L-Phenylalanyl-D-proline methyl ester trifluoroacetate (**7b**; 1.17 g, 3.0 mmol) was dissolved in 30 mL of chloroform and chilled to 0 °C. Triethylamine (0.42 mL, 3.0 mmol) and (*tert*-butyloxycarbonyl)-L-alanyl-α-aminoisobutyric acid (**21b**; 0.9 g, 3.3 mmol, in 10 mL DMF) were added to the solution. 1-Hydroxybenzotriazole monohydrate (0.50 g, 3.3 mmol, in 5 mL of DMF) was added followed by a solution containing dicyclohexylcarbodiimide (0.68 g, 3.3 mmol, in 5 mL of chloroform). The reaction was stirred for 2 h at 0 °C, and stirring was continued at room temperature for 2 days. The reaction mixture was then chilled and filtered, and the filtrate was worked up as described in procedure C. The resulting oil was purified by column chromatography (gravity, silica gel 60) with 3% methanol in chloroform. The appropriate fractions were pooled and evaporated to yield **22a** as amorphous solid: 1.31 g (82%); TLC R_f 0.3 (solvent C); $[\alpha]^{23}_D$ +20.2° (*c* 1.73, methanol); ^{1}H NMR ($CDCl_3$) δ 1.33 (d, 3 H, *J* = 7.5 Hz), 1.43 (s, 9 H), 1.50 (s, 6 H), 1.71–2.04 (complex, 4 H), 2.88–3.08 (m, 2 H), 3.41–3.63 (m, 2 H), 3.67 (s, 3 H), 3.94–4.42 (complex, 2 H), 4.76–5.04 (m, 1 H), 5.23 (d, 1 H, *J* = 8.4 Hz), 6.74 (br s, 1 H), 6.95 (d, 1 H, *J* = 10.8 Hz), 7.18 (br s, 5 H). Anal. Calcd for $C_{27}H_{40}N_4O_7$: C, 60.88; H, 7.57; N, 10.53. Found: C, 60.94; H, 7.79; N, 10.36.

(*tert*-Butyloxycarbonyl)-L-phenylalanyl-D-prolyl-L-alanyl-α-aminoisobutyric Acid Methyl Ester (23a). (*tert*-Butyloxycarbonyl)-L-phenylalanyl-D-proline methyl ester **7a** was saponified according to general procedure B-1. The free acid **7b** was crystallized from ether: yield 73%; mp 170–172 °C.

(*tert*-Butyloxycarbonyl)-L-alanyl-α-aminoisobutyric acid methyl ester (**21a**) was deprotected according to general procedure A-1. The resulting trifluoroacetate salt (**21b**) of the dipeptide was crystallized from ether: yield 85%; mp 176–177 °C; $[\alpha]^{25}_D$ +15.0° (*c* 2, methanol). These appropriately deprotected dipeptides were then used directly in the following fragment coupling procedure.

L-Alanyl-α-aminoisobutyric acid methyl ester trifluoroacetate (**21b**; 1.0 g, 3.3 mmol) was dissolved in 25 mL of dimethylformamide and chilled to −10 °C in a salted ice bath. Triethylamine (0.46 mL, 3.3 mmol), (*tert*-butyloxycarbonyl)-L-phenylalanyl-D-proline (**7b**; 1.08 g, 3 mmol), 1-hydroxybenzotriazole monohydrate (0.50 g, 3.3 mmol), and dicyclohexylcarbodiimide (0.68 g, 3.3 mmol) were added in the order given. The reaction mixture was stirred at −10 °C for 1 h, and stirring was continued at room temperature for 2 days. The reaction mixture was filtered, and the filtrate was diluted with 250 mL of ethyl acetate and worked up as described in procedure C to give **23a** as a white crystalline solid, 1.32 g (82.6%). Recrystallization from chloroform/Skelly B gave the product: 1.05 g (66%); mp 212–213 °C. This material contained a small amount of impurity (probably DCU), so it was further purified by column chromatography (gravity, silica gel 60) with 3% methanol in chloroform to give the product: 0.98 g (61%); mp 214 °C; TLC R_f 0.25 (solvent C); $[\alpha]^{23}_D$ +12.8° (*c* 1.06, methanol); ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3 H, *J* = 6.6 Hz), 1.41 (s, 9 H), 1.52 (s, 6 H), 1.62–2.18 (complex, 4 H), 3.01 (d, 2 H, *J* = 6.9 Hz), 3.45–3.63 (m, 2 H), 3.71 (s, 3 H), 4.17–4.69 (complex, 3 H), 5.22 (d, 1 H, *J* = 7.5 Hz), 6.83 (br s, 1 H), 7.02 (d, 1 H, *J* = 6.6 Hz), 7.25 (br s, 5 H). Anal. Calcd for $C_{27}H_{40}N_4O_7$: C, 60.88; H, 7.57; N, 10.52. Found: C, 60.97; H, 7.65; N, 10.51.

Synthesis of Succinimide Esters 22c and 23c. Peptides **22a** and **23a** were saponified according to general procedure B-1 by using 2 equiv of sodium hydroxide. The yields of free acid tetrapeptides were 77.5% **22b** and 98% **23b**. The TLC R_f was 0.55 (solvent E) for peptide **22** and 0.45 (solvent B) for peptide **23**.

The free acid tetrapeptides were dissolved in an appropriate amount of methylene chloride and chilled to 0 °C. *N*-Hydroxysuccinimide (1.1 equiv, 3 equiv for Pro C-terminal) and dicyclohexylcarbodiimide (1.2 equiv) were added. The reaction mixtures were stirred at room temperature for 4 h. The reaction mixtures were then chilled to 0 °C and filtered to remove the dicyclohexylurea. The filtrates were evaporated to dryness. The resulting material was not further purified but was deprotected directly to yield the trifluoroacetate salts according to general procedure A-1. Peptide **22c** (TFA salt of OSu ester): yield 81.6%; mp 153–155 °C; TLC R_f 0.2 (solvent E). Peptide **23c** (TFA salt of OSu ester): yield 40%.

***cyclo*(L-Alanyl-α-aminoisobutyryl-L-phenylalanyl-D-prolyl) (2) from 22c and 23c.** The TFA salts of **22c** and **23c** were dissolved in dimethylformamide/ethyl acetate (~1:3, ~10-mL total volume) and cyclized according to general procedure E. After purification by preparative TLC as described, the products were isolated: yield 44% from **22c** and 2% from **23c**; ^{1}H NMR and TLC identical with those obtained for compound **2** from sequences **11** and **19**; $[\alpha]^{23}_D$ −90.9° (*c* 0.77, methanol).

Acknowledgment. This work was supported in part by grants from the NIH (CA 27985) and by a Fellowship to J.S. from Eli Lilly and Co.

Rearrangements of Oxygen-Functionalized Cyclopropylcarbinyl Substrates: An Approach to Oxygenated α-Methylene-γ-butyrolactones

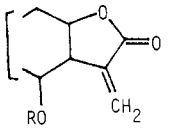
Paul F. Hudrlik,* David T.-W. Chou, and Maurice A. Stephenson

Department of Chemistry, Howard University, Washington, DC 20059

Received January 28, 1982

Keto diester **6** (prepared from 2-bromocyclohexenone, dimethyl malonate, and KH) was converted to the keto cyclopropylcarbinyl substrates **10–13** and the methoxycyclopropylcarbinyl substrates **17–20**. The keto substrates were relatively unreactive to rearrangement; however, under some conditions, lactone **23** and diene **24** were formed. Rearrangement of the methoxy substrates gave lactone **25**.

