An Improved Procedure to Homochiral Cyclic Statines

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Abstract: Chiral tetramic acids were prepared in high yields by the reaction of N-protected amino acids with Meldrum's acid employing DCC as a carboxyl activating agent. Reduction or hydrogenation of these tetramic acids produced homochiral cyclic statines.
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(3S,4S)-3-hydroxy-4-amino acids, represented by statine [(3S,4S)-4-amino-3-hydroxy-6-methyl-heptanoic acid] **1** and its congener (3S,4S)-4-amino-3-hydroxy-5-cyclohexylpentanoic acid (ACPPA) **2**, have attracted a great deal of synthetic attention during the last decade[1-4]. This interest stems from their wide applications in the design and synthesis of inhibitors of aspartyl proteases such as renin, a key enzyme in the renin-angiotensin system, and HIV protease. It has been accepted that these γ-amino acids are recognized to mimic the transition state structure of substrate when interacting with an enzyme and only the β-hydroxy γ-amino acids of the syn configuration can generally adopt a suitable conformation.
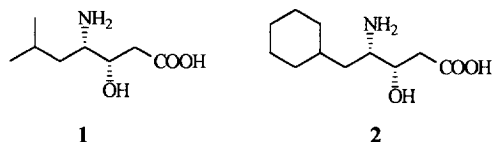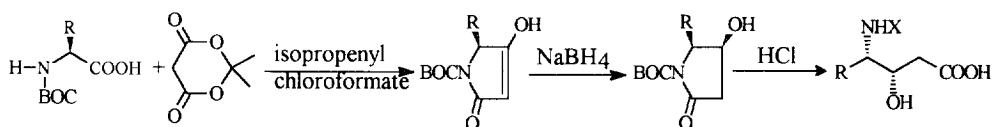

Scheme I

To date there have appeared three major methods for the preparation of (3S,4S)-3-hydroxy-4-amino acids. The first one is by acylation of ester enolates or magnesium malonates with acylamino acid derivatives followed by diastereoselective reduction of the β-oxo esters[1]; the second one is by stereoselective aldol condensation of ester enolates with N-protected α-amino aldehydes[2]; the third one is by stereocontrolled reduction of enantiomerically pure tetramic acids[3]. It is believed that the third one is best because the former two need more steps, give a mixture of syn and anti isomers in most cases and are not suitable for a large scale preparation.

Success of the third method highly depends on the appearance of a method preparing enantiomerically pure tetramic acids, which was reported in 1987[3b]. Jouin and Castro found that the condensation of BOC-amino acids and Meldrum's acid followed by deprotection and decarboxylation could produce tetramic acids

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without racemization (Scheme II). This method has been applied to the synthesis of several biologically active molecules[5-7]. However, one drawback of this method is the activating reagent; isopropenyl chloroformate is very expensive and the reaction conditions are rather critical, while other cheaper carboxyl activating agents such as DCC was found to give much lower yields[3b]. These results led to other efforts to synthesize enantiomerically pure tetramic acids from N-protected amino acids through multstep conversions[8]. Very recently, Joullie and coworkers tested twelve selected carboxyl activating reagents to find a more economical reagent for the Jouin's reaction. In their work DCC was still found not to be a suitable reagent because it led to the lower yield [6a].

Scheme II

In the course of total synthesis of (+)-preussin[9], we required the tetramic acid **5j** as a key intermediate. We thought that the Jouin's reaction was a better way to obtain this intermediate and reinvestigated this reaction. After carefully checking and analyzing each operation step, we found an improved procedure, which allowed us to obtain enantiomerically pure tetramic acids in good to excellent yields even by employing DCC as a carboxyl activating agent.

