UNIVERSITÄT DES SAARLANDES

Asymmetric synthesis of myrtucommulone derivatives and synthesis of a biotin-linked myrtucommulone for affinity based target identification

Dissertation

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The great tragedy of Science — the slaying of a beautiful hypothesis by an ugly fact.

Thomas H. Huxley

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At last, I would like to give a kiss to my “little thing” Maria Augusta who has been there for me when no one else was and keeps making my life sunnier every day.

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Abstract

Myrtucommulones, originally discovered in the Mediterranean shrub *Myrtus communis*, are a class of natural active compounds nowadays well known in the literature. They offer indeed various alternatives to the treatment of pain, inflammation and cancer. Unfortunately, the pharmaceutical world still remains reluctant towards its industrial application. Our incomplete knowledge of the isomeric composition of these compounds as well as the cost-effectiveness, feasibility and safety of the procedure are the most probable issues. On this account, it is of interest to further improve the understanding of the synthesis and mode of action of these substances.

The present work concentrates mainly on the asymmetry of myrtucommulones. This includes the determination of the absolute configurations of myrtucommulone A and B, the achievement, through metal catalysis, of the first enantiomeric excess in the synthesis of myrtucommulone derivatives, and the development of an organocatalysed diastereoselective synthesis of this class of compounds.

Simultaneously, new synthetic methods emerged and gave access to a whole new range of possibilities for the preparation of these active compounds. The syntheses of myrtucommulone derivatives under mild conditions or through a One-Pot reaction are described here.

Finally, a new derivative of myrtucommulone bound to a biotin moiety through a polyamide linker was also synthesised to help identify new cellular targets for compounds of this type.

Zusammenfassung

Myrtucommulone wurden ursprünglich aus Myrte (*Myrtus communis*) isoliert und stellen heutzutage eine gut untersuchte Naturstoffklasse dar, die zahlreiche pharmakologische Eigenschaften besitzt. Sie erwiesen sich beispielweise als besonders wirksam für die Hemmung von Proteinen, die bei der Schmerzentstehung beteiligt sind oder für die Auslösung des Zelltodes von Krebszellen verantwortlich sind. Trotz dieser Fähigkeiten zögert die pharmazeutische Industrie, diese Wirkstoffe in Medikamenten zu verwenden. Die Gründe dafür sind wahrscheinlich zum einen, das unvollständige Wissen über die Isomerenzusammensetzung der Myrtucommulon-Derivate, und zum anderen, die Schwierigkeiten, diese Substanzen in größerem Maßstab herzustellen.

Um das allgemeine Wissen über die Myrtucommulone zu erweitern, hat sich diese Arbeit hauptsächlich mit der Asymmetrie dieser Verbindungen beschäftigt. Zuerst wurden die Absolutkonfigurationen von Myrtucommulon A und B bestimmt. Mittels Metallkatalyse, konnten verschiedene Derivate enantioselektiv hergestellt werden. Anschließend wurden durch Organokatalyse einige Myrtucommulone mit interessanten Diastereomeren-überschüssen synthetisiert.

Gleichzeitig wurden neue Methoden entwickelt, um Myrtucommulon-Derivate bei milden Reaktionsbedingungen oder durch eine Eintopfsynthese herzustellen.

Schließlich wurde das Myrtucommulon-Grundgerüst über einen Polyamid-Linker an Biotin gebunden, um neue therapeutische Targets in Zellen identifizieren zu können.

Résumé

Les myrtucommulones, d'abord découvertes dans le myrte commun (*Myrtus communis*), un arbuste persistant de la région méditerranéenne, sont aujourd'hui une famille de molécules bien étudiée dans la littérature. Ce type de composé actif offre de nombreuses alternatives en ce qui concerne le traitement de la douleur ou de certains cancers. Pourtant, l'industrie pharmaceutique rechigne à y voir là de possibles médicaments. Cela peut s'expliquer entre autre par notre connaissance incomplète de la composition isomérique de ces molécules ainsi que par les coûts et le manque de garanties lors de leur fabrication.

Afin de peaufiner nos connaissances dans ce domaine, une grande partie du travail présenté se consacre à l'étude de l'asymétrie de ces composés. Dans un premier temps, ont été déterminées les configurations absolues des myrtucommulones A et B. Ensuite, des dérivés de myrtucommulone possédant un excès énantiomérique ont été synthétisés par catalyse asymétrique grâce à l'utilisation de complexes métalliques. Puis, une première synthèse diastéréosélective a pu être réalisée par organocatalyse.

Parallèlement, de nouvelles méthodes ont été développées, permettant la préparation des myrtucommulones dans des conditions douces ainsi que par une synthèse monotope.

Pour finir, un nouveau dérivé, liant la structure de la myrtucommulone A à la biotine par une chaine polyamide, a pu être formé afin d'identifier de nouvelles cibles protéiques pour ces composés.

List of abbreviations

A	Acetone
Ac	Acetyl
ACN	Acetonitrile
ALB	$AlLi(BINOL)_2$
APG	Acetyl phloroglucinol
Ar	Aromatic
AUA	11-Aminoundecanoic acid
AUMe	11-Aminoundecanoic acid methyl ester
AUPG	11-Amino-undecanoyl-phloroglucinol
BtABA	4-Biotinamido-butan-1-aminium trifluoroacetate
BINOL	1,1'-Bi-2-naphthol
Boc	*tert*-Butoxycarbonyl
Boc-DAB	*tert*-Butyl-4-aminobutylcarbamate
Boc-DAB-Bt	*tert*-Butyl-4-biotinamidobutylcarbamate
brs	broad singlet
BrUP	11-Bromo-undecanoyl-phloroglucinol
BtA	Biotinamide
BtAUMe	Methyl 11-(biotinamido)undecanoate
Bz	Benzoyl
c	Concentration in g/100mL
CD	Cinchonidine
CN	Cinchonine
COX	Cyclooxygenase
CPD	Cupreidine
CPN	Cupreine
d	doublet
DAB	1,4-Diaminobutane
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
de	diastereomeric excess
DIC	N,N'-Diisopropylcarbodiimide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide

d.r.	diastereomeric ratio
DT101	Anhydrous mixture of DCM/THF, 10/1, v/v
EA	Ethyl acetate
EC_{50}	Half maximal effective concentration
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
Et	Ethyl
Exp. Data Tab.	Experimental data table
Fig.	Figure
GP	General procedure
HOBT	Hydroxybenzotriazole
HODPP	(*S*)-5-(hydroxydiphenylmethyl)pyrrolidin-2-one
HPG	Hexanoyl phloroglucinol
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
IBA	Isobutyraldehyde
IBIND	Isobutylidene indandione
IBPG	Isobutyryl phloroglucinol
IBPGlate	Isobutyryl phloroglucinolate
IBSA	Isobutylidene syncarpic acid
IC_{50}	Half maximal inhibitory concentration
*i*Pr	Isopropyl
LAH	Lithium aluminium hydride
LC	Liquid chromatography
LLB	$LaLi_3(BINOL)_3$
LO	Lipoxygenase
m	multiplet
MA	Meldrum's acid
MC	Myrtucommulone
MCA, MCB, MCC, MCD, MCE, MCF, MCG, MCH, MCI, MCJ, MCK, MCL, MCM	Myrtucommulone A, B, C, D, E, F, G, H, I, J, K, L, M
MCPA	5-myrtucommulone-pentanoic acid
Me	Methyl
MOM	Methoxymethyl
mPGES-1	microsomal Prostaglandin E_2 Synthase-1
MS	Mass Spectrometry
Ms	Mesyl

n-Bu	*n*-Butyl
NMR	Nuclear magnetic resonance
NSMC	Norsemimyrtucommulone
NSMCF	Norsemimyrtucommulone F
PE	Petroleum ether
PG	Phloroglucinol
PGE_2	Prostaglandin E_2
Piv	Pivaloyl
PLL	Poly-L-Leucine
PMC	Pentacyclic myrtucommulone
PMCA	Pentacyclic myrtucommulone A
PMCPA	5-pentacyclic myrtucommulone-pentanoic acid
PPA	Polyphosphoric acid
PTC	Phase transfer catalyst
pTsOH	*para*-Toluenesulfonic acid
q	quartet
Q	Quinine
QD	Quinidine
quint	quintet
ROS	Reactive oxygen species
r.t.	Room temperature
s	singlet
SA	Syncarpic acid
SAMP	(*S*)-aminomethoxymethylpyrrolidine
sept	septet
sext	sextet
SMC	Semimyrtucommulone
t	triplet
Tab.	Table
TADDOL	Tetraaryl-1,3-dioxolane-4,5-dimethanol
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
XRD	X-Ray diffraction

1. Introduction

1.1. Discovery of myrtucommulones

1.1.1. Walking around the Mediterranean sea

Whoever already wandered through the hills of the Mediterranean region, in the south of France, in Corsica, or in North Africa, may have passed by a large amount of green bushes looking alike and with very fine fragrances. One of these evergreen shrubs can reach up to three meters in height and live more than three centuries. It possesses shiny acuminate coriaceous leaves, and the late spring till late summer walker will enjoy its exquisite star-like white flowers bearing numerous white stamens (Fig. 1). From January till March the ovoid blue-black berries are harvested in Corsica to be used in various preparations. This plant is known as common (or true) myrtle (*Myrtus communis*) and belongs to the Myrtaceae family.[1]

a) b)

Fig. 1 Myrtle with a) flowers and b) berries.[2]

Those who do not fancy hiking may be interested to know that this plant has a lot of culinary applications. As a matter of fact, one makes very fine *liqueur* or *schnapps* from myrtle (Fig. 2). Myrtle jelly, myrtle-flavoured honey (Fig. 2) or *terrine* also have a place in a traditional Corsican grocery store.[3] It is possible as well to directly season one meal with dry myrtle leaves and give a very specific taste.

a) b)

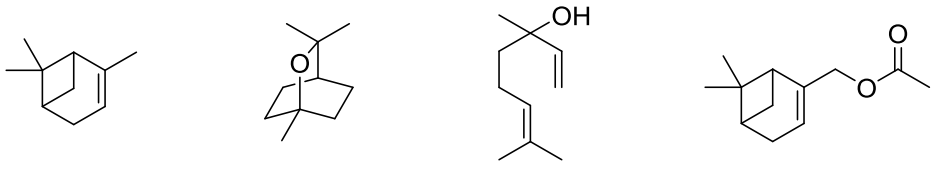
Fig. 2 a) Liqueur and b) jelly made from Myrtle.[3]

1.1.2. A well known plant

Myrtus communis is a widespread bush in the whole Mediterranean area. ALIPOUR *et al.* reported it in Southern Europe, North Africa and Western Asia mostly.[4] It has been known for millenaries, since HIPPOCRATES himself referred to it in his work as a possible remedy.[5] ELFELLAH et al. spoke about it as a known hypoglycaemic agent in the Libyan folk medicine,[6] BONJAR mentioned its antiseptic use in the Iranian traditional medicine,[7] and AKIN *et al.* related about the use of common myrtle decoctions as folk remedies in Italy.[8]

In these works it is always referred to “myrtle extracts” as the active substance. Many other research group focus on the various medicinal use of “myrtle extracts” but since it is not the main topic of this work we will only cite as reference the good and extensive work from ALIPOUR *et al.*[4] This review embraces most, if not all, known properties of myrtle extracts. The anti-inflammatory and anti-oxidative effects are there well described, as well as the hypoglycaemic or anti-bacterial potency. Other very different uses such as treatment of impotence, or hair loss or also depicted in this work.

The composition of myrtle extracts has been the subject of many studies, which mostly concentrated on the water distilled extracts of the leaves. It was possible to determinate major constituents of the myrtle oils such as α-pinene (**1**) and 1,8-cineol (**2**) (Fig. 3).[9] However, the various studies highlighted the fact that the composition is extremely dependent on the geographic region, the period of harvest and the length of distillation (Tab. 1).[4]



1 **2** **3** **4**

Fig. 3 Structures of α-pinene (**1**), 1,8-cineol (**2**), linalool (**3**), myrtenyl acetate (**4**). In the articles cited hereafter,[8-10] no comments were made on the enantiomeric composition of the following compounds.

As an example OZEK *et al.*[10a] reported 1,8-cineol (**2**), linalool (**3**) and myrtenyl acetate (**4**) as major constituents of Turkish myrtle oil whereas BRADESI *et al.*[10b] registered α-pinene (**1**) and 1,8-cineole (**2**) as major constituents of Corsican *Myrtus communis* (Fig. 3).[9] In the common myrtle growing in Northern Cyprus, AKIN *et al*.[8] found no α-pinene (**1**) but more than 50 % of 1,8-cineole (**2**) and linalool (**3**) as major compounds of the essential oil.

Tab. 1 Percentage composition (main constituents) of *Myrtus communis* oil from three different geographic regions.

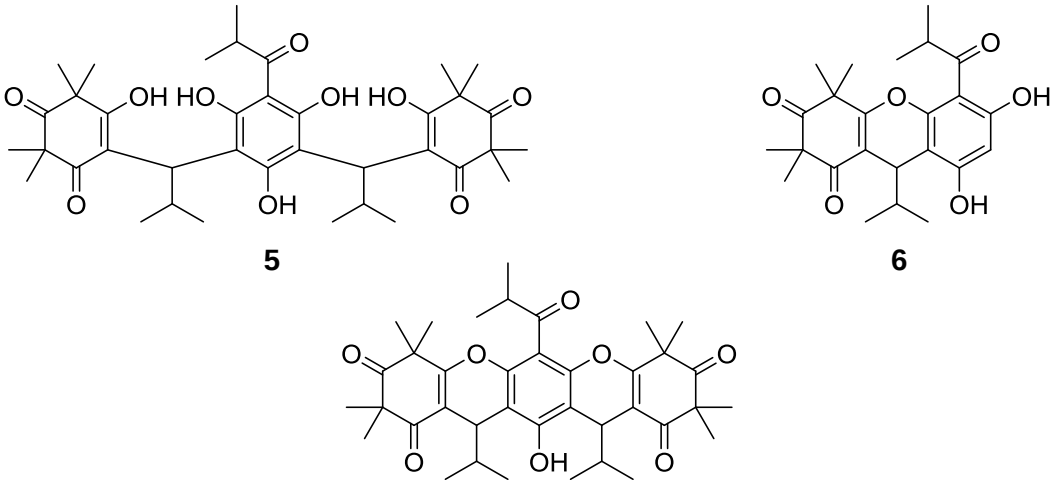
Components	Turkey (leaves)[10a]	Corsica (aerial parts)[10b]	Northern Cyprus (leaves)[8]
α-pinene (**1**)	6.4	**51.2**	x
1,8-cineole (**2**)	**18.2**	**23.6**	**50.1**
linalool (**3**)	**16.3**	2.4	**12.7**
myrtenyl acetate (**4**)	**14.5**	-	-
limonene	3.4	5.9	4.3
α-terpineol	6.5	3.8	7.6
geranyl acetate	5.5	1.9	-
neryl acetate	1.1	-	3.9

- : not mentioned, x : not found.

1.1.3. Myrtucommulones and structure-related products

1.1.3.1 About myrtucommulones

Aware of the antibacterial potency of myrtle extracts, KASHMAN *et al.* isolated for the first time in 1974 two new nonprenylated acyl phloroglucinol compounds that they named myrtucommulone A (MCA) (**5**) and B (MCB) (**6**) (Fig. 4).[11]



5 **6** **7**

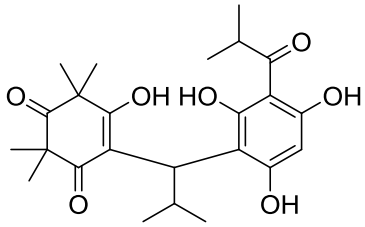
Fig. 4 Structure of MCA (**5**), MCB (**6**) and PMCA (**7**).

After a conscientious analysis by means of NMR and mass spectrometry,[11a] they tested the effects of the newly discovered species on several bacterial strains and found that MCA (**5**) affected the growth of gram-positive bacteria to the same extent as penicillin or

streptomycin.[11b] They could also highlight the importance of the phenolic nature of MCA (**5**) since its pentacyclic derivative PMCA (**7**) (Fig. 4), where several phenolic hydroxyl groups were removed, as well as MCB (**6**) showed much less anti-bacterial activity.

A few years later, LOUNASMAA *et al*. isolated myrtucommulone A (**5**) from *Callistemon lanceolatus*, a shrub from the Myrtaceae family endemic to Australia but grown in India.[12]

In 1998, a French patent described a myrtle extract based preparation in which some myrtucommulones were identified and in particular a hydrated version of MCB (**6**) that was called myrtucommulone B' (MCB') (**8**) (Fig. 5).[13] In 2006, APPENDINO's group, wrote about myrtucommulones again and isolated a new compound very similar to MCB' (**8**) that they named semimyrtucommulone (SMC) (**9**) (Fig. 5).[14] Although the only difference between the compounds **8** and **9** is a methyl group in the *meta*-position of the isobutyryl group, they were not named consequently and the succeeding literature rather took over the term from APPENDINO. Therefore we will, for more clarity, name the compound **8** norsemimyrtucommulone (NSMC) in accordance with **9**.



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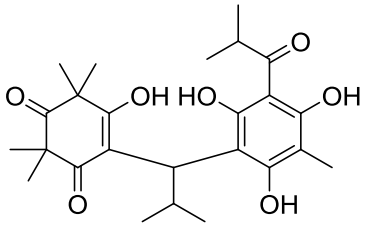

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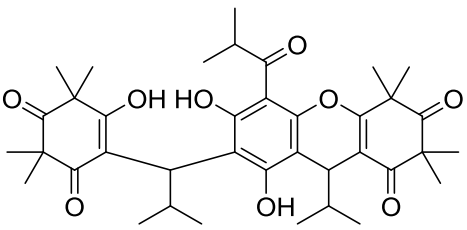
Fig. 5 Structures of norsemimyrtucommulone (NSMC) (**8**) and semimyrtucommulone (SMC) (**9**).

That same year, SHAHEEN *et al.* isolated from Pakistani *Myrtus communis* three new myrtucommulones: MCC (**10**) (Fig. 6), MCD (**11**) and MCE (**12**) (for the structures of the latter two, see § 1.1.3.3: "Pharmacological studies").[15] Two years later, QUINN *et al.* discovered MCA (**5**) and D (**11**) along with four new myrtucommulones (myrtucommulone F (MCF) (**13**) (Fig. 6), and MCG to MCI) in the Australian eucalyptus tree *Corymbia scabrida.*[16]



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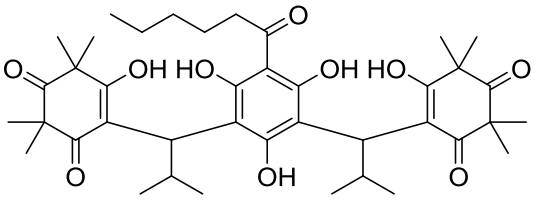

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Fig. 6 Structures of MCC (**10**) and MCF (**13**).

More recently COTTIGLIA and co-workers[17] reported myrtucommulones J (MCJ) (**14**) to L and again SHAHEEN *et al*. extracted myrtucommulone M and myrtucommuacetalone (**15**) from *Myrtus communis* (for the structures of compounds **14** and **15**, see § 1.1.3.3).[18]

Finally in 2014, NICOLETTI *et al.* brought myrtucommulones to a new dimension since they could spot MCA (**5**) and MCD (**11**) in a fungus, endophytic in myrtle, called *Neofusicoccum australe*.[19] The availability of a fungal strain to be cultured *in vitro* could indeed provide access to larger amounts of these derivatives, making them even more inviting for the pharmacological industry.

1.1.3.2 About other structure-related compounds

Because they were not isolated from myrtle, a lot of natural compounds where given other names. Nevertheless their structures are clearly related to myrtucommulones. For this reason, is given here a non exhaustive insight of these other products.

One of the closest examples is the one of the molecules extracted from *Kunzea ericoides* from New Zealand. BLOOR discovered in 1992,[20] two new non-prenylated phloroglucinol derivatives **16** and **17** that he did not name but which have structures very similar to NSMC (**8**) (Fig. 7).

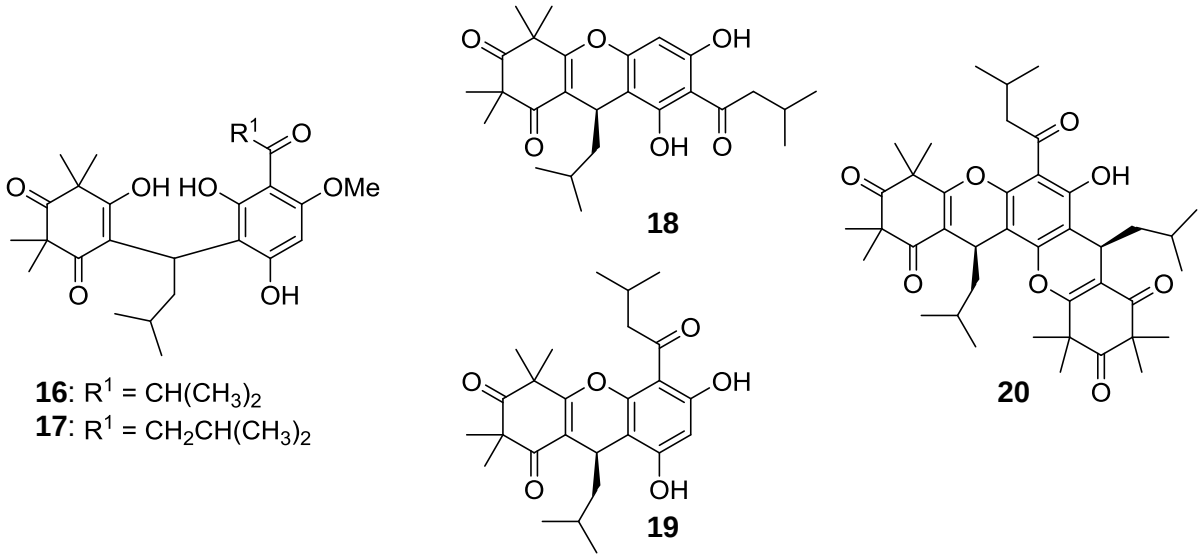


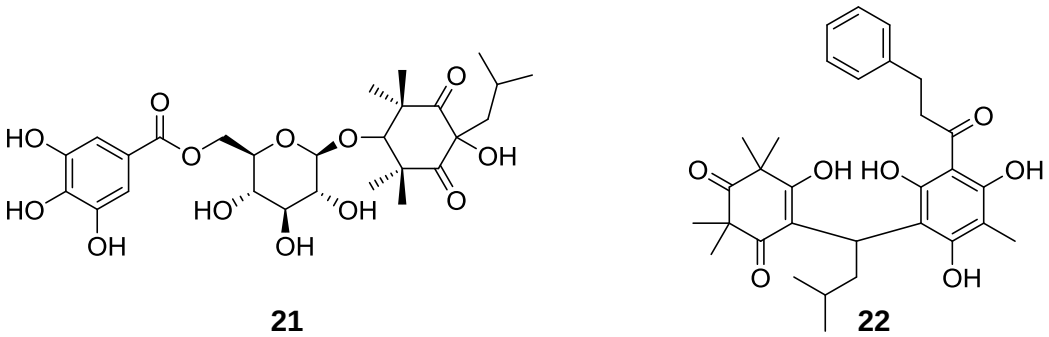
Fig. 7 Structures of phloroglucinol derivatives **16**, **17**, rhodomyrtone (**18**), rhodomyrtosone B (**19**) and rhodomyrtosone C (**20**).

Other very closely related compounds were isolated from *Rhodomyrtus tomentosa* from Southeast Asia. Rhodomyrtone (**18**) and rhodomyrtosone B (**19**) and C (**20**) present

structures very close to the one of myrtucommulone B (**6**) and myrtucommulone E (**12**) (Fig. 7).[21] It is noteworthy that both plants belong to the same family as common myrtle (Myrtaceae).

Gallomyrtucommulones isolated by APPENDINO *et al.*[22] are also worth being cited since they include a syncarpic acid moiety and were extracted from *Myrtus communis.* Despite their related name, these compounds are constitutionally a little more distant from MCs since they possess a galloylglucose moiety. Among them, gallomyrtucommulone B (**21**) showed interesting anti-bacterial activity (Fig. 8).

Finally, QUINN *et al*.[23] isolated corymbones A and B (**22**) from *Corymbia peltata* which again are non-prenylated phloroglucinols having very strong similarities with myrtucommulones and were shown to be possible candidates for the treatment of pain (Fig. 8).



21 **22**

Fig. 8 Structures of gallomyrtucommulone B (**21**) and corymbone B (**22**)

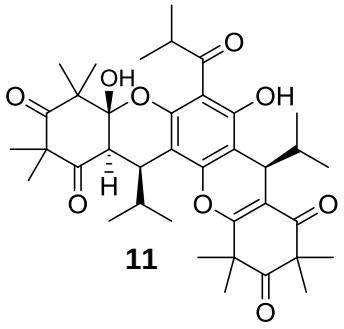
1.1.3.3 Pharmacological studies

As written above, the isolation of new molecules from *Myrtus communis* was motivated by the search for new natural products with biological activity.[11] The arising of this new class of nonprenylated acyl phloroglucinol derivatives led to numerous pharmacological studies.

Anti-bacterial effect

The first results of KASHMAN and co-workers[11] in which MCA (**5**) showed a growth inhibiting effect on gram-positive bacteria such as *Staphylococcus aureus*, *Bacillus subtilis* or *Streptococcus faecalis* were confirmed almost thirty years later by APPENDINO *et al.*[14] who studied the effect of MCA (**5**) and SMC (**9**) on various *Staphylococcus aureus* strains. Later SHAHEEN *et al.*[15] pointed out the efficacy of myrtucommulone D (**11**) and E (**12**) on the same

type of bacteria (Fig. 9) and COTTIGLIA *et al.*[17] underlined the specificity of myrtucommulone J (**14**) against it.



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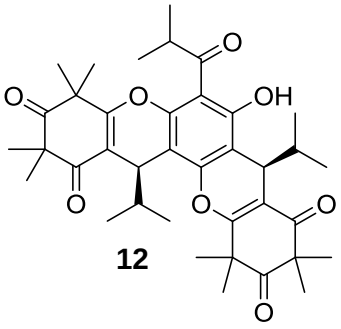

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Fig. 9 Structures of myrtucommulone D (**11**) and myrtucommulone E (**12**).

Recently, the French company PIERRE FABRE DERMO-COSMÉTIQUE developed a dermatologic preparation from myrtle extracts destined to prevent the growth of *Propionibacterium acnes*, a slow growing bacterium linked to acne. They identified MCA (**5**), MCB (**6**), MCD (**11**), NSMC (**8**), and SMC (**9**) as major constituents of their extract.[24]

Anti-inflammatory and analgesic effect

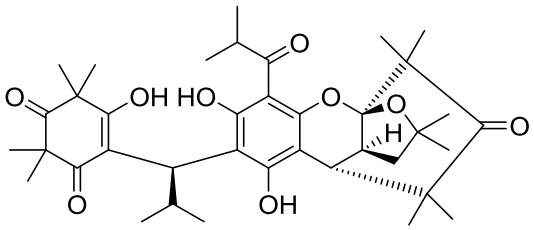
Cyclooxygenases (COXs) and 5-lipooxygenase (5-LO) are key enzymes for the biosynthesis of prostaglandins and leukotrienes respectively. These hormones are believed to be directly involved in the inflammatory response leading to pain and fever. In 2005, WERZ and co-workers[25] published their work showing that MCA (**5**) and to a lesser extent SMC (**9**) directly inhibit cyclooxygenase-1 (COX-1) and 5-lipooxygenase (5-LO).

The inhibition of COX enzymes leads to the non-formation of all products of the cyclooxygenase pathway, but it is known that some prostaglandins possess important physiological functions.[26] A few years later, WERZ *et al.*[26a] identified microsomal prostaglandin E2 synthase-1 (mPGES-1) as a new target for MCA (**5**).[26] They discovered that mPGES-1 was indeed inhibited in a concentration dependent manner without significant inhibition of COX enzymes. This provides a real advantage in the treatment of inflammatory diseases since it directly suppresses the formation of PGE_2, a prostaglandin responsible for inflammation, pain and fever without preventing the formation of the other important prostaglandins.[26]

According to QUINN *et al.*[16] MCA (**5**), MCD (**11**), MCF (**13**) and MCG-I showed specific binding activity to THR receptor-2, a brain hormone receptor that has been proposed as a therapeutic target to treat pain.

Anti-oxidative activity

ROSA *et al.*[27] concentrated on the anti-oxidative properties of these compounds and showed that SMC (**9**) is more powerful than MCA (**5**) in scavenging hydroxyl and peroxyl radicals (Reactive Oxygen Species, ROS) responsible for damaging cells and tissues. This property seems to be directly related to the hydrogen-donating activity of its phenolic hydroxyl group. Similarly, myrtucommuacetalone (**15**) was found to possess an inhibitory effect on ROS generation (Fig. 10).[18]



15

Fig. 10 Structure of myrtucommuacetalone (**15**).

Hypoglycaemic activity

α-Glucosidase inhibitors are used in the management on non-insulin dependent diabetes mellitus (Type 2, most common form of diabetes) to inhibit certain enzymes catalysing the transformation of starch and sucrose in absorbable monosaccharides therefore delaying the postprandial blood glucose peak. Myrtucommulone B (**6**), D (**11**), E (**12**) and especially C (**10**) were found to be all more potent inhibitors than widely prescribed acarbose and standard inhibitor deoxynojirimycin.[15]

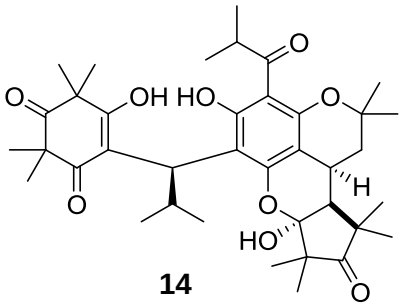
Cytotoxic activity

The most inspiring property of myrtucommulones is probably the selective induction of apoptosis in cancer cell lines.[17,28] Apoptosis is the process of programmed cell death. Deregulation of apoptosis may disrupt the delicate balance between cell proliferation and cell death leading to the formation of tumours. Two major pathways can be distinguished for apoptosis, the extrinsic pathway, triggered through so called death receptors and the intrinsic pathway, involving mitochondria.[28] WERZ *et al.* studied the influence of MCA (**5**) and SMC (**9**) on various cancer cell lines. They found out that MCA (**5**) causes loss of the mitochondrial membrane potential, releasing cytochrome c from mitochondria. Cytosolic cytochrome c

interacts with the adaptor protein Apaf-1 recruiting caspase-9 which then activates caspase-3 leading to cell death.[28]

In cooperation with the present work, a recent study from IZGI *et al.*[29] demonstrated that MCA (**5**) induces both extrinsic and intrinsic apoptosis pathways in 4T1 cancer cells.

COTTIGLIA *et al.*[17] also proved that MCJ (**14**) exhibits an even better activity than MCA (**5**) against MT-4 tumour cell lines (Fig. 11).

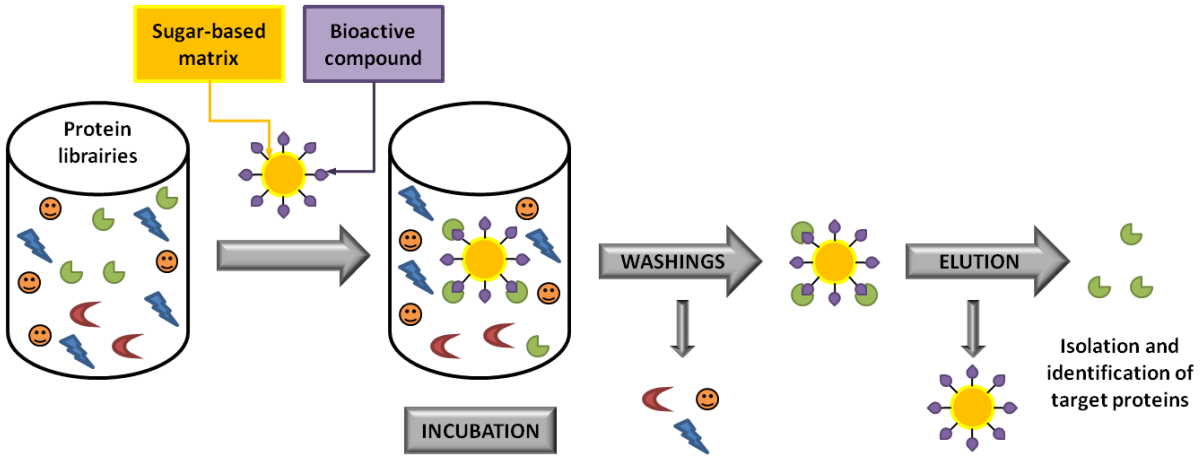


14

Fig. 11 Structure of myrtucommulone J (**14**).

1.1.3.4 Affinity-based target identification

As described above, the possibilities of pharmaceutical use of MCs are numerous. To discover new cellular targets of bioactive molecules, affinity-based purification (also known as target fishing) is one of the most commonly used methods. It relies on the direct interaction/binding between the active compound and the protein.[30] Typically, the drug is attached to a suitable affinity moiety (such as biotin) or directly immobilized on a resin such as agarose beads through a linker. The affinity probe is then incubated with cell extracts and thoroughly washed to remove non-specifically bound proteins. The bound proteins are then eluted and separated with SDS-PAGE and identified by mass spectrometry or peptide sequencing (Scheme 1).[30c,31]



Scheme 1 Outline of affinity chromatography using mobile affinity matrices.[31]

The affinity probe consists principally of three parts: the ligand (or drug), the linker (with or without a functional tag) and the sorting part (matrix). Sugar-based matrices such as agarose (e.g. Affigel-10) or sepharose (e.g. EAH Sepharose 4B™) have been frequently used as solid support in the literature.[32] In 2012, HANDA *et al.*[31] successfully developed high-performance affinity beads composed of multiple ferrite particles coated with a special polymer. These so called “FG-beads” have the main advantage that they can be recovered magnetically.

The linker may affect non specific protein binding as well as the accession of the target to the drug. Differing length of polymethylene and polyethylene glycol are commonly used. The linker may be tagged with fluorescent molecules for visual observation of the target compound. Biotin (**23**), also known as vitamin B_7, B_8 or H, is a widely used functional tag due to its very strong interaction with avidin or streptavidin (avidin is a protein found in the white of the eggs of birds or reptiles, streptavidin has a similar structure and is produced by *Streptomyces avidinii*).[30c,33] As described in Fig. 12, biotin is bound through a linker to the active compound and after incubation, bound proteins can be precipitated with streptavidin-beads.

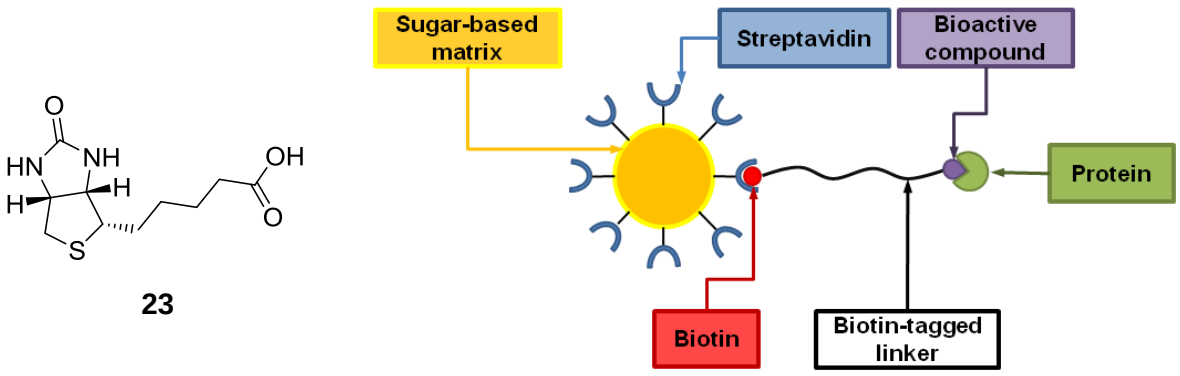
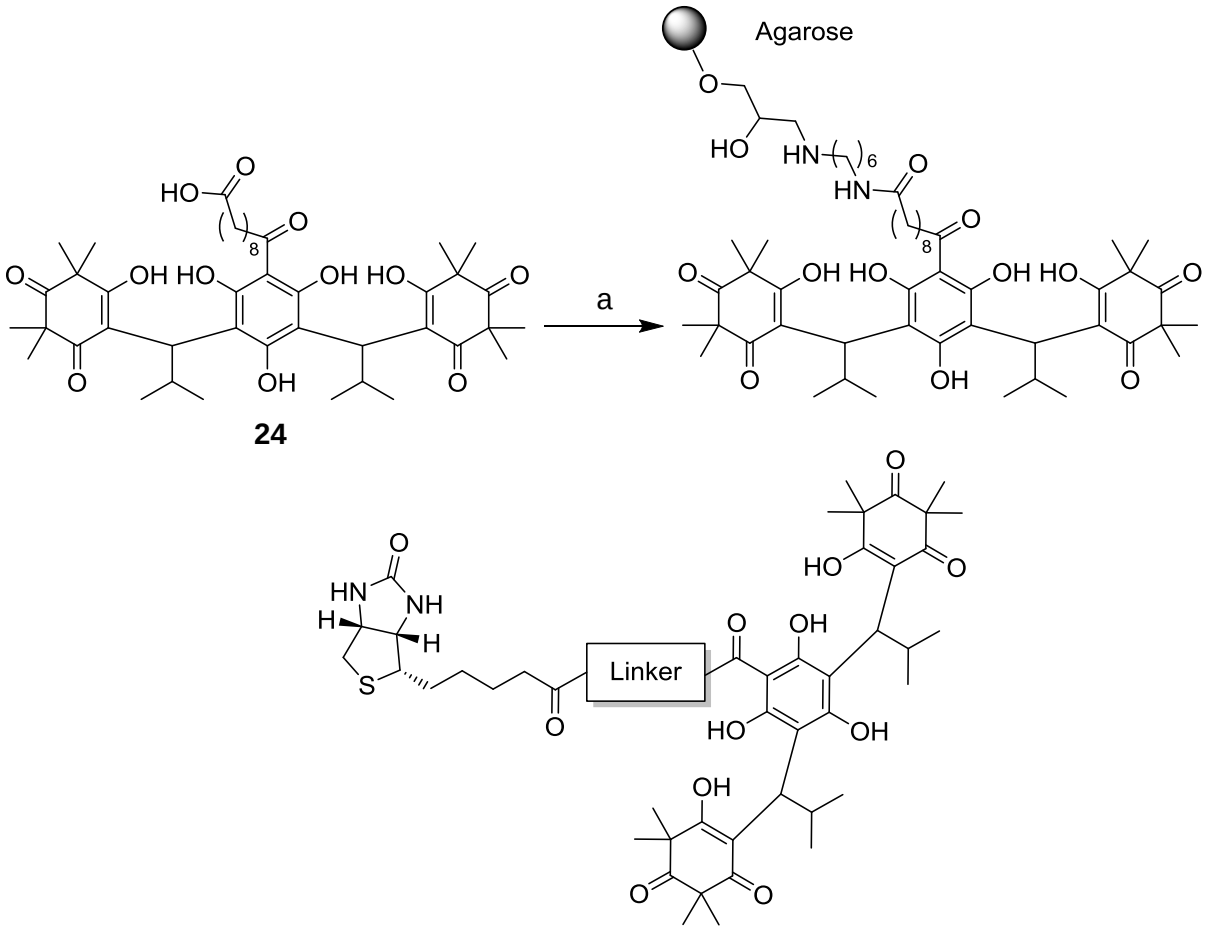


Fig. 12 Representation of biotin (**23**) and its use as functional tag.

During his PhD-Thesis,[34] H. MÜLLER bound a “sebacoyl myrtucommulone” (**24**) to EAH Sepharose 4B™, which possesses a primary amine, to form an amide bond and immobilise the myrtucommulone moiety on agarose beads (Scheme 2). The identification of new targets for MC-derivatives by the research group of Prof. WERZ in Jena is still in progress.

To pursue similar investigations but in different conditions, we came to the idea of making a different compound, namely a biotin-bound myrtucommulone. We therefore dedicated a part of the present work to the search for a suitable linker to bind a myrtucommulone moiety and biotin together (Scheme 2).

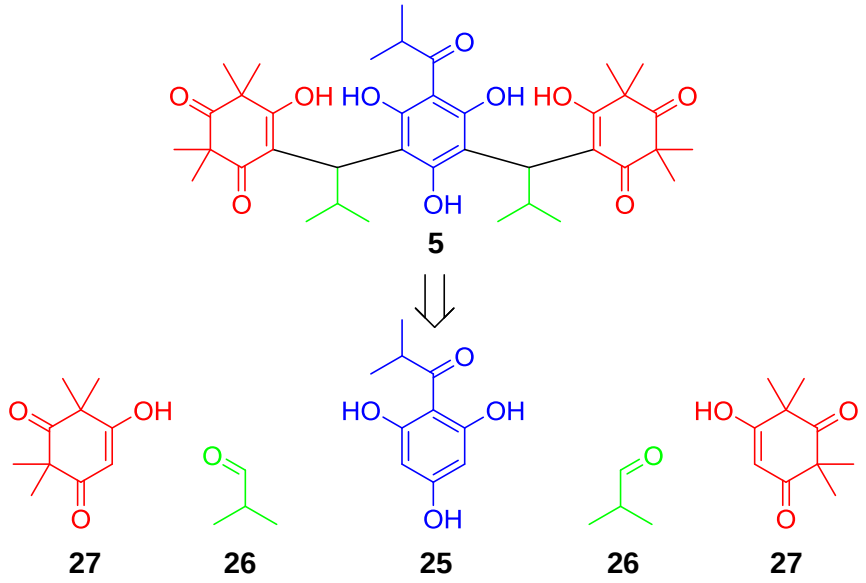


Scheme 2 Formation of Sepharose-bound myrtucommulone and structure of biotin-bound myrtucommulone. a) EAH Sepharose 4B™, EDCI, dioxane/H_2O, r.t., 96 h.

1.2. Total synthesis of myrtucommulones

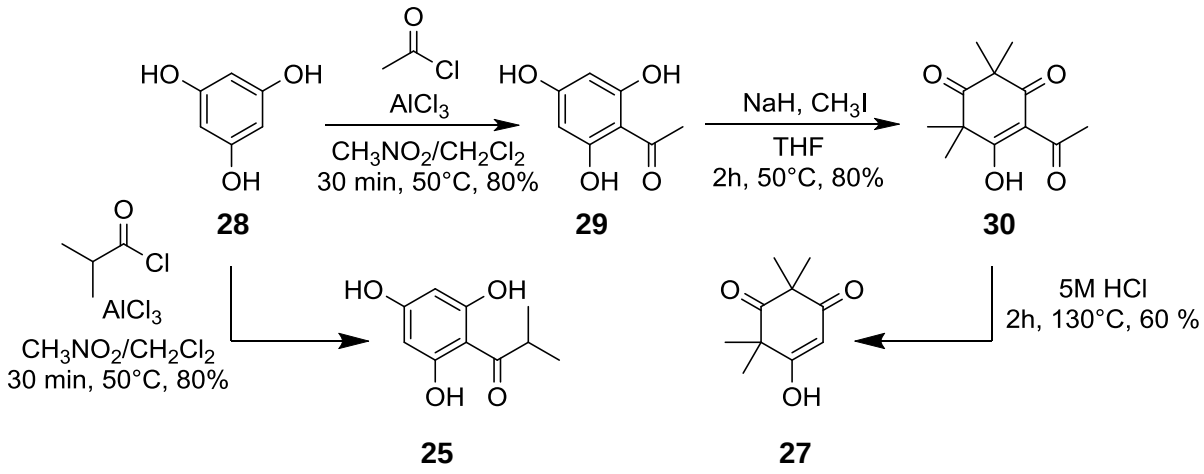
1.2.1. First total syntheses of some myrtucommulone derivatives

As an answer to the rising interest for myrtucommulones, JAUCH *et al.*[35] proposed in 2010 the first total synthesis of myrtucommulone A (**5**), B (**6**), C (**10**), F (**13**) and some derivatives. Myrtucommulone A (**5**) was retrosynthetically divided in three main exchangeable units: isobutyryl phloroglucinol (IBPG) (**25**), isobutyraldehyde (IBA) (**26**), and syncarpic acid (SA) (**27**) (Scheme 3).



Scheme 3 Retrosynthetical approach of MCA (**5**)

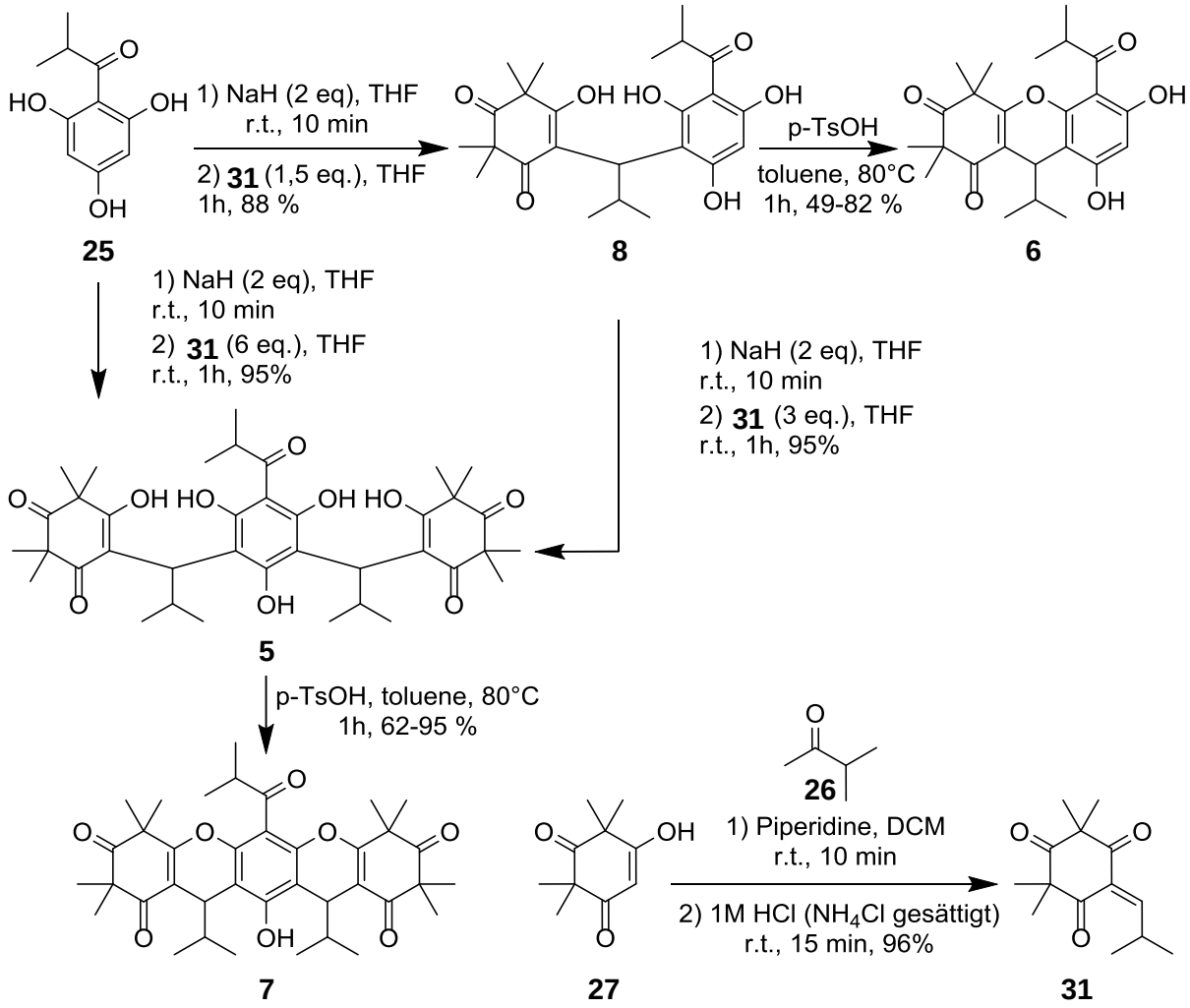
SA (**27**) is a naturally occurring compound that can be easily synthesised in the laboratory from phloroglucinol (PG) (**28**). The starting material **28** was acylated on the one hand to form the central unit **25**, and on the other hand to form acetyl phloroglucinol (APG) (**29**) for the synthesis of the unit **27** (Scheme 4).



Scheme 4 Synthesis of syncarpic acid (**27**) and isobutyryl phloroglucinol (**25**).

APG (**29**) was then methylated four times with methyl iodide to **30**, and the acetyl group was removed through boiling in hydrochloric acid (5M) to give syncarpic acid (**27**) (Scheme 4).

Isobutylidene syncarpic acid (IBSA) (**31**) was formed through a Knoevenagel condensation of SA (**27**) and IBA (**26**) shortly before use to avoid its isomerisation in the dienol-isomer, which is unreactive in the present reaction (Scheme 5).[35a] Isobutyryl phloroglucinol (IBPG) (**25**) was then deprotonated with sodium hydride and 6 equivalents of **31** (for a better yield) were needed to form MCA (**5**) in two successive Michael additions (Scheme 5). In order to synthesise NSMC (**8**), only 1.5 equivalents of the Michael acceptor **31** were added. NSMC (**8**) can also be seen as an intermediate to MCA (**5**). It can be isolated and used again in another reaction to reach MCA (**5**) (Scheme 5). This could also be used to synthesise non-symmetric MCs like MCC (**10**) (from MCB (**6**)) or artificial derivatives as shown in the JAUCH publication[35a] or in the PhD-thesis of MÜLLER.[34]



Scheme 5 Synthesis of myrtucommulone A (**5**) and isobutylidene syncarpic acid (**31**)

The NMR analysis of such compounds is made difficult by the presence of stereoisomers and the number of possible tautomers and rotamers stabilised through hydrogen bonds.[35a]

In order to be analysed fully, MCA (**5**) as well as NSMC (**8**) were cyclised to PMCA (**7**) and MCB (**6**) respectively, by stirring in refluxing toluene in the presence of p-TsOH (Scheme 5). Pharmacologically, the newly synthesised MCA (**5**) showed very similar potency to inhibit the above cited mPGES-1 or induce apoptosis, which justified the usefulness of this synthetic path.[35]

1.2.2. Synthesis of other pharmacologically active derivatives

After the success of the first synthesis of MCA (**5**) and a few naturally occurring derivatives, JAUCH and co-workers focused on synthetic derivatives. They could successfully identify unique compounds showing an improved anti-inflammatory activity or a better apoptosis-inducing potency.[34-36] Listed below are the various building blocks that were combined for the synthesis of derivatives (Fig. 13).

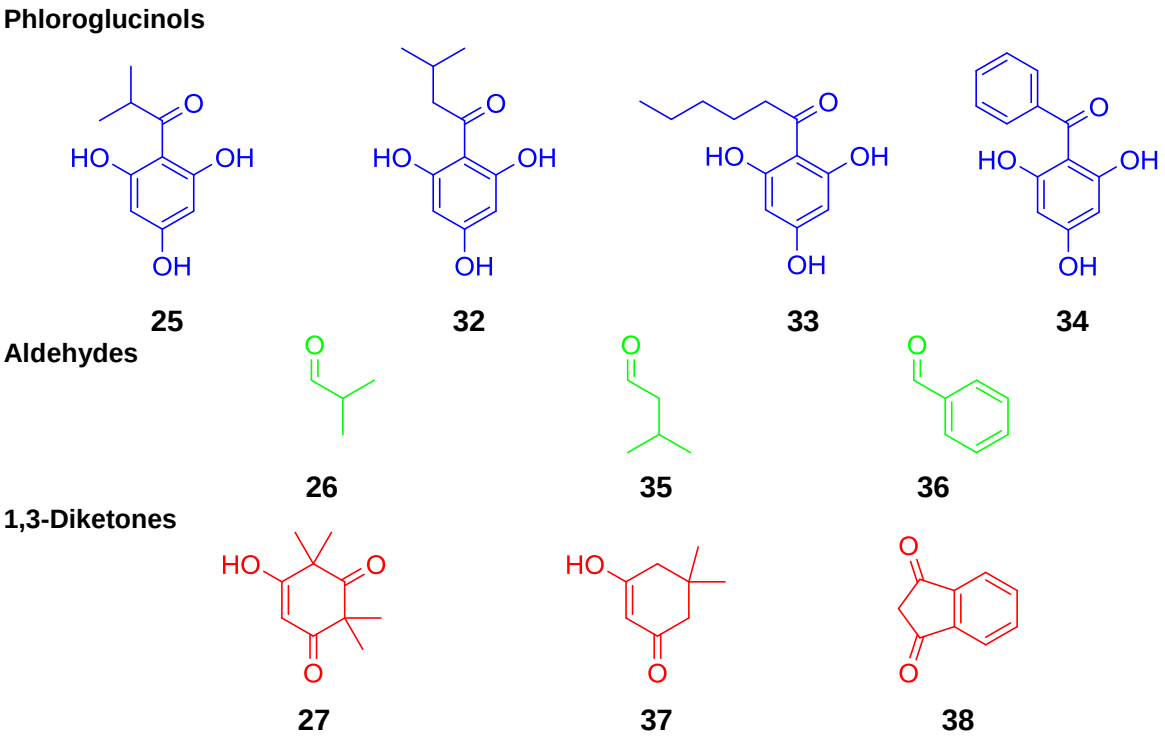
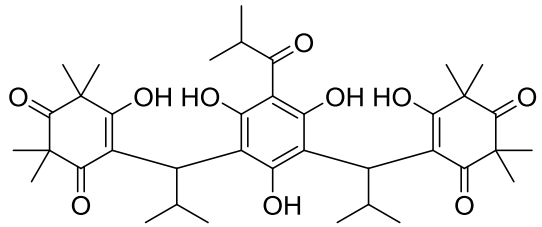


Fig. 13 Various building blocks used for the synthesis of derivatives

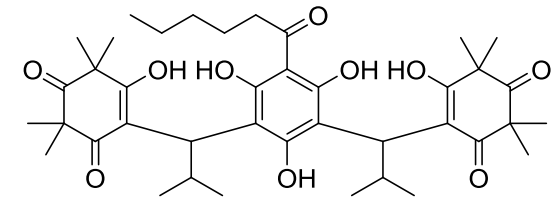
In Fig. 14 are depicted the derivatives with the most efficacy. Interestingly, the IC_{50} value for the inhibition of mPGES-1 (one enzyme included in the pain process, see § 1.1.3.3, Anti-inflammatory and analgesic effects), decreases when a longer chain replaces the isobutyryl group, when isovaleraldehyde (IVA) (**35**) is used and with the use of 1,3-indandione (**38**) as a Michael acceptor. The combination of hexanoyl phloroglucinol (HPG) (**33**) and 1,3-indandione (**38**) to form the myrtucommulone derivative **39** led to an extremely efficient

compound showing an IC_{50} value of only 0.08 µmol/L (almost 10 times lower than for MCA (**5**)). Regrettably, no compound of this kind also including IVA (**35**) could be synthesised to this day. According to the existing results, we could hope to achieve an even better IC_{50} for the myrtucommulone-derivative **41** with the structure depicted in Fig. 14.



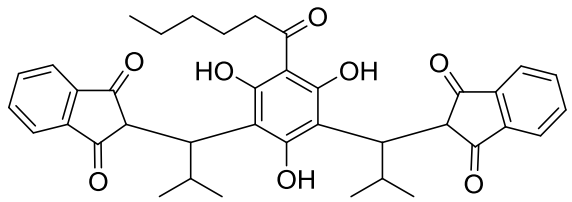
MCA (**5**)

IC_{50}(mPGES-1) = 0.70 µmol/L
IC_{50}(5-LO cell based assay) = 3.20 µmol/L



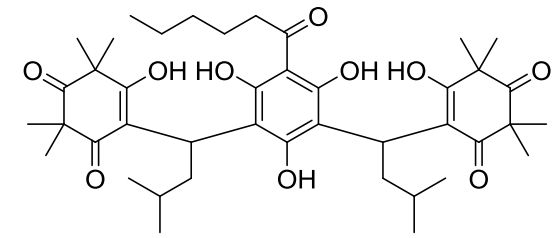
MCF (**13**)

IC_{50}(mPGES-1) = 0.60 µmol/L
IC_{50}(5-LO cell based assay) = 3.10 µmol/L



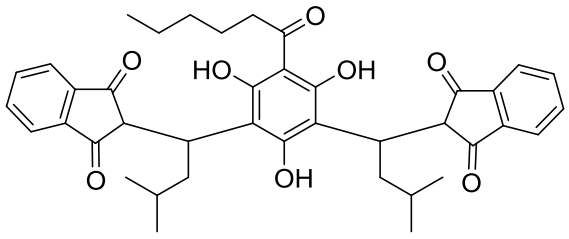
39

IC_{50}(mPGES-1) = 0,08 µmol/L
IC_{50}(5-LO cell based assay) = 1.46 µmol/L



40

IC_{50}(mPGES-1) = 0.24 µmol/L
IC_{50}(5-LO cell based assay) = 0.46 µmol/L



41

Fig. 14 Structure and IC_{50} of the most potent mPGES-1 and 5-LO inhibitors

It is noteworthy as well that the compounds which show a good anti-inflammatory potency are relatively different from the one who happened to be good cytotoxic agents. In the Fig. 15 we depicted the molecules with the best EC_{50} values for the induction of apoptosis. Half-cyclised compounds like MCC (**10**) and **44** are around 3 times more efficient than MCA (**5**) and molecules where the syncarpic acid moiety has been replaced by a dimedone unit (**37**) showed similar potency. Moreover, it is pleasant to see that even MCB (**6**) which is “only” a half-bodied myrtucommulone is of interest in this case.

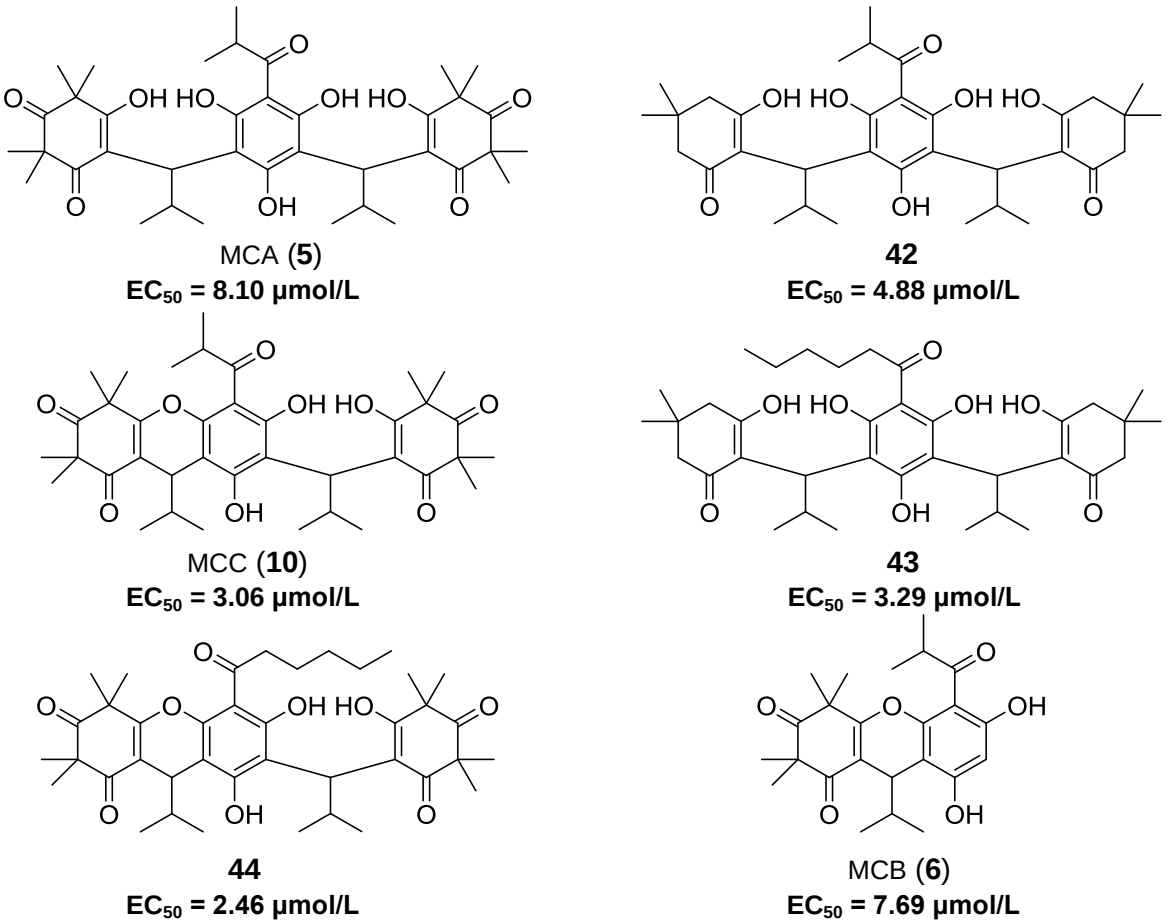


Fig. 15 Structure and EC_{50} of the most potent apoptosis inductors.

1.2.3. Limits of the synthesis

Although this synthesis is extremely efficient and led to the identification of several new artificial derivatives with excellent pharmaceutical properties,[34,36] it has the inconvenience that it uses hydrides and needs therefore dry conditions. This makes the realisation of this reaction in a larger scale costly and dangerous. Despite the obvious interest of MCs for the pharmaceutical industry, this could be a major drawback to their mass production. Likewise, it is disadvantageous that the instable acceptor (**31**) needs to be prepared shortly before use and cannot be stored. This would lead again to complications in an industrial environment.

In this regard, it was interesting to develop an alternative synthesis for myrtucommulones. The first concern was to identify a new class of catalysts for more security and flexibility. The second was to find a more comfortable method to synthesise the myrtucommulones with less effort.

1.3. Asymmetric synthesis

1.3.1. Asymmetry of myrtucommulone A

Since myrtucommulone A (**5**) possesses two constitutionally identical stereocenters, two enantiomers (*R*,*R* and *S*,*S*) and a so called *meso* form are expected (Fig. 16). However, due to the extreme complexity and variability of its structure (stabilisation of the different tautomers and rotamers through hydrogen bonding),[35a] it was not possible to isolate and identify them.

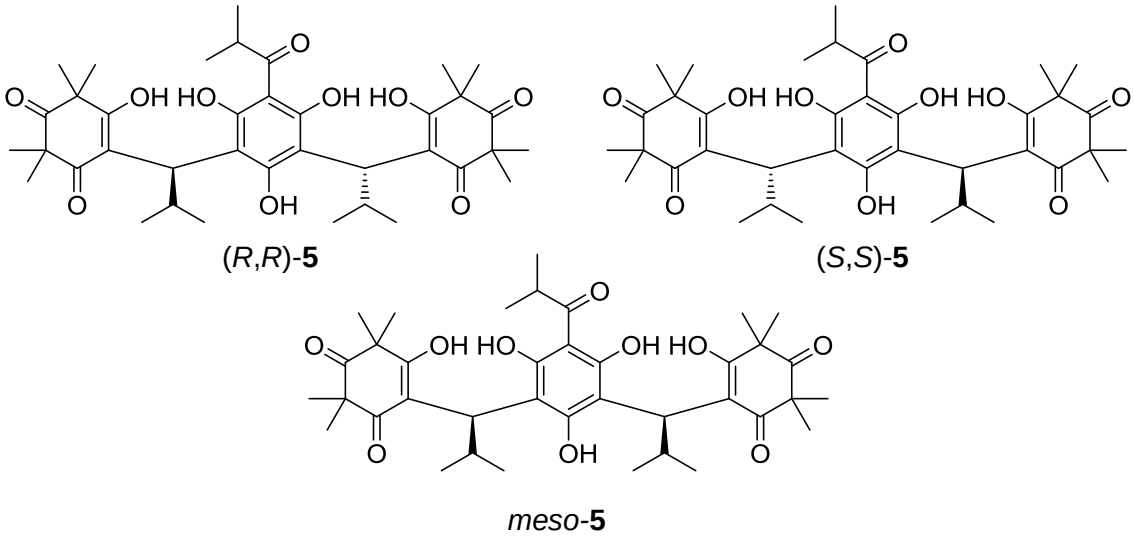
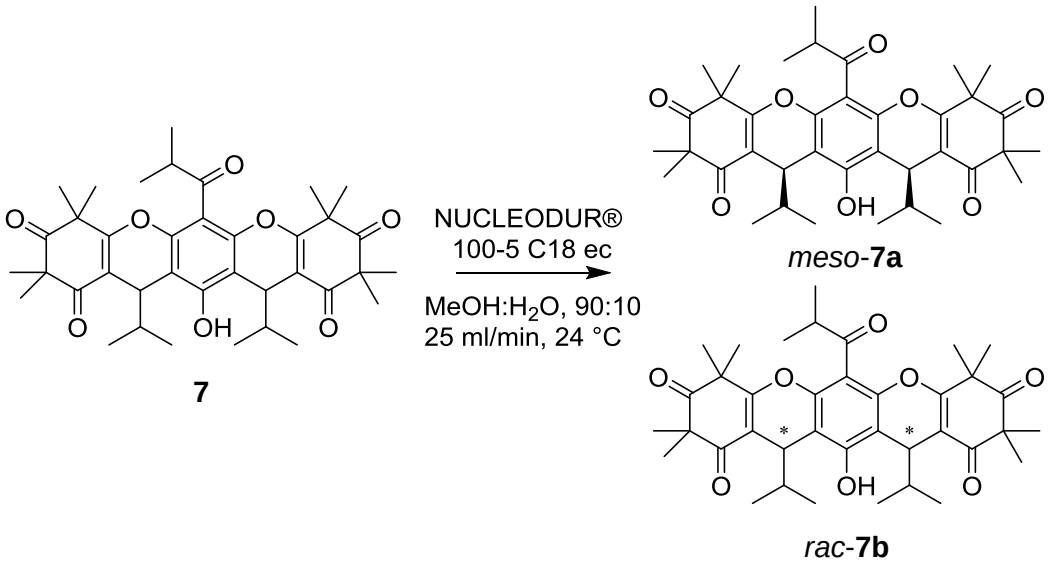


Fig. 16 Structure of the three stereoisomers of myrtucommulone A (**5**)

In his work from 2008,[16] QUINN *et al*. claimed that their MCA from *Corymbia scabrida* should have the configuration *R** and provided an optical rotation value of $[\alpha]_D^{17.6}$ = + 42.1 (*c* = 0.066, MeOH). In the same paper, another myrtucommulone, myrtucommulone D (MCD) (**11**) was isolated from the same plant and provided a small rotatory power: $[\alpha]_D^{17.6}$ = + 13.9 (*c* = 0.13, MeOH). In their publication from 2006 SHAHEEN *et al.*[15] found in *Myrtus Communis* a MCD (**11**) with an optical rotation of $[\alpha]_D^{30}$ = + 375 (*c* = 0.8, $CHCl_3$). On this, QUINN et al. commented that, whereas their low value is rather in favour of a chemically controlled production, the high value of SHAHEEN *et al.* rather speaks for an enzymatic control. One should notice though, that the two values were not measured in the same solvent and should not be compared directly.

In their work on the total synthesis from 2010, JAUCH *et al.* cyclised MCA (**5**) to PMCA (**7**) and separated chromatographically the *meso*-form (*meso*-**7a**) from the racemic mixture of the (*R*,*R*) and (*S*,*S*) enantiomers (*rac*-**7b**) (Scheme 6).[35] Later in this work, if the ratio of the

(*R*,*R*) and (*S*,*S*) enantiomers is not 1:1 or just not known, we will refer to the mixture as **7b**, or **5b** if we speak about uncyclised **5** (the same nomenclature applies for other derivatives). They found that the ratio between *rac*-**7b** and *meso*-**7a** was 54:46 giving another hint concerning diastereomeric composition of synthetic and natural MCA (**5**). But a doubt still remained since it was conceivable that racemisation takes place during the cyclisation process.



Scheme 6 Chromatographic resolution of PMCA (**7**)

To extend and clarify the knowledge on the stereoisomers of myrtucommulone derivatives and possibly draw conclusions about the biosynthesis of this class of compounds, the JAUCH group concentrated on the asymmetric synthesis of such compounds.

First of all it should allow to collect some data concerning the enantiomers of MCs and confirm or not that the isolated compounds are pure or mixtures of stereoisomers. This would also state if racemisation takes place during cyclisation. Then it should help discovering if the efficacy of myrtucommulone is due to its chirality or not. Finally this should allow better understanding of the formation process of myrtucommulones in the plant or the fungus.

1.3.2. Strategies to the asymmetric synthesis

There are numerous strategies for the preparation of enantiopure compounds. As suggested by SINGH *et al.*,[37] it is possible to divide them into two categories: chiral resolution, and asymmetric synthesis (Fig. 17). The first means the isolation of one specific enantiomer from a racemic mixture. The second signifies to selectively synthesise an enantiomerically pure compound. Three approaches to asymmetric synthesis can be distinguished: use of the

chiral pool, use of chiral auxiliaries, or use of chiral catalysts. The latter has an edge over the other due to its cost effectiveness and environmental friendliness. Theoretically, a single molecule of a chiral catalyst can lead to the production of millions of target molecules.[37]

At the beginning of this thesis no chromatographic resolution could be achieved for the uncyclised products, which meant that the different enantiomers of MCA (**5**) were not accessible through this method. Our first move towards asymmetric synthesis was made through the chiral auxiliary method in my own Diploma-thesis and will be discussed briefly in the next paragraph.[38] As these attempts were not especially successful, we then decided to concentrate on metal-catalysis with which we achieved a good enantiomeric excess (*ee*) and later on organocatalysis which led to a good diastereomeric excess (*de*).

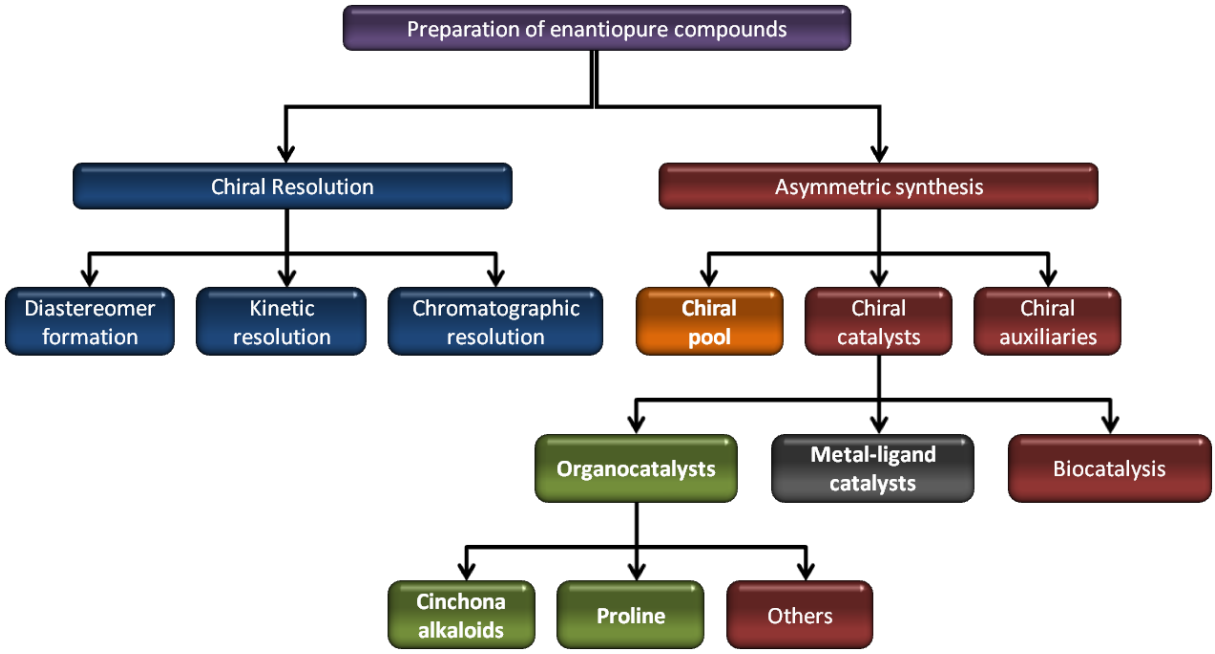


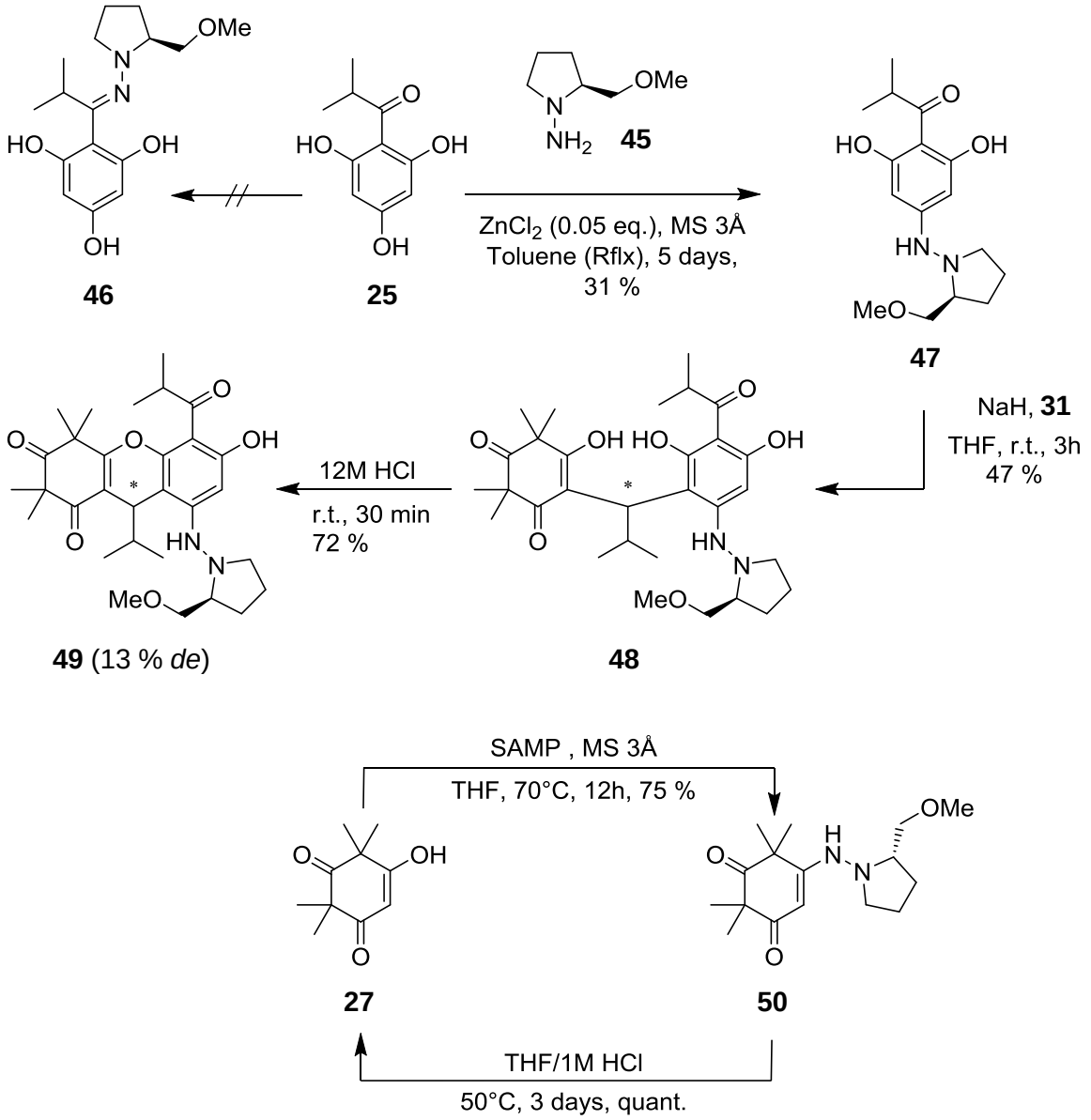
Fig. 17 Strategies for the preparation of enantiopure compounds.

1.3.3. Work toward the asymmetric synthesis of myrtucommulone A using a chiral auxiliary

The first attempts of asymmetric synthesis were performed in my Diploma-thesis.[38] The chiral auxiliary method was chosen and the Ender's auxiliary called SAMP ((*S*)-1-amino-2-methoxymethylpyrrolidine) (**45**) was preferred. It was intended to synthesise the SAMP-hydrazone (**46**) of isobutyryl phloroglucinol (**25**) (Scheme 7). Due to the high electron density on the carbonyl group, it came out that we could not synthesise the hydrazone, but the *para*-substituted IBPG (*para*-SAMP-IBPG) **47**. Nevertheless, para-SAMP-NSMC (**48**) could be

synthesised and cyclised to **49**. It was possible to read the diastereomeric excess (*de*) directly on the NMR but only 13% were observed (Scheme 7).

In another attempt, the SAMP-hydrazone of syncarpic acid (**50**) could be formed and the chiral auxiliary could be removed under mild conditions (Scheme 7). We then tried this new product in our synthesis but no myrtucommulone-derivative could be detected.



Scheme 7 Work towards the asymmetric synthesis of myrtucommulones using SAMP (**45**).

1.4. Objectives of this work

The possibility to use myrtucommulones (MCs) as drugs is obvious. To better understand the mode of activity of myrtucommulones and discover new targets, one objective of this work was the binding of biotin to the MC main structure for the needs of affinity-based chromatography. From the industrial point of view, the costs of the starting materials and the feasibility of the procedure are often limiting factors. Therefore, one goal of this work was to further study and improve the synthesis of this class of compounds.

The enantiomeric composition of MCs is unclear; the previous work on this theme was so far unsuccessful[38] and research groups do not agree on the purity of the isolated compounds. There is no data on perfectly identified enantiomers and the biosynthetic pathway in the plant or in the fungus is ambiguous. Besides it is still unknown if the activity of MCs is due to its chirality or if this has no influence on its efficacy. For all these reasons, this work mainly focuses on the asymmetric synthesis of MCs (especially NSMC (**8**) and MCA (**5**)).

For a start, we determined the absolute configuration of the enantiomers of MCB (**6**) (and later NSMC (**8**)) and the diastereomers of PMCA (**7**) (and later MCA (**5**)). As MCA (**5**) possesses two stereocenters, we focused first on the enantioselective formation of NSMC (**8**) which only has one. After some promising results, the reactions were also performed on MCA (**5**). To proceed with the asymmetric synthesis, we first came back to our previous work using chiral auxiliaries.[38] Then we concentrated on the metal-ligand catalysis achieving good enantioselectivities. Afterwards, the reaction was modified for the use of organocatalysts to synthesise directly myrtucommulones derivatives in a One-Pot synthesis or in similar mild conditions affording very good diastereomeric excess. At the end, the synthesis of a myrtucommulone derivative bound to biotin was achieved.

2. Results and Discussion

2.1. Absolute configuration of myrtucommulone B and pentacyclic myrtucommulone A

2.1.1. Preliminary chromatographic work

Before starting the investigation of the asymmetry of myrtucommulones, we had to define a reliable method to identify any *ee*. After unsuccessful attempts to separate the enantiomers of NSMC (**8**) or MCA (**5**), we could achieve the first separation of the enantiomers of MCB (**6**) using the CHIRALCEL OD-H chiral chromatography column (Fig. 18a).

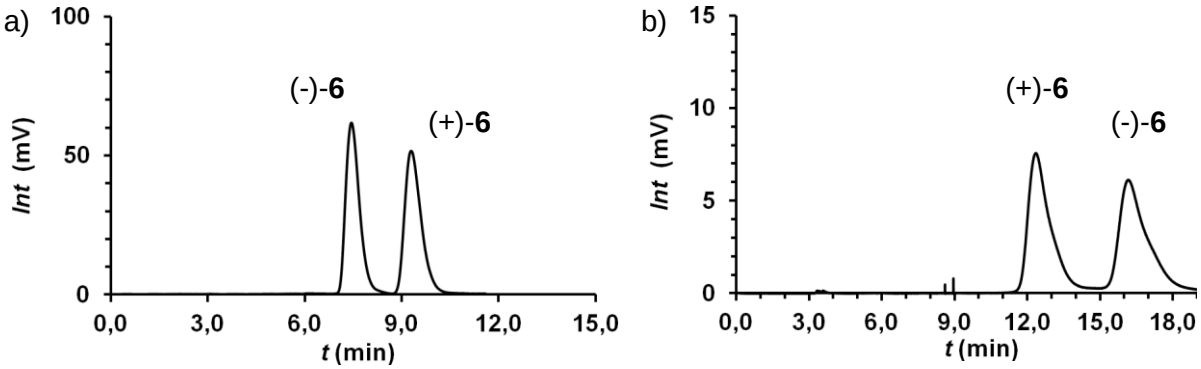


Fig. 18 Chromatographic separation of MCB enantiomers a) on CHIRALCEL OD-H, *i*PrOH/*n*-hexane 20:80, 0.5 mL/min, 15°C, (-)-**6** (t_R = 7.44 min), (+)-**6** (t_R = 9.29 min) and b) on Reprosil 100 Chiral-NR, *i*PrOH/*n*-hexane 5:95, 1.0 mL/min, 24°C, (+)-**6** (t_R = 12,37 min), (-)-**6** (t_R = 16.18 min).

Thanks to the parallel work of M. HANS on the Reprosil 100 Chiral-NR chiral chromatography column, the MCB (**6**) enantiomers could be as well separated and isolated after processing the compound on the preparative version of the same column (Fig. 18b).[39] It is noteworthy that the enantiomers come in a different order depending on the column used.

Likewise the pentacyclic derivatives *rac*-**7** and *meso*-**7** were separated through preparative HPLC according to the method described above and the *rac*-PMCA enantiomers (+)-**7** and (-)-**7** could be likewise identified (Fig. 19).

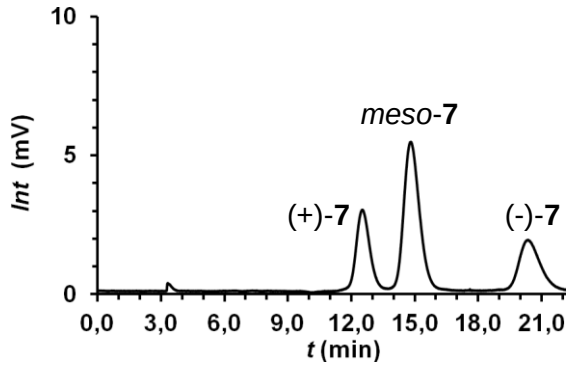


Fig. 19 Chromatographic separation of PMCA stereoisomers on Reprosil 100 Chiral-NR, *i*PrOH/*n*-hexane 5:95, 1.0 mL/min, 24°C, (+)-**7** (t_R = 12,51 min), *meso*-**7** (t_R = 14.82 min), (-)-**7** (t_R = 20.37 min).

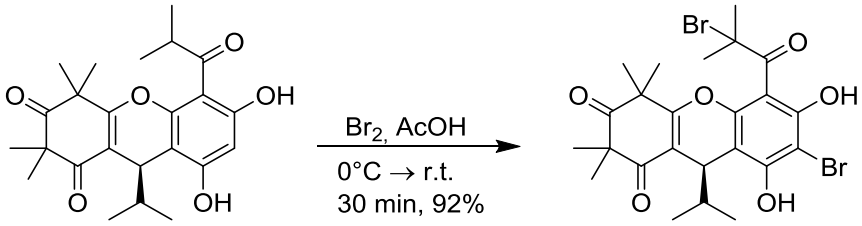
2.1.2. Derivatisation of cyclic myrtucommulones

Thanks to the work of M. HANS from the JAUCH group, a consequent amount of each enantiomer could be soon isolated to further characterise these compounds. It was then possible to determinate the absolute configuration of each peak by derivatising them with different methods, growing crystals from each and analysing it by means of X-ray diffraction.[40]

2.1.2.1 Bromination of (+)-myrtucommulone B

The first isolated peak from MCB (**6**) (on Reprosil 100 Chiral-NR) was identified to be (+)-MCB ((+)-**6**) ($[\alpha]_D^{24}$ = +213 (*c* = 1.0, $CHCl_3$). It appeared to us that determination of the absolute configuration thanks to the resonant scattering effects in X-Ray Diffraction (XRD) was the most appropriate method.[41] This effect can be achieved by introducing a heavy atom (e. g. Br) in the molecule and submitting it to XRD of a single crystal. When X-Rays are incident on an atom, they are scattered in different directions with the same wave length. BRAGG *et al.*[42] figured out that certain specific wave length and incident angles produced peaks of reflexion of strong intensity. They considered the crystal as a set of parallel planes and suggested that these peaks would appear if the reflected peaks interfere constructively. A set of planes of the same direction is described with the Miller indices *(hkl)*.
According to Friedel's[43] law the intensities of one reflexion *hkl* (e.g. (1 0 0)) and its opposite, noted $\overline{hkl}$ (e.g. ($\overline{1}$ 0 0)) are the same. Using a wavelength that only excites one atom (e. g. Br) creates a phase lag in the scattering of this atom, which leads to the loss of equivalence of these intensities. This can be measured and subsequent calculations allow to determine the relative positions of the atoms hence revealing the absolute configuration.

Bromine was hence added to a sample of (+)-MCB ((+)-**6**) to form a dibrominated product, which eventually showed the same optical rotation sign than its precursor, we called (+)-dibromomyrtucommulone B ((+)-DiBrMCB) ((+)-**51**, $[\alpha]_D^{24}$ = + 39.5 (*c* = 1.0, $CHCl_3$) (Scheme 8).[44] After conscientious crystallisation from dichloromethane, white needles were obtained and submitted to anomalous X-ray scattering (Fig. 20).[40]



(+)-(*R*)-**6** (+)-(*R*)-**51**

Scheme 8 Synthesis of (+)-dibromomyrtucommulone B (**51**)

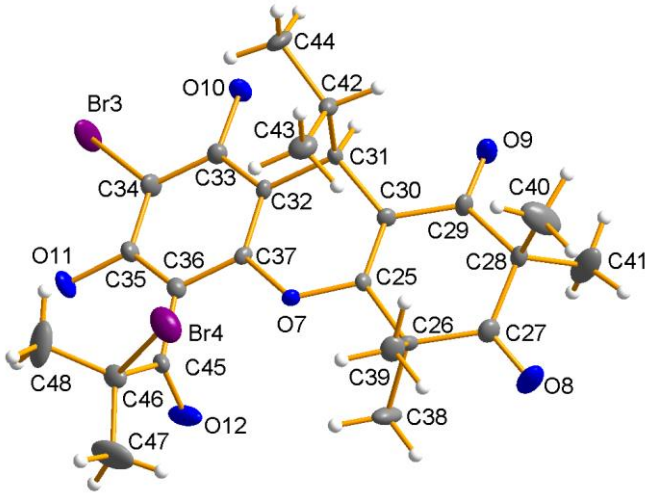
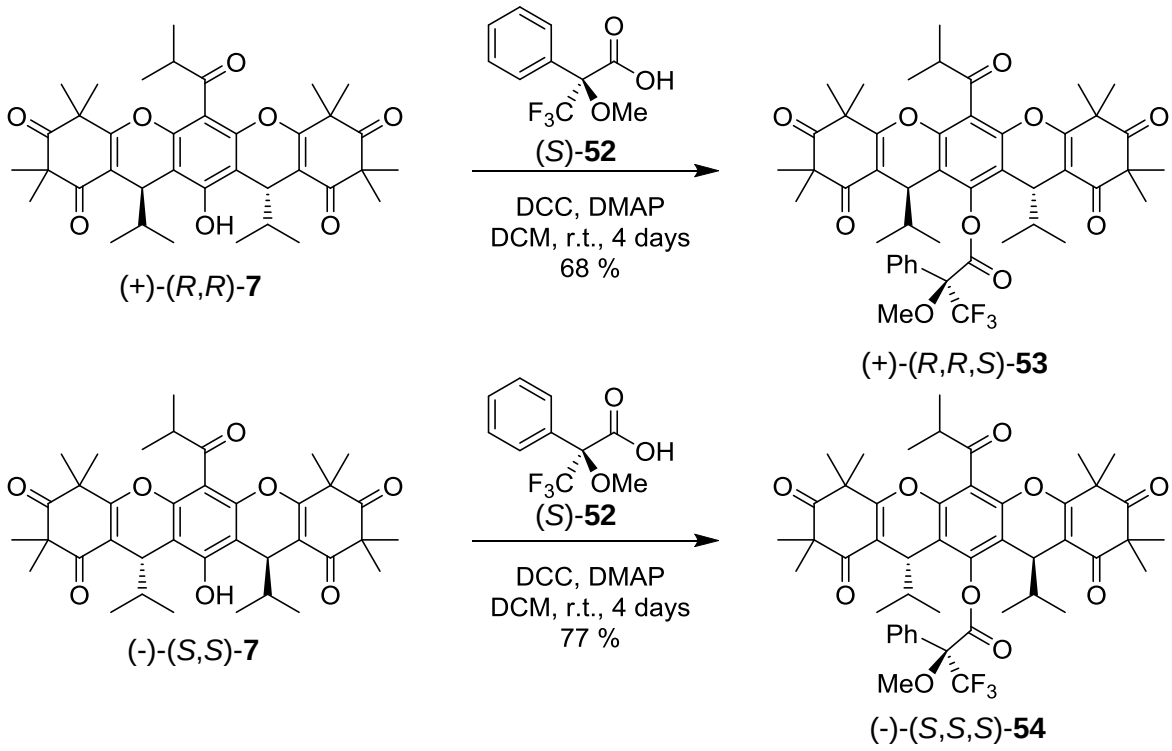


Fig. 20 X-ray structure of (+)-(R)-dibromomyrtucommulone B (**51**); ellipsoids at the 50 % probability level.

The configuration of the only stereocenter of (+)-DiBrMCB (**51**) was found to be *R* implying that the configuration of (+)-MCB ((+)-**6**) is also *R*. Consequently, the other enantiomer of myrtucommulone B (**6**) is (-)-(*S*)-MCB ((-)-(*S*)-**6**).

2.1.2.2 Formation of the Mosher ester of pentacyclic myrtucommulone A

Given that PMCA (**7**) possesses a single phenolic alcohol, the formation of an ester of the Mosher acid (**52**) was preferred.[41a] As described above, the enantiomers of *rac*-PMCA (*rac*-**7**) were separated, and to each one was added a mixture of (*S*)-Mosher acid ((*S*)-**52**), DCC and DMAP to yield after a several days the desired esters **53** and **54** (Scheme 9).[45]



Scheme 9 Synthesis of the Mosher derivatives (+)-**53** and (-)-**54**

The pentacyclic myrtucommulone (+)-**7** led to (+)-PMCA-(*S*)-Mosher ester ((+)-**53**) which showed an optical rotation of $[\alpha]_D^{24}$ = + 40.2 (*c* = 1.0, $CHCl_3$) and (-)-**7** led to (-)-PMCA-(*S*)-Mosher ester ((-)-**54**) which provided an optical rotation of $[\alpha]_D^{24}$ = -15.5 (*c* = 1.0, $CHCl_3$). After several attempts, only the (+)-**53** derivative gave needle-shaped white crystals, which revealed the absolute configuration of (+)-**7** to be *R*,*R* (Fig. 21).[40] As a consequence, the non-crystallised diastereomer is (-)-(*S*,*S*,*S*)-PMCA-Mosher ester ((-)-**54**), which means that the configuration of the (-)-**7** enantiomer is *S*,*S*.

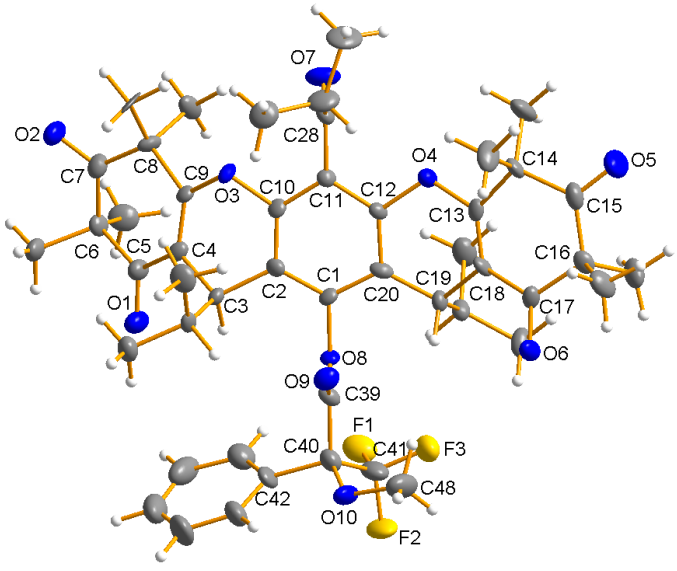


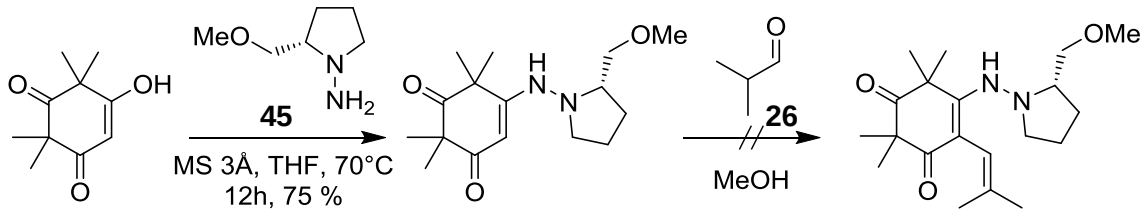
Fig. 21 X-ray structure of (+)-(*R*,*R*)-PMCA-(*S*)-Mosher ester ((+)-(*R*,*R*,*S*)-**53**); ellipsoids at the 50 % probability level.

2.2. Investigation of various synthetic pathways

Additionally to the two main methods used for our asymmetric synthesis (metal catalysis and organocatalysis), other synthetic pathways were also considered. We first came back to the chiral auxiliary method and intended the synthesis of a norsemimyrtucommulone derivative bound to an auxiliary through three different strategies. Another alternative synthesis including an asymmetric alkylation was also investigated.

