NOE data ($CDCl_3$) peak irradiated (ppm)	NOE observed (ppm)
4.14 (H-3)	1.21 (Me-1)
3.61 (H-2)	1.21 (Me-1), 5.26 (NH), 2.46 (H-4)
2.46 (H-4)	4.14 (H-3), 3.61 (H-2)
1.21 (Me-1)	5.26 (NH), 3.61 (H-2), 4.14 (H-3)

Conversion of 4 and 8 to L-Alanine. Compounds 4 and 8 (12 mg each) in parallel experiments were dissolved in MeOH (1 mL) and ozonized at −78 °C in a dry ice–acetone bath.[12] A saturated solution of starch and KI was used as indicator for excess ozone. The reaction product was quenched with Me_2S and the solvent was evaporated to dryness under a stream of N_2. The oily residue was dissolved in CH_2Cl_2 and reacted with DBU (10 μL) in the presence of 4-Å molecular sieves at room temperature for 12 h. The product was passed through a silica BondElut cartridge with EtOAc and an α,β-unsaturated aldehyde mixture was obtained together with some starting material (4 mg from 8 and 7 mg from 4), as judged by TLC and ^1H NMR spectra.

A second ozonolysis was carried out separately on the above reaction products in CH_2Cl_2 (1 mL). Starch/KI indicator was used to monitor excess ozone at −78 °C. The products were quenched with Me_2S and the solvent was evaporated under a stream of nitrogen. The residues were separately dissolved in *t*-BuOH (2 mL) and 2-methyl-2-butene (100 μL) was added to each reaction mixture. A solution of $NaClO_2$ (20 mg) and NaH_2PO_4 (20 mg) in H_2O (0.5 mL) was added dropwise to each vial and stirred for 18 h at room temperature. The solvent was removed and the residues were dissolved in H_2O (5 mL) and acidified with HCl (6 N) and separately extracted with CH_2Cl_2 (3 × 2 mL), which resulted in crude reaction products (1.4 mg from 8 and 4 mg from 4).

Portions of these residues were hydrolyzed (0.7 mg from 8 and 0.4 mg from 4) in sealed tubes with 6 N HCl (200 μL) at 110 °C for 24 h. The solvents were evaporated and the residues were dried under vacuum and dissolved in H_2O (200 μL). An aliquot from each (50 μL from 8 and 100 μL from 4) was reacted with 1-fluoro-2,4-dinitrophen-5-yl-L-alanine amide (FDAA) (Pierce) (20 μL of a 1% solution for 8, and 10 μL of a 1% solution for 4) in the presence of 1 M $NaHCO_3$ (10 μL) for 1 h at 40 °C. The reaction mixtures were quenched with 2 M HCl (10 μL) and the solutions were diluted with 200 μL of DMSO. The final solution was mixed well and chromatographed by HPLC on a 5-μm RP-18 column (10 cm) and eluted by a gradient from 10% MeCN in 0.05 M $(Et_3NH)_3PO_4$ (pH 3) to 40% MeCN in 0.05 M $(Et_3NH)_3PO_4$ (pH 3) in 45 min. The peak retention times were compared with those of standard alanine derivatives, which were prepared by using the same procedure. Further confirmation was achieved by coinjections. Both acetates gave peaks corresponding to L-alanine derivatives.

compound(s) injected	retention time (min:s)
authentic L-alanine derivative	17:06
authentic D-alanine derivative	21:45
alanine derivative from 4	17:15
L-alanine and alanine derivative from 4	17:06
alanine derivative from 8	17:24
L-alanine and alanine derivative from 8	17:15

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Registry No. 2, 117828-55-4; 3, 117828-56-5; 4, 117828-57-6; 5, 117828-58-7; 6, 117828-59-8; 7, 117860-01-2; 8, 117860-02-3; 9, 117860-03-4; 10, 117828-60-1.

Stereospecificity and Regiospecificity of the Phosphorus Oxychloride Dehydration of Sterol Side Chain Alcohols

José-Luis Giner, Christian Margot, and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

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Stigmasta-5,23(*E*)-dien-3β-ol (**2**) and stigmasta-5,23(*Z*)-dien-3β-ol (**3**), sterols of potential biosynthetic interest, were synthesized by phosphorus oxychloride dehydration. High stereospecificity and regiospecificity in this reaction is evident in the dehydrations of several steroidal side chain alcohols. A two-step hydroboration–phosphorus oxychloride dehydration procedure is described for reversing the geometry of trisubstituted double bonds. Surprisingly facile borane migration with retention of the configuration at C24 was observed in the hydroboration of steroidal side chain olefins. Phosphorus oxychloride dehydration was used to introduce deuterium into the vinylic position of isofucosterol (**15**) via its *i*-methyl ether.

The sponge *Calyx Nicaeensis* contains, as its principal sterol, calysterol (**1**),[1] one of the few cyclopropenes found in nature. (*E*)- and (*Z*)-stigmasta-5,23-dien-3β-ol (**2A** and **3A**), minor sterol components of the same sponge,[2] were prepared for feeding experiments to test whether they serve as biosynthetic precursors to this unusual marine sterol. It was found that phosphorus oxychloride dehydration of the epimeric 23-alcohols (**4A** and **5A**) yielded **2A** and **3A**, respectively, as the exclusive products (Figure 1). Herein we describe the preparative utility of this stereo- and regiospecific reaction applied to the synthesis of unsaturated sterols.

