STEREOCHEMISTRY OF THE OPENING OF CYCLOPROPANES BY MERCURY(II) AND TRANSMETALLATION OF THE INTERMEDIATE ORGANOMERCURIALS WITH TRANSITION METALS

by

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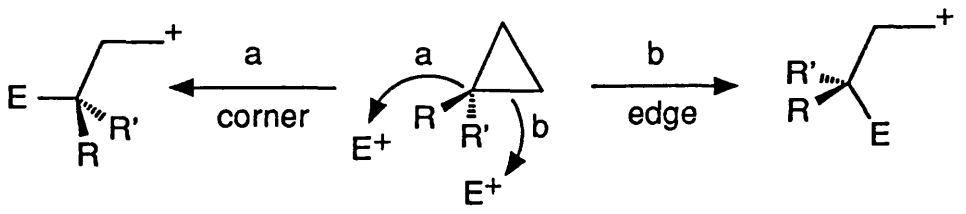
1. Introduction

Activation of organic substrates by both transition and non-transition 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 transmetallation,[1,3] a methodology that combines (often in one pot) the benefits of specific reactivities of two or more metals in tandem reactions.

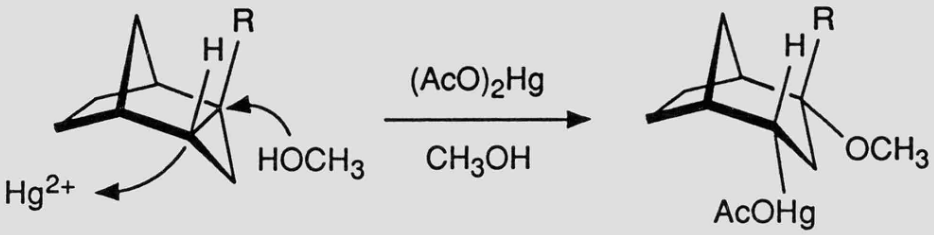
Stereocontrolled cyclopropanation,[4,5] catalysed by various metals,[6] followed by ring-opening,[4] is an attractive strategy for construction of up to three contiguous chiral centres.[2] However, the mechanism of cleavage of the cyclopropane ring was only little understood until very recently,[7] which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

Scheme I



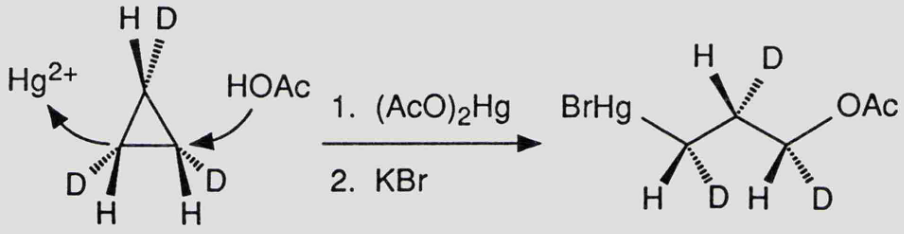
Revitalization of interest in cyclopropane scission in the last few years has led to defining certain relations between the mechanism and the reagent employed.[7] Thus, electrophilic opening by reagents capable of back donation, such as transitions metals (Pd, Pt, and Rh)[8] and halogens (Cl and Br),[9] 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 I). 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 had been a subject of controversy. However very recently "corner" opening was observed with poor back-donors, namely with a proton[11] and with mercury(II);[11,12,13] tricyclic derivatives **1** and **2** (and their congeners with an exo-annulated cyclopropane ring) and stereospecifically trideuterated cyclopropane **5** have been employed to demonstrate this exclusive mechanism (Scheme II).[11,12,13]

Scheme II



1, R = H
2, R = CH_3

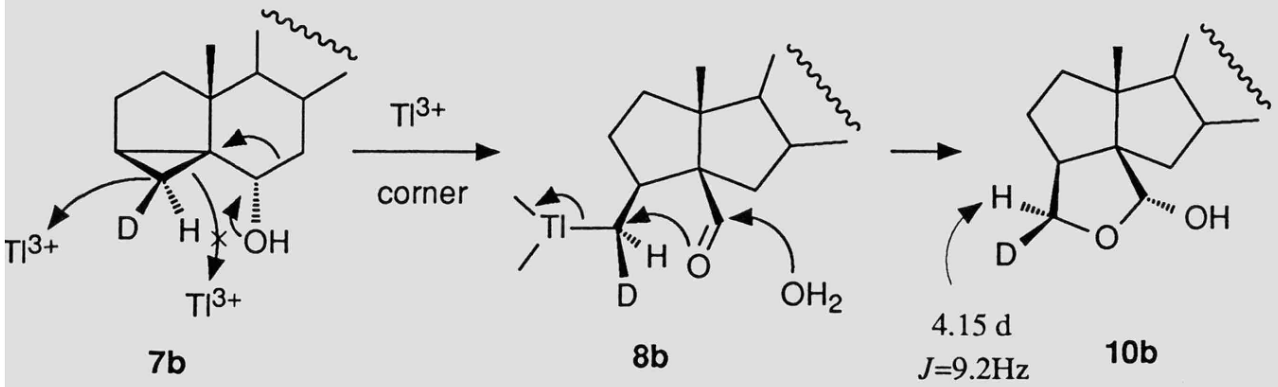
3, R = H
4, R = CH_3



5 **6**

Using double isotopic labelling (^2H and ^{18}O), thallium(III) has been recently shown, for the first time, to be capable of stereospecific "corner" activation and a unique skeletal rearrangement (Scheme II) of 3α,5-cyclo-5α-cholestan-6α-ol (**7** → **8** → **10**) has been described (Scheme III).[14]

Scheme III



7b **8b** **10b**

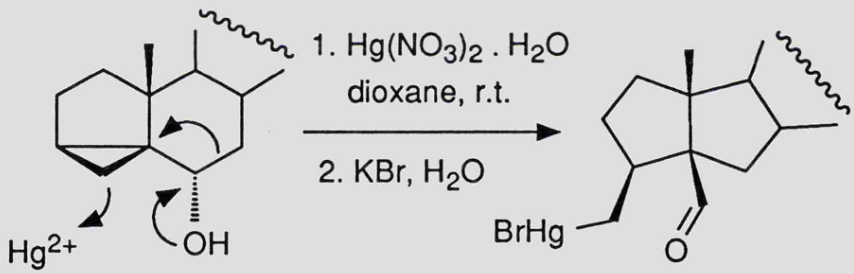
My Thesis can be divided into the two parts. The first part concerns stereochemistry of the cleavage of cyclopropanes by Hg(II) salts. The second part shows further utilization of the resulting organomercurials.

