pyruvate is the more stable compound in solution and is, as a result, the easier to handle.[10] PPase-catalyzed hydrolysis of pyrophosphate was employed to drive the UDPGP-catalyzed reaction. Glucose 6-phosphate was used as a starting material, instead of glucose 1-phosphate, because G-6-P is more stable and more readily available than G-1-P, and because PGM is inexpensive and stable. The good stability and high recovery observed for the enzymes used in the system and the satisfactory turnover number for UTP render the costs of these components acceptable for practical-scale synthesis.

The value of this synthesis lies in its demonstration that enzymatic catalysis can be used to prepare substantial quantities of a representative disaccharide on starting from unprotected sugars and utilizing the enzymes of the Leloir pathway.[17] Although a number of nucleoside diphosphate sugars are required to satisfy all the requirements for syntheses based on this pathway and although the enzymes required for any particular synthesis of interest will be more or less available, the nucleoside triphosphate cofactors involved in all of these syntheses can now be considered to be readily available, and the regeneration schemes for these cofactors function well. The general area of practical-scale, polysaccharide synthesis based on cofactor-requiring enzymes thus now seems amenable for development by synthetic organic chemists.

(17) Beyer, T. A.; Sadler, J. E.; Rearick, J. I.; Paulson, J. C.; Hill, R. L. *Adv. Enzymol.* **1981**, *52*, 24-175.

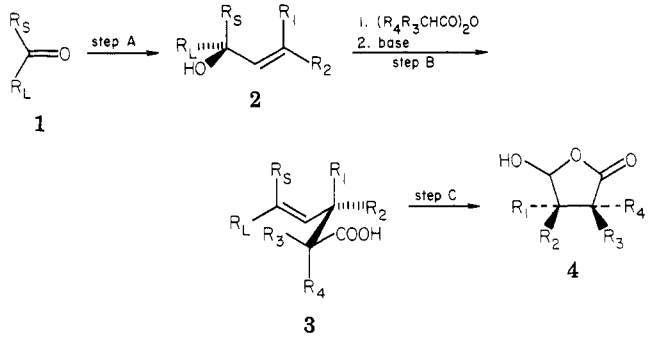
Chi-Huey Wong, Sharon L. Haynie[2]
George M. Whitesides*
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received October 19, 1982

A Nonresolutive Approach to the Preparation of Configurationally Pure Difunctional Molecules

Summary: Treatment of menthone (**5**) with organometallic reagents affords axial tertiary alcohols of type **6** with high diastereoselectivity. Propionate **12**, derived from *trans*-**11**, undergoes an enolate Claisen rearrangement with complete transfer of chirality. The use of these two observations in the nonresolutive synthesis of configurationally pure difunctional molecules such as **15**, **16**, and **19** is discussed.

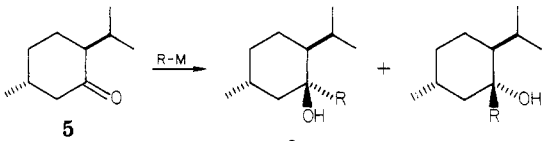
Sir: The phenomenon of transfer of chirality has been documented for a number of [2,3] and [3,3] sigmatropic rearrangements.[1] Until recently, one of the major obstacles to using these rearrangements in asymmetric synthesis was the inavailability of configurationally pure allylic fragments possessing the structural features required to observe transfer of chirality.[2] In this communication we describe the initial results of an approach to the nonresolutive synthesis of tertiary allylic alcohols that transfer chirality in enolate Claisen rearrangements.[3a] In addition, our progress toward establishing a protocol for the synthesis of configurationally pure 1,4-difunctional molecules will be discussed.

