Methylation and Hydroxymethylation of Allylic Alcohols via Radical Cyclization. Methodology for Stereoselective Construction of an Aliphatic Chain in Application to Sterol Synthesis

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Reductive free-radical cyclization of (bromomethyl)dimethylsilyl derivatives (**6b–9b**) of allylic alcohols (**6a–9a**) was studied to evaluate the scope of a novel method of methylation and hydroxymethylation of allylic alcohols. Treatment of (bromomethyl)dimethylsilyl derivatives of primary alcohols **6a** and **7a** with tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile, followed by protiodesilylation of the respective cyclization products, gave in both cases a mixture of saturated methyl derivatives **11a** and **12a** in a ca. 1:1 ratio. Under analogous conditions (bromomethyl)dimethylsilyl derivatives of secondary alcohols **8a** and **9a** afforded the methylation products—sterols **13** and **14**, respectively. Treatment of (bromomethyl)dimethylsilyl derivative of allylic alcohol **6a** with tri-*n*-butyltin hydride and azobisisobutyronitrile, followed by oxidation (H_2O_2–KF–dimethylformamide) of the intermediate product, gave diol **21**; the latter product was transformed via oxetane **22** into (20*S*)-25-hydroxycholesterol **26**. Starting allylic alcohols **6a–9a** were synthesized from α,β-unsaturated ester **15**. Inversion of configuration at the double bond in **15**, leading to *Z* isomer **18**, was accomplished by means of phenylselenylation of saturated ester **16** and fragmentation of the corresponding phenylselenyl oxide. Regio- and stereoselectivity of radical cyclization is discussed.

Recently, Nishiyama et al.[1] and Stork et al.[2,3] have invented a method for methylation and hydroxymethylation of allylic alcohols which involves as a key step cyclization of the free-radical generated from the respective (bromomethyl)dimethylsilyl derivatives (Scheme I). Potentially, this method may be applied for the synthesis of aliphatic branched chains with hydroxy groups, being a structural element of many natural products, e.g. isoprenoids. Its practical utility depends, however, upon the regio- and stereoselectivity of the formation of new bonds.

Radical cyclizations of carbon compounds are known for their regioselectivity which may be predicted from Baldwin–Beckwith rules[4-6] (provided that the reaction is under kinetic control). Hex-5-en-1-yl radical and many substituted hexenyl radicals, amongst others the 2,2-dimethylhexenyl radical,[7,8] cyclize preferentially in the 5-exo mode to afford a 5-membered ring. The replacement of a CH_2 group in the hexenyl chain by O or N atoms does not affect the cyclization mode.[6] Silahexenyl radicals have received considerably less attention, and the results of the reported studies are less consistent.

In an exploratory work Wilt[9] has found that the hexenyl radical with the dimethylsilyl function in the α-position to the radical center differs from the parent system in: (1) markedly lower regioselectivity of cyclization and (2) predominance of the 6-endo product (6-endo:5-exo, ca. 2:1). The origin of the difference has been attributed to the length of the C–Si bond (being ca. 25% longer than the C–C bond) which influences the stereoelectronic factors.[9,10] Studies of analogous cyclization of radical species comprising silicon, phosphorus, or sulfur have suggested[10-12] that exceptions from Baldwin–Beckwith rules arise when a second-row atom is incorporated into the new ring. Calculations by the force-field method also predict for 2-silahexenyl radical preferential 6-endo cyclization.[13] On the other hand, a number of aliphatic 3-oxa-2-silahexenyl radicals cyclize with the predominance, at large, of the 5-exo mode.[1] The mode of cyclization of unsaturated radicals in polycyclic, conformationally rigid systems is a reflection of the stereoelectronic and steric factors. It has been reported[2,3] that oxasilahexenyl radicals comprising a decaline element, for example that generated from (bromomethyl)dimethylsilyl ether **1** (Scheme II), gave with complete regioselectivity the respective 5-exo products (e.g. **2** and subsequently **3**). In contrast, cyclization of the radical corresponding to the bromo derivative **4** has afforded exclusively the 6-endo product **5** (Scheme II).[14] As concerns the stereochemistry of new-bond formation, it is noteworthy that in both cases considered (**1** and **4**) the formation of C–C and C–H bonds is diastereoselective, the latter bond being oriented toward the less hindered side of the respective reaction site (hydrogen atom approaching from the less shielded side).

From the above quoted reports one may conclude that silahexenyl radicals are more flexible than the respective all-carbon systems. It appeared to us that the scrutiny of cyclization of radicals generated from (bromomethyl)dimethylsilyl derivatives of structurally similar allylic alcohols **6a**, **7a**, **8a**, and **9a** (Chart I) may contribute to understanding the subtle factors governing the regio- and diastereoselectivity of formation of new C–C and C–H bonds. The pair of alcohols **6a** and **7a** was chosen for evaluation of the effect of steric shielding of the double

(1) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298.
(2) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.
(3) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826.
(4) Baldwin, J. *J. Chem. Soc., Chem. Commun.* **1971**, 734.
(5) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. Beckwith, A. L. J.; Meijs, G. F. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1535. Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811.
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(7) Beckwith, A. L. J.; Lawrence, T. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1535; 5-exo:6-endo, 99:1.
(8) House, H. O.; Weeks, P. D. *J. Am. Chem. Soc.* **1975**, *97*, 2778.
(9) Wilt, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 5251; *Tetrahedron* **1985**, *41*, 3979.
(10) Chryssostomos, C.; Woynar, H.; Ingold, K. U.; Davis, A. G. *J. Chem. Soc., Perkin Trans. 2* **1983**, 555.
(11) Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 281.
(12) Barton, T. J.; Revis, A. *J. Am. Chem. Soc.* **1984**, *106*, 3802.
(13) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373.
(14) Koreeda, M.; George, J. *J. Am. Chem. Soc.* **1986**, 8098.

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Scheme I

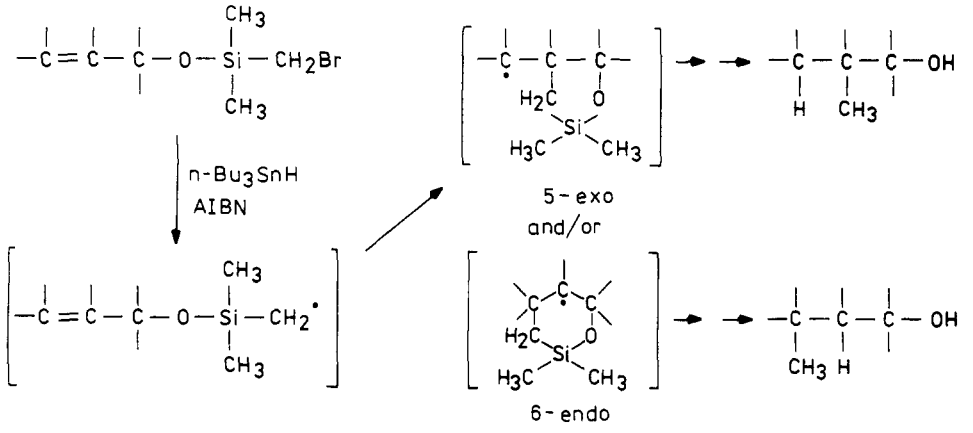
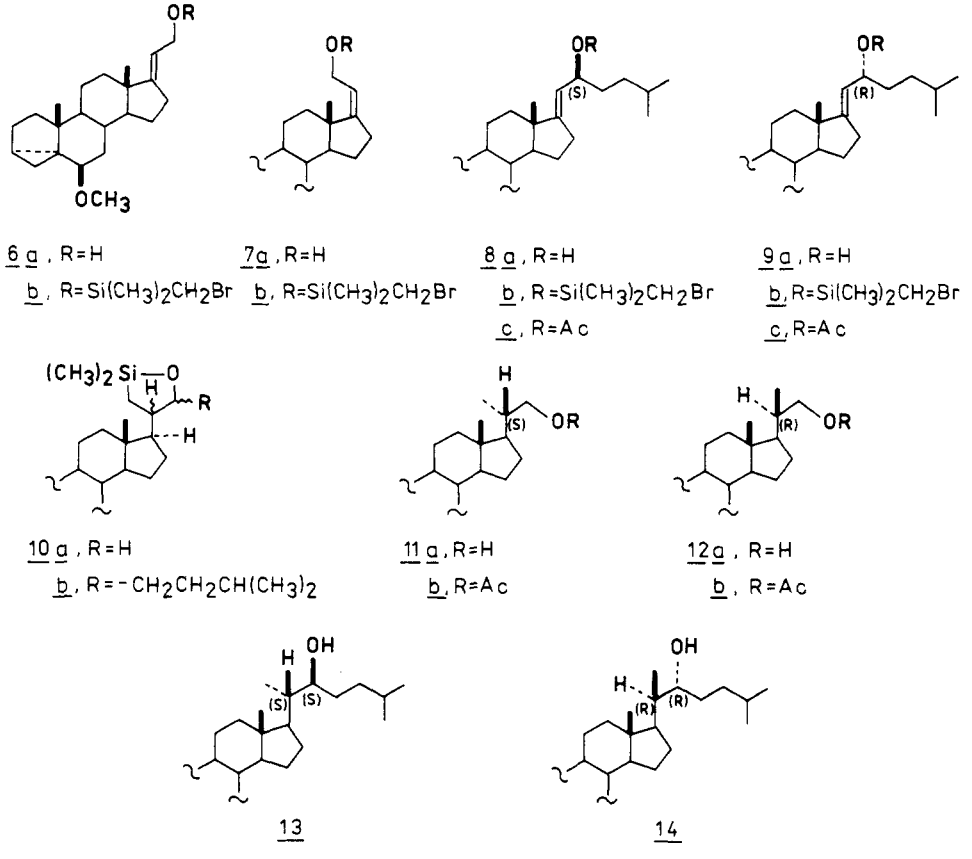


