d, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 9.7 (q), 16.6 (q), 16.7 (q), 16.8 (q), 17.7 (q), 25.7 (q), 26.2 (t), 29.0 (s), 30.6 (s), 39.5 (t), 54.1 (t), 54.7 (t), 62.3 (t), 91.1 (s), 117.5 (d), 123.4 (d), 131.7 (s), 143.2 (s), 167.2 (s), 178.0 (s).

(*S*)-(*E*)-[1-^{2}H]-3,7-Dimethyl-2,6-octadien-1-yl Camphanate ([1-^{2}H]Geranyl Camphanate, 48). In a fashion similar to that described for **47**, 141 mg (0.65 mmol) of camphanoyl chloride was added to a solution of 39 mg (0.26 mmol) of (*S*)-1-deuteriogeraniol **46** and 67 mg (0.55 mmol) of 4-(*N*,*N*-dimethylamino)pyridine in 0.45 mL of dichloromethane. The reaction was monitored and worked up as described for **45**. The resultant oily residue was purified by flash chromatography on a 1.0 cm × 16.5 cm silica gel flash column to yield 66.5 mg (78%) of a white crystalline solid: TLC, R_f 0.21 (1:5.7 ethyl acetate/hexanes); IR (CCl_4) 2970, 2930, 2870, 2150, 1795, 1755, 1725, 1445, 1375, 1160, 1095, 1055, 1010 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3 H, s), 1.03 (3 H, s), 1.15 (3 H, s), 1.61 (3 H, s), 1.69 (3 H, s), 1.74 (3 H, s), 1.96 (2 H, m), 2.08 (4 H, m), 2.48 (2 H, m), 4.76 (1 H, d, J = 7.3 Hz), 5.08 (1 H, s), 5.39 (1 H, d, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 9.8 (q), 16.6 (q), 16.7 (q), 16.8 (q), 17.7 (q), 25.7 (q), 26.3 (t), 29.0 (s), 30.7 (s), 39.5 (t), 54.5 (t), 55.1 (t), 62.3 (dt, $J_{^2H,C}$ = 22.7 Hz), 90.8 (s), 117.5 (d), 123.5 (d), 131.7 (s), 143.4 (s), 167.2 (s), 178.0 (s); ^{2}H NMR (46 MHz, $CHCl_3$) δ 4.71 (s).

Rate of Pyrophosphorylation of Isopentenyl Tosylate (7). Into a dry 5-mm NMR tube, was added a solution of 90 mg (0.1 mmol) of recrystallized tris(tetra-*n*-butylammonium) hydrogen pyrophosphate (**1**) in 0.4 mL of dry acetonitrile by syringe. To this clear colorless solution was added, by syringe, 0.1 mL of a 0.5 M stock solution of 3-methyl-3-buten-1-yl *p*-toluenesulfonate in acetonitrile that was prepared by diluting 120 mg (0.5 mmol) of isopentenyl tosylate (**7**) into 1 mL of dry acetonitrile. The rate of the reaction was monitored by integration, at 15–20-min intervals, of the AA′XX′ resonances for starting material (AA′ at 7.44 ppm and XX′ at 7.78 ppm) and product AA′ at 7.56 ppm and XX′ at 7.13 ppm).

Rate of Pyrophosphorylation of Geranyl Chloride (11). A. Following a procedure that is similar for that described for **7**, 90 mg (0.1 mmol) of **1** was treated with 0.1 mL of a slightly turbid, 0.5 M solution of **11** in acetonitrile that was prepared by diluting 86 mg (0.5 mmol) of **11** into 1 mL of dry acetonitrile. The rate of the reaction was monitored by integration, at 15–20-min intervals, of the resonances for the protons at C1 of the starting material [4.05 ppm (2 H, d, J = 9.0 Hz)] and product [4.47 ppm (2 H, dd, J = 6.5 Hz, $J_{H,P}$ = 6.5 Hz)].

B. Following a procedure similar for that described for **7**, 90 mg (0.1 mmol) of **1** in 0.30 mL of dry acetonitrile was treated with 0.20 mL of a slightly turbid, 0.5 M solution of **11** in acetonitrile that was prepared as above. The rate of chloride displacement was monitored by integration, at 15–20-min intervals, of the resonances for the protons at C1 of the starting material [4.05 ppm (2 H, d, J = 9.0 Hz)] and product [4.47 ppm (2 H, dd, J = 6.5 Hz, $J_{H,P}$ = 6.5 Hz)].

Enzymatic Hydrolysis of 49. To a solution of 0.46 mg (200 units) of *E. coli* alkaline phosphatase in 2.5 mL of 0.2 mL of 0.2 M lysine buffer, pH 10.4, containing 2.0 mM magnesium chloride was added 46 mg (0.13 mmol) of (*S*)-[1-^{2}H]geranyl diphosphate (**34**). This mixture was incubated at 37 °C for 7 h with addition of enzyme (0.23 mg, 10.1 units) and magnesium chloride (5 μL of a 1.0 M stock solution) at 2-h intervals. The reaction mixture was transferred to a separatory funnel and extracted with four 2-mL portions of dichloromethane. The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford 16.7 mg (86%) of the desired *S* alcohol. This material was converted to its camphanate ester as described for the authentic camphanate ester **47**.

Acknowledgment. We are grateful for support of this work by the Institute of General Medical Sciences (Grants GM-25521 and GM-21328). The 300-MHz NMR spectrometer utilized in this study was acquired with National Science Foundation and National Institutes of Health instrumentation grants. Mass spectrometry is supported by National Science Foundation (Grants CHE-8100424 and CHE-8310031) and the University of Utah Instrument Funds Committee.

