The chemistry of 5β,6β-epoxy-4,4-dimethylcholest-1-en-3-one. Approaches to the synthesis of 1α,5α-cyclosteroids. Part II[1]

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Received September 24, 1992

PARIS E. GEORGHIOU and YI REN. Can. J. Chem. **71**, 364 (1993).

Epoxidation of 4,4-dimethylcholesta-1,5-dien-3-one (**9**) with MCPBA gives a mixture of the corresponding epimeric 5α,6α and 5β,6β epoxides. The major product is the 5β,6β epimer **6**, in contradiction to what has been reported by others. The unambiguous assignment of the structures of these epoxides is based upon NMR NOED experiments. The chemistry of the 5β,6β epoxide is described in the context of unsuccessful attempts at synthesizing the corresponding 1α,5α cyclosteroids. Reductive methods using lithium – liquid ammonia, lithium–ethylamine, or tri-*n*-butyl- or triphenyltin–AIBN gave products in which the α,β-unsaturated carbonyl system and the epoxide were reduced. When **6** was treated with BF_3·etherate a *B*-nor derivative **27** was formed, presumably via a pinacol-type rearrangement.

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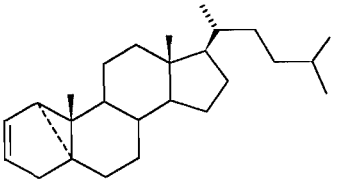
L'époxydation de la 4,4-diméthylcholesta-1,5-dièn-3-one (**9**) par l'AMCPB conduit à un mélange des époxydes épimères correspondants 5α,6α et 5β,6β. Contrairement à ce qui a été rapporté par d'autres, le produit majeur est l'épimère 5β,6β (**6**). L'attribution non-ambiguë des structures de ces époxydes est basée sur des expériences de RMN «NOED». On décrit la chimie de l'époxyde 5β,6β dans le contexte d'essais infructueux de synthèse des 1α,5α cyclostéroïdes correspondants. Les réductions à l'aide de lithium – ammoniac liquide, de lithium–èthylamine ou des tri-*n*-butyl- ou triphényl-étain–AIBN conduisent à des produits dans lesquels le système carbonyle α,β-insaturé et l'èpoxyde sont réduits. Le traitement du produit **6** par du BF_3·ether conduit à la formaton du dérivé *B*-nor **27**, probablement par un réarrangement de type pinacolique.

[Traduit par la rédaction]

Introduction

The 1α,5α cyclocholesterols are relatively rare. Laing and Sykes (1, 2) reported the synthesis of 1α,5α-cyclocholest-2-ene (**1**), and 3β-acetoxy-1α,5α-cyclocholestan-6-one (**2**) (3). The synthesis of **2** could not, however, be duplicated (4). Christensen and Reusch (5) synthesized 1-hydroxy-1α,5α-cyclocholestan-7-one (**3**) via lithium – liquid ammonia reduction of cholest-5-ene-1,7-dione. More recently we succeeded in synthesizing 4,4-dimethyl-1α,5α-cyclocholestane-3,7-dione (**4**) via an intramolecular reductive coupling of the *bis*-α,β-unsaturated diketone **5** (6).



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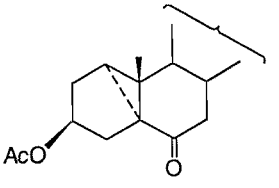

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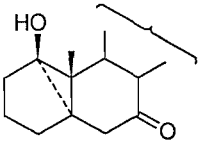

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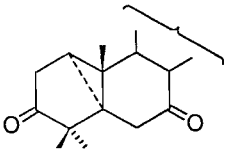

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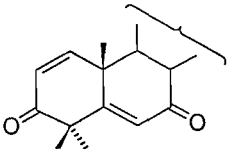

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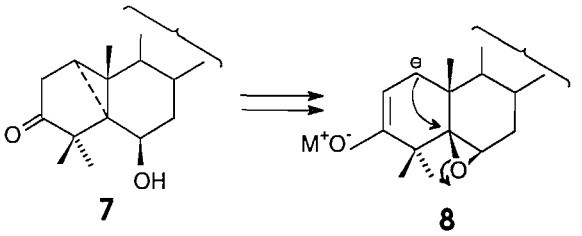
5β,6β-Epoxy-4,4-dimethylcholest-1-en-3-one (**6**) can be envisioned as a potential precursor for the synthesis of the cyclosteroid **7**. As depicted in Scheme 1, **7** could in principle be formed via an intramolecular ring opening of the epoxy group by the intermediate dianion **8** generated by metal – liquid ammonia reduction (7). We were unable to synthesize **7** but the results of our experiments on the chemistry of **6** form the subject of this paper.

Results and discussion

4,4-Dimethylcholesta-1,5-dien-3-one (8) (**9**) was prepared by benzeneselenenic anhydride (8) oxidation of 4,4-dimethylcholest-5-en-3-one (**10**). Reaction of **9** with

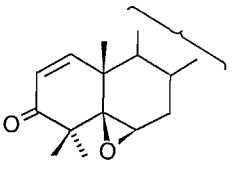
[1]Part I, see ref. 22.
[2]Author to whom correspondence may be addressed.



7 8

SCHEME 1

m-chloroperoxybenzoic acid (MCPBA) in refluxing dichloromethane solution for 4 h gave a mixture of the 5β,6β and 5α,6α epoxides, **6** and **11**, respectively, and a small amount (12%) of the epoxy-lactone **12**. The mixture comprised the major product **6** (71%) and the 5α,6α epoxide **11** (only 9%). The assignment of structures to the epimeric epoxides was initially based on the observations of Cross (9) and Halsall *et al.* (10) of the C-6 proton chemical shift values of other 5β,6β and 5α,6α epoxides. The major product had the lower field chemical shift value for the C-6 proton and was assigned structure **6**. Nuclear Overhauser effect difference (NOED) experiments on both epoxides were in agreement with this assignment. Separate, selective irradiation of both the α and β C-4 methyl groups of the 5α,6α epoxide at δ 0.93 and 1.36, respectively, each enhanced the C-6 proton signal at δ 3.10 (16% and 3%, respectively). By contrast, only when the α C-4 methyl group of the 5β,6β epoxide at δ 0.94 was irradiated was there any enhancement of the C-6 proton signal at δ 3.32 (20%). No corresponding enhancement was observed when the β C-4 methyl group at δ 1.33 on **6** was irradiated.



