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Formal Semisynthesis of Demethylgorgosterol Utilizing a Stereoselective Intermolecular Cyclopropanation Reaction

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In this study, we report a convenient and high yielding formal semisynthesis of demethylgorgosterol, a marine steroid with an intriguing sidechain containing a cyclopropane unit. This was achieved through the synthesis of an advanced ketone intermediate. The synthetic route features a total of ten steps, starting from commercially available stigmasterol, with an overall yield of 27%. The key step was a stereoselective intermolecular cyclopropanation reaction. This reaction proceeded in 82% yield, the resulting cyclopropane carboxylic ester shows a trans/cis ratio of 89:11, with a diastereomeric ratio for the trans-diastereomers of >99:1. A reduction/oxidation sequence afforded the corresponding aldehyde, which was used in a Grignard reaction. A final oxidation step then yielded the desired ketone. This novel route presents a platform to further investigate the medicinal applications of gorgosterol-type steroids and to fully understand their role in coral symbiosis.

Introduction

Corals and coral reefs, despite only covering about 1% of the ocean floor, are the most diverse aquatic ecosystems.[1] They are associated with an estimated 25% of all marine species and rivaled in biodiversity only by rain forests.[2] Their ecological, as well as economic impact, is of global scale,[3] and they are a source of countless natural products.[4] Yet, they are endangered by climate change in multiple ways,[5] as well as by environmental pollution,[5a] amongst others.[6]

One of these many natural products, gorgosterol (**1 a**), was first isolated by Bergmann et al. in 1943 from the soft coral *Plexaura flexuosa*.[7] Gorgosterol is also found in various other animals and their symbionts.[8] It had chemists puzzled due to its unusual properties,[7,9] until its structure was elucidated unambiguously,[10] and its first derivative demethylgorgosterol (**1 b**) was discovered.[11] Nowadays, a plethora of derivatives are known, e.g. **2**–**5** (Figure 1), showing a multitude of biological activities.[12] These include cytotoxicity against various cancer cell lines,[12c,13] reversal of multidrug resistance in cancer cells,[14] antitubercular activity[15], and antifungal activity.[16] A common feature of these steroids is their distinctive sidechain, containing

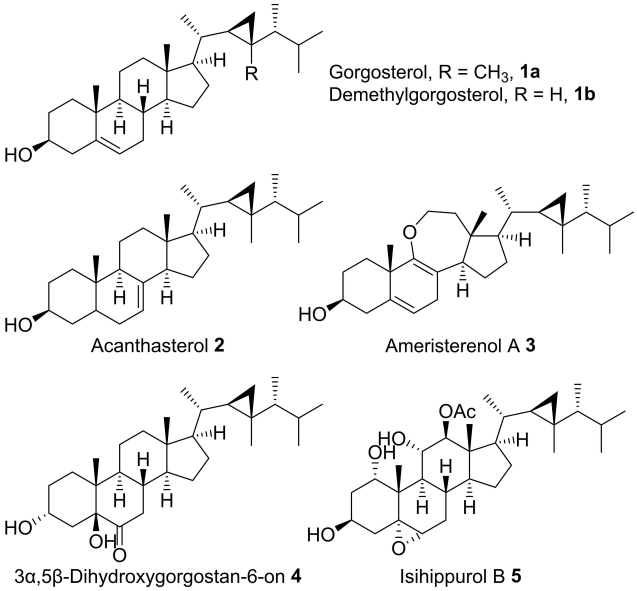

Figure 1. Structures of Gorgosterol (**1 a**), Demethylgorgosterol (**1 b**), and selected derivatives **2**–**5**.

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a C22/C23 cyclopropane ring and additional methyl groups at C23 and C24.

The exact mechanism of the biosynthesis of the gorgosterol family has not been fully elucidated yet. Several plausible routes have been proposed and discussed, with no final conclusion.[19] However, biosynthesis is believed to be part of the complex symbiotic relationship between corals and algae. Recently, it was shown that corals depend on sterols provided by their symbionts and that their sterol composition varies substantially to symbiont species and even cell line.[20] The biological function of gorgosterol is unknown, but it exhibits activity as a growth inhibitor of human colon tumor cell lines.[21] Additionally, it was identified as a new chemotype of farnesoid-X-receptor (FXR) antagonist,[12d] making it a potential target for the treatment of cholestasis.[22]

