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# Syntheses and Equilibrations of 6- and 7-Carbomethoxy-*trans*-2-oxadecalins[1]

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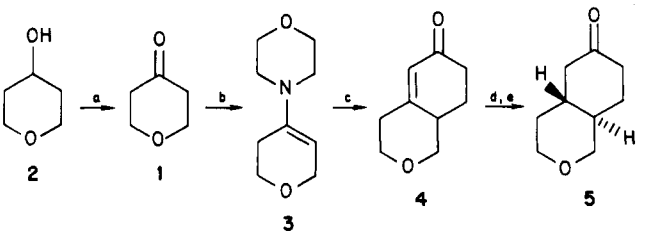
Syntheses of the title compounds based on a Robinson annulation scheme utilizing tetrahydropyran-4-one are described. The 6-substituted system is elaborated by using Wittig methodology, while the 7-substituted ester is prepared via regioselective enolate formation. The regioselectivity of the latter is verified by preparation of a 5-isomer by reductive carboxylation of the original annulation product. Base-catalyzed equilibrations indicate a slightly smaller preference for the equatorial position than in the 2-decalyl analogue, with entropy contributing little to the conformational free energies.

Synthetic approaches to trans-fused 6- and 7-substituted 1- and 2-heteradecalins may be subdivided into three general protocols: (1) manipulation of available bicyclic materials, (2) construction of the heterocyclic ring onto a preformed carbocyclic system, and (3) construction of the carbocyclic ring onto a preformed heterocyclic system. Our earlier approaches to 1-oxadecalins[2] and 1-azadecalins[3] probed the first two possibilities, especially where the carbocyclic ring was aromatic. Utilization of aromatic precursors has not been fruitful in the syntheses of 2-heteradecalins.[4] We have therefore become more interested in those processes beginning with a heterocyclic precursor and involving construction of the carbocyclic ring.[5] We wish herein to report our utilization of a Robinson annulation scheme[6-8] with tetrahydropyran-4-one (1) to prepare the title compounds.

The initial target structure was *trans*-2-oxa-6-decalone (**5**)[9] (Scheme I) since this compound could subsequently be elaborated to the required 6-ester by using Wittig methodology and to the required 7-ester via enolate chemistry. While tetrahydropyran-4-one (**1**) is commercially available, tetrahydropyran-4-ol (**2**) is significantly less expensive and can be oxidized to this ketone in high yield with pyridinium chlorochromate (PCC).[10,11]

Scheme I[a]




[a] (a) PCC, $CH_2Cl_2$, room temperature; (b) morpholine, toluene, reflux; (c) MVK, dioxane, NaOAc-HOAc buffer; (d) Li/liquid $NH_3$, THF, *t*-BuOH, $NH_4Cl$; (e) 8 N $H_2CrO_4$, acetone, 0-5 °C.

Morpholine enamine **3** was formed in good yield only when the catalytic amount of *p*-TsOH ordinarily utilized[13] was omitted. Annulation with methyl vinyl ketone (MVK) in refluxing benzene followed by hydrolysis at reflux with 50% aqueous acetone, a procedure utilized for the sulfur analogue,[14] gave a poor yield of desired conjugated ketone **4**, β,γ-isomer **6**, and ketol **7**. While ketol **7** could be de-

(1) A portion of this work was presented at the 18th Middle Atlantic Regional Meeting of the American Chemical Society, Newark, NJ, May 22, 1984.
(2) Hirsch, J. A.; Schwartzkopf, G. *J. Org. Chem.* **1974**, *39*, 2040.
(3) Hirsch, J. A.; Schwartzkopf, G. *J. Org. Chem.* **1974**, *39*, 2044.
(4) Anzalone, L. Ph.D. Dissertation, Seton Hall University, South Orange, NJ 1984.
(5) For a Diels–Alder approach to 1-thiadecalins, see: Hirsch, J. A.; Kosley, R. W., Jr.; Morin, R. P.; Schwartzkopf, G.; Brown, R. D. *J. Heterocycl. Chem.* **1974**, *12*, 785.
(6) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Reading, MA, 1972.
(7) House, H. O.; Trost, B. M.; Magin, R. W.; Carlson, R. G.; Frank, R. W.; Rasmusson, G. H. *J. Org. Chem.* **1964**, *30*, 2513.
(8) Augustine, R. L.; Caputo, J. A. *Org. Synth.* **1964**, *45*, 80.
(9) The stereochemical designations at the bridgeheads and all other positions are not meant to imply absolute configurations.
(10) Corey, E. J.; Bogen, D. L. *Tetrahedron Lett.* **1978**, *28*, 2461.
(11) Jones oxidation conditions[12] are less satisfactory, primarily because both the ketone and alcohol are water soluble.
(12) Kanojiia, R. M.; Adams, R. E. *Org. Prep. Proced. Int.* **1972**, *4*, 59.
(13) Stork, G.; Brizzolara, H.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
(14) Hutter, G. F.; Hirsch, J. A., unpublished observations with sulfur analogues.

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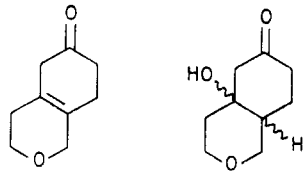
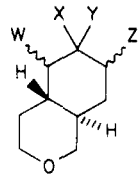


6 7

hydrated[15] in moderate yields to enone 4 and enone 6 could be converted by acid or base[16] to a mixture enriched in conjugated isomer 4, the annulation reaction using enamine 3 or the corresponding pyrrolidine enamine was studied[4] in an attempt to achieve optimal yields. The more polar solvent dioxane combined with hydrolysis in sodium acetate–acetic acid buffer[13] was most satisfactory, providing an enone mixture readily separable by flash chromatography.[17]

With enone 4 in hand, reduction was investigated. Hydrogenation over Pd/C in absolute ethanol[18] or in 95% ethanol containing traces of tetrahydrofuran, the latter having been successful with the thia analogue,[14] produced mixtures of cis-fused (8) and trans-fused (5) isomers which could not be efficiently separated to give pure minor component.[4] Reducing-metal conditions,[6,19–21] which should preferentially produce the saturated ketone with the more stable configuration at the β-carbon, which would presumably be the trans-fused isomer,[2,3] were equally unsatisfactory but were chosen for more extensive study.[4] Use of liquid ammonia in tetrahydrofuran in the presence of a slight excess of *tert*-butyl alcohol[20] produced a crude mixture of ketones and of isomeric alcohols which was subsequently subjected to Jones oxidation. Pure trans-fused ketone 5 was obtained in 72% yield.

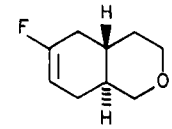


**5**, W=Z=H; XY=O
**9**, W=Z=H; XY=CHOCH$_3$
**10**, W=Z=H; XY=H, CHO
**11**, W=Z=H; XY=H, CO$_2$H
**12**, W=Z=H; XY=H, CO$_2$CH$_3$
**13**, W=Z=H; XY=H, CH$_2$OH
**14**, W=H, Z=C(O)C(O)OCH$_3$; XY=O
**15**, W=H, Z=CO$_2$CH$_3$; XY=O
**16**, W=X=Y=H; Z=CO$_2$CH$_3$
**18**, W=CO$_2$H; Z=H; XY=O
**19**, W=CO$_2$CH$_3$; Z=H; XY=O

Conversion of ketone 5 to 6-carbomethoxy-*trans*-2-oxadecalin (12) could be effected without difficulty. Homologation with (methoxymethylene)triphenylphosphorane[14,16,22] led to vinyl ether 9, which was then hydrolyzed to aldehyde 10, shown by GLC analysis to be a 4:1 mixture of equatorial and axial epimers.[16] Jones oxidation[23] followed by esterification with either diazomethane[24] or trimethyl orthoformate[25] produced an epimeric mixture of trans-fused 12. The epimeric mixture could not be separated by column chromatography, but the epimers were distinguishable by GLC and $^1$H NMR (see following).

