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AN ASYMMETRIC SYNTHESIS OF 5-METHOXY-3-SUBSTITUTED ACIDS AND THEIR RELATED LACTONES IN HIGH ENANTIOMERIC PURITY

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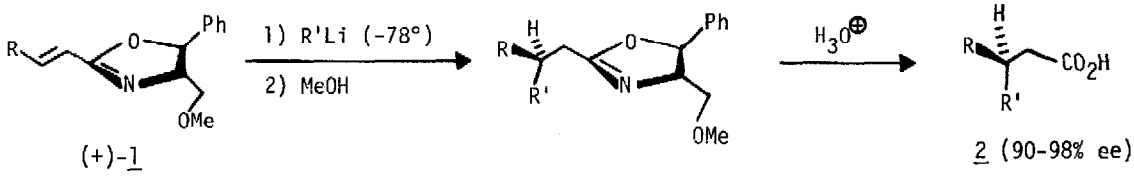
As part of a general program on developing efficient asymmetric syntheses of a variety of functionalized organic compounds, we recently reported that 1,4-addition of organolithium reagents to chiral alkenyl oxazolines 1 leads to 3-substituted acids 2 in high enantiomeric purity.[1] This method allows the preparation of either optical antipode, in predictable fashion, by merely reversing the order of introduction of R and R'. We now report that further studies have led to chiral ω-methoxy-β-substituted acids which were readily transformed into chiral valerolactones. The

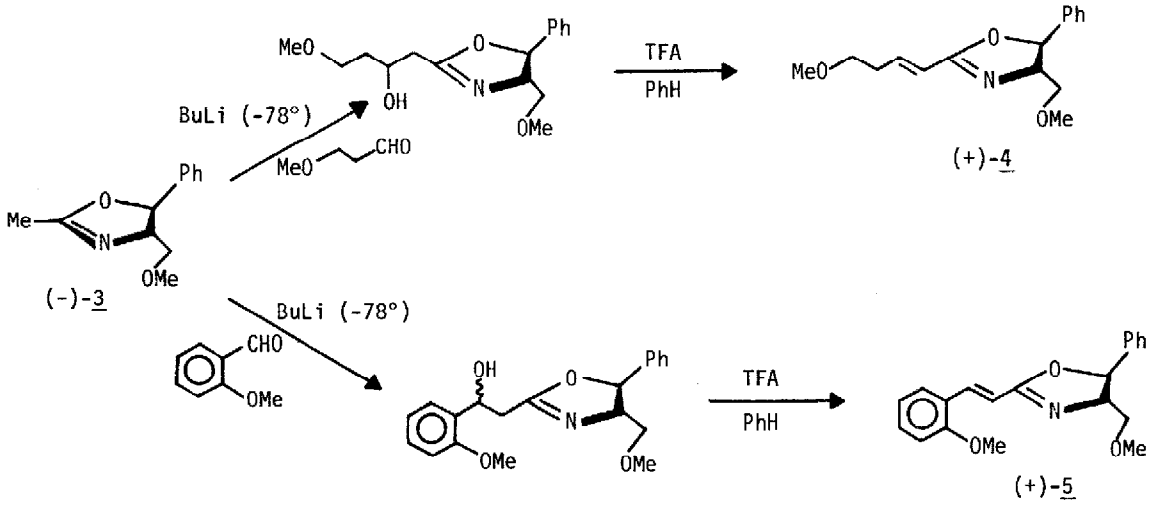


(+)-1 2 (90-98% ee)

