Facile syntheses of (+)-gabosines A, D, and E†‡

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(+)-Gabosines A (**12**), D (**4**), and E (**5**), which share the same trihydroxycyclohexenone skeleton, were synthesized from enone **11** as the common intermediate. The key building block **11** was accessed by an intramolecular aldol cyclization of a diketone derived from D-glucose (**8**).

Introduction

Gabosines belong to a family of multi-hydroxylated cyclohexenones and hexanones that may be classified as pseudo- or carba-sugars (Fig. 1).[1] They have been shown to display antibiotic,[1b] anticancer,[2] and weak DNA binding properties.[1c] A total of 14 gabosines have been identified since the first isolation of gabosine C (**1**) and its crotonyl ester COTC (**2**) from *Streptomyces* strains in 1974.[1a] The structures and the absolute configurations have been established for gabosines A–G, I, L, N, and O. Syntheses of the gabosines have been achieved by the construction of the carbocyclic framework from carbohydrates[3–8] or by a Diels–Alder reaction.[9,10] Other syntheses employed starting materials with the carbocyclic ring already present,[11–16] *e.g.* (–)-quinic acid.

Construction of (–)-gabosine A (**3**) has been accomplished by a chemoenzymatic synthesis from iodobenzene[14] and an enantiospecific synthesis from (–)-quinic acid.[13] The most concise route was conducted by R. Madsen *et al.* using a ring-closing olefin metathesis as the key step from D-ribose with 13.9% overall yield in 9 steps.[7]

(+)-Gabosine D (**4**) has been synthesized by T. Shinada *et al.* from (–)-quinic acid in 11 steps with 13.3% overall yield.[13]

(+)-Gabosine E (**5**) has also been prepared from (–)-quinic acid[13] and D-ribose *via* an intramolecular nitrile-oxide cycloaddition as the key step.[3] The former synthesis, which was also achieved by T. Shinada *et al.*, afforded (+)-gabosine E (**5**) in 11 steps with 11.7% overall yield.[13]

Our previous endeavors have already furnished enantiospecific syntheses of COTC (**2**) from (–)-quinic acid,[11] as well as (–)-gabosines G (**6**) and I (**7**) from δ-D-gluconolactone *via* an intramolecular Horner–Wadsworth–Emmons olefination.[8] In this paper, the enone **11**, constructed from D-glucose (**8**) *via* an intramolecular aldol cyclization of a diketone **9**, was further elaborated to other gabosines (Scheme 1).[17,18]

The present study was inspired by the structure/chirality similarity between (+)-gabosines A (**12**), D (**4**) and E (**5**), all of which share the same trihydroxycyclohexenone framework. We recognized that the advanced intermediate **11** was well suited for their syntheses (Scheme 2).

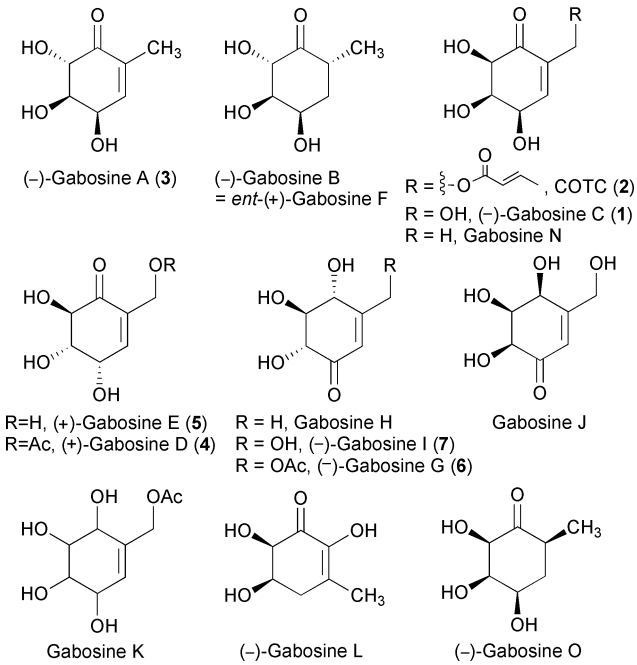
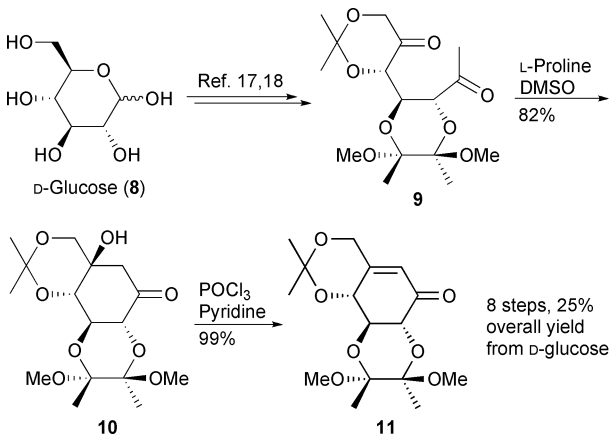


Fig. 1 The gabosine family.



