Formal Synthesis of (+)-Grandisol from Levoglucosenone

Koji OKANO,* Takashi EBATA, Koshi KOSEKI, Hiroshi KAWAKAMI, Katsuya MATSUMOTO and Hajime MATSUSHITA

Life Science Research Laboratory, Japan Tobacco Inc., 6–2 Umegaoka, Midori-ku, Yokohama, Kanagawa 227, Japan. Received October 20, 1992

(+)-Grandisol, which is a component of the male-produced pheromone of the boll weevil, *Anthonomus grandis*, was synthesized from levoglucosenone. The key steps in the synthesis are the intramolecular diastereoselective four-membered ring construction and the Baeyer–Villiger oxidation. The 17-step procedure led to a known synthetic intermediate of (+)-grandisol.

Keywords grandisol; levoglucosenone; pheromone; four-membered ring

The use of chiral building blocks is one of the most widely used methods for the synthesis of natural products. Levoglucosenone (**1**, 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose)[1] is a well-known pyrolytic product of cellulose. Its unique structure, featuring a rigid and highly functionalized bicyclic system, inspired us to use it for the synthesis of chiral compounds. We have already synthesized some natural products starting from levoglucosenone[2] as shown in Fig. 1.

As another demonstration of its usefulness, we describe here a formal synthesis of (+)-grandisol [**2**, (1*R*,2*S*)-(+)-2-isopropenyl-1-methylcyclobutane ethanol)].[3] (+)-Grandisol is one of the components of the male-produced pheromone of the boll weevil, *Anthonomus grandis*, an important pest of cotton crops in the south of the U.S.A. (Fig. 2). Because of its biological activity and unique structure, many synthetic studies have been reported.[4]

Our synthetic plan is illustrated in Chart 1. Introduction of a methyl group into the C-4 position of levoglucosenone would afford the enone (**5**). The four-membered ring construction at the C-3, 4 positions of **5** should take place from the bottom of the pyranone ring because of the steric hindrance of the 1,6-anhydro bridge, leading to **13**. The Baeyer–Villiger oxidation[5] of **13** would give the lactone (**14**). Finally, introduction of dimethyl groups into **14** and removal of the unnecessary secondary hydroxyl group would afford the known synthetic intermediate (**19**).[6]

The practical synthesis is as follows (Chart 2): the thiophenyl ether (**3**) was prepared by the reported procedure[7] from levoglucosenone. The oxidation of **3** with *N*-chlorosuccinimide (NCS) in CCl_4 afforded the enone (**4**) in 95% yield. This enone was treated with Me_2CuLi in tetrahydrofuran (THF) at −78 °C. The major product (**5**) was obtained in 62% yield along with the dimethyl compound.

Although various conditions of [2+2]cycloaddition, for example, dichloroketene, ketene dithioacetal with Lewis

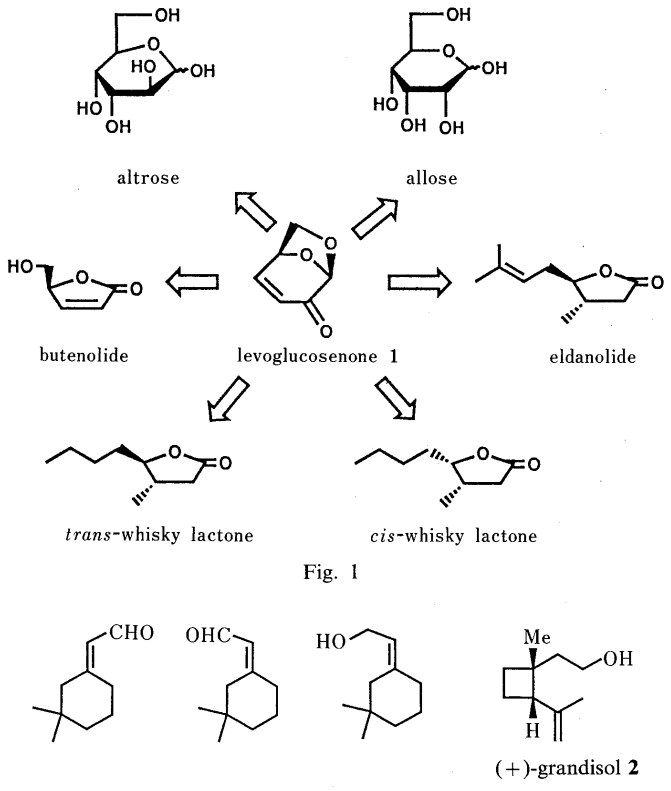


Fig. 1

Fig. 2. Sex Pheromone Complex (Grandlure)

