A New, Versatile and Stereospecific Route to Unusual Amino Acids: The Enantiospecific Total Synthesis of Statine Amide and Its Three Stereoisomers

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Total syntheses of statine amide [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanamide] and its three stereoisomers are described in order to illustrate the versatility of a new route to β-hydroxy-γ-amino acids. The enantioselective Sharpless epoxidation of a racemic allylic alcohol is used to generate chiral intermediates. The allylic alcohol, 3-hydroxy-5-methyl-1-hexene, can be prepared in at least two different ways from readily available materials. The methodology that is described should prove applicable to the synthesis of other analogues of statine.

Introduction

A number of recently characterized, potentially therapeutic small peptides all incorporate the unusual β-hydroxy-γ-amino acid statine [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid] or one of its analogues.[1] How biologically active the peptides are has been found to depend mainly on which statine-like amino acid has been incorporated.[2] Thus, considerable effort has been devoted to developing syntheses of statine and its analogues. Most syntheses so far described have involved the addition of a nucleophile to a chiral *N*-protected amino aldehyde derived from one of the usual naturally occurring amino acids.[3] However, such an approach, although it straightforwardly yields statine and some of its analogues, suffers from an obvious shortcoming: only a relatively few compounds can serve as starting materials. Other approaches, relatively few in number, do allow the synthesis of analogues of statine in which the alkyl group at the γ-carbon can be other than isobutyl. However, they either require the separation of diastereoisomers[4] or give a product whose configuration is preordained by that of the starting material.[5]

We recently described a new route to statine,[6] one which combines enantiospecific reactions with flexibility as to the choice of starting materials and which thus overcomes the limitations of previously reported methods. We have since achieved the total synthesis of the amides of all four stereoisomeric 4-amino-3-hydroxy-6-methyl-heptanoic acids by applying the methodology developed during the course of our synthesis of statine.

Results and Discussion

The enantioselective epoxidation[7] of the racemic allylic alcohol **1** gave, in the presence of D-diisopropyl tartrate, the epoxy alcohol (2*R*,3*R*)-**2** and, in the presence of L-diisopropyl tartrate, the epoxy alcohol (2*R*,3*S*)-**3**. It is worth noting that **1** can be obtained in at least two different ways, i.e., by the addition of vinyl magnesium bromide to isovaleraldehyde and by the addition of isobutyllithium to acrolein. It should be possible to similarly prepare a virtually unlimited number of analogues of **1**, thus providing starting materials for the synthesis of analogues of statine which incorporate different alkyl and aryl groups at the γ-carbon. The kinetic resolution of **1** was effected by epoxidation at −20 °C with a titanium tetraisopropoxide to tartrate to allylic alcohol ratio of 0.6:0.5:1. Attempts to effect epoxidation under normal (1:1:1 ratio) or catalytic[8] conditions gave unsatisfactory results. The optical purity of the products was established[9] by the results of inspecting the high-field ^{1}H NMR spectra (300 MHz) of solutions of **2** and **3** which also contained a chiral shift reagent[10] and by the observation that the specific rotations of **2** and **3** were of the same magnitude but of different sign. Inversion of the hydroxylated carbon of both **2** and **3** was achieved via a Mitsunobu reaction,[11] in which *p*-nitrobenzoic acid served as the nucleophile.[12] That complete inversion had occurred was shown by the fact that no stereoisomers of the products, the epoxy *p*-nitrobenzoates **4** and **5**, respectively, were detected by either TLC or ^{13}C NMR analysis. The two epoxy esters were then individually saponified by treatment with dilute methanolic sodium methoxide to give the epoxy alcohols **6** and **7**, re-

