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Application of a tandem seleno-michael/aldol reaction in the total syntheses of (+)-Pericosine B, (+)-Pericosine C, (+)-COTC and 7-chloro-analogue of (+)-Gabosine C

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ABSTRACT

Synthesis of (+)-Pericosine B, (+)-Pericosine C, (+)-COTC and a 7-chloro-analogue of (+)-Gabosine C was achieved via tandem *seleno*-Michael/aldol reactions as key steps. The carbasugar linear precursor was obtained from cheap and readily available D-ribose in 7 steps which included resolution of the D-ribo-pyranose and the D-ribofuranose forms. Further transformation of the cyclic product involving a regio-selective Steglich esterification or methylation of the secondary hydroxyl group gave rise to protected (+)-COTC, (+)-Pericosine B and (+)-Pericosine C. Deprotection of benzyl ethers at −78 °C gave the titled compounds in satisfactory yields.

1. Introduction

Carbasugars [1] are important carbohydrate analogues in which the ring oxygen is replaced with a methylene group. This structural difference leads to the absence of a hemiacetal linkage which makes them more stable than their parent *true sugars*.

The first carbasugar, 5a-carba-α-DL-talopyranose, was synthesized by prof. G.E McCasland's group in 1966 [2]. A few years later 5a-carba-α-D-galactopyranose was isolated from a natural source of a fermentation broth of *Streptomyces* sp. MA-4145 [3]. Since then, interest in these compounds has increased dramatically, mainly because of their interesting and unique biological properties such as antitumor, antibacterial, antiviral and enzyme inhibitory activity [1,4–8].

Pericosines (A-E) are a subclass of carbasugars which have been isolated from the fungus *Perconia byssoides* (OUPS—N133), originally separated from sea hare, *Aplysia kurodai* (Fig. 1) [9]. They have been shown to display a wide range of interesting biological activities such as significant cytotoxicity against P388 lymphocytic human cancer cells, growth inhibition of tumor cell lines HBC-5 and SNB-75 and inhibition of some enzymes including human topoisomerase II or protein kinase EGFR [10].

In 1974 (−)-Gabosine C was isolated from a culture broth of *Streptomyces filipensis* and is identical to a known antibiotic KD16-U1 [11]. The crotonic ester of (−)-Gabosine C known as a (−)-COTC was isolated one year later and was reported to possess cytotoxic and cancerostatic activity [12,13].

The valuable biological activities of carbasugars attracts the attention of both biologists and chemists. The majority of synthetic approaches for the total synthesis of Pericosines start from shikimic acid or quinic acids, which are relatively expensive and have limited availability [14,15]. Other synthetic strategies involve multistep D-ribose transformation and an RCM strategy of carbocylic ring construction [16–20] or functionalization of the carbocyclic core from commercially available enantiopure bromocyclohexadiene diol [21,22].

Synthetic strategies for the preparation of carbasugars from the Gabosine family have been more extensively studied, mainly due to more diversification in that group of bioactive compounds. Total syntheses of Gabosines were reviewed in 2012 by Mac and co-workers [23]. From that time some novel interesting approaches arose including transformation of δ-D-gluconolactone and aldol type cyclization [24,25], demethylative construction of functionalized cyclohexenecarbaldehyde by vinylogous ketal cleavage prepared from inositols [26] or tandem *seleno*-Michael/aldol type

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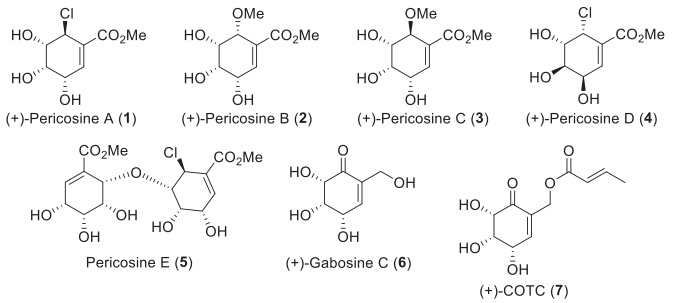


Fig. 1. Structures of naturally occurring Pericosines, (+)-Gabosine C and (+)-COTC.

carbocyclization of monosaccharide derived precursors [27,28].

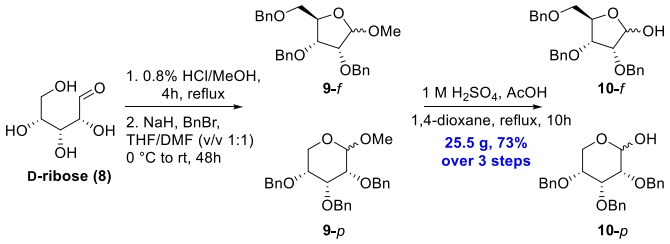
In this work we present our recent studies of the application of the tandem *seleno*-Michael/aldol process in carbasugar synthesis involving D-ribose as a readily available and cheap starting material.

2. Results and discussion

Compounds **2**, **3** and **7** were synthesized using the method initially proposed by us in 2018 in the total synthesis of *β*-(+)-valienamine, where the carbasugar precursor was obtained in 5-steps from naturally occurring D-xylose [28]. In our first approach we planned to prepare linear precursor **12** in a similar way from D-ribose. After cyclization of **12** under optimized conditions we were going to methylate the obtained carbasugar, yielding protected (+)-Pericosine B (**2**) and C (**3**) or perform a selective reduction of the allylic methyl ester, conduct esterification on the crotonic acid derivative and finally oxidize the remaining hydroxyl group, resulting in protected (+)-COTC (**7**) (Scheme 1).

Our initial studies focused on the preparation of precursor **12**. Starting from D-ribose we prepared protected D-ribopyranose (Scheme 2) [29].

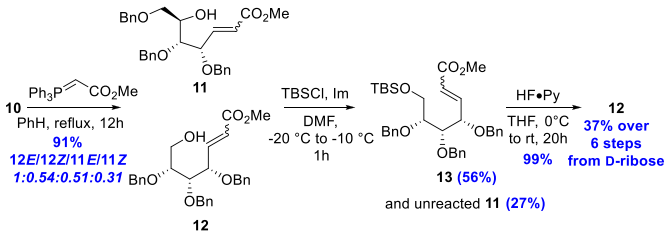
Unfortunately, regardless of the great effort put into chromatographic purification of the pyranose form from the furanose one, we were not able to separate them on a satisfactory scale. After 3 steps we obtained a complex mixture of **10** in 73% yield and we decided to use it without further purification in the next step. The Wittig reaction of **10** with the appropriate phosphonium ylide results in a mixture of E/Z-diastereoisomers derived from both pyranose and furanose forms with a total yield 91%. Oxo-Michael



