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Synthesis of the C_5–C_{30} fragment of cyclodidemniserinol trisulfate via I_2-mediated deprotection and ring closure tandem reaction

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ABSTRACT

The marine natural product cyclodidemniserinol trisulfate displayed moderate HIV-1 integrase inhibitory activity. Its novel structure triggered our interest to synthesize it. In our total synthesis effort, the natural product was dissected into four fragments based on the rational retrosynthetic analysis. All four fragments were successfully prepared with orthogonal protection. And the assembly of fragment A and B furnished the C_5–C_{30} key subunit by employing the I_2-mediated deprotection and intramolecular ketal formation tandem reaction in the presence of $NaHCO_3$ in MeCN. Our work provided flexible and practical approaches to synthesize and derive the 3,5,7-trisubstituted 6,8-dioxabicyclo [3.2.1] octane based analogs to search for new structure HIV-1 integrase inhibitors.

1. Introduction

Cyclodidemniserinol trisulfate (Scheme 1) was isolated and characterized in 2000 from extracts of marine invertebrates, the Palauan ascidian *Didemnum guttatum*.[1] With respect to the structure, this natural product is closely related to didemniserinolipid A from an Indonesian *Didemnum* sp.,[2] whose total synthesis was already accomplished.[3] However, the most notable difference between the two natural products is the presence of a 22-membered additional ring containing a glycine unit and the existence of sulfate groups in cyclodidemniserinol trisulfate. The special structure exhibited both inhibition of the HIV-1 integrase with an IC_{50} of 60 μg/mL and inhibition of the MCV topoisomerase with an IC_{50} of 72 μg/mL. The HIV-1 integrase has been recognized as an attractive target for HIV-1 chemotherapy intervention, and one HIV-1 integrase inhibitor has been developed into the clinically useful *anti*-AIDS drug.[4] So we were intrigued to synthesize the natural product HIV-1 integrase inhibitor, cyclodidemniserinol trisulfate. On one hand, the novel structure can serve as a template to derive structurally diverse HIV-1 integrase inhibitors. Natural product-based combinatorial library is an efficient approach for the innovative drug discovery.[5] On the other hand, the absolute configuration of this natural product has not been reported yet, therefore, total synthesis in a stereoselective manner will help determining the uncertain stereochemistry.

We reported herein our approach to synthesize the cyclodidemniserinol trisulfate. Based on our retrosynthetic analysis (Scheme 1), we have established the methodology to synthesize all four constituting fragments and have successfully assembled fragment A with fragment B to generate C_5–C_{30} subunit of the natural product, which contained the dioxabicyclo octane core structure with the necessary side chain substituents.

2. Results and discussion

The retrosynthetic strategy for cyclodidemniserinol trisulfate is shown in Scheme 1. The final assembly of **1** consists of combining fragments C_1–C_5 (**3**) and C_{31}–C_{33} (**4**) to the relatively large C_5–C_{30} fragment **2**, because the macrocyclic portion can be obtained by macrolactonization[6] or intramolecular Wittig–Horner reaction.[7] The C_5–C_{30} fragment can be further disconnected into smaller subunits **5** (epoxide fragment) and **6** (thioacetal fragment), which can be joined by an S_N2 epoxide opening reaction followed by an I_2-mediated deprotection and intramolecular ketal formation tandem reaction according to our established approaches in the early exploration work.[8]

So, our approach disconnects the natural product into four parts: Fragment A (**5**), which contained an epoxide group and could be synthesized from D-tartaric acid; Fragment B (**6**), containing a thioacetal group and two undetermined chiral centers; Fragment C (**3**), bearing a phosphonate at one terminus and a carboxylic acid at the other; Fragment D (**4**), the serine derivative. Because the structurally simple fragments **3** and **4** were conveniently synthesized by using the literature reported methods,[9,10] we reported

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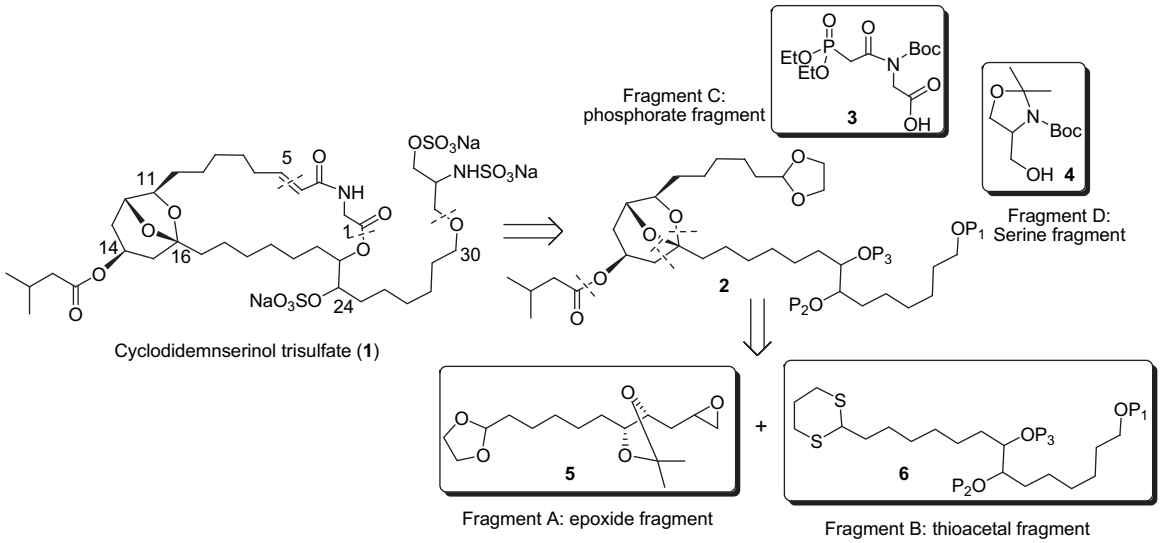


Scheme 1. Retrosynthetic analysis of cyclodidemniserinol trisulfate.

