A Facile Synthesis of N-Protected Statine and Analogues via a Lipase-Catalyzed Kinetic Resolution

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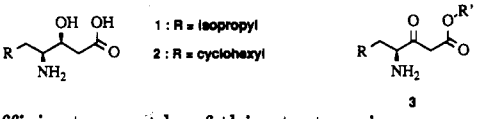
A new synthesis of N-protected statine **4a** and its analogue **4b** is presented. *cis*-(±)-Butyric acid 2-isobutyl-5-oxopyrrolidin-3-yl ester (**10a**) and *cis*-(±)-butyric acid 2-benzyl-5-oxopyrrolidin-3-yl ester (**10b**) were prepared from methyl (*E*)-4-chloro-3-methoxybut-2-enoate (**5**) and subsequently resolved via a kinetic resolution catalyzed by Candida Cylindracea lipase. The desired enantiomers were isolated in excellent enantiomeric excess and good yield. These products were then converted to the *N*-BOC-protected hydroxy amino acids **4a** and **4b**.

(3*S*,4*S*)-4-Amino-3-hydroxy-6-methylheptanoic acid (statine) (**1**) is a key element of the naturally occurring aspartic protease inhibitor pepstatin.[1] Due to the physiological significance of such peptides, particularly as therapeutic agents for human hypertension, substantial effort is being directed toward an efficient synthesis of **1** and its analogues,[2] especially (3*S*,4*S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (**2**). This analogue of statine, in which the isobutyl group has been replaced by a cyclohexylmethyl group, is a fragment of several highly potent renin inhibitors (Chart I).[3]

Previous methods of synthesizing these types of compounds proceed through organometallic additions to the N-protected α-amino aldehydes derived from the α-amino acids.[2a-g] A serious drawback of this approach is the easy racemization of α-amino aldehydes, particularly on a large scale.[4] Another approach is the diastereoselective reduction of an N-protected derivative of **3** (R = isopropyl, phenyl, cyclohexyl), usually the *N*-BOC derivative, but in one case the *N*,*N*-dibenzyl-protected **3** was used.[2l] The most efficient example of this strategy is an asymmetric hydrogenation using BINAP,[2h,i] as reductions of **3** with borohydrides lead to diastereomeric mixtures, which are not easily separated.[2j-l] An alternative strategy is based on the more efficient diastereoselective reduction of cyclic substituted tetramic acids derived from L-amino acids.[5]

Chart I



In this paper we would like to describe alternative syntheses of *N*-BOC-protected statine **4a** and its phenyl analogue **4b**, which proceed via tetramic acid intermediates[5] and have as their key steps kinetic resolutions catalyzed by Candida Cylindracea lipase. The starting material is methyl (*E*)-4-chloro-3-methoxybut-2-enoate (**5**), a compound whose chemistry we have been investigating for several years.[6,7]

Reaction of methyl (*E*)-4-chloro-3-methoxybut-2-enoate (**5**) with aqueous ammonia afforded 1,5-dihydro-4-methoxypyrrol-2-one (**6**).[6] This intermediate **6** was, without isolation, directly condensed in basic media with the appropriate aldehyde (isobutyraldehyde, benzaldehyde) to give the desired carbon skeleton **7**. The isobutylidene substituted intermediate **7a** could be isolated in 80% yield after a simple filtration (the (*Z*)-double bond geometry of **7a** was proved by ^{1}H NMR NOE experiments). Subsequent hydrolysis in concentrated HCl gave **8a** in 92% yield (74% from **5**). In contrast, intermediate **7b** was directly hydrolyzed under acidic conditions to **8b**, which could be isolated by filtration in 88% yield based on **5**. Facile dimerization of C3 or C5 unsubstituted tetramic acids is known to be a problem,[8] but with these 5-substituted tetramic acids no difficulties were encountered. These tetramic acid intermediates **8a** and **8b** were then converted into the corresponding enol butyrates in good yield by reacting them with butyryl chloride and triethylamine in dichloromethane (84% yield for **9a** and 73% for **9b**, after

