TOWARDS SYNTHESIS OF CALYSTEROLS, MARINE STEROLS WITH CYCLOPROPENE MOIETY IN THE SIDE CHAIN: SYNTHESIS OF 26,27-DINOR-23*H*-ISOCALYSTEROL

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Dedicated to Dr Jan Fajkos on the occasion of his 75th birthday.

26,27-Dinor-23*H*-isocalysterol **24** has been synthesized in 19% yield (6 steps) from ethyl 6β-methoxy-3α,5-cyclo-5α-pregnan-21-oate (**18**). For construction of the side chain, alkylation of lithium salt of ester **18** with 1-bromo-1,2-dimethyl-*c*-3-iodomethyl-*c*-2-(trimethylsilyl)cyclopropane **16** was used. It has been shown that reduction of the ester group in position 21 and rearrangement of the 3,5-cyclosteroid system are compatible with the sidechain functionalities. It has been found that methylation of 1,1-dibromo-2-(trimethylsilyl)cyclopropane is accompanied by an rearrangement involving 1,2-migration of the trimethylsilyl group.

Key words: Steroids; Cyclopropanes; Cyclopropenes; Steroid side chain construction; Marine natural products; Total synthesis.

Calysterols are a class of marine sterols[1] of considerable interest because of their unusual structure and assumed biological function as a cell membrane component[2]. Calysterol (**1**) (first reported by the Napoli group[3]), and its isomers differing in the double bond position: (23*R*)-23*H*-isocalysterol[4] (**2a**) and (24*S*)-24*H*-isocalysterol[5] (**3**), have been isolated from the Mediterranean sponge *Calyx niceaensis* where they occur as the principal sterol constituents. The 23-epimer of compound **2a**, (23*S*)-23*H*-isocalysterol (**2b**), together with compounds **1** and **3** and 5,6-dihydro derivatives of compounds **1**, **2b** and **3**, have been isolated from the Bahamas sponge *Calyx podatypa*[6]. Studies by Djerassi and coworkers on marine sterols have resulted in the elucidation of calysterol biosynthesis[7] and have contributed a great deal to the understanding of their chemical and spectral properties[8].

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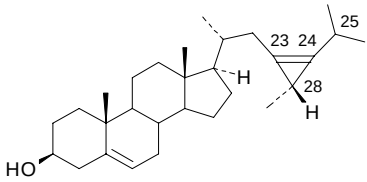
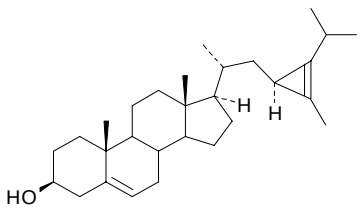
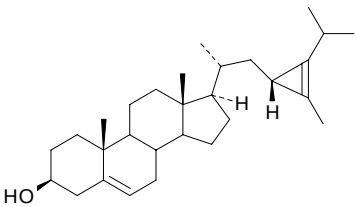
Calysterols have not yielded to synthesis from a readily available steroid starting material[9]. The difficulties in the unsuccessful attempts[10] ensue mainly from the high reactivity of the cyclopropene system[11]. On the other hand, the cyclopropene double bond in these compounds is sterically shielded by the isopropyl group and the large steroid fragment. This suggested that steric congestion may be another major obstacle in assembling the properly functionalized, cyclopropene-containing side chain in synthetic intermediates.



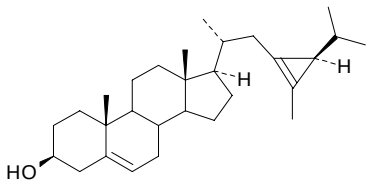
Calysterol **1**



(23*R*)-23*H*-Isocalysterol **2a**



(23*S*)-23*H*-Isocalysterol **2b**

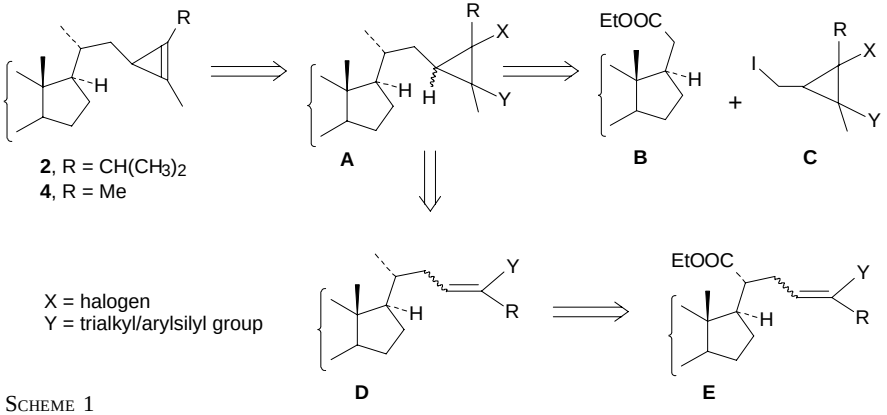


(24*S*)-24*H*-Isocalysterol **3**

In work aimed at the synthesis of a representative calysterol we have chosen 23*H*-isocalysterol (**2**, 23,28-cyclostigmasta-5,24(28)-dien-3β-ol) as the target compound since both its C-23 epimers **2a** and **2b** are fully characterized. To handle the chemical instability of the cyclopropene moiety, it was planned to introduce the double bond into cyclopropane ring at the terminal stages of synthesis using a preformed cyclopropane intermediate **A** (Scheme 1). Elimination of halogen atom and the adjacent trialkyl/arylsilyl group appeared most promising with regard to mildness of the reaction conditions[12] although elimination of two halogen atoms (X and Y = halogen) could lead to the goal as well[13]. Two alternative approaches to the intermediate **A** were considered: (i) construction of the suitable cyclopropane precursor **C** and its coupling with steroid building block **B** and (ii) assembling the side chain stepwise which would involve cyclopropanation of the double bond in the intermediate **D**; the latter would be prepared from **B** *via* **E**.

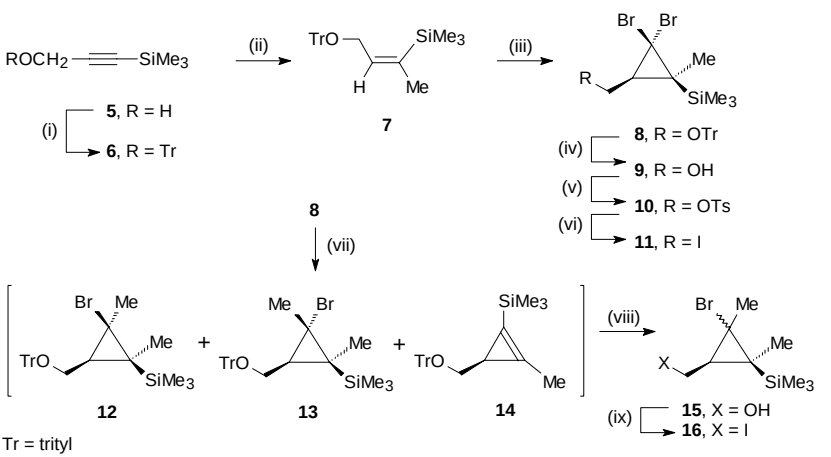
In practical terms, it was expected that analytical monitoring of the intermediate **A** (R = 2-propyl) would be extremely difficult due to the presence of several isomers (3 stereogenic centers in the cyclopropane ring). Under these circumstances, a study on

synthesis of the model cyclopropene derivative **4** (with the hydroxy group and the double bond in rings A and B protected) could provide a useful guidance. The respective intermediate **A** (R = Me) would be formed as a mixture of isomers. However, elimination of XY would remove the stereogenic centers in the cyclopropane ring and afford a single and relatively easy to characterize cyclopropene derivative (**4**). In this paper we describe our studies on synthesis of compounds of type **4**.