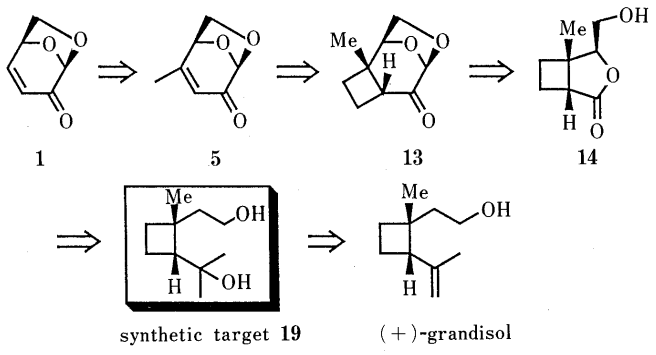


Chart 1

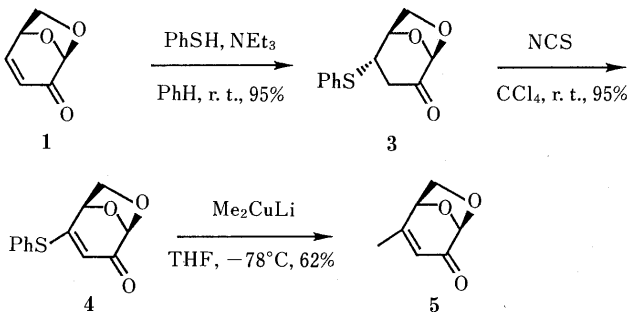


Chart 2

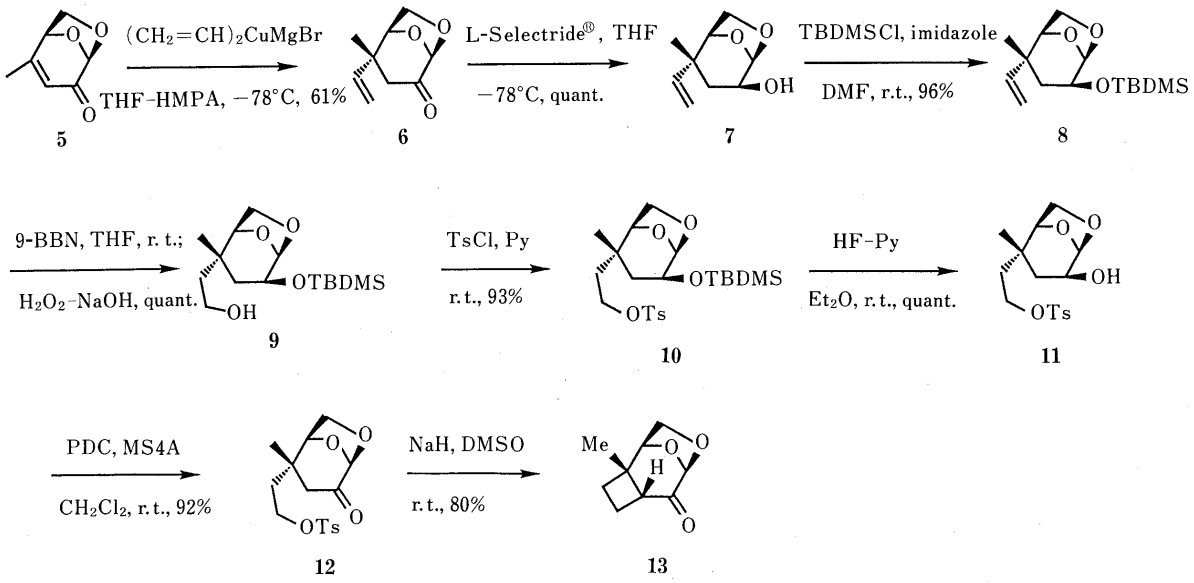


Chart 3

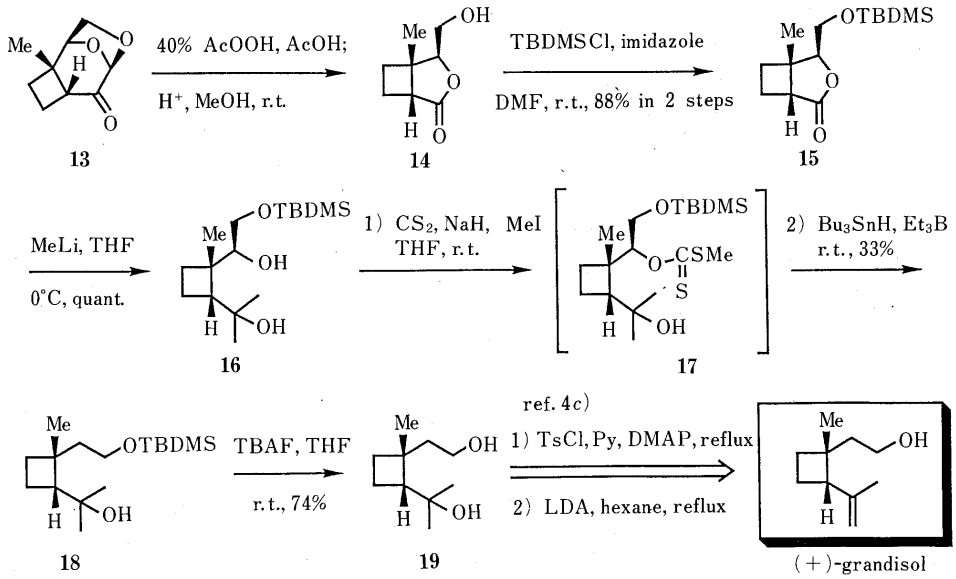
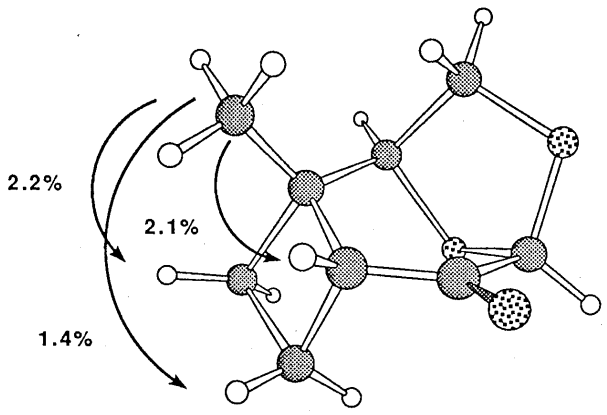


Chart 4

acid and so on, were examined, they did not afford the desired four-membered ring product. The next approach to form the cyclobutane ring was the intramolecular route (Chart 3). Conjugate addition of the divinyl cuprate in THF–hexamethylphosphoramide (HMPA) to the enone **5** gave **6** in 61% yield as a single product. The carbonyl group of **6** was reduced with L-Selectride® in THF at −78 °C to give the alcohol (**7**) in 99% yield as a crystalline product. The hydroxy group of **7** was protected with a *tert*-butyl dimethylsilyl (TBDMS) group to give **8** in 96% yield. The hydroboration of the vinyl group of **8** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidative work-up gave the alcohol (**9**) in quantitative yield. Treatment of **9** with *p*-toluenesulfonyl chloride (TsCl) in pyridine afforded the tosylate (**10**) in 93% yield. The silyl protective group of **10** was deprotected with HF–pyridine complex in ether to give the alcohol (**11**) in 96% yield, and this was oxidized with pyridinium dichromate (PDC) in



NOE analysis

Fig. 3

CH_2Cl_2 to give the keto-tosylate (**12**) in 92% yield. The four-membered ring construction was accomplished by treatment of **12** with NaH in dimethyl sulfoxide (DMSO) to afford **13** in 80% yield. The stereochemistry of the ring junction was confirmed by nuclear Overhauser effect (NOE) analysis of **13** and the result is shown in Fig. 3.

