Synthesis of a Valuable Cyclopropyl Chiron for Preparations of 2,3-Methanoamino Acids

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The potential value of cyclopropane amino acids was recognized sometime ago,[1] but developments in the field were, until recently, constrained by the lack of convenient access to optically pure materials. Recently, we reported asymmetric syntheses of all four stereoisomers of 2,3-methanomethionine (**cyclo-Met**)[2] and a route to both enantiomers of (*Z*)-**cyclo-Orn** and of (*Z*)-**cyclo-Arg** in protected forms suitable for peptide syntheses.[3] These preparations began with conversion of glycidol (1) to the corresponding triflate **2**, followed by reaction of this with di-*tert*-butyl malonate anion, Scheme I. Unfavorable features of this approach are that (i) commercially available glycidol generally is not optically pure; (ii) both triflic anhydride and enantioenriched glycidol are relatively expensive; and (iii) formation of lactone **3** from triflate **2** is a capricious transformation which is difficult to scale up and obtain yields approaching 50%. Our attempts to prepare large batches of optically active lactone **3** from glycidol via this route have been unsatisfactory due to the cost and experimental difficulties. This paper describes a new synthesis of lactone **3**, one that can provide multigram quantities of optically pure material without use of chromatography.

D-Mannitol was converted to diol **4** using a literature route (Scheme II)[4] that does not require any inconvenient purifications. Given the low cost of D-mannitol, it is relatively easy to obtain tens of grams of diol **4** in a relatively short time. Reaction of this diol with thionyl chloride followed by oxidation gave sulfate **5** via the corresponding sulfite (not shown). Crude sulfate **5** formed in this reaction was pure enough to use in the next step without purification. Displacement of the sulfate was achieved via reaction with di-*tert*-butyl malonate anion in refluxing 1,2-dimethoxyethane (DME); formation of a cyclopropane via a similar method has been reported previously.[5] Hydrogenolysis of the benzyl protecting group from cyclopropane **6** gave an isolable alcohol that cyclizes to the desired lactone when treated with catalytic amounts of *p*-toluenesulfonic acid.

No chromatography was required for any of the steps shown in Scheme II: the product was purified via recrystallization and the intermediates were distilled (where necessary). Indeed, it is a distinct advantage that the crude material obtained by the route shown above is crystalline, whereas samples from glycidol triflate were oils which only crystallized after chromatography. The specific rotation of the product [$[\alpha]^{25}_D = -135.1°$ (c = 1.3, CH_2Cl_2)] was higher than that of any sample obtained via glycidol triflate [*cf.* in previous work[2] $[\alpha]^{25}_D = 105°$ (c = 1.3, CH_2Cl_2)],[6] and no trace of the optical antipode could be detected in ^1H NMR experiments with Eu(hfc)$_3$ [by observing the C(CH_3)$_3$ resonance which is clearly resolved for racemic samples].

The synthesis described herein provides relatively easy access to multigram quantities of crystalline, optically pure lactone **3**. Diol **4** can be converted to its enantiomer via a simple three-step process;[7] hence, the chemistry described here can be adapted to give both optical isomers of lactone **3**. Work in progress indicates it should be possible to form several cyclopropyl analogs of protein amino acids from this material, in addition to those already reported.

Experimental Section

General Procedures. High-field NMR spectra were recorded on a Bruker AF300 (^1H at 300 MHz, ^{13}C at 75.4 MHz), a Bruker AC250 (^1H at 250 MHz, ^{13}C at 62.9 MHz), or a Varian XL200 (^1H at 200 MHz, ^{13}C at 50 MHz), ^1H chemical shifts are reported in δ ppm relative to $CHCl_3$ (7.25 ppm) as internal standard, and ^{13}C chemical shifts are reported in ppm relative to $CHCl_3$ (77.0 ppm) unless specified otherwise. Multiplicities in ^1H NMR are reported as (s) singlet, (d) doublet, (t) triplet, (q) quartet, and (m) multiplet. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from Whatman. Dimethoxyethane was distilled immediately before use from sodium benzophenone ketyl. 3-*O*-Benzyl-*sn*-glycerol was prepared from D-mannitol in five steps according to literature procedures.[4,8,9] Other chemicals were purchased from commercial suppliers.

