Total Synthesis Refutes the Postulated Structure of Leucogenenol

Robert G. Salomon,* Mary F. Salomon, Michael G. Zagorski, James M. Reuter, and Daniel J. Coughlin

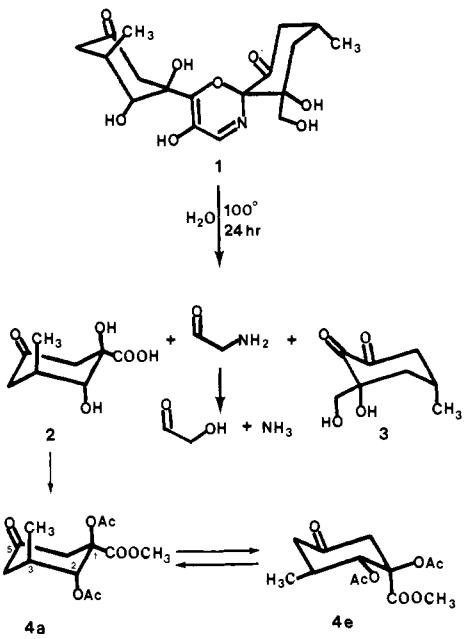
Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106. *Received September 2, 1981*

Abstract: Total syntheses are reported for all four possible stereoisomers of methyl 1,2-diacetoxy-3-methyl-5-oxocyclohexanecarboxylate. The nonidentity of any of these isomers with a keto triester obtained from leucogenenol refutes a structure proposed in 1971 for this natural product. The syntheses exploit reduction–protodesilylation of a benzylsilane to provide a key intermediate, 4-methylene-2-methylcyclohexanone.

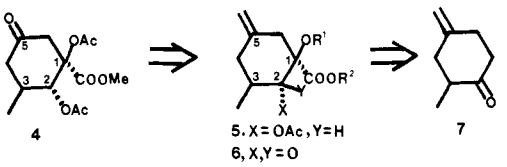
An acidic substance, named leucogenenol because of its presumed enolic structure and because it induces an increase in the white blood cell count (leucocytosis) in rabbits, was first isolated from the metabolic solution of surface cultures of a mold[1] and later from human and bovine liver.[2] Our interest was piqued by claims that leucogenenol stimulates replication and maturation of leucocytes[3] and probably other cells[4] by regulating their metabolic processes.[5] Also, leucogenenol is believed to facilitate antibody production.[6] Although concentrated mainly in the liver, leucogenenol is also found in the thyroid, thymus, testes, and adrenals.[2] Especially fascinating was the claim that the concentration of leucogenenol in human blood is normally 2–4 μg/L but varies with disease.[2b] The concentration is increased (45–75 μg/L) in inflammatory diseases such as systemic lupus erythematosis and rheumatoid arthritis, but depressed (0.13–0.36 μg/L) in the leukemias. All of these interesting results on leucogenenol were reported by Rice and co-workers at the American University, Washington, D.C.[7]

Knowledge of the molecular structure of leucogenenol is important for a fundamental understanding of its biochemistry. Extensive studies by Rice led to postulation of structure **1** for leucogenenol (Scheme I).[8,9] Thus, leucogenenol was characterized spectroscopically, by preparation of derivatives, by degradation to simple products, and by synthesis of one of the fragments. Hydrolysis with boiling water is reported to afford "ammonia and aminoacetaldehyde, a monobasic carboxylic acid $C_8H_{12}O_5$, and a dione $C_8H_{12}O_4$, these products accounting for all the carbon atoms in the molecule".[8] A structure **3** (Scheme I) was proposed for the dione based on spectroscopic and chemical studies and confirmed by total synthesis.[9] The structure **2** (Scheme I) suggested for the "monobasic carboxylic acid" was supported by spectroscopic and extensive degradation studies. These were claimed to include oxidative degradation to (−)-methylsuccinic acid and another sequence leading to 5-methylhexanoic acid.[8] Nevertheless, confirmation of the identity of the product derived from leucogenenol by total synthesis of **2** seemed warranted for several reasons. Thus, the assignment of relative stereochemistry to the methyl group at C-3 rested on the observation of a change in the chemical shift of the methyl protons from δ 1.30 to δ 1.35 upon acetylation of the methyl ester of **2**. It was argued that such a change "indicates a 1,3-diaxial relationship between the C-methyl and the tertiary hydroxy-group". However, this requires a large preference for conformer **4a** over **4e**. It is not obvious to

Scheme I



Scheme II



(1) (a) Rice, F. A. H. *Proc. Soc. Exp. Biol. Med.* **1966**, *123*, 189. (b) Rice, F. A. H.; Barrow, M. *Appl. Microbiol.* **1967**, *15*, 790.
(2) (a) Rice, F. A. H.; Shaikh, B. *Biochem. J.* **1970**, *116*, 709. (b) Rice, F. A. H.; McCurdy, J. D. *Johns Hopkins Med. J.* **1973**, *132*, 282. (c) Rice, F. A. H.; Shaikh, B.; Chen, C. G. *Ibid.* **1975**, *135*, 336. (d) Rice, F. A. H.; Griffin, B. R.; Dass, P. D. *Ibid.* **1975**, *136*, 239.
(3) (a) Rice, F. A. H. *J. Infect. Dis.* **1968**, *118*, 76. (b) Rice, F. A. H.; Darden, J. H. *Ibid.* **1968** *118*, 289. (c) Rice, F. A. H.; McCurdy; Aziz, K. *Proc. Soc. Exp. Biol. Med.* **1971**, *136*, 56. (d) Rice, F. A. H.; Connolly, J.; Aziz, K.; McCurdy, J. D. *J. Infect. Dis.* **1971**, *123*, 117.
(4) (a) Rice, F. A. H.; Lepick, J.; Darden, J. H. *J. Radiat. Res.* **1968**, *36*, 144. (b) Rice, F. A. H. *Proc. Soc. Exp. Biol. Med.* **1976**, *152*, 549. (c) Rice, F. A. H.; Chen, C. G.; Rene, A. A. *Radiat. Res.* **1973**, *56*, 507.
(5) (a) Rice, F. A. H.; Blum, M. L.; Rene, A. A. *Proc. Soc. Exp. Biol. Med.* **1970**, *135*, 623. (b) Rice, F. A. H.; McCurdy, J. D. *Ibid.* **1971**, *137*, 1483. (c) Rice, F. A. H.; McCurdy, J. D. *Johns Hopkins Med. J.* **1973**, *132*, 151.
(6) (a) Rice, F. A. H.; Lepick, J.; Hepner, P. *Radiat. Res.* **1970**, *42*, 164. (b) Rice, F. A. H.; Ciavarra, R. *Proc. Soc. Exp. Biol. Med.* **1971**, *137*, 567. (c) Rice, F. A. H.; Das, N. D.; Koo, M-J. *Ibid.* **1972**, *141*, 222.
(7) Some work from other groups was reported: (a) Elliot, S. C.; Jacoby, A. N.; Barnhill, M. A.; Howard, W. E. *J. Natl. Cancer Inst. (U.S.)* **1973**, *51*, 1135. (b) Fumarola, D.; DeRinaldis, P.; Marcuccio, L. *Atti Relaz. Accad. Pugliese Sci., Parte 2*, **1969**, *27*, 163. (c) Fumarola, D.; DeRinaldis, P.; Marcuccio, G. *Batteriol. Virol. Imunol.* **1970**, *18*, 11. (d) Fossali, G. C.; Fumarola, D.; Cerra, E.; Cavalieri, E. *Riv. Emoter, Immunoematol.* **1969**, *16*, 91. (e) Fumarola, D.; Giordano, D.; Scuderi, N. *Ann. Sclavo* **1973**, *14*, 284. (f) Giordano, D.; Scuderi, N.; Marcuccio, L. *Pathologica* **1973**, *65*, 29. (g) Fumarola, D.; Marcuccio, L; DeRinaldis, P. *Pharmacology* **1972**, *7*, 12.
(8) Rice, F. A. H. *J. Chem. Soc. C* **1971**, 2599.
(9) Rice, F. A. H. *Carbohyd. Res.* **1972**, *21*, 65.