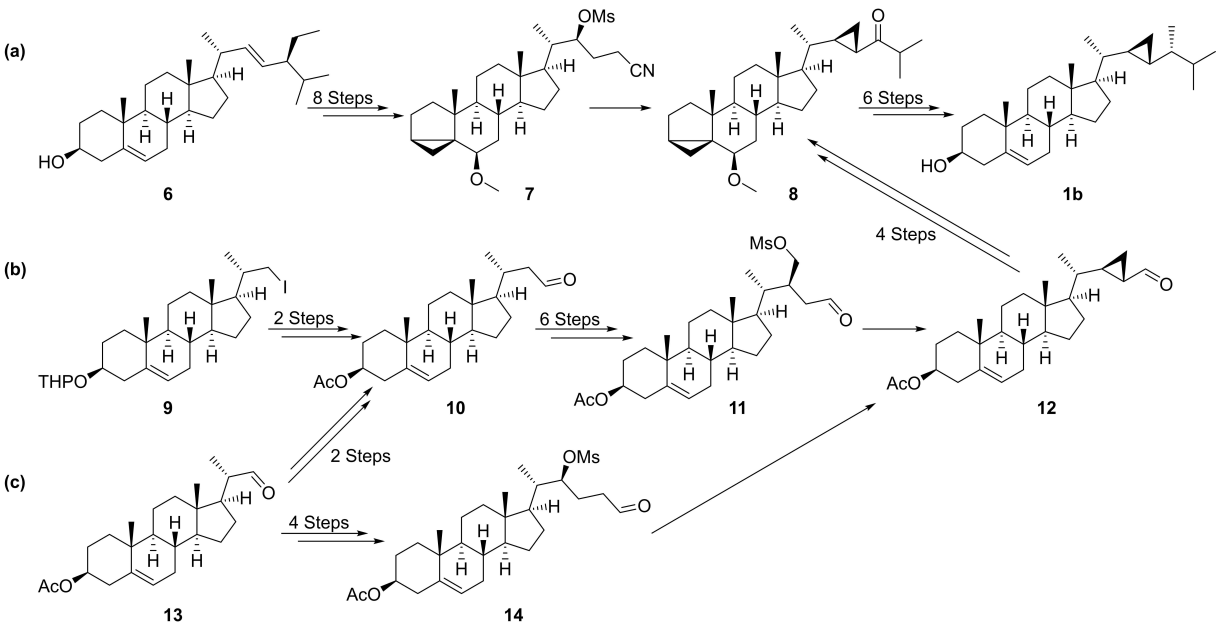
In the past, several semisyntheses of demethylgorgosterol (**1b**) and its stereoisomers, as well as one of gorgosterol (**1a**), were achieved by the groups of Djerassi and Ikekawa. The first attempts to methylenate a suitable precursor using either a Simmons-Smith reaction or a Corey-Chaykovsky reaction did not yield the desired configuration.[23] All of the following syntheses used an intramolecular 3-exo-tet ring-closure strategy to form the cyclopropane moiety in the desired configuration (Scheme 1). The shortest route, developed by Djerassi et al., consists of a total of 15 steps. The key step was a domino cyclization/alkylation-reaction of **7** to **8** (Scheme 1a). However, the overall yield of the above-mentioned semisynthesis was very low.[17] Ikekawa et al. developed three different routes, all leading to ketone **8** eventually and converging into Djerassi's route. Starting from steroid **9**, which was transformed into aldehyde **11** and then cyclized yielding **12**. The cyclized aldehyde **12** was then transformed into the known ketone **8** (Scheme 1b).[18a] Alternatively, starting material **13** could either be transformed into **10** to join route (b) or into **14**, which was then cyclized to yield the known aldehyde **12** (Scheme 1c). These routes, despite involving more steps, produced the intermediary ketone **8** in a higher yield.[18] Ikekawa et al. also presented a stereoselective semisynthesis of gorgosterol (**1b**) using a similar 3-exo-tet cyclization.[24]

Results and Discussion

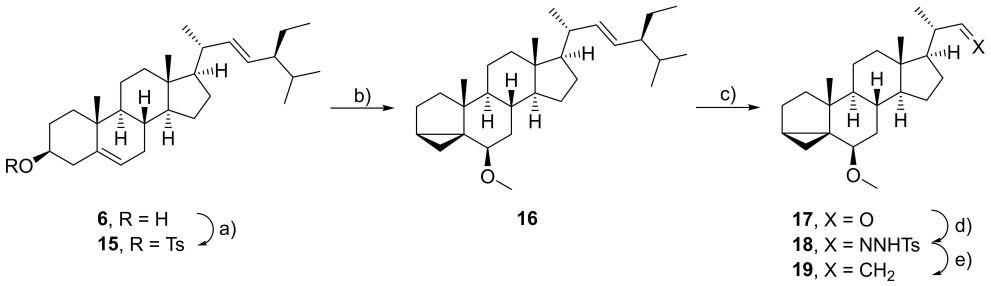
The starting point for our semisynthesis was the commercially available stigmasterol (**6**). The latter phytosterol was transformed into the alkene **19**, which was needed for the enantio- and diastereoselective intermolecular cyclopropanation, according to known procedures in five steps (Scheme 2). The first two steps were necessary to protect the steroidal A- and B-rings in the form of the *i*-steroid methyl ether **16**.[25] This was followed by the cleavage of the side chain by ozonolysis,[26] and subsequent transformation of the resulting aldehyde **17**.[23] A Julia-like, two-step alkene synthesis was employed, rather than one step procedures like the Wittig reaction, since this resulted in higher yields.[27] Alkene **19** was obtained from stigmasterol (**6**) in up to 52% yield on a multi-gram scale.

Since rhodium-based catalysts often show poor selectivity and yields for the cyclopropanation of aliphatic alkenes,[28] and asymmetric Corey-Chaykovsky- and Simmons-Smith-type reactions were chemically not applicable to alkene **19**, we opted for Iwasa's ruthenium-based procedure.[29] From their model for the chiral induction in this Ru-pheox catalyzed cyclopropanation we deduced that the (R)-configured catalyst would produce the desired stereochemistry. The ligand **21** and catalyst **22** were synthesized according to literature from (R)-2-phenylglycinol (**20**) in yields of 73% and 88% respectively (Scheme 3).[30]

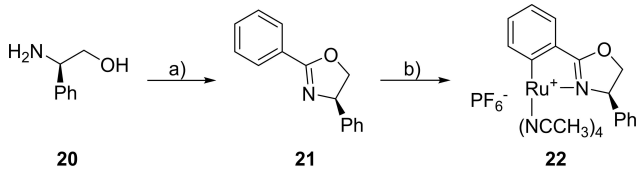
Scheme 4 shows the cyclopropanation carried out under optimized reaction conditions. A yield of 82% was achieved,



