# Synthesis of (23*R*)- and (23*S*)-23*H*-Isocalysterols, Marine Sterols with a Cyclopropene Moiety in the Side Chain

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A synthesis of (23*R*)- and (23*S*)-23*H*-calysterols **2a** and **2b** from pregnanoic ester **10** is reported. Alkylation of **10** with dibromide **19b**, followed by reduction of the carboethyloxy group to a methyl group, afforded (*Z*)-vinylic bromide **22**. Dibromocyclopropanation of **22** yielded the diastereomeric tribromocyclopropane derivatives **15c** and **15d**. The corresponding 3-hydroxy-5-ene **17c** was transformed into **2a** via **25** and a cyclopropenyllithium intermediate. An alternative synthetic route involving vinylsilane **13** and (*E*)-vinylic bromide **14** has also been examined.

## Introduction

Many marine natural products[1,2] show structural features rarely occurring in those of terrain origin, posing new questions regarding their biosynthesis, structure–biological activity relationships, and synthesis. Calysterols are unusual sterols in that they have cyclopropene moieties incorporated in their structures. The first compound of this group, calysterol **1** [(28*R*), Figure 1 ], isolated from the Mediterranean sponge *Calyx niceaensis*, was reported[3] in 1975. It has since been shown that certain other sponges contain calysterol along with isomers differing in the position of the double bond in the cyclopropene ring (**2** and **3**) as well as the respective 5,6-dihydro derivatives.[4–6] Two diastereomeric 23*H*-isocalysterols have been identified, **2a** (23*R*) isolated from *Calyx niceaensis*[6] and **2b** (23*S*)[7] obtained from the Caribbean sponge *Calyx podatypa*. Cyclopropene derivatives are scarce in Nature; as far as we are aware, the only reported examples are calysterols, sterculic acid and few other fatty acids,[8,9] the antibiotic penitricin,[10] and two sesquiterpenes.[11]

For a study of calysterol synthesis, we have chosen 23*H*-isocalysterols **2** since both epimers of this compound differing in the configuration at the stereogenic center in the cyclopropane ring (C-23) are known. Difficulties encountered in the unsuccessful attempts to synthesize calysterols have stemmed mainly from the high reactivity of the cyclopropene system.[17–19] For this reason, we planned to introduce the double bond into a preformed cyclopropane intermediate in the final stages of the synthesis. Our retrosynthetic analysis is illustrated in Scheme 1. It was envisaged that calysterols could be generated by methylation of the lithiocyclopropenyl derivative ***i***, which, in turn, could be obtained from the *gem*-dihalo intermediate ***iii***, where X = halogen and Y = trimethylsilyl group or halogen. The latter represent the products of dihalocyclopropanation of olefin ***iv***, where Y = trimethylsilyl group or halogen. It was anticipated that ***iv*** could be prepared stereoselectively by alkylation of the easily accessible pregnanoic ester ***v*** using an allylic bromide bearing an appropriate substituent Y ***vi***. Alternatively, a precursor with the methyl group at the cyclopropane ring ***ii***, where X = halogen or other leaving

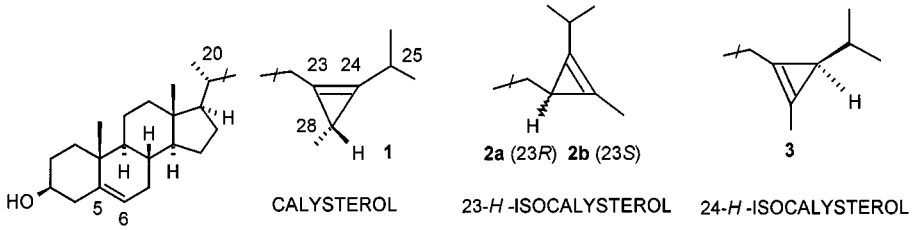


Figure 1. Structures of isomeric calysterols isolated from sponges *Calyx niceaensis* and *Calyx podatypa*

Studies by Djerassi and co-workers on marine sterols have led to the elucidation of the biosynthetic pathways leading to calysterols[12,13] and have contributed a great deal to the understanding of their chemical and spectroscopic properties.[14] An account of the efforts made towards constructing a cyclopropene-containing sterol side-chain has been published,[15] but none of the calysterols have hitherto been synthesized.[16]

group and Y = halogen or trimethylsilyl group, was considered. It was assumed that the intermediate ***ii*** could be obtained from ***iii*** by methylation. Some model experiments verified important points of this plan and also indicated that an ***i***-steroid system (6β-methoxy-3α,5-cyclo-) could be used for temporary protection of the latent C-3 hydroxy group and the C-5,C-6 double bond in isocalysterol.[20]

In a first series of experiments, we set out to synthesize a dibromo-trimethylsilyl intermediate corresponding to ***iii***, where Y = $SiMe_3$ and X = Br (Scheme 1). Its methyl-

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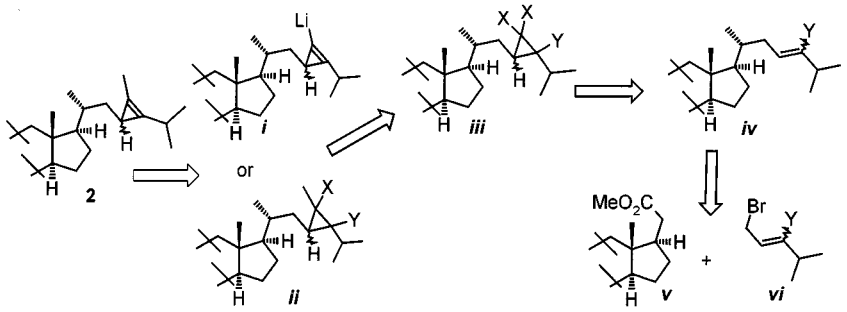
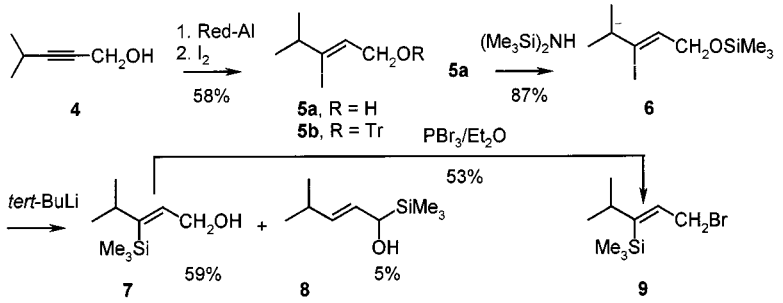


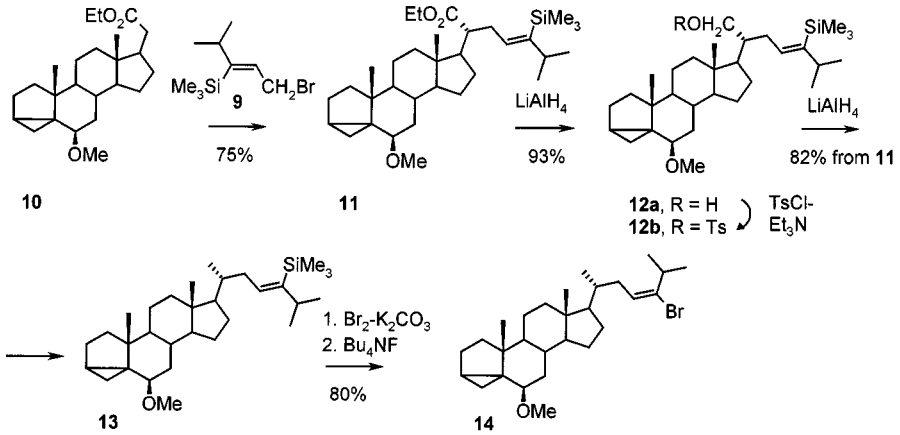
Scheme 1. Retrosynthetic analysis of compounds **2**



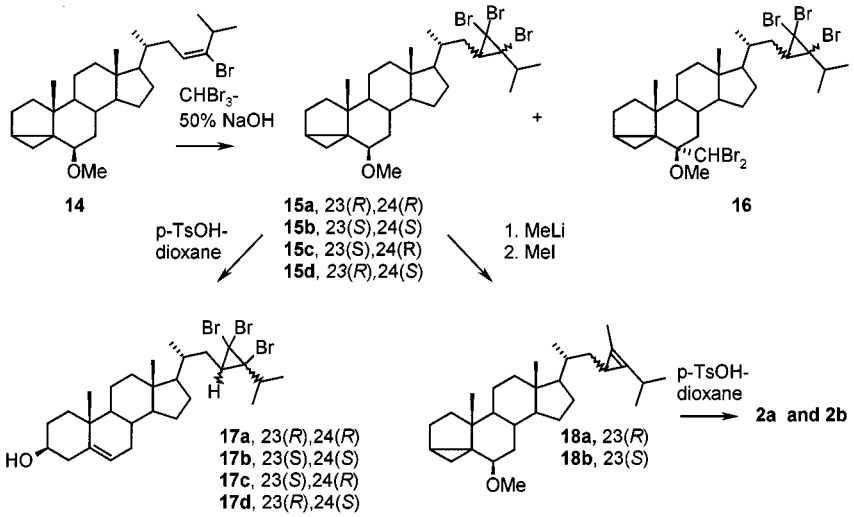
Scheme 2. Synthesis of the side chain building block **9**

ation[21–23] was to be followed by halodesilylation, which appeared to be the most promising method for generating the double bond.[24,25] Accordingly, 4-methylpent-2-yn-1-ol **4**[26,27] (Scheme 2) was treated with Red-Al® and then with iodine[28] to yield vinylic iodide **5a**. After protecting the hydroxy group as a trityl derivative to give **5b**, this was treated with two molar equivalents of *tert*-butyllithium in order to effect iodine–lithium exchange, and then with an excess of trimethylsilyl chloride. No silylation product could be detected. However, when the alcohol **5a** was first transformed into the trimethylsilyl ether **6** and the latter was treated with *tert*-butyllithium (2.1 molar equivalents), a 1,4-shift of the silyl group proceeded smoothly[29] providing vinylsilane **7** in 59% yield along with ca. 5% of the"retro-Brook" product **8**[30] and some desilylated product [(*E*)-4-methylpent-2-en-1-ol]. Alcohol **7** was transformed into bromide **9** using phosphorus tribromide.

