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Note

Enantiospecific synthesis of (*R*)-1,6-dioxaspiro[4.5]decane from a derivative of D-fructose *

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Spiroketal structures are of widespread occurrence, as such or as substructures, in many biologically active natural products[2]. We have reported[3] on the enantiospecific synthesis of several spiroketal compounds (micotoxines and pheromones) with a 1,7-dioxaspiro[5.5]undecane structure, starting from D-fructose.

The title compound (**1**) is the basic framework of several insect pheromones for which different syntheses of the racemic compound[2,4] have been reported, as has one enantiospecific synthesis[5]. We now describe an enantiospecific synthesis of **1** from 3-(1,2:3,4-di-*O*-isopropylidene-β-D-arabinopyranosyl)propanol[6] (**2**), obtainable in five steps from D-fructose.

Reaction of **2** with aqueous trifluoroacetic acid hydrolysed the isopropylidene groups and promoted intramolecular glycosidation to give the spiroketal (5*R*,8*R*,9*R*,10*S*)-8,9,10-trihydroxy-1,6-dioxaspiro[4.5]decane (**3**). The configuration at the spirano centre reflects the dispositions of substituents in the pyranose ring (cf. ref 2) and the anomeric effect[7].

Acetonation of **3** gave the 8,9-*O*-isopropylidene derivative **4**, which was transformed into its 10-xanthate **5**. Deoxygenation[8] of **5** afforded (5*R*,8*R*,9*S*)-8,9-isopropylidenedioxy-1,6-dioxaspiro[4.5]decane (**6**). Cautious hydrolysis of **6** removed the 8,9-isopropylidene group and gave the diol **7**, which was dideoxygenated through the thiocarbonyl derivative (**8**) by the Corey method[9] to produce an olefin, presumably (*R*)-1,6-dioxaspiro[4.5]dec-8-ene (^{1}H NMR evidence), that was not further investigated but hydrogenated to yield **1**. The low yields in the last two steps are probably due to losses because of the high volatility of these spiroketals.

* Enantiospecific Synthesis of Spiroacetals, Part IV. For Part III, see ref 1.
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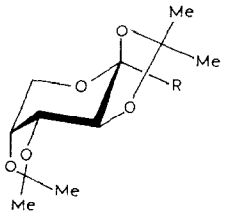
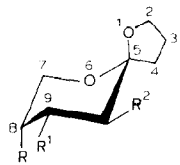


2 R = $CH_2CH_2CH_2OH$



1 R = R^1 = R^2 = H
3 R = R^1 = R^2 = OH
4 R, R^1 = O,O-CMe_2, R^2 = OH
5 R, R^1 = O,O-CMe_2, R^2 = OCSSMe
6 R, R^1 = O,O-CMe_2, R^2 = H
7 R = R^1 = OH, R^2 = H
8 R, R^1 = O,O-C=S, R = H

The ^1H and ^{13}C NMR data for **1**, and its mass spectrum, accorded with those reported by Iwata et al.[5] and Francke et al.[4], respectively. The discrepancy between the reported[5] $[\alpha]_D$ value for **1** (see Experimental) reflects the higher optical purity of the compound now described.

EXPERIMENTAL

General methods.—Solutions were dried over $MgSO_4$ before concentration under diminished pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AM-300 and WP-80 CW 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 Perkin–Elmer 141 polarimeter. GLC was performed at 115°C on a Perkin–Elmer 8410 gas chromatograph equipped with a flame-ionisation detector and a steel column (2 m × 0.125 in. i.d.) packed with 5% OV-17 on Chromosorb W (100–120 mesh). The N_2 flow rate was 30 mL/min, the injection port temperature was 250°C, and the zone-detector temperature was 250°C. TLC was performed on Silica Gel G (Merck) with detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734).