SCHEME 1

Our first objective was the synthesis of iodide **16** (Scheme 2). Silylated propargylic alcohol[14] **5** was transformed in the usual way into the highly crystalline trityl derivative[15] **6**. The latter compound was subjected first to hydroalumination with diisobutyl-



(i) TrCl/pyridine; (ii) a) diisobutylaluminium hydride/ether-toluene, b) MeLi/ether, c) MeI; (iii) $CHBr_3$, 50% aq. NaOH, Cetrimide, EtOH/CH_2Cl_2; (iv) MeOH, Amberlist®; (v) TsCl/pyridine; (vi) NaI/Me_2CO; (vii) a) MeI/THF-HMPA, b) butyllithium/hexanes; (viii) MeOH, reflux; (ix) a) TsCl/pyridine, b) NaI/Me_2CO

SCHEME 2

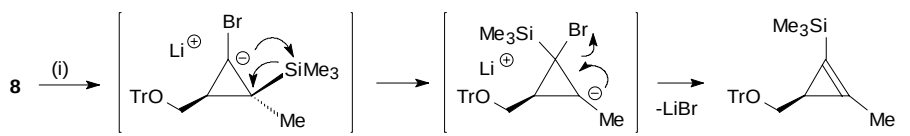
aluminium hydride, then the intermediate was treated with methyllithium (to effect formation of an "ate" complex) and then with methyl iodide[16]. Product **7** with *Z* configuration of the double bond was obtained exclusively. Transformation of **7** into **8** was conducted by the method of Makosza and Fedorynski[17] using bromoform, 50% NaOH and benzyltriethylammonium chloride or Cetrimid® as the phase-transfer catalyst.

Treatment of a solution of **8** and methyl iodide in tetrahydrofuran (THF) containing hexamethylphosphoric triamide (HMPA) with 1-butyllithium at –95 °C according to the general procedure of Kitatani *et al.*[18] yielded a mixture of three products in 5.4 : 2.6 : 1 ratio (98%) which were separated by chromatography. To the major product, the structures **12** and **13** were assigned on the basis of their ^{1}H NMR spectra. In the spectrum of **12**, the cyclopropane proton signal appeared at δ 0.70 ppm, as dd, J = 7.6 and 6.4 Hz, whereas the corresponding signal in the spectrum of **13**, at δ 1.55 ppm, dd, J = 8.7 and 6.7 Hz. Chemical shifts of these protons are in agreement with those described for similar compounds[18a]. Compound **13** decomposed on storage at –18 °C during a few days in contrast to its isomer **12** which was virtually completely stable. Chemical instability of **13** supports the assigned structure with *trans* oriented and strongly interacting by the push-pull mechanism bromine atom and the trimethylsilyl group.

The minor component of the mixture was devoid of bromine atoms. Its molecular formula obtained from high resolution mass spectrum corresponded to the cyclopropene derivative **14**. This structure was fully confirmed by ^{1}H and ^{13}C NMR measurements, including C–C spin–spin coupling constants[19].

Proportion of the methylation (**12** and **13**) to the rearrangement product (**14**) depended upon the temperature, reaction scale and amount of HMPA. Thus, the reaction at –78 °C afforded a larger amount of the cyclopropene derivative with the ratio of **12**/**13**/**14** being 3.1 : 2.2 : 1, starting from 0.6 mmol of **8** and 2.2 : 1.4 : 1, starting from 6 mmol of **8**. When a mixture of **8** and methyl iodide was treated with BuLi (at –78 °C) with no HMPA added, cyclopropene **14** was formed as the only product (isolated in 92% yield). However, all our attempts to exclude completely formation of **14** failed.

Mechanism of formation of cyclopropene **14** and the role HMPA in this reaction deserve a comment. The postulated mechanism of debromination is illustrated in Scheme 3. An anion-induced silyl group 1,2 migration is followed by bromide anion elimination. The presence of HMPA in the reaction medium activates methyl iodide as external electrophile whereas it does not affect significantly the carbon–silicon bond in **8**.



(i) butyllithium/THF

SCHEME 3

This explains the crucial role of HMPA for the proportion of methylation and rearrangement products. When our work was in progress a mechanistically similar rearrangements occurring with a silyl group migration have been reported[20].

Having in mind the synthesis of calysterols **2a** and **2b**, we have briefly examined isopropylation of **8**. With replacement of methyl iodide with isopropyl iodide or triflate in the above discussed reaction (–95 °C, THF–HMPA), only the rearrangement product **14** was obtained. No trace of the isopropyl analogue of **12** could be detected.

Our next goal on the synthetic route was to remove the protecting trityl group in **12** and **13** and transform the respective alcohols into iodides **16**. For these reactions, we have used the crude mixture of alkylation products since the relative stereochemistry of the bromine atom and the trimethylsilyl group in the cyclopropane ring had no consequences for the final product stereochemistry.

Our initial attempts to cleave the trityloxy group in **12** and accompanying products under conditions of acid-catalyzed hydrolysis yielded complex mixtures of products. Ultimately, it was found that heating of the mixture of trityl ethers in anhydrous methanol results in transestherification. Chromatography of the crude product gave tritylmethyl ether and the desired alcohols **15** (5.2 : 1 ratio by ^{1}H NMR, 74% yield). The fate of the minor component in the starting mixture, **14**, was not followed.

The mixture of alcohols was tosylated and the crude unstable tosylates were immediately subjected to the reaction with sodium iodide in acetone. The iodide **16** was obtained in 61% yield (one isomer, as shown by ^{1}H NMR).

With iodide **16** in hand the stage was set for the alkylation reaction. Ester **18** (Scheme 4), prepared as previously described[21] was treated with lithium diisopropylamide and then with 2 equivalents of **16** in the presence of HMPA. The reaction was rather slow and was accompanied by decomposition of the iodide. However, the alkylation product **19** was obtained in sufficient yield (32%) to study further transformations.

