2 N aqueous sodium hydroxide. The solution was acidified with dilute hydrochloric acid and extracted thoroughly with ether. The solution was dried ($MgSO_4$) and filtered, and the solvent was removed at reduced pressure to afford a solid which was recrystallized from acetone to yield **23** (0.27 g, 1.3 mmol, 59%): mp 205 °C; IR ($CHCl_3$, cm^{-1}) 3600–2800, 1715, 1698, 1420, 1167; ^1H NMR (Me_2CO-d_6, 200 MHz) δ 11.3 (1 H, br), 7.4–7.0 (4 H, m), 3.44 (1 H, dd, J = 8.6, 6.0 Hz), 2.84 (1 H, t, J = 8.6 Hz), 2.64 (1 H, dd, J = 8.6, 6.0 Hz).

Methyl 2-Oxo-3,4-benzobicyclo[3.1.0]hex-3-ene-6-*endo*-carboxylate (24). Keto acid **23** was esterified as described for **22**. Recrystallization of the solid product from ether afforded pure **24** (no yield was obtained): mp 104 °C; IR ($CHCl_3$, cm^{-1}) 1735, 1712, 1605, 1200, 1161; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.6–7.2 (4 H, m), 3.39 (3 H, s), 3.30 (1 H, X of ABX, $J_{AX} = J_{BX}$ = 7.3 Hz), 2.68 (2 H, AB of ABX, J_{AB} = 7.3 Hz); ^{13}C NMR (C_6D_6, 15.04 MHz) δ 197.7, 167.8, 146.7, 137.4, 133.2, 125.9, 123.2, 51.7, 41.4, 31.4, and 28.7 (one aromatic carbon is obscured by solvent); mass spectrum, m/e (M^+) calcd 202.0630, obsd 202.0638.

4-Oxa-6,7-benzotricyclo[3.3.0.0^{2,8}]oct-6-en-3-one (25). Keto acid **23** (118 mg, 0.631 mmol) was dissolved in 10 mL of dry THF, and the solution was cooled to −40 °C. Methyllithium (1.2 mL of a 1.05 M solution, 1.26 mmol) was added dropwise and stirring was continued for 2 h at −40 °C. The cooling bath was allowed to expire, and the solution was stirred at room temperature for 8 h. Acidification of the solution with dilute hydrochloric acid and extraction with ether followed by drying ($MgSO_4$) and removal of the ether at reduced pressure afforded a solid product. The solid was dissolved in 5 mL of acetone and cooled to 0 °C. A solution of triethylamine (97 μL, 0.69 mmol) and methyl chloroformate (59 μL, 0.76 mmol) in 1 mL of acetone was added dropwise via syringe. Stirring was continued for 90 min at 0 °C and 30 min at room temperature. The acetone was removed at reduced pressure, and ether was added. The ether solution was washed sequentially with water and brine and dried (Na_2SO_4) and the solvent removed at reduced pressure to yield a yellow oil which was subjected to flash chromatography (15 × 3 cm column, 30% acetone in hexanes v/v). Slightly yellow **25** was eluted in 10-mL fractions 5 through 10. Removal of the solvent at reduced pressure afforded **25** (50 mg, 0.27 mmol, 42%): mp (ether/hexane) 103 °C; IR ($CDCl_3$, cm^{-1}) 1757, 1255, 998; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.4–7.1 (4 H, m), 3.35 (1 H, t, J = 6.0), 2.97 (1 H, dd, J = 6.0, 8.0 Hz), 2.75 (1 H, dd, J = 6.0, 8.0 Hz), 1.93 (3 H, s); ^{13}C NMR (C_6D_6, 15.04 MHz) δ 170.8, 146.7, 140.7, 129.2, 127.1, 125.1, 121.1, 91.6, 45.0, 39.4, 33.4, 18.9; mass spectrum, m/e (M^+) calcd 186.0681, obsd 186.0681.

Photolysis of 25. A solution of lactone **25** (10 mg, 0.05 mmol) and CD_3CN (0.5 mL) was placed in a 5-mm o.d. quartz tube and deoxygenated by purging with a slow stream of nitrogen. The tube was then placed in the cavity of a Rayonet photochemical reactor and irradiated at 254 nm. After 16 h of irradiation, ca. 50% conversion to 1-methylnaphthalene was observed by ^1H NMR. No other products were observed.

Photolysis of 19. A solution of anhydride **19** (10 mg, 0.05 mmol) and CD_3CN (0.5 mL) was placed in a 5-mm o.d. quartz tube and deoxygenated by purging with a slow stream of nitrogen. The tube was then placed in the cavity of a Rayonet photochemical reactor and irradiated at 254 nm. After 20 min of irradiation, ca. 4% conversion to **25** was observed by ^1H NMR. A trace of 1-methylnaphthalene was observable by capillary GC. No other products were observed. Photolysis for 16 h resulted in 30% conversion to lactone **25**, and a trace of (ca. 1%) of 1-methylnaphthalene was observable by ^1H NMR. No other products were observed.

Solution Thermolysis of 25. A solution of lactone **25** (10 mg, 0.05 mmol) and solvent (0.5 mL) was sealed in a 5-mm o.d. Pyrex tube and heated in a silicone oil bath. The tube was then opened and its contents were analyzed by ^1H NMR. If necessary, the tube was resealed for further thermolysis. In both Me_2CO-d_6 and C_6D_6 **25** was found to be stable at temperatures below 200 °C. Lactone **25** was found to decompose to unidentifiable products over a period of several hours at 200 °C.

Vapor-Phase Thermolysis of 25. A sample of lactone **25** was sublimed (90 °C, 0.2 mmHg) through a 300 °C Pyrex tube (20 cm × 1.5 cm) packed loosely with quartz wool. The pyrolysate consisted of a yellow oil which was collected in a cold trap at −78 °C. Analysis by ^1H NMR showed 1-methylnaphthalene to be the sole identifiable product (ca. 30%).

Acknowledgment. We thank the National Science Foundation (CHE 8117381), the Camille and Henry Dreyfus Foundation, and the Research Corporation for generous support of this work. We thank Prof. H. Whitlock for the use of the Wisconsin Interactive Molecular Processor (WIMP) program.

Synthesis of Stereoisomeric 4,9a-Dimethylhydrodicyclopenta[*a*,*d*]cycloocten-1-ones Related to the Ophiobolins and Ceroplastins via Annelative Ring Expansion of Hydrindene Precursors

Robert M. Coates,* Jack W. Muskopf, and Peter A. Senter

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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Synthesis of several stereoisomeric ketones possessing the tricyclic 5-8-5 nucleus characteristic of the ophiobolin and ceroplastin sesterterpenes is described. Hydrindenebutenolides **15a,b** and **16a,b** bearing epimeric butenyl and (*E*)-pentenyl side chains were prepared from *trans*-hydrindanone **6** via the bromo Vilsmeier reaction, Grignard addition, and lithiation–carboxylation and were separated by chromatography. Sensitized irradiation of **15a,b** and **16a,b** effected intramolecular [2 + 2] cycloaddition to tetracyclic lactones **17a,b**, **20a,b** and **21a,b**. The corresponding keto acids underwent reductive cleavage of the cyclobutane ring with lithium–ammonia to form 5-8-5 keto esters **19** or acids **25**, **35**, and **40**. Iododecarboxylation followed by removal of iodine by either reductive replacement or dehydroiodination afforded a stereoisomeric series of dodecahydro-4,9a-dimethyldicyclopenta-[*a*,*d*]cyclooctan-1-ones (**27**, **28**, **30**, **37**, and **43**) and decahydro-4,9a-dimethyldicyclopenta[*a*,*d*]cyclooct-4(or 5)-en-1-ones (**29**, **38**, and **39a**, and **42**). The anti or syn relationship of the C-3a/C-9a (C-6/C-11 by ophiobolane numbering) substituents and the complete stereochemistry of the anti 5-8-5 ketones were established through an X-ray crystal analysis of one iodo ketone (**26c**) and various interconversions. The stereochemistry of reactions at C-8 and C-2, A/B ring fusion equilibrations, and the conformation of various 5-8-5 ketones are discussed.

The ophiobolins (e.g., ophiobolin F, **1**)[1] and the ceroplastins (e.g., ceroplastol I, **2**)[2] comprise two families of naturally occurring sesterterpenes that have in common a tricyclic dicyclopenta[*a*,*d*]cyclooctene nucleus bearing

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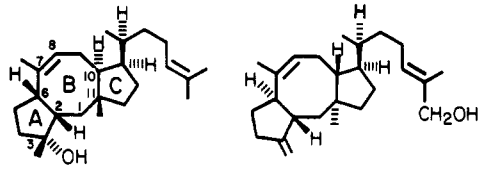
a steroid-type sidechain at C-14.[3,4] The three rings in the ophiobolins have the cis/syn/trans stereochemistry at C-6/C-2/C-11/C-10, whereas the trans/anti/trans orientation obtains in the ceroplastins. The same angular 5-8-5 ring system, albeit with different locations of double bonds, is found in the fusicoccin (e.g., fusicoccin A, **3**, R = sugar),[5,6] cotylenins (similar to **3**),[7] and cycloaranosene (**4**)[8] diterpenes.



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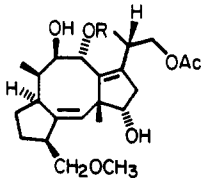

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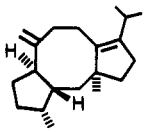

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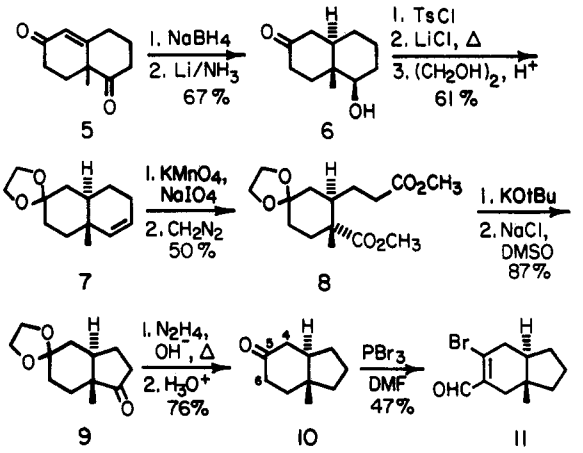
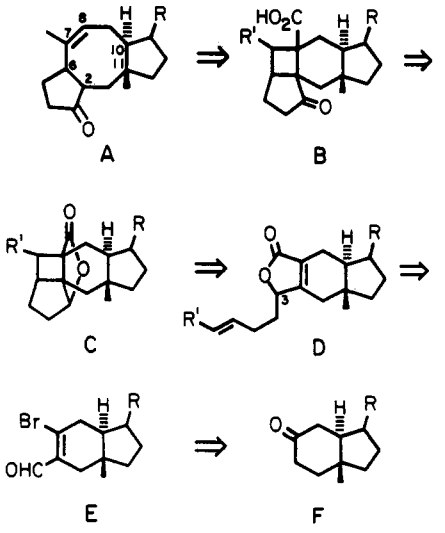
The novel structures, intriguing biosynthetic origins, and wide-ranging biological activities of these isoprenoid metabolites have stimulated efforts to synthesize the basic 5-8-5 ring system.[9-11] Important problems to be addressed in this connection are methods for forming the medium-sized B ring, stereochemical control at the ring-juncture positions, and regioselective placement of double bonds and/or functionality. Key reactions previously used to construct the central eight-membered ring include enamine–acetylene ring expansion of a *trans*-hydrindanone ester,[9] nucleophile-induced fragmentation of bridged tricylcic keto tosylates,[10] and oxy-Cope rearrangement of

Scheme I



divinyl cyclobutanols.[11] However, none of the reported syntheses have succeeded in establishing the stereochemistry of the ophiobolins or ceroplastins at all four ring-juncture positions.

We have developed an alternative synthetic approach to the 5-8-5 nucleus based on annelative two-carbon ring expansion[12] of a *trans*-hydrindanone precursor (F). Thus,



butenolide **D**, available via Grignard addition and carboxylation of bromo aldehyde **E**, should undergo [2 + 2] photocycloaddition to **C**. Reductive cleavage of the cyclobutane ring in the derived keto acid **B** gives rise to the 5–8–5 nucleus (e.g., **A**). It will be noted that the stereochemistry at C-6 is dictated by the configuration of the alkenyl sidechain at C-3 in butenolide **D**, which is in turn established by a Grignard addition to **E**. Although this approach does not afford an opportunity to control the C-6 stereochemistry, access would be gained to both configurational forms. Another concern in this scheme is regioselective introduction of the 7,8-double bond of the ophiobolins and ceroplastins. Initially it was hoped that this could be accmplished via an allenyl lactone **D**[12] and methylene cyclobutanes **C** and **B** (R′ = =CH_2). The purposes of the research described below were to synthesize 5-8-5 ketones having both the syn and anti C-6/C-11 relative configurations via the annelative ring-expansion approach and to determine the stereochemistry and thermodynamic stability of A/B ring-fusion isomers.

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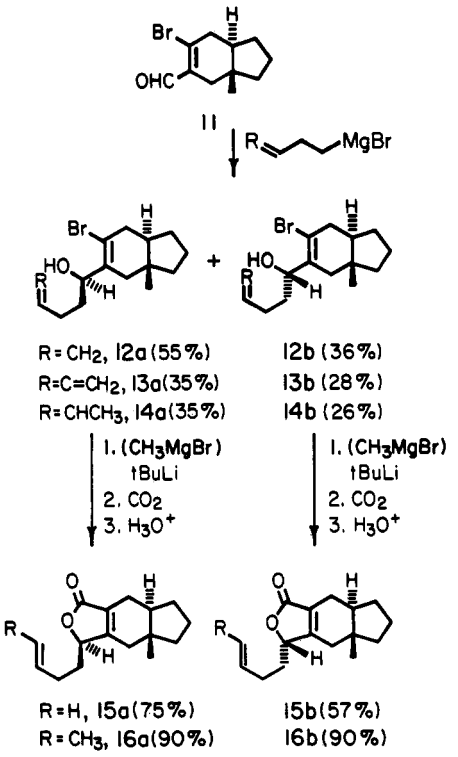
Scheme II



Synthesis of Hydrindene Butenolides

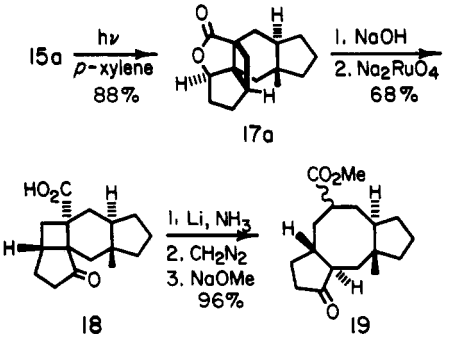
The previously known[13] *trans*-hydrindanone **10** was prepared in 11 steps (13.5% overall yield) from the Wieland–Mischer ketone (**5**)[14,15] as outlined in Scheme I. Lithium chloride induced elimination[16] of the *p*-toluenesulfonate of **6** followed by ketalization afforded octalone ketal **7**. Oxidation of **7** by the Lemieux–Rudolf method,[17] Dieckmann cyclization of the resulting diester, and chloride-induced decarboxylation[18] furnished ketal **9**. The carbonyl group on the five-membered ring was removed by Wolff–Kishner reduction, and the cyclohexanone was liberated by hydrolysis with hydrochloric acid. The bromo Vilsmeier reaction[19] of hydrindanone **10** provided a single crystalline bromo aldehyde **11** in 47–52% yield. It was initially assumed that the Vilsmeier reaction would occur via the 5,6-enol (rather than the 4,5-enol) to give **11** (rather than its regioisomer), in accord with the well-documented tendency of *trans*-decalones and 5α-cholestan-3-ones to undergo preferential enolization at C-2.[20] This assumption was subsequently verified by X-ray crystallography (see below).

Addition of 3-butenyl-, 3,4-pentadienyl-, and (*E*)-4-pentenylmagnesium bromides[12] to aldehyde **11** afforded mixtures (ratios 1.2–1.5:1) of epimeric bromo alcohols **12a,b**, **13a,b** and **14a,b**, respectively (Scheme II). The polarity difference (ΔR_f 0.03) of the isomers on silica gel was sufficient to allow complete separation by medium-pressure liquid chromatography or partial separation by flash chromatography.[21] The less polar and predominant isomer in each case exhibits a somewhat lower field singlet for the angular methyl group ($\Delta\delta^{CDCl_3}$ = 0.03–0.05) in the NMR spectrum. The stereochemistry of **14a** and **14b** was established by an X-ray crystallographic analysis to be presented later. The stereochemistry of **12a,b** and **13a,b** is assigned by analogy. A small amount (ca. 10%) of the primary alcohol resulting from competing reduction of **11** by the homoallylic Grignard reagents was separated in the chromatography and reoxidized to **11** with pyridinium chlorochromate (95%).[22]

Metallation of the bromo alcohols **12a,b** and **14a,b** with 3.5 equiv of *tert*-butyllithium in tetrahydrofuran (THF) from −95 to −45 °C followed by inverse addition to carbon dioxide in THF at −78 °C and hydrolysis[12] afforded the corresponding alkenyl butenolides **15a,b** and **16a,b** in 57–75% yield. Also formed was 10–20% of the debrominated alcohol, evidently arising from self-protonation of initially formed vinyllithium reagent by the hydroxyl proton.[23] This side reaction was suppressed and the yields of **16a,b** were improved to 90% by preformation of the magnesium salt of **14a,b** with methylmagnesium bromide. Attempts to prepare lactones bearing allenyl side chains from **13a,b** or the corresponding tetrahydropyranyl ether of **13a** were uniformly unsuccessful, in contrast to the corresponding cyclohexenyl analogue.[12b] Evidently the allene group undergoes rapid addition (or cyclization?) with the organolithium reagents, affording a complex mixture of byproducts. The inability to obtain the allenyl butenolides was unfortunate, and raised uncertainty over the prospects for regioselective introduction of the 7,8-double bond.