2. Stereochemistry of the Cyclopropane Opening.

2.1. Cyclopropane ring opening by Hg(II) and Tl(III) in the steroidal derivative 7.

Treatment of steroidal cyclopropyl alcohol[15] **7a** with $Hg(NO_3)_2.H_2O$ in DME/CH_3CN (2:5) at room temperature for 1.5 h led, after KBr workup, to a single product **9a**[16] in 97% isolated yield (Scheme IV).

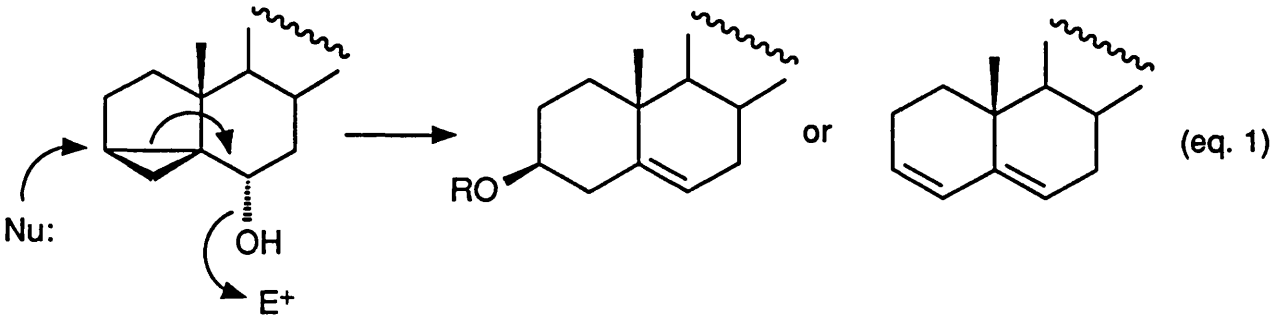
Scheme IV



7 **9**

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 the Tl(III).[14] In contrast to the Tl(III)-mediated reaction,[14] where the organothalliated species **8a** undergoes an instantaneous conversion to lactol **10a**, the organomercurial **9a** 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).[21,22] Other isoelectronic cations (Au^+ and Pb^{4+}) 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 **7a** 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 to be either inert (possibly due to steric hindrance in **7**) 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 $PdCl_2$ (eq. 1).

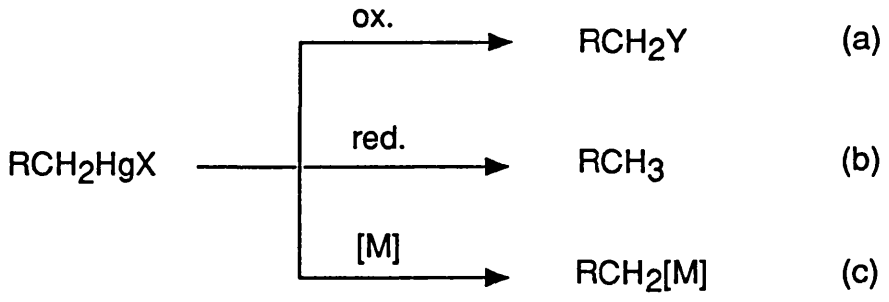


(eq. 1)

Aiming our work to prove the stereochemistry of the cyclopropane fission, we assumed that this mechanism could be established in a way analogous to that it has been employed for thallium,[14] i.e. by using stereospecifically deuterated cyclopropyl alcohol **7b**.[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 **9a**, 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)-(4) bond so that the assignment was not possible at this stage.[26] Hence, transformation of **9a** to a compound in which the C(3)-(4) bond was conformationally fixed, was required.

It is pertinent to note how different types of organometallics can differ ; while alkyl lithiums, Grignard reagents, organocuprates etc. are highly reactive, other organometallics like R-Hg, R-B and R-Sn are relatively stable. This fact has given us a very useful tool for further tuning of reactivity. Until very recently only a few types of transformation of organomercurials have been known (Scheme V).[22]

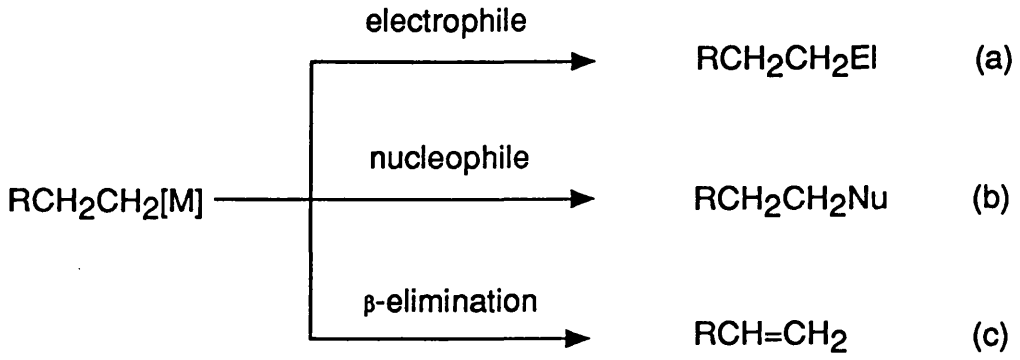
Scheme V



Neither reaction **a** nor **b** could satisfy us since they are believed to be radical and,

therefore, non-stereohomogeneous.[22] By contrast, reactions of the type **c** - transmetallation has been found as a stereohomogenous.[1,3,27,28a-d] Moreover the fact that these reactions have been carried out in the majority of cases with retention of configuration[3,27,28a-d] has given us a useful tool to reach our aim. The intermediate R-CH_2[M] may further react in three possible ways (Scheme VI):

