(±)-Hysterin: Revised Structure and Total Synthesis

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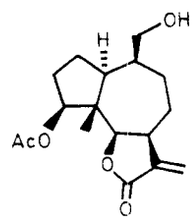
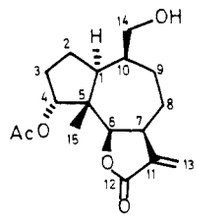
Received July 13, 1979

The total synthesis of the pseudoguaianolide (±)-hysterin (1) has led to the revision of the originally assigned structure 2. Both 1 and 2 were obtained from diol 6β via routine transformations. Unexpectedly, 6β was found to be the minor isomer at C-10 upon catalytic hydrogenation of butenolide 5. The latter product was synthesized from synthon 3 via a four-step sequence, involving inter alia a selective Wittig reaction with (methoxymethylene)triphenylphosphorane on diketone 3.

Hysterin, isolated from *Parthenium bipinnatifidum*,[3-5] is a representative of a group of pseudoguaianolides[6] known as the ambrosanolides (β configuration at C-10)[7] and has been identified as 2 on the basis of chemical transformations and biogenetic considerations.[8] During the course



1

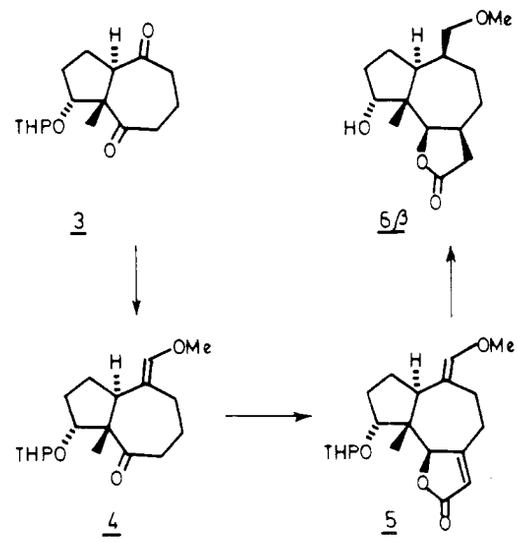


2

of our efforts directed toward the synthesis of 2 we found structure 2 to be incorrect. We also report the revised structure 1 for hysterin and its total synthesis.

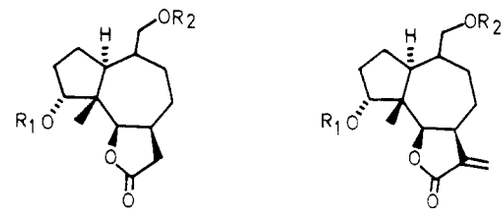
In connection with our synthetic work on pseudoguaianolides we have described an efficient synthesis of the hydroazulenic dione 3 and its potential use in total synthesis.[9] A number of considerations make a total synthesis of "(±)-hysterin-2" starting from key product 3 (via the alcohol 6β[10]) particularly attractive (Scheme I). The presence of a carbonyl group at C-10 allows for the introduction of an oxygenated one-carbon unit (future

Scheme I



3 6β 4 5

Chart I



6; R_1 = H, R_2 = Me
8; R_1 = Ac, R_2 = Me
9; R_1 = Ac, R_2 = H
10; R_1 = R_2 = H

11; R_1 = R_2 = H
12; R_1 = R_2 = Ac

α; α-(C-10)
β; β-(C-10)

(1) Bursary of the IWONL.

(2) Bevoegdverklaard Navorser of the NFWO.

(3) A. Romo de Vivar, E. A. Bratoeff, and T. Ríos, *J. Org. Chem.*, 31, 673 (1966).

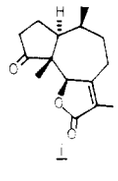
(4) It has been suggested that the original report of the isolation of hysterin from *Parthenium hysterophorus*[3] was in fact for *P. bipinnatifidum*; see W. Herz, "Recent Advances in Phytochemistry", T. J. Mabry, Ed., Appleton-Century-Crafts, New York, 1968. This view was later confirmed.[5]

(5) E. Rodriguez, H. Yoshioka, and T. J. Mabry, *Phytochemistry*, 10, 1145 (1971).

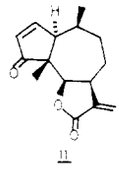
(6) H. Yoshioka, T. J. Mabry, and B. N. Timmerman, "Sesquiterpene Lactones", University of Tokyo Press, Tokyo, Japan, 1973; J. Romo and H. R. de Vivar, *Prog. Chem. Org. Nat. Prod.*, 25, 90 (1976).