Photocyclization of Hydrindene Butenolides

A preliminary investigation into the photochemistry and reductive ring opening was first conducted with butenolides **15a,b** to avoid stereochemical complications from the additional methyl group in **16a,b**. Irradiation of **15a** in *p*-xylene and **15b** in acetone effected smooth [2 + 2] cycloaddition to **17a** (88%) and the stereoisomeric **17b** (66%, structure not shown). Lactone **17a** was converted to keto acid **18** by hydrolysis and oxidation of the carboxylate



anion with sodium ruthenate.[12,24] The IR spectrum of **18** displays peaks at 1735 and 1700 cm^{-1} for the cyclopentanone and carboxylic acid carbonyl groups, consistent

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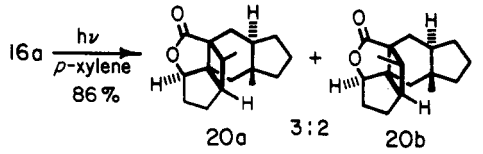
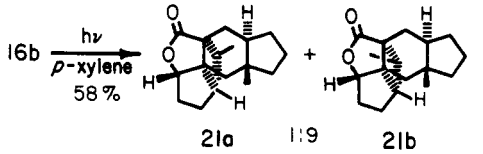
with the fused (rather than bridged) mode of cycloaddition.

Keto acid 18 was reduced with lithium in liquid ammonia, and the product was esterified with diazomethane, affording a 4:2:1 mixture of isomeric keto esters according to GC analysis. Equilibration of the mixture with 0.1 M sodium methoxide in methanol at reflux gave predominantly one isomer, tentatively assigned a trans A/B ring fusion in analogy with results described below.

Irradiation of **16a** in *p*-xylene proceeded at a rate comparable to that of **15a** and **15b**, giving a 3:2 mixture of isomeric lactones **20a** and **20b** (86%) differing in the





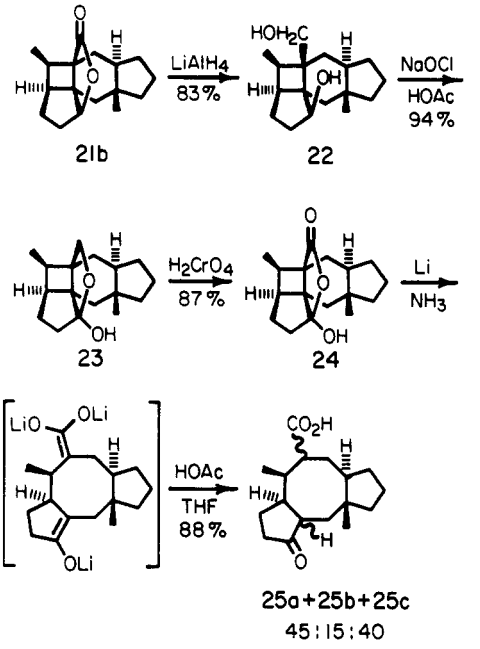
configuration at the secondary methyl group. In contrast **16b** underwent photocyclization at about one-third the rate of **16a** and afforded a 1:9 mixture of lactones **21a** and **21b** in somewhat lower yield (58%). The major isomer (**21b**), mp 141–144 °C, was readily obtained in pure form by crystallization. A small amount of the minor isomer was isolated by chromatography and crystallization.

The stereochemistry of photo lactones **21a** and **21b** follows from the X-ray structure determination of iodo ketone **26c**. The configuration of the secondary methyl group in **20a** and **20b** is assigned on the basis of NMR chemical shifts. The methyl group lying over the lactone π system is assumed to be the one at higher field ($\delta_{CDCl_3}^{CH_3}$ **20a**, = 1.16, **20b** = 0.93; **21a** = 1.29, **21b** = 0.94). This assignment, albeit tentative, is consistent with the apparently slower hydrolysis of **20b**[25] owing to steric hindrance of the lactone carbonyl by the eclipsed methyl group and the stereoselectivities observed in the subsequent reactions of the methyl epimers (see below). It is apparent that loss of the original *E* double bond configuration occurred in these photocyclizations. Presumably bond rotation of a diradical intermediate is competitive with or faster than ring closure.[12,26] The predominant formation of stereomutated cycloadduct **21b** probably reflects steric interactions in the transition state for cyclization to its isomer **21a**. It is reasonable to suppose that the cyclobutane ring will pucker so as to enhance the axial and equatorial alignment of the vicinal, exocyclic bonds with respect to the cyclohexane ring. In the case of **20a** this deformation relieves steric congestion by twisting the secondary methyl away from the cyclohexane ring, whereas in **21a** puckering increases steric repulsion by forcing the methyl group over the ring.

5-8-5 Ketones (C-6/C-11 Anti)

The conversion of crystalline lactone **21b** to 5-8-5 ketones having the anti relationship between the C-6 hydrogen and the C-11 methyl will be discussed first. All attempts to hydrolyze **21b** to water-soluble carboxylates

Scheme III



salts for ruthenate oxidation were unsuccessful, evidently owing to steric congestion of the carboxyl group and/or insolubility of this highly crystalline substance. However, this oxidation could be achieved efficiently in three steps (overall yield, 68%) as shown in Scheme III. Reduction of **21b** with lithium aluminum hydride in THF (80 °C, 1.5 h) furnished diol **22**, which was selectively oxidized in high yield to cyclic hemiketal **23** with sodium hypochlorite in dioxane–acetic acid at 25 °C.[27] Oxidation of diol **22** with either chromic acid in acetone[28] or pyridinium chlorochromate[22] in dichloromethane gave predominantly lactone **21b** as well as other unidentified products. The desired keto acid **24** was obtained by chromic acid oxidation[28] of **23**. The lack of a carbonyl stretching frequency in the IR spectrum of **23** and the presence of only one carbonyl absorption at 1754 cm^{-1} in the IR spectrum of **24** indicate that these compounds exist in the cyclic forms shown.

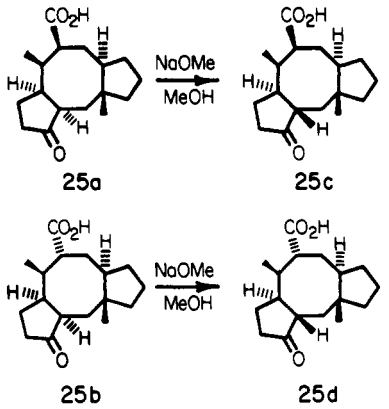
Reduction of lactol **24** with a minimum amount (3 equiv) of lithium in refluxing ammonia–THF provided a 45:15:40 mixture of keto acids **25a**, **25b**, and **25c** in good yield. The presence of three of the four possible isomeric keto acids was evident in the 0.5 and 1.1 ppm region ($CHCH_3$ and CH_3 groups) of the 360-MHz ^1H NMR spectra. The mixture of isomers was equilibrated with sodium methoxide in methanol at increasingly higher temperatures (0–50 °C), and the change in the isomer content was monitored by ^1H NMR. A final 85:15 mixture of keto acids **25c** and **25d** was formed, and the ratio did not change even after prolonged heating. Recrystallization of this 85:15 mixture provided a pure sample of keto acid **25c**, mp 180–181 °C, as well as a 70:30 mixture of C-8 epimers **25c** and **25d**. Since keto acid **25c** remained unchanged when treated with sodium methoxide in methanol at 50 °C, it appears that no carboxyl epimerization occurred under these conditions. The assignments of the configuration of **25a–d** with respect to the ring-juncture stereochemistry seems secure on the basis of the correlations discussed below. A tentative assignment of stereochemistry at the carboxyl bearing carbons is based on the prediction that

(25) A pure sample of **20a** was recovered after hydrolysis and sodium ruthenate oxidation of the **20a,b** mixture. Presumably the recovery of **20a** occurred because of a slower, incomplete hydrolysis in the first step.

(26) Becker, D.; Nagler, M.; Hirsh, S.; Raman, J. *J. Chem. Soc., Chem. Commun.* **1983**, 371–3.

(27) Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030–2.

(28) Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547–49.



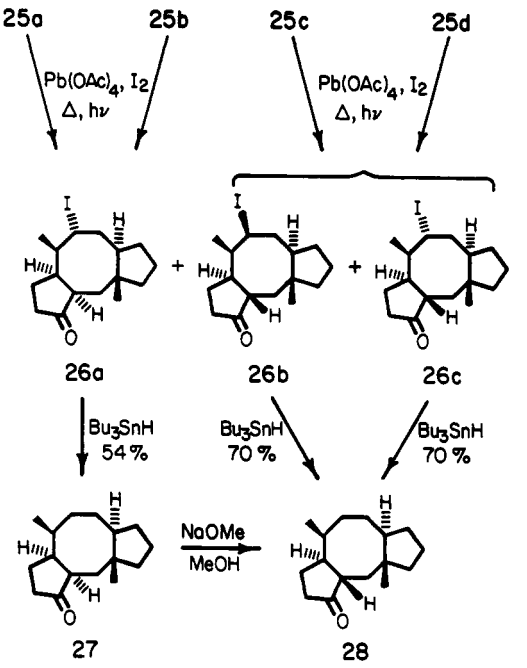
the major products **25a** and **25c** would be those derived from protonation of the carboxylate dianion from the presumed least hindered direction, i.e., syn to the C-7 proton. The 45:15:40 ratio appears to be the result of kinetically controlled protonations since a variety of quenching procedures, such as inverse addition of the trianion into a solution of a proton source, failed to improve the percentage of cis-fused keto acids **25a** and **25b** that was formed in the reductive-cleavage reaction.

Iododecarboxylation[29] of three different mixtures of keto acids **25** with lead tetraacetate and iodine in carbon tetrachloride afforded mixtures of iodo ketones **26a–c** (Scheme IV). The iodides were separated by high-performance liquid chromatography on an analytical silica gel column. The structure and stereochemistry of each iodide (except for **26a** at C-8) were determined by the correlations discussed below. It is clear from entries 2 and 3 (Table I) that keto acids **25c** and **25d** differ only at the carboxyl-bearing carbon and that the configuration at C-8 in the keto acid has no influence on the ratio of the products. The generally accepted mechanism for this type of iododecarboxylation proceeds via a radical intermediate; thus, the stereochemistry of the resulting iodides should be independent of the configuration of the carboxyl group from which it was derived.[29c]

In contrast to the trans-fused isomers, the cis-fused keto acids **25a** and **25b** furnished only one iodo ketone **26a**, as shown in entry 1. This experiment also showed that no equilibration occurred under the reaction conditions. The configuration of the iodo group in **26a** is assigned on the assumption that radical capture would occur syn to the hydrogens at C-2, C-6, C-7, and C-10. Deiodination[30] of iodo ketones **26b** and **26c** with tri-*n*-butyltin hydride in THF at 25 °C furnished the same ketone (**28**) as shown by comparisons of the ^{1}H NMR and GC–mass spectra, as well as TLC, GC, and HPLC characteristics. Reduction of iodide **26a** afforded the cis-fused ketone **27**, which was equilibrated to **28** with sodium methoxide in methanol at 25 °C.

Dehydroiodination of iodo ketone **26b** with tetra-*n*-butylammonium bromide in refluxing acetone[31] gave the trisubstituted enone **29** (Scheme V). The AB ring fusion of **29** was shown to be the same as ketone **28** by palladium-catalyzed hydrogenation of the double bond. A 2:1 mixture of **28** and its C-7 epimer **30** was formed as determined by the 360-MHz ^{1}H NMR spectral properties and

Scheme IV



Scheme V

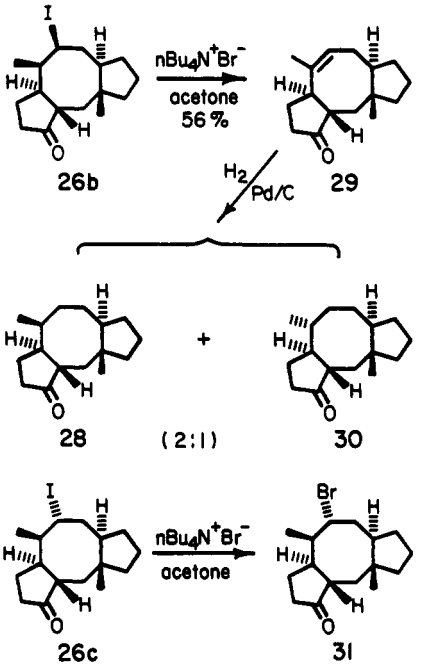


Table I. Ratios and Yields of Iodo Ketones 26a–c from Iododecarboxylation of Keto Acids 25a–d with Lead Tetraacetate and Iodine in Refluxing Carbon Tetrachloride (Scheme IV)

entry	keto acids (ratio)[a]	iodo ketones (ratio)[a]	yield, %
1	**25a** + **25b** + **25c** (45:15:40)	**26a** + **26b** + **26c** (50:20:30)	53
2	**25c**	**26b** + **26c** (40:60)	70
3	**25c** + **25d** (70:30)	**26b** + **26c** (40:60)	80

[a] Ratios determined by integration of 360-MHz ^{1}H NMR spectra. Error estimated to be ±5%.

chromatographic comparisons. Attempted dehydroiodination of iodo ketone **26c** effected only nucleophilic substitution of iodide to give bromo ketone **31** with apparent retention of configuration. The stereochemistry of the bromine is tentatively assigned on the basis of the similarity of the NMR spectra of **26c** and **31**. The retentive

(29) (a) Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2215–26. (b) Barton, D. H. R.; Faro, H. P.; Serebryakov, E. P.; Woollsey, N. F. *J. Chem. Soc.* **1965**, 2438–44. (c) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279–421.

(30) Seyferth, D.; Yamazaki, H.; Alleston, D. L. *J. Org. Chem.* **1963**, *28*, 703–6.

(31) (a) Lloyd, D. J.; Parker, A. J. *Tetrahedron Lett.* **1971**, 637–40. (b) McLenhah, D. J. *Tetrahedron* **1975**, *31*, 2999–3010.

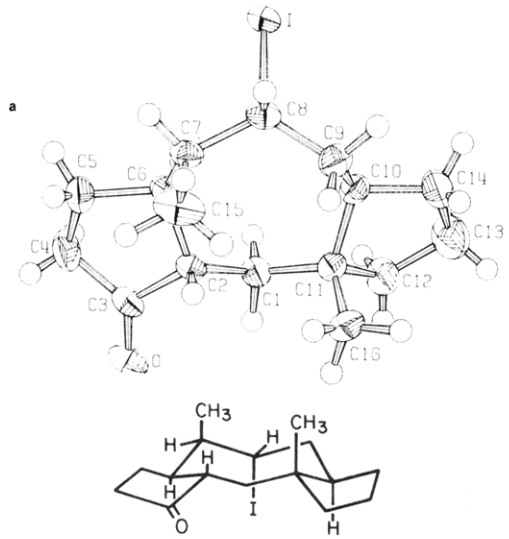


Figure 1. (a) ORTEP plot of the molecular structure of iodo ketone **26c** from a single-crystal X-ray analysis. The non-hydrogen atoms are depicted as 35% probability ellipsoids; the hydrogen atoms were assigned small arbitrary thermal coefficients to avoid overlap problems. (b) Line drawing of **26c** showing crown conformation.

