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From (S)-α-Amino β-Hydroxyacids To (R)-α,β-Diamino-γ-Hydroxyacid N-Carboxyanhydrides via β-Lactams

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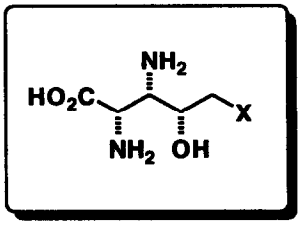
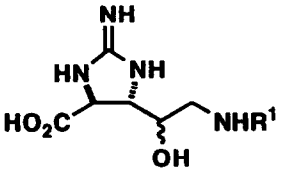
Abstract.: A new synthesis of α,β-diamino-γ-hydroxyacids through optically pure non-naturally available amino acid-derived N-carboxyanhydrides (NCAs) is described.

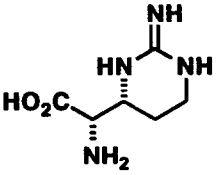
In the preceding paper we have described a new approach to α-amino-β-hydroxyacid N-carboxyanhydrides from β-lactam frameworks generated via cycloaddition reaction[1]. It seemed obvious to us that repetition of this process starting from α-amino-β-hydroxy acids, produced by this NCA methodology, should render substituted β-lactams with predictable stereochemistry as precursors of α,β-diamino-γ-hydroxyacid N-carboxyanhydrides. In particular, a new route to guanidino amino acid derivatives, as found in streptothricin and capreomycin type antibiotics, could be easily envisaged[2].



X: OH
X: NHR

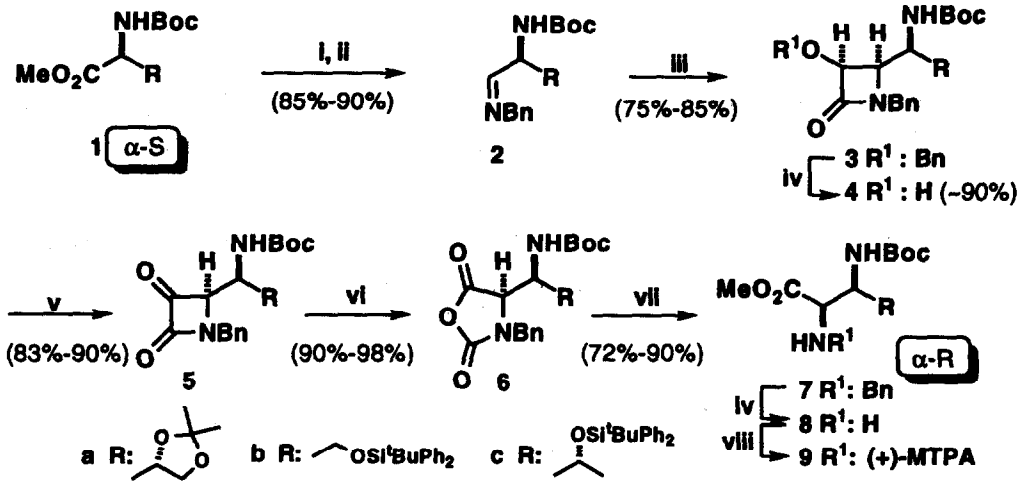


R^1: H Streptolidine Cγ*(R)
R^1: Me Cγ*(R or S)



