Acknowledgment. We are grateful to Dr. Michal Sabat, Department of Chemistry, Northwestern University, Evanston, IL, for his assistance in obtaining the crystallographic data.

Registry No. (*E*)-1-(*N*,*N*-Dimethylamino)-2-nitroethene, 73430-27-0; (*Z*)-1-(*N*,*N*-dimethylamino)-2-nitroethene, 87446-70-6; (*N*,*N*-dimethylamino)ethene, 5763-87-1; 1-(*N*-pyrrolidino)cyclopentene, 7148-07-4; 1-(*N*-pyrrolidino)cyclohexane, 1125-99-1; 1-(*N*-morpholino)cyclopentane, 936-52-7; 1-(*N*-hexamethyleneimino)cyclopentane, 7374-91-6; 1-(*N*-morpholino)-2-nitroethene, 101419-83-4; 1-(*N*-morpholino)-2-nitropropene, 102631-85-6; 1-(2,6-dimethylmorpholino)-2-nitroethene, 119656-36-9; 1-(2,6-dimethylmorpholino)-2-nitropropene, 119656-37-0; 1-(*N*-methylanilino)-2-nitroethane, 61404-93-1; 1-(*N*-ethylanilino)-2-nitroethene, 99068-20-9.

Supplementary Material Available: Complete crystallographic data for 1-(*N*-morpholino)-2-nitroethene (positional parameters, bond lengths, bond angles, and dihedral angles) (5 pages). Ordering information is given on any current masthead page.

Observations on the Reactions of Chiral Pyruvates. Synthesis of (-)- and (+)-Citramalic Acid

James K. Whitesell,* Kathy Nabona, and Don Deyo

Department of Chemistry, University of Texas at Austin, Austin, Texas 78712

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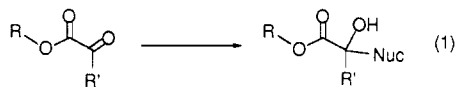
In 1983 we reported on the reduction, nucleophilic addition, and ene reactions (eq 1) of α-keto esters derived from 8-phenylmenthol (**1**)[1] (Figure 1). Unfortunately, the report of an ene reaction between the pyruvate ester and 1-hexene in the presence of $SnCl_4$ was in error as in fact the main products from that reaction appear to be those resulting from aldol reaction–condensation of the pyruvate with itself. Use of other Lewis acids ($EtAlCl_2$, $AlCl_3$, BF_3)



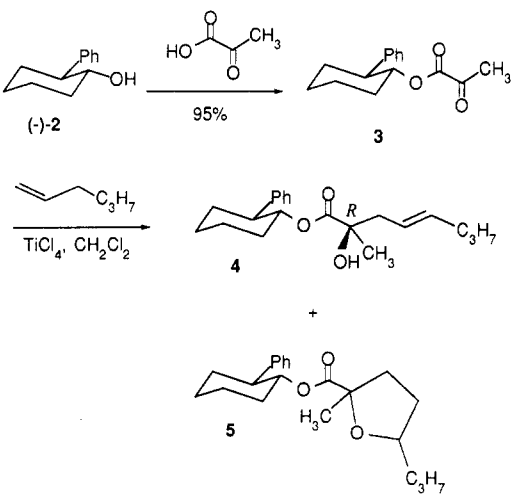
(1)

did not result in significant ene reaction. Apparently, the rate of proton loss from the complex of the pyruvate and the Lewis acid is faster than the addition of the alkene, and the addition of this enol derivative to the complex is faster yet.

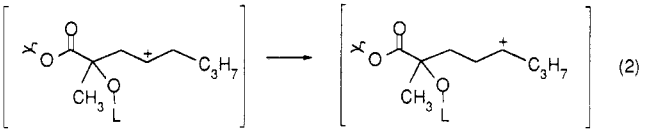
On the other hand, we have found that the corresponding keto esters derived from *trans*-2-phenylcyclohexanol (**2**)[2] undergo ene reactions with good to excellent levels of stereochemical control.[3] Thus, reaction of the pyruvate ester of *trans*-2-phenylcyclohexanol (**3**) with 1-hexene in the presence of $TiCl_4$ afforded adduct **4** with acceptable chemical yield and level of stereochemical control (Scheme I). Interestingly, and in contrast to reaction with the corresponding glyoxylate esters,[4] 2 equiv of the Lewis acid are required—use of only 1 equiv resulted

Figure 1.

