Chemoenzymatic Synthesis of D-*N*-Boc-3,5-dihydroxy-4-methoxyphenylglycine

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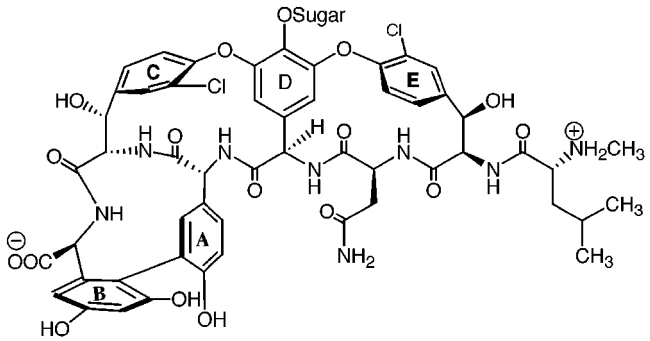
Received February 9, 1998

Vancomycin (**1**, Figure 1) and related glycopeptide antibiotics, by virtue of their important antibacterial activities, have spurred multidisciplinary interest over the last four decades.[1] Fully characterized in 1983,[2] the architectural complexity of vancomycin has captured the imagination of synthetic chemists, and research in this field has resulted in numerous new synthetic methodologies.[3] The intramolecular S_NAr-based cycloetherification reaction has been developed during the last several years as a powerful synthetic methodology for the construction of structurally diverse macrocycles with endo aryl−aryl[4−6] and aryl−alkyl ether[7] linkages. To apply this reaction in the synthesis of vancomycin, an easy access to D-*N*-Boc-3,5-dihydroxy-4-methoxyphenylglycine (**2**), the central unit of its structure, was a prerequisite. Indeed, several asymmetric syntheses of this moiety have been reported. Thus, Boger et al.[8] have devised a synthesis of **2** in which Sharpless asymmetric dihydroxylation[9] served to introduce the required stereochemistry. Pearson[10] and our group[11] have independently developed a synthetic scheme wherein Evans's electrophilic azidation methodology[12] was implemented as a key step for introducing both the chirality and the amino function. In an earlier effort, we have accomplished a concise synthesis of **2**[13] by way of a diastereoselective Strecker reaction using (*S*)-phenylglycinol as chiral auxiliary.[14] Described herein is an efficient new chemoenzymatic synthesis of this nonproteinogenic amino acid (**2**).



vancomycin **1**

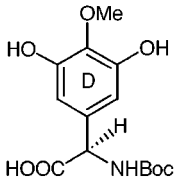


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Figure 1.

The Strecker reaction was used for the synthesis of racemic amino acid derivatives **6a** and **6b** (Scheme 1). Methyl 3,5-bis(isopropyloxy)-4-methoxybenzoate (**3a**), readily available in large quantities from methyl gallate,[15] was converted into the corresponding aldehyde (**4a**) by a standard reduction−oxidation sequence. Treatment of this aldehyde with TMSCN in MeOH saturated with NH_3[16] gave the α-amino nitrile (**5a**), which was then transformed into compound **6a** by way of methanolysis and trifluoroacetylation. Compound **6b** (R = Me) was synthesized following the same synthetic sequence starting from ester **3b**. Chemoselective removal of isopropyl groups from **6a** (BCl_3, CH_2Cl_2) afforded compound **7** in 98% yield.[17,18]

While important progress has been made in the enzymatic synthesis of chiral amino acid derivatives in general, studies on the resolution of arylglycine are relatively rare, and the conditions developed have been often less than satisfactory and limited in scope.[19] One exception is the highly efficient dynamic resolution of hydantoins by D-specific hydantoinases. However, the low availability, high cost, and instability at elevated temperature of hydantoinases compared to other hydrolases have significantly limited their potential applications in organic synthesis.[20] In preliminary experiments, we first examined the protease (from *Bacillus licheniformis*, P5459 from Sigma)-mediated ester hydrolysis[21,22] of **6b** (R = Me) in phosphate buffer and with various organic cosolvents such as CH_2Cl_2, 1,4-dioxane, MeCN,

