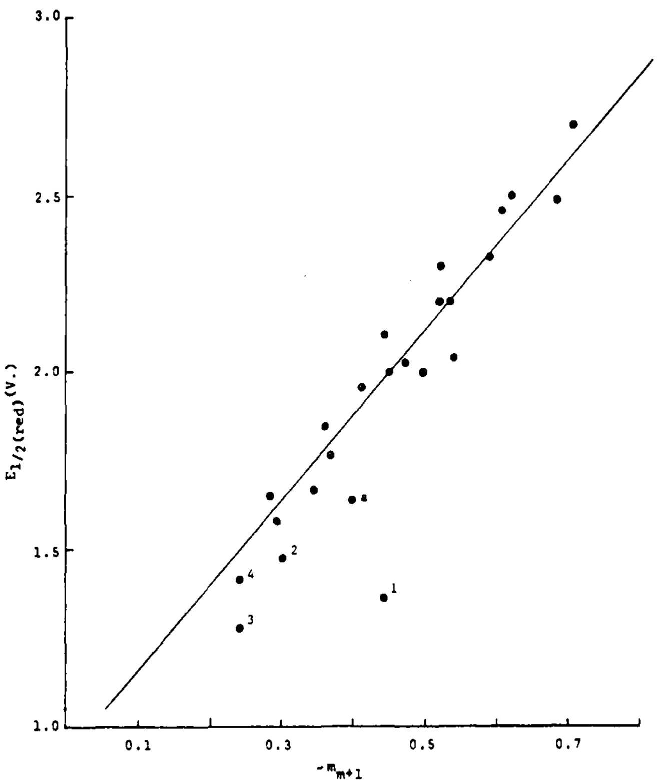


Figure 1. Half-wave reduction potentials *vs.* energies of lowest vacant orbitals for azulene (a), azupyrene (1), 4-methyl-*as*-azupyrene (2), aceheptylene (3), and 3,5,8,10-tetramethylaceheptylene (4) in acetonitrile, and benzenoid hydrocarbons[7] in aqueous dioxane.

It has been pointed out[6a] that different values of β, which will change $-m_{m+1}$, may be required when the bond lengths in a conjugated system are not equal. The value of $-m_{m+1}$ used for azulene (0.40) in Figure 1 was obtained by the simple HMO method using a standard length of 1.4 Å. We have checked this and also calculated the corresponding value for $-m_{m+1}$ (0.47) using bond lengths found by the X-ray diffraction analysis of azulene-1,3-dipropionic acid.[18] The use of unequal bond lengths thus causes the point for azulene to be farther from the line for benzenoid aromatics. CNDO/2 calculations for azulene using equal bond lengths and the X-ray data gave $-m_{m+1}$ values of 0.27 and 0.40, respectively, and thus show the same directional trend in magnitude.[19] The values of $-m_{m+1}$ for the benzenoid compounds in Figure 1 were also calculated using equal bond lengths, and the use of alternating, unequal bond lengths might result in comparable corrections. As a check it was determined for naphthalene, and qualitatively for anthracene and phenanthrene, that the corrections would not be significant.[20] The assumption of standard, equal bond lengths for **1**, **2**, and **3** therefore seems not to be responsible for the location of their points on the graph below the line for the benzenoid hydrocarbons.

Compounds **2** and **4** have methyl substituents and the effect of these groups must be considered. Comparison of **3** and **4** shows a difference of 0.14 V due to four methyl groups, and this suffices to put the point for **4** within the distribution for benzenoid compounds. A study[21] on a series of methylazulenes showed that the substituent effects in these compounds amounted to 0.01–0.12 V, which did not agree well with calculated potential changes. These results suggest that the reduction potential of the parent system of **2** would be slightly lower than that of **2**, and thus still farther below the line.

Acknowledgments. The authors wish to express their gratitude to Professor K. Hafner for providing compounds **2**, **3**, and **4**, and also to Professors E. R. Davidson and N. Epiotis and to Mr. W. Cherry for assistance with the calculations.

Registry No.—**1**, 193-85-1; **2**, 781-30-6; **3**, 209-42-7; **4**, 17597-70-5.