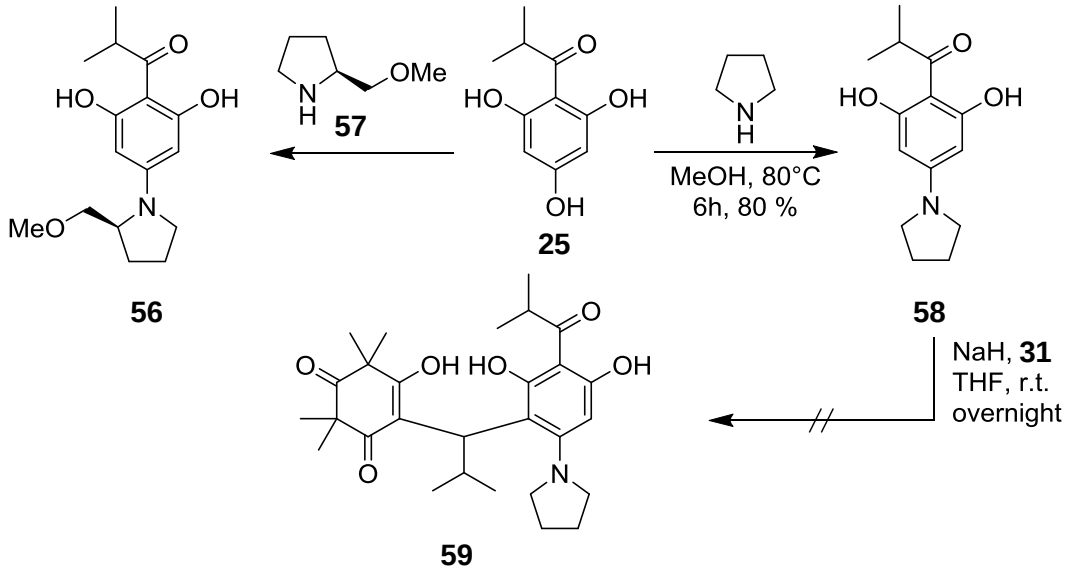
2.2.1. The chiral auxiliary method

The previously synthesised SAMP derivative of syncarpic acid **50** was used again to try to form the isobutylidene derivative **55** by mixing it with IBA (**26**) but no transformation or any consumption of the starting material could be observed.[38] Varying the solvent and the temperature or using some additives like piperidine to enhance the Mannich reaction did not have any influence (Scheme 10).



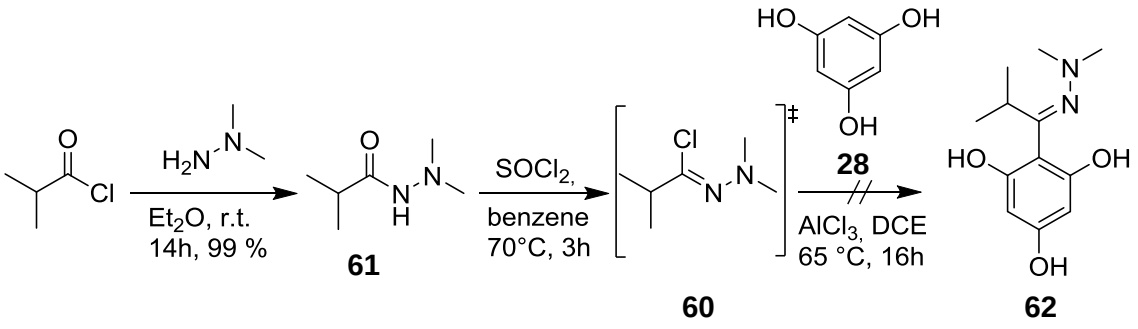
Scheme 10 Attempt to synthesise the Michael acceptor **55** from the SAMP derivative **50**.

As it was so far the first success in the asymmetric synthesis of NSMC (**8**) (13% *de* in the diastereomeric mixture of para-SAMP-MCB (**49**)),[38] another try was given to the *para*-substituted version of IBPG. The *para*-SAMP-IBPG (**47**) possessed two rotational axes along the C-N and the N-N axes. The idea was to suppress one rotational axis for the auxiliary and hence allow less degree of freedom. We aimed for **56**, a derivative of SMP (*S*-methoxymethylpyrrolidine) (**57**) and IBPG (**25**) (Scheme 11). Not to waste an expensive auxiliary, pyrrolidine was used first to form *para*-pyrrolidinyl-IBPG (**58**). Although it was no problem to synthesise **58** by stirring the starting materials in boiling methanol,[46] no reaction took place when it was deprotonated and IBSA (**31**) was added to synthesise the NSMC derivative **59**. Various attempts were run in different solvents and with different temperatures but the starting material was never consumed.



Scheme 11 Synthesis of *para*-pyrrolidinyl-IBPG (**58**) and attempt to synthesise the derivative **59**.

In previous attempts to use a chiral auxiliary, it was tried to add a hydrazine, for example N,N-dimethylhydrazine, as the hydrazonyl chloride **60** to phloroglucinol (**28**) through a Friedel-Crafts reaction.[47] Then, we would replace N,N-dimethylhydrazine by SAMP (**45**) for instance to induce stereoselectivity. First N',N'-dimethylisobutyrohydrazide (**61**) was synthesised from isobutyryl chloride and N,N-dimethylhydrazine (Scheme 12).[47c] We used thionyl chloride in refluxing benzene to get to the intermediate **60** and used it without purification in a Friedel-Crafts type reaction with PG (**28**).[47a,b] All isolated products included the phloroglucinol structure and some of them the isopropyl group from **60** but they had lost the methyl groups and no product **62** could be identified. It is most probable that the hydrazone was hydrolysed. This path was not further investigated.

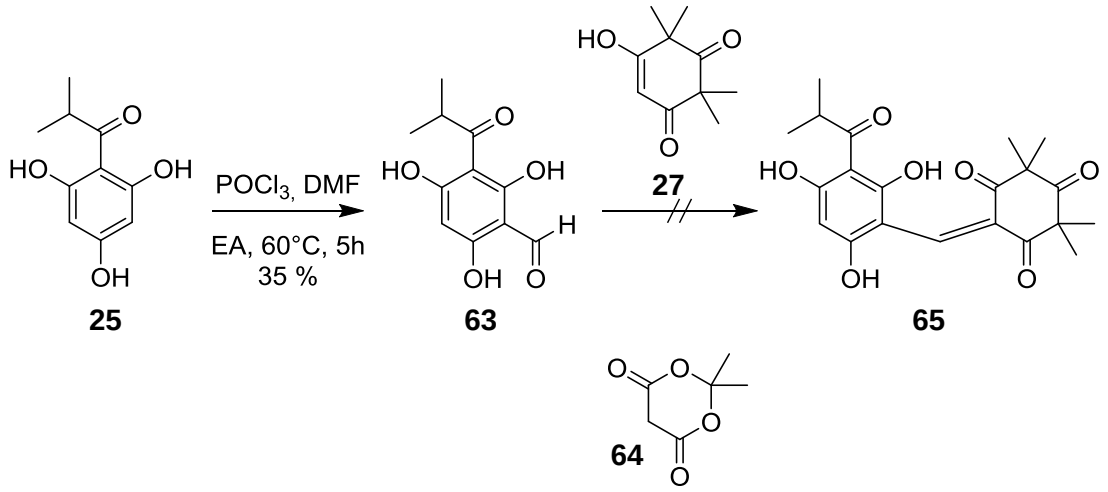


Scheme 12 Attempts to synthesise the hydrazone **62**.

2.2.2. Formation of an intermediate for an asymmetric alkylation

As an alternative to the known synthesis of myrtucommulone derivatives (§ 1.2), it was thought to add a formyl group to IBPG (**25**) to form **63** in order to perform a Knoevenagel type reaction with syncarpic acid (**27**). The idea was to afterwards alkylate stereoselectively the newly formed α,β-unsaturated ketone. For this, we based on the idea of WALKER *et al.*[48] who condensed Meldrum's acid (MA) (**64**) (Scheme 13), whose structure is close to SA (**27**), with a formyl-arene to then perform a Zn-mediated asymmetric alkynylation. We planned to use diisopropyl zinc and copper-ligand additives to reproduce the conditions found in the literature to insert an isopropyl group.[49]

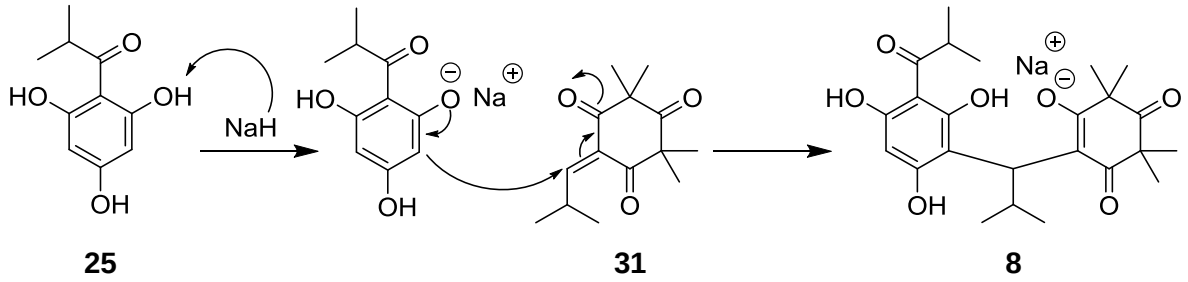
Formyl-IBPG (**63**) was synthesised with a poor yield through a Vilsmeier-Haack type reaction (Scheme 13).[50] On the other hand, no reaction could be observed between the derivative **63** and syncarpic acid (**27**), neither in the presence of an acid (camphersulfonic acid) nor a base (DMAP, piperidine), nor using a dehydrating agent (molecular sieves) and heat.
The reaction did not run either in other solvents or with higher temperatures. It is however surprising that absolutely no consumption of the starting material was observed, not even to form the aldol product of the aldehyde **63** and the enolised ketone **27**. This confirmed once again the results obtained formerly,[38] that is to say that the electrophilicity of any carbonyl group attached to the phloroglucinol ring is weakened by the delocalised aromatic electrons, which means that the formyl group is unreactive in this conditions.



Scheme 13 Synthesis of Formyl-IBPG (**63**) and structure of MA (**64**) for comparison. Attempt to synthesise compound (**65**)**.**

2.3. Metal catalysed asymmetric synthesis

After the unsuccessful tries with alternative pathways to synthesise MCs, we decided to come back to the simple principle of the known synthesis.[35a] We hence looked for methods to perform stereoselectively a Friedel-Crafts reaction (from the point of view of the central unit) or a Michael reaction (from the point of view of the isobutylidene unit). Mechanistically regarded, once the hydride deprotonated the central unit (**25**), the sodium cation stays bound to the alcoholate as an ion pair (Scheme 14). Therefore, we decided to simply modify the base to achieve a stereoselective synthesis.

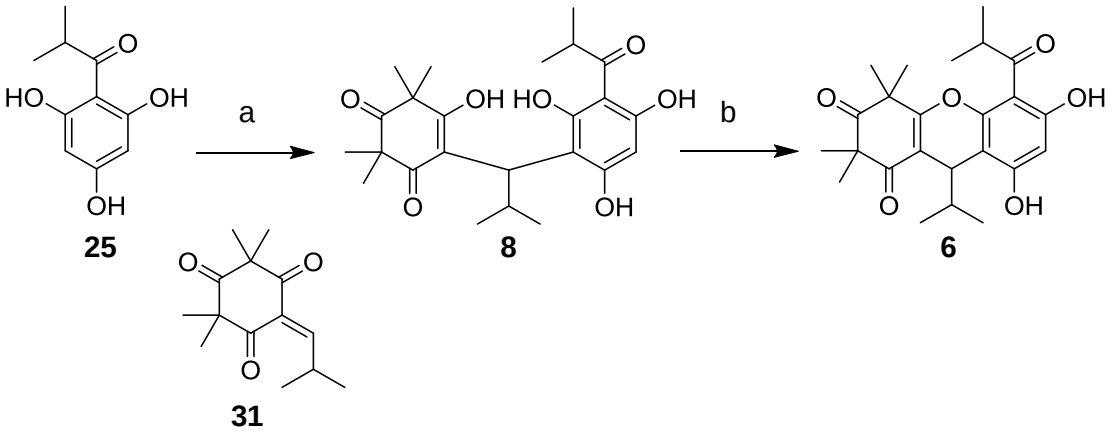


25 **31** **8**

Scheme 14 Mechanistic view of the Michael reaction to the formation of NSMC (**8**)

2.3.1. Setting the reaction conditions

We set up standard reaction conditions to synthesise NSMC (**8**) that we then varied to induce and improve stereoselectivity. Unless otherwise specified the catalyst (**66a-r**, see § 2.3.2) had to be prepared shortly before use under nitrogen atmosphere. It was then added to IBPG (**25**), and stirred one hour before IBSA (**31**) was added to the mixture at 0°C. The NSMC (**8**) formed was then cyclised to MCB (**6**) to allow the determination of its isomeric composition (*ee*) (Scheme 15).



25 **8** **6**

31

Scheme 15 Standard reaction conditions for the asymmetric synthesis of NSMC (**8**) and MCB (**6**)
a.1) Catalyst (**66a-r**), THF, r.t., 1h a.2) IBSA (**31**), THF, 0°C, 1-1,5 h. b) pTsOH, Toluene, 95°C, 1-2h.

Several experiments were performed to find out the best concentration of acceptor **31** and the right temperature. First we figured out that a small excess of the reagent **31** (1.2-1.6 eq.) was needed because of its instability.[35a]

Then, we found out that the reaction of the formation of NSCM (**8**) or MCA (**5**) does not need to be catalysed to happen. After 3 days of reaction at room temperature and without any catalyst, NSCM (**8**) could be synthesised with almost 70 % yield. In the case of MCA (**5**), 10 days were needed.

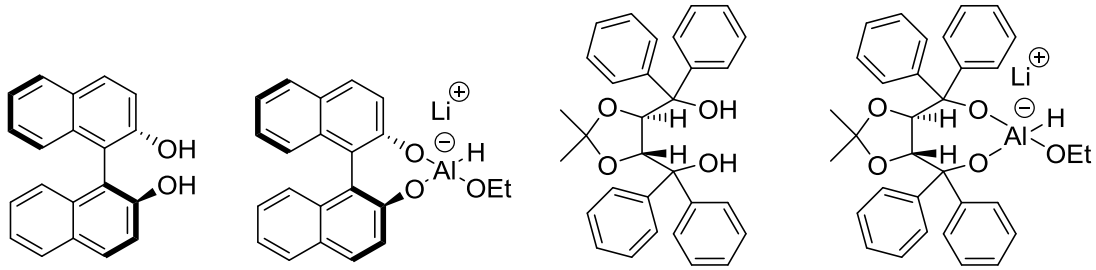
At 0°C the addition of 1 eq. of the Michael acceptor **31** to the Michael donor **25** to form the intermediate **8** without catalyst takes place very slowly and the succeeding one, which would lead to MCA (**5**), almost does not happen. A lower temperature than 0°C made the reaction of the formation of **8** last over more than a week, making the synthesis of the final product **5** very improbable. That is why the reaction was cooled down to 0°C to favour the formation of NSMC (**8**) over MCA (**5**) on the one hand, and to favour the catalysed reaction of **8** over the non-catalysed reaction on the other hand.

2.3.2. Heterobimetallic complexes

Heterobimetallic complexes have proved to be catalysts of choice for the aldol[51] and nitroaldol[52] reactions but more importantly for the Michael[53] and Friedel-Crafts reactions.[54] In most cases, the complexes we used have the general formula $(Ligand)_nM^1M^2$, ligands being generally BINOL (**67**) or derivatives, M^1 a metal or a lanthanide and M^2 an alkali metal.[55] These catalysts function simultaneously as a base ("BINOLate") and a Lewis acid (M^1). As a consequence, each unit of the catalyst as well as the solvent play an important role in its efficiency. Likewise, experimentation demonstrated that the temperature, the size of the BINOL-derivatives and their number on the catalyst can have a great influence on the yield and stereoselectivity of the reaction.[55]

2.3.2.1 First *ee* and absolute configuration of norsemimyrtucommulone

BinAl-H (**66a**) (Fig. 22) was developed by the Nobel prize winner NOYORI as a powerful agent for the asymmetric hydrogenation of ketones.[56] This bimetallic complex is made of an aluminium core, a BINOL (**67**) ligand, an ethoxy group and a hydride. In the presence of labile hydrogen atoms, it can also work as a base. Its use in the synthesis of NSMC (**8**) brought a first *ee* for this compound (Tab. 2).[57]



(*S*)-**67** (*S*)-**66a** (*R*,*R*)-**68** (*R*,*R*)-**66b**

Fig. 22 Structure of BINOL (**67**), TADDOL (**68**) and their respective Al-complexes **66a** and **66b**

At first only one equivalent of BinAl-H was used, which provided a very small *ee* of only 5%. The increase of the number of equivalents up to 3 eq. more than quadrupled the *ee* up to 25 % (Tab. 2, entry 1 to 5). Overloading the reaction mixture with 6 eq. of catalyst improved only slightly the *ee* delivering a highest *ee* to this point of 34 %.[57]

Tab. 2 Results of the tries using the catalysts **66a-d** in various concentrations.[a]

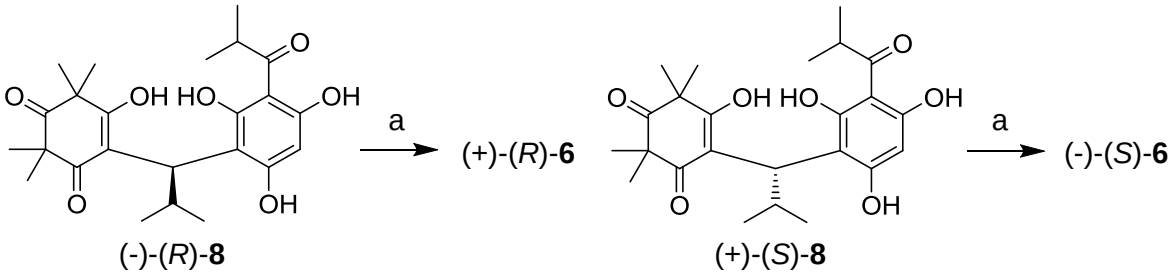
Entry	Catalyst	Number of eq.	T(°C)	Solvent	Yield (%)	$[\alpha]_D^{24}$ of NSMC (**8**)[b]	$[\alpha]_D^{24}$ of MCB (**6**)[c]	*ee*[d] (%)
1	(*S*)-**66a**	1.0	0	THF	47	x	+ 15 [2.8]	5
2	(*S*)-**66a**	2.0	0	THF	70	-3 [3.3]	+ 30 [1.9]	11
3	(*S*)-**66a**	3.0	0	THF	77	- 5 [3.8]	+ 48 [2.9]	25
4	(*R*)-**66a**	3.0	0	THF	64	+ 4 [3.8]	- 44 [2.7]	28
5	(*S*)-**66a**	6.0	0	THF	64	- 5 [4.5]	+ 54 [2.7]	34
6	(*S*)-**66a**	3.0	0	Toluene	41	x	x	2
7	(*S*)-**66a**	3.0	r. t.	THF	52	- 4 [4.5]	+ 50 [2.5]	27
8	(*S*)-**66a**	3.0	-30[e]	THF	64	0 [4.1]	x	3
9	(*R*,*R*)-**66b**	1.0	0	THF	60	0 [5.2]	0 [3.1]	0
10	(*R*,*R*)-**66b**	3.0	0	THF	72	0 [5.1]	0 [3.1]	0
11	(*R*)-**66c**	0.5	0	THF	70	0 [6.0]	0 [3.3]	2
12	(*R*)-**66c**	1.0	0	THF	77	+ 1 [4.8]	-10 [3.1]	15
13	(*R*)-**66c**	2.0	0	THF	58	x	x	16
14	(*S*)-**66d**	3.0	0	THF	60	x	x	2

a) Reaction time : 1h starting when IBSA (**31**) was added, b) in MeOH, [*c*], c) in $CHCl_3$, [*c*], d) determined on MCB (**6**) through HPLC on CHIRALCEL OD-H, *i*PrOH/*n*-hexane 20:80, 0.5-0.6 mL/min, 15°C. e) reaction time: 2h.

A change of solvent resulted in a very poor yield, given that none of the starting materials could dissolve well in toluene (Tab. 2, entry 6). This was in this case a very limiting factor, because the solvent had to be polar enough to dissolve everything, a problem rarely observed in the literature.

Interestingly, a lower temperature than 0°C did not improve the *ee*. The reaction at room temperature resulted in a slightly higher *ee* but a lower yield due to the increased formation of undesired MCA (**5**) (Tab. 2, entry 4, 7-8). Depending on the asymmetry of the ligand **67**, the *ee* could be shifted to one or the other direction. The use of (*S*)-BINOL ((*S*)-**67**) led to the formation of (-)-NSMC ((-)-**8**) which then cyclised to (+)-**6**. The use of (*R*)-BINOL ((*R*)-**67**) led to the formation of (+)-**8** which then cyclised to (-)-MCB ((-)-**6** (Tab. 2, entry 3 and 4).

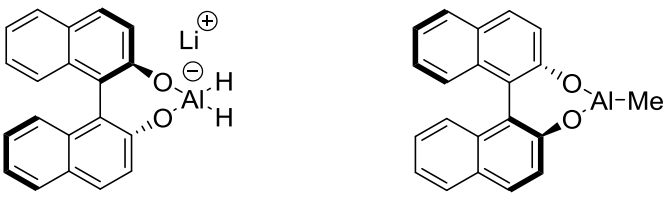
These first results in the asymmetric synthesis helped defining the sign and absolute configuration of NSMC (**8**). (-)-NSMC ((-)-**8**) was then known to have the *R* configuration and (+)-NSMC ((+)-**8**) the *S* configuration (Scheme 16). Besides, since we could obtain different *ee* with different concentrations of the catalyst, we could assert that racemisation does not take place during the cyclisation and assume that the *ee* value of **6** is the *ee* value of **8**.



Scheme 16 Absolute configuration of (-)-**8** and (+)-**8**. a) pTsOH·H_2O, Toluene, 95°C, 1h.

Since TADDOL (**68**) can be used similarly to BINOL (**67**),[58] TaddAlH ((*R*,*R*)-**66b**) (Fig. 22) was tried as a catalyst but provided no *ee* independently of the amount of equivalents used (Tab. 2, entry 9-10).

In addition, the catalyst **66c** (Fig. 23), mentioned by NOYORI in his paper from 1984,[56c] where only one molecule of the diol **67** is added to lithium aluminium hydride (LAH), was chosen and provided a small *ee* of 15% with one equivalent, but no more with 0.5 eq. or 2.0 eq (Tab. 2, entry 11-13).



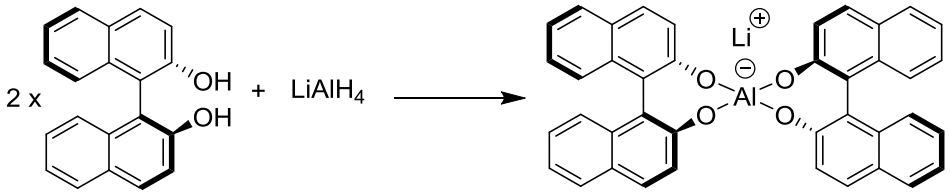
(*R*)-**66c** (*S*)-**66d**

Fig. 23 Structure of catalysts (*R*)-**66c** and (*S*)-**66d**

Finally, the catalyst **66d**,[59] made of trimethylaluminium and (*S*)-**67**, was used but no *ee* could be observed (Fig. 23) (Tab. 2, entry 14).

2.3.2.2 ALB and maximum *ee* for norsemimyrtucommulone

The heterobimetallic complex that brought the best results is without doubt, the aluminium-lithium-BINOL catalyst (ALB) (**66e**) developed by SHIBASAKI and easily obtained from LAH and two equivalents of BINOL (**67**) (Scheme 17).[53b,d]



(*S*)-**67** (*S*,*S*)-**66e**

Scheme 17 Synthesis of the ALB catalyst (*S*,*S*)-**66e**.

0.6 or 1.0 eq. of the catalyst **66e**, used in the standard conditions described above (§ 2.3.1), provided almost no stereoselectivity (Tab. 3, entry 1-2).[53d] On the other hand, a dramatic increase of the enantioselectivity was observed with 2 and 3 eq. (Tab. 3, entry 3-5) affording the MCB (**6**) with 62% *ee* (Fig. 24).[57]

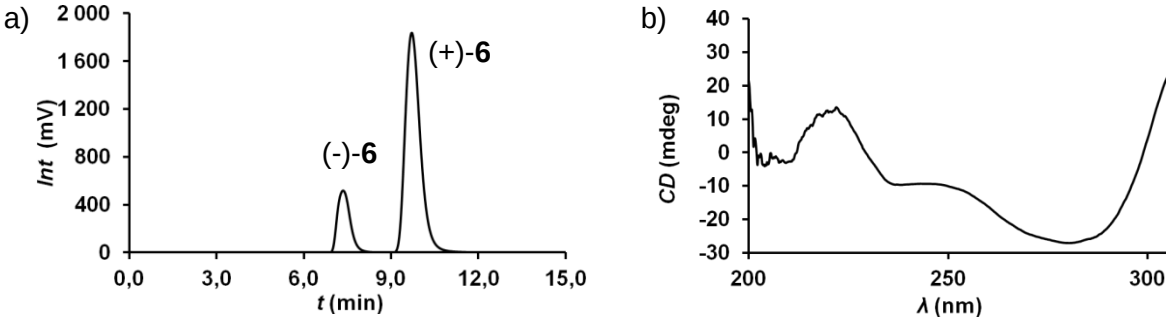


Fig. 24 a) HPLC chromatogram of (+)-**6** with 62% *ee* (ChiralCelOD-H, *i*PrOH/n-hexane, 30:70, 0.5 mL/min, 15°C), b) corresponding circular dichroism spectrum (0.1 mg/mL, MeOH, 20°C).

4 eq. of the catalyst did not improve the asymmetric induction (Tab. 3, entry 6). As seen before, the use of BINOLs (**67**) with opposite optical rotations to form the catalyst, led to an opposite sign of the optical activity of the products. The use of a lower temperature (-20°C) led to a significant loss of yield (despite longer reaction time) but did not influence the stereoselectivity (Tab. 3, entry 3-4).

Tab. 3 Use of the ALB catalyst (**66e**).[a]

Entry	Catalyst	Number of eq.	T(°C)	Solvent	Yield (%)	$[\alpha]_D^{24}$ of NSMC (**8**)[b]	$[\alpha]_D^{24}$ of MCB (**6**)[c]	*ee*[d] (%)
1	(*S*,*S*)-**66e**[e]	0.6	0	THF	57	x	x	0
2	(*S*,*S*)-**66e**	1.0	0	THF	69	x	x	4
3	(*S*,*S*)-**66e**	2.0	-20[f]	THF	57	-8 [4.7]	+ 70 [3.0]	41
4	(*S*,*S*)-**66e**	3.0	-20[f]	THF	55	-13 [4.6]	+ 107 [3.4]	62
5	(*R*,*R*)-**66e**	3.0	0	THF	65	+ 11 [4.8]	- 105 [3.0]	62
6	(*R*,*R*)-**66e**	4.0	0	THF	74	+11 [5.0]	-96 [3.2]	56
7	(*S*,*S*)-**66e**	3.5	0	DCM	62	x	x	63
8	(*S*,*S*)-**66e**	3.2	0	DT101[g]	88	x	x	62
9[g]	(*R*,*R*)-**66e**	3.2	0	DT101[g]	81	+ 16 [3.0]	- 117 [2.9]	72
10[h]	(*R*,*R*)-**66e**	3.4	0	DT101[g]	83	x	x	65

a) Reaction time : 1.5-2h starting when IBSA (**31**) was added, b) in MeOH, [*c*], c) in $CHCl_3$, [*c*], d) determined on MCB (**6**) through HPLC on CHIRALCEL OD-H, *i*PrOH/*n*-hexane 20:80, 0.5-0.6 mL/min, 15°C, e) tBuOK (0.9 eq.) was added according to literature,[53d] f) the reaction was run overnight g) DT101 :mixture of DCM:THF, 10:1, v:v, g) a fresh bottle of 1.0 M $LiAlH_4$ was used, h) the same solution of 1.0 M $LiAlH_4$ was used, three months later.

A reaction in pure dichloromethane led to the same yield and *ee* as in THF, nevertheless the use of a mixture of DCM:THF, 10:1, v:v (DT101) clearly improved the yield of the reaction (Tab. 3, entry 7-8). Thus, using a fresh solution of 1.0 M $LiAlH_4$, and taking particularly care that the reaction took place under very dry conditions, **72 % ee** could be obtained for MCB (**6**) (Tab. 3, entry 9, Fig. 25). The use of the same solution kept under argon for three months resulted in a slight loss of enantioselectivity (Tab. 3, entry 10).

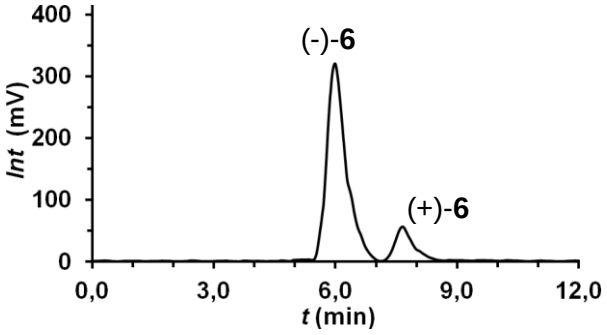


Fig. 25 HPLC chromatogram of (-)-**6** with 72% *ee* (ChiralCelOD-H, *i*PrOH/n-hexane, 20:80, 0.6 mL/min, 15°C)

These results, along with the ones of the section 2.3.2, provided the first and best results concerning the asymmetry of norsemimyrtucommulone (**8**) and myrtucommulone B (**6**).[57] They proved as well that no racemisation of the molecule takes place during the cyclisation

process, validating its utility. This also means that the observed asymmetry is also the one of its precursor NSMC (**8**), which is in what we were interested in the first place.

2.3.2.3 Other heterobimetallic complexes

Given that ALB (**66e**) gave good results towards the enantioselective synthesis of NSMC (**8**), we modified different aspects of its structure to improve its efficiency (Tab. 4).

Tab. 4 Variations of the ALB catalyst[a]

Entry	Catalyst	Description	Number of eq.	Solvent	Yield (%)	*ee*[b] (%)
1	(*R*)-**66f**	$Al_2Li_2(BINOL)_3$	1.0	DT101	71	4
2	(*S*)-**66g**	$AlLi(BINOL)_{2.45}$	3.2	DT101	81	50
3	(*S*)-**66h**	$AlLi_3(BINOL)_3/Al_2(Bu)_2(BINOL)_2$	3.3	THF	67	0
4	(*R*,*R*)-**66i**	$AlNa(BINOL)_2$	3.2	THF	72	2
5	(*S*)-**66j**	$LaLi_3(BINOL)_3$	3.2	THF	60	6
6	(*S*,*S*)-**66k**	La(linked-BINOL)	3.3	THF	66	47
7	(*R*,*R*)-**66l**	$Ti(BINOL)_2$	4.0	Toluene	79	1
8	(*R*)-**66m**	$Ti(O\textit{i}Pr)_2(BINOL)$	4.0	DCM	68	4
9	(*S*,*S*)-**66n**	AlLi(linked-BINOL)	3.2	DT101	62	0
10	(*R*,*R*)-**66o**	$AlLi(TADDOL)_2$	3.4	DT101	37	4
11	(*R*,*R*)-**66p**	$AlLi(6,6'\text{-}Br_2BINOL)_2$	3.3	DT101	88	41
12	(*R*,*R*)-**66q**	$AlLi(3,3'\text{-}Br_2BINOL)_2$	3.3	DT101	72	5
13	(*R*,*R*)-**66r**	$AlLi(6\text{-}BrBINOL)_2$	3.3	DT101	69	61

a) Reaction time : 1.5 h starting when IBSA (**31**) was added, at 0°C, b) determined on MCB (**6**) through HPLC on CHIRALCEL OD-H, *i*PrOH/*n*-hexane 20:80, 0.5-0.6 mL/min, 15°C.

Taking into account the work of SHIBASAKI *et al.*,[53a] it was first intended to form a catalyst with a new ratio of 2:3 for LAH:BINOL to obtain the dimeric structure of **66f** (Fig. 26).[60] It was not possible with our data to confirm the exact structure of the catalyst, but as it showed no asymmetric induction, it was not further investigated (Tab. 4, entry 1).

In their publication from 1997, FERINGA *et al.*[61] found out that 2.45 eq. of BINOL (**67**) in regard to LAH, was the best ratio to form the most efficient "ALB-catalyst" (**66g**) for their Michael addition of α-nitroesters to α,β-unsaturated ketones. In our case no improvement of the enantioselectivity could be observed (Tab. 4, entry 2).

One year Later, SHIBASAKI *et al.*[62] investigated another catalyst of the aluminium-lithium-BINOL type. They added a strong base (*n*-BuLi, NaO-*t*-Bu) to their ALB (**66e**) to afford a mixture of a hexacoordinated and a tetracoordinated aluminium complex which led to an excellent selectivity for the reaction between Horner-Wadsworth-Emmons reagents and cyclic enones. Given the similarity between ALB (**66e**) and $AlLi_3(BINOL)_3/Al_2(Bu)_2(BINOL)_2$ **66h** (Fig. 26) we used it in our asymmetric synthesis but it had no asymmetric influence on the synthesis of NSMC (**8**) (Tab. 4, entry 3).

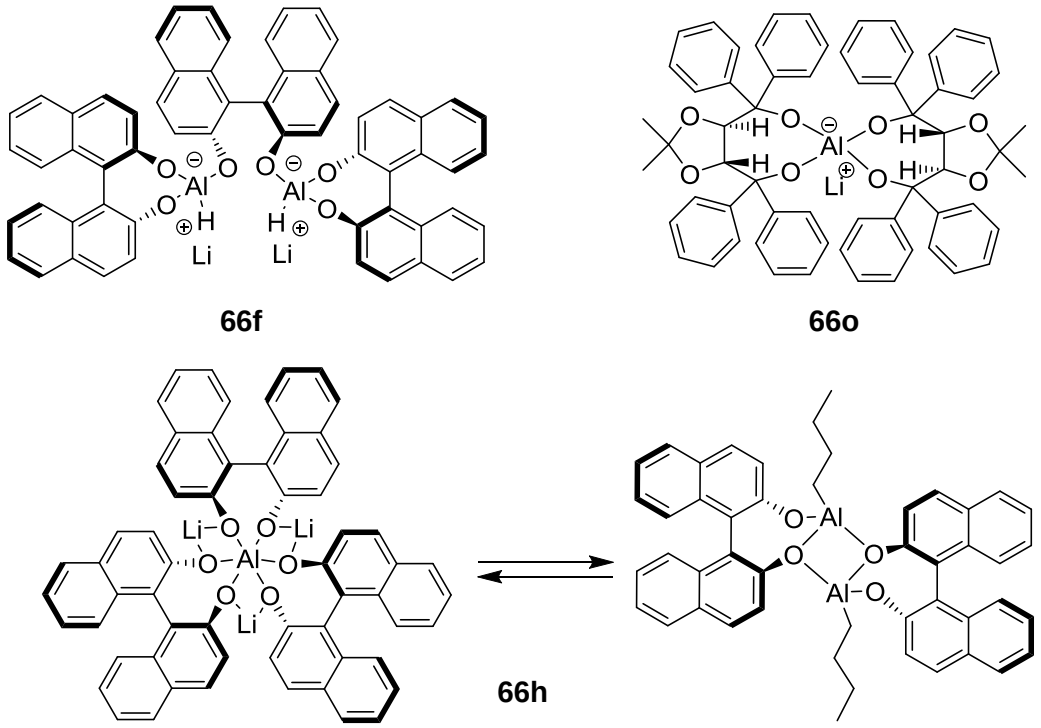
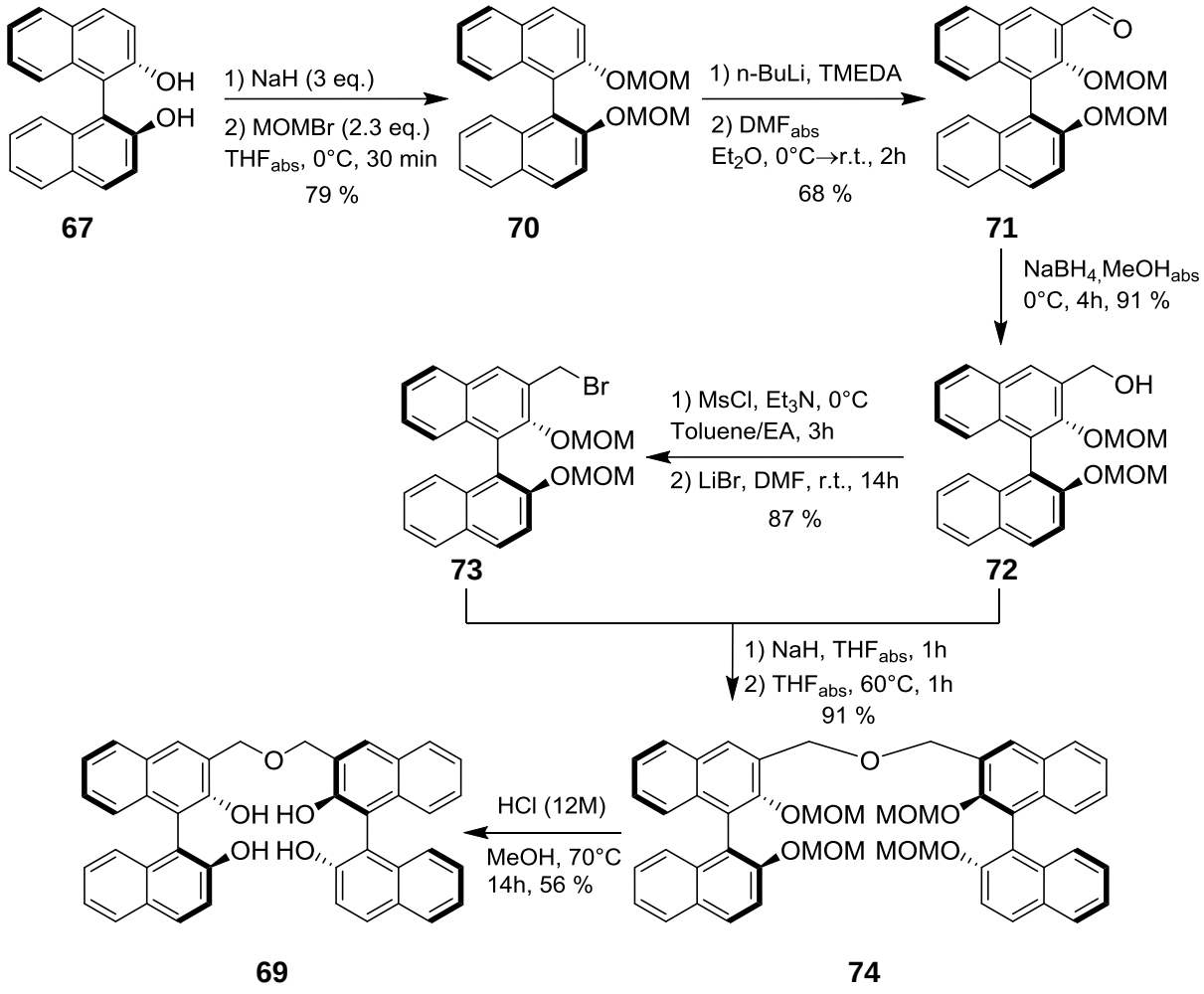


Fig. 26 Structures of **66f**, **66h** and **66o**.

The next attempt concerned the lithium ion included in the catalyst. The result from SHIBASAKI[53b] with ALB (**66e**) showed that the exchange of lithium through sodium in the catalyst had no influence on the enantioselectivity of the Michael reaction between cyclohexenone and dibenzylmalonate. Surprisingly, the reaction between IBPG (**25**) and IBSA (**31**) catalysed through the aluminium-sodium-BINOL-catalyst (ASB) (**66i**) showed no stereoselectivity (Fig. 27) (Tab. 4, entry 4). This underlines the prime importance of lithium for this reaction.

A lot of studies concerning heterobimetallic complexes consider lanthanides as the central metal. Lanthanum is the most commonly used [51-53,55,63] but other rare-earth metals such as praseodymium (Pr), neodymium (Nd) or europium (Eu) have been investigated.[52,55,63] We focused on La and first prepared the so called LLB (Lanthanum-Lithium-BINOL) catalyst (**66j**) where three lithium ions and three BINOL-ligands surround the lanthanum atom (Fig. 27).[51]

We then prepared a catalyst closely related to ALB (**66e**) but less air sensitive for using lanthanum as a central metal (**66k**) (Fig. 27).[53c] It has the particularity that it is lithium free and the two BINOLs surrounding the lanthanum are linked through an ether bridge (linked-BINOL) (**69**). To make this ligand, we had to protect (*S*)-BINOL ((*S*)-**67**) with MOM to form **70**,[64] then formylate through an ortho-lithiation followed by addition of DMF in presence of TMEDA[65] to yield **71** and reduce the aldehyde with $NaBH_4$ to the methyl alcohol **72**.[66] After that, a part of methanol-BINOL (**72**) was transformed into a good leaving group with mesyl chloride and LiBr was added to the reaction to synthesise bromomethyl-BINOL (**73**). Both ligand **72** and **73** were then bound together through a simple nucleophilic substitution and the "linked-ligand" **74** was deprotected in boiling methanol in presence of a few millilitres of concentrated hydrochloric acid to yield the desired linked-BINOL (**69**) (Scheme 18).[66]

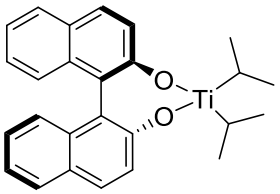


Scheme 18 Synthesis of the linked-BINOL ligand (**69**).

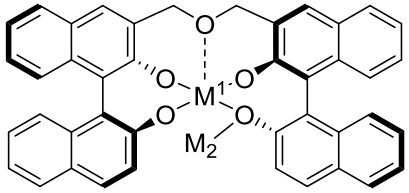
The use of lanthanum led to almost no enantioselectivity in the case of LLB (**66j**) but the La-linked-BINOL catalyst (*S*,*S*)-**66k** provided an interesting *ee* of 47% for MCB (**6**) (Tab. 4, entry 5 and 6). Based on the promising results of the linked-BINOL ligand **69**, we prepared the

catalyst (*S*,*S*)-**66n**, using this ligand and LAH (Fig. 27). In this case the catalyst did not show the expected influence on the stereoselectivity (Tab. 4, entry 9).

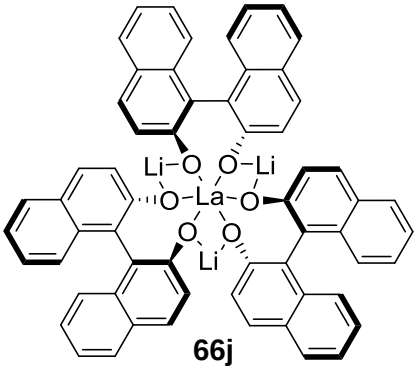
After using La as a central metal, a try was given to a transition metal. Titanium showed excellent enantioselectivities for the aldol[67] or Friedel-Craft reaction.[68] Two different catalysts were tried: **66l** was a mixture of titanium isopropoxide and 2 eq. of BINOL (**67**) and **66m** was a mixture of the same compounds but in a 1:1 ratio (Fig. 27). None of them showed any interesting potency (Tab. 4, entry 7 and 8).[68-69]



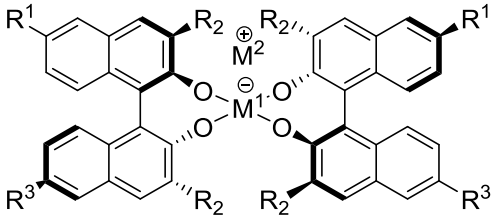
66m



66k : M^1 = La, M^2 = H
66n : M^1 = Al, M^2 = Li



66j

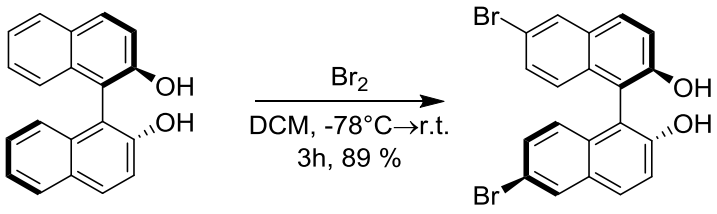


66i : M^1 = Al, M^2 = Na, R^1 = H, R_2 = H, R_3 = H
66l : M^1 = Ti, R^1 = H, R_2 = H, R_3 = H
66p : M^1 = Al, M^2 = Li, R^1 = Br, R_2 = H, R_3 = Br
66q : M^1 = Al, M^2 = Li, R^1 = H, R_2 = Br, R_3 = H
66r : M^1 = Al, M^2 = Li, R^1 = Br, R_2 = H, R_3 = H

Fig. 27 Structure of some catalysts used for the asymmetric synthesis of NSMC (**8**).

Based on the same principle, we further varied the shape of the ligand. We tried again without success to use TADDOL (**68**) as a ligand (Catalyst **66o** (Fig. 26), Tab. 4, entry 10).

A first bromine derivative **75** was synthesised with bromine in the 6,6'-positions of BINOL (**67**) by simply mixing it with bromine in DCM at -78°C (Scheme 19).[70]

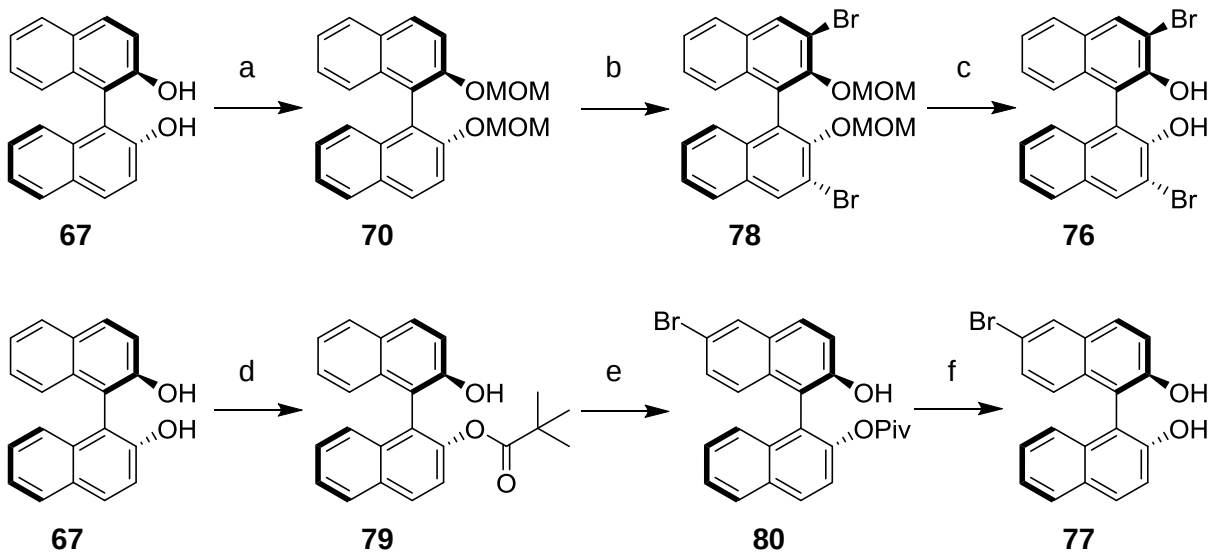


67 **75**

Scheme 19 Formation of 6,6'-dibromo-BINOL (**75**)

Thanks to the work of K. HUWIG two additional ligands (**76** and **77**) could be synthesised and tested for the asymmetric synthesis.[71] Ligand **76** possesses two bromines in the 3,3'-positions of BINOL. This was achieved by ortho-lithiation of MOM-protected BINOL (**70**) followed by addition of bromine to form **78** and subsequent deprotection in acidic medium (Scheme 20).

For ligand **77**, one of the OH-groups of BINOL (**67**) was protected with pivaloyl chloride to give **79** and subsequent bromination led exclusively to the mono-brominated product **80** which was deprotected under basic conditions (Scheme 20). The pivaloyl protecting group (Piv) plays here a double role since its bulkiness prevents esterification of both naphtol moieties during the protection process and its electron withdrawing character deactivates the 6'-position to only afford the formation of 6-bromo-BINOL (**77**).[72]



Scheme 20 Synthesis of 3,3'-dibromo-BINOL (**76**) and 6-bromo-BINOL (**77**). a.1) NaH (3 eq.), THF_{abs}, 0°C, 1h, a.2) MOMBr (2.3 eq.), THF_{abs}, 0°C, 30 min, 79 %, b.1) *n*-BuLi (2,4 eq.), -78°C→0°C, b.2) Br_2 (3.0 eq.), hexane, -78°C→r.t., 14h, 60 %, c) conc. HCl (2.0 eq.), 1,4-dioxane, 50°C, 14h, d) PivCl (1.0 eq.), NEt_3 (3.0 eq.), CH_3CN, 0°C→r.t., 3h, 89 %, e) Br_2 (2.0 eq.), CH_3CN, 0°C, 3h, 90%, f) KOH (3.0 eq.), H_2O/THF, r.t., 23h, 78 %.

The use of the catalyst **66p** bearing the ligand **75** resulted in a small diminution of the *ee* compared to **66e** (Tab. 4, entry 11). The slightly different dihedral angle between the two naphtaline rings due to the steric effects but also the electronic influence of bromine have, in our case, a negative influence on the enantioselectivity.[67] The use of the catalyst **66q** (ligand **76**) where bromine atoms are in the 3,3'-positions led to almost no enantioselectivity (Tab. 4, entry 12). As observed in the literature for titanium complexes,[67] the bromination of the 3,3'-position are very disadvantageous for our aluminium catalyst. The asymmetry of the reaction

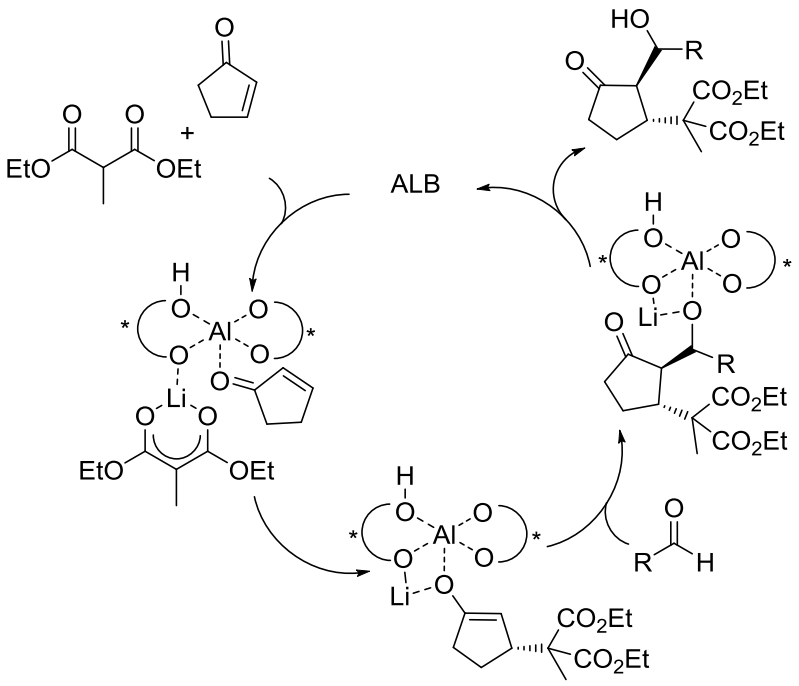
was only slightly influenced by the use of the catalyst **66r** (ligand **77**), where only one bromine is at the 6-position, providing MCB (**6**) with an *ee* of 61 % (Tab. 4, entry 13).[64a,71-73] In conclusion, neither the electronic effects nor the increased steric hindrance of the bromine derivatives of BINOL led to an improvement of the enantioselectivity.

Eventually, no variation of our catalyst **66e** led to an improvement of the *ee* for the Michael/Friedel-Crafts reaction. The best way we found to synthesise enantiomerically enriched NSMC (**8**) and the closely related MCB (**6**) was to use 3 eq. of ALB (**66e**) providing 72 % *ee* for the target molecule.

2.3.2.4 Mechanistic investigations

Synthetic investigations

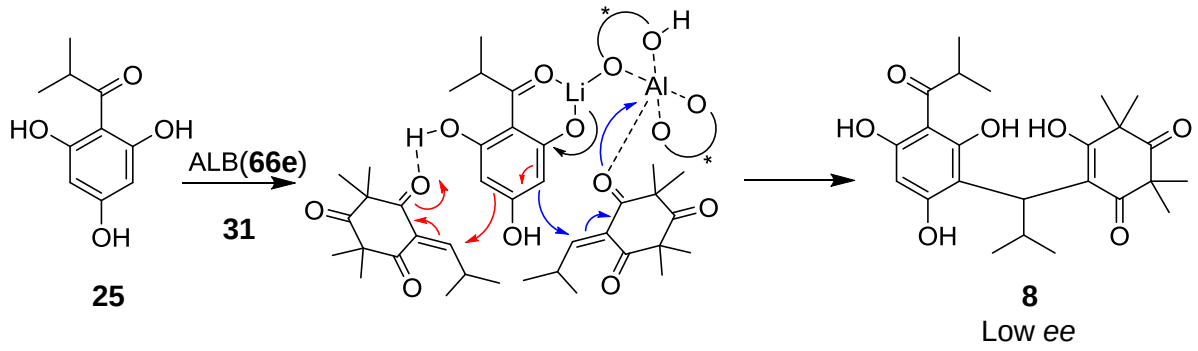
In order to understand the mechanism of the reaction and the reason why 3 eq. were needed we realised some complementary experiments. SHIBASAKI[53b] proposed a mechanistic path for his Michael reaction catalysed by ALB (**66e**) where a lithium enolate is formed with the Michael donor while the Michael acceptor is pre-coordinated to the catalyst through an aluminium-oxygen connection. The Michael reaction should then take place and lead to an intermediary aluminium enolate. They could prove it by adding an electrophilic aldehyde to their reaction [53b] that caught the enolate (Scheme 21).



Scheme 21 Mechanism for a Michael-Aldol reaction catalysed by ALB proposed by SHIBASAKI.[53b]

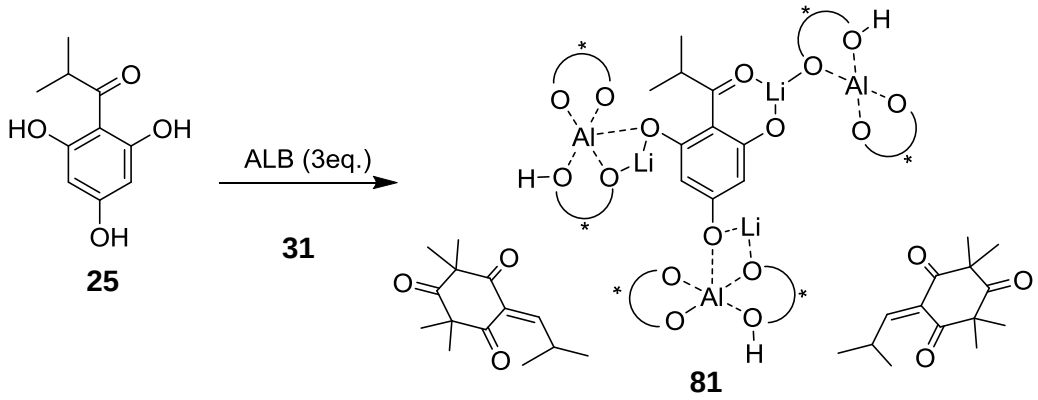
In the case of the reaction between a phloroglucinol derivative and isobutylidene syncarpic acid (**31**), three equivalents of the catalyst **66e** were needed to achieve good enantioselectivities. SHIBASAKI[53b] only used 10 mol% or less. This can be explained by the fact that isobutyryl phloroglucinol (**25**) includes three highly acidic phenolic protons in a conjugated system.

Indeed, if the catalyst coordinates once to IBPG (**25**), it catalyses the reaction on any of the two nucleophilic positions of the phloroglucinol ring. This makes the site free from catalyst (red path) as well more reactive and the reaction can happen “far away” from the catalyst (Scheme 22). As a solution, 3 equivalents were used in the reaction to occupy all the phenolic oxygen atoms and enhance the asymmetric induction.



Scheme 22 Possible reaction pathways for the Michael acceptor (**31**), either with the activated side of IBPG or the other because of the conjugation in IBPG.

Based on the principle that the Michael donor would bind to the catalyst through the lithium ion after having been deprotonated, we supposed we would obtain an intermediate like **81** where lithium is coordinated to one of the phenolic oxygen atoms and to the keto group. The two other equivalents of ALB (**66e**) probably deprotonate and bind over lithium with the two other phenolic oxygen atoms (Scheme 23). This way, the space surrounding the IBPG is overloaded with chiral catalysts, forcing the asymmetric induction.



Scheme 23 Possible complexation of the three aluminium-complexes with IBPG (**25**)

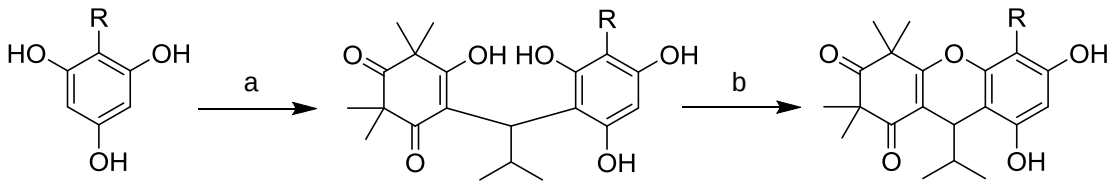
To corroborate this hypotheses a few other experiments were realised. As we already know, lithium plays a crucial role for the efficiency of the catalyst, since its exchange through sodium led to no enantioselectivity (§ 2.3.2.3, Tab. 4, entry 4).
The reaction was then carried out in the reverse order (Tab. 5, entry 2) and provided an *ee* of only little more than half of the maximum ee of 72 % (Tab. 5, entry 1). This result underlines the fact that the efficiency of the catalyst relies on the primary coordination of the aluminium complex on the Michael donor.

Tab. 5 Experiments to better understand the mechanism of the asymmetric catalysis.[a]

Entry	Michael donor	Michael acceptor	Catalyst	Number of eq.	Product (Yield, %)	*ee*[c] (%)
1	**25**	**31**	(*R*,*R*)-**66e**	3.2	**8** (81)	72
2[d]	**25**	**31**	(*R*,*R*)-**66e**	3.5	**8** (65)	38
3	**33**	**31**	(*S*,*S*)-**66e**	3.2	**82** (60)	55
4	**28**	**31**	(*S*,*S*)-**66e**	0.5	**84** (59)	6
5	**28**	**31**	(*S*,*S*)-**66e**	3.5	**84** (75)	28
6	**25**	**86**	(*S*,*S*)-**66e**	3.2	**87** (35)	6[e]

a) Reaction time : 1.5-2h starting when IBSA (**31**)/ IBIND (**86**) was added at 0°C c) determined on the cyclised derivative of the product through HPLC on CHIRALCEL OD-H, *i*PrOH/*n*-hexane 20:80, 0.5-0.6 mL/min, 15°C, d) the starting materials were given in the reverse order, e) determined on the cyclised derivative of the product through HPLC on Reprosil NR, *i*PrOH/*n*-hexane 10:90, 1.0 mL/min, 24°C

To verify the importance of the coordination to the keto group we first carried out the reaction using hexanoyl phloroglucinol (HPG) (**33**), to synthesise norsemimyrtucommulone F (**82**) which was cyclised to **83** (Scheme 24). The only difference here is the long linear pentyl chain of **33** instead of the isopropyl group of IBPG (**25**). Both reactions were performed under the optimised conditions and it is noteworthy that the *ee* dropped to 17 % with the use of HPG (**33**) showing that the form of the acyl chain of the phloroglucinol moiety influences the enantioselectivity (Tab. 5, entry 3).



33 : R = $CO(CH_2)_4CH_3$
28 : R = H

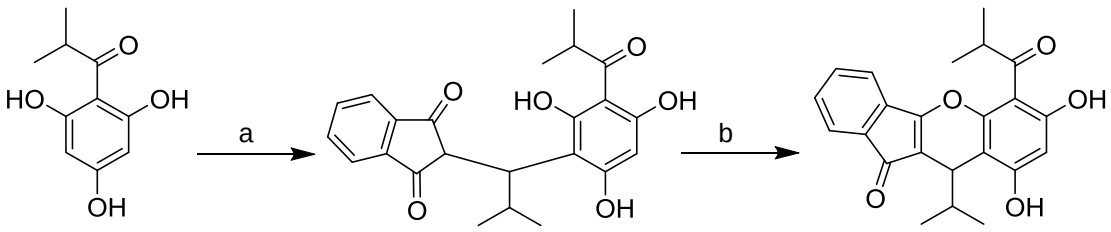
82 : R = $CO(CH_2)_4CH_3$
84 : R = H

83 : R = $CO(CH_2)_4CH_3$
85 : R = H

Scheme 24 Synthesis of the NSMC (**82** and **84**) and MCB derivatives (**83** and **85**) to observe the influence of the keto group on the enantioselectivity. a)1) **66e**, DT101, r.t., 1h 2) IBSA (**31**), DT101, 0°C, 1,5 h. b) pTsOH·H_2O, Toluene, 95°C, 1h.

We went further and removed the keto group, using phloroglucinol (**28**) as a starting material to form **84** (cyclised to **85**, Scheme 24). The reaction with only 0.5 eq. of catalyst showed, as observed before, no selectivity. And the reaction under the standard conditions revealed that the *ee* dropped to 28% (Tab. 5, entry 4-5). This last experiment highlights the essential character of the ketone for the stability of the ALB-Michael donor intermediate.

A final attempt was made where we simply used isobutylidene 1,3-indandione (IBIND) (**86**) instead of SA (**31**) as a Michael acceptor to yield the indandione derivative **87** which was then cyclised to **88** (Scheme 25). A dramatic loss of enantioselectivity was observed since only 6% *ee* were measured (Tab. 5, entry 6). This implies first that the bulky character of IBSA (**31**) participates in the chiral induction and second that our conditions are very specific to NSMC synthesis.



25 **87** **88**

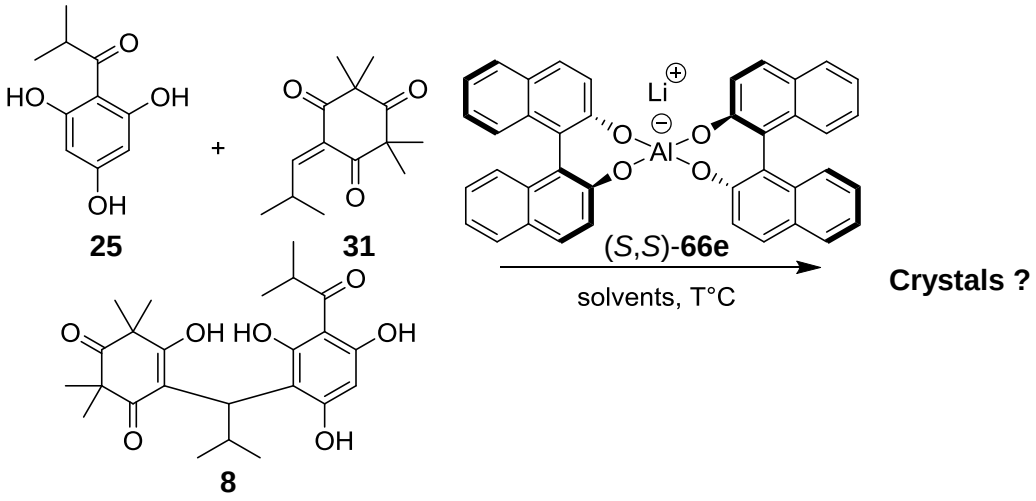
Scheme 25 a.1) **66e**, DT101, r.t., 1h, a.2) IBIND (**86**), DT101, 0°C, 1,5 h. b) pTsOH·H_2O, toluene, 95°C, 1h.

Crystallisation attempts

Thus, it is now known that the keto group and the lithium ion participate in an essential manner to the enantioselective process. However this is not enough in order to know how the 3 eq. of ALB (**66e**) are positioned in space when the reaction takes place. To get a better picture of it we made several crystallisation experiments of the intermediate state when the aluminium is still coordinated.

Basically IBPG (**25**) and 3 eq. of the catalyst (*S*,*S*)-**66e** were mixed in THF or DT101 under the usual conditions and the mixture was then incubated either at room temperature or at 4°C and then -20°C (Tab. 6, entry 1-2, 5). Other attempts were made mixing both Michael donor (**25**) and acceptor (**31**) with (*S*,*S*)-ALB ((*S*,*S*)-**66e**) in different solvent mixtures (Tab. 6, entry 3-4). The catalyst (*S*,*S*)-**66e** was also directly mixed with the product of the reaction NSMC (**8**) but unfortunately no crystal of any coordinated state could be obtained (Tab. 6, entry 6).

Tab. 6 Conditions of the different crystallisation attempts.

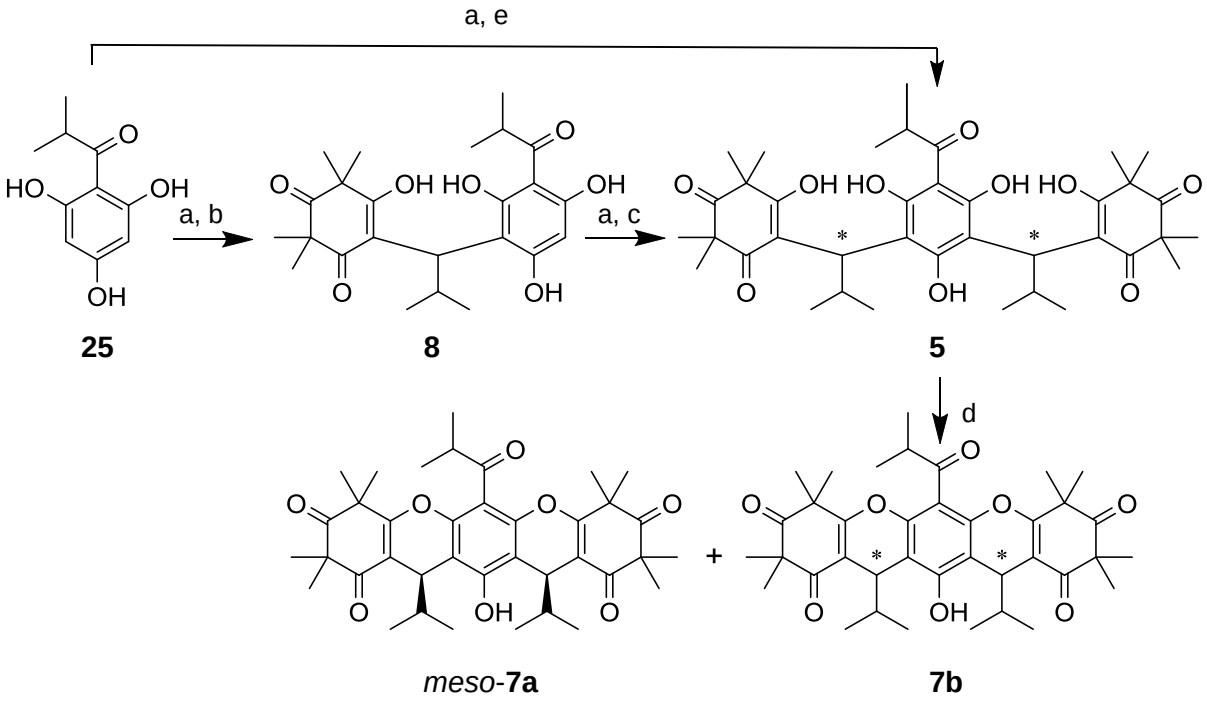


Entry	Starting materials	Solvent	Temperature	time
1	**25**	THF	r.t.	7 days
2	**25**	DT101	r.t.	7 days
3	**25** + **31**	THF	r.t.	3 days then concentrated
4	**25** + **31**	DT101	r.t.	3 days then concentrated
5	**25**	DT101	1) 4°C 2) -20°C	1) 7 days 2) 30 days
6	**8**	DT101	1) 4°C 2) -20°C	1) 7 days 2) 30 days

In these studies we could highlight the essential character of the lithium ion, the keto group and the 1,3-diketone concerning the efficiency of the asymmetric induction. We could also prove that the order used to add the starting materials is of importance and suggest a possible intermediate state for our synthesis. However, we could not verify the exact position of the catalyst in the molecule.

2.3.2.5 Synthesis of myrtucommulone A and limitation of the method

Having extensively investigated the asymmetric synthesis of NSMC (**8**) achieving a maximum *ee* of 72%, we then concentrated on the synthesis of our target molecule based on the optimised conditions (Tab. 7). The aim was to improve the already achieved enantiomeric enrichment and create diastereomeric excess (*de*) in MCA which bears two stereocenters. Since we were not able to separate the enantiomerically enriched MCA **5b** (consisting of (*S*,*S*)-**5** and (*R*,*R*)-**5** in an unknown ratio) from its *meso* form (*meso*-**5a**), we carried out, similarly to NSMC (**8**), the cyclisation reaction to give the pentacyclic derivatives **7b** and *meso*-**7a** (Scheme 26). Since we know from above (§ 2.3.2) that racemisation does not take place, we can consider the *ee* of **7** as the one of **5**.



Scheme 26 Asymmetric synthesis of MCA (**5**) a) Catalyst, DT101, r.t., 1h b) IBSA (**31**) (1,5 eq.), DT101, 0°C, 1,5 h. c) IBSA (**31**) (2 eq.), DT101, 0°C, 44 h, d) pTsOH, toluene, 95°C, 1h. e) IBSA (**31**) (3 eq.), DT101, r.t., 16 h.

Given that MCA (**5**) needs longer reaction time, we first chose to perform the reaction at room temperature. We used once IBPG (**25**) as a starting material to which we added 3 eq. of the Michael acceptor (**31**) to get directly the myrtucommulone A (**5**) (Scheme 26). IBSA (**31**) was added at 0°C and the reaction was left at room temperature overnight. Both NSMC (**8**) and MCA (**5**) were isolated. NSMC (**8**) showed an *ee* of 65 % in accordance with the previous results. MCA (**5**) showed a slight loss of *ee* which signified that the ALB (**66e**) had no or not much influence on the induction of enantioselectivity in the target molecule **5** (Tab. 7, entry 1). Moreover no *de* was observed which confirmed that the influence of the catalyst **66e** is limited once NSMC (**8**) has been formed.

In order to check if the *ee* from the enantiomerically enriched (+)-(*S*)-**8** (62% ee) could be sufficient to induce stereoselectivity in MCA (**5**), we made an experiment with only sodium hydride as a base catalyst (Tab. 7, entry 2). The reaction ran very fast but neither a significant improvement of the *ee* nor an induction of any *de* could be observed .

Tab. 7 Asymmetric synthesis of myrtucommulone A (**5**)

Entry	Starting material (*ee*)	Catalyst (eq.)	T(°C)	Time (h)	Product (Yield, %)	*ee* [a] (%)	*de* [b] (%)
1	**25**	(*S*,*S*)-**66e** (3.3 eq.)	0 /r.t	16	**8** (40 %)	65	-
					5 (46 %)	60	0
2	(+)-(*S*)-**8** (62%)	NaH (2 eq.)	r.t	1.5	**5** (67 %)	64	4
3	(-)-(*R*)-**8** (62%)	(*S*,*S*)-**66e** (3.3 eq.)	0 /r.t	16	**5** (62 %)	55	2
4	(-)-(*R*)-**8** (62%)	(*R*,*R*)-**66e** (3.3 eq.)	0 /r.t	16	**5** (77 %)	70	2
5	(+)-(*S*)-**8** (62%)	(*S*,*S*)-**66e** (2.2 eq.)	r.t	16	**5** (61 %)	65	2
6	(+)-(*S*)-**8** (62%)	(*S*,*S*)-**66e** (3.3 eq.)	r.t	16	**5** (57 %)	70	4
7	(-)-(*R*)-**8** (64%)	(*R*,*R*)-**66e** (3.3 eq.)	0	44	**5** (45 %)	81	3

a) determined on **7b**: HPLC on CHIRALCEL OD-H, *i*PrOH/*n*-hexane 20:80, 0.6 mL/min, 15°C, b) read on NMR

Two parallel experiments were run where the same sample of (-)-(*R*)-**8** (62% ee) was used on the one hand with (*S*,*S*)-ALB ((*S*,*S*)-**66e**) and on the other hand with (*R*,*R*)-ALB ((*R*,*R*)-**66e**) (Tab. 7, entry 3-4).[57] In the first case (entry 3) we obtained 55 % ee for **5b** (mismatched) and only 2 % *de*. In the second case (entry 4), **5b** showed an *ee* of 70% (matched) with 3 % *de*, which meant again that no diastereoselectivity was reached (Fig. 28).

Both of the reactions of (-)-(*R*)-**8** with either (*S*,*S*)-**66e** or (*R*,*R*)-**66e** are typical for double-diastereodifferentiation as explained in Scheme 27.[57]

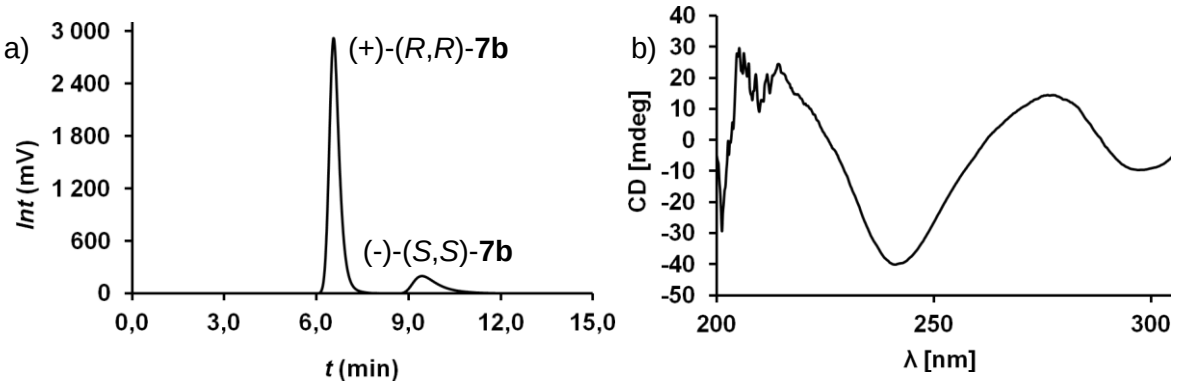
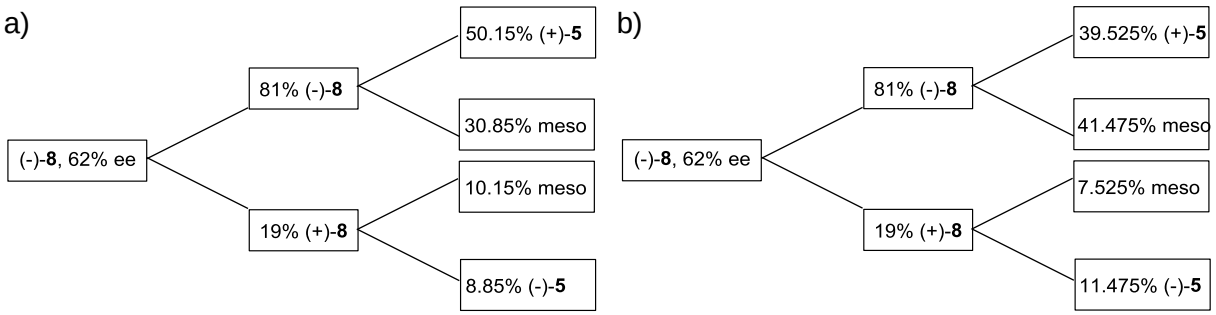


Fig. 28 a) HPLC chromatogram of (+)-(*R*,*R*)-**7b** with 70% *ee* (ChiralCelOD-H, *i*PrOH/n-hexane, 30:70, 0.5 mL/min, 15°C), b) corresponding circular dichroism spectrum (0.1 mg/mL, MeOH, 20°C).



Scheme 27 Results of the matched (a) and the mismatched (b) double-diastereodifferentiating second Michael addition from (-)-**8** to (+)-**5b**.

Given our results on NSMC (**8**) where the number of equivalents used in the synthesis had a crucial influence on the stereoselectivity, we also run parallel experiments with 2.2 and 3.2 eq. of the catalyst (*S*,*S*)-**66e** (Tab. 7, entry 5-6). In this case it seemed to have only little influence since we only observed a 5% difference in the *ee*.

At last we repeated the reaction under optimal conditions at 0°C which seemed more appropriate for a good enantioselectivity since we could reach **81 % *ee*** (Tab. 7, entry 7). On the other hand, even after 44h, the yield stayed low (45%) and still no diastereoselectivity could be achieved. At this point, thanks to the arduous work of M. Hans[39] a new method had been developed and it was possible to read directly the *ee* on the chromatogram of the uncyclised product (Fig. 29).

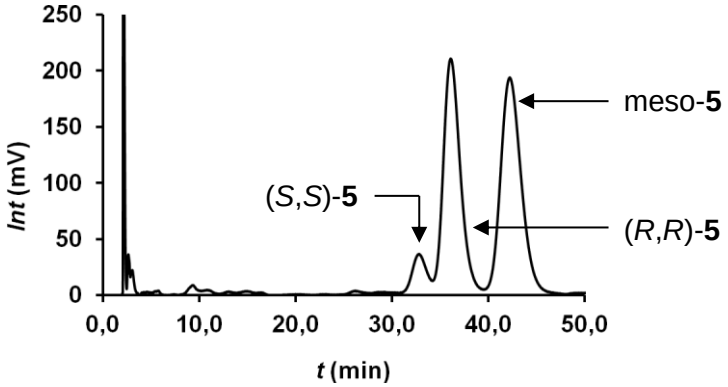


Fig. 29 HPLC chromatogram of **5** with 81% *ee* (Reprosil 100 Chiral-NR, ACN: Buffer (35:65), Buffer: 30mM NH_4OAc, pH9 DEA), 1.0 mL/min, 24°C)

This *ee* of 81 % may look moderate at first sight but it is relatively good compared to published results concerning significantly sterically hindered substrates like **31**. In systems where the Michael acceptor has a similar steric hindrance, either the *ee* value is comparable to ours and the chemical yield is rather low[74] or the chemical yield is moderate and the *ee* value is zero.[57,75]

2.3.2.6 NMR-particularity

NMR-spectrum splitting due to “self induced non-equivalence” or “solute-solute diastereomeric interactions” is a known but seldom reported phenomenon.[76] WILLIAMS *et al*.[77] were the first to report in 1969 two sets of peaks for the same proton in the NMR-spectrum of dihydroquinine. More extensive research from the same authors and other groups revealed that this phenomenon is due to the dimeric association in solution of the different enantiomers of the compounds.[78] Basically, in presence of two enantiomers (+) and (-), three equilibria are expected :

$$(+) + (+) \rightleftharpoons (+)(+) \quad \text{Homochiral dimer}$$
$$(+) + (-) \rightleftharpoons (+)(-) \quad \text{Heterochiral dimer}$$
$$(-) + (-) \rightleftharpoons (-)(-) \quad \text{Homochiral dimer}$$

The homochiral dimers (+)(+) and (-)(-) are enantiomers and are diastereomeric to the heterochiral dimer (+)(-)/(-)(+). If there is an excess of one of the enantiomers, the chiral average environment experienced by the (+) isomer is then different than the one experienced by the (-) isomer and two signals are then reported. In the case of a racemic mixture only one signal in then observed.[76]

One signal corresponds to the weighted average of the population of the (+), (+)(+) and (+)(-) species and the other to the weighted average of (-), (-)(-) and (-)(+). Both weighted averages are related to the total concentration of each isomer. As a consequence, it is possible to directly read the enantiomeric excess of a compound by measuring the integration (I_1 and I_2) of each peak on the NMR spectrum.[76,78a,b]

$$ee\ (\%) = \frac{|I_1 - I_2|}{|I_1 + I_2|} .100$$

Luckily, this phenomenon happened in the case of the cyclised derivatives **6** and **7** of NSMC and MCA respectively. We observed “self-induced non equivalence” even with the slightest *ee.* As an example are depicted in Fig. 30, the NMR signals (in $CDCl_3$) for protons H5 and H1’ of (-)-(*S*)-MCB (**6**) in the case of a racemic mixture (a), a 34% *ee* (b), and with 72 % *ee* (c). All these *ee* were confirmed on HPLC, with the usual methods (Fig. 30, d, e).

One can notice here that the bigger the *ee*, the larger the distance between the peaks. In the spectrum of the 34 % *ee* mixture, the peaks still overlap making it impossible to determine the enantioselectivity of the reaction without HPLC. It is noteworthy as well that the NMR shift (δ) of the splitted peaks is also directly influenced by the *ee,* although the concentration of the solute is also involved.[76,78a]

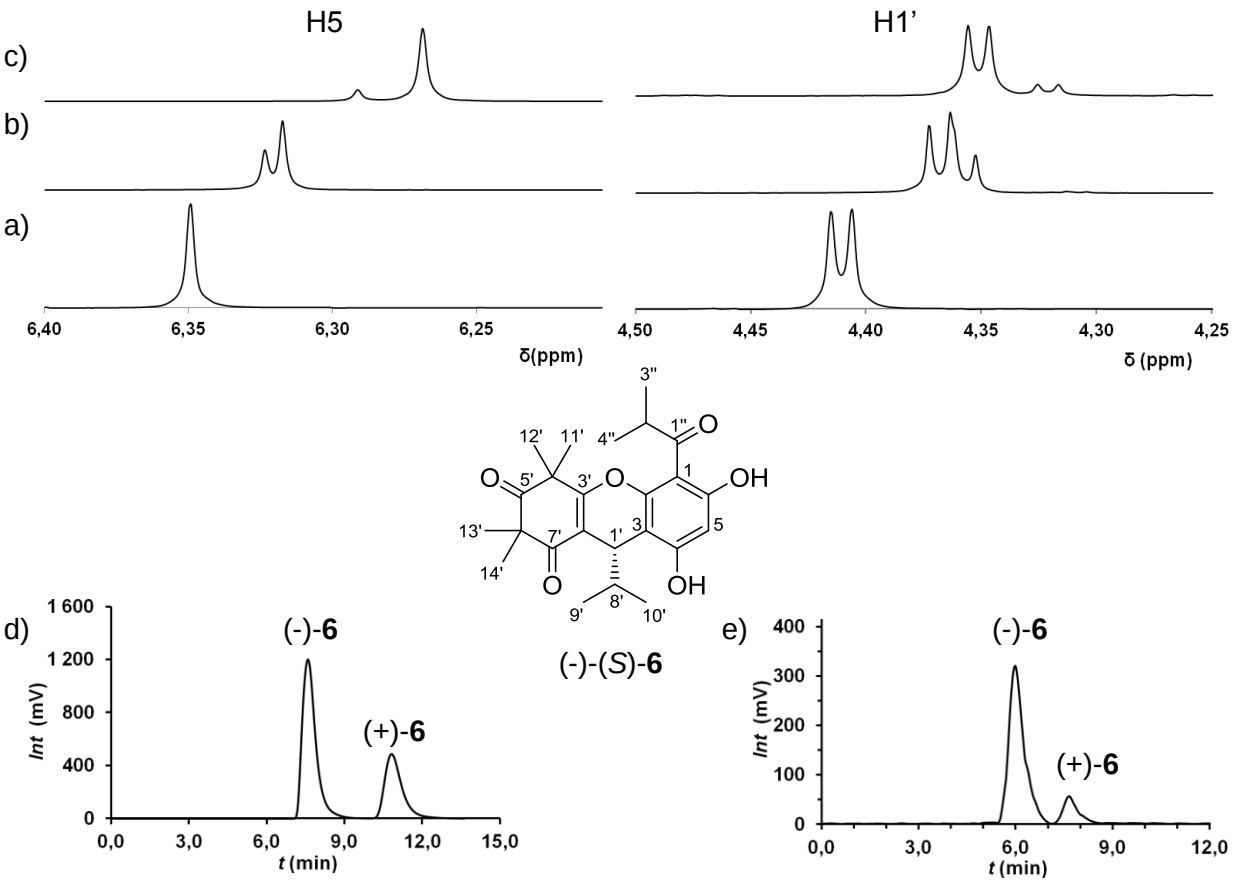


Fig. 30 Comparison of the splitting of the NMR-signals (in $CDCl_3$) of H5 and H1' in the spectrum of MCB (**6**) for with ee of a) 0 %, b) 34 % and c) 72 %. HPLC chromatogram of (-)-(*S*)-MCB (**6**) with d) 34 % *ee* and e) 70 % *ee* (ChiralCelOD-H, *i*PrOH/n-hexane, 30:70, 0.5 mL/min, 15°C)

As suggested by WILLIAMS *et al*.[76] for cannabinoid derivatives or by FENG *et al.*[78c] for urea and amide derivatives, the dimers possibly form over hydrogen bonding in the solution. BERGMAN *et al*.[78a] reported NMR-splittings due to π-stacking interactions of polycyclic aromatic ligands. In the case of myrtucommulone B (**6**) both are possible, that's why we proposed two different ways of forming the dimer in Fig. 31.

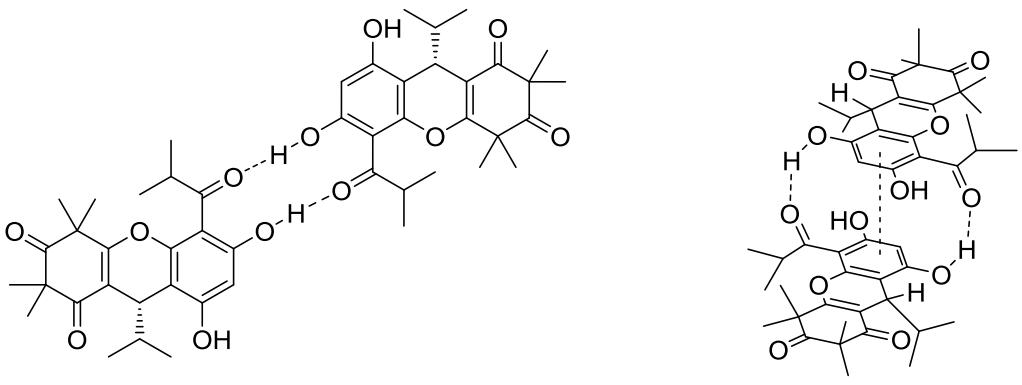
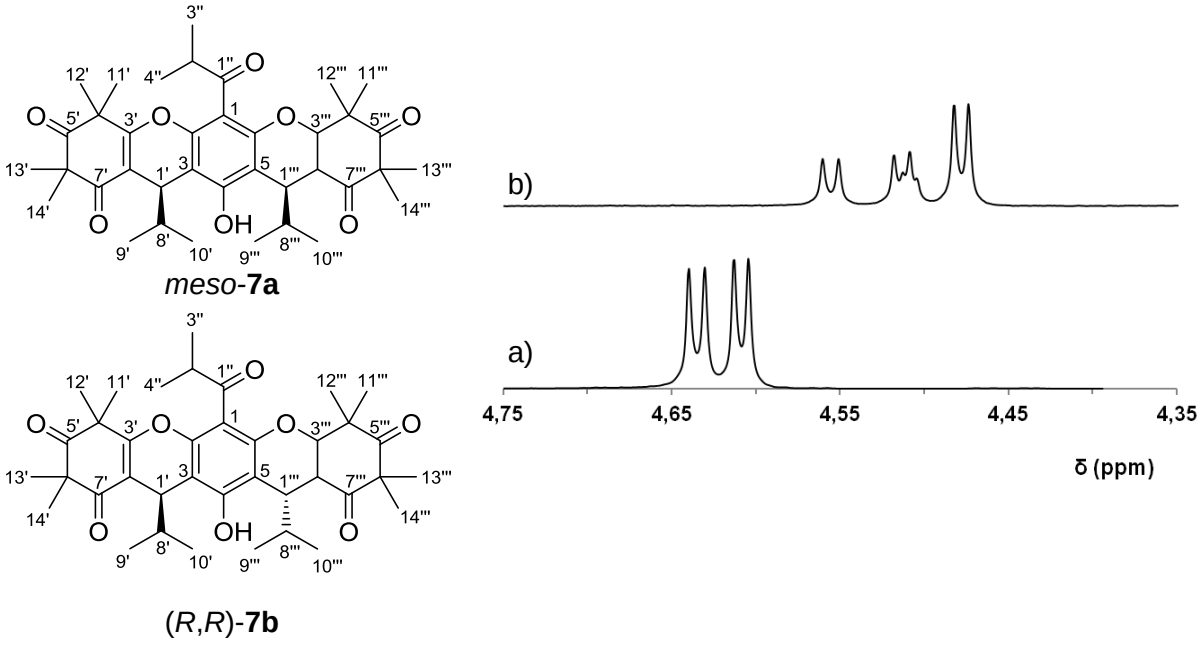


Fig. 31 Possible homochiral dimers of (-)-(*S*)-(**6**).

We could also observe this phenomenon on the NMR spectrum of cyclised MCA (**7**) on a mixture of the diastereomers *meso*-**7a** and **7b**, making it possible to not only read the *ee* but also the *de* of the mixture in the signal of one single proton (Fig. 32).



meso-**7a**

(*R*,*R*)-**7b**

Fig. 32 Comparison of the NMR signals (in $CDCl_3$) of proton H1' and H1''' in a) a 1:1 mixture of *meso*-**7** and *rac*-**7**, b) 1:1 mixture of *meso*-**7a** and **7b** (with 70 % ee).

As expected, in a 1:1 mixture of *meso*-**7a** and *rac*-**7b**, the hydrogen atoms H1' and H1''' are equivalent and appear as one doublet for each diastereomer. In an enantiomerically enriched mixture though, they happen to give a similar splitting to the one observed for MCB (**6**) for the **7b** compound (with 70% *ee*). In addition to that, the signal for the *meso*-form (*meso*-**7a**) is also splitted giving a sum of four doublets with integrations corresponding to the actual ratio of the products. This means that the *meso*-form probably participate to the formation of chiral dimers or "polymer" leading to the observed splitting.

2.3.3. Conclusion on the metal catalysis

In conclusion on the metal catalysis, we developed an enantioselective synthesis capable of providing norsemimyrtucommulone (**8**) and myrtucommulone B (**6**) with 72 % *ee* and myrtucommulone A (**5**) with 81 % *ee*. We started from the achiral isobutyryl phloroglucinol (**25**) and isobutylidene syncarpic acid (**31**) and used ALB (**66**) as a chiral catalyst. This synthesis offers a reliable alternative for the enantioselective Michael/Friedel-Craft reactions, in the case of strongly sterically hindered Michael acceptors.

We also demonstrated that no racemisation takes place during the cyclisation process, thus confirming the prior results from JAUCH *et al*.[35a] We can even now conclude that since no racemisation occurs, the 1:1:2 ratio that was obtained for: (*R*,*R*)-PMCA (**7b**):(*S*,*S*)-PMCA (**7b**):*meso*-PMCA (**7a**) is also valid for MCA (**5**). This shows that natural as well as synthetic MCA from *Myrtus Communis* have a 1:1 ratio between a *meso* form and a racemate.

Moreover we showed the extreme specificity of this system, since it accepts only minor modifications. This specificity is especially due to the steric importance of its substrates and also to the rapidity of the background reaction making any asymmetric catalysis effort laborious.

To find out if enantiomerically enriched MCA is more potent than the racemic one, these compounds were sent to be tested for pharmacological activity but the results are not known yet.

At the end the enantioselectivities obtained are good but no diastereoselectivity could be observed. That is why we turned to the trendy organocatalysis.

2.4. Organocatalysed syntheses of myrtucommulone derivatives

Already in 1912, BREDIG reported a weakly enantioselective synthesis of a cyanohydrin catalysed through an alkaloid.[79] But the development in the early 1970's of the Hajos-Parrish-Eder-Sauer-Wiechert reaction marked a watershed in asymmetric organocatalysis. Two different industrial groups reported the first enantioselective proline-catalysed intramolecular aldol reactions.[79-80] Because of their cost effectiveness and availability, proline and *Cinchona* alkaloids have been for many years the favourite organocatalysts. Nowadays a very broad spectrum of reactions has been described with a wide choice of catalysts. Aldol, Michael, and Mannich reactions are the most widely investigated, but Diels-Alder, Baylis-Hillman, Friedel-Crafts, and aza-Henry reactions have also been reported. Typical catalysts are, in addition to the ones mentioned above, phosphoric acid-binaphtyl derivatives, chiral thioureas as dual hydrogen bond donors or synthetic peptides.[37,79-81]

The work on organocatalysed reactions was divided in two parts. First we designed a new One-Pot synthesis of myrtucommulones derivatives using mostly proline as a catalyst. Then we focused on the development of the reaction conditions to synthesise myrtucommulones asymmetrically. In the first part some stereoselectivity is observed but remains relatively low. In the second, are depicted the various catalysts, including *Cinchona* alkaloids, that were used and the asymmetry is discussed more in details.

