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Synthesis of β-Alkylserine-N-Carboxyanhydrides Through β-Lactams via Cycloaddition Reaction of Alkoxyketenes to Chiral α-Alkoxyaldehyde-derived Imines.

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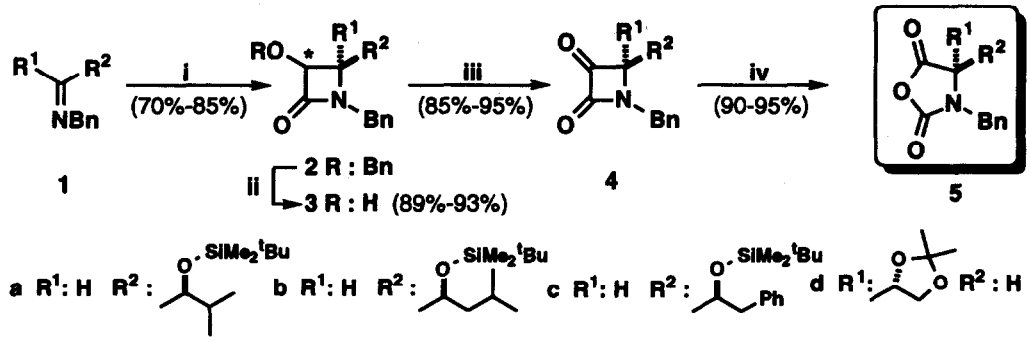
Abstract.: A new synthesis of α-amino-β-hydroxy acid-N-carboxyanhydrides from non-α-amino acid precursors is described.

α-Amino acid-N-carboxyanhydrides[1], NCAs, are useful as synthetic tools in the chemistry of α-amino acids because they offer both amino group protection and carboxylate activation simultaneously. As a result, since the first work of Leuchs[2] in the early 1900's numerous procedures have been reported to synthesize NCAs, all of them involving reaction between an α-amino acid and dehydrating agents, particularly phosgene and its synthetic equivalents[3]. Recently, we undertook a study on the synthesis of this particular class of mixed anhydrides and found that Baeyer-Villiger rearrangement of α-keto β-lactams constituted an efficient alternative to the usual Leuchs procedure[4]. In this paper we disclose our initial results on the application of this methodology to the synthesis of α-amino-β-hydroxy acid-N-α-carboxyanhydrides whose significance as building blocks of β-alkylserine derivatives could be easily anticipated. Although now there are a number of methods for the synthesis of such a class of α-amino acids[5], the key to our approach is the diastereoselective cycloaddition reaction of alkoxyketenes to chiral O-protected α-hydroxyaldehyde derived imines[6].

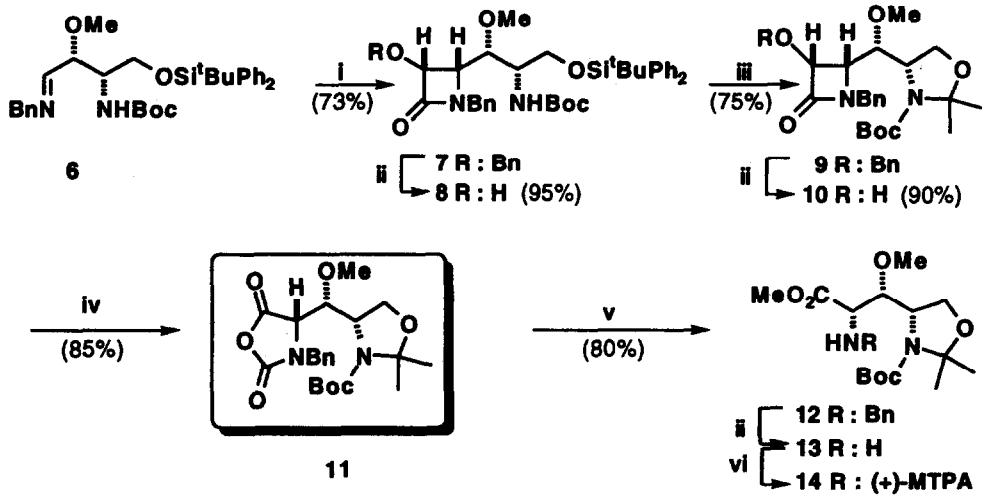
As shown in Scheme 1, some representative examples were selected to illustrate the approach. Thus, treatment of imines **1a, 1b** and **1c** with benzyloxyacetyl chloride and triethylamine in methylene chloride at -78°C to room temperature overnight, led to the formation of β-lactams **2a, 2b** and **2c** in excellent yields. In each case, a single diastereomer was detected by ^{1}H NMR analysis of the reaction crudes and the assignation of the depicted stereochemistry was effected by analogy with the observed stereochemical outcome in closely related reactions[6], and also taking into account the coupling constant between the C_3 and C_4 protons (J = 5Hz), indicating a *cis*- relationship. After removal of the benzyloxy group in each compound **2**, the resulting α-hydroxy β-lactam **3** was subjected to oxidation with P_2O_5 in DMSO as solvent[7] to give the azetidine-2,3-diones **4** generally as oils. Subsequent Baeyer-Villiger rearrangement of each α-keto β-lactam **4** furnished the expected NCAs **5a, 5b** and **5c** in almost quantitative yields[8]. In particular, the NCA **5a**, which is the activated form of the amino acid β-isopropyl serine (3-hydroxyleucine), illustrates the potential significance of the methodology presented for the synthesis of amino acid derivatives found in naturally occurring peptide antibiotics[9]. A further example which defines the scope of the present β-lactam-derived NCA methodology is exemplified by the formation of the NCA **5d** having opposite α-configuration to that of the above NCAs **5a-c**. Thus, the readily available Bose-Manhas's β-lactam **3d**[10], easily prepared from the (D)-glyceraldehyde acetonide imine **1d**, upon oxidation of the hydroxy group and further Baeyer-Villiger