Alkylation of ester **10**[31,32] (Scheme 3) with bromide **9** afforded virtually stereoselectively product **11** with a cholestane carbon skeleton, which was transformed into the corresponding C-21 methyl derivative **13** in the standard manner via alcohol **12a** and tosylate **12b**. Vinylsilane **13** was envisaged as the key intermediate for the cyclopropanation reaction. However, all our attempts to carry out its reaction with bromoform under the phase-transfer conditions[33,34] were unsuccessful. Similarly, **13** resisted reaction with phenyl(tribromomethyl)mercury.[35] The synthesis of steroids with cyclopropane-bearing side-chains by dichloro-[36,37] or dibromocarbene[12,38] addition to olefins under phase-transfer conditions has been widely studied. It has been shown that trisubstituted alkenes afford the corresponding dihalocyclopropanes in good yields. On the other hand, 4-methyl-1-trimethylsilylcyclohex-1-ene has been found to react readily with dichlorocarbene[39] and our own model experiments concerning the addition of dibromocarbene to some vinylsilanes were encouraging.[20] The lack of reactivity of compound **13** suggests that the combined steric effect of the trimethylsilyl and isopropyl



Scheme 3. Attempted synthesis of calysterols via the vinylsilane derivative **13**




Scheme 4. Synthesis of calysterols via the vinyl bromide derivative **14**

groups prevents the reagent from gaining access to the double bond.

The above experiments prompted a revision of our initial choice of the Y group in the key intermediates ***iii*** and ***iv*** (Scheme 1). We turned our attention to the intermediates where Y = Br, in the expectation that the less hindered vinylic bromide ***iv***, Y = Br, would be better suited for the cyclopropanation reaction. In an initial examination of the modified scheme, (*Z*)-vinylsilane **13** was treated with bromine in carbon tetrachloride solution and then the crude dibromo derivative was reacted with tetrabutylammonium fluoride. (*E*)-Vinylic bromide **14** was obtained stereospecifically in 80% yield (inversion of configuration). The (23*E*)-configuration was assigned to this product by direct comparison with the (*Z*)-isomer (**22**) obtained by a stereochemically unambiguous route (vide infra). The stereoselectivity of the bromodesilylation reaction of the sterically congested vinylsilane **13** is noteworthy. It has been reported that silylstyrenes[40,41] and some sterically hindered β,β-disubstituted vinylsilanes[42,43] afford the corresponding vinylic halides with retention of the double-bond configuration. Only unhindered vinylsilanes tend to react with inversion of configuration.[44]

Vinylic bromide **14** was subjected to dibromocyclopropanation by the method of Mąkosza and Fedoryński[33] in a small scale reaction in which magnetic stirring was supplemented by sonication[45] (ultrasonic cleaning tank, 140 W). The reaction proceeded relatively rapidly (ca. 2 h) to afford an inseparable mixture of two dibromocyclopropanes in a ratio of ca. 1:1, to which structures **15a** and **15b** [(23*R*,24*R*) and (23*S*,24*S*), respectively] (Scheme 4) were assigned. The respective alcohols **17a** and **17b**, obtained after hydrolysis of the protecting grouping (TsOH/aqueous dioxane[46]), were separated (HPLC) and fully identified. Ultimately, all four diastereomeric tribromides corresponding to the structure **17** were characterized in the course of this work (vide infra).

From some side products formed in the dibromocyclopropanation reaction, a fraction consisting mainly of one compound was isolated by column chromatography (ca. 10% yield). On the basis of its MS data (5 bromine atoms) and its $^1$H-NMR spectrum (which lacked a 6-H signal), this compound was assigned the structure **16**, resulting from a carbene insertion into the C(6)–H bond.

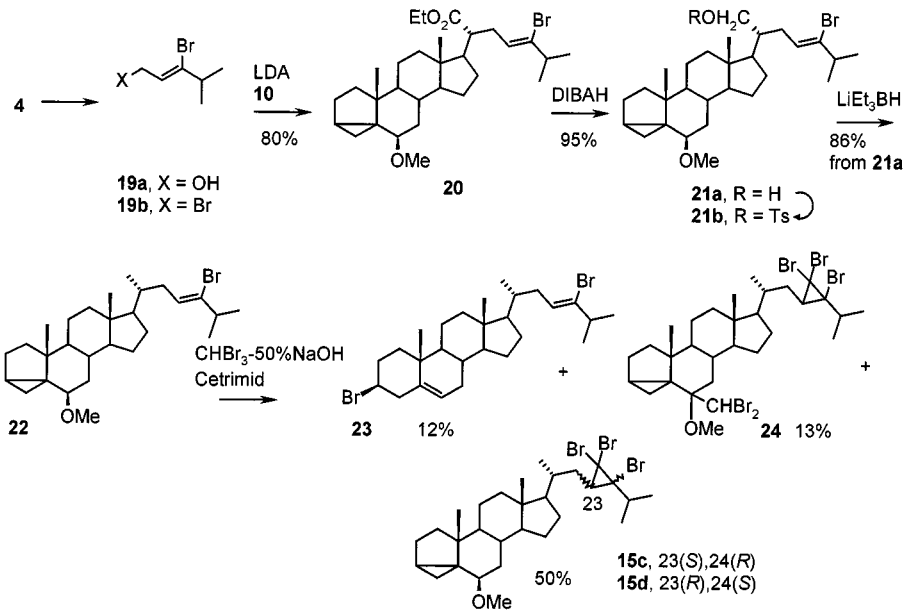
Transformation of the tribromocyclopropanes **15** into the corresponding methylcyclopropene derivative was carried out using the method developed by Baird and coworkers.[47,48] Thus, **15a** and **15b** were treated with an excess of methyllithium in diethyl ether at –70 °C. The reaction mixture was allowed to warm to room temperature so as to generate the intermediate cyclopropenyl anion (corresponding to ***i***, Scheme 1), which was then quenched with methyl iodide. Two diastereomeric calysterol derivatives **18a** and **18b** were obtained in 44% overall yield. The structures of these products were confirmed by their high-resolution MS data and their $^1$H-NMR spectra, in particular by the presence in the latter of two doublets at δ = 1.99 and 2.01, $J$ = 1.6 Hz. These chemical shifts and coupling constant are in good agreement with the signals of cyclopropene methyl group protons reported for calysterols.

Having completed the construction of the cyclopropene-bearing side-chain, we attempted to hydrolyse the ***i***-steroid grouping in **18a**–**b**. Compounds **18a**–**b** were heated at 93–95 °C in aqueous dioxane containing some TsOH. It was gratifying to find that the product consisted of a mixture of calysterols, which could be separated by HPLC using a reversed-phase analytical column. Pure compounds **2a** and **2b** were identified by their $^1$H- and $^{13}$C-NMR spectra as well as by MS data and were shown to be identical to the natural products (Table 1 and 2; see Experimental Section).

The cyclopropene derivatives were found to decompose upon storage in a refrigerator for a few days. Decomposition products of **18** could be detected by HPLC and by MS analysis; the mass spectrum of an aged sample of **18** fea-

Table 1. $^1$H-NMR data (500 MHz) of synthetic 23*H*-isocalysterols **2a** and **2b**, and reported[7] data (400 MHz) for the natural products

| H | **2a** (23*R*) | | | **2b** (23*S*) | | |
|---|---|---|---|---|---|---|
| | recorded | reported | Δδ | recorded | reported | Δδ |
| 18 | 0.694 (s) | 0.689 (s) | 0.005 | 0.687 (s) | 0.681 (s) | 0.006 |
| 21 | 1.009 (d, 6.2) | 1.004 (d, 6.5) | 0.005 | 1.012 (d, 6.5) | 1.005 (d, 6.5) | 0.007 |
| 19 | 1.012 (s) | 1.007 (s) | 0.005 | 1.012 (s) | 1.006 (s) | 0.006 |
| 27 | 1.102 (d, 7.0) | 1.098 (d, 6.8) | 0.004 | 1.094 (d, 6.9) | 1.088 (d, 6.9) | 0.006 |
| 26 | 1.117 (d, 6.9) | 1.113 (d, 6.7) | 0.004 | 1.119 (d, 6.9) | 1.114 (d, 6.9) | 0.005 |
| 29 | 1.993 (d, 1.5) | 1.990 (d, 1.6) | 0.003 | 2.013 (d, 1.5) | 2.009 (d, 1.6) | 0.004 |
| 25 | 2.660 (sept, q, 6.8, 1.5) | 2.654 (sept, q, 6.9, 1.6) | 0.006 | 2.632 (sept, q, 6.8, 1.5) | 2.626 (sept, q, 6.8, 1.6) | 0.006 |
| 3 | 3.470–3.560 (m) | 3.521 (m) | | 3.470–3.570 (m) | 3.520 (m) | |
| 6 | 5.320–5.370 (m) | 5.349 (m) | | 5.330–5.370 (m) | 5.349 (m) | |



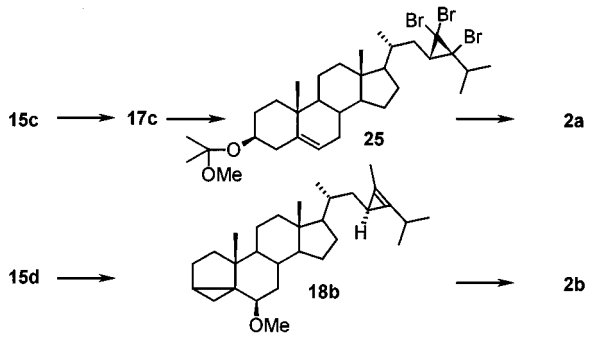

Scheme 5. Improved synthesis of calysterols **2a** and **2b**

tured an ion corresponding to [$M^+$ + O] as well as ions of higher mass. Oxidation[49] and dimerization[50,51] are well-known reactions of cyclopropene derivatives.

