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Asymmetric Syntheses of 3-Amino-2-methylpentanoic Acids. Configurations of the β-Amino Acid in Majusculamide C, 57-Normajusculamide C and Dolastatins 11 and 12

Robert B. Bates* and Sanjeev Gangwar

Department of Chemistry, University of Arizona, Tucson, Arizona 85721, USA

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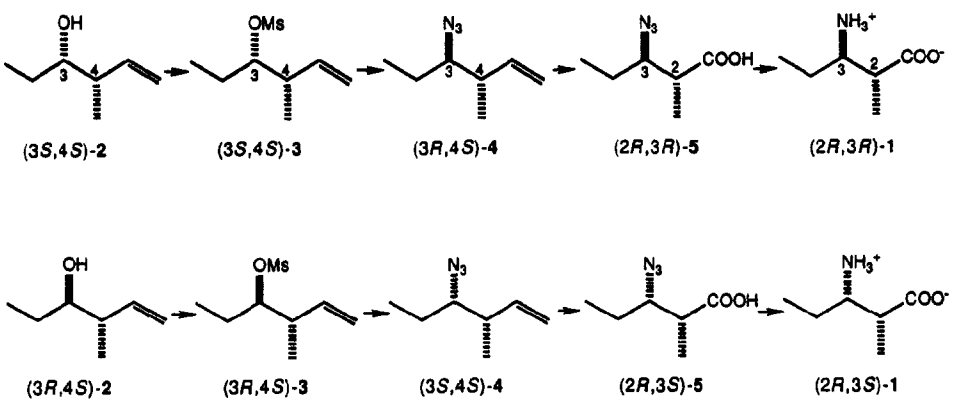
Abstract: The first synthesis of 3-amino-2-methylpentanoic acids is reported. Comparison of the synthetic 2R,3R and 2R,3S acids with 3-amino-2-methylpentanoic acid obtained by degradation of the antifungal depsipeptide majusculamide C indicates that majusculamide C, 57-normajusculamide C, and the antitumor agents dolastatins 11 and 12 have the 2S,3R configurations at the chiral centers in their β-amino acid component.

A 3-amino-2-methylpentanoic acid (**1**) is incorporated into closely related depsipeptides from marine organisms: The antifungal agents majusculamide C[1] and 57-normajusculamide C[2] and the antitumor agents dolastatins 11 and 12.[3] As part of a project to synthesize these depsipeptides and to establish their remaining unknown configurations, two of which are in **1**, we wish to report the first synthesis of two of the four stereoisomers of **1** and that the stereoisomer obtained by hydrolysis of majusculamide C is (2S,3R)-**1**.



Synthetic route 2→3→4→5→1, which could give all of the possible stereoisomers, was used. The four stereoisomeric homoallylic alcohols 2 were each made in ca. 70% yield using highly stereoselective one-pot reactions developed by Brown and Bhat for the synthesis of the corresponding alcohols containing methyl instead of ethyl groups.[4] By NMR, diastereoselectivities were 97% for (3S,4S)-and (3R,4R)-2, and 96% for (3R,4S)- and (3S,4R)-2. Enantioselectivities were probably very close to the 95-96% observed by Brown and Bhat.[4] Small amounts of the impurities isopinocampheol (12-16%) and α-pinene (ca. 3%) were carried through the next several steps since the byproducts they gave later were easily removed: The neutral azide from isopinocampheol was separated by extraction from the azido acid 5, and cis-pinonic acid from α-pinene was separated from the amino acid 1 by extraction.

(3S,4S)-and (3R,4S)-2 were converted into mesylates 3 followed by displacement with sodium azide to the azides 4. Oxidation to the azido acid 5 with $RuCl_3/NaIO_4$[5] proceeded in higher yield (68% vs. 46%) than $O_3/(C_6H_5)_3P/Ag_2O$.[6] Reduction of azido acids 5 with H_2/Pd gave β-amino acids 1. While 2-5 were volatile liquids from which solvents had to be removed by careful distillation and not rotary evaporation, 1·HCl crystallized to give enantiomerically pure final materials. This was supported in the case of (2R,3S)-1 by observing only one product by NMR when it was attached to a chiral dipeptide.[7]

