A Synthesis of 3β-Hydroxy-5β,14α-bufa-20,22-dienolide from Deoxycorticosterone

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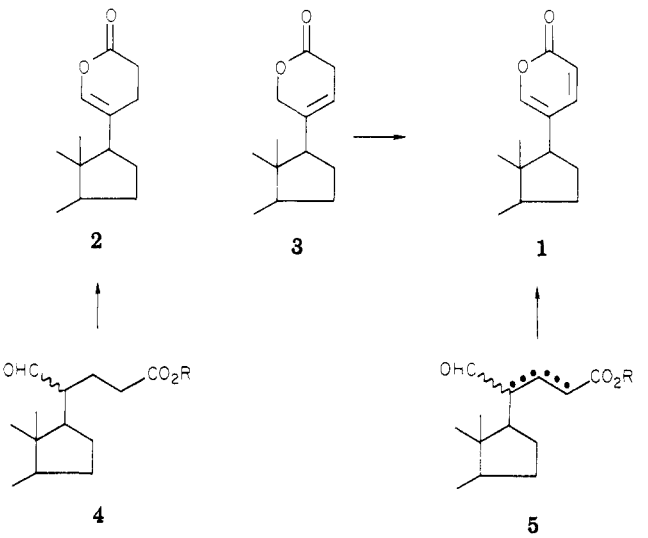
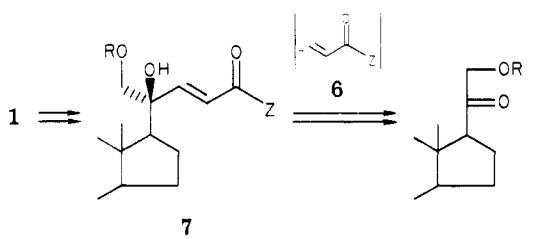
A new procedure for the synthesis of γ-hydroxy-α,β-unsaturated thiol esters from ketones employed 1-(phenylthio)-1-(trimethylsilyl)-2-propene as an unsaturated homoenolate anion equivalent, and this procedure served as a key step in a synthesis of the α-pyrone ring characteristic of bufadienolides. In particular, the regio- and stereoselective trapping of various pregnan-20-ones by the anion of 1-(phenylthio)-1-(trimethylsilyl)-2-propene furnished (20*S*,23*Z*)-20-hydroxy-24-(phenylthio)-24-(trimethylsilyl)-23-cholenes and subsequent regioselective oxygenation of the dianions of these adducts provided *S*-phenyl (20*S*,22*E*)-20-hydroxychol-22-ene-24-thioates. Application of this procedure to 3β-hydroxy-21-methoxy-5β,14α-pregnan-20-one furnished *S*-phenyl (20*S*,22*E*)-3β,20-dihydroxy-21-methoxy-5β-chol-22-ene-24-thioate, which was subsequently cyclized to 3β-hydroxy-5β,14α-bufa-20,22-dienolide.

The bufadienolides[1] isolated from plants and amphibians comprise an intriguing class of steroids that exhibit antineoplastic[2] and cardiac-stimulant[3] properties. Prior synthetic work has focused on the elaboration of the α-pyrone ring characteristic of bufadienolides 1 by a variety of elegant pathways.[4-9] Among these approaches are two recurring problems: either the dehydrogenation of 20-bufenolide **2**[4c,6,7a,9] and 20(22)-bufenolide **3**[8] precursors or the cyclization of saturated esters **4**[6] and unsaturated esters **5**[4a,b,d,7b] proceed in modest yield as shown in Scheme I. To address these problems, we sought to develop a synthetic scheme based on the retroanalysis shown in Scheme II.

Scheme I



Scheme II



This approach demanded the development of an unsaturated homoenolate anion equivalent[10] **6** that (1) would append a three-carbon unit to a pregnan-20-one at the appropriate level of oxidation for closure to an α-pyrone, (2) would accommodate hydroxyl groups and double bonds elsewhere in the steroid without requiring protection, and (3) would furnish an intermediate **7** that would cyclize to an α-pyrone in acceptable yield. We herein report our

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(2) (a) Kupchan, S. M.; Moniot, J. L.; Sigel, C. W.; Hemingway, R. J. *J. Org. Chem.* **1971**, *36*, 2611. (b) Kupchan, S. M.; Hemingway, R. J.; Hemingway, J. C. *Ibid.* **1969**, *34*, 3894. (c) Hartwell, J. L.; Abbott, B. J. *Adv. Pharmacol. Chemother.* **1969**, *7*, 117.

(3) (a) Chem, K. K.; Kovarikova, A. *J. Pharm. Sci.* **1967**, *56*, 1535. (b) Murase, H. *Jpn. J. Pharmacol.* **1965**, *15*, 72. (c) Foester, W. *Acta Biol. Med. Ger.* **1962**, *9*, 341 (*Chem. Abstr.* **1963**, *58*, 11846). (d) Tamm, C. "Proceedings of the First International Pharmacological Meeting"; Wilbrandt, W., Lindgren, P., Ed.; Pergamon Press: London, 1963; Vol. 3, pp 11-26.

(4) Synthesis of scillarenin from 15α-hydroxyprogesterone: (a) Radscheit, K.; Stache, U.; Haede, W.; Fritsch, W.; Ruschig, H. *Tetrahedron Lett.* **1969**, 3029. (b) Stache, U.; Radscheit, K.; Fritsch, W.; Kohl, H.; Haede, W.; Ruschig, H. *Ibid.* **1969**, 3033. (c) Haede, W.; Fritsch, W.; Radscheit, K.; Stache, U.; Ruschig, H. *Justus Liebigs Ann. Chem.* **1970**, *741*, 92. (d) Stache, U.; Radscheit, K.; Fritsch, W.; Haede, W.; Kohl, H.; Ruschig, H. *Ibid.* **1971**, *750*, 149. (e) Kohl, H.; Fritsch, W.; Haede, W.; Radscheit, K.; Stache, U. S. African Patent 69 02 400, 1969 (*Chem. Abstr.* **1970**, *72*, 11729a).

(5) Synthesis of bufalin and resibufogenin from 14α-hydroxycortexolone: (a) Sondheimer, F.; McCrae, W.; Salmond, W. G. *J. Am. Chem. Soc.* **1969**, *91*, 1228. (b) Sondheimer, F.; Wife, R. L. *Tetrahedron Lett.* **1973**, 765.

(6) Synthesis of bufalin and resibufogenin: (a) Pettit, G. R.; Houghton, L. E.; Knight, J. C.; Bruschweiler, F. *J. Chem. Soc., Chem. Commun.* **1970**, 93. (b) Pettit, G. R.; Houghton, L. E.; Knight, J. C.; Bruschweiler, F. *J. Org. Chem.* **1970**, *35*, 2895.

