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CONSTRUCTION OF OPTICALLY PURE TRYPTOPHANS FROM SERINE DERIVED AZIRIDINE-2-CARBOXYLATES

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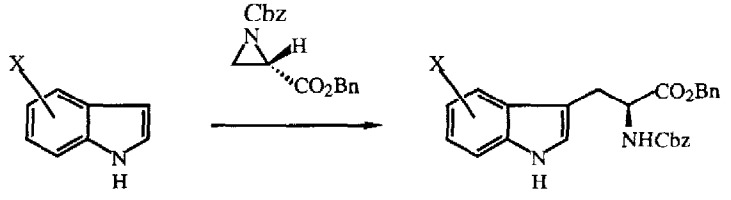
SUMMARY: The possibility of preparing optically pure tryptophan derivatives from various substituted indoles and (2*R*)- or (2*S*)-2-aziridinecarboxylates has been examined. Zinc triflate was found to be the only Lewis acid capable of bringing about this reaction in moderate yields.

During efforts aimed at the synthesis of various analogues of lyngbyatoxin A[1] for use in studies pertaining to the modulation of protein kinase C activity,[2] we became interested in the possibility of procuring optically pure tryptophan derivatives directly from indoles by reaction with optically pure aziridines (Equation 1).



(Equation 1)

While reports of related reactions can be found in the literature,[3] such examples are few in number, and no examples pertaining to the use of (optically pure) aziridinecarboxylates have been published.

Initially we surveyed the possibility of carrying out this reaction using benzyl (2S)-1-benzyloxycarbonyl-2-aziridinecarboxylate[4] (**3a**), indole, and a number of different Lewis acids. The structures, method of preparation, and optical rotations of the aziridines used in this study are displayed in Table 1.

No desired reaction was observed to take place under a range of reaction temperatures, times, and solvents when $AlCl_3$, $EtAlCl_2$, Me_2AlCl, $TiCl_4$, $SnCl_4$, $Mg(OTf)_2$, $ZnBr_2$, $BF_3{\cdot}OEt_2$, or BBr_3 were employed to activate the aziridine to ring opening. Only a single Lewis acid, *zinc triflate*, was in fact found to promote the desired amidoethylation reaction. Typically, the reaction was carried out in a test tube with screw cap at 78 °C for 18 h in chloroform as solvent. The zinc triflate (2-6 equivalents) and the indole (1.5 - 2 equivalents) were used in excess.

The results of the present study are compiled in Table 2. To ascertain the optical purity of the tryptophan derivative generated in entry 1 of Table 2, an authentic sample was prepared from L-tryptophan benzyl ester. The rotations of these two compounds were found to be identical. Additionally, the synthetic tryptophan derivative was reduced by lithium borohydride to the amide alcohol, and both the (S)-MTPA and (*R*)-MTPA ester derivatives were prepared. 500 MHz NMR analysis of the MTPA ester derivatives revealed an optical purity of >95%. While indole derivatives containing electron releasing groups (e.g., 5-methyl, 4- or 5-methoxy) reacted under these conditions to afford the desired tryptophan products, indoles bearing an

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electron withdrawing substitutent (e.g., 4-nitro, 6-chloro or 4-carbaldehyde) gave rise to little if any of the expected tryptophan products. The 4,7-disubstituted indole **4i**, an intermediate in the synthesis of various lyngbyatoxin analogues,[1b] also reacted only poorly with **3c** (entry 13).

The aziridine chemistry described herein thus offers in certain instances a useful method for gaining access to optically pure tryptophan derivatives. While the yields obtainable by this one pot reaction are only moderate, the method does nonetheless compare favorably with the multi-step procedures required to procure such compounds by asymmetric hydrogenation. In this regard it is of interest to compare the earlier literature on the synthesis of the sweetening agent 6-chloro-D-tryptophan with the method of entry 10.[10]

Procedures for preparing the previously unknown aziridine **3c** and the Cbz derivative of L-tryptophan methyl ester follow.

Methyl (2S)-1-Benzyloxycarbonyl-2-aziridinecarboxylate (3c).