Chart I



6a, R=H
b, R=Si(CH3)2CH2Br

7a, R=H
b, R=Si(CH3)2CH2Br

8a, R=H
b, R=Si(CH3)2CH2Br
c, R=Ac

9a, R=H
b, R=Si(CH3)2CH2Br
c, R=Ac

10a, R=H
b, R=-CH2CH2CH(CH3)2

11a, R=H
b, R=Ac

12a, R=H
b, R=Ac

13

14

bond whereas the pair **8a** and **9a** was used for demonstration of the conformational effects of the aliphatic chain. In this paper we report the synthesis of compounds **6a–9a**, intramolecular cyclization of radicals generated from the respective (bromomethyl)dimethylsilyl derivatives **6b–9b**, as well as the utilization of cyclization products **10** for stereoselective synthesis of sterols **13**, **14**, and **26** (Scheme IV), which are difficult to obtain by another route.[15]

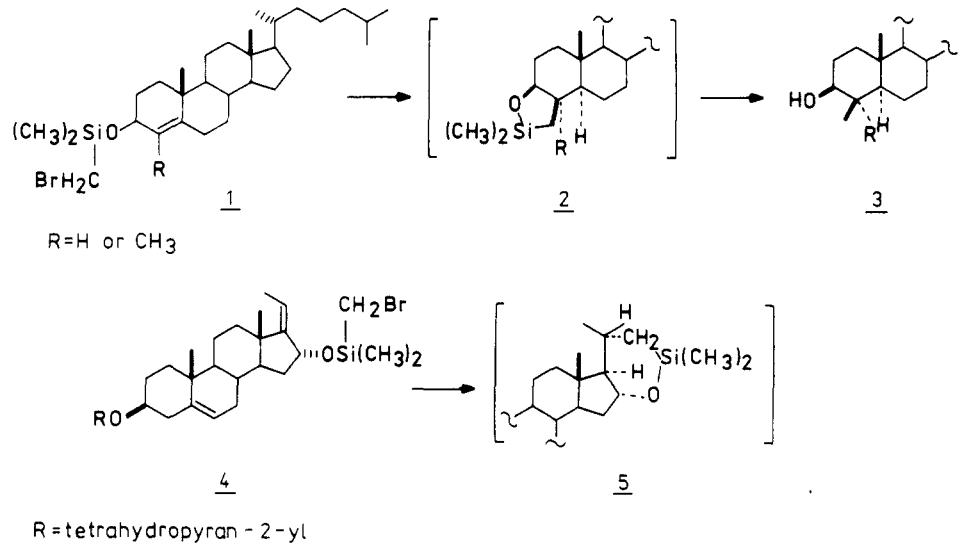
Results and Discussion

Synthesis of Allylic Alcohols 6a–9a. Readily available[16] unsaturated ester **15** (Scheme III) was used as starting material for the synthesis of all allylic alcohols required in the present studies. For the synthesis of *Z* alcohol **7a**, the configuration of the double bond in **15** was inverted by a procedure based upon the known[17] diastereoselectivity of alkylation of 21-pregnenoic acid esters and upon the known[18] preferential cis elimination of the phenylselenyl moiety with the neighboring proton. The saturated ester[17] **16** was deprotonated and treated with phenylselenyl chloride. The phenylselenyl derivative **17** was obtained as a single diastereomer. This product **17** was oxidized to the corresponding phenylselenyl oxides, which underwent fragmentation to unsaturated *Z* ester **18**. Conventionally performed reduction of *E* and *Z* esters **15** and **18** gave allylic alcohols **6a** and **7a**, respectively.

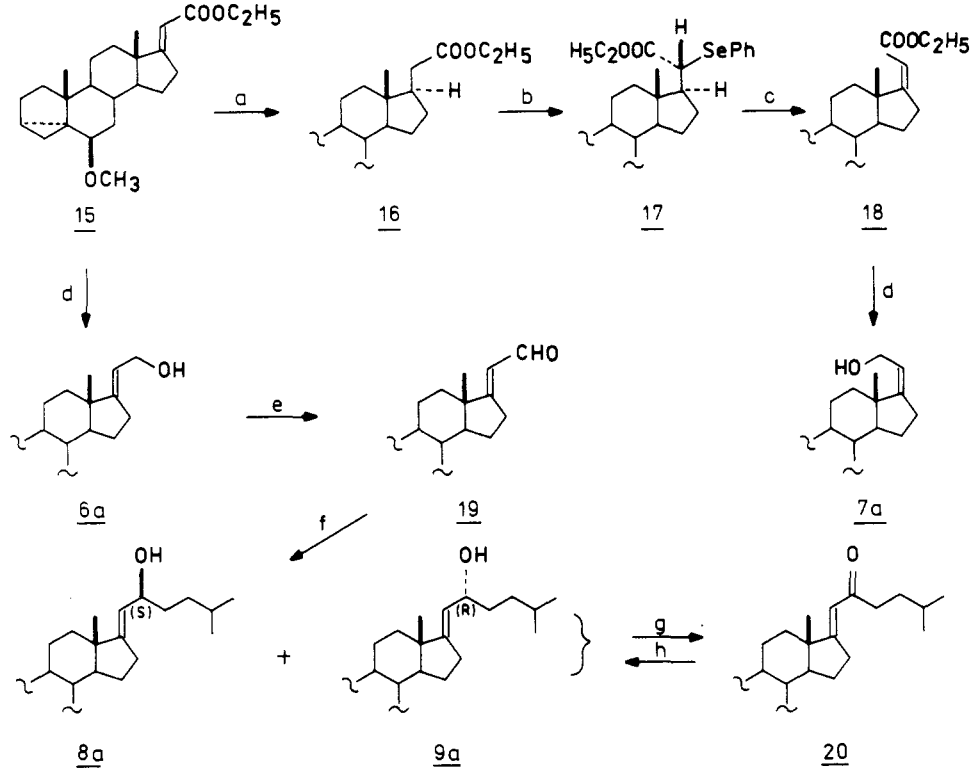
An attempt to reduce ester **15** with diisobutylaluminum hydride (DIBAL) directly to aldehyde **19** failed; oxidation of crude alcohol **6a** with chromic anhydride in hexa-

(15) Some results were reported as a preliminary communications: Kurek-Tyrlik, A.; Wicha, J.; Snatzke, G. *Tetrahedron Lett.* **1988**, *29*, 4001.
(16) Wicha, J.; Bal, K.; Piekut, S. *Synth. Commun.* **1977**, *7*, 215.
(17) Wicha, J.; Bal, K. *J. Chem. Soc., Chem. Commun.* **1975**, *968*; *J. Chem. Soc., Perkin Trans. 1* **1978**, 1282.
(18) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 13. Cf.: Kingsburry C. A.; Cram, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1810.

Scheme II



Scheme III[a]



[a] (a) H_2/Pt/EtOH, 100% yield; (b) LDA/THF then PhSeCl, 62%; (c) H_2O_2/AcOH/THF, −5 °C and then heating, 68%; (d) $LiAlH_4/Et_2O$, 95%; (e) CrO_3/HMPA, 63% (from **15**); (f) i-$C_5H_{11}MgBr$, chromatography; (g) CrO_3/H_2O/py, 77%; (h) see the text.

methylphosphotriamide (HMPA)[19] gave, however, the required product (**19**) in 65% overall yield. Treatment of aldehyde **19** with an excess of isoamylmagnesium bromide yielded a mixture of equal amounts of epimeric alcohols **8a** and **9a**, which were separated by column chromatography (for assignment of the configuration, vide infra). Interestingly, the ^1H NMR spectra of pairs of alcohols (22*S*)-**8a**–(22*R*)-**9a**, and the corresponding acetates, **8c**–**9c**, are virtually superimposable with the exception of signals of C_{16} protons. In the spectrum of **8a** this signal appeared at δ 2.32 ppm as a multiplet ($W/2$ = 20 Hz), whereas in the spectrum of **9a** the signal appeared at δ 2.45 ppm as a quartet of triplets (J_{gem} = 19 Hz, $J_{16\beta,15\beta}$ = 10 Hz, $J_{16\beta,15\alpha} = J_{16\beta,20}$ = 2 Hz), tentatively assigned to 16β-H, and at δ 2.23 ppm as a quartet of triplets (J_{gem} = 19 Hz, $J_{16\alpha,15\alpha} = J_{16\alpha,15\beta}$ = 9 Hz, $J_{16\alpha,20}$ = 2 Hz), tentatively assigned to 16α-H. Likewise, within the pair of epimers **8c**–**9c** the difference in chemical shift of C_{16}-protons is larger for the latter compound.[20]

In order to develop a stereoselective approach to 22-hydroxy-21-norcholestanes, **8a** and **9a**, the product of the above described Grignard reaction was oxidized (CrO_3–pyridine[21]) to ketone **20**, and reduction of the latter was

(19) Cardillo, G.; Orena, M. Sandri, S. *Synthesis* **1976**, 394.

(20) Cf.: Bhacca, N. S.; Williams, D. W. *Application of NMR in Organic Chemistry*; Holden-Day: San Francisco, 1964; p 112.

Table I. Methylation of Allylic Alcohols via Reductive Cyclization of Their Respective (Bromomethyl)dimethylsilyl Ethers and Protiodesilylation of the Intermediate Silaoxolanes

allylic alcohol	bromomethyl ether	product(s)	yield, %, calcd against the alcohol	isomer ratio
6a	**6b**	**11a** and **12a**	48	57:43
7a	**7b**	**11a** and **12a**	55	51:49
8a	**8b**	**13**	56	only product
9a	**9b**	**14**	62	only product

investigated. Several achiral reducing agents including lithium tri-*sec*-butylborohydride (L-Selectride, Aldrich) and DIBAL were virtually unselective. Reduction with (*R*)-(+)-1,1′-bi-2-naphthol-modified lithium aluminum hydride (Noyori reagent)[22] afforded a mixture of alcohols **8a** (22*S*) and **9a** (22*R*) with rather low selectivity, the pure components being isolated in 29 and 53% yield (35:65 ratio), respectively. Eventually, the use of the *S*-(−) Noyori reagent met the purpose, affording the isomers 22*S* and 22*R* in 87 and 7% yield (92:8 ratio), respectively. Reduction of ketone **20** with the *R* and *S* Noyori reagent provides a remarkable example of "double asymmetric induction"[23] in creation of a chiral center.

Methylation of Allylic Alcohols 6a–9a. Allylic alcohols **6a**, **7a**, **8a**, and **9a** (Chart I) were converted to their respective (bromomethyl)dimethylsilyl ethers **6b–9b**. These derivatives were purified by chromatography on silica gel and treated with tri-*n*-butyltin hydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN), in accordance with the procedure.[3] Cyclization products **10a,b** were without purification subjected to protiodesilylation (potassium *tert*-butoxide–dimethyl sulfoxide)[24] to afford the methyl derivatives **11a**, **12a**, **13**, and **14**. The results are presented in Table I.

