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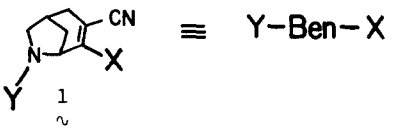
AMINO ACID DERIVATIVES THAT STABILIZE SECONDARY STRUCTURES OF POLYPEPTIDES--IV. PRACTICAL SYNTHESIS OF 4-ALKYLAMINO-3-CYANO-6-AZABICYCLO[3.2.1]OCT-3-ENES (BEN DERIVATIVES) AS γ-TURN TEMPLATES

D.S. Kemp* and Jeffery S. Carter
Department of Chemistry Rm 18-027
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Abstract

Ben derivatives have been prepared in five steps from 4-hydroxyproline by Barton cyanoethylation, ring closure, and derivitization. Proof of absolute configuration and practical synthesis of pure Ben enantiomers are described.

In the accompanying communication we note that β-enaminonitriles can mimic secondary amides and therefore have promise as building blocks for conformationally restricted analogs of polypeptides. Monocyclic β-enaminonitriles have the disadvantages of partial flexibility and



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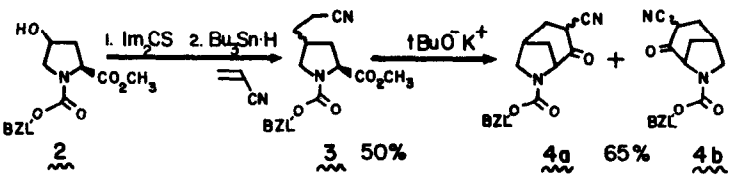
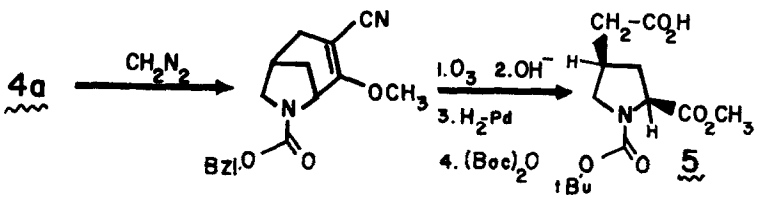
SCHEME I



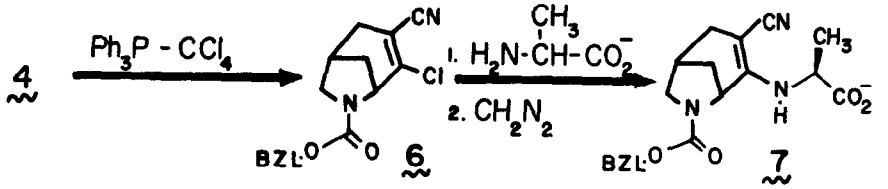
2 3 50% 4a 65% 4b

ease of epimerization, and we therefore examined more rigid bicyclic structures in which Bredt's rule inhibits epimerization processes. For a first study of bicyclic β-enaminonitriles we were attracted to 1, formed from L-hydroxyproline by the synthesis outlined in Scheme 1, which makes use of the Barton cyanoethylation procedure[1].

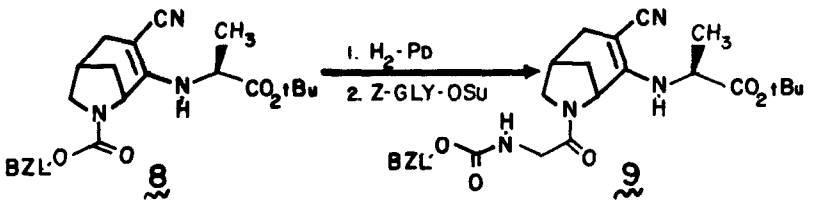
Although the reactions of the Scheme convert 2 to 4ab[2] in two steps with an overall yield of 33%, the route has the unattractive feature that it generates 4ab as a racemate from chiral 2. Not surprisingly the cyanoethylation step proceeds to give a 1:1 mixture of epimers at C-4, and subsequent epimerization at C-2 occurs during the t-butoxide-catalyzed ring closure step, allowing a high conversion efficiency for the overall process but at the expense of loss of the potential for sterochemical control provided by the chirality at C-2 of 2. Treatment of the epimeric mixture 3 with LDA at -78°C in THF, followed by quenching with acetic acid resulted in the formation of a 9:1 mixture of 4a and 4b ($[\alpha]_{405}$ + 265°C), but in only 10% yield. Evidently under these conditions, formation of the conjugate base of the ester occurs substantially more slowly than that of the nitrile, and ring closure occurs only with the cis-diastereomer of 3. In principle, a 50% yield of 4a might be achievable under optimal conditions from the epimeric mixture 3; unfortunately all attempts to modifiy reaction conditions with the aim of increasing the yield while maintaining the chiral purity of the product failed. Given the separation process to be outlined below, the higher yield of racemic product obtained with t-butoxide was the preferable result. Demonstration that 4a had the indicated configuration was achieved by reaction with diazomethane and ozonolysis to generate 5, independently synthesized by a multistep route from 2.