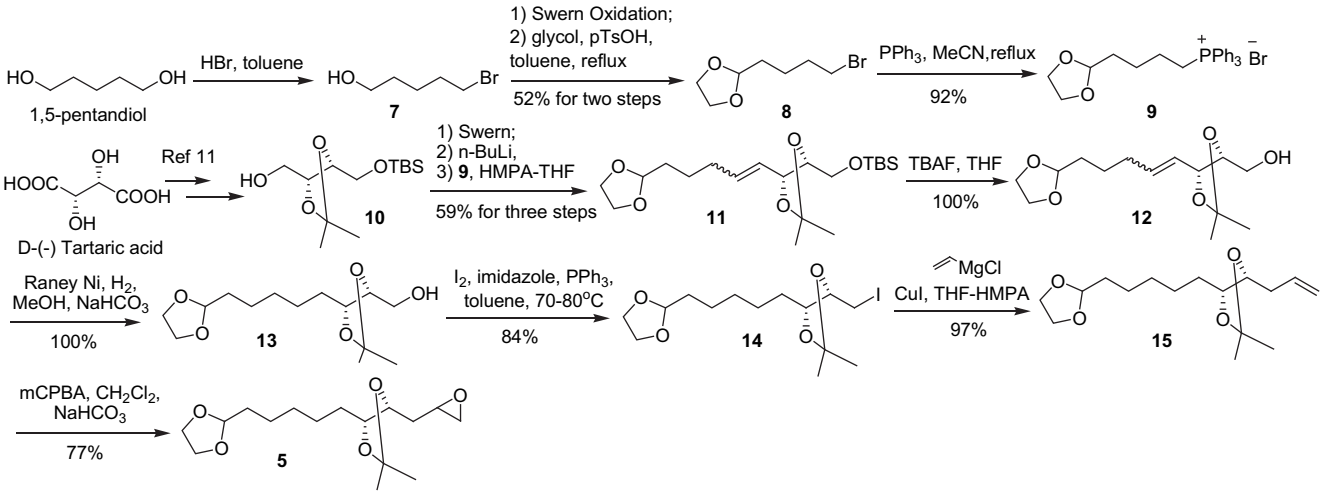
herein the synthesis of fragments **5** and **6** and the following construction of the key portion C_5–C_{30}.

2.1. Synthesis of fragment A

The synthetic approach to fragment **A** commenced from commercially available 1,5-pentadiol and D-(−)-tartaric acid, as depicted in Scheme 2. Firstly, the acetal substituted Wittig reagent **9** was prepared from the 1,5-pentadiol via bromination, Swern oxidation, ethylene acetal protection and formation of triphenylphosphonium bromide. Then the monosilylated D-(−)-threitol acetonide (**10**) was prepared from D-(−)-tartaric acid according to Ref. 11. Swern oxidation of the alcohol **10** followed by treatment with Wittig reagent **9**[12] afforded the key intermediate **11** in 59% yield. However, the hydrogenation of the alkene functionality in **11** with Pd–C as catalyst failed, due in part to the presence of the sulfate group, which was left from the previous Swern oxidation thus caused catalyst poisoning. An alternative approach was to change the reaction sequence or use Raney Ni as the catalyst. Consequently, we adopted the combined strategy, i.e., changing both the reaction sequence and the catalyst. Deprotection of the TBS group with TBAF followed by hydrogenation (Raney Ni as the catalyst or Pd–C, which worked in the new reaction sequence) gave the alcohol **13**. Considering the acidic lability of the acetal group in **12**, we added small amount of $NaHCO_3$ (1.5% mol) in the hydrogenation reaction to avoid acetal removal. The transformation of the hydroxyl group to the iodide proceeded smoothly by iodine in the presence of imidazole and triphenylphosphine. The resulting iodide **14** was coupled with vinyl Grignard reagent by the catalysis of CuI to afford terminal alkene **15** in an excellent yield. Treatment of **15** with mCPBA in the presence of $NaHCO_3$ furnished the epoxide **5** in a non-stereoselective manner. Because of the weak 1,3-induction by the chiral substrate, we obtained a mixture of both diastereomers, which were not differentiated either by TLC monitering or by NMR data.

2.2. Synthesis of fragment B

Fragment B is a fifteen carbon-length moiety. A thioacetal group and a hydroxyl group were positioned at the two ends of the fragment, respectively. In the middle of the fragment, there was



Scheme 2. Synthetic route toward Fragment **A**: epoxide fragment **5**.

a 1,2-diol functional group. It is of note that these two hydroxyl groups should be separately protected with different protecting groups because of their different roles in the following synthesis.

First, we prepared the building blocks for the synthesis of Fragment B (Scheme 3). The (*R*)-glyceraldehyde acetonide **16** was readily synthesized from D-mannitol.[13] Protection of the hydroxyl group in 6-bromohexanol with TBS produced another building block **17**.[14] The 1,6-hexandiol was converted to acetal substituted pentanebromide **18**, which was treated with PPh_3 in the acetonitrile to afford Wittig reagent **19**.[15] Then, the coupling of the wittig reagent **19** with aldehyde **16** furnished compound **20** in 40% yield. Because of the immediate hydrogenation of the resulting double bond in **20**, the *E*/*Z* configuration of the olefine was not determined further. Hydrogenation with Pd–C as catalyst gave a nine-carbon-length intermediate **21** quantitatively. Acetal deprotection and transformation into thioacetal occurred to **21** in the presence of $BF_3 \cdot Et_2O$. In order to achieve selective protection of the secondary alcohol over the primary alcohol, the resulting diol **22** was reacted with 4-methoxybenzaldehyde to afford acetal **23**. However, it was difficult to separate the acetal **23** from the remaining 4-methoxybenzaldehyde by column chromatography. Furthermore, due to the acidic lability of the acetal **23**, the conventional reagent $NaHSO_3$ (aq) was not suitable here to remove the unreacted aldehyde. Finally we employed LAH reduction of the reaction mixture to remove the residual 4-methoxybenzaldehyde clearly without deprotection of acetal **23**. Chemoselective reduction of the 2-(4-methoxyphenyl)-1,3-dioxolane derivative **23** with DIBAL-H achieved selective deprotection of primary alcohol thus affording the secondary hydroxy-protected compound **24**. The Swern oxidation of **24** followed by the coupling with the Grignard reagent, which was generated from compound **17**, produced the precursor of Fragment B. The Grignard reaction occurred in a stereoselective manner according to Cram's chelate rule, and the chirality of the generated hydroxyl group on **25** was supposed to be '*S*' configuration predominately. However, we only found one spot on the TLC, and we obtained only one compound by gel column chromatography instead of two diastereomers. So, we just described the hydroxyl group as an uncertain chirality. The subsequent hydroxyl protection of **25** with allylic group afforded compound **6** successfully, as Fragment B.

