Total Synthesis of (−)-Tetrodotoxin from D-Glucose: A New Route to Multi-Functionalized Cyclitol Employing the Ferrier(II) Reaction toward (−)-Tetrodotoxin

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Total synthesis of (−)-tetrodotoxin (TTX) from D-glucose is described. As a critical transformation step for synthesizing TTX, a key multi-functionalized cyclitol was prepared from D-glucose employing the Ferrier(II) reaction. Stereospecific introduction of three functionalized branched chains were achieved via Peterson olefination and spiro α-chloroepoxidation of the corresponding carbonyl derivatives.

The structure of tetrodotoxin (TTX), a toxic principle in puffer fish poisoning, was reported in 1964 by four separate research groups: Tsuda's,[1a] Hirata's,[1b] Woodward's,[1c] and Mosher's[1d] groups. TTX is a useful biological tool in neurophysiology due to its specificity for blocking voltage-gated Na^+ ion channels in nervous systems.[2] Recently, TTX and several analogs have been found and isolated (Figure 1), not only from aquatic organisms such as puffer fish, but also from terrestrial animals.[3,4] TTX and its analogs can provide important insights into pharmaceutical studies, elucidation of structure–activity relationships, and biological roles.[5] Accordingly, the ability to synthesize larger amounts of TTX and its analogs has grown in importance, however still remains as an extremely difficult, yet fascinating, challenge.[6] In 2003, the Isobe and Du Bois groups both succeeded in the synthesis of (−)-TTX.[7a,7d,7e] In the following year, Isobe's group reported

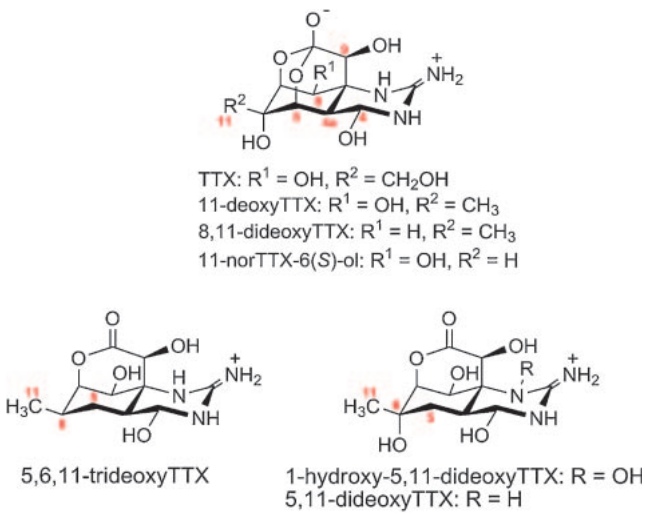

Figure 1.[18] Tetrodotoxin and its analogs.[1,3]

an improved route with fewer steps.[7b,7c,7f] We also achieved the total synthesis of (±)-TTX from *myo*-inositol in 2005,[8a] and (−)-TTX from D-glucose employing the Henry reaction (intramolecular nitro aldol reaction) in 2008.[8b] Moreover, recently Noheda filed a patent application for a synthetic method for TTX, analogs, and its intermediates.[9]

In this area, a practical synthetic route for TTX and its analogs to satisfy biological and pharmacological needs has been increasingly in demand. Particularly, development of a convergent synthetic method to prepare the multi-functionalized cyclitol of the TTX skeleton rather than a linear protocol is required. Herein, we describe our success in another convergent new route for synthesizing (−)-TTX from D-glucose via the multi-functionalized cyclitol **10a** employing the Ferrier(II) reaction[10] as the key skeleton construction. Our synthetic plan was based on our prior experiences in the total synthesis of (±)-TTX from *myo*-inositol[8a] (Scheme 1). Both total syntheses were successfully carried out using the common intermediate **D**, with the later work accomplished in an enantiospecific manner. Compound **D** was derived from D-glucose in the following manner. Compound **D** can be synthesized from multi-functionalized cyclitol **F**,[8] which can be prepared by the reaction of enol acetate **G** employing the Ferrier(II) reaction.[10] Compound **G** can be obtained by standard transformations of D-glucose by using stereoselective introduction of the branched chain at the C-3 of D-glucose (at the C-6 of TTX). The transformation of **D** into (−)-TTX, via compound **C**, **B**, and **A**, were accomplished in a similar manner as reported in the previous paper.[8]

Results and Discussion

The total synthesis of (−)-TTX from D-glucose is shown in Scheme 2. Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosid-3-ulose (**1**) was prepared by regioselective benzylation[11] followed by the Swern oxidation of methyl 4,6-*O*-

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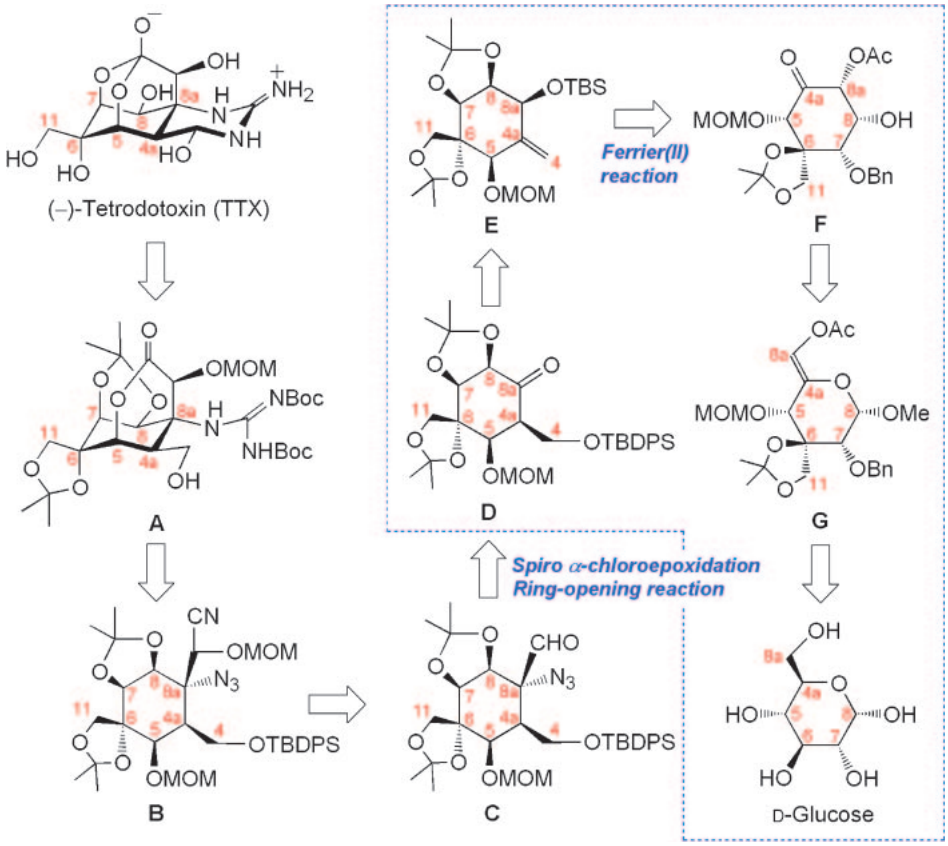
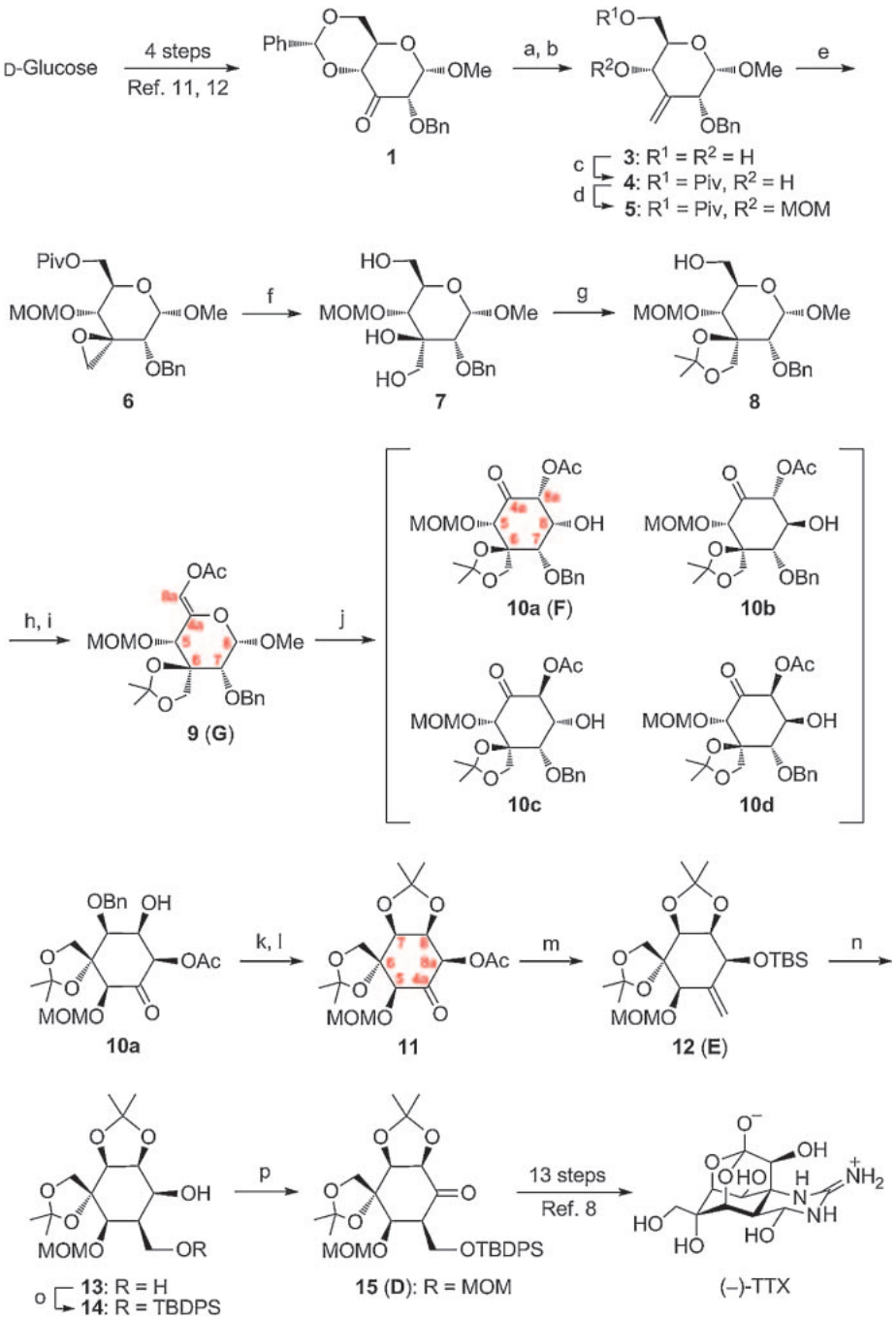