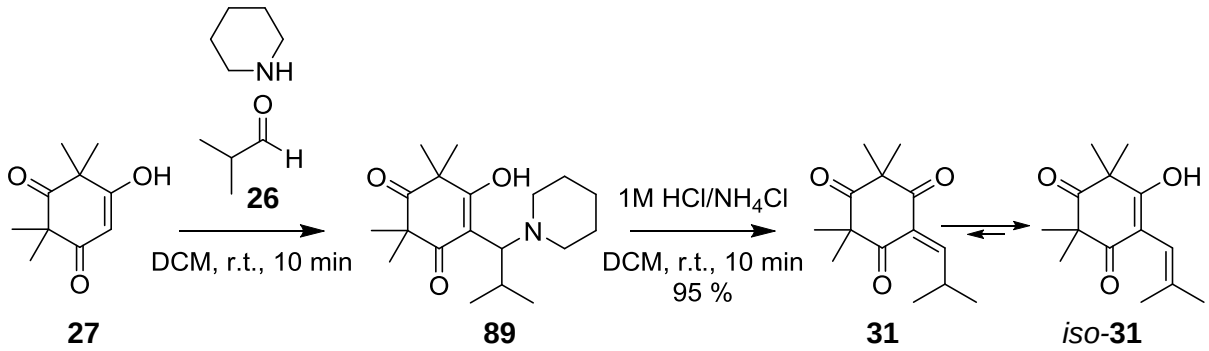
2.4.1. One-Pot synthesis of myrtucommulones

2.4.1.1 The tandem Knoevenagel-Michael reaction.

The first challenge was to determine if the reaction of formation of myrtucommulone derivatives can be efficiently enhanced with organocatalysts. In his dissertation, H. MÜLLER[34] already considered the One-Pot synthesis of myrtucommulone derivatives but it remained unsuccessful.

In the synthesis from 2010, JAUCH *et al.*[35] form the Mannich base **89** from syncarpic acid (**27**) in the presence of isobutyraldehyde (**26**) and piperidine (Scheme 28). After a quick work-up using a 1M HCl solution saturated with ammonium chloride, the Michael acceptor **31** could be obtained. This method is straight forward but has a few drawbacks: first it includes two

practical steps and second, once the product **31** is formed, it isomerises slowly but ineluctably to *iso*-**31** which is unreactive.[35]

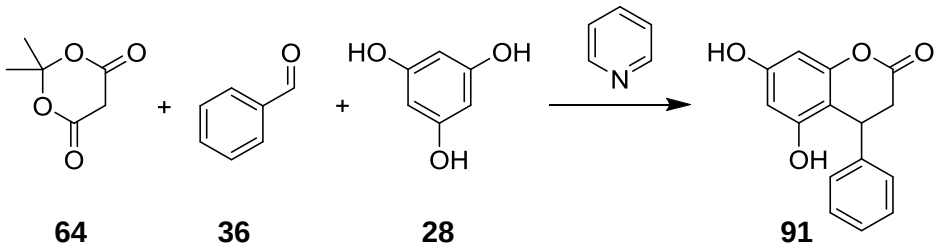


Scheme 28 Previous synthesis of isobutylidene syncarpic acid (**31**).

A broad variety of organic reactions such as Mannich and aldol reactions but also Michael additions are known to be catalysed by (*S*)-proline (**90**) and other amino acids.[80,81i,j,82] Knoevenagel condensations as well are described in the literature.[83] 1,3-Diketones are known to be pretty easily enolised and are used for multicomponent syntheses to form heterocycles or to perform a Knoevenagel reaction in combination with a Michael addition.[84]

The Knoevenagel-Michael tandem reactions are described for dimedone (**37**)[85] or Meldrum's acid (MA) (**64**)[86] but nothing had been found concerning SA (**27**). The literature cited here for the condensation of aldehydes on MA (**64**) precisely uses proline (**90**) as a catalyst.[86]

In a publication from 1987, NAIR reported the pyridine-catalysed condensation of Meldrum's acid (**64**), benzaldehyde (**36**) and PG (**28**) to form the dihydrocoumarin **91** (Scheme 29).[87] After MA (**64**) condensed with the aldehyde **36**, PG (**28**) reacts though a Michael addition on the intermediate to give after transesterification, acetal cleavage and decarboxylation of the MA (**64**), the expected product. One clearly sees here the parallel with the formation of myrtucommulones.



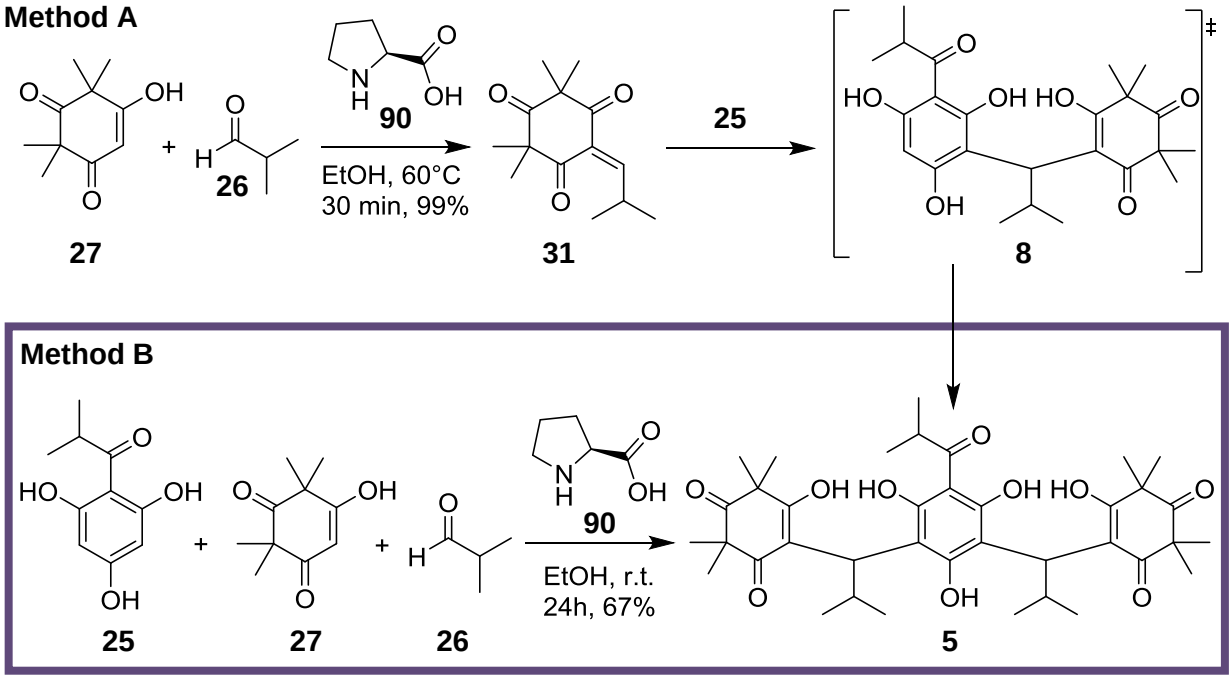
Scheme 29 Synthesis of dihydrocoumarin (**91**) according to NAIR.[87]

Based on this, we found out that (*S*)-proline catalyses the Knoevenagel-condensation of syncarpic acid (**27**) with isobutyraldehyde (**26**) as well (Scheme 30). Isobutylidene syncarpic acid (**31**) could be synthesised in quantitative yields in a few minutes at 60°C or overnight at room temperature (Tab. 8). Very interestingly, the isomerisation of **31** seemed to be much more equilibrated in MeOH, since we obtained at first almost only the desired isomer. Later, we could figure out with reactions lasting up to a week that **31** finally isomerises to *iso*-**31** but extremely slowly.

Tab. 8 Formation of the Michael Acceptor (**31**)

Catalyst	Temperature	Time	Yield
(*S*)-Proline (**90**)	60°C	30 min	97 %
(*S*)-Proline (**90**)	r.t.	14 h	99 %

When IBPG (**25**) was added to the mixture directly after the formation of the acceptor **31**, it reacted immediately to NSMC (**8**) and gave MCA (**5**) after several hours in 72 % yield (Method A) (Tab. 9, entry 2, Scheme 30). By mixing IBPG (**25**), IBA (**26**), SA (**27**), and proline (**90**) in one single vial, we could achieve the first one-pot-synthesis of myrtucommulone A (Method B) in 24h with 67 % yield (Tab. 9, entry 4, Scheme 30).



Scheme 30 One-pot synthesis of myrtucommulone A (**5**). Number of equivalents of the starting materials: IBPG (**25**) (1): SA (**27**) (6): IBA (**26**) (8): proline (**90**) (0.5).

If the Michael donor **25** is in the reaction mixture from the beginning (Method B), there is the possibility that it is consumed by the aldehyde; this would explain the slightly lower yield for

the One-Pot method. When only 0.5 eq. of the catalyst were used, the reaction needed twice as much time (Tab. 9, entry 1,3).

We further investigated the new One-Pot method by choosing other amino acids as catalysts. We chose phenylalanine (Phe) for its neutral side chain, glutamic acid (Glu) for its acidic part and histidine (His) for its basic section. None of them could replace proline to catalyse our one-pot reaction (Tab. 9, entry 5-7). We could indeed isolate some product in the reaction with Phe but only small amounts. It was observed on TLC that Glu did not catalyse the formation of IBSA (**31**), and His enhanced the formation of the Michael acceptor **31** but also the reaction between IBPG (**25**) and IBA (**26**) which consumed the starting material did not lead to any product. This highlights the importance of the secondary amine character of proline. As described in the literature,[80,81d,f,j,82] the formation of the Michael acceptor **31** probably proceeds over an iminium/enamine intermediate.

Tab. 9 Formation of myrtucommulone A (**5**) under different conditions.

Entry	Method	Catalyst (eq.)	Solvent	T(°C)	Time	Product (yield, %)	*de*[b] *(%)*
1	A[a]	**90** (0.5 eq.)	MeOH	r.t.	48 h	**5** (67)	5
2	A[a]	**90** (1 eq.)	EtOH	r.t.	31 h	**5** (72)	24
3	B	**90** (0.5 eq.)	MeOH	r.t.	48 h	**5** (66)	12
4	B	**90** (1 eq.)	EtOH	r.t.	24 h	**5** (66)	12
5	B	Phe (1 eq.)	EtOH	r.t.	24 h	**5** (12)	8
6	B	Glu (1 eq.)	EtOH	r.t.	48 h	x	-
7	B	His (1 eq.)	EtOH	r.t.	48 h	x	-

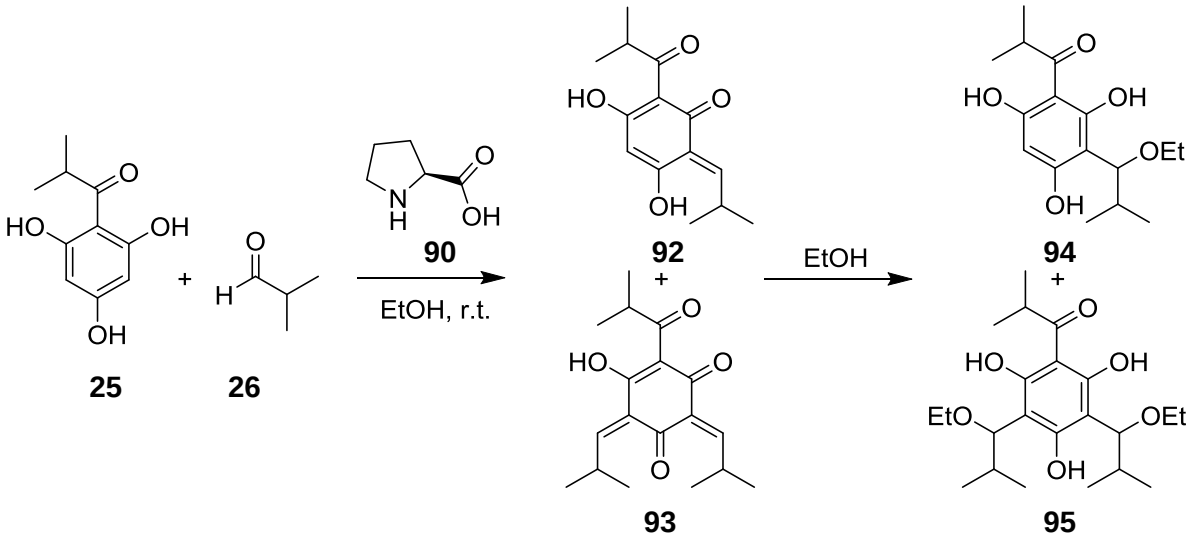
a) time was taken when IBPG (**25**) was added, b) determined on the NMR spectrum of the cyclised derivative.

The last column of the Tab. 9 lists the diastereomeric excess that could be observed on the NMR of each sample of PMCA (**7**). With the Method B and one equivalent of proline (**90**), an encouraging *de* of 24 % was observed and let expect more with other bulkier catalysts. However, every optical rotation measured for these samples was found to be 0. This means that no *ee* was achieved.

Attention was given to the products formed from IBA (**26**) and IBPG (**25**). Different conditions were tried to isolate the isobutylidene derivatives **92** and **93** of IBPG but the only products that could be identified were the two derivatives **94** and **95** (Scheme 31).

These derivatives confirmed that a Knoevenagel condensation takes place between IBPG and IBA, but the isobutylidene derivatives formed were captured by the solvent (EtOH) to form unreactive derivatives. Hereby, we could demonstrate how IBPG is consumed in the

reaction mixture by isobutyraldehyde. Since we could not isolate the desired derivatives in other solvents either, the isobutylidene IBPGs were not further investigated.

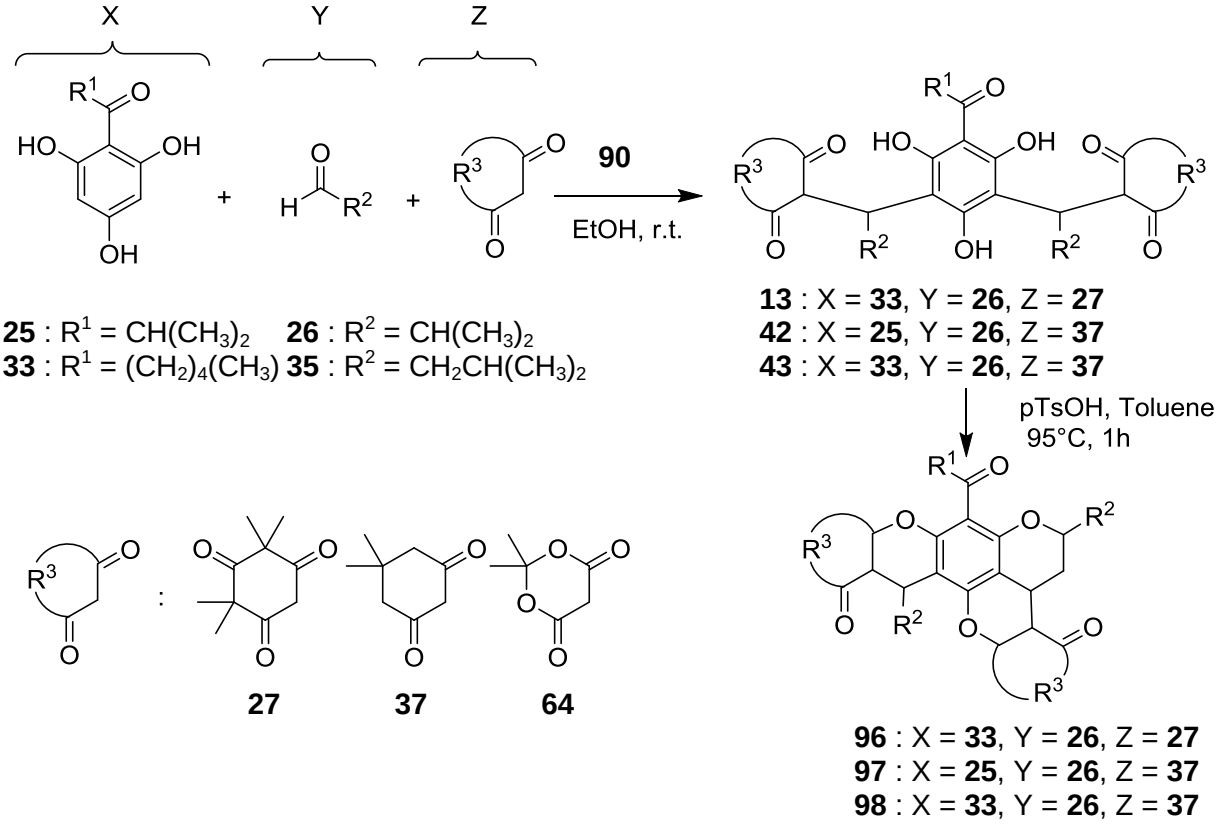


Scheme 31 Synthesis of the IBPG derivatives **94** and **95**.

2.4.1.2 One-Pot Synthesis of myrtucommulone-derivatives

Several myrtucommulone derivatives were synthesised with the one-pot method (Method B) to show the scope of the One-Pot reaction conditions (Tab. 10). Among the derivatives, MCF (**13**) could be synthesised with a fair yield (Tab. 10, entry 1) and a very interesting *de* of 38 %. The dimedone derivatives **42** and **43** which exhibit cytostatic potency (§ 1.2.2) gave the best yields (up to 95 % for **42** (Tab. 10, entry 2-3) but showed only insignificant *de* of 5 and 7 % respectively. The derivatives **13**, **42** and **43** were cyclised to their dehydrated pentacyclic derivatives respectively **96**, **97**, and **98** for analysis.

Tab. 10 One-pot synthesis of myrtucommulone derivatives.



25 : $R^1 = CH(CH_3)_2$ **26** : $R^2 = CH(CH_3)_2$
33 : $R^1 = (CH_2)_4(CH_3)$ **35** : $R^2 = CH_2CH(CH_3)_2$

13 : X = **33**, Y = **26**, Z = **27**
42 : X = **25**, Y = **26**, Z = **37**
43 : X = **33**, Y = **26**, Z = **37**

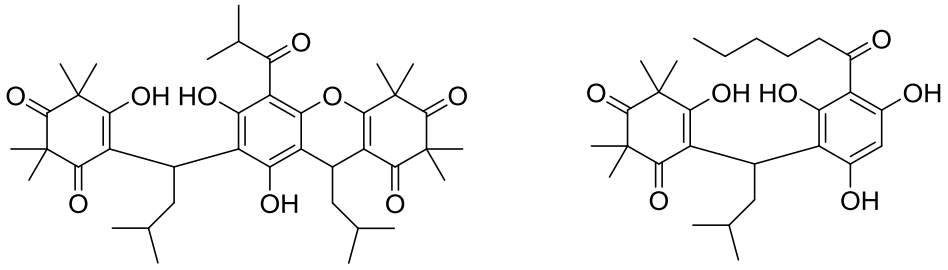
27 **37** **64**

96 : X = **33**, Y = **26**, Z = **27**
97 : X = **25**, Y = **26**, Z = **37**
98 : X = **33**, Y = **26**, Z = **37**

Entry	X	Y	Z	Time	Product	Yield	de[a] (%)
1	**33**	**26**	**27**	48 h	**13**	60 %	38
2	**25**	**26**	**37**	24 h	**42**	95 %	5
3	**33**	**26**	**37**	16 h	**43**	79 %	7
4	**25**	**35**	**27**	40 h	**99**	10 %	-
5	**33**	**35**	**27**	40 h	**100**	14 %	-
6	**25**	**26**	**64**	16 h	**101**	-	-

a) determined on the NMR spectrum of the cyclised derivative

Unfortunately, the use of isovaleraldehyde (**35**) did not lead to the expected derivatives. Only traces of product could be isolated. In the case of entry 4, the product **99** was found to have the molecular weight of 678.8 g/mol which corresponds to one half-cyclised derivative of the expected product (Fig. 33). As for entry 5, we could only isolate the product **100** with the molecular mass corresponding to a product where the Michael addition took place only once between hexanoyl phloroglucinol and isopentylidene syncarpic acid, and again with a poor yield (33).



33 Structures of the isolated products **99** and **100**.

We also tried our reaction with Meldrum's acid (**64**) and first thought we had the expected product since we obtained in 16 h a clear spot on the TLC plate and the starting materials had disappeared. However, after mass analysis, we were forced to reconsider our results since we could only observe masses of 256.4 and 292.1 g/mol in the mass spectra, which is way below the expected mass. Eventually we could get crystals of our main product and submit it to XRD (the structure was determined with a high R-factor but is still reliable). We obtained product **101**, confirmed by NMR, which is the result of a condensation of the MA (**64**) and IBA (**26**), on which acetone added (Fig. 34). We could then identify the second mass to be probably the typical dihydrocoumarin product **102** already observed by NAIR,[87] when mixing a phloroglucinol, and MA (**64**) in the presence of an aldehyde. We could not isolate the desired product because of the extreme instability of the Meldrum's acid.

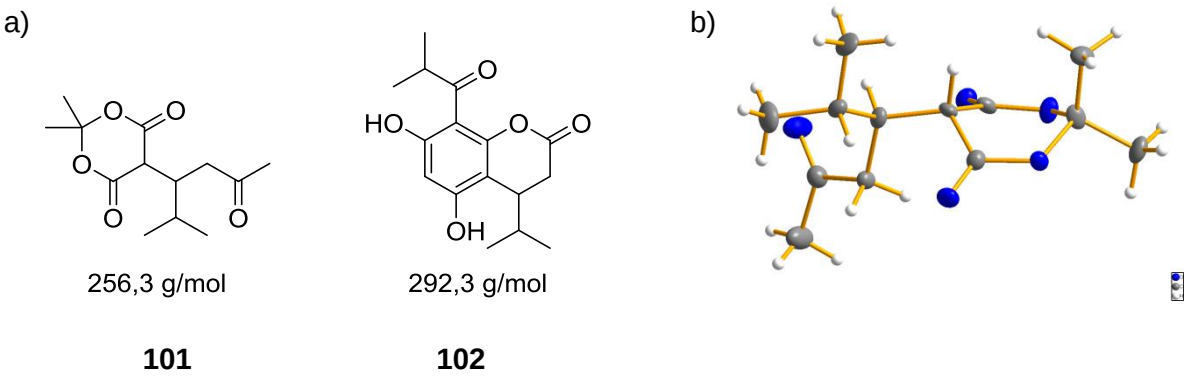


Fig. 34 a) Structure of the products obtained with Meldrum's acid (**64**), b) crystal structure of **101.**

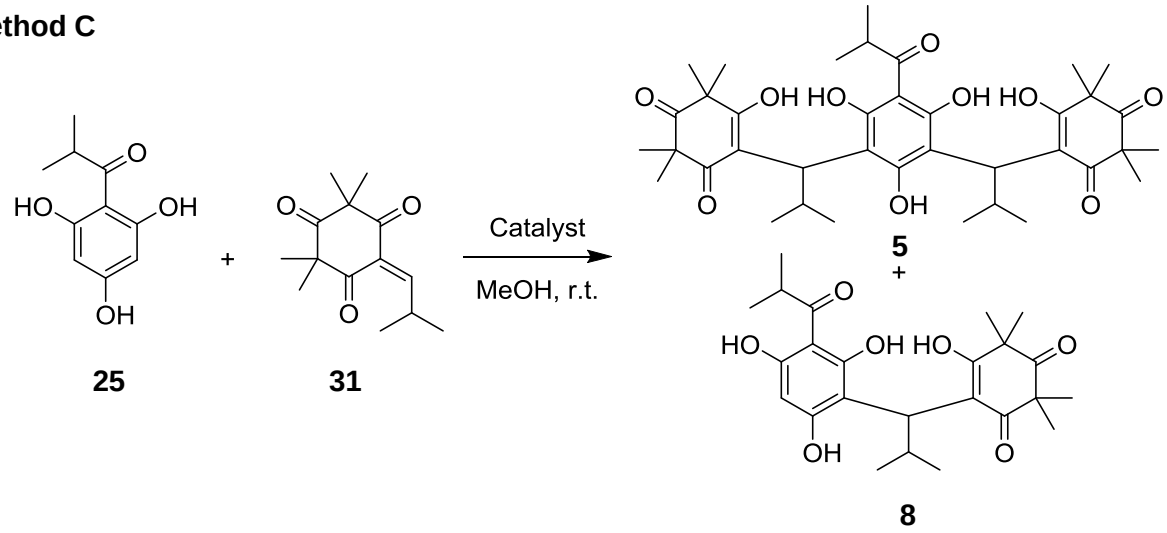
Even if the study is non exhaustive, we could say that the one-pot synthesis is worth being used in the case of the dimedone and syncarpic acid derivatives. The shape of the central phloroglucinol does not seem to have much influence on the synthesis. However, the use of the Meldrum's acid and isovaleraldehyde did not lead to any satisfying results.

2.4.2. Development of the organocatalysed synthesis.

2.4.2.1 Classic synthesis of myrtucommulones in mild conditions

To further investigate the possibilities of these mild reaction conditions, we made some experiments where the formation of MCA (**5**) is independent of the formation of the Michael acceptor (**31**). Therefore, we synthesised IBSA (**31**) either with the published method,[35] or with the method described in Scheme 30, isolated it and added it to a new reaction mixture containing IBPG (**25**) and a catalyst (Scheme 32).

Method C



Scheme 32 Classic synthesis of MCA (**5**) catalysed by proline (**90**). Number of equivalents of the starting materials : IBPG (**25**) (1): SA (**27**) (6): proline (**90**) (0.5).

Thanks to the work of J. SCHMITT,[88] we could selectively synthesise NSMC (**8**) with proline (**90**) by adding only 1.2 eq. of the acceptor **31**. Besides, the use of the achiral piperidine in DCM also led to a good yield offering another cheap alternative for the synthesis of the intermediate **8** (Tab. 11, entry 1-2). Similarly to the results of Method A, MCA (**5**) was obtained with 72 % yield with proline (**90**) and 70 % yield with the achiral pyrrolidine with the Method C (Tab. 11, entry 3-4).

Tab. 11 Formation of MCA (**5**) and NSMC (**8**) with the Method C in different conditions.

Entry	Method	Catalyst (eq.)	T(°C)	Time	Product (yield, %)	*ee*[c] (%)	*de*[d] (%)
1	C[a]	Proline (**90**) (0.5 eq.)	r.t.	48 h	**8** (87)	3	
2	C[a, b]	Piperidine (0,5 eq.)	r.t.	48 h	**8** (79)	-	-
3	C	Proline (**90**) (0.5 eq.)	r.t.	72 h	**5** (72)		5
4	C	Pyrrolidine (0,5 eq.)	r.t.	72 h	**5** (70)	-	-
5	C	**-**	r.t.	72 h	**5** (18) + **8** (69)	-	-
6	C	**-**	r.t.	10 days	**5** (68)	-	-
7	A[b]	Piperidine (0.5 eq.)	65°C	72 h	**5** (56)	-	-
8	C	Proline (**90**) (0.5 eq.)	-20°C	7 days	**5** (35) + **8** (60)	0	8

a) only 1.2 eq. of IBSA (**31**) was added, b) the reaction was run in DCM c) time was taken when IBPG (**25**) was added, c) determined on MCB (**6**) through HPLC on CHIRALCEL OD-H, *i*PrOH/*n*-hexane 20:80, 0.5-0.6 mL/min, 15 °C, d) determined on the NMR spectrum of PMCA (**7**)

We then tested these new reaction conditions without catalyst to evaluate its influence on the product formation (Tab. 11, entry 5-6). As mentioned before, NSMC (**8**) was synthesised without the effort of a catalyst in three days with good yields. Moreover, MCA (**5**) could be isolated after 10 days even if no catalyst was present.

If the reaction was heated, we observed a fast formation of MCA (**5**) in the presence of piperidine. However the heat also favoured the formation of *iso*-**31** which is unreactive and limited the reaction to lower yields (Tab. 11, entry 7). Looking for conditions to favour the asymmetric reaction, we also run the reaction at -20°C and observed a very slow formation of the products but no significant asymmetric induction at this point. Only 8 % *de* could be read on the NMR spectrum of PMCA (**7**) and both optical rotations of NSMC (**8**) and MCA (**5**) were found to be zero (Tab. 11, entry 8).

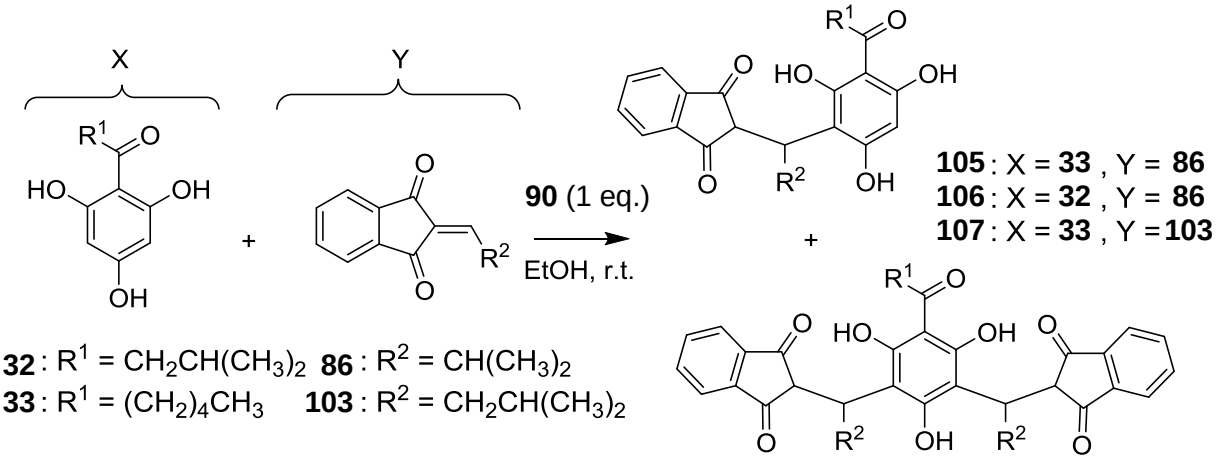
2.4.2.2 Synthesis of indandione-derivatives

We next concentrated on the synthesis of some indandione-derivatives to extend the scope of the reaction (Tab. 12). Isobutylidene 1,3-indadione (IBIND) (**86**), already used in the patent of JAUCH,[36] and a new isopentylidene indandione **103** were used to afford two derivatives described in the same publication (**39** and **104**) and a new one **41** made of the Michael acceptor **103** and hexanoyl phloroglucinol (**33**).

We could form the indandione derivatives in moderate to fair yields. However, the reaction mixture always included the semi-derivatives, where the Michael reaction took place only

once, independently of the time of reaction and in a hardly extricable mixture. As for the synthesis of MCF (**13**), the use of proline (**90**) induced a non negligible diastereomeric excess of 35 and 34 % for the isobutylidene indandione derivative **39** and **104** respectively, where the *meso* form is preponderant (**39a** and **104a**). Interestingly, in the case of the isopentylidene indandione derivative **41**, the excess is smaller but in the other direction making the chiral part of the molecule the major product (**41b**) (see § 4.6.5).

Tab. 12 Formation of indandione-derivatives with Method C.

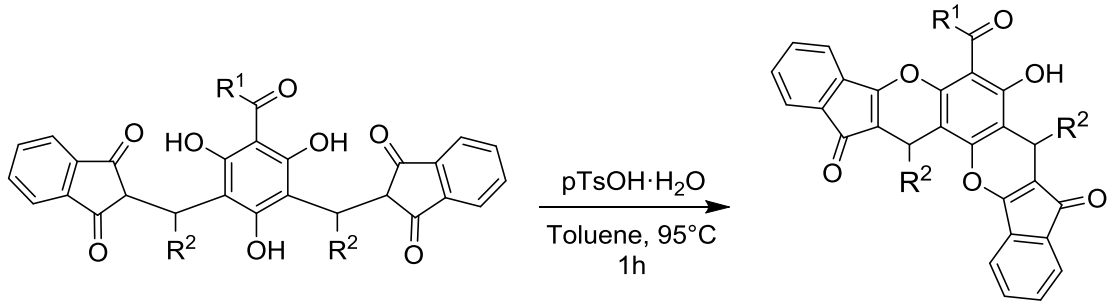


32 : $R^1 = CH_2CH(CH_3)_2$ **86** : $R^2 = CH(CH_3)_2$
33 : $R^1 = (CH_2)_4CH_3$ **103** : $R^2 = CH_2CH(CH_3)_2$

Entry	X	Y	Time	Product	de[a] (%)
1	**33**	**86**	18	**39** (72 %) + **105** (22 %)	35
2	**32**	**86**	48	**104** (71 %) + **106** (23 %)	34
3	**33**	**103**	18	**41** (49 %) + **107** (39 %)	22[b]

a) the *de* was calculated on the amount of each diastereomer isolated, b) in this case **41b** is the major product.

The complete products **39**, **104**, and **41** were cyclised for analysis to their dehydrated forms, **108, 109**, and **110** respectively (Scheme 33). We could then grow crystals from our derivative **110** which helped us confirm its structure (Fig. 35).



39 : $R^1 = (CH_2)_4CH_3$, $R^2 = CH(CH_3)_2$
104 : $R^1 = CH_2CH(CH_3)_2$, $R^2 = CH(CH_3)_2$
41 : $R^1 = (CH_2)_4CH_3$, $R^2 = CH_2CH(CH_3)_2$

108 : $R^1 = (CH_2)_4CH_3$, $R^2 = CH(CH_3)_2$
109 : $R^1 = CH_2CH(CH_3)_2$, $R^2 = CH(CH_3)_2$
110 : $R^1 = (CH_2)_4CH_3$, $R^2 = CH_2CH(CH_3)_2$

Scheme 33 Cyclisation of the indandione-derivatives **39**, **104**, and **41**

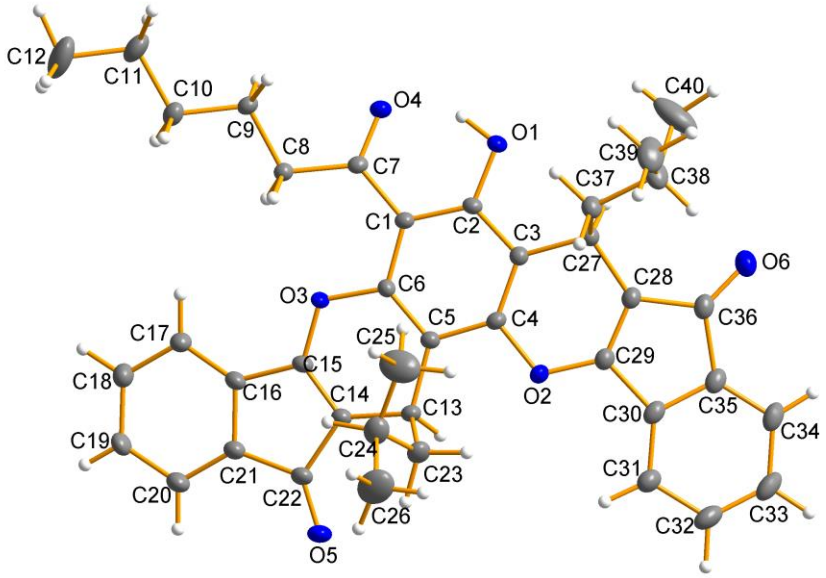


Fig. 35 X-ray structure of the indandione-derivative *syn*-**110a**; ellipsoids at the 50 % probability level.

2.4.2.3 Alternative catalysts

Miscellaneous

Looking to improve the efficiency and the stereoselectivity of the reaction, we varied the polarity, size and structure of the catalysts with the Method C (Tab. 13).

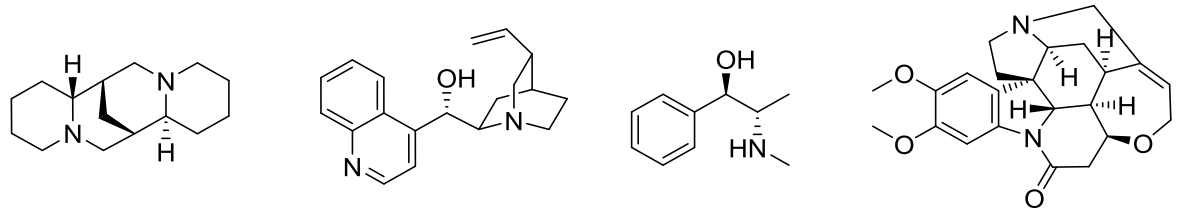
Tab. 13 Variation of the catalyst in the Method C of formation of MCA (**5**) and NSMC (**8**).[a]

Entry	Catalyst (eq.)	Solvent	Time	Product (yield, %)	*ee* (%)	*de* (%)
1	(*S*)-Phe (0,5 eq.)	MeOH	72 h	**5** (70)	-	8[b]
2	(*S*)-Glu (0,5 eq.)	MeOH	72 h	**5** (69) + **8** (10)	-	1[b]
3	(*S*)-His (0,5 eq.)	MeOH	72 h	**5** (42) + **8** (11)	-	-
4	(*S*)-Tyr (0,5 eq.)	MeOH	144 h	**5** (55) + **8** (37)	-	-
5	(*S*)-Trp (0.5 eq.)	MeOH	144 h	**5** (70) + **8** (12)	-	-
6[c]	Sparteine (**111**) (1 eq.)	DCM	19 h	**8** (96)	1[d]	-
7	CN (**112a**) (0,5 eq.)	MeOH	72 h	**5** (77)	13[e]	36[e]
8	CN (**112a**) (1 eq.)	MeOH	24 h	**5** (92)	7[e]	2[e]
9	(-)-Ephedrine (**113**) (0,5 eq.)	MeOH	96 h	**5** (80)	0[e]	2[e]
10	Brucine (**114**) (0.5 eq.)	DCM	114h	**5** (49)	0[e]	12[e]
11	HODPP (**115**)	MeOH	118 h	**5** (10[f])	0[e]	13[e]

a) all reactions were performed at room temperature, b) determined on the NMR spectrum of PMCA (**7**), c) only 1.2 eq. of IBSA (**31**) was added, d) determined on MCB (**6**) through HPLC on CHIRALCEL OD-H, *i*PrOH/*n*-hexane 20:80, 0.5-0.6 mL/min, 15°C, e) determined on MCA (**5**) by HPLC on Reprosil 100 Chiral-NR, ACN: Buffer (35:65), Buffer: 30mM NH_4OAc, pH9 DEA, 1.0 mL/min, 24°C, f) the poor yield here is only due to a massive loss of product during the work-up.

To the list of the three previously tested amino acids (for Method B) were added tryptophan (Trp) and tyrosine (Tyr) (Tab. 13, entry 1-5). Although histidine and tyrosine afforded moderate yields, phenylalanine, glutamic acid and tryptophan catalysed the Michael addition to myrtucommulone A with yields of 69-70 %, however with longer reaction times. Since the yields or the reaction times were not satisfactory, the stereoselectivity was not considered.

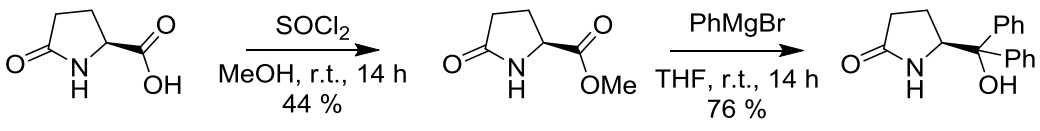
We then got interested in other natural products such as, sparteine (**111**), (+)-cinchonine (CN) (**112a**), (-)-ephedrine (**113**) and brucine (**114**) as catalysts (Fig. 36) (Tab. 13, entry 6-10). The use of sparteine (**111**) (J. SCHMITT[88]) in DCM in combination with a stœchiometric amount of the IBSA (**31**) led to an excellent yield of 96 % of NSMC (**8**) (Tab. 13, entry 1). As for proline, the use of 1 eq. of CN (**112a**) afforded the product in excellent yield (92 %) in only 24 h (Tab. 13, entry 8). Ephedrine (**113**) provided a very good yield as well but not brucine (**114**). Among them, only cinchonine (**112a**) showed a non negligible stereoselective induction affording MCA (**5**) with 13 % *ee* and 36 % *de.* It was so far the best diastereoselective achievement for MCA (**5**). We hence decided to concentrate more closely on *Cinchona* alkaloids in the next section (§ 2.4.2.4).



111 **112a** **113** **114**

Fig. 36 Structures of sparteine (**111**), (+)-cinchonine (**112a**), (-)-ephedrine (**113**), and brucine (**114**).

Since CN (**112a**) provided encouraging results, we aimed for a catalyst also containing the β-hydroxy-amine motif. 5-(hydroxydiphenylmethyl)pyrrolidin-2-one (HODPP) (**115**), was made in two simple steps. Pyroglutamic acid (**116**) was transformed into its methyl ester **117** and two phenyl groups were added through a Grignard reagent to afford **115** (Scheme 34).[89] With this reagent, we wanted to have the hydrogen bonding hydroxyl group surrounded by big bulky groups. Unfortunately this reagent was also ineffective for our Michael reaction (Tab. 14, entry 11).



116 **117** **115**

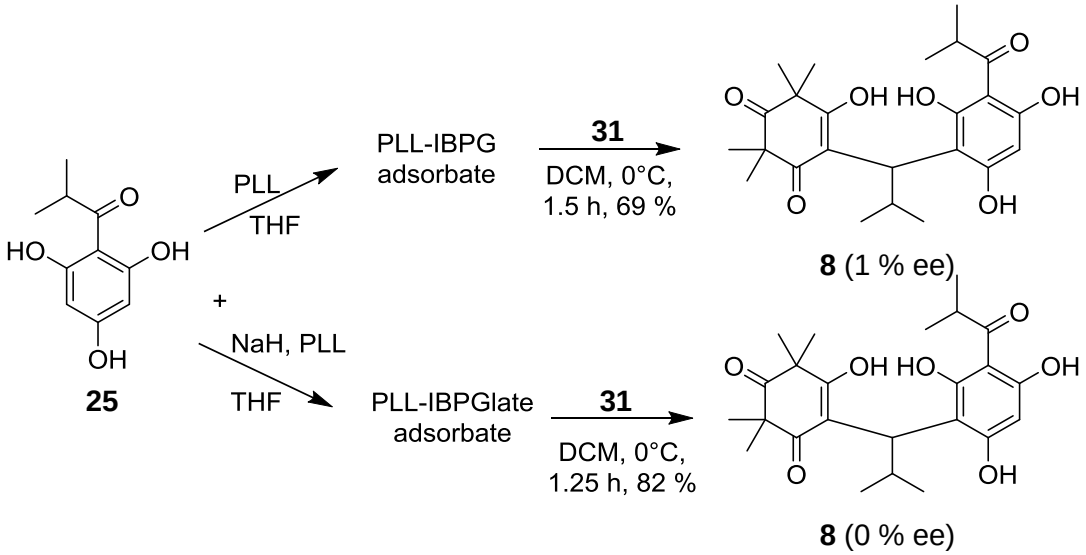
Scheme 34 Synthesis of the catalyst **115**.

The fact that the Michael addition can be catalysed indifferently by tertiary, secondary, and primary amines, brought us to the conclusion that the Michael addition is not enhanced by the iminium/enamine catalysis but rather by the Brønsted character of the bases used. This probably also explains the lack of stereoselectivity observed with small “bases” like the amino acids.

Synthetic peptides

As mentioned above, amino acids and synthetic peptides have been used to perform asymmetrically a wide range of asymmetric reaction in the literature. The aldol condensation, Michael addition, Mannich reaction are the most common.[81g,i] The Julia-Colonna epoxidation of a chalcone also proceeds with Poly-L-Leucine (PLL) in presence of hydrogen peroxide and sodium hydroxide in a triphasic mixture with toluene.[81g,90]

In our mild reaction conditions developed in § 2.4.2.1, the PLL was used as a catalyst but only 16 % MCA (**5**) and 39 % NSMC (**8**) could be isolated after 72 h and none of them showed any asymmetric enrichment. We then performed two experiments where the Michael donor **25** was primarily adsorbed on PLL, by mixing it in THF and evaporating the solvent until we obtained a powder. In the first case we adsorbed IBPG (**25**) directly on PLL and in the second IBPG (**25**) was first deprotonated prior to adsorption to form an “isobutyryl phloroglucinolate” (IBPGlate) adsorbed on PLL (Scheme 35).



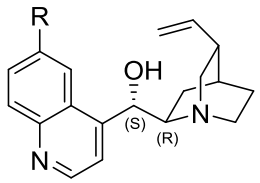
Scheme 35 Synthesis of NSMC with help of Poly-L-Leucine.

In both cases the formation of NSMC (**8**) was then achieved in DCM which is a solvent that should not dissolve the adsorbed molecule, to force it to stay close or stuck on the PLL. In

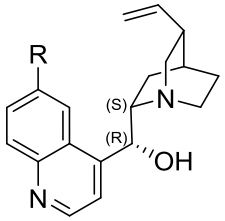
these conditions the intermediate **8** could be synthesised quickly and with good yields but PLL did not induced enantiomeric excess in the product.

2.4.2.4 *Cinchona* alkaloids derivatives

Cinchona trees have been extensively investigated since centuries to look for treatment of malaria.[91] The first unambiguous isolation of the well-known quinine (Q) (**112c**) was realised by PELLETIER and CAVENTOU in 1820.[92] Around 30 different *Cinchona* alkaloids (**112**) were isolated from the *Cinchona* trees, the best known being cinchonine (CN) (**112a**), its pseudo-enantiomer cinchonidine (CD) (**112b**), quinine (Q) (**112c**) and its pseudo-enantiomer quinidine (QD) (**112d**) (Fig. 37).[93] It is noteworthy that, for historical reasons, cinchonidine (**112b**) and quinine (**112c**) have the same absolute configuration, whereas the logic would have wanted the names cinchonidine (**112b**) and quinidine (**112d**), terms in "–idine", to be chemically related.



112a: R = H : cinchonine (CN)
112d: R = OMe : quinidine (QD)

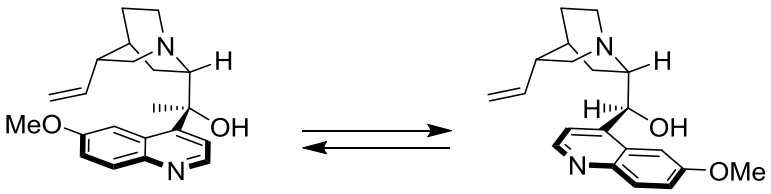


112b : R = H : cinchonidine (CD)
112c : R = OMe : quinine (Q)

Fig. 37 Structure of the four Cinchona alkaloids CN (**112a**), CD (**112b**), Q (**112c**), QD (**112d**).

Cinchona alkaloids and their derivatives have been used as catalysts to perform a wide range of organic reactions.[94] Among them, it is easy to find reports about the Michael reaction.[95] As an example, CHEN *et al.* reported the addition of 1,3-dicarbonyl compounds (comparable with our phloroglucinol moiety) to α,β-unsaturated ketones (comparable with our Michael acceptor **31**) with enantioselectivity between 89 and 99 %.[96]

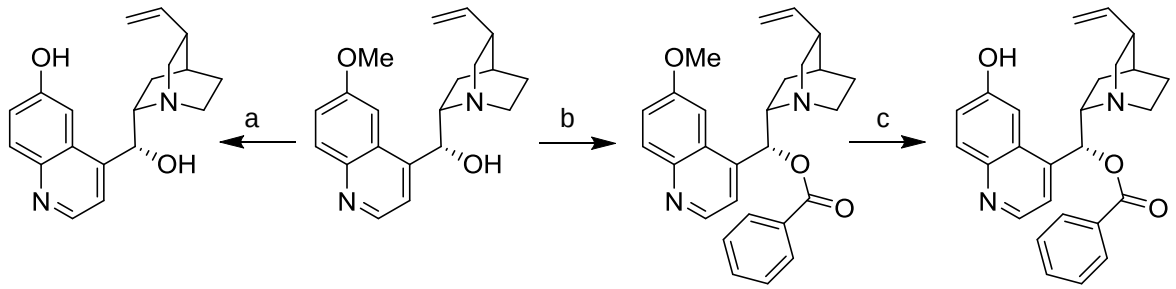
In most examples using this class of molecules, the alkaloids were used as bases.[94b] In other cases however, the bifunctional character of the β-hydroxy-amine motif was exploited.[94d,97] The quinuclidine nitrogen acts as a base while the vicinal free hydroxyl group can coordinate to other parts of the substrate through hydrogen bonding. The stereoselectivity observed is then depending on the conformational isomerism of the alkaloid. In Fig. 38 are depicted the hypothetical two most favoured conformers of quinidine (**112d**) in polar solvents.[98]



anti-closed **112d** *syn-closed* **112d**

Fig. 38 Two different conformers of QD (**112d**) favoured in polar solvents.[98]

Now, by converting the methoxy group on the 6' position into a free hydroxyl group, a new class of catalysts saw the light, including a new possibility of hydrogen-bonding. They are derived from quinine (**112c**) and quinidine (**112d**) and referred as cupreine (CPN) (**118**) and cupreidine (CPD) (**119**) respectively.[94d,95e] Most interestingly, SHI *et al.*[95e] found out that in the case of the Michael reaction of anthrone to nitroalkenes catalysed by CPN (**118**) or benzoyl cupreine (Bz-CPN) (**120**), the enantioselectivity obtained is the opposite of the one observed with quinine (**112c**). Cupreine (**118**) was easily formed by deprotecting the phenolic hydroxyl group of Q (**112c**) by means of sodium thioethanolate. Bz-CPN (**120**) was obtained by benzoylating the C-9 hydroxyl group of Q (**112c**) to benzoyl-quinine (Bz-Q) (**121**) and then removing the phenolic methoxy group with boron tribromide (Scheme 36).



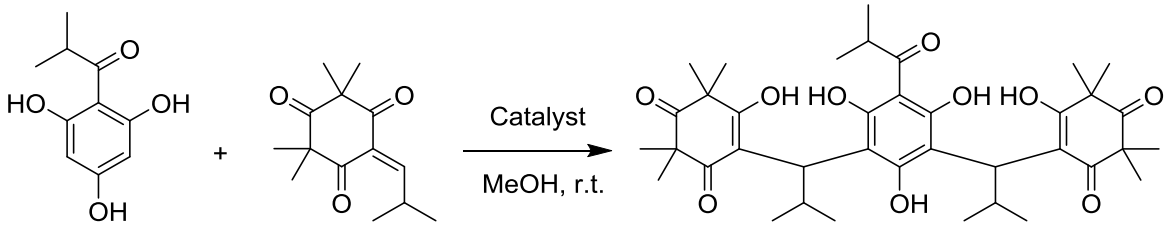
CPN (**118**) Q (**112c**) Bz-Q (**121**) Bz-CPN (**120**)

Scheme 36 Synthesis of CPN (**118**), Bz-Q (**121**), Bz-CPN (**120**). a) NaSEt, DMF, 110°C, 6h, 86 %, b) PhCOCl, 30 % w/w NaOH solution in water, DCM, r.t., 4h, 99 %, c) BBr_3, DCM, -78°C→r.t., 14h, 56 %.

Improvement of the diastereomeric excess

As mentioned before (§ 2.4.2.3), (*S*)-proline and various amino acids were already used as catalysts to synthesise myrtucommulone A (5) from IBPG (**25**) and IBSA (**31**). (*S*)-Proline provided only a poor diastereomeric excess (*de*) of 12 % (Tab. 14, entry 1). Likewise cinchonine (**112a**) was utilised and a *de* of 36 % (diastereomeric ratio (*d.r.*) of approximately 2:1) could be determined thanks to the HPLC method developed by M. HANS,[39] where *meso*-**5** was the major product and **5b** had an *ee* of 13 % (Tab. 14, entry 2) (Fig. 39a).

Tab. 14 Screening of different *Cinchona* alkaloids for the diastereoselective synthesis of MCA (**5**).



25 **31** **5**

Entry	Catalyst (0.5 eq.)	Description	Time	Yield	*ee*[a]	*de*[a]
1[b]	**90**	(*S*)-proline	72 h	72	1	12
2	**112a**	CN	72 h	77	13	36
3	**112b**	CD	96 h	46	28	82
4	**112b** + (*S*)-**67**	CD+ (*S*)-BINOL	72 h	64	22	45
5	**112c**	Q	69 h	60	22	45
6	**118**	CPN	72 h	67	14	44
7	**120**	Bz-Q	72 h	60	14	36
8	**121**	Bz-CPN	72 h	68	23	39

a) determined by HPLC on Reprosil 100 Chiral-NR, ACN: Buffer (35:65), Buffer: 30mM NH_4OAc, pH9 DEA, 1.0 mL/min, 24°C, b) One-Pot method.

We then started screening different *Cinchona* alkaloids looking to improve our diastereoselectivity. We used CD (**112b**), the pseudo-enantiomer of CN (**112a**), and achieved an astonishing leap up to a diastereomeric ratio (*d.r.*) of 91:9 (**5a**:**5b**) (82 % *de*) and an enantiomeric excess of 28 % (Tab. 14, entry 3). The HPLC spectrum given below in Fig. 39 confirmed the first efficient diastereoselective synthesis of MCA (**5**).

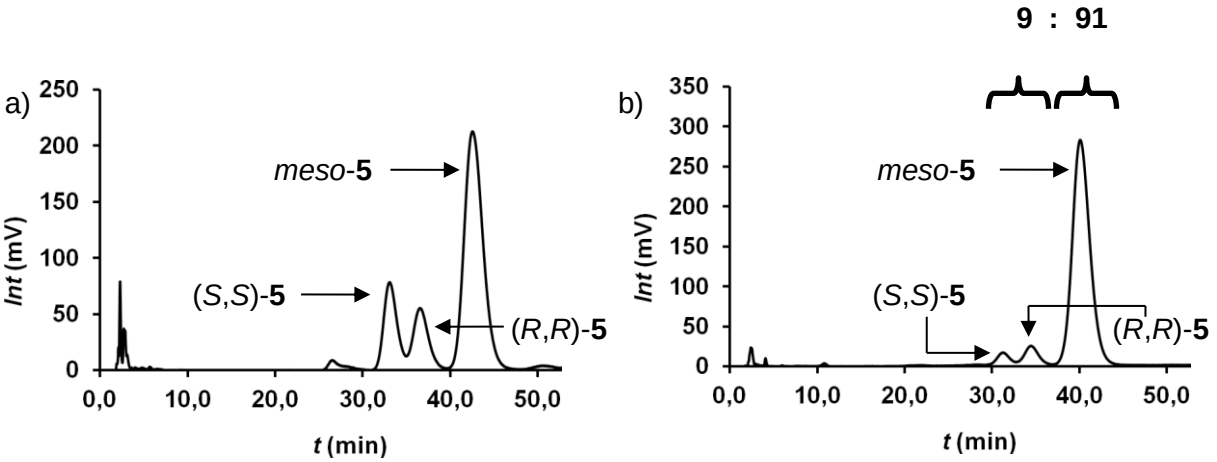


Fig. 39 HPLC chromatogram of **5** a) with 36% *de*, b) with 82 % *de* (Reprosil 100 Chiral-NR, ACN: Buffer (35:65), Buffer: 30mM NH_4OAc, pH9 DEA), 1.0 mL/min, 24°C)

On the other hand quinine (**112c**), which has the same absolute configuration as cinchonidine (**112b**) (see Fig. 37), gave only a slightly better *de* that cinchonine (**112a**) (Tab. 14, entry 5). Based on the work of ZHOU *et al.*[99] who added BINOL (**67**) to their proline-catalysed aldol reaction to enhance the enantioselectivity (71 % *ee* with (*S*)-proline, 94 % *ee* with (*S*)-proline + (*S*)-BINOL), we as well added the diol (*S*)- **67** to our reaction mixture. However, we got with 45 % *de* a much worse result than the one obtained with the use of only CD (**112b**) (Tab. 14, entry 4).

After having synthesised the different quinine derivatives as described above, we tried to either improve our diastereoselectivity or reverse it by using them. But although CPN (**118**) and Bz-CPN (**120**) offer different hydrogen bonding possibilities than CD (**112b**), they could only provide diastereoselectivity less than half as good and the main product was still the meso-form of MCA (**5**). Likewise Bz-Q (**121**) which does not have any hydrogen to donate in a hydrogen bonding, only showed a slightly lower diastereoselectivity than Q (**112c**) (Tab. 14, entry 5-8)

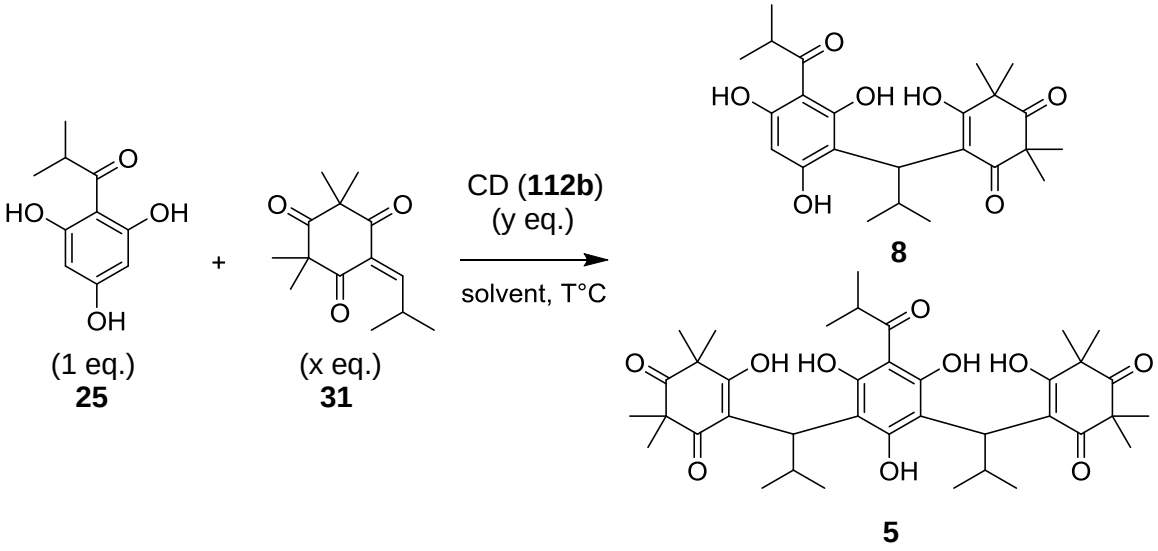
Investigation of the reaction catalysed by cinchonidine

Having obtained our best results with CD (**112b**), we intended to improve the diastereoselectivity and the yield of our reaction by modifying our reaction conditions (Tab. 15). First was varied the number of equivalents (y) of the catalyst. We figured out that 0.5 eq. was the best amount for our catalysis with 82 % *de* Tab. 15, entry 1-4). 0.25 eq. of catalyst led to an interesting 65 % *de*, but 0.33 eq. only provided 38 % *de*, and 1.5 eq. a negligible 3 %. Another attempt (not listed here) was also run with only 0.1 eq. of CN (**112a**) to catalyse the same reaction and disregarding the much longer reaction time, we obtained exactly the same *de* of 36% as with 0.5 eq. (Tab. 14, entry 2).

The variation of the solvent did not improve the *de* either but showed a dramatic influence on the stereoselectivity. The use of THF led to only weak inductions since, 26 % *ee* and 25 % *de* were obtained. On the other hand the use of DCM and toluene led to 41 % and 49 % *ee* respectively. These values were the first example of direct enantioselective organocatalytic synthesis of MCA (**5**) (Tab. 15, entry 5-7).
Motivated by these results, we repeated the synthesis in MeOH and toluene but at 0°C and with a limited amount of the Michael acceptor **31** to enhance the formation of the semimyrtucommulone derivative **8**. As already observed, the organocatalysis at low temperature needed much longer but did not provide any significant *ee* for NSMC (**8**) (Tab. 15, entry 8, 10). As for the formation of myrtucommulone A, the lower temperature seems to

completely inhibit the asymmetric catalysis in MeOH since only 2 % *de* could be observed. In the case of toluene, 40 % *ee* were reached, which is again less than at room temperature.

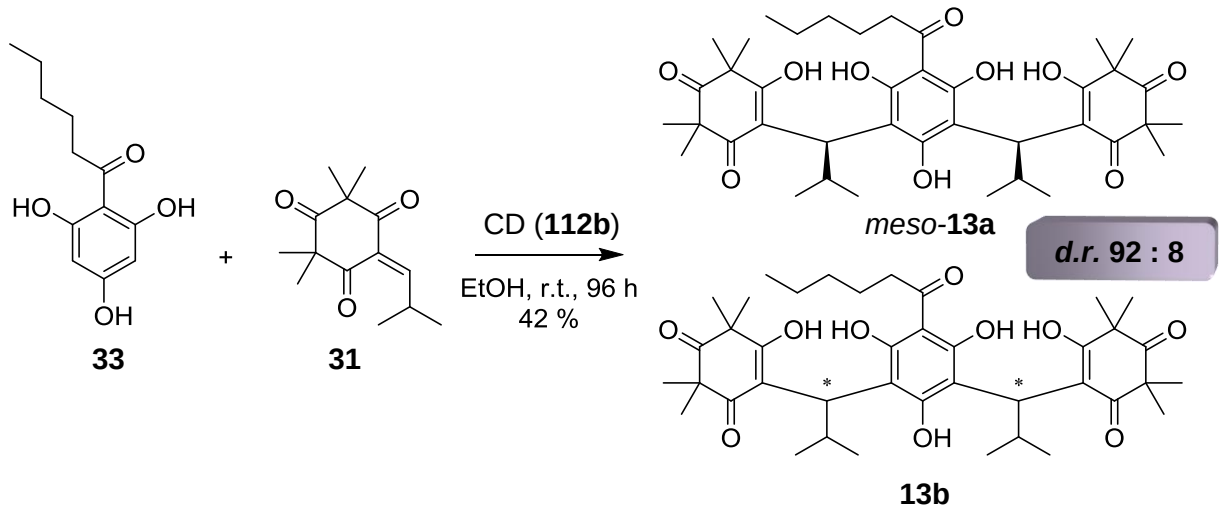
Tab. 15 Investigation of the reaction catalysed by cinchonidine.



Entry	x	y	Solvent	T°C	Time	Product (Yield)	*ee*[a]	*de*[a]
1	4.4	0.5	MeOH	r.t.	96 h	**5** (46)	28	82
2	4.4	0.25	MeOH	r.t.	94 h	**5** (40)	14	65
3	4.4	0.33	MeOH	r.t.	96 h	**5** (69)	16	38
4	4.4	1.5	MeOH	r.t.	90 h	**5** (73)	9	3
5	4.4	0.5	THF	r.t.	6 days	**5** (36)	26	25
6	4.4	0.5	DCM	r.t.	27 h	**5** (94)	41	2
7	4.4	0.5	Toluene	r.t.	72 h	**5** (86)	49	8
8	1.4	0.5	MeOH	0°C	10 days	**8** (48)	2[b]	-
9	4.4	0.5	MeOH	0°C	10 days	**5** (44)	2	2
10	1.4	0.5	Toluene	0°C	96 h	**8** (56)	13[b]	-
11	4.4	0.5	Toluene	0°C	96 h	**5** (64)	40	5

a) determined by HPLC on Reprosil 100 Chiral-NR, ACN: Buffer (35:65), Buffer: 30mM NH_4OAc, pH9 DEA, 1.0 mL/min, 24°C, b) determined on MCB (**6**) by HPLC on ChiralCelOD-H, *i*PrOH/n-hexane, 20:80, 0.5 mL/min, 15°C

An attempt was made with HPG (**33**) as a starting material (Scheme 37). As expected, we could observe a diastereoselectivity similar to the one obtained with IBPG (**25**). Despite a poor yield, 84 % *de* and 18 % *ee* were measured for MCF (**13**), confirming our reaction to be an excellent possibility to synthesise the *meso*-form with a very good *de*.



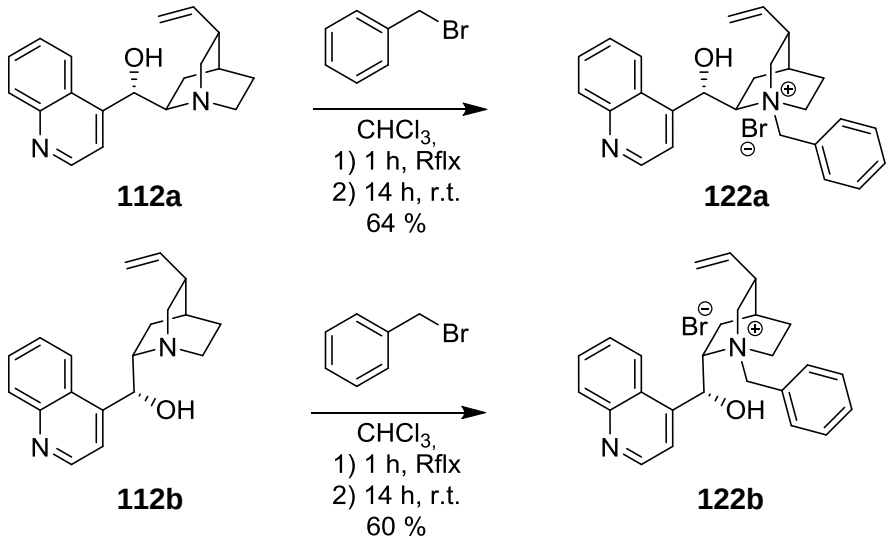
Scheme 37 Synthesis of *meso*-MCF (*meso*-**13a**) with 84 % *de.*

Phase transfer catalysis

Because they possess an easily quaternisable tertiary amine, *Cinchona* alkaloids have been extensively exploited in the development of phase transfer catalysts (PTC). They are known to catalyse various types of epoxidations of enones, using different oxidising agents such as hydrogen peroxide or hypochlorite.[81f]

The Weitz-Scheffer epoxidation of isoflavones by hydroperoxide in the presence of a simple *Cinchona* alkaloid-based PTC was reported by ADAM et al.[100] and provided an epoxide with *ee* values up to 98 %. DIEZ-IBARRA *et al*.[101] published a short study on the Michael addition of different enolisable ketones on α,β-unsaturated ketones under phase transfer conditions and reported *ee* up to 70 %. Likewise COLONNA *et al*.[102] reported Michael additions of thioalkanes or nitroalkanes on enones with PTC and KF as a co-catalyst but with restricted efficiency. In their work on asymmetric alkylation, DOLLING *et al.* could observe an excellent enantioselectivity (92 % *ee*) on the methylation of 2-phenyl-1-indanone catalysed by a *Cinchona* based-PTC and NaOH in toluene.

Based on this reports, we applied the principle of phase transfer catalysis to our Michael reaction in different conditions. Two PTCs were synthesised: N-benzylcinchoninium bromide (BnCNBr) (**122a**) derived from cinchonine (**112a**) and N-benzylcinchonidinium bromide (BnCDBr) (**122b**) derived from cinchonidine (**112b**). In both cases, the *Cinchona* alkaloid and benzyl bromide were dissolved in chloroform and stirred overnight at room temperature after a short period at reflux (Scheme 38).[103]



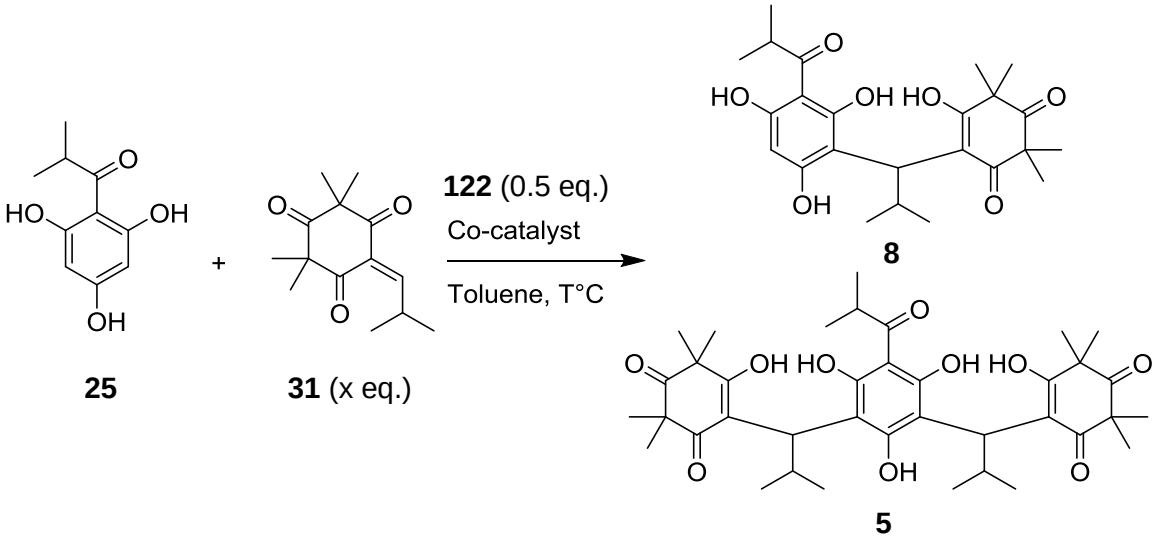
Scheme 38 Synthesis of the phase transfer catalysts BnCNBr (**122a**) and BnCDBr (**122b**)

Our Michael addition was first performed with only 1.4 eq. of the Michael acceptor **31** to synthesise the semimyrtucommulone intermediate **8**. As a reference the reaction was run with the catalyst **122a** at 0°C without any added base in a homogeneous phase (i.e. without phase transfer) and yielded in less than 2 hours 89 % of product (Tab. 16, entry 1). This proved that the PTC is an excellent catalyst for the reaction. As a comparison, the same reaction in toluene with CD (**112b**) as a catalyst yielded 56 % of **8** after 96 h (Tab. 15, entry 10).

Following the procedures of ADAM *et al.*[100] (1 M KOH) and COLONNA *et al.* (KF), we then used alkaline co-catalysts in a water/toluene mixture but despite their obvious efficiency for catalysing the Michael reaction, they did not induce any asymmetry (Tab. 16, entry 2-3).

Next, we repeated the reactions with more equivalents of the isobutylidene syncarpic acid (**31**) to obtain MCA (**5**) as a product (Tab. 16, entry 4-5). In that case the reaction times were in accordance with the one observed with CD (**112b**) as a catalyst. The reaction without any base provided only low *ee* and *de.* Interestingly, when enhanced with 1 M KOH, the yield, reaction time, and stereoselectivities were improved, the last remaining though pretty low compared to the reaction with the natural *Cinchona* alkaloids (Tab. 15, entry 10).

Tab. 16 Synthesis of MCA (**5**) and NSMC (**8**) with Cinchona-based PTCs (**122**).



25 **31** (x eq.)

Entry	Catalyst (0.5 eq.)	Co-catalyst (eq.)	x	T°C	Time	Product (Yield)	*ee*	*de*
1	**122a**	-	1.4	0°C	1.75 h	**8** (89)	1[a]	-
2	**122a**	1 M KOH (2 eq.)	1.4	0°C	1.75 h	**8** (84)	0[a]	-
3	**122a**	KF (1.1 eq.)	1.4	0°C	1 h	**8** (86)	1[a]	-
4	**122b**	-	4.8	r.t.	120 h	**5** (58)	18[b]	13[b]
5	**122b**	1 M KOH (2 eq.)	4.8	r.t.	67 h	**5** (93)	28[b]	11[b]

a) determined by HPLC on Reprosil 100 Chiral-NR, ACN: Buffer (35:65), Buffer: 30mM NH_4OAc, pH9 DEA, 1.0 mL/min, 24°C,
b) determined on the cyclised product by HPLC on ChiralCelOD-H, *i*PrOH/n-hexane, 20:80, 0.5 mL/min, 15°C

2.4.3. Conclusion on the organocatalysis

Changing the conditions of the previously published synthesis of myrtucommulones,[35a] we could develop three new methods to obtain these products. Method A and B consist of a three component one-pot reactions catalysed by proline where a Knoevenagel reaction and two successive Michael additions take place. This is to our knowledge the first report of such tandem reaction with syncarpic acid. We could prove that the duality of proline which can act as a nucleophile but also as a base was essential for this synthesis. Moreover we could use this one-pot reaction condition to synthesise some dimedone derivatives (**42** and **43**) which have shown interesting cytotoxic activity.[34]

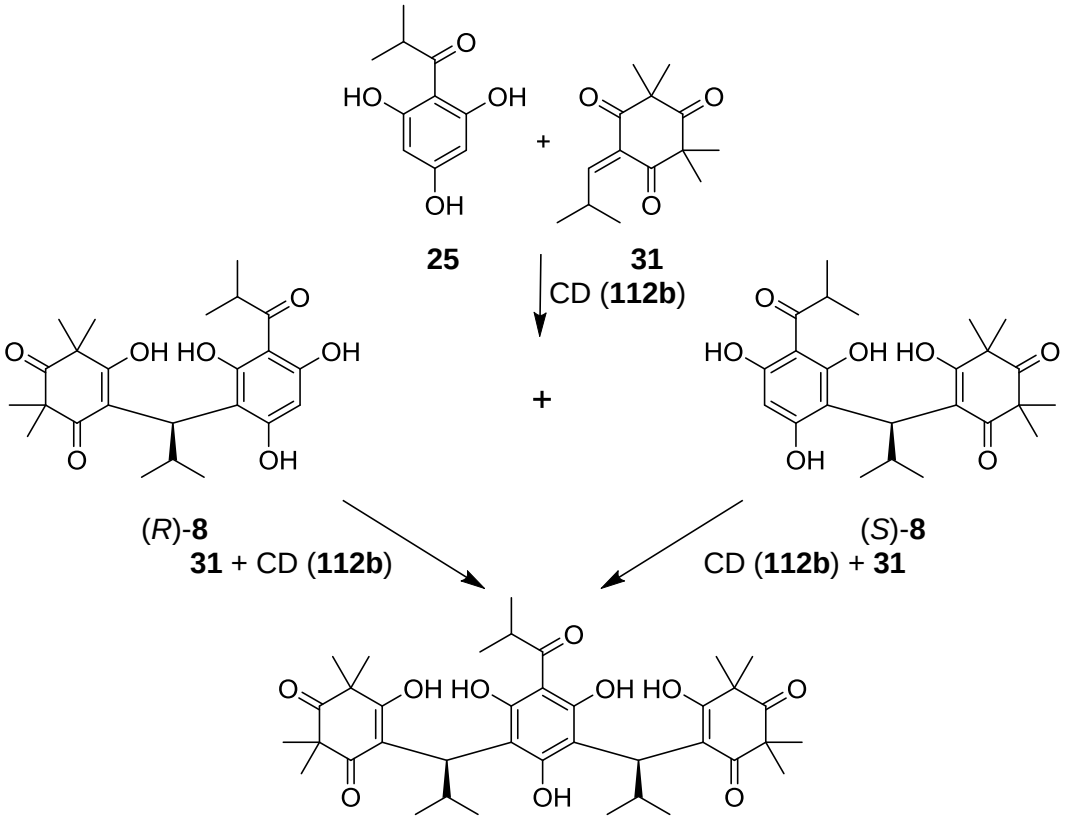
In addition, the fact that we could observe the formation of myrtucommulones by simply mixing the starting materials together with an amino acid as a catalyst (or without catalyst), gave us a hint on the biosynthesis of myrtucommulones. As a matter of fact, even if the formation of the isobutylidene derivative in the plant or the fungus (if it happens so) would need the intervention of proline (definitely present), the rest of the reaction can be catalysed by any weak base present around. This, along with the fact that we only isolated mixtures of stereoisomers, pleads in favour of a non specific pathway for the biosynthesis of MCs. However, it is interesting to note that instances in which an enzyme produces both enantiomers are known.[104]

Method C led to more knowledge about the chemical formation of MCs. We could synthesise norsemimyrtucommulone (**8**) and myrtucommulone A (**5**) in good to excellent yields and some indandione-derivatives (**39**, **41** and **104**), including a new potentially important active compound, in fair yields. Moreover, the One-Pot conditions as well as the Method C conditions offer a new cheap, secure and environmentally friendly alternative to synthesise the myrtucommulone derivatives, making them even more attractive for the pharmaceutical industry.

Thanks to *Cinchona* alkaloids, we could directly synthesise myrtucommulone A (**5**) with good diastereomeric excesses in methanol (up to 82 %) and interesting *ee* (up to 49 %) in dichloromethane or toluene. This was principally realised through the use of cinchonidine (**112b**) which afforded the best diastereomeric ratio (92:8) for MCF (**13**). The use of synthetic peptides or phase transfer catalysts did not provide satisfying results.

Unfortunately, the main compound obtained was always the *meso*-form **5a** of MCA and despite several variations of the catalyst (e.g. cupreines, PTC), we could not synthesise

preferentially **5b** which is the mixture of *R*,*R* and *S*,*S* enantiomers. The experimentation showed as well that in methanol, the reaction is weakly enantioselective for MCA (**5**) and not at all for NSMC (**8**). For this reason, one can conclude that the stereodifferentiation takes place on an almost racemic mixture of NSMC (**8**) and that cinchonidine (**112b**) favours the synthesis of the second stereocenter with the opposite absolute configuration of the one already present. In other words, both (*R*)-NSMC ((*R*)-**8**) and (*S*)-NSMC ((*S*)-**8**) are formed in the reaction mixture in more or less equal amounts. From (*R*)-**8**, the cinchonidine (**112b**) catalyses preferentially the formation of (*R*,*S*)-MCA ((*R*,*S*)-**5a**) and from (*S*)-**8**, CD (**112b**) favours the formation of (*S*,*R*)-MCA ((*S*,*R*)-**5a**), both being one and the same molecule because of the symmetry of the compound, namely *meso*-**5a** (Scheme 39).



Scheme 39 Diastereoselectivity in the formation of MCA (**5**) catalysed by CD (**112b**).

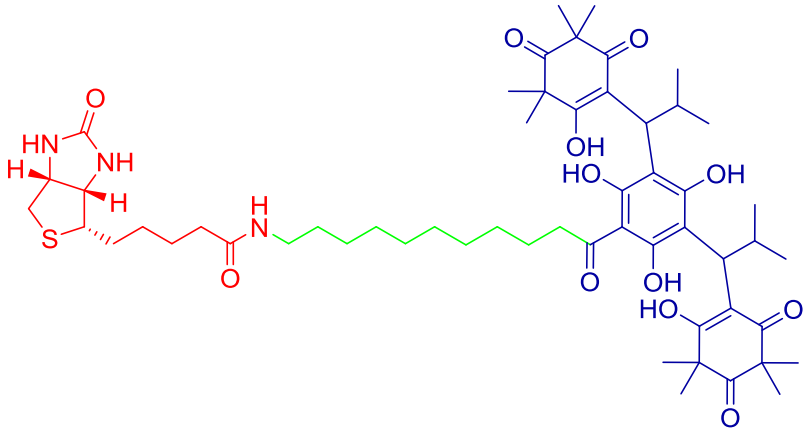
As a matter of fact, if we found a method to form the racemate preferentially, we could think about combining our metal-catalysed reaction with good *ee* with an organocatalytic method to reach almost enantiopure compounds (see § 3 Conclusion and Perspectives).

2.5. Synthesis of a biotin-linked myrtucommulone

As described in the introduction (§ 1.1.3.4), in order to perform affinity based chromatography (also known as target fishing) experiments, we busied ourselves with the formation of a biotin-linked myrtucommulone. Two strategies were considered principally: the first concerned the introduction of an alkyl linker and the other the use of a diamine spacer to bind biotin and myrtucommulone through peptide bonds.

2.5.1. Attempts with an alkyl linker

To form a biotin-bound myrtucommulone we first aimed for a synthesis where the linker is as simple as possible and where we could use as little as possible of the expensive biotin (**23**) As depicted in Fig. 40 the first goal was to introduce a decyl chain (green) between the myrtucommulone moiety (in this section (§ 2.5) the part in blue on Fig. 40 will be referred as myrtucommulone) and an amide bound biotin (red) (10-biotinamido-1-myrtucommulone-decane (**123**)).

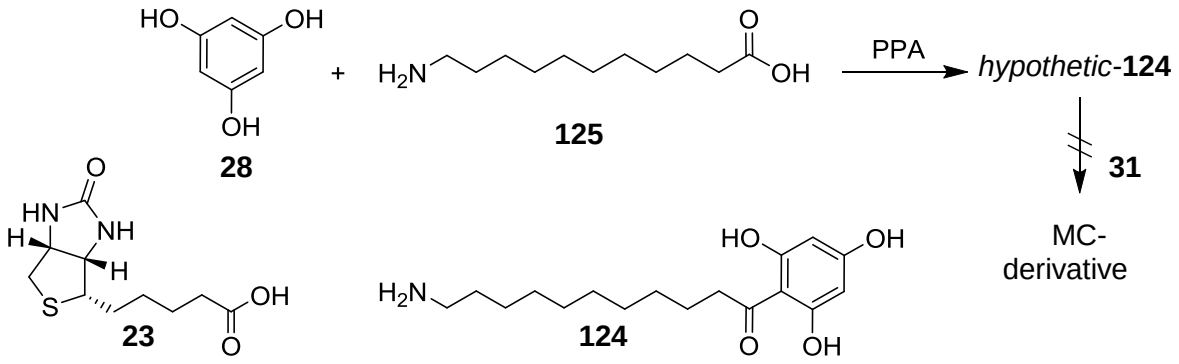


123

Fig. 40 Structure of the aimed 10-biotinamido-1-myrtucommulone-decane (**123**)

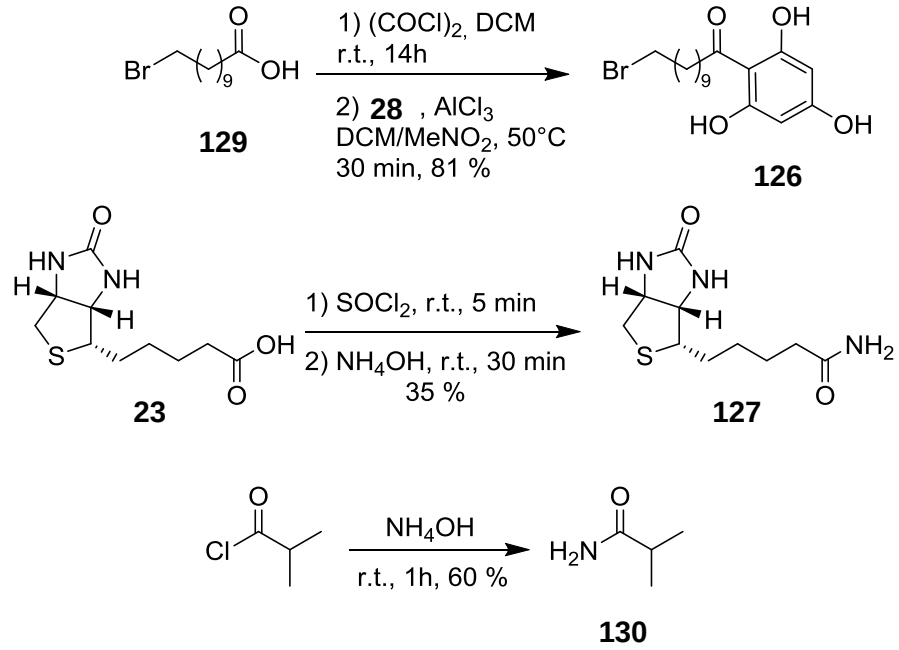
Our first attempt consisted in synthesising 11-amino-undecanoyl-phloroglucinol (AUPG) (**124**) to then directly form an amide bond with biotin (**23**). It based on a German patent from 1963 which used a warm solution of polyphosphoric acid (PPA), obtained by stirring phosphoric acid (85% wt. in water) together with phosphorus pentoxide at 200°C for 2h,[105] to bind 11-aminoundecanoic acid (AUA) (**125**) and phenol.[106] AUA (**125**) and phloroglucinol (**28**) were then mixed in PPA to form the desired amino-undecanoyl-phloroglucinol (**124**) (Scheme 40). Unfortunately, our efforts to form AUPG (**124**) led to a hardly manageable product (*hypothetic*-**124**), insoluble in most solvents making it unidentifiable with the common

methods. Since no formation of myrtucommulone-derivative (MC-derivative) was observed in presence of the Michael acceptor **31** under different conditions, we did not further investigate this unidentified product and changed our synthetic strategy.



Scheme 40 Attempts using the PPA method and structure of expected AUPG (**124**) for an amide bonding with biotin (**23**).

Our next attempt was directed to 11-bromo-undecanoyl-phloroglucinol (BrUP) (**126**) that would then be bound to biotinamide (BtA) (**127**) through a nucleophilic substitution of the bromine to form 11-biotinamido-undecanoyl-phloroglucinol (**128**). To begin with, 11-bromoundecanoic acid (**129**) was transformed into its acyl chloride with oxalyl chloride and added to PG (**28**) in presence of aluminium trichloride for an aromatic electrophilic substitution on the aromatic ring to obtain BrUP (**126**) (Scheme 41).[107]

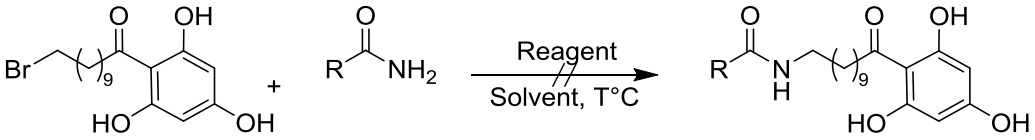


Scheme 41 Preparation of the starting material for the alkylation attempts of biotinamide (**127**).

Next, biotin was dissolved in thionyl chloride and an ammonium chloride solution was added after removing the excess of thionyl chloride to afford biotinamide (**127**) with poor yield due to the work up procedure.[108] Not to waste the expensive biotinamide, isobutyramide (**130**) was also synthesised from isobutyryl chloride with a similar procedure but a better yield (Scheme 41).[109]

Then, following the procedure of LELE *et al.*[110] for the preparation of acrylamides, we mixed BtA (**127**) and BrUP (**126**) in presence of aluminium trichloride in acetone but only one of the isolated products showed some of the characteristic biotin peaks in the NMR-spectrum but in improbable proportion to the rest of the hydrogen atoms (Tab. 17, entry 1). We repeated the reaction with isobutyramide (**130**) and different amounts of aluminium trichloride but only got similar products (Tab. 17, entry 2). Raising the reaction temperature to 80°C and changing the solvent to DMF did not lead to any product formation (Tab. 17, entry 3).[111] Finally with added KOH to a mixture of the starting materials in DME but even though we could see the consumption of the starting material, no main product could be identified (Tab. 17, entry 4).[112]

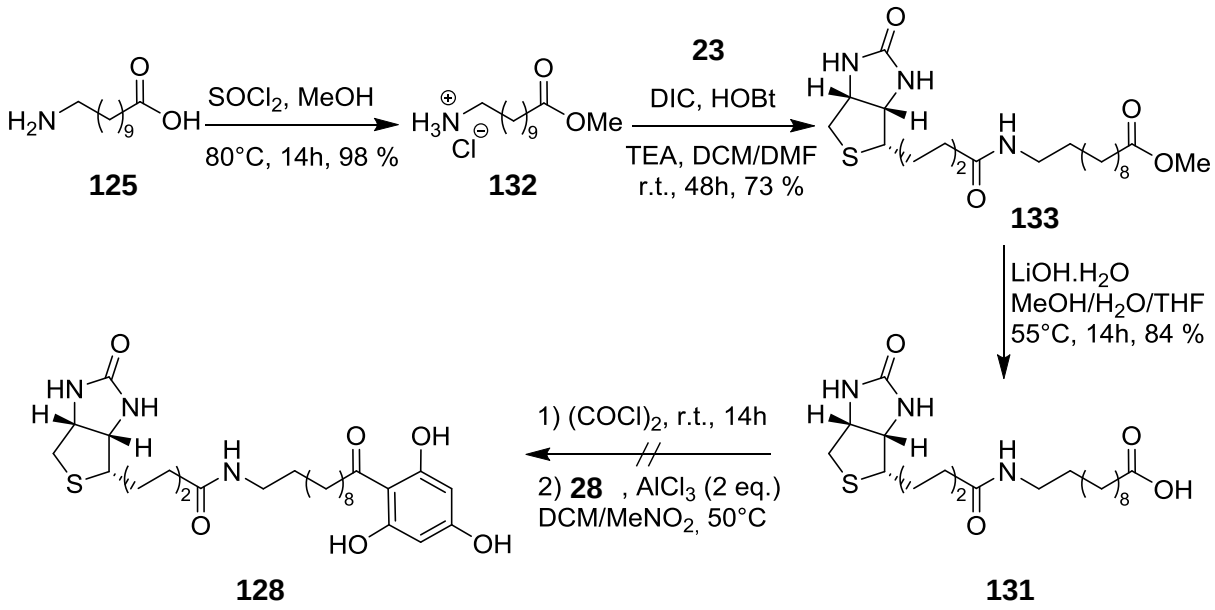
Tab. 17 Attempts to bind an amide to 11-bromo-undecanoyl-phloroglucinol (**126**).



126 **127**: R = "Biotin" **130**: R = *i*Pr **128**: R = "Biotin"

Entry	$RCONH_2$	Reagent	Solvent	T°C
1	**127**	$AlCl_3$ (4 eq.)	$Acetone_{abs}$	50°C
2	**130**	$AlCl_3$ (2 eq.)	$Acetone_{abs}$	50°C
3	**130**	-	DMF	80°C
4	**130**	KOH (2.5 eq.)	DME	75°C

Since we did not isolate the desired product we changed our plans and decided to first add biotin (**23**) on the alkyl moiety and then bind it to the phloroglucinol unit. For this new route, we synthesised in three steps 11-biotinamido-undecanoic acid (**131**). We first had to esterify AUA (**125**) by using thionyl chloride in methanol to synthesise 11-amino-undecanoic acid methyl ester (AUMe) (**132**),[113] then bind biotin (**23**) through an amide bond to the amino-ester to form **133** using diisopropylcarbodiimide (DIC) and hydroxybenzotriazole (HOBT)[114] and finally deprotect the acid function in basic aqueous medium (Scheme 42).[113] Unfortunately, our efforts to synthesise the desired biotin-phloroglucinol derivative **128** through a Friedel-Crafts type reaction remained unsuccessful.

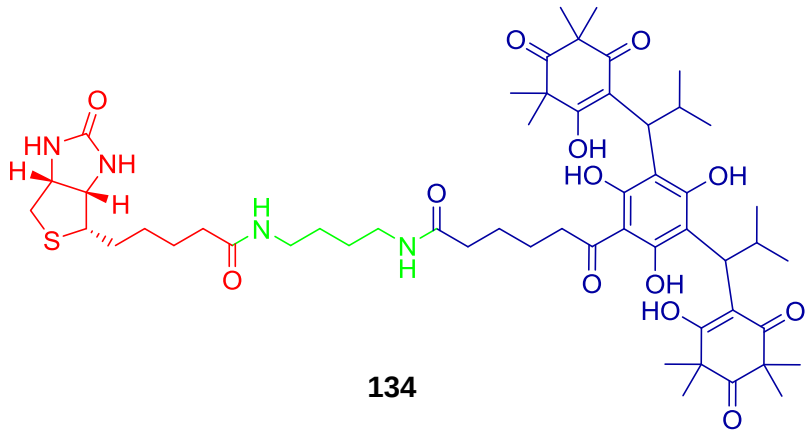


Scheme 42 Formation of 11-biotinamido-undecanoic acid (**131**) and attempt to synthesise **128**.

Several starting materials were synthesised but attempts to bind biotin (**23**) to the phloroglucinol moiety led to undefined products. Attempts to bind biotin (**23**) to an alkyl chain over a peptide bond worked pretty well, however no derivative like **124** could be obtained. Therefore we decided to change our target molecule and focused on the reliability of the peptide bond formation.

2.5.2. Introduction of a polyamide linker

We knew from the prior work of H. MÜLLER that it is possible to bind "sebacoyl-myrtucommulone" (**24**) through a peptide bond to agarose-beads with free amines. Besides, it is not unusual to find biotin bound to different diamino-alkanes such as 1,4-diaminobutane or 1,6-diaminohexane in the literature.[115] In consequence, we aimed for a new compound called N-(4-(biotinamido)butyl)-5-myrtucommulone-pentanamide (biotin-linked-MC) (**134**). In this molecule, the myrtucommulone-oxopentane moiety (blue) is bound to a small spacer (green) through an amide bond on the one hand, and biotin (red) is bound likewise to the other side of the spacer on the other hand (Fig. 41).

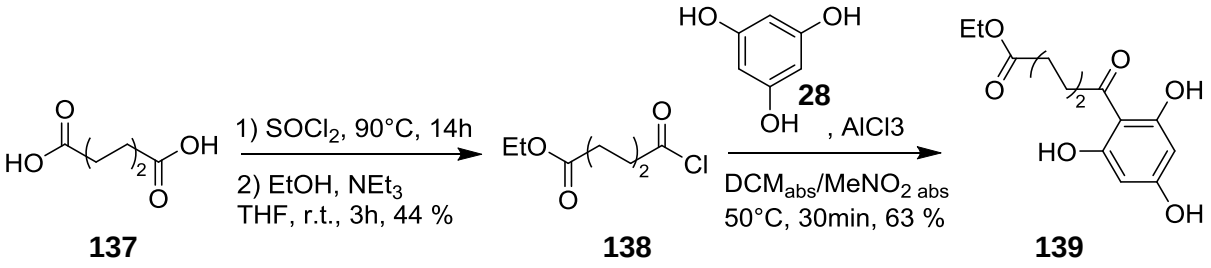


134

Fig. 41 Structure of biotin-linked-MC (**134**)

We focused on the myrtucommulone moiety first und synthesised over 4 steps 5-myrtucommulone-pentanoic acid (MCPA) (**135**) that was derivatised for better analysis to its pentacyclic derivative **136** (PMCPA).

