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Synthesis of 8-Desmethoxy Psymberin: A Putative Biosynthetic Intermediate Towards the Marine Polyketide Psymberin

Max Bielitza and Jörg Pietruszka*[a]

Abstract: The synthesis of a putative biosynthetic precursor of psymberin including a formal synthesis of the natural product is described. The key step towards the densely functionalized tetrahydropyran core was an enantioselective catalytic Mukaiyama aldol reaction using a titanium(IV)–BINOL catalyst system. *syn*-Selective reduction followed by ozonolysis led to a rapid assembly of the tetrahydropyran ring. This flexible approach also allows the synthesis of similar fragments of other complex molecules such as bryostatins and pederins. The *syn*-selective coupling between the tetrahydropyran and the aromatic aldehyde was achieved using a boron-mediated aldol reaction which was followed by further transformations to complete the synthesis of the precursor as well as the formal synthesis of the natural product.

Keywords: biosynthesis · cytotoxin · formal synthesis · Mukaiyama aldol · natural product

Introduction

Psymberin (**1**) (**Ps**ammocinia, **symb**iont, ped**erin**), also known as irciniastatin A (**1**), is a marine cytotoxin which displays high potency. It belongs to the pederins, a group of 36 natural products which may be of either terrestrial or marine origin.[1] Since its independent isolation in 2004 from two genera of sponges by Crews[2] (*Psammocinia*) and Pettit[3] (*Ircinia ramose*), the synthesis of psymberin (**1**) has created enormous attention. There are several total syntheses,[4] a formal synthesis[5] and partial syntheses[6] reported so far. Such interest is due to the unique structural motifs for example, the dihydroisocoumarin unit (DHIC), the *N*,*O*-hemiaminal structure and the densely functionalized tetrahydropyran (THP) core, its selective antitumor activity and its paucity in nature.

It was initially tested for 60 human cell lines and displays excellent efficacy ($LC_{50} < 2.5 \times 10^{-9}$ M) especially against some melanoma, breast and colon cancer cell lines. In contrast, leucemia cell lines are relatively immun ($LC_{50} > 2.5 \times 10^{-5}$ M). The cytotoxic activity of the *Psammocinia* extracts has already been known since 1990, but could not be attributed to a substance until Crews[2] suggested a structure which possessed such a high cytotoxicity and was proven and further characterized by De Brabander[4a] and Williams.[6a] Interestingly, it is believed that psymberin (**1**) is not produced by the sponges themselves, but by symbiotic bacteria.[7]

Psymberin analogues were prepared and tested for their biological activities revealing new potent structures.[4e,f,8] In particular, pedastatin (**2**), a hybrid which combines fragments from psymberin (**1**) and pederin (**3**), turned out to be very potent against colon cell line HCT116. Furthermore, molecular conformational and hydrogen-bonding models of complexes between psymberin-related structures [pederin (**3**), mycalamide A—not shown] and ribosomes have assisted to comprehend the functions of defined structural motifs of the molecules.[4f]

The Piel group has shed light on most of the steps of the biosynthesis of psymberin (**1**), but a few are still unknown.[7] Of particular interest is the order of introduction of the hydroxyl group in 5- and the methoxy group in 8-position (see structure **4**, Figure 1) during the biosynthetic pathway, respectively. It is assumed that 8-desmethoxy psymberin (**5**) is possibly that penultimate intermediate. Therefore, we decided to synthesize the putative biosynthetic precursor to help evaluate these last steps. It should be noted that intermediate **5** is already a highly cytotoxic compound which is more readily accessible and presumably more stable, albeit not as potent as psymberin (**1**) itself.[4i] Herein, we present our different approaches towards the construction of the THP core, which also allows for synthesizing similar THP units from other natural products, for example, pederin (**3**) or bryostatin 1 (**6**), the aromatic unit and the following reaction sequences that enabled us to synthesize 8-desmethoxy psymberin (**5**) as well as the N_7–C_{25} fragment of psymberin (**1**), which even led to complete a formal synthesis.

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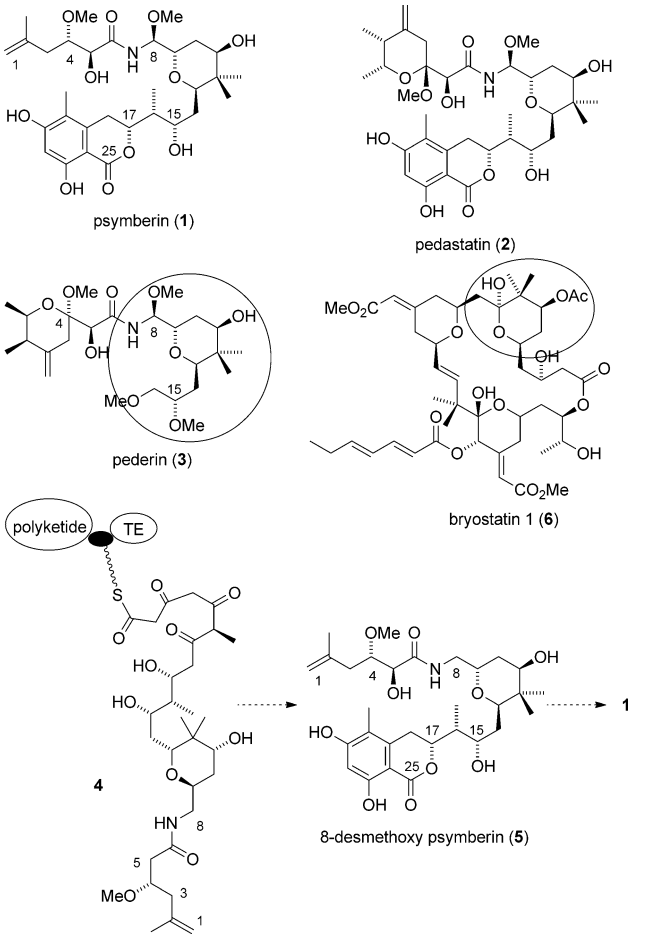
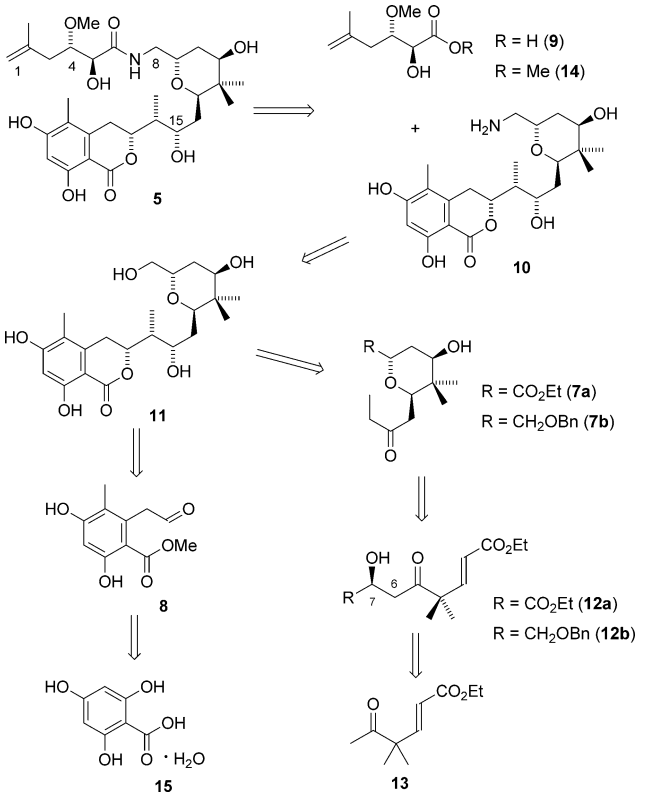