Scheme VI

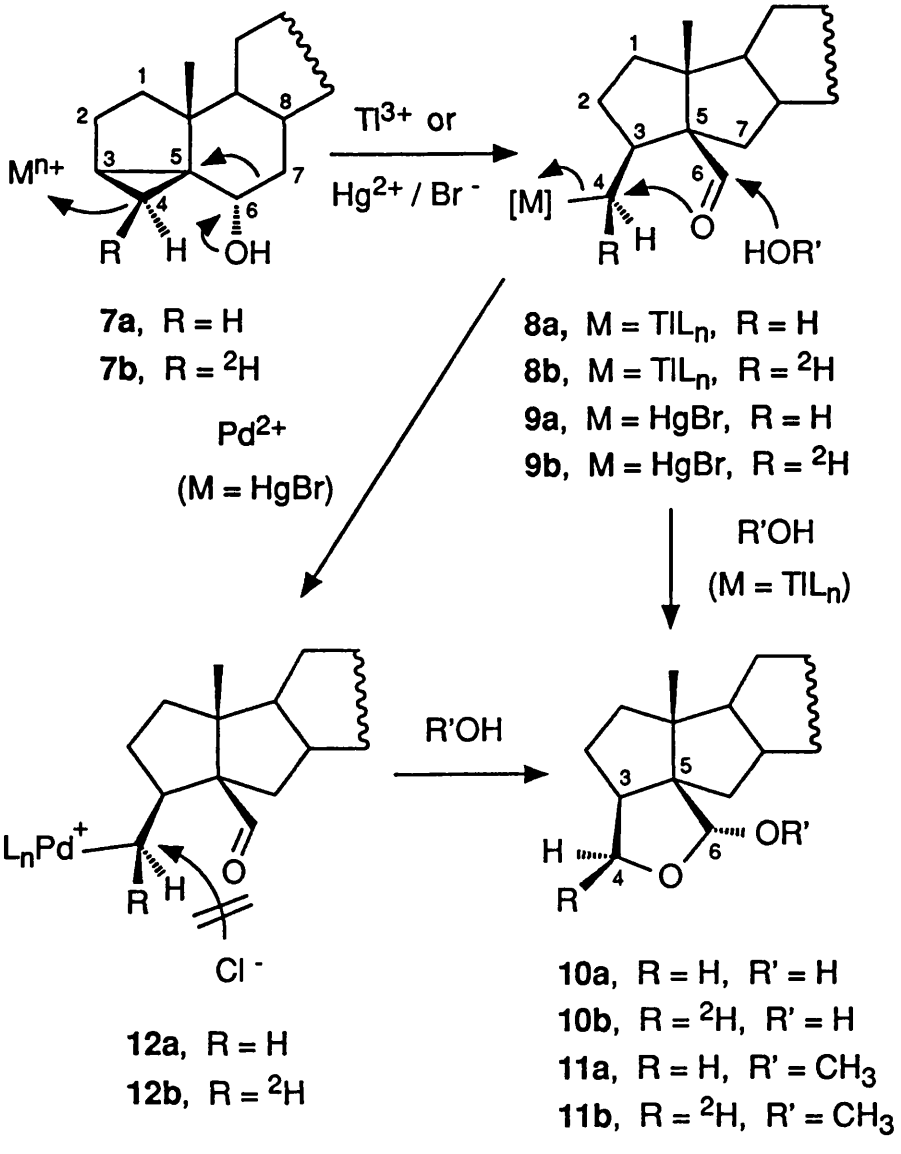


2.1.1. Transmetallation of organomercurial 9 by palladium. Considering all facts we turned our attention to transmetallation of organomercurial **9** by palladium. In this case only pathways (b) and (c) of Scheme VI are possible. The ***syn***-mechanism of β-elimination (pathway c) of organopalladiums has been well established [1,3] and therefore anticipated to assist the determination of configuration at C(4). On the other hand, according to pathway (b) Scheme VI, we could anticipate reaching our aim to obtain products **10** or **11** by analogy to that in previously published studies.[13] After much experimentation, Pd(II) was found to convert **9a** to lactol **10a** or acetal **11a** (via **12a**), in which 4α-H and 4β-H were easily identified (Scheme VII).[29]

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 labelled compounds. Stereospecifically labelled cyclopropyl derivative **7b** was treated with $Hg(NO_3)_2.H_2O$ in the same way as was the unlabelled analogue **7a** and the reaction was quenched with aqueous KBr. Analysis of the ^1H NMR spectrum of the product **9b** revealed the absence of the lower field resonance (2.05 ppm), while the up-field signal at 1.93 ppm was changed to a doublet (J = 8.7 Hz). This indicated that the reaction was stereohomogeneous (≥ 98%). Catalytic