(7) W. Herz, *Proc. Nobel Symp., 25th, 1973*, 153 (1973).

(8) From the observation[3] that i, obtained from hysterin, was identical in all respects (spectroscopic data, melting point, $[\alpha]_D$) with i obtained from ambrosin (ii), the structure of which has been confirmed by X-ray analysis, it may be concluded that the chiral centers at C-1, C-5, and C-6 have the absolute configuration as shown in iii. The three remaining centers were assigned the configuration shown in 2 on the basis of sound biogenetic considerations (C-7 and C-10) and chemical transformations (C-4).[3]



i



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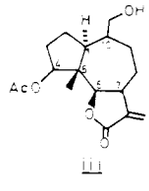

iii

(9) (a) D. Termont, P. De Clercq, D. De Keukeleire, and M. Vandewalle, *Synthesis*, 46 (1977); (b) G. P. Rozing, P. De Clercq, and M. Vandewalle, *ibid.*, 225 (1978); (c) P. De Clercq and M. Vandewalle, *J. Org. Chem.*, 42, 3447 (1977); (d) P. Kok, P. De Clercq, and M. Vandewalle, *Bull. Soc. Chim. Belg.*, 87, 615 (1978); (e) M. Vandewalle, P. De Clercq, M. Demuynck, P. Kok, G. Rozing, and F. Scott, "Stereoselective Total Synthesis of Natural Products", W. Bartmann and G. Winterfeldt, Eds., Excerpta Medica, 1979, p 130; (f) P. Kok, P. De Clercq, M. Vandewalle, J. P. Declercq, G. Germain, and M. Van Meerssche, *Tetrahedron Lett.*, 2063 (1979).

(10) For the sake of clarity we will use α and β throughout the paper to indicate the stereochemistry at C-10: α for the α configuration, β for the β configuration.

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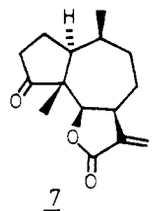
C-14), provided both ketone functions are sufficiently differentiated.[11] This approach stands in contrast with other syntheses of pseudoguaianolides which all aim at products with a methyl group at C-10.[12] Of the six chiral centers present in target **2** (and in **6β**) three (at C-1, C-4, and C-5) already possess the required configuration in the starting material **3**. The β-oriented cis-fused lactone[13] at C-6–C-7 and the remaining chiral center at C-10 of **2** (and **6β**) can be constructed by following a strategy centering about the butenolide **5**; it involves the stereospecific synthesis of **5** from the hydroazulenic ketone **4** and the simultaneous reduction of both double bonds in **5** by catalytic hydrogenation to yield a cis-fused lactone with a β-configuration at C-6, C-7, and C-10. The final transformation of **6β** into our present target (**2**) would only necessitate the introduction[14] of an α-methylene function on the γ-lactone and refunctionalizations at C-4 and C-14. Especially in view of the successful use of this strategy (**3** → **4** → **5** → **6β**, with H instead of OMe) in our total synthesis of (±)-damsin (**7**) no major difficulties were expected;[9c] as it turned out, however, this synthetic journey provided us some surprises.

