J. Am. Chem. Soc. 1994, 116, 186–197

Corner Opening of Cyclopropanes by Mercury(II) and Thallium(III) and Transmetalation of the Intermediate Organomercurials. A Novel, Stereoselective Approach to Cyclobutanes and Cyclopropanes

Pavel Kočovský,*,[†] Jiří Šrogl,[†] Milan Pour,[‡] and Adolf Gogoll[§]

Contribution from the Department of Chemistry, University of Leicester, Leicester LE1 7RH, England, Research School of Chemistry, Australian National University, Canberra ACT 2601, Australia, and Department of Organic Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala, Sweden

Received July 19, 1993[⊗]

Abstract: The reactivity of the two isoelectronic cations (Hg^{2+} and Tl^{3+}) toward the cyclopropane ring is compared, and further evidence for the exclusive corner selectivity for Hg^{2+} is provided by isotope labeling. Cleavage of cyclopropyl derivative **1** with $Hg(NO_3)_2$, followed by KBr quenching, afforded the stable, rearranged organomercurial **3**, whose transmetalation has been studied. Whereas reaction of **3** with Pd(II) afforded lactol **4**, treatment with Me_2CuLi resulted in the formation of cyclobutanol derivative (**3** → **29**); analogous conjugate addition has also been accomplished (**32** → **35**). Similarly, the organomercurial **22**, obtained from **21** as the major product on the Hg(II)-mediated ring-opening, reacted with Me_2CuLi or $AlCl_3$ to give the ring-closure product **21**. These reactions represent a novel method for the stereoselective construction of four- and three-membered rings. The stereochemistry of the key steps of these transformations has been established by using stereospecifically deuterated substrates **1b**, **3b**, **21b**, and **22b**.

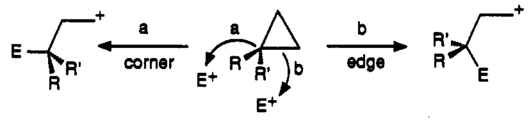
Introduction

Activation of organic substrates by both transition and nontransition metals[1] has the promise of controlling reactivity, enhancing selectivity and efficiency of chemical transformations, and achieving synthetic goals that cannot be attained by traditional methods.[2] Further avenues can be opened by transmetalation,[1,3] a methodology that combines (often in one pot) the benefits of specific reactivities of two or more metals in tandem reactions.

Stereocontrolled cyclopropanation,[4,5] catalyzed by various metals,[6] followed by ring-opening,[4] is an attractive strategy for construction of up to three contiguous chiral centers.[2] However, the mechanism of cleavage of the cyclopropane ring was only little understood until very recently,[7] which has considerably hampered a wider synthetic application of this reaction.

Revitalization of interest in cyclopropane scission in the last few years has led to defining certain relations between the mechanism and the reagent employed.[7] Thus, electrophilic opening by reagents capable of back-donation, such as transition metals (Pd, Pt, and Rh)[8] and halogens (Cl and Br),[9] is now known to occur via a stereospecific "edge" attack, resulting in retention of configuration at the carbon to which the electrophile becomes linked (Scheme 1). Alternative "corner" opening has also been considered,[7,10] but there was a lack of direct evidence in support of this mechanism and this issue has been a subject of controversy. Using double isotopic labeling (^2H and ^{18}O), we have recently shown, for the first time, that thallium(III) is capable of stereospecific "corner" activation and have decribed a unique skeletal rearrangement (Scheme 2) of 3α,5-cyclo-5α-cholestan-6α-ol (**1** → **2** → **4**).[11] While this project was in progress, exclusive "corner" opening was also observed with other poor back-donors, namely, with a proton[12] and with mercury(II).[12–14]

Scheme 1



[†] University of Leicester.

[‡] Australian National University.

[§] University of Uppsala.

[⊗] Abstract published in *Advance ACS Abstracts*, December 15, 1993.

(1) (a) Davies, S. G. *Organotransition Metal Chemistry. Applications to Organic Synthesis*; Pergamon Press: Oxford, 1983. (b) Yamamoto, A. *Organotransition Metal Chemistry. Fundamental Concepts and Applications*; J. Wiley: New York, 1986. (c) Harrington, P. J. *Transition Metals in Total Synthesis*; J. Wiley: New York, 1990.

(2) (a) Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC Press: Boca Raton, FL, 1986; Vols. I and II. (b) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; J. Wiley: New York, 1989. (c) Morrison, J. D., Ed. *Asymmetric Synthesis*; Academic Press: New York, 1983–1985; Vols. 1–5. (d) Bartman, W., Trost, B. M., Eds. *Selectivity—a Goal for Synthetic Efficiency*; Verlag Chemie: Weinheim, 1984 (e) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320.

(3) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Application of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

(4) Rappoport, Z., Ed. *The Chemistry of the Cyclopropyl Group*; J. Wiley and Sons: London, 1987.

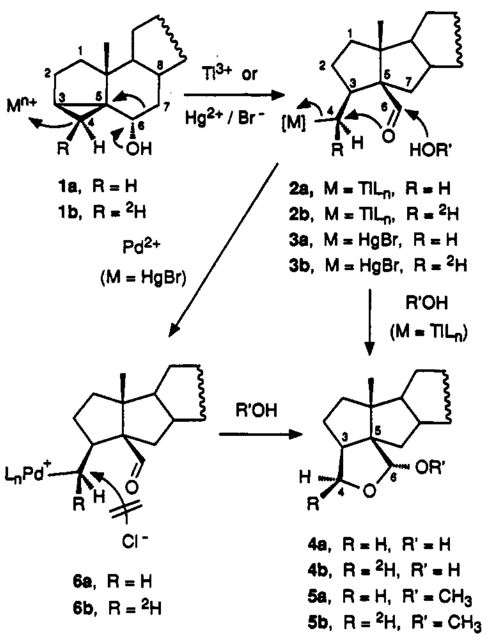
(5) (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (b) Ginsig, R.; Cross, A. D. *J. Am. Chem. Soc.* **1965**, *87*, 4629. (c) Wiechert, R.; Engelfried, O.; Kerb, U.; Laurent, H.; Müller, H.; Schulz, G. *Chem. Ber.* **1966**, *99*, 1118. (d) Dauben, W. G.; Laug, P.; Berezin, G. H. *J. Org. Chem.* **1966**, *31*, 3869. (e) Ellison, R. H. *J. Org. Chem.* **1980**, *45*, 2509. (f) Mohamadi, F.; Still, W. C. *Tetrahedron Lett.* **1986**, *27*, 893 and references cited therein. (g) Molander, G. A.; Etter, J. B.; *J. Org. Chem.* **1987**, *52*, 3942. (h) Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745. (i) Winkler, J. D.; Gretler, E. A. *Tetrahedron Lett.* **1991**, *41*, 5733. (j) Sugimura, T.; Katagiri, T.; Tai, A. *Tetrahedron Lett.* **1992**, *33*, 367. (k) Hamdouchi, C. *Tetrahedron Lett.* **1992**, *33*, 1701. (l) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(6) (a) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839 and references cited therein. (b) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553. (c) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 60. (d) Pfaltz, A. *Bull. Soc. Chim. Belg.* **1990**, *99*, 729. (e) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (f) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (g) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373. (h) O'Malley, S.; Kodadek, T. *Tetrahedron Lett.* **1991**, *32*, 2445. (i) Carfanga, C.; Mariani, L.; Musco, A.; Sallese, G.; Santi, R. *J. Org. Chem.* **1991**, *56*, 3924. (j) Cimetière, B. *Synlett* **1991**, 271. (k) Gai, Y.; Julia, M.; Verpeaux, J.-N. *Synlett* **1991**, 269. (l) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron lett.* **1992**, *33*, 2575. (m) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1992**, *57*, 798. (n) Maxwell, J. L.; O'Malley, S.; Brown, K. C.; Kodadek, T. *Organometallics* **1992**, *11*, 645. (o) O'Malley, S.; Kodadek, T. *Organometallics* **1992**, *11*, 2299. (p) Koskinen, A. M. P.; Hassila, H. *J. Org. Chem.* **1993**, *58*, 4479.

(7) (a) Coxon, J. M.; Battiste, M. A. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; J. Wiley and Sons: London, 1987; Chapter 6. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245.

0002-7863/94/1516-0186$04.50/0

Scheme 2



Herein we compare the reactivity of the two isoelectronic cations (Tl^{3+} and Hg^{2+}) in cyclopropane ring-opening, offer further evidence for the preferential corner selectivity for Hg^{2+}, and report on the outcome of transmetalation with various metals (Pd, Li, and Cu) of the stable organomercurials arising from the cyclopropane opening. In this study we have employed three readily available cyclopropyl derivatives **1**, **7**, and **21**.

Results

Cyclopropane Ring-Opening by Hg(II) and Tl(III) in Steroidal Derivative 1. Treatment of steroidal cyclopropyl alcohol[15] **1a** with $Hg(NO_3)_2\cdot H_2O$ in DME–CH_3CN (2:5) at room temperature for 1.5 h led, after KBr workup, to a single product **3a**[16] in 97% isolated yield (Scheme 2).[21] In contrast to the Tl(III)-mediated reaction,[11] where the organothalliated species **2a** undergoes an instantaneous conversion to lactol **4a**, the organomercurial **3a** could be isolated as a stable compound.

This reaction appears to be unique as it is limited solely to Hg^{2+} and Tl^{3+} (strong, soft Lewis acids[22]). Other isoelectronic cations (Au^+ and Pb^{4+}) and those of high redox potential as well as other ions (Ce^{4+}, Cu^+, Cu^{2+}, Ag^+, Mn^{3+}, Al^{3+}, In^{3+}, and Ti^{4+}) were found either to be inert or to convert **1a** to cholesterol or its esters (acetate, nitrate, etc.). Cholesteryl tosylate was formed on reaction with PhI(OH)OTs. Transition metals, such as Pd, Pt, and Rh, turned out either to be inert (presumably due to steric hindrance in **1**) or to trigger a rearrangement to cholesteryl derivatives (e.g. with $PdCl_2$) at higher temperature and prolonged reaction time. The latter reaction can be ascribed to the inherent acidity of $PdCl_2$.

Mechanism of Hg(II)-Mediated Ring-Opening in Cyclopropyl Alcohol 1 and Transmetalation of Hg for Pd in Organomercurial 3. We assumed that the stereochemistry of cyclopropane fission could be established in a way analogous to that which we have employed for thallium,[11] i.e. by using stereospecifically deuterated cyclopropyl alcohol **1b**.[23] To this end, we needed to assign the NMR signals of the two diastereotopic protons at C(4) in the product of cleavage. In the spectrum of **3a**, they appeared at 1.93 ppm (dd, J = 8.7 and J = 11.7 Hz) and 2.05 (dd, J = 8.1 and J = 11.7 Hz), respectively. However, the similarity in their coupling constants was suggestive of relatively free rotation about the C(3)–C(4) bond so that the assignment was not possible at this stage.[26] Hence, transformation of **3a** to a compound in which the C(3)–C(4) bond was conformationally fixed was required. After much experimentation, Pd(II) was found to convert **3a** to lactol **4a** or acetal **5a** (via **6a**), in which 4α-H and 4β-H were easily identified.[27] Similarly, excess of Br_2 (or NBA) transformed **3a** to the corresponding lactone.

Having found the means for an unequivocal assignment of the NMR signals for the two protons at C(4), we could now carry out experiments with labeled compounds. Stereospecifically labeled cyclopropyl derivative **1b** was treated with $Hg(NO_3)_2\cdot H_2O$ and quenched with aqueous KBr in the same way as was the unlabeled analogue **1a**. Analysis of the ^1H NMR spectrum of the product **3b** revealed the absence of the lower field resonance (2.05 ppm), while the upfield signal at 1.93 ppm was changed to a doublet (J = 8.7 Hz). This indicated that the reaction was stereohomogeneous (≥98%). Catalytic reaction with Li_2PdCl_4 (5 mol %; generated from $PdCl_2$ and LiCl) and $CuCl_2$ (5 equiv) in DME/H_2O, which is assumed to proceed with retention of

---

(8) (a) Dominelli, N.; Oehlschlager, A. C. *Can. J. Chem.* **1977**, *55*, 364. (b) Green, M.; Hughes, R. P. *J. Chem. Soc., Dalton Trans.* **1976**, 1880. (c) Wilhelm, D.; Bäckvall, J.-E.; Nordberg, R. E.; Norin, T. *Organometallics* **1985**, *4*, 1296 and references cited therein. (d) Bäckvall, J.-E.; Björkman, E. E.; Petersson, L.; Siegbahn, P.; Strich, A. *J. Am. Chem. Soc.* **1985**, *107*, 7408. (e) Nielsen, W. D.; Larsen, R. D.; Jennings, P. W. *J. Am. Chem. Soc.* **1988**, *110*, 8657. (f) Hoberg, J. O.; Larsen, R. D.; Jennings, P. W. *Organometallics* **1990**, *9*, 1334. (g) Hoberg, J. O.; Jennings, P. W. *Organometallics* **1992**, *11*, 3452. (h) Ikura, K.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 1520. (i) Stewart, F. F.; Neilsen, W. D.; Ekeland, R. E.; Larsen, R. D.; Jennings, P. W. *Organometallics* **1993**, *12*, 4585. (j) With strongly positive Pd reagents, competition of edge and corner pathways can be encountered in certain instances: Blomberg, M. R. A.; Siegbahn, P. E. M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1987**, *109*, 4450.

(9) Lambert, J. B.; Chelius, E. C.; Schulz, W. J., Jr.; Carpenter, M. E. *J. Am. Chem. Soc.* **1990**, *112*, 3156.

(10) (a) Baird, R. L.; Aboderin, A. A. *J. Am. Chem. Soc.* **1964**, *86*, 252. (b) Collum, D. B.; Mohamadi, F.; Hallock, J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6882. (c) Rood, I. D. C.; Klump, G. W. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 303. (d) Wiberg, K. B.; Kass, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 988. (e) Battiste, M. A.; Coxon, J. M. *Tetrahedron Lett.* **1986**, *27*, 517. (f) Dewar, M. J. S.; Healy, E. F.; Ruiz, J. M. *J. Chem. Soc., Chem. Commun.* **1987**, 943. (g) Koch, W.; Liu, B.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 3479. For an alternative, closely related zigzag mechanism, see: (h) Yamabe, S.; Minato, T.; Seki, M.; Inagaki, S. *J. Am. Chem. Soc.* **1988**, *110*, 6047.

(11) Kočovský, P.; Pour, M.; Gogoll, A.; Hanuš, V.; Smrčina, M. *J. Am. Chem. Soc.* **1990**, *112*, 6735.

(12) (a) Coxon, J. M.; Steel, P. J.; Whittington, B. J.; Battiste, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 2988; *J. Org. Chem.* **1989**, *54*, 1383. (b) Coxon, J. M.; Steel, P. J.; Whittington, B. I. *J. Org. Chem.* **1990**, *55*, 4136.

(13) Lambert, J. B.; Chelius, E. C.; Bible, R. H., Jr.; Hajdu, E. *J. Am. Chem. Soc.* **1991**, *113*, 1331.

(14) DePuy, C. H.; McGuirk, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 2366.

