Table VI. NMR Data of 7 in Various Solvents

	^1H	^{13}C
C_6D_6	2.44 (s, 6 H), 1.23 (s, 6 H), 1.18 (s, 9 H)	83.78, 67.26, 38.87, 27.02, 22.95
C_7D_8	2.44 (s, 6 H), 1.21 (s, 6 H), 1.18 (s, 9 H)	83.79, 67.32, 38.88, 27.07, 23.03
CD_3CN	2.36 (s, 6 H), 1.14 (s, 9 H), 1.10 (s, 6 H)	84.41, 67.75, 38.95, 27.11, 22.57
CD_3OD	2.42 (s, 6 H), 1.19 (s, 9 H), 1.14 (s, 6 H)	85.21, 68.44, 38.90, 27.11, 21.77

stirred at 0 °C for 5 min, the mixture was stirred with ether at room temperature for 2 h. The ether layer was separated and dried with K_2CO_3 and Na_2SO_4. After rotary evaporation of the solvent, the yellow residue (6 g) was relatively clean 7 as shown by NMR analysis. Vacuum distillation gave the pure azoalkane, bp 66.5–67.5 °C (~25 mm). NMR data in four solvents are listed in Table VI. MS (45 eV): 85 (60), 70 (100), 59 (12), 57 (17), 56 (42), 55 (25), 44 (13), 43 (13), 42 (23), 41 (37), 39 (18), 28 (25), 15 (30).

Acetone Dimethylenamine (9) was prepared according to the literature procedure,[71] NMR (C_6D_6) δ 3.88 (br s, 1 H), 3.73 (s, 1 H), 2.38 (s, 6 H), 1.72 (d, 3 H, J = 0.6 Hz). Crude 9 polymerized on attempted distillation, and it degraded into a mixture on standing for 4 days in the freezer under nitrogen. Attempts to purify 9 by GC gave 10 instead: NMR (C_6D_6) δ 5.78 (m, 1 H), 4.06 (s, 1 H), 4.01 (d, 1 H, J = 0.8 Hz), 2.45 (s, 6 H), 1.79 (d, 3 H, J = 1.1 Hz), 1.61 (d, 3 H, J = 1.3 Hz); MS (70 eV) 125 (17), 110 (100), 95 (30), 94 (22), 42 (27), 39 (20), 15 (43).

2-(Dimethylamino)-2,3,3-trimethylbutane (8) was synthesized as described in the literature.[72] The crude product was purified by preparative GC: ^1H NMR (C_6D_6) δ 2.30 (s, 6 H), 0.96 (s, 9 H), 0.93 (s, 6 H); ^{13}C NMR (C_6D_6) δ 59.96, 42.29, 40.49, 27.07, 21.09.

Thermolysis Kinetics. Thermolysis kinetics were done in sealed 1-cm Pyrex UV cells in a constant-temperature oil bath shielded from fluorescent lights. Solutions were degassed by at least three freeze–thaw cycles. The bath temperature was recorded by a platinum thermometer and a HP Model 3456 $6^1/_2$ digit volmeter. The reaction was followed by the decay of the UV absorption maximum around 380 nm.

Thermolysis Product Study. All solutions for thermolysis were degassed by at least three freeze and thaw cycles. Product analysis was done in sealed NMR tubes heated at an appropriate temperature (110–130 °C) in the same bath as used for kinetics. A dry solution of 7 in CD_3CN was obtained by stirring the wet solution with CaH_2 followed by trap to trap distillation on the vacuum line into an NMR tube. In the trapping experiment, tetrabutylammonium cyanide was first placed in the NMR tube and pumped to dryness. Dried 7 solution (see above) in CD_3CN was then distilled into the NMR tube, and the reaction was followed by NMR spectroscopy. In the reaction of 7 with acetic acid, the HOAc–C_6D_6 solution and the solution of 7–C_6D_6 were degassed separately. The acetic acid solution was then distilled into the frozen 7 solution at −196 °C. The combined solution was first allowed to react at room temperature for 30 h in the dark and was then heated at 100 °C for 20 min to complete the reaction. For GC–MS analysis, the tube was usually opened after thermolysis, and the reaction mixture was analyzed immediately to avoid air oxidation of the products and escape of volatile components. Products were identified by ^1H and ^{13}C NMR analyses, or by GC–MS comparison with authentic material. The product ratio was estimated from NMR peak area or peak height. Nitrogen volumes were obtained on a Töpler pump and the gas purity was checked by GC on a 5-Å molecular sieves column. An NMR tube sealed to a 7/25 standard taper joint was used for the nitrogen yields.

Photolysis of 7. All photolyses were done in degassed solution in sealed NMR tubes using an Oriel 500-W high-pressure mercury lamp with a 2,7-dimethyl-3,6-diazacyclohepta-1,6-diene perchlorate filter. Products were identified and quantified by the same methods used in thermolysis.

Quantum Yield. A Hanovia 450-W medium-pressure mercury lamp with 366-nm light filter was used for this purpose. The quantum yield was obtained from the nitrogen volume ratio of 7 relative to DTBD standard with NMR tubes on a merry-go-round apparatus at an average temperature of 20 °C. Solutions of 0.3 M 7–C_6D_6 and 0.82 M DTBD–C_6D_6 were used. The tubes were removed frequently for NMR analysis. Caution was exercised to make sure that all light was absorbed by the samples during the photolysis. After the photolysis, about 25% of DTBD and 63% of 7 were decomposed.

Acknowledgment. Financial support from the National Science Foundation and the Robert A. Welch Foundation is gratefully acknowledged. We thank Professor Joachim G. Shantl for helpful discussions.

Supplementary Material Available: NMR spectra of 7 and its decomposition products as described in ref 32 (7 pages). Ordering information is given on any current masthead page.

(71) Ahlbrecht, H.; Raab, W. *Synthesis* **1980**, 320.
(72) Vejdelek, Z. J.; Trcka, V. *Experientia* **1959**, *15*, 215; *Chem. Abstr.* **1960**, *54*, 3177i.

Synthesis of Polyquinanes. 3. Total Synthesis of (±)-Hirsutene: The Intramolecular Diels–Alder Approach[1,2]

Daniel D. Sternbach*[,3] and Carol L. Ensinger[4]

Department of Chemistry, Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received May 1, 1989

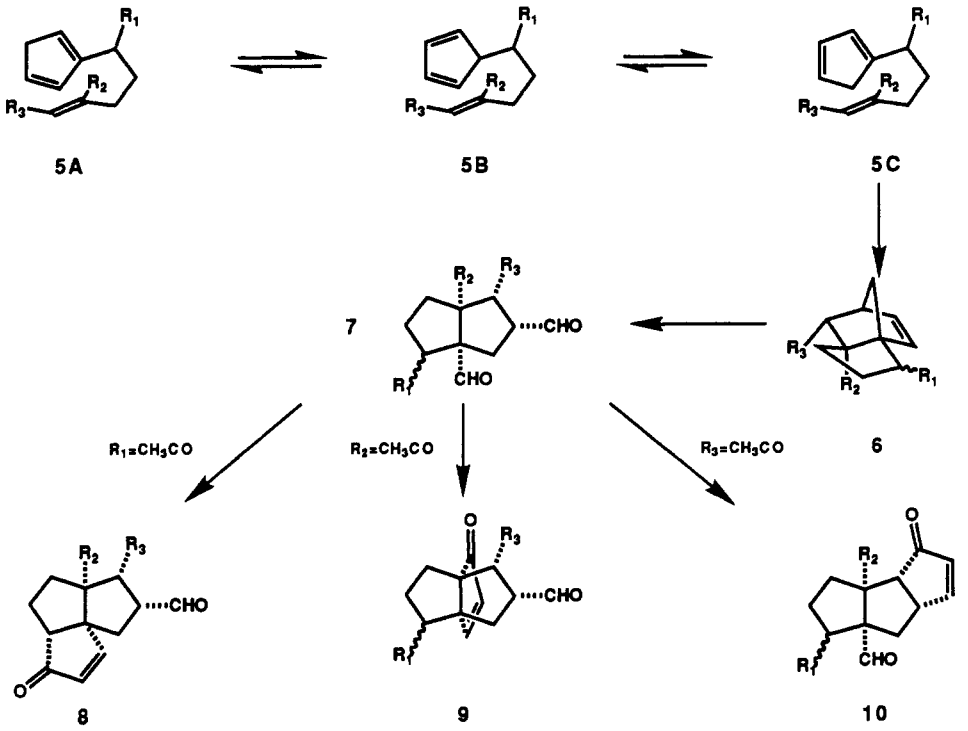
The highly efficient (19% overall yield) 20-step synthesis of the linearly fused triquinane (±)-hirsutene (11) is described. The key step in this sequence is an intramolecular Diels–Alder reaction of the substituted cyclopentadiene **16d**, which contains all but two of the carbon atoms found in hirsutene. During this intramolecular Diels–Alder reaction, two of the three carbocyclic rings found in hirsutene are formed. The third ring is formed by the aldol cyclization of **29**. The successful synthesis of (±)-hirsutene demonstrates the synthetic utility of the intramolecular Diels–Alder strategy for the synthesis of linearly fused triquinanes.

Over the last 15 years much effort has been devoted to the syntheses of polyquinane natural products as well as to the application of the intramolecular Diels–Alder reaction to problems of general synthetic interest. In the

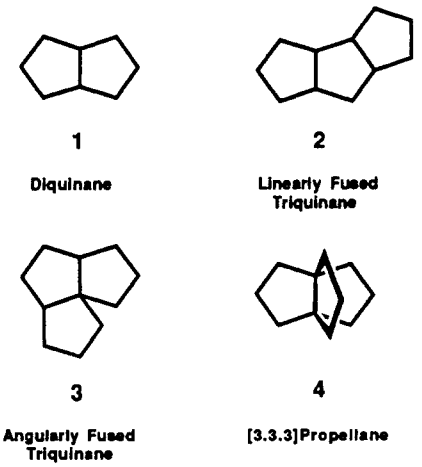
(1) For Part 2 of this series, see: Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Banks, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 2149.
(2) Taken from the doctoral dissertation of Carol Lee Ensinger, Duke University, February, 1988.

0022-3263/90/1955-2725$02.50/0

Scheme I



case of polyquinanes, this attention has been the result of the intriguing and varied structures of these molecules and the potent biological properties that some of these compounds possess. On the other hand, the implementation of the intramolecular Diels–Alder reaction has been due to the inherent advantages of this method over its bimolecular counterpart.[5] As part of a our research program, we have coupled these two areas of endeavor in an attempt to establish a general method of constructing cyclopentanoid natural products of the types 1–4.



Strategy

The strategy to be employed for the synthesis of hirsutene is an outgrowth of our generalized method for the construction of cyclopentanoids. This method is based on the single observation that all polyquinanes, regardless of substitution or presence of rings of other sizes, are built around a core bicyclo[3.3.0]octane (diquinane) ring system. Our approach uses as the key step the intramolecular Diels–Alder (IMDA) reaction of a cyclopentadiene and a dienophile tethered by a three-carbon chain (Scheme I). It has previously been shown that in cases where rapid 1,5-hydride shifts can occur to one of the three possible isomers **5a–c**, only the 1-substituted isomer (**5c**) cyclizes. Moreover, these examples demonstrated an exclusive preference for the tethering chain to possess the exo orientation in the product (**6**).[1,6] As a result of this regio- and stereochemical control, cleavage of the olefin in **6** would lead to a cis-fused diquinane (**7**) possessing defined relative stereochemistry of R_2, R_3, and the newly generated aldehydes. With respect to the syntheses of triquinane natural products, judicious placement of an acetyl group (as R_1, R_2, or R_3) or its equivalent in the IMDA precursor (**5**) should permit aldol cyclization with one of the aldehydes in **7** to lead to either **8**, **9**, or **10**. Herein we wish to describe the successful application of this strategy to the total synthesis of (±)-hirsutene (**11**).

Results and Discussion

The mold metabolite hirsutene (**11**) was first isolated from the hydrocarbon extracts of fermented micelium of *Coriolus consors*.[7] Its structure was determined through a combination of spectral analysis and original synthesis.[7] Considerable interest has been devoted of late to the synthesis of **11**.[7,8] While much of this is due to its rela-

(3) Present address: Glaxo Research Laboratories, 5 Moore Drive, Research Triangle Park, NC 27709.

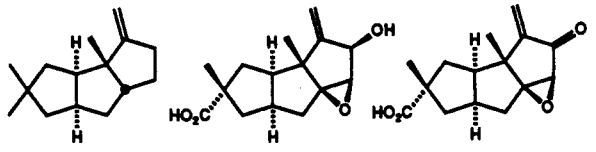
(4) Present address: Pharmaceuticals Research and Development, Medical Products Department, E. I. Dupont de Nemours & Co., Experimental Station, Wilmington, DE 19880–0402.

(5) For some recent reviews, see: Ciganek, E. *Org. React.* **1984**, *32*, 1. Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183.

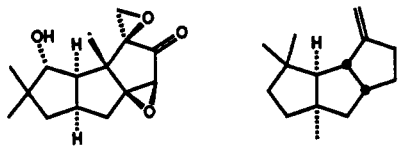
(6) (a) Corey, E. J.; Glass, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 2600. (b) Fallis, A. G.; Breitholle, E. G. *J. Org. Chem.* **1978**, *43*, 1964. (c) Landry, D. W. *Tetrahedron* **1983**, *39*, 2761. (d) For an example in which the IMDA reaction was carried out at temperatures where 1,5-hydride shifts were slow relative to cyclization, see: Wallquist, O.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 1891.

(7) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, 195.

tionship to the antitumor and antibiotic congeners hirsutic acid[9] (12), complicatic acid[10] (13), and coriolin[11] (14), some is also the result of the close similarity between the hirsutane and capnellane families of sesquiterpenes (compare 11 and capnellene 15).

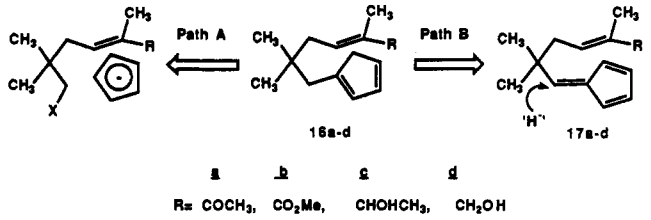


11 12 13



14 15

The synthetic plan called for the construction of a generalized Diels–Alder precursor (16) that might be generated by either of two possible modes where R represents either acetyl or an equivalent (eq 1). In the first



(1)

method (path A), alkylation of cyclopentadiene anion with a suitable halide or sulfonate alkylating agent would give the IMDA precursor directly, assuming that the dienophile is not susceptible to nucleophilic attack. By the second method (path B), condensation of the anion with an appropriate aldehyde would provide a fulvene (17), the exocyclic double bond of which would require reduction for conversion to 16. Once again, the dienophile would have to be resistant to nucleophiles and, additionally, reducing agents. Path A, although appealing for its directness, was not likely to be successful since the requisite alkylating agent would be neopentylic. Path B, on the other hand, necessitated two steps, but appeared to be a viable alternative since we have previously demonstrated[1,12] the feasibility of adding alkyllithiums to sterically hindered fulvenes.