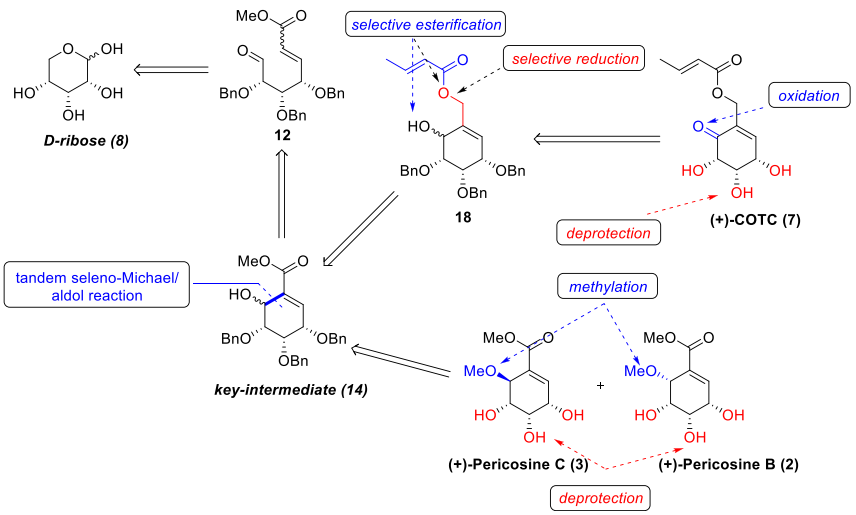
Scheme 2. Preparation of mixture of protected D-ribopyranose and D-ribofuranoses.

products were not observed under refluxing. Attempts of chromatographic separation of desired **11** from **12** were unsuccessful.

In order to separate **11** from **12**, we turned our attention to reagents selective towards primary hydroxyl groups. Initial attempts were performed using the most typical approaches, being the reaction with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of imidazole or triphenylmethyl chloride (TrCl) in pyridine and catalytic amounts of 4-dimethylaminopyridine (DMAP). However, even those reactions carried out with an excess of TrCl or TBDPSCl for 24 h, resulted in poor installation of the appropriate ether (based on TLC plate, and NMR analysis of crude products). We searched for alternative reagents and chose the less hindered and more reactive *tert*-butyldimethylsilyl chloride which was initially rejected in order to avoid additional installation on the secondary group. Maintaining a low temperature and monitoring the reaction by TLC allowed us to obtain a satisfactory yield of **13** (56%) and recover a significant amount of unreacted **11** (27%) via chromatography (Scheme 3). The removal of the TBS-ether with an excess of Olah's reagent was quantitative and allowed the desired **12** to be obtained in 37% yield over 6 steps from D-ribose. Oxidation of the



Scheme 3. Synthesis and resolution of **12**.



Scheme 1. Retrosynthetic analysis of (+)-Pericosine B, (+)-Pericosine C and (+)-COTC from D-ribose.

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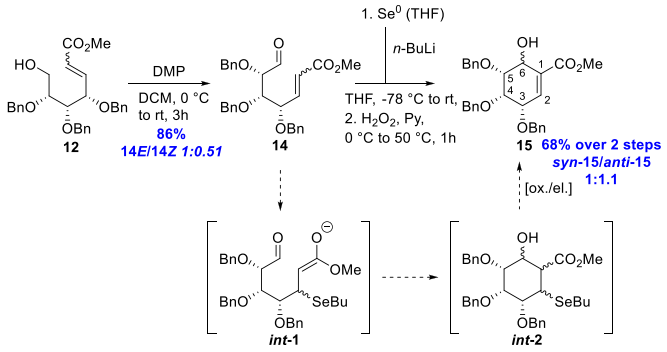


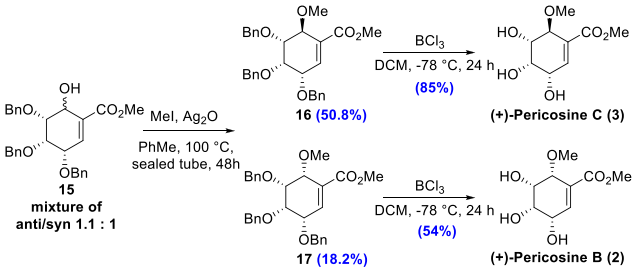
Scheme 4. Preparation of carbasugar precursor and cyclization step.

primary hydroxyl group with Dess-Martin periodinane gave carbasugar precursor **14** as a mixture of diastereoisomers (E/Z 0.51:1) in a very good yield. Further cyclization under tandem seleno/Michael aldol reaction conditions and consecutive oxidation-elimination steps allowed us to obtain the carbocyclic core **15** in 68% yield as a nearly equimolar mixture of *syn* and *anti* diastereoisomers (Scheme 4).

Initially we assumed that the major diastereoisomer would have a relative configuration of C5 and C6 centers *anti*, which was indicated by the relatively high $J_{H5\text{-}H6}$ (7.8 Hz versus 4.4 Hz for *syn*-**15**) in the ^{1}H NMR spectrum. Our theory was confirmed in the total syntheses of natural products derived from both diastereoisomers and by comparison of the obtained ^{1}H and ^{13}C NMR spectra. (+)-Pericosine B (**2**) and (+)-Pericosine C (**3**) were obtained from **15** by methylation with excess MeI/Ag_2O in a sealed tube at 100 °C (Scheme 5). Initial attempts were conducted under much milder conditions and are summarized in Table 1. Only long-term heating in a sealed tube in toluene allowed both diastereoisomers to undergo the reaction to give **16** and **17** in 69% yield.

We postulate that the difference in reactivity of said diastereoisomers could be caused by the fact that the secondary hydroxyl group of **17** is in a pseudo-axial position is more sterically hindered and less reactive than the pseudo-equatorial group in **16** (Scheme 6). The difference is significant to the extent that under very mild conditions (DCM/40 °C, excess of MeI/Ag_2O) *anti*-**15** was completely consumed when *syn*-**15** was fully recovered from the reaction. Fortunately, after the methylation step, **16** and **17** were easily separated by simple column chromatography, while the mixture of *anti*/*syn*-**15** was inseparable.

The final step of the synthesis of (+)-Pericosine B (**2**) and C (**3**) involved deprotection with BCl_3. Due to the presence of an α,β-unsaturated ester fragment, we were limited solely to non-hydrogenolysis methods of benzyl ether removal [30]. After a few unsuccessful attempts, we found that it was crucial to quench the reaction with $NaHCO_3$ and MeOH at −78 °C to avoid a side reaction or decomposition of products. The deprotection step allowed us to



Scheme 5. Preparation of (+)-Pericosine B and (+)-Pericosine C.

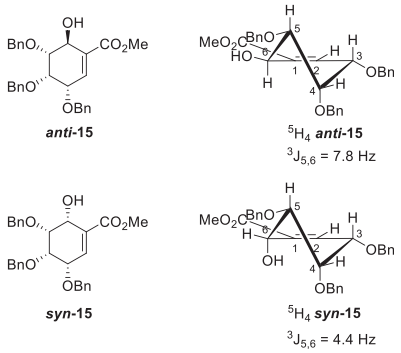
Table 1
Optimization of methylation reaction.

