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Stereoselective Synthesis from D-Glucose of (-)-∂-Multistriatin (Component of the European Elm Bark Beetle, *Scolytus Multistriatus*, Aggregation Pheromone).

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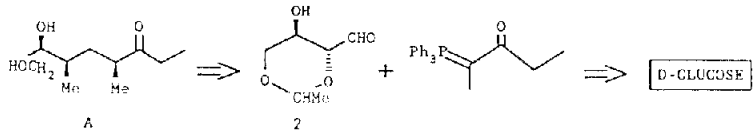
Abstract: A six step stereoselective synthesis of (-)-∂-multistriatin [(1S,2S,4S,5R)-5-ethyl-2,4-dimethyl-6,8-dioxabicyclo[3.2.1]octane, **1**] is presented, starting from 2,4-O-ethylidene-D-erythrose (**2**), which is readily available from D-glucose.

The bicyclic ketal (-)-∂-multistriatin (**1**) is one of three essential components of the aggregation pheromone of the smaller European elm bark beetle, *Scolytus multistriatus*[1], with its absolute stereochemistry having been established by Silverstein *et al.*[2] as (1S,2S,4S,5R)-5-ethyl-2,4-dimethyl-6,8-dioxabicyclo[3.2.1]octane. Several syntheses of optically active **1** have been reported[3] but only two of them used carbohydrates, derivatives of D-glyceraldehyde[4] and cellulose[5], as chiral starting materials.

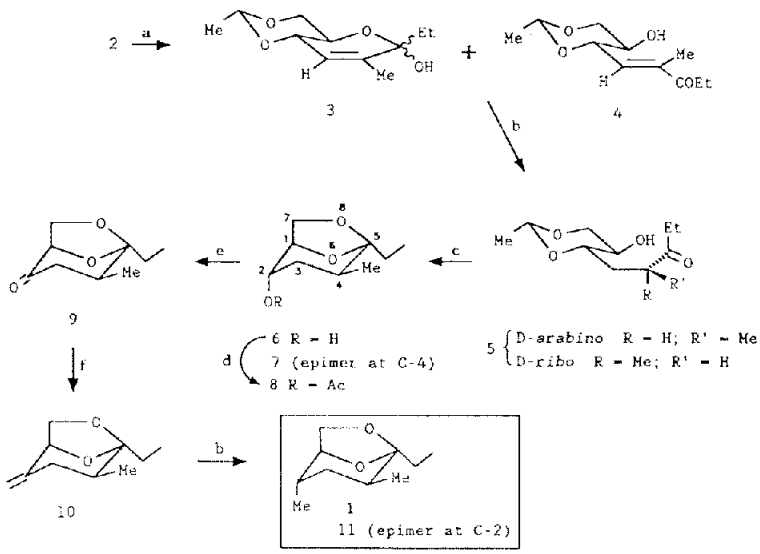
As a part of our continuing efforts on the synthesis of optically active pheromones using sugar derivatives as chiral building blocks[6], we report herein on the stereoselective synthesis of the title compound (**1**) from 2,4-O-ethylidene-D-erythrose (**2**)[7]. Retrosynthesis of **1** (see scheme I) showed that **2**, easily available in two steps from D-glucose, has the required configuration at C-3 as well suitable functional groups to allow not only the lengthening of the carbon chain but the introduction of the required branchings in order to obtain the ketone **A**, precursor of **1**.

