Cyclopentanone Synthesis by Intramolecular Carbon-Hydrogen Insertion of Diazo Ketones.[1] A Diterpene-to-Steroid Skeleton Conversion

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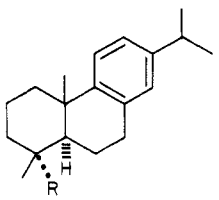
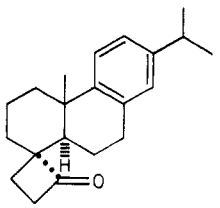
Intramolecular carbon-hydrogen insertion on cupric sulfate assisted decomposition of diazomethyl ketones derived from four 1-methylcycloalkanecarboxylic acids and (hexahydrophenyl)acetic, homopivalic, and enanthic acids is shown to yield mostly cyclopentanones. The yields are appreciable in the conformationally favorable cases, and insertion in the solvent cyclohexane can be avoided by the use of Freon TF as the solvent. The conversion of a pimaradienic diterpene into a 14-iso-16-androstanone derivative shows the power of the new method of cyclopentanone synthesis.

Some time ago an investigation in the diterpene field required homodehydroabietic acid as a starting material. When as a consequence dehydroabietic acid (**1a**) was ex-



1a, R = CO_2H
b, R = $COCHN_2$
c, R = CH_2CO_2Me
d, R = $COCH_2OMe$



2

posed to the traditional Arndt-Eistert synthesis method of homologation, including interaction of diazo ketone **1b** to silver oxide in methanol solution in the Wolff-rearrangement step, there was isolated not only the homologous ester **1c** and some α-methoxy ketone **1d** but also cyclobutanone **2**.[1] The unexpected, last compound was a product of intramolecular carbon-hydrogen insertion in a metal-catalyzed thermal decomposition of a diazomethyl ketone, for which there was little precedent.[7] This observation suggested the new reaction might serve conceivably as a general method of cycloalkanone synthesis, when carried out under more ideal conditions than those of the standard Wolff rearrangement. In order to test this view, we initiated a study of the thermal decomposition of diazomethyl ketones in cyclohexane solution over anhydrous cupric sulfate.

Scheme I

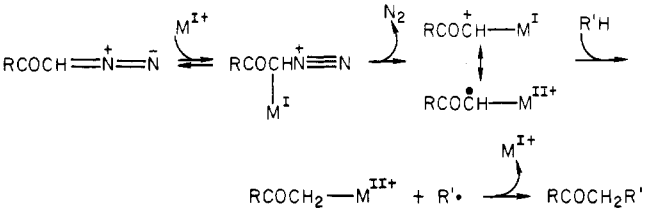
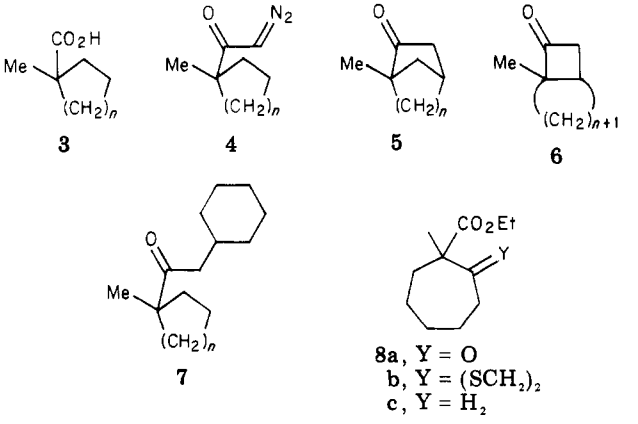


Chart I[a]



3 **4** **5** **6**

7

8a, Y = O
b, Y = $(SCH_2)_2$
c, Y = H_2

[a] For **3-7**: **a**, $n = 4$; **b**, $n = 3$; **c**, $n = 2$; **d**, $n = 1$.

The choice of diazo ketones was predicated on the working hypothesis of Scheme I (vide infra) representing the mechanism of the insertion process (depicted for univalent metal catalysis). An intramolecular variant thereof, constrained by the need for proximity of the two reaction sites, could be expected to favor 1,5 hydrogen shifts similar to those involved in the Barton reaction (the photolytic conversion of nitrites into nitroso alcohols)[8] and the Mihailović reaction (the transformation of alcohols into

(1) For earlier communications see E. Wenkert, B. L. Mylari, L. L. Davis, *J. Am. Chem. Soc.*, **90**, 3870 (1968); R. R. da Silva, M. S. dissertation, Indiana University, 1969.
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(4) Predoctoral fellow, 1962-1966.
(5) Postdoctoral fellow: (a) 1971-1972; (b) summers of 1967 and 1968.
(6) Public Health Service Fellow, 1970-1971.
(7) (a) F. Greuter, J. Kalvoda, and O. Jeger, *Proc. Chem. Soc., London*, 349 (1958); (b) P. T. Lansbury and J. G. Colson, *Chem. Ind. (London)*, 821 (1962); (c) H. O. House, S. G. Boots, and V. K. Jones, *J. Org. Chem.*, **30**, 2519 (1965). For an early intramolecular insertion of an α-diazo ketone, other than a diazomethyl ketone, see: (d) P. Yates and S. Danishefsky, *J. Am. Chem. Soc.*, **84**, 879 (1962); (e) P. Yates and R. J. Crawford, *Ibid.*, 88, 1562 (1966).
(8) R. H. Hesse, *Adv. Free-Radical Chem.*, **3**, 83 (1967); D. H. R. Barton, R. H. Hesse, M. M. Pechet, and L. C. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1159 (1979).

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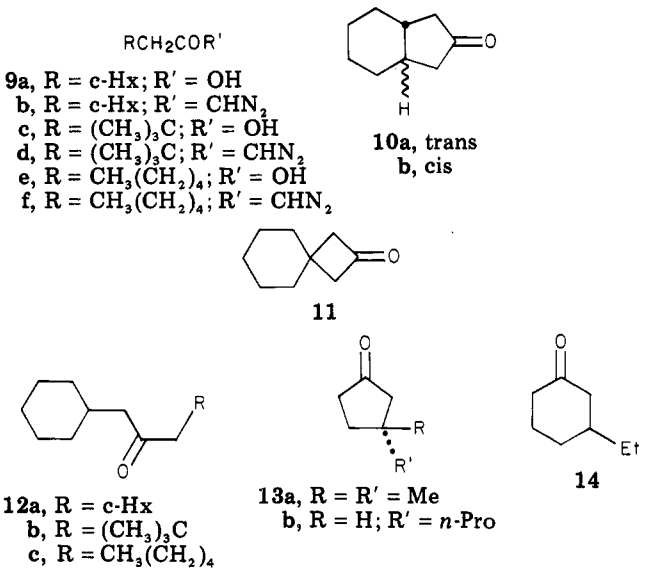
Chart II



tetrahydrofurans on oxidation with lead tetraacetate)[9] and thus to produce predominantly cyclopentanones. Furthermore, the intramolecular reaction was anticipated to proceed best on saturated carbocycles containing an axial diazoacetyl group attachment and an axial hydrogen in a 1,3 relationship to the side chain.