Scheme 1 Preparation of enone **11** from D-glucose (**8**).[17,18]

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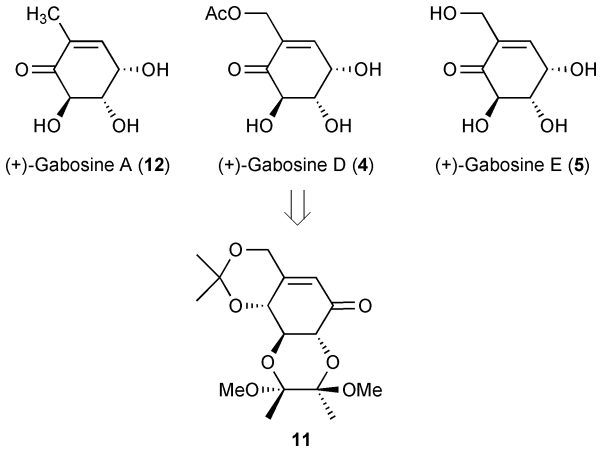
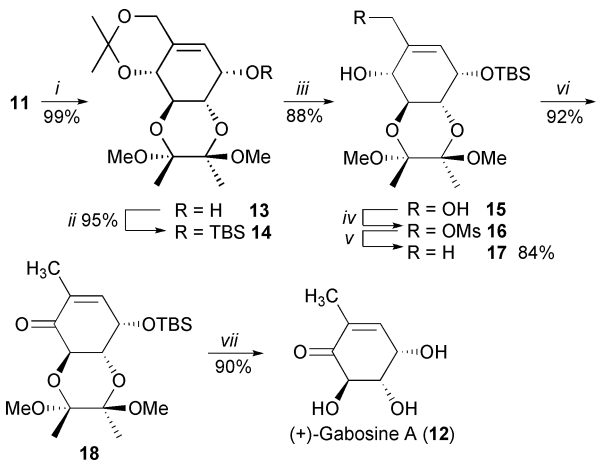
‡ Electronic supplementary information (ESI) available: General experimental; ^{1}H, ^{13}C and DEPT NMR spectra of **4**, **5**, **12**–**15** and **17**–**22**. See DOI: 10.1039/b911810a



Scheme 2 Retrosynthetic analysis.

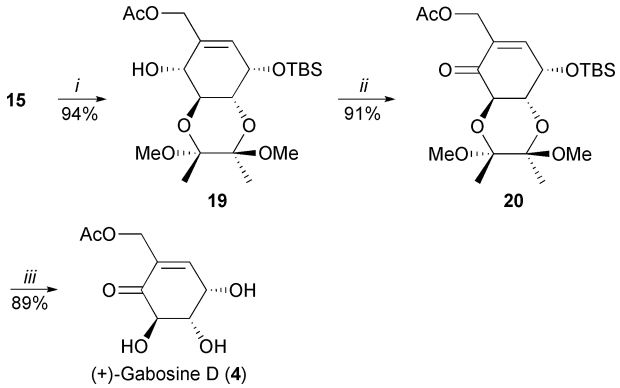
Results and discussion

The synthesis of (+)-gabosine A (**12**) from enone **11** is shown in Scheme 3. Diastereoselective 1,2-reduction of the enone **11** with K-selectride resulted in the exclusive production of α-alcohol **13**, which was protected with TBSCl and imidazole to give silyl ether **14**. The isopropylidene blocking group in **14** was selectively removed with 80% aqueous acetic acid to afford diol **15**. Regioselective mesylation of the primary hydroxy group[19] in diol **15** was realized with methanesulfonyl chloride and 2,4,6-collidine at −78 °C to generate mesylate **16** which was displaced with Super hydride® ($LiEt_3BH$)[20] to give alcohol **17** in 84% overall yield from the diol **15**. PDC oxidation of the alcohol **17** in CH_2Cl_2 afforded enone **18** in a high yield. (+)-Gabosine A (**12**), produced after acid hydrolysis of **18**, was thus constructed from D-glucose (**8**) in 15 steps with 14.4% overall yield with the optical rotation, ^1H and ^{13}C NMR spectral data in accord with the literature values.[1b]



Scheme 3 Synthesis of (+)-gabosine A (**12**). *Reagents and conditions*: *i* K-selectride, THF, −78 °C; *ii* TBSCl, imidazole, DMF; *iii* 80% AcOH; *iv* MsCl, 2,4,6-collidine, CH_2Cl_2, −78 °C; *v* $LiEt_3BH$, THF, −78 °C; *vi* PDC, 3Å MS, CH_2Cl_2; *vii* TFA, H_2O, CH_2Cl_2.