We noticed that the reaction of an organic acid with Meldrum's acid activated by DCC gave the corresponding ketone in a good yield[10]. In fact, when we used an N-protected amino acid to run this reaction, it was found that the reaction worked very well and gave a single spot on TLC after 4 hours at room temperature. After workup we used the crude product directly to run the second step, the cyclization reaction just by following the Jouin's procedure. At this time it was found that the reaction mixture gave many spots on TLC. Thus we considered to try to improve this reaction by changing substrates and reaction conditions. Initially, we thought that a BOC group might be too hindered for cyclization, while a smaller protecting group probably facilitates this step. Accordingly, we chose ethyl carbamate-protected amino acid **3a** to begin the synthesis of the corresponding tetramic acid. After finishing the coupling reaction and filtering off the resulting solid, we found that the filtrate was quite easy to solidify, which brought some trouble for further operation-- washing with 5% aqueous potassium hydrogen sulfate. We solved this problem just by adding more ethyl acetate and then washing to remove DMAP. After evaporation of the solvent, we found the remaining solid had little impurity checked by TLC. After heating this solid in methanol at reflux for 30 min., we saw a new and single spot by TLC. The white solid obtained after removing the methanol, was identified as the tetramic acid **5a** by its NMR and MS spectral data, which was then reduced with sodium borohydride to produce cyclic statine analogue **6a** in 62% yield.

Table I: Synthesis of Chiral Cyclic Statines
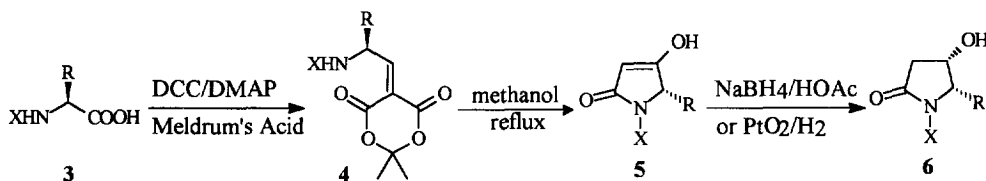
Entry	R	X	yield of 5 (%)[a]	yield of 6 (%)[a, b]
a	CH$_2$Ph	COOEt	81[b]	62[d]
b	i-Propyl	COOMe	96[c]	75[e]
c	i-Propyl	COOEt	98[c]	79[e]
d	i-Propyl	Boc	95[c]	74[e]
e	i-Propyl	Cbz	96[c]	75[d]
f	CH$_2$OBn	COOEt	94[c]	72[d]
g	CH$_2$OTBS	COOEt	89[c]	65[e]
h	i-Butyl	COOEt	98[c]	80[e]
i	CH$_2$Ph	COOMe	80[c]	55[d]
j	CH$_2$Ph	Boc	90[c]	66[d]
k	CH$_2$Ph	Cbz	94[c]	72[d]

a) Based on the starting N-protected amino acid. b) Isolated yield. c) Crude yield. d) Reduction of tetramic acid derivatives by NaBH$_4$ in HOAc and CH$_2$Cl$_2$. e) Reduction of tetramic acid derivatives by H$_2$ catalyzed by PtO$_2$.

Encouraged by the above results, we examined the synthesis of other cyclic statines by employing different N-protected amino acids through the similar procedure. As showed in Table I, in each case the tetramic acid was obtained as a crude product in good yield. Sodium borohydride reduction or PtO$_2$-catalyzed hydrogenation of these tetramic acids gave the corresponding cyclic statines in 55-80% yields. As mentioned above, we had also made a slight change in work-up step of the first reaction. To check if the above results were obtained by this change or by size reducing of the protecting groups, we used BOC-protected L-valine **3d** to run the same sequence of the reactions. It was found that even in this case we could still get cyclic statine **6d** in 74% yield. Compared with entries b, c, and e, these results ruled out the role of the smaller protecting groups.

The intermediates **4** are very unstable to acidic conditions because even dilute acetic acid could cause cleavage of their 1,3-dioxane-4,6-dione rings and subsequent decarboxylation[11]. This isthe reason why Jouin had mentioned that the washing step should process very quickly and use a cold solvent. In the present case, the diluted organic layer might avoid more contact of **4** with an inorganic acid and thus prevent their decompositions. This simple reason may lead to the present success.