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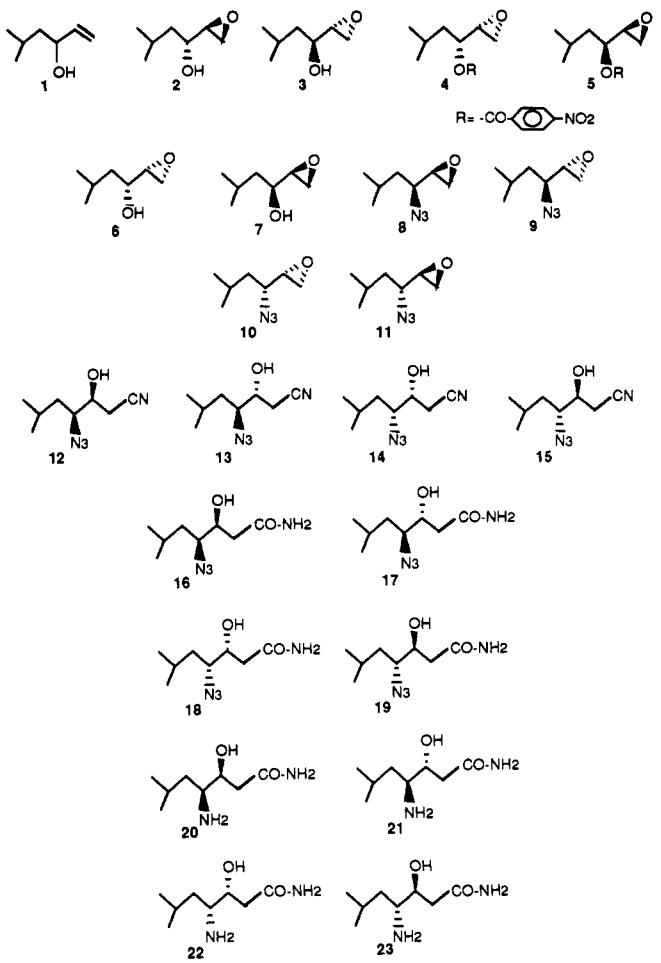

spectively. The stereoisomeric epoxy alcohols **2**, **6**, **3**, and **7** were then individually subjected to the same set of reactions. First, a Mitsunobu reaction in which an azide nucleophile was employed[13] gave the epoxy azides **8**, **9**, **10**, and **11**, respectively. It should be noted that when hydrazoic acid served as the nucleophile, satisfactory results were obtained only with compounds **2** and **3**. The threo epoxy alcohols **6** and **7** are apparently more acid-sensitive and gave mostly products of ring-opening. However, good yields of the desired products were obtained from the latter two compounds when the nonacidic zinc azide bis(pyridine) complex was used in place of hydrazoic acid.[14] Next, opening of the epoxide ring, by treatment with ethanolic potassium cyanide gave, regioselectively, compounds **12–15**, respectively. Hydrolysis of the cyano group to a carboxyl group was then attempted. However, both acid-catalyzed hydrolysis and alcoholysis gave intractable mixtures of products, a result, probably, of the instability of the azido group under the strongly acidic conditions that were employed. Attempts to selectively reduce the azido group to an amino group and then hydrolyze the cyano group also failed. γ-Amino nitriles were in fact produced, but they proved unstable and rapidly decomposed. The hydrolysis of compounds **12–15** in the presence of alkaline hydrogen peroxide gave what at first seemed to be satisfactory results. However, we subsequently found that hydrolysis to the corresponding azido acids could not be reliably reproduced. In most instances, only hydration to the azido amides **16–19**, respectively, was observed.[15] Catalytic hydrogenation of the azido amides gave the corresponding amino amides, compounds **20–23**. In order to avoid the inversion step on the epoxy alcohols **2** and **3**, we sought a more straighforward route: formation of an oxazoline on the amino amide compounds **20** and **22** with inversion of the hydroxylated carbon and subsequent hydrolysis of the heterocyclic ring to give the amino amides **21** and **23**, respectively. However, the oxazoline formation on compounds **20** and **22** led mostly to elimination products.

Thus, we have described a novel enantiospecific synthesis not only of statine amide but also of its three stereoisomers. Furthermore, the methodology that was used appears to be sufficiently flexible to consider applying it to the synthesis of analogues of statine not previously obtainable. The synthesis of such compounds and appropriate biological studies of them are currently under way in our laboratory.

