Partial Synthesis of (20*R*,22*R*)-20,22-Dihydroxycholesterol

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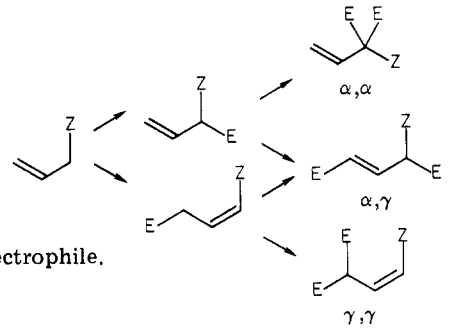
A new procedure for assembling the cholestane side chain from 20-oxopregnanes involved the sequential construction of the C-20,22 and C-24,25 bonds via the sequential α,γ-dialkylation of 1-(phenylthio)-1-(trimethylsilyl)-2-propene. A stereoselective, partial synthesis of (20*R*,22*R*)-20,22-dihydroxycholesterol served to test the validity of this approach.

In contrast to the extensive studies of the monoalkylation of unsymmetrically substituted allylic anions,[1] the sequential dialkylation of such species has attracted little attention. A priori, the dialkylation of an allylic anion could proceed with α,α-, γ,γ-, or α,γ-regioselectivity as illustrated in Scheme I. The latter possibility offered an attractive opportunity for elaborating substituted carbon chains in which different electrophilic partners are attached to either terminus of a three-carbon, binucleophilic reagent.

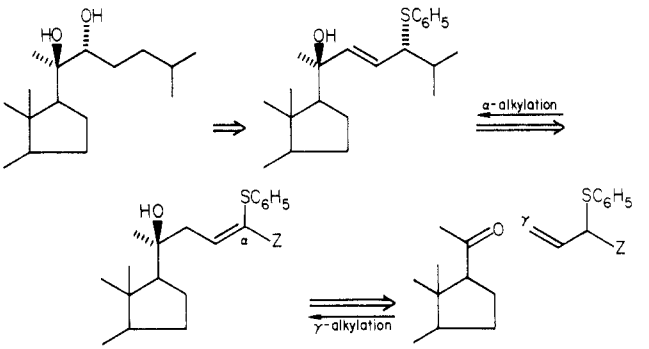
Scheme I[a]



[a] E = electrophile.

Such an approached appeared well-suited to the synthetic problem of assembling functionalized sterol side chains where the disconnection of the C-20,22 and C-24,25 bonds would result in readily available electrophilic partners. To demonstrate the value of such an approach, we investigated the synthesis of the cholestane side chain bearing the (20*R*,22*R*)-20,22-diol functionality. This particular sterol side chain represented a recurring structural element within a family of steroids including the insect ecdysones[2] the related phytoecdysones,[2,3] and cholesterol metabolites such as (20*R*,22*R*)-20,22-dihydroxycholesterol[4] (1). Our retroanalysis of this problem displayed in Scheme II required a sequential γ- and α-alkylation of a phenylthio-substituted allyllithium reagent as the key features of the proposed route.

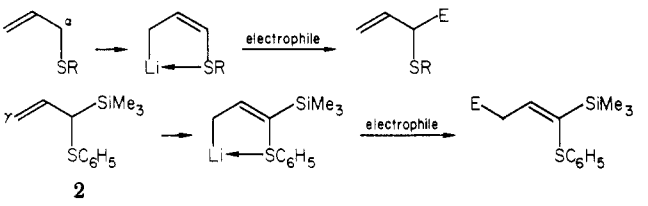
Scheme II



Discussion

Formation of the C-20,22 Bond. The initial objective in our approach required the coupling of a 20-oxo steroid and a phenylthio-substituted allyllithium reagent with γ regioselectivity and 20*S* stereoselectivity.[5] However, (arylthio)- or (alkylthio)allyllithium reagents intercept electrophiles with a high degree of α regioselectivity.[1b,c] To invert this selectivity, we examined the reactions of 1-(phenylthio)-1-(trimethylsilyl)-2-propene (**2**, Scheme III)

Scheme III



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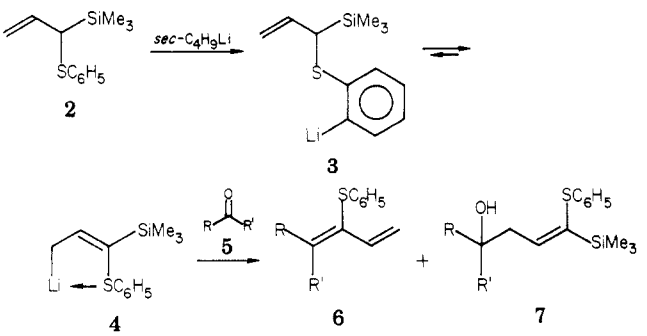
Scheme IV



2 **3**

4 **6** **7**

in which the steric influence of the trimethylsilyl group would direct alkylation to the γ site. An alternative method for achieving this same γ regioselectivity involves the use of thioacrolein dianion.[1a]

Metalation of 1-(phenylthio)-1-(trimethylsilyl)-2-propene (**2**) with *sec*-butyllithium in 5% hexamethylphosphor-

(1) (a) Geiss, K.; Seuring, B.; Pieter, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 479. (b) Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 7926. (c) Oshima, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1567. (d) Lansbury, P. T.; Britt, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 4577. (e) Still, W. C.; Macdonald, T. L. *Ibid.* **1974**, *96*, 5561. (f) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *Ibid.* **1974**, *96*, 5560. (g) Oppolzer, W.; Snowden, R. L. *Tetrahedron Lett.* **1976**, 4187. (h) Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Org. Chem.* **1978**, *43*, 2551. (i) Kuwajima, I.; Kato, M. *J. Chem. Soc.*, Chem. Commun. **1979**, 708. (j) Sturtz, G.; Corbel, B.; Paugam, J.-P. *Tetrahedron Lett.* **1976**, 47. (k) Evans, D. A.; Takacs, J. M.; Hurst, K. M. *J. Am. Chem. Soc.* **1979**, *101*, 371. (l) Jacobsen, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395. (m) Jacobsen, R. M.; Clader, J. W. *Tetrahedron Lett.* **1980**, 1205. (n) Ahlbrecht, H.; Eichler, J. *Synthesis* **1974**, 672. (o) Ahlbrecht, H.; Vonerheid, C. *Ibid.* **1975**, 512. (p) Seebach, D.; Renger, B. *Chem. Ber.* **1977**, 110, 2334. (q) Martin, S. F.; DuPriest, M. T. *Tetrahedron Lett.* **1977**, 3925. (r) Ayalon-Chass, D.; Ehlinger, E.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1977**, 772. (s) Kow, R.; Rathke, M. W. *J. Am. Chem. Soc.* **1973**, *95*, 2715. (t) Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570. (u) Wada, M.; Nakamura, H.; Taguchi, T.; Takei, H. *Chem. Lett.* **1977**, 345.

(2) Hikino, H.; Hikino, Y. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 256.

(3) Prakash, A.; Ghosal, S. *J. Sci. Ind. Res.* **1979**, *38*, 632.

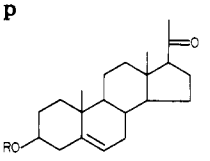
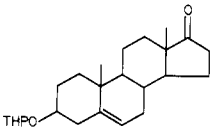
(4) Shimizu, K.; Gut, M.; Dorfman, R. I. *J. Biol. Chem.* **1962**, *237*, 699.

(5) The 20*S* designation for the stereochemistry of the initial adduct **7r** corresponds ultimately to the 20*R* designation for the correct stereochemistry in (20*R*,22*R*)-20,22-dihydroxycholesterol (1).