As a conclusion, we have found a straightforward and economical way to chiral cyclic statines. Since chiral cyclic statines serve as useful building blocks in the synthsis of different class of biologically active molecules, the present results represent an important contribution to this field.

Experimental Section

(4S,5S)-1-ethoxycarbonyl-5-benzyl-4-hydroxy-2-oxopyrrolidine 6a. To a solution of N-ethoxycarbonyl-L-phenylalanine **3a** (1.19 g, 5.0 mmol), Meldrum's acid (0.75 g. 5.0 mmol), DMAP (0.90 g, 7.4 mmol) in 20 mL of methylene chloride was added DCC (1.20 g, 5.8 mmol) at room temperature. The resulting mixture was stirred for 3 h at the same temperature after which it was filtered and the filter was washed with ethyl acetate (20 mL). The combined filtrates were diluted with 200 mL of cold ethyl acetate and washed with cold 5% aqueous potassium hydrogen sulphate, water, and brine, respectively. The organic layer was dried, evaporated under a reduced pressure to give a white solid, which was dissolved in 50 ml of MeOH and heated at reflux for 0.5 h. The solvent was removed and the residual solid was recrystallized from hexane/ether to afford 1.09 g of **5a**, which was dissolved in a mixture of dichloromethane (20 mL) and acetic acid (2 mL). The acidic solution was cooled in an ice-bath and sodium borohydride (315 mg, 8.3 mmol) was added to this solution over 0.5 h under vigorous stirring. The mixture was then maintained for additional 3 h at the same temperature. The resulting solution was poured into a cold water and the organic layer was washed with 10% aqueous $NaHCO_3$, water and brine, dried, then evaporated. The chromatography of the residue on silica gel yielded 0.82 g (62% yield from **3a**) of **6a** as an oil. $[\alpha]^{23}_D = +27.4$ (c 1.0 CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.28~7.16 (m, 5H), 4.47 (m, 1H), 4.20 (m, 3H), 3.15 (d, 2H, $J = 5.4$ Hz), 2.59 and 2.40 (ABq, dd, 2H, $J = 17.1, 7.0, 7.2$ Hz), 1.31 (t, 3H, $J = 7.1$ Hz); MS m/z 263 (M⁺), 245, 172, 91; HRMS calcd. for $C_{14}H_{17}NO_4$: 263.116, Found: 263.117.

Following the similar procedures, crude **5b-5k** were prepared, without further purification, these compounds were subjected to $NaBH_4$ reduction mentioned above or PtO_2-catalyzed hydrogenation to produce **6b-6k**.

Typical procedure for PtO₂-catalyzed hydrogenation: The crude product **5** (1 mmol) was dissolved in ethyl acetate (5 ml), and hydrogenated in the presence of Adam's catalyst in a Parr reactor under 25 atm at room temperature for 20 h. The mixture was then filtered and the filtrate was evaporated. The pure oxopyrrolidine was obtained by column chromatography on silica gel eluting with 1/1ethyl acetate/petroleum ether.

(4S,5S)-1-methoxycarbonyl-5-*iso*-propyl-4-hydroxy-2-oxopyrrolidine 6b. 75% yield from **3b** $[\alpha]^{23}_D = +78.6$ (c 1.0 CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.68 (q, 1H, $J = 8.5$ Hz), 4.19 (dd, 1H, $J = 7.5, 4.8$ Hz), 3.84 (s, 3H), 2.70 and 2.66 (ABq, dd, 2H, $J = 17.4, 9.8, 8.5$ Hz), 2.30 (m, 1H), 2.0 (br s, 1H), 1.07 (d, 3H, $J = 7.0$ Hz), 1.03 (d, 3H, $J = 7.0$ Hz); MS m/z 201 (M⁺), 184, 158; Anal. calcd. for $C_9H_{15}NO_4$: C, 53.70; H, 7.52, N, 6.96; found: C, 53.50; H, 7.71; N, 6.93.