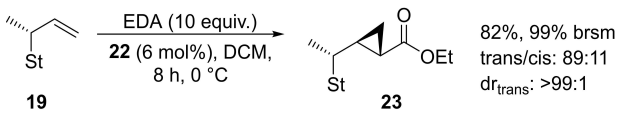
Scheme 1. Previous semisyntheses of demethylgorgosterol (**1b**). Routes developed by (a) Djerassi et al.[17] and (b), (c) Ikekawa et al.[18]



Scheme 2. Synthesis of the alkene **19** starting from commercially available stigmasterol (**6**). Reaction conditions: a) TsCl, pyridine, rt, 16 h, quant. b) MeOH, pyridine, reflux, 4 h, 78%. c) i) O_3, DCM, MeOH, −78 °C, 45 min; ii) Zn, HOAc, rt, 1 h, 80%. d) $TsNHNH_2$, MS 3 Å, ethanol, rt, 30 min, 50 °C, 30 min, 95%. e) Dimethyl sulfone, *n*BuLi, THF, 0 °C to rt, 16 h, 88%.



Scheme 3. Synthesis of (R)-Ru-pheox **22** from (R)-2-phenylglycinol (**20**). Reaction conditions: a) i) benzoyl chloride, Et_3N, DCM, 0 °C to rt, 16 h. ii) $SOCl_2$, $CHCl_3$, 0 °C to rt, 24 h. iii) 2.5 M NaOH, 1,4-dioxan, 0 °C to rt, 4 h, 73%. b) benzeneruthenium(II) chloride dimer, 1 M NaOH, KPF_6, MeCN, 80 °C, 48 h, 88%.



Scheme 4. Cyclopropanation of **19** using optimized reaction conditions.

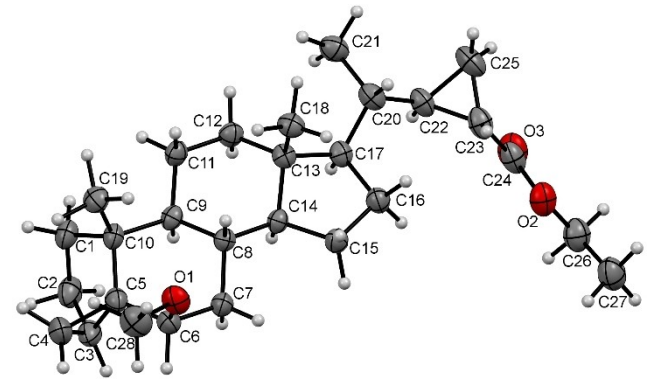
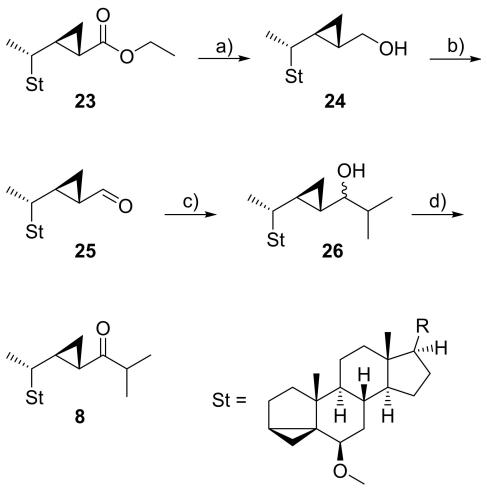


Figure 2. ORTEP-style representation of ester **23**. Thermal ellipsoids are shown at a 50% probability level. The absolute configuration was determined crystallographically.



Scheme 5. Transformation of ester **23** into the known ketone **8** in four steps. Reaction conditions: a) $LiAlH_4$, THF, reflux, 4 h, quant. b) IBX, DMSO, rt, 16 h, 92% c) *i*PrMgBr, THF, −18 °C, 2 h, 83%. d) PCC, DCM, 2 h, 84%.

factoring in recovered starting material it rose to a nearly quantitative yield of 99%. Key optimization steps from Iwasa's procedure were a prolonged addition time and an increased alkene concentration. Detailed information on the optimization of the cyclopropanation procedure can be found in chapter 3 of the supporting information.

Single-crystal x-ray analysis revealed that the main diastereomer had the desired (1*S*,2*R*) configuration at the newly constructed cyclopropane unit (Figure 2). The stereoselectivity of the reaction was further investigated using GC/MS. The trans/cis ratio was found to be 89:11 with a diastereomeric ratio for the two trans-diastereomers of >99:1. Only one of the two possible cis-diastereomers was detected, for which we deduced a (1*S*,2*S*) configuration in agreement with the chiral induction model for the catalyst system. Separation of the minor diastereomers is possible but quite tedious. Therefore, we decided to do so at a later stage.

The ester **23** was then transformed in four steps into the known ketone **8** (Scheme 5).[17] Ester **23** was reduced with $LiAlH_4$, giving the alcohol **24** in a quantitative yield. The latter one was then oxidized using 2-iodoxybenzoic acid (IBX) to afford the aldehyde **25** in a yield of 92%. The direct reduction of the ester **23** to the aldehyde **25** was also tested, but product mixtures along with unreacted ester were obtained in every case. Since very good yields were achieved with the two-step procedure, this was not pursued further. As for the ester, it is possible to separate the minor diastereomers on both stages, but more easily for the alcohol. However, it is still tedious and

they were only separated after the next step. The aldehyde **25** was very similar to the known aldehyde **12** used by Ikekawa et al. in their semisynthesis, the only difference being the protecting group for the A/B-ring.[18b] Therefore, the same procedures were used to synthesize the ketone **8** from the aldehyde **25**.