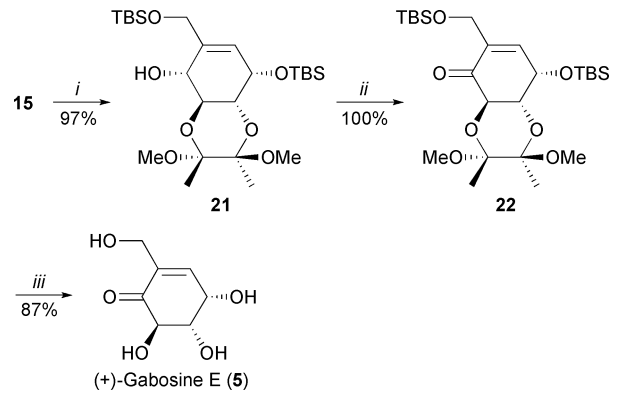
The synthesis of (+)-gabosine D (**4**) is shown in Scheme 4. The primary alcohol in diol **15** was selectively masked by acetyl chloride and 2,4,6-collidine[21] at −30 °C to give acetate **19** which



Scheme 4 Synthesis of (+)-gabosine D (**4**). *Reagents and conditions*: *i* AcCl, 2,4,6-collidine, CH_2Cl_2, −78 °C; *ii* PDC, 3Å MS, CH_2Cl_2; *iii* TFA, H_2O, CH_2Cl_2.

then underwent PDC oxidation to produce enone **20**. Acid hydrolysis of enone **20** then furnished (+)-gabosine D (**4**) without incident. The number of steps and the overall yield for the synthesis of (+)-gabosine D (**4**) from D-glucose (**8**) was 14 and 15.8%, respectively. The physical constant (specific rotation) and the spectral data (^1H and ^{13}C NMR) of synthetic (+)-gabosine D (**4**) were consistent with those reported for the natural compound.[1b]

Scheme 5 shows the synthesis of (+)-gabosine E (**5**). Regioselective silylation of the primary alcohol in diol **15** gave disilyl ether **21** which was oxidized with PDC to generate enone **22**. Acid hydrolysis of the enone **22** provided (+)-gabosine E (**5**) in 87% yield. (+)-Gabosine E (**5**) was thus harvested from D-glucose (**8**) in 14 steps with 17.5% overall yield. The specific rotation and spectral data (^1H and ^{13}C NMR) of synthetic **5** were in accord with those reported previously.[1b]



Scheme 5 Synthesis of (+)-gabosine E (**5**). *Reagents and conditions*: *i* TBSCl, imidazole, CH_2Cl_2; *ii* PDC, 3Å MS, CH_2Cl_2; *iii* TFA, H_2O, CH_2Cl_2.

Conclusions

In summary, the syntheses of (+)-gabosines A (**12**), D (**4**) and E (**5**) have been accomplished from cheap starting material D-glucose (**8**) in better overall yields than those reported previously. The common intermediate enone **11**, readily available from D-glucose (**8**), demonstrates the versatility of intramolecular direct aldol cyclization of carbohydrates in the enantiospecific synthesis of biologically interesting polyhydroxylated carbocyclic natural

products. Application of this strategy to the construction of other cyclohexa(e)noid natural products is in progress.

Experimental

General experimental procedures are described in the ESI‡

(+)-Gabosine D (4)

To a solution of the enone **20** (54.2 mg, 0.122 mmol) in CH_2Cl_2 (3 mL) were added trifluoroacetic acid (TFA) (0.2 mL) and H_2O (0.05 mL) and the mixture was stirred at room temperature for 20 h. The solvent was removed under reduced pressure and flash chromatography ($CHCl_3$:MeOH, 20:1) of the residue afforded (+)-gabosine D (**4**) (23.4 mg, 89%) as a colorless oil; $[\alpha]_D^{20}$ +71.2 (*c* 0.54 in MeOH) {lit.[1b] $[\alpha]_D^{20}$ +86.2 (*c* 1.0 in MeOH)}; R_f 0.5 (^{t}BuOH:AcOH:H_2O 4:1:5, upper phase);[1b] δ_H (300 MHz; CD_3OD) 2.06 (3H, s, Me), 3.78 (1H, dd, $J = 9.6$, 3.9 Hz), 4.32 (1H, d, $J = 9.6$ Hz), 4.48 (1H, t, $J = 4.2$ Hz), 4.73 (2H, d, $J = 0.9$ Hz), 6.91–6.93 (1H, m); δ_C (75 MHz; CD_3OD) 20.6 (CH_3), 61.6 (CH_2), 67.0 (CH), 73.8 (CH), 75.1 (CH), 135.1 (C), 144.8 (CH), 172.2 (C), 198.8 (C); HRMS (ESI, $[M+Na]^+$) Found 239.0524, Calcd for $C_9H_{12}O_6$ 239.0526; *m*/*z* (ESI): 239 ($[M+Na]^+$, 100%).