Obviously, the choice of R group had to be made carefully. Functional groups **a**–**d** (eq 1) quickly emerged as the best choices. The unmasked acetyl group **a** was most desirable since this would provide an activated dienophile and obviated the need for functional group manipulation after the Diels–Alder reaction. However, the activated dienophile was potentially susceptible to nucleophilic attack by cyclopentadiene anion and/or a wide variety of reducing agents. These potential complications thus precluded the use of carboxyl group **b** as well. Therefore, fully reduced equivalents of the acetyl and carboxyl moieties such as **c** and **d** were possibilities. The primary alcohol **d** suffered from the obvious drawbacks that it needed to be both oxidized and homologated before aldolization. This left secondary alcohol **c** as the best available option, needing only to be oxidized to be suitable for the aldol cyclization. Potentially, this oxidation might be combined with the Diels–Alder reaction, providing directly a tricyclic product analogous to **6**, since the resultant enone should be an extremely active dienophile.

We began our synthesis with the construction of IMDA precursor **16c** (Scheme II). The known aldehyde[13] **18** was protected as its acetal (95%) and ozonolyzed to yield **19** (100%). Homologation of **19** with diethyl 2-oxobutane-3-phosphonate[14] in refluxing THF gave (88%) of the desired (*E*)-enone, which was reduced using the conditions developed by Luche[15] ($NaBH_4/CeCl_3 \cdot 7H_2O$) to provide an 88% yield of an allylic alcohol as the sole product. Removal of the acetal protecting group with 1:1 10% HCl/THF generated the aldehyde **20** needed for fulvene formation, in quantitative yield. Condensation with cyclopentadiene using the slightly modified conditions of Little[16] (pyrrolidine, MeOH, Na_2SO_4) afforded fulvene **17c** (96%). Reduction of the exocyclic double bond of the fulvene[17] with $LiAlH_4$ in THF proceeded smoothly to provide the Diels–Alder precursors **16c** as a mixture of double-bond regioisomers in 99% yield. The overall yield for this seven-step protocol from **18** was 70%.

After several unsuccessful attempts to oxidize **16c** with concomitant cyclization, the Oppenauer oxidation[18] was tried, using acetone as the hydride acceptor and $Al(O\text{-}i\text{-}Pr)_3$ as catalyst in refluxing toluene. This reaction provided the tricyclic ketone **21** directly in 47% yield.

Ozonolytic cleavage of the double bond in **21** yielded the keto dialdehyde as the expected[19] mixture of hydrates. Unfortunately aldol cyclization of **22** yielded, at most, only a trace of the desired enone **23**.

Presumably the angular aldehyde was too sensitive to withstand the aldol conditions. With the hope of making a more stable derivative, the dialdehyde was oxidized to the diacid (**24**) with Jones reagent (89% yield). We hoped to carry out cyclization to the linearly fused triquinane by using a protocol developed by Coates and co-workers in

(8) (a) Cossy, J.; Belotti, D.; Pete, J. P. *Tetrahedron Lett.* **1987**, 4547. (b) Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443. (c) Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1049. (d) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (e) Funk, R. L.; Bolton, G. L.; Daggett, J. U.; Hansen, M. M.; Horcher, L. H. M. *Tetrahedron* **1985**, *41*, 3479. (f) Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088. (g) Disanayaka, B. W.; Weedom, A. C. *J. Chem. Soc., Chem. Commun.* **1985**, 1282. (h) Ley, S. V.; Murray, P. J.; Palmer, B. D. *Tetrahedron* **1985**, *41*, 4765. (i) Hewson, A. T.; MacPherson, D. T. *J. Chem. Soc., Perkin Trans. I* **1985**, 2625. (j) Dawson, B. A.; Ghosh, A. K.; Jurlina, J. L.; Stothers, J. B. *J. Chem. Soc., Chem. Commun.* **1983**, 204. (k) Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1982**, 3983. (l) Magnus, P.; Quagliato, D. A. *Organometallics* **1982**, *1*, 1243. (m) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744. (n) Greene, A. E. *Tetrahedron Lett.* **1980**, 3059. (o) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351. (p) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1979**, *101*, 6116.

(9) (a) Comer, F. W.; McCapra, F.; Qureshi, I. H.; Scott, A. I. *Tetrahdron* **1967**, *23*, 4761. (b) Comer, F. W.; Trotter, J. *J. Chem. Soc. B* **1966**, 11.

(10) Mellows, G.; Mantle, P. G.; Feline, T. C.; Williams, D. J. *Phytochemistry* **1973**, *12*, 2717.

(11) (a) Takeuchi, T.; Takahashi, S.; Iinuma, H.; Umezawa, H. *J. Antibiot.* **1971**, *24*, 631. (b) Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215.

(12) Sternbach, D. D.; Hughes, J. W.; Burdi, D. F. *J. Org. Chem.* **1984**, *49*, 201.

(13) (a) Salomon, R. G.; Ghosh, S. *Org. Synth.* **1984**, *62*, 125. (b) Magnus, P. D.; Nobbs, M. S. *Synth. Commun.* **1980**, *10*, 273. These procedures work best when the Vigreaux column described in ref 13a is used.

(14) Corbel, B.; Medinger, L.; Haelters, J. P.; Sturtz, G. *Synthesis* **1985**, 1048.

(15) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

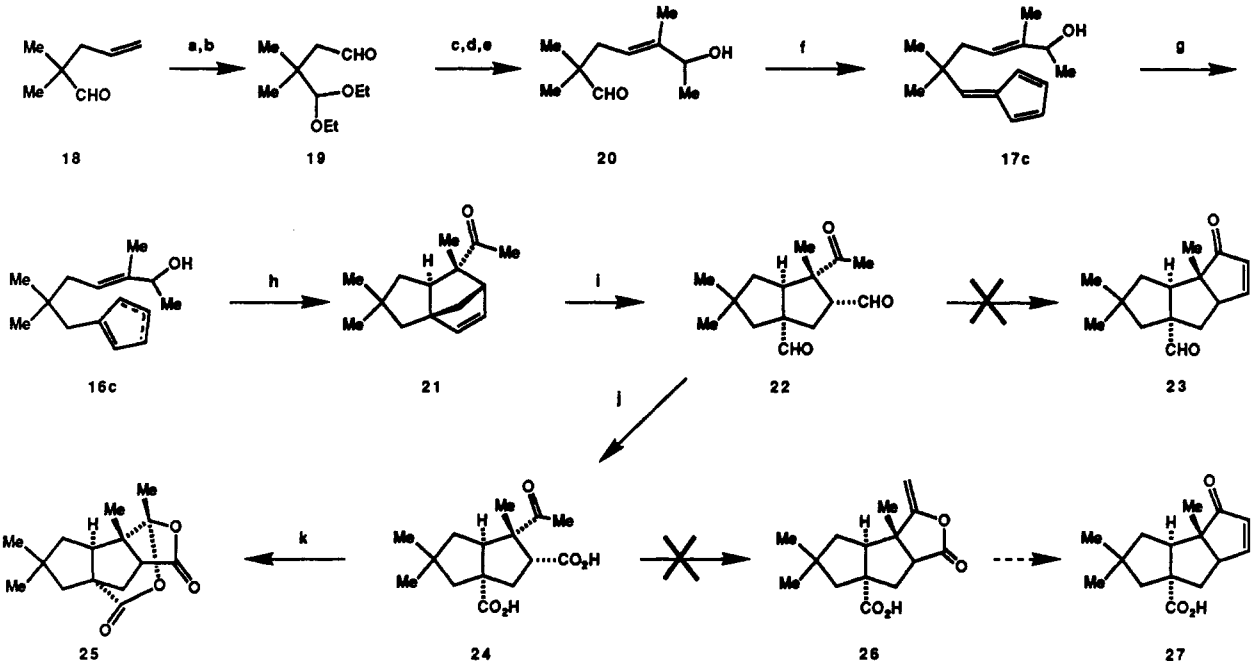
(16) Little, R. D.; Stone, K. J. *J. Org. Chem.* **1984**, *49*, 1849. We wish to thank Professor Little for providing a preprint of this publication.

(17) Little, W. F.; Koestler, R. C. *J. Org. Chem.* **1961**, *26*, 3247.

(18) Djerassi, C. *Org. React.* **1951**, *6*, 207.

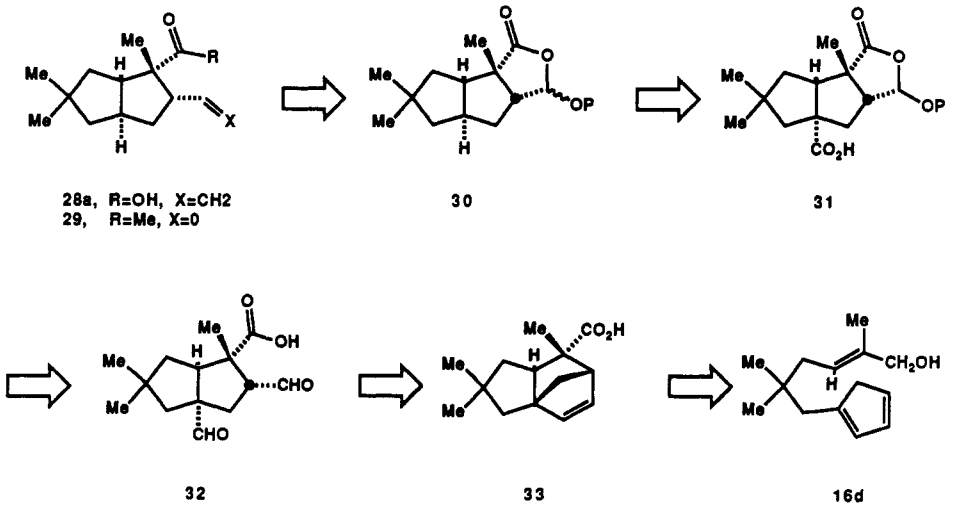
(19) For another example of hydrate formation, see ref 1 and also Martel, A.; Just, G. *Tetrahedron Lett.* **1973**, 1517.

Scheme II. Approaches to Hirsutene through Precursor 16c[a]



[a] (a) $HC(OEt)_3$, EtOH, *p*-TsOH, reflux, 6 h, 95%; (b) O_3, CH_2Cl_2, −78 °C; Ph_3P, CH_2Cl_2, −78 °C to room temperature, 100%; (c) diethyl 2-oxobutane-3-phosphonate, NaH, THF, 0 °C, 45 min; **19**, THF, reflux, 5.5 h, 88%; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, room temperature, 30 min, 88%; (e) 10% HCl, THF, room temperature, 30 min, 100%; (f) cyclopentadiene, pyrrolidine, Na_2SO_4, MeOH, room temperature, overnight, 96%; (g) $LiAlH_4$, THF, room temperature, 1 h, 99%; (h) $Al(O\text{-}i\text{-}Pr)_3$, PhMe, reflux, 1 h; acetone, reflux, 7 h, 47%; (i) O_3, CH_2Cl_2, −78 °C; DMS, −78 °C room temperature, 99%; (j) Jones reagent, acetone, 0 °C, 1 h, 89%; (k) Ac_2O, $HClO_4$, CH_2Cl_2, 0 °C, 1 h.

Scheme III. Revised End Strategy for Synthesis of Hirsutene



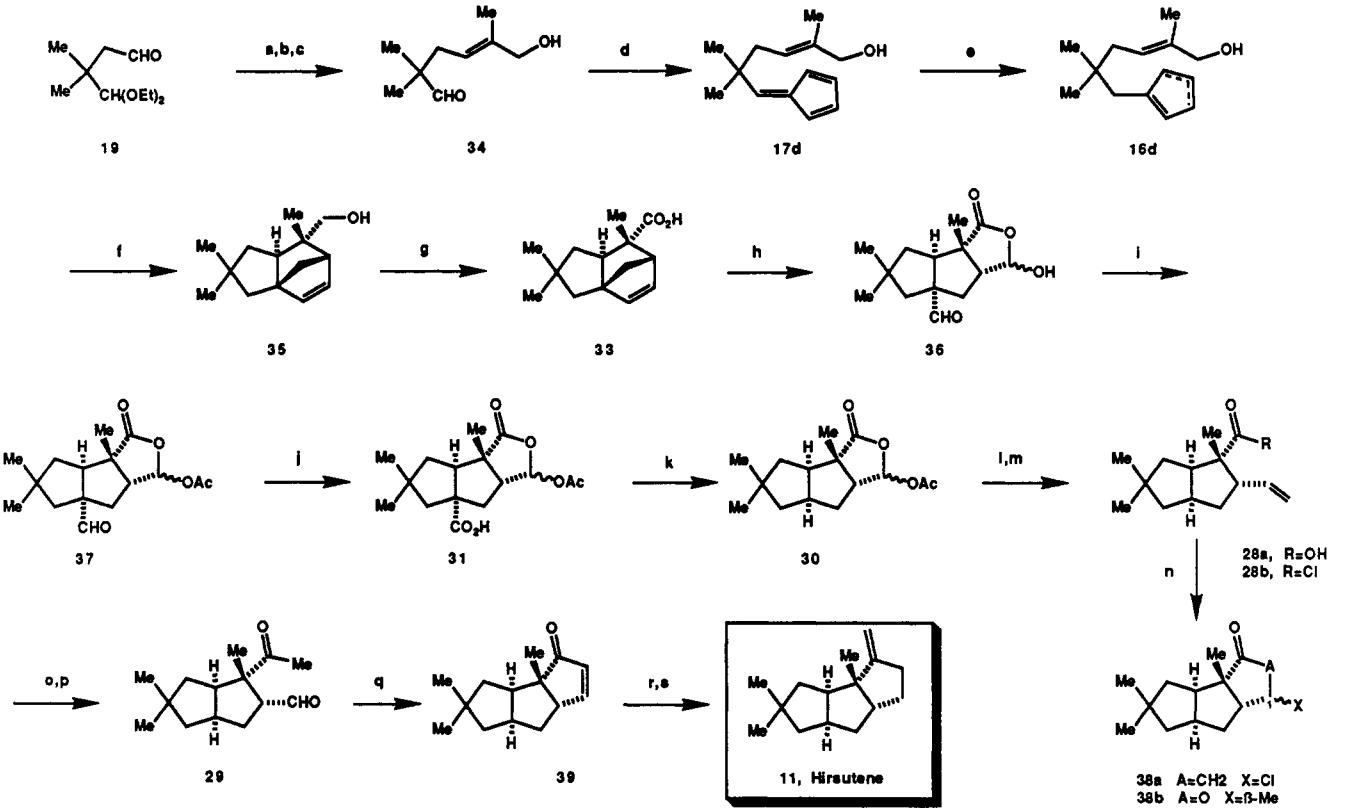
their gymnomitrol synthesis.[20] The basic premise was that diisobutylaluminum hydride reduction of an enol lactone, in this case **26**, would form the aldehyde and an aluminum enolate that would undergo subsequent aldol cyclization. To this end the diacid **24** was reacted with Ac_2O and a catalytic amount of $HClO_4$ in an attempt to form the desired enol lactone **26**. A facile reaction occurred, but instead of the expected enol lactone, the bis-lactone **25** was cleanly formed (85%). This novel structure was supported by the spectral evidence (^1H NMR, ^{13}C NMR, and IR, see Experimental Section). Most importantly the ^{13}C NMR spectrum displayed the absorption at 113.34 ppm due to the quaternary ketal carbon. Unfortunately, selective reaction of one of the carbonyls in the bis-lactone **25** proved difficult. In light of these diappointments, we decided to try a different approach that would allow the selective reaction of the two termini of the double bond in the IMDA adduct. This led us to the approach outlined in Scheme III, which makes use of the hemilactone **31** to differentially protect each of the aldehyde groups in **32** and allow selective removal of the angular one.

