Tetrahedron 69 (2013) 1830–1840

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of C(27)–C(38) fragment of aflastatin A

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ARTICLE INFO

Article history:
Received 16 October 2012
Received in revised form 14 December 2012
Accepted 26 December 2012
Available online 3 January 2013

Keywords:
Aflastatin
Epoxide–alkyne coupling
ω-Alkynone cycloisomerization
Palladium catalysis
Hydroboration

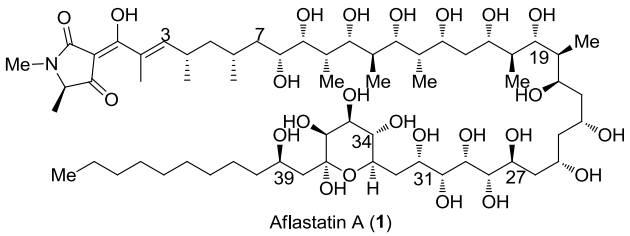
ABSTRACT

Efforts at finding out a strategy for the synthesis of the densely hydroxylated C(27)–C(48) fragment of aflastatin A have been described. The initial studies dealing with alkyne–epoxide coupling using a linear polyol epoxide resulted in a debenzylative cycloetherification leading to a *C*-arabinoside derivative. This problem has been addressed by applying an epoxide pendant on a furanosyl unit. With the model alkyne, the epoxide–alkyne coupling proceeded smoothly. Subsequently, following a sequence of [Pd]-mediated alkynone cycloisomerization/stereoselective hydroboration–oxidation, the synthesis of the central C(27)–C(38) fragment has been executed. When employed, the original C(33)–C(48) alkyne, the coupling and the cycloisomerizations are facile. However, the resulting glycals are unstable, thus warranting a revision in our approach.

1. Introduction

Aflatoxins are the naturally occurring mycotoxins produced by *Aspergillus* fungi such as *Aspergillus flavus* and *Aspergillus parasiticus*.[1] These fungi are the contaminants in a wide variety of food and feeds and the aflatoxins are the most significant environmental carcinogens in mammals.[2] The rapid development of drug resistant strains of *Aspergillus* fungi is a major concern, which warranted the discovery of novel specific inhibitors for the aflatoxin production.[3] In 1996, Sakuda and co-workers reported the isolation of aflastatin A (**1**)[4] and revealed it as a potent and specific inhibitor for aflatoxin biosynthesis, which worked without notably affecting the growth of *A. parasiticus* from *Streptomyces* sp. MRI142.[5] The putative structure of aflastatin A has been proposed by the Sakuda group with the help of chemical degradation and intensive NMR studies.[6] However, the same group has revised its structure, as shown in Fig. 1 in 2007.[7] Aflastatin A (**1**) is an architecturally complex polyol natural product, which comprises a tetramic acid derivative with a highly oxygenated long alkyl side chain, as well as a densely functionalized tetrahydropyran ring. The presence of 29 contiguous stereogenic centers demonstrates the complexity of this molecule from a synthetic point of view.

The stereochemical and structural complexity coupled with potent inhibitory activity makes aflastatin A an attractive target for total synthesis. The groups of Evans[8] and McDonald[9] have reported the synthesis of the C(9)–C(27) fragment. The synthesis of the left



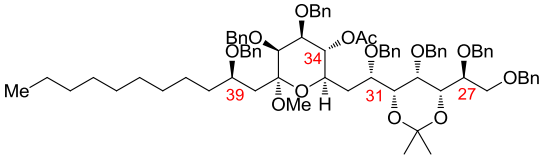


Fig. 1. Structure of aflastatin A (**1**) and the targeted C(26)–C(48) fragment **2**.

over part of the molecule, i.e., the fully functionalized tetrahydropyran moiety remain untouched by the synthetic community due to its complex structural outlay. Inspired by the challenges associated with the construction of the tetrahydropyran unit with requisite stereochemistry, as well as our interest in the synthesis of polyol natural products and cycloisomerization on sugar building blocks,[10] aflastatin A has been selected for the synthetic exercise. Our initial success in this regard was constructing the central tetrahydropyran unit, employing ω-alkynone cycloisomerization and stereoselective hydroboration–oxidation, which have been amply

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http://dx.doi.org/10.1016/j.tet.2012.12.065

applied to synthesize the C(31)–C(48) fragment of aflastatin A.[11] In continuation, our next concern was the construction of the C(26)–C(48) fragment with a keen interest to look at the applicability of a metal mediated cycloisomerization on a densely functionalized polyol template. Herein, we document our efforts in this direction, which reveals the applicability and the limitations of the key ω-alkynone cycloisomerization and hydroboration–oxidation in the synthesis of the above-mentioned fragment of aflastatin A.

2. Result and discussions

Fig. 2 reveals the salient features of our retrosynthetic disconnections for constructing the protected C(26)–C(48) fragment **2**. The key reaction in this regard was an ω-alkynone cycloisomerization[11,12] and a face selective hydroboration–oxidaton[13] that addresses the construction of the central tetrahydropyran core. The key alkynone intermediate **4** would be assembled from the TBS ether **5**, which in turn, could be synthesized by addition of the alkyne **6** to epoxide **7**.[14] In our earlier report, we have documented the synthesis of key alkyne **6** from D-ribose.[11] Inspection of stereochemical details of the epoxide fragment **7** led us to identify the α-D-glucoheptanoic-γ-lactone, where the configuration of the hydroxyl groups at C(2)–C(5) matches perfectly with the stereochemistry of the hydroxyl groups at C(27)–C(30) in aflastatin A. The stereochemistry at C(6) of α-D-glucoheptanoic-γ-lactone can be inverted during the formation of key epoxide **7**, the functional unit that was opted for, in order to address the C(32)–C(33) bond formation.

The terminal 1,2-diol was then selectively protected as the pentylidene ketal **15** by treatment of tetraol **11** at 0 °C with H_2SO_4 in 3-pentanone. The formation of dipentylidene ketal **14** as the side-product was found to be temperature and time dependent. The benzylation of the two free hydroxyl groups in compound **15**, followed by acid hydrolysis of resulting compound **16**, afforded the diol **17** in good yields. Next, the treatment of diol **17** with benzoyl chloride followed by methanesulfonyl chloride delivered compound **19**, which, upon exposure to lithium hydroxide, resulted in the key epoxide building block **20** in 78% yield. Spectral and analytical data of **20** were in good agreement with the assigned structure. The characteristic methine protons of the oxirane ring were found to resonate as two dd at 1.94 and 2.22 ppm in the ^1H NMR spectrum.

Having the required epoxide **20** in hand, the next concern was its opening with the alkyne **6**. In our earlier report dealing with the synthesis of the C(31)–(C48) fragment, the easily accessible alkyne **21** has been used for the optimization studies. However, in that case, the epoxide used was the simple ethylene oxide. As the synthesis of key alkyne **6** involves a sequence of 12 linear steps,[11] our initial intention was to use the alkyne **21** for optimizing the sequence and then proceed with the alkyne **6** in order to arrive at the desired objective. The attempted epoxide opening reaction with alkyne **21** using *n*-BuLi and $BF{\cdot}Et_2O$ failed to give the required product **22** (Scheme 2). Under various reaction conditions explored (Table 1), this reaction led to either formation of the epoxide-rearranged product **23** or isolation of trace amounts of the required product **22**. The rearranged product **23** was expected to be formed by $BF_3{\cdot}Et_2O$ mediated debenzylative cycloetherification, a commonly encountered problem when the reacting groups are in a 1,4-position.[16] Compound **23** was converted to the corresponding acetate **24** for the purpose of characterization.

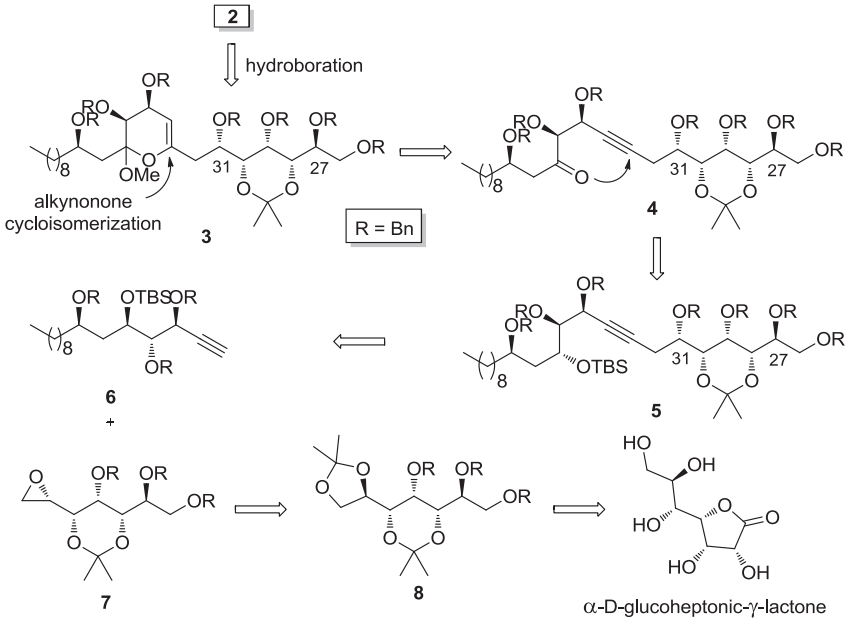
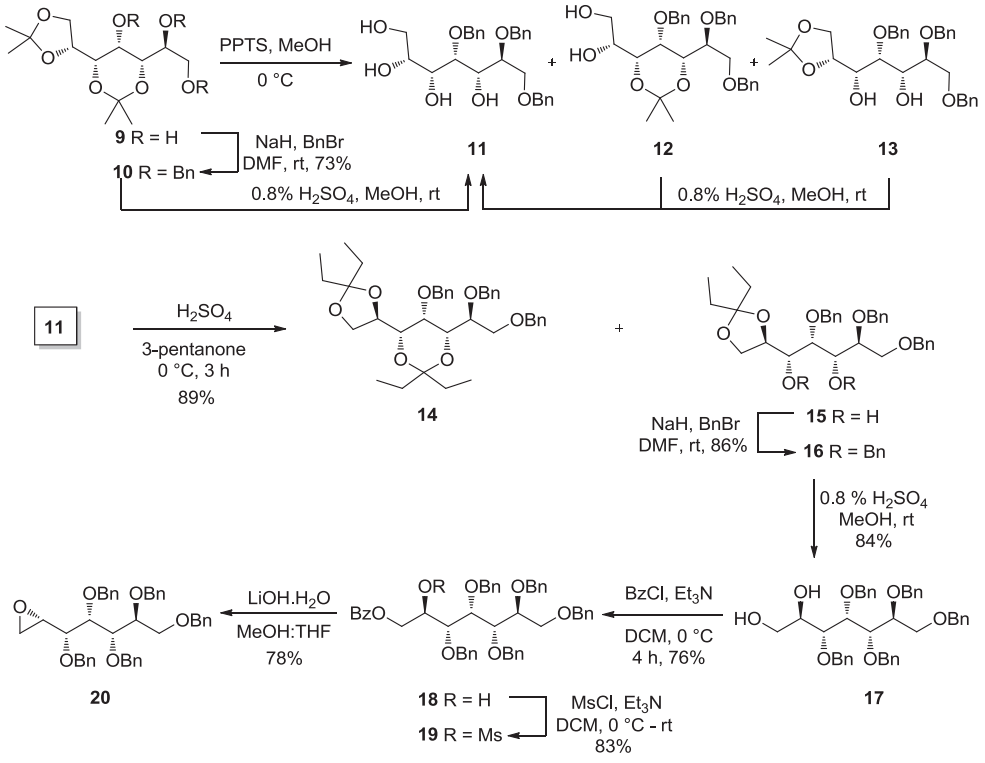


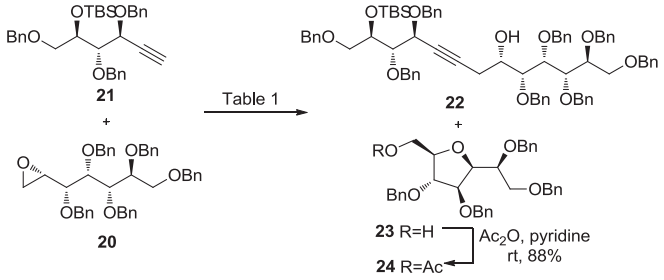
Fig. 2. Retrosynthetic disconnections for C(26)–C(48) fragment of aflastatin A.

