Supplementary Material (ESI) for Chemical Communications

ELECTRONIC SUPPLEMENTARY INFORMATION (ESI)

The First Enantioselective Total Synthesis of the Anti-*Helicobacter Pylori* Agent (+)-Spirolaxine Methyl Ether

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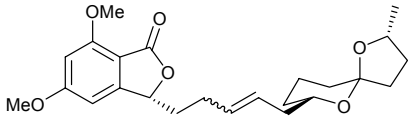
Experimental Details

(*3R, 2''R, 5''R, 7''R*)-5,7-Dimethoxy-3-[5'-(2''-methyl-1'',6''-dioxaspiro[4.5]dec-7''-yl)pent-3'-enyl]-3*H*-isobenzofuran-1-one



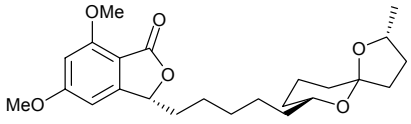
Sulphone **3** (150 mg, 0.39 mmol) was dissolved in tetrahydrofuran (7.5 cm^{-3}) and cooled to -78 °C under an atmosphere of nitrogen. To this stirred solution was added dropwise lithium diisopropylamine (0.43 cm^{-3}, 0.43 mmol, 1 mol dm^{-3}). The resultant deep yellow solution was stirred for 0.75 h before the dropwise addition of aldehyde **4** (98 mg, 0.39 mmol) in tetrahydrofuran (2.5 cm^{-3}). After stirring at -78 °C for 4 h the solution was allowed to slowly warm to room temperature and was stirred for a further 0.75 h. The reaction was quenched by the addition of brine (3 cm^{-3}) and the aqueous layer was extracted with ethyl acetate (3 x 15 cm^{-3}). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed *in vacuo*. The resultant oil was purified by flash column chromatography using hexane-ethyl acetate (9:1-1:1) as the eluent to give the *title compound* (65 mg, 40%) as a yellow oil; $[\alpha]_D$ +58.6 (*c* 0.97 in CH_3Cl); ν_{max}(film)/cm^{-1} 2929, 1758s (CO), 1613s, 1462, 1338, 1218, 1159, 1056 and 980; δ_H (400 MHz, $CDCl_3$): 1.08-1.30 (2 H, m, H8"$_a$ and H8"$_a$*), 1.21 (3 H, d, J = 6.3 Hz, Me), 1.22 (3 H, d, J = 6.3 Hz, Me*), 1.34-1.42 (2 H, m, H3"$_a$ and H3"$_a$*), 1.55-1.59 (2 H, m, H8"$_b$ and H8"$_b$*), 1.62-1.67 (6 H, m, H9"$_a$, H9"$_a$*, H10" and H10"*), 1.70-1.79 (4 H, m, H4"$_a$, H4"$_a$*, H1'$_a$ and H1'$_a$*), 1.80-1.89 (4 H, m, H4"$_b$, H4"$_b$*, H9"$_b$ and H9"$_b$*), 1.96-2.03 (2 H, m, H1'$_b$ and H1'$_b$*), 2.03-2.11 (4 H, m, (*E*)-H5'$_a$, (*E*)-H5'$_a$*, H3"$_b$ and H3"$_b$*), 2.12-2.17 (4 H, m, (*E*)-H5'$_b$, (*E*)-H5'$_b$*, (*Z*)-H5' and (*Z*)-H5'*), 2.18-2.25 (4 H, m, (*E*)-H2',