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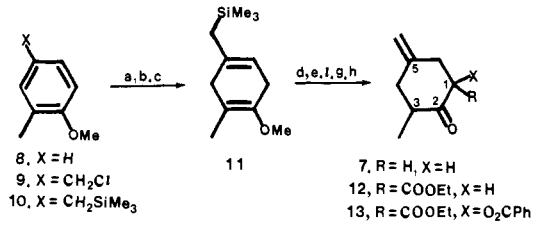
Scheme III



8, X = H
9, X = CH_2Cl
10, X = CH_2SiMe_3

11

7, R = H, X = H
12, R = COOEt, X = H
13, R = COOEt, X = O_2CPh

[a] HCl/CH_2O. [b] $Mg/Me_3SiCl/THF$ (91%). [c] $Li/NH_3/EtOH$ (88%). [d] $HCl/H_2O/THF$ (60%). [e] NaOEt/EtOH/$(EtOOC)_2$. [f] 150 °C (−CO). [g] NaH. [h] $(PhCO_2)_2$.

us that such a preference would be obtained. Furthermore, a δ 1.35 resonance seemed unusually low field for the ring-methyl group in **4** regardless of conformational preference. It seemed possible that the "monobasic carboxylic acid" degradation product from leucogenenol does not correspond to any stereoisomer of **4**. Only preparation of all four possible diastereomers of **4** could provide conclusive evidence refuting the structure proposed for leucogenenol.

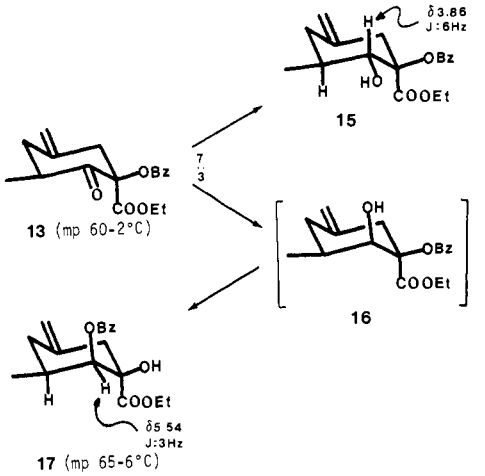
We now report the synthesis of **4** and its three diastereoisomers. Our studies show that a downfield change of 0.10–0.14 ppm for a ring-methyl group upon acetylation of the corresponding diol is observed in **4** and its stereoisomers regardless of relative stereochemistry at C-1 and C-3. This change can be understood as the influence of a vicinal hydroxyl or acetoxyl substituent on an equatorial ring-methyl group, and not as the result of a 1,3-diaxial interaction. Most importantly, our syntheses do not confirm the structure **4** suggested for the degradation product and therefore refute the structure **1** proposed for leucogenenol.

Results and Discussion

The β-hydroxy ketone array in **2** should be prone to retroaldol cleavage or dehydration,[10] and β-acetoxy ketones such as **4** are expected to readily eliminate acetic acid. Therefore, our strategy for the synthesis of **4** and its diastereomers (Scheme II) carried the C-5 carbonyl group in *latent* form as a methylene group (i.e., **5**) until the last step of the synthesis. Since methods exist for stereocontrolled reduction of cyclohexanones to favor production of either an axial or equatorial hydroxyl, a ketone **6** might serve as a common intermediate for either C-2 isomeric acetate. Since the C-5 carbonyl of **4** is only present in latent form in **6**, the C-2 carbonyl can be exploited to activate the adjacent methylene in methyl ketone **7** for regioselective acylation[11] and introduction of oxygen.

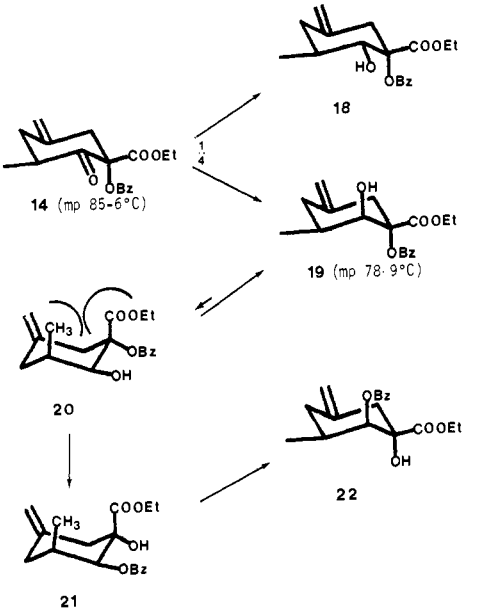
The key intermediate **7** was prepared by a new general method for synthesis of methylenecyclohexanes from benzylsilanes as outlined in Scheme III.[12] Chloromethylation of cresyl methyl ether (**8**) is known to afford **9**.[13] Benzylsilane **10** was obtained from **9** by a Wurtz-type coupling reaction with Me_3SiCl.[14] Conversion of **10** to **7** by Birch reduction–hydrolysis–protodesilylation affords the exocyclic olefin regiospecifically. Acylation of **7** also proceeds regiospecifically as expected[11] and affords **12**.

Introduction of a benzoyloxy substituent at C-1 by treatment of the sodium enolate of **12** with benzoyl peroxide[15] produced a mixture of two isomeric α-benzoyloxy ketones, **13** and **14**, which were separated chromatographically on silica gel. The relative stereochemistries indicated in **13** and **14** for the lower and higher melting isomers respectively were inferred from a 1,2-benzoyl shift observed upon reduction of **13**. Thus, reaction of ketone **13** with sodium borohydride in methanol followed by thin-layer chromatography on silica gel affords two alcohols in a ratio of 7:3. The



major alcohol is assigned structure **15** with an equatorial hydroxyl configuration owing to the large hyperfine coupling of the proton NMR resonance at δ 3.86 which is presumed to indicate an axial proton α to the hydroxyl substituent at C-2 coupled with an axial proton α to an equatorial methyl group at C-3. The minor product is *not* the epimeric alcohol **16**. Rather, a ^1H NMR resonance at δ 5.54 indicates a proton α to a benzoyloxy substituent at C-2. The small hyperfine coupling of this resonance shows that this proton is equatorial and therefore that the benzoyloxy substituent is axial as in structure **17**. Formation of **17** involves a benzoyl migration[16] from the tertiary hydroxyl at C-1 to the vicinal secondary hydroxyl at C-2. Since such migrations occur much more readily from vicinal gauche hydroxyl groups on a six-membered ring when in the cis rather than the trans relationship,[17] the benzoyloxy and hydroxyl substituents in **16** and **17** are presumed to be cis. The configuration at C-1 in **13** and **15** is necessarily the same as in **17**.