The synthesis of the epoxide **7** was commenced through the preparation of triol **9** using the reported procedures from α-D-glucoheptanoic-γ-lactone.[15] The benzylation of triol **9** using NaH and benzyl bromide in DMF at room temperature gave the tribenzyl derivative **10** (Scheme 1). Our initial attempts to selectively hydrolyze the terminal acetonide of compound **10** under various conditions met with the isolation of the three possible hydrolysis products **11**–**13** in varying amounts. This led us to attempt the hydrolysis of both the acetonide groups followed by selective protection of the terminal diol unit. Thus, the treatment of **10** with 0.8% H_2SO_4 in methanol gave the tetraol **11** in quantitative yields.

Since improving the yield of requisite product **22** proved difficult, we next intended to use an epoxide that had been appended on a furanoside unit so that the chances of intramolecular epoxide opening could be reduced. According to the revised tactic, the epoxide **25** was selected as a suitable precursor for the next synthetic exercise. Epoxide **25** was equipped from D-glucose by the literature



Scheme 1. Synthesis of epoxide fragment **20**.



Scheme 2. Attempts for alkyne–epoxide cross-coupling reaction.

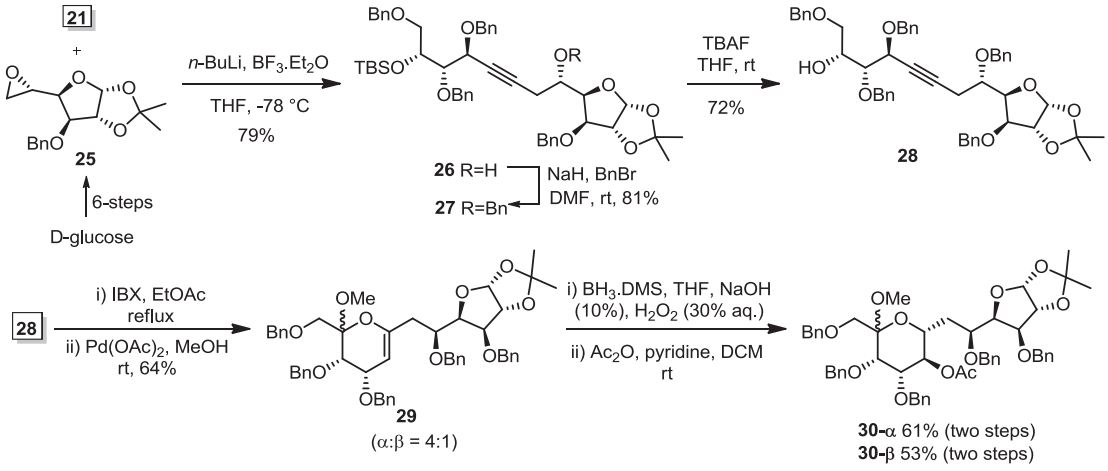
Table 1
Reaction conditions and results for alkyne–epoxide cross-coupling reaction

Sr. no.	Reagents used	Temperature	Results
1	*n*-BuLi (2 equiv), $BF_3{\cdot}Et_2O$ (3 equiv)	−78 °C	72% (**23**)
2	*n*-BuLi (2 equiv), $BF_3{\cdot}Et_2O$ (2 equiv)	−78 °C	68% (**23**)
3	*n*-BuLi (1 equiv), $BF_3{\cdot}Et_2O$ (1.1 equiv)	−78 °C	64% (**23**) and 3% (**22**)
4	*n*-BuLi (1 equiv)	−78 °C to rt	S.M. recovered
5	*n*-BuLi (1 equiv), CuCN (2 equiv)	−40 °C	S.M. recovered
6	*n*-BuMgBr (2 equiv), CuCN (3 equiv)	−40 °C to rt	S.M. recovered
7	*n*-BuMgBr (2 equiv), CuI (3 equiv)	−40 °C to rt	S.M. recovered
8	*n*-BuLi (2 equiv), $MgBr_2$ (2 equiv)	0 °C to rt	S.M. recovered
9	*n*-BuLi (2 equiv), ZnI_2 (2 equiv)	0 °C to rt	S.M. recovered
10	*n*-BuLi (2 equiv), $ZnTf_2$ (1 equiv)	0 °C to rt	S.M. recovered
11	*n*-BuLi (2 equiv), $ScTf_3$ (1 equiv)	0 °C to rt	S.M. recovered

procedures[17] and treated with alkyne **21** using *n*-BuLi and $BF_3{\cdot}Et_2O$ at −78 °C in THF to procure compound **26** in 79% yield (Scheme 3). The protection of the resulting alcohol **26** as its benzyl ether **27** followed by TBS deprotection delivered the alkynol intermediate **28** in good yields. The crude alkynone obtained from the oxidation of alkynol **28** using IBX in refluxing ethyl acetate was subjected for alkynone cycloisomerization employing $Pd(OAc)_2$ in anhydrous methanol to afford anomeric mixture of glycals **29-α** and **29-β** in a 4:1 proportion and in 64% collective yield. Both the anomers were separated by column chromatography and were proceeded independently for hydroboration–oxidation and acetylation to get the required products (**30-α**, 61% yield and **30-β**, 53% yield). The assigned structures were confirmed with the help of extensive NMR studies. The proton connectivities were fixed with the help of the COSY spectrum and the stereochemistry of anomeric center was established by NOESY correlations. For example, the anomeric C(37)–OMe of **30-α** showed NOE with C(33)–H whereas in **30-β**, a similar NOE effect was not observed (Fig. 3).

After having executed successfully the synthesis of the C(27)–C(38) fragment, the next eventual synthetic goal was the assembly of the C(27)–C(48) fragment, utilizing the epoxide **25** and the key alkyne **6** as the starting points. The opening of the epoxide **25** with alkyne **6** proceeded smoothly and provided **31** (Scheme 4). The benzylation of free –OH in **31** followed by TBS deprotection of the resulting compound **32** gave the alkynol fragment **33** in good yields. The alkynol thus obtained was converted to an alkynone **34** by oxidation, employing IBX in ethyl acetate under reflux conditions. The assigned structure of alkynone **34** was established with the help of spectral and analytical techniques. The presence of signals in ^1H and ^{13}C NMR was consistent with the allocated structure. Finally, HRMS spectral data also secured the structure of alkynone **34**.

The glycals **35-α** and **35-β** were obtained in 56% yield (α/β=3:1 proportion) by alkynone cycloisomerization of **34** in presence of $Pd(OAc)_2$ in MeOH at room temperature. Both the anomers were separable by column chromatography. However the characterization of these compounds proved a demanding task. Both the compounds were found to be unstable during NMR analysis and were hydrolyzed easily to give the dicarbonyl compound **36** as was evident from the presence of characteristic signals in ^1H and ^{13}C NMR spectra. In ^1H NMR, the absence of



Scheme 3. Synthesis of C(27)–C(38) fragment.

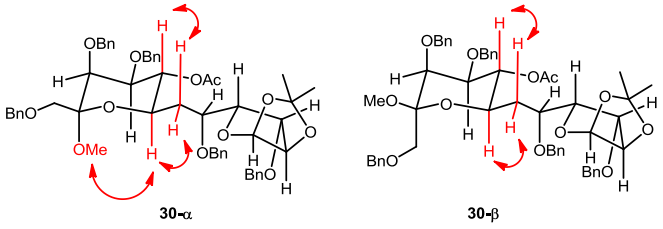
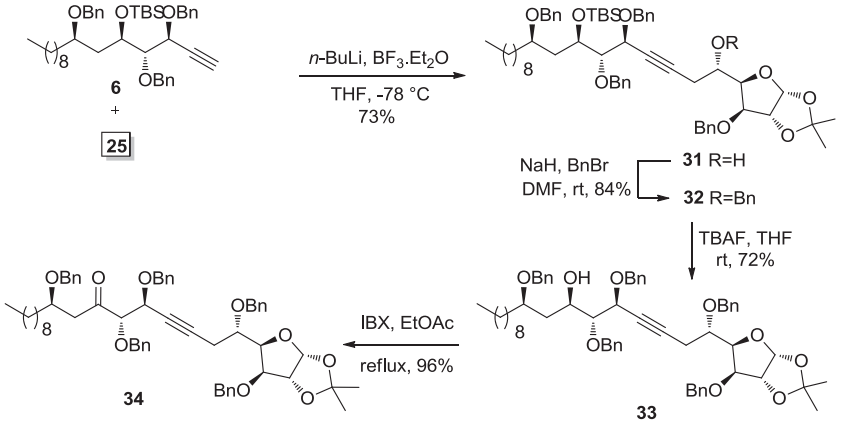


Fig. 3. Characteristic NOEs in **30-α** and **30-β**.

compounds may not be stable enough to do hydroboration–oxidation. After these disappointing results, the alkynone was subjected for sequential cycloisomerization, hydroboration–oxidation, and acetylation as done earlier in the previous report (Scheme 5);[11] but regrettably we ended up with the formation of an intractable mixture of compounds. The consistent results obtained even with various other boranes explored led to a conclusion that construction of the key tetrahydropyran unit should be placed in the early stages of the synthetic program.



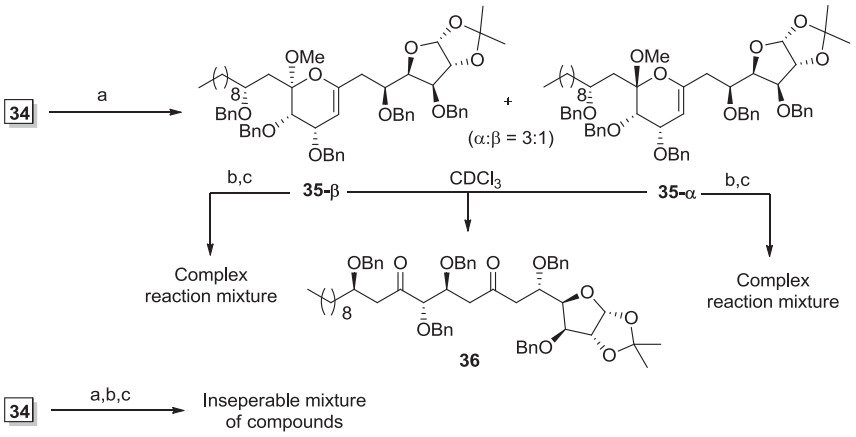
Scheme 4. Synthesis of alkynone **34** by using oxirane opening reaction.

singlet corresponding to –OMe at ≈3.33 ppm (in **35-α** and **35-β**) and the presence of signals at δ 2.44 (dd, J=4.7, 17.5 Hz, 1H), 2.53 (dd, J=5.6, 17.5 Hz, 1H), 2.58–2.70 (m, 1H), 2.72–2.89 (m, 1H), 3.05 (dd, J=7.5, 17.6 Hz, 1H), and 3.85 (dd, J=3.4, 6.1 Hz, 1H) clearly indicated that the dihydropyran was completely hydrolyzed into dione **36**. Also the presence of two carbonyl carbons at 205.8 and 210.3 ppm in the ^{13}C NMR spectrum further supported the assigned structure of **36**. After quick analysis of the freshly prepared samples of **35-α** and **35-β**, we were able to get the analytical data for **35-α** whereas **35-β** was found to be very unstable compared to **35-α**, making the data difficult to record. ^{1}H and ^{13}C NMR spectra of **35-β** always showed the peaks of dione **36** along with **35-β**.

Our attempts involving the direct hydroboration–oxidation and acetylation of freshly prepared **35-α** and **35-β** led to formation of a complex reaction mixture (Scheme 5), which indicates that the

3. Conclusion

In conclusion, the synthesis of the C(27)–C(38) fragment of aflastatin A has been executed by employing the ω-alkynone cycloisomerization and stereoselective hydroboration–oxidation as focal transformations. Apart from this, the Yamaguchi oxirane opening reaction also played a significant role in C–C bond formation by coupling the epoxide and alkyne fragments. Also, we have attempted the synthesis of the C(27)–C(48) fragment by utilizing the same protocol. Though achieving the desired fragment proved difficult, our studies in that direction have opened a new door for the construction of fully functionalized tetrahydropyran unit. Further studies aiming to develop a convergent approach that involves the construction of the key tetrahydropyran unit with minimum number of carbons and subsequent chain elongations are in progress and will be reported in due course.



