Pergamon

Tetrahedron Letters 42 (2001) 183–185

TETRAHEDRON LETTERS

An efficient asymmetric synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-β-hydroxyornithine

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Received 22 September 2000; accepted 2 November 2000

Abstract—Asymmetric syntheses of (2*S*,3*S*)- and (2*R*,3*R*)-β-hydroxyornithine have been achieved in four steps and 46% overall yield. The key step in this synthesis involved an aldol reaction between a chiral glycine boron enolate and (3-oxo-propyl)-carbamic acid benzyl ester. © 2000 Elsevier Science Ltd. All rights reserved.

β-Hydroxyornithine in its various stereoisomeric forms **1a**–**d** (Fig. 1) has been previously investigated as a potential biosynthetic precursor to both the β-lactamase inhibitor clavulanic acid (**2**) and the antibiotic and anticancer agent acivicin (**3**). Clavulanic acid has been shown to be derived from (2*S*,3*R*)-proclavaminic acid **4**, a molecule that is structurally similar to β-hydroxyornithine.[1] In addition, both (2*S*,3*R*)- and (2*S*,3*S*)-β-hydroxyornithine have been shown by Gould et al. not to be incorporated into acivicin.[2] Recently, it has been suggested that a new antibiotic xanthobaccin A could also be derived from this unusual amino acid.[3]

Along with these biosynthetic investigations, efforts have been made to develop efficient syntheses of the *erythro*- and *threo*-forms of β-hydroxyornithine. Gould et al.[4] and Townsend et al.[5] have accessed both diastereomers of 2*S*-β-hydroxyornithine via the dipolar cycloaddition of vinyl glycine derivatives with a suitable nitrone. Misiti and co-workers developed a synthesis of (2*S*,3*R*)-β-hydroxyornithine, starting from D-serine.[6] More recently, Gurjar and co-workers synthesized the same enantiomer as that reported by Misiti by opening an enantiomerically pure epoxy alcohol with benzyl isocyanate.[7] Baldwin, Baggaley, and Wakamiya have used aldol chemistry to synthesize protected forms or derivatives of β-hydroxyornithine.[1,8]

Given the important roles that various isotopomers of β-hydroxyornithine have played in biosynthetic studies, an efficient asymmetric synthesis of both (2*S*,3*S*)- and (2*R*,3*R*)-β-hydroxyornithine that is compatible with various simple strategies to incorporate both stable- and radioisotopes was deemed justified. Herein, we

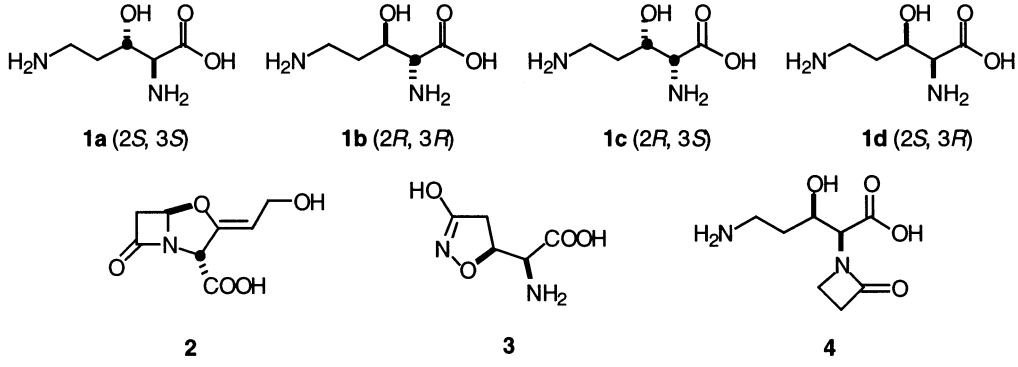

Figure 1.