On the basis of the above considerations, diazo ketones **4** (Chart I), constructed from the acids **3** by successive treatments with thionyl chloride and diazomethane, were used as starting materials for the thermal decomposition study. Whereas three of the four 1-methylcycloalkane-1-carboxylic acids were known compounds, 1-methylcycloheptane-1-carboxylic acid (**3a**) had to be synthesized. It was prepared by the thioketalation of keto ester **8a**,[10] desulfurization, and saponification of the resultant saturated ester **8c**.

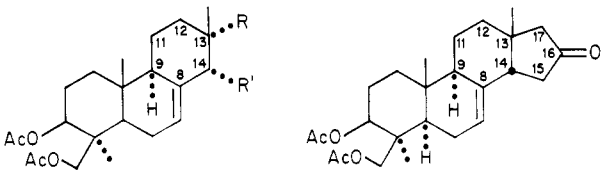
Decomposition of diazo ketones **4** over cupric sulfate in cyclohexane solution produced mixtures of cyclopentanones **5**, cyclobutanones **6**, and solvent-insertion products **7**. Except for the reaction of 1-(diazoacetyl)-1-methylcyclobutane (**4d**), which yielded mostly **7d** and some **5d**, the cyclopentanones **5** were the major products, the cyclopentanone–cyclobutanone ratios being 8–16:1 and the solvent insertion being a minor side reaction. Whereas the yields of cyclopentanones **5a,b** were appreciable (35–70%), those of **5c,d** dropped, reflecting a conformationally determined lowering of the proximity of the two reacting sites in the smaller ring framework.

In an attempt to test the importance of conformation on the intramolecular insertion process, we exposed diazo ketones **9b,d** (Chart II) to cupric sulfate assisted thermolysis. In neither case was the diazo carbon close to a carbon–hydrogen bond in the most favored conformation, although minimal carbon–carbon bond rotation could place the carbenoid unit proximate to more than one hydrogen for cyclopentanone formation. Decomposition of diazo ketone **9b** led to a mixture of ketones **10a,b**, **11**, and **12a**. Unfortunately, the total yield of the bicycles amounted to only 15%, the cyclopentanones (**10a,b**) predominating. Decomposition of diazo ketone **9d** yielded 3,3-dimethylcyclopentanone (**13a**) as the sole intramolecular insertion product, albeit in only 1% yield, and ketone **12b**. In view of the derivation of cyclopentanones from conformationally unfavorable diazo ketones, it was of interest to discover whether cycloalkanones are the products of decomposition of even acyclic, unbranched diazomethyl ketones. When as a consequence 1-diazo-2-octanone (**9f**) was heated over cupric sulfate, there was obtained solvent-insertion product **12c** accompanied by 3-*n*-propylcyclopentanone (**13b**) and 3-ethylcyclohexanone (**14**) in 6% and 1% yields, respectively.

Since solvent insertion represented a serious side reaction plaguing especially those reactions in which the intramolecular process had taken place to only a low extent, cyclohexane was replaced as the solvent by a fluorocarbon, Freon TF. Repetition of the decompositions of diazo ketones **4d** and **9b,d,f**, all low-yielding cyclopentanone-forming reactions, in the latter solvent led only to intramolecular insertion products in somewhat increased yields.

The above observations indicate that a metal-catalyzed thermolysis of diazomethyl ketones constitutes a simple method of cyclopentanone synthesis and a fast procedure for the construction of complex polycyclic compounds (e.g., **5**). Hence it is not surprising that the reaction has been used frequently[11] since its potential general applicability first was recognized.[1] The recent partial synthesis of hibaene illustrates its use in natural products synthesis.[11p] The following discussion portrays its efficacy in a conversion of a diterpene into the steroid nucleus.

The isopimaradiene system, e.g., virescenol B diacetate (**15a**),[12] appears to be an ideal candidate for conversion into a steroid skeleton in view of the possible utilization of the 13α-vinyl group in the construction of the steroid ring D. Hence with the help of **15a** as an isopimaradiene model,



15a, R = C_2H_3; R' = H
b, R = CH_2CH_2OH; R' = H
c, R = CH_2CO_2H; R' = H
d, R = CH_2COCHN_2; R' = H
e, R = CH_2CO_2Me; R' = H
f, R = R' = CH_2CO_2Me

the side chain was transformed into a diazo ketone function. Treatment of virescenol B diacetate (**15a**) with borane–tetrahydrofuran complex and subsequently with alkaline hydrogen peroxide yielded the hydroxy ester **15b**, whose Jones oxidation gave the acid ester **15c**. Successive exposures of the latter to oxalyl chloride and diazomethane

(9) K. Heusler and J. Kalvoda, *Angew. Chem., Int. Ed. Engl.*, **3**, 525 (1964).

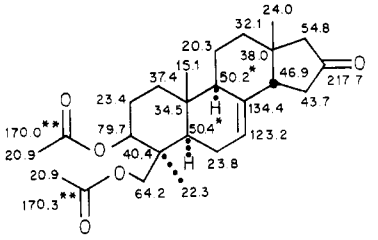
(10) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkeit, *Tetrahedron*, **19**, 1625 (1963).