(7) A synthesis of 3β-acetoxy-5α,14α-bufa-20,22-dienolide from 3β-acetoxy-5α-androstan-17-one: (a) Engel, C. R.; Bouchard, R.; de Krassny, A. F.; Ruest, L.; Lessard, J. *Steroids* **1969**, *14*, 637. (b) Engel, C. R.; Dionne, G. *Can. J. Chem.* **1978**, *56*, 424.

(8) Synthesis of bufalin and resibufogenin from 3β-hydroxy-5β-pregn-14-en-20-one acetate: Yoshii, E.; Oribe, T.; Koizumi, T.; Hayashi, I.; Tumura, K. *Chem. Pharm. Bull.* **1977**, *25*, 2249.

(9) Synthesis of 5β,14α-bufa-20,22-dienolide from cholic acid: Sarel, S.; Shalon, Y.; Yanuka, Y. *J. Chem. Soc., Chem. Commun.* **1970**, 80, 81. The quantitative yield reported for the 2,3-dichloro-5,6-dicyanoquinone-mediated dehydrogenation of the enol lactone to the α-pyrone has been questioned: see ref 8.

(10) For recent references, see (a) Corey, E. J.; Noyori, R. *Tetrahedron Lett.* **1970**, 311. (b) Corey, E. J.; Erickson, B. W.; Noyori, R. *J. Am. Chem. Soc.* **1971**, *93*, 1724. (c) Leroux, Y.; Mantione, R. *J. Organomet. Chem.* **1971**, *30*, 295. (d) Carlson, R. G.; Mardis, W. S. *J. Org. Chem.* **1975**, *40*, 817. (e) Cohen, T.; Bennett, D. A.; Mura, A. J., Jr. *Ibid.* **1976**, *41*, 2506. (f) Schmidt, R. R.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 171. (g) Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1977**, *99*, 263. (h) Wada, M.; Nakamura, H.; Taguchi, T.; Takei, H. *Chem. Lett.* **1977**, 345. (i) Martin, S. F.; Garrison, P. J. *Tetrahedron Lett.* **1977**, 3875. (j) Debal, A.; Cuvigny, T.; Larchêveque, M. *Ibid.* **1977**, 3187.

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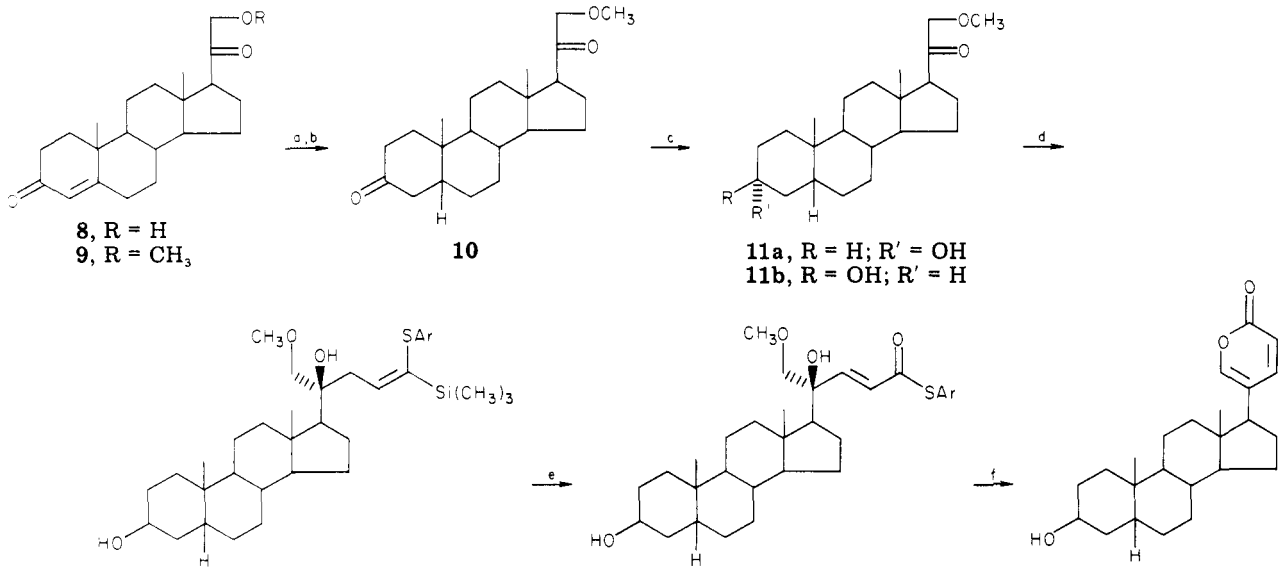
Scheme III [a]



[a] a, CH_3I, Ag_2O; b, H_2, Pd-C, Py; c, $IrCl_6$, $P(OCH_3)_3$, 90% aq i-C_3H_7OH; d, sec-C_4H_9Li, **12**; e, sec-C_4H_9Li followed by O_2; f, HBr, CH_3CN.

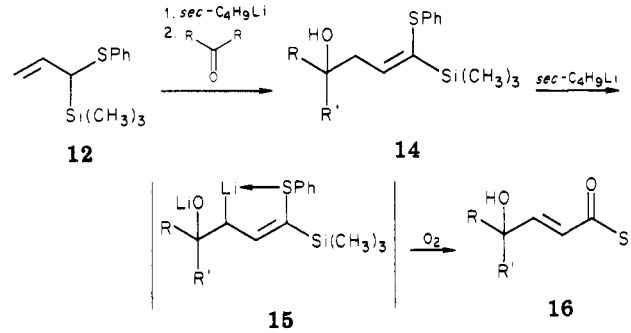
initial efforts to achieve these goals.

Discussion

A suitable pregnan-20-one to test this approach was prepared from deoxycorticosterone (**8**) in three steps[11] as shown in Scheme III. Conversion of the C-21 hydroxyl group in **8** to a methyl ether and stereoselective reduction of 21-methoxypregn-4-ene-3,20-dione[12] (**9**) using palladium on carbon in pyridine[13] furnished 21-methoxy-5β-pregnane-3,20-dione (**10**). The ^{13}C NMR spectrum of **10** displayed C-5 and C-19 at 44.9 and 22.6 ppm, respectively, and confirmed the 5β-stereochemical assignment.[14] Further stereo- and regioselective reduction[15,16] of the C-3 carbonyl group in **10** employed Henbest's iridium chloride–trimethyl phosphite procedure[15] to obtain the 3β- and 3α-alcohols **11b** and **11a** in a 91:9 ratio. The chromatographic separation of **11a** and **11b** proved difficult although the benzoate derivative of each isomer was readily separated and fully characterized. Evidence for the 3β stereochemistry in the major isomer **11b** was again obtained from the ^{13}C NMR spectrum that displayed C-1, C-3, and C-5 at 30.3, 67.3, and 36.9 ppm, respectively.[14] Typically, however, the mixture of diastereomers **11a** and **11b** were not separated but carried forward to the next stage in the synthesis where chromatography gave pure 3β-hydroxyl-containing material.