The aldehyde **25** was first subjected to a Grignard reaction with *i*PrMgBr. Due to the newly formed stereogenic center at C24, this resulted in three pairs of epimers. Nevertheless, separation of this mixture was easily achieved, yielding the alcohol **26** in 83%. The diastereomeric ratio determined by ^{1}H-NMR was found to be 4.9:1, with the main epimer showing (24*S*) configuration, as evidenced by single-crystal x-ray analysis. The alcohol **26** was then oxidized with pyridinium chlorochromate (PCC) providing the known ketone **8** in 84% yield. The melting point of 104–106 °C (Lit. 106–106.5 °C) and optical rotation value of $[\alpha]^{20}_{D} = +115.7°$ (Lit. $+116.7°$) match those reported by Djerassi et al.[17] Additionally, the desired configuration was again proven by single-crystal x-ray analysis (Figure 3) showing that no epimerization of the C23 stereogenic center occurs under the chosen reaction conditions. We also explored the possibility of the direct conversion of ester **23** to ketone **8** by the addition of one equivalent of Grignard reagent, but no conversion was observed. The overall yield for the conversion of ester **23** to ketone **8** was 64% over four steps.

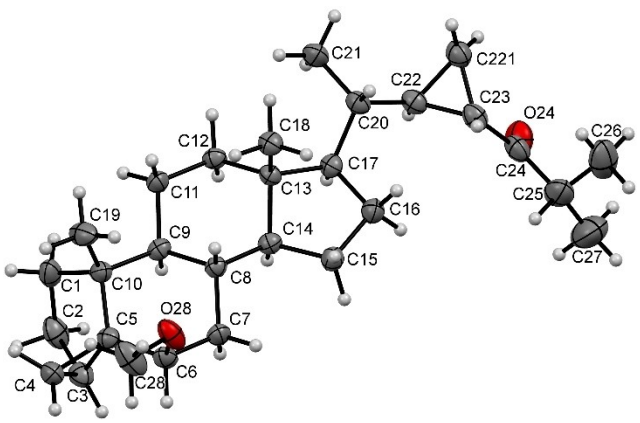


Figure 3. ORTEP-style representation of one of the crystallographic independent molecules of the ketone **8**. Thermal ellipsoids are shown at a 50% probability level. The absolute configuration was determined crystallographically.

Table 1. Comparison of synthetic routes for the synthesis of the intermediary ketone **8**.

Entry	Route	No. of steps	Starting material	Yield of **8** [%]
1	This work	10	**6**	27.4/33.1[a]
2	Djerassi et al.[17]	9	**6**	3.7/5.1[a]
3	Ikekawa et al.[18]	14+[b]	**13**	11.0
4	Ikekawa et al.[18]	14+[b]	**9**	21.9
5	Ikekawa et al.[18a]	9+[b]	**13**	15.2

[a] Based on the recovered starting material. [b] Starting material not commercially available.

In total, our synthesis of the intermediary ketone **8** consists of ten steps in a linear sequence starting from the commercially available stigmasterol **6** (Table 1, entry 1). The key step, the cyclopropanation of the alkene **19**, proceeds with good stereocontrol and exceptional yield. For the complete sequence, a yield of 27.4% and 33.1% based on recovered starting material was achieved. In contrast, Djerassi's route achieved the synthesis of ketone **8** in just nine steps, again starting from **6** (Entry 2). However, the achieved yield was an order of magnitude lower at only 3.7% and 5.1% yield, partly since the stereodefining step proceeded with very low selectivity.[17] Ikekawa et al. presented three different syntheses, with two differing only in the first two steps. These two routes consist of fourteen steps each. However, the route starting from **9** produces about twice as much of ketone **8** as the route starting from **13**, with a yield of 21.9% (Entries 3 and 4). The third synthetic route again starts at **13** but reaches **8** in just ten steps with a yield of 15.1% (Entry 5). The starting materials **13** and **9** used by Ikekawa et al. are not commercially available, and potentially require a multi-step synthesis themselves, which was not factored into the yields given in Table 1.[18]

Conclusion

In conclusion, a short formal semisynthesis of demethylgorgosterol was achieved through the synthesis of the advanced ketone intermediate **8**, following a novel route and using only easily available starting materials and reagents. The key step of this novel route was the stereoselective cyclopropanation of steroidal alkene **19** in a high yield and stereoselectivity. Compared to previous syntheses, our work represents a new optimum in the number of steps and yield, with 10 steps and 33.1% yield for the synthesis of ketone **8**.

Experimental Section

The starting materials, solvents, and reagents were purchased from commercial sources and used without further purification. All reactions containing air- and moisture-sensitive compounds were performed under an argon atmosphere, using oven or flame dried glassware applying standard Schlenk-techniques. All reactions were monitored by thin-layer chromatography (TLC) using silica gel coated aluminum plates (*Merck*, silica gel 60, F_{254}). The detection was performed with UV light (254 nm) or by staining with Seebach solution.[31] NMR spectra were recorded on a *Bruker* Avance 400 or a *Bruker* Avance DRX 500 as solutions at room temperature. Chemical shifts are expressed in parts per million (δ, ppm), downfield from tetramethylsilane (TMS). References for ^{1}H NMR and ^{13}C NMR were the residual solvent peaks of chloroform-d_1 (^{1}H: $\delta = 7.26$ ppm, ^{13}C: $\delta = 77.16$ ppm), dichloromethane-d_2 (^{1}H: $\delta = 5.32$ ppm, ^{13}C: $\delta = 53.84$ ppm), or acetonitrile-d_3 (^{1}H: $\delta = 1.94$ ppm, ^{13}C: $\delta = 1.32$ ppm). All coupling constants are absolute values and expressed in Hertz (*J*, Hz). The spectra were analyzed according to first-order and the descriptions of signals include: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet. The ^{13}C signal structure was analyzed by multiplicity-edited HSQC (*heteronuclear single quantum correlation*) and is described as follows: + = primary or tertiary C-atom (positive signal), − = secondary C-atom (negative