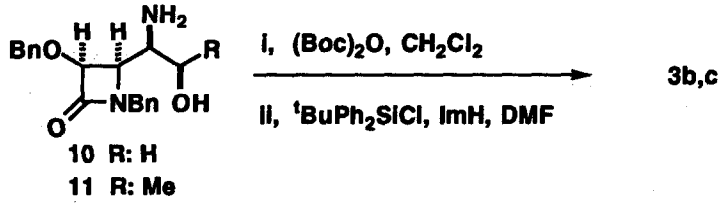
Capreomycidine

To explore the viability of the approach, the α-aminoester **1a**, obtained as previously described[1], was first transformed into the imine **2a**, via the corresponding N-Boc -α-aminoaldehyde, and this subjected to treatment with benzyloxyacetyl chloride and triethylamine in methylene chloride overnight under established conditions[3]. The resulting β-lactam **3a** was then converted in the usual way into the hydroxy derivative **4a** [m.p.: 203-205°C (MeOH), $[\alpha]_D^{25}$ = -44.0 (c = 1.03, CH_2Cl_2)] in 72% overall yield from **2a**. In a similar way, β-lactams **3b** [viscous oil, $[\alpha]_D^{25}$ = -19.20 (c = 1.16, CH_2Cl_2)] and **3c** [m.p.: 44-46°C (Hexane-AcOEt), $[\alpha]_D^{25}$ = -11.8 (c = 1.00, CH_2Cl_2)] obtained from the corresponding imines **2b** and **2c**, were converted into **4b** [73% yield, m.p.: 53-55°C (Hexane-AcOEt), $[\alpha]_D^{25}$ = -30.4 (c = 0.82, CH_2Cl_2)] and **4c** [80% overall yield, m.p.: 65-67°C (Hexane-AcOEt), $[\alpha]_D^{25}$ = -3.8 (c = 1.01, CH_2Cl_2)] respectively. To determine univocally the stereochemical course of these reactions, β-lactams **10** and **11**, whose absolute stereochemistries had previously been established[3], were transformed into **4b** and **4c** respectively and the absolute stereochemistry of **4a** was assigned by analogy.



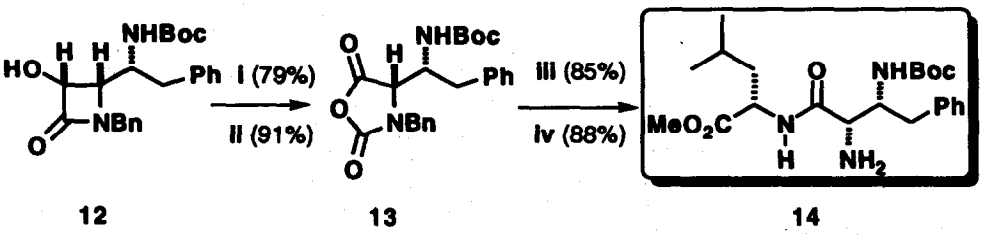
Scheme 1. Reagents and Conditions: i, DIBAL, toluene, -78°C ii, $PhCH_2NH_2$, CH_2Cl_2, $MgSO_4$, 0°C, 4h iii, $BnOCH_2COCl$, NEt_3, CH_2Cl_2, -78°C → r.t., 20-24h iv, HCO_2NH_4, Pd-C, MeOH, reflux. v, DMSO, P_2O_5, r.t., 24hr. vi, m-CPBA, CH_2Cl_2, -40°C, vii, MeOH, reflux. viii, (+)-MTPA-Cl, NEt_3, CH_2Cl_2.

Finally, each compound **4** was oxidized to the corresponding α-keto β-lactam **5** and the resulting crude compound subjected to Baeyer-Villiger rearrangement to furnish the expected NCAs **6a**, **6b** and **6c**. Although practically pure, NCAs could be obtained by trituration of the crude compounds with diethyl ether or mixtures of diethyl ether and hexane, this procedure resulted in a somewhat lower yield of the desired compounds. Therefore, at this stage, each crude NCA was submitted to methanolysis to give the corresponding methyl esters **7a**, **7b** and **7c** in 88%, 77% and 71% overall yields, respectively. Further exposure of these compounds to hydrogenolysis afforded the corresponding free α-amino esters **8** in 85%, 83% and 87% yields respectively, which were acylated using (+)-MTPA acid chloride in the presence of triethylamine[4]. Subsequent analysis of the resulting (+)-MTPA amide derivatives **9** provided the overall diastereomeric purity for β-lactam formation and derivatization sequences[5].



From these representative examples it was clear that a wide variety of differentially protected polyfunctional NCAs whose preparation by the standard Leuchs procedure would be troublesome, might be easily obtained via this approach. As it is evident, the method is also convenient for the synthesis of non-

functionalyzed α,β-diaminoacid-N-carboxyanhydrides by simply choosing the corresponding natural as well as non-natural R or S α-amino acid starting material. For instance, Scheme 2, (R)-phenylalanine methyl ester was converted in the usual way into the corresponding N-(Boc)-α-amino imine and this subjected to treatment with benzyloxyacetyl chloride and triethylamine[3], followed by removal of the benzyloxy group in the resulting cycloadduct.



12 13 14

Scheme 2. Reagents and Conditions: i, DMSO, P_2O_5, r.t., 24hr. ii, m-CPBA, CH_2Cl_2, -40°C. iii, (S)-leucine methyl ester, CH_2Cl_2, r.t. iv, HCO_2NH_4, Pd-C, MeOH, reflux.

