Syntheses of α- and β-Sorigenin Methyl Ethers

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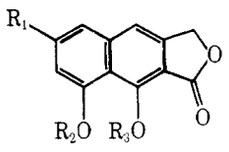
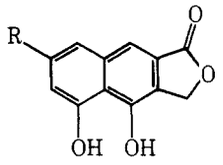
New, abbreviated syntheses of β- and α-sorigenin methyl ethers (**1a** and **1b**) have been accomplished using our recently reported synthetic strategy and reaction sequence for the regioselective construction of linear polynuclear aromatic systems.[1]

The first examples of natural products with a naphthalene nucleus, two primosides, α- and β-sorinin and their aglycones, β-sorigenin (**1c**) and α-sorigenin (**1d**), were isolated by Nikuni

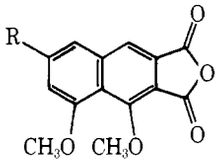


1a, $R_1 = H$; $R_2 = R_3 = CH_3$
b, $R_1 = OCH_3$; $R_2 = R_3 = CH_3$
c, $R_1 = R_2 = R_3 = H$
d, $R_1 = OCH_3$; $R_2 = R_3 = H$



2a, R = H
b, R = OCH_3

in 1938 from the bark of *Rhamus japonica*.[2,3] Initially, structures **2a** and **2b** were proposed for the sorigenins, but these were later revised to **1c** and **1d** by Haber, Nikuni, et al.[4] Lengthy syntheses of the sorigenin methyl ethers by Horii et al.[5,6] followed, but these preparations, performed through anhydrides **3a** and **3b**, failed to establish the disposition of the



3a, R = H
b, R = OCH_3

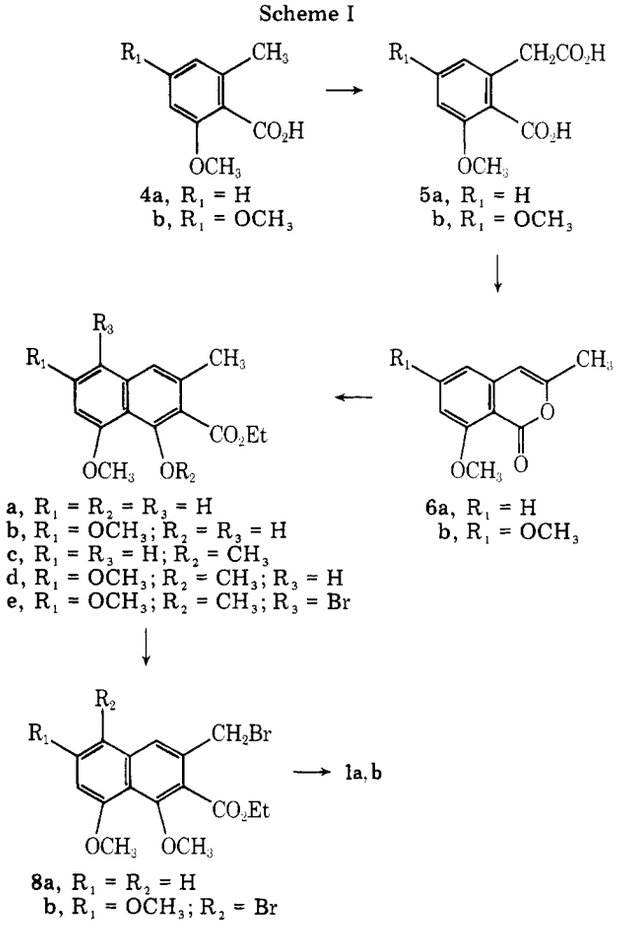
lactone moiety. Finally, Nikuni et al.[7] and Horii et al.[6] independently published unequivocal but protracted syntheses of the sorigenin methyl ethers.