Reagents & conditions: a) $Pd(OAc)_2$, MeOH, rt, 56%; b) BH_3.DMS, THF, 0°C then, H_2O_2 and aq. NaOH, 0 °C - rt; c) Ac_2O, pyridine, DCM, rt

Scheme 5. Attempted synthesis of C(27)–C(48) fragment.

4. Experimental section

4.1. General

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. All anhydrous solvents were distilled prior to use: dichloromethane and DMF from CaH_2; methanol from Mg cake; THF on Na/benzophenone; triethylamine and pyridine over KOH; acetic anhydride from sodium acetate. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem silica gel. Optical rotations were determined on a Jasco DIP-370 digital polarimeter. Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1}. ^1H and ^{13}C NMR spectroscopy measurements were carried out on Bruker AC 200 MHz or Bruker DRX 400 MHz spectrometers, and TMS was used as an internal standard. ^1H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) downfield from chloroform-*d* (δ=7.25) or TMS and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. The multiplicity of ^{13}C NMR signals was assigned with the help of DEPT spectra and the abbreviations used: s=singlet, d=doublet, t=triplet, and q=quartet, represent C (quaternary), CH, CH_2, and CH_3, respectively. Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and 4800 plus MALDI TOF/TOF Applied Biosystem spectrometer.

4.2. (4*S*,5*R*,6*R*)-5-(Benzyloxy)-4-((*S*)-1,2-bis(benzyloxy)ethyl)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-1,3-dioxane (10)

At 0 °C, a solution of triol **9** (10 g, 34.2 mmol) and benzyl bromide (12.6 mL, 106 mmol) in anhydrous DMF (100 mL) was treated with sodium hydride (5.47 g, 60% oil emulsion, 137 mmol) and stirred at room temperature for 6 h. The reaction mixture was cooled and the excess NaH was quenched by adding cold water. The reaction mixture was partitioned between ethyl acetate (250 mL) and water (100 mL). The separated organic layer was washed with water (4×100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (230–400 mesh silica gel, 1.5:8.5 ethyl acetate/petroleum ether) to obtain compound **10** (16.8 g, 87%) as pale yellow syrup. R_f (15% EtOAc/petroleum ether) 0.45; $[\alpha]_D^{25}$ +10.2 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$): 3011, 2928, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.41 (s, 3H), 3.63–3.66 (m, 1H), 3.68–3.70 (m, 1H), 3.79–3.83 (m, 2H), 3.86 (dd, *J*=2.3, 8.5 Hz, 1H), 3.88 (dt, *J*=2.0, 8.4 Hz, 1H), 4.04–4.10 (m, 2H), 4.23–4.28 (m, 1H), 4.36 (dd, *J*=2.0, 11.3 Hz, 1H), 4.52 (dd, *J*=1.5, 12.3 Hz, 1H), 4.56 (d, *J*=1.5 Hz, 1H), 4.62 (br d, *J*=12.3 Hz, 1H), 4.71 (dd, *J*=1.6, 11.3 Hz, 1H), 4.84 (dd, *J*=2.1, 11.8 Hz, 1H), 7.21–7.37 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (q), 25.1 (q), 26.9 (q), 29.4 (q), 67.4 (t), 67.43 (t), 69.7 (d), 70.6 (d), 71.2 (t), 73.3 (t), 73.4 (d), 74.0 (t), 74.4 (d), 76.5 (d), 98.6 (s), 109.1 (s), 127.1 (d, 3C), 127.4 (d, 2C), 127.6 (d, 2C), 127.7 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.24 (d, 2C), 138.3 (s), 138.34 (s), 139.1 (s); HRMS (MALDI-TOF) calcd for $C_{34}H_{42}O_7$ ($[M+Na]^+$) 585.2829, found 585.2813.

4.3. Acetonide hydrolysis of 10

Pyridinium *p*-toluenesulfonate (50 mg) was added to a solution of compound **10** (1.0 g) in methanol (10 mL) at 0 °C and the reaction mixture was stirred at same temperature for 1 h. The TLC showed formation of new three slower moving spots along with starting material. Therefore reaction mixture was basified with triethylamine and solvent was evaporated under reduced pressure to get a mixture of **11**–**13**, which was separated by column chromatography (100–200 mesh silica gel, 2:8 to 9:11 ethyl acetate/petroleum ether) to procure pure compounds **11** (211 mg, 37%), **12** (141 mg, 23%), **13** (107 mg, 17%), and starting material **10** (338 mg, all yields are based on starting material recovered).

*4.3.1. Characterization data of **11**.* R_f (70% EtOAc/petroleum ether) 0.12; $[\alpha]_D^{25}$ +9.1 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): 3460, 3010, 2918, 1452, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.95 (br s, 1H), 3.10 (br s, 1H), 3.39 (br s, 1H), 3.46 (br s, 1H), 3.62 (br s, 1H), 3.64–3.75 (m, 3H), 3.72 (dd, *J*=4.5, 10.5 Hz, 1H), 3.73–3.75 (m, 1H), 3.83 (dd, *J*=3.3, 10.5 Hz, 1H), 3.95 (t, *J*=6.6 Hz, 1H), 4.02 (t, *J*=2.8 Hz, 1H), 4.40 (d, *J*=11.5 Hz, 1H), 4.52 (d, *J*=11.7 Hz, 2H), 4.56 (d, *J*=12.1 Hz, 1H), 4.66 (d, *J*=11.5 Hz, 1H), 4.69 (d, *J*=11.5 Hz, 1H), 7.24–7.34 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 63.7 (t), 69.2 (t), 71.6 (d), 71.7 (t), 72.3 (d), 73.5 (t), 73.6 (d), 74.6 (t), 76.4 (d), 78.0 (d), 127.7 (d), 127.7 (d), 127.8 (d, 2C), 127.9 (d, 3C), 128.0 (d, 2C), 128.4 (d, 4C), 128.5 (d, 2C), 137.9 (s), 137.95 (s), 137.97 (s); HRMS (MALDI-TOF) calcd for $C_{28}H_{34}O_7$ ($[M+Na]^+$) 505.2203, found 505.2184.

*4.3.2. Characterization data of **12**.* R_f (60% EtOAc/petroleum ether) 0.51; $[\alpha]_D^{25}$ −2.1 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$): 3440, 2998, 2910,

1110 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.38 (s, 3H), 1.39 (s, 3H), 3.58 (dd, J=3.8, 10.7 Hz, 1H), 3.66–3.71 (m, 4H), 3.82 (s, 1H), 3.87 (dd, J=1.8, 10.7 Hz, 1H), 3.91 (ddd, J=1.8, 3.4, 9.1 Hz, 1H), 4.09 (dd, J=1.0, 9.1 Hz, 1H), 4.40 (d, J=11.4 Hz, 1H), 4.54 (d, J=12.2 Hz, 1H), 4.60 (d, J=12.2 Hz, 1H), 4.68 (d, J=11.4 Hz, 1H), 4.73 (d, J=12.0 Hz, 1H), 4.83 (d, J=11.4 Hz, 1H), 7.24–7.34 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1 (q), 29.4 (q), 63.9 (t), 67.6 (t), 68.7 (d), 69.4 (d), 71.0 (t), 71.1 (d), 73.37 (t), 73.38 (d), 73.6 (t), 76.5 (d), 98.8 (s), 127.5 (d), 127.6 (d), 127.66 (d, 3C), 127.67 (d, 2C), 127.8 (d, 2C), 128.3 (d, 2C), 128.34 (d, 2C), 128.4 (d, 2C), 138.3 (s), 138.4 (s), 138.7 (s); HRMS (MALDI-TOF) calcd for $C_{31}H_{38}O_7$ ($[M+Na]^+$) 545.2516, found 545.2519.

*4.3.3. Characterization data of **13**.* R_f (60% EtOAc/petroleum ether) 0.62; $[\alpha]_D^{25}$ +9.4 (c 0.6, $CHCl_3$); IR ($CHCl_3$): 3410, 2995, 2928, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 3H), 1.40 (s, 3H), 2.92 (d, J=6.1 Hz, 1H), 2.97 (br s, 1H), 3.64 (dt, J=3.6, 7.8 Hz, 1H), 3.71–3.75 (m, 2H), 3.85 (dd, J=3.2, 10.5 Hz, 1H), 3.93–3.98 (m, 2H), 4.03 (*t*, J=2.5 Hz, 1H), 4.07–4.10 (m, 2H), 4.44 (d, J=11.7 Hz, 1H), 3.54–3.56 (m, 3H), 4.72 (d, J=11.3 Hz, 1H), 4.73 (d, J=11.7 Hz, 1H), 7.28–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.3 (q), 26.8 (q), 67.3 (t), 69.4 (t), 71.8 (t), 73.1 (d), 73.5 (t), 74.7 (t), 75.3 (d), 75.4 (d), 76.2 (d), 78.0 (d), 109.5 (s), 127.7 (d, 4C), 127.8 (d, 3C), 127.9 (d, 2C), 128.37 (d, 2C), 128.4 (d, 2C), 128.42 (d, 2C), 138.0 (s), 138.1 (s), 138.12 (s); HRMS (MALDI-TOF) calcd for $C_{31}H_{38}O_7$ ($[M+Na]^+$) 545.2516, found 545.2532.

4.4. (2*R*,3*R*,4*S*,5*S*,6*S*)-4,6,7-Tris(benzyloxy)heptane-1,2,3,5-tetraol (11)

To a solution of compound **10** (15 g, 26.6 mmol) in methanol (150 mL) was added 0.8% solution of H_2SO_4 in methanol (15 mL) and stirring was continued for 8 h at room temperature. After completion of the reaction, as indicated by TLC, the contents were cooled in an ice bath and neutralized with solid K_2CO_3. The reaction mixture was filtered through Celite pad and the filtrate was evaporated under reduced pressure. The crude was purified by column chromatography (100–200 mesh silica gel, 9:11 ethyl acetate/petroleum ether) to afford tetrol **11** (10.8 g, 84% yield) as colorless gum.

4.5. Selective protection of terminal diol

To an ice-cold solution of tetrol **11** (5 g, 10.4 mmol) in 3-pentanone (50 mL), were added five drops of concentrated H_2SO_4 and stirring was continued at same temperature for next 3 h [formation of dipentylidene derivative **14** was also observed if the temperature increases above 5 °C]. After complete consumption of starting material, the reaction mixture was basified by triethylamine (2 mL) and the solvent was evaporated under reduced pressure. The resulting crude was purified by column chromatography (230–400 mesh silica gel, 3:7 ethyl acetate/petroleum ether) to isolate pure product **15** (4.9 g, 86%) as pale yellow gum.

*4.5.1. Characterization data of **15**.* R_f (15% EtOAc/petroleum ether) 0.71; $[\alpha]_D^{25}$ +9.4 (c 0.6, $CHCl_3$); IR ($CHCl_3$): 3396, 3009, 2891, 1121 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.89 (t, J=7.5 Hz, 6H), 1.59–1.65 (m, 4H), 2.90 (d, J=6.9 Hz, 1H), 2.96 (d, J=4.8 Hz, 1H), 3.63 (ddd, J=3.4, 4.6, 7.9 Hz, 1H), 3.70–3.72 (m, 1H), 3.73 (dd, J=4.6, 10.5 Hz, 1H), 3.85 (dd, J=3.3, 10.5 Hz, 1H), 3.89 (dd, J=5.9, 7.9 Hz, 1H), 3.94 (dt, J=2.3, 7.3 Hz, 1H), 4.06 (t, J=2.5 Hz, 1H), 4.07–4.11 (m, 1H), 4.14 (dd, J=6.3, 7.9 Hz, 1H), 4.41 (d, J=11.6 Hz, 1H), 4.54 (d, J=11.3 Hz, 1H), 4.56 (br s, 2H), 4.73 (d, J=11.6 Hz, 1H), 7.27–7.34 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.1 (q), 8.3 (q), 29.1 (t), 29.6 (t), 68.1 (t), 69.4 (t), 71.8 (t), 73.3 (d), 73.6 (t), 74.8 (t), 75.5 (d), 75.9 (d), 76.4 (d), 78.1 (d), 113.2 (s), 127.7 (d, 4C), 127.8 (d, 2C), 127.86 (d), 127.9 (d, 2C), 128.4 (d, 2C), 128.42 (d, 2C), 128.5 (d, 2C), 138.1 (s), 138.17 (s), 138.19 (s); HRMS (MALDI-TOF) calcd for $C_{33}H_{42}O_7$ ($[M+Na]^+$) 573.2829, found 573.2790.

