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Synthesis of highly substituted tetrahydropyrans: preparation of the C20–C28 moiety of phorboxazoles

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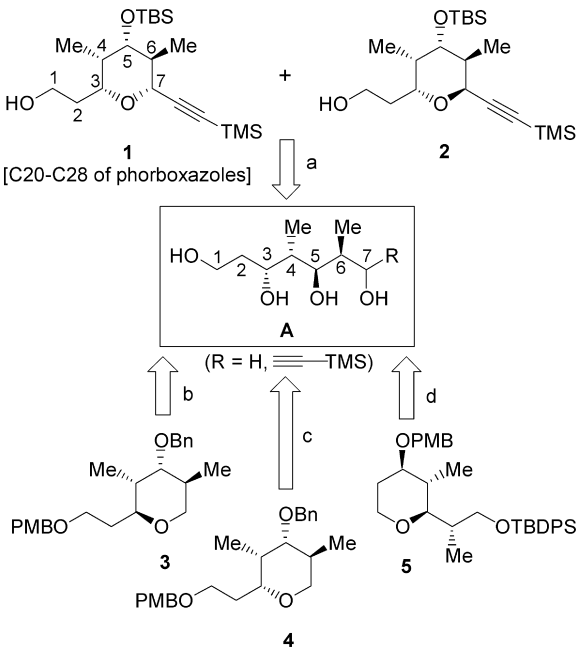
Abstract—A propionate-derived polyketide building block **A** whose 2-methyl-1,3-diol moiety was built by a Ti(III)-mediated ring opening reaction of a trisubstituted 2,3-epoxy alcohol precursor was employed as a common starting material for the syntheses of highly substituted tetrahydropyrans **1**–**5**, the first one being the C20–C28 fragment of cytotoxic natural products, phorboxazoles.

1. Introduction

Saturated oxygen heterocycles are important structural moieties of large number of organic natural products.[1] Total synthesis of these natural products depend largely on the efficient stereoselective construction of these essential cyclic components.[2] In this paper, we describe a new strategy for the synthesis of highly substituted tetrahydro-2*H*-pyrans[3] **1**–**5** starting from a common intermediate **A**, a propionate-derived polyketide unit. Compound **1** constitutes the C20–C28 moiety of phorboxazoles,[4] the most cytotoxic natural products that have attracted wide attention of synthetic chemists.[5]



Scheme 1. Cyclization modes. (a) C3–OH→C7–OX; (b) C7–OH→C3–OX; (c) C3–O^-→C7–OX; (d) C5–O^-→C1–OX (X=Ms, Ts).

Keywords: epoxy alcohols; Sharpless epoxidation; epoxide opening; 2-methyl-1,3-diol; phorboxazoles.

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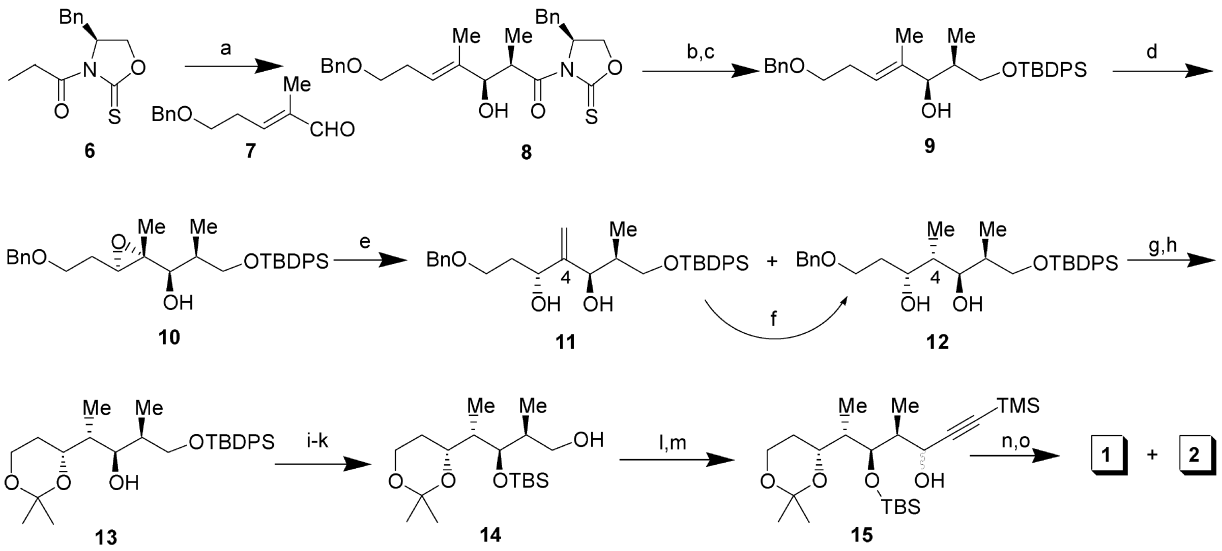
The salient feature of our strategy is the facile 6-*exo* S_N2 type ring closure reaction mediated by different hydroxyl groups present in the acyclic precursor **A**. By carefully choosing the requisite nucleophilic oxygen and a suitable leaving group at δ-position, various tetrahydropyran frameworks were constructed as shown in Scheme 1. For the synthesis of the key building block **A**, a Ti(IV)-mediated 'non-Evans' Crimmins aldol reaction[6] was employed to construct its C5- and C6-stereocentres. The remaining chiral centers at C3- and C4-positions were subsequently fixed by Sharpless epoxidation[7] followed by a radical-mediated epoxide opening reaction, developed by us earlier for the synthesis of 2-methyl-1,3-diols, using $cp_2Ti(III)Cl$.[8]

2. Results and discussion

Scheme 2 outlines in detail the synthesis of tetrahydropyrans **1** and **2**. Asymmetric aldol addition of the titanium enolate derived from the *N*-propanoyl oxazolidinethione **6**,[9] to aldehyde **7**[10] gave the non-Evans *syn* aldol product **8** as the only isolable diastereomer in 78% yield. The relative and absolute stereochemistry of the product were assigned on the basis of earlier reported work.[6] The *syn*-relationship between the C5-hydroxyl and C6-methyl groups was supported by the relatively small value of the corresponding vicinal coupling constant of 3.8 Hz. Reductive removal of the chiral auxiliary using $NaBH_4$ gave an intermediate

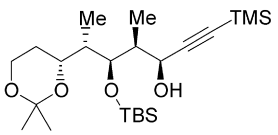
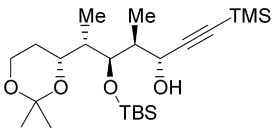


Scheme 2. Stereoselective synthesis of **1** and **2**. *Reagents and conditions*: (a) **6** (1.3 equiv.), $TiCl_4$ (2 equiv.), DIPEA (1.1 equiv.), CH_2Cl_2, −78–0°C, 0.5 h, then **7** (1 equiv.), −78–0°C, 1 h, 78%; (b) $NaBH_4$ (2 equiv.), EtOH, 0°C, 15 min; (c) TBDPSCl (1.1 equiv.), Et_3N (1.5 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, 0°C to room temperature, 4 h, 68% in 2 steps; (d) $Ti(O^iPr)_4$ (1 equiv.), (−)-DIPT (1.1 equiv.), TBHP (2.5 equiv.), CH_2Cl_2, 4 Å MS, −20°C, 3 h, 81%; (e) cp_2TiCl_2 (3 equiv.), Zn (6 equiv.), $ZnCl_2$ (3 equiv.), THF, −20°C to room temperature, 12 h; (f) H_2, 10% Pd–C, CH_3COONH_4 (0.1 equiv.), MeOH, room temperature, 0.5 h, 65% yield of **12** (combined, steps e and f); (g) H_2, 10% Pd–C, MeOH, room temperature, 24 h; (h) 2,2-dimethoxypropane (1.1 equiv.), CSA (0.1 equiv.), CH_2Cl_2, 0°C, 1 h, 56% in 2 steps; (i) TBAF (1.5 equiv.), THF, 0°C to room temperature, 4 h; (j) TBS-OTf (2.5 equiv.), 2,6-Lutidine (4 equiv.), CH_2Cl_2, 0°C, 0.5 h; (k) HF–py, THF, 0°C to room temperature, 18 h, 58% in 3 steps; (l) SO_3–py (5 equiv.), Et_3N (5 equiv.) DMSO:CH_2Cl_2 (2:1.6), 0°C, 0.5 h; (m) (trimethylsilyl)acetylene (5 equiv.), *n*-BuLi (4 equiv.), THF, −78°C to room temperature, 1 h, then aldehyde (1 equiv.), 0°C, 15 min, 76% in 2 steps; (n) MsCl (1.5 equiv.), DMAP (0.1 equiv.), pyridine, 0°C, 0.5 h; (o) CSA (0.1 equiv.), CH_2Cl_2, 0°C to room temperature, 3 h, 37% of **1** and 21% of **2** (in 2 steps from **15**).