Entry	Solvent	T [°C]	t [h]	16	17	*syn*-15
•1[a]	•DCM	•rt	•24	•traces	•traces	• –
•2[b]	•DCM	•40	•24	•52%	•traces	•48%
•3[b,c]	•PhMe	•100	•24	•37%	•21%	•21%
•4[b,c]	•PhMe	•100	•48	•51%	•18%	•traces

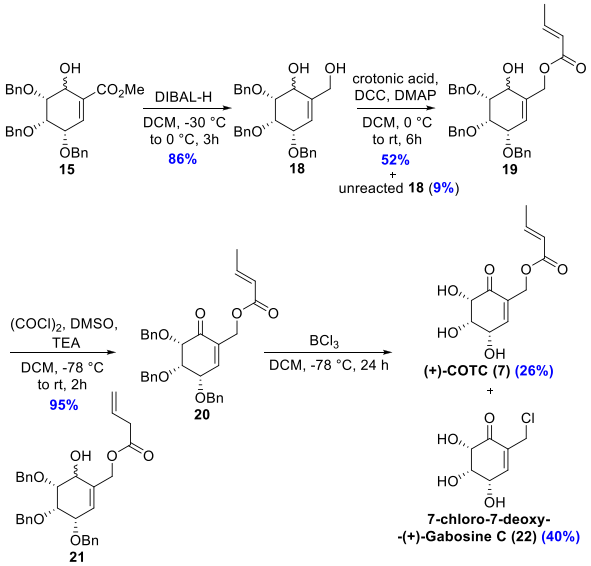
Conditions: 100 mg scale, [a] 10 equiv. MeI, 1.1 equiv. Ag_2O [b] 20 equiv. MeI, 5 equiv. Ag_2O, [c] reaction was performed in a sealed tube.

obtain (+)-Pericosine C (**3**) and (+)-Pericosine B (**2**) in 85% and 54% yield, respectively. ^{1}H and ^{13}C NMR spectra of obtained products are comparable to literature values [17].

Finally, we turned our attention to the synthesis of (+)-COTC (**7**) from carbocyclic intermediate **15** (Scheme 7). In the first step a mixture of diastereoisomers **15** was selectively reduced with DIBAL-H resulting in a mixture of **18**. In the next step different conditions for esterification of the primary hydroxyl group with the crotonyl fragment were examined. Initial attempts of conducting the reaction with crotonic acid and BF_3 or crotonyl chloride and a base catalyst failed. The first method resulted in a complex mixture of products mainly containing the product with two ester fragments. Application of crotonyl chloride and an organic base (pyridine or TEA) led to single esterification of the substrate in moderate



Scheme 6. Possible conformation of compound **15**.



Scheme 7. Final steps of synthesis of (+)-COTC and 7-chloro-7-deoxy-(+)-Gabosine C.

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yield (66%). However, the product was found to have an unexpected structure and only the rearrangement product whit a terminal alkene **21** was observed.

After optimization of the conditions of both processes we decided to focus on a different method of preparing the ester. We turned our attention to the Steglich reaction, which is known as an effective and mild method for ester synthesis. Initial attempts at selective esterification with a stoichiometric amount of crotonic acid and 1.5 equiv. of DCC resulted in very poor yields, even when running the reaction for 24 h. After optimization of the conditions we found a good balance between conversion of substrate and the appearance of an over-esterified product. For effective preparation of **19** a 1.5 M excess of crotonic acid and addition of 0.2 equiv. of DMAP were crucial. This combination resulted in a 52% yield and recovery of 9% of unreacted substrate. Tri-*O*-benzylated (+)-COTC **20** was obtained by Swern oxidation of the remaining hydroxyl group in quantitative yield. Other oxidation strategies, including oxidation with Dess-Martin periodinane, even at increased temperature resulted in selective oxidation of only one diastereoisomer of **19,** leaving the other untouched. This could be explained by the same effect of an axial sterically hindered hydroxyl group, which makes it much less reactive, as was the case in the methylation process.

The final deprotection step with boron trichloride turned out to be extremely difficult due to the presence of the crotonic ester and the other carbonyl group in the molecule. Treatment of **20** with boron trichloride under previously optimized conditions led to a mixture of unprotected (+)-COTC (**7**) and the 7-chloro-analogue of (+)-Gabosine C (**22**) in 26% and 40% yield, respectively. We have not further examined the deprotection step.

3. Conclusion

In summary, we have synthesized three known carbasugars: (+)-Pericosine B, (+)-Pericosine C, (+)-COTC (unnatural) and novel derivative 7-chloro-7-deoxy-(+)-Gabosine C using intramolecular *seleno*-Michael/aldol reactions as key steps. The developed procedure seems to be a good method for synthesis of the carbasugar core in general. The newly obtained 7-chloro-analogue of (+)-Gabosine C could be an interesting building block for the preparation of more complex carbasugar structures.

4. Experimental section

4.1. General information

All starting materials and reagents were purchased from commercial sources and were used without purification. Reactions were monitored using TLC on silica [alu-plates (0.2 mm)]. Plates were visualized with UV light (254 nm) and by treatment with: aqueous cerium (IV) sulfate solution with molybdic and sulfuric acid followed by heating. All organic solutions were dried over anhydrous magnesium sulfate. Reaction products were purified by column chromatography using silica gel 60 (240–400 mesh). Optical rotations were measured at room temperature with a digital polarimeter. $CDCl_3$, D_2O, CD_3OD, $(CD_3)_2CO$ were used as NMR solvents. ^1H NMR spectra were recorded at 600 or 300 MHz, and referenced relative to: $CDCl_3$ – solvent residual peak ($\delta = 7.26$ ppm); D_2O – solvent residual peak ($\delta = 4.79$ ppm); CD_3OD – solvent residual peak ($\delta = 3.31$ ppm); $(CD_3)_2CO$ – solvent residual peak ($\delta = 2.05$ ppm). Data are reported as follows: chemical shift in parts per million (ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dd = doublet of doublet of doublets, ddd = doublet of doublet of doublet of doublets, m = multiplet), coupling constants (in hertz) and integration. ^{13}C NMR spectra were measured at 150 and 75 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard: $CDCl_3$ ($\delta = 77.16$ ppm); CD_3OD ($\delta = 49.00$ ppm); $(CD_3)_2CO$ ($\delta = 206.26$ ppm). High-resolution mass spectra were acquired using ESI-TOF method.