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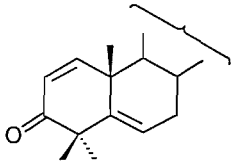
Brynjolffssen *et al.* (11) reported obtaining a 60% yield of **11** when they treated **9** with MCPBA in refluxing dichloromethane. The melting point and NMR data of what they presumed to be the 5α,6α epoxide were identical with our data for **6**. In addition to our NOE data, direct proof by X-ray crystallographic analysis was obtained. Although both **6** and **11** were crystalline, only crystals of **11** were suitable for X-ray crystallography. The structure obtained[3] confirmed our original assignment that **11** was indeed that 5α,6α epoxide and that the assignment of Brynjolffssen *et al.* was incorrect. Using their conditions **11** was obtained only as a minor product. The major product was different from the expected 5β,6β epoxide **6**. Spectral and mass data of this compound were consistent with it being the epoxy-lactone **12**. Compound **12** is most likely formed by a Baeyer–Villager oxidation of **6** since the MCPBA used is in excess.



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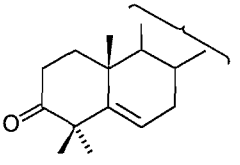

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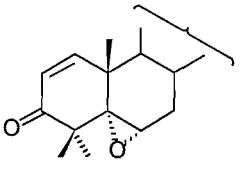

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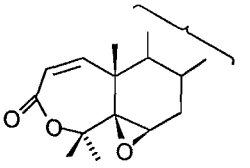

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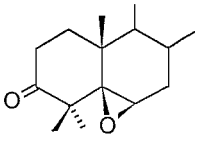

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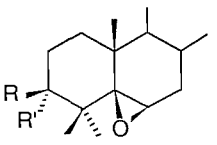
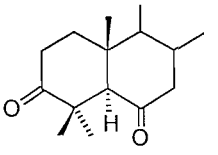


14*a*: R=H; R'=OH
14*b*: R=OH; R'=H



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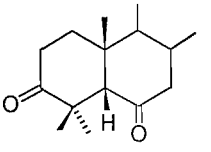


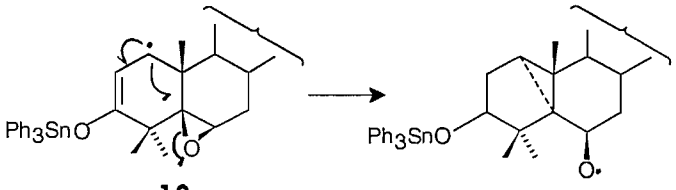
16

Epoxide **6** was reacted with lithium in liquid ammonia under several different conditions, each giving the same results. These were mixtures that could be separated by flash chromatography to afford 5β,β-epoxy-4,4-dimethylcholestan-3-one (**13**), and a mixture of the corresponding epimeric 3α and 3β alcohols **14***a* and **14***b*. Reaction of **6** with ytterbium in liquid ammonia (12) gave the same results as were found with lithium in liquid ammonia. Thus, although the α,β-unsaturated carbonyl system could be reduced, presumably via the dicarbanion **8**, cyclization to **7** via transannular opening of the epoxide did not occur.

The desired intramolecular cyclization can be envisioned as an example of a favoured 3-*exo-tet* or 5-*exo-tet* ring closure (13). It is possible, however, that cyclization did not occur because pyramidalization of the carbanion at C-1 was preferentially formed on the β-face as a result of interactions (14) with the σ-framework.

Reductions employing sodium or lithium in ethylamine can yield different results than when they are employed in liquid ammonia (15, 16). Hallsworth and Henbest (16) found that the course of reductive ring opening of 5β,6β-epoxycholestane could be altered when ethylamine was used with

[3]X-ray crystallographic analysis on **11** confirmed the assigned structure (P. E. Georghiou, Y. Ren, and J. N. Bridson, unpublished data).



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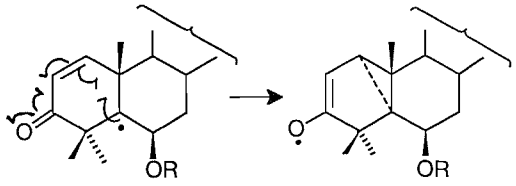
SCHEME 2

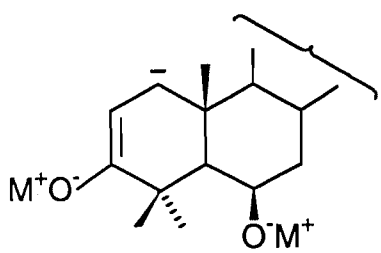


SCHEME 3

lithium. They proposed that the C-5 carbanion was formed directly by the reductive ring opening of the epoxide under these conditions.

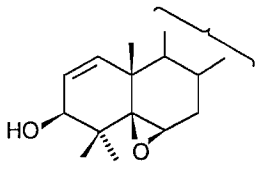
Epoxide **6** was therefore treated with lithium in ethylamine at 0°C. A more complex mixture was obtained than those from the corresponding lithium – liquid ammonia reductions. The mixture could be simplified considerably by oxidation with pyridinium chlorochromate (PCC) to afford only three compounds, none, however, being the desired cyclosteroid. The compounds identified were the C-5 epimeric 4,4-dimethylcholestane-3,6-diones (**15**, **16**) and 4,4-dimethylcholest-5-en-3-one (**10**). The 5α dione **15** was the major product (50%). The 5β dione **16** was obtained in 32% yield. Thus, both the α,β-unsaturated carbonyl system and the epoxide were reduced under these conditions.