diol that was selectively protected at its primary hydroxyl as *tert*-butyldiphenylsilyl (TBDPS) ether to furnish **9** in 68% yield from **8**. The *E*-allylic alcohol **9** was then subjected to Sharpless asymmetric epoxidation[7] using (−)-diisopropyl tartrate (DIPT) in presence of $Ti(O^iPr)_4$ and *tert*-butyl-hydroperoxide (TBHP) and 4 Å molecular sieves in CH_2Cl_2 at −20°C furnishing the desired epoxy alcohol **10** in 81% isolated yield and 83% de, determined by ^1H NMR studies of the crude product. With the trisubstituted chiral epoxide **10** in hand, the stage was now set to carry out the radical-mediated ring opening reaction. However, treatment of **10** with cp_2TiCl, generated in situ according to the procedure reported by us earlier[8] gave the desired '2-methyl-1,3-diol' containing compound **12** along with an unexpected β-hydrogen eliminated compound **11** as the major product. The ^1H NMR spectrum of **11** showed the characteristic methylene protons as two singlets at 5.15 and 5.20 ppm with C3–H appearing as a triplet at δ 4.22 (^3J=4.8 Hz) and C5–H as a doublet at δ 4.38 (^3J=2.4 Hz). The formation of such olefins during the Ti(III)-mediated epoxide opening reaction has been observed earlier by us in certain sterically hindered substrates[11] and also by others.[12] Efforts to suppress the unwanted β-hydrogen elimination using H_2O as additive according to a reported procedure,[12] led to the decomposition of the Ti(III)-species and the starting epoxy alcohol **10** remained unchanged. Fortunately, diastereo-selective reduction of the olefin moiety of **11** with H_2 using 10% Pd/C as a catalyst in the presence of ammonium acetate transformed it into the desired product **12** with the requisite stereochemistry at the C4 methyl group leading to a combined yield of 65% of **12**. The stereochemistry of **12** was ascertained by NMR study of its acetonide. While the ^{13}C NMR spectrum with acetonide methyl signals at 24.9 and 23.8 ppm and that of ketal carbon at 100.3 ppm proved 3,5-*anti* relationship of the molecule,[13] its ^1H NMR spectrum with $^3J_{3H,4H}$=4.0 Hz, $^3J_{4H,5H}$=9.7 Hz confirmed the assigned stereochemistry of the C4–Me group having the expected 3,4-*syn* and 4,5-*anti* orientations.[14] Next, debenzylation of **12** and selective acetonide protection of the C1–C3 diol gave intermediate **13** in 56% yield from **12**. The small amount of C3–C5 acetonide formed during the acetonide protection step could be easily separated. Routine functional group manipulations transformed **13** into **14** in 3 steps in 58% overall yield. The primary hydroxyl group of **14** was then oxidized and the resulting aldehyde was treated with lithium trimethylsilylacetylide to get the propargylic alcohol **15** as a mixture of isomers. Finally, the C7–OH of **15** was mesylated and subsequently treated with a catalytic amount of (±)-camphorsulphonic acid (CSA) to give the desired products **1** and **2**, in 37 and 21% yields (from **15**), respectively, which were separated easily by standard silica gel column chromatography and fully characterized.

Although, our efforts to achieve diastereofacial selectivity during the addition of trimethylsilylacetylide to the aldehyde derived from **14** were not very successful, subjection of the resulting mixture of alcohols **15** to a two step process, oxidation followed by hydride reduction led to the desired diastereoselectivity. The results of this study are summarized in Table 1. While reduction with L-selectride resulted in the best selectivity in favour of the *anti* isomer with an α-hydroxyl group at C7, reduction with $Zn(BH_4)_2$ favored the formation of the *syn* isomer as the major product. The formation of the *anti* isomer as the major product using L-selectride and DIBAL-H can be explained by non-chelate controlled Felkin–Anh model.[15] A chelate

Table 1. Results of the diastereoselective hydride reduction of the C7-keto intermediate, derived from **14** by SO_3–py oxidation, using various reagents

Hydride reagent	Solvent, temperature	Products	
		 *syn*	 *anti*
L-selectride	THF, −78°C	1	4
DIBAL-H	Toluene, −78°C	1	3
$NaBH_4$	MeOH, −78°C	2	3
$LiBH_4$	THF, −78°C	3	2
$Zn(BH_4)_2$	Et_2O, −30°C	2	1

controlled six-membered transition state,[16] on the other hand, can rationalize the formation of the *syn* isomer during the reduction with $Zn(BH_4)_2$.

The ^{1}H NMR chemical shifts and coupling constants of **1** are comparable to those reported earlier for similar units of phorboxazoles.[5] In the energy-minimized[17] chair conformation of **1** (Fig. 1), while the C4–Me occupied an axial position, the remaining substituents on the tetrahydropyran ring, C3–(C2–C1), C5–OTBS, C6–Me and C7(≡–TMS), were all in equatorial positions. This was supported by the ^{1}H NMR spectrum of **1** where the C5–H signal appeared at 3.33 ppm as a dd with coupling constants $^3J_{5H,6H}$=10.1 Hz (*a*,*a*) and $^3J_{5H,4H}$=4.8 Hz (*a*,*e*). The chemical shift of C7–H at 3.72 ppm was a doublet with a large (*a*,*a*) coupling, $^3J_{6H,7H}$=10.7 Hz. The C3–H signal at 3.57 ppm was a ddd with 10.1, 3.1 and 2.0 Hz coupling constants. The chemical shifts of the remaining protons and their splitting patterns confirmed the proposed structure of **1**, representing the C20–C28 moiety of phorboxazoles. Inversion of the C7-center made the C7(≡–TMS) group occupy axial position in compound **2** (Fig. 1) with the other substituents in the ring orienting in the same way in a chair conformation as in **1**. This is reflected in the ^{1}H NMR signal of C7–H at δ 4.52 that showed a doublet with $^3J_{6H,7H}$=5.5 Hz. The dd peak of C5–H at 3.75 ppm had coupling constants $^3J_{5H,6H}$= 10.3 Hz (*a*,*a*) and $^3J_{5H,4H}$=4.9 Hz (*a*,*e*). The remaining protons showed peaks in accordance with the structure.