Figure 1. Structures of psymberin (**1**), pedastatin (**2**), pederin (**3**), 8-desmethoxy psymberin (**5**), bryostatin 1 (**6**), and a segment **4** from the biosynthesis of psymberin (**1**).

Results and Discussion

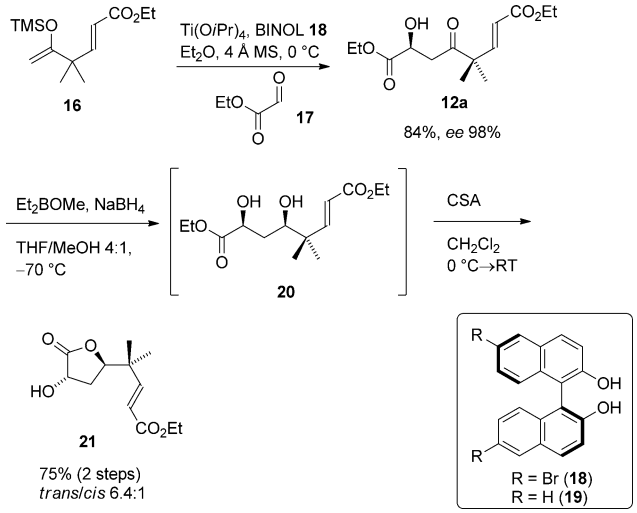
Retrosynthetic plan: Our strategy is based on a general approach to synthesize intermediates that lead to the synthesis of 8-desmethoxy psymberin (**5**) and related molecules by chemical transformations and also allows us to apply our knowledge of enzymatic transformations in future. For the construction of the THP-moiety **3** we wanted to apply our initial results[9] with sterically demanding ketones in enantioselective Mukaiyama aldol reactions.[10]

Therefore, we disconnected the molecule into three units similar to the De Brabander group:[4a] the THP-core **7**, the highly-substituted aromatic system **8** and psymberic acid (**9**) (Scheme 1). A late stage coupling of amine **10** and psymberic acid (**9**) should establish the amide group. Amine **10** should arise from alcohol **11** and the latter from a diastereoselective aldol coupling reaction between THP-unit **7** and aldehyde **8** followed by further transformations. As mentioned above an enantioselective Mukaiyama aldol reaction should set the first stereogenic center to give β-hydroxy ketone **12**. Therefore, we envisioned that the C–C disconnection between C_6 and C_7 would lead to ketone **13** and allow for a possible synthetic pathway towards the THP-core **7**. Psymberic acid (**9**) should be synthesized from psymberic acid methylester (**14**), which had previously been synthesized within our group via chemical and chemoenzymatic transformations[6g,h] and which was readily available. Aldehyde **8** could be disconnected to commercially available phloroglucinol-carboxylic acid monohydrate (**15**) as starting material.



Scheme 1. Retrosynthetic analysis.

Synthesis of the THP core: Our synthesis of the THP-unit **7a** (Scheme 2) started off by preparing silylenol ether **16**.[11] As described before,[9] it was synthesized in four steps from isobutyraldehyde in multigram quantities. The enoate functionality displayed a masked aldehyde and was also chosen because of polarity reasons of the desired aldol product. Thereby, chromatographic separation from the BINOL ligand was readily possible. For the electrophilic component of the aldol reaction, our first choice was commercially available ethyl glyoxalate (**17**). Having prepared the racemic reference materials using LDA for enolate formation, we implemented our initially established results.[9] The titanium(IV)–BINOL **18** system that proved to be superior to the one using the unsubstituted BINOL **19**, provided the aldol product **12a** in excellent enantioselectivity (*ee* 98%) and yield (84%). The next steps should be a diastereoselective *syn*-reduction.[12] But as previously shown, the linear product **20** could not be obtained in a pure fashion because of cyclization to the corresponding lactone **21**. Continuation on that



Scheme 2. First enantioselective approach towards the THP unit.

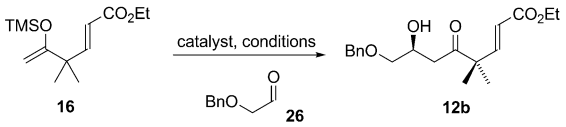
strategy would not have led to the intended coupling partner. However, the lactone is a known, potential intermediate towards psymberin (**5**).[6i]

Thus, cyclization to THP **22** was performed by ozonolysis first (Scheme 3). After spontaneous cyclization and acetylation with acetic anhydride, THP **23** could be obtained as a 5.5:1 diastereomeric mixture in 81% yield over two steps. The next step turned out to be more difficult than anticipated. The reduction of ketones **22** and **23** (available by allylation of **22**) to the secondary alcohols **24** and **25** was performed with different reagents, but the use of sodium borohydride led only to traces of the undesired diastereomer. The relative configuration of **23** could not be resolved until the reduction step and this finding showed that the allylation reaction had furnished the undesired 2,6-*cis* isomer. The use of L-selectride caused a considerable formation of side products and proved to be unhelpful.

Due to the dead ends of the first two attempts we pursued a different route. For this purpose we switched from ethyl glyoxalate (**17**) to 2-(benzyloxy) acetaldehyde (**26**) as the electrophile in the aldol reaction to avoid cyclization to the corresponding five-membered ring. The latter could either be purchased or prepared by double benzyl protection of (*Z*)-but-2-ene-1,4-diol followed by dihydroxylation with subsequent oxidative cleavage.[13] We made use of our initial results and directly applied the titanium(IV)–BINOL **19** catalyst system to our substrates. To our delight, the simple, unsubstituted BINOL ligand **19** proved to give already satisfying results.