From **30**, two cyclization strategies could be envisioned following deprotection of the lactol. Methylene Wittig homologation would provide acid **28a**, a possible Friedel-Crafts acylation substrate. Alternatively, the acid function could be homologated to the methyl ketone and the olefin cleaved to generate aldol precursor **29**. Acid dialdehyde **32** would be the immediate product of ozonolysis of tricyclic **33** which, in turn, would arise in two steps from Diels-Alder precursor **16d**.

Synthesis of this revised IMDA precursor began with

(20) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765 and references cited therein.

Scheme IV. Final Route to Hirsutene[a]



[a] (a) $Ph_3PC(CH_3)CO_2Et$, PhH, reflux, 6 h, 81%; (b) $LiAlH_4$, Et_2O, 0 °C, 15 min, 99%; (c) 10% HCl, THF, room temperature, 25 min, 100%; (d) cyclopentadiene, pyrrolidine, Na_2SO_4, MeOH, 24–36 h, 99%; (e) $LiAlH_4$, THF, room temperature, 1 h, 93%; (f) mesitylene, reflux, 24 h, 70%; (g) Jones reagent, acetone, 0 °C, 1 h, 97%; (h) O_3, CH_2Cl_2, −78 °C; DMS, −78 °C to room temperature, 99%; (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 4 h, 90%; (j) Jones reagent, acetone, room temperature, 45 min, 95%; (k) $(COCl)_2$, DMF, PhH, room temperature, 2 h; 2-mercaptopyridine *N*-oxide, sodium salt, *t*-BuSH, DMAP, PhMe, reflux, 45 min, 82%; (l) MeOH, H_2O, Et_3N (5:4:1), room temperature, 1 h, 95%; (m) Ph_3PCH_3Br, KHMDS, THF, 0 °C, 30 min, 86%; (n) NaH, PhH, room temperature, 1 h; $(COCl)_2$, room temperature, 3 h; $SnCl_4$, 1,2-DCE, 0 °C to room temperature, 7 h, 60%; (o) NaH, PhH, room temperature, 1 h; $(COCl)_2$, room temperature, 3 h; Me_2CuLi, Et_2O, −78 °C to 0 °C, 97%; (p) O_3, CH_2Cl_2, −78 °C; DMS, −78 °C to room temperature, 80%; (q) 5% KOH, Et_2O, THF, (1:1:2), 40% *n*-Bu_4NOH, reflux, overnight, 97%; (r) PtO_2, H_2, EtOAc, room temperature, 20 min, 100%; (s) Ph_3PCH_3Br, KH, PhH, *t*-BuOH (5:1), room temperature to reflux, 5 h, 93%.

Wittig homologation of the previously employed aldehyde **19** using commercially available (carbethoxyethylidene)-triphenylphosphorane (Scheme IV). The α,β-unsaturated ester so obtained (81%) was reduced to the allylic alcohol and hydrolyzed to afford the aldehyde **34** (99%). Condensation of this aldehyde with cyclopentadiene once again using the slightly modified conditions of Little yielded the fulvene **17d** (99%). Reduction of the exocyclic double bond of the fulvene with $LiAlH_4$ in THF gave IMDA precursor **16d**.

The crucial IMDA reaction was conducted at 160 °C in refluxing mesitylene to provide (70%), after 24 h, the tricyclic product **35**. Subsequent treatment with Jones reagent generated carboxylic acid **33**. Ozonolysis of **33** and workup with DMS provided a compound to which was assigned the lactol structure **36** (99%) on the basis of spectral data.

The lactol was protected as its acetate **37** (Ac_2O, Et_3N, DMAP) to generate a 90:10 mixture of anomers (90%) that was used as such. Oxidation of the remaining aldehyde group to its acid **31** with Jones reagent (95%) set the stage for radical decarboxylation by the method of Barton.[21] Thus, activation of the acid as its acid chloride followed by conversion to the thiohydroxamic ester (2-mercaptopyridine *N*-oxide sodium salt; DMAP, PhMe, reflux) and in situ fragmentation with *n*-Bu_3SnH and AIBN provided in only poor yield (27%) the desired noralkane **30**. Efforts were made to improve this recovery, but the best that was obtained was 40%. However, by employing Barton's own modification[21] of this procedure by substituting *t*-BuSH as the hydrogen donor, yields of **30** dramatically improved (82%).

Excluding the exocyclic olefin of **11**, intermediate **30** required incorporation of only one more carbon to complete the basic triquinane system of the natural product. We envisioned utilizing either of two very different protocols based on direct introduction of a carbon at the anomeric center or, alternatively, manipulation of the lactol in such a way as to permit addition of a methyl group to the carboxyl group. As alluded to previously (Scheme III), these options would lead, respectively, to final ring closure by Friedel–Crafts acylation or, in keeping with our original strategy, aldolization. Conveniently, both strategies might be addressed from common intermediate **28a** where the olefin would serve directly in a Friedel–Crafts reaction or as a latent aldehyde. At the outset, the intramolecular acylation appeared the more attractive of the two routes since the β-substituted cyclopentanone anticipated to be the product of this reaction might be transformed to **11** through Wittig homologation and reductive removal of the β-substituent. Accordingly, construction of olefin acid **28a** was accomplished by hydrolysis of **30** (95%) followed by treatment of the resultant lactol with 5 equiv of Wittig

(21) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

reagent (Ph_3PCH_3Br, KHMDS, THF, 0 °C, 86%).

We were thus ready to test the viability of the Lewis acid cyclization strategy. The sodium salt of **28a** was converted to its acid chloride derivative **28b**, which was treated immediately with $SnCl_4$ in 1,2-dichloroethane, giving 60% of a single new product. On the basis of mass spectral analysis, however, this material could not be assigned the desired β-chlorocyclopentanone structure **38a** since the fragmentation pattern lacked the characteristic halide isotopic doubling. Instead, the spectrum displayed a molecular ion at 222, indicating that the product was isomeric with **28a**. Considering all other spectral data, the product was assigned lactone structure **38b**, where it should be noted that the C-1 methyl has exclusively the β configuration. The formation of this lactone presumably arose from the presence of adventitious water during the reaction or on workup.

Having tried unsuccessfully to introduce the third ring of **11** by several different methods, we considered as the only remaining option modification of the original aldol strategy. This eventuality had been anticipated with the construction of **28a** in which the olefin could serve as a masked aldehyde while the acid was homologated to a methyl ketone. This avenue was first explored by treating the acid with 2 equiv of MeLi in Et_2O at 0 °C, but in all attempts the desired ketone was isolated as the minor component in a mixture with the tertiary alcohol resulting from overaddition and unreacted **28a**. However, addition of Me_2CuLi to the acid chloride **28b** did afford the methyl ketone in high yield (97%).

Ozonolysis of the vinyl moiety followed by a reductive workup provided the keto aldehyde **29** (80%), which, on the basis of ^1H NMR, existed entirely as a mixture of epimeric aldehyde hydrates. This mixture underwent smooth aldol condensation using Paquette's[22] conditions (5% KOH in gently refluxing THF/Et_2O (2:1) containing a catalytic amount of 40% n-Bu_4NOH) to give enone **39** in 97% yield. After repeated trials of this reaction, it was found that the optimal quantity of phase-transfer catalyst was scale dependent. Smaller runs required relatively *more* catalyst than larger runs. To consistently achieve high yields on a large scale, it proved advisable to use at the outset only a slight amount of catalyst and then to add it in small increments until cyclization was just induced. The enone **39** was then converted by hydrogenation over PtO_2 to the known hirsutene norketone in quantitative yield. Finally, treatment of hirsutene norketone with excess methylene ylide[23] (Ph_3PCH_3Br, KO-t-Bu, t-BuOH, PhH, reflux) cleanly provided 93% of hirsutene (**11**). The identities of **11** as well as hirsutene norketone were verified by superposition of their 300-MHz ^1H NMR spectra with those of authentic materials.[24]

In summary, we have described a highly efficient (19% overall yield) 20-step synthesis of (±)-hirsutene that demonstrates the utility of the cyclopentadiene IMDA strategy for the synthesis of linearly fused triquinanes.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. In some cases ^1H NMR assignments were supported by appropriate homonuclear decoupling and homo- and heteronuclear correlation experiments (COSY and HETCOR, respectively). ^{13}C NMR assignments were aided by the use of the DEPT pulse sequence and the ADEPT method of spectral manipulation to determine peak multiplicities.

GC-MS analyses and exact mass measurements were obtained at an ionization energy of 70 eV. All reactions were carried out under an atmosphere of dry N_2 or Ar in flame-dried glassware.

Flash chromatography refers to the method developed by W. C. Still and was performed on 230–400-mesh silica gel. The ratio of silica gel to sample was 20–30:1 (w/w). Deactivated silica was prepared by treating 230–400-mesh silica gel with water (12% w/w). Preparative layer chromatography (PLC) was performed on glass plates coated with a 0.25-mm layer of silica gel 60 F-254 purchased from Merck. Thin layer chromatography (TLC) was performed on aluminum plates coated with a 0.02-mm layer of silica gel 60 F-254 purchased from Merck.

Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use. Diethyl ether was used out of freshly opened cans purchased from Mallinckrodt. Benzene, toluene, and mesitylene were distilled from CaH_2 and stored over molecular sieves. Methanol was distilled from Mg turnings and stored over molecular sieves. Methylene chloride, acetonitrile, and dimethylformamide were all dried and stored over sieves.

1,1-Diethoxy-2,2-dimethyl-4-pentene. A solution of 18 (50 g, 0.45 mol), triethyl orthoformate (89 mL, 0.53 mol, 1.20 equiv), and p-TsOH (2.2 g, 0.01 mol, 0.03 equiv) in absolute EtOH (300 mL) was refluxed for 6 h. The resulting yellow solution was cooled to ambient temperature and the EtOH was evaporated. The residue was diluted with ether in a separatory funnel and washed with saturated aqueous $NaHCO_3$ (2×) and with brine (1×) and dried (Na_2SO_4). Filtration, evaporation, and pot-to-pot distillation at ambient temperature under high vacuum (35 °C at 0.05 mm) provided 79 g (95%) of analytically pure acetal as a colorless mobile liquid: ^1H NMR ($CDCl_3$, 300 MHz) 0.89 (s, 6 H), 1.22 (t, 6 H, ^3J = 6.7 Hz), 2.07 (d, 2 H, ^3J = 8.0 Hz, C_3Hs), 3.50 (dq, 2 H, ^3J = 6.7, 8.5 Hz), 3.81 (dq, 2 H, ^3J = 6.7, 9.0 Hz), 3.99 (s, 1 H, C_1H), 5.00 (m, 2 H, ^3J = 15.9, 7.5 Hz, ^2J = 2.00 Hz), 5.83 (m, 1 H, ^3J = 7.5, 8.0, 15.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 15.44 (q), 21.9 (q), 39.34 (s), 42.55 (t), 66.02 (t), 110.44 (d), 116.85 (t), 135.44 (d); IR ($CDCl_3$) 2990 w, 2890 s, 2850 m, 2810 m, 2790 m, 1590 w, 1400 w, 1320 w, 1300 w, 1070 s, 1010 s. Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.9; H, 11.9. Found: C, 70.81; H, 11.79.

4,4-Diethoxy-3,3-dimethylbutanal (19). A solution of 1,1-diethoxy-2,2-dimethyl-4-pentene (5.00 g, 26.8 mmol) in CH_2Cl_2 (250 mL) was thoroughly cooled to −78 °C and treated with a stream of O_3 until the blue color persisted. The reaction was purged of excess O_3 with a stream of Ar, and a solution of Ph_3P (7.04 g, 26.8 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added gradually while maintaining good stirring. After being warmed to ambient temperature overnight, the solvent was evaporated to leave a solid residue, which was triturated 3× with cold pentane. The combined pentane washings were concentrated and the residue was distilled at reduced pressure (75 °C/0.7mm) to provide 5.05 g (100%) of analytically pure aldehyde **19**: R_f = 0.22 (5:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 1.05 (s, 3 H), 1.07 (s, 3 H), 1.22 (m, 6 H), 2.31 (d, 2 H, ^3J = 2.76 Hz, C_2Hs), 3.53 (m, 2 H), 3.82 (m, 2 H), 4.08 (s, 1 H, C_4H), 9.81 (t, 1 H, ^3J = 2.76 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 15.22, 15.29, 22.97, 23.44, 42.19, 51.50, 66.11, 66.36, 109.84, 203.32; IR ($CDCl_3$) 2900 s, 2750 s, 1690 s, 1080 s, 1020 s. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.8; H, 10.7. Found: C, 63.69; H, 10.89.