Alcohols with the bisnorcholane skeleton, **11a** and **12a**, were identified by their analytical and spectral data;[25,26] the assignment of the configuration at C_{20} was confirmed by the difference in chemical shift of C_{21} protons in ^1H NMR spectra of free alcohols **11a** and **12a** as well as of the corresponding acetates, **11b** and **12b** (see the Experimental Section). It has been well documented that the derivatives of the "20-iso series" exhibit the signal of C_{21} protons at δ by 0.05–0.1 ppm higher, as compared with the respective derivatives of the "20-normal" series.[27] Among the four possible cholestane derivatives differing in the configuration on C_{20} and C_{22}, two with the "normal" configuration on C_{20} have been recently described by Ourisson et al.[28] The cholestane derivative obtained in the present work by methylation of allylic alcohol **8a** displayed signals in a high-resolution ^1H NMR spectrum in good agreement with those described[28] for the 20*S*,22*S* isomer. Accordingly, we assigned to this compound the structure **13** and to its precursor, allylic alcohol **8a**, configuration 22*S*. Since

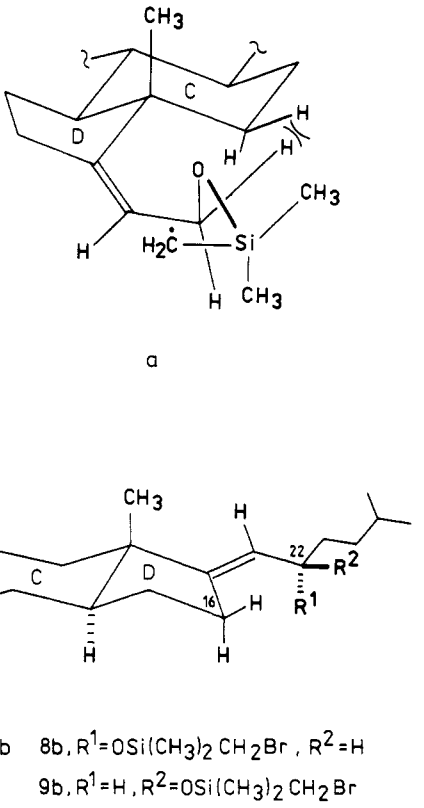


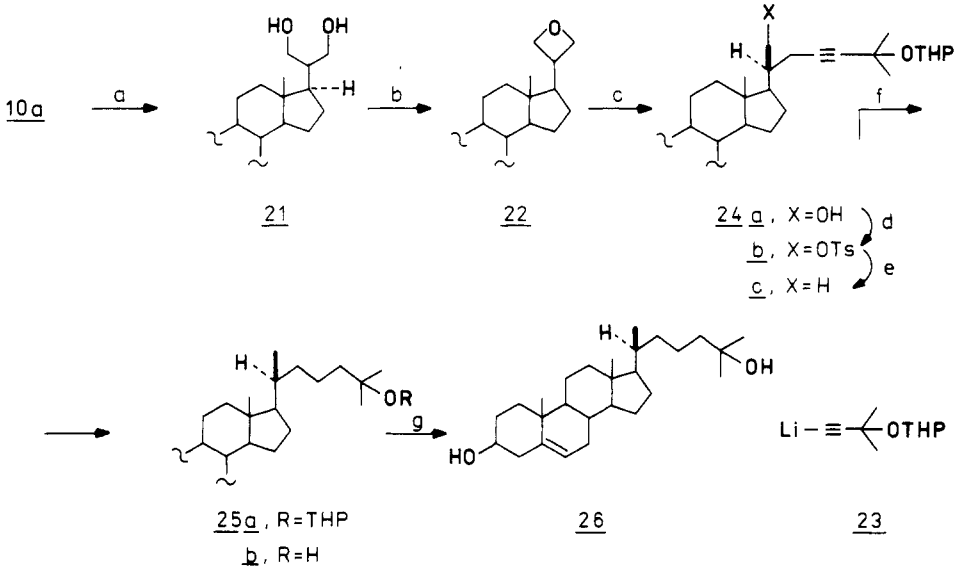
Figure 1.

allylic alcohols **8a** and **9a** differ only in the configuration at the C_{22} carbon atom, alcohol **9a** must have the 22*R* configuration; consequently, the respective methylation product **14** has the 22*R* configuration. It remained to clarify the C_{20} configuration of the product **14**. The diastereomer with the 20*S*,22*R* configuration has been described;[28] we found that the described ^1H NMR spectrum of this isomer differs distinctly from that recorded for **14**. This indicates that sterol **14** has the 20*R*,22*R* configuration. The difference in the chemical shift of C_{21} protons between the described 20*S*,22*R* epimer ("natural") and 20*R*,22*R* epimer, **14**, amounts to 0.09 ppm, confirming the assignment.

The results summarized in Table I require some comments. (1) Cyclization of free radicals derived from each of bromo ethers **6b–9b** occurred regioselectively in the 5-exo mode. The carbon-centered radical added to the double bond at the less substituted and clearly less hindered position.[29,30] (2) The addition of a hydrogen atom to the double bond occurred in all investigated cases stereoselectively from the less hindered side of the molecule (17-α). These observations are in line with the results of other authors.[3,4,14] (3) Cyclization of the derivative of primary *E* alcohol (**6b**), followed by protiodesilylation, afforded a mixture of 20*R* and 20*S* products, **11a** and **12a**, respectively, in almost equal amounts. This is an expected consequence of free rotation around the C_{20}–C_{22} bond and of the relatively small difference in steric hindrance between the α- and β-side of the double bond (in the case of the radical approach in the plane which contains the two olefinic carbon atoms and is perpendicular to C_{17}–C_{20}–C_{21} plane, in the direction laid out by the bond which will be formed).[10] Cyclization of *Z* isomer **7b**, followed by

(21) Cornforth, R. H.; Cornforth, J. W.; Popják, G. *Tetrahedron* **1962**, *18*, 1351.
(22) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.
(23) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(24) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. *J. Am. Chem. Soc.* **1982**, *104*, 6809.
(25) Vanderah, D. J.; Djerassi, C. *J. Org. Chem.* **1978**, *43*, 1442.
(26) Dasgupta, S. K.; Crump, D. R.; Gut, M. *J. Org. Chem.* **1974**, *39*, 1658.
(27) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199 and references quoted therein.
(28) Amann, A.; Ourisson, G., Luu, B. *Synthesis* **1987**, 1002. See also: Posner, J. P.; Ourisson, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2061.
(29) Julia, M.; Descoins, C.; Baillarge, M.; Jaquet, B.; Uguen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 1737.
(30) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482.

Scheme IV[a]



[a] (a) H_2O_2/KF/DMF; (b) *n*-BuLi/THF, −5 °C, TsCl then *t*-BuOK, 82% yield; (c) **23**, −73 °C, BF_3·Et_2O, 83%; (d) TsCl/py, 94%; (e) $LiAlH_4$/THF, 83%; (f) H_2/Pd-on-carbon/$NaHCO_3$/dioxane, 75%, pTSA/aqueous dioxane, 98%.

protiodesilylation, afforded a product with similar isomer composition as in the case of *E* isomer. Examination of molecular models indicated that in **7b** the approach to the double bond from the α-side is rather not hindered; the approach from the β-side is, however, substantially more hindered than in **6b**, owing to interactions of the $CH_2OSi(CH_3)_2CH_2$• moiety with the angular methyl group and C_{12} hydrogen atoms (Figure 1a). In this connection, the cyclization result seems to indicate that radical cyclizations are relatively slightly affected by the nonbonding interactions which do not involve interactions between the structural elements of the new ring. (4) Cyclization of the derivatives of secondary allylic alcohols **8b** and **9b** occurred with stereoselective formation of the C–C bond to afford 20*S* and 20*R* products, respectively. The stereoselectivity of this reaction reflects the preference of the side-chain conformation indicated in Figure 1b, with minimal interactions of C_{16} hydrogen atoms with the substituents at C_{22}.[31]

Synthesis of Sterol 26. Methylation of allylic alcohols **8a** and **9a** provided an approach to 22-hydroxysterols **13** and **14** of 20*S* and 20*R* configuration, respectively. On account of continuous interest in stereoselective construction of the sterol side chain,[32] it was challenging to develop a methodology for stereoselective synthesis of cholesterol derivatives from isomeric silaoxolanes **10a**. The difficulties resulting from the lack of stereoselectivity in free-radical cyclization of **6b** and **7b** were circumvented as follows. The intermediate **6b** was cyclized to afford crude **10a** (a mixture of isomers), as described above. These isomers were (without isolation) oxidized according to Tamao et al.[33] to give in an excellent yield diol **21** devoid of the chiral center at C_{22} (Scheme IV). The diol **21** was converted to oxetane **22** using a two-step procedure.[34] It

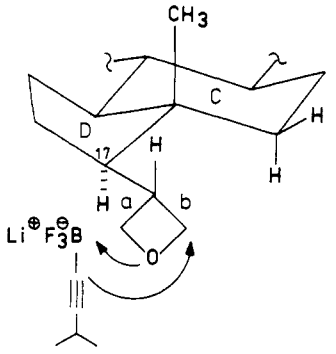


Figure 2.

was expected that nucleophilic displacement of the oxetane C–O bond would allow for stereodifferentiation of the oxetane α-positions. Indeed, treatment of oxetane **22** with lithium acetylenide **23** and boron trifluoride etherate[35,36] gave an adduct as a single isomer at C_{20} in 83% yield. To this product the structure **24a** was assigned on the basis of the below-described transformations.

The hydroxy group in compound **24a** was removed by reduction of the corresponding tosylate **24b** with lithium aluminum hydride. In the ^1H NMR spectrum of the 21-deoxy derivative **24c**, among other signals there appeared a slightly broadened doublet for 3 H at δ 0.94 ppm, J = 7 Hz. This signal was assigned to protons of the C_{21} methyl group, the broadening being attributed to the presence of isomers related to the chiral center in the tetrahydropyranyl moiety. The 20*R* epimer of compound **24c** has been synthesized by the Roche group;[37] the reported chemical shift for C_{21} protons is δ 1.03 ppm (J = 7 Hz). The difference in these values (0.09 ppm) is consistent with the 20*S* configuration of the intermediate **24c**.