Since there existed literature precedent[16] for formation of a single alcohol epimer on reduction of a related carbocyclic aldehyde with NaBH$_4$, such a reduction was attempted on the epimeric mixture of aldehydes 10. Alcohol 13 was obtained. However, pyridinium dichromate (PDC) oxidation[26] of 13 followed by esterification with diazomethane resulted in a 94:6 mixture of the epimeric esters 12.

Preparation of the 7-carbomethoxy isomer 15 may be conceived along the following lines. Utilization of enamine or enolate chemistry could lead to electrophilic attack α to the carbonyl. Subsequent functional group manipulation and deoxygenation of the original carbonyl function would then lead to 16. Aside from the need to find an effective electrophile, the key question is the regioselectivity in the formation of the initial enolate or enamine. Precedent in *trans*-decalin systems is that a double bond as in structure 17 is energetically favored[27] over its regioisomer and that *trans*-2-decalone systems are preferentially alkylated at the 3-position[28,29] via an enolate isomer similar to 17 under conditions of kinetic control.



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Condensation of ketone 5 with dimethyl oxalate[30] produced an oil which exhibited high enolic content. Decarbonylation of this material (presumed to be 14) using soft powdered glass[30] was effected at 180–190 °C to produce pure β-keto ester after chromatography. This highly enolic material (60% enolic by $^1$H NMR) was assigned structure 15.

Deoxygenation of β-keto esters using sodium cyanoborohydride reduction of the corresponding tosylhydrazones[31] was probed by using 2-carboethoxycyclohexanone[32] as a model. The usual one-pot procedure[31] appeared to be quite satisfactory on this model system, but β-keto ester 15 reacted in only low yield to produce a 1:1 mixture of epimers of 16. Higher yields resulted when the tosylhydrazone intermediate was isolated and reduced in separate steps. The desired ester 16 was obtained as a roughly 1:1 mixture of epimers, a mixture considerably enriched in the axial epimer (see following). Formation of the ethylene thioketal of β-keto ester 15 followed by Raney nickel desulfurization[33,34] also produced ester 16 but in lower yield than the cyanoborohydride route.

The epimers of 16 were separable by flash chromatography and could be easily distinguished by their $^1$H NMR

(15) Spencer, T. A.; Schmiegel, K. K.; Williamson, K. L. *J. Am. Chem. Soc.* **1963**, *85*, 3785.
(16) Petrilka, M.; Schleich, K. *Helv. Chim. Acta* **1982**, *65*, 1242.
(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(18) Augustine, R. L. *J. Org. Chem.* **1958**, *23*, 1853.
(19) Stork, G.; Darling, S. D. *J. Am. Chem. Soc.* **1964**, *86*, 1761.
(20) House, H. O.; Geise, R. W.; Kronberger, K.; Kaplan, J. P.; Simeone, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2800.
(21) Smith, H. A.; Huff, B. J. L.; Powers, W. J.; Caine, D. J. *J. Org. Chem.* **1967**, *32*, 2851.
(22) Wittig, G.; Boll, W.; Kruck, K. H. *Chem. Ber.* **1963**, *95*, 2514.
(23) Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.
(24) Block, T. H. *Aldrichimica Acta* **1983**, *16*, 3.
(25) Fredericks, G. R.; Hirsch, J. A., unpublished observations with sulfur analogues.
(26) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *29*, 399.
(27) Turner, R. B.; Meador, W. R.; Winkler, R. E. *J. Am. Chem. Soc.* **1957**, *79*, 4122.
(28) Caine, D. J. *J. Org. Chem.* **1964**, *29*, 1868.
(29) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341.
(30) Kuehne, M. E. *J. Org. Chem.* **1970**, *35*, 171.
(31) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.
(32) Krapcho, A. P.; Diamanti, J.; Cayen, C.; Bingham, R. *Org. Synth.* **1967**, *47*, 20.
(33) Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945.
(34) Spencer, T. A.; Weaver, T. D.; Villarica, R. M.; Friary, R. J.; Posler, J. Schwartz, M. A. *J. Org. Chem.* **1968**, *33*, 712.

**Table I. Equilibration of Esters 12 and 16**

| compd. | T, K | % axial | K |
|---|---|---|---|
| 12 | 363 | 16.20 | 5.17 |
| | 342 | 15.25 | 5.56 |
| | 323 | 13.89 | 6.20 |
| 16 | 363 | 15.87 | 5.30 |
| | 342 | 14.69 | 5.81 |
| | 323 | 14.24 | 6.02 |

spectra. The epimer with the axial ester group was associated with an ill-defined multiplet at $\delta$ 2.83 for the hydrogen at C-7 (because of small and comparable $J_{ae}$ and $J_{ee}$ gauche couplings), while the epimer with the equatorial ester group exhibited a triplet of triplets centered at $\delta$ 2.45 for that same hydrogen with coupling constants characteristic of gauche (3.5 Hz) and anti (11.5 Hz) splittings as required for an axial hydrogen.

In order to more firmly confirm that acylation of ketone **5** had indeed occurred at C-7 with the desired regiochemistry, the regioisomeric ester **19** was prepared. The enolate anion formed in the lithium–ammonia reduction of enone **4** was trapped with carbon dioxide[34,35] to produce the system where the carboxyl group would be placed at the $\alpha$-carbon of the original $\alpha,\beta$-unsaturated system (C-5). Esterification of this $\beta$-keto acid **18** yielded 5-carbomethoxy-*trans*-2-oxa-6-decalone (**19**), which produced only a very faint green color with ferric chloride[34,36] and which did not exhibit any enol content by $^1$H NMR. The $^1$H NMR spectra of **19** and of the two epimers of **16**[41] were all clearly different and consistent with the assignments given.

**Equilibrations.** Sicher[37] had used the *trans*-2-decalyl system as an anancomeric group to evaluate the conformational free energy of the carbomethoxy group. When equilibrated with sodium methoxide in methanol (NaOMe–MeOH), the carbocyclic decalyl ester exhibited $\Delta G°$ of 1.27 kcal mol$^{-1}$, favoring the equatorial epimer at 90 °C (14.7% of axial epimer).

Equilibrations of esters **12** and **16** were carried out with NaOMe–MeOH at 50, 69, and 90 °C, with the temperatures maintained within ±1 °C. Solutions were 0.05 M in substrate. All equilibria were approached from both pure epimers (**16**) or from two drastically different mixtures of epimers (**12**) and were replicated. Compositions were analyzed by GLC.

Results of the equilibration experiments are given in Table I. Enthalpy and entropy values for **12** were obtained from a plot of ln $K$ vs. $1/T$ ($\Delta G°_{90\,°C} = -1.17 \pm 0.03$ kcal mol$^{-1}$, $\Delta H° = -1.12 \pm 0.06$ kcal/mol$^{-1}$, $\Delta S° = 0.15 \pm 0.22$ eu, $r = 0.998$). At 90 °C, the preference for the equatorial position in **12** is slightly smaller than in the decalin itself (1.17 vs. 1.27 kcal/mol$^{-1}$) and is in the range of generally accepted values for a carbomethoxy group in related systems (1.1–1.2 kcal mol$^{-1}$).[38] As in related ester systems,[39] entropy contributes little to the conformational free energy. For ester **16**, slight amounts of decomposition products were detected and the plot of ln $K$ vs. $1/T$ was not linear ($r = 0.961$).

## Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Boiling points are also uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 567 grating infrared spectrophotometer. $^1$H NMR spectra were routinely obtained with a Varian T-60 instrument and, in certain cases, with a Varian XC-200 NMR spectrometer. Unless otherwise noted, all spectra were recorded with $CDCl_3$ as solvent. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The coupling constants are given in hertz. Chemical shifts are reported in parts per million downfield from tetramethylsilane as the internal reference. $^{13}$C NMR spectra were measured on a JEOL-MX90 Fourier transform NMR instrument. Mass spectral analysis were determined on a LKB Model 9000 at 70 eV. "Flash chromatography" refers to the technique developed by Still,[17] and the silica used was E. Merck 230–400 mesh. Thin-layer chromatography was performed on precoated silica gel glass plates (E. Merck). Spots were visualized under 254-nm UV light and/or by spraying with a solution of 3% aqueous ceric ammonium sulfate in 10% sulfuric acid or a solution of 5% ethanolic phosphomolybdic acid or a saturated potassium permanganate solution. VPC analysis were performed on Varian 5020 thermal conductivity GC instrument. The columns used were SE-30 and Carbowax 20M. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany. Reduced pressure refers to water aspirator pressure followed by a short time under vacuum pump pressure. Solvents were purified according to Armarego.[40]

**Tetrahydro-4*H*-pyran-4-one (1).** To a stirred suspension of PCC[10] (Aldrich, 15.5 g, 71.9 mmol) in dry $CH_2Cl_2$ (100 mL) was added in one batch a solution of tetrahydro-4*H*-pyran-4-ol (**2**) (Aldrich, 98%, 5.0 g, 47.9 mmol) in 10 mL of dry $CH_2Cl_2$. After the mixture was stirred at room temperature for 2.5 h, ether (100 mL) was added, the mixture was decanted, and the insoluble residue was washed with ether (3 × 80 mL) until it became granular. The combined organic solutions were filtered through a short pad of Florisil, and the solvent was removed. Distillation at 60 °C (17 mm) afforded 4.10 g (85%) of product. Most of the time, the oxidized product was used without purification: IR (neat) 1720, 1220, 1160 cm$^{-1}$; $^1$H NMR $\delta$ 3.98 (t, 4 H, $J$ = 6 Hz, $CH_2OCH_2$), 2.48 (t, 4 H, $J$ = 6 Hz, $CH_2COCH_2$).

**Morpholine Enamine of Tetrahydro-4*H*-pyran-4-one (3).** A solution of tetrahydro-4*H*-pyran-4-one (**1**) (15.4 g, 154 mmol) and freshly distilled morpholine (Aldrich, 23 g, 264 mmol) in dry toluene (60 mL) was heated to boiling for 6 h, under a reflux condenser, and in a 250-mL round-bottomed flask to which was attached a Dean–Stark trap. The amber reaction solution was concentrated, yielding 23 g of product as a yellowish low-melting solid (88%).

In one of the runs, the resulting solid was distilled at 70 °C (0.2 mm) to give a clear liquid (84.5% yield), which quickly solidified: mp 42–43 °C; IR (neat) 1650 (C=C), 1450 cm$^{-1}$ (C–O–C); $^1$H NMR $\delta$ 4.58 (t, 1 H, $J$ = 3 Hz, C=CH), 4.20 (m, 2 H, $C{=}CCH_2O$), 3.73 (m, 6 H, $CH_2OCH_2$ and $CH_2O$), 2.81 (m, 4 H, $CH_2NCH_2$), 2.13 (m, 2 H, $CH_2C{=}C$).

**$\Delta^{4a}$-2-Oxaoctal-6-one (4).** Crude enamine **3** (22 g, 132 mmol) was dissolved in 70 mL of purified dioxane under argon. To the yellow solution was added dropwise, over a period of 15 min, methyl vinyl ketone (Aldrich, 9.9 g, 141 mmol, freshly distilled), followed by 20 mL of purified dioxane. During the addition, the temperature was kept at 18–20 °C with external cooling. The solution was stirred at ambient temperature for 1.25 h and then boiled at gentle reflux for 4.75 h. The cooled, deep red mixture was hydrolyzed with a buffer solution consisting of 7 g of sodium acetate trihydrate and 14 mL of glacial acetic acid dissolved in 23 mL of $H_2O$. It was stirred for 0.5 h at 25 °C and then refluxed gently for 5.5 h (92 °C). The solution was concentrated to three-fourth of its volume and partitioned between $H_2O$ (30 mL) and ether (150 mL). The aqueous layer was saturated with NaCl and extracted with chloroform (4 × 100 mL). The combined organic layers were washed with 100 mL of 5% HCl solution, 100 mL of saturated $NaHCO_3$, 100 mL of $H_2O$, and 100 mL of saturated NaCl solution and dried ($Na_2SO_4$), and the solvent was evaporated to give 12.3 g of a yellowish solid. By salting out the aqueous solutions and extracting with chloroform, an additional

(35) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1963**, *87*, 275.
(36) Wenkert, E.; Jackson, B. G. *J. Am. Chem. Soc.* **1959**, *81*, 5601.
(37) Tichy, M.; Sipos, F.; Sicher, J. *Collect. Czech. Chem. Commun.* **1966**, *31*, 2889.
(38) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.
(39) Eliel, E. L.; Reese, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 1560.
(40) Perrin, D. P.; Armarego, W. F. L.; Perrin, D. R. "Purification of Laboratory Chemicals"; Pergamon Press: New York, 1966.

2.5 g of the yellowish solid was recovered, for a total of 14.8 g (73.7%). Flash chromatography of 5.5 g of the crude solid with 3:2 hexane–EtOAc afforded 4.0 g of GLC-pure $\alpha,\beta$-unsaturated ketone **4** as a solid, mp 59–61 °C, and 0.3 g, of $\beta,\gamma$-isomer **6** as a liquid (53.6% yield of $\alpha,\beta$-enone, 4% of $\beta,\gamma$-enone).

**Spectral Data for $\alpha,\beta$-Enone 4**: IR (neat) 1670 (C=O conjugated), 1625 $cm^{-1}$ (C=C conjugated); $^1H$ NMR $\delta$ 5.93 (s, 1 H), 4.13 (m, 2 H), 3.48 (t of t, 1 H, $J$ = 3, 10 Hz), 3.08 (t, 1 H, J = 10 Hz), 2.63 (m, 2 H), 2.45 (m, 2 H), 2.38 (1 H), 1.97 (sharp m, 1 H), 1.56 (sharp m, 1 H); MS, $m/e$ (relative intensity) 152 (26), 134 (5), 123 (7), 108 (52), 41 (100). Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.92; H, 7.89.

**Spectral Data for $\beta,\gamma$-Enone 6**: IR (neat) 1710 (C=O), 1620 $cm^{-1}$ (C=O); $^1H$ NMR $\delta$ 4.06 (br s, 2 H), 3.83 (t, 2 H, $J$ = 5 Hz), 2.83 (br s, 2 H), 4.20 (m, 4 H), 2.06 (m, 2 H). Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.84; H, 7.86.

This enone **6** was converted to a mixture of isomers by refluxing in THF–2 N HCl[16] for 6 h. The mixture was highly in favor of the desired $\alpha,\beta$-unsaturated compound (9:1 as per GLC, Carbowax 20M, 180 °C).

When the hydrolysis was effected with 50% aqueous acetone at reflux, a solid identified as the ketol **7** was obtained along with the enone mixture. This solid was recrystallized from methanol: mp 190–193 °C; IR (Nujol) 3300 (OH), 1725 $cm^{-1}$ (C=O); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 4.66 (s, 1 H, disappeared with $D_2O$), 3.53 (m, 4 H), 2.38 (m, 5 H), 1.63 (m, 4 H). Anal. Calcd for $C_9H_{14}O_3$: C, 63.50; H, 8.29. Found: C, 63.31; H, 8.35.