Table II. Internal Cyclooctane Dihedral Angles Observed for Iodo Ketone 26c in the Solid State and Calculated for Idealized Chair–Chair and Crown Conformers of Cyclooctane

	dihedral angle, deg[a]		
C–C bond	keto iodide[b] **26c**	chair–chair[c] cyclooctane	crown[c] cyclooctane
C-1/C-2	82.1	66	87.5
C-2/C-6	96.5	105	87.5
C-6/C-7	82.3	105	87.5
C-7/C-8	63.8	66	87.5
C-8/C-9	73.4	66	87.5
C-9/C-10	92.3	105	87.5
C-10/C-11	83.2	105	87.5
C-11/C-1	70.5	66	87.5

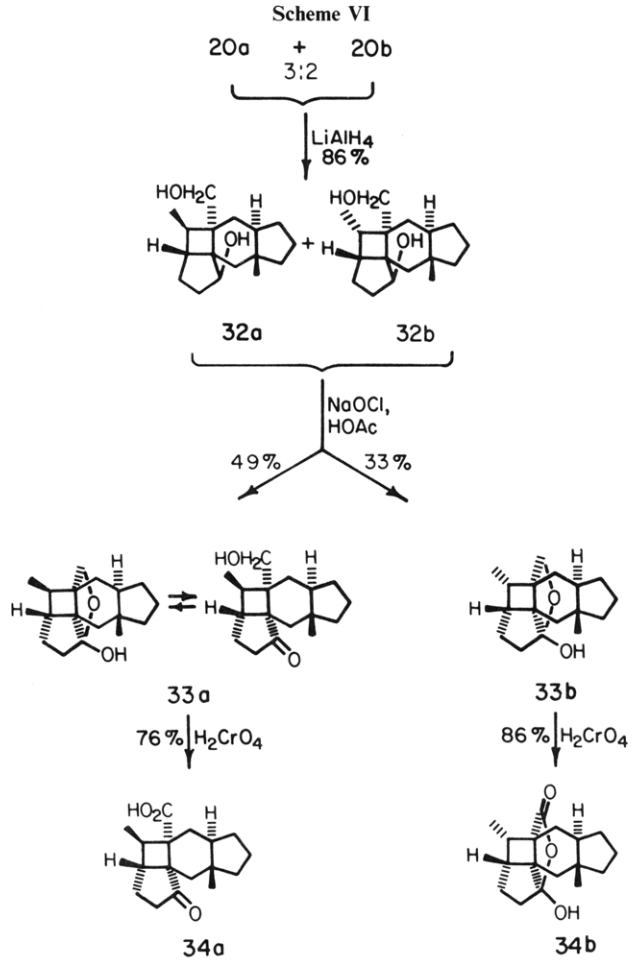
[a] The absolute values of the internal dihedral angle are given. [b] Data are taken from X-ray analysis. [c] Data from ref 33a.

substitution apparently observed in this reaction may be attributed to 1,5-hydrogen participation, a well-precedented phenomenon in the solvolysis of cyclooctyl derivatives.[32]

The structure and relative stereochemistry of iodo ketone **26c** were rigorously established by an X-ray crystallographic analysis. An ORTEP plot and an approximate conformational representation of the molecule are shown in Figure 1. The eight-membered ring adopts a crown-like conformation which appears to be a hybrid between the idealized chair–chair and crown conformations of cyclooctane.[33] Table II lists the dihedral angles of the internal cyclooctane bonds determined from the X-ray analysis and the corresponding dihedral angles calculated for the chair–chair and crown conformers of cyclooctane.[33a]

The 360-MHz ^{1}H NMR spectrum for **26c** in solution exhibits an 8-line multiplet for the proton on carbon bearing iodine with J = 5.4, 4.3, and 2.5 Hz. These are in rough agreement with coupling constants predicted from the dihedral angles between the C-8 proton and the axial

Scheme VI



C-9 proton, the equatorial C-7 proton, and the equatorial C-9 proton, in the solid state using the Karplus equation:[34] ϕ = 39.2, 55.7, 75.2°; J_{calcd} = 5, 2, 0.2, Hz. Thus, the solution conformation is probably quite similar to that in the crystalline state. The epimeric iodo ketone, **26b**, presumably has a similar conformation with an equatorial iodide. Using dihedral angles between H_a at C-8 and H_a at C-9 (179°), H_e at C-7 (49°), and H_e at C-9 (64°), one can predict the following coupling constants for the C-8 proton: J_{calcd} = 9, 4, 2 Hz. The good agreement with the observed values (J_{obsd} = 9, 3, 3 Hz) supports the presumption that **26b** and **26c** have similar conformations. The NMR spectrum of the cis iodo ketone **26a** displays a multiplet for the CHI group with J = 12.6, 9.4, 3.6 Hz (ϕ = 180, 180, 51°) which indicates a boat–boat (or twisted boat–boat) conformation for the cyclooctane ring (C-6/C-10 and C-1/C-8, opposing bow positions), assuming the configuration of the iodo group is correctly assigned.

5-8-5 Ketones (C-6/C-11 Syn)

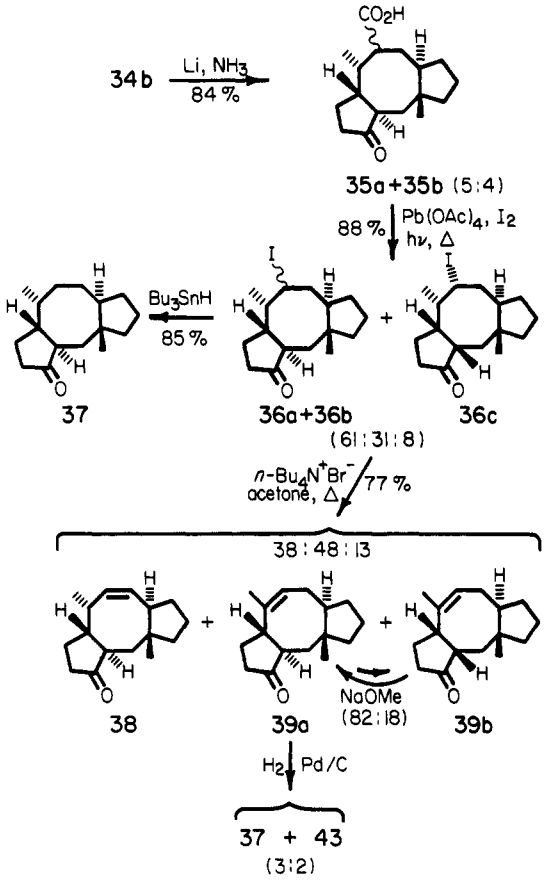
Conversion of lactones **20a** and **20b** to 5-8-5 ketones having the syn relationship between the C-6 proton and the C-11 methyl was carried out by the same reactions discussed in the previous section. Although ruthenate oxidation of the 3:2 mixture of lactones **20a** and **20b** directly to a mixture of keto acids **34a** and **34b** was successful (64%) in this case, the purification and analysis of products from subsequent reactions were complicated by the mixture of the methyl epimers. These difficulties were al-

(32) Nordlander, J. E.; Owuor, P. O.; Cabral, D. J.; Haky, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 201–6, and refs cited therein.

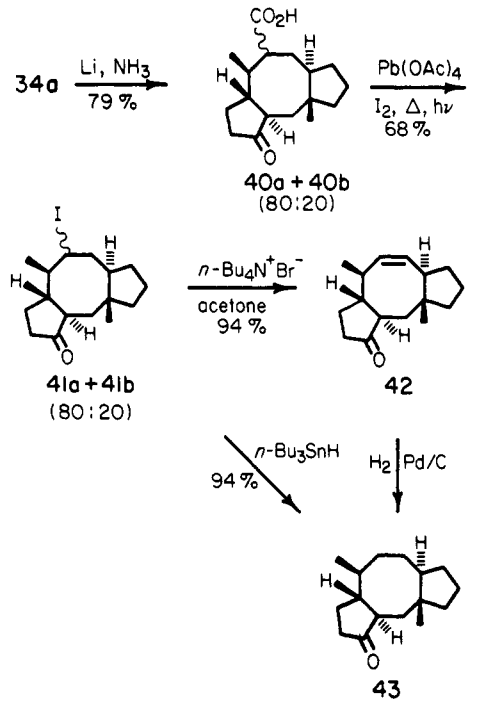
(33) (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 7043–46. (b) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J.; Van-Catledge, F. A. *Ibid.* **1968**, *90*, 1199–1210. (c) Anet, F. A. L.; Basus, V. J. *Ibid.* **1973**, *95*, 4424–26.

(34) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Ed.; Pergamon Press: Oxford, 1969; 280–283.

Scheme VII



Scheme VIII



leviated when the three-step oxidation procedure described above for lactone **21b** was adopted and a chromatographic separation of ketols **33a** and **33b** was achieved (Scheme VI). Reduction of the 3:2 mixture of lactones **20a**, and **20b** with lithium aluminum hydride in THF (50 °C, 10 min) furnished a mixture of chromatographically inseparable diols, **32a** and **32b**. Hydrochlorite oxidation of the mixture and separation of the two diastereomers by flash chromatography (ΔR_f 0.04) on silica gel afforded the corresponding ketols **33a** and **33b**. Although TLC and GC analyses indicated that the crystalline ketol (**33a**, mp 141–144 °C) was pure, the ^{1}H NMR spectrum of **33a** in chloroform-*d* revealed a 1:1 equilibrium mixture of the hemiketal and ketol. Oxidation of **33a** and **33b** with chromic acid in acetone proceeded smoothly at 25 °C, although lactol **34b** (IR 1745 cm^{-1}) was formed at a rate approximately one-tenth that of keto acid **34a** (IR 1740, 1705 cm^{-1}). The lower rate of oxidation of hemiketal **33b** can be attributed to a combination of the apparent lower concentration of **33b** in the ketol form as well as the steric hindrance of the α-CH_3 group.

Reductive cleavage of lactol **34b** with lithium in refluxing ammonia afforded a 5:4 mixture of keto acids **35a** and **35b** in 84% yield (Scheme VII). The appearance of the ^{1}H NMR spectrum was unchanged after treatment of a portion of the mixture with sodium methoxide in methanol at 50 °C for 80 min. This presumably indicates that the isomers have the stable A/B ring fusion stereochemistry. Iododecarboxylation of the original 5:4 mixture of keto acids **35a** and **35b** with lead tetraacetate and iodine provided a 61:31:8 mixture of inseparable iodo ketones **36a–c**, as determined from the relative areas of the CHI signals in the 4.1–4.9 ppm region of the 360-MHz ^{1}H NMR spectrum. Deiodination of this mixture of iodo ketones with tri-*n*-butyltin hydride in THF (25 °C, 30 min) afforded a 93:7 mixture of ketone **37** and its C-2 epimer. Ketone **37** was found to be stable in a solution of sodium methoxide in methanol. It is clear from these results that keto acids **35a,b**, iodo ketones **36a,b**, and ketone **37** each possess the more stable A/B ring fusion and that only a small amount (8%) of the C-2 epimer was present. The A/B stereochemistry of the stable isomers is tentatively assigned as trans on the basis of greater stability of A/B trans 5-8-5 ketones in the C-6/C-11 anti series (see previous section) and literature precedent for similar 5-8 and 5-8-5 ketones.[11,35]

Dehydrohalogenation of iodo ketones **36a–c** with tetra-*n*-butylammonium bromide in refluxing acetone afforded a 38:48:13 mixture of olefins **38**, **39a**, and **39b** in good yield. Partial separation of the isomers was effected by flash chromatography on silica gel impregnated with 10% silver nitrate. Pure samples of enones **38** (mp 81–84 °C) and **39a** (mp 65.5–68 °C) were obtained by crystallization and characterized by their IR, ^{1}H NMR, and mass spectral properties. Enone **38** was stable to sodium methoxide in methanol, but enones **39a** and **39b** (contaminated with 15% **39a**) were each equilibrated to an 82:18 mixture of **39a** and **39b** under these conditions. The A/B ring fusion of **39a** was shown to be the same as ketone **37** by palladium-catalyzed hydrogenation of the double bond. A 3:2 mixture of ketones **37** and **43**, along with unreacted enone **39a**, was formed as determined by inspection of the 360-MHz ^{1}H NMR and chromatographic comparisons. These conditions evidently do not equilibrate ketone isomers judging from the hydrogenation of enones **42** and **45** described below.

Reductive cleavage of keto acid **34a** with lithium in refluxing ammonia afforded an 80:20 mixture of keto acids **40a** and **40b** (Scheme VIII). Equilibration of the 80:20 mixture with sodium methoxide in methanol left the major keto acid unchanged and partially converted the minor isomer (75% conversion) to a new isomer. These conclusions are based on changes observed in the 0.6 to 1.05 ppm

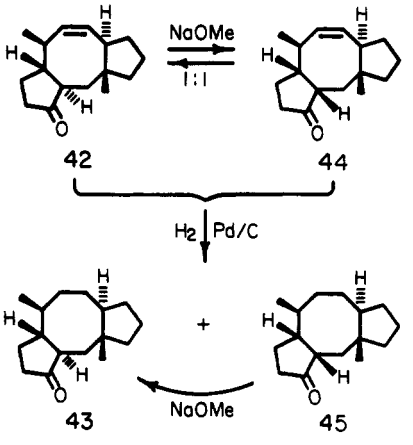
(35) (a) Umehara, M.; Takayanagi, H.; Ogura, H.; Hishida, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3277–81. (b) Begley, M. J.; Mellor, M.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1979**, 235–36.

region of the 360-MHz ^1H NMR spectra.

Iododecarboxylation of the original 80:20 mixture of keto acids **40a** and **40b** yielded an 80:20 mixture of iodo ketones **41a** and **41b**. Reduction of this mixture of iodo ketones with tri-*n*-butyltin hydride in THF afforded only one ketone (**43**) which was stable to sodium methoxide in methanol. The conditions used for the formation of iodo ketones **41a,b** and ketone **43** had previously been demonstrated to be nonequilibrating for related compounds having the C-6/C-11 anti stereochemistry (Scheme IV). Therefore keto acids **40a,b**, iodo ketones **41a,b**, and ketone **43** all presumably have the same A/B ring juncture, which is again tentatively assigned as trans. Since keto acids **40a** and **40b** differed in stereochemistry only at C-8, it is clear from the partial equilibration of **40b** that the relative stability of the A/B ring-juncture isomers can be affected by the relative stereochemistry of substituents on the eight-membered ring.

Attempts to introduce a 7,8-double bond by elimination reactions with iodo ketones **41a,b** were not successful. Dehydroiodination of **41a,b** with tetra-*n*-butylammonium iodide afforded the disubstituted 8,9-enone **42** in 94% yield. Careful inspection of the 360-MHz NMR spectrum of the crude product revealed the complete absence of the 7,8-enone, even though the minor iodo ketone (**41b**) should have the proper stereochemistry for anti elimination toward C-7. Palladium-catalyzed hydrogenation of enone **42** gave the same saturated ketone (**43**) obtained from the tin hydride reduction mentioned previously.

Equilibrium of enone **42** with sodium methoxide in methanol at 50 °C yielded a 1:1 mixture of enones **42** and **44**. This suggests that the conditions used in the dehydroiodination do not effect equilibration of the A/B ring juncture of the starting materials or enone products. Palladium-catalyzed hydrogenation of a mixture of enones **42** and **44** afforded a mixture of ketones **43** and **45**. Since



ketone **43** was previously demonstrated to be the thermodynamically more stable isomer, it is clear that the hydrogenation conditions were nonequilibrating.

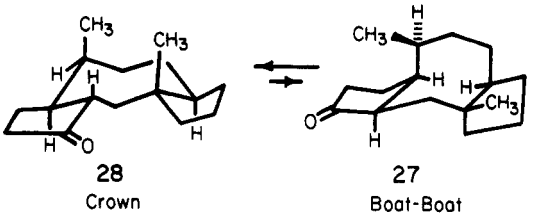
Stereochemistry and Conformation

It is appropriate to conclude by pointing out some apparent generalizations regarding the reaction stereochemistry and conformation of the various 5-8-5 ketones. Carboxy enolate protonations and free-radical capture of iodine at C-8 apparently occurred preferentially on the α-face. Moderately high α stereoselectivities ($\geq$4:1) were observed when the adjacent methyl groups at C-7 was β whereas lower ratios (ca. 1–2:1) were obtained when the C-7 methyl group was α oriented. One exception to this generalization is the iododecarboxylation of **25c,d** (7β CH_3) which resulted in a relatively low (60:40) α/β capture ratio.

The conformations available to 7,8-enes **29** and **39a** are more restricted than those of the saturated 5-8-5 ketones. Thus, it was somewhat surprising that only modest α-selectivities (1.5–2:1) were observed in the catalytic hydrogenations of these tri-substituted double bonds. Presumably this indicates that the reactive conformation(s) is (are) chair-like (rather than tub-like) so that both π-faces are relatively accessible. In contrast, methyl ceroplastate (**2**, CO_2CH_3 in place of CH_2OH) undergoes exclusive epoxidation from the α-face,[36] in accord with the prediction of peripheral attack of reagents on cyclooctenes.[37]

The kinetic protonations of 2,3-enolates following reductive ring opening of keto acids **24**, **34a**, and **34b** result in α-attack, with α/β selectivities varying from 5–10:1 to 53:47, the latter ratio in the formation of **25a** + **25c** from **24**. In the C-6/C-11 anti case (**24**) α-protonation leads predominantly to the thermodynamically less stable cis A/B ring fusion. However, protonations of the C-6/C-11 syn enolates from **34a** and **34b** afford principally the thermodynamically more stable configuration at C-2 which is assumed to be C-6 α with the trans A/B ring juncture. The α-selectivity of these enolate protonations probably arises from partial shielding of the β-face of enolate by the angular methyl group at C-11.

Base-catalyzed equilibrations of 5-8-5 ketones afford potentially useful information on the relative stability of the cis and trans isomers with respect to the A/B ring fusion. In the C-6/C-11 anti series, cis-fused ketones **25a**, **25b**, and **27** isomerized completely ($\geq$95%) to the corresponding trans isomers, **25c**, **25d**, and **28**. Although it is



tempting to conclude that the trans,syn,trans (C-6/C-2/C-11/C-10) stereochemistry is inherently more thermodynamically stable than the cis,anti,trans alternative, the energy difference between the two isomers may be affected by the β-methyl group at C-7. In fact, the boat–boat conformation of **27** would appear to be destabilized to some extent by interactions of the C-7 methyl group with the cyclopentanone ring. Unfortunately no information is available for the α-methyl epimers in this series. Analogous bicyclic 5-8 ketones are also thermodynamically more stable with a trans stereochemistry.[35]

It is likely that the conformations of **27** and **28** are similar to those of the related iodo ketones, **26a** and **26c**. The X-ray crystal structure revealed that the cyclooctane ring of **26c** adopts a crown-like conformation whereas NMR coupling constants indicated a boat–boat (or twisted boat–boat) conformation for **26a**. The alternating staggered relationships of the crown conformation nicely accommodate the trans,syn,trans disposition of the attached cyclopentane rings (see **28** crown). However, neither crown nor chair–chair conformations are accessible to cis,anti, trans ketones such as **27**. Transannular interactions involving the C-7 methyl group appear to destabilize a boat–chair conformation and may explain the ostensible preference for the boat–boat conformation (**27** boat–boat, or a twisted variant).