Registry No. **1**, 76947-02-9; **3**, 65094-22-6; **5**, 78715-61-4; **6**, 104714-96-7, 781-03-3; **8**, 104714-97-8; **9**, 104714-98-9; **10**, 100566-23-2; **11**, 5389-87-7; **12**, 104714-99-0; **13**, 104759-81-1; **14**, 67023-84-1; **15**, 68799-82-6; **16**, 870-63-3; **17**, 104715-00-6; **18**, 104715-01-7; **19**, 104715-02-8; **20**, 104715-03-9; **21**, 3415-48-3; **22**, 104715-04-0; **23**, 22679-02-3; **24**, 104715-05-1; **25**, 104715-06-2; **26**, 104715-07-3; **27**, 104715-08-4; **28**, 104715-09-5; **29**, 104715-10-8; **30**, 104715-11-9; **31**, 104715-12-0; **32**, 104715-13-1; **33**, 104715-14-2; **34**, 104715-15-3; **35**, 104715-16-4; **36**, 104715-17-5; **37**, 104715-18-6; **38**, 104715-19-7; **39**, 104715-20-0; **40**, 104715-21-1; **41**, 104738-00-3; **42**, 104715-22-2; (*E*)-**43**, 32659-21-5; (*Z*)-**43**, 32659-20-4; (*E*)-**44**, 32637-86-8; (*Z*)-**44**, 32637-85-7; **45**, 141-27-5; **46**, 104715-23-3; **47**, 41809-74-9; **48**, 104715-24-4; CH_2=$C(CH_3)CH_2CH_2OH$, 763-32-6; $(CH_3)_2C$=$CHCH_2OH$, 556-82-1; $(CH_3)_2CHCH_2CH_2OH$, 123-51-3; $FCH_2CH(CH_3)CH_2CH_2OH$, 104715-25-5; CH_2=$C(CH_2F)CH_2CH_2OH$, 104715-26-6; (*Z*)-$FCH_2C(CH_3)$=$CHCH_2OH$, 5944-19-4; (*E*)-$FCH_2C(CH_3)$=$CHCH_2OH$, 5944-60-5; (*Z*)-$F_2CHC(CH_3)$=$CHCH_2OH$, 104715-27-7; (*E*)-$F_2CHC(CH_3)$=$CHCH_2OH$, 104715-28-8; $(CH_3)_2NCH_2CH_2OH$, 108-01-0; (*E*)-$(CH_3)_2C$=$CHCH_2CH_2C(CH_3)$=$CHCH_2OH$, 106-24-1; (*Z*)-$(CH_3)_2C$=$CHCH_2CH_2C(CH_3)$=$CHCH_2OH$, 106-25-2; (*E*,*E*)-$(CH_3)_2C$=$CH(CH_2)_2(C(CH_3)$=$CH(CH_3)$=$CH(CH_2)_2)_2C(CH_3)$=$CHCH_2OH$, 106-28-5; $(CH_3)_2CH(CH_2)_3(CH(CH_3)(CH_2)_3)_2CH(CH_3)(CH_2)_2OH$, 645-72-7; $(CH_{32}C$=$CH(CH_2)_2(C(CH_3)$=$CHCH_2CH_2)_2C(CH_3)$=$CHCH_2OH$, 24034-73-9; $(CH_3)_2CHCH_2CH_iBr$, 107-82-4; $(CH3)_2NCH_2CH_2Cl$, 107-99-3; tris(tetra-*n*-butylammonium) hydrogen methanediphosphonate, 93978-76-8; butyl difluoromethanediphosphonate, 74860-86-9; ethyl difluoromethanediphosphonate, 78715-58-9; dibutyl phosphite sodium salt, 2244-27-1; triethyl phosphite, 122-52-1; dibromofluoromethane, 1868-53-7; bromotrimethylsilane, 2857-97-8; linalool, 78-70-6; 6-methyl-5-hepten-2-one, 110-93-0; triethyl phosphonoacetate, 867-13-0.

Auxiliary Structure and Asymmetric Induction in the Ene Reactions of Chiral Glyoxylates

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Received November 15, 1985

A variety of chiral auxiliaries (**1a–13a**) were prepared and tested for levels of asymmetric induction control in the ene reaction of chiral glyoxylates. Structural features required for high levels of control were defined by systematic modification of the auxiliary, providing systems with induction levels that ranged from 1.2 to 1 to better than 99.9 to 0.1.

In 1982 we reported a new method for the control of absolute stereochemistry using the ene reactions of chiral glyoxylates (eq 1).[1] This method represents by far the most powerful method so far reported for the formation

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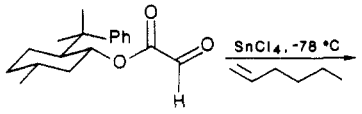
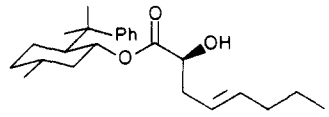


1d

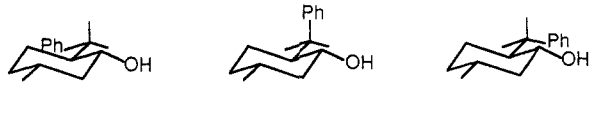


(1)

1e

of α-hydroxy esters and homoallylic alcohols with control of absolute stereochemistry.[2] We have recently detailed the properties of this reaction that are important to its application in synthesis using the chiral auxiliary 8-phenylmenthol.[3] The phenomenal degree of control observed (1000:1) in this process led us to search, through structural modification, for those features of the chiral auxiliary which are critical for high level stereochemical control.

Achmatowicz,[4] using menthol (**2a**) as the chiral auxiliary, was the first to demonstrate asymmetric induction in ene reactions of chiral glyoxylates. His results for carbon–carbon bond formation were impressive in that period of time but were not of synthetic significance. By employing Corey's chiral auxiliary 8-phenylmenthol (**1a**), and tin tetrachloride ($SnCl_4$) as a Lewis acid, we were able to dramatically improve these results and while it is obvious that the structural difference between **1** and **2** is the replacement of a hydrogen with a phenyl group, it was at first unclear as to how this modification so dramatically influenced the face selectivity in the ene reaction. Based strictly on steric interactions, it might be anticipated that conformation A would dominate over B and C and lead to a favoring of the transition state in which the backface of the glyoxylate moiety would be blocked only by a methyl group (Figure 1). However, with the auxiliary **3a** where the back face is always blocked by a methyl group (because of local symmetry), the level of induction was only marginally improved over that obtained with **2a**. Making the reasonable assumption that conformations A and B would result in diastereofacial selectivity in transition states little different than that obtained with **3**, it becomes clear that only conformation C could be involved in the reaction of **1a**. At first it appeared reasonable that there was π–π interaction in the transition state between the phenyl group and the glyoxylate moiety complexed with the Lewis acid catalyst. This argument had previously been invoked by Oppolzer to rationalize his results in the Diels–Alder reaction of the acrylate ester of **1**. In an attempt to influence the donor ability of the phenyl group, auxiliaries **4a** and **5a** were prepared. Unfortunately, the diastereomeric products from the ene reactions of the corresponding glyoxylates **4d** and **5d** were insufficiently resolved chromatographically to allow a precise assessment of the levels of inductions. Based on careful ^{13}C analysis, we can set a minimum level of induction in both cases of 95:5 but, unfortunately, this method does not allow for sufficient precision to assess the influence of the substituent fluoro and methoxy groups.



A B C

Figure 1.

E F

Figure 2.