A large number of sesquiterpenes and other naturally occurring compounds possess the α-methylene-γ-butyrolactone ring. Many of these compounds have biological activity, and some have tumor-inhibiting activity; consequently there has been considerable work on the synthesis of α-methylene-γ-butyrolactones.[1] About half of the naturally occurring α-methylene-γ-butyrolactones, including most of those with tumor-inhibiting activity, have an additional oxygen function at the homoallylic position as shown in partial structure **1** (R = H or acyl).[2]

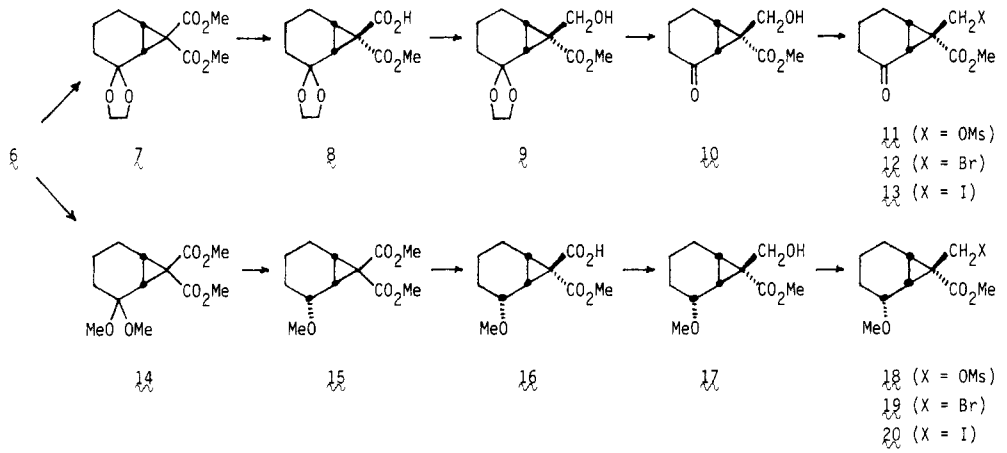


1

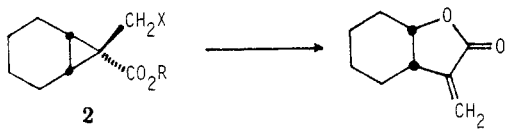
(1) For reviews, see: (a) Grieco, P. A. *Synthesis* **1975**, 67–82. (b) Gammill, R. B.; Wilson, C. A.; Bryson, T. A. *Synth. Commun.* **1975**, *5*, 245–268. (c) Newaz, S. S. *Aldrichimica Acta* **1977**, *10*, 64–71.

0022-3263/82/1947-2987$01.25/0

Scheme I



We have previously reported a new approach to the synthesis of the α-methylene-γ-butyrolactone ring involving rearrangements of carboxy- or carboalkoxy-substituted cyclopropylcarbinyl derivatives (e.g., **2** → **3**).[3] The

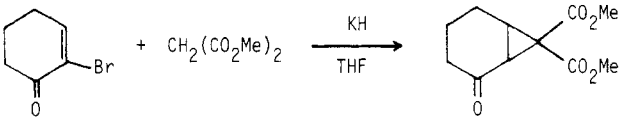


mechanistic rationale for these reactions was based on the rearrangements of cyclopropylcarbinyl cations with interception of the homoallyl form by the neighboring carboxyl group.[4] Although mixtures of isomeric lactones would have been possible from cyclopropanes not having a plane of symmetry, we found the regiochemistry of the rearrangements could be controlled by a suitably placed double bond in the substrate (e.g., **4** → **5**).[3b] About one-fourth of the naturally occurring α-methylene-γ-butyrolactones have the additional double bond of **5**.

With a view toward extending these reactions to the formation of α-methylene-γ-butyrolactones having the homoallylic oxygen function (as in **1**), we have now studied the rearrangements of some oxygen-functionalized cyclopropylcarbinyl substrates.[5]

Preparation of the Cyclopropylcarbinyl Substrates

We have prepared cyclopropylcarbinyl substrates substituted with keto and methoxy groups. The key intermediate for the preparation of these substrates was the keto diester **6**. Several methods for the preparation of



compound **6** were investigated. As expected,[6] copper-catalyzed reactions of dimethyl diazomalonate with cyclohexenone were not successful. Reactions of cyclohexenone with dimethyl bromomalonate[7] gave variable mixtures of products. Compound **6** was successfully prepared by the reaction of 2-bromocyclohexenone with dimethyl malonate in the presence of KH. This reaction, presumably, involving a Michael addition followed by proton transfer and intramolecular alkylation, is potentially a useful and general method for forming cyclopropane rings. This type of reaction was first reported by Michael in 1887[8] but has been used little since then.[9,10]

The preparation of the keto cyclopropylcarbinyl sub-

(2) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147–1152. See also references cited in ref 1 and 3.

(3) (a) Hudrlik, P. F.; Rudnick, L. R.; Korzeniowski, S. H. *J. Am. Chem. Soc.* **1973**, *95*, 6848–6850. (b) Hudrlik, P. F.; Takacs, J. M.; Chou, D. T.-W.; Rudnick, L. R. *J. Org. Chem.* **1979**, *44*, 786–793.

(4) For other applications of cyclopropylcarbinyl rearrangements to the synthesis of α-methylene-γ-butyrolactones, see: (a) Ziegler, F. E.; Marino, A. F.; Petroff, O. A. C.; Studt, W. L. *Tetrahedron Lett.* **1974**, 2035–2038. (b) Hiyama, T.; Saimoto, H.; Nishio, K.; Shinoda, M.; Yamamoto, H.; Nozaki, H. *Ibid.* **1979**, 2043–2046. See also: (c) Mueller, L. G.; Lawton, R. G. *J. Org. Chem.* **1979**, 44, 4741–4742.

(5) First presented at the 15th Middle Atlantic Regional Meeting, American Chemical Society, Washington, D.C., Jan 1981, abstr 308.

(6) Peace, B. W.; Carman, F.; Wulfman, D. S. *Synthesis* **1971**, 658–661.

(7) Warner, D. T. *J. Org. Chem.* **1959**, *24*, 1536–1539.

(8) Michael, A. *Am. Chem. J.* **1887**, *9*, 112–124; *J. Prakt. Chem.* **1887**, *35*, 132–136; *Ibid.* **1887**, *35*, 349–356. Cited by Fuson (Fuson, R. C. "Advanced Organic Chemistry"; Wiley: New York, 1950; p 486). We are grateful to Professor R. R. Sauers for bringing this reference to our attention.

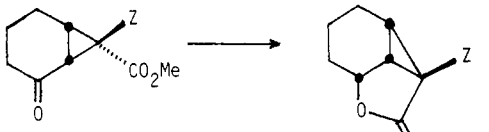
(9) For some examples of this type of reaction, see: (a) Schmidt, U. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 238. Schmidt, U.; Schröer, R.; Hochrainer, A. *Justus Liebigs Ann. Chem.* **1970**, *733*, 180–186. (b) Payne, G. B.; Johnson, M. R. *J. Org. Chem.* **1968**, *33*, 1285–1287. (c) Kawakami, Y.; Tsuruta, T. *Tetrahedron Lett.* **1971**, 1173–1176; Kawakami, Y.; Tajima, K.; Tsuruta, T. *Tetrahedron* **1973**, *29*, 1179–1183. (d) Saegusa, T.; Yonezawa, K.; Murase, I.; Konoike, T.; Tomita, S.; Ito, Y. *J. Org. Chem.* **1973**, *38*, 2319–2328. (e) Kocôr, M.; Kroszczyński, W. *Synthesis* **1976**, 813–814. (f) Shapiro, E. L.; Page, G.; Weber, L.; Gentles, M. J.; McPhail, A. T.; Onan, K. D. *Tetrahedron Lett.* **1977**, 3553–3556. Shapiro, E. L.; Gentles, M. J.; Weber, L.; Page, G.; McPhail, A. T.; Onan, K. D. *Ibid.* **1977**, 3557–3560. (g) Takei, H.; Fukuda, Y.; Sugaya, K.; Taguchi, T.; Kawara, T. *Chem. Lett.* **1980**, 1307–1310. (h) Kocôr, M.; Kroszczyński, W.; Pietrzak, J. *Synthesis* **1980**, 742–743. (i) Babler, J. H.; Invergo, B. J. *Tetrahedron Lett.* **1981**, *22*, 2743–2746. (j) Nickisch, K.; Laurent, H.; Wiechert, R. *Tetrahedron Lett.* **1981**, *22*, 3833–3834.