The relative configuration at C-1 of **14** is epimeric with that of **13**. Sodium borohydride reduction of **14** affords two alcohols in a ratio of 1:4. As expected no benzoyl migration occurs in



the reduction products from **14** since the **19** → **22** rearrangement requires the less favorable[17] migration (**20** → **21**) between gauche

(10) (a) Kristensen-Reh, M. *Bull. Soc. Chem. Fr.* **1956**, 822. (b) Ziegler, F. E.; Condon, M. E. *Tetrahedron Lett.* **1969**, 2315; *J. Org. Chem.* **1971**, *36*, 307.

(11) Ruzicka, L.; Koolhaas, D. R.; Wind, A. H. *Helv. Chim. Acta* **1931**, *14*, 1163.

(12) Salomon, R. G.; Coughlin, D. J. *J. Org. Chem.* **1979**, *44*, 3784.

(13) Wenner, W. *J. Chem. Soc.* **1951**, *16*, 457. Mndzhoyan, A. L.; Aroyan, A. A. *Izv. Akad. Nauk Arm. SSR Ser. Fiz.-Mat. Nauk* **1955**, *8*, 29; Cf. *Chem. Abstr.* **1956**, *50*, 11982i.

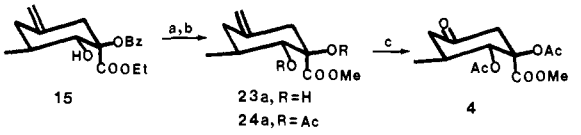
(14) Eaborn, C.; Jackson, R. A.; Pearce, R. *J. Chem. Soc., Perkin Trans.* 1 **1975**, 470.

(15) Cf. Lawesson, S.; Andersson, M.; Berglund, C. *Ark. Kemi* **1961**, *17*, 429.

(16) Ness, R. K.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 4710.

(17) Lemieux, R. U. In "Molecular Rearrangements", Paul de Mayo, Ed.; Interscience: New York, 1964; Part II, pp 765–6.

Scheme IV



15 23a, R=H 24a, R=Ac 4

[a] $MeOH/Ba(OMe)_2$ (79%). [b] $Ac_2O/Py/DMAP$ (95%). [c] O_3 (89%).

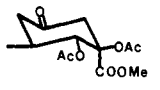
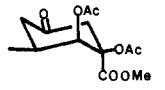
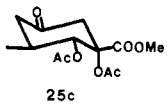
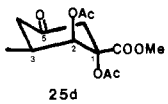
trans hydroxyl groups. Furthermore, the required conformer **20** is disfavored by steric hinderance between bulky 1,3-diaxial substituents. The assignment of configuration to the C-2 hydroxyl, equatorial and axial, to the minor and major products **18** and **19**, respectively, is based on ^1H NMR spectral comparisons of the derived ketodiacetates **25c** and **25d** (vide infra). Benzoyl shift in **15** or **18** from the tertiary to secondary hydroxyl is not expected since the equatorial hydroxyl at C-2 is severely crowded by three vicinal gauche substituents. This congestion is evident from the refractoriness of **23a** and **23c** toward acetylation compared with **23b** and **23d** (see Experimental Section).

Preparation of **4** from **15**, which only requires functional group manipulations and generation of the latent carbonyl at C-5, was achieved as outlined in Scheme IV. Ester exchange and debenzoylation was achieved with barium methoxide in methanol.[18] This reagent is especially effective showing little tendency to generate the carboxylic acid corresponding to **23a** since $Ba(OH)_2$ is insoluble in methanol. Acetic anhydride in pyridine was ineffective for acetylation of the resulting diol **23a**. However, with the acylation catalyst 4-(*N*,*N*-dimethylamino)pyridine,[19] acetylation was readily achieved in excellent yield. Generation of the carbonyl group at C-5 from the methylene group in diacetate **24a** was performed in good yield by ozonolysis and reduction with zinc in acetic acid. Characteristic resonances in the ^1H NMR spectrum of **4** are compared in Table I with those of the keto triester from leucogenenol which was assumed to have structure **4**. Clearly this assumption was incorrect. In particular, the unusually *low* field δ 1.30 resonance for the presumed ring-methyl substituent in the product from leucogenenol does not coincide with the δ 0.98 chemical shift observed for this methyl group in **4**. On the other hand, the δ 5.15 resonance in the product from leucogenenol occurs at *higher* field than the δ 5.27 resonance observed in **4**. Furthermore, this proton is presumably equatorial (J = 4 Hz) in the product from leucogenenol but axial (J = 8 Hz) in **4**. Other ring proton resonances reported[8] for the product from leucogenenol [δ 2.10 (H, d, J = 10 Hz), 2.60 (H, m, J = 6 Hz, and H uncertain), 3.90 (H, d, J = 10 Hz), 4.6 (H, dd, J = 2 and 14 Hz)] are unambiguously different than those observed for **4** [δ 1.9–2.6 (3 H, m), 2.53 (H, d, J = 15 Hz), and 3.47 (H, d, J = 15 Hz)].

The three other possible stereoisomers **25b–d** of **4** were prepared similarly from **17–19**. ^1H NMR spectral comparison of these stereoisomers with the keto triester from leucogenenol is also presented in Table I. None of these stereoisomers show a ring-methyl resonance above δ 1.07 in contrast with the unusually low field δ 1.30 resonance observed for the product from leucogenenol. The isomers **4** and **25c** are presumed to have axial C-2 protons since J = 8 and 10 Hz for the resonances at 5.27 and 5.22, respectively. The isomers **25b** and **25d** are presumed to have equatorial C-2 protons since J = 4 Hz for their δ 5.46 and 5.38 resonances, respectively. The discrepencies between the ^1H NMR spectrum of the keto triester from leucogenenol and **4** and its stereoisomers are readily apparent and are not explicable in terms of a linear displacement of the spectrum. Direct comparison of our spectra with the original spectra for the keto triester from leucogenenol was not possible since these spectra could not be located. Direct comparison with an authentic sample of the product from leucogenenol was also foiled since F. A. H. Rice failed in several attempts over the past 3 years to isolate a sample of leucogenenol for us from his mold.

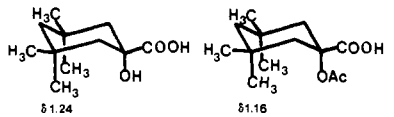
(18) Isbell, H. S. *Natl. Bur. Stand. (U.S.) 1930, 5*, 1179.
(19) Steglich, W.; Hofle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.

Table I. ^1H NMR Spectral Comparison of 4 and Its Isomers with the Keto Triester from Leucogenenol[a]

	CCH_3	OAc	OCH_3	α to OAc
 **4**	0.98 d,J=7Hz	1.96 2.03	3.68	5.27 d,J=8Hz
 **25b**	0.90 d,J=6Hz	1.96 2.12	3.68	5.46 whh=4Hz
 **25c**	1.07 d,J=7Hz	2.11 2.12	3.70	5.22 d,J=10Hz
 **25d**	1.03 d,J=6Hz	2.05 2.13	3.68	5.38 whh=4Hz
Ketotriester from Leucogenenol[b]	1.30 d,J=6Hz	2.08 2.18	3.75	5.15 d,J=4Hz

[a] All spectra are of solutions in $CDCl_3$. [b] Data from ref 8.