Scheme I



1 2 3 4

Table I. Preparation of Configurationally Pure Allylic and Propargyllic Alcohols



5 6 7

entry	R-M/solvent	major product[f]	% yield of adduct (6/7)[c]
1	$HC{\equiv}CLi/NH_3$ [a]	8	53 (9:1)[d]
2	$CH_3C{\equiv}CLi/NH_3$ [a]	9	25 (7:1)[d]
3	$CH_2{=}CHMgBr/THF$	10	77 (6 only)
4	$CH_3CH{=}CHMgBr/THF$ [b]	11	76 (6 only)[e]
5	$CH_3CH{=}CHLi/Et_2O$ [b]	11	90 (6 only)[e]

[a] Enolization of 5 was a competitive process. [b] A mixture of cis and trans organometallic reagents was used. [c] Isolated yields of 6 + 7 after separation. [d] The stereoisomers were easily separated by column chromatography. [e] Obtained as a mixture of cis and trans isomers. [f] In all cases the major product had the stereochemistry depicted by general structure **6**.

The general approach we have pursued is outlined in Scheme I. We hoped to identify readily available configurationally pure carbonyl compounds **1** that would react with appropriate organometallic reagents to give allylic alcohols **2** of defined absolute stereochemistry and olefin geometry (step A). In evaluating candidates for **1** it was important that R_L and R_S differ in size such that transfer of chirality would be observed in subsequent Claisen rearrangements (step B).[3b] Finally, if these requirements could be met, we felt it would be a simple task to liberate configurationally pure 1,4-difunctional molecules of type **4** by oxidative cleavage of rearrangement products **3** (step C).

Although a number of candidates for carbonyl compound **1** were considered, we soon focused on menthone (**5**) for several reasons. First, configurationally pure menthone was readily available on a large scale from Brown oxidation of menthol.[4] In addition, there was

(1) For a lead reference on intramolecular transfer of chirality, see: Scott, J. W.; Valentine, D. *Synthesis* **1978**, 329 and references cited therein.

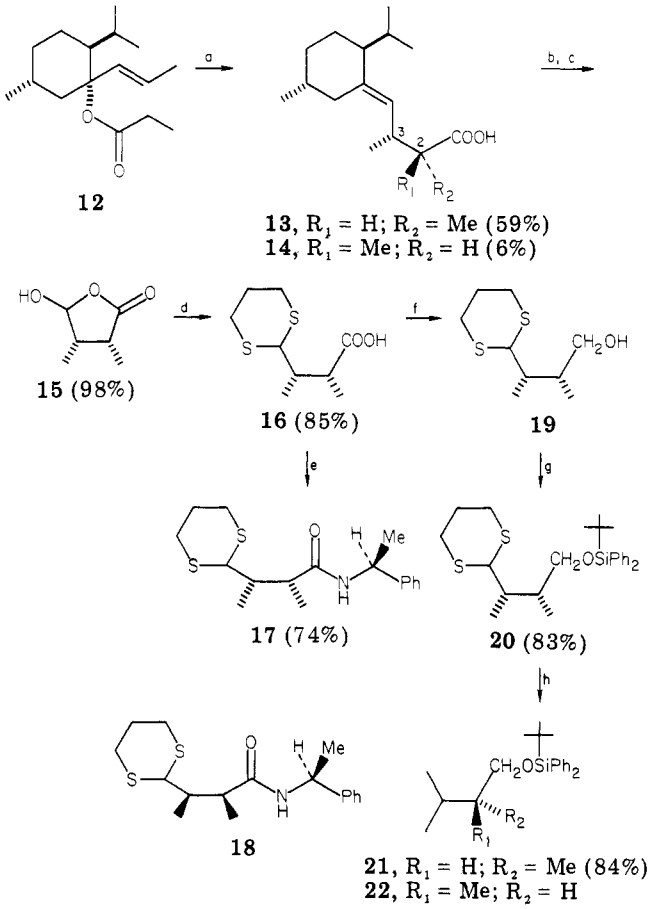
(2) Recent reports that alkyl alkynyl ketones can be reduced enantioselectively in principle now render optically active allylic alcohols readily available: Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. Vigneron, J.-P.; Bloy, V. *Tetrahedron Lett.* **1979**, 2683. Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. For other relevant studies, see: Mori, K.; Akao, H. *Tetrahedron* **1980**, *36*, 91. Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. *Chem. Lett.* **1979**, 447. Terashima, S.; Tanno, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1980**, 1026. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(3) (a) This work is taken in part from the M.S. thesis of D. K. Hutchinson, The Ohio State University, Columbus, OH, 1980. (b) For a discussion that outlines criteria needed to observe transfer of chirality in Claisen rearrangements, see: Perrin, C. L.; Faulkner, D. J. *Tetrahedron Lett.* **1969**, 2783.

