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Natural Products

The Psymberin Story—Biological Properties and Approaches towards Total and Analogue Syntheses**

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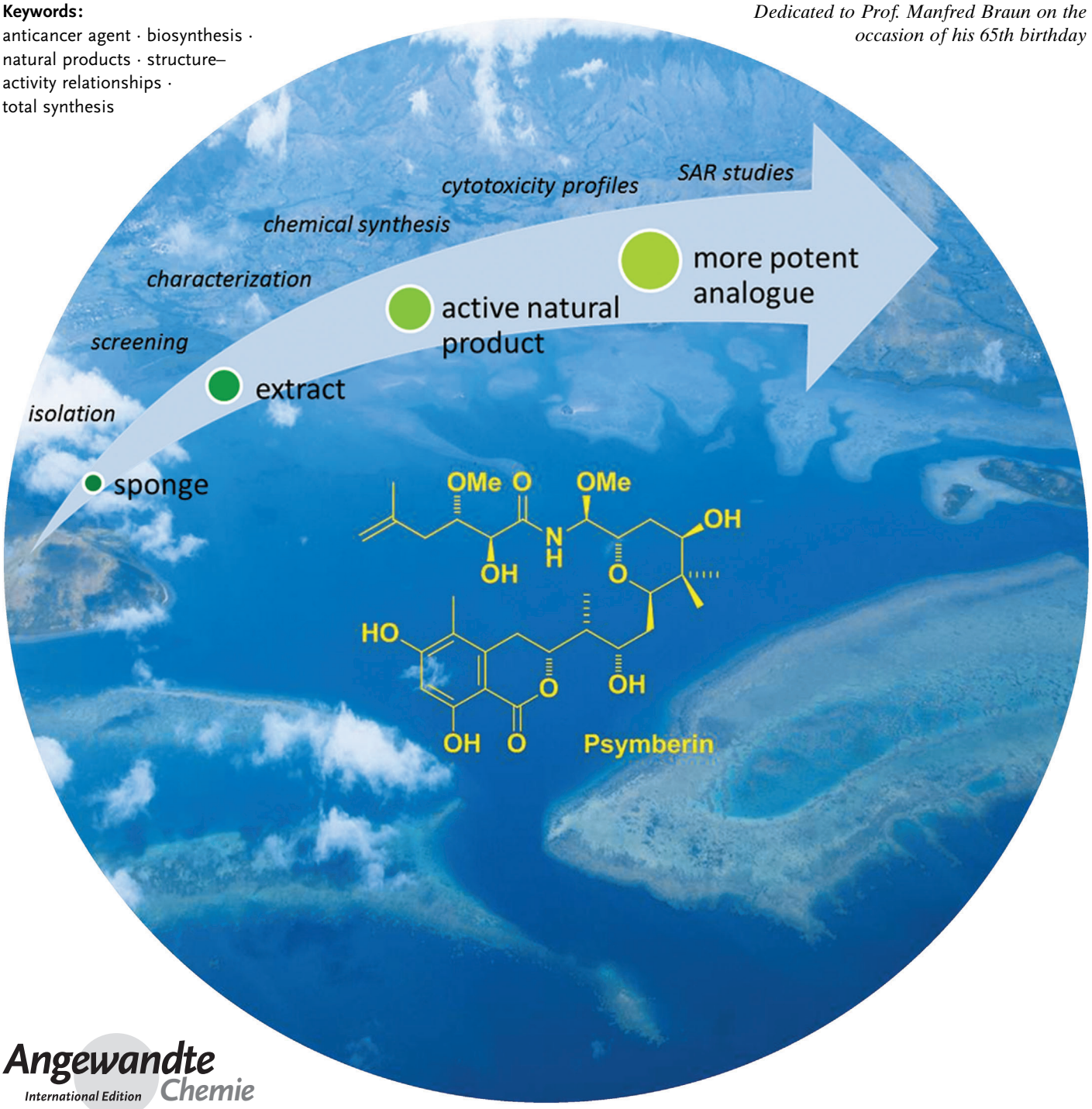
Dedicated to Prof. Manfred Braun on the occasion of his 65th birthday



Psymberin is a marine natural product which has attracted a great deal of interest since its isolation: While the highly cytotoxic compound was detected early on as an ingredient in a marine sponge, it took over a decade and 600 additional samples for the structure to eventually be assigned. In the last eight years fascinating synthetic and biosynthetic investigations have led to a more detailed understanding as well as a new starting point for structure–activity studies towards new antitumor compounds. The Review gives an in-depth insight into the progress in the field of the marine polyketide psymberin and demonstrates how organic synthesis is influencing neighboring scientific subjects.

From the Contents

1. Introduction

A group of biologically active natural products of immense pharmacological interest are the polyketides. This structurally diverse family contains compounds that can either be of marine or terrestrial origin. Figure 1 shows three examples that underline its diversity: 6-methylsalicylic acid is quite a simple compound, while aflatoxin B1 and erythromycin are much more complex. Very complex structures, for example, that of palytoxin, are often produced by marine organisms.[1]

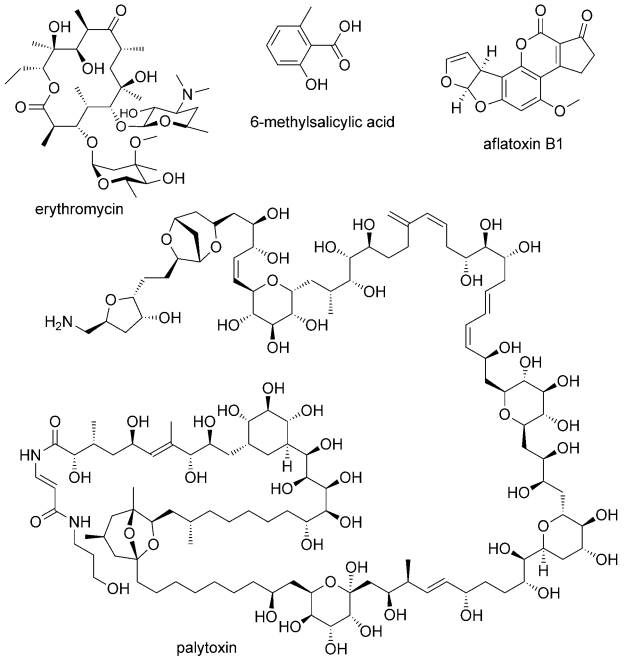


Figure 1. Selected structures of polyketides.

The pederin family is an example of a group of polyketides. Some of these structures are displayed in Figure 2. The group consists currently of 36 compounds,[2] which are either of terrestrial [for example, pederin (**1**)] or of marine origin [for example, mycalamides A–D (**2a–d**)]. The family obtained its name from pederin (**1**), which had already been isolated by Netolitzky in 1919 from *Paederus fuscipes*, a Japanese beetle.[3] However, Netolitzky just mentioned the vesicant property of the natural product. In 1953, it was Pavan and Bo, who isolated more substance from about 25 million beetles (the compound weighs about 0.025% of the beetle), and named it pederin (**1**).[4] With sufficient substance in hand, more studies were conducted in the 1960s by Quilico, Cardani et al., who determined the chemical formula and provisional structure.[5,6] A slightly different structure was suggested by Matsumoto, Furusaki et al., which was confirmed by X-ray analysis.[7,8]

The properties of these beetle extracts have, however, been known for a much longer time.[9] The Chinese (AD 739) already knew about the toxic effect of the components, which led to skin irritation and used these extracts to cure blains, nasal polyps, and lichens. During the last decades some dermatitis cases were reported in Africa, Asia, and South America that were caused by *Paederus* beetles. In 1961 a large beetle population caused many cases of dermatitis in Uganda because people and beetles came into direct contact.[10] There were other cases reported in Okinawa (1966),[11] Central Africa (1993),[12] Northern Kenia (1993),[13] and Sierra Leone (2002).[14] In the Guilan province (Iran) the *Paederus* derma-

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[**] Abbreviations are given in the appendix.

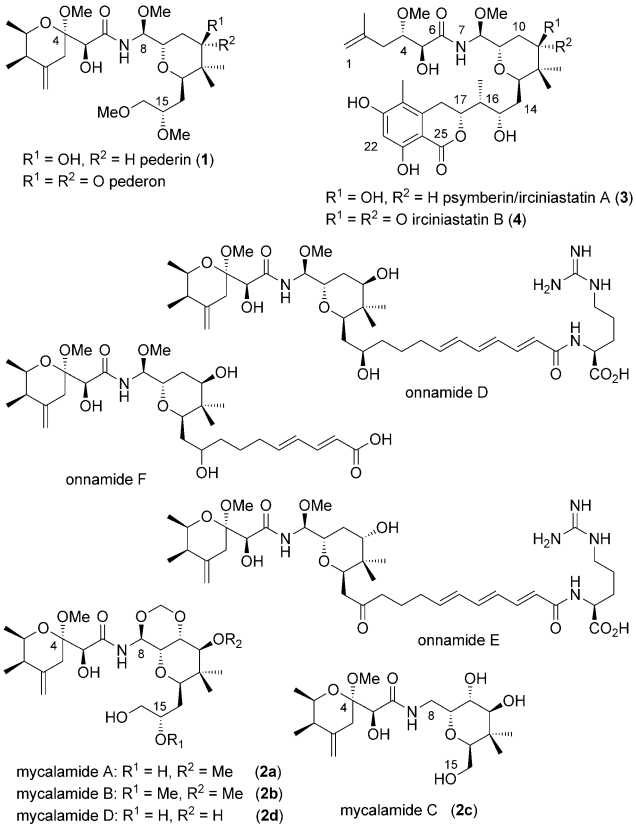


Figure 2. Some members of the pederin family.

titis has been known for some decades and it is called "Dracula",[15] which shows the misunderstanding of the people of the origin of the disease. Even more interesting is the mention[16] that the beetles were responsible for three of the ten biblical plagues[17] (numbers three, four, and six).

The family of the *Paederus* beetles is quite large with about 600 species. These beetles prefer a warm climate and live in huge swarms. They do not expel the toxic extracts when they are flying around people, only when they are harmed and injured. Then, the blood can leak from the wound.[14] It is believed that pederin (**1**) is used as a chemical deterrent that protects the beetles' larvae from spiders. Pederin (**1**) blocks mitosis even in low concentrations (about 1 ng mL^{-1}) by the inhibition of protein and DNA synthesis without influencing RNA synthesis.[9] Pederin (**1**) shows cytotoxicity against various tumor cell lines in vitro and in vivo.[18] All these properties incited many research groups to focus on the natural product.[19]

Recently, there were intensive genetic studies concerned with the biosynthesis of pederin (**1**) and it is believed that it is not produced by the *Paederus* beetles themselves but by symbiotic living bacteria.[20] There are analogous indications for other members of the pederin family. One of them is psymberin (**3**; ***Ps****ammocinia* s**ymb**iont ped**erin**). It was independently discovered in 2004 by the research groups of Crews[2] and Pettit[21] from the sponges *Psammocinia sp.* and *Ircinia ramose*, respectively, and it has turned out to be a marine natural product of immense interest since its isolation.

This interest is due to its complex architecture, biological properties, and paucity in nature, which resulted in a multitude of synthetic and biological investigations and analogue studies in several laboratories around the world. In particular, the dihydroisocoumarin unit and psymberic acid distinguish psymberin (**3**) from the other pederins, and result in excellent cytotoxicity values which exceed the others. This unique unit calls for a partially different biosynthesis. Pederin-like molecules show similar, less-selective profiles of cytotoxicity, while psymberin (**3**) sets itself apart from the others. Table 1 shows the impact of psymberin (**3**) on different human cancer cell lines.[2]

Table 1: LC_{50} values of different cell lines to psymberin (**3**) according to the NCI Developmental Therapeutics In Vitro Screening Program.[2]

Cell line	LC_{50} [M]	Cell line	LC_{50} [M]
leucemia		**melanoma**	
CCRF-CEM	$>2.5\times10^{-5}$	LOX IMVI	$>2.5\times10^{-5}$
HL-60 (TB)	$>2.5\times10^{-5}$	MALME-3 M	$<2.5\times10^{-9}$
K-562	$>2.5\times10^{-5}$	SK-MEL-2	$>2.5\times10^{-5}$
MOLT-4	$>2.5\times10^{-5}$	SK-MEL-5	$<2.5\times10^{-9}$
PRMI-8226	$>2.5\times10^{-5}$	SK-MEL-28	1.41×10^{-5}
SR	$>2.5\times10^{-5}$	UACC-257	$>2.5\times10^{-5}$
		UACC-62	$<2.5\times10^{-9}$
breast cancer		**colon cancer**	
MCF7	$>2.5\times10^{-5}$	HCC-2998	3.76×10^{-7}
HS 578T	$>2.5\times10^{-5}$	HCT-116	$<2.5\times10^{-9}$
MDA-MB-435	$<2.5\times10^{-9}$	HAT29	$>2.5\times10^{-5}$
NCI/ADR-RES	1.9×10^{-5}	SW-620	$>2.5\times10^{-5}$
T-47D	1.36×10^{-5}		

Max Bielitza studied chemistry at the University of Düsseldorf (diploma 2008) and completed his PhD (2012) under the supervision of Prof. Dr. J. Pietruszka at the Research Center Jülich on the synthesis of psymberin and derivatives thereof. Afterwards, he investigated new lead structures by laccase-catalyzed reactions in the Pietruszka group. Currently, he is a postdoctoral researcher with Dr. Davioud-Charvet at Strasbourg University, France, where he is involved in medicinal chemistry issues.

Jörg Pietruszka studied chemistry at the University of Hamburg where he obtained his PhD in 1993 (Prof. Dr. W. A. König). After postdoctoral research with Prof. Dr. S. V. Ley (Cambridge, UK), he moved to the University of Stuttgart, where he finished his Habilitation in 2001. Since 2004 he has held the position of full professor of bioorganic chemistry at the Heinrich-Heine-University Düsseldorf.

Psymberin (**3**) was tested against 60 cell lines and displayed high cytotoxicity values against melanoma, breast, and colon cancer cell lines ($LC_{50} < 2.5 \times 10^{-9}$ M), while leucemia cell lines are relatively immune to it ($LC_{50} > 2.5 \times 10^{-5}$ M). All these highly different values ($> 10^4$) reflect psymberin's high, but selective biological activity, which makes it unique among the pederins. All these properties prove psymberin (**3**) to be a potential candidate for clinical evaluation. In this Review, we highlight the isolation of psymberin (**3**), its biosynthesis, the mode-of-action, and discuss the chemical syntheses that also laid the foundation for the synthesis of further analogues.

2. Isolation, Structure Elucidation, Biosynthesis, and Biological Studies

2.1. Isolation and Structure Elucidation

Since the 1990s it has been known that extracts from the sponge *Psammocinia sp.* show cytotoxic activity. However, for a long time it was not possible to assign these activities to a substance. Crews and co-workers isolated different substances, for example, a halogenated hexapeptide, swinholide A, and brominated phenolic ether, but these were not responsible for the biologic activity. So, they combined all 600 *Psammocinia* fractions collected from 1990 until 2001 off the coast of Papua New Guinea and submitted them to a bioassay-guided fractionation against HCT-116, a human colon cancer cell line. They obtained the natural product which accounts for only about 9.16×10^{-5} wet wt% of the sponge. Crews and co-workers were then able to elucidate almost the complete structure on the basis of MS, multidimensional NMR, and chiroptical methods, except for the configuration at C4.[2] The full structure elucidation was then completed by Kiren and Williams, who had synthesized C4/C5 *anti* and *syn* model compounds. The crystal structure data obtained suggested the *anti*-configuration.[22]

Pettit et al. extracted a sponge from the species *Ircinia ramose*, which had been collected in 1991 in Malaysia, with a dichloromethane/methanol mixture (1:1). This dichloromethane fraction was submitted to a solvent partition separation and the resulting dichloromethane fraction was further separated by gel permeation and partition column chromatography, which were guided by a P388 leucemia cell line assay. The last step was the purification by reversed-phase HPLC to yield both irciniastatin A and B (**3** + **4**) as colorless amorphous powders.[21] After Pettit et al. had isolated the new cytotoxic compound they named it irciniastatin A (**3**) and it was believed that psymberin (**3**) and irciniastatin A (**3**) were diastereomers with respect to the configuration at C8. However, it later turned out that both molecules are identical and feature the structure proposed by Crews and co-workers. Additionally, irciniastatin B (**4**) also shows excellent GI_{50} values against different cancer cell lines. The biological properties will be discussed in Section 8.

