Significantly, the tertiary alcohol, 1-methylcyclohexanol, is readily formylated by these mixed formic anhydrides (Table II). These results are consistent with earlier experiments which indicate high selectivity of nucleophiles for the formyl carbonyl in mixed formic anhydrides, especially those with the second carbonyl deactivated via steric and/or electronic factors. Formate ester synthesis is extremely sensitive to the presence of acids and bases.[6,19] We find that formylation of both amines and alcohols occurs most cleanly in the absence of any catalyst (Table II).

A detailed investigation of the synthesis and synthetic applications of mixed formic anhydrides is underway in our laboratory. A full report of the work will be made available when it is completed.

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## Spiro Asymmetric Induction. Synthesis of Optically Pure α-Hydroxy Acid Derivatives by Alkylation of a Chiral Glycolate Enolate

*Summary:* The enolates of spiro-fused dioxolanones **4A** and **4B** serve as chiral glycolate enolate equivalents, providing either enantiomer of the α-substituted α-hydroxy esters **13** upon alkylation and hydrolysis.

*Sir:* Optically pure hydroxy acids are not only important biological substances but are valuable starting materials for the asymmetric synthesis of natural products.[2] In conjunction with another synthetic project, we required optically pure α-hydroxy acids of considerable complexity. In this paper, we report a route to such compounds based on the alkylation of chiral glycolate enolates.[3] Either

(1) Recipient of a Dreyfus Foundation Grant for Newly Appointed Faculty in Chemistry, 1984-1989.
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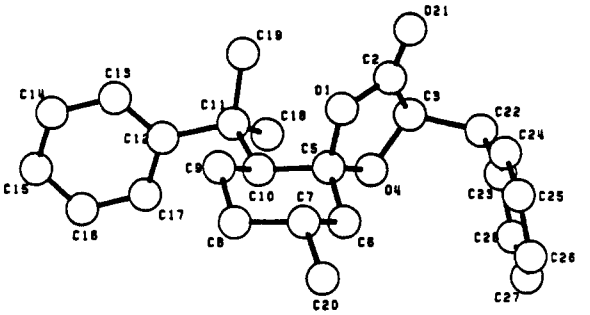
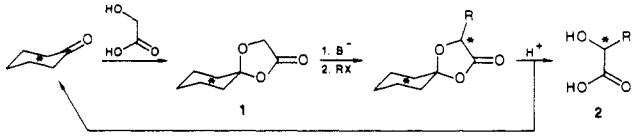



**Figure 1.** Structure and numbering scheme for 11C.

enantiomer of several α-hydroxy esters are produced in 100% optically pure form using a recyclable chiral auxilliary.

A survey of the literature revealed that chiral glycolic acid enolates are known[4,17] and rely on attachment of a chiral auxilliary to either the hydroxyl or carboxyl group, resulting in variable degrees of asymmetric induction. We reasoned that rigid attachment of the chiral auxilliary to both functional groups would result in a more defined steric environment. To this end, we have examined the enolate chemistry of 1,3-dioxolan-4-ones **1** derived from glycolic acid by spiro fusion to a chiral cyclohexanone. Alkylation followed by hydrolysis should afford hydroxy acid **2** accompanied by recovered chiral auxilliary (eq 1).




(1)

It should be noted that Seebach[5] and Frater[6] have reported the alkylation of chiral dioxolanones derived from α-branched optically active α-hydroxy acids and pivaldehyde, providing α,α-disubstituted α-hydroxy acid derivatives ("self-reproduction of chirality"). However, this method is conceptually different from that presented herein, since the chiral starting material is fully incorporated into the products.

