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DIASTEREOSELECTIVE SYNTHESIS OF α-AMINO-β-HYDROXYACIDS[1]

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Summary: *threo*-α-Dibenzylamino-β-hydroxyesters (**2**) have been synthesised with high diastereoselectivity through the $NaBH_4$ reduction of α-dibenzylamino-β-oxoesters (**4**) and then tranformed into *threo*-α-amino-β-hydroxyacids.

α-Amino-β-hydroxyacids are derivatives of primary importance both as enzymatic inhibitors,[2] and as starting material for β-lactam antibiotics synthesis.[3] Although some stereoselective syntheses of these compounds have been described,[2,4] the preparation of the *threo*[5] isomers still appears to be troublesome.

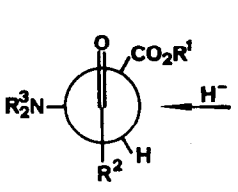
We have now prepared a series of α-amino-β-hydroxyacids using methyl- or *t*-butyl-*N*,*N*-dibenzylglycinate (**1a,b**) as starting material. Both the condensation of lithium enolates derived from (**1a,b**) with aldehydes (method A) and the acylation of the same enolates followed by $NaBH_4$ reduction of the resulting β-oxoesters (**4**) (method B), gave α-dibenzylamino-β-hydroxyesters (**2**) and (**3**) in good yield (see Scheme 1).[6] However, the acylation-reduction procedure appeared to be much more stereoselective affording *threo* compounds (**2**) with d.e. up to ≥98%. Stereochemical results are listed in the Table.[7]

In a typical procedure for method B a solution of the lithium enolate derived from (**1**) (LDA, THF, -60°C) was added to a THF solution of the appropriate acyl chloride (-60°C) to afford oxoesters (**4**) in yields ranging from 60 to 90%. The reduction was thence carried out in aqueous EtOH[9] buffered with an excess of NH_4Cl, by addition of an excess of $NaBH_4$. It is interesting to note that in the absence of NH_4Cl the reaction did not occur.[10]

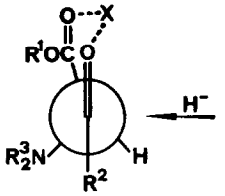
While for methyl esters (**4a**) the reaction was in every case complete, *t*-butyl esters (**4b**) could be reduced only in part, and, for R^2 = *t*-Bu, the reaction did not take place at all. In these cases, probably because of steric inhibition, the rate of reduction was lower and $NaBH_4$ decomposition became competitive.

The stereochemical course of the reaction is in agreement either with a Felkin model

(figure I) or with a Cram cyclic model in which an electrophile (X)[11] is chelated by the carbonyl and carboxyl oxygens (figure II).[13]



I



II

R^3 = $PhCH_2$

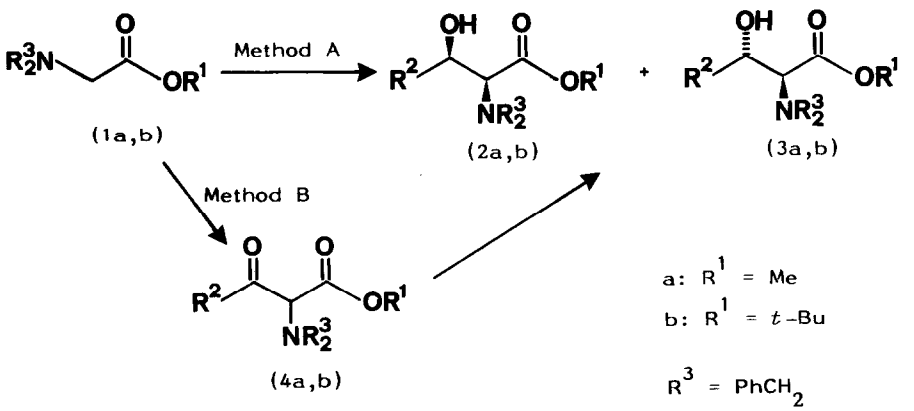
The relative configuration of (2) for R^2 = Me and Ph was unambiguously established by their conversion into *d,l*-threonine and *d,l*-phenylserine respectively (*vide infra*). The other products were correlated to these by t.l.c. comparisons (*n*-hexane-diethyl ether) and by means of ^1H and ^{13}C n.m.r. spectra.

α-Dibenzylamino-β-hydroxyesters (2) and (3) were then transformed into corresponding acids (5) by acid hydrolysis (CF_3COOH, 0°C, 70%) for (**2b**) and (**3b**), and mild saponification (0.5 N KOH, MeOH-H_2O 7:3, 85%) for (**2a**) and (**3a**) (see Scheme 2). In no instance was epimerisation detected by t.l.c. and ^1H n.m.r.. The mildness of these two complementary ester hydrolyses enable the present methodology to be used for a wide range of compounds.