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PII: S0040-4039(00)01945-6

report an efficient and stereoselective synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-β-hydroxyornithine. In order to arrive at the desired hydroxy amino acid, an aldol reaction between the benzyloxycarbonyl protected 3-amino-propanal **6** and the commercially available chiral oxazinone **7a** was investigated (Scheme 1).[9] Upon treatment of 3-amino-propanol with dibenzyl dicarbonate in refluxing 10% triethylamine in methanol, a quantitative yield of the desired benzyloxycarbamate **5** was achieved. Treatment of **5** under Dess–Martin periodinane conditions resulted in a 98% yield of the requisite (3-oxo-propyl)-carbamic acid benzyl ester **6**. Lactone **7a** was then treated with di-*n*-butyl boron triflate to yield the resulting boron enolate. Addition of aldehyde **6** to this enolate provided the expected aldol product **8a** in 69% yield with a diastereoselectivity of 8:1 (^{1}H NMR). The undesired diastereomer was easily removed by recrystallization of **8a** from ethyl acetate and hexanes. Hydrogenolysis of the benzyloxycarbonyl groups as well as the chiral auxiliary was achieved by treatment of **8a** with palladium chloride and hydrogen. The dihydrochloride salt of the amino acid, obtained from this protocol, was neutralized with ammonium hydroxide (pH 6.5); recrystallization from water/ethanol, afforded (2*S*,3*S*)-β-hydroxyornithine **1a** in 68% yield and >99.5:0.5 er as determined by chiral HPLC analysis.

Using the commercially available antipode of the oxazinone (**7b**)[10] the enantiomeric (2*R*,3*R*)-β-hydroxyornithine **1b** was prepared in a similar manner. Full experimental details are provided.

It has been demonstrated that both (2*S*,3*S*)- and (2*R*,3*R*)-β-hydroxyornithine can be prepared from commercially available starting materials in an efficient and stereocontrolled manner. The synthetic approach described herein, maintaining a 46% overall yield, compares favorably with other published syntheses that contain longer sequences, lower overall yields, and lower stereoselectivity.

Experimental

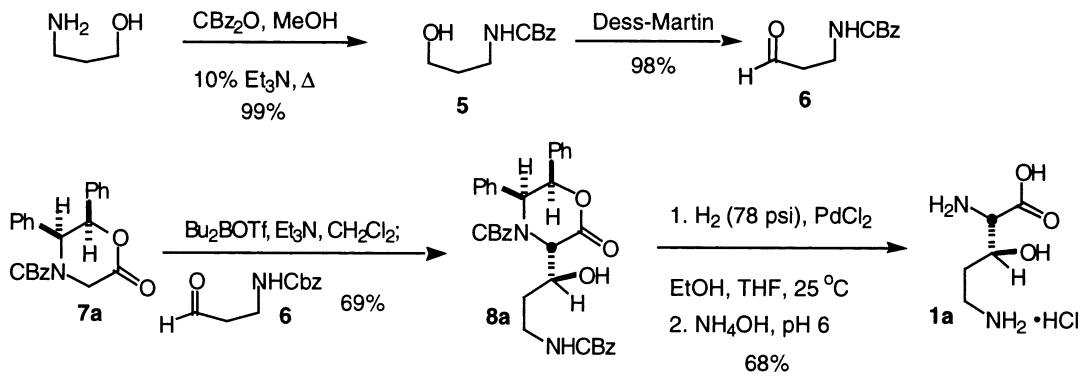
Compound **5**: To a 10% solution of triethylamine in methanol (2 mL) was added 3-aminopropanol (150 mg, 2.00 mmol, 1 equiv.) and dibenzyl dicarbonate (802 mg, 2.80 mmol, 1.4 equiv.). The resulting solution was refluxed under argon for 1 h, at which time the solvent was removed in vacuo resulting in a clear oil. Silica gel chromatography of the crude oil (eluted with 75:20:5 CH_2Cl_2:EtOAc:MeOH) provided 427 mg (99%) of **5** as a white solid. Mp 51–52°C (recryst. CH_2Cl_2:EtOAc).