(36) Quijano, L.; Calderon, J.; Rios, T. *Chem. Ind. (London)* **1978**, 584–85.
(37) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981–96.

In the absence of independent evidence regarding the C-2 stereochemistry in the C-6/C-11 syn series of 5-8-5 ketones, we have assumed that the more stable isomers (**37**, **39a**, and **43**) have trans-A/B fusions. This assumption is based upon the known stability of trans-fused bicyclic 5-8 ketones.[35] The decrease in the energy difference between the cis and trans isomers when double bonds are present in the 7,8- or 8,9-positions is noteworthy. Thus, the equilibrium ratios for epimeric 5-8-5 enones **39a**/**39b** and **42**/**44** are 82:18 and 1:1, respectively. The origin of the very different relative stabilities of the 8,9-enone epimers **42**/**44** and the corresponding saturated ketones **43**/**45** is not apparent from inspection of Dreiding models. Crown or chair–chair conformations of the cyclooctane ring are not available to the trans,anti,trans 5-8-5 ketones (e.g., **37** and **43**), but various twisted boat–chair configurations appear favorable. Both ceroplastol I (**2**) *p*-bromobenzoate[2] and a trans-fused 5-8 diketone[35a] assume boat–chair conformations in the solid state.

Experimental Section

General Aspects. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian Associates EM-390 (90 MHz, continuous wave mode) spectrometer, if unspecified, or Nicolet NT-360 (360 MHz, FT mode) spectrometer, as specified. The 90-MHz spectra were recorded by using an internal lock on tetramethylsilane, and the 360-MHz spectra were recorded with an internal lock on the deuterium resonance of the solvent. Infrared spectra were obtained with a Perkin-Elmer Model 137 spectrometer. Mass spectra were run on Varian-MAT CH-5, 311A (GC/MS), and 731 mass spectrometers by Carter Cook and associates. Elemental analyses were performed at the University of Illinois Microanalytical Laboratory by J. Nemeth and associates. Melting points were determined on a Reichert hot stage microscope, and are uncorrected.

Analytical gas chromatography (GC) was performed on a Varian Model 3700 instrument equipped with a flame-ionization detector and using helium as the carrier gas at the indicated column temperature. The following standard operating conditions were used: 230 °C injector temperature, 300 °C detector temperature, and a 40 mL/min carrier gas flow rate. Analyses were carried out with either column A: 1.8 m × 6 mm glass column packed with 3% OV-17 on 100/120 mesh Gas Chrom Q; or column B: 3.6 m × 6 mm glass column packed with 3% OV-17 on 100/120 mesh Gas Chrom Q.

Flash chromatography was performed as described by Still,[21] on Woelm 32–63 micron silica gel supplied by Universal Scientific, Atlanta, GA. Preparative medium-pressure liquid chromatography (MPLC) was performed with a system developed in this laboratory by Dr. William Baker, as previously described.[38] The column was packed with Woelm 32–63 μm silica gel. Analytical thin-layer chromatography (TLC) was conducted on either Brinkmann Polygram plastic plates precoated with 0.25 mm of silica gel GF-254 or Merck glass plates precoated with 0.25 mm of silica gel GF-254. Thin-layer chromatograms were visualized with 5% phosphomolybdic acid reagent in 95% ethanol, iodine vapors, and/or UV light. High-pressure liquid chromatography (HPLC) was performed on a Waters Model 6000A system equipped with a Schoeffel Instruments Corp. variable wavelength UV detector and a silica gel column.

All reactions, except those performed in aqueous solvents, were carried out in a dry nitrogen or argon atmosphere with use of standard techniques for the exclusion of moisture. Glassware used in water-sensitive reactions was dried in a circulating oven at 130 °C for at least 1 h.

Tetrahydrofuran (THF) was purified by distillation from sodium–benzophenone ketyl. Dry ammonia and absolute methanol were prepared by distillation from sodium. Ethereal diazomethane was generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald), supplied by Aldrich Chemical Co., by using the procedure provided on the container.

(38) Baker, W. R.; Coates, R. M. *J. Org. Chem.* **1979**, *44*, 1022–1024.

(4aβ,5β,7aα)-Octahydro-5-hydroxy-4a-methyl-2(1*H*)-naphthalenone (6). Naphthalenedione **5**[14,15] was reduced with sodium borohydride by the method of Boyce and Whitehurst.[39] The yield of hydroxy enone was 131 g (82%): bp 150–155 °C (0.2 mm) [lit.[39] 140 °C (0.2 mm)].

A portion of the hydroxy enone was reduced with lithium in ammonia.[40] A solution of 7.57 g (1.09 mol) of lithium in 2 L of ammonia was stirred mechanically and maintained at reflux as a solution of 89.1 g (0.495 mol) of the enone alcohol in 1000 mL of THF was added over 65 min. Stirring was continued for 30 min, after which the excess lithium was destroyed with isoprene. A solution of 40 mL of acetic acid in 250 mL of THF was added over 3 min, and the ammonia was evaporated under a stream of nitrogen. The residue was suspended in 250 mL of water, and the aqueous layer was extracted twice with ether. The combined organic fractions were washed with 10% hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. Evaporation of the dried ($MgSO_4$) solution and simple distillation of the residue furnished 73.4 g (82%) of the ketol **6**, bp 127–135 °C (0.3 mm), as a colorless oil, which solidified on standing. Recrystallization from ether provided an analytical sample: mp 71–72 °C [lit.[40] mp 68–70 °C]; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 3 H, CH_3), 1.15–1.92 (m, 9 H), 2.00–2.54 (m, 4 H, two $CH_2C{=}O$), 3.14–3.46 (m, 1 H, C*H*OH).

(4aβ,8aα)-3,4,4a,7,8,8a-Hexahydro-4a-methylspiro[1,3-dioxolane-2,2′(1*H*)-naphthalene] (7). Ketol **6** was dehydrated by the method of Heathcock and co-workers.[16] Simple distillation of the crude product afforded 59.3 (63%) of the enone, bp 130–140 °C (0.8 mm), which formed a white solid on standing. Recrystallization of a portion provided an analytical sample: mp 53–55 °C (lit.[16] mp 54–55 °C).

A mixture of 47.50 g (0.29 mol) of keto olefin, 35.9 g (0.58 mol) of ethylene glycol, and 250 mg of *p*-toluenesulfonic acid hydrate in 300 mL of benzene was heated at reflux for 4 h in a flask equipped with a Dean–Stark trap. The cooled solution was poured into 150 mL of ether, the ether–benzene solution was extracted with 50 mL of saturated sodium carbonate, and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated sodium chloride and dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue through an 18-cm Vigreux column afforded 53.50 g (89%) of ketal olefin **7** as a yellow liquid, bp 92–98 °C (0.8 mm), which solidified on cooling. Recrystallization of a portion from pentane afforded white needles: mp 39–39.5 °C; IR (film) ν_{max} 2940 (CH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3 H, CH_3), 1.22–1.93 (m, 8 H), 3.92 (s, 4 H, OCH_2CH_2O), 5.48 (s, 2 H, HC=CH).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.94; H, 9.70. Found: C, 75.03; H, 9.65.

Methyl 8α-Carbomethoxy-8β-methyl-1,4-dioxaspiro[4.5]decane-7β-propanoate (8). The oxidation of 64.8 g (0.31 mol) of ketal olefin **7** was carried out by using the procedure of Milewich and Axelrod[17] with several modifications. The initial 64.8 g of starting material was divided into two 20.8-g (0.1 mol) portions and one 23.2-g (0.11 mol) portion. Each portion was oxidized individually because of the large reaction volumes the procedure required, but the crude acids were later combined during the esterification step. Since all three oxidations were carried out in the same manner, only one oxidation is described in detail.

A solution of 20.8 g (0.1 mol) of olefin **7** and 18.7 g (0.15 mol) of potassium carbonate in 830 mL of *tert*-butyl alcohol was vigorously stirred at 25 °C with a mechanical stirrer as solutions of 128 g (0.60 mol) of sodium metaperiodate in 1600 mL of water and 2.5 g (15.8 mmol) of potassium permanganate in 330 mL of water were simultaneously added. The metaperiodate solution was added over 1.5 h, and the permanganate solution was added over 3 h. The progress of the reaction was monitored by GC (column A, 200 °C). The oxidation was complete, as indicated by the disappearance of starting material and the appearance of diacid, 30 min after the metaperiodate solution had been completely added. The excess oxidizing agents were reduced by the addition of 23 g of sodium bisulfite. The pH was adjusted to 9–10 with potassium carbonate, and the suspension was stirred and

(39) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1960**, 2680–6.
(40) Birch, A. J.; Pride, E.; Smith, H. *Ibid.* **1958**, 4688–93.

cooled at 0 °C for 6 h. After the precipitated salts were removed by filtration, the volume of solvent was reduced to ~500 mL by evaporation (0.5 mm, 40 °C). The light yellow solution was extracted once with ether, cooled at 5 °C, and acidified to pH 2–3 with 50% sulfuric acid. The mixture was extracted four times with ether and once with dichloromethane. The combined ether layers and the dichloromethane layer were each washed with saturated sodium chloride and were dried (Na_2SO_4).

The other two portions of ketal olefin **7** were treated similarly, and the resulting ether and methylene chloride solutions were combined. Following evaporation of the solvent, the residue was esterified with excess diazomethane in ether at 0 °C. GC analysis indicated the presence of ~30% of unketalized ketone; therefore the ether was evaporated, and a mixture of 10 g of ethylene glycol, 0.2 g of *p*-toluenesulfonic acid, and 600 mL of benzene was added. The mixture was heated at reflux for 20 min as the water was removed via a Dean–Stark trap. After cooling to 0 °C, the mixture was washed with saturated sodium bicarbonate and saturated sodium chloride and was dried (Na_2SO_4). Evaporation of the solvent afforded 46.6 g (50%) of **8** as a white solid, mp 98–106 °C. A portion was recrystallized from ether and provided an analytical sample: mp 104–106 °C [lit.[41] mp 105–105.5 °C]; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3 H, CH_3), 1.23–1.90 (m, 7 H), 1.92–2.42 (m, 4 H), 3.67 (s, 3 H, $COOCH_3$), 3.70 (s, 3 H, $COOCH_3$), 3.98 (s, 4 H, OCH_2CH_2O).

(3aα,7aβ)-Hexahydro-7a-methylspiro[1,3-dioxolane-2,5′-(3*H*)-inden]-1′(2*H*)-one (9). A solution of 20.00 g (67 mmol) of diester **8** in 250 mL of benzene was added to a rapidly stirred suspension of 14.96 g (130 mmol) of potassium *tert*-butoxide in 300 mL of benzene over 45 min. The mixture was heated at reflux for 4 h and cooled to room temperature. The yellow solution was poured into ice-cold 10% hydrochloric acid, and the aqueous layer was extracted with three 30-mL portions of ether. The combined organic layers were washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated, leaving a mixture of keto esters as a light yellow solid.

A mixture of the solid and 3.89 g (67 mmol) of sodium chloride in 200 mL of dimethyl sulfoxide and 2.4 mL of water (0.13 mol) was heated at 160 °C for 4 h and cooled to room temperature.[18] The solution was poured into about 300 mL of saturated sodium chloride, and the aqueous mixture was extracted with several portions of ether. The combined ether extracts were washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. Distillation of the residue through a 7-cm Vigreux column afforded 10.73 g (77%) of ketone **9** as a colorless oil, bp 113–119 °C (0.6 mm), which solidified on standing. Recrystallization from pentane provided an analytical sample: mp 41–49 °C; IR (film) ν_{max} 1735 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3 H, CH_3), 1.17–2.67 (m, 11 H), 3.94 (s, 4 H, OCH_2CH_2O).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.53; H, 8.64. Found: C, 68.81; H, 8.58.

(3aα,7aβ)-Octahydro-7a-methyl-5*H*-inden-5-one (10). A solution of 10.60 g (50 mmol) of ketone **9** and 34 g of potassium hydroxide in 220 mL of diethylene glycol and 65 mL of 85% hydrazine hydrate was stirred and heated at 120 °C (oil bath temperature) for 3 h in a flask equipped with a variable reflux distillation head.[42] The oil bath temperature was increased to 210 °C, and heating was continued for 6 h while distillate was collected. The remaining solution was cooled and combined with the distillate, about 300 mL of water was added, and the aqueous mixture was extracted with several portions of ether. The combined ethereal extracts were washed with saturated sodium chloride and evaporated. A solution of the residue in 80 mL of tetrahydrofuran and 40 mL of 10% hydrochloric acid was heated at reflux for 2 h. The cooled solution was diluted with saturated sodium chloride and extracted with several positions of ether. The combined ethereal extracts were washed with saturated sodium bicarbonate and saturated sodium chloride and were dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue through a 7-cm Vigreux column afforded 6.75 g (88%) of the known[13] hydrindanone **10** as a colorless oil: bp 75–85 °C (3 mm); IR (film) ν_{max} 2910 (C-H), 2835 (C–H), 1710 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3 H, CH_3), 1.13–2.13 (m, 9 H), 2.13–2.58 (m, 4 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.88; H, 10.61. Found: C, 78.62; H, 10.55.

(3aβ,7aα)-6-Bromo-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-indene-5-carboxaldehyde (11). Method A. Bromo Vilsmeier Reaction. The Arnold modification[19] of the Vilsmeir reaction was used to prepare bromo aldehyde **11**. A solution of 11.52 g (0.158 mol) of *N,N*-dimethylformamide in 40 mL of anhydrous trichloroethylene was cooled in an ice bath while 38.48 g (0.142 mol) of phosphorus tribromide was added dropwise over 20 min. The resulting white suspension was warmed to room temperature and stirred for 30 min. A solution of 8.00 g (52.64 mmol) of hydrindanone **10** in 10 mL of trichloroethylene was added via syringe, and the syringe was washed with two 10-mL portions of trichloroethylene. The mixture was stirred and heated at 80 °C for 3 h, cooled to room temperature, and poured onto ice. Solid sodium bicarbonate was carefully added to neutralize the acids, and the mixture was extracted with several portions of ether. The combined ethereal extracts were washed with saturated sodium chloride and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography on 100 g of silica gel, using 1:12 ethyl acetate–hexane as eluant, furnished 6.67 g (52%) of **11** as a light yellow oil, which solidified on standing. Recrystallization from pentane gave colorless rods: mp 46–47.5 °C; IR (film ν_{max} 1675 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 3 H, CH_3), 1.08–2.20 (m, 7 H), 2.39–3.12 (m, 4 H, two allylic CH_2), 10.04 (s, 1 H, CHO).

Anal. Calcd for $C_{11}H_{15}BrO$: C, 54.33; H, 6.23; Br, 32.86. Found: C, 54.63; H, 6.32; Br, 33.07.

Method B. Oxidation of Bromoindenemethanol. A solution of 2.77 g (11.31 mmol) of the bromoindenemethanol (see below) in 10 mL of dichloromethane was added to a stirred suspension of 3.66 g (16.96 mmol) of pyridinium chlorochromate in 20 mL of dichloromethane.[22] The mixture was stirred for 2 h, after which the solvent was decanted from the chromium salts. The salts were washed with several portions of ether. The dichloromethane solution and ethereal extracts were combined, the solution was filtered through a short pad of Florisil, and the Florisil was eluted with ether. Evaporation of the filtrate and purification of the green residue by flash chromatography on a 20-mm column with 1:9 ethyl acetate–hexane as eluant afforded 2.61 g (95%) of bromo aldehyde **11**, as a fine white powder. The TLC, GC, and ^{1}H NMR characteristics are identical with those of the sample prepared in method A.

(1*R,3aβ,7aα)-1-(6-Bromo-2,3,3a,4,5,5a-hexahydro-3a-methyl-1*H*-inden-5-yl)-4-penten-1-ol (12a) and (1*S**,3aβ,7aα)-1-(6-Bromo-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-inden-5-yl)-4-penten-1-ol (12b).** A mixture of 0.66 g (27.16 mmol) of magnesium turnings and 5.28 g (28.07 mmol) of 1,2-dibromoethane in 20 mL of anhydrous tetrahydrofuran was stirred and heated at reflux under an atmosphere of dry argon.[43] After 1 h, the mixture was cooled to room temperature, and 2.05 g (52.51 mmol) of potassium metal was added. The mixture was stirred vigorously and heated at reflux for 1.5 h. The resulting suspension of highly reactive magnesium was cooled to −78 °C and stirred as 3.55 g (26.26 mmol) of 4-bromobutene was added. After the mixture was stirred an additional 30 min at −78 °C, a solution of 2.20 g (9.05 mmol) of bromo aldehyde **11** in 5 mL of tetrahydrofuran was added via syringe. The syringe was washed with three 4-mL portions of tetrahydrofuran, and the mixture was warmed to room temperature. Saturated ammonium chloride was added, and the aqueous layer was extracted with several portions of ether. The combined organic extracts were washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. The isomeric alcohols were separated by medium-pressure liquid chromatography on 450 g of silica gel, using 8% ether in hexane as eluant. The first product to be eluted from the column was bromo alcohol **12a** which was obtained as a pale yellow viscous oil that solidified on standing: yield, 1.38 g (51%); mp 34–40 °C; IR ($CHCl_3$) ν_{max} 3510 (OH), 1650 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.73 (s, 3 H, CH_3), 1.03–2.97 (m, 16 H), 4.66–5.18 (m, 3 H, CH=CH_2, C*H*OH), 5.60–6.11 (m, 1 H, C*H*=CH_2).

