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Supplementary Material Available: Experimental data for II, III, **RS7**, **RS8**, **S11**, and **21** and NMR spectra for **RRR5**, **RSS5**, **SS6**, **RR6**, **S11**, racemic 11, **SS17**, and **RR17** (11 pages). Ordering information is given on any current masthead page.

A Novel Strategy for the Stereoselective Total Synthesis of C-17 Spiro Steroids. Total Synthesis of 19-Norcanrenone, a Formal Total Synthesis of 19-Norspironolactone

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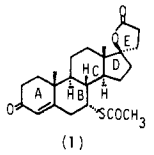
Abstract: The intramolecular (4 + 2) cycloaddition reactions of olefinic *o*-quinodimethanes, generated in situ by the thermolysis of olefinic benzocyclobutenes, lead stereoselectively to A-nor B-aromatic C-17 spiro steroids. This is a new and general methodology for the stereoselective synthesis of biologically important C-17 spiro steroids. This method yields the total synthesis of 19-norcanrenone, constituting a formal total synthesis of 19-norspironolactone.

Herein, we provide full details for the highly efficient stereocontrolled approach to steroids that have an unsymmetrically substituted spiro ring at C-17 position via intramolecular (4 + 2) cycloaddition reaction as a key stereodirecting process. This leads to a total synthesis of 19-norcanrenone.

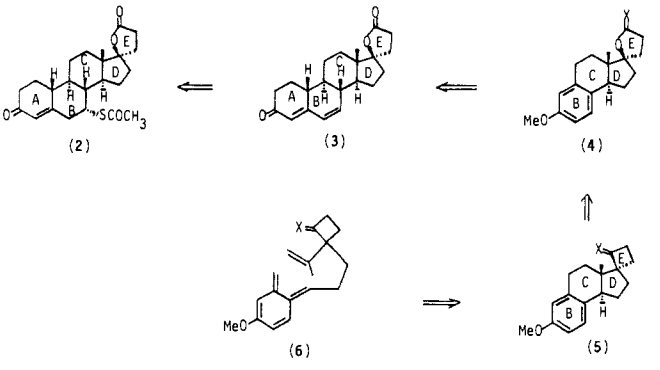
Since the first reports[1] on the synthesis and the antialdosterone activity of the steroidal spironolactone in the late 1950s, numerous efforts have been devoted[2] to the study of structurally diverse steroids, mainly because of the clinical importance of this type of steroids for the treatment of primary hyperaldosteronism, diseases related to secondary hyperaldosteronism (edema), and hypertension. Correlations of biological activity with variations in the structure of the spiro ring have indicated that the oxygen atom should be β oriented[2a] and that substituent rings with more than five members display decreased activity.[2c,e] Of these reported, spironolactone (**1**) has emerged as the most effective representative that is capable of eliciting this type of biological response and that has been to date the only orally active aldosterone antagonist on the market since its discovery.



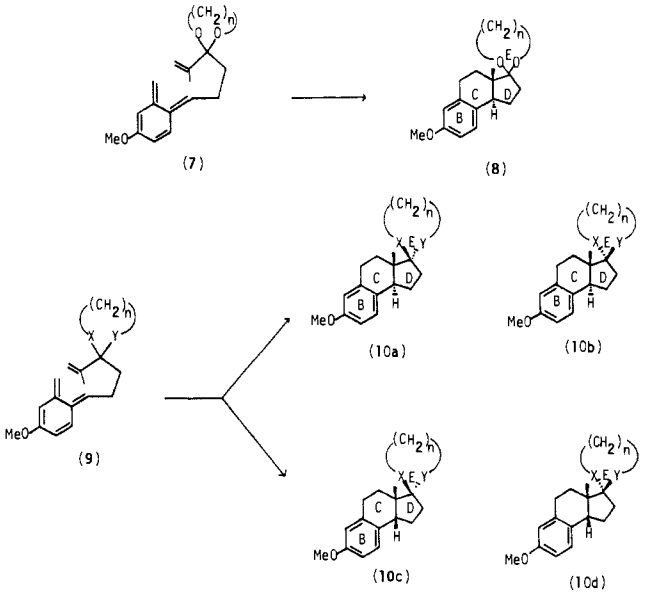
(1)

These facts and the distinctive structural feature—spirolactone group at C-17 and thioacetyl group at C-7 positions—have stimulated us to explore an effective methodology for the synthesis of 19-norspironolactone (**2**), which is more difficult to prepare and is expected to be more effective than its normal analogue **1**.[2m] Our synthetic strategy for this unique steroid **2** is characterized by the one-step creation of B, C, D, and E rings (**5**) in a stereoselective manner (Scheme I). Namely, stereoselective introduction of three successive chiral centers, C_{13}, C_{14}, and C_{17} (steroid numbering), is achieved by using an intramolecular (4 + 2) cycloaddition reaction of the olefinic *o*-quinodimethane **6** as the key step and then the E-ring transformation (**5** → **4**) and functionalization at C-7 position, followed by A-ring formation (**4** → **3**). Conceptually this strategy contrasts to the traditional methods[2]

Scheme I



Scheme II



[†] Tohoku University.
[‡] Hoshi University.

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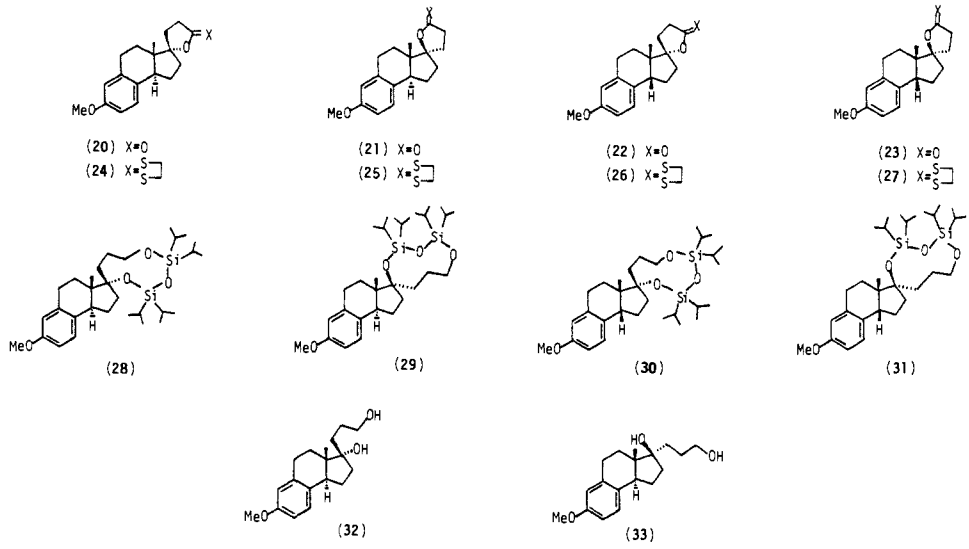
Chart I



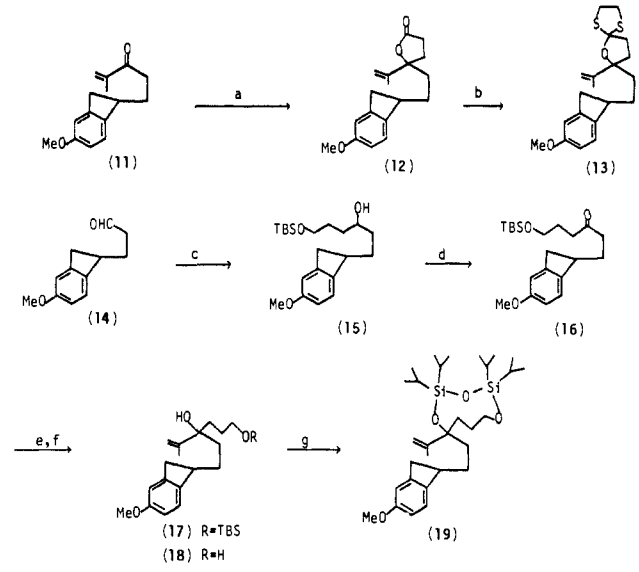
in which the spirolactone ring is created by the manipulation on the preformed C-17 keto steroids.

Results and Discussion[3]

Intramolecular (4 + 2) Cycloaddition Reaction of Olefinic *o*-Quinodimethanes. We learned in a preceding study[4] that A-nor B-aromatic steroid **8**, having symmetrical spiro ring E at the C-17 position with trans-C,D ring juncture, could be formed in a highly stereoselective manner by an intramolecular (4 + 2) cycloaddition reaction of olefinic *o*-quinodimethane **7**, which had no chiral center (Scheme II). However, information about the stereochemical course of such a reaction of an olefinic *o*-quinodimethane **9**, which has a tertiary-substituted chiral center and leads to four possible A-nor B-aromatic steroids (**10a–d**), is not yet available. Therefore, we sought first to demonstrate the effect of the substituents (X, Y) on the cycloaddition reaction of **9**.