(*E*)-H2'*, (*Z*)-H2'$_a$ and (*Z*)-H2'$_a$*), 2.26-2.34 (2 H, m, (*Z*)-H2'$_b$ and (*Z*)-H2'$_b$*), 3.71-3.80 (2 H, m, H7'' and H7''*), 3.89 (3 H, s, OMe), 3.89 (3 H, s, OMe*), 3.95 (6 H, s, OMe and OMe*), 4.13 (1 H, qd, *J* = 6.3 and 6.3 Hz, H2''), 4.15 (1 H, qd, *J* = 6.3 and 6.3 Hz, H2''*), 5.31 (1 H, dd, *J* = 8.3 and 3.4 Hz, H3), 5.33 (1 H, dd, *J* = 8.3 and 3.4, H3*), 5.41-5.55 (4 H, m, H3', H3'*, H4' and H4'*), 6.40-6.41 (2 H, m, H6 and H6*), 6.42 (2 H, s, H4 and H4*); δ_C (100 MHz, $CDCl_3$): 20.3 (CH_2, C9''), 20.3 (CH_2, C9''*), 21.1 (CH_3, Me), 21.2 (CH_3, Me*), 22.8 (CH_2, (*Z*)-C2'), 27.8 (CH_2, (*E*)-C2'), 30.4 (CH_2, C8''), 31.3 (CH_2, C3''), 33.4 (CH_2, C10''), 33.5 (CH_2, C10''*), 34.0 (CH_2, (*Z*)-C5'), 34.8 (CH_2, C1'), 34.8 (CH_2, C1'*), 38.0 (CH_2, C4''), 38.0 (CH_2, C4''*), 39.5 (CH_2, (*E*)-C5'), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 69.9 (CH, C7''), 73.6 (CH, C2''), 73.7 (CH, C2''*), 79.0 (CH, C3), 79.2 (CH, C3*), 97.3 (CH, C6), 98.7 (CH, C4), 106.1 (quat., C5''), 106.8 (quat., C7a), 106.9 (quat., C7a*), 127.9 (CH, C3'), 128.8 (CH, C3'*), 129.0 (CH, C4'), 129.9 (CH, C4'*), 155.1 (quat., C3a), 155.2 (quat., C3a*), 159.6 (quat., C7), 166.7 (quat., C5), 168.5 (quat., C1); *m/z* (EI): 416 (M^+, 3%), 398 (11), 316 (7), 262 (14), 207 (42), 193 (50), 155 (100), 137 (39), 111 (47), 98 (25), 95 (26), 55 (38), 41 (36); HRMS (EI): Found M^+, 416.21999. $C_{24}H_{32}O_6$ requires *M*, 416.21989.

Notes

- The use of * is used to denote either (*E*) or (*Z*) isomers.
- The ratio of (*E*):(*Z*) isomers was unable to be determined and was not relevant to the synthesis.

(*3R, 2''R, 5''R, 7''R*)-5,7-Dimethoxy-3-[5'-(2''-methyl-1'',6''-dioxaspiro[4.5]dec-7''-yl)pentyl]-3*H*-isobenzofuran-1-one (2)



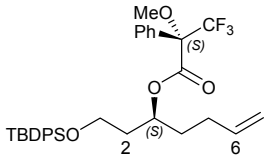
The above alkene (10 mg, 0.02 mmol) was dissolved in tetrahydrofuran (10 cm^{-3}) and stirred under a double balloon containing hydrogen in the presence of PtO_2 (1 mg) for 6 h. The catalyst was removed by filtration through a pad of Celite® and the solvent removed under reduced pressure. Purification of the resultant oil by flash column

chromatography using pentane-diethyl ether (4:6-2:8) as the eluent gave the *title compound* **2** (10 mg, 99%) as a yellow oil; $[\alpha]_D$ +63.7 (*c* 0.85 in CH_3Cl) (lit.[2] $[\alpha]_D$ +62 (c = 0.22, $CHCl_3$); ν_{max}(film)/cm^{-1} 2933, 2860, 1756s (CO), 1605s, 1494, 1459, 1432, 1336, 1218, 1158, 1052, 1029 and 980; δ_H (400 MHz, $CDCl_3$): 1.14 (1 H, dddd, *J* = 13.0, 13.0, 13.0 and 3.8 Hz, H8"$_a$), 1.23 (3 H, d, *J* = 6.6 Hz, Me), 1.25-1.48 (7 H, m, H3', H4', H5' and H3"$_a$), 1.51-1.56 (1 H, m, H8"$_b$), 1.59-1.72 (4 H, m, H1'$_a$, H9"$_a$ and H10"), 1.74 (1 H, ddd, *J* = 12.7, 10.4 and 6.6 Hz, H4"$_a$), 1.80-1.89 (2 H, m, H4"$_b$ and H9"$_b$), 1.94-2.01 (1 H, m, H1'$_b$), 2.12 (1 H, dddd, *J* = 11.9, 8.8, 6.6 and 6.6 Hz, H3"$_b$), 3.66-3.72 (1 H, m, H7"), 3.89 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.14 (1 H, qd, *J* = 6.6 and 6.6 Hz, H2"), 5.30 (1 H, dd, *J* = 7.8 and 3.8 Hz, H3), 6.40 (1 H, s, H6), 6.42 (1 H, d, *J* = 1.7 Hz, H4); δ_C (100 MHz, $CDCl_3$): 20.4 (CH_2, C9"), 21.3 (CH_3, Me), 24.5 (CH_2, C2'), 25.4 (CH_2, C4'), 29.3 (CH_2, C3'), 30.9 (CH_2, C8"), 31.3 (CH_2, C3"), 33.5 (CH_2, C10"), 34.8 (CH_2, C1'), 36.1 (CH_2, C5'), 38.0 (CH_2, C4"), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 69.9 (CH, C7"), 73.9 (CH, C2"), 79.9 (CH, C3), 97.3 (CH, C6), 98.6 (CH, C4), 106.0 (quat., C5"), 107.0 (quat., C7a), 155.2 (quat., C3a), 159.6 (quat., C7), 166.6 (quat., C5), 168.5 (quat., C1); *m/z* (EI): 418 (M^+, 6%), 361 (28), 318 (41), 293 (22), 290 (15), 261 (18), 207 (46), 193 (66), 155 (44), 111 (29), 98 (100), 57 (45), 55 (41), 43 (34), 41 (45); HRMS (EI): Found M^+, 418.23585. $C_{24}H_{34}O_6$ requires *M*, 418.23554. This data was in agreement with that reported in the literature.[1,2]