(31) For a discussion on conformations of the sterol side chain, see: Zeelen, F. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 245.

(32) For some recent works, see: (a) Giner, J. L.; Margot, C.; Djerassi, C. *J. Org. Chem.* **1989**, *54*, 2117. (b) Kim, D.; Han, G. H.; Kim, K. *Tetrahedron Lett.* **1989**, *30*, 1989. (c) Jarzebski, A.; Wicha, J. *Synth. Commun.* **1989**, *19*, 63. (d) Ibuka, I.; Taga, T.; Shinugu, T.; Saito, M.; Nishii, S.; Yamamoto, Y. *J. Org. Chem.* **1988**, *53*, 3947.

(33) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics*, **1983**, *2*, 1694. Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120.

(34) Picard, P.; Leclercq, D.; Bates, J. P.; Moulines, J. *Synthesis* **1981**, 550.

(35) Cf.: Yamaguchi, M.; Nobayashi, Y.; Hirao, I. *Tetrahedron* **1984**, *40*, 426.

(36) For a review on BF_3-assisted reactions of organometallics, see: Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, 947.

(37) Partridge, J. J.; Faber, S.; Uskokovic, M. R. *Helv. Chim. Acta* **1974**, *57*, 764. Narwid, T. A.; Cooney, K. E.; Uskokovic, M. R. *Ibid.* **1974**, *57*, 771.

For the completion of the sterol synthesis, acetylene **24c** was hydrogenated, and the saturated derivative **25a** was treated with *p*-toluenesulfonic acid (pTSA) in ethanol at 0 °C. Finally, the 25-hydroxy intermediate **25b** (δ 0.84 ppm, J = 6.0 Hz, sharp d for C_{21}-H) was heated in aqueous dioxane containing pTSA in order to remove the tetrahydropyranyl group.[37] (20*S*)-25-Hydroxycholesterol **26** ("unnatural configuration" at C_{20}) was obtained (62% yield); its physical and spectroscopic properties were in good agreement with those reported.[37]

Examination of molecular models indicated that in the most stable conformation of oxetane **22** the C_{20}–H bond is oriented parallel to the C–C bond of the angular methyl group (Figure 2), and that the methylene groups a and b, bonded to prochiral center C_{20}, differ in steric shielding. Initially, we had expected that the organometallic reagent would displace the C–O bond at the less shielded position (C_a) to give the 20*R* product and, eventually, 25-hydroxycholesterol ("natural" configuration at C_{20}). A posteriori, we rationalize the result by assuming that the "ate" reagent approach from the less shielded side (C_a) is followed by the formation of a O–B bond oriented toward the less shielded side and by transfer of the acetylene moiety to C_b.[38]

It is noteworthy that stereoselective syntheses involving reduction of the intermediate ketone **20** with (*S*)-BINAH and that using oxetane **22** are complementary, leading to (20*S*)- and (20*R*)-sterols, respectively.

In conclusion, cyclization of silahexenyl radicals derived from allylic alcohols **6a–9a** occurs with high regioselectivity in the 5-exo mode with the formation of a new bond at the less substituted and less shielded side of the double bond. In the case of secondary alcohols **8a** and **9a** the methylation is completely diastereoselective. The corresponding transformations of primary alcohols **6a** and **7a** result in diastereoselective formation of a new C–H bonds and unselective formation of a new a C–C bonds.

Experimental Section

General. Melting points were determined on a Kofler hot-stage apparatus. The spectra were recorded using the following instruments: IR, Beckmann 4240 or Unicam SP 200 spectrophotometers (unless otherwise stated, $CHCl_3$ solutions); ^1H NMR, Varian EM 360 (60 MHz), Bruker 80, AM 400 and AM 500 spectrometers (in $CDCl_3$ solutions); mass, LKB 2091 spectrometer (at 75 eV ionization potential); high-resolution mass, Varian 731 spectrometer. Chemical shifts are reported in δ units, downfield from $(CH_3)_4Si$. Column chromatography was performed on silica gel, Merck, and TLC, on silica gel G, Merck. Organic solvents were dried over anhydrous Na_2SO_4, and solvents were removed under reduced pressure using a rotary evaporator. Microanalyses were performed at our analytical laboratory (Warsaw).

Ethyl 6β-Methoxy-3α,5α-cyclopregnan-21-oate (16). A mixture of unsaturated *E* ester[16] **15** (15 g), 96% ethanol (200 mL), and platinum oxide (1.2 g) was stirred under hydrogen until absorption of gas ceased. Workup gave saturated ester **16** (15 g): oil; ν_{max} 1740 and 1250 cm^{-1}; δ_H (60 MHz) 4.08 (2 H, q, J = 7 Hz, OCH_2CH_3), 3.31 (3 H, s, OCH_3), 2.78 (1 H, br s, C_6-H), 1.25 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.02 (3H, s, C_{19}-H), 0.68 (3 H, s, C_{18}-H); high-resolution mass spectrum, calcd for $C_{24}H_{38}O_3$ (M^+) 374.2821, found 374.2821.

Ethyl (20*R*)-6β-Methoxy-20-(phenylselenyl)-3α,5α-cyclopregnan-21-oate (17). To a mixture of diisopropylamine (2.6 mL, 18 mmol) and THF (10 mL) stirred under argon at −10 °C was added a solution of *n*-BuLi in hexane (1.5 M, 11.6 mL, 17.5 mmol). Stirring at −10 °C was continued for 15 min, the mixture was cooled to −78 °C, and a solution of ester **16** (1.64 g, 4.38 mmol) in THF (5 mL) containing HMPA (2.5 mL) was added. The resulting solution was stirred at −78 °C for 1 h 40 min, whereupon addition was made of phenylselenyl bromide (5.16 g, 21.9 mmol) in THF (8 mL). Stirring was continued for 30 min while the mixture was allowed to warm to −30 °C, and the reaction was quenched with an aqueous soln of NH_4Cl. Workup gave a product (dark oil, 5.8 g), which was chromatographed on SiO_2 (60 g, 230–400 mesh, hexanes–acetone, 99.8:0.2) to give phenylselenyl derivative **17** (1.46 g, 62% yield): ν_{max} 1745 (C=O), 1595, 1490, 750, and 700 cm^{-1}; δ_H (60 MHz, CCl_4) 7.80–7.00 (5 H, m, aromatic H), 3.90 (2 H, q, J = 7 Hz, OCH_2CH_3), 3.57–3.05 (1 H, m, C_{20}-H), 3.24 (3 H, s, OCH_3), 2.65 (1 H, br s, C_6-H), 1.11 (3 H, t, J = 7 Hz, OCH_2CH_3), 0.95 (3 H, s, C_{19}-H), 0.73 (3 H, s, C_{18}-H); mass spectrum, m/z 530 (M^+ + 2, relative intensity 100), 528 (M^+, 57), 515 (8), 475 (9), 373 (16), 341 (90); high-resolution mass spectrum, calcd for $C_{30}H_{42}SeO_3$ (M^+) 528.2307, found 528.2307.

Ethyl (*Z*)-6β-Methoxy-3α,5α-cyclopregn-17(20)-en-21-oate (18). To a solution of selenide **17** (0.600 g) in THF (20 mL) stirred at −5 °C were added acetic acid (0.1 mL) and hydrogen peroxide (30%, 1.5 mL). The mixture was stirred at room temperature for 1 h and heated at the boiling temperature for ca. 5 min. After cooling, the solution was diluted with toluene (20 mL) and washed successively with water, an aqueous solution of sodium metabisulfite, and water. The solvent was evaporated, and the residue (0.516 g, oil) was chromatographed on SiO_2 (15 g, 70–230 mesh, hexanes–acetone, 99.7:0.3) to give unsaturated ester **18** (0.290 g, 68% yield), identical with an authentic sample.[16]

(*E*)-6β-Methoxy-3α,5α-cyclopregn-17(20)-en-21-ol (6a). A mixture of *E* ester **15** (0.350 g), anhydrous ether (20 mL), and lithium aluminum hydride (0.200 g) was stirred at room temperature for 2 h, and the reagent excess was decomposed with saturated aqueous Na_2SO_4. Workup gave the crude product (0.331 g), which was chromatographed on SiO_2 (35 g, 230–400 mesh, hexanes–acetone, 97:3) to give alcohol **6a** (0.291 g, 94% yield): oil; δ_H (60 MHz, CCl_4) 5.20 (1 H, m, C_{20}-H), 4.01 (2 H, d, J = 8 Hz, C_{21}-H), 3.32 (3 H, s, OCH_3), 2.75 (1 H, br s, C_6-H), 1.00 (3 H, s, C_{19}-H), 0.81 (3 H, s, C_{18}-H).

(*Z*)-6β-Methoxy-3α,5α-cyclopregn-17(20)-en-21-ol (7a). Reduction of *Z* ester **18** (0.355 g) with lithium aluminum hydride in ether, analogically as described above, gave *Z* allylic alcohol **7a** (0.300 g, 95% yield): oil; δ_H (60 MHz, CCl_4) 5.20 (1 H, t, J = 8 Hz, C_{20}-H), 4.05 (2 H, d, J = 8 Hz, C_{21}-H), 3.25 (3 H, s, OCH_3), 2.67 (1 H, br s, C_6-H), 1.00 (3 H, s, C_{19}-H), 0.95 (3 H, s, C_{19}-H).

(*E*)-6β-Methoxy-3α,5α-cyclopregn-17(20)-en-21-one (19). To a solution of *E* ester **15** (3.58 g, 9.62 mmol) in anhydrous ether (50 mL) was added lithium aluminum hydride (0.70 g, 18 mmol), and the mixture was heated under reflux for 30 min. Workup with saturated aqueous Na_2SO_4 gave alcohol **6a** (2.89 g). The latter product (2.7 g, ca. 8.2 mmol) was treated with CrO_3 (1.63 g, 16.3 mmol) in HMPA (7 mL) at room temperature for 24 h. The mixture was diluted with cold water and extracted with ether. The extract was washed with 5% aqueous NaOH and evaporated. The residue (2.4 g) was chromatographed on SiO_2 (25 g, 230–400 mesh, hexane) to give aldehyde **19** (1.92 g, 65% yield): mp 98–101 °C (methanol–water); ν_{max} (KBr) 1680 (C=O), 1640 (C=C), 1140, and 1090 cm^{-1}; λ_{max} (C_2H_5OH) 245 nm (ϵ = 16 439); δ_H (60 MHz, CCl_4) 9.9 (1 H, d, J = 8 Hz, CHO), 5.9–5.4 (1 H, m, C_{20}-H), 3.31 (3 H, s, OCH_3), 1.03 (3 H, s, C_{19}-H), 0.93 (3 H, s, C_{18}-H); mass spectrum, m/z 328 (40), 313 (85), 296 (56), 281 (89), 273 (100); high-resolution mass spectrum calcd for $C_{22}H_{32}O_2$ (M^+) 328.2402, found 328.2402.

