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A HIGHLY EFFECTIVE ASYMMETRIC SYNTHESIS OF α-HYDROXY ACIDS BY ALKYLATION OF CHIRAL N-(BENZYLOXYACETYL)-TRANS-2,5-BIS(METHOXYMETHOXYMETHYL)PYRROLIDINE

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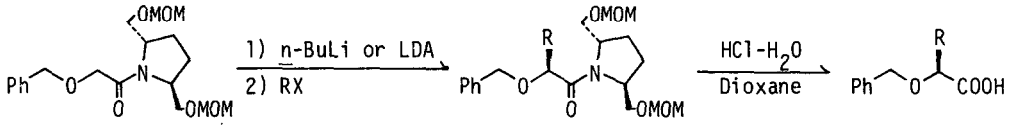
Summary: Alkylation of lithiated N-(benzyloxyacetyl)-trans-2,5-bis(methoxymethoxymethyl)-pyrrolidine proceeded with high stereoselectivity (≥96% de) and subsequent transformations of the alkylated products gave synthetically useful α-benzyloxy acids or α-hydroxy acids of high enantiomeric purity.

α-Hydroxy acids which exist mostly in chiral forms, not only constitute an important class of biological substances but also serve as convenient building blocks for the synthesis of natural products. Asymmetric synthesis of the compounds has, thus, attracted considerable attention and methods of increasing effectiveness have been published in the last few years.[1] Recently, we developed a chiral auxiliary, trans-2,5-bis(methoxymethoxymethyl)pyrrolidine, which was quite useful for α-alkylation,[2] α-acylation,[3] and aldolization[4] of the corresponding amide enolates derived from simple carboxylic acids. Here, we wish to describe a general and very effective asymmetric synthesis of α-hydroxy acids by using the same auxiliary through diastereoselective alkylation of its N-(benzyloxyacetyl) derivative (**1**), giving the highest de values so far reported in the asymmetric alkylation of glycolic acid derivatives.[1a]

The amide (**1**)[5] was lithiated in THF with n-BuLi[6] (1.6 mol dm^{-3} in hexane, 1.05 eq, at -78°C) or with LDA (0.7 mol dm^{-3} in THF, 1.05 eq, at -78°C and then at -20°C), and the alkylating agent (1.1 eq) was added to this at -78°C. Methyl iodide or benzyl bromide reacted smoothly, but other primary iodides required the elevation of temperature to -20°C for the completion of the reaction. While the alkylation with isopropyl iodide did not proceed, isopropyl triflate[7] gave the alkylated product in high yield. Hydrolysis of the alkylated amides (**2**) to the acids (**3**) was carried out without detectable racemization by refluxing them in a mixture (1:1) of aqueous HCl (1 mol dm^{-3}) and dioxane for 4 h,[8] followed by neutralization with saturated aqueous $NaHCO_3$ at rt. These results are summerized in Table 1. Configurations at the α-carbon atoms determined appropriately on some of the products, showed that the (2S,5S)-auxiliary gave (S)-products predominantly and that the asymmetric induction occurred in the same sense as observed in the alkylation and acylation previously reported.[2,3] Thus, the good overall yield, the excellent enantiomeric purity, and the predictable stereochemistry of the products are the most attractive features of the present method and it is considered to provide a useful tool for the synthesis of optically active α-hydroxy acids of various types.

The N-(phenoxyacetyl) analogue gave a reduced selectivity (90% de) in methylation and the N-(t-butyldimethylsiloxyacetyl) analogue gave a surprisingly low de (35%). It is noteworthy that without the protection of the α-hydroxyl group, á selectivity of 90% de was attained in the methylation of the corresponding enediolate (use of 2.1 eq of LDA).



1 2 3

Table 1. Asymmetric Alkylation of (2S,5S)-1 in THF and Subsequent Hydrolysis

Entry	RX	Base	Reaction Temp.(°C)	Alkylated Amide (2)[a] Yield(%)	$[\alpha]_D$ (EtOH)	%de[c]	Hydrolyzed Product (3)[b] Yield(%)[d]	$[\alpha]_D$ (EtOH)	Config.
1	CH_3I	n-BuLi	-78	92	-95° c=4.43	97	88	-86° c=0.96	S[e)f)]
2	$PhCH_2Br$	n-BuLi	-78	91	-38° c=5.45	98	89	-81° c=2.24	S[f)]
3	C_4H_9I	n-BuLi	-78～-20	77	-79° c=4.29	96	83	-73° c=1.19	S[f)]
4	$C_8H_{17}I$	LDA	-78～-20	72	-70° c=0.54	96	73	-55° c=0.41	(S)
5	$PhCH_2O(CH_2)_6I$	LDA	-78～-20	65	-58° c=1.32	96[g)]	84	-46° c=1.30	(S)
6	$(CH_3)_2CHI$	LDA	-78～-20	trace					
7	$(CH_3)_2CHOTf$	LDA	-20	76	-63° c=0.95	97	65	-74° c=1.01	S[f)]