Comparison of the NMR spectra of synthetic (2R,3R)- and (2R,3S)-1·HCl with that of the degradation product of majusculamide C[1] (especially 2-CH at δ2.94, 3-CH at δ3.52) clearly showed that the latter is the (2R,3S)- or (2S,3R)-isomer (2-CH at δ2.93, 3-CH at 3.52) rather than one of the other two stereoisomers (2-CH at δ3.19, 3-CH at δ3.46). Since 1·HCl from degradation of majusculamide C had a + plain ORD curve from 220-300 nm[8] and synthetic (2R,3S)-1·HCl had a - plain ORD curve in the same spectral region, it is (2S,3R)-1 which is incorporated into majusculamide C,[1] 57-normajusculamide C,[2] and dolastatins 11 and 12.[3,8] Thus we assign these four depsipeptides the 2S,3R-configurations at the centers in their β-amino acid units.

This route may prove useful for the asymmetric synthesis of other β-amino acids.

Experimental Section

(3S,4S)-4-Methyl-5-hexen-3-ol ((3S,4S)-2). To a stirred mixture of KO-t-Bu (2.8 g, 25 mmol), THF (10 mL) and cis-2-butene (4.5 mL, 50 mmol), n-butyllithium in THF (2.3 M, 25 mmol) was added at -78 °C. After stirring 1 h, (+)-MDB in ether (1 M, 30 mmol) was added dropwise. After stirring 30 min, BF_3-Et_2O (4 mL, 33.5 mmol) was added dropwise, followed by propionaldehyde (2.2 mL, 35 mmol). After stirring 3 h, NaOH (3 N, 18.3 mL, 55 mmol) was added followed by H_2O_2 (30%, 7.5 mL, 63 mmol). After refluxing 1 h, the organic layer was separated, washed with water (50 mL) and brine (40 mL), dried ($MgSO_4$), evaporated, and vacuum distilled (to remove the bulk of the isopinocampheol) to give (3S,4S)-2 (bp ca. 35 °C/1 mm, 2.9 g, 72%), with diastereoselectivity 97% based on the completely resolved 3-CH proton absorptions in the NMR. (3S,4S)-and (3R,4R)-2 [obtained using (-)-MDB] had ^{1}H NMR δ0.96 (t, J = 7.4 Hz, 1-Me), 1.03 (d, J = 6.8 Hz, 4-Me), 1.3-1.6 (m, 2-CH_2), 2.28 (br sextet, J = 6.5 Hz, 4-CH), 3.40 (dt, J = 7.7, 5.0 Hz, 3-CH), 5.06 (d, J = 10.8 Hz) and 5.09 (d, J = 16.8 Hz, 6-CH_2), 5.80 (ddd, J = 16.8, 10.8, 7.0 Hz, 5-CH). For (3S,4S)-2, $[\alpha]_D^{25}$ -28.8° (c 0.35, $CHCl_3$) and for (3R,4R)-2, $[\alpha]_D^{25}$ +27.9 (c 0.3, $CHCl_3$).

(3R,4S)-4-Methyl-5-hexen-3-ol ((3R,4S)-2). Using trans-2-butene and (-)-MDB, the recipe above gave (3R,4S)-2 in 70% yield with a diastereoselectivity of 96%. (3R,4S)- and (3S,4R)-2 [obtained using (+)-MDB] had ^{1}H NMR δ0.97 (t, J = 7.4 Hz, 1-Me), 1.03 (d, J = 6.9 Hz, 4-Me), 1.3-1.6 (m, 2-CH_2), 2.22 (br sextet, J = 7.4 Hz, 4-CH), 3.33 (ddd, J = 8.1, 6.0, 3.9 Hz, 3-CH), 5.11 (d, J = 16.9 Hz) and 5.12 (d, J = 10.8 Hz, 6-CH_2), 5.76 (ddd, J = 16.9, 10.8, 8.2 Hz, 5-CH). For (3R,4S)-2, $[\alpha]_D^{25}$ -8.7 (c 0.3, $CHCl_3$) and for (3S,4R)-2, $[\alpha]_D^{25}$ +8.8 (c 0.2, $CHCl_3$).