(15) Wagner, A. F.; Wallis, E. S. *J. Am. Chem. Soc.* **1950**, *72*, 1047.

(16) The structure was determined by NMR spectra using H,H-COSY, P.E. COSY, and NOESY,[17] HMQC, HSQC, and multiple bond HSQC,[18], HMBC,[18] and DEPT and selective INEPT.[19] ^1H NMR: 9.72 (s, 1 H, CHO). ^{13}C NMR: 34.78 (CH_2HgBr), 206.22 (CHO). ^{199}Hg NMR: −1063 ppm.[20] The full assignment of carbon signals in the ^{13}C NMR spectrum has been achieved.

(17) (a) Bax, A.; Freeman, R.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 164. (b) Mueller, L. *J. Magn. Reson.* **1987**, *72*, 191. (c) States, D. J.; Haberkorn, R. A.; Ruben, D. J. *J. Magn. Reson.* **1982**, *48*, 286.

(18) (a) Summers, M. F.; Marzilli, L. G.; Bax, A. *J. Am. Chem. Soc.* **1986**, *108*, 4285. (b) Cavanagh, J.; Hunter, C. A.; Jones, D. N. M.; Keeler, J.; Sanders, J. K. M. *Magn. Reson. Chem.* **1988**, *26*, 867. (c) Bodenhausen, G.; Ruben, D. J. *Chem. Phys. Lett.* **1980**, *69*, 185. (d) Kövér, K. E.; Prakash, O.; Hruby, V. J. *Magn. Reson. Chem.* **1993**, *31*, 231.

(19) (a) Doddrell, D. B.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323. (b) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.

(20) For typical NMR Hg-shifts of organomercurials, see, for example: Reischl, W.; Kalchhauser, H. *Tetrahedron Lett.* **1992**, *33*, 2451.

(21) Much slower reaction was observed with $(CF_3CO_2)_2Hg$; $(AcO)_2Hg$ did not react at rt at all. For Hg^{2+}, a DME–MeCN mixture was found to be superior to dioxane, which, in turn, was the solvent of choice for Tl(III).[11]

(22) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223.

(23) Deuterated **1b** was prepared in four steps[11] from 4β-^2H-cholesterol.[24,25]

(24) Nambara, T.; Ikegawa, S.; Ishizuka, T.; Goto, J. *J. Pharm. Bull.* **1974**, *22*, 2656.

(25) For recent synthesis of 4α-^2H-cholesterol, see: Rabinowitz, M. H. *Tetrahedron Lett.* **1991**, *32*, 6081.

(26) Chemical correlation carried out with deuterated compounds (see below) allowed the two signals to be assigned *post festum*: the upfield resonance to *pro*-(*S*)-H and the downfield signal to *pro*-(*R*)-H.

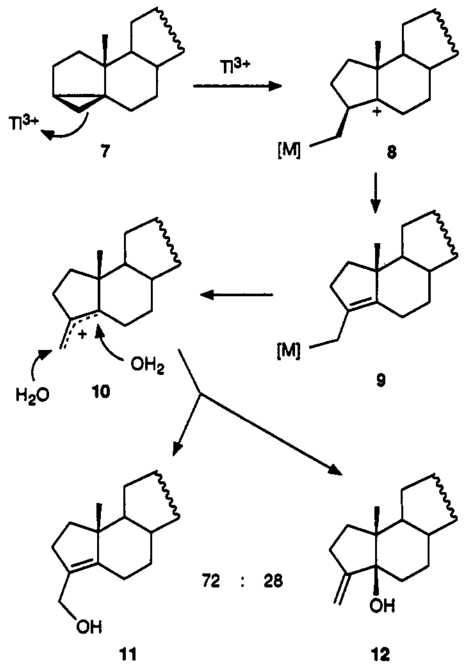
(27) In the ^1H NMR spectrum of unlabeled **4a** the 4α-H appears at 4.17 ppm (dd, J = 8.6 and 9.1 Hz) and 4β-H at 3.40 ppm (dd, J = 8.6 and 4.9 Hz); the upfield signal exhibits an NOE (0.2%) with the acetal proton (δ 5.17), while the downfield signal shows an NOE (15%) with 3α-H.

configuration[28,29] via **6b**, furnished lactol **4b**, while in the presence of MeOH, methyl acetal **5b** was formed. A stoichiometric reaction, in which only Li_2PdCl_4 (1.1 equiv) was added, gave the same result. The configuration of deuterium as being 4β was inferred from the ^{1}H NMR spectra of the respective products: in the labeled compounds, the absence of the higher field signal (3.40 ppm) and the conversion of the lower field doublet of doublets at 4.17 ppm into a doublet (J = 9.2 Hz) are compatible only with the 4β-^{2}H configuration;[27] the other stereoisomer could not be detected.[30]

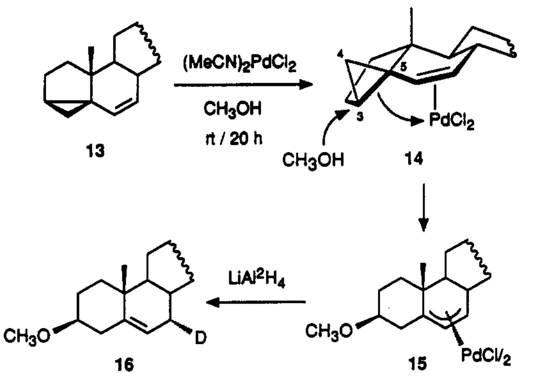
Heumann and Bäckvall have shown[28] that Pd-σ-complexes generated, for example, from organomercurials by the $PdCl_2/CuCl_2$ method undergo S_N2 substitution by Cl^- to give alkyl chlorides. Hence, lactol **4b** could be conjectured to arise from the initially formed chloride by a second inversion. To rule out this possibility, the reaction was run under the chloride-free conditions, with a stoichiometric amount of palladium triflate, generated *in situ* from $(AcO)_2Pd$ and CF_3SO_3H. The product (**4b**) was identical with that formed by the $PdCl_2/CuCl_2$ method. Apparently, the intramolecular S_N2 substitution is highly favored in **6** by the steric arrangement which suppresses the intervention of Cl^-.[31,32,34] These experiments thus provided conclusive evidence for the mechanism of the whole sequence and showed that opening of the cyclopropane ring in **1** by Hg(II) occurred solely in a *corner* fashion.

Cyclopropane Ring-Opening by Hg(II) and Tl(III) in Steroidal Hydrocarbon 7. In the absence of the 6α-hydroxy group, as in the hydrocarbon **7**, the reaction with $(AcO)_2Hg$ has been reported to proceed via a simple ring-opening followed by elimination to give the acetate of the corresponding allylic alcohol **11** (Scheme 3).[35] The reaction was believed to be initiated by an *edge* attack of Hg(II).[35] In light of the evidence accumulated by us and by other investigators,[12-14] this interpretation seems doubtful. Now, we have found that Tl(III) reacts in a similar way, giving a 72:28 mixture of allylic alcohols **11** and **12**,[36] presumably via allylic cation **10**.[38] These reactions demonstrate that the presence of the 6α-hydroxy group is not a prerequisite for the regioselective cleavage between the most (C-5) and the least substituted (C-4) carbon of the cyclopropyl ring. The initial formation of the most stable carbocation **8** appears to be the driving force for the reaction. While here the elimination (**8** → **9**) seems to be the energetically cheapest subsequent process, in the case of cleavage of **1** the initial ring-opening is followed by Wagner–Merrwein migration of C-7.

Scheme 3



Scheme 4



Cyclopropane Ring-Opening by Pd(II) in Cyclopropyl Olefin 13. While on treatment with Pd(II) cyclopropyl alcohol **1a** gave only cholesteryl derivatives due to preferential attack on hydroxyl (see above), hydrocarbon **7** was either inert to the same reagents (at room temperature) or afforded an intractable mixture of lipophilic products (at elevated temperature). On the other hand, introduction of a double bond in the 6,7-position, as in **13**, had a dramatic effect (Scheme 4).[39] Thus, on treatment with $(CH_3CN)_2PdCl_2$ in methanol at room temperature for 20 h, **13** was converted into the η^3-complex **15** (93%). The structure of **15** was corroborated by combination of spectral methods (namely NMR) and chemical correlation: reduction of **15** with $LiAl^2H_4$ (which is assumed to proceed stereoselectively via a syn-delivery of hydride from Pd)[1] afforded deuterated olefin **16**, for which the 7α-^{2}H configuration was confirmed by the coupling constant $J_{6\text{-H},7\beta\text{-H}}$ = 5.4 Hz. The ring-opening in **13** is apparently boosted by initial coordination of Pd(II) to the double bond (**14**) and occurs via an edge attack on the C(3)–C(5) bond.

Mercury(II)-Mediated Ring-Opening in Cyclopropyl Derivative 21. In order to further explore the reactivity of the cyclopropane

---

(28) Heumann, A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 207.

(29) (a) Bäckvall, J.-E. *Tetrahedron Lett.* **1977**, 467. (b) Bäckvall, J.-E.; Åkermark, B.; Ljungren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411. (c) Bäckvall, J.-E.; Nordbegr, R. E. *J. Am. Chem. Soc.* **1980**, *102*, 393. (d) Bäckvall, J.-E.; Björkman, E. J.; Pettersson, L.; Siegbahn, P. *J. Am. Chem. Soc.* **1984**, *106*, 4369; **1985**, *107*, 7265.

(30) The bromine-mediated conversion of **3b** to the corresponding lactone turned out to be nonstereospecific, producing a 1:1 mixture of the C(4)-epimers.

(31) For assessment of the intramolecular nucleophilicities of various functional groups, see, for example: (a) Kočovský, P.; Stieborová, I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1969. (b) Kurth, M. J.; Beard, R. L.; Olmstead, M.; Macmillan, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3712.

(32) Nucleophilic S_N2-type displacement of the palladium appears to be a common reaction and is well documented.[28,29] Another mechanism for the formation of **4** from **6**, which would involve the carbonyl oxygen coordination to Pd followed by reductive elimination, is extremely unlikely in light of the results of Bäckvall[28,29] and others.[33]

(33) (a) Wieber, G. M.; Hegedus, L. S.; Åkermark, B.; Michalson, E. T. *J. Org. Chem.* **1989**, *54*, 4649. (b) Åkermark, B.; Zetterberg, K. *J. Am. Chem. Soc.* **1984**, *106*, 5560. (c) Hegedus, L. S.; Åkermark, B.; Zetterberg, K.; Olsson, L. F. *J. Am. Chem. Soc.* **1984**, *106*, 7122. (d) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474. (e) Brown, J. M.; James, A. P. *J. Chem. Soc., Chem. Commun.* **1987**, *181*. (f) Brown, J. M.; Maddox, P. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1277.

(34) In the presence of a π-acid (maleic anhydride, *p*-benzoquinone, acrylonitrile, or 2-cyclohexenone), the reaction takes a different course: Kočovský, P.; Šrogl, J.; Gogoll, A.; Hanuš, V.; Polášek, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1086.

(35) Blossey, E. C. *Steroids* **1969**, *14*, 727.

(36) The structure of the products was deduced from their NMR spectra and verified by comparison with authentic samples of **11**[35] and **12**[37] prepared by the known methods.[35,37]

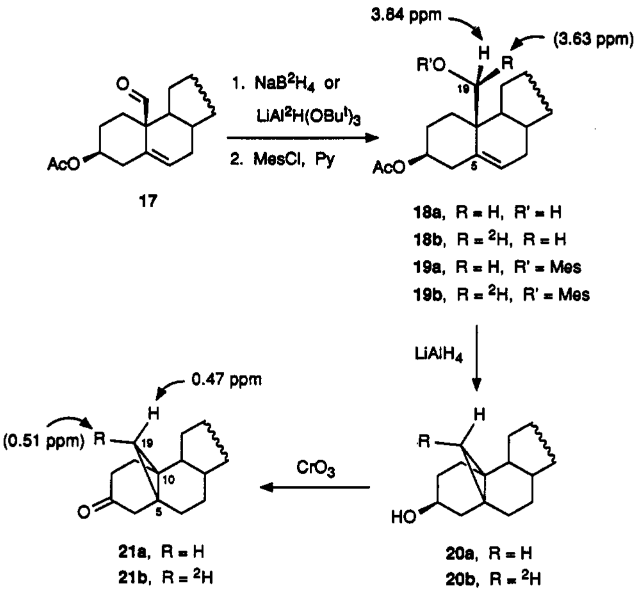
(37) Pradhan, S. K.; Girijarallabhan, V. M. *Steroids* **1969**, *13*, 11.

(38) For another Tl(III)-mediated generation of an allylic cation followed by quenching with hydroxylic solvents, see: Kočovský, P.; Langer, V.; Gogoll, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1026.

(39) Pour, M. Thesis, Charles University, Prague, 1988.

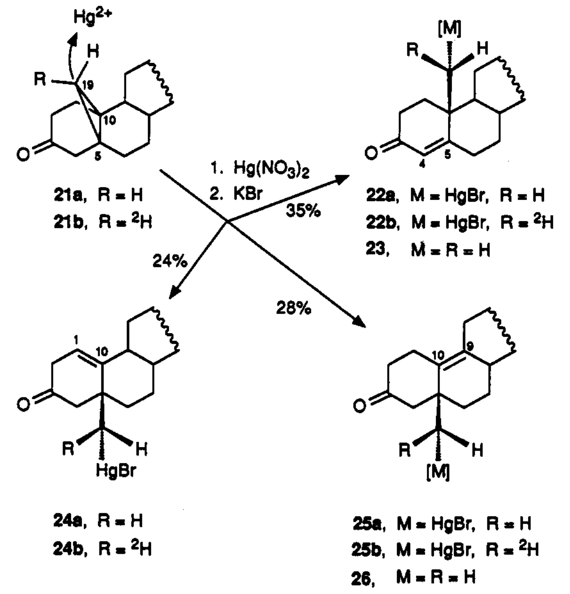
(40) Santaniello, E.; Caspi, E. *J. Steroid Biochem.* **1976**, *7*, 223.

Scheme 5[a]



[a]Mes = CH_3SO_2.

Scheme 6



ring toward Hg(II) and the transmetalation of the resulting organomercurials, another model compound has been synthesized, namely, **20** (Scheme 5).[40] In this case, preferential cleavage of the C(5)–C(19) and/or C(10)–C(19) bond was anticipated[41] in accordance with the apparently general regioselectivity observed, e.g., with **1** (the bond between the most and the least substituted carbon). This cleavage would create an electron-deficient center at C(5) and/or C(10), whose stabilization by proton elimination could produce up to four isomeric olefins. In order to minimize the number of expected products, we have prepared ketone **21a** because, in this instance, the C(5)-cation should produce only a conjugated ketone. The deuterated derivative **21b** was prepared from the aldehyde **17** employing a literature procedure (Scheme 5):[40,42] reduction of aldehyde **17** with NaB^{2}H$_4$ afforded the deuterated alcohol **18b** as a 70:30 mixture of C(19)-epimers.[42] Mesylation followed by reaction with LiAlH$_4$ afforded cyclopropyl alcohol **20b**,[43] oxidation of which with Jones' reagent furnished the desired ketone **21b** as a 68:32 mixture of C(19)-epimers.[44] We have now found that the aldehyde **17** can be reduced with LiAl^{2}H(OBu^t)$_3$ (generated *in situ* from 1 mol of LiAl^{2}H$_4$ and 3 mol of *tert*-butyl alcohol) to give **18b** as an 85:15 epimeric mixture. The latter alcohol was converted to the cyclopropyl ketone **21b** (84:16) using the same procedure as before (Scheme 5).