A mixture of **1c** (0.94g, 2.7 mmol) in chloroform (10 mL) and methanol (2.3 mL) was treated with trifluoroacetic acid (4.6 mL) for 2 h at -10 °C. The solvent was removed *in vacuo*, and the residue was dissolved in chloroform (10 mL). Triethylamine (0.95 mL, 6.8 mmol) and benzyl chloroformate (0.39 mL, 2.7 mmol) were added. After being stirred for 2 h at 0 °C, the reaction mixture was diluted with water, adjusted to a pH of 8 with aq. $NaHCO_3$, and extracted with dichloromethane. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified with flash chromatography on silica gel with 4:1 hexane-ethyl acetate as eluent to provide 0.52 g (81%) of **3c** as an oil.

Cbz-L-Trp-OMe (entry 3, Table 2).

A mixture of **3c** (39.0 mg, 0.166 mmol), indole **4a** (35 mg, 0.30 mmol) and $Zn(OTf)_2$ (121 mg, 0.332 mmol) in chloroform (0.5 mL) was placed in a tightly capped test tube, and stirred for 18 h at 78 °C. The reaction mixture was diluted with water and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using first 4:1 then 2:1 hexane-ethyl acetate as eluent to give 20 mg of recovered **4a**, 13 mg of recovered **3c**, and 15.9 mg (27%, 41% based on aziridine consumed) of **Cbz-L-Trp-OMe** as a gum.[11]

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11. Representative R_f and ^1H NMR data for the products of entries 1, 6, 7, and 10 of Table 2 follow:

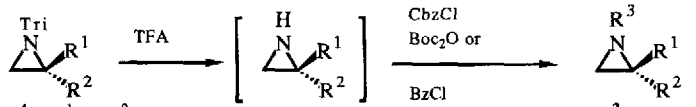
entry 1: R_f = 0.37 (2:1 hexane/ethyl acetate); ^1H NMR δ ($CDCl_3$) 7.93 (br s, 1 H), 7.51 (d, 1 H, J = 7.9 Hz), 7.15 - 7.40 (m, 12 H), 7.07 (t, 1 H, J = 7.6 Hz), 6.78 (s, 1 H), 5.32 (d, 1 H, J = 8.9 Hz), 5.04 - 5.25 (m, 4 H), 4.78 (dt, 1 H, J_d = 8.9 Hz, J_t = 5.3 Hz), 3.31 (d, 2 H, J = 5.3 Hz).

entry 6: R_f = 0.35 (2:1 hexane/ethyl acetate); ^1H NMR δ ($CDCl_3$) 7.86 (br s, 1 H), 7.15 - 7.35 (m, 12 H), 7.01 (d, 1 H, J = 8.3 Hz), 6.74 (s, 1 H), 5.32 (d, 1 H, J = 8.2 Hz), 5.10 (s, 2 H), 5.04 (s, 2 H), 4.77 (dt, 1 H, J_d = 8.2 Hz, J_t = 5.3 Hz), 3.29 (d, 2 H, J = 5.3 Hz), 2.40 (s, 3 H).

entry 7: R_f = 0.18 (2:1 hexane/ethyl acetate); ^1H NMR δ ($CDCl_3$) 7.92 (br s, 1 H), 7.20 - 7.40 (m, 6 H), 6.96 (d, 2 H, J = 10.1 Hz), 6.85 (dd, 1 H, J = 2.3, 8.7 Hz), 5.32 (d, 1 H, J = 8.2 Hz), 5.10 (s, 2 H), 4.73 (dt, 1 H, J_d = 8.2 Hz, J_t = 5.2 Hz), 3.80 (s, 3 H), 3.19 (s, 3 H), 3.28 (d, 2 H, J = 5.2 Hz).

entry 10: R_f = 0.38 (2:1 hexane/ethyl acetate); ^1H NMR δ ($CDCl_3$) 7.91 (br s, 1 H), 7.15 - 7.40 (m, 12 H), 7.00 (dd, 1 H, J = 1.6, 8.5 Hz), 6.73 (s, 1 H), 5.30 (d, 1 H, J = 8.1 Hz), 4.90 - 5.10 (m, 4 H), 4.74 (dt, 1 H, J_d = 8.1 Hz, J_t = 5.3 Hz), 3.27 (d, 2 H, J = 5.3 Hz).