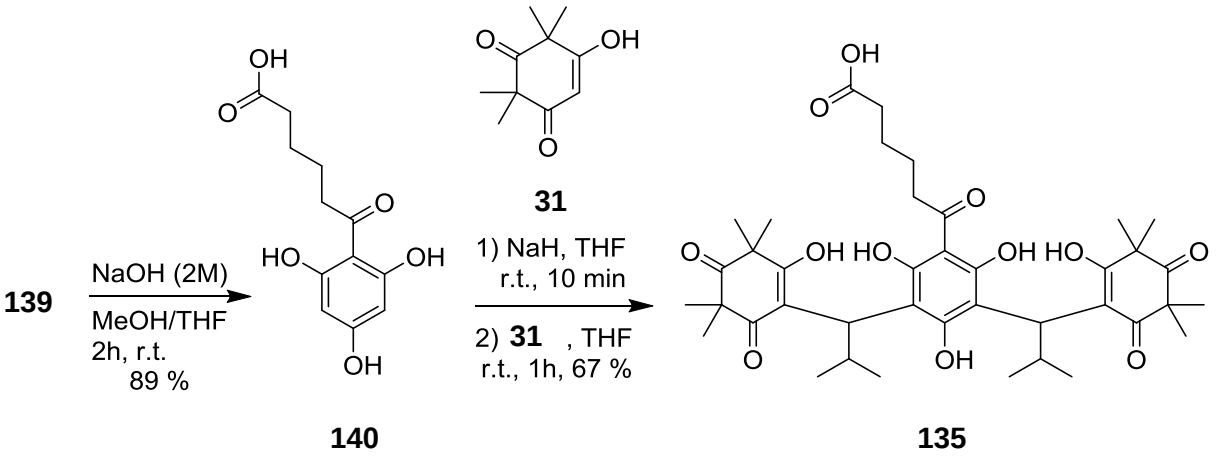
Starting from adipic acid (**137**) that we transformed to its diacyl chloride,[116] the monoester of adipoyl chloride was formed (**138**), through slow addition of an ethanol/triethylamine mixture.[117] Despite special attention, a mixture of the monoester and the diester was obtained, which explains the low yield. Phloroglucinol (**28**) was then acylated under Friedel-Crafts conditions to form 6-oxo-6-phloroglucinol-hexanoic acid ethyl ester (**139**) (Scheme 43).[107b]



137 **138** **139**

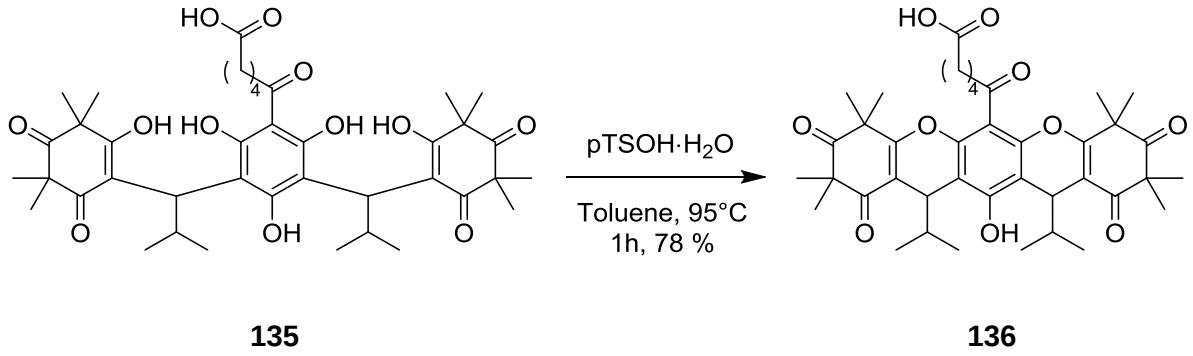
Scheme 43 Synthesis of 6-phloroglucinol-hexanoic acid ethyl ester (**139**)

The ester was subsequently saponified in presence of sodium hydroxide to **140**.[118] After that, two equivalents of isobutylidene syncarpic acid (**31**) were added to **140** which had been deprotonated with sodium hydride to form MCPA (**135**) with a yield of 67 % (Scheme 44).[35a]



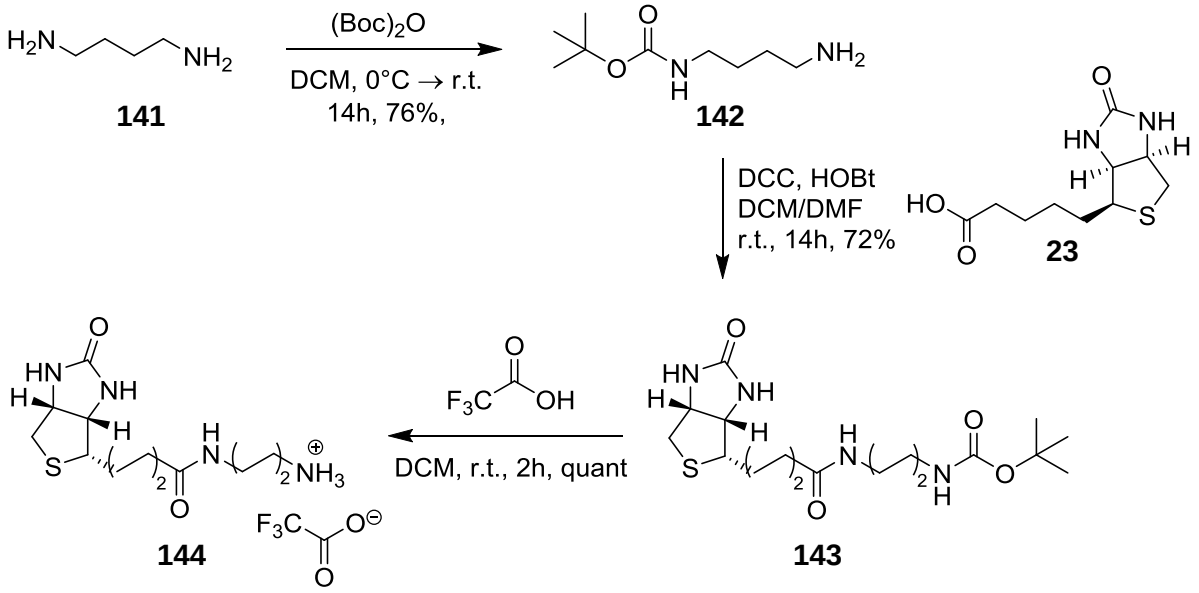
Scheme 44 Synthesis of MCPA (**135**)

Like other MCs, the NMR-analysis was only made possible on the cyclic derivative. As usually done for myrtucommulone derivatives, the product **135** was cyclised using pTsOH in hot toluene to yield its pentacyclic derivative **136** (Scheme 45).



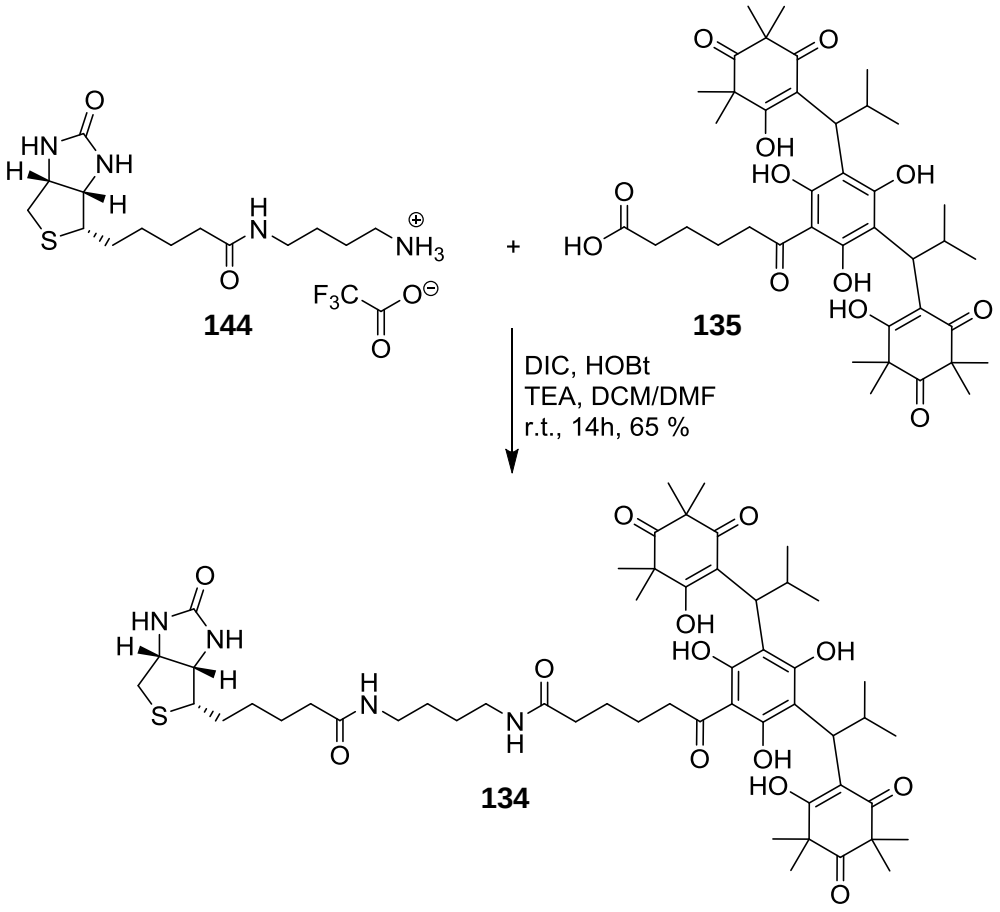
Scheme 45 Cyclisation of MCPA (**135**) to PMCPA (**136**).

We then concentrated on the other side of the product, namely the biotin-bound-spacer (Scheme 46). As depicted above in green, 1,4-diaminobutane (DAB) (**141**), one of the molecules responsible for the bad smell of decayed flesh, was chosen as a spacer. It was first protected on one side with Boc anhydride to form the carbamate (Boc-DAB) (**142**).[115a] Using the conditions described by POOLE *et al.*[115a] biotin (**23**) was then bound to the amino-carbamate **142** in presence of HOBT and DCC to synthesise *tert*-butyl-4-biotinamido-butylcarbamate (**143**) with 72 % yield. The amine was then deprotected to afford 4-biotinamido-butylamine (BtABA) in form of its trifluoroacetate salt (**144**).[115d]



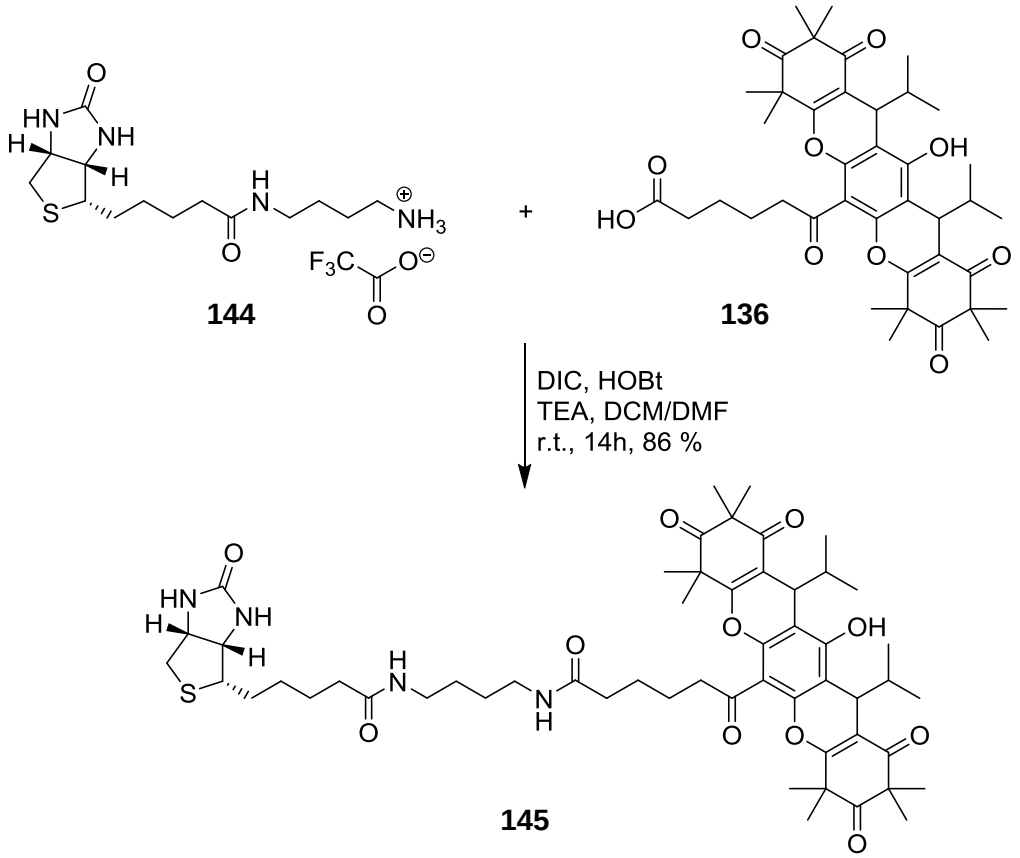
Scheme 46 Synthesis of the Biotin-spacer moiety (**144**).

Once both parts were ready, BtABA (**144**) and MCPA (**135**) were put together following the previously used procedure from SOURAL *et al.*[114] for peptide bond formation. After 14 h stirring and appropriate purifying, biotin-linked-MC (**134**) could be isolated with 47 % total yield based on biotin (Scheme 47).



Scheme 47 Synthesis of biotin-linked-MC (**134**)

Because of the myrtucommulone moiety, whose analysis is complicated, but also because of the general the size of the molecule, NMR-analysis was challenging for this compound. However, high resolution mass spectrometry confirmed the mass of each molecule. As a comparison, the cyclised derivative **136** was used in presence of BtABA (**144**) in the same conditions as **135** to afford biotin-linked-PMC with a very good yield (**145**) (Scheme 48).



Scheme 48 Synthesis of biotin-linked-PMC (**145**).

After some unsuccessful attempts to bind biotin and myrtucommulone through a simple alkyl ligand by different means, the longer but more efficient approach where biotin is bound over a diaminobutyl spacer afforded the expected product. The compound was then sent to the research group of Prof. WERZ for the so called affinity based chromatography experiments. Unfortunately, until the compilation of this work the results of these experiments were not available.

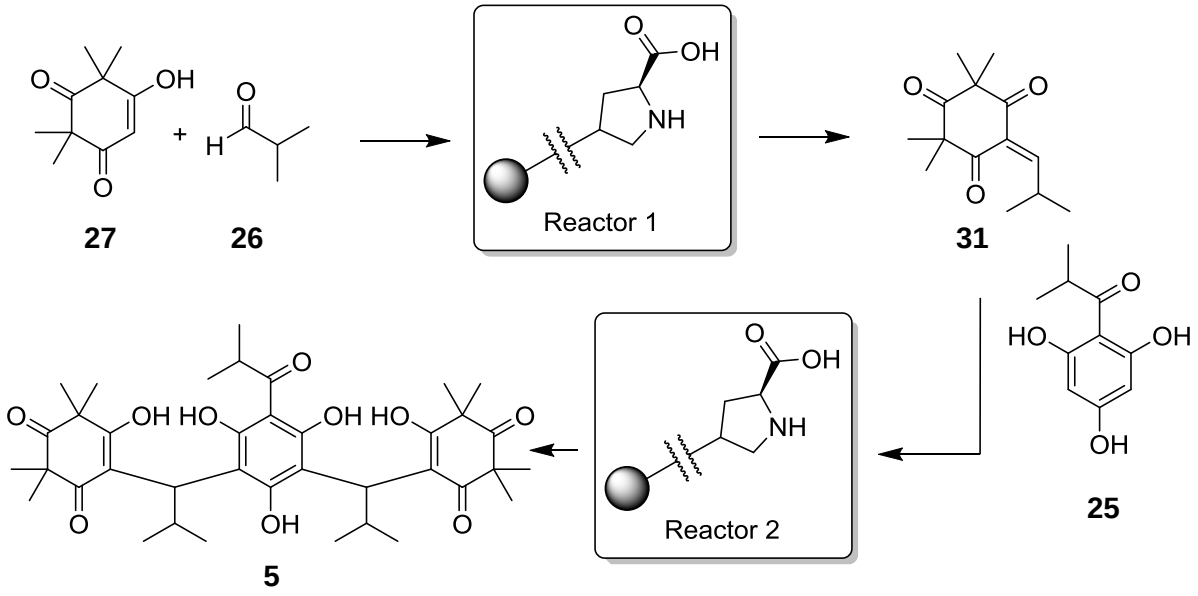
3. Conclusion and perspectives

The objectives of this work were to further investigate the different methods for the synthesis of myrtucommulone-derivatives, search for an asymmetric synthesis of such compounds (together with the determination of the absolute configuration). One part is dedicated to the synthesis of a new biotin-linked myrtucommulone for pharmacological experiments.

The development of new mild reaction conditions using amino acids as catalysts for the synthesis of MC-derivatives in ethanol brought additional knowledge about this class of compounds. We could observe the slow formation of NSMC (**8**) and MCA (**5**) without the need of any catalyst, which gave us a hint concerning the biosynthesis of this type of molecules. It is indeed thinkable that isobutyryl phloroglucinol (**25**), syncarpic acid (**27**) and isobutyraldehyde (**26**) are synthesised in the plant and react together thanks to the intervention of free amino acids, especially proline, without the interference of an enzyme. At this time, further investigations are in progress to know whether myrtle itself or the newly found endophytic fungus[19] (or both together) are responsible for the synthesis of MCs.

Furthermore, the development of One-Pot reaction conditions, which are so far the first known example of a tandem Knoevenagel-Michael reaction using syncarpic acid as a 1,3-diketone, allowed the direct formation of some MC-derivatives avoiding tedious isolation steps.

The use of environmentally-friendly solvents such as ethanol and non-hazardous catalysts such as amino acids or cheap natural products is a real advantage for the possible industrial synthesis of myrtucommulones. Moreover, the possibility to use continuous flow processes,[119] rather unusual in the laboratory, could largely improve the yields. As an example, if the Michael acceptor **31** is continuously synthesised in a reactor containing the immobilised catalyst (e.g. proline) and dropped to another reactor with the Michael donor **25**, the consumption of the phloroglucinol **25** by the aldehyde **26** is avoided. Besides, one could imagine that IBSA (**31**) can be added at such a rate that it is consumed without having much time to isomerise (Scheme 49).

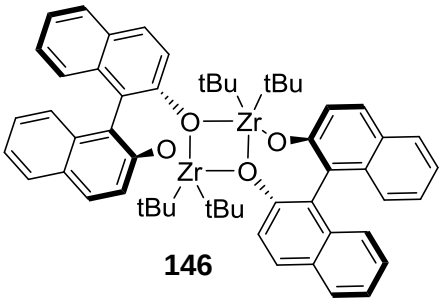


Scheme 49 Possible industrial conception of MCA (**5**).

Two new important derivatives were synthesised: the indandione derivative **41** (§ 2.4.2.2), from which great therapeutic potency is expected due to compounds with similar structure, and the biotin-linked myrtucommulone **134** (§ 2.5.2) for the research for new cellular targets for MCs. Unfortunately, the results concerning the usefulness of these compounds are not known yet.

Finally, the main focus of this work was the investigation of the stereoselective synthesis of MCs and especially NSMC (**8**) and MCA (**5**). The first achievement was to determine the absolute configuration of MCB (**6**) and PMCA (**7**) which, after the first success of the asymmetric catalysis, also gave access to the absolute configuration of NSMC (**8**) and MCA (**5**) respectively.

After arduous work, NSCM (**8**) and likewise MCB (**6**) were synthesised with 72 % *ee* using the heterobimetallic complex ALB (**66e**). Numerous variations of the catalyst, including variations of the central metal, the counterion, the size and shape of ligands led to the conclusion that 3 eq. of ALB (in regard to the Michael donor) in a DCM/THF mixture at 0°C were the optimal conditions for this reaction. However, other variations, such as the zinc-BINOL complex **146** (Scheme 50)[120] used for the Michael addition of unmodified ketones on enones or the zirconium-BINOL complexes (**147**),[54,121] very efficient for the Friedel-Crafts reaction between indoles and α,β-unsaturated ketones can still be considered (Scheme 50). Likewise salen ligands like **148** or **149** made of BINOL and/or aluminium, have shown a great asymmetric influence on the Michael reaction (Scheme 50).[122]



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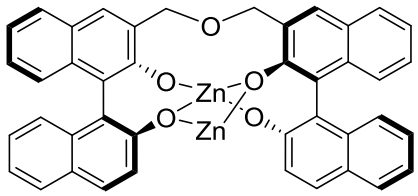

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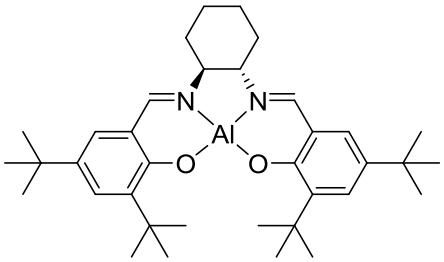

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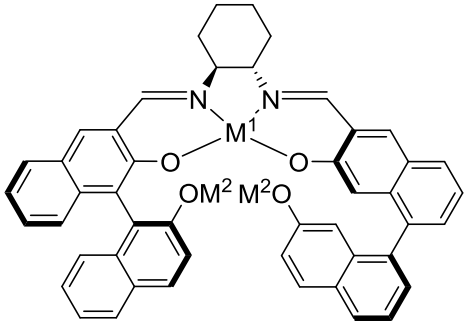


149

Scheme 50 Structures of the possible catalysts **146**, **147**, **148** and **149** for the enantioselective Michael reaction. (M^1 = transition metal M^2 = alkali or earth alkali metal).

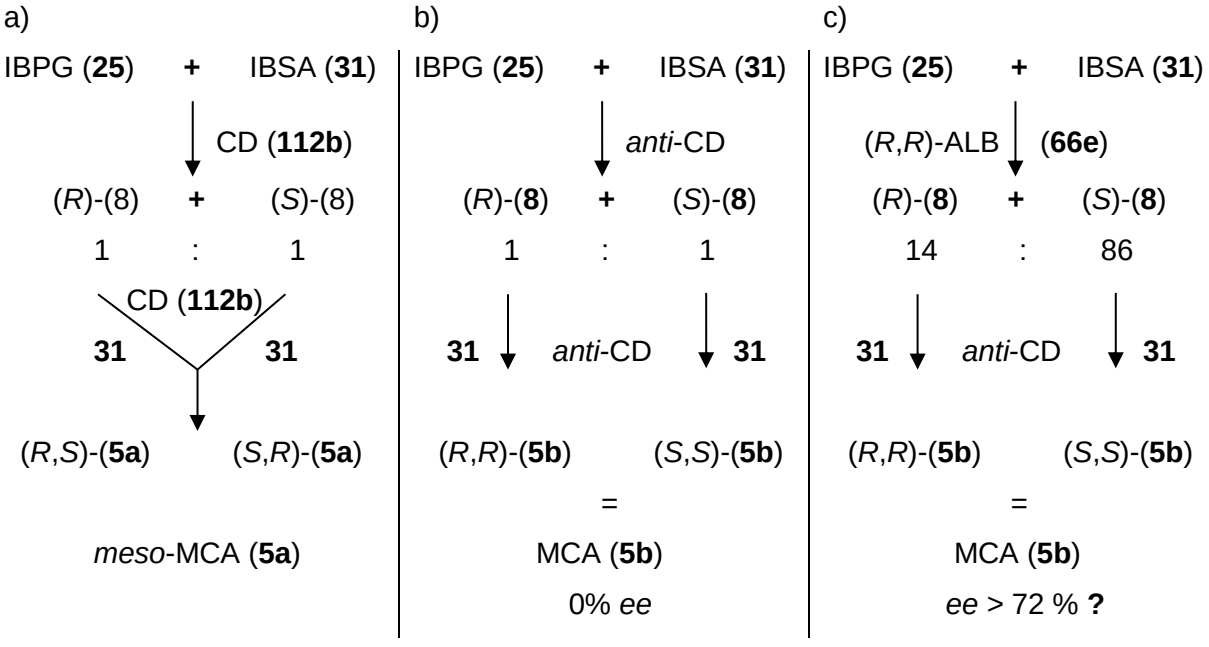
Generally speaking, this enantioselective Michael addition offers an interesting possibility to couple a sterically hindered acceptor with a donor with more than one reaction site. However the mechanistic investigations showed the limits of the reaction since the keto-group of the acyl-phloroglucinol derivative seemed to directly participate in the asymmetric catalysis. Likewise the syncarpic acid moiety showed to be essential for good enantioselectivity.

Nevertheless this is the only example of enantioselective synthesis of a myrtucommulone-derivative to this day.[57] For this reason, the same conditions were used to form MCA (**5**) and likewise PMCA (**7**) with 81 % *ee*. Unfortunately, we do not know yet if the enantiomerically enriched MCA (**5**) shows a better efficacy than racemic MCA (**5**) from the pharmacological point of view.

The metal-catalysis was only enantioselective, and all the attempts afforded only insignificant diastereomeric excess. For this reason we concentrated also on organocatalysis. After some unsuccessful experiments with synthetic peptides and various natural products, the *Cinchona* alkaloids happened to be remarkably efficient to synthesise MCA (**5**) enantio- and diastereoselectively. As a matter of fact MCA (**5**) and MCF (**13**) could be obtained with *d.r.* of 91:9 (**5a**: **5b**) and 92:8 (**13a**:**13b**) respectively by adding cinchonidine (**112b**) to the mixture of the starting materials in methanol. Additionally, the use of cinchonidine (**112b**) in toluene led to an *ee* of 49 % in the direct synthesis of MCA (**5**). Unfortunately only *meso*-**5a** was made

accessible under these conditions, and the diastereomeric ratio could not be inverted towards a major formation of **5b**, independently of the variations of the catalysts (cupreines, PTC).

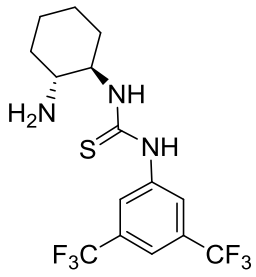
Hence, two different reaction conditions were developed to synthesise MCA (**5**): on the one hand enantioselectively and on the other hand diastereoselectively. Regrettably, it was not possible to combine both to form only one enantiomer of MCA. Indeed the organocatalysed reaction only led to *meso*-**5** as summarised in Scheme 51a and never **5b**. Otherwise, it would have been conceivable that the use of the enantiomerically enriched NSMC (**8**), made through metal-catalysis, with a diastereoselective organocatalyst would lead to the formation of one enantiomer of myrtucommulone preferentially. If we had an organocatalyst which has the reverse diastereomeric effect than cinchonidine (**112b**), that we would call *anti*-cinchonidine (*anti*-CD), we would be able to produce the racemic mixture preferentially (Scheme 51b). Now if we applied it on (*S*)-NSMC ((S)-**8**) with 72 % *ee* (ratio 86:14), we can imagine in the case of a matched stereodifferentiation that we would obtain (*S*,*S*)-**5b** with a good *de* and an *ee* superior to 72 % (Scheme 51c).



Scheme 51 Possible selective synthesis of the **5b** a) with CD (**112b**) b) and c) with a hypothetic *anti*-CD.

A good way to start looking for "*anti*-CD" would be the use of thiourea derivatives widely used in the literature for Michael reactions especially the ones including a nitro compound,[37,81h,123] but not necessarily.[124] Various papers report *Cinchona* alkaloids-derived thioureas as organocatalysts of choice due to the hydrogen bonding ability of thiourea combined with the

basicity and rigidity of the *Cinchona* alkaloids structure (see compounds **150** and **151** Fig. 42).[37,123,125]



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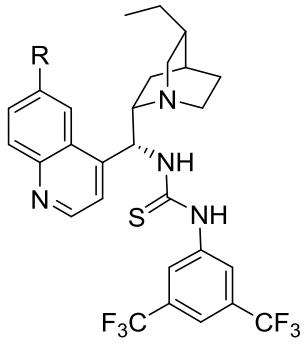


151

Fig. 42 Structures of the possible thiourea catalysts **150** and **151** for the Michael addition.

A final suggestion would be another combination of both methods used in this work. This would imply the synthesis of an aluminium catalyst with *Cinchona* alkaloids ligand such as the one used in the work of FENG *et al.*[126] for the Michael addition of malonitrile to chalcone. Similarly the use a mixture of both BINOL and *Cinchona* alkaloid as bifunctional metal/organo-catalyst has been already described in the literature.[127]

To conclude with, this work treated most of the set objectives with the success and troubles that go along with such projects. Some room remains for further investigations on the theme of myrtucommulones and their derivatives, for instance by improving the asymmetric synthesis or refining the direct formation of MC-derivatives under mild conditions.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a AV II BRUKER FT-NMR spectrometer (400 MHz and 101 MHz respectively) The spectra were processed with the MestRec 4.9.9.6 software of the MESTRELAB RESEARCH S.L. company. Chemical shifts (δ) are reported in ppm, relative to the following internal standards: chloroform-d ($CDCl_3$, ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.00 ppm), acetone-d6 ($CO(CD_3)_2$,^{1}H: δ = 2.05 ppm, ^{13}C: δ = 30.83 ppm), methanol-d4 (CD_3OD, ^{1}H: δ = 3.31 ppm, ^{13}C: δ = 49.05 ppm), and dimethylsulfoxide-d6 (DMSO-D_6, ^{1}H: δ = 2.50 ppm, ^{13}C : 39.43 ppm). The coupling constants are given in Hertz (Hz) and the multiplicities of the signals as follow: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; sept, septet; m, multiplet.

High Pressure Liquid Chromatography (HPLC) analysis was performed on :

- A SYKAM equipment consisting of a S7121 Reagent Organizer, a S1122 Solvent Delivery System, a S8111 Low Press Gradient Mixer, a S3210 UV/Vis Detector, and a Rheodyne 7725i Injector Valve. The processing of the data was realised with the Chromstar 6.3 Software from SCPA GMBH.
- A BECKMANN System Gold® HPLC equipment consisting of a 127 NM Solvent Module, a 166 NM Detector and a Rheodyne 7125 Injector Valve. The data was treated with the Clarity Lite 2.6.4.402 Software from DATA APEX.

For reversed phase (RP) non chiral chromatography, the columns NUCLEODUR® 100-5 C_{18} ec (250 x 4 mm, MACHEREY-NAGEL) and Chromolith® Performance 100-4.6 (MERCK) were used. The Reprosil 100 Chiral-NR (250 x 4.6 mm, DR. MAISCH GMBH) column was used for chiral chromatography on RP and normal phase (NP). For chiral chromatography on normal phase, the CHIRALCEL® OD-H (250 x 4.6 mm, DAICEL CHEMICAL INDUSTRIES) column was used as well. UV detection was performed at 210 nm, 254 nm and 292 nm.

High Resolution Mass Spectra (HRMS) were recorded by TOBIAS DIER on a SolariX FTMS 7.0 T (BRUKER) equipment and analysed with Data Analysis 4.2 (BRUKER) in cooperation with the bio analytics group of Prof. VOLMER, Universität des Saarlandes.

Liquid Chromatography-Low Resolution Mass Spectrometry was performed on a LC-MS equipment from SHIMADZU composed of an Auto-Injector SIL-6B coupled to a System Controller SCL-6B, a Liquid Chromatography system using a LC-AT10 vp pump coupled to a SCL-10 A vp System Controller and a Diode Array Detector SPD M10A vp. The masses

were recorded on the mass spectrometer LC/MS-2020 and the spectra were interpreted with LabSolutions 5.65 from SHIMADZU. EC 250x4 NUCLEODUR® 100-5 C_{18} ec (MACHEREY-NAGEL). and Chromolith® Performance 100-4.6 (MERCK) were used as chromatographic columns.

Thin Layer Chromatography (TLC) was performed on silicagel Si 60 F_{254} glass plates (MERCK). The solvents used are abbreviated as follow: acetone (A), petroleum ether (PE), ethyl acetate (EA), dichloromethane (DCM), methanol (MeOH) and the mixtures are given in volume ratios. The compounds were detected with UV-light or the following stains:

- Phosphomolybdic acid
- Eckert's Reagent (anisaldehyde, acetic acid, sulphuric acid, methanol, 0.5:10:5:85, v:v:v:v)
- Ehrlich's Reagent (p-dimethylaminobenzaldehyde, methanol, HCl, 1:25:75, m:v:v)
- Dragendorff's Reagent (solution (1): $Bi(NO_3)_3$ (0.11 g), tartaric acid (1.25 g), water (5 mL); solution (2): KI (2.0 g), water (5 mL); reagent : (1) (5 mL) + (2) (5 mL) + tartaric acid (20 g) + water (100 mL))

Flash Column Chromatography was carried out on Silicagel 60 (40-63 µm) from MERCK company. Solvents were distilled before use and are abbreviated as detailed above.

Crystallographic Data was obtained through single crystal X-Ray Diffraction on a CCD-Detector-X8 Apex II from BRUKER AXS. The data was calculated with a Micro Vax II-computer form the DIGITAL EQUIPMENT CORPORATION. The following software was used :

- Space group determination : XPREP
- Structure identification: SHELXS-97
- Structure refinement: SHELXL-97

The graphical projections were realised with the MOLECULAR GRAPHICS and DIAMOND 2.1 software.

Optical Rotations were measured on a 241 MC Polarimeter (PERKIN-ELMER) equipped with a sodium-vapour lamp (D-line, λ = 589.3 nm) in 0.1, 0.2 or 1.0 dm cells. Concentrations (*c*) are given in g/100 mL.

Melting points were measured with a capillary melting point apparatus BÜCHI 150 and are uncorrected.

Solvents and chemicals were purchased at the ZENTRALES CHEMIKALIENLAGER DER UNIVERSITÄT DES SAARLANDES (ZCHL), from SIGMA-ALDRICH, ACROS ORGANICS or ABCR GMBH and used without purification unless otherwise specified. Anhydrous solvents were prepared according to the general methods under nitrogen atmosphere. Tetrahydrofurane, diethyl ether and toluene were distilled over sodium with benzophenone as an indicator. Methanol was dried over magnesium, and dichloromethane over calcium hydride. Anhydrous dimethylformamide was purchased from SIGMA-ALDRICH and stored on molecular sieves.

4.2. General Procedures

4.2.1. Preparation of standard starting materials

The frequently used acyl phloroglucinols such as acetyl phloroglucinol (APG) (**29**), isobutyryl phloroglucinol (**25**), isovaleryl phloroglucinol (**32**) and hexanoyl phloroglucinol (HPG) (**33**) were synthesised routinely with the general procedure ***GP 1***. The obtained analytical data was in agreement with the literature.

GP 1: Preparation of acyl phloroglucinols[107b]

In a flame dried equipment, were suspended phloroglucinol (**28**) (1.0 eq.) and aluminium trichloride (2.0 eq.) in anhydrous dichloromethane (1mL/mmol PG (**28**)). Nitromethane (0.3 mL/mmol PG (**28**)) was added dropwise under nitrogen atmosphere to dissolve the aluminium trichloride and the mixture was heated to 50°C. The acyl chloride (1.0 eq.) was dissolved in anhydrous dichloromethane (0.4 mL/mmol acyl chloride) and added dropwise to the warm solution. The completion of the reaction was confirmed by TLC. The reaction mixture was poured on an ice/1M HCl mixture (1/1, v/v, ≈ 30 mL/mmol PG (**28**)) and evaporated for 1h under reduced pressure (50°C/15 mbar) to remove the solvents. The aqueous phase was then extracted with ethyl acetate (1 x 30 mL, 2 x 15 mL for 1 mmol PG (**28**)) and the organic layer was dried over magnesium sulfate. After filtration, the solvents were removed under vacuum and the product was purified by flash chromatography on silica gel to yield the desired acyl phloroglucinol. In the case of acetyl phloroglucinol (**29**), it could be easily purified by recrystallization from water.

GP 2: Preparation of syncarpic acid[107b]

In a flame-dried equipment, sodium hydride (11.9 g, 297 mmol, 5.0 eq.) was washed twice with anhydrous THF (2 x 50 mL). APG (**29**) (10.0 g, 59 mmol, 1.0 eq.), prepared according to the general procedure ***GP 1***, was dissolved in anhydrous THF (30 mL) and added dropwise to the mixture under nitrogen atmosphere. After stirring for 1h at room temperature, methyl iodide (37 mL, 594 mmol, 10.0 eq.) was added dropwise and the mixture was stirred overnight at room temperature. A 1 M HCl solution, saturated with NH_4Cl, was added to the mixture and the aqueous phase was extracted with Et_2O (3 x 300 mL). The combined organic extracts were washed with a saturated solution of sodium thiosulfate, a saturated solution of sodium chloride and then dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the crude product was fully loaded on a broad silica gel column (diameter: 7.5

cm, length: 15 cm) washed with 500 mL petroleum ether and eluted with a Et_2O/PE (1/9) mixture to give acetyl syncarpic acid (**30**) (10.2 g, 45 mmol, 77 % yield) as a yellowish white sticky solid.

Acetyl syncarpic acid (**30**) (10.2 g, 45 mmol) was suspended in 2 M HCl and heated to 140°C (oil temperature) overnight (if needed, HCl was added and the reaction was run for a few more hours). The reaction was then cooled down to room temperature and placed at 4°C overnight. The yellowish white crystals were filtered off and dried *in vacuo* overnight to give syncarpic acid (**27**) (7.0 g, 0.38 mmol) with 85 % yield. The analytical data was in agreement with the literature.

GP 3a: Preparation of isobutylidene syncarpic acid in DCM (classic method)[35a]

Syncarpic acid (**27**) (1.0 eq.) was suspended in DCM (3 mL/mmol) and piperidine (2.0 eq.) and isobutyraldehyde (**26**) (1.5 eq.) were added. After stirring for 10 min at room temperature, a solution of 1M HCl, saturated with ammonium chloride, was added and the biphasic mixture was vigorously stirred for 15 min. The layers were separated and the aqueous phase was extracted once with DCM. The organic layers were combined, filtrated through a 5 cm thick pad of silica gel (PE/A, 2:1) and the eluent was removed by evaporation under reduced pressure. Isobutylidene syncarpic acid (IBSA) (**31**) was obtained with 95-99 % yield as a clear yellow oil and was used without further purification.

GP 3b: Preparation of isobutylidene syncarpic acid in MeOH (new method)

Syncarpic acid (**27**) (1.0 eq.) was dissolved in MeOH (1.5 mL/mmol) and proline (**90**) (0.3 eq.) and isobutyraldehyde (**26**) (1.5 eq.) were added. After stirring for 30-40 min at 60°C (TLC monitoring), a solution of 1M HCl, saturated with ammonium chloride, was added and the aqueous phase was extracted twice with DCM. The organic layers were combined and filtered through a 5 cm thick pad of silica gel (PE/A, 2:1). The eluent was removed by evaporation under reduced pressure to afford isobutylidene syncarpic acid (IBSA) (**31**) with 95-99 % yield as a clear yellow oil which was used without further purification.

GP 4: Preparation of the alkylidene indandiones[34,128]

In a round bottom flask fitted with an inverse Dean-Stark apparatus, 1,3-indandione (**38**) (1.0 eq.) and ammonium acetate (0.2 eq.) were dissolved in chloroform (2 mL/mmol of **38**) before glacial acetic acid (0.5 eq.) and the aldehyde (1.5 eq.) were added. The mixture was refluxed

until no more water separated. The dark mixture was washed with water containing a few drops of sodium bicarbonate until neutrality was reached, then washed with water. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to afford the crude alkylidene indandione which was used without further purification in the next step.

4.2.2. Preparation of myrtucommulone derivatives

GP 5: One-Pot preparation of myrtucommulone derivatives (Method B)

The 1,3-diketone (4.0-6.0 eq.), proline (**90**) (0.5 eq.) and the acyl phloroglucinol (1.0 eq.) were dissolved in EtOH (8 mL/mmol of acyl phloroglucinol). After the addition of the aldehyde (8.0 eq.), the mixture was stirred at room temperature until completion of the reaction was observed by TLC. Diethyl ether (40 mL/mmol of acyl phloroglucinol) and a saturated solution of ammonium chloride (same volume) were added. The layers were separated and the aqueous phase was extracted twice with the same volume of Et_2O. The combined organic layers were dried over magnesium sulfate, filtrated and the solvents were removed under reduced pressure. The crude product was purified on silica gel column chromatography.

GP 6: Preparation of myrtucommulone derivatives using different catalysts (Method C)

The acyl phloroglucinol (1.0 eq.) and the catalyst (0.5 eq., variable) were dissolved in the solvent (4 mL/mmol acyl phloroglucinol) and brought to the desired temperature. The alkylidene 1,3-diketone (1.5-6.0 eq.), prepared according to the general procedures ***GP 3a*** or ***GP 3b***, was dissolved in the solvent (0.5 mL/mmol alkylidene) and added to the mixture. The reaction was stirred at room temperature until completion of the reaction was observed on TLC. After the reaction was hydrolysed with a saturated solution of ammonium chloride, the crude product was extracted with diethyl ether (3 x 20 mL). The product was then dried with magnesium sulfate and the solvent was evaporated under reduced pressure. The product was purified by column chromatography on silica gel.

GP 7: Preparation of myrtucommulone derivatives using phase transfer catalysts (PTC)[100,102,129]

The acyl phloroglucinol (1.0 eq.) and the PTC (**122**) (0.5 eq.) were suspended in toluene (4 mL/mmol acyl phloroglucinol) and a base (1M KOH or KF) was added. After stirring for 15 min, the solution was brought to the desired temperature and the isobutylidene syncarpic

acid (**31**) (1.5-4.8 eq.), which had been prepared according to the general procedures ***GP 3a*** or ***GP 3b***, was dissolved in toluene (0.25 mL/mmol **31**) and added to the mixture. The reaction was stirred at room temperature until completion of the reaction was observed by TLC. After the reaction was hydrolysed with a saturated solution of ammonium chloride, the crude product was extracted with diethyl ether (3 x 20 mL). The product was then dried with magnesium sulfate and the solvent was evaporated under reduced pressure. The product was purified by column chromatography on silica gel.

GP 8: Preparation of myrtucommulone derivatives using metal catalysis

The phloroglucinol derivative (1 eq.) was dissolved in the solvent (2 mL/mmol) under N_2 and slowly added to the freshly prepared solution of the catalyst (**66**) (0.15-0.25 M solution) by syringe. The resulting suspension was stirred at room temperature for an additional hour. Then the alkylidene 1,3-diketone (0.60-0.75 M solution), freshly prepared according to the general procedures ***GP 3a***, ***GP 3b*** or ***GP 4***, was added dropwise at the desired temperature (usually 0°C). Stirring was continued for several hours (monitored by TLC, A/PE, 1/1) and then the reaction mixture was quenched with 1M HCl (aqueous solution saturated with NH_4Cl). The mixture was extracted with diethyl ether (3 x 50 mL), and the combined organic extracts were dried with $MgSO_4$. Filtration and evaporation of the solvent gave the crude product, which was purified by flash chromatography (PE/A) to give the desired myrtucommulone derivative.

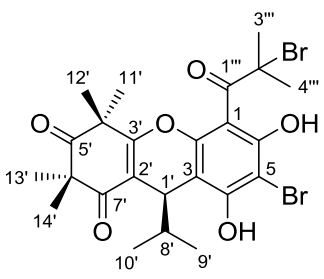
GP 9: Cyclisation of myrtucommulone derivatives.

The myrtucommulone derivative (1.0 eq.) was suspended in toluene (1 mL/10 mg) and a few drops of acetone were added to dissolve it completely. $pTsOH \cdot H_2O$ (3.0 eq. for derivatives with only one condensation site, 6.0-7.0 eq. otherwise) was added and the mixture was stirred at 95°C (bath temperature) until completion of the reaction (monitored by TLC, usually 1h). The solvents were removed under reduced pressure and the residue was directly transferred on a silica gel chromatography column for purification.

4.3. Elucidation of the absolute configuration of the enantiomers of myrtucommulone B and pentacyclic myrtucommulone A

*(+)-(R)-Dibromo-MCB (**51**)*[44]

(+) MCB ((+)-**6**) (121 mg, 0.29 mmol, 1.0 eq.) was dissolved in acetic acid (3 mL) and 0.4 mL of a 1.7 M solution of Br_2 (0.69 mmol, 2.4 eq.) in acetic acid was slowly added to the mixture. After 30 minutes of vigorous stirring, the reaction mixture was poured on a saturated sodium thiosulfate solution and stirred for 5 more minutes. Sodium bicarbonate was then added until the gas formation had ceased and the product was extracted with diethyl ether, dried using magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (A/PE, 1:5, R_f = 0.16) to yield 152 mg (0.27 mmol, 92% yield) of (+)-(*R*)-Dibromo-MCB (**51**) as a white foam which was crystallised from dichloromethane to afford thin white needles (mp = 179-181°C). $[\alpha]_D^{24}$ = + 40.2 ($CHCl_3$, c = 1.0)

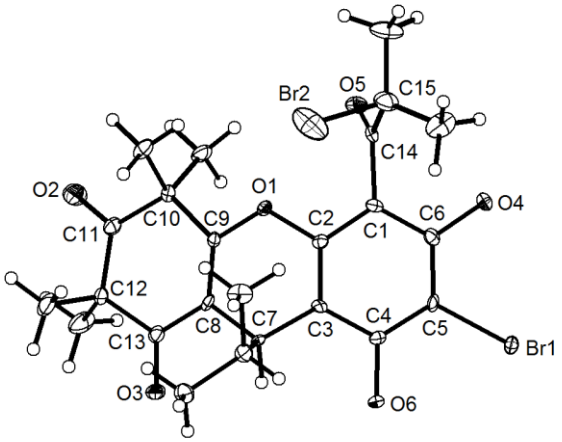


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.91 (s, 1 H, C6-OH), 5.77 (s, 1H, C4-OH), 4.36 (d, $^3J_{H1',H8'}$ = 3.5 Hz, 1H, H1'), 2.064, 2.059 (2 x s, 6 H, H3''', H4'''), 1.98 (dsept, $^3J_{H8',H9'-10'}$= 6.8 Hz and $^3J_{H8',H1'}$ = 3.5 Hz, 1H, H8'), 1.55 (s, 3H, H12'), 1.41 (s, 3H, H14'), 1.36 (s, 3H, H11'), 1.35 (s, 3H, H13'), 0.84 (d, $^3J_{H8',H9'}$ = 7.0 Hz, 3H, H9'), 0.79 (d, $^3J_{H8',H10'}$ = 7.0 Hz, 3 H, H10') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 211.9 (C5'), 198.9 (C1'''), 197.7 (C7'), 168.4 (C3'), 151.0 (C4), 149.0 (C6), 147.3 (C2), 111.3 (C2'), 108.5 (C1), 105.6 (C3), 95.5 (C5), 65.2 (C2'''), 56.1 (C6'), 47.5 (C4'), 34.8 (C8'), 33.1 (C1'), 30.54, 30.51 (C3''', C4'''), 25.2 (C12'), 24.7 (C14'), 24.5, 24.3 (C11', C13'), 19.0 (C10'), 18.9 (C9') ppm.

HRMS (ESI^+) calcd. for $C_{24}H_{29}Br_2O_6^+$ $[M+H]^+$: 571.0331, found: 571.0312

Crystal Structure Data : (for the complete data see Appendix 1)



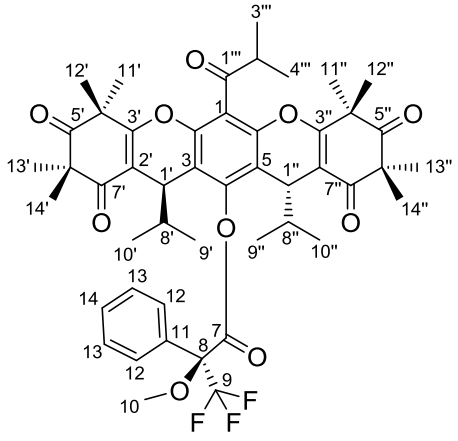
Exp. Data Tab. 1 Crystal data and structure refinement for **51** (sh3343).

Identification code	sh3343	
Empirical formula	C24 H28 Br2 O6 * 0.5 C H2 Cl2	
Formula weight	612.73	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.7566(2) Å	α= 90°.
	b = 19.1985(4) Å	β= 90°.
	c = 27.6028(5) Å	γ = 90°.
Volume	5170.34(18) $Å^3$	
Z	8	
Density (calculated)	1.574 Mg/m^3	
Absorption coefficient	3.276 mm^{-1}	
F(000)	2472	
Crystal size	0.43 x 0.26 x 0.18 mm^3	
Theta range for data collection	1.29 to 26.37°.	
Index ranges	-11<=h<=12, -23<=k<=23, -34<=l<=28	
Reflections collected	38038	
Independent reflections	10541 [R(int) = 0.0316]	
Completeness to theta = 26.37°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5932 and 0.3345	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10541 / 220 / 650	
Goodness-of-fit on F^2	1.097	
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.1275	
R indices (all data)	R1 = 0.0487, wR2 = 0.1305	
Absolute structure parameter	0.004(8)	
Largest diff. peak and hole	0.793 and -1.437 e.$Å^{-3}$	

*(+)-(S,R,R)-PMCA-Mosher ester (**53**)*[45]

To (+)-PMCA ((+)-**7**) (50 mg, 0.08 mmol, 1.00 eq.) in a 4 mL-vial were added 1.1 mL of a 0.09 M solution of (*S*)-Mosher acid (**52**) (23.5 mg, 0.1 mmol, 1.25 eq.) in dichloromethane, 1.5 mL of a 0.07 M solution of DCC (21 mg, 0.1 mmol, 1.25 eq.) in dichloromethane, and several crystals of DMAP. After 24 h, additional (*S*)-Mosher acid (**52**) (13 mg, 0.06 mmol, 0.75 eq.) and DCC (12 mg, 0.06 mmol, 0.75 eq.) were added. After 4 days, the reaction was judged complete by TLC. A saturated solution of ammonium chloride was added, the mixture was extracted with diethyl ether, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel (A/PE, 1/9, R_f = 0.16) to yield 46 mg (0.05 mmol, 68% yield) of (+)-(*S*,*R*,*R*)-PMCA-Mosher ester (**53**) as a white foam which was crystallised from dichloromethane to afford thin white needles (*mp* = 224-230°C). $[\alpha]_D^{24}$ = + 39.5 ($CHCl_3$, *c* = 1.0)

Two different conformers are observed in the NMR-spectrum:

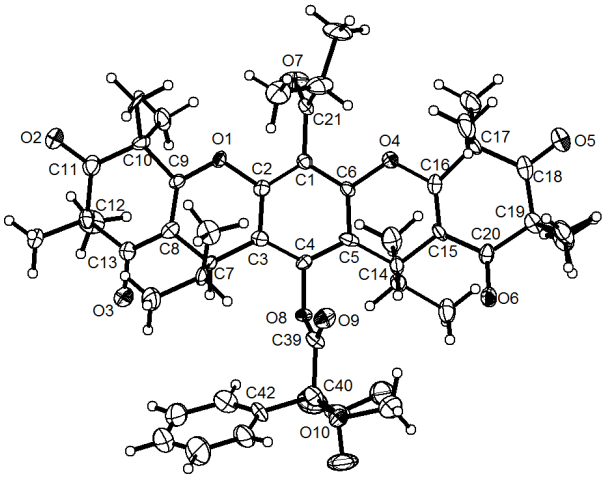


^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 7.82 (d, $^3J_{H12,H13}$ = 7.8 Hz, 1.67H, H12), 7.73 (d, $^3J_{H12,H13}$ = 7.8 Hz, 0.37H, H12), 7.66-7.60 (m, 2H, H13), 7.56-7.50 (m, 1H, H14), 4.19 (brs, 1.35H, H1', H1''), 4.07 (d, $^3J_{H1',H8'}$ = 4.5 Hz, 0.22 H, H1'), 4.04 (d, $^3J_{H1'',H8''}$ = 4.3 Hz, 0.22H, H1''), 3.86 (s, 2.47H, H10), 3.67 (s, 0.52H, H10), 3.12 (sept, $^3J_{H2''',H3'''-H4'''}$ = 7.0 Hz, 1H, H2'''), 1.85-1.76 (m, 0.40H, H8', H8''), 1.73-1.65 (m, 1.70H, H8', H8''), 1.53 (s, 4.80H, H12', H11''), 1.51 (s, 1.20H, H12', H11''), 1.43-1.33 (m, 18H, H11', H12'', H13', H13'', H14', H14''), 1.27 (d, $^3J_{H3''',H2'''}$ = 7.0 Hz, 3H, H3'''), 1.26 (d, $^3J_{H4''',H2'''}$ = 7.3 Hz, 3H, H4'''), 0.70-0.49 (m, 12H, H9', H9'', H10', H10'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : *δ* = 211.71, 211.67 (C5', C5''), 203.6 (C1'''), 197.2, 197.0 (C7', C7''), 167.9, 167.82, 167.78, 167.76 (C3', C3''), 165.1 (C7), 147.33, 147.26 (C2, C6), 144.8 (C4), 130.1 (C14), 129.21, 129.15 (C11; C13), 127.9, 127.8 (C12), 124.5, 121.6 (C9), 116.8, 116.6 (C3, C5), 116.4, 115.9, 115.5 (C1), 110.5, 110.2, 110.0, 109.6 (C2', C2''), 85.1, 84.9 (C8), 56.1, 56.0 (C6', C6''), 55.9 (C10), 47.5, 47.43, 47.42 (C4', C4''), 43.1, 42.7 (C2'''), 35.4, 35.3 (C8', C8''), 33.31, 33.25, 32.7 (C1', C1''), 25.7, 25.3, 25.0, 24.94, 24.90, 24.85, 24.7, 24.6, 24.1, 24.0, 23.8, 23.7 (C12', C11'', C13', C14'', C11', C12'', C14', C13''), 20.8, 19.9, 19.8, 19.3, 19.1, 16.6 (C9', C9'', C10', C10''), 17.9, 17.8, 17.50, 17.45 (C3''', C4''') ppm.

HRMS (ESI$^+$) calcd. for $C_{48}H_{56}F_3O_{10}^+$ $[M+H]^+$: 849.3825, found: 849,3830

Crystal Structure Data: (for the complete data see Appendix 2)

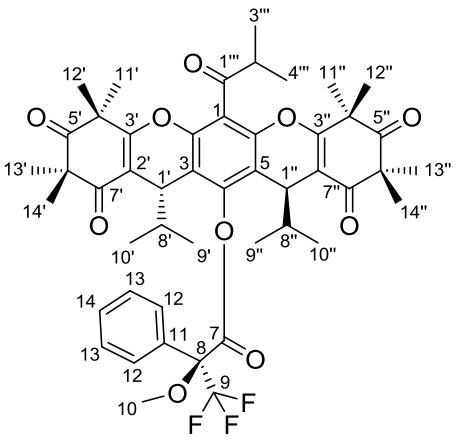


Exp. Data Tab. 2 Crystal data and structure refinement for **53** (sh3365).

Identification code	sh3365	
Empirical formula	C48 H55 F3 O10	
Formula weight	848.92	
Temperature	122(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 6.4479(10) Å	α= 90°.
	b = 40.961(5) Å	β= 91.687(8)°.
	c = 17.888(3) Å	γ = 90°.
Volume	4722.3(11) $Å^3$	
Z	4	
Density (calculated)	1.194 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	1800	
Crystal size	0.806 x 0.120 x 0.064 mm^3	
Theta range for data collection	0.994 to 26.357°.	
Index ranges	-8<=h<=7, -47<=k<=50, -21<=l<=21	
Reflections collected	27828	
Independent reflections	15089 [R(int) = 0.0825]	
Completeness to theta = 25.242°	93.4 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15089 / 399 / 1149	
Goodness-of-fit on F^2	1.230	
Final R indices [I>2sigma(I)]	R1 = 0.0915, wR2 = 0.1989	
R indices (all data)	R1 = 0.1333, wR2 = 0.2133	
Absolute structure parameter	0.2(8)	
Extinction coefficient	0.0050(7)	
Largest diff. peak and hole	0.609 and -0.362 e.$Å^{-3}$	

*(-)-(S,S,S)-PMCA-Mosher ester (**54**)*[45]

54 was synthesised according to the same procedure as for (+)-(S,R,R)-PMCA-Mosher ester (**53**) starting from (-)-PMCA ((-)-**7**) (50 mg, 0.08 mmol, 1.00 eq.) and (*S*)-Mosher acid (**52**). The crude product was purified by flash chromatography (A/PE, 1/9, R_f = 0.13) to give (-)-(*S*,*S*,*S*)-PMCA-Mosher ester (**54**) (52 mg, 0.06 mmol) with 77 % yield as a shiny white solid (mp = 226-229°C). $[\alpha]_D^{24}$ = - 15.5 ($CHCl_3$, *c* = 1.0)



^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 7.79 (d, $^3J_{H12,H13}$ = 7.8 Hz, 2H, H12), 7.64-7.58 (m, 2H, H13), 7.54-7.48 (m, 1H, H14), 4.10 (brs, 2H, H1', H1''), 3.54 (s, 3H, H10), 3.12 (sept, $^3J_{H2''',H3'''\text{-}H4'''}$ = 7.0 Hz, 1H, H2'''), 1.66-1.57 (m, 2H, H8', H8''), 1.52 (s, 6H, H12', H11''), 1.40 (s, 12H, H13', H13'', H14', H14''), 1.37 (s, 6H, H11', H12'') 1.26 (d, $^3J_{H3''',H2'''}$ = 7.0 Hz, 3H, H3'''), 1.25 (d, $^3J_{H4''',H2'''}$ = 7.3 Hz, 3H, H4'''), 0.56 (d, $^3J_{H9',H8'}$ = $^3J_{H9'',H8''}$ = 7.0 Hz, H, H9', H9''), 0.50 (d, $^3J_{H10',H8'}$ = $^3J_{H10'',H8''}$ = 7.0 Hz, H, H10', H10'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : *δ* = 211.7 (C5', C5''), 203.7 (C1'''), 197.1 (C7', C7''), 167.8, (C3', C3''), 164.8 (C7), 147.3 (C2, C6), 144.9 (C4), 130.3 (C14), 129.7 (C11) 129.3 (C13), 128.1 (C12), 124.8, 121.9 (C9), 116.6 (C3, C5), 116.3 (C1), 109.7 (C2', C2''), 85.1, 84.8 (C8), 55.9 (C6', C6''), 55.1 (C10), 47.5 (C4', C4''), 42.7 (C2'''), 35.2 (C8', C8''), 32.6 (C1', C1''), 25.5, 25.3, 24.7, 23.9, 23.8 (C12', C11'', C13', C14'', C11', C12'', C14', C13''), 19.8, 16.6 (C9', C9'', C10', C10''), 17.9, 17.5 (C3''', C4''') ppm.

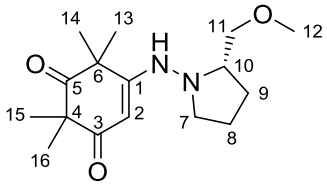
HRMS (ESI^+) calcd. for $C_{48}H_{56}F_3O_{10}^+$ $[M+H]^+$: 849.3825, found: 849,3815

4.4. Synthesis of various intermediates

*Syncarpic acid SAMP-hydrazone (**50**)*[38]

Syncarpic acid (**27**) (650 mg, 3.6 mmol, 1.0 eq.) was dissolved in hot THF_{abs} and molecular sieves were added under nitrogen atmosphere. SAMP (**45**) (489 mg, 0.50mL, 3.6 mmol, 1.0 eq.) was added and the mixture was stirred overnight at 70°C (bath temperature). The molecular sieves were filtered off and the filtrate was concentrated *in vacuo.* The residue was dissolved in DCM and water was added. The layers were separated and the aqueous layer was extracted 4 more times with DCM. The combined organic extracts were washed with brine and dried with magnesium sulfate. The crude product was purified by column chromatography on silica gel (A/PE, 1/5, R_f = 0.17) to afford syncarpic acid SAMP-hydrazone (**50**) (780 mg, 2.7 mmol, 75 % yield) as shiny white needles (*mp* = 154-155°C). $[\alpha]_D^{24}$ = + 58.5 (MeOH, *c* = 1.1)

MS (ESI^+) for $C_{16}H_{27}N_2O_3^+$ $[M+H]^+$: 295.3 (100).

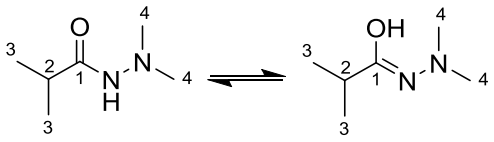


^{1}H-NMR (400 MHz, $CO(CD_3)_2$): δ = 7.11 (s, 1H, NH), 5.75 (s, 1H, H2), 3.42 (dd, $^2J_{H11a,H11b}$ = 9.5H, $^3J_{H11a,H10}$ = 4.8 Hz, 1H, H11a), 3.28 (dd, $^2J_{H11b,H11a}$ = 9.5H, $^3J_{H11b,H10}$ = 6.5 Hz, 1H, H11b), 3.25 (s, 3H, H12), 3.24-3.20 (m, 1H, H7a), 3.11-3.03 (m, 1H, H10), 2.70 (q, *J* = 8.5 Hz, 1H, H7b), 2.01-1.93 (m, 1H, H9a), 1.85-1.77 (m, 2H, H8), 1.69-1.59 (m, 1H, H9b), 1.46 (s, 3H, H13), 1.44 (s, 3H, H14), 1.24 (s, 3H, H15), 1.23 (s, 3H, H16) ppm.

^{13}C-NMR (101 MHz, $CO(CD_3)_2$): δ = 215.7 (C5), 196.7 (C3), 167.2 (C1), 95.0 (C2), 76.6 (C11), 66.5 (C10), 60.1 (C12), 56.2 (C7), 55.6 (C4), 47.3 (C6), 28.3 (C9), 27.2, 27.0 (C13, C14), 26.2, 25.9 (C15, C16) ppm.

*N',N'-dimethylisobutyrohydrazide (**61**)*[47c]

N,N-dimethyl-hydrazine (0.55 mL, 7.1 mmol, 1.0 eq.) and triethylamine (1.10 mL, 7.2 mmol, 1.0 eq.) were mixed in anhydrous diethyl ether (35 mL) under nitrogen atmosphere. The mixture was cooled to 0°C and isobutyryl chloride (0.77 mL, 7.1 mmol, 1.0 eq.) was added dropwise. The resultant suspension was then stirred overnight at room temperature. The precipitate was filtered off to afford a colourless solution which was concentrated under vacuum to give the hydrazide **61** (863 mg, 6.6 mmol, 93 % yield) as shiny white needles after recrystallization from diethyl ether (*mp* = 96-98°C, Lit.[47c] 94-96°C).



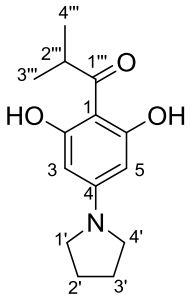
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.21 (brs, 0.52H, NH), 5.96 (brs, 0.40H, NH), 3.14 (sept, $^{3}J_{H2,H3}$ = 6.8 Hz, 0.44H, H2), 2.58 (s, 3.34H, H4), 2.51 (s, 2.66H, H4), 2.21 (sept, $^{3}J_{H2,H3}$ = 6.8 Hz, 0.57H, H2), 1.13 (d, $^{3}J_{H3,H2}$ = 6.8 Hz, 3.36H, H3), 1.11 (d, $^{3}J_{H3,H2}$ = 6.8 Hz, 2.65H, H3) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 180.1, 174.5 (C1), 48.9, 47.5 (C2), 34.1, 29.6 (C4), 19.4, 19.1 (C3) ppm.

*para-pyrrolidinyl-IBPG (**58**)*[46]

IBPG (**25**) (787 mg, 4.0 mmol, 1.0 eq.) was suspended in methanol (3 mL) and pyrrolidine (0.33 mL, 4.0 mmol, 1 eq.) was added. The mixture was stirred and refluxed for 6h and the solvent was evaporated under reduced pressure. The residue was transferred directly onto a silica gel column and chromatographically purified (A/PE, 1/5, R_f = 0.24) to give 794 mg of para-pyrrolidinyl-IBPG (**58**) (3.2 mmol, 80 % yield) as a brownish yellow powder (*mp* = 178-180°C).

MS (ESI^+) for $C_{14}H_{20}NO_3^+$ $[M+H]^+$: 250.2 (100).



^{1}H-NMR (400 MHz, $CO(CD_3)_2$): δ = 11.69 (s, 2H, OH), 5.59 (s, 2H, H3, H5), 3.96 (sept, $^{3}J_{H2'''',H3''''-H4''''}$ = 6.8 Hz, 1H, H2''''), 3.31-3.25 (m, 4H, H1', H4'), 2.02-1.94 (m, 4H, H2', H3'), 1.12 (d, $^{3}J_{H3''''-H4'''',H2''''}$ = 6.8 Hz, 6H, H3'''', H4'''') ppm.

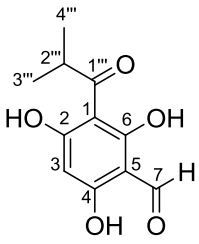
^{13}C-NMR (101 MHz, $CO(CD_3)_2$): δ = 209.7 (C1'''), 165.8 (C4), 154.8 (C2, C6), 102.3 (C1), 92.8 (C3, C5), 49.0 (C1', C4'), 39.9 (C2'''), 26.9 (C2', C3'), 20.8 (C3''', C4''') ppm.

*Formyl-IBPG (**63**)*[50]

To the solution of IBPG (**25**) (980 mg, 5.0 mmol, 1.0 eq.) in ethyl acetate (75 mL) were added molecular sieves, dimethylformamide (0.39 mL, 5.0 mmol, 1.0 eq.) and phosphoryl chloride (0.51 mL, 5.5 mmol, 1.1 eq.) at room temperature under nitrogen atmosphere. The reaction mixture was further stirred for 5h at 60°C. A saturated solution of NH_4Cl was added, the phases were separated, and the aqueous layer was extracted with ethyl acetate (4 x 100 mL). The ethyl acetate layer was washed with brine, dried over Na_2SO_4 and concentrated to afford the crude product. Column chromatography over silica gel using (A/PE, 1/5, R_f = 0.14)

provided formyl-isobutyryl-phloroglucinol (**63**) (405 mg, 1.8 mmol, 35 % yield) as a white powder (*mp* = 114-123°C).

HRMS (ESI$^+$) calcd. for $C_{11}H_{13}O_5^+$ $[M+H]^+$: 225,0763, found: 225,0763.



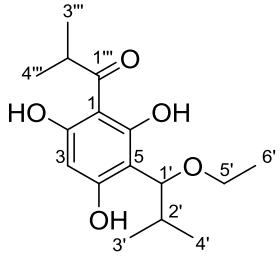
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 15.49 (brs, 0.23H, OH), 15.18 (brs, 0.52H, OH), 14.35 (s, 0.63H, OH), 12.64 (brs, 0.20H, OH), 10.14 (s, 0.29H, H7), 10.06 (s, 0.68H, H7), 7.89 (brs, 0.82H, OH), 5.88 (s, 0.66H, H3), 5.83 (s, 0.30H, H3), 3.98-3.77 (m, 1H, H2'''), 1.20 (d, $^3J_{H3'''\text{-}H4'''',H2''''}$ = 6.8 Hz, 6H, H3'''', H4'''') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 211.5 (C1'''), 191.2 (C7), 174.4 (C6), 169.7 (C4), 165.2 (C2), 104.0 (C1), 103.5 (C5), 95.6 (C3), 39.5 (C2'''), 19.0, 18.9 (C3''', C4''') ppm.

*Isobutyryl phloroglucinol derivatives **94** and **95***

Isobutyryl phloroglucinol (IBPG) (**25**) (200 mg, 1.0 mmol, 1.0 eq.), histidine (170 mg, 1.1 mmol, 1.1 eq.) and isobutyraldehyde (**26**) (100 µL, 1.1 mmol, 1.1 eq.) were mixed in ethanol (4 mL) and stirred at room temperature for 24 h. A solution of ammonium chloride was added, the product was extracted with ethyl acetate (3 x 20 mL) and dried using magnesium sulfate. The solvents were evaporated under reduced pressure and the residue was purified through column chromatography on silica gel (A/PE, 1/9) to afford 35 mg of the derivative **94** and 41 mg of the derivative **95**.

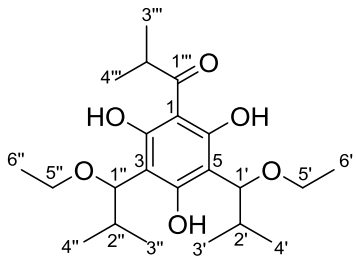
*Derivative **94***



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 14.28 (brs, 0.48H, OH), 13.96 (brs, 0.31H, OH), 10.19 (s, 0.34H, OH), 9.66 (brs, 0.46H, OH), 6.71 (brs, 0.76H, OH), 5.83 (brs, 1H, H3), 4.61 (brs, 1H, H1'), 3.91 (sept, $^3J_{H2'''',H3'''\text{-}H4''''}$ = 6.5 Hz, 1H, H2'''), 3.59-3.58 (m, 1H, H5a'), 3.56-3.46 (m, 1H, H5b'), 2.06-1.95 (m, 1H, H2'), 1.23 (t, $^3J_{H6'',H5''}$ = 6.8 Hz, 3H, H6''), 1.18 (d, $^3J_{H3'''\text{-}H4''',H2''''}$ = 6.8 Hz, 3H, H6''), 1.00 (d, $^3J_{H3'',H2''}$ = 6.5 Hz, 3H, H3''), 0.92 (d, $^3J_{H4'',H2''}$ = 6.8 Hz, 3H, H4'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 210.9, 210.8, 208.9 (C1'''), 172.1 (C2), 164.7, 163.1, 163.0, 162.9, 159.1, 159.0 (C4, C2), 110.0 (C5), 104.8, 104.7 (C1), 95.4 (C3), 82.5 (C1'), 66.0 (C5'), 39.2 (C2'''), 33.4 (C2'), 19.3, 19.2, 19.0, 18.1, 17.9 (C3', C4', C3''', C4'''), 14.9 (C6') ppm.

*Derivative **95***



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 14.29-14.17 (m, 1H, OH), 13.96 (brs, 0.31H, OH), 10.08 (s, 1H, OH), 9.77, 9.76 (2 x s, 1H, OH), 4.71-4.63 (m, 1H, H1', H1''), 4.62-4.54 (m, 1H, H1', H1''), 3.93 (sept, $^{3}J_{H2''',H3'''-H4'''}$ = 6.5 Hz, 1H, H2'''), 3.71-3.59 (m, 1.66H, H5', H5''), 3.59-3.43 (m, 2.59H, H5', H5''), 2.11-1.91 (m, 2H, H2', H2''), 1.28-1.14 (m, 12H, H3''', H4''', H6', H6''), 1.06-0.84 (m, 12H, H3', H3'', H4', H4'') ppm.

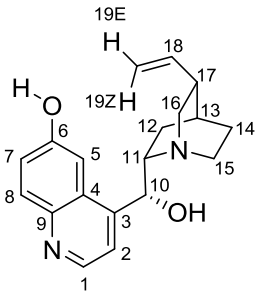
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 211.1 (C1'''), 163.4, 163.2 (C2, C6), 161.2, 161.1 (C4), 159.9, 159.7 (C2, C6), 103.63, 103.59 (C1), 103.02, 102.98, 102.5 (C3, C5), 82.6, 82.4 (C1', C1''), 66.1, 65.8 (C5', C5''), 39.3 (C2'''), 33.5, 33.4 (C2', C2''), 19.5, 19.4, 19.3, 19.1, 19.0, 18.9, 18.8, 18.7, 18.0, 17.7 (C3', C4', C3'', C4'', C3''', C4'''), 15.0, 14.8 (C6') ppm.

4.5. Synthesis of the catalysts

4.5.1. Synthesis of the catalysts for the organocatalysis

*Cupreine (CPN) (**118**)*[94b]

In a flame dried equipment under nitrogen atmosphere, quinine (**112c**) (649 mg, 2.00 mmol, 1.0 eq.) and NaSEt (670 mg, 90 % technical grade, 8 mmol, 4.0 eq.) were suspended in dry DMF (12.5 mL) and stirred at 110°C until a TLC analysis showed that the starting material was completely consumed (5.5h). The reaction mixture was cooled down to room temperature and mixed with a saturated NH_4Cl solution (12.5 mL) and H_2O (10 mL). The pH value of the solution was determined to be around 8. The resulting mixture was extracted with ethyl acetate (2 x 50 mL). The organic phase was washed with brine, dried over Na_2SO_4 overnight and concentrated *in vacuo*. The residue was subjected to flash chromatography (EA/MeOH/TEA, 100/2/3, R_f = 0.19) on silica gel to afford CPN (**118**) (533 mg, 1.72 mmol) as a yellowish white solid (*mp* = 192°C (decomposition)) with 86 % yield.
$[\alpha]_D^{24}$ = - 159.6 (EtOH, *c* = 1.0), Lit.[94b] $[\alpha]_D^{25}$ = - 162.8 (EtOH, *c* = 0.93)



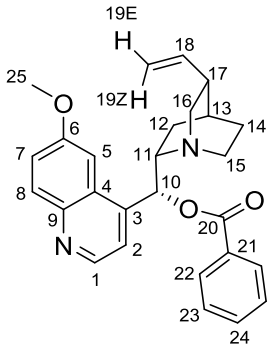
^{1}H-NMR (400 MHz, CD_3OD): δ = 8.59 (d, $^3J_{H1,H2}$ = 4.5 Hz, 1H, H1), 7.90 (d, $^3J_{H8,H7}$ = 9.3 Hz, 1H, H8), 7.63 (d, $^3J_{H2,H1}$ = 4.5 Hz, 1H, H2), 7.36-7.29 (m, 2H, H5, H7), 5.74 (ddd, $^3J_{H18,H19Z}$ = 17.6 Hz, $^3J_{H18,H19E}$ = 10.5 Hz, $^3J_{H18,H17}$ = 7.5 Hz, 1H, H18), 5.56 (d, $^3J_{H10,H11}$ = 3.0 Hz, 1H, H10), 4.98 (dt, $^3J_{H19Z,H18}$ = 17.3 Hz, $^2J_{H19Z,H19E}$ = 1.3 Hz, 1H, H19Z), 4.91 (dt, $^3J_{H19E,H18}$ = 10.3 Hz, $^2J_{H19E,H19Z}$ = 1.3 Hz, 1H, H19E), 3.76 (dddd, $^2J_{H15a,H15b}$ = 13.3 Hz, $^3J_{H15a,H14a}$ = 10.5 Hz, $^3J_{H15a,H14b}$ = 5.0 Hz, $^4J_{H15a,H13}$ = 2.5 Hz, 1H, H15a), 3.20-3.11 (m, 2H, H11, H16a), 2.83-2.69 (m, 2H, H15b, H16b), 2.44-2.35 (m, 1H, H17), 1.95-1.84 (m, 1H, H12a, H14a), 1.84-1.79 (m, 1H, H13), 1.67-1.57 (m, 1H, H14b), 1.49-1.40 (m, 1H, H12b) ppm.

^{13}C-NMR (101 MHz, CD_3OD): δ = 157.9 (C6), 149.5 (C3), 147.5(C1), 144.0 (C9), 142.3 (C18), 131.5 (C8), 128.4 (C4), 123.3 (C7), 119.9 (C2), 115.2 (C19), 105.2 (C5), 71.9 (C10), 61.1 (C11), 57.4 (C16), 44.4 (C15), 40.7 (C17), 29.2 (C13), 27.9 (C14), 21.6 (C12) ppm.

LC-MS (ESI^-) for $C_{19}H_{21}N_2O_2^-$ $[M-H]^-$: 309.20.

*O-benzoyl-quinine (Bz-Q) (**121**)*[95e]

To a stirred solution of quinine (**112c**) (1.298 g, 4.00 mmol, 1.0 eq.) in anhydrous DCM (40 mL), were sequentially added benzoyl chloride (2.3 mL, 20 mmol, 5.0 eq.) and a 30% w/w NaOH solution (5.6 mL) at room temperature. After 4 hours of vigorous stirring, H_2O and DCM were added. The two layers were separated and the aqueous layer extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography. (EA/TEA = 50/1, R_f = 0.27) to give Bz-Q (**121**) (1.624 g, 3.95 mmol, 99% yield) as a white solid (*mp* = 122-123°C).



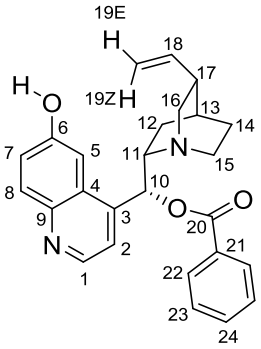
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, $^3J_{H1,H2}$ = 4.5 Hz, 1H, H1), 8.13-8.07 (m, 2H, H22), 8.02 (d, $^3J_{H8,H7}$ = 9.3 Hz, 1H, H8), 7.63-7.57 (m, 1H, H24), 7.52 (d, $^4J_{H5,H7}$ = 2.8 Hz, 1H, H5), 7.50-7.47 (m, 2H, H23), 7.43 (d, $^3J_{H2,H1}$ = 4.5 Hz, 1H, H2), 7.38 (dd, $^3J_{H7,H8}$ = 9.3 Hz, $^4J_{H7,H5}$ = 2.8 Hz, 1H, H7), 6.74 (d, $^3J_{H10,H11}$ = 6.8 Hz, 1H, H10), 5.84 (ddd, $^3J_{H18,H19Z}$ = 17.3 Hz, $^3J_{H18,H19E}$ = 10.3 Hz, $^3J_{H18,H17}$ = 7.3 Hz, 1H, H18), 5.02 (dt, $^3J_{H19Z,H18}$ = 17.3 Hz, $^2J_{H19Z,H19E}$ = 1.3 Hz, 1H, H19Z), 5.00 (dt, $^3J_{H19E,H18}$ = 10.3 Hz, $^2J_{H19E,H19Z}$ = 1.3 Hz, 1H, H19E), 3.98 (s, 3H, H25), 3.54-3.45 (m, 1H, H11), 3.21 (dddd, $^2J_{H15a,H15b}$ = 13.5 Hz, $^3J_{H15a,H14a}$ = 10.3 Hz, $^3J_{H15a,H14b}$ = 5.5 Hz, $^4J_{H15a,H13}$ = 2.5 Hz, 1H, H15a), 3.09 (dd, $^2J_{H16a,H16b}$ = 13.9 Hz, $^3J_{H16a,H17}$ = 10.3 Hz, 1H, H16a), 2.75-2.62 (m, 2H, H15b, H16b), 2.34-2.26 (m, 1H, H17), 1.98-1.87 (m, 2H, H13, H12a), 1.83-1.67 (m, 2H, H12b, H14a), 1.63-1.52 (m, 1H, H14b) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 165.5 (C20), 158.0 (C6), 147.5 (C1), 144.7 (C3), 143.7 (C9), 141.7 (C18), 133.4 (C24), 131.8 (C8), 129.7 (C21), 129.6 (C22), 128.6 (C23), 126.9 (C4), 121.9 (C7), 118.7 (C2), 114.5 (C19), 101.4 (C5), 74.6 (C10), 59.4 (C11), 56.7 (C16), 55.6 (C25), 42.6 (C15), 39.7 (C17), 27.9 (C14), 27.6 (C13), 24.2 (C12) ppm.

*O-benzoyl-cupreine (**120**)*[95e]

O-benzoyl-quinine (**121**) (428 mg, 1.00 mmol, 1.0 eq.) was dissolved in 20 mL of anhydrous DCM under nitrogen atmosphere and cooled to -75°C in an acetone/dry ice bath. A solution of BBr_3 (0.38 mL, 4.00 mmol, 4.0 eq.) in anhydrous DCM (3 mL), prepared under nitrogen atmosphere, was slowly added to the cooled solution. While stirring, the reaction mixture was allowed to slowly warm to room temperature (3h) and subsequently refluxed at 40°C for 1.5 h and then cooled to 0°C. While maintaining the temperature of the mixture below 5°C, a solution of 40% NH_4OH (10 mL) was slowly added (after 1 mL, temperature evolution

ceased). After 30 minutes of vigorous stirring, H_2O and DCM were added. The two layers were separated and the aqueous layer extracted with 1-butanol, the combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure (10 mbar/50°C). The residue was purified by flash chromatography. (EA/MeOH/TEA = 50/2/1, R_f = 0.20) to give Bz-CPN (**120**) (232 mg, 0.56 mmol, 56% yield) as a white solid (*mp* = 132°C (decomposition)). $[\alpha]_D^{24}$ = + 114.0 (CH_2Cl_2, *c* = 1.0), Lit.[95e] $[\alpha]_D^{20}$ = + 115.8 (CH_2Cl_2, *c* = 0.63)



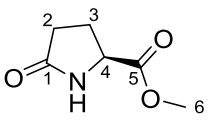
^{1}H-NMR (400 MHz, DMSO-D$_6$): δ = 10.14 (s, 1H, OH), 8.62 (d, $^3J_{H1,H2}$ = 4.5 Hz, 1H, H1), 8.09-8.04 (m, 2H, H22), 7.89 (d, $^3J_{H8,H7}$ = 9.0 Hz, 1H, H8), 7.72-7.66 (m, 1H, H24), 7.60-7.53 (m, 3H, H5, H23), 7.51 (d, $^3J_{H2,H1}$ = 4.5 Hz, 1H, H2), 7.32 (dd, $^3J_{H7,H8}$ = 9.0 Hz, $^4J_{H7,H5}$ = 2.5 Hz, 1H, H7), 6.44 (d, $^3J_{H10,H11}$ = 7.5 Hz, 1H, H10), 5.94 (ddd, $^3J_{H18,H19Z}$ = 17.6 Hz, $^3J_{H18,H19E}$ = 10.5 Hz, $^3J_{H18,H17}$ = 7.8 Hz, 1H, H18), 5.06-4.96 (m, 2H, H19Z, H19E), 3.54-3.42 (m, 1H, H11), 3.14-3.01 (m, 1H, H15a), 3.09 (dd, $^2J_{H16a,H16b}$ = 13.5 Hz, $^3J_{H16a,H17}$ = 10.3 Hz, 1H, H16a), 2.59-2.40 (m, 2H, H15b, H16b), 2.28-2.19 (m, 1H, H17), 1.98-1.90 (m, 1H, H12a), 1.81-1.77 (m, 1H, H13), 1.73-1.63 (m, 1H, H14a), 1.61-1.43 (m, 2H, H12b, H14b) ppm.

^{13}C-NMR (101 MHz, DMSO-D$_6$): δ = 165.5 (C20), 155.7 (C6), 146.6 (C1), 143.30 (C3), 143.25 (C9), 142.3 (C18), 133.7 (C24), 131.4 (C8), 129.3 (C22), 129.2 (C21), 128.9 (C23), 126.9 (C4), 121.9 (C7), 119.0 (C2), 114.4 (C19), 104.5 (C5), 74.7 (C10), 59.3 (C11), 56.0 (C16), 41.7 (C15), 39.2 (C17), 27.3 (C14), 27.2 (C13), 24.7 (C12) ppm.

LC-MS (ESI$^-$) for $C_{52}H_{51}N_4O_6^-$ [2M-H]$^-$: 827.45.

*Pyroglutamic acid methyl ester (**117**)*[89a]

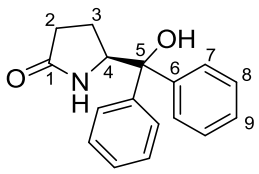
To a stirred solution of (*S*)-pyroglutamic acid (**116**) (5.0 g, 39 mmol, 1.0 eq.) in anhydrous methanol (125 mL) at -15°C was added thionyl chloride (3.4 mL, 5.6 g, 46 mmol, 1.2 eq.) dropwise. The mixture was stirred 30 min at -15°C, slowly warmed to r.t. and stirred overnight. The mixture was concentrated *in vacuo* and the remaining yellow oil was purified by column chromatography on silica gel (A/PE, 1/1, R_f = 0.21) yielding the product **117** as a colourless oil (2.5 g, 17 mmol, 44 % yield).



^{1}H-NMR (400 MHz, CDCl$_3$): δ = 6.18 (brs, 1H, NH), 4.26 (dd, $^3J_{H4,H3a}$ = 5.0 Hz, $^3J_{H4,H3b}$ = 8.5 Hz, 1H, H4), 3.77 (s, 3H, H6), 2.55-2.44 (m, 1H, H3a), 2.44-2.32 (m, 2H, H2), 2.31-2.19 (m, 1H, H3b) ppm.

*(S)-5-(hydroxydiphenylmethyl)pyrrolidin-2-one (HODPP) (**115**)*[89]

In a flame dried round bottom flask, magnesium turnings (1.67 g, 69.6 mmol, 4.0 eq.) were suspended in anhydrous THF (24 mL) under nitrogen atmosphere. A first portion of bromobenzene (2.3 mL, 3.44 g, 21.9 mmol, 1.3 eq.) was then added dropwise and the reaction was heated with a heat gun until it started. The second portion of bromobenzene (5.0 mL, 7.48 g, 47.6 mmol, 2.8 eq.), dissolved in 4 mL anhydrous THF, was then added over 15 min and the mixture was stirred for 2h at reflux. The reaction was then cooled to 0°C and the ester **117** (2.46 g, 17.2 mmol, 1.0 eq.), dissolved in anhydrous THF (10 mL), was added over 15-20 min. The mixture was then allowed to warm to room temperature and stirred overnight. The reaction was hydrolysed with a saturated solution of ammonium chloride and extracted with ethyl acetate (6 x 30 mL). The combined organic extracts were dried using magnesium sulfate and the solvents were evaporated under reduced pressure. After recrystallisation from hot ethanol, HODPP (**115**) (3.51 g, 13.1 mmol, 76 % yield) was obtained as a white solid (*mp* = 185-186°C, decomposition, Lit.[89a] 190°C, decomposition).

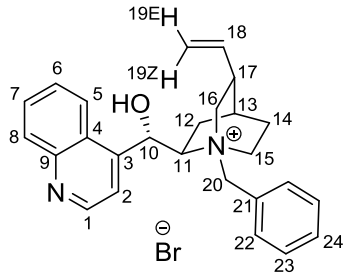


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50-7.42 (m, 4H, H7), 7.35-7.26 (m, 4H, H8), 7.26-7.17 (m, 2H, H9), 5.45 (brs, 1H, NH), 4.70 (dd, $^{3}J_{H4,H3a}$ = 4.8 Hz, $^{3}J_{H4,H3b}$ = 8.3 Hz, 1H, H4), 3.87 (s, 1H, OH), 2.34 (ddd, $^{2}J_{H2a,H2b}$ = 17.1 Hz, $^{3}J_{H2a,H3a}$ = 10.3 Hz, $^{3}J_{H2a,H3b}$ = 6.3 Hz, 2H, H2), 2.23 (ddd, $^{2}J_{H2b,H2a}$ = 17.1 Hz, $^{3}J_{H2b,H3a}$ = 10.3 Hz, $^{3}J_{H2b,H3b}$ = 6.3 Hz, 2H, H2), 2.15-2.03 (m, 1H, H3a), 1.98-1.87 (m, 1H, H3b) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 179.3 (C1), 145.2, 143.2 (C6), 128.8, 128.3 (C8), 127.5, 127.0 (C9), 125.8, 125.6 (C7), 78.7 (C5), 60.6 (C4), 30.2 (C2), 21.6 (C3) ppm.

*Benzylcinchoninium bromide (**122a**)*[103]

Cinchonine (**112a**) (588 mg, 2.0 mmol, 1.0 eq.) was suspended in dry chloroform (12 mL) in a flame dried round-bottom flask containing molecular sieves (3Å). Benzyl bromide (250 µL, 360 mg, 2.1 mmol, 1.1 eq.) was added and the mixture was heated to reflux for 1 hour resulting in a dark red solution which was stirred at r.t. overnight. Molecular sieves were filtered off and the solvent was removed under reduced pressure. The residue was stirred with acetone/MeOH (10/1) for 5 min and filtered off. The solid was then stirred again in acetone for 15 min, filtered off and dried *in vacuo* to afford 598 mg of the PTC **122a** (1.3 mmol, 64 % yield) as a pale yellow solid (*mp* = 230°C, decomposition).



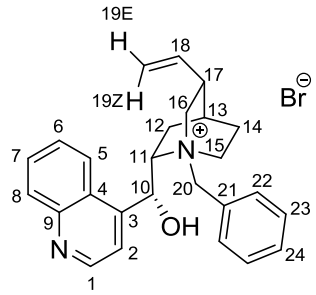
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.81 (d, $^{3}J_{H1,H2}$ = 4.5 Hz, 1H, H1), 8.30-8.24 (m, 1H, H8), 7.85 (d, $^{3}J_{H2,H1}$ = 4.5 Hz, 1H, H2), 7.58 (d, $^{3}J_{H22,H23}$ = 7.0 Hz, 1H, H22), 7.54-7.49 (m, 1H, H6), 7.19-7.12 (m, 1H, H24), 7.11-7.05 (m, 2H, H23), 7.04-6.94 (m, 2H, H5, H7), 6.59 (d, $^{3}J_{H10,H11}$ = 5.5 Hz, OH), 6.50-6.43 (m, 1H, H10), 6.14 (d, $^{2}J_{H20a,H20b}$ = 11.5 Hz, 1H, H20a), 5.81 (ddd, $^{3}J_{H18,H19Z}$ = 17.3 Hz, $^{3}J_{H18,H19E}$ = 10.3 Hz, $^{3}J_{H18,H17}$ = 7.0 Hz, 1H, H18), 5.34 (d, $^{2}J_{H20b,H20a}$ = 11.8 Hz, 1H, H20b), 5.20 (d, $^{3}J_{H19E,H18}$ = 10.3 Hz, 1H, H19E), 5.15 (d, $^{3}J_{H19Z,H18}$ = 17.3 Hz, 1H, H19Z), 4.48-4.38 (m, 1H, H16a), 4.24-4.07 (m, 2H, H11, H15a), 3.26 (t, $^{3}J_{H16b,H16a}$ = 11.5 Hz, 1H, H16b), 2.78-2.65 (m, 1H, H15b), 2.25 (q, ^{3}J = 8.8 Hz, 1H, H17), 2.11-2.01 (m, 1H, H14a), 1.77-1.63 (m, 3H, H12a, H12b, H13), 0.74-0.63 (m, 1H, H14b) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 149.4 (C1), 147.0 (C9), 144.3 (C3), 135.2 (C18), 134.0 (C22), 129.9 (C24), 129.4 (C6), 128.6 (C23), 128.2 (C7), 127.1 (C5), 126.9 (C21), 123.4 (C4), 123.2 (C8), 119.7 (C2), 118.0 (C19), 66.6 (C11), 65.6 (C10), 61.3 (C20), 56.2 (C16), 53.5 (C15), 38.0 (C17), 27.2 (C13), 23.7 (C14), 21.8 (C12) ppm.

HRMS (ESI^+) calcd. for $C_{26}H_{29}N_2O^+$ $[M]^+$: 385,2280; found 385,2261.

*Benzylcinchonidinium bromide (**122b**)*[103]

Cinchonidine (**112b**) (588 mg, 2.0 mmol, 1.0 eq.) was suspended in dry chloroform (12 mL) in a flame dried round-bottom flask containing molecular sieves. Benzyl bromide (250 µL, 360 mg, 2.1 mmol, 1.1 eq.) was added and the mixture was heated to reflux for 1 hour resulting in a dark red solution which was stirred at r.t. overnight. Molecular sieves were filtered off and the solvent was removed under reduced pressure. The residue was stirred with Et_2O/MeOH (2/1) overnight and filtered off. The solid was then stirred again in the same mixture (1h), filtered off and dried *in vacuo* to afford 559 mg of the PTC **122b** (1.2 mmol, 60 % yield) as a pale yellow solid (*mp* = 168-170°C).



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, $^{3}J_{H1,H2}$ = 4.5 Hz, 1H, H1), 8.16 (d, $^{3}J_{H8,H7}$ = 7.8 Hz, 1H, H8), 7.80 (d, $^{3}J_{H2,H1}$ = 4.5 Hz, 1H, H2), 7.68 (d, $^{3}J_{H22,H23}$ = 7.0 Hz, 1H, H22), 7.64 (d, ^{3}J = 7.8 Hz, 1H, H6), 7.24-7.11 (m, 5H, H5, H7, H23, H24), 6.57-6.48 (m, 2H, H10, OH), 5.90 (d, $^{2}J_{H20a,H20b}$ = 12.0 Hz, 1H, H20a), 5.55 (d, $^{2}J_{H20b,H20a}$ = 12.0 Hz, 1H, H20b), 5.41 (ddd, $^{3}J_{H18,H19Z}$ = 17.3 Hz, $^{3}J_{H18,H19E}$ = 10.3 Hz, $^{3}J_{H18,H17}$ = 5.8 Hz, 1H, H18), 5.26 (d, $^{3}J_{H19Z,H18}$ = 17.3 Hz, 1H, H19Z), 4.91 (d, $^{3}J_{H19E,H18}$ = 10.3 Hz, 1H, H19E), 4.67-4.56 (m, 1H, H15a), 4.12 (t, ^{3}J = 9.0 Hz,

1H, H11), 3.88 (d, $^3J_{H16a,H15b}$ = 12.8 Hz, 1H, H16a), 3.17-3.04 (m, 2H, H15b, H16b), 2.50-2.40 (m, 1H, H17), 2.14-2.00 (m, 1H, H14a), 1.93-1.83 (m, 2H, H12a, H13), 1.63-1.52 (m, 1H, H14b), 1.10-0.98 (m, 1H, H12b) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 149.5 (C1), 147.1 (C9), 144.5 (C3), 136.0 (C18), 134.0 (C22), 130.0 (C24), 129.6 (C6), 128.7 (C23), 128.5 (C7), 127.3 (C5), 126.9 (C21), 123.6 (C4), 122.9 (C8), 119.9 (C2), 117.8 (C19), 67.1 (C11), 65.0 (C10), 62.2 (C20), 60.1 (C16), 50.3 (C15), 37.8 (C17), 26.5 (C13), 25.1 (C14), 22.3 (C12) ppm.

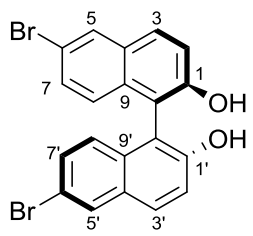
HRMS (ESI^+) calcd. for $C_{26}H_{29}N_2O^+$ $[M]^+$: 385,2280; found 385,2290.

