SYNTHESIS OF OPTICALLY ACTIVE β-METHYLTRYPTOPHANS FROM AZIRIDINE-2-CARBOXYLATES[1)]

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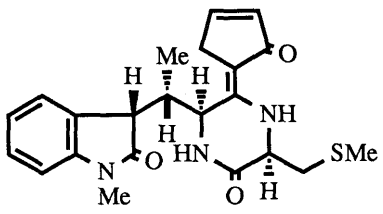
Some (αR,βR)-1,β-dimethyltryptophans (5) were prepared by the reaction of aziridine-2-carboxylates (4), derived from D-threonine, and N-alkylindoles in the presence of $BF_3 \cdot OEt_2$.

KEYWORDS platelet-activating factor(PAF); PAF inhibitor; indole; D-threonine; diketopiperazine; regiospecificity; diastereospecificity

We have recently described the structure of FR900452 (1), a potent PAF (platelet-activating factor) inhibitor isolated from a microorganism.[2)] During investigations aimed at the synthesis of structurally simpler analogues (represented by 2), we have needed a diastereospecific synthesis of (αR,βR)-1,β-dimethyltryptophan 3.[3)] Although reports concerning the synthesis of β-methyltryptophans have appeared,[4)] there has been no practical method for preparing optically active ones. We now report the stereospecific synthesis of optically pure 1,β-dimethyltryptophans by the reaction of indoles and aziridine-2-carboxylates.[5)]

In executing our strategy for preparing (αR,βR)-1,β-dimethyltryptophans, we needed appropriately substituted aziridine intermediates 4a,b, which were prepared from D-threonine according to the method described for L-threonine.[6,7)] Initially we examined the reaction of the Cbz-protected aziridine 4a, with N-methylindole (1 equiv) in the presence of $BF_3 \cdot OEt_2$[8)] (1 equiv) at 0°C for 30 min, which yielded, after alkaline



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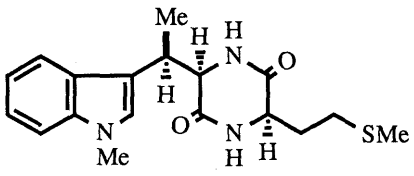

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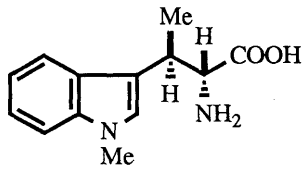

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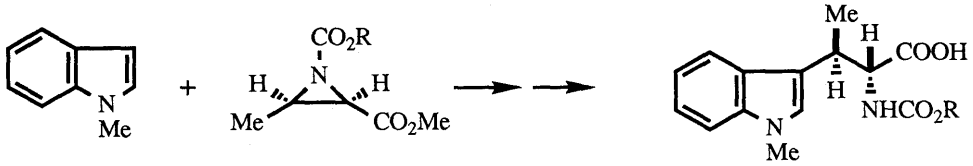