References and Notes

(1) From the Ph.D. Thesis of G. M. Masada, University of Washington, 1972.
(2) Supported in part by grants from the National Science Foundation.
(3) National Institutes of Health Predoctoral Fellow, 1968–1970.
(4) E. Hückel, International Conference on Physics, London, 1934, Vol. II, The Physical Society, London, 1935.
(5) A. Maccoll, *Nature (London)*, **163**, 178 (1949).
(6) For further discussion cf. (a) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, Chapter 7, and references cited therein; (b) G. J. Hoijtink, *Chem. Weekbl.*, **56**, 54 (1960).
(7) Reference 6a, pp 177–181.
(8) J. A. Nelson, Ph.D. Thesis, University of Washington, 1950.
(9) A. G. Anderson, Jr., A. A. MacDonald, and A. F. Montana, *J. Amer. Chem. Soc.*, **90**, 2993 (1968); A. G. Anderson, Jr., G. M. Masada, and A. F. Montana, *J. Org. Chem.*, **38**, 1439 (1973); A. G. Anderson, Jr., A. F. Montana, A. A. MacDonald, and G. M. Masada, *ibid.*, **38**, 1445 (1973).
(10) K. Hafner, R. Fleischer, and K. Fritz, *Angew. Chem., Int. Ed. Engl.*, **4**, 69 (1965).
(11) K. Hafner, unpublished results.
(12) W. H. Wong, Ph.D. Thesis, University of Washington, 1970.
(13) S. Wawzonek and H. A. Laitinen, *J. Amer. Chem. Soc.*, **64**, 2365 (1942).
(14) G. J. Hoijtink and J. van Schooten, *Recl. Trav. Chim. Pays-Bas*, **71**, 1089 (1952); G. J. Hoijtink, J. van Schooten, E. de Boer, and W. I. Aalbersberg, *ibid.*, **73**, 355 (1954); G. J. Hoijtink, *ibid.*, **73**, 895 (1954); **74**, 1525 (1955).
(15) P. H. Given, *J. Chem. Soc.*, 2684 (1958).
(16) L. H. Chopard-dit-Jean and E. Heilbronner, *Helv. Chim. Acta*, **36**, 144 (1953).
(17) E. S. Pysh and N. C. Yang, *J. Amer. Chem. Soc.*, **85**, 2124 (1963), have suggested that the deviation of the analogous plot of the oxidation potential for azulene against the molecular orbital parameters for the highest occupied orbital is due primarily to enhanced solvent stabilization of the cation radical.
(18) H. A. Ammon and M. Sundaralingam, *J. Amer. Chem. Soc.*, **88**, 4794 (1966).
(19) The HMO and CNDO/2 calculations were performed by Mr. Taran Tober.
(20) This point was raised by a referee. We thank Professor N. Epiotis for carrying out these calculations.
(21) R. Zahradnik, J. Michl, and J. Paneir, *Tetrahedron*, **22**, 1355 (1966).

4-Methylnorcamphor and Its Carbon-13 Nuclear Magnetic Resonance Spectrum

Robert L. Cargill,* Dean F. Bushey, and Paul D. Ellis

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

Steven Wolff and William C. Agosta

Laboratories of The Rockefeller University, New York, New York 10021

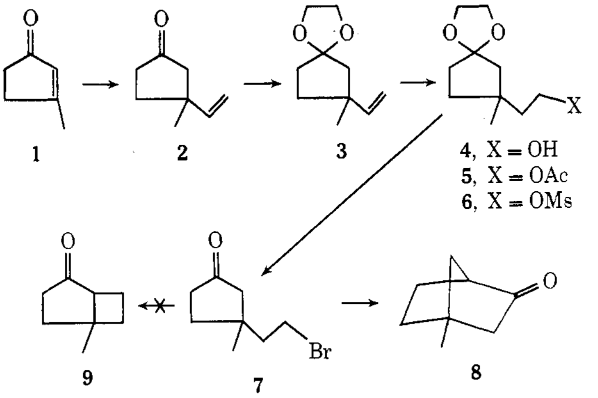
Received August 29, 1973

Although interest in the chemistry of bicyclo[2.2.1]heptanes has been widespread over a number of years, the 1,3-disubstituted derivatives of this ring system have remained scarce. Indeed, a search of the 8th Decennial Index of Chemical Abstracts revealed 13 entries covering seven different 1,3-disubstituted norbornanes. 4-Substituted norcamphors, which are specific examples of 1,3-disubstituted norbornanes, are unknown. We now report that 4-methylnorcamphor (**8**), the only previously undescribed methylnorcamphor,[1] may be prepared from 3-methylcyclopentenone by a route that should be applicable to the synthesis of a variety of 4-substituted norcamphors.