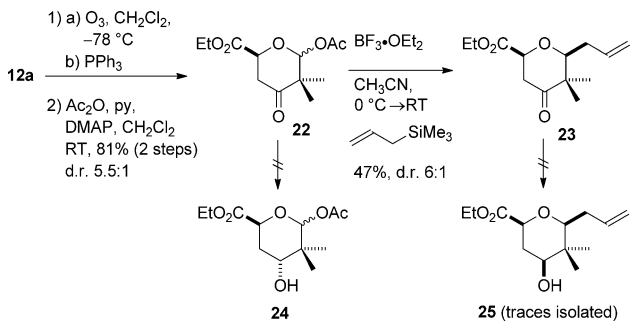
The aldol product **12b** was always obtained with high enantiomeric excess (≥95% *ee*), but yields relied heavily on the temperature. At lower temperatures (−40 °C, Table 1, entry 4) the conversion was low yielding only 44%, at room temperature (entry 1) the yield was also only 45%, because of increased side product formation of which one turned out to be the Evans–Tishchenko[14] product **27**. Therefore, the reaction was run at 0 °C as a compromise between reactivity and selectivity to give the product in 65% yield and an *ee* of ≥97% (entry 2). We based our assumptions that the (*S*)-BINOL ligand should lead to the desired (*S*)-aldol product on our results and those of Keck[15] and Mikami.[16] Unfortunately, the configuration could not be assigned at that stage, because Mosher ester preparation was obviously not possible due to the formation of elimination products.

Table 1. Enantioselective Mukaiyama aldol reactions.



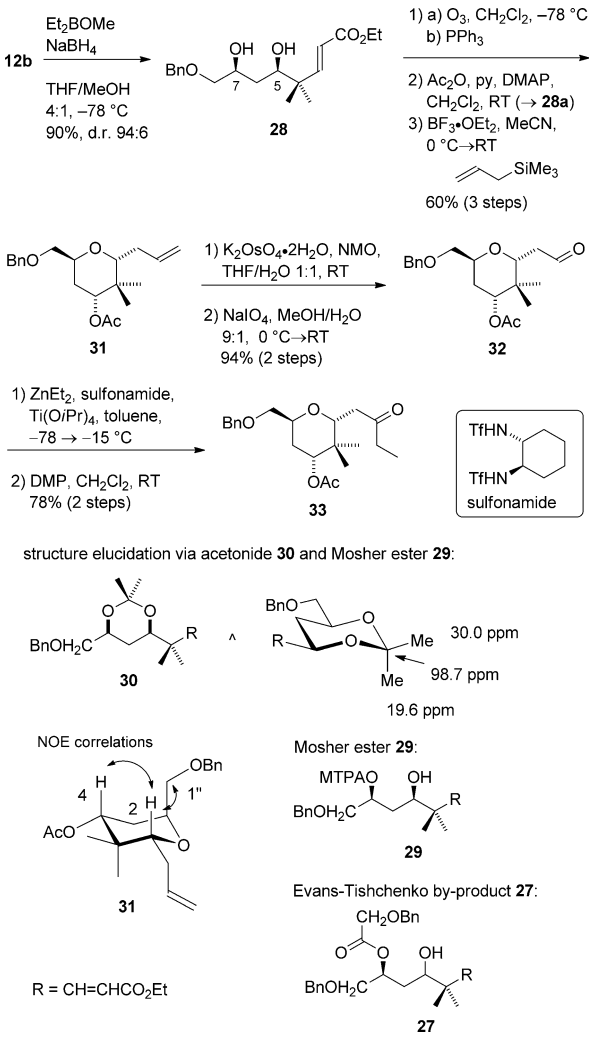
Entry	Conditions[a]	Catalyst [20 mol%]	Yield [%][b]	*ee* [%][c]
1	RT, Et_2O, 4 Å MS	Ti(O*i*Pr)$_4$, BINOL **19**	45	≥95
2	0 °C, Et_2O, 4 Å MS	Ti(O*i*Pr)$_4$, BINOL **19**	65	≥97
3	−15 °C, Et_2O, 4 Å MS	Ti(O*i*Pr)$_4$, BINOL **19**	59	≥97
4	−40 °C, Et_2O, 4 Å MS	Ti(O*i*Pr)$_4$, BINOL **19**	44	97

[a] 0.50 mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC.

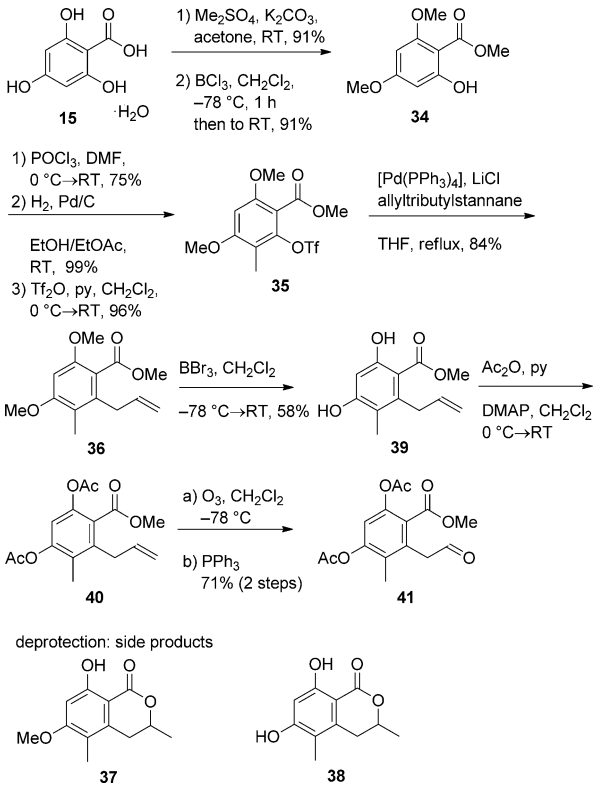


Scheme 3. Different synthetic attempts towards the THP unit.

Aldol **12b** was reduced under Prasad conditions[12] using diethylmethoxyborane and sodium borohydride to yield diol **28** in high yield (90%) and diastereoselectivity (d.r. 94:6) (Scheme 4). Its Mosher ester[17] **29** and dimethyl acetal[18] **30** were prepared proving the expected *S* configuration at C_7 and the *syn*-relation of both hydroxyl groups at C_5 and C_7 (Scheme 4, for more details see Supporting Information). Ozonolysis and double acetylation of diol **28** followed by diastereoselective allylation[19] using allyltrimethylsilane and $BF_3{\cdot}OEt_2$ furnished smoothly THP-core **31** in 60% yield over three steps. NOESY correlations confirmed the relative configuration. This unit displays a useful building block for other members of the pederin family. Alkene **31** was transformed to aldehyde **32** by dihydroxylation and oxidative cleavage. The nucleophilic addition of diethylzinc under the conditions reported by Kobayashi[20] afforded an alcohol that was submitted to Dess–Martin oxidation[21] to provide ketone **33** in 78% yield over two steps.



Scheme 4. Synthesis of THP-core **33** from aldol **12b**.