(11) Inter alia: (a) M. Kitadani, K. Ito, and Y. Yoshikoshi, *Bull. Chem. Soc. Jpn.*, **44**, 3431 (1971); (b) U. R. Ghatak and S. Chakrabarty, *J. Am. Chem. Soc.*, **94**, 4756 (1972); (c) S. Wolff and W. C. Agosta, *J. Org. Chem.*, **38**, 1694 (1973); (d) R. B. Mane and G. S. Krishna Rao, *J. Chem. Soc., Perkin Trans. 1*, 1806 (1973); (e) J. P. Tresca, J. L. Fourrey, J. Polonsky, and E. Wenkert, *Tetrahedron Lett.*, 895 (1973); (f) W. Burns, M. A. McKervey, and J. J. Rooney, *J. Chem. Soc., Chem. Commun.*, 965 (1975); (g) S. Chakrabarty, J. K. Ray, D. Mukherjee, and U. R. Ghatak, *Synth. Commun.*, **5**, 275 (1975); (h) W. C. Agosta and S. Wolff, *J. Org. Chem.*, **40**, 1027 (1975); (i) S. A. Godleski, P. v. R. Schleyer, and E. Osawa, *J. Chem. Soc., Chem. Commun.*, 38 (1976); (j) P. R. Vijayasarathy and G. S. Krishna Rao, *Chem. Ind. (London)*, 161 (1976); (k) U. R. Ghatak and S. Chakrabarty, *J. Org. Chem.*, **41**, 1089 (1976); (l) I. Kuwajima, Y. Iguchi, H. Iwasawa, and T. Sato, *Chem. Lett.*, 1271 (1976); (m) U. R. Ghatak, J. K. Ray, and S. Chakrabarty, *J. Chem. Soc., Perkin Trans. 1*, 1975 (1976); (n) D. Fărcaşiu, H. Bohm, and P. v. R. Schleyer, *J. Org. Chem.*, **42**, 96 (1977); (o) Y. Inamoto, K. Aigami, N. Takaishi, Y. Fujikura, K. Tsuchihashi, and H. Ikeda, *Ibid.*, **42**, 3833 (1977); (p) B. L. Buckwalter, I. R. Burfitt, H. Felkin, M. Joly-Goudket, K. Naemura, M. F. Salomon, E. Wenkert, and P. M. Wovkulich, *J. Am. Chem. Soc.*, **100**, 6445 (1978).

(12) J. Polonsky, Z. Baskevitch, N. Cagnoli Bellavita, and P. Ceccherelli, *Bull. Soc. Chim. Fr.*, 1912 (1970).

led to diazo ketone **15d**. Decomposition of the diazo compound in a 1,2-dimethoxyethane solution of dirhodium(II) tetraacetate at room temperature produced a cyclopentanone-containing tetracycle in 59% yield.[13,14] Whereas, in principle, the intramolecular insertion could have occurred at anyone of three sites [C(12), C(14), or the C(13) methyl group], it was expected to take place at the C(14)–H(14α) bond site in view of the double bond participation in the quasi-axial allylic hydrogen bond rupture. Hence the product was assumed to possess structure **16**.

The first data confirming formula **16** as the correct configuration of the cyclization product came from its ^{13}C NMR spectral analysis. The chemical shift assignment was facilitated by an earlier designation of the δ values of a 16-deoxo-15-oxa analogue of the tetracycle[15] and proved the new carbon–carbon bond, formed in the diazo ketone decomposition, to reside between C(14) and C(15). As a comparison of the carbon shifts [δ values in parts per million downfield from Me_4Si [$\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm]; asterisked values may be interchanged] of the new tetracycle and 16-androstanone,[16] portrayed on formulas **17** and **18**, respectively, indicated that C(9) and C(12) of



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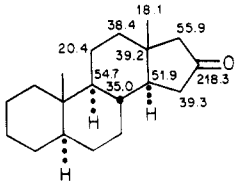

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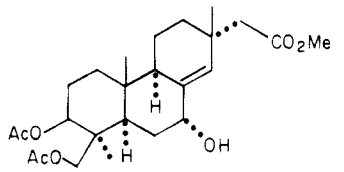
the keto ester are shielded vis-à-vis the model and that the 13-methyl group is deshielded. These shift alterations can be ascribed to a change in the C(14) stereochemistry, since a C/D *cis*-hydrindane relationship places C(15) into an axial orientation on ring C, thus exerting γ effects on C(9) and C(12) while removing one from the 13-methyl group.

Whereas the spectral analysis had confirmed structure **16** for the new tetracycle, more proof was deemed desirable. Hence the compound was synthesized by the following means. Treatment of acid ester **15c** with diazomethane yielded ester **15e**, whose sensitized photooxygenation, followed by iodide reduction of the resultant hydroperoxide, gave hydroxy ester **19**.[15,17] Heating of a mixture



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of the latter, triethyl orthoacetate, and propionic acid produced ester **15f**,[18] whose Dieckmann condensation under the influence of potassium *tert*-butoxide, reacetylation, and subsequent alumina-induced hydrolysis and decarboxylation[19] afforded a tetracyclic keto ester identical in all respects with compound **16**.

Experimental Section

Infrared spectra were determined on Perkin-Elmer 137 and Beckman Acculab 5 spectrophotometers and ^1H NMR spectra of deuteriochloroform solutions on Varian A-60 and EM-360 spectrometers. ^{13}C NMR spectra were recorded on a Varian XL-100 FT spectrometer. Melting points were obtained on a Kofler micro hot stage and are uncorrected. All organic extracts were dried over anhydrous sodium sulfate.

Ethyl 1-Methyl-2-oxocycloheptanecarboxylate Ethylene Thioketal (8b). A solution of 15.0 g of ethyl 1-methyl-2-oxocycloheptanecarboxylate (**8a**)[10] [^1H NMR δ 1.25 (t, 3, J = 7 Hz, Me of Et), 1.31 (s, 3, Me), 1.4–2.3 (m, 8, methylenes), 2.4–2.9 (m, 2, CH_2CO), 4.17 (q, 2, J = 7 Hz, OCH_2)] and 6 mL of boron trifluoride etherate in 30 mL of 1,2-ethanedithiol was stirred for 12 h and then poured into ice-cold 5% sodium hydroxide solution. The organic solution was washed with 5% sodium hydroxide solution and water and dried. Distillation of the residue at 125–130 °C (0.25–0.40 torr) yielded 18.5 g (89%) of liquid ester **8b**, IR (neat) 5.82 μm (s, C=O).

Anal. Calcd for $C_{13}H_{22}O_2S_2$: C, 56.93; H, 8.03. Found: C, 56.93; H, 8.20.

Ethyl 1-Methylcycloheptanecarboxylate (8c). A mixture of 5.0 g of thioketal **8b** and 45 g of Raney nickel (W. R. Grace No. 28, washed with absolute ethanol) in 150 mL of absolute ethanol was refluxed with stirring for 48 h. It was filtered and the solid washed with absolute ethanol. The combined filtrate and washings were evaporated, and the residue was distilled [85–94 °C (5 torr)]. Since a ^1H NMR spectral analysis of the distillate showed the presence of olefinic material, its solution in 40 mL of absolute ethanol was hydrogenated over 150 mg of 10% palladium/charcoal at 40 psi of H_2 for 2 h. The mixture was filtered and the filtrate evaporated. Distillation of the residue yielded 3.0 g (89%) of liquid ester **8c**: bp 82–84 °C (4.5 torr); IR (neat) 5.79 μm (s, C=O); ^1H NMR δ 1.13 (s, 3, Me), 1.21 (t, 3, J = 7 Hz, Me of Et), 1.4–1.7 (m, 12, methylenes), 4.10 (q, 2, J = 7 Hz, OCH_2).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.85; H, 10.86. Found: C, 71.65; H, 10.88.