Results and Discussion

Thirty years ago, the phosphorus oxychloride dehydration was shown in studies of the dehydration of constrained cyclic and bicyclic tertiary alcohols to proceed via an anti elimination reaction with a late transition state.[3] Yet until now the high stereoselectivity and regioselectivity of this simple reaction has been largely unappreciated as a method of preparative utility.

The 22- and 23-alcohols in the (24*R*)-stigmastane (**A**) and (24*S*)-ergostane (**B**) series were prepared by epoxidation of stigmasterol *i*-methyl ether (**6A**) or brassicasterol *i*-methyl ether (**6B**) followed by reduction with

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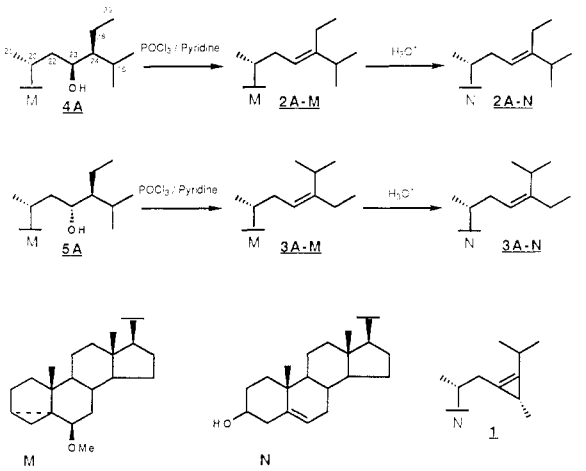

Figure 1. Synthesis of *E* and *Z* stigmasta-5,23-dienols **2A-N** and **3A-N**.

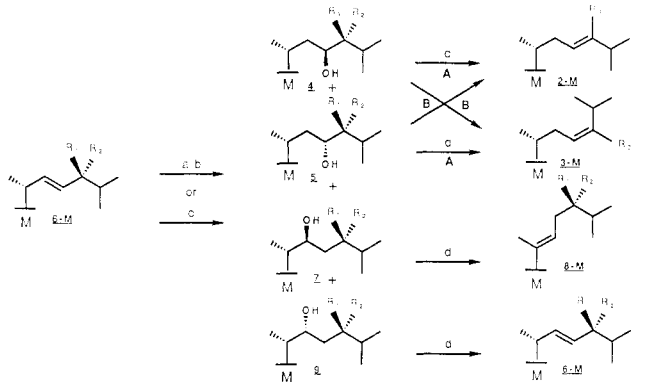

Figure 2. Products of phosphorus oxychloride dehydration of steroidal 22- and 23-alcohols. **A**: R_1 = Et, R_2 = H, R_3 = Et. **B**: R_1 = H, R_2 = Me, R_3 = Me. (a) MCPBA; (B) **A**, $LiAlH_4/AlCl_3$, **B**, $LiAlH_4$; (c) B_2H_6, $H_2O_2/NaOH$; (d) $POCl_3$/pyridine.

lithium aluminum hydride/aluminum chloride or lithium aluminum hydride, respectively. The structures of the products were assigned by correlation with the known epoxides[4] and the ketones derived by oxidation. Alternatively, hydroboration of **6A** and **6B** gave rise to the same products.

In the (24*R*)-stigmastane series phosphorus oxychloride dehydration of 23-alcohols **4A** and **5A** led to the *E* (**2A**) and *Z* (**3A**) isomers of the Δ^{23}-olefin. In the (24*S*)-ergostane series the configuration of the products was reversed, alcohol **4B** leading to the *Z* olefin **3B**[5] and alcohol **5B** to the *E* olefin **2B**[4,5] (Figure 2). Dehydration of 22-(*S*)-alcohol **7** gave the 20(22) *E* olefin 8. However, dehydration of 22(*R*)-alcohol **9** did not produce the 20(22) *Z* olefin, but rather stigmasterol or brassicasterol *i*-methyl ether (**6**) together with a product thought, based on the mass spectrum, to be the 22-chloride. This result can be rationalized on the basis of unfavorable steric interactions in the transition state leading to the $\Delta^{20(22)}$ product (Figure 3).

The phosphorus oxychloride dehydration of tertiary alcohols does not display as great a regioselectivity as it

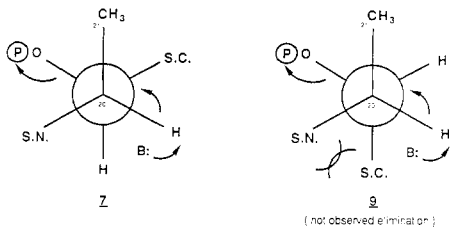

Figure 3. Steric effects in the transition states of phosphorus oxychloride dehydration of 22-alcohols **7** and **9**. S.N. = sterol nucleus; S.C. = sterol side chain.

does with secondary alcohols. Thus (23*S*,24*R*)-23-methyl-23-hydroxyergostane *i*-methyl ether (**10a**) gave rise to a mixture of (24*R*)-23-methyleneergost-5-en-3β-ol (**11**),[9] (23*E*)-23-methylergosta-5,23-dien-3β-ol (**12**),[10] and 4-demethyl-5-dehydrodinosterol (**13**)[11] as their *i*-methyl ethers (Figure 4).