The transformation reaction of the levoglucosenone skeleton to the γ-lactone skeleton was well studied by our group[5] (Chart 4). The Baeyer–Villiger oxidation of **13** with 40% AcOOH in AcOH gave the crude lactone (**14**), which was contaminated with dimethylsulfone derived from dimethylsulfide used for destroying excess peracid. The hydroxyl group of **14** was protected with a TBDMS group to give the silyl ether (**15**) in 88% yield in two steps. Compound **15** was treated with MeLi in ether to afford the diol (**16**) in quantitative yield. The secondary hydroxyl group of **16** was removed by Oshima's method.[8] Compound **16** was converted to the dithioester (**17**) by treatment with NaH, CS_2 and MeI in THF, and **17** was subjected to the next reaction without purification. Treatment of **17** with n-Bu_3SnH and Et_3B at room temperature afforded the dehydroxylated compound (**18**) in 33% yield in two steps. Deprotection of **18** with tetrabutylammonium fluoride (TBAF) in THF gave the alcohol (**19**) in 74% yield. The spectral data for **19** are identical to the reported values.[4c]

The formal synthesis of (+)-grandisol was achieved in 17 steps from levoglucosenone in 3.7% yield.

Experimental

General Procedures IR spectra were measured on a Jasco FT/IR-5000 spectrophotometer. ^{1}H-NMR spectra were recorded at 300 MHz and ^{13}C-NMR spectra at 75 MHz, on a Brucker AC-300P spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane for ^{1}H-NMR and relative to $CDCl_3$ (77.0 ppm) for ^{13}C-NMR. Optical rotations were measured on a Jasco DIP-370 polarimeter. Mass spectra were taken on VG AutoSpecQ and ZAB-HF mass spectrometers. Elemental analysis was performed on a Yanagimoto CHN corder MT-3. Melting points were measured with a Yanagimoto melting point apparatus and are uncorrected.

For column chromatography, silica gel 70—230 mesh (Merck, Kieselgel 60) was used. Thin layer chromatography was performed on Silica gel 60 F-254 plates (Merck).

All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate unless otherwise stated.

1,6-Anhydro-3,4-dideoxy-4-phenylthio-β-D-*glycero*-hex-3-enopyranos-2-ulose ((−)-4) NCS (27.76 g, 0.30 mol) was added to a stirred solution of (−)-**3** (44.61 g, 0.189 mol) in CCl_4 (500 ml) at 0 °C. After 2.5 h, the precipitate was filtered off. The filtrate was washed with 5% aqueous $NaHCO_3$ and brine, and then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (500 g). The fraction eluted with 20—30% AcOEt in hexane (v/v) gave (−)-**4** (42.0 g, 95%) as a yellow oil. $[\alpha]_D^{23}$ −395.3° (c=0.63, $CHCl_3$). IR (neat): 1684 (C=O), 1566 (C=C), 1479, 1441, 1294, 1108, 992, 969, 901 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.92 (1H, d, J=7.0 Hz, C6-H), 3.99 (1H, dd, J=4.8, 7.0 Hz, C5-H_a), 4.94 (1H, d, J=4.7 Hz, C5-H_b), 5.34 (1H, d, J=1.0 Hz, C3-H), 5.14 (1H, s, C1-H), 7.3—7.6 (5H, m, Ar–H). ^{13}C-NMR ($CDCl_3$) δ: 68.02 (C1), 74.84 (C5), 101.39 (C1), 116.40, 126.17, 130.17, 130.68, 135.02, 165.43 (C4), 186.77 (C2). High-resolution mass spectrum (HRMS) $(M)^+$ m/z: Calcd for $C_{12}H_{10}O_3S$: 234.0351. Found: 234.0354.

1,6-Anhydro-3,4-dideoxy-4-methyl-β-D-*glycero*-hex-3-enopyranos-2-ulose((−)-5) MeLi (1.5 M in ether, 1.02 ml, 1.54 mmol) was added dropwise to a suspension of CuI (146 mg, 0.77 mmol) in THF (2 ml) at 0 °C under an Ar atmosphere. After 15 min stirring, the reaction mixture was cooled to −78 °C. A solution of **4** (180 mg, 0.77 mmol) in THF (1 ml) was added and the whole was stirred for 10 min at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and the precipitate was filtered off. The filtrate was separated and the water layer was extracted with ether. The combined organic layer was washed, dried, and concentrated *in vacuo* to afford an oily residue. It was subjected to column chromatography on silica gel. The fraction eluted with 20—40% AcOEt in hexane (v/v) gave (−)-**5** (67 mg, 62%) as a pale yellow oil. $[\alpha]_D^{26}$ −467° (c=1.95, $CHCl_3$). IR (neat): 1690 (C=O), 1630, 1437, 1381, 1315, 1296, 1257, 1108, 990, 963 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, d, J=1.6 Hz, C4-Me), 3.72 (1H, d, J=6.8 Hz, C6-H_a), 3.91 (1H, dd, J=4.8, 6.8 Hz, C6-H_b), 4.83 (1H, d, J=4.8 Hz, C5-H), 5.31 (1H, d, J=1.5 Hz, C1-H), 5.86 (1H, m, C3-H). ^{13}C-NMR ($CDCl_3$) δ: 20.00 (C4-Me), 66.31 (C6), 75.75 (C5), 100.70 (C1), 122.33 (C5), 189.17 (C2). HRMS $(M)^+$ m/z: Calcd for $C_7H_8O_3$: 140.0473. Found: 140.0468.