1-Methylcycloheptanecarboxylic Acid (3a). A mixture of 2.10 g of ester **8c** and 5.0 g of potassium hydroxide in 40 mL of 4:1 ethylene glycol–water was stirred and refluxed for 12 h. Water (50 mL) was added and the mixture extracted with ether. The aqueous solution was acidified with hydrochloric acid and extracted with ether. Drying of this extract and evaporation yielded 1.35 g (76%) of solid, whose crystallization from pentane and from ethanol–water gave acid **3a**: mp 46.5–47 °C; IR (CCl_4) 3.30 (br m, OH) 3.85 (br s, OH), 5.92 μm (s, C=O); ^1H NMR δ 1.20 (s, 3, Me), 1.4–1.7 (m, 12, methylenes).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.48; H, 10.26.

Diazo Ketones. A mixture of 2.30 g of acid **3a** and 8.5 mL of oxalyl chloride was stirred at room temperature for 6 h, whereupon the excess reagent was removed under vacuum. Distillation of the residual liquid yielded 1-methylcycloheptanecarbonyl chloride: bp 60 °C (1 torr); IR (CCl_4) 5.58 μm (s)]. A solution of the latter in 4 mL of anhydrous ether was added dropwise over a 2-h period to a stirring solution of a threefold molar excess of diazomethane in 10 mL of anhydrous ether cooled in an ice bath. Evaporation of the solvent yielded 2.31 g (83%) of liquid diazo ketone **4a**: IR (CCl_4) 4.75 (s, C=N_2), 6.12 μm (s, C=O). This procedure was utilized for the preparation of all other diazo ketones.

Liquid diazo ketone **4b**: bp 56–57 °C (0.04 torr); IR (neat) 4.78 (s, C=N_2) 6.13 μm (s, C=O); ^1H NMR δ 1.12 (s, 3, Me), 1.3–1.6

(13) By the time the diterpene to steroid conversion was underway (1979–1980), the rhodium(II) salt had become a popular catalyst for diazo ketone and diazoacetic ester decompositions, especially in connection with cyclopropanation processes [cf. A. Hubert, A. F. Noels, A. J. Anciaux, and P. Teyssié, *Synthesis*, 600 (1976)]. The cupric sulfate catalyzed decomposition of **15d** yielded **16** in poor yield.

(14) Since the completion of the present work[13] a (albeit intermolecular) carbon–hydrogen insertion with ethyl diazoacetate under the influence of dirhodium(II) tetrakis(trifluoroacetate) has been reported: A. Demonceau, A. F. Noels, A. J. Hubert, and P. Teyssié, *J. Chem. Soc., Chem. Commun.*, 688 (1981).

(15) E. Wenkert, M. S. Raju, P. Ceccherelli, M. Curini, M. Tingoli, and R. Pellicciari, *J. Org. Chem.*, **45**, 741 (1980).

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(19) A. E. Greene, A. Cruz, and P. Crabbé, *Tetrahedron Lett.*, 2707 (1977); R. Pellicciari, B. Natalini, M. Taddei, A. Ricci, G. Alunni Bistocchi, and G. De Meo, *J. Chem. Res., Synop.*, 142 (1979).

(m, 10, methylenes), 5.62 (s, 1, CH).

Anal. Calcd for $C_9H_{14}ON_2$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.94; H, 8.41; N, 16.82.

Liquid diazo ketone **4c**: bp 79–80 °C (1 torr); IR (CCl_4) 4.76 (s, C=N_2) 6.11 μm (s, C=O); ^{1}H NMR δ 1.19 (s, 3, Me), 1.5–1.8 (m, 8, methylenes), 5.46 (s, 1, CH).

A hexane solution of *n*-butyllithium (30 mmol) was added by syringe to a stirring solution of 3.00 g (30 mmol) of diisopropylamine in 40 mL of tetrahydrofuran at −20 °C under nitrogen, and the stirring was continued at this temperature for 10 min.[20] Cyclobutanecarboxylic acid (734 mg, 7.3 mmol) was added in one portion and the mixture refluxed for 3 h. Dropwise addition of 2.84 g (20 mmol) of methyl iodide over a 10-min period was followed by the mixture being stirred at room temperature for 10 min and then refluxed for 2 h. The mixture was acidified with hydrochloric acid and extracted with ether. The extract was dried and evaporated. Chromatography of the residue on 25 g of silica gel and elution with 100:2:1 hexane–ether–acetic acid yielded 750 mg (90%) of acid **3d**.[21]

Liquid diazo ketone **4d**: bp 76 °C (0.35 torr); IR (neat) 4.76 (s, C=N_2), 6.12 μm (s, C=O); ^{1}H NMR δ 1.38 (s, 3, Me), 1.6–2.6 (m, 6, methylenes), 5.42 (s, 3, CH).

Anal. Calcd for $C_7H_{10}ON_2$: C, 60.85; H, 7.30; N, 20.27. Found: C, 60.67; H, 7.42; N, 20.10.

Liquid diazo ketone **9b**: bp 65–66 °C (0.04 torr); IR (neat) 4.74 (s, C=N_2), 6.11 μm (s, C=O); ^{1}H NMR δ 0.8–2.4 (m, 13, methylenes, CH), 5.38 (s, 1, CHN_2).

Anal. Calcd for $C_9H_{14}ON_2$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.84; H, 8.48; N, 16.90.

Liquid diazo ketone **9d**: bp 58 °C (0.5 torr); IR (neat) 4.72 (s, C=N_2), 6.12 μm (s, C=O); ^{1}H NMR δ 1.07 (s, 9, 3 Me), 2.23 (s, 2, CH_2), 5.37 (s, 1, CH).

Anal. Calcd for $C_7H_{12}ON_2$: C, 59.98; H, 8.63; N, 17.64. Found: C, 60.05; H, 8.59; N, 17.75.

