Tetrahedron Letters, Vol. 34, No. 16, pp. 2593-2596, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Towards the Synthesis of HIV-Protease Inhibitors. Synthesis of Optically Pure 3-Carboxyl-decahydroisoquinolines.

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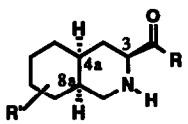
Summary: The synthesis of optically pure decahydroisoquinoline **1**, a component of HIV-protease inhibitors, was accomplished in 30-33% overall yield from the readily available optically pure monoacid **4**.

Decahydroisoquinoline-3-carboxylic acid derivatives, **A**, have received increasing attention in recent years due to their usefulness in the preparation of therapeutic agents[1] especially N-methyl-D-aspartic acid antagonists.[2]

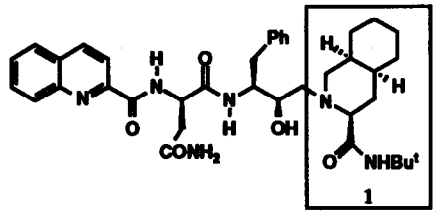
Recently, the N-tert-butyldecahydroisoquinoline-3-carboxamide **1** has been incorporated in the structure of the HIV protease inhibitor **B**, a potentially useful candidate for the treatment of the Acquired Immune Deficiency Syndrome (AIDS).[3]



R'= O, H

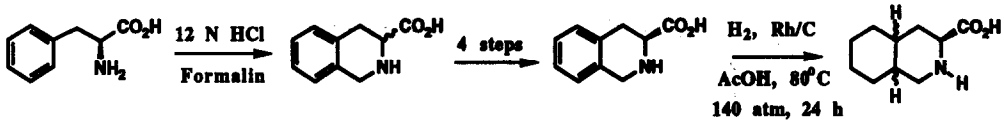
R= OH, NHBu^t, O-alkyl

A



B

The previous synthesis of **1** involved the Pictet-Spengler reaction[4] using L-phenylalanine and formalin in concentrated hydrochloric acid at 95 °C to give the tetrahydroisoquinoline-3-carboxylic acid derivative which had suffered epimerization at the C-3 position (ca. 30%). Resolution (4 steps) to

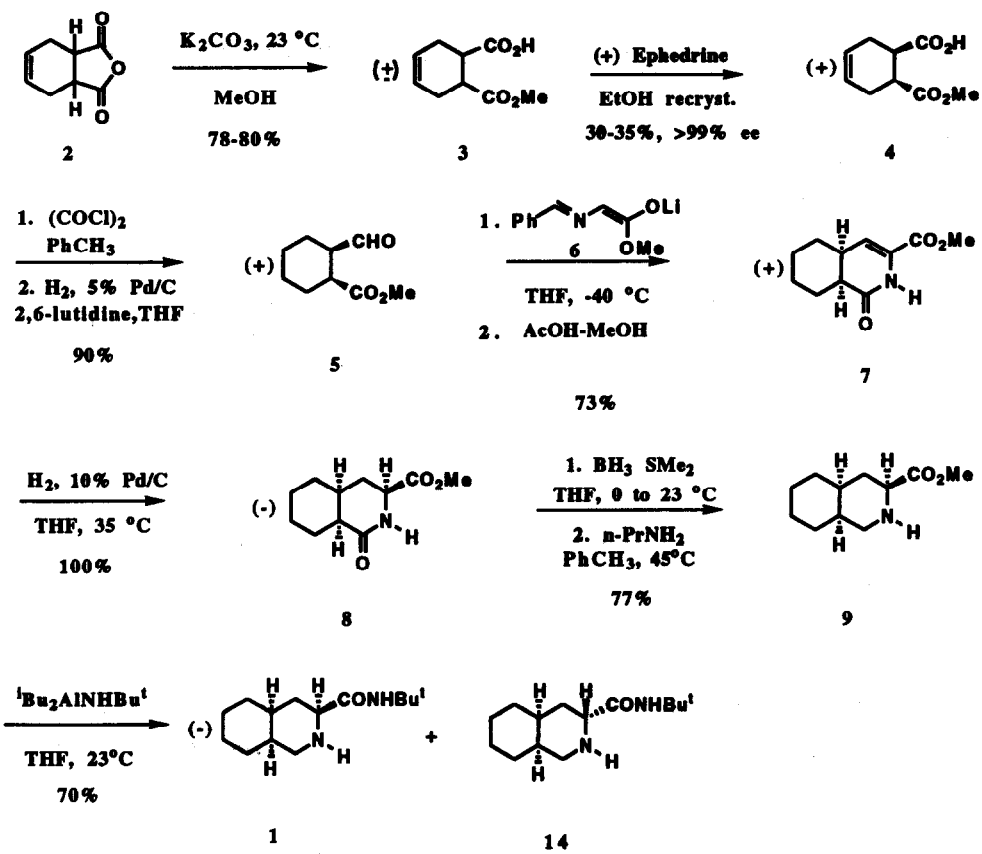


the required 3-S enantiomer and hydrogenation of the phenyl ring, produced the four possible diastereomers of **A** (4aR,8aR; 4aS,8aR; 4aR,8aS; 4aS,8aS) from which the desired diastereomer (3-S, 4aS, 8aS) could be obtained in low overall yield (ca. 8%).[5] We now report a convenient synthesis of **1** which affords the product in 30-33% overall yield, on a multigram-scale, from the readily available optically pure mono-acid **4**. The synthetic sequence is depicted in Scheme 1.