(6) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

0022-3263/81/1946-5182$01.25/0

Table I. Yields of γ-Adducts 7 from the Addition of 3-Lithio-1-(phenylthio)-1-(trimethylsilyl)-1-propene (4) to Carbonyl Compounds 5

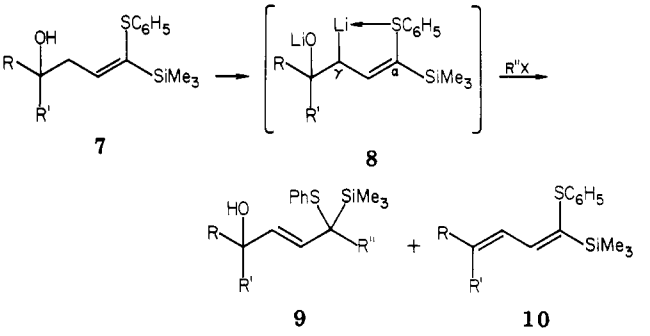
	R	R′	isolated yield of 7, %
5a	H	t-C_4H_9	62
b	H	c-C_6H_{11}	67
c	H	$CH_2CH(CH_3)CH_2CH_2CH=C(CH_3)_2$	50
d	H	C_6H_5	67
e	H	2-$CH_3OC_6H_4$	68
f	H	4-$CH_3OC_6H_4$	72
g	H	2-ClC_6H_4	65
h	H	4-$CH_3C_6H_4$	64
i	H	4-$(C_6H_5)C_6H_4$	57
j	H	$C_6H_5CH=CH$	45
k	H	α-naphthyl	66
l	CH_3	CH_3	78
m	$CH_2CH_2C_6H_5$	$CH_2CH_2C_6H_5$	65
n		$-(CH_2)_{11}-$	59[a]
o	C_2H_5	C_6H_5	62
p	C_6H_5	C_6H_5	77
 5q, R = t-Bu			56
r, R = THP			57
 5s			43[b]

[a] Normal mode of addition produces higher yields of γ-adducts than inverse addition for several cyclic ketones. [b] 17β-Hydroxyl isomer.

amide–tetrahydrofuran at −78 °C initially furnished the ortho-lithiated derivative[6] **3** which subsequently equilibrated in favor of the allylic anion **4** after 2.5 h as shown in Scheme IV. Model studies involving the condensation of **4** with *p*-anisaldehyde (**5f**) revealed that the inverse addition of the anion **4** to **5f** furnished the α adduct **6f** and the γ adduct **7f** in a 1:72 ratio. Deletion of hexamethylphosphoramide, the use of other ether solvents, the direct addition of **5f** to the anion **4**, or the addition of various chelating metal ions (CuI, $ZnCl_2$) decreased the γ/α ratio and reduced the product yields. As shown in Table I, addition of the anion **4** to various aldehydes and ketones **5** provided moderate yields of the desired γ adducts **7**. In the case of carbonyl compounds, the principal side reaction was deprotonation to generate the enolates of **5**. Of particular interest was the addition of **4** to pregnenolone tetrahydropyranyl ether (**5r**) to secure predominantly the 20*S*,23*Z* stereoisomer **7r**. The 20*R* epimer of **7r** was not detected. Spectral and chromatographic data indicated **7r** was a single stereoisomer and in accord with literature precedent, both the 20*S* stereochemistry[7] and 23*Z* stereochemistry[1e] seemed most likely. The former assumption was confirmed by the synthesis of **1**, and the latter assumption was consistent with literature values[8] for the chemical shift of similar vinyl protons.

Formation of the C-24,25 Bond. To complete the carbon skeleton of the cholestane nucleus, we next required a method for regioselectively attaching a three-carbon electrophile to the α-carbon of the adduct **7r**. As shown in Scheme V, we anticipated that the dimetalation of the adduct **7** would furnish the dianion **8** and that the steric

Scheme V

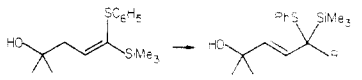
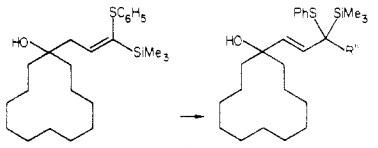
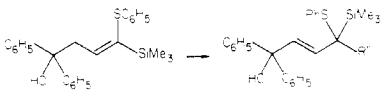
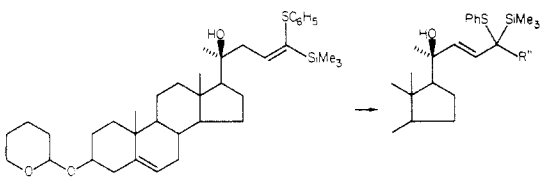


and/or electrostatic interactions involved in the reaction of a second electrophile at the γ site would direct attack to the α site of the dianion **8**. Although the alkylation of the dianion **8** with alkyl halides generated a remarkably encumbered sp^3 center at C-24, the reaction proceeded with exclusive α regioselectivity with a variety of primary and secondary alkyl halides to give the α,γ adducts **9**. The only observable byproduct in such alkylations was the diene **10** which presumably derived from sequential O-alkylation and elimination. In the case of the dianion **8r** derived from the γ adduct **7r**, the reaction with isopropyl iodide furnished the α,γ adduct **9g** with the desired regioselectivity and high but undetermined stereoselectivity at C-24. Judicious control of experimental conditions in the alkylation of the dianion **8r** with isopropyl iodide restricted the yield of the undesired diene **10r** to less than 15%. Extension of this alkylation procedure to a variety of systems provided a general route to similar α,γ adducts **9** as shown in Table II.

Partial Synthesis of (20*R*,22*R*)-20,22-Dihydroxycholesterol. Interest in the catabolism of cholesterol to pregnenolone led to the development of synthetic ap-

(7) For analogous stereochemical results from organometallic additions to 20-oxo steroids, see: Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199.
(8) (a) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1981**, 239. (b) Grobel, B.-T. Seebach, D. *Chem. Ber.* **1977**, *110*, 852.

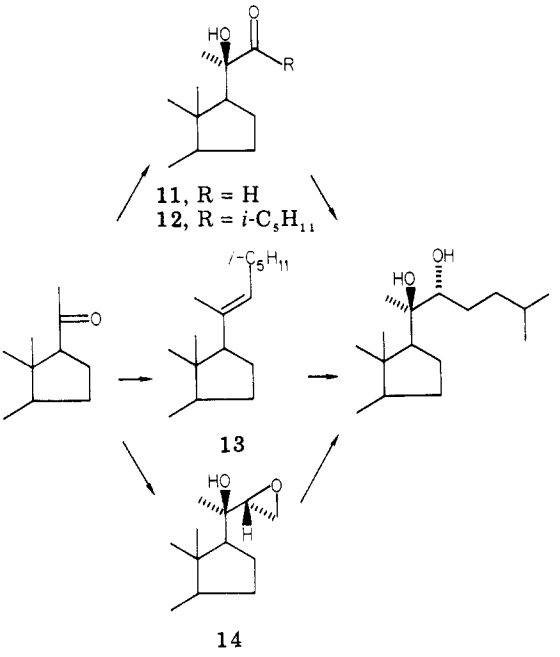
Table II. Alkylation of the Dianions 8 Derived from the Adducts 7 with Alkyl Halides R″X

adduct 7	alkyl halide	product 9	isolated yield, %
			
7l	*i*-Pr	9a, R″ = *i*-Pr	51
7l	$C_6H_5CH(CH_3)CH_2CH_2Br$	9b, R″ = $CH_2CH_2CH(CH_3)C_6H_5$	67
7l	cycloheptyl bromide	9c, R″ = c-C_7H_{13}	42
			
7n	$C_6H_5CH_2Br$	9d, R″ = $CH_2C_6H_5$	43
			
7p	c-$C_6H_{11}CH_2Br$	9e, R″ = CH_2-c-C_6H_{11}	73
7p	*trans*-cinnamyl bromide	9f, R″ = $CH_2CH{=}CHC_6H_5$	36
			