The stereoselective sequence syn hydroboration–anti dehydration offers a convenient method for the isomerization of trisubstituted olefins. Fucosterol (**14**) has been converted to isofucosterol (**15**) by the epoxidation–lithium diphenylphosphinide procedure.[12] The same isomerization was carried out by hydroboration to the 24*R*,28*S* and 24*S*,28*R* alcohols (**16a** and **16b**)[13] followed by phosphorus oxychloride dehydration (Figure 5). However, 16% of the product of the two-step sequence was fucosterol *i*-methyl ether. When the major product of hydroboration **16** was purified prior to dehydration, only isofucosterol (**15**) *i*-methyl ether was obtained. We believe that the incomplete stereospecificity of this procedure is due to isomerization of the intermediate alkylborane. Generally borane migration has been carried out at temperatures of 100–160 °C. It is surprising to observe this reaction at 0 °C; however, it is known that excess borane and sterically bulky alkyl groups increase the rate of the reaction.[14] In the hydroboration reactions of stigmasterol and brassicasterol *i*-methyl ethers (**6A** and **6B**), products of borane migration were also observed. Because hydroboration of *i*-methyl stigmasterol was reported to give incomplete reaction,[15] we heated the reaction mixture at 67 °C for 1 h. In addition to the desired alcohols we found 30% of the product to be a 1:1 mixture of the 24*R*,28*S* 28-alcohol **16a** and the 24*R*,28*R* isomer **16c** (Figure 6). It is interesting to note that the stereocenter at C24 was conserved in the borane migration. In the hydroboration of the brassicasterol side chain (**6B**)[16] at room temperature, 8% of the product was a single isomer of the 25-alcohol (**17**). In this case the configuration at C24 was also conserved as was demonstrated by phosphorus oxychloride dehydration to a 1:1 mixture of codisterol (**18**) and 24-methyldesmosterol (**19**).

Phosphorus oxychloride dehydration also provides a convenient method for the introduction of hydrogen iso-

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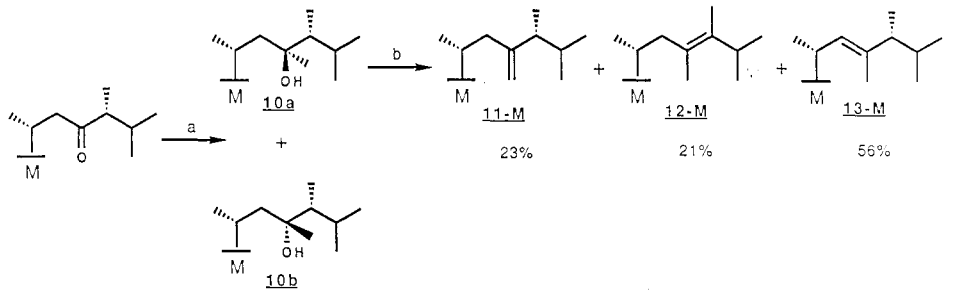

Figure 4. Phosphorus oxychloride dehydration of (23*S*,24*R*)-23-methyl-23-hydroxyergostane *i*-methyl ether (**10a**). (a) MeLi; (b) $POCl_3$/pyridine.

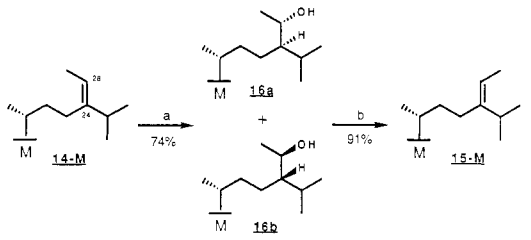

Figure 5. Isomerization of fucosterol *i*-methyl ether (**14-M**) to isofucosterol *i*-methyl ether (**15-M**). (a) B_2H_6, H_2O_2/NaOH; (b) $POCl_3$/pyridine.

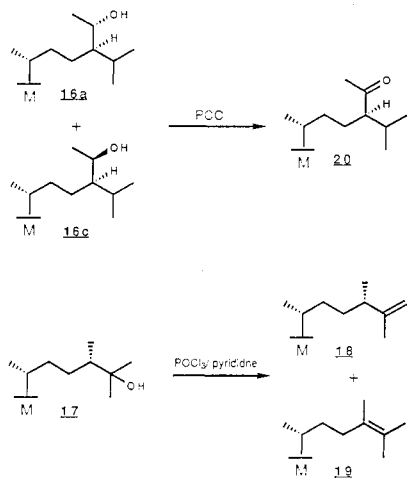

Figure 6. Side products of hydroboration of stigmasterol (**6A-M**) and brassicasterol (**6B-M**) *i*-methyl ethers.