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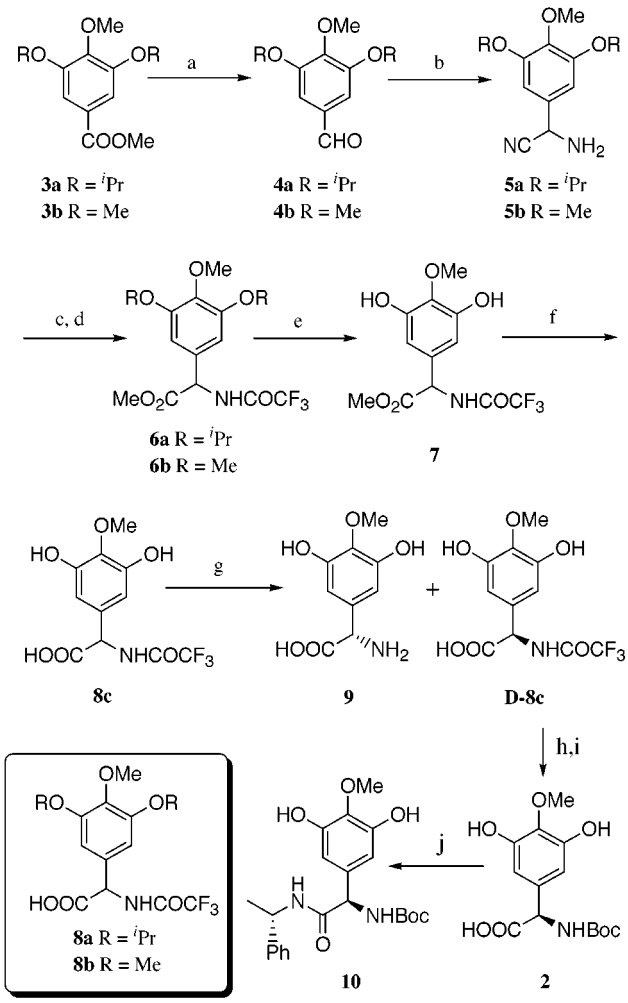
S0022-3263(98)00233-3 CCC: $15.00
Published on Web 07/17/1998

and DMF. Among these, only DMF was found to be suitable, leading to the acid **8b**, with moderate enantioselectivity. However, under identical conditions, compound **6a** (R = *i*-Pr) was resistant to hydrolysis, while compound **7** was transformed into the corresponding acid **8c** in high chemical yield (>95%, 6 h) without enantioselectivity. These results indicated that the phenoxy protecting groups can dramatically influence both the reactivity and the enantioselectivity of the enzymatic process.[23] Although no chiral discrimination was observed, this protease-catalyzed hydrolysis of **7** was found to be the method of choice to prepare acid **8c** (Scheme 1) as other chemical methods (e.g., HOAc/4N HCl = 1/1, 65 °C, 65%) gave only moderate yields due to the lability of the trifluoroacetyl group under both basic and acidic conditions.

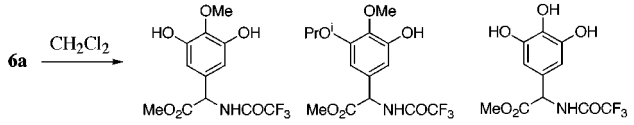
We then turned our attention to the aminoacylase-catalyzed[24] hydrolysis of *N*-(trifluoroacetyl)amino acids **8a**−**c**[25] based on Goldsworthy's work[26] concerning the enzymatic resolution of *N*-(chloroacetyl)-3,5-dihydroxyphenylglycine. The trifluoroacetyl group was chosen since it can be removed under much milder conditions[22] than the chloroacetyl function, whose chemical hydrolysis leads to the erosion of enantiopurity.[26] Experimentally, large differences in the hydrolysis rate of compounds **7** and **8a**−**c** were once again observed under a given set of conditions. Indeed, hydrolysis of **7** and **8a** employing the acylase AMANO 30000[27] under various conditions was not appreciable even after prolonged reaction time, while compounds **8b** and **8c** were smoothly hydrolyzed. For the present purpose, the hydrolysis of **8c** was studied in detail since this would directly furnish the amino acid required for further synthetic elaboration. Thus, hydrolysis of **8c** in phosphate buffer (pH 7) with acylase AMANO 30000 in the presence of a catalytic amount of $CoCl_2$ and NaN_3 at 25 °C[26] gave L-**9** and unhydrolyzed amide D-**8c** in 48% yield. Hydrolysis was initially followed by reversed-phase HPLC and was found to be highly stereoselective. In fact, under these conditions, the enantiomer selectivity is so high that no tedious HPLC monitoring was required, making the resolution step very practical. Removal of the trifluoroacetyl group from D-**8c** under mild acidic conditions followed by formation of *N*-(*tert*-butyloxy)carbamate gave then D-*N*-Boc-3,5-dihydroxy-4-methoxyphenylglycine (**2**) [$[\alpha]_D$ = −90° (MeOH, *c* 2.0); lit.[8] $[\alpha]_D$ = −89° (MeOH, *c* 0.8); lit[10] $[\alpha]_D$ = −86° (MeOH, *c* 0.5)]. Both D-**2** and its racemic form DL-**2** were transformed into the corresponding L-α-methylbenzylamide. Inspection of the ^{1}H NMR spectra (in DMSO) of **10** and its diastereoisomeric amide revealed that the de of **10**, hence the ee of D-**2**, was about 90%.