4.5.2. Synthesis of the catalysts for the metal catalysis

4.5.2.1 Synthesis of the ligands

*6,6'-dibromo-BINOL (**75**)*[70]

In a flame-dried round-bottom flask was dissolved (*R*)-BINOL ((*R*)-**67**) (2.30 g, 8.0 mmol, 1 eq.) in 40 mL dry dichloromethane under nitrogen. The system was cooled to -78°C in an acetone/dry ice bath and bromine (1.1 mL, 3.41 g, 21.4 mmol, 2.7 eq.) dissolved in 4 mL DCM_{abs} was added dropwise over 20-25 min. The mixture was stirred for 2.5 h while warming up to room temperature and stirred for another half an hour at r.t. before the excess of Br_2 was destroyed with a saturated solution of sodium thiosulfate. The layers were separated and the organic phase was washed with brine and dried using magnesium sulfate. The solvents were removed under reduced pressure to afford 3.14 g of 6,6'-dibromo-BINOL (**75**) (7.1 mmol, 89 % yield) as a white brownish powder (mp = 95-100°C, Lit.[64a] 93-95°C).
R_f = 0.25 (PE/A, 5/1), $[\alpha]_D^{24}$ = - 132 ($CHCl_3$, c = 0.8)[70]



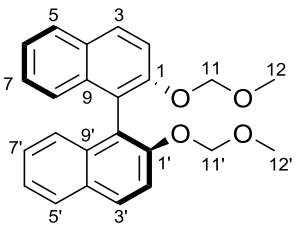
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, $^3J_{H5,H7}$ = $^3J_{H5',H7'}$ = 2.0 Hz, 2H, H5, H5'), 7.87 (d, $^3J_{H3,H2}$ = $^3J_{H3',H2'}$ = 9.0 Hz, 2H, H3, H3'), 7.37 (d, $^3J_{H2,H3}$ = $^3J_{H2',H3'}$ = 9.0 Hz, 2H, H2, H2'), 7.36 (dd, $^3J_{H7,H8}$ = $^3J_{H7',H8'}$ = 9.0 Hz, $^4J_{H7,H5}$ = $^4J_{H7',H5'}$ = 2.0 Hz, 2H, H7, H7'), 6.96 (d, $^3J_{H8,H7}$ = $^3J_{H8',H7'}$ = 9.0 Hz, 2H, H8, H8'), 5.10 (brs, 2H, OH) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 152.9 (C1, C1'), 131.9 (C4, C4'), 130.9 (C7, C7'), 130.6 (C3, C3'), 130.5 (C9, C9'), 130.4 (C5, C5'), 125.9 (C8, C8'), 119.0 (C2, C2'), 118.0 (C6, C6') 110.7 (C10, C10') ppm.

HRMS (ESI$^+$) calcd. for $C_{20}H_{12}Br_2NaO_2^+$ [M+Na]$^+$: 464.9101; found 464.9089.

*(S)-MOM-BINOL (**70**)*[64b]

In a flame dried reaction flask, NaH (3.77 g, 60% dispersion in mineral oil, 94.3 mmol, 3.0 eq.) was washed with THF_{abs} (2 x 50 mL) under nitrogen and stirred in 100 mL THF_{abs}. (*S*)-BINOL ((*S*)-**67**) (9.00 g, 31.4 mmol), dissolved in 50 mL THF_{abs} was added dropwise at 0°C to the stirred suspension of NaH in THF_{abs}. 30 min after the hydrogen evolution had ceased (approx. 1h), bromomethyl methyl ether (9.00 g, 72.0 mmol, 2.3 eq.) was added dropwise and the reaction was further stirred for 1 h at room temperature. It was then diluted with ether (200 mL), washed with a saturated solution of ammonium chloride, brine and then dried over magnesium sulfate. After the mixture was filtered and the solvents removed under vacuum the crude product was purified through flash chromatography on silica gel (A/PE, 1:15, R_f = 0.16) to yield 79 % of (*S*)-MOM-BINOL (**70**) (9.30 g, 24.8 mmol) as a white powder (*mp* = 99-102°C, Lit.[64a] 103-104°C). $[\alpha]_D^{24}$ = - 84.0 ($CHCl_3$, *c* = 1.0)[64b]



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, $^3J_{H3,H2}$ = $^3J_{H3',H2'}$ = 9.0 Hz, 2H, H3, H3'), 7.89 (d, $^3J_{H5,H6}$ = $^3J_{H5',H6'}$ = 8.3 Hz, 2H, H5, H5'), 7.60 (d, $^3J_{H2,H3}$ = $^3J_{H2',H3'}$ = 9.0 Hz, 2H, H2, H2'), 7.36 (ddd, $^3J_{H7,H8}$ = $^3J_{H7',H8'}$ = 8.0 Hz, $^3J_{H7,H6}$ = $^3J_{H7',H6'}$ = 6.5 Hz, $^4J_{H7,H5}$ = $^4J_{H7',H5'}$ = 1.3 Hz, 2H, H7, H7'), 7.27-7.22 (m, 2H, H6, H6'), 7.20-7.16 (m, 2H, H8, H8'), 5.11 (d, $^2J_{H11a,H11b}$ = $^2J_{H11'a,H11'b}$ = 6.8 Hz, 2H, H11a, H11a'), 5.00 (d, $^2J_{H11b,H11a}$ = $^2J_{H11'b,H11'a}$ = 6.8 Hz, 2H, H11b, H11b'), 3.16 (s, 6H, H12, H12') ppm.

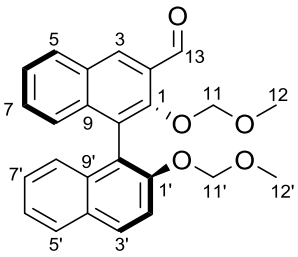
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 152.6 (C1, C1'), 134.0 (C4, C4'), 129.8 (C9, C9'), 129.4 (C3, C3'), 127.8 (C5, C5'), 126.3 (C6, C6'), 125.5 (C8, C8'), 124.0 (C7, C7'), 121.3 (C10, C10'), 117.2 (C2, C2'), 95.1 (C11, C11'), 55.8 (C12, C12') ppm.

LC-MS (ESI$^+$) for $C_{24}H_{22}NaO_4^+$ [M+Na]$^+$: 397.10.

*(S)-3-Formyl-MOM-BINOL (**71**)*[65]

In a thoroughly dried, 1 L single-necked, round-bottomed flask equipped with a magnetic stirring bar, fitted with a three way nitrogen inlet, was dissolved (*S*)-MOM-BINOL (**70**) (8.35 g, 22.3 mol, 1.0 eq.) in 350 mL anhydrous diethyl ether and the mixture was cooled to 0°C with an ice-water bath. Tetramethylethylenediamine (TMEDA) (3.3 mL, 2.55 g, 22.0 mmol, 1.0

eq.) was added and *n*-BuLi (2.5 M in hexane, 9.8 mL, 24.5 mmol, 1.1 eq.) was added dropwise by syringe to the stirring mixture over 10-15 min at 0°C. After stirring for 10 min at 0°C, the mixture was allowed to warm to room temperature and stirred for 2 h, which produced a grey slurry mixture. The mixture was cooled to 0°C again and dry N,N-dimethylformamide (DMF) (2.1 mL, 26.8 mmol, 1.2 eq.) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 h under nitrogen atmosphere. A 1M HCl (200 mL) solution was slowly added to the flask at 0°C and the aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. The residue was fully loaded onto a silica gel column and was eluted with PE/DCM/EA (20/3/1, R_f = 0.18) to give 68 % of (*S*)-3-Formyl-MOM-BINOL (**71**) (6.14 g, 15.2 mmol) as a yellow solid (*mp* = 121-122°C, Lit.[130] 110-112°C).
$[\alpha]_D^{24}$ = - 70.5 ($CHCl_3$, *c* = 1.1) (Lit.[130] - 83.5 ($CHCl_3$, *c* = 0.4))



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.59 (brs, 1H, H13), 8.57 (s, 1H, H3), 8.04 (d, $^3J_{H5,H6}$ = 8.3 Hz, 1H, H5), 8.00 (d, $^3J_{H3',H2'}$ = 9.0 Hz, 1H, H3'), 7.89 (d, $^3J_{H5',H6'}$ = 8.0 Hz, 1H, H5'), 7.61 (d, $J_{H2',H3'}$ = 9.3 Hz, 1H, H2'), 7.47 (ddd, $^3J_{H6,H5}$ = 8.0 Hz, $^3J_{H6,H7}$ = 6.8 Hz, $^4J_{H6,H8}$ = 1.0 Hz, 1H, H6), 7.38 (ddd, $^3J_{H7',H8'}$ = 8.3 Hz, $^3J_{H7',H6'}$ = 6.8 Hz, $^4J_{H7',H5'}$ = 1.3 Hz, 1H, H7'), 7.36 (ddd, $^3J_{H7,H8}$ = 8.5 Hz, $^3J_{H7,H6}$ = 6.8 Hz, $^4J_{H7,H5}$ = 1.3 Hz, 1H, H7), 7.28 (ddd, $^3J_{H6',H5'}$ = 8.0 Hz, $^3J_{H6',H7'}$ = 6.8 Hz, $^4J_{H6',H8'}$ = 1.3 Hz, 1H, H6'), 7.23 (d, $^3J_{H8,H7}$ = 8.5 Hz, 1H, H8), 7.15 (d, $^3J_{H8',H7'}$ = 8.3 Hz, 1H, H8'), 5.15 (d, $^2J_{H11'a,H11'b}$ = 7.0 Hz, 1H, H11a'), 5.04 (d, $^2J_{H11'b,H11'a}$ = 7.0 Hz, 1H, H11b'), 4.75 (d, $^2J_{H11a,H11b}$ = 5.8 Hz, 1H, H11a), 4.63 (d, $^2J_{H11b,H11a}$ = 5.8 Hz, 1H, H11b), 3.16 (s, 3H, H12'), 3.00 (s, 3H, H12) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 191.2 (C13), 153.8 (C1), 152.9 (C1'), 145.4 (C2), 137.0 (C9), 133.7 (C9'), 131.0 (C3), 130.3 (C3'), 130.17 (C5), 130.16 (C10), 129.6 (C4'), 129.0 (C7), 128.0 (C5'), 126.9 (C6'), 126.8 (C4), 126.0 (C8), 125.9 (C6), 125.2 (C8'), 124.3 (C7'), 119.5 (C10'), 116.4 (C2'), 100.2 (C11), 94.9 (C11'), 57.1 (C12), 56.0 (C12') ppm.

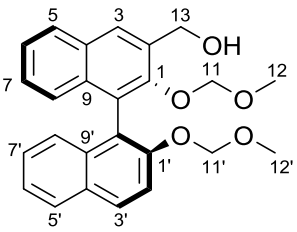
LC-MS (ESI^+) for $C_{25}H_{22}NaO_5^+$ $[M+Na]^+$: 425.15.

*(S)-3-hydroxymethyl-MOM-BINOL (**72**)*[66]

In a flame-dried round-bottom flask, was suspended (*S*)-3-Formyl-MOM-BINOL (**71**) (3.62 g, 9.0 mmol, 1.0 eq.) in anhydrous methanol (30 mL) under nitrogen atmosphere. The mixture was cooled down to 0°C and $NaBH_4$ (1.14 g, 30.2 mmol, 3.2 eq.) was added in small

portions. After stirring for 2 h, water (10 mL) was added to quench the reaction and the product was extracted with ethyl acetate (3 x 30 mL) and dried over $MgSO_4$. After filtration, the organic solvent was removed under reduced pressure to afford (*S*)-3-hydroxymethyl-MOM-BINOL (**72**) (3.30 g, 8.1 mmol) with 91 % yield as a white sticky solid.

R_f = 0.32 (PE/EE, 4/1), $[\alpha]_D^{24}$ = - 56.8 ($CHCl_3$, *c* = 1.1) (Lit.[66] + 63.5 ($CHCl_3$, *c* = 1.0 for the (*R*)-3-hydroxymethyl-MOM-BINOL)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00-7.97 (m, 2H, H3, H3'), 7.90, 7.89 (2 x d, $^3J_{H5,H6}$ = $^3J_{H5',H6'}$ = 8.0 Hz, 2H, H5, H5'), 7.60 (d, $J_{H2',H3'}$ = 9.0 Hz, 1H, H2'), 7.40, 7.37 (2 x ddd, $^3J_{H7,H8}$ = $^3J_{H7',H8'}$ = 8.3 Hz, $^3J_{H7,H6}$ = $^3J_{H7',H6'}$ = 6.8 Hz, $^4J_{H7,H5}$ = $^4J_{H7',H5'}$ = 1.3 Hz, 2H, H7, H7'), 7.30-7.20 (m, 2H, H6, H6'), 7.19-7.13 (m, 2H, H8, H8'), 5.12 (d, $^2J_{H11'a,H11'b}$ = 7.0 Hz, 1H, H11a'), 5.04 (d, $^2J_{H11'b,H11'a}$ = 7.0 Hz, 1H, H11b'), 4.98-4.86 (m, 2H, H13), 4.68 (d, $^2J_{H11a,H11b}$ = 6.0 Hz, 1H, H11a), 4.48 (d, $^2J_{H11b,H11a}$ = 6.0 Hz, 1H, H11b), 3.55-3.42 (m, 1H, OH), 3.25 (s, 3H, H12), 3.16 (s, 3H, H12') ppm.

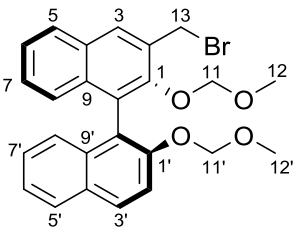
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 153.2 (C1), 152.7 (C1'), 134.3 (C9), 133.74 (C9'), 133.72 (C10), 131.0 (C2), 130.0, 129.1 (C3, C3'), 129.7 (C4'), 128.0, 127.9 (C5, C5'), 126.8, 126.2 (C6, C6'), 125.6, 125.3 (C8, C8'), 125.2, 124.2 (C7, C7'), 125.5 (C4), 120.4 (C10'), 116.5 (C2'), 99.3 (C11), 94.7 (C11'), 62.1 (C13), 57.0 (C12), 56.0 (C12') ppm.

LC-MS (ESI^+) for $C_{25}H_{24}NaO_5^+$ $[M+Na]^+$: 427.20.

*(S)-3-bromomethyl-MOM-BINOL (**73**)*[66]

To a solution of (*S*)-3-hydroxymethyl-MOM-BINOL (**72**) (1.82 g, 4.5 mmol, 1.0 eq.), dissolved in toluene (30 mL) and ethyl acetate (30 mL), was added triethylamine (1.4 mL, 9.4 mmol, 2.0 eq.) at 0°C. Mesyl chloride (0.45 mL, 6.0 mmol, 1.3 eq.) was slowly added and the mixture was stirred for 2 h before being filtrated. The filtrate was concentrated under reduced pressure and the residue was dissolved in DMF (20 mL) before lithium bromide (4.3 g, 50 mmol) was added triggering an exothermic reaction. DMF (10 mL) was added to dilute the viscous mixture and the reaction was stirred overnight at room temperature. Water was added (20 mL), the product was extracted with EA (3 x 50 mL), and after evaporation of the solvents, the residue was purified by silica gel column chromatography (EA/PE, 1/8, R_f = 0.22) to yield 87 % of (*S*)-3-bromomethyl-MOM-BINOL (**73**) (1.84 g, 3.9 mmol) as a greyish white powder (*mp* = 79-89°C).

$[\alpha]_D^{24}$ = - 60.5 ($CHCl_3$, *c* = 1.1) (Lit.[66] + 60.0 ($CHCl_3$, *c* = 1.0 for the (*R*)-3-bromomethyl-MOM-BINOL)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, H3), 7.99 (d, $^3J_{H3',H2'}$ = 9.0 Hz, 1H, H3'), 7.88 (d, $^3J_{H5,H6}$ = $^3J_{H5',H6'}$ = 8.3 Hz, 2H, H5, H5'), 7.60 (d, $J_{H2',H3'}$ = 9.0 Hz, 1H, H2'), 7.44-7.34 (m, 2H, H7, H7'), 7.32-7.22 (m, 2H, H6, H6'), 7.21-7.15 (m, 2H, H8, H8'), 5.13 (d, $^2J_{H11'a,H11'b}$ = 7.0 Hz, 1H, H11a'), 5.07 (d, $^2J_{H11'b,H11'a}$ = 7.0 Hz, 1H, H11b'), 4.90 (d, $^2J_{H13a,H13b}$ = 11.5 Hz, 1H, H13a), 4.88 (d, $^2J_{H13b,H13a}$ = 11.5 Hz, 1H, H13b), 4.71 (d, $^2J_{H11a,H11b}$ = 5.5 Hz, 1H, H11a), 4.48 (d, $^2J_{H11b,H11a}$ = 5.5 Hz, 1H, H11b), 3.20 (s, 3H, H12'), 3.04 (s, 3H, H12) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 152.8 (C1), 152.0 (C1'), 134.1 (C9), 133.8 (C9'), 131.0 (C2), 130.8 (C3), 130.7 (C10), 130.0 (C3'), 129.6 (C4'), 128.0, 127.9 (C5, C5'), 126.9, 126.8 (C6, C6'), 125.9 (C4), 125.8, 125.4 (C8, C8'), 125.3, 124.2 (C7, C7'), 120.2 (C10'), 116.4 (C2'), 99.2 (C11), 94.8 (C11'), 62.1 (C13), 56.8 (C12), 56.0 (C12') ppm.

LC-MS (ESI^+) for $C_{25}H_{23}BrNaO_4^+$ $[M+Na]^+$: 489.25.

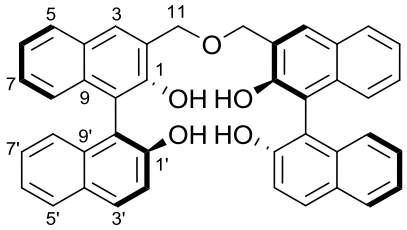
*(S,S)-linked-BINOL (**69**)*[66]

In a flame-dried round-bottom flask, was suspended NaH (0.28 g, 7.0 mmol, 2.0 eq.) in THF_{abs} (30 mL) and (*S*)-3-hydroxymethyl-MOM-BINOL (**72**) (1.42 g, 3.5 mmol, 1.0 eq.) dissolved in THF_{abs} (50 + 10 mL) was added slowly under nitrogen atmosphere. After stirring for 1 h at room temperature, (*S*)-3-bromomethyl-MOM-BINOL (**73**) (1.64 g, 3.5 mmol, 1.0 eq.), dissolved in THF_{abs} (40 + 10 mL), was added and the mixture was refluxed for 22 h. The reaction was quenched with water (30 mL) and after extraction with ethyl acetate (3 x 100 mL) and evaporation of the solvents, 2.56 g (3.2 mmol) of the crude (*S*,*S*)-linked-MOM-BINOL (**74**) were obtained as a white solid (91 % yield).

The solid was dissolved in methanol (170 mL) and 1mL of HCl (12 M) was added before the mixture was refluxed for one hour. Since no difference was seen on the TLC plate, 15 mL HCl were added in portions and the solution was stirred overnight at room temperature. Water was added and the aqueous phase was saturated with ammonium chloride and separated. The organic solvents were removed under reduced pressure and the residue was dissolved in DCM. The organic phase was washed with water (3 x 100 mL) until neutrality was reached, then washed with brine and dried over magnesium sulfate. The residue was

purified by silica gel column chromatography (EA/PE, 1/4, R_f = 0.14) to afford 1.08 g (1.7 mmol, 56 % yield) of (*S*,*S*)-linked-BINOL (**69**) as a brownish white solid (*mp* = 148°C, decomposition)

$[\alpha]_D^{24}$ = - 56.5 ($CHCl_3$, *c* = 1.0) (Lit.[66] + 60.6 ($CHCl_3$, *c* = 1.0 for the (*R*,*R*)-linked-BINOL)



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 2H, H3), 7.87 (d, $^3J_{H3',H2'}$ = 8.8 Hz, 1H, H3'), 7.82 (t, $^3J_{H5,H6}$ = $^3J_{H5',H6'}$ = 7.5 Hz, 4H, H5, H5'), 7.35-7.30 (m, H2, H6), 7.30-7.21 (m, 6H, H7, H7', H2'), 7.21-7.15 (m, 2H, H6), 7.10, 7.07 (2 x d, $J_{H8,H7}$ = $J_{H8',H7'}$ = 8.5 Hz, 4H, H8, H8'), 6.33 (brs, 2H, OH), 5.04 (brs, 2H, OH), 5.00 (s, 4H, H11) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 152.2 (C1), 151.8 (C1'), 133.6, 133.4 (C4, C4'), 130.8, 130.0 (C3, C3'), 129.3, 128.9 (C9, C9'), 128.3, 128.2 (C5, C5'), 127.4, 127.1 (C6, C6'), 125.5 (C2), 124.4 (C8, C8'), 124.2, 123.7 (C7, C7'), 117.7 (C2'), 112.5, 112.1 (C10, C10'), 70.3 (C11) ppm.

LC-MS (ESI^+) for $C_{42}H_{30}NaO_5^+$ $[M+Na]^+$: 637.50.

4.5.2.2 Formation of the catalysts

***GP 10: Preparation of BinAlH type catalysts according to the known procedure from NOYORI*[56c]**

In a flame dried round bottom flask, $LiAlH_4$ (308 mg, 8.1 mmol, 1.0 eq.) was suspended in anhydrous THF (5 mL, 1.62 M solution) under nitrogen atmosphere. Absolute EtOH (0.47 mL, 8.1 mmol, 1.0 eq.) was added dropwise and the mixture was stirred for 5 min at room temperature. (*S*)-BINOL ((*S*)-**67**) (2.29 g, 8.0 mmol, 1.0 eq.) was dried under vacuum for 3h at 70°C prior use. It was then dissolved in dry THF (13 mL, 0.6 M solution) and added dropwise to the LAH/EtOH mixture leading to a cloudy 0.38 M solution of (*S*)-BinAlH ((*S*)-**66a**).

(*R*)-BinAlH ((*R*)-**66a**) and TaddAlH (*R*,*R*)-**66b** were prepared according to the same procedure

GP 11: Preparation of $LiAlH_4$ based catalysts:

The ligand (1.1 or 2.2 eq.) was dried overnight under vacuum at 50-60°C. It was dissolved in the appropriate solvent (2.2 mL/mmol of ligand) under nitrogen atmosphere and added dropwise to a 1.0 M solution of $LiAlH_4$ (1.0 eq.) at room temperature. After stirring for 1h at room temperature, the catalyst was cooled to 0°C. The 0.15-0.25 M solution of the catalyst was then directly used for metal catalysed synthesis.

*Preparation of (R,R)-ALB ((R,R)-**66e**) and related catalysts*[53d]

Following the general procedure ***GP 11***, (*R*)-BINOL (**67**) (3.850 mg, 13.44 mmol, 2.1 eq.) dissolved in DT101 (30 mL) was mixed with a 1.0 M solution of LAH (6.4 mL, 6.4 mmol, 1.0 eq.) to give a 0.21 M solution of the catalyst (*R*,*R*)-ALB ((*R*,*R*)-**66e**) as cloudy suspension ready to be used for metal catalysis.

The same procedure was repeated with TADDOL (**68**), 6,6'-dibromo-BINOL (**75**), 3,3'-dibromo-BINOL (**76**), 6-bromo-BINOL(**77**) as ligands to form the catalysts **66o**, **66p**, **66q**, **66r** respectively.

Likewise, when $NaAlH_4$, $Ti(OiPr_4)$, $Al(Me)_3$ were used instead of LAH, the catalysts **66d 66i**, **66l**, **66m** could be obtained. By varying the ratio of BINOL and LAH, the catalysts **66c, 66f** and **66g** were prepared.

Preparation of the Al-Li-linked-BINOL catalyst

Following the general procedure ***GP 11***, (*S*,*S*)-linked-BINOL (**69**) (959 mg, 1.56 mmol, 1.1 eq.) dissolved in DT101 (12 mL) was mixed with a 1.0 M solution of LAH (1.4 mL, 1.4 mmol, 1.0 eq.) to give a 0.1 M solution of the catalyst **66n** as cloudy suspension ready to be used for metal catalysis.

*Preparation of the La-linked-BINOL catalyst (**66k**)*[53c]

(*S*,*S*)-linked-BINOL (**69**) (890 mg, 1.45 mmol, 1.0 eq.) was dried for 3h under vacuum, dissolved in anhydrous THF (10 mL) and cooled down to -78°C under nitrogen atmosphere. Lanthanum isopropoxide (458 mg, 1.45 mmol, 1.0 eq.) was suspended in anhydrous THF (8.5 mL) and added to the ligand. The cooling bath was removed and the mixture was stirred

at room temperature for 5h. The solvent was evaporated to afford the catalyst **66k** in quantitative yield.

*Preparation of the LLB catalyst (**66h**)*[51]

(*S*)-BINOL ((*S*)-**67**) (1.376 g, 4.8 mmol, 3.0 eq.) was dried under vacuum for 3h at 70°C, dissolved in dry THF (20 mL) and cooled to 0°C and *n*-BuLi (1.92 mL of a 2.5 M solution in hexane, 4.8 mmol, 3.0 eq.) was slowly added under nitrogen atmosphere to give a milky suspension. After stirring for 1h at 0°C, La(O*i*Pr)$_3$ was suspended in dry THF (4 mL) and added to the mixture which became clearer. It was stirred overnight at room temperature and used directly for metal-catalysed synthesis

*Preparation of $Al_3Li_3BINOL_3$ (**66h**)*[62]

(*R*)-BINOL ((*R*)-**67**) (1.840 g, 6.4 mmol, 2.0 eq.) was dried under vacuum for 3h at 70°C. After the flask had cooled down to room temperature, it was dissolved in THF_{abs} (12 mL) and slowly added under nitrogen atmosphere to a solution of $LiAlH_4$ (128 mg, 3.2 mmol, 1.0 eq.) in THF (2 mL). After stirring for 1h at room temperature, *n*-BuLi (1.28 mL of a 2.5 M solution in hexane, 3.2 mmol, 1.0 eq.) was slowly added and the solution was stirred overnight to give the catalyst ***66h***.

4.6. Syntheses of myrtucommulone derivatives

Due to the reasons explained in the introduction (§ 1.2, rotamer and tautomer mixture),[35a] the NMR analyses of MCA (**5**) and similar uncyclised derivatives are not always significant. Therefore, for some derivatives, only the ^{1}H-NMR spectrum is given. In general, the NMR spectra of the uncyclised derivatives cannot be precisely interpreted. The complete and precise peak assignments are made on the cyclised derivatives.

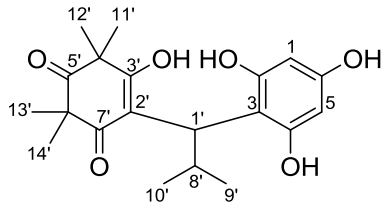
4.6.1. Syncarpic acid derivatives

4.6.1.1 Preparation and cyclisation of the semimyrtucommulone derivative 84

*Semimyrtucommulone derivative **84***

According to ***GP 8***, PG (**28**) (60 mg, 0.48 mmol, 1.0 eq.) was dissolved in a 1/1 mixture of DCM_{abs}/THF_{abs} (2 mL) and added dropwise to the freshly prepared (*S*,*S*)-ALB ((*S*,*S*)-**66e**) (9.1 mL of a 0.18 M solution in DT101, 1.6 mmol, 3.3 eq.). IBSA (0.9 mL of a 0.83 M solution in DT101, 0.75 mmol, 1.6 eq.) was added dropwise to the mixture at 0°C. After 1.5h stirring at 0°C, the reaction was quenched and the product extracted and dried. After purification by column chromatography on silica gel (A/PE, 1/2 (400 mL)-1/1 (600 mL)-3/2 (600 mL), R_f = 0.13 (A/PE, 1/1)), 130 mg of the semimyrtucommulone derivative **84** (0.36 mmol, 75 % yield) were obtained as a pale brownish yellow powder (mp = 171-172°C, decomposition).

HRMS (ESI$^+$) calcd. for $C_{20}H_{27}O_6^+$ $[M+H]^+$: 363.1807, found: 363.1798.

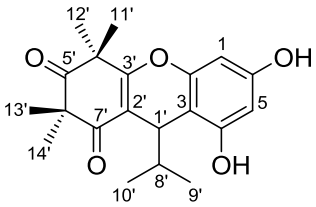


^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 5.82-5.79 (m, 1H, H3, H5), 5.79-5.76 (m, 1H, H3, H5), 4.21, 4.16 (2 x sept, $^{3}J_{H2''',H3'''\text{-}H4'''}$ = 6.9 Hz, 1H, H2'''), 3.85 (d, $^{3}J_{H1',H8'}$ = 11.0 Hz, 1H, H1'), 3.25 (dsept, $^{3}J_{H8',H1'}$ = 11.0 Hz, $^{3}J_{H8',H9'\text{-}H10'}$ = 6.5 Hz, 1H, H8'), 1.30–1.19 (m, 12H, H11', H12', H13', H14'), 0.82 (d, $^{3}J_{H9',H8'}$ = 6.5 Hz, 3H, H9'), 0.71 (d, $^{3}J_{H10',H8'}$ = 6.5 Hz, 3H, H10') ppm.

^{13}C-NMR (101 MHz, CO(CD$_3$)$_2$): δ = 218.1 (C5'), 198.9, 197.5 (C7'), 159.8, 159.7, 158.2 (C4, C6, C3', C2), 114.2 (C3), 112.8 (C2'), 106.8, 106.2 (C1), 98.2, 97.3 (C3, C5), 53.4 (C4', C6'), 43.0 (C-1'), 27.6 (C8'), 27.0, 26.6, 25.9 (C11', C12', C13', C14'), 23.9, 23.8 (C9', C10') ppm.

*Tricyclic semimyrtucommulone derivative **85** (28 % ee)*

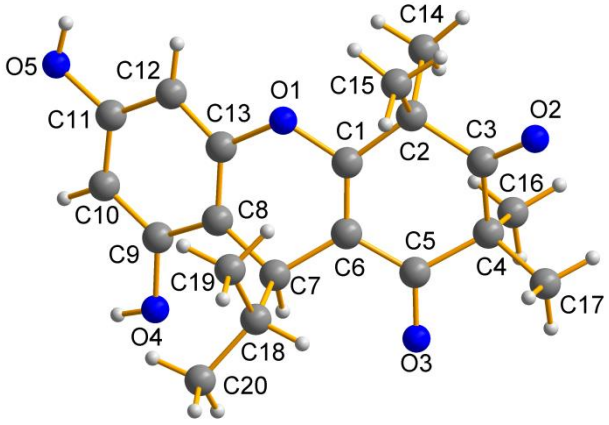
Following the ***GP 9*** procedure, semimyrtucommulone derivative **84** (80 mg, 0.22 mmol, 1.0 eq.) and pTsOH (126 mg, 0.66 mmol, 3.0 eq.) were heated to 95 °C in toluene (8 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9, R_f = 0.13), 37 mg of the cyclised derivative **85** (0.11 mmol, 49 % yield). It was dissolved in a DCM/PE (1/9) mixture and evaporated under reduced pressure to afford a white powder (*mp* > 245°C).



^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 8.66 (brs, 1H, OH), 8.44 (brs, 1H, OH), 6.31, (d, $^4J_{H1,H5}$ = 2.3 Hz, 1H, H1), 6.21, (d, $^4J_{H5,H1}$ = 2.3 Hz, 1H, H5), 4.26 (d, $^3J_{H1',H8'}$ = 3.8 Hz, 1H, H1'), 1.93 (dsept, $^3J_{H8',H1'}$ = 3.8 Hz, $^3J_{H8',H9'-10'}$= 6.8 Hz, 1H, H8'), 1.55 (s, 3H, H12'), 1.42 (s, 3H, H14'), 1.36 (s, 3H, H11'), 1.30 (s, 3H, H13'), 0.79 (d, $^3J_{H9',H8'}$ = 7.0 Hz, 3H, H9'), 0.75 (d, $^3J_{H10',H8'}$ = 7.0 Hz, 3H, H10') ppm.

^{13}C-NMR (101 MHz, CO(CD$_3$)$_2$): δ = 213.8 (C5'), 198.8 (C7'), 170.3 (C3'), 158.9, 157.5 (C4, C6), 155.5 (C2), 113.2 (C2'), 105.4 (C3), 101.2 (C1), 96.3 (C5), 57.3 (C6'), 49.0 (C4'), 36.6 (C8'), 33.9 (C1'), 26.6 (C11', C12'), 25.7, 25.3 (C13', C14'), 20.7, 20.1 (C9', C10') ppm.

Crystal Structure: (for the complete data see Appendix 3)



Exp. Data Tab. 3 Crystal data and structure refinement for **85** (sh3169).

Identification code	sh3169
Empirical formula	C20 H24 O5
Formula weight	344.39
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic

Space group	Pna2(1)	
Unit cell dimensions	a = 11.642(3) Å	α= 90°.
	b = 17.302(4) Å	β= 90°.
	c = 9.182(2) Å	γ = 90°.
Volume	1849.5(8) $Å^3$	
Z	4	
Density (calculated)	1.237 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	736	
Crystal size	0.48 x 0.07 x 0.05 mm^3	
Theta range for data collection	2.11 to 27.52°.	
Index ranges	-14<=h<=15, -13<=k<=22, -7<=l<=11	
Reflections collected	8555	
Independent reflections	3300 [R(int) = 0.1492]	
Completeness to theta = 27.52°	99.3 %	
Absorption correction	None	
Max. and min. transmission	0.9953 and 0.9592	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3300 / 1 / 233	
Goodness-of-fit on F^2	0.951	
Final R indices [I>2sigma(I)]	R1 = 0.0744, wR2 = 0.1092	
R indices (all data)	R1 = 0.2271, wR2 = 0.1524	
Absolute structure parameter	2(3)	
Extinction coefficient	0.0081(10)	
Largest diff. peak and hole	0.337 and -0.311 e.$Å^{-3}$	

4.6.1.2 Preparation of norsemimyrtucommulone (NSMC) (8)

According to general procedure *GP 6*[88]

According to the general procedure ***GP 6***, isobutyryl phloroglucinol (IBPG) (**25**) (98 mg, 0.50 mmol, 1.0 eq.), sparteine (**111**) (115 µL, 0.50 mmol, 1.0 eq.), and isobutylidene syncarpic acid (IBSA) (**31**) (354 mg, 1.50 mmol, 1.5 eq.), were mixed in DCM (4 mL) and stirred at room temperature for 19h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/2 (400 mL), 1/1 (1000 mL), R_f = 0.15 (A/P, 1/1)) to afford 209 mg of NSMC (**8**) (0.48 mmol, 96 % yield) as a brownish yellow powder. $[\alpha]_D^{24}$ = 0.0 (MeOH, *c* = 2.0)

NSMC (**8**) was also synthesised according to ***GP 6*** using piperidine (Tab. 13, entry 2), poly-L-leucine (PLL) (§ 2.4.2.3) and cinchonidine (**112b**) (Tab. 15, entry 8, 10) as catalysts.

Attempts with Poly-L-Leucine

IBPG (**25**) (98 mg, 0.50 mmol, 1.0 eq.) was dissolved in THF_{abs} (6 mL) and NaH (52 mg, 60 % dispersion on mineral oil, 1.30 mmol, 2.5 eq.) was added. After stirring for 10 min at room temperature, PLL (324 mg, ≈ 5.6 eq.) was added and the mixture was stirred for another 15 min. The solvent was removed under reduced pressure until a brownish powder formed. The residue was stirred in DCM_{abs} (2 mL) and IBSA (**31**), dissolved in DCM (2 mL), was added at 0°C to the mixture. After 1h, the completion of the reaction was observed on TLC and the reaction was hydrolysed with a saturated solution of ammonium chloride. The crude product was extracted with diethyl ether (3 x 20 mL) and then dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the purification on silica gel column chromatography (A/PE, 1/2 (400 mL), 1/1 (1000 mL)) afforded 181 mg of NSMC (**8**) (0.42 mmol, 82 % yield) as a yellow powder.

With a phase transfer catalyst (PTC)[102]

According to the general procedure ***GP 7***, isobutyryl phloroglucinol (IBPG) (**25**) (100 mg, 0.51 mmol, 1.0 eq.) was mixed with the PTC **122a** (302 mg, 0.65 mmol, 1.3 eq.) and KF (38 mg, 0.65 mmol, 1.3 eq.).The mixture was brought to 0°C before isobutylidene syncarpic acid (IBSA) (**31**) (183 mg, 0.77 mmol, 1.5 eq.) was added. After stirring for 1h, the reaction was worked up (use of $CaCl_2$ to catch fluoride ions) and the product was purified through column chromatography on silica gel (A/PE, 1/2 (400 mL), 1/1 (1000 mL)) to afford 190 mg of NSMC (**8**) (0.44 mmol, 86 % yield) as a pale yellow powder.

Typical metal catalysed synthesis

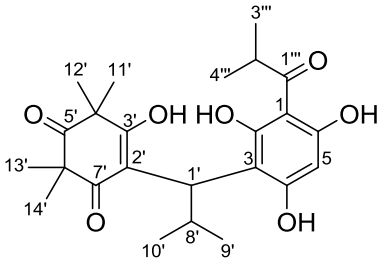
According to ***GP 8***, IBPG (**25**) (390 mg, 2.0 mmol, 1.0 eq.) was dissolved in DT101 (8 mL) and added dropwise to the freshly prepared (*R*,*R*)-ALB ((*R*,*R*)-**66e**) (36.4 mL of a 0.18 M solution in DT101, 6.4 mmol, 3.2 eq.). IBSA (654 mg, 2.77 mmol, 1.4 eq.) was dissolved in DT101 (5.5 mL, 0.68 M solution) and added dropwise to the mixture at 0°C. After 2h stirring at 0°C, the reaction was quenched and the product extracted and dried. After purification by column chromatography on silica gel (A/PE, 1/2 (400 mL), 1/1 (1000 mL), R_f = 0.15 (A/P, 1/1)), 661 mg of NSMC (**8**) (1.53 mmol, 81 % yield) were obtained as a pale yellow powder.
$[\alpha]_D^{24}$ = + 16.1 (MeOH, *c* = 2.98).

HRMS (ESI^+) calcd. for $C_{24}H_{32}NaO_7^+$ $[M+Na]^+$: 455.2045, found: 455.2030.

The same procedure was repeated for every attempted metal-catalysed reaction, changing the catalyst, the number of equivalents of the catalyst, the solvent, and the temperature.

Characterisation

Since the NMR spectra showed no difference relatively to the method used for the synthesis of NSMCs (**8**), only one NMR spectrum is displayed here. Two sets of peaks are observed in both ^{1}H and ^{13}C NMR-spectra probably related to two different rotamers.[57]



^{1}H-NMR (500 MHz, $CO(CD_3)_2$): δ = 14.36 (brs, 0.46H, OH), 13.75-13.60 (brs, 1H, OH), 13.49 (brs, 0.31H, OH), 13.04 (brs, 0.35H, OH), 5.67, 5.66 (2 x s, 1H, H5), 4.21, 4.16 (2 x sept, $^{3}J_{H2''',H3'''\text{-}H4'''}$ = 6.9 Hz, 1H, H2'''), 3.85, 3.82 (2 x d, $^{3}J_{H1',H8'}$ = 11.0 Hz, 1H, H1'), 3.30, 3.25 (2 x dsept, $^{3}J_{H8',H1'}$ = 11.0 Hz, $^{3}J_{H8',H9'\text{-}H10'}$ = 6.3 Hz, 1H, H8'), 1.31-1.25 (m, 6H, H11', H12', H13', H14'), 1.22-1.17 (s, 6 H, (m, 6H, H11', H12', H13', H14'), 1.14, 1.13 (2 x d, $J_{H3''',H2'''}$ = 6.9 Hz, 3H, H3'''), 1.09, 1.08 (2 x d, $J_{H4''',H2'''}$ = 6.9 Hz, 3H, H4'''), 0.83, 0.82 (2 x d, $^{3}J_{H9',H8'}$ = 6.3 Hz, 3H, H9'), 0.71, 0.67 (2 x d, $^{3}J_{H10',H8'}$ = 6.3 Hz, 3H, H10') ppm.

^{13}C-NMR (125 MHz, $CO(CD_3)_2$): δ = 218.7 (C5'), 212.1, 211.8 (C1'), 195.0, 192.5 (C7'), 167.39, 166.36 (C4), 166.64, 166.58 (C6), 164.1, 163.5 (C3', C2), 114.2, 113.7 (C3), 113.3, 113.1 (C2'), 106.8, 106.2 (C1), 98.4, 97.4 (C5), 56.5, 53.54, 53.4, 53.34, 53.26 (C4', C6'), 43.6, 43.4 (C-1'), 40.25, 40.18 (C2'''), 27.5, 27.19 (C8'), 27.3, 27.24, 26.9, 26.8, 26.72, 26.65 (C11', C12', C13', C14'), 23.9, 23.8, 23.76, 23.74, 23.68 (C4''', C3'''), 21.4, 21.2 (C9'), 20.7, 20.3 (C10') ppm.

NSMC (**8**) was dissolved in DCM with a drop of acetone and precipitated with PE before being evaporated under vacuum to obtain a pale yellow powder (*mp* = 170°C, decomposition).

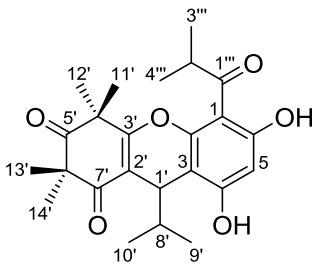
HRMS (ESI^+) calcd. for $C_{24}H_{33}O_7^+$ $[M+H]^+$: 433.2221, found: 433.2220.

4.6.1.3 Preparation of myrtucommulone B (6)

Following the ***GP 9*** procedure, NSMC (**8**) (70 mg, 0.16 mmol, 1.0 eq.) and pTsOH (93 mg, 0.49 mmol, 3.0 eq.) were heated to 95°C in toluene (7 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9, R_f = 0.08), 43 mg of MCB (**6**) (0.10 mmol, 65 % yield). It was dissolved in a DCM/PE (1/9) mixture and evaporated under reduced pressure to afford a white foam.

In the case of MCB (**6**), the experimental properties are dependent on the *ee* of the sample. For this reason two examples are given. In the 2% *ee* sample, two very close sets of peaks can be observed in ^{1}H-NMR but also on some peaks of the ^{13}C-NMR spectrum. Likewise, in the 72 % *ee* sample, two more distinguishable sets of peaks are visible but sometimes not in the ^{13}C-NMR spectrum where the concentration of the less concentrated peak is too low.

Sample with 2% *ee*



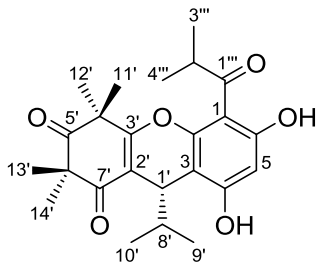
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 13.39 (s, 1H, C6- OH), 7.71 (brs, 1H, C4-OH), 6.339, 6.336 (2 x s, 1H, H5), 4.40, 4.39 (d, $^{3}J_{H1',H8'}$ = 3.5 Hz, 1H, H1'), 3.90 (sept, $^{3}J_{H2''',H3'''-H4'''}$ = 6.8 Hz, 1H, H2'''), 1.92 (dsept, $^{3}J_{H8',H1'}$ = 3.5 Hz, $^{3}J_{H8',H9'-10'}$ = 6.8 Hz, 1H, H8'), 1.62 (s, 3H, H12'), 1.46 (s, 3H, H14'), 1.43 (s, 3H, H11'), 1.40 (s, 3H, H13'), 1.25 (d, $^{3}J_{H4''',H2'''}$ = 6.5 Hz, 3H, H4'''), 1.24 (d, $^{3}J_{H3''',H4'''}$ = 7.0 Hz, 3H, H3''), 0.83, 0.82 (2 x d, $^{3}J_{H9',H8'}$ = 7.3 Hz, 3H, H9'), 0.79 (d, $^{3}J_{H10',H8'}$ = 7.0 Hz, 3H, H10') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 211.8 (C5'), 208.9 (C1'''), 199.2, 199.1 (C7'), 168.41, 168.37 (C3'), 164.7 (C4), 159.9 (C6), 153.4 (C2), 112.1 (C2'), 103.9 (C3), 103.7 (C1), 100.6 (C5), 56.1 (C6'), 47.3 (C4'), 39.6 (C2'''), 34.8 (C8'), 31.4 (C1'), 25.2, 25.0 (C12'), 24.97 (C14'), 24.94 (C11'), 24.2 (C13'), 20.9 (C3'''), 18.9 (C9'), 18.6 (C10'), 17.7 (C4''') ppm.

HRMS (ESI$^+$) calcd. for $C_{24}H_{31}O_6^+$ $[M+H]^+$: 415.2121, found: 415.2112, mp = 85-95°C

Sample with 72% *ee: (-)-(S)-MCB (6)*

In this NMR spectrum, the “self induced non-equivalence” discussed in § 2.3.2.6 (NMR particularity) can be clearly observed.



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 13.40 (s, 1H, C6-OH), 7.98 (brs, 1H, C4-OH), 6.36 (s, 0.13H, H5), 6.33 (s, 0.82H, H5), 4.42 (d, $^{3}J_{H1',H8'}$ = 3.8 Hz, 0.84H, H1’), 4.39 (d, $^{3}J_{H1',H8'}$ = 3.8 Hz, 0.14H, H1’), 3.95-3.83 (m, 1H, H2’’’), 1.92 (dsept, $^{3}J_{H8',H1'}$ = 3.8 Hz, $^{3}J_{H8',H9'\text{-}10'}$= 6.8 Hz, 1H, H8’), 1.62 (s, 3H, 12’), 1.46 (s, 3H, H14’), 1.44 (s, 0.50H, H11’), 1.42 (s, 2.71H, H11’), 1.39 (s, 3H, H13’), 1.26 (d, $^{3}J_{H4''',H2'''}$ = 6.5 Hz, 3H, H4’’’), 1.24 (d, $^{3}J_{H3''',H2'''}$ = 7.0 Hz, 3H, H3’’’), 0.84 (d, $^{3}J_{H8',H9'}$ = 6.8 Hz, 3H, H9’), 0.80 (d, $^{3}J_{H8',H10'}$ = 6.8 Hz, 3H, H10’) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 211.8 (C5’), 208.9 (C1’’’), 199.3 (C7’), 168.5, 168.3 (C3’), 164.72, 164.69 (C4), 160.02, 159.97 (C6), 153.4, 153.3 (C2), 112.2, 112.1 (C2’), 103.9, 103.8 (C3), 103.63, 103.58 (C1), 100.6 (C5), 56.14, 56.11 (C6’), 47.3 (C4’), 39.6 (C2’’’), 34.8, 34.7 (C8’), 31.41, 31.37 (C1’), 25.1 (C12’), 25.03 (C14’), 24.95, 24.92 (C11’), 24.15, 24.10 (C13’), 20.9 (C3’’’), 18.91, 18.86 (C9’), 18.6, 18.5 (C10’), 17.7 (C4’’’) ppm.

HRMS (ESI^+) calcd. for $C_{24}H_{31}O_6^+$ $[M+H]^+$: 415.2121, found: 415.2112 (different measure from the one above), mp = 168-174°C, $[\alpha]_D^{24}$ = - 117.1 ($CHCl_3$, c = 2.92).

4.6.1.4 Preparation of myrtucommulone A

One-Pot Method

According to the general procedure ***GP 5***, isobutyryl phloroglucinol (IBPG) (**25**) (98 mg, 0.50 mmol, 1.0 eq.), proline (**90**) (57 mg, 0.50 mmol, 1.0 eq.), syncarpic acid (**27**) (550 mg, 3.02 mmol, 6.0 eq.) and isobutyraldehyde (**26**) (0.36 mL, 3.94 mmol, 8.0 eq.) were mixed in ethanol (4 mL) and stirred at room temperature for 24 h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/2, R_f = 0.15) to afford 219 mg of MCA (5) (0.33 mmol, 66 % yield) as a pale yellow powder (mp = 160-185°C, Lit.[35a] 150-180°C). $[\alpha]_D^{24}$ = 0.0 (MeOH, c = 3.0)

HRMS (ESI^+) calcd. for $C_{38}H_{53}O_{10}^+$ $[M+H]^+$: 669.3638, found: 669.3666.

According to the general procedure *GP 6*

a) *High yielding unstereoselective synthesis*

According to the general procedure ***GP 6***, isobutyryl phloroglucinol (IBPG) (**25**) (98 mg, 0.50 mmol, 1.0 eq.), cinchonine (**112a**) (147 mg, 0.5 mmol, 1.0 eq.), and isobutylidene syncarpic acid (IBSA) (**31**) (732 mg, 3.1 mmol, 6.2 eq.), were mixed in MeOH (5 mL) and stirred at room temperature for 27h. The reaction was worked-up and the product was purified through column chromatography on silica gel (A/PE, 1/2) to afford 309 mg of MCA (**5**) (0.46 mmol, 92 % yield) as a pale yellow powder. $[\alpha]_D^{24}$ = 0.0 (MeOH, *c* = 2.0) This sample has an *ee* of 7% and a *de* of 2 %.

b) *Diastereoselective synthesis*

According to the general procedure ***GP 6***, isobutyryl phloroglucinol (IBPG) (**25**) (98 mg, 0.50 mmol, 1.0 eq.), cinchonidine (**112b**) (73.6 mg, 0.25 mmol, 0.5 eq.), and isobutylidene syncarpic acid (IBSA) (**31**) (520 mg, 2.2 mmol, 4.4 eq.), were mixed in MeOH (5 mL) and stirred at room temperature for 91h. The reaction was worked-up and the product was purified through column chromatography on silica gel (A/PE, 1/2) to afford 151 mg of MCA (5) (0.23 mmol, 46 % yield) as a pale yellow powder. $[\alpha]_D^{24}$ = + 2.0 (MeOH, *c* = 2.05). This sample showed an *ee* of 28 % and *de* of 82 %. *mp* = 162-185°C (Lit.[35a] 150-180°C)

This procedure was repeated with piperidine, pyrrolidine, proline (**90**), Phe, His, Glu, Tyr, Trp, CN (**112a**), Q (**112c**), CPN (**118**), Bz-Q (**121**), Bz-CPN (**120**), brucine (**114**), ephedrine (**113**), and HODPP (**115**).

HRMS (ESI^+) calcd. for $C_{38}H_{53}O_{10}^+$ $[M+H]^+$: 669.3638, found: 669.3649.

With a phase transfer catalyst (PTC)[100,129]

According to the general procedure ***GP 7***, isobutyryl phloroglucinol (IBPG) (**25**) (98 mg, 0.50 mmol, 1.0 eq.) was mixed with the PTC **122b** (116 mg, 0.25 mmol, 0.5 eq.) and a 1.0 M KOH solution (1.0 mmol, 2.0 eq.) was added. After the addition of isobutylidene syncarpic acid (IBSA) (**31**) (570 mg, 2.4 mmol, 4.8 eq.), the mixture was stirred at room temperature for 67h before being worked-up. The crude product was purified through column chromatography on silica gel (A/PE, 1/2) to afford 309 mg of MCA (**5**) (0.46 mmol, 92 % yield) as a pale yellow powder.

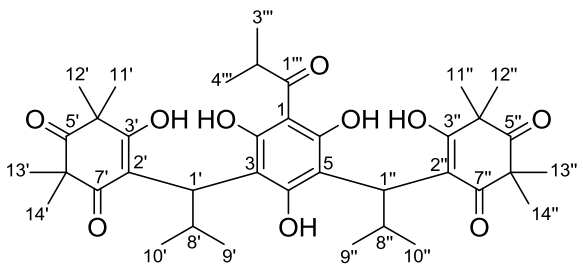
Typical metal catalysed synthesis[57]

According to ***GP 8***, (-)-(*R*)-NSMC ((*R*)-**8**) (183 mg, 0.42 mmol, 1.0 eq.) was dissolved in DT101 (0.8 mL) and added dropwise to the freshly prepared (*R*,*R*)-ALB ((*R*,*R*)-**66e**) (7.6 mL of a 0.18 M solution in DT101, 1.38 mmol, 3.3 eq.). IBSA (1.1 mL of a 0.73 M solution, 0.80 mmol, 2.0 eq.) was added dropwise to the mixture at 0°C and the reaction was stirred at this temperature for 10h then at room temperature for 6h. The reaction was quenched and the product extracted and dried. After purification by column chromatography on silica gel (A/PE, 1/2), 216 mg of MCA (**5**) (0.32 mmol, 77 % yield) were obtained as a pale yellow powder with 70% *ee*. $[\alpha]_D^{24}$ = + 22.1 (MeOH, *c* = 2.08).

HRMS (ESI^+) calcd. for $C_{38}H_{53}O_{10}^+$ $[M+H]^+$: 669.3638, found: 669.3628.

Characterisation

Since the NMR spectra showed no difference relatively to the method used for the synthesis of MCA (**5**), only one NMR spectrum is displayed here.



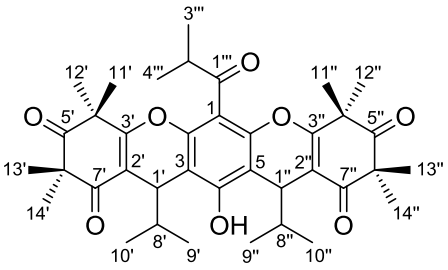
^{1}H-NMR (400 MHz, $CO(CD_3)_2$): δ = 15.80 (brs, 0.38H, OH), 15.41 (brs, 0.51H, OH), 14.54-14.08 (m, 0.33H, OH), 13.93-13.59 (m, 0.11H, OH), 13.14-12.77 (m, 0.85H, OH), 4.47-4.26 (m, 0.58H), 4.22 (d, ^3J =11.3 Hz, 1.08H, H1', H1''), 4.16-4.03 (m, 0.96H, H2'''), 3.81 (dd, ^3J=6.0 Hz, J= 2.0 Hz, 0.08H), 3.28-2.99 (m, 1.78H, H8', H8''), 1.47-1.06 (m, 30.0H, H3''' H4''', H11', H12', H13', H14'', H11'', H12'', H13'', H14''), 0.89-0.64 (m, 12H, H9', H10', H9'', H10'') ppm.

^{13}C-NMR (101 MHz, $CO(CD_3)_2$): δ = 216.1, 212.9, 200.0, 180.6, 180.5, 162.81, 162.78, 157.5, 148.5, 147.4, 119.8, 119.7, 119.4, 118.8, 112.3, 101.9, 97.5, 92.4, 91.4, 55.4, 51.2, 41.4, 40.4, 36.4, 28.3, 28.1, 26.9, 26.8, 26.2, 26.0, 23.6, 23.43, 23.38, 23.34, 21.1 ppm.

4.6.1.5 Preparation of pentacyclic myrtucommulone A (7)

Following the ***GP 9*** procedure, MCA (**5**) (150 mg, 0.22 mmol, 1.0 eq.) and pTsOH (270 mg, 1.42 mmol, 6.5 eq.) were heated to 95°C in toluene (14 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9), 116 mg of PMCA (**7**) (0.18 mmol, 83 % yield). This white foam is obtained as a mixture of a *linear* cyclised MCA: *l*-PMCA (*l*-**7**) (104 mg, 0.16 mmol, 75 % yield, R_f = 0.19), and an *angular* cyclised MCA: *a*-PMCA (*a*-**7**) (11 mg, 0.02 mmol, 8 % yield, R_f = 0.36).

***l*-PMCA (*l*-7): sample with a *d.r.* of 56:44 (*meso:rac*)**

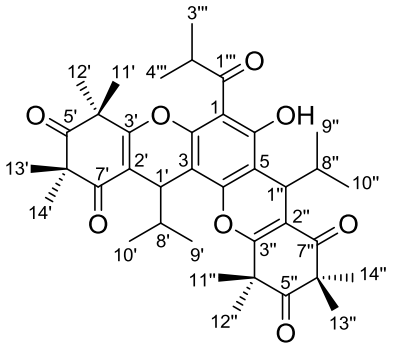


^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 8.07 (brs, 0.55 H, OH-*meso*), 7.91 (brs, 0.42H, OH-*rac*), 4.64 (d, $^3J_{H1',H8'}$ = $^3J_{H1'',H8''}$ = 3.8 Hz, 1.04H, H1', H1'', *meso*), 4.61 (d, $^3J_{H1',H8'}$ = $^3J_{H1'',H8''}$ = 3.5 Hz, 0.79H, H1', H1'', *rac*), 3.19, 3.17 (2 x sept, $^3J_{H2''',H3'''}$ = $^3J_{H2''',H4'''}$ = 7.0 Hz, $^3J_{H2''',H3'''}$ = $^3J_{H2''',H4'''}$ = 6.8 Hz, 1H, H2'''), 2.03-1.90 (m, 2H, H8', H8''), 1.54 (s, 2.40H, H12', H11'', *rac*), 1.52 (s, 3.06H, H12', H12'', *meso*), 1.48-1.40 (m, 12H, *rac:* H11', H12'', H13', H14'', H13'', H14', *meso:* H13', H13''), 1.38 (s, 6H, H11', H11'', *meso*), 1.36 (s, 6H, H14', H14'', *meso*), 1.29 (d, J = 7.0 Hz, 3H, H3''', H4''', *meso*), 1.24 (t, J = 7.5 Hz, 3H, H3''', H4''', *rac*), 0.89-0.85, 0.80-0.74 (2 x m, 3.79H, 8.25H, H9', H9'', H10', H10'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 211.78, 211.75 (C5', C5''), 205.3 (C1'''-*meso*), 204.3 (C1'''-*rac*), 198.9 (C7', C7'', *rac*), 198.8 (C7', C7'', *meso*), 169.2 (C3', C3'', *meso*), 168.9 (C3', C3'', *rac*), 152.5 (C4, *meso*), 152.1 (C4, *rac*), 147.5 (C2, C6, *rac*), 147.45 (C2, C6, *meso*), 111.3 (C3, C5, *meso*), 110.9 (C3, C5, *rac*), 110.4 (C1, *meso*), 110.0 (C1, *rac*), 108.8 (C2', C2'', *rac*), 108.5 (C2', C2'', *meso*), 55.9 (C6', C6'', *meso*), 55.8 (C6', C6'', *rac*), 47.53, 47.51 (C4', C4''), 43.3 (C2''', *meso*), 42.7 (C2''', *rac)*, 35.10, 35.09 (C8', C8''), 32.4 (C1', C1'', *meso*), 32.2 (C1', C1'', *rac*), 25.2 (C12', C11'', *rac*), 24.88, 24.85, 24.78, 24.76 (*meso*: C11', C11'', C12', C12'', C14', C14'', *rac:* C12'', C11', C13', C14''), 24.3 (C14', C13'', *rac*), 24.2 (C13', C13'', *meso*), 19.3, 19.1 (C10', C10''), 18.8, 18.5 (C9', C9''), 18.0, 17.7 (C3''', C4''') ppm.
15

HRMS (ESI$^+$) calcd. for $C_{38}H_{49}O_8^+$ $[M+H]^+$: 633.3422, found: 633.3415.
$[\alpha]_D^{24}$ = 0.0 ($CHCl_3$, *c* = 0.7)

***a*-PMCA (*a*-7):**



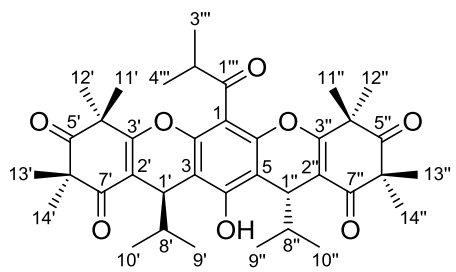
^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 13.56 (s, 0.12H, OH), 13.29 (s, 0.78 H, OH), 4.48 (d, $^{3}J_{H1',H8'}$ = 2.8 Hz, 0.12H, H1'), 4.43 (d, $^{3}J_{H1'',H8''}$ = 3.3 Hz, 0.17H, H1''), 4.41 (d, $^{3}J_{H1',H8'}$ = 3.3 Hz, 0.76H, H1'), 4.37 (d, $^{3}J_{H1'',H8''}$ = 3.5 Hz, 0.79H, H1''), 3.92 (sept, $^{3}J_{H2''',H3'''\text{-}H4'''}$ = 6.8 Hz, 1H, H2'''), 2.06 (dsept, $^{3}J_{H8',H1'}$ = 3.3 Hz, $^{3}J_{H8',H9'\text{-}H10'}$ = 7.0 Hz, 1H, H8'), 1.93. (dsept, $^{3}J_{H8'',H1''}$ = 3.5 Hz, $^{3}J_{H8'',H9''\text{-}H10''}$ = 6.8 Hz, 1H, H8''), 1.67-1.64 (m, 3H), 1.62 (s, 2.40H), 1.59 (1.24), 1.51-1.48 (m, 3.05), 1.46-1.40 (m, 9H), 1.38 (s, 3.45H), 1.35 (s, 2.49H), 1.30-1.26 (m, 5.45H) (H11', H12', H13', H14', H11'', H12'' H13'', H14''), 0.94-0.90, 0.84-0.65 (2 x m, 3.15H,9.10H, H9', H9'', H10', H10'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 211.8, 211.5, (C5', C5''), 209.5 (C1'''), 197.6, 197.4 (C7', C7''), 167.6, 167.2 (C3', C3''), 161.0 (C6), 153.2, 151.0 (C2, C4), 111.8, 111.7 (C3, C5), 110.2 (C1), 106.1 (C2'), 103.0 (C2''), 56.2, 56.1 (C6', C6''), 47.53, 47.51 (C4', C4''), 40.2 (C2'''), 35.3, 34.2 (C8', C8''), 32.1, 31.8 (C1', C1''), 25.4, 25.2, 25.1, 25.0, 24.9, 23.9, 23.8 (C11', C11'', C12', C12'', C13', C13'', C14', C14''), 20.7, 19.7, 19.4, 18.5, 18.4 (C9', C9'', C10', C10''), 17.7 (C3''', C4''') ppm.

$[\alpha]_D^{24}$ = +2.3 ($CHCl_3$, *c* = 0.6)

The preparation of PMCA (**7**) from (+)-MCA (**5**) with 70 % *ee* (see above) led to a similar mixture of isomers from which we isolated *l*-**7a** and *l*-**7b** whose NMR data is listed below. In the ^{1}H-NMR spectrum of *l*-**7b**, the "self induced non-equivalence" discussed in § 2.3.2.6 (NMR particularity) can be observed.

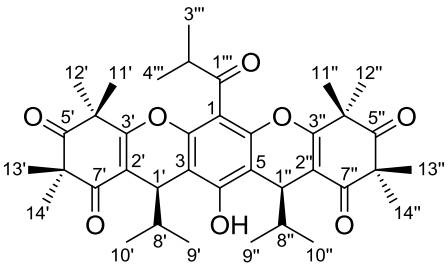
***l*-PMCA (*l*-7b): sample with an *ee* 70 %**



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.91 (brs, 1H, OH), 4.53 (d, $^{3}J_{H1',H8'}$ = $^{3}J_{H1'',H8''}$ = 3.5 Hz, 0.27H, H1', H1''), 4.47 (d, $^{3}J_{H1',H8'}$ = $^{3}J_{H1'',H8''}$ = 3.3 Hz, 1.65H, H1', H1''), 3.24-3.11 (m, 1H, H2'''), 2.02-1.89 (m, 2H, H8', H8''), 1.54 (s, 6H, H12', H11''), 1.45 (m, 6H, H13', H14''), 1.44-1.38 (m, 12H, H11', H12'', H14', H13''), 1.28-1.22 (m, 6H, H3''', H4'''), 0.88-0.74 (m, 12H, H10', H10'', H9', H9'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 211.8 (C5', C5''), 204.30 (C1'''), 198.4 (C7', C7''), 168.6 (C3', C3''), 151.8 (C4), 147.6 (C2, C6), 110.9 (C3, C5), 110.0 (C1), 108.5 (C2', C2''), 55.9 (C6, C6''), 47.5 (C4', C4''), 42.7 (C2'''), 35.1 (C8', C8''), 32.4 (C1', C1''), 25.2 (C12', C11''), 24.81 (C13', C14''), 24.79 (C11', C12''), 24.4 (C14', C13''), 19.1 (C10', C10''), 18.7 (C9', C9''), 18.0 (C3''', C4''') ppm.

_l_-meso-PMCA (_l_-7a):



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81 (brs, 1H, OH), 4.59 (d, $^{3}J_{H1',H8'}$ = $^{3}J_{H1'',H8''}$ = 3.8 Hz, 2H, H1', H1''), 3.19 (sept, $^{3}J_{H2'',H3''\text{-}4''}$ = 7.0 Hz 1H, H2'''), 2.06-1.90 (m, 2H, H8', H8''), 1.52 (s, 6H, H12', H12''), 1.44 (s, 6H, H13', H13''), 1.38 (s, 6H, H11', H11''), 1.36 (s, 6H, H14', H 14''), 1.29 (d, J = 6.8 Hz, 6H, H3''', H4'''), 0.86 (d, J = 6.8 Hz, 6H, H9', H9''), 0.79 (d, J = 6.8 Hz, 6H, H10', H10'') ppm.

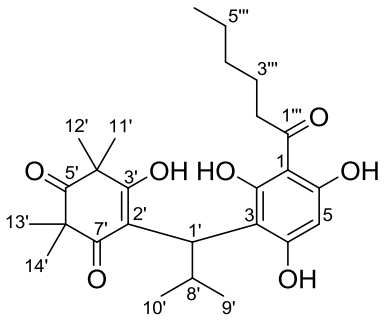
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 211.8 (C5', C5''), 205.30 (C1'''), 198.6 (C7', C7''), 169.1 (C3', C3''), 152.4 (C4), 147.5 (C2, C6), 111.2 (C3, C5), 110.4 (C1), 108.5 (C2', C2''), 56.0 (C6', C6''), 47.5 (C4', C4''), 43.3 (C2'''), 35.1 (C8', C8''), 32.4 (C1', C1''), 24.9 (C12', C12''), 24.77 (C14', C14'), 24.75 (C11', C11''), 24.3 (C13', C13''), 19.1 (C10', C10''), 18.8 (C9', C9''), 17.7 (C3''', C4''') ppm.

4.6.1.6 Preparation and cyclisation of norsemimyrtucommulone F

*Norsemimyrtucommulone F (NSMCF) (**82**)*

According to ***GP 8***, HPG (**33**) (224 mg, 1.0 mmol, 1.0 eq.) was dissolved in DT101 (4 mL) and added dropwise to the freshly prepared (*S*,*S*)-ALB ((*S*,*S*)-**66e**) (18.2 mL of a 0.18 M solution in DT101, 3.2 mmol, 3.2 eq.). IBSA (**31**) (2.4 mL of a 0.62 M solution in DT101, 1.5 mmol, 1.5 eq.) was added dropwise to the mixture at 0°C. After 2h stirring at 0°C, the reaction was quenched and the product extracted and dried. After purification by column chromatography on silica gel (A/PE, 1/2 (500 mL), 1/1 (1000 mL), R_f = 0.19 (A/PE, 1/1)), 322 mg of (-)-NSMCF (**82**) (0.70 mmol, 70 % yield) were obtained as a pale yellow powder (mp = 186°C, decomposition). $[\alpha]_D^{24}$ = - 10.7 (MeOH, *c* = 3.0).

HRMS (ESI^+) calcd. for $C_{26}H_{37}O_7^+$ $[M+H]^+$: 461.2539, found: 461.2532.



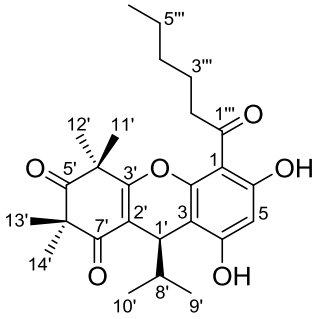
^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 14.24 (brs, 0.53H, OH), 13.64 (brs, 0.79H, OH), 5.69 (s, 1H, H5), 3.83 (m, 1H, H1'), 3.34-3.20 (m, 1H, H8'), 3.15-3.00 (m, 2H, H2'''), 1.71-1.60 (H3''') 1.38-1.32 (m, 4H, H4''', H5'''), 1.31-1.18 (m, 12 H, H11', H12', H13', H14'), 0.93-0.87 (m, 3H, H6'''), 0.83, 0.82 (2 x d, $^{3}J_{H9',H8'}$ = 6.3 Hz, 3H, H9'), 0.71, 0.68 (2 x d, $^{3}J_{H10',H8'}$ = 6.5 Hz, 3H, H10') ppm.

^{13}C-NMR (101 MHz, CO(CD$_3$)$_2$): δ = 218.0 (C5'), 209.6, 208.1, 207.7 (C1', C7'), 167.3, 166.0, 165.1, 164.4, 154.7, 111.9, 98.3, 97.4 (C5), 53.4, 53.3 (C4', C6'), 45.7, 45.5 (C2'''), 43.3, 43.2 (C1'), 33.6 (C4'''), 27.6 (C8'), 27.2, 27.1, 26.8, 26.7, 26.6 (C11', C12', C13', C14'), 24.5 (C5'''), 23.72, 23.69, (C9', C10'), 15.3 (C6''') ppm.

*Tricyclic NSMCF (**83**) (55% ee)*

Following the ***GP 9*** procedure, (-)-NSMCF (**82**) (85 mg, 0.18 mmol, 1.0 eq.) and pTsOH (105 mg, 0.55 mmol, 3.0 eq.) were heated to 95°C in toluene (8.5 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9, R_f = 0.14), 55 mg of the cyclised product (+)-(*R*)-**83** (0.12 mmol, 69 % yield) with 55 % *ee*. It was dissolved in a DCM/PE (1/9) mixture and evaporated under reduced pressure to afford a white foam (mp = 68-81°C). $[\alpha]_D^{24}$ = +90.4 ($CHCl_3$, *c* = 2.92).

HRMS (ESI$^+$) calcd. for $C_{26}H_{35}O_6^+$ $[M+H]^+$: 443.2433, found: 443.2422.



^{1}H-NMR (400 MHz, CDCl$_3$): δ = 13.49 (s, 1H, C6-OH), 7.67 (brs, 1H, C4-OH), 6.33 (s, 0.21H, H5), 6.32 (s, 0.71H, H5), 4.40 (d, $^{3}J_{H1',H8'}$ = 3.8 Hz, 0.73H, H1'), 4.38 (d, $^{3}J_{H1',H8'}$ = 3.8 Hz, 0.20H, H1'), 3.31-3.20 (m, 1H, H2a'''), 3.09-2.97 (m, 1H, H2b'''), 1.91 (dsept, $^{3}J_{H8',H1'}$ = 3.8 Hz, $^{3}J_{H8',H9'-10'}$= 6.8 Hz, 1H, H8'), 1.83-1.69 (m, 2H, H3'''), 1.66 (s, 3H, 12'), 1.48-1.43 (m, 6H, H11', H14'), 1.40 (s, 3H, H13'), 1.39-1.33 (m, 4H, H4''', H5'''), 0.94-0.88 (m, 3H, H6'''), 0.83 (d, $^{3}J_{H8',H9'}$ = 6.8 Hz, 3H, H9'), 0.79 (d, $^{3}J_{H8',H10'}$ = 7.0 Hz, 3H, H10') ppm.

^{13}C-NMR (101 MHz, CDCl$_3$): δ = 211.8 (C5'), 204.5, 204.4 (C1'''), 199.3, 199.1 (C7'), 168.5, 168.3 (C3'), 164.4 (C4), 160.0, 159.9 (C6), 153.7 (C2), 112.2 112.1 (C2'), 104.8 (C3), 103.9, 103.8 (C1), 100.4 (C5), 56.11, 56.08 (C6'), 47.4 (C4'), 44.6 (C2'''), 34.9, 34.8 (C8'), 31.42,

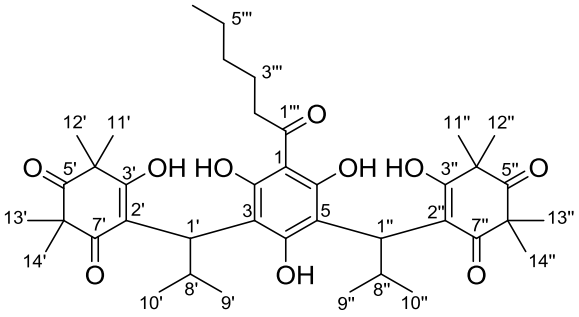
31.38 (C1', C5'''), 25.3, 25.0 (C12', C14', C11'), 24.14, 24.10, 24.0 (C13', C3'''), 22.6 (C4'''), 18.92, 18.89, 18.63, 18.57 (C9', C10'), 13.9 (C6''') ppm.

4.6.1.7 Preparation and cyclisation of myrtucommulone F

*Preparation of myrtucommulone F (MCF) (**13**) (38 % de)*

According to the general procedure ***GP 5***, hexanoyl phloroglucinol (HPG) (**33**) (112 mg, 0.50 mmol, 1.0 eq.), proline (**90**) (57 mg, 0.50 mmol, 1.0 eq.), syncarpic acid (**27**) (550 mg, 3.02 mmol, 6.0 eq.) and isobutyraldehyde (**26**) (0.36 mL, 3.94 mmol, 8.0 eq.) were mixed in ethanol (4 mL) and stirred at room temperature for 48 h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/2, R_f = 0.19) to afford 202 mg of MCF (**13**) (0.30 mmol, 60 % yield) as a light yellow powder (*mp* = 147-180°C, decomposition).

LC-MC (ESI^-) for $C_{40}H_{55}O_{10}^-$ [M-H]$^-$: 696.80



^{1}H-NMR (400 MHz, $CO(CD_3)_2$): δ = 15.86 (brs, 0.34H, OH), 15.47 (brs, 0.64H, OH), 14.67-14.15 (m, 0.30H, OH), 14.06-13.80 (m, 0.08H, OH), 13.23-12.75 (m, 1.09H, OH), 4.51-4.25 (m, 0.41H), 4.21 (d, ^3J = 11.0 Hz, 1.30H, H1', H1''), 4.09-3.90 (m, 0.12H), 3.82-3.77 (m, 0.04H), 3.23-3.00 (m, 3.77H, H8', H8'', H2'''), 1.70-1.60 (m, 2H, H3'''), 1.45-1.10 (m, 29H, H4''', H5''', H11', H12', H13', H14'', H11'', H12', H13'', H14''), 0.94-0.65 (m, 15H, H6''', H9', H10', H9'', H10'') ppm.

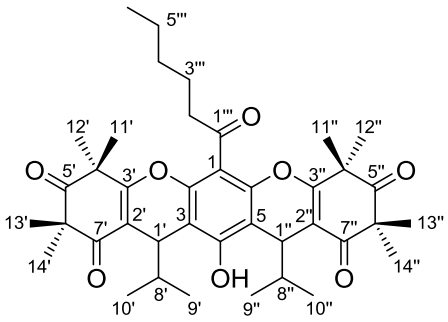
^{13}C-NMR (101 MHz, $CO(CD_3)_2$): δ = 216.1, 200.1, 181.7, 167.3, 162.8, 145.0, 116.0, 115.4, 112.3, 112.2, 111.9, 106.4, 55.5, 55.4, 51.2, 45.6 (C2'''), 41.3 (C1', C1''), 33.6 (C4'''), 28.3 (C8', C8''), 28.1, 26.8 (C3'''), 26.7, 26.4, 26.3, 26.1, 24.4, 23.6, 23.5, 23.4, 23.3, 23.1, 20.3, 15.3 ppm.

*Pentacyclic MCF (PMCF) (**96**)*

Following the ***GP 9*** procedure, MCF (**13**) (90 mg, 0.13 mmol, 1.0 eq.) and pTsOH (176 mg, 0.93 mmol, 6.5 eq.) were heated to 95°C in toluene (9 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9, R_f = 0.17), 65 mg of PMCF (7) (0.10 mmol, 76 % yield) as a white foam. (mp = 105-158°C)

LC-MC (ESI$^-$) for $C_{42}H_{51}O_8^-$ [M-H]$^-$: 659.75

→ A *d.r.* of 69:31 (*meso*:*rac)* can be seen in the NMR-spectrum



^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 8.00 (brs, 0.57 H, OH-*meso*), 7.79 (brs, 0.42H, OH-*rac*), 4.62 (d, $^3J_{H1',H8'}$ = $^3J_{H1'',H8''}$ = 3.5 Hz, 1.20H, H1', H1'', *meso*), 4.59 (d, $^3J_{H1',H8'}$ = $^3J_{H1'',H8''}$ = 3.5 Hz, 0.72H, H1', H1'', *rac*), 2.93 (t, $^3J_{H2''',H3'''}$ = 7.3 Hz, 1.36H, H2'''), 2.90-2.74 (m, 0.56H, H2''') 2.04-1.88 (m, 2H, H8', H8''), 1.84-1.69 (m, 2H, H3'''') 1.56 (s, 2.10H, H12', H11'', *rac*), 1.54 (s, 3.60H, H12', H12'', *meso*), 1.48-1.30 (m, 22H, H4''', H5''', H11', H11'', H12'', H13', H14'', H13'', H14'), 0.92-74 (m, 15H, H6''', H9', H9'',H10',H10'') ppm.

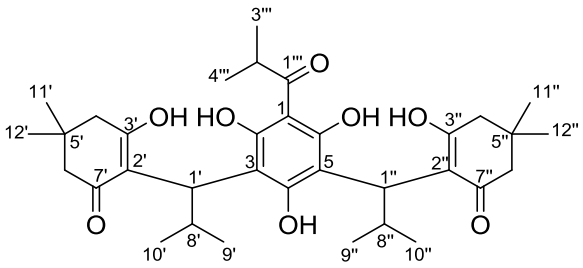
^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 211.76 (C5', C5''), 201.6, 200.6 (C1'''), 198.8 (C7', C7'', *rac*), 198.7 (C7', C7'', *meso*), 169.2 (C3', C3'', *meso*), 169.0 (C3', C3'', *rac*), 152.6 (C4, *meso*), 152.1 (C4, *rac*), 147.6 (C2, C6, *meso*), 147.5 (C2, C6, *meso*), 111.3 (C3, C5, *meso*), 111.0 (C3, C5, *rac*), 110.9 (C1, *meso*), 110.8 (C1, *rac*), 108.8 (C2', C2'', *rac*), 108.6 (C2', C2'', *meso*), 55.94 (C6', C6'', *meso*), 55.84 (C6', C6'', *rac*), 47.55 (C4', C4'', *meso*), 47.53 (C4', C4'', *rac*), 45.8 (C2''', *meso*), 45.7 (C2''', *rac)*, 35.2 (C8', C8'', *meso*), 35.1 (C8', C8'', *rac*), 32.4 (C1', C1'', *meso*), 32.3 (C1', C1'', *rac*), 31.6 (C5''', *meso*), 31.4 (C5''', *rac*), 25.3, 25.0, 24.9, 24.8, 24.7, 24.3, 24.2, 24.04, 23.96 (C11', C11'', C12', C12'', C13', C13'', C14', C14''), 22.5 (C4'''), 19.3, 19.1, 18.8, 18.5 (C9', C9'', C10', C10''), 13.8 (C6''') ppm

4.6.2. Dimedone myrtucommulone derivatives

4.6.2.1 Preparation and cyclisation of the myrtucommulone derivative 42

*Dimedone-myrtucommulone derivative **42***

According to the general procedure ***GP 5***, isobutyryl phloroglucinol (IBPG) (**25**) (98 mg, 0.50 mmol, 1.0 eq.), proline (**90**) (57 mg, 0.50 mmol, 1.0 eq.), dimedone (**37**) (420 mg, 3.00 mmol, 6.0 eq.) and isobutyraldehyde (**26**) (0.36 mL, 3.94 mmol, 8.0 eq.) were mixed in ethanol (4 mL) and stirred at room temperature for 24 h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/5, R_f = 0.25) to afford 278 mg of the dimedone derivative **42** (0.48 mmol, 95 % yield) as a yellow powder (*mp* = 80-125°C).



^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): *δ* = 13.59-11.32 (m, 0.60H, OH), 10.94-9.52 (m, 0.21H, OH), 6.57 (s, 0.77H, OH), 5.84 (brs, 0.74H, OH), 4.21 (d, ^3J= 5.5 Hz, 0.08H), 4.17-4.05 (m, 0.63H, H2'''), 4.00-3.79 (m, 1.26H, H1', H1''), 3.12-2.90 (m, 1.75H, H8', H8''), 2.55 (d, ^2J = 15.3 Hz, 1.04H, H6a', H6a''), 2.49-2.33 (m, 4.37H, H4', H4'', H6', H6''), 2.21 (d, ^2J = 15.3 Hz, 0.97H, H6b', H6b''), 1.96 (dd, ^2J = 13.8 Hz, ^4J = 0.8 Hz, 0.89H, H4a', H4a''), 1.67 (d, ^2J = 13.8 Hz, 0.97H, H4b', H4b'') 1.39, 1.27 (2 x s, 6H, H11', H11''), 1.20-1.02 (m, 14.72H, H3''', H4''', H9', H12', H12''), 1.00 (s, 3H, H12', H12''), 0.94-0.83 (m, 5.09H), 0.80 (d, ^3J = 6.5 Hz, 0.76H), 0.74 (d, ^3J = 6.5 Hz, 1.25H), 0.71 (d, ^3J = 6.5 Hz, 0.73H), 0.65 (d, ^3J = 6.5 Hz, 0.32H), 0.62 (d, ^3J = 6.5 Hz, 0.51H) (H9', H10', H9'', H10'') ppm.

^{13}C-NMR (101 MHz, CO(CD$_3$)$_2$): *δ* = 199.2, 162.0, 147.3, 139.3, 137.2, 118.0, 117.9, 117.6, 117.5, 117.4, 111.7, 106.7, 106.4, 98.5, 79.8, 75.9, 56.4, 55.2, 53.7, 45.9, 41.0, 40.9, 40.7, 40.4, 33.0, 32.9, 32.8, 32.7, 32.5, 32.0, 31.5, 28.6, 28.2, 28.14, 28.06, 27.9, 27.6, 25.1, 24.4, 23.7, 23.6, 23.5, 23.3, 23.2, 23.1, 23.0, 22.9, 21.3, 20.8, 20.7, 20.6, 20.2, 19.6 ppm.

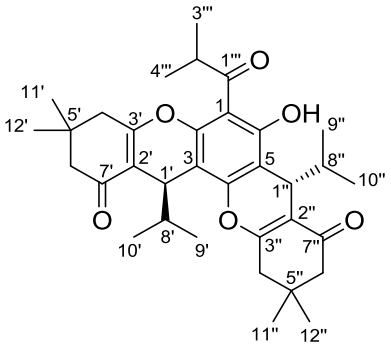
LC-MC (ESI$^-$) for $C_{34}H_{47}O_8^-$ [M-H]$^-$: 583.75

*Pentacyclic dimedone derivative (**97**)*

Following the ***GP 9*** procedure, the dimedone derivative **42** (110 mg, 0.19 mmol, 1.0 eq.) and pTsOH (250 mg, 1.32 mmol, 6.9 eq.) were heated to 95°C in toluene (11 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/10), 59 mg of the pentacyclic derivative **97** (0.11 mmol, 57 % yield) as a white foam. This product cyclised *orthogonally* as two isolable products: *anti*-**97** (28 mg, 0.05 mmol, 27 %, R_f = 0.17) and *syn*-**97** (31 mg, 0.06 mmol, 30 %, R_f = 0.07).

*Characterisation of anti-**97***

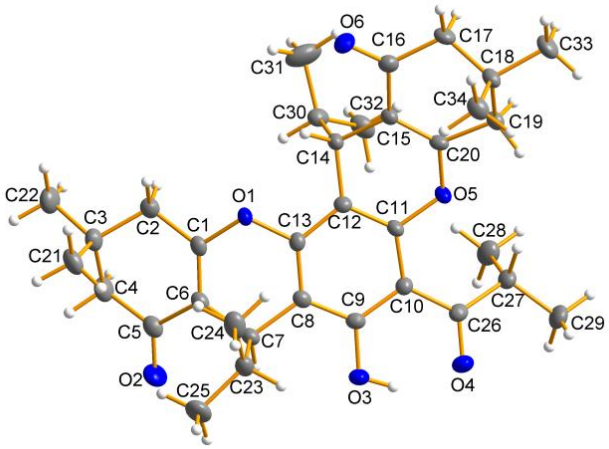
LC-MC (ESI^-) for $C_{34}H_{43}O_6^-$ $[M-H]^-$: found: 547.65, (*mp* = 95-135°C)



^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 13.56 (s, 1H, OH), 4.26 (d, $^3J_{H1',H8'}$ = 3.5 Hz, 1H, H1'), 4.19 (d, $^3J_{H1'',H8''}$ = 4.0 Hz, 1H, H1''), 3.75 (sept, $^3J_{H2''',H3'''-H4'''}$ = 6.8 Hz, 1H, H2'''), 2.64-2.50, 2.48-2.24 (2 x m, 8H, H4', H4'', H6', H6''), 1.96 (dsept, $^3J_{H8'-H1'}$ = 3.5 Hz, $^3J_{H8',H9'-H10'}$ = 7.0 Hz, 1H, H8'), 1.88 (dsept, $^3J_{H8'',H1''}$ = 4.0 Hz, $^3J_{H8'',H9''-H10''}$ = 6.8 Hz, 1H, H8''), 1.23 (d, $^3J_{H3'''-H4''',H2'''}$ = 6.8 Hz, 6H, H3''', H4'''), 1.21, 1.174, 1.168, 1.12 (4 x s, 4 x 3H, H11', H11'', H12', H12''), 0.79-0.72 (m, 9H), 0.69 (d, $^3J_{H9'-H10'-H8'}$ = 6.8Hz, 3H) (H9', H9'', H10', H10'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 210.0 (C1'''), 196.92, 196.9 (C7', C7''), 165.8, 165.6 (C3', C3''), 161.4 (C6), 153.4 (C4), 151.0 (C2), 113.9, 113.3 (C2', C2''), 110.7 (C5), 106.2 (C1), 103.8 (C3), 50.95, 50.87 (C6', C6''), 41.2, 41.1 (C4', C4''), 40.2 (C2'''), 35.2 (C8''), 34.5 (C8'), 32.0, 31.9 (C5', C5''), 31.4 (C1'), 31.0 (C1''), 30.0, 29.7 (C11', C11''), 27.1, 27.0 (C12', C12''), 19.33, 19.29 (C3''', C4'''), 20.0, 18.7 (C9', C9'', C10', C10'') ppm.

Crystal Structure: (for the complete data see Appendix 4)

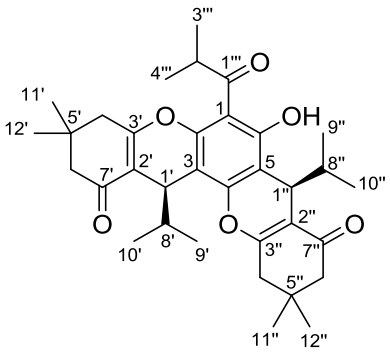


Exp. Data Tab. 4 Crystal data and structure refinement for *anti*-**97** (sh3587a).

Identification code	sh3587a	
Empirical formula	C34 H44 O6 x C H2 Cl2	
Formula weight	633.62	
Temperature	152(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 13.4239(5) Å	α= 90°.
	b = 21.6721(8) Å	β= 105.9659(19)°.
	c = 11.9123(4) Å	γ = 90°.
Volume	3331.9(2) $Å^3$	
Z	4	
Density (calculated)	1.263 Mg/m^3	
Absorption coefficient	0.238 mm^{-1}	
F(000)	1352	
Crystal size	0.382 x 0.337 x 0.078 mm^3	
Theta range for data collection	1.578 to 27.955°.	
Index ranges	-17<=h<=17, -28<=k<=27, -15<=l<=15	
Reflections collected	31543	
Independent reflections	7919 [R(int) = 0.0511]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.7100	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7919 / 0 / 399	
Goodness-of-fit on F^2	1.463	
Final R indices [I>2sigma(I)]	R1 = 0.0782, wR2 = 0.1934	
R indices (all data)	R1 = 0.1302, wR2 = 0.2120	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.243 and -1.153 $e.Å^{-3}$	

*Characterisation of syn-**97***

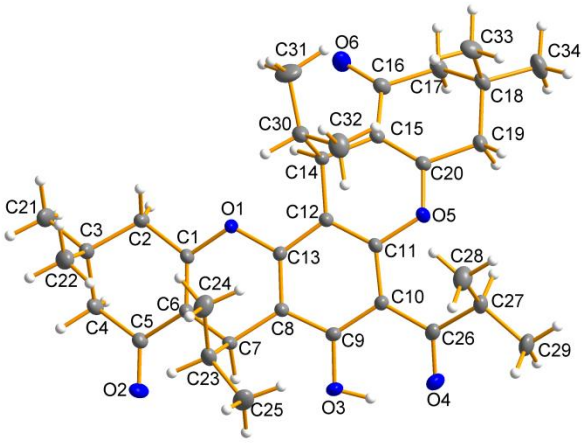
LC-MC (ESI$^-$) for $C_{34}H_{43}O_6^-$ [M-H]$^-$: 547.70, (*mp* = 85-135°C)



^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 13.53 (s, 1H, OH), 4.23 (d, $^3J_{H1',H8'}$ = 3.5 Hz, 1H, H1'), 4.15 (d, $^3J_{H1'',H8''}$ = 3.5 Hz, 1H, H1''), 3.75 (sept, $^3J_{H2''',H3'''-H4'''}$ = 6.8 Hz, 1H, H2'''), 2.60-2.44, 2.42-2.22 (2 x m, 8H, H4', H4'', H6', H6''), 2.02 (dsept, $^3J_{H8'-H1'}$ = 3.8 Hz, $^3J_{H8',H9'-H10'}$ = 7.0 Hz, 1H, H8'), 1.91 (dsept, $^3J_{H8'',H1''}$ = 3.8 Hz, $^3J_{H8'',H9''-H10''}$ = 7.0 Hz, 1H, H8''), 1.25 (d, ^3J = 6.8 Hz, 3H), 1.19 (d, ^3J = 6.8 Hz, 9H), 1.17-1.10 (m, 6H) (H3''', H4''', H11', H11'', H12', H12''), 0.84, 0.81, 0.78, 0.75 (4 x d, $^3J_{H9'-H10',H8'}$ = $^3J_{H9''-H10'',H8''}$ = 7.0 Hz, 12H, H9', H9'', H10', H10'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 210.0 (C1'''), 197.0, 196.9 (C7', C7''), 165.7, 165.4 (C3', C3''), 161.2 (C6), 153.7 (C4), 151.7 (C2), 113.7, 113.4 (C2', C2''), 110.3 (C5), 106.0 (C1), 103.8 (C3), 51.0, 50.9 (C6', C6''), 41.4, 41.1 (C4', C4''), 40.2 (C2'''), 35.2 (C8''), 34.3 (C8'), 32.0, 31.8 (C5', C5''), 31.4 (C1'), 31.2 (C1''), 29.9, 29.6 (C11', C11''), 27.1, 27.0 (C12', C12''), 20.1, 19.6, 19.5, 19.1, 18.9, 18.6 (C3''', C4''', C9', C9'', C10', C10'') ppm.

Crystal Structure: (for the complete data see Appendix 5)



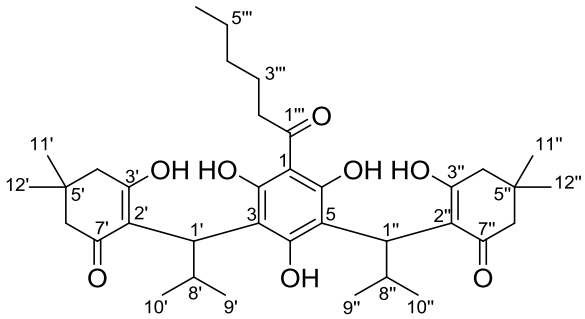
Exp. Data Tab. 5 Crystal data and structure refinement for *syn*-**97** (sh3590).

Identification code	sh3590	
Empirical formula	C34 H44 O6	
Formula weight	548.69	
Temperature	152(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.7960(5) Å	α= 103.800(2)°.
	b = 11.1104(5) Å	β= 108.9765(19)°.
	c = 13.6046(6) Å	γ = 91.466(2)°.
Volume	1489.13(12) $Å^3$	
Z	2	
Density (calculated)	1.224 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	592	
Crystal size	0.667 x 0.276 x 0.196 mm^3	
Theta range for data collection	1.640 to 33.178°.	
Index ranges	-16<=h<=16, -17<=k<=16, -20<=l<=20	
Reflections collected	41676	
Independent reflections	11328 [R(int) = 0.0323]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7465 and 0.6947	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11328 / 0 / 537	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0458, wR2 = 0.1164	
R indices (all data)	R1 = 0.0735, wR2 = 0.1325	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.445 and -0.245 e.$Å^{-3}$	

4.6.2.2 Preparation and cyclisation of the myrtucommulone derivative 43

*Dimedone-myrtucommulone derivative **43***

According to the general procedure ***GP 5***, hexanoyl phloroglucinol (HPG) (**33**) (112 mg, 0.50 mmol, 1.0 eq.), proline (**90**) (57 mg, 0.50 mmol, 1.0 eq.), dimedone (**37**) (550 mg, 3.02 mmol, 6.0 eq.) and isobutyraldehyde (**26**) (0.36 mL, 3.94 mmol, 8.0 eq.) were mixed in ethanol (4 mL) and stirred at room temperature for 16 h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/15, R_f = 0.08) to afford 243 mg of the dimedone derivative **43** (0.40 mmol, 79 % yield) as a yellow oil.



^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 13.73-11.40 (m, 0.92H, OH), 11.73-8.92 (m, 0.29H, OH), 6.57 (s, 0.46H, OH), 5.84 (brs, 0.41H, OH), 3.99-3.79 (m, 1.96H, H1', H1''), 3.27-2.88 (m, 6.16H, H8', H8'', H2'''), 2.55 (d, ^2J = 15.0 Hz, 0.95H, H6a', H6a''), 2.46-2.28 (m, 7.07H, H4', H4'', H6', H6''), 2.21 (d, ^2J = 15.0 Hz, 0.80H, H6b', H6b''), 1.96 (dd, ^2J = 13.8 Hz, ^4J = 0.8 Hz, 1.02H, H4a', H4a''), 1.72-1.62 (m, 2.55H, H3'', H4b', H4b''), 1.42-1.32 (m, H11', H11'', H4'''), 1.27 (s, 1.69, H11', H11''), 1.15 (s, 2.12H, H12', H12'') 1.14-1.02 (m, 12.35H, H11', H11'', H12', H12'', H5'''), 1.00 (s, 3H, H12', H12''), 0.96-0.86 (m, 9.83H), 0.80 (d, ^3J = 6.5 Hz, 1.10H), 0.74 (d, ^3J = 6.5 Hz, 2.11H), 0.69 (d, ^3J = 6.5 Hz, 1.11H), 0.65 (d, ^3J = 6.5 Hz, 0.59H), 0.62 (d, ^3J = 6.5 Hz, 1.23H) (H9', H10', H9'', H10'') ppm.