rearrangement of the resulting α-keto β-lactam **4d** led to the NCA **5d** in 85% overall yield from **3d**. These examples demonstrate that protected α-amino-β-hydroxyacid-derived NCAs with desired L or D configurations can be obtained from non-α-amino acid precursors.



Scheme 1. Reagents and Conditions: i, $BnOCH_2COCl$, NEt_3, CH_2Cl_2, -78°C→r.t., 20h ii, Pd-C, HCO_2NH_4, MeOH, reflux. iii, DMSO, P_2O_5, r.t., 24hr. iv, m-CPBA, CH_2Cl_2, -40°C.

The potential utility of this method for the synthesis of higher functionalized NCAs was also examined (Scheme 2). For this purpose, we choose to use the β-lactam **8** easily prepared in 70% overall yield as single diastereomer from the imine **6**[11], via cycloaddition and further hydrogenolysis of the resulting β-lactam **7** [$[\alpha]_D^{25}$ = +30.6 (c = 1.01, CH_2Cl_2)].



Scheme 2. Reagents and conditions: i, $BnOCH_2COCl$, NEt_3, CH_2Cl_2, -78°C→r.t., 20h ii, Pd-C, HCO_2NH_4, ^iPrOH, reflux. iii, NBu_4F, THF, r.t., then, $Me_2C(OMe)_2$, 4-$MeC_6H_4SO_3H$ (cat.), C_6H_6, reflux. iv, DMSO, P_2O_5,16h, r.t. then m-CPBA, CH_2Cl_2, -40°C, v, MeOH, reflux, 2h vi, (+)-MTPA-Cl, NEt_3, CH_2Cl_2, r.t., 2.5h.

Nonetheless, our first attempts to oxidize the α-hydroxy β-lactam **8** into the corresponding α-keto derivative were unsuccessful. However, oxidation of **10**, easily prepared from **7** in two steps, led to the required α-keto β-lactam, which was then treated with m-CPBA. Finally, the resulting NCA **11** was transformed into the α-amino ester **12** [m.p: 91-93°C (hexane); $[\alpha]_D^{25}$ = -36.3 (c = 0.50, CH_2Cl_2)] to check its optical purity[12].

In summary, the results presented here serve to illustrate that the approach is an alternative to the conventional Leuchs procedure[2], is very simple in execution and easily extensible to further applications.

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8.- Initial attempts to purify NCAs by crystallization or column chromatography on silica gel were unfruitful and led to partial decomposition of the products. In general, the resulting NCAs were of sufficient purity for use in next steps.

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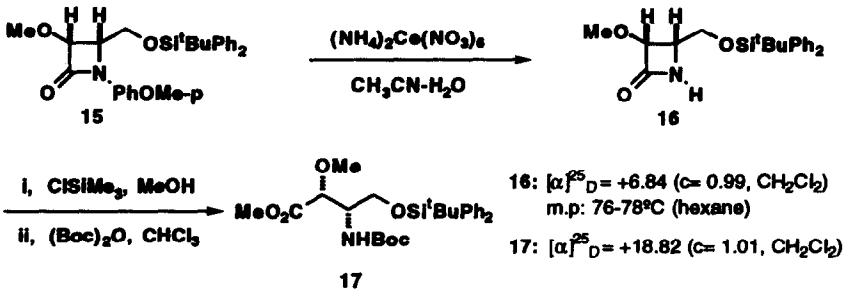
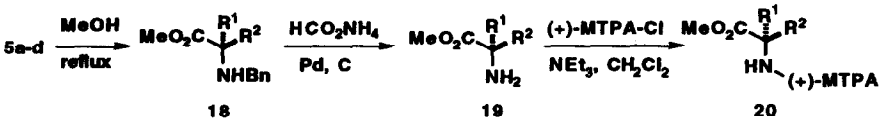
11.- The imine **6** was prepared in the usual way (see ref. 6i) from the corresponding ester **17** which was obtained from the β-lactam **15** in few steps.