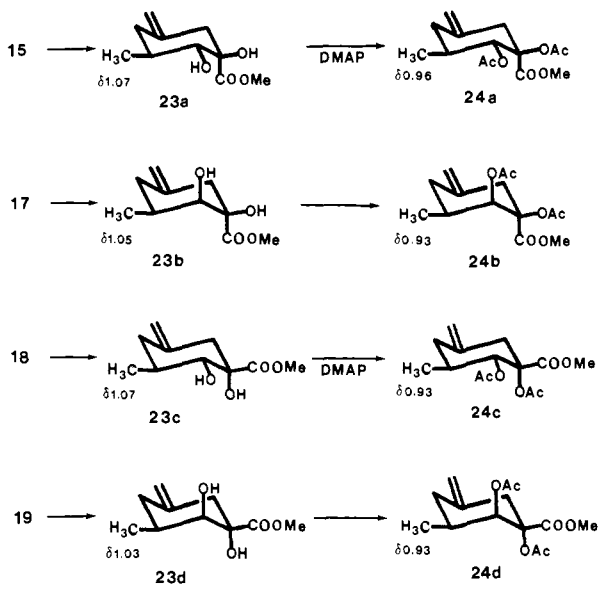
We prefer not to speculate on possible alternative structures which might accommodate the data reported for the keto triester of the "monobasic acid" hydrolysis product from leucogenenol.[20] Certainly the low field position of the presumed ring-methyl substituent must be considered. This resonance occurs at δ 1.35 in the methyl ester of the "monobasic acid" and at δ 1.30 for the corresponding diacetate.[8] Similar chemical shift changes are indeed found for axial methyl groups on a cyclohexyl ring bearing an axial hydroxyl in a 1,3 relationship as in **26** and **27**.[21] However,



26 **27**

our present studies provide evidence against the view that the observation of such a change in chemical shift "indicates a 1,3-diaxial relationship between the C-methyl and the tertiary hydroxy-group".[8] Thus, all four diastereomers of **23** were prepared from **15–19** and acetylated to afford the corresponding diacetates **24**. Acetylation of every diastereomer of **23** was accompanied by an 0.10–0.14 ppm upfield shift of the ring-methyl ^1H NMR resonance. Since this chemical shift change occurs with isomers of **23** in which the C-1 hydroxyl and C-3 methyl are trans as well as cis, this change cannot be taken as proof for "a 1,3-diaxial relationship between the C-methyl and the tertiary hydroxyl". We believe that the observed change results from interactions of the C-3 methyl with a vicinal hydroxyl in **23** or acetoxyl in **24**. If the methyl is equatorial in all four diasteriomers of **23** and **24**, then the C-2 hydroxyl or acetoxyl and C-3 methyl will be gauche whether the vicinal substituent is cis or trans. In other words,

(20) In our opinion, this compound and its degradation products must be prepared again and NMR spectral data should be obtained on modern instruments with high dispersion and sensitivity before further synthetic studies are undertaken. Comparison of the putative degradation products (–)-methylsuccinic acid and 5-methylhexanoic acid with authentic samples is mandatory.
(21) Harnden, M. R. *J. Chem. Soc. C* **1969**, 960.



the observation of such a chemical shift change upon acetylation may indicate a gauche relationship between a ring-methyl and a vicinal hydroxyl group.

Experimental Section

General. Proton magnetic resonance spectra were recorded at 60 MHz with a Varian A60A spectrometer unless 100-MHz spectra, recorded with a Varian HA-100 spectrometer, are indicated. Mass spectra were recorded with a DuPont Model 21-094 GC–MS instrument with an interfaced computer. High-resolution mass spectra were obtained with an AEI/Kratos MS-30 double focusing mass spectrometer with an AEI/Kratos DS-50 data system. Microanalyses were preformed by Chemalytics Inc., Tempe, AZ and Spang Microanalytical Laboratories, Eagle Harbor, MI.

Materials. Tetrahydrofuran (THF) used for all Grignard reactions and Birch reduction was freshly distilled from potassium benzophenone ketyl. Diethyl ether used in the Birch reductions was freshly distilled from lithium aluminum hydride.

[(4-Methoxy-3-methylphenyl)methyl]trimethylsilane (10). A flame-dired 2-L three-necked round-bottomed flask, equipped with a mechanical stirrer, reflux condenser, N_2 inlet, and 1-L addition funnel, was charged with dry magnesium turnings (24 g, 1 mol), dry tetrahydrofuran (100 mL), and chlorotrimethylsilane (127 mL, 108.7 g, 1.0 mol). A solution of 4-methoxy-3-methylbenzyl chloride[11] (0.9 mol) in dry THF (900 mL) was added slowly, at a rate to maintain gentle reflux. After addition was complete, the mixture was heated under reflux 2 h, cooled, and poured into 1 L of cold water. Pentane (700 mL) was added and the pentane layer washed with cold water (3 × 600 mL) and saturated NaCl solution (500 mL), dried ($MgSO_4$), and then concentrated by rotary evaporation of solvents. Distillation under reduced pressure gave **10**: bp 73–78 °C (12 mm) (91%); ^{1}H NMR (CCl_4) δ 0.00 (s, 9 H), 1.94 (s, 2 H), 21.9 (s, 3 H), 3.82 (s, 3 H), 6.68–6.87 (m, 3 H).

Anal. Calcd for $C_{12}H_{20}OSi$: C, 69.17; H, 9.67. Found: C, 68.92; H, 9.42.

[(4-Methoxy-5-methyl-1,4-cyclohexadien-1-yl)methyl]trimethylsilane (11). [(4-Methoxy-3-methylphenyl)methyl]trimethylsilane (**10**) (18.2 g, 0.087 mol) was reduced with lithium (7.5 g, 1.07 mol) wire in liquid ammonia (600 mL), dry diethyl ether (100 mL), and absolute ethanol (71 g, 90 mL, 1.54 mol). Ammonium chloride (65 g, 1.2 mol) was added in small portions, care being taken to avoid foaming of the liquid NH_3. The dry ice condenser was removed, and the liquid NH_3 allowed to evaporate from the flask. Ether (500 mL) was added to the flask, followed by water (1 L). The layers were separated and the ether layer washed with water (2 × 500 mL) and with saturated sodium chloride solution (500 mL), dried ($MgSO_4$), and freed of solvents by rotary evaporation. Distillation under reduced pressure afforded **11** [bp 120–125 °C (12 mm) (6.1 g, 88%)] which by ^{1}H NMR appeared to be a mixture of [(4-methoxy-5-methyl-1,4-cyclohexadien-1-yl)methyl]trimethylsilane (**11**) (~70%) and dihydrobenzene isomers (~30%). **1H** NMR ($CDCl_3$) δ 0.00 (s, 9 H), 1.42 (s, 2 H), 1.58 (s, 3 H), 2.48–2.85 (m, 4 H), 3.46 (s, 3 H), 5.16 (m, 1 H).

4-Methylene-2-methylcyclohexanone (7) was prepared by hydrolysis of [(4-methoxy-5-methyl-1,4-cyclohexadien-1-yl)methyl]trimethylsilane (**11**, 18 g), in THF (400 mL), concentrated HCl (36 mL), and H_2O (18 mL) at room temperature for 30 h. Workup with water, extraction into ether, and careful distillation through a glass helices packed column gave the ketone **7** (60%): bp 67–68 °C (12 mm); ^{1}H NMR ($CDCl_3$) δ 1.06 (3 H, d, J = 6 Hz, CH_3), 2.08–2.8 (7 H), 4.88 (2 H, s, olefinic CH_2).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.42; H, 9.73.