(*E*)-1,1-Diethoxy-2,2,5-trimethyl-4-hepten-6-one. Under a stream of N_2, NaH (1.82g, 80% dispersion in mineral oil, 60.7 mmol) was washed with hexane (3×), suspended in 85 mL of dry THF, and cooled to 0 °C. To this suspension was added dropwise a solution of diethyl 2-oxobutane-3-phosphonate (12.05g, 57.8 mmol) in dry THF (27 mL). Stirring was continued at 0 °C for 45 min until H_2 evolution ceased. A solution of **19** (9.18 g, 48.2 mmol) in dry THF (9 mL) was added. The reaction was removed immediately from the ice bath and brought to reflux. After being heated for 5.5 h, the mixture was cooled to ambient temperature, poured into saturated NH_4Cl, and extracted 3× with ether. The combined organic extracts were washed sequentially with saturated NH_4Cl (1×) and brine (2×) and dried ($MgSO_4$). Filtration, evaporation, and distillation at reduced pressure (110 °C at 0.5 mm) provided 10.36 g (88%) of analytically pure enone as a slightly yellow liquid: R_f = 0.18 (5:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 0.96 (s, 6 H), 1.23 (t, 6 H, ^3J = 7.2 Hz), 1.77

(22) Paquette, L. A.; Stevens, K. E. *Tetrahedron Lett.* **1981**, 4393.
(23) Paquette, L. A.; Stevens, K. E. Personal Communication.
(24) We thank Professor Curran for supplying us with ^1H NMR, IR, and mass spectra that he had available for hirsutene norketone as well as hirsutene itself, including data he had originally received from Professor Magnus.

(s, 3 H), 2.29 (d, 2 H, ^3J = 7.98 Hz), 2.32 (s, 3 H), 3.51 (dq, 2 H, ^2J = 16.15 Hz, ^3J = 7.14 Hz), 3.83 (dq, 2 H, ^2J = 13.97 Hz, ^3J = 7.14 Hz), 4.02 (s, 1 H, C_1H), 6.83 (t, 1 H, ^3J = 7.98 Hz, C_4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.16, 15.39, 22.73, 25.43, 36.83, 40.29, 66.09, 110.57, 134.70, 141.40, 199.92; IR ($CDCl_3$) 2910 s, 2830 s, 1630 s, 1340 m, 1230 m, 1090 m, 1020 s, 1000 s. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.4; H, 10.8. Found: C, 69.31; H, 10.85.

(*E*)-1,1-Diethoxy-2,2,5-trimethyl-4-hepten-6-ol. To a solution of the preceding enone (10.36 g, 42.7 mmol) in MeOH (105 mL) was added $CeCl_3 \cdot 7H_2O$ (15.91g, 42.7 mmol) in one portion at ambient temperature while maintaining good stirring. To the rapidly stirred suspension was added in small portions $NaBH_4$ (1.62 g, 42.7 mmol). The addition was accompanied by vigorous hydrogen evolution. After 30 min at ambient temperature, saturated aqueous $NaHCO_3$ was added slowly with vigorous evolution of CO_2. The thick mixture was stirred until gas evolution ceased, poured into a separatory funnel, diluted with H_2O until just mobile, and extracted with EtOAc (4×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1×) and with brine (2×) and dried (Na_2SO_4). Filtration and evaporation provided 9.13 g (88%) of pure allylic alcohol. This material was used without further purification: R_f = 0.17 (silica, 1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 0.88 (s, 6 H), 1.21 (d, 3 H, ^3J = 6.7 Hz, C_5Me), 1.25 (t, 6 H, ^3J = 5.76 Hz), 1.63 (s, 3 H), 2.04 (d, 2 H, ^3J = 7.36 Hz, C_3Hs), 3.49 (dq, 2 H, ^2J = 1.69 Hz, ^3J = 6.67 Hz), 3.80 (dq, 2 H, ^2J = 1.82 Hz, ^3J = 6.62 Hz), 4.00 (s, 1 H, C_1H), 4.24 (q, 1 H, ^3J = 6.31 Hz, C_6H), 5.49 (t, 1 H, ^3J = 7.36 Hz, C_4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.52, 15.36, 21.71, 21.93, 35.23, 40.05, 65.91, 73.55, 110.48, 121.13, 140.06; IR ($CDCl_3$) 3550 w, 3400 br w, 2900 s, 2810 s, 1650 w, 1420 m, 1340 m, 1220 m, 1090 s, 1020 s. Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.79; H, 11.57. Found: C, 68.95; H, 11.41.

(*E*)-6-Hydroxy-2,2,5-trimethyl-4-heptenal (20). To a solution of (*E*)-1,1-diethoxy-2,2,5-trimethyl-4-hepten-6-ol (5.63 g, 23.0 mmol) in THF (5.6 mL) was added 10% HCl (5.6 mL). The resulting biphasic mixture was stirred rapidly for 20–30 min at ambient temperature until a homogeneous solution was obtained. The reaction was quenched by the slow addition of saturated aqueous $NaHCO_3$ and was extracted with EtOAc (3×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1×) and with brine (2×) and dried ($MgSO_4$). Filtration and evaporation provided 3.9 g (100%) of essentially pure aldehyde **20** as an oil, which was used without further purification: R_f = 0.11 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 1.03 (s, 6 H), 1.20 (d, 3 H, ^3J = 6.45 Hz, C_7Hs), 1.59 (br s, 3 H, C_5Me), 2.16 (d, 2 H, ^3J = 7.55 Hz, C_3Hs), 4.17 (q, 1 H, ^3J = 6.45 Hz, C_6H), 5.31 (t, 1 H, ^3J = 7.55 Hz, C_4H), 9.43 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.84, 21.23, 21.81, 34.84, 46.54, 73.18, 118.75, 141.74, 205.83; IR ($CDCl_3$) 3600 w, 3410 br, 2970 s, 2940 s, 2860 m, 2800 w, 2700 w, 1725 s, 1420 w, 1365 w, 1250 w, 1040 m.

7-(2,4-Cyclopentadien-1-ylidene)-3,6,6-trimethyl-3-hepten-2-ol (17c). To a rapidly stirred suspension of aldehyde **20** (3.75 g, 22.0 mmol), cyclopentadiene (4.86 mL, 58.8 mmol, 2.67 equiv), and anhydrous Na_2SO_4 (1.0 g, 6.0 mmol, 0.30 equiv) in dry MeOH (75 mL) was added dropwise at ambient temperature pyrrolidine (2.94 mL, 35.3 mmol, 1.5 equiv). The reaction mixture, which became yellow within several minutes, was stirred rapidly overnight at ambient temperature. The reaction was treated with AcOH (3.7 mL, 64.7 mmol, 1.8 equiv based on pyrrolidine), diluted with H_2O, and extracted with four large portions of ether. The combined ether extracts were washed with brine until the washes were colorless and then simultaneously decolorized and dried with a combination of Norit neutral charcoal, $MgSO_4$, and K_2CO_3. Filtration through Celite and evaporation provided 4.59 g (96%) of essentially pure fulvene **17c** as a bright yellow-orange oil. This material was used without further purification: R_f = 0.27 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 1.22 (d, 3 H, ^3J = 6.21 Hz, C_1Hs), 1.61 (br s, 3 H, C_3Me), 2.24 (d, 2 H, ^3J = 7.37 Hz, C_5Hs), 4.19 (q, 1 H, ^3J = 6.21 Hz, C_2H), 5.43 (t, 1 H, ^3J = 7.37 Hz, C_4H), 6.14 (m, 1 H), 6.38 (m, 2 H), 6.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.78, 21.69, 28.57, 28.77, 39.94, 41.45, 73.43, 119.99, 120.77, 128.40, 128.49, 134.19, 140.99, 152.42; IR ($CDCl_3$) 3600 m, 3425 m, 3050 w, 2960 s, 2940 s, 2875 s, 1600 w, 1440 m, 1370 s, 1260 m, 1180 m, 1090 s.

7-(1,3-Cyclopentadienyl)-3,6,6-trimethyl-3-hepten-2-ol (16c). To a suspension of $LiAlH_4$ (0.67 g, 17.8 mmol, 1.1 equiv) in dry THF (67 mL) was added very slowly dropwise at ambient temperature a solution of **17c** (3.53 g, 16.2 mmol) in dry THF (67 mL). The vigorous and somewhat exothermic reaction was stirred for 1 h after completion of the addition and was then carefully quenched by the sequential addition of H_2O (0.67 mL), 10% NaOH (0.67 mL), and H_2O (1.34 mL). After 1 h, the mixture was filtered through Celite and the cake was washed generously with ether. Evaporation provided 3.56 g (99%) of essentially pure **16c** as a pale yellow oil. This material was used immediately without further purification: R_f = 0.16 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 0.79 (s, 3 H), 1.19 (d, 3 H, ^3J = 6.15 Hz, C_1Me), 1.53 (br s, 3 H, C_3Me), 1.86 (d, 2 H, ^3J = 7.62 Hz, C_5Hs, major), 1.95 (d, 2 H, ^3J = 7.51 Hz, C_5Hs, minor), 2.19 (br s, 2 H, C_7Hs, major), 2.24 (br s, 2 H, C_7Hs, minor), 2.88 (br s, 2 H, major), 3.41 (br s, 2 H, minor), 4.16 (q, 1 H, ^3J = 6.15 Hz, C_4H), 5.43 (br t, 1 H) 6.27 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.73, 21.83, 27.04, 35.01, 35.23, 35.44, 39.69, 39.79, 41.26, 42.18, 42.83, 45.97, 58.41, 73.64, 113.42, 120.77, 121.54, 121.66, 129.44, 129.61, 130.85, 132.39, 136.61, 139.86, 143.97, 146.46; IR ($CDCl_3$) 3600 w, 2960 s, 2940 s, 2850 m, 1630 m, 1450 m, 1360 m, 1250 m, 1080 m, 880 m.

(3aβ,6β,7aα,7aα)-(±)-7-Acetyl-1,2,3,6,7,7a-hexahydro-2,2,7-trimethyl-3a,6-methano-3a*H*-indene (21). A suspension of $Al(O\text{-}i\text{-}Pr)_3$ (1.19 g, 5.8 mmol, 1.7 equiv) in dry toluene (65 mL) was heated at reflux until the catalyst was almost completely dissolved. To the refluxing mixture was added a solution of **16c** (0.75 g, 3.4 mmol) in dry toluene (5 mL). After 1 h, acetone (7 mL) was added gradually through the top of the condenser to the refluxing solution. After an additional 8 h at reflux, the mixture was cooled to ambient temperature, poured into ice-cold 10% HCl, diluted with ether, and shaken vigorously. The organic extract was washed with an additional portion of cold 10% HCl and then with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Filtration, evaporation, and gravity chromatography on activity grade III neutral alumina eluting with 10:1 hexane/ether provided 0.35 g (47%) of analytically pure ketone **21** as a colorless oil: R_f(**21**) = 0.43 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 1.01 (s, 3 H), 1.05 (s, 3 H) 1.19 (s, 3 H), 1.23 (dd, 1 H, ^2J = 12.4 Hz, ^3J = 12.8 Hz, $C_1H\beta$), 1.26 (dd, 1 H, ^4J = 2.04 Hz, ^2J = 8.48 Hz, C_8Hsyn), 1.45 (d, 1 H, ^2J = 13.86 Hz, $C_3H\beta$), 1.47 (dd, 1 H, ^2J = 12.4 Hz, ^3J = 6.79 Hz, $C_1H\alpha$), 1.63 (d, 1 H, ^2J = 8.48 Hz, C_8Hanti), 1.66 (d, 1 H, ^2J = 13.86 Hz, $C_3H\alpha$), 2.02 (s, 3 H), 2.41 (ddd, 1 H, ^4J = 2.04 Hz, ^3J = 6.79, 12.8 Hz, $C_{7a}H$), 2.69 (d, 1 H, ^3J = 2.40 Hz, C_6H), 5.88 (dd, 1 H, ^3J = 2.40, 5.37 Hz, C_5H), 6.04 (d, 1 H, ^3J = 5.37 Hz, C_4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 21.42 (q), 25.77 (q), 31.14 (q), 31.78 (q), 42.51 (s) 42.89 (t), 43.0 (t), 50.0 (d), 50.96 (t), 53.82 (d), 58.14 (s), 62.95 (s), 133.52 (d), 143.16 (d), 212.11 (s); IR ($CDCl_3$) 2900 m, 1640 s, 1420 w, 1340 w. Anal. Calcd for $C_{15}H_{22}O$: C, 82.5; H, 10.2. Found: C, 82.37; H, 10.36.

(1α,2α,3aα,6aα)-(±)-1-Acetyloctahydro-1,5,5-trimethyl-2,3a-pentalenedicarboxaldehyde (22). A solution of **21** (250 mg, 1.14 mmol) in 12 mL of dry CH_2Cl_2 was cooled to −78 °C and treated with a stream of O_3 until the blue color persisted. After the solution was purged of excess ozone with a stream of Ar, the mixture was treated dropwise with dimethyl sulfide (500 μL, 6.84 mmol, 6 equiv) at −78 °C. The reaction was allowed to slowly reach ambient temperature, whereupon it was poured into brine and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine (2×) and dried (Na_2SO_4). After filtration and evaporation, the remaining volatiles were removed under high vacuum to provide 280 mg (99%) of dialdehyde **22** as a slightly yellow foamy residue. This material was used immediately without further purification: R_f = 0.29 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 0.79 (s, 3 H), 1.04 (s, 3 H) 1.37 (s, 3 H), 2.15 (s, 3 H), 0.93–1.67 (m, 4 H), 1.80 (dd, 1 H, J = 7.94, 13.55 Hz), 2.09–2.5 (m, 2 H), 3.19 (dd, 1 H, J = 7.52, 11.29 Hz), 9.45 (s, 1 H), 9.81 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.01, 15.59, 19.01, 24.95, 25.8, 28.39, 28.82, 29.9, 35.68, 36.21, 39.85, 40.33, 43.69, 44.93, 50.56, 50.93, 52.94, 55.37, 55.79, 62.47, 64.31, 105.95, 201.73, 202.24, 203.14.

(1α,2α,3aα,6aα)-(±)-1-Acetyloctahydro-1,5,5-trimethyl-2,3a-pentalenedicarboxylic Acid (24). To a solution of **22** (570 mg, 2.3 mmol) in 25 mL of reagent grade acetone was added Jones reagent (1.3 mL, ca. 2.7 M) dropwise at 0 °C. The resulting suspension was stirred for 1 h at 0 °C and then treated dropwise with isopropyl alcohol until the dark blue-green color persisted. Enough water to dissolve the solids was added and the mixture

was transferred to a separatory funnel and extracted with ether (4×). The combined organic layers were washed with brine (2×) and dried ($MgSO_4$). Filtration and evaporation provided 580 mg (89%) of **24** as a white solid (mp = 156–157 °C). This material was used without further purification: R_f = 0.13 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 1.01 (s, 3 H), 1.14 (s, 3 H), 1.2 (s, 3 H), 1.60 (s, 3 H), 0.95–1.36 (m, 2 H), 1.72–2.41 (m, 4 H), 2.81 (dd, 1 H, J = 3.14, 11.89 Hz), 3.28 (dd, 1 H, J = 5.96, 12.07 Hz); IR ($CDCl_3$) 3040–2450 br, 2950 s, 2860 m, 1790 s, 1760 s, 1710 s, 1440 w, 1395 w, 1290 s, 1260 s.

