Tetrahedron Letters No. 2, pp 103 - 106.

0040-4039/79/0108-0103$02.00/0

POLARITY REVERSED PRELOG REACTIONS

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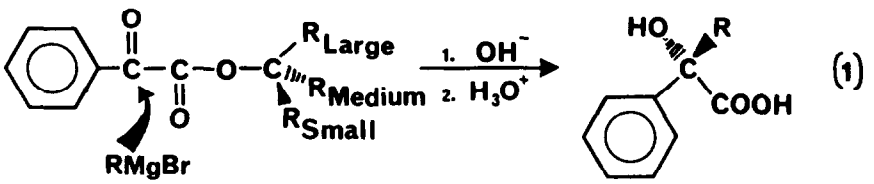
Stereocontrolled carbon-carbon bond formation is a continuing challenge in synthetic organic chemistry. Asymmetric syntheses in which carbon-carbon bonds form by reaction of chiral electrophiles and achiral nucleophiles are well established, predictable synthetic reactions. Related asymmetric syntheses of carbon-carbon bonds using chiral nucleophiles and achiral electrophiles have recently received more attention and have been quite successful.[1-6] Here we report an asymmetric synthesis of α-hydroxy carboxylic acid esters. This reaction between a chiral alkoxy enediolate and an achiral alkyl halide[7] employs a reactivity sense opposite to that of a conventional Prelog reaction and in the cases studied proceeds in a predictable fashion.

Prelog reactions (eq 1) are known to give α-hydroxy carboxylic acid esters of predictable configuration based on a hypothetical transition state. The po-



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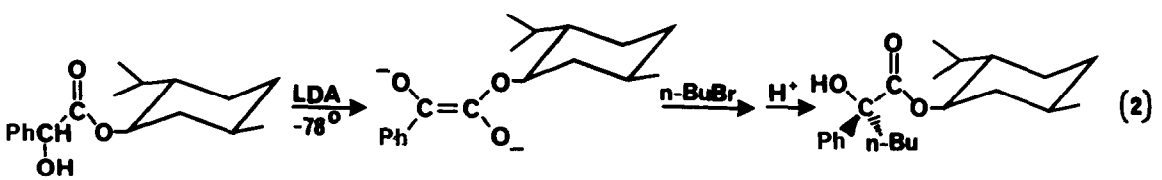
larity reversed or "umpolung" Prelog reaction we have discovered proceeds in a similar fashion (eq 2). Alkylation of chiral alkoxy enediolates gives good



(2)

synthetic yields and modest (up to 50% ee) stereoselectivities (see Table I). The stereoselectivities of each alkylation reaction using chiral alkoxy enediolates were determined by integration of the diastereomeric hydroxylic protons of the product α-hydroxy carboxylic acid ester or by integration following the use of europium shift reagents to separate the diastereotopic peaks. In every case, the peak from the predominant diastereomer was shifted further downfield and has been assigned to the (R) product. In two cases, menthyl α-ethyl mande-

late and menthyl α-butylmandelate, the product of the asymmetric synthesis was hydrolyzed and the resulting hydroxy carboxylic acid analyzed polarimetrically. The observed rotation for α-ethyl mandelic acid ($[\alpha]_D^{25} = -9.0°$ ($c=3.0$, C_2H_5OH)) corresponds to an R configuration at the chiral center and 27% ee based on the rotation reported for optically pure α-ethyl mandelic acid.[8] The rotation for α-butyl mandelic acid was also negative indicating that the predominant enantiomer is R. The stereoselectivities in these alkylation reactions was highest with 1-bromobutane. Surprisingly, the lowest stereoselectivity was observed with a more hindered alkylating agent, iodocyclohexane (7% ee).

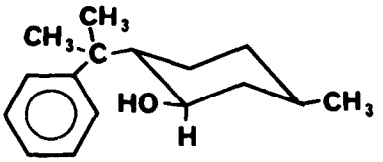
Table I. Asymmetric Syntheses of Substituted Mandelic Acid Esters

Starting Material[a]	Alkylating Agent[b]	Synthetic Yield (%)[c]	Stereoselectivity (%)[d]
Menthyl Mandelate	n-C_4H_9Br	32	50
Menthyl Mandelate	n-C_4H_9I	69-75	36-41
Menthyl Mandelate	$CH_2=CHCH_2Br$	73	31
Menthyl Mandelate	c-$C_6H_{11}I$	68	7
Menthyl Mandelate	CH_3CH_2I	49	27
(S)-Menthyl Mandelate[e]	CH_3I	46	10
(R)-Menthyl Mandelate[e]	CH_3I	46	10
(S)-Menthyl Mandelate[e]	n-C_4H_9I	57	37
(R)-Menthyl Mandelate[e]	n-C_4H_9I	43	33
Menthyl Mandelate	$C_6H_5CH_2Br$	41-53	14-22

[a]Starting materials contained two diastereomeric menthyl mandelates unless otherwise noted and were all prepared from pure ℓ-menthol. [b]Alkylation occurred while warming the reaction mixtures from -78° to 0°. Experimental procedures were otherwise identical to those described in reference 7. [c]Isolated yields of products characterized by ^1H NMR. [d]Determined by ^1H NMR by integration of diastereomeric -OH proton peaks of the product or by integration of diastereomeric protons after addition of the europium shift reagent $Eu(fod)_3$. [e]The indicated stereochemistry refers to the configuration of the mandelic acid portion of the ester.

