Enantioselective Synthesis of *S*-(+)-Pantolactone

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Supporting Information

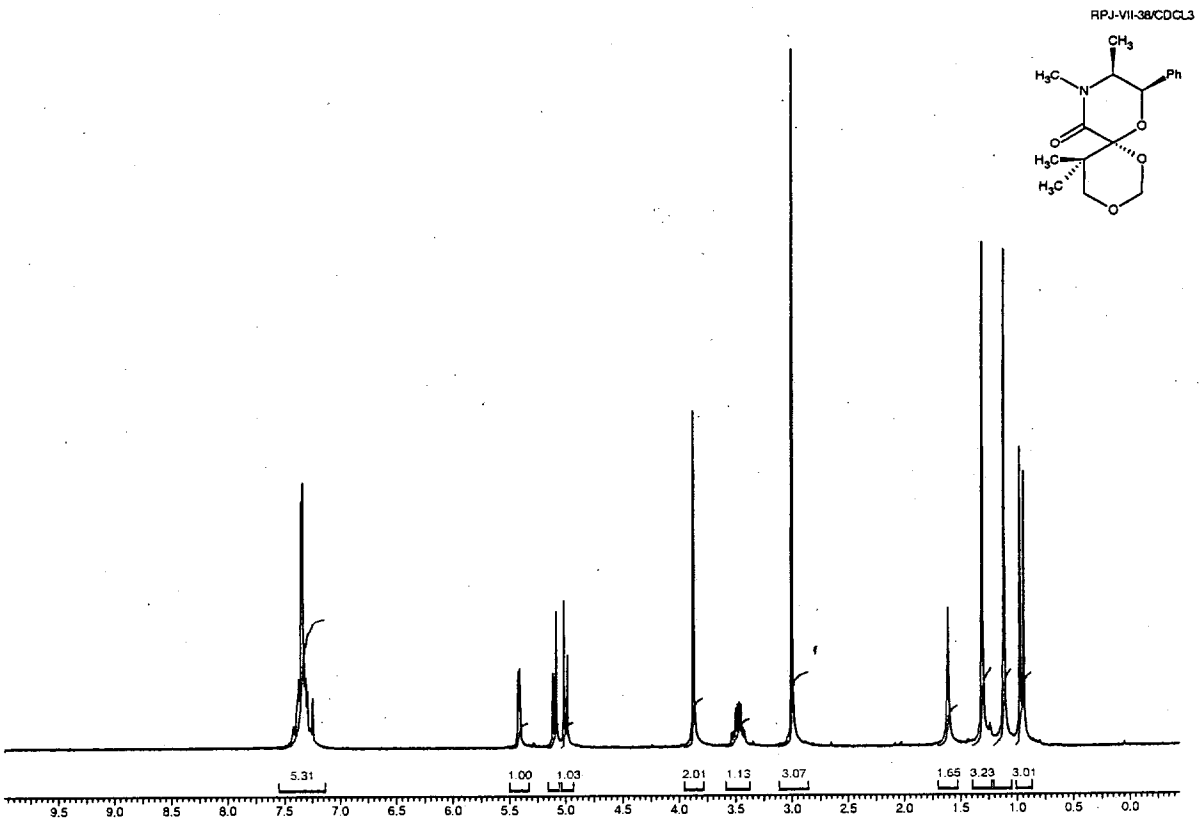
8*R*,6*R*,9*S*,5,5,9,10-Tetramethyl-1,3,7-trioxa-10-aza-spiro[5,5]undecan-11-one:
Prins reaction of 2 with $(CH_2O)_n/H_2SO_4$ in CH_3COOH: Conc. H_2SO_4 (0.25 g, 2.55 mmol) was added to a mixture of the alkylidene morpholinone (1.2 g, 4.9 mmol) and paraformaldehyde (0.735 g, 24.5 mmol) in glacial acetic acid (20 mL) and the reaction mixture was heated at an oil bath tempereture of 75-80°C for 1 h. It was neutralized with saturated aq. $NaHCO_3$ and extracted with ether. The ether layer was washed with water, 2N HCl followed by water and dried over Na_2SO_4. Removal of the solvent under reduced pressure furnished 1.234 g of the crude product as clear colourless gum. Purification by flash chromatography over silica gel (petroleum ether/ethyl acetate 7/3) furnished 1.086g (72%) of the spiro acetal **3** as a white solid. IR ($CHCl_3$): 3017, 2982, 1655, 1479, 1215, 1178, 1150, 1132, 1097, 1036, 1013, 976 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.5-7.2 (m, 5H, Ar*H*), 5.4 (d, 1H, *J* = 3.4, PhC*H*), 5.1 (d, 1H, *J* = 5.9, OCH_2O), 5.0 (d, 