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The first asymmetric synthesis of (2*S*)- and (2*R*)-amino-3,3-dimethoxypropanoic acid

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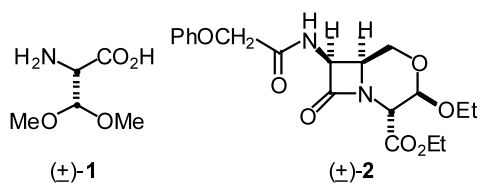
Abstract—The first asymmetric synthesis of (2*S*)-, and (2*R*)-amino-3,3-dimethoxypropanoic acid (α-formylglycine dimethylacetal) has been achieved in two steps and 91% overall yield. The key step involved the quenching of a chiral glycine titanium enolate with trimethyl orthoformate.

The unnatural amino acid 2-amino-3,3-dimethoxypropanoic acid or α-formylglycine dimethylacetal (±)-**1** has been utilized in a wide variety of synthetic transformations (Fig. 1).[1] This compound and its diethylacetal counterpart, until now, have only been synthesized in racemic form via a variety of tedious approaches. In many of the literature references using this compound, the stereogenic center present in α-formylglycine dimethylacetal is destroyed such as, in cases where a dehydroamino acid moiety is constructed. Doyle and co-workers demonstrated the usefulness of α-formylglycine diethylacetal in their synthesis of isocepham (±)-**2** (Fig. 1).[2] Although, in this case, the stereogenic center from the α-formylglycine diethylacetal portion was retained in the final product, compound **2** was synthesized in racemic form.

Our desire to prepare both enantiomers of α-formylglycine dimethylacetal is related to our investigations on the total synthesis of capreomycin IB (**3**) (Fig. 2). Shiba, in his total syntheses of the capreomycins and the structurally similar tuberactinomycins, used racemic α-formylglycine diethylacetal as a precursor to the enamidourea functionality present in both of these cyclic pentapeptides.[3] Our goal was to synthesize both diastereomers of our macrocyclization precursor arising from the incorporation of both enantiomers of α-formylglycine dimethylacetal. This was desired so that we could investigate whether or not one diastereomeric hexapeptide undergoes more facile macrocyclization than the other.



(±)-**1** (±)-**2**

Figure 1.

Adapting chemistry developed by Evans to our strategy, chiral glycinate (−)-**4** was treated with $TiCl_4$ at −78°C, followed by the addition of triethylamine (Scheme 1).[4] After allowing the enolate to form, trimethylorthoformate was added, and the mixture was allowed to warm to 0°C over an hour. The result was a single diastereomer of the desired dimethylacetal (+)-**5** in 93% yield. Hydrogenolysis of the lactone adduct, followed by trituration with ether to remove the dibenzyl byproduct provided (2*R*)-amino-3,3-dimethoxypropanoic acid (−)-**1** in 98% yield. Treatment of (−)-**1** with refluxing methanolic HCl resulted in the formation of (+)-**6** in 99% yield. The ee of (+)-**6** was found to be >95% by Mosher's amide analysis (^{1}H NMR). In addition, both enantiomers of α-formylglycine dimethylacetal (**1**) can be prepared from the commercially available antipodes of oxazinone **4**.[5]

The amino functionality of compound **1** can also be protected for use in peptide synthesis strategies as illustrated with the example in Scheme 2. Treatment of (+)-**1** with TeocONSu[6] and triethylamine in dioxane:water provided the trimethylsilylethyl carbamate (−)-**7** in 77% yield.[7]

In summary, a titanium enolate/trimethyl orthoformate condensation with chiral glycine template **4** has been

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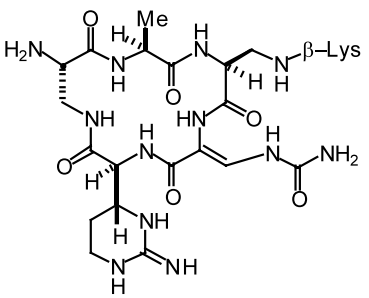
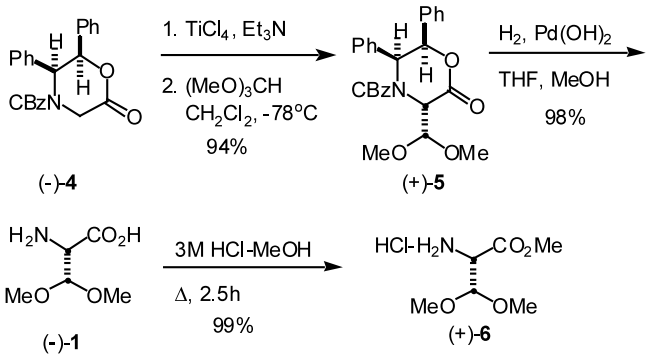
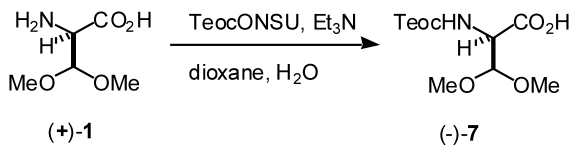