**Dehydration of Ketol 7.** A mixture[15] of ketol **7** (0.55 g, 3.3 mmol) and *p*-TsOH (trace) in dry benzene (50 mL) was refluxed under a water separator for 2 h. The cooled mixture was washed with saturated $NaHCO_3$ solution and saturated NaCl solution and dried ($MgSO_4$), and the solvent evaporated to yield 0.25 g (50%) of product as a mixture of isomers (88:12 $\alpha,\beta$-enone–$\beta,\gamma$-enone Carbowax 20M, 180 °C).

***cis*-2-Oxa-6-decalone (8).** A solution of enone **4** (0.28 g, 1.84 mmol), 9 mL of absolute ethanol, and 0.5 mL of 10% aqueous HCl was added slowly to a 250-mL Parr bottle containing 0.08 g of 5% Pd/C (MBI). The theoretical amount of $H_2$ was absorbed within 1 h. Filtration through Celite, rinsing with 2 × 10 mL of absolute ethanol, and evaporation of solvent gave a residue which was dissolved in ether (10 mL), washed with 5% aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated. The resulting 0.24 g of product (84.6% yield) was one spot on TLC but a mixture of 10% trans-fused **5** and 90% cis-fused **8** by GLC (Carbowax 20 M, 190 °C). Pure *cis*-**8** exhibited the following spectra: IR 1710, 1470, 1210 $cm^{-1}$; $^1H$ NMR $\delta$ 3.84 (t of t, 1 H, $J$ = 4, 11 Hz), 3.71 (d of d, 1 H, $J$ = 2, 11 Hz), 3.54 (d of d, 1 H, $J$ = 3, 12 Hz), 3.33 (t of t, 1 H, $J$ = 3, 11 Hz), 2.49 (d of d, 1 H, $J$ = 6, 14 Hz), 2.41–1.33 (9 H); $^{13}C$ NMR $\delta$ 210.92, 70.91, 67.54, 46.27, 40.15, 36.20, 34.92, 27.68, 25.38; MS, $m/e$ (relative intensity) 154 (15), 136 (22), 126 (3), 121 (3), 109 (32), 98 (18), 95 (26), 83 (35), 67 (55), 55 (89), 41 (95), 39 (100).

***trans*-2-Oxa-6-decalone (5).** To 250 mL of liquid $NH_3$ (redistilled from Na) was added Li (0.9 g, 0.13 mol) in small pieces (weighed in xylene and rinsed in anhydrous ether). The cold blue solution was stirred under reflux while a solution of enone **4** (5.96 g, 39.2 mmol) and freshly distilled *tert*-butyl alcohol (7.5 mL, 79 mmol) in freshly distilled THF (50 mL) were added dropwise.[20] After the resulting mixture had been stirred under reflux for 1.5 h, the blue color was discharged with solid $NH_4Cl$ (11 g). The $NH_3$ was allowed to evaporate overnight and then under reduced pressure. The yellowish residue was partitioned between ether (210 mL) and $H_2O$ (50 mL). The aqueous layer was saturated with NaCl, and extracted with ether (5 × 40 mL). The combined etheral layers were washed with 2 N HCl solution, $H_2O$, and saturated NaCl solution and dried ($Na_2SO_4$), and the solvent was evaporated to obtain 5.87 g of yellow solid (mixture of alcohol and ketone, as per GC and IR). The crude product was dissolved in purified acetone, and the resulting solution was cooled to 4 °C. Dropwise, with the aid of a burette, a slight excess of aqueous 8 N $H_2CrO_4$[23] was added, and then the mixture was treated with isopropyl alcohol to destroy the excess reagent. The reaction mixture was filtered, and the solid was washed well with acetone. After the solvent was concentrated under reduced pressure, the resulting residue was dissolved in ether (200 mL), and the ethereal solution was washed with 5% $NaHCO_3$ solution, $H_2O$, and saturated NaCl solution. It was dried ($Na_2SO_4$), and the solvent was evaporated to yield 4.8 g of yellowish solid. Flash chromatography through silica gel using 3:2 hexane–EtOAc gave 4.4 g (72.7%) of white solid. Recrystallization from hexane gave needle-like crystals: mp 58–59.5 °C (GLC Carbowax 20M, 190 °C, $R_t$ 9.8 min); IR (film) 1705, 1470, 1205, 1180 $cm^{-1}$; NMR $^1H$ (100 MHz) $\delta$ 4.02 (m, 2 H), 3.42 (t of t, 1 H, $J$ = 3, 11 Hz), 3.08 (m, 1 H), 2.43 (m, 3 H), 2.16 (m, 1 H), 1.91 (m, 1 H), 1.59 (m, 4 H), 1.32 (sharp m, 1 H); $^{13}C$ NMR $\delta$ 209.78, 72.14, 67.56, 47.67, 40.93, 40.72, 40.60, 33.51, 27.94; MS, $m/e$ (relative intensity) 154 (83), 136 (3), 125 (6), 111 (11), 98 (86), 39 (100). Anal. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 69.91; H, 9.02.

**Vinyl Ether 9.** To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride[16] (5.3 g, 15.5 mmol, Aldrich) in 27 mL of dry tetrahydrofuran (THF) was added 8.8 mL of 1.6 N *n*-BuLi in hexane (Aldrich, 14 mmol) dropwise. The mixture was allowed to stir at room temperature for 10 min before cooling to −40 °C. At this temperature, a solution of ketone **5** (1.2 g, 7.8 mmol) in dry THF (10 mL) was added dropwise over a 15-min interval. The reaction mixture was allowed to warm slowly to room temperature and left stirring for 12 h. The mixture was quenched with cold acetic acid and diluted with 5% $Na_2CO_3$ solution (10 mL). It was extracted with ether (5 × 50 mL), and the aqueous layer was saturated with NaCl and then extracted with additional ether (3 × 50 mL). The combined ethereal solutions were washed with 50 mL of saturated $Na_2CO_3$ solution, 50 mL of $H_2O$, and 50 mL of saturated NaCl solution and dried ($Na_2SO_4$), and the solvent was evaporated to obtain a yellow semicrystalline residue. This residue was triturated with warm hexane (250 mL) and the mixture placed in the refrigerator overnight. The next morning the solid was removed by filtration, and the filtrate was concentrated under reduced pressure to yield 2.34 g of yellow liquid. In one of the runs, the resulting yellow liquid was chromatographed on silica gel with 15:1 hexane–ether as the eluting solvent to yield the product as a clear liquid (plus some triphenylphosphine). GLC analysis (Carbowax 20M, 170 °C) showed the chromatographed sample to be greater than 96% pure ($R_t$ 12 min, with small peak at 17.3 min): IR (neat) 1225 $cm^{-1}$ (=C—O—C); $^1H$ NMR $\delta$ 5.78 (s, 1 H, =CH), 4.12 (m, 1 H), 3.89 (br s, 1 H), 3.69 (br d, 1 H, $J$ = 10 Hz), 3.53 (s, 3 H, $OCH_3$), 3.05 (m, 3 H), 2.06–1.53 (8 H).