*4.5.2. Characterization data of **14**.* R_f (15% EtOAc/petroleum ether) 0.25; $[\alpha]_D^{25}$ +15.7 (c 1.0, $CHCl_3$); IR ($CHCl_3$): 3011, 2916, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.79–0.92 (m, 12H), 1.54–1.66 (m, 6H), 1.71–1.81 (m, 2H), 3.67 (dd, J=3.4, 10.6 Hz, 1H), 3.72 (br d, J=8.5 Hz, 1H), 3.77–3.84 (m, 3H), 3.89 (ddd, J=2.1, 3.2. 9.1 Hz, 1H), 4.06 (dd, J=1.0, 9.1 Hz, 1H), 4.09 (dd, J=6.5, 8.3 Hz, 1H), 4.25 (dt, J=6.2, 8.3 Hz, 1H), 4.35 (d, J=11.4 Hz, 1H), 4.52 (d, J=12.3 Hz, 1H), 4.58 (d, J=13.0 Hz, 1H), 4.61 (d, J=12.3 Hz, 1H), 4.73 (d, J=11.5 Hz, 1H), 4.87 (d, J=12.1 Hz, 1H), 7.23–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 7.1 (q), 8.1 (q), 8.15 (q), 8.3 (q), 21.1 (t), 29.0 (t), 29.7 (t), 30.7 (t), 67.6 (t), 68.3 (t), 69.7 (d), 70.0 (d), 71.2 (t), 73.4 (t), 73.8 (t), 73.9 (d), 74.0 (d), 76.6 (d), 101.9 (s), 113.1 (s), 126.7 (d, 2C), 127.0 (d), 127.5 (d), 127.52 (d), 127.6 (d, 2C), 127.8 (d, 2C), 128.1 (d, 2C), 128.3 (d, 4C), 138.3 (s), 138.5 (s), 139.4 (s); HRMS (MALDI-TOF) calcd for $C_{38}H_{50}O_7$ ($[M+Na]^+$) 641.3455, found 641.3453.

4.6. (*R*)-2,2-Diethyl-4-((1*R*,2*R*,3*S*,4*S*)-1,2,3,4,5-pentakis(benzyloxy)pentyl)-1,3-dioxolane (16)

To a solution of diol **15** (4 g, 7.3 mmol) in anhydrous DMF (40 mL) was added benzyl bromide (1.8 mL, 15.3 mmol) at room temperature and the reaction mixture was cooled to 0 °C. To this, sodium hydride (871 mg, 21.8 mmol) was added portion wise. After complete addition, reaction mixture was allowed to stir at room temperature for 4 h. The reaction mixture was cooled and the excess NaH was quenched by adding cold water. The reaction mixture was partitioned between ethyl acetate (100 mL) and water (50 mL). The separated organic layer was washed with water (4×50 mL), brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to obtain **16** (4.9 g, 92%) as pale yellow syrup. R_f (20% EtOAc/petroleum ether) 0.60; $[\alpha]_D^{25}$ +2.9 (c 1.7, $CHCl_3$); IR ($CHCl_3$): 3021, 2917, 1448, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, J=7.5 Hz, 3H), 0.86 (t, J=7.5 Hz, 3H), 1.53–1.64 (m, 4H), 3.73 (dd, J=5.1, 10.0 Hz, 1H), 3.77–3.82 (m, 2H), 3.83–3.88 (m, 2H), 3.92 (*t*, J=4.7 Hz, 1H), 3.96 (dd, J=6.3, 7.9 Hz, 1H), 4.04 (dd, J=4.6, 6.3 Hz, 1H), 4.10 (dt, J=5.6, 8.0 Hz, 1H), 4.45 (d, J=11.9 Hz, 1H), 4.51 (d, J=12.1 Hz, 1H), 4.55 (d, J=12.1 Hz, 1H), 4.59 (d, J=11.6 Hz, 1H), 4.62 (d, J=11.4 Hz, 1H), 4.65–4.74 (m, 3H), 4.76 (d, J=11.4 Hz, 1H), 7.24–7.33 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 8.3 (q, 2C), 28.5 (t), 29.5 (t), 66.7 (t), 69.7 (t), 71.9 (t), 73.3 (t), 74.0 (t), 74.4 (t), 75.2 (t), 76.8 (d), 79.4 (d), 79.5 (d), 79.7 (d), 80.5 (d), 112.2 (s), 127.4 (d, 3C), 127.5 (d, 4C), 127.6 (d, 2C), 127.7 (d, 2C), 127.9 (d, 2C), 128.0 (d, 2C), 128.2 (d, 4C), 128.23 (d, 4C), 128.3 (d, 2C), 138.3 (s), 138.5 (s), 138.54 (s), 138.6 (s), 138.8 (s); HRMS (MALDI-TOF) calcd for $C_{47}H_{54}O_7$ ($[M+Na]^+$) 753.3768, found 753.3756.

4.7. (2*R*,3*R*,4*S*,5*S*,6*S*)-3,4,5,6,7-Pentakis(benzyloxy)heptane-1,2-diol (17)

To a solution of compound **16** (4.5 g, 6.7 mmol) in methanol (50 mL) was added 0.8% solution of H_2SO_4 in methanol (5 mL) and stirred for 6 h before neutralizing with solid K_2CO_3. The contents were filtered through Celite bed and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (230–400 mesh silica gel, 3:7 ethyl acetate/petroleum ether) to afford **17** (3.3 g, 82%) as colorless gum. R_f (30% EtOAc/petroleum ether) 0.26; $[\alpha]_D^{25}$ +2.9 (c 1.1, $CHCl_3$); IR ($CHCl_3$): 3398, 3012, 2921, 1451, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.59 (dd, J=4.3, 11.4 Hz, 1H), 3.66 (dd, J=3.2, 11.4 Hz, 1H), 3.70–3.73 (m, 2H), 3.79 (dd, J=4.1, 7.6 Hz, 1H), 3.84 (dd, J=3.5,

10.3 Hz, 1H), 3.86–3.90 (m, 2H), 4.06 (t, J=4.3 Hz, 1H), 4.47 (d, J=12.0 Hz, 1H), 4.50–4. 57 (m, 6H), 4.68 (br d, J=11.7 Hz, 2H), 4.77 (d, J=11.2 Hz, 1H), 7.24–7.31 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 63.6 (t), 69.5 (t), 71.8 (d), 72.0 (t), 73.3 (t), 73.4 (t), 74.0 (t, 2C), 76.5 (d), 78.2 (d), 78.6 (d), 78.9 (d), 127.5 (d), 127.6 (d, 2C), 127.6 (d, 2C), 127.7 (d, 2C), 127.8 (d), 127.9 (d), 128.0 (d, 2C), 128.1 (d, 2C), 128.3 (d, 6C), 128.35 (d, 2C), 128.4 (d, 4C), 137.7 (s), 137.8 (s), 138.2 (s, 2C), 138.5 (s); HRMS (MALDI-TOF) calcd for $C_{42}H_{46}O_7$ ([M+Na]$^+$) 685.3142, found 685.3163.

4.8. (2*R*,3*R*,4*S*,5*S*,6*S*)-3,4,5,6,7-Pentakis(benzyloxy)-2-hydroxyheptyl benzoate (18)

At 0 °C, a solution of diol **17** (3 g, 4.5 mmol) and Et_3N (0.76 mL, 5.4 mmol) in anhydrous CH_2Cl_2 (30 mL) was added benzoyl chloride (0.5 mL, 4.5 mmol) and the contents stirred at the same temperature for 2.5 h. Then reaction mixture was partitioned between CH_2Cl_2 (100 mL) and water (60 mL). The organic layer was separated, washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue obtained was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to procure **18** (2.9 g, 83%) as colorless syrup. R_f (15% EtOAc/petroleum ether) 0.45; $[\alpha]_D^{25}$ +6.4 (c 1.4, $CHCl_3$). IR ($CHCl_3$): 3421, 2998, 2912, 1732, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.72–3.77 (m, 2H), 3.87 (dd, J=3.1, 10.2 Hz, 1H), 3.89–3.99 (m, 2H), 4.04–4.13 (m, 2H), 4.35 (dd, J=5.7, 11.6 Hz, 1H), 4.44–4.54 (m, 6H), 4.62 (br s, 2H), 4.69 (d, J=11.6 Hz, 1H), 4.71 (d, J=11.4 Hz, 1H), 4.78 (d, J=11.4 Hz, 1H), 7.22–7.32 (m, 25H), 7.39–7.42 (m, 2H), 7.53–7.55 (m, 1H), 7.99–8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.3 (t), 69.5 (t), 70.4 (d), 72.0 (t), 73.2 (t), 73.4 (t), 74.1 (t), 74.2 (t), 76.6 (d), 78.3 (d), 78.5 (d), 78.9 (d), 127.5 (d), 127.6 (d, 2C), 127.7 (d, 3C), 127.8 (d, 2C), 128.1 (d, 2C), 128.14 (d, 2C), 128.3 (d, 6C), 128.4 (d, 7C), 129.7 (d, 2C), 130.1 (d), 132.9 (d, 2C), 137.6 (s), 137.8 (s, 2C), 138.1 (s), 138.2 (s), 138.5 (s), 166.6 (s); HRMS (MALDI-TOF) calcd for $C_{49}H_{50}O_8$ ([M+Na]$^+$) 789.3404, found 789.3425.

4.9. (2*R*,3*S*,4*R*,5*S*,6*S*)-3,4,5,6,7-Pentakis(benzyloxy)-2-((methyl sulfonyl)oxy)heptylbenzoate (19)

At 0 °C, a solution of compound **18** (2.5 g, 3.3 mmol) and Et_3N (0.6 mL, 4.2 mmol) in anhydrous CH_2Cl_2 (30 mL) was treated with methanesulfonyl chloride (0.3 mL, 3.6 mmol) and the contents were stirred at room temperature for 2.5 h. The crude product isolated after the usual aqueous workup was purified by column chromatography (230–400 mesh silica gel, 1.5:8.5 ethyl acetate/petroleum ether) to afford **19** (2.1 g, 78%) as colorless gum. R_f (5% EtOAc/toluene) 0.70; $[\alpha]_D^{25}$ +17.5 (c 2.3, $CHCl_3$); IR ($CHCl_3$): 3011, 2913, 1461, 1121 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.74 (s, 3H), 3.71 (dd, J=6.1, 11.4 Hz, 1H), 3.85–3.90 (m, 3H), 3.96 (t, J=5.1 Hz, 1H), 4.16 (dd, J=2.8, 5.9 Hz, 1H), 4.50 (br d, J=11.2 Hz, 3H), 4.58 (dd, J=8.3, 12.7 Hz, 1H), 4.65–4.69 (m, 6H), 4.72 (dd, J=2.4, 12.7 Hz, 1H), 4.75 (d, J=11.4 Hz, 1H), 5.20 (dt, J=2.4, 8.3 Hz, 1H), 7.15–7.32 (m, 25H), 7.42 (t, J=7.8 Hz, 2H), 7.54–7.57 (m, 1H), 8.02–8.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 38.4 (q), 63.7 (t), 69.4 (t), 72.1 (t), 73.3 (t), 73.8 (t), 74.9 (t), 75.0 (t), 78.3 (d), 78.7 (d), 79.5 (d), 80.3 (d), 81.3 (d), 127.5 (d), 127.6 (d), 127.63 (d), 127.7 (d, 3C), 127.8 (d, 3C), 128.1 (d, 2C), 128.2 (d), 128.22 (d, 4C), 128.3 (d, 2C), 128.32 (d, 5C), 128.4 (d, 2C), 129.0 (d), 129.7 (d), 129.72 (d, 2C), 133.1 (d), 137.7 (s), 137.8 (s), 138.1 (s), 138.2 (s), 138.3 (s), 138.4 (s), 166.1 (s); HRMS (MALDI-TOF) calcd for $C_{50}H_{52}O_{10}S$ ([M+Na]$^+$) 867.3179, found 867.3156.