As a preliminary investigation, the thermolysis of three different types of compound, the olefinic γ-lactone **12**, its thioacetal **13**, and nine-membered disiloxane **19**, was carried out. All of these have ring E or rings readily convertible to ring E corresponding to the ring E of the compound **2**. The syntheses of these benzocyclobutenes, **12**, **13**, and **19**, were straightforward (Scheme III). The reaction of the enone **11**[4] with allyl tetramethylphosphorodiamidate[5] in the presence of *n*-butyllithium followed by acid treatment gave directly the olefinic lactone **12** in 38% yield. The conversion of this lactone **12** into the lactonic thioacetal **13** was achieved in 82% yield by the treatment with bis(dimethylaluminum) 1,2-ethanedithiolate.[6] Grignard reaction of the aldehyde **14**[7] with [1-[*tert*-butyldimethylsilyl)oxy]-3-propyl]magnesium bromide afforded in 49% yield the alcohol **15**, which was oxidized with pyridinium chlorochromate (PCC) to give the ketone **16** in 79% yield. Barbier reaction of **16** with 2-bromopropene in the presence of lithium afforded the isopropenyl alcohol **17** in 61% yield. The diol **18**, obtained in 97% yield by the deprotection of the *tert*-butyldimethylsilyl ether **17** with tetra-*n*-butylammonium fluoride, was treated with 1,3-dichloro-1,1,3,3-tetraisopropyl-

Scheme III[a]



[a] Steps: (a) $CH_2{=}CHCH_2OP(O)(NMe_2)_2$, *n*-BuLi, THF, −50 °C → −20 °C, then **9**, reflux, 3.5 h; concentration HCl, MeOH, 40 °C, 2 h; (b) $Me_2AlS(CH_2)_2SAlMe_2$, CH_2Cl_2, −40 °C → room temperature, 1 h; (c) $TBSO(CH_2)_3MgBr$, THF, room temperature, 15 min; (d) PCC, CH_2Cl_2, room temperature, 5 h; (e) $CH_2{=}C(CH_3)Br$, Li, ultrasound, Et_2O, room temperature, 10 min; (f) n-$Bu_4{}^+NF^-$, THF, room temperature, 15 min; (g) $(i\text{-}Pr_2SiCl)_2O$, DMAP, imidazole, DMF, room temperature, 1 h.

Table I[a]

entry	substrate	time, h	product ratio[b]
1	**12**	11	**20**:**21** (94:6)
2	**13**	1.5	**24**:**25** (93:7)
3	**19**	5	**28**:**29** (96:4)

[a] All reactions were run under an inert atmosphere (argon) in boiling *o*-dichlorobenzene. [b] Determined by ^1H NMR analysis of the sample obtained from the thermolysis for entry 1, the hydrolysis of the initial products **24** and **25** for entry 2, and the deprotection of the initial products **28** and **29**, followed by oxidation of the resulting diols **32** and **33** for entry 3.

(1) (a) Cella, J. A.; Kagawa, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 4808. (b) Cella, J. A.; Tweit, R. C. *J. Org. Chem.* **1959**, *24*, 1109. (c) Kagawa, C. M. *Endocrinology* **1960**, *67*, 125.

(2) (a) Kagawa, C. M.; Celloa, J. A.; Van Arman, C. G. *Science (Washington, D.C.)* **1957**, *126*, 1015. (b) De Stevens, G. *Diuretic Chemistry and Pharmacology*; Academic: New York **1963**, Chapter 7. (c) Arth, G. E.; Schwam, H.; Sarett, L. H.; Glitzer, M. *J. Med. Chem.* **1963**, *6*, 617. (d) Nickisch, K.; Bittler, D.; Casals-Stenzel, J.; Laurent, H.; Nickolson, R.; Nishino, Y.; Petzoldt, K.; Wiechert, R. *Ibid.* **1985**, *28*, 546. (e) Tweit, R. C.; Brown, E. A.; Kraychy, S.; Mizuba, S.; Muir, R. D.; Nicholson, R. T. *Chem. Pharm. Bull.* **1964**, *12*, 859. (f) Bertin, D.; Perronnet, J. *Bull. Soc. Chim. Fr.* **1964**, 564. (g) Johns, W. F.; Brown, E. A. *J. Org. Chem.* **1966**, *31*, 2099. (h) Krapcho, A. P. *Synthesis* **1978**, 77. (i) Cain, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 883. (j) Ehlinger, E.; Magnus, P. *Ibid.* **1980**, *21*, 11. (k) Wieland, P. *Helv. Chim. Acta* **1979**, *62*, 2276. (l) Johnson, W. S.; Dumas, D. J.; Berner, D. *J. Am. Chem. Soc.* **1982**, *104*, 3510. (m) Cella, J. A.; Brown, E. A.; Burtner, R. R. *J. Org. Chem.* **1959**, *24*, 743.

(3) All the compounds in the synthetic sequence are racemic. To clarify the stereochemical presentation, only one enantiomer is depicted.

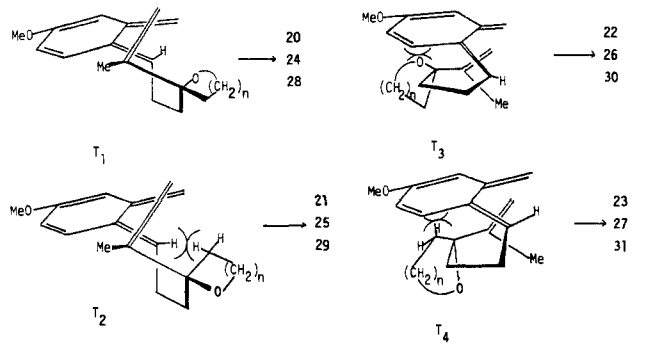
(4) Nemoto, H.; Nagai, M.; Moizumi, M.; Fukumoto, K.; Kametani, T., submitted for publication in *J. Org. Chem.*

(5) Sturtz, G.; Yaouanc, J.-J.; Krausz, F.; Labeeuw, B. *Synthesis* **1980**, 289.

(6) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5869.

(7) Nemoto, H.; Nagai, M.; Abe. Y.; Moizumi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc. Perkin Trans. I* **1987**, 1727.

Chart II



disiloxane to furnish the nine-membered cyclic disiloxane **19** in 82% yield.

The thermal reactions of these olefinic benzocyclobutenes, **12**, **13**, and **19**, were conducted in boiling *o*-dichlorobenzene. The results, which are summarized in Table I, show that all of these reactions proceeded with high stereoselectivity, leading to the preferred formation of trans-anti[8] isomers **20**, **24**, and **28** rather than the trans-syn isomers **21**, **25**, and **29** (Chart I). None of the cis-anti isomers **22**, **26**, and **30**, and cis-syn isomers **23**, **27**, and **31** were detected. The initial and tentative stereochemical assignments of each of the isomers were based on spectroscopic properties,[9] and the unambiguous confirmation of the assignments was derived from a comparison with an authentic sample, which was prepared alternatively.[11]

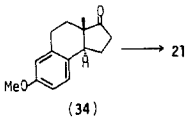
From these results, it seemed possible that the high stereoselectivity for trans-anti isomers **20**, **24**, and **28** might reflect the severe steric interactions present in the endo transition states T_3 and T_4 and the exo transition state T_2 relative to the exo transition state T_1 (Chart II). We expected the trans selectivity in this type of cycloaddition reaction on the basis of the previous study.[4] However, the high anti selectivities, which might be a function of the substitution pattern at positions 1 and 4[12] for **12** and **13** and positions 1 and 8 for **19**, could not have been estimated. The fact that the substituent at position 2 (**12** and **13**) and the ring size (**19**) did not affect the stereochemical course of this reaction should also be noted.

(8) For convenience, the trans-anti, trans-syn, cis-anti, and cis-syn representations of stereoisomers refer to the CD ring juncture and the relative arrangements of the angular methyl and oxygen at spiro position, respectively.

(9) These isomer (**20** and **21**) ratios were determined by ^{1}H NMR integration of the angular methyl signals in the product. In the A-nor B-aromatic steroids,[4] signals of CD trans isomers were observed at much higher field, because of the shielding effect of the aromatic ring in its preferred boatlike conformation,[10] than that of CD cis isomers. Of these trans and cis isomers, this signals of syn isomers should be observed at lower field than that of anti isomers, because of the deshielding effect of oxygen, respectively. Thus, the angular methyl groups of **20** and **21** were observed at 0.61 and 0.88 ppm, respectively. This was also confirmed by the lower field resonance (3.21 ppm) for C_{14} (steroid numbering) hydrogen of **20** than that of **21** attributable to the deshielding effect of C_{17} oxygen in its 500-MHz NMR spectrum. This was very diagnostic and was used for the products' analysis in the thermal reactions. The same kind of argument was found to be the case for cis analogues **22** and **23**.

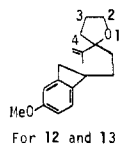
(10) Nemoto, H.; Nagai, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1985**, *50*, 2764.

(11) The trans ketone **34**[4] was treated successively with allyl tetramethylphosphorodiamidate[5] in the presence of *n*-butyllithium and acid to give the trans-syn lactone **21** in 76% yield.

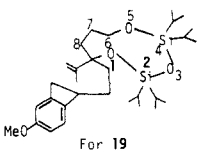


(34)

(12) The numberings cited here are as follows.