^{13}C-NMR-APT (101 MHz, CO(CD$_3$)$_2$): δ = 197.6, 139.3, 53.8, 45.9, 45.8, 41.0, 40.7, 40.3, 33.4, 33.0, 32.9, 32.8, 32.5, 31.5, 28.5, 28.2, 28.14, 27.9, 27.4, 26.3, 26.2, 25.1, 24.4, 24.3, 23.6, 23.5, 23.3, 23.2, 23.1, 22.9, 15.3 ppm.

LC-MC (ESI$^-$) for $C_{36}H_{51}O_8^-$ [M-H]$^-$: found: 611.80

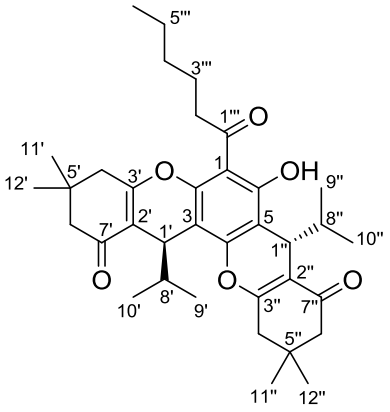
*Pentacyclic dimedone derivative (**98**)*

Following the ***GP 9*** procedure, the dimedone derivative **43** (100 mg, 0.16 mmol, 1.0 eq.) and pTsOH (217 mg, 1.14 mmol, 7.1 eq.) were heated to 95°C in toluene (10 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/15), 43 mg of the pentacyclic derivative **98** (0.07 mmol, 46 % yield) as a white foam. This product cyclised orthogonally as two

isolable products: *anti*-**98** (23 mg, 0.04 mmol, 25 %, R_f = 0.14) and *syn*-**98** (20 mg, 0.03 mmol, 21 %, R_f = 0.10).

*Characterisation of anti-**98***

LC-MC (ESI$^-$) for $C_{36}H_{47}O_6^-$ [M-H]$^-$: 575.75, (*mp* = 80-140°C)

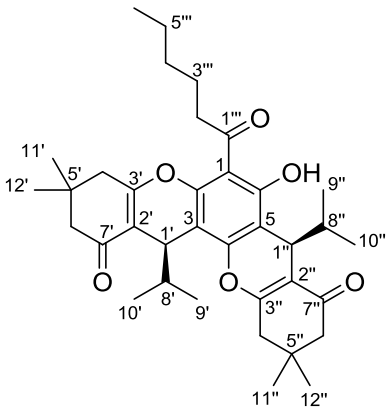


^{1}H-NMR (400 MHz, CDCl$_3$) : δ = 13.66 (s, 1H, OH), 4.26 (d, $^3J_{H1',H8'}$ = 3.3 Hz, 1H, H1'), 4.18 (d, $^3J_{H1'',H8''}$ = 4.0 Hz, 1H, H1''), 3.10 (dt, $^2J_{H2a''',H2b'''}$ = 16.6 Hz, $^3J_{H2a''',H3'''}$ = 7.3 Hz, 1H, H2a'''), 3.10 (dt, $^2J_{H2b''',H2a'''}$ = 16.6 Hz, $^3J_{H2b''',H3'''}$ = 7.5 Hz, 1H, H2b'''), 2.66-2.51, 2.49-2.24 (2 x m, 8H, H4', H4'', H6', H6''), 2.02-1.88 (m, 1H, H8'), 1.81-65 (m, 3H, H3''', H8''), 1.42-1.36 (m, 4H, H4''', H5'''), 1.22-1.10 (m, 12H, H11', H11'', H12', H12''), 0.96-0.89 (m, 3H, H6'''), 0.88-0.72 (m, 9H), 0.70 (d, $^3J_{H9'-H10',H8'}$ = 6.8Hz, 3H) (H9', H9'', H10', H10'') ppm.

^{13}C-NMR (101 MHz, CDCl$_3$) : δ = 205.0 (C1'''), 196.9 (C7', C7''), 165.8, 165.6 (C3', C3''), 161.2 (C6), 153.4 (C4), 151.4 (C2), 114.0, 113.4 (C2', C2''), 110.5 (C5), 106.8 (C1), 103.8 (C3), 50.94, 50.87 (C6', C6''), 44.8 (C2''') 41.3, 41.2 (C4', C4''), 35.2 (C8''), 34.5 (C8'), 31.96, 31.94 (C5', C5''), 31.6 (C4''), 31.3 (C1'), 31.0 (C1''), 30.0, 29.7 (C11', C11''), 27.1 (C12', C12''), 24.4 (C3'''), 22.6 (C5'''), 19.9, 19.3, 18.8 (C9', C9'', C10', C10''), 14.0 (C6''') ppm.

*Characterisation of syn-**98***

LC-MC (ESI$^-$) for $C_{36}H_{47}O_6^-$ [M-H]$^-$: 575.75, (*mp* = 75-95°C)

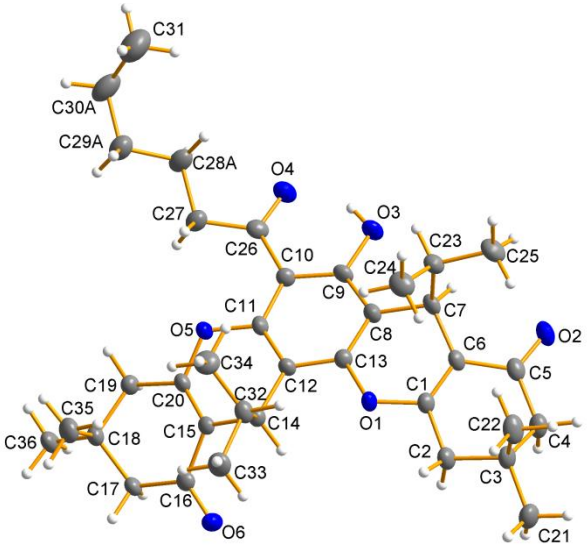


^{1}H-NMR (400 MHz, CDCl$_3$) : δ = 13.63 (s, 1H, OH), 4.26 (d, $^3J_{H1',H8'}$ = 3.5 Hz, 1H, H1'), 4.18 (d, $^3J_{H1'',H8''}$ = 3.8 Hz, 1H, H1''), 3.08 (dt, $^2J_{H2a''',H2b'''}$ = 16.6 Hz, $^3J_{H2a''',H3'''}$ = 7.5 Hz, 1H, H2a'''), 3.05 (dt, $^2J_{H2b''',H2a'''}$ = 16.6 Hz, $^3J_{H2b''',H3'''}$ = 7.5 Hz, 1H, H2b'''), 2.60-2.44, 2.42-2.18 (2 x m, 8H, H4', H4'', H6', H6''), 2.01 (dsept, $^3J_{H8'-H1'}$ = 3.5 Hz, $^3J_{H8',H9'-H10'}$ = 6.8 Hz, 1H, H8'), 1.90 (dsept, $^3J_{H8'',H1''}$ = 3.8 Hz, $^3J_{H8'',H9''-H10''}$ = 6.8 Hz, 1H, H8''), 1.76-1.67 (m, 2H, H3'''), 1.41-1.34 (m, 4H, H4''', H5'''), 1.20, 1.18, 1.15, 1.11 (4 x s, 12H, H11', H11'', H12', H12''), 0.95-

0.90 (m, 3H, H6‘‘‘), 0.84, 0.81, 0.79, 0.75 (4 x d, $^{3}J_{H9'\text{-}H10',H8'}$ = $^{3}J_{H9''\text{-}H10'',H8''}$ = 6.8 Hz, 12H, H9’, H9’’, H10’, H10’’) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 205.8 (C1’’’), 197.0, 196.9 (C7’, C7’’), 165.7, 165.6 (C3’, C3’’), 161.0 (C6), 153.8 (C4), 151.0 (C2), 113.7, 113.4 (C2’, C2’’), 110.2 (C5), 106.8 (C1), 103.8 (C3), 51.0, 50.9 (C6’, C6’’), 44.9 (C2’’’) 41.4, 41.3 (C4’, C4’’), 35.3 (C8’’), 34.3 (C8’), 32.0, 31.8 (C5’, C5’’), 31.6 (C4’’’), 31.4, 31.2 (C1’, C1’’), 29.8, 29.6 (C11’, C11’’), 27.3, 27.1 (C12’, C12’’), 24.5 (C3’’’), 22.6 (C5’’’), 20.0, 19.5, 18.9, 18.6 (C9’, C9’’, C10’, C10’’), 13.8 (C6’’’) ppm.

Crystal Structure: (for the complete data see Appendix 6)



Crystal data and structure refinement for syn-**98** (sh3583).

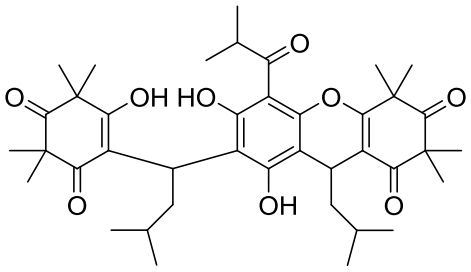
Identification code	sh3583	
Empirical formula	C36 H48 O6	
Formula weight	576.74	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.2643(8) Å	α= 71.787(5)°.
	b = 11.9208(8) Å	β= 87.308(5)°.
	c = 13.4429(10) Å	γ = 66.348(4)°.
Volume	1564.2(2) Å^3	
Z	2	
Density (calculated)	1.224 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	624	
Crystal size	0.247 x 0.182 x 0.040 mm^3	
Theta range for data collection	1.601 to 29.065°.	
Index ranges	-14<=h<=15, -14<=k<=16, -18<=l<=18	
Reflections collected	31788	

Independent reflections	8286 [R(int) = 0.0870]
Completeness to theta = 25.242°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7458 and 0.6952
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8286 / 94 / 417
Goodness-of-fit on F^2	0.968
Final R indices [I>2sigma(I)]	R1 = 0.0617, wR2 = 0.1212
R indices (all data)	R1 = 0.1563, wR2 = 0.1559
Extinction coefficient	n/a
Largest diff. peak and hole	0.316 and -0.282 e.Å^{-3}

4.6.3. Derivatives made with isovaleraldehyde

*Isovaleryl-myrtucommulone derivative **99***

According to the general procedure ***GP 5***, isobutyryl phloroglucinol (IBPG) (**25**) (98 mg, 0.50 mmol, 1.0 eq.), proline (**90**) (57 mg, 0.50 mmol, 1.0 eq.), syncarpic acid (**27**) (550 mg, 3.02 mmol, 6.0 eq.) and isovaleraldehyde (**35**) (0.43 mL, 4.01 mmol, 8.0 eq.) were mixed in ethanol (4 mL) and stirred at room temperature for 40 h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/2, R_f = 0.10) to afford 35 mg of the derivative **99** (0.05 mmol, 10 % yield) as a brownish white powder (*mp* = 142°C, decomposition).



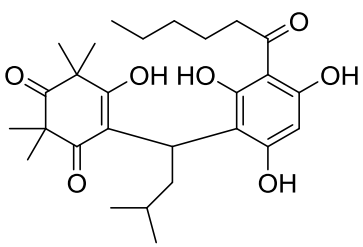
^{1}H-NMR (400 MHz, $CO(CD_3)_2$): δ = 4.86-4.72 (m, 0.13H), 4.64-4.50 (m, 0.49H), 4.32-4.18 (m, 0.83H), 4.16-3.95 (m, 0.42H), 3.65-3.36 (m, 0.93H), 2.55 (brs, 0.53H), 2.38-2.23 (1.12H), 1.96-1.84 (m, 0.56H) 1.70-1.49 (m, 3.29H) 1.48-1.18 (m, 28.10H), 1.18-1.08 (m, 6.08H), 0.91-0.74 (m, 9.64H) ppm.

LC-MC (ESI^-) for $C_{40}H_{53}O_9^-$ $[M-H]^-$: 677.80

*Isovaleryl-myrtucommulone derivative **100***

According to the general procedure ***GP 5***, hexanoyl phloroglucinol (HPG) (**33**) (112 mg, 0.50 mmol, 1.0 eq.), proline (**90**) (57 mg, 0.50 mmol, 1.0 eq.), syncarpic acid (**27**) (550 mg, 3.02 mmol, 6.0 eq.) and isovaleraldehyde (**35**) (0.43 mL, 4.01 mmol, 8.0 eq.) were mixed in ethanol (4 mL) and stirred at room temperature for 48 h. The reaction was worked up and the

product was purified through column chromatography on silica gel (A/PE, 1/2, R_f = 0.13) to afford 33 mg of the derivative **100** (0.07 mmol, 14 % yield) as a brownish white powder (*mp* = 122-145°C).



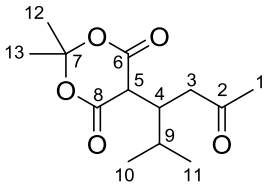
^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 4.89-4.74 (m, 0.49H), 4.55-4.35 (m, 0.11H), 4.32-4.17 (m, 0.08H), 4.16-3.95 (m, 0.42H), 3.23-3.07 (m, 1.17H), 2.55 (brs, 0.39H), 2.41-2.17 (1.00H), 1.72-1.58 (m, 2.12H), 1.47-1.15 (m, 20.29H), 0.93-0.87 (m, 2.59H), 0.86-0.73 (m, 6.00H) ppm.

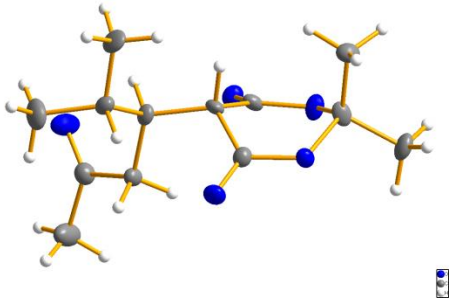
LC-MC (ESI$^-$) for $C_{27}H_{37}O_7^-$ [M-H]$^-$: 473.35.

4.6.4. Attempt with Meldrum's acid

*Meldrum's acid-myrtucommulone derivative **101***

According to the general procedure ***GP 5***, isobutyryl phloroglucinol (IBPG) (**25**) (98 mg, 0.50 mmol, 1.0 eq.), proline (**90**) (57 mg, 0.50 mmol, 1.0 eq.), Meldrum's acid (423 mg, 2.93 mmol, 6.0 eq.) and isobutyraldehyde (**26**) (0.32 mL, 3.51 mmol, 7.0 eq.) were mixed in ethanol (4 mL) and stirred at room temperature for 7 h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/6, R_f = 0.06) to afford 144 mg of the Meldrum's acid derivative **101** (0.56 mmol) as a white powder (*mp* = 81-88°C). The crystal structure could not be refined because of the bad quality of the crystals but was confirmed by mass spectroscopy and NMR (the crystal data is not provided here).





^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 4.02 (d, $^3J_{H5,H4}$ = 1.3 Hz, H5). 2.88-2.77 (m, 3H, H3, H4), 2.09 (s, 3H, H1), 2.00-1.86 (m, 1H, H9), 1.80 (s, 3H, H12), 1.71 (s, 3H, H13), 0.91 (d, $^3J_{H10,H9}$ = 6.8 Hz, 3H, H10), 0.87 (d, $^3J_{H11,H9}$ = 6.8 Hz, 3H, H11) ppm.

^{13}C-NMR (101 MHz, CO(CD$_3$)$_2$): δ = 209.4 (C2), 167.4 (C6, C8), 106.4 (C7), 49.0 (C3), 45.4 (C5), 40.9 (C1), 32.0 (C9), 31.1 (C4), 29.5, 28.0 (C12, C13), 22.2, 21.9 (C10, C11) ppm.

LC-MC (ESI$^-$) for $C_{13}H_{19}O_5^-$ [M-H]$^-$: 255.40

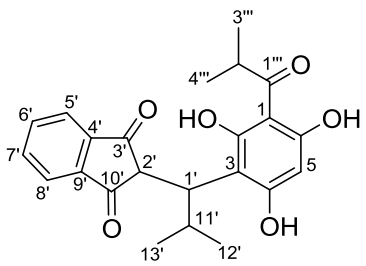
4.6.5. Indandione derivatives

4.6.5.1 Preparation and cyclisation of the semimyrtucommulone derivative 87

*Semimyrtucommulone derivative **87***

According to ***GP 8***, IBPG (**25**) (196 mg, 1.0 mmol, 1.0 eq.) was dissolved in DT101 (4 mL) and added dropwise to the freshly prepared (*S*,*S*)-ALB ((*S*,*S*)-**66e**) (18.2 mL of a 0.18 M solution in DT101, 3.2 mmol, 3.2 eq.). Isobutylidene indandione (IBIND) (**86**) (240 mg, 1.2 mmol, 1.2 eq.) was dissolved in DT101 (1.5 mL, 0.80 M solution) and added dropwise to the mixture at 0°C. The mixture was allowed to warm up to room temperature and was stirred for 24h more. The reaction was quenched and the product extracted and dried. After purification by column chromatography on silica gel (A/PE, 1/2-1/1), 142 mg of the derivative **87** (0.36 mmol, 36 % yield) were obtained as a yellow solid (*mp* = 114-138°C, decomposition). $[\alpha]_D^{24}$ = + 1.7 (MeOH, *c* = 2.88).

HRMS (ESI$^+$) calcd. for $C_{23}H_{25}O_6^+$ [M+H]$^+$: 397.1651, found: 397.1643.



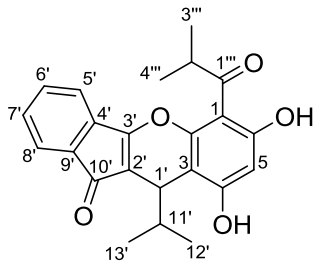
^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 14.19 (brs, 0.22H, OH), 14.04 (s, 0.39H, OH), 13.26 (s, 0.33H, OH), 9.80-9.38 (m, 0.89H, OH), 9.26 (brs, 0.23H, OH), 8.02 (d, *J* = 7.8 Hz, 0.36H, H_{Ar}), 7.96 (d, *J* = 7.8 Hz, 0.46H, H_{Ar}), 7.91-7.84 (m, 0.41H, H_{Ar}), 7.84-7.73 (m, 1.28H, H_{Ar}), 7.70-7.65 (m, 0.28H, H_{Ar}), 7.57-7.52 (m, 1.43H, H_{Ar}), 5.98 (s, 0.32H, H5), 5.86 (s, 0.28H, H5), 5.83 (s, 0.40H, H5), 4.27 (sept, *J* = 6.8 Hz, 0.41H, H2'''), 3.94-3.81 (m, 1H), 3.58-3.48 (m, 1H), 3.41 (d, *J* = 2.0 Hz , 0.34H, H2'), 3.41 (d, *J* = 1.5 Hz , 0.39H, H2'), 2.89-2.78 (m, 0.38H), 2.36-2.25 (m, 0.38H), 2.25-2.16 (m, 0.44H), 1.19, 1.18 (2 x d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 1.66H), 1.10 (d, *J* = 6.8 Hz, 1.58H), 1.07-1.03 (m, 2.11H), 1.02 (d, *J* = 6.5 Hz, 1.15H), 0.99 (d, *J* = 6.8 Hz, 0.70H), 0.93, 0.92 (2 x d, *J* = 6.8 Hz, 2.27H), 0.73 (d, *J* = 6.8 Hz, 0.76H).

^{13}C-NMR (101 MHz, CO(CD$_3$)$_2$): δ = 219.2, 218.4, 212.7, 211.6, 203.6, 166.8, 165.7, 164.3, 163.3, 161.5, 160.7, 157.1, 154.7, 154.2, 153.8, 137.7, 137.6, 137.4, 137.1, 136.9, 136.1, 125.5, 125.4, 124.2, 123.9, 123.8, 123.7, 110.1, 109.1, 108.0, 106.5, 99.1, 98.2, 96.2, 58.2, 57.9, 56.7, 40.8, 40.5, 40.4, 40.1, 39.5, 32.7, 32.2, 28.5, 23.9, 23.6, 22.7, 22.3, 22.21, 22.16, 22.0, 20.7, 20.53, 20.48, 19.4,

*Tetracyclic semimyrtucommulone derivative **88** (6% ee)*

Following the ***GP 9*** procedure, the derivative **87** (70 mg, 0.18 mmol, 1.0 eq.) and pTsOH (100 mg, 0.53 mmol, 3.0 eq.) were heated to 95°C in toluene (7 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9, R_f = 0.08), 48 mg of the tetracyclic derivative ***88*** (0.13 mmol, 70 % yield) as a yellow solid (*mp* = 185-220°C, decomposition).
$[\alpha]_D^{24}$ = - 23.0 (MeOH, *c* = 2.88)

HRMS (ESI$^+$) calcd. for $C_{23}H_{23}O_5^+$ $[M+H]^+$: 379.1540, found: 379.1542.



^{1}H-NMR (400 MHz, CDCl$_3$): δ = 13.55 (s, 1H, OH), 7.50 (d, $^3J_{H8',H7'}$ = 7.0 Hz, 0.52H, H8'), 7.46 (d, $^3J_{H8',H7'}$ = 7.0 Hz, 0.56H, H8'), 7.44-7.37 (m, 0.71H, H6'), 7.35 (d, ^3J = 7.5 Hz, 0.89H, H6', H7'), 7.33-7.27 (m, 0.76H, H7'), 7.21 (d, $^3J_{H5',H6'}$ = 7.0 Hz, 0.54H, H5'), 7.15 (d, $^3J_{H5'',H6''}$ = 7.0 Hz, 0.54H, H5''), 6.31 (s, 0.45H, H5), 6.22 (s, 0.48H, H5), 4.04 (d, $^3J_{H1',H11'}$ = 3.0 Hz, 1H, H1'), 3.98 (d, $^3J_{H1'',H11''}$ = 3.0 Hz, 0.46H, H1''), 3.93 (sept, $^3J_{H2''',H3'''-H4'''}$ = 6.5 Hz, 1H, H2'''), 2.26-2.17 (m, 0.75H, H11''), 2.13 (dsept, $^3J_{H11'',H1''}$ = 3.0 Hz, $^3J_{H11'',H12''-H13''}$ = 6.8 Hz, 0.56H, H11''), 1.34 (d, $^3J_{H12',H11'}$ = 6.8 Hz, 1.63H, H12'), 1.31 (d, $^3J_{H12',H11'}$ = 6.8 Hz, 1.78H, H12'), 1.22, 1.21 (2 x d, $^3J_{H3''',H2'''}$ = 6.8 Hz, 3H, H3'''), 1.07-1.03 (m, 3H, H4'''), 0.72 (d, $^3J_{H13',H11'}$ = 6.8 Hz, 3H, H13'), 0.66 (d, $^3J_{H13'',H11''}$ = 6.8 Hz, 3H, H13'') ppm.

^{13}C-NMR (101 MHz, CDCl$_3$): δ = 211.2, 209.5 (C1'''), 1200.8, 197.2 (C10'), 170.7 (C3'), 164.9, 163.7, 159.9, 157.8, 156.3, 153.2 (C6, C4, C2), 136.6, 136.5 (C9'), 132.6, 132.4 (C6'), 132.2 (C4'), 130.3, 130.1 (C7'), 122.2, 121.9 (C8'), 117.8, 117.7 (C5'), 110.5, 110.4, 110.0 (C2'), 106.9, 106.4 (C1), 105.1 (C3), 100.9, 95.6 (C5), 40.3, 39.8 (C2'''), 34.0, 33.3, 33.2, 33.1 (C1', C11'), 29.0, 28.9, 27.7, 22.6, 21.3, 21.0, 20.4, 19.6, 19.4, 19.2, 19.1, 18.7 (C12', C3''', C4'''), 17.5, 17.3 (C13'), 14.3, 11.4 (C3''', C4''') ppm.

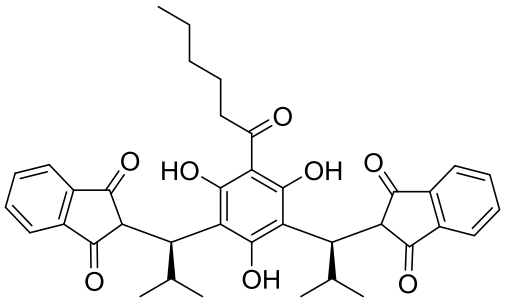
4.6.5.2 Preparation and cyclisation of the myrtucommulone derivative 39

*Indandione-myrtucommulone derivative **39***

According to the general procedure ***GP 6***, hexanoyl phloroglucinol (HPG) (**33**) (112 mg, 0.50 mmol, 1.0 eq.), proline (**90**) (57 mg, 0.50 mmol, 1.0 eq.) and IBIND (**86**) (600 mg, 3.00 mmol, 6.0 eq., prepared according to ***GP 4***) were mixed in ethanol (4 mL) and stirred at room temperature for 18h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/3 to 1/1) to afford 224 mg of the derivative **39** (0.36 mmol, 72 % yield) in two portions: 73 mg of **39b** (0.12 mmol, 24 % yield, R_f = 0.32) and 151 mg of *meso*-**39a** (0.24 mmol, 48 % yield, R_f = 0.32) were separated both as orange powders. Besides 48 mg of the semi-derivative **105** (0.11, 22 %, R_f = 0.41) were also isolated.

Since the NMR-spectra of the non cyclised molecules are challenging to interpret due to their numerous possible conformers and tautomers, only the ^{1}H-NMR spectrum of *meso*-**39** is given.

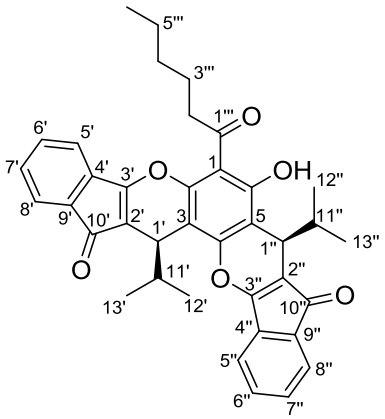
LC-MS (ESI^-) for **105** ($C_{25}H_{27}O_6^-$) $[M-H]^-$: 423.25.
LC-MS (ESI^-) for **39b** ($C_{38}H_{39}O_8^-$) $[M-H]^-$: 625, 35.
HRMS (ESI^+) calcd. for *meso*-**39a** ($C_{38}H_{41}O_8^+$) $[M+H]^+$: 625,2801 found: 625,2817.



^{1}H-NMR (400 MHz, $CO(CD_3)_2$): δ = 13.77 (s, 0.67H, OH), 8.23 (d, *J* = 7.8 Hz, 0.67H, H_{Ar}), 8.01 (d, *J* = 7.8 Hz, 1.05H, H_{Ar}), 7.98-7.91 (m, 0.45H, H_{Ar}), 7.89-7.83 (m, 1H, H_{Ar}), 7.80-7.76 (m, 1H, H_{Ar}), 7.59-7.46 (m, 4H, H_{Ar}), 7.19-7.00 (m, 68H, OH), 3.57 (dd, *J* = 1.3 Hz, *J* = 8.8 Hz, 0.86H), 3.40-3.28 (m, 2.41H), 3.27-3.22 (m, 0.82H), 3.08 (dt, *J* = 17.8 Hz, *J* = 7.3 Hz, 1.27H), 1.67-1.50 (m, 3H), 1.38-1.26 (m, 4.81H), 1.02 (d, *J* = 6.8 Hz, 2.18H), 0.93-0.86 (m, 4H), 0.80 (d, *J* = 6.8 Hz, 2H), 0.66 (d, *J* = 6.8 Hz, 2.17H), 0.19 (d, *J* = 6.8 Hz, 2.17H) ppm.

*Heptacyclic indandione-myrtucommulone derivative syn-**108***

Following the ***GP 9*** procedure, the indandione derivative **39b** (80 mg, 0.13 mmol, 1.0 eq.) and pTsOH (190 mg, 1.00 mmol, 7.6 eq.) were heated to 95°C in toluene (8 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9, R_f = 0.29), 47 mg of the heptacyclic derivative *syn*-**108** (0.08 mmol, 61 % yield) as a yellow solid (*mp* = 205-215°C).

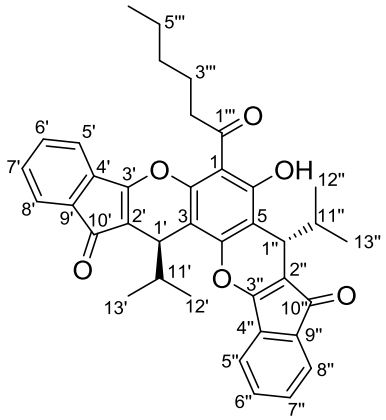


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 13.77 (s, 1H, OH), 7.51 (d, $^3J_{H8',H7'}$ = 7.0 Hz, 1H, H8'), 7.47 (d, $^3J_{H8'',H7''}$ = 7.0 Hz, 1H, H8''), 7.45-7.40 (m, 2H, H6', H6''), 7.39-7.31 (m, 2H, H7', H7''), 7.29 (d, $^3J_{H5',H6'}$ = 7.0 Hz, 1H, H5'), 7.17 (d, $^3J_{H5'',H6''}$ = 7.0 Hz, 1H, H5''), 4.18 (d, $^3J_{H1',H11'}$ = 3.0 Hz, 1H, H1'), 4.06 (d, $^3J_{H1'',H11''}$ = 2.8 Hz, 1H, H1''), 3.35 (dt, $^2J_{H2a''',H2b'''}$ = 17.6 Hz, $^3J_{H2a''',H3'''}$ = 7.5 Hz, 1H, H2a'''), 3.24 (dt, $^2J_{H2b''',H2a'''}$ = 16.6 Hz, $^3J_{H2b''',H3'''}$ = 7.3 Hz, 1H, H2b'''), 2.22 (dsept, $^3J_{H11'-H1'}$ = 3.0 Hz, $^3J_{H11',H12'-H13'}$ = 6.8 Hz, 1H, H11'), 2.15 (dsept, $^3J_{H11'',H1''}$ = 3.0 Hz, $^3J_{H11'',H12''-H13''}$ = 7.0 Hz, 1H, H11''), 1.87-1.75 (m, 2H, H3'''), 1.49-1.38 (m, 4H, H4''', H5'''), 1.12 (d, $^3J_{H12',H11'}$ = 6.8 Hz, 3H, H12'), 1.06 (d, $^3J_{H12'',H11''}$ = 7.0 Hz, 3H, H12''), 0.95 (t, $^3J_{H6'''-H5'''}$ = 7.0 Hz, 3H, H6'''), 0.80 (d, $^3J_{H13',H11'}$ = 6.8 Hz, 3H, H13'), 0.66 (d, $^3J_{H13'',H11''}$ = 6.8 Hz, 3H, H13'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 205.9 (C1'''), 192.6, 192.4 (C10', C10''), 169.8, 169.7 (C3', C3''), 161.2 (C6), 153.8 (C4), 151.3 (C2), 136.4 (C9', C9''), 132.5, 132.4 (C6', C6''), 132.1, 132.0 (C4', C4''), 130.4, 130.2 (C7', C7''), 122.2, 121.9 (C8', C8''), 117.8, 117.7 (C5', C5''), 111.5 (C5), 110.2, 109.8 (C2', C2''), 107.5 (C1), 105.3 (C3), 45.5 (C2'''), 35.2 (C11''), 33.64, 33.55 (C1', C1''), 33.0 (C11'), 31.6 (C4'''), 23.9 (C3'''), 22.6 (C5'''), 21.2, 20.9, (C12', C12''), 17.8, 17.3 (C13', C13''), 14.0 (C6''') ppm.

*Heptacyclic indandione-myrtucommulone derivative anti-**108***

Following the ***GP 9*** procedure, the indandione derivative *meso*-**39a** (80 mg, 0.13 mmol, 1.0 eq.) and pTsOH (190 mg, 1.00 mmol, 7.6 eq.) were heated to 95°C in toluene (8 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9, R_f = 0.28), 38 mg of the heptacyclic derivative *anti*-**108** (0.06 mmol, 49 % yield) as a yellow solid.



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 13.87 (s, 1H, OH), 7.53 (d, $^3J_{H8',H7'}$ = 7.0 Hz, 1H, H8'), 7.49 (d, $^3J_{H8'',H7''}$ = 7.0 Hz, 1H, H8''), 7.46-7.41 (m, 2H, H6', H6''), 7.40-7.32 (m, 2H, H7', H7''), 7.25 (d, $^3J_{H5',H6'}$ = 7.0 Hz, 1H, H5'), 7.19 (d, $^3J_{H5'',H6''}$ = 7.0 Hz, 1H, H5''), 4.28 (d, $^3J_{H1',H11'}$ = 3.0 Hz, 1H, H1'), 4.11 (d, $^3J_{H1'',H11''}$ = 3.3 Hz, 1H, H1''), 3.39 (ddd, $^2J_{H2a''',H2b'''}$ = 17.3 Hz, $^3J_{H2a''',H3a'''}$ = 8.0 Hz, $^3J_{H2a''',H3b'''}$ = 6.8 Hz, 1H, H2a'''), 3.26 (ddd, $^2J_{H2b''',H2a'''}$ = 17.3 Hz, $^3J_{H2b''',H3a'''}$ = 8.0 Hz, $^3J_{H2b''',H3b'''}$ = 6.8 Hz, 1H, H2b'''), 2.20 (dsept, $^3J_{H11'-H1'}$ = 3.3 Hz, $^3J_{H11',H12'-H13'}$ = 7.0 Hz, 1H, H11'), 2.06 (dsept, $^3J_{H11'',H1''}$ = 3.0 Hz, $^3J_{H11'',H12''-H13''}$ = 7.0 Hz, 1H, H11''), 1.89-1.77 (m, 2H, H3'''), 1.50-1.39 (m, 4.89H, H4''', H5'''), 1.14 (d, $^3J_{H12',H11'}$ = 6.8 Hz, 3H, H12'), 1.06 (d, $^3J_{H12'',H11''}$ = 7.0 Hz, 3H, H12''), 0.96 (t, $^3J_{H6'''-H5'''}$ = 7.0 Hz, 3H, H6'''), 0.70 (d, $^3J_{H13',H11'}$ = 7.0 Hz, 3H, H13''), 0.64 (d, $^3J_{H13'',H11''}$ = 6.8 Hz, 3H, H13') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 205.9 (C1'''), 192.6, 192.5 (C10', C10''), 170.06, 170.05 (C3', C3''), 161.7 (C6), 153.7 (C4), 151.6 (C2), 136.4 (C9', C9''), 132.6, 132.5 (C6', C6''), 132.1 (C4', C4''), 130.4, 130.2 (C7', C7''), 122.3, 122.0 (C8', C8''), 117.7, 117.5 (C5', C5''), 111.8 (C5), 110.2, 109.9 (C2', C2''), 107.7 (C1), 105.2 (C3), 45.5 (C2'''), 34.7 (C11''), 33.7, 33.6 (C1', C1''), 33.2 (C11'), 31.6 (C4'''), 24.0 (C3'''), 22.6 (C5'''), 21.3, 21.2, (C12', C12''), 17.4, 17.3 (C13', C13''), 14.0 (C6''') ppm.

4.6.5.3 Preparation and cyclisation of the myrtucommulone derivative 104

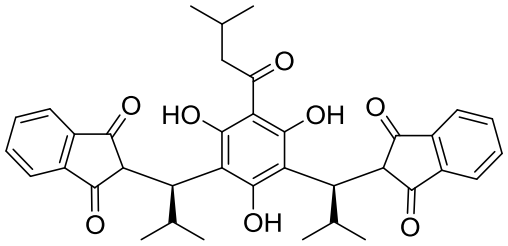
*Indandione-myrtucommulone derivative **104***

According to the general procedure ***GP 6***, isovaleryl phloroglucinol (**32**) (105 mg, 0.50 mmol, 1.0 eq.), proline (**90**) (57 mg, 0.50 mmol, 1.0 eq.), IBIND (**86**) (600 mg, 3.00 mmol, 6.0 eq., prepared according to ***GP 4***) were mixed in ethanol (4 mL) and stirred at room temperature for 48h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/2) to afford 216 mg of the derivative **104** (0.36 mmol,

71 % yield) in two portions: 71 mg of **104b** (0.12 mmol, 24 % yield, R_f = 0.50 (A/PE,1/1)) and 145 mg of *meso*-**104a** (0.24 mmol, 48 % yield, R_f = 0.34 (A/PE, 1/1)) were separated both as orange powders. Besides, 47 mg of the semi-derivative **106** (0.12 mmol, 23 %, R_f = 0.62, (A/PE,1/1)) were also isolated.

Since the NMR-spectra of the non cyclised molecules are challenging to interpret due to their numerous possible conformers and tautomers, only the ^{1}H-NMR spectrum of *meso*-**104** is given.

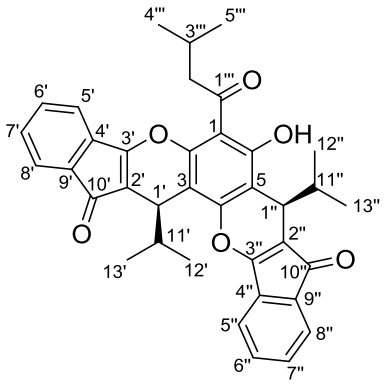
LC-MS (ESI$^-$) for *meso*-**104a** ($C_{37}H_{37}O_8^-$) [M-H]$^-$: 609, 70.



^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 13.77 (s, 0.97H, OH), 8.22 (d, *J* = 7.8 Hz, 0.67H, H_{Ar}), 8.01 (d, *J* = 7.8 Hz, 1.11H, H_{Ar}), 7.89-7.84 (m, 1H, H_{Ar}), 7.81-7.76 (m, 1.16H, H_{Ar}), 7.61-7.44 (m, 4.93H, H_{Ar} + OH), 7.17-7.01 (m, 0.90H, OH), 3.60-3.54 (m, 1H), 3.40-3.25 (m, 2.74H), 3.24 (s, 0.68H), 2.92 (d, *J* = 6.8 Hz, 0.75H), 2.87 (d, *J* = 6.8 Hz, 0.62H), 2.19 (sept, *J* = 6.8 Hz, 1.42H), 2.12-2.05 (m, 1H), 1.64-1.51 (m, 1H), 1.19-1.07 (m, 2.45H), 1.02 (d, *J* = 6.8 Hz, 2.18H), 0.97 (d, *J* = 6.8 Hz, 3.15H), 0.96-0.88 (m, 5.28H), 0.80 (d, *J* = 6.8 Hz, 2.30H), 0.67 (d, *J* = 6.8 Hz, 2.59H), 0.17 (d, *J* = 6.8 Hz, 1.98H) ppm.

*Heptacyclic indandione-myrtucommulone derivative syn-**109***

Following the ***GP 9*** procedure, the indandione derivative **104b** (60 mg, 0.10 mmol, 1.0 eq.) and pTsOH (114 mg, 0.60 mmol, 6.0 eq.) were heated to 95°C in toluene (6 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9, R_f = 0.18), 27 mg of the heptacyclic derivative *syn*-**109** (0.05 mmol, 47 % yield) as a yellow solid (*mp* = 218-221°C).



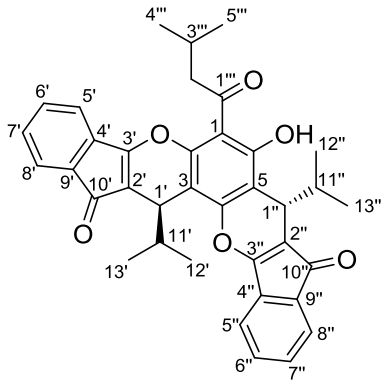
^{1}H-NMR (400 MHz, CDCl$_3$) : δ = 13.81 (s, 1H, OH), 7.52 (d, $^3J_{H8',H7'}$ = 7.0 Hz, 1H, H8'), 7.47 (d, $^3J_{H8'',H7''}$ = 7.0 Hz, 1H, H8''), 7.45-7.40 (m, 2H, H6', H6''), 7.39-7.31 (m, 2H, H7', H7''), 7.29 (d, $^3J_{H5',H6'}$ = 7.0 Hz, 1H, H5'), 7.19 (d, $^3J_{H5'',H6''}$ = 7.0 Hz, 1H, H5''), 4.19 (d, $^3J_{H1',H11'}$ = 3.0 Hz, 1H, H1'), 4.07 (d, $^3J_{H1'',H11''}$ = 3.0 Hz, 1H, H1''), 3.28 (dd, $^2J_{H2a''',H2b'''}$ = 17.3 Hz, $^3J_{H2a''',H3'''}$ = 6.8 Hz, 1H, H2a'''), 3.13 (dd, $^2J_{H2b''',H2a'''}$ = 17.3 Hz, $^3J_{H2b''',H3'''}$ = 6.8 Hz, 1H, H2b'''), 2.38 (sept, $^3J_{H3''',H4'''\text{-}H5'''}$= 6.8 Hz, 1H, H3'''), 2.23 (dsept, $^3J_{H11'',H1'''}$ = 3.0 Hz, $^3J_{H11'',H12''\text{-}H13''}$ =

7.0 Hz, 1H, H11‘‘), 2.16 (dsept, $^{3}J_{H11'\text{-}H1'}$ = 3.0 Hz, $^{3}J_{H11',H12'\text{-}H13'}$ = 7.0 Hz, 1H, H11’), 1.12 (d, $^{3}J_{H12',H11'}$ = 6.8 Hz, 3H, H12‘), 1.09 (d, $^{3}J_{H4'''',H3''''}$ = 6.5 Hz, 3H, H4‘‘‘), 1.06 (d, $^{3}J_{H5'''',H3''''}$ = 6.8 Hz = $^{3}J_{H12'',H11''}$, 6H, H4‘‘‘, H12‘‘), 0.81 (d, $^{3}J_{H13',H11'}$ = 6.8 Hz, 3H, H13‘), 0.67 (d, $^{3}J_{H13'',H11''}$ = 6.8 Hz, 3H, H13‘‘) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 205.4 (C1’’’), 192.6, 192.5 (C10’, C10’’), 169.81, 169.77 (C3’, C3’’), 161.5 (C6), 153.8 (C4), 151.2 (C2), 136.5 (C9’, C9’’), 132.54, 132.45 (C6’, C6’’), 132.1, 132.0 (C4’, C4’’), 130.4, 130.2 (C7’, C7’’), 122.2, 122.0 (C8’, C8’’), 117.8, 117.7 (C5’, C5‘’), 111.6 (C5), 110.3 (C2’’), 109.9 (C2’), 107.8 (C1), 105.3 (C3), 54.3 (C2’’’), 35.3 (C11’), 33.7, 33.6 (C1’, C1’’), 33.1 (C11’’), 24.6 (C3’’’), 22.89, 22.86 (C4’’’, C5’’’), 21.2, 21.0 (C12’, C12’’), 17.9, 17.4 (C13’, C13’’) ppm.

*Heptacyclic indandione-myrtucommulone derivative anti-**109***

Following the ***GP 9*** procedure, the indandione derivative *meso*-**104** (90 mg, 0.15 mmol, 1.0 eq.) and pTsOH (190 mg, 1.00 mmol, 6.7 eq.) were heated to 95°C in toluene (9 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/9, R_f = 0.25), 41 mg of the heptacyclic derivative *anti*-**109** (0.07 mmol, 49 % yield) as a yellow solid (*mp* = 195°C, decomposition).



^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 13.83 (s, 1H, OH), 7.52 (d, $^{3}J_{H8',H7'}$ = 6.8 Hz, 1H, H8’), 7.49 (d, $^{3}J_{H8'',H7''}$ = 6.8 Hz, 1H, H8‘’), 7.46-7.40 (m, 2H, H6‘, H6‘‘), 7.39-7.31 (m, 2H, H7‘, H7‘‘), 7.25 (d, $^{3}J_{H5',H6'}$ = 7.0 Hz, 1H, H5’), 7.20 (d, $^{3}J_{H5'',H6''}$ = 7.0 Hz, 1H, H5‘’), 4.27 (d, $^{3}J_{H1',H11'}$ = 3.0 Hz, 1H, H1’), 4.11 (d, $^{3}J_{H1'',H11''}$ = 3.0 Hz, 1H, H1‘’), 3.33 (dd, $^{2}J_{H2a''',H2b'''}$ = 17.1 Hz, $^{3}J_{H2a''',H3'''}$ = 6.3 Hz, 1H, H2a‘‘‘), 3.11 (dd, $^{2}J_{H2b''',H2a'''}$ = 17.1 Hz, $^{3}J_{H2b''',H3'''}$ = 7.0 Hz, 1H, H2b‘‘‘), 2.39 (sept, $^{3}J_{H3''',H4'''\text{-}H5'''}$= 6.8 Hz, 1H, H3‘‘‘), 2.20 (dsept, $^{3}J_{H11'',H1''}$ = 3.0 Hz, $^{3}J_{H11'',H12''\text{-}H13''}$ = 7.0 Hz, 1H, H11‘’), 2.06 (dsept, $^{3}J_{H11'\text{-}H1'}$ = 3.0 Hz, $^{3}J_{H11',H12'\text{-}H13'}$ = 7.0 Hz, 1H, H11’), 1.17-1.12 (m, 3H, H12‘), 1.09 (d, $^{3}J_{H4''',H3'''}$ = 6.5 Hz, 3H, H4‘‘‘), 1.06 (d, $^{3}J_{H5''',H3'''}$ = 6.5 Hz, 3H, H4‘‘‘), 1.05 (d, $^{3}J_{H12'',H11''}$ = 7.0 Hz, 3H, H12‘‘), 0.71 (d, $^{3}J_{H13',H11'}$ = 6.8 Hz, 3H, H13‘), 0.64 (d, $^{3}J_{H13'',H11''}$ = 6.8 Hz, 3H, H13‘‘) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 205.4 (C1’’’), 192.51, 192.46 (C10’, C10’’), 170.04, 170.01 (C3’, C3’’), 161.6 (C6), 153.7 (C4), 151.6 (C2), 136.4 (C9’, C9’’), 132.5 (C6’, C6’’), 132.1 (C4’, C4’’), 130.4, 130.2 (C7’, C7’’), 122.2, 122.0 (C8’, C8’’), 117.7, 117.5 (C5’, C5‘’), 111.8 (C5), 110.2, 109.9 (C2’, C2’’), 107.9 (C1), 105.2 (C3), 54.2 (C2’’’), 34.7 (C11’), 33.7, 33.6

(C1', C1''), 33.2 (C11''), 24.8 (C3'''), 23.0, 22.8 (C4''', C5'''), 21.3, 21.1 (C12', C12''), 17.4, 17.3 (C13', C13'') ppm.

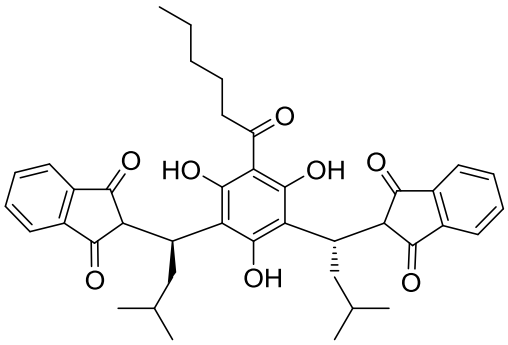
4.6.5.4 Preparation and cyclisation of the myrtucommulone derivative 41

*Indandione-myrtucommulone derivative **41***[128]

According to the general procedure **GP 6**, HPG (**33**) (224 mg, 1.00 mmol, 1.0 eq.), proline (**90**) (115 mg, 1.00 mmol, 1.0 eq.), isopentylidene indandione (**103**) (1.5 g, 6.93 mmol, 6.9 eq., prepared according to ***GP 4***) were mixed in ethanol (8 mL) and stirred at room temperature for 18h. The reaction was worked up and the product was purified through column chromatography on silica gel (A/PE, 1/3 to 1/1) to afford 320 mg of the indandione derivative **41** (0.49 mmol, 49 % yield) in two portions: 125 mg of *meso*-**41a** (0.19 mmol, 19 % yield, R_f = 0.34 (A/PE, 1/2)) and 195 mg of **41b** (0.30 mmol, 30 % yield, R_f = 0.22 (A/PE, 1/2)) were separated both as orange powders. Besides 169 mg of the semi-derivative **107** (0.39, 39 %, R_f = 0.36 (A/PE, 1/2)) were also isolated.

LC-MS (ESI^-) for **107** ($C_{26}H_{29}O_6^-$) $[M-H]^-$: 437.20.
LC-MS (ESI^-) for *meso*-**41a** ($C_{40}H_{43}O_8^-$) $[M-H]^-$: 651.30.
HRMS (ESI^+) calcd. for **41b** ($C_{40}H_{45}O_8^+$) $[M+H]^+$: 653.3114 found: 653.3136

Since the NMR-spectra of the non cyclised molecules are not meaningful due to their numerous possible conformers and tautomers, only the ^{1}H-NMR spectrum of *rac*-**41** is given.

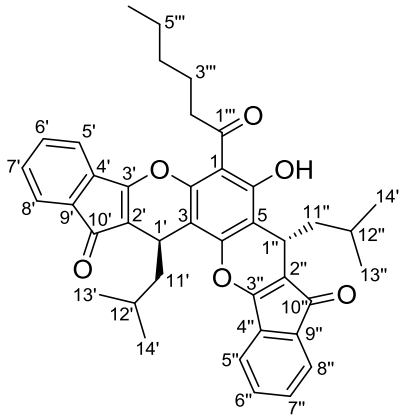


^{1}H-NMR (400 MHz, $CO(CD_3)_2$): δ = 14.28 (brs, 0.15H, OH), 13.69 (brs, 0.15H, OH), 13.63 (brs, 0.14H, OH), 13.42-13.36 (m, 0.07H, OH), 10.01-9.75 (m, 0.13H, OH), 9.68 (brs, 0.14H, OH), 9.40 (s, 0.14H, OH), 8.26 (d, *J* = 7.5 Hz, 0.25H, H_{Ar}), 8.17-7.76 (m, 5.60H, H_{Ar}), 7.76-7.43 (m, 1.93H, H_{Ar}), 7.39 (t, *J* = 8.0 Hz, 0.25H, H_{Ar}), 5.04-4.94 (m, 0.15H), 4.87-4.57 (m, 0.51H), 4.46 (brs, 0.35H), 4.20 (d, *J* = 5.8 Hz, 0.17H), 4.17-4.09 (m, 0.18H), 4.08-3.93 (m, 0.47H), 3.93-3.78 (m, 0.28H), 3.78-3.64 (m, 0.16H), 3.56-3.35 (m, 0.61H), 3.34-3.11 (m, 2.41H), 3.11-2.97 (m, 0.91H), 2.92 (dd, *J* = 7.8 Hz, *J* = 6.8 Hz, 0.32H), 2.14-1.53 (m, 5.58H), 1.46-1.06 (m, 8.31H), 1.05-0.65 (m, 14.41), 0.64-0.50 (m, 1.37H) ppm.

*Heptacyclic indandione-myrtucommulone derivative anti-***110**

Following the ***GP 9*** procedure, the indandione derivative *meso*-**41a** (80 mg, 0.12 mmol, 1.0 eq.) and pTsOH (135 mg, 0.71 mmol, 5.9 eq.) were heated to 95°C in toluene (8 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/6), 15 mg of the heptacyclic derivative *anti*-**110** (0.02 mmol, 20 % yield, R_f = 0.44) as a yellow solid (*mp* = 195-200°C).

HRMS (ESI$^+$) calcd. for *anti*-**110** ($C_{40}H_{40}NaO_6^+$) $[M+Na]^+$: 639.2717 found: 639.2718.



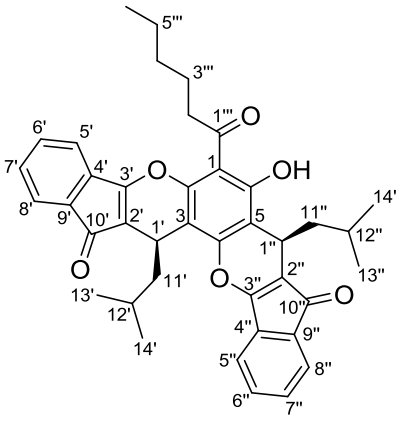
^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 13.83 (s, 1H, OH), 7.54-7.51 (m, 1H, H8'), 7.50 (d, $^3J_{H8'',H7''}$ = 7.5 Hz, 1H, H8''), 7.47-7.40 (m, 2H, H6', H6''), 7.40-7.32 (m, 2H, H7', H7''), 7.31 (d, $^3J_{H5',H6'}$ = 7.0 Hz, 0.73H, H5'), 7.31 (d, $^3J_{H5',H6'}$ = 7.0 Hz, 0.32H, H5'), 7.18 (d, $^3J_{H5'',H6''}$ = 6.8 Hz, 1H, H5''), 4.33 (d, $^3J_{H1',H11'}$ = 3.8 Hz, 0.32H, H1'), 4.31 (d, $^3J_{H1',H11'}$ = 3.5 Hz, 0.34H, H1''), 4.28-4.23 (m, 0.27H, H1', H1''), 4.21 (d, ^3J = 5.8 Hz, 0.21H, H1', H1''), 4.14 (d, ^3J = 3.3 Hz, 0.34H, H1', H1''), 4.12 (d, ^3J = 3.0 Hz, 0.34H, H1', H1''), 4.10 (d, ^3J = 3.3 Hz, 0.14H, H1', H1''), 4.08 (d, ^3J = 3.0 Hz, 0.14H, H1', H1''), 3.43-3.21 (m, 2H, H2'''), 1.89-1.77 (m, 2H, H3'''), 1.73-1.52 (m, 6H, H11', H11'', H12', H12''), 1.50-1.39 (m, 4H, H4''', H5'''), 1.21-1.16 (m, 3H, H13', H13''), 1.07-1.01 (m, 3.16H, H13', H13''), 0.97 (t, $^3J_{H6'''-H5'''}$ = 7.0 Hz, 3H, H6'''), 0.84 (d, $^3J_{14',H12'}$ = 6.3 Hz, 0.91H, H14'), 0.78 (d, $^3J_{14',H12'}$ = 6.0 Hz, 0.94H, H14''), 0.77-0.71 (m, 4.08, H14', H14'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 205.9 (C1'''), 192.6, 192.5 (C10', C10''), 168.7, 168.4 (C3', C3''), 161.8 (C6), 153.0 (C4), 151.6 (C2), 136.6 (C9', C9''), 132.5 (C6', C6''), 132.0 (C4', C4''), 130.4, 130.2 (C7', C7''), 122.3, 122.0 (C8', C8''), 117.83, 117.80 (C5', C5''), 115.3 (C5), 113.0, 112.8, 112.4 (C2', C2''), 107.9 (C1), 106.4 (C3), 47.4, 45.53 (C11', C11''), 45.49 (C2'''), 31.6 (C4'''), 26.1, 26.0, 25.9 (C1', C1''), 25.5, 25.3 (C12', C12''), 24.1, 24.0, 23.9 (C3''', C14', C14''), 22.7 (C5'''), 22.23, 22.15 (C13', C13''), 14.0 (C6''') ppm.

*Heptacyclic indandione-myrtucommulone derivative syn-***110**

Following the ***GP 9*** procedure, the indandione derivative **41b** (90 mg, 0.14 mmol, 1.0 eq.) and pTsOH (157 mg, 0.83 mmol, 5.9 eq.) were heated to 95°C in toluene (9 mL) for 1h to yield, after purification on column chromatography (A/PE, 1/6), 30 mg of the heptacyclic derivative *syn*-**110** (0.05 mmol, 35 % yield, R_f = 0.34) as a yellow solid (*mp* = 198-202°C).

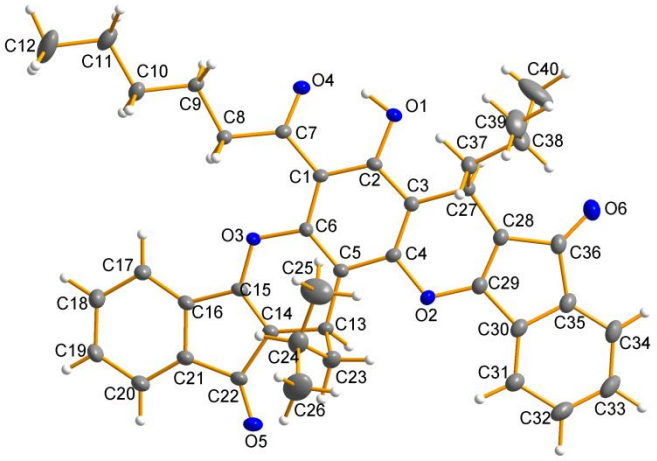
HRMS (ESI$^+$) calcd. for *syn*-**110** ($C_{40}H_{41}O_8^+$) $[M+H]^+$: 617.2897 found: 617.2908



^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 13.83 (s, 1H, OH), 7.49 (d, $^3J_{H8'',H7''}$ = 7.0 Hz, 1H, H8''), 7.47-7.44 (m, 1H, H8''), 7.43-7.31 (m, 4H, H6', H6'', H7', H7''), 7.27-7.23 (m, 1H, H5'), 7.15 (d, $^3J_{H5'',H6''}$ = 7.0 Hz, 1H, H5''), 4.18-4.13 (m, 1H, H1', H1''), 4.02 (d, ^3J = 3.0 Hz, 0.45H, H1', H1''), 4.00 (d, ^3J = 3.0 Hz, 0.46H, H1', H1''), 3.33 (dt, $^2J_{H2a''',H2b'''}$ = 17.6 Hz, $^3J_{H2a''',H3'''}$ = 7.5 Hz, 1H, H2a'''), 3.22 (dt, $^2J_{H2b''',H2a'''}$ = 17.6 Hz, $^3J_{H2b''',H3'''}$ = 7.3 Hz, 1H, H2b'''), 1.94 (sept, ^3J = 6.8 Hz, 0.63H, H12'), 1.85-1.76 (m, 2H, H3'''), 1.69-1.61 (m, 4H, H11', H11''), 1.77-1.70 (m, 1.22H, H12', H12''), 1.48-1.39 (m, 4H, H4''', H5'''), 1.15 (d, $^3J_{13',H12'}$ = 6.3 Hz, 3H, H13'), 1.03-1.00 (m, 3H, H13''), 0.99-0.93 (m, 3H, H6'''), 0.80 (d, $^3J_{14',H12'}$ = 6.5 Hz, 0.91H, H14'), 0.75 (d, $^3J_{14'',H12''}$ = 6.0 Hz, 3H, H14'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$) : δ = 205.8 (C1'''), 192.5, 192.4 (C10', C10''), 168.4, 168.1 (C3', C3''), 161.7 (C6), 153.0 (C4), 150.6 (C2), 136.54, 136.50 (C9', C9''), 132.6 (C6', C6''), 132.0, 131.9 (C4', C4''), 130.4, 130.2 (C7', C7''), 122.1, 121.9 (C8', C8''), 117.9, 117.8 (C5', C5''), 113.1 (C5), 112.32, 112.28 (C2', C2''), 107.7 (C1), 106.4 (C3), 45.6, 45.5 (C11', C11''), 37.1 (C2'''), 31.6 (C4'''), 26.0 (C1', C1''), 28.8 (C3'''), 25.5, 25.4 (C12', C12''), 23.92, 23.89, 23.87 (C14', C14''), 22.7, 22.5 (C5'''), 22.3, 22.0 (C13', C13''), 14.0 (C6''') ppm.

Crystal Structure: (for the complete data see Appendix 7)



Exp. Data Tab. 6 Crystal data and structure refinement for *syn*-**110** (sh3552).

Identification code	sh3552	
Empirical formula	C40 H40 O6	
Formula weight	616.72	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.2500(8) Å	α = 90°.
	b = 19.6628(13) Å	β = 96.290(2)°.
	c = 15.0044(10) Å	γ = 90°.
Volume	3299.1(4) $Å^3$	
Z	4	
Density (calculated)	1.242 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	1312	
Crystal size	0.545 x 0.379 x 0.120 mm^3	
Theta range for data collection	1.714 to 30.574°.	
Index ranges	-16<=h<=14, -28<=k<=18, -21<=l<=17	
Reflections collected	39027	
Independent reflections	10077 [R(int) = 0.0380]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7461 and 0.7140	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10077 / 0 / 575	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2sigma(I)]	R1 = 0.0523, wR2 = 0.1322	
R indices (all data)	R1 = 0.0790, wR2 = 0.1490	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.621 and -0.251 $e.Å^{-3}$	

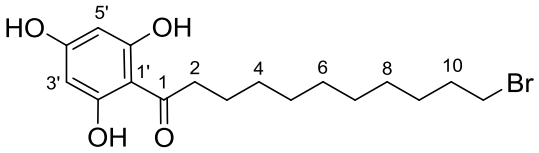
4.7. Synthesis of the myrtucommulone-biotin derivative

4.7.1. Syntheses for the introduction of an alkyl linker

*11-Bromo-undecanoyl-phloroglucinol (BrUP) (**126**)*[107]

11-bromo-undecanoic acid (**129**) (2.0 g, 7.5 mmol, 1.0 eq.) was dissolved in 4 mL DCM_{abs} and oxalyl chloride (1.0 mL, 1.5 g, 11.6 mmol, 1.5 eq.) was added slowly. After stirring for 2h the solvent and excess oxalyl chloride were removed under reduced pressure to yield 2.0 g (7.0 mmol, 94 % yield) of the crude 11-bromo-undecanoyl chloride that was used without purification.

According to the general procedure ***GP 1***, 11-bromo-undecanoyl chloride (2.0 g, 7.0 mmol, 1.0 eq.) was added to phloroglucinol (**28**) (897 mg, 7.12 mmol, 1.0 eq.) and aluminium trichloride (1.898 g, 14.24 mmol, 2.0 eq.) dissolved in anhydrous dichloromethane (7 mL) and nitromethane (2.3 mL). After purification by flash chromatography on silica gel (A/PE, 1/3, R_f = 0.16) 11-bromo-undecanoyl-phloroglucinol (**126**) (2.166 g, 5.79 mmol) as a white solid (*mp* = 150-151°C) with 82 % yield.



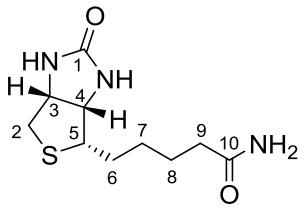
^{1}H-NMR (400 MHz, $CO(CD_3)_2$): δ = 11.73 (brs, 2H, C2'-OH, C6'-OH), 9.19 (brs, 1H, C4'-OH), 5.92 (s, 2H, H3', H5'), 3.48 (t, $^3J_{H11,H10}$ = 6.8 Hz, 2H, H11), 3.06 (m, 2H, H2), 1.88-1-80 (m, 2H, H10), 1.66 (quint, $^3J_{H3,H2}$ = $^3J_{H3,H4}$ = 7.0 Hz, 2H, H3), 1.48-1.40 (m, 2H, H9), 1.37-1.29 (m, 10H, H4, H5, H6, H7, H8) ppm.

^{13}C-NMR (101 MHz, $CO(CD_3)_2$): δ = 207.5 (C1), 166.4 (C2', C6'), 166.1 (C4'), 106.1 (C1'), 96.8 (C3', C5'), 45.4 (C2), 35.6 (C11), 34.6 (C10), 31.4, 31.2, 31.1, 30.4, 29.8, 26.5 (C3, C4, C5, C6, C7, C8, C9) ppm.

HRMS (ESI^+) calcd. for $C_{17}H_{26}BrO_4^+$ $[M+H]^+$: 373.1014; found 373.1001.

*Biotinamide (**127**)*[108]

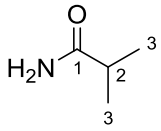
Biotin (**23**) (311 mg, 1.27 mmol) was dissolved in thionyl chloride (6 mL) and stirred 5 min at room temperature in the absence of moisture. The excess thionyl chloride was co-evaporated twice with dichloromethane under reduced pressure. To the crude acyl chloride were then added 10 mL of aqueous ammonia releasing white fumes. After stirring for 30 minutes, the precipitate was washed with cold water and cold methanol (which dissolved partially the product) to yield 35 % of biotinamide (**127**) (107 mg, 0.44 mmol).



^{1}H-NMR (400 MHz, SO(CD$_3$)$_2$): δ = 7.22 (s, 1H, NH_2), 6.68 (s, 1H, NH_2), 6.42 (s, 1H, NH), 6.35 (s, 1H, NH), 4.33-4.27 (m, 1H, H3), 4.15-4.09 (m, 1H, H5), 3.14-3.06 (m, 1H, H5), 2.82 (dd, $^2J_{H9a,H9b}$ = 12.3 Hz and $^3J_{H9a,H8}$ = 5.0 Hz, 1H, H2a), 2.69 (d, $^2J_{H9b,H9a}$ = 12.3 Hz, 1H, H2b), 2.03 (t, $^3J_{H2,H3}$ = 7.3 Hz, 2H, H9), 1.66-1.41 (m, 4H, H6, H8), 1.38-1.24 (m, 2H, H7) ppm.

*Isobutyramide (**130**)*[109]

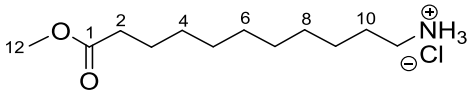
Isobutyryl chloride (2.0 mL, 2.0 g, 19.0 mmol) was slowly added to 8 mL aqueous ammonia. The milky mixture was then stirred for 1h and evaporated to dryness under reduced pressure. The white residue was then boiled in 10 mL ethyl acetate filtrated quickly on a hot funnel. This process was repeated twice with the same amount of ethyl acetate and the combined organic extracts were cooled to 0°C. Crystalline isobutyramide (**130**) which had precipitated was removed by filtration. The filtrate was concentrated to a third and cooled down again to collect a second fraction of the product. The shiny needles of isobutyramide (**130**) were dried under vacuum to yield 1.0 g (11.5 mmol, 60 % yield) of the product.



^{1}H-NMR (400 MHz, SO(CD$_3$)$_2$): δ = 7.19 (s, 1H, NH_2), 6.63 (s, 1H, NH_2), 2.31 (sept, $^3J_{H2,H3}$ = 7.0 Hz,1H, H2), 0.98 (d, $^3J_{H3,H2}$ = 7.0 Hz,1H, H3) ppm.

mp = 124-127°C (Lit. [109] 127-129°C)

*11-Aminium chloride-undecanoic acid methyl ester (AUMe) (**132**)*[113]



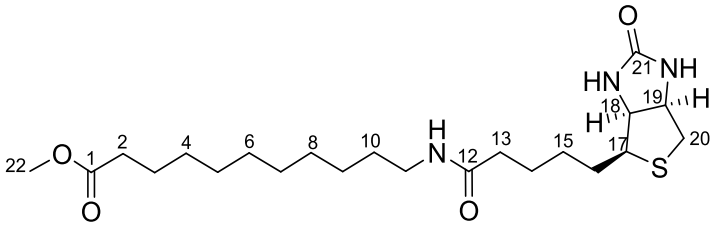
11-Aminoundecanoic acid (1.85 g, 9.19 mmol, 1.0 eq.) was suspended in 9 mL anhydrous methanol. The mixture was cooled to 0°C and thionyl chloride (2.0 mL, 27.57 mmol, 3.0 eq.) was added dropwise. The resulting solution was then heated to reflux overnight and the methanol and thionyl chloride in excess were then removed under reduced pressure. 11-aminium chloride-undecanoic acid methyl ester (**132**) was obtained as a yellowish white powder (2.26 g, 8.98 mmol, 98 % yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.25 (brs, 3H, NH_3^+), 3.65 (s, 3H, H12), 2.97 (brs, 2H, H11), 2.29 (t, $^{3}J_{H2,H3}$ = 7.5 Hz, 2H, H2), 1.76 (brs, 2H, H10), 1.60 (quint, $^{3}J_{H3,H2}$ = $^{3}J_{H3,H4}$ =7.3 Hz, 2H, H3), 1.43-1.33 (m, 2H, H9), 1.33-1.22 (m, 10H, H4, H5, H6, H7, H8) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 174.3 (C1), 51.4 (C12), 40.0 (C11), 34.1 (C2), 29.3, 29.2, 29.1, 28.9 (C4, C5, C6, C7, C8), 27.6 (C10), 26.5 (C9), 24.9 (C3) ppm.

*Methyl 11-(biotinamido)undecanoate (BtAUMe) (**133**)*[113-114]

Biotin (**23**) (150 mg, 0.61 mmol, 1.0 eq.) was dissolved in DMF_{abs} at 70°C and the solution was cooled to room temperature. DIC (380 µL, 2.44 mmol, 4.0 eq.) and HOBT (118 mg, 84-89 % as a hydrate, ≥0.73 mmol, 1.2 eq.) were added to the mixture and stirred 1h at room temperature. AUMe (**132**) (184 mg, 0.73 mmol, 1.2 eq.) was suspended in DMF_{abs} and TEA (140 µL, 1.0 mmol, 1.6 eq.) stirred until the ester was dissolved. The solution was then transferred with a syringe into the flask containing biotin (**23**) and stirred at room temperature overnight. Water (10 mL) was added to the mixture, and the crude product was extracted with DCM (3 x 10 mL). The organic layer was washed with a 1M HCl solution, a saturated solution of $NaHCO_3$ and brine. After drying with sodium sulfate, the mixture was filtrated and the solvent was removed under reduced pressure. The crude product was purified with silica gel column chromatography (DCM/MeOH, 95/5, R_f = 0.15) to afford 192 mg of methyl 11-(biotinamido)-undecanoate (BtAUMe) (**133**) (0.44 mmol, 73 % yield) as a white powder.

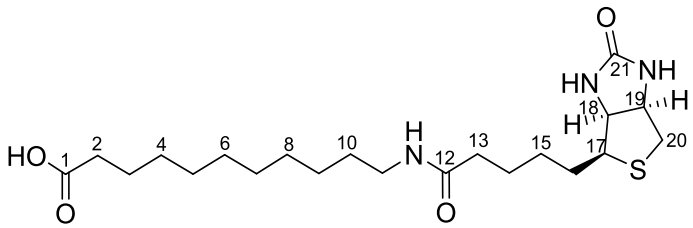


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.39 (brs, 1H, C18-NH), 6.00 (t, $^{3}J_{HN,H11}$ = 5.8 Hz, 1H, C11-NH), 5.55 (brs, 1H, C19-NH), 4.50 (dd, $^{3}J_{H19,H18}$ = 7.8 Hz, $^{3}J_{H19,H20a}$ = 5.0 Hz, 1H, H19), 4.32-4.28 (m, 1H, H18), 3.65 (s, 3H, H22), 3.23-3.17 (m, 2H, H11), 3.14 (dt, $^{3}J_{H17,H18}$ = 4.8, $^{3}J_{H17,H16}$ =7.3 Hz, 1H, H17) 2.90 (dd, $^{2}J_{H20a,H20b}$ = 12.8 Hz, $^{3}J_{H20a,H19}$ = 5.0 Hz, 1H, H20a), 2.73 (d, $^{2}J_{H20b,H20a}$ = 12.8 Hz, 1H, H20b), 2.29 (t, $^{3}J_{H2,H3}$ = 7.5 Hz, 2H, H2), 2.19 (t, $^{3}J_{H13,H14}$ = 7.5 Hz, 2H, H13), 1.80-1.54 (m, 6H, H3, H14, H16), 1.51-1.38 (m, 4H, H15, H10), 1.33-1.22 (m, 12H, H4, H5, H6, H7, H8, H9) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 174.3 (C1), 173.1 (C12), 163.9 (C21), 61.2 (C18), 60.2 (C19), 55.6 (C17), 51.4 (C22), 40.5 (C20), 39.5 (C11), 36.1 (C13), 34.1 (C2), 29.6, 29.4, 29.31, 29.25, 29.2, 29.1, 28.2, 28.1, 26.9, 25.7, 24.9, (C3, C4, C5, C6, C7, C8, C9, C10, C14, C15, C16) ppm.

*11-Biotinamido-undecanoic acid (BtAU) (**131**)*[113]

BtAUMe (**133**) (190 mg, 0.43 mmol, 1.0 eq.) was suspended in a mixture of MeOH (4.3 mL), water (2.6 mL) and THF (1.5 mL), and lithium hydroxide hydrate (36 mg, 0.85 mmol, 2.0 eq.) was added in one portion. The mixture was then stirred overnight at 55°C. After removal of the majority of the solvents under vacuum, the mixture was acidified to pH 2.0 with 1M HCl. The precipitation was filtered off and washed with cold water and cold ether subsequently, before being dried under vacuum to give 11-biotinamido-undecanoic acid (**131**) (154 mg, 0.36 mmol) with 84 % yield as a hardly soluble white solid.



^{1}H-NMR (400 MHz, CD_3OD): δ = 4.47 (dd, $^{3}J_{H19,H18}$ = 7.8 Hz, $^{3}J_{H19,H20a}$ = 5.0 Hz, 1H, H19), 4.28 (dd, $^{3}J_{H18,H19}$ = 7.8 Hz, $^{3}J_{H18,H17}$ = 4.3 Hz, 1H, H18), 3.21-3.17 (m, 2H, H17), 3.14 (dt, $^{3}J_{H11,H10}$ = 7.3, $^{3}J_{H11,H9}$ = 2.0 Hz, 2H, H11), 2.91 (dd, $^{2}J_{H20a,H20b}$ = 12.8 Hz, $^{3}J_{H20a,H19}$ = 5.0 Hz,

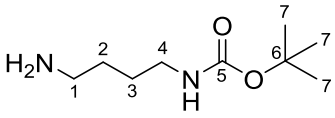
1H, H20a), 2.69 (d, $^{2}J_{H20b,H20a}$ = 12.8 Hz, 1H, H20b), 2.17 (q, ^{3}J = 7.0 Hz, 4H, H2, H13), 1.78-1.52 (m, 6H, H3, H14, H16), 1.52-1.36 (m, 4H, H15, H10), 1.34-1.26 (m, 12H, H4, H5, H6, H7, H8, H9) ppm.

^{13}C-NMR (101 MHz, CD_3OD): δ = 176.0 (C12), (C1 not seen), 166.2 (C21), 63.4 (C18), 61.7 (C19), 57.1 (C17), 41.1 (C20), 40.5 (C11), 36.7 (C13), 30.8, 30.7, 30.6, 30.5, 29.8, 29.6, 28.1, 27.5, 27.0 (C2, C3, C4, C5, C6, C7, C8, C9, C10, C14, C15, C16) ppm.

4.7.2. Syntheses for the introduction of a polyamide linker

*tert-Butyl-4-aminobutylcarbamate (Boc-DAB) (**142**)*[115a]

1,4-Diamino-butane (DAB) (**141**) (11.2 g, 127 mmol, 10 eq.) was melted at 50°C (*mp* = 25-28°C) on the hot plate, transferred to a flame dried flask with dropping funnel a under nitrogen atmosphere and dissolved in 170 mL anhydrous DCM. Boc anhydride (2.8 g, 13 mmol, 1.0 eq.) was dissolved in DCM under nitrogen atmosphere and added to the dropping funnel. The DAB (**141**) solution was cooled down to 0°C and the anhydride wad added over 1h, stirred 2h more at 0°C after completion of the addition, and overnight at room temperature. The reaction was quenched with water, washed with brine, the organic layer was separated washed with sodium sulfate and the solvents were evaporated. The N-Boc-diaminobutane (Boc-DAB) (**142**) (1.9 g, 10 mmol) was obtained with 76 % yield as a viscous white oil.



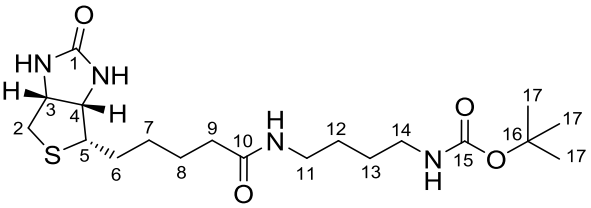
^{1}H-NMR (400 MHz, $CDCl_3$): δ =4.65 (brs, 1H, NH) 3.18-3.04 (m, 2H, H4), 2.70 (t, $^{3}J_{H4,H3}$ = 6.8 Hz, 2H, H1), 1.56-1.45 (m, 4H, H2, H3), 1.44 (s, 9H, H7), 1.21 (brs, 1H, NH_2) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 156.0 (C5), 78.9 (C6), 41.7 (C3), 40.4 (C4), 30.8 (C2), 28.3 (C7), 27.4 (C3) ppm.

*tert-Butyl-4-biotinamidobutylcarbamate (Boc-DAB-Bt) (**143**)*[115a]

In a flame dried equipment, biotin (**23**) (200 mg, 0.82 mmol, 1.0 eq.) was dissolved in anhydrous DMF (6.6 mL) at 70°C. After the reaction was cooled down to room temperature, molecular sieves (3Å), and hydroxybenzotriazole (26 mg, 84-89 % as hydrate, 0.16 mmol, 0.2 eq.) were added and the mixture was stirred 5 minutes before DCC (0.9 mL of a 1.0 M solution in DCM, 0.90 mmol, 1.1 eq.) was slowly added. After stirring for 3h, Boc-DAB (**142**)

and a few crystals of DMAP were dissolved in 2 mL DCM_{abs}/DMF_{abs} (1/1) and added to the biotin (**23**) mixture. The reaction mixture was then stirred 4h at 60°C and overnight at room temperature. Molecular sieves were separated by filtration and washed with a DCM/MeOH, 1/1 solution before the solvents were removed under reduced pressure (10 mbar/50°C). The residue was then submitted to flash chromatography on silica gel (DCM/MeOH, 90/10 to 85/15, R_f = 0.19 (DCM/MeOH, 9/1)) to give the biotinamidobutyl-carbamate (Boc-DAB-Bt) **143** (244 mg, 0.59 mmol) with 72 % yield as a white solid (*mp* = 176-181°C, Lit.[115a] 178-180°C). $[\alpha]_D^{24}$ = 0.0 (MeOH, *c* = 1.0)



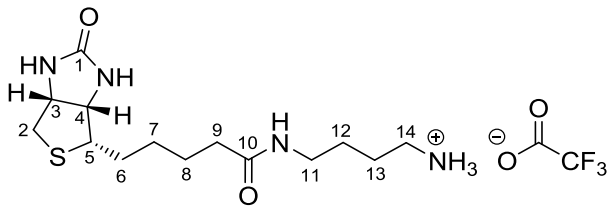
^{1}H-NMR (400 MHz, CD_3OD): δ = 4.49 (dd, $^3J_{H3,H4}$ = 7.8 Hz, $^3J_{H3,H2a}$ = 5.0 Hz, 1H, H3), 4.31 (dd, $^3J_{H4,H3}$ = 7.8 Hz, $^3J_{H4,H5}$ = 4.5 Hz, 1H, H4), 3.24-3.15 (m, 3H, H5, H11), 3.07-3.02 (m, 2H, H14), 2.93 (dd, $^2J_{H2a,H2b}$ = 12.8 Hz, $^3J_{H2a,H3}$ = 5.0 Hz, 1H, H2a), 2.71 (d, $^2J_{H2b,H2a}$ = 12.8 Hz, 1H, H2b), 2.22 (t, $^3J_{H9,H8}$ = 7.4 Hz, 2H, H9), 1.79-1.55 (m, 4H, H6, H8), 1.54-1.47 (m, 4H, H12, H13), 1.46-1.39 (m, 11H, H7, H17) ppm.

^{13}C-NMR (101 MHz, CD_3OD): δ = 176.0 (C10), 166.1 (C1), 158.6 (C15), 79.9 (C16) 63.4 (C4), 61.7 (C3), 57.0 (C5), 41.1 (C14), 41.0 (C2), 40.1 (C11), 36.9 (C9), 29.8 (C7), 29.5 (C6), 28.8 (C17), 28.4, 27.8 (C12, C13), 26.9 (C8) ppm.

HRMS (ESI^+) calcd. for $C_{19}H_{35}N_4O_4S^+$ $[M+H]^+$: 415.2379; found 415.2379

*4-Biotinamido-butan-1-aminium trifluoroacetate (BtABA) (**144**)*[115d]

Boc-DAB-Bt (**143**) (465 mg, 1.12 mmol) was suspended in DCM, 2 mL TFA were added and the mixture was stirred at room temperature for 2h before the solvent were removed under vacuum. The product was dried in an exsiccator filled with KOH pellets to remove the excess trifluoroacetic acid. BtABA (**144**) (489 mg, 96 % purity based on ^{19}F-NMR, 1.09 mmol) was obtained as its trifluoroacetate salt (white solid) in slightly over-quantitative yield, because TFA could not be removed completely, but it did not matter for the following reaction.
R_f = 0.21 (DCM/MeOH, 4/1), *mp* = 83-102°C, $[\alpha]_D^{24}$ = + 4.0 (MeOH, *c* = 1.0)



^{1}H-NMR (400 MHz, CD_3OD): δ = 4.50 (dd, $^{3}J_{H3,H4}$ = 8.0 Hz, $^{3}J_{H3,H2a}$ = 5.0 Hz, 1H, H3), 4.31 (dd, $^{3}J_{H4,H3}$ = 8.0 Hz, $^{3}J_{H4,H5}$ = 4.5 Hz, 1H, H4), 3.24-3.18 (m, 3H, H5, H11), 2.98-2.92 (m, 2H, H14), 2.93 (dd, $^{2}J_{H2a,H2b}$ = 12.8 Hz, $^{3}J_{H2a,H3}$ = 5.0 Hz, 1H, H2a), 2.71 (d, $^{2}J_{H2b,H2a}$ = 12.8 Hz, 1H, H2b), 2.21 (t, $^{3}J_{H9,H8}$ = 7.4 Hz, 2H, H9), 1.79-1.54 (m, 8H, H6, H8, H12, H13), 1.46-1.39 (m, 2H, H7) ppm.

^{13}C-NMR (101 MHz, CD_3OD): δ = 176.3 (C10), 166.2 (C1), 162.1 (CF_3**C**(O)O^-), 63.5 (C4), 61.7 (C3), 57.1 (C5), 41.1 (C14), 40.4 (C2), 39.5 (C11), 36.8 (C9), 29.8 (C7), 29.5 (C6), 27.5, 26.9 (C12, C13), 25.9 (C8) ppm.

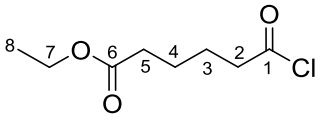
^{19}F-NMR (377 MHz, CD_3OD): δ = -76.83 (s, 1.00F, trifluoroacetic acid), -77.20 (s, 28.34F, trifluoroacetate) ppm.

HRMS (ESI$^+$) calcd. for $C_{14}H_{27}N_4O_2S^+$ $[M+H]^+$: 315.1854; found 315.1845.

*Adipoyl chloride monoethylester (**138**)*[116-117]

Adipic acid (**137**) (5.0 g, 34.2 mmol) was suspended in thionyl chloride (7.0 mL, 96.5 mmol) in absence of moisture and was heated at 90°C overnight under nitrogen atmosphere. The excess thionyl chloride was removed under vacuum to afford 6.23 g of crude adipoyl chloride that was used without further purification.

In a flame-dried round-bottom flask containing molecular sieves (3Å) and fitted with a dropping funnel, was dissolved the acyl chloride (6.23 g, ≈ 34.2 mmol) in anhydrous THF (60 mL). 59 mL of an equimolar 0.58M solution of ethanol (2.00 mL, 34.2 mmol) and triethylamine (4.80 mL, 34.2 mmol) were then added dropwise over 2h and the mixture was stirred 1.5h more after the end of the addition. The ammonium chloride salt that had formed during the reaction was filtrated through a hot funnel and the solvents were evaporated under reduced pressure. 6.3 g of crude product was obtained containing 2.9 g of the monoester (**138**) (15.0 mmol, determined on NMR) representing 44 % yield. The rest of the mixture includes unreacted dichloride, the diester and diethyl sulfite.

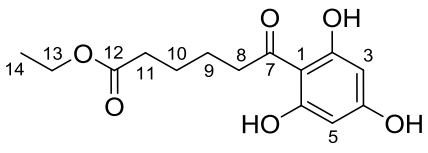


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.19 (q, ^{3}J = 7.3 Hz, 0.5 H, $\underline{CH_2}CH_3$, $SO(OEt)_2$), 4.13, 4.12 (2 x q, ^{3}J = 7.0 Hz, 2H, H7, mono- and diester), 2.97-2.98 (m, 2H, H2**,** monoester and dichloride), 2.35-2.26 (m, 2.8 H, H5, monoester, diester, dichloride), 1.80-1.63 (m, 4H, H3, H4, monoester, diester, dichloride), 1.28 (t, ^{3}J = 7.0 Hz, $CH_2\underline{CH_3}$, $SO(OEt)_2$), 1.254, 1.248 (2 x t, ^{3}J = 7.0 Hz, 3H, H8, mono- and diester) ppm.

^{13}C-NMR (101 MHz, CD_3OD): δ = 173.5, 173.4, 173.3, 172.9 (C1, C6, monoester, diester, dichloride), 61.4, 60.5, 60.3 (C7, monoester, diester, diethylsulfite), 46.7, 46.4 (C2, monoester, dichloride), 33.9, 33.6 (C5, monoester, diester), 24.5, 24.4 (C3, C4, mono- and diester), 23.8, 23.7 (C3, C4, monoester, dichloride), 14.20, 14.15 (C8, monoester, diester, diethylsulfite) ppm.

*Phloroglucinol adipic acid ethyl ester (**139**)*[107b]

According to the general procedure ***GP 1***, to phloroglucinol (**28**) (2.9 g, 23 mmol, 1.5 eq.) and aluminium trichloride (8.4 g, 63 mmol, 2.7 eq.) dissolved in anhydrous dichloromethane (21 mL) and nitromethane (7 mL), was added the acyl chloride **138** (2.9 g, 15 mmol, 1.0 eq.). After purification by flash chromatography on silica gel (A/PE, 1/2, R_f = 0.25) phloroglucinol adipic acid ethyl ester (**139**) (2.65 g, 9.4 mmol) was obtained with 63 % yield as a light yellow solid (*mp* = 136-139°C).



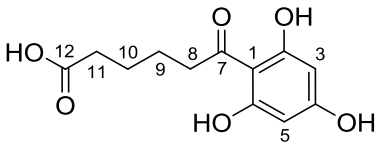
^{1}H-NMR (400 MHz, $CO(CD_3)_2$): δ = 11.63 (brs, 2H, C6-OH, C2-OH), 9.51 (brs, 1H, C4-OH), 5.92 (s, 2H, H3, H5), 4.07 (q, $^{3}J_{H13,H14}$ = 7.0 Hz, 2H, H13), 3.11-3.05 (m, 2H, H8), 2.35-2.29 (m, 2H, H11), 1.74-1.63 (m, 4H, H9, H10), 1.20 (t, $^{3}J_{H14,H13}$ = 7.0 Hz, 3H, H14) ppm.

^{13}C-NMR (101 MHz, $CO(CD_3)_2$): δ = 207.1 (C7), 174.5 (C12), 166.4 (C2, C6), 166.2 (C4), 106.1 (C1), 96.8 (C3, C5), 61.4 (C13), 45.0 (C8), 35.6 (C11), 26.5, 25.9 (C9, C10), 15.5 (C14) ppm.

HRMS (ESI^+) calcd. for $C_{14}H_{19}O_6^+$ $[M+H]^+$: 283.1182; found 283.1169.

*6-oxo-6-phloroglucinol-hexanoic acid (**140**)*[118]

The ethyl ester **139** (2.6 g, 9.2 mmol) was dissolved in a MeOH (14 mL)/THF (14 mL) mixture and 21 mL of NaOH 2M were added. The yellow solution turned dark green. After stirring for 2h at room temperature, the volatile components were evaporated under vacuum. The aqueous phase was acidified with 2 M HCl and the crude product was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtrated and evaporated. The residue was purified on silica gel column chromatography (A/PE, 1/1, + 1% AcOH, R_f = 0.45) to afford 2.1 g of the free acid (**140**) (8.2 mmol, 89 % yield) as a pale yellow powder (*mp* = 188-194°C).



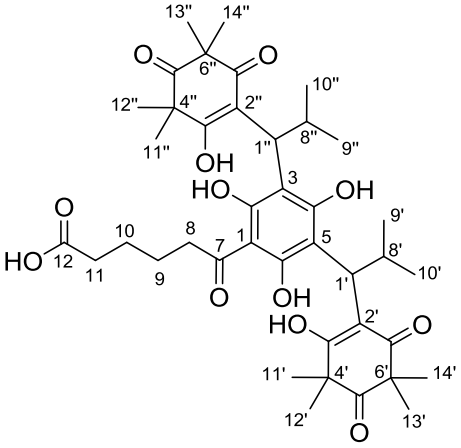
^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 10.73 (brs, 4H, C6-OH, C2-OH, C4-OH, C(O)OH), 5.93 (s, 2H, H3, H5), 3.13-3.07 (m, 2H, H8), 2.36-2.32 (m, 2H, H11), 1.75-1.64 (m, 4H, H9, H10), ppm.

^{13}C-NMR (101 MHz, CO(CD$_3$)$_2$): δ = 207.1 (C7), 175.9, 175.8 (C12), 166.4 (C2, C6), 166.1 (C4), 106.1 (C1), 96.8 (C3, C5), 61.4 (C13), 45.0 (C8), 35.1, 34.9 (C11), 26.5, 26.1, 26.0 (C9, C10), 15.5 (C14) ppm.

HRMS (ESI$^+$) calcd. for $C_{12}H_{15}O_6^+$ $[M+H]^+$: 255.0869; found 255.0862.

*5-myrtucommulone-pentanoic acid (MCPA) (**135**)*[35a]

In a flame-dried round-bottom flask, the phloroglucinol **140** (254 mg, 1.00 mmol, 1.0 eq.) was dissolved in anhydrous THF (5 mL) under nitrogen atmosphere. Sodium hydride (132 mg, 60 % dispersion in mineral oil, 3.30 mmol, 3.3 eq.) was added in one portion and the mixture was stirred for 10 min before IBSA (**31**) (1.31 g, 5.5 mmol), prepared according to the general method ***GP 3*** and dissolved in 5 mL anhydrous THF, was added as well. After stirring for 1h at room temperature, almost no reaction was observed. 132 mg of NaH (3.3 mmol, 3.3 eq.) were added and the completion of the reaction could be confirmed by TLC after 1h. A 1M HCl solution, saturated with ammonium chloride, was then added and the crude product was extracted with ethyl acetate (3 x 50 mL). After drying the combined organic layers with Na_2SO_4, the mixture was filtrated and evaporated under vacuum. The residue was purified by silica gel column chromatography (A/PE, 1/1, R_f = 0.40) to afford 489 mg of 5-myrtucommulone-pentanoic acid (**135**) (0.67 mmol, 67 % yield) as a pale yellow powder (*mp* = 146°C, decomposition).



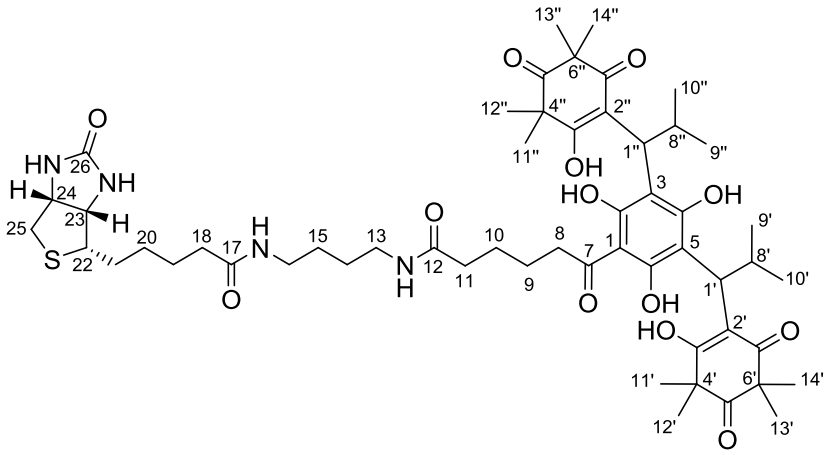
^{1}H-NMR (400 MHz, CO(CD$_3$)$_2$): δ = 15.85 (s, 0.5H), 15.47 (s, 0,5H), 12.95 (brs, 1H), 4.40 (brs, 0.4H), 4.25-4.14 (m, 1.32H, H1', H1''), 4.02 (brs, 0.23H), 3.25-2.97 (m, 4H, H8, H8', H8''), 2.38-2.28 (m, 2H, H11), 1.75-1.65 (m, 4H, H9, H10), 1.40-1.17 (m, 24H, H11', H12', H13', H14', H11'', H12'', H13'', H14''), 0.89-0.55 (m, 12 H, H9', H10', H9'', H10'') ppm.

^{13}C-NMR (101 MHz, CO(CD$_3$)$_2$): δ = 216.1, 216.0 (C5', C5''), 200.4, 200.1 (C7', C7''), 195.2 (C7), 181.6, 181.5 (C3', C3''), 175.9, 175.8 (C12), 162.8 (C2, C6), 160.5 (C4), 115.9, 115.4 (C1), 112.33, 112.25 (C3, C5), 106.4, 104.0 (C2', C2''), 55.5, 55.4 (C6', C6''), 51.21, 51.18 (C4', C4''), 45.2 (C8), 41.32, 41.30 (C1', C1''), 35.4 (C11), 28.3, 28.1 (C8', C8''), 26.9, 26.8, 26.7, 26.4, 26.3, 26.1, 26.0 (C9, C10, C11', C12', C13', C14', C11'', C12'', C13'', C14''), 23.9, 23.6, 23.3, 23.1 (C9', C10', C9'', C10'') ppm

HRMS (ESI$^+$) calcd. for $C_{40}H_{51}O_{10}^+$ $[M+H]^+$: 727.3694, found: 727.3695.

*N-(4-biotinamidobutyl)-5-myrtucommulone-pentanamide (biotin-linked-MC) (**134**)*[113-114]

MCPA (**135**) (155 mg, 0.21 mmol, 1.0 eq.) was dissolved in DMF_{abs} (1.5 mL). Molecular sieves (3Å), and hydroxybenzotriazole (41 mg, 84-89 % as a hydrate, ≥0.26 mmol, 1.2 eq.) were added and the mixture was stirred 5 minutes before DIC (160 µL, 1.02 mmol, 4.9 eq.) was added and the reaction mixture was stirred for another hour at room temperature. In another round-bottom flask, BtABA (**144**) (110 mg, 0.25 mmol, 1.2 eq.) was suspended in DMF_{abs}/DCM_{abs} (1/2, 3.0 mL) and TEA (53 µL, 0.39 mmol, 1.9 eq.) was added and the mixture stirred for 10 min. The solution containing MCPA (**135**) was then transferred with a syringe into the flask containing BtABA (**144**) and stirred at room temperature overnight. Water (10 mL) was added to the mixture, and the crude product was extracted with DCM (10 mL) and ethyl acetate (2 x 10 mL). The combined organic layers were treated with a 1M HCl solution, saturated with NH_4Cl, and brine. After drying with sodium sulfate, the mixture was filtrated and the solvents were removed under reduced pressure. The crude product was purified with silica gel column chromatography (DCM/MeOH, 90/10 to 80/20, R_f = 0.20 (DCM/MeOH, 85/15)) to afford 141 mg of biotin-linked-MC (**134**) (0.14 mmol, 65 % yield) as a pale yellow powder (*mp* = 110°C, decomposition). $[\alpha]_D^{24}$ = + 20.0 (MeOH, *c* = 1.1).