(+)-Gabosine E (5)

To a solution of the enone **22** (99.7 mg, 0.193 mmol) in CH_2Cl_2 (3 mL) were added trifluoroacetic acid (TFA) (1 mL) and H_2O (0.05 mL) and the mixture was stirred at room temperature for 19 h. The solvent was removed under reduced pressure and flash chromatography ($CHCl_3$:MeOH, 10:1) of the residue afforded (+)-gabosine E (**5**) (29 mg, 87%) as a colorless oil; $[\alpha]_D^{20}$ +136 (*c* 0.46 in MeOH) {lit.[1b] $[\alpha]_D^{20}$ +148 (*c* 0.95 in MeOH)}; R_f 0.33 (^{t}BuOH:AcOH:H_2O 4:1:5, upper phase);[1b] δ_H (300 MHz; CD_3OD) 3.76 (1H, dd, $J = 9.9$, 3.9 Hz), 4.20 (1H, d, $J = 15.9$ Hz), 4.26 (1H, d, $J = 15.3$ Hz), 4.34 (1H, d, $J = 9.9$ Hz), 4.81 (1H, t, $J = 4.5$ Hz), 6.91 (1H, dt, $J = 5.4$, 1.8 Hz); δ_C (75 MHz; CD_3OD) 59.5 (CH_2), 67.1 (CH), 73.9 (CH), 75.1 (CH), 139.9 (C), 141.8 (CH), 199.7 (C); HRMS (ESI, $[M+Na]^+$) Found 197.0425, Calcd for $C_7H_{10}O_5$ 197.0420; *m*/*z* (ESI): 197 ($[M+Na]^+$, 100%).

(+)-Gabosine A (12)

To a solution of the enone **18** (36.2 mg, 0.0936 mmol) in CH_2Cl_2 (3 mL) were added trifluoroacetic acid (TFA) (0.2 mL) and H_2O (0.05 mL) and the mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure and flash chromatography ($CHCl_3$:MeOH, 20:1) of the residue afforded (+)-gabosine A (**12**) (13.3 mg, 90%) as a colorless oil; $[\alpha]_D^{20}$ +146 (*c* 0.64 in MeOH) {lit.[1b] enantiomer of **12** had $[\alpha]_D^{20}$ −132 (*c* 1.0 in MeOH)}; R_f 0.51 (^{t}BuOH:AcOH:H_2O 4:1:5, upper phase);[1b] δ_H (300 MHz; CD_3OD) 1.80 (3H, d, $J = 0.9$ Hz, Me), 3.72 (1H, dd, $J = 9.9$, 3.9 Hz), 4.31 (1H, d, $J = 9.9$ Hz), 4.38 (1H, t, $J = 4.8$ Hz), 6.73–6.75 (1H, m); δ_C (75 MHz; CD_3OD) 15.6 (CH_3), 67.4 (CH), 73.9 (CH), 75.1 (CH), 136.9 (C), 143.0 (CH), 200.4 (C); HRMS (ESI, $[M+Na]^+$) Found 181.0477, Calcd for $C_7H_{10}O_4$ 181.0471; *m*/*z* (ESI): 181 ($[M+Na]^+$, 100%).

(1*S*,2*S*,3*S*,4*R*)-2,3-[(2*R*,3*R*)-2,3-Dimethoxybutan-2,3-dioxy]-5-(hydroxymethyl)-4,6-di-*O*-isopropylidene-5-cyclohexene-1,2,3,4-tetraol 13. To a solution of the enone **11** (2.01 g, 6.12 mmol) in THF (35 mL) at −78 °C was added 1M THF solution of K-selectride (9 mL, 9 mmol) over 30 min and the mixture was stirred for 12 h at room temperature. The reaction was quenched with saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$ and filtered. Concentration of the filtrate followed by flash chromatography (hexane:EtOAc, 1:1) gave α-alcohol **13** (2 g, 99%) as a colorless oil; $[\alpha]_D^{20}$ –118 (*c* 1.51 in $CHCl_3$); $R_f = 0.33$ (hexane:EtOAc, 1:1); ν_{max} (film)/cm^{-1} 3469, 2994, 2950, 1645, 1455, 1376, 1140 and 754; δ_H (300 MHz; CD_3OD) 1.33 (6H, s, 2 × Me), 1.38 (3H, s, Me), 1.49 (3H, s, Me), 3.27 (6H, s, 2 × Me), 3.62 (1H, dd, $J = 11.1$, 4.2 Hz), 4.06 (1H, dd, $J = 11.1$, 8.1 Hz), 4.14–4.22 (2H, m), 4.38–4.43 (2H, m), 5.59 (1H, d, $J = 4.2$ Hz); δ_C (75 MHz; $CDCl_3$) 18.1 (CH_3), 18.2 (CH_3), 20.8 (CH_3), 28.3 (CH_3), 48.4 (CH_3), 48.6 (CH_3), 63.2 (CH_2), 65.6 (CH), 67.2 (CH), 68.3 (CH), 70.3 (CH), 99.4 (C), 99.7 (C), 100.1 (C), 119.6 (CH), 136.8 (C); HRMS (ESI, $[M+Na]^+$) Found: 353.1579, Calcd for $C_{16}H_{26}O_7$ 353.1571; *m*/*z* (ESI): 353 ($[M+Na]^+$, 100%).