Scheme 1 [a]



[a] Key: (a) (i) LAH, THF; (ii) PDC, CH_2Cl_2, 85−90%; (b) NH_3, MeOH, TSCN; (c) MeOH, HCl; (d) TEA, trifluoroacetic anhydride, CH_2Cl_2, 88%; (e) BCl_3, CH_2Cl_2, 98% from **6a**; (f) protease from *Bacillus licheniformis* (Sigma), phosphate buffer, DMF, (g) AMANO 30000, phosphate buffer, NaN_3, $CoCl_2$, 42% for two enzymatic steps; (h) HOAc, 6 N HCl; (i) Boc_2O, dioxane, H_2O, Na_2CO_3, 83%; (j) L-α-methylbenzylamine, EDC, HOBt, CH_2Cl_2, 90%.

(18) A significant difference in reactivity between BCl_3 in CH_2Cl_2 and BCl_3 in hexane (1 M solution, both from Aldrich) was observed. While the former displayed excellent chemoselectivity leading to the formation of compound **7** in quantitative yield [1 equiv (mol ratio: BCl_3/**6a** = 2/1) of BCl_3, room temperature, 3 h], the latter afforded a mixture of **7**, **A**, and **B** depending upon the reaction temperature.



	Temp.	7	A	B
BCl_3 in CH_2Cl_2	rt	98%	0%	0%
BCl_3 in hexane	-78°C to 5°C	50%	50%	0%
BCl_3 in hexane	rt	50%	0%	50%

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(25) Compounds **8a** and **8b** were prepared in moderate yield by treatment of esters **6a** and **6b**, respectively, with acid (HOAc/4 N HCl = 1/1, 65 °C). Alternatively, full deprotection of **6a** and **6b** to the corresponding free amino acid (6 N HCl, reflux) followed by reprotection of amine as the trifluoroacetamide (ethyl trifluoroacetate, triethylamine, MeOH) gave **8a** and **8b** in similar yields (60%). See: Curphey, T. J. *J. Org. Chem.* **1979**, *44*, 2805−2807.

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A one-pot sequential treatment of amino ester **7** by protease (from *B. licheniformis*) followed by acylase was also briefly investigated. However, it seems that the catalytic property of acylase was poisoned by the presence of the protease as only optically inactive acid **8c** ($[\alpha]_D = 0$) was isolated with this two-enzyme, one-reactor procedure.

In summary, we have described an efficient synthesis of nonproteinogenic amino acid **2**, an important building block in the synthesis of vancomycin-type antibiotics. The chirality was introduced by AMANO acylase-catalyzed enantioselective hydrolysis, and the overall yield of **2** was 36% starting from aldehyde **4a**. It was observed in the course of these studies that the efficiency of both protease- and acylase-catalyzed hydrolysis reactions depends significantly on the protecting groups used for the two phenoxy functions on the aromatic ring. Besides the steric reason, the beneficial effect of the free hydroxy groups in compound **8c** may be attributed to their hydrogen bonding donor property as well as to the possible dipole−dipole interactions in the binding region of the enzyme.[23] To the best of our knowledge, the trifluoroacetyl group has been used for the first time as the acyl group in aminoacylase-catalyzed hydrolysis of amides, the main advantages being its easy preparation and mild chemical hydrolysis. The synthetic route described here is amenable to the synthesis of D-**2** on a multigram scale.

Experimental Section

General procedures and methods for characterization of new compounds have been described previously. Melting points are uncorrected.[28]