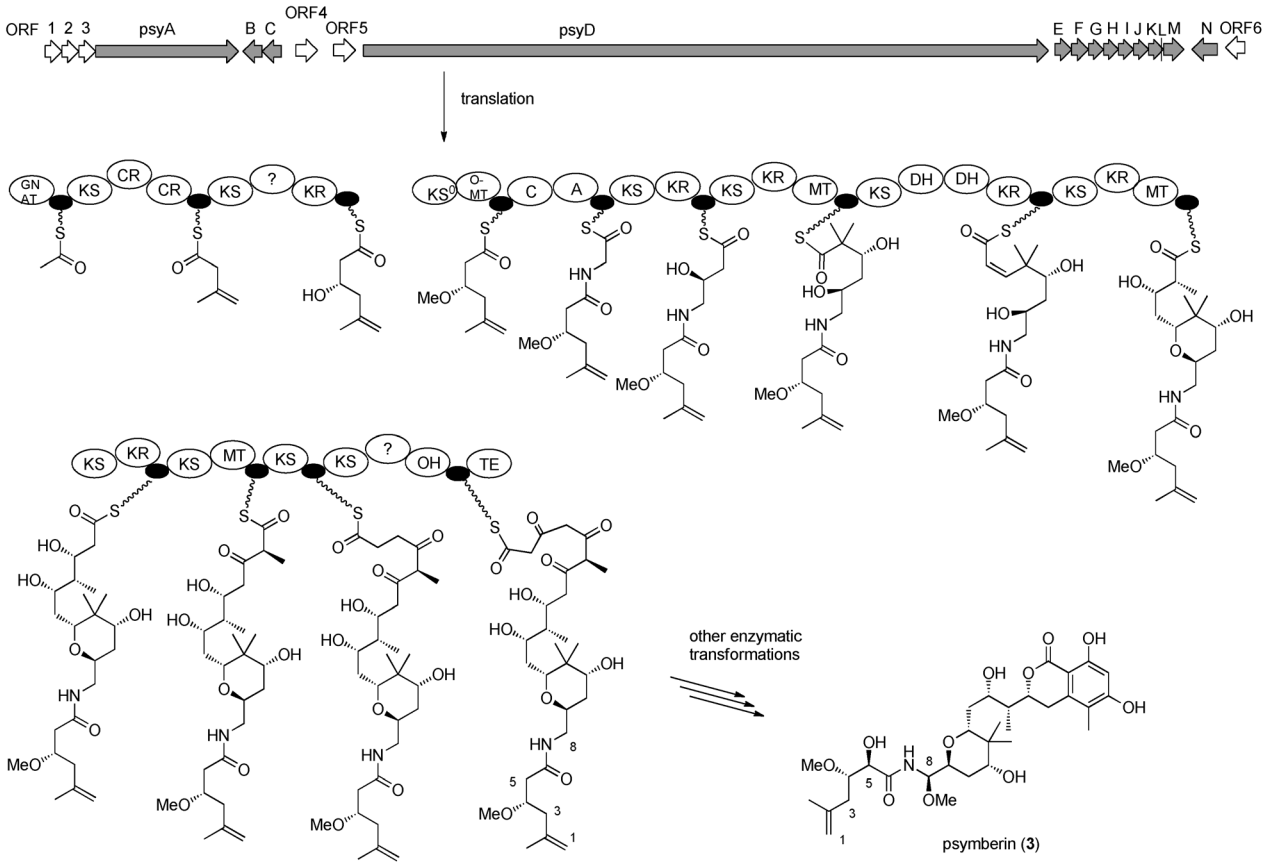
2.2. Biosynthesis

The initial biological investigations concerning the pederin group were performed by Cardani et al. in 1973.[23] They investigated the biosynthesis of pederin (**1**) by feeding experiments with radioactively labeled molecules ([1-^{14}C]-acetate, [2-^{14}C]-acetate, [1,2-^{14}C]-glycine, and [2-^{14}C]-propionate). They proposed the pederin structure to be formed by polyketide biosynthesis. Further investigation was carried out by the Piel research group.[20] They were able to identify the genes of the non-cultivatable symbiont *Pseudomonas sp.*, which lives with the beetle *Paederus fuscipes*. These genes encode for the huge, multifunctional polyketide synthase enzymes which are responsible for the biosynthesis of polyketides.

Again, it was the Piel research group that published analogous studies about the biosynthesis of psymberin (**3**) in 2005. They were able to isolate the polyketide synthase cluster from the sponge *Psammocinia aff. bulbosa*.[24] The proposed biosynthesis is shown in Scheme 1. Starting from acetic acid thioester, the psymberic acid unit is built first by the typical reactions of polyketide synthesis (e.g. keto reduction, crotylation, dehydration). Then, the chain is elongated by further transformations until cyclization and aromatization occur. It is currently unknown how the last steps proceed. It is believed that chemo- and stereoselective oxidations take place in the 5- and 8-positions followed by O-methylation in the 8-position to complete the synthesis. Piel and co-workers also discovered that parts of the psymberin gene cluster were identical to the ones from a different sponge, *Discodermia dissolute*,[25] which had been found about 16000 kilometers away from Papua New Guinea in Curacao.[20,26,27] As mentioned above, a psymberin-containing sponge was found in Malaysia.[21] The actual studies and investigations indicate more and more that it is not the sponges or beetles themselves that are the producers of the natural products, but non-cultivatable symbiotic-living bacteria. Further investigations towards the elucidation of the biosynthesis and the heterologic expression are underway to allow a sustainable production of these highly potent, pharmacologically interesting molecules.

2.3. Biological Studies

The properties of the pederins mentioned above have drawn considerable attention from different research groups to unravel their molecular mechanisms. It was shown that some mycalamides are inhibitors of protein biosynthesis[28] and p21 synthesis, a cyclin-dependent, cell growth regulating kinase inhibitor.[29] Richter et al. found out that pederin (**1**) and several mycalamides cause necrosis in squamous cell carcinoma but not in fibroblasts.[30] Other studies showed that these molecules activate c-Jun kinase (JKN) and p31 mitogen-activating protein kinase, thereby causing apoptosis within a multitude of cell lines.[31,32] Furthermore, the 60S subunit of the ribosome could be identified as the potential target of pederin (**1**).[33] Psymberin (**3**) induces protein kinase activation (similar to JKN and p38), probably with the help of reactive oxygen species from mitochondria. Alternatively,



Scheme 1. Proposed biosynthesis of psymberin (**3**) by Piel and co-workers.[24] The gray arrows indicate the genes of the pederin cluster. GNAT: GCN5-related *N*-acetyltransferase family; CR: crotonase superfamily, KR: ketoreductase; KS^0: non-elongating KS; OMT: *O*-methyltransferase; C: nonribosomal peptide synthetase (NRPS) condensation domain; A: NRPS adenylation domain; MT: methyltransferase; DH: dehydratase; TE: thioesterase; ?: unknown.

after JKN activation, caspase-8 could cause apoptosis. The exact mechanism for cell death has not yet been elucidated.[34]

Floreancig and co-workers investigated different binding modes of model complexes of pederin (**1**) and the ribosome which was derived from crystal-structure data of the structurally related mycalamide A (**2a**) and the ribosome.[35] This investigation provided them with information about the function of the different structural units of the molecules, which resulted in newly designed second-generation analogues (see Section 8).

Just recently, an interesting publication appeared on biochemical and genetic studies to identify the mode of action of psymberin (**3**).[36] Wu et al. conducted a genetic screen in the well-studied nematode worm *Caenorhabditis elegans* (Figure 3): After determining the minimum concentration of psymberin (**3**) where no larva (wild-type, wt) could grow or survive (5 μM), worms at the young adult stage were genetically altered by random mutagenesis (treatment with ethyl methanesulfonate). Resistance to psymberin (**3**) was observed in seven cases, and the drug-resistant mutation was identified in one case (strain DA2312)—a proline to leucine transition (P65L)

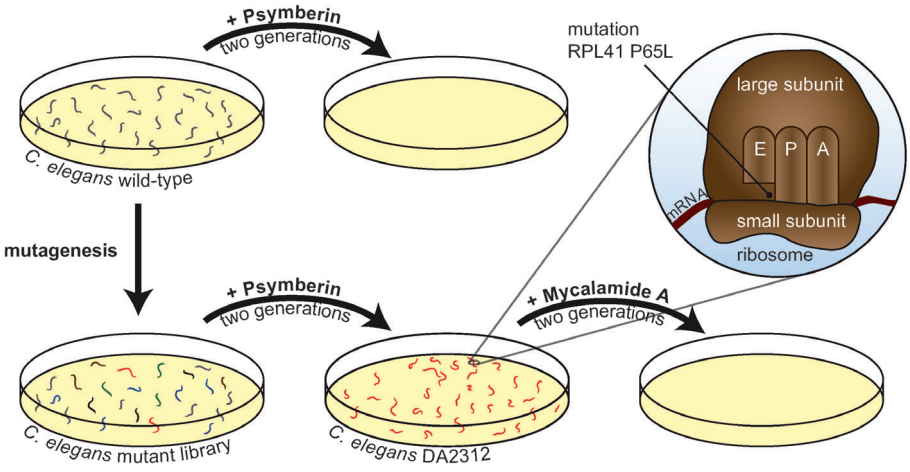
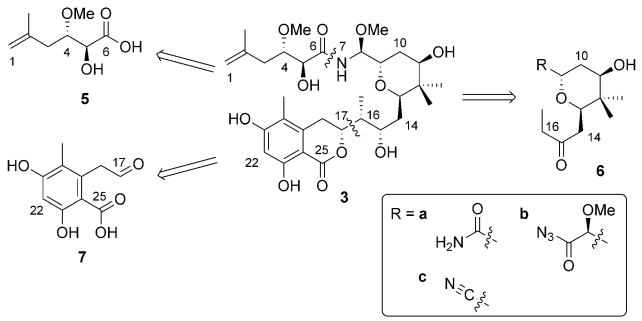


Figure 3. Target identification assay: Schematic overview.[36]

in the ribosomal large subunit protein (RPL41), a protein that is orthologous to human RPL36a and RPL36al. Furthermore, experiments suggested that mycalamide A (**2a**) and psymberin (**3**) bind to the same molecular target, but in a different way. Wu et al. also found that the accumulation to psymberin (**3**) within the cells depended on the stereochemistry of the substituents in the C4- and C8-positions and the presence of the dihydroisocoumarin group. Thus, it could be explained why these analogues lose their cytotoxic activity but keep the activity in cell-free in vitro assays. In contrast to pederin (**1**) and other pederins, psymberin (**3**) is not a blistering agent. A more detailed discussion concerning structure–activity relationships is the topic of Section 8.

3. Retrosynthetic Approaches

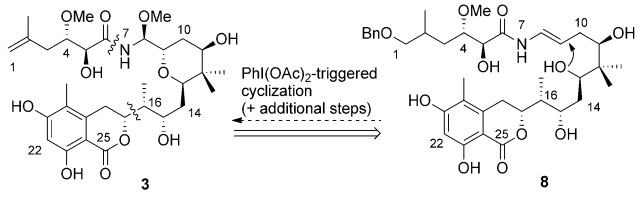
To synthesize a natural product one has to come up with a well-planned retrosynthesis which enables the synthetic chemist to construct the desired molecule in a short and efficient manner. The most often used retrosynthetic disconnections for the polyketide psymberin (**3**) turned out to be between C6 and N7 and between C16 and C17, thereby leading to the three fragments shown in Scheme 2: psymberic



Scheme 2. Common retrosynthetic approach to psymberin (**3**).

acid (**5**), tetrahydropyran core **6**, and aromatic aldehyde **7**. A major difference in the syntheses was the strategies used for the construction of the *N,O*-hemiaminal functionality, and led to the functional groups displayed in Scheme 2 (with R = a–c) which finally proved to be successful.

First, the different approaches towards the three fragments are shown, including some variations that differ from the ones mentioned above. Second, the strategies for connecting the three units are explained, followed by further



Scheme 3. Retrosynthetic approach of Huang et al.[37]

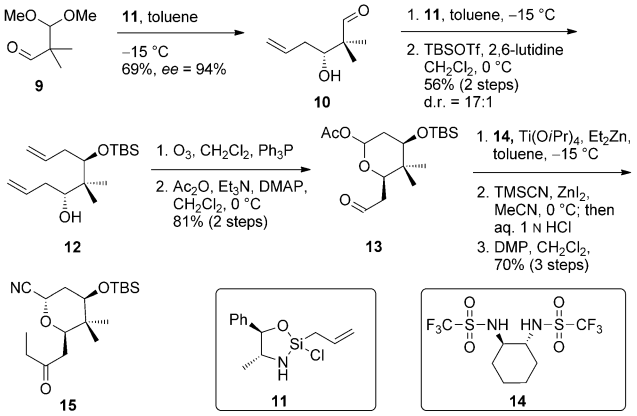
transformations that result in the total synthesis of the natural product.

One of the total syntheses varies significantly from the others. Huang et al. developed a late-stage oxidative cyclization from enamide **8** to tetrahydropyran **3** (Scheme 3), which turned out to be the key step in their synthesis.[37] This approach will also be shown in Section 7.

4. Syntheses of the Tetrahydropyran Core

Organic chemists have been striving for new tetrahydropyran syntheses for years because of its abundance in a variety of natural products, for example, bryostatin 1[38] and maitotoxin-1.[39,40] The tetrahydropyran core is the central unit of psymberin (**3**). It is highly substituted, contains a *gem*-dimethyl group, three stereogenic centers, and bears a 2,6-*trans* relationship which is thermodynamically less favored than the 2,6-*cis* arrangement.[41] There is a multitude of tetrahydropyran syntheses in the literature,[42–44] including the ones that lead to the synthesis of other pederins, but only a few apply here. Therefore, new concerted syntheses had to be developed to build the tetrahydropyran core of psymberin. In the following, these approaches are presented in detail.

De Brabander and co-workers published the first total synthesis of psymberin (**3**) in 2005, which led to the complete stereochemical assignment and proved that psymberin (**3**) and irciniastatin A (**3**) are identical.[45] Their tetrahydropyran synthesis is described in Scheme 4. Starting from monopro-

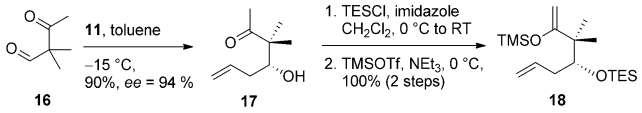


Scheme 4. Tetrahydropyran synthesis by De Brabander and co-workers.[45]

tected bisaldehyde **9**, the transformation to alcohol **10** was performed with Leighton's allylsilane **11** in 69% yield and 94% *ee*. The other aldehyde functionality was deprotected during work-up and was further reacted with Leighton's reagent **11** in a highly diastereoselective manner (d.r. = 17:1; →**12**). Tetrahydropyran core **13** could then be obtained after ozonolysis, acetate protection, followed by an asymmetric diethylzinc addition. The last step was run under Kobayashi conditions with the chiral diamine ligand **14**. A subsequent acetate replacement by a cyanide and a Dess–Martin

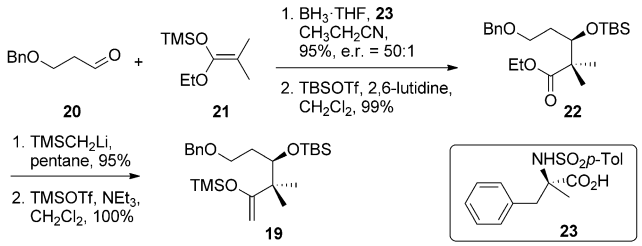
oxidation to the corresponding ketone provided **15**. Starting from **9** the coupling unit **15** could be obtained in 8 steps and 30% overall yield.

The partial synthesis of psymberin (**3**) by Rech and Floreancig started with aldehyde **16**.[46] They pursued a different strategy, where the ring closure was achieved after coupling to the aromatic fragment. Similar to the approach used by the De Brabander research group, aldehyde **16** was converted into alcohol **17** in 90% yield and 94% *ee*. After protecting alcohol **17** with a TES group, the silyl enol ether **18** was formed in quantitative yield (Scheme 5). The tetrahydropyran structure can already be recognized in **18**.