Scheme 1.[18] Retrosynthetic analysis of (−)-TTX from D-glucose.

benzylidene-α-D-glucopyranoside[12] derived from D-glucose. Peterson's olefination[13] of **1** followed by treatment with aqueous acetic acid solution gave the methylene derivative **3** via trimethylsilyl derivative **2**. Regioselective protections of **3** with pivaloyl and methoxymethyl groups gave **5**, which was oxidized using *m*-chloroperbenzoic acid via the same stereochemical course as reported[14] to afford epoxide **6**. Alkaline hydrolysis of **6** yielded triol **7**, which was then converted into the acetonide **8**. Oxidation of **8** resulted in an unstable aldehyde, which was immediately converted into enol acetate **9** (**G**) as a single geometrical isomer. The (*Z*)-configuration at C-8a of **9** was determined by NOESY spectrum (Figure 2). This selectivity was likely due to steric hindrance of the C-5 substituent.

The crucial key reaction of the intramolecular cyclization (Ferrier(II) reaction)[10] of enol acetate **9** was carried out as follows. Enol acetate **9** was treated with several mercury reagents in aqueous acetic acid–acetone solution at room temperature. The results are shown in Table 1. As a result, the desired stereoisomer **10a** (**F**) was obtained in 58% yield using $Hg(OAc)_2$ (**10a**:**10b**:**10c**:**10d** = 6:2:1:0) under the conditions listed in Entry 4. On the other hand, the Ferrier(II) reaction using $PdCl_2$[10c] afforded a complex mixture. It seems that (π-allyl)palladium complex as a reaction intermediate was not smoothly generated therefore the starting enol acetate gradually decomposed during heating. Finally, we decided that $Hg(OAc)_2$ was the most suitable reagent for this enol acetate **9**. The structures of the four stereoisomers **10a**–**10d** were confirmed by ^{1}H NMR analysis. The chemical shifts and *J* values of **10a** are shown in Figure 2: H-8a, 5.21, $J_{8a,8} = 3.3$ Hz; H-8, 4.21, $J_{8,7} = 2.2$ Hz, $J_{8,OH} = 1.5$ Hz; H-7, 4.02, $J_{7,5} = 0$ Hz; H-5, 4.31, $J_{8a,5} = 1.0$ Hz). Furthermore, the configurations at C-6 and C-8a in TTX numbering of **10a** were verified by X-ray crystal structure analysis of **11** (Figure 3). In spite of many efforts toward transforming **10b**–**10d** into **10a** or others, it could not be achieved. It seems that some side reactions, especially β-elimination, occurred during the stereochemical inversion of hydroxy substituents at C-8 and -8a. Protected diol **11** was obtained by catalytic debenzylation of **10a**, followed by isopropylidenation. Compound **11** was then transformed into **12** (**E**) by Peterson olefination[13] and subsequent *O*-silylation. Methylene derivative **12** was converted into the corresponding hydroxymethyl derivative **13** in a hydroboration–oxidation and de-*O*-silylation sequence. Selective protection of the primary hydroxy group of **13** using a *tert*-butyldiphenylsilyl group afforded the corresponding monohydroxy compound **14**, which was then oxidized with Dess–Martin periodinane[15] to give optically active ketone **15** (**D**), a key intermediate in the synthesis of TTX. The further transformation of **15** into (−)-TTX was performed along to our established route[8] including the successive spiro α-chloroepoxide formation and ring-opening with an azide anion[16] as a crucial key step. Full synthetic details including the stereochemistry and the final transformation of **15** into (−)-TTX are available in Supporting Information and previous papers.[8] The spectral data (^{1}H and MS) for the synthetic TTX was in good agreement with that of natural TTX.[7a,7b,8]



Scheme 2.[18] Total synthesis of (−)-TTX from D-glucose. Reagents and conditions: a) $TMSCH_2MgCl$, Et_2O–CH_2Cl_2 (94%); b) 60% AcOH aq (99%); c) PivCl, Py., CH_2Cl_2 (94%); d) P_2O_5, $CH_2(OCH_3)_2$, CH_2Cl_2, (82%); e) *m*-CPBA, $(CH_2Cl)_2$ (75%); f) *n*-Bu_4NOH, THF (83%); g) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, CH_2Cl_2 (75%); h) TFAA, DMSO, Et_3N, CH_2Cl_2; i) K_2CO_3, Ac_2O, CH_3CN (72%, 2 steps); j) $Hg(OAc)_2$, AcOH aq–acetone, then NaCl aq (58%); k) 20% $Pd(OH)_2$–C, H_2, EtOH (quant.); l) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, acetone–CH_2Cl_2 (66%); m) [i] $TMSCH_2MgCl$, Et_2O (56%); [ii] TBS-Cl, imidazole, CH_2Cl_2 (88%); n) [i] BH_3·THF, THF, then 10% NaOH aq, 30% H_2O_2 aq; [ii] *n*-Bu_4NF, THF (74%, 2 steps); o) *tert*-butyldiphenylsilyl chloride (TBDPS-Cl), imidazole, CH_2Cl_2 (92%); p) Dess–Martin periodinane, CH_2Cl_2 (99%).

Conclusion

The total synthesis of (−)-TTX from D-glucose featuring the Ferrier(II) reaction as the key skeleton construction was successfully carried out using effective and stereoselective steps. In studies of TTX synthesis, our group has achieved the total synthesis of TTX in three routes.[8] The proper selection of these synthetic methodologies may useful for not only compounds related to TTX (including enabled derivatives), but also other highly complex multi-functionalized cyclitols bearing branched chain structures such as cyclophellitol, mytillitol, and laminitol.[17]

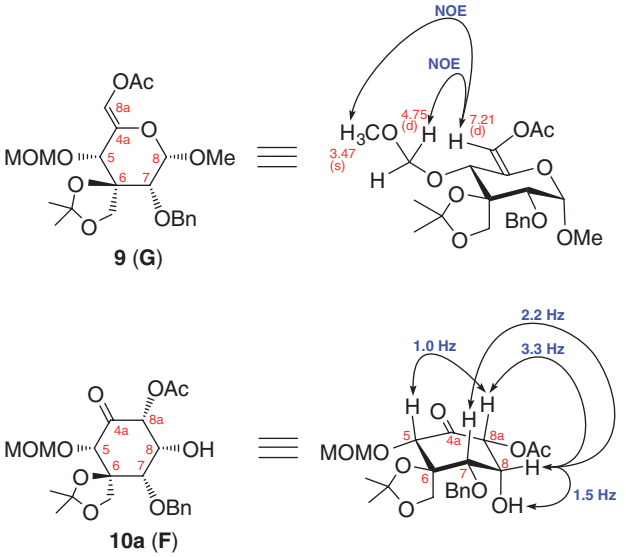


Figure 2.[18] Structure assignments of enol acetate **9** and cyclitol **10a** (Chemical shifts, split pattern, NOE correlation of **9**, and *J* values of **10a** with the corresponding TTX numbering).

Table 1. The Ferrier(II) Reaction Conditions and Products Yields

Entry	Reagent	Time /h	Ratio[a] **10a**:**10b**:**10c**:**10d**	Isolated yield of **10a**/%
1	$Hg(OCOCF_3)_2$	0.3	6:0:1:3	33
2	$HgCl_2$	4	0:0:1:2	trace
3	HgO	5	5:0:2:1	48
4	$Hg(OAc)_2$	1.5	6:2:1:0	58

a) Determined by ^{1}H NMR spectrum.

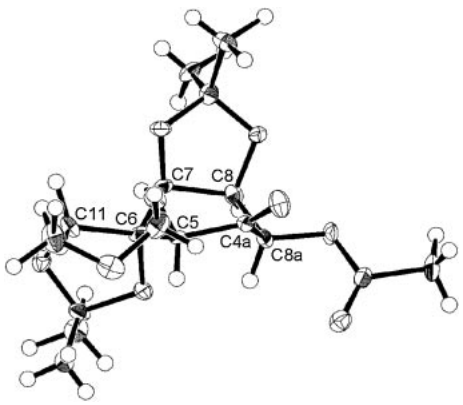


Figure 3.[18] ORTEP drawing of **11** with the corresponding TTX numbering. Thermal ellipsoids were scaled to enclose 30% probability.