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Experimental Section

General Methods. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions (unless otherwise noted) were recorded, at 300.13 and 75.47 MHz, respectively. TMS served as the internal standard, unless otherwise noted. Assignment of all the signals was made possible by applying homonuclear spin decoupling techniques. Shift experiments used $CDCl_3$ as the solvent and tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III) as the chiral shift reagent. GLC analysis of volatile compounds was performed using a 12-m fused silica capillary column (coated with BP1 nonpolar phase). Reaction progress was monitored by TLC on plastic sheets coated with 0.2-mm-thick silica gel 60 F254 (Merck). The compounds were visualized by spraying the sheets with anisaldehyde/H_2SO_4 in EtOH and subsequent heating. Pure compounds were obtained by flash chromatography on Chromagel (S.D.S., 60 Å, 200–400 mesh). Specific rotations were measured at room temperature with sodium D light. Microanalyses were performed by the Centre National de Microanalyses du CNRS, Vernaison, France.

3-Hydroxy-5-methyl-1-hexene (1). Method A. A solution of isovaleraldehyde (86 g; 1 mol in dry THF (200 mL) was added, with stirring, to ice-cold vinylmagnesium bromide (1 M, 500 mL of a 2 M solution in THF), at such a rate that the temperature did not exceed 5 °C. The mixture was stirred for an additional 30 min at a temperature below 5 °C. Saturated aqueous $NaHSO_4$ (50 mL) was cautiously added, and stirring was continued for 15 min. The resulting suspension was filtered through Celite. The filtrate was diluted with hexane (300 mL) and was washed (1 × 100 mL saturated aqueous $NaHSO_4$, 2 × 100 mL of brine), dried ($MgSO_4$), and concentrated. Fractional distillation of the residue gave **1** (60 g; 50%): bp 48–50 °C (15 mmHg).

Method B. *i*-BuLi (100 mL of a 2 M solution in THF) was slowly added to a cold (−50 °C) solution of freshly distilled acrolein (11 g; 0.2 mol) in THF (100 mL). The mixture was stirred for 30 min at −50 °C, and then it was allowed to come to 0 °C. Aqueous NaH_2PO_4 (5 mL, 1 M) was cautiously added. The mixture was diluted with hexane (200 mL) and was worked up as in method A. Distillation gave pure **1** (13.5 g; 60%): ^1H NMR δ 0.93, 0.95 (2d, 6 H), 1.32 (ddd, J = 13.6 Hz, 1 H), 1.47 (ddd, J = 13.7 Hz, 1 H), 1.73 (m, 1 H), 1.9 (bs, 1 H), 4.17 (dd, J = 6.6 Hz, 1 H), 5.08 (dd, J = 17.2 Hz, 1 H), 5.21 (dd, J = 10.38 Hz, 1 H), 5.86 (ddd, J = 16.94, 10.35, 6.28 Hz, 1 H); ^{13}C NMR δ 22.38, 23.07, 24.56, 46.29, 71.53, 114.32, 141.72. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.43; H, 12.41.

(2*S*,3*R*)-1,2-Epoxy-3-hydroxy-5-methylhexane (2). The racemic alcohol **1** (11 g, 96.5 mmol) was dissolved in dry CH_2Cl_2 (200 mL), and then diisopropyl D-tartrate (13.5 g, 58 mmol) was added. The mixture was cooled under N_2 to −20 °C. Titanium tetraisopropoxide (14.26 mL, 48 mmol) was added, and the mixture was stirred for 15 min at −20 °C. Then anhydrous *tert*-butyl hydroperoxide (52 mL of a 3.7 M solution in toluene) was added. The mixture was left at −20 °C until reaction was complete (GLC analysis after 4.5 h showed 50% conversion). The reaction mixture was then diluted with Et_2O (500 mL) and was poured into an ice-cooled solution of ferrous sulfate (30 g) in 10% aqueous tartaric acid (100 mL). The mixture was then stirred