The readily available meso-cis-anhydride **2** underwent smooth methanolysis with K_2CO_3 in MeOH to give **3** in 78-80% yield after extractive work-up. Formation of the ephedrine salt, followed by two recrystallizations from EtOH, afforded **4** (>99% ee) in 30-35% yield from +/- **3**.[6] Alternatively, **4** was obtained from the enzymatic hydrolysis (ca. 95% ee) of the corresponding diester with Pig Liver Esterase according to known procedures.[7]

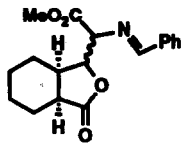
The monoacid was converted to aldehyde **5** by the sequence:[8] (a) treatment of **4** with oxalyl chloride (1.1 equiv) in toluene at 23 °C for 18 hours with a continuous N_2 purge, to remove the HCl formed, followed by concentration in vacuo to give the acid chloride (b) hydrogenation of the latter (5% Pd/C, 40 psi, 25°C) in THF in the presence of 2,6-lutidine (1.1 equiv) followed by extractive workup to give the pure monoaldehyde ester **5** ($[\alpha]^{25}$ = +40.3°; c=1, MeOH) in 90% yield from **4**. The aldehyde **5** was added to a solution of the enolate **6**[9] [formed by treatment of the benzylimine protected glycine methyl ester with LiHMDS in THF] at -40 °C. The mixture was quenched after 30 minutes with AcOH in anhydrous methanol and concentrated in vacuo. The residue, identified as the lactone **10** (mixture of

Scheme 1

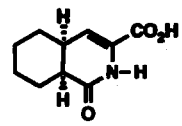


diastereomers by ^1H NMR), was treated with AcOH (10 equiv.) in anhydrous MeOH for 36 hours at 23 °C to effect tandem imine deprotection-cyclization to the hexahydroisoquinolinone **7** in 73% yield after chromatographic purification ($[\alpha]^{25} = +58.0°$; c=1, MeOH).

Reduced yields of **7**, due to hydrolysis to **11**, resulted when excessive amounts of H_20 were present in the reaction medium.

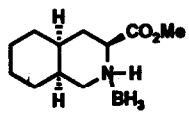


10

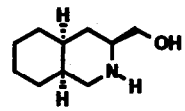


11

Hydrogenation of **7** (10% Pd/C, THF, 35°C, 40 psi, 24 hours) proceeded smoothly to give **8** ($[\alpha]^{23} = -9.2°$C; c=1, MeOH) as a single diastereomer in quantitative yield. In a solution of the amide **8** in THF was slowly added neat BH_3·SMe_2 (2.5 equiv)[10] at 0 °C, and the reaction mixture was allowed to stir at 23 °C for 2 hours. Quenching with MeOH at 0 °C and concentration in vacuo afforded the amine-borane complex **12** as the only detectable product in the ^1H NMR spectrum.[11] Complete decomplexation of **12** to give **9** was accomplished by treatment of the former with n-propylamine (n-$PrNH_2$) (5 equiv) in toluene at 45 °C. The product **9** was isolated in 77% yield by the following work-up: (a) partitioning of the residue between hexane and 0.25 M HCl (5 equiv) at 0°C (b) treatment of the aqueous layer with 1N NaOH to pH 10 at 0 °C (c) extraction with EtOAc. Use of dilute acid and maintenance of the temperature at 0 °C during the work up was essential in obtaining the optimum yield, since the product was shown to be sensitive to strong acid. The use of BH_3·THF as the reducing agent or addition of BH_3·SMe_2 at higher temperature (>25°C) produced substantial amounts of the overreduced product **13**.



12



13

Weinreb amidation[12] to generate **1** was accomplished by a minor modification of the published procedure: (a) initial formation of the aluminum reagent by treatment of triisobutylaluminum (1 M solution in toluene) with t-$BuNH_2$ in THF-$PhCH_3$ (1:1) at 45 °C for 30 min (b) concentration of the solvent in vacuo and dissolution of the residue in dry THF and (c) addition of **9** in THF and stirring the reaction mixture at 23 °C for 24 hours. Quenching with Na,K tartrate and chromatographic purification (1:1 EtOAc-hexane on flash SiO_2 deactivated with Et_3N) afforded the desired amide **1** in 70% yield ($[\alpha]^{28} =$ -69.5°; c=0.52, MeOH). A small amount of the a C-3 diastereomer **14** (ca. 5%) was detected in the ^1H

NMR spectrum of the crude reaction mixture. The degree of epimerization increased with increasing amounts of toluene (12% when THF: $PhCH_3$= 1:1) while complete epimerization at C-3 was observed when the reaction was run at higher temperatures (50°C).

In conclusion, the synthesis of the decahydroisoquinoline derivative **1**[13] was accomplished in good overall yield from **2**. The synthetic sequence developed allows for the synthesis of analogues with potentially interesting pharmacological profiles.

Acknowledgment. We acknowledge Ms. Pamela Simpson for determination of enantiomeric purity of **4**. We thank Drs. D. Richard Sidler, Joseph Armstrong and Steven King for helpful discussions. We also thank Mr. Greg McManemin for the mass spectral determinations.

References and notes:

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13. All new compounds gave satisfactory ^1H , ^{13}C NMR and Mass spectra. The structure and absolute stereochemistry of the final product (**1**) was established by comparison with an authentic sample provided by Dr. Wayne Thompson whom we gratefully acknowledge.

(Received in USA 10 November 1992; accepted 16 February 1993)