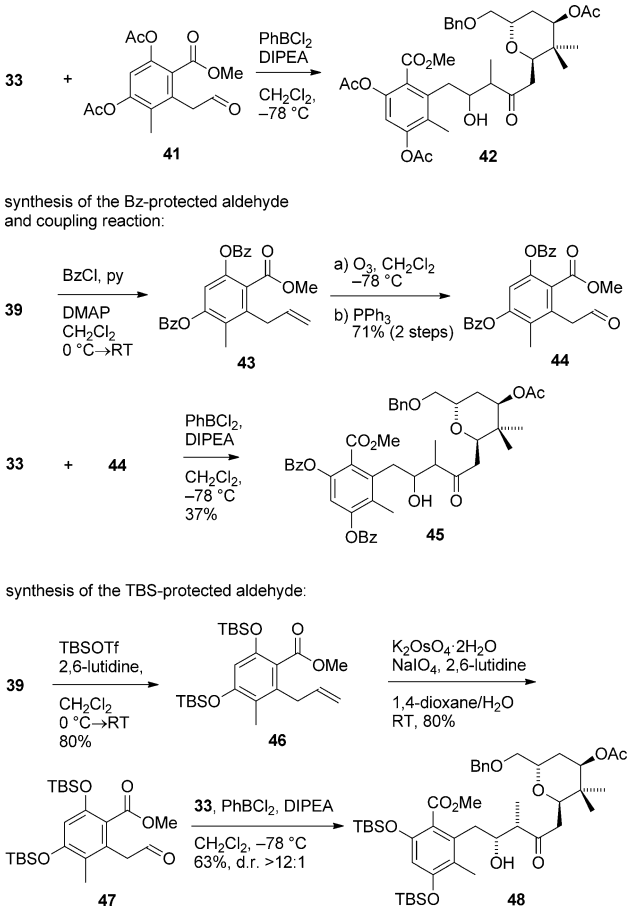
Scheme 5. Construction of the aromatic unit.

Synthesis of the DHIC unit: The synthesis of aryl fragment **8** began with phloroglucinol carboxylic acid monohydrate (**15**) as an inexpensive starting material (Scheme 5). Permethylation and regioselective deprotection of one methoxy group furnished phenol **34** in 83% yield over two steps.[22] It was formylated under Vilsmeier–Haack conditions[23] and reduced with hydrogen and Pd/C to install the methyl group in 3-position.[24]

In the following reaction sequence a protocol from Huang et al.[4b] was applied: formation of triflate **35** provided us with a suitable substrate for cross-coupling reactions. Under Stille conditions allyl product **36** was available in 84% yield. A Suzuki reaction using $[Pd(dppf)Cl_2]CH_2Cl_2$ as catalyst and allylboronic acid pinacol ester led to similar results (80% yield), but the reaction time could be decreased to 8 h.[25] The deprotection of the two methoxy groups of **36** proved to be difficult due to side product formation (**37** and **38**, Scheme 5) and phenol **39** could only be obtained in satisfying yield of 58% after work-up optimisation.

Next, we had to decide upon the protecting group strategy. Our plan was to keep one kind of protecting group throughout the sequence, then to cleave them all at once at the end. First, we converted resorcin **39** into its bisacetate **40** followed by ozonolysis to obtain aldehyde **41** in 71% yield over two steps.

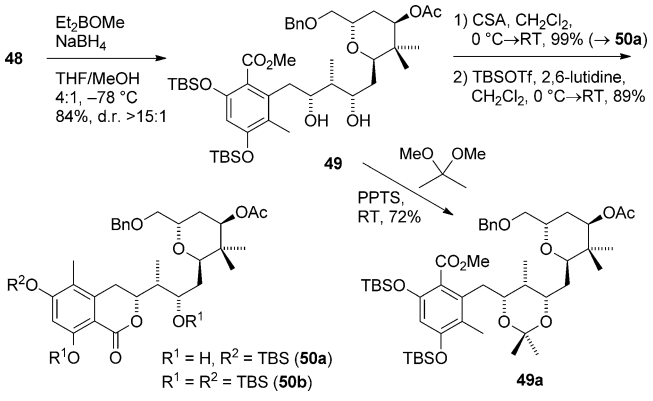
Fragment coupling: Then we focused on the boron mediated aldol reaction (Scheme 6).[26] In analogy to the De Brabander protocol,[4a] boron enolate derived from ketone **33** and dichlorophenyl borane reacted with aldehyde **41** at –78°C to give aldol **42** with good selectivity albeit modest conversion. Furthermore, separation of the two diastereomers and by-products was not possible by column chromatography. We thought that switching to a more stable protective group (acetate to benzoate, **39**→**43**, **44**) could solve the problem of the low conversion. Unfortunately, that was not the case and separation of the diastereomers of **45** could still not be achieved. We revised the protective group strategy and chose the TBS group for the protection of both phenolic hydroxy groups. Reaction of resorcin **39** with TBSOTf/2,6-lutidine provided the fully protected aromatic compound **46** in 80% yield which was subjected to ozonolysis as realized before. But it turned out that oxidative double bond cleavage caused the considerable formation of by-products and therefore could not be used. Presumably, TBS protection increased the electron density in such a way that the aromatic system could be oxidized. Instead we performed an oxidative cleavage to generate the aldehyde which was done by one-pot dihydroxylation with potassium osmate and diol cleavage with sodium periodate[27] to obtain aldehyde **47** in



Scheme 6. Syntheses of different aromatic aldehydes and their coupling reactions to THP **33**.

80% yield. Then we turned our attention to the coupling reaction according to our previous attempts. This time aldol **48** was obtained in good yield (63%) and good stereoselectivity (d.r. >12:1). Furthermore, the diastereomers could be separated by column chromatography.

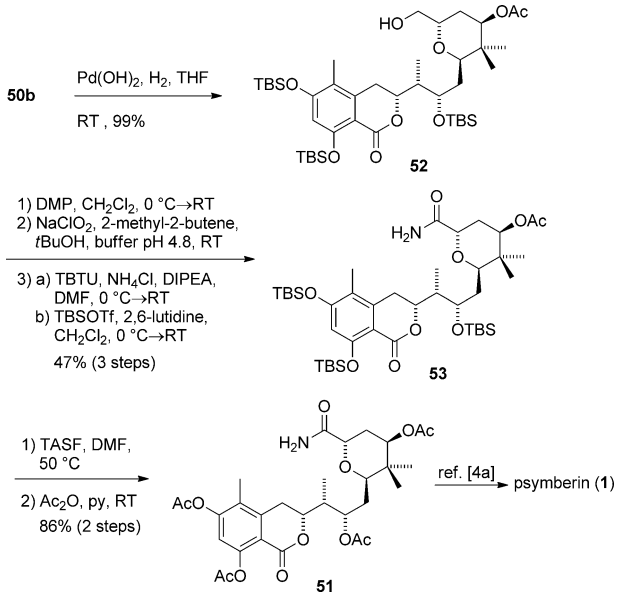
The following steps were performed as planned at the beginning (Scheme 7). The *syn*-reduction with sodium borohydride in the presence of diethylmethoxyborane furnished



Scheme 7. Fragment coupling and the synthesis of DHIC **50b**.

diol **49** in good yield (84%) and high diastereoselectivity (d.r. >15:1). Its all-*syn* configuration was proven by Rychnovsky's acetonide method (conversion to its dimethyl acetal **49a**; see Supporting Information for detailed NMR data). The DHIC moiety was installed in the next step by cyclization under acidic conditions with camphor sulfonic acid (CSA) (99%) giving an alcohol (→**50a**) which was TBS protected (TBSOTf, 2,6-lutidine) in 89% yield (→**50b**).

