Asymmetric Synthesis of α-Amino-acid Derivatives by Alkylation of a Chiral Schiff Base

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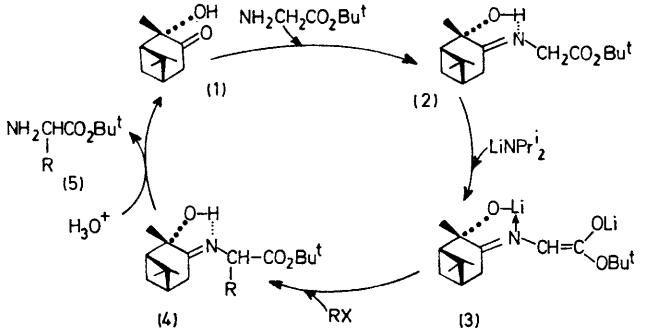
Summary An efficient asymmetric synthesis of D-α-amino-acid derivatives has been achieved by alkylation of a Schiff base prepared from glycine t-butyl ester and (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one.

ALTHOUGH numerous attempts to achieve the asymmetric synthesis of α-amino-acids have been reported,[1] very few[2] have a practical value and satisfy the following criteria: (i) good asymmetric and material yields, (ii) catalytic processes or recycle of the chiral reagents, and (iii) simplicity. We report the asymmetric synthesis of α-amino-acid derivatives by asymmetric alkylation of the carbanion (**3**) produced from the chiral Schiff base (**2**), which may satisfy these criteria.

Condensation of glycine t-butyl ester with (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one (**1**),[3] m.p. 31—32 °C, $[\alpha]_D^{25}$ − 38·9° (*c* 2·64, $CHCl_3$),† prepared from (+)-α-pinene, in the presence of BF_3–Et_2O in benzene furnished the required chiral Schiff base (**2**), b.p. 125—130 °C at 10^{-1} Torr, in 83% yield. Its i.r. spectrum showed the presence of an intramolecular hydrogen bond (3542 cm^{-1} in CCl_4). Lithiation of the Schiff base (**2**) with 2 equiv. of lithium di-isopropylamide[4] in tetrahydrofuran gave the dilithio salt, which can probably be formulated as (**3**).[5] Treatment of (**3**) with methyl iodide afforded the monomethylated Schiff base (**4a**). Hydrolysis with 15% aqueous citric acid in tetrahydrofuran gave alanine t-butyl ester (**5a**), which was directly treated with hydrogen chloride to produce alanine hydrochloride in an overall yield of 52%. Benzoylation of alanine t-butyl ester with benzoyl chloride–pyridine afforded benzoyl-D-alanine t-butyl ester, m.p. 62—67 °C, $[\alpha]_D^{25}$ − 32·3° (*c* 1·04, $CHCl_3$), the optical purity of which was 83% based on the specific rotation of optically pure benzoyl-L-alanine t-butyl ester, $[\alpha]_D^{25}$ + 38·9° (*c* 1·06, $CHCl_3$), prepared by benzoylation of L-alanine t-butyl ester. The ketol (**1**) was also recovered after hydrolysis with citric acid, in 75% yield without loss of optical purity, and hence may be used directly again.



SCHEME

Similar treatment of the dilithio salt (**3**) with isobutyl iodide, benzyl bromide, and 3,4-dimethoxybenzyl bromide, respectively, using hexamethylphosphoric triamide as a cosolvent[4] afforded the corresponding monoalkylated Schiff bases (**4b—d**). Hydrolysis of the isobutylated Schiff base (**4b**) with aqueous citric acid followed by benzoylation yielded benzoyl-D-leucine t-butyl ester with 83% optical purity in 50% overall yield. The aromatic D-amino-acid t-butyl esters (**5c—d**) were obtained by treatment of the Schiff bases (**4c—d**) with hydroxylamine acetate in ethanol since cleavage with aqueous citric acid was slow. The ketol (**1**) was recovered as its ketoxime, m.p. 115—116 °C. The results are summarized in the Table. Interestingly none of dialkylated products were obtained in any case even when an excess of alkylating agents was used.

TABLE

	Alkylating agent, RX	Product	Overall yield (%)[a]	Optical yield (%)[b]
a	MeI	H-D-Ala-OH·HCl	52[c]	83[c]
b	Bu^tI	Bz-D-Leu-OBu^t	50	83[d]
c	$PhCH_2Br$	H-D-Phe-OBu^t	79	72
d	3-4-$(MeO)_2$-$PhCH_2Br$	H-D-3,4-$(MeO)_2$-Phe-OBu^t	62	66[e]

[a] Based on (**2**). [b] Based on products purified, without attempted resolution, by use of a silica gel column. [c] See text. [d] Based on the specific rotation of optically pure Bz-L-Leu-OBu^t, m.p. 99—100 °C, $[\alpha]_D^{25}$ + 26·2° (*c* 1·15, $CHCl_3$), prepared by benzoylation of H-L-Leu-OBu^t. [e] The t-butyl ester (**5d**) was further converted into its *N*-acetyl derivative, $[\alpha]_D^{25}$ − 44·3° (*c* 1·24, $CHCl_3$). The optical purity of the latter was 66% based on the specific rotation of optically pure Ac-L-3,4-$(MeO)_2$Phe-OBu^t, m.p. 79·5—81 °C, $[\alpha]_D^{25}$ + 67·6° (*c* 1·24, $CHCl_3$), prepared from *N*-formyl-L-3,4-$(MeO)_2$Phe-OH[6] by successive treatment with 10% aqueous HCl, 10% aqueous NH_3, Ac_2O, and isobutene.

These preliminary results demonstrate an efficient and general approach to α-amino-acids of high optical purity. The method may allow the asymmetric synthesis of both D- and L-isomers, because α-pinene, and consequently the ketol (**1**), is available from natural sources in both optically active forms.

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† Prepared by permanganate oxidation of (+)-α-pinene, $[\alpha]_D^{20}$ + 47·5° (neat), 93% optical purity, by the procedure in ref. 3, and recrystallised four times from n-pentane. The optical purity of the ketol (**1**) was estimated to be > 97% based on the specific rotation of chromatographically purified, non-recrystallised material. However, M. Delépine, A. Horeau, and M. Grandperrin-Harispe, *Ann. Chim.* (*France*), 1943, **18**, 250 reported the preparation of the ketol (**1**) with $[\alpha]_D$ − 41·2° (*c* 0·04, $CHCl_3$) from (+)-α-pinene, $[\alpha]_D$ +45·9° (neat).

[1] J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions,' Prentice-Hall, Englewood Cliffs, New Jersey, 1971, Ch. 7; J. W. Scott and D. Valentine, Jr., *Science*, 1974, **184**, 943.
[2] E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Amer. Chem. Soc.*, 1970, **92**, 2476; E. J. Corey, H. S. Sachdev, J. Z. Gougoutas, and W. Saenger, *ibid.*, p. 2488; W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *ibid.*, 1975, **97**, 2567; W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *Chem. Technol.*, 1972, **2**, 590.
[3] R. G. Carlson and J. K. Pierce, *J. Org. Chem.*, 1971, **36**, 2319.
[4] *Cf.* S. Yamada, T. Oguri, and T. Shioiri, *J.C.S. Chem. Comm.*, 1972, 623; T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (*Japan*), 1975, **23**, 167, 173.
[5] *Cf.* M. W. Rathke and D. F. Sullivan, *J. Amer. Chem. Soc.*, 1973, **95**, 3050.
[6] A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.*, 1957, **79**, 3827.