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CONFORMATIONALLY RESTRICTED AMINO ACIDS: DIASTEREOSELECTIVE SUBSTITUTION AT THE β-POSITION OF L-TRYPTOPHAN

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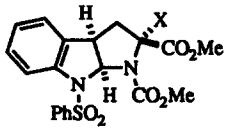
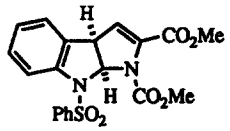
Summary : Higher order cuprates add with extreme exo-facial selectivity to the chiral tetrahydropyrroloindole **3**, itself prepared in enantiomerically pure form from L-tryptophan: treatment of the adducts with trifluoroacetic acid provides diastereo- and enantiomerically pure β-substituted tryptophan derivatives.

α-Disubstituted and β-substituted amino acids are of interest owing to the properties that they confer on peptides into which they are incorporated. These, often advantageous, properties include the limitation of conformational mobility, increased lipophilicity, and increased resistance to exo and endo peptidases as well as to chemical hydrolysis. Much effort has been put into the enantioselective synthesis of α-disubstituted amino acids[1] but rather less, with the exception of the β-hydroxy-α-amino acids, into substitution at the β-position.[2] Tryptophan occupies a special position in so far as, although 2S,3R-β-methyltryptophan has interesting biological activity, both alone and as a peptide component,[3] little or no effort has been described for the asymmetric synthesis of its β-substituted derivatives. Racemic syntheses of conformationaly restricted analogues of the related biogenic amine serotonin have recently been described.[4] We describe herein preliminary experiments on a fully stereocontrolled synthesis of β-substituted tryptophan derivatives and of an α,β-methanotryptophan derivative by a logical extension of our recent approach to the enantiospecific α-alkylation of tryptophan.[5]

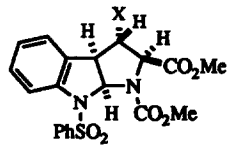
Treatment of the hexahydro[2,3b]pyrrolindole **1**, prepared as previously described[5,6] from L-tryptophan, in THF under a nitrogen atmosphere with LDA and, after 60 min at -78 °C, with phenylselenyl chloride gave the crystalline selenide **2** as a single diastereoisomer in 70% isolated yield. That substitution at C2 has occurred with retention of configuration is readily discernable from the typical upfield chemical shift of the C2 CO_2Me group (δ 3.15) which is a result of its proximity to the endo surface of the molecule and so shielding by the aromatic ring current. Oxidation of **2** with excess magnesium monoperoxyphthalate at room temperature in THF enables isolation, by simple extraction, of the essentially pure dehydro derivative **3** in 98% yield. This substance, a white foam, is perfectly air stable showing no tendency to undergo aromatization in more than a year at room temperature.