Table I
^{13}C Chemical Shifts of 4-Methylnorcamphor
(CS_2 Scale)

C-1	141.2	C-3	141.8	C-5	158.6	C-7	149.2
C-2	−21.8	C-4	150.0	C-6	167.1	CH_3	172.0

Conjugate addition of lithium divinylcopper[2] to 3-methylcyclopentenone (**1**) gave 3-methyl-3-vinylcyclopentanone (**2**). The copper reagent has been prepared previously by reaction of vinyllithium with preformed and purified copper iodide-tributylphosphine complex.[3] We found that this preparation could be considerably simplfied by treating a suspension of copper iodide in ether first with tributylphosphine and then at low temperature with vinyllithium. Ketone **2** was converted into its ethylene ketal **3** and thence by hydroboration-oxidation into alcohol **4**. Owing to the decomposition of **4** upon standing, the derived acetate **5** is the preferred form for storage. Alcohol **4** was converted into the methanesulfonate **6**, and thence by treatment of **6** with lithium bromide in acetone into bromo ketone **7** (61% from **3**). Presumably the ketal function is removed by an acid-catalyzed transketalization reaction with the acetone solvent. Methanesulfonic acid, a trace of which could be generated by an elimination reaction leading to **3**, probably serves as the catalyst for the transketalization. When **7** was stirred at 25° with potassium *tert*-butylate in *tert*-butyl alcohol overnight, 4-methylnorcamphor (**8**) was obtained as the sole product in 65% yield.[4] Identification of 4-methylnorcamphor was made by analysis of its ir and proton nmr spectra (see Experimental Section), and its nonidentity on glpc with authentic 5-methylbicyclo[3.2.0]heptan-2-one (**9**).[5]



The ^1H noise decoupled ^{13}C nmr spectrum of **8** determined in benzene-d_6 exhibits eight resonances whose chemical shifts and assignments are shown in Table I. These assignments are consistent with those of Roberts, *et al.*,[1] for the other nine methylnorcamphors.

Experimental Section[6]

3-Methyl-3-vinylcyclopentanone (2). To a suspension of cuprous iodide (27.6 g, 0.145 mol) (Fisher Chemical) in anhydrous THF, magnetically stirred under an argon atmosphere, was added tributylphosphine (29.3 g, 0.145 mol, 36.2 ml). The mixture was cooled to −78° before vinyllithium (97 ml of 2.9 *M* solution, 0.28 mol) was added at a rate such that the reaction temperature did not exceed −50°. When the addition was complete, the temperature of the thick, wine-colored solution dropped below −70°, and was allowed to warm to −60° before 11.5 g (0.120 mol) of 3-methylcyclopent-2-enone (1) was added dropwise in anhydrous ether; the temperature of the reaction was allowed to rise to −50° during the addition, and, after its completion, to −30° where it was maintained for 1 hr. The reaction mixture was poured into saturated NH_4Cl containing a few milliliters of NH_4OH with vigorous stirring (gas evolution). The black mixture was filtered through Celite; the organic phase was separated; and the aqueous phase was extracted twice with ether. The combined organic phases were washed twice with saturated NH_4Cl and brine and dried over $MgSO_4$. Solvents were removed *in vacuo* and the residue was distilled to give 9.75 g (66%) of **2**: bp 63–64° (14 Torr); ir 1750, 1640, 990, 910 cm^{-1}; nmr (CCl_4) δ 6.02 (q, 1 H), 5.08 (m, 2 H), 2.54–1.45 (m, 6 H), 1.21 (s, 3 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.30; H, 9.74.