Scheme I



in no reaction. Significant amounts of a cyclic product (**5**) were also formed.[5] Optimum conditions for stereochemical control (extended time at low temperature) were also those that afforded the poorest ratio of **4** to **5** (Table I). Presumably, an initially formed cation intermediate suffers 1,2-hydrogen shift to form a regioisomeric cation that is captured internally by oxygen (eq 2) in competition with proton loss to form the adduct **4**. On the other hand, the



(2)

reaction between the pyruvate ester **3** (derived from (–)-**2**) and 3-(trimethylsilyl)-1-propene in the presence of tin tetrachloride at −78 °C afforded the adduct as a single diastereomer (de greater than 99⁺%) (Scheme II). As in the reaction with 1-hexene, a small quantity (<5%) of a cyclic byproduct (**7**), presumably resulting from 1,2-shift of the silyl group in an intermediate cation, was also obtained.[5]

Conversion of adduct **6** to citramalic acid[6] illustrates the potential of this method for stereochemical control and, as well, provided an avenue by which the *absolute* sense of stereochemical direction could be readily determined. Thus, oxidation of the alkene linkage in **6** with potassium permanganate/sodium periodate[13] afforded the ester–acid

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(2) Whitesell, J. K.; Chen, H.-H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663. Whitesell, J. K.; Lawrence, R. M. *Chimia* **1986**, *40*, 318.

(3) In contrast to the high level of stereochemical control observed in the reaction with alkenes, reaction of **3** with allyl magnesium bromide afforded both diastereomers of **6** with little selectivity (1.3:1).

(4) Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc. Chem. Commun.* **1982**, 989. Whitesell, J. K. *Acct. Chem. Res.* **1985**, 280. 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.

(5) Neither the proton nor the carbon NMR spectra are of significant use in assigning the relative stereochemistry within the tetrahydrofuranyl rings of byproducts **5** and **7** as one of the centers in this five-membered ring is quaternary.

(6) Enantiomerically pure citramalic acid is available as a microbial metabolite[7] and has been synthesized previously with good to excellent control of absolute stereochemistry. A number of syntheses of this acid have been reported,[8-13] where Eliel's synthesis[11] of both enantiomers of dimethyl 2-acetyl citramalate in 96% ee represents the highest level of control in setting absolute stereochemistry and Wynberg's[10] potentially the most practical because of its application of catalytic asymmetric induction.

(7) Barker, H. A.; Blair, A. H. *Biochem. Prep.* **1962**, *9*, 21.
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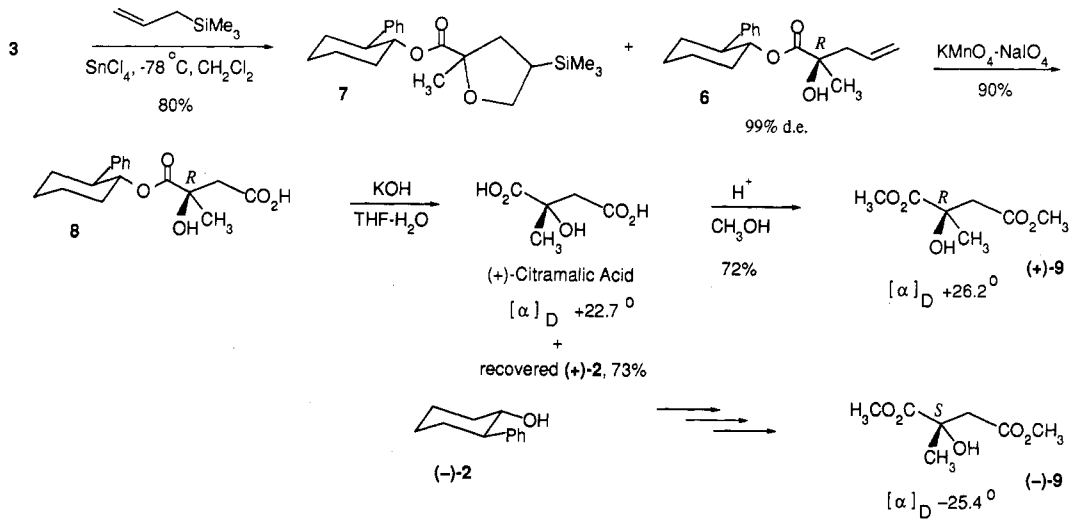
0022-3263/89/1954-2258$01.50/0

Table I

equiv of $TiCl_4$	equiv of 1-hexene	time, min	temp, °C	yield, %	4:5	de (4), %
2	8	60	0	58	12:1	82
2	6	15	0	85	15:1	86
2	6	45	−78	85	1.8:1	91

Scheme II



8, which was readily cleaved with hydroxide to produce citramalic acid as well as recovered chiral auxiliary. Purification by crystallization afforded material with an optical purity of 96%. Conversion to the corresponding diester (HCl–methanol) resulted in (−)-dimethyl citramalate with an optical purity of 93%. The (+)-enantiomer of the chiral auxiliary was carried through the same sequence of reactions to form the enantiomeric citramalic acid, which was again converted to the diester (96% optical purity).