Formal synthesis: To assure the configurational assignments proposed before and to complete the formal synthesis of psymberin (**1**) we could also synthesize the N_7–C_{27} fragment **51** (Scheme 8). For the conversion of the alcohol functionali-

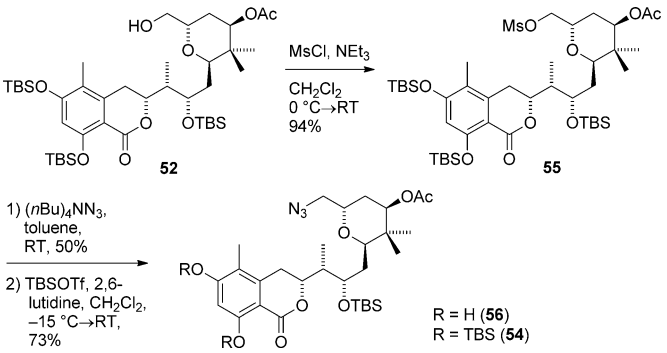


Scheme 8. Completion of the formal synthesis. tris(dimethylamino)sulfonium difluorotrimethylsilylsilicate (TASF).

ty to the corresponding primary amide, benzyl ether **50b** had to be deprotected using Pearlman's catalyst.[28] This transformation was performed in 99% yield. Alcohol **52** was oxidized in a two-step sequence using Dess–Martin and Pinnick[29] conditions. Amide formation proved to be difficult due to the lability of the phenolic TBS groups towards any nucleophiles. The reaction of the acid with ammonium acetate under peptide coupling conditions[30] [*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*,*N*-tetramethyluronium tetrafluoroborate (TBTU), Huenig's base] followed by treatment with TBSOTf afforded the desired fragment **53** in 47% yield over three steps. To complete the formal synthesis the protective groups were switched from TBS to acetate to give peracetylated amide **51** in 86% over two steps. The analytical data were all in full agreement with those reported previously.[4a,5]

Final steps towards the title compound: With alcohol **52** in hand and the configuration unambiguously confirmed, a

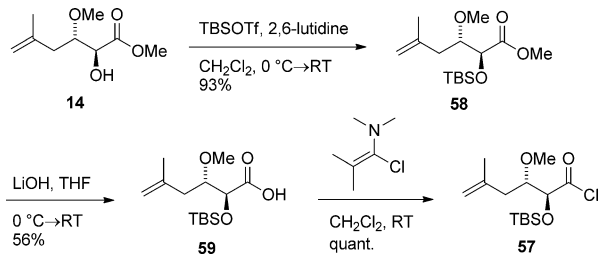
one-step conversion to azide **54** was initially intended employing Mitsunobu conditions[31] [diethyl azadicarboxylate (DEAD), PPh_3, diphenylphosphoryl azide (DPPA)], but no conversion was observed. The use of DPPA and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[32] was also not successful. Thus, we turned to a two-step procedure, first generating a good leaving group followed by a subsequent displacement by a nucleophile (Scheme 9). The conversion of



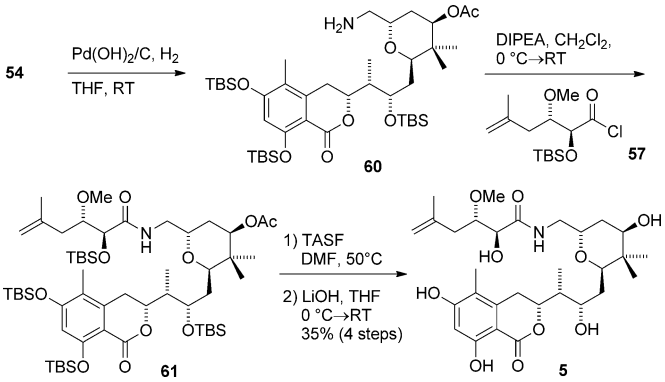
Scheme 9. Synthesis of azide **54** starting from alcohol **52**.

alcohol **52** to the corresponding triflate worked, but the product hydrolyzed during work-up. Next, we tried to introduce a mesylate under standard conditions. Having successfully obtained **55** in 94% yield (with minor impurities of mesyl chloride), two different azide reagents were tested. The use of NaN_3[33] only caused deprotection of TBS groups while $(Bu_4N)N_3$[34] provided the azide along with cleavage of both TBS groups on the aromatic system (→**56**). Deprotection could not be avoided, but the protective groups could be reintroduced under standard conditions yielding azide **54** in 37% yield over two steps.

The synthesis was continued generating the acid chloride of psymberic acid **57** in three steps from psymberic acid methyl ester[6h] (**14**) (Scheme 10). TBS protection (→**58**, hydrolysis with aqueous LiOH (→**59**) and the use of Ghosez's reagent[35] furnished acid chloride **57** in 52% yield (over 3 steps). Simultaneouly, azide **54** was hydrogenated to amine **60** and coupled to acid chloride **57** (Scheme 11). The slightly impure coupling product **61** was directly deprotected in a two-step sequence. All TBS groups were cleaved using tris-(dimethylamino)sulfonium difluorotrimethylsilylsilicate



Scheme 10. Preparation of psymberic acid chloride **57**.



Scheme 11. Amide formation between **60** and **57** followed by global deprotection yielded 8-desmethoxy psymberin (**5**).

(TASF)[36] followed by acetate hydrolysis to yield 8-desmethoxy psymberin (**5**)[4f] in 35% over four steps.

Conclusion

In summary, 8-desmethoxy psymberin (**5**), a putative biosynthetic precursor of psymberin (**1**), could be successfully synthesized in 25 steps (longest linear sequence) and was submitted for further testing. 8-Desmethoxy psymberin (**5**) might cast light on the final steps of the biosynthesis of psymberin (**1**). Additionally, our strategy enabled us to verify all stereochemical assignments by completing a formal synthesis of the natural product in 24 steps. The fragments **31** and **47** were accessible from simple starting materials. The application of a highly enantioselective aldol reaction paved the way for a rapid assembly of the highly functionalized THP-core **33**. Our flexible reaction sequence also displays a possible approach to similar tetrahydropyran units of other natural products such as pederin. The synthesis of aldehyde **47** describes a further development towards this coupling unit. The work being presented lays the foundation for the synthesis of related molecules and will be considered for further developments.