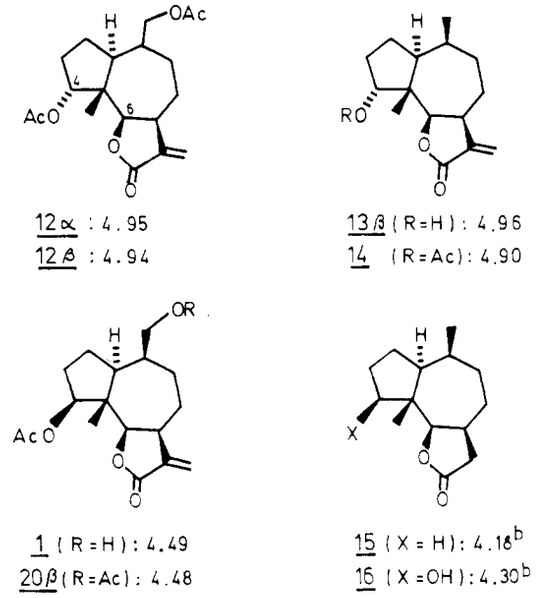


7

Reaction of diketone **3** with (methoxymethylene)triphenylphosphorane (5.0 equiv; from (methoxymethyl)-triphenylphosphonium chloride and *n*-butyllithium) in tetrahydrofuran yielded **4** as a mixture of *E* and *Z* isomers in 68% yield.[15] The conversion of ketone **4** to the butenolide **5** proceeded via a three-step sequence[13] involving treatment of the enolate of **4** (lithium diisopropylamide, tetrahydrofuran) with ethyl bromoacetate–hexamethylphosphoric triamide (81%), saponification of the resulting ester (potassium hydroxide, methanol) to the corresponding acid (90%), and finally treatment with sodium acetate in acetic anhydride (61%). The catalytic hydrogenation of butenolide **5** (5% Pt/C, ethanol) yielded directly alcohol **6** as a mixture of two diastereoisomers (ratio 7:3, 90% yield) and the stereodishomogeneous center was assigned to C-10 on the basis of previous results.[9c]

Although we were confident at that time that the major isomer had the β configuration at C-10 (**6β**) especially due to the expected steric interference of the angular methyl group, that expectation was later found to be wrong (vide infra). After suitable protection of the free hydroxyl group in **6** (acetic anhydride, pyridine; 89%), acetate **8** was treated with boron tribromide in methylene chloride (−25 °C), yielding alcohol **9** in 82% yield. After acid hydrolysis (75%) the resulting diol **10** was subjected to Danishefsky's[16] three-step procedure for the introduction of the α-methylene unit on the γ-lactone: reaction with lithium diisopropylamide (15 equiv), followed by Eschenmoser's salt[17] (20 equiv) in tetrahydrofuran–hexamethylphosphoric triamide, treatment of the resulting amine with methyl iodide in dioxane, and finally elimination with base (sodium bicarbonate in ethyl acetate) gave **11** in 25% yield.

Chart II[a]



[a] ^{1}H NMR chemical shift values of H-6 obtained at 360 MHz (90 MHz for **13β** and **14**; 60 MHz for **15** and **16**) with Me_4Si as internal standard (ppm) in chloroform-*d* (unless otherwise stated). [b] In CCl_4.

As our first objective we undertook the synthesis of the corresponding acetate of "hysterin-**2**" (**12β**) which had been tentatively[18] identified in *Parthenium bipinnatifidum*; diol **11** was therefore converted to the corresponding diacetate **12** (acetic anhydride–pyridine; 62%). Comparison of the ^{1}H NMR spectral properties of the synthetic mixture of **12α** and **12β** with natural hysterin acetate[19] showed unambiguously the latter product to be different from both isomers, the chemical shift of H-6 being especially indicative: 4.48 ppm for hysterin acetate, 4.95 and 4.94 ppm for **12α** and **12β**, respectively (360 MHz, $CDCl_3$). This observation raised serious doubts about the correctness of structure **2** for hysterin and more specifically about the assigned configuration at C-4. Indeed, from the comparison of the chemical shift values of H-6 in products **13β** and **14**[9c] and products **15**[13] and **16**[12b] it may be inferred that the α-oriented H-6 is strongly deshielded (about 0.5 ppm) by the presence of an adjacent α-OH (OAc) at C-4 (Chart II); the appearance at high field of H-6 in hysterin and its acetate (4.49 and 4.48 ppm, respectively) points to the β configuration at C-4 for both products as shown in **1** and **20β**, in contrast with the originally assigned structure **2**. Final confirmation of this and of the β configuration at C-10 (an absolute α configuration at C-7 being highly im-

(11) A few other C-14 oxygenated ambrosanolides are also known, e.g. tetraneurin-A, -E, and -F and conchosin-A and -B.[6]

(12) For other syntheses of pseudoguaianolides, see: (a) R. A. Kretchmer and W. J. Thompson, *J. Am. Chem. Soc.*, **98**, 3379 (1976); (b) P. A. Grieco, Y. Ohfune, and G. Majetich, *ibid.*, **99**, 7393 (1977); (c) J. A. Marshall and R. H. Gillison, *ibid.*, **98**, 4312 (1976); (d) M. F. Semmelhack, A. Yamashita, J. C. Tomesch, and K. Ilirotsu, *ibid.*, **100**, 5565 (1978); (e) P. A. Grieco, T. Oguri, S. Burke, E. Rodriguez, G. T. DeTitta, and S. Fortier, *J. Org. Chem.*, **43**, 4552 (1978); (f) P. A. Wender, M. A. Eissenstat, and M. P. Filosa, *J. Am. Chem. Soc.*, **101**, 2196 (1979); (g) Y. Ohfune, P. A. Grieco, C.-L. J. Wang, and G. Majetich, *ibid.*, **100**, 5946 (1978).