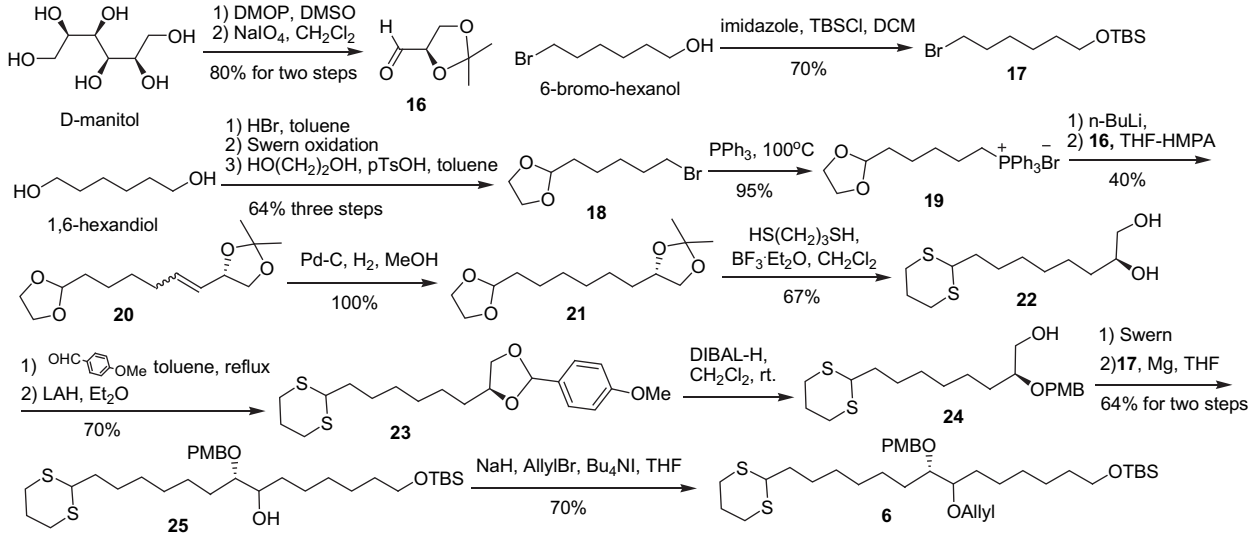
It is worthwhile noting that all the protecting groups in the Fragment B were orthogonal.[16] The thioacetal can be removed by iodine in the intramolecular ketal formation step, but stable in most reaction conditions. The PMB group could be removed by oxidation with DDQ or hydrogenation, and also stable in other conditions. The TBS group was sensitive to fluoride and acid, but resistant to other reaction conditions. For the allylic group, it is tolerant for most reaction conditions, and was designed to be removed in the end of the synthesis by using Pd reagent. The globally orthogonal protecting group strategy is advantageous in affording more options for the future total synthesis and structural derivatization study.

2.3. Synthesis of the key skeleton C_5–C_{30}

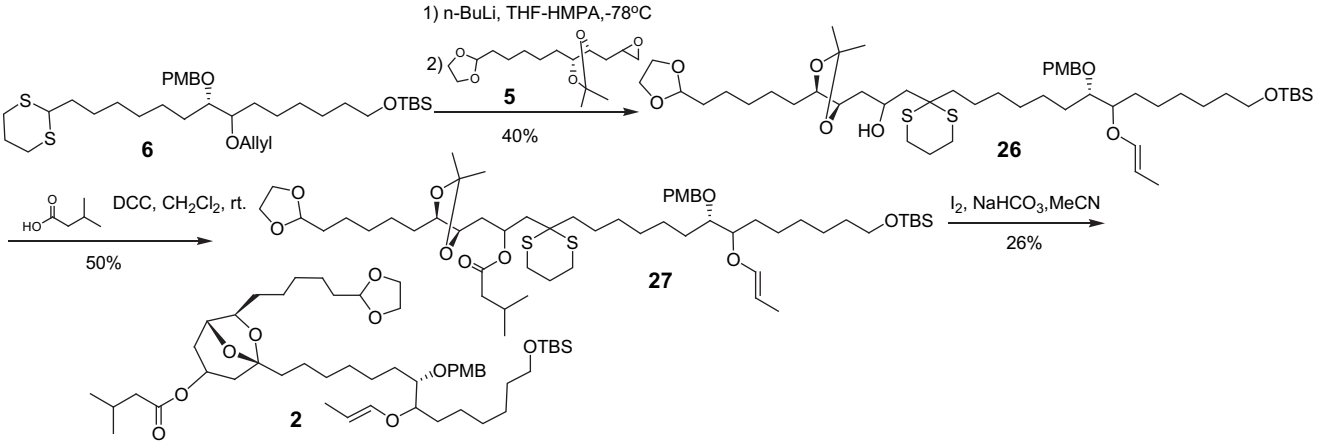
With Fragments A (**5**) and B (**6**) in hand, we started to try the construction of C_5–C_{30} subunit via an alkylation reaction, as outlined in Scheme 4. However, during the S_N2 epoxide opening reaction, the protective group allylic ether was isomerized into the vinyl ether. The isomerization of allylic ethers was reported to take place during Pd-catalyzed reaction[17] or treatment with *t*BuOK/DMSO.[18] In our case, the n-BuLi/HMPA–THF system was also observed to induce such allylic isomerization. Since the vinyl ether can be removed under acidic condition, we continued the following coupling reaction with the isomerized compound. Taking advantage of our previous synthetic study results,[8] the generated hydroxyl group in **26** was protected as isovaleric ester, because isovaleroate group served as a stable protective group to resist the epimerization, furthermore, the isovaleroate group was naturally occurring on the natural product of cyclodidemniseriol.

We used to make much effort on constructing the core structure of 3,5,7-trisubstituted 6,8-dioxabicyclo [3.2.1] octane,[8,19] and have tried proton acid in polar solvent (such as HCl in MeOH) or Lewis acid in non-proton solvent (such as $BF_3 \cdot Et_2O$ in Et_2O) to catalyze the intramolecular ketal formation reaction. Finally, by judiciously making use of the special reactivity of iodine reagent, which can remove both thioketal group and ketal group,[20] we successfully established an efficient methodology to synthesize the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane, featured with an I_2-mediated deprotection and ring closure tandem reaction, including thioketal deprotection, acetonide deprotection and intramolecular ketal formation in one pot.[8]

However, the I_2-mediated formation of the 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane was achieved only on the simple structure with small substituent groups, how about the complex structure bearing long hydrocarbon chain and functional substituent such as compound **27**? Considering the acid labile groups



Scheme 3. Synthesis route toward Fragment B: thioacetal fragment **6**.



Scheme 4. Synthesis route toward C_5–C_{30} subunit.

existing in the precursor **27**, we modified the I_2-based methodology by adding $NaHCO_3$ into the I_2-acetonitrile system. Then we applied the modified I_2-mediated deprotection and ring closure tandem reaction to the synthesis of 3,5,7-trisubstituted-6,8-dioxabicyclo [3.2.1] octane containing C_5–C_{30} subunit. As a result, the construction of C_5–C_{30} portion of cyclodidemniserinol trisulfate was smoothly accomplished by treatment with iodine carefully in the presence of $NaHCO_3$ in MeCN, affording the key skeleton **2** with essential side chain functional groups for further structural extension.