topes to the vinyl position of a double bond.[17] Thus 28-deuterio 24*R*,28*S* alcohol **16** (from lithium aluminum deuteride reduction of (24*R*)-stigmastan-28-one *i*-methyl ether[13]) was dehydrated to 28-deuterioisofucosterol *i*-methyl ether (**15**).[18]

Summary

The high stereospecificity and regiospecificity of the phosphorus oxychloride dehydration of secondary alcohols, due to anti elimination and a transition state with considerable product character, is a synthetically useful reaction. Biosynthetically interesting marine sterols (*E*)- and (*Z*)-stigmasta-5,23-dien-3β-ol (**2** and **3**) were synthesized in pure form in two steps from stigmasterol *i*-methyl ether by this method. When coupled to the syn stereochemistry of hydroboration, this provides a convenient means to interconvert double bond isomers. It was noted that borane migration in the hydroboration reaction can take place under surprisingly mild conditions with retention of stereochemistry. Phosphorus oxychloride dehydration also provides a convenient method for isotopically labeling olefins.

Experimental Section

General Methods. High-pressure liquid chromatography (HPLC) was carried out on a Waters Associates HPLC system (M 6000 pump, R403 differential refractometer) with two Altex Utrasphere ODS 5-μm columns (10 mm i.d. × 25 cm) in series with methanol as the mobile phase (3 mL/min). Low-resolution mass spectra were obtained with either a Finnigan MAT-44 spectrometer; a Hewlett-Packard GC/MS system consisting of a Model 5890A gas chroamtograph with a SE-54 coated fused silica capillary column (0.32 mm i.d. × 15 m), a Model 5970 mass spectrometer, and a 9133 system for data acquisition; or a Hewlett-Packard Model 5995 GC/MS in the direct inlet mode. Melting points were determined on a Thomas-Hoover "Unimelt" capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (NMR) were recorded on a Varian XL-400 instrument. All NMR spectra are referenced to the solvent peak ($CHCl_3$).

Synthesis of 22- and 23-Hydroxy-6β-methoxy-3α,5-cyclo-5α-stigmastanes. (22*R*,23*R*)-22,23-Epoxy-6β-methoxy-3α,5-cyclo-5α-stigmastane[4] (0.3 g) was treated in 15 mL of THF with a mixture of 0.3 g of $LiAlH_4$ and 0.4 g of $AlCl_3$ at reflux under Ar for 2 h. The reaction was quenched by pouring into saturated $(NH_4)_2SO_4$ and extracted with ether. Silica gel chromatography (eluent: hexanes/ethyl acetate, 24:1) gave 0.29 g (96%) of a mixture of (23*S*,24*S*)-6β-methoxy-3α,5-cyclo-5α-stigmastan-23-ol (**4A**) and (22*S*,24*R*)-6β-methoxy-3α,5-cyclo-5α-stigmastan-22-ol (**7A**). Separation by reverse-phase HPLC gave the following.

(23*S*,24*S*)-6β-Methoxy-3α,5-cyclo-5α-stigmastan-23-ol (4A) (74%): TLC R_f = 0.49 (hexanes/ether, 2:1); HPLC t_R 26 min; ^1H NMR (400 MHz) δ ($CDCl_3$) 3.907 (m, 1 H, C23), 3.324 (s, 3 H, OMe), 1.020 (s, 3 H, C19), 0.978 (d, *J* = 6.3 Hz, C21), 0.960 (t, *J* = 7.4 Hz, 3 H, C29), 0.951 (d, *J* = 6.6 Hz, 3 H, C26 or 27), 0.945 (d, *J* = 6.6 Hz, 3 H, C26 or 27), 0.724 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 444 (M^+, $C_{30}H_{52}O_2$, 33), 429 (57), 412 (44), 389 (92), 327 (51), 207 (52), 55 (100).

(22*S*,24*R*)-6β-Methoxy-3α,5-cyclo-5α-stigmastan-22-ol (7A) (26%): TLC R_f = 0.55 (hexanes/ether, 2:1); HPLC t_R 23 min; ^1H NMR (400 MHz) δ ($CDCl_3$) 3.751 (m, 1 H, C22), 3.329 (s, 3 H, OMe), 1.026 (s, 3 H, C19), 0.899 (d, *J* = 6.5 Hz, C21), 0.879 (t, *J* = 7.3 Hz, 3 H, C29), 0.844 (d, *J* = 6.6 Hz, 3 H, C26 or 27), 0.831 (d, *J* = 6.6 Hz, 3 H, C26 or 27), 0.731 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 444 (M^+, $C_{30}H_{52}O_2$, 35), 429 (58), 412 (51), 389 (100), 301 (24), 284 (41), 69 (88).

Treatment of (22*S*,23*S*)-22,23-epoxy-6β-methoxy-3α,5-cyclo-5α-stigmastane[4] as above gave the following.