a) All the new compounds gave satisfactory ^1H NMR and elementary analyses. b) Epimerization was not detected by ^1H NMR examination (90 MHz instrument, S/N～100/1) of the corresponding methyl ester (CH_2N_2) in C_6D_6 under the presence of a chiral shift reagent, Eu(hfc)$_3$. c) Diastereomeric ratios were determined from intensities of relevant ^1H NMR signals. d) Yield based on the alkylated amide (2). e) $[\alpha]_D$ of the (S)-enantiomer has been reported to be -92° without specification of the solvent: H.Ott, A.J.Frey, and A.Hofmann, Tetrahedron, **19**, 1675 (1963). f) Configuration was determined from the sign of optical rotation after debenzylation (H_2/Pd on C in EtOH, quantitative) to the corresponding hydroxy acid, by comparison with authentic data: M.Winitz, L.B.Frankenthal, N.Izumiya, S.M.Birnbaum, C.G.Baker, and G.P.Greenstein, J. Am. Chem. Soc., **78**, 2423 (1956). g) The ratio was deduced from the optical purity [^1H NMR, Eu(hfc)$_3$] of the corresponding methyl ester, after successive hydrolysis and esterification.

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References and Notes

1) a) K.A.Lutomski and A.I.Meyers, in "Asymmetric Synthesis," ed by J.D.Morrison, John Wiley and Sons, New York (1984), Vol. 3, p. 213; T.R.Keily and A.Arvanitis, Tetrahedron Lett., **25**, 39 (1984); G.Helmchen, and R.Wierzchowski, Angew. Chem. Int. Ed. Engl., **23**, 60 (1984). b) J.W.Apsimon and R.P.Segiom, Tetrahedron, **35**, 2797 (1979); A.Ohno, M.Ikeguchi, T.Kimura, and S.Oka, J. Chem. Soc., Chem. Commun., **1978**, 328; J.K.Whitesell, Abhattacharya, D.A.Aguilar, and K.Henke, ibid., **1982**, 989; M.M.Midland and P.E.Lee, J. Org. Chem., **46**, 3933 (1981); J.D.Elliot, V.M.F.Choi and W.S.Johnson, ibid., **48**, 2294 (1983). 2) Y.Kawanami, Y.Ito, T.Kitagawa, Y.Taniguchi, T.Katsuki, and M.Yamaguchi, Tetrahedron Lett., **25**, 857 (1984). 3) Y.Ito, T.Katsuki, and M.Yamaguchi, Tetrahedron Lett., in press. 4) T.Katsuki and M.Yamaguchi, in preparation. 5) The amide (**1**) was prepared by stirring (2S,5S)-trans-bis-(methoxymethoxymethyl)pyrrolidine and mixed benzyloxyacetic pivalic anhydride (formed in situ from benzyloxyacetic acid, pivaloyl chloride, and Et_3N in CH_2Cl_2 at 0°C) in CH_2Cl_2 in the presence of Et_3N and a catalytic amount of 4-dimethylaminopyridine at 0°C～rt; yield 79%, $[\alpha]_D^{19}$ -48.9° c=10.0 (EtOH). Benzyloxyacetic acid was conveniently prepared by refluxing bromoacetic acid and NaH (2 equiv.) in benzyl alcohol for 4 h. [cf. H.O.L.Fischer, and B.Gohlke, Helv. Chim. Acta, **16**, 1130 (1933).] 6) In cases where n-BuLi was used as a base, a small amount (<7%) of 1-benzyloxy-2-hexanone was formed as a by-product. A partial attack of n-BuLi on the amide carbonyl seems to have occurred during the enolate formation step. 7) A pentane solution was prepared according to the reported method [C.D.Beard, K.Baum, and V.Grakauskas, J. Org. Chem., **38**, 3673 (1973)] using pentane as a solvent. 8) A partial debenzylation (ca 50%) occurred when the methylated product was treated with aqueous HCl (1 mol dm^{-3}) at 100°C for 4 h.

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