For the synthesis of compounds **3** and **4**, the intermediate diol **12** was first debenzylated as shown in Scheme 3 and the C1–C3 diol moiety was protected as PMP–acetal to furnish **16** in 63% yield from **12**. Small amount of the other benzylidene from C3–C5 diol was also formed that could be easily separated chromatographically. The C5–OH was protected next as Bn-ether by treating a solution of **16** and

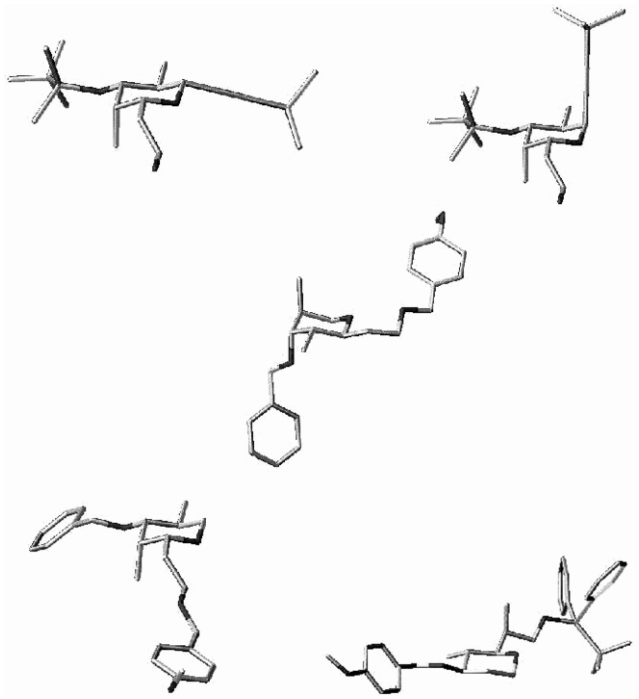
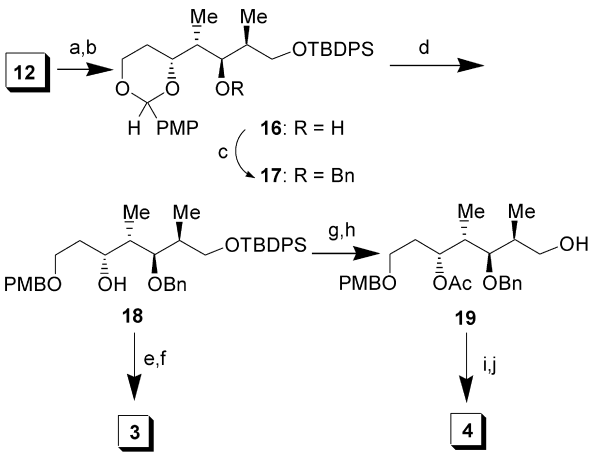


Figure 1. Energy-minimized structures of **1** (top-left), **2** (top-right), **3** (centre), **4** (bottom-left) and **5** (bottom-right).

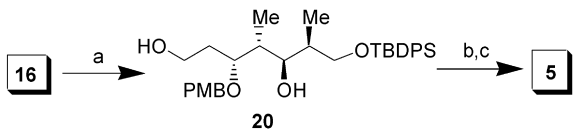


Scheme 3. Stereoselective synthesis of **3** and **4**. *Reagents and conditions*: (a) H_2, 10% Pd–C, MeOH, room temperature, 24 h; (b) *p*-methoxybenzaldehyde dimethylacetal (1.1 equiv.), CSA (0.01 equiv.), CH_2Cl_2, 0°C, 1 h, 63% in 2 steps; (c) BnBr (1.2 equiv.), NaHMDS (1.2 equiv.), THF:DMF (2:1), 0°C, 45 min, 85%; (d) $NaCNBH_3$ (6 equiv.), TMS–Cl (6 equiv.) CH_3CN, 4 Å MS, 0°C, 15 min, 62%; (e) MsCl (1.5 equiv.), DMAP (0.1 equiv.), pyridine, 0°C, 0.5 h; (f) TBAF (1.5 equiv.), THF, 0°C to room temperature, 24 h, 87% in 2 steps; (g) Ac_2O (1.5 equiv.), Et_3N (1.5 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, 0°C to room temperature, 8 h; (h) TBAF (1.5 equiv.), THF, 0°C to room temperature, 5 h, 91% in 2 steps; (i) TsCl (1.1 equiv.), Et_3N (2 equiv.), 0°C to room temperature 5 h; (j) K_2CO_3 (3 equiv.), MeOH, 0°C to room temperature, 24 h, 85% in 2 steps.

BnBr with NaHMDS to furnish **17** in 85% yield. Reduction of **17** with $NaCNBH_3$ and TMS–Cl in anhydrous CH_3CN gave selectively the primary-protected substrate **18** in 62% yield.[18] The minor product with C3–OPMB could be easily removed by column chromatography. Mesylation of the C3–OH followed by deprotection of the TBDPS group using TBAF led to a concomitant cycloetherification reaction in which the C7–alkoxide ion intramolecularly displaced the C3–OMs in S_N2 fashion leading to the formation of the tetrahydropyran **3** in 87% yield.

The small vicinal coupling constants, 3.0 and 1.2 Hz, of its C7-protons with C6–H suggest an equatorial disposition of the latter as shown in its energy-minimized structure in Figure 1. This, in turn, leads to an equatorial orientation of the adjacent C5–H as reflected in the absence of any large diaxial coupling in its chemical shift at 3.24 ppm. Protection of the C3–OH of **18** as an acetate and subsequent silyl deprotection gave the intermediate **19** in 91% yield from **18**. The primary hydroxyl of **19** was then tosylated and finally base-catalyzed cyclization furnished the desired product **4** in 85% yield. In compound **4**, the C3, C5 and C6 substituents occupy equatorial positions with an axial orientation of the C4–Me (Fig. 1). This is reflected in the large vicinal diaxial coupling of 11.2 Hz of the C7–H(axial) that resonated at 2.96 ppm. The dd peak of its C5–H at 3.12 ppm with coupling constants $^3J_{5H,6H}$=10.3 Hz (*a*,*a*) and $^3J_{5H,4H}$= 4.9 Hz (*a*,*e*) further corroborated the structure.

The PMP–acetal **16** served as the starting material for the synthesis of **5** as outlined in Scheme 4. Reduction of **16** with $NaCNBH_3$ and TMS–Cl gave the diol **20** as the minor product in 35% yield. The major product had the primary hydroxyl group PMB-protected. Uses of other hydride reagents did not help in reversing the selectivity. Selective tosylation of the primary hydroxyl of **20** was followed by facile intramolecular cyclization initiated by the C5–O^- leading to the expected product **5** in 65% yield. In compound **5**, all the three substituents on the ring occupy equatorial positions in a chair conformation as shown in its energy-minimized structure in Figure 1. The C5–H (numberings according to **A**) signal at 3.69 ppm with large diaxial vicinal coupling of 9.1 Hz points to its axial position. The dt peak at 3.11 ppm belonged to C3–H that showed two diaxial couplings of 10.3 Hz and one (*a*,*e*)-coupling of 4.8 Hz providing further supports for the proposed structure.



Scheme 4. Stereoselective synthesis of **5**. *Reagents and conditions*: (a) $NaCNBH_3$ (6 equiv.), TMS–Cl (6 equiv.), CH_3CN, 4 Å MS, 0°C, 15 min, 35%; (b) TsCl (1.1 equiv.), Et_3N (2 equiv.), CH_2Cl_2, 0°C to room temperature, 3 h; (c) NaH (6 equiv.), toluene, 0°C to reflux, 3 h, 65% in 2 steps.

In conclusion, a versatile synthon **A** has been successfully and very efficiently exploited to construct a wide variety of structurally diverse chiral tetrahydropyran frameworks, including the one that bears the C20–C28 unit **1** of phorboxazoles. The protocol will be very useful in the synthesis of many such natural products that contain similar substituted tetrahydropyran moieties.

3. Experimental

3.1. General procedures

All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Melting points are uncorrected. IR spectra were recorded as neat liquids or KBr pellets. Mass spectra were obtained under electron impact ionisation (EI), liquid secondary ion mass spectrometric (LSIMS) technique, electron spray ionisation (ESI) and MALDI techniques. NMR spectra were recorded on 500, 300 and 200 MHz spectrometers at 30°C with 2–10 mM solutions in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded on 75 and 50 MHz spectrometers with complete proton decoupling.