Liquid diazo ketone **9f**: bp 54–55 °C (0.1 torr); IR (neat) 4.76 (s, C=N_2), 6.10 μm (s, C=O); ^{1}H NMR δ 0.88 (t, 3, J = 7 Hz, Me), 1.1–1.9 (m, 8, methylenes), 2.35 (t, 2, J = 7 Hz, $COCH_2$), 5.45 (s, 1, CH).

Anal. Calcd for $C_8H_{14}ON_2$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.50; H, 9.15; N, 17.96.

1-Methylbicyclo[4.2.1]nonan-8-one (5a) and 1-Methylbicyclo[5.2.0]nonan-9-one (6a). A solution of 2.30 g of 1-(diazoacetyl)-1-methylcycloheptane (**4a**) in 350 mL of cyclohexane (distilled from lithium aluminum hydride) was added dropwise over a 4.5-h period to a stirred suspension of 8.00 g of anhydrous cupric sulfate (prepared by commercial anhydrous copper sulfate being dried at 100 °C for 24 h and just before use being heated over a free flame, while swirling, until totally colorless) in 200 mL of dry cyclohexane, and the stirred mixture was refluxed for 0.5 h. It was filtered, and the filtrate was washed with water, dried, and freed from solvent by distillation. Chromatography of the residue on Guilini alumina (activity I) and elution with ether yielded 2.2 g of a ketone mixture, whose infrared spectrum showed it to be composed of mostly a cyclopentanone and cyclobutanone. (The <5% of solvent-insertion product **7a** was not isolated.) GC analysis on a 10 ft × $^3/_8$ in. 30% FFAP column at 180 °C revealed two major components of 12.8- and 14.2-min retention times which were collected by preparative GC. The first fraction led to 206 mg (9%) of liquid ketone **6a**: IR (CCl_4) 5.63 μm (s, C=O); ^{1}H NMR δ 1.23 (s, 3, Me), 1.3–2.4 (m, 11, 5 CH_2, CH), 2.54 (dd, 1, J = 6, 18 Hz, H of $COCH_2$), 3.24 (dd, 1, J = 9, 18 Hz, other H of $COCH_2$); semicarbazone, 208–209 °C (from ethanol).

Anal. Calcd for $C_{11}H_{19}ON_3$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.40; H, 9.02; N, 20.02.

The second fraction led to 1.48 g (72%) of liquid ketone **5a**: IR (neat) 5.75 μm (s, C=O); ^{1}H NMR δ 1.02 (s, 3, Me), 1.2–2.7 (m, 13, 6 CH_2, CH).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.83; H, 10.65.

5a semicarbazone, mp 210–212 °C (from aqueous ethanol).

Anal. Calcd for $C_{11}H_{19}ON_3$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.32; H, 9.21; N, 20.14.

The yield ranges for ketones **5a** and **6a** were 50–75% and 5–10%, respectively.

1-Methylbicyclo[3.2.1]octan-7-one (5b) and 1-Methylbicyclo[4.2.0]octan-8-one (6b). Decomposition of 1-(diazoacetyl)-1-methylcyclohexane (**4b**) under the conditions described above for the like reaction of **4a**, chromatography of the crude product on Guilini alumina (activity II), and elution with 50:1 pentane–ether gave an oil, whose infrared spectrum showed it to be predominantly a cyclopentanone. Elution with 30:1 pentane–ether afforded an oil, whose preparative GC purification on a SE-30 column at 230 °C produced an 18% yield of liquid 1-(cyclohexylacetyl)-1-methylcyclohexane (**7b**): IR (neat) 5.83 μm (s, C=O); ^{1}H NMR δ 1.03 (s, 3, Me), 1.1–2.1 (m, 21, 10 CH_2, CH), 2.31 (d, 2, J = 7 Hz, $COCH_2$); mass spectrum, calcd for $C_{15}H_{26}O$ m/e 222.1984, found m/e 222.1981.

GC collection of the cyclopentanone-containing fraction on an 8 ft × 0.25 in. 10% SE-30 column at 200 °C yielded an oil, which appeared homogeneous on five different GC columns but contained some cyclobutanone on the basis of IR and ^{1}H NMR spectral analyses. Two successive, slow chromatographic separations on Woelm alumina (activity III) and elution with 100:1 hexane–ether (accompanied by IR spectral monitoring) resulted first in a 4% yield of liquid ketone **6b**: IR (neat) 5.63 μm (s, C=O); ^{1}H NMR δ 1.17 (s, 3, Me), 1.3–3.0 (m, 11, 5 CH_2, CH); mass spectrum, calcd for $C_9H_{14}O$ m/e 138.1045, found m/e 138.1037.

Separation of the second fraction gave a 58% yield of liquid ketone **5b**: IR (neat) 5.75 μm (s, C=O); ^{1}H NMR δ 0.98 (s, 3, Me), 1.2–2.6 (m, 11, 5 CH_2, CH); semicarbazone, mp 221–223 °C (from ethanol).

Anal. Calcd for $C_{10}H_{17}ON_3$: C, 61.51; H, 8.78. Found: C, 61.45; H, 8.89.

1-Methylbicyclo[2.2.1]heptan-2-one (5c) and 1-Methylbicyclo[3.2.0]heptan-7-one (6c). Decomposition of 1-(diazoacetyl)-1-methylcyclopentane (**4c**) under the conditions of the like reaction of **4a** (vide supra), chromatography of the crude product on Guilini alumina (activity I), elution with ether, distillation of the eluates, and collection of two fractions boiling at 49–57 °C (8 torr) and 87 °C (0.45 torr) gave two fractions. GC analysis of the second fraction on a 5 ft × $^3/_8$ in. 20% Carbowax 20M column (200 mL/min flow rate) at 170 °C revealed one major component (28.5-min retention time), whose collection led to a 9% yield of liquid 1-(cyclohexylacetyl)-1-methylcyclopentane (**7c**): IR (CCl_4) 5.83 μm (s, C=O); ^{1}H NMR δ 1.17 (s, 3, Me), 1.2–2.4 (m, 21, 10 CH_2, CH); semicarbazone, mp 174 °C (from ethanol).

Anal. Calcd for $C_{15}H_{27}ON_3$: C, 67.88; H, 10.25; N, 15.83. Found: C, 68.04; H, 10.19; N, 15.80.

GC analysis of the low-boiling fraction (140 °C, otherwise same conditions) revealed major components with 4.7- and 6-min retention times. Collection of the first fraction led to a 3% yield of ketone **6c**:[22] IR (CCl_4) 5.63 μm (s, C=O); ^{1}H NMR δ 1.24 (s, 3, Me), 1.5–2.3 (m, 7, 3 CH_2, CH), 2.45 (dd, 1, J = 5, 19 Hz, COCH), 3.18 (dd, 1, J = 10, 19 Hz, COCH); 2,4-dinitrophenylhydrazone, mp 93–95 °C (from ethanol); semicarbazone, mp 176–178 °C (from ethanol).