1H, *J* = 5.9, OCH_2O), 3.85 (s, 2H, OCH_2C), 3.45 (dq, 1H, *J* = 3.4, 6..3, CH_3C*H*), 3.00 (s, 3H, NCH_3), 1.30 (s, 3H, CCH_3), 1.1 (s, 3H, CCH_3), 0.95 (d, 3H, *J* = 6.3, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0 (*C*=O), 137.2 (Ar*C*), 128.4 (Ar*C*H), 127.6 (Ar*C*H), 125.4 (Ar*C*H), 99.4 (O*C*O (quat)), 88.3 (O-*C*H_2-O), 74.5 (C*C*H_2O), 70.7 (Ph*C*H), 58.9 (CH_3*C*H), 38.0 ((CH_3)$_2$*C*), 33.5 (N*C*H_3), 22.0 (C*C*H3), 21.3 (C*C*H_3), 12.4 (CH*C*H_3); MS (70 eV) m/z 91 (8), 105 (3), 118 (100), 146 (4), 220 (3), 305 (M^+, 3). HRMS (CI, NH_3): for $C_{17}H_{24}NO_4$ $[M + H]^+$ calcd 306.1706, found 306.1707.

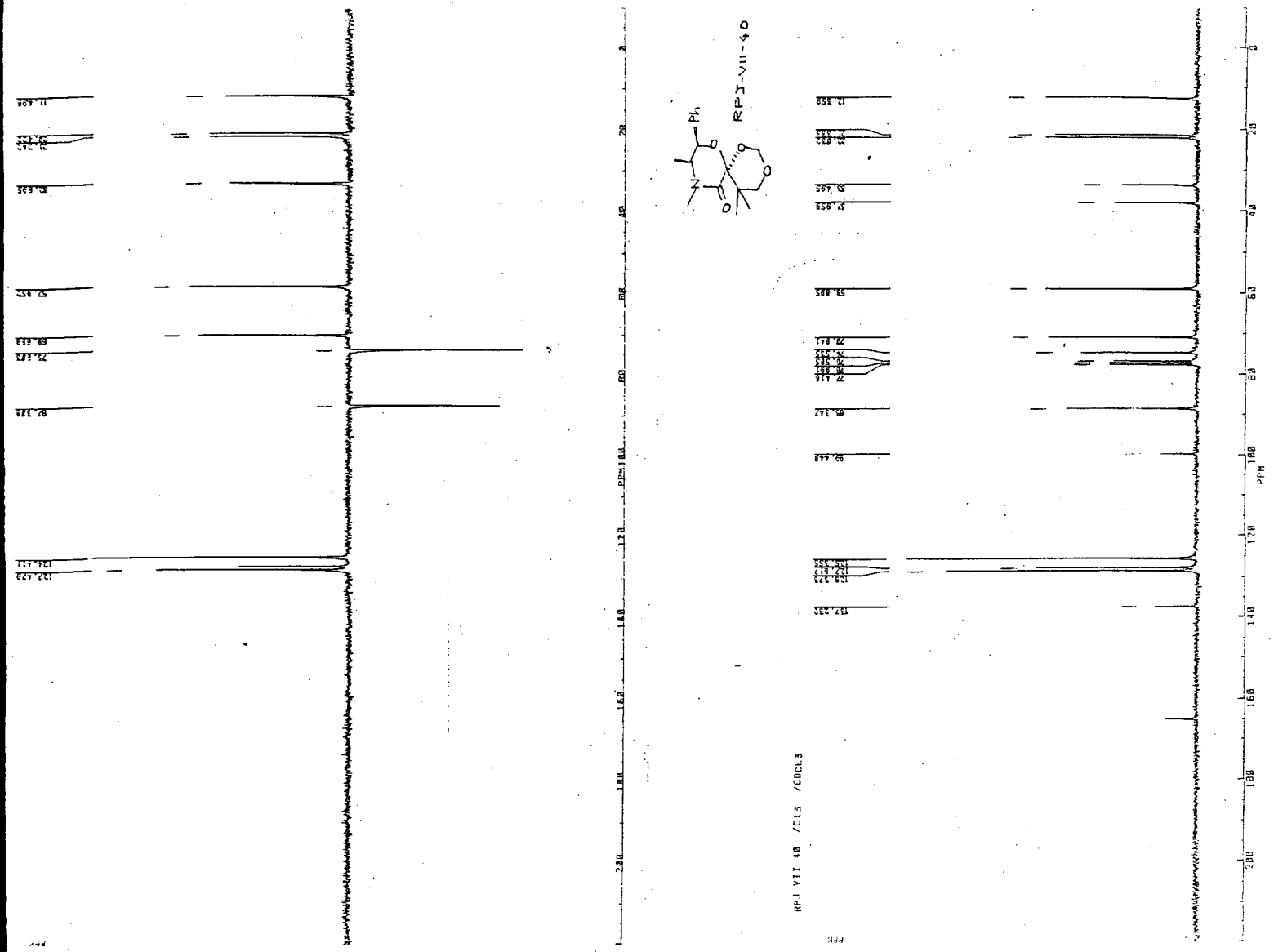
2*S*,5*S*,6*R*-4,5-Dimethyl-6-phenyl-2-(1,1-dimethyl-2-methoxy ethyl) morpholin-3-one:
Reductive cleavage of spiro acetal 3 with $TiCl_4/Et_3SiH$: To the solution of **3** (1.08 g, 3.54 mmol) in dichloromethane (30 mL) at -78°C was added Et_3SiH (11.3 mL, 70.8 mmol) followed by $TiCl_4$ (4.65 mL, 42.48 mmol) and the reaction mixture was slowly warmed to and stirred at ambient temperature for 24 h. It was then cooled to 0 °C, saturated aqueous NH_4Cl was added and the mixture was warmed up to ambient temperature. Water was added to dissolve precipitated