Experimental

Melting points were measured using a Yanaco Model MP-J3 micro-melting point apparatus, and are uncorrected. IR spectra were recorded using a SHIMADZU IR Prestige-21 spectrometer in KBr. ^{1}H and ^{13}C NMR spectra were measured with JEOL JNM-ECA500 and -600 spectrometers in $CDCl_3$ or 3% CD_3COOD/D_2O solution with tetramethylsilane used as internal standard. Specific rotations were measured in 0.5 dm tubes using a JASCO P-1020 polarimeter in $CHCl_3$ or 3% CD_3COOD/D_2O. Mass spectra were obtained on a SHIMADZU JMS-T100CS. X-ray diffraction was measurement by Rigaku Saturn 70 diffractometer with graphite monochromated Mo Kα radiation. Structure solution and refinement were performed using CrystalStructure 3.8. Crystallographics data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-644815 for compound No. 11. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-α-D-glucopyranosid-3-ulose (1). To a stirred solution of trifluoroacetic anhydride (1.12 mL, 8.07 mmol) in dry CH_2Cl_2 (10 mL), dimethyl sulfoxide (0.96 mL, 13.5 mmol) was added at −78 °C under argon. After 30 min, a solution of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside[10] (1.00 g, 2.69 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture at −78 °C. After 15 min, triethylamine (2.61 mL, 18.8 mmol) was added dropwise to the above mixture and stirred for 5 min. After the disappearance of 2-*O*-benzylglucopyranoside on TLC with toluene–acetone (8:1 v/v), the reaction mixture was poured into saturated aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give **1**, which was purified by recrystallization from hexane–EtOAc; mp 177.0–178.0 °C (colorless needles, hexane–EtOAc); $R_f = 0.38$ (toluene–acetone = 8:1 v/v); $[\alpha]_D^{25}$ −32.4° (*c* 0.73, $CHCl_3$); IR (KBr, disk): ν 1748 cm^{-1} (C=O); ^{1}H NMR (600 MHz): δ 7.51–7.31 (10H, m, Ph*H*), 5.53 (1H, s, PhC*H*), 5.06 (1H, d, $J_{2,1} = 4.1$ Hz, H-1), 4.97, 4.60 (2H, each d, $J_{A,B} = 12.2$ Hz, –CH_2Ph), 4.39 (1H, dd, $J_{6eq,6ax} = 10.2$ Hz, $J_{6eq,5} = 4.8$ Hz, H-6eq), 4.20 (1H, dd, $J_{4,5} = 9.8$ Hz, $J_{4,2} = 1.4$ Hz, H-4), 4.14 (1H, dd, $J_{2,1} = 4.1$ Hz, $J_{2,4} = 1.4$ Hz, H-2), 4.09 (1H, ddd, $J_{5,4} = 9.8$ Hz, $J_{5,6eq} = 4.8$ Hz, $J_{5,6ax} = 10.4$ Hz, H-5), 3.87 (1H, dd, $J_{6ax,6eq} = 10.2$ Hz, $J_{6ax,5} = 10.4$ Hz, H-6ax), 3.44 (3H, s, OCH_3). ^{13}C NMR (150 MHz): δ 196.27, 136.9, 136.3, 129.3, 128.6, 128.2, 128.2, 126.4, 102.5, 101.9, 82.1, 79.6, 72.6, 69.4, 65.4. Anal. Calcd for $C_{21}H_{22}O_6$ (370.40): C, 68.10; H, 5.99%. Found: C, 68.43; H, 6.33%.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-*C*-trimethylsilylmethyl-α-D-allopyranoside (2). To a solution of 3-ulose **1** (781 mg, 2.1 mmol) in a mixture of dry CH_2Cl_2–Et_2O (1:1 v/v, 70 mL), trimethylsilylmethylmagnesium chloride (0.45 M in Et_2O, 7.0 mL, 3.15 mmol) was added and stirred for 1 h under argon. After the disappearance of starting compound **1** on TLC with hexane–EtOAc (2:1 v/v), the mixture was poured into saturated aq NH_4Cl solution, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, evaporated to give **2** (913 mg, 94% yield), which was purified on a column of silica gel with hexane–EtOAc (4:1 v/v). colorless syrup; $R_f = 0.25$ (hexane–EtOAc = 4:1 v/v); $[\alpha]_D^{25}$ +32.9° (*c* 1.07, $CHCl_3$); IR (KBr, neat): ν 3511 cm^{-1} (OH); ^{1}H NMR (600 MHz): δ 7.52–7.31 (10H, m, Ph*H*), 5.48 (1H, s, PhC*H*), 4.73 (1H, d, $J_{1,2} = 3.4$ Hz, H-1), 4.68 (2H, s, CH_2-Ph), 4.32 (1H, dd, $J_{6eq,6ax} = 10.3$ Hz, $J_{6eq,5} = 5.2$ Hz, H-6eq), 4.10 (1H, ddd, $J_{5,6eq} = 5.2$ Hz, $J_{5,6ax} = 10.3$ Hz, $J_{5,4} = 9.2$ Hz, H-5), 3.69 (1H, dd, $J_{6ax,5} = 10.3$ Hz, $J_{6ax,6eq} = 10.3$ Hz, H-6ax), 3.49 (1H, s, O*H*), 3.39 (3H, s, OCH_3), 3.38 (1H, d, $J_{2,1} = 3.4$ Hz, H-2), 3.36 (1H, d, $J_{4,5} = 9.2$ Hz, H-4), 1.36, 1.26 (2H, each d, $J_{A,B} = 14.9$ Hz, CH_2Si(CH$_3$)$_3$), 0.00 (9H, s, CH$_2$Si(CH_3)$_3$). ^{13}C NMR (150 MHz): δ 137.7, 137.3, 129.0, 128.5, 128.1, 128.0, 126.5, 102.2, 98.5, 82.6, 78.9, 74.9, 72.3, 69.1, 59.4, 55.7, 24.4,

0.39. NOE correlation: H-5–OH; H-3′–H-2, –H-4. Anal. Calcd for $C_{25}H_{34}O_6Si$ (458.62): C, 65.47; H, 7.47%. Found: C, 65.22; H, 7.28%.

Methyl 2-*O*-Benzyl-3-deoxy-3-methylene-α-D-*ribo*-hexopyranoside (3). Compound **2** (98.4 mg, 0.214 mmol) was dissolved in 60% aq acetic acid solution (3 mL), and stirred for 4 h at 70 °C. After the disappearance of starting compound **2** on TLC with hexane–EtOAc (4:1 v/v), the reaction mixture was evaporated to give olefin **3** (59.4 mg, 99% yield), which was purified on a column of silica gel with hexane–EtOAc (1:4 v/v). Colorless syrup; $R_f = 0.55$ (hexane–EtOAc = 1:4 v/v); $[\alpha]_D^{25}$ +21.1° (*c* 1.45, $CHCl_3$); IR (KBr neat): ν 3445 cm^{-1} (OH), 1661 cm^{-1} (C=C); ^{1}H NMR (600 MHz): δ 7.38–7.29 (5H, m, Ph*H*), 5.41–5.31 (2H, m, H-3′), 4.80, 4.59 (2H, each d, $J_{A,B} = 12.5$ Hz, CH_2Ph), 4.71 (1H, d, $J_{1,2} = 3.6$ Hz, H-1), 4.07 (1H, dd, $J_{6a,5} = 7.4$ Hz, $J_{6a,6b} = 9.3$ Hz, H-6a), 3.93 (1H, m, H-2), 3.85 (2H, m, H-6b, H-4), 3.50 (1H, ddd, $J_{5,6a} = 7.4$ Hz, $J_{5,6b} = 4.0$ Hz, $J_{5,4} = 8.9$ Hz, H-5), 3.40 (3H, s, OCH_3), 2.28 (1H, d, $J_{OH,4} = 7.2$ Hz, 4-O*H*), 2.05 (1H, s, 6-O*H*). ^{13}C NMR (150 MHz): δ 143.5, 137.9, 128.5, 128.1, 127.9, 127.7, 105.3, 98.7, 97.7, 76.5, 73.7, 72.1, 68.6, 62.6, 55.3. Anal. Calcd for $C_{15}H_{20}O_5$ (280.32): C, 64.27; H, 7.19%. Found: C, 64.15; H, 7.16%.