4.10. (*S*)-2-((1*R*,2*S*,3*S*,4*S*)-1,2,3,4,5-Pentakis(benzyloxy)pentyl) oxirane (20)

Solid lithium hydroxide (300 mg, 7.1 mmol) was added to a solution of compound **19** (2 g, 2.4 mmol) in THF/MeOH (7:3, 20 mL) at 0 °C. After 30 min stirring at 0 °C, the reaction mixture was stirred for next 7 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue obtained was purified by column chromatography (230–400 mesh silica gel, 1.5:8.5 ethyl acetate/petroleum ether) to obtain **20** (1.2 g, 79%) as a colorless gum. R_f (20% EtOAc/petroleum ether) 0.64; $[\alpha]_D^{25}$ −27.2 (c 1.5, $CHCl_3$); IR ($CHCl_3$): 3055, 2921, 1131 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.94 (dd, J=2.4, 4.8 Hz, 1H), 2.22 (dd, J=4.0, 4.8 Hz, 1H), 3.06–3.11 (m, 2H), 3.63 (dd, J=5.2, 9.7 Hz, 1H), 3.70 (dt, J=3.5, 5.2 Hz, 1H), 3.76 (dd, J=3.1, 7.0 Hz, 1H), 3.85 (dd, J=5.2, 9.7 Hz, 1H), 4.18 (dd, J=3.5, 7.0 Hz, 1H), 4.40–4.46 (m, 3H), 4.53 (d, J=12.0 Hz, 1H), 4.54 (d, J=11.7 Hz, 1H), 4.59 (br d, J=11.6 Hz, 1H), 4.75 (d, J=11.3 Hz, 1H), 4.77 (d, J=11.6 Hz, 1H), 4.85 (br d, J=12.0 Hz, 2H), 7.22–7.36 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 42.4 (t), 53.3 (d), 67.5 (t), 71.8 (t), 72.0 (t), 73.4 (t), 74.5 (t), 74.8 (t), 78.9 (d), 79.7 (d), 80.1 (d), 80.6 (d), 127.3 (d, 2C), 127.4 (d, 2C), 127.6 (d), 127.7 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.25 (d, 4C), 128.3 (d, 2C), 128.4 (d, 2C), 128.6 (d, 2C), 138.1 (s), 138.13 (s), 138.3 (s), 138.6 (s), 138.9 (s); HRMS (MALDI-TOF) calcd for $C_{42}H_{44}O_6$ ([M+Na]$^+$) 667.3036, found 667.3065.

4.11. Addition of alkyne 21 to the epoxide 20

At −78 °C, a solution of alkyne **21** (493 mg, 0.9 mmol) in anhydrous THF (6 mL) was treated with n-BuLi (0.2 mL, 1.6 M in hexane, 0.3 mmol) and stirred for 20 min and then introduced a solution of $BF_3\cdot Et_2O$ (48 mg, 0.3 mmol) and stirred at −78 °C for 20 min. To this, a solution of epoxide **20** (200 mg, 0.3 mmol) in anhydrous THF (2 mL) was added slowly at −78 °C and the contents were stirred for 2.5 h at the same temperature. Reaction mixture was quenched by adding saturated sodium bicarbonate (1 mL) and partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with brine (20 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude compound was purified by column chromatography (silica 230–400 mesh, 25% ethyl acetate in petroleum ether) to afford compound **22** (11 mg, 3% yield) as colorless syrup and compound **23** (112 mg, 64% yield) as pale yellow gum.

*4.11.1. Characterization data of **22**.* R_f (15% EtOAc/petroleum ether) 0.33; $[\alpha]_D^{25}$ +27.1 (c 2.2, $CHCl_3$); IR ($CHCl_3$): 3398, 3013, 2912, 1441, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.05 (s, 6H), 0.85 (s, 9H), 2.24 (ddd, J=1.9, 5.7, 16.5 Hz, 1H), 2.52 (ddd, J=1.9, 7.7, 16.5 Hz, 1H), 2.63 (br s, 1H), 3.55 (dd, J=5.2, 10.0 Hz, 1H), 3.60 (dd, J=2.8, 10.0 Hz, 1H), 3.75 (dd, J=4.5, 10.1 Hz, 1H), 3.77–3.82 (m, 3H), 3.91–3.95 (m, 3H), 4.01 (dd, J=3.0, 7.4 Hz, 1H), 4.04 (ddd, J=3.0, 5.2, 8.2 Hz, 1H), 4.42–4.6 (m, 4H), 4.47–4.59 (m, 5H), 4.66 (d, J=11.6 Hz, 1H), 4.68 (d, J=12.0 Hz, 1H), 4.69 (d, J=11.6 Hz, 1H), 4.75 (d, J=11.5 Hz, 1H), 4.76 (d, J=11.4 Hz, 1H), 4.77 (d, J=11.2 Hz, 1H), 4.80 (d, J=12.0 Hz, 1H), 4.90 (d, J=11.5 Hz, 1H), 7.21–7.34 (m, 40H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ −5.0 (q), −4.3 (q), 18.0 (s), 25.8 (q, 3C), 69.5 (d), 69.8 (t), 70.8 (t), 71.1 (d), 71.9 (t, 2C), 72.3 (d), 73.2 (t), 73.3 (t), 73.5 (t), 74.4 (t, 2C), 74.7 (t), 74.9 (t), 78.0 (d), 78.8 (s), 79.1 (d), 79.4 (d), 80.1 (d), 81.7 (d), 84.6 (s), 127.3 (d), 127.4 (d, 2C), 127.5 (d, 2C), 127.54 (d), 127.6 (d, 2C), 127.7 (d, 6C), 127.8 (d, 2C), 128.0 (d, 2C), 128.02 (d, 2C), 128.1 (d, 4C), 128.16 (d, 2C), 128.19 (d, 2C), 128.26 (d, 5C), 128.3 (d, 7C), 137.9 (s), 138.2 (s, 2C), 138.3 (s), 138.4 (s), 138.43 (s), 138.6 (s), 138.7 (s); HRMS (MALDI-TOF) calcd for $C_{75}H_{86}O_{10}Si$ ([M+Na]$^+$) 1197.5888, found 1197.5919.

*4.11.2. Characterization data of **23**.* R_f (15% EtOAc/petroleum ether) 0.18; $[\alpha]_D^{25}$ +37.2 (c 6.4, $CHCl_3$); IR ($CHCl_3$): 3427, 3022, 2913, 1127 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.62 (dd, J=4.2, 11.7 Hz, 1H), 3.67 (dd, J=5.6, 10.7 Hz, 1H), 3.73 (dd, J=3.1, 11.7 Hz, 1H), 3.87 (dd, J=1.9, 10.7 Hz, 1H), 3.99–4.08 (m, 4H), 4.14 (dd, J=3.1, 9.1 Hz,

1H), 4.39 (d, *J*=11.4 Hz, 1H), 4.46 (d, *J*=11.9 Hz, 1H), 4.49 (d, *J*=11.4 Hz, 1H), 4.50–4.56 (m, 4H), 4.78 (d, *J*=11.5 Hz, 1H), 7.20–7.33 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 63.1 (t), 70.9 (t), 71.6 (t), 71.7 (t), 72.5 (t), 73.4 (t), 75.8 (d), 80.3 (d), 81.7 (d), 82.5 (d), 85.1 (d), 127.4 (d, 2C), 127.5 (d, 4C), 127.6 (d, 2C), 127.9 (d, 4C), 128.2 (d, 4C), 128.5 (d, 4C), 137.2 (s), 137.5 (s), 138.4 (s), 138.7 (s); HRMS (MALDI-TOF) calcd for $C_{35}H_{38}O_6$ ([M+Na]$^+$) 577.2566, found 577.2577.

4.12. ((2*R*,3*R*,4*S*,5*S*)-3,4-Bis(benzyloxy)-5-((*S*)-1,2-bis(benzyloxy)ethyl)tetrahydrofuran-2-yl)methylacetate (24)

To a solution of compound **23** (80 mg, 0.2 mmol) in pyridine (1 mL), acetic anhydride (1 mL) was added slowly at 0 °C. The contents were stirred for 3 h at room temperature. The reaction mixture was diluted with ethyl acetate (10 mL), washed with water (5 mL), brine (5 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (230–400 mesh silica gel, 1.5:8.5 ethyl acetate/petroleum ether) to procure compound **24** (79 mg, 91%) as colorless gum. R_f (20% EtOAc/petroleum ether) 0.55; $[\alpha]_D^{25}$ +33.1 (*c* 3.4, $CHCl_3$); IR ($CHCl_3$): 3022, 2931, 1731, 1461, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.00 (s, 3H), 3.70 (dd, *J*=5.6, 10.6 Hz, 1H), 3.84–3.91 (m, 2H), 4.03–4.06 (m, 1H), 4.09–4.13 (m, 4H), 4.19 (dd, *J*=3.3, 9.0 Hz, 1H), 4.42–4.53 (m, 5H), 4.59 (br s, 2H), 4.81 (d, *J*=11.4 Hz, 1H), 7.24–7.34 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.8 (q), 64.6 (t), 71.0 (t), 71.4 (t), 71.7 (t), 72.5 (t), 73.3 (t), 76.0 (d), 80.5 (d), 81.9 (d), 82.0 (d), 83.0 (d), 127.4 (d, 2C), 127.6 (d, 8C), 127.7 (d), 127.9 (d), 128.2 (d, 4C), 128.4 (d, 2C), 128.5 (d, 2C), 137.5 (s), 137.7 (s), 138.6 (s), 138.8 (s), 170.7 (s); HRMS (MALDI-TOF) calcd for $C_{37}H_{40}O_7$ ([M+Na]$^+$) 619.2672, found 619.2660.

4.13. (1*S*,5*S*,6*S*,7*R*)-5,6,8-Tris(benzyloxy)-1-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-7-((*tert*-butyldimethylsilyl)oxy)oct-3-yn-1-ol (26)

A solution of alkyne **21** (2.72 g, 5.1 mmol) in anhydrous THF (20 mL) was treated with *n*-BuLi (3.2 mL, 1.6 M in hexane, 5.1 mmol) at −78 °C for 20 min and then $BF_3\cdot Et_2O$ (680 mg, 4.8 mmol) was added. Stirring was continued at −78 °C for 20 min then to this, a solution of epoxide **25** (50Z0 mg, 1.7 mmol) in anhydrous THF (3 mL) was added slowly at −78 °C and the contents were stirred for 2 h at the same temperature. Reaction mixture was quenched by adding saturated sodium bicarbonate (2 mL) and extracted with ethyl acetate (100 mL) and water (40 mL). The organic layer was washed with brine (40 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude was purified by column chromatography (silica 230–400 mesh, 1:4 ethyl acetate/petroleum ether) to afford compound **26** (1.1 g, 79%) as pale yellow thick oil. R_f (25% EtOAc/petroleum ether) 0.32; $[\alpha]_D^{25}$ +19.1 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$): 3468, 3021, 2931, 1099 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ −0.01 (s, 3H), 0.01 (s, 3H), 0.80 (s, 9H), 1.32 (s, 3H), 1.42 (s, 3H), 2.50 (dd, *J*=5.8, 16.8 Hz, 1H), 2.60 (dd, *J*=7.1, 16.8 Hz, 1H), 3.52 (dd, *J*=5.0, 10.1 Hz, 1H), 3.58 (dd, *J*=2.7, 10.1 Hz, 1H), 3.79 (dd, *J*=4.2, 6.5 Hz, 1H), 3.97–3.99 (m, 2H), 4.08 (dd, *J*=6.2, 10.9 Hz, 1H), 4.34 (t, *J*=3.8 Hz, 1H), 4.42–4.53 (m, 5H), 4.63–4.73 (m, 3H), 4.81 (d, *J*=11.9 Hz, 1H), 4.90 (d, *J*=11.6 Hz, 1H), 6.00 (d, *J*=3.8 Hz, 1H), 7.23–7.36 (m, 20H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ −5.0 (q), −4.3 (q), 18.0 (s), 23.9 (t), 25.8 (q, 3C), 26.4 (q), 26.9 (q), 68.9 (d), 70.8 (t), 71.0 (d), 71.8 (t, 2C), 72.2 (d), 73.2 (t), 74.3 (t), 78.8 (s), 80.5 (d), 81.4 (d), 82.3 (d), 83.1 (d), 83.9 (s), 104.9 (d), 111.9 (s), 127.3 (d, 2C), 127.5 (d), 127.7 (d, 2C), 127.8 (d, 2C), 127.9 (d, 2C), 128.1 (d, 2C), 128.13 (d, 2C), 128.2 (d, 2C), 128.3 (d, 3C), 128.7 (d, 2C), 136.6 (s), 137.9 (s), 138.4 (s), 138.7 (s); HRMS (MALDI-TOF) calcd for $C_{49}H_{62}O_9Si$ ([M+Na]$^+$) 845.4061, found 845.3998.