solids and the solution was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to furnish 1.22 g crude product which on purification by flash chromatography on silica gel furnished 990 mg (96%) of **5** as clear colourless gum. IR (neat): 2976, 2932, 2874, 1651, 1477, 1452, 1396, 1379, 1308, 1252, 1150, 1111, 1063 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.5-7.2 (m, 5H, Ar*H*), 4.9 (d, 1H, *J* = 2.9, PhC*H*), 4.25 (s, 1H, C*H*O), 3.55 (d, 1H, *J* = 8.8, CH_2), 3.45 (d, 1H, *J* = 8.8, CH_2), 3.48 (dq, 1H, *J* = 2.9, 6.6, MeC*H*), 3.35 (s, 3H, OCH_3), 3.0 (s, 3H, NCH_3), 1.15 (s, 6H, C(CH_3)$_2$), 0.95 (d, 3H, *J* = 6.6, CHCH_3); ^{13}CNMR (22.5 MHz, $CDCl_3$): δ 168.3 (*C*=O), 138.0 (Ar*C*), 127.9, 127.1, 125.1 (Ar*C*H),81.3 (*C*H-O), 79.4 (*C*H_2O), 76 (Ph*C*H), 58.7, 58.4 (O*C*H_3,

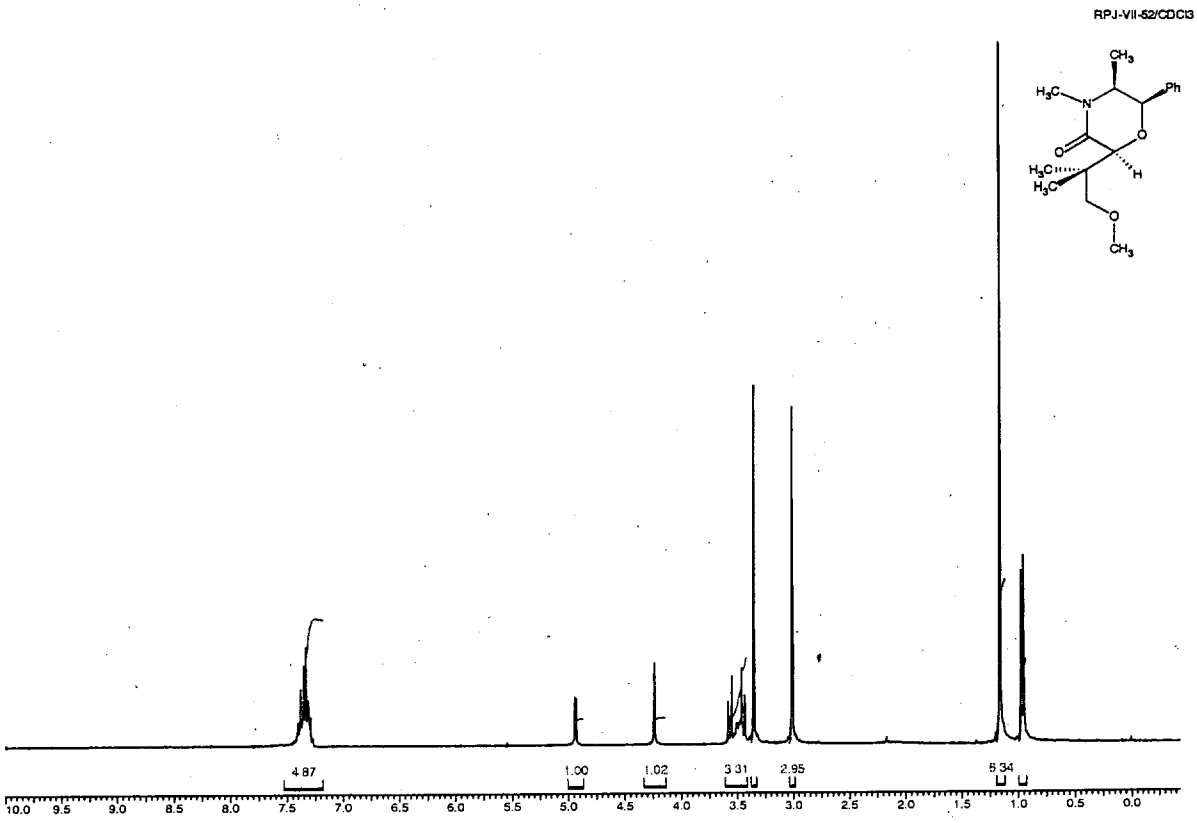
CH_3CH), 39.8 (N*C*H_3), 33 (*C*(CH$_3$)$_2$), 21.7 (C(*C*H_3)$_2$), 12.7 (*C*H_3CH); MS (70eV) m/z 58 (7), 84 (33), 118 (100), 140 (15), 148 (7), 205 (70), 276 (1), 291 (M^+, 1); HRMS (CI, NH_3): for $C_{17}H_{26}NO_3$ $[M + H]^+$ calcd 292.1913, found 292.1913.

2*S*-3,3-Dimethyl-2-hydroxy-4-methoxybutanoic acid *N*-methyl amide:
Dissolving metal reduction of 5: To anhydrous liquid ammonia (25 mL, distilled over sodium) was added Na metal (0.8 g, 34.7 mmol) at -78 °C and the mixture stirred for 15 minutes. To the resulting blue solution was added a solution of **5** (0.98 g, 3.36 mmol) in anhydrous THF (2 mL) and the mixture was stirred for 10-15 sec. Anhydrous ammonium chloride (6 g) was added and the mixture was warmed to ambient temperature to remove ammonia. The resulting solid mass was extracted with hot ethyl acetate to furnish 0.8 g of the crude product. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 2/8 furnished 369 mg (62%) of **6**. IR ($CHCl_3$): 3431, 2964, 2936, 2880, 2251, 1666, 1541, 1477, 1414, 1101, 1074, 908 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.8 (br s, 1H, N*H*), 4.45 (d, 1H, J = 3.6, O*H*), 4.00 (d, 1H, *J* = 3.6, C*H*), 3.35 (s, 3H, OC*H*$_3$), 3.35 (d, 1H, *J* = 9.2, C*H*$_2$), 3.25 (d, 1H, *J* = 9.2, C*H*$_2$), 2.85 (d, *J* = 5.1, 3H, NC*H*$_3$), 1.00 (s, 6H, C(C*H*$_3$)$_2$). ^{13}CNMR (22.5 MHz, $CDCl_3$): d 172.9 (*C*=O), 81.7 (*C*HOH), 77.9 (O*C*H$_2$), 59.1 (O*C*H$_3$), 38.4 (*C*(CH$_3$)$_2$), 25.0, 25.3 (N*C*H$_3$), 21.6 (C(*C*H$_3$)$_2$), 20.2 (C(*C*H$_3$)$_2$); HRMS (CI, NH_3): for $C_8H_{18}NO_3$ $[M + H]^+$ calcd 176.1287, found 176.1288.