The auxiliaries **6a** and **7a** were prepared in the anticipation that they would represent more readily accessible chiral auxiliaries than **1a**, especially since both enantiomeric forms would be equally accessible. It should be noted that while these have not yet been resolved, the influence of this auxiliary on stereochemical control can nonetheless be evaluated with the racemate since in all cases we are evaluating the level of control through internal reference (either spectroscopic or chromatographic) between the newly formed center and the chiral auxiliary. In both cases, however, the level of control was dramatically reduced. This result can be rationalized on the basis of serious steric interactions in those conformations (E and F) where the phenyl groups are suitably positioned to block the back face of the glyoxylate moiety (Figure 2). Such an interaction is also present when the phenyl group in **1** is suitably disposed (conformation C). However, the important difference is that **1** has a similar interaction present in all of its conformations while this is not the case with **6** and **7**.

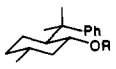
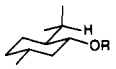
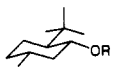
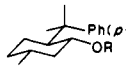
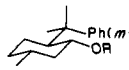
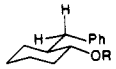
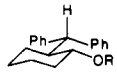
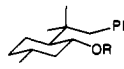
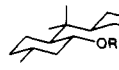
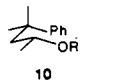
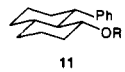
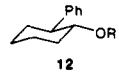
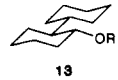
Auxiliary **8a** was prepared since it was anticipated that π–π stacking of the phenyl group with the glyoxylate unit would not be as favorable. Indeed, the results obtained are inferior to those from **1a**. However, there is still a residual influence of the aromatic group as the increase in level observed with **8** relative to **3** reflects a significant energy difference. That this is not due to steric interaction can be seen from the result with **9** (in which the phenyl group of **1** has been fully saturated) where the results are essentially identical with those obtained with **3**.

The auxiliary **10a** is commercially available (Aldrich) and, as would be expected, the enhanced conformational freedom present in **10** relative to **1** results in dramatically reduced levels of stereochemical control.

It should be noticed (Table I) that there are relatively dramatic differences in the proton shifts of the glyoxylates, as well as for the precursor bromoacetate and (nitrooxy)acetate esters. Indeed, the level of induction obtained with the auxiliaries **1a–7a** roughly correlates with the absorption of the glyoxylate proton. The upfield position of this proton in **1d**, **4d** and **5d** relative to **2d** and **3d** is presumably due to magnetic shielding by the aromatic ring and clearly indicates that in the ground state the conformer with the phenyl behind the glyoxylate is significantly populated. Notice, however, that both **7** and **8** do not fit directly into this pattern. In order to use the anisotropic shift effect of the phenyl group to estimate conformational populations, it was necessary to examine a system where the phenyl group is held rigidly in a position equivalent to that in conformer C. To this end we prepared the glyoxylate derived from the bicyclic auxiliary **11a**. Since the shift of the glyoxylate proton in **1d** relative to **2d** and **3d** is only approximately $^1/_2$ that of **11d**, we presume that the ground-state conformation in **1d** is populated to only the extent of approximately 50% by conformation C.

(1) Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989.
(2) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
(3) Whitesell; J. K.; Bhattacharya, A.; Buchanan, C. M.; Chen, H.-H.; Deyo, D.; James, D.; Liu, C.-L.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993.
(4) Achmatowicz, O., Jr.; Szechner, B. *J. Org. Chem.* **1972**, *37*, 964.

Table I

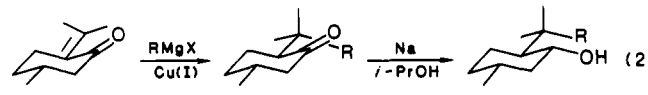
a, R = OH	de (%)	chemical shift (δ) $OCCH_2Br$ (b)	$OCCH_2ONO_2$ (c)	OCCHO (d)
 1	99.9:0.1	2.94	4.23/3.80	8.50
 2	2:1			9.30
 3	3.9:1	3.76		9.37
 4	>95:5	3.16	4.29/4.05	8.65
 5	>95:5	3.13	4.39/3.92	8.47
 6	1.5:1	3.72		9.18
 7	4.5:1	3.24/3.12	4.35/3.94	8.77
 8	8:1	3.72	4.70	9.36
 9	3.5:1			9.38
 10	2.3:1	3.26	4.37/4.09	8.75
 11	99.3:0.7	2.47/2.70	3.99/3.24	8.13
 12	>95:5	3.40	4.42/4.57	8.91
 13	1.2:1			9.42

Clearly then, the transition states for these processes differ significantly from the ground states and this would be anticipated if indeed the phenyl group is serving as a ligand for the Lewis acid. It would also be anticipated that changes in the Lewis acid could dramatically affect such interactions. Unfortunately, except for titanium tetrachloride (which affords results similar to those observed with tin tetrachloride), all other Lewis acids (Et_2AlCl, $EtAlCl_2$, BF_3, $ZnCl_2$, $FeCl_3$, and $MgBr_2$) examined in this reaction either afforded low yields of ene adducts contaminated with severl byproducts or were not effective in inducing the reaction.

Finally, we note the results with **12** where the phenyl group is in a dramatically different spatial position relative to the glyoxylate. Again, the importance of the aromatic system was demonstrated by comparison of the results of the fully saturated **13** with those for **12**.

While we cannot conclude from our results precisely how the aromatic group of these chiral auxiliaries influences asymmetric induction, it is clear that the aromatic moiety of the auxiliary is critically important for high levels of asymmetric induction and presumably is intimately involved at the transition state either directly with the glyoxylate unit or with the stannic ion to which it is complexed.

Synthesis of the Auxiliaries. The preparation of **1a** has previously been described and **2a** and **10a** are commercially available. Auxiliaries **3a**, **4a**, **5a**, and **8a** were prepared by the same general route (eq 2) used for 1:



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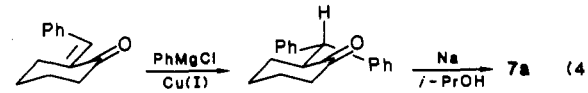

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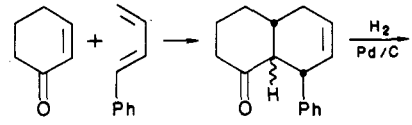
conjugate addition to pulegone followed by dissolving metal reduction of the resulting ketone. Auxiliaries **6a**, **12a** and **13a** were prepared by the Grignard opening of cyclohexene oxide (eq 3). Auxiliary **7a** was prepared in a manner analogous to **1a** except that benzylidenecyclohexanone was used in place of pulegone (eq 4). Auxiliary **9a** was prepare by catalytic reduction of **1a**. The *trans*-decalin **11a** was prepared by the Diels–Alder route illustrated in eq 5.[5]