4.14. *tert*-Butyldimethyl(((2*R*,3*S*,4*S*,8*S*)-1,3,4,8-tetrakis(benzyloxy)-8-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)oct-5-yn-2-yl)oxy)silane (27)

To a solution alcohol **26** (1 g, 1.2 mmol) in anhydrous DMF (15 mL) was added benzyl bromide (0.16 mL, 1.3 mmol) at room temperature and the reaction mixture was cooled to 0 °C. To this, sodium hydride (97 mg, 60% oil emulsion, 2.4 mmol) was added portion wise. After complete addition, reaction mixture was allowed to stir at room temperature for 6 h. Reaction mixture was quenched and partitioned between ethyl acetate (80 mL) and water (30 mL). The separated organic layer was washed with water (4×30 mL), brine (30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude was purified by column chromatography (230–400 mesh silica gel, 1.5:8.5 ethyl acetate/petroleum ether) to obtain compound **27** (903 mg, 81%) as pale yellow syrup. R_f (20% EtOAc/petroleum ether) 0.61; $[\alpha]_D^{25}$ +23.1 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): 3028, 2913, 1451, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.01 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 1.33 (s, 3H), 1.44 (s, 3H), 2.46 (ddd, *J*=1.6, 6.3, 17.1 Hz, 1H), 2.57 (ddd, *J*=1.7, 4.3, 17.1 Hz, 1H), 3.56 (dd, *J*=4.8, 9.9 Hz, 1H), 3.61 (dd, *J*=3.0, 9.9 Hz, 1H), 3.80 (dd, *J*=4.3, 6.3 Hz, 1H), 3.92 (dt, *J*=4.7, 6.6 Hz, 1H), 4.00–4.04 (m, 2H), 4.40–4.49 (m, 6H), 4.60–4.66 (m, 3H), 4.71 (d, *J*=11.9 Hz, 1H), 4.78 (d, *J*=11.5 Hz, 1H), 4.83 (d, *J*=11.9 Hz, 1H), 4.92 (d, *J*=11.9 Hz, 1H), 5.99 (d, *J*=4.0 Hz, 1H), 7.22–7.36 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.9 (q), −4.3 (q), 18.0 (s), 21.6 (t), 25.9 (q, 3C), 26.6 (q), 27.0 (q), 70.6 (t), 71.00 (d), 71.7 (t), 72.0 (t), 72.2 (d), 72.9 (t), 73.2 (t), 74.3 (t), 76.5 (d), 78.0 (s), 81.7 (d), 82.3 (d), 82.4 (d), 82.6 (d), 84.3 (s), 105.1 (d), 112.0 (s), 127.3 (d, 2C), 127.35 (d), 127.4 (d), 127.7 (d, 4C), 127.8 (d, 2C), 127.9 (d, 2C), 127.95 (d, 2C), 128.0 (d), 128.1 (d, 2C), 128.13 (d, 2C), 128.2 (d, 2C), 128.24 (d, 2C), 128.5 (d, 2C), 137.1 (s), 138.0 (s), 138.4 (s), 138.8 (s), 138.9 (s); HRMS (MALDI-TOF) calcd for $C_{56}H_{68}O_9Si$ ([M+Na]$^+$) 935.4531, found 935.4512.

4.15. (2*R*,3*R*,4*S*,8*S*)-1,3,4,8-Tetrakis(benzyloxy)-8-((3a*R*,5*R*,6-*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3] dioxol-5-yl)oct-5-yn-2-ol (28)

To an ice cooled solution of TBS ether **27** (900 mg, 1.0 mmol) in anhydrous THF (10 mL) was added a solution of TBAF (386 mg, 1.5 mmol) in anhydrous THF (2 mL) under argon atmosphere and allowed to stir at room temperature for 4 h. Reaction mixture was concentrated and the residue was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to afford compound **28** (601 mg, 76% yield) as a colorless gum. R_f (20% ethyl acetate/petroleum ether) 0.28; $[\alpha]_D^{25}$ +30.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3442, 3038, 2943, 1451, 1081 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.32 (s, 3H), 1.44 (s, 3H), 2.43 (dd, *J*=6.1, 17.1 Hz, 1H), 2.53 (dd, *J*=3.3, 17.1 Hz, 1H), 2.65 (br s, 1H), 3.59 (dd, *J*=5.7, 9.6 Hz, 1H), 3.65 (dd, *J*=2.8, 9.6 Hz, 1H), 3.76 (dd, *J*=3.6, 7.5 Hz, 1H), 3.91 (dt, *J*=3.6, 6.5 Hz, 1H), 3.95 (br s, 1H), 4.00 (d, *J*=3.6 Hz, 1H), 4.40–4.42 (m, 2H), 4.47 (d, *J*=11.8 Hz, 1H), 4.48 (d, *J*=11.7 Hz, 1H), 4.51 (d, *J*=11.8 Hz, 1H), 4.52–4.54 (m, 1H), 4.57–4.64 (m, 3H), 4.70 (d, *J*=11.6 Hz, 1H), 4.79 (d, *J*=11.6 Hz, 1H), 4.86 (d, *J*=12.2 Hz, 1H), 4.88 (d, *J*=11.6 Hz, 1H), 5.99 (d, *J*=3.9 Hz, 1H), 7.20–7.37 (m, 25H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.6 (t), 26.5 (q), 26.9 (q), 70.8 (d), 70.82 (t), 70.9 (t), 71.4 (d), 71.7 (t), 73.0 (t), 73.3 (t), 73.9 (t), 76.4 (d), 77.6 (s), 80.5 (d), 82.1 (d), 82.3 (d), 82.7 (d), 84.7 (s), 105.1 (d), 112.0 (s), 127.3 (d), 127.5 (d), 127.6 (d), 127.7 (d, 3C), 127.8 (d, 2C), 127.83 (d, 4C), 128.0 (d, 3C), 128.16 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 128.5 (d, 2C), 137.0 (s), 137.8 (s), 138.0 (s), 138.5 (s), 138.8 (s); ESI-MS: *m*/*z* 821.43 ([M+Na]$^+$).

4.16. Pd-mediated cycloisomerization

IBX (52 mg, 0.2 mmol) was added to a solution of an alcohol **28** (100 mg, 0.1 mmol) in ethyl acetate (10 mL) at room temperature and stirring was continued at reflux temperature for 3 h. After the complete consumption of starting material, the reaction mixture was cooled in ice bath, filtered through Celite bed, washed with ethyl acetate, and the combined filtrate was evaporated under reduced pressure. The residual crude ketone (91 mg) was dissolved in anhydrous methanol (10 mL) and the solution was degassed by passing argon for 45 min. To this, $Pd(OAc)_2$ (5 mg, 22.8 μmol) was added and stirred for 2.5 h. After consumption of starting material, the reaction mixture was filtered through Celite bed and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to obtain **29-α** (52 mg, 53% yield) and 2**9-β** (13 mg, 14% yield) as colorless gums.

4.16.1. Characterization data of ***29-α****.* R_f (15% EtOAc/petroleum ether) 0.46; $[\alpha]_D^{25}$ +9.2 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): 3019, 2928, 1455, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 3H), 1.43 (s, 3H), 2.19–2.35 (m, 2H), 3.09 (s, 3H), 3.45 (d, *J*=10.3 Hz, 1H), 3.71 (d, *J*=10.3 Hz, 1H), 3.90 (d, *J*=3.7 Hz, 1H), 3.95 (dt, *J*=4.6, 7.7 Hz, 1H), 4.04 (dd, *J*=1.8, 4.1 Hz, 1H), 4.24 (dd, *J*=3.8, 7.4 Hz, 1H), 4.29 (d, *J*=12.2 Hz, 1H), 4.44 (m, 2H), 4.50 (d, *J*=11.7 Hz, 1H), 4.53–4.57 (m, 3H), 4.60–4.63 (m, 3H), 4.65 (d, *J*=12.2 Hz, 1H), 4.87 (d, *J*=11.4 Hz, 1H), 4.90 (br s, 1H), 5.95 (d, *J*=4.0 Hz, 1H), 7.15–7.36 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.5 (q), 26.9 (q), 36.0 (t), 48.7 (q), 64.7 (t), 70.7 (d), 70.8 (t), 71.8 (t), 72.4 (d), 73.3 (t), 73.5 (t), 74.9 (t), 75.3 (d), 82.1 (d), 82.7 (d), 83.2 (d), 100.4 (d), 101.6 (s), 105.1 (d), 111.8 (s), 127.1 (d), 127.2 (d, 2C), 127.3 (d, 2C), 127.6 (d, 2C), 127.8 (d), 127.9 (d, 3C), 128.0 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.32 (d, 2C), 128.4 (d, 2C), 128.5 (d, 2C), 137.2 (s), 137.6 (s), 138.6 (s), 138.8 (s), 139.1 (s), 146.8 (s); HRMS (MALDI-TOF) calcd for $C_{51}H_{56}O_{10}$ ($[M+Na]^+$) 851.3771, found 851.3724.

4.16.2. Characterization data of ***29-β****.* R_f (15% EtOAc/petroleum ether) 0.42; $[\alpha]_D^{25}$ −8.5 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 3014, 2923, 1451, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.33 (s, 3H), 1.46 (s, 3H), 2.18 (dd, *J*=8.7, 14.3 Hz, 1H), 2.28 (dd, *J*=2.9, 14.3 Hz, 1H), 3.34 (s, 3H), 3.67 (d, *J*=10.0 Hz, 1H), 3.87–3.89 (m, 2H), 3.92 (d, *J*=3.4 Hz, 1H), 4.01 (d, *J*=4.1 Hz, 1H), 4.05 (dt, *J*=3.4, 8.2 Hz, 1H), 4.24 (dd, *J*=3.4, 7.7 Hz, 1H), 4.43 (d, *J*=12.0 Hz, 1H), 4.46 (d, *J*=11.8 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 4.52 (d, *J*=12.3 Hz, 1H), 4.54 (d, *J*=12.1 Hz, 1H), 4.61–4.64 (m, 3H), 4.67 (d, *J*=11.1 Hz, 1H), 4.69 (d, *J*=11.4 Hz, 1H), 4.82 (d, *J*=11.1 Hz, 1H), 4.86 (d, *J*=4.8 Hz, 1H), 6.01 (d, *J*=4.1 Hz, 1H), 7.16–7.39 (m, 25H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 26.5 (q), 26.9 (q), 36.1 (t), 50.0 (q), 69.0 (t), 70.4 (t), 71.6 (t), 72.4 (t), 73.3 (t), 73.5 (t), 73.9 (d), 76.0 (d), 81.9 (d), 82.1 (d), 83.3 (d), 98.1 (d), 100.4 (s), 105.1 (d), 111.8 (s), 127.2 (d), 127.4 (d), 127.5 (d), 127.6 (d, 3C), 127.9 (d, 5C), 128.0 (d), 128.1 (d, 4C), 128.2 (d, 6C), 128.3 (d, 2C), 128.5 (d, 2C), 137.0 (s), 137.9 (s), 138.1 (s), 138.8 (s), 139.0 (s), 149.8 (s); HRMS (MALDI-TOF) calcd for $C_{51}H_{56}O_{10}$ ($[M+Na]^+$) 851.3771, found 851.3724.