signal), and C_q. = quaternary C-atom (no signal). Assignments were made based upon the IUPAC numbering system for steroids. EI-MS and FAB (3-NBA) were performed by using a *Finnigan* MAT 90 (70 eV). The molecular fragments are reported as mass-to-charge-ratio (*m/z*). GC-MS measurements were performed on an *Agilent Technologies* 6890 N (electron impact ionization), equipped with an *Agilent* HP-5MS column and a 5975B VL MSD detector.

Ethyl (1*S*,2*R*)-2-(6β-Methoxy-3α,5-cyclopregnan-20*R*-yl)cyclopropanecarboxylate (23): Alkene **19** (631 mg, 1.84 mmol, 1.00 equiv.) and Ru-catalyst **22** (70.0 mg, 111 μmol, 6 mol%) were weight in an oven-dried vial, evacuated and backfilled with argon three times. Dry DCM (2.4 mL) was added and the solution was cooled to 0 °C. Ethyl diazoacetate (2.60 g, 2.40 mL, 19.4 mmol, 10.5 equiv.) was added over a period of 8 h by syringe pump, while the reaction was kept at 0 °C. After complete addition, the reaction was stirred over night at room temperature. DCM was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography (pentane/Et_2O 10:1). Volatile dimerization products were removed under high vacuum to yield a yellowish solid which was recrystallized from acetone/water to yield the pure ester **23** as a colorless crystalline solid (649 mg, 1.51 mmol, 82%, 99% brsm). Compound **23** was obtained with a 89.0:10.7:0.3 diastereomeric ratio as determined by GC-MS using a HP-5MS column; 120 °C, 3 min, 20 °C/min, 270 °C, 30 min; $\tau_{(1S,2R)}$ = 20.8 min, $\tau_{(1S,2S)}$ = 21.1 min, $\tau_{(1R,2S)}$ = 21.6 min. Recrystallization from acetone/H_2O afforded crystals suitable for X-ray crystallographic analysis (CCDC 2040692). R_f = 0.28 (pentane/Et_2O 10:1). $[\alpha]^{20}_D$ = +68.4° (c = 0.56, $CHCl_3$). Mp: 99–100 °C. ^{1}H NMR (500 MHz, CD_2Cl_2): δ [ppm] = 4.13–4.03 (m, 2H, OC*H*$_2$CH$_3$), 3.28 (s, 3H, OCH_3), 2.74 (t, *J* = 2.9 Hz, 1H, 6-CH), 1.96 (dt, *J* = 12.5, 3.4 Hz, 1H, CH*H*), 1.90–1.60 (m, 5H), 1.54–1.36 (m, 6H), 1.36–1.26 (m, 1H, CH), 1.22 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.20–0.96 (m, 12H, contains 1.01 (d, *J* = 6.7 Hz, 3H, 21-CH_3), 0.99 (s, 3H, 19-CH_3)), 0.92–0.80 (m, 4H), 0.67 (s, 3H, 18-CH_3), 0.63–0.58 (m, 2H), 0.40 (dd, *J* = 8.0, 5.0 Hz, 1H, 4-CH*H*). ^{13}C NMR (126 MHz, CD_2Cl_2): δ [ppm] = 174.4 (C_q, COOEt), 82.7 (+, CH-6), 60.5 (−, OCH_2CH_3), 58.2 (+, CH), 56.7 (+, OCH_3), 56.5 (+, CH), 48.4 (+, CH), 43.7 (C_q), 43.2 (C_q), 40.4 (−, CH_2), 39.8 (+, CH_2), 35.7 (C_q, C-5), 35.4 (+, CH_2), 33.7 (+, CH_2), 31.0 (+, CH), 30.6 (+, CH), 28.1 (−, CH_2), 25.3 (−, CH_2), 24.6 (−, CH_2), 23.1 (−, CH_2), 22.6 (+, CH), 21.9 (+, CH), 19.8 (+, CH_3-21), 19.5 (+, CH_3-19), 14.6 (+, OCH_2CH_3), 13.3 (−, CH_2-4), 12.9 (−, CH_2), 12.3 (+, CH_3-18). MS (FAB, 3-NBA): m/z (%) = 429 (13) $[M+H]^+$, 428 (21) $[M]^+$, 427 (31) $[M–H]^+$, 413 (11) $[M–CH_3]^+$, 397 (100) $[M–OCH_3]^+$, 396 (18) $[M–CH_3OH]^+$, 255 (12) $[C_{19}H_{27}]^+$, 253 (17) $[C_{19}H_{25}]^+$, 213 (10) $[C_{16}H_{21}]^+$. HRMS (FAB, 3-NBA, m/z): calcd. for $C_{28}H_{44}O_3$, $[M]^+$: 428.3290; found: 428.3289. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2942 (m), 2932 (m), 2870 (m), 1717 (vs), 1458 (w), 1333 (s), 1204 (m), 1170 (vs), 1098 (vs), 1038 (m), 1014 (m), 990 (w), 867 (m), 744 (w), 615 (w), 569 (vw). EA ($C_{28}H_{44}O_3$, 428.6): calcd.: C 78.46, H 10.35; found: C 78.46, H 10.06.