The complex mixture that was initially formed resulted from the fact that a new stereogenic centre at C-3 is produced and two of the existing ones at C-5 and C-6 are modified during the reduction. PCC oxidation removed the two stereogenic centres at C-3 and C-6 by converting the epimeric alcohols into the corresponding ketones. That **10** was obtained indicated that an elimination of the epoxy oxygen had also occurred during this reaction. Hallsworth and Henbest (17) reported an analogous finding with 5β,6β-epoxycholesterol under similar conditions. In our case, reduction of the epoxide ring was observed but it is likely that the α,β-unsaturated ketone was reduced more rapidly, thereby precluding the intramolecular Michael addition of a C-5 carbanion. Carbanion formation at C-5 would not be inhibited as was presumed to have been the case with 5β,6β-epoxycholesterol (17) because the enolate oxyanion at C-3 of the intermediate **17** is sufficiently distant from C-5. However, it is recognized that the desired cyclization in this case would have required a type of ring closure that can be viewed as being both a disfavoured 5-*endo-trig* and a favoured 3-*exo-trig* type.



17

Triphenyltin hydride (TPTH) and tri-*n*-butyltin hydride (TBTH) reduce α,β-unsaturated ketones via a radical mechanism (18, 19). It was therefore of interest to determine whether a radical-induced intramolecular cyclization (20) could be effected with our system via a tin enolate radical **18** (see Scheme 2). When a dilute solution of **6** was treated with TPTH and azobisisobutyronitrile (AIBN), a mixture of four compounds was obtained. The major product surprisingly was the epoxide **19** (76%), followed by the keto-epoxide **13** (14%) and small amounts (3 and 4%, respectively) of the corresponding epoxide ring-opened products, the dihydroxy **20** and the hydroxy-ketone **21**. The fact that **20** and **21** were obtained, albeit in small amounts, indicated that the epoxide ring could be opened by TPTH/AIBN.



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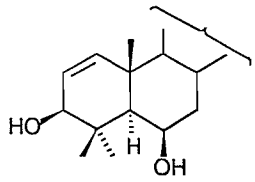

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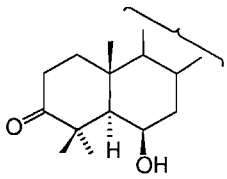

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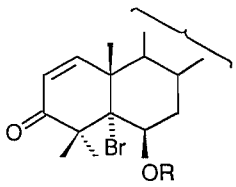
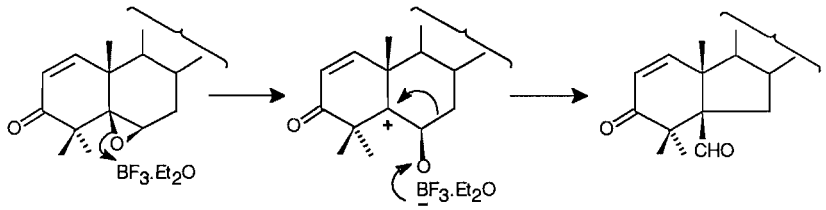


22 R = H
23 R = Ac

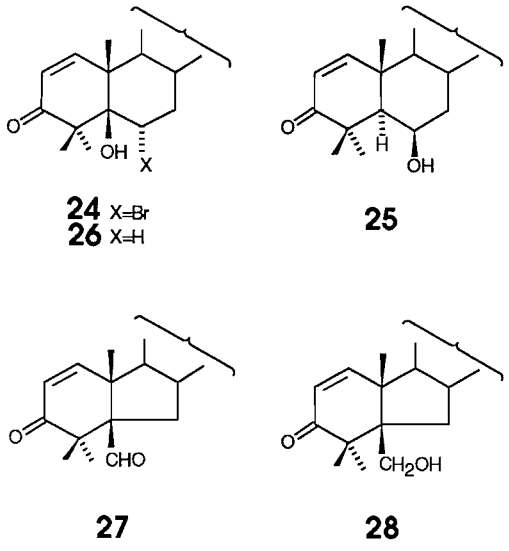
Since we were unable to effect transannular cyclization using reductive methods on the α,β-unsaturated ketone-epoxide **6**, we explored the potential for a more typical radical cyclization–coupling (21) route as depicted in Scheme 3. Reaction of **6** with HBr in acetic acid gave the bromohydrin **22**, its corresponding acetate **23**, and the 6α-bromo-5β-hydroxy bromohydrin **24**. Since the bromohydrins were unstable the crude bromohydrin mixture was isolated and, without purification, was treated with TBTH/AIBN in dilute refluxing benzene. The resulting product mixture consisted of three compounds whose spectral properties are consistent with the structures **21**, **25**, and **26**, and an unstable fourth compound that could not be characterized. The major product (48%) was identical with **21**, indicating that the bromine atom of the bromohydrin could indeed be removed by TPTH to afford a radical at C-5 but that it did not add internally to the α,β-unsaturated ketone at C-1—C-3. It is possible that the α,β-unsaturated ketone was reduced first. However, as **25** and **26** were also isolated, this could imply that radical formation occurred at C-5 from bromohydrin **21** and at C-6 from bromohydrin **24**, respectively, whilst the α,β-unsaturated ketone was still present. Cycli-



SCHEME 4

zation could apparently not be effected under these conditions either, for similar reasons to those proposed above for **17**. Compound **26** was presumably formed from **24**, which would have been formed as the minor product of the HBr-induced ring opening of **6**. Compound **26** was found to be inert to PCC oxidation, confirming the presence of a tertiary hydroxy group. It is interesting that when the 5β,6β epoxide group was present as in **6**, the major product of TPTH reduction was that in which the C-3 carbonyl group was reduced. Without the epoxide group present, however, normal reduction of the carbon–carbon double bond was preferred.

The reaction of **6** with BF_3·etherate was also examined during the course of our investigations. A mixture of several compounds was obtained, the major one (77%) being the *B*-nor-enone-5β aldehyde **27** presumably formed via a pinacol-type rearrangement. A similar *B*-nor keto-aldehyde was obtained by Halsall *et al.* (10) and Blunt *et al.* (23) with



5β,6β-epoxy-4,4-dimethylcholestan-3-one **13**. These authors, however, did not unambiguously assign the stereochemistry to the aldehyde at C-5.