(10) For some examples of a related type of reaction in which the activating group for the Michael addition *becomes* the leaving group, see: (a) Gosselck, J.; Schmidt, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 456–457. (b) Johnson, C. R.; Lockard, J. P. *Tetrahedron Lett.* **1971**, 4589–4592. (c) Takaki, K.; Agawa, T. *J. Org. Chem.* **1977**, *42*, 3303–3304. (d) Takaki, K.; Negoro, K.; Agawa, T. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1490–1493. (e) Johnson, C. R.; Lockard, J. P.; Kennedy, E. R. *J. Org. Chem.* **1980**, *45*, 264–271. (f) Shimizu, M.; Kuwajima, I. *Ibid.* **1980**, *45*, 2921–2923. (g) Chow, Y. L.; Bakker, B. H.; Iwai, K. *J. Chem. Soc., Chem. Commun.* **1980**, 521–522, and references cited in each of the above. For a review of more conventional methods for making cyclopropane rings, see: Yanovskaya, L. A.; Dombrovskii, V. A. *Russ. Chem. Rev.* **1975**, *44*, 154–169.

strates **10–13** and the methoxycyclopropylcarbinyl substrates **17–20** from keto diester **6** is shown in Scheme I. Methoxy diester **15**[11] was prepared from the dimethyl ketal **14** by reduction with $NaBH_3CN$ in methanol containing HCl[12] (generated in situ by the addition of acetyl chloride). Diesters **15** and **7** were converted to the cyclopropylcarbinyl substrates by routes analogous to those used in our earlier work.[3]

The stereochemistry of the substrates was assigned in part by analogy to the previously described selective saponification of norcarane diesters.[3,13] The stereochemistry of the keto substrates **10–13** was confirmed by formation of the known lactone mesylate **22**[4a] in the reduction of keto mesylate **11** with $NaBH_4$. The stereochemistry of the methoxy group in substrates **17–20** was tentatively assigned on the expectation that reduction of **14** to **15** would take place predominantly from the less hindered side and on the basis of the 220-MHz NMR spectrum of the crystalline acid ester **16**, which showed a coupling constant J = 6 Hz between the CH–OMe and the adjacent cyclopropane hydrogen, consistent with the cis stereochemistry. (The stereochemistry of the methoxy group was ultimately confirmed by the independent synthesis of lactone **25**, discussed below.)

Attempts to prepare the analogous cyclopropylcarbinyl substrates having a hydroxyl group on the six-membered ring were unsuccessful. Reduction of keto diester **6** with $NaBH_4$ gave the known lactone **21**;[4a] the similar reduction of **11** to **22** was mentioned above.

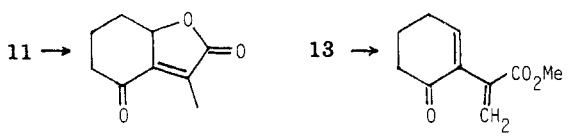


6, Z = CO_2Me
11, Z = CH_2OMs

21, Z = CO_2Me
22, Z = CH_2OMs

Rearrangements

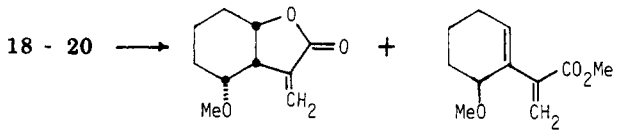
The solvolytic, acid-catalyzed, and silver ion induced rearrangements of the cyclopropylcarbinyl substrates **10–13** and **17–20** were examined by using a number of conditions similar to those used earlier[3] for the simple (i.e., **2**) and unsaturated (i.e., **4**) substrates. Attempted rearrangements of the keto substrates **10–13** under conditions used successfully for the analogous unsaturated substrates (**4**) led predominantly to recovered starting material. Use of longer reaction times and/or more vigorous conditions with hydroxy ester **10** and with bromo ester **12** led to decomposition; however, with mesylate ester **11** and iodo ester **13**, rearrangement products were formed. When mesylate **11** was treated with $LiClO_4$ in dioxane at reflux, unsaturated lactone **23**[14] was formed, and when iodide **13** was



23 24

treated with $AgClO_4$ in dioxane with added water, diene ester **24** was formed. Although no α-methylene-γ-butyrolactones were observed, compounds **23** and **24** most likely were formed via cyclopropane ring opening in the desired manner (i.e., that necessary to produce α-methylene lactones having a homoallylic oxygen function).

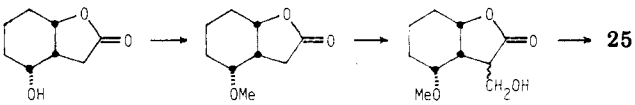
The methoxy-substituted cyclopropylcarbinyl derivatives **17–20** were reactive to conditions similar to those used for rearrangements of the analogous unsaturated substrates (**4**), and under some conditions, the oxygen-functionalized α-methylene-γ-butyrolactone **25** could be isolated. Hydroxy ester **17** underwent reaction with $HClO_4$ in dioxane to give an unidentified mixture of products. Mesylate ester **18** underwent solvolysis with $LiClO_4$ in dioxane to give the α-methylenelactone **25** contaminated with a considerable amount (~25%) of a byproduct believed to be diene ester **26** (or an isomer) on the basis of the GC–mass spectrum and the NMR spectrum of the mixture. Bromo ester **19** and iodo ester **20** underwent $AgClO_4$-induced rearrangement to give α-methylene lactone **25** in crude yields of 65–85%, contaminated with less (5–15%) of the diene byproduct. The product from **20** was chromatographed to give pure α-methylene lactone **25** in 39% yield.



25 26

The structure of α-methylene lactone **25** was supported by its 220-MHz NMR spectrum, which showed the lactone CH at δ 4.57 as a doublet of triplets (rather than the doublet of doublets expected for the regioisomeric lactone). The cis-lactone stereochemistry is in accord with the lactone-forming cyclopropylcarbinyl rearrangements in our earlier work,[3] and the stereochemistry of the methoxy group follows from that assigned to the methoxycyclopropylcarbinyl substrates **17–20**.

So that its structure and stereochemistry could be confirmed, lactone **25** was synthesized by an independent and unambiguous method. The known[15] hydroxylactone **27**



27 28 29

was converted to the methyl ether **28** by treatment with methyl iodide and silver oxide in the presence of dry $CaSO_4$.[16] (Attempted preparation of **28** from **27** with methyl iodide in the presence of NaH or KH was unsuccessful.) The α-methylene group was introduced by the method of Grieco.[17] The product was identical with the α-methylene-γ-butyrolactone **25** obtained from the cyclopropylcarbinyl rearrangements.