(13) J. A. Marshall and W. R. Snyder, *J. Org. Chem.*, **40**, 1656 (1975).

(14) P. A. Grieco, *Synthesis*, 67 (1975).

(15) (Alkoxymethylene)triphenylphosphoranes have been found to decompose (ether, 45 °C, 20 h): see, G. Wittig and W. Böll, *Chem. Ber.*, **95**, 2526 (1962). The use of several equivalents and a lower reaction temperature allow, however, for a normal conversion.

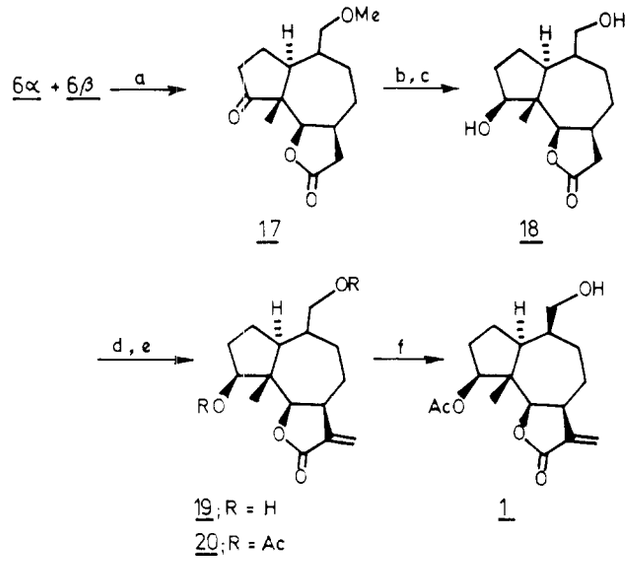
(16) S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976).

(17) J. Schreiber, M. Haag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, **10**, 330 (1971).

(18) From *P. bipinnatifidum* there has been isolated a 3:2 mixture of two substances which were tentatively identified as neoambrosin and hysterin acetate.[5]

(19) Obtained from hysterin by treatment with acetic anhydride and 4-(dimethylamino)pyridine (room temperature, 70% yield).

Scheme II[a]



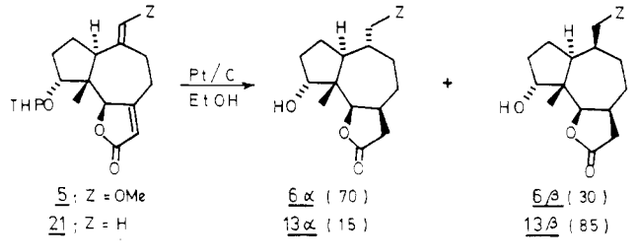
[a] a, Jones oxidation, acetone; b, BBr_3, CH_2Cl_2 (−25 °C); c, $NaBH_4$, MeOH (−20 °C); d, $CH_2{=}NMe_2I$, LDA, THF, HMPA; MeI, dioxane; $NaHCO_3$, EtOAc; e, Ac_2O, 4-$C_5H_4NNMe_2$; f, K_2CO_3, MeOH (30 min).

probable)[8,20] was obtained by a single-crystal X-ray diffraction study[21] of natural hysterin, which unequivocally established the revised structure of the title compound as **1**.

As a consequence, our further synthetic investigation toward hysterin (**1**) necessitated an inversion at C-4. This reaction and the further sequence leading to the title compound is illustrated in Scheme II. Jones oxidation of the alcohol **6** (isomeric mixture) gave the corresponding ketone **17** in 90% yield. Cleavage of the methyl ether, followed by reduction with sodium borohydride at −20 °C yielded diol **18** (51% overall yield), with a β-oriented hydroxyl group at C-4 (δ 4.5 for H-6). Danishefsky's α-methylenation procedure[16] led to diol **19** in 25% yield. Conversion of the latter product to the diacetate (acetic anhydride, 4-(dimethylamino)pyridine; 68% yield) afforded an unseparable mixture[22] of **20α** and **20β** (ratio 75:25). Much to our surprise comparison of the ^1H NMR spectrum of this mixture with the spectrum of authentic hysterin acetate allowed easy identification of the minor isomer as **20β** or (±)-hysterin acetate. We were nevertheless extremely gratified to find that upon treatment of **20** (isomeric mixture) with potassium carbonate in methanol (1 molar equiv; 30 min) only **20β** was saponified selectively[23] to the corresponding primary alcohol, thus yielding an easily separable mixture of **20α** and (±)-hysterin (**1**). From comparison of TLC behavior and spectral properties (^1H NMR), **1** was found to be identical with an authentic sample of hysterin.