(4S,5S)-1-ethoxycarbonyl-5-*iso*-propyl-4-hydroxy-2-oxopyrrolidine 6c: 79% yield from **3c**. $[\alpha]^{23}_D$ = +87.3 (c 1.0 CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.68 (q, 1H, $J = 9.6$ Hz), 4.29 (m, 2H), 4.19 (dd, 1H, $J =$

7.6, 4.9 Hz), 2.70 and 2.65 (ABq, 2H, dd, $J = 17.4$, 9.5, 8.1Hz), 2.45 (m, 1H), 1.63 (br s, 1H), 1.33 (t, 3H, $J = 7.1$ Hz), 1.08 (d, 3H, $J = 6.9$ Hz), 1.04 (d, 3H, $J = 7.1$ Hz); MS m/z 215 (M$^+$), 198, 172, 100. Anal. calcd. for $C_{10}H_{17}NO_4$: C, 55.78; H, 7.96, N, 6.51; found: C, 55.89; H, 8.09; N, 6.43.

(4S,5S)-1-*tert*-butoxycarbonyl-5-*iso*-propyl-4-hydroxy-2-oxopyrrolidine 6d: 75% yield from **3d**. $[\alpha]^{23}_D = + 80.0$ (c 0.7 CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.68 (q, 1H, $J = 8.4$ Hz), 4.15 (dd, 1H, $J = 7.0$, 5.0 Hz), 2.65 (m, 2H), 2.35~2.29 (m, 1H), 2.0 (br s, 1H), 1.52 (s, 9H), 1.10 (d, 3H, $J = 7.0$ Hz), 1.05 (d, 3H, $J = 7.1$ Hz); MS m/z 243 (M$^+$), 226, 210; Anal. calcd. for $C_{12}H_{21}NO_4$: C, 59.22; H, 8.70, N, 5.76; found: C, 59.36; H, 9.01; N, 5.91.

(4S,5S)-1-benzyloxycarbonyl-5-*iso*-propyl-4-hydroxy-2-oxopyrrolidine 6e. 74% yield from **3e**. $[\alpha]^{23}_D = + 64.9$ (c 0.6 CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (m, 5H), 5.27 (s, 2H), 4.68 (q, 1H, $J = 8.4$ Hz), 4.20 (dd, 1H, $J = 7.8$, 4.9 Hz), 2.69 (m, 2H), 2.33 (m, 1H), 2.0 (br s, 1H), 1.05 (d, 3H, $J = 7.0$ Hz), 1.02 (d, 3H, $J = 7.0$ Hz); MS m/z 277 (M$^+$), 259, 143, 91; Anal. calcd. for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.91, N, 5.05, found: C, 64.95; H, 7.09; N, 5.11.

(4S,5S)-1-ethoxycarbonyl-5-benzyloxymethyl-4-hydroxy-2-oxopyrrolidine 6f. 72% yield from **3f**. $[\alpha]^{23}_D = + 60.3$ (c 1.0 CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.32 (m, 5H), 4.55 (m, 3H), 4.28 (m, 3H), 3.96 and 3.90 (ABq, dd, 2H, $J = 10.2$, 3.7, 2.6 Hz), 2.78 and 2.71 (ABq, dd, 2H, $J = 17.4$, 8.6, 8.5 Hz), 2.65 (br s. 1H), 1.30 (t, 3H, $J = 7.1$ Hz); MS m/z 294 (M$^+$ + H$^+$), 276, 187, 91; HRMS calcd. for $C_{15}H_{19}NO_5$ 293.126, found 293.126.