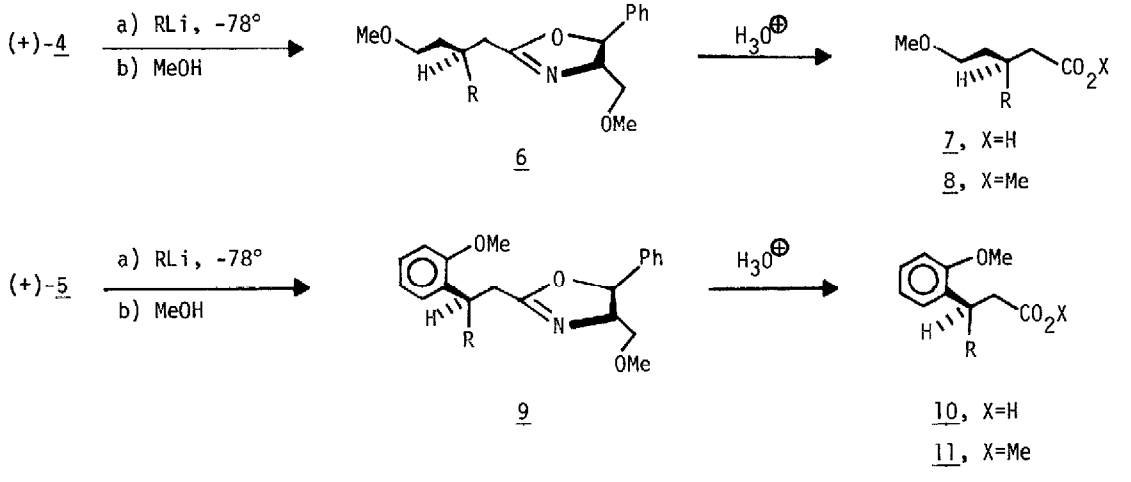
method is demonstrated for two series of compounds, 4 and 5, prepared from commercially available 3[2] as outlined in Scheme 1. These methoxy-substituted oxazolines were subjected to low temperature reaction with 1.5 equiv of an organolithium reagent (2 h) and then quenched with methanol (-78°). The work-up gave the crude alkylated oxazolines 6 and 9 which were usually not purified[3] prior to proceeding to the next step. Aqueous hydrolysis (3M H_2SO_4, reflux 6 h) gave the chiral methoxy acids 7 and 10. Pertinent details are given in Table 1. Since none of these acids had been previously reported, their % enantiomeric excess was determined using chiral shift reagents (Eu-Optishift I and Eu-Optishift II).[4]

Examination of the acids 7 and 10 or their methyl esters 8[5] and 11 with the chiral shift reagents gave no clear separation of enantiomers. This could have been due to (a) inadequate asymmetric complexation of the product with the shift reagent or (b) a very high enantiomeric excess.

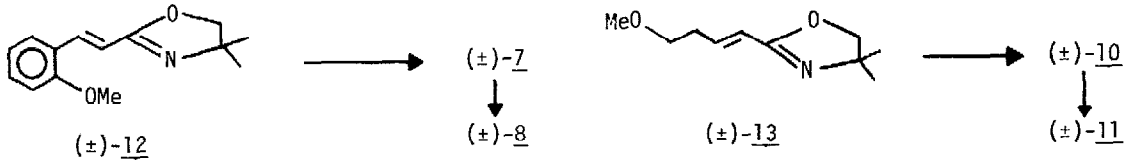
SCHEME I



Thus, the racemic acids 7 and 10 and their corresponding esters 8 and 11 were prepared using the achiral oxazolines 12 and 13 and subjected to shift reagent analysis. In both series, the corres-



ponding methyl esters (racemic 8 and 11) showed very clean separation of the respective methoxy signals (R-OMe and R-C(=O)-OMe) in 1:1 ratios. A slight (<10%) peak was observed on the shift reagent nmr spectra of chiral 8 and 11 and when these samples were admixed with an equal quantity of racemic 8 and 11, the %ee could be determined. These are given in Table 1.[6]



The chiral methoxy acids 7 and 10 were treated with boron tribromide (each series required slightly different reaction conditions) and gave the corresponding valerolactones 14 and 15. Yields, rotations and % ee are given in Table 2.