(*S*)-4-[(Benzyloxy)methyl]-2,2-dioxo-1,3,2-dioxathiolane (5). A 1-L, two-necked, round-bottomed flask equipped with a reflux condenser, a $CaCl_2$ drying tube connected to a HCl trap, and a rubber septum was charged with 3-*O*-benzyl-*sn*-glycerol (40.1 g, 220 mmol) and CCl_4 (220 mL). Thionyl chloride (19.3 mL, 264 mmol) was added slowly via a syringe, and the resulting mixture was heated under reflux for 1 h. The solution was then cooled to 0 °C and diluted with CH_3CN (220 mL). $RuCl_3 \cdot 3H_2O$ (35.2 mg, 0.132 mmol), $NaIO_4$ (70.5 g, 330 mmol), and then water (330 mL) were added. The resulting mixture was stirred at 25 °C for 1 h. The mixture was diluted with Et_2O (1760 mL), and the two phases were separated. The organic layer was washed with water (90 mL), saturated $NaHCO_{3(aq)}$ (2 × 90 mL), and brine (90 mL), dried over $MgSO_4$, and filtered through a pad of silica gel to remove the brown color. Removal of the solvent gave crude **5** (50 g, 93%) which was used for the next reaction without further purification: R_f 0.46 (33% acetone/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.04 (m, 1H), 4.58–4.71 (m, 4H), 3.76 (d, J = 4.9 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 136.7, 128.6, 128.2, 127.6, 79.8, 73.8, 69.7, 67.4.

(*R*)-(−)-Di-*tert*-butyl 2-[(Benzyloxy)methyl]cyclopropane-1,1-dicarboxylate (6). Di-*tert*-butyl malonate (40.0 g, 185 mmol) was added dropwise to a well-stirred solution of sodium hydride (19.53 g, 406.9 mmol) in dry dimethoxyethane (925 mL) at 25 °C under nitrogen. The cyclic sulfate **5** (49.69 g, 203.4 mmol) was added slowly, and the solution was refluxed for 22 h at ca. 83–85 °C. The reaction mixture was cooled to 25 °C, and brine (300 mL) was added followed by Et_2O (500 mL). After the two layers were separated, the aqueous solution was extracted with Et_2O (3 × 500 mL). The combined organic layers were dried over Na_2SO_4, and removal of the solvent under reduced pressure gave compound **6** as a dark brown oil. The crude product was purified by distillation (132–142 °C, 0.25 mmHg) to give **6** (50.8 g, 76%) as a colorless oil: R_f 0.71 (20% acetone/hexane); ^1H NMR (200

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(6) The rotation of the material obtained in the present work was checked several times. The rotation reported originally (ref 2) is lower than that calculated by taking 100% ee as equivalent to $[\alpha]_D = 135°$, probably due to solvent impurities in the original work.
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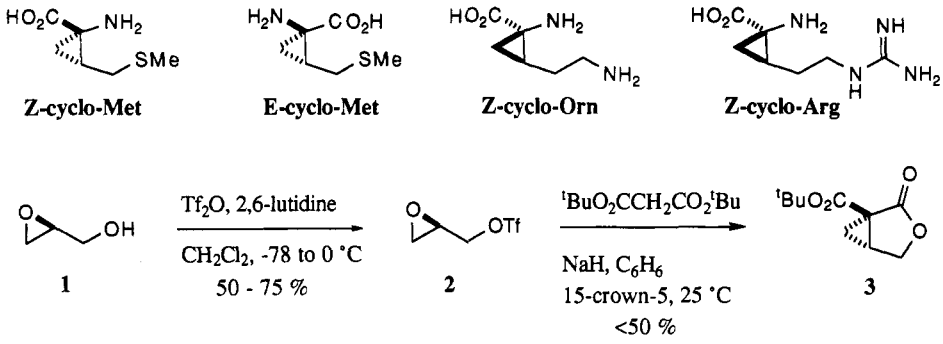
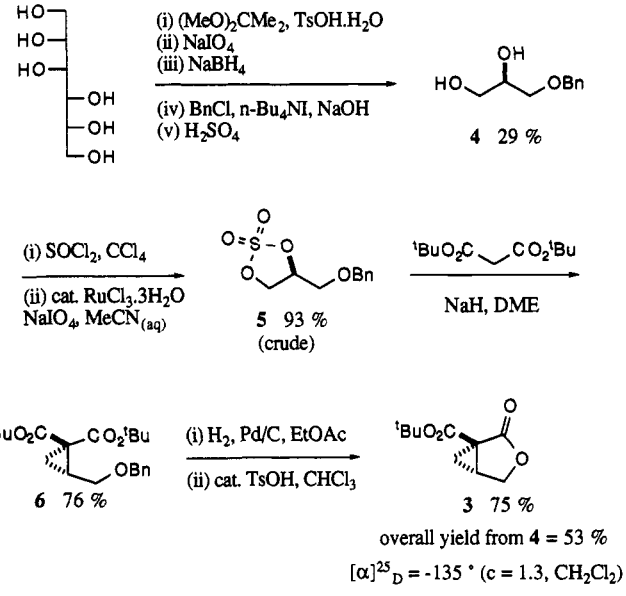
Scheme I