3.1.1. Synthesis of 8. To a solution of *N*-propanoyl oxazolidinethione **6**[9] (2.54 g, 10.19 mmol) in CH_2Cl_2 (40 mL) at 0°C, $TiCl_4$ (1.67 mL, 15.69 mmol) was added dropwise. After 5 min, DIPEA (1.5 mL, 8.63 mmol) was slowly added and stirring was continued for another 20 min at 0°C. It was cooled to −78°C, aldehyde **7**[10] (1.6 g, 7.84 mmol) in CH_2Cl_2 (20 mL) was added and stirred at −78°C for 1 h. The reaction mixture was warmed to 0°C and quenched with saturated aqueous NH_4Cl solution. It was diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 15–18% EtOAc in petroleum ether eluant) gave pure compound **8** (2.77 g, 78%) as colorless oil. R_f=0.4 (silica gel, 25% EtOAc in petroleum ether). $[\alpha]_D^{20}$=+80.1 (*c* 1.8, $CHCl_3$); IR (neat): ν_{max} 3446, 2928, 2860, 1707, 1453, 1321, 1196, 1095, 960, 775, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.18 (m, 10H, aromatic), 5.62 (br t, *J*=7.2 Hz, 1H, olefinic), 5.05 (dq, *J*=6.8, 3.8 Hz, 1H, C*H*C=O), 4.96 (ddt, *J*=10.2, 6.4, 3.8 Hz, 1H, C4′–*H*), 4.53 (m, 1H, allylic C*H*OH), 4.496 (s, 2H, OCH_2Ph), 4.33–4.26 (m, 2H, C5′–H_2), 3.50 (t, *J*=7.2 Hz, 2H, BnOCH_2–), 3.28 (dd, *J*=13.2, 3.8 Hz, 1H, PhC*H*), 2.704 (dd, *J*=13.2, 10.2 Hz, 1H, PhC*H*′), 2.638 (d, *J*=3.4 Hz, 1H, O*H*), 2.406 (m, 2H, allylic CH_2), 1.70 (s, 3H, =CCH_3), 1.15 (d, *J*=6.8 Hz, 3H, CHCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 185.08, 177.79, 138.43, 135.65, 135.17, 129.27, 128.99, 128.29, 127.56, 127.45, 127.40, 122.56, 96.08, 75.15, 72.86, 70.17, 69.71, 59.90, 40.40, 37.71, 28.35, 13.62, 10.75; MS (LSIMS): *m*/*z* (%): 436 (38)

$[M+H-H_2O]^+$; HRMS (LSIMS): calcd for $C_{26}H_{32}NO_4S$ $[M+H]^+$: 454.2052, found: 454.2074.

3.1.2. Synthesis of 9. To a solution of **8** (8.86 g, 19.55 mmol) in EtOH (120 mL), $NaBH_4$ (1.48 g, 39.1 mmol) was added at 0°C and stirred at the same temperature for 15 min. The reaction mixture was quenched with saturated NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The resulting alcohol was used directly in the next step. It was dissolved in CH_2Cl_2 (60 mL), Et_3N (4.08 mL, 29.32 mmol) and TBDPSCl (5.51 mL, 21.5 mmol) were added sequentially at 0°C. Next, a catalytic amount of DMAP (239 mg, 1.95 mmol) was added to the reaction mixture. After being stirred for 4 h at room temperature the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 8–10% EtOAc in petroleum ether eluant) gave pure compound **9** (6.68 g, 68% in 2 steps) as clear oil. R_f=0.5 (silica gel, 15% EtOAc in petroleum ether); $[\alpha]_D^{20}$=+7.2 (*c* 2.22, $CHCl_3$); IR (neat): ν_{max} 3444, 3072, 2941, 2858, 1475, 1423, 1368, 1107, 1004, 815, 738, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.67–7.27 (m, 15H, aromatic), 5.47 (t, *J*=6.8 Hz, 1H, olefinic), 4.50 (s, 2H, OCH_2Ph), 4.2 (d, *J*=3.7 Hz, 1H, C5–*H*), 3.65 (dd, *J*=10.5, 4.9 Hz, 1H, C7–*H*), 3.63 (dd, *J*=10.5, 5.6 Hz, 1H, C7–*H'*), 3.46 (t, *J*=6.8 Hz, 2H, C1–H_2), 2.37 (m, 2H, C2–H_2), 1.84 (m, 1H, C6–*H*), 1.55 (s, 3H, C4–CH_3), 1.06 (s, 9H, ^{t}Bu), 0.89 (d, *J*=6.8 Hz, 3H, C6–CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.41, 137.39, 135.57, 135.49, 133.29, 133.15, 129.66, 129.64, 128.26, 127.63, 127.56, 127.43, 121.13, 77.77, 72.80, 69.80, 67.66, 37.67, 28.25, 26.79, 19.14, 13.14, 10.60; MS (LSIMS): *m/z* (%): 503 (5) $[M+H]^+$.

3.1.3. Synthesis of 10. To a suspension of activated powdered 4 Å molecular sieves (1.06 g, 20 wt%) in CH_2Cl_2 (25 mL), $Ti(O^iPr)_4$ (3.13 mL, 10.52 mmol) and (−)-DIPT (2.46 mL, 11.57 mmol) were added sequentially at −20°C. After being stirred for 20 min, TBHP (3.73 M solution in toluene, 7.05 mL, 26.3 mmol) was added and stirring continued for another 30 min at the same temperature. To the above solution, compound **9** (5.28 g, 10.52 mmol) in CH_2Cl_2 (10 mL) was added and stirred for 3 h at −20°C. The reaction mixture was quenched with water (60 mL), warmed to room temperature and stirred for 1 h. After re-cooling to 0°C, an aqueous solution of NaOH (30% (w/v), 16 mL), saturated with NaCl, was added to it and stirred at 0°C for 10 min. CH_2Cl_2 was removed under reduced pressure, the compound was extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, 10–13% EtOAc in petroleum ether eluant) afforded pure compound **10** in 83% de (4.41 g, 81%) as colorless oil. R_f=0.6 (silica gel, 15% EtOAc in petroleum ether); $[\alpha]_D^{20}$=−0.5 (*c* 1.89, $CHCl_3$); IR (neat): ν_{max} 3470, 3059, 2957, 2929, 2855, 1486, 1439, 1393, 1341, 1258, 1211, 1107, 1004, 815, 735, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.68–7.27 (m, 15H, aromatic), 4.52 (ABq, *J*=11.8 Hz, 2H, OCH_2Ph), 4.02 (d, *J*=1.2 Hz, 1H, C5–*H*), 3.74 (dd, *J*=9.9, 8.0 Hz, 1H, C7–*H*), 3.64 (t, *J*=6.2 Hz, 2H, C1–H_2) 3.61 (dd, *J*=9.9, 5.6 Hz, 1H, C7–*H'*), 3.28 (t, *J*=6.2 Hz, 1H, C3–*H*), 2.07 (br s, 1H, O*H*), 1.89 (m, 3H, C2–H_2, C6–*H*), 1.24 (s, 3H, C4–CH_3), 1.06 (s, 9H, ^{t}Bu), 0.79 (d, *J*=6.8 Hz, 3H, C6–CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.10, 135.52, 133.70, 133.59, 129.55, 128.29, 127.58, 73.09, 71.19, 67.39, 66.79, 61.77, 56.66, 37.02, 28.86, 26.83, 19.17, 15.17, 9.44; MS (MALDI): *m/z* (%): 542 (48) $[M+H+Na]^+$, 558 (19) $[M+H+K]^+$.

3.1.4. Synthesis of 12. To a suspension of cp_2TiCl_2 (5.018 g, 20.16 mmol) in dry THF (90 mL) at room temperature, freshly fused $ZnCl_2$ (2.75 g, 20.16 mmol), Zn powder (2.63 g, 40.3 mmol) were added under N_2 atmosphere and stirred at room temperature for 1 h. To the above solution, epoxy alcohol **10** (3.48 g, 6.72 mmol) in dry THF (10 mL) was added at 0°C. The reaction mixture was warmed to room temperature and stirred for 10–12 h. The reaction was quenched by slow addition of 1N HCl and extracted with EtOAc. The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 18–35% EtOAc in petroleum ether eluant) eluted first compound **12** (735 mg, 21%) followed by **11** (2.62 g, 75%) as colorless oils.