(4) Brown, H. C.; Garg, C. P.; Liu, K. T. *J. Org. Chem.* **1971**, *36*, 387.

0022-3263/82/1947-5418$01.25/0

Scheme II[a]

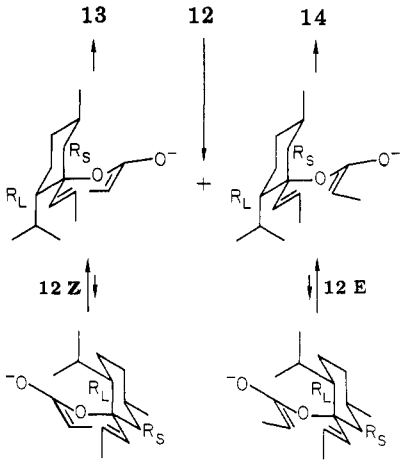


[a] (a) LCIA, THF; (b) O_3, CH_2Cl_2; (c) Me_2S; (d) $HS(CH_2)_3SH$, HCl; (e) DPPA, Et_3N, (S)-PhCH(NH_2)Me; (f) $LiAlH_4$; (g) $Ph_2(t\text{-Bu})SiCl$, DMF, imidazole; (h) W-2 RaNi.

reason to believe that menthone would meet the diastereoselectivity requirements set forth in step A of Scheme I.[5] Finally, we felt that menthone adducts would be good mimics for **2** where R_S = Me and R_L = *t*-Bu (vide infra).[6]

In fact, treatment of menthone with several vinylic and acetylenic organometallic reagents did give axial alcohols **6** with high diastereoselectivity as shown in Table I.[7,8] Although geometrically pure vinylic lithium compounds were not used in this study, entry **5** suggests that this will ultimately offer the most expedient route to configurationally and geometrically pure tertiary allylic alcohols of type **6**. For the current study geometrically pure samples of *cis*-**11** and *trans*-**11** were prepared by catalytic hydrogenation ($Pd/BaSO_4$, pyridine, H_2, 85%)[9] and $LiAlH_4$–NaOMe reduction (80%)[10] of **9**, respectively.

Scheme III



We next turned to a study of Claisen rearrangements of derivatives of allylic alcohols **11**.[11] Not unexpectedly, both *cis*- and *trans*-**11** were extremely hindered[12] and did not undergo vinyl ether formation[13] or Claisen rearrangement under the Johnson[14] conditions. Propionate **12**, however, was prepared by sequential treatment of *trans*-**11** with methylmagnesium bromide and propionic anhydride (60%).[15] Treatment of **12** with lithium cyclohexylisopropylamide (−70 → 25 °C, 5 h) afforded a mixture of acids **13** and **14** in 59% and 6% yields, respectively.[16,17] The relative relationship of the two new asymmetric centers in **13** was determined by degradation to *meso*-2,3-dimethylsuccinic acid[18] and the stereochemical relationship between **13** and **14** was established by interconversion of the corresponding methyl esters upon treatment with sodium methoxide in methanol.