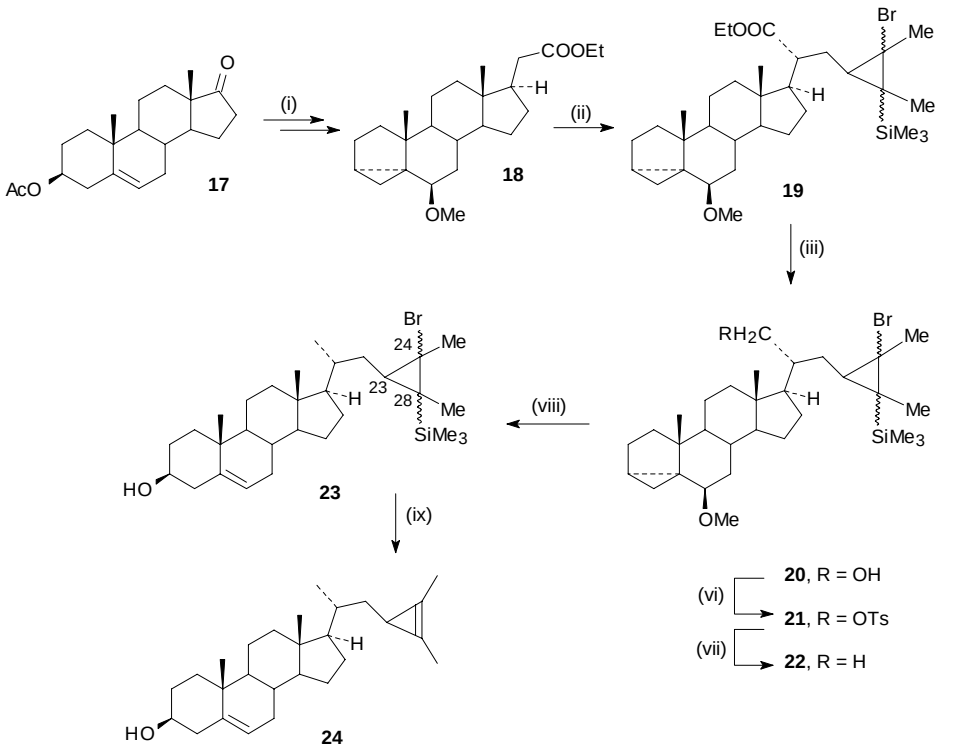
Reduction of the ester group in **19** with diisobutylaluminium hydride yielded alcohol **20** which was further reduced into the methyl derivative **22** *via* tosylate **21**. The signals of C-21 protons in the NMR spectra of alcohol **20**, tosylate **21** and the methyl derivative **22** indicated that the alkylation was completely stereoselective with respect to the stereogenic center at C-20.

After obtaining the intermediate **22** with the pre-prepared cyclopropene unit, we approached removal of the protecting 3,5-cyclo-steroid system. Hydrolysis of methyl ether **22** with 4-toluenesulfonic acid in aqueous dioxane under reflux[22] yielded smoothly the corresponding homoallylic alcohol **23**.

It was of interest to investigate coupling of ester **18** with cyclopropene building block at earlier stages of transformation. To this end, dibromide **8** was subjected to methanolysis to give alcohol **9** which was then transformed into iodide **11** in the usual way. Our attempts to couple ester **18** and iodide **11** under alkylation reaction conditions

were unsuccessful. The reaction was sluggish even at higher temperature (–20 to 0 °C); the only product that could be isolated was ester **18** with bromine in position 20.

Finally, treatment of **23** with tetrabutylammonium fluoride followed by flash chromatography of the product provided the target calysterol analogue **24** (100% yield). In its ^{1}H NMR spectrum six proton singlet at δ 1.95 ppm appeared corresponding to the methyl groups on the cyclopropene ring. The cyclopropene derivative **24** could be stored as an oil for a few hours without a visible decomposition as could be judged from its ^{1}H NMR spectra.



(i) ref. [21]; (ii) a) lithium diisopropylamide/THF, b) **16**, HMPA; (iii) diisobutylaluminium hydride/CH_2Cl_2-toluene; (iv) TsCl/pyridine; (v) $LiEt_3BH$/THF; (vi) TsCl/pyridine; (vii) $LiEt_3BH$/THF; (viii) TsOH/aqueous dioxane; (ix) tetrabutylammonium fluoride/THF

SCHEME 4

In conclusion, calysterol analogue **24** has been synthesized by a convergent route involving separate preparation of cyclopropane building block **16**. It has been shown that reduction of the ester group into the methyl group (**19**→**22**) and the deprotection of the 3,5-cyclo-steroid system (**22**→**23**) are compatible with the side chain functionality. However, a low yield of the coupling of the steroid and cyclopropane building blocks

suggests using a stepwise construction of the side chain in an approach to 23*H*-isocalysterols. An interesting migration of the trimethylsilyl group in the cyclopropane ring has been noted.

EXPERIMENTAL

Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ solutions, ^1H at 200 MHz and ^{13}C at 50 MHz with Varian Gemini instrument and ^1H at 500 MHz and ^{13}C at 125 MHz with Bruker AMX. Chemical shifts are reported in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra were recorded on Perkin–Elmer 1670 FT unit, wavenumbers in cm^{-1}. Mass spectra (electron impact, 70 eV) were taken on AMD 604 (AMD Intectra GmbH, Germany). Anhydrous solvents were obtained by distillation from benzophenone ketyl (ether, THF) or calcium hydride (dioxane, 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 on a rotary evaporator. Column chromatography was performed on Merck silica gel 60, 230–400 mesh, and TLC on Merck aluminium sheets, silica gel 60 F_{254} G. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter using a 1 ml capacity cell (10 cm path length) for $CHCl_3$ solutions and are given in 10^{-1} deg. For preparative HPLC, column Macherey–Nagel Duren Nucleosil®, flow 8 ml/min, was used.

1-Trimethylsilyl-3-trityloxyprop-1-yne (**6**)

A mixture of tritylchloride (11.58 g, 41.5 mmol), pyridine (3.4 ml, 42 mmol), alcohol[14] **5** (5.35 g, 41.5 mmol) and CH_2Cl_2 (17 ml) was stirred at room temperature for 10 h. Then CH_2Cl_2 (180 ml), cold aqueous 3% HCl (15 ml) and ice (*ca* 5 g) were added. The organic layer was separated and washed successively with saturated aqueous $NaHCO_3$ solution (20 ml) and water (45 ml). The solvent was evaporated, the residue dissolved in hexane and filtered through silica gel (30 g) to give **6** (14.9 g, pure by TLC). This product was crystallized from methanol (130 ml)/water (2 ml) and dried in high vacuum to give **6** (11.57 g, 75%), m.p. 93–94 °C, identical in all respects with an authentic sample[15].