Having synthesized isocalysterols from the steroidal building block **10** via the vinylsilane **13** and the vinylic bromide **14**, we then attempted to synthesize these natural products by a shorter and more efficient synthetic route. (*Z*)-Dibromide[52] **19b** was prepared from propargyl alcohol **4** via bromo alcohol **19a** (Scheme 5) in a manner analogous to that used for the preparation of iodide **5a**. The (*Z*)-configuration of the double bond in **19b** follows from the established mechanism of hydroalumination–bromination reactions.[28,53,54] Alkylation of ester **10** with dibromide **19b** gave **20** in 80% yield. For transforming **20** into **22**, DIBAH was used to reduce the ester group, while L-Selectride® was used for the tosylane reduction. With these reagents, the vinylic bromide (*Z*)-**22** was obtained (82% overall yield), isomeric to the previously prepared compound (*E*)-**14**.

Bromoolefin **22** was subjected to dibromocyclopropanation using Cetrimid® (Aldrich) as a phase-transfer catalyst. Chromatography of the crude product on a silica gel column afforded, in order of elution, 3β,24-dibromide **23** (12% yield), the carbene insertion product **24** (13%), and the desired dibromocyclopropane derivatives **15**. The bulk of the latter product was eluted as a mixture of diastereomers (42%). Small amounts of pure **15c** (more mobile, 5%) and **15d** (3%) were also collected. Diastereomers **15c** and **15d** could be completely separated by preparative HPLC. An (*R*) configuration at C-23 was subsequently established for the isomer **15d** through its transformation to (23*S*)-23*H*-isocalysterol **2b**. This allowed configurational assignments for **15c** and **15d** of (23*S*,24*R*) and (23*R*,24*S*), respectively.

Diastereomer **15d** was subjected to the Baird elimination–methylation procedure to give ***i*-methyl ether **18b** (Scheme 6) in 53% yield. Acid hydrolysis of the protective group provided crude (23*S*)-23*H*-isocalysterol **2b** in 31% yield and purification of this product by HPLC yielded a sample identical to that already prepared. In order to minimize material losses during ***i*-steroid hydrolysis in cyclopropene ring-containing intermediates, it is best carried out at the stage of tribromocyclopropane derivatives. Two isomeric 3-hydroxy-tribromocyclopropanes, **17a** and **17b**, had already been prepared by hydrolysis of the respective ***i*-steroids **15** followed by HPLC separation. Since it was tempting to synthesize all four diastereomers of **17**, which would confirm the diastereoselectivity of the cyclopropanation reac-




Scheme 6

tion, pure tribromide **15d** was treated with TsOH in aqueous dioxane to give free alcohol **17d** in 96% yield. In an analogous manner, **15c** was transformed into **17c**. Comparison of the four isomeric tribromides **17** by HPLC confirmed their isomeric purities.

Alcohol **17c** was treated with 2-methoxypropene to provide a temporary protection of the hydroxy group. The derivative **25** (Scheme 6), without isolation, was treated with methyllithium and then with methyl iodide. The crude reaction product was hydrolyzed with methanol in the presence of pyridine-deactivated[55] Amberlyst-15 to give (23*R*)-23*H*-isocalysterol **2a** in 73% yield. A sample purified by preparative HPLC showed $[\alpha]_{589}^{20} = -44.4$, in accord with the reported [38] value $[\alpha]_{589}^{22} = -47.3$. The melting point of 109–111 °C determined for the synthetic material (the quantity was insufficient for recrystallization) was somewhat lower than that reported for the natural product (115–116 °C).

In the modified synthetic cycle, the diastereoisomeric tribromides **15c** and **15d** were obtained in 66% yield from pregnanoic ester **10**, and calysterol **2a** was obtained from **15c** in 68% yield. The overall synthetic sequence from **10** to **2a** involves 9 steps.

In conclusion, a simple synthesis of representative calysterols **2a** and **2b** from the readily available steroidal intermediate **10** has been developed. Some methods for the generation of the cyclopropane moiety have been evaluated and adapted to multi-step transformations.

## Experimental Section

**General:** Melting points were determined on a hot-stage apparatus and are uncorrected. – Optical rotations were measured on a Perkin–Elmer model 141 polarimeter using 1 mL capacity cells (5 cm path length). – NMR spectra were recorded in $CDCl_3$ solutions, $^1H$ at 200 MHz and $^{13}C$ at 50 MHz on a Varian Gemini instrument, or $^1H$ at 500 MHz and $^{13}C$ at 125 MHz on a Bruker AMX. Chemical shifts are reported in δ units. TMS was used as an internal standard, except with compounds bearing a trimethylsilyl group and with isocalysterols **2a** and **2b**, where chloroform was used ($CHCl_3$, $^1H$-NMR δ = 7.26; $CDCl_3$, $^{13}C$-NMR δ = 77.00). In the $^{13}C$-NMR spectra, multiplicities of signals were assigned using the DEPT technique. – IR spectra were recorded on Perkin–Elmer 1640 FT spectrophotometer. – MS (electron impact, 70 eV) were recorded on an AMD 604 (AMD Intectra GmbH). – HPLC analyses were performed using a Shimadzu LC-8A chromatograph equipped with an SPD-6A variable-wavelength detector. – Column chromatography was performed on Merck silica gel 60, 230–400 mesh, deactivated with 0.1% $Et_3N$ in hexane. – TLC was performed on aluminum-backed sheets, Merck silica 5554. – Anhydrous solvents were obtained by distillation from benzophenone ketyl (diethyl ether, THF) or calcium hydride ($CH_2Cl_2$, pyridine, toluene). – Air-sensitive reactions were performed in oven- or flame-dried glassware under argon. – Organic extracts were dried with anhydrous $Na_2SO_4$ and solvents were evaporated in a rotary evaporator. – Microanalyses were performed at our analytical laboratory.

**(*Z*)-3-Iodo-4-methylpent-2-en-1-ol (5a):** To a stirred mixture of Red-Al® (29 mL, 98.7 mmol, 3.4 M in toluene) and diethyl ether (40 mL), a solution of alcohol **4**[26] (5.7 g, 58.1 mmol) in diethyl ether (40 mL) was added over a period of 40 min. at –5 °C. The mixture was set aside at room temp. until the starting material had been consumed (TLC, hexane/AcOEt, 3:1; ca. 4 h) and was then cooled to –78 °C, whereupon iodine (36.6 g, 114 mmol) was added. After 30 min., the mixture was partitioned between diethyl ether and satd. aq. potassium sodium tartrate solution. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with satd. aq. $Na_2S_2O_7$ solution. The solvent was then evaporated and the residue (12.5 g) was distilled (48–50 °C/0.05–0.1 Torr) to give iodide **5a** (7.6 g, 58%). – $^1H$ NMR: δ = 1.06 (d, *J* = 6.6 Hz, 6 H, *i*Pr), 1.70 (br. s, 1 H, OH), 2.30 (sept, *J* = 6.6 Hz, 1 H, *i*Pr), 4.22 (d, *J* = 5.7 Hz, 2 H, $CH_2$), 5.9 (t d, *J* = 5.7, 0.9 Hz, 1 H, C=CH). – $^{13}C$ NMR: δ = 23.05 (*i*Pr), 41.37 (*i*Pr), 67.25 ($CH_2$), 121.40 (CI), 131.06.

**(*Z*)-3-Iodo-4-methyl-*O*-tritylpent-2-en-1-ol (5b):** To a solution of TrCl (3.29 g, 11.8 mmol) in $CH_2Cl_2$ (10 mL) containing pyridine (1 mL), alcohol **5a** (2.68 g, 11.8 mmol) was added at 0 °C. The resulting mixture was set aside at room temp. for 18 h and then partitioned between diethyl ether and 0.25 M aq. HCl. The organic phase was washed with satd. aq. sodium hydrogen carbonate solution and then the solvent was evaporated. The residue was filtered through $SiO_2$ (50 g; hexane) to give the ether **5b** (5.08 g, 92%); m.p. 75–78 °C (hexane). – $^1H$ NMR: δ = 1.01 (d, *J* = 6.6 Hz, 6 H) and 2.22 (sept, *J* = 6.6 Hz, 1 H, *i*Pr), 3.76 (br. d, *J* = 5.0 Hz, 2 H, $CH_2$), 5.89 (td, *J* = 5.0, 0.8 Hz, 1 H, C=CH), 7.1–7.6 (m, 15 H, Tr). – $^{13}C$ NMR: δ = 23.07 and 41.22 (*i*Pr), 69.32 ($CH_2$), 86.97 (Ph*C*), 119.09 (CI), 126.99 ($C_p$), 127.83 ($C_m$), 128.69 ($C_o$), 129.96 (C=*C*H), 143.96 ($C_{ipso}$). – $C_{25}H_{25}OI$ (468.38): calcd. C 64.11, H 5.38, I 27.10; found C 64.11, H 5.41, I 27.11.

**(*Z*)-4-Methyl-3-trimethylsilylpent-2-en-1-ol (7):** To a solution of alcohol **5a** (4.1 g, 18.1 mmol) in $CH_2Cl_2$ (5 mL), HMDS (6.1 mL, 29.6 mmol) was added at 5 °C. The resulting mixture was stirred for 1 h at room temp., the solvent was then evaporated, and the residue was distilled. The fraction distilling at 74–75 °C/1.8 Torr was collected to give trimethylsilyl ether **6** (4.7 g, 87%). After preparing further batches, **6** (5.6 g, 18.9 mmol) was dissolved in THF (74 mL), the solution was cooled to –78 °C, and then *tert*-BuLi (30.5 mL, 1.3 M in pentane, 39.7 mmol) was added. The resulting mixture was stirred for 30 min. at –78 °C, then allowed to warm to room temp. and poured into a satd. aq. $NH_4Cl$/ice mixture. The product was extracted with diethyl ether. The combined extracts were washed with brine and the solvent was evaporated. The residue was chromatographed on $SiO_2$ (80 g; hexane/diethyl ether, 50:1 and then 25:1). The major fraction (TLC, hexane/AcOEt, $R_f$ = 0.36) was distilled (94–100 °C/13 Torr) to give alcohol **7** (1.93 g, 59%). – $^1H$ NMR (200 MHz): δ = 0.16 (s, 9 H, $Me_3Si$), 1.00 (d, *J* = 6.9 Hz, 6 H, *i*Pr), 1.40 (br. s, 1 H, OH), 2.43 (sept, *J* = 6.8 Hz, 1 H, *i*Pr), 4.21 (d, *J* = 6.9 Hz, 2 H, $CH_2$), 6.14 (td, *J* = 6.9, 0.9 Hz, 1 H, C=CH). – $^{13}C$ NMR (50 MHz): δ = 0.61 ($Me_3Si$), 23.07 (Me),

32.59 (*i*Pr), 62.33 ($CH_2$), 136.34 (CH), 150.56. – MS: *m*/*z* (%) = 173 [$MH^+$] (0.1), 157 [$M^+$ – Me] (6), 154 [$M^+$ – $H_2O$] (8), 139 [$M^+$ – Me – $H_2O$] (5), 129 [$M^+$ – *i*Pr] (6), 82 [$MH^+$ – $H_2O$ – $Me_3Si$] (26), 75 [$Me_2SiOH^+$] (100), 72 [$Me_3Si^+$] (55), 67 (39). – HRMS: $C_9H_{20}OSi$ [$M^+$]: calcd 172.12834; found 172.12829.