Data for **12**. R_f=0.45 (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{20}$=+12.7 (*c* 2.62, $CHCl_3$); IR (neat): ν_{max} 3439, 3055, 2949, 2918, 2850, 1485, 1436, 1381, 1107, 811, 735, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.67–7.27 (m, 15H, aromatic), 4.53 (ABq, *J*=12.4 Hz, 2H, OCH_2Ph), 4.03 (br d, *J*=10.5 Hz, 1H, C5–*H*), 3.9 (dd, *J*=9.3, 1.2 Hz, 1H, C3–*H*), 3.76 (dd, *J*=9.9, 4.3 Hz, 1H, C7–*H*), 3.75–3.68 (m, 3H, C1–H_2, C7–*H'*), 3.61 (br s, 1H, O*H*), 3.52 (br s, 1H, O*H*), 1.98–1.91, 1.84–1.77, 1.75–1.72 and 1.66–1.62 (m, 4H, C2–H_2, C4–*H*, C6–*H*), 1.06 (s, 9H, ^{t}Bu), 0.96 (d, *J*=6.8 Hz, 3H, CH_3), 0.78 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.04, 135.64, 135.52, 133.17, 133.00, 129.74, 128.37, 127.69, 127.64, 75.70, 73.26, 69.70, 69.00, 39.78, 36.63, 32.57, 29.64, 26.84, 19.14, 11.97, 9.35; MS (MALDI): *m/z* (%): 543 (13) $[M+Na]^+$, 559 (5) $[M+K]^+$; HRMS (LSIMS): calcd for $C_{32}H_{45}O_4Si$ $[M+H]^+$: 521.3087, found: 521.3077.

To a solution of **11** (2.62 g, 5.05 mmol) in MeOH (5 mL), 10% Pd–C and catalytic amount of NH_4OAc (38 mg, 0.5 mmol) were added and the mixture was hydrogenated using a H_2-filled balloon for 0.5 h. It was then filtered through a short pad of Celite and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated. Purification by column chromatography (SiO_2, 18–22% EtOAc in petroleum ether eluant) eluted compound **12** (1.54 g, 58%) as colorless oil.

3.1.5. Synthesis of 13. To a solution of **12** (2.07 g, 3.98 mmol) in MeOH (5 mL), 10% Pd–C was added and the mixture was hydrogenated using a H_2-filled balloon for 24 h. It was then filtered through a short pad of Celite and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated in vacuo. The residue was used directly in the next step.

It was dissolved in dry CH_2Cl_2 (12 mL), 2,2-dimethoxypropane (0.54 mL, 4.37 mmol) and CSA (92 mg,

0.39 mmol) were added sequentially at 0°C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 14–16% EtOAc in petroleum ether eluant) gave the compound **13** (1.05 g, 56% in 2 steps) as clear oil. R_f=0.6 (silica gel, 20% EtOAc in petroleum ether); $[\alpha]_D^{20}$=+8.9 (*c* 2.0, $CHCl_3$); IR (neat): ν_{max} 3486, 3070, 2965, 2921, 2847, 1459, 1422, 1374, 1196, 1102, 968, 818, 740, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.66–7.25 (m, 10H, aromatic), 4.18 (dd, *J*=11.9, 2.2 Hz, 1H, C5–*H*), 3.99–3.74 and 3.69–3.64 (m, 5H, C1–H_2, C7–H_2, C3–*H*), 3.29 (br s, 1H, O*H*), 1.97–1.76 and 1.75–1.62 and 1.32–1.17 (m, 4H, C2–H_2, C4–*H*, C6–*H*), 1.45 (s, 3H, acetonide Me), 1.35 (s, 3H, acetonide Me), 1.06 (s, 9H, ^{t}Bu), 0.86 (d, *J*=6.8 Hz, 3H, CH_3), 0.78 (d, *J*=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 135.63, 135.57, 133.83, 133.69, 129.58, 127.61, 98.49, 72.78, 71.25, 67.69, 60.17, 39.12, 37.52, 29.92, 26.91, 26.45, 19.23, 19.05, 11.35, 9.31; MS (MALDI): *m/z* (%): 494 (10) $[M+H+Na]^+$; HRMS (LSIMS): calcd for $C_{28}H_{43}O_4Si$ $[M+H]^+$: 471.2931, found: 471.2956.

3.1.6. Synthesis of 14. To a solution of **13** (658 mg, 1.4 mmol) in dry THF (5 mL), TBAF (1 M in THF, 2.1 mL, 2.1 mmol) was added at 0°C. The reaction mixture was warmed to room temperature and stirred for 4 h. It was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAC, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was used directly in the next step.

It was dissolved in CH_2Cl_2 (5 mL), 2,6-lutidine (0.65 mL, 5.6 mmol) and TBS–OTf (0.8 mL, 3.5 mmol) were added at 0°C. After being stirred for 0.5 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, washed with saturated aqueous $CuSO_4$ solution, water, brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in dry THF (5 mL) and treated with HF–py complex (40%, 0.17 mL) at 0°C. It was warmed to room temperature and stirred for 18 h. The reaction mixture was cautiously poured into aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 16–18% EtOAc in petroleum ether) afforded compound **14** (281 mg, 58% in 3 steps) as clear oil. R_f=0.5 (silica gel, 20% EtOAc in petroleum ether); $[\alpha]_D^{20}$=+5.5 (*c* 1.48, $CHCl_3$); IR (neat): ν_{max} 3455, 2952, 2925, 2855, 2746, 1455, 1368, 1242, 1193, 1083, 1028, 968, 826, 757, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.94 (dt, *J*=12.4, 3.1 Hz, 1H, C1–*H*), 3.89 (dd, *J*=4.9, 1.8 Hz, 1H, C5–*H*), 3.825 (m, 2H, C1–*H*′, C3–*H*), 3.43 (dd, *J*=10.5, 8.6 Hz, 1H, C7–*H*), 3.38 (dd, *J*=10.5, 5.6 Hz, 1H, C7–*H*′), 1.78, 1.7–1.58 and 1.40–1.35 (m, 4H, C2–H_2, C4–*H*, C6–*H*), 1.37 (s, 3H, acetonide Me), 1.29 (s, 3H, acetonide Me), 0.91 (d, *J*=6.8 Hz, 3H, CH_3), 0.84 (s, 9H, ^{t}Bu), 0.81 (d, *J*=6.8 Hz, 3H, CH_3), 0.011 and 0.001 (two s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 98.08, 72.39, 69.99, 66.49, 59.81, 44.65, 38.16, 29.81, 29.55, 25.92, 19.48, 18.23, 11.67, 10.69, −4.19, −4.51; MS (LSIMS): *m/z* (%): 347 (8) $[M+H]^+$.

3.1.7. Synthesis of 15. To a solution of **14** (115 mg, 0.33 mmol) in dry CH_2Cl_2 (1 mL) and DMSO (0.8 mL), Et_3N (0.23 mL, 1.66 mmol) and SO_3–py complex (264.5 mg, 1.66 mmol) were added sequentially at 0°C under N_2 atmosphere. After 30 min of stirring at 0°C, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with petroleum ether. The organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was used directly in the next step.

To a solution of (trimethylsilyl)acetylene (0.23 mL, 1.66 mmol) in dry THF (5 mL), *n*-BuLi (1.6 M in hexane, 0.83 mL, 1.32 mmol) was added at −78°C. After stirring for 30 min at −78°C, the reaction mixture was warmed to room temperature and stirred for another 30 min. It was then cooled to 0°C and the above aldehyde in THF (1 mL) was added to it. After 15 min, it was quenched with saturated aqueous NH_4Cl solution at 0°C, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 6–8% EtOAc in petroleum ether eluant) afforded compound **15** (112 mg, mixture of isomers, 76% in 2 steps) as clear oil. R_f=0.5 (silica gel, 15% EtOAc in petroleum ether); IR (neat): ν_{max} 3420, 2949, 2926, 2842, 2647, 2173, 1448, 1381, 1239, 1075, 1007, 831, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz, mixture of isomers): δ 4.19–3.71 (m, 5H, C*H*–O), 2.06–2.01 and 1.85–1.58 (m, 4H, C2–H_2, C4–*H*, C6–*H*), 1.41 (s, 3H, acetonide CH_3), 1.31 (s, 3H, acetonide CH_3), 1.01 (d, *J*=6.8 Hz, 3H, CH_3), 0.94 (d, *J*=6.8 Hz, 3H, CH_3), 0.88 and 0.878 (two s, 9H, ^{t}Bu), 0.16, 0.15 and 0.07 (three s, 15H, SiMe); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 106.92, 106.65, 98.16, 90.84, 90.00, 77.21, 72.72, 70.98, 70.14, 66.74, 66.11, 59.79, 45.07, 44.87, 42.52, 41.69, 29.87, 29.61, 29.56, 25.97, 19.54, 18.31, 18.26, 11.75, 10.72, 10.67, 10.37, −0.14, −0.23, −4.03, −4.11, −4.32, −4.39; MS (ESIMS): *m/z* (%): 465 (100) $[M+Na]^+$.