Since the crystals of **27** that were obtained were not suitable for X-ray crystallography, NOED experiments on **27** were undertaken. Irradiation of the signal due to the aldehyde proton at δ 9.57 enhanced the signals due to both the C-19 methyl and the β C-4 methyl groups by 1%. This evidence ruled out the possibility of an α configuration for the aldehyde group since in this case only the 4α-methyl could be expected to be positively enhanced. However, since the C-19 and β C-4 methyl signals overlap and only a small NOED was observed, the aldehyde **27** was selectively reduced with $NaBH_4$ to the corresponding carbinol **28**. NOED experiments on **28** confirmed the structure assigned. Irradiation of the signal due to the methylene protons of the carbinol group at δ 3.71 enhanced the signals due to the C-19 methyl group at δ 1.21 and the β C-4 methyl group at δ 1.09 by 1.7 and 2.3%, respectively. A likely mechanism for the formation of **27** can be envisioned in Scheme 4, and is in agreement with the mechanism proposed by Blunt *et al.* (23).

In summary, we have shown that epoxidation of 4,4-dimethylcholesta-1,5-dien-3-one with MCPBA leads to the formation of 5β,6β epoxide **6** as the major product. This is in contrast to what was previously reported by others. We were unable to transform this epoxide into the corresponding 1α,5α cyclosteroid **7** using several alternative reductive methods. It is likely that the α,β-unsaturated carbonyl system undergoes reduction more rapidly than intramolecular cyclization occurs, or that the cyclization is reversible, favouring the uncyclized carbanion **8**, or radical **18**.

Experimental

Melting points (mp) were determined on a Fisher–Johns apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Mattson Polaris FT instrument. Mass spectral (MS) data were from a V.G. Micromass 7070HS instrument. ^{1}H NMR spectra were recorded with a GE GN-3OONB spectrometer at 300 MHz. ^{13}C NMR spectra were recorded with the same instrument at 75.47 MHz. The solvents used are noted in the experimental details. Proton nuclear Overhauser effect difference (NOED) spectra were obtained from zero-filled 32K data tables to which a 1–2 Hz exponential line-broadening function had been applied. A set of four "dummy" scans was employed to equilibrate the spins prior to data acquisition. No relaxation delay was applied between successive scans of a given frequency. Ultraviolet (UV) spectra were determined on a Unicam SP.8OO ultraviolet spectrophotometer. Microanalyses were performed by the Canadian Microanalytical Service Ltd., Delta, B.C.

5β,6β-Epoxy-4,4-dimethylcholest-1-en-3-one (6) and 5α,6α-epoxy-4,4-dimethylcholest-1-en-3-one (11)

A solution of dienone **9** (8) (1.05 g, 2.55 mmol) in 20 mL CH_2Cl_2 was refluxed under argon. *m*-Chloroperoxybenzoic acid, 50–60% (865 mg, 2.76 mmol), in 20 mL CH_2Cl_2 was added dropwise over 0.5 h. The mixture was stirred at reflux for 4 h. The solution was extracted with ether (×4) and the combined organic layers were washed with 10% $NaHCO_3$ (×3) and saturated NaCl (×4), dried ($MgSO_4$), and concentrated. Chromatography (10% benzene in hexane over aluminium oxide, Grade III) yielded the lactone **12** (142 mg, 12%), 5β,6β epoxide **6** (776 mg, 71%), and 5α,6α epoxide **11** (99 mg, 9%). For **6**, mp 101–102°C; $\nu_{max}(CCl_4)/cm^{-1}$: 1687 (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$): 0.67(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.86(3H, d, J = 6.6 Hz, 27-Me), 0.90(3H, d, J = 6.5 Hz, 21-Me), 1.77–1.90(1H, m), 0.94(3H, s, 4α-Me), 1.27(3H, s, 19-Me), 1.33(3H, s, 4β-Me), 2.01(1H, dt, J = 3.4, 12.7 Hz), 2.14(1H, ddd, J = 2.2, 4.3, 14.9 Hz, 7-H), 3.32(1H, s, 6-H), 5.93(1H, d, J = 10.5 Hz, 2-H), 6.90(1H, d, J = 10.5 Hz, 1-H); m/z(%): 426(65, M^+), 398(25), 383(15), 356(10), 339(4), 295(5), 247(17), 161(19), 136(82), 107(58), 81(61), 43(100). Anal. calcd. for $C_{29}H_{46}O_2$: C 81.63; H, 10.87%; found C 81.79 H 10.44%. For α-epoxide **11**, mp 132.0–

135.0°C; $\nu_{max}(CCl_4)/cm^{-1}$: 1681(α,β-unsaturated ketone); δ_H(300 MHz; $CDCl_3$): 0.65(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.86(3H, d, J = 6.6 Hz, 27-Me), 0.90(3H, d, J = 6.6 Hz, 21-Me), 0.93(3H, s, 4α-Me), 1.31(3H, s, 19-Me), 1.36(3H, s, 4β-Me), 3.10(1H, d, J = 3.6 Hz, 6-H), 6.00(1H, d, J = 10.3 Hz, 2-H), 7.11(1H, d, J = 10.3 Hz, 1-H); m/z(%): 426(21, M^+), 411(9), 383(13), 365(4), 343(3), 300(3), 275(10), 247(15), 43(100). Anal. calcd. for $C_{29}H_{46}O_2$: C 81.63; H, 10.87%; found C 81.69 H 10.79%.

*5β,6β-Epoxy-4,4-dimethyl-4-oxa-*A*-homocholest-1-en-3-one lactone (**12**)*

A solution of dienone **9** (51 mg, 0.12 mmol) in 10 mL CH_2Cl_2 was refluxed under argon. *m*-Chloroperoxybenzoic acid, 50–60% (300 mg, ca. 0.96 mmol), in 10 mL CH_2Cl_2 was added dropwise over 0.5 h. The mixture was stirred at reflux for 12 h. The solution was extracted with ether (×4) and the combined organic layers were washed with 10% $NaHCO_3$ (×3) and saturated NaCl (×4), dried ($MgSO_4$), and concentrated. Chromatography (10% benzene in hexane over aluminium oxide) yielded the lactone **12** (27 mg, 48%), and a mixture containing 5α,6α epoxide **11** (6 mg, 12%). For lactone **12**, mp 177.5–178.5°C; $\nu_{max}(CCl_4)/cm^{-1}$: 1754 (ε-lactone); δ_H(300 MHz; $CDCl_3$): 0.64(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.86(3H, d, J = 6.6 Hz, 27-Me), 0.89(3H, d, J = 6.6 Hz, 21-Me), 1.19(3H, s, Me), 1.31(3H, s, Me), 1.40(3H, s, Me), 1.77–1.90(1H, m), 1.98(1H, dt, J = 3.4, 12.6 Hz), 2.13(1H, dt, J = 3.2, 14.0 Hz, 7-H), 3.20(1H, br d, J = 1.9 Hz, 6-H), 5.19(1H, d, J = 7.3 Hz, 2-H), 6.26(1H, d, J = 7.3 Hz, 1-H); m/z(%): 442(1, M^+), 427(3), 399(13), 371(10), 353(2), 329(3), 287(3), 262(7), 175(6), 153(25), 123(40), 43(100). Anal. calcd. for $C_{29}H_{46}O_3$: C 78.68; H, 10.47%; found C 78.24 H 10.09%.