For 12 and 13



For 19

Scheme IV

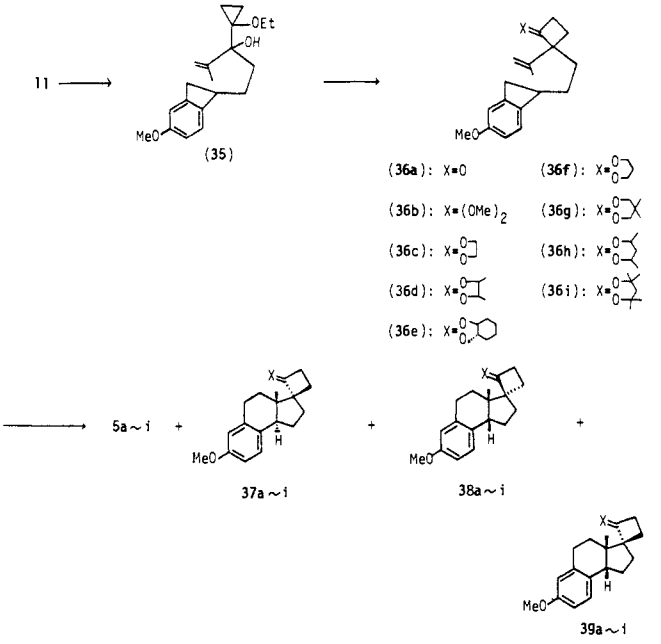


Table II[a]

entry	substrate	product ratio[b] **5a:37a:38a**	isolated yield,[c] %
1	**36a**	28:60:12	97
2	**36b**	88:3:9	56
3	**36c**	60:21:19	73
4	**36d**	59:22:19	97
5	**36e**	59:23:18	97
6	**36f**	65:15:20	82
7	**36g**	62:13:25	75
8	**36h**	66:15:19	99
9	**36i**	61:20:19	90

[a] All reactions were run under an inert atmosphere (argon) in boiling *o*-dichlorobenzene for 9 h as described in the Experimental Section. [b] Determined by ^{1}H NMR analysis.[16] [c] All yields are based on purified product by passing through a short column (SiO_2). For entries 2–9, the initial products are hydrolyzed and then purified.

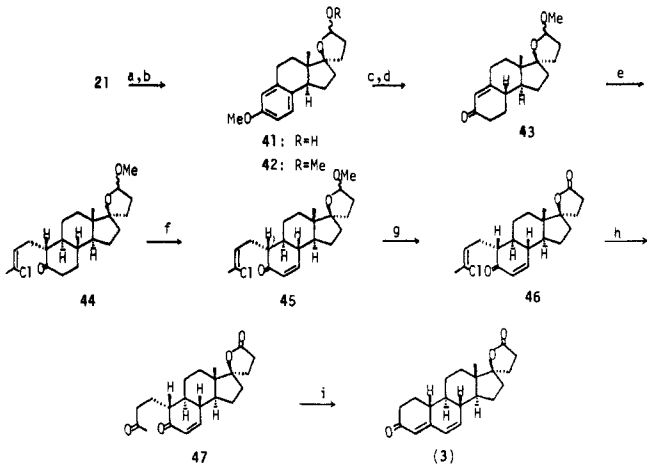
Thus, we obtained information about the stereochemical course of the cycloaddition reactions of olefinic *o*-quinodimethanes that have tertiary-substituted chiral centers, which lead to unsymmetrically substituted spiro compounds, although the observed trans-anti selectivity leading to **20**, **24**, and **28** was not what we had expected to achieve preliminary to the synthesis of spironolactones. In these cycloaddition reactions, the syn or anti selectivity is strictly controlled by the bulk of position 1 or 4 (for **12** and **13**) and position 1 or 8 (for **19**) and not affected by the bulk at position 2 to a detectable degree, despite large steric bulk (1,2-dithiane ring for **13** and diisopropylsilyl group for **19**).

On the basis of the above-described outcome, our efforts were then directed toward the studies for the cycloaddition reaction of the olefinic *o*-quinodimethanes **6**, which have a cyclobutane ring with various substituents (X), because it was expected that the bond having a bulky substituent (X) on the cyclobutane ring in the product **5** was syn. Thus, the cyclobutanone acetals were suitable candidates for this steric demand. Furthermore, the functional group is versatile for further synthetic transformations, which lead to spironolactones.

The preparation of the requisite benzocyclobutenes **36**, sources of *o*-quinodimethanes **6**, was straightforward (Scheme IV). Reaction of the enone **11**[4] with (1-ethoxycyclopropyl)lithium, generated by metalation of 1-ethoxycyclopropyl bromide[13] with *tert*-butyllithium afforded quantitatively the cyclopropyl alcohol **35**, which was then subjected to acid (42% HBF_4) catalyzed

(13) Gadwood, R. C. *Tetrahedron Lett.* **1984**, *25*, 5851.

Scheme V[a]



[a] Steps: (a) Dibal, toluene–THF, −78 °C, 1 h; (b) BF_3·Et_2O, MeOH, THF, room temperature, 27 h; (c) Li, liquid NH_3, EtOH, THF, −78 °C, 1 h; (d) 10% HCl, MeOH, room temperature, 3 h; (e) Li, liquid NH_3, THF, −78 °C → −20 °C, 1 h; $BrCH_2CH{=}CCH_3Cl$, THF, −20 °C, 2 h; (f) TMSCl, LDA, THF, −78 °C, 1 h; $Pd(OAc)_2$, DDQ, CH_3CN, room temperature, 36 h; (g) Jones reagents, acetone, 0 °C, 40 min; (h) $Hg(OCOCF_3)_2$, CH_2Cl_2, room temperature, 1 h; (i) concentrated HCl, AcOH, H_2O, room temperature, 90 h.

rearrangement to produce the cyclobutanone **36a** in quantitative yield. A standard acetalization [camphorsulfonic acid (CSA), $HC(OMe)_3$, MeOH, for **36b**] followed by transacetalization of **36b** with the diols gave quantitatively the corresponding acetals **36c–i**.[14] Thermolyses of these cyclobutanone derivatives **36a–i** were conducted in refluxing *o*-dichlorobenzene. Table II summarizes the distribution[16] of the products for each substrate.

The observed trans-anti[17] (for entry 1) and trans-syn (for entry 2–9) selectivities could be again most conveniently rationalized by invoking the same explanation of the stereoselectivity in the thermolytic reaction of **12**, **13**, and **19** (vide supra), although the selectivity was somewhat decreased with the decrease of ring size from five- and nine-membered rings to a four-membered ring in this case. In the most predominant isomers, the bulky substituents at the spiro position (methylene rather than ketone for entry 1 and acetals rather than methylenes for entry 2–9) were located in a syn mode in their preferred trans isomers.

The straightforward synthesis of 19-norcanrenone (**3**) illustrates of the power of the methodology that constitutes a formal synthesis of 19-norspironolactone (**2**).

Total Synthesis of 19-Norcanrenone (3). The tetracyclic cyclobutanone **5a** was prepared in a stereoselective manner by the thermolysis of the olefinic cyclobutanone acetals (the best yield for trans-syn isomer was obtained in entry 8) followed by acid treatment. This cyclobutanone was subjected to the Baeyer–Villiger oxidation as described previously to give the lactone **21**. The lactone **21** thus obtained was reduced in 92% yield with diisobutylaluminum hydride (Dibal) to give the lactol **41**, which was converted in 99% yield into the acetal **42** by treating with boron trifluoride etherate in methanol (Scheme V). Birch reduction of **42** followed by acid treatment afforded in 71% yield the enone **43**. Enone **43** was reductively alkylated by lithium in liquid ammonia–THF followed by trapping the in situ generated anion with Wichtere's reagent to give in 73% yield the alkylated ketone **44**. This ketone was then subjected to Saegusa's[18] dehydrogenation procedures to give the enone **45** in 69% yield. The lactonic vinyl chloride **46**, prepared in 84% yield by Jones oxidation of **45**, was hydrolyzed in the presence of mercuric trifluoroacetate to afford the diketone **47** in 98% yield. Acid treatment of **47** furnished in 54% yield the pentacyclic dienone, 19-norcanrenone (**3**), which was identical with an authentic sample[21] in its H^1 NMR (500 MHz, $CDCl_3$) and IR ($CHCl_3$) spectral comparisons. Since (±)-19-norcanrenone (**3**) has been converted[21] into *dl*-19-norspironolactone (**2**), this work constitutes a formal total synthesis of (±)-19-norspironolactone (**2**).

A novel and efficient methodology for the stereoselective synthesis of A-nor B-aromatic C-17 spiro steroids, which leads to a formal total synthesis of 19-norspironolactone (**2**), has been achieved.

Experimental Section

General Procedures. All reactions were carried out under dry nitrogen unless indicated. Column chromatography was carried out with silica gel (Wako gel C-200). All new compounds described in this Experimental Section were homogeneous on TLC. The phrase "residue upon workup" refers to the residue obtained when the organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure.

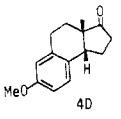
2-Isopropenyl-2-[2-(4-methoxybenzocyclobutenyl)ethyl]-5-oxotetrahydrofuran (12). To a stirred solution of allyl tetramethylphosphorodiamidate[5] (154 mg, 0.8 mmol) in 0.5 mL of THF was added dropwise *n*-butyllithium (1.39 M solution in *n*-hexane, 1.5 mL, 2.1 mmol) at −50 °C. After stirring had been continued for 1 h at −20 °C, a solution of the enone **11**[4] (92 mg, 0.4 mmol) in 1 mL of THF was added at the same temperature, and then the reaction mixture was refluxed for 3.5 h. The residue upon evaporation of the solvent was dissolved in 1.2 mL of methanol, adjusted to pH 1 by adding concentrated hydrochloric acid, and stirred for 2 h at 40 °C. Evaporation of the solvent left the residue, which was dissolved in 10 mL of ether. The organic layer was washed with saturated aqueous NH_4Cl and NaCl solution and dried ($MgSO_4$). The residue upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (33:1 v/v) to give the lactone **12** (44 mg, 38%) as a colorless oil: IR ($CHCl_3$) 1765 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.27 (3 H, br s, $CH_2{=}CCH_3$), 3.83 (3 H, s, OCH_3), 4.88, 5.02 (2 H, each br s, $CH_2{=}CCH_3$), 6.50–6.97 (3 H, m, Ar H); mass spectrum, *m/z* 286 (M^+). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.53; H, 7.69.