3.1.8. Synthesis of 16. To a solution of **12** (1.268 g, 2.44 mmol) in MeOH (5 mL), 10% Pd–C was added and the mixture was hydrogenated using a H_2-filled balloon for 24 h. It was then filtered through a short pad of Celite and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated in vacuo. The residue was used directly in the next step.

It was dissolved in dry CH_2Cl_2 (8 mL), *p*-methoxybenzaldehyde dimethylacetal (0.5 mL, 2.7 mmol) and CSA (6 mg, 0.024 mmol) were added sequentially at 0°C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 16–18% EtOAc in petroleum ether eluant) gave the compound **16** (842 mg, 63% in 2 steps) as colorless oil. R_f=0.6 (silica gel, 20% EtOAc in petroleum ether); $[\alpha]_D^{20}$=−5.2 (*c* 1.185, $CHCl_3$); IR (neat): ν_{max} 3502, 3062, 2952, 2929, 2844, 2714, 1593, 1502, 1467, 1420, 1384, 1289, 1242, 1107, 1011, 984, 823, 738, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.65–7.33 (m, 10H, aromatic), 7.34, 6.84 (two d, *J*=8.2 Hz, 4H, PMP *ortho* and *meta*-H), 5.47 (s, 1H, C*H*PMP), 4.34–4.18, 4.02–3.86 and 3.75–3.62 (m, 6H, C1–H_2, C3–*H*, C5–*H*, C7–H_2), 3.79 (s, 3H,

OCH_3), 3.02 (br s, 1H, OH), 2.17–1.96, 1.75–1.61 and 1.32–1.25 (m, 4H, C2–H_2, C4–H, C6–H), 1.07 (s, 9H, ^{t}Bu), 0.91 (d, J=6.7 Hz, 3H, CH_3), 0.87 (d, J=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.81, 135.65, 135.52, 133.41, 133.23, 131.42, 129.68, 129.63, 127.64, 127.30, 113.51, 101.22, 77.61, 73.01, 68.39, 67.19, 55.21, 40.04, 36.71, 27.38, 26.87, 19.15, 10.86, 8.93; MS (LSIMS): m/z (%): 549 (4) $[M+H]^+$; HRMS (LSIMS): calcd for $C_{33}H_{45}O_5Si$ $[M+H]^+$: 549.3036, found: 549.3018.

3.1.9. Synthesis of 17. To a solution of **16** (338 mg, 0.616 mmol) in THF:DMF (2:1, 3 mL), benzyl bromide (0.088 mL, 0.74 mmol) was added. The reaction mixture was cooled to 0°C and treated by dropwise addition of NaHMDS (2 M in THF, 0.37 mL, 0.74 mmol). After being stirred for 45 min at 0°C, it was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 6–8% EtOAc in petroleum ether eluant) afforded compound **17** (334 mg, 85%) as colorless oil. R_f=0.7 (silica gel, 20% EtOAc in petroleum ether); $[\alpha]_D^{20}$=−58.1 (c 0.86, $CHCl_3$); IR (neat): ν_{max} 3439, 3070, 2960, 2925, 2842, 1608, 1514, 1475, 1381, 1234, 1157, 1102, 1036, 815, 733, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.68–7.20 (m, 15H, aromatic), 7.40 and 6.85 (two d, J=8.9 Hz, 4H, PMP *ortho* and *meta-H*), 5.37 (s, 1H, CHPMP), 4.60 (ABq, J=11.1 Hz, 2H, OCH_2Ph), 4.32–4.16 and 4.04–3.88 (m, 4H, C7–H_2, C5–H, C3–H), 3.82 (s, 3H, OCH_3), 3.705 (t, J=9.7 Hz, 1H, C1–H), 3.57 (dd, J=9.7, 5.9 Hz, 1H, C1–H'), 2.2–1.84, 1.77–1.61 and 1.26–1.21 (m, 4H, C2–H_2, C4–H, C6–H), 1.06 (s, 9H, ^{t}Bu), 0.95 (d, J=6.7 Hz, 3H, CH_3), 0.79 (d, J=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.34, 139.26, 135.53, 133.81, 131.79, 129.53, 128.24, 127.59, 127.48, 127.26, 127.10, 113.47, 100.44, 78.42, 75.83, 74.76, 67.25, 66.52, 55.23, 40.32, 37.56, 28.52, 26.91, 19.24, 10.51, 9.22; MS (LSIMS): m/z (%): 639 (6) $[M+H]^+$; HRMS (LSIMS): calcd for $C_{40}H_{51}O_5Si$ $[M+H]^+$: 639.3506, found: 639.3527.

3.1.10. Synthesis of 18. To a solution of **17** (307 mg, 0.48 mmol) in dry CH_3CN (10 mL), activated and powered molecular sieves (4 Å, 62 mg) were added at room temperature. After being stirred for 5 min, the reaction mixture was cooled to 0°C and $NaCNBH_3$ (181 mg, 2.89 mmol) and TMS–Cl (0.37 mL, 2.89 mmol) were added sequentially. The resulting solution was stirred for 15 min before quenching with saturated aqueous NH_4Cl solution and extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, 13–15% EtOAc in petroleum ether eluant) provided compound **18** (191 mg, 62%) as a clear oil. R_f=0.6 (silica gel, 30% EtOAc in petroleum ether); $[\alpha]_D^{20}$=−2.3 (c 1.76, $CHCl_3$); IR (neat): ν_{max} 3499, 3039, 2960, 2930, 2839, 1607, 1510, 1447, 1234, 1102, 823, 746, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66–7.24 (m, 15H, aromatic), 7.22 and 6.84 (two d, J=8.7 Hz, 4H, PMP *ortho* and *meta-H*), 4.625 (ABq, J=11.2 Hz, 2H, OCH_2Ar), 4.407 (ABq, J=11.8 Hz, 2H, OCH_2Ar), 4.09 (br d, J=9.3 Hz, 1H, C5–H), 3.78 (s, 3H, OCH_3), 3.734 (dd, J=7.4, 4.3 Hz, 1H, CH–O), 3.662 (dd, J=10.5, 7.4 Hz, 1H, CH–O), 3.606–3.531 (m, 3H, CH–O), 3.08 (br s, 1H, OH), 1.98, 1.86, 1.66, 1.52 (four m, 4H, C2–H_2, C4–H, C6–H), 1.07 (s, 9H, ^{t}Bu), 0.923 (d, J=6.9 Hz, 3H, CH_3), 0.913 (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.16, 138.81, 135.56, 133.75, 130.42, 129.58, 129.15, 128.29, 127.62, 127.42, 113.79, 82.61, 75.20, 72.77, 69.65, 68.77, 66.75, 55.21, 40.32, 38.37, 34.91, 26.94, 19.27, 11.21, 10.93; MS (MALDI): m/z (%): 664 (30) $[M+H+Na]^+$, 680 (8) $[M+H+K]^+$; HRMS (LSIMS): calcd for $C_{40}H_{53}O_5Si$ $[M+H]^+$: 641.3662, found: 641.3656.