7r	*i*-PrI	9g, R″ = *i*-Pr	45
7r	cyclopentyl bromide	9h, R″ = c-C_5H_9	43
7r	*n*-hexyl bromide	9i, R″ = *n*-C_6H_{13}	45

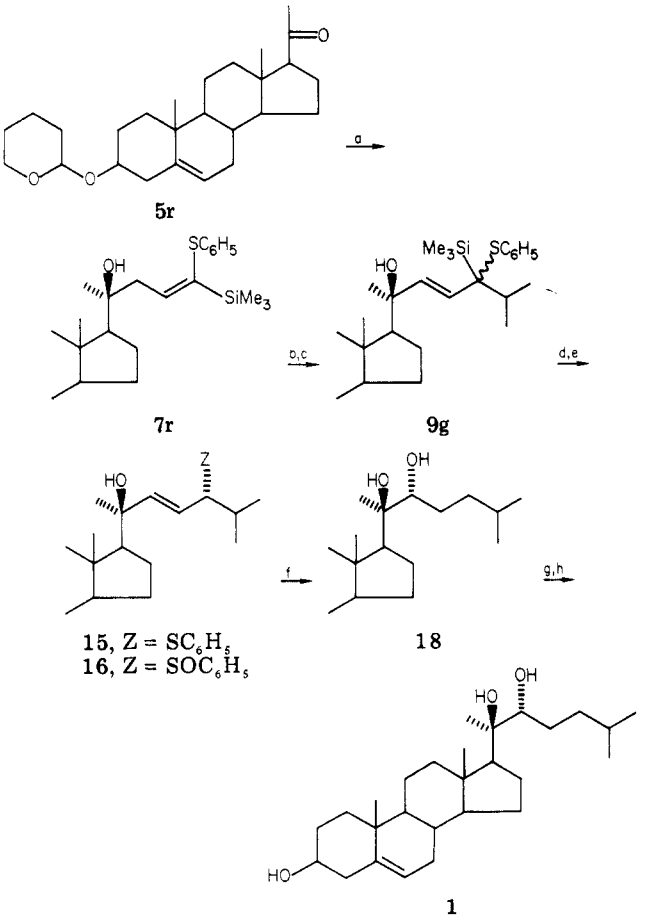
proaches to the four diastereomers of 20,22-dihydroxycholesterol of which the 20*R*,22*R* isomer was identified as the naturally occurring intermediate.[4] Concurrent interest in the synthesis of the side chain of ecdysones resulted in a stereoselective synthesis of the (20*R*,22*R*)-diol functionality.[9] This approach involved the addition of a Grignard reagent to a (20*S*)-20-hydroxy-20-carboxaldehyde **11** (Scheme VI) and was subsequently adapted for a stereoselective synthesis of (20*R*,22*R*)-20,22-dihydroxycholesterol[10] (**1**). Alternate approaches to **1** involving the reduction of the α-hydroxy ketone[4,10a,11] **12** or the hydroxylation of the *E* olefin[10b,12] **13** lacked stereoselectivity for the (20*R*,22*R*)-diol. Finally, the addition of lithium diisobutylcuprate to the epoxy alcohol[10c] **14** proved to be stereo- and regioselective, but the epoxy alcohol itself was unavailable by an efficient, stereoselective pathway.

After assembly of the carbon skeleton of cholesterol via the route shown in Scheme VII, it was necessary only to introduce the C-22 hydroxyl group and to adjust the oxidation level in the side chain in order to achieve a partial

Scheme VI



Scheme VII[a]



[a] (a) 4; (b) *sec*-C_4H_9Li, 5% HMPA-THF, −78 °C; (c) *i*-C_3H_7I; (d) KF, CH_3OH; (e) MCPBA; (f) heat, $P(OCH_3)_3$; (g) H_2, $Pd/CaCO_3$; (h) *p*-TsOH, CH_3OH.

synthesis of (20*R*,22*R*)-20,22-dihydroxycholesterol (**1**). We employed potassium fluoride in methanol in order to cleave the carbon–silicon bond in **9g** and to obtain the β,γ-unsaturated sulfide **15**. Oxidation of **15** with *m*-chloroperoxybenzoic acid furnished the sulfoxide **16** and a small amount of the α,β-unsaturated isomer **17**. The [2,3] sig-

(9) Huppi, G.; Siddall, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 6790.
(10) (a) Koreeda, M.; Koizumi, N.; Teicher, B. A. *Tetrahedron Lett.* **1976**, 4565. (b) Byon, C.; Gut, M. *J. Org. Chem.* **1976**, *41*, 3716. (c) Morisaki, M.; Sato, S.; Ikekawa, N. *Chem. Pharm. Bull.* **1977**, *25*, 2576.
(11) (a) Chaudhuri, N. K.; Nickolson, R.; Kimball, H.; Gut, M. *Steroids* **1970**, *15*, 525. (b) Koreeda, M.; Koizumi, N.; Teicher, B. A. *J. Chem. Soc., Chem. Commun.* **1976**, 1035.
(12) Bannai, K.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2116.

matropic rearrangement of **16** in the presence of trimethyl phosphite[13] or the isomerization–rearrangement of **17** in the presence of trimethyl phosphite and diethylamine afforded the unsaturated diol **18**. The selective generation of the 22*R*,23*E* stereoisomer of the unsaturated diol **18** required either the 24*S*,22*E* or 24*R*,22*Z* stereoisomer of the β,γ-unsaturated sulfoxide **16**. Since infrared[14] evidence suggested that **16** possessed 22*E* stereochemistry, we inferred that **16** also possessed the 24*S* stereochemistry shown in Scheme VII. Finally, selective hydrogenation[15] of the 23*E* double bond and methanolysis of the tetrahydropyranyl ether furnished (20*R*,22*R*)-20,22-dihydroxycholesterol (**1**).

In summary, we have developed a new procedure for assembling the cholestane side chain from a 20-oxopregnane which involves the sequential α,γ-dialkylation of 1-(phenylthio)-1-(trimethylsilyl)-2-propene (**2**). To test the viability of this approach, we completed a stereoselective, partial synthesis of (20*R*,22*R*)-20,22-dihydroxycholesterol (**1**). We are presently investigating the adaptation of this reagent **2** as a pivot on which to synthesize other complex sterol side chains.

Experimental Section

Infrared spectra were determined on a Beckman Microlab 600 spectrophotometer. The abbreviation TF denotes thin film. NMR spectra were determined on a Varian HA-100 or CFT-20 or on a Nicolet NT-360 spectrometer. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined by using a Thomas-Hoover Apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

1-(Phenylthio)-1-(trimethylsilyl)-2-propene (2). To 22.6 g (150 mmol) of 1-(phenylthio)-2-propene[16] in 112 mL of anhydrous THF under a nitrogen atmosphere at −78 °C was added 108 mL of *sec*-butyllithium in cyclohexane (1.40 M, 150 mmol). The solution was stirred for 3 h at −78 °C; 38 mL (300 mmol) of chlorotrimethylsilane was added rapidly over a 1 min period; and the mixture was stirred an additional 1.5 h at −78 °C. The reaction mixture was quenched by cautious addition of 200 mL of water, and the organic layer was separated. The aqueous layer was extracted with three 75-mL portions of ether. The combined organic phases were washed with two 100-mL portions of H_2O and dried over anhydrous magnesium sulfate. Evaporation of solvent afforded a pale yellow liquid which was fractionally distilled over a 5-h period to yield 22.0 g (66%) of **2**: bp 57–58 °C (0.13 mm); IR (TF) 3.25, 6.16, 6.32, 6.77, 8.01 μm (Si–CH); NMR ($CDCl_3$) δ 0.15 (s, 9, $Si(CH_3)_3$), 3.17 (d, J = 9.0 Hz, 1, allylic H), 4.76–4.95 (m, 3, vinylic H), 6.95–7.32 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 222 (M^+, 21), 207 (17), 113 (15), 73 (100). Anal. ($C_{12}H_{18}SSi$) C, H. A higher boiling fraction than fraction containing 5 furnished 4.98 g (15%) of 1-(phenylthio)-3-(trimethylsilyl)-1-propene: bp 76–77 °C (0.13 mm); IR (TF) 3.24, 6.31, 6.77, 8.01 (Si–CH), 10.47 μm; NMR ($CDCl_3$) δ 0.17 (s, 9, $Si(CH_3)_3$), 1.67 (m, 2, allylic H), 5.63–6.18 (m, 2, vinylic H), 6.93–7.30 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 222 (M^+, 33), 207 (14), 149 (38), 113 (6), 73 (100). Anal. ($C_{12}H_{18}SSi$) C, H.