*5β,6β-Epoxy-4,4-dimethylcholestan-3-one (**13**)*

Freshly condensed ammonia (30 mL, dried over sodium at −78°C) was allowed to distill into a stirring suspension of lithium (20 mg, 2.9 mmol) in anhydrous THF (5 mL) at −78°C and the stirring continued until the metal had dissolved. A solution of 5β,6β epoxide (**6**) (190 mg, 0.45 mmol) in anhydrous THF (5 mL) was added dropwise over 1 h and the solution stirred at −78°C for another 1 h. Sufficient NH_4Cl was added to discharge the blue colour and the ammonia was allowed to evaporate. Upon the addition of 30 mL of ether and 20 mL of water the aqueous layer was extracted with ether. The combined ether solutions were washed, dried, and evaporated as usual. Chromatography of the residue and gradient elution with hexane – ethyl acetate yielded 5β,6β-epoxy-4,4-dimethylcholestan-3-one (**13**) (124 mg, 65%) and a mixture of the corresponding epimeric 3α and 3β alcohols **14*a***, **14*b*** (48 mg, 25%). For compound **13**, mp 197.0–198.0°C (needles from hexane–methanol (lit. (10) mp 197–200°C); $\nu_{max}(CCl_4)/cm^{-1}$: 1716 (saturated ketone); δ_H(300 MHz; $CDCl_3$): 0.64(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.87(3H, d, J = 6.6 Hz, 27-Me), 0.87(3H, s, Me), 0.89(3H, s, Me), 0.90(3H, d, J = 6.4 Hz, 21-Me), 1.21(3H, s, Me), 1.78–1.90(1H, m), 1.98(1H, dt, J = 3.4, 12.5 Hz), 2.01–2.06(2H, m), 2.15(1H, dt, J = 3.2, 14.2 Hz, 7-H), 2.40–2.58(2H, m), 3.07(1H, s, 6-H); m/z(%): 428(32, M^+), 400(15), 385(10), 343(14), 330(9), 301(2), 273(4), 247(9), 137(100), 107(47), 81(50), 55(94).

*PCC oxidation of **14**a and **14**b*

The mixture of the epimeric 3α and 3β alcohols **14*a*** and **14*b*** (40 mg, 0.09 mmol) was suspended in anhydrous CH_2Cl_2 (10 mL) and pyridinium chlorochromate (41 mg, 0.19 mmol) was added in one portion to the stirred solution. After 2 h the reaction solution was put on the top of a short silica gel column and was washed by a sufficient amount of ether. Evaporation of the ether yielded 5β,6β-epoxy-4,4-dimethylcholestan-3-one (**13**) (34 mg, 84%).

*Hydrogenation of 5β,6β epoxide **6***

To a solution of 5β,6β epoxide **6** (51 mg, 0.12 mmol) in ethyl acetate (100 mL) was added Pd–C (5%, 15 mg) and the mixture stirred under a H_2 atmosphere (1 atm; (= 101.3 kPa)) for 2 h. The reaction solution was applied onto a silica gel column and eluted with sufficient ether. Evaporation of the ether gave 5β,6β-epoxy-4,4-dimethylcholestan-3-one (**13**) in quantitative yield.

*Reaction of **6** with lithium–ethylamine*

Lithium (108 mg, 15.5 mmol) was added to a solution of 5β,6β epoxide **6** (200 mg, 0.47 mmol) in ethylamine (anhydrous, 99%, 15 mL) with stirring at 0°C. The mixture was stirred at 0°C for 1.5 h and then moist ether was added to discharge the blue colour. After the addition of 30 mL of ether and 20 mL of water the aqueous layer was extracted with ether. The combined ether solutions were washed, dried, and evaporated as usual. Thin-layer chromatography (TLC) showed the residue to be a complex mixture that was difficult to separate. The crude residue was suspended in CH_2Cl_2 (10 mL) and PCC (700 mg, 3.25 mmol) and CH_3COONa (200 mg, 2.44 mmol) were added together in one portion to the stirred solution. After 2 h the reaction mixture was placed directly onto a short silica gel column and was eluted with ether. Evaporation of the ether yielded a mixture of three major products. Silica gel chromatography using a gradient solvent system of hexane – ethyl acetate gave 4,4-dimethylcholest-5-en-3-one (**10**) (21 mg, 11%), 4,4-dimethyl-5α-cholestane-3,6-dione (**15**) (100 mg, 50%), and 4,4-dimethyl-5β-cholestane-3,6-dione (**16**) (65 mg, 32%). For **15**, mp 139.5–140.5°C (plates from acetone–methanol) (lit. (10) mp 141–142°C); $\nu_{max}(CCl_4)/cm^{-1}$: 1714 (saturated ketones); δ_H(300 MHz; $CDCl_3$): 0.68(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.87(3H, d, J = 6.6 Hz, 27-Me), 0.91(3H, d, J = 6.5 Hz, 21-Me), 1.12(3H, s, Me), 1.13(3H, s, Me), 1.50(3H, s, Me), 1.95(1H, t, J = 12.5 Hz, 7α-H), 2.22(1H, ddd, J = 2.8, 4.2, 14.4 Hz, 2α-H), 2.31(1H, dd, J = 4.2, 12.5 Hz, 7β-H), 2.40(1H, s, 5-H), 2.81(1H, dt, J = 5.9, 14.6 Hz, 2β-H); m/z(%): 428 (37, M^+), 413(9), 400(3), 371(35), 315(9), 273(11), 262(4), 231(9), 165(40), 137(67), 43(100). For **16**, mp 118–119°C (lit. (10) mp 112–114°C); $\nu_{max}(CCl_4)/cm^{-1}$: 1707 (saturated ketones); δ_H(300 MHz; $CDCl_3$): 0.67(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.87(3H, d, J = 6.6 Hz, 27-Me), 0.91(3H, d, J = 6.5 Hz, 21-Me), 0.96(3H, s, Me), 1.15(3H, s, Me), 1.17(3H, s, Me), 1.93–2.09(3H, mm), 2.38(1H, d, J = 1.5 Hz, 5-H), 2.44(1H, t, J = 4.2 Hz), 2.50(1H, dd, J = 1.7, 4.2 Hz). m/z(%): 428(17, M^+), 400(5), 373(2), 331(100), 302(3), 273(10), 247(8), 191(15), 83(62), 43(74).