for 1 h, and then the organic phase was decanted, dried ($MgSO_4$), and concentrated. Fractional distillation of the residue under reduced pressure gave the (3*S*)-allylic alcohol (bp 50 °C (15 mmHg)) and the epoxide **2** (bp 80–85 °C (15 mmHg), 6 g, 96%).[16] **2**: $[\alpha]^{20}_D$ +11° (*c* 1, MeOH); ^{1}H NMR δ 0.95, 0.96 (2d, 6 H), 1.30–1.46 (m, 2 H), 1.87 (m, 1 H), 2.04 (bs, 1 H), 2.72 (dd, *J* = 4.30 Hz, 1 H), 2.81 (dd, *J* = 2.75 Hz, 1 H), 3.0 (m, *J* = 3.18, 6.85 Hz, 1 H), 3.92 (m, *J* = 7.1, 9.01 Hz, 1 H); ^{13}C NMR δ 22.01, 23.54, 24.43, 42.51, 43.55, 55.06, 66.87. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.36; H, 10.57.

(2*R*,3*S*)-1,2-Epoxy-3-hydroxy-5-methylhexane (3). Epoxidation of **1** (11 g, 96.5 mmol) in the same manner, but in the presence of L-diisopropyl tartrate, gave **3** (6.1 g, 98%):[16] $[\alpha]^{20}_D$ −11.2° (*c* 1, MeOH).

(2*S*,3*S*)-1,2-Epoxy-5-methyl-3-(4′-nitrobenzoyl)hexane (5). Epoxide **2** (0.65 g, 5 mmol) was dissolved in benzene (5 mL), and then PPh_3 (3.9 g, 15 mmol) and *p*-nitrobenzoic acid (2.3 g, 13.5 mmol) were added. Diethyl azodicarboxylate (2.34 mL, 15 mmol) in benzene (5 mL) was then added drop-by-drop. After 20 min, the mixture was concentrated. The residue was purified by flash chromatography on silica gel (hexane/EtOAc (95:5)) to give **5** as a yellowish liquid (0.97 g, 70%): $[\alpha]^{20}_D$ +5.8° (*c* 1, MeOH); ^{1}H NMR δ 0.89, 0.92 (2d, 6 H), 1.50–1.58 (m, 1 H), 1.6–1.73 (m, 1 H), 1.73–1.8 (m, 1 H), 2.64 (dd, *J* = 2.6, 4.83 Hz, 1 H), 2.82 (dd, *J* = 4.65, 4.26 Hz, 1 H), 3.2 (ddd, *J* = 2.59, 4.11, 6.4 Hz, 1 H), 5.12 (ddd, *J* = 4.18, 6.24, 10.02 Hz, 1 H), 8.15–8.25 (m, 4 H); ^{13}C NMR δ 22.28, 23.02, 24.57, 40.22, 45.03, 53.26, 74.39, 123.57, 130.66, 135.46, 150.65, 164.06. Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.38; H, 5.95; N, 5.18.

(2*R*,3*R*)-1,2-Epoxy-5-methyl-3-(4′-nitrobenzoyl)hexane (4). Similar treatment of **3** (0.64 g, 4.9 mmol) gave **4** (1.13 g, 82%): $[\alpha]^{20}_D$ −6° (*c* 1, MeOH).

(2*S*,3*S*)-1,2-Epoxy-3-hydroxy-5-methylhexane (7). The *p*-nitrobenzoate **5** (1.5 g, 5.38 mmol) was dissolved in MeOH (20 mL), and then sodium methoxide (0.5 mL of a 1.1 M solution in MeOH) was added. After 1.5 h the mixture was neutralized by treating it with IR 120 Amberlite resin (H^+-form). Filtration of the mixture, concentration of the filtrate, and flash chromatography of the residue gave **7** (0.65 g, 95%): $[\alpha]^{20}_D$ −10° (*c* 1, MeOH); ^{1}H NMR δ 0.93, 0.95 (2d, 6 H), 1.35 (ddd, *J* = 4.7, 8.5, 13.4 Hz, 1 H), 1.46 (ddd, *J* = 5.68, 9.09, 13.93 Hz, 1 H), 1.84 (m, 1 H), 2.72 (dd, *J* = 2.76, 4.92 Hz, 1 H), 2.83 (dd, *J* = 4.18, 4.82 Hz, 1 H), 2.97 (ddd, *J* = 2.49, 3.93, 4.99 Hz, 1 H), 3.48 (bs, 1 H), 3.53 (dd, *J* = 4.92, 9.48 Hz, 1 H); ^{13}C NMR δ 22.10, 23.38, 24.38, 43.37, 45.24, 55.80, 69.98. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.35; H, 10.62.

