Polymer-aided stereodivergent synthesis (PASS): A new concept for the discrete preparation of optical antipodes

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Supporting information

Optically pure glycerol monotosylate 6

p-Toluenesulfonyl chloride (2.922 g, 15.7 mmol) was dissolved in pyridine (4 ml) and slowly added to a cooled (0°C) sample of (*S*)-(+)-solketal (2.228 g, 16.9 mmol). The reaction mixture was kept at room temperature for 5 hours, subsequently dichloromethane (75 ml) was added and the solution was washed with an aqueous copper sulfate solution (0.16 M, 50 ml, 5×) and water (50 ml, 1×) respectively. The organic layer was concentrated in vacuo and treated with TFA/water (2/1, 10 ml) for 15 minutes. Azeotropic evaporation (toluene, 20 mL, 5×) of the solvent yielded slightly yellow oil that was purified by flash column chromatography (ethyl acetate/hexane = 1/1, v/v, 250 ml followed by ethyl acetate) to give 3.166 g (84 %) of **6** as colorless oil that solidified upon standing.

Quasi-meso compound 7

A sample of polymer bound sulfonyl chloride (1.000 g, 1.34 mmol; PS-TsCl, Argonaut Technologies Inc.) was suspended in dichloromethane (10 mL). Successively, 1,2-diol **6** (824 mg, 3.35 mmol) and triethylamine (271 mg, 2.68 mmol) were added and the mixture was allowed to stir overnight at room temperature. The resin was filtered off and washed with dichloromethane (25 mL, 3×), methanol (25 mL, 3×) and dichloromethane (25 mL, 3×), and dried in vacuo for 6 hours. The resin obtained (1.144 g) was suspended in dichloromethane (10 mL) and phenyl isocyanate (428 mg, 3.59 mmol) and triethylamine (12 mg, 0.12 mmol) were added. The mixture was stirred at room temperature overnight. The resin was filtered and thoroughly washed with dichloromethane (25 mL, 5×), dichloromethane/methanol (1/1, 25 mL, 5×), methanol (25 mL, 5×), dichloromethane/methanol (1/1, 25 mL, 5×), dichloromethane (25 mL, 5×), and dried in vacuo for 6 hours to give 1.215 g of resin **7**.

Cyclization to quasi-enantiomers 8 and 9

Resin **7** (1.000 g, maximum theoretical loading: 0.93 mmol/g) was suspended in dichloromethane (10 mL) and DBN (115 mg, 0.93 mmol) was slowly added. The mixture was stirred at room temperature for 2 hours. The resin was filtered off and washed with dichloromethane (10 mL, 3×), dry diethyl ether (10 mL, 3×), and dichloromethane (10 mL, 3×). The filtrate was concentrated in vacuo and the product obtained was filtered through a short plug of (60H) silica gel (eluent: ethyl acetate/heptane = 1/1, v/v) giving 32 mg (23% overall, starting from PS-TsCl, of maximum of 50%) of a white solid consisting of a mixture of tosylate **9** and chloride **12** (ratio **9**/**12** = 1/2, GC-MS analysis). The resin obtained was thoroughly washed with dichloromethane (25 mL, 5×), dichloromethane/methanol (1/1, 25 mL, 5×), methanol (25 mL, 5×), dichloromethane/methanol (1/1, 25 mL, 5×), dichloromethane (25 mL, 5×), and dried in vacuo for 6 hours to give 977 mg of resin **8**.

Synthesis of (*S*)-enantiomers 10 and 11 from quasi-enantiomer 8 — general procedure

Resin **8** (900 mg, maximum theoretical loading: 0.48 mmol/g) was suspended in wet DMF (10 mL) and lithium chloride (147 mg, 3.46 mmol) or sodium azide (85 mg, 1.30 mmol) was added. The reaction mixture was heated (55°C) and stirred for 5h. The resin was filtered off and washed with dichloromethane (10 mL, 3×), methanol (10 mL, 3×), and dichloromethane (10 mL, 3×) and the filtrate was concentrated under high vacuum. The product obtained was filtered through a short plug of (60H) silica gel (eluent: ethyl acetate/heptane = 1/1, v/v) giving 23 mg (21% overall, starting from PS-TsCl, of maximum of 50%) of **10** as a white solid or 17 mg (15% overall, starting from PS-TsCl, of maximum of 50%) of **11** as a white solid.

Synthesis of (*S*)-enantiomer 12 from a mixture of quasi-enantiomer 9 and compound 12

A sample of the compound mixture of **9** and **12** (30 mg, ratio **9**/**12** = 1/2, 0.12 mmol) was dissolved in wet DMF, lithium chloride (49 mg, 1.17 mmol) was added and the reaction mixture was heated (55°C) and stirred for 5h. Next, the solvent was evaporated under high vacuum and the product obtained was filtered through a short plug of (60H) silica gel (eluent: ethyl acetate/heptane = 1/1, v/v) giving 24 mg (96% for this step; 22% overall, starting from PS-TsCl, of maximum of 50%) of a white solid.

Synthesis of (*R*)-enantiomer 13 from a mixture of quasi-enantiomer 9 and compound 12

A sample of the compound mixture of **9** and **12** (30 mg, ratio **9**/**12** = 1/2, 0.12 mmol) was dissolved in wet DMSO, sodium azide (76 mg, 1.17 mmol) was added and the reaction mixture was heated (75°C) and stirred overnight. Next, the solvent was evaporated under high vacuum and the product obtained was filtered through a short plug of (60H) silica gel (eluent: ethyl acetate/heptane = 1/1, v/v) giving 25 mg (quantitative for this step, 23% overall, starting from PS-TsCl, of maximum of 50%) of a white solid.