Discussion

The reactions described here are not likely to compete with other methods for the synthesis of oxygenated α-methylene-γ-butyrolactones. However, it is interesting to note that all of the products observed from the rearrangements of both the keto cyclopropylcarbinyl substrates **10–13** and the methoxycyclopropylcarbinyl substrates

(11) An attempt to prepare compound **15** by copper-catalyzed reaction of dimethyl diazomalonate with 3-methoxycyclohexene gave a mixture of products.
(12) Adapted from the procedure of Horne and Jordan (Horne, D. A.; Jordan, A. *Tetrahedron Lett.* **1978**, 1357–1358).
(13) Musso, H. *Chem. Ber.* **1968**, *101*, 3710–3720.
(14) Jacobi and Craig have reported lactone **23** and the ethyl ester corresponding to **24** and have shown the latter can be converted to lactone **23** on treatment with aqueous acid: Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748–7750.
(15) Grieco, P. A.; Marinovic, N.; Miyashita, M. *J. Org. Chem.* **1975**, *40*, 1670–1672.
(16) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6404–6408.
(17) Grieco, P. A.; Hiroi, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1317–1318. See also ref 15.

17–20 were formally derived from breaking the cyclopropane bond farthest from the oxygen function. This apparent directing effect is consistent with the powerful inductive and resonance electron-withdrawing effect of the carbonyl group and the inductive electron-withdrawing effect of the methoxy group.[18] The contrast with the rearrangements of the cyclopropylcarbinyl substrates (4), in which the product was derived from breaking the cyclopropane bond adjacent to the double bond, is noteworthy.

Experimental Section

General Procedures. All reactions except saponification reactions were carried out under a nitrogen atmosphere. The verb "concentrated" refers to the evaporation of solvent under reduced pressure (water aspirator) using a rotary evaporator. The term "evaporative distillation" refers to bulb to bulb distillation in a Kugelrohr apparatus under oil pump vacuum; the temperature following in parentheses refers to the oven temperature.

All vapor-phase chromatographic (VPC) analyses were performed on a Varian Aerograph Model 90-P instrument using helium as the carrier gas at the column temperature indicated;[19] the retention time of a hydrocarbon standard under the given conditions is included. For VPC peaks, the retention time is followed by the percentage of total peak area and where possible the probable assignment. Proton nuclear magnetic resonance (NMR) spectra were obtained with a Varian EM-360 spectrometer or a Varian T-60 spectrometer. Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane (0.00) as an internal reference. Infrared (IR) spectra were obtained with a Beckman IR-33 spectrometer or a Perkin-Elmer Model 727 B infrared spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer Model RMU-7E instrument or a Finnigan Model 3200-E automated GC–MS instrument. Exact mass determinations were carried out at Rutgers University, University of Illinois, and Massachusetts Institute of Technology. Melting points were determined on a Fisher-Johns hot-stage melting-point apparatus or a Thomas Hoover capillary melting-point apparatus. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL. Thin-layer chromatography (TLC) was performed on microscope slides with Silica Gel G; TLC plates were visualized with iodine vapor.

Materials. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Dioxane and triethylamine were distilled from calcium hydride. Pyridine was distilled from barium oxide. Acetone was distilled from sodium sulfate. Absolute methanol was obtained by distillation of methanol from magnesium and a trace of iodine.

2-Keto-7,7-bis(carbomethoxy)norcarane (6). Potassium hydride (12.53 g of a 24% slurry in oil, 0.124 mol) was washed three times with petroleum ether. To the residue was added 160 mL of THF, and the resulting mixture was cooled in ice. A solution of 9.71 mL (85 mmol) of dimethyl malonate in 80 mL of THF was added, the reaction mixture was warmed to room temperature, and a solution of 11.55 g (66 mmol) of 2-bromo-2-cyclohexen-1-one[20] in 80 mL of THF was added dropwise. The resulting mixture was stirred for 2.5 h, and then added to ice-cold saturated NH_4Cl overlaid with ether. The aqueous layer was extracted four times with ether. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed quickly through 220 g of Florisil with 3% ether in methylene chloride. The product was evaporatively distilled (120 °C) to remove dimethyl malonate, leaving 6.176 g of **6** as a yellow liquid, which was used directly for the preparation of dimethyl ketal **14**.

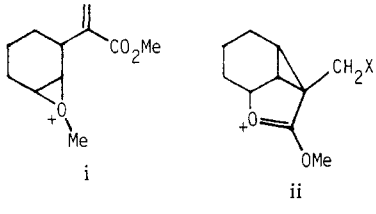
In smaller scale runs, the yields were higher, and chromatography to remove colored impurities was not necessary. Thus, from 25 mmol of KH, 1.37 mL (12 mmol) of dimethyl malonate, 2.1 g (12 mmol) of 2-bromo-2-cyclohexen-1-one, and 70 mL of THF, the crude product was evaporatively distilled (125 °C) to remove dimethyl malonate, and the residue was evaporatively distilled (168 °C) to give 2.255 g (83%) of keto diester **6** as a colorless liquid: IR (CCl_4) 2950, 1735, 1440, 1260 cm^{-1}; NMR (CCl_4) δ 1.0–2.4 (m, 8 H), 3.17 (s, 0.4 H, impurity), 3.6 (s, 6 H); mass spectrum, *m/e* 226 (M^+), 194, 166, 163, 162, 139, 79, 59. VPC analysis[19a] (158 °C, $C_{17}H_{36}$ = 3.7 min) showed the major peak at 3.8 min (>97% of total peak area). The 2,4-DNP derivative (recrystallized from ethanol) had mp 139–140 °C. Anal. Calcd for $C_{17}H_{18}N_4O_8$: C, 50.25; H, 4.46. Found: C, 50.47; H, 4.41.

2,2-Ethylenedioxy-7,7-bis(carbomethoxy)norcarane (7). To a solution of 0.272 g (1.2 mmol) of keto diester **6** and 0.78 mL (4.68 mmol) of ethyl orthoformate in 0.39 mL (6.9 mmol) of ethylene glycol were added a few crystals of *p*-toluenesulfonic acid monohydrate. The resulting mixture was heated with vigorous stirring at 145 °C for 2.5 h, cooled, and added to saturated NaCl overlaid with petroleum ether. The layers were separated, and the organic layer was dried (Na_2SO_4), concentrated, and evaporatively distilled (110 °C) to remove ethylene glycol and ethyl orthoformate. The residue was evaporatively distilled (170 °C) to give 0.273 g (84%) of **7** as a colorless liquid: IR (film) 2950, 1730, 1260, 1120 cm^{-1}; NMR (CCl_4) δ 0.8–2.2 (m, 8 H), 3.5 (s, 6 H), 3.75 (br s, 4 H). VPC analysis[19a] (154 °C, $C_{18}H_{38}$ = 8.2 min) showed the major peak at 7.2 min (98% of total peak area). The product from a similar experiment was purified by preparative VPC followed by evaporative distillation. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.48; H, 6.77.

2,2-Ethylenedioxy-*exo*-7-carboxy-*endo*-7-(carbomethoxy)norcarane (8). To a solution of 0.822 g (3.04 mmol) of ketal diester **7** in 15 mL of methanol was added a solution of 0.205 g (3.10 mmol) of potassium hydroxide (85%) in 5 mL of water, and the resulting solution was stirred at room temperature for 25 h. The solution was diluted with 6 mL of water and extracted four times with methylene chloride. The combined organic layers were washed with saturated $NaHCO_3$ and discarded. The aqueous layers were combined and added to 20 mL of methylene chloride, and the resulting mixture was stirred in an ice bath and carefully acidified to pH 3 with 3 M H_2SO_4. The layers were separated, and the aqueous layer was extracted four times with methylene chloride and twice with ether. The organic layers were combined and washed with brine, dried ($MgSO_4$), and concentrated to give 0.593 g (76%) of ketal acid **8** as a colorless liquid, which solidified after several days in the freezer (mp 88–90 °C): IR ($CHCl_3$) 3600–2400 (br), 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.5 (m, 8 H), 3.76 (s, 3 H), 4.00 (br s, 4 H), 9.4 (s, 1 H).