We then developed 1-(phenylthio)-1-(trimethylsilyl)-2-propene[17] (**12**) as the appropriate unsaturated homoenolate anion equivalent **6**. As shown in Scheme IV, the anion of this reagent **12** condensed with various ketones **13** to provide the adducts **14**. Application of this condensation reaction to various simple ketones as well as selected pregnan-20-ones gave the desired adducts **14** displayed in Table I. Subsequently, the dianions **15** derived from the adducts **14** were exposed to oxygen to afford the γ-hydroxy-α,β-unsaturated thiol esters **16**. As shown in Table I, this oxidative desilylation procedure converted a variety of adducts **14** to unsaturated thiol esters **16** in modest yield. Although the mechanism is unclear, we suspect that a radical–anion process is involved in which electrostatic considerations dictate the selective trapping of oxygen at C-24 rather than at C-22. The yields clearly varied with structure in a fairly unpredictable fashion, and the other major component in most oxidation reactions was unreacted starting material. The oxidation procedure was, as expected, compatible with hydroxyl groups, isolated double bonds and 1,3-dioxane protecting groups but not with tetrahydropyranyl ethers or 1,3-dioxolanes.[18]

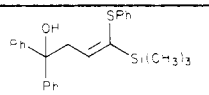
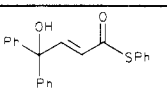
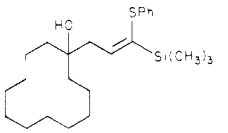
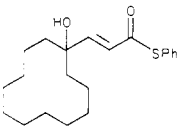
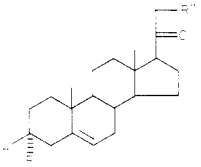
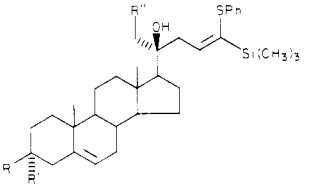
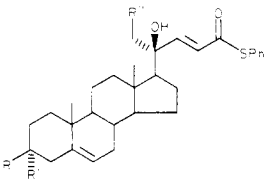
Scheme IV



As shown in Scheme III, application of this sequence to the bufadienolide precursor, 3β-hydroxy-21-methoxy-5β-pregnan-20-one (**11b**) initially furnished the adduct **17** in

(11) This regioselective route should be contrasted with a much longer route involving C-20 carbonyl protection: Bach, G.; Capitaine, J.; Engel, C. R. *Can. J. Chem.* **1968**, *46*, 733.
(12) Cole, W. G.; Williams, D. H. *J. Chem. Soc. C* 1968, 1849.
(13) Tsuji, N.; Suzuki, J.; Shiota, M.; Takahashi, I.; Nishimua, S. *J. Org. Chem.* **1980**, *45*, 2729.
(14) Blunt, J. W.; Stothers, J. B. *Org. Magn. Reson.* **1977**, *9*, 439.
(15) (a) Hadda, Y. M. Y.; Henbest, H. B.; Husbands, Mrs. J.; Mitchell, T. R. B. *Proc. Chem. Soc.* 1964, 361. (b) Browne, P. A.; Kirk, D. N. *J. Chem. Soc. C* **1969**, 1653. (c) Henbest, H. B.; Mitchell, T. R. B. *Ibid.* **1970**, 785. (d) Pettit, G. R.; Dias, J. R. *J. Org. Chem.* **1971**, *36*, 3207. (e) Valcavi, U.; Innocenti, S. *Farmaco, Ed. Sci.* **1974**, *29*, 194.
(16) For an alternate rhodium-catalyzed hydrogenation, see Nishimura, S. *Strem. Chem.* **1978**, *6*, 7.
(17) Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1981**, *46*, 5182.
(18) (a) Heathcock, C. H.; Ellis, J. E.; Badger, R. A. *J. Heterocycl. Chem.* **1969**, *6*, 139. (b) Mallory, R. A.; Rovinski, S.; Kohen, F.; Scheer, I. *J. Org. Chem.* **1967**, *32*, 1417 and references therein.

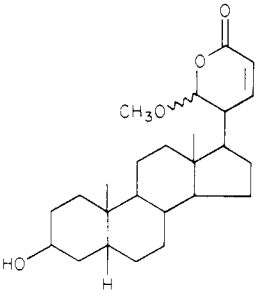
Table I. Addition of 1-(Phenylthio)-1-(trimethylsilyl)-2-propene (12) to Ketones 13 and Oxidative Desilylation of Adducts 14

ketone 13	adduct 14	isolated yield of 14, %	unsaturated thiol ester 16	isolated yield of 16, %
a, $C_6H_5COC_6H_5$		77 [a]		54
b, cyclododecanone		59 [a]		39
				
c, R = OTHP; R′ = R″ = H		57 [a]		74 [c]
d, R = OCH_3; R′ = R″ = H		69		51
e, R = R′ = $O(CH_2)_2O$; R″ = OCH_3		60		30
f, R = R′ = $O(CH_2)_3O$; R″ = OCH_3		*b*		34

[a] *J. Org. Chem.* **1981**, *46*, 5182. [b] The adduct **14f** was prepared by an acid-catalyzed exchange with use of **14e** and 1,3-propandiol. [c] The tetrahydropyranyl ether group in **14c** was lost during the oxidation to give **16c** where R = OH, R′ = H.

48% yield. The recovery of unreacted starting material **11b** raised the yield of **17** to 72%, and the recycling of this material routinely gave good overall yields of the adduct **17**. The oxygenation step, however, involved one additional complicating factor in that we needed to generate a *trianion* from the adduct **17**. Problems associated with balancing the insolubility of this trianion species or its ion aggregates at −78 °C against the instability of the allyllithium portion of the trianion at somewhat higher temperatures than −78 °C caused considerable difficulty. Ultimately, the metalation of **17** using *sec*-butyllithium in a 10% hexamethylphosphoramide–tetrahydrofuran solution containing 12-crown-4 at −78 °C and subsequent exposure of the trianion to oxygen gave a 39% yield of the thiol ester **19** in Scheme III. Again, recovered starting material raised the yield of **19** to 59%. Variation of the solvent, temperature, oxidizing agents such as oxodiperoxymolybdenum hexamethylphosphoramide pyridine[19] and other additives such as *N,N,N′,N′*-tetramethylethylenediamine proved futile. Similarly, variation of substrate structure such as the 2-(methoxyphenyl)thio analogue **18** afforded no improvement in the yield of the oxidation step.

