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STEREOSELECTIVE ADDITION OF LITHIOETHYL ACETATE TO BOC-L-PROLINAL. A CONVENIENT CHIRAL SYNTHETIC BUILDING BLOCK FOR THE PYRROLIZIDINE ALKALOID RING SYSTEM

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Summary: *Aldol condensation of lithioethyl acetate with Boc-L-prolinal proceeds stereoselectively to give R,S diastereomer* **2**. *Acidolysis of the Boc group and lactamization gives crystalline* **3** *which possesses the pyrrolizidine alkaloid skeleton. Saponification and acidolysis of* **2** *yields* **7**, *a novel GABA analogue.*

Statine (**1**) [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid] is a key component of the microbial enzyme inhibitor pepstatin[1] and the 3*R*,4*S* isomer is present in the antiviral didemnins,[2] two important natural products under current study for their therapeutic potential. Naturally occurring statine as well as its unnatural analogues have been incorporated into peptides to produce renin inhibitors;[3] these compounds are being vigorously prosecuted as medicinal agents for the treatment of hypertension.[4] We wish to report here a stereoselective synthesis of the novel statine analogue β-(*R*)-hydroxy-2-(*S*)-pyrrolidinepropionic acid ((*R*,*S*)-**HPPA**-OH) as the *N*-Boc ethyl ester **2** (Boc-(*R*,*S*)-**HPPA**-OEt) and the trifluoroacetate salt **7** (tfa•(*R*,*S*)-**HPPA**-OH). We also report a single crystal X-ray structure determination of pyrrolizidinone **3**, which proves the configuration at the hydroxymethine carbon of **2**. Compound **3** represents a novel chiral entry into the pyrrolizidine alkaloid nucleus. **HPPA** was prepared[5] to probe the effects of conformational restriction on renin inhibition.

The synthetic chemistry[6] is shown in Scheme 1: Boc-L-proline methyl ester was reduced (DIBAL, toluene, -78°) to Boc-L-prolinal **4**; the freshly prepared aldehyde **4** reacts stereoselectively with lithioethyl acetate (THF,-78°) to produce a mixture containing predominantly *R*,*S* Boc-**HPPA**-OEt **2** along with *S*,*S* epimer **5** (70% combined yield).[7] Reverse phase HPLC analysis [Supelco LC18, 60:40 methanol-water, 1 mL/min] indicates an 80:20 ratio of compounds **2** [rt = 11.5min] and **5** [rt =

SCHEME 1 *

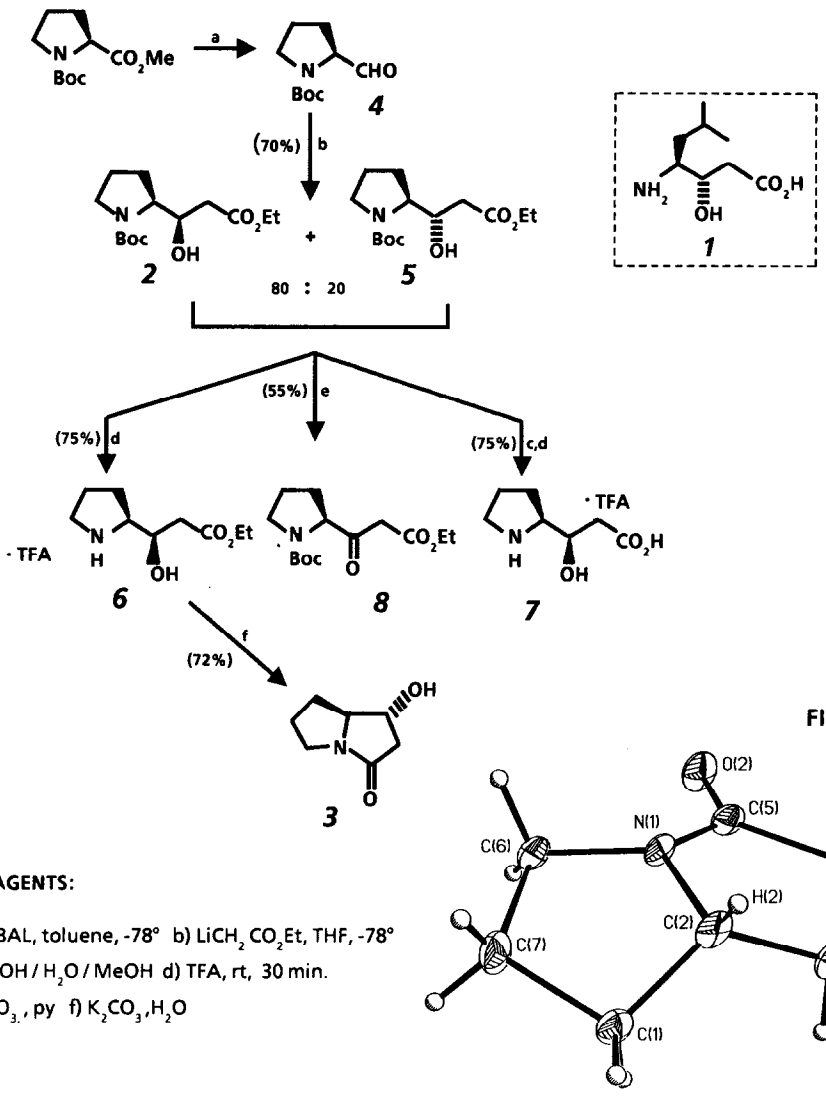

FIGURE 1

*** REAGENTS:**

a) DIBAL, toluene, -78° b) $LiCH_2CO_2Et$, THF, -78°
c) NaOH / H_2O / MeOH d) TFA, rt, 30 min.
e) CrO_3, py f) K_2CO_3, H_2O