2,2-Ethylenedioxy-*exo*-7-(hydroxymethyl)-*endo*-7-(carbomethoxy)norcarane (9). Sodium hydride (0.272 g of a 50% dispersion in oil, 5.6 mmol) was washed three times with petroleum ether. To the residue were added 6 mL of THF followed by a solution of 0.499 g (1.95 mmol) of ketal acid ester **8** in 14 mL of THF. The mixture was stirred for 15 min, and then a solution of 0.196 mL (2.54 mmol) of methyl chloroformate in 7 mL of THF was added. The resulting mixture was stirred for 2.5 h and then cooled in an ice bath, and 0.593 g (15.6 mmol) of sodium borohydride was added. The resulting mixture was stirred at ice temperature for 10 min, and then 2.5 mL of methanol was added dropwise. The resulting mixture was stirred at ice temperature for 2 h and then poured into 40 mL of water. The mixture was stirred for 0.5 h and then extracted with four 20-mL portions of methylene chloride and three 20-mL portions of ether. The

(18) In principle the methoxy group might have played the role of a neighboring group (see i) or a leaving group (see ii). Both processes would be much more likely in compounds having an exo-methoxy group; neither would be expected to lead to lactone **25**.



i ii

(19) The following columns were used for VPC analysis: (a) 3% SE-30 on Varaport 30, 5 ft × 1/4 in. stainless steel; (b) 10% SE-30 on Chromosorb W, 10 ft × 3/8 in. stainless steel; (c) 10% SE-30 on Chromosorb W, 10 ft × 1/4 in. aluminum; (d) 5% SE-30 on Chromosorb W, 5 ft × 1/4 in. aluminum; (e) 10% DC-550 on Chromosorb W, 10 ft × 1/4 in. aluminum; (f) 3% SE-30 on Chromosorb W, 5 ft × 1/4 in. aluminum.

(20) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 2544–2550.

combined organic layers were dried ($MgSO_4$) and concentrated to give 0.394 g (83%) of **9** as a cloudy liquid: IR (film) 3400 (br), 2950, 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.2 (m, 9 H), 3.02 (br s, 1 H, OH), 3.53 (s, CH_2O), 3.75 (s, CO_2CH_3), 4.00 (s, OCH_2CH_2O) (total 9 H). VPC analysis[19b] (180 °C, $C_{17}H_{36}$ = 15.1 min) showed the major peak at 16.8 min (>99% of total peak area).

2-Keto-*exo*-7-(hydroxymethyl)-*endo*-7-(carbomethoxy)-norcarane (10). To a solution of 0.295 g (1.22 mmol) of ketal alcohol ester **9** in 15 mL of THF was added 0.41 mL (1.23 mmol) of 3 M H_2SO_4. The resulting solution was stirred at room temperature for 1.3 h and then poured into saturated $NaHCO_3$ overlaid with ether. The layers were separated, and the aqueous layer was extracted twice with ether and twice with methylene chloride. The combined organic layers were dried ($MgSO_4$), concentrated, and evaporatively distilled (165 °C) to give 0.159 g (66%) of **10** as a colorless liquid: IR (film) 3400, 2950, 1732, 1696, 1170 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.6 (m, 8 H), 3.78 (s, CO_2CH_3) overlapping with 3.1–4.1 (m) (total 6 H); mass spectrum, *m/e* 198.0893 (M^+) (calcd for $C_{10}H_{14}O_4$ 198.0892), 170, 167, 148, 137, 120, 93, 79, 55. VPC analysis[19c] (180 °C, $C_{17}H_{36}$ = 17.7 min) showed the major peak at 17.3 min (97% of total peak area).

Mesylate (11) of Keto Alcohol 10. To a solution of 1.132 g (5.7 mmol) of the keto alcohol ester **10** in 55 mL of methylene chloride was added 1.2 mL (8.6 mmol) of triethylamine, and the solution was stirred in an ice bath for 20 min. To the resulting solution was added 0.49 mL (6.3 mmol) of methanesulfonyl chloride, and the mixture was stirred at 0 °C for 1.6 h. The mixture was then diluted with 40 mL of methylene chloride, washed successively with 35-mL portions of cold water, 10% HCl, saturated $NaHCO_3$, and saturated NaCl, then dried ($MgSO_4$), and concentrated (using a water bath at room temperature). The residue was placed under oil pump vacuum for 1 h to give 1.575 g (100%) of crude mesylate ester **11** as a light yellow solid, mp 86–89 °C. Recrystallization from pentane–methylene chloride gave 1.072 g (68%) of white crystals, mp 103–106 °C: IR ($CHCl_3$) 1735, 1705, 1356, 1170, 910 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.6 (m, 8 H), 3.08 (s, 3 H, CH_3SO_2), 3.75 (s, CO_2CH_3) overlapping with 3.94 (d, J = 11 Hz, CHOMs) (total 4 H), 4.47 (s, 0.3 H, impurity), 4.65 (d, J = 11 Hz, 1 H, CHOMs). Further recrystallization from pentane–methylene chloride gave white crystals, mp 107–108.5 °C. Anal. Calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.83. Found: C, 47.70; H, 5.82.

2-Keto-*exo*-7-(bromomethyl)-*endo*-7-(carbomethoxy)norcarane (12). To a solution of 0.914 g (3.30 mmol) of mesylate ester **11** in 30 mL of acetone was added 1.21 g (13.9 mmol) of lithium bromide. The resulting solution was stirred at room temperature for 72 h (precipitate formed) and then was added to saturated NaCl overlaid with ether. The layers were separated, and the aqueous layer was extracted three times with ether and once with methylene chloride. The combined organic layers were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 0.663 g (77%) of bromide **12** as a yellow liquid: IR (film) 2970, 1733, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.7 (m, 8 H), 3.10 (d, J = 11 Hz, 1 H, CHBr), 3.76 (s, CO_2CH_3) overlapping with 3.97 (d, J = 11 Hz, CHBr) (total 4 H). TLC showed one spot (R_f 0.62, 1% MeOH/$CHCl_3$; for iodide **13**, R_f 0.56; mesylate **11**, R_f 0.43).

2-Keto-*exo*-7-(iodomethyl)-*endo*-7-(carbomethoxy)norcarane (13). To a solution of 0.212 g (0.765 mmol) of the mesylate ester **11** in 11 mL of acetone was added 0.40 g (2.67 mmol) of sodium iodide. The resulting solution was stirred at room temperature for 20 h (precipitate formed). The reaction mixture was then added to saturated NaCl overlaid with ether. The layers were separated, and the aqueous layer was extracted three times with ether and twice with methylene chloride. The combined organic layers were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 0.218 g (92%) of iodide **13** as a brown liquid: IR (film) 2965, 1730, 1700, 1196 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.7 (m, 8 H), 2.99 (d, J = 11 Hz, 1 H, CHI), 3.79 (s, CO_2CH_3) overlapping with 3.76 (d, J = 11 Hz, CHI) (total 4 H).

Rearrangement of Mesylate Ester 11 in the Presence of Lithium Perchlorate in Dioxane: Formation of Lactone 23. To a solution of 0.240 g (0.87 mmol) of the mesylate ester **11** in 6.5 mL of dioxane was added 1.17 g (11.0 mmol) of anhydrous lithium perchlorate, and the resulting mixture was heated at reflux (bath temperature 100 °C) for 17.4 h. The mixture was then poured into 25 mL of water overlaid with ether. The layers were separated, and the aqueous layer was extracted three times with ether and once with methylene chloride. The combined organic layers were washed with saturated $NaHCO_3$, dried ($MgSO_4$), concentrated, and evaporatively distilled (162 °C) to give 70 mg of a light yellow liquid (which solidified in the freezer) which was identified as lactone **23**[14] by its IR (1760, 1696 cm^{-1}) and NMR spectra. The mass spectrum showed *m/e* 166.0631 (M^+) (calcd for $C_9H_{10}O_3$ 166.0630). VPC analysis[19a] (147 °C, $C_{16}H_{34}$ = 2.9 min) showed the major peak at 2.7 min (91.5% of peak area).