Methyl 2-*O*-Benzyl-3-deoxy-3-methylene-6-*O*-pivaloyl-α-D-*ribo*-hexopyranoside (4). To a solution of olefin **3** (104 mg, 0.37 mmol) in dry CH_2Cl_2 (2.5 mL) and pyridine (0.5 mL), pivaloyl chloride (92 μL, 0.74 mmol) was added and stirred at 0 °C. After 80 min, pivaloyl chloride (46 μL, 0.37 mmol) was added to the above mixture at rt. After the disappearance of starting compound **3** on TLC with hexane–EtOAc (1:1 v/v), EtOH (5 mL) was added to the above reaction mixture and stirred for 10 min. The above mixture was poured into water, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, evaporated to give **4** (126 mg, 94% yield), which was purified on a column of silica gel with hexane–EtOAc (3:1 v/v). Mp 65.2–67.3 °C (hexane–EtOAc); $R_f = 0.21$ (hexane–EtOAc = 3:1 v/v); $[\alpha]_D^{26}$ +27.0° (*c* 3.00, $CHCl_3$); IR (KBr, disk): ν 3474 cm^{-1} (OH), 1721 cm^{-1} (C=O); ^{1}H NMR (600 MHz): δ 7.38–7.30 (5H, m, Ph*H*), 5.42–5.37 (2H, m, H-3′), 4.79, 4.59 (2H, each d, $J_{A,B} = 12.5$ Hz, CH_2Ph), 4.72 (1H, d, $J_{1,2} = 3.8$ Hz, H-1), 4.50 (1H, dd, $J_{6a,5} = 5.0$ Hz, $J_{6a,6b} = 12.2$ Hz, H-6a), 4.27 (1H, dd, $J_{6b,5} = 2.2$ Hz, $J_{6b,6a} = 12.2$ Hz, H-6b), 3.91 (1H, m, H-2), 3.81 (1H, br dd, $J_{4,OH} = 6.4$ Hz, $J_{4,5} = 9.3$ Hz, H-4), 3.63 (1H, ddd, $J_{5,4} = 9.3$ Hz, $J_{5,6a} = 5.0$ Hz, $J_{5,6b} = 2.2$ Hz, H-5), 3.40 (3H, s, OCH_3), 2.71 (1H, d, $J_{OH,4} = 6.4$ Hz, O*H*), 1.22 (9H, s, C(CH_3)$_3$). ^{13}C NMR (150 MHz): δ 179.4, 142.6, 137.8, 130.1, 128.6, 128.5, 128.4, 128.2, 127.9, 127.7, 105.9, 98.5, 76.6, 72.7, 72.5, 72.2, 68.2, 63.8, 63.7, 55.2, 38.9, 27.2. Anal. Calcd for $C_{20}H_{28}O_6$ (364.43): C, 65.91; H, 7.74%. Found: C, 65.83; H, 7.88%.

Methyl 2-*O*-Benzyl-3-*O*-deoxy-4-*O*-methoxymethyl-3-methylene-6-*O*-pivaloyl-α-D-*ribo*-hexopyranoside (5). To a solution of compound **4** (267.4 mg, 0.74 mmol) in dry CH_2Cl_2 (4 mL), dimethoxymethane (3.27 mL, 37 mmol), Molecular Sieves 4A (945 mg), and P_2O_5 (650 mg, 4.52 mmol) were added and stirred at rt for 5 h. After the disappearance of starting compound **4** on TLC with hexane–EtOAc (1:1 v/v), the reaction mixture was poured into saturated $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, evaporated to give **5** (245.3 mg, 82% yield), which was purified on a column of silica gel with hexane–EtOAc (4:1 v/v). Colorless syrup; $R_f = 0.47$ (hexane–EtOAc = 2:1 v/v); $[\alpha]_D^{25}$ +123.0° (*c* 1.80, $CHCl_3$); IR (KBr, neat): ν 1732 cm^{-1} (C=O); ^{1}H NMR (600 MHz): δ 7.38–7.30 (5H, m, Ph*H*), 5.39–5.27 (2H, m, H-3′), 4.79, 4.57 (2H, each d, $J_{A,B} = 12.4$ Hz, CH_2Ph), 4.74, 4.66 (2H, each d, $J_{A,B} = 6.9$ Hz, OCH_2OCH$_3$), 4.71 (1H, d, $J_{1,2} = 3.8$ Hz, H-1), 4.40 (1H, dd, $J_{6a,5} = 2.1$ Hz, $J_{6a,6b} = 11.9$ Hz, H-6a), 4.18 (1H, dd, $J_{6b,5} = 5.7$ Hz, $J_{6b,6a} = 11.9$ Hz, H-6b), 3.98 (1H, br d, $J_{4,5} = 9.8$ Hz, H-4), 3.91 (1H, m, H-2), 3.75 (1H, ddd, $J_{5,4} = 9.8$ Hz, $J_{5,6a} = 2.1$ Hz, $J_{5,6b} = 5.7$ Hz, H-5), 3.42, 3.39 (6H, each s, 2 × OCH_3), 1.21 (9H, s, C(CH_3)$_3$). ^{13}C NMR (150 MHz): δ 178.2, 140.7, 137.9, 128.5, 127.9, 127.7, 106.4, 98.2, 76.9, 73.4, 72.1, 71.2, 63.3, 56.5, 55.1, 38.9, 27.2. Anal. Calcd for $C_{22}H_{32}O_7$ (408.49): C, 64.69; H, 7.90%. Found: C, 64.74; H, 8.16%.

Methyl 2-*O*-Benzyl-4-*O*-methoxymethyl-6-*O*-pivaloyl-α-D-glucopyranoside-3-spiro-2′-oxirane (6). To a solution of **5** (53 mg, 0.13 mmol) in dry $(CH_2Cl)_2$ (1 mL), *m*-chloroperbenzoic acid (44.9 mg, 0.26 mmol) was added and stirred at 55 °C under argon for 3 h. After the disappearance of starting compound **5** on TLC with hexane–MeOH (5:1 v/v), the reaction mixture was poured into saturated aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, evaporated to give epoxide **6** (41 mg, 75% yield), which was purified on a column of silica gel with hexane–EtOAc (4:1 v/v). Colorless syrup; $R_f = 0.48$ (hexane–EtOAc = 2:1 v/v); $[\alpha]_D^{26}$ +91.5° (*c* 1.26, $CHCl_3$); IR (KBr, neat): ν 1732 cm^{-1} (C=O); ^{1}H NMR (600 MHz): δ 7.37–7.28 (5H, m, Ph*H*), 4.78, 4.52 (2H, each d, $J_{A,B} = 12.2$ Hz, CH_2Ph), 4.72, 4.51 (2H, each d, $J_{A,B} = 6.7$ Hz, OCH_2OCH$_3$), 4.69 (1H, d, $J_{1,2} = 3.6$ Hz, H-1), 4.41 (1H, dd, $J_{6a,5} = 2.1$ Hz, $J_{6a,6b} = 11.9$ Hz, H-6a), 4.17 (1H, dd, $J_{6b,6a} = 11.9$ Hz, $J_{6b,5} = 5.7$ Hz, H-6b), 3.88 (1H, ddd, $J_{5,4} = 10.1$ Hz, $J_{5,6a} = 2.1$ Hz, $J_{5,6b} = 5.7$ Hz, H-5), 3.79 (1H, d, $J_{4,5} = 10.1$ Hz, H-4), 3.70 (1H, m, H-2), 3.39, 3.36 (6H, each s, 2 × OCH_3), 3.13, 3.06 (2H, each d, $J_{a,b} = 5.8$ Hz, H-3′), 1.21 (9H, s, C(CH_3)$_3$). ^{13}C NMR (150 MHz): δ 178.2, 137.8, 129.8, 128.4, 127.9, 98.9, 97.6, 73.9, 73.5, 70.4, 69.3, 63.1, 60.6, 56.4, 55.2, 45.4, 38.9, 27.2. Anal. Calcd for $C_{22}H_{32}O_8$ (424.48): C, 62.25; H, 7.60%. Found: C, 62.23; H, 7.57%.

Methyl 2-*O*-Benzyl-3-*C*-hydroxymethyl-4-*O*-methoxymethyl-α-D-glucopyranoside (7). To a solution of epoxide **6** (41 mg, 97.0 μmol) in dry THF (1 mL), tetra-*n*-butylammonium hydroxide (40 wt % in aqueous solution, 315 μL, 0.485 mmol) was added and refluxed for 30 h. After the disappearance of starting compound **6** on TLC with hexane–EtOAc (1:4 v/v), the reaction mixture was poured into saturated aq NH_4Cl solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, evaporated to give diol **7** (29 mg, 83% yield), which was purified on a column of silica gel with hexane–EtOAc (1:4 v/v). Colorless syrup; $R_f = 0.31$ (hexane–EtOAc = 1:4 v/v); $[\alpha]_D^{26}$ +75.7° (*c* 0.75, $CHCl_3$); IR (KBr, neat): ν 3474 cm^{-1} (OH); ^{1}H NMR (600 MHz): δ 7.36–7.30 (5H, m, Ph*H*), 4.90, 4.69 (2H, each d, $J_{A,B} = 6.4$ Hz, OCH_2OCH$_3$), 4.78, 4.68 (2H, each d, $J_{A,B} = 11.9$ Hz, CH_2Ph), 4.62 (1H, d, $J_{1,2} = 4.1$ Hz, H-1), 4.18 (1H, dd, $J_{6a,OH} = 6.7$ Hz, $J_{6a,6b} = 11.9$ Hz, H-6a), 3.95 (1H, dd, $J_{6b,6a} = 11.9$ Hz, $J_{6b,OH} = 7.2$ Hz, H-6b), 3.91 (1H, d, $J_{OH,3'} = 2.1$ Hz, O*H*), 3.80, 3.77 (2H, each ddd, $J_{3',OH} = 2.1$ Hz, $J_{3',OH} = 6.5$ Hz, $J_{a,b} = 12.2$ Hz, H-3′), 3.67 (1H, d, $J_{4,5} = 10.4$ Hz, H-4), 3.66 (1H, d, $J_{5,4} = 10.4$ Hz, H-5), 3.59 (1H, d, $J_{2,1} = 4.1$ Hz, H-2), 3.45, 3.36 (6H, each s, OCH_3), 2.95 (1H, dd, $J_{OH,6a} = 7.2$ Hz, $J_{OH,6b} = 7.2$ Hz, CH$_2$O*H*), 2.45 (1H, dd, $J_{OH,3'a} = 6.7$ Hz, $J_{OH,3'b} = 6.7$ Hz, O*H*). ^{13}C NMR (150 MHz): δ 137.6, 128.5, 128.1, 128.0, 99.2, 98.3, 81.5, 79.4, 75.2, 74.1, 69.1, 62.9, 61.7, 56.5, 55.5. Anal. Calcd for $C_{17}H_{26}O_8$ (358.38): C, 56.97; H, 7.31%. Found: C, 56.76; H, 7.37%.