(*Z*)-3-Trimethylsilyl-1-trityloxybut-2-ene (**7**)

To a stirred solution of **6** (3.7 g, 9.96 mmol) in ether (18 ml) a solution of 1.2 M diisobutylaluminium hydride in toluene (10 ml, 11.95 mmol) was added dropwise at 4 °C and the mixture was stirred at room temperature until the starting material was consumed (TLC, hexane/toluene/ethyl acetate 10 : 1 : 0.02, *ca* 5 h). Then the mixture was cooled to 0–5 °C and was treated with 1.6 M methyllithium in ether (8.1 ml, 12.95 mmol) followed (after 30 min) with methyl iodide (2.1 ml, 32.4 mmol). The mixture was stirred at room temperature for 22 h and then heated at the reflux for 1 h. After cooling, the reaction was quenched by careful by careful addition of ice water. The mixture was partitioned between ether (70 ml) and 1 M HCl (40 ml). The aqueous layer was extracted with ether (2 × 20 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and water. The solvent was evaporated and the residue was dissolved in hexane and filtered through silica gel (38 g) to give **7** (3.6 g, 94%). An analytical sample was crystallized from methanol: m.p. 73–74 °C. ^1H NMR spectrum (200 MHz) : 0.12 (s, 9 H, $(CH_3)_3Si$); 1.82 (dt, J = 1.5, 1.3, 3 H, CH_3); 3.61 (dq, J = 6.5, 1.3, 2 H, CH_2); 6.31 (tq, J = 6.5, 1.7, 1 H, C=CH); 7.19–7.53 (m, 15 H, arom. H). ^{13}C NMR spectrum (50 MHz): –0.85 ($(CH_3)_3Si$)); 24.31 (**C**CH_3); 63.89 (CH_2); 86.68 (Ph**C**); 127.04 (C_p); 127.90 (C_m); 128.90 (C_o); 138.48 (C=**C**H); 138.73 (C=**C**Si); 144.50 (C_{ipso}). For $C_{26}H_{30}OSi$ (386.61) calculated: 80.77% C, 7.82% H; found: 80.81% C, 7.79% H.

1,1-Dibromo-2-methyl-*r*-2-trimethylsilyl-*c*-3-(trityloxymethyl)cyclopropane (**8**)

A mixture of **7** (2.55 g, 6.59 mmol), CH_2Cl_2 (3.5 ml), bromoform (2.3 ml, 26.4 mmol), Cetrimide (46 mg), 50% aqueous NaOH (2.85 g, 71.3 mmol) and ethanol (20 μl) was vigorously stirred (with a mechanical stirrer) at room temperature for 1 h and then at 50 °C for 18 h and then it was cooled to __ °C and partitioned between water (15 ml) and CH_2Cl_2 (50 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 ml). The combined organic extracts were washed with HCl (3%, 2 ml) and then with saturated aqueous $NaHCO_3$ solution (3 ml) and water (20 ml). The solvent was evaporated and the residue was dissolved in hexane and filtered through silica gel (30 g). The filtrate was concentrated and the precipitate collected to give **8** (2 g, 68%). An analytical sample was recrystallized twice from hexane, m.p. 149–151 °C. ^{1}H NMR spectrum (200 MHz): 0.03 (s, 9 H, $(CH_3)_3Si$); 1.30 (s, 3 H, CH_3); 1.48 (dd, *J* = 7.4, 6.7, 1 H, CH); 3.23 (dd, *J* = 10.8, 6.7, 1 H, CH_2); 3.40 (dd, *J* = 10.8, 7.4, 1 H, CH_2); 7.20–7.53 (m, 15 H, arom. H). ^{13}C NMR spectrum (50 MHz): 0.34 ($(CH_3)_3Si$); 24.43 (CH_3**C**Si); 25.87 (CH_3); 41.71 (CH); 44.77 (CBr_2); 64.33 (CH_2); 87.04 (Ph_3C); 127.03 (C_p); 127.80 (C_m); 128.84 (C_o); 144.50 (C_{ipso}). Mass spectrum, *m/z* (%): 558 (M^+); 481, 368, 243 ($C_6H_5I_3C^+$, 100); 165, 75. For $C_{27}H_{30}Br_2OSi$ (558.42) calculated: 58.07% C, 5.42% H; found: 58.19% C, 5.21% H.

1,1-Dibromo-*c*-3-hydroxymethyl-2-methyl-*r*-2-(trimethylsilyl)cyclopropane (**9**)

A mixture of **8** (2.33 g, 4.18 mmol), methanol (25 ml) and Amberlyst-15 (100 mg) was heated under reflux for 1 h, cooled and the precipitate (Ph_3COMe) was removed and washed with methanol. The filtrate was evaporated and the residue was chromatographed on silica gel (20 g). Elution with hexane–ether, (20 : 1), gave some additional Ph_3COMe and elution with hexane–ether (6 : 1) afforded **9** (1.23 g, 93%). A sample was purified by sublimation at 65 °C/65 Pa), m.p. 103–104 °C. ^{1}H NMR spectrum (200 MHz): 0.23 (s, 9 H, $(CH_3)_3Si$); 1.33 (s, 3 H, CH_3); 1.58 (dd, *J* = 9.1, 6.1, 1 H, CH); 3.79 (part B of ABX system, *J* = 11.7, 6.1, 1 H, CH_2); 3.87 (part A of ABX system, *J* = 11.7, 9.1, 1 H, CH_2). ^{13}C NMR spectrum (50 MHz): 0.70 (CH_3Si); 25.08 (CH_3**C**Si); 25.97 (CH_3); 43.87 (CH); 44.54 (CBr_2); 63.01 (CH_2). IR spectrum: 3 640. For $C_8H_{16}Br_2OSi$ (316.1) calculated: 30.39% C, 5.11% H; found: 30.39% C, 5.14% H.

1,1-Dibromo-2-methyl-*c*-3-tosyloxymethyl-*r*-2-(trimethylsilyl)cyclopropane (**10**)

A mixture of **9** (520 mg, 1.63 mmol), tosyl chloride (390 mg, 2 mmol) and pyridine (2 ml) was stirred at 5 °C for 16 h and then partitioned between ether (25 ml) and ice-cold 4 M HCl (8 ml). The aqueous layer was extracted with ether (2 × 20 ml) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine. The solvent was evaporated and the residue was chromatographed on silica gel (10 g, 0.3% of ethylacetate in hexane) to give **10** (480 mg, 62%). ^{1}H NMR spectrum (200 MHz): 0.19 (s, 9 H, $(CH_3)_3Si$); 1.28 (s, 3 H, CH_3); 1.59 (dd, *J* = 7.8, 7.6, 1 H, CH); 2.46 (s, 3 H, tosyl); 4.15 (dd, *J* = 10.8, 7.6, 1 H, CH_2); 4.34 (dd, *J* = 10.8, 7.8, 1 H, CH_2); 7.36 (d, *J* = 8.6, 2 H, tosyl); 7.83 (d, *J* = 8.6, 2 H, tosyl). $C_{15}H_{22}Br_2O_3SSi$ (470.3) calculated: 38.31% C, 4.72% H; found: 38.60% C, 4.72% H.