Rearrangement of Iodo Ester 13 with Silver Perchlorate in Dioxane: Formation of Keto Diene Ester 24. To a solution of 0.332 g (1.08 mmol) of the iodo ester **13** in 14 mL of dioxane was added 1.01 g (4.88 mmol) of anhydrous silver perchlorate. The resulting mixture was stirred at room temperature for 16 h. Water (36.4 μL, 2.02 mmol) was added, and the mixture was stirred for 23 h and then poured into a mixture of saturated NaCl and $NaHCO_3$ overlaid with ether. The layers were separated, and the aqueous layer was extracted three times with ether and once with methylene chloride. The combined organic layers were dried ($MgSO_4$) and concentrated to give 0.225 g of a white solid–yellow liquid mixture. VPC analysis[19a] (143 °C, $C_{16}H_{34}$ = 2.8 min) showed the major peak at 2.2 min (~80% of total peak area). (It should be noted that VPC analysis of iodo ester **13** under the same conditions showed the major peak at 2.2 min, suggesting rearrangement on the column.) This mixture was chromatographed on 12.5 g of Florisil. Elution with ether–methylene chloride (1:1) gave 61 mg of oil, which showed one spot on TLC (R_f 0.60, 1% MeOH/$CHCl_3$) and was identified as keto diene ester **24** by its IR (1731, 1680 cm^{-1}) and NMR[14] spectra. The mass spectrum showed *m/e* 180.0787 (M^+) (calcd for $C_{10}H_{12}O_3$ 180.0786), 165, 152, 121, 91.

2,2-Dimethoxy-7,7-bis(carbomethoxy)norcarane (14). To a solution of 2.096 g (9.26 mmol) of keto diester **6** in 20 mL of absolute MeOH at room temperature was added dropwise 2.45 mL (22.39 mmol) of methyl orthoformate in 20 mL of absolute MeOH over a period of 10 min.[21] The mixture was stirred for 5 min and then cooled to 0 °C. *p*-Toluenesulfonic acid monohydrate (0.24 g, 1.26 mmol) was added, and the mixture was stirred for 10 min, then warmed to room temperature, and stirred for another 5 min. The mixture was then allowed to stand without stirring at room temperature for 12 days. A solution of sodium methoxide in MeOH was added until the mixture reached pH 8. The mixture was then concentrated and evaporatively distilled (140 °C) to give 2.055 g (81%) of ketal **14** as a colorless liquid: IR (film) 2970, 1730, 1255 cm^{-1}; NMR ($CDCl_3$) δ 0.7–2.5 (m, 8 H), 3.23 (s, 3 H), 3.31 (s, 3 H), 3.74 (s) and 3.78 (s) (total 6 H); mass spectrum, *m/e* 272 (M^+), 257, 241, 240, 209, 208, 149, 148, 121, 109, 108, 91, 77. VPC analysis[19d] (165 °C, $C_{17}H_{36}$ = 3.4 min) showed the major peak at 2.8 min (99% of total peak area).

***endo*-2-Methoxy-7,7-bis(carbomethoxy)norcarane (15).** To a solution of 0.184 g (0.68 mmol) of dimethyl ketal diester **14** in 10 mL of absolute MeOH at 0 °C was added 85.7 mg (1.36 mmol) of sodium cyanoborohydride, and the mixture was stirred for 10 min.[12] Then acetyl chloride was added slowly until the pH came to 2 (0.06 mL total). The reaction was monitored by VPC and in this case was found to be complete in 2 h. The remaining reaction mixture was poured into ice and extracted four times with pentane and twice with ether. The combined organic layers were washed with saturated $NaHCO_3$, dried (K_2CO_3), and concentrated to give 0.152 g (93%) of compound **15** as a colorless liquid: IR (film) 2960, 1730, 1255 cm^{-1}; NMR ($CDCl_3$) δ 0.6–2.6 (m, 8 H), 3.40 (s, 3 H), 3.69 (s) and 3.75 (s) overlapping with broad multiplet (CHOMe) (total 7 H); mass spectrum, *m/e* 242 (M^+), 227, 210, 195, 184, 152, 110, 91, 79, 59. VPC analysis[19a] (150 °C, $C_{16}H_{34}$ = 1.3 min) showed the major peak at 1.3 min (98% of total peak area). From a similar experiment, an analytical sample was prepared by chromatography and distillation. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.30; H, 7.48.

***endo*-2-Methoxy-*exo*-7-carboxy-*endo*-7-(carbomethoxy)-norcarane (16).** With use of a procedure similar to that used for the conversion of **7** to **8**, 2.310 g (9.53 mmol) of methoxy diester **15** in 50 mL of methanol was treated with 0.82 g (12.34 mmol)

(21) Eliel, E. L.; Badding, V. G.; Rerick, M. N. *J. Am. Chem. Soc.* **1962**, *84*, 2371–2377.

of potassium hydroxide (85%) in 38 mL of water. After workup was obtained 2.092 g of a colorless liquid, which solidified in the freezer. Recrystallization from pentane–methylene chloride gave 1.20 g (mp 107.5–108.5 °C) and 0.636 g (mp 105–106.5 °C) of the acid ester **16** as white crystals (total yield 84%): IR ($CHCl_3$) 3500–2500 (br), 1734, 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.7–2.6 (m, 8 H), 3.42 (s, 3 H), 3.77 (s) overlapping with 3.7–4.2 (m) (total 4 H), 9.7 (s, 1 H). The 220-MHz NMR spectrum ($CDCl_3$) showed the methine proton on the carbon bearing the methoxy group at δ 3.90 as a doublet (J = 10.5 Hz) of triplets (J = 6 Hz) and the adjacent proton on the ring junction carbon at δ 2.22 as a doublet of doublets (J = 6, 9 Hz). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89, H, 7.07. Found: C, 57.65; H, 6.93.

***endo*-2-Methoxy-*exo*-7-(hydroxymethyl)-*endo*-7-(carbomethoxy)norcarane (17).** With use of a procedure similar to that used for the conversion of **8** to **9**, 0.328 g (1.44 mmol) of methoxy acid ester **16** was treated successively with sodium hydride (4.37 mmol) in 33 mL of THF, 0.145 mL (1.87 mmol) of methyl chloroformate in 15 mL of THF, 0.44 g (11.6 mmol) of sodium borohydride, and 2 mL of methanol. Workup and evaporative distillation (145 °C) as before yielded 0.200 g (65%) of the hydroxy ester **17** as a colorless liquid: IR (film) 3440, 2960, 1735, 1200 cm^{-1}; NMR ($CDCl_3$) δ 0.7–2.3 (m, 8 H), 3.38 (s) overlapping with 3.57 (m, CHOMe and CH_2OH) and 3.73 (s) (total 10 H); mass spectrum, m/e 214.1207 (M^+) (calcd for $C_{11}H_{18}O_4$ 214.1205), 196, 181, 137, 105, 91. VPC analysis[19e] (176 °C, $C_{17}H_{36}$ = 8.3 min) showed the major peak at 8.7 min (>99% of total peak area).

