JOC The Journal of Organic Chemistry

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Asymmetric Total Synthesis of (+)-Didemniserinolipid B via Achmatowicz Rearrangement/Bicycloketalization

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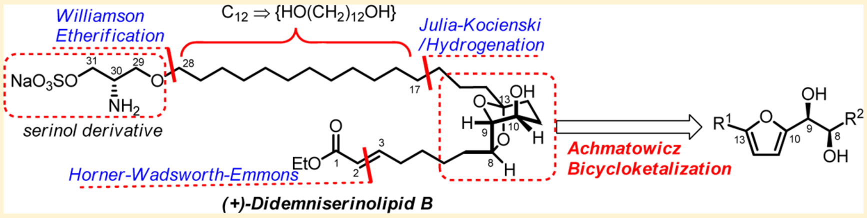
S *Supporting Information*



ABSTRACT: A new synthetic strategy was developed for the asymmetric total synthesis of (+)-didemniserinolipid B in 19 linear steps, featuring a highly efficient and enantioselective construction of 6,8-dioxabicyclo[3.2.1]octane (6,8-DOBCO) framework via a rarely explored Achmatowicz rearrangement/bicycloketalization strategy. In addition, the first total synthesis of the proposed (+)-didemniserinolipid C was accomplished with 41.6% yield in 4 steps from a common advanced intermediate **18**, and a possible revised structure of (+)-didemniserinolipid C was proposed. The new convergent synthetic strategy greatly expedites the entry to the didemniserinolipids and their analogues for biological activity evaluation.

INTRODUCTION

Didemniserinolipids A−C (Figure 1) as the first serinolipids from marine organisms were reported in 1999 by Jiménez and co-workers from the methanol extract of marine tunicate *Didemnum* sp.[1] The initial methanolic extract indicated a potent cytotoxic activity against several tumor cell lines, while the CH_2Cl_2 partition from this extract was found to have the most cytotoxic potency (IC_{50} = 0.25 μg/mL) against tumor cell lines including P388, A549, and HT29.

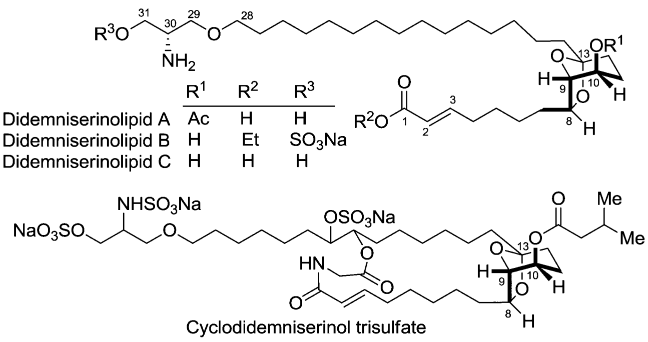


Figure 1. Didemniserinolipids and cyclodidemniserinol trisulfate.

Unfortunately, the pure individual didemniserinolipids from chromatography purification of the CH_2Cl_2 partition showed no cytotoxicity in the same assays. In contrast to the lack of known biological activity for the didemniserinolipids, the structurally related cyclodidemniserinol trisulfate isolated from *Didemnum guttatum* inhibited HIV-1 integrase with an IC_{50} of 60 μg/mL and MCV topoisomerase with an IC_{50} of 72 μg/mL.[2] Interestingly, many simple alkylated 6,8-dioxabicyclo[3.2.1]octanes (6,8-DOBCOs) such as brevicomin, frontalin, and multistriatin are insect pheromones,[3] while many natural products containing the 6,8-DOBCO moiety were reported to be biologically active.[4] Therefore, further biological activity evaluation of didemniserinolipids would be desirable, and consequently their synthetic studies (e.g., total synthesis) could be of paramount importance.

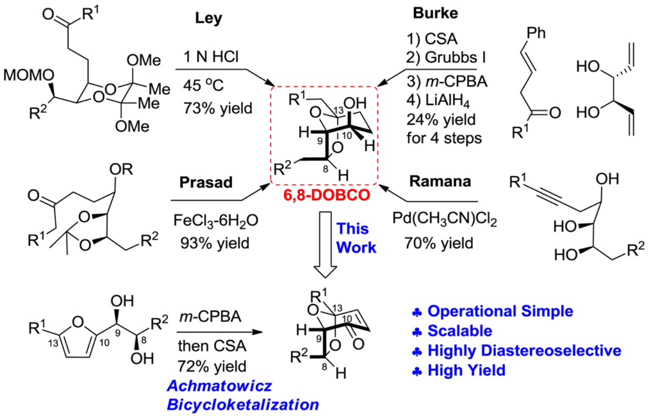
Not surprisingly, the didemniserinolipids with the structurally interesting and intriguing 6,8-DOBCO core attracted much interest in the synthetic community (Scheme 1).[5] In particular, Ley's pioneering synthetic studies culminated in the first total synthesis and structural revision of didemniserinolipid B, in which O-sulfate at C31 was identified and the stereochemistry at C30 was unambiguously determined by chemical synthesis.[5a] It was also noteworthy that the second total synthesis of didemniserinolipid B was elegantly achieved by Burke[5b,c] and co-workers through full exploitation of an efficient, nontraditional ketalization/ring-closing metathesis strategy to access the 6,8-DOBCO moiety.

Our interest in didemniserinolipids was triggered by the central 6,8-DOBCO framework, which was prepared conventionally by intramolecular dehydrative ketalization of a keto diol.[6] We envisioned that such bicyclic ketal core (isolevoglucosenone) could be readily synthesized by oxidative rearrangement (Achmatowicz rearrangement[7]) of furfuryl diol followed by dehydrative ketalization (Scheme 1), a process originally developed by Ogasawara[8] for diastereoselective synthesis of

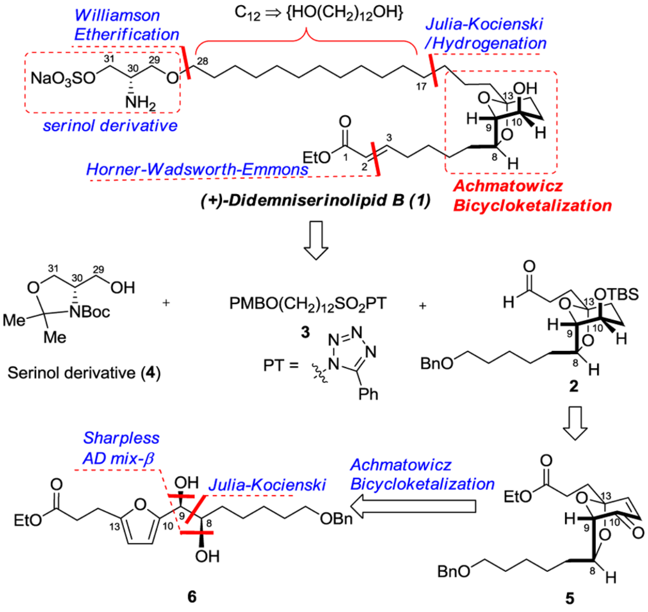
Received: May 20, 2014
Published: July 14, 2014

dx.doi.org/10.1021/jo501142q | *J. Org. Chem.* 2014, 79, 6987−6995

Scheme 1. Key Strategies for Synthesis of 6,8-Dioxabicyclo[3.2.1]octane (6,8-DOBCO)



Scheme 2. Retrosynthetic Analysis of (+)-Didemniserinolipid B



saccharides. Reduction of the isolevoglucosenone through Pd-catalyzed hydrogenation and diastereoselective reduction of the resulting ketone would provide the 6,8-DOBCO moiety of didemniserinolipids, which is complementary to all previous synthetic strategies. This rarely explored protocol for the synthesis of 6,8-DOBCO, however, offers many practical synthetic benefits including readily accessible substrate (2,5-disubstituted furan), simple operation, scalability, reproducibility, and high diastereoselectivity.[9] One of the most compelling advantages over previous syntheses is that the chiral centers (C8, C9, C10, and C13) of 6,8-DOBCO are derived directly or indirectly from the well-established, highly enantioselective Sharpless asymmetric dihydroxylation.[10] If successful, such strategy to construct the 6,8-DOBCO would enable an efficient and modular synthesis of didemniserinolipids, their analogues, and the recently isolated, structurally closely related siladenoserinols,[11] which were found to be inhibitors of p53−Hdm2 interaction.