(1α,3aβ,5aα,8aβ,8bβ)-Hexahydro-3a,7,7,8b-tetramethyl-5*H*-1,5a-methanocyclopenta[*d*]furo[2,3-*b*]pyran-2,5(1*H*)-dione (25). To a solution of **24** (280 mg, 1.0 mmol) and Ac_2O (510 μL, 5.4 mmol, 5.4 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added 70% $HClO_4$ (1.2 μL, 0.01 mmol, 0.01 equiv). After 1 h at 0 °C, the reaction was washed with saturated aqueous $NaHCO_3$ (2×) and with brine (1×) and dried ($MgSO_4$). Filtration and evaporation yielded an off-white solid, which was recrystallized at −20 °C from ether/hexane to provide 225 mg (85%) of the analytically pure bis-lactone **25** as white needles (mp = 183 °C): R_f = 0.36 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 1.06 (s, 3 H), 1.19 (s, 3 H) 1.25 (s, 3 H), 1.32 (t, 1 H, $^2J = {}^3J$ = 12.55 Hz, $C_8H\beta$), 1.65 (s, 3 H), 1.66 (dd, 1 H, ^3J = 6.45, 12.69 Hz, $C_{8a}H$), 1.79 (d, 1 H, ^2J = 14.21 Hz, $C_6H\beta$), 2.06 (d, 1 H, ^2J = 14.21 Hz, $C_6H\alpha$), 2.20 (dd, 1 H, ^2J = 15.0 Hz, ^3J = 3.35 Hz, $C_9H\beta$), 2.36 (dd, 1 H, ^2J = 12.88 Hz, ^3J = 6.45 Hz, $C_8H\alpha$), 2.42 (dd, 1 H, ^2J = 15.0 Hz, ^3J = 12.0 Hz, $C_9H\alpha$), 2.85 (dd, 1 H, ^3J = 3.35, 12.0 Hz, C_1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 17.20 (q), 20.75 (q), 31.67 (q), 32.26 (q), 37.52 (t), 40.40 (s), 41.93 (t), 45.03 (t), 47.99 (d), 51.79 (d), 56.30 (s), 56.89 (s), 113.94 (s), 172.70 (s), 175.83 (s); IR ($CDCl_3$) 2900 m, 2860 w, 1790 s, 1760 s, 1280 m, 1060 m, 900 m. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.64. Found: C, 67.97; H, 7.58.

Ethyl (*E*)-6,6-Diethoxy-2,5,5-trimethyl-2-hexenoate. To a solution of **19** (25.0 g, 132.8 mmol) in dry benzene (1.3 L) was added neat in one portion (carbethoxyethylidene)triphenylphosphorane (51.02 g, 140.8 mmol, 1.06 equiv). The resultant yellow mixture was stirred for 10 min at ambient temperature to dissolve the solids and then heated at reflux for 6 h. The mixture was cooled to ambient temperature and the benzene removed by rotary evaporation, leaving a waxy residue. The solid was triturated with 400 mL of cold pentane and let stand for 30 min at 0 °C. The suspension was filtered, and the cake was washed with an additional 200 mL of cold pentane. The combined filtrates were evaporated and distillation of the residue at reduced pressure (85 °C at 0.05 mm) provided 29.3 g (81%) of analytically pure α,β-unsaturated ester as a colorless, sweet-smelling oil: R_f = 0.63 (silica, 1:1 hexane/ether);^1H NMR ($CDCl_3$, 300 MHz) 0.89 (s, 3 H), 1.18 (t, 6 H, ^3J = 7.0 Hz), 1.26 (t, 3 H, ^3J = 7.12 Hz), 1.80 (br s, 3 H, C_2Me), 2.17 (d, 2 H, ^3J = 7.81 Hz, C_4Hs), 3.45 (q, 2 H, ^3J = 7.00 Hz), 3.77 (q, 2 H, ^3J = 7.0 Hz), 3.97 (s, 1 H, C_6H), 4.15 (q, 2 H, ^3J = 7.12 Hz), 6.85 (t, 1 H, C_3H, ^3J = 7.81 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 12.44, 14.26, 15.38, 22.3, 36.55, 40.28, 60.32, 66.06, 110.24, 128.86, 139.33, 168.29; IR ($CDCl_3$) 3000 s, 2960 s, 2920 s, 2900 s, 1710 s, 1650 m, 1480 m, 1380 m, 1260 s, 1120 s, 1060 s. Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.38. Found: C, 66.24; H, 10.21.

(*E*)-1,1-Diethoxy-2,2,5-trimethyl-4-hexen-6-ol. To a suspension of $LiAlH_4$ (2.37g, 62.4 mmol) in dry ether (650 mL) cooled to 0 °C was added slowly by means of a dropping funnel a solution of the preceding ester (17.0 g, 62.4 mmol) in dry ether (450 mL) over 5.5 h. After the addition was complete, the reaction was stirred for an additional 15 min at 0 °C and then quenched at the same temperature by the careful sequential addition of H_2O (2.37 mL), 10% NaOH (2.37 mL), and H_2O (4.74 mL). The mixture was stirred overnight at ambient temperature and filtered through Celite. The filter cake was washed with ether (300 mL) and the combined filtrates were dried over a 50/50 mixture of $MgSO_4$ and K_2CO_3. Filtration and evaporation provided 14.23 g (99%) of analytically pure allylic alcohol as the sole product: R_f = 0.23 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 0.86 (s, 6 H), 1.19 (t, 6 H, ^3J = 7.02 Hz), 1.64 (br s, 3 H, C_5Me), 2.04 (d, 2 H, ^3J = 7.62 Hz, C_3Hs), 3.48 (q, 2 H, ^3J = 7.02 Hz), 3.80 (q, 2 H, ^3J = 7.02 Hz), 3.97 (s, 1 H, C_1H), 4.00 (br s, 2 H, C_6Hs), 5.46 (t, 1 H, ^3J = 7.62 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 13.70, 15.33, 21.89, 35.42, 39.98, 65.91, 68.98, 110.38, 122.32, 136.18; IR ($CDCl_3$) 3600 m, 3450 br w, 2980 s, 2930 s, 2860 s, 1460 m, 1380 m, 1110 s, 1060 s. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.77; H, 11.40. Found: C, 67.99; H, 11.14.

(*E*)-6-Hydroxy-2,2,5-trimethyl-4-hexenal (34). To a solution of the preceding alcohol (51.4 g, 223.1 mmol) in THF (65 mL) was added at room temperature 10% HCl (65 mL). The biphasic mixture was stirred for 25 min at ambient temperature until a homogeneous solution resulted. The reaction was quenched with saturated aqueous $NaHCO_3$ until gas evolution ceased. The mixture was diluted with a small amount of H_2O and extracted with ether (3×). The combined organic phases were washed with brine (2×) and dried ($MgSO_4/K_2CO_3$). Filtration and evaporation provided 35 g (100%) of analytically pure aldehyde **34** as a colorless oil: R_f = 0.18 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 1.04 (s, 6 H), 1.63 (br s, 3 H, C_5Me), 2.19 (d, 2 H, ^3J = 7.62 Hz, C_3Hs), 3.97 (br s, 2 H, C_6Hs), 5.33 (t, 1 H, ^3J = 7.62 Hz, C_4H), 9.45 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 13.73, 21.10, 34.80, 46.44, 68.40, 119.67, 137.91, 206.20; IR ($CDCl_3$) 3600 m, 3450 m, 2950 s, 2925 s, 2860 s, 2700 m, 1720 s, 1460 m, 1380 m, 1000 s. Anal. Calcd for $C_9H_{16}O_2$: C, 69.18; H, 10.34. Found: C, 69.52; H, 10.31.

6-(2,4-Cyclopentadien-1-ylidene)-2,5,5-trimethyl-2-hexen-1-ol (17d). To a rapidly stirred suspension of **34** (19.87 g, 127.2 mmol), freshly distilled cyclopentadiene (26 mL, 318.7 mmol, 2.5 equiv), and anhydrous Na_2SO_4 (9.0 g, 63.6 mmol, 0.50 equiv) in reagent-grade MeOH (440 mL) was added dropwise pyrrolidine (16 mL, 191.5 mmol, 1.5 equiv). The reaction, which became yellow within 5 min, was stirred at ambient temperature for 24–36 h. When complete, the very dark reaction was quenched by the addition of AcOH (12 mL, 203.2 mmol, 1.06 equiv based on pyrrolidine) and stirred for another 15 min. In a separatory funnel, the mixture was diluted with H_2O (75 mL) and ether (350 mL). After equilibration, the layers were separated, and the aqueous phase was extracted with ether (two–three 350-mL portions) until the extracts were colorless. The combined organic fractions were washed with brine (two–three 100-mL portions) until the washes were colorless, then simultaneously decolorized and dried over Norit neutral charcoal, $MgSO_4$, and K_2CO_3. After standing for 1 h, filtration through Celite and evaporation provided 25.7 g (99%) of **17d** as a bright yellow-orange oil. This material was used without further purification: R_f = 0.28 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 1.27 (s, 6 H), 1.63 (br s, 3 H, C_2Me), 2.28 (d, 2 H, ^3J = 7.44 Hz, C_4Hs), 3.96 (br s, 2 H, C_1Hs), 5.41 (t, 1 H, ^3J = 7.44 Hz, C_3H), 6.13 (m, 1 H), 6.37 (m, 2 H), 6.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 13.84, 28.52, 31.01, 39.69, 41.53, 68.61, 119.97, 121.71, 128.41, 128.52, 134.21, 137.15, 143.15, 152.60; IR ($CDCl_3$) 3600 w, 3400 br m, 2925 s, 2860 s, 1630 m, 1440 m, 1360 m, 1100 s. Anal. Calcd for $C_{14}H_{20}O$: C, 82.23; H, 9.89. Found: C, 82.00; H, 9.91.

6-(1,3-Cyclopentadienyl)-2,5,5-trimethyl-2(*E*)-hexen-1-ol (16d). To a well-stirred suspension of $LiAlH_4$ (4.91g, 129.3 mmol, 1.05 molar equiv) in dry THF (375 mL) at ambient temperature was added slowly by means of a dropping funnel a solution of **17d** (25.27 g, 123.7 mmol) in dry THF (375 mL) over 5 h. After completion of the addition, the mixture was stirred for 1 h at ambient temperature and then quenched by the careful sequential addition of H_2O (4.91 mL), 10% NaOH (4.91 mL), and H_2O (9.82 mL). The thick mixture was stirred overnight and filtered through Celite, and the filter cake was washed with ether (200 mL). The combined filtrates were dried ($MgSO_4/K_2CO_3$), which after filtration and evaporation provided 23.86 g (93%) of cyclopentadiene **16d** as a slightly yellow oil. This material was used immediately without further purification: R_f = 0.33 (1:1 hexane/ether); ^1H NMR ($CDCl_3$, 300 MHz) 0.84 (s, 6 H), 1.62 (br s, 3 H, C_2Me), 1.93 (d, 2 H, ^3J = 7.57 Hz, C_4Hs), 2.25 and 2.29 (br s, 2 H, C_6Hs, different isomers), 2.91 (m, 2 H), 4.00 (br s, 2H, C_1Hs), 5.50 (t, 1 H, ^3J = 7.57 Hz, C_3H), 5.77–6.43 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 13.87, 26.92, 27.08, 39.79, 39.90, 41.19, 42.07, 42.71, 45.91, 69.08, 122.96, 129.53, 129.67, 132.44, 136.13, 136.69, 144.04; IR ($CDCl_3$) 3600 m, 3450 br m, 2900 s, 1440 m, 1360 m, 980 m.

(3aβ,6β,7α,7aα)-(±)-1,2,3,6,7,7a-Hexahydro-2,2,7-trimethyl-3a,6-methano-3a*H*-indene-7-methanol (35). A solution of **16d** (5.2 g, 25.2 mmol) in dry mesitylene (500 mL) was heated at reflux for 24 h. After cooling to ambient temperature, the mesitylene was distilled off pot-to-pot under high vacuum at ambient temperature. The orange residue was purified by flash chromatography on deactivated silica with 5:1 hexane/ether, providing 3.65 g (70%) of **35** as a slightly yellow residue, which

hardened to a waxy solid on standing. A sample for analysis was prepared by sublimation under high vacuum (35 °C at 0.02 mm), giving white feathers (mp (sealed tube) = 65 °C). This material could be used without purification in the next reaction without any measurable difference in yield for the two steps: R_f = 0.29 (1:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.99 (s, 3 H), 1.08 (s, 3 H), 1.13 (s, 3 H), 1.23–1.51 (m, 5 H), 1.66 (m, 2 H), 2.45 (br s, 1 H, C_6H), 3.18 (d, 1 H, ^2J = 10.50 Hz), 3.25 (d, 1 H, ^2J = 10.50 Hz), 5.99 (dd, 1 H, ^3J = 2.93, 5.62 Hz, C_5H), 6.10 (d, 1 H, ^3J = 5.62 Hz, C_4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 20.91, 26.89, 31.03, 31.65, 42.13, 42.98, 43.13, 45.09, 51.28, 51.92, 52.88, 63.29, 71.89, 134.02, 142.06; IR ($CDCl_3$) 3650 m, 3400 br w, 3050 w, 2950 s, 2925 s, 2860 s, 1450 m, 1390 m, 1010 m. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.77. Found: C, 81.42; H, 10.57.