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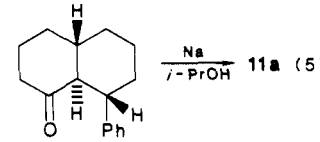
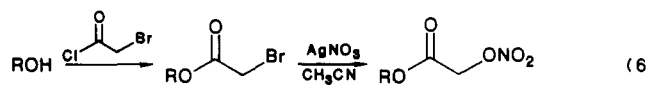


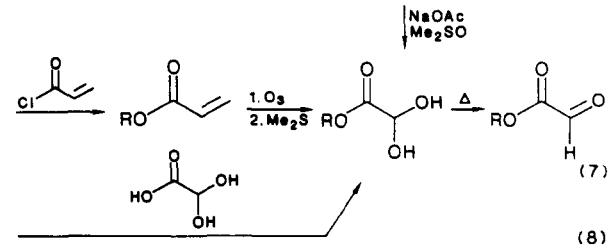
(5)

17

Conversion of the auxiliary alcohols to the glyoxylate esters was effectecd by using three different routes: through the bromo- and (nitrooxy)acetates (eq 6), by ozonolytic cleavage of the derived acrylate esters (eq 7), or by direct esterification with glyoxylic acid (eq 8). Yield data for these transformations and for the ene reactions with 1-hexene are provided in Table II.



(6)



(7)

(8)

(5) Ketone **17** had been previously prepared as a minor product from the catalytic reduction of the $\Delta^{4,8}$ isomer of **16**. See: House, H. O.; Thompson, H. W. *J. Org. Chem.* **1963**, *28*, 360.

Table II. Yields for the Synthesis for the Auxiliaries 3a–13a and the Synthesis and Ene Reactions of Glyoxylates 3d–13d

series	a	a → b	b → c	a → c	c → d	a → d	route	e
3	61			76	74	56	A	76
4	52	87	85		54	40	A	83
5	64	90	82		60	44	A	87
6	20					65	A	78
7				65	89	58	A	83
8	41	81	86		64	45	A	76
9	73					61	B	81
10		95	85		91	73	A	81
11	39					53	C	72
12	81			65	70	45	A	78
13	45					52	B	45

Experimental Section

Materials. Ether and tetrahydrofuran (THF) were distilled prior to use from a deep-blue solution resulting from benzophenone and sodium. Skelly-B (hexane) was stirred with sulfuric acid and then solid sodium carbonate and distilled before use. All other solvents and reagents were used as obtained from commercial sources.

Procedures. Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. Organic solutions of products were dried with molecular sieves (unless otherwise noted) prior to concentration in vacuo. Solutions are aqueous unless otherwise indicated. Some crude products were passed through short columns of silica gel with the indicated ratio of Skelly-B and EtOAc. Reference to purification by HPLC refers to the use of a Water Prep-500 system with two silica gel cartridges. Analytical HPLC analyses were performed on a Waters 6000A pump with a refractive index detector and a Microporasil column.

Spectra. ^{13}C NMR data were obtained on either a Nicolet NT-360 or a Varian FT-80A instrument. ^1H NMR were obtained on either a Nicolet NT-360, Nicolet NT-200, or a Varian EM-390 spectrophotometer. Both proton and carbon NMR were obtained with $CDCl_3$ as solvent and values are reported in ppm downfield from tetramethylsilane as internal standard. For the proton spectra, only those absorptions distinct from the broad band at 2.2–0.5 ppm are individually reported. Infrared (IR) spectra were obtained on dilute, dichloromethane solutions on a Perkin-Elmer 237B or 298 instrument. Low-resolution (EI) mass spectra were obtained on a Bell and Howell Model 21-491 instrument. High-resolution (EI) mass spectra were recorded with a CEC 21-110B instrument.

(1*R*,2*S*,5*R*)-2-*tert*-Butyl-5-methylcyclohexanol (3a). 1. (2*S*,5*R*)-2-*tert*-Butyl-5-methylcyclohexanone. To a solution of 384 mL (0.595 mol) of a 1.55 M ethereal solution of methyllithium in 600 mL of ether at 0 °C was added 57.1 g (0.30 mol) of anhydrous cuprous chloride and the resulting mixture was stirred for 10 min. A solution of 31.0 g (0.204 mol) of (*R*)-(+)-pulegone in 50 mL of ether was then added via syringe (ca 20 min), and the mixture was stirred for 2 h at 0 °C and then 12 h at room temperature. The reaction mixture was poured into 500 mL of ice-cold 2 N HCl with rapid stirring. The ether layer was separated and the aqueous layer was extracted (3×) with ether. The organic layers were combined, washed with brine, dried, concentrated, filtered through silica gel (10:1), and concentrated to afford 32.1 (94%) of a yellow liquid. The liquid was dissolved in 200 mL of methanol and 2 mL of 2 N NaOH was added. The mixture was stirred at room temperature for 3 days. The solvent was removed and the residue was dissolved in 300 mL of ether and washed with brine. After back-extracting the aqueous layer (2×) with ether, the combined organic layers were dried, concentrated, filtered through silica gel (10:1), and concentrated to afford 31.6 g (92%) of the desired ketone. ^{13}C NMR (20 MHz) 210.8 (s), 59.3 (d), 52.4 (t), 36.3 (d), 34.9 (t), 31.7 (s), 28.6, 27.7, 22.4 (q).

2. A mixture of 5.16 g (225 mmol) of sodium and 100 mL of toluene was heated at reflux for 20 min and then cooled to 0 °C. A solution of 12.6 g (74.9 mmol) of the ketone prepared above and 21.0 g (350.0 mmol) of isopropyl alcohol was added over a period of 15 min. The mixture was allowed to warm to room temperature and stir for 12 h. The isopropyl alcohol was removed under vacuum and the residue was added to 200 mL of brine and extracted (3×) with ether. The combined organic layers were dried, concentrated, filtered through silica gel (10:1), and concentrated to afford 11.8 g. Preparative HPLC (10:1) afforded 7.80 g (61%) of **3a**: ^{13}C NMR (20 MHz) 73.0 (d), 53.3 (d), 46.9 (t), 35.2 (t), 33.0 (s), 31.9 (t), 29.4 (q), 26.7 (d), 22.0 (q); ^1H NMR (90 MHz) 3.53 (dt, J = 4, 10 Hz, 1 H), 0.99 (s, 9 H); IR 3596, 2948, 2911, 2865, 1448, 1359, 1012 cm^{-1}; MS, m/z 170 (M^+), 152 (M – H_2O), 137, 113, 96, 81, 57; HRMS, m/z calcd for $C_{11}H_{22}O$ 170.1670, found 170.1665.