The final step in the synthesis of 3β-hydroxy-5β,14α-bufa-20,22-dienolide (**21**) involved the cyclization[20] of the thiol ester **19**. Exposure of **19** to hydrobromic acid in refluxing acetonitrile converts **19** to **21** in 51% yield. Although the exact sequence of steps in this conversion is uncertain, the overall process involves the hydrolysis of the thiol ester group, dehydration of the C-20 hydroxyl,[21] isomerization of the C-22 double bond, lactonization, and loss of methanol to give the α-pyrone. The interruption of this reaction after a short time interval allowed the isolation of the carboxylic acid derived from **19** but none of the aldehyde **5**. The improved yield in the cyclization of **19** relative to the reported yields[4a,b,c,7b] for the cyclization of **5** suggests an alternate pathway possibly involving the acetal **22** as an intermediate.[22] The ^{13}C NMR data for

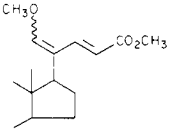


22

(19) Minoun, H.; Seree de Roch, L.; Sajus, L. *Bull. Soc. Chim. Fr.* **1969**, 1481.

(20) For examples of acid-catalyzed cyclizations leading to δ-lactones (including α-pyrones), see (a) Wiley, R. H.; Hart, A. J. *J. Am. Chem. Soc.* **1954**, *76*, 1942. (b) Kochetkov, N. K.; Kudryashov, L. J.; Gottich, B. P. *Tetrahedron* **1961**, *12*, 63. (c) Korte, F.; Scharf, D. *Chem. Ber.* **1962**, *95*, 443. (d) Fujita, T.; Watanabe, S.; Suga, K.; Kuramochi, T.; Tsukagoshi, F. *J. Chem. Tech. Biotechnol.* **1979**, *29*, 31.

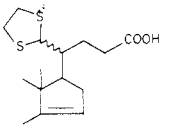
(21) Prior efforts to prepare the intermediate dienol ether i



i

by a Wittig reaction of methyl 20-oxo-21-norchol-22-en-24-oate with the ylide from (methoxymethyl)triphenylphosphonium chloride was unsuccessful: Pettit, G. R.; Green, B.; Dunn, G. L.; Sunder-Plassmann, P. *J. Org. Chem.* 1970, *35*, 1385.

(22) A 20(22)-saturated analogue of the hypothetical acetal intermediate in the cyclization was prepared by the mercuric chloride catalyzed methanolysis of the dithioacetal ii: ref 6b.



ii

Table II. Selected ^{13}C NMR Data[a,b]

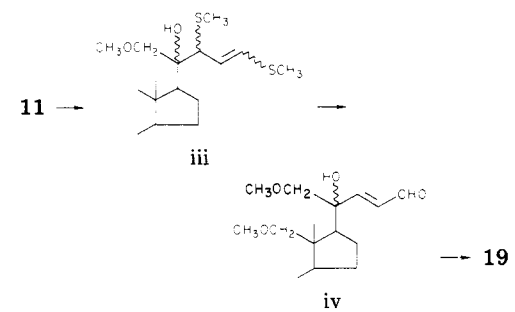
carbon	10	11b	11b (benzoate)	11a (benzoate)	17	18	19	20	21
C-1	37.1[a]	30.3	30.8	31.9	29.9	29.9	29.9	30.0	30.8
C-2	37.0[a]	28.3	25.2	24.5	27.8	27.8	27.8	27.9	25.0
C-3	212.8	67.3	71.2	70.6	67.1	67.1	67.1	67.1	70.6
C-4	42.3	33.9	31.1	33.2	33.5	33.5	33.5	33.6	30.6
C-5	44.9	36.9	37.6	35.9[a]	36.5	36.5	36.5	36.6	37.4
C-6	25.7[b]	26.7[a]	26.2[a]	26.3	26.1	26.1	26.2	26.2	26.2
C-7	26.5[b]	27.0[a]	26.5[a]	28.2	26.6	26.6	26.6	26.6	26.4
C-8	35.5	35.6	35.8	35.5[a]	35.1	35.1	35.1	35.1	35.0
C-9	40.7	40.1	40.0	40.4	39.9	39.9	39.8	40.2	37.9
C-10	34.9	36.1	35.0	32.9[a]	35.0	35.0	35.1	35.1	36.0
C-11	21.4	21.5	24.0	20.8	20.9	20.9	20.9	20.9	20.7
C-12	38.9	39.6	39.1	38.9	39.7	39.7	40.1	39.8	40.1
C-13	44.1	45.4	45.0	44.9	42.9	42.9	43.5	43.5	44.2
C-14	56.7	59.4	59.0	58.9[b]	56.8	56.7	56.5	56.5	51.2
C-15	24.5	24.3	24.6	54.2	23.9	23.9	23.9	23.9	23.8
C-16	22.9	23.2	22.9	22.8	23.6	23.6	23.9	23.9	24.2
C-17	59.2[c]	57.5	57.0	56.9[b]	55.4	55.5	55.7	56.0	55.8
C-18	13.6	14.1	13.7	11.4	13.7	13.6	14.5	14.4	12.9
C-19	22.6	25.0	21.2	13.7	22.3	22.3	22.8	22.8	25.3
C-20	208.0	208.7	208.3	208.2	76.6	76.6	77.7	77.7	118.5
C-21	78.7	79.1	78.7	78.7	76.9	76.5	77.9	78.0	148.6
C-22					34.8	39.5	148.4	147.9	145.4
C-23					135.7	134.8	129.3	131.5	115.4
C-24					148.3	149.0	188.0	187.4	162.2
OCH_3	58.8[c]	59.7	59.2	59.2[b]	59.0	59.0	59.4	59.4	
COC_6H_5			165.9	165.9					
$Si(CH_3)_3$					−1.0	−1.1			
$CH_3OC_6H_4$						55.8		55.8	
aromatic C-1			132.7	132.7	137.7	128.2	134.5	136.8	
aromatic C-2			129.5	129.5	128.1	156.3	127.7	159.4	
aromatic C-3			130.2	131.2	128.5	125.8	129.1	126.3	
aromatic C-4			128.3	128.3	125.1	110.3	126.2	111.6	
aromatic C-5						120.7		115.9	
aromatic C-6						125.9		121.1	

[a] a, b, c, assignments may be reversed. [b] The central $CDCl_3$ signal was set at δ 77.00.

compounds in this study appear in Table II.