Methyl 2-*O*-Benzyl-3-*C*-hydroxymethyl-4-*O*-methoxymethyl-α-D-glucopyranoside-3-spiro-4′-(2′,2′-dimethyldioxolane) (8).

To a solution of diol **7** (2.52 g, 7.07 mmol) in CH_2Cl_2 (75 mL), acetone dimethylacetal (4.3 mL, 35.4 mmol) and *p*-toluenesulfonic acid monohydrate (54 mg, 0.28 mmol) were added and stirred for 20 min. After the disappearance of starting compound **7** on TLC with hexane–EtOAc (1:4 v/v), triethylamine (1 mL) was added to the reaction mixture and stirred 5 min. The above mixture was poured into saturated aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give acetonide **8** (2.10 g, 75% yield), which was purified on a column of silica gel with hexane–EtOAc (1:1 v/v). Colorless syrup; $R_f = 0.25$ (hexane–EtOAc = 1:1 v/v); $[\alpha]_D^{26}$ +94.7° (*c* 0.82, $CHCl_3$); IR (KBr, neat): ν 3480 cm^{-1} (OH); ^1H NMR (500 MHz): δ 7.37–7.28 (5H, m, Ph*H*), 4.90, 4.71 (2H, each d, $J_{A,B} = 6.5$ Hz, OCH_2OCH_3), 4.83, 4.56 (2H, each d, $J_{A,B} = 12.4$ Hz, CH_2Ph), 4.41 (1H, d, $J_{1,2} = 3.4$ Hz, H-1), 4.35, 4.01 (2H, each d, $J_{a,b} = 9.3$ Hz, H-3′), 3.92 (1H, br ddd, $J_{6a,5} = 2.2$ Hz, $J_{6a,OH} = 5.2$ Hz, $J_{6,6'} = 12.7$ Hz, H-6a), 3.70 (1H, br ddd, $J_{6b,6a} = 12.7$ Hz, $J_{6b,5} = 2.2$ Hz, $J_{6b,OH} = 8.9$ Hz, H-6b), 3.57 (1H, d, $J_{4,5} = 10.1$ Hz, H-4), 3.53 (1H, d, $J_{2,1} = 3.4$ Hz, H-2), 3.45 (3H, s, OCH_3), 3.43 (1H, ddd, $J_{5,4} = 10.1$ Hz, $J_{5,6a} = 2.2$ Hz, $J_{5,6b} = 2.2$ Hz, H-5), 3.28 (3H, s, OCH_3), 3.08 (1H, br dd, $J_{OH,6a} = 5.2$ Hz, $J_{OH,6b} = 8.9$ Hz, O*H*), 1.48, 1.44 (6H, each s, $C(CH_3)_2$). ^{13}C NMR (150 MHz): δ 137.9, 128.5, 128.5, 128.2, 128.0, 109.2, 100.2, 98.9, 85.8, 78.2, 78.1, 74.4, 70.4, 64.5, 61.5, 56.5, 55.3, 26.9, 25.9. Anal. Calcd for $C_{20}H_{30}O_8$ (398.45): C, 60.29; H, 7.59%. Found: C, 59.97; H, 7.52%.

Methyl 6-*O*-Acetyl-2-*O*-benzyl-4-*O*-methoxymethyl-α-D-*xylo*-hex-5-enopyranoside-3-spiro-4′-(2′,2′-dimethyldioxolane) (9). To a stirred solution of trifluoroacetic anhydride (200 µL, 1.36 mmol) in dry CH_2Cl_2 (30 mL), dimethyl sulfoxide (170 µL, 2.4 mmol) was added at −78 °C under argon. After 15 min, a solution of alcohol **8** (94.8 mg, 0.24 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture at −78 °C. After 30 min, triethylamine (400 µL, 2.88 mmol) was added dropwise to the above mixture, and stirred for 5 min. After the disappearance of starting compound **8** on TLC with toluene–acetone (8:1 v/v), the reaction mixture was warm to rt, poured into saturated aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give unstable aldehyde. Following, to a solution of aldehyde in dry CH_3CN (5 mL), potassium carbonate (199 mg, 1.44 mmol) and acetic anhydrous (227 µL, 2.4 mmol) were added and refluxed for 6 h. After the disappearance of starting aldehyde on TLC with hexane–EtOAc (1:1 v/v), the reaction mixture was poured into saturated aq NH_4Cl solution, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give enol acetate **9** (75.2 mg, 2 steps 72% yield), which was purified on a column of silica gel with hexane–EtOAc (1:1 v/v). Mp 50.0–51.0 °C (colorless plates, hexane–EtOAc); $R_f = 0.47$ (hexane–EtOAc = 2:1 v/v); $[\alpha]_D^{26}$ −10.6° (*c* 0.97, $CHCl_3$); IR (KBr, disk): ν 1755 cm^{-1} (C=O), 1639 cm^{-1} (C=C); ^1H NMR (600 MHz): δ 7.39–7.31 (5H, m, Ph*H*), 7.21 (1H, d, $J_{6,4} = 1.9$ Hz, H-6), 4.88, 4.61 (2H, each d, $J_{A,B} = 12.4$ Hz, CH_2Ph), 4.87, 4.75 (2H, each d, $J_{A,B} = 6.5$ Hz, OCH_2OCH_3), 4.53 (1H, $J_{1,2} = 3.4$ Hz, H-1), 4.21, 3.98 (2H, each d, $J_{a,b} = 9.3$ Hz, H-3′), 4.03 (1H, d, $J_{4,6} = 1.9$ Hz, H-4), 3.64 (1H, d, $J_{2,1} = 3.4$ Hz, H-2), 3.47, 3.41 (6H, each s, 2 × OCH_3), 2.14 (3H, s, $COCH_3$), 1.48, 1.44 (6H, each s, $C(CH_3)_2$). ^{13}C NMR (150 MHz): δ 167.2, 137.8, 135.0, 128.5, 128.2, 128.1, 123.7, 109.9, 100.4, 98.2, 85.4, 77.4, 76.2, 74.7, 64.4, 56.9, 56.4, 26.7, 25.7, 20.5. Anal. Calcd for $C_{22}H_{30}O_9$ (438.47): C, 60.26; H, 6.90%. Found: C, 60.50; H, 6.87%.

Aldehyde (Methyl (5*R*)-2-*O*-Benzyl-4-*O*-methoxymethyl-α-D-*gluco*-hexodialdopyranoside-3-spiro-4′-(2′,2′-dimethyldioxolane)): Colorless syrup; $R_f = 0.25$ (toluene–acetone = 8:1 v/v); ^1H NMR (270 MHz): δ 9.63 (1H, d, $J_{CHO,5} = 2.3$ Hz), 8.28–7.23 (5H, m, Ph*H*), 4.89, 4.67 (2H, each d, $J_{A,B} = 12.2$ Hz, CH_2Ph), 4.85, 4.56 (2H, each d, $J_{A,B} = 6.6$ Hz, OCH_2OCH_3), 4.46 (1H, $J_{1,2} = 3.3$ Hz, H-1), 4.33, 4.09 (2H, each d, $J_{a,b} = 9.5$ Hz, H-3′), 3.87 (1H, dd, $J_{5,CHO} = 2.3$ Hz, $J_{5,4} = 10.2$ Hz, H-5), 3.65 (1H, d, $J_{4,5} = 10.2$ Hz, H-4), 3.53 (1H, d, $J_{2,1} = 3.3$ Hz, H-2), 3.30, 3.29 (6H, each s, 2 × OCH_3), 1.47, 1.44 (6H, each s, $C(CH_3)_2$). ^{13}C NMR (150 MHz): δ 197.0, 137.7, 128.6, 128.2, 128.2, 109.6, 99.7, 99.0, 85.4, 78.0, 77.7, 74.6, 74.6, 74.2, 64.5, 56.3, 55.9, 26.8, 25.8. ESI-TOF-MS Calcd for $C_{20}H_{29}O_8$ m/z $[M + H]^+$: 397.1862. Found: 397.1865.

2D-(2,3,4,6/5(OH))-2-*O*-Acetyl-4-*O*-benzyl-5-*C*-hydroxymethyl-5,5′-*O*-isopropylidene-6-*O*-methoxymethyl-2,3,4,5,6-pentahydroxycyclohexanone (10a), 2D-(2,4,6/3,5(OH))-2-*O*-Acetyl-4-*O*-benzyl-5-*C*-hydroxymethyl-5,5′-*O*-isopropylidene-6-*O*-methoxymethyl-2,3,4,5,6-pentahydroxycyclohexanone (10b), 2L-(3,4,6/2,5(OH))-2-*O*-Acetyl-4-*O*-benzyl-5-*C*-hydroxymethyl-5,5′-*O*-isopropylidene-6-*O*-methoxymethyl-2,3,4,5,6-pentahydroxycyclohexanone (10c), and 2L-(4,6/2,3,5(OH))-2-*O*-Acetyl-4-*O*-benzyl-5-*C*-hydroxymethyl-5,5′-*O*-isopropylidene-6-*O*-methoxymethyl-2,3,4,5,6-pentahydroxycyclohexanone (10d). To a solution of enol acetate **9** (218 mg, 0.497 mmol) in a mixture of acetone–H_2O–AcOH (500:200:7 v/v/v, 6 mL), mercury(II) acetate (205 mg, 0.464 mmol) was added and stirred at 70 °C for 1 h. After the disappearance of starting compound **9** on TLC with hexane–EtOAc (1:1 v/v), the reaction mixture was cooled to rt, saturated aq NaCl solution (3 mL) was added to the above mixture, and stirred for 5 min. After the end of reaction as determined by TLC with hexane–EtOAc (1:1 v/v), the mixture was extracted with $CHCl_3$, washed with brine and water, and evaporated to give a residue. The remaining residue was purified on a column of silica gel with hexane–EtOAc (4:1 v/v) to give cyclitol **10a** (122 mg, 58% yield) and its diastereomers **10b** (18 mg, 23% yield) and **10c** (9.2 mg, 9% yield), respectively.