(1*R*,2*S*,5*R*)-2-*tert*-Butyl-5-methylcyclohexyl Bromoacetate (3b). A mixture of 7.0 g (41.1 mmol) of **3a**, 14.3 g (103 mmol) of 1-bromoacetic acid, 0.20 g (1.1 mmol) of *p*-toluenesulfonic acid monohydrate, and 100 mL of benzene was heated at reflux for 24 h with azeotropic removal of water and then cooled to room temperature and poured into 200 mL of cold saturated $NaHCO_3$. The aqueous layer was extracted (3×) with ether. The combined organic layers were washed with brine, dried, and concentrated to afford the crude ester: ^{13}C NMR (20 MHz) 167.1 (s), 77.6 (d), 44.9 (d), 41.1 (t), 34.3 (t), 32.5 (s), 31.1 (d), 29.0 (q), 26.2 (t), 21.7 (q); ^1H NMR (90 MHz) 4.80 (dt, J = 4, 10.5 Hz, 1 H), 3.76 (s, 1 H), 0.90 (s, 9 H).

(1*R*,2*S*,5*R*)-2-*tert*-Butyl-5-methylcyclohexyl (Nitrooxy)acetate (3c). The bromoacetate ester **3b** was dissolved in 100 mL of acetonitrile and to this solution 20.9 g (123.0 mmol) of silver nitrate was added. The mixture was stirred at room temperature for 48 h and concentrated at 30 °C, and the residue was extracted with 100 mL of ether. The solid (silver bromide) was removed and washed with ether. The combined organic layers were washed (2×) with water, dried, concentrated, filtered through silica gel (15:1), and concentrated to afford 26.3 g (76% from **3a**) of **3c**: ^{13}C NMR (20 MHz) 165.1, 77.4, 67.7, 50.0, 41.6, 34.6, 32.7, 31.4, 29.0, 26.6, 21.8.

(1*R*,2*S*,5*R*)-2-*tert*-Butyl-5-methylcyclohexyl Glyoxylate (3d). A mixture of 8.54 g (31.2 mmol) of (nitrooxy)acetate **3c** and 4.25 g (31.2 mmol) of sodium acetate trihydrate dissolved in 150 mL of dimethyl sulfoxide was stirred at room temperature for 1 h and then poured into 150 mL of ice–salt water. The solution was extracted (5X) with ether and the combined organic layers were washed with brine, dried, and concentrated. The resulting liquid was heated at 80 °C under vacuum (10 mmHg) for 1 h and then transferred at 78 °C under vacuum (0.15 mmHg) to afford 5.24 g (74%) of **3d**: ^{13}C NMR (20 MHz) 184.0 (d), 159.1 (small doublet), 78.1 (d), 49.9 (d), 41.3 (t), 34.5 (t), 32.8 (s), 31.4 (d), 29.0 (q), 26.5 (t), 21.7 (q); ^1H NMR (90 MHz) 9.37 (s, 1 H), 4.93 (dt, J = 4.5, 10 Hz, 1 H), 0.89 (s, 9 H); MS, m/z 153 (M – COOCOH), 137, 97, 81, 57 (base).

(1*R*,2*S*,5*R*)-2-*tert*-Butyl-5-methylcyclohexyl (2*S*)- and (2*R*)-2-Hydroxy-4(*E*)-octenoate (3e). To 1.06 g (4.68 mmol) of glyoxylate **3d** in 20 mL of CH_2Cl_2 at −78 °C was added via syringe 0.55 mL (4.69 mmol) of $SnCl_4$ over 1 min. After 5 min, 1.17 mL (9.36 mmol) of 1-hexene was added and the solution was stirred for 40 min after which 0.474 g (9.36 mmol) of trimethylamine was added to quench the reaction. The reaction mixture was then added to 50 mL of ether, washed with brine, dried, filtered through silica gel (10:1), and concentrated to afford 1.1 g (76%) of **3e**. HPLC analysis (3 Microporasil columns, 15:1, 0.5 mL/min) showed one large peak with a shoulder (t_R 34 min, α 1.05). Because of this poor resolution, the 3.9:1 ratio of the two diastereomers was calculated from the carbon-13 NMR spectrum: ^{13}C NMR (20 MHz) 173.9 (173.6), 134.4, 124.0 (124.2), 76.5 (77.0), 70.7 (71.0), 50.1 (49.9), 42.0 (41.8), 37.6 (37.0), 34.8, 32.7, 31.4, 29.1, 26.5, 22.5 (22.7), 21.8, 13.7 (14.1) (the absorptions in parentheses refer to the minor diastereomer); ^1H NMR (90 MHz) 5.51 (m, 2

H), 4.88 (dt, J = 4.5, 10.5 Hz, 1 H), 4.15 (t, J = 5 Hz, 1 H), 3.03 (bs, 1 H), 0.87 (s, 9 H); IR 3532, 3031, 2925, 2860, 1726, 1494, 1450, 1210 cm^{-1}; MS, m/z 152, 137, 113, 109, 97, 81, 57 (base); HRMS (CI),[6] m/z calcd for $C_{19}H_{34}O_3$ 310.2495, found 310.2499.

(1*R*,2*S*,5*R*)-2-(1-Methyl-1-(*m*-methoxylphenyl)ethyl)-5-methylcyclohexyl glyoxylate (5d) was prepared from **5c** in 60% yield by the same procedure used for **3d**: ^{13}C NMR (20 MHz) 183.4 (d), 159.1 (s), 157.6 (small d), 152.7 (s), 128.6 (d), 117.7 (d), 112.1 (d), 109.7 (d), 76.1 (d), 54.7 (q), 50.3 (d), 41.0 (t), 39.2 (s), 34.1 (t), 31.0 (d), 29.2 (q), 25.9 (t), 22.6 (q), 21.4 (q); ^1H NMR (90 MHz) 8.47 (s, 1 H), 7.27–6.53 (m, 4 H), 4.97 (dt, J = 4.5, 10.5 Hz, 1 H), 3.73 (s, 3 H), 1.27 (s, 3 H), 1.20 (s, 3 H), 0.87 (d, J = 6 Hz, 3 H); MS, m/z 318 (M^+), 244 (M – HCOOCOH), 229, 149 (base).

(1*R*,2*S*,5*R*)-2-(1-Methyl-1-(*m*-methoxylphenyl)ethyl)-5-methylcyclohexyl (2*S*)-2-hydroxy-4(*E*)-octenoate (5e) was prepared from **5d** and 1-hexene in 87% yield by the same conditions as for the previous ene reaction: ^{13}C NMR (20 MHz) 173.9, 159.4, 153.4, 134.3, 128.8, 123.7, 118.0, 112.3, 109.6, 75.9, 69.8, 55.2, 50.4, 41.7, 39.6, 37.1, 34.6, 34.5, 31.3, 28.7, 26.4, 23.9, 22.4, 21.7, 13.6; ^1H NMR (90 MHz) 7.35–6.65 (m, 4 H), 5.65–5.10 (m, 2 H), 4.88 (dt, J = 4.5, 10.5 Hz, 1 H), 3.80 (s, 3 H), 3.41 (t, J = 6 Hz, 1 H), 2.57 (bs, 1 H), 1.27 (s, 3 H), 1.14 (s, 3 H); IR 3540, 2960, 2928, 2870, 1722, 1600, 1582 cm^{-1}; MS, m/z 402 (M^+), 253, 245, 229, 149 (base); HRMS, m/z calcd for $C_{25}H_{38}O_4$ 402.2770, found 402.2778.