5,5-(Ethylenedithio)-2-isopropenyl-2-[2-(4-methoxybenzocyclobutenyl)ethyl]tetrahydrofuran (13). A solution of the lactone **12** (66 mg, 0.23 mmol) in 3 mL of methylene chloride was added to a solution of bis(dimethylaluminum) 1,2-ethanedithiolate[6] [prepared from trimethylaluminum (1.0 M *n*-hexane solution, 0.51 mL, 0.51 mmol) and 1,2-ethanedithiol (0.02 mL, 0.25 mmol)] in 1 mL of methylene chloride

(14) Since the yield for the acetal **36i** by following the general procedure as for the acetals **36c–h** was not satisfactory, the Noyori procedure[15] was applied for this transformation.

(15) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(16) These isomers' (**5a**, **37a**, and **38a**) ratio was determined by ^1H NMR integration of the angular methyl signals. Because of the same reasons for the chemical shifts differences of the angular methyl signals in the H^1 NMR spectrum of the isomers **20** and **21** as noted previously (see note 9), the signals [^1H NMR (500 MHz)] appearing at 0.77, 0.68, and 0.96 ppm could be assigned to the angular methyl group of the isomers **5a**, **37a**, and **38a**, respectively. This was also supported by the presence of the low field signals [^1H NMR (500 MHz)] (3.13 and 3.05 ppm) attributable for the C_{14} (steroid numbering) hydrogens of **37a** and **38a**, respectively (cis to the carbonyl group of cyclobutanone ring), and the absence of such low field signal for **5a** (trans to the carbonyl group of cyclobutanone ring). Unambiguous structure determination of these isomers has been made as follows. Analytically pure samples of **5a**, **37a**, and **38a** were subjected to Baeyer–Villiger oxidation (*t*-BuOOH, 10% NaOH) to give the corresponding lactones **21**, **20**, and **23**, respectively. The lactones **20** and **21** were identified with authentic samples obtained previously by the thermolysis of **12**. In the ^1H NMR (500 MHz) spectrum of **23**, the angular methyl group resonated at the lowest field (0.98 ppm) of the other isomers (**20** and **21**), and the signal due to C_{14} (steroid numbering) hydrogen was observed at low field (3.13 ppm), suggesting the relative stereochemistry to be cis-syn (see note 8). The ring junction to be cis was confirmed by the definite NOE enhancement (9.1%) observed for C_{14} hydrogen upon irradiation of the angular methyl group. The relative stereochemistry at spiro position of **23** was also supported by the comparison of the angular methyl group and C_{14} hydrogen with that of cis-anti isomer **22**, which was prepared by the direct lactonization of the known ketone **40**[4] by following the same procedure as for the transformation of **34** to **21**.



(17) The trans-anti, trans-syn, cis-anti, and cis-syn representations of stereoisomers refer to the C,D ring junction and the relative arrangements of the angular methyl and ketone or acetal containing bonds at spiro position, respectively.

(18) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

at −40 °C, and then stirring was continued for 1 h at room temperature. The residue upon evaporation of the solvent was dissolved in 5 mL of ether, treated with moist Na_2SO_4, and then dried (Na_2SO_4). The crude product upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (9:1 v/v) to give the dithiolane ortho lactone **13** (68 mg, 82%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.73 (3 H, br s, CH_2=CCH_3), 3.38, 3.45 (3 H, m, SCH_2CH_2S), 3.76 (3 H, s, OCH_3), 4.91, 5.00 (2 H, each br s, CH_2=CCH_3), 6.68–7.04 (3 H, m, Ar H); mass spectrum, *m/z* 362 (M^+); exact mass calcd for $C_{20}H_{26}O_2S_2$ 362.1373 (M^+), found 362.1356.

6-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-1-(4-methoxybenzocyclobutenyl)hexane (15). To a stirred solution of the aldehyde **14**[7] (278.5 mg, 1.47 mmol) in 6 mL of THF was added a solution of [1-[(*tert*-butyldimethylsilyl)oxy]-3-propyl]magnesium bromide [prepared from [1-[(*tert*-butyldimethylsilyl)oxy]-3-propyl] bromide (456 mg, 1.8 mmol) and magnesium (52.8 mg, 2.2 mmol)] in 5 mL of THF at room temperature. After stirring was continued for 15 min at the same temperature, the reaction mixture was treated with 20 mL of saturated aqueous NH_4Cl solution and extracted with ether (50 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried (Na_2SO_4). The residue upon workup was chromatographed on silica gel (10 g) with *n*-hexane–ethyl acetate (93:7 v/v) to give the alcohol **15** (260 mg, 49%) as a colorless oil: IR ($CHCl_3$) 3400 (OH) cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ 0.07 [6 H, s, $Si(CH_3)_2$], 0.90 [9 H, s, $SiC(CH_3)_3$], 3.68 (3 H, s, OCH_3), 6.50–6.90 (3 H, m, Ar H); mass spectrum, *m/z* 364 (M^+). Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95. Found: C, 68.78; H, 9.90.

6-[(*tert*-Butyldimethylsilyl)oxy]-3-oxo-1-(4-methoxybenzocyclobutenyl)hexane (16). A solution of the alcohol **15** (260 mg, 0.7 mmol) in 2 mL of methylene chloride was added with stirring to a mixture of pyridinium chlorochromate (230 mg, 1.07 mmol), Florisil (230 mg), and 8 mL of methylene chloride at room temperature, and stirring was continued for 5 h at the same temperature. To this end, the reaction mixture was diluted with 50 mL of methylene chloride and filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ and NaCl solutions and dried ($MgSO_4$). The residue upon workup was chromatographed on silica gel (10 g) with *n*-hexane–ethyl acetate (19:1 v/v) to give the ketone **16** (204.4 mg, 79%) as a colorless oil: IR ($CHCl_3$) 1705 (C=O) cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ 0.07 [6 H, s, $Si(CH_3)_2$], 0.93 [9 H, s, $SiC(CH_3)_3$], 3.76 (3 H, s, OCH_3), 6.53–6.97 (3 H, m, Ar H); mass spectrum, *m/z* 362 (M^+). Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.57; H, 9.45. Found: C, 69.37; H, 9.85.

1-[3-[(*tert*-Butyldimethylsilyl)oxy]propyl]-1-isopropenyl-3-(4-methoxybenzocyclobutenyl)propanol (17). A mixture of the ketone **16** (204 mg, 0.564 mmol), isopropenyl bromide (0.06 mL, 0.677 mmol), lithium (18.7 mg, 2.7 mmol), and 6 mL of ether was irradiated in an ultrasound cleaner for 10 min at room temperature. The reaction mixture was then treated with saturated aqueous NH_4Cl solution and extracted with ether (20 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). The residue upon workup was chromatographed on silica gel (5 g) with *n*-hexane–ethyl acetate (1:24 v/v) to give the alcohol **17** (140 mg, 61%) as a colorless oil: IR ($CHCl_3$) 3375 (OH) cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ 0.07 [6 H, s, $Si(CH_3)_2$], 0.93 [9 H, s, $SiC(CH_3)_3$], 1.67 (3 H, br s, CH_2=CCH_3), 3.70 (3 H, s, OCH_3), 4.82, 4.97 (2 H, each br s, CH_2=CCH_3), 6.50–6.97 (3 H, m, Ar H); mass spectrum, *m/z* 404 (M^+). Anal. Calcd for $C_{24}H_{40}O_3Si$: C, 71.24; H, 9.96. Found: C, 71.18; H, 10.10.

1-(3-Hydroxypropyl)-1-isopropenyl-3-(4-methoxybenzocyclobutenyl)propanol (18). To a stirred solution of the *tert*-butyldimethylsilyl ether **17** (140 mg, 0.344 mmol) in 2 mL of THF was added tetra-*n*-butylammonium fluoride (1.0 M THF solution, 0.52 mL, 0:52 mmol) at room temperature. The mixture was then diluted with 10 mL of water and extracted with methylene chloride (20 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). The residue upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (7:3 v/v) to give the diol **18** (99 mg, 99%) as a colorless oil: IR ($CHCl_3$) 3375 (OH) cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.63 (3 H, br s, CH_2=CCH_3), 3.71 (3 H, s, OCH_3), 4.84, 4.97 (2 H, each br s, CH_2=CCH_3), 6.53–6.95 (3 H, m, Ar H); mass spectrum, *m/z* 290 (M^+). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.08; H, 9.08.

1-Isopropenyl-1-[2-(4-methoxybenzocyclobutenyl)ethyl]-3,3,5,5-tetraisopropyl-3,5-disila-2,4,6-trioxacyclononane (19). To a stirred solution of the diol **18** (48 mg, 0.164 mmol), imidazole (47.7 mg, 0.164 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in 3 mL of dimethylformamide was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.057 mL, 0.180 mmol) at room temperature. After stirring had been continued for 1 h at the same temperature, the reaction mixture was diluted with 6 mL of water and extracted with ether (6 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried (Na_2SO_4). The residue upon workup was chromatographed on silica gel (2.0 g) with *n*-hexane–ethyl acetate (3:17 v/v) to give the siloxane **19** (71 mg, 82%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.04 [24 H, br s, 4 $CH(CH_3)_2$], 3.78 (3 H, s, OCH_3), 4.90, 5.02 (2 H, each br s), 6.69–7.06 (3 H, m, Ar H); exact mass calcd for $C_{30}H_{52}O_4Si_2$ 532.3401 (M^+), found 532.3429.