D,L-*N*-(Trifluoroacetyl)-3,5-bis(isopropyloxy)-4-methoxyphenylglycine Methyl Ester (6a). To a solution of 3,5-bis(isopropyloxy)-4-methoxybenzaldehyde (**4a**) (12.00 g, 47.62 mmol) in MeOH (100 mL) saturated with NH_3 was added TMSCN (71.43 mmol, 9.55 mL) dropwise at 0 °C. The resulting solution was then heated to 45 °C for 5 h and evaporated in vacuo to dryness. The crude amino nitrile **5a**, dissolved in dry MeOH (80 mL), was saturated with gaseous hydrogen chloride. After being stirred at room temperature for 12 h, thionyl chloride (4 mL) was added, and the solution was heated to 55 °C for 3 h in order to convert a small amount of free amino acid to the desired amino ester. The volatile was removed under reduced pressure to give the analytically pure hydrogen chloride salt of amino ester: ^{1}H NMR (CD_3OD) δ 1.31 (d, J = 6.1 Hz, 6H), 1.34 (d, J = 6.1 Hz, 6H), 3.76 (s, 3H), 3.80 (s, 3H), 4.59 (septet, J = 6.1 Hz, 2H), 5.10 (br s, 1H), 6.75 (s, 2H). To a solution of the hydrogen chloride salt of amino ester in CH_2Cl_2 (120 mL) were added triethylamine (13.24 mL, 95.24 mmol) and trifluoroacetic anhydride (13.45 mL, 95.24 mmol), successively. After being stirred at room temperature for 2 h, the reaction mixture was diluted with aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Purification by flash chromatography (SiO_2, eluent: CH_2Cl_2) gave **6a** as white crystals (17.06 g, 88% overall yield from aldehyde **4a**): mp 109−110 °C (CH_2Cl_2−pentane); IR ($CHCl_3$) ν 3412, 1735, 1600, 1450, 1285, 1175, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J = 6.1 Hz, 12 H), 3.78 (s, 3H), 3.81 (s, 3H), 4.51 (septet, J = 6.1 Hz, 2H), 5.41 (d, J = 7.1 Hz, 1H), 6.53 (s, 2H), 7.28 (d, J = 7.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 21.9, 52.5, 56.5, 59.5, 70.6, 108.5, 115.7 (q, J = 285.0 Hz), 129.6, 139.9, 151.2, 156.2 (q, J = 38.0 Hz), 169.6; MS (CI) m/z 408 [M + 1], 366, 324. Anal. Calcd for $C_{18}H_{24}F_3NO_6$: C, 53.07; H, 5.94; N, 3.44. Found: C, 53.05; H, 5.91; N, 3.80.

D,L-*N*-(Trifluoroacetyl)-3,5-dihydroxy-4-methoxyphenylglycine Methyl Ester (7). To a solution of compound **6a** (7.00 g, 17.20 mmol) in dry CH_2Cl_2 (60 mL) was added, at −78 °C, a solution of BCl_3 in CH_2Cl_2 (1 M, 36.12 mL, 36.12 mmol). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 3 h before being recooled to 0 °C and quenched by careful addition of dry MeOH. Removal of volatile at reduced pressure gave compound **7** (5.44 g, 98%): mp 148−150 °C ($CHCl_3$); IR ($CHCl_3$) ν 3600, 3400, 1735, 1600, 1525, 1170 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.71 (s, 3H), 3.78 (s, 3H), 5.37 (d, J = 7.0 Hz, 1H), 6.48 (s, 2H), 8.21 (br s, 2H), 8.95 (br d, 1H); ^{13}C NMR (DMSO-d_6) δ 52.6, 56.7, 59.8, 107.6, 115.9 (q, J = 286.5 Hz), 129.5, 135.9, 151.0, 156.5 (q, J = 37.5 Hz), 169.8; MS (CI) m/z 324 [M + 1]. Anal. Calcd for $C_{12}H_{12}F_3NO_6$: C, 44.59; H, 3.74; N, 4.33. Found: C, 44.46; H, 3.91; N, 4.23.

Protease (from *B. licheniformis*)-Catalyzed Hydrolysis of 7: d,L-*N*-(Trifluoroacetyl)-3,5-dihydroxy-4-methoxyphenylglycine (8c). To a solution of compound **7** (5.00 g, 15.48 mmol) in DMF (20 mL) and phosphate buffer pH = 7 (500 mL) was added protease (from *B. licheniformis*, Sigma) (15 mL). After being stirred at 37 °C overnight, the reaction mixture was acidified to pH = 3 and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to dryness, which was used directly for the next enzymatic reaction.