General Procedure for the Reaction of 1-(Phenylthio)-1-(trimethylsilyl)-2-propene (2) with Aldehydes and Ketones. 4-Hydroxy-4-(4-methoxyphenyl)-1-(phenylthio)-1-(trimethylsilyl)-1-butene (7f). To 289 mg (1.3 mmol) of **2** in 2.0 mL of anhydrous THF under a nitrogen atmosphere at −78 °C was added 0.93 mL of *sec*-butyllithium in cyclohexane (1.40 M, 1.3 mmol) followed by 0.1 mL of anhydrous hexamethylphosphoramide. After being stirred for 2.5 h at −78 °C, the yellow solution was transferred via a syringe in a dry ice-filled jacket to a solution of 136 mg (1.0 mmol) of *p*-anisaldehyde (**5f**) in 0.5 mL of anhydrous THF at −78 °C and stirred 3.0 h at −78 °C. The mixture was quenched at −78 °C with 1.0 mL of water, diluted with 50 mL of ether, washed successively with 50 mL of 1 M aqueous hydrochloric acid, 50 mL of water, and 50 mL of brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded a pale yellow oil which was chromatographed on two 20 × 20 cm Merck silica gel F254 preparative layer plates in dichloromethane.

A band (R_f 0.31) was eluted to afford 258 mg (72%) of **7f**: IR (TF) 2.92, 6.20, 6.73, 7.97 μm (Si–CH); NMR ($CDCl_3$) δ 0.14 (s, 9, $Si(CH_3)_3$), 2.64 (s, 1, OH), 2.94 (t, J = 7 Hz, 2, allylic H), 3.78 (s, 3, OCH_3), 4.79 (t, J = 7 Hz, 1, CHOH), 6.68 (t, J = 7 Hz, 1, vinylic H), 6.84–7.29 (m, 9, aromatic H): mass spectrum (70 eV), m/e (relative intensity) 358 (M^+, 3.6), 340 (2), 222 (48), 137 (100), 94 (11), 91 (7). Anal. ($C_{20}H_{26}O_2SSi$) C, H.

A band (R_f 0.80) was eluted to afford 3.1 mg (1%) of **6f** as a mixture of *E*/*Z* isomers: IR (TF) 6.25, 6.33, 6.64 μm; NMR ($CDCl_3$) δ 3.63 and 3.66 (2 s, 3, OCH_3 of *E*/*Z* isomers), 4.95–5.85 (m, 2, vinylic H), 6.24–7.75 (m, 10, aromatic and vinylic H); mass spectrum (70 eV), m/e (relative intensity) 268 (M^+, 100), 159 (74), 144 (42), 115 (74). Anal. ($C_{17}H_{16}OS$) C, H.

Spectral Data for γ Adducts 7. 7a: IR (TF) 2.87, 6.32, 6.78, 7.97 μm (Si–CH); NMR ($CDCl_3$) δ 0.11 (s, 9, $Si(CH_3)_3$), 0.91 (s, 9, $C(CH_3)_3$), 1.72 (s, 1, OH), 2.61 (m, 2, allylic H), 3.32 (d, J = 10 Hz, 1, CHOH), 6.76 (t, J = 7 Hz, 1, vinylic H), 7.11–7.32 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 308 (M^+, 22), 222 (63), 167 (48), 151 (15), 74 (100). Anal. ($C_{17}H_{28}OSSi$) C, H.

7b: IR (TF), 2.94, 6.32, 6.77, 8.02 μm (Si–CH); NMR ($CDCl_3$) δ 0.11 (s, 9, $Si(CH_3)_3$), 0.9–1.95 (br m, 12, CH, CH_2, and OH), 2.61 (m, 2, allylic H), 3.49 (m, 1, CHOH), 6.71 (t, J = 7 Hz, 1, vinylic H), 7.06–7.20 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 334 (M^+, 11), 222 (51), 167 (33), 91 (19), 69 (100). Anal. ($C_{19}H_{30}OSSi$), C, H.

7c: IR (TF) 2.90, 6.32, 6.78, 8.02 μm (Si–CH); NMR ($CDCl_3$) δ 0.09 (s, 9, $Si(CH_3)_3$), 0.94 (d, J = 6Hz, 3, $CHCH_3$), 1.66 (d, J = 8 Hz, 6, vinylic CH_3), 2.60 (t, J = 7 Hz, 2, $CH_2CH{=}C(SPh)$), 3.86 (m, 1, CHOH), 5.08 (m, 1, $CH{=}C(CH_3)_2$), 6.69 (t, J = 7 Hz, $CH{=}C(SPh)$), and 6.99–7.38 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 376 (M^+, 11), 222 (54), 167 (40), 155 (38), 73 (100). Anal. ($C_{22}H_{36}OSSi$) C, H.

7d: IR (TF) 2.95, 6.31, 6.78, 8.00 μm (Si–CH); NMR ($CDCl_3$) δ 0.12 (s, 9, $Si(CH_3)_3$), 2.52 (s, 1, OH), 2.95 (t, J = 7 Hz, 2, allylic H), 4.80 (t, J = 7 Hz 1, CHOH), 6.68 (t, J = 7 Hz, 1, vinylic H), 7.13 (s, 5, aromatic H), 7.29 (s, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 328 (M^+, 6), 222 (55), 167 (27), 151 (15), 107 (22), 73 (100). Anal. ($C_{19}H_{24}OSSi$) C, H.

7e: IR (TF) 2.93, 6.29, 6.69, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.13 (s, 9, $Si(CH_3)_3$), 2.90 (s, 1, OH), 3.02 (t, J = 7 Hz, 2, allylic H), 3.76 (s, 3 OCH_3), 5.06 (t, J = 7 Hz, 1, CHOH), 6.68–7.43 (m, 10, vinylic and aromatic H); mass spectrum (70 eV), m/e (relative intensity) 358 (M^+, 3), 340 (3), 222 (29), 167 (9), 137 (100), 73 (46). Anal. ($C_{20}H_{26}O_2SSi$) C, H.

7g: IR (TF) 2.92, 6.32, 6.78, 8.02 μm (Si–CH); NMR ($CDCl_3$) δ 0.24 (s, 9, $Si(CH_3)_3$), 2.49 (s, 1, OH), 2.99 (t, J = 7 Hz, 2, allylic H), 5.41 (t, J = 7 Hz, 1, CHOH), 6.81 (t, J = 7 Hz, 1, vinylic H), 7.16–7.79 (m, 9, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 364 (M^+ + 2, 2.3), 362 (M^+, 7.0), 222 (30), 151 (18), 141 (15), 73 (100). Anal. ($C_{19}H_{23}ClOSSi$) C, H.

7h: IR (TF) 2.96, 6.32, 6.78, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.20 (s, 9, $Si(CH_3)_3$), 2.28 (s, 1, OH), 2.46 (s, 3, aromatic CH_3), 3.00 (t, J = 7 Hz, 2, allylic H), 4.88 (t, J = 7 Hz, 1, CHOH), 6.75 (t, J = 7 Hz, vinylic H), 7.12–7.63 (m, 9, aromatic H); mass

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spectrum (70 eV), m/e (relative intensity) 342 (M^+, 4), 222 (87), 167 (35), 121 (68), 73 (100). Anal. ($C_{20}H_{26}OSSi$) C, H.