In summary, we have developed 1-(phenylthio)-1-(trimethylsilyl)-2-propene (**12**) as an unsaturated homoenolate anion equivalent that generates a γ-hydroxy-α,β-unsaturated carbonyl compound at an oxidation level different than the oxidation level of other homoenolate anion equivalents.[23] The reagent was applied to an expeditious, six-step synthesis of 3β-hydroxy-5β,14α-bufa-20,22-dienolide that contrasts favorably with other somewhat longer syntheses of the α-pyrone ring in bufadienolides. We are presently investigating other reagents both to improve the efficiency of this process and to accommodate a C-14 double bond necessary for the synthesis of naturally occurring bufadienolides.

(23) Other unsaturated homoenolate anion equivalents such as Corey's 1,3-bis(methylthio)propene[10b] could, in principle, be used to prepare the unsaturated thiol ester as shown below. In order to compare this method with the oxidative desilylation method, we prepared the unsaturated aldehyde iv in 50% overall yield, which is comparable to the overall yield of thiol ester **19** in the oxidative desilylation procedure. Some difficulty was experienced in purifying the diastereomers iii and in oxidizing iv where C-20/C-21 bond cleavage occurred.



Experimental Section

Infrared spectra were determined on a Beckman Microlab 600 spectrometer. The abbreviation TF denotes thin film. NMR spectra were determined on a JEOL 270-MHz SC spectrometer. Mass spectra were determined on either a Varian MAT CH5 or a Du Pont CEC 21-10B mass spectrometer. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. GA.

General Condensation Procedure for the Preparation of Adducts 14. (3β,20*S*,23*Z*)-20-Hydroxy-3-methoxy-24-(phenylthio)-24-(trimethylsilyl)chola-5,23-diene (14d). The procedure of Kyler and Watt[17] was repeated with 330 mg (1.0 mmol) of pregnenolone methyl ether[25] (**13d**) and 287 mg (1.3 mmol) of 1-(phenylthio)-1-(trimethylsilyl)-2-propene (**12**) except that the anion of **12** was added to a solution of **13d** in anhydrous THF at 0 °C rather than at −78 °C to afford, after preparative-layer chromatography on Merck silica gel F254 in 1:3:5 ether–hexane–dichloromethane, 325 mg (59%) of **14d**: mp 116–117 °C; IR (KBr) 3476, 1578 cm^{-1}; NMR ($CDCl_3$) δ 0.12 (s, 9, $Si(CH_3)_3$), 0.93 (s, 3, C-18 angular CH_3), 1.07 (s, 3, C-19 angular CH_3), 1.39 (s, 3, C-21 CH_3), 3.43 (s, 3, OCH_3), 5.44 (m, 1, C-6 vinyl H), 6.78 (t, 1, J = 5 Hz, C-23 vinyl H), 7.1–7.5 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 534 ($M^+ - H_2O$, 2), 331 (7), 313 (4), 299 (8), 222 (100). Repetition of this experiment on a 10-mmol scale gave a 69% yield of **14d**.

Anal. Calcd for $C_{34}H_{52}O_2SSi$: C, 73.85; H, 9.48. Found: C, 73.92; H, 9.57.

Data for Adducts 14: 14a–c are described elsewhere.[17]

14e: mp 118–119.5 °C; IR (KBr) 3480, 1583 cm^{-1}; NMR ($CDCl_3$) δ 0.03 (s, 9, $Si(CH_3)_3$), 0.84 (s, 3, C-18 angular CH_3), 1.02 (s, 3, C-19 angular CH_3), 3.37 (s, 3, OCH_3), 3.32, 3.43 (AB q, J = 8.8

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Hz, 2, CH_2OCH_3), 3.95 (m, 4, OCH_2CH_2O), 5.37 (m, 1, C-6 vinylic H), 6.65 (t, 1, C-23 vinylic H), 7.08–7.48 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 610 (M^+, 0.2), 592 (5), 565 (4), 389 (100), 222 (20), 99 (20); exact mass spectrum calcd for $C_{36}H_{54}O_4SSi$ 610.3512, found 610.3506.

14f: mp 154.5–156 °C; IR (KBr) 3460, 1583 cm^{-1}; NMR ($CDCl_3$) δ 0.04 (s, 9, $Si(CH_3)_3$), 0.84 (s, 3, C-18 angular CH_3), 1.02 (s, 3, C-19 angular CH_3), 3.38 (s, 3, OCH_3), 3.32, 3.44 (AB q, J = 9.2 Hz, 2, CH_2OCH_3), 3.77–4.16 (m, 4, $OCH_2CH_2CH_2O$), 5.37 (m, 1, C-6 vinylic H), 6.65 (t, 1, C-23 vinylic H), 7.08–7.48 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 624 (M^+, 0.5), 606 (0.5), 579 (1), 403 (77), 222 (52), 113 (100); exact mass spectrum calcd for $C_{37}H_{56}O_4SSi$ 624.3668, found 624.3665.

Anal. Calcd for $C_{37}H_{56}O_4SSi$: C, 71.10; H, 9.15. Found: C, 71.40; H, 9.18.

General Oxidative Desilylation Procedure. *S*-Phenyl (3β,20*S*,22*E*)-20-Hydroxy-3-methoxychola-5,22-diene-24-thioate (16d). To 138 mg (0.25 mmol) of **14d** in 1.5 mL of anhydrous THF at −78 °C under a nitrogen atmosphere was added 0.56 mL of 1.08 M *sec*-butyllithium in cyclohexane followed by 0.15 mL of anhydrous hexamethylphosphoramide. The orange solution was stirred at −78 °C for 3 h and exposed to a slow oxygen stream for 30 min. The reaction was quenched with 1.0 mL of water, diluted with ether, washed with water, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on two 20 × 20 cm Merck silica gel F254 preparative-layer plates in 1:3:5 ether–hexane–dichloromethane to afford 62.5 mg (51%) of **16d**: mp 146–147 °C; IR (KBr) 3500, 1663, 1624 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (s, 3, C-18 angular CH_3), 0.99 (s, 3, C-19 angular CH_3), 1.39 (3, s, C-21 CH_3), 3.35 (s, 3, OCH_3), 6.38 (m, 1, C-6 vinyl H), 6.39 (d, 1, J = 15 Hz, C-23 vinyl H), 7.06 (d, 1, J = 15 Hz, C-22 vinyl H), 7.33–7.62 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 494 (M^+, 0.1), 385 (75), 353 (100), 255 (44), 159 (64), 145 (61), 125 (56), 119 (38); exact mass spectrum calcd for $C_{31}H_{42}O_3S$ 495.2855, found 494.2886.