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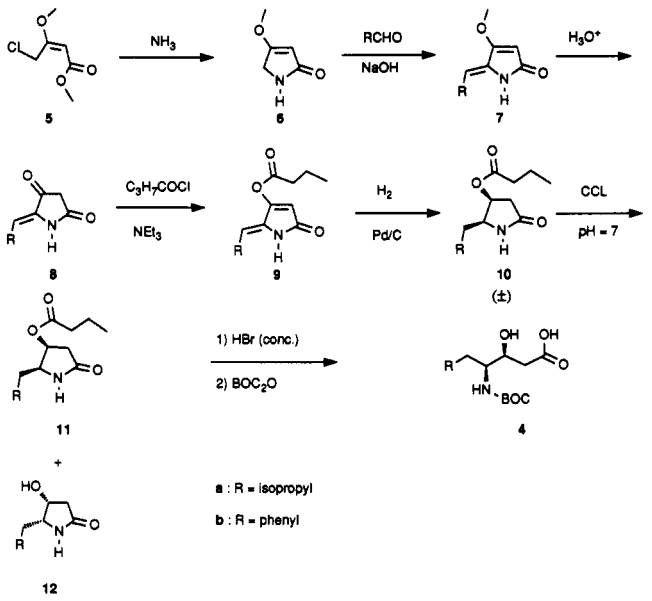
Scheme I



recrystallization). Hydrogenation of these enol esters in toluene over a Pd/C catalyst afforded, after crystallization, the racemic butyrates **10a** and **10b** in 77% and 69% yield, respectively. The cis stereochemistry of the corresponding acetate of **10a** was proved by ^{1}H NMR NOE experiments. The trans-substituted diastereomer and the hydrogenolysis byproduct were removed in the crystallization. It is known that the reduction of 5-substituted tetramic acids has a bias toward the cis-substituted diastereomer.[5]

These racemic butyrates **10** were then subjected to a lipase-catalyzed kinetic resolution. Lipase screening showed that Candida Cylindracea lipase at rt and pH 7 gives excellent selectivity in the hydrolysis of **10a** and **10b**. Preliminary lipase screening experiments were also carried out with the corresponding acetate of **10a**, but the rate of hydrolysis was much slower than for the butyrate **10a**. For substrate **10b** toluene was added as a cosolvent, in order to achieve a similar activity and selectivity as for **10a**. Comparable effects have been noted by earlier workers[9] with several lipases. After approximately 50% conversion the hydrolysis rate of both substrates decreased significantly, indicating the high stereoselectivity of the process. Especially gratifying was the facile separation of the product alcohol **12** from the unreacted ester **11** by a toluene extraction. The alcohol (**12a** or **12b**) remains completely in the aqueous phase, whereas the unreacted ester (**11a** or **11b**) is extracted with toluene. In both cases the (*R*,*R*)-enantiomer was hydrolyzed. The desired (*S*,*S*)-butyrates (**11a** and **11b**) were isolated in high yield (43% crude yield) and excellent optical purity (the crude products had a >99% ee according to GC or HPLC analysis on chiral columns). The absolute stereochemistry of **11a** and **11b** was established by converting them to the *N*-BOC-protected amino acids **4a** and **4b** (optical rotations and melting points were identical to literature values[2a,5a]). This conversion was achieved by hydrolyzing the ester and lactam ring in **11** with concd HBr at 75 °C, in a fashion similar to that of Katsuki.[10] *N*-BOC protection was carried out *in situ*.[11]

The conversion of **4b** into the (3*S*,4*S*)-4-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-5-cyclohexylpentanoic acid via a Rh-catalyzed hydrogenation is described in the literature[2b] and proceeds in quantitative yield.[11]

The advantages of these syntheses are the cheap starting materials and the high yield and selectivity in the resolution step. Furthermore, all intermediates are crystalline and easy to purify, where necessary. **4a** could be isolated in 11% and **4b** in 9% overall yield from **5**. The whole process should be suitable for scaling up.