Treatment of **21a** with Hg(NO$_3$)$_2$·H$_2$O in DME at 0 °C for 2 h led, after KBr workup, to a mixture of three olefinic organomercurials **22a**, **24a**, and **25a** (Scheme 6).[45] The structures of **22a** and **25a** were corroborated by chemical correlation: upon Bu$_3$SnH reduction, **22a** furnished the known cholest-4-en-3-one (**23**), while **25a** afforded the Westphalen-type ketone **26**, identicalwith an authentic sample.[46,47] The structure of **24a** was deduced from spectral data.[48]

The reaction of the deuterated cyclopropyl derivative **21b** with Hg(NO$_3$)$_3$ proceeded analogously giving **22b**, **24b**, and **25b**. The reaction was highly stereospecific: starting from a 68:32 mixture of **21b** and its C(19)-epimer, **22b** turned out to be a 65:35 mixture of C(19)-epimers as revealed by ^{2}H NMR; a similar composition was detected for **24b** (68:32).[49] This outcome corresponds to 96% and 100% diastereoselectivity, respectively, which is within the experimental error of the ratio determination by ^{1}H and ^{2}H NMR. Since the configuration at C(19) of these organomercurials could not be safely established from their NMR spectra, we sought a suitable chemical correlation that would address this issue. We reasoned that a stereospecific ring-closure reaction employing the carbon adjacent to mercury, as a nucleophile, and an electrophilic neighboring group (C=O or C=CC=O) might provide the required tool. Utilizing **3b** (of known configuration at C-4) as a model compound, we have therefore endeavored to find conditions under which such reactions occur.

Transmetalation of Hg for Li and Cu in Organomercurial 3 and Construction of a Cyclobutane Ring. In order to bring about an intramolecular addition to the aldehyde group which would construct a four-membered ring in a novel way, we have attempted a transmetalation of **3a** that would generate a more reactive organometallic species.[50,52] Organolithium reagents (MeLi, *n*-BuLi, and *t*-BuLi) proved unrewarding as they produced complex mixtures. We reasoned that intermediates derived from

---

(41) Langbein, G.; Siemann, H.-J.; Gruner, I.; Müller, C. *Tetrahedron* **1986**, *42*, 937.

(42) Arigoni, D.; Battaglia, R.; Akhtar, M.; Smith, T. *J. Chem. Soc., Chem. Commun.* **1975**, 185.

(43) This reaction employs π-electrons of the double bond as an internal nucleophile and has been shown to proceed via an S$_N$2-like inversion at C(19).[40,42] For nucleophiles other than H$^-$, see: (a) Tadanier, J. *J. Org. Chem.* **1966**, *31*, 2124. (b) Kojima, M.; Maeda, M.; Ogawa, H.; Nitta, K.; Ito, T. *J. Chem. Soc., Chem. Commun.* **1975**, 47. (c) Bite, P.; Moravcsik, I. *Acta Chim. Acad. Sci. Hung.* **1977**, *95*, 311.

(44) In the ^{1}H NMR spectrum of **21a** the *pro-R*-H appears at δ 0.51 (d, J = 5.7 Hz), while the *pro-S*-H at 0.47 (d). In the spectrum of **21b**, two signals appeared as singlets at 0.51 and 0.47, respectively, in a 32:68 ratio. This assignment is based on the stereochemistry of the reduction of aldehyde **17** and assuming S$_N$2 inversion at C(19) in the cyclopropane formation (**19b** → **20b**).[42,43]

(45) In contrast to **1a**, carrying the reaction in a DME–MeCN mixture resulted in the formation of a complex mixture of olefinic products, indicating that the C(10)-cation has further migrated along the backbone of the skeleton. For a review on backbone rearrangements, see: Kočovský, P. *Chem. Listy* **1979**, *73*, 583.

(46) Kočovský, P.; Černý, V. *Collect. Czech. Chem. Commun.* **1976**, *41*, 2620.

(47) The LiAlH$_4$ reduction of **22a** produced cholest-4-en-3β-ol as the major product, while **25a** afforded 19-nor-5-methyl-5β-cholest-9-en-3β-ol (ca. 60%), identical with an authentic sample,[46] along with its C(3)-epimer.

(48) Both ^{1}H and ^{13}C NMR spectra were indicative of a trisubstituted double bond; treatment with a trace of aqueous HBr led to a conjugated ketone, as revealed by UV absorption of the product.

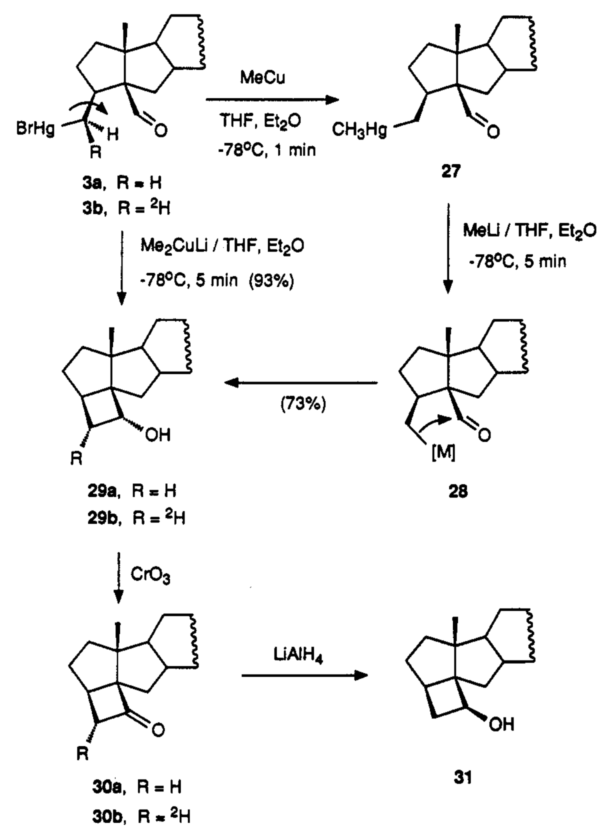
(49) The ratio was determined by integration of the signals of 19-^{2}H in the ^{2}H NMR spectrum for each pair of 19-epimers. For **22b** the ratio of 2.53 ($W/2$ = 13.8 Hz) to 2.23 ($W/2$ = 12.0) was 65:35; for **24b**, the signals at 2.42 ($W/2$ = 18.0 Hz) and 2.12 ($W/2$ = 13.8 Hz) were in a 32:68 ratio.

(50) As expected,[51] attempted radical cyclizations failed: reduction of **3a** with NaBH$_4$ or Bu$_3$SnH furnished only the corresponding demercurated alcohol. No cyclobutane ring-closure was observed.[52] For occasional reports on cyclobutane or cyclopropane formation via a radical addition, see: Jung, M.; Trunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719 and references therein.

(51) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986; p 143.

(52) Kočovský, P.; Šrogl, J. *Org. Chem.* **1992**, *57*, 4565.

Scheme 7

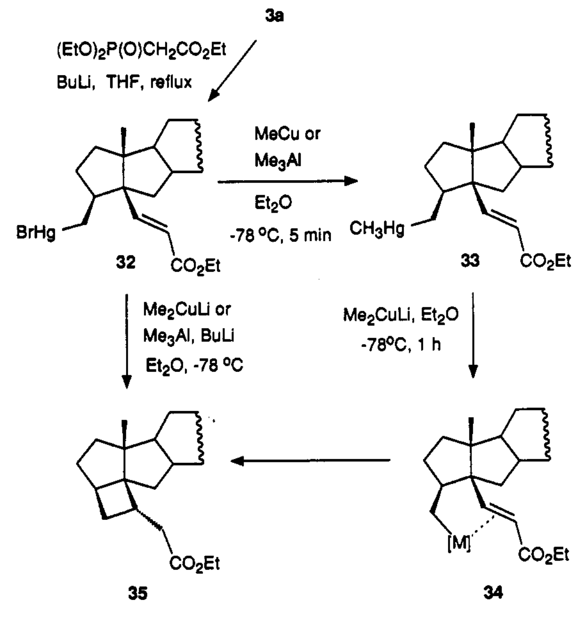


softer metals might be more promising, and after several unsuccessful attempts using various transition metals, we turned our attention to copper[53] (Scheme 7). Rather surprisingly, MeCu effected clean methylation on mercury, providing the MeHg derivative **27** (94%). This result itself may represent a new method for the preparation of dialkyl mercury derivatives RHgR′ from the readily available organomercury halides RHgBr. Other reagents that also gave high yields of **27** were Me_3Al (69%) and Me_2Zn (91%).

Subsequent treatment of **27** with MeLi at low temperature resulted in the formation of the desired cyclobutanol **29a** (73%). Alternatively, **29a** was obtained in one pot on reaction of **3a** with Me_2CuLi in an excellent yield (93%). This reaction can be understood in terms of the Lipshutz equilibrium between a cuprate and alkyllithium ($2Me_2CuLi \rightleftarrows MeLi + Me_3Cu_2Li$).[54,55]

The stereostructure of cyclobutanol **29a** was corroborated by combination of NMR spectroscopy and chemical transformations: (1) Upon irradiation of 10β-CH_3, an NOE (5.7%) was observed for C*H*OH which is compatible only with an α-configuration for the hydroxyl. (2) Alcohol **29a** was oxidized with Jones' reagent to ketone **30a**, whose $\nu_{C=O}$ = 1750 cm^{-1} was in the range typical for cyclobutanones.[57] (3) On reduction with $LiAlH_4$, ketone **30a** furnished alcohol **31**,[59] epimeric with **29a**, for which no NOE for C*H*OH and 10β-CH_3 could be observed.

Scheme 8



When deuterated organomercurial **3b** was subjected to the reaction with Me_2CuLi, a stereospecifically deuterated cyclobutanol **29b** was obtained. In this case, the 4α-configuration of deuterium was determined in ketone **30b**,[60] which was prepared from **29b** by Jones' oxidation. The ^1H NMR spectrum of **30b** also revealed a ca. 86% diastereoisomeric purity, which in view of the label content, indicates ≥90% overall retention of configuration at C(4). This result is compatible with double retention of configuration at C(4) through the whole sequence and with a mechanism for the cyclization step comprising intramolecular coordination of the metal to the carbonyl oxygen.

Having thus successfully accomplished intramolecular addition to the C═O bond to produce cyclobutanol **29**, we explored the possibility of an intramolecular conjugate addition to an activated C═C bond. The required substrate, α,β-unsaturated ester **32**, was prepared from aldehyde **3a** on Horner–Emmons olefination with $(EtO)_2P(O)CH_2CO_2Et$ and BuLi in refluxing THF (Scheme 8). Although the reaction was rather slow (reflux for 12 h) due to steric hindrance, the yield of **32** was good (73%). To our knowledge, this is the first successful Wittig-type olefination in the presence of an HgBr group in the substrate molecule.[61] The organomercurial **32** was first methylated with MeCu or Me_3Al to give **33** (in 91% and 95% yield, respectively). In contrast to **27**, however, reaction of **33** with MeLi or BuLi produced a complex mixture; Me_2CuLi proved more efficient, furnishing the desired cyclobutane derivative **35** (40%). A much better yield of **35** (75%) was obtained in one pot from **32** on reaction with Me_2CuLi. This behavior suggests that the actual reactive species **34** involves copper. Although the structure of **34** is speculative, it seems reasonable to assume[53] that M = $CuLiCH_3$ or $CuHgLiCH_3$ and that the more suitably positioned C(4) in the complex **34** adds across the double bond in preference to the CH_3 group.

---

[53] (a) For transmetalation R-HgX → R-Cu, see: Bergbreiter, D. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 4937. (b) For transmetalation ArHgX → ArLi, see for example: Wittig, G.; Bickelhaupt, F. *Chem. Ber.* **1958**, *91*, 883. (c) For a review on transmetalations in organocopper chemistry, see: Wipf, P. *Synthesis* **1993**, 537.

[54] Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197.

[55] Similarly, CH_2═$MoCl_3$, generated *in situ* from MeLi and $MoCl_5$,[56] also converted **27** to **29a** in good yield.

[56] Kauffmann, T.; Fiegenbaum, P.; Wieschollek, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 531.

[57] It is pertinent to note that the carbonyl group of ketone **30a** proved extremely hindered. Thus, for instance, attempts at Wittig or Peterson olefination were unsuccessful; only Cp_2Ti═CH_2 (Tebbe reagent)[58] was reactive enough to convert this carbonyl into an *exo*-methylene group.

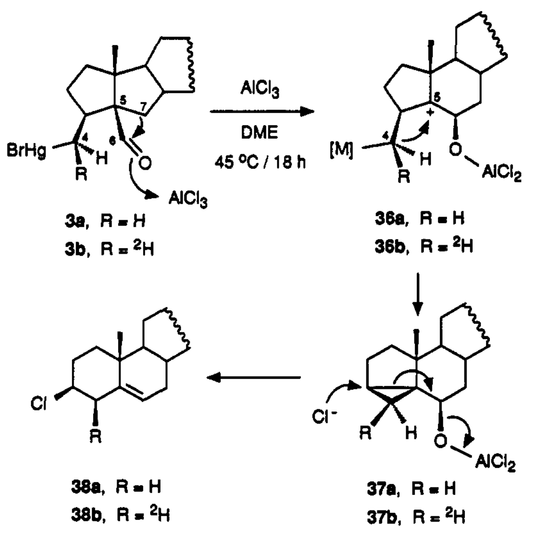
[58] (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

[59] This reduction can be easily understood as occurring from the convex side of the molecule. The resulting alcohol **31** was also reoxidized to ketone **30a** to make sure that no skeletal rearrangement had occurred on reduction.

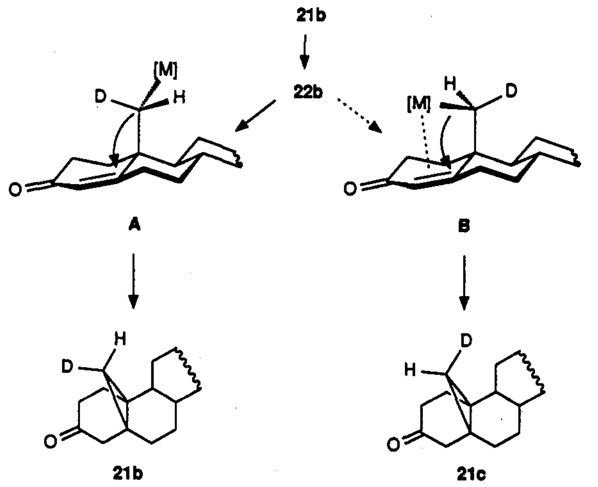
[60] The signals of C(4)-protons were much better resolved in ketone **30a** than in the parent alcohol **29a**. Thus, in the ^1H NMR spectrum of **30a**, 4α-H appears at 2.90 ppm (dd, *J* = 17.6 and 8.6 Hz), while 4β-H gives a signal at 2.61 ppm (dd, *J* = 17.6 and 6.8 Hz). In the spectrum of **30b**, the signal of 4α-H was reduced to ca. 14% relative to the 4β-H signal. In view of the total deuterium content (≥94%, as evidenced by MS) in ketone **30b**, the corrected integration of the relative intensities of 4α-H and 4β-H is indicative of a ca. 90:10 ratio of **30b** to its 4-epimer.