4.1.1. Synthesis of methyl (4S,5R,6R)-4,5,7-tris(benzyloxy)-6-hydroxyhept-2-enoate (11) and methyl (4S,5S,6R)-4,5,6-tris(benzyloxy)-7-hydroxyhept-2-enoate (12)

To a methanolic solution of 0.8% HCl (prepared by dropwise addition of $SOCl_2$ (2 mL) to anhydrous methanol (125 mL)) D-ribose (12.50 g, 83.26 mmol) was added in one portion, and the resulting mixture was refluxed for 4 h under argon (reaction was monitored by TLC DCM/MeOH v/v = 10:1). The reaction mixture was allowed to cool to room temperature, neutralized by addition of solid $NaHCO_3$ (8.50 g, 0.101 mol) and concentrated under reduced pressure. The residue was dissolved in ethanol (100 mL) and concentrated to half of the original volume, toluene (50 mL) was added, and the mixture was concentrated to dryness. The residual crude oil was used without further purification in the next step. The viscous oil from the previous step was dissolved in anhydrous DMF (125 mL) and anhydrous THF (125 mL) and in five portions was added to a 60% NaH suspension in mineral oil (16.63 g, 0.416 mol) cooled to 0 °C. After hydrogen evolution was complete, the mixture was treated with BnBr (39.56 mL, 0.333 mol) and stirred for 48 h in room temperature (reaction was monitored by TLC Hex/EA v/v = 4:1). The reaction mixture was carefully quenched with 10% cold, aqueous solution of NH_4Cl (65 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were washed with water (3 × 80 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (Hex/EA v/v 3:1) allowed to remove major impurities before the next step. The partially purified mixture of ribosides from the previous step was heated under reflux for 10 h with 1 M H_2SO_4 (105 mL), AcOH (120 mL), and 1,4-dioxane (110 mL). The mixture was cooled to room temperature. The aqueous layer was extracted with ethyl acetate (2 × 125 mL), and the combined organic layers were washed with water (3 × 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography (Hex/EA v/v = 3:1) gave the complex mixture of pyranoses and furanoses **10** as a yellowish syrup (73%, 25.50 g, 60.64 mmol). ^1H NMR spectrum is attached in SI.

To a solution of **10** (2.50 g, 5.95 mmol) in anhydrous benzene (20 mL) methyl (triphenylphosphoranylidene)acetate (3.98 g, 11.89 mmol) was added in one portion, and the mixture was stirred at reflux for 8 h (reaction was monitored by TLC Hex/EA v/v = 3:1). After the indicated time, the next portion of methyl (triphenylphosphoranylidene) acetate (1.99 g, 5.95 mmol) was added and heating at reflux was continued for the next 4 h. The reaction mixture was cooled to room temperature and benzene was evaporated under reduced pressure. Triphenylphosphine oxide was precipitated from the mixture of Hex/Ether v/v = 1:1 and filtered by suction. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (Hex/EA v/v = 2:1). The product as a mixture of primary and secondary alcohols **11** and **12 (12*E*/12*Z*/11*E*/11*Z* 1:0.54:0.51:0.30)** was obtained as a colorless oil (91%, 2.58 g, 5.41 mmol). ^1H NMR (*only key signals*) (300 MHz, $CDCl_3$) δ 7.05 (dd, $J = 15.9$, 6.8 Hz, 0.51H ***11E***), 6.95 (dd, $J = 15.8$, 6.5 Hz, 1H ***12E***), 6.45 (dd, $J = 11.8$, 9.1 Hz, 0.30H ***11Z***), 6.32 (dd, $J = 11.8$, 8.5 Hz, 0.54H ***12Z***), 6.14 (dd, $J = 15.9$, 1.1 Hz, 0.51H ***11E***), 6.03 (dd, $J = 11.8$, 1.1 Hz, 0.30H ***11Z***), 5.95 (dd, $J = 15.9$, 1.2 Hz, 1H ***12E***), 5.92 (dd, $J = 11.8$, 1.3 Hz, 0.54H ***12Z***).

To a solution of **11** and **12** (2.58 g, 5.41 mmol) in anhydrous DMF (35 mL) was added *tert*-butyldimethylsilyl chloride (0.82 g,

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5.41 mmol) and imidazole (0.73 g, 10.82 mmol) at −20 °C. The mixture was allowed to reach −10 °C. After 1 h the reaction mixture was carefully quenched with aqueous solution of NH_4Cl (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 40 mL), and the combined organic layers were washed with water (2 × 50 mL) and brine (40 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (Hex/EA v/v = 10:1) to give the titled compound **13** as a mixture of diastereoisomers (*E/Z* 1:0.50) as a colorless oil. (56%, 1.79 g, 3.03 mmol) and an unreacted mixture of secondary alcohols **11** (E/Z: 1:0.71) as a colorless oil (27%, 0.705 g, 1.48 mmol). **Methyl (4S,5S,6R)-4,5,6-tris(benzyloxy)-7-((tert-butyldimethylsilyl)oxy) hept-2-enoate (13):** Yield after 5 steps = 37.2%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36−7.26 (m, 22.5H), 6.97 (dd, *J* = 15.8, 6.6 Hz, 1H *E*-isomer), 6.32 (dd, *J* = 11.8, 8.6 Hz, 0.5H Z-isomer), 5.96 (dd, *J* = 15.9, 1.2 Hz, 1H *E*-isomer), 5.87 (dd, *J* = 11.8, 1.3 Hz, 0.5H *Z*-isomer), 5.45 (dd, *J* = 8.6, 3.0, 1.3 Hz, 0.5H *Z*-isomer), 4.83 (d, *J* = 11.5 Hz, 0.5H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.75−4.71 (m, 1.5H), 4.65 (d, *J* = 11.6 Hz, 0.5H), 4.63 (d, *J* = 11.4 Hz, 1H), 4.60−4.54 (m, 1.5H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.34 (dd, *J* = 6.5, 3.9, 1.3 Hz, 1H), 3.95 (dd, *J* = 10.9, 2.3 Hz, 0.5H), 3.90 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.86 (dd, *J* = 6.4, 3.9 Hz, 1H), 3.82 (dd, *J* = 7.1, 3.0 Hz, 0.5H), 3.78−3.73 (m, 1.5H), 3.72−3.69 (m, 2H), 3.73 (s, 3H CH_3-*E*-isomer), 3.72−3.69 (m, 0.5H), 3.63 (s, 1.5H CH_3-*Z*-isomer), 3.58 (dd, *J* = 6.4, 5.4, 3.3 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 4.5H), 0.03 (s, 6H), 0.01 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.6, 166.4, 148.4, 145.7, 139.0, 138.8, 138.8, 138.5, 138.4, 138.1, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.3, 123.2, 120.9, 81.1, 80.3, 79.7, 79.5, 79.1, 75.5, 74.1, 73.1, 72.7, 72.5, 71.7, 71.5, 63.5, 62.8, 51.7, 51.4, 26.0, 18.4. **HRMS** (ESI): calcd. for $C_{35}H_{46}NaO_6Si$ $[M+Na]^+$ 613.2956, found 613.2956. **Methyl (4S,5R,6R)-4,5,7-tris(benzyloxy)-6-hydroxyhept-2-enoate (11)**: Yield after 5 steps = 17.9%; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37−7.21 (m, 25.5H), 7.04 (dd, *J* = 15.9, 6.8 Hz, 1H), 6.44 (dd, *J* = 11.9, 9.0 Hz, 0.7H), 6.13 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.02 (dd, *J* = 11.9, 1.2 Hz, 0.7H), 5.41 (dd, *J* = 9.1, 2.2, 1.1 Hz, 0.7H), 4.88 (d, *J* = 11.3 Hz, 0.7H), 4.76 (d, *J* = 11.3 Hz, 1H), 4.66−4.57 (m, 2.7H), 4.57−4.47 (m, 4.4H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.40−4.36 (m, 0.7H), 3.86 (dd, *J* = 8.8, 2.3 Hz, 0.7H), 3.81−3.51 (m), 3.75 (s, 3H CH_3-*E*-isomer), 3.72 (s, 2.1H CH_3-*Z*-isomer).