The preponderant formation of **6α** upon catalytic hydrogenation of butenolide **5** stands in sharp contrast with the stereochemical result we had previously obtained for

Scheme III[a]



[a] Values between parentheses indicate relative percent as determined from ^1H NMR spectroscopy.

the reduction of the similar butenolide **21**, where the major reduction product was found to be **13β** (Scheme III).[9c] No rationale for this observation is presently available. Our attempts to obtain **6β** in higher yield by using other approaches (e.g., hydroboration of **21**, followed by hydrogenation) have so far met with complete failure. We are currently investigating the course of the catalytic hydrogenation of butenolides such as **5** and **21**, as well as the possibility of obtaining the β configuration at C-4 at an earlier stage of the sequence, since the spatial orientation of the group located at that carbon could have a determining influence on the stereochemical outcome of the hydrogenation.

Experimental Section

Reaction products were isolated by the addition of water and extracted with ether or ethyl acetate. The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solutions on a rotary evaporator. R_f values are quoted for Merck silica gel 60 GF_{254} TLC plates of thickness 0.25 mm. IR spectra were recorded on a Perkin-Elmer 337 spectrometer, mass spectra on an AEI MS-50, and ^1H NMR spectra on a Varian EM-390 spectrometer or a Bruker 360 spectrometer ($CDCl_3$). Melting points are uncorrected. Stereochemical designations of substituents in bicyclic compounds are indicated by *c* (cis) and *t* (trans) relative to a reference substituent (*r*).

***t*-5-Methyl-10-(methoxymethylene)-*c*-4-[(2-tetrahydropyranyl)oxy]-*r*-1*H*-bicyclo[5.3.0]decan-6-one (4).** To a suspension of (methoxymethylene)triphenylphosphorane (from 43.5 g (0.125 mol) of (methoxymethyl)triphenylphosphonium chloride and 76.5 mL of 1.6 M *n*-butyllithium–hexane solution) in 150 mL of tetrahydrofuran was added a solution of 7.0 g (0.025 mol) of diketone **3** in 25 mL of tetrahydrofuran at room temperature. After 45 min the reaction mixture was poured into a saturated ammonium chloride solution. Workup and purification by column chromatography on silica gel, using 5% ethyl acetate–isooctane, yielded 5.2 g (68%) of **4** as a mixture of *E* and *Z* isomers: R_f (ethyl acetate–isooctane (3:7)) 0.4; IR (film) 2950, 1700, 1680, 1200–1150 cm^{-1}; NMR (90 MHz) δ_{Me_4Si} 5.94 and 5.80 (s, exo-CH vinyl H), 3.56 and 3.45 (s, OCH_3), 0.87–1.03 (4 s, C-5 CH_3); MS *m/z* 223 (18), 167 (30), 85 (100), 31 (12).

[*t*-6-Hydroxy-*t*-5-methyl-10-(methoxymethylene)-*c*-4-[(2-tetrahydropyranyl)oxy]-*r*-1*H*-bicyclo[5.3.0]dec-7-ylidene]acetic Acid γ-Lactone (5). To a solution of 4.76 mL (0.034 mol) of *N,N*-diisopropylamine in 60 mL of tetrahydrofuran was added at −78 °C 21.05 mL (0.034 mol) of 1.6 M *n*-butyllithium–hexane solution. The temperature was slowly raised to 0 °C over 30 min. A solution of 5.2 g (0.0169 mol) of ketone **4** in 12 mL of tetrahydrofuran was added at −78 °C and stirring was continued for 3 h at room temperature. Finally a solution of 4.15 mL (0.037 mol) of ethyl bromoacetate and 6.4 mL (0.037 mol) of hexamethylphosphoric triamide in 24 mL of tetrahydrofuran was added at −78 °C. After 30 min of stirring, the mixture was poured into a saturated ammonium chloride solution. Workup and purification by column chromatography on silica gel, using ethyl acetate–isooctane (1:9), yielded 5.4 g (81%) of ethyl [*t*-5-methyl-10-(methoxymethylene)-6-oxo-*c*-4-[(2-tetrahydropyranyl)oxy]-*r*-1*H*-bicyclo[5.3.0]dec-7-yl]acetate: R_f (isooctane–ethyl acetate (7:3)) 0.4; IR 3000, 1745, 1705, 1680, 1200, 1120, 1060, 1010 cm^{-1}; NMR