3. Conclusion

In conclusion, we disconnected the natural product HIV-1 integrase inhibitor, cyclodidemniserinol trisulfate into four fragments based on the rational retrosynthetic analysis. All four fragments were successfully prepared with orthogonal protection. And assembly of fragment A with B afforded the C_5–C_{30} subunit of the natural product by employing the I_2-mediated deprotection and intramolecular ketal formation tandem reaction in the presence of $NaHCO_3$ in MeCN as the key step. Our work provided flexible and practical approaches to synthesize and derive the 3,5,7-trisubstituted 6,8-dioxabicyclo [3.2.1] octane based analogs to search for new structure HIV-1 integrase inhibitors.

4. Experimental Section

4.1. General

Anhydrous solvents were obtained by standard procedures according to 'Purification of Laboratory Chemicals (fourth Edition)'. Flash column chromatography was performed over silica gel H (100–200 or 200–300 mesh). Proton and carbon NMR spectra were recorded on either 300 MHz or 400 MHz spectrometer. NMR chemical shifts were reported in δ (ppm) using the δ 7.26 signal of $CDCl_3$ (^{1}H NMR) and the δ 77.2 signal of $CDCl_3$ (^{13}C NMR) as internal standards. Mass spectra were recorded using either electron ionization or electron spray ionization.

*4.1.1. 2-(4-Bromobutyl)-1,3-dioxolane (**8**).* The mixture of 1,5-pentanediol (5.6 mL, 50 mmol) and HBr (7.84 mL, 50 mL, 40% aq) in toluene (250 mL) was heated to reflux and removed H_2O. After all the H_2O was removed out, the mixture was cooled to rt. The organic layer was washed with $NaHCO_3$ (aq), and dried over Na_2SO_4. After the mixture was evaporated to 50 mL, the resulting mixture was used directly for next step, due to the low bp of the product.

To a solution of oxalyl chloride (6.6 mL, 75 mmol) in CH_2Cl_2 (150 mL) was added a solution of DMSO (7.1 mL, 100 mmol) in CH_2Cl_2 (50.0 mL) at −78 °C under N_2 over 10 min. After stirring for another 30 min, a solution of the alcohol **7** in toluene and CH_2Cl_2 (1:1,70 mL) was added over 10 min, and the reaction mixture was stirred at the same temperature for another 2 h. Et_3N (35.0 mL, 250 mmol) was then added, and the mixture was gradually warmed to room temperature and stirred for another 1.5 h. After diluted with ether, the mixture was poured into satd $NaHCO_3$ solution, and the aqueous layer was extracted with ether twice. The combined organic layers were dried over Na_2SO_4, and concentrated to give crude aldehyde. The crude aldehyde was used directly.

The mixture of aldehyde, glycol (8.4 mL, 150 mL), and *p*-TsOH (0.48 g, 2.5 mmol) in toluene (250 mL) was refluxed to remove water. After cooled to rt, the mixture was poured into satd $NaHCO_3$ solution. The aqueous layer was extracted with ether twice, and the combined organic layers were dried over Na_2SO_4. After the solvent removal, the residue was purified with gel column chromatography (EtOAc/petroleum ether, 1:50), and the compound **8** (5.45 g, 52%) was obtained as bright yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54–1.70 (m, 4H), 1.86–1.96 (m, 2H), 3.41 (t, J=6.9 Hz, 2H), 3.82–3.99 (m, 4H), 4.86 (t, J=4.5 Hz, 1H).

*4.1.2. (4-(1,3-Dioxolan-2-yl)butyl)triphenylphosphonium bromide (**9**).* The mixture of bromide **8** (5.45 g, 26 mmol), $NaHCO_3$ (a few), and PPh_3 (6.83 g, 26 mmol) in MeCN (100 mL) was refluxed for 36 h. After cooled to the rt, the mixture was washed with PE. Removed solvent, and the Wittig reagent **9** (11.29 g, 92%) was obtained as brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.61 (m, 2H), 1.66–1.73 (m, 2H), 1.78–1.88 (m, 2H), 3.54 (t, J=6.9 Hz, 2H), 3.82–3.99 (m, 4H), 4.86 (t, J=4.5 Hz, 1H), 7.29 (m, 10H), 7.46–7.92 (m, 5H).

*4.1.3. (((4R,5R)-5-(5-(1,3-Dioxolan-2-yl)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)(tert-butyl)dimethylsilane (**11**).* To a solution of oxalyl chloride (0.74 mL, 8.4 mmol) in CH_2Cl_2 (20 mL) was added a solution of DMSO (0.80 mL, 11.2 mmol) in CH_2Cl_2 (5 mL) at −78 °C under N_2. After the mixture was stirred for another 30 min, a mixture of the alcohol **10** (1.55 g, 5.6 mmol) in CH_2Cl_2 (5 mL) was added, and the reaction mixture was stirred at the same temperature for another 2 h. Et_3N (3.90 mL, 28.1 mmol) was then added to the mixture, and the mixture was gradually warmed to room temperature and stirred for another 1.5 h. After

diluted with ether, the mixture was poured into satd NH_4Cl solution, and the aqueous layer was extracted with ether (×2). The combined organic layer was dried over Na_2SO_4, and concentrated to give crude aldehyde. The crude aldehyde was used directly without further purification.

To a solution of Wittig reagent **9** (2.6 g, 5.5 mmol) in THF (25 mL) was added n-BuLi (3.6 mL, 5.8 mmol, 1.60 M in hexane) under N_2 atmosphere at −78 °C. After 0.5 h stirring at rt, the mixture was cooled to the −78 °C again, and a solution of aldehyde in THF (5.0 mL) was added followed by the addition of HMPA (3 mL). The mixture was allowed to warm to rt, and stand overnight. The reaction was quenched by satd NH_4Cl solution, and the aqueous layer was extracted with ether (×2). After drying over Na_2SO_4 and solvent removal, the residue was purified with gel column chromatography (EtOAc/petroleum ether, 1:10), and the compound **11** (1.27 g, 59%) was obtained as bright yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (d, J=3.9 Hz, 6H), 0.90 (s, 9H), 1.40 (s, 6H), 1.48–1.57 (m, 2H), 1.64–1.71 (m, 2H), 2.09–2.26 (m, 2H), 3.60–3.69 (m, 2H), 3.76–3.98 (m, 4H), 4,75 (m, 1H), 4.84 (t, J=5.1 Hz, 1H), 5.40–5.44 (m, 1H), 5.61–5.71 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.2, 18.5, 24.1, 26.1, 27.1, 27.5, 27.7, 33.6, 61.7, 65.0, 73.0, 82.0, 104.5, 108.9, 127.2, 135.5. MS (EI, m/z): 386 (M^+). HRMS calcd for $C_{20}H_{38}O_5Si$ [M^+] 386.2489, found 386.2487. $[\alpha]_D^{22}$ +1.9 (*c* 1.1, $CHCl_3$).