Experimental Section

Chemicals being used were purchased from the companies Sigma–Aldrich/Fluka, TCI International, Alpha Aesar and VWR International/Merck. Pure solvents were either purchased or distilled prior to use. Absolute solvents were either taken from a drying machine (MBraun (model MB SPS-800) (THF, Et_2O, CH_2Cl_2, toluene), distilled using common methods (MeOH, NEt_3, DIPEA) (according to W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, *Vol. 5*, Butterworth-Heinemann, Burlington, **2003**) or purchased (DMF, pyridine, 2,6-lutidine). Evaporation of solvents was performed on Buechi rotary evaporators (heating bath temperature: 30–40 °C) and on high vacuum pumps. Usually, reactions were conducted under N_2-atmosphere in Schlenk flasks or tubes, which were previously heated at 120 °C overnight. NMR spectra were recorded on a Bruker–Avance/Drx 600 instrument (^1H at 600 MHz; ^{13}C at 151 MHz). Chemical shifts (δ) are reported relative to chloroform (^1H: 7.26 ppm; ^{13}C: 77.00 ppm) or acetonitrile (^1H: 1.94 ppm; ^{13}C:

118.69 ppm). The multiplicities are reported with the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, m_c = centered multiplet, brs = broad singlet). Higher order chemical shifts and *J* values are not corrected. Where it was necessary DEPT 135, COSY, HSQC, HMBC and NOESY spectra were recorded for structure elucidation. Structures **30**, **49a**, **50a**, **50b**, **51**–**56**, **61** and **5** were not numbered according to IUPAC. Instead, the DHIC-unit was given highest priority due to ease of comparison of NMR data. Diasteromeric ratios were determined by ^{1}H NMR or HPLC. Infrared spectra were recorded using a PerkinElmer SpectrumOne IR-spectrometer. Silica gel 60 M (0.040–0.063 mm, 230–400 mesh) from Macherey–Nagel was used for flash-column chromatography. Eluents are stated for each substance in the experimental section. Thin layer chromatography (TLC) was conducted on POLYGRAM SIL G/UV254 plates with fluorescence indicator. Detection was either by UV absorption or treatment with ceric ammonium molybdate solution followed by heating. HPLC measurements were performed on a chiral stationary phase using a Dionex machine with analytical column (Chiralpak IC) from Daicel. Substances were detected by UV at wavelengths of 205, 225 and 254 nm, respectively. Optical rotations were determined using a PerkinElmer (type 341) polarimeter. Mass spectra were either measured using GC-MS (instrument: Thermo Elektron MAT 95, ionization by EI (70 eV), column: HP-5 ms (30 m × 250 μm × 0.25 μm) from Agilent) or MS (instrument: Finnigan MAT LC-Q, ionization by ESI). High-resolution mass (HRMS) spectra were measured by the Biospec group of the Research Center Juelich. Measurements were recorded on a LTQ-FT Ultra machine from Thermo Fisher. Samples were dissolved in MeOH and ionized by ESI. Melting points were determined using a Buechi instrument (type: melting point B-540). Elemental analyses were either measured at the central analytical department (ZCH) of the Research Center Juelich or at the institute for Organic Chemistry of the University of Stuttgart.

Details for all other compounds can be found in the Supporting Information.

(2*R*,4*R*,6*S*)-6-(Azidomethyl)-2-((2*S*,3*S*)-3-((*R*)-6,8-bis(*tert*-butyldimethylsilyloxy)-5-methyl-1-oxoisochroman-3-yl)-2-(*tert*-butyldimethylsilyloxy)-butyl)-3,3-dimethyl-tetrahydro-2*H*-pyran-4-yl acetate (54): Azide **56** (10.0 mg, 16.5 μmol) was dissolved in CH_2Cl_2 (1.00 mL). The solution was cooled to −15 °C and was then treated with 2,6-lutidine (19.0 μL, 165 μmol) and TBSOTf (19.0 μL, 82.5 μmol) and warmed to room temperature overnight. Further 2,6-lutidine (25.0 μL, 215 μmol) and TBSOTf (25.0 μL, 87.0 μmol)were added to complete conversion. After 3 h the reaction mixture was quenched by adding saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The organic layers were combined and washed with brine. The crude product was purified by column chromatography (petrol ether/ethyl acetate 80:20) to yield azide **54** (10.0 mg, 12.0 μmol, 73 %). R_f (petroleum ether/ethyl acetate 70:60) = 0.78; $[\alpha]_D^{20} = +45.5\ cm^3\,g^{-1}\,dm^{-1}$ (*c* = 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.03 (s, 3H, Si-CH_3), 0.11 (s, 3H, Si-CH_3), 0.22 (s, 3H, Si-CH_3), 0.24 (s, 3H, Si-CH_3), 0.24 (s, 3H, Si-CH_3), 0.24 (s, 3H, Si-CH_3), 0.83 (s, 9H, Si-C(CH_3)$_3$), 0.91 (s, 3H, 3″-CH_{3a}), 1.01 (s, 9H, Si-C(CH_3)$_3$), 1.02 (s, 9H, Si-C(CH_3)$_3$), 1.03 (s, 3H, 3″-CH_{3b}), 1.10 (d, $^3J_{1',2'}$ = 6.7 Hz, 3H, 1′-H), 1.69 (ddd, $^2J_{5''ax,5''eq}$ = 13.9 Hz, $^3J_{5''ax,4''}$ = 6.7 Hz, $^3J_{5''ax,6''}$ = 4.4 Hz, 1H, 5″-H_{ax}), 1.73 (ddd, $^2J_{4'a,4'b}$ = 14.6 Hz, $^3J_{4'a,3'}$ = 9.8 Hz, $^3J_{4'a,2''}$ = 2.0 Hz, 1H, 4′-H_a), 1.80 (ddd, $^2J_{5''eq,5''ax}$ = 13.9 Hz, $^3J_{5''eq,6''}$ = 7.5 Hz, $^3J_{5''eq,4''}$ = 3.9 Hz, 1H, 5″-H_{eq}), 1.98–2.04 (m, 1H, 2′-H), 2.07 (s, 3H, OCOCH_3), 2.08 (s, 3H, 5-CH_3), 2.07–2.15 (m, 1H, 4′-H_b), 2.68 (dd, $^2J_{4a,4b}$ = 16.3 Hz, $^3J_{4a,3}$ = 12.0 Hz, 1H, 4-H_a), 3.05 (dd, $^2J_{4b,4a}$ = 16.3 Hz, $^3J_{4b,3}$ = 2.4 Hz, 1H, 4-H_b), 3.28 (dd, $^2J_{1'''a,1'''b}$ = 12.9 Hz, $^3J_{1'''a,6}$ = 3.9 Hz, 1H, 1‴-H_a), 3.41 (dd, $^2J_{1'''b,1'''a}$ = 12.9 Hz, $^3J_{1'''b,6}$ = 8.6 Hz, 1H, 1‴-H_b), 3.43 (dd, $^3J_{2'',4'b}$ = 12.9 Hz, $^3J_{2'',4'a}$ = 1.8 Hz, 1H, 2″-H), 3.97–4.03 (m_c, 1H, 6″-H), 4.19 (ddd, $^3J_{3',4'a}$ = 9.7 Hz, $^3J_{H,H}$ = 3.8 Hz, $^3J_{H,H}$ = 3.2 Hz, 1H, 3′-H), 4.25 (ddd, $^3J_{3,4a}$ = 11.9 Hz, $^3J_{3,2'}$ = 7.9 Hz, $^3J_{3,4b}$ = 2.4 Hz, 1H, 3-H), 4.79 (dd, $^3J_{4'',5''ax}$ = 6.7 Hz, $^3J_{4'',5''eq}$ = 3.9 Hz, 1H, 4-H), 6.31 ppm (s, 1H, 7-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = −4.9 (Si-CH_3), −4.4 (Si-CH_3), −4.4 (Si-CH_3), −4.3 (Si-CH_3), −4.2 (Si-CH_3), −3.5 (Si-CH_3), 8.7 (C-1′), 11.6 (5-*C*H_3), 14.1 (3″-*C*H_{3a}), 18.0 (Si-*C*(CH_3)$_3$), 18.3 (Si-*C*(CH_3)$_3$), 18.6 (Si-*C*(CH_3)$_3$), 21.2 (OC(O)*C*H_3), 25.2 (3″-*C*H_{3b}), 25.7 (Si-C(*C*H_3)$_3$), 25.8 (Si-C(*C*H_3)$_3$), 26.0 (Si-C(*C*H_3)$_3$), 29.1 (C-5″), 29.8 (C-4), 32.5 (C-4′), 36.5 (C-3″), 39.9 (C-2′), 53.6 (C-1‴), 66.9 (C-6″), 68.9 (C-3′), 74.2 (C-4″), 75.7 (C-2″), 78.8 (C-3), 110.6 (arom. C), 110.7 (C-7), 118.7, 141.2, 156.9, 158.3 (arom. C), 163.5 (C-1), 170.3 ppm (O*C*(O)CH_3); IR (film) $\tilde{\nu}$ = 2955, 2930, 2858, 2098, 1726, 1593, 1569, 1472, 1413, 1351, 1247, 1200, 1167, 1069, 1033, 1006, 938, 837, 808, 779, 674 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{42}H_{75}N_3O_8Si_3$: 834.4935; found: 834.4938 [*M*+H$^+$].