1,1-Dibromo-*c*-3-iodomethyl-2-methyl-*r*-2-(trimethylsilyl)cyclopropane (**11**)

A mixture of **10** (470 mg, 1 mmol), NaI (220 mg, 1.5 mmol) and acetone (16 ml) was heated under reflux for 2 h. After cooling, the solvent was evaporated and the residue was chromatographed on silica gel (10 g, hexane) to give **11** (360 mg, 85%). ^{1}H NMR spectrum (200 MHz): 0.30 (s, 9 H, $(CH_3)_3Si$); 1.32 (s, 3 H, CH_3); 1.80 (dd, *J* = 8.7, 7.6, 1 H, CH); 3.26 (dd, *J* = 10.1, 8.7, 1 H, CH_2); 3.48 (dd, *J* = 10.1, 7.6, 1 H, CH_2). ^{13}C NMR spectrum (50 MHz): 0.88 ($(CH_3)_3Si$); 5.68 (CH_2); 26.00 (CH_3); 28.92 (CH_3**C**Si); 45.41 (CH); 48.16 (CBr_2). Mass spectrum, *m/z* (%): 347, 345 (M^+ – Br,

<0.1); 301, 299, 297 ($M^+ - I$, 0.2); 73 (Me_3Si^+, 100). For $C_8H_{15}Br_2ISi$ (426.0) calculated: 22.55% C, 3.55% H; found: 22.63% C, 3.69% H.

Reaction of Ester **18** with Iodide **11**

To a solution of lithium diisopropylamide, prepared from diisopropylamine (39 μl, 0.28 mmol) and 1.6 M butyllithium in hexanes (175 μl, 0.28 mmol), in THF (250 μl) a solution of **18** (30 mg, 0.08 mmol) in THF (250 μl) was added at –78 °C. The mixture was stirred for 1 h and then a solution of **11** (80 mg, 0.19 mmol) in THF (100 μl) and HMPA (100 μl) was added. Stirring at –70 °C was continued for 2.5 h and the mixture was set aside at 0 °C for 12 h. The reaction was quenched with water and the product was extracted with hexane (2 × 20 ml). The solvent was evaporated and the residue was chromatographed on SiO_2 (1 g, toluene/hexane 2 : 1) to give ethyl (20 *R/S*)-bromo-6β-methoxy-3α,5-cyclo-5α-pregnan-21-oate (10 mg, 30%) and a mixed fraction consisting of this product and **18** (14 mg).

Ethyl (20 R/S)-bromo-6β-methoxy-3α,5-cyclo-5α-pregnan-21-oate. ^{1}H NMR spectrum (200 MHz): 0.41 (dd, *J* = 8.1, 5.2, 1 H, 4α-H); 0.62 (t, *J* = 4.4, 1 H, 4β-H); 0.74 (s, 3 H, 3 × 18-H); 0.98 (s, 3 H, 3 × 19-H); 1.29 (t, *J* = 7.1, 3 H, C**H**$_3$CH$_2$O); 2.72–2.77 (m, 1 H, 6-H); 3.30 (s, 3 H, CH$_3$O); 4.14 (d, *J* = 9.1, 1 H, CHBr); 4.18 (dq, *J* = 7.1, 1.3, 2 H, CH$_3$C**H**$_2$O). IR spectrum (film): 1 740, 1 755. Mass spectrum, *m/z* (%): 454, 452 (M^+, 27); 439, 437 ($M^+ - CH_3$, 57); 422, 420 ($M^+ - CH_3OH$, 59); 399, 397 ($M^+ - C_4H_7$, 100); 359 (M – Br – CH_3, 12); 342 (M^+ – Br – CH_3OH, 54).

Methylation of Dibromocyclopropane **8**

To a mixture of **8** (136 mg, 0.24 mmol), HMPA (270 μl, 1.6 mmol), methyl iodide (126 μl, 1.92 mmol) and THF stirred at –95 °C, (1.8 ml) 1.4 M butyllithium in hexanes (345 μl, 0.48 mmol) was added. After 2 h at –95 °C ether (5 ml) was added followed by water (0.5 ml). The mixture was partitioned between ether (20 ml) and water (15 ml). The aqueous layer was extracted with ether (20 ml). The combined extract was evaporated and the residue was dissolved in hexane and filtered through silica gel (1.5 g) to give a mixture of **12**, **13** and **14** in a ratio of 5.4 : 2.6 : 1 (120 mg, 98%). The products were separated by preparative HPLC (0.2% ethylacetate in hexane, detection at λ 253 nm).

r-1-Bromo-1,2-dimethyl-c-2-trimethylsilyl-c-3-(trityloxymethyl)cyclopropane (**12**). R_t 17.49 min. ^{1}H NMR spectrum (200 MHz): –0.03 (s, 9 H, $(CH_3)_3Si$); 0.70 (dd, *J* = 7.6, 6.4, 1 H, CH); 1.06 (s, 3 H, $(CH_3)CSi$); 1.90 (s, 3 H, $(CH_3)CBr$); 3.30 (dd, *J* = 10.0, 6.4, 1 H, CH_2); 3.38 (dd, *J* = 10.0, 7.6, 1 H, CH_2); 7.15–7.55 (15 H, arom. H). ^{13}C NMR spectrum (50 MHz): 0.52 ($(CH_3)_3Si$); 19.53 ((CH_3)**C**Si); 20.14, 28.01 ($(\mathbf{C}H_3)CBr$) and ($(\mathbf{C}H_3)CSi$); 37.54 (CH); 49.20 ((CH_3)**C**Br); 65.40 (CH_2); 86.79 (Ph_3C); 126.88 (C_p); 127.69 (C_m); 128.84 (C_o); 144.38 (C_{ipso}). Mass spectrum, *m/z* (%): 494, 492 (M^+); 382, 332, 243 (Ph_3C^+, 100); 165 (25); 73 ($(CH_3)_3Si^+$, 52). HR MS, for $C_{28}H_{33}BrOSi$ calculated: 492.14840; found: 492.14791.

r-1-Bromo-1,2-dimethyl-t-2-(trimethylsilyl)-t-3-(trityloxymethyl)cyclopropane (**13**). R_t 16.76 min. ^{1}H NMR spectrum (200 MHz): –0.13 (s, 9 H, $(CH_3)_3Si$); 1.32 (s, 3 H, $(CH_3)CSi$); 1.55 (dd, *J* = 8.7, 6.7, 1 H, CH); 1.70 (s, 3 H, CH_3CBr); 2.96 (dd, *J* = 9.9, 6.7, 1 H, CH_2); 3.17 (dd, *J* = 9.9, 8.7, 1 H, CH_2); 7.15–7.50 (15 H, arom. H). ^{13}C NMR spectrum (50 MHz): 0.38 ($(CH_3)_3Si$); 19.28 ((CH_3)**C**Si); 25.49, 26.38 ($(\mathbf{C}H_3)CSi$) and ($(\mathbf{C}H_3)CBr$); 39.31 (CH); 50.81 ((CH_3)**C**Br); 61.95 (CH_2); 86.57 (Ph_3C); 126.96 (C_p); 127.79 (C_m); 128.66 (C_o); 144.15 (C_{ipso}).