To demonstrate the synthetic utility of the Achmatowicz rearrangement/bicycloketalization (AR/BCK) strategy to access the 6,8-DOBCO framework in the context of complex natural products, we elected to undertake the total synthesis of (+)-didemniserinolipid B (DslB, **1**), whose molecular structure including relative and absolute configurations was revised and fully confirmed by a previous total synthesis.[5] Our key synthetic strategies are shown in Scheme 2 in a retrosynthetic manner. Specifically, DslB (**1**) could be derived from the union of three functionalized fragments, i.e., serinol derivative (**4**),[5] 1,12-dodecanediol derivative (**3**), and the 6,8-DOBCO (**2**), through Williamson etherification and Julia−Kocienski olefination[12]/hydrogenation. The convergence of such design would permit facile variations of these fragments for potential analogue preparation. The key 6,8-DOBCO fragment (**2**) would arise from hydrogenation and diastereoselective ketone reduction of the bicyclic acetal **5**, which could be provided by the key AR/BCK sequence of the optically pure furfuryl diol **6**. Julia−Kocienski olefination would be utilized again to introduce the six-carbon chain (1,6-hexanediol derivative) with *trans*-alkene (C8−C9) for Sharpless asymmetric dihydroxylation, which yielded the key substrate **6** for the AR/BCK sequence.

■ RESULTS AND DISCUSSION

Our synthesis (Scheme 3) began with preparation of aldehyde **8** by Vilsmeier−Haack formylation[13] of the commercial furan **7** with 90% yield. Julia−Kocienski olefination of aldehyde **8** with sulfone **9** using KHMDS as the base at −78 °C provided a *E*/*Z* mixture of alkene **10** in 90% yield with good *E*/*Z* selectivity (*E*/*Z* = 9/1), which could not be separated by flash column chromatography on silica gel and was directly used for Sharpless asymmetric dihydroxylation with AD mix-*β* to enantioselectively install the vicinal diol of furan (−)-**6** (97% ee by HPLC) in 84% yield. It was noted that the desired, enantiomerically pure **6** was easily separated from the undesired, minor diastereomer derived from the *Z*-isomer of **10** through flash column chromatography on silica column. The AR/BCK sequence of furan (−)-**6**, to our delight, was effectively promoted by *m*-CPBA and then CSA to provide the desired bicyclic acetal (−)-**5** as a single diastereomer in 72% yield on a multigram scale (>6.4 g obtained). Pd-catalyzed chemoselective hydrogenation of enone **5** using EtOAc as the optimal solvent for 2 h gave the ketone **11** in excellent yield (87% yield). Chemo- and diastereoselective reduction of ketone **11** to alcohol **12a** was found to be very challenging because delivery of hydride from the less hindered convex gave the *pseudo*-equatorial alcohol (**12b**) as the major undesired product (Table 1, entries 2−7), except in case of K-selectride (Table 1, entry 1) where it produced a 1:1 mixture of diastereomers in excellent yield. After two cycles of recovery of the undesired **12b** via Dess−Martin periodinane (DMP) oxidation[14] and K-selectride reduction, **12a** could be obtained in 54% overall yield from ketone **11**. It should be noted that Mitsunobu inversion[15] of the secondary alcohol of **12b** under various conditions resulted in a complex mixture. Alternatively, reduction of enone (−)-**5** with various reducing agents followed by palladium-catalyzed saturation of the double bond did not provide better diastereoselectivity or yields of **12a** (see Supporting Information). Compound **12a** was then converted to aldehyde **2** in two steps via TBS silylation and DIBAL-H reduction. Julia−Kocienski olefination of aldehyde **2** with the 12-carbon sulfone **3** was promoted by LiHMDS in THF at −78 °C to provide the alkene **14** as inconsequent 2:1 *E*/*Z* isomers. Removal of the PMB protecting group with DDQ in a pH 7.0 buffered solution gave the alcohol **15**, which was

Scheme 3. Asymmetric Total Synthesis of (+)-Didemniserinolipid B

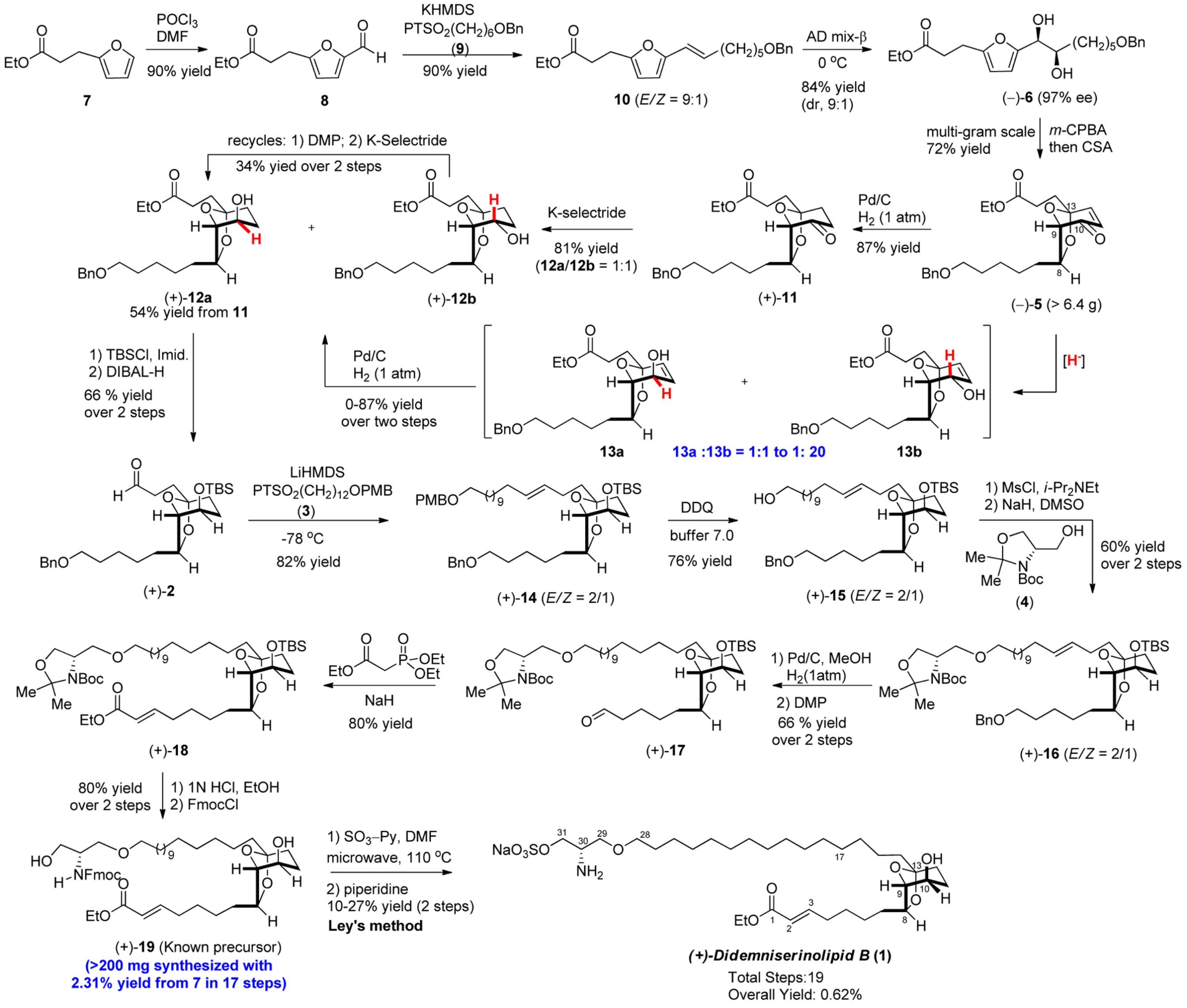


Table 1. Diastereoselective Reduction of Ketone 11[a]