4a R = CH_2Ph
b R = CMe_3

5a R = CH_2Ph
b R = CMe_3

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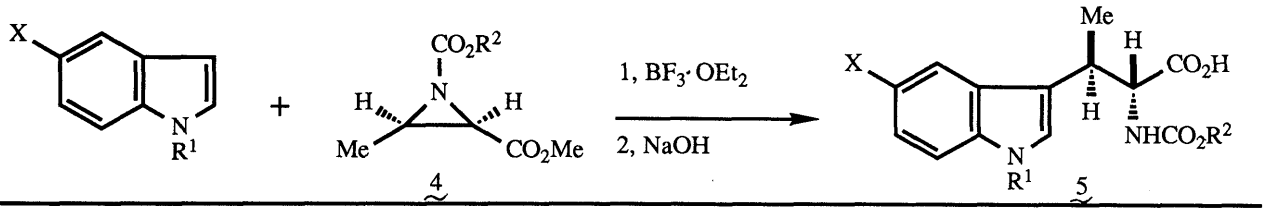
hydrolysis (10% aq NaOH/MeOH, r.t., 2 h), the desired tryptophan derivative 5a (37.1% yield, $[\alpha]_D$ -48.8° (c 1.6,MeOH)). Apparently the reaction occurred via the BF_3 activation of the aziridine ring of 4a, followed by nucleophilic attack of N-methylindole at the β-position of 4a with inversion of the configuration. The best yields (58.5-59.6%) were obtained when aziridine 4a, N-methylindole, and $BF_3 \cdot OEt_2$ were used in a ratio of 1:3:0.5-1 (Table I). Similarly, the Boc-protected aziridine 4b also gave the corresponding Boc derivative 5b of the tryptophan (Table II).[9] To confirm the optical purity, 5b was converted to the free amino acid 3 by deprotection of the Boc group (TFA, r.t., 30 min).[10] The amino acid 3 was identified by comparison with an authentic racemic sample[4] in spectroscopic properties except for melting points and optical rotations, and proved to be optically pure (>95%) on HPLC coupled with a chiral derivatization method using 2,3,4,6,-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate.[11,12] The Boc-protected amino acid 5b also led, by condensation[3] with D-methionine methyl ester, to the diketopiperazine derivative 2, which was identified with the sample prepared previously,[3] which proved to be a single diastereomer. The Cbz-protected amino acid 5a was also converted to 2 (1. methyl methionate/DCC/CH_2Cl_2; 2. H_2/10%Pd-C/MeOH; 3. NH_3/EtOH), which was identical with the sample obtained from 5b.

Thus we have been able to achieve the regio- and stereospecific synthesis of (αR,βR)-1,β-dimethyltryptophan (3). Using this procedure, we also prepared some other tryptophan derivatives with substituents on the indole nucleus under the conditions

Table I. Synthesis of (αR,βR)-N^{α}–Carbobenzyloxy-1,β-Dimethyltryptophan (5a)

Entry	Ratio			Isolation Yield (%)
	4a	N-Methylindole	BF_3 OEt	
1	1	1	1	37.1
2	1	2	1	49.5
3	1	3	1	59.6
4	1	3	0	0
5	1	3	0.5	58.5
6	1	3	2	42.3

Table II. Synthesis of (αR,βR)-β-Methyltryptophan Derivatives (5b-h)



Entry	Compound	X	R^1	R^2	Yield (%)	$[\alpha]_D$ (°)
1	5b	H	Me	CMe_3	60.0	-40.6 (c 2.3, MeOH)
2	5c	H	Et	CH_2Ph	67.4	-39.2 (c 1.0, MeOH)
3	5d	OMe	Me	CH_2Ph	44.2	-54.6 (c 1.0, MeOH)
4	5e	OMe	Me	CMe_3	61.1	-46.8 (c 1.8, MeOH)
5	5f	Me	Me	CH_2Ph	56.3	-38.8 (c 1.9, MeOH)
6	5g	F	Me	CH_2Ph	69.2	-38.8 (c 1.4, MeOH)
7	5h	Cl	Me	CMe_3	52.4	-46.3 (c 1.8, MeOH)

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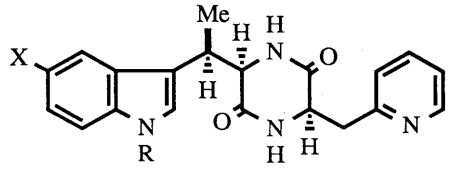
used for the best yield of 5 (entry 3 and 5 in Table I). The results are given in Table II. The stereospecificity in this reaction was ascertained by the fact that the products produced diketopiperazines as single isomers (>95% enantiometric purities) when coupled with a certain amino acid.[13] Details will be reported in due course.

The effect of the present reaction is to replace the hydroxy group of threonine by indoles with complete retention of the enantiometric configurations of threonine. This provides a useful methodology for preparing various optically active β-methyltryptophans.