(1*S*,2*R*)-2-(6β-Methoxy-3α,5-cyclopregnan-20*R*-yl)cyclopropanemethanol (24): A flame-dried round bottom flask was charged with ester **23** (1.00 g, 2.33 mmol, 1.00 equiv.) and $LiAlH_4$ (354 mg, 9.33 mmol, 4.00 equiv.). 28 mL of abs. THF were added and the mixture was refluxed for 4 h under argon atmosphere. After cooling to room temperature, excess $LiAlH_4$ was quenched by slow addition of KOH (50%). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3×25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (pentane/EtOAc 5:1 to 3:1) to yield the alcohol **24** as a colorless solid (902 mg, 2.33 mmol, quant.). Recrystallization from acetone/H_2O afforded crystals suitable for X-ray crystallographic analysis (CCDC 2041206). R_f = 0.23 (pentane/EtOAc 4:1). $[\alpha]^{20}_D$ = +44.0° (c = 0.50, $CHCl_3$). Mp: 150–155 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.64 (dd, *J* = 11.1, 6.0 Hz, 1H, CH*H*OH), 3.32 (s, 3H, OCH_3), 3.25 (dd, *J* = 11.2, 7.8 Hz, 1H, C*H*HOH), 2.77 (t, *J* = 2.9 Hz, 1H, 6-CH), 2.00–1.86 (m, 3H), 1.80–1.58 (m, 4H), 1.55–1.46 (m, 3H), 1.44–1.36 (m, 2H), 1.26 (q, *J* = 9.7 Hz, 1H, CH), 1.19–0.97 (m, 11H, contains 1.01 (s, 3H, 19-CH_3), 0.99 (d, *J* = 6.7 Hz, 3H, 21-CH_3)), 0.92–0.71 (m, 4H), 0.69–0.62 (m, 4H, contains 0.66 (s, 3H, 18-CH_3)), 0.46–0.36 (m, 2H), 0.29 (dt, *J* = 8.9, 4.7 Hz, 1H, 22^1-CH*H*), 0.23 (dt, *J* = 8.2, 5.0 Hz, 1H, 22^1-C*H*H). ^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 82.5 (+, CH-6), 67.3 (−, CH_2OH), 58.3 (+, CH), 56.7 (+, OCH_3), 56.3 (+, CH), 48.2 (+, CH), 43.5 (C_q), 43.1 (C_q), 40.3 (−, CH_2), 40.1 (+, CH), 35.4 (C_q, C-5), 35.2 (−, CH_2), 33.5 (−, CH_2), 30.7 (+, CH), 28.2 (−, CH_2), 25.14 (−, CH_2), 25.10 (+, CH), 24.4 (−, CH_2), 23.2 (+, CH), 22.9 (−, CH_2), 21.6 (+, CH), 20.1 (+, CH_3-21), 19.4 (+, CH_3-19), 13.2 (−, CH_2-4), 12.4 (+, CH_3-18), 7.9 (−, CH_2-22^1). MS (FAB, 3-NBA): m/z (%) = 386 (28) $[M]^+$, 385 (37) $[M–H]^+$, 371 (16) $[M–CH_3]^+$, 355 (100) $[M–OCH_3]^+$, 338 (24) $[M–OCH_3–OH]^+$, 337 (86) $[M–OCH_3–H_2O]^+$, 255 (24) $[C_{19}H_{27}]^+$, 253 (28) $[C_{19}H_{25}]^+$, 213 (22) $[C_{16}H_{21}]^+$. HRMS (FAB, 3-NBA, m/z): calcd. for $C_{26}H_{42}O_2$, $[M]^+$: 386.3185; found: 386.3186. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3425 (w), 3058 (vw), 2931 (vs), 2863 (vs), 1453 (m), 1383 (m), 1329 (w), 1268 (w), 1201 (w), 1054 (vs), 1030 (vs), 970 (m), 857 (m), 612 (m). EA ($C_{26}H_{42}O_2$, 386.6): calcd.: C 80.77, H 10.95; found: C 80.80, H 11.03.