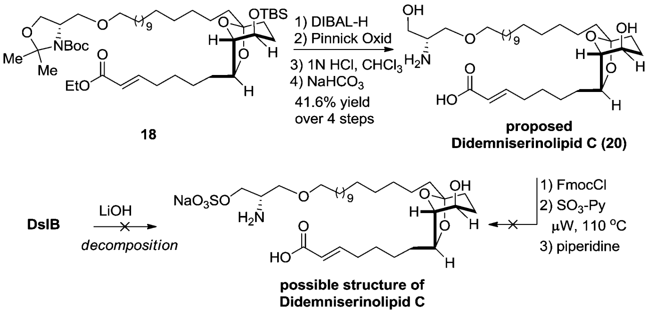
entry	[H⁻]	temp (°C)	ratio (12a/12b)	yield (total, %)
1	**K-selectride**	−78	**1/1**	**81**
2	$NaBH_4$	−78	<1/20	89
3	$LiAlH(Ot\text{-}Bu)_3$	−78	1/3	79
4	SmI_2/*i*-PrOH	rt	1/5	52
5	CBS/BH_3	−20	<1/20	81
6	(*R*)-alpine/BH_3	rt	<1/20	50
7	(*S*,*S*)-Ru* Et_3N/HCO_2H	rt	<1/20	71

[a] The diastereomeric ratio was determined by ^{1}H NMR of the crude products, isolated yield. CBS: Corey−Bakshi−Shibata catalyst. (*S*,*S*)-Ru*: RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN].

subjected to mesylation followed by Williamson etherification with serinol derivative **4**. Under the condition developed previously for Williamson etherification of similar substrates,[5] the union of the functionalized 6,8-DOBCO (**15**) and serinol derivative **4** proceeded efficiently to provide compound **16** with the full-carbon side chain of DslB. Pd-catalyzed hydrogenation of **16** in methanol at room temperature saturated the double bond on the side chain and simultaneously removed the protecting group. The resulting primary alcohol was oxidized with Dess−Martin periodinane (DMP) to yield the aldehyde **17**, which upon treatment of the *in situ* generated stabilized phosphonate anion underwent Horner−Wadsworth−Emmons olefination[16] to provide the conjugate ester **18** as a single *trans*-isomer. Global deprotection of **18** with 1.0 N HCl in ethanol and protection of the resulting amino group with FmocCl provided the known DslB precursor **19** (>200 mg synthesized with 2.31% yield in 17 steps), which was further elaborated to DslB by following the protocols developed by Ley and co-workers.[5a] It should be noted that the sulfation of **19** in our hand was still not efficient (10−27% yield) after many unsuccessful attempts. Nonetheless, we eventually achieved the third total synthesis of DslB using a unique Achmatowicz rearrangement/bicycloketalization strategy. The spectroscopic data of our synthetic DslB were in good agreement with those reported previously for natural and synthetic DslB.[17]

In addition, we have attempted to synthesize didemniserinolipid C from the advanced intermediate **18** (Scheme 4). To this end, **18** was elaborated in a 4-step sequence including

Scheme 4. Total Synthesis of the Proposed (+)-Didemniserinolipid C



18

proposed Didemniserinolipid C (20)

possible structure of Didemniserinolipid C

reduction with DIBAL-H, Pinnick oxidation, global deprotection with 1 N HCl and neutralization with $NaHCO_3$ to furnish didemniserinolipid C (DslC, **20**) in 41.6% overall yield. Unfortunately, the ^{1}H- and ^{13}C NMR spectra of our synthetic DslC was not consistent with those reported for the natural DslC. This finding suggested that the structure of natural DslC might be incorrectly proposed. We suspected that DslC might have the O-sulfate on the side chain, similar to the corresponding side chain for DslB identified by Ley et al. Therefore, the identical sulfation protocol was applied to the synthetic proposed DslC; however, we could not isolate any desired product. Alternatively, DslB was subjected to saponification, which unfortunately resulted in decomposition, and no desired DslC could be detected by NMR. More synthetic work is needed to reach a conclusion for the true structure of the natural DslC.

■ CONCLUSION

We have developed a new synthetic strategy for the asymmetric total synthesis of (+)-didemniserinolipid B with 0.62% yield in 19 steps from commercially available materials, featuring a novel Achmatowicz rearrangement/bicycloketalization strategy for the construction of the key 6,8-dioxabicyclo[3.2.1]octane substructure. The first total synthesis of the proposed structure of (+)-didemniserinolipid C was accomplished with 41.6% yield in 4 steps from a common advanced intermediate **18** and a new possible structure for (+)-didemniserinolipid C was proposed. Most importantly, the new, convergent synthetic strategy would greatly expedite the entry to the didemniserinolipids and their analogues for biological activity evaluation. Further application of the new Achmatowicz rearrangement/bicycloketalization strategy to the 6,8-DOBCOs in total synthesis of siladenoserinols is ongoing and will be reported in a due course.

■ EXPERIMENTAL SECTION

NMR spectra were recorded on a 400 MHz spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) as values relative to the internal chloroform (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). Infrared (IR) spectra were recorded as neat samples (liquid films on KBr plates). HRMS spectra were recorded with a TOF detector (LD+: MALDI ionization). Normal phase HPLC was used to determine enantiomeric excess of chiral compounds with eluents of hexane/*i*-PrOH. Reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled before use from sodium using benzophenone as indicator. Dichloromethane (DCM) was freshly distilled before use from calcium hydride (CaH_2). All other anhydrous solvents were dried over 3 or 4 Å molecular sieves.

Ethyl 3-(5-Formylfuran-2-yl)propanoate (8). To a solution of *N*,*N*-dimethylformamide (DMF, 8.10 g, 110 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was added phosphorus oxychloride ($POCl_3$, 15.4 g, 100 mmol). After 30 min, ethyl 3-(furan-2-yl)propanoate **7** (8.40 g, 50.0 mmol) was added to this solution slowly. After the completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for additional 6 h. Then the reaction was quenched by addition of saturated aqueous Na_2CO_3 solution (100 mL). The organic fractions were collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic fractions were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired product **8** (8.64 g, 45.0 mmol, 90% yield) as a yellow oil. The analytical data were identical to those reported in the literature.[7b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 7.13 (d, J = 3.5 Hz, 1H), 6.26 (d, J = 3.5 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.03 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 171.7, 161.3, 151.9, 109.0 (2 × C), 60.6, 31.8, 23.6, 14.0.