*4.1.4. (4R,5R)-[5-(5-[1,3]Dioxolan-2-yl-1-pentenyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol (**12**).* A solution of TBAF in THF (0.85 mL, 0.85 mmol) was added to the solution of compound **11** (220 mg, 0.57 mmol) in THF (2.5 mL) at rt, and the resulting mixture stood overnight. The mixture was poured into satd NH_4Cl solution, and the aqueous layer was extracted with ether twice. After drying over Na_2SO_4 and the solvent removal, the residue was purified with gel column chromatography (EtOAc/petroleum ether, 1:3) to produce compound **12** (155 mg, 100%) as colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 6H), 1.41–1.54 (m, 2H), 1.65–1.70 (m, 2H), 1.80 (m, 1H), 2.17–2.21 (m, 2H), 3.55 (m, 1H), 3.80–3.99 (m, 5H), 4,70 (m, 1H), 4.86 (t, J=5.1 Hz, 1H), 5.41 (m, 1H), 5.68 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.1, 26.1, 27.2, 27.4, 27.5, 27.6, 29.7, 33.1, 33.3, 33.9, 60.7, 62.2, 65.0, 72.7, 77.0, 81.5, 81.7, 104.5, 104.7, 109.2, 126.6, 136.2. MS (EI, m/z): 272 (M^+). $[\alpha]_D^{25}$ +8.2 (*c* 0.6, $CHCl_3$).

*4.1.5. (4R,5R)-[5-(5-[1,3]Dioxolan-2-yl-pentyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol (**13**).* The mixture of compound **12** (2.0 g, 7.4 mmol), $NaHCO_3$ (10 mg), and Raney Ni (200 mg) in MeOH (40 mL) was hydrogenated under H_2 atmosphere overnight. After filtration and solvent removal, the crude product **13** (2.0 g, 100%) was yielded as colorless oil, used directly without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36–1.43 (m, 10H), 1.55–1.67 (m, 5H), 1.88–1.92 (m, 1H), 3.54–3.62 (m, 1H), 3.73–3.81 (m, 2H), 3.80–3.99 (m, 5H), 4.84 (t, J=4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.0, 26.1, 27.2, 27.6, 29.8, 33.1, 34.0, 62.3, 65.0, 77.1, 81.7, 104.8, 108.7. MS (EI, m/z): 273 $(M-H)^-$. HRMS calcd for $C_{14}H_{26}O_5$ [M^+] 274.178, found 274.1759. $[\alpha]_D^{25}$ +20.4 (*c* 0.34, $CHCl_3$).

*4.1.6. (4S,5R)-[5-(5-[1,3]Dioxolan-2-yl-pentyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methyl iodide (**14**).* To the mixture of crude **13** (2.0 g, 7.3 mmol), PPh_3 (4.78 g, 18 mmol), and imidazole (2.49 g, 36 mmol) in toluene (27 mL) was added I_2 (4.64 g, 18 mmol) at 0 °C. The resulting mixture was warmed to 80–90 °C. After 2 h stirring, the reaction mixture was cooled to rt, then quenched with satd aqueous $Na_2S_2O_3$ solution. The water layer was extracted with ether, and the combined organic layers were dried over Na_2SO_4. Usual work-up and purification with gel column chromatography (EtOAc/petroleum ether, 1:5) afforded compound **14** (2.35 g, 84%) as pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38–1.41 (m, 11H), 1.57–1.68 (m, 5H), 3.18–3.30 (m, 2H), 3.59–3.64 (m, 1H), 3.71–3.75 (m, 1H), 3.80–3.97 (m, 4H), 4.83 (t, J=4.8 Hz, 1H). MS (EI, m/z): 383 $(M-H)^-$.

*4.1.7. 2-(5-((4R,5R)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)pentyl)-1,3-dioxolane (**15**).* Vinylmagnesium chloride (0.1 mL, 0.16 mmol, 1.60 M in the THF) was added to CuI (1 mg) at −40 °C followed by the addition of the precooled iodide **14** (25 mg, 0.065 mmol) in THF–HMPA (6:1, 0.35 ml). The mixture was allowed to warm to rt. After stirring overnight at rt, the reaction was quenched by satd NH_4Cl solution at 0 °C. The solid was removed by filtration, and the organic layer was washed with brine. After drying over Na_2SO_4, the solvent was removed in vacuo. The residue was purified with gel column chromatography (EtOAc/petroleum ether, 1:10) to give 18 mg (97%) of **15** as colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32–1.43 (m, 12H), 1.45–1.58 (m, 2H), 1.61–1.69 (m, 2H), 2.30–2.35 (m, 2H), 3.61–3.68 (m, 2H), 3.84–3.99 (m, 4H), 4.84 (t, J=4.8 Hz, 1H), 5.08–5.16 (m, 2H), 5.78–5.90 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.1, 26.2, 27.4, 27.5, 29.8, 32.9, 34.0, 37.4, 65.0, 80.2, 80.6, 104.5, 104.8, 108.1, 117.5, 134.3. MS (EI, m/z): 283 $(M-H)^-$. $[\alpha]_D^{25}$ +22.3 (*c* 0.6, $CHCl_3$).

*4.1.8. 2-(5-((4R,5R)-2,2-Dimethyl-5-(oxiran-2-ylmethyl)-1,3-dioxolan-4-yl)pentyl)-1,3-dioxolane (**5**).* mCPBA (47 mg, 0.27 mmol) was added to a mixture of alcohol **15** (26 mg, 0.09 mmol) and $NaHCO_3$ (76 mg) in dry CH_2Cl_2 (1 mL) at 0 °C and the reaction mixture was warmed to rt and stand overnight. Quenched the reaction by adding Na_2SO_3 solution, extracted with CH_2Cl_2 (×3), the combined organic layer was washed with satd $NaHCO_3$ solution and brine, dried over Na_2SO_4. Concentrated and the residue was purified with gel column chromatograph (EtOAc/petroleum ether, 1:5) to give 21 mg (77%) of **5** as colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32–1.45 (m, 9H), 1.58–1.70 (m, 7H), 1.79–1.83 (m, 2H), 2.50–2.55 (m, 1H), 2.77–2.84 (m, 1H), 3.08–3.11 (m, 1H), 3.62–3.78 (m, 2H), 3.80–3.99 (m, 4H), 4.84 (t, J=4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.8, 26.0, 27.1, 27.2, 27.3, 29.5, 32.3, 33.7, 34.8, 36.5, 46.5, 47.3, 49.1, 49.6, 64.7, 77.9, 78.3, 80.1, 80.9, 104.5, 108.2. MS (ESI, m/z): 323.2 $(M+Na)^+$. HRMS calcd for $C_{16}H_{28}O_5Na$ [$M+Na^+$] 323.1834, found 323.1807.