(20) J. B. Hendrickson, *Tetrahedron*, 7, 82 (1959).
(21) J. P. Declercq, G. Germain, M. Van Meerssche, M. Demuynck, P. De Clercq, and M. Vandewalle, *Acta Crystallogr., Sect. B*, submitted for publication.
(22) In fact the only compound in which the epimers at C-10 could be separated by column chromatography was **11** (silica gel, ethyl acetate–isooctane (3:2) as eluent: R_f 0.28 for **11β**, R_f 0.26 for **11α**).
(23) The fast selective hydrolysis of the primary acetate in (±)-hysterin acetate (**20β**), compared to the hydrolysis of **20α**, could be due to the accompanying relief of steric congestion. Natural hysterin acetate[19] was similarly converted to hysterin (90% yield).

(90 MHz) δ_{Me_4Si} 0.90–0.85 (C-5 CH_3); MS m/z 213 (14), 207 (25), 185 (35), 85 (100), 43 (25).

A solution of 5.4 g (0.014 mol) of this ester and 3.1 g (0.054 mol) of potassium hydroxide in 80 mL of dry methanol was heated at reflux for 4 h. The solution was cooled and concentrated in vacuo, and water was added to the residue. After being washed with ether, the solution was acidified to pH 4 with acetic acid. Workup yielded 4.5 g (90%) of [*t*-5-methyl-10-(methoxymethylene)-6-oxo-*c*-4-[(2-tetrahydropyranyl)oxy]-*r*-1*H*-bicyclo[5.3.0]dec-7-yl]-acetic acid as a semisolid oil: R_f (ethyl acetate–isooctane 1:1)) 0.38; IR (melt) 3400–2500, 1750, 1705, 1670, 1200 cm^{-1}; NMR (90 MHz) δ_{Me_4Si} 5.9 and 5.73 (s, exo-CH vinyl H), 1.00–0.87 (4 s, C-5 CH_3); MS m/z 209 (22), 177 (8), 108 (10), 85 (86), 56 (100). Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.0; H, 8.15.

A solution of this acid (4.5 g) and 16.2 g (0.197 mol) of sodium acetate in 135 mL of acetic anhydride was heated at reflux for 2 h and then cooled to 0 °C, and 150 mL of methanol was carefully added. The solution was stirred for 2 h at 0 °C and then poured into water, and the product was extracted with ether. The product was freed from acetic acid by azeotropic distillation in vacuo with toluene. Purification by column chromatography on silica gel, using ethyl acetate–isooctane (1:1) as eluent, yielded 2.6 g (61%) of the butenolide **5**: R_f (isooctane–ethyl acetate (1:1)) 0.27; IR (KBr) 3100, 1770, 1680, 1640, 1200 cm^{-1}; NMR (90 MHz) δ_{Me_4Si} 3.6 and 3.5 (s, OMe), 0.56–0.47 (C-5 CH_3); MS m/z 249 (12), 151 (25), 107 (32), 97 (100), 85 (12).

Catalytic Hydrogenation of Butenolide 5. Lactones 6α and 6β. A suspension of 2.6 g (75×10^{-4} mol) of the butenolide **5** and 870 mg of 5% platinum-on-carbon in 50 mL of dry ethanol was hydrogenated at room temperature under a pressure of 4 bar. After 70 h the reaction mixture was filtered and concentrated in vacuo. Column chromatography on silica gel, using 35% ethyl acetate–isooctane, yielded 1.8 g (90%) of **6** as a yellow oil, which solidified on standing: R_f (ethyl acetate–isooctane (1:1)) 0.33; IR (KBr) 3500–3300, 2950, 1770, 1150, 1090, 890 cm^{-1}; NMR (90 MHz) δ_{Me_4Si} 4.96 (d, C-6 methine), 3.95 (m, C-4 methine), 3.30 (s, CH_2OCH_3), 0.83 (s, C-5, CH_3); MS m/z at 218 (15), 205 (22), 159 (20), 119 (25), 81 (42), 55 (35), 45 (100). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.17; H, 8.9. Found: C, 67.3; H, 8.7.