(*E*)-6β-Methoxy-3α,5α-cyclo-21-norcholest-17(20)-en-22-ols [(22*S*)-8a and (22*R*)-9a]. To a solution of isoamylmagnesium bromide, prepared from magnesium (0.276 g, 11.4 mg-atom) and isoamyl bromide (1.58 g, 10.5 mmol) in ether (3 mL), was added dropwise a solution of aldehyde **19** (1.92 g) in ether (1 mL). The mixture was heated under reflux for 30 min and set aside for 16 h. The reagent excess was decomposed with saturated aqueous NH_4Cl; the organic layer was filtered through Celite, dried with K_2CO_3, and evaporated. The residue (2.29 g) was chromatographed on SiO_2 (50 g, 230–400 mesh, hexanes–acetone, 98:2) to give: (1) 22*S* alcohol **8a** (0.67 g, 29% yield) (TLC, *n*-hexane–acetone, 4:1, R_f = 0.48); (2) a mixed fraction (0.04 g) consisting of **8a** and **9a**; (3) 22*R* alcohol **9a** (0.70 g, 30% yield) (TLC, the same system, R_f = 0.44).

22*S* Alcohol 8a: oil; δ_H (500 MHz) 4.975 (1 H, dt, $J_{20,22}$ = 9.0 Hz, $J_{20,16\alpha} = J_{20,16\beta}$ = 2.3 Hz, C_{20}-H), 4.182 (1 H, dt, $J_{22,20}$ = 9.0

(38) Brown, H. C.; Racherla, U. R.; Singh, S. M. *Tetrahedron Lett.* **1984**, *25*, 2411.

Hz, $J_{22,23}$ = 6.4 Hz, C_{22}-H), 3.320 (3 H, s, OCH_3), 2.779 (1 H, t, J = 2.7 Hz, C_6-H), 2.32 (2 H, m, $W/2$ = 20 Hz, C_{16}-H), 1.022 (3 H, s, C_{19}-H), 0.857 and 0.854 (6 H, 2 d, J = 6.8 Hz, C_{26}- and C_{27}-H), 0.783 (3 H, s, C_{18}-H), 0.640 (1 H, t, J = 5.0 Hz), and 0.420 (1 H, dd, J_1 = 8 Hz, J_2 = 5 Hz, cyclopropane H); mass spectrum, m/z 400 (M^+, 9), 382 (23), 368 (23), 350 (20), 335 (46), 297 (72), 286 (29), 279 (40), 253 (48), 213 (72), 81 (100); high-resolution mass spectrum calcd for $C_{27}H_{44}O_2$ 400.3341, found 400.3345.

22*S* Acetate 8c (prepared using acetic anhydride and pyridine): δ_H (500 MHz) 5.273 (1 H, dt, $J_{22,20}$ = 9.1 Hz, $J_{22,23}$ = 6.9 Hz, C_{22}-H), 4.915 (1 H, dt, $J_{20,22}$ = 9.2 Hz, $J_{20,16\alpha}$ = $J_{20,16\beta}$ = 2.4 Hz, C_{20}-H), 3.337 (3 H, s, OCH_3), 2.781 (1 H, t, J = 2.8 Hz, C_6-H), 2.509 (1 H, qt, $J_{16\alpha,16\beta}$ = 17.5 Hz, $J_{16\alpha,15\alpha}$ = $J_{16\alpha,15\beta}$ = 8.8 Hz, $J_{16\alpha,20}$ = 2.3 Hz, $C_{16\alpha}$-H), 2.3444 (1 H, br qt, $J_{16\beta,16\alpha}$ = 16.7, $J_{16\beta,15\beta}$ = 10.0 Hz, $J_{16\beta,20}$ = $J_{16\beta,15\alpha}$ = 3 Hz, $C_{16\beta}$-H), 2.013 (3 H, s, CH_3CO), 1.94 (1 H, dt, J_1 = 13.5 Hz, J_2 = 3 Hz), 1.042 (3 H, s, C_{19}-H), 0.870 and 0.869 (6 H, 2 d, J = 6.6 Hz, C_{26}- and C_{27}-H), 0.808 (3 H, s, C_{18}-H), 0.650 (1 H, t, J = 5 Hz), and 0.450 (1 H, dd, J_1 = 5 Hz, J_2 = 8 Hz, cyclopropane H).

Decouplings: (1) irradiation at δ 5.27 → δ 4.9 (t, J = 2.5 Hz), δ 2.50 → δ 4.9 (dd, J_1 = 9.2, J_2 = 1.9), δ 2.35 → δ 4.9 (dd, J_1 = 9.2, J_2 = 1.9).

22*R* Alcohol 9a: oil; δ_H (500 MHz) 4.990 (1 H, dt, $J_{20,22}$ = 8.5 Hz, $J_{20,16\alpha}$ = $J_{20,16\beta}$ = 2 Hz, C_{20}-H), 4.157 (1 H, dt, $J_{22,20}$ = 8.5 Hz, $J_{22,23}$ = 6.5 Hz, C_{22}-H), 3.318 (3 H, s, OCH_3), 2.768 (1 H, t, J = 2.9 Hz, C_6-H), 2.45 (1 H, qt, $J_{16\alpha,16\beta}$ = 19 Hz, $J_{16\beta,15\beta}$ = 10 Hz, $J_{16\beta,15\alpha}$ = $J_{16\beta,20}$ = 2 Hz, $C_{16\beta}$-H), 2.23 (1 H, qt, $J_{16\alpha,16\beta}$ = 19 Hz, $J_{16\alpha,15\alpha}$ = $J_{16\alpha,15\beta}$ = 9 Hz, $J_{16\beta,20}$ = 2 Hz, $C_{16\alpha}$-H), 1.022 (3 H, s, C_{19}-H), 0.864 and 0.860 (6 H, 2 d, J = 6.6 Hz, C_{26}- and C_{27}-H), 0.809 (3 H, s, C_{18}-H), 0.64 (1 H, t, J = 5 Hz), and 0.42 (1 H, dd, J = 5 Hz, J_2 = 8, Hz, cyclopropane H); mass spectrum, z/e 400 (9), 382 (24), 368 (23), 350 (32), 335 (54), 297 (70), 286 (26), 279 (41), 253 (53), 213 (76), 81 (100); high-resolution mass spectrum calcd for $C_{27}H_{44}O_2$ (M^+) 400.3341, found 400.3352.

22*R* Acetate 9c (prepared using acetic anhydride and pyridine): δ_H (500 MHz) 5.320 (1 H, dt, $J_{22,20}$ = 9.0 Hz, $J_{22,23}$ = 6.8 Hz, C_{22}-H), 4.933 (1 H, dt, $J_{20,22}$ = 9.0 Hz, $J_{20,16\alpha}$ = $J_{20,16\beta}$ = 3.0 Hz, C_{20}-H), 3.337 (3 H, s, OCH_3), 2.785 (1 H, t, J = 2.8 Hz, C_6-H), 2.570 (1 H, qt, $J_{16\alpha,16\beta}$ = 18.0 Hz, $J_{16\beta,15\beta}$ = 11.0 Hz, $J_{16\beta,20}$ = 3 Hz, $J_{16\beta,15\alpha}$ = 4 Hz, $C_{16\beta}$-H), 2.261 (1 H, qt, $J_{16\alpha,16\beta}$ = 18.0 Hz, $J_{16\alpha,15\alpha}$ = $J_{16\alpha,15\beta}$ = 9 Hz, $J_{16\alpha,20}$ = 2.3 Hz, $C_{16\alpha}$-H), 2.019 (3 H, s, OCH_3), 1.953 (1 H, dt, J_1 = 13.5 Hz, J_2 = 3.0 Hz), 1.043 (3 H, s, C_{19}-H), 0.875 and 0.872 (6 H, 2 d, J = 6.6 Hz, C_{26}- and C_{27}-H), 0.812 (3 H, s, C_{18}-H), 0.650 (1 H, t, J = 5 Hz), and 0.450 (1 H, dd, J = 5 Hz, J = 8 Hz, cyclopane H).

(*E*)-6β-Methoxy-3α,5α-cyclo-21-norcholest-17(20)-en-22-one (20). To a solution of alcohols **8a** and **9a** (the crude product of the above described Grignard reaction, 0.71 g, ca. 1.8 mmol) in pyridine (6.5 mL), cooled in an ice bath and stirred was added to a solution of CrO_3 (0.55 g, 5.5 mmol) in water (0.35 mL). The mixture was stirred at room temperature for 8 h, diluted with ether (20 mL), and filtered through an 1-cm layer of SiO_2. The filtrate was washed successively with cold 5% aqueous HCl, water, and saturated $NaHCO_3$ and dried (K_2CO_3). The solvent was evaporated, and the residue (0.65 g) was chromatographed on SiO_2 (20 g, 230–400 mesh, hexanes–acetone, 99.5:0.5) to give ketone **20** (0.54 g, 77% yield): ν_{max} 1685 (C=O) cm^{-1}; λ_{max} (C_2H_5OH) 242 nm (ϵ = 15785); δ_H (80 MHz) 5.88 (1 H, t, J = 3 Hz, C_{20}-H), 3.30 (3 H, s, OCH_3), 1.02 (3 H, s, C_{18}-H), 0.89 (6 H, d, J = 7 Hz, C_{26}- and C_{27}-H), 0.82 (3 H, s overlapping downfield part of d, C_{19}-H); high-resolution mass spectrum calcd for $C_{27}H_{42}O_2$ (M^+) 398.3185, found 398.3185.