3.1.11. Synthesis of 19. To a solution of **18** (126 mg, 0.196 mmol) in dry CH_2Cl_2 (1 mL), Et_3N (0.04 mL, 0.294 mmol), Ac_2O (0.027 mL, 0.294 mmol), catalytic amount of DMAP (2.4 mg, 0.02 mmol) were added at 0°C. After being stirred for 8 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was used directly in the next step.

It was dissolved in dry THF (1 mL), TBAF (1 M in THF, 0.294 mL, 0.294 mmol) was added at 0°C, the reaction mixture was warmed to room temperature and stirred for 5 h. It was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 30% EtOAc in petroleum ether eluant) afforded compound **19** (80 mg, 91% in 2 steps) as a clear oil. R_f=0.5 (silica gel, 40% EtOAc in petroleum ether); $[\alpha]_D^{20}$=+7.1 (c 1.01, $CHCl_3$); IR (neat): ν_{max} 3439, 3289, 2937, 2866, 1744, 1615, 1525, 1368, 1239, 1083, 1023, 850, 773, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.21 (m, 5H, aromatic), 7.174 and 6.761 (two d, J=9.5 Hz, 4H, PMP *ortho* and *meta-H*), 5.41 (m, 1H, C3–H), 4.565 and 4.45 (ABq, J=10.7 Hz, 2H, OCH_2Ar), 4.35 (ABq, J=11.8 Hz, 2H, OCH_2Ar), 3.758 (s, 3H, OMe), 3.601–3.514 and 3.494–3.376 (m, 5H, C1–H_2, C7–H_2, C5–H), 2.0 (s, 3H, OCOCH_3), 2.02–1.73 (m, 4H, C2–H_2, C4–H, C6–H), 1.7 (br s, 1H, OH), 0.91 (d, J=6.8 Hz, 3H, CH_3), 0.86 (d, J=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.84, 159.05, 138.81, 130.46, 129.22, 128.22, 127.74, 127.36, 113.68, 79.99, 74.35, 72.68, 71.61, 67.17, 65.95, 55.21, 39.46, 37.67, 33.39, 21.24, 10.35, 10.19; MS (ESIMS): m/z (%): 445 (3.3) $[M+H]^+$, 467 (12.5) $[M+Na]^+$, 483 (7) $[M+K]^+$; HRMS (LSIMS): calcd for $C_{26}H_{37}O_6$ $[M+H]^+$: 445.2590, found: 445.2580.

3.1.12. Synthesis of 20. To a solution of **16** (340 mg, 0.62 mmol) in dry CH_3CN (13 mL), activated and powered molecular sieves (4 Å, 70 mg) were added at room temperature. After being stirred for 5 min, the reaction mixture was cooled to 0°C; to the above solution, $NaCNBH_3$ (234 mg, 3.72 mmol) and TMS–Cl (0.47 mL, 3.72 mmol) were added sequentially. After being stirred for 15 min the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (SiO_2, 25–30% EtOAc in petroleum ether eluant) provided compound **20** (119 mg, 35%) as a clear oil. R_f=0.4 (silica gel, 35% in petroleum ether); $[\alpha]_D^{20}$=+26.5 (c 1.13, $CHCl_3$); IR (neat): ν_{max} 3451, 3070, 2960, 2925, 2834, 1607, 1502, 1420, 1242, 1107, 1047, 811, 730, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$,

300 MHz): δ 7.7–7.33 (m, 10H, aromatic), 7.27 and 6.87 (two d, J=8.4 Hz, 4H, PMP *ortho*- and *meta-H*), 4.65, 4.48 (ABq, J=11.2 Hz, 2H, OCH_2PMP), 3.78 (s, 3H, OCH_3), 3.95–3.89 and 3.76–3.64 (m, 6H, C1–H_2, C3–*H*, C5–*H*, C7–H_2), 3.64 (br s, 1H, O*H*), 2.11 (br s, 1H, O*H*), 1.99–1.85 and 1.8–1.74 and 1.71–1.61 (m, 4H, C2–H_2, C4–*H*, C6–*H*), 1.06 (s, 9H, ^{t}Bu), 0.9 (d, J=6.8 Hz, 3H, CH_3), 0.78 (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.32, 135.61, 135.53, 133.66, 133.50, 130.18, 129.64, 129.61, 127.63, 113.88, 79.65, 73.30, 71.93, 67.94, 60.62, 55.21, 37.15, 37.07, 33.25, 26.86, 19.21, 11.87, 8.71; MS (ESIMS): *m/z* (%): 551 (17) $[M+H]^+$; HRMS (LSIMS): calcd for $C_{33}H_{47}O_5Si$ $[M+H]^+$: 551.3193, found: 551.3189.

3.1.13. Synthesis of 1 and 2. To a solution of compound **15** (72 mg, 0.162 mmol) in dry pyridine (1 mL), MsCl (0.08 mL, 0.244 mmol) and DMAP (2 mg, 0.016 mmol) were added sequentially at 0°C. After being stirred for 30 min at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with saturated aqueous $CuSO_4$ solution, water, brine, dried (Na_2SO_4) and concentrated in vacuo. It was used directly in the next step.

The residue was dissolved in dry MeOH (1 mL), CSA (3.8 mg, 0.016 mmol) was added at 0°C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 3 h. It was quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 7–8% EtOAc in petroleum ether eluant) eluted first compound **2** (13 mg, 21% in 2 steps) and followed by **1** (23 mg, 37% in 2 steps).

Data for compound **1**. R_f=0.4 (20% EtOAc in petroleum ether); $[\alpha]_D^{20}$=+54.8 (*c* 0.22, $CHCl_3$); IR (neat): ν_{max} 3426, 2941, 2841, 2158, 1468, 1384, 1252, 1084, 1052, 843, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, numbering as in **A**): δ 3.76 (t, J=5.6 Hz, 2H, C1–H_2), 3.72 (d, J=10.7 Hz, 1H, C7–*H*), 3.57 (ddd, J=10.1, 3.1, 2.0 Hz, 1H, C3–*H*), 3.33 (dd, J=10.1, 4.8 Hz, 1H, C5–*H*), 2.17 (br s, 1H, O*H*), 1.95, 1.74, 1.68 and 1.49 (four m, 4H, C2–H_2, C4–*H*, C6–*H*), 0.97 (d, J=6.5 Hz, 3H, CH_3), 0.93 (d, J=6.8 Hz, 3H, CH_3), 0.88 (s, 9H, ^{t}Bu), 0.14 (s, 9H, $SiMe_3$), 0.037 (s, 3H, SiMe), 0.017 (s, 3H, SiMe); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 103.37, 89.96, 78.56, 76.85, 73.52, 61.23, 39.94, 38.42, 35.25, 25.80, 18.09, 14.34, 6.10, −0.14, −4.15, −4.85; MS (LSIMS): *m/z* (%): 385 (31) $[M+H]^+$; HRMS (LSIMS): calcd for $C_{20}H_{41}O_3Si_2$ $[M+H]^+$: 385.2594, found: 385.2584.

Data for compound **2**. R_f=0.45 (20% EtOAc in petroleum ether); $[\alpha]_D^{20}$=+104.6 (*c* 0.66, $CHCl_3$); IR (neat): ν_{max} 3453, 2951, 2169, 1463, 1388, 1335, 1253, 1076, 973, 844, 777, 674 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, numbering as in **A**): δ 4.52 (d, J=5.5 Hz, 1H, C7–*H*), 4.215 (dt, J=10.9, 2.4 Hz, 1H, C3–*H*), 3.76 (t, J=5.5 Hz, 2H, C1–H_2), 3.75 (dd, J=10.3, 4.9 Hz, 1H, C5–*H*), 2.24 (br s, 1H, O*H*), 1.97–1.85, 1.74 and 1.54–1.49 (m, 4H, C2–H_2, C4–*H*, C6–*H*), 0.93 (d, J=6.7 Hz, 3H, CH_3), 0.92 (d, J=6.8 Hz, 3H, CH_3), 0.91 (s, 9H, ^{t}Bu), 0.19 (s, 9H, $SiMe_3$), 0.07 (s, 3H, SiMe), 0.05 (s, 3H, SiMe); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 101.90, 93.65, 73.65, 73.43, 70.85, 61.62, 40.01, 34.87, 34.76, 25.84, 18.13, 13.92, 5.79, −0.09, −4.29, −4.84; MS (LSIMS): *m/z* (%): 386 (33) $[M+H]^+$; HRMS (LSIMS): calcd for $C_{20}H_{41}O_3Si_2$ $[M+H]^+$: 385.2594, found: 385.2594.