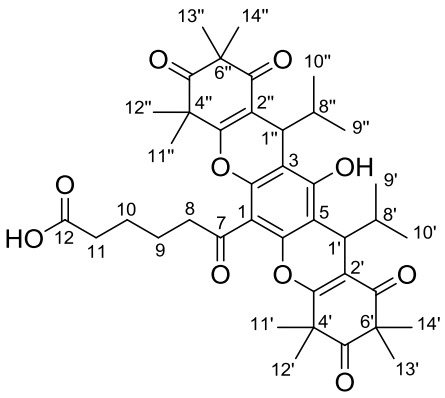
[1]H-NMR (400 MHz, CD_3OD): δ = 4.50 (dd, $^3J_{H24,H23}$ = 8.0 Hz and $^3J_{H24,H25a}$ = 5.0 Hz, 1H, H24), 4.31 (dd, $^3J_{H23,H24}$ = 8.0 Hz and $^3J_{H23,H22}$ = 4.5 Hz, 1H, H23), 4.26-4.00 (m, 1.7H, H1', H1''), 3.24-3.11 (m, 6H, H8, H13, H16, H22), 3.11-2.96 (m, 2H, H8', H8''), 2.92 (dd, $^2J_{H25a,H25b}$ = 12.8 Hz and $^3J_{H25a,H23}$ = 4.8 Hz, 1H, H25a), 2.70 (d, $^2J_{H25b,H25a}$ = 12.8 Hz, 1H, H25b), 2.31-2.16 (m, 2H, H11), 2.21 (t, $^3J_{H18,H19}$ = 7.4 Hz, 2H, H18), 1.80-1.58 (m, 8H, H14, H15, H19, H21),1.57-1.48 (H9, H10), 1.46-1.40 (m, 2H, H20), 1.40-1.11 (m, 24H, H11', H12', H13', H14', H11'', H12'', H13'', H14''), 0.96-0.62 (m, 12H, H9', H10', H9'', H10'') ppm.

[13]C-NMR (101 MHz, CD_3OD): δ =219.1, 216.1, 215.7, 214.8, 214. 5, 202.9 (C5', C5'', C7), 199.9, 199.5 (C7', C7''), 188.3 (C3', C3''), 176.2, 176.0, 171.3, 171.1 (C12, C17), 169,4 (C3', C3''), 166.0 (C26), 160.5 (C2, C6), 157.3 (C4), 112.8, 112.7 (C3, C5), 102.4 (C2', C2''), 63.4 (C23), 61.7 (C24), 57.1, 57.0 (C22), 55.0 (C6', C6''), 53.2, 53.0 (C4', C4''), 44.9 (C8), 41.1 (C25), 41.0, 40.9 (C1', C1''), 39.9 (C13, C16), 37.2, 36.9 (C11, C18), 32.7, 32.4 (C1', C1''), 29.8, 29.5 (C19, C20, C21), 27.93, 27.90, 27.8 (C9, C10, C8', C8''), 27.0, 26.9, 26.7, 26.4, 25.9, 25.8, 25.7, 24.9, 24.5, 23.7 (C11', C12', C13', C14', C11'', C12'', C13'', C14''), 22.7, 22.5, 22.3 (C9', C10', C9'', C10'') ppm.

HRMS (ESI$^+$) calcd. for $C_{54}H_{79}N_4O_{13}S^+$ $[M+H]^+$: 1023.5364, found: 1023.5351.

*5-pentacyclic-myrtucommulone-pentanoic acid (PMCPA) (**136**)*[35a]

The pentacyclic derivative **136** was synthesised according to the general procedure ***GP 9*** starting from 5-myrtucommulone-pentanoic acid (**135**) (146 mg, 0.20 mmol, 1.0 eq.) and using pTsOH (267 mg, 1.41 mmol, 7.0 eq.) as a reagent. After purification over column chromatography on silica gel (Ac/PE, 1/2, R_f = 0.14), 107 mg of PMCPA (**136**) (0.16 mmol, 78 % yield) were synthesised as a white solid (*mp* = 140°C, decomposition).



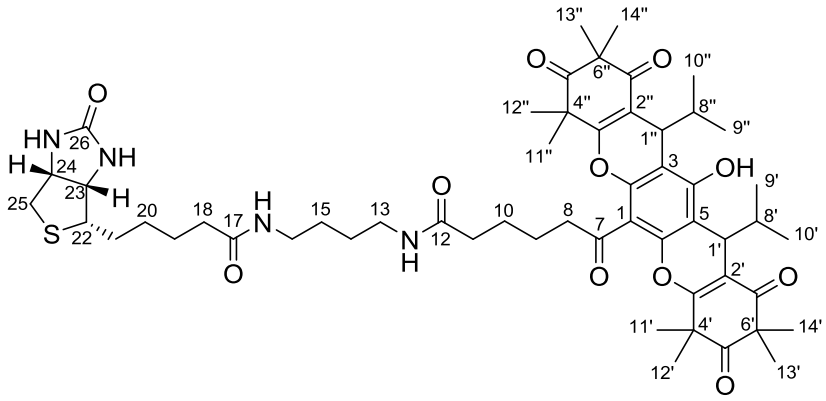
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 4.61, (d, $^{3}J_{H1',H8'} = {}^{3}J_{H1'',H8''}$ = 3.8 Hz, 1H, H1', H1'', *meso*), 4.57 (d, $^{3}J_{H1',H8'} = {}^{3}J_{H1'',H8''}$ = 3.8 Hz, 1H, H1', H1'', *rac*), 3.03-2.79 (m, 2H, H8), 2.42 (q, $^{3}J_{H11,H10}$ = 6.8 Hz, 2H, H11), 2.02-1.89 (m, 2H, H8', H8''), 1.87-1.71 (m, 4H, H9, H10), 1.56 (s, 3H, H12', H11'', *rac*), 1.53 (s, 3H, H12', H12'', *meso*), 1.46 (s, 3H, H13', H14'', *rac*), 1.44 (s, 3H, H13', H13'', meso), 1.43-1.38 (s, 9H, *meso*: H11', H11'', *rac*: H11', H12'', H13'', H14'), 1.36 (s, 3H, H14', H 14'', *meso*), 0.87-0.84 (m, 3H,) and 0.81-0.75 (m, 9H) (H9', H9'', H10', H10'') ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 211.7 (C5', C5''), 200.7, 199.8 (C7), 198.8 (C7', C7''), 178.51, 178.49 (C12), 169.2, 168.9 (C3', C3''), 152.7, 152.3 (C4), 147.7, 147.6 (C2, C6), 111.4, 111.0 (C3, C5), 110.7, 110.6 (C1), 108.9, 108.7 (C2', C2''), 55.93, 55.91 (C6', C6''), 47.54, 47.49 (C4', C4''), 45.3, 45.2 (C8), 35.1, 35.0 (C8', C8'') 33.7 (C11), 32.4, 32.3 (C1', C1''), 25.3 (C12', C11'', *rac*), 25.0 (C13', C14'', *rac)*, 24.9 (C12', C12'', *meso*), 24.8, 24.70, 24.67, 24.4, 24.1 (*meso*: C11', C11'', C13', C13'', C14', C14'', *rac:* C11', C12'', C13'', C14'), 24.36, 24.2, 23.6, 23.5 (C9, C10), 19.3, 19.1, 18.9, 18.5 (C9', C10', C9'', C10'') ppm.

HRMS (ESI^+) calcd. for $C_{40}H_{55}O_{12}^+$ $[M+H]^+$: 691.3482, found: 691,3487.

*N-(4-biotinamidobutyl)-5-myrtucommulone-pentanamide (biotin-linked-PMC) (**145**)*

Following the same procedure as the one used for the synthesis of biotin-linked-MC (**134**), 70 mg of PMCPA (**136**) (0.101 mmol, 1.0 eq.) was mixed with molecular sieves, HOBT (20 mg, 0.12 mmol, 1.2 eq.) and DIC (65 µL, 0.40 mmol, 4.0 eq.), and then added to BtABA (**144**) (80 mg, 0.18 mmol, 1.8 eq.) and TEA (50 µL, 0.39 mmol, 4.0 eq.) in a DCM_{abs}/DMF_{abs} mixture. The reaction was stirred overnight at room temperature. Subsequent purification through column chromatography on silica gel (DCM/MeOH, 9/1, R_f = 0.24) provided the biotin-linked-PMC (**145**) (86 mg, 0.087 mmol) as a yellowish white powder (mp = 153-160°C, decomposition) with 86 % yield. $[\alpha]_D^{24}$ = +15.0 (MeOH, *c* = 1.0)



[1]H-NMR (400 MHz, CD_3OD): δ = 4.49 (dd, $^3J_{H24,H23}$ = 7.8 Hz and $^3J_{H24,H25a}$ = 5.0 Hz, 1H, H24), 4.44, (d, $^3J_{H1',H8'}$ = $^3J_{H1'',H8''}$ = 4.0 Hz, 1H, H1', H1'', *meso*), 4.40 (d, $^3J_{H1',H8'}$ = $^3J_{H1'',H8''}$ = 3.8 Hz, 1H, H1', H1'', *rac*), 4.30 (dd, $^3J_{H23,H24}$ = 7.5 Hz and $^3J_{H23,H22}$ = 4.5 Hz, 1H, H23), 3.24-3.14 (m, 5H, H13, H16, H22), 3.00-2.88 (m, 2H, H8), 2.92 (dd, $^2J_{H25a,H25b}$ = 12.5 Hz and $^3J_{H25a,H24}$ = 5.0 Hz, 1H, H25a), 2.70 (d, $^2J_{H25b,H25a}$ = 12.5 Hz, 1H, H25b), 2.26-2.17 (m, 4H, H11, H18), 1.98-1.87 (m, 2H, H8', H8''), 1.80-1.58 (m, 8H, H9, H10, H19, H21), 1.56-1.49 (s, 10H, H14, H15, *rac*: H12', H11'', *meso*: H12', H12''), 1.47-1.41 (m, 2H, H20), 1.41-1.37 (m, 12H, *meso*: H11', H11'', H13', H13'' *rac*: H11', H12'', H13', H14''), 1.34 (s, 3H, *rac*: H13'', H14'), 1.32 (s, 3H *meso*: H14', H 14''), 0.88-0.73 (m, 12H) (H9', H9'', H10', H10'') ppm.

[13]C-NMR (101 MHz, CD_3OD): δ = 213.1, 210.1 (C5', C5''), 203.0, 202.6 (C7), 199.40, 199.36 (C7', C7''), 176.0, 175.58, 175.56 (C12, C17), 169.8 (C3', C3''), 166.1 (C26), 154.7, 154.4 (C4), 149.03, 148.98 (C2, C6), 112.6, 112.3 (C3, C5), 111.72, 111.65 (C1), 111.1, 110.6 (C2', C2''), 63.4 (C23), 61.7 (C24), 57.14, 57.09 (C6', C6''), 57.0 (C22), 48,7 (C4', C4''), 46.6, 46.5 (C8), 41.1 (C25), 40.04, 40.02 (C13, C16), 37.00, 36.95, 36.7 (C11, C18), 36.3, 36.2 (C8', C8''), 33.7, 33.6 (C1', C1''), 29.8 (C20), 29.5 (C19, C21), 27.8 (C14, C15), 26.93, 26.90, 26.8 (C9, C10), 25.8, 25.64, 25.58, 25.2 (*rac:* C11', C12'', C11'', C12', C13', C14'', *meso*: C11', C11'', C12', C12'', C13', C13''), 25.0, 24.9 (C9, C10), 24.6 (*rac*: C13'', C14', *meso*: C14', C14''), 20.0, 19.7, 19.3, 18.8 (C9', C10', C9'', C10'') ppm.

HRMS (ESI^-) calcd. for $C_{54}H_{73}N_4O_{11}S^-$ $[M-H]^-$: 985.4997, found: 985.4959.

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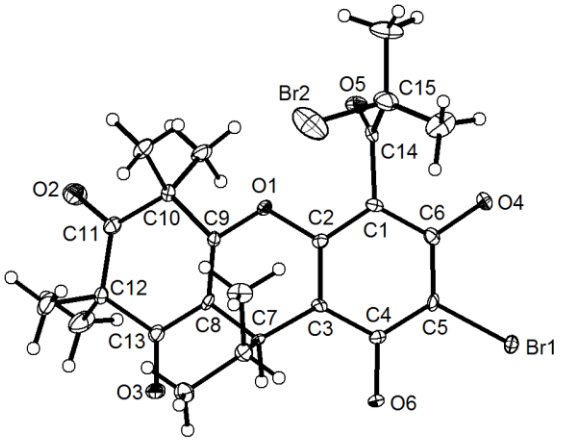
6. Appendices

6.1. Appendix 1: crystal data for 51



Exp. Data Tab. 7 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **51** (sh3343). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Br(1)	6773(1)	3076(1)	8840(1)	16(1)
Br(2A)	6810(1)	6618(1)	8442(1)	47(1)
Br(2B)	6018(12)	6798(5)	8135(6)	96(3)
O(1)	4436(3)	5937(2)	9128(1)	12(1)
O(2)	731(4)	7067(2)	9873(1)	35(1)
O(3)	3306(4)	5432(2)	10743(1)	21(1)
O(4)	6304(3)	3874(2)	9814(1)	13(1)
O(5)	5912(4)	4176(2)	8076(1)	20(1)
O(6)	3871(4)	5663(2)	8053(1)	21(1)
C(1)	3735(5)	6053(2)	9548(2)	10(1)
C(2)	2620(5)	6584(2)	9460(2)	11(1)
C(3)	1727(5)	6696(2)	9907(2)	17(1)
C(4)	2072(5)	6375(2)	10395(2)	14(1)
C(5)	3175(5)	5806(2)	10385(2)	13(1)
C(6)	4058(4)	5728(2)	9967(2)	10(1)
C(7)	5264(5)	5228(2)	9981(1)	10(1)
C(8)	5426(5)	4915(2)	9486(2)	9(1)
C(9)	5943(4)	4239(2)	9412(2)	10(1)
C(10)	6105(5)	3987(2)	8941(2)	12(1)
C(11)	5802(5)	4407(2)	8539(2)	12(1)
C(12)	5321(5)	5083(2)	8608(2)	11(1)
C(13)	5082(4)	5296(2)	9080(2)	10(1)
C(14)	1684(6)	6341(2)	9043(2)	19(1)
C(15)	3291(6)	7289(2)	9322(2)	19(1)
C(16)	755(6)	6087(3)	10624(2)	29(1)
C(17)	2666(7)	6969(3)	10715(2)	29(1)
C(18)	6625(5)	5576(2)	10152(2)	15(1)
C(19)	7133(5)	6147(3)	9819(2)	20(1)

C(20)	6502(6)	5841(2)	10677(2)	20(1)
C(21)	5042(5)	5560(2)	8181(2)	15(1)
C(22)	6250(5)	5923(3)	7937(2)	24(1)
C(23A)	5835(7)	6334(4)	7496(2)	34(2)
C(24A)	7520(7)	5497(4)	7848(3)	37(2)
C(23B)	5960(60)	5770(30)	7411(6)	41(5)
C(24B)	7670(17)	5730(30)	8114(18)	29(4)
Br(3)	-2352(1)	380(1)	8031(1)	39(1)
Br(4)	1760(1)	3183(1)	7396(1)	34(1)
O(7)	360(3)	3119(2)	8458(1)	13(1)
O(8)	947(6)	4847(2)	9642(2)	46(1)
O(9)	982(5)	2521(2)	10091(1)	36(1)
O(10)	-596(4)	793(2)	8921(1)	21(1)
O(11)	-2273(4)	1735(2)	7404(1)	23(1)
O(12)	-1910(5)	3471(2)	7699(1)	35(1)
C(25)	662(4)	3277(2)	8928(2)	11(1)
C(26)	837(5)	4049(2)	8991(2)	14(1)
C(27)	1031(5)	4251(2)	9524(2)	19(1)
C(28)	1368(5)	3708(2)	9910(2)	17(1)
C(29)	1026(5)	2963(2)	9769(2)	18(1)
C(30)	838(5)	2775(2)	9260(2)	13(1)
C(31)	891(5)	2016(2)	9123(2)	14(1)
C(32)	-10(5)	1927(2)	8678(2)	12(1)
C(33)	-702(5)	1297(2)	8584(2)	16(1)
C(34)	-1457(5)	1233(2)	8159(2)	20(1)
C(35)	-1540(5)	1778(2)	7823(2)	16(1)
C(36)	-877(5)	2405(2)	7919(2)	14(1)
C(37)	-159(4)	2458(2)	8355(2)	11(1)
C(38)	-394(6)	4452(3)	8786(2)	28(1)
C(39)	2141(5)	4279(3)	8714(2)	21(1)
C(40)	2939(6)	3699(4)	9968(3)	44(2)
C(41)	690(9)	3911(3)	10394(2)	45(2)
C(42)	2399(5)	1789(2)	9044(2)	16(1)
C(43)	3142(6)	2214(3)	8658(2)	26(1)
C(44)	2523(6)	1009(2)	8927(2)	26(1)
C(45)	-1053(5)	3041(2)	7604(2)	15(1)
C(46)	-163(5)	3158(3)	7155(2)	18(1)
C(47)	-425(8)	3851(4)	6922(2)	44(2)
C(48)	-249(8)	2572(4)	6797(2)	43(2)
C(49)	4848(12)	3971(6)	6980(4)	82(3)
Cl(1)	5933(3)	4595(2)	6715(1)	76(1)
Cl(2)	5576(4)	3136(2)	6935(2)	118(1)

Exp. Data Tab. 8 Bond lengths for **51** (sh3343).

Bond	Length [Å]	Bond	Length [Å]
Br(1)-C(10)	1.886(4)	C(24B)-H(24E)	0.9960
Br(2A)-C(22)	2.007(6)	C(24B)-H(24F)	0.9980
Br(2B)-C(22)	1.782(11)	Br(3)-C(34)	1.890(5)
O(1)-C(1)	1.364(5)	Br(4)-C(46)	1.991(5)
O(1)-C(13)	1.388(5)	O(7)-C(25)	1.366(5)

O(2)-C(3)	1.208(6)	O(7)-C(37)	1.395(5)
O(3)-C(5)	1.226(5)	O(8)-C(27)	1.194(6)
O(4)-C(9)	1.360(5)	O(9)-C(29)	1.230(6)
O(5)-C(11)	1.357(5)	O(10)-C(33)	1.346(6)
O(6)-C(21)	1.212(6)	O(11)-C(35)	1.362(5)
C(1)-C(6)	1.351(6)	O(12)-C(45)	1.205(6)
C(1)-C(2)	1.510(6)	C(25)-C(30)	1.342(6)
C(2)-C(3)	1.524(6)	C(25)-C(26)	1.503(6)
C(2)-C(14)	1.542(6)	C(26)-C(27)	1.533(7)
C(2)-C(15)	1.552(6)	C(26)-C(38)	1.536(7)
C(3)-C(4)	1.520(6)	C(26)-C(39)	1.550(7)
C(4)-C(5)	1.534(6)	C(27)-C(28)	1.527(7)
C(4)-C(16)	1.536(7)	C(28)-C(29)	1.519(6)
C(4)-C(17)	1.556(7)	C(28)-C(40)	1.541(8)
C(5)-C(6)	1.447(6)	C(28)-C(41)	1.541(7)
C(6)-C(7)	1.519(6)	C(29)-C(30)	1.463(6)
C(7)-C(8)	1.501(6)	C(30)-C(31)	1.506(6)
C(7)-C(18)	1.560(6)	C(31)-C(32)	1.520(6)
C(7)-H(7)	1.0000	C(31)-C(42)	1.550(7)
C(8)-C(13)	1.380(6)	C(31)-H(31)	1.0000
C(8)-C(9)	1.408(6)	C(32)-C(37)	1.362(6)
C(9)-C(10)	1.396(6)	C(32)-C(33)	1.410(6)
C(10)-C(11)	1.403(6)	C(33)-C(34)	1.391(7)
C(11)-C(12)	1.393(6)	C(34)-C(35)	1.399(6)
C(12)-C(13)	1.385(6)	C(35)-C(36)	1.391(6)
C(12)-C(21)	1.518(6)	C(36)-C(37)	1.396(6)
C(14)-H(14A)	0.9800	C(36)-C(45)	1.509(6)
C(14)-H(14B)	0.9800	C(38)-H(38A)	0.9800
C(14)-H(14C)	0.9800	C(38)-H(38B)	0.9800
C(15)-H(15A)	0.9800	C(38)-H(38C)	0.9800
C(15)-H(15B)	0.9800	C(39)-H(39A)	0.9800
C(15)-H(15C)	0.9800	C(39)-H(39B)	0.9800
C(16)-H(16A)	0.9800	C(39)-H(39C)	0.9800
C(16)-H(16B)	0.9800	C(40)-H(40A)	0.9800
C(16)-H(16C)	0.9800	C(40)-H(40B)	0.9800
C(17)-H(17A)	0.9800	C(40)-H(40C)	0.9800
C(17)-H(17B)	0.9800	C(41)-H(41A)	0.9800
C(17)-H(17C)	0.9800	C(41)-H(41B)	0.9800
C(18)-C(19)	1.515(6)	C(41)-H(41C)	0.9800
C(18)-C(20)	1.540(6)	C(42)-C(43)	1.525(7)
C(18)-H(18)	1.0000	C(42)-C(44)	1.536(6)
C(19)-H(19A)	0.9800	C(42)-H(42)	1.0000
C(19)-H(19B)	0.9800	C(43)-H(43A)	0.9800
C(19)-H(19C)	0.9800	C(43)-H(43B)	0.9800
C(20)-H(20A)	0.9800	C(43)-H(43C)	0.9800
C(20)-H(20B)	0.9800	C(44)-H(44A)	0.9800
C(20)-H(20C)	0.9800	C(44)-H(44B)	0.9800
C(21)-C(22)	1.525(7)	C(44)-H(44C)	0.9800
C(22)-C(24A)	1.504(7)	C(45)-C(46)	1.529(6)
C(22)-C(23A)	1.506(6)	C(46)-C(47)	1.499(8)
C(22)-C(23B)	1.508(10)	C(46)-C(48)	1.501(7)

C(22)-C(24B)	1.513(10)	C(47)-H(47A)	0.9800
C(23A)-H(23A)	0.9800	C(47)-H(47B)	0.9800
C(23A)-H(23B)	0.9800	C(47)-H(47C)	0.9800
C(23A)-H(23C)	0.9800	C(48)-H(48A)	0.9800
C(24A)-H(24A)	0.9800	C(48)-H(48B)	0.9800
C(24A)-H(24B)	0.9800	C(48)-H(48C)	0.9800
C(24A)-H(24C)	0.9800	C(49)-Cl(2)	1.758(12)
C(23B)-H(23D)	0.9800	C(49)-Cl(1)	1.760(12)
C(23B)-H(23E)	0.9800	C(49)-H(49A)	0.9900
C(23B)-H(23F)	0.9800	C(49)-H(49B)	0.9900
C(24B)-H(24D)	0.9999		

Exp. Data Tab. 9 Angles for **51** (sh3343).

Bonds	Angles [°]	Bonds	Angles [°]
C(1)-O(1)-C(13)	116.9(3)	H(23E)-C(23B)-H(23F)	109.5
C(6)-C(1)-O(1)	122.4(4)	C(22)-C(24B)-H(24D)	112.3
C(6)-C(1)-C(2)	128.0(4)	C(22)-C(24B)-H(24E)	110.1
O(1)-C(1)-C(2)	109.6(3)	H(24D)-C(24B)-H(24E)	107.3
C(1)-C(2)-C(3)	112.2(3)	C(22)-C(24B)-H(24F)	111.3
C(1)-C(2)-C(14)	110.0(3)	H(24D)-C(24B)-H(24F)	107.7
C(3)-C(2)-C(14)	107.9(4)	H(24E)-C(24B)-H(24F)	107.9
C(1)-C(2)-C(15)	108.9(4)	C(25)-O(7)-C(37)	118.3(3)
C(3)-C(2)-C(15)	108.5(4)	C(30)-C(25)-O(7)	121.1(4)
C(14)-C(2)-C(15)	109.2(4)	C(30)-C(25)-C(26)	128.0(4)
O(2)-C(3)-C(4)	119.1(4)	O(7)-C(25)-C(26)	110.8(4)
O(2)-C(3)-C(2)	118.7(4)	C(25)-C(26)-C(27)	112.0(4)
C(4)-C(3)-C(2)	122.2(4)	C(25)-C(26)-C(38)	111.4(4)
C(3)-C(4)-C(5)	115.4(4)	C(27)-C(26)-C(38)	108.9(4)
C(3)-C(4)-C(16)	109.0(4)	C(25)-C(26)-C(39)	108.4(4)
C(5)-C(4)-C(16)	109.7(4)	C(27)-C(26)-C(39)	107.6(4)
C(3)-C(4)-C(17)	106.8(4)	C(38)-C(26)-C(39)	108.4(4)
C(5)-C(4)-C(17)	105.7(4)	O(8)-C(27)-C(28)	118.7(4)
C(16)-C(4)-C(17)	110.0(4)	O(8)-C(27)-C(26)	119.7(5)
O(3)-C(5)-C(6)	121.3(4)	C(28)-C(27)-C(26)	121.6(4)
O(3)-C(5)-C(4)	118.4(4)	C(29)-C(28)-C(27)	114.6(4)
C(6)-C(5)-C(4)	120.3(4)	C(29)-C(28)-C(40)	103.6(4)
C(1)-C(6)-C(5)	119.8(4)	C(27)-C(28)-C(40)	107.1(4)
C(1)-C(6)-C(7)	119.5(4)	C(29)-C(28)-C(41)	111.5(4)
C(5)-C(6)-C(7)	120.4(4)	C(27)-C(28)-C(41)	109.8(4)
C(8)-C(7)-C(6)	108.2(3)	C(40)-C(28)-C(41)	109.9(5)
C(8)-C(7)-C(18)	111.0(4)	O(9)-C(29)-C(30)	121.3(4)
C(6)-C(7)-C(18)	113.4(3)	O(9)-C(29)-C(28)	118.1(4)
C(8)-C(7)-H(7)	108.0	C(30)-C(29)-C(28)	120.5(4)
C(6)-C(7)-H(7)	108.0	C(25)-C(30)-C(29)	119.6(4)
C(18)-C(7)-H(7)	108.0	C(25)-C(30)-C(31)	121.9(4)
C(13)-C(8)-C(9)	117.3(4)	C(29)-C(30)-C(31)	118.4(4)
C(13)-C(8)-C(7)	120.0(4)	C(30)-C(31)-C(32)	106.9(4)
C(9)-C(8)-C(7)	122.7(4)	C(30)-C(31)-C(42)	109.8(4)
O(4)-C(9)-C(10)	123.6(4)	C(32)-C(31)-C(42)	113.8(4)
O(4)-C(9)-C(8)	116.6(4)	C(30)-C(31)-H(31)	108.7

C(10)-C(9)-C(8)	119.7(4)	C(32)-C(31)-H(31)	108.7
C(9)-C(10)-C(11)	120.9(4)	C(42)-C(31)-H(31)	108.7
C(9)-C(10)-Br(1)	119.8(3)	C(37)-C(32)-C(33)	118.0(4)
C(11)-C(10)-Br(1)	119.3(3)	C(37)-C(32)-C(31)	120.5(4)
O(5)-C(11)-C(12)	117.4(4)	C(33)-C(32)-C(31)	121.5(4)
O(5)-C(11)-C(10)	122.7(4)	O(10)-C(33)-C(34)	124.1(4)
C(12)-C(11)-C(10)	119.8(4)	O(10)-C(33)-C(32)	116.9(4)
C(13)-C(12)-C(11)	117.5(4)	C(34)-C(33)-C(32)	119.0(4)
C(13)-C(12)-C(21)	121.5(4)	C(33)-C(34)-C(35)	121.6(4)
C(11)-C(12)-C(21)	121.0(4)	C(33)-C(34)-Br(3)	118.6(3)
C(8)-C(13)-C(12)	124.4(4)	C(35)-C(34)-Br(3)	119.8(3)
C(8)-C(13)-O(1)	120.2(4)	O(11)-C(35)-C(36)	117.3(4)
C(12)-C(13)-O(1)	115.3(4)	O(11)-C(35)-C(34)	123.2(4)
C(2)-C(14)-H(14A)	109.5	C(36)-C(35)-C(34)	119.6(4)
C(2)-C(14)-H(14B)	109.5	C(35)-C(36)-C(37)	117.4(4)
H(14A)-C(14)-H(14B)	109.5	C(35)-C(36)-C(45)	122.5(4)
C(2)-C(14)-H(14C)	109.5	C(37)-C(36)-C(45)	119.7(4)
H(14A)-C(14)-H(14C)	109.5	C(32)-C(37)-O(7)	120.6(4)
H(14B)-C(14)-H(14C)	109.5	C(32)-C(37)-C(36)	124.3(4)
C(2)-C(15)-H(15A)	109.5	O(7)-C(37)-C(36)	115.1(4)
C(2)-C(15)-H(15B)	109.5	C(26)-C(38)-H(38A)	109.5
H(15A)-C(15)-H(15B)	109.5	C(26)-C(38)-H(38B)	109.5
C(2)-C(15)-H(15C)	109.5	H(38A)-C(38)-H(38B)	109.5
H(15A)-C(15)-H(15C)	109.5	C(26)-C(38)-H(38C)	109.5
H(15B)-C(15)-H(15C)	109.5	H(38A)-C(38)-H(38C)	109.5
C(4)-C(16)-H(16A)	109.5	H(38B)-C(38)-H(38C)	109.5
C(4)-C(16)-H(16B)	109.5	C(26)-C(39)-H(39A)	109.5
H(16A)-C(16)-H(16B)	109.5	C(26)-C(39)-H(39B)	109.5
C(4)-C(16)-H(16C)	109.5	H(39A)-C(39)-H(39B)	109.5
H(16A)-C(16)-H(16C)	109.5	C(26)-C(39)-H(39C)	109.5
H(16B)-C(16)-H(16C)	109.5	H(39A)-C(39)-H(39C)	109.5
C(4)-C(17)-H(17A)	109.5	H(39B)-C(39)-H(39C)	109.5
C(4)-C(17)-H(17B)	109.5	C(28)-C(40)-H(40A)	109.5
H(17A)-C(17)-H(17B)	109.5	C(28)-C(40)-H(40B)	109.5
C(4)-C(17)-H(17C)	109.5	H(40A)-C(40)-H(40B)	109.5
H(17A)-C(17)-H(17C)	109.5	C(28)-C(40)-H(40C)	109.5
H(17B)-C(17)-H(17C)	109.5	H(40A)-C(40)-H(40C)	109.5
C(19)-C(18)-C(20)	111.0(4)	H(40B)-C(40)-H(40C)	109.5
C(19)-C(18)-C(7)	113.7(4)	C(28)-C(41)-H(41A)	109.5
C(20)-C(18)-C(7)	111.2(4)	C(28)-C(41)-H(41B)	109.5
C(19)-C(18)-H(18)	106.8	H(41A)-C(41)-H(41B)	109.5
C(20)-C(18)-H(18)	106.8	C(28)-C(41)-H(41C)	109.5
C(7)-C(18)-H(18)	106.8	H(41A)-C(41)-H(41C)	109.5
C(18)-C(19)-H(19A)	109.5	H(41B)-C(41)-H(41C)	109.5
C(18)-C(19)-H(19B)	109.5	C(43)-C(42)-C(44)	109.7(4)
H(19A)-C(19)-H(19B)	109.5	C(43)-C(42)-C(31)	113.6(4)
C(18)-C(19)-H(19C)	109.5	C(44)-C(42)-C(31)	112.2(4)
H(19A)-C(19)-H(19C)	109.5	C(43)-C(42)-H(42)	107.0
H(19B)-C(19)-H(19C)	109.5	C(44)-C(42)-H(42)	107.0
C(18)-C(20)-H(20A)	109.5	C(31)-C(42)-H(42)	107.0
C(18)-C(20)-H(20B)	109.5	C(42)-C(43)-H(43A)	109.5

H(20A)-C(20)-H(20B)	109.5	C(42)-C(43)-H(43B)	109.5
C(18)-C(20)-H(20C)	109.5	H(43A)-C(43)-H(43B)	109.5
H(20A)-C(20)-H(20C)	109.5	C(42)-C(43)-H(43C)	109.5
H(20B)-C(20)-H(20C)	109.5	H(43A)-C(43)-H(43C)	109.5
O(6)-C(21)-C(12)	119.5(4)	H(43B)-C(43)-H(43C)	109.5
O(6)-C(21)-C(22)	121.7(4)	C(42)-C(44)-H(44A)	109.5
C(12)-C(21)-C(22)	118.7(4)	C(42)-C(44)-H(44B)	109.5
C(24A)-C(22)-C(23A)	112.0(5)	H(44A)-C(44)-H(44B)	109.5
C(24A)-C(22)-C(23B)	84(3)	C(42)-C(44)-H(44C)	109.5
C(23A)-C(22)-C(23B)	43(2)	H(44A)-C(44)-H(44C)	109.5
C(24A)-C(22)-C(24B)	34(2)	H(44B)-C(44)-H(44C)	109.5
C(23A)-C(22)-C(24B)	129.2(14)	O(12)-C(45)-C(36)	120.5(4)
C(23B)-C(22)-C(24B)	116(3)	O(12)-C(45)-C(46)	118.0(4)
C(24A)-C(22)-C(21)	117.4(4)	C(36)-C(45)-C(46)	121.5(4)
C(23A)-C(22)-C(21)	112.9(5)	C(47)-C(46)-C(48)	111.9(5)
C(23B)-C(22)-C(21)	101(2)	C(47)-C(46)-C(45)	112.5(4)
C(24B)-C(22)-C(21)	117.1(14)	C(48)-C(46)-C(45)	113.0(4)
C(24A)-C(22)-Br(2B)	131.8(6)	C(47)-C(46)-Br(4)	106.4(4)
C(23A)-C(22)-Br(2B)	73.7(7)	C(48)-C(46)-Br(4)	106.8(4)
C(23B)-C(22)-Br(2B)	117(3)	C(45)-C(46)-Br(4)	105.6(3)
C(24B)-C(22)-Br(2B)	104(3)	C(46)-C(47)-H(47A)	109.5
C(21)-C(22)-Br(2B)	101.4(5)	C(46)-C(47)-H(47B)	109.5
C(24A)-C(22)-Br(2A)	104.5(4)	H(47A)-C(47)-H(47B)	109.5
C(23A)-C(22)-Br(2A)	106.6(4)	C(46)-C(47)-H(47C)	109.5
C(23B)-C(22)-Br(2A)	148(2)	H(47A)-C(47)-H(47C)	109.5
C(24B)-C(22)-Br(2A)	72(3)	H(47B)-C(47)-H(47C)	109.5
C(21)-C(22)-Br(2A)	102.0(3)	C(46)-C(48)-H(48A)	109.5
Br(2B)-C(22)-Br(2A)	36.3(5)	C(46)-C(48)-H(48B)	109.5
C(22)-C(23A)-H(23A)	109.5	H(48A)-C(48)-H(48B)	109.5
C(22)-C(23A)-H(23B)	109.5	C(46)-C(48)-H(48C)	109.5
C(22)-C(23A)-H(23C)	109.5	H(48A)-C(48)-H(48C)	109.5
C(22)-C(24A)-H(24A)	109.6	H(48B)-C(48)-H(48C)	109.5
C(22)-C(24A)-H(24B)	109.4	Cl(2)-C(49)-Cl(1)	110.4(7)
C(22)-C(24A)-H(24C)	109.4	Cl(2)-C(49)-H(49A)	109.6
C(22)-C(23B)-H(23D)	109.5	Cl(1)-C(49)-H(49A)	109.6
C(22)-C(23B)-H(23E)	109.5	Cl(2)-C(49)-H(49B)	109.6
H(23D)-C(23B)-H(23E)	109.5	Cl(1)-C(49)-H(49B)	109.6
C(22)-C(23B)-H(23F)	109.5	H(49A)-C(49)-H(49B)	108.1
H(23D)-C(23B)-H(23F)	109.5		

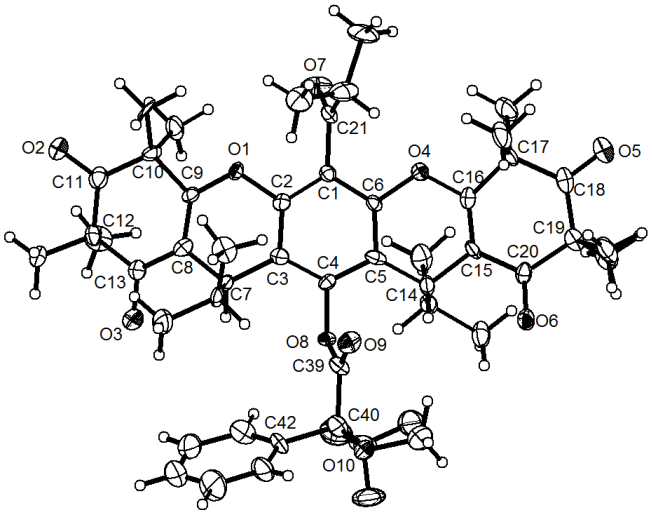
Exp. Data Tab. 10. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **51** (sh3343). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	22(1)	11(1)	14(1)	-1(1)	5(1)	5(1)
Br(2A)	65(1)	47(1)	29(1)	-1(1)	7(1)	-38(1)
Br(2B)	83(6)	50(4)	155(8)	-7(5)	31(6)	-18(4)
O(1)	14(2)	10(1)	13(1)	2(1)	2(1)	4(1)
O(2)	33(2)	50(3)	22(2)	5(2)	2(2)	28(2)
O(3)	25(2)	22(2)	15(2)	7(1)	7(1)	11(2)

O(4)	20(2)	11(2)	10(1)	3(1)	-1(1)	4(1)
O(5)	28(2)	21(2)	10(2)	-2(1)	0(1)	9(2)
O(6)	23(2)	25(2)	15(2)	3(1)	-5(1)	6(2)
C(1)	13(2)	8(2)	10(2)	-2(2)	1(2)	1(2)
C(2)	11(2)	10(2)	13(2)	-2(2)	0(2)	1(2)
C(3)	17(2)	17(2)	17(2)	0(2)	-3(2)	8(2)
C(4)	17(2)	12(2)	14(2)	0(2)	5(2)	6(2)
C(5)	15(2)	10(2)	14(2)	-1(2)	-1(2)	0(2)
C(6)	11(2)	6(2)	14(2)	-2(2)	-3(2)	2(2)
C(7)	11(2)	9(2)	9(2)	1(2)	-3(2)	5(2)
C(8)	8(2)	11(2)	8(2)	3(2)	4(2)	-2(2)
C(9)	6(2)	12(2)	12(2)	4(2)	2(2)	2(2)
C(10)	10(2)	11(2)	14(2)	-3(2)	2(2)	5(2)
C(11)	9(2)	17(2)	11(2)	-1(2)	3(2)	1(2)
C(12)	11(2)	14(2)	8(2)	2(2)	-1(2)	0(2)
C(13)	11(2)	8(2)	12(2)	1(2)	0(2)	-3(2)
C(14)	22(2)	15(2)	20(2)	1(2)	-8(2)	6(2)
C(15)	21(2)	10(2)	25(2)	1(2)	-3(2)	1(2)
C(16)	23(3)	27(3)	37(3)	14(2)	12(2)	10(2)
C(17)	43(3)	15(2)	28(3)	-7(2)	-12(2)	11(2)
C(18)	15(2)	15(2)	15(2)	-1(2)	-3(2)	-1(2)
C(19)	18(3)	21(2)	22(2)	4(2)	-8(2)	-11(2)
C(20)	28(3)	16(2)	15(2)	-3(2)	-6(2)	-2(2)
C(21)	22(2)	15(2)	8(2)	-1(2)	4(2)	6(2)
C(22)	26(3)	28(3)	18(2)	6(2)	4(2)	-1(2)
C(23A)	37(4)	43(4)	24(3)	20(3)	2(3)	-4(3)
C(24A)	28(3)	36(4)	47(4)	21(3)	30(3)	9(3)
C(23B)	38(10)	59(10)	27(6)	28(7)	12(7)	-7(10)
C(24B)	21(6)	38(9)	27(10)	35(9)	27(8)	-13(8)
Br(3)	58(1)	24(1)	36(1)	8(1)	-27(1)	-26(1)
Br(4)	20(1)	55(1)	27(1)	5(1)	4(1)	-5(1)
O(7)	16(2)	8(1)	14(1)	2(1)	-2(1)	-2(1)
O(8)	95(4)	12(2)	31(2)	-1(2)	-2(2)	-1(2)
O(9)	75(3)	14(2)	19(2)	1(2)	-11(2)	-3(2)
O(10)	30(2)	14(2)	19(2)	6(1)	-6(2)	-10(1)
O(11)	27(2)	25(2)	18(2)	3(1)	-12(1)	-10(2)
O(12)	46(3)	38(2)	20(2)	12(2)	16(2)	27(2)
C(25)	9(2)	12(2)	12(2)	-1(2)	-2(2)	-2(2)
C(26)	14(2)	8(2)	20(2)	2(2)	-3(2)	-1(2)
C(27)	22(3)	14(2)	21(2)	-1(2)	0(2)	-6(2)
C(28)	24(3)	14(2)	13(2)	-2(2)	-1(2)	-2(2)
C(29)	26(3)	12(2)	15(2)	-2(2)	-3(2)	-5(2)
C(30)	13(2)	10(2)	16(2)	1(2)	-1(2)	-4(2)
C(31)	20(2)	10(2)	11(2)	0(2)	-5(2)	-2(2)
C(32)	15(2)	11(2)	12(2)	-2(2)	-1(2)	-3(2)
C(33)	18(2)	13(2)	16(2)	0(2)	0(2)	-3(2)
C(34)	24(3)	14(2)	21(2)	0(2)	-8(2)	-8(2)
C(35)	19(2)	16(2)	15(2)	0(2)	-5(2)	-1(2)
C(36)	11(2)	17(2)	14(2)	0(2)	0(2)	-1(2)
C(37)	8(2)	9(2)	15(2)	-2(2)	0(2)	-2(2)
C(38)	24(3)	13(2)	45(3)	0(2)	-17(2)	3(2)

C(39)	22(3)	17(2)	24(2)	2(2)	2(2)	-9(2)
C(40)	31(3)	45(4)	55(4)	21(3)	-19(3)	-21(3)
C(41)	83(5)	21(3)	30(3)	0(2)	23(3)	-10(3)
C(42)	17(2)	13(2)	19(2)	-2(2)	-5(2)	2(2)
C(43)	21(3)	22(2)	34(3)	-1(2)	3(2)	2(2)
C(44)	32(3)	13(2)	34(3)	-6(2)	-5(2)	7(2)
C(45)	19(2)	16(2)	10(2)	-1(2)	-2(2)	2(2)
C(46)	16(2)	24(2)	16(2)	2(2)	4(2)	1(2)
C(47)	45(4)	53(4)	34(3)	29(3)	13(3)	8(3)
C(48)	46(4)	56(4)	27(3)	-21(3)	19(3)	-20(3)
C(49)	78(7)	87(6)	80(7)	-8(6)	-15(6)	-4(5)
Cl(1)	69(2)	79(2)	81(2)	-7(1)	-1(1)	-5(1)
Cl(2)	109(2)	68(2)	176(4)	-7(2)	-6(2)	-6(2)

6.2. Appendix 2: crystal data for 53



Exp. Data Tab. 11 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **53** (sh3365). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	3102(9)	6440(1)	6678(3)	21(1)
O(2)	4179(12)	6416(1)	9273(4)	42(2)
O(3)	5526(12)	7381(1)	7950(3)	38(2)
O(4)	4409(10)	6268(1)	4154(3)	24(1)
O(5)	4367(14)	5991(2)	1623(4)	53(2)
O(6)	4246(11)	7104(1)	2359(3)	34(2)
O(7)	4324(12)	5823(1)	5783(4)	42(2)
O(8)	4923(10)	7364(1)	5155(3)	20(1)
O(9)	1722(10)	7444(1)	4660(3)	30(2)
O(10)	2644(12)	8073(1)	4283(3)	40(2)
C(1)	3690(14)	6368(2)	5413(4)	19(2)
C(2)	3624(13)	6584(2)	6003(5)	18(2)
C(3)	3902(14)	6915(2)	5936(5)	20(2)
C(4)	4463(13)	7025(2)	5240(4)	17(2)
C(5)	4714(14)	6827(2)	4619(5)	22(2)
C(6)	4290(14)	6501(2)	4730(4)	17(2)
C(7)	3544(14)	7131(2)	6619(4)	18(2)
C(8)	4043(14)	6931(2)	7315(5)	21(2)
C(9)	3781(14)	6606(2)	7303(5)	18(2)
C(10)	4102(15)	6372(2)	7951(5)	23(2)
C(11)	4549(15)	6555(2)	8672(5)	28(2)
C(12)	5540(15)	6890(2)	8683(5)	25(2)
C(13)	5015(16)	7086(2)	7964(5)	28(2)
C(14)	5469(14)	6942(2)	3879(4)	22(2)
C(15)	4810(15)	6700(2)	3272(5)	22(2)
C(16)	4431(13)	6392(2)	3430(4)	19(2)
C(17)	3855(16)	6114(2)	2901(5)	26(2)
C(18)	4260(15)	6210(2)	2097(5)	29(2)

C(19)	4465(14)	6565(2)	1855(5)	24(2)
C(20)	4486(14)	6813(2)	2497(4)	22(2)
C(21)	3153(15)	6014(2)	5484(5)	22(2)
C(22)	1029(17)	5914(2)	5211(6)	40(2)
C(23)	-515(17)	6034(2)	5746(6)	40(3)
C(24)	870(20)	5545(2)	5044(7)	53(3)
C(25)	1331(14)	7276(2)	6596(4)	21(2)
C(26)	883(18)	7481(2)	7289(5)	38(3)
C(27)	-374(15)	7020(2)	6502(6)	34(2)
C(28)	6005(18)	6153(2)	7776(5)	35(2)
C(29)	2209(18)	6149(2)	8014(5)	37(3)
C(30)	4790(19)	7083(2)	9371(5)	41(3)
C(31)	7865(16)	6851(2)	8720(6)	39(2)
C(32)	7845(15)	6999(2)	3942(5)	24(2)
C(33)	8988(17)	6690(2)	4198(5)	37(2)
C(34)	8756(17)	7124(2)	3195(5)	34(2)
C(35)	5010(20)	5802(2)	3100(6)	51(3)
C(36)	1498(18)	6049(3)	2929(6)	43(3)
C(37)	6558(17)	6597(2)	1474(6)	42(3)
C(38)	2713(18)	6644(2)	1285(6)	40(3)
C(39)	3378(15)	7557(2)	4841(5)	23(2)
C(40)	4028(16)	7915(2)	4781(5)	32(2)
C(41)	6210(20)	7953(2)	4497(6)	42(2)
F(1)	7731(10)	7865(1)	4985(4)	52(2)
F(2)	6599(12)	8266(1)	4332(4)	61(2)
F(3)	6492(11)	7778(1)	3877(3)	55(2)
C(42)	3794(18)	8072(2)	5556(5)	35(2)
C(43)	2105(18)	8285(2)	5647(6)	41(3)
C(44)	1800(30)	8430(3)	6297(7)	73(4)
C(45)	3140(30)	8355(3)	6914(7)	70(4)
C(46)	4730(20)	8138(3)	6856(6)	61(3)
C(47)	5040(20)	8001(2)	6154(6)	45(3)
C(48)	2400(20)	7961(2)	3508(6)	60(4)
O(11)	-570(10)	8593(1)	-395(3)	28(2)
O(12)	2(13)	7454(1)	-271(4)	45(2)
O(13)	740(13)	8087(1)	1912(4)	48(2)
O(14)	1189(10)	9693(1)	-751(3)	26(1)
O(15)	920(12)	10811(1)	-1350(4)	39(2)
O(16)	835(14)	10486(2)	1143(4)	53(2)
O(17A)	1510(20)	9146(4)	-1811(8)	30(5)
O(17B)	1720(20)	8955(4)	-1645(8)	51(5)
O(18)	156(12)	9309(1)	1755(4)	38(2)
O(19)	3147(13)	9076(2)	2071(4)	50(2)
O(20)	2494(15)	9151(2)	3512(5)	65(2)
C(49)	272(15)	9142(2)	-552(5)	25(2)
C(50)	-155(15)	8898(2)	-63(5)	24(2)
C(51)	-186(14)	8934(2)	709(5)	18(2)
C(52)	408(14)	9241(2)	976(5)	20(2)
C(53)	933(14)	9505(2)	517(5)	23(2)
C(54)	829(15)	9441(2)	-247(5)	26(2)
C(55)	-833(14)	8656(2)	1195(5)	22(2)

C(56)	-287(13)	8339(2)	778(5)	18(2)
C(57)	-294(15)	8322(2)	36(5)	21(2)
C(58)	67(14)	8027(2)	-438(5)	23(2)
C(59)	232(16)	7718(2)	43(5)	29(2)
C(60)	848(15)	7724(2)	867(5)	25(2)
C(61)	435(16)	8059(2)	1242(6)	28(2)
C(62)	1780(14)	9826(2)	808(5)	23(2)
C(63)	1243(14)	10086(2)	239(5)	23(2)
C(64)	1136(15)	10013(2)	-499(5)	26(2)
C(65)	895(16)	10238(2)	-1150(5)	29(2)
C(66)	734(15)	10596(2)	-881(5)	29(2)
C(67)	190(18)	10674(2)	-88(5)	35(2)
C(68)	843(16)	10422(2)	475(5)	28(2)
C(69)	110(20)	9083(2)	-1402(6)	41(3)
C(70A)	-1480(50)	9222(15)	-1947(14)	75(5)
C(71A)	-480(90)	9243(13)	-2695(19)	80(6)
C(70B)	-2110(30)	9054(4)	-1728(10)	74(5)
C(71B)	-2120(40)	8890(4)	-2487(9)	82(5)
C(72)	-3440(30)	9330(3)	-1724(9)	97(5)
C(73)	-3152(15)	8672(2)	1366(5)	30(2)
C(74)	-3831(19)	8400(2)	1905(6)	45(3)
C(75)	-4563(16)	8670(2)	664(6)	40(2)
C(76)	2104(16)	8069(2)	-867(6)	37(2)
C(77)	-1786(16)	7995(2)	-1010(5)	34(2)
C(78)	-431(17)	7470(2)	1260(6)	41(3)
C(79)	3141(16)	7651(2)	945(5)	32(2)
C(80)	4142(15)	9795(2)	1015(6)	38(2)
C(81)	5032(19)	10105(3)	1382(6)	52(3)
C(82)	5380(17)	9707(3)	339(6)	47(3)
C(83)	-1021(18)	10156(2)	-1648(6)	45(3)
C(84)	2830(20)	10214(3)	-1617(7)	53(3)
C(85)	-2276(18)	10675(2)	-98(6)	46(3)
C(86)	950(19)	11013(2)	141(6)	43(3)
C(87)	1561(19)	9215(2)	2229(6)	36(2)
C(88)	1054(18)	9316(2)	3041(5)	36(2)
C(89)	-1120(20)	9205(3)	3238(7)	60(3)
C(90)	1570(16)	9681(2)	3124(5)	27(2)
C(91)	3351(18)	9767(2)	3535(6)	45(3)
C(92)	3910(20)	10097(3)	3583(7)	59(3)
C(93)	2620(20)	10329(3)	3282(7)	60(3)
C(94)	850(20)	10242(2)	2896(6)	53(3)
C(95)	310(20)	9921(2)	2819(5)	42(3)
C(96)	2510(30)	8790(3)	3525(9)	88(5)
F(4)	-1410(18)	9269(2)	3968(4)	115(4)
F(5)	-1572(15)	8905(2)	3095(4)	89(3)
F(6)	-2641(13)	9384(2)	2863(5)	80(2)

Exp. Data Tab. 12 Bond lengths for **53** (sh3365).

Bond	Length [Å]	Bond	Length [Å]
O(1)-C(9)	1.370(10)	O(12)-C(59)	1.224(10)

O(1)-C(2)	1.395(9)	O(13)-C(61)	1.214(11)
O(2)-C(11)	1.246(10)	O(14)-C(64)	1.386(10)
O(3)-C(13)	1.255(9)	O(14)-C(54)	1.394(10)
O(4)-C(16)	1.391(10)	O(15)-C(66)	1.225(10)
O(4)-C(6)	1.408(9)	O(16)-C(68)	1.223(11)
O(5)-C(18)	1.238(10)	O(17A)-C(69)	1.205(15)
O(6)-C(20)	1.222(9)	O(17B)-C(69)	1.252(14)
O(7)-C(21)	1.204(10)	O(18)-C(87)	1.280(13)
O(8)-C(39)	1.377(10)	O(18)-C(52)	1.434(10)
O(8)-C(4)	1.432(9)	O(19)-C(87)	1.212(13)
O(9)-C(39)	1.200(11)	O(20)-C(88)	1.408(13)
O(10)-C(40)	1.401(12)	O(20)-C(96)	1.479(13)
O(10)-C(48)	1.463(12)	C(49)-C(50)	1.360(12)
C(1)-C(2)	1.379(11)	C(49)-C(54)	1.388(11)
C(1)-C(6)	1.403(11)	C(49)-C(69)	1.539(13)
C(1)-C(21)	1.493(11)	C(50)-C(51)	1.391(12)
C(2)-C(3)	1.372(10)	C(51)-C(52)	1.397(11)
C(3)-C(4)	1.382(11)	C(51)-C(55)	1.499(11)
C(3)-C(7)	1.532(11)	C(52)-C(53)	1.405(11)
C(4)-C(5)	1.387(11)	C(53)-C(54)	1.391(12)
C(5)-C(6)	1.379(10)	C(53)-C(62)	1.509(11)
C(5)-C(14)	1.500(12)	C(55)-C(73)	1.536(13)
C(7)-C(8)	1.518(11)	C(55)-C(56)	1.543(11)
C(7)-C(25)	1.545(12)	C(56)-C(57)	1.329(12)
C(8)-C(9)	1.342(11)	C(56)-C(61)	1.482(12)
C(8)-C(13)	1.448(12)	C(57)-C(58)	1.499(11)
C(9)-C(10)	1.513(11)	C(58)-C(59)	1.532(12)
C(10)-C(11)	1.511(12)	C(58)-C(76)	1.550(13)
C(10)-C(29)	1.531(12)	C(58)-C(77)	1.556(13)
C(10)-C(28)	1.560(13)	C(59)-C(60)	1.517(13)
C(11)-C(12)	1.514(12)	C(60)-C(79)	1.511(13)
C(12)-C(31)	1.507(14)	C(60)-C(78)	1.513(12)
C(12)-C(13)	1.546(12)	C(60)-C(61)	1.553(11)
C(12)-C(30)	1.551(12)	C(62)-C(63)	1.506(11)
C(14)-C(15)	1.522(11)	C(62)-C(80)	1.563(13)
C(14)-C(32)	1.550(13)	C(63)-C(64)	1.354(12)
C(15)-C(16)	1.317(11)	C(63)-C(68)	1.467(12)
C(15)-C(20)	1.471(12)	C(64)-C(65)	1.489(12)
C(16)-C(17)	1.519(11)	C(65)-C(84)	1.524(14)
C(17)-C(35)	1.517(12)	C(65)-C(83)	1.540(14)
C(17)-C(18)	1.521(13)	C(65)-C(66)	1.548(12)
C(17)-C(36)	1.545(15)	C(66)-C(67)	1.505(13)
C(18)-C(19)	1.524(12)	C(67)-C(68)	1.494(13)
C(19)-C(20)	1.534(12)	C(67)-C(86)	1.522(12)
C(19)-C(38)	1.534(13)	C(67)-C(85)	1.590(16)
C(19)-C(37)	1.535(13)	C(69)-C(70A)	1.51(2)
C(21)-C(22)	1.498(14)	C(69)-C(70B)	1.53(2)
C(22)-C(23)	1.485(15)	C(70A)-C(72)	1.41(2)
C(22)-C(24)	1.545(13)	C(70A)-C(71A)	1.51(2)
C(25)-C(27)	1.526(13)	C(70B)-C(72)	1.418(18)
C(25)-C(26)	1.531(12)	C(70B)-C(71B)	1.52(2)

C(32)-C(33)	1.529(12)	C(73)-C(75)	1.529(13)
C(32)-C(34)	1.561(12)	C(73)-C(74)	1.543(12)
C(39)-C(40)	1.530(12)	C(80)-C(82)	1.512(15)
C(40)-C(41)	1.517(15)	C(80)-C(81)	1.532(14)
C(40)-C(42)	1.540(13)	C(87)-C(88)	1.554(14)
C(41)-F(3)	1.338(11)	C(88)-C(89)	1.523(17)
C(41)-F(2)	1.342(10)	C(88)-C(90)	1.540(11)
C(41)-F(1)	1.343(13)	C(89)-F(5)	1.290(12)
C(42)-C(47)	1.350(15)	C(89)-F(4)	1.351(14)
C(42)-C(43)	1.410(14)	C(89)-F(6)	1.382(16)
C(43)-C(44)	1.324(15)	C(90)-C(95)	1.374(13)
C(44)-C(45)	1.42(2)	C(90)-C(91)	1.391(14)
C(45)-C(46)	1.36(2)	C(91)-C(92)	1.400(14)
C(46)-C(47)	1.394(15)	C(92)-C(93)	1.361(18)
O(11)-C(57)	1.359(9)	C(93)-C(94)	1.365(18)
O(11)-C(50)	1.405(9)	C(94)-C(95)	1.366(14)

Exp. Data Tab. 13 Bonds angles for **53** (sh3365).

Bonds	Angle [°]	Bonds	Angle [°]
C(9)-O(1)-C(2)	114.6(6)	C(88)-O(20)-C(96)	119.5(10)
C(16)-O(4)-C(6)	115.9(6)	C(50)-C(49)-C(54)	116.8(8)
C(39)-O(8)-C(4)	116.7(7)	C(50)-C(49)-C(69)	120.8(7)
C(40)-O(10)-C(48)	120.5(8)	C(54)-C(49)-C(69)	122.4(7)
C(2)-C(1)-C(6)	115.5(7)	C(49)-C(50)-C(51)	124.8(7)
C(2)-C(1)-C(21)	123.0(7)	C(49)-C(50)-O(11)	114.9(7)
C(6)-C(1)-C(21)	121.4(7)	C(51)-C(50)-O(11)	120.3(7)
C(3)-C(2)-C(1)	124.1(7)	C(50)-C(51)-C(52)	115.0(7)
C(3)-C(2)-O(1)	122.0(7)	C(50)-C(51)-C(55)	120.5(7)
C(1)-C(2)-O(1)	113.8(6)	C(52)-C(51)-C(55)	124.4(7)
C(2)-C(3)-C(4)	116.0(7)	C(51)-C(52)-C(53)	124.2(8)
C(2)-C(3)-C(7)	118.6(7)	C(51)-C(52)-O(18)	117.9(7)
C(4)-C(3)-C(7)	125.4(7)	C(53)-C(52)-O(18)	117.1(7)
C(3)-C(4)-C(5)	124.8(7)	C(54)-C(53)-C(52)	115.1(7)
C(3)-C(4)-O(8)	118.2(7)	C(54)-C(53)-C(62)	120.5(8)
C(5)-C(4)-O(8)	116.9(7)	C(52)-C(53)-C(62)	124.0(8)
C(6)-C(5)-C(4)	114.9(7)	C(49)-C(54)-C(53)	123.9(7)
C(6)-C(5)-C(14)	120.2(7)	C(49)-C(54)-O(14)	116.4(7)
C(4)-C(5)-C(14)	124.9(7)	C(53)-C(54)-O(14)	119.6(7)
C(5)-C(6)-C(1)	124.3(7)	C(51)-C(55)-C(73)	111.8(7)
C(5)-C(6)-O(4)	122.3(7)	C(51)-C(55)-C(56)	106.7(7)
C(1)-C(6)-O(4)	113.3(6)	C(73)-C(55)-C(56)	111.7(7)
C(8)-C(7)-C(3)	108.0(6)	C(57)-C(56)-C(61)	120.8(7)
C(8)-C(7)-C(25)	113.7(7)	C(57)-C(56)-C(55)	122.1(7)
C(3)-C(7)-C(25)	111.3(7)	C(61)-C(56)-C(55)	116.9(7)
C(9)-C(8)-C(13)	119.9(8)	C(56)-C(57)-O(11)	121.4(7)
C(9)-C(8)-C(7)	119.9(8)	C(56)-C(57)-C(58)	127.5(7)
C(13)-C(8)-C(7)	119.9(7)	O(11)-C(57)-C(58)	111.0(7)
C(8)-C(9)-O(1)	123.0(7)	C(57)-C(58)-C(59)	111.1(7)
C(8)-C(9)-C(10)	126.9(8)	C(57)-C(58)-C(76)	109.8(7)
O(1)-C(9)-C(10)	110.0(6)	C(59)-C(58)-C(76)	108.9(8)

C(11)-C(10)-C(9)	111.0(7)	C(57)-C(58)-C(77)	108.1(7)
C(11)-C(10)-C(29)	111.3(7)	C(59)-C(58)-C(77)	109.8(7)
C(9)-C(10)-C(29)	110.1(7)	C(76)-C(58)-C(77)	109.2(8)
C(11)-C(10)-C(28)	108.9(8)	O(12)-C(59)-C(60)	119.0(7)
C(9)-C(10)-C(28)	107.6(7)	O(12)-C(59)-C(58)	117.8(8)
C(29)-C(10)-C(28)	107.8(7)	C(60)-C(59)-C(58)	123.0(7)
O(2)-C(11)-C(10)	118.3(8)	C(79)-C(60)-C(78)	111.5(7)
O(2)-C(11)-C(12)	119.6(8)	C(79)-C(60)-C(59)	108.2(8)
C(10)-C(11)-C(12)	122.0(7)	C(78)-C(60)-C(59)	108.0(8)
C(31)-C(12)-C(11)	108.8(7)	C(79)-C(60)-C(61)	108.4(7)
C(31)-C(12)-C(13)	106.6(8)	C(78)-C(60)-C(61)	107.8(7)
C(11)-C(12)-C(13)	112.2(7)	C(59)-C(60)-C(61)	113.0(7)
C(31)-C(12)-C(30)	110.6(8)	O(13)-C(61)-C(56)	121.2(7)
C(11)-C(12)-C(30)	109.3(7)	O(13)-C(61)-C(60)	119.0(8)
C(13)-C(12)-C(30)	109.2(7)	C(56)-C(61)-C(60)	119.8(8)
O(3)-C(13)-C(8)	120.9(8)	C(63)-C(62)-C(53)	108.0(7)
O(3)-C(13)-C(12)	117.8(8)	C(63)-C(62)-C(80)	114.9(7)
C(8)-C(13)-C(12)	121.3(7)	C(53)-C(62)-C(80)	110.6(7)
C(5)-C(14)-C(15)	109.5(7)	C(64)-C(63)-C(68)	119.0(7)
C(5)-C(14)-C(32)	109.2(7)	C(64)-C(63)-C(62)	120.4(7)
C(15)-C(14)-C(32)	113.9(7)	C(68)-C(63)-C(62)	120.6(8)
C(16)-C(15)-C(20)	118.8(7)	C(63)-C(64)-O(14)	121.7(7)
C(16)-C(15)-C(14)	121.4(7)	C(63)-C(64)-C(65)	128.8(7)
C(20)-C(15)-C(14)	119.7(7)	O(14)-C(64)-C(65)	109.5(7)
C(15)-C(16)-O(4)	123.8(7)	C(64)-C(65)-C(84)	108.8(9)
C(15)-C(16)-C(17)	128.9(7)	C(64)-C(65)-C(83)	112.4(8)
O(4)-C(16)-C(17)	107.3(6)	C(84)-C(65)-C(83)	108.8(9)
C(35)-C(17)-C(16)	112.1(8)	C(64)-C(65)-C(66)	110.5(7)
C(35)-C(17)-C(18)	110.0(7)	C(84)-C(65)-C(66)	107.1(8)
C(16)-C(17)-C(18)	110.5(7)	C(83)-C(65)-C(66)	109.1(8)
C(35)-C(17)-C(36)	108.8(9)	O(15)-C(66)-C(67)	121.5(8)
C(16)-C(17)-C(36)	109.4(7)	O(15)-C(66)-C(65)	117.4(8)
C(18)-C(17)-C(36)	105.8(8)	C(67)-C(66)-C(65)	120.9(7)
O(5)-C(18)-C(17)	118.4(8)	C(68)-C(67)-C(66)	114.8(8)
O(5)-C(18)-C(19)	119.3(8)	C(68)-C(67)-C(86)	111.4(8)
C(17)-C(18)-C(19)	122.3(7)	C(66)-C(67)-C(86)	111.5(8)
C(18)-C(19)-C(20)	114.7(7)	C(68)-C(67)-C(85)	105.8(8)
C(18)-C(19)-C(38)	108.7(8)	C(66)-C(67)-C(85)	104.5(8)
C(20)-C(19)-C(38)	110.4(7)	C(86)-C(67)-C(85)	108.3(8)
C(18)-C(19)-C(37)	107.0(7)	O(16)-C(68)-C(63)	119.2(8)
C(20)-C(19)-C(37)	106.6(7)	O(16)-C(68)-C(67)	120.2(8)
C(38)-C(19)-C(37)	109.1(8)	C(63)-C(68)-C(67)	120.2(8)
O(6)-C(20)-C(15)	120.7(7)	O(17A)-C(69)-C(70A)	91.9(16)
O(6)-C(20)-C(19)	119.7(7)	O(17B)-C(69)-C(70B)	127.5(11)
C(15)-C(20)-C(19)	119.6(7)	O(17A)-C(69)-C(49)	122.5(12)
O(7)-C(21)-C(1)	121.7(8)	O(17B)-C(69)-C(49)	112.1(11)
O(7)-C(21)-C(22)	121.4(8)	C(70A)-C(69)-C(49)	127.2(15)
C(1)-C(21)-C(22)	116.7(8)	C(70B)-C(69)-C(49)	114.9(11)
C(23)-C(22)-C(21)	108.9(8)	C(72)-C(70A)-C(69)	122.3(16)
C(23)-C(22)-C(24)	114.1(9)	C(72)-C(70A)-C(71A)	130(3)
C(21)-C(22)-C(24)	112.6(9)	C(69)-C(70A)-C(71A)	107(3)

C(27)-C(25)-C(26)	108.3(8)	C(72)-C(70B)-C(71B)	111.6(14)
C(27)-C(25)-C(7)	113.6(7)	C(72)-C(70B)-C(69)	119.7(13)
C(26)-C(25)-C(7)	112.7(8)	C(71B)-C(70B)-C(69)	110.9(15)
C(33)-C(32)-C(14)	111.3(7)	C(75)-C(73)-C(55)	113.3(8)
C(33)-C(32)-C(34)	109.8(8)	C(75)-C(73)-C(74)	109.7(8)
C(14)-C(32)-C(34)	112.5(7)	C(55)-C(73)-C(74)	112.9(8)
O(9)-C(39)-O(8)	121.1(7)	C(82)-C(80)-C(81)	109.9(9)
O(9)-C(39)-C(40)	126.5(9)	C(82)-C(80)-C(62)	111.3(9)
O(8)-C(39)-C(40)	112.4(8)	C(81)-C(80)-C(62)	112.7(8)
O(10)-C(40)-C(41)	108.5(8)	O(19)-C(87)-O(18)	124.9(10)
O(10)-C(40)-C(39)	108.5(8)	O(19)-C(87)-C(88)	123.0(10)
C(41)-C(40)-C(39)	112.4(8)	O(18)-C(87)-C(88)	112.0(10)
O(10)-C(40)-C(42)	107.7(7)	O(20)-C(88)-C(89)	108.3(9)
C(41)-C(40)-C(42)	112.0(9)	O(20)-C(88)-C(90)	105.7(8)
C(39)-C(40)-C(42)	107.6(8)	C(89)-C(88)-C(90)	117.7(10)
F(3)-C(41)-F(2)	107.4(8)	O(20)-C(88)-C(87)	106.3(9)
F(3)-C(41)-F(1)	106.2(9)	C(89)-C(88)-C(87)	110.9(9)
F(2)-C(41)-F(1)	105.1(9)	C(90)-C(88)-C(87)	107.3(7)
F(3)-C(41)-C(40)	111.9(9)	F(5)-C(89)-F(4)	109.8(10)
F(2)-C(41)-C(40)	110.8(9)	F(5)-C(89)-F(6)	104.7(12)
F(1)-C(41)-C(40)	114.9(9)	F(4)-C(89)-F(6)	104.4(11)
C(47)-C(42)-C(43)	119.0(9)	F(5)-C(89)-C(88)	116.3(11)
C(47)-C(42)-C(40)	123.5(10)	F(4)-C(89)-C(88)	108.8(11)
C(43)-C(42)-C(40)	117.3(9)	F(6)-C(89)-C(88)	112.1(9)
C(44)-C(43)-C(42)	121.0(12)	C(95)-C(90)-C(91)	119.9(9)
C(43)-C(44)-C(45)	118.9(12)	C(95)-C(90)-C(88)	122.1(9)
C(46)-C(45)-C(44)	121.7(11)	C(91)-C(90)-C(88)	117.9(9)
C(45)-C(46)-C(47)	117.4(12)	C(90)-C(91)-C(92)	118.7(10)
C(42)-C(47)-C(46)	121.9(12)	C(93)-C(92)-C(91)	120.0(12)
C(57)-O(11)-C(50)	117.8(6)	C(92)-C(93)-C(94)	120.4(10)
C(64)-O(14)-C(54)	118.8(7)	C(93)-C(94)-C(95)	120.7(11)
C(87)-O(18)-C(52)	119.1(8)	C(94)-C(95)-C(90)	120.1(11)

Exp. Data Tab. 14 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **53** (sh3365) The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

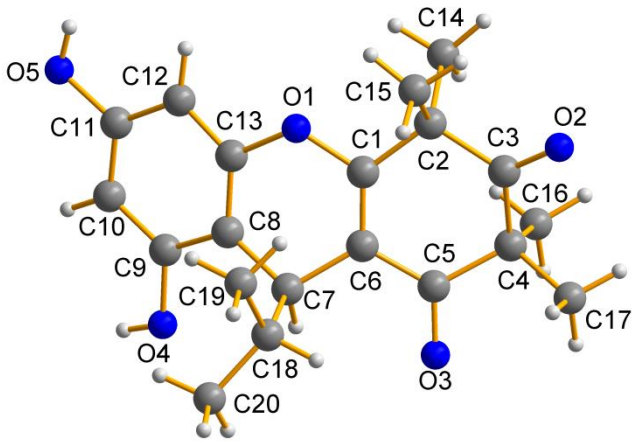
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	27(4)	24(3)	13(3)	3(2)	0(2)	-9(2)
O(2)	68(6)	35(4)	23(4)	4(3)	5(3)	-8(3)
O(3)	58(6)	30(3)	26(4)	4(3)	-1(3)	-6(3)
O(4)	33(4)	20(3)	19(3)	-1(2)	-1(3)	1(2)
O(5)	89(7)	41(4)	30(4)	-12(3)	5(4)	-7(4)
O(6)	59(5)	26(3)	17(3)	0(3)	-2(3)	8(3)
O(7)	39(5)	23(3)	64(5)	9(3)	-10(4)	-1(3)
O(8)	23(4)	14(3)	23(3)	0(2)	3(3)	-6(2)
O(9)	25(4)	33(3)	32(4)	6(3)	-5(3)	1(3)
O(10)	72(6)	25(3)	22(4)	6(3)	-5(3)	1(3)
C(1)	21(5)	18(4)	19(4)	-2(3)	-3(4)	-2(3)
C(2)	12(5)	22(4)	20(4)	1(3)	2(3)	-6(3)
C(3)	15(5)	19(4)	25(4)	-1(3)	3(4)	1(3)

C(4)	14(5)	19(4)	19(4)	4(3)	0(3)	-4(3)
C(5)	22(6)	14(4)	29(5)	-3(3)	-6(4)	-2(3)
C(6)	19(5)	15(4)	16(4)	-3(3)	-6(3)	1(3)
C(7)	22(5)	19(4)	14(4)	3(3)	2(3)	-4(3)
C(8)	16(5)	24(4)	23(4)	6(3)	1(3)	0(3)
C(9)	19(5)	18(4)	19(4)	3(3)	3(3)	-5(3)
C(10)	31(6)	18(4)	21(4)	8(3)	-9(4)	-4(3)
C(11)	27(6)	35(5)	23(5)	0(4)	3(4)	-7(4)
C(12)	32(6)	27(4)	15(4)	-3(3)	-4(4)	-1(4)
C(13)	41(7)	26(5)	18(5)	1(3)	-3(4)	-3(4)
C(14)	26(5)	25(4)	14(4)	-3(3)	1(3)	-1(4)
C(15)	30(6)	19(4)	17(4)	-9(3)	-6(4)	5(3)
C(16)	11(5)	30(4)	16(4)	-1(3)	2(3)	2(3)
C(17)	36(6)	19(4)	23(4)	-9(3)	3(4)	5(4)
C(18)	23(6)	41(5)	22(5)	-9(4)	1(4)	3(4)
C(19)	18(5)	28(4)	25(5)	-5(3)	-5(4)	6(4)
C(20)	21(6)	30(4)	15(4)	2(3)	-1(3)	6(4)
C(21)	27(6)	19(4)	20(5)	-6(3)	2(4)	-1(3)
C(22)	36(7)	30(5)	54(7)	5(5)	-5(5)	-17(4)
C(23)	30(7)	46(6)	46(7)	1(5)	-4(5)	-11(5)
C(24)	65(10)	27(5)	67(8)	-7(5)	-7(6)	-27(5)
C(25)	29(6)	25(4)	9(4)	2(3)	-2(3)	7(3)
C(26)	47(8)	37(5)	29(6)	-2(4)	10(5)	8(5)
C(27)	16(6)	46(6)	41(6)	-4(4)	-3(4)	5(4)
C(28)	54(7)	32(5)	18(5)	-3(4)	-9(4)	16(4)
C(29)	61(7)	34(5)	15(5)	14(4)	6(5)	-25(5)
C(30)	72(9)	32(5)	19(5)	3(4)	9(5)	-2(5)
C(31)	25(6)	41(6)	49(7)	0(5)	-11(5)	-2(4)
C(32)	26(5)	25(4)	22(5)	-6(4)	5(4)	-6(4)
C(33)	32(7)	48(6)	30(6)	-4(4)	-7(5)	11(4)
C(34)	31(7)	49(6)	22(5)	-6(4)	1(4)	-11(4)
C(35)	90(10)	26(5)	36(6)	-8(4)	1(6)	19(5)
C(36)	48(7)	54(6)	27(6)	-17(5)	2(5)	-24(5)
C(37)	39(7)	47(6)	40(6)	-13(5)	20(5)	-9(5)
C(38)	51(7)	38(5)	30(6)	-15(4)	-13(5)	6(5)
C(39)	25(6)	19(4)	26(6)	-7(3)	-4(4)	1(3)
C(40)	36(6)	27(4)	32(5)	-6(4)	5(4)	4(4)
C(41)	51(7)	20(5)	55(7)	-3(4)	13(5)	-6(4)
F(1)	39(4)	42(3)	76(5)	-5(3)	4(3)	-7(3)
F(2)	80(6)	24(3)	79(5)	6(3)	38(4)	-13(3)
F(3)	71(5)	39(3)	55(4)	-4(3)	31(3)	2(3)
C(42)	57(8)	23(5)	24(5)	-11(4)	4(4)	1(4)
C(43)	48(8)	33(5)	41(6)	-11(4)	14(5)	5(4)
C(44)	111(13)	51(7)	59(8)	-7(6)	39(7)	32(7)
C(45)	122(14)	46(7)	42(7)	-14(6)	28(7)	-17(7)
C(46)	103(11)	48(7)	31(6)	1(5)	-7(6)	-27(6)
C(47)	54(8)	36(6)	46(6)	-7(5)	2(5)	-4(5)
C(48)	105(12)	37(6)	36(6)	8(5)	-10(6)	3(6)
O(11)	40(5)	14(3)	29(4)	-3(2)	-3(3)	0(3)
O(12)	70(6)	15(3)	48(5)	-11(3)	-21(4)	-1(3)
O(13)	85(7)	25(3)	32(4)	3(3)	-19(4)	-1(4)

O(14)	34(4)	22(3)	21(3)	2(2)	1(3)	5(3)
O(15)	58(6)	27(3)	33(4)	7(3)	-4(3)	-8(3)
O(16)	103(8)	26(4)	30(4)	-3(3)	-6(4)	6(4)
O(18)	57(6)	19(3)	38(4)	3(3)	-1(3)	-5(3)
O(19)	60(6)	47(4)	42(5)	-7(3)	-13(4)	12(4)
O(20)	92(7)	38(4)	66(5)	3(4)	-16(5)	4(4)
C(49)	35(7)	21(4)	21(4)	-1(3)	7(4)	-1(4)
C(50)	28(6)	15(4)	27(5)	-4(3)	-11(4)	-1(3)
C(51)	16(5)	18(4)	20(4)	3(3)	0(3)	2(3)
C(52)	18(6)	28(4)	16(4)	-1(3)	4(3)	5(3)
C(53)	16(5)	25(4)	29(5)	-5(3)	-5(4)	1(3)
C(54)	30(6)	21(4)	26(5)	2(3)	1(4)	-3(4)
C(55)	21(5)	14(4)	29(5)	1(3)	2(4)	-6(3)
C(56)	11(5)	18(4)	27(4)	0(3)	3(3)	-4(3)
C(57)	29(6)	11(4)	23(5)	1(3)	-1(4)	3(3)
C(58)	21(5)	14(4)	34(5)	-5(3)	-2(4)	-4(3)
C(59)	28(6)	18(4)	41(5)	-2(4)	-12(4)	2(4)
C(60)	25(6)	12(4)	37(5)	2(3)	0(4)	-4(3)
C(61)	33(6)	16(4)	36(5)	-1(4)	5(4)	2(3)
C(62)	11(5)	25(4)	32(5)	1(3)	-7(4)	-3(3)
C(63)	18(6)	22(4)	29(5)	5(3)	-2(4)	3(3)
C(64)	21(6)	19(4)	39(5)	-1(3)	0(4)	-1(3)
C(65)	31(6)	25(4)	32(5)	-2(4)	-2(4)	-4(4)
C(66)	27(6)	22(4)	37(5)	1(4)	-3(4)	-7(4)
C(67)	60(7)	18(4)	25(5)	0(4)	-4(5)	2(4)
C(68)	35(6)	18(4)	32(5)	2(4)	0(4)	-6(4)
C(69)	72(8)	21(5)	30(5)	-3(4)	-7(5)	1(5)
C(70A)	115(11)	74(11)	35(8)	-15(8)	-37(8)	46(9)
C(71A)	122(14)	80(13)	37(9)	-13(10)	-36(10)	37(12)
C(70B)	114(11)	72(10)	32(7)	-14(7)	-40(7)	53(8)
C(71B)	122(12)	85(10)	37(8)	-18(7)	-39(7)	29(9)
C(72)	90(12)	82(10)	117(14)	-28(9)	-20(9)	24(8)
C(73)	21(6)	31(5)	37(6)	-7(4)	6(4)	-11(4)
C(74)	53(9)	42(6)	40(6)	-5(4)	27(5)	-19(5)
C(75)	23(6)	39(6)	57(6)	-12(5)	-4(5)	1(4)
C(76)	30(6)	40(5)	43(6)	-8(5)	14(5)	-4(4)
C(77)	38(7)	31(5)	32(6)	-6(4)	-16(4)	-2(4)
C(78)	32(7)	26(5)	64(7)	6(5)	10(5)	-7(4)
C(79)	29(6)	34(5)	33(6)	1(4)	0(4)	3(4)
C(80)	14(6)	38(5)	61(7)	16(5)	-11(4)	-3(4)
C(81)	47(8)	67(7)	40(7)	18(5)	-10(5)	-36(6)
C(82)	17(6)	47(6)	77(8)	7(5)	4(5)	1(5)
C(83)	53(8)	30(5)	49(7)	9(5)	-25(5)	-7(5)
C(84)	52(8)	52(6)	56(8)	5(5)	26(6)	5(5)
C(85)	45(7)	43(6)	51(7)	-10(5)	3(5)	-3(5)
C(86)	65(9)	24(5)	40(6)	11(4)	-2(5)	-7(5)
C(87)	41(7)	25(5)	43(5)	-4(4)	4(5)	-3(4)
C(88)	65(7)	23(4)	21(5)	-2(4)	-4(4)	-21(4)
C(89)	68(8)	49(7)	63(8)	-4(6)	20(6)	-17(6)
C(90)	34(6)	25(4)	23(5)	-1(4)	6(4)	-10(4)
C(91)	42(7)	31(5)	60(8)	-17(5)	-9(5)	2(4)

C(92)	57(9)	51(6)	68(9)	-15(6)	-7(6)	-26(5)
C(93)	94(11)	28(6)	58(9)	-18(5)	7(7)	-5(5)
C(94)	103(11)	37(5)	19(6)	1(5)	1(6)	6(6)
C(95)	67(9)	34(5)	23(6)	4(4)	-13(5)	1(5)
C(96)	131(16)	40(6)	93(12)	8(7)	15(10)	18(8)
F(4)	156(10)	132(7)	61(5)	-35(5)	66(5)	-64(7)
F(5)	118(8)	63(4)	88(6)	-4(4)	25(5)	-48(4)
F(6)	43(5)	102(5)	98(6)	-15(4)	28(4)	-5(4)

6.3. Appendix 3: crystal data for 85



Exp. Data Tab. 15 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **85** (sh3169). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	1190(3)	3379(2)	2485(5)	26(1)
O(2)	-523(4)	1695(3)	-880(6)	50(2)
O(3)	1990(4)	3562(2)	-2533(5)	35(1)
O(4)	4107(3)	5168(2)	1105(5)	29(1)
O(5)	3632(3)	4443(2)	6097(5)	31(1)
C(1)	1121(5)	3133(3)	1046(8)	26(2)
C(2)	407(5)	2406(3)	986(8)	26(2)
C(3)	257(6)	2145(3)	-600(8)	28(2)
C(4)	1052(6)	2417(4)	-1784(8)	33(2)
C(5)	1550(5)	3214(4)	-1490(8)	29(2)
C(6)	1598(5)	3525(4)	-44(8)	19(2)
C(7)	2154(5)	4308(3)	193(7)	23(2)
C(8)	2584(5)	4338(3)	1736(8)	18(2)
C(9)	3539(5)	4774(3)	2184(7)	20(2)
C(10)	3892(6)	4805(3)	3637(7)	24(2)
C(11)	3282(5)	4392(3)	4646(8)	25(2)
C(12)	2372(5)	3913(4)	4259(7)	21(2)
C(13)	2073(5)	3910(3)	2826(7)	19(2)
C(14)	994(6)	1734(4)	1821(9)	44(2)
C(15)	-769(5)	2558(4)	1687(9)	41(2)
C(16)	2087(6)	1860(3)	-1807(9)	52(2)
C(17)	444(6)	2401(4)	-3251(9)	65(3)
C(18)	1277(5)	4949(3)	-219(8)	33(2)
C(19)	311(6)	5027(4)	890(9)	54(2)
C(20)	1860(6)	5723(3)	-476(9)	52(3)

Exp. Data Tab. 16 Bond lengths [Å] for **85** (sh3169).

Bond	Length [Å]	Bond	Length [Å]
O(1)-C(1)	1.390(7)	C(10)-H(10)	0.9500
O(1)-C(13)	1.414(6)	C(11)-C(12)	1.391(8)
O(2)-C(3)	1.224(7)	C(12)-C(13)	1.361(8)
O(3)-C(5)	1.242(7)	C(12)-H(12)	0.9500
O(4)-C(9)	1.373(6)	C(14)-H(14A)	0.9800
O(4)-H(4)	0.8400	C(14)-H(14B)	0.9800
O(5)-C(11)	1.396(8)	C(14)-H(14C)	0.9800
O(5)-H(5)	0.8400	C(15)-H(15A)	0.9800
C(1)-C(6)	1.330(8)	C(15)-H(15B)	0.9800
C(1)-C(2)	1.508(8)	C(15)-H(15C)	0.9800
C(2)-C(3)	1.534(9)	C(16)-H(16A)	0.9800
C(2)-C(15)	1.535(8)	C(16)-H(16B)	0.9800
C(2)-C(14)	1.553(9)	C(16)-H(16C)	0.9800
C(3)-C(4)	1.503(9)	C(17)-H(17A)	0.9800
C(4)-C(5)	1.519(8)	C(17)-H(17B)	0.9800
C(4)-C(17)	1.522(10)	C(17)-H(17C)	0.9800
C(4)-C(16)	1.544(9)	C(18)-C(20)	1.519(8)
C(5)-C(6)	1.434(9)	C(18)-C(19)	1.523(9)
C(6)-C(7)	1.518(8)	C(18)-H(18)	1.0000
C(7)-C(8)	1.504(8)	C(19)-H(19A)	0.9800
C(7)-C(18)	1.555(8)	C(19)-H(19B)	0.9800
C(7)-H(7)	1.0000	C(19)-H(19C)	0.9800
C(8)-C(13)	1.379(8)	C(20)-H(20A)	0.9800
C(8)-C(9)	1.405(8)	C(20)-H(20B)	0.9800
C(9)-C(10)	1.397(8)	C(20)-H(20C)	0.9800
C(10)-C(11)	1.368(8)		

Exp. Data Tab. 17 Bond angles [°] for **85** (sh3169).

Bonds	Angles [°]	Bonds	Angles [°]
C(1)-O(1)-C(13)	116.9(5)	C(11)-C(12)-H(12)	121.8
C(9)-O(4)-H(4)	109.5	C(12)-C(13)-C(8)	126.0(6)
C(11)-O(5)-H(5)	109.5	C(12)-C(13)-O(1)	113.8(6)
C(6)-C(1)-O(1)	122.3(6)	C(8)-C(13)-O(1)	120.1(6)
C(6)-C(1)-C(2)	128.9(7)	C(2)-C(14)-H(14A)	109.5
O(1)-C(1)-C(2)	108.8(6)	C(2)-C(14)-H(14B)	109.5
C(1)-C(2)-C(3)	110.0(6)	H(14A)-C(14)-H(14B)	109.5
C(1)-C(2)-C(15)	109.5(5)	C(2)-C(14)-H(14C)	109.5
C(3)-C(2)-C(15)	110.3(6)	H(14A)-C(14)-H(14C)	109.5
C(1)-C(2)-C(14)	111.3(5)	H(14B)-C(14)-H(14C)	109.5
C(3)-C(2)-C(14)	107.3(5)	C(2)-C(15)-H(15A)	109.5
C(15)-C(2)-C(14)	108.2(6)	C(2)-C(15)-H(15B)	109.5
O(2)-C(3)-C(4)	120.2(7)	H(15A)-C(15)-H(15B)	109.5
O(2)-C(3)-C(2)	118.1(6)	C(2)-C(15)-H(15C)	109.5
C(4)-C(3)-C(2)	121.6(6)	H(15A)-C(15)-H(15C)	109.5
C(3)-C(4)-C(5)	113.0(6)	H(15B)-C(15)-H(15C)	109.5
C(3)-C(4)-C(17)	110.4(6)	C(4)-C(16)-H(16A)	109.5
C(5)-C(4)-C(17)	110.6(6)	C(4)-C(16)-H(16B)	109.5

C(3)-C(4)-C(16)	107.1(5)	H(16A)-C(16)-H(16B)	109.5
C(5)-C(4)-C(16)	105.7(5)	C(4)-C(16)-H(16C)	109.5
C(17)-C(4)-C(16)	109.8(6)	H(16A)-C(16)-H(16C)	109.5
O(3)-C(5)-C(6)	121.1(6)	H(16B)-C(16)-H(16C)	109.5
O(3)-C(5)-C(4)	117.4(6)	C(4)-C(17)-H(17A)	109.5
C(6)-C(5)-C(4)	121.3(6)	C(4)-C(17)-H(17B)	109.5
C(1)-C(6)-C(5)	119.3(6)	H(17A)-C(17)-H(17B)	109.5
C(1)-C(6)-C(7)	121.7(6)	C(4)-C(17)-H(17C)	109.5
C(5)-C(6)-C(7)	118.9(6)	H(17A)-C(17)-H(17C)	109.5
C(8)-C(7)-C(6)	107.9(6)	H(17B)-C(17)-H(17C)	109.5
C(8)-C(7)-C(18)	115.1(6)	C(20)-C(18)-C(19)	110.9(6)
C(6)-C(7)-C(18)	108.8(5)	C(20)-C(18)-C(7)	111.9(5)
C(8)-C(7)-H(7)	108.3	C(19)-C(18)-C(7)	112.6(5)
C(6)-C(7)-H(7)	108.3	C(20)-C(18)-H(18)	107.0
C(18)-C(7)-H(7)	108.3	C(19)-C(18)-H(18)	107.0
C(13)-C(8)-C(9)	114.7(6)	C(7)-C(18)-H(18)	107.0
C(13)-C(8)-C(7)	121.4(6)	C(18)-C(19)-H(19A)	109.5
C(9)-C(8)-C(7)	123.9(6)	C(18)-C(19)-H(19B)	109.5
O(4)-C(9)-C(10)	121.9(5)	H(19A)-C(19)-H(19B)	109.5
O(4)-C(9)-C(8)	115.9(6)	C(18)-C(19)-H(19C)	109.5
C(10)-C(9)-C(8)	122.2(6)	H(19A)-C(19)-H(19C)	109.5
C(11)-C(10)-C(9)	118.3(6)	H(19B)-C(19)-H(19C)	109.5
C(11)-C(10)-H(10)	120.9	C(18)-C(20)-H(20A)	109.5
C(9)-C(10)-H(10)	120.9	C(18)-C(20)-H(20B)	109.5
C(10)-C(11)-C(12)	122.2(6)	H(20A)-C(20)-H(20B)	109.5
C(10)-C(11)-O(5)	117.5(6)	C(18)-C(20)-H(20C)	109.5
C(12)-C(11)-O(5)	120.2(6)	H(20A)-C(20)-H(20C)	109.5
C(13)-C(12)-C(11)	116.4(6)	H(20B)-C(20)-H(20C)	109.5
C(13)-C(12)-H(12)	121.8		

Exp. Data Tab. 18 Anisotropic displacement parameters ($Å^2 x\ 10^3$ for **85** (sh3169). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

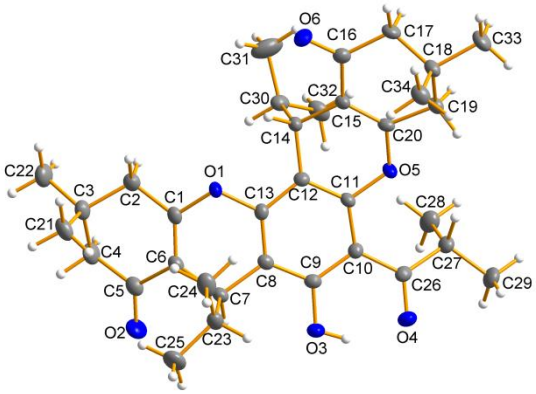
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	26(3)	29(3)	23(3)	0(2)	-2(2)	-10(2)
O(2)	63(3)	49(3)	37(3)	-5(3)	2(3)	-35(3)
O(3)	48(3)	38(3)	19(3)	-6(3)	2(3)	-21(2)
O(4)	40(3)	25(2)	22(3)	-2(3)	3(3)	-16(2)
O(5)	41(3)	33(3)	20(3)	7(3)	0(3)	-12(2)
C(1)	29(4)	24(4)	25(5)	-8(4)	-12(4)	8(3)
C(2)	25(4)	25(4)	28(5)	-3(4)	4(4)	-10(3)
C(3)	35(4)	20(4)	29(5)	6(4)	-3(4)	-12(3)
C(4)	42(5)	32(4)	26(5)	3(4)	3(4)	-11(4)
C(5)	32(4)	30(4)	23(5)	-4(4)	-7(4)	-3(3)
C(6)	23(4)	16(3)	19(4)	1(3)	-1(3)	-8(3)
C(7)	28(4)	22(4)	19(4)	-3(3)	1(4)	2(3)
C(8)	22(3)	16(3)	18(4)	-4(3)	4(3)	-2(3)
C(9)	20(3)	11(3)	27(5)	10(3)	4(3)	-4(3)
C(10)	25(4)	22(4)	25(4)	2(4)	-3(3)	-10(3)
C(11)	22(4)	25(4)	28(5)	-5(4)	-4(3)	1(3)
C(12)	25(4)	21(4)	17(4)	0(3)	4(3)	-5(3)

C(13)	20(4)	8(3)	29(5)	3(3)	-6(3)	-5(3)
C(14)	61(5)	22(4)	48(5)	10(4)	-15(5)	-8(4)
C(15)	33(4)	47(5)	42(5)	-10(4)	6(4)	-16(4)
C(16)	74(6)	23(4)	58(6)	-18(4)	26(5)	-12(4)
C(17)	98(7)	68(6)	28(5)	3(5)	-12(6)	-53(5)
C(18)	41(4)	18(4)	39(5)	8(4)	-7(4)	1(3)
C(19)	47(5)	52(5)	63(7)	6(5)	4(5)	27(4)
C(20)	64(5)	19(4)	73(7)	18(4)	-18(5)	-4(4)

Exp. Data Tab. 19 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **85** (sh3169).