(3aβ,6β,7α,7aα)-(±)-1,2,3,6,7,7a-Hexahydro-2,2,7-trimethyl-3a,6-methano-3a*H*-indene-7-carboxylic Acid (33). A solution of **35** (5.81 g, 28.1 mmol) in reagent-grade acetone (280 mL) was treated at 0 °C with Jones reagent (21 mL of ca. 2.7 M, 2 equiv). After completion of the addition, the mixture was stirred at 0 °C for 1 h. The excess Jones reagent was consumed with isopropyl alcohol and the resulting solids were dissolved with H_2O. The blue-green solution was extracted with ether (3×). The combined organic fractions were washed with brine (2×) and brine ($MgSO_4$). Filtration and evaporation gave the acid **33** as a white solid. Recrystallization from ether/hexane provided 6.0 g (97%) of pure material (mp = 156 °C). On small-scale (<1.0 g) runs of this reaction, pure material was conveniently obtained by gravity chromatography on Silicar CC-4 Special silica gel with 3:1 hexane/ether. In runs where crude **35** was used in this step, yields of 60–65% were achieved over two steps from **16d**. A sample for analysis was prepared by converting a small portion of **33** to its methyl ester derivative (vide infra): R_f = 0.35 (1:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 1.04 (s, 3 H), 1.09 (s, 3 H) 1.26 (t, 1 H, ^2J = ^3J = 12.45 Hz, $C_1H\beta$), 1.30 (dd, 1 H, ^2J = 8.79 Hz, ^4J = 1.77 Hz, C_8Hsyn), 1.37 (s, 3 H), 1.49 (d, 1 H, ^2J = 13.80 Hz, $C_3H\beta$), 1.54 (dd, 1 H, ^2J = 6.87, 12.21 Hz, $C_1H\alpha$), 1.64 (d, 1 H, ^2J = 8.79 Hz, C_8Hanti), 1.71 (d, 1 H, ^2J = 13.80 Hz, $C_3H\alpha$), 2.41 (ddd, 1 H, ^2J = 6.87, 12.60 Hz, ^4J = 1.77 Hz, $C_{7a}H$), 2.75 (br s, 1 H, C_6H), 6.02 (dd, 1 H, ^2J = 2.93, 5.61 Hz, C_5H), 6.16 (d, 1 H, ^2J = 5.61 Hz, C_4H); ^{13}C NMR ($CDCl_3$, 75 MHz) 22.51, 31.09, 31.76, 42.49, 42.61, 42.79, 50.85, 51.15, 51.38, 54.08, 62.95, 134.53, 143.29, 183.62; IR ($CDCl_3$) 3200–2400 br, 2950 s, 2925 m, 2860 m, 1740 m, 1700 s, 1240 w.

Methyl (3aβ,6β,7α,7aα)-(±)-1,2,3,6,7,7a-Hexahydro-2,2,7-trimethyl-3a,6-methano-3a*H*-indene-7-carboxylate (Methyl Ester of 33). To a suspension of **32** (105.7 mg, 0.48 mmol) and trimethyloxonium tetrafluoroborate (78.1 mg, 0.53 mmol, 1.1 equiv) in CH_2Cl_2 (7.5 mL) was added diisopropylethylamine (84 μL, 0.48 mmol, 1.0 equiv). The resulting slightly yellow mixture was stirred at ambient temperature for 24 h, then washed with 10% HCl (2×), saturated aqueous $NaHCO_3$ (2×), and brine (1×), and dried ($MgSO_4$). Filtration and evaporation, followed by gravity chromatography on Silicar CC-4 Special silica with 10:1 hexane/ether, provided 105.8 mg (94%) of analytically pure methyl ester as an oil: R_f = 0.40 (5:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 1.04 (s, 3 H), 1.08 (s, 3 H), 1.22 (dd, 1 H, ^4J = 1.91 Hz, ^2J = 6.60 Hz), 1.25 (t, 1 H, ^2J = ^3J = 12.45 Hz), 1.30 (s, 3 H), 1.48 (d, 1 H, ^2J = 13.80 Hz), 1.55 (dd, 1 H, ^2J = 12.24 Hz, ^3J = 6.86 Hz), 1.70 (d, 1 H, ^2J = 13.80 Hz), 2.43 (ddd, 1 H, ^3J = 6.86, 12.65 Hz, ^4J = 1.91 Hz), 2.73 (br s, 1 H), 3.58 (s, 3 H), 5.92 (dd, 1 H, ^3J = 2.93, 5.61 Hz), 6.12 (d, 1 H, ^3J = 5.61 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 22.48, 31.14, 31.81, 42.41, 42.65, 42.84, 50.73, 51.31, 51.50, 51.60, 54.19, 62.91, 134.41, 143.18, 178.49; IR ($CDCl_3$) 2950 s, 2925 s, 2860 m, 1715 s, 1445 m, 1245 m, 1200 m, 1110 m, 890 s. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.81. Found: C, 76.66; H, 9.85.

(3aβ,3bα,6aα,7aβ)-(±)-1-Hydroxyoctahydro-3a,5,5-trimethyl-3-oxopentaleno[1,2-*c*]furan-6a(1*H*)-carboxaldehyde (36). A solution of **33** (1.73 g, 7.8 mmol) in CH_2Cl_2 (80 mL) was cooled thoroughly to −78 °C and treated with a stream of O_3 until the blue color persisted. After the reaction was purged of excess ozone with a stream of Ar, the mixture was treated dropwise with dimethyl sulfide (3.5 mL, 47.0 mmol, 6 equiv) at −78 °C. The reaction was allowed to slowly reach ambient temperature, whereupon it was poured into brine and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were washed with brine (2×) and then dried ($MgSO_4$). After filtration and evaporation, the remaining volatiles were removed under high vacuum to provide 1.95 g (99%) of essentially pure **36** as a colorless residue, which crystallized on standing. This material was used immediately without further purification: R_f = 0.04 (1:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.98 (s, 3 H), 1.06 (s, 3 H), 1.13 (s, 3 H), 1.21 (s, 3 H), 1.37 (s, 3 H), 1.18–1.71 (m, 9 H), 1.87–1.99 (m, 2 H), 2.37 (dd, 1 H, J = 4.88, 14.83 Hz), 2.42–2.60 (m, 2 H), 3.05 (dd, 1 H, J = 6.96, 12.15 Hz), 3.16 (t, 1 H, J = 9.80 Hz), 5.21 (s, 1 H), 5.62 (s, 1 H), 5.69 (d, 1 H, J = 7.16 Hz), 6.03 (d, 1 H, J = 6.27 Hz), 9.35 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 17.07, 20.32, 28.46, 29.14, 30.08, 30.42, 31.06, 33.97, 40.20, 40.98, 41.06, 42.66, 44.16, 47.11, 48.05, 48.38, 49.29, 50.06, 51.78, 54.38, 56.83, 65.94, 98.47, 100.64, 182.23, 202.02; IR ($CDCl_3$) 3600 w, 2950 m, 2860 w, 1770 s, 1715 m, 1450 w, 1380 w, 1090 w.

(3aβ,3bα,6aα,7aβ)-(±)-1-(Acetyloxy)octahydro-3a,5,5-trimethyl-3-oxopentaleno[1,2-*c*]furan-6a(1*H*)-carboxaldehyde (37). To a solution of **36** (250 mg, 0.99 mmol) in dry CH_2Cl_2 (10 mL) was added in sequence at ambient temperature DMAP (24.7 mg, 0.20 mmol, 0.2 equiv), Et_3N (210 μL, 1.49 mmol, 1.5 equiv), and Ac_2O (120 μL, 1.29 mmol, 1.3 equiv). After 4 h, the mixture was poured into cold saturated aqueous $NaHCO_3$ and shaken vigorously. The layers were separated and the aqueous phase was extracted with one portion of CH_2Cl_2. The combined organic fractions were washed with brine (2×) and dried (Na_2SO_4). Filtration and evaporation provided 258.4 mg (90%) of analytically pure **37** as a white solid: R_f = 0.52 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.85 (s, 3 H), 0.96 (s, 3 H), 1.07 (s, 3 H), 1.11 (s, 3 H), 1.27 (s, 3 H), 1.33 (s, 3 H), 1.13–1.71 (m, 7 H), 2.05 (s, 3 H), 2.10 (s, 3 H), 1.91–2.16 (m, 3 H), 2.44 (dd, 1 H, J = 4.98, 14.86 Hz), 2.50 (dd, 1 H, J = 7.67, 15.24 Hz), 2.62, (dd, 1 H, J = 4.98, 10.84 Hz), 2.87 (m, 1 H), 3.04 (dd, 1 H, J = 6.92, 12.24 Hz), 3.18 (dd, 1 H, J = 7.32, 11.72 Hz), 6.32 (s, 1 H), 6.54 (d, 1 H, J = 4.94 Hz), 9.33 (s, 1 H), 9.42 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 18.21, 19.96, 20.67, 20.81, 27.03, 28.38, 29.30, 30.02, 33.14, 35.28, 36.83, 40.72, 41.01, 43.76, 44.20, 48.40, 49.24, 49.30, 50.54, 52.54, 52.91, 54.40, 60.28, 64.71, 94.15, 98.26, 168.75, 169.01, 178.04, 180.40, 200.87, 201.12; IR ($CDCl_3$) 2960 s, 2870 m, 1790 s, 1720 s, 1460 m, 1370 m, 1220 s, 1185 s, 1120 s, 1070 s, 980 s. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.28; H, 7.55. Found: C, 65.02; H, 7.57.

(3aβ,3bα,6aα,7aβ)-(±)-1-(Acetyloxy)octahydro-3a,5,5-trimethyl-3-oxopentaleno[1,2-*c*]furan-6a(1*H*)-carboxlyic Acid (31). To a solution of **37** (4.17 g, 14.2 mmol) in reagent-grade acetone (140 mL) was added dropwise Jones reagent (5 mL) at ambient temperature. The reaction mixture, which became slightly warm, was stirred for 45 min at ambient temperature. The excess Jones reagent was consumed with isopropyl alcohol and the resulting heavy blue solids were dissolved by the addition of H_2O. The mixture was then extracted with CH_2Cl_2 (3×). The combined organic fractions were washed with brine (2×) and dried ($MgSO_4$). Filtration and evaporation provided 4.21g (95%) of essentially pure acid **31** as a white solid (mp = 142–148 °C). A sample for analysis was prepared by converting a small portion of the acid to its methyl ester derivative (vide infra). In general, this material was used without further purification: R_f = 0.24 and 0.32 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.98 (s, 3 H), 1.06 (s, 3 H), 1.09 (s, 3 H), 1.12 (s, 3 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 1.27–1.42 (m, 1 H), 1.53 (d, 1 H, J = 13.86 Hz) 1.60 (d, 1 H, J = 13.68 Hz), 1.72 (dd, 1 H, J = 7.23, 11.38 Hz), 2.10 (s, 3 H), 2.14 (s, 3 H), 2.22 (d, 1 H, J = 13.57 Hz), 2.62 (m, 1 H), 2.88 (dt, 1 H, J = 6.12, 9.26 Hz), 3.37 (dd, 1 H, J = 7.08, 12.45 Hz), 3.53 (dd, 1 H, J = 7.49, 11.81 Hz), 6.32 (s, 1 H), 6.57 (d, 1 H, J = 5.73 Hz); IR ($CDCl_3$) 3500–2400 br, 2970 s, 2870 w, 1790 s, 1760 s, 1700 s, 1460 w, 1385 w, 1370 w, 1265 s, 1220 s, 1200 s, 1180 s.

Methyl (3aβ,3bα,6aα,7aβ)-(±)-1-(Acetyloxy)octahydro-3a,5,5-trimethyl-3-oxopentaleno[12-*c*]furan-6a(1*H*)-carboxylate (Methyl Ester of 31). To a well-stirred suspension of **31** (100.0 mg, 0.32 mmol) in dry ether (3.5 mL) at 0 °C was added dropwise via a fire-polished pipet a solution of CH_2N_2 in ether until the yellow color persisted. The mixture was stirred overnight with warming to ambient temperature. Evaporation of the volatiles and gravity chromatography on Silicar CC-4 Special silica with 10:1 hexane/EtOAc provided 89.9 mg (90%) of the methyl ester as a white solid. This material did not give a satisfactory combustion analysis, but its molecular weight was

confirmed by GC-MS: R_f = 0.22 and 0.28 (1:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.97 (s, 3 H), 1.05 (s, 3 H), 1.19–1.31 (m, 2 H), 1.50 (d, 1 H, J = 13.67 Hz), 1.63 (dd, 1 H, J = 7.05, 12.24 Hz), 2.04 (s, 3 H), 2.08 (s, 3 H), 2.08 (d, 1 H, J = 13.56 Hz), 2.49–2.58 (m, 2 H), 3.23 (dd, 1 H, J = 6.87, 12.43 Hz), 3.59 (s, 3 H), 3.61 (s, 3 H), 6.26 (s, 1 H), 6.50 (d, 1 H, J = 5.86 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 20.86, 22.56, 31.49, 40.57, 42.15, 51.23, 52.34, 52.58, 53.13, 57.03, 60.39, 93.87, 98.56, 168.88, 176.68, 180.73; mass spectrum (CI, NH_3) 344 (M + 2 + NH_3, 0.3), 343 (M + 1 + NH_3, 0.20), 342 (M + NH_3, 100), 300 (0.09), 265 (0.3) 255 (0.03), 220 (0.05), 194 (0.02), 149.15 (0.04), 126 (0.03); IR ($CDCl_3$) 2960 s, 2940 s, 2870 m, 1790 s, 1760 s, 1730 s, 1455 m, 1435 m, 1380 m, 1370 m, 1260 s, 1230 s, 1210 s, 1170 s, 1100 s, 1070 s, 1000 s.

(3aβ,3bα,6aα,7aβ)-(±)-1-(Acetyloxy)octahydro-3a,5,5-trimethyl-3-oxopentaleno[1,2-*c*]furan (30). To a solution of **31** (3.11 g, 10.0 mmol) and dry DMF (10 microdrops) in dry benzene (50 mL) was added slowly dropwise oxalyl chloride (5.02 mL, 57.5 mmol, 5.75 equiv). The reaction was stirred at ambient temperature for 2 h, evaporated to dryness, redissolved in dry benzene (50 mL), and evaporated to dryness once again to give crude acid chloride, which was used immediately. In a separate flask, equipped with a combined condenser/analytical still head, 2-mercaptopyridine *N*-oxide sodium salt (1.99 g, 12.0 mmol, 1.2 equiv, 90% pure) and DMAP (120 mg, 1.0 mmol, 0.10 equiv) were suspended in dry toluene (100 mL). The suspension was brought to reflux and 5 mL of azeotrope were removed through the still head. The still head was then replaced with an efficient reflux condenser and *tert*-butyl mercaptan (5.0 mL, 44.5 mmol, 4.5 equiv) was added to the refluxing mixture. The acid chloride, as a solution in dry toluene (50 mL), was added via a dropping funnel at such a rate as to not slow the rate of reflux. When the addition was complete, the reaction was heated another 45 min and then cooled to ambient temperature. The resulting greenish suspension was diluted with ether, washed with H_2O (5×) and with brine (2×), and dried ($MgSO_4$). Filtration, evaporation, and immediate flash chromatography on deactivated silica with a 20:1 to 10:1 hexane/EtOAc gradient provided 2.19 g (82%) of analytically pure **30** as a white solid (mp = 104–114 °C): R_f = 0.43 and 0.46 (1:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.92 (s, 3 H) 1.07 (s, 3 H) 1.17 (dd, 1 H, ^3J = 5.16 Hz, ^2J = 13.17 Hz, $C_6H\beta$), 1.23 (t, 1 H, ^2J = ^3J = 12.01 Hz, $C_4H\beta$), 1.35 (s, 3 H), 1.50 (ddd, 1 H, ^4J = 1.03 Hz, ^3J = 7.40 Hz, ^2J = 12.09 Hz, $C_4H\alpha$), 1.68 (ddd, 1 H, ^4J = 1.03 Hz, ^3J = 8.18 Hz, ^2J = 13.17 Hz, $C_6H\alpha$), 1.85 (t, 2 H, ^2J = ^3J = ^3J = 8.06 Hz, $C_7H\alpha,\beta$), 2.50 (m, 1 H, $C_{6a}H$), 2.53 (t, 1 H, ^3J = ^3J = 7.81 Hz, $C_{7a}H$), 2.80 (dt, 1 H, ^3J = 7.40, 11.69 Hz, $C_{3b}H$), 6.23 (s, 1 H, C_1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 19.61 (q), 20.96 (q), 28.55 (q), 30.52 (q), 37.65 (t), 40.73 (s), 42.44 (d), 42.95 (t), 47.62 (t), 50.79 (d), 52.57 (d), 53.10 (s), 98.21 (d), 169.12 (s), 181.97 (s); IR ($CDCl_3$) 2900 m, 2870 w, 1790 s, 1750 s, 1220 m, 1200 m, 1000 m, 990 m. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.63; H, 8.34. Found: C, 67.81; H, 8.17.