5-(6-(Benzyloxy)hexylsulfonyl)-1-phenyl-1*H*-tetrazole (9). To a solution of 1,6-hexane-diol (11.8 g, 100 mmol) in dry THF (100 mL) at 0 °C was added sodium hydride (NaH, 4.40 g, 110 mmol, ca. 60 wt %) slowly. After 30 min at 0 °C, benzyl bromide (BnBr, 17.1 g, 100 mmol) and tetrabutylammonium iodide (TBAI, 3.90 g, 10.0 mmol) were added to this solution dropwise. After the completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for additional 10 h. Then reaction was quenched by addition of saturated aqueous NH_4Cl solution (100 mL). The organic phase was collected, and the aqueous phase was extracted with EtOAc (3 × 80 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired monobenzylated alcohol (11.4 g, 54.5 mmol, 55% yield) as a colorless oil. To a solution of the alcohol (10.0 g, 48.0 mmol) in THF (400 mL) at 0 °C were added PPh_3 (26.3 g, 96.0 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, 17.8 g, 96.0 mmol), and diisopropyl azodicarboxylate (DIAD, 20.2 g, 96.0 mmol). The reaction mixture was stirred at room temperature for 6 h and then evaporated directly in vacuo. The residue was dissolved in saturated aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford the desired sulfide product (16.1 g, 43.2 mmol, 90% yield) as a colorless oil. To a solution of the sulfide obtained above (16.1 g, 43.2 mmol) in CH_2Cl_2 (500 mL) at 0 °C were added $NaHCO_3$ (20.0 g, 240 mmol) and 3-chloroperbenzoic acid (*m*-CPBA, 19.5 g, 96.0 mmol, ca. 85 wt %). The reaction mixture was stirred overnight at room temperature. The reaction was quenched by addition of saturated aqueous Na_2SO_3 solution (100 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford the desired sulfone product **9** (18.3 g, 45.0 mmol, 82% yield) as a colorless oil. IR (neat, cm^{-1}): 3029, 2859, 2360, 2341, 1737, 1595, 1340, 1151, 1100, 763, 689. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70−7.68 (m, 2H), 7.65−7.56 (m, 3H), 7.39−7.31 (m, 4H), 7.31−7.25 (m, 1H), 4.50 (s, 2H), 3.81−3.64 (m, 2H), 3.47 (t, J = 6.3 Hz, 2H), 2.02−1.89 (m, 2H), 1.68−1.59 (m, 2H), 1.57−1.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 138.5, 133.0, 131.4, 129.7 (2 × C), 128.4 (2 × C), 127.6 (2 × C), 127.5, 125.1 (2 × C), 72.9, 69.9, 55.9, 29.3, 27.9, 25.6, 21.9. HRMS (TOF, LD$^+$) m/z calcd for $C_{20}H_{24}N_4O_3SNa$, $[M + Na]^+$ 423.1467, found 423.1461.

Ethyl 3-(5-(7-(Benzyloxy)hept-1-enyl)furan-2-yl)propanoate (10). To a solution of sulfone **9** (12.3 g, 30.0 mmol) in dry THF (200 mL) at −78 °C was added potassium bis(trimethylsilyl)amide

(KHMDS, 0.5 M in toluene, 84.0 mL, 42.0 mmol) slowly. The reaction mixture was stirred at −78 °C for 30 min, and the aldehyde **8** (8.67 g, 45.0 mmol) was added very slowly. After the completion of addition, the reaction mixture was stirred at −78 °C for additional 2 h. Then, the reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL). The organic phase was collected, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1) to afford the desired alkene product **10** (10.0 g, 27.0 mmol, 90% yield, ratio of *E*/*Z* isomers 9/1) as a pale yellow oil. IR (neat, cm^{-1}): 2926, 2853, 2360, 2341, 1734, 1647, 1373, 732, 696. ^1H NMR (400 MHz, C_6D_6): δ 7.33 (d, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 6.32−6.18 (m, 1H), 6.11 (d, *J* = 15.8 Hz, 1H), 5.94 (d, *J* = 3.2 Hz, 1H), 5.88 (d, *J* = 3.2 Hz, 1H), 4.35 (s, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.30 (t, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.03 (dt, *J* = 6.8, 7.2 Hz, 2H), 1.60−1.50 (m, 2H), 1.37−1.29 (m, 2H), 1.25−1.19 (m, 2H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 171.7, 153.6, 152.6, 139.5, 130.2, 128.5 (2 × C), 127.6 (2 × C), 127.5, 119.2, 101.1, 107.2, 72.9, 70.4, 60.1, 33.0, 30.1, 29.6, 29.2, 26.4, 23.9, 14.1. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{23}H_{30}O_4$, $[M]^+$ 370.2144, found 370.2152.

Ethyl 3-(5-((1*S*,2*R*)-7-(Benzyloxy)-1,2-dihydroxyheptyl)furan-2-yl)propanoate ((−)-6). To a solution of alkene **10** (10.0 g, 27.0 mmol) in *t*-BuOH/H_2O (1/1, 100 mL/100 mL) solution at 0 °C were added sequentially K_2CO_3 (11.0 g, 81.0 mmol), $K_3Fe(CN)_6$(26.0 g, 81.0 mmol), $(DHQD)_2PHAL$(0.21 g, 0.27 mmol), $K_2OsO_4\cdot(H_2O)_2$ (99 mg, 0.27 mmol), and $MeSO_2NH_2$(2.6 g, 27 mmol). The reaction mixture was stirred at 0 °C for 4 days. The reaction was quenched by addition of saturated aqueous Na_2SO_3 (50 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 2:1) to afford the desired diol (−)-**6** (9.16 g, 22.7 mmol, 84% yield, 97 ee %) as a yellow oil. HPLC data: Daicel CHIRALPAK AD-H Column, 10% *i*-PrOH in hexane, t_1 = 12.6 min (98.31%), t_2 = 13.9 min (1.69%). $[\alpha]_D^{20}$ = −6.1 (*c* 0.80, $CHCl_3$). IR (neat, cm^{-1}): 3421, 3030, 2859, 2360, 1733, 1455, 1186, 1097, 1019, 789, 737, 698. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.29 (m, 4H), 7.29−7.25 (m, 1H), 6.18 (d, *J* = 3.1 Hz, 1H), 5.96 (d, *J* = 3.1 Hz, 1H), 4.48 (s, 2H), 4.37 (d, *J* = 6.2 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.85 (dd, *J* = 10.4, 7.0 Hz, 1H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.82 (br s, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.59 (dd, *J* = 13.5, 6.7 Hz, 2H), 1.53−1.44 (m, 1H), 1.44−1.31 (m, 5H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 154.0, 152.7, 138.5, 128.3 (2 × C), 127.5 (2 × C), 127.4, 108.3, 106.0, 73.2, 72.8, 71.0, 70.2, 60.5, 32.7, 32.6, 29.5, 26.0, 25.3, 23.4, 14.1. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{23}H_{32}O_6Na$, $[M + Na]^+$ 427.2097, found 427.2089.

Ethyl 3-((1*R*,7*R*)-7-(5-(Benzyloxy)pentyl)-2-oxo-6,8-dioxabicyclo[3.2.1]oct-3-en-5-yl)propanoate ((−)-5). To a solution of diol (−)-**6** (9.0 g, 22 mmol) in CH_2Cl_2 (50 mL) was added 3-chloroperbenzoic acid (*m*-CPBA, 5.4 g, 27 mmol, ca. 85 wt %) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, and then CSA (5.1 g, 22 mmol) was added. The reaction mixture was stirred at 0 °C for additional 20 min. Then the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (30 mL) and $NaHCO_3$ solution (30 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford the desired product (−)-**5** (6.5 g, 16 mmol, 72% yield) as a yellow oil. $[\alpha]_D^{20}$ = −23.2 (*c* 0.74, $CHCl_3$). IR (neat, cm^{-1}): 3030, 2937, 2361, 1734, 1700, 1372, 1229, 1093, 1028, 899, 737, 698. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.31 (m, 4H), 7.29 (dd, *J* = 9.0, 4.2 Hz, 1H), 6.96 (d, *J* = 9.8 Hz, 1H), 6.04 (d, *J* = 9.8 Hz, 1H), 4.51 (s, 2H), 4.32 (s, 1H), 4.25−4.08 (m, 2H), 3.80 (t, *J* = 6.6 Hz, 1H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.64−2.47 (m, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.71−1.59 (m, 4H), 1.47−1.38 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 172.8, 150.1, 138.6, 128.3 (2 × C), 127.6 (2 × C), 127.5, 126.2, 104.3, 84.3, 75.8, 72.9, 70.1, 60.6, 33.9, 29.6, 29.4, 27.2, 25.9, 25.5, 14.2. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{23}H_{30}O_6Na$, $[M + Na]^+$ 425.1940, found 425.1948.