The observed stereoselectivity of up to 50% is high considering the two step nature of this asymmetric synthesis (*vide infra*) and the relatively poor stereoselectivities normally associated with the use of menthol as a chiral auxillary. Preliminary experiments support the expectation that other more discriminating chiral esters may significantly improve the overall stereoselectivity. Specifically, the use of alcohol 1 instead of menthol in a man-

delate ester in an asymmetric synthesis like equation 2 raises the stereoselectivity observed in methylation to 42% (51% synthetic yield).[9] However, a similar increase in the stereoselectivity was not observed in butylation with 1-iodobutane (in fact, a slight decrease in stereoselectivity (43%) was noted).



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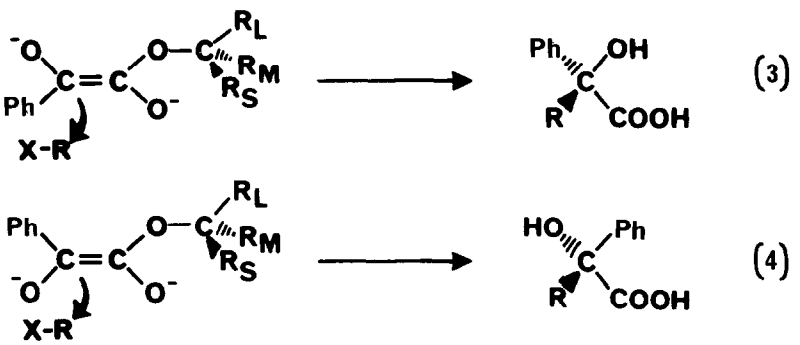
These polarity reversed Prelog reactions are more successful at forming chiral tetrasubstituted carbon centers than most other electrophilic asymmetric syntheses.

Interpretation of the mechanism of this asymmetric syntheses is clouded by our inability to determine accurately the alkoxy enediolate geometry. We have assumed it is Z (see equation 2) because the product configuration is then correlated with the Prelog generalization. It is important to note that these alkoxy enediolates probably do not rotate about the pseudo carbon-carbon double bond.[10,11] Since the isomeric Z- and E- alkoxy enediolates are predicted to yield enantiomeric mixtures of products after alkylation and hydrolysis (cf. eq 3 and 4), stereoselectivity in the lithio anion formation could be the limiting step in our asymmetric syntheses.[12] Research is presently underway to clarify this point and to ascertain the Z- or E- geometry of the intermediate alkoxy enediolates.



ACKNOWLEDGEMENT: We thank the Texas A&M University NIH Biomedical Sciences Support Grant for funding this research.

References and Notes

1. J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, New Jersey (1971), and D. Valentine and J.W. Scott, Synthesis 329 (1978).

2. J.K. Whitesell and S.W. Felman, J.Org.Chem., 42, 1663 (1977), and S. Yamada, K. Hiroi, and K. Achiwa, Tetrahedron Lett., 4233 (1969).
3. D. Enders, and H. Eichenauer, Angew.Chem.Int.Ed.,Engl., 15, 549 (1976); D. Enders and H. Eichenauer, Tetrahedron Lett., 191 (1977).
4. D. Mea-Jacheet and A. Horeau, Bull.Soc.Chim.Fr., 4571 (1968); M. Kitamoto, K. Hiroi, S. Terashima, and S. Yamada, Chem.Pharm.Bull., 22, 459 (1974); A.I. Meyers, D.R. Williams, and M. Druelinger, J.Am.Chem.Soc., 98, 3032 (1976); J.K. Whitesell and M.A. Whitesell, J.Org.Chem., 42, 377 (1972); and A.I. Meyers, G.S. Poindexter, and Z. Brich, J.Org.Chem., 43, 892 (1978).
5. S. Yamada, T. Oguri, and T. Shiori, J.Chem.Soc., Chem.Commun., 136 (1976) and Y. Schollkopf, H.-H. Hausberg, I. Hoppe, M. Segal, and U. Reiter, Angew.Chem.Int.Ed.Engl., 17, 117 (1978).
6. A.I. Meyers, G. Knaus, K. Kamata, and M.E. Ford, J.Am.Chem.Soc., 98, 567 (1976) and A.I. Meyers and E.D. Mihelich, Angew.Chem.Int.Ed.Engl., 15, 270 (1976).
7. L.J. Ciochetto, D.E. Bergbreiter, and M. Newcomb, J.Org.Chem., 42, 2948 (1977).
8. T.R. Emerson, D.F. Ewing, W. Klyne, D.G. Neilsen, D.A. Peters, C.H. Rooch, and R.J. Swan, J.Chem.Soc., 4007 (1965).
9. E.J. Corey and H.E. Ensley, J.Am.Chem.Soc., 97, 6908, (1975) and H.E. Ensley, C.A. Parnell, and E.J. Corey, J.Org.Chem., 43, 1610 (1978).
10. Other carbanions stabilized by carbonyl groups exist as stable geometrical isomers on a synthetic time scale, cf. M. Newcomb and D.E. Bergbreiter, J.Chem.Soc., Chem.Commun., 486 (1977) and references therein.
11. There is experimental evidence that vicinal enediolates derived from α-hydroxy ketones do not rotate, cf. D.P. Bauer and R.S. Macomber, J.Org.Chem, 41, 2640 (1976).
12. Recent work has demonstrated that stereoselectivity in proton abstraction is an essential feature of other asymmetric syntheses, e.g. alkylation of chiral oxazoline lithio anions.[13]
13. M.A. Hoobler, D.E. Bergbreiter, and M. Newcomb, J.Am.Chem.Soc., 100, 0000 (1978); and A.I. Meyers, E.S. Snyder, and J. J.H. Ackerman, J.Am.Chem.Soc., 100, 0000 (1978).

(Received in USA 2 November 1978)