(4*R*)-1,6-Anhydro-3,4-dideoxy-4-*C*-methyl-4-*C*-vinyl-β-D-*glycero*-hexopyranos-2-ulose ((−)-6) Vinylmagnesium bromide (0.93 M in THF, 4.3 ml, 4.0 mmol) was added dropwise to a suspension of CuI (381 mg, 2.0 mmol) in THF (3 ml) at −20 °C under an Ar atmosphere. After 15 min stirring, the reaction mixture was cooled to −78 °C. A solution of **5** (140 mg, 1.0 mmol) and HMPA (0.35 ml, 2.0 mmol) in THF (1 ml) was added and the whole was stirred for 15 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl and the precipitate was filtered off. The filtrate was separated and the water layer was extracted with AcOEt. The combined organic layer was washed, dried, and concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 15% AcOEt in hexane (v/v) gave (−)-**6** (103 mg, 61%) as a colorless oil. $[\alpha]_D^{24}$ −314.9° (c=0.43, $CHCl_3$). IR (neat): 1742 (C=O), 1642 (C=C), 1120, 1015, 977, 911 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, s, C4-Me), 2.39 (1H, d, J=15.9 Hz, C3-H_a), 2.45 (1H, d, J=15.9 Hz, C3-H_b), 3.92 (1H, dd, J=5.3, 8.2 Hz, C6-H_a), 4.25 (1H, d, J=4.0 Hz, C6-H_b), 4.26 (1H, d, J=7.3 Hz, C5-H), 5.07 (1H, s, C1-H), 5.13 (1H, d, J=17.2 Hz, C=CH_2), 5.17 (1H, d, J=10.2 Hz, C=CH_2), 5.97 (1H, dd, J=10.9, 17.5 Hz, CH=). ^{13}C-NMR ($CDCl_3$) δ: 22.75 (C4-Me), 42.62 (C3), 44.64 (C4), 64.33 (C6), 80.23 (C5), 100.44 (C1), 114.27 (=CH_2), 142.03 (C=), 199.91 (C2). HRMS $(M)^+$ m/z: Calcd for $C_9H_{12}O_3$: 168.0786. Found: 168.0788.

(4*R*)-1,6-Anhydro-3,4-dideoxy-4-*C*-methyl-4-*C*-vinyl-β-D-*threo*-hexopyranose ((−)-7) L-Selectride® (1 M in THF, 1.0 ml, 1.0 mmol) was added to a stirred solution of (−)-**6** (84 mg, 0.5 mmol) in THF (1 ml) at −78 °C under an Ar atmosphere. The reaction mixture was stirred for 1.5 h, then quenched with H_2O and extracted with AcOEt. The extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 20% AcOEt in hexane (v/v) gave (−)-**7** (84 mg, 99%) as colorless crystals. mp 161—161.5 °C (ether–hexane). $[\alpha]_D^{26}$ −38.8° (c=0.425, $CHCl_3$). IR (KBr): 3414 (OH), 1638, 1390, 1325, 1156, 1120, 1029, 928, 913 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s, Me), 1.71 (1H, dd, J=4.3, 14.9 Hz, C3-H_a), 1.80 (1H, m, C3-H), 2.14 (1H, br d, J=11.3 Hz, C2-H), 3.48 (1H, m, OH), 3.71 (1H, dd, J=5.3, 7.8 Hz, C6-H_a), 4.00 (1H, d, J=7.8 Hz, C6-H_b), 4.24 (1H, dd, J=1.9, 5.3 Hz, C5-H), 5.14 (1H, dd, J=0.7, 10.9 Hz, C=CH), 5.25 (1H, s like, C1-H), 5.33 (1H, dd, J=0.6, 17.5 Hz, C=CH), 6.03 (1H, dd, J=11.0, 17.8 Hz, CH=). ^{13}C-NMR ($CDCl_3$) δ: 25.43 (Me), 34.70 (C4), 38.41 (C3), 64.09 (C6), 67.94 (C2), 79.43 (C5), 101.67 (C1), 113.83 (=CH_2), 145.65 (CH=). HRMS $(M)^+$ m/z: Calcd for $C_9H_{14}O_3$: 170.0943. Found: 170.0943.

(4*R*)-1,6-Anhydro-2-*O*-*tert*-butyldimethylsilyl-3,4-dideoxy-4-*C*-methyl-4-*C*-vinyl-β-D-*threo*-hexopyranose ((−)-8) Imidazole (139 mg, 2.05 mmol) and TBDMSCl (154 mg, 1.02 mmol) were added to a stirred solution of (−)-**7** (87 mg, 0.51 mmol) in dimethylformamide (DMF) (2 ml) at room temperature under an Ar atmosphere. The whole was stirred overnight, then the reaction was quenched with H_2O and the mixture was extracted with ether. The extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 10% AcOEt in hexane (v/v) gave (−)-**8** (140 mg, 96%) as a colorless oil. $[\alpha]_D^{22}$ −54.5° (c=0.945, $CHCl_3$). IR (neat): 1638 (C=C), 1257, 1122, 1085, 1064 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.00, 0.17 (3H each s, Si–Me), 0.89 (9H, s, *tert*-Bu), 0.90 (3H, s, C4-Me), 1.44 (1H, dd, J=1.2, 14.5 Hz, C3-H_a), 1.70 (1H, dd, J=4.5, 14.5 Hz, C3-H_b), 3.58 (1H, m, C2-H), 3.65 (1H, dd, J=5.3, 7.7 Hz, C6-H), 3.98 (1H, d, J=11.7 Hz, C6-H), 3.99 (1H, m, C5-H), 4.95 (1H, d, J=2.1 Hz, =CH), 5.00 (1H, dd, J=1.1, 8.8 Hz, =CH), 5.18 (1H, s, C1-H), 6.70 (1H, dd, J=11.0, 17.7 Hz, CH=). ^{13}C-NMR ($CDCl_3$) δ: −4.95 (Si–Me), −4.92 (Si–Me), 17.98 (quaternary carbon of *tert*-Bu), 22.25 (Me), 25.72 (3 Me carbons in *tert*-Bu), 37.03 (C4), 37.96 (C3), 64.18 (C6), 67.53 (C2), 80.38 (C5), 102.08 (C1), 110.89 (=CH_2), 145.47 (CH=). HRMS $(M+H)^+$ m/z: Calcd for $C_{15}H_{29}O_3Si$:

285.1908. Found: 285.1906.

(4*S*)-1,6-Anhydro-2-*O*-*tert*-butyldimethylsilyl-3,4-dideoxy-4-*C*-methyl-4-*C*-hydroxyethyl-β-D-*threo*-hexopyranose ((−)-9) A solution of 9-BBN (0.5 M in THF, 2.1 ml, 1.05 mmol) was added to a stirred solution of (−)-**8** (298 mg, 1.05 mmol) in THF (3 ml) at room temperature under an Ar atmosphere. After 1 h, then a further portion of 9-BBN (2.1 ml) was added. The whole was stirred for 1 h, then a mixture of H_2O, 3 M NaOH solution and 30% H_2O_2 was added to the reaction mixture and the whole was stirred for 1 h at 40—45 °C. After cooling, the reaction mixture was extracted with AcOEt. The extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 20% AcOEt in hexane (v/v) gave (−)-**9** (316 mg, 100%) as a colorless oil. $[\alpha]_D^{25}$ −30.0° (*c*=0.585, $CHCl_3$). IR (neat): 3405 (OH), 1473, 1464, 1386, 1363, 1257, 1170, 1127, 1089, 1064, 1035, 944, 926 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.19, 0.32 (3H each, s, Si–Me), 0.80 (3H, s, C4-Me), 0.87 (9H, s, *tert*-Bu), 1.5—1.6 (2H, m, C3-H), 1.89 (1H, br s, OH), 2.00 (1H, dt, *J*=6.5, 13.8 Hz, CH_a–C–O), 2.16 (1H, dt, *J*=6.5, 13.8 Hz, CH_b–C–O), 3.56 (1H, m, C2-H), 3.62 (1H, dd, *J*=5.5, 7.5 Hz, C6-H), 3.74 (2H, t, *J*=6.4 Hz, CH_2–O), 3.93 (1H, d, *J*=7.6 Hz, C6-H), 4.05 (1H, d, *J*=5.3 Hz, C5-H), 5.14 (1H, s, C1-H). ^{13}C-NMR ($CDCl_3$) δ: −4.98 (Si–Me), −4.95 (Si–Me), 18.01 (quaternary carbon of *tert*-Bu), 23.65 (Me), 25.76 (3 Me carbons in *tert*-Bu), 34.49 (C3), 34.99 (C4), 40.39 (CH_2–C–O), 59.46 (CH_2–O), 63.65 (C6), 67.81 (C2), 80.03 (C5), 101.89 (C1). HRMS $(M+H)^+$ *m/z*: Calcd for $C_{15}H_{31}O_4Si$: 303.1856. Found: 303.1924. *Anal.* Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.26; H, 9.91.

(4*S*)-1,6-Anhydro-2-*O*-*tert*-butyldimethylsilyl-3,4-dideoxy-4-*C*-methyl-4-*C*-*p*-toluenesulfonyloxyethyl-β-D-*threo*-hexopyranose ((−)-10) TsCl (3.69 g, 19 mmol) and 4-dimethylaminopyridine (DMAP, catalytic amount) were added to a stirred solution (−)-**9** (5.315 g, 17.6 mmol) in pyridine (60 ml) at room temperature. The whole was stirred overnight, then quenched with H_2O and extracted with ether. The extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 20% AcOEt in hexane (v/v) gave (−)-**10** (7.247 g, 93%) as a colorless oil. $[\alpha]_D^{20}$ −23.0° (*c*=0.225, $CHCl_3$). IR (neat): 1601 (C=C), 1464, 1363, 1257, 1178, 1125, 1058, 944 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.14, −0.04 (3H each, s, Si–Me), 0.79 (3H, s, C4-Me), 0.81 (9H, s, *tert*-Bu), 1.35 (1H, br d, *J*=5.0 Hz, C3-H_a), 1.51 (1H, dd, *J*=4.5, 15.0 Hz, C3-H_b), 2.11 (1H, dt, *J*=6.9, 14.5 Hz, CH_a–C–O), 2.25 (1H, dt, *J*=6.5, 14.5 Hz, CH_b–C–O), 2.42 (3H, s, Ar–Me), 3.50 (1H, br t, *J*=2.2 Hz, C2-H), 3.61 (1H, dd, *J*=5.4, 7.7 Hz, C6-H_a), 3.91 (1H, d, *J*=7.7 Hz, C6-H_b), 3.94 (1H, m, C5-H), 4.16 (2H, m, CH_2–O), 5.10 (1H, s, C1-H), 7.31 (2H, d, *J*=8.4 Hz, Ar–H), 7.76 (2H, d, *J*=8.2 Hz, Ar–H). ^{13}C-NMR ($CDCl_3$) δ: −5.04 (Si–Me), −4.98 (Si–Me), 17.89 (quaternary carbon of *tert*-Bu), 21.59 (Ar–Me), 23.47 (Me), 25.70 (3 Me carbons in *tert*-Bu), 34.50 (C3), 34.95 (C4), 35.82 ($\underline{C}H_2$–CH_2O), 63.64 (C6), 67.45 (CH_2–O), 68.21 (C2), 79.58 (C5), 101.97 (C1), 127.86 (Ar), 129.79 (Ar), 138.15 (Ar), 144.61 (Ar). HRMS $(M+H)^+$ *m/z*: Calcd for $C_{22}H_{37}O_6SSi$: 457.2080. Found: 457.2121.