(23*R*,24*S*)-6β-Methoxy-3α,,5-cyclo-5α-stigmastan-23-ol (5A) (70%): TLC R_F = 0.40 (hexanes/ether, 2:1); HPLC t_R 32 min; ^1H NMR (400 MHz) δ ($CDCl_3$) 3.713 (m, 1 H, C23), 3.318 (s, 3 H, OMe), 1.018 (s, 3 H, C19), 0.958 (d, *J* = 6.4 Hz, C21), 0.936 (t, *J* = 7.2 Hz, 3 H, C29), 0.909 (d, *J* = 6.6 Hz, 3 H, C26 or 27), 0.892 (d, *J* = 6.6 Hz, 3 H, C26 or 27), 0.751 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 444 (M^+, $C_{30}H_{52}O_2$, 28), 429 (41), 412 (33), 389 (80), 327 (36), 207 (28), 55 (100).

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(22*R*,24*R*)-6β-Methoxy-3α,5-cyclo-5α-stigmastan-22-ol (9A) (30%): TLC R_f = 0.38 (hexanes/ether, 2:1); HPLC t_R 27.5 min; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 3.710 (m, 1 H, C22), 3.321 (s, 3 H, OMe), 1.024 (s, 3 H, C19), 0.916 (d, *J* = 7.2 Hz, C21), 0.889 (d, *J* = 6.8 Hz, 3 H, C26 or 27), 0.881 (t, *J* = 7.2 Hz, 3 H, C29), 0.792 (d, *J* = 6.8 Hz, 3 H, C26 or 27), 0.741 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 444 (M^+, $C_{30}H_{52}O_2$, 25), 429 (40), 412 (29), 389 (77), 301 (24), 284 (52), 69 (100), 55 (92).

The above alcohols were correlated by their pyridinium chlorochromate oxidation products. Thus **7A** and **9A** were oxidized to give the following.

(24*R*)-6β-Methoxy-3α,5-cyclo-5α-stigmastan-22-one: ^{1}H NMR (400 MHz) δ ($CDCl_3$) 3.321 (s, 3 H, OMe), 1.080 (d, *J* = 6.9 Hz, 3 H, C21), 1.021 (s, 3 H, C19), 0.844 (t, *J* = 7.4 Hz, 3 H, C29), 0.833 (d, *J* = 6.8 Hz, 3 H, C26 or 27), 0.805 (d, *J* = 6.7 Hz, 3 H, C26 or 27), 0.736 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 442 (M^+, $C_{30}H_{50}O_2$, 12), 427 (17), 410 (18), 387 (34), 326 (10), 283 (14), 255 (16), 213 (16), 127 (50), 109 (53), 55 (100).

Similarly **4A** and **5A** gave the following upon pyridinium chlorochromate oxidation.

(24*S*)-6β-Methoxy-3α,5-cyclo-5α-stigmastan-23-one: ^{1}H NMR (400 MHz) δ ($CDCl_3$) 3.319 (s, 3 H, OMe), 1.015 (s, 3 H, C19), 0.926 (d, *J* = 6.2 Hz, C21), 0.863 (d, *J* = 7.7 Hz, 6 H, C26 and 27), 0.808 (t, *J* = 7.4 Hz, 3 H, C29), 0.755 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 442 (M^+, $C_{30}H_{50}O_2$, 10), 427 (20), 410 (17), 387 (38), 314 (15), 299 (11), 282 (42), 85 (100).

Synthesis of 22- and 23-Hydroxy-6β-methoxy-3α,5-cyclo-5α-ergostanes. (22*R*,23*R*)-22,23-Epoxy-6β-methoxy-3α,5-cyclo-5α-ergostane[4] (60.3 mg) was treated in 3 mL of THF with 50 mg of $LiAlH_4$ for 48 h under Ar at 55 °C. The reaction mixture was quenched with ethyl acetate, poured into water, and extracted with ether. Silica gel chromatography gave 50.0 mg (83%) of (23*S*,24*R*)-6β-methoxy-3α,5-cyclo-5α-ergostan-23-ol (**4B**) and (22*S*,24*S*)-6β-methoxy-3α,5-cyclo-5α-ergostan-22-ol (**7B**). Separation by reverse-phase HPLC gave the following.

(23*S*,24*R*)-6β-Methoxy-3α,5-cyclo-5α-ergostan-23-ol (4B) (34%): TLC R_f = 0.49 (hexanes/ether, 2:1); HPLC t_R 27.5 min; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 3.612 (m, 1 H, C23), 3.323 (s, 3 H, OMe), 1.046 (d, *J* = 6.5 Hz, 3 H, C24), 1.017 (s, 3 H, C19), 0.908 (d, *J* = 6.9 Hz, C21), 0.839 (d, *J* = 6.7 Hz, 3 H, C26 or 27), 0.791 (d, *J* = 6.8 Hz, 3 H, C26 or 27), 0.726 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 430 (M^+, $C_{29}H_{50}O_2$), 79), 415 (57), 398 (70), 389 (77), 375 (69), 327 (18), 135 (32), 105 (29), 71 (54), 57 (72), 55 (59), 43 (100).

(22*S*,24*S*)-6β-Methoxy-3α,5-cyclo-5α-ergostan-22-ol (7B)[19] (66%): TLC R_f = 0.55 (hexanes/ether, 2:1); HPLC t_R 24 min.

Treatment of (22*S*,23*S*)-22,23-epoxy-6β-methoxy-3α,5-cyclo-5α-ergostane[4] as above gave the following.