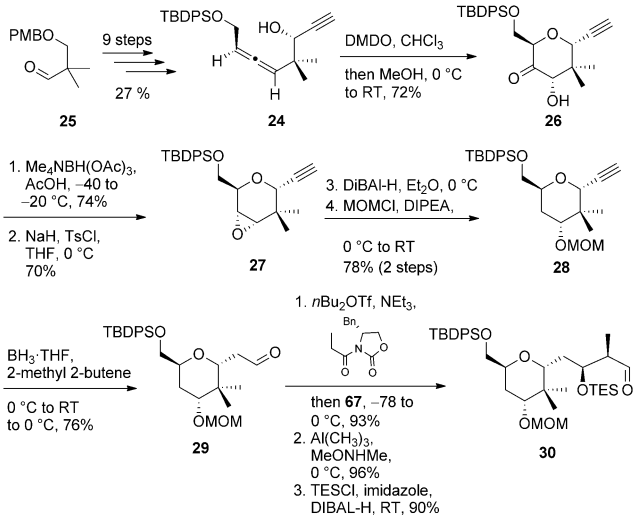
Scheme 5. Approach towards the tetrahydropyran core by Rech and Floreancig.[46]

Similar to the Floreancig research group, Huang et al. conducted the ring closure after coupling to the aromatic unit. Therefore, silyl enol ether **19** was needed. As a key step, they performed a Masamune aldol reaction of aldehyde **20** with trimethylsily enol ether **21** to obtain **22**. They achieved an excellent enantiomeric ratio of 50:1 by using chiral ligand **23**. After two more steps they could obtain **19** in 94% yield. Ring closure was performed later in the synthesis (Scheme 6).[37]



Scheme 6. Synthesis of the tetrahydropyran core by Huang et al.[37]

Shangguan et al. also pursued an interesting strategy (Scheme 7).[47] The key step towards the pyran unit was the oxidation of a 1,3-disubstituted allene **24** via a spiro diepoxide intermediate. Allene **24** could be obtained in nine steps and a total yield of 27% from protected, commercially available aldehyde **25**. Cyclization was possible by using dimethyldioxirane (DMDO) and product **26** could be isolated in 72% yield. Then a sequence of diastereoselective reduction using tetrabutylammonium trisacetoxyborohydride and tosylation with subsequent nucleophilic replacement provided epoxide **27**. The latter could be regioselectively opened with DiBAl-H and the resulting alcohol protected with a MOM group to furnish **28** (78% over two steps). A hydroboration reaction furnished aldehyde **29** in 67% yield, which was submitted to an asymmetric propionate aldol reaction using the Evans

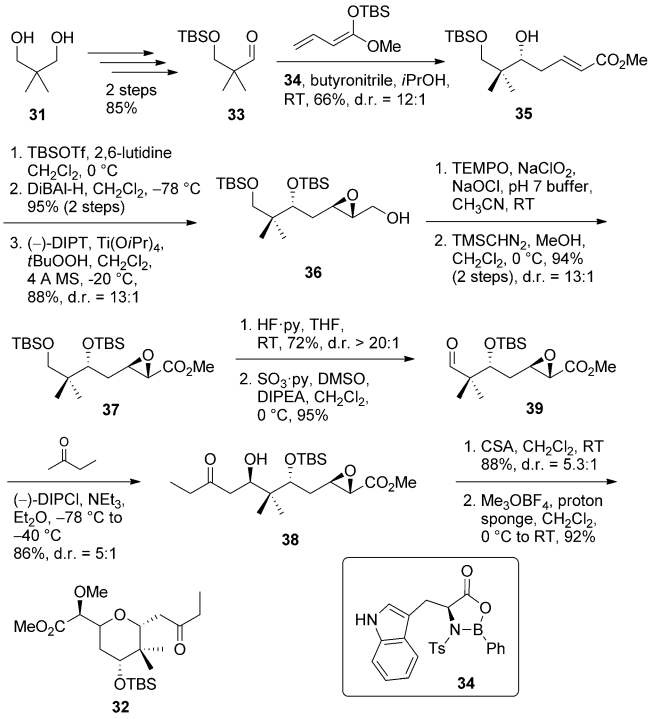


Scheme 7. Tetrahydropyran synthesis by Shangguan et al.[47]

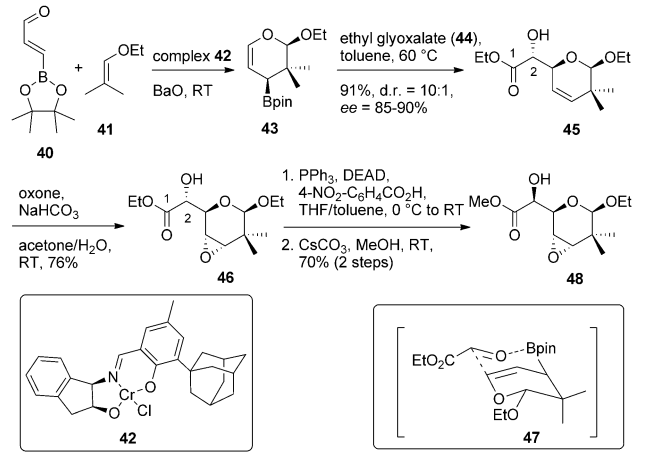
auxiliary. The auxiliary was then transformed into the corresponding Weinreb amide. Protection with a TES group followed by reduction provided aldehyde **30** as the coupling partner, which was obtained in 80% yield over the last three steps.

The Smith research group published their total synthesis in 2008.[48] Starting from diol **31**, they synthesized tetrahydropyran unit **32** in 13 steps. Alcohol **31** was transformed to aldehyde **33** in two steps and this was submitted to a vinylogous Mukaiyama aldol reaction using oxaborolidinone **34** as the chiral catalyst. The product alcohol **35** was obtained in 66% yield and transformed into epoxide **36** in three steps and a total yield of 84% and a diastereomeric ratio of 13:1. The epoxide was oxidized to the corresponding acid and then methylated in 94% yield over two steps to obtain ester **37**. Afterwards aldol **38** was synthesized in three more steps via aldehyde **39** followed by cyclization to the tetrahydropyran core. The last step was accomplished in 88% yield and a diastereomeric ratio of 5.3:1. The final methylation using Meerwein's salt provided ketone **32** in 92% yield (Scheme 8).

Hall and co-workers focused on a hetero-Diels–Alder reaction between 3-boronoacroleine **40** and vinyl ether **41** and the following allylation as key steps for the enantio- and diastereoselective construction of the tetrahydropyran unit (Scheme 9).[49] They used the chromium complex **42** developed by Jacobsen and co-workers[50] as the catalyst for the cycloaddition. After a short work-up, product **43** was directly treated with ethyl glyoxalate (**44**) to obtain alcohol **45** in 91% yield, 85–90% *ee*, and a diasteromeric ratio of 10:1. A highly stereoselective epoxidation with DMDO then afforded epoxide **46**. The observed selectivity was due to steric factors. Since the allyl addition to ethyl glyoxalate (**44**) (presumably via transition state **47**) had delivered the expected but undesired *R* stereoisomer, a Mitsunobu conversion at the 2-position had to be performed to give epoxide **48**, which turned out to be an advanced intermediate towards the anticipated synthesis.

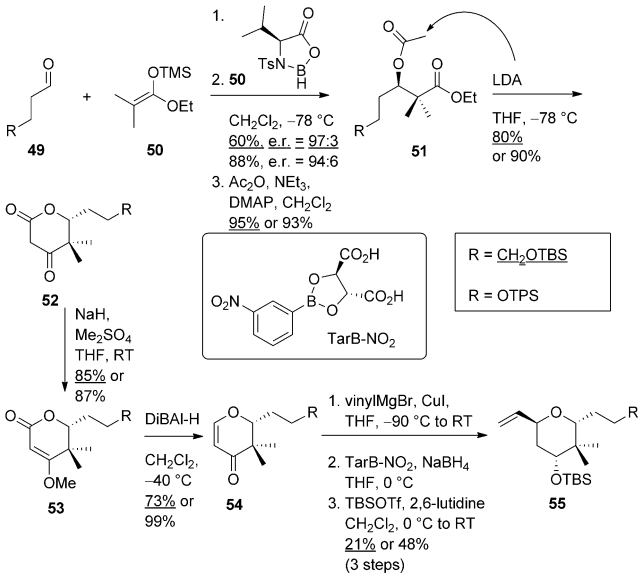


Scheme 8. The tetrahydropyran synthesis by Smith III et al.[48]



Scheme 9. Approach to tetrahydropyran **48** by Hall and co-workers.[49]

Konopelski and co-workers used an oxaborolidine-catalyzed aldol reaction of aldehyde **49** and silyl enol ether **50** for the construction of the first stereogenic center (Scheme 10).[51] Depending on the substituents (R = CH_2OTBS or OTPS), products could be isolated in 60 and 88% yield and 97:3 and 94:6 *ee*, respectively. After acetylation (→**51**), deprotonation in the α-position of the acetyl group was induced by LDA that led to nucleophilic attack at the ethyl ester group and cyclization (Dieckmann condensation) (→**52**). Then, vinyl ether **53** was formed which was subsequently reduced to furnish α,β-unsaturated ketone **54**, which was submitted to vinylation, reduction, and TBS protection to obtain tetrahydropyran **55**. Interestingly, a substrate-induced diastereoselective reduction of ketone **54** was not possible. Therefore, reduction with sodium borohydride in the presence of the chiral boronic ester TarB-NO_2 was necessary. The product was obtained with good selectivity (d.r. = 19:1) but a modest yield of 55%. All substances with R = CH_2OTBS turned out to be quite sensitive throughout the whole sequence. Therefore, a more-stable protective group (R = OTPS) was chosen. The Konopelski research group synthesized all the fragments necessary for the psymberin (**3**) synthesis, but problems occurred during the coupling reactions. So far, no further results have been published.

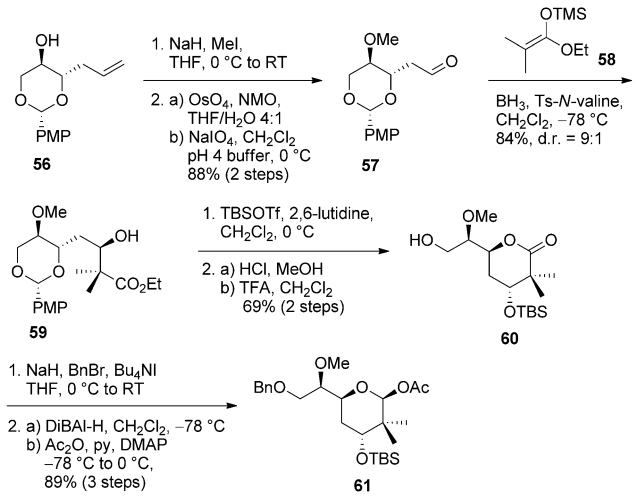


Scheme 10. Tetrahydropyran core synthesis by Konopelski and co-workers.[51]

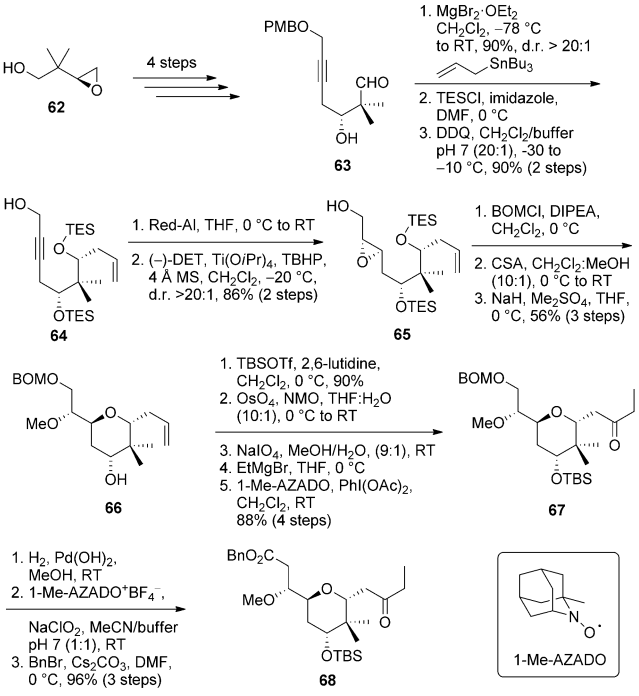
The tetrahydropyran synthesis by the Crimmins research group began with the well-known allyl compound **56**, which could be obtained in two steps from 2-deoxy-D-ribose. After methylation and oxidative cleavage of the double bond, aldehyde **57** was submitted to a Kiyoo aldol reaction with trimethylsilyl enol ether **58**. The chiral information resulted from an oxaborolidine catalyst which had been prepared in situ from borane and *N*-tosylated valine. Aldol product **59** was obtained in 84% yield and with a diastereoselectivity of 9:1 in favor of the isomer shown. The protecting groups were then switched and the cyclization to lactone **60** was induced by TFA (two steps, 69%). Lactone **60** was benzylated and then diastereoselectively reduced to the corresponding lactol with DiBAl-H. A final acetylation furnished tetrahydropyran **61** in 89% yield over the last three steps (Scheme 11).[52]

In 2011, Watanabe et al. published their total synthesis of psymberin (**3**).[53] To construct the tetrahydropyran unit they started from epoxide **62**, which could be synthesized from (−)-pantolactone, and converted it into aldehyde **63** in four steps and a total yield of 55% (Scheme 12). Aldehyde **63** was treated with allyltributylstannane to obtain the corresponding alcohol with a diastereomeric ratio of > 20:1 and 90% yield.

Having prepared alkine **64** in two steps, it was reduced to an alkene, which was epoxidized under Sharpless conditions.



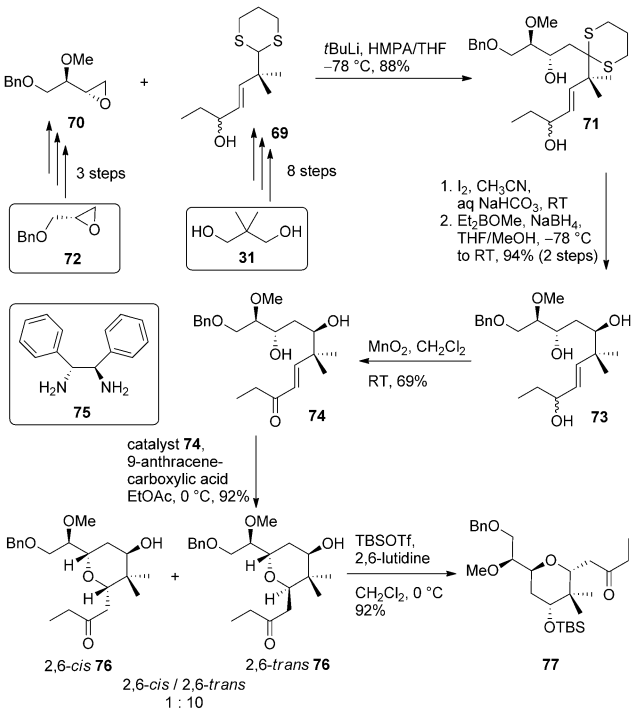
Scheme 11. Tetrahydropyran synthesis by Crimmins et al.[52]



Scheme 12. The synthetic approach towards the tetrahydropyran core by Watanabe et al.[53]

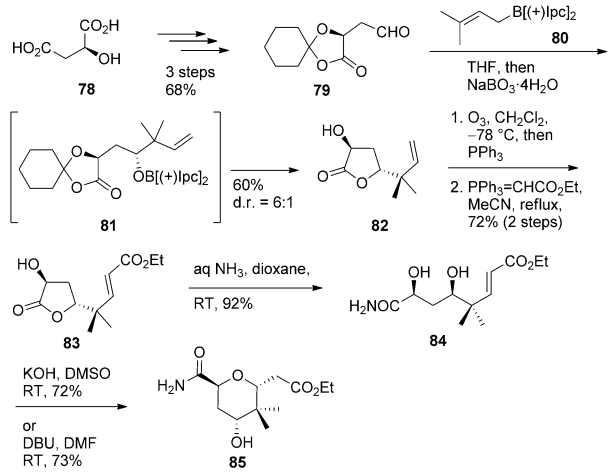
Epoxy alcohol **65** was obtained in 86% yield over two steps with a diastereomeric ratio of >20:1. A subsequent protection as a BOM ether and acid-catalyzed cyclization to the tetrahydropyran core was then carried out (along with TES cleavage). Afterwards, the product was methylated to obtain alkene **66**. The transformation to ketone **67** was achieved in five steps. The alkene **66** was first protected with a TBS group. The double bond was then dihydroxylated and oxidatively cleaved to generate the corresponding aldehyde, which was treated with ethylmagnesium bromide. Further oxidation with 1-methyl-AZADO/PhI(OAc)$_2$ provided ketone **67** in excellent yield. The last steps consisted of BOM cleavage, oxidation to the acid, and esterification with benzyl bromide to provide the desired coupling partner **68** in 96% yield over three steps.

For the construction of the tetrahydropyran unit, Byeon et al. added dithiane **69** to epoxide **70**, which led to diol **71**[54] (epoxide **70** was synthesized from (*S*)-glycidylic benzyl ether (**72**) in three steps; dithiane **69** had been prepared from 2,2-dimethylpropane-1,2-diol (**31**) in eight steps). Subsequent cleavage of the thio protecting group with iodine followed by stereoselective reduction delivered *syn*-diol **73**. Triol **73** was then oxidized at the allylic position to obtain ketone **74** in 69% yield. The innovative key step in the synthesis was an organocatalytic oxa-Michael addition. Having optimized the reaction conditions (9-anthracenecarboxylic acid in combination with diamine **75** proved to be best), tetrahydropyran **76** was synthesized in 92% yield and a diastereomeric ratio of 10:1 in favor of the desired 2,6-*trans* isomer. Final TBS protection of alcohol **76** led to ketone **77**, which was the desired coupling partner (Scheme 13).



Scheme 13. Tetrahydropyran synthesis by Byeon et al.[54]

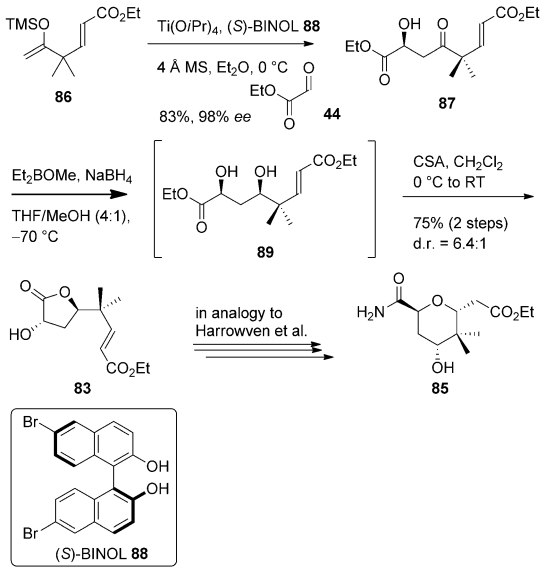
The tetrahydropyran synthesis of Harrowven and coworkers is described next (Scheme 14).[55] Starting from (*S*)-malic acid (**78**), aldehyde **79** could be synthesized in three steps (68% yield). Aldehyde **79** was then treated with Brown's allylborane **80** to obtain complex **81**, which was cyclized to lactone **82** after work-up and column chromatography. The reaction yielded **82** in 60% yield and a diastereomeric ratio of 6:1 in favor of the desired *trans* diastereomer



Scheme 14. Tetrahydropyran synthesis by Harrowven and co-workers.[55]

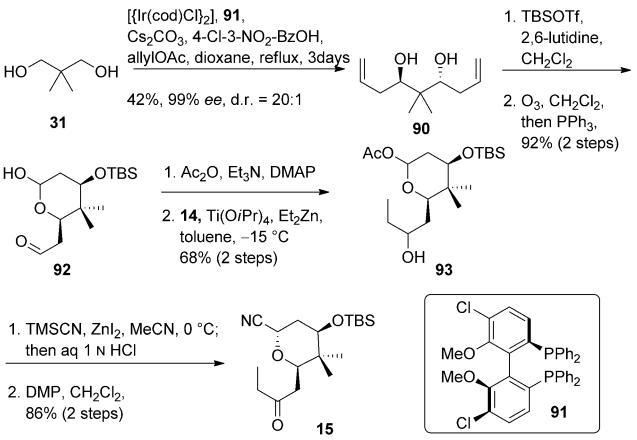
82. For the following steps it was necessary to first introduce an electron-withdrawing group and then carry out an oxidative cleavage of the double bond. The resulting aldehyde was treated in a Horner–Wadsworth–Emmons reaction to furnish lactone **83** in 72% yield. This lactone was opened with aqueous ammonia (→**84**, 92% yield) followed by a base-catalyzed Michael reaction. Tetrahydropyran **85** was obtained in 73% yield after separation from its diastereomers (crude product d.r. = 14:1). A total synthesis has not yet been reported.