*4.1.9. (R)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (**16**).* The reaction mixture of mannitol (54.6 g, 0.3 mol), dimethoxyl propane (87.7 mL, 0.75 mol) and, *p*-TsOH (0.57 g, 3 mmol) in DMSO (100 mL) was stirred at rt for 48 h. The mixture was poured into satd $NaHCO_3$ solution, and the water layer was extracted with EtOAc (×3). The combined organic layer was washed with brine. After drying over Na_2SO_4, the solvent was removed. The resulting solid (63.4 g, 80%) was used directly without further purification.

To the mixture of protected mannitol (3.96 g, 15 mmol) in CH_2Cl_2 (40 mL) and satd $NaHCO_3$ solution (4 mL) the $NaIO_4$ (4.80 g, 22.5 mmol) was added. After 2 h reacting, the Na_2SO_4 was added. Filtered about 20 min later, and concentrated to give the crude aldehyde **16** (3.90 g 100%), which was used directly for the next step without further purification.

*4.1.10. (6-Bromohexyloxy)(tert-butyl)dimethylsilane (**17**)*[14]. After the mixture of 6-bromohexanol (12.67 g, 70 mmol), imidazole (10.4 g, 153 mmol), and TBSCl (13.84 g, 92 mmol) in CH_2Cl_2 (120 mL) was stirred at rt for 13 h, the reaction mixture was poured into saturated NH_4Cl (aq). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with water and brine. After dried over Na_2SO_4, the solvent was removed and the residue was purified with the gel column chromatography (petroleum ether) to afford **17** (16.40 g, 70%). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 6H), 0.89

(s, 9H), 1.32–1.52 (m, 6H), 1.84 (m, 2H), 3.40 (t, J=6.9 Hz, 2H), 3.60 (t, J=6.6 Hz, 2H).

*4.1.11. 2-(5-Bromo-pentyl)-[1,3]dioxolane (**18**).* The preparation procedure was the same as compound **8**. Yield: 64% for three steps. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44 (m, 4H), 1.65 (m, 2H), 1.88 (m, 2H), 3.40 (t, J=6.9 Hz, 2H), 3.81–3.99 (m, 4H), 4.84 (t, J=4.8 Hz, 1H).

*4.1.12. (5-[1,3]Dioxolan-2-yl-pentyl)-triphenyl-phosphonium bromide (**19**)*[15]. The mixture of compound **18** (5.67 g, 25.5 mmol), PPh_3 (6.69 g, 25.5 mmol), and K_2CO_3 (10 mg) was heated to 100 °C and stirred under N_2 protection. After the mixture was solidified, it was cooled to rt and solved with MeCN. The petroleum ether was used to wash the resultant solution, in order to removed unreacted reactant. Concentration and the result compound **19** (11.72 g, 95%) was used directly without further purification.

*4.1.13. (S)-4-(6-(1,3-Dioxolan-2-yl)hexenyl)-2,2-dimethyl-1,3-dioxolane (**20**).* To a solution of Wittig reagent **19** (11.72 g, 24 mmol) in THF (100 mL) at −78 °C under N_2 atmosphere was added n-BuLi (18 mL, 28.8 mmol, 1.60 M in hexane). The result mixture was stirred at rt for 1 h before HMPA (12 mL) and the solution of **16** (3.90 g, 30 mmol) were added successively. The reaction was allowed to warm to rt and stood overnight. To quench the reaction, the H_2O was added. The water layer was extracted with Et_2O, and the combined organic layer was dried over Na_2SO_4. Concentration and the residue was purified with the gel column chromatography (EtOAc/petroleum ether, 1:10) to afford alkene **20** (2.51 g, 40%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35–1.48 (m, 11H), 1.59–1.65 (m, 2H), 2.10–2.16 (m, 1H), 3.51 (m, 1H), 3.82–4.00 (m, 4H), 4.06 (m, 1H), 4.84 (m, 2H), 5.41 (m, 1H), 5.81 (m, 1H). MS (EI, m/z): 255 $(M-H)^-$. HRMS calcd for $C_{14}H_{23}O_4$ [$M-H^+$] 255.1596, found 255.1601. $[\alpha]_D^{22}$ −14 (c 0.25, $CHCl_3$).

*4.1.14. (S)-4-(6-(1,3-Dioxolan-2-yl)hexyl)-2,2-dimethyl-1,3-dioxolane (**21**).* The alkene **20** was hydrogenated under H_2 atmosphere in the presence of Pd–C and $NaHCO_3$. Filtered and the residue **21** (2.52 g, 100%) was used directly without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27–1.48 (m, 16H), 1.60–1.67 (m, 2H), 3.48–3.53 (m, 1H), 3.84–4.05 (m, 4H), 4.08–4.10 (m, 2H), 4.83 (t, J=4.8 Hz, 1H).

*4.1.15. (S)-8-(1,3-Dithian-2-yl)octane-1,2-diol (**22**).* To the mixture of **21** (2.40 g, 9.3 mmol), 1,3-propandithiol (1.96 mL, 19.5 mmol) in the CH_2Cl_2 (50 mL) was added $BF_3\cdot Et_2O$ (catalyst amount) at 0 °C. The resultant mixture was allowed to warm to rt and stirred overnight. The mixture was poured into NaOH (10% aq) and separated. The water layer was extracted with CH_2Cl_2, and the combined organic layer was dried over Na_2SO_4. Concentration and the residue was purified with the gel column chromatography (EtOAc/petroleum ether, 1:5 to EA) to afford **22** (1.65 g, 67%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20–1.35 (m, 6H), 1.38–1.55 (m, 5H), 1.64–1.90 (m, 3H), 2.06–2.12 (m, 1H), 2.77–2.91 (m, 5H), 3.36–3.42 (m, 1H), 3.60–3.67 (m, 2H), 4.02 (t, J=6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.6, 26.2, 26.6, 29.2, 29.5, 30.6, 33.2, 35.5, 47.7, 66.9, 72.4. MS (EI, m/z): 264 (M^+). HRMS calcd for $C_{12}H_{24}O_2S_2$ [M^+] 264.1218, found 264.1225; $[\alpha]_D^{25}$ +5 (c 0.10, $CHCl_3$).