Surprisingly, the absolute sense of stereochemical induction in the reaction of allyltrimethylsilane and pyruvate **3** derived from (−)-**2** to form **6** is the same as that observed with the corresponding gloxylate ester of (−)-**2** but *opposite* to that observed for the same reaction with the gloxylate of 8-phenylmenthol where the spatial relationship of the phenyl groups is the same. We feel that this reversal in stereochemical direction may be the result of different roles played by the phenyl groups in the two auxiliaries. We have previously suggested that there is the possibility for the aromatic ring to act as a π-donor in 8-phenylmenthol systems, an interaction that seems less likely with *trans*-2-phenylcyclohexanol as the auxiliary. It should be noted in this regard that there is a upfield shift of the olefinic protons (5.07 and 4.52 δ) for the major diastereomer of **4** (and **6**) relative to analogous compounds derived from the glyloxylate of 8-phenylmenthol (5.4 δ) as well as alcohols lacking the aromatic ring. This effect contrasts with that observed, for example, on the bromoacetate esters where the aromatic ring of 8-phenylmenthol causes a larger upfield shift of the acetate hydrogens (2.94 δ) as compared with *trans*-2-phenylcyclohexanol (3.40 δ).[4]

Experimental Section

Materials. Ether and tetrahydrofuran (THF) were distilled prior to use from a deep-blue solution resulting from benzophenone and sodium. Benzene and methanol were stored over molecular sieves. Methylene chloride and triethylamine were distilled from calcium hydride and stored over molecular sieves. Skelly-B was stirred first with concentrated sulfuric acid and then with solid sodium carbonate, filtered through alumina, and distilled before use. All other solvents and reagents were used as obtained from commercial sources unless stated otherwise.

Procedures. Reactions were routinely carried out under dry nitrogen or argon atmospheres with magnetic stirring. Preparative chromatography was carried out with use of recycling techniques with either a Waters Prep-500 system with two normal-phase silica gel cartridges or a Waters 600A HPLC with two 7.8 mm × 60 cm Porasil A silica gel semiprep columns with a refractive index detector.

Spectra. Carbon NMR spectra were obtained by using either a Nicolet NT-360 spectrometer at 90 MHz or a Varian FT-80A at 20 MHz. Proton NMR spectra were obtained with a Nicolet NT-360 at 361 MHz. Both carbon and proton NMR spectra were obtained in chloroform-*d*, and chemical shift values are reported in ppm downfield shift from TMS as an internal standard. IR spectra were obtained on dilute (5%) methylene chloride solutions with a Beckman Acculab 8 or a Perkin-Elmer 298 infrared spectrophotometer, with use of polystyrene's absorption at 1601.4 cm^{-1} as a reference. Low-resolution mass spectra in EI mode were recorded using a Bell and Howell Model 21-491 spectrometer at 70 eV and those in CI mode using a Finnigan-MAT 4023 GC/MS with methane. High-resolution mass spectra were recorded with a CEC 21-110B instrument in EI mode. Only m/Z values greater than or m/Z greater than or equal to 90 amu are reported. Optical rotations were measured with a Perkin-Elmer 141 polarimeter using the sodium D line.

***trans*-2-Phenylcyclohexyl Pyruvate (3).** A solution of 4.41 g (25 mmol) of *trans*-2-phenylcyclohexanol (**2**), 7.28 g (83 mmol) of pyruvic acid, and 0.27 g (1.6 mmol) of *p*-toluenesulfonic acid in 100 mL of benzene was heated at reflux with azeotropic removal of water for 3 h. The reaction mixture was cooled and then washed with saturated sodium bicarbonate, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (magnesium sulfate) and filtered through silica gel (10:1 Skelly-B–ethyl acetate), and the solvent was removed to afford 5.80 g (94%) of pyruvate **3** as a pale yellow oil: ^{13}C NMR δ 192.1 (s), 160.1 (s), 142.3 (s), 128.4 (d), 127.6 (d), 126.8 (d), 79.0 (d), 49.7 (d), 33.3 (t), 31.9 (t), 26.5 (q), 25.6 (t), 24.7 (t); ^1H NMR δ 7.32–7.10 (m, 5 H), 5.06 (dt, J = 5, 11 Hz, 1 H), 2.77 (dt, J = 4, 11 Hz, 1 H), 2.20–1.20 (m, 8 H), 2.12 (s, 3 H); IR 2930, 2860, 1725, 1145, 1120 cm^{-1}; HRMS m/e calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1247.