Bielitza and Pietruszka also synthesized intermediate **83** by a different synthetic approach (Scheme 15).[56] They performed a highly enantioselective Mukaiyama-aldol reaction between silyl enol ether **86** and ethyl glyoxalate (**44**) and obtained aldol **87** in 83% yield and 98% *ee*. The chirality was obtained by using the chiral BINOL ligand **88**. In a two-step sequence (*syn* reduction (→**89**) and acid-catalyzed cyclization), aldol **87** could be transformed into lactone **83** in 75% yield and a diastereomeric ratio of 6.4:1. Lactone **83** can be transformed into tetrahydropyran **85** in an analogous manner as that used by Harrowven and co-workers.



Scheme 15. Approach towards the tetrahydropyran core **85** by Bielitza and Pietruszka.[56]

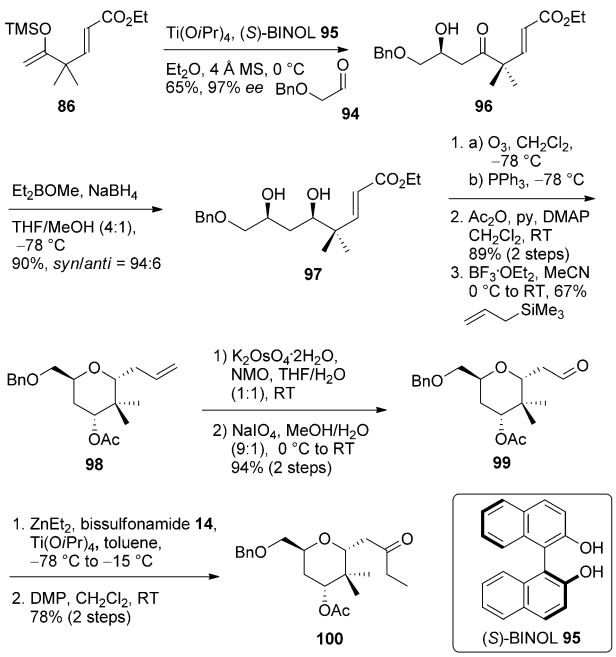
De Brabander and co-workers developed a second approach towards tetrahydropyran unit **15** (Scheme 16).[57]



Scheme 16. Second generation tetrahydropyran synthesis by De Brabander and co-workers.[57]

2,2-Dimethylpropane-1,3-diol (**31**) was converted into the C2-symmetrical diol **90** according to a procedure by Krische. This highly stereoselective double allylation was performed by using an iridium catalyst with chiral ligand **91** and allyl acetate. Product **90** was obtained in a moderate yield of 42%, but with an excellent enantiomeric excess of 99% and a diastereomeric ratio of 20:1. Monoprotection of diol **90** with a TBS group and a subsequent ozonolytic cleavage of both double bonds generated aldehyde **92** in 92% yield over two steps. The following steps (via alcohol **93**) were very similar to the ones from the first sequence published. This second route proved to be more effective.

In their second approach towards the tetrahydropyran core of psymberin (**3**) Bielitza and Pietruszka used 2-(benzyloxy)acetaldehyde (**94**) instead of ethyl glyoxalate (**44**) for the aldol reaction with silyl enol ether **86** to circumvent cyclization to the five-membered lactone. By using the chiral BINOL ligand **95**, aldol product **96** was obtained with an excellent $\geq$97% *ee*. The yield of the reaction was 65%. Aldol **96** was reduced under Prasad conditions to furnish diol **97** in high yield (90%) and with a diastereoselectivity of 94:6. Ozonolysis and double acetylation of diol **97** followed by subsequent allylation with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ provided tetrahydropyran core **98** in 60% yield over three steps. Alkene **98** was transformed to aldehyde **99** by dihydroxylation and oxidative cleavage. The nucleophilic addition of diethylzinc under the conditions reported by Kobayashi afforded an alcohol that was submitted to Dess–Martin oxidation to provide ketone **100** in 78% yield over two steps (Scheme 17).[58]



Scheme 17. Alternative approach towards the tetrahydropyran core of psymberin by Bielitza and Pietruszka.[58]

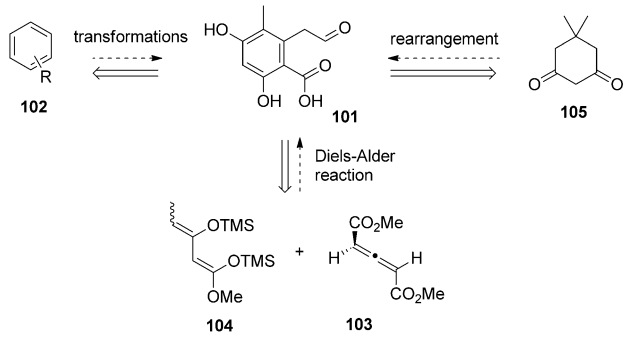
5. Syntheses of the Aromatic Unit

The dihydroisocoumarin unit of psymberin is characterized by its high substitution pattern. Such pentasubstituted dihydroisocoumarins are, of course, not commercially available and have to be synthesized by long synthetic routes. In principle, there are a number of methods that can be used for their construction.[59–77] However, the two phenolic hydroxy groups in particular cannot be introduced selectively at a late stage of the synthesis, which causes many of the above-cited methods to fail.

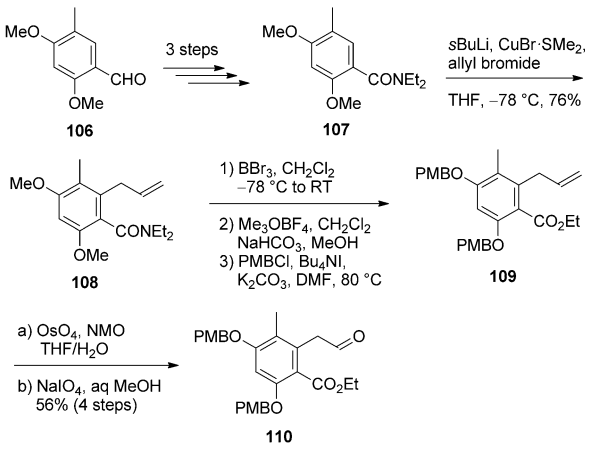
Some strategies have already been developed for the concerted synthesis of the dihydroisocoumarin unit of psymberin. The one that was used most often was the construction of aldehyde **101** as an intermediate from simple aromatic precursors. The aldehyde was mostly connected to the tetrahydropyran unit through an aldol reaction or by crotylation with concomitant oxidative cleavage of the double bond to obtain a homologous aldehyde. A subsequent cyclization furnished the dihydroisocoumarin unit. An alternative approach made use of the addition of the aromatic compound to an aliphatic aldehyde. For this, the benzyl anion was generated by deprotonation with a strong base. After this addition, the alkoxide that formed immediately closed the ring in situ.

Retrosynthetically, three different routes were pursued to obtain aldehyde **101** as a coupling partner: on the one hand aldehyde **101** could be synthesized starting from differently substituted aromatic molecules **102** by the introduction of substituents or on the other hand aldehyde **101** could be constructed by cycloaddition of allene dicarboxylate **103** and diene **104**. The third route was based on the acid-catalyzed rearrangement of dimedone (**105**) to the corresponding aromatic compound. The three strategies are illustrated in Scheme 18.

De Brabander and co-workers used the known aldehyde **106** as the starting material (Scheme 19).[46] After oxidation and amidation (→**107**) an *ortho*-lithiation/allylation sequence



Scheme 18. Retrosyntheses of the aromatic unit **101**.

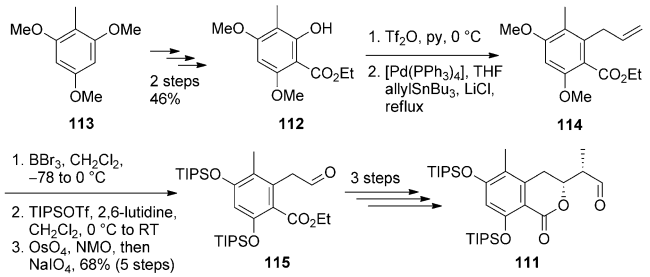


Scheme 19. Synthesis of aldehyde **110** by De Brabander and co-workers.[46]

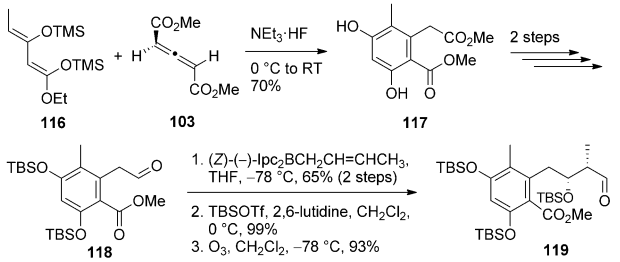
was performed (76% yield) to provide allyl compound **108**. Then protecting groups were switched, the amide function was converted into an ester (→**109**), and oxidative cleavage of the double bond furnished the PMB-protected aldehyde **110** ready for coupling.

The synthesis of aldehyde **111** started from the well-known phenol **112**, which was prepared in 46% yield over two steps from 2,4,6-trimethoxytoluene (**113**; Scheme 20). Huang et al. formed the corresponding triflate, which was then coupled in a Stille reaction to allyltributylstannane (→**114**). Aldehyde **115** was obtained after deprotection and cleavage of the diol. Next, a Brown crotylation and two more reactions were performed to build up dihydroisocoumarin **111**, which was used for the following coupling reaction.[37]

An elegant approach was used by the Floreancig research group (Scheme 21).[47] The approach was based on the cycloaddition of allene dicarboxylate **103** (available in one



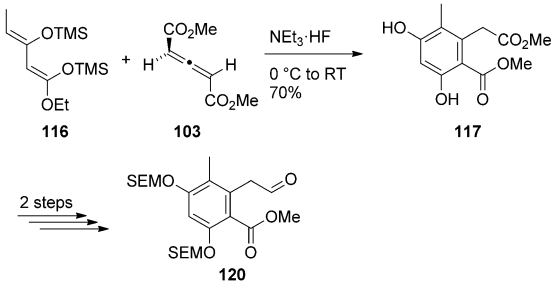
Scheme 20. Synthetic steps towards aldehyde **111** by Huang et al.[37]



Scheme 21. A cycloaddition approach towards the aromatic unit.[47]

step from acetone 1,3-dicarboxylate) and bis(silyl enol ether) **116** (available in two steps from 3-oxopentanoic acid methyl ester) to construct arene **117** in 70% yield by using HF-triethylamine. This step was based on an earlier study by Langer and Kracke.[78] After protection with TBS groups and chemoselective reduction, aldehyde **118** was obtained, which was submitted to a Brown crotylation, deprotection, and ozonolysis. This sequence furnished aldehyde **119** as the coupling unit in 60% yield over the last four steps.

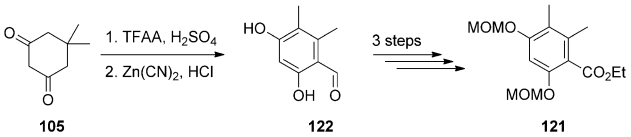
In analogy to the approach used by Floreancig and co-workers, the Smith research group synthesized the aromatic coupling unit (Scheme 22). They obtained aldehyde **120** in two steps. In principle, the choice of protecting group was the only difference (TBS versus SEM).[48]



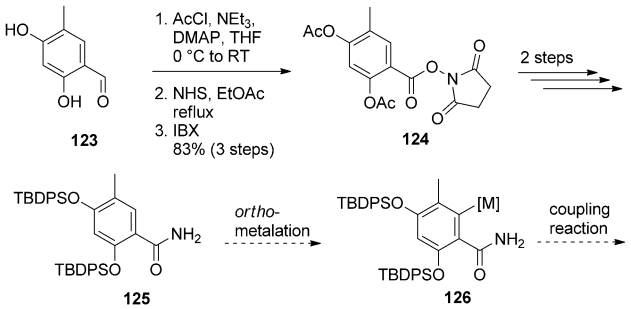
Scheme 22. Synthesis of the aromatic unit by Smith et al.[48]

Next, the syntheses of Shangguan et al.[47] and the Konopelski research group[51] are introduced. Shangguan et al. needed ester **121**, which was deprotonated in the benzylic position with LDA and then added to an aldehyde. To do so, dimedone (**105**) had been transformed into aldehyde **122** by an acid-catalyzed rearrangement and formylation. Product **122** was then protected with MOM groups, oxidized, and transformed into ester **121** (Scheme 23).

Konopelski and co-workers began their synthesis with resorcin **123** (Scheme 24). It was acetylated, oxidized and



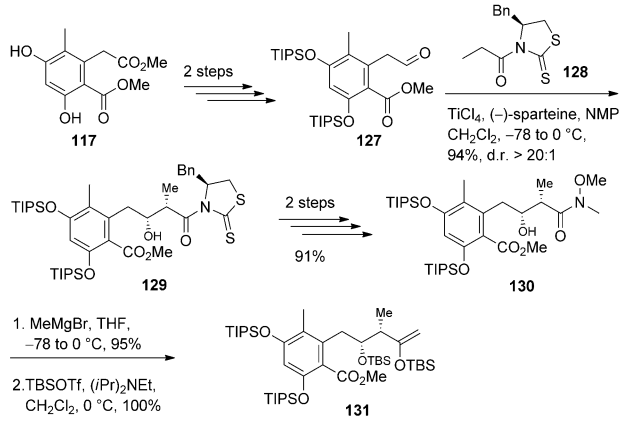
Scheme 23. Synthesis of aromatic unit **121** by Shangguan et al.[47]



Scheme 24. Approach towards the synthesis of the aromatic unit of psymberin by Konopelski and co-workers.[51]

transformed into the activated ester **124** (83% yield over 3 steps). The ester was then converted into amide **125** in two more steps. Nucleophilic attack of the *ortho*-metalated amide **126** at the aldehyde group led to coupling to the tetrahydropyran unit. As a consequence of problems experienced with the following ring closure, the strategy needed to be revised.

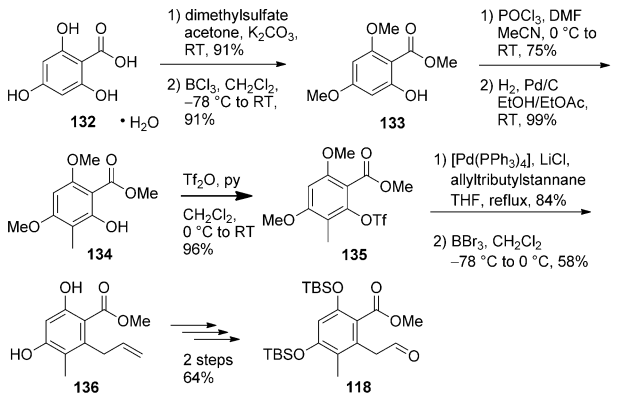
Diester **117** was synthesized according to a literature method and was then used as the starting material in the synthesis by Crimmins et al. (Scheme 25).[52] It was converted into TIPS-protected aldehyde **127**. For the following *syn*-selective aldol reaction they used thiazolidinthione **128** to



Scheme 25. Synthetic steps towards enol ether **131** by Crimmins et al.[52]

obtain product **129** in 94% yield and with a diastereoselectivity of > 20:1. After conversion into Weinreb amide **130** (91% yield) in two steps, it could be further treated with methylmagnesium bromide to obtain the corresponding ketone in 95% yield. Aromatic compound **131** could be synthesized quantitatively after formation of the silyl enol ether.