**(*E*)-4-Methyl-1-trimethylsilylpent-2-en-1-ol (8):** This was obtained from the less polar fractions (TLC, $R_f$ = 0.47). – $^1H$ NMR (200 MHz): δ = 0.02 (s, 9 H, $Me_3Si$), 0.98 (d, *J* = 6.8 Hz, 6 H) and 2.15–2.45 (m, 1 H, *i*Pr), 3.87–3.93 (m, 1 H, CHOH), 5.35–5.62 (m, 2 H, C=CH). – $^{13}C$ NMR (50 MHz): δ = –4.22 ($Me_3Si$), 22.75 (*i*Pr), 30.99 (*i*Pr), 68.32 (CHOH), 128.19, 134.77.

**(*Z*)-1-Bromo-4-methyl-3-trimethylsilylbut-2-ene (9):** To a stirred mixture of alcohol **7** (1.06 g, 6.16 mmol), diethyl ether (6 mL), and pyridine (195 μL), a mixture of $PBr_3$ (250 μL, 2.58 mmol) and diethyl ether (2 mL) was added dropwise at –40 °C. Stirring was continued at –40 to –30 °C for 45 min. and then a few drops of methanol were added. The mixture was partitioned between diethyl ether and satd. aq. ammonium sulfate solution. The organic layer was collected, washed with water, and concentrated. The residue (1.4 g) was redissolved in pentane and filtered through $SiO_2$ (14 g; pentane). The crude product (0.82 g) was distilled and the fraction distilling at 118–126 °C/29 Torr was collected to afford bromide **9** (0.77 g, 53%). – $^1H$ NMR (200 MHz): δ = 0.19 (s, 9 H, $SiCH_3$), 0.98 (d, *J* = 6.7 Hz, 6 H, *i*Pr), 2.43 (sept d, *J* = 6.7, 0.9 Hz, 2 H, *i*Pr), 4.08 (d, *J* = 8.5 Hz, 2 H, $CH_2Br$), 6.18 (td, *J* = 8.5, 1.1 Hz, 1 H, C=CH).

**Ethyl (23*Z*)-6β-Methoxy-24-(trimethylsilyl)-3α,5-cyclo-5α-cholest-23-en-21-oate (11):** To a stirred solution of LDA [prepared from diisopropylamine (300 μL, 2.14 mmol) and *n*-BuLi (1.8 M in hexane, 2.01 mmol) in THF (2.5 mL)], a solution of ester **10**[31] (657 mg, 1.76 mmol) in THF (4 mL) was added over a period of 10 min. at –72 °C. The resulting mixture was stirred for 1 h at –72 °C and then the temp. was gradually allowed to rise to –35 °C, whereupon bromide **9** (358 mg, 1.52 mmol) was added. The mixture was stirred for 2 h and was then allowed to warm to 0 °C over ca. 30 min. The reaction was then quenched by the addition of satd. aq. ammonium sulfate solution and the mixture was partitioned between hexane and water. The organic layer was washed with satd. aq. ammonium sulfate solution and water, and then the solvent was evaporated. The residue (915 mg) was chromatographed on $SiO_2$ (20 g; hexane/AcOEt, 99.5:0.5) to give compound **11** (600 mg, 75%) and unchanged **10** (70 mg). **11:** IR (film): $\tilde{\nu}$ = 1732 (C=O), 1613 (C=C) $cm^{-1}$. – $^1H$ NMR (200 MHz): δ = 0.14 (s, 9 H, $SiCH_3$), 0.42 (dd, *J* = 7.9, 5.0 Hz, 1 H, 4α-H), 0.64 (t, *J* = 4.5 Hz, 1 H, 4β-H), 0.75 (s, 3 H, 18-H), 0.92 and 0.95 (2 d, *J* = 5.7 Hz, 6 H, 26- and 27-H), 1.00 (s, 3 H, 19-H), 1.25 (t, *J* = 7.1 Hz, 3 H, OEt), 2.20–2.42 (m, 3 H, 22- and 25-H), 2.76 (t, *J* = 2.8 Hz, 1 H, 6-H), 3.32 (s, 3 H, $OCH_3$), 4.07 (m, 2 H, OEt), 5.85 (t, *J* = 6.5 Hz, 1 H, 23-H). – MS: *m*/*z* (%) = 528 (28), 513 (100), 473 (18), 446 (35), 241 (56), 199 (44), 123 (12), 73 (27). – $C_{33}H_{56}O_3Si$ (528.83): calcd. C 74.94, H 10.67; found C 75.01, H 10.73.

**(23*Z*)-6β-Methoxy-24-(trimethylsilyl)-3α,5-cyclo-5α-cholest-23-en-21-ol (12a):** To a solution of ester **11** (500 mg, 0.95 mmol) in diethyl ether (25 mL), $LiAlH_4$ (130 mg, 3.4 mmol) was added portionwise over a period of 4 h. The excess reagent was then decomposed by adding wet diethyl ether. The solution was washed with 0.1 N NaOH and water. The solvent was evaporated to give alcohol **12a** (427 mg, 93%). – IR (film): $\tilde{\nu}$ = 3467 (OH), 1608 (C=C) $cm^{-1}$. – $^1H$ NMR (200 MHz): δ = 0.16 (s, 9 H, $SiCH_3$), 0.43 (dd, *J* = 8.0, 5.0 Hz, 1 H, 4α-H), 0.65 (t, *J* = 4.7 Hz, 1 H, 4β-H), 0.76 (s, 3 H, 18-H), 0.98 (d, *J* = 6.8 Hz, 6 H, 26- and 27-H), 1.02 (s, 3 H, 19-H), 2.08–2.49 (m, 3 H, 22- and 25-H), 2.77 (t, *J* = 2.5 Hz, 1 H, 6-H), 3.32 (s, 3 H, $OCH_3$), 3.59–3.80 (m, 2 H, 21-H), 6.07 (t, *J* = 6.8 Hz, 1 H, 23-H). – $C_{31}H_{54}O_2Si$ (486.80): calcd. C 76.48, H 11.18; found C 76.23, H 11.23.

**(23*Z*)-6β-Methoxy-24-(trimethylsilyl)-3α,5-cyclo-5α-cholest-23-ene (13):** To a solution of **12a** (405 mg, 0.833 mmol) in $CH_2Cl_2$ (10 mL), $Et_3N$ (1.6 mL), TsCl (534 mg, 2.8 mmol), and DMAP (5 mg) were added. The resulting mixture was set aside for 48 h and then partitioned between hexane (20 mL) and water (10 mL). The aqueous layer was extracted with hexane (20 mL) and the combined organic extracts were washed with saturated aq. $NaHCO_3$ solution and water. The solvent was then evaporated to leave the tosylate **12b** (552 mg). – $^1H$ NMR (200 MHz): δ = 0.10 (s, 9 H, $SiCH_3$), 0.43 (dd, *J* = 7.9, 4.9 Hz, 1 H, 4α-H), 0.66 (s, 3 H, 18-H), 0.83 and 0.85 (2 d, *J* = 6.7 Hz, 6 H, 26- and 27-H), 1.00 (s, 3 H, 19-H), 2.43 (s, 3 H, Ts), 2.76 (t, *J* = 2.6 Hz, 1 H, 6-H), 3.31 (s, 3 H, $OCH_3$), 4.05 (d, *J* = 3.7 Hz, 2 H, 21-H), 5.71 (t, *J* = 6.7 Hz, 1 H, 23-H), 7.32 (d, *J* = 8.5 Hz, 2 H, Ts), 7.78 (d, *J* = 8.4 Hz, 2 H, Ts). Crude **12b** (528 mg) was dissolved in THF (5 mL) and this solution was added to a suspension of $LiAlH_4$ (203 mg) in THF (5 mL). The resulting mixture was heated under reflux for 20 min., then cooled, and the excess reagent was decomposed by adding satd. aq. $Na_2SO_4$ solution. The mixture was diluted with hexane and successively washed with 1 N NaOH solution and water. The solvent was then evaporated and the residue (380 mg) was chromatographed on $SiO_2$ (2 g; hexane) to give the cholestane derivative **13** (308 mg, 82%). – IR (film): $\tilde{\nu}$ = 1610 $cm^{-1}$ (C=C). – $^1H$ NMR: δ = 0.13 (s, 9 H, $SiCH_3$), 0.74 (s, 3 H, 18-H) 0.89 (d, *J* = 6.4 Hz, 3 H, 21-H), 0.98 (d, *J* = 6.7 Hz, 6 H, 26- and 27-H), 1.03 (s, 3 H, 19-H), 2.77 (t, *J* = 2.6 Hz, 1 H, 6-H), 3.32 (s, 3 H, $OCH_3$), 5.93 (ddd, *J* = 8.3, 6.2, 0.5 Hz, 1 H, 23-H). – MS: *m*/*z* (%) = 470 (10), 455 (12), 438 (10), 415 (25), 283 (58), 253 (100), 73 (28). – $C_{31}H_{54}OSi$: calcd. 470.39439; found 470.39442 (MS).