***trans*-2-Phenylcyclohexyl 2-Hydroxy-2-methyl-4-octenoate (4).** The experimental conditions that gave the highest ratio of **4** to **5** are as follows. To a stirred solution of 0.90 g (3.7 mmol) of the pyruvate **3** in 25 mL of methylene chloride under a nitrogen atmosphere at 0 °C was added 1.41 g (7.4 mmol) of titanium tetrachloride, causing the mixture to turn dark orange. After 5 min, 2.0 g (23 mmol) of 1-hexene was added. After 15 min, the

reaction was quenched by the addition of several mL of a saturated, aqueous sodium bicarbonate solution. The mixture was washed with water and dried (magnesium sulfate). The solvent was removed, and the product was filtered through silica gel (10:1 SkB–ethyl acetate) to afford as a clear oil 1.04 g (85%) of a 15:1 mixture (by HPLC analysis) of **4** (as a 6.1:1 diastereomeric mixture) and the cyclic product **5**. The two adducts, **4** and **5**, were separated by semipreparative HPLC (15:1 SkB–ethyl acetate). Higher diastereomeric selectivity (10.2:1) in the formation of **4** was obtained when the reaction was initiated at and held at −78 °C for 45 min. These conditions gave a combined 85% yield of **4** and **5** in a 1.8:1 ratio.

For **4**: ^{13}C NMR δ 175.7 (s, C1), 143.0 (s), 134.9 (d, C5), 128.4 (d), 127.5 (d), 126.6 (d), 123.5 (d, C4), 77.8 (d), 73.9 (s, C2), 49.8 (d), 43.2 (t, C3), 34.5 (t, C6), 33.9 (t), 32.2 (t), 25.8 (t), 25.1 (q, C2 Me), 24.7 (t), 22.5 (t, C7), 13.6 (q, C8); ^{1}H NMR δ 7.30–7.15 (m, 5 H), 5.07 (dt, J = 16, 7 Hz, 1 H), 4.97 (dt, J = 5, 11 Hz), 4.52 (dt, J = 16, 7 Hz, 1 H), 2.83 (b s, 1 H), 2.71 (dt, J = 5, 11 Hz, 1 H), 2.20–2.08 (m, 2 H), 1.98–1.71 (m, 5 H), 1.62–1.13 (m, 7 H), 1.22 (s, 3 H), 0.84 (t, J = 8 Hz, 3 H); IR 3540, 2935, 1725, 1205 cm^{-1}; HRMS m/e calcd for $C_{21}H_{30}O_3$ 330.2195, found 330.2201.

For **5**: ^{13}C NMR δ 174.4 (s, C1), 143.2 (s), 128.3 (d), 127.6 (d), 126.4 (d), 83.0 (s, C2) 79.6 (d, C5), 76.3 (d), 50.1 (d), 38.1 (t, C6), 35.7 (t, C3), 34.0 (t), 32.2 (t), 30.3 (t, C4), 25.8 (t), 24.8 (q, C2 Me), 24.5 (t), 19.0 (t, C7), 14.1 (q, C8); ^{1}H NMR δ 7.30–7.10 (m, 5 H), 5.03 (dt, J = 5, 11 Hz, 1 H), 3.78 (quin, J = 7 Hz, 1 H), 2.68 (dt, J = 4, 9 Hz, 1 H), 2.10 (m, 1 H), 2.00–1.75 (m, 3 H), 1.60–1.15 (m, 12 H), 1.22 (s, 3 H), 0.88 (t, J = 7 Hz, 3 H); IR 2940, 1730, 1185, 1120 cm^{-1}; HRMS m/e calcd for $C_{21}H_{30}O_3$ 330.2195, found 330.2204.