Reduction of Ketone 20 with 1,1'-Bi-2-naphthol-Modified Lithium Aluminum Hydride. A. With *R*-(+) Reagent.[38] To a solution of lithium aluminum hydride in THF (0.98 M, 1 mL),[39,40] stirred at room temperature, was added ethanol (0.050 g, 1.08 mmol) in THF (1 mL), followed by the binaphthol (0.289 g, 1.01 mmol) in THF (1 mL). After 1 h the solution was cooled to −100 °C, and ketone **20** (0.132 g, 0.331 mmol) in THF (1 mL) was added during 5 min by means of a syringe. The mixture was stirred at −100 °C for 1 h and then at −78 °C for 2 h, and the reagent excess was decomposed with wet ether. The mixture was filtered through Celite, and the solvent was evaporated. The residue was dissolved in benzene, washed three times with 3% aqueous NaOH, and dried (K_2CO_3). After evaporation of benzene, the residue (0.11 g) was chromatographed on SiO_2 (4 g, 230–400 mesh, hexanes–acetone, 98.5:1.5) to give: (1) 22*S* alcohol **8a** (0.039 g, 29% yield), (2) 22*R* alcohol **9a** (0.071 g, 53% yield). Total yield: 82%; isomer ratio 22*S*:22*R* = 35:65.

B. With *S*-(−) Reagent.[38] Ketone **20** (0.055 g, 0.138 mmol) was reduced with the use of (*S*)-(−)-binaphthol (0.123 g, 0.43 mmol) analogically as described above to give: (1) 22*S* alcohol **8a** (0.048 g, 87% yield), (2) 22*R* alcohol **9a** (0.004 g, 7% yield).

(*E*)-21-(((Bromomethyl)dimethylsilyl)oxy)-6β-methoxy-3α,5α-cyclopregn-17(20)-ene (6b). To a mixture of *E* alcohol **6a** (0.460 g, 1.4 mmol), triethylamine (1.5 mL), and methylene chloride (7 mL), stirred under argon at room temperature, was added dropwise (bromomethyl)chlorodimethylsilane (0.3 mL). Stirring was continued for 40 min (until TLC indicated almost complete consumption of the alcohol); the mixture was diluted with methylene chloride (20 mL) and poured into an ice-cold aqueous Na_2HCO_3 solution. The organic layer was separated, washed with brine, and dried; the solvent was evaporated. The residue was chromatographed on SiO_2 (24 g, 100–200 mesh, hexanes–acetone, 99.5:0.5) to give silyl derivative **6b** (0.383 g, 57% yield) and starting alcohol **6a** (0.166 g, 36%).

Silyl ether was used immediately after preparation in the subsequent step.

(*Z*)-21-(((Bromomethyl)dimethylsilyl)oxy)-6β-methoxy-3α,5α-cyclopregn-17(20)-ene (7b). To a mixture of *Z* alcohol **7a** (0.238 g, 0.72 mmol), triethylamine (0.75 mL), and methylene chloride (4.5 mL), stirred under argon at room temperature, was added (bromomethyl)chlorodimethylsilane (0.18 mL). Stirring was continued for 1 h, whereupon the mixture was worked up analogically as described above for the *E* isomer. The product was chromatographed on SiO_2 (4 g, 70–230 mesh, hexanes–acetone, 99.5:0.5) to give the silyl derivative **7b** (0.281 g, 81% yield) and starting alcohol **7a** (0.039 g, 16%).

Silyl ether was immediately after preparation used in the subsequent step.

(*E*)-(22*R*)-22-(((Bromomethyl)dimethylsilyl)oxy)-6β-methoxy-3α,5α-cyclo-21-norcholest-17(20)-ene (9b). To a solution of alcohol **9a** (0.137 g, 0.34 mmol) in methylene chloride (3 mL), stirred under argon at 0 °C, was added triethylamine (0.45 mL, 3.23 mmol), followed by (bromomethyl)chlorodimethylsilane (0.120 mL, 0.88 mmol). The mixture was stirred for 1 h at room temp and poured into a cold aqueous solution of $KHCO_3$. The organic layer was separated, washed with water, and evaporated. The residue was chromatographed on SiO_2 (2 g, 140–270 mesh, hexanes–acetone, 99.5:0.5) to give the derivative **9b** (0.167 g, 88% yield): oil; δ_H (80 MHz) 4.95 (1 H, dt, $J_{20,22}$ = 7 Hz, $J_{20,16}$ = 3 Hz, C_{20}-H), 4.19 (1 H, m, C_{22}-H), 3.32 (3 H, s, OCH_3), 2.76 (1 H, t, J = 3 Hz, C_6-H), 2.42 (2 H, s, $SiCH_2Br$), 1.02 (3 H, s, C_{18}-H), 0.84 (6 H, d, J = 7 Hz, C_{26}- and C_{27}-H), 0.80 (3 H, s, C_{19}-H), 0.21 (6 H, s, SiCH).

This product was used immediately after the preparation in the subsequent step.

(*E*)-(22*S*)-22-(((Bromomethyl)dimethylsilyl)oxy)-6β-methoxy-3α,5α-cyclo-21-norcholest-17(22)-ene (8b). Similarly as described above, from alcohol **8a** (0.076 g, 0.19 mmol), using (bromomethyl)chlorodimethylsilane (0.15 mL, 0.73 mmol) and triethylamine (0.3 mL), the derivative **8b** (0.088 g, 84% yield) was prepared: δ_H (80 MHz) 4.95 (1 H, dt, $J_{20,22}$ = 7 Hz, $J_{20,16}$ = 3 Hz, C_{20}-H), 4.20 (1 H, m, C_{22}-H), 3.31 (3 H, s, OCH_3), 2.77 (1 H, t, J = 3 Hz, C_6-H), 2.42 (2 H, s, $SiCH_2Br$), 1.03 (3 H, s, C_{18}-H), 0.85 (6 H, d, J = 7 Hz, C_{26}- and C_{27}-H), 0.78 (3 H, s, C_{19}-H), 0.22 (6 H, s, SiCH).

This product was used immediately after the preparation in the subsequent step.

6β-Methoxy-3α,5α-cyclobisnorcholan-22-ols [(20*S*)-11a and (20*R*)-12a]. A. Preparation from 6b. To a solution of ether **6b** (0.340 g, 0.7 mmol) in benzene (1.5 mL), at reflux temperature, were added tributyltin hydride (97%, 0.55 mL, 1.98 mmol) and AIBN (0.013 g, 0.08 mmol) in benzene (1.5 mL) dropwise during 2 h. The mixture was refluxed for an additional 2 h and left overnight at room temperature. The solvent was evaporated, and the residue was dissolved in Me_2SO (4.5 mL) containing potassium *tert*-butoxide (95%, 0.532 g, 4.5 mmol). The mixture was heated

(39) Purchased from Aldrich.
(40) Determined iodometrically, according to Felkin, H. *Bull. Soc. Chim. Fr.* **1951**, *18*, 347.

at 95–105 °C for 16 h, cooled, and diluted with water. The crude product (0.6 g, oil) was isolated with chloroform and chromatographed on SiO_2 (10 g, 100–200 mesh, hexanes–acetone, 98:2) to give three fractions of products contaminated with tin compounds: (1) 0.050 g, *R* alcohol **12a**; (2) 0.040 g, *R* and *S* alcohols **12a** and **11a**; (3) 0.070 g, *S* alcohol **11a**.

Rechromatography of each of these fractions, using the eluting system indicated above and combining the appropriate fractions, gave:

(1) 20*R* alcohol **12a** (0.056 g, 23% yield): ν_{max} 3640 (OH) cm^{-1}; δ_H (80 MHz) 3.85–3.40 (2 H, m, C_{22}-H), 3.34 (3 H, s, OCH_3), 2.76 (1 H, m, C_6-H), 1.00 (3 H, s, C_{19}-H), 0.94 (3 H, d, J = 7 Hz, C_{21}-H), 0.74 (3 H, s, C_{18}-H); mass spectrum, m/z 346 (M^+, 28), 331 (47), 314 (65), 291 (100); high-resolution mass spectrum calcd for $C_{23}H_{38}O_2$ (M^+) 346.2872, for $C_{19}H_{31}O_2$ ($M^+ - C_4H_7$) 291.2324; found 346.2872, 291.2324 [described[25] δ_H 3.60 (2 H, m), 3.30 (3 H, s), 2.77 (1 H, br t), 1.00 (3 H, s), 0.93 (3 H, d, J = 6 Hz), 0.72 (3 H, s), 0.7–0.3 (3 H, m)].

(2) 20*S* alcohol **11a** (0.075 g, 31% yield): ν_{max} 3620 (OH) cm^{-1}; δ_H (80 MHz) 3.80–3.20 (2 H, m, C_{22}-H), 3.30 (3 H, s, OCH_3), 2.75 (1 H, m, C_6-H), 1.03 (3 H, d, J = 7 Hz, C_{21}-H), 1.00 (3 H, s, C_{19}-H), 0.74 (3 H, s, C_{18}-H); mass spectrum, m/z 346, 331, 314, 291; high-resolution mass spectrum calcd for $C_{23}H_{38}O_2$ (M^+) 346.2872, for $C_{19}H_{31}O_2$ ($M^+ - C_4H_7$) 291.2324; found 346.2872, 291.2324 [described[25] 3.50 (2 H, m), 3.30 (3 H, s), 2.77 (1 H, t), 1.03 (3 H, d, J = 6 Hz), 1.01 (3 H, s), 0.72 (3 H, s), 0.7–0.3 (3 H, s); mp 84.5–86 °C].

Acetates **12b** and **11b** were prepared from the respective alcohols using acetic anhydride and pyridine.

(20*R*)-6β-Methoxy-3α,5α-cyclobisnorcholan-22-ol acetate (12b): ν_{max} 1740 and 1240 cm^{-1}; δ_H (500 MHz) 4.200 (1 H, dd, J_{AB} = 10.8 Hz, J_{AX} = 3.6 Hz) and 3.823 (1 H, dd, J_{AB} = 10.8 Hz, J_{BX} = 7.7 Hz, C_{22}-H), 3.324 (3 H, s, OCH_3), 2.770 (1 H, t, J = 2.7 Hz, C_6-H), 2.054 (3 H, s, $COCH_3$), 1.018 (3 H, s, C_{19}-H), 0.927 (3 H, d, J = 6.7 Hz, C_{21}-H), 0.746 (3 H, s, C_{18}-H), 0.438 (1 H, dd, J_1 = 5.1 Hz, J_2 = 7.9 Hz, cyclopropane H).