(2*S*,3*S*)-2-(*Tert*-butyldimethylsilyloxy)-3-methoxy-5-methylhex-5-enoyl chloride (57): 1-Chloro-*N*,*N*-2-trimethyl-1-propenylamine (411) (9 μL, 69 μmol) was added to a stirred solution of acid **59** (9.8 mg, 34 μmol) in CH_2Cl_2 (0.25 mL) at 0 °C. The reaction mixture was stirred for 10 min and then warmed to room temperature: After 3 h the solvent was evaporated and the residue dried under high vacuum. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.10 (s, 3H, Si-CH_3), 0.11 (s, 3H, Si-CH_3), 0.93 (s, 9H, Si-C(CH_3)$_3$), 1.78 (s, 3H, 5-CH_3), 2.26 (dd, $^2J_{4a,4b}$ = 14.6 Hz, $^3J_{4a,3}$ = 4.4 Hz, 1H, 4-H_a), 2.31 (dd, $^2J_{4b,4a}$ = 14.7 Hz, $^3J_{4b,3}$ = 8.0 Hz,1H, 4-H_b), 3.42 (s, 3H, 3-OCH_3), 3.74 (ddd, $^3J_{3,4b}$ = 8.1 Hz, $^3J_{3,4a}$ = 4.5 Hz, $^3J_{3,2}$ = 4.2 Hz, 1H, 3-H), 4.47 (d, $^3J_{2,3}$ = 4.1 Hz, 1H, 2-H), 4.81–4.83 (m, 1H, 6-H_a), 4.84–4.86 ppm (m, 1H, 6-H_b); ^{13}C NMR (151 MHz, $CDCl_3$): δ = −5.2 (Si-CH_3), −5.1 (Si-CH_3), 18.1 (Si-*C*(CH_3)$_3$), 22.8 (5-*C*H_3), 25.5 (Si-C(*C*H_3)$_3$), 38.4 (C-4), 58.4 (3-O*C*H_3), 73.6 (C-3), 81.4 (C-2), 113.6 (C-6), 141.6 (C-5), 175.2 ppm (C-1).

(2*R*,4*R*,6*S*)-2-((2*S*,3*S*)-3-((*R*)-6,8-Bis(*tert*-butyldimethylsilyloxy)-5-methyl-1-oxoiso-chroman-3-yl)-2-(*tert*-butyldimethylsilyloxy)butyl)-6-(((2*S*,3*S*)-2-(*tert*-butyl-dimethylsilyloxy)-3-methoxy-5-methylhex-5-enamido)methyl)-3,3-dimethyltetra-hydro-2*H*-pyran-4-yl acetate (61): $Pd(OH)_2$ (0.7 mg) was added to a stirred solution of azide **48** (2.5 mg, 3.0 μmol) in THF (0.50 mL) and the suspension was hydrogenated for 4 h. It was filtered over celite and the solvent was removed in vacuo. Meanwhile, acid chloride **57** was prepared from its acid **59** (4.00 mg, 14 μmol). Acid chloride **57** was placed in a flask, diluted with CH_2Cl_2 (0.30 mL) and charged with Huenig's base (6.00 μL). The resulting solution was cooled to 0 °C and the a solution of the crude amine in CH_2Cl_2 (0.20 mL) was added dropwise. The reaction mixture was stirred for 2 h and then warmed to room temperature and stirred for 1 h. It was diluted with CH_2Cl_2 and quenched by the addition of aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (1×), brine (1×) and dried over $MgSO_4$. The solvents were evaporated and the product was obtained as a colorless solid (1.1 mg) after column chromatography (petrol ether/ethyl acetate 80:20) with impurities. R_f (petroleum ether/ethyl acetate 70:60) = 0.76; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.02 (s, 3H, Si-CH_3), 0.07 (s, 3H, Si-CH_3), 0.09 (s, 3H, Si-CH_3), 0.13 (s, 3H, Si-CH_3), 0.22 (s, 3H, Si-CH_3), 0.23 (s, 3H, Si-CH_3), 0.24 (s, 6H, Si-CH_3), 0.89 (s, 9H, Si-C(CH_3)$_3$), 0.92 (s, 9H, Si-C(CH_3)$_3$), 1.01 (s, 9H, Si-C(CH_3)$_3$), 1.01 (s, 3H, 3-CH_{3a}), 1.02 (s, 9H, Si-C(CH_3)$_3$), 1.04 (s, 3H, 3-CH_{3b}), 1.10 (d, $^3J_{16\text{-}CH3,16}$ = 6.8 Hz, 3H, 16-CH_3), 1.70 (s, 3H, 2-CH_3), 1.71 (m, 2H), 1.82 (m, 1H), 1.98 (m, 1H), 2.07 (m, 1H), 2.07 (s, 3H, OCOCH_3), 2.08 (s, 3H, 20-CH_3), 2.25 (dd, $J_{H,H}$ = 14.4 Hz, $J_{H,H}$ = 8.3 Hz, 1H), 2.63 (dd, $^2J_{H,H}$ = 16.4 Hz, $^3J_{H,H}$ = 12.3 Hz, 1H, 18-H_a), 3.03 (dd, $^2J_{H,H}$ = 16.2 Hz, $^3J_{H,H}$ = 2.2 Hz, 1H, 18-H_b), 3.10 (ddd, $J_{H,H}$ = 14.6 Hz, $J_{H,H}$ = 7.2 Hz, $J_{H,H}$ = 4.9 Hz, 1H), 3.20 (ddd, $J_{H,H}$ = 13.3 Hz, $J_{H,H}$ = 6.8 Hz, 5.1 Hz, 1H), 3.37 (s, 3H, 4-OCH_3), 3.45 (dd, $J_{H,H}$ = 11.5 Hz, $J_{H,H}$ = 2.4 Hz, 1H), 3.61–3.69 (m, 4H), 3.89 (m, 1H), 4.23 (ddd, $^3J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 2.2 Hz, 1H, 15-H), 4.37 (d, $^3J_{5,4}$ = 1.9 Hz, 1H, 5-H), 4.72 (m, 1H, 1-H_a), 4.75 (m, 1H, 1-H_b), 4.86 (dd, $^3J_{11,10ax}$ = 5.8 Hz, $^3J_{11,10eq}$ = 3.7 Hz, 1H, 11-H), 6.31 ppm (s, 1H, 22-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = −5.4, −4.8, −4.5, −4.4, −4.4, −4.3, −4.2, −3.6, 8.9, 11.8, 14.1, 18.0, 18.2, 18.3, 18.6, 21.2, 22.6, 22.7, 25.7, 25.8, 25.9, 25.9, 25.9, 27.1, 28.6, 31.9, 34.8, 37.4, 40.2, 45.8, 57.8, 64.9, 69.2, 74.2, 74.3, 78.1, 78.7, 110.6, 110.7, 112.5, 141.0, 142.4, 150.0, 150.5, 156.9, 158.4, 171.8, 171.9 ppm; IR (film) $\tilde{\nu}$ = 2952, 2827, 2856, 1735, 1679, 1593, 1570, 1472, 1350, 1360, 1249, 1168, 1067, 862, 839, 780 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for $C_{56}H_{103}NO_{11}Si_4$: 1078.6681; found: 1078.6676 [*M*+H$^+$].