Ketone 17. To a solution of 1 g (37×10^{-4} mol) of the alcohol **6** in 5 mL of dry acetone was added at 0 °C Jones reagent until the red color persisted. The mixture was quenched with isopropyl alcohol, solid sodium hydrogen carbonate was added, and the mixture was filtered and concentrated in vacuo. The usual workup and column chromatography on silica gel, using 30% ethyl acetate–isooctane, yielded 0.9 g (90%) of ketone **17**: R_f (ethyl acetate–isooctane (7:3)) 0.15; IR (melt) 3000, 1780, 1750, 1180, 1120, 1000 cm^{-1}; NMR (90 MHz) δ_{Me_4Si} 4.52 (d, J = 6.5 Hz, C-6 methine), ~3.3 (CH_2OCH_3), 1.13 (s, C-5 CH_3 in **17α**), 1.07 (s, C-5 CH_3 in **17β**); MS m/z 266 (M^+, 2), 251 (30), 161 (6), 124 (8), 109 (9), 88 (10), 45 (60), 28 (100).

Diol 18. To a stirred solution of 0.25 g (94×10^{-5} mol) of **17** in 4 mL of dry dichloromethane was added at −78 °C a solution of 0.30 mL of BBr_3 (27×10^{-4} mol) in 1 mL of dichloromethane. After 1 h the mixture was warmed to −25 °C. The reaction was monitored by TLC; after completion, the mixture was quenched with saturated sodium hydrogen carbonate. The usual workup yielded 0.2 g of the crude keto alcohol which was added at −20 °C to a solution of 0.11 g (28×10^{-4} mol) of sodium borohydride in 2 mL of absolute methanol. The mixture was stirred for 1 h and then poured into a saturated ammonium chloride solution. Workup and purification by column chromatography on silica gel, using 70% ethyl acetate–isooctane, yielded 0.122 g (51% overall) of **18**: R_f (ethyl acetate–isooctane (9:1)) 0.2; IR (melt) 3600–3300, 3000, 1780, 1050, 1000 cm^{-1}; NMR (90 MHz) δ_{Me_4Si} 4.5 (d, J = 8.5 Hz, C-6 methine), 0.92 (s, C-5 CH_3 of **18α**), 0.86 (s, C-5 CH_3 of **18β**); MS m/z 221 (20), 145 (41), 120 (28), 105 (55), 81 (90), 55 (75), 41 (100).

α-Methylene γ-Lactone 19. To a solution of 1.65 mL (11.8×10^{-3} mol) of *N,N*-diisopropylamine in 40 mL of tetrahydrofuran, at −78 °C, was added 7.16 mL (11.8×10^{-3} mol) of a 1.58 M solution of *n*-butyllithium in hexane during 10 min. After 20 min a solution of 0.20 g (0.787×10^{-3} mol) of lactone **18** in 15 mL of tetrahydrofuran and 2.7 mL (15.7×10^{-3} mol) of hexamethylphosphoric triamide was added dropwise over a period of 1 h. The solution was stirred for 45 min at −78 °C and for 15 min at −42 °C and was then added through a syringe to 3 g (15.7×10^{-3} mol) of the Eschenmoser reagent in 10 mL of tetrahydrofuran. The reaction mixture was stirred for 45 min at −42 °C and for 30 min at room temperature and was then acidified with 5% hydrochloric acid to pH 2 and made alkaline with potassium carbonate. Six milliliters of water was added and the product extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was taken up in 5 mL of dioxane, 15 mL of methyl iodide was added, and the mixture was heated at reflux for 24 h. The solvents were evaporated in vacuo; the residue was washed with eight 10-mL portions of ether and then taken up in 18 mL of an 8% sodium bicarbonate solution and 72 mL of ethyl acetate. The suspension was stirred for 30 min, the organic phase was separated, and a new portion of 45 mL of ethyl acetate was added to the water layer. After 30 min of stirring, the combined ethyl acetate solutions were dried on magnesium sulfate and the solvent was removed in vacuo. Purification by column chromatography on silica gel, using 80% ethyl acetate–isooctane, yielded 0.05 g (25%) of diol **19**: R_f (ethyl acetate–isooctane (1:1)) 0.2; IR (melt) 3600–3200, 2950, 1750, 1650, 1450, 1290, 1200, 980 cm^{-1}; NMR (360 MHz) δ_{Me_4Si} 6.23 (d, J = 3.5 Hz, C-13 vinyl H), 5.52 (d, J = 3.5 Hz, C-13 vinyl H), 4.57 (d, J = 9.2 Hz, C-6 methine of **19α**), 4.52 (d, J = 9.2 Hz, C-6 methine of **19β**), 0.81 (s, C-5 CH_3 of **19α**), 0.74 (s, C-5 CH_3 of **19β**).