(3S,4S)-4-Methyl-5-hexen-3-yl mesylate ((3S,4S)-3). To (3S,4S)-2 (360 mg, 3.30 mmol) in 4 mL pyridine at 0 °C was added mesyl chloride (1.12 mL, 9.9 mmol). After stirring 1 h at 0 °C and 4 h at 25 °C, ether (100 mL) was added and the organic layer was washed with water (4 x 30 mL) and then saturated NaCl (20 mL), dried ($MgSO_4$), and the solvent carefully distilled off, leaving (3S,4S)-3 (587 mg, 93%), $[\alpha]_D^{25}$ +12.0 (c 0.13, $CHCl_3$), ^{1}H NMR δ1.00 (t, J = 7.4 Hz, 1-Me), 1.08 (d, J = 6.9 Hz, 4-Me), 1.6-1.9 (m, 2-CH_2), 2.60 (br sextet, J = 6.9 Hz, 4-CH), 3.02 (s, SMe), 4.58 (q, J = 5.7 Hz, 3-CH), 5.12 (d, J = 10.6 Hz) and 5.14 (d, J = 17.9 Hz, 6-CH_2), 5.79 (ddd, J = 17.9, 10.6, 7.3 Hz, 5-CH).

(3R,4S)-4-Methyl-5-hexen-3-yl mesylate ((3R,4S)-3). (3R,4S)-3 had $[\alpha]_D^{25}$ +22.5 (c 0.45, $CHCl_3$) and ^{1}H NMR δ0.99 (t, J = 7.4 Hz, 1-Me), 1.10 (d, J = 6.9 Hz, 4-Me), 1.21 (pentet, J = 7.4 Hz, 2-CH_2), 2.60 (br sextet, J = 6.9 Hz, 4-CH), 3.02 (s, SMe), 4.57 (q, J = 6.2 Hz, 3-CH), 5.12 (d, J = 10.6 Hz) and 5.14 (d, J = 17.7 Hz, 6-CH_2), 5.79 (ddd, J = 17.7, 12.4, 7.9 Hz, 5-CH).

(3R,4S)-4-Methyl-5-hexen-3-yl azide ((3R,4S)-4). To a stirred solution of (3S,4S)-3 (587 mg, 3.3 mmol) in DMF (20 mL) at room temperature was added sodium azide (680 mg, 10 mmol). After stirring for 72 h, ether (50 mL) was added. The ether layer was washed with water (4 x 25 mL), dried ($MgSO_4$), and the solvent carefully distilled off to give (3R,4S)-4 (445 mg, 97%), $[\alpha]_D^{25}$ -16.1 (c 0.05, $CHCl_3$), ^{1}H NMR δ1.00 (t, J = 7.4 Hz, 1-Me), 1.07 (d, J = 6.8 Hz, 4-Me), 1.4-1.7 (m, 2-CH_2), 2.39 (br sextet, J = 7.0 Hz, 4-CH), 3.13 (dt, 8.3, 4.2 Hz, 3-CH), 5.05 (m, 6-CH_2), 5.75 (ddd, J = 17.7, 9.8, 7.2 Hz, 5-CH).

(3S,4S)-4-Methyl-5-hexen-3-yl azide ((3S,4S)-4). (3S,4S)-4 had $[\alpha]_D^{25}$ 18.3 (c 0.12, $CHCl_3$), ^{1}H NMR δ1.00 (t, J = 7.4 Hz, 1-Me), 1.07 (d, J = 6.8 Hz, 4-Me), 1.4-1.7 (m, 2-CH_2), 2.33 (br sextet, J = 6.9 Hz, 4-CH), 3.10 (m, 3-CH), 5.06 (d, J = 10.2 Hz) and 5.08 (d, J = 17.2 Hz, 6-CH_2), 5.79 (ddd, J = 17.2, 10.2, 7.2 Hz, 5-CH).