***S*-(+)-Pantolactone (7)**: To the solution of **6** (0.1 g, 0.57 mmol) in CH_2Cl_2 (4 mL) was added at -78°C BBr_3 (2M in CH_2Cl_2, 2.5 mL) and the resulting mixture was slowly warmed to and stirred at -15°C for 2h. Water (2 mL) was added and the reaction mixture was stirred for an additional 10 min after which 2 mL of ice cold 6M H_2SO_4 was added dropwise and the reaction mixture was slowly warmed to and stirred at ambient temperature for 12 h. It was cooled (ice bath) and neutralized by addition of small portions of solid $NaHCO_3$. The resulting semi-solid residue was extracted with hot CH_2Cl_2 to furnish 72 mg of the crude lactone as clear colorless oil. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 6/4 furnished 51 mg (68%) of *S*-(+)-pantolactone as a white solid. IR ($CHCl_3$): 3445, 1782, 1113, 1007 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.1 (d, 1H, J = 3.7, C*H*OH), 4.03 (d, 1H, *J* = 9.2, C*H*$_2$), 3.95 (d, 1H, *J* = 9.2, C*H*$_2$), 2.82 (d, 1H, *J* = 3.7, O*H*), 1.24 (s, 3H, C*H*$_3$), 1.08 (s, 3H, C*H*$_3$); MS (70eV) m/z 57 (19), 68 (15), 71 (100), 85 (2), 130 (M^+, 1); $[\alpha]_D^{25}$ = +51.6 (*c* 2, H_2O).



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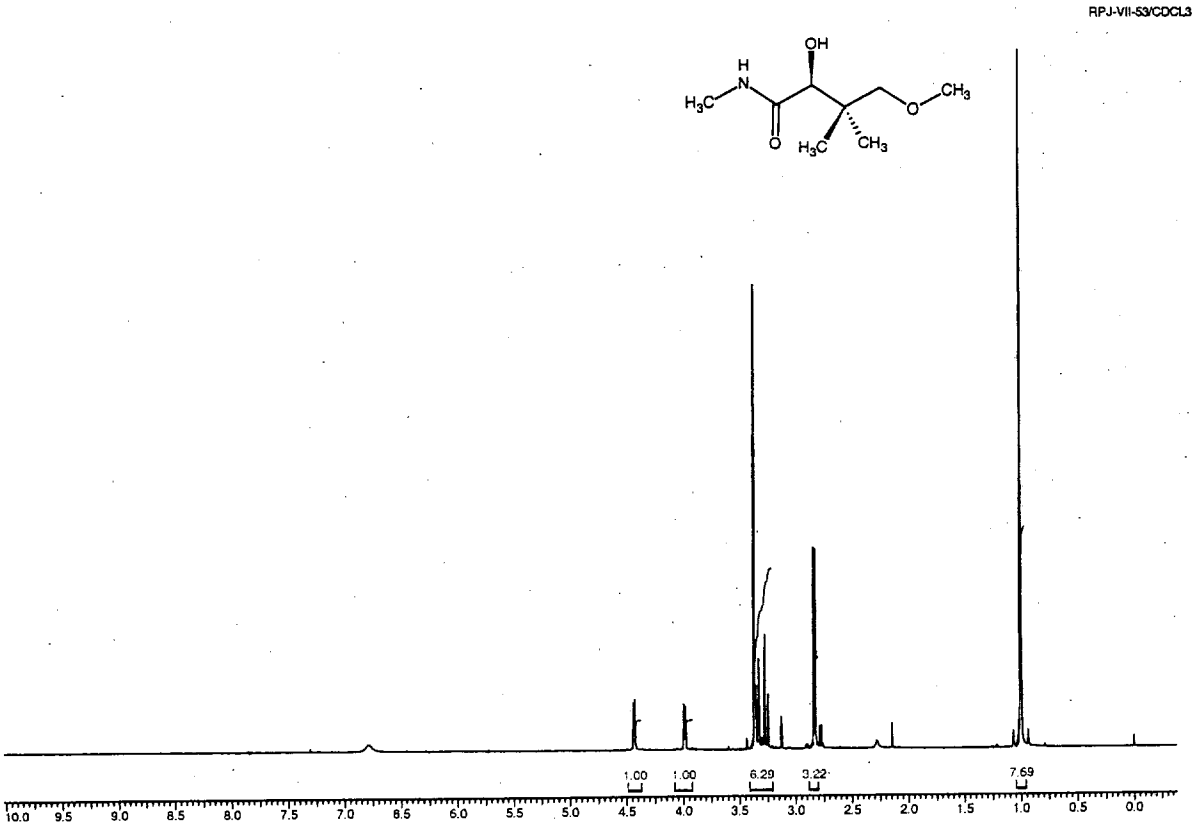
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