Bielitza and Pietruszka used phloroglucinol carboxylic acid hydrate (**132**) as the starting material for their synthesis of aldehyde **118** (Scheme 26).[58] After permethylation and

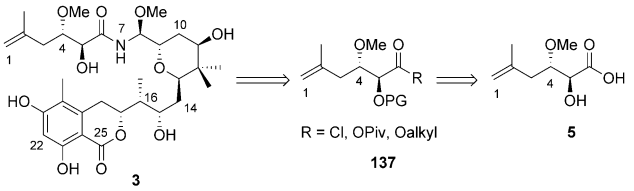


Scheme 26. Synthesis of aldehyde **118** by Bielitza and Pietruszka.[58]

regioselective monodeprotection, phenol **133** could be obtained in 83% yield over two steps. The methyl group in the 3-position was introduced in a two-step sequence by using a Vilsmeier–Haack formylation followed by catalytic hydrogenation. Product **134** was obtained in 74% yield. The allylic side chain was introduced by a Stille reaction from triflate **135**, which had been synthesized previously in 96% yield under standard conditions. The corresponding cross-coupling product was obtained in 84% yield and subjected to a deprotection reaction using boron tribromide. The yield of 58% for **136** was moderate because of the formation of some by-products. Resorcin **136** was protected with TBS groups, and the double bond was oxidatively cleaved to furnish aldehyde **118** in 64% yield over the last two steps.

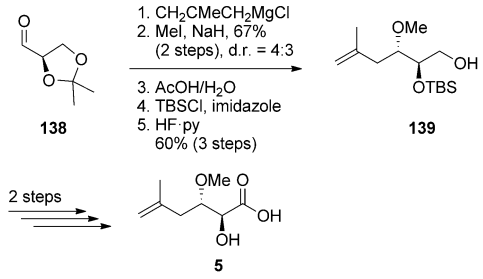
6. Syntheses of Psymberic Acid

The structure elucidation of psymberin (**3**) by Crews and co-workers was based on various multidimensional ^{1}H and ^{13}C experiments as well as on the correlations of chiroptic data with those of other pederins. However, the configuration at C4 was not solved. It was Kiren and Williams who synthesized the C4/C5-*anti* and -*syn* model compounds to elucidate the correct structure and concluded from crystal-structure data that the *anti*-configuration was correct. In the following, the different synthetic approaches are described that led to the construction of psymberic acid (**5**) and derivatives **137** thereof (Scheme 27). Many different retrosynthetic approaches were developed to construct psymberic acid (**5**). The most used retrosynthetic disconnection was between C3 and C4, but others (between C4 and C5 or between C2 and C3) were also feasible.



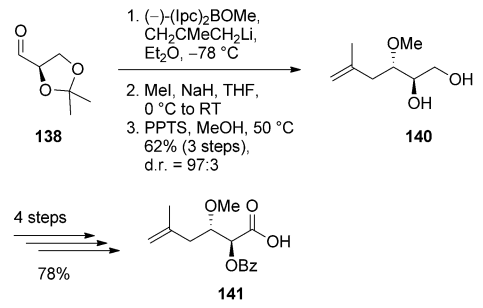
Scheme 27. Retrosynthesis towards psymberic acid (**5**).

Kiren and Williams used aldehyde **138** as the starting material, which is available from mannitol in two steps. Aldehyde **138** was treated with methallylmagnesium chloride followed by methylation to give the product in 67% yield but a low diastereomeric ratio (4:3). A protecting-group switch then furnished primary alcohol **139**, which was oxidized to psymberic acid (**5**) in two steps (Scheme 28). Acid **5** was converted into its corresponding diisopropylamide for crystal-structure analysis.[22]



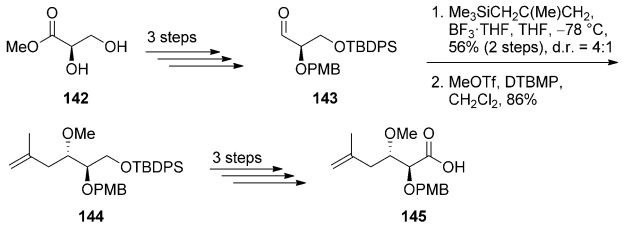
Scheme 28. The psymberic acid synthesis of Kiren and Williams.[22]

Only a few weeks later De Brabander and co-workers published the first total synthesis of psymberin (**3**).[46] Their synthetic strategy was similar to the one above. They used an asymmetric methallylation, which provided the product in an excellent diastereomeric ratio of 97:3 (Scheme 29). The next steps consisted of methylation, protecting-group manipulation (→**140**), and a two-step oxidation to obtain acid **141**. From their total synthesis of psymberin (**3**) and its C4, epimer as well as comparison of the analytical data with that of the isolated natural product they were able to elucidate the correct configuration.



Scheme 29. Synthesis of protected psymberic acid **141** by De Brabander and co-workers.[46]

Almost simultaneously Floreancig and co-workers proved the absolute and relative configuration of psymberic acid by natural product degradation and comparison with synthetic material.[79] Their synthesis began with D-glyceric acid methyl ester (**142**), which could either be synthesized from serine by diazotization or by hydrolytic kinetic resolution. Aldehyde **143** was isolated after introduction of the protecting groups and reduction of the ester group. The addition of methallyl(trimethyl)silane under Felkin–Anh control (d.r. = 4:1) then furnished an alcohol, which was methylated to provide ether **144**. After three more synthetic steps, Floreancig and co-workers obtained the PMB-protected psymberic acid **145** (Scheme 30).

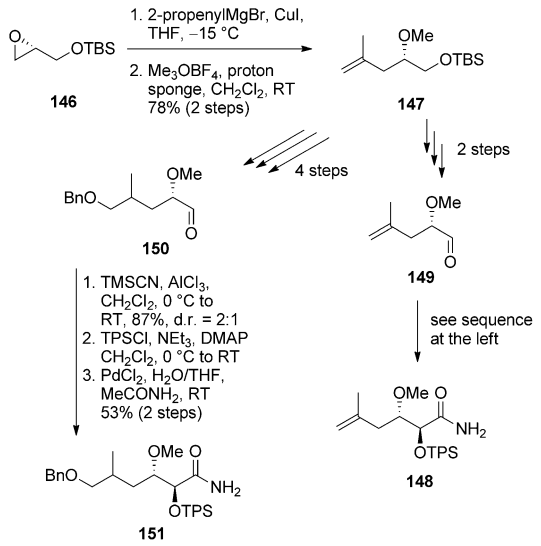


Scheme 30. Synthesis of PMB-protected psymberic acid **145** by Floreancig and co-workers.[79]

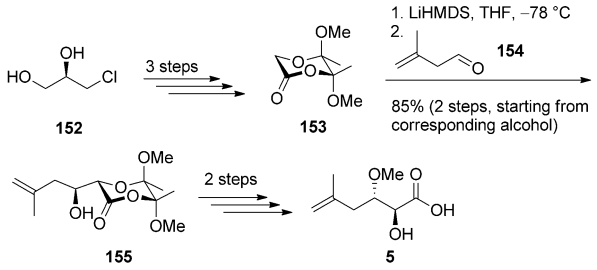
Having synthesized epoxide **146** according to a literature method, Huang et al. opened it with 2-propenylmagnesium bromide and methylated the corresponding alcohol directly afterwards (→**147**).[37] Unfortunately, they could not use psymberic acid or its amide **148** (via aldehyde **149**) for the $PhI(OAc)_2$-triggered cyclization because of a side reaction on the terminal double bond. Therefore, they synthesized aldehyde **150** from alkene **147** in four steps. TMSCN was subsequently added (87% yield and a diastereomeric ratio of 2:1). After protection as a TPS ether, the nitrile was hydrolyzed to amide **151** with palladium(II)chloride in a mixture of water and THF. The steps towards the synthesis of **148** were performed in analogy to those before for amide **151** (Scheme 31).

Pietruszka and co-workers used a highly diastereoselective aldol reaction (no *syn* product could be detected) to form the *anti*-configured product (Scheme 32).[80] They converted diol **152** into the BDA-protected glycolic acid **153** according to the procedure by Ley et al.,[81,82] and then treated it with aldehyde **154** to obtain aldol **155**. The free psymberic acid (**5**) was obtained after methylation and hydrolysis.

Furthermore, the same research group developed a unique chemoenzymatic strategy.[83] Starting from racemic, BDA-protected glycolic acid, they performed an aldol and methylation reaction. The free hydroxy group needed to be protected as a PMB ether (→**156**) for the enzymatic, kinetic resolution. The ether was treated with different hydrolases (Table 2), and the best results were obtained with esterase BS3 (89% *ee* for PMB-protected acid **145** and an *E* value of 67) and esterase 001 (98% *ee* for **145** and an *E* value of >100). This approach was used later by the Floreancig research group for their total synthesis of psymberin (**3**).

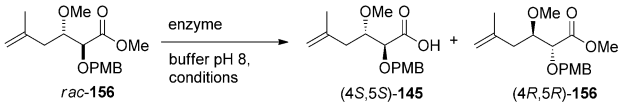


Scheme 31. Synthetic route towards amide **151** by Huang et al.[37]



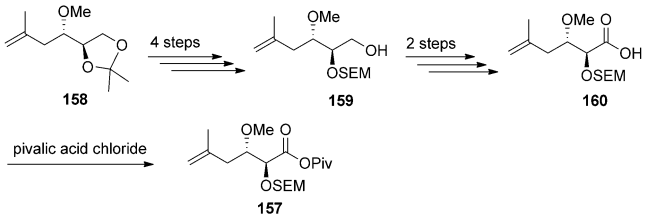
Scheme 32. Psymberic acid synthesis by the Pietruszka research group.[80]

Table 2: Chemoenzymatic approach used by Pietruszka and Simon.[83]



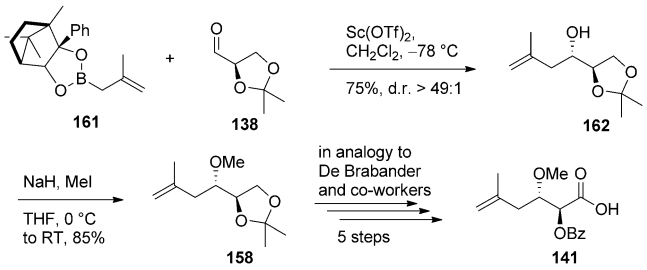
Enzyme	*T* [°C]	*t* [h]	*ee* (4*S*,5*S*)-**145**	*ee* (4*R*,5*R*)-**156**	Conv.	*E* value
esterase BS3	30	26	89%	96%	52%	67
esterase BS3	40	16	>83%	>95%	53%	48
esterase 001	25	65	98%	>94%	49%	>100

The synthesis of SEM-protected psymberic acid anhydride **157** by Smith et al. started from acetonide **158**, which was known from the De Brabander synthesis. Acetonide **158** was converted into SEM-protected alcohol **159** in four steps. The alcohol **160** was then oxidized to an acid in two steps followed by conversion into the mixed anhydride **157** by using pivalic acid chloride. Anhydride **157** was used in the coupling reaction with the tetrahydropyran core later in the synthesis (Scheme 33).[48]



Scheme 33. Psymberic acid synthesis by Smith et al.[48]

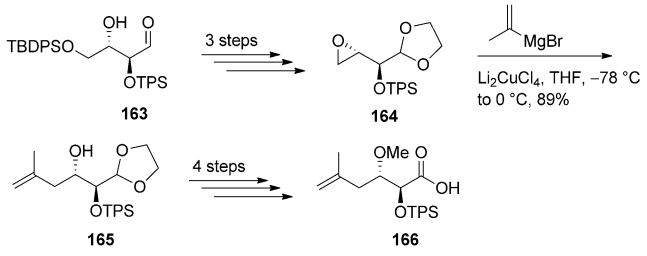
The Hall research group[49] used a similar strategy to that of Kiren and Williams and of De Brabander and co-workers. The idea was to use different methallylboronic esters under various conditions (Scheme 34). The substrate-induced dia-



Scheme 34. Synthesis of psymberic acid **141** by the Hall research group.[49]

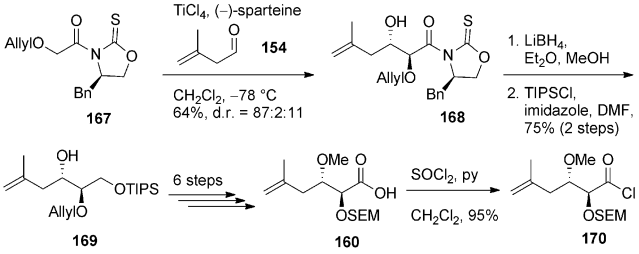
stereoselectivity was low (5:4) when using achiral boronic esters. This was the reason why they used the chiral camphordiol boronate **161** to obtain the product through a double induced diastereoselectivity. The reaction worked smoothly and provided product **162** in 75% yield and a ratio of >49:1 in favor of the *anti*-product. Alcohol **162** was then methylated (→**158**) and converted into Bz-protected psymberic acid **141**, as De Brabander and co-workers had done previously.

Another approach was published by Konopelski and co-workers (Scheme 35).[51] They began with MacMillan's aldehyde **163**, which could be obtained in 93% *ee* and with a diastereomeric ratio of 9:1 by a proline-catalyzed homo-aldol reaction of 2-(*tert*-butyldiphenylsilyloxy)acetaldehyde.[84,85] Aldehyde **163** was converted in three steps into epoxide **164**, which was opened with 2-propenylmagnesium bromide (→**165**). Four more steps (methylation, deprotection, double oxidation) were necessary to provide TPS-protected psymberic acid **166**.



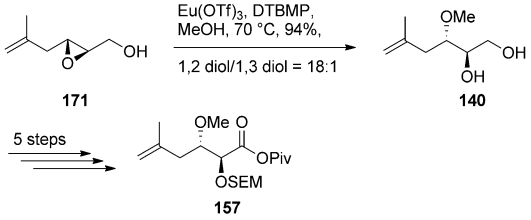
Scheme 35. Approach towards psymberic acid **166** by Konopelski and co-workers.[51]

Crimmins et al. constructed the two stereogenic centers of psymberic acid by performing an asymmetric *anti*-selective aldol reaction with a chiral oxazolidinthione. Glycol **167** was treated with aldehyde **154** to afford aldol product **168** in 64% yield and a diastereomeric ratio of 87:2:11. Subsequent cleavage of the auxiliary and regioselective TIPS protection furnished alcohol **169**, which was converted into SEM-protected psymberic acid **160** (protection-group manipulation, oxidation) in six steps. Conversion into its acid chloride **170** was possible by using thionyl chloride (Scheme 36).[52]



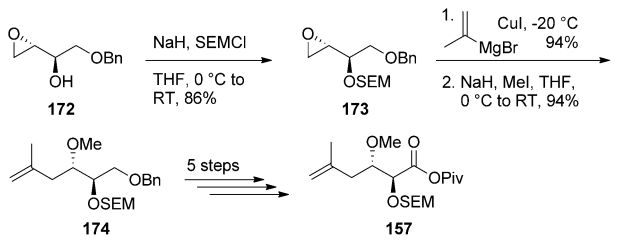
Scheme 36. Synthesis of psymberic acid by Crimmins et al.[52]

Watanabe et al. also needed SEM-protected psymberic acid anhydride **157** for their total synthesis of psymberin (**3**).[53] Therefore, they started off with epoxy alcohol **171** and opened it under Lewis acid catalysis with methanol (→**140**). After extensive optimization, they found that europium trifluoromethanesulfonic acid provided the best results. By adding di-*tert*-butyl-4-methylpyridine they could reduce the amount of Lewis acid to 20 mol% without lowering the selectivity (>20:1 versus 18:1). The following steps consisted of protection group chemistry, a one-pot oxidation of the alcohol to an acid, and a conversion into pivaloate **157** (Scheme 37).



Scheme 37. The approach towards **157** by Watanabe et al.[53]

Finally, the synthesis route of Byeon et al. is described (Scheme 38).[54] A SEM group was introduced (→**173**) into epoxide **172**, and the epoxide function was opened with isopropenylmagnesium bromide and the resulting alcohol methylated (→**174**). The yield was 88% over the two steps. The last five steps consisted of the deprotection of the primary hydroxy group and further transformation, in analogy to the approach used by Smith et al. to obtain mixed anhydride **157**.



Scheme 38. Synthesis of **157** by Byeon et al.[54]

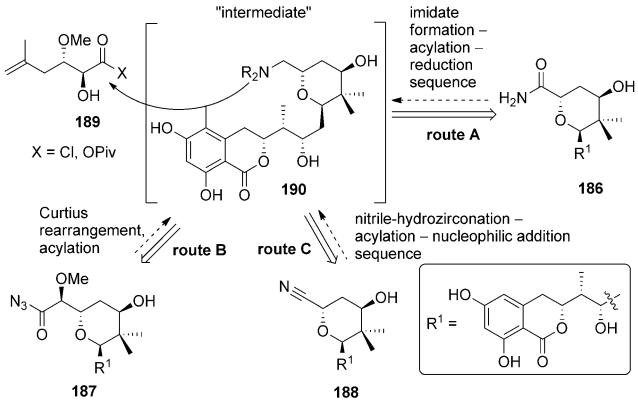
7. Coupling Reactions and Total Syntheses

The most prominent retrosynthetic approach of psymberin (**3**) was the disconnection into three subunits. This section describes the coupling reactions between the tetrahydropyran core and the aromatic compound to obtain compound **175** as well as the coupling reactions between **175** and psymberic acid derivatives. Finally, the approaches will be shown that varied significantly from the ones shown above.

As described before, the three fragments, psymberic acid, tetrahydropyran unit, and the aromatic unit were coupled in the same order, which means the coupling of tetrahydropyran units **176**–**180** with the aromatic compounds **181**–**185** followed by coupling to the activated psymberic acid. The reason for that probably lies in the instability of the *N*,*O*-hemiaminal structure, which proved to be labile in contact with bases, acids, and harsh reaction conditions. To avoid such decomposition, the construction of the hemiaminal was done at a late stage of the synthesis.