Reaction of **2** with triphenyl(1-propionylethylidene)phosphorane[8] gave a mixture of (*Z*)- (**3**) and (*E*)-1,2,4,5-tetradeoxy-6,8-O-ethylidene-4-*C*-methyl-D-*erythro*-oct-4-ene-3-ulose (**4**) in a 1:6 ratio, respectively. The *Z* and *E* configurations in **3** and **4** were established on the basis of their spectroscopic data. Thus, the IR spectrum of **3** showed no carbonyl absorption band and its ^{1}H-NMR spectrum contained signals of **3** as a mixture of

Scheme I



cyclic anomers, as could be expected for such a structure. However **4** showed an intense conjugate carbonyl absorption band (1665 cm^{-1}), with ^{1}H- and ^{13}C-NMR spectra in accordance with the proposed structure. Hydrogenation of a mixture of **3** and **4** gave the corresponding 1,2,4,5-tetradeoxy-6,8-O-ethylidene-4-*C*-methyl-D-*ribo*- and -D-*arabino*-3-octuloses as an inseparable mixture (**5**), whose ^{1}H-NMR spectrum showed no vinylic protons and an up-field shift of the signal of methyl group at C-4 (d, 1.05 ppm, J 6 Hz).



a: $Ph_3P{=}CMeCOEt$; b: $Pd/C, H_2$; c: p-TsOH, $MeCHOHCH_2OH$;
d: Ac_2O, py; e: PCC, 4 A MS, CH_2Cl_2; f: $Ph_3P{=}CH_2$

Treatment of **5** with *p*-toluenesulfonic acid and 1,2-propylene glycol caused the loss of the ethylidene group by transketalisation and promoted intramolecular double cyclisation to produce a mixture of (1R,2S,4S,5R)-5-ethyl-2-hydroxy-4-methyl-6,8-dioxabicyclo[3.2.1]octane (**6**) and its epimer at C-4 (**7**) in a ≈ 40:1 ratio (GLC-MS, analysis), respectively. The high stereoselectivity found in the latter reaction was in agreement with that reported[9] for an analogous compound and could be explained through an acid catalysed process where the intermediate with a S configuration at C-4 led to the most stable bicycloketal due to the equatorial disposition of the methyl group. The structure of **6** was also confirmed through its 2-O-acetyl derivative (**8**).

The target molecule **1** was obtained from **6** by oxidation with PCC by the Antonakis procedure[10] to the previously unknown ketone **9**, subsequent reaction with methylenetriphenylphosphorane to yield the vinylic compound **10** and finally hydrogenation over Pd/C to afford **1** as the major component and its C-2 epimer (**11**) in a 94:6 ratio (GLC-MS, evidence), respectively. This finding was in accord with an equatorial attack of the hydrogen to the exocyclic methylene group in **10** to give preferentially the axial product.

We can conclude that transformation **5** → **6**, as well as **10** → **1** were crucial in establishing the stereocontrol of the whole synthesis of the title compound.

Experimental

General: Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AM-300 and WP-80 WC spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin-Elmer 782 instrument and mass spectra with a Hewlett-Packard HP-5988-A mass spectrometer. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. GLC was performed on a Perkin-Elmer 8410 gas chromatograph equipped with a flame-ionisation detector and a steel column (2 m x 0.125 in. i.d.) packed with 5% OV-17 on Chromosorb W (100-120 mesh): (*A*) at 130° C, program 10°C/min, to 230°C, 2 min; (*B*) at 90° C, program 10°C/min, to 130°C, 2 min; (*C*) column (2 m x 0.250 in. i.d.) packed with 3% OV-225 on Chromosorb W (80-100 mesh) at 120° C. The N_2 flow rate was 30 mL/min (*A* and *B*), and 80 mL/min (*C*), the injection port and the zone-detector temperatures were (*A*) 280° C; (*B*) and (*C*) 180° C. TLC was performed on Silica G (Merck) with detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds, for which elemental analyses were not obtained were shown to be homogeneous by chromatography and characterised by NMR and mass spectrometry.