Scheme I shows our parallel reaction sequences followed to transform 2-methoxy-6-methylbenzoic acid[9] (**4a**) and dimethylorsellinic acid[10] (**4b**) to β- and α-sorigenin methyl ethers (**1a** and **1b**), respectively. A high-yield, one-pot transformation of benzoic acid **4a** to homophthalic acid **5a** was described by us earlier.[11] Under identical conditions, dimethylorsellinic acid[10] (**4b**) was efficiently transformed to homophthalic acid **5b** in 76% yield.[12] Preparations of isocoumarins **6a**[18] and **6b**[13,16] from homophthalic acids **5a** and **5b** have been described. The best yields (65–70%) were obtained using the three-step sequence outlined by Wendler et al.[13]

Substantially improved yields over those reported for transformation of isocoumarins to ethyl 1-hydroxy-2-naphthoates by Reformatsky reaction were achieved by dropwise addition of the precursor ethyl bromoacetate rather than batch addition.[19] Employing the modified conditions, naphthoates **7a** and **7b** were obtained in 72 and 34% yield respectively from isocoumarins **6a** and **6b**.[20] Naphthoates **7a** and **7b** were converted in quantitative yield to their corresponding methyl ethers **7c** and **7d** employing potassium carbonate and dimethyl sulfate.

Final conversion of naphthalene **7c** to β-sorigenin methyl ether was accomplished by initial bromination of the 3-methyl group of **7c** with *N*-bromosuccinimide (NBS) to give bromomethyl compound **8a**. Treatment of **8a** with sodium hydroxide resulted in initial bromide displacement followed by anchimerically assisted hydrolysis of the ortho ester functionality furnishing β-sorigenin methyl ether in 85% yield.

Scheme I



4a, $R_1 = H$
b, $R_1 = OCH_3$

5a, $R_1 = H$
b, $R_1 = OCH_3$

a, $R_1 = R_2 = R_3 = H$
b, $R_1 = OCH_3$; $R_2 = R_3 = H$
c, $R_1 = R_3 = H$; $R_2 = CH_3$
d, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = H$
e, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = Br$

6a, $R_1 = H$
b, $R_1 = OCH_3$

8a, $R_1 = R_2 = H$
b, $R_1 = OCH_3$; $R_2 = Br$

A more circuitous route was necessary to convert naphthalene **7d** to α-sorigenin methyl ether (**1a**). Treatment of naphthalene **7d** with an equivalent of NBS resulted in nearly exclusive formation of ring-brominated product **7e**. Successful bromination of the 3-methyl group of **7e** to bromomethyl compound **8b** was accomplished with a second equivalent of NBS. Treatment of **8b** with sodium hydroxide followed by catalytic reduction with palladium on charcoal to cleave the arylbromine gave α-sorigenin methyl ether **1b**. The overall yield of **1b** from **7d** was 53% after purification.

These syntheses demonstrate that the synthetic strategy and reaction sequence described earlier by us[1] have general applicability and can be used to regiospecifically construct highly functionalized naphthalenes. Further studies on the preparation of more complex polynuclear aromatic systems are in progress.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 337 spectrophotometer. Ultraviolet spectra were run on a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Model HA-100, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in δ units. TLC analyses were performed on silica gel using 5% ethyl acetate–chloroform as the eluent.

2-Carboxy-3,5-dimethoxybenzeneacetic Acid (5b). Benzeneacetic acid **5b** was prepared in a manner analogous to that described for **5a**.[11] From orsellinic acid (**4b**) (10 g, 50 mmol), there was obtained, after recrystallization (acetone–hexane), 9.3 g (76%) of pure **5b** with mp 171–173 °C (lit.[13] mp 171–173 °C).

8-Methoxy-3-methyl-1*H*-2-benzopyran-1-one (6a) and 6,8-Dimethoxy-3-methyl-1*H*-2-benzopyran-1-one (6b). Pyridine (2.5 mL) was added to a magnetically stirred mixture of benzeneacetic acid

5a (5.0 g, 23.8 mmol) in acetic anhydride (13 mL) under nitrogen. The solids instantly dissolved to give a greenish orange solution and within 10 min crystals began to separate. Dry ether (75 mL) was added to facilitate stirring, which was continued overnight. The reaction was diluted with additional dry ether (100 mL) and filtered and the cake of acetylated chromandione was washed repeatedly with ether to remove traces of acetic anhydride and pyridine.

The dried cake was suspended in water (40 mL) and the solution was magnetically stirred and heated on the steam bath. A sodium hydroxide solution (10%) was added dropwise so that the carbon dioxide effervescence did not create excessive foaming. When the foaming ceased, additional sodium hydroxide solution was added to a final pH 9–10. Stirring and heating of the reaction was continued for another hour at which time the solution was acidified to pH 1 with hydrochloric acid. The reaction was extracted with ethyl acetate (2 × 100 mL). The organic extract was dried ($MgSO_4$) and filtered.