1. For the ^1H and ^{13}C NMR data of natural spirolaxine methyl ether: M. A. Gaudliana, L. H. Huang, T. Kaneko, and P. C. Watts, *PCT Int. Appl.*, 1996, WO 9605204; CAN 125:58200.
2. For the IR and optical rotation +62° (c = 0.22, $CHCl_3$) of *semi-synthetic* spirolaxine methyl ether (prepared by methylation of natural spirolaxine): T. Adaci, I. Takagi, K. Kondo, A. Kawashima, A. Kobayashi, I. Taneoka, S. Morimoto, B. M. Hi, and Z. Chen, *PCT Int. Appl.*, 1996, WO 9610020; CAN 125:86482.

Supplementary Material (ESI) for Chemical Communications

(*2'S*)-((*3S*)-1-(*tert*-butyldiphenylsilyloxy)hept-6-en-3-yl)-3',3',3'-trifluoro-2'-methoxy-2'-phenylpropanoate



To a suspension of (*S*)-2-methoxy-2-trifluoromethyl-2-phenylacetic acid (48 mg, 0.20 mmol), 4-dimethylaminopyridine (3 mg, 0.03 mmol) and dicyclohexylcarbodiimide (70 mg, 0.34 mmol) in dichloromethane (1 cm^{-3}) was added alcohol (50 mg, 0.14 mmol) in dichloromethane (1 cm^{-3}). After stirring at room temperature for 72 h the reaction was quenched by the addition of brine (2 cm^{-3}). The mixture was diluted with diethyl ether (5 cm^{-3}) and the aqueous layer extracted with diethyl ether (3 x 5 cm^{-3}). The combined extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Flash column chromatography using hexane-diethyl ether (9:1) as the eluent gave the *title compound* (65 mg, 82%) as a colourless oil; δ_H (300 MHz, $CDCl_3$): 1.05 (9 H, s, Si^t*Bu*Ph_2), 1.67-1.74 (2 H, m, H4), 1.82-1.89 (2 H, m, H2), 1.90-2.02 (2 H, m, H5), 3.45 (3 H, s, OMe), 3.70 (2 H, t, *J* = 6.3 Hz, H1), 4.92-4.98 (2 H, m, H7), 5.36 (1 H, q, *J* = 6.2 Hz, H3), 5.71 (1 H, dddd, *J* = 17.6, 9.7, 6.5 and 6.5 Hz, H6), 7.38-7.42 (9 H, m, Si^{t}Bu*Ph*$_2$, *p* and *m* and ArH, *p* and *o* or *m*), 7.50-7.52 (2 H, m, ArH, *o* or *m*), 7.62-7.66 (4 H, m, Si^{t}Bu*Ph*$_2$, *o*); δ_F (282 MHz, $CDCl_3$) -72.47 (0.09F, CF_3), -72.29 (2.91F, CF_3). Integration of these resonances established the enantiomeric excess to be 94%.