(5R,8R,9R,10S)-8,9,10-Trihydroxy-1,6-dioxaspiro[4.5]decane (**3**).—A solution of **2**[6] (7.8 g, 27 mmol) in aq 70% CF_3CO_2H (40 mL) was kept at room temperature overnight. TLC (5:1 $CHCl_3$–MeOH) then showed the absence of **2** and the presence of a slower-running product. The solvent was evaporated under vacuum, and a solution of the residue in EtOH (25 mL) was neutralised with solid K_2CO_3, filtered, and concentrated. Column chromatography ($CHCl_3 \rightarrow$ 10:1 $CHCl_3$–MeOH) of the residue gave **3** (4.95 g, 96.5%); mp 131–134°C (from $CHCl_3$); $[\alpha]_D$ −132° (*c* 1.1, MeOH); ν_{max}^{KBr} 3400, 3359, and 3350 (OH), 2984, 2955, 2936, and 2887

TABLE I

^{13}C NMR data for **1** and **3–8**

Compound	C-2	C-3	C-4	C-5	C-7	C-8	C-9	C-10	CMe_2	CMe_2	C–S	S–Me
1	67.01	23.74	33.51	105.65	61.67	25.29	20.35	37.68				
3	69.48	23.83	34.58	109.82	64.93	72.50	71.17	71.17				
4	68.83	23.89	33.52	107.33	59.70	72.04	73.93	78.11	109.21	28.64 26.22		
5	68.65	23.74	33.64	106.26	59.73	74.33 [a]	75.09 [a]	80.54	109.68	27.80 26.46	217.18	19.30
6	67.18	23.82	35.91	105.80	60.88	70.60 [b]	71.75 [b]	38.30	108.54	27.83 25.94		
7	67.53	23.38	36.63	106.76	63.80	66.60	67.88	37.49				
8	67.55	23.95	33.19	104.74	59.28	78.29	76.92	38.38			191.52	

[a,b] Assignments may be interchanged.

(C–H), 1116, 1105, 1085, 1033, 977, and 974 cm^{-1} (C–O–C). ^1H NMR data (CD_3OD): δ 3.98–3.86 (m, 2 H, H-9,10), 3.84–3.81 (m, 1 H, H-8), 3.84 (dd, 1 H, $J_{7a,8}$ 1.5 Hz, H-7a), 3.71 (bd, 2 H, H-2a,2b), 3.54 (dd, 1 H, $J_{7a,7b}$ 12.5, $J_{7b,8}$ 2 Hz, H-7b), 2.26–2.15 and 2.04–1.79 (2 m, 4 H, relative intensity 1:3, H-3a,3b,4a,4b). For the ^{13}C NMR data (CD_3OD), see Table I. Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.65; H, 7.35.

(5R,8R,9R,10S)-10-Hydroxy-8,9-isopropylidenedioxy-1,6-dioxaspiro[4.5]decane (**4**).—A solution of **3** (620 mg, 3.3 mmol) and *p*-toluenesulfonic acid (50 mg) in dry acetone (25 mL) was stirred for 50 h at room temperature with anhyd $CuSO_4$ (1 g). TLC (5:1 $CHCl_3$–MeOH) then revealed the presence of a compound of higher mobility. The mixture was neutralised (K_2CO_3), filtered, and concentrated. Column chromatography (3:2 ether–hexane) of the residue yielded **4** (400 mg, 53%) that crystallised on storage, mp 72–75°C; $[\alpha]_D$ −164.5° (*c* 0.8); ν_{max}^{film} 3518 (OH), 3001, 2992, 2957, 2934, 2886, and 2873 (C–H), 1393 and 1377 (CMe_2), 1251, 1232, 1216, 1165, 1130, 1117, 1100, 1079, 1028, 999, 986, 945, and 849 cm^{-1} (C–O–C and 1,3-dioxolane ring). ^1H NMR data: δ 4.16 (dd, 1 H, $J_{7a,8}$ 2.4, $J_{8,9}$ 5.7 Hz, H-8), 4.07 (dd, 1 H, $J_{9,10}$ 7.6 Hz, H-9), 3.98 (dd, 1 H, $J_{7a,7b}$ 13.4 Hz, H-7a), 3.90 (d, 1 H, H-7b), 3.98–3.85 (m, 2 H, H-2a,2b), 3.60 (t, 1 H, $J_{10,OH}$ 7.6 Hz, H-10), 2.23 (d, 1 H, HO-10), 2.27–2.14, 2.09–1.93, and 1.93–1.78 (3 m, 4 H, relative intensities 1:1:2, H-3a,3b,4a,4b), 1.52 and 1.36 (2 s, 6 H, CMe_2). For the ^{13}C NMR data, see Table I. Mass spectrum: *m/z* 216 (1%, $M^+ + 1 - Me$,), 215 (5, $M^+ - Me$), 212 (1, $M^+ - H_2O$,), 155 (1, $M^+ - Me - AcOH$), 145 (9), 143 (6), 101 (10, $C_5H_9O_2^+$), 100 (52, $C_5H_8O_2^+$), 87 (100), 85 (73, $C_5H_8O_2^+ - Me$), 69 (21), 59 (37, Me_2COH^+), and 43 (48, Ac^+). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.29; H, 7.95.