Experimental Section

General. Solvents and reagents were purchased from Fluka, except methyl (*E*)-4-chloro-3-methoxybut-2-enoate (**5**), which is made by Lonza. Candida Cylindracea lipase was purchased from Biocatalysts (85 000 u/g). ^{1}H NMR were measured at 400 MHz and ^{13}C NMR at 100.6 MHz in $CDCl_3$ unless otherwise stated. Chemical shifts δ in ppm are reported with reference to tetramethylsilane; coupling constants (J) are given in Hz. The ee was determined for **11a** by GC (Lipodex D; Macherey Nagel) and for **11b** by HPLC (Chiralcel (OD); Daicel). The pH of the lipase-catalyzed kinetic resolutions was kept constant by adding 1 M NaOH through an autotitrator.

In cases where synthetic intermediates were isolated by "aqueous workup (aqueous solution, organic solvent)", the procedure was to quench the reaction mixture with the indicated aqueous solution, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic extracts over $MgSO_4$, and remove the solvent in vacuo.

(*Z*)-1,5-Dihydro-5-isobutylidene-4-methoxypyrrol-2-one (7a). Methyl (*E*)-4-chloro-3-methoxybut-2-enoate (**5**) (120 g, 95% pure, 0.69 mol) was added over 3 h to concd ammonia (25%, 200 mL) at 65–70 °C. During the addition NH_3 was bubbled through the solution. After the addition of **5** the mixture was kept at 65–70 °C for another 1.5 h. Then the reaction mixture was heated at reflux for 0.5 h. After the mixture was cooled to rt, 1 M NaOH (450 mL) was added and the pH was adjusted to pH = 13 by adding 33% NaOH. Isobutyraldehyde (50 g, 0.69 mol) was added, and the reaction mixture was stirred at 60 °C for 6 h. After the mixture was cooled to rt, the resultant precipitate was filtered, washed with cold water, and dried under vacuum to afford **7a** (93.2 g, 80%). This product was used for the next step without further purification: mp 140.5–141.1 °C (Et_2O); ^{1}H NMR (300 MHz) δ 1.09 (d, J = 6.6, 6H), 2.65–2.73 (m, 1H), 3.85 (s, 3H), 5.13 (s, 1H), 5.29 (d, J = 10, 1H), 9.02 (br s, 1H); MS m/z 167 ($M^{\bullet+}$) (53), 152 (100), 124 (10), 120 (60), 109 (11), 92 (20), 69 (35), 41 (20).

(*Z*)-5-Isobutylidenepyrrolidine-2,4-dione (8a). To finely pulverized **7a** (50 g, 299 mmol) was added concd HCl (500 mL). This mixture was stirred at rt for 5 h. After the mixture was cooled to 0 °C, 14% NaOH (1 L) was slowly added. The precipitate was filtered, washed with cold water, and dried under vacuum to yield **8a** as a yellow powder (42 g, 92%). This product was used for the next step without further purification: mp 134–136 °C (THF/hexane); ^{1}H NMR (300 MHz) δ, 1.09 (d, J = 6.5, 6H), 2.41–2.55 (m, 1H), 3.09 (s, 2H), 5.57 (d, J = 10, 1H), 8.85 (br s, 1H); MS m/z 153 ($M^{\bullet+}$) (100), 138 (57), 125 (17), 121 (21), 120 (12), 110 (41), 96 (14), 82 (55), 69 (17), 68 (92), 67 (11), 56 (12), 55 (19), 43 (31), 42 (47), 41 (74), 40 (12), 39 (40).