(Z)- (3) and (E)-1,2,4,5-Tetradeoxy-6,8-O-ethylidene-4-C-methyl-D-erythro-oct-4-ene-3-ulose (4)

To a stirred solution of 2,4-O-ethylidene-D-erythrose[7] (**2**, 6.41 g, 43.9 mmol) in dichloromethane (75 mL), triphenyl(1-propionylethylidene)phosphorane[8] (16.5 g, 47.7 mmol) was added and the reaction mixture left at room temperature overnight. TLC (ether-hexane, 3:1), then revealed the presence of two new products of higher mobility. Concentration of the solvent gave a residue that was extracted with ether and the extracts concentrated. Flash chromatography (ether-hexane, 2:3) of the residue yielded first **3** (0.96 g, 10%) as a syrup. IR (neat): 3434 (OH), 2979, 2942, and 2868 (C-H), 1683 and 1633 (C=C), 1260, 1120, 1079, 1035, 843 and 818 cm^{-1} (C-O-C and 1,3-dioxane ring). The ^1H-nmr spectrum, showed that **3** was a mixture of two cyclic anomers.

Eluted second was **4** (5.47 g, 58%) that crystallised on standing, mp.: 57-59°C (ether-hexane). $[\alpha]_D^{25}$: -55 (c=0.8). IR (KBr): 3516 (OH), 2988, 2978, 2942 and 2880 (C-H), 1665 (C=O, conjugated), 1623 (C=C, conju-

gated), 1256, 1142, 1097, 1085, 1041 and 791 cm^{-1} (C-O-C and 1,3-dioxane ring). NMR data: ^1H (80 MHz), ∂ 6.40 (dq, 1 H, $J_{5,6}$ 8, $J_{5,Me}$ 1 Hz, H-5), 4.70 (q, 1 H, $J_{H,Me}$ 2.5 Hz, H-acetalic), 4.25 (t, 1 H, $J_{6,7}$ 8 Hz, H-6), 4.05-4.30 (m, 1 H, H-8e), 3.45 (dd, 1 H, $J_{8a,8e}$ 14, $J_{7,8a}$ 9 Hz, H-8a), 3.45-3.75 (m, 1 H, H-7), 2.68 (q, 2 H, $J_{1,2}$ 7 Hz, H-2,2), 2.38 (d, 1 H, $J_{OH,7}$ 4.5 Hz, OH), 1.85 (d, 3 H, Me-4), 1.30 (d, 3 H, Me acetalic) and 1.05 (t, 3 H, H-1,1,1); ^{13}C, ∂ 203.54 (C-3), 140.74 (C-4), 136.49 (C-5), 98.70 (C-acetalic), 78.64 (C-6), 70.54 (C-8), 65.36 (C-7), 30.72 (C-2), 20.44 (Me-4), 12.81 (Me acetalic) and 8.44 (C-1). Mass spectrum (c.i., CH_4): m/z 215 (100%, M^++1), 197 (52, M^++1-H_2O), 171 (80, M^++1-MeCHO), 153 (57, M^++1-H_2O-MeCHO), 141 (11, M^+-MeCHO-Et), 127 (11, $C_7H_{11}O_2^+$), 97 (15, $C_5H_5O_2^+$), 87 (7, $C_4H_7O_2^+$) and 57 (6, $C_3H_5O^+$); $C_{11}H_{18}O_4$ (214.25) Calcd: C 61.66 H 8.47 found: C 61.83 H 8.39.

(1R,2S,4S,5R)-5-Ethyl-2-hydroxy-4-methyl-6,8-dioxabicyclo[3.2.1]octane (6)

A mixture of **3** and **4** (1:7 ratio) (1.89 g, 8.82 mmol) in methanol (50 mL), was hydrogenated at 4 atm over 10% Pd/C (200 mg) for 15 min. GLC (**A**), then indicated that **3** (T_R 7.05 min) and **4** (T_R 7.62 min) had disappeared and that a new compound (T_R 6.20 min) was present. The catalyst was filtered off, washed with methanol and the filtrate concentrated. Flash chromatography (ether-hexane, 2:3) of the residue gave 1,2,4,5-tetradeoxy-6,8-O-ethylidene-4-C-methyl-D-*ribo*- and -D-*arabino*-3-octulose (**5**, 1.46 g, 77%) as a colourless syrup. The ^1H-nmr spectrum showed no vinylic protons and shielding of the Me resonance signal (1.05 ppm) at C-4.