The requisite dioxolanones were prepared from menthone[7] and 8-phenylmenthone[8] with trimethylsilyl ((tri-

(3) For good leading references concerning other methods for the asymmetric synthesis of α-hydroxy acids, see: (a) Kelly, T. R.; Arvanitis, A. *Tetrahedron Lett.* **1984**, *25*, 39. (b) Gamboni, R.; Mohr, P.; Waespe-Sarcevic, N.; Tamm, C. *Tetrahedron Lett.* **1985**, *26*, 203. (c) Oppolzer, W.; Dudfield, P. *Helv. Chim. Acta* **1985**, *68*, 216. See also the following papers and work cited therein: (d) Meyers, A. I.; Knaus, G.; Kendall, P. M. *Tetrahedron Lett.* **1974**, 3495. (e) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294. (f) Mukaiyama, T.; Tomimori, K.; Oriyama, T. *Chem. Lett.* **1985**, 813. (g) Soai, K.; Hasegawa, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 769. (h) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. (i) Solladie-Cavallo, A.; Suffert, J. *Tetrahedron Lett.* **1985**, *26*, 429. (j) Davis, F. A.; Vishwakarma, L. C. *Ibid.* **1985**, *26*, 3539. (k) Frye, S. V.; Eliel, E. L. *Ibid.* **1985**, *26*, 3907. (l) Boireau, G.; Korenova, A.; Deberly, A.; Abenhaim, D. *Ibid.* **1985**, *26*, 4181.
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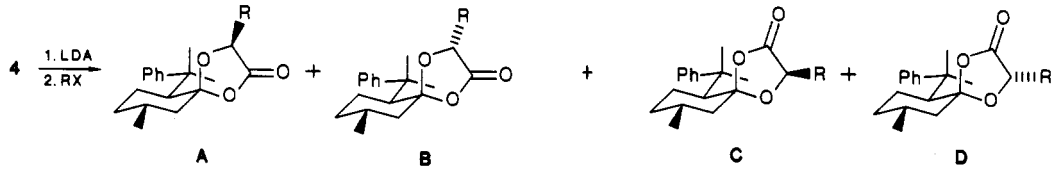
(5) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704. This concept has now been extended to the synthesis of singly branched α-hydroxy acids: D. Seebach, private communication.
(6) Frater, G.; Muller, U.; Gunther, W. *Tetrahedron Lett.* **1981**, *22*, 4221.
(7) Brown, H. C.; Carg, C. P. *J. Am. Chem. Soc.* **1961**, *83*, 2952.

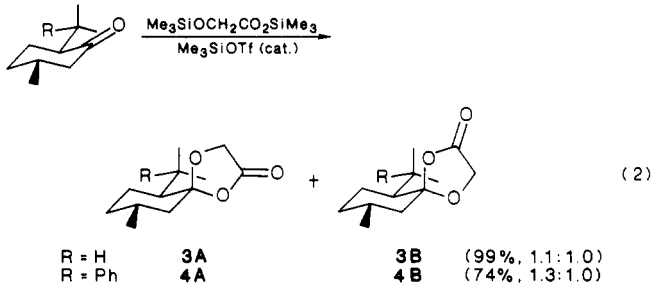
0022-3263/86/1951-3746$01.50/0 

**Table I. Alkylation of Dioxolanones 4a and 4b**




| dioxolanone | RX | yield (%) | products | ratio (A:B) | ratio (C:D) |
|---|---|---|---|---|---|
| 4A | $CH_3I$ | 97 | 5 | 14:1 | |
| 4A | $CH_2$=$CHCH_2I$ | 97 | 6 | 42:1 | |
| 4A | $PhCH_2Br$ | 96 | 7 | 58:1 | |
| 4A | *n*-BuI | 85 | 8 | 24:1 | |
| 4B | $CH_3I$ | 99 | 9 | | 24:1 |
| 4B | $CH_2$=$CHCH_2I$ | 96 | 10 | | 123:1 |
| 4B | $PhCH_2Br$ | 92 | 11 | | >123:<1 |
| 4B | *n*-BuI | 82 | 12 | | 28:1 |

methylsilyl)oxy)acetate[9] and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf).[10-12] The dioxolanones were formed in each case as a mixture of diastereomers (eq 2). Chemical transformations and