(1*S*,2*R*,3*S*,4*R*)-1-*O*-*tert*-Butyldimethylsilyl-5-(hydroxymethyl)-4,6-di-*O*-isopropylidene-2,3-[(2*R*,3*R*)-2,3-dimethoxybutan-2,3-dioxy]-5-cyclohexene-1,2,3,4-tetraol 14. A solution of the alcohol **13** (506 mg, 1.53 mmol), imidazole (312 mg, 4.58 mmol) and *tert*-butyl dimethyl silyl chloride (TBSCl) (345 mg, 2.30 mmol) in dry DMF (5 mL) was stirred at room temperature for 24 h. The mixture was quenched with saturated $NaHCO_3$ solution and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et_2O, 1:1) to afford silyl ether **14** (649 mg, 95%) as a white solid; mp 83–85 °C (from EtOAc); $[\alpha]_D^{20}$–46.9 (*c* 0.79 in $CHCl_3$); R_f 0.5 (hexane:Et_2O, 1:1); ν_{max} (film)/cm^{-1} 2990, 2947, 1463, 1374, 1131 and 836; δ_H (300 MHz; $CDCl_3$) 0.07 (3H, s, Me), 0.09 (3H, s, Me), 0.89 (9H, s, 3 × Me), 1.28 (3H, s, Me), 1.30 (3H, s, Me), 1.40 (3H, s, Me), 1.50 (3H, s, Me), 3.24 (6H, s, 2 × Me), 3.48 (1H, dd, $J = 10.8$, 3.6 Hz), 4.06–4.14 (2H, m), 4.17 (1H, t, $J = 4.2$ Hz), 4.37–4.42 (2H, m), 5.44 (1H, d, $J = 5.1$ Hz); δ_C (75 MHz; $CDCl_3$) –4.2 (CH_3), –4.1 (CH_3), 18.1 (CH_3), 18.3 (CH_3), 18.9 (C), 20.6 (CH_3), 26.3 (CH_3), 28.7 (CH_3), 48.2 (CH_3), 48.3 (CH_3), 63.5 (CH_2), 66.7 (CH), 67.4 (CH), 68.5 (CH), 71.0 (CH), 98.9 (C), 99.6 (C), 121.6 (CH), 133.9 (C); HRMS (ESI, $[M+Na]^+$) Found 467.2440, Calcd for $C_{22}H_{40}O_7Si_1$ 467.2436; *m*/*z* (ESI): 467 ($[M+Na]^+$, 100%).

(1*S*,2*R*,3*S*,4*R*)-1-*O*-*tert*-Butyldimethylsilyl-5-(hydroxymethyl)-2,3-[(2*R*,3*R*)-2,3-dimethoxybutan-2,3-dioxy]-5-cyclohexene-1,2,3,4-tetraol 15. A solution of the silyl ether **14** (361 mg, 0.812 mmol) in 80% aqueous AcOH (5 mL) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc, 1:1) to afford diol **15** (289 mg, 88%) as a white solid; mp 123–125 °C (from EtOAc); $[\alpha]_D^{20}$ –37.2 (*c* 0.46 in $CHCl_3$); R_f 0.28 (hexane:EtOAc, 1:1); ν_{max} (film)/cm^{-1} 3474, 2928, 2854, 1645, 1462, 1126 and 1037; δ_H (300 MHz; $CDCl_3$) 0.07 (3H, s, Me), 0.10 (3H, s, Me), 0.88 (9H, s, 3 × Me), 1.28 (3H, s, Me), 1.31 (3H, s, Me, 2.33 (1H, brs), 2.75 (1H, brs), 3.24 (3H, s, Me), 3.26 (3H, s, Me), 3.43 (1H, dd, $J = 11.1$, 3.9 Hz), 4.06 (1H, dd, $J = 11.1$, 8.1 Hz), 4.18–4.28 (3H, m), 4.34 (1H, d, $J = 8.1$ Hz), 5.70 (1H, d, $J = 4.5$ Hz); δ_C (75 MHz; $CDCl_3$) –4.2 (CH_3), –4.1 (CH_3), 18.1 (CH_3), 18.3

(CH_3), 18.8 (C), 26.3 (CH_3), 48.2 (CH_3), 48.4 (CH_3), 64.7 (CH_2), 66.5 (CH), 68.4 (CH), 69.8 (CH), 72.7 (CH), 99.1 (C), 99.6 (C), 125.3 (CH), 139.8 (C); HRMS (ESI, $[M+Na]^+$) Found 427.2119, Calcd for $C_{19}H_{36}O_7Si_1$ 427.2123; *m/z* (ESI): 427 ($[M+Na]^+$, 100%).