The α-hydroxy β-lactam **12** [m.p: 248-249°C (THF-MeOH), $[\alpha]_D^{25}$ = +26.0 (c = 0.5, DMSO)] was then oxidized to the α-keto β-lactam and the crude compound treated with m-CPBA in methylene chloride to give the NCA **13** in 72% overall yield from **12**. Subsequent treatment of this NCA compound with (S)-leucine methyl ester led to the dipeptide (2S,3S)-**14**, the protected form of aminodeoxybestatin[6], an AP-M inhibitor equipotent to the known bestatin[7]. In addition, the ^{13}C-NMR and HPLC analysis of the dipeptide product did not reveal either diastereomeric cross-contaminants or detectable epimerization[8].Remarkably, the present method allows the synthesis of (R)-α-aminoacid-N-carboxyanhydrides from (S)-α-amino acids and *vice versa*, with complete predictable stereochemical control and optical purity. This aspect constitutes a further important, and essential feature of the approach as compared with the traditional Leuchs procedure.

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5.- Representative data: Compound 5b: Viscous oil; $[\alpha]^{25}_{D}$ = -48.3 (c=1.28,CH_2Cl_2); IR (liquid film) υ 3330 (NH),1823,1765,1710 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 90°C) δ 7.71-7.30(m, 15H, arom.); 6.57(s_{br}, 1H, OCONH); 5.02(d, 1H, J=15.3Hz, HCHN); 4.60(d, 1H, J=15.3Hz, HCHN); 4.42(d, 1H, J=4.9Hz, C_4H); 4.03(m, 1H, CHNHBoc); 3.65(m, 2H, CH_2OSi); 1.42(s, 9H, OC(CH_3)$_3$); 1.02(s, 9H, SiC(CH_3)$_3$). Compound 5c: M.p 56°C (hexane-ethyl acetate); $[\alpha]^{25}_{D}$= +1.29 (c=1.0, CH_2Cl_2); IR(CH_2Cl_2) υ 3410 (NH), 1818,1742,1728,1709 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 90°C) δ 7.65-7.23(m, 15H, arom.); 6.40(d_{br}, 1H, J=4.0Hz, OCONH); 5.00(d, 1H, J=15.5Hz, HCHN); 4.47(d, 1H, J=15.5Hz, HCHN); 4.41(d, 1H, J=6.4Hz, C_4H); 3.96(m, 1H, CHCH$_3$); 3.89(m, 1H, CHNHBoc); 1.38(s, 9H, OC(CH_3)$_3$); 0.95(s, 9H, SiC(CH_3)$_3$); 0.75(d, 3H, J=6.3Hz, CHCH_3). Anal. Calcd for $C_{34}H_{44}N_2O_5Si$: C, 69.60; H, 7.21; N, 4.77. Found: C,69.20; H,7.45; N,4.46. Compound 7a: Oil; ^{1}H-NMR ($CDCl_3$) δ : 5.26 (d, 1H, NH, J=9.49); 4.36-4.30 (m, 1H, OCHCH_2O); 4.12-4.01 (m, 1H, CHNHCOOC(CH_3)$_3$); 4.05 (dd, 1H, J=6.54, J=8.29, OCHCHHO); 3.74 (s, 3H, H_3OC); 3.78-3.69 (m, 1H, OCHCHHO); 2.20 (m, 2H, NH_2); 1.43 (s, 12H, CH_3, (CH_3)$_3$C); 1.34 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$) δ : 174.0, 155.8, 109.7, 79.7, 76.4, 66.5, 56.7, 52.7, 52.4, 28.2, 26.2, 25.1. Compound 7b: Viscous oil; $[\alpha]^{25}_{D}$ = -10.6 (c=1.11,CH_2Cl_2); IR (liquid film) υ 3320 (NH),1732,1714 (C=O) cm^{-1};^{1}H-NMR ($CDCl_3$) δ 7.68-7.24(m, 15H, arom.); 4.70(d_{br}, 1H, J=9.0Hz, OCONH); 4.20(br m, 1H, C_3H); 3.85(d, 1H, J=13.0Hz, HCHN); 3.73(s, 3H, CO_2CH_3); 