REFERENCES AND NOTES

1) This work was presented in part at the Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii, Dec. 1987. Symposium Abst. p. 134.
2) S.Takase, N.Shigematsu, I.Shima, I.Uchida, M.Hashimoto, T.Tada, S.Koda, and Y.Morimoto, J. Org. Chem., 52, 3485 (1987).
3) N.Shimazaki, I.Shima, K.Hemmi, and M.Hashimoto, J. Med. Chem., 30, 1706 (1987).
4) S.J.Gould, C.C.Chang, D.S.Darling, J.D.Roberts and M.Squiliacote, J. Am. Chem. Soc., 102, 1707 (1980).
5) A similar synthetic procedure for tryptophan derivatives has appeared: K. Sato and A. P. Kozikowski, Tetrahedron Lett., 30, 4073 (1989).
6) K.Okawa and K.Nakajima, Biopolymers, 20, 1811 (1981); K.Nakajima, M.Neya, S.Yamada and K.Okawa, Bull. Chem. Soc. Jpn., 55, 3049 (1982).
7) Compound 4a, oil, $[\alpha]_D$ 62.5° (c=1.0,MeOH); compound 4b, mp 34-35°C, $[\alpha]_D$ 71.3° (c=1.0,MeOH).
8) The reaction was also effected with $AlCl_3$, $FeCl_3$, $TiCl_4$, $SnCl_4$, $BF_3 \cdot SMe_2$, etc. in place of $BF_3 \cdot OEt_2$, but with less satisfactory results.
9) Selected ^1H NMR data for 5a and 5b. 5a: δ($CDCl_3$) 1.47(3H,d,J=7.5Hz,β-Me), 3.71(3H,s,1-Me), 3.82(1H,m,β-H), 4.67(1H,m,α-H), 5.10(2H,s), 5.25(1H,d,J=9Hz), 6.87(1H,s), 7.05(1H,m), 7.1-7.35(7H,m), 7.66(1H,d,J=8Hz).
5b: δ($CDCl_3$) 1.41(12H,s,β-Me and t-Bu), 3.71(3H,s,1-Me), 3.73(1H,m,β-H), 4.55(1H,m, α-H), 4.98(1H,m), 6.89(1H,s), 7.05(1H,t,J=8Hz), 7.20(2H,m), 7.65(1H,d,J=8Hz).
10) (αR,βR)-1,β-Dimethyltryptophan 3: mp 235-238°C, $[\alpha]_D$ -41.8° (c 0.5, 1N HCl). For data of dl-erythro-β-methyltryptophan, see ref. 3.
11) For the chiral derivation method, see N.Nimura, A.Toyama, and T. Kinoshita, J. Chromatogr. 316, 547 (1984).
12) HPLC conditions: column, Beckman Ultrasphere ODS (5μ) (4.6 x 250 mm); eluent, 0.1% aqueous H_3PO_4-MeOH (1:1); flow rate, 1.5 ml/min: Column temperature, 50°C; detection, UV 254 nm; retention time, compound 3 25.4 min, dl-erythro isomer (αR,βR and αS,βS) 17.1 and 25.4 min, dl-threo isomer (αR,βS and αS,βR) 16.9 and 23.1 min.
13) The N-protected tryptophan derivatives 5 obtained were coupled with ethyl D-β-(2-pyridyl)alanate dihydrochloride (mp 201-203°C; $[\alpha]_D$ -20.5° (c 1.0, MeOH)) to yield the corresponding diketopiperazine derivatives 6: 6a (X=H, R=Me), mp 230-232°C; 6b (X=H, R=Et), mp 237-240°C; 6c (X=OMe, R=Me), mp 220-222°C; 6d (X=R=Me), mp 256-257°C; 6e (X=F, R=Me), mp 242-248°C; 6f (X=Cl, R=Me), mp 229-234°C. Compounds 5a and 5b gave the same diketopiperazine derivative 6a, and 5d and 5e yielded 6c. The preparation of ethyl D-β-(2-pyridyl)alanate dihydrochloride and diketopiperazines 6 will be reported in a forthcoming full paper.



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(Received November 15, 1989)

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