To the magnetically stirred ethyl acetate extract was added acetic anhydride (10 mL) and perchloric acid (3–5 drops); the solution darkened immediately on addition of the acid. The reaction was stirred for 1 to 2 h before a saturated bicarbonate solution (50 mL) was added. When the foaming ceased, the organic layer was separated, dried ($MgSO_4$), and evaporated at reduced pressure. Residual acetic anhydride was removed by taking the residue up in ethyl acetate (200 mL) and adding small portions of bicarbonate solution until no further carbon dioxide evolution was observed. The organic layer was again separated, dried, and evaporated to give a brown oil which slowly crystallized. Final purification was effected by chromatography (100 g, silica gel, 3% EtOAc–CH_2Cl_2) and gave 3.08 g (68%) of pure **6a** with mp 109 °C (lit. mp 109.5–110.5 °C).

Using the above procedure, benzeneacetic acid **5b** was converted to benzopyran **6b** in 70% yield, mp 151–152 °C (lit.[13] mp 151–152 °C).

Ethyl 1-Hydroxy-8-methoxy-3-methyl-2-naphthalenecarboxylate (7a) and Ethyl 6,8-Dimethoxy-1-hydroxy-3-methyl-2-naphthalenecarboxylate (7b). A solution of ethyl bromoacetate (14.8 g, 88.4 mmol) in benzene (225 mL) was added dropwise (drop/7–10 s) to a magnetically stirred refluxing mixture of dry, acid washed zinc (14.5 g, 221 mmol, 20 mesh) and benzopyran **6a** (4.2 g, 22.1 mmol) in benzene (20 mL). Approximately 30 min after the addition was started, yellow crystals began forming in the reaction. After the addition was completed, the solution was refluxed for 1 h, cooled, diluted with ethyl acetate (200 mL), and acidified with hydrochloric acid. The organic layer was separated and washed with water (2 × 100 mL), sodium bicarbonate solution (200 mL), water (100 mL), and brine (100 mL). The solution was dried ($MgSO_4$), filtered, and evaporated to give a brown oil which slowly crystallized.

Final purification was accomplished by chromatography (100 g, silica gel, benzene to 3% EtOAc–benzene) and gave 4.1 g (72%) of pure **7a** with mp 59 °C: NMR ($CDCl_3$) δ 1.40 (t, J = 6 Hz, 3, CH_2CH_3), 2.42 (s, 3, $ArCH_3$), 3.96 (s, 3, OCH_3), 4.4 (q, J = 6 Hz, 2, OCH_2CH_3), 6.68 (d, J = 4 Hz, 1, ArH), 6.72 (d, J = 4 Hz, 1, ArH), 7.05 (s, 1, ArH), 7.30 (t, J = 4 Hz, 1, ArH), 10.30 (s, 1, OH). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.17; H, 6.26.

An identical reaction performed on benzopyran **6b** gave a 34% yield of naphthoate **7b** with mp 68–70 °C: NMR (CCl_4) δ 1.40 (t, J = 6 Hz, 3, CH_2CH_3), 2.40 (s, 3, $ArCH_3$), 3.80 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 4.35 (q, J = 6 Hz, 2, OCH_2CH_3), 6.23 (d, J = 4 Hz, 1, ArH), 6.38 (d, J = 4 Hz, 1, ArH), 6.74 (s, 1, ArH). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.26; H, 6.27.