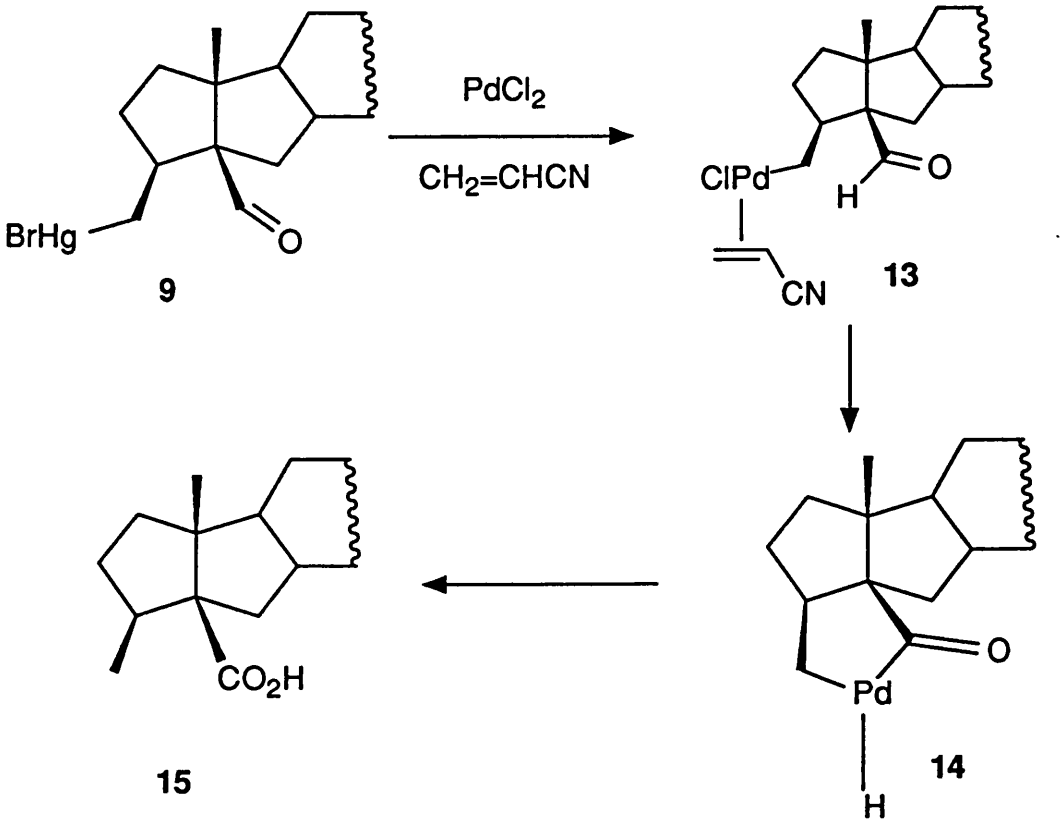
reaction with Li_2PdCl_4 (5 mol%; generated from $PdCl_2$ and LiCl) and $CuCl_2$ (5 equiv.) in DME/H_2O, which is assumed to proceed with retention of configuration[27,28a-d] via **12b**, furnished lactol **10b**, while in the presence of MeOH, methyl acetal **11b** was formed. A stoichiometric reaction, 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 ^1H NMR spectra of the respective products: in the labelled 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 to a doublet (J = 9.2 Hz) are compatible only with the 4β-^2H configuration;[29] the other stereoisomer could not be detected.[30]

Scheme VII



Heumann and Bäckvall have shown[28] that Pd-σ-complexes generated, e.g., from organomercurials by the $PdCl_2/CuCl_2$ method, undergo S_N2 substitution by Cl^- to give alkyl chlorides. Hence lactol **10b** 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(II) triflate, generated *in situ* from $(AcO)_2Pd$ and CF_3SO_3H. The product (**10b**) was identical with that formed by the $PdCl_2/CuCl_2$ method. Apparently, the intramolecular S_N2 substitution is highly favoured in **12** by the steric arrangement and suppresses the intervention of Cl^-.[31,32] These experiments thus provided conclusive evidence for the mechanism of the whole sequence and showed that opening of the cyclopropane ring in **7** by Hg(II) occurred solely in a *corner* fashion.

Scheme VIII

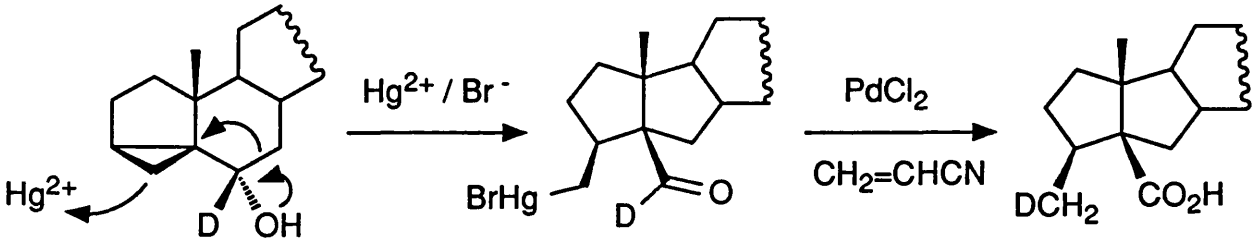


When the transmetallation of the organomercurial **9** with Li_2PdCl_4 was attempted in the presence of a π-acid, such as maleic anhydride, acrylonitrile or 2-cyclohexen-1-one, acid **15** was isolated as the sole or major product, rather than the lactol **10**. Apparently, the

coordination to a π-acid dramatically changed the reactivity of Pd.[34] This rather unexpected reaction can be rationalized as follows. Instead of undergoing the 5(O)$^{\pi,n}$-*exo-Tet* ring closure[31] to **10**, in this instance the transient organopalladium **13** preferred an intramolecular insertion into the C-H bond of the aldehyde group.[35] This step generated palladacycle **14** (a highly unstable Pd(IV)-species), which eventually collapsed to the acid **15** via a hydrogen transfer from Pd to C(4) (reductive elimination) followed by hydrolysis of the acyl-Pd bond (presumably via acyl chloride)[3] and formation of Pd(0).[36] In order to verify this mechanism, deuterated aldehyde **9c** was prepared from 6β-^{2}H-alcohol **7c** (Scheme IX), which in turn was synthesized by a highly stereoselective reduction of 3α,5-cyclo-5α-cholestan-6-one with $LiAl^2H_4$.