*Epimerization of **16** to **15***

To a solution of **16** (20 mg) in dry methanol (50 mL) was added sodium and and the mixture was stirred at room temperature for 3 h. Water (10 mL) was added in to quench the reaction. The solution was extracted with ether and the combined ether layers were washed, dried, and evaporated to gave the 5α epimer **15** in quantitative yield.

*Reaction of 5β,6β epoxide **6** with triphenyltin hydride*

A solution of 5β,6β epoxide **6** (113 mg, 0.265 mmol) in dry benzene (50 mL) was refluxed under argon while triphenyltin hydride (TPTH) (435 mg, 1.24 mmol) and a trace amount of AIBN (7 mg, 0.04 mmol) in dry benzene (30 mL) was added dropwise over 20 h. The mixture was stirred at reflux for 50 h. A small amount of water was then added to quench the reaction. The residue obtained after evaporating the solvent was placed directly onto a silica gel column. Elution, first with pure benzene, removed the TPTH derivatives completely. Subsequent elution using a hexane – ethyl acetate gradient solvent system gave, in the following order: 5β,6β-epoxy-4,4-dimethylcholestan-3-one (**13**) (15 mg, 14%); 6β-hydroxy-4,4-dimethylcholestan-3-one (**21**) (5 mg, 4%); 3β-hydroxy-5β,6β-epoxy-4,4-dimethylcholest-1-ene (**19**) (87 mg, 76%); and 3β,6β-dihydroxy-4,4-dimethylcholest-1-ene (**20**) (3 mg, 3%). For **19**, mp 158.0–159.0°C; $\nu_{max}(CCl_4)/cm^{-1}$: 3632, 3611 (O-H); δ_H(300 MHz; $CDCl_3$): 0.63(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.86(3H, d, J = 6.8 Hz, 27-Me), 0.88(3H, s, Me), 1.02(3H, s, Me), 1.08(3H, s, Me), 1.76–1.88(1H, m), 1.96(1H, dt, J = 3.4, 12.6 Hz), 2.14(1H, ddd, J = 2.1, 4.4,

14.8 Hz, 7-H), 3.28(1H, s, 6-H), 4.08(1H, s, 3-H), 5.50(1H, dd, J = 1.4, 10.4 Hz, 2-H), 5.87(1H, dd, J = 2.5, 10.4 Hz); m/z(%): 428(9, M^+), 410(8), 395(4), 360(7), 331(3), 273(2), 227(3), 175(7), 121(43), 95(52), 43(100). Anal. calcd. for $C_{29}H_{48}O_2$: C 81.25, H 11.29%; found: C 81.37, H 11.18%. For **20**, $\nu_{max}(CCl_4)/cm^{-1}$: 3624 (two free O-H); δ_H(300 MHz; $CDCl_3$): 0.70(3H, s, 18-Me), 0.86(3H, d, J = 6.6Hz, 26-Me), 0.86(3H, d, J = 6.6 Hz, 27-Me), 0.91(3H, d, J = 6.5 Hz, 21-Me), 1.09(3H, s, Me), 1.14(3H, s, Me), 1.28(3H, s, Me), 1.76(1H, s, 5α-H), 1.78–1.83(2H, m), 2.01(1H, dt, J = 3.4, 12.6 Hz), 3.81(1H, d, J = 8.2 Hz, 3-H), 4.41(1H, s, 6-H), 5.36(1H, dd, J = 1.6, 10.4 Hz, 1-H), 5.74(1H, dd, J = 2.3, 10.4 Hz, 2-H). For **21**, mp 152.5–153.5°C; $\nu_{max}(CCl_4)/cm^{-1}$: 3621(free O-H), 1707(saturated ketone); δ_H(300 MHz, $CDCl_3$): 0.71(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.87(3H, d, J = 6.6 Hz, 27-Me), 0.91(3H, d, J = 6.5 Hz, 21-Me), 1.15(3H, s, Me), 1.38(3H, s, Me), 1.43(3H, s, Me), 1.68(1H, s), 1.75–1.86(3H, mm), 1.95(1H, ddd, J = 3.0, 6.0, 13.1 Hz), 2.01(1H, dt, J = 3.3, 12.8 Hz), 2.26(1H, ddd, J = 3.0, 4.6, 14.9 Hz, 2-H), 2.76(1H, dt, J = 6.0, 14.6, 14.6 Hz, 2-H), 4.34(1H, s, 6-H); m/z(%): 430(4, M^+), 412(18), 397(4), 357(4), 327(3), 257(12), 187(17), 145(15), 107(27), 81(36), 43(100). Anal. calcd. for $C_{29}H_{50}O_2$: C 80.87, H 11.70%; found: C 81.00, H 11.54%.

Sodium borohydride reduction of 5β,6β epoxide ***6***

To a solution of **6** (100 mg, 0.24 mmol) in methanol (30 mL) was added $NaBH_4$ (53 mg, 1.4 mmol) and $CeCl_3 \cdot 7H_2O$ (100 mg, 0.27 mmol). The mixture was stirred at room temperature for 45 min before a small amount of water was added to quench the reaction. The mixture was extracted with ether and the combined ether layers were washed, dried, and evaporated as usual. Silica gel chromatography of the residue and elution with a hexane – ethyl acetate gradient solvent system yielded 3β-hydroxy-5β,6β-epoxy-4,4-dimethylcholest-1-ene (**19**) (89 mg, 87%).