**6-Formyl-*trans*-2-oxadecalin (10).** Vinyl ether **9** (crude, 2.34 g) was stirred at room temperature with 20 mL of 4:1 THF–2 N HCl for 6.5 h. The mixture was then diluted with $H_2O$ (20 mL) and extracted with ether (4 × 50 mL). The aqueous layer was saturated with NaCl and extracted with ether (2 × 60 mL). The ethereal extracts were washed with a 5% $NaHCO_3$ solution (50 mL), $H_2O$ (50 mL), and a saturated NaCl solution and dried ($Na_2SO_4$), and the solvent was evaporated to yield 2.1 g of slightly yellow liquid. Chromatography performed on silica gel with 1:1 hexane–ether solvent mixture resulted in 0.70 g of clear liquid (53% starting from the ketone). GLC analysis (Carbowax 20M, 170 °C) indicated a mixture of two products (13:87): IR (neat) 2720, 1725 $cm^{-1}$; $^1H$ NMR $\delta$ 9.80 (s, 0.2 H), 9.66 (s, 0.8 H), 4.11 (br s, 1 H), 3.93 (br s, 1 H), 3.75 (br s, 1 H), 3.50 (m, 1 H), 3.20 (m, 2 H), 2.50–1.03 (9 H).

**6-Carboxy-*trans*-2-oxadecalin (11).** To a vigorously stirred solution of aldehyde **10** (0.64 g, 3.8 mmol) in purified acetone (50 mL) was added, dropwise, 2 mL of 4 N $H_2CrO_4$[23] solution at 10 °C. The mixture was allowed to stir for 20 min at room temperature after the addition. Appropriate workup yielded 0.68 g (86%) of slightly yellow liquid, which quickly solidified.

This solid (35 mg) was placed in a sublimation apparatus. The product condensed on the cold finger as a semisolid material, which solidified afterward (mp 62–72 °C). The solid left behind melted at 70–76 °C. The combined solids were recrystallized from hexane to give a powdery material melting at 87–88.5 °C (this was subjected to elemental analysis): IR (Nujol) 3600–2600 (br, OH acid), 1730 and 1700 $cm^{-1}$ (C=O); $^1H$ NMR (100 MHz) $\delta$ 9.45 (br s, 1 H), 3.99 (d of t, asymmetrical, 1 H, $J$ = 6, 2 Hz), 3.82 (d of d, 1 H, $J$ = 9, 3 Hz), 3.43 (t of d, 1 H, $J$ = 3, 10 Hz), 3.02 (t, 1 H, $J$ = 10 Hz), 2.81 (br s, 0.2 H, $W/2$ = 10 Hz), 2.42 (t of t, 0.8 H, $J$ = 8 Hz), 2.04 (m, 2 H), 1.64–1.06 (7 H), 1.00 (t of d, 1 H, $J$ = 4, 11 Hz). Anal. Calcd for $C_9H_{16}O_2$: C, 65.19; H, 8.75. Found: C, 64.99; H, 8.57.

**6-Carbomethoxy-*trans*-2-oxadecalin (12). Method I: Esterification with Diazomethane.**[24] To a cold solution of KOH (4 g) in water (10 mL) was added ether (50 mL) and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG, Aldrich, 97%, 1.0 g). The organic layer turned bright yellow. After the addition, the ethereal layer was decanted into a plastic flask containing KOH pellets. This container was also kept cold. The aqueous layer was washed with several portions of ether, and the etheral layers were combined. The diazomethane solution thus prepared was added slowly to a stirred solution of crude acid **11** (0.57 g) in ether (5 mL) until the bright yellow color persisted. Under the hood, the diazomethane was flushed with nitrogen, and the clear solution was dried ($Na_2SO_4$) and the solvent evaporated to yield 0.56 g of slightly yellow liquid.

GLC analysis (Carbowax 20M, 170 °C) showed the product to be a mixture. Two peaks were observed, $R_t$ 13 and 17.7 min. GC/MS indicated that the two peaks were epimers of the product (18% and 82%). Flash chromatography of the product using 3:1 hexane–EtOAc solvent mixture gave several fractions of clear liquid: fraction 5, 0.14 g (65% equatorial, 35% axial); fraction 6, 0.21 g (89.3% equatorial, 10.7% axial; fraction 7, 0.06 g (93.6% equatorial, 6.4% axial); fraction 8, 0.01 g (98% equatorial); total, 0.42 g (65.6%). IR (neat) 1735, 1440, 1260 $cm^{-1}$.

Fraction 8 (equatorial epimer): $^1H$ NMR (100 MHz) $\delta$ 3.99 (d of m, 1 H, $J$ = 11 Hz), 3.90 (d of d, 1 H, $J$ = 3.5, 11 Hz), 3.64 (s, 3 H), 3.42 (t of t, 1 H, $J$ = 3.5, 11 Hz), 3.01 (t, 1 H, $J$ = 11 Hz), 2.40 (t of t, 1 H, $J$ = 3, 11.5 Hz), 2.20 (m, 1 H), 1.95 (m, 1 H), 1.45 (m, 4 H), 1.21 (m, 3 H), 0.98 (t of t, 1 H, $J$ = 3.5, 12 Hz); $^{13}C$ NMR $\delta$ 175.7, 72.7, 68.4, 51.5, 43.1, 41.7, 40.2, 35.0, 33.0, 28.2, 27.0; MS, $m/e$ (relative intensity) 198 (6), 168 (26), 152 (16), 138 (30), 121 (27), 94 (100). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.63; H, 9.15. Found: C, 66.41; H, 9.17.

Fraction 8 (axial epimer[41]): $^{13}C$ NMR $\delta$ 175.3, 72.8, 68.5, 51.5, 42.3, 39.2, 37.0, 33.5, 33.2, 26.7, 24.3. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.63; H, 9.15. Found: C, 66.44; H, 9.11.

**Method II: Esterification with Trimethyl Orthoformate.**[25] A mixture of acid **11** (0.19 g, 1.1 mmol), freshly distilled trimethyl orthoformate (10 mL, Aldrich), *p*-TsOH (0.10 g), and dry methanol (10 mL) was stirred at room temperature for 30 h. Solid $Na_2CO_3$ was then added, and the mixture was stirred an additional 0.5 h. The carbonate was removed by filtration and the solution was concentrated to approximately one-fourth of its original volume and diluted with ether. The organic solution was washed consecutively with 5% $NaHCO_3$, $H_2O$, and saturated NaCl solution and dried ($Na_2SO_4$), and the solvent was evaporated to get 0.23 g of yellow liquid. TLC developed with saturated $KMnO_4$ solution showed two spots, $R_f$ 0.3 and 0.04. The solvent system was a mixture of hexane–EtOAc.

**Attempt To Synthesize the Equatorial Epimer of 12 Exclusively.** Epimeric aldehyde **10** (0.2 g, 1.19 mmol) was placed in a 25-mL round-bottomed flask with 10 mL of 0.1 N methanolic KOH solution.[16] The resulting mixture was cooled, and an excess of $NaBH_4$ (0.4 g) was added in small portions. Aqueous quenching and workup of $CH_2Cl_2$ solutions yielded 0.3 g of yellow oil. TLC eluted with 2:1 hexane–EtOAc gave one spot at $R_f$ 0.17, along with another spot at the origin. Preparative TLC with the same solvent system gave 0.12 g of the alcohol **13**. GLC analysis (Carbowax 20M, 190 °C) showed only one peak with $R_t$ 16.5 min: IR (neat) 3300 $cm^{-1}$ (OH).

To alcohol **13** (80 mg, 0.5 mmol) in freshly distilled dimethylformamide (DMF, 1.6 mL) was slowly added pyridinium dichromate (PDC, 0.65 g, 10 mmol).[26] The orange suspension was stirred at room temperature overnight. The next morning, $H_2O$ (7 mL) was added, and the solution was extracted with ether (3 × 20 mL). The combined ethereal layers were washed with $H_2O$ and saturated NaCl solution and dried ($Na_2SO_4$), and the volatiles were evaporated to yield 70 mg of crude acid as a yellowish powder. This solid was dissolved in an ethereal solution of diazomethane (see preceding) at 0 °C and stirred for 15 min. The excess diazomethane was flushed out with nitrogen (under the hood), and the now clear solution was concentrated to furnish 60 mg of slightly yellow liquid. GLC analysis (Carbowax 20M, 175 °C) indicated an epimeric mixture consisting of approximately 94% of the equatorial isomer.