Thermolysis of the Olefinic Lactone 12. A solution of the lactone **12** (144 mg, 0.5 mmol) in 15 mL of *o*-dichlorobenzene was heated at 180 °C for 11 h. Removal of the solvent gave the crude product, which was subjected to flash chromatography on silica gel (1 g) with *n*-hexane–ethyl acetate (1:99 v/v) to afford the cyclized product (97 mg, 85%) as a colorless oil. Analysis of this product by ^{1}H NMR indicated a 94:6 mixture of **20**/**21**. This mixture was separated by careful column chromatography on silica gel with *n*-hexane–ethyl acetate (25:1 v/v) to give the analytically pure samples of **20** and **21**, respectively.

***trans*-4,5-(4-Methoxybenzo)-7aβ-methylhydrindan-1-spiro-2′-(1′β-5′-oxotetrahydrofuran) (20):** colorless needles; mp 126–127 °C (ether); IR ($CHCl_3$) 1770 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.61 (3 H, s), 1.53–1.56 (1 H, m), 1.65–1.72 (1 H, m), 1.98–2.11 (2 H, m), 2.15–2.36 (4 H, m), 2.53–2.66 (2 H, m), 2.85–3.00 (2 H, m), 3.21 (1 H, dd, J = 6.4 and 12.5 Hz), 3.79 (3 H, s), 6.70 (1 H, s), 6.72 (1 H, d, J = 8.8 Hz), 6.95 (1 H, d, J = 8.8 Hz); mass spectrum, *m/z* 286 (M^+). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.35; H, 7.68.

***trans*-4,5-(4-Methoxybenzo)-7aβ-methylhydrindan-1-spiro-2′-(1′α-5′-oxotetrahydrofuran) (21):** colorless needles; mp 117–118 °C (ether); IR ($CHCl_3$) 1760 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3 H, s), 1.73–1.83 (3 H, m), 1.98–2.08 (2 H, m), 2.14–2.21 (1 H, m), 2.41–2.48 (2 H, m), 2.53–2.67 (2 H, m), 2.79 (1 H, dd, J = 7.1 and 11.4 Hz), 2.94 (2 H, dd, J = 5.7 and 8.5 Hz), 3.79 (3 H, s), 6.70 (1 H, s), 6.72 (1 H, d, J = 8.8 Hz), 6.95 (1 H, d, J = 8.8 Hz); mass spectrum, *m/z* 286 (M^+).

Thermolysis of the Dithiolane Ortho Lactone 13 and the Products' Analysis. A mixture of the crude products (**24** and **25**), which were obtained by the thermolysis of the dithiolane ortho lactone **13** (54.4 mg, 0.15 mmol) by following the same procedure for the olefinic lactone **12** under the conditions described in Table I, mercuric chloride (30.5 mg, 0.116 mmol), calcium carbonate (13.3 mg, 0.133 mmol), 1.4 mL of acetonitrile, and 0.3 mL of water was stirred for 15 min at room temperature. The residue upon evaporation of acetonitrile was extracted with chloroform (5 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). Evaporation of the solvent afforded the residue, which was subjected to flash chromatography on silica gel (500 mg) with *n*-hexane–ethyl acetate (1:99 v/v) to give a mixture of **20** and **21** (13.2 mg, 30% overall yield from **13**).

Thermolysis of the Siloxane 19 and the Products' Analysis. A solution of the crude products (a mixture of **28** and **29**), which were obtained by the thermolysis of the siloxane **19** (31 mg, 0.058 mmol) by following the same procedure for **12** under the conditions described in Table I, and tetra-*n*-butylammonium fluoride (1.0 M THF solution, 0.1 mL, 0.1 mmol) in 1 mL of THF was stirred for 10 min at room temperature. The residue upon evaporation of the solvent was dissolved in 5 mL of chloroform, washed with saturated aqueous NaCl solution, and dried ($MgSO_4$). To a solution of the crude product, which was obtained by the evaporation of the solvent, in 3 mL of acetone was added Jones reagent (0.06 mL, 0.085 mmol) at 0 °C. After stirring had been continued for 20 min at the same temperature, the reaction mixture was treated with 0.3 mL of 2-propanol and concentrated to give the residue, which was diluted with 1 mL of water and extracted with chloroform (5 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). The residue upon workup was subjected to flash chromatography on silica gel (1 g) with *n*-hexane–ethyl acetate (1:99 v/v) to give a mixture of **20** and **21** (12 mg, 70%).

Alternative Synthesis of 21 via the Lactonization of the Trans Ketone (34). To a stirred solution of allyl tetramethylphosphorodiamidate[5] (84.5 mg, 0.44 mmol) in 1 mL of THF was added dropwise *n*-butyllithium (1.54 M solution in *n*-hexane, 0.57 mL, 0.88 mmol) at −50 °C. After stirring had been continued for 1 h at −20 °C, a solution of the ketone **34**[4] (24.3 mg, 0.11 mmol) in 1 mL of THF was added at the same temperature, and then the reaction mixture was refluxed for 3.5 h. The residue obtained upon evaporation of the solvent was dissolved in 3 mL of methanol, adjusted to pH 1 by adding concentrated hydrochloric acid, and stirred for 2 h at 40 °C. Evaporation of the solvent left the residue, which was dissolved in 50 mL of ether. The organic layer was washed with saturated aqueous NH_4Cl and NaCl solutions and dried ($MgSO_4$). The crude product obtained upon evaporation of the solvent was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (3:17 v/v) to afford the lactone **21** (23 mg, 76%, as colorless needles), mp 117–118 °C (ether), which was identical with the sample obtained by the thermolysis of the olefinic lactone **12** in its IR ($CHCl_3$) and NMR ($CDCl_3$) spectral comparison and also mixed melting point test.

1-(1-Ethoxycyclopropyl)-1-isopropenyl-3-(4-methoxybenzocyclobutenyl)propanol (35). To a stirred solution of *tert*-butyllithium (1.7 M solution in *n*-hexane, 26 mL, 44 mmol) in 70 mL of ether was added 1-bromo-1-ethoxycyclopropane[13] (2.89 mL, 23.4 mmol) at −78 °C. After stirring had been continued for 5 min at the same temperature, a solution of the enone **11** (3.37 g, 14.7 mmol) in a mixture of 25 mL of ether and 10 mL of THF was added, and stirring was continued for 10 min at the same temperature. The reaction mixture was stirred for 10 min at 0 °C, quenched with 30 mL of saturated aqueous NH_4Cl solution, and extracted with ether (50 mL × 3). The residue upon workup was chromatographed on silica gel (80 g) with *n*-hexane–ethyl acetate (24:1 v/v) to give the alcohol **35** (4.65 g, 100%) as a colorless oil: IR ($CHCl_3$) 3550 (OH) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.81–0.92 (4 H, m, c-C_3H_5), 1.05 (3 H, t, J = 7.5 Hz, OCH_2CH_3), 1.57 (3 H, br s, CH_2=CCH_3), 3.53 (2 H, q, J = 7.5 Hz, OCH_2CH_3), 3.75 (3 H, s, OCH_3), 4.94, 5.11 (2 H, each br s, C=CH_2), 6.05–6.99 (3 H, m, Ar H); mass spectrum, m/z 316 (M^+). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.82; H, 9.15.

2-Isopropenyl-2-[2-(4-methoxybenzocyclobutenyl)ethyl]cyclobutanone (36a). After a solution of the alcohol **35** (1.02 g, 3.22 mmol) and 2 mL of 42% aqueous tetrafluoroboric acid in 35 mL of ether had been stirred for 40 h at room temperature, the reaction mixture was diluted with 20 mL of saturated aqueous $NaHCO_3$ solution and extracted with ether (50 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). The residue upon workup was chromatographed on silica gel (20 g) with *n*-hexane–ethyl acetate to give the cyclobutanone (**36a**) (0.83 g, 95%) as a colorless oil: IR ($CHCl_3$) 1770 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.78 (3 H, br s, H_2C=CCH_3), 2.95 (2 H, t, J = 9.0 Hz, O=CCH_2), 3.75 (3 H, s, OCH_3), 4.90 (2 H, br s, H_2C=CCH_3), 6.66–7.00 (3 H, m, Ar H); mass spectrum, m/z 270 (M^+). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.78; H, 8.24.

2,2-Dimethoxy-1-isopropenyl-1-[2-(4-methoxybenzocyclobutenyl)-ethyl]cyclobutane (36b). A mixture of the cyclobutanone **36a** (438 mg, 1.62 mmol), a catalytic amount of camphorsulfonic acid, methyl orthoformate (0.71 mL, 6.48 mmol), and 10 mL of methanol was stirred for 3 h at room temperature. The reaction mixture was then basified with $NaHCO_3$, concentrated, treated with 10 mL of water, and extracted with ether (30 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated to give the residue, which was chromatographed on neutral alumina (2 g) with *n*-hexane–ethyl acetate (1:99 v/v) to afford the dimethyl acetal **36b** (513.4 mg, 100%) as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 1.79 (3 H, br s, CH_2=CCH_3), 3.19, 3.31 (6 H, each s, 2 OCH_3), 3.76 (3 H, s, $ArOCH_3$), 4.67, 4.93 (2 H, each br s, CH_2=CCH_3), 6.67–7.06 (3 H, m, Ar H); mass spectrum, m/z 285 ($M^+ - 31$). Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.11; H, 9.18.