Acylase-Catalyzed Enantioselective Hydrolysis of Acid DL-8c. To a solution of crude acid dl-**8c**, so obtained from the above protease-mediated hydrolysis of **7**, in phosphate buffer pH = 7 (400 mL) were added $CoCl_2$ (7 mL, 2.5 mM in water), NaN_3 (1 mL, 154 mM), and acylase AMANO 30000 (1.4 g), successively. After being stirred at 25 °C overnight (no monitoring was required as the hydrolysis is highly enantioselective), the reaction was acidified by addition of aqueous citric acid solution, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Purification by flash chromatography (SiO_2, eluent heptane/EtOAc/AcOH = 2/1/0.01) gave D-**8c** as a colorless oil (2.01 g, 42% based on compound **7**): $[\alpha]_D = -110°$ (MeOH, c 0.4); ^{1}H NMR (DMSO-d_6) δ 3.44 (s, 3H), 4.91 (d, J = 6.1 Hz, 1H), 6.16 (s, 2H), 9.02 (br s, 2H), 9.80 (d, J = 6.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 56.7, 59.9, 107.6, 107.8, 116.0 (q, J = 286.0 Hz), 130.4, 135.8, 150.9 (2C), 156.4 (q, J = 37.5 Hz), 174.5; MS (CI) m/z 310 [M + 1], 266. Anal. Calcd for $C_{11}H_{10}F_3NO_6$: C, 42.73; H, 3.26. Found: C, 42.89; H, 3.33.

D-*N*-Boc-3,5-dihydroxy-4-methoxyphenylglycine (2). A solution of D-**8c** (1.00 g, 3.24 mmol) in HOAc (10 mL) and 6 N HCl (10 mL) was heated to 65 °C for 6 h. Evaporation of the volatile at reduced pressure gave the hydrogen chloride salt of crude amino acid that was redissolved in dioxane (40 mL), and a solution of Na_2CO_3 (687.0 mg, 6.48 mmol) in H_2O (20 mL) and Boc_2O (1.41 g, 6.48 mmol) were added successively. After being stirred at room temperature for 3 h, the reaction mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Purification by flash chromatography (SiO_2, eluent heptane/EtOAc/HOAc = 2/1/0.01) gave D-**2** (843 mg, 83%): $[\alpha]_D = -90°$ (MeOH, c 0.2) [lit.[8] $[\alpha]_D = -89°$ (MeOH, c 0.8); lit.[10] $[\alpha]_D = -86°$ (MeOH, c 0.5)]; mp 85−87° (ether); IR ($CHCl_3$) ν 3530, 3440, 3240, 1724, 1600, 1500, 1370, 1164 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 1.39 (s, 9H), 3.77 (s, 3H), 5.08 (d, J = 7.7 Hz, 1H), 6.38 (br d, J = 7.7 Hz, 1H), 6.51 (s, 2H); ^{13}C NMR (CD_3OD) δ 28.4, 28.6, 59.0, 60.5, 80.7, 107.4, 108.0, 133.9, 136.5, 151.6 (2C), 157.2, 174.2; MS (FAB NaCl) m/z 336 [M + 23], 258. Anal. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.38; H, 6.14; N, 4.43.

[(1-Phenylethylcarbamoyl)(3,5-dihydroxy-4-methoxyphenyl)methyl]carbamic Acid *tert*-Butyl Ester (10). To a solution of D-**2** (31.0 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) were added, at 0 °C, L-α-methylbenzylamine (20 μL, 0.15 mmol), EDC (21 mg, 0.11 mmol), and HOBt (15 mg, 0.11 mmol) successively. After being stirred at 0 °C for 4 h, the reaction mixture was diluted with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Purification by flash chromatography (SiO_2, eluent heptane/EtOAc = 1/1) gave amide **10** (37.5 mg, 90%): de 90%; $[\alpha]_D = -55°$ (MeOH, c 0.3); mp 80−85° (ether); IR ($CHCl_3$) ν 3550, 3430, 1710, 1680, 1500, 1360, 1270 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.29 (d, J = 7.0 Hz, 3H), 1.35 (s, 9H), 3.63 (s, 3H), 4.84 (q, J = 7.0 Hz, 1H), 4.99 (d, J = 8.6 Hz, 1H), 6.34 (s, 2H), 6.89 (d, J = 8.6 Hz, 1H), 7.28

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(m, 5H), 8.50 (d, J = 7.7 Hz, 1H), 9.00 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 22.6, 28.4, 48.4, 56.6, 59.9, 77.8, 106.5, 128.3, 126.9, 128.5, 134.4, 136.0, 144.5, 150.7, 156.0, 169.5; MS (CI) m/z 417 [M + 1]. Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.44; H, 6.78; N, 6.72. Found: C, 63.06; H, 7.10; N, 6.46.

Acknowledgment. We are grateful to Dr. J. Ouazzani of this institute for helpful discussions and a generous gift of AMANO 30000. **Note Added in Proof**. Very recently, an elegant synthesis of D-*N*-Boc-3,5-dihydroxy-4-methoxyphenylglycine (**2**) was reported from Professor Davis's group; see: Davis, F. A.; Fanelli, D. L. *J. Org. Chem*. **1998**, *63*, 1981−1985.

JO980233X