(3aβ,3bα,6aα,7aβ)-(±)-1-Hydroxyoctahydro-3a,5,5-trimethyl-3-oxopentaleno[1,2-*c*]furan. A suspension of **30** (250 mg, 0.94 mmol) in reagent-grade MeOH (7.5 mL) was stirred for 15–30 min at ambient temperature until homogeneous. To this solution were added in quick succession H_2O (6.0 mL) and Et_3N (1.5 mL) to make a 5:4:1 mixture of MeOH/H_2O/Et_3N. After 1 h at ambient temperature, the MeOH and Et_3N were removed by rotary evaporation. The aqueous residue was extracted with CH_2Cl_2 (3×) and the combined organic fractions were washed with brine (1×) and dried briefly over $MgSO_4$. Filtration and evaporation provided 200.4 mg (95%) of analytically pure hemiacetal as a white solid (mp = 110–113 °C): R_f = 0.22 (1:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.87 (s, 3 H), 1.01 (s, 3 H), 1.08 (dd, 1 H, ^3J = 5.83 Hz, ^2J = 13.16 Hz, $C_6H\beta$), 1.18 (t, 1 H, ^2J = ^3J = 11.90 Hz, $C_4H\beta$), 1.28 (s, 3 H), 1.43 (dd, 1 H, ^3J = 7.42 Hz, ^2J = 12.12 Hz, $C_4H\alpha$), 1.58–1.84 (m, 3 H, $C_6H\alpha$, $C_7H\alpha,\beta$), 2.40–2.47 (m, 2 H, $C_{6a}H$, $C_{7a}H$), 2.79 (dt, 1 H, ^3J = 7.76 Hz, ^2J = 11.64 Hz, $C_{3b}H$), 5.83 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 19.76, 15.30, 36.42, 40.69, 42.17, 42.79, 47.78, 52.11, 52.65, 54.53, 109.52, 183.71; IR ($CDCl_3$) 3600 w, 3550–3100 br w, 2960 s, 2875 m, 1775 s, 1465 m, 1370 m, 1180 m, 1120 m. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.60; H, 9.01. Found: C, 69.80; H, 8.84.

(1α,2α,3aα,6aα)-(±)-1-Acetyloctahydro-1,5,5-trimethyl-2-vinylpentalene (28a). To a suspension of Ph_3PCH_3Br (190 mg, 535 mmol, 1.2 equiv based on KHMDS) in dry THF (4.5 mL) was added dropwise at 0 °C KHMDS in toluene (890 μL, 445 mmol, 5 equiv, a 0.5 M solution). The intensely yellow mixture was stirred at 0 °C for 10 min, then at ambient temperature 20 min. The supernatant was then transferred via syringe to a stirred solution of the preceding hemiacetal (20 mg, 0.089 mmol) in dry THF (5.5 mL) at 0 °C. After 30 min at 0 °C, the reaction was poured into ice-cold 10% HCl and diluted with ether. The aqueous fraction was extracted with ether (2×) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (1×) and with brine (1×) and dried ($MgSO_4$). Filtration, evaporation, and gravity chromatography on Silicar CC-4 silica with 1:1 hexane/ether provided 17.1 mg (86%) of analytically pure acid **28a** as an off-white solid (mp = 73–74 °C dec): R_f = 0.47 (1:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.84 (s, 3 H), 0.98 (s, 3 H), 1.08 (s, 3 H), 0.87–1.36 (m, 4 H), 1.70 (ddd, 1 H, J = 2.46, 8.61, 12.39 Hz), 1.95 (dt, 1 H, J = 9.32, 12.62 Hz), 2.37 (dt, 1 H, J = 7.49, 12.33 Hz), 2.65–2.89 (m, 2 H), 4.96–5.03 (m, 2 H), 5.71 (ddd 1 H, ^3J = 8.22, 10.31, 16.90 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 18.00 (q), 25.96 (q), 28.90 (q), 37.58 (t), 40.52 (s), 40.67 (d), 43.69 (t), 49.88 (t), 50.93 (d), 51.79 (d), 54.80 (s), 116.15 (t), 137.60 (d), 183.13 (s); IR ($CDCl_3$) 3450–2300 br, 3080 m, 2960 s, 2870 m, 1690 s, 1580 m, 1560 m, 1450 m, 1420 m, 1365 m, 1250 m, 1120 m. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.99. Found: C, 75.81; H, 9.84.

(3aβ,3bα,6aα,7aβ)-(±)-1-(Acetyloxy)octahydro-1,3a,5,5-tetramethyl-3-oxopentaleno[1,2-*c*]furan (38b). To a stirred suspension of NaH (6.9 mg, 0.23 mmol, 1.0 equiv, 80% in mineral oil) in dry benzene (1.0 mL) was added **28a** (50.0 mg, 0.23 mmol) in dry benzene (1.3 mL). After 1 h at ambient temperature, the slightly turbid, pale yellow solution was treated dropwise with oxalyl chloride (120 μL, 1.38 mmol, 6.0 equiv). The reaction was stirred for 3 h at ambient temperature, then filtered through Celite, and evaporated. The resulting crude acid chloride was then immediately dissolved in dichloroethane (18 mL) and cooled to 0 °C. To the cold solution was added $SnCl_4$ (40 μL, 0.35 mmol, 1.5 equiv) upon which the reaction turned yellow. After being stirred for 1 h at 0 °C and 6 h at ambient temperature, the reaction was poured into brine and diluted with ether. The mixture was shaken vigorously until the layers separated and the organic fractions were washed alternately with saturated aqueous $NaHCO_3$ and brine until the $NaHCO_3$ washes were no longer milky. The organic fractions were then washed with brine (2×), dried ($MgSO_4$), filtered, and evaporated. Flash chromatography on deactivated silica with 10:1 hexane/ether provided 32 mg (60%) of analytically pure **38b** as a white solid (mp = 65–67 °C): R_f = 0.61 (5:1 benzene/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.90 (s, 3 H), 0.96 (dd, 1 H, ^3J = 9.18 Hz, ^2J = 12.67 Hz, $C_6H\beta$), 1.03 (s, 3 H), 1.14 (t, 1 H, ^2J = ^3J = 11.54 Hz, $C_4H\beta$), 1.19 (s, 3 H), 1.32 (d, 3 H, ^3J = 6.53 Hz, C_1Me), 1.46 (ddd, 1 H, ^3J = 2.70, 8.29 Hz, ^2J = 13.96 Hz, $C_7H\beta$), 1.50 (ddd, 1 H, ^4J = 2.37 Hz, ^3J = 8.00 Hz, ^2J = 12.39 Hz, $C_4H\alpha$), 1.65 (ddd, 1 H, ^4J = 2.37 Hz, ^3J = 8.34 Hz, ^2J = 12.67 Hz, $C_6H\alpha$), 1.74 (dt, 1 H, ^3J = ^3J = 9.65 Hz, ^2J = 13.96 Hz, $C_7H\alpha$), 2.38 (ddd, 1 H, ^3J = 4.43, 8.29, 9.65 Hz, $C_{7a}H$), 2.58 (dquintet, 1 H, 4^3J = 8.90 Hz, ^3J = 2.70 Hz, $C_{6a}H$), 2.96 (dt, 1 H, ^3J = ^3J = 8.41 Hz, ^3J = 11.29 Hz, $C_{3b}H$), 4.64 (dq, 1 H, ^3J = 4.43, 6.53 Hz, C_1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 15.84 (q), 16.93 (q), 26.39 (q), 29.14 (q), 31.02 (t), 40.47 (s), 41.18 (d), 43.29 (t), 48.55 (t), 49.14 (d), 49.57 (d), 56.21 (s), 75.58 (d), 182.98 (s); IR ($CDCl_3$) 2960 s, 2940 s, 2870 m, 1760 s, 1260 m, 1195 m, 1125 m, 810 m. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.99. Found: C, 75.80; H, 9.80.

(1α,2α,3aα,6aα)-(±)-1-Acetyloctahydro-1,5,5-trimethyl-2-vinylpentalene. As previously detailed for the formation of lactone **38b**, **28a** (262.5 mg, 1.18 mmol) was converted to its acid chloride derivative and used immediately as described below.

To a suspension of CuI (674.2 mg, 3.54 mmol) in dry ether (2.5 mL) cooled to 0 °C was added MeLi (5.1 mL, 7.08 mmol, 2.0 equiv, 1.4 M in ether). After the CuI was consumed (15–30 min), the solution was cooled to −78 °C and a solution of the freshly prepared acid chloride in dry ether (7.0 mL) was added. After 1 h at −78 °C, the reaction was allowed to warm slowly to 0 °C. It was then quenched by the addition of saturated NH_4Cl and stirred at ambient temperature for 15 min. The mixture was extracted with ether (3×), and the combined extracts were washed with brine (2×) and dried ($MgSO_4$). Filtration, evaporation, and flash elution of the residue through a short plug of silica with 5:1 hexane/ether provided 256.0 mg (97%) of analytically pure methyl ketone as

an oil: R_f = 0.43 (5:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.85 (s, 3 H), 0.87 (dd, 1 H, J = 9.06, 12.43 Hz), 0.98 (s, 3 H), 1.04 (t, 1 H, J = 11.53 Hz), 1.11 (s, 3 H), 1.25–1.33 (m, 2 H), 1.64–1.74 (m, 1 H), 1.73 (dt, 1 H, J = 12.49, 9.03 Hz), 1.99 (s, 3 H), 2.33 (dt, 1 H, J = 11.63, 7.49 Hz), 2.65 (dquintet, 1 H, J = 1.84, 8.83 Hz), 2.73 (dt, 1 H, J = 11.00, 8.51 Hz), 4.99 (m, 2 H, ^4J = 0.97 Hz, ^3J = 10.45, 17.05 Hz, ^2J = 1.98 Hz), 5.68 (ddd, 1 H, ^3J = 8.37, 10.45, 17.05 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 18.35 (q), 26.04 (q), 28.93(q), 29.03 (q), 37.07 (t), 40.44 (d), 40.70 (s), 43.59 (t), 49.62 (d), 49.81 (t), 52.26 (d), 60.54 (s), 115.91 (t), 138.16 (d), 213.31 (s); IR ($CDCl_3$) 2960 s, 2940 s, 2870 m, 1695 s, 1460 w, 1360 w, 1265 m, 1100 m, 1015 m, 810 m. Anal. Calcd for $C_{15}H_{24}O$: C, 81.74; H, 11.00. Found: C, 81.54; H, 11.23.

(1α,2α,3aα,6aα)-(±)-1-Acetyloctahydro-1,5,5-trimethyl-2-pentalenecarboxaldehyde (29). A solution of the preceding ketone (176 mg, 0.80 mmol) in CH_2Cl_2 (8.0 mL) was treated at −78 °C with a stream of ozone until the blue color persisted. The excess ozone was purged from the solution with a stream of argon, and dimethyl sulfide (350 μL, 4.80 mmol, 6.0 equiv) was added dropwise. The reaction was allowed to warm slowly to ambient temperature, at which point it was diluted with CH_2Cl_2 and washed with brine (3×). The combined brine washes were extracted with CH_2Cl_2 (1×) and the combined organics were dried ($MgSO_4$). Filtration, evaporation, and gravity chromatography on silica with 5:1 hexane/ether provided 142.0 mg (80%) of analytically pure **29** as an oil. On the basis of ^{1}H NMR, this material was judged to exist entirely as a mixture of epimeric aldehyde hydrates because of the absence of an aldehyde resonance, the presence of the signals at 5.0–5.5 ppm, and the doubling of the methyl peaks: R_f = 0.31 (5:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.82–1.04 (m, 2 H), 0.91 (s, 3 H), 1.02 (s, 6 H), 1.10–1.22 (m, 2 H), 1.24 (s, 3 H), 1.29 (s, 3 H), 1.32–1.44 (m, 4 H), 1.69–1.79 (m, 2 H), 1.90–2.04 (m, 4 H), 2.13 (s, 3 H), 2.14 (s, 3 H), 2.58–2.74 (m, 4 H), 4.98 (s, 1 H), 5.04 (s, 1 H), 5.08 (s, 1 H), 5.12 (s, 1 H), 5.33 (d, 1 H, ^3J = 6.60 Hz), 5.39 (d, 1 H, ^3J = 7.25 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 19.63 (q), 20.06 (q), 26.07(q), 26.16 (q), 27.54 (q), 27.80 (q), 28.87 (q), 34.29 (t), 34.53 (t), 40.00 (s), 40.06 (d), 40.49 (d), 43.11 (t), 48.81 (d), 49.68 (t), 51.13 (d), 51.22 (d), 58.54 (s), 59.29 (s), 93.75 (t), 93.91 (t), 104.08 (d), 104.67 (d), 212.47 (s), 212.84 (s); IR ($CDCl_3$) 2960 s, 2900 m, 2775 m, 1700 s, 1470 m, 1380 w, 1375 m, 1360 m, 1115 m, 1080 s, 970 m. Anal. Calcd for $C_{14}H_{22}O_2 \cdot H_2O$: C, 69.9; H, 10.1. Found: C, 70.14; H, 9.99.