Transmetallation of **9c** under the same conditions as applied to its unlabelled counterpart (i.e. Li_2PdCl_4, CH_2=CHCN, DME, H_2O r.t.) resulted in the formation of acid **15b** labelled in the methyl group. The mass and ^{13}C NMR spectra revealed an almost quantitative transfer of deuterium from the aldehyde group to the methyl,[37] which is in an excellent agreement with the proposed mechanism.[38]

Scheme IX

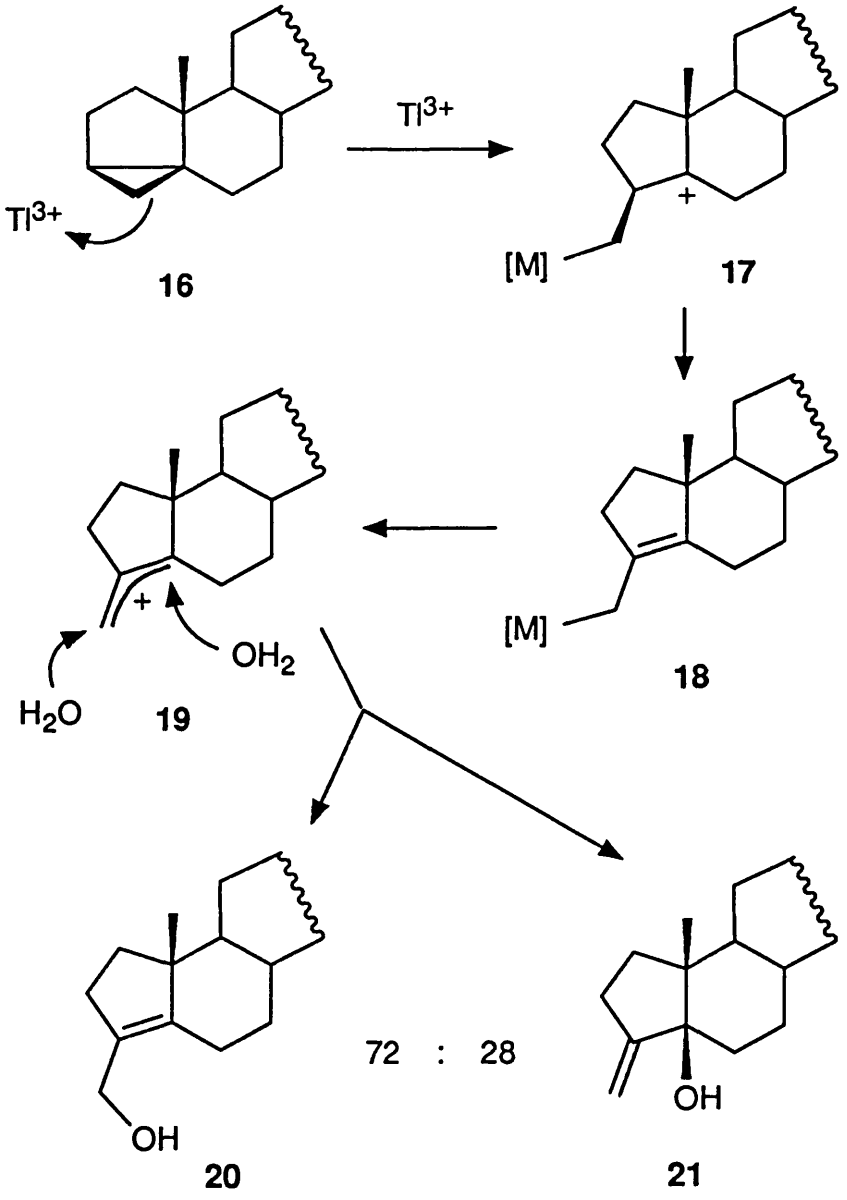


7c **9c** **15b**

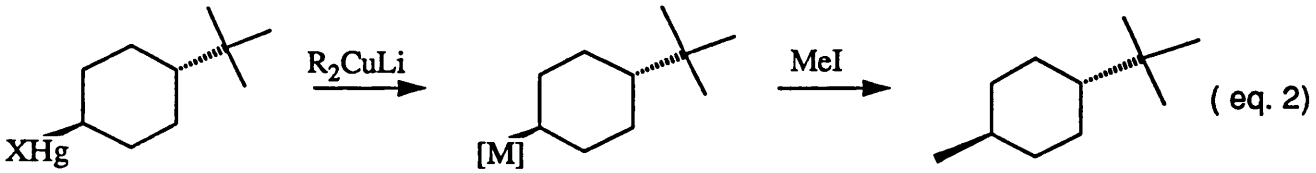
2.1.2. Cyclopropane ring opening by Hg(II) and Tl(III) in steroidal hydrocarbon 16. In the absence of the 6α-hydroxy group (**16**), the reaction with $(AcO)_2Hg$ has been reported to proceed via a simple ring-opening followed by elimination to give the acetate of the corresponding allylic alcohol **20** (Scheme X).[39] The reaction was believed to be initiated by an *edge* attack of Hg(II).[39] 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 **20** and **21**,[40] presumably via the allylic cation **19**.[42] 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 **17** appears to be the driving force for the reaction. While here the elimination (**17** → **18**) seems to be the energetically cheapest subsequent process, in the case of cleavage of **7** the initial cleavage is followed by Wagner-Meerwein migration of C-7.