The ^{13}C NMR spectra of **13** and **14** exhibited only 16 signals, suggesting that each compound was configurationally pure at the two new asymmetric centers. To determine the degree of configurational purity and the absolute configuration of the new asymmetric centers, we performed the degradations outlined in Scheme II. Ozonolysis of **13** in dichloromethane followed by workup with dimethyl sulfide gave lactol **15** (98%). Thioketalization of **15** (propane-1,3-dithiol, HCl, $CHCl_3$; 85%) gave acid **16**, which was converted to the hygroscopic amide **17** (mp 141–142 °C) upon treatment with (S)-α-phenylethylamine, triethylamine, and diphenylphosphoryl azide[19] in dichloromethane. None of the diastereomeric amide **18** was detected by 200-MHz ^1H NMR analysis.[20] Thus the

(5) Watanabe, S.; Suga, K.; Suematsu, Y.; Suzuki, T. *Aust. J. Chem.* **1968**, *21*, 531.

(6) In preliminary studies we showed that the acetate, propionate, and isobutyrate of *tert*-butylmethylvinylcarbinol undergo enolate–Claisen rearrangements to afford the geometrically pure (*E*)-5,6,6-trimethyl-, (*E*)-2,5,6,6-tetramethyl-, and (*E*)-2,2,5,6,6-pentamethyl-4-hexenoic acids, respectively. On the basis of these results, we expected optically active mimics of **2** (R_S = Me, R_L = *t*-Bu) to undergo Claisen rearrangements with high transfer of chirality.[3b]

(7) Stereochemical assignments for the alcohols were based on relative TLC mobilities (Barton, D. H. R. *J. Chem. Soc.* **1953**, 1027. Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562), ^1H-NMR studies (Chapman, O. L.; King, R. W. *J. Am. Chem. Soc.* **1964**, *86*, 1256. Ficini, J.; Maujean, A., *Bull. Soc. Chim. Fr.* **1971**, 219) and are supported by the stereochemical results described herein.

(8) For a review discussing the stereochemical course of carbonyl addition reactions, see Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

(9) Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518.

(10) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245. Molloy, B. B.; Hauser, K. L. *J. Chem. Soc., Chem. Commun.* **1968**, 1017.

(11) For reviews of the Claisen rearrangement, see: Rhoads, S. J.; Raulins, N. R. In "Organic Reactions"; Dauben, W. G., Ed.; Wiley: New York, 1975. Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.

(12) *cis*-**11** and *trans*-**11** both showed significant non-hydrogen-bonded OH stretching absorptions in their *neat film* infrared spectra.

(13) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828.

(14) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(15) Starting alcohol was recovered in a 24% yield. All attempts to esterify **11** via DMAP catalayzed methods met with failure.

(16) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868 and references cited therein.

(17) Approximately 10% of alcohol *trans*-**11** was also formed, presumably via enolate fragmentation.

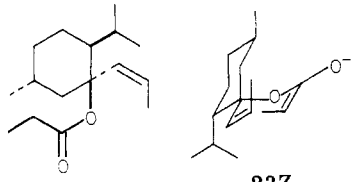
(18) Ozonolysis of **13** followed by an oxidative workup gave meso-2,3-dimethylsuccinic acid, mp 192–194 °C (lit. mp 194 °C; Vittorelli, P.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1293).

(19) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

enolates derived from **12** rearrange with nearly complete transfer of chirality. To determine the sense of the chirality transfer, we converted acid **16** to *tert*-butyldiphenylsilyl ether **21** via a straightforward reaction sequence (Scheme II). Comparison of the specific rotation of **21** ($[\alpha]^{20}_D$ −3.7° ($CHCl_3$)) with that of **22**, ($[\alpha]^{20}_D$ +3.3° ($CHCl_3$)) prepared from (*S*)-2,3-dimethylbutyric acid,[21,22] established the absolute configuration at C(2) and, by extrapolation, at C(3) of **13**.