1 X = H
2 X = SePh

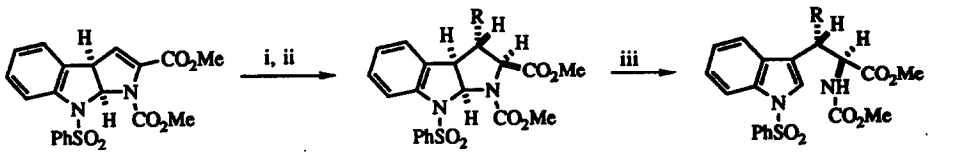


3



4 X = SPh
5 X = $NHCH_2Ph$

Reaction of **3** with either thiophenol or benzylamine in methanol at room temperature in the presence of triethylamine gave the Michael adducts **4** and **5**, as single diastereoisomers, both in 70% isolated yield. As anticipated both reaction steps, Michael addition and enolate quenching, took place with very high selectivity on the exo-face of the diazabicyclo[3.3.0]octane framework to the extent that, although we are able to identify a number of minor byproducts in the crude reaction mixture these do not include alternative diastereoisomers of the major products. Once again the stereochemistry at C2 is readily identified by the diagnostic shielded ester Me group. Stereochemical elucidation at C3 is facilitated, in **4**, by the singlet nature of H3 which implies that the torsion angles H3-C3-C3a-H3a and H2-C2-C3-H3 are both close to 90°. This information can only be accommodated by the designated configuration and with the terminal heterocyclic ring adopting such a conformation as to minimize $A^{1,3}$ strain[7] between the putative $N1^{+}{=}C(O^{-})OMe$ double bond and the substituent at C2. This conformation (Fig. 1), found in solution for all derivatives of **1** prepared so far and verified crystallographically in certain cases,[5] is also found in carbamates of the related amino acid proline.[8] The same logic is used to assign configurations to all the Michael adducts to **3** described here with the only ^{3}J scalar couplings to H3 observed being those to the newly introduced group at C3. Alkyl groups were introduced by means of TMSCl assisted[9] Lipshutz higher order cuprate technology[10] as indicated in scheme 1. In each case only a single diastereoisomer was found. Following the protocol previously developed[5] each of the adducts **6 - 9** was then dissolved in neat trifluoroacetic acid to bring about ring opening to the tryptophan system. With the simple unsubstituted system **1** this reaction is complete in 5 min at room temperature and with α-alkylated derivatives of **1**[5] in a similar time. However, the β-methyl derivative **6** and the β-butyl derivative **7** required between 3 and 4 days, and the β-phenyl derivative **8** 14 days for greater than 90% conversion to the tryptophans **10- 12** respectively under similar conditions. The β-t-butyl derivative **9** was recovered unchanged after 10 days in trifluoroacetic acid at room temperature. Clearly the 3exo-alkyl groups in **6-9** have a profound effect on the ring opening reaction to the extent that we have been unable to obtain samples of **10-12** completely free from traces of these ring closed tautomers. If the ring opening process is viewed as protonation of the carbamate followed by anticlockwise rotation about the C2 - C3 bond, as in figure 2, the retardation in **6 - 9** is seen to be the result of a gauche interaction between the newly introduced C3-substituent and the carbamate. Whatever the reason, the acid stability of **9** opens up the possibility of the asymmetric synthesis of physostigmine derivatives unsubstituted at C3a.



3

6 R = Me (56%) 8 R = Ph (65%)
7 R = ^{n}Bu (60%) 9 R = ^{t}Bu (70%)

10 R = Me (94%) 12 R = Ph (92%)
11 R = ^{n}Bu (94%) 13 R = ^{t}Bu (0%)

i) R(2-th)CuCNLi$_2$; ii) NH_4Cl; iii) CF_3CO_2H

Scheme 1

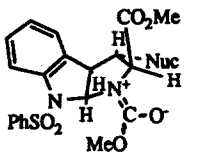


Figure 1

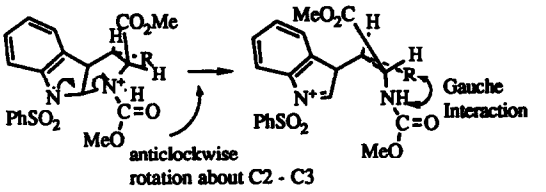
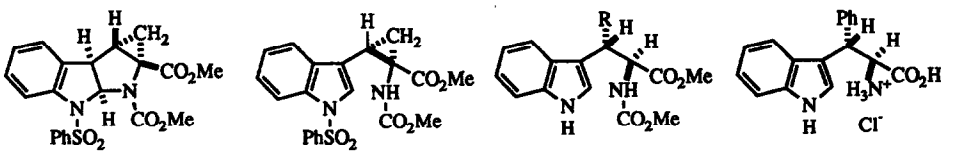


Figure 2

Treatment of 3 with trimethylsulfoxonium iodide and dimsyl sodium in DMSO at room temperature results in the isolation of the tetracyclic system 14 in 56% yield. The extra strain inherent in 14 is immediately apparent from its reaction with a 25% solution of trifluoroacetic acid in chloroform which results in complete ring opening to the cyclopropatryptophan derivative 15 within 30 min at room temperature. Despite the current widespread interest in cyclopropaamino acids[11] to our knowledge this is the first example of such a derivative of tryptophan.



14 15 16 R = Me 17 R = Ph 18

Products 10 and 11 were desulfonylated by photolysis in the presence of anisole and ascorbic acid as described by Yonemitsu[12] to give 16 and 17 respectively. The enantiomeric purity of 16 and 17 was verified spectroscopically with a chiral lanthanide shift reagent[13] and found to be greater than 95% in both cases. Finally 17 was completely deprotected by heating to reflux for 30h in 6N HCl to give 18[14] in 87% yield.

In conclusion, we have demonstrated that the 1,3a,8,8a-tetrahydropyrrolo[2,3b]indole **3** is stable, readily prepared, compound subject to highly stereoselective conjugate addition reactions, and that it is a suitable precursor to a number of diastereo- and enantiomerically pure derivatives of tryptophan. We anticipate that this chemistry will be of considerable use in the preparation of conformationally restricted analogues of tryptophan, serotonin, and of peptide mimetics.

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14. **18**, a glass, had $[\alpha]_D$ = +43° (c = 4.3, MeOH); δ_H (300 MHz, CD_3OD) 4.65(1 H, d, *J* = 9.3 Hz, H_β), 4.73(1 H, d, *J* = 9.3 Hz, H_α); δ_C (75 MHz, CD_3OD) 48.1(C_β), 58.2(C_α).

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