7i: IR (TF) 2.97, 6.32, 6.74, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.21 (s, 9, $Si(CH_3)_3$), 2.53 (s, 1, OH), 3.05 (t, J = 7 Hz, 2, allylic H), 4.95 (t, J = 7 Hz, CHOH), 6.76 (t, J = 7 Hz, 2, vinylic H), 7.16–8.01 (m, 14, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 404 (M^+, 3), 222 (85), 183 (61), 167 (35), 73 (100). Anal. ($C_{25}H_{28}OSSi$) C, H.

7j: IR (TF) 2.96, 5.97, 6.29, 6.75, 7.97 μm (Si–CH); NMR ($CDCl_3$) δ 0.15 (s, 9, $Si(CH_3)_3$), 1.98 (s, 1, OH), 2.83 (t, J = 6 Hz, 2, allylic H), 4.45 (q, J = 6 Hz, 1, CHOH), 6.07–6.77 (m, 3, vinylic H), 7.05–7.40 (m, 10, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 354 (M^+, 7), 336 (3), 222 (26), 167 (22), 151 (19), 133 (35), 115 (15), 73 (100). Anal. ($C_{21}H_{26}OSSi$) C, H.

7k: IR (TF) 2.97, 6.32, 6.74, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.25 (s, 9, $Si(CH_3)_3$), 2.65 (s, 1, OH), 3.10 (t, J = 7 Hz, 2, allylic H), 5.69 (t, J = 7 Hz, 1, CHOH), 6.80 (t, J = 7 Hz, 1, vinylic H), 7.22–7.80 (m, 12, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 378 (M^+, 5), 360 (3), 222 (77), 183 (68), 167 (58), 73 (100). Anal. ($C_{23}H_{26}OSSi$) C, H.

7l: mp 55–56 °C; IR (KBr) 2.93, 6.32, 6.77, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.12 (s, 9, $Si(CH_3)_3$), 1.26 (s, 6, $CH_2C(OH)(CH_3)_2$), 1.92 (s, 1, OH), 2.65 (d, J = 7 Hz, 2, allylic H), 6.73 (t, J = 7 Hz, vinylic H), 7.17 (s, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 280 (M^+, 11), 222 (43), 167 (39), 151 (17), 75 (24), 73 (100). Anal. ($C_{15}H_{24}OSSi$) C, H.

7m: IR (TF) 2.91, 6.25, 6.32, 6.72, 6.78, 8.02 μm (Si–CH); NMR ($CDCl_3$) δ 0.32 (s, 9, $Si(CH_3)_3$, 1.79 (s, 1, OH), 1.92–2.17 (m, 4, CH_2CH_2Ph), 2.77–3.07 (m, 4, benzylic H), 2.94 (d, J = 7 Hz, 2, allylic H), 6.94 (t, J = 7 Hz, 1, vinylic H), 7.24–7.57 (m, 15, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 460 (M^+, 2), 443 (4), 239 (19), 222 (65), 167 (12), 91 (15), 73 (100). Anal. ($C_{29}H_{36}OSSi$) C, H.

7n: IR (TF) 3.04, 6.32, 6.80, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.17 (s, 9, $Si(CH_3)_3$), 1.40 (br s, 23, CH_2, OH), 2.61 (d, J = 7 Hz, 2, allylic H), 6.85 (t, J = 7 Hz, 1, vinylic H), 7.22 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 404 (M^+, 6), 222 (100), 183 (55), 167 (50), 73 (99). Anal. ($C_{24}H_{40}OSSi$) C, H.

7o: IR (TF) 2.88, 6.32, 6.78, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.10 (s, 9, $Si(CH_3)_3$), 1.01 (t, J = 7.5 Hz, 3, CH_2CH_3), 2.05 (q J = 7.5 Hz, 2, CH_2CH_3), 2.09 (s, 1, OH), 3.07 (d, J = 7 Hz, 2, allylic H), 6.60 (t, J = 7 Hz, 1, vinylic H), 7.10–7.55 (m, 10, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 356 (M^+, 3), 339 (3), 222 (99), 167 (44), 135 (100), 73 (92). Anal. ($C_{21}H_{28}OSSi$) C, H.

7p: IR (TF) 2.90, 6.29, 6.76, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.16 (s, 9, $Si(CH_3)_3$), 2.54 (s, 1, OH), 3.61 (d, J = 7 Hz, 2, allylic H), 6.72 (t, J = 7 Hz, 1, vinylic H), 7.16–7.63 (m, 15, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 404 (M^+, 1), 387 (5), 222 (46), 183 (100), 105 (55), 73 (38). Anal. ($C_{25}H_{28}OSi$) C, H.

7q: mp 156.5–157 °C; IR (KBr) 2.89, 6.09, 6.32, 6.78, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.12 (s, 9, $Si(CH_3)_3$), 0.82 and 1.05 (2 s, 6, C-18 and C-19 CH_3), 1.17 (s, 9, $C(CH_3)_3$), 1.30 (s, 3, C-21 CH_3), 2.55 (d, J = 7 Hz, C-22 CH_2), 5.20–5.30 (m, 1, C-6 vinylic H), 6.64 (t, J = 7 Hz, 1, C-23 vinylic H), 7.07–7.22 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 594 (M^+, 1), 576 (2), 355 (12), 310 (33), 222 (100), 73 (41). Anal. ($C_{37}H_{58}O_2SSi$) C, H.

7r: mp 174–174.5 °C; IR (KBr) 2.88, 6.10, 6.29, 6.79, 8.03 μm (Si–CH); NMR ($CDCl_3$) δ 0.14 (s, 9, $Si(CH_3)_3$), 0.81 and 1.07 (2 s, 6, C-18 and C-19 CH_3), 1.36 (s, 3, C-21 CH_3), 2.62 (m, 2, C-22 CH_2), 4.73 (m, 1, H-2′ in THP), 5.38 (m, 1, C-6 vinylic H), 6.71 (t, J = 7 Hz, 1, C-23 vinylic H), 7.14–7.34 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 622 (M^+, 0.5), 604 (1), 401 (22), 300 (15), 222 (100), 85 (78), 73 (39). Anal. ($C_{38}H_{58}O_3SSi$) C, H.

7s: mp 152.5–153.5 °C; IR (KBr) 2.93, 5.97, 6.33, 6.80, 8.04 μm (Si–CH); NMR ($CDCl_3$) δ 0.12 (s, 9, $Si(CH_3)_3$), 0.89 and 1.04 (2 s, 6, C-18 and C-19 CH_3), 2.70 (d, J = 7 Hz, 2, C-20 CH_2), 4.69 (m, 1, H-2′ in THP), 5.30 (m, 1, C-6 vinylic H), 6.82 (t, J = 7 Hz, C-21 vinylic H), 7.04–7.20 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 594 (M^+, 1), 576 (1), 373 (27), 222 (100), 85 (63), 73 (41). Anal. ($C_{36}H_{54}O_3SSi$) C, H.