Mesylate (18) of Methoxy Alcohol 17. With use of a procedure similar to that used for the conversion of **10** to **11**, an ice-cooled solution of 0.480 g (2.24 mmol) of the methoxy alcohol ester **17** in 25 mL of methylene chloride was treated with 0.48 mL (3.44 mmol) of triethylamine followed by 0.202 mL (2.61 mmol) of methanesulfonyl chloride. The product was worked up as described for the preparation of **11** and concentrated by using a room-temperature bath to give 0.629 g (96%) of mesylate **18** as a light, cloudy liquid: IR (film) 2960, 1741, 1360, 1175, 940 cm^{-1}; NMR ($CDCl_3$) δ 0.7–2.5 (m, 8 H), 3.04 (s, 3 H), 3.36 (s, 3 H), 3.73 (s, CO_2CH_3) overlapping with 3.7–4.1 (m, CHOMe) and 3.87 (d, J = 10.5 Hz, CHOMs) (total 7 H), 4.65 (d, J = 10.5 Hz, 1 H, CHOMs). TLC (3% MeOH/$CHCl_3$) showed one spot with R_f 0.76.

***endo*-2-Methoxy-*exo*-7-(bromomethyl)-*endo*-7-(carbomethoxy)norcarane (19).** With use of a procedure similar to that used for the conversion of **11** to **12**, a solution of 0.523 g (1.79 mmol) of mesylate ester **18** in 22 mL of acetone was treated with 0.64 g (7.39 mmol) of lithium bromide at room temperature for 16 h. After workup, the crude product was placed under oil pump vacuum for 0.5 h at 0 °C, giving 0.439 g (89%) of bromide **19** as a light yellow solid (mp 48–50 °C): IR ($CHCl_3$) 2960, 1740, 1440, 1345, 1175 cm^{-1}; NMR ($CDCl_3$) δ 0.7–2.4 (m, 8 H), 3.07 (d, J = 10.5 Hz, 1 H, CHBr), 3.38 (s, 3 H), 3.74 (s, CO_2CH_3) overlapping with 3.7–4.1 (m, CHOMe) and 4.03 (d, J = 10.5 Hz, CHBr) (total 5 H). TLC (1% MeOH/$CHCl_3$) showed one spot with R_f 0.71.

***endo*-2-Methoxy-*exo*-7-(iodomethyl)-*endo*-7-(carbomethoxy)norcarane (20).** To a solution of 0.106 g (0.363 mmol) of the mesylate ester **18** in 9 mL of acetone was added 0.272 g (1.82 mmol) of sodium iodide, and the mixture was stirred at room temperature for 8 h (precipitate formed) and then poured into saturated $NaHCO_3$ overlaid with ether. The layers were separated, and the aqueous layer was extracted three times with ether and twice with methylene chloride. The combined organic layers were dried ($MgSO_4$), concentrated, and placed under oil pump vacuum at 0 °C for 0.5 h, giving 95 mg (81%) of iodide **20** as a light yellow liquid: IR (film) 2960, 1742, 1360, 1200, 1100 cm^{-1}; NMR ($CDCl_3$) δ 0.7–2.3 (m, 8 H), 2.87 (d, J = 10 Hz, 1 H, CHI), 3.07 (s, 0.4 H, impurity), 3.38 (s, 3 H), 3.74 (s, CO_2CH_3) overlapping with 3.85 (d, J = 10 Hz, CHI) and 3.60–4.10 (m, CH–OMe) (total 5 H). TLC (1% MeOH/$CHCl_3$) showed one spot with R_f 0.66.

Rearrangement of Iodo Ester 20 with Silver Perchlorate in Dioxane: Isolation of α-Methylene Lactone 25. To a solution of 426 mg (1.31 mmol) of iodo ester **20** in 6 mL of dioxane was added 600 mg (2.90 mmol) of anhydrous silver perchlorate, and the resulting mixture was stirred at room temperature for 1.75 h (light green precipitate formed). The mixture was poured into aqueous NaCl and $NaHCO_3$ overlaid with ether. The layers were separated, and the aqueous layer was extracted three times with ether and three times with methylene chloride. The combined organic layers were dried ($MgSO_4$) and concentrated to give 0.200 g of crude lactone **25** as a brown liquid. VPC analysis[19e] (175 °C, $C_{17}H_{36}$ = 9.2 min) showed the major peak at 11.6 min (88%, **25**) with a minor peak at 3.9 min (5%, **26**). The crude product was chromatographed on 14 g of Florisil; elution with 3% ether in methylene chloride gave four major fractions: (1) 33 mg, 82% pure by VPC; (2) 38 mg, >99% pure by VPC; (3) 40 mg, >99% pure by VPC; (4) 16 mg, >99% pure by VPC (total yield of fractions 2–4 = 39%). The third fraction was evaporatively distilled (145 °C) to give 33 mg of lactone **25** as a colorless liquid: IR (film) 2960, 1767, 1101 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.2 (m, 6 H), 3.36 (s, OCH_3) overlapping with 3.2–3.7 (m, MeOCHCHC=C) (total 5 H), 4.57 (br m, 1 H, CHOCO), 5.93 (m, 1 H), 6.26 (m, 1 H). The 220-MHz NMR spectrum ($CDCl_3$) showed the multiplet at δ 4.57 to be a doublet (J = 5.6 Hz) of triplets (J = 7.2 Hz). The mass spectrum showed m/e 182.0915 (M^+) (calcd for $C_{10}H_{14}O_3$ 182.0943), 164, 150, 122, 97, 71.

***cis*-2-Hydroxy-*cis*-(6-methoxycyclohexyl)acetic Acid Lactone (28).** To a solution of 1.52 g (9.73 mmol) of hydroxy lactone **27**[15] in 15 mL of methyl iodide were added 4.89 g (36 mmol) of $CaSO_4$ (dried overnight at 105–110 °C) followed by 3.67 g (15.8 mmol) of Ag_2O.[16] The resulting mixture was stirred vigorously at room temperature for 36 h, at which point VPC analysis of an aliquot indicated that reaction was complete. The reaction mixture was filtered through Celite (using 150 mL of methylene chloride as wash). The filtrate was concentrated and evaporatively distilled (162–164 °C) giving 1.47 g (89%) of **28** as a colorless oil: IR (film) 2960, 1770, 1170, 1110, 960 cm^{-1}; NMR (CCl_4) δ 1.0–2.1 (m, 7 H), 2.1–3.0 (m, 3 H), 3.30 (s, OCH_3) overlapping with 3.1–3.5 (m, CHOMe) (total 4 H), 4.4 (m, 1 H); mass spectrum, m/e 170.0916 (M^+) (calcd for $C_9H_{14}O_3$ 170.0943), 138, 110, 97, 71. VPC analysis[19f] (120 °C, $C_{16}H_{34}$ = 2.8 min) showed the major peak at 1.56 min (96% of total peak area).

2-(*cis*-2-Hydroxy-*cis*-6-methoxycyclohexyl)propenoic Acid Lactone (25). A solution of 0.221 g (1.3 mmol) of methoxy lactone **28** in 15 mL of THF was added dropwise over 20 min to a solution (at −78 °C) of lithium diisopropylamide in THF [prepared from 0.24 mL (1.70 mmol) of diisopropylamine, 1.20 mL (1.73 mmol) of n-butyllithium (1.44 M in hexane), and 10 mL of THF]. The resulting mixture was stirred for 1.5 h at −78 °C, then warmed to −24 °C, and treated with formaldehyde. [Paraformaldehyde (dried overnight under vacuum) (0.585 g, 19.5 mmol as CH_2O) was heated at 155–160 °C while passing the resulting formaldehyde into the reaction mixture with a stream of nitrogen.] The reaction mixture was then stirred an additional 1.5 h at −24 °C and then quenched with saturated NH_4Cl. The resulting mixture was placed under water pump vacuum to remove THF, and the aqueous residue was extracted four times with methylene chloride and four times with ether. The combined organic extracts were washed with saturated NaCl, dried ($MgSO_4$), and concentrated. The residue was chromatographed on 25 g of silica gel. Elution with 3:1 ether–methylene chloride gave 0.138 g (53%) of the hydroxymethylated lactone **29**: IR (film) 3400, 2960, 1765 cm^{-1}. The NMR spectrum ($CDCl_3$) showed several broad absorptions at δ 1–5 and a singlet at δ 3.40 (OCH_3). VPC analysis[19f] (95 °C, $C_{18}H_{38}$ = 5.2 min) showed the major peak at 6.7 min (93% of peak area).