10a: colorless syrup; $R_f = 0.34$ (hexane–EtOAc = 1:1 v/v); $[\alpha]_D^{25}$ −8.74° (*c* 2.31, $CHCl_3$); IR (KBr neat): ν 3543 cm^{-1} (OH), 1748, 1732 cm^{-1} (C=O); ^1H NMR (600 MHz): δ 7.41–7.35 (5H, m, Ph*H*), 5.21 (1H, dd, $J_{2,6} = 1.0$ Hz, $J_{2,3} = 3.3$ Hz, H-2), 4.92, 4.73 (2H, each d, $J_{A,B} = 11.9$ Hz, CH_2Ph), 4.78, 4.75 (2H, each d, $J_{A,B} = 6.7$ Hz, OCH_2OCH_3), 4.31 (1H, d, $J_{6,2} = 1.0$ Hz, H-6), 4.26, 3.90 (2H, each d, $J_{A,B} = 9.5$ Hz, H-5′), 4.21 (1H, ddd, $J_{3,2} = 3.3$ Hz, $J_{3,4} = 2.2$ Hz, $J_{3,OH} = 1.5$ Hz, H-3), 4.02 (1H, d, $J_{4,3} = 2.2$ Hz, H-4), 3.43 (3H, s, OCH_3), 2.29 (1H, d, $J_{OH,3} = 1.5$ Hz, O*H*), 2.20 (3H, s, $COCH_3$), 1.52, 1.46 (6H, each s, $C(CH_3)_2$). ^{13}C NMR (150 MHz): δ 197.0, 169.4, 137.1, 128.7, 128.4, 128.1, 110.2, 96.9, 87.2, 81.1, 77.8, 74.7, 74.5, 69.4, 64.6, 56.5, 26.6, 26.0, 20.5. Anal. Calcd for $C_{21}H_{28}O_9$ (424.44): C, 59.43; H, 6.65%. Found: C, 59.34; H, 7.05%. ESI-TOF-MS Calcd for $C_{21}H_{28}NaO_9$ m/z $[M + Na]^+$: 447.1631. Found: 447.1596.

10b: colorless syrup; $R_f = 0.48$ (hexane–EtOAc = 1:1 v/v); $[\alpha]_D^{25}$ −14.4° (*c* 1.01, $CHCl_3$); IR (KBr neat): ν 3468 cm^{-1} (OH), 1755, 1748 cm^{-1} (C=O); ^1H NMR (600 MHz): δ 7.40–7.33 (5H, m, Ph*H*), 5.23 (1H, dd, $J_{2,6} = 1.0$ Hz, $J_{2,3} = 10.3$ Hz, H-2), 5.03, 4.80 (2H, each d, $J_{A,B}$ =11.7 Hz, OCH_2OCH_3), 4.77 (2H, s, CH_2Ph), 4.47 (1H, d, $J_{6,2} = 1.0$ Hz, H-6), 3.98, 3.81 (2H, each d, $J_{a,b} = 8.4$ Hz, H-5′), 3.92 (1H, d, $J_{4,3} = 9.5$ Hz, H-4), 3.48 (1H, d, $J_{3,4} = 9.5$ Hz, H-3), 3.43 (3H, s, OCH_3), 2.50 (1H, br s, O*H*), 2.18 (3H, s, $COCH_3$), 1.52, 1.48 (6H, each s, $C(CH_3)_2$). ^{13}C NMR (150 MHz): δ 197.0, 169.7, 137.6, 128.9, 128.4, 127.9, 111.7, 96.7, 84.6, 81.6, 80.2, 77.3, 76.5, 71.1, 64.3, 56.5, 26.4, 26.3, 20.5. ESI-

TOF-MS Calcd for $C_{21}H_{28}NaO_9$ m/z $[M + Na]^+$: 447.16310. Found: 447.1602.

10c: colorless syrup; $R_f = 0.23$ (hexane–EtOAc = 1:1 v/v); $[\alpha]_D^{25}$ +8.9° (*c* 0.1, $CHCl_3$); IR (KBr neat): ν 3495 cm^{-1} (OH), 1744, 1742 cm^{-1} (C=O); ^1H NMR (600 MHz): δ 7.40–7.34 (5H, m, Ph*H*), 6.00 (1H, d, $J_{2,3} = 3.3$ Hz, H-2), 4.83, 4.64 (2H, each d, $J_{A,B} = 11.9$ Hz, CH_2Ph), 4.69, 4.67 (2H, each d, $J_{A,B} = 6.7$ Hz, OCH_2OCH$_3$), 4.43 (1H, ddd, $J_{3,4} = 3.6$ Hz, $J_{3,OH} = 9.6$ Hz, $J_{3,2} = 3.3$ Hz, H-3), 4.22, 3.99 (2H, each d, $J_{a,b} = 9.6$ Hz, H-5′), 3.98 (1H, d, $J_{6,4} = 1.7$ Hz, H-6), 3.50 (1H, dd, $J_{4,3} = 3.6$ Hz, $J_{4,6} = 1.7$ Hz, H-4), 3.39 (3H, s, OCH_3), 3.13 (1H, d, $J_{OH,3} = 9.6$ Hz, O*H*), 2.23 (3H, s, COCH_3), 1.41, 1.32 (6H, each s, C(CH_3)$_2$). ^{13}C NMR (150 MHz): δ 200.2, 170.0, 136.9, 128.6, 128.3, 128.0, 112.5, 96.5, 85.2, 82.6, 79.8, 74.9, 73.4, 73.0, 69.2, 56.5, 26.6, 26.2, 20.7. ESI-TOF-MS Calcd for $C_{21}H_{28}NaO_9$ m/z $[M + Na]^+$: 447.1631. Found: 447.1662.

10d: colorless syrup; $R_f = 0.6$–0.2 tailing (hexane–EtOAc = 1:1 v/v); $[\alpha]_D^{26}$ +10.3° (*c* 0.1, $CHCl_3$); IR (KBr neat): ν 3468 cm^{-1} (OH), 1745, 1741 cm^{-1} (C=O); ^1H NMR (600 MHz): δ 7.43–7.27 (5H, m, Ph*H*), 5.37 (1H, dd, $J_{2,3} = 4.1$ Hz, $J_{2,4} = 3.3$ Hz, H-2), 5.14 (1H, dd, $J_{3,4} = 4.3$ Hz, $J_{3,OH} = 7.0$ Hz, H-3), 4.89, 4.68 (2H, each d, $J_{A,B} = 12.0$ Hz, CH_2Ph), 4.67, 4.65 (2H, each d, $J_{A,B} = 6.7$ Hz, OCH_2OCH$_3$), 4.26, 3.85 (2H, each d, $J_{a,b} = 9.6$ Hz, H-5′), 3.95 (1H, d, $J_{6,4} = 1.2$ Hz, H-6), 3.94 (1H, dd, $J_{4,6} = 1.2$ Hz, $J_{4,3} = 4.3$ Hz, H-4), 3.37 (3H, s, OCH_3), 3.20 (1H, d, $J_{OH,3} = 7.0$ Hz, O*H*), 2.00 (3H, s, COCH_3), 1.36, 1.13 (6H, each s, C(CH_3)$_2$). ^{13}C NMR (150 MHz): δ 205.6, 170.5, 137.0, 128.5, 128.4, 128.2, 128.0, 111.5, 97.0, 84.7, 82.5, 74.9, 73.3, 69.6, 69.0, 56.5, 26.7, 26.1, 20.9. ESI-TOF-MS Calcd for $C_{21}H_{28}NaO_9$ m/z $[M + Na]^+$: 447.1631. Found: 447.1643.

2D-(2,3,4,6/5(OH))-2-*O*-Acetyl-5-*C*-hydroxymethyl-3,4:5,5′-di-*O*-isopropylidene-6-*O*-methoxymethyl-2,3,4,5,6-pentahydroxycyclohexanone (11). A solution of cyclitol **10a** (146 mg, 0.344 mmol) in EtOH (7 mL) was hydrogenated in the presence of a catalytic amount of 20% Pd(OH)$_2$–C (116 mg) under H_2 gas at rt for 2 h. After the disappearance of starting compound **10a** on TLC with toluene–acetone (1:1 v/v), catalyst was filtered off, and evaporated to quantitatively give diol. To a solution of this diol (10.6 mg, 31.7 μmol) in a mixture of acetone–CH_2Cl_2 (1:1 v/v) (0.4 mL), 2,2-dimethoxypropane (40 μL, 0.317 mmol) and *p*-toluenesulfonic acid monohydrate (5.5 mg, 3.17 μmol) were added and stirred at rt for 1 h. After the disappearance of starting diol on TLC with toluene–acetone (2:1 v/v), the reaction mixture was quenched with saturated aq $NaHCO_3$ solution, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give diacetonide **11** (7.8 mg, 66% yield), which was purified on a column of silica gel with hexane–EtOAc (2:1 v/v). Mp 145.0–146.0 °C (colorless prism, hexane–EtOAc); $R_f = 0.41$ (hexane–EtOAc = 1:1 v/v); $[\alpha]_D^{25}$ −152.4° (*c* 1.03, $CHCl_3$); IR (KBr disk): ν 1759, 1741 cm^{-1} (C=O); ^1H NMR (600 MHz): δ 5.70 (1H, d, $J_{2,3} = 4.5$ Hz, H-2), 5.03, 4.72 (2H, each d, $J_{a,b} = 6.9$ Hz, OCH_2OCH$_3$), 4.84 (1H, dd, $J_{3,2} = 4.5$ Hz, $J_{3,4} = 6.8$ Hz, H-3), 4.43 (1H, d, $J_{4,3} = 6.8$ Hz, H-4), 4.35, 4.24 (2H, each d, $J_{A,B} = 9.8$ Hz, H-5′), 4.18 (1H, s, H-6), 3.46 (3H, s, OCH_3), 2.24 (3H, s, COCH_3), 1.48, 1.45, 1.39, 1.35 (12H, each s, 2 × C(CH_3)$_2$). ^{13}C NMR (150 MHz): δ 200.6, 170.0, 111.7, 111.5, 97.9, 82.1, 80.2, 77.4, 75.9, 73.8, 69.3, 56.6, 27.1, 25.9, 25.6, 24.4, 20.6. Anal. Calcd for $C_{17}H_{26}O_9$ (374.38): C, 54.54; H, 7.00%. Found: C, 54.41; H, 7.24%.