***trans*-2-Phenylcyclohexyl 2-Hydroxy-2-methyl-4-pentenoate (6).** To a solution of 2.03 g (8.3 mmol) of the pyruvate **3** in 50 mL of methylene chloride under a nitrogen atmosphere at −78 °C was added 2.58 g (9.9 mmol, 1.16 mL) of tin tetrachloride. After 10 min, 2.36 g (21 mmol, 3.28 mL) of trimethylallylsilane in 5 mL of methylene chloride was added to the yellow reaction mixture. After being stirred for 45 min, the reaction mixture was quenched with 4 mL of triethylamine. Upon warming to room temperature, the reaction mixture was washed once with water, dried (magnesium sulfate), and concentrated. The resulting residue was filtered through a short silica gel column (10:1 Skelly-B–ethyl acetate) and concentrated to afford 1.90 g (80%) of a yellow oil. The product was very clean by spectral analysis. Only one diastereomer was seen by HPLC (30:1 Skelly-B–ethyl acetate) and NMR spectral analysis. A small amount of **7** (16%) was also formed.

For **6**: ^{13}C NMR δ 175.8 (s), 142.7 (s), 132.4 (d), 128.4 (d), 127.5 (d), 126.6 (d), 118.8 (t), 77.9 (d), 73.9 (s), 50.1 (d), 44.3 (t), 33.9 (t), 32.3 (t), 25.8 (t), 25.2 (q), 24.7 (t); ^{1}H NMR δ 7.27 (m, 2 H), 7.19 (m, 3 H), 5.00 (m, 2 H), 4.78 (dd, J = 2.5, 10 Hz, 1 H), 4.65 (dd, J = 2, 16 Hz, 1 H), 2.85 (br, 1 H), 2.70 (t, J = 4, 11 Hz, 1 H), 2.16 (m, 1 H), 2.00–1.30 (m, 9 H), 1.25 (s, 3 H); IR 3545, 2940, 1730, 1228, 1165 cm^{-1}; HRMS m/e calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1736. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.02; H, 8.43.

For **7**: ^{13}C NMR δ 174.6 (s), 143.1 (s), 128.2 (d), 127.6 (d), 126.5 (d), 82.7 (s), 76.5 (d), 71.9 (t), 50.0 (d), 38.7 (t), 33.8 (t), 32.2 (t) 26.9 (d), 25.8 (t), 24.7 (t), 24.6 (q), −2.9 (q); ^{1}H NMR δ 7.25–7.00 (m, 5 H), 5.18 (dt, J = 5, 11 Hz, 1 H), 3.84 (t, J = 7.7 Hz, 1 H), 3.55 (dd, J = 10, 13 Hz, 1 H), 2.82 (td, J = 5, 11 Hz, 1 H), 2.02 (m, 1 H), 1.90–1.10 (m, 10 H), 1.05 (s, 3 H), −0.24 (s, 9 H); IR 3510, 2935, 1730, 1210, 1120 cm^{-1}; HRMS m/e calcd for $C_{21}H_{32}O_3Si$ 360.2121, found 360.2120.

***trans*-2-Phenylcyclohexyl Citramalate (8).** A solution of 320 mg (1.1 mmol) of the adduct **6**, 30 mg (0.17 mmol) of potassium permanganate, and 1.41 g (6.6 mmol) of sodium periodate in 35 mL of water was stirred at room temperature for 20 h, during which time it lost its dark purple color and became brick-red. The reaction mixture was extracted six times with ether, and the organic layers were combined, dried, and concentrated. The resulting oil was filtered through a short silica gel column (1:1 SkB–EtOAc) to give a clear oil. NMR analysis of the product showed that the acid **8** was contaminated with about 25% of unreacted **6**. Flash chromatography on a silica gel column (5:1 SkB–EtOAc) afforded 90 mg of **6** followed by elution with 5:1 SkB–acetone with 5% acetic acid to afford 230 mg of the acid **8**. The unreacted **6** was subjected to the same reaction conditions as described above, affording an additional 80 mg for a combined yield 310 mg (90%) of **8**: ^{13}C NMR δ 175.9 (s), 174.5 (s), 142.6 (s), 128.4 (d), 127.4 (d), 126.7 (d), 78.4 (d), 72.1 (s), 49.8 (d), 43.3 (t), 33.8 (t), 31.9 (t), 25.8 (t), 25.7 (q), 24.7 (t); ^{1}H NMR δ 7.30–7.08 (m, 5 H), 4.96 (dt, J = 5, 11 Hz, 1 H), 2.71 (dt, J = 4, 11 Hz, 1 H), 2.57 (d, J = 16 Hz, 1 H), 2.39 (J = 16 Hz, 1 H), 2.25–1.20 (m, 8 H), 1.17 (s, 3 H); IR 3510, 3000–2500, 2940, 2860, 1730, 1450, 1210 cm^{-1}.