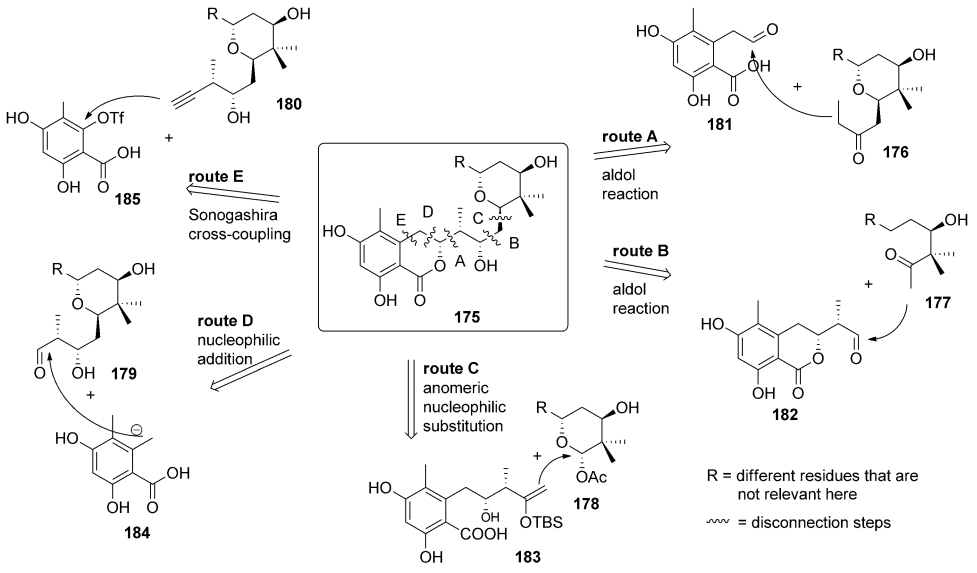
First, the synthesis of compound **175** will be discussed (Scheme 39). The C–C bond-forming reaction that has widely been used to connect tetrahydropyran and aromatic unit is the aldol reaction. This connection was done in either the A or B position. Route C was based on a nucleophilic substitution reaction of silyl enol ether **183** to the anomeric carbon atom of acetate **178**. The access to all of the corresponding coupling partners was described in Sections 5 and 6. The coupling reaction between aromatic compound **184** and aliphatic aldehyde **179** (D position) is also the topic of this section. This strategy of C–C bond formation by adding a benzyl anion to the carbonyl group of **179** was used by Shangguan and Williams. As an alternative, the aromatic compound **185** could also be connected to alkyne **180** (route E) by a cross-coupling reaction.

After generating the tetrahydropyran fragments **186**–**188** and the psymberic acid derivative **189**, the research groups investigated the coupling reactions. In the following the strategies towards the *N*,*O*-hemiaminal are discussed (Scheme 40). In one variant, amide **186** was converted into the corresponding methyl imidate. This was then acylated by the activated psymberic acid **189** (route A). Afterwards the *N*-acyl aminal had to be reduced to obtain the natural product. In another variant, acid azides **187** were used in a Curtius rearrangement and directly coupled to the activated psymberic acid **189** (route B). Another approach used nitrile **188** for the coupling reaction (route C). After hydrozirconation and acylation with **189**, methanol was added to form the *N*,*O*-hemiaminal. Here the term intermediate **190** was used as a general compound for simplification because of the various approaches described above.



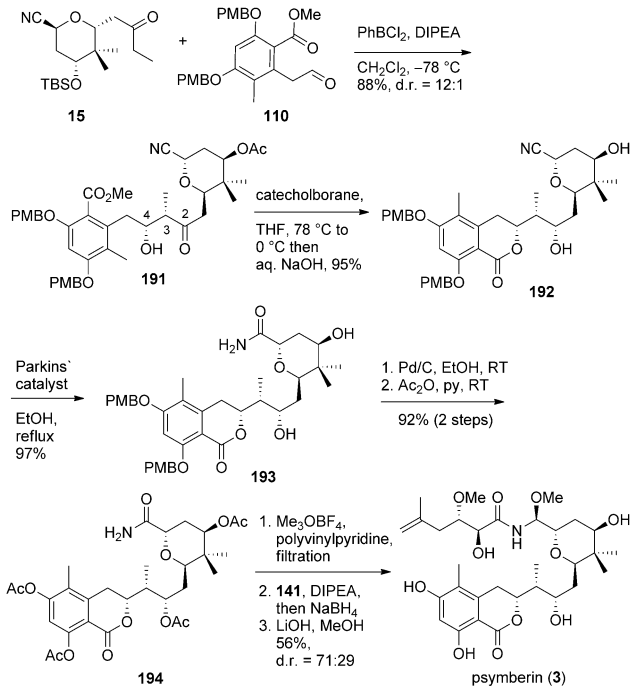
Scheme 40. Different approaches towards the *N*,*O*-hemiaminal structure of psymberin (**3**).

The individual syntheses are now described in detail by presenting the coupling reactions and the most important steps towards the natural product. This is done in the chronological order of the publications.



Scheme 39. Overview of the coupling reactions between the tetrahydropyran core and the aromatic unit.

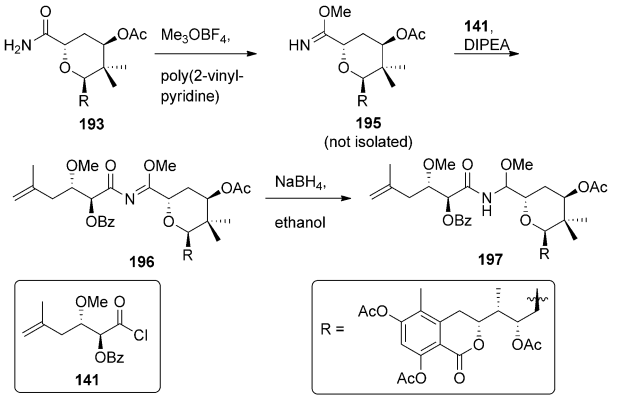
The first synthesis that is described is the impressive total synthesis of psymberin (**3**) by De Brabander and co-workers in 2005 (Scheme 41).[46] Their approach, based on a *syn*-selective aldol reaction between ketone **15** and aldehyde **110**, laid the basis for other total syntheses. Generating the *Z*-



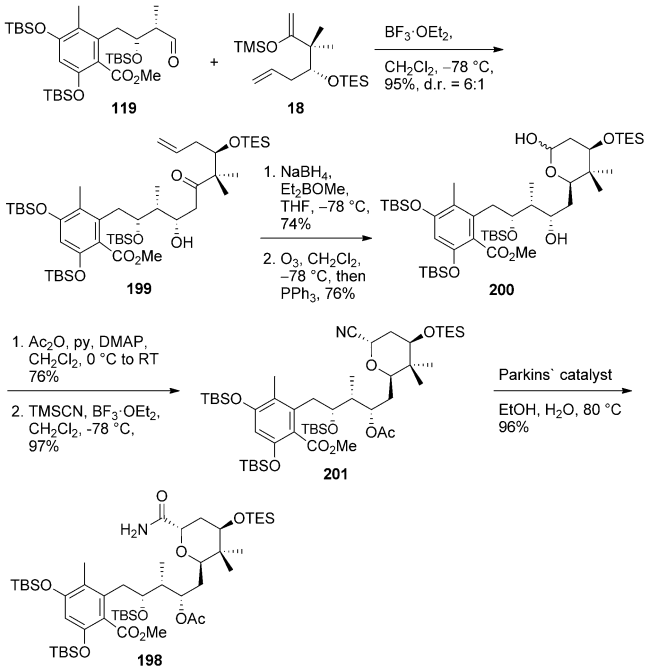
Scheme 41. Total synthesis of psymberin (**3**) by De Brabander and co-workers.[46]

enolate in a highly selective manner controlled the *syn*-relationship at C3 and C4. The 1,4-stereoinformation was induced by the β-alkoxy substituent as Evans and Calter had reported earlier in their studies.[86] The C–C coupling reaction was performed in 88% yield and with a diastereomeric ratio of 12:1. Afterwards, the aldol product **191** was reduced with catecholborane to selectively form the diol, which spontaneously cyclized to dihydroisocoumarin **192** in a high yield of 95%. The nitrile group could be hydrolyzed in the presence of the Parkins catalyst to amide **193** with concomitant protection-group switch from PMB to acetate (→**194**). The synthesis was completed by the formation of methyl imidate **195** by using the Meerwein salt and basic conditions (for more details see Scheme 42). The reaction proved to be difficult to perform and the use of immobilized poly(vinyl-2-pyridine) as the base was essential. Then, imidate **195** was acylated with Bz-protected psymberic acid chloride **141**. The product **196** was first reduced (→**197**) and then hydrolyzed to furnish psymberin (**3**) in 56% yield and with a diastereoselectivity of 71:29. Thus, the first total synthesis was completed within about one year after the structure of psymberin (**3**) had been published!

In 2005 Rech and Floreancig published the synthesis of the N7–C25 fragment **198** of psymberin (**3**; Scheme 43).[46] Enol ether **18** and aldehyde **119** were submitted to



Scheme 42. Mechanistic view of the coupling reaction between the tetrahydropyran core **193** and psymberic acid chloride **141**.

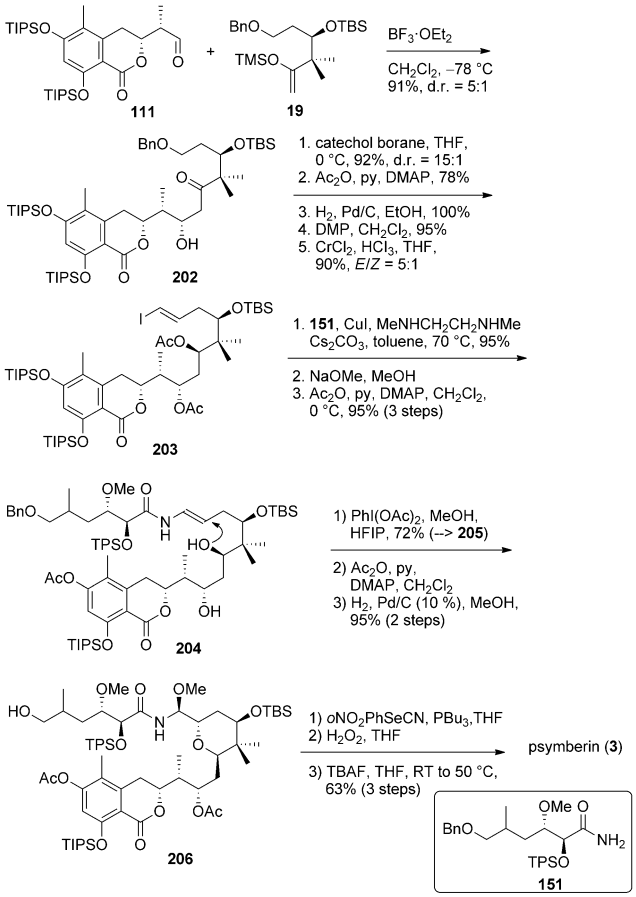


Scheme 43. The synthesis of the N7–C25 fragment **198** of psymberin (**3**) by Rech and Floreancig.[46]

a Mukaiyama aldol reaction with boron trifluoride etherate used as the Lewis acid. They isolated aldol product **199** in 95% yield and with a diastereoselectivity of 6:1. It was followed by a reduction and an ozonolysis to form lactol **200** in 56% yield over two steps. Lactol **200** was acetylated and submitted to an anomeric substitution by a cyanide ion to furnish nitrile **201**, which could be hydrolyzed with the Parkins catalyst. Fragment **198** was isolated in 71% yield over three steps. These initial studies laid the foundation for the total synthesis published in 2011.

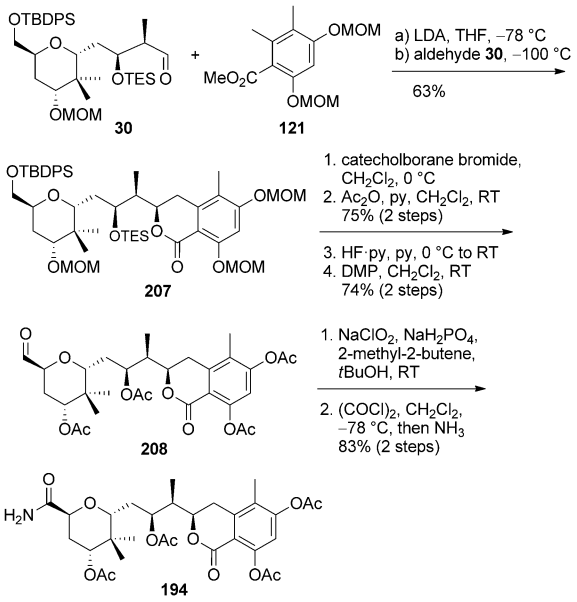
Huang et al. continued their unique synthetic approach by treating silyl enol ether **19** with aldehyde **111** in a Mukaiyama aldol reaction. Aldol product **202** could be reduced in a *syn* fashion by applying catecholborane followed by acetylation. Then they cleaved the benzyl protecting group to obtain an

alcohol, which was oxidized with the Dess–Martin reagent to the corresponding aldehyde. The latter was submitted to a Takai olefination to generate vinyl iodide **203**. This iodide **203** was coupled to amide **151** in the presence of a Cu^{I} catalyst to furnish an *N*-acylamine in an excellent yield of 95%. Cleavage of all the acetate groups was accompanied by an unwanted cleavage of the TIPS group. However, regioselective introduction of an acetate group delivered **204**, which was then submitted to a $PhI(OAc)_2$-triggered oxidative cyclization to construct the tetrahydropyran core.[37,87] The ring closure was successful and product **205** was obtained in 72% yield. Huang et al. needed to manipulate the protection groups and then obtained alcohol **206**. The final steps consisted of the construction of the terminal double bond by applying 2-nitrophenyl selenocyanate and hydrogen peroxide. Global deprotection with tetrabutylammonium fluoride provided the natural product (Scheme 44).



Scheme 44. The total synthesis of psymberin (**3**) by Huang et al.[37]

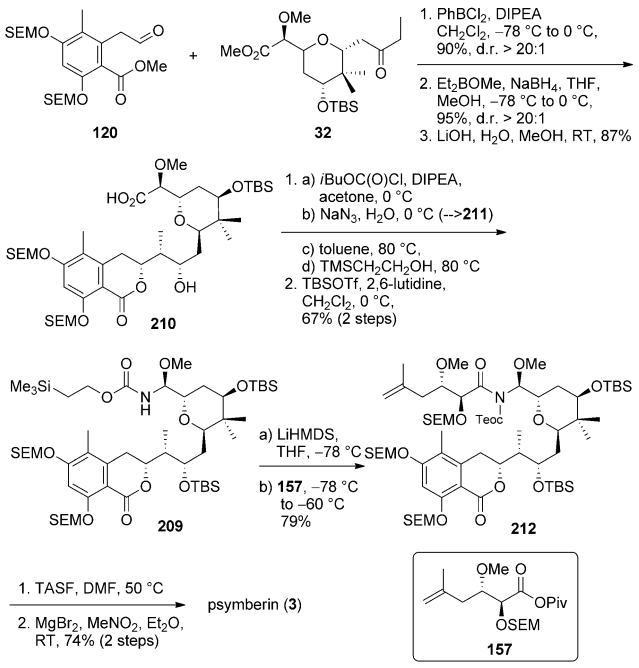
Shangguan et al. connected tetrahydropyran **30** and aromatic compound **121** by nucleophilic addition of the benzyl anion of derivative **121**, generated by deprotonation with LDA, to aldehyde **30**. The addition product cyclized spontaneously, forming dihydroisocoumarin **207**. The diastereoselectivity was 3:1 in favor of the desired isomer. The cyclization was followed by protection-group manipulation and oxidation to generate aldehyde **208** in four steps and a total yield of 56%. The latter was oxidized to its corresponding acid, which was then transformed into amide **194** (Scheme 45).[47] Compound **194** was identical that from the De Brabander synthesis.