8-Desmethoxy psymberin (5): Amide **61** (1.1 mg) was dissolved in DMF (0.10 mL) and placed in a 2 mL Eppendorf vial. The solution was charged with TASF (5.2 mg, 19 μmol) at room temperature and placed in an oil bath at 50 °C. The reaction mixture was stirred overnight, quenched with aqueous NH_4Cl and stirred for 5 min. It was diluted with ethyl acetate and H_2O. The layers were separated and the aqueous layer was extracted

with ethyl acetate (5×). The combined organic layer was washed with brine (1×) and dried over $MgSO_4$. Column chromatography (petrol ether/ethyl acetate 30:70 → CH_2Cl_2/MeOH 95:5) yielded the desilylated amide (0.7 mg), which was taken up in THF (0.20 mL) and treated with aqueous LiOH (1.50 mL, 0.5 M) at 0 °C. After 10 min the solution was allowed to warm to room temperature overnight. It was quenched by the addition of saturated aqueous NH_4Cl and then diluted with ethyl acetate and H_2O. The layers were separated. The aqueous layer was extracted with ethyl acetate (3×). The organic layers were combined and dried over $MgSO_4$. The crude was purified by column chromatography (*n*-pentane/ethyl acetate 10:90 → 0:100) to yield amide **5** (0.6 mg, 1.04 μmol, 35% over 4 steps) as a colourless solid. R_f (ethyl acetate) = 0.08; $[\alpha]_D^{20} = +50.0\ cm^3\,g^{-1}\,dm^{-1}$ (c = 0.06, MeOH) (lit. [4f]: $[\alpha]_D^{20} = +34.8$ (c = 0.27, MeOH); ^{1}H NMR (600 MHz, CH_3OD): δ = 0.89 (s, 3H, 12-CH_{3a}), 0.97 (s, 3H, 12-CH_{3b}), 1.11 (d, $^3J_{16\text{-}CH3,16}$ = 7.0 Hz, 1H, 16-CH_3), 1.57–1.63 (m, 1H), 1.71 (s, 3H, 2-CH_3), 1.68–1.74 (m, 2H), 1.84 (ddd, $J_{H,H}$ = 18.1, 11.5, 6.7 Hz, 1H), 1.91–1.96 (m, 1H), 2.01–2.06 (m, 1H), 2.10 (s, 3H, 20-CH_3), 2.26 (dd, $J_{H,H}$ = 14.4, 9.2 Hz, 1H), 2.90 (dd, $J_{H,H}$ = 16.4, 12.0 Hz, 1H), 3.12 (dd, $J_{H,H}$ = 13.9, 4.7 Hz, 1H), 3.14 (dd, $J_{H,H}$ = 15.4, 2.9 Hz, 1H), 3.24 (s, 3H, 4-OCH_3), 3.55 (dd, $J_{H,H}$ = 9.7, 2.4 Hz, 1H), 3.58 (dd, $J_{H,H}$ = 11.2, 4.7 Hz, 1H), 3.66 (ddd, $J_{H,H}$ = 9.4, 3.2 Hz, $J_{H,H}$ = 3.2 Hz, 1H), 3.85 (dd, $J_{H,H}$ = 13.9, 9.9 Hz, 1H), 4.00–4.04 (m, 1H), 4.07–4.13 (m, 1H), 4.30 (d, $^3J_{5,4}$ = 2.9 Hz, 1H, 5-H), 4.50 (ddd, $J_{H,H}$ = 12.1, 5.9, 3.0 Hz, 1H), 4.69–4.71 (m, 1H, 1-H_a), 4.72–4.75 (m, 1H, 1-H_b), 6.25 ppm (s, 1H, 22-H); ^{13}C NMR (151 MHz, CD_3OD): δ = 8.9, 10.5, 13.1, 22.7, 23.5, 29.3, 30.9, 33.2, 38.3, 40.4, 40.4, 42.8, 57.1, 71.4, 72.1, 72.4, 72.6, 78.2, 82.2, 101.4, 112.8, 115.7, 141.3, 143.9, 164.4, 164.8, 172.8, 175.1 ppm; IR (film): $\tilde{\nu}$ = 3357, 2922, 1659, 1631, 1467, 1262, 1100 cm^{-1}; HRMS (ESI+): m/z calcd for $C_{30}H_{45}NO_{10}$: calcd 580.3116; found: 580.3114 [M+H$^+$].

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