^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.71 (2H, m); 2.47 (1H, bs); 3.36 (2H, bm); 3.69 (2H, t); 5.09 (1H, bs); 5.12 (2H, s); 7.32–7.38 (5H, m). ^{13}C NMR (75 MHz) ($CDCl_3$) δ 32.6, 38.0, 59.7, 66.9, 128.1, 128.2, 128.6, 136.5, 157.4. IR (NaCl, Neat) 3326, 3030, 2955, 2931, 2873, 1684, 1651, 1586, 1535, 1499, 1489, 1454, 1374, 1327, 1298, 1266, 1216, 1144, 1116, 1086, 1066, 1023, 984, 966 cm^{-1}. HRMS (FAB) calcd for $C_{11}H_{15}NO_3$ (MH^+) 210.1130; found 210.1125.

Compound **6**: To a solution of **5** (427 mg, 2.04 mmol, 1 equiv.) in non-distilled methylene chloride (17 mL) was added the Dess–Martin periodinane (1.47 g, 3.47 mmol, 1.7 equiv.). The resulting heterogeneous mixture was stirred overnight at room temp. Upon taking up the reaction mixture in diethyl ether (70 mL) and satd. aq. $NaHCO_3$ (70 mL), sodium thiosulfate (6.03 g, 24.3 mmol, 11.9 equiv.) was added, and the biphasic solution was stirred for 30 min. After removing the organic layer via separatory funnel, the aqueous layer was extracted twice more with ether. The organic layers were combined and dried over anhydrous $MgSO_4$. Filtration followed by removal of solvent under reduced pressure provided a crude white solid that was purified by silica gel chromatography (eluted with 1:1 EtOAc:hexanes) to provide 416 mg (98%) of **6** as a white solid. Mp 53–54°C (recryst. EtOAc/hexanes).

^{1}H NMR (300 MHz) ($CDCl_3$) δ 2.75 (2H, t); 3.50 (2H, q); 5.09 (2H, s); 5.18 (1H, bs); 7.32–7.37 (5H, m); 9.81 (1H, s). ^{13}C NMR (75 MHz) ($CDCl_3$) δ 34.7, 44.3, 66.9, 128.2, 128.3, 128.6, 136.5, 156.4, 201.2. IR (NaCl, Neat) 3449, 3054, 2986, 2305, 2254, 1720, 1512, 1422, 1265, 1144, 1094, 1027, 909 cm^{-1}. HRMS (FAB) calcd for $C_{11}H_{13}NO_3$ (MH^+) 208.0974; found 208.0975.

Compound **8a**: Under argon atmosphere, compound **7a** (624 mg, 1.61 mmol, 1 equiv.) was dissolved in dry methylene chloride (19 mL). The resulting solution is then cooled to −5°C (ice/acetone bath). Di-*n*-butyl-



Scheme 1.

boron triflate (1 M in CH_2Cl_2) (3.22 mL, 3.22 mmol, 2 equiv.) was added via syringe followed by addition of triethylamine (673 μL, 4.83 mmol, 3 equiv.). The mixture was stirred 15 min at −5°C then cooled to −78°C. In a separate flask, compound **6** (400 mg, 1.93 mmol, 1.2 equiv.) was dissolved in methylene chloride (3.5 mL) and the resulting aldehyde solution was added via canula to the boron enolate, and the reaction was stirred one hour at −78°C. The reaction was quenched by the addition of 0.025 M pH 7 potassium phosphate buffer at −78°C, and the mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted twice more with methylene chloride. The organic layers were combined and dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure produced an orange oil that was purified by silica gel chromatography (eluted with 30% EtOAc in hexanes). This initial separation resulted in co-elution of both the aldehyde and aldol product. A second silica gel chromatographic separation (eluted with 3:1:1 CH_2Cl_2:EtOAc:hexanes) resulted in the isolation of 657 mg (69%) of **8a** as an 8:1 mixture of diastereomers (^{1}H NMR). The minor diastereomer was removed by recrystallization from EtOAc/hexanes. Mp 175°C (recryst. EtOAc/hexanes).