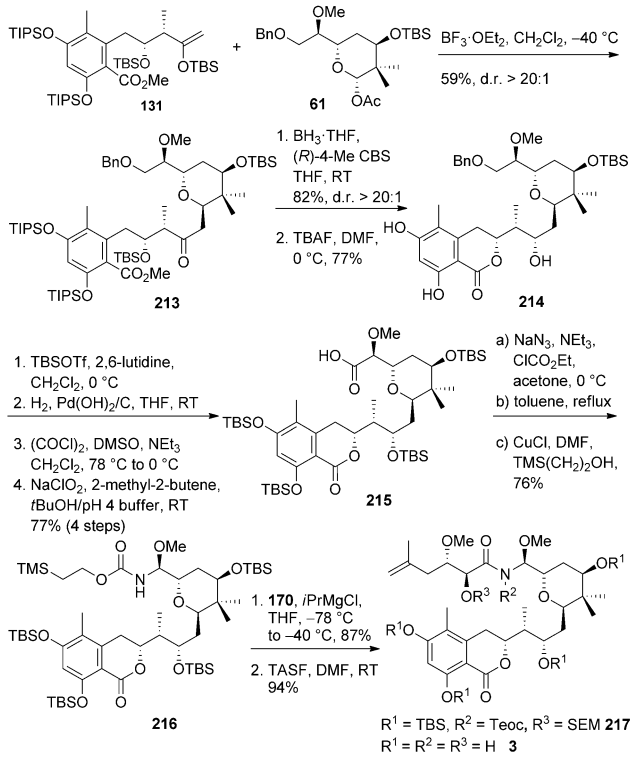
Scheme 45. Formal synthesis by Shangguan et al.[47]

Smith et al. developed an innovative approach for the coupling of fragment **209** with activated psymberic acid **157**. The key step towards the synthesis was a Curtius rearrangement with concomitant acylation. First, ketone **32** and aldehyde **120** were connected in an aldol reaction. This afforded product in 90% yield and >20:1 diastereoselectivity. Second, a *syn* reduction under Prasad conditions and an ester hydrolysis were conducted. Then, the corresponding acid **210** was transformed into its mixed anhydride followed by formation of an acid azide (→**211**). The latter underwent rearrangement when heated to form an isocyanate, which was treated with 2-trimethylsilylethanol to form a carbamate in situ. After protecting it with a TBS group, carbamate **209** was acylated with psymberic acid **157** in 79% yield (→**212**). The deprotection of all the silyl groups was done in a two-step sequence with TASF and $MgBr_2$, which provided psymberin (**3**) in 74% yield over the last two steps (Scheme 46).[48]

Crimmins et al. coupled silyl enol ether **131** to acetal **61** (Scheme 47). Boron trifluoride etherate was used as the catalyst and product **213** was obtained in 59% yield and an excellent diastereomeric ratio of >20:1. The selectivity was explained by a pseudoaxial addition of the silyl enol ether to the in situ formed oxocarbenium ion. The corresponding diol was subsequently obtained by CBS reduction and was then cyclized to dihydroisocoumarin **214** (after deprotection). The benzyl protecting group was cleaved by reduction to furnish an alcohol, which was oxidized to acid **215**. After formation of the corresponding acid azide and Curtius rearrangement, the isocyanate was treated with 2-trimethylsilylethanol to afford carbamate **216**. For the following acylation carbamate **216** was



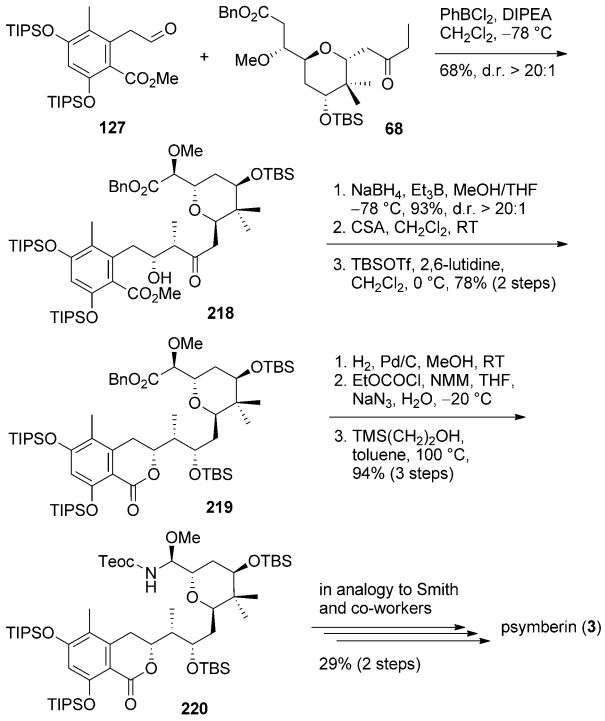
Scheme 46. Total synthesis of psymberin (**3**) by Smith et al.[48]



Scheme 47. Total synthesis of psymberin (**3**) by Crimmins et al.[52]

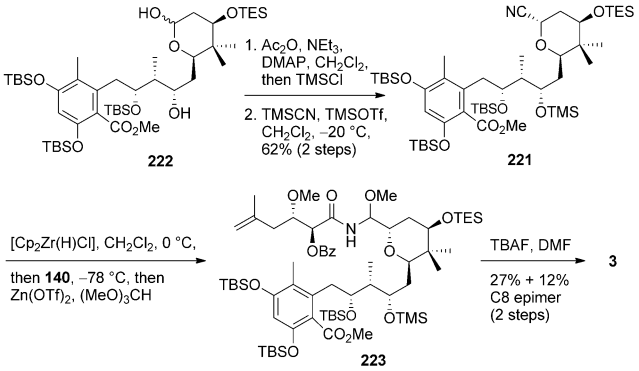
deprotonated with isopropylmagnesium chloride and then coupled to **170** to give amide **217** in 87% yield. After cleavage of all the silyl groups with TASF, psymberin (**3**) was obtained in 94% yield.[52]

Watanabe et al. also used an aldol reaction for the coupling of aldehyde **127** and ketone **68**, which yielded aldol **218** in 68% yield (diastereomeric ratio >20:1).[53] After Prasad reduction, the corresponding *syn*-diol was cyclized to the dihydroisocoumarin by using CSA and then protected with TBS groups (→**219**). The following steps were similar to the ones used by the Smith research group. The formation of the acid azide, Curtius rearrangement, and addition of TMS-ethanol furnished protected amine **220**. This was acylated with **157** to complete the total synthesis. Psymberin (**3**) was isolated in 27% yield over the last five steps (Scheme 48).

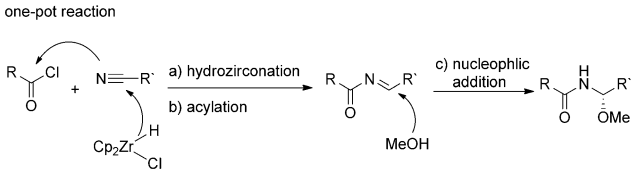


Scheme 48. Approach towards psymberin (**3**) by Watanabe et al.[53]

The studies on the total synthesis of psymberin (**3**) by the Floreancig research group were concerned with a different strategy for the coupling of the tetrahydropyran fragment and the activated psymberic acid.[35] They performed an impressive one-pot coupling reaction (see Schemes 49 and 50) on the basis of preliminary studies from their group[88–91] and from Erker et al.[92] as well as Maraval et al.[93] This effective procedure enabled Floreancig and co-workers to use it as a flexible, diverse approach towards the synthesis of various related compounds, for example, pederin (**1**) and different analogues. To synthesize nitrile **221**, they used their fragment synthesis described above to obtain lactol **222** (Scheme 49). After acetylation and anomeric substitution by cyanide, the nitrile compound **221** was obtained. Then the hydrozirconation/acylation/addition sequence (for a mechanistic view see Scheme 50) was performed to furnish product **223**, which after deprotection provided psymberin (**3**) in 27% yield (+12% C8 epimer). Initial studies towards that sequence with methanol generated the product, but with the unfavorable diastereoselectivity (1:3) at C8. The addition of magnesium



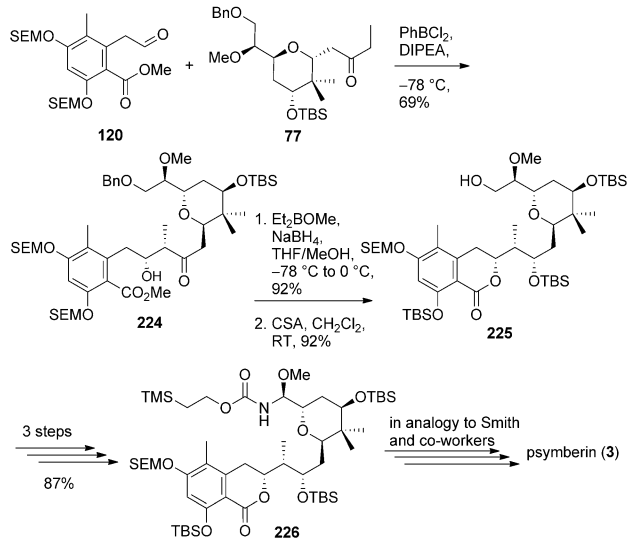
Scheme 49. Total synthesis by Floreancig and co-workers.[35]



Scheme 50. The hydrozirconation/acylation/addition sequence in detail.

perchlorate altered the selectivity (3:1), but caused the yield to deteriorate. Finally, a combination of orthoformic acid methyl ester (as the source of methanol) and zinc(II) triflate afforded the best results (27% psymberin (**3**) and 12% C8-*epi*-psymberin (C8-*epi* **3**)).

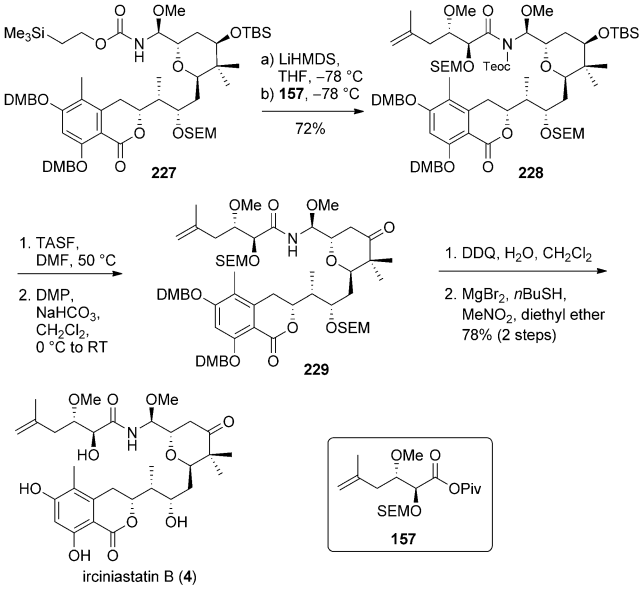
The final steps of the total synthesis of Byeon et al. are shown in Scheme 51.[54] Clearly, the synthesis shows great resemblance to the ones used by the research groups of Smith, Crimmins, and Watanabe. An aldol reaction was used to couple aldehyde **120** to ketone **78** to obtain product **224**. Then



Scheme 51. The synthetic approach towards psymberin (**3**) by Byeon et al.[54]

syn reduction, cyclization (→**225**), oxidation, and a Curtius rearrangement were used to furnish **226**. The final coupling between psymberic acid **157** and compound **226** was conducted in analogy to Smith's synthesis.

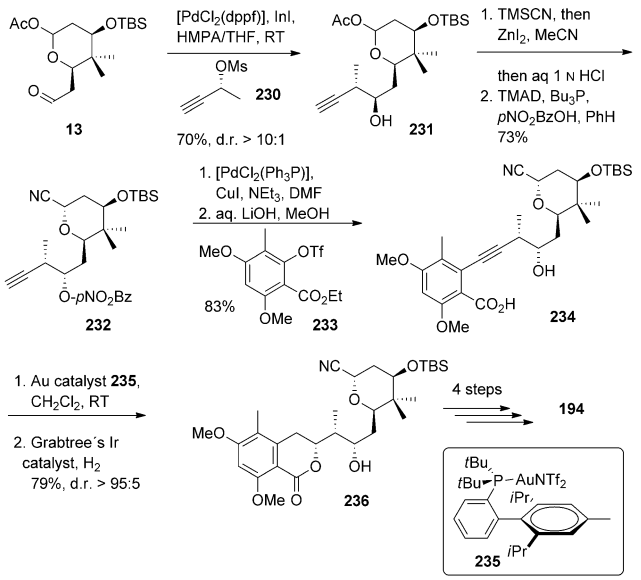
Recently, the Smith research group has published the first total synthesis of irciniastatin B (**4**; Scheme 52).[94] They used



Scheme 52. The total synthesis of irciniastatin B (**4**) by the Smith research group.[94]

the same strategy they had developed for the synthesis of psymberin (**3**) except for the protecting groups on the dihydroisocoumarin fragment (DMB versus SEM) to synthesize compound **227**. This switch allowed for compound **228** to be synthesized in 72% yield from carbamate **227**. After cleavage of the silyl groups, the secondary alcohol was oxidized with the Dess–Martin reagent to give ketone **229**. A final two-step deprotection furnished irciniastatin B (**4**) in 78% yield over two steps. The structure was validated by reducing irciniastatin B (**4**) to psymberin (**3**) with sodium borohydride.

In 2012, De Brabander and co-workers published their second approach towards the total synthesis of psymberin (**3**) and derivatives thereof (Scheme 53).[57] Starting from aldehyde **13**, they performed a Marshall coupling with alkyne **230** to obtain alcohol **231** in 70% yield with a diastereomeric ratio of $>10{:}1$ in favor of the shown diastereomer. After stereoselective substitution of the anomeric acetate by a cyanide ion, the configuration of the secondary alcohol needed to be inverted by a Mitsunobu reaction to furnish the *syn* compound **232**. A Sonogashira cross-coupling reaction between alkyne **232** and triflate **233** was then successfully applied to obtain coupling product **234** in 83% yield after ester hydrolysis. The interesting key step was the gold-catalyzed cyclization with subsequent reduction to form the dihydroisocoumarin unit, which was unique among all the syntheses. After optimization of the reaction conditions, gold complex

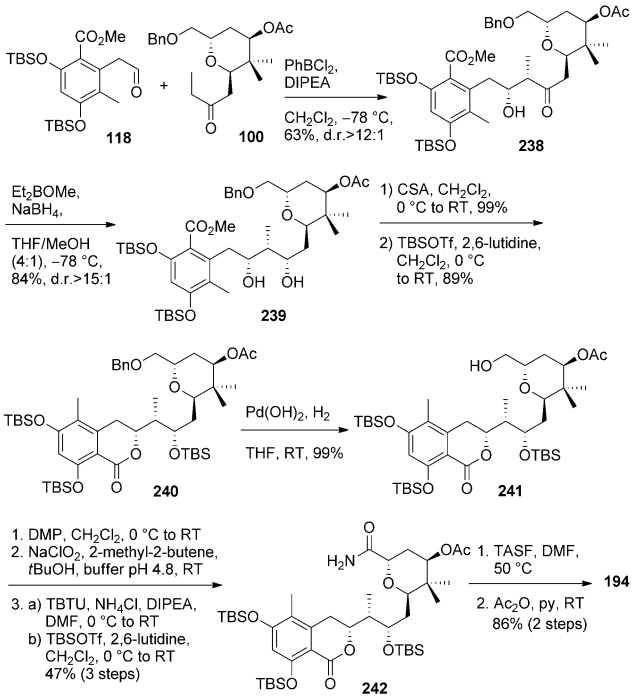


Scheme 53. The second-generation total synthesis of psymberin (**3**) by the De Brabander research group.[57]

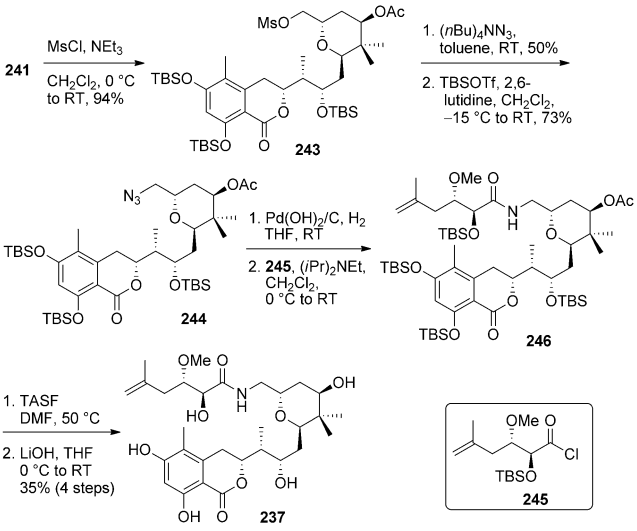
235 was found to give the best results. Reduction with hydrogen and Crabtree's catalyst provided dihydroisocoumarin **236** in 79% over two steps and with an excellent diastereomeric ratio of >95:5. A further four steps led to amide **194**, which was a known intermediate from their first total synthesis. This coupling strategy seems to be very valuable for synthesizing analogues that differ in the substitution pattern of the aromatic unit.

Bielitza and Pietruszka published the synthesis of 8-desmethoxypsymberin (**237**) along with a formal synthesis of psymberin (**3**) in 2013 (Scheme 54).[58] After an aldol reaction between ketone **100** and aldehyde **118** (→**238**) followed by *syn* reduction (→**239**), the lactone ring was closed by using CSA. The product needed to be protected again to furnish the desired lactone **240** in 88% yield over two steps. After deprotection of the primary alcohol (→**241**), it was oxidized in a two-step sequence by Dess–Martin and Pinnick oxidation. The corresponding acid was subsequently transformed into amide **242** under peptide coupling conditions. The three-step sequence afforded **242** in 47% yield. A final deprotection and peracetylation furnished the known, advanced compound **194** in 86% yield over two steps.

As mentioned above, Bielitza and Pietruszka synthesized 8-desmethoxypsymberin (**237**), a putative precursor of the natural product, to contribute to the elucidation of the biosynthesis. They continued the sequence with alcohol **241**, which was mesylated to obtain **243** in 94% yield. After replacement of the mesyl group by an azide group, it was protected again with TBS groups to furnish compound **244** in 73% yield. A final azide reduction, coupling to psymberic acid chloride **245** (→**246**), prepared beforehand in three steps from psymberic acid methyl ester, and deprotection furnished the desired product **237** in 35% yield over four steps (Scheme 55).



