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A SYNTHON FOR CHIRAL GLYCOLATE ENOLATE (ROCHCOOR'): A CAMPHOR-BASED OXAZOLINE

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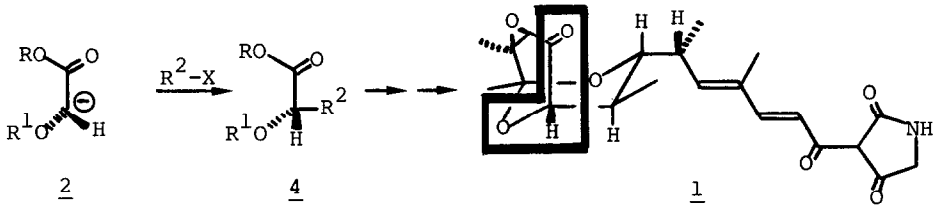
Summary: Alkylations of the anion (7a) derived from a camphor-based oxazoline proceed in good yield. Hydrolysis affords the corresponding α-hydroxy acids in high ee.

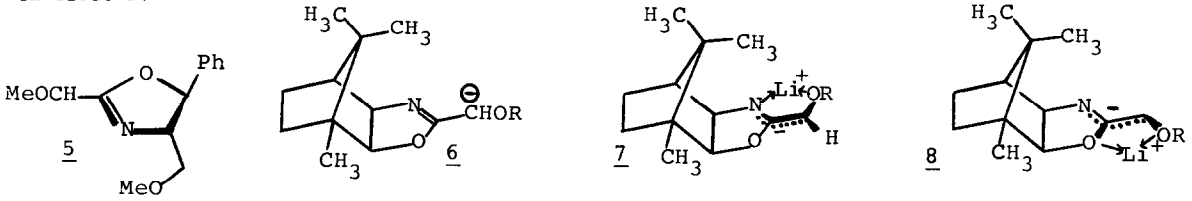
In the course of studies directed toward the synthesis of the family of molecules typified by tirandamycin (1),[1,2] we envisioned that the "boxed" portion of 1 might be generated by alkylation of a suitably protected enolate (e.g., 2) of glycolic acid (3, $HOCH_2COOH$) as indicated in Equation 1. The achirality of 2 suggested, however, that the likelihood of achieving practical levels of stereochemical control during the course of the alkylation (2 → 4) was small even if chirality in R^2 afforded the possibility of kinetic resolution. Consequently, it became desirable to incorporate into 2 features which would ordain the desired outcome.



2 4 1 (Eq. 1)

Of the technologies available at the time this project was initiated,[3] only Meyers' oxazoline-based approach offered a potentially applicable solution.[4] Unfortunately, however, while chiral oxazolines have been impressive in their overall[4] contribution to asymmetric synthesis, their application[5] to the fabrication of chiral α-alkoxy acids had proved more of a Waterloo than a watershed. Specifically,[5a] employ of 5 as a synthon for 3 failed to afford satisfactory degrees of enantiomeric excess, with %ee's ranging from 12 to 42% in the examples reported.

Nonetheless, an oxazoline-based method still appeared highly attractive in principle. Analysis suggested that for a useful degree of ee to obtain only two objectives need be met: 1) anion generation must be, at a minimum, highly stereoselective and 2) once generated, the anion should exhibit high diastereofacial selectivity. Examination of models indicated that 6 should meet the second criterion[6] because the methyl group endo to the oxazoline ring shields the β-face of the anion; and consideration of chelation effects led to the expectation that 6 might well exist largely with the stereochemistry shown in 7. We now report the realization of both of the above expectations, as evidenced by the ee's and absolute configuration given in Table 1.