A mixture of both diastereomers was prepared by a thermal ene reaction. To a thick Pyrex tube were added 400 mg (1.26 mmol) of glyoxylate **5d**, 1.0 mL (8.00 mmol) of 1-hexene, and 7 mL of CH_2Cl_2. The tube was placed in liquid nitrogen and after the solution solidified the tube was sealed under vacuum. The tube was placed in an oven and heated at 190 °C for 20 h. The reaction mixture was removed and concentrated to afford 230 mg (58%). HPLC analysis (2 Microporasil columns, 15:1, 0.5 mL/min) showed two major peaks (α 1.50) in a 1:1 ratio. The more polar compound was identical with the single diastereomer observed from the Lewis acid catalyzed ene reaction. For the less polar diastereomer: ^{13}C NMR (20 MHz) 172.6, 159.5, 153.7, 134.3, 128.9, 124.2, 118.1, 112.5, 109.6, 76.0, 71.2, 55.2, 50.1, 41.7, 39.8, 36.6, 34.7, 32.0, 31.4, 28.4, 26.6, 24.6, 22.5, 21.7, 13.7; ^1H NMR (90 MHz) 7.36–6.66 (m, 4 H), 5.66–5.05 (m, 2 H), 4.90 (dt, J = 4, 10.5 Hz, 1 H), 3.80 (s, 3 H), 3.77 (m, 1 H).

(±)-(4aβ,8aα)-Decahydro-8α-phenyl-1α-naphthalenyl Glyoxylate (11d). A mixture of 2.62 g (11.4 mmol) of the alcohol **11a**, 2.11 g (28.4 mmol) glyoxylic acid hydrate, 0.5 g of *p*-toluenesulfonic acid, and 100 mL of benzene was heated at reflux with azeotropic removal of water. After 3 h an additional 1.0 g of glyoxylic acid was added and heating was continued for another 1.5 h. The reaction mixture was cooled and poured into 100 mL of ice water and the aqueous layer was separated and extracted (3×) with ether. The combined organic layers were washed with brine, dried, filtered through silica gel (2:1), and concentrated to afford 3.60 g. Preparative HPLC (3.3:1) afforded 0.61 g of recovered alcohol and a liquid that by ^1H NMR analysis was a mixture of glyoxylate and glyoxylate hydrate. The mixture was then heated at 100 °C under vacuum (0.4 mmHg) for 2 h to afford 1.73 g (53%) of **11d** as a white solid: mp 115–117 °C; ^{13}C NMR (20 MHz) 183.0 (d), 157.7 (small d), 147.2 (d), 128.1 (d), 125.8 (d), 78.6 (d), 50.6 (d), 49.6 (d), 41.8 (d), 37.0 (t), 33.6 (t), 33.3 (t), 32.7 (t), 26.1 (t), 23.6 (t); ^1H NMR (90 MHz) 8.13 (s, 1 H), 7.2–6.9 (m, 5 H), 4.85 (dt, J = 4, 10 Hz, 1 H), 2.35 (dt, J = 3, 10 Hz, 1 H); MS, m/z 286 (M^+), 213 (M – COOCOH), 117, 91 (base); HRMS, m/z calcd for $C_{18}H_{22}O_3$ 286.1568, found 286.1559.

(±)-(4aβ,8aα)-Decahydro-8α-phenyl-1α-naphthalenyl *trans*,*trans*-2-hydroxy-4(*E*)-octenoate (11e) was prepared from glyoxylate **11b** and 1-hexene in 72% yield by the same conditions as for the previous ene reactions. HPLC analysis (1 Microporasil, 15:1, 1 mL/min) on this liquid showed a major peak (11.7 min) and two minor peaks att 8.9 (α 1.59) and 9.1 min in 100:0.7:0.5 ratio: ^{13}C NMR (20 MHz) 174.2, 147.9, 133.8, 128.1, 127.2, 125.6, 124.0, 77.9, 68.7, 50.5, 49.6, 41.9, 37.7, 36.9, 34.7, 33.7, 33.6, 33.1, 26.2, 23.7, 22.5, 13.6; ^1H NMR (200 MHz) 7.31–7.16 (m, 5 H), 5.37 (dt, J = 16.2, 7.4 Hz, 1 H), 5.14 (dt, J = 16.2, 7.4 Hz, 1 H), 4.74 (dt, J = 4.4, 10.3 Hz, 1 H), 2.56 (dt, J = 4.6, 4.5 Hz, 1 H), 2.34 (dt, J = 3.8, 10.7 Hz, 1 H), 2.28 (d, J = 4.6 Hz, 1 H), 0.86 (t, J = 7.4 Hz, 3 H); IR 3532, 2922, 2851, 1720 cm^{-1}; MS, m/z 370 (M^+), 352 (M – 18), 212 (base), 117, 91; HRMS, m/z calcd for $C_{24}H_{34}O_3$ 370.2507, found 370.2515.

A thermal ene reaction under same conditions as the previous thermal ene reaction afforded an 81% yield of two diastereomers. HPLC analysis (1 Microporasil column, 15:1, 1 mL/min) showed two peaks (α 1.51) in 2.5:1 ratio. The two products were separated by semipreparative chromatography (25:1). NMR analysis showed the major product from both the Lewis acid catalyzed and thermal one reactions were identical. For the minor diastereomer: ^1H NMR (200 MHz) 7.33–7.15 (m, 5 H), 5.40 (dt, J = 14.7, 6.3 Hz, 1 H), 5.22 (dt, J = 14.7, 6.3 Hz, 1 H), 4.78 (dt, J = 4.4, 10.3 Hz, 1 H), 3.32 (t, J = 4.6 Hz, 1 H), 2.37 (dt, J = 3.8, 11.3 Hz, 1 H), 0.85 (t, J = 7.4 Hz, 3 H); IR 3559, 2922, 2850, 1725 cm^{-1}.