Diol (2D-(2,3,4,6/5(OH))-2-*O*-Acetyl-5-*C*-hydroxymethyl-5,5′-*O*-isopropylidene-6-*O*-methoxymethyl-2,3,4,5,6-pentahydroxycyclohexanone): Mp 66.5–67.3 °C (hexane–EtOH); $R_f = 0.27$ (toluene–acetone = 1:1 v/v); $[\alpha]_D^{25}$ +19.4° (*c* 3.40, $CHCl_3$); IR (KBr, disk): ν 3458 cm^{-1} (OH), 1730, 1714 cm^{-1} (C=O); ^1H NMR (600 MHz): δ 5.33 (1H, d, $J_{2,3} = 3.4$ Hz, H-2), 4.76 (2H, each d, $J_{A,B} = 6.7$ Hz, OCH_2OCH$_3$), 4.46 (1H, br dd, $J_{3,OH} = 2.8$ Hz, $J_{3,2} = 2.8$ Hz, H-3), 4.41 (1H, s, H-6), 4.30, 3.96 (2H, each d, $J_{a,b} = 9.8$ Hz, H-5′), 4.22 (1H, br s, H-4), 3.32 (3H, s, OCH_3), 2.84 (1H, br d, $J_{OH,4} = 3.4$ Hz, O*H*), 2.64 (1H, br s, O*H*), 2.23 (3H, s, COCH_3), 1.49 (6H, s, C(CH_3)$_2$). ^{13}C NMR (150 MHz): δ 197.6, 169.7, 110.1, 97.0, 87.5, 80.0, 75.3, 71.8, 71.2, 64.3, 56.8, 26.8, 26.3, 20.7. Anal. Calcd for $C_{14}H_{22}O_9$ (334.32): C, 50.30; H, 6.63%. Found: C, 49.99; H, 6.92%.

1D-(1,2,3,5/4(OH))-1-*O*-*tert*-Butyldimethylsilyl-4-*C*-hydroxymethyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-6-*C*-methylene-1,2,3,4,5-cyclohexanepentol (12). To a solution of diacetonide **11** (60 mg, 0.16 mmol) in dry Et_2O (10 mL), trimethylsilylmethylmagnesium chloride (1.0 M in Et_2O solution, 2.88 mL, 2.88 mmol) was added dropwise at 0 °C, and stirred for 20 h. After the disappearance of starting compound **11** on TLC with hexane–EtOAc (1:1 v/v), the reaction mixture was poured into saturated aq NH_4Cl solution, extracted with EtOAc, washed with brine and water, dried over anhyd $MgSO_4$, and evaporated to give olefin (30 mg, 56% yield), which was purified on a column of silica gel with hexane–EtOAc (3:2 v/v). To a solution of resulting olefin (30 mg, 80 μmol) in dry CH_2Cl_2 (4 mL) *tert*-butyldimethylsilyl chloride (78 mg, 0.51 mmol) and imidazole (52 mg, 0.77 mmol) were added and stirred for 22 h. After the disappearance of starting olefin on TLC with hexane–EtOAc (2:1 v/v), the reaction mixture was poured into saturated aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, and evaporated to give silyl ether **12** (28.8 mg, 88% yield), which was purified on a column of silica gel with hexane–EtOAc (4:1 v/v). Colorless syrup; $R_f = 0.36$ (hexane–EtOAc = 4:1 v/v); $[\alpha]_D^{25}$ −48.4° (*c* 3.38, $CHCl_3$); IR: Characteristic absorption was not observed; ^1H NMR (600 MHz): δ 5.43, 5.31 (2H, each m, H-6′), 4.79, 4.75 (2H, each d, $J_{A,B} = 6.7$ Hz, OCH_2OCH$_3$), 4.53 (1H, m, H-1), 4.41 (1H, dd, $J_{2,1} = 4.5$ Hz, $J_{2,3} = 6.9$ Hz, H-2), 4.21 (1H, d, $J_{3,2} = 6.9$ Hz, H-3), 4.15 (2H, each s, H-4′), 4.14 (1H, br s, H-5), 3.43 (3H, s, OCH_3), 1.47, 1.43, 1.40, 1.33 (12H, each s, 2 × C(CH_3)$_2$), 0.94 (9H, s, SiC(CH_3)$_3$), 0.14, 0.12 (6H, each s, Si(CH_3)$_2$). ^{13}C NMR (150 MHz): δ 143.1, 112.1, 110.2, 109.8, 96.5, 83.3, 79.2, 77.6, 69.5, 67.7, 56.1, 26.9, 26.3, 26.0, 25.7, 24.8, 18.6, 13.7, −4.6, −4.9. Anal. Calcd for $C_{22}H_{40}O_7Si$ (444.63): C, 59.43; H, 9.07%. Found: C, 59.62; H, 8.85%.

Olefin (1D-(1,2,3,5/4(OH))-4-*C*-Hydroxymethyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-6-*C*-methylene-1,2,3,4,5-cyclohexanepentol): Mp 55.5–56.5 °C (colorless needles, hexane–EtOAc); $R_f = 0.40$ (hexane–EtOAc = 1:1 v/v); $[\alpha]_D^{25}$ −104.3° (*c* 0.45, $CHCl_3$); IR (KBr disk): ν 3487 cm^{-1} (OH), 1659 cm^{-1} (C=C); ^1H NMR (600 MHz): δ 5.37, 5.33 (2H, each m, H-6′), 4.79, 4.75 (2H, each d, $J_{A,B} = 6.7$ Hz, OCH_2OCH$_3$), 4.48 (1H, dd, $J_{4,5} = 4.8$ Hz, $J_{4,3} = 6.7$ Hz, H-2), 4.36 (1H, br ddd, $J_{5,4} = 4.8$ Hz, $J_{5,1} = 1.9$ Hz, $J_{5,OH} = 9.8$ Hz, H-5), 4.28 (1H, dd, $J_{3,4} = 6.7$ Hz, $J_{3,1} = 0.7$ Hz, H-3), 4.26, 4.16 (2H, each d, $J_{A,B} = 9.5$ Hz, H-4′), 4.24 (1H, br d, $J_{1,3} = 0.7$ Hz, H-1), 3.45 (3H, s, OCH_3), 2.43 (1H, d, $J_{OH,5} = 9.8$ Hz, O*H*), 1.44, 1.43, 1.41, 1.35 (12H, each s, 2 × C(CH_3)$_2$). ^{13}C NMR (150 MHz): δ 143.6, 112.3, 110.5, 110.1, 97.1, 81.8, 79.5, 78.3, 76.1, 68.6, 68.3, 56.4, 27.0, 26.2, 25.6, 25.0. Anal. Calcd for $C_{16}H_{26}O_7$ (330.37): C, 58.17; H, 7.93%. Found: C, 57.90; H, 8.20%.

1D-(1,2,3,5,6/4(OH))-4,6-Di-*C*-hydroxymethyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-1,2,3,4,5-cyclohexanepentol (13). To a solution of olefin **12** (215 mg, 0.484 mmol) in dry THF (15 mL), Borane–THF complex (1.0 M in THF solution, 1.45 mL,