Ethyl 3-((1*R*,7*R*)-7-(5-(Benzyloxy)pentyl)-2-oxo-6,8-dioxabicyclo[3.2.1]octan-5-yl)propanoate ((+)-11). To a solution of enone (−)-**5** (6.48 g, 16.1 mmol) in ethyl acetate (EtOAc, 50 mL) was added Pd/C (0.85 g, 0.81 mmol, 10.0 wt % Pd on activated carbon) under N_2 (g) at room temperature. The reaction flask was flushed by H_2 (balloon) for 10 min, then the gas outlet was closed, and the reaction mixture was stirred under H_2 (balloon, 1 atm) atmosphere at room temperature for 2 h before filtration through Celite. The solvent (EtOAc) was removed under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:1) to afford (+)-**11** (5.65 g, 14.0 mmol, 87% yield) as yellow oil. $[\alpha]_D^{20}$ = +18.4 (*c* 0.95, $CHCl_3$). IR (neat, cm^{-1}): 3445, 2936, 2858, 2360, 1732, 1635, 1365, 1027, 737, 698. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.29 (m, 4H), 7.29−7.23 (m, 1H), 4.49 (s, 2H), 4.20−4.10 (m, 2H), 4.08 (s, 1H), 4.01 (t, *J* = 6.7 Hz, 1H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.55−2.36 (m, 4H), 2.23−2.13 (m, 2H), 2.13−2.02 (m, 2H), 1.63−1.56 (m, 2H), 1.51−1.29 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.8, 173.2, 138.6, 128.3 (2 x C), 127.6 (2 x C), 127.5, 108.4, 83.9, 78.9, 72.9, 70.1, 60.5, 34.5, 34.4, 32.4, 31.4, 29.6, 28.2, 25.9, 25.3, 14.2. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{23}H_{32}O_6Na$, $[M + Na]^+$ 427.2097, found 427.2099.

Ethyl 3-((1*S*,2*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)propanoate ((+)-12a). To a solution of ketone (+)-**11** (5.60 g, 14.0 mmol) in dry THF (50 mL) at −78 °C was added K-selectride (1.0 M in toluene, 28 mL, 28.0 mmol) slowly. After the completion of addition, the reaction mixture was stirred at −78 °C for 2 h. Then, the reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL). The organic phase was collected, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired alcohol product (+)-**12a** (2.40 g, 5.90 mmol, 42% yield) as a pale yellow oil and *pseudo*-equatorial alcohol (+)-**12b** (2.21 g, 5.45 mmol, 39% yield), which was recycled to afford (+)-**12a** in two steps as follows. To a solution of recycled *pseudo*-equatorial alcohol (+)-**12b** (2.1 g, 5.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added $NaHCO_3$ (2.2 g, 25 mmol) and Dess−Martin periodinane (DMP, 4.2 g, 10 mmol). The reaction mixture was stirred for 2 h at 0 °C. Then, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford the desired ketone product (+)-**11** (1.8 g, 4.4 mmol, 90% yield) as a pale yellow oil. To a solution of ketone (+)-**11** (1.8 g, 4.4 mmol) in dry THF (20 mL) at −78 °C was added K-selectride (1.0 M in toluene, 8.8 mL, 8.8 mmol) slowly. After the completion of addition, the reaction mixture was stirred for 2 h at −78 °C. Then the reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL). The organic phase was collected, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired alcohol product (+)-**12a** (0.68 g, 1.7 mmol, 38% yield) as a pale yellow oil and *pseudo*-equatorial alcohol (+)-**12b** (0.65 g, 1.6 mmol, 37% yield). After two cycles of recovery *pseudo*-equatorial alcohol (+)-**12b**, desired (+)-**12a** could be obtained in 54% overall yield (3.1 g, 7.5 mmol) from ketone (+)-**11**. (+)-**12a**: $[\alpha]_D^{20}$ = +27.0 (*c* 1.00, $CHCl_3$). IR (neat, cm^{-1}): 3629, 2935, 2858, 2361, 1733, 1366, 1235, 1114, 1027, 736, 698. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 7.1, 5.8 Hz, 4H), 7.28 (dd, *J* = 8.5, 3.8 Hz, 1H), 4.49 (s, 2H), 4.18−4.07 (m, 2H), 4.04 (s, 1H), 3.92−3.83 (m, 1H), 3.59 (s, 1H), 3.46 (t, J = 6.5 Hz, 2H), 2.53−2.35 (m, 3H), 2.13−1.92 (m, 3H), 1.87−1.75 (m, 1H), 1.69−1.52 (m, 5H), 1.48−1.37 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 138.5, 128.3 (2 × C), 127.5 (2 × C), 127.4, 108.3, 82.3, 78.0, 72.8, 70.1, 66.1, 60.3, 34.9, 31.5, 30.6, 29.6, 27.6, 25.9, 25.37, 24.9, 14.1. HRMS (TOF, LD$^+$) m/z calcd for $C_{23}H_{34}O_6Na$, $[M + Na]^+$ 429.2253, found 429.2246.

Ethyl 3-((1*S*,2*R*,7*R*)-7-(5-(Benzyloxy)pentyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)propanoate ((+)-12b). $[\alpha]_D^{20}$ = +21.4 (c 0.95, $CHCl_3$). IR (neat, cm^{-1}): 3445, 2970, 2858, 2360, 1733, 1647, 1419, 1026, 697. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.31 (m, 4H), 7.31−7.25 (m, 1H), 4.49 (s, 2H), 4.21−4.17 (m, 1H), 4.17−4.06 (m, 2H), 3.91 (s, 1H), 3.88 (t, J = 4.8 Hz, 1H), 3.47 (t, J = 6.5 Hz, 2H), 2.51−2.34 (m, 2H), 2.08−1.97 (m, 3H), 1.91 (t, J = 5.7 Hz, 1H), 1.79 (br s, 1H), 1.68−1.58 (m, 6H), 1.49−1.36 (m, 4H), 1.24 (t, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 138.5, 128.3 (2 × C), 127.6 (2 × C), 127.4, 107.3, 80.8, 75.8, 72.8, 70.2, 66.2, 60.3, 34.9, 34.2, 30.8, 29.6, 27.9, 26.4, 25.9, 25.4, 14.2. HRMS (TOF, LD$^+$) m/z calcd for $C_{23}H_{34}O_6Na$, $[M + Na]^+$ 429.2253, found 429.2256.