To a stirred solution of **5** (2.06 g, 9.55 mmol) in anhydrous ether (120 mL), *p*-toluenesulfonic acid (3.6 g, 0.83 mmol) and 1,2-propylene glycol (3.06 g, 53 mmol) were added. The stirring was maintained at room temperature for 24 h. GLC (**A**) then revealed no **5** and the presence of two new products (T_R 3.03, 97.5% and 3.35 min, 2.5%) indentified as **6** (see below) and its epimer at C-4 (**7**) (GLC-MS evidence), respectively. The reaction mixture was neutralised (solid $NaHCO_3$) and concentrated. Column chromatography (ether-hexane, 1:2) of the residue only allowed the isolation of **6** (1.06 g, 64.5%) as a colourless syrup. $[\alpha]_D^{26}$: -94.2 (c=1). IR (neat): 3445 (OH), 2975, 2941 and 2887 (C-H), 1240, 1197, 1098, 1059, 1045, 915, 899 and 869 cm^{-1} (C-O-C and 1,3-dioxolane ring). NMR data: ^1H: ∂ 4.41 (m, 1 H, H-1), 3.79 (dd, 1 H, $J_{7exo,7endo}$ 7.6, $J_{1,7exo}$ 5.4 Hz, H-7*exo*), 3.71 (dd, 1 H, $J_{1,7endo}$ 1 Hz, H-7*endo*), 3.60 (dt, 1 H, $J_{1,2}$ = $J_{2,3e}$ = 2, $J_{2,3a}$ 4.1 Hz, H-2), 2.53 (bs, 1 H, OH), 1.97 (ddq, 1 H, $J_{4,11}$ 6.7, $J_{3a,4}$ 11.8, $J_{3e,4}$ 5.3 Hz, H-4), 1.70 (dq, 2 H, $J_{9,10}$ 7.4, J 1.8 Hz, H-9,9), 1.63 (ddt, 1 H, $J_{3e,3a}$ 14.5, $J_{1,3e}$ = $J_{2,3e}$ = 2 Hz, H-3e), 1.49 (ddd, 1 H, H-3a), 0.90 (t, 3 H, H-10,10,10) and 0.80 (d, 3 H, H-11,11,11); ^{13}C: ∂ 111.52 (C-5), 78.14 (C-1), 67.80 (C-2), 67.42 (C-7), 33.91 (C-3), 33.77 (C-4), 27.09 (C-9), 16.04 (C-11) and 7.01 (C-10). Mass spectrum (c.i., CH_4): m/z 173 (100%, M^++1), 157 (2, M^+-Me), 155 (37, M^+-H_2O), 143 (1, M^+-Et), 137 (4, M^+-2H_2O), 85 (6, $C_5H_9O^+$), 79 (22, $C_6H_7^+$) and 57 (12, $C_3H_5O^+$).

(1R,2S,4S,5R)-2-Acetoxy-5-ethyl-4-methyl-6,8-dioxabicyclo[3.2.1]octane (8)