Conversion of 4 to 1 was efficiently carried out by reaction of amino acid tetraalkylammonium salts with 6, which can in turn be formed by reaction of 4 with CCl_4/Ph_3P[3,4].



When the racemic 4ab is carried through the above conversion, the resulting diasteromeric mixture of esters 1 is reproducible separable by MPLC on silica on gram scale. Acid hydrolysis regenerates 4a and 4b, which can be separately reconverted to the enantiomers of 6[5] and hence to optically pure diastereomers of 1 by reaction with amino acid salts. As tests of the degree of epimerization of the amino acid group itself, L-isoleucine and L-alanine were separately subjected to the above reaction sequence, the resulting products were hydrolyzed, and the isolated amino acids were analyzed for racemic or epimeric content. In the case of Ile, less than 0.2% of allo-Ile was found; with alanine, the recovered Ala was allowed to react with Leu N-carboxyanhydride[6], and the resulting dipeptide was found to contain less than 0.25% of H-L-Leu-D-Ala-OH.



Hydrogenolysis and peptide acylation of Ben derivatives can be carried out without difficulty as indicated by the transformation of 7 to 8. The major restriction in the compatibility of the Ben function with the standard operations of peptide synthesis results from its lability to acids. Thus treatment of 7 with trifluoroacetic acid results in partial hydrolysis of the enamine function. Selective and complete t-butyl ester cleavage resulted when 7 was exposed to $BF_3 \cdot OEt_2$ - acetic acid in CH_2Cl_2[7]. Coupling of the resulting acid with H-L-Phe-OMe in the presence of equivalents of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole generated Z-Ben-L-Ala-L-Phe-OMe in 41% yield. As a test of the racemizing tendency of the enamino portion of a Ben derivative, 7 was exposed to triethylamine and/or acetic acid in solvents ranging from methanol to DMSO under a variety of conditions. No epimerization was seen under any of the basic conditions. Acetic acid with or without bases in methanol or DMSO for 18h at 50°C gave no detectable epimerization, but 14% of epimer was

observed in CH_2Cl_2 in 24h at 23°C in the presence of dichloroacetic acid, the optimum conditions reported for enamine formation in the accompanying communication. Under more rigorous conditions, simple carboxylic acids have been reported to be potent catalysts for the epimerization of simple amino acids as well[8].

In this paper we have demonstrated a short, practical route to Ben derivatives and have demonstrated their compatibility with many of the operations of peptide synthesis. The conformational properties of Ben derivatives when incorporated into short linear and cyclic peptides are under study and will be reported subsequently.

Acknowledgement

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References

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2. 4ab waxy glass after Kugelrohr distillation (190°C, 0.05 mm). IR ($CHCl_3$): 3020, 3005, 2260, 1745, 1705; MS (m/e) 284 (M^+,2), 256 (36), 158 (54), 91 (100).
3. Lee, J.B., J. Am. Chem. Soc. (1966), 88, 3340.
4. 6, waxy solid, mp 86-92°C; IR ($CHCl_3$) 2985, 2900, 2220, 1690; MS (m/e) 302 (M^+,11), 267 (6), 186 (14), 150 (55), 91 (100). Anal. Calcd for $C_{16}H_{15}N_2ClO_2$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.49; H, 5.21; N, 9.22. Owing to rotational isomerism at the urethane C-N bond, the ^1H NMR spectra were complex, and peak positions above were relatively useless for purposes of characterization.
5. For the (6R,2S) series: 4a $[\alpha]_{405}$ + 319° (EtOAc); 6a $[\alpha]_{405}$ -294° (EtOAc);
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