Ethyl 1,8-Dimethoxy-3-methyl-2-naphthalenecarboxylate (7c) and Ethyl 3-Methyl-1,6,8-trimethoxy-2-naphthalenecarboxylate (7d). A magnetically stirred mixture of naphthoate **7a** (4.8 g, 18.5 mmol), dimethyl sulfate (3.50 g, 27.8 mmol), and anhydrous potassium carbonate (5.10 g, 37 mmol) in acetone (125 mL) was refluxed until TLC analysis indicated that the naphthoate was completely converted to methyl ether product **7c** (5–7 h). The solution was cooled, filtered, and evaporated to give an oil. Excess dimethyl sulfate was removed by dissolving the oil in ether (200 mL), adding triethylamine (5 mL), and allowing the turbid solution which formed to stand for 1 h. The ether solution was washed with water (2 × 50 mL), hydrochloric acid (50 mL), and brine (50 mL) and finally dried ($MgSO_4$). Evaporation of the solvent gave 5.04 g (100%) of pure **7c** as an oil: NMR (CCl_4) δ 1.36 (t, J = 7 Hz, 3, CH_2CH_3), 2.33 (s, 3, $ArCH_3$), 3.79 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 4.36 (q, J = 7 Hz, 2, OCH_3), 6.62 (d, J = 5 Hz, 1, ArH), 6.67 (d, J = 5 Hz, 1, ArH), 7.16 (s, 1, ArH), 7.0 (t, J = 5 Hz, ArH).

A similar preparation was performed on **7b** to give **7d** (100%): NMR (CCl_4) δ 1.34 (t, J = 7 Hz, 3, CH_2CH_3), 2.29 (s, 3, $ArCH_3$), 3.73 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 4.33 (q, J = 7 Hz, 2, CH_2CH_3), 6.31 (d, J = 5 Hz, 1, ArH), 6.46 (d, J = 5 Hz, 1, ArH), 7.07 (s, 1, ArH).

8,9-Dimethoxynaphtho[2,3-c]furan-1(3H)-one (1a). Naphthoate **7c** (700 mg, 2.6 mmol), *N*-bromosuccinimide (480 mg, 2.6 mmol), and a catalytic amount (~5 mg) of benzoyl peroxide in carbon tetrachloride (50 mL) were refluxed while irradiating with a sunlamp until the *N*-bromosuccinimide had been consumed. The solution was cooled and then filtered to remove succinimide. An ^1H NMR spectrum of the crude product showed that approximately 87% reaction had occurred and that a new singlet at δ 4.56 ppm ($ArCH_2Br$) was present. Evaporation of the solvent gave 1.1 g of bromo product **8a** which was dissolved in dioxane (20 mL) without further purification. Sodium hydroxide (500 mg) in water (20 mL) was added and the solution was refluxed under nitrogen for 2 h; TLC analysis indicated that all of the bromo compound had reacted. The dioxane was removed at reduced pressure and the remaining aqueous solution was acidified with concentrated hydrochloric acid. The aqueous solution of hydroxy acid was then heated on the steam bath to effect lactonization. While hot, the aqueous layer was extracted with ethyl acetate (2 × 100 mL), which was then washed with water (50 mL) and brine and finally dried ($MgSO_4$). The semisolid which remained after evaporation of the ethyl acetate was further purified by thick-layer chromatography (silica gel; 5% EtOAc–CH_2Cl_2) to give 529 mg (85%) of pure **1a** as a powder. A sample recrystallized from acetone–hexane had: mp 174.5–176 °C (lit.[8] mp 176–177.5 °C); NMR (acetone-d_6) δ 4.01 (s, 3, OCH_3), 4.03 (s, 3, OCH_3), 5.37 (s, 2, $ArCH_2O$), 7.0 (d, J = 6 Hz, 1, ArH), 7.03 (d, J = 6 Hz, 1, ArH), 7.70 (s, 1, ArH), 7.53 (t, J = 3 Hz, 1 ArH).

6,8,9-Trimethoxynaphtho[2,3-c]furan-1(3H)-one (1b). Naphthoate **7b** (1.4 g, 4.6 mmol) was brominated with *N*-bromosuccinimide (910 mg, 5.1 mmol) and then isolated in the same manner that was described for naphthoate **8a**. The ^1H NMR spectrum of the product (**7e**) showed that exclusive nuclear bromination had occurred: NMR (CCl_4) δ 1.37 (t, J = 7 Hz, 3, CH_2CH_3), 2.39 (s, 3, $ArCH_3$), 3.70 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 4.45 (q, J = 7 Hz, 2, OCH_2CH_3), 6.41 (s, 1, ArH), 7.71 (s, 1, ArH).