PCC oxidation of hydroxy-ketone ***21***

To a solution of 6β-hydroxy-4,4-dimethylcholestan-3-one (**21**) (10 mg, 0.024 mmol) in anhydrous CH_2Cl_2 (10 mL) was added PCC (10 mg, 0.049 mmol) in one portion and the mixture was stirred at room temperature for 2 h. The reaction solution was placed onto a silica gel column and was eluted with ether. Evaporation of the ether yielded 4,4-dimethyl-5α-cholestane-3,6-dione (**15**) (9 mg, 92%).

Preparation of bromohydrin acetate ***23***

To a solution of **6** (100 mg, 0.24 mmol) in dry glacial acetic acid (10 mL) with stirring at 10°C was added a solution of hydrogen bromide (3.7%) in acetic acid (9 mL, 0.41 mmol) by syringe over 30 min. After stirring at 10°C for 8 h, the reaction mixture was poured onto ice-water and extracted with ether. The combined ether layers were washed, dried, and evaporated as usual. Silica gel chromatography of the residue and elution with a hexane – ethyl acetate gradient solvent system afforded **6** (89 mg, 85%), bromohydrin acetate **23** (13 mg, 10%), and a compound (5 mg) whose structure was not determined. For **23**, mp 180–182°C (needles from acetone–water); $\nu_{max}(CCl_4)/cm^{-1}$: 1747(ester carbonyl), 1692(α,β-unsaturated ketone); δ_H(300 MHz, $CDCl_3$): 0.73(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.87(3H, d, J = 6.6 Hz, 27-Me), 0.92(3H, d, J = 6.5 Hz, 21-Me), 1.45(3H, s, Me), 1.52(3H, s, Me), 1.69(3H, s, Me), 2.09(1H, dt, J = 3.3, 12.8 Hz), 2.14(3H, s, acetate methyl), 2.20–2.34(2H, m), 5.59(1H, br s, 6-H), 5.94(1H, d, J = 10.3 Hz, 2-H), 6.83(1H, d, J = 10.5 Hz, 1-H); m/z(%): 426(2, M^+-Br,CH_3CO), 410(7), 408(8), 395(3), 393 (6), 367(3), 365(5), 339(5), 337(2), 149(11), 147(8), 81(38), 79(24), 43(100).

In-situ *reaction of* ***21*** *with triphenyltin hydride*

To a solution of **6** (100 mg, 0.24 mmol) in dry glacial acetic acid (10 mL) with stirring at 10°C was added a solution of hydrogen bromide (3.7%) in glacial acetic acid (0.8 mL, 0.37 mmol) by syringe over 30 min. After stirring at 10°C for 90 min, the reaction mixture was poured onto ice-water. The precipitate was filtered and washed with ice-water to remove all traces of acetic acid. The colourless residue was vacuum-dried and then was dissolved in dry benzene (50 mL) and refluxed. Tri-*n*-butyltin hydride (TBTH) (97%, 0.06 mLl, 0.22 mmol) in dry benzene (10 mL), and a catalytic amount of AIBN were then added dropwise over 1 h. The mixture was stirred at reflux for 2 h. A small amount of water was added to the reaction solution to quench the reaction. The residue after evaporation of the solvent was placed directly onto a silica gel column. Elution, first with pure benzene removed the TBTH derivatives. Subsequent elution with the hexane – ethyl acetate gradient solvent system gave 6β-hydroxy-4,4-dimethylcholestan-3-one (**21**) (49 mg, 48%), 6β-hydroxy-4,4-dimethyl-5α-cholest-1-en-3-one (**25**) (3 mg, 3%), 5β-hydroxy-4,4-dimethylcholest-1-en-3-one (**26**) (18 mg, 18%), and an unstable compound (17 mg, 17%). For **25**, $\nu_{max}(CCl_4)/cm^{-1}$: 3622 (free O-H), 1676 (α,β-unsaturated ketone); δ_H(300 MHz, $CDCl_3$): 0.74(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.87(3H, d, J = 6.6 Hz, 27-Me), 0.92(3H, d, J = 6.5 Hz, 21-Me), 1.22(3H, s, Me), 1.39(3H, s, Me), 1.41(3H, s, Me), 1.64(1H, d, J = 1.4 Hz, 5-H), 1.77–1.90(2H, m), 2.07(1H, dt, J = 3.3, 3.3, 12.9 Hz, 8-H), 4.40(1H, s, 6-H), 5.82(1H, d, J = 10.3 Hz, 2-H), 6.97(1H, d, J = 10.3 Hz, 1-H). For **26**, $\nu_{max}(CCl_4)/cm^{-1}$: 3626(free O-H), 1686(α,β-unsaturated ketone); δ_H(300 MHz, $CDCl_3$): 0.70(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.86(3H, d, J = 6.6 Hz, 27-Me), 0.91(3H, d, J = 6.5 Hz, 21-Me), 1.22(3H, s, Me), 1.30(3H, s, Me), 1.37(3H, s, Me), 2.03(1H, dt, J = 3.3, 12.9 Hz), 2.14(1H, ddd, J = 2.1, 4.5, 14.1 Hz), 5.88(1H, d, J = 10.5 Hz, 2-H), 6.56(1H, d, J = 10.4 Hz, 1-H).