Scheme X



2.1.3. Transmetallation of Hg for Li and Cu in organomercurial 9 and 27.[43] In order to bring about an intramolecular addition to the aldehyde group (to construct a four-membered ring), we attempted a transmetallation of **9a** that would generate a more reactive species[22] (Pathway b, Scheme VI). Organolithium reagents (MeLi, *n*-BuLi, and *t*-BuLi) proved unrewarding as they produced complex mixtures. We reasoned that intermediates derived from softer metals might be more promising, and after several unsuccessful attempts using various transition metals, we turned our attention to copper[43] (Scheme XI). Although in the last two decades organocuprates have been used as a very powerful tool for organic chemists, their ability to transmetalate organomercurials has been investigated in one case only.[44] Authors in this paper have declared stereohomogeneity of the above reaction (retention of configuration of transmetallation)(eq. 2).



(eq. 2)

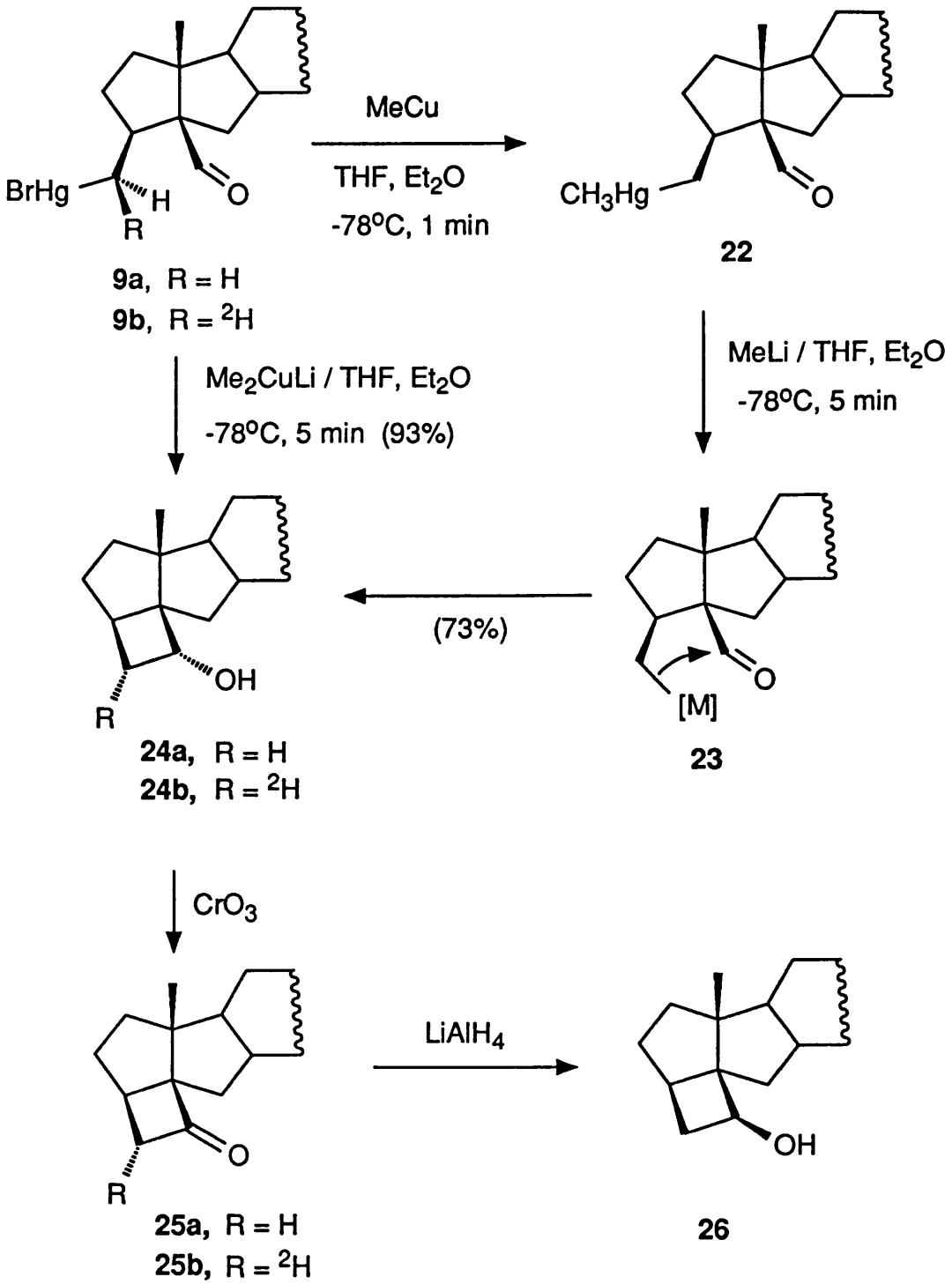
In due course, MeCu effected clean methylation on mercury, providing the MeHg-derivative **22** (94%). This result itself may represent a new method for the preparation of dialkyl mercury derivatives RHgR' from the readily available organomercury halides RHgBr. Other reagents that also gave high yields of **22** were Me_3Al (69%) and Me_2Zn (91%).

Subsequent treatment of **22** with MeLi at low temperature resulted in the formation of the desired cyclobutanol **24a** (73%). Alternatively, **24a** was obtained in one pot on reaction of **9a** with Me_2CuLi in an excellent yield (93%). This reaction can be understood in terms of the Lipshutz observation of an equilibrium between a cuprate and alkyllithium (2 $Me_2CuLi \rightleftarrows$ MeLi + Me_3Cu_2Li).[45] Similarly, CH_2=$MoCl_3$, generated in situ from MeLi and $MoCl_5$,[46] also converted **22** to **24a** in a good yield.

The stereostructure of cyclobutanol **24a** was corroborated as follows. (1) An NOE (5.7%), observed for C*H*-OH upon irradiation of 10β-CH_3, is compatible only with an α-configuration for the hydroxyl. (2) Alcohol **24a** was oxidized with Jones' reagent to ketone

25a, whose $\nu_{C=O}$ = 1750 cm^{-1} was in the range typical for cyclobutanones.[47] (3) On reduction with $LiAlH_4$, ketone **25a** furnished alcohol **26**,[49] epimeric with **24a**, for which no NOE for C*H*OH and 10β-CH_3 could be observed.