[61] No reaction of aldehyde **3a** was observed with Ph_3P═CHR (R = H, Me, or OMe) or with Ph_3As═CH_2, presumably due to the lower reactivity of these reagents and/or preferential coordination of P or As to Hg.

Scheme 9



Scheme 10



Finally, treatment of **33** (first generated *in situ* from **32** by means of Me$_3$Al) with Me$_3$Al/*n*-BuLi furnished **35** in 92% isolated yield.[62,63]

Stereoselective Skeletal Rearrangement of Organomercurial 3 by Means of Lewis Acids. In the previous paragraph, we have described stereoselective ring-closures (**3** → **29** and **32** → **35**) via activating the nucleophilic component in the molecule (C—Hg). Another possibility was to activate the electrophilic group (C═O) by coordination to a Lewis acid. As mentioned above, Me$_3$Al (a weak Lewis acid) only effected methylation on mercury (**3a** → **27a** and **32** → **33**). By contrast, we have now found that the reaction of **3a** with AlCl$_3$ (a strong Lewis acid) takes a completely different course, producing **38a** (Scheme 9). Similar reaction was also observed with MoCl$_5$[64] and SiCl$_4$. This unexpected outcome can be rationalized as follows: the reagent (AlCl$_3$) apparently activated the C═O group in **3a** by coordination to the oxygen. However, instead of closing a four-membered ring by reacting with the nucleophilic carbon C(4), this coordination triggered a stereoelectronically controlled Wagner–Meerwein migration of C(7) from C(5) to C(6), generating carbocation **36a**. The latter cationic species is likely to form a bond between C(4) and C(5), which may, presumably, occur with *inversion* at C(4), as suggested by the geometry of **36a** (this sequence may well be concerted). The resulting cyclopropyl intermediate **37a** subsequently collapses to cholesteryl chloride (**38a**) via the well-known[65] "*iso*-steroid" rearrangement.

The mechanism was verified by labeling. The deuterated organomercurial **3a** was treated with AlCl$_3$ in Et$_2$O as was its unlabeled counterpart. Analysis of the ^{1}H NMR spectrum of the resulting deuterated cholesteryl chloride **38b** established the configuration of deuterium as being 4β[66] and revealed that the whole reaction sequence was remarkably stereoselective, as no other diastereoisomer could be detected. The 4β-^{2}H configuration is compatible with inversion of configuration at C(4) in the C(4)–C(5) bond-forming step (**36b** → **37b**).[67]

Transmetalation of Hg for Li and Cu in Organomercurial 22 and Construction of a Cyclopropane Ring. Having found the means for the stereoselective construction of a C–C bond between the carbon adjacent to mercury and an electrophilic center (C═O, C═CC═O, or C$^+$), which worked remarkably well for **3** and **32**, we set out to explore the reactivity of the unlabeled organomercurial **22a** with the aim to close up a cyclopropane ring. To our delight, Me$_2$CuLi was found to induce cyclization, resulting in the formation of **21a** (86%). This highly efficient ring-closure represents a novel way for the construction of cyclopropyl derivatives and was also accomplished with AlCl$_3$ and/or SiCl$_4$ in good yields (93% and 80%, respectively).

Unfortunately, the cuprate-mediated cyclization of **22b** turned out to be nonstereospecific. Thus, starting from the 65:35 mixture of **22b** and its C(19)-epimer, which originated from the ring-opening of **21b** (68:32 mixture; Scheme 6), a mixture of **21b** and **21c** in a 53:47 ratio was formed (Scheme 10), as revealed by integration of the signals of cyclopropane protons in the ^{1}H NMR spectrum (singlets at 0.47 for **21b** and 0.51 for **21c**). This is in sharp contrast with the highly stereohomogeneous cyclobutane ring-closure **3b** → **29b** (Scheme 7), where no more than 10% scrambling was observed:[68] while retention of configuration at the nucleophilic carbon largely dominated the cyclobutane ring formation (Scheme 7), this pathway (**22b** → **B** → **21c**; Scheme 10) was considerably suppressed at the expense of a competing mechanism (**22b** → **A** → **21b**).

The latter mechanism would be in line with the inversion of the configuration at C(4) in the AlCl$_3$-mediated cyclopropane ring-closure **36b** → **37b**. Therefore, the cyclization of **22b** by means of AlCl$_3$ (although much slower than that with cuprate) was also explored. In this case we have observed acceptable stereoselectivity since the resulting cyclopropyl derivative turned out to be a 62:38 mixture of **21b** and **21c**, which corresponds to 95% de for the ring-closure and 91% de overall for the two-step sequence (**21b** → **22b** → **21b**). Since transmetalation of Hg for

---

[62] We believe that, in this instance, the Lewis acid (Me$_3$Al) accelerates the conjugate addition, as in its absence only a complex mixture was obtained.

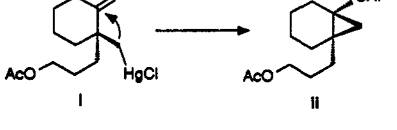
[63] Attempted radical cyclization of **32**, using NaBH$_4$ or Bu$_3$SnH, gave only the demercurated product. Attempted intramolecular Heck coupling, using various Pd(II) reagents, resulted solely in β-elimination. This is in sharp contrast to the analogous cyclizations that occur readily to produce five-membered rings.[67]

[64] Šrogl, J.; Kočovský, P. *Tetrahedron Lett.* **1992**, *33*, 5591.

[65] Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: Amsterdam, 1968.

[66] Diagnostic was the signal of 3α-H (at 3.77 ppm). While the width of this multiplet was 32.7 Hz for **38a**, in the spectrum of the deuterated compound **38b** (in which ≥95% of deuterium was revealed by HRMS) it was only 19.7 Hz, which indicated that one large (i.e. axial) coupling was missing. This is only compatible with the 4β-^{2}H configuration. Compared to the spectrum of **38a**, where the C(4)-protons appear at 2.48 (4α-H) and 2.55 (4β-H) ppm, the latter signal is absent in the spectrum of **38b**, and the former has lost its geminal coupling (13.6 Hz). For a detailed description of the ^{1}H NMR patterns in 4α-^{2}H- and 4β-^{2}H-cholesterol, see ref 25.

[67] A recent precedent suggests that the carbon atom adjacent to HgX can serve as an effective nucleophile to quench an electron-deficient center (**i** → **ii**), even in preference to the nucleophilic AcO group: Takemoto, Y.; Ohra, T.; Yonetoku, Y.; Imanishi, T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 192.



[68] Racemization has also been observed with another Hg → Cu transmetalation.[53a]

Al is unlikely, we can conclude that the crucial ring-closure occurred predominantly with inversion at C(19) (**22b** → A → **21b**; M = HgBr), which is in line with the previously observed stereochemistry (**36** → **37**; Scheme 9). In view of these mechanistic considerations we can assign a (19*S*) configuration to the organomercurial **22b** (major epimer), which is consistent with a stereospecific corner opening of the cyclopropane ring in **21b** (Scheme 6).

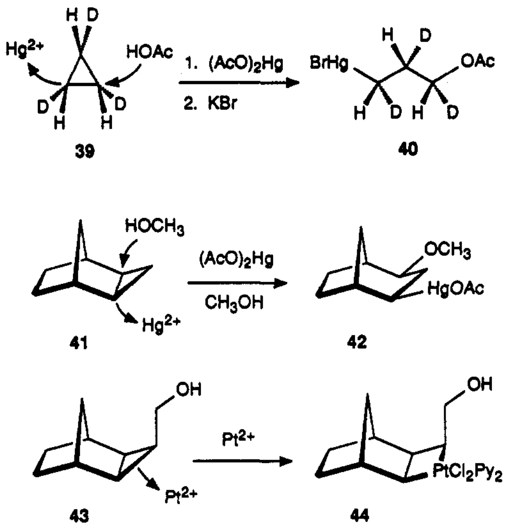
Since **21b** was recovered (after the opening and ring-closure) as a 62:38 mixture of C(19)-epimers (Scheme 10), one can possibly argue that this ratio may reflect some sort of thermodynamic equilibration rather than a stereodefined transformation. We reasoned that this issue can be addressed by carrying out the sequence of ring-opening and ring-closure again with cyclopropane derivative **21b** of higher epimeric purity (such as 84:16; see above). Treatment of the enriched derivative **21b** (84:16) with $Hg(NO_3)_2$ gave organomercurial **22b** (Scheme 6), which was converted back to **21b** on reaction with aluminum chloride. ^1H NMR analysis (namely the integration of the 19-H signals for the major and the minor isomer) revealed a 79:21 epimeric ratio. This corresponds to 94% diastereoselectivity for the two-step sequence, which is in excellent agreement with the overall stereoselectivity obtained for the lower isomeric ratio (91% de; see above). Hence, it can be concluded that the originally observed ratio reflected the stereoselectivity of the ring-closure rather than a thermodynamic equilibration. The above rationalization is thus further confirmed.

Discussion

The observed behavior of mercury(II) parallels the reactivity of thallium(III) in both the stereo- and regioselectivity of the cyclopropane ring-opening. These results also demonstrate that both metals favor *stereospecific corner opening*[69] and a *fission of the C–C bond between the most and the least substituted carbon*. This appears to be a general feature (at least for Hg) as the same reactivity has now been observed for several structurally different compounds: for **1** and **21** (this report), for the parent cyclopropane **39**[13] and its methylated counterpart[14] (Scheme 11), and for **41** (and its *endo*-annulated isomer).[12] Unfortunately, direct comparison of the reactivity of Hg and Tl with the behavior of transition metals (Pd, Pt, etc.) and Br_2 could not be made with our model compounds **1** and **21** as they either are inert to these reagents or undergo different transformations (namely the conversion to cholesterol or its derivatives; see above). However, reaction of the cyclopropyl derivative **13** with Pd(II) demonstrates that edge opening is indeed possible with our type of compounds, i.e. that the polycyclic structure itself does not preclude the reagent approach on the edge. Moreover, for example, the cyclopropyl derivative **43**, very closely related to **41** (which is known to be corner-opened[12] with Hg^{2+}), has been cleaved by Pt (a transition metal) with exclusive edge selectivity[8c] (Scheme 11). In view of this experimental evidence, we are confident that the mechanism of opening (corner or edge) is dictated by the nature of the reagent rather than by the substrate structure.

The preferential edge opening by transition metals and halogens has been attributed to the back-donation from the electrophile to the LUMO Walsh orbitals, which stabilizes the transition state.[12,13] By contrast, electrophiles incapable of back-donation (H^+, Hg^{2+}, and Tl^{3+}) cannot provide such a stabilization, which results in the preferential corner opening. This mechanism may be further boosted by simultaneous stabilization of the developing positive charge on the other carbon of the C–C bond being split via a homologous S_N2-like reaction with an external nucleophile (**39** → **40** or **41** → **42**) or by the Wagner–Meerwein migration (**1** → **2** or **3**).

Scheme 11



The two isoelectronic cations (Tl^{3+} and Hg^{2+}) not only share the same reactivity in the initial step but in the following events as well, namely, the unique skeletal rearrangement (**1** → **2** or **3**). The difference between Tl and Hg is only seen in the fate of the organometallics generated in this way. While the organomercurial **3** is fairly stable and can be isolated in pure state and used for subsequent transformations, its thalliated counterpart is more reactive and undergoes the nucleophilic ring-closure (**2** → **4**). This divergence in behavior serves as a clear example of how a choice of metal can be used for delicate control of the reactivity.

The reactions of organomercurials with MeLi or Me_2CuLi, presumably occurring via transmetalation, represent a novel methodology for cyclobutane annulation (**3** → **29** and **32** → **35**) that may be of general use in view of the rather limited number of alternative approaches[70,71] and of the failure of radical reactions. The relatively high configurational stability of the organometallic species such as **28** (at −78 °C) is noteworthy as it contrasts, for example, with the recently reported[72] isomerization of an R-Li intermediate (at −78 °C), generated from the corresponding R-SMe compound.

A remarkable dichotomy has been observed for the steric course of the C–C bond-forming ring-closure reactions: retention of configuration at the nucleophilic carbon in the formation of the cyclobutane ring induced by cuprates (Scheme 7) and a non-stereospecific reaction or predominant inversion of configuration in cyclopropane formation when cuprates or Lewis acids are used, respectively (compare Schemes 9 and 10). Since no difference in hybridization at the carbon atom adjacent to mercury has been observed for **3a** and **22a**,[73] the difference in reactivity must originate elsewhere. In the cyclobutane ring formation, one can assume frontal interaction of the σ-orbital of the C–[M] bond

---

[69] The stereostructures of the products of cyclopropane cleavage are most consistent with the corner activation. However, an initial edge attack cannot rigorously be excluded, provided that the initially formed edge-metalated intermediate quickly stereomutates to the corner-metalated species via a trigonal bipyramid.[13]

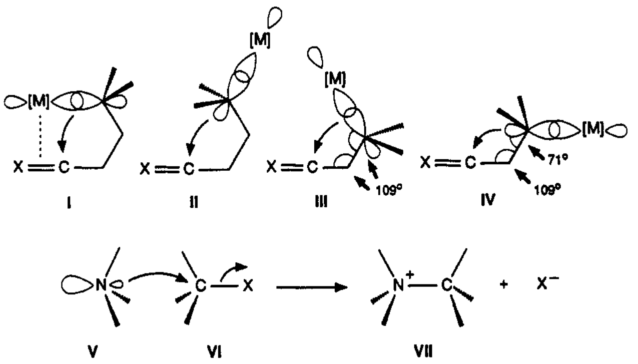
[70] For methods of construction of four-membered rings, see ref 2a (Vol. 1, pp 39, 96, 145) and (a) Trost, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 1, p 843; Vol. 3, pp 588, 620; Vol. 5, pp 63, 123, 899. For a recent enantioselective approach, see: (b) Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* **1992**, *57*, 1707.

[71] (a) Recently, an ionic, intramolecular addition across a conjugated double bond to form a cyclobutane ring has been reported; the reactive nucleophilic species was generated by I/Li exchange: Cooke, M. P., Jr. *J. Org. Chem.* **1992**, *57*, 1495. For an analogous cyclization involving a triple bond, see: (b) Crandall, J. K.; Ayers, T. A. *Organometallics* **1992**, *11*, 473. (c) Harms, A. E.; Stille, J. R. *Tetrahedron lett.* **1992**, *33*, 6565. (d) Bailey, W.F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080. (e) Cooke, M. P., Jr. *J. Org. Chem.* **1993**, *58*, 6833.

[72] Krief, A.; Hobe, M.; Dumont, W.; Badaoui, E.; Guittet, E.; Evrard, G. *Tetrahedron Lett.* **1992**, *33*, 3381.

[73] This is evidenced by almost identical ^{13}C–H coupling constants at the carbon adjacent to mercury: $^1J_{C-H}$ = 135.3 Hz for **3a** and $^1J_{C-H}$ = 135.6 Hz for **22a**.