capreomycin IB (3)

Figure 2.



Scheme 1.



Scheme 2.

accomplished in excellent yield. This has served as the key step in the first asymmetric synthesis of (2*S*)- and (2*R*)-amino-3,3-dimethoxypropanoic acid. This work constitutes the first example of the successful deployment of a titanium enolate generated from **4** that may find other useful applications in amino acid synthesis. In addition, the condensation product **5** is a potentially useful chiral building block, and studies are currently underway to explore other uses for this substance.

Experimental

Compound (+)-**5**: A solution of (−)-**4** (1.24 g, 3.2 mmol, 1 equiv.) is dissolved in CH_2Cl_2 (50 mL) and cooled to −78°C. While stirring, $TiCl_4$ (700 μL, 6.4 mmol, 2 equiv.) was added, followed by triethylamine (900 μL, 6.4 mmol, 2 equiv.) to provide a dark blue enolate solution. After stirring for 15 min, trimethyl orthoformate (2.1 mL, 19.2 mmol, 6 equiv.) was added, and the solution warmed slowly to 0°C. After stirring 45 min at 0°C, 0.025 M pH 7 phosphate buffer was added and stirred 30 min. The quenched reaction was filtered through Celite, diluted with CH_2Cl_2, and washed twice with brine. Upon drying the organic layer over anhydrous sodium sulfate, the solution was filtered and evaporated to provide an off white solid. Silica gel chromatography (eluted with 6:3:1 CH_2Cl_2:hexanes:EtOAc) provided 1.37 g (93%) of pure (+)-**5** as a white solid.

^{1}H NMR (300 MHz) (DMSO-d_6, 393K) δ DMSO: 3.50 (3H, bs); 3.51 (3H, s); 4.87 (1H, d, $J=2.9$ Hz); 5.02 (2H, broad m); 5.14 (1H, d, $J=2.9$ Hz); 5.28 (1H, d, $J=3.3$ Hz); 6.28 (1H, d, $J=3.3$ Hz); 6.61 (2H, d, $J=7.0$ Hz); 7.01–7.29 (13H, m). IR (NaCl, neat) 3031, 2940, 2837, 1753, 1706, 1454, 1401, 1348, 1288, 1267, 1250, 1207, 1189, 1109, 1081 cm^{-1}. HRMS (FAB$^+$) calcd for $C_{27}H_{28}NO_6$ (MH$^+$) 462.1917; found 462.1917. (+)-**5**. $[\alpha]_D^{25}=+1.7$ ($c=1.0$, CH_2Cl_2). (−)-**5**. $[\alpha]_D^{25}=-1.8$ ($c=1.0$, CH_2Cl_2).

Compound (−)-**1**: A solution of (+)-**5** (472 mg, 1.02 mmol, 1 equiv.) in 3:1 THF:MeOH (32 mL) was purged with argon for 10 min. To this solution in a pressure tube, 20% $Pd(OH)_2$ on activated carbon (360 mg, 0.51 mmol, 0.5 equiv.) was added, and the tube filled with hydrogen gas to 95 psi. The pressure was released, and the tube refilled. This was repeated 4 times more. The pressurized tube was then stirred for 2 days at room temperature. After the 2 days, the pressure was released, the solution purged with argon, and the 20% $Pd(OH)_2$ on activated carbon removed by filtration through Celite. Evaporation of the filtrate and trituration of the residue with ether provided 152 mg (99%) of (−)-**1** as an oily solid.