Citramalic Acid. A solution of 100 mg (0.31 mmol) of the acid **8** and 90 mg (1.6 mmol) of potassium hydroxide in 5 mL of THF and 5 mL of water was heated at 60 °C for 24 h, diluted with 15 mL of water, and extracted with one 15-mL portion of ether. The organic layer was dried (magnesium sulfate) and concentrated to afford 40 mg (73%) of the recovered chiral auxiliary **2**. The aqueous layer was acidified with 2 N hydrochloric acid to a pH of 2 and then concentrated to a light brown solid. The solid was rinsed with acetone five times to remove the citramalic acid, leaving behind inorganic salts. Evaporation of the acetone gave a pale yellow solid, which was identified as crude citramalic acid. The crude acid was dissolved in 5 mL of water and treated with 0.01 g of charcoal. After filtration through Celite, the colorless solution was concentrated and dehydrated by the addition of two 50-mL portions of ethyl acetate–benzene (1:1) and concentrated. The crude sample was then diluted with 5 mL of ethyl acetate and transferred to an Erlenmeyer flask, and 2.5 mL of Skelly-B was added. Crystallization and then recrystallization from the same solvents afforded 40 mg (87%) of citramalic acid.

From (+)-*trans*-2-phenylcyclohexanol was obtained diacid with the following: $[\alpha]_D$ +22.7° (c = 0.0156, H_2O) [lit $[\alpha]_D$ +23.7° (c = 0.0156, H_2O)]; ^{13}C NMR (referenced to dioxane at 67.4) δ 179.3 (s), 174.8 (s), 73.4 (s), 44.8 (t), 26.4 (q); ^{1}H NMR δ 3.08 (d, J = 15 Hz, 1 H), 2.75 (d, J = 15 Hz, 1 H), 1.49 (s, 3 H).

Dimethyl Citramalate (9). A sample of the crude acid was dissolved in 150 mL of methanol and 2 mL of concentrated hydrochloric acid, and the mixture was heated at 55 °C for 48 h. The mixture was concentrated, and the resulting product was partitioned between 100 mL of saturated sodium bicarbonate and 100 mL of ether. The aqueous layer was extracted with four 50-mL portions of ether, and the combined organic layers were dried (magnesium sulfate) and concentrated to afford 1.14 g (72%) of dimethyl citramalate as a yellow oil.

From (+)-*trans*-2-phenylcyclohexanol was obtained diester **9** with the following properties: $[\alpha]_D$ +26.15° (c = 1.95, $CHCl_3$), $[\alpha]_D$ +57.6° (c = 10.0, CH_3OH) [lit.[10] $[\alpha]_D$ +27.23° (c = 2.11, $CHCl_3$)].

From (−)-*trans*-2-phenylcyclohexanol was obtained diester **9** with the following properties: $[\alpha]_D$ −25.40° (c = 2.25, $CHCl_3$), $[\alpha]_D$ −55.2° (c = 10.0, CH_3OH); ^{13}C NMR δ 176.0 (s), 171.4 (s), 72.7 (s), 52.8 (q), 51.8 (q), 44.2 (t), 26.3 (q); ^{1}H NMR δ 3.83 (s, 3 H), 3.72 (s, 3 H), 3.00 (d, J = 16.1 Hz, 1 H), 2.70 (d, J = 16.1 Hz, 1 H), 1.46 (s, 3 H); MS m/e 176 (M^+), 158, 117 (base), 91, 85, 43.

Acknowledgment. The research efforts that led to these results have been generously supported by the National Institutes of Health (Grant GM-31750) and the Robert A. Welch Foundation (Grant F-626).

Registry No. (−)-**2**, 98919-68-7; **3**, 119695-99-7; **4** (isomer 1), 119696-00-3; **4** (isomer 2), 119785-83-0; **5**, 119696-01-4; **6**, 119696-02-5; **7**, 119696-03-6; **8**, 119696-04-7; (−)-**9**, 81426-68-8; (+)-**9**, 38574-61-7; (−)-citramalic acid, 6236-09-5; (+)-citramalic acid, 6236-10-8; pyruvic acid, 127-17-3; 1-hexene, 592-41-6; trimethylallylsilane, 762-72-1.