2-Carboethoxy-4-methylene-6-methylcyclohexanone (12).[12] A solution of NaOEt in ethanol (45 mL) was prepared from sodium (2.7 g, 118 mmol) in a 100-mL three-necked flask fitted with a mechanical stirrer, inlet for dry nitrogen, and a rubber septum. The ketone **7** (15 g, 120 mmol) dissolved in diethyl oxalate (19.2 mL) was added dropwise at −10 °C. The resulting mixture was stirred at 0 °C (2 h) and at 25 °C (15 h), and then poured into an ice cold solution of concentrated HCl (30 mL) in water (200 mL). The mixture was extracted with ether (3 × 60 mL). The combined extracts were dried (Na_2SO_4). Solvents were removed by rotary evaporation and the crude oily product was distilled under reduced pressure to remove volatile impurities (up to 100 °C (15 mm)). The residual oil was heated to 180 °C under a blanket of nitrogen until evolution of gas ceased. After cooling, the product was distilled under reduced pressure to afford **12**: bp 155–165 °C (15 mm) (17 g, 72%). The ^{1}H NMR spectrum of this product corresponds to a 3:7 mixture of enol and ketone tautomers of **12**: NMR (CCl_4) δ 1.0–1.6 (6 H), 1.7–3.4 (6.7 H), 4.0–4.5 (2 H, m, OCH_2), 4.77 (0.6 H, olefinic CH_2 of enol tautomer), 4.9 (1.4 H, olefinic CH_2 of keto tautomer), 12.25 (0.3 H, s, OH).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.42; H, 8.26.

Ethyl 1-Benzoyloxy-5-methylene-3-methyl-2-oxocyclohexanecarboxylates 13 and 14.[13] In a 100-mL three-necked flask fitted with a mechanical stirrer, inlet for dry nitrogen, and rubber septum a 57% dispersion of sodium hydride in mineral oil (0.72 g, 17 mmol) was washed with dry pentane (2 × 5 mL) and then suspended in benzene (15 mL) freshly distilled from sodium benzophenone ketyl. The keto ester **12** (2.94 g, 15 mmol) was added dropwise over 10 min with a syringe. The resulting mixture was stirred for 30 min at 25 °C and then cooled to 0 °C. A solution of benzoyl peroxide (3.66 g, 15 mmol) in benzene (30 mL) was added over 1 h. The resulting mixture was stirred at 25 °C for an additional hour, and then poured into water (75 mL). The phases were separated and the aqueous phase was extracted with ether (2 × 75 mL). The combined organic extracts were washed with water (3 × 50 mL) until neutral and dried (Na_2SO_4). Rotary evaporation of solvents gave a crude oily product which was purified by chromatography on silica gel (700 g, Baker 60–200 mesh) with chloroform as eluting solvent. Fractions affording pure **13** (0.63 g), pure **14** (1.13 g), and a mixture of these isomers (2.33 g) were obtained. The overall yield of **14** + **15** was 87%. The chromatography was monitored by TLC [0.25 mm silica gel, chloroform, R_f (**14**) 0.39, R_f (**13**) 0.49, R_f (starting material) **12** 0.59]. **13** can be separated from starting material via preparative TLC [0.50 mm silica gel, 1:4 ethyl acetate/isooctane, R_f (**13**) 0.37, R_f (starting material) **12** 0.52]. The relative amounts of **13** and **14** can be easily determined by NMR in benzene-d.[6] The rationale for assigning a *trans*-3-methyl stereochemistry to the less polar ketone **13** and a *cis*-3-methyl stereochemistry to the more polar ketone **14** is discussed in the results section.

Ethyl 1-Benzoyloxy-*trans*-3-methyl-5-methylene-2-oxocyclohexanecarboxylate (13). The less polar ketone (R_f 0.49) showed mp 60–62 °C: ^{1}H NMR (benzene-d,[6] 100 MHz) δ 0.98 (3 H, t, J = 7 Hz, ester CH_3), 1.03 (3 H, d, J = 6 Hz, $CHCH_3$), 1.92 (1 H, br d, J = 14 Hz, eq H-3), 2.40 (1 H, ddd, J = 3, 6, 13 Hz, ax H-5), 2.72 (1 H, br d, J = 13 Hz, eq H-5), 3.26 (1 H, dd, J = 13, 3 Hz, ax H-3), 3.57 (1 H, quintet, J = 6 Hz, ax H-6), 4.10 (2 H, q, J = 7 Hz, ester CH_2), 4.87 (2 H, m, olefinic), 7.0–7.4 (3 H, m, aromatic), 8.1–8.4 (2 H, m, aromatic); mass spectrum (70 eV) m/e (relative intensity) 316 (M, 0.6), 194 (5), 106 (6), 105 (100), 77 (16); high-resolution mass spectrum (M), calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1279.

Ethyl 1-Benzoyloxy-*cis*-3-methyl-5-methylene-2-oxocyclohexanecarboxylate (14). The more polar ketone (R_f 0.39) showed mp 85–86 °C: ^{1}H NMR, (benzene-d,[6] 100 MHz) δ 0.94 (3 H, d, J = 6 Hz, $CHCH_3$), 0.96 (3 H, t, J = 7 Hz, ester CH_3), 1.83 (1 H, br d, J = 13 Hz, eq H-5), 2.22 (1 H, ddd, J = 3, 6, 13 Hz, ax 5-H), 2.94 (1 H, quintet, J = 6 Hz, ax H-6), 3.05 (1 H, br d, J = 14 Hz, eq H-3), 3.70 (1 H, dd, J = 3, 14 Hz, ax H-3), 4.13 (2 H, q, J = 7, ester CH_2), 4.66 (2 H, m, olefinic), 6.95–7.35 (3 H, m, aromatic), 7.95–8.2 (2 H, m, aromatic); mass spectrum m/e (rel intensity) 316 (M, 0.3), 106 (6.4), 105 (100), 77 (17); high-resolution mass spectrum (M), calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1266.

Borohydride Reduction of α-Benzyloxy-β-keto Esters 13 and 14. Ketone **14** (80 mg) was dissolved in methanol (3 mL) under nitrogen and was cooled to 0 °C. Sodium borohydride (30 mg) was added and the reaction was stirred at 0 °C for 0.5 h. Aqueous HCl (10%, 1 mL) was added dropwise (foaming!) followed by water (20 mL). The solution was

saturated with sodium chloride and extracted with ether (3 × 30 mL), dried ($MgSO_4$), and concentrated. The crude product was placed on two silica gel thin-layer plates (0.5 mm) and developed four times with 4:1 isooctane:ethyl acetate. Product **18** (10.7 mg, 13%) had an R_f of 0.21–0.28, while product **19** (39 mg, 49%) had an R_f of 0.28–0.42. The configurations at C-2 of the alcohols were assigned on the basis of the NMR spectra of the corresponding diacetates (see below).