To a solution of **6** (50 mg, 0.3 mmol) in dry pyridine (0.5 mL), acetic anhydride (0.25 mL) was added and the mixture left at room temperature for 24 h. Work-up of the reaction as usual gave after column chromatography (ether-hexane, 1:1) **8** (52 mg, 81%) as a colourless syrup; T_R 4.95 min (A). IR (neat): 2984, 2943 and 2883 (C-H), 1739 (C=O), 1274, 1187, 1128, 1044, 980 and 897 cm^{-1} (C-O-C and 1,3-dioxolane ring). NMR data: ^1H ∂ 4.69 (dt, 1 H, $J_{1,2} = J_{2,3e} = 2$, $J_{2,3a}$ 4.2 Hz, H-2), 4.53 (dt, 1 H, $J_{1,7exo}$ 2, $J_{1,7endo}$ 7.7 Hz, H-1), 3.80 (t, 1 H, $J_{7endo,7exo} = J_{1,7endo}$ 7.7 Hz, H-7*endo*), 3.79 (dd, 1 H, H-7*exo*), 2.09 (s, 3 H, CH_3CO), 2.01 (dquin, 1 H, $J_{4,11} = J_{3e,4} = 6.5$, $J_{3a,4}$ 15.5 Hz, H-4), 1.80-1.54 (m, 4 H, H-3a,3e,9,9), 0.91 (t, 3 H, $J_{9,10}$ 7.4 Hz, H-10,10,10) and 0.81 (d, 3 H, H-11,11,11); ^{13}C: ∂ 170.99 (MeCO), 111.43 (C-5), 75.67 (C-1), 70.11 (C-2), 67.57 (C-7), 34.59 (C-4), 31.19 (C-3), 27.04 (C-9), 21.48 (MeCO), 16.04 (C-11) and 6.82 (C-10). Mass spectrum (c.i., CH_4): m/z 215 (47%, M^++1), 155 (100, M^++1-AcOH), 79 (33, $C_6H_7^+$) and 57 (12, $C_4H_5O^+$).

(1R,4S,5R)-5-Ethyl-4-methyl-2-methylene-6,8-dioxabicyclo[3.2.1]octane (10)

To a stirred solution of **6** (300 mg, 1.74 mmol) in dry dichloromethane (30 mL), molecular sieve (4 Å, 1 g) and pyridinium chlorochromate (750 mg, 3.5 mmol) were added. Stirring was continued for 2 h at room temperature. GLC (A) then showed that **6** had disappeared and that a new compound (T_R 2.71 min) was present. The reaction mixture was concentrated and the residue was extracted with ether (3 x 20 mL) and then concentrated. Column chromatography (ether-hexane, 1:2) of the residue gave **9** (293 mg, quantitative) as a colourless syrup, that was not further investigated, but its IR and NMR spectra showed that **9** was partially hydrated.

To a stirred suspension of methyltriphenylphosphonium bromide (5 g, 13.86 mmol) in anhydrous ether (25 mL) a 1.6 M methyl lithium solution (7.6 mL, 12.21 mmol) in the same solvent was added, and the resulting deep yellow solution left for 30 min at room temperature, under Ar. Then, a solution of **9** (1.13 g, 6.6 mmol) in anhydrous ether (25 mL) was added dropwise. After 15 min the GLC (A) analysis revealed the absence of **9** and the presence of a new compound (T_R 2.08 min). The reaction mixture was quenched with ether saturated with water, filtered through a cellite pad and the filtrated was washed with brine, water and then concentrated. Flash chromatography (ether-hexane, 1:6) of the residue gave **10** (450 mg, 45%) as a colourless syrup. $[\alpha]_D^{24}$: -43.5 (c=1, hexane). IR (neat): 2975, 2941 and 2884 (C-H), 1661 (C=C), 1242, 1182, 1169, 1126, 1043, 1031, 979, 916 and 903 cm^{-1} (C-O-C and 1,3-dioxolane ring). NMR data: ^1H: ∂ 4.80 (t, 1 H, $J_{3a,12} = J_{12,12'}$ 2 Hz, H-12), 4.73 (t, 1 H, $J_{3a,12'}$ 2 Hz, H-12'), 4.65 (d, 1 H, $J_{1,7exo}$ 4.8 Hz, H-1), 3.87 (dd, 1 H, $J_{7exo,7endo}$ 7 Hz, H-7*exo*), 3.82 (d, 1 H, H-7*endo*), 2.24 (dd, 1 H, $J_{3e,4}$ 5.7, $J_{3e,3a}$ 14 Hz, H-3e), 2.09 (ddt, 1 H, $J_{3a,4}$ 11 Hz, H-3a), 1.92 (m, 1 H, H-4), 1.74 (q, 2 H, $J_{9,10}$ 7.4 Hz, H-9,9), 0.93 (t, 3 H, H-10,10,10) and 0.88 (d, 3 H, $J_{4,11}$ 6.6 Hz, H-11,11,11); ^{13}C, ∂ 144.66 (C-2), 110.69 (C-5), 108.48 (C-12), 78.92 (C-1), 69.78 (C-7), 39.50 (C-4), 34.17 (C-3), 26.92 (C-9), 16.17 (C-11) and 7.03 (C-10). Mass spectrum: m/z 168 (9%, M^+), 140 (1, M^+-CO), 139 (3, M^+-Et), 138 (5, M^+-2 Me), 112 (15, M^+-CO-C_2H_4), 109 (11, $C_6H_5O_2^+$), 94 (20, $C_7H_{10}^+$), 79 (89, $C_6H_7^+$) and 57 (100, $C_5H_5O^+$).