(1*S*,2*R*,3*S*,4*R*)-1-*O*-*tert*-Butyldimethylsilyl-2,3-[(2*R*,3*R*)-2,3-dimethoxybutan-2,3-dioxy]-5-methyl-5-cyclohexene-1,2,3,4-tetraol 17. To a solution of the diol **15** (55.8 mg, 0.138 mmol) and 2,4,6-collidine (0.05 mL, 0.378 mmol) in dry CH_2Cl_2 (4 mL) at −78 °C was added methanesulfonyl chloride (MsCl) (0.012 mL, 0.155 mmol) slowly. The resultant solution was allowed to warm to 0 °C slowly. The reaction mixture was stirred for 6 h at 0 °C and then quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to afford **16** as a colorless oil. To a solution of **16** in THF (5 mL) was added a 1M THF solution of $LiEt_3BH$ (1.2 mL, 1.2 mmol) dropwise at −30 °C under N_2. The reaction mixture was stirred for 6 h at room temperature. Water was then added slowly at 0 °C to destroy the excess of hydride and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et_2O, 3:1) to afford alkene **17** (45 mg, 84%) as a white solid; mp 91–92 °C (from EtOAc); $[\alpha]_D^{20}$ −40.4 (*c* 0.6 in $CHCl_3$); R_f 0.53 (hexane: EtOAc, 2:1); ν_{max} (film)/cm^{-1} 3457, 2952, 2891, 1460, 1085 and 834; δ_H (300 MHz; $CDCl_3$) 0.06 (3H, s, Me), 0.08 (3H, s, Me), 0.88 (9H, s, 3 × Me), 1.28 (3H, s, Me), 1.31 (3H, s, Me), 1.79 (3H, s, Me), 3.24 (3H, s, Me), 3.25 (3H, s, Me), 3.43 (1H, dd, J = 10.2, 3.6 Hz), 3.97–4.07 (2H, m), 4.11 (1H, t, J = 4.8 Hz), 5.46 (1H, dt, J = 5.7, 1.5 Hz); δ_C (75 MHz; $CDCl_3$) −4.2 (CH_3), −4.1 (CH_3), 18.1 (CH_3), 18.3 (CH_3), 18.8 (C), 19.1 (CH_3), 26.3 (CH_3), 48.1 (CH_3), 48.3 (CH_3), 66.8 (CH), 68.6 (CH), 70.0 (CH), 73.6 (CH), 99.0 (C), 99.5 (C), 124.4 (C), 137.9 (CH); HRMS (ESI, $[M+Na]^+$) Found 411.2177, Calcd for $C_{19}H_{36}O_6Si_1$ 411.2173; *m/z* (ESI): 411 ($[M+Na]^+$, 100%).

(4*S*,5*R*,6*R*)-4-*O*-*tert*-Butyldimethylsilyl-5,6-[(2*R*,3*R*)-2,3-dimethoxybutan-2,3-dioxy]-2-methyl-2-cyclohexen-1-one 18. A mixture of 3Å molecular sieves (*ca.* 82 mg) and pyridinium dichromate (PDC) (72 mg, 0.191 mmol) was added to a solution of the alcohol **17** (50.1 mg, 0.129 mmol) in dry CH_2Cl_2 (3 mL) under N_2 at 0 °C. The mixture was stirred for 12 h at room temperature. The mixture was then filtered through a pad of celite and the residue was washed with EtOAc until no product was observed in the eluent (checked with TLC). Concentration of the filtrate followed by flash chromatography (hexane:Et_2O, 5:1) yielded enone **18** (45.8 mg, 92%) as a white solid; mp 79–80 °C (from EtOAc); $[\alpha]_D^{20}$ +11.2 (*c* 1.45 in $CHCl_3$); R_f 0.24 (hexane:Et_2O, 3:1); ν_{max} (film)/cm^{-1} 2952, 2933, 1703, 1462, 1381, 1131 and 980; δ_H (300 MHz; $CDCl_3$) 0.10 (3H, s, Me), 0.14 (3H, s, Me), 0.89 (9H, s, 3 × Me), 1.29 (3H, s, Me), 1.36 (3H, s, Me), 1.80 (3H, d, J = 0.6 Hz, Me), 3.21 (3H, s, Me), 3.24 (3H, s, Me), 3.82 (1H, dd, J = 10.8, 3.3 Hz), 4.35 (1H, dd, J = 5.7, 3.3 Hz), 4.73 (1H, d, J = 11.1 Hz), 6.53 (1H, dd, J = 6, 1.2 Hz); δ_C (75 MHz; $CDCl_3$) −4.3 (CH_3), −4.2 (CH_3), 16.1 (CH_3), 18.0 (CH_3), 18.1 (CH_3), 18.8 (C), 26.2 (CH_3), 48.3 (CH_3), 48.5 (CH_3), 66.3 (CH), 69.2 (CH), 69.9 (CH), 99.6 (C), 100.1 (C), 136.6 (C), 140.3 (CH), 195.6 (C); HRMS (ESI, $[M+Na]^+$) Found 409.2013, Calcd for $C_{19}H_{34}O_6Si_1$ 409.2017; *m/z* (ESI): 409 ($[M+Na]^+$, 100%).