^{1}H NMR (300 MHz) (DMSO-d_6, 393 K) δ DMSO: 1.84–2.06 (2H, m); 3.30 (2H, m); 4.29 (1H, m); 4.87 (1H, d, $J = 1.8$ Hz); 5.02 (1H, 1/2 ABq, $J = 12.9$ Hz); 5.07 (1H, 1/2 ABq, $J = 12.9$ Hz); 5.12 (2H, s); 5.30 (1H, d, $J = 3.3$ Hz); 5.62 (1H, bs); 6.55 (1H, d, $J = 3.3$ Hz); 6.64–7.41 (21H, m). IR (NaCl, Neat) 3365, 3032, 2951, 1750, 1734, 1700, 1684, 1653, 1540, 1404, 1274, 1120, 967 cm^{-1}. Anal. calcd for $C_{35}H_{34}N_2O_7$: C, 70.69; H, 5.76; N, 4.71. Found C, 70.50; H, 6.02; N, 4.89. Compound **8a**. $[\alpha]_D^{25} = -5.7$ ($c = 1.5$, CH_2Cl_2). Compound **8b**. $[\alpha]_D^{25} = +5.7$ ($c = 1.5$, CH_2Cl_2).

Compound 1a (mono-HCl salt): A pressure tube containing **8a** (100 mg, 0.17 mmol, 1 equiv.) in dry THF (4 mL) and absolute ethanol (2 mL) was purged with argon for 15 min. $PdCl_2$ (60 mg, 0.34 mmol, 2 equiv.) was added to this solution and the tube pressurized to 78 psi with hydrogen gas. The reaction was stirred at room temperature for 4 days. The catalyst was removed by filtration through Celite. The Celite pad was washed several times with a 2:1 THF:EtOH solution. Into a separate flask, the Celite pad was washed with five volumes of deionized water. The water volume was reduced by lyophilization and brought to pH 6.5 with NH_4OH. Addition of EtOH resulted in a white precipitate that was collected by filtration and dried to yield 21 mg (68%) of **1a** as the mono-HCl salt.

^{1}H NMR (300 MHz) (D_2O) δ 1.82–2.04 (2H, m); 3.18 (2H, sym m); 3.89 (1H, d, $J = 3.7$ Hz); 4.26 (1H, ddd, $J = 3.3$, 3.3, 10.6 Hz).^{13}C NMR (100 MHz) (D_2O) δ 29.0, 37.7, 59.5, 68.0, 171.6. IR (NaCl, 1% KBr) 3074, 1612, 1576, 1529, 1508, 1431, 1358, 1325, 1180, 1140, 1065, 1032 cm^{-1}. Mp 232°C dec (lit.[5] mp 232°C dec). Compound **1a**. $[\alpha]_D^{25} = +24.1$ ($c = 0.56$, 6N HCl) [lit.[5] $[\alpha]_D = +18.0$ ($c = 2.2$, 6N HCl)]. Compound **1b**. $[\alpha]_D^{25} = -20.2$ ($c = 0.47$, 6N HCl). The enantiomeric purities of **1a** and **1b** were determined to be >99.5:0.5 er by chiral HPLC analysis (Daicel Chiral Pak WH, column temperature 50°C, 0.25 mM $CuSO_4$ mobile phase, Waters 600 HPLC, dual wavelength UV detection at 210 and 254 nm).

Acknowledgements

This work was supported by the National Science Foundation (Grant CHE 9731947).

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10. Lactones **7** are commercially available from Aldrich Chemical Co.; **7a**: catalog #33-185-6; **7b** catalog #33,187-2.