General Procedure for the Reaction of Dianions (8) with Alkyl Halides. (3β,20*S*,22*E*)-24ξ-(Phenylthio)-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-24ξ-(trimethylsilyl)cholesta-5,22-dien-20-ol (9g). To 311 mg (0.5 mmol) of **7r** in 4.0 mL of anhydrous THF at −78 °C under a nitrogen atmosphere was added 0.88 mL of *sec*-butyllithium in cyclohexane (1.25 M, 1.1 mmol) followed by 1.2 mL of anhydrous hexamethylphosphoramide. After the mixture was stirred 2.5 h at −78 °C, 170 mg (1.0 mmol) of 2-iodopropane was added, and the solution was stirred an additional 3 h at −78 °C and 1.5 h at 25 °C. The mixture was quenched with 1 mL water, diluted with 50 mL ether, washed successively with 50 mL of 1 M aqueous hydrochloric acid, 50 mL of water, and 50 mL of brine, and dried over anhydrous magnesium sulfate. Evaporation of solvent afforded a colorless oil which was chromatographed on two 20 × 20 Merck silica gel F254 preparative layer plates in 1:3:5 ether–hexane–dichloromethane. A band (R_f 0.60) was eluted to give 150 mg (45%) of **9g** as a white powder: mp 71–73 °C; IR (KBr) 2.86, 5.81, 6.29, 6.78, 8.03 (Si–CH), 10.28 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.21 (s, 9, $Si(CH_3)_3$), 0.83 and 1.01 (2 s, 6, C-18 and C-19 CH_3), 1.12 (d, 6, J = 7 Hz, C-26 and C-27 CH_3), 1.31 (s, 3, C-21 CH_3), 4.70 (m, 1, H-2′ in THP), 5.22–5.69 (m, 3, C-22, 23 vinylic H, J = 16 Hz, and C-6 vinyl H), 7.01–7.58 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 664 (M^+, 3), 646 (1), 573 (100), 299 (65), 263 (27). Anal. ($C_{41}H_{64}O_3SSi$) C, H. A second band (R_f 0.81) was eluted to give 49 mg (15%) of **10r**: mp 51–52 °C; IR (KBr) 6.08, 6.31, 6.78, 9.71 μm; NMR ($CDCl_3$) 0.60 and 1.01 (2 s, 6, C-18 and C-19 CH_3), 1.10 (d, 6, J = 7.5 Hz, C-26 and C-27 CH_3), 1.62 (s, 3, C-21 CH_3), 4.66 (m, 1, H-2′ in THP), 5.31 (m, 1, C-6 vinylic H), 6.10 and 6.31 (2 d, 2, J = 10 Hz, C-22 and C-23 vinylic H), 7.06–7.47 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 574 (M^+, 2), 489 (1), 243 (25), 218 (31), 135 (100). Anal. ($C_{38}H_{54}O_2S$) C, H.

Spectral Data for α,γ-Alkylated Adducts 9. 9a: IR (TF) 2.93, 6.11, 6.33, 6.79, 8.02 (Si–CH), 10.42 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.12 (s, 9, $Si(CH_3)_3$), 0.96 and 1.07 (2 d, 6, J = 7 Hz, $CH(CH_3)_2$), 1.10 (s, 6, $C(OH)(CH_3)_2$), 1.38 (s, 1, OH), 2.19 (m, 1, $CH(CH_3)_2$), 5.30 and 5.55 (2 d, J = 16 Hz, 2, vinylic H), 7.02–7.44 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 322 (M^+, 10), 307 (47), 247 (63), 232 (86), 155 (29), 123 (50), 73 (100). Anal. ($C_{18}H_{30}OSSi$) C, H.

9b: IR (TF) 2.92, 6.11, 6.28, 6.32, 6.71, 6.80, 8.01 (Si–CH), 10.49 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.28 (s, 9, $Si(CH_3)_3$), 1.22 (s, 6, $C(OH)(CH_3)_2$), 1.40 (d, 3, J = 7 Hz, $CH(CH_3)Ph$), 1.5–2.52 (m, 5, CH_2CH_2 and OH), 2.73 (m, 1, benzylic H), 5.16 and 5.80 (2 d, J = 16 Hz, 2, vinylic H), 7.09–7.39 (m, 10, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 412 (M^+, 16), 379 (11), 321 (58), 204 (58), 95 (26), 73 (100). Anal. ($C_{25}H_{36}OSSi$) C, H.

9c: IR (TF) 2.91, 6.13, 6.33, 6.85, 8.02 μm (Si–CH); NMR ($CDCl_3$) δ 0.24 (s, 9, $Si(CH_3)_3$), 1.21 (s, 6, $C(OH)(CH_3)_2$), 1.22–2.22 (br m, 14, CH, CH_2, OH), 6.23 and 6.70 (2 d, J = 16 Hz, 2, vinylic H), 7.10–7.60 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 376 (M^+, 5), 358 (9), 285 (31), 209 (32), 177 (26), 95 (55), 73 (100). Anal. ($C_{22}H_{36}OSSi$) C, H.

9d: IR (TF) 2.89, 6.12, 6.27, 6.34, 6.70, 6.80, 8.03 (Si–CH), 10.53 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.09 (s, 9, $Si(CH_3)_3$), 1.40 (br s, 22, CH_2) 3.16 (m, 2, benzylic H), 3.46 (s, 1, OH), 5.52 and 5.90 (2 d, J = 16 Hz, 2, vinylic H), 7.13–7.71 (m, 10, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 494 (M^+, 1), 476 (1), 404 (43), 314 (15), 222 (73), 167 (30), 73 (100). Anal. ($C_{31}H_{46}OSSi$) C, H.

9e: IR (TF) 2.90, 6.13, 6.26, 6.33, 6.72, 6.78, 8.02 (Si–CH), 10.36 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.26 (s, 9, $Si(CH_3)_3$), 0.96–2.26 (br m, 13, CH and CH_2), 2.21 (s, 1, OH), 5.75 and 6.01 (2 d, J = 16 Hz, 2 vinylic H), 7.13–7.54 (m, 15, aromatic H); mass spectrum (70 eV) m/e (relative intensity) 500 (M^+, 1), 482 (1), 409 (100), 183 (64), 73 (89). Anal. ($C_{32}H_{40}OSSi$) C, H.

9f: IR (TF) 2.89, 6.12, 6.27, 6.35, 6.71, 6.78, 8.02 (Si–CH), 10.34 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.22 (s, 9, $Si(CH_3)_3$), 1.13 (s, 1, OH), 2.66 (m, 2, allylic H), 5.54–6.65 (m, 4, vinylic H), 6.95–7.53 (m, 20, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 520 (M^+, 2), 502 (4), 429 (25), 222 (37), 183 (65), 105 (72), 73 (100). Anal. ($C_{34}H_{36}OSSi$) C, H.

9h: IR (TF) 2.87, 6.08, 6.30, 6.77, 8.04 (Si–CH), 10.27 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.21 (s, 9, $Si(CH_3)_3$), 0.84 and 1.03 (2 s, 6, C-18 and C-19 CH_3), 1.23 (s, 3, C-21 CH_3), 4.70 (m, 1, H-2′ in THP), 5.33 (m, 1, C-6 vinylic H), 5.42 and 5.69 (2 d, J = 16 Hz, C-22 and C-23 vinylic H), 7.09–7.62 (m, 5, aromatic H); mass spectrum (70 eV), m/e (relative intensity) 690 (M^+, 1),

Table III. Comparison of ^{13}C NMR (C_5D_5N) Data[a] for 1, (20R,22R)-20,22-Dihydroxy-5α-cholestanol (i), (20R,22S)-20,22-Dihydroxy-5α-cholestanol (ii), and Ponasterone A (iii)

	1	i[17]	ii[17]	iii[18]
C-18	14.1	14.1	14.1	17.9
C-19	12.5	12.5	12.5	24.4
C-20	76.5	76.5	76.5	76.7
C-21	21.1	21.1	21.9	21.1
C-22	76.6	76.5	78.3	76.7
C-23	30.1	30.1	29.3	30.2
C-24	37.1	37.1	37.5	37.1
C-25	28.2	28.2	28.6	28.1
C-26	22.5	22.5	22.8	22.3
C-27	23.2	23.2	23.1	23.3

[a] In parts per million from Me_4Si.

672 (2), 599 (38), 290 (41), 73 (100). Anal. ($C_{43}H_{66}O_3SSi$) C, H.