(1*S*,2*R*,3*S*,4*R*)-5-Acetoxymethyl-1-*O*-*tert*-butyldimethylsilyl-2,3-[(2*R*,3*R*)-2,3-dimethoxybutan-2,3-dioxy]-5-cyclohexene-1,2,3,4-tetraol 19. To a solution of the diol **15** (87.6 mg, 0.216 mmol) and 2,4,6-collidine (0.086 mL, 0.649 mmol) in dry CH_2Cl_2 (3 mL) at −78 °C was added acetyl chloride (AcCl) (0.018 mL, 0.253 mmol) slowly. The reaction mixture was stirred for 18 h at −78 °C and quenched with water (3 mL). The resultant solution was allowed to warm to room temperature. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were then washed with cold 1 N HCl (2 × 5 mL), cold deionized water (5 mL) and cold diluted $NaHCO_3$ (5 mL). The organic layer was washed with brine (2 × 5 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography (hexane:Et_2O, 1:1) gave acetate **19** (90.4 mg, 94%) as a colorless oil; $[\alpha]_D^{20}$ −44.2 (*c* 0.71 in $CHCl_3$); R_f 0.66 (hexane:EtOAc, 1:1); ν_{max} (film)/cm^{-1} 3486, 2948, 2892, 1742, 1130 and 835; δ_H (300 MHz; $CDCl_3$) 0.06 (3H, s, Me), 0.09 (3H, s, Me), 0.87 (9H, s, 3 × Me), 1.28 (3H, s, Me), 1.31 (3H, s, Me), 2.06 (3H, s, Me), 2.76 (1H, brs), 3.24 (3H, s, Me), 3.26 (3H, s, Me), 3.46 (1H, dd, J = 10.8, 3.6 Hz), 4.06 (1H, dd, J = 10.8, 8.1 Hz), 4.17–4.20 (2H, m), 4.48 (1H, d, J = 12.9 Hz), 4.90 (1H, d, J = 12.6 Hz), 5.77 (1H, d, J = 5.1 Hz); δ_C (75 MHz; $CDCl_3$) −4.3 (CH_3), −4.2 (CH_3), 18.1 (CH_3), 18.3 (CH_3), 18.8 (C), 21.4 (CH_3), 26.2 (CH_3), 48.1 (CH_3), 48.4 (CH_3), 64.6 (CH_2), 66.3 (CH), 68.3 (CH), 69.7 (CH), 70.7 (CH), 99.1 (C), 99.6 (C), 127.9 (CH), 136.6 (C), 171.6 (C); HRMS (ESI, $[M+Na]^+$) Found 469.2230, Calcd for $C_{21}H_{38}O_8Si_1$ 469.2228; *m/z* (ESI): 469 ($[M+Na]^+$, 100%).

(4*S*,5*R*,6*R*)-2-Acetoxymethyl-4-*O*-*tert*-butyldimethylsilyl-5,6-[(2*R*,3*R*)-2,3-dimethoxybutan-2,3-dioxy]-2-cyclohexen-1-one 20. A mixture of 3Å molecular sieves (*ca.* 121 mg) and pyridinium dichromate (PDC) (93 mg, 0.247 mmol) was added to a solution of the alcohol **19** (73.9 mg, 0.165 mmol) in dry CH_2Cl_2 (5 mL) under N_2 at 0 °C. The mixture was stirred for 24 h at room temperature. The mixture was then filtered through a pad of celite and the residue was washed with EtOAc until no product was observed in the eluent (checked with TLC). Concentration of the filtrate followed by flash chromatography (hexane:Et_2O, 1:1) yielded enone **20** (66.5 mg, 91%) as a colorless oil; $[\alpha]_D^{20}$ −11.6 (*c* 0.51 in $CHCl_3$); R_f 0.34 (hexane: Et_2O, 1:1); ν_{max} (film)/cm^{-1} 2932, 2855, 1764, 1704, 1377, 1124 and 835; δ_H (300 MHz; $CDCl_3$) 0.12 (3H, s, Me), 0.16 (3H, s, Me), 0.89 (9H, s, 3 × Me), 1.30 (3H, s, Me), 1.37 (3H, s, Me), 2.08 (3H, s, Me), 3.22 (3H, s, Me), 3.26 (3H, s, Me), 3.86 (1H, dd, J = 11.1, 3.6 Hz), 4.44 (1H, dd, J = 5.7, 3.6 Hz), 4.70–4.81 (3H, m), 6.74 (1H, d, J = 6 Hz); δ_C (75 MHz; $CDCl_3$) −4.3 (CH_3), −4.2 (CH_3), 17.9 (CH_3), 18.0 (CH_3), 18.8 (C), 21.3 (CH_3), 26.2 (CH_3), 48.4 (CH_3), 48.6 (CH_3), 61.0 (CH_2), 65.9 (CH), 69.0 (CH), 69.8 (CH), 99.8 (C), 100.2 (C), 134.9 (C), 142.0 (CH), 170.9 (C), 193.9 (C); HRMS (ESI, $[M+Na]^+$) Found 467.2078, Calcd for $C_{21}H_{36}O_8Si_1$ 467.2072; *m/z* (ESI): 467 ($[M+Na]^+$, 100%).