(5R,8R,9R,10S)-8,9-Isopropylidenedioxy-10-[(methylthio)thiocarbonyloxy]-1,6-dioxaspiro[4.5]decane (**5**).—To a stirred suspension of NaH (390 mg, 13 mmol; 80% oil dispersion), washed free of oil with hexane, in anhyd tetrahydrofuran (15

mL) under N_2 was added dropwise a solution of imidazole (40 mg) and **4** (1.47 g, 6.37 mmol) in the same solvent (15 mL). The mixture was boiled under reflux for 30 min, and CS_2 (0.9 mL, 14.5 mmol) and MeI (0.7 mL, 14.5 mmol) were added dropwise to the solution after 0.5 and 1 h, respectively. After a total period of 2 h, TLC (ether) then revealed the absence of **4** and the presence of a faster-running compound. The excess of NaH was destroyed with ether saturated with water (40 mL) and water (10 mL). The organic phase was separated and the aqueous phase was extracted with ether (2 × 10 mL). The combined extracts were washed with water and concentrated. Column chromatography (CH_2Cl_2) of the residue gave **5** (1.81 g, 89%); mp 180–182°C (from CH_2Cl_2–ether); $[\alpha]_D$ −167° (*c* 1); ν_{max}^{KBr} 2993, 2982, 2961, 2952, 2932, and 2895 (C–H), 1385 and 1374 (CMe_2), 1243, 1224, 1209 (C=S), 1162, 1129, 1111, 1101, 1077, 1033, 1024, 991, 976, 947, 923, and 847 cm^{-1} (C–O–C, C–S–C, and 1,3-dioxolane ring). ^1H NMR data: δ 6.10 (d, 1 H, $J_{9,10}$ 8 Hz, H-10), 4.42 (dd, 1 H, $J_{8,9}$ 5.4 Hz, H-9), 4.24 (dd, 1 H, $J_{7a,8}$ 2.4 Hz, H-8), 4.05 (dd, 1 H, $J_{7a,7b}$ 13.4 Hz, H-7a), 3.97 (d, 1 H, H-7b), 3.95 (dd, 1 H, *J* 5.4, $J_{2a,2b}$ 8 Hz, H-2a), 3.88 (dd, 1 H, *J* 5.4 Hz, H-2b), 2.56 (s, 3 H, SMe), 2.04–1.74 (m, 4 H, H-3a,3b,4a,4b), 1.56 and 1.33 (2 s, 6 H, CMe_2). For the ^{13}C NMR data, see Table I. Mass spectrum: *m/z* 305 (1%, M^+ − Me), 245 (4, M^+ − Me − AcOH), 213 (21, M^+ − OCSSMe), 212 (71, M^+ − OCS − MeSH), 182 (98), 154 (47, M^+ − OCS − MeSH − Me_2CO), 143 (21), 111 (29), 99 (72), 91 (100, $MeSCS^+$), 85 (64), 83 (57), 71 (73), and 43 (45, Ac^+). Anal. Calcd for $C_{13}H_{20}O_5S_2$: C, 48.75; H, 6.29. Found: C, 48.68; H, 6.36.