9i: IR (TF) 2.89, 6.07, 6.36, 6.85, 8.02 (Si–CH), 10.27 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.20 (s, 9, $Si(CH_3)_3$), 0.80 and 1.01 (2 s, 6, C-18 and C-19 CH_3), 1.32 (s, 3, C-21 CH_3), 4.69 (m, 1, H-2′ in THP), 4.98–5.95 (m, 3, C-6, C-22 and C-23 vinylic H), 7.08–7.48 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 706 (M^+, 1), 688 (4), 615 (26), 331 (28), 85 (100), 73 (51). Anal. ($C_{44}H_{70}O_3SSi$) C, H.

(3β,20S,22E,24S)-24-(Phenylthio)-3-[(tetrahydro-2H-pyran-2-yl)oxy]cholesta-5,22-dien-20-ol (15). To 100 mg (0.15 mmol) of **9g** in 4.0 mL of anhydrous methanol was added 87 mg (1.5 mmol) of anhydrous potassium fluoride and 1 mg of 18-crown-6. The mixture was refluxed for 13 h, cooled, diluted with 50 mL of ether, washed successively with 50 mL of 0.1 M aqueous hydrochloric acid, 50 mL of water, and 50 mL of brine, and dried over anhydrous magnesium sulfate. Evaporation of solvents afforded a crude semisolid which was chromatographed on two 20 × 20 cm Merck silica gel F254 preparative layer plates to afford 76 mg (85%) of **15**: mp 102–104 °C; IR (KBr) 2.88, 6.02, 6.33, 6.78, 9.79, 10.31 μm (*trans*-CH=CH); NMR ($CDCl_3$) 0.84 and 0.98 (2 s, 6, C-18 and C-19 CH_3), 1.04 (d, 6, J = 7 Hz, C-26 and C-27 CH_3), 1.20 (s, 3, C-21 CH_3), 4.66 (m, 1, H-2′ in THP), 5.28–5.68 (m, 3, C-6, C-22, and C-23 vinylic H), 7.06–7.42 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 592 (M^+, 0.5), 574 (1), 483 (16), 299 (18), 193 (75), 73 (100). Anal. ($C_{38}H_{56}O_3S$) C, H.

(3β,20S,22E,24S)-24-(Phenylsulfinyl)-3-[(tetrahydro-2H-pyran-2-yl)oxy]cholesta-5,22-dien-20-ol (16). To 592 mg (1 mmol) of **15** in 4.0 mL of dichloromethane at 0 °C was added 223 mg (1.1 mmol) of *m*-chloroperoxybenzoic acid. After being stirred for 4 h at 0 °C, the mixture was diluted with 50 mL of ether, washed successively with 50 mL of saturated sodium bicarbonate solution, 50 mL of water, and 50 mL of brine, and dried over anhydrous magnesium sulfate. Evaporation of solvent gave a crude pale yellow solid which was chromatographed on eight 20 × 20 cm Merck silica gel F254 preparative layer plates in 1:1 ethyl acetate–dichloromethane.

A band (R_f 0.42) was eluted to afford 347 mg (57%) of **16**: mp 82–83.5 °C; IR (KBr) 2.93, 6.02, 6.35, 6.85, 9.76 (S=O), 10.28 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.66 and 0.95 (2, s, 6, C-18 and C-19 CH_3), 1.00 (d, 6, J = 7 Hz, C-26 and C-27 CH_3), 4.62 (m, 1, H-2′ in THP), 5.10–5.67 (m, 3, C-6, C-22, and C-23 vinylic H), 7.18–7.69 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 608 (M^+, 1) 590 (2), 465 (12), 383 (32), 73 (100). Anal. ($C_{38}H_{56}O_4S$) C, H.

A band (R_f 0.55) was eluted to afford 115 mg (19%) of **17**: mp 95–98 °C; IR (KBr) 2.90, 6.12, 6.33, 9.74 μm (S=O); NMR ($CDCl_3$) δ 0.88 and 0.98 (2 s, 6, C-18 and C-19 CH_3), 1.01 (d, 6, J = 6 Hz, C-26 and C-27 CH_3), 1.32 (s, 3, C-21 CH_3), 4.64 (m, 1, H-2′ in THP), 5.26 (m, 1, C-6 vinylic H), 5.47 (t, 1, J = 7 Hz, C-23 vinylic H), 7.20–7.66 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 608 (M^+, 0.5), 590 (1), 465 (27), 299 (21), 73 (100). Anal. ($C_{38}H_{56}O_4S$) C, H.

(3β,20R,22R,23E)-3-[(Tetrahydro-2H-pyran-2-yl)oxy]cholesta-5,23-diene-20,22-diol (18). To 150 mg (0.25 mmol) of **16** in 3.0 mL of anhydrous methanol was added 0.5 mL of trimethyl phosphite. The mixture was refluxed for 1.5 h, concentrated, and chromatographed on two 20 × 20 cm Merck silica gel F254 preparative plates in 1:1 ethyl acetate–dichloromethane. A band (R_f 0.73) was eluted to give 79.5 mg (63%) of **18**: mp 147–147.5 °C; IR (KBr) 2.89, 6.03, 9.78, 10.32 μm (*trans*-CH=CH); NMR ($CDCl_3$) δ 0.87 and 0.97 (2 s, 6, C-18 and C-19 CH_3), 0.95 (d, 3, J = 7 Hz, C-26 and C-27 CH_3), 1.19 (s, 3, C-21 CH_3), 3.82 (d, 1, J = 7 Hz, C-22 H), 4.66 (m, 1, H-2′ in THP), 5.12–5.78 (m, 3, C-6, C-23 and C-24 vinylic H); mass spectrum (70 eV), *m/e* (relative intensity) 500 (M^+, 0.5), 467 (0.5), 401 (33), 383 (12), 314 (20), 73 (100). Anal. ($C_{32}H_{52}O_4$) C. H. Coincidence of chemical shifts for C-6, C-23, and C-24 vinylic resonances from 5.12 to 5.78 ppm was not amenable to a rigorous interpretation of the coupling parameters. Only one portion of the complex pattern, a quartet of doublets centered at 5.69 ppm was sufficiently distinct to interpret as the C-23 proton, and the coupling constant $J_{23,24}$ = 16 Hz was consistent with the 23*E* stereochemistry.

(3β,20R,22R)-3-[(Tetrahydro-2H-pyran-2-yl)oxy]-cholest-5-ene-20,22-diol (19). To 20 mg (0.04 mmol) of **18** in 1.5 mL of 1:2 THF–methanol was added 4 mg of 5% palladium on calcium carbonate. Hydrogenation under a slightly positive pressure of hydrogen commenced after the catalyst turned black in color; ca. 1 mL of hydrogen was absorbed within 20 min. The progress of the hydrogenation was monitored by thin-layer chromatography with silver nitrate impregnated silica gel plates in 1:2 ethyl acetate–hexane. The product was filtered from the catalyst, and the catalyst was washed with three 10-mL portions of THF. The crude product was concentrated and chromatographed on a 20 × 20 cm Merck silica gel F254 preparative layer plate in 1:2 ethyl acetate–hexane to afford 17.2 mg (86%) of **19**: mp 153–153.5 °C; IR (KBr) 2.88 μm; NMR ($CDCl_3$) δ 0.88 (s, 3, C-18 CH_3), 0.97 (d, 6, C-26 and C-27 CH_3; C-19 CH_3 buried under this envelope), 1.21 (s, 3, C-21 CH_3), 4.70 (m, 1, H-2′ in THP), 5.31 (m, 1, C-6 vinylic H); mass spectrum (70 eV), *m/e* (relative intensity); mass spectrum (70 eV), *m/e* (relative intensity) 502 (M^+, 0.5), 484 (1), 401 (68), 383 (29), 299 (100), 151 (28). Anal. ($C_{32}H_{54}O_4$) C, H.