Ethyl 1-Benzoyloxy-*cis*-2-hydroxy-*trans*-3-methyl-5-methylenecyclohexanecarboxylate (18). The minor isomer was the more polar alcohol which shows: ^1H NMR ($CDCl_3$, 100 MHz) δ 1.17 (3 H, d, J = 6 Hz, $CHCH_3$), 1.30 (3 H, t, J = 7 Hz, ester CH_3), 1.4–2.8 (5 H), 3.47 (1 H, d, J = 13 Hz), 3.74 (1 H, br s), 4.31 (2 H, q, J = 7 Hz, ester CH_2), 4.70 (1 H, narrow m, olefinic), 4.78 (1 H, narrow m, olefinic), 7.45–7.83 (3 H, m, aromatic), 7.95–8.29 (2 H, aromatic).

Ethyl 1-Benzoyloxy-*trans*-2-hydroxy-*trans*-3-methyl-5-methylenecyclohexanecarboxylate (19). The major isomer was the less polar alcohol, mp 78–79 °C, which shows: ^1H NMR ($CDCl_3$, 100 mHz) δ 1.06 (3 H, d, J = 6 Hz, $CHCH_3$), 1.25 (3 H, t, J = 7 Hz, ester CH_3), 1.6–2.4 (3 H, m), 2.53 (1 H, sharp d, J = 15 Hz), 3.02 (1 H, slightly br d, J = 15 Hz), 3.07–3.35 (1 H, br s), 4.26 (2 H, q, J = 7 Hz, ester CH_2), 4.28 (1 H, partly buried), 4.78 (1 H, narrow m, olefinic), 4.82 (1 H, narrow m, olefinic), 7.25–7.66 (3 H, m, aromatic), 7.84–8.13 (2 H, m, aromatic).

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.86; H, 7.02.

The less polar ketone **13** (R_f 0.49) (46 mg) was reduced with sodium borohydride by a procedure analogous with that used for reducing the more polar ketone **14** (R_f 0.39). The crude product was placed on a silica gel thin layer chromatography plate (0.25 mm) and developed two times with 4:1 isooctane:ethyl acetate. The major product **15** (21 mg, 46%) has an R_f of 0.22–0.35 and the minor product **17** (10 mg, 22%) has an R_f of 0.35–0.43. The configuration at C-2 of the products was deduced on the basis of ^1H NMR spectra of the derived diacetates (see below). The major product is not the expected alcohol **16**. Instead, a benzoyloxy group at C-2 is indicated by the chemical shift of the C-2 proton at δ 5.54 in **17**.

Ethyl 1-Benzoyloxy-*cis*-2-hydroxy-*trans*-3-methyl-5-methylenecyclohexanecarboxylate (15). The major isomer shows: ^1H NMR ($CDCl_3$) δ 1.10 (3 H, d, J = 6 Hz, $CHCH_3$), 1.24 (3 H, t, J = 7 Hz, ester CH_3), 1.7–2.6 (4 H, m), 3.22–3.46 (2 H, m), 3.86 (1 H, br d, J = 8 Hz), 4.24 (2 H, q, J = 7 Hz, ester CH_2), 4.86 (2 H, br s, olefinic), 7.30–7.67 (3 H, m, aromatic), 8.02 (2 H, dd, J = 2, 8 Hz, aromatic).

Ethyl *trans*-2-Benzoyloxy-1-hydroxy-*trans*-3-methyl-5-methylenecyclohexanecarboxylate (17). The minor isomer has mp 65–66 °C and shows: ^1H NMR ($CDCl_3$) δ 1.08 (3 H, d, J = 6 Hz, $CHCH_3$), 1.24 (3 H, t, J = 7 Hz, ester CH_3), 3.35 (1 H, s, OH), 2.1–3.2 (5 H), 4.22 (2 H, q, J = 7 Hz, ester CH_2), 4.86 (2 H, olefin), 5.54 (H, d, J = 3 Hz, C-2), 7.34–7.70 (3 H, m, aromatic, 7.98–8.16 (2 H, m, aromatic).

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 68.04; H, 6.97.

Methyl 1,2-Dihydroxy-3-methyl-5-methylenecyclohexanecarboxylates (23). Methanolysis and transesterification of hydroxy benzoates **15** and **17–19** afford the corresponding diols **23**. In a representative procedure the benzoate (18 mg) was placed in a flame-dried round-bottomed flask (10 mL) with magnetic stirrer under nitrogen. The flask was stoppered with a septum cap and anhydrous methanol (1 mL) was added followed by methanolic $Ba(OMe)_2$[18] (14 μL of a 1.4 M solution). [The methoxide was prepared by stirring chunk BaO with anhydrous methanol for 3 days. The methoxide goes into solution, the hydroxide is insoluble.] The reaction was stored at 8 °C and monitored periodically by silica gel TLC [ethyl acetate, starting materials R_f 0.72, products R_f around 0.55]. After TLC indicated that the reaction was complete, the reaction was stirred with Amberlyst 15 (H^+ cation exchange resin for nonaqueous solvents, Rohm and Haas, approximately 100–150 mg) until the pH was neutral (5 min). The solution was filtered, the amberlyst washed well with metahnol, and the combined metanolic solutions concentrated. The resulting diol methyl esters were separated from traces of methyl benzoate or starting benzoate by preparative thin-layer chromatography prior to acetylation.

Methyl 1,*cis*-2-Dihydroxy-*trans*-3-methyl-5-methylenecyclohexanecarboxylate (23a). The reaction was worked up after 7 days. NMR indicated some extra benzoate present (besides methyl benzoate) so crude product was purified by preparative TLC [1 development 2:1 ethyl acetate:isooctane, R_f 0.35, eluting the product with ethyl acetate]. Diol **23a** was obtained in 79% yield from benzoate **15**. ^1H NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 6 Hz, $CHCH_3$), 1.7–2.5 (4 H), 2.67 (1 H, br d, J = 14 Hz), 3.1–3.7 (3 H, m), 3.75 (3 H, s, OMe), 4.68 (1 H, br s, olefinic), 4.75 (1 H, dr s, olefinic).

Methyl 1,*trans*-2-Dihydroxy-*trans*-3-methyl-5-methylenecyclohexanecarboxylate (23b). The reaction was complte in 3 days to afford pure diol **23b** in 100% yield from benzoate **17**. ^1H NMR ($CDCl_3$) δ 1.05 (3 H, d, J = 6 Hz, $CHCH_3$), 2.18 (3 H, br s), 2.50 (2 H, br s), 3.13 (2 H, br s), 3.80 (3 H, s, OMe), 3.97 (1 H, d, J = 3 Hz, C*H*OH), 4.80 (2 H, br s, olefinic).

Methyl 1,*trans*-2-Dihydroxy-*cis*-3-methyl-5-methylenecyclohexanecarboxylate (23c). The reaction was worked up after 3 days. The NMR indicates that the reaction was 70% complete. The crude product was purified by preparative TLC [0.25 mm plate, 1 development 1:1 hexane:ethyl acetate, R_f 0.3]. Diol **23c** was obtained in 68% yield from benzoate **18**. ^1H NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 6 Hz, $CHCH_3$), 1.6–2.9 (6 H), 3.5–3.8 (2 H, m), 3.83 (3 H, s, OMe), 4.72–4.92 (2 H, m, olefinic).

Methyl 1,*cis*-2-Dihydroxy-*cis*-3-methyl-5-methylenecyclohexanecarboxylate (23d). The reaction was worked up after 7 days. There was still some benzoate present (besides methyl benzoate). The curde product was purified by preparative TLC [1 development 1:1 ethyl acetate:hexane, R_f 0.3]. Diol **23d** was obtained in 42% yield from benzoate **19**. ^1H NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 6 Hz, $CHCH_3$), 2.0–2.4 (4 H), 2.6–3.1 (3 H), 3.72 (1 H, br s), 3.83 (3 H, s, OMe), 4.7–4.9 (2 H, m, olefinic).