*4.1.16. (4S)-4-(6-(1,3-Dithian-2-yl)hexyl)-2-(4-methoxyphenyl)-1,3-dioxolane (**23**).* The mixture of **22** (654 mg, 2.48 mmol), 4-methoxybenzaldehyde (0.45 mL, 3.72 mmol), and p-TsOH (catalyst amount) in toluene (20 mL) was warmed to reflux and H_2O was removed. The mixture was allowed to rt, and treated with LAH in the Et_2O as co-solvent. 30 min later, the reaction was quenched by H_2O. Then it was filtered, concentrated and the residue was purified with the gel column chromatography (EtOAc/petroleum ether, 1:10) to afford **23** (660 mg, 70%) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28–1.40 (m, 4H), 1.45–1.64 (m, 4H), 1.68–1.95 (m, 4H), 2.00–2.18 (m, 2H), 2.76–2.88 (m, 4H), 3.64 (m, 1H), 3.80 (s, 3H), 4.00–4.15 (m, 2H), 4.15–25 (m, 1H), 5.50 (m, 1H), 6.80 (m, 2H), 7.40 (m, 2H).

*4.1.17. (S)-2-(4-Methoxybenzyloxy)-8-(1,3-dithian-2-yl)octanal (**24**).* To a solution of **23** (660 mg, 1.73 mmol) in the CH_2Cl_2 (8.5 mL) at 0 °C was added DIBAL-H (2.6 mL, 2.6 mmol, 1.0 M in toluene). The mixture was allowed to warm to rt and stirred overnight. The reaction was quenched by H_2O, and the water layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4. Concentration and the residue was purified with the gel column chromatography (EtOAc/petroleum ether, 1:1) to afford **24** (590 mg, 90%), as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16–1.21 (m, 7H), 1.41–1.68 (m, 3H), 1.60–1.78 (m, 2H), 1.80–1.97 (m, 1H), 2.04–2.20 (m, 1H), 2.76–2.96 (m, 4H), 3.40 (m, 2H), 3.68 (m, 1H), 3.81 (s, 3H), 4.03 (t, J=6.6 Hz, 1H), 4.46 (q, J=10.8 Hz, 2H), 6.90 (d, J=8.1 Hz, 2H), 7.28 (d, J=6.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.3, 26.1, 26.6, 29.1, 29.5, 30.5, 30.8, 35.5, 47.7, 55.3, 64.3, 71.2, 79.4, 113.9, 129.5, 130.6, 159.3. MS (EI, m/z): 384 (M^+). HRMS calcd for $C_{20}H_{32}O_3S_2$ [M^+] 384.1793, found 384.1802. $[\alpha]_D^{22}$ +7.5 (c 2.9, $CHCl_3$).

*4.1.18. ((8S)-8-(4-Methoxybenzyloxy)-7-hydroxyl-14-(1,3-dithian-2-yl)tetradecyloxy)(tert-butyl)dimethylsilane (**25**).* To a solution of $(COCl)_2$ (0.1 mL, 1.17 mmol) in CH_2Cl_2 (5 mL) was added DMSO (0.11 mL, 1.56 mmol) at −78 °C, under N_2 protection. After stirring at the same temperature for 30 min, the solution of **24** (0.30 g, 0.78 mmol) in CH_2Cl_2 was added. The Et_3N (0.54 mL, 3.91 mmol) was added, after reacting at −78 °C for another 1.5 h. The mixture was allowed to warm to the rt and reaction was continued for 2 h more. The reaction mixture was poured into H_2O, and the water layer was extracted with CH_2Cl_2. The combined organic layer was dried, after wash with brine. Concentrated and the residue was used without further purification.

To the solution of the aldehyde in the THF (1 mL), the Grignard reagent, which was prepared from **17** (1.072 g 4 mmol) and Mg (106 mg, 4.4 mmol) in the ether (5 mL), was added dropwise at 0 °C under N_2 atmosphere. The mixture was allowed to warm to rt and stirred overnight. The reaction was quenched by H_2O, and the water layer was extracted with ether. The combined organic layer was dried over Na_2SO_4. Concentration and the residue was purified with the gel column chromatography (EtOAc/petroleum ether, 1:10) to afford coupling product **25** (0.30 g, 64%), as pale yellow oil. MS (ESI, m/z): 621.4 ($M+Na^+$), 637.4 ($M+K^+-H^+$).

*4.1.19. ((8S)-8-(4-Methoxybenzyloxy)-7-propenyloxyl-14-(1,3-dithian-2-yl)tetradecyloxy)(tert-butyl)dimethylsilane (**6**).* To a solution of alcohol **25** (98 mg, 0.16 mmol) in the THF (1 mL) at 0 °C under N_2 atmosphere was added NaH (7 mg, 0.18 mmol, 60% in the oil), and the mixture was allowed to stir at rt for 30 min. The allylic bromide (0.021 mL, 0.25 mmol) and Bu_4NI (catalyst amount) were added successively. After the mixture was stirred for another 30 h, the reaction was quenched with H_2O, and the water layer was extracted with ether. The combined organic layer was dried over Na_2SO_4. Concentration and the residue was purified with the gel column chromatography (EtOAc/petroleum ether, 1:15) to afford **6** (70 mg, 70%), as pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.20–1.38 (m, 12H), 1.38–1.60 (m, 6H), 1.65–1.80 (m, 3H), 1.80–1.95 (m, 1H), 2.00–2.20 (m, 2H), 2.88–2.95 (m, 4H), 3.25–3.45 (m, 2H), 3.59 (t, J=6.3 Hz, 2H), 3.80 (s, 3H), 3.90–4.10 (m, 3H), 4.40–4.60 (m, 2H), 5.20–5.30 (m, 2H), 5.95 (m, 1H), 6.86 (d, J=6.9 Hz, 2H), 7.25 (d, J=6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.1, 18.6, 26.0, 26.1, 26.2, 26.8, 29.4, 29.7, 29.8, 30.1, 30.2, 30.7, 33.1, 35.6, 47.8, 55.5, 63.5, 72.0, 72.5, 80.0, 80.4, 113.9, 116.8, 119.5,

129.7, 131.2, 135.7. MS (ESI, *m*/*z*): 661.5 ($M+Na^+$), 678.4 ($M+K^+$). HRMS calcd for $C_{35}H_{62}O_4S_2SiNa$ [$M+Na^+$] 661.3757, found 661.3710.