From these results we conclude that the rearrangement of ester **12** to acids **13** and **14** proceeds as outlined in Scheme III. In accord with Ireland's numerous studies,[16] enolization of **12** affords a mixture of **12Z** and **12E** in which the former predominates. Each enolate could rearrange from a number of conformations only two of which are shown in Scheme III. We suggest that rearrangement of **12Z** (**12E**) via a chair–chair transition state in which R_L occupies a pseudoequatorial site affords the observed product **13** (**14**). An examination of the chair–chair conformations of **12Z** and **12E** shown in Scheme III reveals that these menthone adducts are excellent mimics for allylic alcohols of type **2** where R_S = Me and R_L = *t*-Bu. In fact, axial substitution at the isopropyl-bearing carbon is unnecessary to produce the required difference in size between the two groups bonded to the carbinol center.

It was disappointing to find that propionate **23**, prepared



23 **23Z**

from *cis*-**11**, did not undergo Claisen rearrangement upon conversion to the corresponding enolate. We suspect that severe pseudo-1,3-diaxial interactions as shown in structure **23Z** are responsible for the decrease in rate of Claisen rearrangement relative to other processes.[23]

In summary, we have established a protocol for the preparation of configurationally pure 1,4-difunctional compounds as depicted in Scheme I. The procedure features a tertiary allylic alcohol Claisen rearrangement that proceeds with complete transfer of chirality and should be adaptable to the synthesis of a variety of compounds by varying substituents in the organometallic and esterification reagents. The sequence, however, is currently not without some operational difficulties. These difficulties are associated with the hindered nature of menthone (e.g., enolization in step A) and the derived alcohols (e.g., difficulties in derivatization and failure of simple Claisen rearrangements). Experiments that address these problems are being pursued.

Acknowledgment. This research was generously supported by a Dow Chemical U.S.A. Grant of Research Corporation.

Registry No. **5**, 14073-97-3; **8** (isomer 1), 24278-73-7; **8** (isomer 2), 24278-67-9; **9** (isomer 1), 33651-09-1; **9** (isomer 2), 33651-10-4; **10**, 33651-06-8; *cis*-**11**, 83803-21-8; *trans*-**11**, 83803-22-9; **12**, 83803-23-0; **13**, 83803-24-1; **14**, 83860-22-4; **15**, 83803-25-2; **16**, 83803-26-3; **17**, 83803-27-4; **18**, 83860-23-5; **19**, 83803-28-5; **20**, 83803-29-6; **21**, 83803-30-9; **22**, 83803-31-0; HC≡CLi, 1111-64-4; $CH_3C{\equiv}CLi$, 4529-04-8; $CH_2{=}CHMgBr$, 1826-67-1; (*E*)-$CH_3CH{=}CHMgBr$, 13154-15-9; $CH_3CH{=}CHLi$, 29283-76-9; (*Z*)-$CH_3CH{=}CHMgBr$, 13154-14-8.

Sandra E. Chillous, David J. Hart*
Douglas K. Hutchinson
Department of Chemistry
The Ohio State University
Columbus, Ohio 43210

Received September 18, 1982

Stereochemical Consequences of Carbanion Asymmetry. An Access to 1,2-Diols

Summary: The enantiofacial discrimination of some asymmetric α-alkoxy carbanions is described, as well as an illustration of their preparative utility.

Sir: Carbon–carbon bond formation resulting from nucleophilic attack upon carbonyl compounds has played a prominent role in the evolution of organic chemistry. The means by which the stereochemical outcome of these condensations may be predictably controlled has continued to be the focus of considerable effort. Stereoselection is most often the result of facial discrimination of the carbonyl function as imposed by chirality residing in either the electrophilic (R_1*) or nucleophilic (R_2*) reaction component (Figure 1), with impressive success documented for both approaches.[1] Acceptable stereoselection is seen to result from the favorable disposition of a number of reaction parameters, including the proximity of resident chirality to the centers of reactivity, the spatial regulation of this resident chirality, as well as the nature of attendant metal species.[2] In the present study, we communicate our preliminary results in optimizing the proximity factor by arranging the coincidence of existent asymmetry with a site of reactivity. More specifically, this investigation represents initial efforts to delineate the *enantiofacial selectivity of a configurationally defined, asymmetric carbanion.*[3,4]