4.1.2. Synthesis of methyl (4S,5S,6R)-4,5,6-tris(benzyloxy)-7-hydroxyhept-2-enoate (12)

A solution of **13** (1.74 g, 2.94 mmol) in anhydrous THF (20 mL) was cooled in an ice bath and Olah's reagent (0.79 mL, ~30 mmol) was added. The resulting mixture was warmed to room temperature and was stirred for 20 h. The reaction mixture was neutralized by addition of solid $NaHCO_3$ and filtered on a thin pad of Celite directly into a separatory funnel with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were washed with water (2 × 30 mL) and brine (30 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (Hex/EA v/v = 2:1) to give the title compound as a mixture of diastereoisomers (*E/Z* 1:0.53) as a colorless oil (99%, 1.39 g, 2.92 mmol); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38−7.21 (m, 23H), 6.94 (dd, *J* = 15.8, 6.6 Hz, 1H *E*-isomer), 6.31 (dd, *J* = 11.8, 8.5 Hz, 0.53H *Z*-isomer), 5.96−5.89 (m, 1.53H E/Z-isomers), 5.49 (dd, *J* = 8.5, 3.0, 1.3 Hz, 1H), 4.84 (d, *J* = 11.5 Hz, 0.53H), 4.77 (d, *J* = 11.3 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 0.53H), 4.67 (d, *J* = 11.3 Hz, 1H), 4.64−4.59 (m, 2H), 4.59−4.56 (m, 1.53H), 4.54 (d, *J* = 11.9 Hz, 0.53H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.26 (dd, *J* = 6.5, 3.7, 1.1 Hz, 1H), 3.90−3.86 (m, 1.53H), 3.81 (dd, *J* = 11.8, 4.8 Hz, 0.53H), 3.78−3.74 (m, 2.5H), 3.74 (s, 3H), 3.72−3.68 (m, 0.53H), 3.67 (s, 1.59H), 3.56 (dt, *J* = 6.8, 4.1 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.2, 166.2, 148.1, 144.9, 138.2, 138.1, 137.8, 137.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 123.4, 121.2, 81.5, 80.7, 78.6, 78.4, 78.1, 75.3, 74.1, 73.1, 71.8, 71.8, 71.5, 61.2, 60.8, 51.6, 51.4; **HRMS** (ESI): calcd. for $C_{29}H_{32}NaO_6$ $[M+Na]^+$ 499.2091, found 499.2091.

4.1.3. Synthesis of methyl (4S,5S,6S,Z)-4,5,6-tris(benzyloxy)-7-oxohept-2-enoate (14)

A solution of **12** (1.36 g, 2.85 mmol) in anhydrous methylene chloride (30 mL) was cooled to 0 °C and Dess−Martin periodinane (1.82 g, 4.82 mmol) was added in one portion and stirred at 0 °C for 15 min. Afterwards the ice bath was removed and reaction mixture was stirred for 3 h at room temperature (reaction was monitored by TLC Hex/EA v/v = 2:1). The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with methylene chloride (3 × 30 mL), and the combined organic layers were washed with water (2 × 100 mL) and brine (100 mL). The organic phase was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (Hex/EA v/v = 6:1) to give the title compound as a mixture of diastereoisomers (E/Z 1:0.51) as a colorless syrup (86%, 1.17 g, 2.47 mmol); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.55 (d, *J* = 1.5 Hz, 0.51H), 9.50 (d, *J* = 1.0 Hz, 1H), 7.36−7.23 (m, 22.5H), 6.92 (dd, *J* = 15.8, 6.2 Hz, 1H), 6.10 (dd, *J* = 11.7, 8.8 Hz, 0.51H), 6.05 (dd, *J* = 15.8, 1.2 Hz, 1H), 5.96 (dd, *J* = 11.7, 1.1 Hz, 0.51H), 5.55 (dd, *J* = 8.7, 5.9, 1.0 Hz, 0.51H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.70−4.65 (m, 2H), 4.62 (s, 1H), 4.59−4.54 (m, 3H), 4.53−4.49 (m, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.32 (dd, *J* = 7.7, 6.3, 1.1 Hz, 1H), 4.10 (dd, *J* = 4.2, 1.5 Hz, 0.51H), 4.05−4.02 (m, 1H), 3.87 (dd, *J* = 5.9, 4.2 Hz, 0.51H), 3.81 (dd, *J* = 7.9, 2.7 Hz, 1H), 3.76 (s, 3H), 3.69 (s, 1.53H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 201.3, 201.3, 166.4, 166.3, 146.8, 145.5, 138.0, 137.7, 137.5, 137.2, 137.2, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 123.6, 123.0, 83.0, 82.5, 82.2, 82.2, 76.7, 73.6, 73.3, 73.1, 73.0, 72.6, 72.0, 51.8, 51.5; **HRMS** (ESI): calcd. for $C_{29}H_{30}NaO_6$ $[M+Na]^+$ 497.1935, found 497.1936.

4.1.4. Synthesis of methyl (3S,4S,5R)-3,4,5-tris(benzyloxy)-6-hydroxycyclohex-1-ene-1-carboxylate (15)

A suspension of elemental selenium (0.373 g, 4.73 mmol) in anhydrous THF (75 mL) was cooled in an ice bath and *n*-BuLi (2.5 M in hexanes, 1.89 mL, 4.73 mmol) was added dropwise (a clear solution was produced) and the mixture was cooled to −78 °C. The solution of **14** (1.87 g, 3.94 mmol in 25 mL of anhydrous THF) was added dropwise and stirring was continued for the next 20 min and then the mixture was allowed to warm to room temperature and was stirred for the next 1 h (reaction was monitored by TLC Hex/EA v/v = 3:1). After towards, the reaction was cooled to 0 °C and a hydrogen peroxide solution (35%, 3.48 mL, 39.4 mmol) and pyridine (1.59 mL, 19.70 mmol) were added. The ice bath was removed and the mixture was heated to 50 °C for 1 h. After that time, water (100 mL) was added and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with water (2 × 150 mL) and brine (150 mL). The organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (Hex/EA v/v = 3.5:1) to give the title product as white solid (68%, 1.27 g, 2.68 mmol); 6 S (anti)/6R (syn) 1.1:1 (based on ^{1}H NMR spectrum); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34−7.17 (m, 31.5H), 6.85 (t, *J* = 1.7 Hz, 1H ***15***-*syn*), 6.77 (d, *J* = 1.3 Hz, 1.1H ***15***-*anti*), 4.90−4.87 (m, 1.1H ***15***-*anti*), 4.82 (dd, *J* = 11.7, 2.7 Hz, 2H), 4.80−4.70 (complex multiplet, 2H (***15***-*syn*) + 4.4H (***15***-*anti*)), 4.60 (d, *J* = 12.0 Hz, 1.1H), 4.54 (s, 2H), 4.50−4.44 (m, 1 (***15***-*syn*) +2.2H (***15***-*anti*)), 4.21 (dd, *J* = 3.4, 1.4 Hz, 1H), 4.10 (dt, *J* = 3.1, 1.6 Hz, 1.1H),