5 6 7 8

a, R=CH_2OCH_3

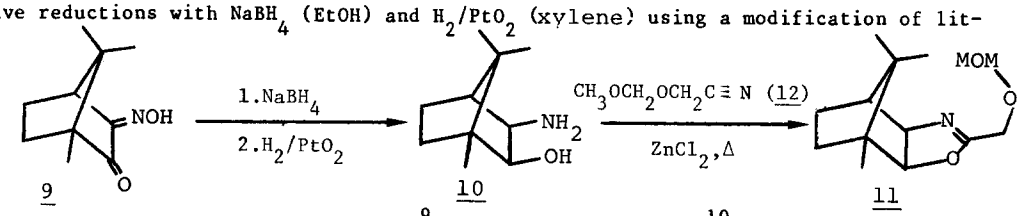
Table 1[13]

Acid	Alkyl Group(R)	Alkylating Agent (17)	%ee of Acid[a]	Configuration of Acid[a]	Overall Yield of Acid(%)[b,c]
14a	$C_6H_5CH_2$-(a)	$C_6H_5CH_2Br$	92%	R	70
14b	$(CH_3)_2CHCH_2$-(b)	$(CH_3)_2CHCH_2I$	88%	R	72
14c	$(CH_3)_2CH$-(c)	$(CH_3)_2CHI$	87%	R	26[c]
14d	$CH_3CH_2CH_2$-(d)	$CH_3CH_2CH_2I$	86%	R	57
14e	CH_3CH_2-(e)	CH_3CH_2I	77%	R	42

a) see text; b) purity $\geq$ 95% except 14c (90%); c) all alkylations proceed in high yield.[a]

The oxazoline precursor to 6a was secured as summarized in Equation 2. Thus 9, prepared[7] by reaction of (+)-camphor with isoamyl nitrite, affords 10 in 72-76% yield upon successive reductions with $NaBH_4$ (EtOH) and H_2/PtO_2 (xylene) using a modification of lit-

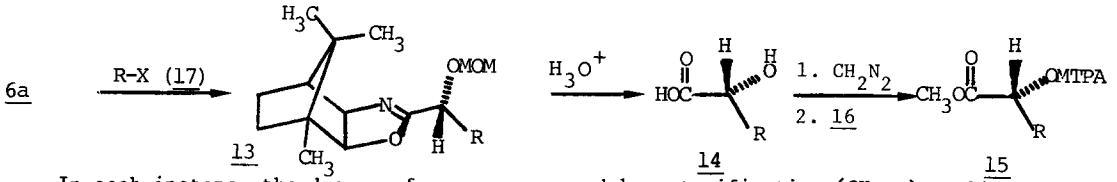
(Eq. 2)



9 10 11

erature[8] procedures. Heating of 10 with 12[9] and a catalytic amount[10] of $ZnCl_2$ for 50 h at 100° gives (48-51%) 11,[11] bp 80°/0.05 torr (Kugelrohr).

Alkylation[12] of the anion (6a) derived (n-BuLi) from 11 with a variety of alkylating agents affords the alkylated oxazolines 13[11] in uniformly high yield. Hydrolysis gives the corresponding hydroxy acids 14 (Table 1),[13] albeit sometimes in disappointing yields - a difficulty which Meyers et al. also encountered.[5a]



In each instance the degree of ee was assessed by esterification (CH_2N_2) of 14 and conversion to the Mosher[14] derivative 15 using (S)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (16) and assay by ^{19}F NMR spectroscopy. In all cases parallel studies using (±)-14 and 16 established that the diastereomeric composition of 15[11] accurately represents the enantiomeric composition of 14. The absolute configuration of each of the hydroxy acids 14 derived from 6a was ascertained by repetition of the 14 → 15 transformation using samples[14] of 14 of known absolute stereochemistry. The reaction conditions[13] which gave the highest degree of ee (Table 1) were arrived at after examining the importance of solvent composition and reaction temperature (Table 2).