Anal. Calcd for $C_9H_{15}ON_3$: C, 59.65; H, 8.34; N, 23.18. Found: C, 59.93; H, 8.35; N, 23.08.

Collection of the second fraction led to a 19% yield of ketone **5c**:[23] IR (CCl_4) 5.74 μm (s, C=O); ^{1}H NMR δ 1.17 (s, 3, Me), 1.2–2.7 (m, 9, 4 CH_2, CH); spectral and GC behavior identical with that of an authentic sample; semicarbazone, mp and mmp 212–214 °C (lit.[23] mp 211–212 °C).

1-Methylbicyclo[2.1.1]hexan-2-one (5d). Except for a longer addition time (9 h) the above procedure for the decomposition of **4a** was followed for the reaction of 1-(diazoacetyl)-1-methylcyclobutane (**4d**). Solvent removal was carried out by slow distillation (bath temperature of 140 °C) through a 12-in. Vigreux column. GC analysis of the crude product, with added acetophenone as an internal standard, on an 8 ft × $^3/_8$ in. 15% Carbowax 20M column at 180 °C indicated the presence of a major component and several minor components. Preparative GC of the major component (retention time of 2 relative to that of

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acetophenone) led to a 29% yield of 1-(cyclohexylacetyl)-1-methylcyclobutane (**7d**): IR (neat) 5.83 μm (s, C=O); ^{1}H NMR δ 1.35 (s, 3, Me), 1.3–2.5 (m, 19, 9 CH_2, CH); mass spectrum, calcd for $C_{13}H_{22}O$ *m/e* 194.1671, found *m/e* 194.1659.

Preparative GC of the minor components showed only one to be a $C_7H_{10}O$ compound. Isolation of this constituent (retention time of 0.2 relative to that of acetophenone) led to a 1% yield of ketone **5d**:[24] IR (neat) 5.67 μm (s, C=O); ^{1}H NMR δ 1.15 (s, 3, Me), 1.4–2.8 (m, 7, 3 CH_2, CH); spectral and GC behavior identical with that of an authentic sample; 2,4-dinitrophenylhydrazone, mp and mmp 179–181 °C (from ethanol) (lit.[24] mp 181–182 °C).

A solution of 800 mg of diazo ketone **4d** in 100 mL of dry Freon TF (1,1,2-trichloro-1,2,2-trifluoroethane by Du Pont, distilled from phosphorus pentoxide) was added dropwise over a 12-h period to a stirring, refluxing suspension of 800 mg of anhydrous cupric sulfate in 100 mL of dry Freon TF, and the refluxing was continued for an additional 12 h. After solvent removal, GC analysis with an internal acetophenone standard, and preparative GC sample collection, ketone **5d** was obtained in 4% yield.

***trans*- (10a) and *cis*-Hexahydroindan-2-one (10b) and Spiro[3.5]nonan-2-one (11).** The procedure for the decomposition of **4d** in cyclohexane (vide supra) was followed for the reaction of diazomethyl hexahydrobenzyl ketone (**9b**). GC analysis of the crude product, with diethyl adipate as an internal standard and on an 8 ft × $^3/_8$ in. 15% Carbowax 20M column at 220 °C, showed the presence of four substances with retention times of 0.55, 0.67, 0.83, and 3.0 relative to that of the internal standard. Preparative GC collection of the first fraction led to a 1% yield of liquid ketone **11**:[25] IR (neat) 5.62 μm (s, C=O); ^{1}H NMR δ 1.3–1.8 (m, 10, methylenes), 2.68 (s, 4, 2 $COCH_2$); spectra identical with those of an authentic specimen.

Preparative GC isolation of the second component led to a 9% yield of liquid ketone **10a**:[26] IR (neat) 5.72 μm (s, C=O); ^{1}H NMR δ 1.0–2.6 (m, 14, 6 CH_2, 2 CH); spectra identical with those reported;[26] semicarbazone, mp and mmp 243 °C (from aqueous ethanol) (lit.[27] mp 243 °C).

Preparative GC separation of the third constituent led to a 5% yield of liquid ketone **10b**:[26] IR(neat) 5.75 μm (s); ^{1}H NMR δ 1.2–1.8, 2.0–2.5 (m, 14, 6 CH_2, 2 CH); spectra identical with those reported; [26] semicarbazone, mp 215–216 °C (from aqueous ethanol) (lit.[27] mp 215–216 °C).

Preparative GC collection of the last fraction led to a 23% yield of bis(hexahydroxybenzyl) ketone (**12a**): IR (CCl_4) 5.82 μm (s, C=O); ^{1}H NMR δ 0.7–1.8 (m, 22, 10 CH_2, 2 CH), 2.25 (d, 4, *J* = 7 Hz, 2 $COCH_2$).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.31; H, 11.85.

Decomposition of diazo ketone **9b** in Freon TF as described for diazo ketone **4d**, followed by GC analysis of the crude product with diethyl adipate as internal standard led to ketones **10a,b** and **11** in the same yields as from the reaction in cyclohexane. Decomposition of diazo ketone **9b** over an equal weight of cupric bis(hexafluoroacetylacetonate) dihydrate[11p,28] in Freon TF gave ketones **10a,b** and **11** in 14%, 7%, and 1% yields, respectively.

3,3-Dimethylcyclopentanone (13a). The aforementioned method of decomposition of **4d** in cyclohexane was followed for the reaction of diazomethyl neopentyl ketone (**9d**). Solvent removal was accomplished by slow distillation (bath temperature of 140 °C) through a 12-in. Vigreux column. GC analysis of the crude product, with diethyl adipate as an internal standard, at 200 °C on the Carbowax column used for the identification of ketones **10** and **11** showed minor products of 0.2 and 2.4 retention times relative to that of the standard. The last component (2%) revealed a GC/MS mass peak of *m/e* 196, characteristic of solvent-insertion product **12b**, but was not investigated further. Preparative GC separation of the first component led to a 1% yield of liquid ketone **13a**: IR (neat) 5.74 μm (s, C=O); ^{1}H NMR δ 1.11 (s, 6, 2 Me), 1.77 (t, 2, *J* = 8 Hz, 2 H-4), 2.03 (s, 2, 2 H-2), 2.30 (t, 2, *J* = 8 Hz, 2 H-5); semicarbazone, mp 178–180 °C (from aqueous ethanol) (lit.[29] mp 179–180 °C); 2,4-dinitrophenylhydrazone, mp 144–145 °C (from aqueous ethanol) (lit.[30] mp 145 °C).