(23*R*,24*R*)-6β-Methoxy-3α,5-ergostan-23-ol (5B) (81%): TLC R_f = 0.33 (hexanes/ether, 2:1), HPLC t_R 33 min; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 3.702 (m, 1 H, C23), 3.321 (s, 3 H, OMe), 1.020 (s, 3 H, C19), 0.960 (d, *J* = 6.5 Hz, 3 H, C24), 0.938 (d, *J* = 6.8 Hz, C21), 0.860 (d, *J* = 6.9 Hz, 3 H, C26 or 27), 0.838 (d, *J* = 6.8 Hz, 3 H, C26 or 27), 0.750 (s, 3 *H*, C18); low-resolution mass spectrum, *m/z* (relative intensity) 430 (M^+, $C_{29}H_{50}O_2$, 50), 415 (38), 398 (48), 375 (46), 255 (12), 213 (10), 71 (66), 55 (59), 43 (89), 41 (100).

(22*R*,24*S*)-6β-Methoxy-3α,5-cyclo-5α-ergostan-22-ol (9B)[19] (19%): TLC R_f = 0.36 (hexanes/ether, 2:1); HPLC t_R 27.5 min.

General Method for Phosphorus Oxychloride Dehydration. To a solution of 5–50 mg of steroidal alcohol in 1 mL of pyridine at 0 °C was added 0.1 mL of $POCl_3$. The mixture was allowed to stand for 2 h at room temperature (48 h in the case of tertiary alcohol **10**) and poured into dilute hydrochloric acid. Extraction with ether and silica gel chromatography (eluent: hexanes/ether, 79:1) gave the *i*-methyl sterols in 85–95% yields. Deprotection of the Δ^5-3β-ol system was accomplished by heating the *i*-methyl ether in a 9:1 dioxane/water mixture containing 0.05% *p*-toluenesulfonic acid under reflux for 1.5 h. See Figure 2 for reaction products.

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(24*R*)-Stigmasta-5,20(22)(*E*)-dien-3β-ol (8A-N): mp 107–109 °C (MeOH); ^{1}H NMR (400 MHz) δ ($CDCl_3$) 5.351 (m, 1 H, C_6), 5.172 (t, *J* = 7.0 Hz, 1 H, C22), 1.623 (s, 3 H, C21), 1.008 (s, 3 H, C19), 0.862 (t, *J* = 7.4 Hz, 3 H, C29), 0.846 (d, *J* = 6.8 Hz, 3 H, C26 or 27), 0.842 (d, *J* = 6.8 Hz, 3 H, C26 or 27), 0.550 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 412 (M^+, $C_{29}H_{48}O$, 83), 397 (6), 379 (15), 314 (11), 299 (19), 271 (25), 258 (17), 229 (18), 213 (19), 211 (17), 123 (33), 55 (41), 43 (100).

(24*S*)-Ergosta-5,20(22)(*E*)-dien-3β-ol (8B-N): mp 126–129 °C (MeOH); ^{1}H NMR (400 MHz) δ ($CDCl_3$) 5.354 (m, 1 H, C6), 5.182 (t, *J* = 7.3 Hz, 1 H, C22), 1.619 (s, 3 H, C21), 1.008 (s, 3 H, C19), 0.875 (d, *J* = 6.8 Hz, 3 H, C26, 27 or 28), 0.825 (d, *J* = 6.8 Hz, 3 H, C26, 27 or 28), 0.795 (d, *J* = 6.8 Hz, 3 H, C26, 27 or 28), 0.556 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 398 (M^+, $C_{28}H_{46}O$, 81), 383 (7), 365 (15), 314 (8), 299 (20), 271 (24), 258 (17), 229 (26), 213 (24), 211 (19), 109 (47), 55 (51), 43 (100).

Dehydration of (23*S*,24*R*)-23-Methyl-6β-methoxy-3α,5-cyclo-5α-ergostan-23-ol (10a). A solution of 39.1 mg of mixed 6β-methoxy-3α,5-cyclo-5α-ergostan-23-ols **4B** and **5B** in 5 mL of CH_2Cl_2 and two drops of pyridine was treated with 190 mg of PCC at room temperature for 45 min. The reaction mixture was filtered through silica gel and purified by silica gel chromatography (eluent: hexanes/ether, 9:1) to give 38.2 mg of the following ketone (97%).

(24*R*)-6β-Methoxy-3α,5-cyclo-5α-ergostan-23-one: ^{1}H NMR (400 MHz) δ ($CDCl_3$) 3.321 (s, 3 H, OMe), 1.019 (s, 3 H, C19), 0.975 (d, *J* = 6.9 Hz, C21), 0.906 (d, *J* = 6.6 Hz, 6 H, C26 and 27), 0.835 (d, *J* = 6.8 Hz, 3 H, C28), 0.757 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 428 (M^+, $C_{29}H_{48}O_2$, 47), 413 (34), 396 (39), 373 (54), 314 (19), 282 (36), 121 (15), 71 (100), 69 (80), 55 (64).