Scheme 12



with the π^*-orbital of the double bond (C=C or C=O), which is presumably boosted by further coordination of [M] to the double bond (Scheme 12). This scenario will result in the retention of configuration (I). By contrast, a mechanism involving inversion (II) would preclude the latter stabilization of the transition state. As a result, retention (I) is favored over inversion (II). The geometric picture for the cyclopropane ring formation is dramatically different: for the retention mechanism (III), coordination of [M] is hardly attainable and the bonding angle (~109°) also disfavors the formation of the cyclopropane ring (where a ~60° angle is required).[74] For the inversion mechanism (IV), at least the bonding angle is much more favorable (~71°). Naturally, inversion at the nucleophilic carbon will be energetically costly. However, it has been shown on rigid nitrogen compounds that the barrier for the flipping is lower than the activation energy of nucleophilic substitution (V + VI → VII).[75] If similar relative energy levels are assumed for the reaction of C–[M] with an electrophilic partner, the preference for inversion in the case of cyclopropane ring-closure (IV) can be understood. Hence, for cuprates capable of coordination, retention is highly favored for the formation of a four-membered ring (I), whereas both retention and inversion mechanisms (III and IV) apparently operate when a three-membered ring is to be closed up. With Lewis acids as activators, no transmetalation is assumed to occur. Since the coordination ability of mercury is expected to be poor as compared to copper, the preferred mechanism seems to correspond to the more suitable geometry of the molecular framework and, as a result, the reaction predominantly occurs with inversion (IV).

Conclusions

In conclusion, we have achieved a unique regio- and stereoselective opening of a cyclopropane ring by Tl(III) or Hg(II), followed by a skeletal rearrangement, to generate a "5,5" system (**1** → **2** or **3**). Stereospecific deuteration (**1b** and **21b**) provided further evidence to support the concept of preferred *corner* opening[69] of the cyclopropane ring by poor back-donors (H^+, Hg^{2+}, and Tl^{3+} known to date).

By virtue of specific transmetalations (with Pd, Li, or Cu) and/or reactions with Lewis acids, we have been able to effect stereoselective transformations of the organomercurials **3** and **22**, initially generated by the cyclopropane ring-opening. Our results have further demonstrated the potential of the transmetalation methodology. Combining the reactivity of Hg^{2+}, which is the only reactive species capable of the cyclopropane ring-opening in this unique way (as illustrated, for example, in Scheme 2), with the reaction potential of other metals, enabled us to achieve different synthetic goals: (1) the Pd-mediated intramolecular S_N2 displacement (**3** → **6** → **4**); (2) the unprecedented Cu-facilitated construction of the cyclobutane ring via the intramolecular addition to a carbonyl group (**3** → **29**) or to an activated double bond (**32** → **35**); (3) the novel cuprate- or Lewis acid-mediated cyclopropane ring-closure via a conjugate addition (**22** → **21**). Although the experiments were confined to the steroidal skeleton, we are confident that our findings are of a general nature and may be used for synthetic purposes, particularly in view of a number of methods for preparation of organomercurials.

Experimental Section

General Methods. Melting points were determined on a Kofler block and are uncorrected. The optical rotations were measured in $CHCl_3$ with a Perkin-Elmer 141 polarimeter at 22 °C with an error of <±1°. The NMR spectra were recorded for $CDCl_3$ solutions at 25 °C on a Varian Unity 400 (operating at 400 MHz for ^1H, 100.6 MHz for ^{13}C, and 61.4 MHz for ^2H), Varian XL-300, or Bruker AM 300 spectrometer. Chemical shifts were indirectly referenced to TMS via the solvent signals (7.26 ppm for ^1H and ^2H and 77.0 ppm for ^{13}C). The ^{199}Hg NMR spectra were recorded on a Varian XL-300 instrument (at 53.7 MHz) and referenced to external Ph_2Hg (DMSO-d_6 solution) at –808.5 ppm. Diastereoisomeric ratios for **22b** and **24b** were determined by ^2H NMR (61.4 MHz); spectra were recorded for $CHCl_3$ solutions (no lock, ^1H broad-band decoupling, 1-s acquisition time, spectral width 1000 Hz, 1000 transients). The areas for the partially overlapping signals of diastereoisomeric deuterons were determined by deconvolution (Lorenzian line-shape). The $^1J_{C-H}$ values were determined from f_2 traces of HMQC spectra.[18a] Standard software supplied by the manufacturer was used throughout. The IR spectra were recorded in $CHCl_3$ on a Perkin-Elmer 621 instrument. The mass spectra was measured on a Jeol JMS D-100 spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were carried out under nitrogen. Standard workup of an ethereal solution means washing with 5% HCl (aqueous), water, and 5% $KHCO_3$ (aqueous) and drying with $MgSO_4$. Petroleum ether refers to the fraction boiling in the range 40–60 °C. The identity of samples prepared by different routes was checked by TLC and IR and NMR spectra. Yields are given for isolated product showing one spot on a chromatographic plate and no impurities detectable in the NMR spectrum.

3β-((Bromomercurio)methyl)-A,B-dinor-5β-cholestane-5-carbaldehyde (3a). To a solution of cyclopropyl alcohol **1a** (200 mg; 0.52 mmol) in DME (8 mL) were added dropwise acetonitrile (20 mL) and then mercury nitrate monohydrate (190 mg; 0.55 mmol). The resulting mixture was stirred at rt for 1 h, while monitored by TLC. The mixture was then quenched with aqueous KBr and diluted with ether (40 mL), and the solution was washed with 5% aqueous $KHCO_3$ (2 × 10 mL) and water (1 × 20 mL), dried with $MgSO_4$, and evaporated. The residue contained pure product **3a** (325 mg; 97%), showing one spot on TLC: mp 149–151 °C (EtOH); $[\alpha]_D$ –9.9° (*c*, 3.9 in $CHCl_3$/EtOH 3:2); IR ($CHCl_3$) ν(CHO) 1703 and 2706 cm^{-1}; ^1H NMR δ 0.61 (s, 3 H, 18-H), 0.860 (d, 3 H, J = 6.5 Hz, 26-H or 27-H), 0.865 (d, 3 H, J = 6.5 Hz, 26-H or 27-H), 0.90 (7α-H), 0.91 (d, 3 H, J = 6.5 Hz, 21-H), 0.95 (s, 3 H, 19-H), 1.09 (17-H), 1.10 (14-H), 1.11 (9-H), 1.27 (11-H), 1.50 (25-H), 1.55 (12-H), 1.60 (8-H), 1.85 (11-H), 1.93 (dd, 1 H, J_{gem} = 11.7 Hz, $J_{3\alpha\text{-H},4\text{-H}}$ = 8.5 Hz, *pro-S*-4-H), 2.05 (m, 2 H, 12-H and *pro-R*-4-H, J_{gem} = 11.7 Hz, $J_{4\text{-H},3\alpha\text{-H}}$ = 8.1 Hz), 2.37 (m, 1 H, 3α-H), 2.47 (dd, $J_{7\alpha\text{-H},7\beta\text{-H}}$ = 12.0 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.9 Hz, 7β-H), 9.72 (s, 1 H, CHO); ^{13}C NMR (75.4 MHz) δ 12.20 (C-18), 18.74 (C-21), 19.68 (C-19), 21.10 (t), 22.54 (C-26 or C-27), 22.80 (C-26 or C-27), 23.86 (t), 24.37 (t), 27.99 (C-25), 28.46 (C-11), 34.78 (C-4), 35.63 (C-20), 36.20 (C-22), 36.93 (C-7), 38.88 (C-2), 39.40 (C-1), 39.46 (C-12 and C-24), 43.71 (C-13), 44.39 (C-8), 53.01 (C-3), 55.70 (C-17), 56.74 (C-14), 58.29 (C-10), 59.19 (C-9), 70.59 (C-5), 206.22 (C-6); ^{199}Hg NMR (53.6 MHz) δ –1063. NOE difference experiments: Irradiation of C*H*O resulted in the increase of 4-H (1%), 4-H′ (3%), 7β-H (1%), and 19-H (3%). Irradiation of 7β-H resulted in the increase of C*H*O (4%) and 7α-H (22%). Irradiation of 3α-H gave an increase of C*H*O (1%), 4-H (4%), and 4-H′ (4%). Anal. Calcd for $C_{27}H_{45}BrHgO$: C, 48.68; H, 6.81; Br, 12.00; Hg, 30.11. Found: C, 48.33; H, 7.16.

[4^{2}H]-3β-((Bromomercurio)methyl)-A,B-dinor-5β-cholestane-5-carbaldehyde (3b): mp 148–150 °C; ^1H NMR δ 0.63 (s, 3 H, 18-H), 1.96 (d, J = 8.7 Hz, 1-H, 4-H), 9.75 (s, 1 H, CH=O); ^{13}C NMR δ 12.17 (q), 18.71 (q), 19.65 (q), 21.07 (t), 22.52 (q), 22.77 (q), 23.82 (t), 24.35 (t), 27.92 (d), 28.42 (t), 35.57 (d), 36.15 (t), 36.77 (t), 38.76 (t), 39.34 (t), 39.40 (2 × t), 43.64 (s), 44.26 (d), 52.89 (d), 55.63 (d), 56.65 (d), 58.22 (s), 59.09 (d), 70.55 (s), 206.24 (d).

---

(74) For discussion of bonding in cyclopropane, see: Hamilton, J. G.; Palke, W. E. *J. Am. Chem. Soc.* **1993**, *115*, 4159 and references cited therein.

(75) Heathcock, C. H.; von Geldern, T. W.; Lebrilla, C. B.; Maier, W. F. *J. Org. Chem.* **1985**, *50*, 968.

Lactol (4a). Method A. To a solution of **1a** (410 mg; 1.06 mmol) in dioxane (12 mL) and water (1 mL) were added 10% aqueous $HClO_4$ (2 mL) and thallium nitrate trihydrate (570 mg; 1.28 mmol), and the mixture was stirred at rt for 24 h. The mixture was then diluted with ether and filtered, and the filtrate was worked up. The residue was chromatographed on silica gel (25 g) using a petroleum ether–ether mixture (98:2) to remove impurities and then with a 90:10 mixture to afford lactol **4a** (269 mg, 63%): mp 155–157 °C (aqueous acetone); IR ($CHCl_3$) ν(OH) 3395, 3620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (s, 3 H, 18-H), 0.92 (s, 3 H, 19-H), 2.40 (m, 1 H, 3α-H), 3.40 (dd, 1 H, J_{gem} = 8.6 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 4.9 Hz, 4β-H), 4.17 (dd, 1 H, J_{gem} = 8.6 Hz, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 9.1 Hz, 4α-H), 5.17 (s, 1 H, 6β-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.21 (q), 18.53 (q), 18.75 (q), 22.18 (t), 22.54 (q), 22.79 (q), 23.82 (t), 24.48 (t), 27.98 (d), 28.44 (t), 28.56 (t), 35.64 (d), 36.10 (t), 36.21 (t), 37.87 (t), 39.47 (t), 39.73 (t), 40.92 (d), 43.66 (s), 49.24 (d), 53.02 (s), 55.04 (d), 55.67 (d), 56.56 (d), 65.44 (s), 71.91 (t), 101.16 (d); HRMS (EI, 70 eV) *m/z* (relative intensity) 402 (26, M$^+$), 385 (17, M$^+$ – OH), 384 (21, M$^+$ – H_2O), 358 (21, M$^+$ – CO_2), 356 (58, $C_{26}H_{44}$). The configuration of hydroxyl was established by ^{1}H NMR, as an appreciable NOE (ca. 8%) can be seen for the acetal proton upon irradiation of the angular methyl. Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.21; H, 11.72.

Method B. To a solution of lithium chloride (30 mg; 5 equiv) in DME (3 mL) was added palladium(II) chloride (1.5 mg; 5 mol %), and the mixture was stirred at rt for 15 min. Copper(II) chloride (100 mg; 5 equiv) was then added, and the mixture was stirred for an additional 15 min. Then a solution of organomercurial **3a** (100 mg; 0.15 mmol) in DME (2 mL) was added, and the mixture was stirred at rt. The reaction reached completion after 12 h (TLC). The mixture was then diluted with ether (20 mL), washed with water (6 × 10 mL), 5% aqueous $KHCO_3$ (1 × 10 mL), and water (1 × 10 mL), and dried with $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on a column of silica gel, using a petroleum ether–ether mixture (9:1) as eluent to give lactol **4a** (56 mg; 93%), identical with an authentic sample: mp 156–158 °C.

Deuterated lactol (4b): mp 152–154 °C (aqueous acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (s, 3 H, 18-H), 0.88 (s, 3 H, 19-H), 4.15 (d, 1 H, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 9.2 Hz, 4α-H), 5.17 (s, 1 H, 6β-H); in NOE difference experiments, irradiation at 4.15 (4α-H) gave 11% enhancement of the signal at 2.39 (3α-H), while irradiation at 2.39 resulted in 17% enhancement of the signal at 4.15 (4α-H); no enhancement of the latter signal was detected upon irradiation at 5.17 (6β-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.27 (q), 18.53 (q), 18.76 (q), 22.20 (t), 22.52 (q), 22.86 (q), 23.83 (t), 24.49 (t), 27.99 (d), 28.40 (t), 28.57 (t), 35.66 (d), 36.10 (t), 36.22 (t), 37.89 (t), 39.48 (t), 39.74 (t), 40.94 (d), 43.68 (s), 49.15 (d), 53.04 (s), 55.09 (d), 55.68 (d), 56.58 (d), 65.49 (s), 101.20 (d); LRMS *m/z* 403 (M$^+$).

Methyl acetal (5a) was prepared from **3a** in the same way as lactol **4a**, using $PdCl_2$, $CuCl_2$, and LiCl in a mixture of DME and methanol (1:1) as a solvent: mp 75–76 °C (dec; $CHCl_3$–acetone); ^{1}H NMR δ (300 MHz, $CDCl_3$) δ 0.64 (s, 3 H, 18-H), 0.88 (s, 3 H, 19-H), 0.91 (d, 3 H, J = 7 Hz, 21-H), 1.80 (m, 2 H, 2α-H and 2β-H), 2.01 (ddd, 1 H, J_{gem} = 12.5 Hz, $J_{11\alpha\text{-H},12\beta\text{-H}}$ = 6.5, $J_{11\beta\text{-H},12\beta\text{-H}}$ = 6.5 Hz, 12β-H), 2.24 (dd, 1 H, J_{gem} = 12.9 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.0, 7β-H), 2.31 (m, 1 H, 3α-H), 3.32 (s, 3 H, CH_3O), 3.37 (dd, 1 H, J_{gem} = 8.5 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 4.4 Hz, 4β-H), 3.98 (dd, J_{gem} = 8.5 Hz, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 9.1 Hz, 4α-H), 4.60 (s, 1 H, 6β-H); ^{13}C NMR δ (75.4 MHz, $CDCl_3$) δ 12.27 (q, C-18), 18.50 (q, C-19), 18.78 (q, C-21), 22.23 (t, C-11), 22.57 (q, C-26), 22.82 (q, C-27), 23.85 (t, C-16), 24.52 (t, C-15), 28.02 (d, C-25), 28.60 (t, C-2), 28.79 (t, C-23), 35.68 (d, C-20), 36.10 (t, C-1), 36.24 (t, C-22), 37.31 (t, C-7), 39.51 (t, C-24), 39.79 (t, C-12), 40.93 (d, C-8), 43.71 (s, C-13), 49.88 (d, C-3), 53.18 (s, C-10), 54.05 (q, CH_3O), 54.90 (d, C-9), 55.70 (d, C-17), 56.68 (d, C-14), 65.99 (s, C-5), 71.75 (t, C-4), 107.61 (d, C-6) (the three CH_2 carbons at 23.85, 24.52, and 28.79 were assigned tentatively and can be interchanged); HRMS (EI, 70 eV) *m/z* (relative intensity) 416 (0.2 M$^+$), 385 (15, M$^+$ – CH_3O), 356 (100, $C_{26}H_{44}$). Anal. Calcd for $C_{28}H_{48}O_2$: C, 80.69; H, 11.63. Found: C, 80.36; H, 11.64.