3-((1*R*,2*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-2-(*tert*-butyldimethylsilyloxy)-6,8-dioxabicyclo[3.2.1]octan-5-yl)propanal ((+)-2). To a solution of (+)-**12a** (1.9 g, 4.7 mmol) in dry DMF (20 mL) at 0 °C were added imidazole (1.4 g, 9.3 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl, 0.63 g, 9.3 mmol). After the completion of addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of water (60 mL). The organic fraction was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford the desired product ester (2.0 g, 3.8 mmol, 82% yield) as a colorless oil. To a solution of ester (2.0 g, 3.8 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added diisobutylaluminum hydride solution (DIBAL-H, 1.0 M, 4.2 mL, 4.2 mmol) dropwise. After stirring at −78 °C for 2 h, the reaction was quenched by addition of saturated aqueous Rochelle salt (sodium potassium tartrate) solution (50 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford desired aldehyde (+)-**2** (1.5 g, 3.1 mmol, 80% yield) as a yellow oil. $[\alpha]_D^{20}$ = +11.1 (c 0.90, $CHCl_3$). IR (neat, cm^{-1}): 3444, 2930, 2856, 2360, 1724, 1646, 1635, 1363, 1028, 834, 774. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.38−7.31 (m, 4H), 7.31−7.24 (m, 1H), 4.50 (s, 2H), 3.93 (s, 1H), 3.84−3.74 (m, 1H), 3.60 (s, 1H), 3.47 (t, J = 6.4 Hz, 2H), 2.56 (t, J = 7.1 Hz, 2H), 2.07 (qd, J = 14.8, 7.4 Hz, 2H), 1.98−1.83 (m, 2H), 1.63 (dt, J = 13.7, 6.8 Hz, 2H), 1.59−1.45 (m, 4H), 1.45−1.35 (m, 4H), 0.90 (s, 9H), 0.07 (d, J = 2.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 138.6, 128.3 (2 × C), 127.6 (2 × C), 127.5, 108.0, 83.1, 78.1, 72.9, 70.2, 66.7, 37.4, 35.0, 30.9, 29.7, 29.2, 26.0, 25.9, 25.8, 25.5, 18.2 (3 × C), −4.6, −4.7. HRMS (TOF, LD$^+$) m/z calcd for $C_{27}H_{44}O_5SiNa$, $[M + Na]^+$ 499.2856, found 499.2870.

5-(12-(4-Methoxybenzyloxy)dodecylsulfonyl)-1-phenyl-1*H*-tetrazole (3). To a solution of 1,12-dodecan-diol (10.0 g, 50.0 mmol) in dry THF (100 mL) at 0 °C, was added NaH (2.4 g, 60 mmol, ca. 60 wt %) slowly. After 30 min at 0 °C, 4-methoxybenzyl chloride (PMBCl, 8.6 g, 55 mmol) and tetrabutylammonium iodide (TBAI, 1.8 g, 5.0 mmol) were added sequentially to this solution dropwise. After the completion of addition, the reaction mixture was allowed to warm to room temperature, and then the reaction was heated to reflux for 10 h. The reaction was quenched by addition of saturated NH_4Cl aqueous solution (100 mL). The organic phase was collected, and the aqueous phase was extracted with EtOAc (3 × 80 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired product PMB-protected alcohol (9.9 g, 31 mmol, 61% yield) as a colorless oil. To a solution of the alcohol (9.9 g, 31 mmol) in THF (200 mL) at 0 °C were added PPh_3 (9.7 g, 37 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, 6.6 g, 37 mmol), and diisopropyl azodicarboxylate (DIAD, 7.4 g, 37 mmol). The reaction mixture was stirred at room temperature for 6 h and then evaporated directly in vacuo. The residue was dissolved in saturated aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford the desired sulfide product (12 g, 25 mmol, 81% yield) as a colorless oil.To a stirred solution of the sulfide (10.9 g, 24.8 mmol) in CH_2Cl_2 (200 mL) were added $NaHCO_3$ (10.4 g, 124 mmol) and 3-chloroperbenzoic acid (*m*-CPBA, 10.0 g, 49.6 mmol, ca. 85 wt %) at 0 °C. The reaction mixture was stirred overnight at room temperature. The reaction was quenched by addition of saturated aqueous Na_2SO_3 solution (100 mL), and reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford the desired sulfone product **3** (9.9 g, 19 mmol, 78% yield) as a colorless oil. IR (neat, cm^{-1}): 3067, 2926, 2853, 1718, 1653, 1558, 1420, 1340, 1152, 1074, 916, 819, 761, 717. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, J = 7.7, 1.5 Hz, 2H), 7.65−7.57 (m, 3H), 7.27 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.45 (s, 2H), 3.81 (s, 3H), 3.78−3.68 (m, 2H), 3.45 (t, J = 6.7 Hz, 2H), 1.95 (dt, J = 12.1, 7.8 Hz, 2H), 1.66−1.55 (m, 2H), 1.55−1.45 (m, 2H), 1.40−1.23 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 159.1, 133.7, 133.0, 131.4, 130.7, 130.2, 129.8, 129.7, 129.2, 128.2, 125.0, 113.7, 72.4, 70.2, 56.0, 55.2, 29.7, 29.5 (3 × C), 29.4, 29.1, 28.9, 28.1, 26.1, 21.9. HRMS (TOF, LD$^+$) m/z calcd for $C_{27}H_{38}O_4N_4SNa$, $[M + Na]^+$ 537.2511, found 537.2524.

((1*R*,2*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-(15-(4-methoxybenzyloxy)pentadec-3-enyl)-6,8-dioxabicyclo[3.2.1]-octan-2-yloxy)(*tert*-butyl)dimethylsilane ((+)-14). To a solution of sulfone **3** (2.9 g, 5.6 mmol) in dry THF (20 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (LiHMDS, 1.0 M in THF, 6.2 mL, 6.2 mmol) slowly. The reaction mixture was stirred at −78 °C for 30 min, and the aldehyde (+)-**2** (1.34 g, 2.80 mmol) was added very slowly. After the completion of addition, the reaction mixture was stirred at −78 °C for additional 2 h. Then, the reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL). The organic phase was collected, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford the desired alkene product (+)-**14** (1.76 g, 2.30 mmol, 82% yield, ratio of E/Z isomers 2/1) as a pale yellow oil. $[\alpha]_D^{20}$ = +20.9 (c 0.60, $CHCl_3$). IR (neat, cm^{-1}): 3048, 2927, 2854, 2360, 1810, 1541, 1437, 1248, 1099, 1172, 868, 774. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 4.3 Hz, 3H), 7.23−7.12 (m, 4H), 6.80 (d, J = 7.9 Hz, 2H), 5.36−5.26 (m,2H), 4.43 (s, 2H), 4.36 (s, 2H), 3.87 (s, 1H), 3.73 (s, 1H), 3.73 (s, 3H, overlap), 3.53 (s, 1H), 3.44−3.32 (m, 4H), 2.14−2.03 (m, 2H), 1.99−1.75 (m, 4H), 1.74−1.62 (m, 2H), 1.62−1.44 (m, 6H), 1.41−1.31 (m, 4H), 1.29−1.14 (m, 18H), 0.84 (s, 9H), 0.02 (d, J = 2.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.6, 130.8, 130.5, 130.2, 129.7, 129.2, 128.3 (2 × C), 127.6 (2 × C), 127.5, 113.7 (2 × C), 108.8, 83.0, 77.7, 72.9, 72.4, 70.4, 70.1, 66.9, 55.2, 37.2, 35.2, 32.6, 30.5, 29.8, 29.7, 29.6 (3 × C), 29.5, 29.4, 29.3, 29.2, 26.1 (3 × C), 26.0, 25.9, 25.5, 18.3, −4.6 (2 × C). HRMS (TOF, LD$^+$) m/z calcd for $C_{47}H_{76}O_6SiNa$, $[M + Na]^+$ 787.5309, found 787.5331.

15-((1*R*,2*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-2-(*tert*-butyldimethylsilyloxy)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadec-12-en-1-ol ((+)-15). To a solution of (+)-**14** (1.76 g, 2.30 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 0.626 g, 2.76 mmol) and buffer (pH = 7.0) solution (2 mL). After the completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by addition of saturated sodium thiosulfate (20 mL). The organic fractions were collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired product (+)-**15** (1.12 g, 1.75 mmol, 76% yield, *E*/*Z* = 2/1) as a colorless oil. $[\alpha]_D^{20}$ = +11.0 (*c* 0.50, $CHCl_3$). IR (neat, cm^{-1}): 2927, 2854, 2360, 2341, 1734, 1608, 1489, 1252, 1058, 868, 774. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.30 (m, 4H), 7.30−7.24 (m, 1H), 5.42−5.32 (m, 2H), 4.49 (s, 2H), 3.93 (s, 1H), 3.84−3.74 (m, 1H), 3.68−3.56 (m, 3H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.25−2.07 (m, 2H), 2.03−1.85 (m, 4H), 1.77−1.69 (m, 2H), 1.67−1.49 (m, 6H), 1.46−1.35 (m, 4H), 1.35−1.25 (m, 18H), 0.91 (s, 9H), 0.07 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 130.4, 130.1, 129.7, 129.2, 128.3 (2 × C), 127.5 (2 × C), 127.4, 108.7, 108.7, 83.0, 83.0, 77.8, 77.7, 77.2, 72.8, 70.2, 66.8, 62.9, 37.2, 35.1, 32.7, 32.6, 30.5, 30.4, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 27.1, 26.0 (3 × C), 25.9, 25.7, 25.4, 20.7, 18.2, −4.6, −4.7. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{39}H_{68}O_5SiNa$, $[M + Na]^+$ 667.4734, found 667.4735.