1-Methyl-2-(trimethylsilyl)-3-(trityloxymethyl)cyclopropene (**14**). R_t 15.90 min. ^{1}H NMR spectrum (200 MHz): 0.13 (s, 9 H, $(CH_3)_3Si$); 1.59 (dd, *J* = 5.6, 4.5, 1 H, C**H**CH_2O); 2.21 (s, 3 H, CH_3); 2.77 (dd, *J* = 9.2, 4.5, 1 H, CH_2); 2.99 (dd, *J* = 9.2, 5.6, 1 H, CH_2); 7.15–7.50 (m, 15 H, arom. H). ^{1}H NMR spectrum (200 MHz, dioxane-d_8): 0.14 (s, 9 H, $(CH_3)_3Si$); 1.59 (dd, *J* = 5.7, 4.3, 1 H, C**H**CH_2O); 2.18 (s, 3 H, CH_3); 2.71 (dd, *J* = 9.2, 4.5, 1 H, CH_2); 3.02 (dd, *J* = 9.2, 5.7, 1 H, CH_2); 7.10–7.60 (m, 15 H, arom. H).

^{13}C NMR spectrum (50 MHz, dioxane-d_8): –0.86 ($(CH_3)_3Si$); 13.48 (CH_3); 20.25 (**C**HCH_2); 72.07 (CH_2); 86.64 (Ph_3C); 112.87 ($(CH_3)_3Si$**C**); 127.31 (C_p); 128.22 (C_m); 129.39 (C_o); 135.84 (C=**C**–C); 145.60 (C_{ipso}). IR spectrum (film): 1 810. Mass spectrum, *m/z* (%): 398 (M^+); 368 ($M^+ - 2(CH_3)$); 243 (75, Ph_3C^+); 165 (65); 155 ($M^+ - Ph_3C$, 40); 125 (M^+–Ph_3COCH_2, 72); 73 ($(CH_3)_3Si^+$, 100). HR MS, for $C_{27}H_{30}OSi$ calculated: 398.20659; found: 398.20655.

An analogous reaction carried out at –78 °C yielded compounds **12**, **13** and **14** in a ratio of 3.1 : 2.2 : 1 (94%). Compound **13** was unstable on storage.

1-Methyl-2-trimethylsilyl-3-(trityloxymethyl)cyclopropene (**14**)

To a mixture of **8** (435 mg, 0.78 mmol), methyliodide (408 μl, 6.24 mmol) and THF (8 ml), stirred at –78 °C, 1.4 M butyllithium in hexanes (1.39 ml, 1.95 mmol) was added dropwise during 10 min. Stirring was continued for 1 h and then the reaction was quenched with ether (5 ml) and water (0.5 ml) and the mixture was partitioned between ether (20 ml) and water (10 ml). The aqueous layer was extracted with ether and the combined organic extract was evaporated. The residue was dissolved in hexane and filtered through silica gel to give **14** (286 mg, 92%) identical with the product described above.

r-1-Bromo-1,2-dimethyl-*c*-3-hydroxymethyl-*c*-2-(trimethylsilyl)cyclopropane (**15a**) and
r-1-Bromo-1,2-dimethyl-*t*-3-hydroxymethyl-*t*-2-(trimethylsilyl)cyclopropane (**15b**)

A mixture of **12**, **13** and **14** (481 mg, in 3.8 : 2.5 : 1 ratio) obtained as described above, was dissolved in methanol (16 ml) and heated under reflux for 1 h. After cooling, the mixture was diluted with toluene (15 ml) and concentrated on a rotary evaporator. The residue (*ca* 10 ml) was transferred onto a silica gel (10 g) column. Elution of the column afforded: Ph_3COCH_3 and some unchanged starting material (hexane/ethylacetate 25 : 1) and a mixture of **15a** and **15b** (156 mg, 74%) in 5.2 : 1 ratio by ^{1}H NMR spectrum (hexane/ethyl acetate 20 : 1).

An analogous reaction of **12** (isolated by HPLC) yielded 68% of **15a**.

r-1-Bromo-1,2-dimethyl-*c*-3-hydroxymethyl-*c*-2-(trimethylsilyl)cyclopropane (**15a**)

^{1}H NMR spectrum (200 MHz): 0.18 (s, 9 H, $(CH_3)_3Si$); 0.83 (dd, J = 8.0, 6.8, 1 H, CH); 1.06 (s, 3 H, $(CH_3)CSi$); 1.90 (s, 3 H, $(CH_3)CBr$); 3.81–3.91 (m, 2 H, CH_2). IR spectrum ($CHCl_3$): 3 620. Mass spectrum, *m/z* (%): 237, 235 ($M^+ - CH_3$); 219, 217 ($M^+ - CH_3 - H_2O$); 171 (M^+ – Br); 162, 160 ($M^+ - (CH_3)_3SiOH$, 18); 81 ($M^+ - (CH_3)_3SiOH$ – Br, 100); 73 ($(CH_3)_3Si^+$, 62). HR MS, for $C_8H_{16}OBrSi$ ($M^+ - CH_3$) calculated: 235.01538; found: 235.01542.

1-Bromo-1,2-dimethyl-*c*-3-iodomethyl-*c*-2-(trimethylsilyl)cyclopropane (**16**)

A mixture of alcohols **15a** and **15b** (in 5.2 : 1 ratio, 245 mg, 0.98 mmol) was dissolved in pyridine (2.3 ml) and treated with tosyl chloride (206 mg, 1.08 mmol) at 0 °C. The mixture was set aside at 0 to 4 °C for 18 h and then was partitioned between ether (20 ml) and water (10 ml). The aqueous layer was extracted with ether (20 ml). The combined organic extract was evaporated. The residue was dissolved in acetone (7 ml), NaI (220 mg, 1.47 mmol) was added and the mixture was heated under reflux for 1.5 h. The solvent was evaporated and the residue was transferred with pentane onto a silica gel (8 g) column. Elution of the column with pentane gave iodides **16** (215 mg, 61%). ^{1}H NMR spectrum (200 MHz): 0.22 (s, 9 H, $(CH_3)_3Si$); 1.07 (s, 3 H, $(CH_3)CSi$); 1.08 (t, J = 7.9, 1 H, CH); 1.87 (s, 3 H, $(CH_3)CBr$); 3.44 (d, J = 7.9, 2 H, CH_2). ^{13}C NMR spectrum (50 MHz): 0.90 ($(CH_3)_3Si$); 9.35 (CH_2); 24.57 ((CH_3)**C**Si); 20.14, 27.36 ((**C**H_3)CSi) and ((**C**H_3)CBr); 41.57 (CH); 53.42

((CH_3)**C**Br). Mass spectrum, *m/z* (%): 281 (M^+ – Br); 235, 233 (M^+ – I); 162, 161 (M^+ – $(CH_3)_3SiI$); 81 (M^+ – $((CH_3)_3SiI$ – Br, 100); 73 ($(CH_3)_3Si^+$, 47). For $C_9H_{18}BrISi$ (361.1) calculated: 29.93% C, 5.02% H; found: 29.98% C, 5.11% H.