Methyl 1,2-Diacetoxy-3-methyl-5-methylenecyclohexanecarboxylates (24). Acetylation of the diols with acetic anhydride in pyridine succeeded with compounds **23b** and **23d**. More powerful conditions, acetic anhydride and 4-(*N*,*N*-dimethylamino)pyridine,[15] were necessary to achieve complete acetylation of the more hindered diols **23a** and **23c** which have three adjacent equatorial substituents. Compounds **24a**, **24b**, and **24d** can be separated by analytical VPC on a 10% FFAP column (5 ft × $^1/_8$ in., 130 °C). The relative retention times **24d**:**24a**:**24b** are 0.80:0.92:1.00. However, the products obtained after removal of the ether solvent (see below) were quite pure, and were used directly for preparation of the corresponding ketones **25**.

Methyl 1,*trans*-2-Diacetoxy-*cis*-3-methyl-5-methylenecyclohexanecarboxylate (24c). Diol **23c** (5 mg, 0.025 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (6 mg, 0.05 mmol) were mixed in anhydrous methylene chloride (1 mL) under nitrogen. Acetic anhydride (distilled 0.075 mmol, 7 μL) was added in one portion and the mixture allowed to stand at room temperature. The reaction, monitored by TLC (1:1 ethyl acetate:hexane), proceeded very slowly. First the monoacetate formed (R_f 0.5, 1 day) and then the diacetate formed (R_f 0.62, 4 days). The reaction was diluted with ether (10 mL), washed with dilute aqueous HCl (5%, 5 mL) and saturated sodium bicarbonate (5 mL), dried ($MgSO_4$), and concentrated to give the diacetate **24c** (90%). ^1H NMR ($CDCl_3$, 100 MHz) δ 0.93 (3 H, d, J = 6 Hz, $CHCH_3$), 1.5–3.2 (5 H), 2.06 (3 H, s, OAc), 2.07 (3 H, s, OAc), 3.68 (3 H, s, OMe), 4.6–5.0 (3 H).

Methyl 1,*cis*-2-Diacetoxy-*cis*-3-methyl-5-methylenecyclohexanecarboxylate (24d). Diol **23d** (21 mg) was allowed to stand 3 days with acetic anhydride (1 mL) and pyridine (1 mL). The long reaction time was necessary to effect complete acetylation. The excess reagents were removed in vacuo and the residue taken up in ether (10 mL), washed with saturated $NaHCO_3$ (5 mL) and saturated cupric sulfate (5 mL), dried ($MgSO_4$), and concentrated to obtain diacetate **24d** (37 mg, 95%). ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 6 Hz, $CHCH_3$), 1.8–2.2 (3 H, m), 2.02 (3 H, s, OAc), 2.05 (3 H, s, OAc), 2.92 (2 H, br s), 3.65 (3 H, s, OMe), 4.70 (1 H, br s, olefinic), 4.77 (1 H, br s, olefinic), 5.20 (1 H, narrow m, whh = 3 Hz, C*H*OAc). The axial–equatorial configuration of the secondary acetate and adjacent methyl groups is indicated by the narrowness of the peak corresponding to C*H*OAc (equatorial–axial coupling).

Methyl 1,*cis*-2-Diacetoxy-*trans*-3-methyl-5-methylenecyclohexanecarboxylate (24a). Diol **23a** (22 mg) was acetylated with acetic anhydride and 4-(*N*,*N*-dimethylamino)pyridine in the same manner used in the preparation of compound **24c** above. Analysis by TLC after 3 h (1:1 ethyl acetate:hexane) indicates one single product and no more starting material. Diacetate **24a** (95%) exhibits ^1H NMR ($CDCl_3$) δ 0.96 (3 H, d, J = Hz, $CHCH_3$), 1.5–2.6 (3 H, m), 1.96 (3 H, s, OAc), 2.00 (3 H, s, OAc), 2.53 (1 H, d, J = 15 Hz), 3.17 (1 H, d, J = 15 Hz), 3.63 (3 H, s, OMe), 4.77 (2 H, br s, olefinic), 4.98 (1 H, d, J = 6 Hz, C*H*OAc). The equatorial–equatorial relationship of the secondary acetate group and the adjacent methyl group is indicated by the large coupling (6 Hz) between C*H*OAc and C*H*Me (axial–axial coupling).

Methyl 1,*trans*-2-Diacetoxy-*trans*-3-methyl-5-methylenecyclohexanecarboxylate (24b). The acetic anhydride/pyridine procedure used in preparation of compound **24d** above was followed starting with diol **23b** except that only an 18 h reaction time was required. Diacetate **24b** (83%) exhibits ^1H NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 6 Hz, $CHCH_3$), 1.96 (3 H, s, OAc), 2.12 (3 H, s, OAc), 2.0–2.6 (3 H, m), 2.70 (2 H, br s), 3.68 (3 H, s, OMe), 4.78 (2 H, br s, olefinic), 5.55 (1 H, d, J = 2 Hz, C*H*OAc). The axial–equatorial relationship between the secondary

acetate and adjacent methyl groups is indicated by the small (2 Hz) coupling between the H geminal to the acetate and the H geminal to the methyl group (equatorial-axial coupling). Mass spectrum (70 eV) *m/e* (realtive intensity) 284 (M, 3), 224 (M - HOAc, 2), 181 (47), 164 (62), 150 (22), 149 (66), 123 (45), 105 (100), 95 (37), 59 (20), 55 (25); high-resolution mass spectrum (M) calcd for $C_{14}H_{20}O_6$ 284.1260, found 284.1238.

Methyl 1,2-Diacetoxy-3-methyl-5-oxocyclohexanecarboxylates (25). Ozonolysis of methylene triesters **24** afforded keto triesters **25**.

General Procedure. Methylene cyclohexane derivative **24d** (10 mg, 0.35 mmol) was dissolved in dry methylene chloride (5 mL) and cooled to -78 °C. Ozone was bubbled into the solution until the blue color of excess ozone persisted in the solution. The ozone stream was removed and a stream of nitrogen was bubbled through the solution at -78 °C until the solution became colorless. After the solution turned colorless, the nitrogen stream was continued for 5 min. Acetic acid (0.25 mL, 4 mmol) was added to the flask followed by zinc dust (13 mg, 0.2 mmol). The solution was allowed to warm to room temperature and stirred for 1 h. The solution was filtered and extracted with ether (3 × 10 mL) and the combined extracts were washed with water (2 × 10 mL), saturated aqueous sodium bicarbonate (2 × 10 mL), water (10 mL), and saturated sodium chloride (2 × 10 mL), dried ($MgSO_4$) and rotary evaporated to afford **25d** (9.7 mg, 97%). The keto diacetates **4** and **25b-d** were fully characterized by ^1H NMR and high-resolution mass spectra as described below.