(41) Stork, G.; Stotter, P. L. *J. Am. Chem. Soc.* **1969**, *91*, 7780–81.
(42) (a) Huang-Minlon *J. Am. Chem. Soc.* **1946**, *68*, 2487–88. (b) Huang-Minlon *Ibid.* **1949**, *71*, 3301–3.
(43) Rieke, R. D.; Bales, S. E.; Hudnall, P. M.; Poindexter, G. S. *Org. Synth.* **1980**, *59*, 85–94.

Anal. Calcd for $C_{15}H_{23}BrO$: C, 60.19; H, 7.76; Br, 26.70. Found: C, 60.24; H, 7.76; Br, 26.70.

Bromo alcohol **12b** eluted second, and was obtained as a colorless oil: yield, 1.07 g (40%); IR (film) ν_{max} 3300 (OH), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (s, 3 H, CH_3), 1.10–2.71 (m, 16 H), 4.68–5.20 (m, 3 H, CH=CH_2, C*H*OH), 5.61–6.09 (m, 1 H, C*H*=CH_2).

Anal. Calcd for $C_{15}H_{23}BrO$: C, 60.19; H, 7.76; Br, 26.70. Found: C, 60.23; H, 7.75; Br, 26.74.

(1*R,3aβ,7aα)-1-(6-Bromo-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-inden-5-yl)-4,5-hexadien-1-ol (13a) and (1*S**,3aβ,7aα)-1-(6-bromo-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-inden-5-yl)-4,5-hexadien-1-ol (13b)** were prepared from 1.00 g (4.12 mmol) of bromo aldehyde **11** and 1.73 g (11.77 mmol) of 5-bromo-1,2-pentadiene[12b] and separated by medium-pressure liquid chromatography as described previously for the preparation of bromo alcohols **12a** and **12b**. Bromo alcohol **13a** eluted first from the column and was obtained as a pale yellow oil: yield, 450 mg (35%); IR (film) ν_{max} 3350 (OH), 1955 (C=C=C), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H, CH_3), 1.02–2.86 (m, 16 H), 4.58–5.00 (m, 3 H, CH=C=CH_2, C*H*OH), 5.06 (quintet, J = 7 Hz, 1 H, C*H*=C=CH_2).

Anal. Calcd for $C_{16}H_{23}BrO$: C, 61.72; H, 7.46; Br, 25.67. Found: C, 61.99; H, 7.70; Br, 25.92.

Bromo alcohol **13b** eluted second, and was obtained as a pale yellow oil: yield, 360 mg (28%); IR (film) ν_{max} 3300 (OH), 1955 (C=C=C), 1640 (C=C) cm^{-1}; ^1H NMR δ 0.70 (s, 3 H, CH_3), 1.04–1.96 (m, 10 H), 1.96–2.73 (m, 6 H, three allylic CH_2), 4.56–4.91 (m, 3 H, CH=C=CH_2, C*H*OH), 5.06 (quintet, J = 7 Hz, 1 H, C*H*=C=CH_2).

Anal. Calcd for $C_{16}H_{23}BrO$: C, 61.72; H, 7.46; Br, 25.67. Found: C, 61.88; H, 7.35; Br, 25.94.

(1*R,3aβ,7aα)-1-(6-Bromo-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-inden-5-yl)-4-hexen-1-ol (14a), (1*S**,3aβ,7aα)-1-(6-Bromo-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-inden-5-yl)-4-hexen-1-ol (14b), and (3aβ,7aα)-6-Bromo-2,3,3a,4,7,7a-hexahydro-3a-methyl-1*H*-indene-5-methanol.** A 2-mL portion of 2.30 g (15.43 mmol) of 5-bromo-2-pentene[12b] in 10 mL of tetrahydrofuran was added to 500 mg (20.58 mmol) of magnesium turnings in 20 mL of tetrahydrofuran. When the mixture became warm, the remainder of the 5-bromo-2-pentene was added over 10 min. The mixture was stirred for 3 h at room temperature to complete the formation of the Grignard reagent, and then cooled to −100 °C. A solution of 2.50 g (10.29 mmol) of bromo aldehyde **11** in 5 mL of tetrahydrofuran was added via syringe, and the syringe was washed with three 5-mL portions of tetrahydrofuran. The reaction mixture was warmed to room temperature after which an excess of saturated ammonium chloride was added, and the aqueous mixture was extracted with several portions of ether. The combined ethereal extracts were washed with saturated sodium chloride and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography on 200 g of silica gel, using 12% ether in hexane, as eluant afforded the following fractions in order of elution: 1.13 g (35%) of bromo alcohol **14a**, 370 mg (11%) of a 1:1 mixture of **14a** and **14b**, 1.01 g (31%) of bromo alcohol **14b**, and 340 mg (11%) of the reduction product. Bromo alcohol **14a** was obtained as a colorless oil: IR (film) ν_{max} 3300 (OH), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (s, 3 H, CH_3), 0.89–2.82 (m, 18 H), 4.76 (t, J = 7 Hz, C*H*OH), 5.21–5.55 (m, 2 H, HC=CH).

Anal. Calcd for $C_{16}H_{25}BrO$: C, 61.33; H, 8.06; Br, 25.50. Found: C, 61.20; H, 8.26; Br, 25.40.

Bromo alcohol **14b** was obtained as a colorless oil which solidified on standing. Recrystallization from pentane afforded an analytical sample, mp 68–70 °C: IR (film) ν_{max} 3300 (OH), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (s, 3 H, CH_3), 0.93–1.89 (m, 12 H), 1.89–2.78 (m, 6 H, three allylic CH_2), 4.75 (t, J = 6 Hz, 1 H, C*H*OH), 5.20–5.57 (2 H, HC=CH).

Anal. Calcd for $C_{16}H_{25}BrO$: C, 61.33; H, 8.06; Br, 25.50. Found: C, 61.37; H, 8.08; Br, 25.68.

The bromoindenemethanol reduction product was obtained as a viscous colorless oil: ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H, CH_3), 1.05–1.94 (m, 7 H), 1.94–2.82 (m, 5 H, two allylic CH_2, CH_2OH), 4.20 (s, 2 H, CH_2OH).

(3β,7aα,4aβ)-3-(4-Penten-1-yl)-3,4,4a,5,6,7,7a,8-octahydro-4a-methyl-1-oxo-1*H*-indeno[5,6-*c*]furan (15a). A solution of 0.600 g (2.01 mmol) of bromo alcohol **12a** in 30 mL of tetrahydrofuran was cooled at −95 °C and stirred as 4.32 mL (7.04 mmol) of 1.63 M *tert*-butyllithium in pentane was added over 10 min. After 20 min, the solution was warmed to −45 °C over 10 min, stirred for 65 min, and then transferred via cannula to a solution of excess anhydrous carbon dioxide in 15 mL of tetrahydrofuran at −78 °C. The solution was warmed to room temperature and poured into ice-cold 10% hydrochloric acid. The aqueous layer was extracted with several portions of ether, and the combined extracts were washed with saturated sodium bicarbonate and saturated sodium chloride and were dried ($MgSO_4$). Evaporation of the solvent and purification of the product by flash chromatography on 30 g of silica gel, using 10% ether in hexane as eluant, afforded 370 mg (75%) of lactone **15a** as a colorless oil, which solidified on standing. Recrystallization from pentane provided an analytical sample: mp 48–52 °C; IR ($CHCl_3$) ν_{max} 1735 (C=O), 1665 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74 (s, 3 H, CH_3), 1.11–2.60 (m, 15 H), 4.70–5.21 (m, 3 H, CH=CH_2, C*H*OR), 5.57–6.05 (m, 1 H, C*H*=CH_2).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.00; H, 9.02. Found: C, 77.72; H, 8.91.

(3α,7aα,4aβ)-3-(4-Penten-1-yl)-3,4,4a,5,6,7,7a,8-octahydro-4a-methyl-1-oxo-1*H*-indeno[5,6-*c*]furan (15b) was prepared from 0.880 g (2.94 mmol) of bromo alcohol **12b** as previously described for lactone **15a**. Purification of the product by chromatography on 80 g of silica gel with 1:8 ether–hexane as eluant afforded 390 mg (57%) of lactone **15a** as a colorless oil which solidified on standing: mp 36–39 °C; IR (film) ν_{max} 1755 (C=O), 1660 (C=C), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (s, 3 H, CH_3), 1.03–2.02 (m, 9 H, ring CH), 2.02–2.61 (m, 6 H, three allylic CH_2), 4.59–4.82 (m, 1 H, CHOR), 4.85–5.15 (m, 2 H, CH=CH_2), 5.54–5.97 (m, 1 H, C*H*=CH_2).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.00; H, 9.02. Found: C, 77.63; H, 9.24.

(3β,4aβ,7aα)-3-(4-Hexen-1-yl)-3,4,4a,5,6,7,7a,8-octahydro-4a-methyl-1-oxo-1*H*-indeno[5,6-*c*]furan (16a). A solution of 2.71 g (8.67 mmol) of bromo alcohol **14a** in 70 mL of THF was stirred and cooled at −78 °C as 3.79 mL (11.75 mmol) of 3.1 M methylmagnesium bromide in ether was added over 2 min. After 5 min, the −78 °C bath was replaced by an ice bath, and the reaction was stirred at 0 °C for 15 min. The solution was cooled again to −78 °C, and 48 mL (73.5 mmol) of 1.55 M *tert*-butyllithium in pentane was added over 10 min. The yellow solution was stirred at −78 °C for 5 min, allowed to warm to −20 to −30 °C over 15 min, and kept in this temperature range for 45 min, before being cooled back to −78 °C. The reaction mixture was transferred via cannula to a flask containing a large excess of anhydrous carbon dioxide in 100 mL of THF cooled at −78 °C. The reaction mixture was added to 100 mL of 10% hydrochloric acid, and the resulting mixture was saturated with sodium chloride. The layers were separated, and the aqueous layer was extracted three times with ether. The combined organic layers were washed with saturated sodium bicarbonate and saturated sodium chloride and were dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography on 70 g of silica gel, using 5% ethyl acetate in hexane as eluant, furnished 2.02 g (90%) of **16a** as a white solid. Recrystallization from ether–hexane provided an analytical sample: mp 63–75 °C: IR (film) ν_{max} 1745 (C=O), 1665 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (s, 3 H, CH_3), 1.05–2.63 (m, 15 H), 1.64 (d, J = 4 Hz, 3 H, CHCH_3), 4.63–4.91 (m, 1 H, CHOR), 5.19–5.57 (m, 2 H, HC=CH).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.40; H, 9.30. Found: C, 78.20; H, 9.28.

(3α,4aβ,7aα)-3-(4-Hexen-1-yl)-3,4,4a,5,6,7,7a,8-octahydro-4a-methyl-1-oxo-1*H*-indeno[5,6-*c*]furan (16b) was prepared from bromo alcohol **14b** as described in the previous procedure. The yield, after flash chromatography, was 1.71 g (90%) of lactone **16b** obtained as a white solid. Recrystallization of a portion from hexane afforded an analytical sample: mp 34–43 °C; IR (film) ν_{max} 1765 (C=O), 1680 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (s, 3 H, CH_3), 1.10–2.72 (m, 15 H), 1.65 (d, J = 5 Hz, 3 H, CHCH_3), 4.61–4.83 (m, 1 H, CHOR), 5.33–5.72 (m, 2 H, HC=CH).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.40; H, 9.30. Found: C, 78.14; H, 9.31.

(2α,5β,7α,9α,13β)-2-Hydroxy-13-methyltetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecane-7-carboxylic Acid Lactone (17a).

A solution of 150 mg (0.61 mmol) of lactone **15a** in 25 mL of *p*-xylene was irradiated for 45 min with a 400-W Hanovia lamp in a water-cooled quartz reactor.[12] Evaporation of the solvent and purification of the residue by flash chromatography on 30 g of silica gel, using 30% ethyl acetate in hexane as eluant, afforded 132 mg (88%) of **17a** as a light yellow solid. Recrystallization from pentane provided an analytical sample: mp 73–73.5 °C; IR ($CHCl_3$) ν_{max} 1755 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3 H, CH_3), 0.99–2.85 (m, 18 H), 4.38–4.57 (m, 1 H, CHOR).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.00; H, 9.02. Found: C, 77.85; H, 8.87.

(2β,5α,7β,9α,13β)-2-Hydroxy-13-methyltetracyclo-[7.5.0.0^{1,5}.0^{9,13}]tetradecane-7-carboxylic Acid Lactone (17b). A solution of 100 mg (0.41 mmol) of lactone **15b** in 20 mL of acetone was irradiated for 15 min, as described before, for the photolysis of lactone **15a**. Purification by flash chromatography on a 10-mm column with 1:4 ethyl acetate–hexane as eluant afforded 66 mg (66%) of **17b** as a fine white solid. Recrystallization from pentane provided an analytical sample: mp 112–118 °C; IR ($CHCl_3$) ν_{max} 1745 (C=O); ^1H NMR ($CDCl_3$) δ 0.64 (s, 3 H, CH_3), 0.89–2.59 (m, 18 H), 4.47 (d, J = 3 Hz, 1 H, CHOR).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.00; H, 9.02. Found: C, 78.00; H, 9.02.

(5β,7α,9α,13β)-13-Methyl-2-oxotetracyclo[7.5.0.0^{1,5}.0^{9,13}]-tetradecane-7-carboxylic Acid (18). A suspension of 89 mg (0.36 mmol) of lactone **17a** in 10 mL of 2 M aqueous sodium hydroxide was heated at 90 °C for 3 h. The solution was cooled to room temperature and stirred as 10 mL (0.414 mmol) of a 0.419 M aqueous sodium ruthenate solution was added.[12,24] After the mixture was stirred for 1.5 h at room temperature, 2 mL of methanol was added to reduce excess ruthenate. The precipitate was collected and washed with water. The filtrate was extracted with two 20-mL portions of ether and acidified with concentrated hydrochloric acid. The mixture was saturated with sodium chloride and extracted with several portions of ether. The combined organic layers were washed with saturated sodium chloride and dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the solid residue (90 mg) from ethyl acetate–hexane afforded 64 mg (68%) of keto acid **18** as a fine white solid: mp 208–211 °C; IR ($CHCl_3$) ν_{max} 2300–3500 (COOH), 1735 (C=O), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3 H, CH_3), 1.00–2.82 (m, 17 H), 2.82–3.20 (m, 1 H).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.24; H, 8.47. Found: C, 73.22; H, 8.26.

(3aβ,6aα,9aβ)-Tetradecahydro-9a-methyl-1-oxodicyclo-penta[*a*,*d*]cyclooctene-5-carboxylic Acid (19). A solution of 6 mg (0.86 mmol) of lithium in 10 mL of anhydrous ammonia was stirred at reflux as a solution of 45 mg (0.17 mmol) of keto acid **18** in 0.5 mL of tetrahydrofuran was added in one portion via syringe. The syringe was washed with three 0.5-mL portions of tetrahydrofuran. After 10 min, excess lithium was destroyed with 0.3 mL of 3-hexyne. A 1-mL portion of 1:1 acetic acid–tetrahydrofuran solution was added, and the ammonia was evaporated under a stream of nitrogen. A suspension of the residue in 10% hydrochloric acid was extracted with several portions of ether. The combined organic extracts were washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated. An ether solution of the residue was esterified with diazomethane at 0 °C. Evaporation of the solvent and purification of the residue by flash chromatography on 8 g of silica gel, using 40% ethyl acetate in hexane as eluant, provided 46 mg (96%) of **19** as a pale yellow oil: IR (film) ν_{max} 2900 (CH), 1720 (C=O) cm^{-1}; 220 MHz ^1H NMR ($CDCl_3$) δ 0.79 (s, 2 H, CH_3), 0.82 (s, 0.4 H, CH_3), 0.87 (s, 0.3 H, CH_3), 0.89 (s, 0.4 H, CH_3), 2.61 (m, 0.5 H), 2.79 (6 line m, ~1 H), 3.68 (s, ~1 H, OCH_3), 3.69 (s, ~2 H, OCH_3). GC analysis (column A, temperature program: 180 °C 2 min, 2 °C/min to 210 °C) revealed three peaks in the ratio 4:2:1. GC–MS analysis of each peak (70 eV) m/e 278 (M^+). High-resolution mass spectrum calcd for $C_{17}H_{26}O_3$: m/e 278.1875. Found: m/e 278.1882.

A solution of sodium methoxide in methanol was prepared from 10 mg (0.43 mmol) of sodium metal and 2 mL of methanol, and 15 mg (0.054 mmol) of the mixture of keto esters in 1 mL of methanol was added. The solution was heated at reflux under a nitrogen atmosphere for 4 h. A GC analysis showed a single peak corresponding in retention time to one of the two minor components originally present. The cooled solution was diluted with saturated sodium chloride, the product was isolated by three extractions with ether, and the ethereal solution was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel with 20% ethyl acetate in hexane as eluant afforded 9 mg (60%) of a colorless oil: 220 MHz ^1H NMR: δ 0.87 (s, 3 H, CH_3), 2.60 (m, ~1 H), 3.68 (s, 3 H, OCH_3). The probable presence of small amounts of other isomers is indicated by the appearance of three small peaks at δ 0.79, 0.82, and 0.85 in the NMR spectrum.

(2α,5β,7α,9α,13β)-2-Hydroxy-6,13-dimethyltetracyclo-[7.5.0.0^{1,5}.0^{9,13}]tetradecane-7-carboxylic Acid Lactones (20a and 20b). A solution of 3.13 g (120.6 mmol) of lactone **16a** in 540 mL of degassed *p*-xylene was divided into two portions of ca. equal size, and each was stirred and irradiated for 145 min with a 400-W medium-pressure Hanovia lamp in a quartz immersion well apparatus. The progress of the photolyses were monitored by GC (column B, temperature program: 180 °C raised to 270 °C at 20 °C/min), and when less than 5% of the starting material remained, the irradiations were terminated.