(1S,2S,4S,5R)-5-Ethyl-2,4-dimethyl-6,8-dioxabyciclo[3.2.1]octano [(-)-∂-multistriatin, 1]

A solution of **10** (289 mg, 1.75 mmol) in anhydrous ether (25 mL), was hydrogenated over 10% Pd/C (30 mg) at 70 psi for 24 h. GLC (**B**) then showed no **10** and the presence of two new products (T_R 4.12, 94% and 4.46 min, 6%) identified as **1** (see below) and its epimer at C-2 (**11**) (GLC-MS analysis), respectively. The catalyst was filtered off, washed with ether and the filtrate cautiously concentrated. Column chromatography (*n*-pentane) of the residue gave **1** (196 mg, 68%) slightly impurified by **11**. Preparative GLC (**C**), allowed the isolation of **1**. $[\alpha]_D^{25}$: -74 (c=0.25, *n*-pentane), [lit.[5] $[\alpha]_D^{23}$: -84.7 (c=0.155, pentane)]. IR (neat): 2971, 2964, 2936 and 2884 (C-H), 1248, 1197, 1049, 1033, 912, 895 and 823 cm^{-1} (C-O-C and 1,3-dioxolane ring). NMR data: ^1H, ∂ 4.22 (m, 1 H, H-1), 3.84-3.79 (m, 2 H, H-7*endo*,7*exo*), 1.89 (ddq, 1 H, $J_{4,11}$ 6.7, $J_{3e,4}$ 5.3, $J_{3a,4}$ 12 Hz, H-4), 1.69 (q, 2 H, $J_{9,10}$ 7.5 Hz, H-9,9), 1.69-1.50 (m, 2 H, H-2,3a), 1.29 (ddt, 1 H, $J_{2,3e} = J_{1,3e}$ = 1.4, $J_{3a,3e}$ 13.7 Hz, H-3e), 1.13 (d, 3 H, $J_{2,12}$ 7 Hz, H-12,12,12), 0.91 (t, 3 H, H-10,10,10) and 0.78 (d, 3 H, H-11,11,11); ^{13}C, ∂ 111.45 (C-5), 78.96 (C-1), 69.97 (C-7), 35.51 and 33.02 (C-2,4), 32.49 (C-3), 27.35 (C-9), 17.96 (C-12), 16.44 (C-11) and 7.15 (C-10). Mass spectrum: m/z 170 (4%, M^+), 155 (0.5, M^+-Me), 140 (2, M^+-2Me), 128 (11), 125 (2, M^+-3Me), 113 (2), 99 (7, $C_6H_{11}O^+$), 96 (21, $C_7H_{12}^+$), 81 (15, $C_6H_9^+$), 71 (18, $C_4H_7O^+$) and 57 (100, $C_3H_5O^+$). The spectral data were identical to those found in the literature[5].

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