Anal. Calcd for $C_{31}H_{42}O_3S$: C, 75.27; H, 8.56. Found: C, 75.30; H, 8.58.

Data for δ-Hydroxy-α,β-unsaturated Thiol Esters 16. 16a: mp 124–126 °C; IR (TF) 3473, 1682, 1671, 1625 cm^{-1}; NMR ($CDCl_3$) δ 2.59 (s, 1, OH), 6.47 (d, 1, J = 15 Hz, CH=C**H**CO), 6.9–7.5 (m, 16, aromatic H, C**H**=CHCO); mass spectrum (70 eV), *m/e* 237 (M^+ − SPh).

Anal. Calcd for $C_{22}H_{18}O_2S$: C, 76.28; H, 5.24. Found: C, 76.21; H, 5.24.

16b: mp 108–109 °C; IR (KBr) 3448, 1675, 1625 cm^{-1}; NMR ($CHCl_3$) δ 1.20–1.80 (m, 22, CH_2), 6.41, 7.04 (2 d, J = 15.2 Hz, 2, C-22 and C-23 vinylic H), 7.36–7.56 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 346 (8), 328 (6), 237 (100); exact mass spectrum calcd for $C_{21}H_{30}O_2S$ 346.1965, found 346.1938.

Anal. Calcd for $C_{21}H_{30}O_2S$: C, 72.78; H, 8.73. Found: C, 72.57; H, 8.81.

16c: mp 157.5–159.5 °C (recrystallized from ether–hexane); IR (KBr) 3480, 1670, 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.80, 0.97 (2 s, 6, C-18 and C-19 angular CH_3), 1.35 (s, 3, C-21 CH_3), 3.35–3.6 (m, 1, C-3α H), 5.28 (m, 1, C-6 vinylic H), 6.31, 6.99 (2 d, J = 16 Hz, 2, C-22 and C-23 vinylic H), 7.33 (s, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 371 (85, M^+ − SPh), 353 (83), 181 (82), 131 (100).

Anal. Calcd for $C_{30}H_{40}O_3S{\cdot}H_2O$: C, 72.26; H, 8.49. Found: C, 72.71; H, 8.49.

An elemental analysis was also obtained on the 3β-tetrahydropyranyl ether derivative of **16c**.

Anal. Calcd for $C_{35}H_{48}O_4S$: C, 74.43; H, 8.57. Found: C, 74.22; H, 8.61.

16e: mp 151.5–153.5 °C (recrystallized from hexane); IR (KBr) 3443, 1684 cm^{-1}; NMR ($CHCl_3$) δ 0.80 (s, 3, C-18 angular CH_3), 1.02 (s, 3, C-19 angular CH_3), 3.38 (s, 3, OCH_3), 3.29, 3.47 (AB q, J = 9.2 Hz, 2, CH_2OCH_3), 3.95 (m, 4, OCH_2CH_2O), 5.35 (m, 1, C-6 vinylic H), 6.47, 7.04 (2 d, J = 15.2 Hz, 2, C- 23 and C-24 vinylic H), 7.32–7.72 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 552 (M^+, 52), 443 (100), 399 (13), 345 (13); exact mass spectrum calcd for $C_{33}H_{44}O_5S$: 552.2909, found 552.2922.

16f: isolated as a foam that could not be induced to crystallize; IR (TF) 3442, 1683 cm^{-1}; NMR ($CHCl_3$) δ 0.80 (s, 3, C-18 angular CH_3), 1.02 (s, 3, C-19 angular CH_3), 3.38 (s, 3, OCH_3), 3.30, 3.48 (AB q, J = 8.6 Hz, 2, CH_2OCH_3), 3.76–4.16 (m, 4, $OCH_2CH_2CH_2O$), 5.37 (m, 1, C-6 vinylic H), 6.47, 7.04 (2 d, J = 15.8 Hz, 2, C-22 and C-23 vinylic H), 7.35–7.64 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 566 (M^+, 0.1), 457 (0.1), 402 (0.1), 149 (20), 133 (11), 119 (25), 113 (54); exact mass spectrum calcd for $C_{34}H_{46}O_5S$ 566.3065, found 566.3015.

21-Methoxy-5β-pregnane-3,20-dione (10). The procedure of Nishimura[13] was repeated, using 2.23 g of recrystallized 21-methoxyprogesterone[12] (**6**) and 290 mg of 10% palladium on carbon in 25 mL of anhydrous pyridine under 30 psi of hydrogen in a Parr shaker for 140 min (final pressure = 21 psi) to afford 1.86 g (83%) of **10**: mp 136–138 °C (recrystallized from acetone–hexane); IR (KBr) 1717, 1703 cm^{-1}; NMR ($CDCl_3$) δ 0.67 (s, 3, C-18 angular CH_3), 1.03 (s, 3, C-19 angular CH_3), 3.41 (s, 3, OCH_3), 4.01 (AB q, J = 17.1 Hz, 2, CH_2OCH_3); mass spectrum (70 eV), *m/e* (relative intensity) 346 (M^+, 4), 301 (100), 273 (18), 255 (56), 203 (12), 107 (14); exact mass spectrum calcd for $C_{22}H_{34}O_3$ 346.2490, found 346.2499.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.27; H, 9.91.

3β-Hydroxy-21-methoxy-5β-pregnan-20-one (11b). The procedure of Browne and Kirk[15b] was repeated, using 1.28 g (3.7 mmol) of **10**, 2.5 mL of distilled trimethyl phosphite and 122 mg of dihydrogen hexachloroiridate(IV) hexahydrate (Alfa) in 32 mL of 90% aqueous isopropyl alcohol under reflux for 93 h to afford, after MPLC chromatography on silica gel with 1:2 dichloromethane–ethyl acetate, 1.13 g (88%) of 90.5:9.5 ratio of 3α-hydroxy-21-methoxy-5β-pregnan-20-one (**11a**) and 3β-hydroxy-21-methoxy-5β-pregnan-20-one (**11b**). The predominant alcohol **11b** had the following: IR (KBr) 3340, 1699 cm^{-1}; NMR ($CDCl_3$) δ 0.63 (s, 3, C-18 angular CH_3), 0.96 (s, 3, C-19 angular CH_3), 3.41 (s, 3, OCH_3), 4.04 (AB q, J = 17.1 Hz, 2, CH_2OCH_3), 4.12 (m, 1, C-3α H); mass spectrum (70 eV), *m/e* (relative intensity) 348 (M^+, 1), 303 (24), 285 (3), 257 (20), 142 (10), 100 (100); exact mass spectrum calcd for $C_{22}H_{36}O_3$ 348.2664, found 348.2639.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.75; H, 10.40.