Scheme XI



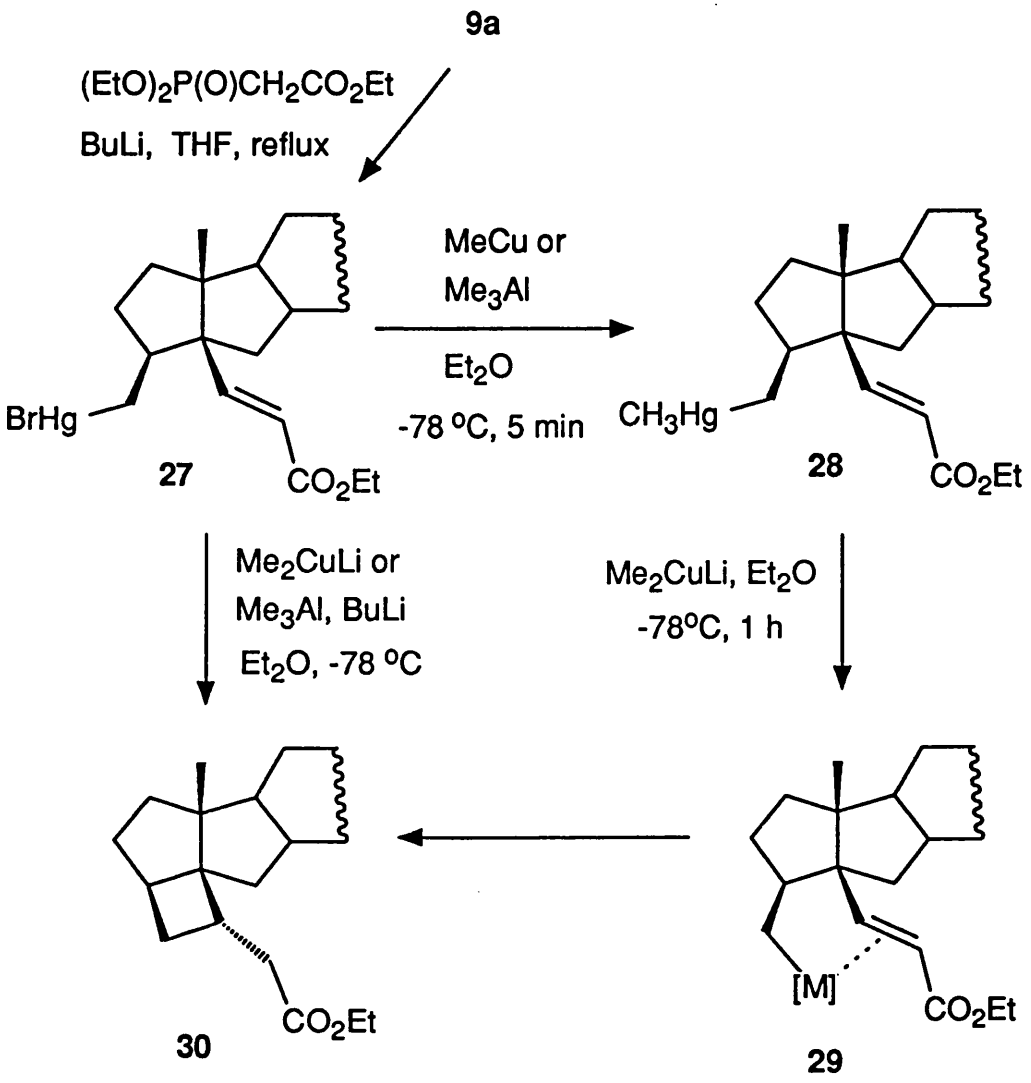
When deuterated organomercurial **9b** was subjected to the reaction with Me_2CuLi, a stereospecifically deuterated cyclobutanol **24b** was obtained. In this case, the 4α-configuration of deuterium was determined in ketone **25b**,[50] that was prepared from **24b** by Jones' oxidation. The ^1H NMR spectrum of **25b** 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. The alternative of double inversion is unlikely in view of the generally accepted mechanism of transmetallation reactions which involves retention of configuration.[3]

Having thus successfully accomplished intramolecular addition to the C=O bond to produce cyclobutanol **24** we explored the possibility of an intramolecular conjugate addition to an activated C=C bond. The required substrate, α,β-unsaturated ester **27**, was prepared from aldehyde **9a** on Horner-Emmons olefination with $(EtO)_2P(O)CH_2CO_2Et$ and BuLi in refluxing THF (Scheme XII).

Although the reaction was rather slow (reflux for 12 h) due to steric hindrance, the yield of **27** 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.[51]

We first explored the reactions with copper reagents.[52] Organomercurial **27** was first methylated with MeCu or Me_3Al to give **28** (in 91% and 95% yield, respectively). In contrast to **22**, however, reaction of **28** with MeLi or BuLi produced a complex mixture; Me_2CuLi proved more efficient, furnishing the desired cyclobutane derivative **30** (40%). A much better yield of **30** (75%) was obtained in one pot from **27** on reaction with Me_2CuLi. This behaviour suggests that the actual reactive species **29** involves copper. Although the structure of **29** is speculative, it seems reasonable to assume[44] that M = $CuLiCH_3$ or $CuHgLiCH_3$ and that the more suitably positioned C(4) in the complex **29** adds across the double bond in preference to the CH_3 group. Finally, treatment of **28** (first generated *in situ* from **27** by means of Me_3Al) with Me_3Al/*n*-BuLi furnished **30** in 92% isolated yield.[54]

Scheme XII



2.1.4. Reaction of organomercurial 9 with $MoCl_5$. Being encouraged by the results described above, we have sought another possibility to enhance the reactivity of the organomercurial **9**. According to the literature,[55] organomercurials are activated by treatment with "highly reactive halogenides". One example of such highly reactive species would be $MoCl_5$ which we have decided to explore. To our surprise, organomercurial **9** was readily converted into cholesteryl chloride **33** in high yield (79%). This unexpected transformation can, *a priori*, be rationalized in two ways (Scheme XIII).