(20*S*)-6β-Methoxy-3α,5α-cyclobisnorcholan-22-ol acetate (11b): ν_{max} 1740 and 1240 cm^{-1}; δ_H (500 MHz) 4.070 (1 H, dd, J_{AB} = 10.7 Hz, J_{AX} = 3.4 Hz) and 3.776 (1 H, dd, J_{AB} = 10.7 Hz, J_{BX} = 7.6 Hz, C_{22}-H), 3.324 (3 H, s, OCH_3), 2.771 (1 H, t, J = 2.7 Hz, C_6-H), 2.053 (3 H, s, $COCH_3$), 1.024 (3 H, s, C_{19}-H), 1.012 (3 H, d, J = 6.7 Hz, C_{21}-H), 0.742 (3 H, s, C_{18}-H), 0.438 (1 H, dd, J_1 = 5.1 Hz, J_2 = 7.9 Hz, cyclopropane H); mp 125–126 °C.

B. Preparation from 7b. To a solution of ether **7b** (0.241 g) in benzene (2 mL), at reflux temperature was added tributyltin hydride (0.40 mL) in benzene (2 mL) containing AIBN (0.011 g, 0.067 mmol) during 100 min. The mixture was refluxed for additional 30 min and left overnight at room temperature. The solvent was evaporated, and the residue was dissolved in Me_2SO (3.5 mL) and treated with potassium *tert*-butoxide (0.450 g). The mixture was stirred at 100 °C for 20 h, cooled, and poured into ice–water. The product (0.40 g), isolated with ethyl acetate, was chromatographed on SiO_2 (4 g, 230–400 mesh, hexanes–acetone, 97:3) to give 20*R* alcohol **12a** (0.0476 g, 28% yield) and 20*S* alcohol **11a** (0.049 g, 29% yield).

(20*S*,22*S*)-6β-Methoxy-3α,5α-cyclocholestan-22-ol (13). To a solution of bromomethylsilyl ether **8b** (0.078 g, 0.14 mmol) in benzene (1.5 mL), boiling under argon, was added a solution of tributyltin hydride (0.19 mL, 0.70 mmol) and AIBN (0.009 g) in benzene (2 mL) during 1 h. The mixture was heated at reflux temperature for an additional hour, and the solvent was evaporated under reduced pressure. The residue was dissolved in Me_2SO (2.5 mL), potassium *tert*-butoxide (0.330 g, 2.9 mmol) was added, and the mixture was stirred at 105 °C for 13 h. Workup with ethyl acetate and chromatography on SiO_2 (1.7 g, 140–270 mesh, hexanes–acetone, 99.7:0.3) gave sterol **13** (0.039 g, 67% yield): oil; ν_{max} 3630 cm^{-1}; δ_H (400 MHz) 3.594 (1 H, dd, J_1 = 8.0 Hz, J_2 = 4.6 Hz, C_{22}-H), 3.294 (3 H, s, OCH_3), 2.743 (1 H, t, J = 2.8 Hz, C_6-H), 0.993 (3 H, s, C_{19}-H), 0.864 (3 H, d, J = 6.3 Hz, C_{21}-H), 0.860 (6 H, d, J = 6.6 Hz, C_{26}- and C_{27}-H), 0.697 (3 H, s, C_{18}-H), 0.650 (1 H, t, J = 4.8 Hz), and 0.438 (1 H, dd, J_1 = 8 Hz, J_2 = 5 Hz, cyclopropane H); mass spectrum, m/z 416 (M^+, 1.6), 401 (1.5), 384 (3.2), 361 (3.8), 358 (0.2), 43 (100); high-resolution mass spectrum calcd for $C_{28}H_{48}O_2$ (M^+) 416.3654, found 416.3660 [described[28] δ_H (200 MHz) 3.63 (1 H, dd, J = 7.5, 4.4 Hz), 3.34 (3 H, s), 2.78 (1 H, t, J = 2.7 Hz), 1.03 (3 H, s), 0.90 (9 H, d, J = 6.5 Hz), 0.74 (3 H, s), 0.44 (1 H, dd, J = 5, 8.2 Hz).[41]

(20*R*,22*R*)-6β-Methoxy-3α,5α-cyclocholestan-22-ol (14). To a solution of 22*R* silyl ether **9b** (0.157 g, 0.28 mmol) in benzene (1.5 mL), boiling under argon, were added tributyltin hydride (0.27 mL, 1.0 mmol) and AIBN (0.006 g, 0.04 mmol) in benzene (1.8 mL) during 1.5 h. The mixture was heated at reflux temperature for additional 2 h, and the solvent was evaporated. The residue was dissolved in Me_2SO (2.5 mL), potassium *tert*-butoxide (0.241 g, 2.15 mmol) was added, and the mixture was stirred at 100 °C for 17 h. Workup with ethyl acetate gave the crude product (0.335 g), which was chromatographed on SiO_2 (3 g, 140–270 mesh, hexanes–acetone, 99.7:0.3) to give sterol **14** (0.084 g, 71% yield): oil; ν_{max} 3640 cm^{-1}; δ_H (400 MHz) 3.845 (1 H, br t, J = 5.8 Hz, C_{22}-H), 3.328 (3 H, s, OCH_3), 2.776 (1 H, t, J = 2.7 Hz, C_6-H), 1.025 (3 H, s, C_{19}-H), 0.863 and 0.850 (6 H, 2 d, J = 6.6 Hz, C_{26}- and C_{27}-H), 0.788 (3 H, d, J = 6.6 Hz, C_{21}-H), 0.703 (3 H, s, C_{18}-H), 0.651 (1 H, t, J = 4.8 Hz), and 0.437 (1 H, dd, J_1 = 8 Hz, J_2 = 5 Hz, cyclopropane H); mass spectrum, m/z 416 (M^+, 42), 401 (53), 384 (62), 361 (88), 358 (21), 55 (100); high-resolution mass spectrum calcd for $C_{28}H_{48}O_2$ (M^+) 416.3654, found 416.3660 [described for 20*S*,22*R* isomer[28] C_{21}-H, δ 0.92 ppm, J = 6.6 Hz].[41]

6β-Methoxy-3α,5α-cyclobisnorcholane-21,22-diol (21). To a solution of ether **6b** (0.915 g, 1.9 mmol) in benzene (3 mL), at reflux temperature, were added tributyltin hydride (97%, 1.25 mL, 4.5 mmol) and AIBN (0.018 g, 0.1 mmol) in benzene (1.5 mL) dropwise during 2 h. The mixture was refluxed for additional 2.5 h, and the solvent was evaporated. The residue **10a** was dissolved in dimethylformamide (10 mL) containing KF (1.7 g, 29.3 mmol) and hydrogen peroxide (30%, 1.2 mL), and the mixture was heated at 80–85 °C for 3 days. Workup and chromatography of the crude product on SiO_2 (15 g, 100–200 mesh, hexanes-acetone, 96:4) gave: (1) alcohol **6a** (0.114 g, 18% yield); (2) diol **21** (0.528 g, 78% yield): ν_{max} 3630 and 3450 (OH) cm^{-1}; δ_H (60 MHz) 4.27–3.44 (4 H, m, C_{21}- and C_{22}-H), 3.32 (3 H, s, OCH_3), 2.80 (1 H, m, C_6-H), 1.01 (3 H, s, C_{19}-H), 0.75 (3 H, s, C_{18}-H); mass spectrum, m/z 362 (M^+, 50), 347 (58), 330 (71), 307 (100); mp 133–134 °C. Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.15; H, 10.71.

6β-Methoxy-21,22-epoxy-3α,5α-cyclobisnorcholane (22). To a solution of diol **21** (0.303 g, 0.84 mmol) in THF (2.5 mL), stirred under argon at −5 °C, was added butyllithium in hexane (1.5 M, 700 μL, 1.05 mmol), whereupon, after 20 min, a solution of tosyl chloride (0.215 g, 1.1 mmol) in THF (2.5 mL) was added. The mixture was allowed to warm to room temperature for ca. 20 min and was left aside for additional 2 h. The product was isolated with toluene. Organic solution was washed with water and evaporated in vacuo. The residue was dissolved in *tert*-butyl alcohol (15 mL), potassium *tert*-butoxide (0.288 g, 2.57 mmol) was added, and the mixture was boiled for 30 min and left at room temperature for 2 h. Workup with toluene and chromatography of the crude product on SiO_2 (10 g, 100–200 mesh, hexanes–acetone, 99.5:0.5) gave oxetane **22** (0.236 g, 82% yield): ν_{max} (KBr) 1100 and 980 (C–O–C) cm^{-1}; δ_H (500 MHz) 4.711 (2 H, m, CH_2O), 4.552 (1 H, dd, J_{AB} = 6.9 Hz, J_{AX} = 6.0 Hz, CH_ACH_BO), 4.501 (1 H, dd, J_{BA} = 6.9 Hz, J_{BX} = 6.0 Hz, CH_AH_BO), 3.323 (3 H, s, OCH_3), 3.092 (1 H, m, C_{20}-H), 2.773 (1 H, t, C_6-H), 1.018 (3 H, s, C_{19}-H), 0.599 (3 H, s, C_{18}-H), 0.625 (1 H, br t, J = 4.8 Hz), and 0.410 (1 H, dd, J_1 = 9 Hz, J_2 = 5 Hz, cyclopropane H); mass spectrum, m/z 344 (37), 329 (64), 289 (100); mp 86–87 °C. Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.89; H, 10.79.