Examination of the data in Table 1 indicates that with the exception of 14e the ee's are identical within experimental error. Were anion 6a to suffer alkylation to a substantial extent on both faces, one would predict significant differences in ee among 17a-17e because their different steric requirements should translate to different ratios of top to bottom-face

Table 2: Effect of Experimental Conditions[a]

Entry	Acid prepared	Solvent[b]	Cation	Internal Temperature	%ee[c]
1	14b	THF	Li	-78°C	73
2	14b	THF	Li	-100	79
3	14b	THF	Li(+1.1 eq LiI[d])	-78	78
4	14b	Et_2O	Li	-78	no rxn[e,f]
5	14b	2:1 Et_2O/THF	Li	-78	79
6	14b	1:2 Et_2O/THF	Li	-78	88
7	14b	1:2 Et_2O/THF	Li	-100	88
8	14b	1:4 Et_2O/THF	Li	-78	88
9	14b	hexane	Li	-78	no rxn[e]
10	14b	hexane	Li	-40	g
11	14b	1:1 hexane/THF	Li	-78	56
12	14b	THF	Li,Mg[h]	-78	no rxn[e]
13	14b	THF	Li,Mg[h]	-40	decomp[e]
14	14d	THF	Li	-78	80
15	14d	1:2 Et_2O/THF	Li	-78	85
16	14d	1:4 Et_2O/THF	Li	-78	86

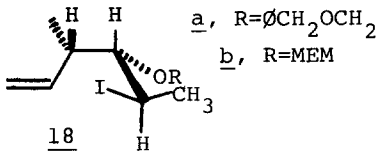
a) reactions were conducted on 1g 11 in a total volume (excluding hexane[b]) of 40mL (assuming volumes[b] are additive).[12] b) in the case of mixed solvents the anion was generated in the solvent listed first; the anion solution was then diluted with the cosolvent; ca. 1.6 mL hexane (from BuLi) was also present. c) determined by conversion to 15 (see text). d) 11 and LiI were stirred 5 min at 20° before BuLi was added at -78°. e) anion formation proven by quenching with D_2O and/or CH_3CH_2CHO. f) anion decomposes at -40°. g) alkylation only 60% complete after 16 h; anion decomposes above -20°C. h) 11 stirred with 1 eq $MgBr_2$ (from Mg + $BrCH_2CH_2Br$) before addition of BuLi.

attack. The lack of variation in ee therefore suggests that alkylation occurs on only one face of the anion. If one assumes, as previously shown for other oxazoline anions,[15] that anion 6a is configurationally stable, it follows that the observed ee is a direct consequence of the stereochemical composition of the anion, which on the basis of 88% ee is thus inferred to be 94:6. It further follows from the R chirality of the acids 14 that 7a is the dominant anion isomer, which is in agreement with the original prediction based on chelation considerations. The lower ee observed in the case of 17e, the least sterically demanding of the alkylating agents, is attributed to intrusion of a small amount (ca. 5%) of top side alkylation of anion 7a.

A number of factors were examined for their role in determining the stereochemical outcome and the results are summarized in Table 2. Values in Table 1 were obtained using conditions optimized for 14b; %ee's of acids 14 prepared from all five alkyl halides (17) using THF as solvent (as in Table 2, entries 1 and 14) were also determined but were uniformly lower, ranging from 73% (14b) to 82% (14a). It thus appears that anion formation in ether results in more selective generation of 7a (addition of THF is necessary for alkylation to occur: see entry 4).

Efforts to further enhance the 7a:8a ratio by using reaction conditions (Table 2) which would afford a tighter chelate (Mg^{++} instead of Li^{+}, hexane as solvent, etc.) generally rendered the anion unreactive toward alkylation.

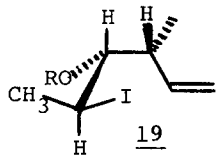
Having demonstrated the efficacy of 7a as an effective surrogate for 2, we turned our attention to its employ in the synthesis of 1. To our dismay, neither 18a and b [prepared from the more available (S)-ethyl lactate as models for their enantiomers 19a and b][16] nor (±)-20[17] is sufficiently reactive to alkylate 7a. Other routes to 1 are presently under investigation.



a, R=ØCH$_2$OCH$_2$

b, R=MEM

18



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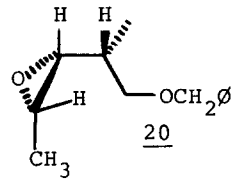

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In summary, 7a serves as an effective synthon for chiral 2, and the concepts underlying its design are vindicated, even though it proved unsuitable for its intended application.[18]

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