(4*S*)-*tert*-Butyl 4-((15-((1*R*,2*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-2-(*tert*-butyldimethylsilyloxy)-6,8-dioxabicyclo[3.2.1]octan-5-yl)-pentadec-12-enyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate ((+)-16). To a solution of alcohol (+)-**15** (1.12 g, 1.75 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added *N*,*N*-diisopropylethylamine (DIPEA, 0.44 g, 3.4 mmol), 4-(dimethylamino)pyridine (DMAP, 20 mg, 0.17 mmol), and methanesulfonyl chloride (MsCl, 0.30 g, 2.6 mmol) slowly. The reaction was allowed to warm to room temperature. After 4 h, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (20 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product (0. 94 g, 1.3 mmol, 78% yield *E*/*Z* = 2/1) as a yellow oil was used directly for the Williamson etherification without further purification. To a solution of serinol derivative **4** (0.60 g, 2.6 mmol) in dry DMSO (5 mL) were added NaH (0.12 g, 2.9 mmol, ca. 60 wt %) and the mesylate (0.94 g, 1.3 mmol). The reaction was allowed to warm to room temperature. After 24 h, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired product (+)-**16** (0.86 g, 1.1 mmol, 77% yield *E*/*Z* = 2/1) as a yellow oil. $[\alpha]_D^{20}$ = +23.3 (*c* 0.55, $CHCl_3$). IR (neat, cm^{-1}): 2928, 2855, 2360, 2341, 1828, 1792, 1365, 1207, 1102, 867, 735. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.30 (m, 4H), 7.29 (s, 1H), 5.43−5.33 (m, 2H), 4.50 (s, 2H), 4.11−3.96 (m, 2H), 3.95−3.87 (m, 2H), 3.85−3.75 (m, 1H), 3.60 (s, 2H), 3.51−3.43 (m, 4H), 3.44−3.36 (m, 1H), 3.33−3.27 (m, 1H), 2.22−2.09 (m, 2H), 2.05−1.89 (m, 4H), 1.71−1.36 (m, 27H), 1.35 1.20 (m, 18H), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 130.5, 130.2, 129.7, 129.4, 128.3 (2 × C), 127.6, 127.4, 108.7, 83.0, 77.7, 73.0, 71.8, 71.5, 70.1, 67.0, 37.3, 35.2, 32.4, 30.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 28.5, 28.4, 27.1, 26.0, 25.9, 25.6, 25.5, 20.2, 18.3, −4.6, −4.7. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{50}H_{87}O_8NSiNa$, $[M + Na]^+$ 880.6099, found 880.6103.

(4*S*)-*tert*-Butyl 4-((15-((1*R*,2*S*,7*R*)-2-(*tert*-Butyldimethylsilyloxy)-7-(5-oxopentyl)-6,8-dioxabicyclo[3.2.1]octan-5-yl)-pentadec-12-enyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate ((+)-17). To a solution of alkene (+)-**16** (0.86 g, 1.1 mmol) in methanol (MeOH, 5 mL) was added Pd/C (53 mg, 0.050 mmol, ca. 10.0 wt % Pd on activated carbon) under N_2 atmosphere at room temperature. The reaction flask was flushed by H_2 gas for 10 min, then the gas outlet was closed, and the reaction mixture under H_2 atmosphere (balloon, 1 atm) was stirred at room temperature for 2 h before filtration through Celite. The solvent was removed under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 8:1) to afford the desired alcohol (0.67 g, 0.87 mmol, 87% yield) as yellow oil. To a solution of the alcohol (0.67 g, 0.87 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C were added $NaHCO_3$ (0.37 g, 4.35 mmol) and Dess−Martin periodinane (DMP, 0.74 g, 1.7 mmol). The reaction mixture was stirred at 0 °C for 2 h. Then, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired aldehyde (+)-**17** (0.51 g, 0.66 mmol, 76% yield) as a pale yellow oil. $[\alpha]_D^{20}$ = +13.5 (*c* 0.65, $CHCl_3$). IR (neat, cm^{-1}): 2927, 2854, 2361, 1731, 1646, 1387, 1365, 1089, 834, 774. ^1H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 4.12−3.96 (m, 2H), 3.96−3.88 (m, 2H), 3.85−3.76 (m, 1H), 3.60 (s, 2H), 3.52−3.36 (m, 2H), 3.35−3.18 (m, 1H), 2.48−2.43 (m, 2H), 2.00−1.79 (m, 2H), 1.76−1.64 (m, 4H), 1.58−1.38 (m, 29H), 1.36−1.18 (m,18H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 109.3 (2 × C), 83.1 (2 × C), 77.4 (2 × C), 71.4 (2 × C), 66.9 (2 × C), 56.5, 43.7, 37.6, 35.1, 30.3, 29.8, 29.6 (6 × C), 29.5 (4 × C), 29.4 (4 × C), 28.4, 26.1, 25.9, 25.8 (3 × C), 25.2, 23.0, 21.9, 18.2, −4.7, −4.6. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{43}H_{81}O_8NSiNa$, $[M + Na]^+$ 790.5629, found 790.5644.

(4*S*)-*tert*-Butyl 4-((15-((1*R*,2*S*,7*R*)-2-(*tert*-Butyldimethylsilyloxy)-7-((*E*)-7-ethoxy-7-oxohept-5-enyl)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadec-12-enyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate ((+)-18). To a solution of NaH (61 mg, 1.5 mmol, ca. 60 wt %) in THF (5 mL) at 0 °C was added triethyl phosphonoacetate (0.32 g, 1.3 mmol). After 30 min of stirring at 0 °C, a solution of aldehyde (+)-**17** (0.51 g, 0.66 mmol) in THF (1 mL) was added dropwise at 0 °C. After the reaction mixture was stirred at 0 °C for 2 h, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (5 mL). The organic phase was collected, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford a single *E* isomer (+)-**18** (0.44 g, 0.52 mmol, 80% yield) as a yellow oil. $[\alpha]_D^{20}$ = +14.3 (*c* 0.65, $CHCl_3$). IR (neat, cm^{-1}): 2927, 2855, 2360, 1721, 1702, 1655, 1463, 1388, 1365, 1257, 1176, 1089, 834, 774. ^1H NMR (400 MHz, $CDCl_3$): δ 6.95 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.80 (d, *J* = 15.6 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.10−3.95 (m, 2H), 3.92 (d, *J* = 6.2 Hz, 2H), 3.83−3.71 (m, 1H), 3.60 (s, 1.5H), 3.53−3.35 (m, 2.5H), 3.35−3.24 (m, 1H), 2.19 (dd, *J* = 13.5, 6.8 Hz, 2H), 2.02−1.75 (m, 2H), 1.74−1.36 (m, 30H), 1.36−1.14 (m, 24H), 0.91 (s, 9H), 0.07 (d, *J* = 3.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 166.6, 148.9, 121.4 (2 × C), 109.24, 83.0, 80.3, 77.5, 71.3, 70.0, 66.8, 60.3, 60.0 (2 × C), 37.5, 35.0, 32.0, 30.2, 29.8, 29.7 (3 × C), 29.6 (3 × C), 29.5, 29.4, 28.4, 27.8, 26.7, 26.1, 26.0, 25.9 (5 × C), 25.1, 24.4, 22.8, 21.0, 18.3, 14.2, 14.1, −4.6, −4.7. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{47}H_{87}O_9NSiNa$, $[M + Na]^+$ 860.6048, found 860.6066.