**7-Carbomethoxy-*trans*-2-oxadecal-6-one (15).** Sodium methoxide was prepared by dissolving Na (0.76 g, 3.3 mmol) in dry methanol (20 mL). The excess solvent was evaporated under reduced pressure. Freshly distilled benzene (30 mL) was added under argon to the white powdery base, followed by freshly distilled dimethyl oxalate (6.0 g, 50 mmol). To the cooled white suspension was added *trans*-2-oxadecal-6-one (**5**) (1.40 g, 9 mmol)[30] over a 10-min period, with the reaction slowly turning yellow-reddish; stringlike precipitate was discernible soon after the addition. More benzene (5 mL) was added at this point. The mixture was stirred at 7 °C for 1 h and then at room temperature for the next 19 h. The mixture was cooled and poured into ice-cold $H_2O$ (50 mL). Cold 2% NaOH solution was added until both layers became clear. The layers were quickly separated. The organic layer was extracted with additional NaOH solution (2 × 50 mL), and the combined basic layers were washed once with ether, acidified to Congo Red with ice-cold 10% HCl while kept cold, and extracted with $CH_2Cl_2$ (5 × 50 mL). The combined organic solutions were washed consecutively with cold $H_2O$ and saturated NaCl solution and dried ($Na_2SO_4$). Evaporation of the solvent under reduced pressure left 2.30 g of thick orange liquid, which produced a purple color with 1% methanolic $FeCl_3$. TLC eluted with 3:1 hexane–EtOAc solvent mixture showed essentially two spots, $R_f$ 0.21 and 0.5. These chromatograms were developed with ceric sulfate solution and under UV light.

In a 25-mL pear-shaped flask containing the crude thick liquid, 4 g of powdered soft glass was added. The flask was then placed in an oil bath preheated to 180 °C. The thick mixture was stirred at first with a glass rod and then with a magnetic stirring bar. The flask was connected to a gas bubbler to monitor gas evolution. Carbon monoxide started to come out at once and ceased after 10 min while the mixture was becoming deep red. The residue was taken up in $CH_2Cl_2$, and the glass powder was removed. Upon evaporation of the solvent, a thick red liquid (1.78 g) was obtained. Green coloration resulted with $FeCl_3$. TLC eluted with 3:1 hexane–EtOAc showed two spots, $R_f$ 0.57 and 0.25. Flash chromatography eluting with 7:3 hexane–EtOAc solvent mixture gave 0.60 g of solid (mp 66–68 °C) and 80 mg of an unidentified yellow enolizable liquid (spot with $R_f$ 0.25).

Spectral data for the solid: IR (Nujol) 3300 (OH enolic), 1760 (C=O), 1730, 1645, 1605 $cm^{-1}$; $^1H$ NMR (100 MHz) $\delta$ 12.13 (s, 0.5 H, C=CH), 4.02 (m, 2 H), 3.78 (s, 3 H, $OCH_3$), 3.43 (t of t, 1 H, $J$ = 2, 12 Hz), 3.12 (t, 1 H, $J$ = 12 Hz), 2.34 (t of t, 2 H, $J$ = 4, 16 Hz), 2.08 (m, 1 H), 1.80–1.35 (6.5 H); $^{13}C$ NMR (carbonyl carbon missing) $\delta$ 170.90, 96.22, 72.51, 67.99, 51.39, 37.22, 35.65, 35.34, 32.60, 24.59, (with satellite peaks at $\delta$ 172.59, 71.74, 67.50, 47.61, 41.25, 39.93, 33.27, and 31.02); MS, $m/e$ (relative intensity) 212 (18), 194 (15), 180 (53), 153 (9), 55 (100). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.59. Found: C, 62.20; H, 7.43.

**Preparation of Ethyl Cyclohexanecarboxylate.** A sample of 2-carbethoxycyclohexanone[32] (0.51 g, 3 mmol) was added under $N_2$ to a solution of tosylhydrazine (0.71 g, 3.75 mmol), *p*-TsOH (0.75 mg) in dry DMF (7 mL), and dry sulfolane (7 mL).[31] The slightly yellow solution was stirred at room temperature for 1 h and then placed in an oil bath (preheated to 100 °C). While at this temperature, sodium cyanoborohydride ($NaBH_3CN$, Aldrich, 0.7 g, 1.19 mmol) in 5 mL of cyclohexane was added. The mixture was kept at 100 °C for 2 h while it was stirred. The cooled mixture was diluted with $H_2O$ (30 mL), extracted with cyclohexane (3 × 30 mL), and dried ($Na_2SO_4$), and the solvent was evaporated to give 0.38 g of slightly yellow oil (solvent present). Tests with 1% methanolic $FeCl_3$ gave no coloration. Spectra matched those of a commercial sample (P & B).

**Deoxygenation of the $\beta$-Keto Ester 15. Method I: Reduction of Tosylhydrazone. 7-Carbomethoxy-*trans*-2-oxadecal-6-one Tosylhydrazone.** A stirred mixture of $\beta$-keto ester **15** (1.29 g, 5.8 mmol) and *p*-toluenesulfonhydrazide (Aldrich, 97%, 1.30 g, 6.9 mmol) in 10 mL of absolute EtOH was heated to reflux for 1.5 h.[31] The resulting white precipitate was removed by filtration from the cooled reaction mixture, washed several times with cold EtOH, and dried under vacuum. The solid weighed 2.14 g (96%) and melted at 185–187 °C: IR (KBr) 3100 (N–H), 1750, 1650, 1600 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 10.33 (s, 1 H), 7.68 (m, 4 H), 3.6 (m), 3.3 (s), 2.8 (m), 2.43 (s), 1.43 (m). Anal. Calcd

(41) These epimers of **16** have subsequently been prepared by a different route: Truc, V. C.; Hirsch, J. A., unpublished observations.

for $C_{18}H_{24}N_2SO_5$: C, 56.82; H, 6.35; N, 7.36. Found: C, 56.73; H, 6.35; N, 7.38.

**7-Carbomethoxy-*trans*-2-oxadecalin (16).** A stirred mixture of the above hydrazone of **15** (2.0 g, 5.25 mmol) and *p*-TsOH (135 mg) in 26 mL of 1:1 DMF–sulfolane solvent mixture was heated to 100 °C. At this temperature, sodium cyanoborohydride[31] (Aldrich, 95%, 1.40 g, 21 mmol) was added at once (quickly dissolved) along with 2 mL of cyclohexane, which produced a blanket of cyclohexane vapor to prevent destruction of the intermediate diazenes by oxygen. The solution was stirred at 100 °C for 2 h and, once cooled, was partitioned between cyclohexane (20 mL) and $H_2O$ (30 mL). The layers were separated, and the aqueous layer was extracted exhaustively with cyclohexane (total volume 200 mL), saturated with NaCl, and extracted with more cyclohexane (3 × 30 mL). The combined organic solutions were washed once with $H_2O$ and dried ($Na_2SO_4$), and the solvent was evaporated to furnish 0.70 g of slightly yellow liquid. GLC analysis (Carbowax 20M, 190 °C) indicated that the liquid was a mixture consisting of three compounds ($R_t$ 9.8, 11.8, and 15.7 min) with percent composition 42.2%, 39.1%, and 18.5%, respectively. The peak at $R_t$ 15.7 min was identified as sulfolane by comparison with an authentic sample. TLC eluted with 4:1 hexane–EtOAc solvent mixture showed one spot ($R_f$ 0.37), along with another spot that stayed at the origin. Chromatograms were developed with saturated $KMnO_4$ solution. Flash chromatography eluting with 7:1 pentane–EtOAc yielded 0.32 g (30.7%) of product as a liquid (70 mg of pure axial, 140 mg of a mixture, and 90 mg of pure equatorial; $R_f$ 11.8 min): IR (neat) 1740 (C=O), 1455 and 1440 $cm^{-1}$ (C–O–C).