(20) Amide **18** was prepared from *dl-erythro*-2,3-dimethyl-4-pentenoic acid[14] [(i) $NaIO_4$, OsO_4, *t*-BuOH–H_2O; (ii) $HSCH_2CH_2CH_2SH$, HCl, $CHCl_3$; (iii) $(PhO)_2P(O)N_3$, Et_3N, (*S*)-$PhCH(NH_2)CH_3$]. Amides **18** [mp 124–125 °C, $[\alpha]^{21}_D$ −30.3° ($CHCl_3$)] and **17** [mp 141–142 °C, $[\alpha]^{21}_D$ −69.1° ($CHCl_3$)] were separable by chromatography and were easily distinguished by ^1H NMR spectroscopy: **17** ($CDCl_3$) δ 1.12 (d, *J* = 7 Hz, 3 H, CH_3), 1.18 (d, *J* = 7 Hz, 3 H, CH_3), 1.50 (d, *J* = 7 Hz, 3 H, Ar $CHCH_3$), 1.7–2.0 (m, 1 H, CH) 2.08–2.23 (m, 2 H, CH_2), 2.42 (dq, *J* = 8, 7 Hz, 1 H, CHCO), 2.83–2.95 (m, 4 H, CH_2S), 4.19 (d, *J* = 5 Hz, 1 H, CHS), 5.14 (dq, *J* = 8, 7 Hz, 1 H, CHN), 5.94 (br d, *J* = 8 Hz, 1 H, NH), 7.27 (m, 5 H, Ar H); **18** ($CDCl_3$) δ 1.02 (d, *J* = 7 Hz, 3 H, CH_3), 1.20 (d, *J* = 7 Hz, 3 H, CH_3), 1.49 (d, *J* = 7 Hz, 3 H, Ar $CHCH_3$), 1.66–2.07 (m, 3 H, CH and CH_2), 2.46–2.8 (m, 5 H, CHCO and CH_2S), 3.94 (d, *J* = 7 Hz, 1 H, CHS), 5.16 (dq, *J* = 8 Hz, 1 H, CHN), 6.08 (br d, *J* = 8 Hz, 1 H, NH), 7.27–7.36 (m, 5 H, ArH).

(21) (*S*)-2,3-Dimethylbutyric acid (91–94% ee based on reported rotation data[22]) was prepared from isovaleric acid via the method of: Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, 4233.

(22) For the absolute configuration of 2,3-dimethylbutyric acid, see: Levene, P. A.; Marker, R. E. *J. Biol. Chem.* **1935**, *111*, 299.

(23) For the sake of clarity, transition states have been represented as ground-state conformations (Scheme III, **23Z**).

(1) For recent studies: (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Heathcock, C. H. *Science* **1981**, *214*, 395. (c) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (d) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(2) For discussion addressing synthetic design, see: (a) Izumi, Y.; Tai, A. "Stereo-Differentiating Reactions"; Academic Press: New York, 1977. (b) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1976**, *10*, 175. (c) Meyers, A. I. *Pure Appl. Chem.* **1979**, *51*, 1255. (d) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109. See also ref 1.

(3) For recent, related examples: (a) Williams, D. R.; Phillips, J. G.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 4101. (b) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1982**, *104*, 2323 and references cited therein.

(4) For an interesting varient wherein the enantiofacial bias of an asymmetric *electrophile* is examined, see: Sauriol-Lord, F.; Grindley, T. B. *J. Org. Chem.* **1981**, *46*, 2831.

0022-3263/82/1947-5420$01.25/0