*4,4-Dimethyl-3-oxo-*B*-norcholest-1-ene-5-carboxaldehyde (27)*

To a solution of **6** (110 mg, 0.26 mmol) in dry benzene (5 mL) with stirring at room temperature was added boron trifluoride etherate (0.1 mL, 0.8 mmol) by syringe. After stirring at room temperature for 30 min, the reaction mixture was quenched by pouring into $NaHCO_3$ solution (3%) and extracted with ether. The combined ether extracts were washed, dried, and evaporated as usual. Silica gel chromatography using the hexane – ethyl acetate gradient solvent system yielded the *B*-nor aldehyde **27** (86 mg, 77%), and two other products that could not be characterized due to their instability. For **27**, mp 103.5–104.5°C (plates from ethanol–water); $\nu_{max}(CCl_4)/cm^{-1}$: 1729 (aldehyde), 1688 (α,β-unsaturated ketone); δ_H(300 MHz, $CDCl_3$): 0.64(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.86(3H, d, J = 6.6 Hz, 27-Me), 0.91(3H, d, J = 6.5 Hz, 21-Me), 1.04(3H, s, 4β-Me), 1.04(3H, s, 19-Me), 1.11(1H, dd, J = 11.2, 13.0 Hz, 7-H), 1.17(3H, s, 4α-Me), 1.83–1.90(1H, m), 2.04(1H, dt, J = 2.8, 12.9 Hz), 2.41(1H, dd, J = 7.0, 13.0 Hz, 7-H), 5.94(1H, d, J = 10.2 Hz, 2-H), 6.63(1H, d, J = 10.2 Hz, 1-H), 9.57(1H, s, 6-H); HRMS for $C_{29}H_{46}O_2$, calcd.: 426.3495; found: 426.3495; m/z(%): 426(7, M+), 397(7), 356(5), 313(3), 261(9), 243(3), 149(35), 43(100). Anal. calcd. for $C_{29}H_{46}O_2$: C 81.63, H 10.87%; found: C 81.51, H 10.78%.

Sodium borohydride reduction of 27

To a solution of the *B*-nor aldehyde **27** (51 mg, 0.12 mmol) and $CeCl_3 \cdot 7H_2O$ (56 mg, 0.15 mmol) was added $NaBH_4$ in small portions over 4 h until the starting material almost disappeared according to TLC. The reaction mixture was stirred at room temperature for an additional hour before a small amount of water was added to quench the reaction. The reaction mixture was extracted with ether and the combined ether layers were washed, dried, and evaporated as usual. Chromatography of the residue and elution with the hexane – ethyl acetate gradient solvent system gave 5β-hydroxymethyl-4,4-dimethyl-*B*-norcholest-1-en-3-one (**28**) (45 mg, 88%). For **28**, mp 150–151°C; $\nu_{max}(CCl_4)/cm^{-1}$: 3630 (free O-H), 3493 (intermolecular and weakly bonded O-H), 1685

(α,β-unsaturated ketone); δ_H(300 MHz, $CDCl_3$): 0.66(3H, s, 18-Me), 0.86(3H, d, J = 6.6 Hz, 26-Me), 0.87(3H, d, J = 6.6 Hz, 27-Me), 0.92(3H, d, J = 6.5 Hz, 21-Me), 1.09(3H, s, 4β-Me), 1.12–1.16(1H, m, 7α-H), 1.21(3H, s, 19-Me), 1.22(3H, s, 4α-Me), 1.35(1H, br s, 7β-H), 1.65–1.75(1H, m), 1.81–1.93(1H, m), 2.04(1H, dt, J = 3.2, 12.8 Hz, 12β-H), 3.71(2H, br s, 6-methylene), 5.82(1H, d, J = 10.2 Hz, 2-H), 6.54(1H, d, J = 10.2 Hz, 1-H); m/z(%): 428(23.6, M^+), 413(8), 410(7), 398(14), 397(34), 385(7), 358(22), 261(12), 166(14), 149(43), 121(66), 43(100). Anal. calcd. for $C_{29}H_{48}O_2$: C 81.25, H 11.29%; found: C 81.05; H 11.17%.

Acknowledgements

The authors wish to express their sincerest appreciation to Dr. C. R. Jablonski and Ms. N. Brunet for their generous contributions in the form of numerous high-quality high-resolution nmr spectra. We thank Dr. D. J. Burnell for many suggestions and for his ongoing encouragement, Dr. B. Gregory and Ms. M. Baggs for their mass spectral contributions, and Dr. J. N. Bridson for X-ray crystallographic analyses. The Department of Chemistry and Memorial University are thanked for their financial assistance in the form of graduate student support to one of us (Y.R.).

1. S. B. Laing and P. J. Sykes. J. Chem. Soc.(C), 421 (1968).
2. S. B. Laing and P. J. Sykes. J. Chem. Soc.(C), 653 (1968).
3. S. B. Laing and P. J. Sykes. J. Chem. Soc.(C), 937 (1968).
4. P. E. Georghiou and G. Just. J. Chem. Soc. Perkin Trans. 1, 70 (1973).
5. J. R. Christensen and W. E. Reusch. J. Org. Chem. **48**, 3741 (1983).
6. P. E. Georghiou, Y. Ren, and J. N. Bridson. J. Org. Chem. **58**, 827 (1993).
7. D. Caine. Org. React. **23**, 1 (1976).
8. D. H. Barton, D. J. Lester, and S. V. Ley. J. Chem. Soc. Perkin Trans. 1, 2209 (1980).
9. A. D. Cross. J. Am. Chem. Soc. **84**, 3206 (1962).
10. T. G. Halsall, E. R. H. Jones, E. L. Tan, and G. R. Chaudhry. J. Chem. Soc.(C), 1374 (1966).
11. J. Brynjolffssen, J. Midgley, and W. B. Whalley. J. Chem. Soc. Perkin Trans. 1, 812 (1977).
12. J. D. White and G. L. Larson. J. Org. Chem. **43**, 4555 (1978).
13. J. E. Baldwin. J. Chem. Soc. Chem. Commun. 738 (1976).
14. S. K. Pradhan. Tetrahedron, **42**, 6351 (1986).
15. R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas. J. Am. Chem. Soc. **77**, 3230 (1975).
16. A. S. Hallsworth and H. B. Henbest. J. Chem. Soc. 4604 (1957).
17. A. S. Hallsworth and H. B. Henbest. J. Chem. Soc. 3571 (1960)
18. M. Pereyre, J.-P. Quintard, and A. Rahm. Tin in organic synthesis, Butterworths, Kent. 1987, and references therein.
19. H. Laurent, P. Esperling, and G. Baude. Liebigs Ann. Chem. 1996 (1983).
20. V. H. Rawal, R. C. Newton, and V. Krishnamurthy. J. Org. Chem. **55**, 5181 (1990).
21. V. M. A. Chambers, W. R. Jackson, and G. W. Young. J. Chem. Soc.(C), 2075 (1971).
22. P. E. Georghiou and M. A. MacDiarmid. Can. J. Chem. **58**, 1759 (1980).
23. J. W. Blunt, M. P. Hartshorn, and D. N. Dirk. J. Chem. Soc. (C), 635 (1968).