Table 1. Preparation of N-Protected-2-Aziridinecarboxylate



1a[4] R^1 = H, R^2 = CO_2Bn
1b[4] R^1 = CO_2Bn, R^2 = H
1c[5] R^1 = H, R^2 = CO_2Me

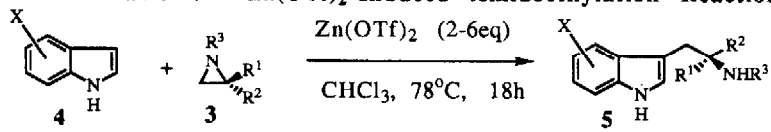
2

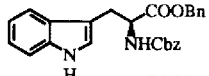
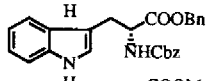
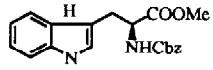
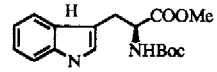
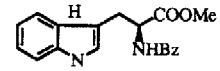
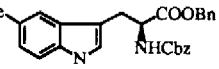
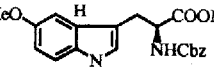
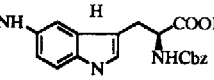
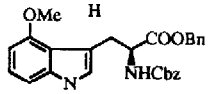
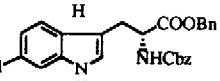
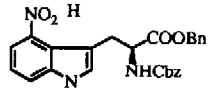
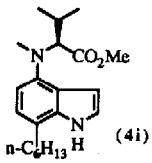
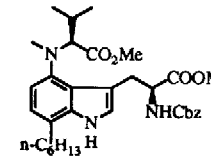
3

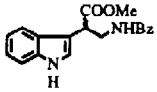
Entry	3	R^1	R^2	R^3	Yield (%)	$[\alpha]_D^{23}$ (MeOH)
1	**3a**	H	CO_2Bn	Cbz	62	-18.8° (*c* 0.785) *lit.*[6,7] -18.1°, -19.0°
2	**3b**	CO_2Bn	H	Cbz	61	+19° (*c* 0.455) *lit.*[7] +20.0°
3	**3c**	H	CO_2Me	Cbz	81	-34.7° (*c* 0.950)
4	**3d**	H	CO_2Me	Boc	74	-68.8° (*c* 0.625)
5	**3e**	H	CO_2Me	Bz	78	-123° (*c* 1.05)

Tri = triphenylmethyl
Bn = benzyl
Bz = benzoyl
Cbz = benzyloxycarbonyl
Boc = *t*-butoxycarbonyl

Table 2. $Zn(OTf)_2$ Induced Amidoethylation Reaction



Entry	4	3	5	Yield(%)[a]	[α]$_D^{23}$(MeOH)[b]
1	H(4a)	3a		44(64)	-8.5° (*c* 0.655) -8.5° (*c* 0.895)[c]
2	4a	3b		33(55)	+8.2° (*c* 0.55)
3	4a	3c		27(41)	-11° (*c* 0.40), *lit.*[8] -11.1 °C
4	4a	3d		30(41)[d]	-4.2° (*c* 0.335) mp. 145-146°C
5	4a	3e		38[e]	-45° (*c* 0.175) amorphous powder *lit.*[9] mp. 108-109 °C
6	5-Me(4b)	3a		46(57)	-7.7° (*c* 0.575)
7	5-OMe(4c)	3c		26(35)	-9.0° (*c* 0.70)
8	4-NHCbz(4d)	3c		15(19)	-6.1° (*c* 0.18)
9	4-OMe(4e)	3a		33(38)	-8.9° (*c* 0.25)
10	6-Cl(4f)	3b		12(36)	+15° (*c* 0.19)
11	4-NO_2(4g)	3a		3(4)	---
12	4-CHO(4h)	3a	no reaction	---	---
13	 (4i)	3c		11(14)[f]	-31° (*c* 0.09)

[a] Yields in parentheses are based on consumed aziridines.
[b] The products were isolated as gums.
[c] An authentic sample was prepared from L-tryptophan benzyl ester.
[d] The reaction temperature was 68 °C.
[e]  (14%) was isolated as a minor product of undetermined stereochemistry.
[f] 4i was treated with 2.5 eq of 3c and 2.5 eq of $Zn(OTf)_2$. Yield in parenthesis is based on consumed 4i.

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