14 15

The absolute configuration of the chiral methoxy acids 7 and 10 as well as the chiral lactones 14 and 15, are assigned on the basis of the mechanism and results obtained for the chiral acids 2. Further verification of the configurational assignment was gathered from the similarity of the CD spectra for these compounds (2, 7, 10). Additional studies are in progress to increase the versatility of this process which should provide a ready source of chiral products in high enantiomeric purity.

TABLE 1 Methoxy Acids 7 and 10

Oxazoline			RLi	Acids			
Compound	$[\alpha]_{578}^{25}$	% Yield		% Yield	$[\alpha]_{578}^{25}$	% ee (±5%)[a]	Conf'n.[d]
4	+34.1 (c 5.78, $CHCl_3$)	40	Et	(7) 56	-1.30 (c 14.5, PhH)	85[b]	S
			n-Bu	(7) 65	+2.38 (neat)	81[b]	S
			Ph	(7) 66	+11.1 (c 11.4, PhH)	89[b]	S
5	+141 (c 5.55, $CHCl_3$)	57	Et	(10) 83	-2.13 (c 11.2, PhH)	75[c]	R
			n-Bu	(10) 70	-21.7 (c 10.3, PhH)	81[c]	R
			Ph	(10) 87	-24.8 (c 10.5, $CHCl_3$)	85[c]	S

a) Determined by use of chiral shift reagent on corresponding methyl esters: 8 (R=Et), $[\alpha]_{578}$ -1.42 (10.9, $CHCl_3$); 8 (R=n-Bu), $[\alpha]_{578}$ +0.33 (10.9, $CHCl_3$); 8 (R=Ph) $[\alpha]_{578}$ +1.78 (9.59, $CHCl_3$); 11 (R=Et), $[\alpha]_{578}$ -10.2 (8.18, PhH); 11 (R=n-Bu), $[\alpha]_{578}$ -11.4 (6.51, PhH); 11 (R=Ph), $[\alpha]_{578}$ -32.5 (4.96, PhH); b) Addition of Eu-Optishift II to 1:1 racemic and chiral esters; c) Addition of Eu-Optishift I to 1:1 racemic and chiral esters; d) Assigned by analogy to synthesis of chiral acids 2.

TABLE 2 Valerolactones 14 and 15

Lactone	Yield %	$[\alpha]_{578}^{25}$	ee[a] %	Conf'n.[a]
14 (R=Et)	42	-28.6 (c 8.30, $CHCl_3$)	85	S
14 (R=n-Bu)	45	-24.2 (c 6.77, $CHCl_3$)	81	S
14 (R=Ph)	62	-12.6 (c 11.4, $CHCl_3$)	89	S
15 (R=Et)	77	+69.8 (c 5.87, PhH)	75	R
15 (R=n-Bu)	72	+74.2 (c 5.04, PhH)	81	R
15 (R=Ph)	67	+43.7 (c 5.58, PhH)	85	S

a) Enantiomeric excess and configuration are assumed to be identical with the corresponding acids.

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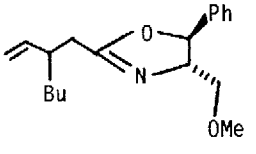
REFERENCES AND FOOTNOTES

1. A. I. Meyers and C. E. Whitten, J. Am. Chem. Soc., 97, 6266 (1975).

2. Aldrich Chemical Co., Milwaukee, Wisc., or Elars Biochemical Co., Ft. Collins, Colo. Preparative details appear in A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, J. Am. Chem. Soc., 98, 567 (1976).

3. In the case of 6 (R=n-Bu), purification (Silica Gel, 0.03-0.06 mm, Woelm; 20% acetone-hexane, 90 psi) was necessary to remove ~15% of a side product found to be:



4. Eu-Optishift I = tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium (III). Eu-Optishift II = tris [3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium (III).

5. The esters were prepared in 90-98% yield using diazomethane in ether.

6. All compounds gave satisfactory elemental, mass, and spectral analyses.