***trans*-2-Phenylcyclohexanol (12a).** To 10.9 g (0.45 mol) of magnesium and 100 mL of THF was added 73.0 g (0.465 mol) of bromobenzene in 100 mL of THF over 1 h. The resulting mixture was stirred for 0.5 h and then 8.85 g (46.5 mmol) of cuprous iodide was added and the mixture was cooled to −30 °C. A solution of 29.45 g (0.30 mol) of cyclohexene oxide in 50 mL of THF was then added dropwise. After the addition was complete, the mixture was stirred for 3 h and then quenched by being poured into 100 mL of cold saturated NH_4Cl. The solution was extracted with ether and the organic layers were combined, dried, and concentrated to afford a liquid that was distilled at 80 °C under vacuum (0.23 mmHg) to afford 43.1 g (81%) of **12a** as a yellow solid which was recrystallized from pentane: mp 56.5–57.0 °C (lit.[7] mp 57–58 °C); ^{13}C NMR (90 MHz) 143.4 (s), 128.7 (d), 127.9 (d), 126.7 (d), 74.3 (d), 53.3 (d), 34.6 (t), 33.4 (t), 26.1 (t), 25.1 (t); ^1H NMR (361 MHz) 7.35–7.17 (m, 5 H), 3.64 (ddd, J = 5.4, 10.8, 10.8 Hz, 1 H), 2.42 (ddd, J = 5.4, 10.8, 16.5 Hz, 1 H), 2.11 (m, 1 H), 1.84 (m, 2 H), 1.76 (m, 1 H), 1.62 (s, 1 H), 1.53–1.25 (bm, 4 H); IR 3592, 3461, 2941, 2863, 1604, 1497, 1451 cm^{-1}; MS, m/z 176 (M^+), 158, 143, 130, 117, 104, 91 (base).

***trans*-2-Phenylcyclohexyl bromoacetate (12b)** was prepared from **12a** by using the procedure used for **3b**: ^{13}C NMR (20 MHz) 166.1 (s), 142.5 (s), 128.3 (d), 127.4 (d), 126.5 (d), 77.8 (d), 49.5 (d), 33.7 (t), 31.9 (t), 25.8 (t), 25.7 (t), 24.6 (t); ^1H NMR (90 MHz) 7.3–7.0 (m, 5 H), 4.98 (dt, J = 5, 10 Hz, 1 H), 3.40 (s, 2 H), 2.65 (dt, J = 4, 10 Hz, 1 H); IR 2934, 2858, 1728, 1281, 1170 cm^{-1}; MS, m/z 158 (M – $COOCH_2Br$), 143, 130, 91.

***trans*-2-Phenylcyclohexyl (nitrooxy)acetate (12c)** was prepared from **12b** in 65% overall yield from **12a** by the same procedure used for **3c**: ^{13}C NMR (20 MHz) 165.1, 142.4, 128.5, 127.4, 126.8, 78.3, 67.0, 49.7, 33.8, 32.2, 25.7, 24.7; ^1H NMR (90 MHz) 7.3–7.0 (m, 5 H), 5.05 (dt, J = 4.5, 10.5 Hz, 1 H), 4.57 (d, J = 17 Hz, 1 H), 4.42 (d, J = 17 Hz, 1 H), 2.65 (dt, J = 4, 11 Hz, 1 H); IR 2934, 2859, 1753, 1659, 1291, 1219 cm^{-1}.

***trans*-2-Phenylcyclohexyl Glyoxylate (12d)** was prepared from **12c** in 70% yield by the same procedure used for **3d**: ^{13}C NMR (20 MHz) 183.6 (d), 158.5 (small d), 142.3 (s), 128.4 (d), 127.5 (d), 126.7 (d), 78.6 (d), 49.4 (d), 33.5 (t), 31.9 (t), 25.6 (t), 24.6 (t); ^1H NMR (90 MHz) 8.91 (s, 1 H), 7.23–6.95 (m, 5 H), 5.08 (dt, J = 4.5, 10.5 Hz, 1 H), 2.74 (dt, J = 4, 10.5 Hz, 1 H); IR 3520, 2943, 2866, 1750, 1726, 1291, 1228 cm^{-1}; MS, m/z 158 (M – COOHCOH), 143, 129, 91 (base). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.09; H, 7.29.

***trans*-2-Phenylcyclohexyl 2-hydroxy-4(*E*)-octenoate (12e)** was prepared from **12d** and 1-hexene in 78% yield by the same conditions for the previous ene reactions: ^{13}C NMR (20 MHz) 173.8, 143.0, 134.3, 128.4, 127.6, 126.7, 123.7, 77.5, 70.1, 49.9, 37.2, 34.6, 34.1, 32.3, 25.8, 24.7, 22.4, 13.6; ^1H NMR (90 MHz) 7.3–7.0 (m, 5 H), 5.36–4.50 (m, 3 H), 3.95 (t, J = 5 Hz, 1 H), 2.67 (dt, J = 4, 11 Hz, 1 H); IR 3548, 3539, 2937, 2860, 1729, 1208 cm^{-1}; MS, m/z 316 (M^+), 298, 203, 176, 158 (base), 91; HRMS: m/z calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2033.

A thermal ene reaction between the hydrate of **12d** and 1-hexene (15 h, 165 °C) afforded a 1:1 diastereomeric mixture of adducts (by carbon-13 NMR), one of which was identical with that obtained above. For the diastereomer: ^{13}C NMR (20 MHz) 173.6, 142.7, 134.5, 128.5, 127.4, 126.6, 123.5, 77.7, 70.0, 49.7, 37.4,

(6) We are grateful to Dr. David Russell (Department of Chemistry, Texas A & M University, College Station, TX 77843) for the HRMS data (chemical ionization) for **3e**.

(7) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *17*, 1503.

34.7, 33.8, 32.3, 25.8, 24.8, 22.5, 13.6.

Acknowledgment. We are grateful for support of this research by the National Institutes of Health (GM-31750) and by the Robert A. Welch Foundation (F-626).