(2*R*,3*R*)-1,2-Epoxy-3-hydroxy-5-methylhexane (6). Similar treatment of **4** (1.4 g, 5.13 mmol) gave **6** (0.6 g, 90%): $[\alpha]^{20}_D$ +10.5° (*c* 1, MeOH).

(2*S*,3*S*)-1,2-Epoxy-3-azido-5-methylhexane (8). The epoxide **2** (1 g, 7.7 mmol) and PPh_3 (4 g, 15.4 mmol) were dissolved in benzene (15 mL). The solution was cooled in an ice bath, and then diethyl azodicarboxylate (2.4 mL, 15.4 mmol) and anhydrous hydrazoic acid (8 mL of a 1.2 M solution in benzene) were successively added, with stirring. The mixture was stirred for 1 h at rt, and then it was diluted with hexane (100 mL) and was washed with 80% aqueous MeOH[17] (2 × 5 mL). Concentration of the benzene/hexane solution and flash chromatography of the residue gave pure **8** (1.1 g, 92%): $[\alpha]^{20}_D$ −8° (*c* 0.1, MeOH); ^{1}H NMR δ 0.91, 0.96 (2d, 6 H), 1.30–1.42 (m, 1 H), 1.52–1.64 (m, 1 H), 1.80 (m, 1 H), 2.68 (dd, *J* = 2.55, 4.78 Hz, 1 H), 2.83 (dd, *J* = 4.7 Hz, 1 H), 3.04 (ddd, *J* = 2.52, 3.94, 6.44 Hz, 1 H), 3.16 (ddd, *J* = 5.11, 6.23, 9.46 Hz, 1 H); ^{13}C NMR δ 21.86, 23.04, 24.76, 39.99, 44.85, 54.70, 61.89. Anal. Calcd for $C_7H_{13}N_3O$; 0.5 H_2O: C, 51.20; H, 8.59; N, 25.59. Found: C, 51.43; H, 8.46; N, 25.49.

(2*R*,3*R*)-1,2-Epoxy-3-azido-5-methylhexane (10). Similar treatment of **3** (1 g, 77 mmol) gave **10** (1.15 g, 95%): $[\alpha]^{20}_D$ +8.1 (*c* 0.1, MeOH).

(2*S*,3*R*)-1,2-Epoxy-3-azido-5-methylhexane (11). Similar treatment of **7** (1 g, 1.1 mmol), but with zinc azide bis(pyridine) (2.8 g, 9.3 mmol) instead of hydrazoic acid gave **11** (1 g, 84%): $[\alpha]^{20}_D$ +11.4° (*c* 0.6, MeOH); ^{1}H NMR δ 0.95, 0.97 (2d, 6 H), 1.37–1.54 (m, 2 H), 1.84 (m, 1 H), 2.78–2.83 (m, 2 H), 3 (ddd, *J* = 2.6, 3.81, 5.27 Hz, 1 H), 3.37 (dd, *J* = 5.08, 9.8 Hz, 1 H); ^{13}C NMR δ 21.77, 23.19, 24.84, 40.75, 44.84, 53.72, 60.83. Anal. Calcd for $C_7H_{13}N_3O$·0.6H_2O: C, 50.65; H, 8.62; N, 25.31. Found: C, 50.72; H, 8.38; N, 24.98.

(2*R*,3*S*)-1,2-Epoxy-3-azido-5-methylhexane (9). Similar treatment of **6** (1 g, 7.7 mmol), but with zinc azide bis(pyridine) (2.8 g, 9.3 mmol) instead of hydrazoic acid gave **9** (1.1 g, 92%): $[\alpha]^{20}_D$ −11.6° (*c* 0.6, MeOH).