(4S,5S)-1-ethoxycarbonyl-5-(*tert*-butyldimethylsillyl)oxymethyl-4-hydroxy-2-oxopyrrolidine 6g. 65% yield from **3g**. $[\alpha]^{23}_D = + 58.9$ (c 1.0 CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.58 (q, 1H, $J = 8.3$ Hz), 4.33 (q, 2H, $J = 7.1$ Hz), 4.26 (dt, 1H, $J = 7.9$, 3.0 Hz), 4.12 (m, 2H), 2.84 and 2.71 (ABq, dd, 2H, $J = 17.6$, 8.7 , 8.3 Hz), 1.75 (br s, 1H), 1.35 (t, 3H, $J = 7.1$ Hz). 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); MS m/z 318 (M$^+$+ H$^+$), 300, 260, 188; Anal. Calcd. for $C_{14}H_{27}NO_5Si$: C, 52.97; H, 8.58, N, 4.42; found: C, 52.95; H, 8.53, N, 4.69.

(4S,5S)-1-ethoxycarbonyl-5-*iso*-butyl-4-hydroxy-2-oxopyrrolidine 6h. 80% yield from **3h**. $[\alpha]^{23}_D = + 82.6$ (c 0.6 CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.56 (q, 2H), 4.33~4.26 (m, 3H), 2.70 and 2.62 (ABq, dd, 2H, $J = 17.4$, 5.3, 4.7 Hz), 2.3~2.1 (br s, 1H), 1.80 (m, 2H), 1.50 (m, 1H), 0.97 (m, 6H); MS m/z 230 (M$^+$ + H$^+$), 212, 173, 100; Anal. Calcd. for $C_{11}H_{19}NO_4$: C, 57.61; H, 8.36, N, 6.11; found: C, 57.74; H, 8.58; N, 6.17.

(4S,5S)-1-methoxycarbonyl-5-benzyl-4-hydroxy-2-oxopyrrolidine 6i. 55% yield from **3i**. $[\alpha]^{23}_D = + 38.6$ (c 1 CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.28~7.19 (m, 5H), 4.46 (m, 2H), 3.77 (s, 3H), 3.15 (d, 2H, $J = 5.8$ Hz), 2.62 and 2.42 (ABq, dd, 2H, $J = 17.3$, 7.7, 7.1 Hz), 2.30 (br s, 1H); MS m/z 249 (M$^+$), 231, 158, 91; HRMS Calcd. for $C_{13}H_{15}NO_4$ 249.100; found: 249.098.

(4S,5S)-1-*tert*-butoxycarbonyl-5-benzyl-4-hydroxy-2-oxopyrrolidine 6j. 72% yield from **3j**. m.p 120-122° (lit[3b] m.p. 120-124°); $[\alpha]^{23}_D = + 42.7$ (c 1.1 MeOH), (lit[3b] $[\alpha]^{23}_D = + 43$ (c 1.0 MeOH)); ^{1}H NMR

(300 MHz, CDCl$_3$) δ 7.36~7.26 (m, 5H), 4.49 (m, 2H), 3.15 (m, 2H), 2.63 and 2.42 (ABq, dd, 2H, J = 16.9, 7.2, 7.1 Hz), 2.05 (br s, 1H), 1.51 (s, 9H); MS m/z 292 (M$^+$ + H$^+$), 235, 191, 100, 91.

(4S,5S)-1-benzyloxycarbonyl-5-benzyl-4-hydroxy-2-oxopyrrolidine 6k. 66% yield from **3k**. $[\alpha]^{23}_D$ = +40.7 (c 1.0 MeOH), ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.43~7.18 (m, 5H), 5.26 (d, 1H, J = 12.2 Hz), 5.18 (d, 1H, J = 12.2 Hz), 4.55~4.44 (m, 2H), 3.15 (m, 2H), 2.60 (dd, 1H, J = 17.1, 7.5 Hz), 2.43 (dd, 1H, J = 17.1, 7.1Hz), 2.55 (br s, 1H); MS m/z 326 (M$^+$ + H$^+$), 308, 282, 234, 190, 91; HRMS Calcd. for C$_{19}$H$_{19}$NO$_4$ 325.131; found: 325.131.

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