A second equivalent of *N*-bromosuccinimide (910 mg, 5.1 mmol) was added, and the bromination and workup were performed as previously described to give 3.8 g of crude dibromo product **8b:** NMR (CCl_4) δ 1.42 (t, J = 7 Hz, 3, CH_2CH_3), 3.71 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 4.40 (q, J = 7 Hz, 2, OCH_2CH_3), 4.62 (s, 2, $ArCH_2Br$), 6.39 (s, 1, ArH), 7.86 (s, 1, ArH).

Dibromoproduct **8b** was hydrolyzed without purification according to the procedure described for the preparation of β-sorigenin methyl ether (**1a**). This gave 1.17 g (81%) of lactone as a fine powder. A sample recrystallized from ethanol had: mp 240–242 °C; NMR (acetone-d_6) δ 4.05 (s, 3, OCH_3), 4.10 (s, 6, OCH_3), 5.42 (s, 2, $ArCH_2O$), 7.02 (s, 1, ArH), 8.04 (s, 1, ArH).

The bromo lactone (0.72 g, 2.5 mmol) was suspended in warm ethyl acetate–ethanol (50 mL, 1:1) with triethylamine (2 mL) and palladium on charcoal (150 mg, 10%) and hydrogenated (30 psi) until reduction ceased. The catalyst was removed by filtration through a celite bed and the solvent was evaporated to give crude lactone **1b.** Final purification was effected by thick-layer chromatography (silica gel; 5% EtOAc–CH_2Cl_2) and gave 510 mg (73%) of pure **1b** as a powder. Recrystallization from acetone–hexane gave colorless needles: mp 184–186 °C (lit.[7,8] mp 185 °C); NMR (acetone-d_6) δ 3.92 (s, 3, OCH_3), 3.98 (s, 3, OCH_3), 4.00 (s, 3, OCH_3), 5.31 (s, 2, $ArCH_2O$), 6.60 (d, J = 3 Hz, 1, ArH), 6.92 (d, J = 3 Hz, 1, ArH), 7.55 (s, 1, ArH).

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Registry No.—**1a,** 63744-12-7; **1b,** 63744-13-8; **1b** bromo derivative, 63744-14-9; **4b,** 3686-57-5; **5a,** 1137-31-1; **5b,** 4778-99-8; **6a,** 830-54-6; **6b,** 18110-66-2; **7a,** 63520-14-9; **7b,** 63744-15-0; **7c,** 63744-16-1; **7d,** 63744-17-2; **7e,** 63744-18-3; **8a,** 63744-19-4; **8b,** 63744-20-7; ethyl bromoacetate, 105-36-2.

References and Notes

(1) F. M. Hauser and R. P. Rhee, *J. Am. Chem. Soc.*, **99,** 4533 (1977).
(2) Z. Nikuni, *Nippon Nogei Kagaku Kaishi,* **14,** 352 (1938).
(3) Z. Nikuni and H. Hitsumoto, *Nippon Nogei Kagaku Kaishi,* **20,** 283 (1944).
(4) R. G. Haber, Z. Nikuni, H. Schmid, and K. Yagi, *Helv. Chem. Acta,* **39,** 1654 (1956).
(5) Z. Horii and T. Tanaka, *Chem. Ind. (London),* 1576 (1959).
(6) Z. Horii, T. Katagi, and Y. Tamura, *Chem. Ind. (London),* 1088 (1960).
(7) M. Matsui, Y. Nakatani, Y. Mori, and Z. Nikuni, *Agric. Biol. Chem.,* **27,** 40 (1962).
(8) Z. Horii, T. Katagi, Y. Tamura, T. Tanaka, and Y. Yamawaki, *Chem. Pharm. Bull.,* **11,** 305, 317 (1963).
(9) Several syntheses of this compound have appeared in the literature. A practical synthesis, adaptable to large-scale preparation, was reported by V. B. Piskov and L. K. Osanova, *Chem. Abstr.,* **65,** 3782c (1965).