4.17. (2*R*,3*R*,4*S*,5*S*,6*S*)-4,5-Bis(benzyloxy)-2-((*S*)-2-(benzyloxy)-2-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethyl)-6-((benzyloxy)methyl)-6-methoxytetrahydro-2*H*-pyran-3-yl acetate (30-α)

To an ice cooled solution of compound **29-α** (45 mg, 54.3 μmol) in anhydrous THF (3 mL) was added neat $BH_3 \cdot DMS$ (15.4 μL, 163 μmol) and stirring was continued at room temperature for 3 h. Then reaction mixture was cooled to 0 °C, treated with 3 N NaOH (0.5 mL) followed by 30% H_2O_2 (0.5 mL) and stirred at room temperature for 8 h. The reaction mixture was concentrated under reduced pressure and the residual material was extracted with diethyl ether (5 mL). The organic layer was washed water (2 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude compound was dissolved in 1 mL anhydrous CH_2Cl_2 and treated with pyridine (0.5 mL) followed by acetic anhydride (0.5 mL). The contents were stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and traces of solvents were removed by co-evaporation with toluene (3×10 mL). Residue was purified by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) to procure compound **30-α** (32 mg, 66% yield) as colorless gum. R_f (20% EtOAc/petroleum ether) 0.40; $[\alpha]_D^{25}$ −16.9 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): 3011, 2933, 1721, 1450, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (s, 6H), 1.47–1.49 (m, 1H), 1.78–1.81 (m, 1H), 1.93 (s, 3H), 3.16 (s, 3H), 3.33 (d, *J*=6.5 Hz, 1H), 3.45 (d, *J*=10.1 Hz, 1H), 3.63 (d, *J*=10.1 Hz, 1H), 3.78–3.90 (m, 2H), 3.95 (dd, *J*=2.8, 6.8 Hz, 1H), 4.07 (d, *J*=2.8 Hz, 1H), 4.37–4.38 (m, 1H), 4.40 (d, *J*=11.0 Hz, 1H), 4.43 (d, *J*=11.7 Hz, 1H), 4.49 (d, *J*=12.5 Hz, 1H), 4.52 (d, *J*=3.7 Hz, 1H), 4.53–4.60 (m, 3H), 4.61–4.66 (m, 2H), 4.72 (d, *J*=12.1 Hz, 1H), 4.91 (d, *J*=11.4 Hz, 1H), 5.13 (t, *J*=10.0 Hz, 1H), 5.94 (d, *J*=3.9 Hz, 1H), 7.20–7.36 (m, 20H), 7.45–7.49 (m, 2H), 7.53–7.56 (m, 1H), 7.64–7.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1 (q), 26.2 (q), 26.7 (q), 33.5 (t), 50.1 (q), 67.1 (t), 70.0 (d), 71.0 (t), 71.6 (d), 71.7 (t), 72.5 (t), 73.4 (t), 74.7 (d), 75.0 (t), 75.4 (d), 77.1 (d), 81.7 (d), 82.3 (d), 83.3 (d), 100.5 (s), 105.2 (d), 111.4 (s), 127.2 (d, 2C), 127.5 (d, 4C), 127.7 (d, 4C), 127.9 (d, 2C), 128.0 (d, 2C), 128.2 (d, 4C), 128.24 (d, 3C), 128.5 (d, 4C), 137.2 (s), 137.6 (s), 138.1 (s), 139.0 (s), 139.2 (s), 169.9 (s); HRMS (MALDI-TOF) calcd for $C_{53}H_{60}O_{12}$ ($[M+Na]^+$) 911.3983, found 911.3994.

4.18. (2*R*,3*R*,4*S*,5*S*,6*R*)-4,5-Bis(benzyloxy)-2-((*S*)-2-(benzyloxy)-2-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethyl)-6-((benzyloxy)methyl)-6-methoxytetrahydro-2*H*-pyran-3-yl acetate (30-β)

Following the above procedure the hydroboration of **29-β** (21 mg, 25 μmol) followed by acetylation gave **30-β** (14 mg, 63% yield) as pale yellow gum. R_f (20% EtOAc/petroleum ether) 0.42; $[\alpha]_D^{25}$ −29.4 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 3010, 2919, 1726, 1452, 1087 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (s, 3H), 1.38 (s, 3H), 1.45–1.49 (m, 2H), 1.92 (s, 3H), 3.22–3.31 (m, 1H), 3.38 (s, 3H), 3.49 (d, *J*=10.8 Hz, 1H), 3.56 (br d, *J*=10.9 Hz, 1H), 3.87–3.90 (m, 2H), 4.04 (d, *J*=3.1 Hz, 1H), 4.10 (d, *J*=3.1 Hz, 1H), 4.22 (d, *J*=12.4 Hz, 1H), 4.33 (dd, *J*=3.1, 8.4 Hz, 1H), 4.40 (d, *J*=12.4 Hz, 1H), 4.44–4.48 (m, 3H), 4.51–4.54 (m, 3H), 4.71 (d, *J*=11.5 Hz, 1H), 4.74 (d, *J*=11.5 Hz, 1H), 4.88 (d, *J*=11.9 Hz, 1H), 5.22 (t, *J*=9.1 Hz, 1H), 5.95 (d, *J*=3.9 Hz, 1H), 7.16–7.24 (m, 10H), 7.27–7.31 (m, 13 H), 7.41–7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1 (q), 26.2 (q), 26.7 (q), 32.3 (t), 48.5 (q), 65.2 (t), 67.1 (d), 71.6 (t), 71.62 (t), 71.7 (d), 72.1 (t), 73.4 (t), 74.8 (d), 74.9 (t), 75.5 (d), 78.4 (d), 81.4 (d), 82.2 (d), 83.6 (d), 101.1 (s), 105.1 (d), 111.2 (s), 127.2 (d, 2C), 127.4 (d, 2C), 127.9 (d), 127.95 (d, 3C), 128.1 (d, 3C), 128.1 (d), 128.3 (d, 3C), 128.4 (d, 4C), 128.5 (d), 131.9 (d), 132.0 (d, 2C), 132.1 (d, 2C), 137.0 (s), 137.7 (s), 138.5 (s), 138.8 (s), 139.2 (s), 170.0 (s); HRMS (MALDI-TOF) calcd for $C_{53}H_{60}O_{12}$ ($[M+Na]^+$) 911.3983, found 911.3994.

4.19. (1*S*,5*S*,6*S*,7*R*,9*R*)-5,6,9-Tris(benzyloxy)-1-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-7-((*tert*-butyldimethylsilyl)oxy)octadec-3-yn-1-ol (31)

A solution of alkyne **6** (3.44 g, 5.1 mmol) in anhydrous THF (30 mL) was treated with *n*-BuLi (3.2 mL, 1.6 M in hexane, 5.1 mmol) at −78 °C for 20 min and then with $BF_3 \cdot Et_2O$ (680 mg, 4.8 mmol) for 20 min. To this, a solution of epoxide **25** (500 mg, 1.7 mmol) in anhydrous THF (3 mL) was added slowly at −78 °C and the contents were stirred for 2 h at same temperature. Reaction mixture was quenched by adding saturated sodium bicarbonate (5 mL) and

extracted with ethyl acetate (150 mL) and water (70 mL). The organic layer was washed with brine (60 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude was purified by column chromatography (silica 230–400 mesh, 1:3 ethyl acetate/petroleum ether) to afford compound **31** (1.35 g, 82%) as colorless gum. R_f (15% EtOAc/petroleum ether) 0.38; $[\alpha]_D^{25}$ +7.5 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 3471, 3009, 2918, 1439, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ −0.01 (s, 6H), 0.82 (s, 9H), 0.86 (t, *J*=4.8 Hz, 3H), 1.24 (br s, 14H), 1.31 (s, 3H), 1.42 (s, 3H), 1.46–1.51 (m, 2H), 1.69–1.75 (m, 1H), 1.95–2.08 (m, 1H), 2.48 (ddd, *J*=1.6, 6.0, 16.7 Hz, 1H), 2.60 (ddd, *J*=1.7, 6.9, 16.7 Hz, 1H), 3.17 (br s, 1H), 3.65 (dd, *J*=2.0, 7.6 Hz, 1H), 3.73 (t, *J*=5.1 Hz, 1H), 3.96–4.17 (m, 3H), 4.26–4.35 (m, 2H), 4.39–4.54 (m, 4H), 4.62–4.71 (m, 3H), 3.74–4.84 (m, 2H), 6.00 (d, *J*=3.8 Hz, 1H), 7.19–7.38 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.5 (q), −4.3 (q), 14.1 (q), 17.9 (s), 22.7 (t, 2C), 23.9 (t), 25.3 (t), 25.9 (q), 25.91 (q), 26.0 (q), 26.4 (q), 26.9 (q), 29.3 (t), 29.6 (t, 2C), 29.7 (t), 29.9 (t), 31.9 (t), 68.9 (d), 70.7 (t), 71.9 (t), 74.2 (t), 74.5 (t), 75.8 (d), 76.3 (d), 77.2 (d), 77.4 (s), 80.4 (d), 82.3 (d), 83.3 (d), 84.1 (d), 85.1 (s), 105.0 (d), 112.0 (s), 127.3 (d, 2C), 127.6 (d), 127.8 (d, 4C), 127.9 (d, 3C), 128.2 (d, 5C), 128.3 (d, 3C), 128.7 (d, 2C), 136.6 (s), 137.8 (s), 139.0 (s), 139.1 (s); HRMS (MALDI-TOF) calcd for $C_{59}H_{82}O_9Si$ ($[M+Na]^+$) 985.5626, found 985.5698.

4.20. *tert*-Butyldimethyl(((1*S*,5*S*,6*S*,7*R*,9*R*)-1,5,6,9-tetrakis(benzyloxy)-1-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)octadec-3-yn-7-yl)oxy)silane (32)

To a solution of alcohol **31** (1 g, 1.0 mmol) in anhydrous DMF (15 mL) was added benzyl bromide (0.14 mL, 1.1 mmol) at room temperature and then sodium hydride (83 mg, 60% oil emulsion, 2.1 mmol) at 0 °C. Usual workup followed by purification by column chromatography (230–400 mesh silica gel, 1:4 ethyl acetate/petroleum ether) gave **32** (893 mg, 82%) as pale yellow syrup. R_f (15% EtOAc/petroleum ether) 0.51; $[\alpha]_D^{25}$ +10.1 (*c* 3.2, $CHCl_3$); IR ($CHCl_3$): 3032, 2911, 1453, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ −0.03 (s, 3H), −0.01 (s, 3H), 0.80 (s, 9H), 0.84 (t, *J*=4.6 Hz, 3H), 1.21 (br s, 14H), 1.29 (s, 3H), 1.42 (s, 3H), 1.51–1.72 (m, 3H), 1.98–2.05 (m, 1H), 2.38 (ddd, *J*=1.7, 6.2, 17.2 Hz, 1H), 2.51 (ddd, *J*=1.9, 4.2, 17.2 Hz, 1H), 3.53–3.63 (m, 1H), 3.70 (t, *J*=5.1 Hz, 1H), 3.85–3.89 (m, 1H), 3.95–3.99 (m, 2H), 4.26–4.42 (m, 6H), 4.58 (d, *J*=3.6 Hz, 1H), 4.60 (d, *J*=4.2 Hz, 1H), 4.63 (d, *J*=11.6 Hz, 1H), 4.65 (d, *J*=11.5 Hz, 1H), 4.72 (d, *J*=10.7 Hz, 1H), 4.75 (d, *J*=11.5 Hz, 1H), 4.80 (d, *J*=11.5 Hz, 1H), 5.96 (d, *J*=4.0 Hz, 1H), 7.15–7.32 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.5 (q), −4.2 (q), 14.1 (q), 21.5 (t), 22.7 (t), 25.3 (t), 25.9 (q, 2C), 26.0 (q), 26.6 (q), 27.0 (q), 29.3 (t), 29.6 (t), 29.7 (t), 29.9 (t), 31.9 (t), 34.5 (t), 37.2 (t), 70.1 (d), 70.6 (d), 70.7 (t), 71.7 (t), 72.9 (t), 74.2 (t), 75.5 (t), 76.3 (d), 76.4 (d), 78.7 (s), 82.3 (d), 82.4 (d), 82.5 (d), 84.0 (s), 84.2 (d), 105.1 (d), 112.0 (s), 127.2 (d), 127.3 (d, 2C), 127.5 (d), 127.7 (d, 2C), 127.8 (d, 5C), 127.9 (d, 2C), 128.0 (d, 2C), 128.1 (d, 4C), 128.2 (d, 2C), 128.3 (d, 2C), 128.5 (d, 2C), 137.1 (s), 137.9 (s), 138.8 (s), 139.1 (s), 139.14 (s); HRMS (MALDI-TOF) calcd for $C_{66}H_{88}O_9Si$ ($[M+Na]^+$) 1075.6096, found 1075.6082.