(3aα,3bβ,6aβ,7aα)-(±)-Octahydro-3a,5,5-trimethyl-3*H*-cyclopenta[*a*]pentalen-1-en-3-one (39). To a biphasic mixture of 5% aqueous KOH (1.4 mL, 1.2 mmol, 13.0 equiv), THF (2.8 mL), and 40% aqueous n-Bu_4NOH (3 drops) was added a solution of **29** (20 mg, 0.09 mmol) in ether (1.4 mL). The mixture was vigorously stirred and heated at reflux overnight. The reaction was cooled to ambient temperature, poured into H_2O, and extracted with ether (4×). The combined organic fractions were washed with brine (2×) and dried ($MgSO_4$). Filtration, evaporation, and flash chromatography on silica with 5:1 hexane/ether provided 18.0 mg (97%) of essentially pure enone **39** as a slightly yellow solid (mp = 69–70 °C): R_f = 0.24 (5:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.87 (s, 3 H), 1.04 (s, 6 H), 1.22 (dd, 1 H, ^3J = 2.65 Hz, ^2J = 13.48 Hz, $C_6H\beta$), 1.37 (m, 2 H, $C_4H\alpha,\beta$), 1.54 (dd, 1 H, ^3J = 8.13 Hz, ^2J = 13.52 Hz, $C_6H\alpha$), 1.62 (ddd, ^3J = 9.09, 11.48 Hz, ^2J = 13.28 Hz, $C_7H\beta$), 1.71 (ddd, 1 H, ^3J = 2.04, 7.84 Hz, ^2J = 13.28 Hz, $C_7H\alpha$), 2.14 (ddq, 1 H, ^3J = 2.65, 11.48 Hz, 3^3J = 7.80 Hz, $C_{6a}H$), 2.46 (dt, 1 H, 2^3J = 7.63 Hz, ^3J = 11.58 Hz, $C_{3b}H$), 2.89 (dq, 1 H, 2^3J = ^4J = 2.19 Hz, ^3J = 9.09 Hz, $C_{7a}H$), 6.04 (dd, 1 H, ^4J = 1.71 Hz, ^3J = 5.62 Hz, C_2H), 7.41 (dd, 1 H, ^3J = 2.89, 5.62 Hz, C_1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 18.51, 30.26, 31.57, 36.18, 40.46, 42.07, 42.34, 45.47, 50.99, 55.67, 56.41, 131.78, 166.68 (no carbonyl carbon observed due to high dilution); IR ($CDCl_3$) 2960 s, 2870 m, 1695 s, 1590 w.

(3aα,3bβ,6aβ,7aα)-(±)-Decahydro-3a,5,5-trimethyl-3*H*-cyclopenta[*a*]pentalen-3-one (Hirsutene Norketone). A suspension of PtO_2 (8.7 mg, 0.038 mmol, 0.1 equiv) in EtOAc (2.0 mL) was treated with a stream of H_2 until the catalyst turned from brown to black (5–10 min). A solution of **39** (78 mg, 0.38 mmol) in EtOAc (2.0 mL) was added dropwise and the resulting suspension was hydrogenated for 20 min. Excess H_2 was purged from the solution with a stream of Ar. The mixture was then filtered through Celite, the cake was washed with EtOAc, and the combined filtrates were concentrated to provide 78.5 mg (100%) of essentially pure hirsutene norketone as the sole product as a colorless oil. The product was forced to crystallize by supercooling it in dry ice and allowing it to warm to ambient temperature under high vacuum (mp = 41–43 °C; lit.[8p] mp = 44–46 °C). This material was used without further purification.

The mass spectrum, IR spectrum, and ^{1}H NMR spectrum obtained for this compound were identical in all respects with those provided by Professor Dennis Curran: R_f = 0.33 (5:1 hexane/ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.86 (s, 3 H), 0.90 (s, 3 H), 0.95 (dd, 1 H, ^3J = 8.82 Hz, ^2J = 12.49 Hz, $C_6H\beta$), 1.00 (s, 3 H), 1.11 (m, 1 H), 1.30–1.43 (m, 2 H), 1.51–1.72 (m, 3 H), 1.95 (dddd, 1 H, ^3J = 6.30, 8.46, 9.84 Hz, ^2J = 13.15 Hz, $C_1H\beta$), 2.16–2.39 (m, 3 H), 2.47 (dquintet, 1 H, ^3J = 3.39 Hz, 4^3J = 8.91 Hz, $C_{6a}H$), 2.75 (dt, 1 H, 2^3J = 8.59 Hz, ^3J = 10.89 Hz, $C_{3b}H$); mass spectrum (EI, 70 eV) 207 (M + 1, 13), 206 (M^+, 84), 188 (13), 162 (54), 149 (47), 107 (base, 100), 93 (70), 79 (62), 67 (17), 55 (16), 41 (17); IR ($CDCl_3$) 2950 s, 2870 s, 1730 s, 1460 m, 1410 w, 1370 m, 1260 w, 1210 w, 1100 w, 1070 w, 1045 w, 1030 w, 1010 w; exact mass calcd for $C_{14}H_{22}O$ 206.1671, found 206.1675.

(3aα,3bβ,6aβ,7aα)-(±)-Decahydro-2,2,3b-trimethyl-4-methylene-1*H*-cyclopenta[*a*]pentalene (Hirsutene) (11). To a suspension of KH (105 mg, 0.91 mmol, 35% in mineral oil) in dry benzene (2.0 mL) was added dropwise at ambient temperature a solution of *tert*-butyl alcohol (1.06 mL, 11.27 mmol) in dry benzene (2.5 mL). After stirring for 30 min at ambient temperature, Ph_3PCH_3Br (260 mg, 0.73 mmol, 5 equiv) was added neat in one portion, and the resulting intensely yellow mixture was stirred for an additional 30 min. A solution of hirsutene norketone (30 mg, 0.15 mmol) in benzene (0.5 mL) was added and the mixture was brought to reflux. After 5 h, the reaction was cooled, poured into H_2O, and extracted with light petroleum ether (3×). The combined extracts were washed with brine (2×) and dried ($MgSO_4$). Filtration, evaporation, and flash chromatography on silica eluting with petroleum ether provided hirsutene contaminated with traces of mineral oil. PLC on silica impregnated with $AgNO_3$ (applied to the plate as a 12.5% aqueous solution) with petroleum ether provided 28 mg (93%) of pure hirsutene as a colorless oil.

The mass spectrum and ^{1}H NMR spectrum obtained for this compound were identical in all respects with those provided by Professor Dennis Curran: R_f = 0.62 (petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) 0.89 (s, 3 H), 0.93 (s, 3 H), 1.00 (dd, 1 H, ^3J = 7.32 Hz, ^2J = 12.20 Hz, $C_1H\beta$), 1.03 (s, 3 H), 1.20 (m, 2 H), 1.37–1.48 (m, 4 H), 1.61 (ddd, 1 H, J = 2.14, 8.30, 12.53 Hz), 1.71 (ddt, 1 H, J = 6.23, 12.65, 8.95 Hz), 2.13 (dddt, 1 H, ^3J = 2.39, 6.06, 11.06, 8.30 Hz, $C_{7a}H$), 2.44 (dddd, 1 H, J = 2.02, 4.53, 6.41, 13.19 Hz), 2.49–2.63 (m, 2 H), 4.75 (dt, 1 H, ^3J = 2.42 Hz, ^2J = 0.92 Hz), 4.80 (ddd, 1 H, ^3J = 2.06, 3.00 Hz, ^2J = 0.92 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 23.16, 26.76, 29.71, 30.85, 38.57, 40.85, 41.80, 44.23, 48.96, 49.86, 53.36, 55.95, 103.50, 162.87; mass spectrum (EI, 70 eV) 204 (M^+, 4), 108 (3), 94 (base, 100), 79 (32); exact mass calcd for $C_{15}H_{24}$ 204.1878, found 204.1876.

Acknowledgment. We acknowledge financial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank Drs. George Dubay and David Millington of the Duke University Mass Spectrometry Facility for conducting the GC-MS and exact mass analyses, respectively. We also thank Professor Dennis Curran for sending complete spectral data of hirsutene norketone and hirsutene.

Registry No. (±)-**11**, 59433-37-3; (±)-**16c** (isomer 1), 125567-64-8; (±)-**16** (isomer 2), 125567-84-2; **16d** (isomer 1), 125567-61-5; **16d** (isomer 2), 125567-85-3; (±)-**17c**, 125567-65-9; **17d**, 125567-62-6; **18**, 5497-67-6; **18** (diethyl acetal), 96302-18-0; **19**, 125567-66-0; (±)-**20**, 125567-67-1; (±)-**20** (diethyl acetal), 125567-57-9; (±)-**21**, 125567-68-2; (±)-**22**, 125567-69-3; (±)-**24**, 125567-71-7; (±)-**25**, 125567-72-8; (±)-**28a**, 125567-73-9; (±)-**28** (X = Me), 125567-60-4; (±)-**29**, 125567-74-0; (±)-**30** (isomer 1), 125567-75-1; (±)-**30** (isomer 2), 125638-52-0; (±)-**30** (lactol, isomer 1), 125567-59-1; (±)-**30** (lactol, isomer 2), 125638-53-1; (±)-**31** (isomer 1), 125567-76-2; (±)-**31** (isomer 2), 125638-50-8; (±)-**31** (methyl ester, isomer 1), 125567-63-7; (±)-**31** (methyl ester, isomer 2), 125638-51-9; (±)-**33**, 125567-77-3; (±)-**33** (methyl ester),

125567-70-6; **34**, 125567-78-4; **34** (diethyl acetal), 125567-58-0; (±)-**35**, 125567-79-5; (±)-**36** (isomer 1), 125567-80-8; (±)-**36** (isomer 2), 125638-48-4; (±)-**37** (isomer 1), 125567-81-9; (±)-**37** (isomer 2), 125638-49-5; (±)-**38b**, 125567-82-0; (±)-**39**, 125567-83-1; (±)-**39** (dihydro derivative), 59372-73-5; (E)-$(EtO)_2CHCMe_2CH_2CH{=}C(Me)COMe$, 125567-56-8; $(\pm)$-$(EtO)_2P(O)CHMeCOMe$, 117653-52-8; $Ph_3P{=}C(Me)CO_2Et$, 5717-37-3; cyclopentadiene, 542-92-7.

Synthesis of Mercapturic Acid Derivatives of Putative Toxic Metabolites of Bromobenzene[1]

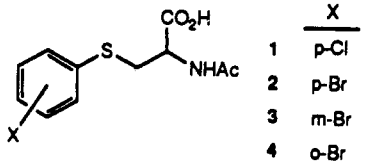
Robert P. Hanzlik,* Paul E. Weller, Jayant Desai, Jiang Zheng, Larry R. Hall, and Donald E. Slaughter

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045-2506

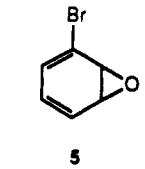
Received July 3, 1989

The synthesis and characterization of nine isomerically defined *S*-arylmercapturic acids of interest in connection with the metabolism of the model hepatotoxin bromobenzene is described. Included are three *S*-(bromophenyl)-, two *S*-(bromohydroxyphenyl)-, and three *S*-(bromodihydroxyphenyl)mercapturic acids of defined substitution pattern. In addition, several related compounds with two or no bromine atoms are described. These syntheses depend on two basic methods, 1,4-addition of various arene thiols to acetamidoacrylic acid or the 1,4-addition of *N*-acetyl-L-cysteine to various benzoquinone derivatives. In addition, we describe a method for efficient conversion of the mercapturic acids to thioanisole derivatives, regioisomers of which can be separated and detected at low levels by capillary gas-liquid chromatography.

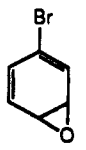
Mercapturic acids are S-substituted derivatives of *N*-acetyl-L-cysteine (e.g., **1**-**4**). They are typically isolated from the urine of animals or humans exposed to electrophilic agents such as epoxides, enones, alkyl halides, etc.



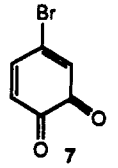
	X
1	p-Cl
2	p-Br
3	m-Br
4	o-Br



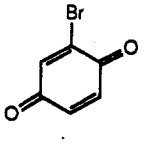
5



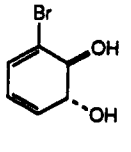
6



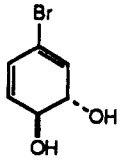
7



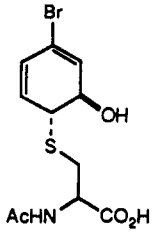
8



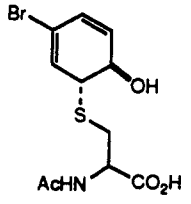
9



10



11



12

Their biosynthesis involves reaction of the electrophile with the sulfhydryl group of glutathione (γ-Glu-Cys-Gly), usually with catalysis by one or more isozymes of glutathione transferase.[2] This is followed by enzymatic hydrolysis of the Glu-Cys and Cys-Gly bonds and N-acetylation.[3] *S*-(*p*-Chlorophenyl)- and *S*-(*p*-bromophenyl)mercapturic acids (**1** and **2**) were first isolated in 1879 from the urine of dogs treated with chloro- or bromobenzene.[4,5] Since then, mercapturic acid metabolites of a great many other drugs and chemicals have been isolated. Contemporary interest in mercapturic acids derives largely from the fact that their excretion implies the previous presence in the animal of an electrophile, many of which have been associated with toxic effects on living cells. With suitably sensitive analytical methods, urinary mercapturic acids can provide an approach to "molecular dosimetry" of workers exposed occupationally to electrophilic compounds or their metabolic precursors. For example, phenylmercapturic acid is found in the urine of workers exposed to benzene.[6]

Our current interest in mercapturic acids stems from a more general interest in the chemical basis for the hepatotoxicity of bromobenzene and certain derivatives of it.[7] Both in vivo and in isolated hepatocytes the toxicity of bromobenzene has been correlated with the covalent binding of one or more of its chemically reactive metabolites to cellular proteins; it is *presumed* that at least *some* of these covalent binding events are deleterious to the cell in which they occur. Both covalent binding and toxicity are enhanced by prior depletion of glutathione.

(1) Financial support for this research was provided by NIH Grant GM-21784. L.R.H. is a NIH Predoctoral Trainee (GM-07775).

(2) Mannervick, B. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1985**, *57*, 357-406.
(3) Jakoby, W. B.; Stevens, J.; Duffell, M. W.; Weisiger, R. A. *Rev. Biochem. Toxicol.* **1984**, *6*, 97-115.
(4) Bauman, E.; Preusse, C. *Chem. Ber.* **1879**, 806-810.
(5) Jaffe, M. *Chem. Ber.* **1879**, 1092-1098.
(6) Jongeneelen, F. J.; Dirven, H. A. A. M.; Leidekkers, C.-M.; Henderson, P. T.; Brouns, R. M. E.; Halm, K. *J. Anal. Toxicol.* **1987**, *11*, 100-104.
(7) Hanzlik, R. P.; Weller, P. E.; Narasimhan, N.; Buben, J. A. *Xenobiotic Metabolism and Disposition*; Kato, R., Estabrook, R. W., Cayen, M. N., Eds.; Taylor & Francis: London, 1989; pp 367-374.

0022-3263/90/1955-2736$02.50/0