(3*S*,4*S*)-4-Azido-3-hydroxy-6-methylheptanenitrile (12). Compound **8** (0.5 g, 3.2 mmol) was dissolved in 90% aqueous EtOH (5 mL), and then KCN (1 g, 16.5 mmol) was added. The mixture was stirred overnight at rt. The mixture was then diluted with EtOAc (50 mL), was washed successively with water[18] (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. Recrystallization of the residue from hexane gave **12** (0.5 g, 85%): mp 55–60 °C, $[\alpha]^{20}_D$ −16.2° (*c* 0.1, MeOH); ^{1}H NMR δ 0.98 (2d, 6 H), 1.42–1.67 (m, 2 H), 1.80 (m, 1 H), 2.60 (AB, *J* = 5.68, 16.84 Hz, 1 H), 2.69 (AB, *J* = 7.02, 16.78 Hz, 1 H), 3.39 (ddd, *J* = 3.62, 4.73, 8.87 Hz, 1 H), 3.94 (ddd, *J* = 3.57, 5.68, 7.03 Hz, 1 H); ^{13}C NMR δ 21.87, 22.99, 23.45, 24.96, 39.13, 62.74, 69.87, 117.34. Anal. Calcd for $C_8H_{14}N_4O$·0.5MeOH: C, 51.50; H, 8.14; N, 28.26. Found: C, 51.66; H, 7.83; N, 28.02.

(3*R*,4*S*)-4-Azido-3-hydroxy-6-methylheptanenitrile (13). Treatment of **9** (0.5 g, 3.2 mmol) in a similar manner gave **13** (0.48 g, 82%): $[\alpha]^{20}_D$ −15.2° (*c* 0.1, MeOH).

(3*R*,4*R*)-4-Azido-3-hydroxy-6-methylheptanenitrile (14). Similar treatment of **10** (0.5 g, 3.2 mmol) gave **14** (0.5 g, 85%): $[\alpha]^{20}_D$ +16° (*c* 0.1, MeOH).

(3*S*,4*R*)-4-Azido-3-hydroxy-6-methylheptanenitrile (15). Treatment of **11** (0.5 g, 3.2 mmol) in a similar manner gave **15** (0.52 g, 88%): $[\alpha]^{20}_D$ +16.5° (*c* 0.1, MeOH); ^{1}H NMR δ 0.97, 0.99 (2d, 6 H), 1.27–1.51 (m, 2 H), 1.75–1.83 (m, 1 H), 2.67 (AB, *J* = 7.52, 16.81 Hz, 1 H), 2.59 (AB, *J* = 4.38, 16.52 Hz, 1 H), 3.56 (m, *J* = 3.99, 9.17 Hz, 1 H), 3.96 (ddd, *J* = 4.81, 7.35, 9.64 Hz, 1 H); ^{13}C NMR δ 21.55, 22.18, 23.32, 25.09, 39.31, 63.94, 70.37, 117.55. Anal. Calcd for $C_8H_{14}N_4O$·0.4MeOH: C, 51.73; H, 8.06; N, 28.73. Found: C, 51.86; H, 7.88; N, 28.54.

(3*S*,4*S*)-4-Azido-3-hydroxy-6-methylheptanamide (16). The nitrile **12** (0.1 g, 0.55 mmol) was dissolved in 60% aqueous *t*-BuOH (8 mL). Aqueous NaOH (0.6 mL of a 1 M solution) and 30% aqueous H_2O_2 (0.1 mL) were then added. The mixture was stirred for 2 h at rt. It was then concentrated, acidified (1 N HCl, 5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The extract was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc). Concentration of the eluate gave **16** (0.1 g, 91%): $[\alpha]^{20}_D$ −21° (*c* 1, H_2O); ^{1}H NMR δ 0.96, 0.97 (2d, 6 H), 1.43 (ddd, *J* = 4.49, 8.75, 13.58 Hz, 1 H), 1.67 (ddd, *J* = 5.33, 9.66, 14.07 Hz, 1 H), 1.83 (m, 1 H), 2.40 (AB, *J* = 2.95, 15.56 Hz, 1 H), 2.59 (AB, *J* = 9.42, 15.58 Hz, 1 H), 3.2 (m, *J* = 4.21, 9.19 Hz, 1 H), 4.06 (ddd, *J* = 3.35, 6.78, 9.45 Hz, 1 H); ^{13}C NMR δ 21.68, 23.09, 24.91, 39.03, 39.67, 63.84, 70.85, 175.18. Anal. Calcd for $C_8H_{16}N_4O_2$; H_2O: C, 44.03; H, 8.31; N, 25.67. Found: C, 44.12; H, 8.33; N, 25.51.