^{1}H NMR (400 MHz) (DMSO-d_6) δ DMSO: 3.35 (3H, s); 3.36 (3H, s); 3.39 (1H, d, $J=2.1$ Hz); 4.71 (1H, d, $J=2.1$ Hz); 6.80–8.40 (3H, bs). ^{13}C NMR (100 MHz) (DMSO-d_6) δ DMSO: 55.0, 55.6, 56.8, 103.7, 166.3. IR (NaCl, neat): 2939, 1641, 1506, 1406, 1342, 1272, 1218, 1194, 1067 cm^{-1}. HRMS (FAB$^+$) calcd for $C_5H_{12}NO_4$ (MH$^+$) 150.0766; found 150.0768. (−)-**1**. $[\alpha]_D^{25}=-7.4$ ($c=0.50$, MeOH). (+)-**1**. $[\alpha]_D^{25}=+7.6$ ($c=0.67$, MeOH).

Compound (+)-**6**: A stirred solution of MeOH (10 mL) at 0°C was treated with acetyl chloride (2 mL, 30 mmol). This mixture was warmed to room temperature and stirred for 20 min. The resulting methanolic HCl solution was added to a round bottomed flask containing (−)-**1** (95 mg, 0.64 mmol, 1 equiv.). After stirring the reaction at reflux for 2.5 h, the solvent was removed in vacuo to provide 126 mg (99%) of (+)-**6** as a clear oil.

^{1}H NMR (400 MHz) (CD_3OD) δ CD_3OD: 3.49 (3H, s); 3.54 (3H, s); 3.86 (3H, s); 4.33 (1H, d, $J=2.8$ Hz); 4.86 (1H, d, $J=2.8$ Hz). ^{13}C NMR (100 MHz) (CD_3OD) δ: 53.9; 56.4; 57.2; 57.7; 103.2; 167.8. IR (NaCl, neat): 3583, 3408, 2956, 2843, 1749, 1643, 1591, 1503, 1443, 1378, 1306, 1241, 1195, 1111, 1070 cm^{-1}. HRMS (FAB$^+$) calcd for $C_6H_{14}NO_4$ (MH$^+$) 164.0923; found 164.0922. (+)-**6**. $[\alpha]_D^{25}=+2.7$ ($c=0.66$, MeOH). (−)-**6**. $[\alpha]_D^{25}=-2.7$ ($c=0.66$, MeOH). The enantiomeric purity of (+)-**6** was found to be >95% ee by formation of the Mosher's amide via both the optically pure and racemic Mosher's acid chlorides and comparison of the resulting diastereomers by ^{1}H NMR. None of the minor

diastereomer was observed in the optically pure Mosher's acid chloride case.

Compound (−)-**7**: To a solution of (+)-**1** (59 mg, 0.40 mmol, 1 equiv.) in 1:1 dioxane:water (3 ml) was added triethylamine (166 μL, 1.19 mmol, 3 equiv.) and the mixture stirred under argon. TeocONSu[6] (109 mg, 0.42 mmol, 1.05 equiv.) was added to the solution, and the reaction stirred overnight at room temperature. The reaction was diluted, acidified to pH 4 with 0.5 M citric acid, and extracted twice with ether. The combined ether layers were washed twice with water, then dried over $MgSO_4$. Removal of the drying agent by filtration and evaporation provided 90 mg (77%) of (−)-**7** as a pale oil.

^{1}H NMR (300 MHz) ($CDCl_3$) δ $CDCl_3$: 0.04 (9H, s); 1.00 (2H, ddd, $J=0$, 8.4, 9.5 Hz); 3.47 (6H, s); 4.19 (2H, ddd, $J=0$, 6.6, 9.5 Hz); 4.61 (1H, d, $J=8.4$ Hz); 4.66 (1H, s); 5.42 (1H, d, $J=7.7$ Hz); 9.29 (1H, bs). ^{13}C NMR (75 MHz) ($CDCl_3$) δ: −1.2, 17.9, 55.9, 56.3, 64.1, 103.9, 156.9, 173.1. IR (NaCl, neat): 3452, 3319, 3107, 2954, 2838, 1725, 1525, 1448, 1415, 1317, 1251, 1214, 1186, 1118, 1068 cm^{-1}. HRMS (FAB$^+$) calcd for $C_{11}H_{24}NO_6Si$ (MH^+) 294.1373; found 294.1379. (−)-**7**. $[\alpha]_D^{25}=-22.2$ ($c=2.0$, CH_2Cl_2).

Acknowledgements

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