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SYNTHESIS VIA OXAZOLINES. VI. AN ASYMMETRIC SYNTHESIS OF β-HYDROXY AND β-METHOXY ALKANOIC ACIDS

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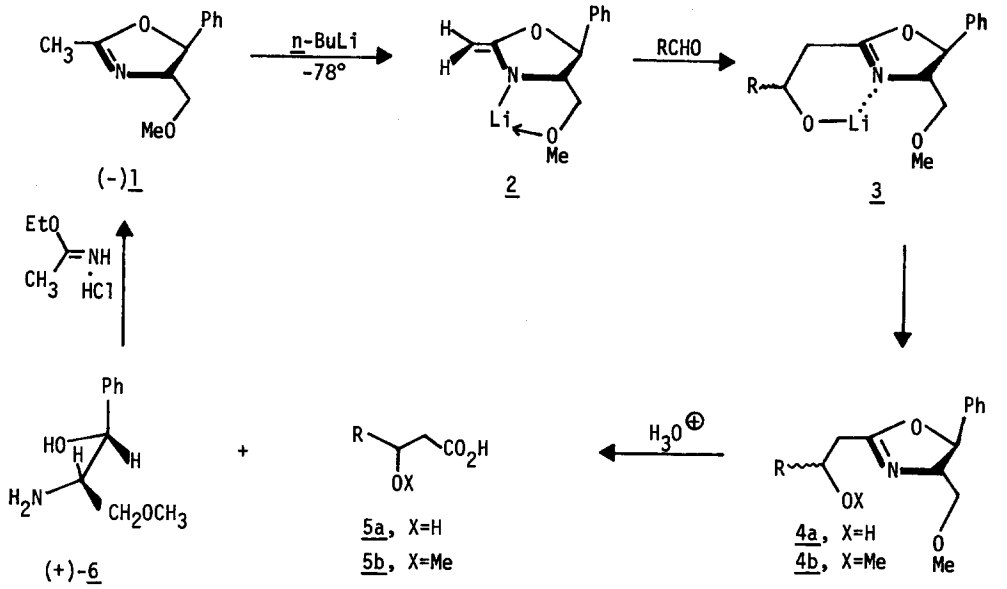
The recently reported asymmetric synthesis of α-methyl alkanoic acids utilizing chiral non-racemic oxazolines[1] has prompted further studies in an effort to evaluate their full synthetic potential. The 2-methyl oxazoline 1[2] was readily obtained from commercially available 1S,2S-(+)-1-phenyl-2-amino-1,3-propane diol 6[3] and the ethyl imidate hydrochloride of acetonitrile[4] by stirring in dichloromethane (0°, 6h), followed by ether formation using sodium hydride-methyl iodide. Treatment of 1 with 1.0 equiv of n-butyllithium (THF, -78°) produced, after a few minutes, a yellow suspension, which is presumed to be the lithio salt 2.[1] Addition of a series of aldehydes gave rapid and efficient alkylated oxazoline adducts 3 which were either quenched in water to the hydroxyalkyl oxazoline 4a or treated with methyl iodide in hexamethyl phosphoramide prior to aqueous quenching to produce the methoxy derivatives 4b. In either case, the alkylation yields were very high (Table 1). Aqueous acidic hydrolysis (3N HCl, 2-4 h, 95°) of the crude oxazolines gave the β-hydroxy acids 5a or the β-methoxy acids 5b respectively in 31-87% overall yields. As in the earlier study,[1] the amino alcohol 6 was recovered completely active and may be recycled to the starting material (-) 1.

Although there have been a variety of studies in which chiral esters and bromoesters have been employed to prepare β-hydroxy acids and esters, these have only been performed successfully on phenyl ketones and benzaldehydes.[5] In fact, the only study which included aliphatic aldehydes resulted in virtually racemic β-hydroxy acids using menthyl esters of α-bromoacetic acid.[6] When



the oxazoline 1 was treated with benzaldehyde, the alkylation proceeded to 4a (R=Ph, X=H) in high yield, however, the acidic hydrolysis resulted in dehydration to cinnamic acid. Similarly, the methoxy oxazoline 4b (R=Ph, X=Me) gave only cinnamic acid upon acidic treatment. Thus, the present technique precludes the use of benzaldehydes (or phenyl ketones) as a route to β-aryl-β-hydroxy acids due to their facile dehydration during the acidic hydrolysis.