Butyric Acid 2,5-Dihydro-2(*Z*)-isobutylidene-5-oxo-1*H*-pyrrol-3-yl Ester (9a). To a suspension of **8a** (31.8 g, 190 mmol) in CH_2Cl_2 (318 mL) were added butyryl chloride (23.22 g, 219 mmol) followed by triethylamine (27.32 g, 270 mmol) at −5 °C. After the addition was complete, stirring at 0 °C was continued for another 10 min. Aqueous workup (5% $NaHCO_3$, CH_2Cl_2, 0.4 M HCl) afforded crude **9a** (46 g). This material was recrystallized from hexane to yield **9a** as a pale yellow amorphous solid (38.8 g, 84%): mp 111–112 °C; ^{1}H NMR δ 1.03 (t, J = 7.5, 3H), 1.12

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(d, J = 6.6, 6H), 1.77 (m, 2H), 2.56 (t, J = 7.5, 2H), 2.78–2.83 (m, 1H), 5.35 (d, J = 10, 1H), 6.15 (s, 1H), 9.91 (br s, 1H); ^{13}C NMR δ 13.52, 18.12, 22.77, 27.22, 36.24, 105.90, 119.87, 131.57, 154.46, 169.08, 172.13; MS m/z 224 (M^+ + 1) 151, 153 (45), 138 (32), 71 (65), 68 (15), 43 (100). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.67; N, 6.30. Found: C, 64.65; H, 7.88; N, 6.66.

***cis*(±)-Butyric Acid 2-Isobutyl-5-oxopyrrolidin-3-yl Ester (10a).** A mixture of **9a** (30 g, 133 mmol) and Pd/C (5%) (3.0 g) in toluene (300 mL) was hydrogenated in a steel autoclave at 20 atm and rt for 24 h. The catalyst was removed by filtration and the filtrate concentrated in vacuo. The crude product was crystallized from hexane to afford **10a** as a white crystalline product (23.50 g, 77%): mp 101.5–102.7 °C; ^{1}H NMR δ 0.91–0.98 (m, 9H), 1.35–1.71 (m, 5H), 2.29–2.36 (m, 3H), 2.71 (dd, J = 6.4, 17.6 1H), 3.88–3.93 (m, 1H), 5.40–5.43 (m, 1H), 7.49 (br s, 1H); ^{13}C-NMR δ 13.66, 18.39, 22.04, 23.29, 25.00, 36.19, 38.04, 38.52, 56.10, 70.63, 172.99, 175.71; MS m/z 228 ($M^{\bullet+}$ + 1) (3), 170 (49), 157 (21), 156 (97), 140 (13), 139 (45), 114 (28), 100 (49), 98 (11), 97 (69), 88 (17), 86 (71), 83 (11), 82 (64), 71 (76), 55 (19), 44 (32), 43 (100), 42 (13).

(2*S*,3*S*)-Butyric Acid 2-Isobutyl-5-oxopyrrolidin-3-yl Ester (11a). Candida Cylindracea lipase (2 g) was added to **10a** (20 g, 88 mmol) in water (100 mL). The mixture was stirred at rt, and the pH was kept constant at pH = 7 by addition of 1 M NaOH. After 53.8% conversion (47.36 mL of 1 M NaOH consumed; 70 h) the mixture was diluted with water (200 mL) and extracted with toluene (1 × 400 mL and 2 × 200 mL). The combined toluene phases were washed with water (3 × 20 mL), evaporated under reduced pressure, and dried in vacuo to yield **11a** as a white amorphous solid (8.55 g, 43%) (GC >98% area; <1% **12a**; ee >99% (GC, Lipodex D)). This crude product was recrystallized from hexane (94%): mp 94.9–95.3 °C; $[\alpha]_D$ −3.9 (c = 1.0, $CHCl_3$); spectral data as for **10a**. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.39; H, 9.31; N, 6.19. Found: C, 63.00; H, 9.51; N, 6.54.

