Asymmetric Synthesis of α-Alkylated Tryptophan Derivatives

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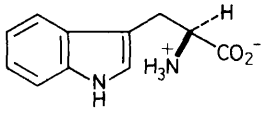
L-Tryptophan has been converted, by the alkylation of the hexahydro[2,3-*b*]pyrroloindole (**7**), followed by ring opening, to α-alkylated tryptophan derivatives with overall retention of configuration.

The asymmetric synthesis of α-alkylated α-amino acids is subject to much current interest owing to the increased stability of peptide bonds[1] and the modified biological activity of peptides[2] conferred by α,α-disubstituted residues, and to the possibility of their use as peptoids.[3]

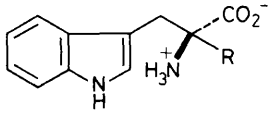
Two substantially different concepts have been developed for the asymmetric α-alkylation of α-amino acids; the Schöllkopf bis-lactim ether method[4] which relies on a second α-amino acid as chiral auxiliary, and the Seebach self-reproduction of chirality method[5] in which the amino acid to be alkylated is itself used as a source of chirality. The amino acid tryptophan (**1**) presents special problems owing to the reactive nature of its side-chain. To our knowledge the only reported syntheses of optically active α-substituted tryptophan analogues (**2**) are due to Seebach[6] and Schöllkopf[7] and involve the alkylation of oxazolidinones (**3**) and the bis-lactim ether (**4**), respectively, with *N*-protected indolylmethyl bromide. α-Alkylation of tryptophan derivatives with concomitant racemisation has been reported.[8] We report here a novel variation of the Seebach method in which, for the first time, positive advantage is taken of the reactive nature of the indole group in tryptophan.

Thus, stirring of N_b-methyloxycarbonyl-L-tryptophan methyl ester (**5**) with 85% phosphoric acid, according to Taniguchi[9] gave the crystalline hexahydropyrrolo[2,3-*b*]indole (**6**)† in 85% yield as a single diastereoisomer. Protection and stabilisation of (**6**) was achieved by reaction with toluene-*p*-sulphonyl chloride in pyridine to give the *N*-tosyl derivative (**7**),‡ again in 85% yield. Deprotonation of (**7**) in tetrahydrofuran at −78 °C with lithium di-isopropylamide to the enolate (**8**) followed by reaction with various electrophiles gave excellent yields of the alkylated derivatives (**9**)—(**14**) in which quenching took place, within the limits of n.m.r. detection, with complete diastereoselectivity from the *exo*-face.

In this manner it proved possible to introduce directly the side-chains of alanine, phenylalanine, and methionine by the use of methyl iodide, benzyl bromide, and 2-(methylthio)ethyl iodide, respectively (Table 1, entries 1,2,3). Quenching with allyl bromide and with ethyl bromoacetate provided the versatile derivative (**12**) and the aspartate derivative (**13**), respectively (Table 1, entries 4 and 5). Finally, quenching with 2-(trimethylsilyl)ethoxymethyl chloride, (SEM-Cl) provided the serine derivative (**14**) in excellent yield. Although the SEM group has been frequently used as a hydroxy protecting group,[10] as well as a combined *N*-protecting and directing group for orthometallation[11] in pyrroles, this is the first time, to our knowledge, that it has been used as a formaldehyde



(**1**)



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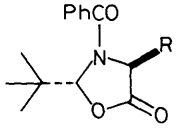

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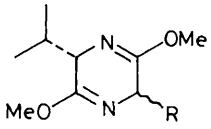

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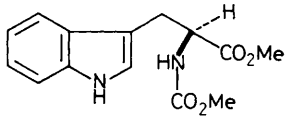
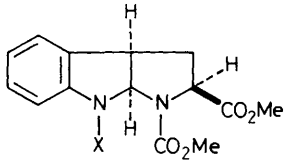
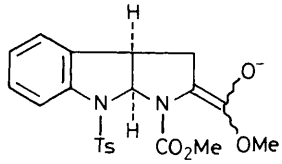


(**5**)

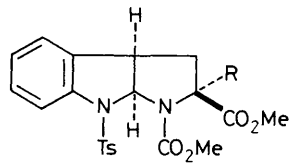


(**6**) X = H
(**7**) X = Ts

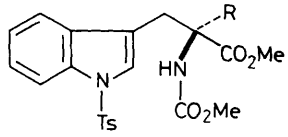
† The enantiomeric purity of (**6**) and (**21**) was verified by ^{19}F n.m.r. studies of Mosher's acid derivatives.[12]



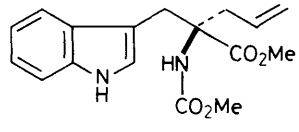
(**8**)



(**9**) R = Me
(**10**) R = CH_2Ph
(**11**) R = CH_2CH_2SMe
(**12**) R = $CH_2CH{=}CH_2$
(**13**) R = CH_2CO_2Et
(**14**) R = $CH_2OCH_2CH_2SiMe_3$



(**15**) R = Me
(**16**) R = CH_2Ph
(**17**) R = CH_2CH_2SMe
(**18**) R = $CH_2CH{=}CH_2$
(**19**) R = CH_2CO_2Et
(**20**) R = CH_2OH



(**21**)

‡ All new compounds gave satisfactory spectroscopic and microanalytical or high resolution mass data.

Ts = $SO_2C_6H_4Me$-*p*

Table 1.

Entry	Electrophile	Hexahydropyrroloindole (%)	Amino acid (%)
1	MeI	(**9**) (80)	(**15**) (90)
2	$PhCH_2Br$	(**10**) (71)	(**16**) (93)
3	$MeSCH_2CH_2I$	(**11**) (44)	(**17**) (84)
4	CH_2=CH–CH_2Br	(**12**) (79)	(**18**) (85)
5	$EtOC(O)CH_2Br$	(**13**) (83)	(**19**) (97)
6	$Me_3SiCH_2CH_2OCH_2Cl$	(**14**) (78)	(**20**) (75)[a]

[a] Ring opening was accompanied by deprotection of the hydroxy group.

equivalent in aldol reactions§ where, in our hands, it is vastly superior to the more traditional gaseous formaldehyde.

That quenching had indeed occurred from the *exo* face of the intermediate enolate ion (**8**) has been demonstrated by nuclear Overhauser enhancement (n.O.e.) difference spectroscopy and by single crystal *X*-ray determination of (**12**), to be reported subsequently in full.

Ring opening of the hexahydrodropyrroloindoles (**9**)—(**14**) was achieved simply by stirring overnight at room temperature in trifluoroacetic acid, providing the α-alkylated tryptophan derivatives (**15**)—(**20**) in excellent yields (Table 1), with the same relative stereochemistry as the starting tryptophan. Removal of the toluenesulphonyl protecting group was best achieved at this stage by reaction with sodium in liquid ammonia, as exemplified by the conversion of (**18**) to (**21**)† in 96% isolated yield.

§ *Note added in proof.* However, for a recent example see: L. A. Paquette, C. S. Ra, and T. W. Silvestri, *Tetrahedron*, 1989, **45**, 3099.

We consider this to be an expedient method for the asymmetric synthesis of α-alkylated L-tryptophan derivatives, which, given the availability of D-tryptophan, may be readily extended to the enantiomeric series.

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