General Procedure for the Preparation of Cyclic Acetals. Preparation of 36c. A solution of the dimethyl acetal **36b** (439 mg, 1.4 mmol) and ethylene glycol (0.4 mL, 7 mmol) in 20 mL of toluene was refluxed for 1 h with Dean–Stark apparatus. After addition of a catalytic amount of camphorsulfonic acid at room temperature, the reaction mixture was stirred for 1 h at room temperature and then refluxed for 1 h. To this end, the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated to give the crude product, which was chromatographed on silica gel (10 g) with *n*-hexane–ethyl acetate (3:47 v/v) to furnish the ethylene acetal **36c** (391 mg, 90%) as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 1.66 (3 H, br s, CH_2=CCH_3), 3.76 (3 H, s, OCH_3), 3.87–3.95 (4 H, m, OCH_2CH_2O), 4.69, 4.92 (2 H, each br s, CH_2=CCH_3), 6.67–7.06 (3 H, m, Ar H); mass spectrum, m/z 314 (M^+). Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.48; H, 8.27.

36d: (100%) colorless oil; ^1H NMR (90 MHz, $CDCl_3$) δ 1.11–1.20 (6 H, m, $CH_3CH(O)CH(O)CH_3$), 1.71 (3 H, br s, CH_2=CCH_3), 3.76 (3 H, s, OCH_3), 3.96–4.35 (2 H, m, $CH_3CH(O)CH(O)CH_3$), 4.68, 4.88 (2 H, each br s, CH_2=CCH_3), 6.68–7.07 (3 H, m, Ar H); mass spectrum, m/z 342 (M^+). Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.06; H, 8.87.

36e: (98%) colorless oil; ^1H NMR (90 MHz, $CDCl_3$) δ 1.74 (3 H, br s, CH_2=CCH_3), 3.76 (3 H, br s, OCH_3), 4.69, 4.90 (2 H, each br s, CH_2=CCH_3), 6.68–7.08 (3 H, m, Ar H); mass spectrum, m/z 368 (M^+). Anal. Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.12; H, 8.95.

36f: (100%) colorless oil; ^1H NMR (90 MHz, $CDCl_3$) δ 1.88 (3 H, br s, CH_2=CCH_3), 3.85 (3 H, s, OCH_3), 3.95–4.07 (4 H, m, $OCH_2CH_2CH_2O$), 4.68, 4.98 (2 H, each br s, CH_2=CCH_3), 6.77–7.16 (3 H, m, Ar H); mass spectrum, m/z 328 (M^+). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.05; H, 8.96.

36g: (100%) colorless oil; ^1H NMR (90 MHz, $CDCl_3$) δ 0.73, 1.23 (6 H, each s, 2 CH_3), 1.72 (3 H, br s, CH_2=CCH_3), 3.76 (3 H, s, OCH_3), 4.58, 4.90 (2 H, each br s, CH_2=CCH_3), 6.66–7.07 (3 H, m, Ar H); mass spectrum, m/z 356 (M^+). Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.26, H, 9.36.

36h: (79%) colorless oil; ^1H NMR (90 MHz, $CDCl_3$) δ 1.10–1.31 (6 H, m, 2 $OCHCH_3$), 1.67 (3 H, br s, CH_2=CCH_3), 3.73 (3 H, s, OCH_3), 3.83–4.37 (2 H, m, 2 $OCHCH_3$), 4.43, 4.71 (2 H, each br s, CH_2=CCH_3), 6.49–7.03 (3 H, m, Ar H); mass spectrum, m/z 356 (M^+). Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.60; H, 9.22.

Preparation of 36i. To a stirred solution of the dimethyl acetal **36b** (61 mg, 0.19 mmol) and 2,4-bis(silyloxy)-2,4-dimethylpentane (106 mg, 0.38 mmol) was added a catalytic amount of trimethylsilyloxy triflate at −78 °C. After having been stirred for 40 min at the same temperature, to this solution was added pyridine (0.04 mL, 0.46 mmol) and saturated aqueous $NaHCO_3$ (2 mL). The reaction mixture was extracted with ether. The organic layer was washed with water and brine and dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was chromatographed on silica gel (1 g) with *n*-hexane-ether (33:1 v/v) to afford 70 mg (95%) of the acetal **36i** as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 1.32 [12 H, br s, 2 $OC(CH_3)_2$], 1.64 (3 H, br s, CH_2=CCH_3), 3.73 (3 H, s, OCH_3), 4.50, 4.72 (2 H, each br s, CH_2=CCH_3), 6.53–7.03 (3 H, m, Ar H); mass spectrum, m/z 384 (M^+). Anal. Calcd for $C_{25}H_{36}O_3$: 78.08; H, 9.44. Found: C, 77.83; H, 9.59.

Thermolysis of the Olefinic Cyclobutanone (36a). A solution of the cyclobutanone **36a** (59.6 mg, 0.22 mmol) in 6 mL of *o*-dichlorobenzene was heated at 180 °C for 9 h. Removal of the solvent gave the crude product, which was subjected to flash chromatography on silica gel (500 mg) with *n*-hexane–ethyl acetate (1:99 v/v) to give the cyclized product (57.8 mg, 97%) as a colorless oil. Analysis of this product by ^1H NMR indicated a 28:60:12 mixture of **5a**–**37a**–**38a**. This mixture was separated by HPLC [silica gel, *n*-hexane–ethyl acetate (1:19 v/v)] to give the analytically pure samples of **5a**, **37**, and **38a**, respectively.

***trans*-4,5-(4-Methoxybenzo)-7aβ-methylhydrindan-1-spiro-2′β-oxocyclobutane (5a)**: colorless needles (Et_2O); mp 113–114 °C; IR ($CHCl_3$) 1760 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 (3 H, s), 1.62–1.74 (3 H, m), 1.93 (1 H, ddd, J = 5.8, 9.1, and 14.6 Hz), 2.02 (1 H, dt, J = 12.7 and 10.2 Hz), 2.19–2.25 (1 H, m), 2.34 (1 H, dt, J = 5.4 and 10.8 Hz), 2.52 (1 H, ddd, J = 3.4, 11.2, and 15.1 Hz), 2.76 (1 H, dd, J = 8.1 and 11.7 Hz), 2.81–2.92 (1 H, m), 2.93–2.96 (2 H, m), 3.78 (3 H, s), 6.68 (1 H, s), 6.69 (1 H, d, J = 8.8 Hz) 6.94 (1 H, d, J = 8.8 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) δ 15.088, 24.012, 25.245, 27.358, 30.177, 34.287, 44.208, 46.146, 47.555, 55.188, 76.734, 111.489, 113.546, 127.636, 131.333, 136.617, 157.748, 213.941; exact mass calcd for $C_{18}H_{22}O_2$ 270.1619 (M^+), found 270.1605.

***trans*-4,5-(4-Methoxybenzo)-7aβ-methylhydrindan-1-spiro-2′α-oxocyclobutane (37a)**: colorless oil; IR ($CHCl_3$) 1755 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.68 (3 H, s), 1.60–1.68 (1 H, m), 1.73–1.78 (2 H, m), 1.84–1.95 (2 H, m), 2.18–2.35 (3 H, m), 2.79–2.92 (4 H, m), 3.13 (1 H, dd, J = 8.4 and 12.0 Hz), 3.77 (3 H, s), 6.66 (1 H, s), 6.68 (1 H, d, J = 8.8 Hz), 6.93 (1 H, d, J = 8.8 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) δ 14.266, 18.845, 24.893, 26.948, 30.353, 32.231, 42.741, 45.830, 46.909, 55.070, 76.734, 111.198, 113.485, 127.049, 131.746, 136.617, 157.513, 215.519; exact mass calcd for $C_{18}H_{22}O_2$ 270.1619 (M^+), found 270.1624.

***cis*-4,5-(4-Methoxybenzo)-7aβ-methylhydrindan-1-spiro-2′β-oxocyclobutane (38a)**: colorless oil; IR ($CHCl_3$) 1760 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (3 H, s), 1.44 (1 H, ddd, J = 1.8, 6.4, and 11.8 Hz), 1.50–1.59 (2 H, m), 1.77–1.82 (1 H, m), 1.89 (1 H, dt, J = 6.4 and 12.7 Hz), 2.07–2.19 (2 H, m), 2.22–2.30 (1 H, m), 2.72 (1 H, dd, J = 6.3 and 17.1 Hz), 2.80–2.88 (2 H, m), 2.96 (1 H, ddd, J = 1.8, 7.2, and 10.8 Hz), 3.05 (1 H, t, J = 9.4 Hz), 3.78 (3 H, s), 6.64 (1 H, s), 6.70 (1 H, d, J = 8.8 Hz), 7.00 (1 H, d, J = 8.8 Hz); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 17.609, 17.826, 25.652, 25.761, 31.739, 32.609, 42.826, 43.587, 47.717, 55.217, 96.596, 112.340, 113.617, 130.638, 131.915, 135.319, 157.447, 216.170; exact mass calcd for $C_{18}H_{22}O_2$ 270.1619 (M^+), found 270.1598.