(4*S*)-1,6-Anhydro-3,4-dideoxy-4-*C*-methyl-4-*C*-*p*-toluenesulfonyloxyethyl-β-D-*threo*-hexopyranose ((−)-11) HF–pyridine complex (1 ml) was added to a stirred solution of (−)-**10** (187 mg, 0.41 mmol) in ether (4 ml) at 0 °C under an Ar atmosphere. The mixture was stirred for 2 h at room temperature, then a further portion of HF–pyridine (0.2 ml) was added. The whole was stirred for 2 h, then diluted with ether. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with AcOEt. The extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 50% AcOEt in hexane (v/v) gave (−)-**11** (138 mg, 96%) as colorless crystals. mp 104.5—105.5 °C (ether–hexane). $[\alpha]_D^{22}$ −27.3° (*c*=0.40, $CHCl_3$). IR (KBr): 3482 (OH), 1332, 1189, 1176, 1123, 1040, 1021, 926 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s, C4-Me), 1.5—1.6 (2H, m, C3-H), 1.96 (1H, br s, OH), 2.07, 2.28 (1H, each, *J*=6.7, 14.0 Hz, CH_2–C–O), 2.45 (3H, s, Ar–Me), 3.60 (1H, dt, *J*=2.2, 4.0 Hz, C2-H), 3.68 (1H, dd, *J*=5.4, 7.8 Hz, C6-H), 3.98 (1H, d like, *J*=8.2 Hz, C6-H), 4.01 (1H, d, *J*=5.4 Hz, C5-H), 4.22 (2H, t, *J*=6.7 Hz, CH_2–O), 5.29 (1H, s, C1-H), 7.36 (2H, d, *J*=7.7 Hz, Ar–H), 7.80 (2H, d, *J*=7.8 Hz, Ar–H). ^{13}C-NMR ($CDCl_3$) δ: 21.58 (Ar–Me), 23.45 (Me), 34.40 (C3, $\underline{C}H_2$–C–O), 36.43 (C4), 63.70 (C6), 67.08 (CH_2–O), 67.85 (C2), 79.81 (C5), 101.60 (C1), 127.83 (Ar), 129.83 (Ar), 132.89 (Ar), 144.80 (Ar). *Anal.* Calcd for $C_{16}H_{22}O_6S$: C, 56.13; H, 6.48. Found: C, 55.73; H, 6.46.

(4*S*)-1,6-Anhydro-3,4-dideoxy-4-*C*-methyl-4-*C*-*p*-toluenesulfonyloxyethyl-β-D-*glycero*-hexopyranos-2-ulose ((−)-12) PDC (1.29 g, 3.4 mmol) and molecular sieves 4A (powder, 2.3 g) were added to a stirred solution of (−)-**11** (782 mg, 2.3 mmol) in CH_2Cl_2 (25 ml) at room temperature. The whole was stirred for 2.5 h, then diluted with ether and filtered with the aid of Celite. The filtrate was concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with hexane : CH_2Cl_2 : ether = 3 : 1 : 1 (v/v) gave (−)-**12** (718 mg, 92%) as colorless crystals. mp 70.5—71 °C (AcOEt–hexane). $[\alpha]_D^{23}$ −132.6° (*c*=0.675, $CHCl_3$). IR (KBr): 1736 (C=O), 1599, 1359, 1174, 1108, 909 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, s, C4-Me), 1.81 (1H, dt, *J*=6.7, 14.9 Hz, CH_a–C–O), 1.95 (1H, dt, *J*=6.4, 14.8 Hz, CH_b–C–O), 2.12 (1H, d like *J*=14.9 Hz, C3-H_a), 2.39 (1H, d, *J*=15.9 Hz, C3-H_b), 2.46 (3H, s, Ar–Me), 3.89 (1H, dd, *J*=5.3, 8.2 Hz, C6-H), 4.1—4.3 (4H, m, CH_2–O, C5-H and C6-H), 5.02 (1H, s, C1-H), 7.36 (2H, dd, *J*=0.6, 8.6 Hz, Ar–H), 7.79 (2H, d, *J*=8.4 Hz, Ar–H). ^{13}C-NMR ($CDCl_3$) δ: 21.62 (Ar–Me), 22.25 (Me), 36.48 (C4), 41.03 (C3), 44.82 ($\underline{C}H_2$–C–O), 64.41 (C6), 66.60 (C–O), 79.36 (C5), 100.39 (C1), 127.96 (Ar), 129.91 (Ar), 132.54 (Ar), 145.08 (Ar), 199.5 (C2). *Anal.* Calcd for $C_{16}H_{20}O_6S$: C, 56.46; H, 5.92. Found: C, 56.52; H, 5.91.

(3*R*,4*S*)-1,6-Anhydro-3,4-dideoxy-3,4-*C*-ethylene-4-*C*-methyl-β-D-*glycero*-hexopyranos-2-ulose ((−)-13) DMSO (5 ml) was added to the washed NaH (50% in oil, 85 mg, 1.76 mmol) and the whole was stirred for 1 h at 60 °C, then allowed to cool. A solution of (−)-**12** (500 mg, 1.47 mmol) in DMSO (1 ml) was added at room temperature. The whole was stirred for 10 min, then the reaction was quenched with H_2O, and the mixture was extracted with AcOEt. The extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 20% AcOEt in hexane (v/v) gave (−)-**13** (198 mg, 80%) as a colorless oil. $[\alpha]_D^{24}$ −193° (*c*=0.35, $CHCl_3$). IR (neat): 1734 (C=O), 1458, 1383, 1290, 1234, 1114, 1038, 1013, 967 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s, C4-Me), 1.70 (1H, m, C8-H_a), 1.97 (1H, m, C7-H_b), 2.49 (1H, m, C7-H_a), 2.58 (1H, m, C3-H), 2.65 (1H, m, C8-H_b), 3.72 (1H, dd, *J*=5.0, 77 Hz, C6-H_b), 4.06 (1H, d, *J*=7.7 Hz, C6-H_a), 4.18 (1H, d, *J*=4.9 Hz, C5-H), 5.11 (1H, s, C1-H). ^{13}C-NMR ($CDCl_3$) δ: 20.82 (C7), 22.26 (Me), 29.11 (C8), 40.20 (C4), 45.00 (C3), 64.46 (C6), 79.85 (C5), 99.04 (C1), 217.90 (C2). HRMS $(M)^+$ *m/z* Calcd for $C_9H_{12}O_3$: 168.0786. Found: 168.0789.