12.- Although the reactions described proceeded without detectable epimerization, as judged by HPLC analysis of the resulting compounds, all of the NCAs prepared were transformed into the corresponding α-amino esters to confirm their optical purities. Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.



Representavite data of selected compounds: Compound.5a:. ^{1}H-NMR ($CDCl_3$) δ 7.50-7.20(m, 5H, arom.); 5.20(d, 1H, J=15.6Hz, CHPh); 4.20(d, 1H, J=15.6Hz, CHPh); 4.10(d, 1H, J=2.2Hz, HCHN); 3.71(dd, 1H, J=2.3Hz, J=8.3Hz, HCOSi); 1.80(sep, 1H, CHMe$_2$); 0.94(d, 3H, J=7.9Hz, CH_3); 0.92(s, 9H, SiC(CH_3)$_3$); 0.66(d, 3H, J=6.7Hz, CH_3); 0.06(s, 3H, CH_3Si), 0.00(s, 3H, CH_3Si).Compound.5c:. ^{1}H-NMR ($CDCl_3$) δ 7.43-7.17(m, 8H, arom.); 6.80-6.73(m, 2H, arom.); 5.08(d, 1H, J=15.9Hz, CHPh); 4.44(d, 1H, J=15.9Hz, CHPh); 4.35-4.29(m, 1H, HCOSi); 4.03(d, 1H, J=1.9Hz, HCHN); 2.85(dd, 1H, J=6.7Hz, J=13.8Hz, CHPh); 2.70(dd, 1H, J=13.7Hz, CHPh); 0.87(s, 9H, SiC(CH_3)$_3$); 0.05(s, 3H, CH_3Si), -0.03(s, 3H, CH_3Si). Compound.18a:. Oil; ^{1}H-NMR ($CDCl_3$) δ 7.33-7.30(m, 5H, arom.); 3.94(d, 1H, J=13.0Hz); 3.72(s, 3H); 3.66(dd, 1H, J=3.0Hz, J=6.3Hz); 3.58(d, 1H, J=13.0Hz); 3.30(d, 1H, J=3.1Hz); 2.00-1.90(m,, 1H); 0.89(d, 3H, J=6.6Hz); 0.88(s, 9H, ^{t}Bu); 0.85(d, 3H, J=6.8Hz); 0.03(s, 3H); -0.05(s,3H). Compound.18c:. Oil; ^{1}H-NMR ($CDCl_3$) δ 7.39-7.08(m, 10H, arom.); 4.25-4.17 (m, 1H), 3.97(d, 2H, J=12.8Hz); 3.67(s, 3H); 3.50(d, 1H, J=12.9Hz); 3.21(d, 1H, J=9.1Hz, J=12.8Hz); 3.08(d, 1H, J=2.1Hz); 2.75(dd, 1H, J=5.3Hz, J=12.8Hz); 0.85(s, 9H, tBu); -0.03(s, 3H, Me); -0.07(s, 3H, Me).^{13}C-NMR ($CDCl_3$) δ 174.1; 140.2; 138.2; 129.5; 128.6; 128.3; 126.9; 126.2; 75.6; 62.3; 52.0; 51.5; 40.5; 25.7; 17.9; -4.6; -6.1. Compound.18d:.Yield 81%. Oil; [α]$^{25}_D$= -47.9 (c=0.53, CH_2Cl_2); IR(CH_2Cl_2) υ 3300 (NH), 1740 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.33-7.31(m, 5H, arom.); 4.36-4.34 (m, 1H), 4.00(d, 2H, J=6.6Hz); 3.98(d, 1H, J=13.4Hz); 3.76(s, 3H); 3.66(d, 1H, J=13.4Hz); 3.27(d, 1H, J=4.3Hz); 1.39(s, 3H); 1.33(s, 3H).^{13}C-NMR ($CDCl_3$) δ 173.3; 139.7; 128.5; 128.4; 127.2; 109.8; 76.4; 66.4; 61.4; 52.2; 52.1; 26.4; 25.4. Compound.20c:.^{19}F-NMR ($CDCl_3$) δ 107.9(s). Compound.20d:.^{19}F-NMR ($CDCl_3$) δ 107.6(s). Compound.14:.^{19}F-NMR ($CDCl_3$) δ 109.4(s).

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