(5R,8R,9S)-8,9-Isopropylidenedioxy-1,6-dioxaspiro[4.5]decane (**6**).—A solution of **5** (1.743 g, 5.4 mmol) and azobis(isobutyronitrile) (50 mg) in dry toluene (25 mL) was added dropwise to a stirred solution of tributyltin hydride (2 mL, 6.9 mmol) in the same solvent (25 mL) boiling under reflux under dry N_2. Boiling under reflux was continued overnight. TLC (3:2 ether–hexane) then revealed that **5** had disappeared and that a compound of lower mobility was present. Concentration of the solvent and column chromatography (1:3 ether–hexane) of the residue afforded **6** (1.03 g, 89%), isolated as a colourless syrup; $[\alpha]_D$ −121° (*c* 1.2); ν_{max}^{film} 2987, 2940, and 2888 (C–H), 1382, and 1371 (CMe_2), 1245, 1218, 1163, 1111, 1065, 1022, 990, and 863 cm^{-1} (C–O–C and 1,3-dioxolane ring). ^1H NMR data: δ 4.40 (q, 1 H, $J_{8,9} = J_{9,10} = 6.7$ Hz, H-9), 4.04 (dt, 1 H, $J_{7a,8} = J_{7b,8} = 1.6$ Hz, H-8), 3.90–3.78 (m, 4 H, H-2a,2b,7a,7b), 2.14–1.98, 1.90–1.77, and 1.74–1.64 (3 m, relative intensities 2:1:1, H-3a,3b,4a,4b), 1.95 (d, 2 H, H-10,10), 1.48 and 1.31 (2 s, 6 H, CMe_2). For the ^{13}C NMR data, see Table I. Mass spectrum: *m/z* 214 (0.2%, M^+), 201 (1.0, M^+ + 2 − Me), 200 (10.8, M^+ + 1 − Me), 199 (93.8, M^+ − Me), 184, (5.0, M^+ − H_2CO), 157 (4.9, M^+ + 1 − Me_2CO), 139 (25.6, M^+ − Me − AcOH), 126 (8.2), 113 (23.4), 100 (26.3, $C_5H_8O_2^+$), 97 (20.0), 85 (37.8, $C_5H_8O_2^+$ − Me), 84 (12.4), 59 (21.9, Me_2COH^+), 55 (16.4) and 43 (100, Ac^+).

(5R,8R,9S)-8,9-Dihydroxy-1,6-dioxaspiro[4.5]decane (**7**).—A solution of **6** (960 mg, 4.5 mmol) in aq 60% acetic acid (15 mL) was heated at 40°C for 1 h. TLC (EtOAc) then revealed the presence of a slower-running product. The solvent was

evaporated and the remaining acetic acid eliminated by repeated codistillation with toluene. Column chromatography (EtOAc) of the residue gave **7**, isolated as a syrup (708 mg, 91%); $[\alpha]_D$ −103° (*c* 0.9); ν_{max}^{film} 3422 (OH), 2942 and 2887 (C–H), 1165, 1087, 1065, 1031, 1005, 976, and 844 cm^{-1} (C–O–C). ^1H NMR data (80 MHz): δ 4.25–3.50 (m, 6 H, H-2a,2b,7a,7b,8,9), 2.75–2.40 (m, 2 H, HO-8,9), and 2.25–1.50 (m, 6 H, H-3a,3b,4a,4b,10a,10b). For the ^{13}C-NMR data, see Table I. Mass spectrum: *m/z* 175 (1%, $M^+ + 1$), 174 (3, M^+), 157 (3, $M^+ - OH$), 143 (62, $M^+ - H_2CO$), 125 (56, $M^+ - H_2CO - H_2O$), 114 (35), 113 (47), 97 (37), 87 (96), 85 (88), 84 (64), 71 (40), and 43 (100, Ac^+).