Axial epimer: $^1H$ NMR (100 MHZ) $\delta$ 4.06 (d of m, 1 H), 3.90 (d of d, 1 H, $J$ = 4, 10 Hz), 3.78 (s, 3 H), 3.50 (t of t, 1 H, $J$ = 3, 11 Hz), 3.05 (t, 1 H, $J$ = 11), 2.83 (br s, 1 H, $W/2$ = 10), 2.27 (m, 1 H), 1.99 (d of q, 1 H, $J$ = 2.5, 12 Hz), 1.67–1.06 (8 H); $^{13}C$ NMR $\delta$ 175.2, 72.9, 68.6, 51.2, 40.9, 39.0, 38.5, 33.1, 29.8, 28.8, 27.0.

Equatorial epimer: $^1H$ NMR $\delta$ 4.07 (d of m, 1 H, $J$ = 12 Hz), 3.87 (d of d, 1 H, $J$ = 6, 11 Hz), 3.72 (s, 3 H), 3.50 (t of t, 1 H, $J$ = 3, 11 Hz), 3.11 (t, 1 H, $J$ = 11 Hz), 2.45 (t of t, 1 H, $J$ = 3.5, 12 Hz), 2.06 (m, 1 H), 1.88–1.01 (9 H); $^{13}C$ NMR $\delta$ 175.9, 72.7, 68.5, 51.5, 42.7, 41.4, 40.3, 33.0, 31.8, 30.2, 28.6; MS, *m/e* (relative intensity) 198 (19), 166 (51), 154 (6), 136 (27), 121 (25), 41 (100).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 66.63; H, 9.15. Found: C, 66.53; H, 9.17. The analytical sample was distilled at 100 °C (0.5 mm).

**Method II: Desulfurization of Dithioketal.** The $\beta$-keto ester **15** (80 mg, 0.3 mmol) dissolved in ethanedithiol (0.2 mL) and ethereal $BF_3$ (Aldrich, 0.1 mL)[33] was stirred at room temperature overnight. The next morning the solution was diluted with ether (10 mL) and washed with 1 N aqueous NaOH solution (2 × 1 mL) and saturated NaCl solution (2 mL). The organic layer was dried ($Na_2SO_4$), filtered (gravity), and concentrated to give 30 mg of yellow residue (very unpleasant odor). Recrystallization from EtOH furnished white crystals (mp 112–115 °C). $^1H$ NMR showed a multiplet centered at $\delta$ 3.0 typical of the ethylene dithioketal protons. A 25-mL round-bottomed flask containing $^1/_4$ tsp of Raney nickel (W-2, Grace)[33] (treated with absolute EtOH) in 3 mL of absolute EtOH was added to a solution of the crude thioketal in i mL of absolute EtOH. The mixture was refluxed for 20 h and then diluted with hot EtOH. The catalyst was removed by filtration through a Celite bed and rinsed several times with hot EtOH. The combined alcoholic solutions were concentrated to yield 15 mg (20%) of a mixture consisting mostly of product **16** as per GLC analysis (Carbowax 20M, 170 °C). Spectral data were similar to those of the material synthesized by method I.

**5-Carbomethoxy-*trans*-2-oxadecal-6-one (19).** To a solution of 0.4 g (0.06 mol) of lithium in 120 mL of liquid $NH_3$ (predistilled from Na) was added dropwise over a 5-min period a solution of $\alpha,\beta$-enone **4** (1.5 g, 9.8 mmol) in 50 mL of ether.[34,36] The ammonia was evaporated (warm water bath) and the residue diluted with ether. The solution was refluxed for 0.5 h in order to remove the last trace of ammonia (the original blue mixture turned grayish white). Carbon dioxide gas was bubbled through this suspension for 4 h. The gas was generated by placing dry ice in a flask connected with Tygon tubing to a Drierite tube attached to a gas dispersion tube. Ether was added throughout the gas addition to maintain a constant volume. The mixture was then cooled to 0 °C and slowly acidified to Congo Red with cold 1 M HCl solution saturated with NaCl. The layers were quickly separated, and the ether layer was washed with saturated NaCl solution, dried rapidly ($Na_2SO_4$), decanted from the drying agent, and poured into an excess of ethereal diazomethane (prepared as previous). The bright orange color was discharged with nitrogen. The original aqueous layer was extracted several times with $CH_2Cl_2$, and the combined extracts were washed with cold saturated NaCl solution and evaporated to yield a yellow solid (1.02 g). This material was dissolved in ether (since not completely soluble, MeOH was added). The solution was cooled to 0 °C and treated with diazomethane as before. Again, the color was discharged with $N_2$, and this ethereal solution was combined with the one above. After the solution was dried ($Na_2SO_4$), the solvent was evaporated to give a yellow liquid. Flash chromatography eluting with 3:2 hexane–EtOAc solvent mixture yielded 0.45 g (22%) of product as yellowish liquid, which solidified on standing. Recrystallization of the resulting solid from hexane gave platelets with mp 72–72.5 °C. Other products isolated were 0.20 g of *trans*-2-oxadecal-6-one (**5**) and 0.60 g of starting enone **4**. A very faint green color was observed upon testing the crude product with 1% methanolic $FeCl_3$: IR (Nujol) 1745, 1715, 1445, 1355, 1270 $cm^{-1}$; $^1H$ NMR (100 MHz) $\delta$ 4.0 (m, 2 H), 3.77 (s, 3 H), 3.43 (t of t, 1 H, $J$ = 2.5, 12 Hz), 3.12 (m, 2 H), 2.51 (m, 2 H), 1.88 (m, 3 H), 1.50 (m, 3 H); $^{13}C$ NMR $\delta$ 203.9, 169.0, 71.5, 66.9, 62.2, 51.5, 42.6, 40.4, 39.0, 31.4, 27.3; MS, *m/e* (relative intensity) 212 (42), 194 (100), 184 (16), 181 (52), 156 (41). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.59. Found: C, 62.20; H, 7.51.

**Table II. Equilibration of 12 at 363 K**

| time, h | % axial | |
|---|---|---|
| | axial side | equatorial side |
| 0 | 35 | 7.2 |
| 4 | 20.8 | 10.2 |
| 12 | 18.6 | 14.7 |
| 24 | 17.5 | 15.1 |
| 48 | 16.7 | 15.8 |
| 60 | 16.6 | 16.2 |
| 90 | 16.2 | 16.2 |

**Table III. Equilibration of 16 at 363 K**

| time, h | % axial | |
|---|---|---|
| | axial side | equatorial side |
| 0 | 49 | 0 |
| 4 | 26.4 | 9 |
| 8 | 19.5 | 12 |
| 24 | 18.1 | 13.5 |
| 48 | 16.6 | 14.7 |
| 60 | 16.1 | 15.4 |
| 72 | 15.9 | 15.6 |
| 90 | 15.9 | 15.9 |

**Equilibrations.** For the most part, samples to be equilibrated were not pure epimers but a mixture rich in one or the other of the two isomers. In all cases equilibrium was approached from both sides.