(1*S*,2*R*,3*S*,4*R*)-1-*O*-*tert*-Butyldimethylsilyl-5-(*tert*-butyldimethylsilyloxymethyl)-2,3-[(2*R*,3*R*)-2,3-dimethoxybutan-2,3-dioxy]-5-cyclohexene-1,2,3,4-tetraol 21. A solution of the diol **15** (102 mg, 0.252 mmol), imidazole (51.2 mg, 0.752 mmol) and *tert*-butyl dimethyl silyl chloride (TBSCl) (46.1 mg, 0.306 mmol) in

dry CH_2Cl_2 (3 mL) was stirred at room temperature for 12 h. The mixture was quenched with saturated $NaHCO_3$ solution and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (hexane:Et_2O, 4:1) to afford silyl ether **21** (127 mg, 97%) as a colorless oil; $[\alpha]_D^{20}$ –32.1 (*c* 0.53 in $CHCl_3$); R_f 0.21 (hexane:Et_2O, 3:1); ν_{max} (film)/cm^{-1} 3474, 2951, 2933, 1464, 1130 and 840; δ_H (300 MHz; $CDCl_3$) 0.06 (3H, s, Me), 0.07 (3H, s, 2 × Me), 0.09 (3H, s, Me), 0.88 (9H, s, 3 × Me), 0.90 (9H, s, 3 × Me), 1.28 (3H, s, Me), 1.32 (3H, s, Me), 2.67 (1H, brs), 3.24 (3H, s, Me), 3.26 (3H, s, Me), 3.45 (1H, dd, J = 11.1, 3.6 Hz), 4.07 (1H, dd, J = 11.1, 8.1 Hz), 4.18 (1H, t, J = 4.2 Hz), 4.22–4.35 (3H, m), 5.69–5.72 (1H, m); δ_C (75 MHz; $CDCl_3$) –4.9 (CH_3), –4.3 (CH_3), –4.1 (CH_3), 18.1 (CH_3), 18.3 (CH_3), 18.8 (C), 26.2 (CH_3), 26.3 (CH_3), 48.1 (CH_3), 48.3 (CH_3), 64.1 (CH_2), 66.4 (CH), 68.5 (CH), 69.9 (CH), 71.9 (CH), 99.0 (C), 99.6 (C), 123.1 (CH), 140.5 (C); HRMS (ESI, $[M+Na]^+$) Found 541.2992, Calcd for $C_{25}H_{50}O_7Si_2$ 541.2987; *m*/*z* (ESI): 541 ($[M+Na]^+$, 100%).

(4*S*,5*R*,6*R*)-4-*O*-*tert*-Butyldimethylsilyl-2-(*tert*-butyldimethylsilyloxymethyl)-5,6-[(2*R*,3*R*)-2,3-dimethoxybutan-2,3-dioxy]-2-cyclohexen-1-one 22. A mixture of 3Å molecular sieves (*ca.* 132 mg) and pyridinium dichromate (PDC) (127 mg, 0.338 mmol) was added to a solution of the alcohol **21** (117 mg, 0.226 mmol) in dry CH_2Cl_2 (3 mL) under N_2 at 0 °C. The mixture was stirred for 3 h at room temperature. The mixture was then filtered through a pad of celite and the residue was washed with EtOAc until no product was observed in the eluent (checked with TLC). Concentration of the filtrate followed by flash chromatography (hexane:Et_2O, 4:1) yielded enone **22** (116 mg, 100%) as a colorless oil; $[\alpha]_D^{20}$ +3.6 (*c* 0.89 in $CHCl_3$); R_f 0.33 (hexane:Et_2O, 3:1); ν_{max} (film)/cm^{-1} 2951, 2933, 1700, 1464, 1382, 1126 and 840; δ_H (300 MHz; $CDCl_3$) 0.06 (3H, s, Me), 0.07 (3H, s, Me), 0.12 (3H, s, Me), 0.15 (3H, s, Me), 0.89 (9H, s, 3 × Me), 0.90 (9H, s, 3 × Me), 1.29 (3H, s, Me), 1.37 (3H, s, Me), 3.22 (3H, s, Me), 3.25 (3H, s, Me), 3.85 (1H, dd, J = 10.8, 3.3 Hz), 4.29 (1H, dd, J = 16.2, 1.8 Hz), 4.37–4.47 (2H, m), 4.76 (1H, d, J = 10.8 Hz), 6.81 (1H, dt, J = 6, 2.1 Hz); δ_C (75 MHz; $CDCl_3$) –4.9 (CH_3), –4.9 (CH_3), –4.3 (CH_3), –4.2 (CH_3), 18.0 (CH_3), 18.1 (CH_3), 18.7 (C), 18.8 (C), 26.1 (CH_3), 26.3 (CH_3), 48.3 (CH_3), 48.5 (CH_3), 60.0 (CH_2), 65.8 (CH), 69.3 (CH), 70.0 (CH), 99.7 (C), 100.2 (C), 138.7 (CH), 139.4 (C), 194.9 (C); HRMS (ESI, $[M+Na]^+$) Found 539.2835, Calcd for $C_{25}H_{48}O_7Si_2$ 539.2831; *m*/*z* (ESI): 539 ($[M+Na]^+$, 100%).

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