(3*R*,4*S*)-4-Azido-3-hydroxy-6-methylheptanamide (17). Similar treatment of **13** (0.096 g, 0.53 mmol) gave **17** (0.095 g, 90%): $[\alpha]^{20}_D$ −17.8° (*c* 1, H_2O).

(3*R*,4*R*)-4-Azido-3-hydroxy-6-methylheptanamide (18). Similar treatment of **14** (0.1 g, 0.55 mmol) gave **18** (0.1 g, 95%): $[\alpha]^{20}_D$ +21.4° (*c* 1, H_2O).

(3*S*,4*R*)-4-Azido-3-hydroxy-6-methylheptanamide (19). Similar treatment of **15** (0.096 g, 0.53 mmol) gave **19** (0.097 g, 92%): $[\alpha]^{20}_D$ +18° (*c* 1, H_2O); ^{1}H NMR δ 0.94, 0.96 (2d, 6 H), 1.24–1.45 (m, 2 H), 1.7–1.85 (m, 1 H), 2.42 (AB, *J* = 3.84, 15.68 Hz, 1 H), 2.54 (AB, *J* = 7.91 Hz, 1 H), 3.51 (m, *J* = 4.22, 8.60 Hz, 1 H), 4.05 (m, *J* = 3.43, 8.15 Hz, 1 H); ^{13}C NMR δ 21.61, 23.35, 25.18, 37.39, 39.34, 64.73, 71.37, 175.57. Anal. Calcd for $C_8H_{16}N_4O_2$·0.8H_2O: C, 44.76; H, 8.26; N, 26.10. Found: C, 44.96; H, 8.42; N, 25.81.

(3*S*,4*S*)-4-Amino-3-hydroxy-6-methylheptanamide (20). The azido compound **16** (0.1 g, 0.5 mmol) was dissolved in MeOH (5 mL). The solution was treated with activated charcoal and

(16) Reported yields for **2** and **3** are related to the reacting allylic alcohol enantiomer.

(17) This washing with methanol removed most of the triphenylphosphine oxide.

(18) The aqueous solution is very toxic and should be disposed of with proper care.

the mixture was filtered. The filtrate was cooled to 0 °C, and 10% Pd/C was added. The mixture was then shaken under H_2 (40 psi) for 3 h at rt. Filtration of the mixture and concentration of the filtrate gave the pure amino amide **20** (0.085 g, 98%): mp 202 °C dec; $[\alpha]^{20}_D$ -20.4° (*c* 1, H_2O); ^1H NMR (D_2O, int. std. 4.78 ppm) δ 0.92, 0.93 (2d, 6 H), 1.35-1.45 (m, 1 H), 1.52-1.64 (m, 1 H), 1.68-1.80 (m, 1 H), 2.50 (AB, *J* = 10.50 Hz, 1 H), 2.53 (AB, *J* = 3.5, 10.7 Hz, 1 H), 3.4 (ddd, *J* = 3.06, 7.14, 9.8 Hz, 1 H), 4.0-4.10 (m, 1 H); ^{13}C NMR (D_2O, CH_3OH int. std. 48.98 ppm) δ 21.01, 22.10, 23.93, 38.50, 41.42, 53.97, 68.27, 178.72. Anal. Calcd for $C_8H_{18}N_2O_2 \cdot H_2O$: C, 49.98; H, 10.49; N, 14.57. Found: C, 49.83; H, 10.49; N, 14.37.