(20*S*)-6β-Methoxy-25-((2′-tetrahydropyranyl)oxy)-23,24-bisdehydro-3α,5α-cyclocholestan-21-ol (24a). To a solution of 3-methyl-3-((2′-tetrahydropyranyl)oxy)but-1-yne **23** (1.075 g, 6.4 mmol) in THF (1 mL), stirred under argon at −78 °C, was added butyllithium in hexane (1.6 M, 4 mL, 6.4 mmol). The mixture was stirred for 10 min, whereupon addition was made of oxetane **22** (0.220 g, 0.64 mmol) in THF (1.5 mL), followed by $BF_3{\cdot}Et_2O$ (0.675 mL, 6.4 mmol). Stirring at −78 °C was continued for 4 h, whereupon the mixture was diluted with saturated aqueous NH_4Cl, and the product was isolated with toluene and chromatographed on SiO_2 (10 g, 70–230 mesh). Elution with hexanes–acetone, 98:2, gave the starting material **22** (0.066 g, 30%). Elution with hexanes–acetone, 95:5, afforded adduct **24a** (0.189 g, 83%

(41) In the described spectrum all signals (0-point) are shifted by 0.04 ppm upfield in relation to our measurements.

yield calculated against the consumed oxetane): ν_{max} (film) 3450 (OH), 2220 (C≡C) cm^{-1}; δ_H (400 MHz) 5.030 (1 H, m, $C_{2'}$-H), 3.926 (1 H, m, $C_{6'}$-H), 3.758 (1 H, dt, $J_{21A,21B}$ = 11.3 Hz, $J_{21A,20} = J_{21A,17}$ = 3 Hz, C_{21A}-H), 3.547 (1 H, br dd, $J_{21B,21A}$ = 11.0 Hz, $J_{21B,20}$ = 7.2 Hz, C_{21B}-H), 3.467 (1 H, ddd, J_1 = 11.0 Hz, J_2 = 5.4 Hz, J_3 = 3 Hz, $C_{6'}$-H), 3.292 (3 H, s, OCH_3), 2.742 (1 H, t, J = 2.7 Hz, C_6-H), 1.481 and 1.434 (6 H, 2 s, C_{26}- and C_{27}-H), 0.992 (3 H, s, C_{19}-H), 0.703 (3 H, s, C_{18}-H), 0.620 (1 H, br t, J = 4.8 Hz), and 0.410 (1 H, dd, J_1 = 9.0 Hz, J_2 = 5.2 Hz, cyclopropane H); mass spectrum, m/z 497 (M^+ - 15, 0.4); high-resolution mass spectrum calcd for $C_{32}H_{43}O_4$ (M^+ - CH_3) 497.3631, found 497.3625.

(20*S*)-6β-Methoxy-25-((2′-tetrahydropyranyl)oxy)-23,24-didehydro-3α,5α-cyclocholestane (24c). A mixture of alcohol **24a** (0.050 g, 0.097 mmol), tosyl chloride (0.147 g, 0.77 mmol), and pyridine (1 mL) was set aside for 16 h. Workup gave tosylate **24b** (0.061 g, 94% yield): ν_{max} (film) 1600 and 1500 (tosyl) cm^{-1}; δ_H (80 MHz) 7.78 and 7.32 (4 H, 2 dd, aromatic H), 4.93 (1 H, m, $C_{2'}$-H), 4.32–3.40 (4 H, m, C_{21}-H and $C_{6'}$-H), 3.31 (3 H, s, OCH_3), 2.75 (1 H, m, C_6-H), 2.44 (3 H, s, C_6H_4-CH_3 overlapping 1 H, m, C_{20}-H), 1.42 and 1.37 (6 H, 2 s, C_{26}- and C_{27}-H), 1.01 (3 H, s, C_{19}-H), 0.68 (3 H, s, C_{18}-H).

To a boiling solution of lithium aluminum hydride (0.324 g, 9 mmol) in THF (1.5 mL) was added tosylate **24b** (0.179 g, 0.27 mmol) in THF (3 mL). The mixture was refluxed for 45 min. Workup with saturated aq Na_2SO_4 afforded the crude product (0.123 g), which was purified on SiO_2 (5 g, 70–230 mesh, hexanes–acetone, 99.5:0.5) to give the derivative **24c** (0.111 g, 83% yield): ν_{max} (film) 2220 (C≡C) cm^{-1}; δ_H (400 MHz) 5.045 (1 H, m, $C_{2'}$-H), 3.933 (1 H, m, $C_{6'}$-H), 3.467 (1 H, m, $C_{6'}$-H), 3.302 (3 H, s, OCH_3), 2.750 (1 H, t, J = 2.6 Hz, C_6-H), 1.493 and 1.494 (3 H, 2 s, C_{26}-H), 1.457 and 1.458 (3 H, 2 s, C_{27}-H), 0.999 (3 H, s, C_{19}-H), 0.952 and 0.947 (3 H, 2 d, J = 6.8 Hz, C_{21}-H), 0.695 (3 H, s, C_{18}-H), 0.626 (1 H, t, J = 4.8 Hz), and 0.411 (1 H, dd, J_1 = 7.3 Hz, J_2 = 4.8 Hz, cyclopropane H); mass spectrum, m/z 496 (M^+, 12), 481 (11), 464 (6), 441 (10), 412 (22), 394 (18), 389 (12), 363 (49), 281 (50), 253 (52), 85 (100); high-resolution mass spectrum calcd for $C_{33}H_{52}O_3$ (M^+) 496.3916, found 496.3916.

(20*S*)-6β-Methoxy-25-((2′-tetrahydropyranyl)oxy)-3α,5α-cyclocholestane (25a). A mixture of acetylene **24c** (0.076 g), $NaHCO_3$ (0.042 g), 10% palladium-on-cabon (0.020 g), and dioxane (3.5 mL) was vigorously stirred under hydrogen for 6 h. Workup and chromatography of the product on SiO_2 (8 g, 230–400 mesh, hexanes–acetone, 99.7:0.3) afforded the saturated product **25a** (0.057 g, 75% yield): oil; δ_H (500 MHz) 4.724 (1 H, m, $C_{2'}$-H), 3.956 (1 H, m) and 3.44 (1 H, m, $C_{6'}$-H), 3.322 (3 H, s, OCH_3), 2.771 (1 H, t, J = 2.5 Hz, C_6-H), 1.208 and 1.190 (6 H, 2 s, C_{26}- and C_{27}-H), 1.021 (3 H, s, C_{19}-H), 0.824 (3 H, d, J = 6.5 C_{21}-H), 0.713 (3 H, s, C_{18}-H), 0.646 (1 H, t, J = 4.9), 0.436 (1 H, dd, J_1 = 7.3 Hz, J_2 = 4.9 Hz, cyclopropane H); mass spectrum, m/z 500 (M^+, 0.7), 485 (1.5), 445 (2.5), 398 (1.3), 367 (8), 85 (100); high resolution mass spectrum for $C_{33}H_{56}O_3$ (M^+) calcd 500.4229, found 500.4229.

(20*S*)-6β-Methoxy-3α,5α-cyclocholestan-25-ol (25b). To a solution of THP–ether **25a** (0.018 g) in methanol (3.5 mL) containing a few drops of chloroform, stirred at 0 °C, was added pTSA (0.003 g). After 1 h at 0 °C an excess of K_2CO_3 was added, and the product was isolated with toluene. Alcohol **25b** (0.013 g, 87% yield) was obtained: ν_{max} 3450 (OH) cm^{-1}; δ_H (500 MHz) 3.322 (3 H, s, OCH_3), 2.767 (1 H, t, J = 2.7 Hz, C_6-H), 1.215 (6 H, s, C_{26}- and C_{27}-H), 1.022 (3 H, s, C_{19}-H), 0.836 (3 H, d, J = 6.6 Hz, C_{21}-H), 0.717 (3 H, s, C_{18}-H), 0.626 (1 H, t, J = 4.8 Hz), and 0.411 (1 H, dd, J_1 = 7.3 Hz, J_2 = 4.8 Hz, cyclopropane H); mass spectrum, m/z 416 (M^+, 21), 401 (33), 366 (15), 361 (42), 343 (13), 324 (13), 301 (11), 255 (23), 59 (100); high-resolution mass spectrum for $C_{28}H_{48}O_2$ (M^+) calcd 416.3654, found 416.3676.

(20*S*)-25-Hydroxycholesterol (26).[37] A mixture of i-cholesterol derivative **25a** (0.060 g), dioxane (4.5 mL), and pTSA (0.008 g) was stirred at 60–80 °C for 4 h and set aside at room temperature for 16 h. Workup and chromatography of the crude product on SiO_2 (5 g, 70–230 mesh, hexanes–acetone, 9:1) gave diol **26** (0.043 g, 89% yield): ν_{max} 3600 cm^{-1}; δ_H (80 MHz) 5.35 (1 H, m, C_6-H), 3.47 (1 H, m, C_3-H), 1.23 (6 H, s, C_{26}- and C_{27}-H), 1.02 (3 H, s, C_{19}-H), 0.84 (3 H, d, J = 6.0 Hz, C_{21}-H), 0.69 (3 H, s, C_{18}-H); mass spectrum, m/z 402 (M^+, 8), 384 (23), 369 (12), 351 (8), 342 (12), 59 (100); mp 189–191 °C [described[37] δ_H 5.34 (1 H, m), 3.45 (1 H, m), 1.22 (6 H, s), 0.84 (3 H, d, J = 6 Hz), 0.68 (3 H, s); mp 189.5–190.5 °C].

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Registry No. **6a**, 119005-00-4; **6b**, 119005-06-0; **7a**, 119068-30-3; **7b**, 119005-07-1; **8a**, 126543-92-8; **8b**, 126543-93-9; **8c**, 126543-94-0; **9a**, 126543-95-1; **9b**, 126543-96-2; **9c**, 126543-97-3; **10a**, 126640-58-2; **11a**, 51231-23-3; **11b**, 53139-47-2; **12a**, 65166-03-2; **12b**, 82210-83-1; **13**, 38379-55-4; **14**, 126640-59-3; **15**, 64338-43-8; **16**, 74348-77-9; **17**, 119005-02-6; **18**, 87726-19-0; **19**, 126543-98-4; **20**, 126543-99-5; **21**, 119005-03-7; **22**, 119005-04-8; **23**, 96354-27-7; **24a**, 119005-05-9; **24b**, 119005-08-2; **24c**, 119068-31-4; **25a**, 126640-60-6; **25b**, 53177-01-8; **26**, 53176-99-1; phenylselenyl bromide, 34837-55-3; isoamyl bromide, 107-82-4; (bromomethyl)chlorodimethylsilane, 16532-02-8.

Supplementary Material Available: Copies of ^1H NMR spectra of compounds **6a**, **7a**, **8a**, **8c**, **9a**, **9c**, **14**, **16–20**, **22**, **24a**, **24c**, **25a**, and **25b** (35 pages). Ordering information is given on any current masthead page.