Decomposition of diazo ketone **9d** in Freon TF as in the above procedure for **4d** and subsequent GC analysis showed ketone **13a** as the sole product in 10% yield.

3-*n*-Propylcyclopentanone (13b) and 3-Ethylcyclohexanone (14). The decomposition of 1-diazo-2-octanone (**9f**) in cyclohexane followed the procedure for the reaction of diazo ketone **4d** above. GC analysis of the crude product, with ethyl phenylacetate as an internal standard, on an 8 ft × $^3/_8$ in. 15% Carbowax 20M column at 220 °C showed three components with 0.37, 0.42, and 1.8 retention times with respect to that of the standard. The last constituent (18%) showed a GC/MS mass peak of *m/e* 210, characteristic of solvent-insertion product **12c**, and was not investigated further. Preparative GC collection of the first component led to a 6% yield of liquid ketone **13b**: IR (neat) 5.73 μm (s, C=O); ^{1}H NMR δ 0.92 (t, 3, *J* = 7 Hz, Me), 1.2–2.5 (m, 11, 5 CH_2, CH); semicarbazone, mp 174–176 °C (aqueous ethanol) (lit.[31] mp 178 °C).

Anal. Calcd for $C_9H_{17}ON_3$: C, 58.99; H, 9.35; N, 22.93. Found: C, 58.70; H, 9.05; N, 22.75.

Preparative GC isolation of the central fraction led to a 1% yield of liquid ketone **14**: IR (neat) 5.83 μm (s, C=O) ^{1}H NMR δ 0.92 (t, 3, *J* = 7 Hz, Me), 1.1–2.7 (m, 11, 5 CH_2, CH); spectrally identical with an authentic sample; semicarbazone, mp and mmp 167–169 °C (from aqueous ethanol) (lit.[32] mp 169–171 °C).

Decomposition of diazo ketone **9f** in Freon TF as in the above procedure for **4d** and subsequent GC analysis showed the presence of ketones **13b** and **14** in 9% and 2% yields, respectively.

15,16-Dihydro-16-hydroxyvirescenol B Diacetate (15b). A 1 M boron hydride–tetrahydrofuran solution (2.5 mL) was added over a 20-min period to a stirring solution of 1.80 g of virescenol B diacetate (**15a**) in 15 mL of tetrahydrofuran at 0 °C under nitrogen, and the mixture was stirred at room temperature for 3 h. It then was treated successively with 2 mL of 3 M sodium hydroxide solution and 1.8 mL of 36% hydrogen peroxide, and the mixture was stirred at 60 °C for 1 h. It was diluted with 50 mL of water and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. Chromatography of the residue (1.9 g) on silica and elution with 20:1 benzene–ethyl acetate gave 250 mg of starting material (**15a**) and 1.50 g of solid. Crystallization from ether gave hydroxy ester **15b**: mp 123–125 °C; ^{1}H NMR δ 0.77, 0.87, 1.00 (s, 3 each, Me), 2.06 (s, 6, 2 $COCH_3$), 3.65 (t, 2, *J* = 8 Hz, OCH_2), 4.17, 4.40 (4-line AB, 2, *J* = 11 Hz, $AcOCH_2$), 4.36 (m, 1, OCH), 5.24 (m, 1, olefinic H).

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.82; H, 9.56.

Diester Acid 15c. A solution of 3.00 mmol of Jones reagent, prepared from a solution of 70 g of chromium trioxide in 500 mL of water, and 61 mL of concentrated sulfuric acid was added slowly to a stirring solution of 1.20 g of hydroxy ester **15b** in 50 mL of acetone at 0 °C and the mixture stirred for an additional 0.5 h. The mixture was treated with excess 5% sodium bisulfite solution, diluted with 200 mL of water, and extracted with ether. The extract was dried ($MgSO_4$) and evaporated. Chromatography of the residue (1.1 g) on silica and elution with 100:1 chloroform–methanol yielded 0.90 g of semisolid acid **15c**: ^{1}H NMR δ 0.90, 0.93, 1.02 (s, 3 each, Me), 2.00 (s, 6, 2 $COCH_3$), 4.17, 4.42 (4-line AB, 2, *J* = 11 Hz, OCH_2), 4.34 (m, 1, OCH), 5.28 (m, 1, olefinic H).

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.68; H, 8.59.

3β-Acetoxy-4β-(acetoxymethyl)-7,8-didehydro-14-iso-4α-

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methyl-16-androstanone (16). After the slow addition of 750 mg of acid **15c** to 8 mL of oxalyl chloride the resultant frothy mixture was stirred for 4 h, and then the excess reagent was removed by vacuum distillation. A solution of the crystalline acid chloride in 100 mL of ether was added dropwise over a 4-h period to a stirred, ice-cold ethereal solution of 0.5 mmol of diazomethane, and the mixture was stirred at 0 °C for 4 h and at room temperature for 12 h. Excess diazomethane was evaporated under a stream of nitrogen and the remaining mixture concentrated to dryness. Chromatography of the residue (700 mg) and elution with 7:1 benzene–ethyl acetate yielded 600 mg of semisolid diazo ketone **15d**: IR ($CHCl_3$) 4.72 (s, C=N_2), 6.10 μm (s, C=O); ^{1}H NMR δ 0.86, 0.88, 1.00 (s, 3 each, Me), 2.00 (s, 6, 2 $COCH_3$), 4.20, 4.40 (4-line AB, 2, J = 11 Hz, OCH_2), 4.25 (m, 1, OCH), 5.10 (s, 1, NCH), 5.22 (m, 1, olefinic H).

A solution of 400 mg of diazo ketone **15d** in 20 mL of 1,2-dimethoxyethane was added dropwise over a 2-h period to a stirred suspension of 50 mg of dirhodium(II) tetraacetate in 50 mL of 1,2-dimethoxyethane under nitrogen, and the stirring was continued at room temperature for 1 h. Water (100 mL) was added and the mixture extracted with ether. The extract was evaporated and the residue (320 mg) chromatographed on silica gel. Elution with 50:1 benzene–ethyl acetate gave 220 mg of a solid, whose crystallization from ether yielded crystalline keto ester **16**: mp 166–168 °C; IR ($CHCl_3$) 5.75 (s, C=O), 5.80 μm (s); ^{1}H NMR δ 0.88, 1.03, 1.10 (s, 3 each, Me), 2.00 (s, 6, 2 $COCH_3$), 4.15, 4.42 (4-line AB, 2, J = 11 Hz, OCH_2), 4.32 (m, 1, OCH), 5.45 (m, 1, olefinic H).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.16; H, 8.86.