3.1.14. Synthesis of 3. To a solution of compound **18** (105 mg, 0.164 mmol) in dry pyridine (1 mL), MsCl (0.02 mL, 0.246 mmol) and DMAP (2 mg, 0.0164 mmol) were added sequentially at 0°C. After being stirred for 0.5 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with saturated aqueous $CuSO_4$ solution, water, brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was used directly in the next step.

It was dissolved in dry THF (1 mL) and TBAF (1 M in THF, 0.246 mL, 0.246 mmol) was added at 0°C. Reaction mixture was warmed to room temperature and stirred for 24 h. It was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 12–14% EtOAc in petroleum ether) afforded compound **3** (55 mg, 87% in 2 steps) as a clear oil. R_f=0.6 (silica gel, 20% EtOAc in petroleum ether); $[\alpha]_D^{20}$=−24.8 (*c* 1.83, $CHCl_3$); IR (neat): ν_{max} 3030, 2855, 1612, 1512, 1458, 1355, 1301, 1244, 1175, 1093, 1037, 839, 745, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, numbering as in **A**): δ 7.34–7.27 (m, 5H, aromatic), 7.25 and 6.86 (two d, J=8.5 Hz, 4H, PMP), 4.61 and 4.42 (ABq, J=12.1 Hz, 2H, OCH_2Ar), 4.43 (ABq, J=12.7 Hz, 2H, OCH_2Ar), 3.88 (dd, J=11.5, 3.0 Hz, 1H, C7–*H*), 3.79 (s, 3H, OCH_3), 3.62–3.52 (m, 3H, C1–H_2, C3–*H*), 3.44 (dd, J=11.5, 1.2 Hz, 1H, C7–H'), 3.24 (t, J=3 Hz, 1H, C5–*H*), 1.95, 1.88, 1.78 and 1.65 (four m, 4H, C2–H_2, C4–*H*, C6–*H*), 1.05 (d, J=6.8 Hz, 3H, CH_3), 0.91 (d, J=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.01, 139.01, 130.75, 129.17, 128.18, 127.38, 127.31, 113.66, 81.17, 75.42, 72.59, 71.21, 67.37, 67.01, 55.17, 34.97, 33.11, 31.72, 15.25, 14.00; MS (ESIMS): *m/z* (%): 385 (17) $[M+H]^+$, 407 (25) $[M+Na]^+$; HRMS (LSIMS): calcd for $C_{24}H_{33}O_4$ $[M+H]^+$: 385.2379, found: 385.2389.

3.1.15. Synthesis of 4. To a solution of **19** (84 mg, 0.189 mmol) in CH_2Cl_2 (1 mL), Et_3N (0.053 mL, 0.378 mmol) and TsCl (39.7 mg, 0.2 mmol) were added sequentially at 0°C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 5 h. It was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was used directly in the next step.

It was dissolved in dry MeOH (1 mL), K_2CO_3 (78.4 mg, 0.567 mmol) was added at 0°C under nitrogen atmosphere. The reaction mixture was allowed to room temperature and stirred for 24 h. It was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 13–15% EtOAc in petroleum ether eluant) afforded compound **4** (62 mg, 85% in 2 steps) as a clear oil. R_f=0.6 (silica gel, 20% EtOAc in petroleum ether); $[\alpha]_D^{20}$=+83.1 (*c* 1.5, $CHCl_3$); IR (neat):

ν_{max} 2947, 2911, 2853, 1612, 1513, 1458, 1359, 1302, 1246, 1177, 1093, 955, 820, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, numbering as in **A**): δ 7.35–7.27 (m, 5H, aromatic), 7.25 and 6.88 (two d, J=9.1 Hz, 4H, PMP *ortho* and *meta-H*), 4.62 and 4.34 (ABq, J=11.5 Hz, 2H, OCH_2Ar), 4.44 (ABq, J=11.5 Hz, 2H, OCH_2Ar), 3.80 (dd, J=11.2, 5.5 Hz, 1H, C7–*H*), 3.79 (s, 3H, OCH_3), 3.57–3.494 (m, 2H, C1–H_2), 3.475–3.445 (m, 1H, C3–*H*), 3.12 (dd, J=10.3, 4.9 Hz, 1H, C5–*H*), 2.96 (t, J=11.2 Hz, 1H, C7–H'), 2.04, 1.89 and 1.66 (m, 4H, C2–H_2, C4–*H*, C6–*H*), 0.92 (d, J=6.7 Hz, 3H, CH_3), 0.86 (d, J=6.7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.08, 138.58, 130.54, 129.16, 128.24, 127.61, 127.41, 113.69, 83.76, 76.16, 72.90, 72.57, 69.57, 66.69, 55.14, 34.44, 33.36, 31.41, 13.46, 5.75; MS (EIMS): *m/z* (%): 293 (10) $[M^+-91]$, 384 (4.3) $[M]^+$; HRMS (LSIMS): calcd for $C_{24}H_{33}O_4$ $[M+H]^+$: 385.2379, found: 385.2365.

3.1.16. Synthesis of 5. To a solution of compound **20** (80 mg, 0.145 mmol) in CH_2Cl_2 (1 mL), Et_3N (0.04 mL, 0.29 mmol) and TsCl (30.5 mg, 0.16 mmol) were added sequentially at 0°C under nitrogen atmosphere. Reaction mixture was warmed to room temperature and stirred for 3 h. It was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was used directly in the next step.

It was dissolved in dry toluene (5 mL), NaH (35 mg, 0.87 mmol) was added at room temperature and heated to reflux. After being stirred for 3 h under reflux, the reaction mixture was cooled to 0°C and quenched by dropwise addition of cold saturated aqueous NH_4Cl solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 8% Et0Ac in petroleum ether eluant) afforded compound **5** (51 mg, 65% in 2 steps) as colorless oil. R_f=0.5 (silica gel, 15% EtOAc in petroleum ether); $[\alpha]_D^{20}=-29.5$ (*c* 1.5, $CHCl_3$); IR (neat): ν_{max} 2928, 2855, 1613, 1513, 1464, 1357, 1248, 1108, 1068, 821, 742, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, numbering as in **A**): δ 7.67–7.27 (m, 10H, aromatic), 7.28 and 6.88 (two d, J=8.5 Hz, 4H, PMP *ortho* and *meta-H*), 4.6 and 4.38 (ABq, J=10.9 Hz, 2H, OCH_2Ar), 3.97 (m, 1H, C1–*H*), 3.81 (s, 3H, OCH_3), 3.69 (t, J=9.1 Hz, 1H, C5–*H*), 3.51 (dd, J=9.7, 6.1 Hz, 1H, C7–*H*), 3.3 (dt, J=11.5, 2.4 Hz, 1H, C1–H'), 3.24 (dd, J=9.7, 1.8 Hz, 1H, C7–H'), 3.11 (dt, J=10.3, 4.8 Hz, 1H, C3–*H*), 2.02, 1.96, 1.66–1.58 and 1.57–1.49 (four m, 4H, C2–H_2, C4–*H*, C6–*H*), 1.05 (s, 9H, ^{t}Bu), 0.925 (d, J=6.7 Hz, 3H, CH_3), 0.775 (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.15, 135.56, 134.12, 130.90, 129.47, 129.43, 129.26, 127.56, 127.53, 113.79, 80.70, 80.27, 70.19, 66.27, 65.75, 55.24, 38.85, 36.52, 31.97, 26.89, 19.28, 12.72, 9.17; MS (ESIMS): *m/z* (%): 533 (7.4) $[M+H]^+$, 555 (10) $[M+Na]^+$.

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