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4.08 (dd, $J = 4.9$, 2.5 Hz, 1.1H), 3.98–3.94 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3.3H), 3.50 (dd, $J = 7.8$, 1.5 Hz, 1.1H), 3.30 (dd, $J = 4.4$, 1.4 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.7, 166.1, 138.7, 138.6, 138.5, 138.0, 137.8, 137.6, 137.5, 137.5, 132.7, 131.7, 128.6, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.9, 127.7, 127.7, 127.7, 127.6, 81.8, 76.7, 76.1, 75.7, 75.1, 74.9, 74.9, 73.7, 73.0, 71.3, 71.0, 70.0, 69.7, 63.8, 52.2, 52.1; **HRMS** (ESI): calcd. for $C_{29}H_{30}NaO_6$ $[M+Na]^+$ 497.1935, found 497.1935.

4.1.5. Synthesis of 3,4,5-tri-O-benzyl-(+)-pericosine B (17) and 3,4,5-tri-O-benzyl-(+)-pericosine C (16)

Procedure I: To solution of **15** (0.20 g, 0.421 mmol) in anhydrous methylene chloride (6 mL) was added silver oxide (0.488 g, 2.11 mmol) and methyl iodide (0.52 mL, 8.43 mmol). The mixture was stirred at 40 °C for 16 h (reaction was monitored by TLC Hex/EA v/v = 3:1). The reaction mixture was filtered through a thin pad of Celite. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (Hex/EA v/v = 3:1) to give **16** as a white solid (52%, 0.107 g, 0.219 mmol) and one diastereoisomer of substrate *syn*-**15** (47%, 0.094 g, 0.198 mmol).

Procedure II: To solution of **15** (0.20 g, 0.421 mmol) in anhydrous toluene (6 mL) was added silver oxide (0.488 g, 2.11 mmol) and methyl iodide (0.52 mL, 8.43 mmol). The mixture was stirred at 100 °C for 24 h in a sealed tube. The reaction mixture was filtered through a thin pad of Celite. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (Hex/EA v/v = 3:1) to give the titled compounds as a white solids (**16**: 37%, 0.076 g, 0.155; **17**: 21%, 0.044 g, 0.090 mmol) and recovered substrate *syn*-**15** (13%, 0.026 g, 0.055 mmol).

3,4,5-tri-*O*-benzyl-(+)-Pericosine C (16) $[\alpha]_D^{24} = +75.5$ (c 0.50, $CHCl_3$); mp: 87–89 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34–7.11 (m, 15H), 6.69–6.64 (m, 1H), 4.76–4.69 (m, 2H), 4.58 (d, $J = 11.8$ Hz, 1H), 4.54 (d, $J = 11.8$ Hz, 1H), 4.52 (s, 2H), 4.39–4.35 (m, 1H), 4.06 (dt, $J = 4.6$, 2.3 Hz, 1H), 4.04 (dt, $J = 3.2$, 1.5 Hz, 1H), 3.68 (s, 3H), 3.57 (dd, $J = 6.9$, 1.6 Hz, 1H), 3.50 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.6, 138.7, 138.3, 137.9, 137.4, 132.5, 128.5, 128.5, 128.3, 128.0, 127.9, 127.7, 127.7, 127.6, 81.5, 78.2, 75.0, 75.0, 73.2, 72.3, 71.5, 60.7, 51.9; **HRMS** (ESI): calcd. for $C_{30}H_{32}NaO_6$ $[M+Na]^+$ 511.2091, found 511.2091.**3,4,5-tri-*O*-benzyl-(+)-Pericosine B (17)** $[\alpha]_D^{24} = -19.2$ (c 1.2, $CHCl_3$); mp: 92.5–93.5 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.27–7.10 (m, 13H), 6.79 (t, $J = 1.5$ Hz, 1H), 4.85 (d, $J = 12.7$ Hz, 1H), 4.79 (d, $J = 12.7$ Hz, 1H), 4.57 (d, $J = 12.0$ Hz, 1H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.49 (d, $J = 12.1$ Hz, 1H), 4.37 (d, $J = 12.1$ Hz, 1H), 4.30 (d, $J = 4.4$ Hz, 1H), 4.15–4.07 (m, 1H), 3.82 (dt, $J = 3.7$, 1.8 Hz, 1H), 3.66 (s, 3H), 3.61 (s, 3H), 3.26 (dd, $J = 4.4$, 1.3 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.4, 139.5, 139.3, 138.1, 138.0, 130.6, 128.6, 128.5, 128.3, 128.1, 127.8, 127.7, 127.6, 127.4, 127.3, 79.1, 75.6, 73.0, 72.3, 71.5, 71.3, 70.5, 61.7, 52.0; **HRMS** (ESI): calcd. for $C_{30}H_{32}NaO_6$ $[M+Na]^+$ 511.2091, found 511.2092. **Methyl (3S,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-hydroxycyclohex-1-ene-1-carboxylate (*syn*-15)** $[\alpha]_D^{24} = +11.2$ (c 0.96, $CHCl_3$); mp: 108.5–110.5 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35–7.17 (m, 15H), 6.85 (t, $J = 1.8$ Hz, 1H), 4.83 (dd, $J = 11.7$, 2.7 Hz, 2H), 4.77 (d, $J = 11.5$ Hz, 1H), 4.72 (s, 1H), 4.55 (s, 2H), 4.49 (d, $J = 11.8$ Hz, 1H), 4.22 (dd, $J = 3.5$, 1.5 Hz, 1H), 3.97–3.95 (m, 1H), 3.73 (s, 3H), 3.30 (dd, $J = 4.4$, 1.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 138.0, 137.8, 137.5, 137.5, 132.7, 128.6, 128.5, 128.4, 128.4, 128.1, 127.9, 127.9, 127.7, 76.7, 76.1, 74.9, 71.3, 69.7, 63.8, 52.2; **HRMS** (ESI): calcd. for $C_{29}H_{30}NaO_6$ $[M+Na]^+$ 497.1935, found 497.1935.