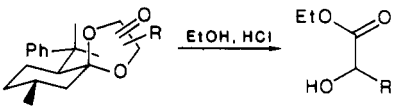

(2)

R = H **3A** **3B** (99%, 1.1:1.0)
R = Ph **4A** **4B** (74%, 1.3:1.0)

X-ray crystallography were utilized to assign the stereochemistry of these compounds (vide infra), since spectroscopic techniques did not allow direct assignment. Easy chromatographic separation of the dioxolanone diastereomers is crucial to the methodology. Whereas isomers **3A** and **3B** were only separated satisfactorily by HPLC, **4A** and **4B** were separated by flash column chromatography.[13]

Deprotonation of the dioxolanones was accomplished with lithium diisopropylamide (LDA) in THF at low temperature. Alkylation of **3B** with methyl iodide afforded a 92% yield of an 8.2:1 mixture of methylated dioxolanones. Separation and ethanolysis (vide infra) of the

**Table II. Hydrolysis of Alkylated Dioxolanones**




**13**

| compd | R | yield (%) | product | % ee | confign |
|---|---|---|---|---|---|
| 5A | $CH_3$ | 86 | 13A | 100 | *S* |
| 6A | $CH_2$=$CHCH_2$ | 83 | 13B | 100 | *S* |
| 7A | $PhCH_2$ | 95 | 13C[16] | 100 | *S* |
| 9C | $CH_3$ | 84 | 13D | 100 | *R* |
| 10C | $CH_2$=$CHCH_2$ | 84 | 13E | 100 | *R* |
| 11C | $PhCH_2$ | 95 | 13F[16] | 100 | *R* |

major isomer provided (*R*)-ethyl lactate, thereby supporting the stereochemical assignment for dioxolanone **3B**. For our purposes, the diastereoselectivity of this alkylation was deemed unsatisfactory. However, alkylation of both isomers of **4** proceeded with excellent diastereofacial selectivity, as shown in Table I.[11,14] Flash chromatography provided the major isomers in excellent yield and diastereomeric purity. At this stage, we were able to assign the stereochemistry of dioxolanone **11C** by X-ray crystallography (Figure 1).

Refluxing ethanolic hydrogen chloride served to liberate the $\alpha$-hydroxy esters **13** in good yield (Table II). The absolute configuration of the products is consistent with the stereochemical assignments for the dioxolanones **4A** and **4B**. Further, the 8-phenylmenthone auxilliary was recovered in 95–99% yield without epimerization or ke-

(8) Prepared by chromic acid oxidation[7] of Corey's 8-phenylmenthol: (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. See also: (b) Whitesell, J. K.; Liu, C.-L.; Buchanan, C. M.; Chen, H.-H.; Minton, M. A. *J. Org. Chem.* **1986**, *51*, 551.

(9) Wissner, A. *Tetrahedron Lett.* **1978**, 2749.

(10) This approach is related to work by Noyori[10a] on the preparation of dioxolanes and work by Jefford[10b] on the synthesis of 1,2,4-trioxan-5-ones: (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (b) Jefford, C. W.; Rossier, J.-C.; Richardson, G. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1064. Although condensation of $\alpha$-branched-$\alpha$-hydroxy acids (e.g., lactic acid) with carbonyl compounds proceeds well under acid-catalyzed conditions, such a route using glycolic acid itself is poor. See: (c) Farines, M.; Soulier, J. *Bull. Soc. Chim. Fr.* **1970**, 332. A full report on the synthesis of these rare dioxolanones will appear elsewhere.

(11) All new compounds were fully characterized by $^1H$ NMR, $^{13}C$ NMR, IR, MS, and combustion analyses (see supplementary material).