Complete separation of the epimeric alcohols was best effected by conversion to their benzoates (2.0 equiv of benzoyl chloride/anhydrous pyridine) and MPLC chromatography on silica gel with use of 1:3:5 ether–hexane–dichloromethane to afford an 8% yield of a noncrystallizable foam, 3α-hydroxy-21-methoxy-5β-pregnan-20-one benzoate: IR (TF) 1716 (br) cm^{-1}; NMR ($CDCl_3$) δ 0.65 (s, 3, C-18 angular CH_3), 0.84 (s, 3, C-19 angular CH_3), 3.41 (s, 3, OCH_3), 4.01 (AB q, J = 17.1 Hz, 2, CH_2OCH_3), 5.29 (m, 1, CHOBz), 7.4–8.2 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 452 (M^+, 1), 407 (100), 257 (71), 105 (34); exact mass spectrum calcd for $C_{29}H_{40}O_4$ 452.2987, found 452.2957.

Anal. Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 77.00; H, 8.93.

Chromatography also afforded a 76% yield of a more polar material, 3β-hydroxy-21-methoxy-5β-pregnan-20-one benzoate: mp 143–144 °C (recrystallized from dichloromethane–hexane); IR (KBr) 1710 (br) cm^{-1}; NMR ($CDCl_3$) δ 0.65 (s, 3, C-18 angular CH_3), 1.02 (s, 3, C-19 angular CH_3), 3.42 (s, 3, OCH_3), 4.01 (AB q, J = 17.1 Hz, 2, CH_2OCH_3), 5.37 (m, 1, CHOBz), 7.4–8.2 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 452 (M^+, 0.4), 407 (100), 257 (97), 105 (67).

Anal. Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 76.93; H, 8.93.

(3β,20*S*,23*Z*)-3,20-Dihydroxy-21-methoxy-24-(phenylthio)-24-(trimethylsilyl)-5β-chol-23-ene (17). To 577 mg (2.6 mmol, 1.3 equiv) of **12** in 4 mL of anhydrous THF under a nitrogen atmosphere was added 2.4 mL (2.6 mmol) of 1.08 M *sec*-butyllithium in cyclohexane followed by 0.2 mL of anhydrous HMPA. The solution was stirred for 4 h at −78 °C. To 348 mg (1 mmol) of **11** in 2 mL of anhydrous THF at 0 °C was added the anion solution dropwise via a syringe packed in dry ice. An immediate gelatinous precipitate was produced that was allowed to stand for 3 h at 0 °C. The reaction was quenched with water, diluted with ether, washed with water, and dried over anhydrous magnesium sulfate. The product was chromatographed on three 20 × 20 cm Merck silica gel F254 plates in 1:3:5 ether–hexane–dichloromethane to afford 275 mg (48%) of **17** isolated as a foam

that could not be induced to crystallize: IR (KBr) 3450, 1580 cm^{-1}; NMR ($CHCl_3$) δ 0.12 (s, 9, $Si(CH_3)_3$), 0.89 (s, 3, C-18 angular CH_3), 1.04 (s, 3, C-19 angular CH_3), 3.45 (s, 3, OCH_3), 4.20 (m, 1, C-3α H), 6.71 (t, 1, C-23 vinylic H), 7.1-7.5 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 552 ($M^+ - H_2O$, 0.5), 525 (2), 415 (1), 331 (34), 257 (34), 222 (100); exact mass spectrum calcd for $C_{34}H_{54}O_3SSi \cdot H_2O$ 552.3457, found 552.3486. The recovery of 115 mg of **11** raised the yield of **17** to 72%.

Anal. Calcd for $C_{34}H_{54}O_3SSi$: C, 71.52; H, 9.53. Found: C, 71.35; H, 9.56.

1-[(2-Methoxyphenyl)thio]-1-(trimethylsilyl)-2-propene. The procedure of Hurd and Greengard[26] was repeated using 10 g (71.4 mmol) of 2-methoxybenzenethiol, 8.64 g (71.4 mmol) of allyl bromide, and 1.64 g (71.4 mmol) of sodium in 50 mL of absolute ethanol to afford 10.3 g (80%) of 2-methoxyphenyl allyl sulfide: bp 79–83 °C (0.3 mm). The procedure of Kyler and Watt[17] was repeated with 5.0 g (27.8 mmol) of this sulfide, 25.5 mL (33.4 mmol, 1.2 equiv) of 1.31 M *sec*-butyllithium in cyclohexane, and 7.25 g (66.7 mmol, 2.4 equiv) of chlorotrimethylsilane to afford 3.61 g (51%) of 1-(2-methoxyphenyl)-1-(trimethylsilyl)-2-propene: bp 97–100.5 °C (0.15 mm): IR (TF) 2953, 1623, 1577 cm^{-1}; NMR ($CDCl_3$) δ 0.19 (s, 9, $Si(CH_3)_3$), 3.28 (d, *J* = 9.3 Hz, 1, $CHCH{=}CH_2$), 3.89 (s, 3, OCH_3), 4.87–5.10 (m, 2, $CHCH{=}CH_2$), 5.64–5.82 (m, 1, $CHCH{=}CH_2$), 6.76–7.29 (m, 4, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 252 (M^+, 14), 167 (14), 165 (14), 73 (100).

Anal. Calcd for $C_{13}H_{20}OSSi$: C, 61.85; H, 7.99. Found: C, 61.75; H, 8.03.

(3β,20*S*,23*Z*)-3,20-Dihydroxy-21-methoxy-24-[(2-methoxyphenyl)thio]-24-(trimethylsilyl)-5β-chol-23-ene (18). The procedure described for the preparation of **17** was repeated with 200 mg (0.575 mmol) of **11b** and 337 mg (1.49 mmol, 1.3 equiv) of 1-[(2-methoxyphenyl)thio]-1-(trimethylsilyl)-2-propene to afford, after chromatography on Merck silica gel F254 in 1:2 dichloromethane–ethyl acetate, 128 mg (37%) of **18**: mp 62–65 °C; IR (TF) 3441, 2924, 1577 cm^{-1}; NMR ($CDCl_3$) δ 0.06 (s, 9, $Si(CH_3)_3$), 0.81 (s, 3, C-18 angular CH_3), 0.96 (s, 3, C-19 angular CH_3), 2.48–2.79 (m, 2, C-22 CH_2), 3.36 (s, 3, CH_2OCH_3), 3.24–3.45 (m, 2, CH_2OCH_3), 3.90 (s, 3, aromatic OCH_3), 6.62–7.13 (m, 4, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 349 ($M^+ - C_{10}H_{19}OSSi$ from C-20, 22 bond cleavage, 20), 252 (100), 73 (42). The recovery of 101 mg of **11b** raised the yield of **18** to 75%.