Methyl 1,*cis*-2-Diacetoxy-*trans*-3-methyl-5-oxocyclohexanecarboxylate (4). The keto diacetate **4** (89% from **24a**) obtained after removal of solvents was quite pure according to ^1H NMR analysis. ^1H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7 Hz, $CHCH_3$), 1.96 (3 H, s, OAc), 2.03 (3 H, s, OAc), 1.9-2.6 (3 H, m), 2.53 (1 H, d, J = 15 Hz), 3.47 (1 H, d partly buried, J = 15 Hz), 3.68 (3 H, s, OMe), 5.27 (1 H, br d, J = 8 Hz, $CHOAc$); mass spectrum (70 eV) *m/e* (relative intensity) no parent peak, 226 (M - HOAc, 5.5), 185 (37), 184 (75), 167 (53), 166 (67), 144 (39), 146 (36), 142 (27), 126 (15) 125 (100), 103 (21), 99 (30), 82 (22), 79 (16), 69 (48), 60 (25), 59 (29), 58 (16), 57 (53), 55 (47); high-resolution mass spectrum (M - HOAc), calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0830.

Further purification of **4** was attempted with preparative TLC (0.25 mm, 1:1 ethyl acetate:hexane). No **4** was recovered from the plate. Only the acetic acid elimination product, methyl *trans*-6-acetoxy-5-methyl-3-oxo-1-cyclohexenecarboxylate (R_f 0.53-0.67), was obtained. NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 7 Hz, $CHCH_3$), 2.10 (3 H, s, OAc), 2.3-2.8 (3 H, m), 3.85 (3 H, s, OMe), 5.76 (1 H, br d, J = 4 Hz, $CHOAc$), 6.80 (1 H, s, olefinic).

Methyl 1,*trans*-2-Diacetoxy-*trans*-3-methyl-5-oxocyclohexanecarboxylate (25b). The keto diacetate **25b** (82% from **24b**) obtained after removal of solvents was quite pure according to ^1H NMR analysis. ^1H NMR ($CDCl_3$) δ 0.90 (3 H, d, J = 6 Hz, $CHCH_3$), 1.8-2.2 (3 H, m), 1.96 (3 H, s, OAc), 2.12 (3 H, s, OAc), 2.48 (1 H, d, J = 15 Hz), 3.28 (1 H, d, J = 15 Hz), 3.68 (3 H, s, OMe), 5.46 (1 H, narrow m, whh = 4 Hz, CHOAc); mass spectrum (70 eV) *m/e* (relative intensity) 226 (M - HOAc, 12), 185 (41), 184 (91), 167 (45), 166 (61), 144 (42), 143 (32), 142 (29), 126 (18), 125 (100), 103 (25), 99 (28), 82 (25), 79 (20), 69 (40), 55 (39); high-resolution mass spectrum (M - HOAc), calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0853.

Methyl 1,*trans*-2-Diacetoxy-*cis*-3-methyl-5-oxocyclohexanecarboxylate (25c). The keto diacetate **25c** (95% from **24c**) obtained after removal of solvents was quite pure according to ^1H NMR analysis. ^1H NMR ($CDCl_3$, 100 MHz) δ 1.07 (3 H, d, J = 7 Hz, $CHCH_3$), 2.0-2.8 (4 H), 2.11 (3 H, s, OAc), 2.12 (3 H, s, OAc), 3.27 (1 H, d, J = 13 Hz), 3.70 (3 H, OMe), 5.22 (1 H, d, J = 10 Hz, $CHOAc$); mass spectrum (70 eV) *m/e* (relative intensity) no parent peak, 226 (M - HOAc, 11), 202 (23), 185 (84), 184 (100), 167 (61), 166 (62), 146 (33), 145 (21), 144 (49), 143 (53), 142 (40), 126 (22), 125 (83), 103 (40), 99 (36), 85 (33), 83 (23), 82 (30), 79 (26), 71 (22), 69 (80), 60 (20), 59 (25), 56 (43), 55 (56); high-resolution mass spectrum (M - HOAc), calcd for $C_{11}H_{14}O_5$ 226.0841, found 226.0825.

Methyl 1,*cis*-2-Diacetoxy-*cis*-3-methyl-5-oxocyclohexanecarboxylate (25d). The keto diacetate **25d** (97% from **24d**) obtained after removal of solvents was quite pure according to ^1H NMR analysis. ^1H NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 6 Hz, $CHCH_3$), 2.05 (3 H, s, OAc), 2.13 (3 H, s, OAc), 1.9-2.6 (3 H, m), 2.97 (1 H, slightly br d, J = 15 Hz), 3.25 (1 H, d, J = 15 Hz), 3.68 (s, OMe), 5.38 (1 H, narrow m, whh = 4 Hz, $CHOAc$); mass spectrum (70 eV) *m/e* (relative intensity) 286 (M, 0.5), 226 (M - HOAc 24) 185 (36) 184 (100), 167 (15), 166 (19), 144 (29), 143 (29), 142 (47), 125 (31), 110 (16), 103 (16), 99 (24), 83 (15), 82 (26), 77 (17), 69 (19), 55 (17); high-resolution mass spectrum (M), calcd for $C_{13}H_{18}O_7$ 286.1052, found 286.1034.

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Registry No. 1, 29101-95-9; **4**, 80448-38-0; **7**, 71435-90-0; **10**, 71435-91-1; **11**, 71435-95-5; **12**, 80448-39-1; **13**, 80448-40-4; **14**, 80448-41-5; **15**, 80448-42-6; **17**, 80448-43-7; **18**, 80482-92-4; **19**, 80482-93-5; **23a**, 80448-44-8; **23b**, 80482-94-6; **23c**, 80482-95-7; **23d**, 80482-96-8; **24a**, 80448-45-9; **24b**, 80482-97-9; **24c**, 80482-98-0; **24d**, 80482-99-1; **25b**, 80483-00-7; **25c**, 80483-01-8; **25d**, 80483-02-9; 4-methoxy-3-methylbenzyl chloride, 60736-71-2; methyl *trans*-6-acetoxy-5-methyl-3-oxo-1-cyclohexenecarboxylate, 80448-46-0.

Low-Temperature Reactions of Metal Atoms with Methyl Bromide

Yasutaka Tanaka, Stephen C. Davis, and Kenneth J. Klabunde*

Contribution from the Department of Chemistry, Kansas State University, Manhattan, Kansas 66506. *Received June 8, 1981*

Abstract: The atoms of a series of metals were codeposited with CH_3Br under matrix isolation conditions (argon diluent at 12 K and pure CH_3Br at 77 K). Oxidative addition of CH_3Br to Fe, Co, Ni, and Pd did not occur upon simple codeposition or upon matrix photolysis, which is rationalized by the formation of a favored CH_3Br-M complex. Cu, Ag, and Au behaved similarly. Main-group metals Mg, Al, Ga, and In did react to form CH_3MBr whereas Zn, Tl, Ge, Sn, and Pb did not. For the group 1B-4B (Cu, Zn, B, C) families the most important reactivity parameter is a low ionization potential. However, a high heat of vaporization of the element also has a positive effect on reactivity. In the case of Mg, clusters may be necessary for high reactivity.

Introduction

Ault[1] has recently provided convincing evidence that Mg atoms react in a low-temperature argon matrix at 15 K with methyl halides to yield CH_3MgX species. This finding seemed remarkable to us in light of the extremely low temperature employed and the report of Skell and Girard[2] suggesting that Mg atoms deposited with pure alkyl halides at 77 K did not yield oxidative addition products (nonsolvated Grignard reagents) until the matrix was

(1) Ault, B. *J. Am. Chem. Soc.* **1980**, *102*, 3480.

(2) Skell, P. S.; Girard, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 5518.

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