Finally the deprotection of the amino moiety was easily obtained by catalytic hydrogenation[16] (H_2, Pd/C, 95% EtOH, 70°C, 90%) to give α-amino-β-hydroxyacids (6).

In summary, the acylation-reduction method here reported represents a new synthetic pathway for achieving 90-100% diastereomerically pure *threo*-α-amino-β-hydroxyacids starting from easily accessible substrates. Further application of *N,N*-dibenzylglycinates to the diastereo- and enantioselective synthesis of polyfunctionalised compounds of biological interest are being developed in our laboratory.

Scheme 1



Scheme 2

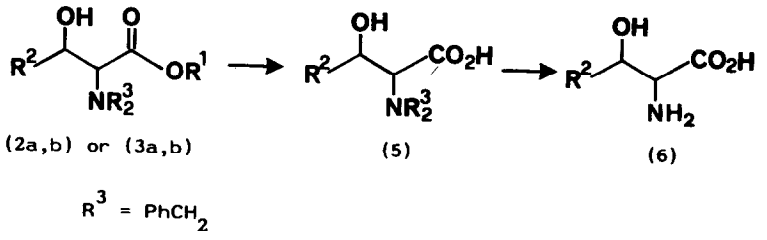


Table. *Stereoselective synthesis of α-dibenzylamino-β-hydroxyesters (2) and (3)*

Entry	R^2	R^1	*via* reduction of β-oxoesters		*via* aldol condensation[a]	
			yield[b] (%)	*threo*:*erythro*[c]	yield[b] (%)	*threo*:*erythro*[c]
1	Me	Me	81	93: 7	89	57:43
2		*t*-Bu	50	89:11	91	60:40
3	Ph	Me	70	⩾99: 1	75	46:54
4		*t*-Bu	57	⩾99: 1	74	18:82
5	*n*-C_6H_{13}	Me	75	96: 4	80	71:29
6		*t*-Bu	52	89:11	86	46:54
7		Me	80	95: 5	78	21:79
8		*t*-Bu	35	90:10	77	16:84
9	*t*-Bu	Me	83	⩾99: 1	65	31:69
10		*t*-Bu	-	-	56	20:80

[a]Aldehydes were added at -60°C to a solution of lithium enolate derived from (1) (LDA, THF, -60°C). [b]After chromatography. [c]Determined by ^1H n.m.r. or standardised spectrodensitometry (254 nm).

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References and Notes

1. Dedicated to Prof. Giuseppe Leandri on the occasion of his 70th birthday.
2. T. Nakatsuka, T. Miwa, and T. Mukaiyama, *Chem. Lett.*, 1981, 279; 1982, 145.
3. P.G. Mattingly and M.J. Miller, *J. Org. Chem.*, 1983, **48**, 3556 and references therein.
4. A. Shanzer, L. Somekh, and D. Butina, *J. Org. Chem.*, 1979, **44**, 3967.
5. We name as *threo* the isomer with the same relative configuration as that of threonine.
6. Here only one enantiomeric form is arbitrarily shown although racemates were obtained.
7. Also the Mukaiyama reaction (ref. 8) between the trimethylsilyl ketene acetal derived from (**1a**) and acetaldehyde catalysed by $TiCl_4$ or BF_3 Et_2O was tested. In both cases low stereoselectivities were observed.
8. T.H. Chan, T. Aida, P.K.W. Lau, V. Gorys, and D.N. Harpp, *Tetrahedron Lett.*, 1979, 4029.
9. 70% (for R^1 = Me) or 95% (for R^1 = *t*-Bu) aqueous EtOH.
10. S.H. Pines, S. Karady, and M. Sletzinger, *J. Org. Chem.*, 1968, **33**, 1758.
11. This can be the sodium ion (see ref. 12) or the ammonium ion (through two hydrogen bonds).
12. R.S. Glass, D.R. Deardorff, and H. Henegar, *Tetrahedron Lett.*, 1980, 2467.
13. Although previous examples of reduction of α-amino- or α-acetylamino-β-oxoesters are known (see ref. 14), they generally show a preference for the *erythro* isomer. It seemed likely that a crucial role in these reductions had to be played by the size of the protective groups on the nitrogen atom. We argued that a bulky group like dibenzylamino would have favoured the formation of the *threo* isomers i) by a higher discrimination between the amino ("large") and the carboxyl ("medium") groups in I; ii) by a larger differentiation between the two sides of attack in II; iii) by preventing the effectiveness of a Cram cyclic model involving chelation by the amino group (see ref. 15).
14. M. Suzuki, T. Iwasaki, K. Matsumoto, and K. Okumura, *Chem. & Ind.*, 1973, 228; W.A. Bolhofer, *J. Amer. Chem. Soc.*, 1952, **74**, 5459; see also ref. 9.
15. M. Tramontini, *Synthesis*, 1982, 605.
16. L. Velluz, G. Amiard, and R. Heymés, *Bulletin Soc. Chim. France*, 1955, 201.

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