(3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-6-methylheptanoic Acid (4a). **11a** (3.0 g, 13.2 mmol) in 48% HBr (30 mL) was heated to 75 °C for 24 h. The mixture was then cooled to rt, diluted with water (30 mL), and extracted with Et_2O (3 × 20 mL). The aqueous phase was cooled to −10 °C, and the pH was adjusted to pH = 10 by adding 33% NaOH. THF (20 mL) was added, followed by BOC_2O (2.9 g, 13.3 mmol). This mixture was stirred at pH = 10 for 94 h at rt. Acidification to pH 1.4 with 16% HCl (aq) followed by aqueous workup (Et_2O) gave crude **4a**, which was purified by column chromatography (hexane/ethyl acetate/acetic acid (6:4:0.1)) on silica gel to yield product **4a** as a white solid (2.09 g, 58%): mp 120.2–120.9 °C (acetone/hexane); $[\alpha]_D$ −40.3 (c = 1.0, CH_3OH); ^{1}H NMR δ (d_6-DMSO) 0.83–0.88 (m, 6H), 1.22–1.29 (m, 2H), 1.38 (s, 9H), 1.53–1.57 (m, 1H), 2.12 (dd, J = 15.5, 9.1, 1H), 2.34 (dd, J = 15.5, 3.8, 1H), 3.49–3.53 (m, 1H), 3.79–3.82 (m, 1H), 6.24 (d, J = 9.1, 1H).

(*Z*)-5-Benzylidenepyrrolidine-2,4-dione (8b). Methyl (*E*)-4-chloro-3-methoxybut-2-enoate (**5**) (75 g, 95% pure, 0.43 mol) was added over 3 h to concd ammonia (25%, 133 g) at 65–70 °C. During the addition NH_3 was bubbled through the solution. After the addition of **5** was complete, the mixture was kept for another 0.75 h at this temperature. Then the reaction mixture was stirred at reflux for 0.5 h. After the mixture was cooled to rt, water (300 mL) was added and the pH was adjusted to pH = 13 by adding 33% NaOH (50 mL). To this mixture was added benzaldehyde (46.4 g, 0.44 mol), and the reaction mixture was stirred at 60 °C for 6 h. After the mixture was cooled to rt, concd HCl (688 mL) was added and the mixture stirred at 40 °C for 22 h. Then the mixture was cooled to rt, and the product was filtered, washed with cold water, and dried under vacuum to yield crude **8b** as a yellow powder (74.7 g, 88%). This product was used for the next step without further purification: mp 186–187 °C (THF/hexane); ^{1}H NMR (300 MHz) δ 3.17 (s, 2H), 6.56 (s, 1H), 7.29–7.47 (m, 5H), 8.46 (br s, 1H); MS m/z 188 ($M^{\bullet+}$ + 1) (11), 187 ($M^{\bullet+}$) (100), 159 (11), 130 (16), 118 (17), 117 (47), 116 (24), 91 (14), 90 (33), 89 (32), 63 (13).

Butyric Acid 2(*Z*)-Benzylidene-2,5-dihydro-5-oxo-1*H*-pyrrol-3-yl Ester (9b). **9b** was prepared in a fashion similar to **9a** from **8b** (67 g, 358 mmol) and gave after recrystallization from toluene a pale yellow amorphous solid (67.3 g, 73%): mp 139.8–141.5 °C; ^{1}H NMR δ 1.03 (t, J = 7.4, 3H), 1.78 (m, 2H), 2.58 (t, J = 6.7, 2H), 6.20 (s, 1H), 6.30 (s, 1H), 7.28–7.50 (m, 5H), 9.20 (br s, 1H); ^{13}C-NMR δ 13.53, 18.12; 36.23, 105.39, 109.17, 128.48, 129.09, 129.25, 131.82, 133.85, 155.49, 168.96, 172.12; MS m/z 257 ($M^{\bullet+}$) (26), 188 (13), 187 (100), 186 (24), 159 (31), 130 (10), 118 (16), 117 (16), 116 (19), 91 (16), 90 (11), 89 (10), 71 (36), 69 (17), 43 (79), 41 (19). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.00; H, 5.88; N, 5.47. Found: C, 69.66; H, 5.92; N, 5.80.