3-Methyl-3-vinylcyclopentanone Ethylene Ketal (3). A mixture of the vinylcyclopentanone (21.56 g, 0.174 mol), ethylene glycol (12.40 g, 0.200 mol, 11.1 ml), benzene (225 ml), and a trace of *p*-toluenesulfonic acid were heated to reflux for 7.25 hr with continuous removal of water (Dean-Stark trap). The reaction mixture was cooled and poured into saturated $NaHCO_3$, the organic layer was separated, and the aqueous phase was extracted once with ether. The organic phases were combined, washed with brine, and dried over $MgSO_4$. Distillation afforded 23.0 g of the ketal: bp 80–85° (14 Torr); ir 1640, 1330, 1095, 905 cm^{-1}; nmr (CCl_4) δ 6.01 (m, 1 H), 5.22–4.77 (m, 2 H), 3.87 (s, 4 H), 2.15–1.25 (m, 6 H), 1.25 (s, 3 H). This material was used directly in the following reaction.

3-(2′-Hydroxyethyl)-3-methylcyclopentanone (4). The hydroboration of 23.0 g (0.137 mol) of **3** in 140 ml of anhydrous THF with externally generated diborane was accomplished following the procedure of Zeifel and Brown.[7] The diborane was prepared from a solution of 1.73 g (45.8 mmol) of sodium borohydride in 45 ml of diglyme to which was added to a solution of 12.1 ml of boron trifluoride etherate in 15 ml of diglyme. After the usual oxidation with sodium hydroxide and hydrogen peroxide and workup, 26.7 g of **4** was obtained as a colorless oil: nmr (CCl_4) δ 3.89 (s, 4 H), 3.70 (t, J = 7.5 Hz, 2 H), 3.0 (br, 1 H), 1.4–2.0 (m, 8 H), 1.08 (s, 3 H).

For purification and long-term storage, the crude alcohol was acetylated with acetic anhydride (26 ml) and pyridine (55 ml). Distillation afforded 27.1 g (87%) of **5**: bp 100–104° (0.5 Torr); ir 1742, 1368, 1333, 1235, 1100, 1030 cm^{-1}; nmr (CCl_4) δ 4.08 (t, J = 7 Hz, 2 H), 3.80 (s, 4 H), 1.95 (s, 3 H), 2.13–1.33 (m, 8 H), 1.22 (s, 3 H).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.02; H, 8.74.

3-(2′-Mesyloxyethyl)-3-methylcyclopentanone Ethylene Ketal (6). To a solution of 9.86 g (53.1 mmol) of crude alcohol **4** in 60 ml of dry pyridine under nitrogen at 25° was added dropwise 6.9 g of methanesulfonyl chloride. A precipitate appeared in a short time, and the mixture was stirred at 25° overnight and then quenched with 6 ml of cold water. Ether (50 ml) was added and the aqueous layer was removed and washed with ether (10 ml). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 50 ml), aqueous $CuSO_4$ solution (8 × 50 ml) (the pyridine is removed when the $CuSO_4$ solution remains light blue), and water (50 ml), dried ($MgSO_4$), and concentrated *in vacuo*, giving 11.7 g (83.4%) of crude oily mesylate **6**: ir (CCl_4) 1370, 1350, 1180 cm^{-1}; nmr (CCl_4) δ 4.2 (t, 2, J = 7 Hz, -CH_2CH_2OMs), 3.8 (s, 4, ketal), 2.95 (s, 3, $ROSO_2CH_3$), 2.0–1.35 (m, 8), 1.1 (s, 3, Me).

3-(2′-Bromoethyl)-3-methylcyclopentanone (7). A solution containing 11.4 g (43.1 mmol) of crude mesylate **6** and 15.0 g (174 mmol) of anhydrous lithium bromide in 200 ml of acetone was refluxed (drying tube) for 5 hr. After the mixture had stood overnight the acetone was removed *in vacuo* and the residue was taken up in a 50:50 ether-water mixture. The aqueous layer was removed and the organic layer was washed with water (50 ml) and saturated Na_2CO_3 (50 ml), dried ($MgSO_4$), concentrated *in vacuo*, and distilled [bath temperature 100° (0.3 Torr)], giving 7.14 g (60.7% from **3**) of bromo ketone **7**: ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 3.53–3.25 (m, 2, RCH_2Br), 2.3–1.7 (m, 8), 1.1 (s, 3, Me).