Anal. Calcd for $C_{35}H_{56}O_4SSi$: C, 69.95; H, 9.39. Found: C, 69.78; H, 9.43.

***S*-Phenyl (3β,20*S*,22*E*)-3,20-Dihydroxy-21-methoxy-5β-chol-22-ene-24-thioate (19).** To 81.5 mg (0.143 mmol) of **18** and 50.4 mg (0.286 mmol, 2 equiv) of 12-crown-4 in 3 mL of anhydrous THF under a nitrogen atmosphere at −78 °C was added 0.48 mL (0.515 mmol, 1.2 equiv) of 1.08 M *sec*-butyllithium in cyclohexane. To this heterogeneous mixture was added 0.3 mL of anhydrous HMPA, and the mixture was stirred for 5 h at −78 °C. Oxygen gas was bubbled into the solution for 30 min, and the reaction was quenched with 1 mL of water. The product was diluted with ether, washed with water, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on a 20 × 20 cm Merck silica gel F254 plate in 1:10 ethyl acetate–dichloromethane to afford 29 mg (39%) of **19** as a foam that could not be induced to crystallize: IR (KBr) 3428, 1683, 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.76 (s, 3, C-18 angular CH_3), 0.95 (s, 3, C-19 angular CH_3), 3.37 (s, 3, OCH_3), 3.29, 3.47 (AB q, *J* = 9.2 Hz, 2, CH_2OCH_3), 4.10 (m, 1, C-3α H), 6.46 (d, *J* = 15.1 Hz, 1, C-23 H), 7.02 (d, *J* = 15.1 Hz, 1, C-22 H), 7.4–7.6 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 403 (M^+ − SPh, 20), 385 (86), 257 (44), 155 (100). The recovery of 27 mg of **18** raised the yield of **19** to 59%.

Anal. Calcd for $C_{31}H_{44}O_5S \cdot CH_3OH$: C, 70.56; H, 8.88. Found: C, 70.72; H, 8.76.

***S*-(2-Methoxyphenyl) (3β,20*S*,22*E*)-3,20-Dihydroxy-21-methoxy-5β-chol-22-ene-24-thioate (20).** The procedure described for the preparation of **19** was repeated with 32.3 mg (0.054 mmol) of **18** to afford 8.8 mg (30%) of **20**: IR (TF) 3558, 2928, 1675, 1628, 1582 cm^{-1}; NMR ($CDCl_3$) δ 0.77 (s, 3, C-18 angular CH_3), 0.96 (s, 3, C-19 angular CH_3), 3.36 (s, 3, CH_2OCH_3), 3.26–3.49 (m, 2, CH_2OCH_3), 3.85 (s, 3, aromatic OCH_3), 4.09 (m, 1, C-3α H), 6.47 (d, *J* = 16 Hz, 1, C-23 vinylic H), 6.95–7.44 (m, 5, aromatic and C-22 vinylic H); mass spectrum (70 eV), *m/e* (relative intensity) 468 (6), 394 (19), 236 (25), 159 (44), 144 (100).

Anal. Calcd for $C_{32}H_{45}O_2S$: C, 70.81; H, 8.54. Found: C, 70.57; H, 8.62.

3β-Hydroxy-5β,14α-bufa-20,22-dienolide (21). To 10.0 mg (0.0195 mmol) of **19** in 1 mL of acetonitrile was added 34 μL of 48% hydrobromic acid. The solution was refluxed for 2.5 h; an additional 34 μL of 48% hydrobromic acid was added; and the solution was refluxed an additional 9 h at which time TLC indicated that the starting material **19** was consumed. The product was diluted with ether, washed successively with aqueous sodium bicarbonate solution, water, and brine, and dried over anhydrous magnesium sulfate. The product was chromatographed on a 20 × 20 cm Merck silica gel F254 plate in 1:1 ethyl acetate–hexane to afford 3.8 mg (51%) of **21** as a gum that could not be induced to crystallize: IR (TF) 3413, 2923, 1718 cm^{-1}; NMR ($CDCl_3$) δ 0.53 (s, 3, C-18 angular CH_3), 0.97 (s, 3, C-19 angular CH_3), 6.28 (d, *J* = 9.2 Hz, 1, C-23 vinylic H). The C-21 and C-22 protons appear as a multiplet at δ 7.2–7.3 that is partially obscured by the $CHCl_3$ signal. NMR (Me_2SO-d_3) δ 0.47 (s, 3, C-18 angular CH_3), 0.90 (s, 3, C-19 angular CH_3), 3.88 (br s, 1, C-3α H), 6.28 (d, *J* = 9.9 Hz, 1, C-23 vinylic H), 7.51 (dd, $J_{22,23}$ = 9.3 Hz, $J_{21,22}$ = 2.6 Hz, C-22 vinylic H), 7.62 (br s, 1, C-21 vinylic H); mass spectrum (70 eV), *m/e* (relative intensity) 370 (M^+, 1), 352 (4), 298 (2), 215 (18), 107 (50); exact mass spectrum calcd for $C_{24}H_{34}O_3$ 370.2509, found 370.2510.

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Registry No. **8**, 64-85-7; **9**, 20380-14-7; **10**, 83862-48-0; **11a**, 83862-49-1; **11a** benzoate, 83862-50-4; **11b**, 83862-51-5; **11b** benzoate, 83862-52-6; **12**, 78905-13-2; **13d**, 511-26-2; **14a**, 83862-53-7; **14b**, 83862-54-8; **14c**, 79409-72-6; **14d**, 83862-55-9; **14e**, 83876-13-5; **14f**, 83862-56-0; **16a**, 83862-57-1; **16b**, 83862-58-2; **16c**, 83862-59-3; **16c**·THP, 83862-60-6; **16d**, 83862-61-7; **16e**, 83862-62-8; **16f**, 83862-63-9; **17**, 83862-64-0; **18**, 83876-14-6; **19**, 83862-65-1; **20**, 83897-12-5; **21**, 83862-66-2; 2-methoxybenzenethiol, 7217-59-6; allyl bromide, 106-95-6; 2-methoxyphenyl allyl sulfide, 38477-80-4; chlorotrimethylsilane, 75-77-4; 1-(2-methoxyphenyl)-1-(trimethylsilyl)-2-propene, 83862-67-3.

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