A suspension of 780 mg of potassium *tert*-butoxide and 180 mg of ester **20** (vide infra) in 30 mL of benzene was refluxed for 4 h and kept at room temperature thereafter for 12 h. The mixture was acidified with 1 N sulfuric acid and extracted with benzene. The extract was dried and evaporated. A solution of the residue (90 mg) and 1.5 mL of acetic anhydride in 4 mL of pyridine was kept at room temperature for 12 h. The usual workup led to 100 mg of crude product, whose chromatography on silica gel and elution with 12:1 benzene–ethyl acetate gave 80 mg of a tetracyclic keto ester mixture. A stirred suspension of 5 g of basic Merck alumina (type I, used for TLC), the latter mixture, and 1.5 mL of water in 12 mL of dioxane was refluxed under nitrogen for 18 h. The mixture was filtered and the alumina washed exhaustively with hot chloroform. The combined washings and filtrate were dried and evaporated. Chromatography of the residue (60 mg) on silica gel and elution with 50:1 benzene–ethyl acetate yielded 40 mg of keto ester **16**, identical with the above sample.

Triester 15e. An ethereal diazomethane solution was added dropwise to a stirred solution of 1.10 g of acid **15c** in 100 mL of ether until a yellow color persisted, and the stirring was continued for 40 min. A few drops of acetic acid were added for the decomposition of excess diazomethane, and the solution was evaporated. Chromatography of the residue (1.1 g) on silica gel and elution with 10:1 benzene–ethyl acetate afforded 1.00 g of semisolid triester **15e**: ^{1}H NMR δ 0.90, 0.90, 1.00 (s, 3 each, Me), 2.06 (s, 6, 2 $COCH_3$), 2.16 (s, 2, $COCH_2$), 3.53 (s, 3, OMe), 4.17, 4.46 (4-line AB, 2, J = 11 Hz, OCH_2), 4.54 (m, 1, OCH), 5.30 (m, 1, olefinic H).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.19; H, 8.71.

Hydroxy Ester 19. A solution of 1.00 g of ester **15e** and 30 mg of eosin in 100 mL of ethanol was irradiated by a 250-W tungsten lamp under a stream of oxygen for 24 h. A solution of 0.4 g of sodium iodide in 20 mL of ethanol and subsequently 150 mL of water were added, and the mixture was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. Chromatography of the residue (950 mg) on silica gel and elution with 4:1 benzene–ethyl acetate yieldeted 280 mg of starting ester (**15e**) and 600 mg of semisolid hydroxy ester **19**: ^{1}H NMR δ 0.80, 1.02, 1.02 (s, 3 each, Me), 2.08 (s, 6, 2 $COCH_3$), 2.26 (s, 2, $COCH_2$), 3.63 (s, 3, OMe), 4.16, 4.40 (4-line AB, 2, J = 11 Hz, OCH_2), 4.21 (m, 1, OCH), 4.60 (m, 1, AcOCH), 5.60 (br, s, 1, olefinic H).

Anal. Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.79; H, 8.43.

Tetraester 15f. A solution of 640 mg of hydroxy ester **19** and 6 mg of propionic acid in 1.60 g of triethyl orthoacetate was stirred at 140 °C for 6 h. Removal of the excess ortho ester by distillation, chromatography of the residue (600 mg) on silica gel, and elution with 12:1 benzene–ethyl acetate yielded 400 mg of semisolid tetraester **15f**: ^{1}H NMR δ 0.90, 1.00, 1.00 (s, 3 each, Me), 1.23 (t, 3, J = 7 Hz, Me of Et), 2.06 (s, 6, 2 $COCH_3$), 3.60 (s, 3, OMe), 4.00 (q, 2, J = 7 Hz, OCH_2 of OEt), 4.20, 4.48 (4-line AB, 2, J = 11 Hz, OCH_2), 4.60 (m, 1, OCH), 5.45 (m, 1, olefinic H).

Anal. Calcd for $C_{29}H_{44}O_8$: C, 66.90; H, 8.52. Found: C, 66.79; H, 8.65.

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Registry No. 3a, 35664-93-8; **3a** acid chloride, 35664-99-4; **3b**, 1123-25-7; **3b** acid chloride, 2890-61-1; **3c**, 5217-05-0; **3c** acid chloride, 20023-50-1; **3d**, 32936-76-8; **3d** acid chloride, 21890-82-4; **4a**, 20609-37-4; **4b**, 20609-36-3; **4c**, 20609-38-5; **4d**, 20609-39-6; **5a**, 20608-94-0; **5a** semicarbazone, 82322-81-4; **5b**, 20608-68-8; **5b** semicarbazone, 82322-82-5; **5c**, 10218-04-9; **5d**, 20609-40-9; **6a**, 20609-41-0; **6a** semicarbazone, 82322-83-6; **6b**, 68212-57-7; **6c**, 57706-99-7; **6c** DNP, 82322-84-7; **6c** semicarbazone, 20609-42-1; **7b**, 82322-85-8; **7c**, 82322-86-9; **7c** semicarbazone, 82322-87-0; **7d**, 82322-88-1; **8a**, 20043-64-5; **8b**, 82322-89-2; **8c**, 82322-90-5; **9a**, 5292-21-7; **9a** acid chloride, 23860-35-7; **9b**, 27473-43-4; **9c**, 1070-83-3; **9c** acid chloride, 7065-46-5; **9d**, 76828-10-9; **9e**, 111-14-8; **9e** acid chloride, 2528-61-2; **9f**, 58237-58-4; **10a**, 16484-17-6; **10b**, 5689-04-3; **11**, 29800-56-4; **12a**, 62221-40-3; **12b**, 82322-91-6; **12c**, 82322-92-7; **13a**, 20500-49-6; **13b**, 82322-93-8; **14**, 22461-89-8; **15a**, 11051-39-1; **15b**, 82337-90-4; **15c**, 82322-94-9; **15d**, 82322-95-0; **15e**, 82322-96-1; **15f**, 82322-97-2; **16**, 82322-98-3; **18**, 963-74-6; **19**, 82322-99-4; 1,2-ethanedithiol, 540-63-6; cyclobutanecarboxylic acid, 3721-95-7.