The above ketone (19.7 mg) was treated with 0.3 mL of 1.4 M MeLi/Et_2O in 2 mL of ether for 1 min at room temperature. The reaction mixture was quenched with water and extracted with ether. Separation of 18.6 mg of mixed alcohols (91%) by preparative TLC (hexanes/ether, 4:1) gave the following.

(23*S*,24*R*)-23-Methyl-6β-methoxy-3α,5-cyclo-5α-ergostan-23-ol (10a) (89%): TLC R_f = 0.39 (hexanes/ether, 2:1); ^{1}H NMR (400 MHz) δ ($CDCl_3$) 3.323 (s, 3 H, OMe), 1.140 (s, 3 H, C29), 1.033 (d, *J* = 6.5 Hz, 3 H, C24), 1.019 (s, 3 H, C19), 0.924 (d, *J* = 6.9 Hz, C21), 0.829 (d, *J* = 7.0 Hz, 6 H, C26 and 27), 0.760 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 444 (M^+, $C_{30}H_{52}O_2$, 1), 429 (4), 426 (2), 394 (9), 373 (41), 323 (26), 283 (46), 253 (33), 69 (100), 55 (73).

(23*R*,24*R*)-23-Methyl-6β-methoxy-3α,5-cyclo-5α-ergostan-23-ol (10b) (11%): TLC R_f = 0.32 (hexanes/ether, 2:1); ^{1}H NMR (400 MHz) δ ($CDCl_3$) 3.324 (s, 3 H, OMe), 1.154 (s, 3 H, C29), 1.076 (d, *J* = 6.4 Hz, 3 H, C24), 1.019 (s, 3 H, C19), 0.913 (d, *J* = 6.8 Hz, C21), 0.836 (d, *J* = 6.8 Hz, 3 H, C26 or 27), 0.808 (d, *J* = 6.7 Hz, 3 H, C26 or 27), 0.760 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 444 (M^+, $C_{30}H_{52}O_2$, 0.6), 429 (2), 426 (2), 394 (6), 373 (31), 323 (20), 283 (37), 253 (24), 69 (100), 55 (71).

Dehydration of the above steroidal alcohol **10a** followed by deprotection as described above gave the mixture described in Figure 4.

(24*R*)-23-Methylergosta-5,23(29)-dien-3β-ol (11-*N*): mp 163–165 °C (MeOH); ^{1}H NMR (400 MHz) δ ($CDCl_3$) 5.351 (m, 1 H, C6), 4.732 (s, 1 H, C29), 4.720 (s, 1 H, C29), 1.012 (s, 3 H, C19), 0.933 (d, *J* = 6.9 Hz, C21), 0.890 (d, *J* = 6.8 Hz, 3 H, C26 or 27), 0.863 (d, *J* = 5.9 Hz, 3 H, C24), 0.783 (d, *J* = 6.7 Hz, 3 H, C26 or 27), 0.712 (s, 3 H, C18); low-resolution mass spectrum, *m/z* (relative intensity) 412 (M^+, $C_{29}H_{48}O$, 1), 394 (4), 379 (2), 300 (69), 283 (23), 282 (29), 267 (43), 207 (25), 105 (56), 93 (46), 81 (57), 69 (62), 55 (100).

Hydroboration of Brassicasterol *i*-Methyl Ether (6B-M). A solution of 67.1 mg of **6B-M** in 4 mL of THF was treated with 3 mL of 1 M BH_3/THF. After 8 h at room temperature the reaction mixture was quenched with a few drops of water and 3 mL of 5% NaOH, and 1.5 mL of 30% H_2O_2 was added. After 3 h at room temperature the mixture was poured into water and extracted with ether. Silica gel chromatography (eluent: hexanes/ether, 4:1) gave 45.1 mg of mixed alcohols (64%). Separation by HPLC gave **7B-M** (24%), **4B-M** (9%), **9B-M** (33%), **5B-M** (23%), and **17** (8%).

(24S)-6β-Methoxy-3α,5-cyclo-5α-ergostan-25-ol (17): ^{1}H NMR (400 MHz) δ ($CDCl_3$) 3.324 (s, 3 H, OMe), 1.165 (s, 3 H, C26 or 27), 1.153 (s, 3 H, C26 or 27), 1.021 (s, 3 H, C19), 0.932 (d, J = 6.5 Hz, C21), 0.892 (d, J = 6.8 Hz, 3 H, C24), 0.714 (s, 3 H, C18); low-resolution mass spectrum, m/z (relative intensity) 430 (M^+, $C_{29}H_{50}O_2$, 8), 415 (7), 398 (9), 375 (14), 255 (14), 213 (12), 105 (59), 59 (100), 55 (67).

Dehydration of (24S)-6β-Methoxy-3α,5-cyclo-5α-ergostan-25-ol (17). Treatment of **17** as described above gave a 1:1 mixture of codisterol (**18**) and 24-methyldesmosterol (**19**) as their *i*-methyl ethers.