**(23*E*)-24-Bromo-6β-methoxy-3α,5-cyclo-5α-cholest-23-ene (14):** To a stirred solution of silane **13** (305 mg, 0.648 mmol) in $CCl_4$ (15 mL) containing powdered $K_2CO_3$ (224 mg, 1.623 mmol), bromine (105 mg) in $CCl_4$ (1.8 mL) was added portionwise over a period of 3 h at –10 °C. The mixture was subsequently partitioned between hexane and water. The organic layer was washed with aq. $Na_2S_2O_4$ solution and water and then the solvent was evaporated. The crude dibromide (429 mg) was redissolved in THF (10 mL) and tetrabutylammonium fluoride (370 mg, 1.117 mmol) was added. The resulting mixture was set aside for 24 h and then partitioned between hexane and water. The organic phase was washed with water and the solvent was evaporated. The residue (300 mg) was chromatographed on $SiO_2$ (10 g; hexane) to give the bromide **14** (248 mg, 80%). – IR (film): $\tilde{\nu}$ = 1636 $cm^{-1}$ (C=C). – $^1H$ NMR: δ = 0.71 (s, 3 H, 18-H), 0.93 (d, *J* = 6.5 Hz, 3 H, 21-H), 1.02 (s, 3 H, 19-H) overlapping 1.03 (d, *J* = 6.5 Hz, 6 H, 26- and 27-H), 2.77 (t, *J* = 2.7 Hz, 1 H, 6-H) overlapping 2.83 (sept., *J* = 6.5 Hz, 1 H, 25-H), 3.32 (s, 3 H, $OCH_3$), 5.75 (dd, *J* = 8.7, 6.8 Hz, 1 H, 23-H). – $C_{28}H_{45}OBr$: calcd. 476.26537; found 476.26611 (MS).

**Reaction of 14 with Dibromocarbene Generated in a Phase-Transfer System: (23*R*,24*R*)- and (23*S*,24*S*)-24-Bromo-23,24-(dibromomethylene)-6β-methoxy-3α,5-cyclo-5α-cholestane (15a and 15b):** A mixture of (*E*)-bromide **14** (132 mg, 0.27 mmol), $CHBr_3$ (2.5 mL), 50% aq. NaOH solution (1.25 mL), TEBACl (1 mg), and EtOH (96%, 2 drops) was stirred and sonicated using a 140 W ultrasonic cleaning bath for 2 h at 25–35 °C and then partitioned between hexane and water. The organic phase was washed with water and then the solvent was evaporated. The residue (orange liquid, ca. 2 mL) was chromatographed on $SiO_2$ (3 g; hexane) to give first a mixture of prod-

ucts incorporating 5 Br atoms (by MS) (19 mg, 12%), to which the structure **16** was tentatively assigned, and then the tribromo derivatives **15a** and **15b** (93 mg, 52%). – MS: *m*/*z* (%) = 652, 650, 648, 646 [$M^+$] (50), 637, 635, 633, 631 [$M^+$ – Me] (52), 620, 618, 616, 614 [$M^+$ – MeOH] (67), 597, 595, 593, 591 [$M^+$ – 55] (100), 539, 537, 535 [$M^+$ – MeOH – Br] (37), 515, 513, 511 [$M^+$ – 55 – Br] (18), 253 (85). – $C_{29}H_{45}O^{79}Br_2{}^{81}Br$: calcd. 648.1000; found 648.0999 (MS).

**(23*R*,24*R*)- and (23*S*,24*S*)-24-Bromo-23,24-(dibromomethylene)-cholest-5-ene-3β-ols (17a and 17b):** A solution of *i*-steroids **15a** and **15b** (8 mg) in a mixture of dioxane and water (8:1, 2.5 mL) containing TsOH (1 mg) was kept at 93–95 °C for 3.5 h. The product was then extracted with $CHCl_3$ to afford a solid material (6 mg), which was chromatographed on $SiO_2$ (320 mg; hexane/AcOEt, 95:5) to give crystalline alcohols **17a** and **17b** (4 mg). – $^1$H NMR (200 MHz): δ = 0.71 and 0.74 (2 s, 3 H, 18-H), 1.02 (s, 3 H, 19-H), 3.4–3.7 (m, 1 H, 3-H), 5.3–5.4 (m, 1 H, 6-H). – MS: *m*/*z* (%) = 638, 636, 634, 632 [$M^+$] (65). – $C_{28}H_{43}Br_3O$: calcd. 632.0864; found 632.0863 (MS). The mixture was separated by HPLC (Merck Lichrospher 100 RP-18, 5 μm, 250 × 4 mm, methanol, 10 mL/min, UV detection, λ = 220 nm) to give a pure diastereomer with $t_R$ = 22.16 min: $^1$H NMR (500 MHz): δ = 0.74 (s, 3 H, 18-H), 1.02 (s, 3 H, 19-H), 1.07 (d, *J* = 6.5 Hz, 6 H, 26- and 27-H), 1.12 (d, *J* = 6.4 Hz, 3 H, 21-H), 3.48–3.57 (m, 1 H, 3-H), 5.33–5.37 (m, 1 H, 6-H). Another diastereomer with $t_R$ = 25.6 min was found to be contaminated with ca. 12% of the more mobile component; notable signals in $^1$H NMR (500 MHz): δ = 0.71, 1.02, 1.10, and 1.11 (2 d, *J* = 6.5 Hz, 3 H each, 26- and 27-H), 1.12 (d, *J* = 6.6 Hz, 3 H, 21-H), 3.48–3.56 (m, 1 H), 5.33–5.37 (m, 1 H, 6-H).

**(23*R*)- and (23*S*)- 6β-Methoxy-3α,5:23,28-dicyclo-5α-stigmasta-24(28)-ene (18a and 18b):** To a stirred solution of tribromides **15a** and **15b** (69 mg, 0.11 mmol) in diethyl ether (1.7 mL), methyllithium (1.5 M in pentane, 600 μL, 0.90 mmol) was added at –70 °C. The resulting mixture was allowed to warm to room temp. (over ca. 2.5 h), then cooled to –60 °C, whereupon methyl iodide (200 μL, 0.32 mmol) was added. The mixture was stirred at –60 °C for 30 min., then allowed to warm to room temp., and subsequently partitioned between hexane and water. The organic phase was washed with water and the solvent was evaporated. The residue (45 mg) was chromatographed on $SiO_2$ (1.5 g; hexane) to give a mixture of cyclopropenes **18a** and **18b** (20 mg, 44%). – $^1$H NMR (200 MHz): δ = 0.42 (dd, *J* = 7.9 Hz, 1 H, 4α-H), 0.65 (t, *J* = 5 Hz, 1 H, 4β-H), 0.72 and 0.73 (2 br. s, 3 H, 18-H), 1.00 (d, *J* = 7.1 Hz, 3 H, 21-H), 1.02 (br. s, 3 H, 19-H), 1.07, 1.08, 1.10, 1.11, 1.12, 1.13 (6 H, 26-, and 27-H), 1.99 and 2.01 (2 d, *J* = 1.6 Hz, 3 H, 29-H), 2.5–2.7 (sept. t, *J* = 6.9, 1.4 Hz, 1 H, 25-H), 2.76 (t, *J* = 2.8 Hz, 1 H, 6-H), 3.32 (s, 3 H, $OCH_3$). – MS: *m*/*z* (%) = 424 [$M^+$] (8), 409 [$M^+$ – Me] (25), 392 [$M^+$ – MeOH] (18), 377 (17), 369 (30), 253 [$M^+$ – side chain – 2H – MeOH] (100), 95 [$C_7H_{11}$] (37). – $C_{30}H_{48}O$ [$M^+$]: calcd. 424.3705; found 424.3700; $C_{26}H_{41}O$ [$M^+$ – $C_4H_7$]: calcd. 369.3157; found 369.3159; $C_7H_{11}$ [$CH_2$–C= $C(CH^+)$*i*Pr]: calcd. 95.0861; found 95.0860 (MS).

**(23*R*)-23*H*-Isocalysterol [(23*R*)-23,28-Cyclostigmasta-5,24(28)-dien-3β-ol] (2a) and (23*S*)-23*H*-Isocalysterol [(23*S*)-23,28-Cyclostigmasta-5,24(28)-dien-3β-ol] (2b):** A solution of *i*-steroids **18a** and **18b** (17 mg, 0.04 mmol) in a mixture of dioxane (8 mL) and water (2 mL) containing TsOH (2 mg) was kept at 93–95 °C for 5 h and then partitioned between chloroform and water. The chloroform phase was then washed with water and the solvent was evaporated. The solid residue (12 mg) was subsequently chromatographed on $SiO_2$ (600 mg; hexane/acetone, 98:2) to give a mixture of calysterols **2a** and **2b** in a ratio of ca. 1:1 (7 mg, 44%). This mixture was separated by HPLC (Merck LiChrospher 100 RP-18, 5 μm, 250 × 4 mm column, 1% $H_2O$ in methanol, flow rate 0.6 mL/min, UV detection, λ = 220 nm) to give **2a** and **2b**; retention times $t_R$ = 19.58 and 18.37 min, respectively. The relative retention times are in agreement with literature data.[14] Chemical shifts and coupling constants in the $^1$H-NMR spectra of synthetic isocalysterols **2a** and **2b** (500 MHz) were in agreement with those reported for the respective natural products; see Table 1. Chemical shifts in the $^{13}$C-NMR spectrum of **2a** (125 MHz) were also in agreement with those reported; see Table 2.