Deuterated Acetal (5b): mp 75–76 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (s, 3 H, 18-H), 0.88 (s, 3 H, 19-H), 4.15 (d, 1 H, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 9.2 Hz, 4α-H), 5.17 (s, 1 H, 6β-H); in NOE difference experiments, irradiation at 4.15 (4α-H) gave 11% enhancement of the signal at 2.39 (3α-H), while irradiation at 2.39 resulted in 17% enhancement of the signal at 4.15 (4α-H); no enhancement of the latter signal was detected upon irradiation at 5.17 (6β-H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 12.27, 18.53, 18.76, 22.20, 22.52, 22.86, 23.83, 24.49, 27.99, 28.40, 28.57, 35.66, 36.10, 36.22, 37.89, 39.48, 39.74, 40.94, 43.68, 49.15, 53.04, 55.09, 55.68, 56.58, 66.49, 101.20.

3-(Hydroxymethyl)-A-nor-cholest-3-ene (11). After isolation of **12**, chromatography was continued with hexane–ether (95:5) to afford **11** (98 mg; 66%): mp 119–120 °C (aqueous acetone; lit.[35] gives 116–117 °C); ^{1}H NMR δ 2.42 (m, 1 H, 6-H), 2.36 (m, 2 H, 2-H), 4.09 and 4.19 (AB system, J = 12 Hz, 2 H, 4-H); ^{13}C NMR δ 12.00 (q), 18.01 (q), 18.70 (q), 22.55 (q), 22.62 (t), 22.82 (q), 22.88 (t), 23.81 (t), 24.38 (t), 28.00 (d), 28.18 (t), 31.21 (t), 32.09 (t), 35.75 (d), 36.07 (d), 36.15 (t), 37.98 (t), 39.50 (t), 39.86 (t), 42.83 (s), 50.20 (s), 54.94 (d), 55.92 (d), 56.15 (d), 59.16 (t), 129.25 (s), 146.71 (s).

3-Methylidene-A-nor-5β-cholestan-5-ol (12). A mixture of **7** (140 mg; 0.38 mmol), thallium nitrate trihydrate (230 mg; 0.52 mmol), and aqueous 10% perchloric acid (0.4 mL) in dioxane (8 mL) was stirred at rt for 4 h. The mixture was diluted with ether, the precipitate was filtered off, and the organic phase was worked up as usual. The crude product was chromatographed on silica (10 g) using hexane, which eluted lipophilic impurities, followed by hexane–ether (97:3) mixture to yield **12** (38 mg; 26%): mp 56–58 °C (aqueous acetone; lit.[37] gives 58 °C); $[\alpha]_D$ +21° (*c* 2.0; lit.[37] gives +20°); ^{1}H NMR δ 0.68 (s, 3 H, 18-H), 1.01 (s, 3 H, 19-H), 1.35 (m, 1 H, 1-H), 1.65 (m, 2 H, 1-H and 6-H), 1.91 (m, 1 H, 6-H), 1.96 (m, 1 H, 12-H), 2.30 (m, 2 H, 2-H), 2.45 (m, 2 H, 2-H), 4.99 (dd, J = 2.2 and 2.2 Hz, 1 H, 4*E*-H), 5.07 (dd, J = 2.5 and 2.5 Hz, 1 H, 4*Z*-H); ^{13}C NMR δ 12.01 (q), 13.75 (q), 18.63 (q), 22.27 (t), 22.54 (q), 22.73 (q), 23.79 (t), 24.18 (t), 27.15 (t), 27.99 (d), 28.84 (t), 28.85 (t), 29.97 (t), 31.08 (t), 34.96 (d), 35.75 (d), 36.12 (t), 39.48 (t), 40.02 (t), 42.53 (s), 45.08 (d), 48.28 (s), 56.15 (d), 56.40 (d), 81.44 (s), 107.33 (t), 155.19 (s).

3α,5-Cyclo-5α-cholest-6-ene (13). A solution of 3α,5-cyclo-5α-cholest-6-one[15,76] (1.50 g; 3.9 mmol) and tosylhydrazine (850 mg; 4.3 mmol; 1.1 equiv) in methanol (30 mL) was refluxed for 5 min and then cooled to rt, and the crystalline tosylhydrazone (1.85 g; 86%) was isolated by suction: mp 203–25 °C (dec) (methanol). The crude tosylhydrazone (1.85 g; 3.4 mmol) was dissolved in ether (30 mL) and cooled to –30 °C, and to this solution was added 1.4 M methyllithium (10 mL; 14 mmol; 4.12 equiv). The mixture was stirred and allowed to warm slowly to rt. The reaction was complete after 2 h (as revealed by TLC). The mixture was decomposed by saturated aqueous NH_4Cl and diluted with ether, and the ethereal solution was worked up to afford **13** (1.20 g; 96%): mp 71–72 °C (lit.[77] gives 73 °C); $[\alpha]_D$ –48° (*c* 1.4; lit.[77] gives –47.2°); IR ν(C=C) 1640, ν(C=CH) 3020, ν(C–H cycloprop) 3060 cm^{-1}; ^{1}H NMR δ 0.46 and 0.48 (AB system, J = 5.1 Hz, 2 H, 4α-H and 4β-H), 0.75 (s, 3 H, 18-H), 0.93 (s, 3 H, 19-H), 5.24 (dd, $J_{6\text{-H},7\text{-H}}$ = 9.8 Hz, $J_{7\text{-H},8\beta\text{-H}}$ = 2.5 Hz, 1 H, 7-H), 5.57 (dd, $J_{6\text{-H},7\text{-H}}$ = 9.8 Hz, $J_{6\text{-H},8\beta\text{-H}}$ = 1.5 Hz, 1 H, 6-H); ^{13}C NMR δ 12.01 (q), 14.49 (t), 17.68 (q), 18.53 (q), 22.16 (t), 22.43 (q), 22.68 (q), 23.78 (t), 24.03 (t), 25.00 (t), 25.63 (d), 27.86 (d), 28.28 (t), 31.35 (t), 35.70 (d), 36.03 (t), 36.36 (d), 36.53 (s), 39.36 (t), 40.15 (t), 42.38 (s), 43.20 (s), 45.93 (d), 54.84 (d), 56.04 (d), 127.42 (d), 131.46 (d).

Palladium Complex (15). A mixture of olefin **13** (110 mg; 0.30 mmol), $(MeCN)_2PdCl_2$ (80 mg; 0.31 mmol), and $CuCl_2$ (10 mg; 0.07 mmol) in methanol (30 mL) was stirred at rt for 20 h under nitrogen and with exclusion of light. The solvent was then evaporated in vacuo, the residue was dissolved in petroleum ether, and the solution was filtered through a pad of aluminum oxide. First, impurities were eluted with a petroleum ether–benzene mixture (1:1). Elution with chloroform furnished a crude product (180 mg), which was chromatographed on silica gel (10 g) with a petroleum ether–ether–acetone mixture (89:10:1) to afford **15** (136 mg; 93%); recrystallization from a benzene–methanol mixture gave pure yellow crystals of **15** (97 mg): mp 106–108 °C (dec); $[\alpha]_D$ –80° (*c* 2.1); ^{1}H NMR 0.66 (s, 3 H, 18-H), 3.36 (s, 3 H, CH_3O), 3.96 (m, $W/2$ = 22 Hz, 3α-H), 4.64 and 5.19 (AB system, $J_{6\text{-H},7\text{-H}}$ = 8 Hz, 2 H, 6-H and 7-H). Anal. Calcd for $C_{56}H_{94}Cl_2O_2Pd_2$: C, 62.09; H, 8.76. Found: C, 61.85; H, 8.80.

[7α-^{2}H]-3β-Methoxycholest-5-ene (16). To a solution of **15** (80 mg; 0.08 mmol) in ether (5 mL) was added lithium aluminum deuteride (20 mg; 0.48 mmol) at –78 °C, and the mixture was stirred at this temperature for 15 min. The excess of reagent was decomposed with water, the mixture was diluted with ether and water, and the organic layer was worked up. The residue was purified by chromatography on a silica gel plate (20 × 20 cm) using a petroleum ether–ether mixture (95:5) to give **16** (35 mg; 53%), identical (TLC) with an authentic sample of the unlabeled

---

(76) Aburatani, M.; Takeuchi, T.; Mori, K. *Synthesis* **1987**, 181.

(77) Riegel, B.; Hager, G. P.; Zenitz, B. L. *J. Am. Chem. Soc.* **1946**, *68*, 2562.

compound: mp 83–84 °C (lit.[78] gives 83.7–84.4 °C); $[\alpha]_D$ −40° (*c* 1.9); ^{1}H NMR δ 0.68 (s, 3 H, 18-H), 2.16 (m, *W* = 29 Hz, 1 H, 4β-H), 2.93 (m, *W* = 20 Hz, 1 H, 4α-H), 3.06 (m, *W* = 32 Hz, 3α-H); 3.35 (s, 3 H, OCH_3), 5.35 (dd, $J_{6\text{-H},7\beta\text{-H}} = 5.4$, $J_{6\text{-H},4\alpha\text{-H}} = 1.9$ Hz, 1-H, 6-H); HRMS *m*/*z* 401 ($M^{\bullet+}$, $C_{28}H_{47}DO$), 386, 369, 354, 330, 302, 275, 256, 242, 228, 199, 185, 161, 149, 129, 111, 97, 83, 71, 57, 43.

(19*S*)-[19^{2}H]-Cholest-5-ene-3β,19-diol 3-Monoacetate (18b). To a solution of lithium aluminum deuteride (280 mg; 7.38 mmol) in ether (70 mL) was added dropwise *tert*-butyl alcohol (1.64 g; 22.13 mmol) in ether (5 mL) at −78 °C. The mixture was stirred at −10 °C for 30 min under argon and then cooled to −78 °C. A solution of aldehyde **17** (300 mg; 0.68 mmol) in ether (10 mL) was added, and the mixture was stirred at −78 °C for 20 min while monitored by TLC. The excess of reagent was decomposed by saturated NH_4Cl (aqueous), and the mixture was diluted by ether and worked up to afford **18b** (290 mg; 96%): ^{1}H NMR δ 0.72 (s, 3 H, 18-H), 1.99 (s, 3 H, CH_3CO_2), 3.56 (s, 0.17 H, 19-H), 3.78 (s, 0.85 H, 19-H), 4.62 (m, *W* = 27.4 Hz, 1 H, 3α-H), 5.71 (d, *J* = 4.6 Hz, 1 H, 6-H).

(19*S*)-[19^{2}H]-Cholest-5-ene-3β,19-diol 3-Acetate 19-Mesylate (19b). To a solution of the alcohol **18b** (290 mg; 0.65 mmol) and triethylamine (0.1 mL) in THF (60 mL) was added mesyl chloride (0.8 mL) at −10 °C, and the mixture was kept at this temperature for 1 h. The mixture was then poured on ice and water, the product was extracted with ether, and the ethereal solution was worked up to yield mesylate **19b** (330 mg, 97%), identical (TLC) with its unlabeled counterpart (**19a**);[42] this product was directly used in the next procedure without further purification.

(19*R*)-[19^{2}H]-5,19-Cyclo-5β-cholestan-3β-ol (20b). The mesylate **19b** (270 mg; 0.52 mmol) in ether (100 mL) was treated with lithium aluminum hydride (250 mg; 6.51 mmol) at rt for 28 h. The mixture was then cooled to −78 °C, the excess of reagent was decomposed with saturated NH_4Cl (aqueous), the product was extracted with ether, and the ethereal solution was worked up. The crude product was chromatographed on silica gel (15 g) with a petroleum ether–ether mixture (8:2) to afford **20b** (176 mg; 88%), identical (TLC) with its unlabeled counterpart (**20a**).[42]

5,19-Cyclo-5β-cholestan-3-one (21a). Method A. The alcohol[42] **20a** (750 mg; 1.94 mmol) was dissolved in acetone–DME mixture (1:1; 50 mL) and oxidized with Jones' reagent at 0 °C for 10 min. The excess of reagent was decomposed with methanol, the mixture was diluted with ether and water, and the product was extracted with ether. The ethereal solution was successively washed with saturated aqueous $KHCO_3$ (3 × 30 mL) and water and dried with $MgSO_4$. Ether was evaporated, and the residue was chromatographed on silica (30 g) using a petroleum ether–ether mixture (95:5) as eluent to yield **21a** (710 mg; 95%): mp 96–98 °C (acetone); $[\alpha]_D$ +47° (*c* 1.7); IR ν(C=O) 1705 cm^{-1}; ^{1}H NMR δ 0.47 (d, *J* = 5.7 Hz, 1 H, 19-H), 0.51 (d, *J* = 5.7 Hz, 1 H, 19-H), 0.70 (s, 3 H, 18-H), 2.51 and 2.57 (AB system, J_{gem} = 18.1 Hz, 2 H, 4α-H and 4β-H); ^{13}C NMR δ 12.13 (q), 17.53 (t, C-19), 18.32 (s), 18.54 (q), 22.43 (q), 22.68 (q), 23.68 (t), 23.93 (t), 25.11 (s), 25.35 (t), 26.38 (t), 27.24 (t), 27.86 (d), 28.10 (t), 31.74 (t), 35.53 (d), 35.60 (d), 36.00 (t), 36.08 (t), 39.35 (t), 39.85 (t), 42.97 (s), 46.44 (d), 48.28 (t), 54.99 (d), 56.28 (d), 212.55 (s). Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.17; H, 11.75.

Method B. To a stirred suspension of copper(I) iodide (270 mg; 1.42 mmol) in dry DME (5 mL) was added dropwise a 1.4 M solution of methyllithium in ether (2 mL; 2.8 mmol) at −78 °C. The mixture was stirred under nitrogen at −10 °C for 10 min and then cooled to −78 °C. At this temperature, a precooled (−20 °C) solution of the organomercurial **22a** (80 mg; 0.12 mmol) in DME (1 mL) was added. The mixture was stirred at −78 °C for 5 min and then quenched with water. The product was extracted with ether, and the ethereal solution was worked up. The crude product was chromatographed on silica (5 g) using a petroleum ether–ether mixture (95:5) as eluent to give pure **21a** (40 mg; 86%): mp 98–99 °C.