Hydroboration of Stigmasterol *i*-Methyl Ether (6A-M). A solution of 392 mg of **6A-M** in 5 mL of THF was treated with 15 mL of 1 M BH_3/THF. After 4.5 h at room temperature and 1 h at 67 °C, the reaction mixture was worked up as described above. Separation by HPLC gave **7A-M** (21%), an unidentified epimeric steroidal side chain alcohol (8%), **4A-M** (6%), **9A-M** (32%), a 1:1 mixture of (24*R*,28*S*)-6β-methoxy-3α,5-cyclo-5α-stigmastan-28-ol (**16a**) and its 24*R*,28*R* epimer (**16c**)[13] (29%), and **5A-M** (4%).

Isomerization of Fucosterol *i*-Methyl Ether (14-M). a Solution of 67.9 mg of **14-M**[20] in 5 mL of THF was treated with 5 mL of 1 M BH_3/THF at 0 °C under Ar. After 6 h 4.5 mL of 5% NaOH and 3 mL of H_2O_2 were added. After 12 h at 0 °C the mixture was worked up as described above to give 52.1 mg of a mixture of (24*R*,28*S*)-6β-methoxy-3α,5-cyclo-5α-stigmastan-28-ol (**16a**) and its 24*S*,28*R* epimer (**16b**).[13] Treatment of 43.3 mg of this mixture with phosphorus oxychloride as described above gave, after chromatography, 37.8 mg of isofucosterol *i*-methyl ether (**15-M**) (91%) containing 16% **14-M**.

Dehydration of (24R,28S)-6β-Methoxy-3α,5-cyclo-5α-stigmastan-28-ol (16a). Treatment of **16a** as described above gave pure **15-M**.

28-Deuterio-6β-methoxy-3α,5-cyclo-5α-stigmasta-24(28)-(Z)-diene (28-*d* 15-M).[18] A solution of (24*R*)-6β-methoxy-3α,5-cyclo-5α-stigmastan-28-one (**20**)[13] in ether was reduced with 5 mg of $LiAlD_4$. After 5 min the reaction was quenched with water and extracted with ether. Separation of the products by preparative TLC (benzene/ether, 9:1) followed by dehydration of the (24*R*,28*S*)-28-deuterio-6β-methoxy-3α,5-cyclo-5α-stigmastan-28-ol (**28-*d* 16a**) gave **28-*d* 15-M**.

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(20) Pure fucosterol *i*-methyl ether was prepared by a copper allyl reaction: Giner, J.-L.; Margot, C.; Djerassi, C. *J. Org. Chem.*, submitted for publication.

Bimolecular Reactions of 3-Methylene-1,4-cyclohexadiene (*p*-Isotoluene), 5-Methylene-1,3-cyclohexadiene (*o*-Isotoluene), 1-Methylene-1,4-dihydronaphthalene (Benzo-*p*-isotoluene), and 9-Methylene-9,10-dihydroanthracene (Dibenzo-*p*-isotoluene)

Joseph J. Gajewski* and Andrea M. Gortva

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

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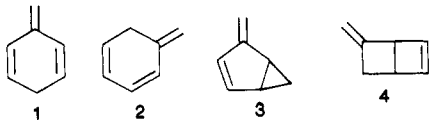
3-Methylene-1,4-cyclohexadiene, **1**, 5-methylene-1,3-cyclohexadiene, **2**, 1-methylene-1,4-dihydronaphthalene, **5**, and 9-methylene-9,10-dihydroanthracene, **8**, react with second-order kinetics in benzene solution. The activation parameters for the reaction of **1**, **5**, and **8**, especially the frequency factor, suggest a nonconcerted reaction with little orientational demand in the transition state. The frequency factor for the reaction of **2** suggests a concerted pathway. The product distribution from each compound reinforces the kinetic observations. The products from the pyrolysis of **1** could be rationalized by a radical cage intermediate, which could combine or disproportionate. The reaction products from **5** indicate a radical chain oligomerization. The reaction of **8** gives an insoluble solid. *o*-Isotoluene (**2**) gives ene dimers.

The existence of alicyclic isomers of toluene, *p*-isotoluene, **1**, *o*-isotoluene, **2**, *m*-isotoluene, **3**, and 5-methylenebicyclo[2.2.0]hexene, seemed unlikely a half century ago,[1] but all four compounds have been synthesized. Not unreasonably, both **1** and **2** are approximately 23 kcal/mol less stable than toluene as judged by gas-phase acidities compared with toluene.[2] However, the sensitivity of these materials to air, acid, and base precluded or obscured earlier efforts to observe their thermal behavior.



1 2 3 4

p-Isotoluene, **1**, was prepared by Plieninger and was reported to convert to toluene smoothly at room temperature. However, the conditions (in the presence of air, acid, or base) under which the isomerization of *p*-isotoluene occurred were not recorded.[3] A possible first-order, thermally allowed 1,5-hydrogen shift pathway for the isomerization of **1** was suggested by Dreiding.[4]

o-Isotoluene was synthesized by different routes by Bailey,[5a] Hasselmann,[5b] Kopecky,[5c] and Pryor.[5d] All previous experimenters reported that **2** forms toluene rapidly. The facile aromatization of *o*-isotoluene might be rationalized by the thermally allowed antarafacial 1,7-sigmatropic hydrogen shift.[4] Both Pryor and Kopecky proposed *o*-

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