Table 2. $^{13}$C-NMR data (125 MHz) of **2a** and recorded data (100 MHz) for the natural product[7]

| | recorded | reported | Δδ | | recorded | reported | Δδ |
|---|---|---|---|---|---|---|---|
| C-1 | 37.27 | 37.26 | 0.01 | C-16 | 28.46 | 28.46 | 0 |
| C-2 | 31.69 | 31.67 | 0.02 | C-17 | 56.57 | 56.56 | 0.01 |
| C-3 | 71.83 | 71.82 | 0.01 | C-18 | 11.87 | 11.87 | 0 |
| C-4 | 42.32 | 42.31 | 0.01 | C-19 | 19.40 | 19.40 | 0 |
| C-5 | 140.77 | 140.75 | 0.02 | C-20 | 36.51[a] | 36.48 | 0.03 |
| C-6 | 121.74 | 121.74 | 0 | C-21 | 19.23 | 19.23 | 0 |
| C-7 | 31.92 | 31.91 | 0.01 | C-22 | 43.53 | 43.53 | 0 |
| C-8 | 31.92 | 31.91 | 0.01 | C-23 | 19.00 | 18.99 | 0.1 |
| C-9 | 50.17 | 50.15 | 0.02 | C-24 | 122.70 | 122.67 | 0.03 |
| C-10 | 36.47[a] | 36.48 | –0.01 | C-25 | 26.40 | 26.40 | 0 |
| C-11 | 21.11 | 21.11 | 0 | C-26 | 21.07 | 21.08 | –0.01 |
| C-12 | 39.82 | 39.81 | 0.02 | C-27 | 21.24 | 21.24 | 0 |
| C-13 | 42.34 | 42.34 | 0 | C-28 | 112.24 | 112.23 | 0.01 |
| C-14 | 56.85 | 56.83 | 0.02 | C-29 | 10.65 | 10.67 | 0.01 |
| C-15 | 24.31 | 24.31 | 0 | | | | |

[a] Alternative assignments.

MS and HR-MS of **2a:** *m*/*z* = 410 [$M^+$] (3), 395 [$M^+$ – $CH_3$] (3), 377 [$M^+$ – $CH_3$ – $H_2O$] (1), 367 [$M^+$ – $CH(CH_3)_2$] (2), 353 (1), 349 (1), 339 (1), 314 [$M^+$ – $C_7H_{11}$] (4), 300 [$M^+$ – $C_7H_{11}$ – $CH_3$] (8), 283 (16), 271 [$M^+$ – side chain – 2 H] (93), 253 [$M^+$ – side chain – $H_2O$ – 2 H] (19), 241 (8), 215 (14), 199 (7), 187 (8), 173 (12), 159 (28), 145 (20), 133 (31), 121 (17), 109 (48), 96 [$C_7H_{12}$] (53), 95 [$C_7H_{11}$] (100), 81 (27), 67 (26), 55 (22), 41 (11). – $C_{29}H_{46}O$ [$M^+$]: calcd. 410.3549; found 410.3545; $C_{28}H_{41}$ [$M^+$ – $CH_3$ – $H_2O$]: calcd. 377.3208; found 377.3203; $C_{26}H_{39}O$ [$M^+$ – $CH(CH_3)_2$]: calcd. 367.3001; found 367.2999; $C_{14}H_{27}O$ [$M^+$ – side chain – 2 H]: calcd. 271.2062; found 271.2066. These data are in agreement with the reported values.[38]

MS and HR-MS of **2b:** 410 [$M^+$] (3), 395 [$M^+$ – $CH_3$] (3), 377 [$M^+$ – $CH_3$ – $H_2O$] (1), 367 [$M^+$ – *i*Pr] (2), 353 [$M^+$ – *i*Pr] (1), 349 [$M^+$ – *i*Pr – $H_2O$] (1), 339 (1), 300 [$M^+$ – $C_6H_{11}$] (7), 283 (16), 271 [$M^+$ – side chain – 2 H] (85), 253 [$M^+$ – side chain – $H_2O$ – 2 H] (17), 241 (7), 215 (14), 199 (7), 187 (9), 173 (11), 159 (26), 145 (20), 133 (29), 121 (16), 109 (47), 96 (53), 95 (100), 81 (27), 67 (26), 55 (21), 41 (10). – $C_{29}H_{46}O$ [$M^+$]: calcd. 410.3549; found 410.3545; $C_{28}H_{41}$ [$M^+$ – $CH_3$ – $H_2O$]: calcd. 377.3208; found 377.3207; $C_{26}H_{39}O$ [$M^+$ – $CH(CH_3)_2$]: calcd. 367.3001; found 367.3000; $C_{14}H_{27}O$ [$M^+$ – side chain – 2 H]: calcd. 271.2062; found 271.2062. These data are in agreement with the reported values.[7][14] For m.p. and optical rotation of **2a**, vide infra.

**(*Z*)-3-Bromo-4-methylpent-2-en-1-ol (19a):** To a stirred mixture of Red-Al® (1.7 M in toluene, 34.4 mL, 117 mmol) and diethyl ether (49 mL), a solution of propargylic alcohol **4** (6.76 g, 68.8 mmol) in diethyl ether (49 mL) was added dropwise over a period of 20 min. at 0 °C. The resulting mixture was set aside at room temp. for 4 h, then cooled to 0 °C once more, whereupon pyridine (16.6 mL, 0.21 mol) was added. The mixture was cooled to –78 °C and then bromine (6.9 mL, 133.6 mmol) in $CH_2Cl_2$ (84 mL) was added dropwise, with the temp. being maintained below –60 °C. Stirring at –78 °C was continued for 20 min. and then the mixture was poured into 1 M NaOH solution and ice. The product was extracted with diethyl ether. The combined extracts were washed with 6 M HCl (50 mL) and satd. aq. $NaHCO_3$ solution. The solvent was then evaporated and the residue was chromatographed on $SiO_2$ (100 g; hexane/$CH_2Cl_2$, 2:1 and then 1:1). The crude product was distilled at 70–86 °C/1.5–2 Torr to give alcohol **19a** (9.36 g, 77%). – IR (film): $\tilde{\nu}$ = 3332 $cm^{-1}$ (OH). – $^1H$ NMR: δ = 1.13 (d, *J* = 6.6 Hz, 6 H, *i*Pr), 2.00 (br. s, 1 H, OH), 2.58 (sept, *J* = 6.7 Hz, 1 H, *i*Pr), 4.27 (d, *J* = 5.9 Hz, 2 H, $CH_2$), 5.96 (dt, *J* = 5.9, 0.8 Hz, 1 H, C=CH). – $^{13}C$ NMR: δ = 21.68 ($CH_3$), 38.92 (CH), 62.32 ($CH_2$), 125.26 (C=CH), 137.79 (CBr). – $C_6H_{11}OBr$ (179.06): calcd. C 40.24, H 6.19, Br 44.63; found C 39.95, H 6.19, Br 44.75.

**(*Z*)-1,3-Dibromo-4-methylpent-2-ene (19b):** To a solution of alcohol **19a** (517 mg, 2.90 mmol) in diethyl ether (2.5 mL) containing pyridine (8 μL), a solution of $PBr_3$ (360 μL, 1.26 mmol) in diethyl ether (1 mL) was added at 4 °C. The resulting mixture was stirred for 20 min. and then the reaction was quenched by adding methanol (0.5 mL) and ice. The aqueous layer was separated and extracted with pentane. The combined extracts were washed with satd. aq. $NaHCO_3$ solution. The pentane was then evaporated and the residue was distilled in a kugelrohr apparatus (100 °C/5 Torr) to yield dibromide **19b** (598 mg, 85%). – $^1H$ NMR: δ = 1.13 (d, *J* = 6.7 Hz, 6 H) and 2.61 (sept, 1 H, *J* = 6.7 Hz, *i*Pr) 4.08 (d, *J* = 7.9 Hz, 2 H, $CH_2$), 6.02 (dt, *J* = 7.9, 0.8 Hz, 1 H, C=CH). – $^{13}C$ NMR: δ = 21.64 ($CH_3$), 30.34 ($CH_2Br$), 39.16 (CH), 122.17 (C=*C*H), 142.25 (CBr). – $C_6H_{10}Br_2$ (241.95): calcd. C 29.78, H 4.17; found C 29.82, H 4.24.

**Ethyl (23*Z*)-24-Bromo-6β-methoxy-3α,5-cyclo-5α-cholest-23-en-21-oate (20):** To a stirred solution of LDA [prepared from diisopropylamine (1.22 mL, 8.72 mmol) in THF (8.3 mL) and *n*-BuLi (1.9 M in hexane, 4.6 mL, 8.74 mmol)], a solution of ester **10**[31] (2.96 g, 7.92 mmol) in THF (24 mL) was added dropwise at –78 °C. The mixture was stirred at –78 °C for 1 h and then bromide **19b** (1.99 g, 8.21 mmol) was added. Stirring at –78 °C was continued for 3.5 h, then the mixture was allowed to warm to room temp. and partitioned between diethyl ether and water. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with satd. aq. ammonium chloride solution and the solvent was evaporated. The residue was chromatographed on $SiO_2$ (200 g; hexane/$CH_2Cl_2$, 2.5:1 2:1) to give ester **20** (3.38 g, 80%). – IR (film): $\tilde{\nu}$ = 1732 $cm^{-1}$ (C=O). – $^1H$ NMR: δ = 0.43 (dd, *J* = 7.9, 4.9 Hz, 1 H, 4α-H), 0.65 (t, *J* = 4.5 Hz, 1 H, 4β-H), 0.76 (s, 3 H, 18-H), 1.01 (s, 3 H, 19-H), 1.07 (d, *J* = 6.7 Hz, 6 H, 26- and 27-H), 1.26 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$CH$_2$O), 2.28–2.43 (m, 3 H, 20- and 22-H), 2.52 (sept, *J* = 6.6 Hz, 1 H, 25-H), 2.73–2.81 (m, 1 H, 6-H), 3.32 (s, 3 H, $CH_3O$), 4.09 (q, *J* = 7.1 Hz, 2 H, $CH_2O$), 5.62 (t, *J* = 6.5 Hz, 1 H, 23-H). MS: *m*/*z* (%) = 536, 534 [$M^+$] (4), 521, 519 [$M^+$ – Me] (11), 504, 502 [$M^+$ – $CH_3OH$] (6), 479, 481 [$M^+$ – $C_4H_7$] (20), 455 [$M^+$ – Br] (100), 397 (12), 253 (14). – $C_{30}H_{47}O_3Br$: calcd. 534.27085; found 534.27014 (MS).