X-ray crystal data: crystals of 3 were monoclinic, space group $P2_1$. The cell parameters were a = 6.819 (2), b = 7.278 (2), c = 7.664 (3) Å, β = 115.35 (2), V = 343.7 (1) Å^3, and d calcd = 1.35g cm^{-3} for z = 2. The intensity data were measured on a Nicolet R3m-E diffractometer with Mo K_α radiation (λ = 0.71079Å) in the θ-2θ mode. The structure was solved using the direct methods routine SOLV of G.M. Sheldrick available from Nicolet. Observed reflections: 623. C,H, and O were anisotropically refined with H's fixed in idealized positions. Refinement: R: 0.052, R_w: 0.050, GOF: 1.5.

10.7min], respectively. This degree of stereoselectivity is significant considering that a similar reported[8] aldol condensation on *acyclic* Boc-leucinal proceeded with little stereoselectivity and in contrast gave a slight excess of the *S,S* diastereomer (60:40). It is interesting to note that when vinyl*magnesium* bromide was substituted for lithioethyl acetate in the above reaction with **4**, no stereoselectivity was obtained and 1:1 mixture of diastereomers resulted. (The identity of the HPLC peaks was determined by preparing pure samples of **2** and **5** as follows: An epimeric mixture of **2** and **5** prepared by the above route was oxidized using an *in situ* Collins reagent[9] to ketone **8** which was subsequently reduced with $NaBH_4$ (EtOH, 25°) to an expected 1:1 mixture of **2** and **5**; these alcohols were separated by chromatography on silica gel [20% EtOAc-hexanes] and analyzed by HPLC.)

The 80:20 epimeric mixture of **2** and **5** was saponified (NaOH, MeOH-H_2O (4:1), 25°, 30min) and the isolated free acid treated with 90% trifluoroacetic acid to give novel GABA analogue **7**, mp 112-113°. To prepare the pyrrolizidine alkaloid building block **3**, the above epimeric mixture of **2** and **5** was treated with 90% TFA (25°) to give a single crystalline amine salt **6**, mp 93-94° (needles from EtOH-Et_2O, 75% yield), $[\alpha]_D^{25}$ -17° (*c*1,EtOH). Compound **6** was neutralized (K_2CO_3-water) and heated on a steam bath to produce hydroxy pyrrolizidinone **3**, mp 84-86° (prisms from EtOAc-hexanes, 72% yield), $[\alpha]_D^{25}$ -91.5° (*c*1,$CHCl_3$). The structure of compound **3** was determined by single crystal X-ray analysis and is shown in figure 1. Thus the major product of the aldol condensation is the *R,S* isomer **2**. Lactam **3** possesses the pyrrolizidine alkaloid skeleton, and thus formally represents a convenient chiral synthon for the preparation of certain members of this class; pyrrolizidine alkaloids have evoked since their discovery in 1909 a great deal of interest[10] as model systems for new methodology in natural product synthesis as well as for their pharmacological activity.

The above synthetic route is convenient and produces pure chiral products after simple recrystallization. The synthetic strategy might be applicable to more complex pyrrolizidines. Subsequent papers will demonstrate the utility of building block **3** for the preparation of optically pure 1-substituted[11] pyrrolizidines.

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References and Notes:

1. Umezawa, H., Aoyagi, T., Morishima, H., Matsuzaki, M., Hamada, M. and Takeuchi, T., *J. Antibiot. Tokyo* **1970**, *23*, 259.

2. Rinehart, K.L., Gloer, J.B., Cook, J.C. Jr., Mizsak, S.A. and Scahill, T.A., *J. Amer. Chem. Soc.* **1981**, *103*, 1857.

3. Bock, M.G., DiPardo, R.M., Evans, B.E., Rittle, K.E., Boger, J.S., Freidinger, R.M. and Veber, D.F., *JCS Chem. Comm.* **1985**, 109 and references cited therein.

4. Hanson, G.J., Baran, J.S., Lindberg, T., Walsh, G.M., Bittner, S.E., Babler, M., Papaioannou, S., Yang, P.-C. and DalCorobbo, M., *Biochem. Biophys. Res. Commun.* **1985**, *132*, 155 and references cited therein.

5. Baran, J.S., Hanson, G.J., Lindberg, T., Sham, H.L., Papaioannou, S., Laos, I., Babler, M. and Rozek, L., "An SAR Study with Analogs of the Renin Inhibitor Pepstatin," 19th National Medicinal Chemistry Symposium (ACS), Tucson, AZ, June **1984**.

6. All new compounds exhibited satisfactory combustion analyses and spectral data consistent with their structures.

7. This mixture was first prepared by H.L. Sham of our laboratories.

8. Rich, D.H., Sun, E.T.O. and Boparai, A.S., *J. Org. Chem.* **1978**, *43*, 3624.

9. Ratcliffe, R. and Rodehorst, R., *J. Org. Chem.* **1970**, *35*, 4000.

10. Zalkow, L.H., Glinski, J.A., Gelbaum, L.T., Fleischmann, T.J., McGowan, L.S. and Gordon, M.S., *J. Med. Chem.* **1985**, *28*, 687.

11. Wilson, S.R. and Sawicki, R.A., *JCS Chem. Comm.* **1977**, 431.

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