(5R,8R,9S)-8,9-Thiocarbonyldioxy-1,6-dioxaspiro[4.5]decane (**8**).—To a stirred solution of **7** (668 mg, 3.8 mmol) in dry toluene (13 mL) was added, 1,1′-thiocarbonyldiimidazole (970 mg, 5.45 mmol), and the mixture was boiled under reflux for 3 h. TLC (EtOAc) then revealed the presence of a new compound of higher mobility. The mixture was cooled, washed with water, and concentrated. Column chromatography (1:3 → 3:1 ether–hexane) of the residue gave **8** (593 mg, 72%); mp 120–122°C (from ether–hexane); $[\alpha]_D$ −72° (*c* 1.1); ν_{max}^{KBr} 2994, 2981, 2965, 2952, and 2899 (C–H), 1389, 1375, 1353, 1341, 1313, 1270, 1242, 1226, 1183, 1163, 1085, 1071, 1047, 1009, 973, and 914 cm^{-1} (C=S and C–O–C). ^1H NMR data: δ 5.18 (dt, 1 H, $J_{8,9}$ 7.7, $J_{9,10}$ 5.7 Hz, H-9), 4.84 (br dt, 1 H, H-8), 3.99 (d, 1 H, $J_{7a,7b}$ 14 Hz, H-7a), 3.92 (dd, 1 H, $J_{7b,8}$ 2 Hz, H-7b), 3.92–3.78 (m, 2 H, H-2a,2b), 2.19 (d, 2 H, H-10,10), 2.15–1.98, 1.97–1.82, and 1.79–1.72 (3 m, 4 H, relative intensities 2:1:1, H-3a,3b,4a,4b). For the ^{13}C NMR data, see Table I. Mass spectrum: *m/z* 218 (4, $M^+ + 2$), 217 (8, $M^+ + 1$), 216 (72, M^+), 174 (6), 139 (12), 130 (16), 113 (20), 87 (68), 84 (100), 70 (50), and 55 (45). Anal. Calcd for $C_9H_{12}O_4S$: C, 50.00; H, 5.60. Found: C, 50.34; H, 5.63.

(R)-1,6-Dioxaspiro[4.5]decane (**1**).—A solution of **8** (580 mg, 2.7 mmol) in trimethyl phosphite (1 mL, 8.5 mmol) was heated under reflux for 2.5 h. TLC (ether) then revealed the presence of a compound of higher mobility. The mixture was diluted with ether (10 mL) and stirred with aq 25% NaOH (2 mL) overnight. The organic phase was separated, washed with water, and concentrated at 15°C. Column chromatography (1:5 ether–pentane) of the residue yielded a fraction (120 mg), which showed a main peak (t_R 3.49 min, 96%) in GLC and which had an ^1H NMR spectrum (80 MHz) that contained signals for vinylic (br d, δ 5.75) and acetalic (m, δ 4.25–3.63) protons as well as for methylene protons. On this basis, the structure of (*R*)-1,6-dioxaspiro[4.5]dec-8-ene was assigned.

A solution of the above compound in ether (10 mL) was hydrogenated over 5% Pd–C (40 mg) in the presence of one drop of Et_3N for 24 h at 4 atm. Monitoring of the reaction by GLC showed the loss of the peak with t_R 3.49 and the appearance of one with t_R 2.68 min. The mixture was filtered and concentrated at 0°C. Column chromatography (1:5 ether–pentane) of the residue gave **1** (32 mg, 10%); $[\alpha]_D$ −101° (*c* 0.3, pentane); lit.[5] $[\alpha]_D$ −44.4° (*c* 0.6, pentane). ^1H NMR data: δ 4.10–3.40 (m, 4 H) and 1.30–2.10 (m, 10 H). For the ^{13}C NMR data, see Table I. Mass spectrum: *m/z* 143 (2%, $M^+ + 1$), 142 (16, M^+), 114 (12), 112 (13),

101 (28), 100 (17), 97 (23), 87 (100), 86 (37), 85 (11), 84 (76), 83 (23), 56 (27), 55 (27), 43 (14, Ac^+), 42 (14), and 41 (14).

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