4.21. (1*S*,5*S*,6*R*,7*R*,9*R*)-1,5,6,9-Tetrakis(benzyloxy)-1-((3a*R*,5*R*,6-*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)octadec-3-yn-7-ol (33)

To an ice cooled solution of TBS ether **32** (900 mg, 0.8 mmol) in anhydrous THF (10 mL) was added a solution of TBAF (335 mg, 1.3 mmol) in anhydrous THF (2 mL) under argon atmosphere and allowed to stir at room temperature for 4 h. Reaction mixture was concentrated and residue was purified by column chromatography (230–400 mesh silica gel, 1:3 ethyl acetate/petroleum ether) to afford compound **33** (601 mg, 75% yield) as a colorless gum. R_f (25% EtOAc/petroleum ether) 0.39; $[\alpha]_D^{25}$ +8.5 (*c* 2.9, $CHCl_3$); IR ($CHCl_3$): 3458, 3014, 2923, 1451, 1129 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J*=4.4 Hz, 3H), 1.25 (br s, 14H), 1.32 (s, 3H), 1.43 (s, 3H), 1.50–1.57 (m, 3H), 1.76–1.91 (m, 1H), 2.41–2.47 (m, 1H), 2.53 (ddd, *J*=2.1, 4.2, 17.1 Hz, 1H), 3.56 (dd, *J*=3.7, 6.5 Hz, 1H), 3.58–3.61 (m, 1H), 3.91–3,95 (m, 2H), 4.00 (br d, *J*=3.3 Hz, 1H), 4.36–4.49 (m, 5H), 4.57 (br d, *J*=11.5 Hz, 1H), 4.61–4.72 (m, 4H), 4.79 (d, *J*=11.1 Hz, 1H), 4.85 (d, *J*=12.1 Hz, 1H), 4.91 (d, *J*=11.7 Hz, 1H), 5.99 (d, *J*=4.0 Hz, 1H), 7.19–7.37 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 21.7 (t), 22.7 (t), 24.6 (t), 26.5 (q), 26.9 (q), 29.3 (t), 29.5 (t), 29.6 (t), 29.9 (t), 31.9 (t), 33.4 (t), 36.6 (t), 70.4 (t), 70.7 (t), 71.1 (d), 71.7 (t), 71.8 (d), 73.1 (t), 74.2 (t), 76.6 (d), 77.9 (s), 80.2 (d), 82.2 (d), 82.4 (d), 82.6 (d), 83.4 (d), 84.5 (s), 105.1 (d), 112.0 (s), 127.3 (d), 127.5 (d, 2C), 127.7 (d, 3C), 127.8 (d, 2C), 127.84 (d, 4C), 128.0 (d, 2C), 128.2 (d, 5C), 128.3 (d, 2C), 128.4 (d, 2C), 128.5 (d, 2C), 137.0 (s), 138.0 (s), 138.1 (s), 138.6 (s), 138.8 (s); HRMS (MALDI-TOF) calcd for $C_{60}H_{74}O_9$ ($[M+Na]^+$) 961.5231, found 961.5281.

4.22. (1*S*,5*S*,6*S*,9*R*)-1,5,6,9-Tetrakis(benzyloxy)-1-((3a*R*,5*R*,6-*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)octadec-3-yn-7-one (34)

To a solution of alcohol **33** (100 mg, 106 μmol) in ethyl acetate (10 mL) was added IBX (45 mg, 160 μmol) at room temperature and stirred at reflux temperature for 3 h. After the complete consumption of starting material, the reaction mixture was cooled in ice bath, filtered through Celite bed, washed with ethyl acetate, and the combined filtrate evaporated under reduced pressure. The crude compound was purified by column chromatography (100–200 mesh silica gel, 1.5:8.5 ethyl acetate/petroleum ether) to procure pure product **34** (94 mg, 94%) as colorless syrup. R_f (25% EtOAc/petroleum ether) 0.44; $[\alpha]_D^{25}$ +7.4 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): 3011, 2919, 1722, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J*=6.0 Hz, 3H), 1.23 (br s, 16H), 1.33 (s, 3H), 1.44 (s, 3H), 2.39–2.52 (m, 3H), 2.72–3.10 (m, 1H), 3.87–4.06 (m, 4H), 4.36–4.47 (m, 6H), 4.51–4.64 (m, 4H), 4.72 (d, *J*=11.9 Hz, 1H), 4.75 (d, *J*=11.7 Hz, 1H), 4.78 (d, *J*=11.7 Hz, 1H), 6.00 (d, *J*=4.1 Hz, 1H), 7.23–7.36 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 21.6 (t, 2C), 22.7 (t), 25.2 (t), 26.5 (q), 26.9 (q), 29.3 (t), 29.6 (t), 29.7 (t), 31.9 (t), 34.5 (t), 44.4 (t), 69.9 (d), 70.6 (t), 71.6 (t), 71.7 (t), 73.0 (t), 73.1 (t), 74.9 (d), 76.4 (d), 77.3 (s), 82.1 (d), 82.3 (d), 82.6 (d), 85.2 (s), 85.7 (d), 105.1 (d), 112.0 (s), 127.4 (d, 2C), 127.7 (d, 3C), 127.8 (d, 2C), 127.9 (d, 2C), 128.0 (d, 4C), 128.2 (d, 5C), 128.3 (s, 5C), 128.5 (d, 2C), 137.0 (s), 137.3 (s), 137.34 (s), 138.7 (s), 138.8 (s), 208.0 (s); HRMS (MALDI-TOF) calcd for $C_{60}H_{72}O_9$ ($[M+Na]^+$) 959.5074, found 959.5085.

4.23. Pd-mediated cycloisomerization

To a solution of alcohol **33** (100 mg, 0.1 mmol) in ethyl acetate (10 mL) was added IBX (45 mg, 0.2 mmol) at room temperature and stirred at reflux temperature for 3 h. After the complete consumption of starting material, the reaction mixture was cooled in ice bath, filtered through Celite bed, and the filtrate was evaporated under reduced pressure. The residual crude ketone **34** (96 mg, 102 μmol) was dissolved in anhydrous methanol (15 mL) and the solution was degassed by passing argon gas for 45 min. To this, $Pd(OAc)_2$ (7 mg, 31 μmol) was added and stirred for 2.5 h. After consumption of starting material, the reaction mixture was filtered through Celite bed and the filtrate was concentrated under reduced pressure. The resulting crude compound was purified by column chromatography (230–400 mesh silica gel, 1:3 ethyl acetate/petroleum ether) to procure compounds **35-α** (55 mg, 55% yield) and **35-β** (18 mg, 18% yield) as colorless gums.

4.23.1. Characterization data of ***35-α****.* R_f (25% EtOAc/petroleum ether) 0.34; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J*=6.2 Hz, 3H), 1.24 (br s, 14H), 1.26–1.28 (m, 2H), 1.32 (s, 3H), 1.37–1.40 (m, 2H), 1.47

(s, 3H), 2.23–2.34 (m, 2H), 3.29 (s, 3H), 3.75–3.84 (m, 2H), 3.95–4.03 (m, 2H), 4.21 (dd, J=1.8, 5.9 Hz, 2H), 4.30–4.34 (m, 2H), 4.37–4.43 (m, 2H), 4.49 (br s, 2H), 4.53–4.59 (m, 2H), 4.61–4.64 (m, 2H), 4.78 (d, J=11.3 Hz, 1H), 4.87 (d, J=4.7 Hz, 1H), 5.99 (d, J=4.0 Hz, 1H), 7.19–7.23 (m, 13H), 7.27–7.35 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.7 (t), 26.5 (q), 26.9 (q), 29.1 (t), 29.4 (t), 29.6 (t), 29.63 (t), 29.7 (t), 29.72 (t), 30.0 (t), 31.9 (t), 36.0 (t), 48.6 (q), 70.7 (t), 71.3 (t), 71.8 (t), 73.4 (t), 74.1 (t), 75.3 (d), 75.8 (d, 2C), 77.2 (d), 82.3 (d), 82.7 (d), 83.2 (d), 99.9 (d), 103.2 (s), 105.1 (d), 111.7 (s), 126.8 (d), 127.0 (d), 127.1 (d), 127.2 (d, 2C), 127.24 (d), 127.3 (d), 127.5 (d), 127.6 (d), 127.7 (d, 2C), 127.75 (d), 127.8 (d), 127.9 (d), 128.03 (d), 128.1 (d, 2C), 128.2 (d, 4C), 128.3 (d), 128.4 (d), 128.41 (d), 128.5 (d), 138.0 (s), 138.8 (s), 139.0 (s), 139.1 (s), 139.4 (s), 151.9 (s); HRMS (MALDI-TOF) calcd for $C_{61}H_{76}O_{10}$ ([M+Na]$^+$) 991.5336, found 991.5309.

4.24. (1*S*,5*S*,6*S*,9*R*)-1,5,6,9-Tetrakis(benzyloxy)-1-((3a*R*,5*R*,6-*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)octadecane-3,7-dione (36)

During the spectral (NMR) analysis both **35-α** and **35-β** were hydrolyzed in to dicarbonyl compound (**36**). R_f (30% EtOAc/petroleum ether) 0.31; $[\alpha]_D^{25}$ −24.7 (c 1.3, $CHCl_3$); IR ($CHCl_3$): 3031, 2938, 1723, 1716, 1451, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, J=6.3 Hz, 3H), 1.25–1.31 (br m, 16H), 1.34 (s, 3H), 1.49 (s, 3H), 2.25–2.40 (m, 1H), 2.44 (dd, J=4.7, 17.5 Hz, 1H), 2.53 (dd, J=5.6, 17.5 Hz, 1H), 2.58–2.70 (m, 1H), 2.72–2.89 (m, 1H), 3.05 (dd, J=7.5, 17.6 Hz, 1H), 3.85 (dd, J=3.4, 6.1 Hz, 1H), 3.92–4.03 (m, 2H), 4.18–4.23 (m, 1H), 4.31–4.41 (m, 3H), 4.43–4.50 (m, 3H), 4.51–4.54 (m, 1H), 4.56–4.63 (m, 3H), 4.64–4.67 (m, 1H), 4.70–4.85 (m, 2H), 6.1 (d, J=3.9 Hz, 1H), 7.20–7.39 (m, 25H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1 (q), 22.7 (t, 2C), 25.2 (t), 26.4 (q), 26.8 (q), 29.3 (t), 29.6 (t), 29.7 (t), 31.9 (t), 34.3 (t), 44.6 (t), 45.1 (t), 45.2 (t), 71.4 (t), 71.6 (t), 72.6 (t), 73.0 (t), 73.9 (t), 74.5 (d), 75.1 (d), 75.8 (d), 77.2 (d), 81.8 (d), 83.1 (d), 86.0 (d), 105.2 (d), 111.8 (s), 127.0 (d), 127.3 (d), 127.4 (d), 127.7 (d), 127.8 (d, 4C), 127.9 (d, 3C), 128.0 (d), 128.1 (d), 128.2 (d), 128.24 (d, 4C), 128.4 (d, 2C), 128.6 (d, 3C), 129.0 (d), 129.7 (d), 136.8 (s), 137.4 (s), 138.0 (s), 138.7 (s), 138.8 (s), 205.8 (s), 210.3 (s); HRMS (MALDI-TOF) calcd for $C_{60}H_{74}O_{10}$ ([M+Na]$^+$) 977.5180, found 977.5149.

Acknowledgements

We thank the Ministry of Science and Technology for funding through the Department of Science and Technology under the Green Chemistry Program (No. SR/S5/GC-20/2007). S.B.N. thanks CSIR, New Delhi for the financial assistance in the form of a research fellowship.

Supplementary data

NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.065.

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