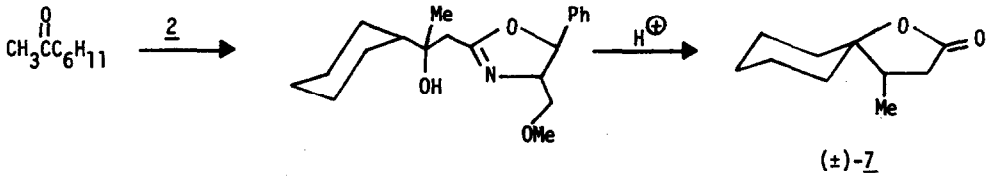
Of the chiral acids 5a and 5b prepared, only the butanoic acid (5a, 5b R=Me) has been reported.[7] It was felt that the use of a chiral shift reagent would provide the enantiomeric excess of the hydroxy acids prepared. A survey of a variety of commercially available shift reagents failed to resolve the hydroxy acids to any meaningful degree. On the other hand, the methoxy acids responded clearly to "Eu-Optishift II" (Table 1, footnote d) and cleanly separated the OMe singlet into two distinct peaks. From this it was feasible to determine the percent enantiomeric excess (18-25%). This determination was rendered valid by also preparing the racemic methoxy acids (using an achiral oxazoline[8]) and observing virtually equal peaks for the OMe group. Since the asymmetric center in 3 would not be expected to be involved in the

Table 1. Reaction of Aldehydes with (-)-1

	β-Hydroxy Acids[a]			β-Methoxy Acids[a]			
R-CHO	%4a	%5a	$[\alpha]_{589}^{25}$(c, $CHCl_3$)	%4b	%5b	$[\alpha]_{589}^{25}$(c,$CHCl_3$)	% enantiomeric excess[d]
Me	92	40	-8.4°(5.0)	88	31	-1.02(neat)	20±2
Et	78	44	-6.6°(11.1)	82	62	-0.89(15.8)	18±2
t-Bu	99	87[b]	-11.6°(12.3)	99	77[c]	-4.3(14.5) -5.0(neat)	25±2
n-Hex	88	54[e]	+3.3°(12.9)	--			
Cyclohexyl	99	48	-2.4°(15.2)	--			
Ph	99	82(cinnamic acid)		94	79(cinnamic acid)		

a) Distilled to dryness to avoid enantiomeric enrichment; b) mp 82°-84°; c) Contained 5-6% α,β-unsaturated acid; d) Determined in $CDCl_3$ using Eu-Optishift II (tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium III; purchased from Willow Brook Laboratories, P. O. Box 526, Waukesha, Wisconsin 53186; e) mp 58°-59°.

methylation to 4b, it is safe to assume that the β-hydroxy acids are also formed in 18-25% enantiomeric excess. The inherent reliability of enantiomeric composition using the shift reagents suggests that the reported value of -11.6° for 3-methoxybutanoic acid (-1.02° observed in this study) is probably too high.[7] Several ketones (2-butanone and acetyl cyclohexane) were also examined in the reaction with (-)1. The β-hydroxy acid derived from 2-butanone was essentially racemic ([α] = +0.05°) while the acetyl cyclohexane gave, upon hydrolysis, the racemic lactone 7.[9] The latter undoubtedly arose from a methyl shift during the acidic hydrolysis in a non-stereoselective manner. Additional synthetic studies involving the chiral oxazolines are presented in the accompanying letters.



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9. Oil, 71%, ir (film) 1740 cm^{-1}, nmr ($CDCl_3$) δ 2.87-2.13 (m, 3), 2.00-0.80 (m, 10), 1.07 (d, J=6.8 Hz, 3).
Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.60.