The two solutions were combined, and the solvent was evaporated. Purification of the residue by flash chromatography on 70 g of silica gel, using 10% ethyl acetate in hexane as eluant, furnished 2.71 g (86%) of a 3:2 mixture of lactones **20a** and **20b**, as determined by 360 MHz ^1H NMR: mp 60–95 °C; IR ($CHCl_3$) ν_{max} 1740 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (s, 2 H, **20a**, CH_3), 0.93 (d, 1 H, J = 6 Hz, **20b**, $CHCH_3$), 0.95 (s, 1 H, **20b**, CH_3), 1.16 (d, 2 H, J = 7 Hz, **20a**, $CHCH_3$), 1.0–2.8 (m, ~20 H), 4.43 (d, 1 H, J = 5 Hz, **20b**, HCOC(O)), 4.52 (dd, 2 H, J = 4.3 and 3.6 Hz, **20a**, HCOC(O)).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.40; H, 9.30. Found: C, 78.12; H, 9.16.

A sample of **20b** was obtained from the incomplete sodium–ruthenate oxidation of a mixture of **20a** and **20b**.[25] Recrystallization of a portion from pentane afforded an analytical sample: mp 76–91 °C; IR ($CHCl_3$) ν_{max} 1745 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.93 (d, 3 H, J = 7 Hz, $CHCH_3$), 0.95 (s, 3 H, CH_3), 1.1–2.2 (m, ~15 H), 2.41 (dd, 1 H, J = 14 and 4 Hz), 2.6–2.8 (m, ~4 H), 4.43 (d, 1 H, J = 5 Hz, HCOC(O)). A minor impurity (<10%) is indicated by a multiplet at 4.45 ppm.

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.40; H, 9.30. Found: C, 78.38; H, 9.03.

(2β,5α,6α,7β,9α,13β)-2-Hydroxy-6,13-dimethyltetracyclo-[7.5.0.0^{1,5}.0^{9,13}]tetradecane-7-carboxylic Acid Lactone (21a) and (2β,5α,6β,7β,9α,13β)-2-Hydroxy-6,13-dimethyl-tetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecane-7-carboxylic Acid Lactone (21b). A solution of 2.71 g (10.4 mmol) of lactone **16b** in 250 mL of *p*-xylene was irradiated as described previously for the synthesis of lactones **20a** and **20b**. The reaction was 96% complete after 5 h and was 97% complete when the irradiation was terminated 2 h later. Evaporation of the solvent and recrystallization of the residue from hexane furnished 1.30 g (43%) of analytically pure lactone **21b**: mp 141–144 °C IR ($CHCl_3$) ν_{max} 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (s, 3 H, CH_3), 0.94 (d, J = 7 Hz, 3 H, $CHCH_3$), 1.07–2.88 (m, 16 H), 4.46 (d, J = 3 Hz, 1 H, CHOR).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.40; H, 9.30. Found: C, 78.24; H, 9.25.

Evaporation of the mother liquor and purification of the residue by flash chromatography on 70 g of silica gel, using 10% ethyl acetate in hexane as eluant, furnished, in order of elution, 0.21 g (7%) of lactone **21b**, 0.21 (7%) of a ~1:1 mixture of **21b** and **21a**, and 0.18 g (6%) of a ~10:90 mixture of **21b** and **21a**. Recrystallization of this last mixture from hexane–ether provided an analytical sample of **21a**: mp 108–109 °C; IR ($CHCl_3$) ν_{max} 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (s, 3 H, CH_3), 1.29 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.07–2.33 (m, 17 H), 4.49 (d, 1 H, J = 2.5 Hz, HCOC(O)).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.29; H, 9.17.

The ratio of **21b**:**21a** in the original mixture was 9:1 based on the isolated amounts of each isomer.

(2β,5α,6β,7β,9α,13β)-7-(Hydroxymethyl)-6,13-dimethyl-tetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecan-2-ol (22). A suspension of 0.416 g (10.7 mmol) of lithium aluminum hydride in 20 mL of THF was stirred at 25 °C as a solution of 0.901 g (3.46 mmol) of lactone **21b** was added over 5 min. The reaction was heated at 80 °C for 1.5 h. After cooling to 0 °C, the excess hydride reagent

was decomposed by the sequential addition of 0.4 mL of water, 0.4 mL of 5% sodium hydroxide, and 1.5 mL of water.[44] The suspension was diluted with ether and filtered through celite, and the filtrate was washed twice with 10% hydrochloric acid and once with saturated sodium chloride and was dried ($MgSO_4$). Evaporation of the solvent and trituration of the residue with hexane furnished 0.755 g (83%) of diol **22** as white crystals, mp 138–140 °C. Recrystallization of a portion from hexane furnished an analytical sample: mp 148–149 °C; IR ($CHCl_3$) ν_{max} 3340 (OH), 2830, 1450, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (s, 3 H, CH_3), 0.77 (d overlapping s, 3 H, J = 7.8 Hz, $CHCH_3$), 1.01–2.22 (m, 16 H), 2.45 (dq, 1 H, J = 7.8 and 8.4 Hz, $CHCH_3$), 3.05 and 4.25 (AB d, 2 H, J = 12 Hz, CH_2OH), 3.67–4.00 (m, 1 H, CHOH), 3.82–4.03 (m, 2 H, OH?).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.85; H, 10.62.

(5α,6β,7β,9α,13β)-7-(Hydroxymethyl)-6,13-dimethyltetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecan-2-one (23) (Hemiketal). A solution of 0.729 g (2.76 mmol) of diol **22** and 1.9 mL of glacial acetic acid in 11 mL of dioxane was stirred at ~15 °C as a solution of 4.08 mL (3.04 mmol) of 0.75 M sodium hypochlorite in water (Clorox bleach) was added over 4 min.[27] After 50 min at 25 °C, 50 mL of ether and 10 mL of water were added. The layers were separated, and the aqueous layer was extracted once with ether. The combined organic layers were washed with saturated sodium bicarbonate, 5% sodium hydroxide, and twice with saturated sodium chloride, and were dried ($MgSO_4$). Evaporation of the solvent and trituration of the solid residue with hexane furnished 0.657 g (90%) of hemiketal **23**. Evaporation of the mother liquor and purification of the residue by flash chromatography on 6 g of silica gel, using 20% ethyl acetate in hexane as eluant, afforded an additional 31 mg (4%) of **23**. Recrystallization of a portion from hexane–ether afforded an analytical sample: mp 169–170.5 °C; IR ($CHCl_3$) ν_{max} 3300 (OH), 2903, 2821, 1449, 1105 (no C=O stretch) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (s, 3 H, CH_3), 0.84 (d, 3 H, J = 6 Hz, $CHCH_3$), 0.96–2.0 (m, 14 H), 2.0–2.6 (m, 4 H), 3.61 and 3.93 (AB d, 2 H, J = 10 Hz, CH_2O).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 78.14; H, 9.68.

(5α,6β,7β,9α,13β)-6,13-Dimethyl-2-oxotetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecane-7-carboxylic Acid (24) (Lactol). A solution of 0.668 g (2.55 mmol) of hemiketal **23** in 37 mL of acetone was stirred at 20 °C as 3 mL (~6 mmol) of Jones' Reagent (prepared from 10.3 g (0.1 mole) of chromium trioxide, 30 mL of water, and 8.7 mL of concentrated sulfuric acid)[28] was added in one portion. After 90 min, the excess oxidizing agent was decomposed with excess isopropyl alcohol. The mixture was extracted with 120 mL of ether, and the ethereal extract was washed three times with saturated sodium chloride and dried ($MgSO_4$). GC analysis (column A, temperature program: 160 °C raised to 300 °C at 20°/min) of an aliquot treated with excess diazomethane indicated the crude product was a 94:6 ratio of keto acid **24** and starting material. The crude product (0.691 g) was dissolved in 20 mL of 5% sodium hydroxide, and the basic solution was extracted with ether. Acidification of the aqueous layer with concentrated hydrochloric acid and extraction of the resulting suspension with ether provided a solution which contained only **24**, by GC analysis of an aliquot. This solution was washed with saturated sodium chloride and dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the residue (0.614 g) from hexane–dichloromethane provided 0.526 g (75%) of lactol **24** as white crystals: mp 212–212.5 °C; IR ($CHCl_3$) ν_{max} 2907, 1750 (C=O), 1205 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.64 (s, 3 H, CH_3), 0.96 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.2–2.2 (m, 15 H), 2.37 (d, 1 H, J = 14 Hz), 2.48 (q, 1 H, J = 8.5 Hz), 2.70 (dq, 1 H, J = 7 and 10 Hz, $CHCH_3$), 3.08 (s, 1 H, OH).

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.96; H, 8.76.

The recovered starting material was oxidized in the same manner and provided an additional 36 mg (5%) of product (mp 212–212.5 °C). Recrystallization of the combined mother liquors provided an additional 48 mg (7%) of lactol **24** (mp 200–212 °C), which was suitable for use in the reductive cleavage step.

(3aα,4β,6aα,9aβ)-Tetradecahydro-4,9a-dimethyl-1-oxodicyclopenta[a,d]cyclooctene-5-carboxylic Acids (25a–d). A solution of 1.8 mg (0.26 mmol) of lithium in 4 mL of ammonia was stirred at reflux as a solution of 24.2 mg (0.088 mmol) of lactol **24** in 0.4 mL of THF was added in one portion via syringe. The syringe was rinsed with two 0.25-mL portions of THF. The color of the reaction mixture was light blue, indicating that only a slight excess of lithium remained. Decomposition of the excess lithium metal was effected by the addition of 1 μL of isoprene, and the enolates were quenched by the addition of a solution of 50 mg (~1 mmol) of glacial acetic acid in 0.25 mL of THF. The solvents were evaporated under a stream of nitrogen, and the remaining solids were dissolved in 1 mL of 10% hydrochloric acid and 2 mL of ether. The acidic aqueous layer was extracted with several portions of ether and dichloromethane. The organic extracts were combined and washed with saturated sodium chloride and were dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography on 3 g of silica gel, using 20% ethyl acetate in hexane as eluant, afforded 21.5 mg (88%) of keto acids **25**, mp 130–180 °C. The 0.7 to 1.1 ppm region of the 360 MHz ^1H NMR spectrum indicated the product was a 45:15:40 mixture of diastereomers. The spectral properties of the mixture in this region are as follows: ^1H NMR (360 MHz, $CDCl_3$) δ 0.82 (s, 1.35 H, **25a**, CH_3), 0.83 (s, 1.23 H, **25c**, CH_3), 0.89 (s, 0.42 H, **25b**, CH_3), 0.91 (d, 0.42 H, **25b**, $CHCH_3$), 0.94 (d, 1.23 H, J = 7 Hz, **25c**, $CHCH_3$), 1.00 (d, 1.35 H, J = 7 Hz, **25a**, $CHCH_3$).

A solution of 8.2 mg (0.029 mmol) of the mixture of keto acids **25a–c** in 0.25 mL (0.04 mmol) of 0.12 M solution of sodium methoxide in methanol was stirred at 0 °C for 10 min, 25 °C for 8 h, and 1 h at 50 °C. The progress of the equilibration was followed by ^1H NMR, and the equilibration was terminated when no change in the ^1H NMR spectrum was observed. The methyl peaks in the 0.7 to 1.1 ppm region of the 360 MHz ^1H NMR spectrum ($CDCl_3$) of the equilibrated diastereomeric mixture are as follows: δ 0.83 (s, 2.55 H, **25c**, CH_3), 0.84 (s, 0.45 H, **25d**, CH_3), 0.94 (d, 2.55 H, J = 7 Hz, **25c**, $CHCH_3$), 0.98 (d, 0.45 H, J = 7 Hz, **25d**, $CHCH_3$).

Recrystallization of 53 mg of a crude 85:15 mixture of keto acids **25c** and **25d** from pentane–ether furnished 18 mg of **25c** as white crystals: mp 180–181 °C; IR ($CHCl_3$) ν_{max} 3600–2450 (b, OH), 2900, 1727 (C=O), 1702 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.83 (s, 3 H, CH_3), 0.94 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.4–1.75 (m, 12 H), 1.8–2.5 (m, 9 H), 2.55 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{17}H_{16}O_3$: C, 73.35; H, 9.41. Found: C, 73.02; H, 9.14.

The mother liquor from the recrystallization was extracted with saturated sodium bicarbonate. The aqueous layer was acidified to pH 2 with concentrated hydrochloric acid and was extracted twice with dichloromethane. Evaporation of the dried ($MgSO_4$) extracts furnished 9 mg of a 70:30 mixture of keto acids **25c** and **25d**. This material was suitable for use in the iodo decarboxylation procedure described below.

The amount of lithium used in the reduction of lactol **24** was varied from the minimum amount reported for this experiment to a maximum of 30 equiv. The highest ratio of cis to trans fusion was obtained in those experiments in which a minimum of lithium was used. In addition, a variety of quenching procedures were tried, e.g., inverse addition of the ammonia solution to a solution of proton source in THF or liquid ammonia. In retrospect, the quench procedure had little effect on the cis:trans ratio of the product.

(3aα,4β,5α,6aα,9aβ,10aα)-Dodecahydro-5-iodo-4,9a-dimethyldicyclopenta[a,d]cycloocten-1(2*H*)-one (26a), (3aα,4β,5β,6aα,9aβ,10aβ)-Dodecahydro-5-iodo-4,9a-dimethyldicyclopenta[a,d]cycloocten-1(2*H*)-one (26b), and (3aα,4β,5α,6aα,9aβ,10aβ)-Dodecahydro-5-iodo-4,9a-dimethyldicyclopenta[a,d]cycloocten-1(2*H*)-one (26c). A solution of 8.2 mg (0.029 mmol) of a 45:15:40 diastereomeric mixture of keto acids **25a**, **25b**, and **25c** and 20.7 mg (0.047 mmol) of lead tetraacetate in 1.5 mL of carbon tetrachloride was stirred and heated at reflux, while simultaneously irradiating with a 400-W tungsten lamp. A saturated solution of iodine in carbon tetrachloride was added at a rate such that the red-pink color persisted.[29] Aliquots were withdrawn and added to a saturated solution of sodium thiosulfate. The mixture was extracted three

(44) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* **1967**, *1*, 581–95.

times with ether, and the combined ethereal extracts were treated with excess diazomethane. The progress of the iodination was followed by GC (column A, 210 °C) analysis of these processed aliquots. The reaction was presumed complete when the keto acids were consumed. After 25 min, the irradiation and heating were terminated, and the cooled suspension was diluted with dichloromethane. The reaction mixture was washed with saturated sodium thiosulfate, saturated sodium bicarbonate, and saturated sodium chloride and was dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography on 1 g of silica gel, using 5% ether in pentane as eluant, afforded 6 mg (53%) of a 50:20:30 mixture of iodo ketones **26a**, **26b**, and **26c**. The ratio was determined by integrating the multiplets of the CHI protons in the 360-MHz ^1H NMR spectrum.

Separation of the diastereomeric iodides was effected by HPLC (1% THF in isooctane, 2.4 mL/min flow rate). A preliminary experiment furnished 16 mg of a 4:4:3 mixture of **26a**, **26b**, and **26c**. This mixture was dissolved in 150 μL of 1% THF in isooctane and injected onto the HPLC column in 5 30-μL portions (3.2 mg of iodides/injection). The total yield of each iodo ketone, in order of elution, was 4.6 mg of **26c**, 4.3 mg of **26b**, and 3.4 mg of **26a**. Each iodo ketone was obtained as a white solid and recrystallized from pentane. The mp and spectral properties are given for each iodide. Iodide **26a**: mp 114–116 °C; IR ($CHCl_3$) ν_{max} 2960, 1732 (C=O), 1448, 1382 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (s, 3 H, CH_3), 1.05 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.2–1.4 (m, ~3 H), 1.4–1.7 (m, ~5 H), 2.1–2.4 (m, ~8 H), 2.68 (bs, 1 H, $W_{1/2h}$ = 33 Hz), 3.41 (bs, 1 H, $W_{1/2h}$ = 25 Hz), 4.64 (ddd, 1 H, J = 12.6, 9.4, and 3.6 Hz, CHI). Iodide **26b**: mp 108–110 °C; IR ($CHCl_3$) ν_{max} 2960, 1734 (C=O) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) δ 0.83 (s, 3 H, CH_3), 1.22 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.28–1.69 (m, 7 H), 1.78–2.60 (m, ~11 H), 4.75 (dt, 1 H, J = 10.2, 2.89, and 2.89 Hz, CHI); mass spectrum (10 eV) m/e (rel intensity) 233 (77, M – I), 215 (100), 159 (29), 133 (32), 121 (38), 109 (34), 107 (34), 95 (67), 81 (60). Iodide **26c**: mp 75–77 °C; IR ($CHCl_3$) ν_{max} 2961, 1733 (C=O) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) 0.88 (s, 3 H, CH_3), 1.03 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.30–2.0 (m, ~13 H), 2.15–2.40 (m, ~4 H), 2.55 (q, 1 H, J = 9 Hz, CHC(O)?), 4.89 (ddd, 1 H, J = 5.4, 4.3, and 2.5 Hz, CHI); mass spectrum (10 eV) m/e (rel intensity) 233 (54, M – I), 215 (63), 187 (11), 173 (9), 107 (45), 95 (91), 81 (100), 77 (25), 55 (97), 41 (77).

