Asymmetric Synthesis of Aziridine-2-carboxylic Acid and the Formation of Chiral Serine

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Summary The alkyl 1-alkylaziridine-2-carboxylates (III) have been asymmetrically synthesized from the alkyl $\alpha\beta$-dibromopropionates (I) and chiral benzylamines (II); optically active serine (V) was obtained by hydration of (III).

SYNTHETIC and stereochemical studies of aziridine-2-carboxylic acids derived from α-bromo-$\alpha\beta$-unsaturated or $\alpha\beta$-dibromocarboxylic acid esters have been reported.[1–5] Aziridine-2-carboxylic acids can be converted into the corresponding α-amino-acids,[2,3,6] and so if an optically active aziridine-2-carboxylic acid[7,8] is synthesized asymmetrically, an optically active amino acid can be obtained.

We describe here the asymmetric synthesis of the alkyl aziridine-carboxylates (III) from the $\alpha\beta$-dibromopropionates (I)† and the chiral benzylamines (II), and the formation of optically active serine (V) by hydration of the aziridine (III), by the route given in the Scheme.

The $\alpha\beta$-dibromopropionates (I) (3 mmol) in ethanol (25 ml) and the chiral benzylamine (II) (3 mmol) in triethylamine (9 mmol) were mixed at -25 to -20 °C and kept at this temperature for 24 h. Silica gel chromato-

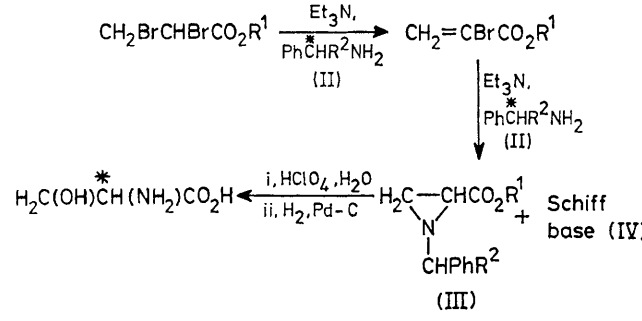
† The $\alpha\beta$-dibromopropionate is easily converted into the α-bromoacrylate in the presence of base, and so the asymmetric synthesis is equivalent to a synthesis starting from the α-bromoacrylate.

TABLE. Formation of chiral serine from asymmetrically synthesized aziridinecarboxylic acids.

R^1 in (I)	Confign. and R^2 of (II)[a]	Yield[b], %	Confign. of Ser.	$[\alpha]_D^{25}$ of isolated Ser. (*c* in 1 M HCl)	Optical purity[c], %	DNP-Ser $[\alpha_D^{25}]$ (*c* in 4% $NaHCO_3$)	Optical purity, %
Me	*R*(+)–Me	32	*S*	+4·0 (1.40)	28	+36·6 (0·42)	29
Me	*S*(−)–Me	35	*R*	−3·9 (1·26)	27	−35·1 (0·40)	28
Et	*R*(+)–Me	43	*S*	+4·2 (1·10)	29	+37·0 (0·63)	29
Et	*S*(−)–Me	39	*R*	−3·7 (1·54)	26	−34·9 (0·48)	28
Pr^i	*R*(+)–Me	71	*S*	+4·8 (1·98)	33	+41·7 (0·98)	33
Pr^i	*S*(−)–Me	69	*R*	−5·3 (1·69)	37	−47·9 (0·45)	38
Pr^i	*R*(+)–Et	65	*S*	+3·7 (1·75)	25	+42·9 (0·78)	34
Pr^i	*S*(−)–Et	67	*R*	−3·9 (1·25)	27	−41·8 (0·86)	33
Bu^t	*R*(+)–Me	53	*S*	+5·5 (1·42)	38	+49·2 (0·64)	39
Bu^t	*S*(−)–Me	50	*R*	−5·3 (1·58)	37	−46·6 (0·40)	37

[a] *R*(+)–Me: *R*(+)-α-methylbenzylamine, $[\alpha]_D^{25}$ + 39·0° neat; *S*(−)–Me: *S*(−)-α-methylbenzylamine, $[\alpha]_D$ −39·0° neat; *R*(+)–Et: *R*(+)-α-ethylbenzylamine, $[\alpha]_D^{25}$ + 21·5° in benzene; *S*(−)–Et: *S*(−)-α-ethylbenzylamine, $[\alpha]$ −21·0° in benzene. The methyl compounds were obtained from Aldrich Chemical Co. Inc., and the ethyl derivatives by a literature method: A. J. Little, J. M'Leau, and F. J. Wilson, *J. Chem. Soc.*, 1940, 337. [b] Based on the αβ-dibromopropionate (I). [c] Based on the maximum rotation: ±14·5° (1 M HCl). [d] Based on the maximum rotation: ±125·8° (4% $NaHCO_3$).

graphy using benzene–ether (1:1) as eluant gave the aziridine (III) and its Schiff base (IV), in a ratio in the range 4:6 to 8:2 depending on the alkyl group of the ester. The separated diastereoisomeric mixture (III) was oily, and did not crystallize. The structure of (III) was confirmed by i.r. and n.m.r. analyses.‡ The diastereoisomeric mixture (III) was hydrated with 20% perchloric acid at 80 °C for 30 h. The resulting *N*-alkylserine was isolated by use of a Dowex 50 column and was hydrogenolysed in aqueous ethanol (1:1 v/v) with palladium hydroxide on charcoal at room temperature for 24 h under hydrogen (1 atm). The product was chromatographed on Dowex 1 and 50 columns in the usual way to purify the optically active serine (V) without fractionation of optical isomers. A part of (V) was treated with 1-fluoro-2,4-dinitrobenzene, and the resulting dinitrophenyl-serine stereoisomers were separated by Celite column chromatography.[9] Yields and optical purities are summarized in the Table. The yields of optically active (V) are in the range 31—71% from (I), with optical purities in range 28—39% depending on the bulk of the alkyl group in the ester (I). Only small differences in the optical purities of (V) are observed when chiral α-methylbenzylamine is replaced by chiral α-ethylbenzylamine.



SCHEME. R^1 = Me, Et, Pr^i or Bu^t; R^2 = Me or Et.

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‡ The n.m.r. spectrum of (III) is complex, since it is a mixture of unequal amounts of diastereoisomers. For n.m.r. analysis of the structure of (III), compound (III) was prepared from racemic α-methylbenzylamine and its n.m.r. spectrum was analysed: δ ($CDCl_3$) 1·26 (d, 3H, CHMe), 1·43—2·14 (AB_2 type, 3H, ring proton), 2·34 (q, 1H, CHMe), 3·49 (s, 3H, CO_2Me), and 7·0—7·38 (m, 5H, ArH).

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