Method C. The organomercurial **22a** (100 mg) was treated with aluminum chloride (40 mg) in dry DME (5 mL) at rt for 12 h and monitored by TLC. The mixture was then cooled to −20 °C, water (1 mL) was added dropwise, and the mixture was allowed to warm to rt. The mixture was extracted with ether, and the ethereal solution was worked up. Chromatography on silica (5 g) with a petroleum ether–ether mixture (95:5) yielded **21a** (54 mg; 93%): mp 95–96 °C.

(19*R*)-[19^{2}H]-5,19-Cyclo-5β-cholestan-3-one (21b): mp 86–87 °C; ^{1}H NMR δ 0.47 (s, 0.84 H, 19-H), 0.71 (s, 3 H, 18-H).

19-(Bromomercurio)cholest-4-en-3-one (22a). The third fraction after isolation of **24a** and **25a** contained **22a** (543 mg; 35%): mp 117–120 °C (DME); $[\alpha]_D$ +67° (*c* 5.5); IR ν(C=O) 1672 cm^{-1}; ^{1}H NMR δ 0.75 (s, 3 H, 18-H), 2.20 and 2.51 (AB system, two d, J_{gem} = 12.1 Hz, 2 × 1 H, 19-H), 5.78 (s, 1 H, 4-H); ^{13}C NMR δ 12.18 (q), 18.61 (q), 21.75 (t), 22.54 (q), 22.80 (q), 23.77 (t), 24.10 (t), 27.98 (d), 28.11 (t), 32.46 (t), 33.27 (t), 33.97 (t), 35.68 (d), 35.92 (d), 36.04 (t), 37.39 (t), 39.44 (t), 39.61 (t), 40.41 (t), 42.40 (s), 42.78 (s), 54.81 (d), 55.88 (d), 55.98 (d), 123.85 (d), 171.55 (s), 197.86 (s). Anal. Calcd for $C_{27}H_{43}BrHgO$: C, 48.83; H, 6.53. Found: C, 48.54; H, 6.30.

(19*S*)-[19^{2}H]-19-(Bromomercurio)cholest-4-en-3-one (22b): ^{1}H NMR δ 0.71 (s, 3 H, 18-H), 2.15 (s, <1 H, 19-H), 5.74 (s, 1 H, 4-H); ^{2}H NMR δ 2.53 (*W*/2 = 13.8 Hz);[49] ^{13}C NMR δ 12.18 (q), 18.60 (q), 21.75 (t), 22.54 (q), 22.80 (q), 23.77 (t), 24.09 (t), 27.98 (d), 28.10 (t), 32.47 (t), 33.27 (t), 33.99 (t), 35.68 (d), 35.92 (d), 36.04 (t), 37.32 (t), 39.44 (t), 39.61 (t), 40.2 (CH^{2}H, $J_{C,D}$ = 21.5 Hz), 42.40 (s), 42.71 (s), 54.81 (d), 55.88 (d), 55.98 (d), 123.85 (d), 171.57 (s), 197.87 (s); ^{199}Hg NMR δ −1011; MS 95 ± 3% ^{2}H (d_1).

Cholest-4-en-3-one (23). To a solution of organomercurial **22a** (120 mg; 0.18 mmol) in toluene (20 mL) was added tributyltin hydride (0.2 mL; 0.74 mmol) in toluene (2 mL). The mixture was stirred at rt for 10 min and then diluted with ether, and the ethereal solution was worked up. The crude product was chromatographed on silica gel (5 g) first with petroleum ether and then with a petroleum ether–ether mixture (8:2) to furnish **23** (52 mg; 75%), identical with an authentic sample: mp 74–77 °C (acetone; Aldrich catalog gives 79–81 °C).

19-Nor-5-((bromomercurio)methyl)-5β-cholest-1(10)-en-3-one (24a). To a solution of **21a** (900 mg; 2.34 mmol) in DME (100 mL) was added mercury(II) nitrate monohydrate (2.6 g; 7.6 mmol) at 0 °C in several portions. The mixture was stirred at 0 °C and monitored by TLC. After 2 h, a saturated aqueous solution of KBr (30 mL) was added, and the mixture was stirred for 5 min. The product was extracted with ether (4 × 50 mL), and the ethereal solution was washed successively with aqueous KBr, 5% aqueous $KHCO_3$, and water and dried with sodium sulfate. The solvent was evaporated to give a crude mixture of isomeric organomercurials. The mixture was chromatographed on silica (52 g) using a petroleum ether–ether mixture (7:3 to 1:1). The first fraction contained **24a** (372 mg; 24%): mp 93–95 °C; $[\alpha]_D$ −30° (*c* 8.8); IR ν(C=O) 1709 cm^{-1}; ^{1}H NMR δ 0.68 (s, 3 H, 18-H), 2.21 and 2.47 (AB system, J_{gem} = 13.8 Hz, 2 × 1 H, 19-H), 3.00 (m, *W* = 10 Hz, 2 H, 2-H), 5.54 (brd, *J* = 2.3 Hz, 1 H, 1-H); ^{13}C NMR δ 11.82 (q), 18.63 (q), 22.51 (q), 22.77 (q), 23.54 (t), 23.74 (two t), 25.60 (t), 27.93 (d), 28.05 (t), 32.89 (d), 35.42 (t), 35.64 (d), 36.07 (t), 39.05 (t), 39.41 (t), 40.21 (t), 40.29 (d), 42.28 (s), 42.52 (s), 47.60 (t), 55.88 (d), 57.36 (t), 57.86 (d), 115.24 (d), 149.12 (s), 210.21 (s). Anal. Calcd for $C_{27}H_{43}BrHgO$: C, 48.83; H, 6.53. Found: C, 48.61; H, 6.74.

(19*R*)-[19^{2}H]-19-Nor-5-((bromomercurio)methyl)-5β-cholest-1(10)-en-3-one (24b): ^{1}H NMR δ 0.66 (s, 3 H, 18-H), 2.37 (s, <1 H, 19-H), 2.99 (m, *W* = 10 Hz, 2 H, 2-H), 5.53 (brd, *J* = 2.3 Hz, 1 H, 1-H); ^{2}H NMR δ 2.12 (*W*/2 = 13.8 Hz);[49] ^{13}C NMR δ 11.9 (q), 11.7 (q), 22.6 (q), 22.8 (q), 23.6 (t), 23.80 (t), 23.82 (t), 25.7 (t), 28.0 (d), 28.1 (t), 33.0 (d), 35.5 (t), 36.1 (d), 37.5 (t), 39.1 (t), 39.5 (t), 40.3 (t), 40.4 (d), 42.3 (s), 42.6 (s), 47.5 (CH^{2}H, $J_{C,D}$ = 22.5 Hz), 56.0 (d), 57.5 (t), 57.9 (d), 115.4 (d), 149.2 (s), 210.0 (s); ^{199}Hg NMR δ 739.16.

19-Nor-5-((bromomercurio)methyl)-5β-cholest-9-en-3-one (25a). The second chromatographic fraction after isolation of **24a** contained **25a** (435 mg; 28%): mp 174–178 °C (acetone); $[\alpha]_D$ +36° (*c* 12.6); IR ν(C=O) 1705 cm^{-1}; ^{1}H NMR δ 0.83 (s, 3 H, 18-H), 2.23 and 2.27 (AB system, two d, J_{gem} = 11.6 Hz, 2 × 1 H, 19-H), 2.70 (d, J_{gem} = 14.00 Hz, 1 H, 4β-H), 3.00 (dd, J_{gem} = 12.5 Hz, $J_{1\beta\text{-H},2\beta\text{-H}}$ = 6.7 Hz, 1 H, 2β-H); ^{13}C NMR δ 11.16 (q), 18.50 (q), 22.44 (q), 22.69 (q), 23. 62 (t), 24.67 (t), 24.79 (t), 25.28 (t), 25.77 (t), 27.86 (d), 28.11 (t), 35.54 (d), 35.92 (t), 38.84 (d), 39.34 (t), 40.02 (t), 41.21 (t), 42.00 (s), 42.35 (t), 43.11 (s), 52.57 (t), 55.93 (d), 56.16 (t), 56.54 (d), 131.62 (s), 135.87 (s), 211.13 (s). Anal. Calcd for $C_{27}H_{43}BrHgO$: C, 48.83; H, 6.53. Found: C, 48.57; H, 6.88.

5-Methyl-19-norcholest-9-en-3-one (26). A solution of **25a** (40 mg; 0.060 mmol) in benzene (5 mL) was refluxed with a 1 M benzene solution of tributyltin hydride (0.3 mL) and a catalytic amount of 2,2′-azoisobutyronitrile for 10 min. The mixture was then diluted with ether, washed with 5% NaF (aqueous) and 5% $KHCO_3$ (aqueous), and dried with Na_2SO_4, and the solvent was evaporated. The residue was chromatographed on silica gel (2 g) with a petroleum ether–ether mixture (9:1) as eluent to give **26** (23 mg; 69%), identical with an authentic sample:[46] $[\alpha]_D$ +18° (*c* 2.0; lit.[46] gives +20°); IR ν(C=O) 1713 cm^{-1}; ^{1}H NMR δ 0.82 (s, 3 H, 18-H), 1.03 (s, 3 H, 5β-methyl).

3β-((Methylmercurio)methyl)-A,B-dinor-5β-cholestane-5-carbaldehyde (27). Method A. To a stirred suspension of copper(I) iodide (266

---

(78) Kosower, E. M.; Winstein, S. *J. Am. Chem. Soc.* **1956**, *78*, 4347.

mg; 1.40 mmol) in dry THF (10 mL) was added dropwise a 1.4 M solution of methyllithium in THF (1 mL; 1.4 mmol) at –35 °C. The mixture was stirred under nitrogen at the same temperature for 10 min, and then a precooled (–20 °C) solution of organomercurial **3a** (260 mg; 0.40 mmol) in THF (5 mL) was added. Since TLC indicated an instantaneous reaction, the mixture was then poured into an ice-cold aqueous solution of NH_4Cl, the product was extracted with ether, and the organic phase was worked up. The solvent was evaporated to give oily methylmercury **27** (225 mg; 94%) showing one spot on TLC: $[\alpha]_D$ –6° (*c* 6.3); IR 1712, 2698 cm^{-1}; ^{1}H NMR δ 0.32 (s, 3 H, CH_3Hg), 0.64 (s, 3 H, 18-H), 0.96 (s, 3 H, 19-H), 9.81 (s, 1 H, CH=O); ^{13}C NMR δ 12.19 (C-18), 18.72 (C-21), 19.57 (C-19), 20.94 (CH_3Hg), 21.07 (t), 22.54 (C-26 or C-27), 22.80 (C-26 or C-27), 23.85 (t), 24.37 (t), 27.98 (d), 28.49 (t), 35.63 (d), 36.20 (t), 36.46 (C-7), 39.46 (t), 39.58 (t), 39.70 (t), 39.90 (t), 42.22 (t), 43.67 (C-13), 44.04 (d), 54.37 (C-3), 55.73 (d), 56.87 (d), 57.38 (C-10), 59.45 (d), 71.57 (s), 207.37 (CH=O); ^{199}Hg NMR δ –161.6; MS (EI, 70 eV) *m/z* 600 (M$^+$, 0.3), 587 (0.2), 559 (3), 385 (100), 367 (20), 341 (24), 247 (13), 217 (33), 215 (32). Anal. Calcd for $C_{28}H_{48}HgO$: C, 55.93; H, 8.05; Hg, 33.36. Found: C, 55.71; H, 7.83.

Method B. To a solution of **3a** (150 mg; 0.23 mmol) in ether (50 mL) was added a 2 M solution of trimethylaluminum in hexane (0.5 mL; 1.1 mmol) at –78 °C. The mixture was stirred at the same temperature for 30 min, the excess of the reagent was then decomposed by 10% HCl (aqueous) at –78 °C, and the mixture was worked up. The crude product was dissolved in ether and was filtered through a pad of silica gel. The filtrate was evaporated to give **27** (121 mg; 69%), identical with the product prepared under method A.

Method C. A 1.4 M solution of methyllithium in THF (2 mL; 2.8 mmol) was added to zinc(II) chloride (200 mg; 1.47 mmol) in THF (50 mL) at –30 °C, and the mixture was stirred at –30 °C for 30 min. The organomercurial **3a** (100 mg; 1.50 mmol) was then added, and the mixture was stirred at –30 °C, then cooled to –78 °C, and decomposed with saturated NH_4Cl (aqueous). The mixture was then diluted with ether and worked up to give pure **27** (82 mg; 91%), identical with the product obtained under method A.

A-Homo-B-nor-3,5-cyclo-5α-cholestan-6α-ol (29a). To a stirred suspension of copper(I) iodide (260 mg; 1.40 mmol) in dry THF (20 mL) was added dropwise a 1.4 M solution of methyllithium in THF (2 mL; 2.8 mmol) at –78 °C. The mixture was stirred under nitrogen at –10 °C for 10 min and then cooled to –78 °C. At this temperature, a precooled (–20 °C) solution of the organomercurial **3a** (300 mg; 0.45 mmol) in THF (5 mL) was added. Since TLC indicated an instantaneous reaction, the mixture was then poured into an ice-cold aqueous solution of NH_4Cl, the product was extracted with ether, and the organic phase was worked up. The solvent was evaporated to give cyclobutanol **29a** (159 mg; 93%), showing one spot on TLC: mp 97–99 °C (Me_2CO); $[\alpha]_D$ +26° (*c* 5.0); IR ν(OH) 3430 and 3600 cm^{-1}; ^{1}H NMR δ 0.66 (s, 3 H, 18-H), 0.94 (s, 3 H, 19-H), 2.42 (ddd, 1 H, 3α-H), 4.19 (dd, 1 H, J = 4.6 and 5.4 Hz, C*H*OH); ^{13}C NMR δ 12.31 (C-18), 17.17 (C-21), 18.78 (C-19), 21.85 (t), 22.56 (C-26 or C-27), 22.81 (C-26 or C-27), 23.83 (t), 24.49 (t), 28.00 (d), 28.56 (t), 28.96 (t), 32.86 (t), 34.95 (t), 35.66 (d), 36.25 (t), 36.30 (t), 39.50 (t), 39.82 (t), 40.96 (d), 43.98 (s, C-13), 45.56 (d), 53.48 (d), 53.62 (s), 55.72 (d), 57.07 (d), 63.82 (s), 68.59 (d). Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.60; H, 12.24.

[4α^{2}H]-A-Homo-B-nor-3,5-cyclo-5α-cholestan-6α-ol (29b): mp 98–99 °C; ^{1}H NMR δ 0.67 (s, 3 H, 18-H), 0.91 (s, 3 H, 19-H), 2.42 (dd, 1 H, $J \cong 2 \times 6.5$ Hz, 3α-H), 4.18 (d, J = 6.8 Hz, C*H*OH); ^{13}C NMR δ 12.31 (q), 17.17 (q), 18.78 (q), 21.85 (t), 22.56 (q), 22.81 (q), 23.83 (t), 24.49 (t), 28.00 (d), 28.56 (t), 28.96 (t), 32.50 (dt, CH^{2}H), 34.93 (t), 35.66 (d), 36.24 (t), 36.31 (t), 39.50 (t), 39.82 (t), 40.96 (d), 43.98 (s), 45.42 (d), 53.49 (d), 53.61 (s), 55.72 (d), 57.08 (d), 63.80 (s), 68.45 (d).