General Procedure for the Thermolysis of the Olefinic Cyclobutanone Acetals and the Hydrolysis of the Products. A solution of the dimethyl acetal **36b** (112.6 mg, 0.356 mmol) in 10 mL of *o*-dichlorobenzene was heated at 180 °C for 9 h. The residue resulting on evaporation of the solvent was dissolved in 5 mL of acetone containing a few drops of 10% hydrochloric acid, and stirring was continued for 15 min at room temperature. The reaction mixture was basified with $NaHCO_3$ and concentrated. The residue was then treated with 5 mL of water and extracted with ether (10 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). Evaporation of the solvent afforded the residue, which was subjected to flash chromatography on silica gel (500 mg) with *n*-hexane–ethyl acetate (1:99 v/v) to give the cyclized product (54.3 mg, 56%) as a colorless oil. Analysis of this product by ^1H NMR indicated a 88:3:9 mixture of **5a**–**37a**–**38a**.

Via the same procedure as described for the compound **36b** under the

conditions described in Table II, the thermolysis and the products' analysis of compounds **36c–i** were conducted and the results were summarized in Table II.

Lactones 21, 20, and 23 via Baeyer–Villiger Reaction on the Cyclobutanones 5a, 37a, and 38a. To a stirred solution of the ketone **5a** (26.8 mg, 0.1 mmol) and 0.06 mL of 10% aqueous NaOH solution in 1 mL of THF was added 0.04 mL of 70% aqueous *tert*-butyl hydroperoxide solution at 0 °C, and stirring was continued for 1.6 h at the same temperature. The reaction mixture was then treated with 2 mL of saturated aqueous Na_2SO_3 solution and extracted with ether (10 mL × 3). The combined extracts were washed successively with saturated aqueous Na_2SO_3 and NaCl solution and dried (Na_2SO_4). The residue upon workup was chromatographed on silica gel (500 mg) with *n*-hexane–ethyl acetate (4:1 v/v) to give the lactone **21** (26 mg, 92%) as colorless needles, mp 117–118 °C (ether). This was identical with the samples obtained previously by the thermolysis of **12** and the direct lactonization of the ketone **34** in its IR ($CHCl_3$) and ^1H NMR (500 MHz, $CDCl_3$) spectral comparisons and mixed melting point test. Via the same procedure described above, the cyclobutanones **37a** and **38a** were converted into the lactones **20** and **23**, respectively.

20: (85%) colorless needles; mp 126–127 °C (ether). This was identical with the sample obtained by the thermolysis of **12** in its IR ($CHCl_3$) and ^1H NMR (500 MHz, $CDCl_3$) spectral comparisons and mixed melting point test.

23: (79%) colorless needles; mp 128–129 °C (ether); IR ($CHCl_3$) 1770 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (3 H, s), 1.43–1.58 (3 H, m) 2.02 (1 H, ddd, J = 5.0, 10.0, and 20.0 Hz), 2.08 (2 H, t, J = 8.3 Hz), 2.26 (1 H, dt, J = 13.0 and 10.0 Hz), 2.31–2.39 (1 H, m), 2.54–2.68 (2 H, m), 2.76 (1 H, ddd, J = 2.3, 5.8, and 20.0 Hz), 2.87 (1 H, ddd, J = 6.3, 11.5, and 20.0 Hz), 3.31 (1 H, t, J = 9.0 Hz), 3.79 (3 H, s), 6.65 (1 H, s), 6.74 (1 H, d, J = 8.8 Hz), 7.01 (1 H, d, J = 8.8 Hz); exact mass calcd for $C_{18}H_{22}O_3$ 286.1568 (M^+), found 286.1580.

Synthesis of 22 via Lactonization of the Cis Ketone 40.[4] By means of the exact procedure as for the synthesis of **21** via the lactonization of the ketone **34**, the lactone **22** was obtained in 61% yield as colorless needles (ether): mp 101–102 °C; IR ($CHCl_3$) 1770 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (3 H, s), 1.54–1.60 (1 H, m), 1.62–1.70 (1 H, m), 1.82–1.89 (2 H, m), 2.03 (1 H, ddd, J = 4.5, 9.0, and 13.5 Hz), 2.14–2.23 (2 H, m), 2.41 (1 H, dt, J = 13.5 and 9.0 Hz), 2.53–2.66 (2 H, m), 2.68–2.76 (2 H, m), 2.81 (1 H, dt, J = 9.0 and 5.4 Hz), 3.78 (3 H, s), 6.66 (1 H, d, J = 2.5 Hz), 6.73 (1 H, dd, J = 2.5 and 10.0 Hz), 7.00 (1 H, d, J = 10.0 Hz); exact mass calcd for $C_{18}H_{22}O_3$ 286.1568 (M^+), found 286.1556.

***trans*-4,5-(4-Methoxybenzo)-7aβ-methylhydrindan-1-spiro-2′-(1′β-5′-hydroxytetrahydrofuran) (41).** To a stirred solution of the lactone **21** (1.29 g, 4.5 mmol) in 15 mL of THF was added Dibal (1.0 M solution in *n*-hexane, 5.40 mL, 5.40 mmol) at −78 °C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with 2 mL of saturated aqueous NH_4Cl solution. The residue obtained on evaporation of the solvent was diluted with 20 mL of water and extracted with methylene chloride (50 mL × 3). The combined extracts were washed with saturated aqueous NH_4Cl solution and NaCl solution and dried ($MgSO_4$). Evaporation of the solvent afforded the residue, which was chromatographed on silica gel (20 g) with *n*-hexane–ethyl acetate (33:1 v/v) as an eluant to give the lactol **41** (1.19 g, 92%) as a colorless powder: IR ($CHCl_3$) 3600 (OH) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.76, 0.80 (3 H, each s, CH_3), 3.76 (3 H, s, OCH_3), 5.50 (1 H, br s, OCHO), 6.46–7.00 (3 H, m, Ar H); mass spectrum, m/z 288 (M^+). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.66; H, 8.37.

***trans*-4,5-(4-Methoxybenzo)-7aβ-methylhydrindan-1-spiro-2′-(1′β-5′-methoxytetrahydrofuran) (42).** A solution of the lactol **41** (1.19 g, 4.12 mmol) and a catalytic amount of boron trifluoride etherate in a mixture of 15 mL of THF and 60 mL of methanol was stirred for 27 h at room temperature. After addition of $NaHCO_3$, the solvent was evaporated to leave the residue, which was diluted with 20 mL of water, extracted with chloroform (50 mL × 3), and dried ($MgSO_4$). Evaporation of the solvent left the residue, which was chromatographed on silica gel (20 g) with *n*-hexane–ethyl acetate (49:1 v/v) as an eluant to give the acetal **42** (1.24 g, 99%) as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 0.78, 0.82 (3 H, each s, CH_3), 3.34 (3 H, s, $C_{5'}OCH_3$), 3.76 (3 H, s, Ar OCH_3), 4.97 (1 H, br s, OCHO), 6.52–7.00 (3 H, m, Ar H); mass spectrum, m/z 302 (M^+). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.22; H, 8.88.

***anti-trans*-4,5-(4-Oxo-1,2,3,4-tetrahydrobenzo)-7aβ-methylhydrindan-1-spiro-2′-(1′β-5-methoxytetrahydrofuran) (43).** To a stirred solution of the acetal **42** (118 mg, 0.39 mmol) in a mixture of 3 mL of THF, 10 mL of liquid ammonia, and 0.3 mL of ethanol was added lithium (10.8 mg, 1.56 mmol) at −78 °C. After stirring had been continued for 1 h at the same temperature, the solvent was concentrated. The residue was diluted with 10 mL of water and extracted with ether (50 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried (Na_2SO_4). The residue obtained on evaporation of the solvent was dissolved in a mixture of 10 mL of methanol and 0.5 mL of 10% hydrochloric acid, and stirring was continued for 3 h at room temperature. Evaporation of the solvent afforded the residue, which was diluted with 10 mL of water and extracted with methylene chloride (20 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). The residue upon workup was chromatographed on silica gel (2 g) with *n*-hexane–ethyl acetate (9:1 v/v) to give the enone **43** (80 mg, 71%) as a colorless powder: IR ($CHCl_3$) 1660 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.02 (3 H, s, CH_3), 3.27 (3 H, s, OCH_3), 5.13 (1 H, br s, OCHO), 6.07 (1 H, br s, C=CH); mass spectrum, m/z 290 (M^+). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.12; H, 9.39.

***trans-anti-trans*-4,5-[5α-(3-Chlorobut-2-enyl)-4-oxo-1,2,3,4,5,6-hexahydrobenzo]-7aβ-methylhydrindan-1-spiro-2′-(1′β-5′-methoxytetrahydrofuran) (44).** To a stirred solution of the enone **43** (116.7 mg, 0.57 mmol) in a mixture of 12 mL of THF and 12 mL of liquid ammonia was added lithium (12 mg, 0.75 mmol) at −78 °C. After stirring had been continued for 1 h at −20 °C, a solution of 1-bromo-3-chloro-2-butene (126 mg, 0.75 mmol) in 5 mL of THF was added dropwise, and the reaction mixture was stirred for 2 h at the same temperature. To this end, the residue that resulted on evaporation of the solvent was diluted with 10 mL of water and extracted with chloroform (20 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). Concentration of the solvent afforded the crude product, which was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (14:1 v/v) as eluant to give the alkylated compound **44** (158.8 mg, 73%) as a colorless oil: IR ($CHCl_3$) 1705 $(C=O)^{-1}$; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95, 0.98 (3 H, s, CH_3), 2.07 (3 H, br s, $C=CClCH_3$), 3.30 (3 H, s, OCH_3), 4.90 (1 H, br s, $OCHOCH_3$), 5.17–5.73 (1 H, m, $CH=CClCH_3$); mass spectrum, m/z 382 ($M^+ + 2$), 380 (M^+); exact mass calcd for $C_{22}H_{33}O_3Cl$ 382.2102 ($M^+ + 2$) and 380.2113 (M^+), found 382.2116 and 380.2118.