Scheme II. Asymmetric Synthesis of Lactone 3



MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.50 (ABq, J = 11.9, 14.2 Hz, 2H), 3.53 (dd, J = 6.8, 10.4 Hz, 1H), 3.40 (dd, J = 6.9, 10.5 Hz, 1H), 2.14 (m, 1H), 1.45 (s, 9H), 1.43 (s, 9H), 1.37 (dd, J = 4.3, 7.1 Hz, 1H), 1.26 (dd, J = 4.6, 9.2 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.1, 167.1, 138.1, 128.3, 127.6, 127.5, 81.5, 81.3, 72.7, 68.5, 35.1, 27.9, 27.8, 25.6, 18.4; IR (neat) 2979, 1719, 1171, 1136 cm^{-1}; $[\alpha]^{25}_D$ -40.6° (c = 1.3, CH_2Cl_2). Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.97; H, 8.59.

(*R*)-(−)-Di-*tert*-butyl 2-(Hydroxymethyl)cyclopropane-1,1-dicarboxylate. To a solution of **6** (29 g, 80 mmol) in EtOAc (534 mL) was added Pd/C (1.70 g, 1.60 mmol), and the reaction mixture was placed under an atmosphere of H_2 (1 atm). After being stirred at 25 °C for 4 d, the reaction mixture was filtered, and the solvent was removed under reduced pressure affording the crude product as a white solid (22 g, 100%) which was used for the next reaction without further purification. An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 33–34 °C; R_f 0.41 (20% acetone/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (dd, J = 5.0, 12.4 Hz, 1H), 3.20 (dd, J = 9.6, 12.3 Hz, 1H), 2.00 (m, 1H), 1.47 (s, 9H), 1.44 (s, 9H), 1.35 (dd, J = 4.9, 9.1 Hz, 1H), 1.16 (dd, J = 4.9, 7.1 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.1, 167.9, 82.2, 82.0, 62.7, 35.9, 29.0, 28.0, 27.6, 17.7; IR (neat) 3527, 2979, 1719, 1171, 1136 cm^{-1}; $[\alpha]^{26}_D$ −23.1° (c = 1.3, CH_2Cl_2). Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.81; H, 9.22.

(1*R*,5*R*)-(−)-1-(*tert*-Butoxycarbonyl)-2-oxo-3-oxabicyclo-[3.1.0]hexane (3). To a solution of crude **(*R*)-(−)-di-*tert*-butyl 2-(hydroxymethyl)cyclopropane-1,1-dicarboxylate** (22 g, 80 mmol) in $CHCl_3$ (800 mL) was added $TsOH{\cdot}H_2O$ (1.52 g, 8 mmol). After being stirred at 25 °C for 60 h, the reaction mixture was washed with saturated $NaHCO_{3(aq)}$ (4 × 100 mL), water (3 × 100 mL), and brine (3 × 100 mL) and dried over Na_2SO_4. Removal of the solvent gave a pale yellow solid which was recrystallized from ethyl acetate/hexane to give white crystals (12.06 g, 75%, >95% ee). The enantiomeric excess of this material was determined by chiral shift experiment using Eu(hfc)$_3$: mp 66–67 °C; R_f 0.35 (20% acetone/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 4.34 (dd, J = 4.8, 9.5 Hz, 1H), 4.15 (d, J = 9.4 Hz, 1H), 2.65 (m, 1H), 1.99 (dd, J = 4.7, 8.0 Hz, 1H), 1.48 (s, 9H), 1.30 (t, J = 5.0 Hz, 1H); $[\alpha]^{25}_D$ −135.1° (c = 1.3, CH_2Cl_2).

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