Iodecarboxylation of 23 mg (0.083 mmol) of keto acid **25c** (>95% pure, mp 181–183 °C), using the procedure described above, furnished 21 mg (70%) of iodo ketones **26b** and **26c** after flash chromatography. The ratio of **26b** to **26c** was 2:3 as determined by ^1H NMR. Iododecarboxylation of 9 mg (0.032 mmol) of a 70:30 mixture of keto acids **25c** and **25d** afforded 9.3 mg (80%) of a 2:3 mixture of iodo ketones **26b** and **26c**, as determined by ^1H NMR.

Single-Crystal X-ray Analysis of Iodo Ketone 26c. Crystals suitable for X-ray diffraction were grown from pentane. The crystal used for data collection was a colorless, transparent prism measuring 0.48 × 0.50 × 1.10 mm. Lattice constants and intensity data were measured at 298 K and λ = 0.71069 Å (MoK_α) on a Syntex $P2_1$ automated four-circle diffractometer equipped with a graphite crystal monochromator. Data were collected from 3.0 < 2θ <55.0°. A total of 4268 reflections was collected (one form, ±h, +k, +l) yielding 3,706 unique intensities and 2,942 reflections with $I > 2.58\sigma(I)$. This set of reflections was used in the structure solution and refinement. Data included corrections for background, extinction, Lorentz and polarization effects, and anomalous dispersion effects. The data were also numerically corrected for absorption; minimum and maximum transmission factors were 0.381 and 0.451, respectively. Systematic absences for $0k0$, k = $2n + 1$, and $h0l$, l = $2n + 1$ unambiguously indicated the space group to be $P2_1/c$ (C_{2h}^5). The cell data are as follows: monoclinic; a = 8.659(3) Å, b = 29.75(1) Å, c = 6.551(3) Å, β = 107.37(3)°, V = 1611(1) Å^3, Pc = 1.485 g cm^{-3}; Z = 4.

Coordinates for the iodine atom were deduced from a Patterson map. A weighted-difference Fourier then revealed correct positions for all but two of the non-hydrogen atoms. Subsequent least-squares-difference Fourier calculations gave positions for the rest of the atoms in the asymmetric unit including the hydrogens. In the final cycle of least squares, all non-hydrogen atomic positions were varied with anisotropic thermal coefficients, and all hydrogen positions were varied with isotropic coefficients. Refinement converged at R = 0.029 (R_w = 0.034). The final difference Fourier map was featureless. An ORTEP drawing[45] of one molecule in the crystal is presented in Figure 1. Calculations were performed on a DEC VAX 11/780 computer system.

(3aα,4β,6aα,9aβ,10aβ)-Dodecahydro-4,9a-dimethyldicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (28). Method A. Reduction of Iodo Ketone 26c. A solution of 4.6 mg (0.013 mmol) of iodo ketone **26c** and 35 μL (0.13 mmol) of tri-*n*-butyltin hydride in 150 μL of THF was stirred at 25 °C under an atmosphere of argon.[30] After 17 h the reduction was complete, as shown by TLC (10% ethyl acetate in hexane). Evaporation of the solvent and purification of the residue by flash chromatography on 0.5 g of silica gel, using pentane as eluant, afforded 2.1 mg (70%) of ketone **28** as a white solid. Recrystallization from pentane afforded an analytical sample: mp 35.5–36.5 °C; IR ($CHCl_3$) ν_{max} 2960, 1730 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.80 (s, 3 H, CH_3), 0.93 (d, 3 H, J = 7 Hz), 1.2–1.6 (m, ~10 H), 1.75–1.95 (m, ~6 H), 2.0–2.15 (m, ~2 H), 2.23–2.38 (6-line m, ~2 H, CHC(O)); GC mass spectrum m/e (rel intensity) 234 (M^+, 26), 177 (6), 163 (8), 149 (10), 137 (20), 123 (40), 109 (26), 95 (50), 83 (75), 55 (90), 41 (100). High-resolution mass spectrum calcd for $C_{16}H_{26}O$: m/e 234.1983. Found: m/e 234.1979.

Method B. Reduction of Iodo Ketone 26b. The preparation of ketone **28** from 3 mg (0.008 mmol) of iodo ketone **26b** was carried out as described in Method A. The yield of **28**, after flash chromatography, was 1.4 mg (70%) of white solid. GC (column A, 90 °C to 220 °C at 10 °C/min), TLC (10% ethyl acetate in hexane) and HPLC (1% THF in isooctane, 2.3 mL/min) comparisons of the product obtained in this reduction with the sample obtained from the reduction of **26c** indicated that they were identical. In addition, the 360-MHz ^1H NMR and GC–mass spectra of each sample were identical.

Method C. Equilibration of Ketone 27. A solution of ~0.5 mg (0.002 mmol) of ketone **27** (see below) in 20 μL of methanol was stirred at 25 °C in a 0.5-mL reacti-vial as 50 μL (0.045 mmol) of 0.9 M sodium methoxide in methanol was added. The progress of the equilibration was monitored by TLC and HPLC. After 2 h, the sodium methoxide was neutralized by the addition of the drop of 10% hydrochloric acid. TLC, HPLC, and ^1H NMR comparisons of this sample to the ketones obtained in Methods A and B established their identity.

(3aα,4β,6aα,9aβ,10aα)-Dodecahydro-4,9a-dimethyldicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (27) was prepared from 3.4 mg (0.009 mmol) of iodo ketone **26c** in the manner described above for the reduction of **26c** to **28**. The yield, after flash chromatography, was 1.2 mg (54%) of a white solid. Recrystallization from pentane afforded an analytical sample: mp 85–86.5 °C; IR ($CHCl_3$) ν_{max} 2950, 1738 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.80 (s, 3 H, CH_3), 0.88 (t, ~1 H, J = 7 Hz), 0.97 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.2–1.8 (m, ~12 H), 1.92–2.04 (m, ~3 H), 2.05–2.17 (5-line m, 1 H), 2.2–2.35 (m, ~4 H), GC–mass spectrum (10 eV) m/e (rel intensity) 234 (M^+, 92), 216 (14), 163 (21), 137 (47), 123 (78), 109 (60), 95 (89), 83 (100), 55 (82). High-resolution mass spectrum calcd for $C_{16}H_{26}O$: m/e 234.1984. Found: m/e 234.1971.

(3aα,6aα,9aβ,10aα)-3,3a,6,6a,7,8,9,9a,10,10a-Decahydro-4,9a-dimethyldicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (29). A solution of 15.4 mg (0.043 mmol) of iodo ketone **26b**, 150 mg (0.45 mmol) of tetra-*n*-butylammonium bromide, and 16 mg (0.154 mmol) of 2,6-dimethylpyridine in 1.5 mL of acetone was stirred and heated at reflux.[31] After 2.5 h the reaction mixture was cooled, and the majority of the acetone was evaporated under a stream of nitrogen. The residue was dissolved in 0.5 mL of 10% hydrochloric acid and 0.5 mL of ether. The aqueous layer was extracted twice with ether, and the combined ethereal extracts were washed with saturated sodium chloride and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography on 0.5 g of silica gel, using 5% ether in pentane as eluent, afforded 5.4 mg (56%) of enone **29** as a white solid. Recrystallization from pentane at –78 °C furnished an analytical sample: mp 38–41.5 °C; IR ($CHCl_3$) ν_{max} 2950, 1732 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.84 (s, 3 H, CH_3), 1.1–1.2 (4-line

(45) Johnson, C. K. "ORTEP-II: A Fortran Thermal Ellipsoid Plot Program", ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1971.

m, ~2 H), 1.29 (t, 1 H, J = 7 Hz), 1.4–1.6 (m, 3 H), 1.74 (s, 3 H, C=CCH_3), 1.75–2.45 (m, 8 H), 2.74 (td, 1 H, J = 10 and 5 Hz, C(O)CH?), 5.56 (t, 1 H, J = 7 Hz, C=CH); GC–mass spectrum m/e (rel intensity) 232 (M^+, 15), 217 (5), 175 (9), 150 (15), 123 (39), 108 (40), 95 (100), 81 (49), 55 (54), 41 (74). High-resolution mass spectrum calcd for $C_{16}H_{24}O$: m/e 232.1827. Found: m/e 232.1837.

A solution of ~2 mg (0.009 mmol) of enone **29** and 4 mg of 10% palladium on carbon in 0.3 mL of absolute ethanol was rapidly stirred under an atmosphere of hydrogen. After 45 min, the mixture was filtered, and the filtrate was evaporated, affording 2 mg of saturated ketones. The 360-MHz ^{1}H NMR spectrum indicated that the product was a 2:1 mixture of the previously prepared ketone **28** and its C-7 isomer **30**. The angular CH_3 and the secondary CH_3 of ketone **30** appear at δ 0.92 and δ 1.03 (J = 7 Hz), respectively. The HPLC (1% THF in isooctane; 1.6 mL/min) retention time of the major isomer (8.3 min) was the same as authentic ketone **28** prepared by the reduction of iodo ketones **26b** and **26c**. The HPLC retention time of the minor isomer was 8.8 min.

(3aα,4β,5α,6aα,9aβ,10aβ)-5-Bromododecahydro-4,9a-dimethyldicyclopenta[a,d]cycloocten-1(2*H*)-one (31) was obtained when 10.0 mg (0.028 mmol) of ketone **26c** was treated with tetra-*n*-butylammonium bromide as described in the preceding procedure. Evaporation of the solvent, after the usual workup, afforded 7 mg (80%) of the crude bromo ketone **31** as a white solid: IR ($CHCl_3$) ν_{max} 2900, 1730 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.84 (s, 3 H, CH_3), 1.16 (d, 3 H, J = 7 Hz, CHCH_3), 1.4–1.7 (m, ~9 H), 1.8–2.55 (m, ~9 H), 4.46 (ddd, 1 H, J = 8, 5.2, and 2.8 Hz, CHBr). A small amount (<10%) of unreacted iodo ketone was present as indicated by the ^{1}H NMR spectrum.

(2α,5β,7α,9α,13β)-7-(Hydroxymethyl)-6,13-dimethyltetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecan-2-ol (32a and 32b). A suspension of 1.17 g (30.8 mmol) of lithium aluminum hydride in 50 mL of THF was stirred at 0 °C as a solution of 2.00 g (7.69 mmol) of a 3:2 mixture of lactones **20a** and **20b** in 20 mL of THF was added in one portion. After heating the stirred suspension at 50 °C for 10 min, the mixture was cooled to 0 °C and the crude product was isolated in the same manner as described previously for the preparation of diol **22**. Purification of the crude product by flash chromatography on 120 g of silica gel, using 30% ethyl acetate in hexane, provided 1.74 g (85%) of diols **32** as a foam. No separation of the two diols was observed in the flash chromatography. Kugelrohr distillation (200 °C oven temperature, 0.5 mm) afforded an analytical sample: IR ($CHCl_3$) ν_{max} 3350 (OH), 2900 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) 0.84 (s, 1.8 H, **32a**, CH_3), 0.89 (d, 1.2 H, J = 7 Hz, **32b**, CHCH_3), 0.90 (s, overlapping d, 1.2 H, **32b**, CH_3), 0.95 (d, 1.8 H, J = 11 Hz, **32b**, CH_2OH), 1.10–2.5 (m, 17 H), 3.13 and 4.26 (AB d, 0.8 H, J = 11 Hz, **32b**, CH_2OH), 3.30 and 3.79 (AB d, 1.2 H, J = 11 Hz, **32a**, CH_2OH), 3.63 (bm overlapping dd, 2 H, OH), 3.70 (dd, 1 H, J = 7 and 5 Hz, C*H*OH).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.40; H, 10.37.

Reduction of a pure sample of **20b** (see the preparation of **20a** and **20b** for the source of this sample) in the above manner afforded 61 mg (85%) of diol **32b**. The GC retention time and the ^{1}H NMR spectra indicated that this compound was identical with the minor isomer in the mixture, namely **32b**.

(5β,6α,7α,9α,13β)-7-(Hydroxymethyl)-6,13-dimethyltetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecan-2-one (33b) and (5β,6β,7α,9α,13β)-7-(Hydroxymethyl)-6,13-dimethyltetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecan-2-one (33a). The oxidation of a 3:2 mixture of ketols **32a** and **32b** was carried out in the manner described above for the preparation of ketol **23**. The TLC (30% ethyl acetate in hexane) R_f values for ketols **33a** and **33b** were 0.36 and 0.40, respectively. Separation of the isomers by flash chromatography on 300 g of silica gel, using 10% ethyl acetate in hexane as eluant, provided 0.512 g (33%) of the less polar ketol (**33b**), 15 mg (1%) of mixed fractions, and 0.745 g (49%) of the more polar ketol (**33a**). Each of the pure samples were obtained a solid, and each was recrystallized from ether–chloroform. The physical and spectral properties follow. Ketol **33b**: mp 154–156 °C; IR ($CHCl_3$) ν_{max} 3300 (w, OH), 2900, 1050, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3 H, J = 6.7 Hz, CHCH_3), 0.95 (s, 3 H, CH_3), 1.2–1.4 (~4 H), 1.4–1.8 (m, ~10 H), 1.95 (5-line m, 1 H), 2.4–2.6 (m, 3 H), 3.53 and 3.77 (AB d, 2 H, J = 9 Hz, CH_2OH).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.71; H, 9.89.

Ketol **33a**: mp 141–144 °C; IR ($CHCl_3$) ν_{max} 3300 (w, OH), 2900, 1710 (w, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 and 0.89 (s, 3 H, CH_3), 1.02 and 1.08 (d, 3 H, J = 7 Hz, CHCH_3), 1.15–2.0 (m, 12 H), 2.06 (dd, 0.5 H, J = 8 and 5 Hz), 2.16 (dd, 0.5 H, J = 13 and 8 Hz), 2.32–2.45 (m, ~2 H), C(O)CH_2?), 2.53–2.65 (m, ~2 H), 3.35–3.45 (m, 1 H, CH_2OH), 3.56 and 3.70 (AB d, 1 H, J = 8 Hz, CH_2O).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.91; H, 10.06.

Oxidation of a pure sample of **32b**, obtained in the previous preparation of diol **32b**, furnished 35 mg (50%) of ketol **33b**. The identity of the compounds obtained here and the previous procedure was established by GC analysis and comparison of their ^{1}H NMR spectra.

(5β,6β,7α,9α,13β)-6,13-Dimethyl-2-oxotetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecane-7-carboxylic Acid (34a). A solution of 0.500 g (1.91 mmol) of ketol **33a** in 25 mL of acetone was stirred at 25 °C as 1.1 mL of the standard Jones' Reagent (see preparation of keto acid **24**) was added in one portion. After 20 min, the oxidation was complete, and the reaction was processed in the manner previously described for the isolation of **24**. Recrystallization of the crude product afforded 0.397 g (76%) of **34a** as white crystals: mp 253–255.5 °C; IR ($CHCl_3$) ν_{max} 3500–2600 (COOH), 2950, 1740 (C=O), 1705 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.88 (s, 3 H, CH_3), 1.10 (bs, 3 H, $W_{1/2h}$ = 17 Hz, CHCH_3), 1.4–2.0 (m, ~10 H), 2.2–2.4 (m, 1 H), 2.5–2.8 (m, 2 H).

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.05; H, 8.59.

(5β,6α,7α,9α,13β)-6,13-Dimethyl-2-oxotetracyclo[7.5.0.0^{1,5}.0^{9,13}]tetradecane-7-carboxylic Acid (34b). A solution of 0.400 g (1.53 mmol) of ketol **33b** in 20 mL of acetone was stirred at 25 °C as 2.8 mL (~5 mmol) of Jones' Reagent (see preparation of keto acid **24**) was added. After 3 h, the reaction was processed in the same manner as described for the preparation of keto acid **24**. The yield of recrystallized keto acid **34b** was 0.361 g (86%): mp 181.5–184.5 °C; IR ($CHCl_3$) ν_{max} 3300 (b, OH), 2900, 1745 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.94 (d, 3 H, J = 7 Hz, CHCH_3), 0.9 (s, 3 H, CH_3), 1.1–2.0 (m, ~12 H), 2.25–2.40 (m, 2 H), 2.72–2.84 (5-line m, ~2 H), 3.44 (bs, 1 H, OH); mass spectrum (10 eV) m/e (rel intensity) 276 (M^+, 1), 248 (M^+ – 18, 100), 233 (12), 161 (36), 95 (44). High-resolution mass spectrum calcd for $C_{17}H_{24}O_3$: m/e 276.1726. Found: m/e 276.1726.

(3aβ,4α,6aα,9aβ,10aα)-Tetradecahydro-4,9a-dimethyl-1-oxodicyclopenta[a,d]cyclooctene-5-carboxylic Acids (35a,b). A solution of 14 mg (2.0 mmol) of lithium in 10 mL of ammonia was stirred at reflux as a solution of 51.8 mg (0.188 mmol) of keto acid **34b** was added via syringe. The syringe was rinsed with 1 mL of THF. After 10 min, the slight excess of lithium was quenched with isoprene, and the reagent mixture was added, via cannula, to a vigorously stirred solution of 1.8 g (34 mmol) of ammonium chloride in 40 mL of ammonia at –33 °C. The product was isolated in the same manner described previously in the preparation of keto acids **25**. The yield, after flash chromatography, was 43.9 mg (84%) of keto acids **35** as a free flowing white solid, mp 140–165 °C. GC analysis (column B, 260 °C) of the methyl esters of **35** (esterification with diazomethane) showed only one peak, but the ^{1}H NMR spectrum revealed that the product was a 4:5 mixture of two diastereomers. The spectral data for the mixture of acids are as follow: IR ($CHCl_3$) ν_{max} 3500–2300 (b, OH), 2910, 1730 (C=O), 1705 (C=O), cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) 0.67 (s, 1.7 H, CH_3), 0.85 (s, 1.3 H, CH_3), 0.98 (d, 1.7 H, J = 6 Hz, CHCH_3), 1.09 (d, 1.3 H, J = 7 Hz, CHCH_3), 1.35–2.0 (m, ~14 H), 2.1–2.81 (m, ~5 H); mass spectrum m/e (rel intensity) 278 (M^+, 6), 260 (28), 232 (31), 204 (43), 137 (89), 163 (85), 95 (88), 81 (82), 67 (80), 55 (95), 41 (100). High-resolution mass spectrum calcd for $C_{17}H_{26}O_3$: m/e 278.1882. Found: m/e 278.1881.