***trans-anti-trans*-4,5-[5α-(3-Chlorobut-2-enyl)-4-oxo-1,4,5,6-tetrahydrobenzo]-7aβ-methylhydrindan-1-spiro-2′-(1′β-5′-methoxytetrahydrofuran) (45).** A solution of the alkylated compound **44** (126.5 mg, 0.33 mmol) in 1.5 mL of THF was added dropwise to a solution of LDA [prepaed from *n*-butyllithium (1.08M solution in *n*-hexane, 0.55 mL, 0.6 mmol) and diisopropylamine (0.084 mL, 0.6 mmol)] in 3 mL of THF at −78 °C. After stirring had been continued for 1 h at the same temperature, a mixture of trimethylsilyl chloride (0.085 mL, 0.66 mmol), triethylamine (0.024 mL, 0.17 mmol), and 2 mL of THF was added. The reaction mixture was then stirred for 1 h at room temperature, treated with 10 mL of saturated aqueous $NaHCO_3$ solution, and extracted with ether (20 mL × 3). The combined extracts were dried ($MgSO_4$) and concentrated to leave the crude product, which was used directly without further purification. To a stirred mixture of $Pd(OAc)_2$ (149 mg, 1.33 mmol), *p*-benzoquinone (71.8 mg, 1.33 mmol), and 6.5 mL of acetonitrile was added the crude silyl enol ether obtained above in 2 mL of acetonitrile at room temperature. After stirring had been continued for 36 h at the same temperature, the reaction mixture was continued for 36 h at the same temperature, the reaction mixture was concentrated, dissolved in 10 mL of benzene, and filtrated through Celite. Evaporation of the filtrate afforded the residue, which was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (12:1 v/v) to give the enone **45** (86.2 mg, 69%) as a colorless oil: IR ($CHCl_3$) 1670 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.97, 1.03 (3 H, each s, CH_3), 2.11 (3 H, br s, $C=CClCH_3$), 3.36 (3 H, s, OCH_3), 4.92 (1 H, br s, $OCHOCH_3$), 5.46 (1 H, m, $CH=CClCH_3$), 6.00 (1 H, dd, J = 10.5 and 2.9 Hz, $COCH=CH$), 6.84 (1 H, d, J = 10.5 Hz, $COCH=CH$); mass spectrum, m/z 380 ($M^+ + 2$), 378 (M^+); exact mass calcd for $C_{22}H_{31}O_3Cl$ 380.1947 ($M^+ + 2$) and 378.1960 (M^+), found 380.1931 and 378.1935.

***trans-anti-trans*-4,5-[5α-(3-Chlorobut-2-enyl)-4-oxo-1,4,5,6-tetrahydrobenzo]-7aβ-methylhydrindan-1-spiro-2′-(1′β-5′-oxotetrahydrofuran) (46).** To a stirred solution of the enone **45** (58 mg, 0.15 mmol) in 5 mL of acetone was added dropwise Jones reagent (0.16 mL, 0.22 mmol) at 0 °C, and stirring was continued for 40 min at the same temperature. The reaction mixture was then quenched with 0.5 mL of 2-propanol and concentrated to leave the crude product, which was diluted with 2 mL of water and extracted with chloroform (10 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). The residue upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (85:15 v/v) to give the lactone **46** (46.4 mg, 84%) as a colorless oil: IR ($CHCl_3$) 1770 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.07 (3 H, s, CH_3), 2.13 (3 H, br s, $C=CClCH_3$), 5.42 (1 H, m, $CH=CClCH_3$), 6.03 (1 H, dd, J = 10.5 and 2.9 Hz, $COCH=CH$), 6.81 (1 H, d, J = 10.5 Hz, $COCH=CH$); mass spectrum, m/z 364 ($M^+ + 2$), 362 (M^+).

***trans*-anti-*trans*-4,5-[5α-(3-Oxobutyl)-4-oxo-1,4,5,6-tetrahydrobenzo]-7aβ-methylhydrindan-1-spiro-2′-(1′β-5′-oxotetrahydrofuran) (47).** A mixture of mercuric trifluoroacetate (53 mg, 0.124 mmol), the lactone **46** (30 mg, 0.08 mmol), and 2 mL of methylene chloride was stirred for 1 h at room temperature. The reaction mixture was diluted with 10 mL of water and extracted with chloroform (20 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution and dried ($MgSO_4$). The residue upon workup was chromatographed on silica gel (1 g) with methylene chloride–chloroform (1:4 v/v) to give the diketone **47** (28 mg, 98%) as a colorless oil: IR ($CHCl_3$) 1760 (C=O), 1705 (C=O), 1665 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.06 (3 H, s, CH_3), 2.15 (3 H, s, O=CCH_3), 6.00 (1 H, dd, J = 10.5 and 2.9 Hz, COCH=C*H*), 6.82 (1 H, d, J = 10.5 Hz, COC*H*=CH); mass spectrum, m/z 344 (M^+); exact mass calcd for $C_{21}H_{28}O_4$ 344.1987 (M^+), found 344.2012 (M^+).

19-Norcanrenone (3). A mixture of the diketone **47** (39 mg, 0.113 mmol), 0.4 mL of concentrated hydrochloric acid, 0.1 mL of water, and 4 mL of acetic acid was stirred for 90 h at room temperatue, diluted with 20 mL of water, and extracted with chloroform (20 mL × 3). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ and NaCl solutions and dried ($MgSO_4$). The residue upon workup was chromatographed on silica gel (1 g) with methylene chloride–chloroform (1:1 v/v) to give 19-norcanrenone (**3**) (20.1 mg, 54%) as colorless prisms (from methylene chloride–*n*-hexane): mp 192–193 °C (lit.[2l] 191–192 °C); IR ($CHCl_3$) 1765 (C=O), 1655 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (1 H, dd, J = 6.0 and 14.0 Hz), 1.03 (3 H, s), 1.10–1.20 (1 H, m), 1.26–1.43 (5 H, m), 1.52–1.65 (2 H, m), 1.85–1.96 (3 H, m), 2.22 (1 H, t, J = 12.5 Hz), 2.28–2.41 (4 H, m), 2.46–2.67 (3 H, m), 5.80 (1 H, s), 6.16 (1 H, d, J = 10.1 Hz), 6.22 (1 H, dd, J = 10.1 and 3.0 Hz); mass spectrum, m/z 326 (M^+); exact mass calcd for $C_{21}H_{26}O_3$ 326.1882 (M^+), found 326.1883 (M^+).

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Biosynthesis and Full NMR Assignment of Fungichromin, a Polyene Antibiotic from *Streptomyces cellulosae*

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Abstract: The biosynthesis and NMR signal assignments of the antifungal polyene antibiotic fungichromin (**1**) were determined. NMR analysis after administration of sodium [1-^{13}C]-, [2-^{13}C]-, and [1,2-$^{13}C_2$]acetates, [1-^{13}C]propionate, and [1-^{13}C]- and [3-^{13}C]octanoates to cultures of *Streptomyces cellulosae* ATCC 12625 showed that **1** is derived from one propionate unit, 12 acetate units, and one intact octanoate unit, condensed in the head-to-tail fashion typical of polyketide biogenesis. The results with octanoate are the first case of incorporation of a fatty acid with more than four carbon atoms as a unit into a polyketide without significant degradation. Incorporation of ethyl [CD_3]oleate gave **1** labeled specifically at C-6′, thereby demonstrating that this unit is produced from oleate. Separate incorporations of sodium [1-^{13}C,$^{18}O_2$]acetate, [1-^{13}C,$^{18}O_2$]propionate, and [1-^{13}C,$^{18}O_2$]octanoate as well as $^{18}O_2$ into **1** followed by ^{13}C NMR analysis indicated retention of intact carbon–oxygen bonds at all expected sites. Diethyl [2-^{13}C]malonate was incorporated into **1** as acetate. Efficient incorporation of a mixture of diethyl [2-^{13}C]- and [1,3-$^{13}C_2$]malonates gave **1**, the 2D INADEQUATE spectrum of which gave "interunit" carbon–carbon connectivities complementary to the "intraunit" connectivities obtained from incorporation of sodium [1,2-$^{13}C_2$]acetate. This technique allowed full assignment of the ^{13}C NMR spectrum of **1** for the positions derived from acetate with small amounts of compound.

Fungichromin (**1**) and filipin III (**2**) belong to the class of macrocyclic polyene antibiotics, a group of over 200 compounds, produced primarily by *Streptomyces* species, that possess antifungal and antiprotozoal activity.[1,2] Structurally, all of these compounds contain a chain of three to eight conjugated double bonds within a macrocyclic lactone ring that also has a corresponding saturated fragment adorned with hydroxyl groups.[1a] Despite their toxicity[1b,3] and the development of other classes of antifungal antibiotics,[4] the polyenes (especially amphotericin B and nystatin) remain the best treatment for many fungal infections in humans.[1b,4a] The antihypercholesterolemic,[3a,5] antitumor,[6] and antiviral[7] activities of such steroid-binding[8] polyenes have also

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