(10) Ethyl orsellinate was prepared according to a procedure described by R. M. Anker and A. H. Cook (*J. Chem. Soc.*, 311 (1945)). After methylation of the phenols with dimethyl sulfate, the ester was hydrolyzed to the acid with aqueous potassium hydroxide and dimethyl sulfoxide.
(11) F. M. Hauser and R. P. Rhee, *Synthesis*, 245 (1977).
(12) This preparation of homophthalic acid **5b** is a considerable improvement over alternate methods of preparation.[13-17]
(13) H. L. Slates, S. Weber, and N. L. Wendler, *Chimia*, **21**, 468 (1967).
(14) H. Nogami, *Yakugaku Zasshi*, **61**, 56 (1941).
(15) E. Hardeger, W. Rieder, A. Walser, and F. Kugler, *Helv. Chim. Acta*, **49**, 1283 (1966).
(16) J. Mukherjee, J. N. Chatterjea, and S. C. Sengupta, *Indian J. Chem.*, **13**, 859 (1975).
(17) R. N. Hurd and D. H. Shah, *J. Org. Chem.*, **38**, 610 (1973).
(18) M. Matsui, K. Mori, and S. Arasaki, *Agric. Biol. Chem.*, **28**, 896 (1964).
(19) M. Pailer and O. Vostrowsky, *Monatsh., Chem.*, **102**, 951 (1971).
(20) 1*H*-2-Benzopyran-1-one was converted to ethyl 1-hydroxy-3-methyl-2-naphthoate in quantitative yield using the improved conditions.

Synthesis via Chloroketene Adducts. Synthesis of Demethylsesquicarene[1]

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Sirenin (**1**) and sesquicarene (**2**) are novel sesquiterpenes with a carbon skeleton that can be considered an isoprenoid homologue of 2-carene. These compounds have been the object of numerous synthetic studies[2] since the initial reports of their isolation and structure.[3] The major consideration in devising a synthesis of sirenin (**1**) and sesquicarene (**2**) is the introduction of the proper stereochemistry at C-7 in the bicyclo[4.1.0]heptane skeleton. We have utilized the stereospecific ring contraction of chlorocyclobutanone **4** to ester **5** for the total synthesis of demethylsesquicarene (**3**), an analogue of the natural products.

Cyclobutanone ring contractions related to the conversion of **4** → **5** have been well documented.[4] However, at the time of our research, the only examples of this rearrangement with cyclobutanones fused to a six-membered ring had involved cine substitution prior to the ring contraction.[4c] Chlorocyclobutanone **4**[5] was obtained in 47% yield by cycloaddition of methylchloroketene to 1,3-cyclohexadiene followed by column chromatography to remove the *exo*-methyl isomer formed in 10% yield. Our initial attempts to ring contract cyclobutanone **4** following established procedures for ketone **6** were unsuccessful. The facile rearrangement of chloro alcohol **7**[4] led us to investigate this procedure for ring contraction. Reduction of chloro ketone **6** has been effected readily by a number of reducing agents.[4g,h] Chloro ketone **4** could not be reduced cleanly with lithium aluminum hydride, sodium borohydride, lithium tri-*tert*-butoxyaluminum hydride, or sodium diethylaluminum hydride. However, treatment of **4** with aluminum hydride or diisobutylaluminum hydride produced a single alcohol in modest yield (40–50%). Rearrangement of this alcohol using sodium hydroxide in aqueous methanol[4g,h] or sodium nitrate in ethanol[7] gave a cyclobutanone product rather than the desired aldehyde **8**. This result as well as spectral evidence suggests that reduction of ketone **4** gives the exo alcohol **10** rather than the endo alcohol **9** necessary for ring contraction.

The observation that reduction of ketone **4** with charged nucleophiles was unsuccessful but reduction could be effected with the Lewis acids, aluminum hydride, and diisobutyl aluminum hydride led to attempts to rearrange ketone **4** under nonbasic conditions. We found that chlorocyclobutanone **4** could be converted cleanly to ester **5** by refluxing in methanolic silver nitrate for 24 h.[6] There was no evidence that a second isomer was formed in the reaction. The use of the lanthanide shift reagent Eu(fod)$_3$[7] confirmed the exo nature of the carbomethoxy group. Creary has recently reported[8] that this ring contraction can be effected with lithium hydroxide to give the acid corresponding to **5**.

Ester **5** was reduced with lithium aluminum hydride to form alcohol **11** in 97% yield. Alcohol **11** appeared to be stable and could be stored under nitrogen at 0 °C for several weeks. Treatment with carbon tetrachloride and hexamethylphosphorus triamide in ether resulted in formation of chloride **12**.[9] This compound was quite unstable and underwent decomposition upon silica gel chromatography.[10] It generally was not purified but was used directly in the next reaction. Sodium