A solution of 15 mg (0.054 mmol) of the mixture of keto acids **35** and 12 mg (0.22 mmol) of sodium methoxide in 0.66 mL of methanol was stirred and heated at 50 °C. After 80 min, the solution was acidified with 10% hydrochloric acid and extracted

with dichloromethane. The extracts were dried, and the solvent was evaporated, yielding 15 mg of the equilibrated keto acids **35**. The ^{1}H NMR spectrum of this material was essentially identical with that of the starting material described above.

(3aβ,4α,6aα,9aβ,10aα)-Dodecahydro-5-iodo-4,9a-dimethyldicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (36a–c). Iododecarboxylation of 89 mg (0.32 mmol) of keto acids **35** was carried out by using the method and conditions described previously for the preparation of iodo ketones **26a–c**. The reaction was complete within 20 min and, after the usual workup and purification by flash chromatography, 101 mg (88%) of a mixture of iodo ketones **36a–c** was obtained. Although only a single spot was observed by TLC (10% ethyl acetate in hexane), HPLC indicated the product was in fact a 2:1 mixture of diastereomers. The ^{1}H NMR confirmed the results of the HPLC analysis, but also indicated the presence of a small amount (8%) of a third isomer. The spectral properties of the mixture are as follows: IR ($CHCl_3$) ν_{max} 2850, 1730 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.67 (s, 0.9 H, CH_3), 0.83 (s, 2 H, CH_3), 0.85 (s, 0.1 H, CH_3?), 1.16 (d overlapping d, 0.9 H, J = 6 Hz, CHCH_3), 1.18 (d overlapping d, 2.0 H, J = 7 Hz, CHCH_3), 1.3–2.0 (m, ~13 H), 2.0–2.6 (m, ~5 H), 2.77 (4 d, ~0.3 H, J = 12, 12, 6, and 2 Hz, CHC(O)?), 2.93 (dq, ~0.7 H, J = 8 and 3 Hz, CHC(O)?), 4.16 (dt, 0.3 H, J = 2 and 9 Hz, CHI), 4.42 (2 d, 0.05 H, J = 6 and 12 Hz, CHI), 4.82 (2 d, 0.65 H, J = 5 and 13 Hz, CHI).

(3aβ,4α,6aα,9aβ,10aα)-Dodecahydro-4,9α-dimethyldicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (37). A solution of 10.0 g (0.028 mmol) of iodo ketones **36** and 97 mg (0.33 mmol, 90 μL) of tri-*n*-butyltin hydride in 0.5 mL of THF was stirred for 30 min at room temperature. The product was isolated in the manner described previously for the preparation of ketone **28**. The yield, after flash chromatography, was 5.5 mg (85%) of ketone **37** as an oil. GC analysis (column B, 260 °C) indicated the product was a 93:7 mixture of diastereomers. The spectral properties follow: IR ($CHCl_3$) ν_{max} 2900, 1725 (C=O), 1155 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.80 (s, 3 H, CH_3), 0.98 (d, 3 H, J = 7 Hz, CHCH_3), 1.2–2.0 (m, ~16 H), 2.0–2.5 (m, ~4 H); GC–mass spectrum (10 eV) m/e (rel intensity) 234 (M$^+$, 80), 216 (8), 201 (5), 191 (10), 177 (12), 163 (12), 123 (50), 45 (55), 81 (60), 67 (70), 55 (85), 41 (100). High-resolution mass spectrum calcd for $C_{16}H_{26}O$: m/e 234.1984. Found: m/e 234.1984.

Equilibration of 3 mg of ketone **37**, in the same manner described previously for ketone **27**, furnished 3 mg of product that was unchanged as indicated by GC analysis and the ^{1}H NMR spectrum.

(3aβ,4α,6aα,9aβ,10aα)-3,3a,4,6a,7,8,9,9a,10,10a-Decahydro-4,9a-dimethyldicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (38) and (3aβ,6aα,9aβ,10aα)-3,3a,6,6a,7,8,9,9a,10,10a-Decahydro-4,9a-dimethyldicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (39a). A solution of 83.3 mg (0.231 mmol) of the 31:61:8 mixture of iodo ketones **36a–c**, 1.14 g (3.53 mmol) of tetra-*n*-butylammonium bromide, and 85 mg (0.8 mmol, 93 μL) of 2,6-dimethylpyridine in 8.5 mL of acetone was heated at reflux. Progress of the elimination was monitored by TLC (10% ethyl acetate in hexane), and after 42 h the reaction was complete. The crude product was isolated in the manner described previously for the synthesis of enone **29**. Purification of the product by flash chromatography on 8 g of silica gel, using 10% ether in hexane as eluant, provided 41.6 mg (77%) of a 38:48:13 mixture of enones **38**, **39a**, and **39b**, respectively. The fractions were analyzed by TLC and GC (column A, 150 °C; retention times of **38**, **39a**, and **39b** were 3.9, 5.3, and 7 min, respectively), and care was taken to insure that all fractions containing enone(s) were combined.

Partial separation of the isomers by flash chromatography on 35 g of silica gel impregnated with 10% silver nitrate, using 10% ethyl acetate in hexane as eluant, provided 8.9 mg of enone **38** (≥98% pure by GC) and 14.3 mg of enone **39a** (~85% pure by GC). One recrystallization of enone **38** from pentane provided colorless crystals: mp 81–84 °C; IR ($CHCl_3$) 2910, 1732 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (s, 3 H, CH_3), 1.15 (d, 3 H, J = 7 Hz, CHCH_3), 1.0–2.0 (m, ~11 H), 2.0–2.7 (m, ~5 H, C(O)CH and C=CCH), 5.28 and 5.91 (2 t, 2 H, J = 10 Hz, HC=CH); GC mass spectrum m/e (rel intensity) 232 (M$^+$, 50), 217 (10), 203 (8), 189 (11), 175 (12), 161 (14), 147 (32), 137 (75), 95 (75), 55 (70), 41 (100). High-resolution mass spectrum calcd for $C_{16}H_{24}O$: m/e 232.1828. Found: m/e 232.1832.

Two recrystallizations from pentane of **39a** contaminated with 15% of **38** furnished 2 mg of the pure isomer: mp 65.5–68 °C; IR ($CHCl_3$) ν_{max} 2900, 1730 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.72 (s, 3 H, CH_3), 1.2–1.6 (m, ~9 H), 1.69 (s, 3 H, C=CCH_3), 1.7–1.9 (10-line m, ~2 H), 1.95–2.1 (10-line m, ~3 H), 1.95–2.5 (13-line m, ~3 H), 3.23 (ddd, 1 H, J = 14, 12, and 5 Hz, C(O)CH), 5.59 (t, 1 H, J = 8 Hz, C=CH); GC mass spectrum m/e (rel intensity) 232 (M$^+$, 18), 217 (8), 175 (12), 135 (12), 123 (30), 108 (35), 95 (100), 79 (30). High-resolution mass spectrum calcd for $C_{16}H_{24}O$: m/e 232.1827. Found: m/e 232.1828.

Evaporation of the mother liquor obtained in the recrystallization of enone **39a** provided 10 mg of a 12:85:3 mixture of enones **38**, **39a**, and **39b**, respectively. A solution of 1 mg of this mixture in 100 μL of 0.45 M sodium methoxide in methanol was stirred at 25 °C for 20 min and at 50 °C for 30 min. Equilibration of the AB ring juncture was complete within 10 min at 25 °C. The final ratio, by GC, was 13:71:15 of enones **38**, **39a**, and **39b**.

The silver nitrate–silica gel chromatography column was stripped with ether, affording 6.9 mg of a 15:85 mixture of enones **39a** and **39b**. The ^{1}H NMR spectrum of the mixture had the following appearance: ^{1}H NMR ($CDCl_3$) δ 0.72 (s, 0.45 H, CH_3), 0.82 (s, 2.55 H, CH_3), 1.51 (s, ~2.55 H, C=CCH_3), 1.0–2.5H (m, ~17 H), 3.42–3.68 (m, 1 H, C(O)CH), 5.50 (t, 1 H, J = 9 Hz, C=CH). Equilibration of 1 mg of this mixture in the same manner as described in the preceding paragraph resulted in an 82:18 mixture of enones **39a** and **39b** by GC analysis.

Equilibration of 3 mg of enone **38** in the same manner afforded 3 mg of enone **38** that was unchanged when analyzed by TLC, GC, and ^{1}H NMR spectroscopy.

(3aβ,4β,6aα,9aβ,10aα)-Tetradecahydro-4,9a-dimethyl-1-oxodicyclopenta[*a*,*d*]cyclooctene-5-carboxylic Acids (40a,b). Reductive cleavage of 51.2 mg (0.186 mmol) of keto acid **34a** was carried out in the exact manner as described in the preparation of **35**. The yield, after flash chromatography, was 40.6 mg (79%) of keto acids **40** as a white solid: mp 165–195 °C; IR ($CDCl_3$) ν_{max} 3500–2400 (b, OH), 2910, 1730 (C=O), 1705 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.70 (s, 0.8 H, CH_3), 0.84 (s, 2.2 H, CH_3), 1.03 (d, 0.8 H, J = 6 Hz, CHCH_3), 1.03 (d, 2.2 H, J = 7 Hz, CHCH_3), 1.2–1.3 (dd, 1 H, J = 8 and 16 Hz), 1.32–2.0 (m, ~13 H), 2.1–2.5 (m, ~4 H), 2.76 (dt, 0.73 H, J = 13, 4, and 4 Hz, C(O)CH), 2.83 (q, 0.27 H, J = 4 Hz, C(O)CH); mass spectrum m/e (rel intensity) 278 (M$^+$, 7), 260 (21), 232 (25), 204 (28), 137 (55), 136 (53), 95 (78), 81 (66), 67 (66), 55 (84), 41 (100). High-resolution mass spectrum calcd for $C_{17}H_{26}O_3$: m/e 278.1882. Found: m/e 278.1881.

Equilibration of 16 mg (0.058 mmol) of the 8:2 diastereomer mixture in the same manner as described previously for keto acids **35** afforded 16 mg of a mixture. The ^{1}H NMR spectrum indicated the major isomer in the starting material was unchanged, but that the minor isomer had equilibrated to a 3:1 mixture of a new isomer and itself. The chemical shift of the angular methyl of the new isomer was 0.73 ppm.

(3aβ,4β,6aα,9aβ,10aα)-Dodecahydro-5-iodo-4,9α-dimethyldicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (41a,b) was prepared from 30.0 mg (0.108 mmol) of keto acids **40a,b** and 100 mg (0.226 mmol) of lead tetraacetate as described for the preparation of iodo ketones **26a–c** and **36a–c**. The yield was 26.4 mg (68%) of iodo ketones **41a,b** after purification. HPLC analysis and the ^{1}H NMR spectrum indicate the product was a 22:78 mixture of two diastereomers. The spectral data for the mixture are as follows: IR ($CHCl_3$) ν_{max} 2900, 1730 (C=O) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.83 (s, 0.7 H, CH_3), 0.86 (s, 2.3 H, CH_3), 1.12 (d, 0.7 H, J = 7 Hz, CHCH_3), 1.21–1.27 (4-line m, ~2 H, J = 8 Hz), 1.35 (d, ~2.3 H, J = 7 Hz, CHCH_3), 1.3–2.0 (m, ~12 H), 2.0–2.45 (m, 7 H), 4.66–4.74 (9-line m, 1 H, CHI).

The ^{1}H NMR spectrum of the crude product indicated the presence (8%) of disubstituted olefin **42**.

(3aβ,4β,6aα,9aβ,10aα)-3,3a,4,6a,7,8,9,9a,10,10a-Decahydro-4,9a-dimethyldicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (42) was obtained from 10.0 mg (0.028 mmol) of a 22:78 mixture of iodo ketones **41a** and **41b** as previously described for the preparation of enones **38** and **39a**. The yield, after flash chromatography, was 6.1 mg (94%) of enone **42** as a white solid that was a single compound by GC (column A, 180 °C) and TLC (10% ethyl acetate in hexane) analyses and ^{1}H NMR spectroscopy. Recrystallization of the product from pentane (–20 °C) afforded 5.3 mg (83%) of colorless crystals: mp 114–119 °C; IR ($CHCl_3$) ν_{max}

2910, 1730 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.75 (s, 3 H, CH_3), 1.11 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.3–1.8 (m, 10 H), 2.0–2.5 (m, 6 H, C(O)CH and C=CCH), 5.34 and 5.43 (6-line m, 2 H, HC=CH); GC mass spectrum m/e (rel intensity) 232 (M^+, 63), 217 (18), 203 (10), 189 (22), 175 (16), 161 (18), 147 (51), 137 (95), 95 (72), 81 (89), 41 (100). High-resolution mass spectrum calcd for $C_{16}H_{14}O$: m/e 232.1827. Found: m/e 232.1823.

Equilibration of 2 mg of enone **42** in 200 μL of 0.5 M sodium methoxide in methanol for 1 h at 50 °C provided 2 mg of crude product that was a 1:1 mixture of diastereomers as indicated by GC analysis (column A, 170 °C) and the 360-MHz ^1H NMR spectrum. The chemical shifts of the angular methyl and the secondary methyl of the C-2 epimer **45** are 0.82 and 1.04 ppm, respectively. The vinyl protons overlap those of the starting material.

(3aβ,4β,6aα,9aβ,10aα)-Dodecahydro-4,9a-dimethyldicyclopenta[a,d]cycloocten-1(2H)-one (43). Method A. Tri-n-butyltin Hydride Reduction of Iodides 41. The reduction of 8.5 mg (0.024 mmol) of a 22:78 mixture of iodo ketones **41a** and **41b** was carried out in the same manner previously described for the preparation of ketone **37**. The yield, after flash chromatography, was 5.1 mg (92%) of ketone **43** as a white solid. GC and TLC analysis and ^1H NMR spectra indicated that the product was one isomer. The spectral properties are as follows: IR ($CHCl_3$) ν_{max} 2900, 1725 (C=O) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.82 (s, 3 H, CH_3), 1.02 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.2–1.8 (m, ~16 H), 2.0–2.5 (m, 4 H, C(O)CH); GC mass spectrum m/e (rel intensity) (M^+, 70), 216 (10), 191 (10), 177 (10), 163 (11), 149 (19), 123 (50), 95 (52), 81 (58), 67 (68), 55 (89), 41 (100). High-resolution mass spectrum calcd for $C_{16}H_{26}O$: m/e 234.1984. Found: m/e 234.1982.

Submission of 2 mg of ketone **43** to the equilibrating conditions (sodium methoxide in methanol) described in detail in the preparation of enones **38** and **39a** afforded 2 mg of product which was identical with the starting material by GC and TLC analyses, and ^1H NMR spectral comparisons.

Method B. Hydrogenation of Enone 42. A suspension of 2 mg (0.0086 mmol) of enone **42** and 0.5 mg of 5% palladium on carbon in 0.5 mL of absolute ethanol was stirred at 25 °C as hydrogen gas was passed slowly across the surface of the reaction mixture. The progress of the reaction was monitored by TLC, and after 1.5 h the reduction was complete. The suspension was filtered through celite, and the solvent was evaporated. The TLC, GC, and ^1H NMR spectral properties of this material were found to be identical with those of the product isolated in Method A.

Method C. Hydrogenation of a 2:1 Mixture of Enones 42 and 44. The reduction of 8 mg (0.034 mmol) of a 2:1 mixture of enones **42** and **44**, obtained by partial equilibration of **42** with sodium methoxide in methanol, was carried out using the conditions described in Method B except that 4 mg of 5% palladium on carbon was used, and the total reaction time was 8 h. The yield, after filtration and evaporation, was 6.5 mg (81%) of a white solid. GC (column B, 160 °C) analysis and ^1H NMR spectra indicated that the product was a 2:1 mixture of ketones **43** and **45**. The chemical shifts assigned to the angular methyl group and the secondary methyl group (J = 6 Hz) of the cis-fused isomer in the 360 MHz ^1H NMR spectrum are 0.85 and 0.97 ppm, respectively.

Method D. Partial Hydrogenation of Enone 39a. A suspension of 1 mg of enone **39a** and 0.5 mg of 5% palladium on carbon in 0.7 mL of absolute ethanol was stirred under an atmosphere of hydrogen for 2 h. The catalyst was removed by filtration, and the filtrate was evaporated, affording ~1 mg of product. The 360-MHz ^1H NMR spectrum indicated that the product was a 76:15:9 mixture of **39a**, **37**, and **43**.

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Supplementary Material Available: Tables (III–VI) of bond distances, bond angles, atomic positional parameters, and atomic thermal parameters for iodo ketone **26c** are included (4 pages). Ordering information is given on any current masthead page.