(23*R**,24*R**,28*R**)-Ethyl 24-Bromo-6β-methoxy-28-(trimethylsilyl)-3α,5:23,28-dicyclo-26,27-dinor-5α-stigmastan-21-oate (**19**)

To a solution of lithium diisopropylamide prepared from diisopropylamine (52 μl, 0.37 mmol) and 1.38 M butyllithium in hexanes (270 μl) in THF (350 μl), stirred at –78 °C, a solution of **18** (68 mg, 0.182 mmol) in THF (540 μl) was added. The mixture was stirred at –78 °C for 1 h and a solution of **16** (128 mg, 0.36 mmol) in THF and HMPA (500 μl and 370 μl, respectively) was added dropwise during 10 min. The mixture was stirred at –23 °C for 3 h and the reaction was quenched with water (2 ml). The mixture was extracted with ether (3 × 20 ml) and the combined extracts were washed with water and brine. The solvent was evaporated and the residue was chromatographed on silica gel (3 g) to give: **16** (hexane), **19** (35.2 mg, 32%, hexane/toluene 3 : 1), **19** contamined with **18** (7.6 mg) and **18** contaminated with unidentified side products (33.6 mg, toluene–acetone 4 : 1).

Compound **19**. ^{1}H NMR spectrum (200 MHz): 0.14 (s, 9 H, $(CH_3)_3Si$); 0.76 (s, 3 H, 3 × 18-H); 0.99 (s, 6 H, 3 × 19-H and 3 × 29-H); 1.26 (m, 3 H); 1.85 (s, 3 H, 3 × 25-H); 2.70–2.80 (m, 1 H, 6-H); 3.30 (s, 3 H, CH_3O); 4.10 (m, 2 H, $CH_3C\mathbf{H}_2O$). IR spectrum (film): 1 730. Mass spectrum, *m/z* (%): 593, 591 (M^+ – (CH_3), 1.4); 563, 561 (M^+ – Et, 1.4); 547 (1); 527 (47); 513 (4); 446 (77); 431 (6); 373 (6); 353 (4); 349 (5); 279 (4); 267 (7); 253 (78); 239 (8); 277 (9); 213 (12); 199 (100); 173 (9); 159 (10); 149 (8); 140 (15); 133 (6); 121 (8); 105 (7); 95 (8); 81 (9); 73 (30). HR MS, for $C_{32}H_{52}O_3BrSi$ (M^+ – CH_3) calculated: 591.28691; found: 591.28639.

(23*R**,24*R**,28*R**)-24-Bromo-6β-methoxy-28-(trimethylsilyl)-3α,5:23,28-dicyclo-26,27-dinor-5α-stigmastan-21-ol (**20**)

To a stirred solution of **19** (116 mg, 0.19 mmol) in CH_2Cl_2 (3.2 ml) 0.75 M diisobutylaluminium hydride in toluene (1 ml, 0.75 mmol) was added at –23 °C. Stirring at –23 °C was continued for 45 min and the reaction was quenched with ether (10 ml) and water (15 ml). The aqueous layer was extracted with ether (3 × 25 ml) and the combined organic extracts were washed with brine. The solvent was evaporated and the residue was chromatographed on silica gel (10 g, 0.6% acetone in hexane) to give **20** (96.5 mg, 90%). ^{1}H NMR spectrum (200 MHz): 0.15 (s, 9 H, CH_3Si); 0.44 (dd, J = 8.0, 4.5, 1 H, 4α-H); 0.66 (t, J = 4.5, 1 H, 4β-H); 0.76 (s, 3 H, 3 × 18-H); 1.01 (s, 3 H, 3 × 19-H); 1.05 (s, 3 H, 3 × 29-H); 1.88 (s, 3 H, 3 × 25-H); 2.72–2.79 (m, 1 H, 6-H); 3.31 (s, 3 H, CH_3O); 3.65–3.90 (m, 2 H, CH_2OH). IR spectrum (film): 3 480. Mass spectrum, *m/z* (%): 566, 564 (M^+, 0.3); 551, 549 (M^+ – CH_3, 0.2); 534, 532 (M^+ – CH_3OH, 0.1); 519, 517 (M^+ – CH_3 – CH_3OH, 0.2); 511, 509 (M^+ – C_4H_7, 0.4); 484 (12); 469 (53); 453 (3); 437 (2); 411 (42); 397 (9); 357 (2); 308 (3); 281 (3); 253 (40); 239 (5); 227 (7); 213 (9); 197 (17); 183 (12); 170 (55); 155 (100); 141 (15); 125 (22); 107 (19); 95 (19); 84.82 (18); 73 (58); 67 (16); 55 (12). HR MS, for $C_{27}H_{46}O_2BrSi$ (M^+ – C_4H_7) calculated: 509.24509; found 509.24474.

(23*R**,24*R**,28*R**)-24-Bromo-6β-methoxy-21-tosyloxy-28-(trimethylsilyl)-3α,5:23,28-dicyclo-26,27-dinor-5α-stigmastane (**21**)

A mixture of **21** (41 mg, 0.073 mmol), pyridine (50 μl, 0.63 mmol), tosyl chloride (43 mg, 0.146 mmol) and CH_2Cl_2 (0.5 ml) was stirred at room temperature for 16 h and then partitioned between ether (20 ml) and water (5 ml). The aqueous layer was extracted with ether (20 ml) and the combined organic extract was washed with water and brine. The solvent was evaporated and the residue was filtered

through silica gel (3 g, 0.7% of acetone in hexane) to give **21** (49.6 mg, 94%). ^{1}H NMR spectrum (200 MHz): 0.12 (s, 9 H, $(CH_3)_3Si$); 0.41 (dd, J = 7.9, 5.2, 1 H, 4α-H); 0.66 (s, 3 H, 3 × 18-H); 0.87 (s, 3 H, 3 × 29-H); 0.98 (s, 3 H, 3 × 19-H); 1.70 (s, 3 H, 3 × 25-H); 2.41 (s, 3 H, tosyl); 2.70–2.78 (m, 1 H, 6-H); 4.14 (q, J = 9.6, 2 H, CH_2OTs); 7.31 (d, J = 8.2, 2 H, tosyl); 7.80 (d, J = 8.2, 2 H, tosyl). Mass spectrum, *m/z* (%): 718 (M^+, 0.1); 705, 703 ($M^+ - CH_3$, 0.1); 689, 687 (0.1); 673, 671 (0.4); 663, 665 (0.1); 638 (0.4); 623 (0.2); 606 (0.2); 593, 591 (0.2); 583 (0.2); 565 (2); 557 (0.3); 551 (0.4); 534 (0.4); 511 (0.7); 499, 501 (0.6); 466 (5); 427 (12.5); 411 (3); 395 (3); 379 (3.5); 361, 363 (3.5); 281 (7); 267 (7); 259 (7); 253 (100); 245 (5); 239 (4); 229 (17); 213 (12); 199 (9); 185 (8); 171 (8); 159 (17); 147, 145 (17); 133 (16); 121 (19); 107 (24); 95 (14); 91 (15); 81 (15); 81 (15); 73 (51); 66 (22).