(1*R*,4*S*,5*S*)-(−)-4-Hydroxymethyl-5-methyl-3-oxabicyclo[3.2.0]heptan-2-one ((−)-14) and (1*R*,4*S*,5*S*)-(−)-4-*tert*-Butyldimethylsilyloxymethyl-5-methyl-3-oxabicyclo[3.2.0]heptan-2-one ((−)-15) Peracetic acid (40%, 0.72 ml) was added to a stirred solution of (−)-**13** (290 mg, 1.73 mmol) in AcOH (3 ml) and the whole was stirred for 4 h at room temperature. To quench the excess peracid, methylsulfide (a few drops) was added, and the mixture was stirred for an additional 0.5 h. After evaporation of AcOH, the residue was dissolved in methanol (5 ml). Aqueous HCl (1 drop) was added to the reaction mixture, then the whole was stirred overnight. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 60% AcOEt in hexane (v/v) gave a mixture of (−)-**14** and dimethylsulfone. This was subjected to the next reaction.

The crude (−)-**14** (279 mg) was treated with TBDMSCI (390 mg, 2.6 mmol) and imidazole (235 mg, 3.45 mmol) in DMF (5 ml). After 1.5 h stirring, usual work-up gave an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 30% AcOEt in hexane (v/v) gave (−)-**15** (411 mg, 88%) as colorless crystals. mp 82—82.5 °C (from hexane). $[\alpha]_D^{25}$ −13.5° (*c*=1.43, $CHCl_3$). IR (KBr): 1754 (C=O), 1464, 1381, 1348, 1305, 1263, 1170, 1114, 1071, 1036, 1013, 961, 930 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.01, 0.02 (3H each s, Si–Me), 0.83 (9H, s, *tert*-Bu), 1.38 (3H, s, Me), 1.81 (1H, m, C6-H_a), 2.02 (1H, m, C7-H_b), 2.27 (1H, m, C7-H_a), 2.50 (1H, m, C1-H), 2.61 (1H, m, C6-H_b), 3.67 (1H, dd, *J*=0.7, 11.3 Hz, CH_a–O), 3.78 (1H, dd, *J*=2.3, 11.4 Hz, CH_b–O), 4.12 (1H, br s, C4-H). ^{13}C-NMR ($CDCl_3$) δ: −5.87 (Si–Me), −5.74 (Si–Me), 17.76 (C6), 17.98 (quaternary carbon of *tert*-Bu), 21.68 (Me), 25.68 (3 Me carbons in *tert*-Bu), 31.89 (C5), 43.74 (C4), 44.69 (C7), 62.26 (C8), 86.51 (C4), 180.67 (C2). HRMS $(M)^+$ *m/z*: Calcd for $C_{14}H_{26}O_3Si$: 270.1651. Found: 270.1653.

In order to afford an analytical pure sample, the TBDMS group of (−)-**15** was removed by the treatment with TBAF. The pure (−)-**14** was obtained as colorless needles. mp 48.5—49 °C (ether–hexane). $[\alpha]_D^{25}$ −26.0 °C (*c*=0.43, $CHCl_3$). IR (KBr): 3400 (OH), 1758 (C=O), 1441, 1346, 1305, 1170, 1145, 1073, 1031 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, s, Me), 1.91 (1H, ddt, *J*=3.2, 9.9, 11.9 Hz, C6-H_a), 2.11 (1H, ddt, *J*=2.6, 9.0, 11.7 Hz, C7-H_b), 2.2—2.4 (2H, m, C1-H, C7-H_b), 2.54 (1H, ddd, *J*=9.6, 11.7, 19.1 Hz, C6-H_b), 2.73 (1H, d like, *J*=9.2 Hz, OH), 3.69 (1H,

ddd, J=3.4, 5.6, 12.5 Hz, CH_a–C–O), 3.88 (1H, ddd, J=2.7, 6.3, 12.5 Hz, CH_b–C–O), 4.26 (1H, t, J=3.0 Hz, C4-H). ^{13}C-NMR ($CDCl_3$) δ: 17.89 (C6), 21.59 (Me), 32.22 (C5), 43.37 (C4), 44.19 (C7), 61.90 (C8), 87.42 (C4), 180.93 (C2). *Anal.* Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.25; H, 7.57.

(1*S*,2*R*)-(+)-1-[(1*S*)-1-Hydroxy-2-*tert*-butyldimethylsilyloxy]ethyl-2-(1-hydroxy-1-methylethyl)-1-methylcyclobutane ((+)-16) MeLi (1.1 M in ether, 0.15 ml, 0.16 mmol) was added to a stirred solution of (−)-**15** (9 mg, 33 mmol) in THF (1 ml) and the whole was stirred for 10 min at 0 °C under an Ar atmosphere. The reaction was quenched with H_2O and the mixture was extracted with AcOEt. The extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 30% AcOEt in hexane (v/v) gave (+)-**16** (10 mg, 100%) as colorless crystals. mp 66.5—67 °C (Et_2O–hexane). $[\alpha]_D^{25}$ +14.9° (c=1.10, $CHCl_3$). IR (KBr): 3374 (OH), 1475, 1381, 1247, 1195, 1108, 1094, 1038, 1006, 942 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s, Si–Me×2), 0.87 (9H, s, *tert*-Bu), 1.04, 1.08, 1.25 (3H each, s, Me), 1.4—1.6 (2H, m), 1.69 (1H, m), 1.8—2.0 (2H, m), 3.34 (1H, br s, OH), 3.50 (1H, dd, J=8.9, 9.8 Hz, CH–O), 3.64 (1H, dd, J=3.0, 9.9 Hz, CH_aH_b–O), 4.15 (1H, dd, J=3.0, 8.8 Hz, CH_aH_b–O), 4.32 (br s, OH). ^{13}C-NMR ($CDCl_3$) δ: −5.40 (Si–Me), −5.34 (Si–Me), 18.23 (quaternary carbon of *tert*-Bu), 18.52 (CH_2), 23.39 (CH_2), 25.85 (3 Me carbons in *tert*-Bu), 26.86 (CH_3), 28.24 (CH_3), 29.18 (CH_3), 45.44 (CH), 57.49 (C), 63.32 (CH_2OH), 70.66 (CHOH), 72.96 (COH). HRMS $(M+H)^+$ m/z Calcd for $C_{16}H_{35}O_3Si$: 303.2355. Found: 303.2354.