4.1.6. Synthesis of (4S,5S,6R)-4,5,6-tris(benzyloxy)-2-(hydroxymethyl)cyclohex-2-en-1-ol (18)

A solution of compound **15** (0.300 g, 0.63 mmol) in anhydrous methylene chloride (10 mL) was cooled to −30 °C and a solution of DIBAL-H (1 M in methylene chloride, 3.79 mL, 3.79 mmol) was added dropwise. When the addition was complete, the mixture was stirred at −10 °C for 2 h. Subsequently, the mixture was warmed to 0 °C and stirred for 1 h (reaction was monitored by TLC Hex/EA v/v = 1:1). The reaction was quenched with methanol (2 mL) and the mixture was stirred at room temperature for 1 h. Afterwards, a few drops of 1 M aqueous HCl were added (to dissolved solidified residue in the flask), followed by addition of water (20 mL). The aqueous phase was extracted with methylene chloride (3 × 10 mL) and the combined organic phases were washed with water (2 × 20 mL), brine (20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Crude oil was purified by column chromatography (Hex/EA v/v = 1 : 1) to give **18** as a white solid as a mixture of diastereoisomers (86%, 0.243 g, 0.54 mmol); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41–7.26 (m, 30H), 5.80–5.77 (m, 1H), 5.74–5.70 (m, 1H), 4.89 (dd, $J = 12.0$, 8.3 Hz, 2H), 4.83 (dd, $J = 11.9$, 4.7 Hz, 3H), 4.81–4.78 (m, 1H), 4.63 (d, $J = 11.7$ Hz, 1H), 4.61–4.56 (m, 5H), 4.46 (d, $J = 11.7$ Hz, 1H), 4.33 (d, $J = 4.6$ Hz, 1H), 4.32–4.28 (m, 3H), 4.26 (dd, $J = 3.5$, 1.3 Hz, 1H), 4.23 (dt, $J = 3.3$, 1.6 Hz, 1H), 4.15 (d, $J = 13.0$ Hz, 1H), 4.10 (dt, $J = 4.6$, 1.6 Hz, 1H), 4.01–3.97 (m, 1H), 3.47 (dd, $J = 8.3$, 1.6 Hz, 1H), 3.42 (dd, $J = 4.5$, 1.4 Hz, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 139.9, 138.6, 138.1, 138.0, 137.9, 137.9, 137.8, 128.6, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.7, 127.7, 127.5, 127.5, 127.5, 124.3, 122.7, 83.1, 76.0, 75.9, 75.0, 74.5, 73.7, 73.5, 71.8, 71.3, 71.0, 70.7, 69.8, 65.9, 64.7, 64.5; **HRMS** (ESI): calcd. for $C_{28}H_{30}NaO_5$ $[M+Na]^+$ 469.1986, found 469.1983.

4.1.7. Synthesis of ((3S,4S,5R)-3,4,5-tris(benzyloxy)-6-hydroxycyclohex-1-en-1-yl)methyl (2e)-but-2-enoate (19)

A solution of **18** (0.145 g, 0.32 mmol) in anhydrous methylene chloride (5 mL) was cooled to 0 °C. DCC (dicyclohexylcarbodiimide) (0.101 g, 0.49 mmol), DMAP (7.9 mg, 0.065 mmol) and crotonic acid (30.8 mg, 0.36 mmol) were added and the mixture was stirred for 4 h at 0 °C (reaction was monitored by TLC Hex/EA v/v = 2:1). The mixture was warmed to room temperature and stirred for 2 h. After that time, the reaction was quenched with methanol (2 mL) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (Hex/EA v/v = 4:1) to give **19** as a white solid as a mixture of diastereoisomers 6S/6R = 1:1 (36%, 0.060 g, 0.117 mmol).; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41–7.24 (m, 30H), 7.04–6.95 (m, 2H), 5.89–5.84 (m, 2H), 5.79 (s, 1H), 5.76 (d, $J = 1.2$ Hz, 1H), 4.94–4.82 (m, 6H), 4.75 (d, $J = 13.2$ Hz, 1H), 4.67–4.60 (m, 3H), 4.60–4.52 (m, 6H), 4.25 (d, $J = 2.2$ Hz, 1H), 4.23–4.20 (m, 1H), 4.08 (s, 1H), 3.99 (s, 1H), 3.47 (dd, $J = 8.1$, 1.5 Hz, 1H), 3.42 (dd, $J = 4.3$, 0.9 Hz, 1H), 1.91–1.85 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.5, 166.1, 145.4, 145.1, 138.8, 138.0, 137.9, 137.8, 136.2, 135.0, 128.5, 128.4, 128.4, 128.4, 128.3, 128.1, 128.0, 127.8, 127.8, 127.7, 127.7, 127.7, 127.5, 127.5, 127.4, 125.7, 124.8, 122.4, 122.3, 82.9, 76.6, 76.0, 75.8, 75.1, 74.5, 73.7, 73.4, 72.2, 71.1, 70.8, 69.9, 69.6, 65.3, 64.2, 63.7, 60.4, 18.0; **HRMS** (ESI): calcd. for $C_{32}H_{34}NaO_6$ $[M+Na]^+$ 537.2248, found 537.2249.

Sample **19** was separated into two pure diastereoisomers by column chromatography (Hex/EA 4:1) to collect pure ^{1}H NMR and ^{13}C NMR spectra. **((3S,4S,5R,6S)-3,4,5-tris(benzyloxy)-6-hydroxycyclohex-1-en-1-yl)methyl (2E)-but-2-enoate (6S-19)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 (d, $J = 7.4$ Hz, 2H), 7.38–7.25 (m, 13H), 7.00 (dq, $J = 13.9$, 6.9 Hz, 1H), 5.87 (dd, $J = 15.5$, 1.7 Hz, 1H), 5.77 (d, $J = 1.1$ Hz, 1H), 4.95–4.84 (m, 3H), 4.65 (dt, $J = 13.3$, 7.9 Hz, 3H), 4.60–4.53 (m, 3H), 4.25–4.20 (m, 1H), 4.09 (s, 1H), 3.48 (dd, $J = 8.1$, 1.4 Hz, 1H), 1.88 (dd, $J = 6.9$, 1.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 145.5, 138.9, 138.2, 135.1, 128.6, 128.5, 128.3, 128.2, 127.9, 127.8, 127.8, 127.6, 127.5, 125.8, 122.5, 83.1, 76.1, 73.9, 73.6, 72.3, 70.9, 69.7, 63.8, 18.1; **((3S,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-hydroxycyclohex-1-en-1-yl)methyl (2E)-but-2-enoate (6R-19)**:

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^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.26 (m, 15H), 6.99 (dq, J = 15.4, 6.9 Hz, 1H), 5.86 (dq, J = 15.4, 1.5 Hz, 1H), 5.79 (s, 1H), 4.89 (d, J = 11.7 Hz, 1H), 4.87–4.82 (m, 3H), 4.75 (d, J = 13.2 Hz, 1H), 4.60–4.53 (m, 3H), 4.27 (dd, J = 14.6, 3.2 Hz, 2H), 3.99 (s, 1H), 3.42 (dd, J = 4.4, 1.0 Hz, 1H), 1.89 (dd, J = 6.9, 1.7 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.2, 145.3, 138.1, 138.0, 137.9, 136.4, 128.6, 128.5, 128.5, 127.9, 127.9, 127.9, 127.7, 124.9, 122.5, 76.7, 75.9, 75.2, 74.6, 71.2, 70.0, 65.4, 64.3, 18.1.