3.67(m, 3H, CH_2OSi and C_2H); 3.60(d, 1H, J=13.0Hz, HCHN); 2.17(br s, 1H, NHCH_2); 1.38(s, 9H, OC(CH_3)$_3$); 1.04(s, 9H, SiC(CH_3)$_3$); ^{13}C-NMR ($CDCl_3$) δ 174.0, 155.5, 139.5, 135.5, 135.4, 133.0, 132.9, 129.7, 128.2, 128.2, 127.7, 127.0, 79.2, 63.0, 59.8, 53.8, 53.0, 52.2, 28.1, 26.7, 19.1 ppm; MS Calcd for $C_{33}H_{44}N_2O_5Si$ (M^+): 576, Found : 298 (MH^+ - CO_2^{t}Bu - $MeO_2CCHNHBn$), 178 ($MeO_2CCHNHBn$). Compound 7c: Viscous oil; $[\alpha]^{25}_{D}$ = +3.7 (c=0.73, CH_2Cl_2); IR (liquid film) υ 3410 (NH),1734,1710 (C=O) cm^{-1};^{1}H-NMR ($CDCl_3$) δ 7.80-7.31(m, 15H, arom.); 4.69(d_{br}, 1H, J=9.3Hz, OCONH); 4.00-3.96(m, 2H, C_3H and C_4H); 3.90(d, 1H, J=13.0Hz, HCHN); 3.76(s, 3H, CO_2CH_3); 3.61(d, 1H, J=13.0Hz, HCHN); 3.50(d, 1H, J=4.2Hz, C_2H); 2.09(br s, 1H, NHCH_2); 1.51(s, 9H, OC(CH_3)$_3$); 1.11(s, 9H, SiC(CH_3)$_3$); 1.09(d, 3H, J=6.0Hz, CHCH_3);^{13}C-NMR ($CDCl_3$) δ 173.8, 155.8, 139.4, 135.8, 134.2, 133.0, 129.7, 129.4, 128.3, 128.1, 127.5, 127.3, 127.0, 79.1, 69.2, 60.7, 58.0, 52.0, 28.2, 26.8, 20.6, 19.1 ppm; MS Calcd for $C_{34}H_{46}N_2O_5Si$ (M^+): 590, Found : 312 (MH^+ - CO_2^{t}Bu - $MeO_2CCHNHBn$), 178 ($MeO_2CCHNHBn$). Representative NMR data of Mosher derivatives: Compound 9a: ^{1}H-NMR ($CDCl_3$) δ : 7.59-7.39 (m, 5H, arom.); 4.95 (d, 1H, NHCOOC(CH_3)$_3$; 4.73 (dd, 1H, J=4.76, J=7.89, H_3OCOCH); 4.18-4.16 (m, 2H, CHNHCOOC(CH_3)$_3$, OCHCH_2O); 4.03 (dd, 1H, J=6.49, J=8.19, OCHCHHO); 3.80 (s, 3H, CH_3O); 3.69 (dd, 1H, J=6.41, J=8.29, OCHCHHO); 3.53 (d, 3H, J_{H-F} = 1.32); 1.42 (s, 9H, (CH_3)$_3$C); 1.38 (3H, s, CH_3); 1.24 (3H, s, CH_3). ^{19}F-NMR ($CDCl_3$) δ : 107.80. Compound 9b: ^{1}H-NMR ($CDCl_3$) δ 7.76(d_{br}, 1H, J=7.0Hz, NH); 7.67-7.31(m, 15H, arom.); 4.90(m_{br}, 2H, NHBoc and C_2H); 4.20(m, 1H, C_3H); 3.77(s, 3H, CO_2CH_3); 3.74-3.59(m, 2H, CH_2OSi); 3.53(d, 3H, J=1.5Hz, OCH_3); 1.43(s, 9H, OC(CH_3)$_3$); 1.10(s, 9H, SiC(CH_3)$_3$). ^{19}F-NMR ($CDCl_3$) δ 107.89. Compound 9c: ^{1}H-NMR ($CDCl_3$) δ 7.68(d_{br}, 1H, J=6.5Hz, NH); 7.61-7.24(m, 15H, arom.); 4.77(m_{br}, 2H, NHBoc and C_2H); 3.85(m, 2H, C_3H and C_4H); 3.60(s, 3H, CO_2CH_3); 3.45(d, 3H, J=1.2Hz, OCH_3); 1.32(s, 9H, OC(CH_3)$_3$); 1.03(d, 3H, J=5.0Hz, CHCH_3);1.01(s, 9H, SiC(CH_3)$_3$). ^{19}F-NMR ($CDCl_3$) δ 107.79. Compound 14: mp: 112-113°C (AcOEt); $[\alpha]^{25}_{D}$= + 11.0 (c=1.0, CH_2Cl_2).

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8.- Although the NCA method has been shown to be virtually recemization-free, *vide infra*, the NCA **13** was also coupled with racemic leucine methyl ester for comparative analyses. See, for example, Manning, J.M.; Moore, S. *J. Biol. Chem.*, **1968**, *243*, 5591.

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