Registry No. **1a**, 65253-04-5; **1b**, 80595-59-1; **1c**, 104197-95-7; **1d**, 84312-20-9; **2a**, 2216-51-5; **2d**, 26315-61-7; **3a**, 75419-02-2; **3b**, 104197-96-8; **3c**, 104197-82-2; **3d**, 104264-93-9; (2*S*)-**3e**, 104197-83-3; (2*R*)-**3e**, 104264-95-1; **4a**, 104197-76-4; **4b**, 104197-97-9; **4c**, 104198-04-1; **4d**, 104198-12-1; **4e**, 104197-84-4; **5a**, 104197-77-5; **5b**, 104197-98-0; **5c**, 104198-05-2; **5d**, 104198-13-2; (2*S*)-**5e**, 104197-85-5; (2*R*)-**5e**, 104264-96-2; **6a**, 5947-19-3; **6b**, 104197-99-1; **6c**, 104198-06-3; **6d**, 104213-46-9; **6e** (isomer 1), 104197-86-6; **6e** (isomer 2), 104264-97-3; **7a**, 104197-78-6; **7b**, 104198-00-7; **7c**, 104198-07-4; **7d**, 104198-14-3; **7e** (isomer 1), 104197-87-7; **7e** (isomer 2), 104264-98-4; **8a**, 104197-79-7; **8b**, 104198-01-8; **8c**, 104198-08-5; **8d**, 104213-47-0; (2*S*)-**8e**, 104197-88-8; (2*R*)-**8e**, 104264-99-5; **9a**, 104197-80-0; **9d**, 104198-15-4; (2*S*)-**9e**, 104197-89-9; (2*R*)-**9e**, 104265-00-1; **10a**, 2035-93-0; **10b**, 104198-02-9; **10c**, 104198-10-9; **10d**, 99457-86-0; **10e** (isomer 1), 104197-90-2; **10e** (isomer 2), 104265-01-2; **11a**, 104197-81-1; **11b**, 104198-03-0; **11c**, 104198-11-0; **11d**, 104198-16-5; **11e** (isomer 1), 104197-91-3; **11e** (isomer 2), 104265-02-3; **12a**, 2362-61-0; **12b**, 104197-93-5; **12c**, 104197-94-6; **12d**, 98779-11-4; **12e** (isomer 1), 104264-94-0; **12e** (isomer 2), 104265-03-4; **13a**, 6531-86-8; **13d**, 104198-17-6; **13e** (isomer 1), 104197-92-4; **13e** (isomer 2), 104265-04-5; **14**, 5682-83-7; **15**, 30614-39-2; **16** (isomer 1), 104198-20-1; **16** (isomer 2), 104198-21-2; **17**, 104265-05-6; $SnCl_4$, 7646-78-8; (1*R*,2*S*,5*R*)-2-*tert*-butyl-5-methylcyclohexanone, 56782-80-0; methyllithium, 917-54-4; (*R*)-(+)-pulegone, 89-82-7; 1-bromoacetic acid, 79-08-3; 1-hexene, 592-41-6; glyoxylic acid, 298-12-4; bromobenzene, 108-86-1; cyclohexene oxide, 286-20-4; para-fluorophenyl bromide, 460-00-4; meta-bromoanisole, 2398-37-0; benzylmagnesium chloride, 6921-34-2; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7; phenylmagnesium chloride, 100-59-4; *cis*-2-diphenylmethylcyclohexanol, 104198-18-7; *cis*-2-diphenylmethylcyclohexyl bromoacetate, 104198-19-8; (1*R*,2*S*,5*R*)-2-(1-methyl-1-cyclohexylethyl)-5-methylcyclohexanol acrylate, 104198-09-6; acryloyl chloride, 814-68-6; 2-cyclohexenone, 930-68-7; *trans*-1-phenyl-1,3-butadiene, 16939-57-4; (±)-(4aα,8aβ)-decahydro-8β-phenyl-1α-naphthalenol, 104265-06-7; cyclohexyl bromide, 108-85-0; *trans*-2-cyclohexylcyclohexyl acrylate, 104198-22-3.

Supplementary Material Available: Experimental details for the preparation of and spectral data for **4a–e**, **6a–e**, **7a–e**, and **8a–e**; **5a–c** and **11a–c**; **9a,d,e**; **10b–e**; **13d,e**; and **14–17** (21 pages). Ordering information is given on any current masthead page.

Synthesis, Electrochemistry, and Xanthine Oxidase Substrate Reactivity of Imidazo[4,5-*g*]quinazoline-4,9-diones. Studies Directed toward the Design of Purine-like Reductive Alkylators

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Received August 22, 1986

The synthesis of imidazo[4,5-*g*]quinazoline-4,9-diones related to hypoxanthine and xanthine, **1** and **2**, respectively, was carried out in conjunction with the design of quinone-like purine mimics. These derivatives may exhibit purine-like binding to enzymes as well as quinone-mediated reactions such as reductive alkylation. Potential reductive alkylators are represented by compounds possessing a leaving group in the 2α-position: 2-(methoxymethyl)-3-methylimidazo[4,5-*g*]quinazoline-4,8,9(3*H*,7*H*)-trione (**1d**); the 2-(bromomethyl) derivative of **1d** (**1e**); and 2-(methoxymethyl)-3-methylimidazo[4,5-*g*]quinazoline-4,6,8,9(3*H*,5*H*,7*H*)-tetrone (**2b**). Reduction of these systems, perhaps in low-potential tumor cells, should activate the leaving group and thereby facilitate the alkylation of purine-utilizing enzymes. Elaboration of the 4,9-dione (benzoquinone) moiety of **1** was carried out by either oxidation of 4-aminoimidazo[4,5-*g*]quinazoline derivatives with Fremy's radical or oxidation of 4,9-unsubstituted derivatives with nitrogen dioxide. The xanthine derivatives were prepared from **1** by xanthine oxidase mediated oxidation. A study of the enzymatic oxidation of **1** → **2** (pH 7.40) indicated that the associated catalytic parameters are comparable to the natural substrates, even though the hypoxanthine derivatives **1** exist largely in the anionic form and the natural substrates do not. Thus, the title quinones are purine mimics, at least in the case of xanthine oxidase oxidation. Comparative electrochemical studies of 2,3-dimethylimidazo-[4,5-*g*]quinazoline-4,8,9(3*H*,7*H*)-trione (**1b**) and 1,2-dimethylbenzimidazole-4,7-dione (**14**) provided insights into the influence of the fused pyrimidine ring on the quinone redox potential. The neutral fused pyrimidine ring has no effect on the potential whereas the anionic form (pK_a of **1b** is 6.15) lowers the potential. The expected low potentials for the title quinones at or above neutrality are desirable in terms of reductive alkylation; reduction will only occur in a low-potential environment. The electrochemical studies also revealed that a high-potential diprotonated quinone species (**1b**·H_2^{2+}) is present in strong-acid solutions. In hydrobromic acid solutions **1b**·H_2^{2+} readily oxidizes bromide to bromine, presumably by two-electron transfer from a bromo adduct. The conclusion of the study is that the design of reductive alkylators directed toward the active sites of purine-utilizing enzymes is feasible; preliminary studies suggest that this is indeed the case.

Although many imidazo[4,5-*g*]quinazolines have been reported in the literature,[1] there are no reports of derivatives bearing 4,9-dione substitution. The work of Leonard and co-workers[1b,2] has shown that analogues of this ring system are purine mimics in many enzymatic reactions. Their findings led to our interest in imidazo[4,5-*g*]-quinazoline-4,9-diones; such derivatives may exhibit purine-like binding to enzymes as well as some of the chemical properties of quinones. Thus, quinone-mediated reactions such as oxygen radical generation,[3] carbonyl addition,[4] and reductive alkylation[5] may be exploited for the

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