1.45 mmol) was added at 0 °C, and stirred at rt. After 1 h, 10 wt % aq NaOH solution (9 mL) was added to the stirred mixture at 0 °C. After 5 min, 30 wt % aq H_2O_2 solution (9 mL) was added and stirred at 0 °C for 1 h. After monitoring of the reaction on TLC with hexane–EtOAc (2:1 v/v), the reaction mixture was poured into saturated aq NH_4Cl solution, extracted with EtOAc, washed with sodium thiosulfate solution, brine, and water, dried over anhyd $MgSO_4$, and evaporated to give residue. To a solution of the remaining residue in tetrahydrofuran (5 mL), tetra-*n*-butylammonium fluoride (1.0 M in THF solution, 0.58 mL, 0.58 mmol) was added and stirred for 1 h at rt. After the disappearance of starting compound **12** on TLC with EtOAc, the reaction mixture was evaporated to give a residue. The remaining residue was purified on a column of silica gel with EtOAc to give diol **13** (126 mg, 74% yield 2 steps). Colorless syrup; $R_f = 0.55$ (EtOAc); $[\alpha]_D^{25}$ +6.59° (*c* 1.8, $CHCl_3$); IR (KBr neat): ν 3464 cm^{-1} (OH); ^1H NMR (600 MHz): δ 4.77, 4.72 (2H, each d, $J_{A,B} = 6.7$ Hz, OCH_2OCH_3), 4.26 (2H, each d, $J_{A,B} = 9.6$ Hz, H-4′), 4.15 (1H, d, $J_{2,1} = 4.8$ Hz, H-2), 4.15 (1H, s, H-3), 4.01 (1H, dd, $J_{6'a,6} = 9.1$ Hz, $J_{6'a,6'b} = 11.3$ Hz, H-6′a), 3.93 (1H, d, $J_{5,6} = 2.4$ Hz, H-5), 3.85 (1H, dd, $J_{6'b,6} = 6.2$ Hz, $J_{6'b,6'a} = 11.3$ Hz, H-6′b), 3.83 (1H, br ddd, $J_{1,2} = 4.8$ Hz, $J_{1,6} = 2.4$ Hz, $J_{1,OH} = 10.8$ Hz, H-1), 3.46 (3H, s, OCH_3), 3.18 (1H, d, $J_{OH,1} = 10.8$ Hz, O*H*), 2.63 (1H, br s, O*H*), 2.10 (1H, dddd, $J_{6,6'a} = 9.1$ Hz, $J_{6,5} = 2.4$ Hz, $J_{6,6'b} = 6.2$ Hz, $J_{6,1} = 2.4$ Hz, H-6), 1.58, 1.41, 1.41, 1.40 (12H, each s, 2 × $C(CH_3)_2$). ^{13}C NMR (150 MHz): δ 110.8, 109.7, 99.5, 80.6, 79.9, 78.3, 75.5, 69.3, 68.2, 61.3, 56.8, 39.7, 27.0, 26.6, 25.8, 25.7. Anal. Calcd for $C_{16}H_{28}O_8$ (348.39): C, 55.16; H, 8.10%. Found: C, 55.0; H, 8.20%.

1D-(1,2,3,5,6/4(OH))-6′-*O*-*tert*-Butyldiphenylsilyl-4,6-di-*C*-hydroxymethyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-1,2,3,4,5-cyclohexanepentol (14). To a solution of diol **13** (1.3 g, 3.73 mmol) in dry CH_2Cl_2 (45 mL) *tert*-butyldiphenylsilyl chloride (1.2 mL) and imidazole (1.0 mg, 14.7 mmol) were added and stirred for 10 min. After the disappearance of starting compound **13** on TLC with EtOAc, the reaction mixture was poured into saturated aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, and evaporated to give silyl ether **14** (2.01 g, 92% yield), which was purified on a column of silica gel with hexane–EtOAc (4:1 v/v). Colorless syrup; $R_f = 0.45$ (hexane–EtOAc = 3:1 v/v); $[\alpha]_D^{26}$ −23.6° (*c* 2.8, $CHCl_3$); IR (KBr, neat): ν 3508 cm^{-1} (OH); ^1H NMR (600 MHz): δ 7.68–7.36 (10H, m, Ph*H*), 4.71, 4.61 (2H, each d, $J_{A,B} = 6.7$ Hz, OCH_2OCH_3), 4.35, 4.30 (2H, each d, $J_{a,b} = 9.6$ Hz, H-4′), 4.14 (1H, d, $J_{3,2} = 5.3$ Hz, H-3), 4.11 (1H, dd, $J_{2,3} = 5.3$ Hz, $J_{2,1} = 5.2$ Hz, H-2), 4.06 (1H, br dd, $J_{5,1} = 0.9$ Hz, $J_{5,6} = 2.2$ Hz, H-5), 4.02 (1H, dd, $J_{6'a,6} = 9.5$ Hz, $J_{6'a,6'b} = 10.3$ Hz, H-6′a), 3.88 (1H, dd, $J_{6'b,6'a} = 10.3$ Hz, $J_{6'b,6} = 6.2$ Hz, H-6′b), 3.76 (1H, dddd, $J_{1,2} = 5.2$ Hz, $J_{1,5} = 0.9$ Hz, $J_{1,6} = 2.1$ Hz, $J_{1,OH} = 11.3$ Hz, H-1), 3.31 (3H, s, OCH_3), 3.30 (1H, d, $J_{OH,1} = 11.3$ Hz, O*H*), 2.09 (1H, dddd, $J_{6,6'b} = 6.2$ Hz, $J_{6,6'a} = 9.5$ Hz, $J_{6,5} = 2.2$ Hz, $J_{6,1} = 2.1$ Hz, H-6), 1.56, 1.45, 1.42, 1.40 (12H, each s, 2 × $C(CH_3)_2$), 1.05 (9H, s, $C(CH_3)_3$). ^{13}C NMR (150 MHz): δ 135.6, 135.5, 133.5, 133.3, 129.7, 129.7, 127.7, 127.7, 110.5, 109.6, 98.9, 80.2, 80.0, 78.2, 75.5, 69.7, 68.1, 62.3, 56.2, 40.3, 26.8, 26.7, 25.8, 25.8, 19.2. NOE correlations: H-2–H-6; H-4′–H-3, H-5. Anal. Calcd for $C_{32}H_{46}O_8Si$ (586.78): C, 65.50; H, 7.90%. Found: C, 65.17; H, 7.98%.

2D-(2,3,5,6/4(OH))-6′-*O*-*tert*-Butyldiphenylsilyl-4,6-di-*C*-hydroxymethyl-2,3:4,4′-di-*O*-isopropylidene-5-*O*-methoxymethyl-2,3,4,5-tetrahydroxycyclohexanone (15). To a solution of compound **14** (0.876 g, 1.49 mmol) in dry CH_2Cl_2 (20 mL), Dess–Martin periodinane (1.268 g, 2.99 mmol) was added and stirred for 15 min at rt. After the disappearance of starting compound **14** on TLC with hexane–EtOAc (4:1 v/v), the reaction mixture was poured into saturated aq $NaHCO_3$ solution, extracted with $CHCl_3$, washed with brine and water, and evaporated to give ketone **15** (865 mg, 99% yield), which was purified on a column of silica gel with hexane–EtOAc (4:1 v/v). Colorless syrup; $R_f = 0.4$ (hexane–EtOAc = 4:1 v/v); $[\alpha]_D^{26}$ +17.0° (*c* 0.83, $CHCl_3$); IR (KBr, neat): ν 1732 cm^{-1} (C=O); ^1H NMR (600 MHz): δ 7.65–7.34 (10H, m, Ph*H*), 4.62, 4.54 (2H, each d, $J_{A,B} = 6.7$ Hz, CH_2OCH_3), 4.44 (1H, dd, $J_{3,2} = 6.0$ Hz, $J_{3,5} = 1.9$ Hz, H-3), 4.43, 4.35 (2H, each d, $J_{A,B} = 9.6$ Hz, H-4′), 4.40 (1H, d, $J_{2,3} = 6.0$ Hz, H-2), 4.37 (1H, dd, $J_{5,6} = 2.1$ Hz, $J_{5,3} = 1.9$ Hz, H-5), 4.01 (1H, dd, $J_{6'a,6} = 4.8$ Hz, $J_{6'a,6'b} = 11.0$ Hz, H-6′a), 3.93 (1H, dd, $J_{6'b,6'a} = 11.0$ Hz, $J_{6'b,6} = 10.3$ Hz, H-6′b), 3.30 (3H, s, OCH_3), 3.28 (1H, ddd, $J_{6,6'a} = 4.8$ Hz, $J_{6,6'b} = 10.3$ Hz, $J_{6,5} = 2.1$ Hz, H-6), 1.51, 1.50, 1.36, 1.34 (12H, each s, 2 × $C(CH_3)_2$), 1.04 (9H, s, $C(CH_3)_3$). ^{13}C NMR (150 MHz): δ 206.2, 135.5, 135.5, 134.8, 133.2, 129.8, 129.6, 127.7, 111.0, 110.8, 98.7, 82.8, 82.3, 79.2, 78.6, 69.8, 58.3, 55.7, 51.5, 26.9, 26.8, 26.8, 26.7, 26.5, 26.2, 19.2, 19.1. Anal. Calcd for $C_{32}H_{44}O_8Si$ (584.77): C, 65.73; H, 7.58%. Found. C, 65.79; H, 7.33%.

(−)-Tetrodotoxin. White powder; $R_f = 0.5$ (1-butanol–AcOH–H_2O = 2:1:1 v/v/v), $R_f = 0.6$ (pyridine–EtOAc–AcOH–H_2O = 15:9:3:6 v/v/v/v); $[\alpha]_D^{28}$ −3.75° (*c* 0.13, 3% AcOH); ^1H NMR (600 MHz, in 3% CD_3COOD/D_2O, referenced to CHD_2COOD (2.06 ppm)): δ 5.50 (d, 1H, $J = 8.9$ Hz, H-4), 4.30 (d, 1H, $J = 2.1$ Hz, H-8), 4.25 (br s, 1H, H-5), 4.09 (t, 1H, $J = 2.1$ Hz, H-7), 4.06, 4.01 (2 × d, 2H, $J = 12.4$ Hz, H-11), 3.96 (s, 1H, H-9), 2.35 (d, 1H, $J = 9.6$ Hz, H-4a). ESI-TOF-MS Calcd for $C_{11}H_{18}N_3O_8$ *m/z* $[M + H]^+$: 320.1094. Found: 320.1085.

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Supporting Information

The copies of ^1H and ^{13}C NMR (PDF). This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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18 The numbering used in all Schemes and Figures of this paper corresponds to that of tetrodotoxin.