Scheme 54. A formal synthesis of psymberin (**3**) by Bielitza and Pietruszka.[58]



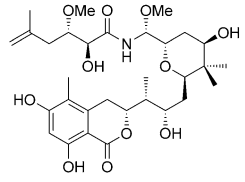
Scheme 55. Synthesis of 8-desmethoxypsymberin (**237**) by Bielitza and Pietruszka.[58]

8. Analogues and Their Biological Properties

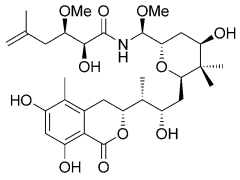
The immense interest in the natural product psymberin (**3**) did not only result in a variety of total and partial syntheses but also in some studies of the structure–activity relationship (SAR). Analogues were prepared containing different variations of structural units and tested for their biological properties. This combinatorial approach is also common in pharmaceutical industry to increase the biological activity of potential lead structures.

The first analogues tested were the ones synthesized by De Brabander and co-workers (Table 3).[95] They obtained the C8 and C4 epimers of psymberin [(C8-*epi*-**3**) and (C4-*epi*-**3**)] during the development of their total synthesis of psymberin (**3**). Those analogues showed good IC_{50} values against the

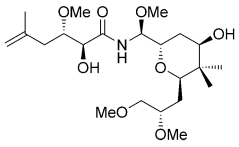
Table 3: Different analogues of psymberin synthesized by the De Brabander research group (Promega CellTiter Glo Assay).[95]



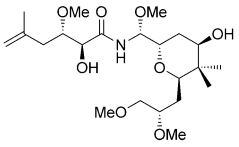
C8-*epi*-**3**



C4-*epi*-**3**



hybrid **247**



C8-*epi*-**247**

	IC_{50} value [nM][a]			
structure	KM12	PC3	SK-MEL-5	T98G
3	0.45 ± 0.01	0.98 ± 0.12	2.29 ± 0.13	1.37 ± 0.06
C8-*epi*-**3**	37.1 ± 5.5	200.2 ± 27.6	352.0 ± 2.1	85.8 ± 48.4
C4-*epi*-**3**	126.08 ± 8.6	346.5 ± 102.8	762.8 ± 70.0	186.7 ± 51.3
hybrid **247**	710.9 ± 35.8	821.8 ± 89.1	> 1000	> 1000
C8-*epi*-**247**	> 1000	255.5 ± 11.4	> 1000	> 1000

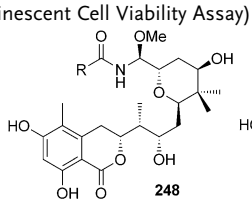
[a] Cell lines: KM12: colon cancer, PC3: prostate cancer, SK-MEL-5: melanoma, T98G: glioblastoma.

tested cell lines, but the values were around 100 times higher than those of the natural product. Two simpler hybrids were synthesized which contained a dimethoxy unit [similar to pederin (**1**)] instead of the dihydroisocoumarin unit. The hybrid **247** and its epimer C8-*epi*-**247** did not show significant biological activity against the tested cell lines. Thus, the dihydroisocoumarin unit seems to be essential for the biological activity of psymberin (**3**).

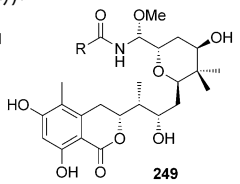
In 2009, another report from the Schering group followed, wherein they described the synthesis and biological evaluation of several derivatives.[96] They focused on variation of the psymberic acid unit. Table 4 shows the seven structures along with their biological properties towards the human lung cancer cell line HOP62. The simplified structures with R = methyl (**248a**, **249a**) and R = 3-phenylpropyl (**248b**, **249b**) showed IC_{50} values of > 10000, while **248c**, **249c**, and **248d** possessed values between 32 and 615 nM. These did not show any improvement compared to the natural product. It seems as if the psymberic acid unit, at least the (4*S*)-methoxy and (5*R*)-hydroxy groups, is important for the cytotoxicity of psymberin (**3**).

Huang et al. also synthesized different C11-deoxy analogues and tested them for their biological properties (Table 5).[96] Interestingly, the values were always slightly better than the natural product. The corresponding diastereomers C8, C9-*epi* **250**, C8-*epi* **250**, and C9-*epi* **250** did not

Table 4: Psymberin analogues from the Huang research group and their IC_{50} values tested in the human lung cancer cell line HOP62 (CellTiter-Glo Luminescent Cell Viability Assay).[96]



248



249

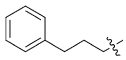
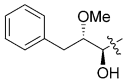
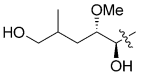
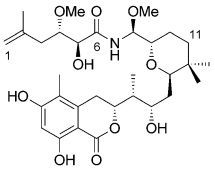
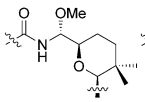
R		IC_{50} (**248a–d**) [nM]	IC_{50} (**249a–d**) [nM]
	a	> 10000	> 10000
	**b**	> 10000	> 10000
	**c**	32 ± 1	615 ± 15
	**d**	260 ± 36	–

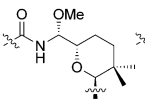
Table 5: Structural variations at the tetrahydropyran core of psymberin (CellTiter-Glo Luminescent Cell Viability Assay).[96]



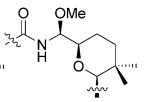
C11-deoxy psymberin (**250**)



C8,C9-*epi*-**250**



C8-*epi*-**250**



C9-*epi*-**250**

		IC_{50} [nM]				
human tissue type	cell line	**3**	**250**	C8,C9-*epi*-**250**	C8-*epi*-**250**	C9-*epi*-**250**
kidney	ACHN	0.76	0.265	n.d.	n.d.	8.7
prostate	DU145	0.30	0.149	n.d.	n.d.	5.9
lung	H226	0.18	0.034	n.d.	n.d.	1.6
lung	HOP62	0.42	0.055	177	46	3.0
breast	MB231	0.27	0.142	n.d.	n.d.	5.3
gastric	MKN45	0.28	0.076	n.d.	n.d.	3.9
prostate	PC3	0.19	0.073	.n.d.	n.d.	2.9
colon	SW620	0.82	0.160	n.d.	n.d.	6.1
normal	NHDF	0.84	0.066	n.d.	n.d.	3.8

show improved values. With this study, Huang et al. deduced that the hydroxy group at C11 is not important for cytotoxicity.

Watanabe et al. constructed the enantiomer of psymberin (*ent*-**3**) and another derivative, the so-called alkymberin (**251**; Figure 4). Enantiomer e*nt*-**3** proved to have no significant GI_{50} values against the tested cell line HeLa, thus indicating an enantiodifferential recognition between psymberin (**3**) and its target in the cell. In contrast, alkymberin (**251**) showed a GI_{50} value of 1.2 nM, which is similar to that of psymberin (**3**). Clearly, minor variations on the psymberic acid site are possible.[53]

In 2011, Floreancig and co-workers published an impressive study of a variety of pederin and psymberin analogues as well as the binding properties of pederin (**1**) to a ribo-

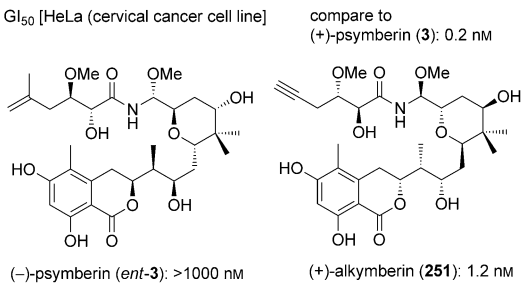


Figure 4. Two synthetic analogues of psymberin.[53]

some.[35,36] In doing so they used the crystal-structure data of mycalamide A (**2a**) and a ribosomal subunit. Their insight into the binding mode enabled them to propose new active agents by modeling studies. By using the same reaction sequences as for the synthesis of the natural product they synthesized 8-desmethoxypsymberin (**237**), pedastatin (**252**), and 10-desmethoxypedastatin (**253**). All of the structures showed similar or even better GI_{50} values towards the colon cancer cell line HCT116 than the natural product (Figure 5).

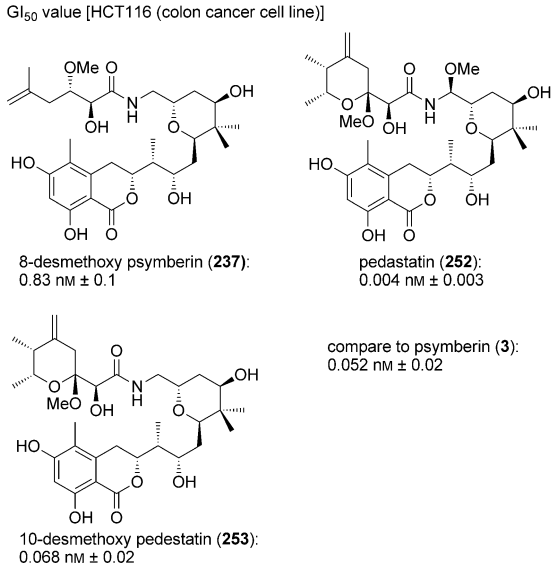


Figure 5. Analogues synthesized by the Floreancig research group.[35]

The combination of structural elements of psymberin (**3**) and pederin (**1**), realized in the structure of pedastatin (**252**), provided the compound with an excellent GI_{50} value of 0.004 nM, which is about 13 times better than that of psymberin (**3**; 0.052 nM). Consequently, pedastatin (**252**) belongs to the most potent cytotoxins known, such as spongistatin 1[97] and meayamycin B, a synthetic analogue of FR901464.[98]

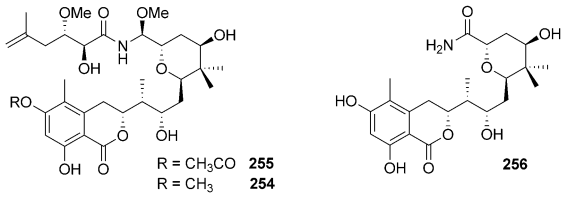
Surprisingly, there have been many synthetic approaches towards psymberin (**3**) since its isolation, but none concerning the structurally similar, but also highly active irciniastatin B (**4**) until 2012. The Smith research group finally synthesized the natural product by slightly altering their synthetic strategy which had led to the synthesis of psymberin (**3**).[94] Irciniastatin B (**4**) inhibits cell growth strongly against the pancreas, breast, and central nervous system (CNS) cell lines (Table 6). In contrast, psymberin (**3**) was more active against lung cancer cell line NCI-H460.

Table 6: Inhibition of cancer cell line growth (GI_{50}, $\mu g\,mL^{-1}$) by psymberin (**3**) and irciniastatin B (**4**).[21]

Human cancer cell line		Psymberin (**3**)	Irciniastatin B (**4**)
pancreas	BXPC-3	0.0038	0.00073
breast	MCF-7	0.0032	0.00050
CNS	SF268	0.0034	0.00066
lung	NCI-H460	<0.0001	0.0012
colon	KM20 L2	0.0027	0.0021
prostate	DU-145	0.0024	0.0016
leukemia	P388	0.00413	0.006
normal endothelial	HUVEC	<0.0005	n.d.

The latest published analogue synthesis was developed by the De Brabander research group.[57] They synthesized methyl- and acetylpsymberin (**254** and **255**) in one step each starting from the natural product. Those and other analogues (e.g. amide **256**) were tested for their cytotoxicity and translation inhibition against human cancer cell lines (Table 7).[36]

Table 7: Cytotoxicity of synthetic analogues of psymberin from Wu et al. (CellTiter-Glo luminescent assay).[36]



	cytotoxicity [IC_{50}, nM]		Translation inhibition [EC_{50}, nM] in vitro	cell-based	
compound	HeLa	SK-MEL-5		HeLa	SK-MEL-5
3	0.064 ± 0.14	0.27 ± 0.04	28 ± 7	2.2 ± 1.4	11 ± 10
255	0.54 ± 0.01	0.35 ± 0.07	142 ± 21	5.8 ± 1.7	4.2 ± 3.2
254	2.34 ± 0.53	1.58 ± 0.42	120 ± 47	9.6 ± 8.9	9.3 ± 8.5
256	>1000	>1000	>10000	>10000	>10000
2a	2.52 ± 1.39	3.79 ± 0.04	3.79 ± 44	59 ± 32	64

There are a couple of conclusions (applies only for the tested cell lines) that can be drawn from the SAR studies shown above (Figure 6):

- Minor structural variations can be made to the psymberic acid unit as long as the (4*S*)-methoxy and (5*R*)-hydroxy functions are present; substitution for pederic acid [pedastatin (**252**)] generates an analogue with the best GI_{50} value towards the colon cancer cell line HCT116.
- Compounds with the pederic acid unit generally show higher activity than those with the psymberic acid unit.
- The C11-hydroxy group is not necessary for cytotoxicity; the C11-oxo analogue [irciniastatin B (**4**)] is also very potent.

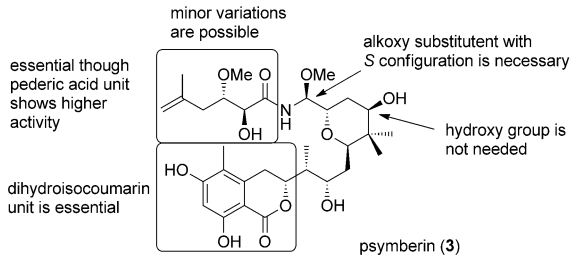


Figure 6. Overview of the observed structure–activity relationship trends.

- Variations of the C8-alkoxy substituent are possible, but it cannot be substituted by hydrogen.
- The dihydroisocoumarin unit is essential for cytotoxicity.
- Inverting the configurations at positions C4 and C8 leads to a dramatic loss of activity.

9. Summary and Outlook

This Review is intended to cast light on the fascinating properties, total syntheses, and analogues of the marine natural product psymberin (**3**). Numerous studies and synthetic efforts helped to evaluate its biosynthesis and resulted in a variety of impressive synthetic approaches. An array of different new methods were developed to prepare structurally unique motives, for example, the *N*,*O*-hemiaminal. It was achieved by four different approaches: 1) acylation of a methylimidate with subsequent hydride reduction, 2) oxidative cyclization of a hydroxy enamide, 3) Curtius rearrangement followed by acylation, and 4) by a hydrozirconation/acylation/addition sequence. The approaches towards the 2,6-*trans*-tetrahydropyran unit of psymberin, described in Section 3, comprise the substitution reactions of anomeric acetates, opening of a spiro epoxide, a $PhI(OAc)_2$-triggered cyclization, an intramolecular cyclization of epoxy alcohols, an addition of enol silanes to oxocarbenium ions, a 1,4-addition of vinylmagnesium bromide to a dihydropyran, a cyclization and organocatalytic and base-catalyzed oxa-Michael reaction. Generally, the oxaborolidinone-catalyzed aldol reaction proved to be a particularly suitable and very reliable method towards advanced precursors of the tetrahydropyran core. To conclude, the stereoselective synthesis of 2,6-*trans*-tetrahydropyrans has been and still will be a challenge because of their lower thermodynamic stability and substitution patterns. The construction of the highly substituted dihydroisocoumarin core can be achieved by transformation of simple, commercially available aromatic starting materials, by cycloaddition of silyl enol ethers with allenes, or by acid-catalyzed rearrangement. Psymberic acid (**5**) and derivatives thereof can be synthesized by a number of different ways. Common approaches were additions of methallyl and vinyl metal compounds to aldehydes or epoxides, allylation, and aldol reactions. Furthermore, SAR studies proved that psymberin (**3**) is a potent lead structure for analogue synthesis. Its inherent properties could even be improved by variation and combination of different structural motives [for example, pedastatin (**252**)]. It is believed that further synthetic efforts will be made that will result in shorter, more efficient total syntheses and new, structurally simpler analogues especially at the dihydroisocoumarin unit. Other prospective studies are intended to elucidate the last steps of the biosynthesis and the mechanism of apoptosis. The possibility to express psymberin (**3**) in a heterologic manner would have a major impact on the supply of this rare natural product to provide sufficient material for further testing. Psymberin (**3**) might indeed become a suitable candidate for clinical evaluation for the treatment of a variety of different cancers.

Appendix: List of Abbreviations

Ac	acetyl
AZADO	2-azaadamantane *N*-oxyl
BDA	butane-2,3-diacetal
BINOL	1,1-bi-2-naphthol
Bn	benzyl
BOM	benzyloxymethyl
Bz	benzoyl
CBS	Corey, Bakshi, Shibata (oxazaborolidine)
CSA	10-camphorsulfonic acid
cod	1,5-cyclooctadiene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DiBAl-H	diisobutylaluminum hydride
DIP	diisopinocampheyl
DIPEA	*N*,*N*-diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMB	2,4-dimethoxybenzyl
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EC	effective concentration
GI	growth inhibition
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
IBX	2-iodoxybenzoic acid
IC	inhibitory concentration
Ipc	isopinocampheyl
LC	lethal concentration
LDA	lithium diisopropylamide
MOM	methoxymethyl
MS	molecular sieves
NHS	*N*-hydroxysuccinimide
NMO	4-methylmorpholine *N*-oxide
NMP	1-methyl-2-pyrrolidinone
OMs	methansulfonate
OTf	trifluoromethanesulfonate
OTs	*p*-toluenesulfonate

Piv	pivaloate
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum dihydride
SEM	2-(trimethyl)silylethoxymethyl
Tar	tartrate
TASF	tris(dimethylamino)sulfonium fluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
Teoc	2-trimethylsilylethyl carbamate
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TIPS	tri(isopropyl)silyl
TMAD	1,1′-azobis(*N*,*N*-dimethylformamide)
TMS	trimethylsilyl
TPS	*tert*-butyldiphenylsilyl

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