(20R,22R)-20,22-Dihydroxycholesterol (1). To 30 mg (0.06 mmol) of **19** in 30 mL of methanol was added <1 mg of *p*-toluenesulfonic acid monohydrate. The solution was stirred for 19 h at 25 °C, concentrated, and chromatographed on a 20 × 20 cm Merck silica gel F254 plate in 1:2 ethyl acetate–hexane.

A band (R_f 0.20) was eluted to afford 25 mg (100%) of (20*R*,22*R*)-20,22-dihydroxycholesterol (1) having infrared, NMR and mass spectra identical with those of an authentic sample. Thin-layer chromatographic comparison of synthetic 1, an authentic sample of 1, and the 20*R*,22*S* diastereomer of 1 in a system reported by Gut to separate the 22*R* and 22*S* diastereomers showed our synthetic material was exclusively 1.

The most diagnostic evidence for the 22*R* stereochemistry in 1 was the ^{13}C NMR which displayed C-22 at 76.6 ppm, which agreed with the chemical shift values for C-22 in related systems bearing the (20*R*,22*R*)-diol but not the (20*R*,22*S*)-diol stereochemistry (Table III).

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Registry No. 1, 596-94-1; 2, 78905-13-2; 4, 79409-52-2; **5a**, 630-19-3; **5b**, 2043-61-0; **5c**, 106-23-0; **5d**, 100-52-7; **5e**, 135-02-4; **5f**, 123-11-5; **5g**, 89-98-5; **5h**, 104-87-0; **5i**, 3218-36-8; **5j**, 104-55-2; **5k**, 66-77-3; **5l**, 67-64-1; **5m**, 5396-91-8; **5n**, 830-13-7; **5o**, 93-55-0; **5p**, 119-61-9; **5q**, 62623-50-1; **5r**, 35961-41-2; **5s**, 19637-35-5; (*E*)-**6f**, 79409-53-3; (*Z*)-**6f**, 79409-54-4; **7a**, 79409-55-5; **7b**, 79409-56-6; **7c**, 79409-57-7; **7d**, 79409-58-8; **7e**, 79409-59-9; **7f**, 79409-60-2; **7g**, 79409-61-3; **7h**, 79409-62-4; **7i**, 79409-63-5; **7j**, 79409-64-6; **7k**, 79409-65-7; **7l**, 79409-66-8; **7m**, 79409-67-9; **7n**, 79409-68-0; **7o**, 79409-69-1; **7p**, 79409-70-4;

7q, 79409-71-5; **7r**, 79409-72-6; **7s**, 79409-73-7; **9a**, 79409-74-8; **9b**, 79409-75-9; **9c**, 79409-76-0; **9d**, 79409-77-1; **9e**, 79409-78-2; **9f**, 79409-79-3; **9g**, 79409-80-6; **9h**, 79409-81-7; **9i**, 79409-82-8; **10r**, 79420-94-3; **15**, 79409-83-9; **16**, 79409-84-0; **17**, 79409-85-1; **18**, 79409-86-2; **19**, 79409-87-3; 1-(phenylthio)-2-propene, 5296-64-0; 1-(phenylthio)-3-(trimethylsilyl)-1-propene, 79409-88-4; isopropyl iodide, 75-30-9; 1-bromo-3-phenylbutane, 5801-17-2; cycloheptyl bromide, 2404-35-5; benzyl bromide, 100-39-0; cyclohexylmethyl bromide, 2550-36-9; *trans*-cinnamyl bromide, 26146-77-0; cyclopentyl bromide, 137-43-9; *n*-hexyl bromide, 111-25-1.

Phase-Transfer-Catalyzed Michaelis–Becker Reaction

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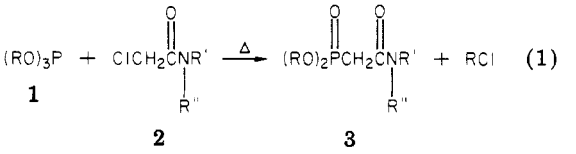
Dialkyl hydrogen phosphonates or dialkylphosphine oxides are conveniently and efficiently alkylated by alkyl chlorides to produce dialkyl alkylphosphonates or trialkylphosphine oxides, respectively, by aqueous sodium hydroxide in a liquid–liquid phase-transfer-catalyzed reaction. Despite the hydrolytic instability of dialkyl hydrogen phosphonates, their reaction with chloroacetamides in the two-phase system can provide dialkyl (carbamoylmethyl)phosphonates $(RO)_2P(O)CH_2C(O)NR'R''$ in 90% yields and crude purities. Many of these products have unique utility as solvent extraction reagents for the fractionation of hazardous radionuclides. The new route is not plagued by the side reactions typical of conventional Arbuzov or Michaelis–Becker syntheses, which seriously limit yields and crude product purities. It does not require anhydrous conditions or the use of alkali metals, alkoxides, or hydrides and provides access to products outside the scope of conventional routes.

The general utility of the reaction of the conjugate bases of dialkyl hydrogen phosphonates, $(RO)_2P(O)H$, and dialkylphosphine oxides, $R_2P(O)H$, with alkylating agents (i.e., the Michaelis–Becker reaction) is limited by the requirement of a strong anhydrous base (e.g., alkali metals, alkoxides, or hydrides) for conjugate base formation. Since such bases are reactive directly with alkylating agents, it is necessary to prepare these reactive organophosphorus alkali metal salts in stoichiometric quantities prior to exposure to the desired alkylating agent. A stepwise procedure such as this which results in high concentrations of these strong nucleophiles can lead to undesirable side reactions (vide infra).

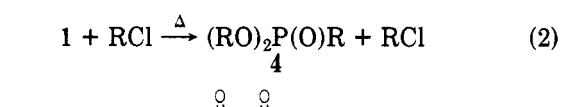
It has been reported that diethyl hydrogen phosphonate reacts with benzyl chloride in the presence of potassium carbonate and a crown ether at 100 °C to afford diethyl benzylphosphonate in 66% yield.[1] This reaction likely proceeds by proton abstraction on the surface of the solid carbonate but demonstrates the capability of a properly activated weak base for this reaction.

This study was undertaken to develop a simple and facile route to elusive dialkyl (carbamoylmethyl)phosphonates **3**, which are unique reagents for the fractionation of radionuclides from nuclear process streams by solvent extraction.[2-9] We now report a convenient method for high-yield preparations of these compounds as well as novel tertiary (carbamoylmethyl)phosphine oxides **10** via a Michaelis–Becker reaction facilitated by liquid–liquid phase-transfer catalysis (PTC),[10,11] a route which substantially relieves the limitatioins described above.

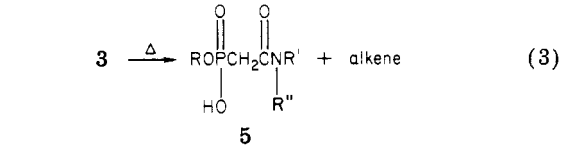
Siddall found the reaction of trialkyl phosphites (**1**) with *N,N*-dialkylchloroacetamides (**2**, eq 1) to be sluggish, requiring forcing conditions.[12] The reactivity of **1** in this example of the Arbuzov reaction is further reduced when R is large, such as when **3** is designed as a solvent extraction reagent and must be very hydrophobic. The reaction is plagued by typical Arbuzov side reactions (eq 2 and 3), and poor yields (40–50%) of difficulty purifiable products inevitably result.[13]



(1)

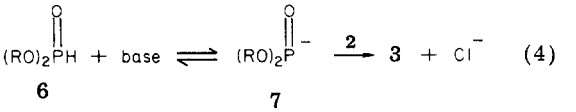


(2)



(3)

The nucleophilic displacement involving **2** and alkali metal salts (**7**) of dialkyl hydrogen phosphonates (**6**, eq 4),



(4)

an example of the Michaelis–Becker reaction, occurs under considerably milder conditions.[14] However, the previously

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