4-Methylnorcamphor (8). The bromo ketone **7** (7.14 g, 34.8 mmol) was dissolved in 100 ml of dry *tert*-butyl alcohol under nitrogen at 25°, and 38 ml (38.0 mmol) of a freshly prepared 1 *M* solution of potassium *tert*-butylate in *tert*-butyl alcohol was added slowly. A yellow color appeared immediately and was followed by precipitation of potassium bromide. This mixture was stirred at 25° overnight and poured into a 50:50 pentane–saturated NaCl solution. The aqueous layer was separated and washed with pentane (20 ml). The combined organic layers were washed with saturated NaCl (30 ml), water (4 × 30 ml), and saturated NaCl (30 ml), dried ($MgSO_4$), concentrated at atmospheric pressure, and distilled [bath temperature 80° (18 Torr)], giving 2.80 g (64.9%) of 4-methylnorcamphor (**8**): ir (CCl_4) 1750 cm^{-1}; nmr (CCl_4) δ 2.50–2.35 (m, 1, bridgehead hydrogen), 1.85–1.40 (m, 8), 1.28 (s, 3, Me); mass spectrum (70 eV) *m/e* (rel intensity) 124 (32), 109 (6), 95 (12), 82 (20), 81 (100), 80 (78), 67 (64), 55 (34), 39 (4).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.50; H, 9.68.

The 2,4-dinitrophenylhydrazone, mp 132–133°, was recrystallized from EtOH.

Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.04; H, 5.40; N, 18.25.

Registry No. 1, 2758-18-1; **2,** 49664-66-6; **3,** 49664-67-7; **4,** 49664-68-8; **5,** 49664-69-9; **6,** 49664-70-2; **7,** 49664-71-3; **8,** 49664-72-4; 8 2,4-dinitrophenylhydrazone, 49664-73-5.

References and Notes

(1) J. B. Grutzner, M. Jautelate, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Amer. Chem. Soc.*, **92,** 7107 (1970), have described the ^{13}C nmr spectra of all methylnorcamphors except that of **8.** This paper provides references for syntheses of the other methylnorcamphors.

(2) G. H. Posner, *Org. React.*, **19,** 1 (1972).

(3) J. Hooz and R. B. Layton, *Can. J. Chem.*, **48,** 1626 (1970).

(4) J. L. Marshall, *Tetrahedron Lett.*, 753 (1971), showed that 3-(2′-tosyloxyethyl)cyclopentanone, obtained in 12% yield from norcamphor, could be cyclized with base to yield norcamphor.

(5) R. L. Cargill, B. M. Gimarc, D. M. Pond, T. Y. King, A. B. Sears, and M. R. Willcott, *J. Amer. Chem. Soc.*, **92,** 3809 (1970); R. L. Cargill, A. B. Sears, J. Boehm, and M. R. Willcott, *ibid.*, **95,** 4346 (1973). The synthesis of **9** from **1** and ethylene and the spectra of **9** are described: R. L. Cargill and B. W. Wright, manuscript in preparation.

(6) Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., Alfred Bernhardt Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany, and S. T. Bella, the Rockefeller University. Boiling points and melting points are uncorrected. The ^{13}C spectra were obtained on a Varian XL-100-15 nmr spectrometer operating at 25.2 MHz in the Fourier transform mode. Carbon-13 chemical shifts were determined with respect to internal benzene-d_6 and then converted to a CS_2 scale by adding 64.8 ppm. Spectra were also determined in CCl_4 solution and no significant medium effects were noted.

(7) G. Zweifel and H. C. Brown, *Org. React.*, **13,** 1 (1963).

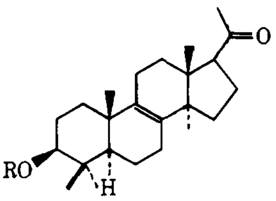
Improved Methods for the Side-Chain Degradation of Lanosterol. The Synthesis of 4,4,14α-Trimethyl-5α-pregn-8-en-20-one Derivatives

Bruce Ganem*[1] and Michael S. Kellogg

Department of Chemistry, Stanford University, Stanford, California 94350

Received October 16, 1973

Although descriptions of steroid side-chain degradations abound in the literature,[2] no such process for lanosterol has been reported which preserves the acid-sensitive Δ^8 olefin.[3] The present note discloses two facile side-chain degradations leading to the 20-keto lanostane derivatives **1** and **2** free of the Δ^7 isomer.