A-Homo-B-nor-3,5-cyclo-5α-cholestan-6-one (30a). The alcohol **29a** (150 mg; 0.39 mmol) in acetone (10 mL) was treated with Jones' reagent at –20 °C for 10 min. The excess of reagent was decomposed by methanol, and the mixture was diluted by ether and water and worked up. The residue was crystallized from aqueous acetone to give ketone **30a** (135 mg; 90%): mp 112–114 °C; $[\alpha]_D$ –9° (*c* 2.4); IR ν(C=O) 1750 cm^{-1}; ^{1}H NMR δ 0.66 (s, 3 H, 18-H), 0.96 (s, 3 H, 19-H), 1.09 (t, 1 H, $J \approx$ 13 Hz, 7α-H), 1.68 (m, 1 H, 8β-H), 2.29 (dd, J_{gem} = 13.4 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 7.4 Hz, 1-H; 7β-H), 2.35 (m, 1 H, 3α-H), 2.61 (dd, 1 H, J_{gem} = 17.6, $J_{4\beta\text{-H},3\alpha\text{-H}}$ = 6.8 Hz, 4β-H) , 2.90 (dd, 1 H, J_{gem} = 17.6 Hz, $J_{4\alpha\text{-H},3\alpha\text{-H}}$ = 8.6 Hz, 4α-H); ^{13}C NMR δ 12.24 (q), 18.77 (q), 19.67 (q), 21.87 (t), 22.56 (q), 22.81 (q), 23.86 (t), 24.29 (t), 28.01 (d), 28.52 (t), 30.40 (t), 35.09 (t), 35.63 (d), 35.77 (t), 36.23 (t), 39.49 (2 × t), 39.90 (d), 41.90 (d), 44.04 (s), 47.24 (t), 53.38 (d), 55.69 (d), 56.74 (d), 58.66 (s), 83.93 (s), 212.93 (C=O). NOE difference experiments: irradiation of 4α-H (at δ 2.90) resulted in the increase of 4β-H (19.6%) and 3α-H (8.6%); irradiation of 4β-H (at δ 2.61) resulted in the increase of 4α-H (21.6%); irradiation of 3α-H (at δ 2.35) resulted in the increase of 4α-H (7.8%) and 7α-H (13.2%). Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.09; H, 11.80.

[4α^{2}H]-A-Homo-B-nor-3,5-cyclo-5α-cholestan-6-one (30b): mp 112–114 °C; ^{1}H NMR δ 0.67 (s, 3 H, 18-H), 2.64 (brd, J = 7 Hz, 1 H, 4β-H); ^{13}C NMR δ 12.24 (q), 18.77 (q), 19.67 (q), 21.86 (t), 22.56 (q), 22.81 (q), 23.85 (t), 24.28 (t), 28.00 (d), 28.51 (t), 30.39 (t), 35.08 (t), 35.62 (d), 35.75 (t), 36.22 (t), 39.48 (2 × t), 39.77 (d), 41.88 (d), 44.02 (s), 46.96 (CHD, C-4), 53.38 (d), 55.68 (d), 56.73 (d), 58.65 (s), 83.93 (s), 212.97 (s); MS ≥ 95% ^{2}H (d$_1$).

A-Homo-B-nor-3,5-cyclo-5α-cholestan-6β-ol (31). Ketone **30a** (210 mg; 0.54 mmol) in dry ether (20 mL) was treated with $LiAlH_4$ (50 mg) at –10 °C for 5 min. The excess of reagent was decomposed with 10% aqueous HCl at –78 °C and worked up. The solvent was evaporated and to give alcohol **31** (201 mg; 96%); showing one spot on TLC: mp 125–127 °C (aqueous acetone); $[\alpha]_D$ +20° (*c* 5.3); ^{1}H NMR δ 0.68 (s, 3 H, 18-H), 1.77 (s, 3 H, 19-H), 4.30 (t, J = 9.0 Hz, 6α-H); ^{13}C NMR δ 12.27 (q), 18.78 (q), 19.54 (q), 21.28 (t), 22.56 (q), 22.81 (q), 23.85 (t), 24.48 (t), 28.00 (d), 28.43 (t), 28.57 (t), 31.62 (t), 35.66 (d), 36.25 (t), 37.69 (t), 39.50 (t), 39.76 (t), 41.08 (d), 41.13 (d), 43.82 (s), 43.99 (t), 54.85 (d), 55.00 (s), 55.69 (d), 57.05 (d), 64.50 (s), 73.83 (d). Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.56; H, 12.33.

3β-((Bromomercurio)methyl)-5-[(*E*)-2′-(Ethoxycarbonyl)ethenyl]-A,B-dinor-5β-cholestane (32). To a stirred solution of triethylphosphonoacetate (1.27 g; 1.5 equiv) in dry THF (100 mL) was slowly added a 1.6 M solution of butyllithium in hexane (2.8 mL; 1.2 equiv) at 0 °C, and the mixture was then stirred at rt for 30 min under nitrogen. A solution of organomercurial **3a** (2.5 g; 0.37 mmol; 1 equiv) in THF (15 mL) was added, and the mixture was refluxed. The progress of reaction was monitored by TLC. After 12 h, the mixture was cooled and diluted with ether and water, and the organic layer was washed with water (1 × 20 mL), 5% aqueous HCl (2 × 20 mL), 5% aqueous $KHCO_3$ (2 × 20 mL), saturated aqueous KBr (1 × 20 mL), and water (2 × 20 mL) and dried with Na_2SO_4. The solvent was evaporated, and the residue was chromatographed on a column of silica first with a petroleum ether–ether mixture (9:1) and then with a petroleum ether–ether–acetone mixture (7:1:2) to give **32** (2.02 g; 73%), showing one spot on TLC: mp 100–105 °C (Me_2CO, H_2O); $[\alpha]_D$ –3° (*c* 2.6); IR ν(C=C) 1631, ν(C=O) 1702 cm^{-1}; ^{1}H NMR δ 0.65 (s, 3 H, 18-H), 0.81 (s, 3 H, 19-H), 1.36 (t, 3 H, J = 7.1 Hz, C*H*$_3$CH$_2$), 4.26 (q, 2 H, J = 7.1 Hz, CH$_3$C*H*$_2$O), 5.92 (d, J = 16.0 Hz, 1 H, CH=C*H*CO$_2$Et), 7.06 (d, 1 H, J = 16.0 Hz, C*H*=CHCO$_2$Et); ^{13}C NMR δ 12.27 (q), 14.32 (q), 18.75 (q), 20.76 (q), 21.44 (t), 22.55 (q), 22.81 (q), 23.88 (t), 24.48 (t), 27.99 (d), 28.50 (t), 32.15 (t), 35.65 (d), 36.22 (t), 37.22 (t), 38.44 (t), 39.47 (t), 39.54 (t), 39.61 (t), 43.56 (d), 43.78 (s), 53.78 (d), 55.71 (d), 56.72 (d), 57.34 (s), 58.98 (d), 60.44 (t), 62.32 (s), 119.57 (d), 151.98 (d), 166.46 (s). Anal. Calcd for $C_{31}H_{51}BrHgO_2$: C, 50.57; H, 6.98; Br, 10.85; Hg, 27.24. Found: C, 50.31; H, 6.74.

3β-((Methylmercurio)methyl)-5-[(*E*)-2′-(Ethoxycarbonyl)ethenyl]-A,B-dinor-5β-cholestane (33). To a solution of **32** (120 mg; 0.16 mmol) in dry ether (10 mL) was added a 2 M solution of trimethylaluminum in hexane (0.2 mL; 2.5 equiv) at –78 °C, and the mixture was stirred at this temperature for 1 h. The excess of reagent was decomposed by 10% aqueous HCl, and the mixture was worked up. The solvent was evaporated, the residue was dissolved in a petroluem ether–ether mixture (9:1), and the solution was filtered through a pad of aluminum oxide. The filtrate was evaporated to afford pure, oily **33** (107 mg; 95%): $[\alpha]_D$ –5° (*c* 3.7); IR ν(C=C) 1640, ν(C=O) 1710 cm^{-1}; ^{1}H NMR δ 0.25 (s, 3 H, CH$_3$-Hg), 0.65 (s, 3 H, 18-H), 0.79 (s, 3 H, 19-H), 1.35 (d, 3 H, J = 7.1 Hz, C*H*$_3$CH$_2$O), 4.25 (d, 2 H, J = 7.1 Hz, CH$_3$C*H*$_2$O), 5.84 (d, 1 H, J = 16.0 Hz, CH=C*H*CO$_2$Et), 7.15 (d, 1 H, J = 16.0 Hz, C*H*=CHCO$_2$Et); ^{13}C NMR δ 12.29 (q), 14.38 (q), 18.78 (q), 20.92 (q), 21.48 (q), 21.56 (t), 22.58 (q), 22.83 (q), 23.89 (t), 24.51 (t), 28.01 (d), 28.56 (t), 35.68 (d), 36.26 (t), 38.19 (t), 38.85 (t), 39.51 (t), 39.77 (t), 39.98 (t), 42.55 (t), 43.43 (d), 43.78 (s), 55.59 (d), 55.77 (d), 56.76 (s), 56.86 (d), 58.98 (d), 60.12 (t), 63.27 (s), 118.03 (d), 154.73 (d), 166.89 (s). Anal. Calcd for $C_{32}H_{54}HgO_2$: C, 57.25; H, 8.11; Hg, 29.88. Found: C, 56.93; H, 7.95.

6α-((Ethoxycarbonyl)methyl)-A-homo-B-nor-3,5-cyclo-5α-cholestane (35). Method A. To a solution of **32** (120 mg; 0.16 mmol) in dry THF (10 mL) was added a 2 M solution of trimethylaluminum in hexane (0.2 mL; 2.5 equiv) at –78 °C. The mixture was stirred at this temperature for 1 h. Then a 1.6 M solution of butyllithium in hexane (0.3 mL; 3

equiv) was added, and the mixture was stirred at –78 °C for 1 h and allowed to warm to rt. The excess of reagent was decomposed by 10% aqueous HCl, the product was extracted with ether, and the ethereal layer was worked up. The solvent was evaporated, and the residue was chromatographed on a column of silica gel with a petroleum ether–ether mixture (97:3) as eluent to give pure **35** (68 mg; 92%): $[\alpha]_D$ +18° (*c* 6.8); IR 1728 cm^{-1}; ^{1}H NMR δ 0.65 (s, 3 H, 18-H), 0.96 (s, 3 H, 19-H), 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 4.15 (q, 2 H, *J* = 7.1 Hz, CH_3CH_2O); ^{13}C NMR δ 12.18 (q), 14.17 (q), 17.28 (q), 18.64 (q), 21.93 (t), 22.42 (q), 22.67 (q), 23.69 (t), 24.37 (t), 26.95 (t), 27.86 (d), 28.43 (t), 29.06 (t), 30.68 (d), 35.52 (d), 36.02 (t), 36.11 (t), 37.46 (t), 39.36 (two t), 39.76 (t), 40.90 (d), 43.82 (s), 46.53 (d), 52.84 (d), 54.09 (s), 55.57 (d), 56.90 (d), 59.93 (t), 60.21 (s), 173.20 (s). Anal. Calcd for $C_{31}H_{52}O_2$: C, 81.52; H, 11.48. Found: C, 81.33; H, 11.21.

Method B. To a stirred suspension of copper(I) iodide (260 mg; 1.40 mmol) in dry THF (5 mL) was added dropwise a 1.4 M solution of methyllithium in THF (2 mL; 2.8 mmol) at –78 °C. The mixture was stirred under nitrogen at –10 °C for 10 min and then cooled to –78 °C. At the same temperature, a precooled (–20 °C) solution of **32** (78 mg; 0.11 mmol) in THF (5 mL) was added. The mixture was stirred at –78 °C for 15 min and then allowed gradually to warm to rt. The excess of reagent was decomposed by aqueous NH_4Cl, the product was taken up into ether, and the ethereal solution was worked up. The solvent was evaporated, and the residue was chromatographed on a column of silica gel with a petroleum ether–ether mixture (9:1) to yield **35** (35 mg; 75%), identical with the product obtained by method A.

3β-Chloro-5-cholestene (38a). A mixture of **3a** (100 mg) and aluminum chloride (20 mg) in dry DME (5 mL) was heated at 45 °C for 18 h and monitored by TLC. The mixture was then cooled to –20 °C, water (1 mL) was added, and the mixture was allowed to warm to rt. The mixture was extracted with ether, and the ethereal solution was worked up. Chromatography on silica (5 g) with petroleum ether yielded **38a** (48 mg; 79%): mp 94–96 °C (ethyl acetate; Fluka catalog gives 94–96 °C); ^{1}H NMR δ 0.68 (s, 3 H, 18-H), 1.04 (s, 3 H, 19-H), 2.49 (ddd, J_{gem} = 13.5, $J_{4\alpha\text{-H},3\alpha\text{-H}}$ = 5.1, $J_{4\alpha\text{-H},6\text{-H}}$ = 2.1 Hz, 1 H, 4α-H), 2.56 (m, 1 H, 4β-H), 3.77 (m, *W* = 32.7 Hz, 1 H, 3α-H), 5.38 (brd, *J* = 5.2 Hz, 6-H); ^{13}C NMR δ 11.87 (q), 18.73 (q), 19.27 (q), 20.97 (t), 22.58 (q), 22.84 (q), 23.85 (t), 24.28 (t), 28.03 (d), 28.23 (t), 31.79 (d), 31.84 (t), 33.39 (t), 35.79 (d), 36.19 (t), 36.38 (s), 39.12 (t), 39.52 (t), 39.71 (t), 42.31 (s), 43.41 (t), 50.07 (d), 56.14 (d), 56.69 9d), 60.33 (d), 122.46 (d), 140.77 (s); MS *m/z* 406 (34, $M^{\bullet +}$), 404 (91).

[4β^{2}H]-3β-Chloro-5-cholestene (38b): mp 94–96 °C; ^{1}H NMR δ 0.71 (s, 3 H, 18-H), 1.06 (s, 3 H, 19-H), 2.50 (m, *W* = 6 Hz, 1 H, 4α-H), 3.80 (m, *W* = 19.7 Hz, 1 H, 3α-H), 5.48 (dd, *J* = 5.5 and 2.0 Hz, 1 H, 6-H); MS ≥ 95% ^{2}H (d_1).

Note added in proof: our conclusions are further supported by the work of Razin et al. (a) Razin, V. V.; Zadonskaya, N. Yu. *Zh. Org. Khim.* **1990**, *26*, 2342; *Chem. Abstr.* **1991**, *115*, 182661q. (b) Razin, V. V.; Genaev, A. M.; Dobonravov, A. N. *Zh. Org. Khim.* **1992**, *28*, 104; *Chem. Abstr.* **1992**, *117*, 170832z.

Acknowledgment. We thank Professors J.-E. Bäckvall and P. Cullis, and Dr. R. D. W. Kemmitt for stimulating discussions, Drs. V. Hanuš and M. Polášek for measurement of mass spectra, and Dr. G. Griffith for obtaining some of the NMR spectra. We also thank Merck Sharp and Dohme, Roche Products Ltd., and Pfizer Ltd. for financial support to J.Š., and the Czechoslovak Academy of Sciences for support to M.P.