(1*S*,2*R*)-2-(6β-Methoxy-3α,5-cyclopregnan-20*R*-yl)cyclopropanecarboxaldehyde (25): Alcohol **24** (459 mg, 1.19 mmol, 1.00 equiv.) and 2-iodoxybenzoic acid (IBX) (1.66 g, 5.94 mmol, 5.00 equiv.) were dissolved in 10 mL of DMSO and stirred overnight at room temperature. 50 mL of water was added to the reaction mixture and the resulting precipitate was filtered and washed thoroughly with diethyl ether. The aqueous phase was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (pentane/EtOAc 10:1) to yield the desired aldehyde **25** as a colorless glass (421 mg, 1.09 mmol, 92% yield). R_f = 0.56 (pentane/EtOAc 5:1). $[\alpha]^{20}_D$ = +50.7° (c = 0.53, $CHCl_3$). ^{1}H NMR (500 MHz, CD_2Cl_2): δ [ppm] = 8.89 (d, *J* = 5.8 Hz, 1H, 24-CHO), 3.27 (s, 3H, OCH_3), 2.73 (t, *J* = 2.9 Hz, 1H, 6-CH), 1.96 (dt, *J* = 12.5, 3.4 Hz, 1H, CH*H*), 1.90–1.59 (m, 6H), 1.54–1.22 (m, 7H), 1.22–1.03 (m, 8H, contains 1.05 (d, *J* = 6.7 Hz, 3H, 21-CH_3)), 1.03–0.81 (m, 8H, contains 0.99 (s, 3H, 19-CH_3)), 0.68 (s, 3H, 18-CH_3), 0.61 (dd, *J* = 5.0, 3.7 Hz, 1H, 4-CH_2), 0.40 (dd, *J* = 8.0, 5.0 Hz, 1H, 4-CH_2). ^{13}C NMR (126 MHz, CD_2Cl_2): δ [ppm] = 201.0 (+, CHO-24), 82.7 (+, CH-6), 58.2 (+, CH), 56.7 (+, OCH_3), 56.4 (+, CH), 48.3 (+, CH), 43.7 (C_q), 43.3 (C_q), 40.5 (−, CH_2), 39.5 (+, CH), 35.7 (C_q, C-5), 35.3 (−, CH_2), 33.7 (−, CH_2), 32.8 (+, CH), 30.9 (+, CH), 29.6 (+, CH), 28.3 (−, CH_2), 25.3 (−, CH_2), 24.6 (−, CH_2), 23.1 (−, CH_2), 21.9 (+, CH-3), 20.0 (+, CH_3-21), 19.5 (+, CH_3-19), 13.2 (−, CH_2-4), 12.3 (+, CH_3-18), 12.0 (−, CH_2-22^1). MS (FAB, 3-NBA): m/z (%) = 384 (21) $[M]^+$, 383 (36) $[M–H]^+$, 369 (15) $[M–CH_3]^+$, 354 (28) $[M–CH_2O]^+$, 353 (100) $[M–OCH_3]^+$, 352 (23) $[M–CH_3OH]^+$, 255 (23) $[C_{19}H_{27}]^+$, 253 (25) $[C_{19}H_{25}]^+$, 213 (14) $[C_{16}H_{21}]^+$. HRMS (FAB, 3-NBA, m/z): calcd. for $C_{26}H_{40}O_2$, $[M]^+$: 384.3028; found: 384.3029. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3058 (vw), 2931 (s), 2867 (s), 2721 (vw), 1704 (vs), 1455 (m), 1381 (w), 1095 (vs), 1016 (s), 863 (m), 613 (w). EA ($C_{26}H_{40}O_2$, 384.6): calcd.: C 81.20, H 10.48; found: C 81.38, H 10.39.

6β-Methoxy-3α,5-cyclo-22*R*,23*S*-methylene-5α-cholestan-24$^{\xi}$-ol (26): A mixture of aldehyde **25** (60.0 mg, 156 μmol, 1.00 equiv.) and *i*PrMgBr (2 M, 156 μL, 312 μmol, 2.00 equiv.) in 1 mL of dry THF was stirred at −18 °C for 2 h under argon atmosphere and then quenched with sat. NH_4Cl. The layers were separated and the aqueous layer was washed with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (pentane/EtOAc 15:1) to give a diastereomeric mixture of the alcohol as an off-white solid (55.7 mg, 130 μmol, 83% yield). Compound (24*S*)-**26** was obtained

with a 4.9:1 diastereomeric ratio as determined by ^{1}H NMR spectroscopy. Recrystallization from isopropanol/H_2O afforded crystals suitable for X-ray crystallographic analysis (CCDC 2041207). R_f = 0.66 (pentane/EtOAc 4:1). $[\alpha]^{20}_D$ = +61.9° (c = 0.52, $CHCl_3$). Mp: 91–94 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.32 (s, 3H, OCH_3), 2.95 (dd, J = 6.7, 4.8 Hz, 1H, 24-C*H*OH), 2.77 (t, J = 2.9 Hz, 1H, 6-C*H*OCH_3), 2.00–1.87 (m, 3H), 1.83–1.67 (m, 3H), 1.67–1.58 (m, 1H), 1.55–1.46 (m, 2H), 1.46–1.33 (m, 3H), 1.27–1.00 (m, 9H, contains 1.02 (s, 3H, 19-CH_3)), 0.97 (d, J = 6.9 Hz, 6H, 26-CH_3 and 27-CH_3), 0.92–0.77 (m, 7H, contains 0.87 (d, J = 6.7 Hz, 3H, 21-CH_3)), 0.69 (s, 3H, 18-CH_3), 0.65 (dd, J = 5.0, 3.7 Hz, 1H, 4-CH*H*), 0.62–0.55 (m, 1H, CH), 0.43 (dd, J = 8.0, 5.0 Hz, 1H, 4-C*H*H), 0.33 (dt, J = 9.0, 4.7 Hz, 1H, 22^1-CH*H*), 0.19 (ddd, J = 8.5, 5.5, 4.5 Hz, 1H, 22^1-*CH*H). Missing Signal (1H, OH) due to H/D exchange. ^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 82.6 (+, CH-6), 79.1 (+, CH-24), 57.8 (+, CH), 56.7 (+, OCH_3), 56.4 (+, CH), 48.2 (+, CH), 43.5 (C_q), 43.0 (C_q), 40.3 (−, CH_2), 38.3 (+, CH), 35.4 (C_q, C-5), 35.2 (−, CH_2), 34.0 (+, CH), 33.5 (−, CH_2), 30.7 (+, CH), 28.3 (−, CH_2), 25.1 (−, CH_2), 24.4 (−, CH_2), 23.5 (+, CH), 23.0 (+, CH), 22.9 (−, CH_2), 21.6 (+, CH), 19.5 (+, CH_3-26 or CH_3-27), 19.4 (+, CH_3-19), 18.3 (+, CH_3-21), 17.4 (+, CH_3-26 or CH_3-27), 13.2 (−, CH_2-4), 12.4 (+, CH_3-18), 5.6 (−, CH_2-22^1). MS (FAB, 3-NBA): m/z (%) = 428 (16) $[M]^+$, 427 (37) $[M–H]^+$, 397 (19) $[M–OCH_3]^+$, 379 (100) $[M–OCH_3–H_2O]^+$, 353 (14) $[M–H_2–C_4H_9O]^+$, 255 (26) $[C_{19}H_{27}]^+$, 253 (45) $[C_{19}H_{25}]^+$, 213 (20) $[C_{16}H_{21}]^+$. HRMS (FAB, 3-NBA, m/z): calcd. for $C_{29}H_{48}O_2$, $[M]^+$: 428.3649; found: 428.3651. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3493 (w), 3060 (vw), 2932 (vs), 2866 (vs), 2846 (s), 1459 (s), 1380 (m), 1252 (w), 1198 (w), 1152 (w), 1086 (vs), 1016 (s), 992 (m), 914 (m), 891 (w), 860 (m), 815 (w), 660 (w), 615 (w), 541 (w). EA ($C_{29}H_{48}O_2$, 428.7): calcd.: C 81.25, H 11.29; found: C 81.14, H 11.40.