**(23*Z*)-24-Bromo-6β-methoxy-3α,5-cyclo-5α-cholest-23-en-21-ol (21a):** To a stirred solution of ester **20** (1.12 g, 2.1 mmol) in $CH_2Cl_2$ (35 mL), DIBAH (0.75 M in hexane, 8.4 mL, 6.3 mmol) was added at –30 to –20 °C. After 30 min., the mixture was diluted with diethyl ether and satd. aq. sodium potassium tartrate solution was added. The aqueous layer was separated and extracted with diethyl ether. The combined organic extracts were concentrated to dryness and the residue was chromatographed on $SiO_2$ (22 g; hexane/acetone, 100:1) to give alcohol **21a** (0.977 g, 95%). – IR (film): $\tilde{\nu}$ = 3451 $cm^{-1}$ (OH). – $^1H$ NMR: δ = 0.44 (dd, *J* = 7.9, 5.2 Hz, 1 H, 4α-H), 0.65 (t, *J* = 4.9 Hz, 1 H, 4β-H), 0.75 (s, 3 H, 18-H), 1.02 (s, 3 H, 19-H), 1.11 (d, *J* = 6.6 Hz, 6 H, 26- and 27-H), 2.15–2.45 (m, 3 H, 20- and 22-H), 2.52 (sept, *J* = 6.6 Hz, 1 H, 25-H), 2.73–2.81 (m, 1 H, 6-H), 3.33 (s, 3 H, $CH_3O$), 3.50–3.80 (m, 2 H, C*H*$_2$OH), 5.62 (t, *J* = 6.5 Hz, 1 H, 23-H). –MS: *m*/*z* (%) = 494, 492 [$M^+$] (37), 479, 477 [$M^+$ – $CH_3$] (56), 462, 460 [$M^+$ – $CH_3OH$] (41), 439, 437 [$M^+$ – $C_4H_7$] (100), 436, 434 (15), 381 (27), 299 (10), 285 (34), 281 (10), 253 (52), 227 (14), 213 (21), 201, 199 (12). – $C_{28}H_{45}O_2Br$: calcd. 492.2603; found 492.2604 (MS).

**(23*Z*)-24-Bromo-6β-methoxy-21-tosyloxy-3α,5-cyclo-5α-cholest-23-ene (21b):** To a solution of alcohol **21a** (1.81 g, 3.68 mmol) in $CH_2Cl_2$ (24 mL) containing pyridine (1.78 mL, 22 mmol), TsCl (1.56 g, 8.22 mmol) was added. The mixture was set aside for 24 h and then partitioned between diethyl ether and water. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with satd. aq. $NH_4Cl$ solution. The solvent was then evaporated and the residue was chromatographed on $SiO_2$ (50 g; hexane/$CH_2Cl_2$, 1:1) to give tosylate **21b** (2.264 g, 95%). – $^1H$ NMR: δ = 0.43 (dd, *J* = 8.2, 5.1 Hz, 1 H, 4α-H), 0.67 (s, 3 H, 18-H), 1.01 (s, 3 H, 19-H), 1.01 (d, *J* = 6.7 Hz, 6 H, 26- and 27-H), 1.98–2.50 (m, 3 H, 22- and 25-H), 2.44 (s, 3 H, MePh), 2.72–2.81 (m, 1 H, 6-H), 3.32 (s, 3 H, $CH_3O$), 3.95–4.10 (m, 2 H, 21-H), 5.43 (t, *J* = 6.7 Hz, 1 H, 23-H), 7.31 (d, *J* = 8.0 Hz, 2 H, Ts), 7.80 (d, *J* = 8.2 Hz, 2 H, Ts). –MS: *m*/*z* (%) = 648, 646 [$M^+$] (4), 633, 631 [$M^+$ – $CH_3$] (8), 616, 614 [$M^+$ – $CH_3OH$] (7), 593, 591 [$M^+$ – $C_4H_7$] (14), 444, 442 [$M^+$ – TsOH – $CH_3OH$] (22), 363 [$M^+$ – TsOH – $CH_3OH$ – Br] (10), 285 (28), 253 [$M^+$ – side chain – $CH_3OH$ – 2 H] (100), 227 (12), 213 (14). – $C_{35}H_{51}O_4BrS$: calcd. 646.2691; found 646.2687 (MS).

**(23*Z*)-24-Bromo-6β-methoxy-3α,5-cyclo-5α-cholest-23-ene (22):** To a stirred solution of tosylate **21b** (1.24 g, 1.92 mmol) in THF (30 mL), $LiEt_3BH$ (1 M in THF, 11.5 mL, 11.52 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 5 h and then partitioned between diethyl ether and water. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with satd. aq. $NH_4Cl$ solution. The solvent was then evaporated and the residue was chromatographed on $SiO_2$ (17 g; hexane/toluene, 6:1) to yield the cholestene derivative **22** (0.84 g, 91%). An analytical sample was crystallized from methanol; m.p. 60–63 °C. – $^1H$ NMR: δ = 0.43 (dd, *J* = 7.7, 5.0 Hz, 1 H, 4α-H), 0.65 (t, *J* = 4.4 Hz, 1 H, 4β-H), 0.73 (s, 3 H, 18-H), 0.93 (d, *J* = 6.5 Hz, 3 H, 21-H), 1.02 (s, 3 H, 19-H), 1.11 (d, *J* = 6.6 Hz, 6 H, 26- and 27-H), 2.55 (sept, *J* = 6.6 Hz, 1 H, 25-H), 2.73–2.81 (m, 1 H, 6-H), 3.33 (s, 3 H, $CH_3O$), 5.67 (t, *J* = 6.7 Hz, 1 H, 23-H). –MS: *m*/*z* (%) = 478, 476 [$M^+$] (41), 463, 461 [$M^+$ – $CH_3$] (50), 446, 444 [$M^+$ – $CH_3OH$] (39), 423, 421 [$M^+$ – $C_4H_7$] (100), 315 [$M^+$ – $C_6H_{10}Br$] (14), 257 (11), 253 (34). – $C_{28}H_{45}OBr$ (477.57): calcd. C 70.31, H 9.75, Br 16.87; found C 70.42, H 9.50, Br 16.73.

**Reaction of 22 with Dibromocarbene Generated in a Phase-Transfer System:** A mixture of vinylic bromide **22** (332 mg, 0.70 mmol), $CH_2Cl_2$ (1.5 mL), bromoform (487 μL, 5.58 mmol), Cetrimid® (4 mg), ethanol (10 μL), and 50% aq. NaOH solution (1.174 mL, 22.306 mmol) was stirred for 50 h and then partitioned between diethyl ether and water. The layers were separated and the aqueous

layer was extracted with further diethyl ether. The combined organic extracts were washed with satd. aq. $NH_4Cl$ solution, the solvent was evaporated, and the residue was chromatographed on $SiO_2$ (10–40 μm, Merck 7736, 24 g). Fractions were collected as follows: elution with hexane gave **23** (58 mg, 12%); elution with hexane/$CH_2Cl_2$, 8:1, gave **24** (76 mg, 13%), followed by (23*S*,24*R*)-**15c** (22 mg), a mixture of **15c** and **15d** (190 mg), and (23*R*,24*S*)-**15d** (15 mg). The chromatography was monitored by TLC (hexane/$CH_2Cl_2$, 2:1, developed 3 times). The combined yield of **15c** and **15d** amounted to 50%. The mixture of products was also separated by preparative HPLC on a Macherey–Nagel Duren Nucleosil® 100–10 C18 column eluting with hexane/$CH_2Cl_2$, 3:1, flow rate 8 mL/min., UV detection at λ = 235 nm.

**(23*R**,24*S**)-3β,24-Dibromo-23,24-(dibromomethylene)cholest-5-ene (23) (Mixture of Diastereoisomers):** $^1$H NMR: δ = 0.70 and 0.73 (s, 3 H, 18-H), 1.04 (s, 3 H, 19-H), 1.09 (d, *J* = 6.5 Hz, 27- and 21-H), 1.10 (d, *J* = 6.6 Hz, 26- and 21-H), 1.17 (d, *J* = 6.4 Hz, 3 H, 27-H), 3.80–4.05 (m, 1 H, CHBr), 5.30–5.42 (m, 1 H, C=CH). – MS: *m*/*z* (%) = 702, 700, 698, 696, 694 [$M^+$] (6), 687, 685, 683, 681, 679 [$M^+ - CH_3$] (8), 621, 619, 617, 615 [$M^+$ – Br] (100), 365, 363 [$M^+ - C_7H_{10}Br_3$] (57), 335, 333 (77), 295, 293 (25), 241, 239, 237 (27), 229, 227, 225, 223 (25), 215, 213 (42).

**(23*R**,24*S**)-24-Bromo-6α-dibromomethyl-23,24-dibromomethylene-6β-methoxy-3α,5-cyclo-5α-cholestane (24):** – $^1$H NMR: δ = 0.78 (s, 3 H, 18-H), 1.06–1.12 (s, 3 H, 19-H coincident with d, 3 H, 21-H), 1.10 (d, *J* = 6.3 Hz, 3 H, 26-H), 1.18 (d, 3 H, *J* = 6.0 Hz, 27-H), 3.31 (s, 3 H, $CH_3O$), 5.75 (s, 1 H, $CHBr_2$). – MS: *m*/*z* (%) = 824, 822, 820, 818, 816, 814 [$M^+$] (3), 712, 710, 708, 706, 704 [$M^+$ – Br – $CH_3OH$] (97), 651, 649, 647, 645 [$M^+ - CHBr_2$] (100), 628 [$M^+ - Br_2 - CH_3OH$] (88), 617, 615, 613, 611, 609 [$C_{22}H_{29}Br_4$] (44), 549, 547, 545 [$M^+ - Br_3 - CH_3OH$] (20). – LSIMS (with NaOAc): *m*/*z* (%) = 849, 847, 845, 843, 841, 839 [M + Na]$^+$ (37), 651, 649, 647, 645 [$M^+ - CHBr_2$] (100).