4.1.8. Synthesis of 3,4,5-tri-O-benzyl-(+)-COTC (20)

A solution of oxalyl chloride (0.030 mL, 0.485 mmol) in anhydrous methylene chloride (5 mL) was cooled to −78 °C. After, DMSO (0.069 mL, 0.972 mmol) was added dropwise and the mixture stirred was for 30 min. A solution of **19** (50.0 mg, 0.097 mmol) in anhydrous methylene chloride (2 mL) was slowly added to the oxidative mixture, and kept at −78 °C for the next 1 h. Triethylamine (0.203 mL, 1.46 mmol) was added, and stirring was continued for 30 min. After the indicated time, the reaction mixture was allowed to slowly warm to room temperature. The reaction was quenched with the addition of saturated NH_4Cl (5 mL), followed by the addition of water (20 mL). The aqueous layer was extracted with methylene chloride (3 × 5 mL) and the combined organic phases were washed with water (2 × 10 mL) and brine (10 mL). The organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure (below 35 °C). The crude product was purified by column chromatography (Hex/EA v/v = 3:1) to give the titled compound as a white solid (95%, 47.5 mg, 0.093 mmol); $[\alpha]_D^{24} = -10.4$ (c 0.50, $CHCl_3$); mp: 87–89 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39–7.26 (m, 15H), 6.99 (dq, J = 15.5, 6.9 Hz, 1H), 6.72 (t, J = 2.1 Hz, 1H), 5.86 (dq, J = 15.5, 1.6 Hz, 1H), 5.03 (d, J = 12.1 Hz, 1H), 4.97 (dd, J = 14.1, 2.3, 1.5 Hz, 1H), 4.88 (d, J = 12.3 Hz, 1H), 4.85–4.77 (m, 2H), 4.60 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.44–4.41 (m, 1H), 4.32–4.29 (m, 1H), 3.99 (d, J = 1.9 Hz, 1H), 1.88 (dd, J = 6.9, 1.7 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 195.3, 166.2, 145.7, 142.9, 138.3, 137.9, 137.4, 134.0, 128.7, 128.7, 128.6, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 122.4, 82.8, 78.9, 75.8, 73.6, 73.1, 71.2, 60.4, 18.3; **HRMS** (ESI): calcd. for $C_{32}H_{32}NaO_6$ $[M+Na]^+$ 535.2091, found 535.2091.

4.2. General procedure for removing benzyl ether with BCl_3

16, **17** or **20** (50 mg) was dissolved in anhydrous methylene chloride (3 mL) and cooled to −78 °C. Subsequently, a 1 M BCl_3 solution in methylene chloride was added dropwise (10 equiv.) and the mixture was stirred for 24 h at −78 °C. After indicated time, the reaction was quenched with solid $NaHCO_3$ (45 equiv.) followed by the addition of anhydrous methanol (1 mL). The reaction mixture was allowed to warm to room temperature and was filtered through a short pad of Celite. The solvent was evaporated under reduced pressure and the products were purified by column chromatography (chloroform/MeOH).

(+)-Pericosine C (3): colorless oil (86%, 19.3 mg, 0.088 mmol) from **16**; $[\alpha]_D^{19} = +64.6$ (c 0.56, EtOH); **^{1}H NMR** (600 MHz, Acetone-d_6/D_2O 6:1) δ 6.69 (d, J = 3.7 Hz, 1H), 4.25 (td, J = 3.8, 1.4 Hz, 1H), 4.17 (d, J = 5.1 Hz, 1H), 3.92 (dd, J = 5.1, 2.1 Hz, 1H), 3.90 (dd, J = 3.9, 2.1 Hz, 1H), 3.72 (s, 3H), 3.45 (s, 3H); **^{13}C NMR** (150 MHz, Acetone-d6/D2O 6 : 1) δ 165.2, 138.1, 128.7, 76.4, 70.4, 68.0, 64.7, 56.9, 49.6.

(+)-Pericosine B (2): colorless oil (64%, 14.3 mg, 0.066 mmol) from **17**; $[\alpha]_D^{19} = +23.2$ (c 0.39, EtOH); **^{1}H NMR** (600 MHz, Acetone-d6/D2O 6:1) δ 6.70 (dd, J = 2.6, 1.4 Hz, 1H), 4.21 (d, J = 4.2 Hz, 1H), 4.17 (t, J = 2.8 Hz, 1H), 3.96–3.93 (m, 1H), 3.81 (dd, J = 4.2, 2.1 Hz, 1H), 3.74 (s, 3H), 3.54 (s, 3H); **^{13}C NMR** (150 MHz, Acetone-d_6/D_2O 6:1) δ 164.6, 139.3, 127.8, 73.9, 69.8, 67.0, 66.7, 58.9, 49.7.

4.2.1. (+)-COTC (7) and 7-chloro-7-deoxy-(+)-gabosine C (22)

20 (40 mg, 0.078 mmol) was dissolved in anhydrous methylene chloride (3 mL) and cooled to −78 °C. Afterwards, a 1 M BCl_3 solution in methylene chloride was added dropwise (0.78 mL, 0.78 mmol) and mixture was stirred for 24 h at −78 °C. After the indicated time, the reaction was quenched with solid $NaHCO_3$ (295 mg, 3.51 mmol) followed by the addition of anhydrous methanol (0.8 mL). The reaction mixture was allowed to warm to room temperature and filtered through a short pad of Celite. The solvent was evaporated under reduced pressure and products were purified by column chromatography (chloroform/MeOH 6:1). **(+)-COTC (7)** was obtained as a white solid (26%, 5.0 mg, 0.021 mmol); $[\alpha]_D^{19} = +94.7$ (c 0.42, MeOH); **^{1}H NMR** (600 MHz, CD_3OD) δ 7.02 (dq, J = 15.5, 6.9 Hz, 1H), 6.70 (td, J = 2.3, 1.2 Hz, 1H), 5.89 (dq, J = 15.5, 1.7 Hz, 1H), 4.87 (dd, J = 2.2, 1.4 Hz, 1H), 4.76 (dt, J = 13.7, 1.6 Hz, 1H), 4.64 (dq, J = 3.9, 2.0 Hz, 1H), 4.37–4.35 (m, 1H), 4.29 (d, J = 2.5 Hz, 1H), 1.89 (dd, J = 6.9, 1.7 Hz, 3H); **^{13}C NMR** (150 MHz, CD_3OD) δ 198.6, 167.5, 147.8, 147.0, 133.4, 123.0, 77.6, 76.8, 69.3, 61.2, 18.0. and **7-chloro-7-deoxy-(+)-Gabosine C (22)** was obtained as a colorless oil (40%, 6.0 mg, 0.031 mmol); $[\alpha]_D^{19} = +88.6$ (c 0.57, EtOH); **^{1}H NMR** (600 MHz, CD_3OD) δ 6.85 (tt, J = 2.3, 1.1 Hz, 1H), 4.68–4.65 (m, 1H), 4.39–4.35 (m, 2H), 4.29 (d, J = 2.5 Hz, 1H), 4.18 (dt, J = 12.3, 1.2 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 198.0, 149.1, 135.1, 77.7, 77.0, 69.3, 40.7; **HRMS** (ESI): calcd. for $C_7H_9ClO_4$ $[M+Na]^+$ 215.0082, found $[M+2+Na]^+$ 217.0057 (32%).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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