(2R,3R)-3-Azido-2-methylpentanoic acid ((2R,3R)-5). To a stirred solution of (3R,4S)-4 (240 mg, 1.53 mmol) in CCl_4 (3 mL), MeCN (3 mL), and water (4.5 mL) at room temperature under argon was added sodium bicarbonate (835 mg, 9.95 mmol), and $NaIO_4$ (1.8 g, 8.42 mmol) was added in small portions over 0.5 h. $RuCl_3$ (53 mg, 0.26 mmol) was added and stirring was continued for 48 h. The mixture was washed with ether (2 x 30 mL) and the aqueous layer was carefully acidified with 10% HCl and extracted with ether (2 x 50 mL). The combined ether solution was dried ($MgSO_4$) and the solvent carefully distilled off to give (2R,3R)-5 (164 mg, 68%), $[\alpha]_D^{25}$ -19.5 (c 0.2, $CHCl_3$), ^{1}H NMR δ1.05 (t, J = 7.3 Hz, 5-Me), 1.23 (d, J = 7.1 Hz, 2-Me), 1.57 and 1.72 (m, CH_2), 2.64 (pentet, J = 7.3 Hz, 2-CH), 3.53 (dt, J = 8.3, 3.6 Hz, 3-CH).

(2R,3S)-3-Azido-2-methylpentanoic acid ((2R,3S)-5). (2R,3S)-5 had $[\alpha]_D^{25}$ +16.4 (c 0.22, $CHCl_3$) and ^{1}H NMR δ1.05 (t, J = 7.4 Hz, 5-Me), 1.25 (d, J = 7.0 Hz, 2-Me), 1.64 (pentet, J = 6.9 Hz, CH_2), 2.61 (pentet, J = 6.9 Hz, 2-CH), 3.65 (q, J = 7.1 Hz, 3-CH).

(2R,3R)-3-Amino-2-methylpentanoic acid ((2R,3R)-1). (2R,3R)-5 (100 mg, 0.64 mmol) in EtOAc (25 mL) and 10% Pd/C (20 mg) was stirred 16 h under H_2 (1 atm). The solvent was evaporated and EtOH (15 mL) and water (50 mL) were added. After heating the mixture to 60 °C and filtering, the solution was evaporated and the residual solid triturated with EtOAc (3 x 20 mL) to remove a small amount of cis-pinonic acid from the oxidation of α-pinene. Crystallization from water gave (2R,3R)-1 (51 mg, 60%), ^{1}H NMR (D_2O) δ0.98 (t, J = 7.4 Hz, 5-Me), 1.21 (d, J = 7.3 Hz, 2-Me), 1.69 (m, CH_2), 2.58 (pentet, J = 7.0 Hz, 2-CH), 3.24 (m, 3-CH). The hydrochloride (2R,3R)-1·HCl, crystallized from water, had mp 246-248 °C dec, $[\alpha]_D^{25}$ -6.7 , $[\alpha]_{400}^{max}$ -257 (c 0.12, H_2O), ^{1}H NMR (D_2O + HCl) δ0.98 (t, J = 7.0 Hz, 5-Me), 1.27 (d, J = 6.4 Hz, 2-Me), 1.76 (pentet, J = 7.0 Hz, CH_2), 3.19 (pentet, J = 6.9 Hz, 2-CH), 3.46 (q, J = 6.3 Hz, 3-CH). Anal. Calcd for $C_6H_{14}NO_2Cl$: C, 42.99; H, 8.42; N, 8.36. Found: C, 43.34; H, 8.36; N, 8.20.

(2R,3S)-3-Amino-2-methylpentanoic acid ((2R,3S)-1). (2R,3S)-1, obtained similarly in 62% yield, had ^{1}H NMR (D_2O) δ0.98 (t, J = 7.4 Hz, 5-Me), 1.16 (d, J = 7.2 Hz, 2-Me), 1.65 (m, CH_2), 2.57 (pentet, J = 6.9 Hz, 2-CH), 3.33 (q, J = 6.3 Hz, 3-CH). The hydrochloride (2R,3S)-1·HCl had mp 274-278 °C dec, $[\alpha]_D^{25}$ -5.5 , $[\alpha]_{250}^{max}$ -140 (c = 0.06, H_2O), and ^{1}H NMR (D_2O + HCl) δ1.00 (t, J = 7.4 Hz, 5-Me), 1.25 (d, J = 7.4 Hz, 2-Me), 1.60-1.85 (m, CH_2), 2.93 (m, 2-CH), 3.52 (m, 3-CH). Anal. Calcd for $C_6H_{14}NO_2Cl$: C, 42.99; H, 8.42; N, 8.36. Found: C, 43.28; H, 8.40; N, 8.43.

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