Hydrogen atom	x	y	z	U(eq)
H(4)	4659	5414	1469	44
H(5)	3202	4168	6618	47
H(7)	2830	4351	-475	28
H(10)	4539	5104	3917	29
H(12)	1981	3605	4957	25
H(14A)	1709	1591	1326	65
H(14B)	477	1287	1846	65
H(14C)	1166	1899	2819	65
H(15A)	-667	2666	2727	61
H(15B)	-1257	2101	1569	61
H(15C)	-1132	3003	1215	61
H(16A)	2496	1891	-875	78
H(16B)	2609	2005	-2599	78
H(16C)	1815	1330	-1960	78
H(17A)	155	1878	-3440	97
H(17B)	985	2548	-4020	97
H(17C)	-200	2765	-3239	97
H(18)	916	4792	-1162	39
H(19A)	629	5198	1824	81
H(19B)	-68	4525	1016	81
H(19C)	-249	5407	543	81
H(20A)	1301	6091	-870	78
H(20B)	2491	5656	-1172	78
H(20C)	2165	5919	447	78

6.4. Appendix 4: crystal data for *anti*-97



Exp. Data Tab. 20 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for *anti*-**97** (sh3587a). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	1646(2)	6090(1)	6360(2)	20(1)
O(2)	1153(2)	4538(1)	3514(2)	37(1)
O(3)	3714(2)	4303(1)	7384(2)	28(1)
O(4)	4467(2)	4061(1)	9493(2)	34(1)
O(5)	3174(2)	5640(1)	10356(2)	21(1)
O(6)	2000(2)	7675(1)	9511(2)	30(1)
C(1)	1212(2)	5851(1)	5265(2)	19(1)
C(2)	301(2)	6217(1)	4621(2)	23(1)
C(3)	-43(2)	6071(1)	3309(2)	25(1)
C(4)	-47(3)	5369(1)	3172(2)	29(1)
C(5)	932(2)	5045(1)	3823(2)	24(1)
C(6)	1579(2)	5341(1)	4886(2)	21(1)
C(7)	2563(2)	5039(1)	5578(2)	21(1)
C(8)	2714(2)	5187(1)	6854(2)	19(1)
C(9)	3292(2)	4805(1)	7732(2)	19(1)
C(10)	3418(2)	4930(1)	8934(2)	20(1)
C(11)	2978(2)	5486(1)	9188(2)	18(1)
C(12)	2389(2)	5876(1)	8345(2)	19(1)
C(13)	2273(2)	5704(1)	7186(2)	18(1)
C(14)	1825(2)	6417(1)	8675(2)	19(1)
C(15)	2419(2)	6630(1)	9876(2)	18(1)
C(16)	2378(2)	7277(1)	10223(2)	22(1)
C(17)	2832(2)	7428(1)	11501(2)	26(1)
C(18)	3825(2)	7073(1)	12070(2)	23(1)
C(19)	3588(2)	6382(1)	11878(2)	21(1)
C(20)	3020(2)	6240(1)	10644(2)	19(1)
C(21)	703(3)	6359(2)	2685(2)	32(1)
C(22)	-1131(3)	6324(2)	2784(3)	37(1)
C(23)	3525(2)	5232(2)	5183(2)	26(1)
C(24)	3709(3)	5923(2)	5253(3)	33(1)
C(25)	3465(3)	4995(2)	3953(3)	40(1)
C(26)	3951(2)	4461(1)	9797(2)	22(1)
C(27)	3802(2)	4420(1)	11013(2)	25(1)

C(28)	2664(3)	4283(2)	10905(3)	35(1)
C(29)	4501(3)	3923(2)	11725(3)	35(1)
C(30)	686(2)	6242(1)	8579(2)	25(1)
C(31)	51(3)	6794(2)	8760(4)	51(1)
C(32)	588(3)	5728(2)	9412(3)	33(1)
C(33)	4170(3)	7211(2)	13381(2)	32(1)
C(34)	4688(2)	7265(2)	11529(2)	29(1)
Cl(1)	1591(2)	2574(1)	4773(2)	173(1)
Cl(2)	3086(2)	3039(1)	3725(3)	177(1)
C(35)	2276(6)	3192(3)	4488(7)	143(3)

Exp. Data Tab. 21 Bond lengths [Å] for *anti*-**97** (sh3587a).

Bond	Length [Å]	Bond	Length [Å]
O(1)-C(1)	1.376(3)	C(19)-H(19A)	0.9900
O(1)-C(13)	1.385(3)	C(19)-H(19B)	0.9900
O(2)-C(5)	1.221(4)	C(21)-H(21A)	0.9800
O(3)-C(9)	1.344(3)	C(21)-H(21B)	0.9800
O(3)-H(3)	0.8400	C(21)-H(21C)	0.9800
O(4)-C(26)	1.225(3)	C(22)-H(22A)	0.9800
O(5)-C(20)	1.375(3)	C(22)-H(22B)	0.9800
O(5)-C(11)	1.384(3)	C(22)-H(22C)	0.9800
O(6)-C(16)	1.217(3)	C(23)-C(24)	1.517(5)
C(1)-C(6)	1.338(4)	C(23)-C(25)	1.534(4)
C(1)-C(2)	1.482(4)	C(23)-H(23)	1.0000
C(2)-C(3)	1.536(4)	C(24)-H(24A)	0.9800
C(2)-H(2A)	0.9900	C(24)-H(24B)	0.9800
C(2)-H(2B)	0.9900	C(24)-H(24C)	0.9800
C(3)-C(22)	1.524(4)	C(25)-H(25A)	0.9800
C(3)-C(4)	1.530(4)	C(25)-H(25B)	0.9800
C(3)-C(21)	1.534(4)	C(25)-H(25C)	0.9800
C(4)-C(5)	1.503(4)	C(26)-C(27)	1.518(4)
C(4)-H(4A)	0.9900	C(27)-C(29)	1.524(4)
C(4)-H(4B)	0.9900	C(27)-C(28)	1.526(4)
C(5)-C(6)	1.471(4)	C(27)-H(27)	1.0000
C(6)-C(7)	1.503(4)	C(28)-H(28A)	0.9800
C(7)-C(8)	1.512(3)	C(28)-H(28B)	0.9800
C(7)-C(23)	1.549(4)	C(28)-H(28C)	0.9800
C(7)-H(7)	1.0000	C(29)-H(29A)	0.9800
C(8)-C(13)	1.376(4)	C(29)-H(29B)	0.9800
C(8)-C(9)	1.390(4)	C(29)-H(29C)	0.9800
C(9)-C(10)	1.421(3)	C(30)-C(31)	1.518(4)
C(10)-C(11)	1.412(4)	C(30)-C(32)	1.521(4)
C(10)-C(26)	1.483(4)	C(30)-H(30)	1.0000
C(11)-C(12)	1.381(4)	C(31)-H(31A)	0.9800
C(12)-C(13)	1.396(3)	C(31)-H(31B)	0.9800
C(12)-C(14)	1.506(4)	C(31)-H(31C)	0.9800
C(14)-C(15)	1.506(4)	C(32)-H(32A)	0.9800
C(14)-C(30)	1.549(4)	C(32)-H(32B)	0.9800
C(14)-H(14)	1.0000	C(32)-H(32C)	0.9800
C(15)-C(20)	1.341(4)	C(33)-H(33A)	0.9800

C(15)-C(16)	1.468(4)	C(33)-H(33B)	0.9800
C(16)-C(17)	1.512(4)	C(33)-H(33C)	0.9800
C(17)-C(18)	1.526(4)	C(34)-H(34A)	0.9800
C(17)-H(17A)	0.9900	C(34)-H(34B)	0.9800
C(17)-H(17B)	0.9900	C(34)-H(34C)	0.9800
C(18)-C(34)	1.530(4)	Cl(1)-C(35)	1.712(6)
C(18)-C(33)	1.532(4)	Cl(2)-C(35)	1.631(6)
C(18)-C(19)	1.536(4)	C(35)-H(35A)	0.9900
C(19)-C(20)	1.490(4)	C(35)-H(35B)	0.9900

Exp. Data Tab. 22 Bond angles [°] for *anti*-**97** (sh3587a).

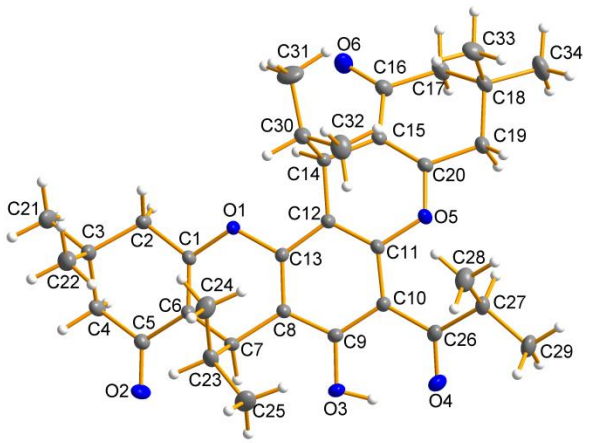
Bonds	Angles [°]	Bonds	Angles [°]
C(1)-O(1)-C(13)	117.5(2)	C(3)-C(21)-H(21A)	109.5
C(9)-O(3)-H(3)	109.5	C(3)-C(21)-H(21B)	109.5
C(20)-O(5)-C(11)	118.6(2)	H(21A)-C(21)-H(21B)	109.5
C(6)-C(1)-O(1)	122.2(2)	C(3)-C(21)-H(21C)	109.5
C(6)-C(1)-C(2)	126.5(2)	H(21A)-C(21)-H(21C)	109.5
O(1)-C(1)-C(2)	111.3(2)	H(21B)-C(21)-H(21C)	109.5
C(1)-C(2)-C(3)	113.0(2)	C(3)-C(22)-H(22A)	109.5
C(1)-C(2)-H(2A)	109.0	C(3)-C(22)-H(22B)	109.5
C(3)-C(2)-H(2A)	109.0	H(22A)-C(22)-H(22B)	109.5
C(1)-C(2)-H(2B)	109.0	C(3)-C(22)-H(22C)	109.5
C(3)-C(2)-H(2B)	109.0	H(22A)-C(22)-H(22C)	109.5
H(2A)-C(2)-H(2B)	107.8	H(22B)-C(22)-H(22C)	109.5
C(22)-C(3)-C(4)	109.8(3)	C(24)-C(23)-C(25)	110.4(3)
C(22)-C(3)-C(21)	109.5(3)	C(24)-C(23)-C(7)	112.8(3)
C(4)-C(3)-C(21)	109.6(3)	C(25)-C(23)-C(7)	111.7(3)
C(22)-C(3)-C(2)	109.3(2)	C(24)-C(23)-H(23)	107.2
C(4)-C(3)-C(2)	107.8(2)	C(25)-C(23)-H(23)	107.2
C(21)-C(3)-C(2)	110.8(2)	C(7)-C(23)-H(23)	107.2
C(5)-C(4)-C(3)	115.6(2)	C(23)-C(24)-H(24A)	109.5
C(5)-C(4)-H(4A)	108.4	C(23)-C(24)-H(24B)	109.5
C(3)-C(4)-H(4A)	108.4	H(24A)-C(24)-H(24B)	109.5
C(5)-C(4)-H(4B)	108.4	C(23)-C(24)-H(24C)	109.5
C(3)-C(4)-H(4B)	108.4	H(24A)-C(24)-H(24C)	109.5
H(4A)-C(4)-H(4B)	107.4	H(24B)-C(24)-H(24C)	109.5
O(2)-C(5)-C(6)	121.1(3)	C(23)-C(25)-H(25A)	109.5
O(2)-C(5)-C(4)	121.0(3)	C(23)-C(25)-H(25B)	109.5
C(6)-C(5)-C(4)	117.7(3)	H(25A)-C(25)-H(25B)	109.5
C(1)-C(6)-C(5)	117.8(3)	C(23)-C(25)-H(25C)	109.5
C(1)-C(6)-C(7)	121.7(2)	H(25A)-C(25)-H(25C)	109.5
C(5)-C(6)-C(7)	120.3(3)	H(25B)-C(25)-H(25C)	109.5
C(6)-C(7)-C(8)	108.3(2)	O(4)-C(26)-C(10)	119.0(3)
C(6)-C(7)-C(23)	113.3(2)	O(4)-C(26)-C(27)	118.3(2)
C(8)-C(7)-C(23)	110.8(2)	C(10)-C(26)-C(27)	122.5(3)
C(6)-C(7)-H(7)	108.1	C(26)-C(27)-C(29)	110.5(2)
C(8)-C(7)-H(7)	108.1	C(26)-C(27)-C(28)	108.8(2)
C(23)-C(7)-H(7)	108.1	C(29)-C(27)-C(28)	111.0(3)
C(13)-C(8)-C(9)	117.7(2)	C(26)-C(27)-H(27)	108.8
C(13)-C(8)-C(7)	120.8(2)	C(29)-C(27)-H(27)	108.8

C(9)-C(8)-C(7)	121.5(2)	C(28)-C(27)-H(27)	108.8
O(3)-C(9)-C(8)	116.4(2)	C(27)-C(28)-H(28A)	109.5
O(3)-C(9)-C(10)	121.4(2)	C(27)-C(28)-H(28B)	109.5
C(8)-C(9)-C(10)	122.1(3)	H(28A)-C(28)-H(28B)	109.5
C(11)-C(10)-C(9)	116.0(2)	C(27)-C(28)-H(28C)	109.5
C(11)-C(10)-C(26)	126.0(2)	H(28A)-C(28)-H(28C)	109.5
C(9)-C(10)-C(26)	118.0(2)	H(28B)-C(28)-H(28C)	109.5
C(12)-C(11)-O(5)	119.8(2)	C(27)-C(29)-H(29A)	109.5
C(12)-C(11)-C(10)	123.7(2)	C(27)-C(29)-H(29B)	109.5
O(5)-C(11)-C(10)	116.5(2)	H(29A)-C(29)-H(29B)	109.5
C(11)-C(12)-C(13)	116.3(2)	C(27)-C(29)-H(29C)	109.5
C(11)-C(12)-C(14)	120.9(2)	H(29A)-C(29)-H(29C)	109.5
C(13)-C(12)-C(14)	122.5(2)	H(29B)-C(29)-H(29C)	109.5
C(8)-C(13)-O(1)	121.0(2)	C(31)-C(30)-C(32)	109.4(3)
C(8)-C(13)-C(12)	124.1(2)	C(31)-C(30)-C(14)	112.2(3)
O(1)-C(13)-C(12)	115.0(2)	C(32)-C(30)-C(14)	113.0(2)
C(12)-C(14)-C(15)	108.3(2)	C(31)-C(30)-H(30)	107.3
C(12)-C(14)-C(30)	110.4(2)	C(32)-C(30)-H(30)	107.3
C(15)-C(14)-C(30)	113.6(2)	C(14)-C(30)-H(30)	107.3
C(12)-C(14)-H(14)	108.1	C(30)-C(31)-H(31A)	109.5
C(15)-C(14)-H(14)	108.1	C(30)-C(31)-H(31B)	109.5
C(30)-C(14)-H(14)	108.1	H(31A)-C(31)-H(31B)	109.5
C(20)-C(15)-C(16)	118.3(2)	C(30)-C(31)-H(31C)	109.5
C(20)-C(15)-C(14)	121.1(2)	H(31A)-C(31)-H(31C)	109.5
C(16)-C(15)-C(14)	120.6(2)	H(31B)-C(31)-H(31C)	109.5
O(6)-C(16)-C(15)	121.4(2)	C(30)-C(32)-H(32A)	109.5
O(6)-C(16)-C(17)	121.6(3)	C(30)-C(32)-H(32B)	109.5
C(15)-C(16)-C(17)	117.0(2)	H(32A)-C(32)-H(32B)	109.5
C(16)-C(17)-C(18)	113.5(2)	C(30)-C(32)-H(32C)	109.5
C(16)-C(17)-H(17A)	108.9	H(32A)-C(32)-H(32C)	109.5
C(18)-C(17)-H(17A)	108.9	H(32B)-C(32)-H(32C)	109.5
C(16)-C(17)-H(17B)	108.9	C(18)-C(33)-H(33A)	109.5
C(18)-C(17)-H(17B)	108.9	C(18)-C(33)-H(33B)	109.5
H(17A)-C(17)-H(17B)	107.7	H(33A)-C(33)-H(33B)	109.5
C(17)-C(18)-C(34)	110.3(2)	C(18)-C(33)-H(33C)	109.5
C(17)-C(18)-C(33)	109.7(2)	H(33A)-C(33)-H(33C)	109.5
C(34)-C(18)-C(33)	109.0(2)	H(33B)-C(33)-H(33C)	109.5
C(17)-C(18)-C(19)	107.7(2)	C(18)-C(34)-H(34A)	109.5
C(34)-C(18)-C(19)	110.6(2)	C(18)-C(34)-H(34B)	109.5
C(33)-C(18)-C(19)	109.5(2)	H(34A)-C(34)-H(34B)	109.5
C(20)-C(19)-C(18)	112.2(2)	C(18)-C(34)-H(34C)	109.5
C(20)-C(19)-H(19A)	109.2	H(34A)-C(34)-H(34C)	109.5
C(18)-C(19)-H(19A)	109.2	H(34B)-C(34)-H(34C)	109.5
C(20)-C(19)-H(19B)	109.2	Cl(2)-C(35)-Cl(1)	115.4(4)
C(18)-C(19)-H(19B)	109.2	Cl(2)-C(35)-H(35A)	108.4
H(19A)-C(19)-H(19B)	107.9	Cl(1)-C(35)-H(35A)	108.4
C(15)-C(20)-O(5)	122.0(2)	Cl(2)-C(35)-H(35B)	108.4
C(15)-C(20)-C(19)	126.2(3)	Cl(1)-C(35)-H(35B)	108.4
O(5)-C(20)-C(19)	111.7(2)	H(35A)-C(35)-H(35B)	107.5

Exp. Data Tab. 23 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for *anti*-**97** (sh3587a). The anisotropicdisplacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	27(1)	18(1)	13(1)	0(1)	2(1)	2(1)
O(2)	46(2)	28(1)	32(1)	-13(1)	2(1)	-2(1)
O(3)	36(1)	23(1)	24(1)	-3(1)	9(1)	9(1)
O(4)	40(1)	31(1)	30(1)	1(1)	10(1)	16(1)
O(5)	32(1)	15(1)	15(1)	-1(1)	5(1)	1(1)
O(6)	38(1)	20(1)	31(1)	1(1)	4(1)	7(1)
C(1)	20(2)	21(2)	15(1)	1(1)	5(1)	-6(1)
C(2)	24(2)	24(2)	22(1)	1(1)	8(1)	-3(1)
C(3)	23(2)	29(2)	20(1)	-1(1)	1(1)	-4(1)
C(4)	29(2)	30(2)	24(1)	-3(1)	0(1)	-8(2)
C(5)	28(2)	24(2)	21(1)	-2(1)	8(1)	-8(1)
C(6)	24(2)	22(2)	17(1)	-1(1)	7(1)	-4(1)
C(7)	25(2)	20(2)	18(1)	-3(1)	8(1)	-1(1)
C(8)	18(2)	20(2)	19(1)	-3(1)	6(1)	-3(1)
C(9)	19(2)	17(1)	23(1)	-3(1)	8(1)	-1(1)
C(10)	21(2)	17(2)	20(1)	0(1)	4(1)	0(1)
C(11)	22(2)	16(1)	16(1)	-3(1)	6(1)	-2(1)
C(12)	22(2)	14(1)	20(1)	-1(1)	6(1)	-1(1)
C(13)	20(2)	17(1)	17(1)	2(1)	4(1)	-3(1)
C(14)	24(2)	17(2)	16(1)	-1(1)	4(1)	2(1)
C(15)	23(2)	17(1)	16(1)	-1(1)	7(1)	0(1)
C(16)	21(2)	21(2)	25(1)	-2(1)	9(1)	0(1)
C(17)	33(2)	20(2)	25(1)	-7(1)	10(1)	0(1)
C(18)	34(2)	19(2)	17(1)	-3(1)	7(1)	-3(1)
C(19)	27(2)	21(2)	17(1)	-1(1)	7(1)	-2(1)
C(20)	24(2)	14(1)	21(1)	-3(1)	10(1)	-1(1)
C(21)	42(2)	36(2)	19(1)	-2(1)	9(1)	-9(2)
C(22)	32(2)	42(2)	29(2)	-2(2)	-4(1)	-1(2)
C(23)	22(2)	35(2)	22(1)	1(1)	8(1)	3(1)
C(24)	27(2)	46(2)	28(2)	4(2)	9(1)	-8(2)
C(25)	41(2)	54(2)	33(2)	-5(2)	21(2)	5(2)
C(26)	22(2)	17(1)	24(1)	-3(1)	2(1)	0(1)
C(27)	32(2)	19(2)	22(1)	3(1)	6(1)	3(1)
C(28)	35(2)	37(2)	34(2)	9(2)	13(2)	2(2)
C(29)	44(2)	30(2)	28(2)	10(1)	4(2)	11(2)
C(30)	23(2)	24(2)	27(1)	-7(1)	5(1)	0(1)
C(31)	25(2)	39(2)	89(3)	-8(2)	16(2)	5(2)
C(32)	34(2)	38(2)	29(2)	-7(1)	15(1)	-9(2)
C(33)	47(2)	29(2)	21(1)	-7(1)	7(1)	-7(2)
C(34)	33(2)	29(2)	26(2)	-3(1)	10(1)	-8(2)
Cl(1)	274(3)	66(1)	263(3)	-14(1)	216(3)	-21(1)
Cl(2)	162(2)	134(2)	303(3)	67(2)	179(2)	51(2)
C(35)	196(8)	58(4)	236(8)	41(5)	162(7)	36(4)

6.5. Appendix 5: crystal data for *syn*-97



Exp. Data Tab. 24 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for *syn*-**97** (sh3590). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	3174(1)	2452(1)	10855(1)	18(1)
O(2)	6578(1)	3896(1)	14212(1)	27(1)
O(3)	5022(1)	6644(1)	11742(1)	21(1)
O(4)	4396(1)	7814(1)	10325(1)	29(1)
O(5)	2113(1)	4682(1)	8179(1)	21(1)
O(6)	1592(1)	313(1)	6873(1)	32(1)
C(1)	4052(1)	2310(1)	11801(1)	16(1)
C(2)	3985(1)	987(1)	11860(1)	19(1)
C(3)	4591(1)	877(1)	13022(1)	21(1)
C(4)	5918(1)	1696(1)	13560(1)	20(1)
C(5)	5829(1)	3037(1)	13511(1)	18(1)
C(6)	4829(1)	3276(1)	12568(1)	16(1)
C(7)	4639(1)	4599(1)	12526(1)	16(1)
C(8)	4036(1)	4616(1)	11363(1)	15(1)
C(9)	4181(1)	5685(1)	11013(1)	16(1)
C(10)	3465(1)	5758(1)	9956(1)	17(1)
C(11)	2727(1)	4638(1)	9232(1)	17(1)
C(12)	2642(1)	3534(1)	9517(1)	16(1)
C(13)	3300(1)	3570(1)	10598(1)	15(1)
C(14)	1826(1)	2372(1)	8715(1)	16(1)
C(15)	1686(1)	2472(1)	7598(1)	17(1)
C(16)	1559(1)	1355(1)	6724(1)	20(1)
C(17)	1470(1)	1549(1)	5639(1)	24(1)
C(18)	762(1)	2673(1)	5392(1)	21(1)
C(19)	1482(1)	3819(1)	6307(1)	23(1)
C(20)	1761(1)	3587(1)	7389(1)	18(1)
C(21)	4816(1)	-480(1)	12995(1)	32(1)
C(22)	3670(1)	1295(1)	13655(1)	28(1)
C(23)	3783(1)	5130(1)	13226(1)	21(1)
C(24)	2364(1)	4518(1)	12745(1)	28(1)

C(25)	3807(1)	6539(1)	13452(1)	31(1)
C(26)	3510(1)	6983(1)	9709(1)	19(1)
C(27)	2458(1)	7307(1)	8786(1)	21(1)
C(28)	1092(1)	7140(1)	8882(1)	31(1)
C(29)	2757(1)	8639(1)	8752(1)	29(1)
C(30)	481(1)	2200(1)	8888(1)	21(1)
C(31)	-318(1)	959(1)	8205(1)	38(1)
C(32)	-339(1)	3271(1)	8702(1)	31(1)
C(33)	-680(1)	2459(1)	5300(1)	29(1)
C(34)	814(1)	2861(1)	4330(1)	34(1)

Exp. Data Tab. 25 Bond lengths [Å] for *syn*-**97** (sh3590).

Bond	Length [Å]	Bond	Length [Å]
O(1)-C(1)	1.3753(10)	C(18)-C(19)	1.5295(14)
O(1)-C(13)	1.3829(10)	C(19)-C(20)	1.4904(13)
O(2)-C(5)	1.2240(11)	C(19)-H(10)	1.020(15)
O(3)-C(9)	1.3439(11)	C(19)-H(11)	1.006(14)
O(3)-H(6)	0.906(16)	C(21)-H(12)	1.011(16)
O(4)-C(26)	1.2388(12)	C(21)-H(13)	0.980(17)
O(5)-C(20)	1.3670(11)	C(21)-H(14)	0.977(17)
O(5)-C(11)	1.3827(11)	C(22)-H(15)	0.962(14)
O(6)-C(16)	1.2226(12)	C(22)-H(16)	1.015(14)
C(1)-C(6)	1.3402(12)	C(22)-H(17)	0.970(15)
C(1)-C(2)	1.4916(13)	C(23)-C(25)	1.5199(15)
C(2)-C(3)	1.5387(13)	C(23)-C(24)	1.5234(16)
C(2)-H(1)	0.995(13)	C(23)-H(18)	0.992(13)
C(2)-H(2)	0.981(14)	C(24)-H(19)	0.977(14)
C(3)-C(21)	1.5271(15)	C(24)-H(20)	0.985(15)
C(3)-C(22)	1.5285(16)	C(24)-H(21)	0.959(17)
C(3)-C(4)	1.5325(14)	C(25)-H(22)	0.996(14)
C(4)-C(5)	1.5114(13)	C(25)-H(23)	0.975(16)
C(4)-H(3)	1.001(13)	C(25)-H(24)	1.005(16)
C(4)-H(4)	0.999(14)	C(26)-C(27)	1.5183(14)
C(5)-C(6)	1.4691(13)	C(27)-C(29)	1.5212(14)
C(6)-C(7)	1.5012(13)	C(27)-C(28)	1.5327(15)
C(7)-C(8)	1.5068(12)	C(27)-H(25)	1.005(13)
C(7)-C(23)	1.5630(14)	C(28)-H(28)	0.991(16)
C(7)-H(5)	1.005(13)	C(28)-H(26)	0.962(16)
C(8)-C(13)	1.3797(12)	C(28)-H(27)	0.959(15)
C(8)-C(9)	1.4036(12)	C(29)-H(29)	0.961(16)
C(9)-C(10)	1.4166(12)	C(29)-H(30)	1.015(17)
C(10)-C(11)	1.4169(12)	C(29)-H(31)	0.979(15)
C(10)-C(26)	1.4804(13)	C(30)-C(31)	1.5215(15)
C(11)-C(12)	1.3805(12)	C(30)-C(32)	1.5227(16)
C(12)-C(13)	1.4010(12)	C(30)-H(32)	1.002(13)
C(12)-C(14)	1.5095(12)	C(31)-H(33)	1.052(16)
C(14)-C(15)	1.5091(12)	C(31)-H(34)	0.974(15)
C(14)-C(30)	1.5587(13)	C(31)-H(35)	1.003(18)
C(14)-H(7)	0.976(13)	C(32)-H(38)	0.979(17)
C(15)-C(20)	1.3414(13)	C(32)-H(37)	1.007(16)

C(15)-C(16)	1.4682(13)	C(32)-H(36)	1.004(15)
C(16)-C(17)	1.5140(14)	C(33)-H(41)	1.015(14)
C(17)-C(18)	1.5298(15)	C(33)-H(39)	0.966(15)
C(17)-H(9)	0.984(15)	C(33)-H(40)	0.999(14)
C(17)-H(8)	1.009(14)	C(34)-H(44)	1.010(17)
C(18)-C(34)	1.5265(14)	C(34)-H(43)	1.012(17)
C(18)-C(33)	1.5280(15)	C(34)-H(42)	0.987(15)

Exp. Data Tab. 26 Bond angles [°] for *syn*-**97** (sh3590).

Bonds	Angles [°]	Bonds	Angles [°]
C(1)-O(1)-C(13)	117.94(7)	C(15)-C(20)-O(5)	122.65(8)
C(9)-O(3)-H(6)	105.2(10)	C(15)-C(20)-C(19)	126.41(9)
C(20)-O(5)-C(11)	118.46(7)	O(5)-C(20)-C(19)	110.94(8)
C(6)-C(1)-O(1)	122.20(8)	C(3)-C(21)-H(12)	110.4(9)
C(6)-C(1)-C(2)	125.97(8)	C(3)-C(21)-H(13)	109.9(10)
O(1)-C(1)-C(2)	111.80(7)	H(12)-C(21)-H(13)	111.9(13)
C(1)-C(2)-C(3)	111.97(8)	C(3)-C(21)-H(14)	111.1(10)
C(1)-C(2)-H(1)	106.9(8)	H(12)-C(21)-H(14)	107.6(13)
C(3)-C(2)-H(1)	111.2(7)	H(13)-C(21)-H(14)	105.8(13)
C(1)-C(2)-H(2)	109.3(8)	C(3)-C(22)-H(15)	111.4(8)
C(3)-C(2)-H(2)	109.5(8)	C(3)-C(22)-H(16)	112.4(8)
H(1)-C(2)-H(2)	107.9(11)	H(15)-C(22)-H(16)	109.1(12)
C(21)-C(3)-C(22)	109.54(9)	C(3)-C(22)-H(17)	109.8(9)
C(21)-C(3)-C(4)	109.20(9)	H(15)-C(22)-H(17)	106.8(12)
C(22)-C(3)-C(4)	109.95(8)	H(16)-C(22)-H(17)	107.1(11)
C(21)-C(3)-C(2)	108.90(8)	C(25)-C(23)-C(24)	109.95(10)
C(22)-C(3)-C(2)	110.47(9)	C(25)-C(23)-C(7)	112.62(8)
C(4)-C(3)-C(2)	108.74(8)	C(24)-C(23)-C(7)	112.79(8)
C(5)-C(4)-C(3)	113.53(8)	C(25)-C(23)-H(18)	107.2(7)
C(5)-C(4)-H(3)	107.0(7)	C(24)-C(23)-H(18)	108.8(7)
C(3)-C(4)-H(3)	110.5(7)	C(7)-C(23)-H(18)	105.2(7)
C(5)-C(4)-H(4)	108.6(8)	C(23)-C(24)-H(19)	110.6(8)
C(3)-C(4)-H(4)	110.7(8)	C(23)-C(24)-H(20)	113.2(9)
H(3)-C(4)-H(4)	106.3(11)	H(19)-C(24)-H(20)	108.2(11)
O(2)-C(5)-C(6)	120.71(8)	C(23)-C(24)-H(21)	109.7(9)
O(2)-C(5)-C(4)	121.83(8)	H(19)-C(24)-H(21)	106.7(13)
C(6)-C(5)-C(4)	117.44(8)	H(20)-C(24)-H(21)	108.2(12)
C(1)-C(6)-C(5)	119.05(8)	C(23)-C(25)-H(22)	111.5(8)
C(1)-C(6)-C(7)	121.61(8)	C(23)-C(25)-H(23)	109.9(9)
C(5)-C(6)-C(7)	119.19(8)	H(22)-C(25)-H(23)	107.9(12)
C(6)-C(7)-C(8)	108.42(7)	C(23)-C(25)-H(24)	109.6(9)
C(6)-C(7)-C(23)	108.86(7)	H(22)-C(25)-H(24)	107.5(12)
C(8)-C(7)-C(23)	113.51(8)	H(23)-C(25)-H(24)	110.4(13)
C(6)-C(7)-H(5)	108.7(7)	O(4)-C(26)-C(10)	118.66(9)
C(8)-C(7)-H(5)	110.5(7)	O(4)-C(26)-C(27)	118.03(8)
C(23)-C(7)-H(5)	106.7(7)	C(10)-C(26)-C(27)	123.11(8)
C(13)-C(8)-C(9)	117.26(8)	C(26)-C(27)-C(29)	110.96(9)
C(13)-C(8)-C(7)	120.63(8)	C(26)-C(27)-C(28)	110.90(8)
C(9)-C(8)-C(7)	122.11(8)	C(29)-C(27)-C(28)	109.60(9)
O(3)-C(9)-C(8)	116.21(8)	C(26)-C(27)-H(25)	107.4(8)

O(3)-C(9)-C(10)	121.74(8)	C(29)-C(27)-H(25)	109.9(8)
C(8)-C(9)-C(10)	122.03(8)	C(28)-C(27)-H(25)	108.0(7)
C(9)-C(10)-C(11)	115.96(8)	C(27)-C(28)-H(28)	109.6(9)
C(9)-C(10)-C(26)	118.33(8)	C(27)-C(28)-H(26)	111.6(9)
C(11)-C(10)-C(26)	125.68(8)	H(28)-C(28)-H(26)	103.0(13)
C(12)-C(11)-O(5)	120.08(8)	C(27)-C(28)-H(27)	112.9(9)
C(12)-C(11)-C(10)	123.82(8)	H(28)-C(28)-H(27)	110.7(12)
O(5)-C(11)-C(10)	116.05(8)	H(26)-C(28)-H(27)	108.6(12)
C(11)-C(12)-C(13)	116.36(8)	C(27)-C(29)-H(29)	109.5(9)
C(11)-C(12)-C(14)	121.59(8)	C(27)-C(29)-H(30)	110.9(9)
C(13)-C(12)-C(14)	121.98(8)	H(29)-C(29)-H(30)	105.9(13)
C(8)-C(13)-O(1)	121.32(8)	C(27)-C(29)-H(31)	110.3(9)
C(8)-C(13)-C(12)	124.03(8)	H(29)-C(29)-H(31)	110.0(12)
O(1)-C(13)-C(12)	114.65(7)	H(30)-C(29)-H(31)	110.1(12)
C(15)-C(14)-C(12)	108.28(7)	C(31)-C(30)-C(32)	110.32(10)
C(15)-C(14)-C(30)	113.52(7)	C(31)-C(30)-C(14)	112.41(9)
C(12)-C(14)-C(30)	109.70(8)	C(32)-C(30)-C(14)	112.46(8)
C(15)-C(14)-H(7)	110.1(7)	C(31)-C(30)-H(32)	108.1(7)
C(12)-C(14)-H(7)	107.6(7)	C(32)-C(30)-H(32)	108.1(7)
C(30)-C(14)-H(7)	107.5(7)	C(14)-C(30)-H(32)	105.2(7)
C(20)-C(15)-C(16)	117.72(8)	C(30)-C(31)-H(33)	112.0(9)
C(20)-C(15)-C(14)	121.11(8)	C(30)-C(31)-H(34)	109.1(9)
C(16)-C(15)-C(14)	121.03(8)	H(33)-C(31)-H(34)	107.0(12)
O(6)-C(16)-C(15)	121.62(9)	C(30)-C(31)-H(35)	112.9(9)
O(6)-C(16)-C(17)	120.91(9)	H(33)-C(31)-H(35)	108.8(13)
C(15)-C(16)-C(17)	117.36(8)	H(34)-C(31)-H(35)	106.8(13)
C(16)-C(17)-C(18)	113.52(8)	C(30)-C(32)-H(38)	111.7(10)
C(16)-C(17)-H(9)	104.9(8)	C(30)-C(32)-H(37)	111.1(10)
C(18)-C(17)-H(9)	109.6(8)	H(38)-C(32)-H(37)	108.6(13)
C(16)-C(17)-H(8)	107.9(8)	C(30)-C(32)-H(36)	109.4(8)
C(18)-C(17)-H(8)	111.9(8)	H(38)-C(32)-H(36)	109.2(13)
H(9)-C(17)-H(8)	108.7(12)	H(37)-C(32)-H(36)	106.8(12)
C(34)-C(18)-C(33)	108.81(9)	C(18)-C(33)-H(41)	110.6(8)
C(34)-C(18)-C(19)	109.41(9)	C(18)-C(33)-H(39)	109.5(8)
C(33)-C(18)-C(19)	111.15(9)	H(41)-C(33)-H(39)	108.9(12)
C(34)-C(18)-C(17)	110.02(9)	C(18)-C(33)-H(40)	109.1(8)
C(33)-C(18)-C(17)	109.96(9)	H(41)-C(33)-H(40)	109.5(11)
C(19)-C(18)-C(17)	107.49(8)	H(39)-C(33)-H(40)	109.2(12)
C(20)-C(19)-C(18)	112.40(8)	C(18)-C(34)-H(44)	111.6(9)
C(20)-C(19)-H(10)	107.1(8)	C(18)-C(34)-H(43)	110.0(9)
C(18)-C(19)-H(10)	110.3(8)	H(44)-C(34)-H(43)	104.5(13)
C(20)-C(19)-H(11)	107.0(8)	C(18)-C(34)-H(42)	109.6(9)
C(18)-C(19)-H(11)	111.5(8)	H(44)-C(34)-H(42)	112.4(13)
H(10)-C(19)-H(11)	108.3(11)	H(43)-C(34)-H(42)	108.5(12)

Exp. Data Tab. 27 Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for *syn*-**97** (sh3590). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	21(1)	14(1)	14(1)	6(1)	-1(1)	-2(1)
O(2)	26(1)	21(1)	22(1)	5(1)	-6(1)	-3(1)

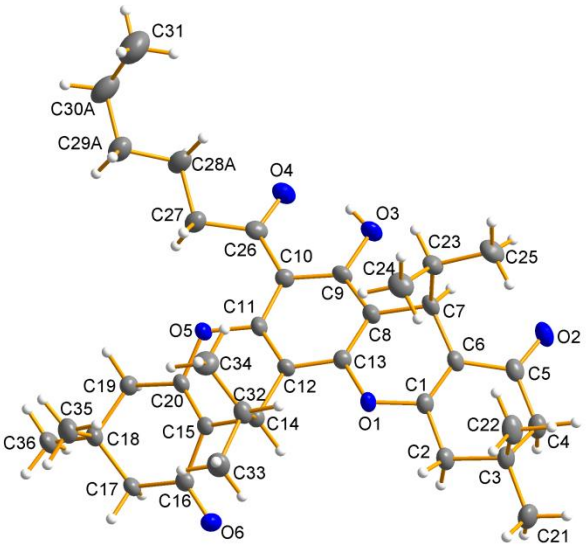
O(3)	25(1)	15(1)	18(1)	3(1)	2(1)	-5(1)
O(4)	35(1)	17(1)	28(1)	8(1)	2(1)	-5(1)
O(5)	31(1)	15(1)	13(1)	5(1)	0(1)	0(1)
O(6)	51(1)	18(1)	22(1)	5(1)	7(1)	7(1)
C(1)	17(1)	16(1)	13(1)	5(1)	1(1)	1(1)
C(2)	22(1)	14(1)	17(1)	4(1)	2(1)	0(1)
C(3)	26(1)	15(1)	17(1)	6(1)	2(1)	1(1)
C(4)	22(1)	18(1)	17(1)	5(1)	1(1)	5(1)
C(5)	18(1)	18(1)	17(1)	5(1)	2(1)	2(1)
C(6)	17(1)	15(1)	15(1)	5(1)	2(1)	1(1)
C(7)	18(1)	13(1)	14(1)	3(1)	1(1)	-1(1)
C(8)	16(1)	14(1)	13(1)	4(1)	2(1)	0(1)
C(9)	18(1)	13(1)	16(1)	2(1)	4(1)	0(1)
C(10)	20(1)	14(1)	15(1)	5(1)	4(1)	0(1)
C(11)	19(1)	16(1)	12(1)	4(1)	2(1)	1(1)
C(12)	17(1)	15(1)	14(1)	4(1)	2(1)	0(1)
C(13)	16(1)	13(1)	15(1)	5(1)	3(1)	0(1)
C(14)	18(1)	13(1)	14(1)	4(1)	2(1)	-1(1)
C(15)	16(1)	17(1)	14(1)	4(1)	2(1)	1(1)
C(16)	21(1)	20(1)	17(1)	4(1)	3(1)	4(1)
C(17)	30(1)	26(1)	17(1)	6(1)	8(1)	10(1)
C(18)	24(1)	23(1)	14(1)	5(1)	3(1)	4(1)
C(19)	27(1)	23(1)	16(1)	8(1)	3(1)	-2(1)
C(20)	19(1)	17(1)	14(1)	4(1)	2(1)	0(1)
C(21)	44(1)	17(1)	28(1)	9(1)	-1(1)	2(1)
C(22)	31(1)	29(1)	24(1)	9(1)	10(1)	-2(1)
C(23)	29(1)	18(1)	16(1)	5(1)	7(1)	5(1)
C(24)	28(1)	25(1)	36(1)	11(1)	16(1)	7(1)
C(25)	46(1)	20(1)	28(1)	2(1)	17(1)	5(1)
C(26)	24(1)	15(1)	18(1)	5(1)	8(1)	2(1)
C(27)	27(1)	18(1)	19(1)	8(1)	8(1)	4(1)
C(28)	27(1)	33(1)	37(1)	18(1)	11(1)	7(1)
C(29)	39(1)	21(1)	30(1)	14(1)	12(1)	5(1)
C(30)	20(1)	24(1)	19(1)	7(1)	4(1)	-2(1)
C(31)	30(1)	34(1)	43(1)	3(1)	10(1)	-13(1)
C(32)	24(1)	39(1)	34(1)	15(1)	13(1)	10(1)
C(33)	22(1)	32(1)	25(1)	5(1)	-1(1)	4(1)
C(34)	48(1)	38(1)	18(1)	12(1)	11(1)	12(1)

Exp. Data Tab. 28. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for *syn*-**97** (sh3590).

Hydrogen atom	x	y	z	U(eq)
H(1)	3039(13)	645(12)	11542(10)	27(3)
H(2)	4451(13)	509(12)	11413(11)	30(3)
H(3)	6563(13)	1366(12)	13204(10)	26(3)
H(4)	6314(13)	1682(13)	14330(11)	34(4)
H(5)	5521(13)	5117(12)	12866(10)	27(3)
H(6)	5045(15)	7228(15)	11381(13)	47(4)
H(7)	2297(12)	1661(12)	8864(10)	23(3)
H(9)	2391(15)	1681(13)	5677(11)	36(4)
H(8)	1035(14)	751(13)	5073(11)	34(4)

H(10)	924(15)	4546(14)	6280(12)	40(4)
H(11)	2353(14)	4089(13)	6260(11)	34(4)
H(12)	3954(16)	-1038(15)	12626(12)	47(4)
H(13)	5466(16)	-730(15)	12646(13)	48(4)
H(14)	5190(16)	-586(15)	13723(13)	51(4)
H(15)	2830(14)	791(13)	13332(11)	34(4)
H(16)	3523(13)	2206(13)	13725(11)	32(3)
H(17)	4048(14)	1197(13)	14379(12)	40(4)
H(18)	4207(12)	4936(12)	13927(10)	25(3)
H(19)	1915(14)	4709(13)	12060(11)	33(3)
H(20)	2292(14)	3605(14)	12621(11)	39(4)
H(21)	1889(16)	4848(14)	13216(13)	49(4)
H(22)	3381(13)	6801(13)	12781(11)	33(3)
H(23)	4716(16)	6930(14)	13768(12)	44(4)
H(24)	3306(15)	6843(14)	13953(12)	44(4)
H(25)	2449(13)	6708(12)	8101(11)	30(3)
H(28)	1053(15)	7766(15)	9522(13)	47(4)
H(26)	417(15)	7336(14)	8298(12)	43(4)
H(27)	858(14)	6313(14)	8909(11)	36(4)
H(29)	2118(15)	8803(14)	8132(12)	42(4)
H(30)	2668(16)	9260(15)	9400(13)	50(4)
H(31)	3644(15)	8767(13)	8726(12)	40(4)
H(32)	716(12)	2202(12)	9664(10)	26(3)
H(33)	-660(16)	923(15)	7381(13)	50(4)
H(34)	-1092(15)	852(14)	8409(12)	43(4)
H(35)	182(17)	225(16)	8313(13)	54(5)
H(38)	131(16)	4073(16)	9178(13)	51(4)
H(37)	-583(16)	3322(15)	7933(13)	50(4)
H(36)	-1188(15)	3122(13)	8831(11)	40(4)
H(41)	-747(14)	2348(13)	6001(12)	38(4)
H(39)	-1123(14)	3169(13)	5137(11)	34(4)
H(40)	-1116(14)	1697(14)	4706(12)	39(4)
H(44)	350(16)	2117(15)	3706(13)	53(5)
H(43)	308(15)	3579(15)	4149(12)	46(4)
H(42)	1738(15)	3059(14)	4395(12)	40(4)

6.6. Appendix 6: crystal data for *syn*-98



Exp. Data Tab. 29 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for *syn*-**98** (sh3583). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	3369(1)	7752(1)	2475(1)	24(1)
O(2)	5260(2)	10220(2)	3386(1)	32(1)
O(3)	3444(2)	11319(2)	-314(1)	30(1)
O(4)	2887(2)	11517(2)	-2149(1)	31(1)
O(5)	2478(1)	8085(1)	-1042(1)	24(1)
O(6)	3998(2)	3925(2)	1424(1)	31(1)
C(1)	3979(2)	8061(2)	3153(2)	22(1)
C(2)	4421(2)	6997(2)	4178(2)	28(1)
C(3)	4681(2)	7446(2)	5066(2)	28(1)
C(4)	5514(2)	8208(2)	4644(2)	29(1)
C(5)	4968(2)	9295(2)	3621(2)	25(1)
C(6)	4139(2)	9158(2)	2894(2)	22(1)
C(7)	3557(2)	10216(2)	1860(2)	23(1)
C(8)	3378(2)	9605(2)	1079(2)	22(1)
C(9)	3257(2)	10217(2)	-5(2)	22(1)
C(10)	2895(2)	9756(2)	-743(2)	21(1)
C(11)	2756(2)	8578(2)	-316(2)	21(1)
C(12)	2916(2)	7903(2)	741(2)	20(1)
C(13)	3225(2)	8459(2)	1408(2)	22(1)
C(14)	2737(2)	6652(2)	1148(2)	21(1)
C(15)	2973(2)	6051(2)	283(2)	19(1)
C(16)	3561(2)	4644(2)	525(2)	23(1)
C(17)	3713(2)	4099(2)	-366(2)	23(1)
C(18)	2804(2)	5002(2)	-1361(2)	25(1)
C(19)	2889(2)	6314(2)	-1650(2)	24(1)
C(20)	2783(2)	6781(2)	-729(2)	21(1)
C(21)	5418(3)	6276(2)	6014(2)	37(1)

C(22)	3392(2)	8290(3)	5391(2)	37(1)
C(23)	2233(2)	11288(2)	1935(2)	26(1)
C(24)	1175(2)	10792(2)	2275(2)	37(1)
C(25)	2362(2)	12009(2)	2659(2)	37(1)
C(26)	2581(2)	10583(2)	-1848(2)	25(1)
C(27)	1788(2)	10415(2)	-2616(2)	30(1)
C(28A)	1218(3)	11634(3)	-3570(2)	35(1)
C(29A)	266(3)	11590(3)	-4303(2)	42(1)
C(30A)	-266(3)	12809(3)	-5260(2)	49(1)
C(28B)	1500(30)	11160(30)	-3794(8)	39(2)
C(29B)	300(30)	12410(20)	-3962(19)	42(2)
C(30B)	332(11)	13290(30)	-5056(19)	45(2)
C(31)	-1104(3)	14035(3)	-5008(3)	78(1)
C(32)	1370(2)	6889(2)	1552(2)	26(1)
C(33)	1224(2)	5628(2)	2073(2)	33(1)
C(34)	268(2)	7802(2)	691(2)	35(1)
C(35)	1413(2)	5139(2)	-1172(2)	36(1)
C(36)	3250(3)	4449(2)	-2264(2)	35(1)

Exp. Data Tab. 30. Bond lengths [Å] for *syn*-**98** (sh3583).

Bond	Length [Å]	Bond	Length [Å]
O(1)-C(1)	1.384(2)	C(23)-C(25)	1.530(3)
O(1)-C(13)	1.396(2)	C(23)-H(23)	1.0000
O(2)-C(5)	1.220(3)	C(24)-H(24A)	0.9800
O(3)-C(9)	1.347(2)	C(24)-H(24B)	0.9800
O(3)-H(3)	0.8400	C(24)-H(24C)	0.9800
O(4)-C(26)	1.239(3)	C(25)-H(25A)	0.9800
O(5)-C(20)	1.374(2)	C(25)-H(25B)	0.9800
O(5)-C(11)	1.389(2)	C(25)-H(25C)	0.9800
O(6)-C(16)	1.227(2)	C(26)-C(27)	1.505(3)
C(1)-C(6)	1.327(3)	C(27)-C(28A)	1.527(3)
C(1)-C(2)	1.490(3)	C(27)-C(28B)	1.529(8)
C(2)-C(3)	1.534(3)	C(27)-H(27A)	0.9900
C(2)-H(2A)	0.9900	C(27)-H(27B)	0.9900
C(2)-H(2B)	0.9900	C(27)-H(27C)	0.9900
C(3)-C(21)	1.522(3)	C(27)-H(27D)	0.9900
C(3)-C(4)	1.529(3)	C(28A)-C(29A)	1.517(3)
C(3)-C(22)	1.535(3)	C(28A)-H(28A)	0.9900
C(4)-C(5)	1.508(3)	C(28A)-H(28B)	0.9900
C(4)-H(4A)	0.9900	C(29A)-C(30A)	1.527(3)
C(4)-H(4B)	0.9900	C(29A)-H(29A)	0.9900
C(5)-C(6)	1.470(3)	C(29A)-H(29B)	0.9900
C(6)-C(7)	1.510(3)	C(30A)-C(31)	1.522(4)
C(7)-C(8)	1.514(3)	C(30A)-H(30A)	0.9900
C(7)-C(23)	1.550(3)	C(30A)-H(30B)	0.9900
C(7)-H(7)	1.0000	C(28B)-C(29B)	1.522(8)
C(8)-C(13)	1.377(3)	C(28B)-H(28C)	0.9900
C(8)-C(9)	1.396(3)	C(28B)-H(28D)	0.9900
C(9)-C(10)	1.418(3)	C(29B)-C(30B)	1.524(8)

C(10)-C(11)	1.411(3)	C(29B)-H(29C)	0.9900
C(10)-C(26)	1.469(3)	C(29B)-H(29D)	0.9900
C(11)-C(12)	1.376(3)	C(30B)-C(31)	1.510(8)
C(12)-C(13)	1.397(3)	C(30B)-H(30C)	0.9900
C(12)-C(14)	1.511(3)	C(30B)-H(30D)	0.9900
C(14)-C(15)	1.508(3)	C(31)-H(31A)	0.9800
C(14)-C(32)	1.554(3)	C(31)-H(31B)	0.9800
C(14)-H(14)	1.0000	C(31)-H(31C)	0.9800
C(15)-C(20)	1.338(3)	C(31)-H(31D)	0.9800
C(15)-C(16)	1.464(3)	C(31)-H(31E)	0.9800
C(16)-C(17)	1.505(3)	C(31)-H(31F)	0.9800
C(17)-C(18)	1.530(3)	C(32)-C(33)	1.518(3)
C(17)-H(17A)	0.9900	C(32)-C(34)	1.526(3)
C(17)-H(17B)	0.9900	C(32)-H(32)	1.0000
C(18)-C(35)	1.526(3)	C(33)-H(33A)	0.9800
C(18)-C(36)	1.529(3)	C(33)-H(33B)	0.9800
C(18)-C(19)	1.532(3)	C(33)-H(33C)	0.9800
C(19)-C(20)	1.490(3)	C(34)-H(34A)	0.9800
C(19)-H(19A)	0.9900	C(34)-H(34B)	0.9800
C(19)-H(19B)	0.9900	C(34)-H(34C)	0.9800
C(21)-H(21A)	0.9800	C(35)-H(35A)	0.9800
C(21)-H(21B)	0.9800	C(35)-H(35B)	0.9800
C(21)-H(21C)	0.9800	C(35)-H(35C)	0.9800
C(22)-H(22A)	0.9800	C(36)-H(36A)	0.9800
C(22)-H(22B)	0.9800	C(36)-H(36B)	0.9800
C(22)-H(22C)	0.9800	C(36)-H(36C)	0.9800
C(23)-C(24)	1.525(3)		

Exp. Data Tab. 31. Bond angles [°] for *syn*-**98** (sh3583).

Bonds	Angle [°]	Bonds	Angle [°]
C(1)-O(1)-C(13)	117.00(17)	C(23)-C(24)-H(24A)	109.5
C(9)-O(3)-H(3)	109.5	C(23)-C(24)-H(24B)	109.5
C(20)-O(5)-C(11)	117.60(16)	H(24A)-C(24)-H(24B)	109.5
C(6)-C(1)-O(1)	123.2(2)	C(23)-C(24)-H(24C)	109.5
C(6)-C(1)-C(2)	126.5(2)	H(24A)-C(24)-H(24C)	109.5
O(1)-C(1)-C(2)	110.38(18)	H(24B)-C(24)-H(24C)	109.5
C(1)-C(2)-C(3)	112.45(19)	C(23)-C(25)-H(25A)	109.5
C(1)-C(2)-H(2A)	109.1	C(23)-C(25)-H(25B)	109.5
C(3)-C(2)-H(2A)	109.1	H(25A)-C(25)-H(25B)	109.5
C(1)-C(2)-H(2B)	109.1	C(23)-C(25)-H(25C)	109.5
C(3)-C(2)-H(2B)	109.1	H(25A)-C(25)-H(25C)	109.5
H(2A)-C(2)-H(2B)	107.8	H(25B)-C(25)-H(25C)	109.5
C(21)-C(3)-C(4)	109.83(19)	O(4)-C(26)-C(10)	119.5(2)
C(21)-C(3)-C(2)	109.75(19)	O(4)-C(26)-C(27)	117.9(2)
C(4)-C(3)-C(2)	106.87(18)	C(10)-C(26)-C(27)	122.3(2)
C(21)-C(3)-C(22)	109.05(19)	C(26)-C(27)-C(28A)	111.2(2)
C(4)-C(3)-C(22)	111.03(19)	C(26)-C(27)-C(28B)	125.8(16)
C(2)-C(3)-C(22)	110.29(19)	C(26)-C(27)-H(27A)	109.4
C(5)-C(4)-C(3)	115.11(19)	C(28A)-C(27)-H(27A)	109.4
C(5)-C(4)-H(4A)	108.5	C(26)-C(27)-H(27B)	109.4

C(3)-C(4)-H(4A)	108.5	C(28A)-C(27)-H(27B)	109.4
C(5)-C(4)-H(4B)	108.5	H(27A)-C(27)-H(27B)	108.0
C(3)-C(4)-H(4B)	108.5	C(26)-C(27)-H(27C)	105.9
H(4A)-C(4)-H(4B)	107.5	C(28B)-C(27)-H(27C)	105.9
O(2)-C(5)-C(6)	121.4(2)	C(26)-C(27)-H(27D)	105.9
O(2)-C(5)-C(4)	120.9(2)	C(28B)-C(27)-H(27D)	105.9
C(6)-C(5)-C(4)	117.5(2)	H(27C)-C(27)-H(27D)	106.2
C(1)-C(6)-C(5)	118.0(2)	C(29A)-C(28A)-C(27)	113.7(2)
C(1)-C(6)-C(7)	121.84(19)	C(29A)-C(28A)-H(28A)	108.8
C(5)-C(6)-C(7)	120.0(2)	C(27)-C(28A)-H(28A)	108.8
C(6)-C(7)-C(8)	108.09(18)	C(29A)-C(28A)-H(28B)	108.8
C(6)-C(7)-C(23)	113.61(18)	C(27)-C(28A)-H(28B)	108.8
C(8)-C(7)-C(23)	109.29(17)	H(28A)-C(28A)-H(28B)	107.7
C(6)-C(7)-H(7)	108.6	C(28A)-C(29A)-C(30A)	112.6(3)
C(8)-C(7)-H(7)	108.6	C(28A)-C(29A)-H(29A)	109.1
C(23)-C(7)-H(7)	108.6	C(30A)-C(29A)-H(29A)	109.1
C(13)-C(8)-C(9)	116.7(2)	C(28A)-C(29A)-H(29B)	109.1
C(13)-C(8)-C(7)	121.1(2)	C(30A)-C(29A)-H(29B)	109.1
C(9)-C(8)-C(7)	122.0(2)	H(29A)-C(29A)-H(29B)	107.8
O(3)-C(9)-C(8)	115.85(19)	C(31)-C(30A)-C(29A)	114.5(3)
O(3)-C(9)-C(10)	121.4(2)	C(31)-C(30A)-H(30A)	108.6
C(8)-C(9)-C(10)	122.7(2)	C(29A)-C(30A)-H(30A)	108.6
C(11)-C(10)-C(9)	115.59(19)	C(31)-C(30A)-H(30B)	108.6
C(11)-C(10)-C(26)	125.9(2)	C(29A)-C(30A)-H(30B)	108.6
C(9)-C(10)-C(26)	118.3(2)	H(30A)-C(30A)-H(30B)	107.6
C(12)-C(11)-O(5)	120.03(19)	C(29B)-C(28B)-C(27)	108.7(15)
C(12)-C(11)-C(10)	124.24(19)	C(29B)-C(28B)-H(28C)	109.9
O(5)-C(11)-C(10)	115.70(18)	C(27)-C(28B)-H(28C)	109.9
C(11)-C(12)-C(13)	115.9(2)	C(29B)-C(28B)-H(28D)	109.9
C(11)-C(12)-C(14)	121.57(19)	C(27)-C(28B)-H(28D)	109.9
C(13)-C(12)-C(14)	122.51(19)	H(28C)-C(28B)-H(28D)	108.3
C(8)-C(13)-O(1)	121.07(19)	C(28B)-C(29B)-C(30B)	105.8(17)
C(8)-C(13)-C(12)	124.8(2)	C(28B)-C(29B)-H(29C)	110.6
O(1)-C(13)-C(12)	114.18(19)	C(30B)-C(29B)-H(29C)	110.6
C(15)-C(14)-C(12)	108.32(17)	C(28B)-C(29B)-H(29D)	110.6
C(15)-C(14)-C(32)	112.69(17)	C(30B)-C(29B)-H(29D)	110.6
C(12)-C(14)-C(32)	110.81(17)	H(29C)-C(29B)-H(29D)	108.7
C(15)-C(14)-H(14)	108.3	C(31)-C(30B)-C(29B)	85.8(13)
C(12)-C(14)-H(14)	108.3	C(31)-C(30B)-H(30C)	114.3
C(32)-C(14)-H(14)	108.3	C(29B)-C(30B)-H(30C)	114.3
C(20)-C(15)-C(16)	117.80(19)	C(31)-C(30B)-H(30D)	114.3
C(20)-C(15)-C(14)	120.92(19)	C(29B)-C(30B)-H(30D)	114.3
C(16)-C(15)-C(14)	120.89(18)	H(30C)-C(30B)-H(30D)	111.5
O(6)-C(16)-C(15)	120.9(2)	C(30A)-C(31)-H(31A)	109.5
O(6)-C(16)-C(17)	120.4(2)	C(30A)-C(31)-H(31B)	109.5
C(15)-C(16)-C(17)	118.49(19)	H(31A)-C(31)-H(31B)	109.5
C(16)-C(17)-C(18)	115.33(18)	C(30A)-C(31)-H(31C)	109.5
C(16)-C(17)-H(17A)	108.4	H(31A)-C(31)-H(31C)	109.5
C(18)-C(17)-H(17A)	108.4	H(31B)-C(31)-H(31C)	109.5
C(16)-C(17)-H(17B)	108.4	C(30B)-C(31)-H(31D)	109.5

C(18)-C(17)-H(17B)	108.4	C(30B)-C(31)-H(31E)	109.5
H(17A)-C(17)-H(17B)	107.5	H(31D)-C(31)-H(31E)	109.5
C(35)-C(18)-C(36)	109.44(19)	C(30B)-C(31)-H(31F)	109.5
C(35)-C(18)-C(17)	110.04(19)	H(31D)-C(31)-H(31F)	109.5
C(36)-C(18)-C(17)	109.53(18)	H(31E)-C(31)-H(31F)	109.5
C(35)-C(18)-C(19)	110.95(19)	C(33)-C(32)-C(34)	110.60(19)
C(36)-C(18)-C(19)	108.70(19)	C(33)-C(32)-C(14)	111.66(18)
C(17)-C(18)-C(19)	108.15(18)	C(34)-C(32)-C(14)	112.62(18)
C(20)-C(19)-C(18)	112.46(18)	C(33)-C(32)-H(32)	107.2
C(20)-C(19)-H(19A)	109.1	C(34)-C(32)-H(32)	107.2
C(18)-C(19)-H(19A)	109.1	C(14)-C(32)-H(32)	107.2
C(20)-C(19)-H(19B)	109.1	C(32)-C(33)-H(33A)	109.5
C(18)-C(19)-H(19B)	109.1	C(32)-C(33)-H(33B)	109.5
H(19A)-C(19)-H(19B)	107.8	H(33A)-C(33)-H(33B)	109.5
C(15)-C(20)-O(5)	122.83(19)	C(32)-C(33)-H(33C)	109.5
C(15)-C(20)-C(19)	125.8(2)	H(33A)-C(33)-H(33C)	109.5
O(5)-C(20)-C(19)	111.33(18)	H(33B)-C(33)-H(33C)	109.5
C(3)-C(21)-H(21A)	109.5	C(32)-C(34)-H(34A)	109.5
C(3)-C(21)-H(21B)	109.5	C(32)-C(34)-H(34B)	109.5
H(21A)-C(21)-H(21B)	109.5	H(34A)-C(34)-H(34B)	109.5
C(3)-C(21)-H(21C)	109.5	C(32)-C(34)-H(34C)	109.5
H(21A)-C(21)-H(21C)	109.5	H(34A)-C(34)-H(34C)	109.5
H(21B)-C(21)-H(21C)	109.5	H(34B)-C(34)-H(34C)	109.5
C(3)-C(22)-H(22A)	109.5	C(18)-C(35)-H(35A)	109.5
C(3)-C(22)-H(22B)	109.5	C(18)-C(35)-H(35B)	109.5
H(22A)-C(22)-H(22B)	109.5	H(35A)-C(35)-H(35B)	109.5
C(3)-C(22)-H(22C)	109.5	C(18)-C(35)-H(35C)	109.5
H(22A)-C(22)-H(22C)	109.5	H(35A)-C(35)-H(35C)	109.5
H(22B)-C(22)-H(22C)	109.5	H(35B)-C(35)-H(35C)	109.5
C(24)-C(23)-C(25)	109.82(19)	C(18)-C(36)-H(36A)	109.5
C(24)-C(23)-C(7)	113.31(18)	C(18)-C(36)-H(36B)	109.5
C(25)-C(23)-C(7)	111.98(18)	H(36A)-C(36)-H(36B)	109.5
C(24)-C(23)-H(23)	107.1	C(18)-C(36)-H(36C)	109.5
C(25)-C(23)-H(23)	107.1	H(36A)-C(36)-H(36C)	109.5
C(7)-C(23)-H(23)	107.1	H(36B)-C(36)-H(36C)	109.5

Exp. Data Tab. 32. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for *syn*-**98** (sh3583). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	35(1)	26(1)	18(1)	-8(1)	1(1)	-18(1)
O(2)	37(1)	34(1)	37(1)	-18(1)	6(1)	-23(1)
O(3)	44(1)	25(1)	27(1)	-6(1)	7(1)	-22(1)
O(4)	41(1)	28(1)	30(1)	-9(1)	11(1)	-20(1)
O(5)	32(1)	20(1)	22(1)	-7(1)	0(1)	-12(1)
O(6)	41(1)	24(1)	25(1)	-4(1)	-3(1)	-13(1)
C(1)	25(1)	27(1)	20(1)	-11(1)	5(1)	-12(1)
C(2)	35(1)	30(1)	25(1)	-13(1)	4(1)	-16(1)
C(3)	36(1)	33(1)	20(1)	-13(1)	4(1)	-18(1)
C(4)	31(1)	38(2)	28(1)	-14(1)	4(1)	-20(1)

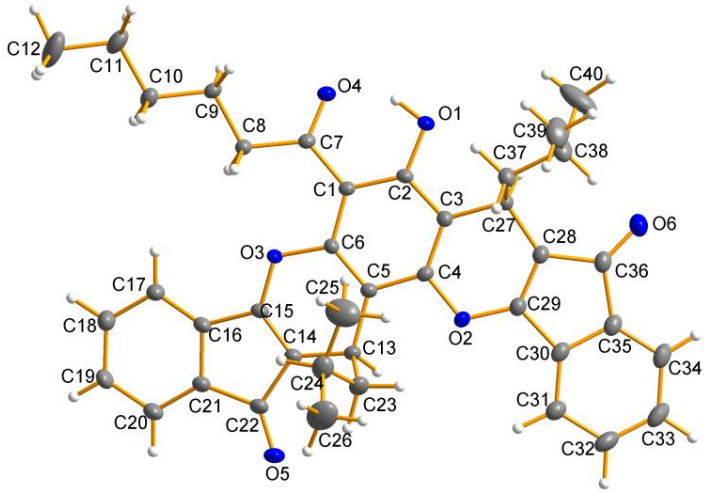
C(5)	24(1)	30(1)	28(1)	-17(1)	9(1)	-13(1)
C(6)	26(1)	24(1)	22(1)	-13(1)	8(1)	-14(1)
C(7)	26(1)	24(1)	28(1)	-13(1)	7(1)	-15(1)
C(8)	23(1)	22(1)	25(1)	-10(1)	4(1)	-12(1)
C(9)	24(1)	19(1)	27(1)	-8(1)	8(1)	-12(1)
C(10)	22(1)	22(1)	20(1)	-8(1)	7(1)	-10(1)
C(11)	22(1)	22(1)	23(1)	-12(1)	3(1)	-9(1)
C(12)	23(1)	19(1)	21(1)	-7(1)	4(1)	-11(1)
C(13)	22(1)	24(1)	20(1)	-8(1)	4(1)	-10(1)
C(14)	24(1)	23(1)	18(1)	-7(1)	2(1)	-11(1)
C(15)	18(1)	20(1)	21(1)	-8(1)	2(1)	-10(1)
C(16)	22(1)	25(1)	24(1)	-8(1)	4(1)	-12(1)
C(17)	28(1)	20(1)	25(1)	-10(1)	3(1)	-10(1)
C(18)	29(1)	24(1)	26(1)	-10(1)	0(1)	-13(1)
C(19)	29(1)	25(1)	21(1)	-9(1)	3(1)	-12(1)
C(20)	23(1)	21(1)	24(1)	-10(1)	2(1)	-11(1)
C(21)	48(2)	42(2)	25(1)	-10(1)	-1(1)	-22(1)
C(22)	41(2)	53(2)	32(1)	-25(1)	14(1)	-25(1)
C(23)	28(1)	22(1)	29(1)	-10(1)	6(1)	-10(1)
C(24)	28(1)	37(2)	48(2)	-19(1)	10(1)	-12(1)
C(25)	42(2)	28(2)	44(2)	-19(1)	10(1)	-13(1)
C(26)	25(1)	22(1)	26(1)	-9(1)	10(1)	-8(1)
C(27)	31(1)	33(2)	25(1)	-4(1)	0(1)	-16(1)
C(28A)	36(2)	40(2)	27(1)	-1(1)	-1(1)	-21(1)
C(29A)	46(2)	45(2)	32(1)	-6(1)	-4(1)	-20(1)
C(30A)	43(2)	63(2)	30(2)	-3(1)	-4(1)	-17(2)
C(28B)	41(3)	43(3)	29(3)	-4(3)	-3(3)	-20(3)
C(29B)	42(3)	49(3)	29(3)	-5(3)	-3(3)	-19(3)
C(30B)	45(3)	52(3)	31(3)	-5(3)	-4(3)	-19(3)
C(31)	75(2)	81(3)	61(2)	-13(2)	-21(2)	-20(2)
C(32)	28(1)	31(1)	25(1)	-14(1)	9(1)	-16(1)
C(33)	34(1)	38(2)	32(1)	-10(1)	9(1)	-23(1)
C(34)	24(1)	36(2)	41(2)	-14(1)	8(1)	-7(1)
C(35)	35(1)	39(2)	41(2)	-16(1)	0(1)	-21(1)
C(36)	56(2)	27(1)	28(1)	-12(1)	3(1)	-20(1)

Exp. Data Tab. 33 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for *syn*-**98** (sh3583).

Hydrogen atom	x	y	z	U(eq)
H(3)	3334	11630	-973	45
H(2A)	5228	6289	4100	33
H(2B)	3748	6649	4370	33
H(4A)	5633	8572	5181	35
H(4B)	6384	7601	4546	35
H(7)	4183	10622	1600	28
H(14)	3408	6052	1750	25
H(17A)	3564	3296	-116	28
H(17B)	4623	3860	-552	28
H(19A)	3729	6241	-1944	29
H(19B)	2183	6957	-2200	29
H(21A)	5589	6567	6576	56

H(21B)	6245	5735	5812	56
H(21C)	4894	5773	6264	56
H(22A)	2893	7771	5685	55
H(22B)	2888	9017	4775	55
H(22C)	3572	8621	5922	55
H(23)	1935	11933	1215	31
H(24A)	1415	10185	2994	56
H(24B)	1083	10349	1799	56
H(24C)	348	11521	2251	56
H(25A)	1539	12755	2605	55
H(25B)	3058	12306	2449	55
H(25C)	2571	11426	3387	55
H(27A)	1073	10214	-2263	36
H(27B)	2345	9678	-2852	36
H(27C)	929	10560	-2336	36
H(27D)	2203	9488	-2558	36
H(28A)	769	12387	-3321	42
H(28B)	1939	11765	-3969	42
H(29A)	-468	11482	-3911	50
H(29B)	707	10830	-4543	50
H(30A)	475	12933	-5629	59
H(30B)	-789	12676	-5749	59
H(28C)	2254	11351	-4070	46
H(28D)	1351	10632	-4175	46
H(29C)	321	12813	-3423	50
H(29D)	-500	12251	-3921	50
H(30C)	867	13785	-5078	54
H(30D)	536	12865	-5604	54
H(31A)	-1903	13971	-4730	116
H(31B)	-1328	14782	-5649	116
H(31C)	-621	14141	-4482	116
H(31D)	-1333	13748	-4288	116
H(31E)	-1606	13877	-5485	116
H(31F)	-1305	14961	-5219	116
H(32)	1288	7313	2102	31
H(33A)	409	5802	2412	49
H(33B)	1958	5042	2603	49
H(33C)	1211	5228	1541	49
H(34A)	351	7441	116	53
H(34B)	315	8646	424	53
H(34C)	-570	7904	981	53
H(35A)	1111	5533	-617	54
H(35B)	1390	4283	-956	54
H(35C)	844	5689	-1822	54
H(36A)	2716	5065	-2915	53
H(36B)	3155	3630	-2105	53
H(36C)	4165	4298	-2350	53

6.7. Appendix 7: crystal data for syn-110



Exp. Data Tab. 34 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for *syn*-**110** (sh3552). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	11949(1)	10118(1)	8918(1)	20(1)
O(2)	8176(1)	11112(1)	7994(1)	21(1)
O(3)	8367(1)	8919(1)	9345(1)	20(1)
O(4)	11972(1)	8983(1)	9718(1)	22(1)
O(5)	4333(1)	9621(1)	9122(1)	29(1)
O(6)	11133(1)	12810(1)	7881(1)	33(1)
C(1)	10162(1)	9470(1)	9114(1)	16(1)
C(2)	10754(1)	10053(1)	8831(1)	16(1)
C(3)	10118(1)	10607(1)	8419(1)	17(1)
C(4)	8884(1)	10572(1)	8343(1)	17(1)
C(5)	8222(1)	10022(1)	8626(1)	17(1)
C(6)	8901(1)	9485(1)	9003(1)	16(1)
C(7)	10893(1)	8893(1)	9502(1)	16(1)
C(8)	10392(1)	8188(1)	9604(1)	17(1)
C(9)	11358(1)	7649(1)	9785(1)	20(1)
C(10)	10832(1)	6941(1)	9850(1)	25(1)
C(11)	11783(2)	6393(1)	10046(1)	37(1)
C(12)	11241(3)	5697(1)	10193(2)	59(1)
C(13)	6859(1)	10051(1)	8552(1)	19(1)
C(14)	6451(1)	9456(1)	9054(1)	19(1)
C(15)	7177(1)	8955(1)	9380(1)	19(1)
C(16)	6561(1)	8413(1)	9825(1)	20(1)
C(17)	6953(1)	7815(1)	10231(1)	24(1)
C(18)	6100(1)	7410(1)	10597(1)	28(1)
C(19)	4908(1)	7600(1)	10541(1)	27(1)
C(20)	4527(1)	8218(1)	10130(1)	27(1)

C(21)	5359(1)	8616(1)	9778(1)	21(1)
C(22)	5242(1)	9289(1)	9289(1)	21(1)
C(23)	6199(1)	10080(1)	7590(1)	26(1)
C(24)	6338(2)	9475(1)	6969(1)	31(1)
C(25)	7548(2)	9443(1)	6619(2)	52(1)
C(26)	5341(2)	9508(1)	6184(2)	51(1)
C(27)	10805(1)	11191(1)	8052(1)	18(1)
C(28)	9955(1)	11777(1)	7917(1)	19(1)
C(29)	8763(1)	11697(1)	7866(1)	19(1)
C(30)	8094(1)	12335(1)	7692(1)	22(1)
C(31)	6885(1)	12475(1)	7553(1)	27(1)
C(32)	6555(2)	13160(1)	7398(1)	33(1)
C(33)	7401(2)	13668(1)	7399(1)	33(1)
C(34)	8626(2)	13517(1)	7550(1)	28(1)
C(35)	8953(1)	12846(1)	7679(1)	22(1)
C(36)	10175(1)	12519(1)	7829(1)	22(1)
C(37)	11290(1)	10958(1)	7174(1)	21(1)
C(38)	12163(2)	11432(1)	6772(1)	31(1)
C(39)	12452(2)	11147(1)	5878(1)	41(1)
C(40)	13295(2)	11541(2)	7388(2)	64(1)

Exp. Data Tab. 35 Bond lengths [Å] for *syn*-**110** (sh3552).

Bond	Length [Å]	Bond	Length [Å]
O(1)-C(2)	1.3425(15)	C(19)-C(20)	1.408(2)
O(1)-H(1)	0.94(2)	C(19)-H(16)	0.87(2)
O(2)-C(29)	1.3499(16)	C(20)-C(21)	1.371(2)
O(2)-C(4)	1.3960(15)	C(20)-H(17)	0.944(19)
O(3)-C(15)	1.3477(16)	C(21)-C(22)	1.5112(19)
O(3)-C(6)	1.3902(15)	C(23)-C(24)	1.530(2)
O(4)-C(7)	1.2343(16)	C(23)-H(18)	1.01(2)
O(5)-C(22)	1.2157(16)	C(23)-H(19)	1.063(19)
O(6)-C(36)	1.2151(18)	C(24)-C(25)	1.513(3)
C(1)-C(6)	1.4113(17)	C(24)-C(26)	1.536(2)
C(1)-C(2)	1.4143(17)	C(24)-H(20)	1.06(2)
C(1)-C(7)	1.4825(17)	C(25)-H(21)	0.98(3)
C(2)-C(3)	1.4080(17)	C(25)-H(22)	1.04(3)
C(3)-C(4)	1.3823(18)	C(25)-H(23)	1.07(3)
C(3)-C(27)	1.5201(18)	C(26)-H(24)	1.01(3)
C(4)-C(5)	1.4041(18)	C(26)-H(25)	1.00(3)
C(5)-C(6)	1.3864(17)	C(26)-H(26)	1.02(3)
C(5)-C(13)	1.5266(18)	C(27)-C(28)	1.4980(18)
C(7)-C(8)	1.5095(18)	C(27)-C(37)	1.5502(19)
C(8)-C(9)	1.5211(18)	C(27)-H(27)	0.965(17)
C(8)-H(2)	1.012(19)	C(28)-C(29)	1.3437(19)
C(8)-H(3)	0.997(16)	C(28)-C(36)	1.4874(18)
C(9)-C(10)	1.5201(19)	C(29)-C(30)	1.4718(18)
C(9)-H(4)	1.030(19)	C(30)-C(31)	1.381(2)
C(9)-H(5)	1.007(17)	C(30)-C(35)	1.396(2)
C(10)-C(11)	1.525(2)	C(31)-C(32)	1.409(2)
C(10)-H(6)	1.008(18)	C(31)-H(28)	0.992(19)

C(10)-H(7)	0.99(2)	C(32)-C(33)	1.379(3)
C(11)-C(12)	1.524(3)	C(32)-H(29)	0.99(2)
C(11)-H(8)	1.256(17)	C(33)-C(34)	1.403(2)
C(11)-H(9)	1.02(2)	C(33)-H(30)	0.97(2)
C(12)-H(10)	1.04(4)	C(34)-C(35)	1.3769(19)
C(12)-H(11)	1.02(3)	C(34)-H(31)	0.934(19)
C(12)-H(12)	1.14(4)	C(35)-C(36)	1.512(2)
C(13)-C(14)	1.4904(18)	C(37)-C(38)	1.526(2)
C(13)-C(23)	1.5499(19)	C(37)-H(32)	1.021(18)
C(13)-H(13)	0.964(19)	C(37)-H(33)	1.011(18)
C(14)-C(15)	1.3387(18)	C(38)-C(40)	1.504(3)
C(14)-C(22)	1.4789(19)	C(38)-C(39)	1.522(2)
C(15)-C(16)	1.4701(18)	C(38)-H(34)	1.01(2)
C(16)-C(17)	1.3760(19)	C(39)-H(35)	0.98(2)
C(16)-C(21)	1.4037(19)	C(39)-H(36)	0.99(2)
C(17)-C(18)	1.404(2)	C(39)-H(37)	1.03(2)
C(17)-H(14)	0.971(19)	C(40)-H(38)	0.96(3)
C(18)-C(19)	1.387(2)	C(40)-H(39)	0.97(3)
C(18)-H(15)	1.00(2)	C(40)-H(40)	0.98(3)

Exp. Data Tab. 36 Bond angles [°] for *syn*-**110** (sh3552).

Bonds	Angles [°]	Bonds	Angles [°]
C(2)-O(1)-H(1)	106.1(14)	O(5)-C(22)-C(14)	127.29(13)
C(29)-O(2)-C(4)	115.68(10)	O(5)-C(22)-C(21)	126.66(13)
C(15)-O(3)-C(6)	116.30(10)	C(14)-C(22)-C(21)	106.05(11)
C(6)-C(1)-C(2)	116.55(11)	C(24)-C(23)-C(13)	117.90(12)
C(6)-C(1)-C(7)	124.75(11)	C(24)-C(23)-H(18)	107.0(11)
C(2)-C(1)-C(7)	118.70(11)	C(13)-C(23)-H(18)	111.1(11)
O(1)-C(2)-C(3)	115.12(11)	C(24)-C(23)-H(19)	108.1(10)
O(1)-C(2)-C(1)	123.14(11)	C(13)-C(23)-H(19)	104.6(10)
C(3)-C(2)-C(1)	121.73(11)	H(18)-C(23)-H(19)	107.7(15)
C(4)-C(3)-C(2)	117.05(11)	C(25)-C(24)-C(23)	113.55(15)
C(4)-C(3)-C(27)	123.65(11)	C(25)-C(24)-C(26)	110.23(17)
C(2)-C(3)-C(27)	119.25(11)	C(23)-C(24)-C(26)	108.61(15)
C(3)-C(4)-O(2)	121.29(11)	C(25)-C(24)-H(20)	107.6(11)
C(3)-C(4)-C(5)	125.08(11)	C(23)-C(24)-H(20)	106.5(11)
O(2)-C(4)-C(5)	113.59(11)	C(26)-C(24)-H(20)	110.2(11)
C(6)-C(5)-C(4)	114.99(11)	C(24)-C(25)-H(21)	113.9(19)
C(6)-C(5)-C(13)	124.22(11)	C(24)-C(25)-H(22)	107.8(15)
C(4)-C(5)-C(13)	120.73(11)	H(21)-C(25)-H(22)	99(2)
C(5)-C(6)-O(3)	121.32(11)	C(24)-C(25)-H(23)	115.4(14)
C(5)-C(6)-C(1)	124.52(12)	H(21)-C(25)-H(23)	111(2)
O(3)-C(6)-C(1)	114.10(10)	H(22)-C(25)-H(23)	109(2)
O(4)-C(7)-C(1)	118.63(11)	C(24)-C(26)-H(24)	106.3(15)
O(4)-C(7)-C(8)	118.24(11)	C(24)-C(26)-H(25)	112.6(14)
C(1)-C(7)-C(8)	123.06(11)	H(24)-C(26)-H(25)	104(2)
C(7)-C(8)-C(9)	113.01(11)	C(24)-C(26)-H(26)	108.3(16)
C(7)-C(8)-H(2)	108.6(10)	H(24)-C(26)-H(26)	111(2)
C(9)-C(8)-H(2)	110.2(10)	H(25)-C(26)-H(26)	115(2)
C(7)-C(8)-H(3)	109.1(9)	C(28)-C(27)-C(3)	106.74(11)

C(9)-C(8)-H(3)	108.9(9)	C(28)-C(27)-C(37)	113.03(11)
H(2)-C(8)-H(3)	106.9(14)	C(3)-C(27)-C(37)	108.97(11)
C(10)-C(9)-C(8)	112.01(12)	C(28)-C(27)-H(27)	108.8(10)
C(10)-C(9)-H(4)	110.4(10)	C(3)-C(27)-H(27)	109.2(10)
C(8)-C(9)-H(4)	107.5(10)	C(37)-C(27)-H(27)	109.9(10)
C(10)-C(9)-H(5)	109.8(10)	C(29)-C(28)-C(36)	106.55(12)
C(8)-C(9)-H(5)	107.9(10)	C(29)-C(28)-C(27)	122.35(12)
H(4)-C(9)-H(5)	109.1(14)	C(36)-C(28)-C(27)	131.09(12)
C(9)-C(10)-C(11)	112.92(13)	C(28)-C(29)-O(2)	126.40(12)
C(9)-C(10)-H(6)	109.5(10)	C(28)-C(29)-C(30)	113.42(12)
C(11)-C(10)-H(6)	107.3(10)	O(2)-C(29)-C(30)	120.13(12)
C(9)-C(10)-H(7)	108.9(11)	C(31)-C(30)-C(35)	121.71(13)
C(11)-C(10)-H(7)	108.9(11)	C(31)-C(30)-C(29)	132.32(13)
H(6)-C(10)-H(7)	109.1(16)	C(35)-C(30)-C(29)	105.97(12)
C(12)-C(11)-C(10)	112.26(17)	C(30)-C(31)-C(32)	116.96(15)
C(12)-C(11)-H(8)	107.9(7)	C(30)-C(31)-H(28)	119.6(11)
C(10)-C(11)-H(8)	115.0(7)	C(32)-C(31)-H(28)	123.5(11)
C(12)-C(11)-H(9)	109.1(12)	C(33)-C(32)-C(31)	121.43(15)
C(10)-C(11)-H(9)	109.9(12)	C(33)-C(32)-H(29)	120.2(12)
H(8)-C(11)-H(9)	102.3(14)	C(31)-C(32)-H(29)	118.3(12)
C(11)-C(12)-H(10)	107.7(19)	C(32)-C(33)-C(34)	120.86(14)
C(11)-C(12)-H(11)	112.7(16)	C(32)-C(33)-H(30)	120.0(12)
H(10)-C(12)-H(11)	103(2)	C(34)-C(33)-H(30)	119.2(12)
C(11)-C(12)-H(12)	112.1(18)	C(35)-C(34)-C(33)	117.89(15)
H(10)-C(12)-H(12)	114(3)	C(35)-C(34)-H(31)	117.0(12)
H(11)-C(12)-H(12)	107(2)	C(33)-C(34)-H(31)	125.1(11)
C(14)-C(13)-C(5)	107.25(10)	C(34)-C(35)-C(30)	121.11(14)
C(14)-C(13)-C(23)	110.92(11)	C(34)-C(35)-C(36)	130.78(14)
C(5)-C(13)-C(23)	116.36(12)	C(30)-C(35)-C(36)	108.10(11)
C(14)-C(13)-H(13)	109.4(11)	O(6)-C(36)-C(28)	127.61(13)
C(5)-C(13)-H(13)	107.4(11)	O(6)-C(36)-C(35)	126.53(13)
C(23)-C(13)-H(13)	105.3(11)	C(28)-C(36)-C(35)	105.86(12)
C(15)-C(14)-C(22)	106.84(12)	C(38)-C(37)-C(27)	117.13(12)
C(15)-C(14)-C(13)	123.58(12)	C(38)-C(37)-H(32)	108.9(10)
C(22)-C(14)-C(13)	129.58(12)	C(27)-C(37)-H(32)	108.3(10)
C(14)-C(15)-O(3)	126.44(12)	C(38)-C(37)-H(33)	107.8(11)
C(14)-C(15)-C(16)	113.57(12)	C(27)-C(37)-H(33)	108.0(10)
O(3)-C(15)-C(16)	119.98(11)	H(32)-C(37)-H(33)	106.1(14)
C(17)-C(16)-C(21)	121.75(13)	C(40)-C(38)-C(39)	110.19(17)
C(17)-C(16)-C(15)	132.55(13)	C(40)-C(38)-C(37)	112.55(17)
C(21)-C(16)-C(15)	105.70(11)	C(39)-C(38)-C(37)	109.32(13)
C(16)-C(17)-C(18)	117.28(13)	C(40)-C(38)-H(34)	110.1(12)
C(16)-C(17)-H(14)	122.9(11)	C(39)-C(38)-H(34)	107.0(12)
C(18)-C(17)-H(14)	119.8(11)	C(37)-C(38)-H(34)	107.5(12)
C(19)-C(18)-C(17)	121.45(14)	C(38)-C(39)-H(35)	110.1(13)
C(19)-C(18)-H(15)	119.2(12)	C(38)-C(39)-H(36)	109.8(13)
C(17)-C(18)-H(15)	119.3(12)	H(35)-C(39)-H(36)	107.1(18)
C(18)-C(19)-C(20)	120.34(14)	C(38)-C(39)-H(37)	111.0(14)
C(18)-C(19)-H(16)	121.3(12)	H(35)-C(39)-H(37)	112.6(19)
C(20)-C(19)-H(16)	118.3(13)	H(36)-C(39)-H(37)	106.2(18)

C(21)-C(20)-C(19)	118.32(14)	C(38)-C(40)-H(38)	109.5(16)
C(21)-C(20)-H(17)	120.3(11)	C(38)-C(40)-H(39)	114.3(16)
C(19)-C(20)-H(17)	121.4(11)	H(38)-C(40)-H(39)	108(2)
C(20)-C(21)-C(16)	120.85(13)	C(38)-C(40)-H(40)	108.3(16)
C(20)-C(21)-C(22)	131.33(13)	H(38)-C(40)-H(40)	109(2)
C(16)-C(21)-C(22)	107.82(12)	H(39)-C(40)-H(40)	107(2)

Exp. Data Tab. 37 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for *syn*-**110** (sh3552). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	12(1)	20(1)	29(1)	4(1)	3(1)	0(1)
O(2)	17(1)	17(1)	28(1)	6(1)	1(1)	2(1)
O(3)	12(1)	17(1)	31(1)	5(1)	5(1)	1(1)
O(4)	14(1)	21(1)	31(1)	3(1)	0(1)	2(1)
O(5)	14(1)	27(1)	44(1)	4(1)	1(1)	3(1)
O(6)	29(1)	23(1)	49(1)	2(1)	7(1)	-4(1)
C(1)	13(1)	17(1)	18(1)	0(1)	2(1)	2(1)
C(2)	12(1)	18(1)	18(1)	-1(1)	3(1)	1(1)
C(3)	16(1)	16(1)	18(1)	1(1)	3(1)	1(1)
C(4)	16(1)	17(1)	19(1)	2(1)	2(1)	3(1)
C(5)	14(1)	17(1)	20(1)	1(1)	2(1)	1(1)
C(6)	14(1)	15(1)	20(1)	1(1)	4(1)	0(1)
C(7)	15(1)	18(1)	16(1)	0(1)	3(1)	3(1)
C(8)	15(1)	17(1)	20(1)	2(1)	3(1)	1(1)
C(9)	17(1)	18(1)	23(1)	3(1)	2(1)	4(1)
C(10)	27(1)	18(1)	29(1)	2(1)	0(1)	2(1)
C(11)	43(1)	21(1)	46(1)	5(1)	-1(1)	10(1)
C(12)	86(2)	22(1)	66(1)	5(1)	-11(1)	4(1)
C(13)	14(1)	18(1)	25(1)	2(1)	1(1)	2(1)
C(14)	14(1)	20(1)	23(1)	1(1)	2(1)	1(1)
C(15)	13(1)	20(1)	24(1)	-1(1)	3(1)	0(1)
C(16)	14(1)	20(1)	25(1)	-1(1)	4(1)	-1(1)
C(17)	18(1)	21(1)	32(1)	3(1)	6(1)	2(1)
C(18)	26(1)	21(1)	38(1)	6(1)	8(1)	1(1)
C(19)	21(1)	24(1)	37(1)	6(1)	9(1)	-4(1)
C(20)	17(1)	26(1)	39(1)	2(1)	5(1)	-1(1)
C(21)	15(1)	21(1)	28(1)	1(1)	2(1)	0(1)
C(22)	14(1)	21(1)	27(1)	0(1)	0(1)	0(1)
C(23)	23(1)	24(1)	28(1)	6(1)	-4(1)	2(1)
C(24)	34(1)	28(1)	29(1)	0(1)	-4(1)	-2(1)
C(25)	46(1)	68(2)	42(1)	-23(1)	7(1)	1(1)
C(26)	55(1)	52(1)	40(1)	-9(1)	-18(1)	2(1)
C(27)	17(1)	16(1)	20(1)	2(1)	3(1)	0(1)
C(28)	21(1)	16(1)	20(1)	2(1)	4(1)	1(1)
C(29)	22(1)	18(1)	19(1)	3(1)	3(1)	1(1)
C(30)	27(1)	20(1)	18(1)	4(1)	4(1)	5(1)
C(31)	26(1)	26(1)	28(1)	7(1)	5(1)	6(1)
C(32)	33(1)	32(1)	33(1)	10(1)	8(1)	14(1)
C(33)	44(1)	24(1)	31(1)	9(1)	12(1)	14(1)
C(34)	40(1)	19(1)	25(1)	6(1)	10(1)	3(1)

C(35)	30(1)	20(1)	19(1)	4(1)	8(1)	3(1)
C(36)	28(1)	18(1)	21(1)	2(1)	7(1)	0(1)
C(37)	22(1)	20(1)	23(1)	1(1)	7(1)	-1(1)
C(38)	33(1)	27(1)	35(1)	-1(1)	18(1)	-4(1)
C(39)	54(1)	36(1)	38(1)	0(1)	28(1)	-3(1)
C(40)	35(1)	100(2)	59(1)	-24(2)	21(1)	-30(1)

Exp. Data Tab. 38 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for *syn*-**110** (sh3552).

Hydrogen atom	x	y	z	U(eq)
H(1)	12250(20)	9736(12)	9244(16)	56(6)
H(2)	9863(16)	8196(9)	10108(13)	31(5)
H(3)	9872(15)	8066(8)	9046(11)	21(4)
H(4)	11890(16)	7671(9)	9269(13)	30(5)
H(5)	11851(15)	7767(8)	10365(12)	24(4)
H(6)	10354(16)	6819(9)	9263(12)	28(4)
H(7)	10299(18)	6937(10)	10330(14)	37(5)
H(8)	12493(14)	6329(8)	9461(11)	18(4)
H(9)	12343(19)	6522(11)	10601(15)	46(6)
H(10)	11940(30)	5346(18)	10280(20)	111(11)
H(11)	10730(30)	5521(14)	9640(20)	82(9)
H(12)	10650(30)	5701(18)	10770(30)	116(12)
H(13)	6643(17)	10466(10)	8837(13)	33(5)
H(14)	7778(17)	7663(9)	10262(12)	31(5)
H(15)	6359(18)	6978(11)	10909(14)	44(6)
H(16)	4373(17)	7341(10)	10754(13)	35(5)
H(17)	3723(17)	8361(9)	10103(12)	30(5)
H(18)	6431(18)	10502(10)	7263(13)	41(5)
H(19)	5279(17)	10124(9)	7685(12)	31(5)
H(20)	6243(18)	9031(10)	7355(14)	42(5)
H(21)	8220(30)	9437(15)	7090(20)	94(10)
H(22)	7710(20)	9913(14)	6336(18)	73(8)
H(23)	7640(20)	9055(13)	6130(18)	72(8)
H(24)	5470(20)	9943(14)	5857(18)	69(8)
H(25)	5420(20)	9146(13)	5723(17)	64(7)
H(26)	4540(30)	9516(14)	6440(19)	82(9)
H(27)	11461(15)	11317(8)	8490(11)	22(4)
H(28)	6300(17)	12098(10)	7552(13)	34(5)
H(29)	5691(19)	13272(10)	7291(14)	41(5)
H(30)	7153(18)	14135(10)	7297(13)	40(5)
H(31)	9242(17)	13836(10)	7565(13)	31(5)
H(32)	10578(16)	10868(9)	6706(12)	28(4)
H(33)	11701(16)	10504(9)	7292(12)	30(5)
H(34)	11742(18)	11878(11)	6643(14)	42(5)
H(35)	13030(20)	11441(11)	5622(15)	50(6)
H(36)	12830(20)	10693(12)	5970(15)	49(6)
H(37)	11680(20)	11074(11)	5447(17)	56(7)
H(38)	13620(20)	11110(14)	7584(18)	64(9)
H(39)	13910(30)	11796(14)	7120(18)	73(8)
H(40)	13100(20)	11801(14)	7910(20)	76(8)