**Typical Run.** To a 5-mL Microflex vial containing 20 mg of the ester **12** or **16** was added, under an inert atmosphere, 2 mL of 0.25 N methanolic NaOMe solution[37] (made by dissolving metallic sodium in freshly distilled MeOH and storing under argon in the refrigerator for no longer than a 2-week period). The vials, properly sealed with Microflex valves, were heated in an oil bath (50–90 °C) for 1–20 days.

The mixtures of esters were quenched with acetic acid and extracted with cyclohexane. The solutions were washed once with $H_2O$, dried, concentrated, and analyzed by GLC on a $^1/_4$ in. × 6 ft 10% Carbowax 20M on 80/100 Chromosorb W AW column (170 °C). To determine the detector response ratio, an analytical sample was prepared consisting of 60% of the axial epimer of **16**. The peak corresponding to this material represented 59 ± 0.5% of the mixture.

Each equilibration was carried out at least twice (see Tables II and III for two examples of each isomer). For the 7-isomer (**16**), hydrolysis problems were encountered. These were alleviated by quenching the basic mixture with NaOAc–AcOH buffer (pH 5) and extracting exhaustively with purified $CCl_4$. This type of workup was also employed with ester **12**. Similar results to those

obtained for the acetic acid procedure were observed with these compounds.

**Registry No.** 1, 29943-42-8; 2, 2081-44-9; 3, 72250-03-4; 4, 96728-48-2; 5, 96728-52-8; 6, 96728-49-3; 7, 96728-50-6; 8, 96728-51-7; 9, 96728-53-9; 10 (isomer 1), 96728-54-0; 10 (isomer 2), 96728-55-1; 11 (isomer 1), 96728-56-2; 11 (isomer 2), 96728-57-3; 12 (isomer 1), 96728-58-4; 12 (isomer 2), 96728-59-5; 13 (isomer 1), 96728-60-8; 13 (isomer 2), 96728-61-9; 14, 96728-63-1; 15, 96728-62-0; 15 (thioketal), 96728-67-5; 16 (isomer 1), 96728-65-3; 16 (isomer 2), 96728-66-4; 19, 96728-68-6; morpholine, 110-91-8; methyl vinyl ketone, 78-94-4; (methoxymethyl)triphenylphosphonium chloride, 4009-98-7; dimethyl oxalate, 553-90-2; ethyl cyclohexanecarboxylate, 3289-28-9; 2-carbethoxycyclohexanone, 1655-07-8; tosylhydrazine, 1576-35-8; 7-carbomethoxy-2-oxadecal-6-one tosylhydrazone, 96728-64-2; ethanedithiol, 540-63-6.

# Enzymic Oxidative Coupling of Urushiol in Sap of the Lac Tree, *Rhus vernicifera*

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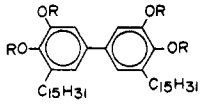
Dimerization of urushiol is a significant initial step of the laccase-catalyzed polymerization of natural lacquer. Urushiol dimers produced during the physiological oxidation of urushiol were thoroughly separated by liquid chromatography. Obtained dimers have been classified into four types of compounds, viz., biphenyls, dibenzofurans, nucleus–side chain bound dimers, and their side chain oxidized products. Dibenzofurans are derived by successive oxidation of biphenyls and the last type of compounds by oxidation of parent dimers. Then it has been established that the dimerization of urushiol in natural sap proceeds through two predominant reaction routes, i.e., phenol coupling and nucleus–side chain coupling. For the first and third types of compounds, product distribution with special regard to the orientation of reactions has been compared to frontier electron densities of possible reaction species. It has been inferred that an attack of urushiol–semiquinone on the urushiol nucleus affords biphenyls. Urushiol–quinone produced by disproportionation of the semiquinone abstracts hydride from the side chain of triolefinic urushiol, 3-[8′(*Z*),11′(*E*),13′(*Z*)-pentadecatrienyl]catechol (**3**), to give the 1,7-disubstituted heptatrienyl cation **24**. Electrophilic substitution of the cation to the urushiol nucleus yields nucleus–side chain bound dimers. In this reaction, C–C coupling occurs exclusively, and derivatives of dihydric phenols are given as dimers of urushiol. This regiospecificity may be due to the slightly acidic reaction medium of natural sap and facilitates subsequent oxidation mediated by polyphenol oxidase laccase.

Sap of the lac tree, *Rhus vernicifera*, dries into a tough and brilliant film and has been used as naturally occuring coating material for thousands of years in the Orient.[1] It is a latex composed of urushiol[2] (60%), water (30%), plant gum[3] (7%), water-insoluble glycoprotein (2%), and copper glycoproteins (laccase[4] and stellacyanin[5]) (ca. 0.1%).

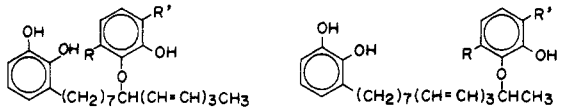
The principal reaction of the film-making process is believed to be oxidative coupling of urushiol under the catalytic action of the oxidoreductase laccase.[6] Quinoid compounds were detected as an intermediate in the course of this process.[7] Symmetric biphenyl was identified in a mildly oxidized sap as the tetraacetate **1**,[8] which was



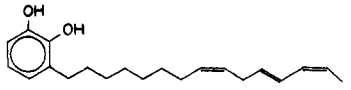

**1**, R = $CH_3CO$

**5**, R = $CH_3O$

derived by phenol coupling of urushiol. In addition, from studies of model reactions between 4-*tert*-butyl-*o*-benzoquinone and certain olefinic compounds, it was speculated[9] that nucleus–side chain C–O coupling compounds (**2a** or **2b**) were given through the reaction between urushiol–




**2a**, R/R′ = H/$C_{15}H_{31}$ **2b**, R/R′ = H/$C_{15}H_{31}$




**3**

quinone and triolefinic urushiol 3-[8′(*Z*),11′(*E*),13′(*Z*)-

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(1) Kumanotani, J. In "Polymer Application of Renewable-Resource Materials"; Carraher, C. E., Jr., Sperling, L. H., Eds.; Plenum Press: New York, 1983; pp 225–248.

(2) (a) Majima, R. *Ber. Dtsch. Chem. Ges. B* **1922**, *55B*, 172–191. (b) Sunthanker, S. V.; Dawson, C. R. *J. Am. Chem. Soc.* **1954**, *76*, 5070–5074. (c) Yamauchi, Y.; Oshima, R.; Kumanotani, J. *J. Chromatogr.* **1982**, *243*, 71–84. (d) Du, Y.; Oshima, R.; Kumanotani, J. *J. Chromatogr.* **1984**, *284*, 463–470.

(3) Oshima, R.; Kumanotani, J. *Carbohydr. Res.* **1984**, *127*, 43–57.

(4) Reinhammer, B. In "The Coordination Chemistry of Metalloenzymes"; Bertini, I., Drago, R. S., Luchinat, C., Eds.; D. Reidel: Dordrecht, The Netherlands, 1983; pp 177–200.

(5) Peisach, J.; Levine, W. G.; Blumberg, W. E. *J. Biol. Chem.* **1967**, *242*, 2847–2858.

(6) Kumanotani, J. *Makromol. Chem.* **1978**, *179*, 47–61.

(7) Kumanotani, J.; Kato, T.; Hikosaka, A. *J. Polym. Sci., Part C* **1968**, *23*, 519–531.

(8) Kato, T.; Kumanotani, J. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2375–2376.

(9) Kato, T.; Kumanotani, J. *J. Polym. Sci., Polym. Chem. Ed.* **1969**, *7*, 1455–1465.

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