(3*R*,4*S*)-4-Amino-3-hydroxy-6-methylheptanamide (21). Similar treatment of **17** (0.1 g, 0.5 mmol) gave **21** (0.083 g, 96%): mp 203 °C dec; $[\alpha]^{20}_D$ -18.1° (*c* 1, H_2O).

(3*R*,4*R*)-4-Amino-3-hydroxy-6-methylheptanamide (22). Treatment of **18** (0.1 g, 0.5 mmol) in a similar manner gave **22** (0.080 g, 92%): $[\alpha]^{20}_D$ +19° (*c* 1, H_2O).

(3*S*,4*R*)-4-Amino-3-hydroxy-6-methylheptanamide (23). Similar treatment of **19** (0.1 g, 0.5 mmol) gave **23** (0.086 g, 99%): $[\alpha]^{20}_D$ +18.3° (*c* 1, H_2O); ^1H NMR (D_2O int. std. 4.78 ppm) δ 0.91 (2d, 6 H), 1.35-1.70 (m, 3 H), 2.4-2.66 (m, 2 H), 3.37-3.48 (m, 1 H), 4.24-4.38 (m, 1 H); ^{13}C NMR (DCl 0.2 N, CH_3OH int. std. 48.95 ppm) δ 17.47, 18.33, 20.34, 34.66, 38.06, 58.01, 67.85, 175.54. Anal. Calcd for $C_8H_{18}N_2O_2 \cdot 0.6H_2O$: C, 51.92; H, 10.46; N, 15.14. Found: C, 51.63; H, 10.42; N, 14.78.

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Supplementary Material Available: ^{13}C NMR spectra for compounds **1**, **2**, **5**, **7**, **8**, **11**, **12**, **15**, **16**, **19**, **20**, and **23** (12 pages). This material is contained in many 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.

Asymmetric Tandem Mannich-Michael Reactions of Amino Acid Ester Imines with Danishefsky's Diene

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Imines **1** derived from aromatic, aliphatic, and functionalized aldehydes and various amino acid esters react with Danishefsky's diene under Lewis acid catalysis via a tandem Mannich-Michael mechanism to give cyclic 6-substituted 2,3-didehydro-4-piperidinones in good to high yields and with diastereomeric ratios reaching from 92:8 up to 97:3. The chiral auxiliary is removed by conversion of the α C atom of the amino acid into an acetalic center, employing a Curtius reaction as the key step. For the elucidation of the absolute configuration, the alkaloids (*S*)-coniine and (*R*)-δ-coniceine are synthesized from the enaminones **5i** and **5r**.

Introduction

Reactions of compounds containing C-N double bonds with dienes to give six-membered azaheterocycles open up a wide variety of opportunities for organic synthesis, in particular for the construction of alkaloids and analogues thereof.[1] The widespread use of these methods has for a long time been hampered by the low reactivity of easily accessible and common unactivated imines, making the application of activated Schiff bases necessary, which carry electron-withdrawing substituents, e.g. CF_3, acyl, and tosyl groups. However, recently Danishefsky et al.[2a-c] demonstrated that unactivated aromatic and aliphatic imines react smoothly with electron-rich dienes like **2** (Danishefsky's diene) in the presence of $ZnCl_2$. The mechanism of this conversion is a matter of debate and may vary with the structure of the heteroanalogous carbonyl compound employed. Whereas Danishefsky et al. seem to favor a Diels-Alder type process, Kunz et al.[3] have substantiated that alternatively a Lewis acid induced addition of the silyl enol ether moiety of **2** followed by a cyclization via nucleophilic intramolecular attack of the amine generated, may occur. The principle has subsequently been applied by several groups for the construction of various heterocyclic frameworks and natural products.[2,3] Despite the great potential of this synthetic method, only isolated efforts have thus far been made to carry out corresponding transformations asymmetrically using removable chiral auxiliary groups, i.e. only a carbohydrate derived amine has been applied for the steric steering of reactions between the diene **2** and respective imines.[3]

In this paper we report on the use of the easily accessible amino acid esters as mediators of chirality in the reaction of unactivated imines with Danishefsky's diene **2**.[5] These esters have already been used as effective chiral auxiliaries

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