(±)-Hysterin Acetate (20β) and Diacetate 20α. A solution of 10 mg (37×10^{-6} mol) of **19** and 50 mg (49×10^{-5} mol) of 4-(dimethylamino)pyridine in 250 μL of acetic anhydride was stirred for 6 h at room temperature. The mixture was poured into ice–water. The usual workup and purification by column chromatography on silica gel, using 60% ethyl acetate–isooctane, yielded 9 mg (68%) of **20α** and **20β** (ratio 7:3, respectively, determined from NMR integration): NMR (360 MHz) 6.18 (d, J = 3.5 Hz, C-13 vinyl H), 5.46 (d, J = 3.5 Hz, C-13 vinyl H of **20α**), 5.47 (d, J = 3.5 Hz, C-13 vinyl H of **20β**), 5.18 (t, J = 8.4 Hz, C-4 methine of **20α**), 5.13 (t, J = 8.8 Hz, C-4 methine of **20β**), 4.52 (d, J = 9.2 Hz, C-6 methine of **20α**), 4.48 (d, J = 9.2 Hz, C-6 methine of **20β**), 3.99 (center of AB of ABX, C-14 methylene of **20α**), 4.27 (center of AB of ABX, C-14 methylene of **20β**), 3.31 (m, C-7 methine), 0.88 (s, C-5 CH_3 of **20α**), 0.85 (s, C-5 CH_3 of **20β**); R_f (ethyl acetate–isooctane (4:1)) 0.47.

(±)-Hysterin (1). A solution of 6 mg (17.1×10^{-6} mol) of the acetate **20** and 6 mg of potassium carbonate (35.1×10^{-6} mol) in 250 μL of dry methanol was stirred for 30 min at room temperature. The reaction mixture was poured into 1% hydrochloric acid and extracted with ethyl acetate. Workup and purification by preparative thin-layer chromatography (repeated elution with ethyl acetate–isooctane (7:3); 5 times) yielded after recrystallization from ethyl acetate ca. 0.5 mg of crystalline (±)-hysterin: mp 173–174 °C; R_f (ethyl acetate–isooctane (4:1)) 0.23; NMR (360 MHz) 6.19 (d, J = 3.5 Hz, C-13 vinyl H), 5.48 (d, J = 3.5 Hz, C-13 vinyl H), 5.13 (t, J = 9.2 Hz, C-4 methine), 4.49 (d, J = 9.2 Hz, C-6 methine), 3.86 (center of AB of ABX, C-14 methylene), 3.34 (m, C-7 methine), 2.11 (s, $OCOCH_3$), 0.83 (s, C-5 CH_3).

Acknowledgment. We are indebted to the National Fonds voor Wetenschappelijk Onderzoek and the Ministerie voor Wetenschapsbeleid for financial support to the laboratory. We thank Professor A. Romo de Vivar for the generous gift of an authentic sample of hysterin. We are grateful to Professor M. Van Meerssche, Dr. J. P. Declercq, and Dr. G. Germain of the University of Louvain-LaNeuve for the X-ray measurement.

Registry No. (±)-**1**, 71883-69-7; (±)-**3**, 62990-79-8; (±)-(*E*)-**4**, 71883-70-0; (±)-(*Z*)-**4**, 71883-71-1; (±)-**5**, 71599-12-7; (±)-**6α**, 71599-11-6; (±)-**6β**, 71623-83-1; (±)-**17α**, 71838-26-1; (±)-**17β**, 71838-27-2; (±)-**18α**, 71838-28-3; (±)-**18β**, 71838-29-4; (±)-**19α**, 71838-30-7; (±)-**19β**, 71838-31-8; (±)-**20α**, 71883-72-2; (±)-**20β**, 71883-73-3; ethyl bromoacetate, 105-36-2; (methoxymethylene)triphenylphosphorane, 20763-19-3; ethyl [±-5-methyl-10-(methoxymethylene)-6-oxo-*c*-4-[(2-tetrahydropyranyl)oxy]-*r*-1*H*-bicyclo[5.3.0]dec-7-yl]acetate, 71838-32-9; [±-5-methyl-10-(methoxymethylene)-6-oxo-*c*-4-[(2-tetrahydropyranyl)oxy]-*r*-1*H*-bicyclo[5.3.0]dec-7-yl]acetic acid, 71838-33-0.