(23*R**,24*R**,28*R**)-24-Bromo-6β-methoxy-28-(trimethylsilyl)-3α,5:23,28-dicyclo-26,27-dinor-5α-stigmastane (**22**)

To a solution of **21** (18.7 mg, 0.026 mmol) in THF (0.4 ml), 1 M $LiEt_3BH$ (Super Hydride®) in THF (0.1 ml, 0.1 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 4.5 h and the reaction was quenched with ether (10 ml) and water (10 ml). The aqueous layer was extracted with ether (2 × 20 ml), and the combined organic extracts were washed with water and brine, the solvent was evaporated and the residue was filtered through silica gel (1.5 g, hexane/toluene 6 : 1) to give **22** (11 mg, 77%). ^{1}H NMR spectrum (200 MHz): 0.19 (s, 9 H, $(CH_3)_3Si$); 0.39–0.52 (m, 2 H, 4α-H and 23-H); 0.67 (t, J = 4.6, 1 H, 4β-H); 0.78 (s, 3 H, 3 × 18-H); 1.02 (d, J = 6.4, 3 H, 3 × 21-H); 1.05 (s, 3 H, 3 × 19-H); 1.08 (s, 3 H, 3 × 29-H); 1.91 (s, 3 H, 3 × 25-H); 2.76–2.84 (m, 1 H, 6-H); 3.35 (s, 3 H, CH_3O). IR spectrum (film): 2 970, 2 890, 1 450, 1 380, 1 245, 1 090, 830. Mass spectrum, *m/z* (%): 548 (M^+, 0.1); 535, 533 ($M^+ - CH_3$, 0.2); 518, 516 ($M^+ - CH_3OH$, 0.1); 503, 501 ($M^+ - CH_3OH - CH_3$, 0.5); 495, 493 ($M^+ - C_4H_7$, 0.3); 468 (2); 453 (0.6); 437, 436 (1); 421 (0.4); 413 (0.9); 396, 395 (1); 381 (3); 364, 363 (2); 349 (2); 341 (4); 335 (0.5); 328 (0.9); 314 (1.6); 311 (0.6); 307 (0.6); 299 (4); 283 (10); 267 (4); 259 (7); 253 (100); 241 (3); 227 (7); 213 (8); 201, 199 (6); 187 (6); 173 (6); 159 (10); 154 (8); 147, 145 (11); 139 (8); 133 (9); 121 (13); 109 (16); 95 (10); 81 (13); 73 (48); 67 (28). HR MS, for $C_{31}H_{53}OBrSi$ ($M^+ - CH_3$) calculated: 533.2814; found: 533.2815.

(23*R**,24*R**,28*R**)-24-Bromo-28-(trimethylsilyl)-23,28-cyclo-26,27-dinorstigmast-5-en-3β-ol (**23**)

A solution of **22** (11 mg, 0.02 mmol) in a mixture dioxane–water 4 : 1 (3 ml) containing a catalytic amount of 4-toluenesulfonic acid, was heated under reflux for 3 h. After cooling, the mixture was diluted with ether (25 ml). The aqueous layer was extracted with ether (25 ml) and the combined organic extract was washed with water and brine. The solvent was evaporated and the residue was chromatographed on silica gel (1 g, hexane/ether 6 : 1) to give **23** (10 mg, 93%). ^{1}H NMR spectrum (200 MHz): 0.14 (s, 9 H, $(CH_3)_3Si$); 0.42 (dd, J = 9.2, 3.8, 1 H, 23-H); 0.69 (s, 3 H, 3 × 18-H); 0.97 (d, J = 5.3, 3 H, 3 × 21-H); 0.99 (s, 3 H, 3 × 19-H); 1.04 (s, 3 H, 3 × 29-H); 1.87 (s, 3 H, 3 × 25-H); 3.40–3.60 (m, 1 H, 3-H); 5.33 (d, J = 5.2, 1 H, 6-H). IR spectrum ($CHCl_3$): 3 620. Mass spectrum, *m/z* (%): 534 (M^+, 0.04); 521, 519 ($M^+ - CH_3$, 0.1); 503, 501 ($M^+ - CH_3OH$, 0.4); 454 (M^+ – HBr, 5); 439 (0.8); 421 (0.4); 381 (1.6); 367 (3); 353 (1); 349 (2); 343 (0.4); 335 (0.3); 325 (0.7); 314 (4); 300 (10); 283 (10); 271 (80); 253 (16); 241 (6); 227 (4); 213 (10); 199 (5); 187 (7); 173 (8); 159 (21); 154 (23); 145 (17); 139 (12); 133 (22); 121 (17); 109 (25); 95 (17); 81 (24); 73 (100); 67 (48); 55 (11); 41 (6). HR MS, for $C_{29}H_{48}OBrSi$ ($M^+ - CH_3$) calculated: 519.26578; found 519.26586.

23,28-Cyclo-26,27-dinorstigmast-5,23(28)-dien-3β-ol (**24**)

To a solution of **23** (3.7 mg, 0.007 mmol) in THF (1 ml) tetrabutylammonium fluoride (26 mg, 0.08 mmol) was added and the mixture was stirred at room temperature for 20 h and then heated under reflux for 1 h. After cooling, the mixture was partitioned between ether (20 ml) and water (5 ml). The aqueous layer was extracted with ether (2 × 20 ml) and the combined organic extracts were washed with water and brine. The solvent was evaporated and the residue was chromatographed on silica gel (1 g, hexane/ether 6 : 1) to give **24** (3.3 mg, 100%). ^{1}H NMR (200 MHz): 0.67 (s, 3 H, 3 × 18-H); 0.98 (d, J = 4.9, 3 H, 3 × 21-H); 0.99 (s, 3 H, 3 × 19-H); 1.95 (s, 6 H, 2 × =C–CH_3); 3.40–3.60 (m, 1 H, 3-H); 5.33 (d, J = 5.3, 1 H, 6-H). Mass spectrum, *m/z* (%): 382 (3, M^+); 367 ($M^+ - CH_3$, 3); 364 ($M^+ - H_2O$, 0.7); 353 (0.9); 349 ($M^+ - CH_3 - H_2O$, 2); 339 (0.3); 336 (0.3); 325 (0.5); 312 (2); 300 (8); 297 (2); 283 (17); 271 (100); 267 (10); 253 (16); 241 (7); 227 (6); 215, 213 (11); 199 (6); 187 (8); 173 (11); 159 (26); 145 (20); 132 (26); 121 (16); 109 (27); 95 (19); 81 (3); 67 (64); 55 (14); 41 (10). HR MS, for $C_{27}H_{42}O$ (M^+) calculated: 382.32356; found: 382.32356.

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