(1*R*,2*R*)-(+)-(2-*tert*-Butyldimethylsilyloxy)ethyl-2-(1-hydroxy-1-methylethyl)-1-methylcyclobutane ((+)-18) A solution of (+)-**16** (35 mg, 0.115 mmol) and imidazole (1 crop) in THF (1 ml) was added to a stirred suspension of the washed NaH (50% in oil, 17 mg, 0.35 mmol) in THF (2 ml) at room temperature under an Ar atmosphere. After 20 min, CS_2 (22 μl, 0.35 mmol) was added in one portion and then the whole was stirred for 30 min. MeI (22 μl, 0.35 mmol) was added to the reaction mixture. After 15 min, the reaction was quenched with AcOH (a few drops). Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to the next reaction. n-Bu_3SnH (47 μl, 0.17 mmol) and Et_3B (1 M in hexane, 170 μl, 0.17 mmol) were added to a stirred solution of the crude product in benzene. After 30 min, the same amounts of n-Bu_3SnH and Et_3B were added and the whole was stirred for 1 h. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 5% AcOEt in hexane (v/v) gave (+)-**18** (11 mg, 33%) as a colorless oil. $[\alpha]_D^{20}$ +12.6° (c=0.45, $CHCl_3$). IR (neat): 3446 (OH), 1464, 1257, 1093, 1031, 1006, 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s, Si–Me×2), 0.88 (9H, s, *tert*-Bu), 1.05, 1.09, 1.20 (3H each, s, Me), 1.4—2.1 (8H, m), 3.5—3.8 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: −5.26 (Si–Me×2), 17.86 (quaternary carbon of *tert*-Bu), 18.36 (CH_2), 26.02 (3 Me carbons in *tert*-Bu), 28.88 (CH_3×2), 29.01 (CH_3), 30.57 (CH_3), 37.40 (CH_2), 41.80 (C), 56.35 (CH), 60.51 (CH_2OH), 71.93 (COH).

(1*R*,2*R*)-(+)-1-(2-Hydroxyethyl)-2-(1-hydroxy-1-methylethyl)-1-methylcyclobutane ((+)-19) TBAF (1 M in THF, 48 μl, 48 mmol) was added to a stirred solution of (+)-**18** (9 mg, 31 mmol) in THF (0.5 ml) at room temperature. After 30 min, the reaction was quenched with H_2O and the mixture was extracted with AcOEt. The extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 60% AcOEt in hexane (v/v) gave (+)-**19** (4 mg, 74%) as colorless crystals. mp 58—59 °C (heptane). $[\alpha]_D^{24}$ +17.2° (c=0.38, $CHCl_3$). IR (KBr): 3374 (OH), 1464, 1379, 1365, 1303, 1232, 1172, 1133, 1064, 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04, 1.06, 1.17 (3H each, s, Me), 1.47 (1H, t lik, J=9.3 Hz, C2-H), 1.6—2.1 (8H, m), 3.60 (1H, ddd, J=5.3, 8.7, 10.3 Hz, CH_2–O), 3.67 (1H, ddd, J=6.7, 8.3, 10.3 Hz, CH_2–O). ^{13}C-NMR ($CDCl_3$) δ: 17.90 (CH_2), 28.26 (CH_3), 28.92 (CH_3), 29.12 (CH_3), 30.53 (CH_2), 37.68 (CH_2), 41.73 (C), 56.04 (CH), 60.06 (CH_2OH), 72.16 (COH). HRMS $(M-18)^+$ m/z: Calcd for $C_{10}H_{18}O$: 154.1358. Found: 154.1353. *Anal.* Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.47; H, 11.77. [lit.[4c] mp 57—61 °C, $[\alpha]_D^{20}$ +18° (c=0.958, $CHCl_3$), ^{1}H-NMR ($CDCl_3$) δ: 1.09, 1.10, 1.23 (3H each, s, Me), 1.5 (1H, m), 1.71 (2H, m), 1.83—2.14 (4H, m), 3.5—3.75 (2H, m), 3.1—4.1 (2H, s, OH). ^{13}C-NMR ($CDCl_3$) δ: 17.96 (CH_2), 28.19 (CH_3), 28.95 (2×CH_3), 30.50 (CH_2), 37.45 (CH_2), 41.65 (C), 56.13 (CH), 59.38 (CH_2OH), 72.08 (COH). IR ($CDCl_3$): 3450, 2970, 2870, 1655, 1545, 1465, 1380 cm^{-1}].

References and Notes

1) Y. Halpern, R. Riffer and A. Broid, *J. Org. Chem.*, **38**, 204 (1973). Levoglucosenone is available from Yuki Gosei Kogyo Co., Ltd.
2) *a*) Whisky lactone and eldanolide; T. Ebata, K. Matsumoto, H. Yoshikoshi, K. Koseki, H. Kawakami and H. Matsushita, *Heterocycles*, **31**, 1585 (1990); *b*) Altrose; K. Matsumoto, T. Ebata, K. Koseki and H. Matsushita, *Bull. Chem. Soc. Jpn.*, **61**, 2309 (1991); *c*) Allose; K. Matsumoto, T. Ebata, K. Koseki and H. Matsushita, *Heterocycles*, **32**, 2225 (1991), and see also ref. 5.
3) J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin and J. P. Minyard, *J. Org. Chem.*, **36**, 2616 (1971).
4) *a*) K. Mori and K. Fukamatsu, *Justus Liebigs Ann. Chem.*, **1992**, 489; *b*) K. Narasaka, H. Kusama and Y. Hayashi, *Bull. Chem. Soc. Jpn.*, **64**, 1471 (1991); *c*) N. Hoffmann and H-D. Scharf, *Justus Liebigs Ann. Chem.*, **1991**, 1273 and references cited herein.
5) K. Koseki, T. Ebata, H. Kawakami, H. Matsushita, Y. Naoi and K. Itoh, *Heterocycles*, **31**, 423 (1990).
6) J. B. Jones, M. A. W. Finch and I. J. Jakovac, *Can. J. Chem.*, **60**, 2007 (1982) and see also 4*c*.
7) F. Shafizadeh, R. H. Furneaux and T. T. Stevenson, *Carbohydr. Res.*, **71**, 169 (1979).
8) K. Nozaki, K. Oshima and K. Utimoto, *Tetrahedron Lett.*, **29**, 6125 (1988).