***cis*-(±)-Butyric Acid 2-Benzyl-5-oxopyrrolidin-3-yl Ester (10b).** A mixture of **9b** (46.7 g, 182 mmol) and Pd/C (5%) (4.67 g) in toluene (467 mL) was hydrogenated in a steel autoclave at 20 atm and rt for 28 h. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure to give a white sticky solid. This was crystallized from diisopropyl ether to afford **10b** as white needles (32.9 g, 69%): mp 85.6–87 °C; ^{1}H NMR δ 0.98 (t, J = 7.3, 3H), 1.69 (sext, J = 7.3, 2H), 2.34–2.41 (m, 3H), 2.68–2.77 (m, 2H), 2.92 (dd, J = 5.1, 14.0, 1H), 4.07–4.18 (m, 1H), 5.40–5.48 (m, 1H), 6.04 (br s, 1H), 7.16–7.34 (m, 5H). ^{13}C NMR δ 13.68, 18.36, 35.86, 36.12, 37.97, 58.83, 70.17, 127.10, 128.97, 129.01, 137.13, 172.96, 174.35; MS m/z 170 ($M^{\bullet+}$ − 91) (85), 120 (10), 100 (20), 91 (30), 82 (100), 71 (65), 65 (12), 55 (10), 43 (55).

(2*S*,3*S*)-Butyric Acid 2-Benzyl-5-oxopyrrolidin-3-yl Ester (11b). Candida Cylindracea lipase (4.0 g) was added to **10b** (20.0 g, 76.5 mmol) in H_2O (137 mL) and toluene (34 mL). The mixture was stirred at rt, and the pH was kept constant at pH = 7 by addition of 1 M NaOH. After 54% conversion (41.3 mL of 1 M NaOH consumed; 71 h), toluene (600 mL) was added to the reaction mixture. This mixture was stirred vigorously for 0.5 h. The phases were separated, and the aqueous phase was extracted with toluene (300 mL). The combined toluene phases were washed with water (3 × 100 mL) and evaporated under vacuum to yield **11b** as a white amorphous solid (8.57 g, 43%) (GC >98% area; <1% **12b**; ee >99% (HPLC, Chiralcel OD)). This crude **11b** was recrystallized from diisopropyl ether (88%): mp 78.9–79.2 °C; $[\alpha]_D$ −89.0 (c = 1.0, $CHCl_3$); spectral data as for **10b**. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.93; H, 7.33; N, 5.38. Found: C, 68.95; H, 7.44; N, 5.72.

(3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-5-phenylpentanoic Acid (4b). **11b** (1 g, 3.8 mmol) in 48% HBr (10 mL) was heated at 80 °C for 20 h. The mixture was then cooled to rt, diluted with water (10 mL), and extracted with Et_2O (3 × 20 mL). The aqueous phase was cooled to −5 °C, and the pH was adjusted to pH = 10 by adding 33% NaOH. THF (20 mL) was added, followed by BOC_2O (0.86 g, 3.9 mmol). This mixture was stirred at pH = 10 for 24 h. Acidification to pH 1 with 1 M HCl immediately followed by aqueous workup (Et_2O) gave crude **4b**, which was purified by colomn chromatography (hexane/ethyl acetate/acetic acid (10:10:0.25)) on silica gel to afford **4b** as a white powder (0.64 g, 54%): mp 153.2–153.4 °C ($CHCl_3$/hexane); $[\alpha]_D$ −37.7 (c = 1.1, CH_3OH); ^{1}H NMR δ ($CDCl_3$; 60 °C) 1.40 (s, 9H), 2.40–2.66 (m, 2H), 2.86–2.96 (m, 2 H), 3.66–3.82 (m, 1H), 3.96–4.07 (m, 1H), 4.82–5.00 (br s, 1H), 7.12–7.35 (m, 5H).

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Supplementary Material Available: GC (**11a**) and HPLC (**11b**) analyses for ee determination (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.