(12) A representative procedure is exemplified by the following preparation of **4A** and **4B**: 8-Phenylmenthone (6.68 g, 29.0 mmol) was added in a dropwise fashion to a solution of trimethylsilyl ((trimethylsilyl)-oxy)acetate (6.97 g, 36.2 mmol) and TMSOTf (0.32 g, 1.45 mmol) in anhydrous dichloromethane (20 mL) at −78 °C, and the solution was warmed to room temperature for 24 h. Pyridine (3 mL) was added, and the solution was poured into saturated aqueous sodium bicarbonate and extracted with ether. The organic phase was dried ($MgSO_4$), concentrated, and flash chromatographed[13] ($SiO_2$, 10% ethyl acetate/hexane) to provide 1.71 g (26%) of starting material and 6.20 g of a mixture of **4A** and **4B** (74%, $R_f$ 0.25) as a colorless oil. This mixture could be separated by flash chromatography ($SiO_2$, 5:15:80 acetonitrile/benzene-/hexane), providing **4A** ($R_f$ 0.24) and **4B** ($R_f$ 0.29) in a 1.3:1 ratio.

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(14) Representative procedure for alkylation and hydrolysis: Dioxolanone **4B** (0.115 g, 0.400 mmol) in THF (2 mL) was added in a dropwise manner to a solution of LDA (0.48 mmol) in THF (6 mL) at −78 °C. After 30 min, benzyl bromide (0.68 g, 4.0 mmol) was added, and the solution was stirred for an additional 2 h. Saturated aqueous sodium bicarbonate was added, and the mixture was extracted twice with ether. The organic layer was dried ($MgSO_4$) and concentrated to provide the crude product **11**, which was shown to be diastereomerically pure (>-123:<1) by capillary GC analysis. (In most cases, an authentic sample of the epimeric diastereomer was prepared in order to test for its presence. For example, LDA deprotonation of **11C** followed by an aqueous ammonium chloride quench at low temperature provided the alternative diastereomer **11D**). Flash chromatography ($SiO_2$, 10% ethyl acetate/hexane, $R_f$ 0.30) and recrystallization from ether/hexane gave 0.140 g (92%) of pure **11C**. Anhydrous hydrogen chloride was bubbled through a solution of **11C** (35 mg, 0.092 mmol) in absolute ethanol (4 mL) for 2 min. After being refluxed for 2 h, the solution was cooled, poured into saturated aqueous sodium bicarbonate, and extracted twice with ether. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography ($SiO_2$, 15% ethyl acetate/hexane) gave 20.5 mg (96%) of 8-phenylmenthone and 17.8 mg (99%) of (*R*)-**13F**, $R_f$ 0.12, $[\alpha]_D^{25}$ +21.40° (*c* 0.43, benzene) [lit.[16] $[\alpha]_D^{18}$ +22.5° (*c* 3.98, benzene)]. Formation of the Mosher's ester derivative[15] and comparison with the corresponding Mosher's derivative of (*S*)-**13C** showed no contamination with the *S* enantiomer by capillary GC and $^1H$ NMR.

(15) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(16) McKenzie, A.; Barrow, F. *J. Chem. Soc.* **1911**, *99*, 1910.

talization and was easily recycled. The hydroxy esters were found to be 100% optically pure by $^1$H NMR and capillary GC analysis of the Mosher's ester[15] derivatives.

Hence, a practical method for the asymmetric alkylation of glycolic acid has been developed, which affords either pure enantiomer of various α-hydroxy acid derivatives. Further, the chiral auxilliary is efficiently recycled. Related studies involving aldol condensations of these enolates and the synthesis of other hetero acids are currently underway.

(17) Note added in proof: A conceptually similar approach to α-hydroxy acids has recently been reported. See: Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *Tetrahedron Lett.* **1986**, *27*, 2731.

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**Supplementary Material Available:** X-ray data for compound **11C**; spectra and analytical data for all new compounds (20 pages); a listing of structure factors (4 pages). Ordering information is given on any current masthead page.

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