**(23*S*,24*R*)-24-Bromo-23,24-dibromomethylene-6β-methoxy-3α,5-cyclo-5α-cholestane (15c):** $R_f$ = 0.44, $t_R$ = 39.18 min. – $^1$H NMR: δ = 0.43 (dd, *J* = 7.9, 5.1 Hz, 1 H, 4α-H), 0.65 (t, *J* = 4.9 Hz, 1 H, 4β-H), 0.74 (s, 3 H, 18-H), 1.03 (s, 3 H, 19-H), 1.09 (d, 3 H, *J* = 5.6 Hz, 21-H), 1.09 (d, 3 H, *J* = 6.6 Hz, 26-H), 1.18 (d, *J* = 6.4 Hz, 3 H, 27-H), 2.74–2.81 (m, 1 H, 6-H), 3.32 (s, 3 H, $CH_3O$). – MS: *m*/*z* (%) = 652, 650, 648, 646 [$M^+$] (51), 637, 635, 633, 631 [$M^+$ – Me] (54), 620, 618, 616, 614 [$M^+ - CH_3OH$] (69), 597, 595, 593, 591 [$M^+ - C_4H_7$] (100), 553 (11). – $C_{29}H_{45}OBr_3$: calcd. 646.102048; found 646.101578 (MS).

**(23*R*,24*S*)-24-Bromo-23,24-dibromomethylene-6β-methoxy-3α,5-cyclo-5α-cholestane (15d):** $R_f$ = 0.41, $t_R$ = 43.24 min. – $^1$H NMR: δ = 0.43 (dd, *J* = 7.9, 5.4 Hz, 1 H, 4α-H), 0.65 (t, *J* = 4.4 Hz, 1 H, 4β-H), 0.79 (s, 3 H, 18-H), 1.03 (s, 3 H, 19-H), 1.09 (d, 3 H, *J* = 6.6 Hz, 21-H), 1.10 (d, *J* = 6.6 Hz, 3 H, 26-H), 1.18 (d, *J* = 6.5 Hz, 3 H, 27-H), 2.73–2.80 (m, 1 H, 6-H), 3.33 (s, 3 H, $CH_3O$). – MS: *m*/*z* (%) = 652, 650, 648, 646 [$M^+$] (50), 637, 635, 633, 631 [$M^+$ – Me] (56), 620, 618, 616, 614 [$M^+ - CH_3OH$] (67), 597, 595, 593, 591 [$M^+ - C_4H_7$] (100), 553 (9). – $C_{29}H_{45}Br_3O$: calcd. 646.10205; found 646.10222 (MS).

**(23*S*)-6β-Methoxy-3α,5:23,28-dicyclo-5α-stigmasta-24(28)-ene (18b):** To a stirred solution of (23*R*,24*S*)-tribromide **15d** (34 mg, 0.053 mmol) in diethyl ether (0.5 mL), MeLi (1.45 M in diethyl ether, 146 μL, 0.212 mmol) was added at –78 °C. The resulting mixture was allowed to warm to room temp., then cooled to –65 °C, whereupon MeI (100 μL, 1.6 mmol) was added. The cooling bath was then removed and, after 2.5 h, the mixture was partitioned between diethyl ether (5 mL) and satd. aq. $NH_4Cl$ solution (5 mL). The aqueous layer was extracted with further diethyl ether and the combined organic extracts were washed with satd. aq. $NaHCO_3$ solution. The solvent was then evaporated and the residue was chromatographed on $SiO_2$ (0.5 g, hexane/diethyl ether, 100:1) to give the calysterol derivative **18b** (12 mg, 53%). – $^1$H NMR: δ = 0.43 (dd, *J* = 8.0, 5.0 Hz, 1 H, 4α-H), 0.65 (t, *J* = 4.4 Hz, 1 H, 4β-H), 0.72 (s, 3 H, 18-H), 0.98–1.14 (d, *J* = 7.0 Hz, 3 H, 21-H coincident with s, 3 H, 19-H), 1.10 (d, *J* = 6.9 Hz, 3 H, 26-H), 1.12 (d, *J* = 6.9 Hz, 3 H, 27-H), 2.02 (d, *J* = 1.6 Hz, 3 H, 29-H), 2.63 (sept q, *J* = 6.8, 1.6 Hz, 1 H, 25-H), 2.74–2.81 (m, 1 H, 6-H), 3.32 (s, 3 H, $CH_3O$). – MS: *m*/*z* (%) = 424 [$M^+$] (2), 409 [$M^+$ – Me] (3), 392 [$M^+ - CH_3OH$] (3), 381 [$M^+ - CH(CH_3)_2$] (7), 377 [$M^+ - CH_3 - CH_3OH$] (2), 369 [$M^+ - C_4H_7$] (5), 349 [$M^+ - CH(CH_3)_2 - CH_3OH$] (2), 283 (10), 253 [$M^+$ – side chain – $CH_3OH$ – 2 H] (100), 227 (8), 213 (9), 199 (8), 187 (8), 173 (10), 159 (18), 155 (12), 143 (12), 121 (17), 109 (17), 95 (35), 91 (12), 77 (12), 65 (10), 51 (5). – $C_{30}H_{48}O$: calcd. 424.3705; found 424.3707 (MS).

**(23*S*)-23*H*-Isocalysterol [(23*S*)-23,28-Cyclostigmasta-5,24(28)-dien-3β-ol] (2b):** A mixture of ***i*-steroid 18b** (12 mg, 0.028 mmol), dioxane (1 mL), water (250 μL), and TsOH (1 mg) was stirred at 80 °C for 1 h, cooled to room temp., and then partitioned between diethyl ether (3 mL) and satd. aq. $NaHCO_3$ solution (2 mL). The aqueous layer was extracted with further diethyl ether and the combined organic extracts were washed with brine. The solvent was then evaporated and the residue was chromatographed on a column packed with silica gel for TLC (10–40 μm, Merck 7736) eluting with hexane/diethyl ether, 15:1, to give isocalysterol **2b** (3.6 mg, 31%) and **2b** contaminated with a UV light-absorbing substance (2.8 mg). An analytical sample was obtained by HPLC ($t_R$ = 18.25 min). Its $^1$H-NMR and mass spectra were identical to those of a sample obtained as described above.

**(23*R*,24*S*)-24-Bromo-23,24-(dibromomethylene)cholest-5-en-3β-ol (17d):** A mixture of ***i*-steroid 15d** (40 mg, 0.062 mmol), dioxane (1.6 mL), water (250 μL), and TsOH (1 mg) was stirred at 81–84 °C for 30 min., allowed to cool to room temp., and then partitioned between diethyl ether and satd. aq. $NaHCO_3$ solution. The aqueous layer was extracted with further diethyl ether and the combined organic extracts were concentrated to dryness. The residue was chromatographed on $SiO_2$ (1 g; hexane/diethyl ether, 6:1) to yield alcohol **17d** (37.7 mg, 96%). An analytical sample was obtained by crystallization from hexane; m.p. 132–135 °C and 149–152 °C. – $^1$H NMR: δ = 0.73 (s, 3 H, 18-H), 1.01 (s, 3 H, 19-H), 1.09 (d, *J* = 6.6 Hz, 3 H, 21-H or 26-H), 1.10 (d, *J* = 6.6 Hz, 3 H, 21-H or 26-H), 1.18 (d, *J* = 6.4 Hz, 3 H, 27-H), 3.40–3.65 (m, 1 H, 3-H), 5.30–5.40 (m, 1 H, 6-H). – $C_{28}H_{43}OBr_3$ (635.35): calcd. C 52.93, H 6.82; found C 53.00, H 6.94.

**(23*S*,24*R*)-24-Bromo-23,24-(dibromomethylene)cholest-5-en-3β-ol (17c):** A mixture of ***i*-steroid 15c** (33 mg, 0.051 mmol), dioxane (1 mL), water (250 μL), and TsOH (1 mg) was stirred at 85 °C for 2 h, then allowed to cool, and worked-up as described above to give alcohol **17c** (31 mg, 95%). – $^1$H NMR: δ = 0.71 (s, 3 H, 18-H), 1.01 (s, 3 H, 19-H), 1.09 (d, *J* = 6.5 Hz, 6 H, 26- and 27-H or 26- and 21-H), 1.17 (d, *J* = 6.5 Hz, 3 H, 21-H or 27-H), 3.40–3.65 (m, 1 H, 3-H), 5.30–5.40 (m, 1 H, 6-H). – MS: *m*/*z* (%) = 638, 636, 634, 632 [$M^+$] (8), 539, 537, 535 [$M^+ - Br - H_2O$] (15), 283 (21), 271, 253, 213 (27), 199 (15). – $C_{28}H_{43}OBr_3$: calcd. 632.0864; found 632.0863 (MS).

**(23*R*)-23*H*-Isocalysterol [(23*R*)-23,28-Cyclostigmasta-5,24(28)-dien-3β-ol] (2a):** To a solution of **17c** (24.5 mg, 0.04 mmol) in $CH_2Cl_2$ (1 mL), 2-methoxypropene (16 μL, 0.16 mmol) and Amberlyst-15H

(10 mg) were added. The mixture was stirred for 2 h and then filtered through $SiO_2$ deactivated with $Et_3N$ (1 g). The filtrate was concentrated to dryness and the residue was dried under high vacuum conditions at 50 °C. The 2-methoxy-2-propyl derivative **25** thus obtained was redissolved in diethyl ether (0.9 mL). This solution was cooled to –75 °C, whereupon MeLi (1.4 M in diethyl ether, 200 μL, 0.28 mmol) was added. The resulting mixture was allowed to warm to room temp. over ca. 15 min. and was then cooled to –70 °C once more, whereupon MeI (100 μL, 1.6 mmol) was added. The cooling bath was removed and after 3 h the reaction was quenched (temp. –40 °C) by adding diethyl ether (5 mL) and water (5 mL). The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with water and brine. The solvent was then evaporated and the crystalline residue was redissolved in a mixture of methanol (1 mL) and diethyl ether (0.5 mL). Amberlyst-15H deactivated with pyridine (23 mg) was added and the mixture was stirred at room temp. for 50 min. The solid was then filtered off, the filtrate was concentrated in stream of Ar, and the residue was chromatographed on $SiO_2$ (1.5 g; hexane/diethyl ether, 12:1) to give isocalysterol **2a** (11.8 mg, 73%). An analytical sample was purified by HPLC under the conditions described above; m.p. 109–111 °C (diethyl ether/methanol); $[\alpha]_{589}^{22} = -44.4$ (3 mg/mL, $CHCl_3$); ref.[38] m.p. 115–116 °C; $[\alpha]_{589}^{20} = -47.3$). Its $^1$H- and $^{13}$C-NMR spectra, as well as the mass spectrum, were identical to those obtained for a sample prepared as described above.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