(*E*)-Ethyl 7-((1*R*,2*S*,7*R*)-5-(15-((*R*)-2-(((9*H*-Fluoren-9-yl)-methoxy)carbonylamino)-3-hydroxypropoxy)pentadec-3-enyl)-2-(*tert*-butyldimethylsilyloxy)-6,8-dioxabicyclo[3.2.1]-octan-7-yl)hept-2-enoate ((+)-19). A solution of (+)-**18** (0.44 g, 0.52 mmol) in EtOH (5 mL) and 1 N HCl (1 mL) was stirred at 45 °C for 12 h. The mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 5:1) to afford the desired product (0.31 g, 0.50 mmol, 96% yield) as a yellow oil. To a solution of the product obtained (0.19 g, 0.31 mmol) in dioxane/H_2O (2 mL/2 mL) were added K_2CO_3 (0.21 g, 1.5 mmol) and 9-fluorenylmethoxycarbonyl chloride (FmocCl, 0.39 g, 1.5 mmol). After the reaction mixture was stirred for 4 h, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (5 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 1:1) to afford desired protected product (+)-**19** (0.21 g, 0.25 mmol, 80% yield) as a yellow oil. $[\alpha]_D^{20}$ = +20.6 (*c* 0.60, $CHCl_3$). IR (neat, cm^{-1}): 3440, 2971, 2360, 2341, 2067, 1737, 1720, 1438, 1228, 1216. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 6.95 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.81 (d, *J* = 15.8 Hz, 1H), 5.47 (d, *J* = 5.6 Hz, 1H), 4.40 (d, *J* = 6.5 Hz, 2H), 4.26−4.14 (m, 3H), 4.05 (s, 1H), 3.92−3.80 (m, 3H), 3.72 (br s, 1H), 3.68−3.56 (m, 3H), 3.44 (t, *J* = 6.3 Hz, 2H), 2.21 (dd, *J* = 13.8, 6.8 Hz, 2H), 2.04−1.92 (m, 2H), 1.84−1.72 (m, 1H), 1.73−1.60 (m, 2H), 1.61−1.36 (m, 12H), 1.36−1.17 (m, 24H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 156.4, 148.8, 143.8 (2 × C), 141.2, 127.5 (2 × C), 126.9 (2 × C), 125.0, 124.9 (2 × C), 121.3, 119.8 (2 × C), 109.5, 82.3, 77.6, 71.7, 71.2, 66.7, 66.1, 63.6, 60.1, 51.7, 47.1, 46.3, 37.4, 34.9, 31.9, 30.0, 29.7, 29.6 (3 × C), 29.5 (3 × C), 29.4, 29.3, 27.7, 25.9, 25.0, 24.9 (2 × C), 22.8, 14.1. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{48}H_{71}O_9NNa$, $[M + Na]^+$ 828.5027, found 828.5051.

(+)-Didemniserinolipid B ((+)-1). According to the procedure reported by Ley et al.,[5a] to a solution of the (+)-**19** (20 mg, 0.025 mmol) in dry DMF (0.4 mL) was added sulfur trioxide pyridine complex (SO_3·Py, 4.8 mg, 0.050 mmol). The reaction was stirred under microwave irradiation at 110 °C for 2 h. The reaction was concentrated under reduced pressure to afford crude product as a yellow oil. The crude product was dissolved in DMF/piperidine (0.4 mL/0.1 mL), and the resulting solution was stirred at room temperature for 2 h. The reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 4:1) to afford (+)-didemniserinolipid B as a yellow oil. This reaction was carried out for several times with isolated yields ranging from 10% (1.7 mg, 2.5 μmol) to 27% (4.6 mg, 6.8 μmol). HRMS (TOF, LD^+) *m*/*z* calcd for $C_{33}H_{60}NO_{10}SNa$, $[M + H]^+$ 686.3914, found 686.3904. Other spectroscopic data were listed in the Supporting Information and compared with those reported in the literature.

Proposed (+)-Didemniserinolipid C (20). To a solution of ester (+)-**18** (25 mg, 0.030 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added diisobutylaluminum hydride solution (DIBAL-H, 1.0 M, 0.036 mL, 0.036 mmol) dropwise. After stirring at −78 °C for 1 h, the reaction was quenched by addition of saturated aqueous Rochelle salt (sodium potassium tartrate) solution (2 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the desired crude aldehyde as a yellow oil. To a solution of the crude aldehyde in THF/*t*-BuOH/H_2O (0.4 mL/0.4 mL/0.1 mL) were added 2-methyl-butene (2.0 M in THF, 0.12 mL, 0.24 mmol), sodium dihydrogen phosphate (NaH_2PO_4, 23 mg, 0.18 mmol), and sodium chlorite ($NaClO_2$, 8.7 mg, 0.096 mmol). The reaction was stirred vigorously for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (2 mL). The organic phase was collected, and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 2:1) to afford the desired carboxylic acid (16 mg, 0.020 mmol, 66% yield over 2 steps) as a yellow oil. A solution of the carboxylic acid (15 mg, 0.019 mmol) in $CHCl_3$ (0.4 mL) and 1 N HCl (0.1 mL) was stirred at 45 °C for 12 h. The reaction mixture was concentrated under reduced pressure to afford the residue as a yellow oil. To the solution of the resulting residue in $CHCl_3$ (0.2 mL) was added saturated aqueous $NaHCO_3$ solution (0.2 mL) and stirred for 2 h. The organic phase was collected, and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1) to afford the desired product (+)-DslC (6.4 mg, 0.012 mmol, 63%) as a yellow oil. $[\alpha]_D^{20}$ = +10.5 (*c* 0.08, $CHCl_3$). IR (neat, cm^{-1}): 3514, 3452, 2926, 2855, 2360, 2340, 1700, 1677, 1630,1461, 1386, 1033, 836, 799. ^1H NMR (400 MHz, CD_3OD): δ 7.10−6.81 (m, 1H), 5.84 (d, *J* = 15.7 Hz, 1H), 4.00 (s, 1H), 3.91−3.88 (m, 1H), 3.77−3.71 (m, 2H), 3.64−3.56 (m, 4H), 3.52−3.48 (m, 2H), 2.23 (d, *J* = 6.8 Hz, 2H), 2.04−1.96 (m, 2H), 1.82 (dd, *J* = 21.0, 6.2 Hz, 2H), 1.66−1.58 (m, 6H), 1.49−1.42 (m, 6H), 1.34−1.25 (m, 22H). ^{13}C NMR (100 MHz, CD_3OD): δ 151.1, 131.2, 121.8, 110.4, 83.7, 79.2, 72.8, 68.8, 66.6, 60.4, 52.1, 36.3, 33.1, 30.8 (4 × C), 30.7 (4 × C), 30.6 (3 × C), 30.5 (3 × C), 30.1, 29.1, 27.2, 26.3. HRMS (TOF, LD^+) *m*/*z* calcd for $C_{31}H_{58}O_7N$, $[M + H]^+$ 556.4213, found 556.4219.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables of NMR data comparison of our synthetic (+)-didemniserinolipid B with those reported in the literature and copies of ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was financially supported by The Hong Kong University of Science and Technology (HKUST R9309) and Research Grant Council of Hong Kong (GRF ECS 605912 and GRF 605113).

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