6β-Methoxy-3α,5-cyclo-22*R*,23*S*-methylene-5α-cholestan-24-one (8): To a solution of alcohol **26** (211 mg, 492 μmol, 1.00 equiv.) in 5 mL of DCM was added 0.2 g of powdered molecular sieve 3 Å, followed by pyridinium chlorochromate (PCC) (165 mg, 765 μmol, 1.56 equiv.). The mixture was stirred at room temperature for 2 h. Diethyl ether was added (10 mL), and the mixture was filtered through a short plug of Florisil. The solvent was removed under reduced pressure to yield the crude ketone, which was purified by silica gel flash column chromatography (pentane/EtOAc 20:1). The ketone **8** was obtained as a colorless solid (176 mg, 413 μmol, 84% yield). Spectroscopic properties were identical to those present in the literature.[17] Recrystallization from methanol/H_2O afforded crystals suitable for X-ray crystallographic analysis (CCDC 2047122). R_f = 0.28 (pentane/EtOAc 20:1). $[\alpha]^{20}_D$ = +115.7° (c = 0.555, $CHCl_3$). Mp: 104–106 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.32 (s, 3H, OCH_3), 2.77 (t, J = 2.9 Hz, 1H, 6-C*H*OCH_3), 2.72 (hept, J = 6.9 Hz, 1H, 25-CH), 1.98–1.85 (m, 3H), 1.84–1.66 (m, 3H), 1.65–1.56 (m, 1H, CH*H*), 1.55–1.47 (m, 2H), 1.47–1.32 (m, 3H), 1.31–1.21 (m, 2H), 1.19–0.96 (m, 17H, contains 1.14 (d, J = 7.0 Hz, 3H, 27-CH_3), 1.11 (d, J = 6.8 Hz, 3H, 26-CH_3), 1.01 (s, 3H, 19-CH_3), 1.00 (d, J = 6.7 Hz, 3H, 21-CH_3)), 0.93–0.78 (m, 4H), 0.70–0.61 (m, 5H, contains 0.67 (s, 3H, 18-CH_3)), 0.43 (dd, J = 8.1, 5.0 Hz, 1H, 4-CH*H*). ^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 214.1 (C_q, CO-24), 82.5 (+, CH-6), 57.8 (+, CH), 56.7 (+, OCH_3), 56.3 (+, CH), 48.1 (+, CH), 43.5 (C_q), 43.0 (C_q), 41.5 (+, CH-25), 40.2 (−, CH_2), 39.6 (+, CH), 35.3 (C_q, C-5), 35.2 (−, CH_2), 33.5 (−, CH_2), 32.6 (+, CH), 30.7 (+, CH), 28.9 (+, CH), 28.2 (−, CH_2), 25.1 (−, CH_2), 24.3 (−, CH_2), 22.9 (−, CH_2), 21.6 (+, CH), 19.7 (+, CH_3-21), 19.4 (+, CH_3-19), 18.8 (+, CH_3-27), 18.0 (+, CH_3-26), 16.2 (−, CH_2-22^1), 13.2 (−, CH_2-4), 12.4 (+, CH_3-18). MS (FAB, 3-NBA): m/z (%) = 426 (38) $[M]^+$, 425 (50) $[M–H]^+$, 411 (12) $[M–CH_3]^+$, 395 (100) $[M–OCH_3]^+$, 371 (13), 297 (25) $[C_{22}H_{33}]^+$, 255 (19) $[C_{19}H_{27}]^+$, 253 (33) $[C_{19}H_{25}]^+$, 213 (10) $[C_{16}H_{21}]^+$. HRMS (FAB, 3-NBA, m/z): calcd. for $C_{29}H_{46}O_2$, $[M]^+$: 426.3492; found: 426.3495. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3060 (vw), 2956 (s), 2919 (vs), 2866 (s), 1687 (vs), 1459 (m), 1446 (m), 1381 (m), 1346 (m), 1181 (w), 1092 (vs), 1062 (vs), 1017 (s), 966 (m), 914 (m), 880 (w), 861 (m), 815 (w), 615 (w). EA ($C_{29}H_{46}O_2$, 426.7): calcd.: C 81.63, H 10.87; found: C 81.35, H 10.72.

Deposition Numbers 2047122 (for **8**), 2041205 (for **15**), 2041206 (for **24**), 2041207 (for **26**), 2040691 (for **18**), and 2040692 (for **23**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Cyclopropanation · Gorgosterol · Steroids · Stereoselective synthesis · Ruthenium

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