*4.1.20. 1-{2-[14-(tert-Butyl-dimethyl-silanyloxy)-7-(7S)-(4-methoxy-benzyloxy)-8-(8S)-propenyloxy-tetradecyl]-[1,3]dithian-2-yl}-3-[5-(5R)-(5-[1,3]dioxolan-2-yl-pentyl)-2,2-dimethyl-[1,3]dioxolan-4-(4R)-yl]-propan-2-ol (**26**).* To a solution of dithioacetal **6** (338 mg, 0.53 mmol) in THF (2 mL) at −78 °C under N_2 atmosphere was added HMPA (0.3 mL) and n-BuLi (0.36 mL, 0.58 mmol, 1.6 M in hexane) successively. After stirring at same temperature for 1 h, the epoxide **5** (159 mg, 0.53 mmol) in THF (1 mL) was added rapidly. The mixture was allowed to warm to rt and stand overnight. The reaction was quenched with water at 0 °C and the water layer was extracted with ether (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, evaporated in vacuo. The residue was purified with gel column chromatography (EtOAc/petroleum ether, 1:3) to give 210 mg (40%) of **26** as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ, 0.06 (s, 6H), 0.95 (s, 9H), 1.20–1.80 (m, 41H), 1.80–2.06 (m, 6H), 2.20–2.40 (m, 1H), 2.70–3.10 (m, 4H), 3.36 (m, 1H), 3.56 (m, 4H), 3.70 (m, 2H), 3.80 (s, 3H), 3.80–4.00 (m, 4H), 4.18 (m, 1H), 4.40–4.60 (m, 2H), 4.80 (t, *J*=4.8 Hz, 1H), 5.96 (m, 1H), 6.85 (d, *J*=8.4 Hz, 2H), 7.25 (d, *J*=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.0, 9.6, 18.6, 22.9, 24.1, 24.2, 25.3, 26.0, 26.2, 26.6, 27.4, 27.5, 27.6, 29.7, 29.8, 29.9, 30.3, 30.5, 32.1, 32.6, 32.7, 33.0, 34.0, 39.8, 40.0, 40.8, 41.2, 42.3, 44.9, 45.3, 52.5, 52.6, 55.5, 63.5, 65.0, 65.8, 66.2, 67.6, 72.8, 76.8, 79.6, 80.6, 81.3, 81.5, 83.8, 99.9, 104.8, 108.3, 108.6, 113.9, 129.0, 129.8, 131.2, 146.6, 158.9, 159.4. MS (ESI, *m*/*z*): 961.7 ($M+Na^+$), 962.6 ($M+Na^++H^+$). HRMS calcd for $C_{51}H_{90}O_9S_2$-SiNa [$M+Na^+$] 961.5693, found 961.5643.

*4.1.21. 3-Methyl-butyric acid 2-{2-[14-(tert-butyl-dimethyl-silanyloxy)-7-(7S)-(4-methoxy-benzyloxy)- 8-(8S)-propenyloxy-tetradecyl]-[1,3]dithian-2-yl}-1-[5-(5R)-(5-[1,3]dioxolan-2-yl-pentyl)-2,2-dimethyl-[1,3]dioxolan-4-(4R)-ylmethyl]-ethyl ester (**27**).* The mixture of compound **26** (200 mg, 0.21 mmol), DDC (439 mg, 2.1 mmol), isovaleric acid (0.232 mL, 2.1 mmol), and DMAP (5 mg) in CH_2Cl_2 (1 mL) was stirred at rt for 24 h. The mixture was purified with gel column chromatography (EtOAc/hexane, 1:5) to give 106 mg (50%) of **27** as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 6H), 0.90 (s, 9H), 0.95 (m, 6H), 1.20–1.60 (m, 35H), 1.65–1.90 (m, 9H), 2.05–2.30 (m, 6H), 2.70–3.10 (m, 4H), 3.36 (m, 1H), 3.50–3.70 (m, 5H), 3.80 (s, 3H), 3.80–4.00 (m, 4H), 4.30 (m, 1H), 4.40–4.60 (m, 2H), 4.80 (t, *J*=4.8 Hz, 1H), 5.19 (m, 1H), 5.96 (m, 1H), 6.85 (d, *J*=8.4 Hz, 2H), 7.25 (m, 2H).

*4.1.22. 3-Methyl-butyric acid 5-[14-(tert-butyl-dimethyl-silanyloxy)-7-(7S)-(4-methoxy-benzyloxy) -8-(8S)-propenyloxy-tetradecyl]-7-(7R)-(5-[1,3]dioxolan-2-yl-pentyl)-(1R)-6,8-dioxa-bicyclo[3.2.1]oct-3-yl ester (**2**).* The iodine (2 mg, 0.0076 mmol) was added to the mixture of compound **27** (9 mg, 0.0088 mmol) and $NaHCO_3$ (1 mg, 0.012 mmol) in MeCN (2 mL) at 0 °C. Stirring was continued at 0 °C for another 5 min before satd Na_2SO_3 solution was added. The mixture was extracted with Et_2O, and the organic layer was washed with brine and dried over Na_2SO_4. After the solvent was evaporated, the residue was purified through gel column chromatography (EtOAc/petroleum ether, 1:3), and compound **2** (2 mg, 26%) was obtained as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 6H), 0.94 (s, 9H), 0.97 (d, *J*=6.9 Hz, 6H), 1.20–1.60 (m, 37H), 2.20–2.40 (m, 5H), 3.40 (m, 2H), 3.60 (m, 2H), 3.72 (m, 1H), 3.80 (s, 3H), 3.80–4.00 (m, 4H), 4.06 (m, 2H), 4.50 (m, 2H), 4.84 (t, *J*=4.8 Hz, 1H), 5.20 (m, 1H), 5.89 (m, 1H), 6.86 (d, *J*=8.4 Hz, 2H), 7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.0, 14.3, 15.5, 18.6, 22.4, 22.7, 22.8, 22.9, 24.1, 24.3, 25.9, 26.0, 26.1, 26.2, 27.0, 27.4, 27.5, 28.5, 29.0, 29.4, 29.7, 29.8, 29.9, 32.0, 32.1, 32.7, 32.8, 33.0, 33.8, 34.0, 35.6, 35.8, 37.7, 37.9, 38.7, 40.2, 44.1, 55.5, 63.4, 65.1, 72.0, 76.1, 79.5, 80.6, 82.0, 82.8, 104.8, 107.5, 108.7, 113.9, 129.7, 131.1, 132.7, 142.2, 200.5. MS (ESI, *m*/*z*): 1045.7 ($M+Na^+$), 1046.7 ($M+Na^++H^+$). HRMS calcd for $C_{50}H_{86}O_{10}SiNa$ [$M+Na^+$] 897.5888, found 897.5873.

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Supplementary data

^{1}H NMR spectra for compound **2**, **5**, **6**, **9**, **11**–**15**, **18**, **20**–**24**, and **26**–**27**. ^{13}C NMR spectra for compound **2**, **5**, **6**, **11**–**13**, **15**, **22**, **24**, and **26**. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.12.024.

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