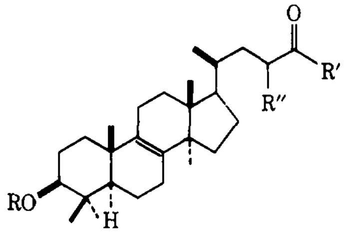


1, R = H
2, R = CH_3CO

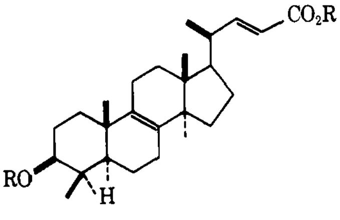
Reaction of lanosterol as its acetate[4] or benzoate[5] with 1 molar equiv of ozone followed by Jones reagent[4] produced the trisnor acids **3** and **6** in about 50% yield. Treatment of **6** with diazomethane gave the methyl ester **7**, which was added to lithium isopropylcyclohexylamide in tetrahydrofuran–hexamethylphosphoric triamide (THF–HMPA) solution at −78°, giving the enolate anion quantitatively after 45 min.[6] Addition of this solution to bromine in THF at −78° afforded the α-bromo ester **8**, which was smoothly dehydrobrominated in HMPA[7] at 120° to the α,β-unsaturated ester **9** in 72% overall yield from **7**. Hydrolysis of the benzoate and reesterification of the sparingly soluble α,β-unsaturated acid **10** by reaction of the sodium salt with ethyl iodide in HMPA[8] afforded an 80% yield of the ethyl ester **11**. Treatment with potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) transformed **11** into the β,γ-unsaturated acid **12** (80% yield),[9] which on ozonolysis (as its methyl ester **13**) afforded the desired 3β-hydroxy-4,4,14α-trimethyl-5α-pregn-8-en-20-one (**1**).[10] None of the Δ^7 isomer could be detected.[11]

An alternative degradation was accomplished by converting the acetoxy acid **3** to its acid chloride **4** and treating this substance with lithium diphenylcopper[12] to produce the phenyl ketone **5** in 50% yield after chromatography. When irradiated at 350 nm in *tert*-butyl alcohol using a Rayonet reactor, this ketone underwent facile Norrish Type II cleavage[13] to afford the 20-methylene derivative **14** in 53% yield. Ozonolysis in this instance generated 3β-acetoxy-4,4,14α-trimethyl-5α-pregn-8-en-20-one (**2**, 47% yield) free of the Δ^7 isomer, and having melting point, ir, and nmr characteristics in full accord with reported values for this compound.[10] Moreover, this substance could be saponified to the hydroxy ketone **1**.

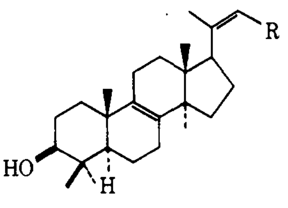
The yield of the final ozonolysis step in both series was disappointing, and could not be improved even by using a slight deficiency of ozone. This is apparently due to a competing, allylic oxidation known to occur in the Δ^8 lanostane system with a variety of oxidizing agents.[14] A comparison of the two degradation schemes reveals that overall yields were somewhat higher for the first route (9.0–9.2%) than for the second (6–6.5%); however, the latter, photochemical sequence may be faster and more convenient.



3, R = CH_3CO; R′ = OH; R″ = H
4, R = CH_3CO; R′ = Cl; R″ = H
5, R = CH_3CO; R′ = C_6H_5; R″ = H
6, R = C_6H_5CO; R′ = OH; R″ = H
7, R = C_6H_5CO; R′ = OCH_3; R″ = H
8, R = C_6H_5CO; R′ = OCH_3; R″ = Br



9, R = C_6H_5CO; R′ = CH_3
10, R = H; R′ = H
11, R = H; R′ = CH_3CH_2



12, R = CH_2CO_2H
13, R = $CH_2CO_2CH_3$
14, R = H (3β-Ac derivative)

Experimental Section

Melting points were determined using a Kofler hot stage microscope. Nmr spectra of deuteriochloroform solutions were recorded on a Varian T-60 spectrometer with tetramethylsilane as internal standard. Ir spectra of chloroform solutions were determined on a Perkin-Elmer 137 spectrophotometer. Gas–liquid chromatographic analyses were carried out on a Hewlett-Packard HP-402 gas chromatograph using 3% XE-60 in 80–100 gas chromatograph Q packed in a 6-ft glass column with a helium flow rate of 40–50 ml/min, unless otherwise stated. Mass spectral measurements