To an ice-cooled solution of 137.6 mg (0.687 mmol) of hydroxymethylated lactone **29** (product from above experiment) in 8 mL of pyridine was added 0.064 mL (0.825 mmol) of methanesulfonyl chloride. The reaction mixture was stirred overnight (approximately 20 h). The solvent was removed in vacuo and the residue dissolved in water and methylene chloride. The aqueous layer was extracted several times with methylene chloride and with ether. The combined organic layers were washed with saturated NaCl, dried ($MgSO_4$), and concentrated, giving 122 mg of the mesylate as a white solid: NMR ($CDCl_3$) δ 0.8–2.8 (m, 8 H), 2.9–3.6 (m, CHOMe) overlapping with 3.07 (s, CH_3SO_2) and 3.40 (s, OCH_3) (total 7 H), 4.65 (m, 3 H, CHOCO and CH_2OMs).

A solution of 122 mg of the mesylate prepared above in 8 mL of pyridine was heated to 135–140 °C for about 8 h. The reaction mixture was then cooled to room temperature and the solvent removed in vacuo. The residue was dissolved in water and methylene chloride, and the aqueous layer was extracted several

times with methylene chloride and with ether. The combined organic layers were dried ($MgSO_4$), concentrated, chromatographed on silica gel, and evaporatively distilled (135–140 °C), giving 88 mg (70% from **29**) of α-methylenelactone **25** as a colorless liquid. The IR, NMR, and mass spectra were essentially identical with those of lactone **25** prepared by rearrangement of iodo ester **20**. VPC analysis[19e] (155 °C, $C_{18}H_{38}$ = 9.8 min) showed a single peak at 10.5 min.

Acknowledgment. We are grateful to Professor Carlyle B. Storm for 220-MHz NMR spectra of compounds **16** and **25**, to Professors Peter A. Jacobi and Frederick E. Zeigler for comparison spectra, to Professor Ronald A. Ruden for suggesting the preparation of compound **6**, and to Dr. Anne M. Hudrlik for assistance with the manuscript. We thank the NIH (Grant No. 2-S06-RR-08016-10 from the MBS Program, DRR/NIH, and Grant No. CA-23037 from the NCI) for financial support.

Registry No. **6**, 81856-97-5; **6** 2,4-DNP deriv., 81856-98-6; **7**, 81856-99-7; **8**, 81857-00-3; **9**, 81857-01-4; **10**, 81857-02-5; **11**, 81857-03-6; **12**, 81857-04-7; **13**, 81857-05-8; **14**, 81857-06-9; **15**, 81857-07-0; **16**, 81857-08-1; **17**, 81857-09-2; **18**, 81857-10-5; **19**, 81857-11-6; **20**, 81857-12-7; **23**, 68961-90-0; **24**, 81857-13-8; **25**, 81857-14-9; **26**, 81857-15-0; **27**, 54911-63-6; **28**, 81857-16-1; **29**, 81857-17-2; **29** mesylate, 81857-18-3; dimethyl malonate, 108-59-8; 2-bromo-2-cyclohexen-1-one, 50870-61-6; ethylene glycol, 107-21-1; methanesulfonyl chloride, 124-63-0.

Notes

Synthesis of the Corticoid Side Chain

Andrzej Robert Daniewski* and Wanda Wojciechowska

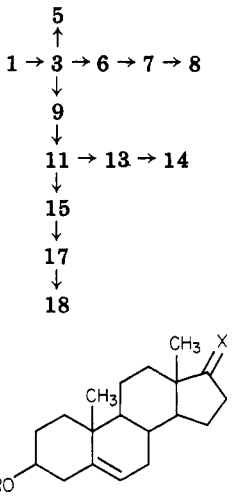
Institute of Organic Chemistry of the Polish Academy of Sciences, 01-224 Warsaw, Poland

Received November 19, 1981

The transformation of androstan-17-one derivatives into corticoids and other compounds like cardenolides or bufadienolides become very important when microbial degradation of the side chain of easy accessible from soya bean sitosterol and campesterol was developed.[1] Recently, efficient methods for syntheses of two-carbon-atom side chains were published,[2-4] but all of them suffer from inconveniences. We present a method of synthesis of pregnane derivatives starting from protected 3β-hydroxy-5-androsten-17-one as a tetrahydropyranyl ether (**1**, Scheme I) or as the 6β-methoxy i-steroid (**2**, Scheme II).

Compounds **1** and **2** were transformed into chloro esters **3** and **4**, respectively, by the Reformatsky-type reaction[5] using ethyl trichloroacetate, zinc, and diethylchloroaluminum. Transformation of chloro ester **3** to compound **6** was accomplished by DIBAL-H reduction, and deprotection of 3β-OH group and acetylation afforded diacetate **8**. Attempts to hydrolyze the vinylic chlorine in compound **8**, in order to obtain compound **14**, by using $HClO_4$, H_2SO_4, $BF_3{\cdot}OEt_2$, and $Hg(OAc)_2$ in acetic acid or in CF_3COOH failed. Refluxing chloro esters **3** and **4** in anhydrous methanol with sodium methoxide gave the methoxy esters **9** and **10**, respectively. The NMR spectra of chloro esters **3** and **4** and methoxy esters **9** and **10** showed that the compounds were pure either *E* or *Z* isomers. The DIBAL-H reduction of methoxy esters **9** and **10** in toluene gave alcohols **11** and **12**, respectively, which on acid hydrolysis gave 3β,21-dihydroxy-5-pregnen-20-one (**13**) in excellent yield. The methoxy alcohols **11** and **12** when treated with MCPBA in methanol at room temperature gave compounds **15** and **16**, respectively, in 95% yield.

Scheme I



1, X = O; R = THP

3, X = $C(Cl)(COOEt)$; R = THP

5, X = $C(Cl)(COOEt)$; R = H

6, X = $C(Cl)(CH_2OH)$; R = THP

7, X = $C(Cl)(CH_2OH)$; R = H

8, X = $C(Cl)(CH_2OAc)$; R = Ac

9, X = $C(OCH_3)(COOCH_3)$; R = THP

11, X = $C(OCH_3)(CH_2OH)$; R = THP

13, X = $COCH_2OH$; 17α-H; R = H
14, X = $COCH_2OAc$; 17α-H; R = Ac
15, X = $COCH_2OH$; 17α-OH; R = THP
17, X = $COCH_2OH$; 17α-OH; R = H
18, X = $COCH_2OAc$; 17α-OH; R = Ac

(1) M. G. Wovcha, F. J. Antosz, J. C. Knight, L. A. Kominek, and T. R. Pyke *Biochim. Biophys. Acta*, **539**, 308 (1978).
(2) V. Van Rheenen, K. P. Shepard, *J. Org. Chem.*, **44**, 1582 (1979).
(3) G. Neef, U. Eder, A. Seeger, and R. Wiechert, *Chem. Ber.*, **113**, 1184 (1980).
(4) M. Gumułka, A. Kurek, and J. Wicha, *Pol. J. Chem.*, in press.
(5) K. Takai, Y. Hotta, K. Oshina, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **53**, 1698 (1980).