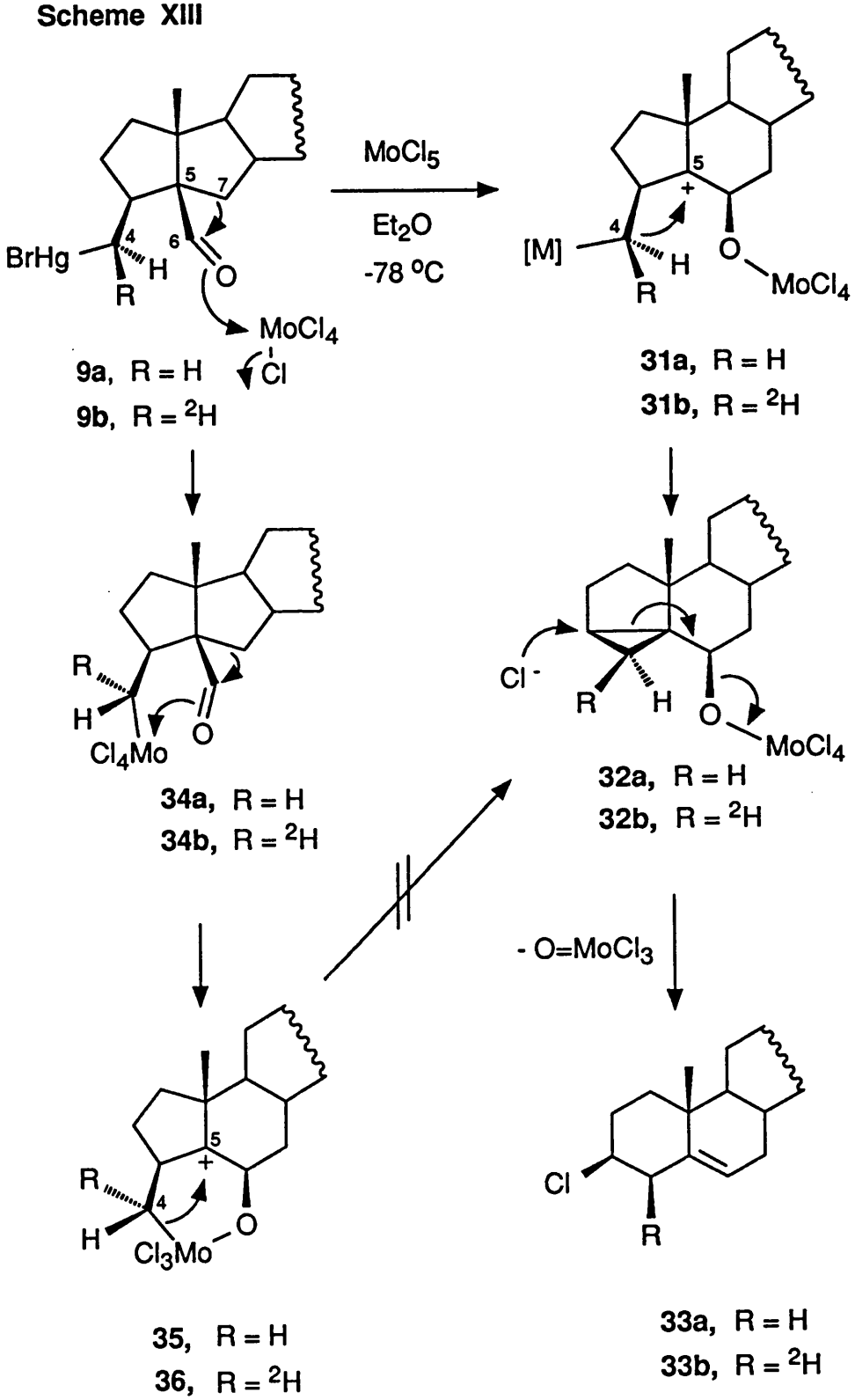
The highly oxophilic Mo(V) can be assumed to first coordinate to the aldehyde oxygen which would trigger a stereoelectronically controlled Wagner-Meerwein migration of C(7) from C(5) to C(6) generating carbocation **31a**. The cationic species **31a** must be extremely unstable and the following event is likely to be the formation of a bond between C(4) and

C(5), which may, presumably, occur with *inversion* at C(4) as suggested by the geometry of **31a** (this sequence may well be concerted). The resulting cyclopropyl intermediate **32a** subsequently collapses to cholesteryl chloride (**33a**) via the well known[56] "*iso*-steroid" rearrangement.[57] Alternatively, if transmetallation is considered as the first event to generate **34a**, the C(7) migration may be initiated by an *intramolecular* coordination of the carbonyl oxygen to molybdenum.[58] The cation **35** generated in this way is likely to produce **32a** with *retention* at C(4).

The question as to which of these two pathways does operate was addressed by labelling. The deuterated organomercurial **9b** was treated with $MoCl_5$ in Et_2O as was its unlabelled counterpart. Analysis of the ^1H NMR spectrum of the resulting deuterated cholesteryl chloride **33b** established the configuration of deuterium as being 4β[59] and revealed that the whole reaction sequence was, again, remarkably stereoselective, as no other diastereoisomer could be detected. The 4β-^2H configuration is compatible with inversion of configuration at C(4) in the C(4)-(5) bond-forming step (**31b** → **32b**). The other pathway (**34b** → **36**) can thus be excluded as it would require retention at C(4). The exact structure of **31** is unknown and it would be premature to make conclusions at this stage as to whether M = Hg or Mo. We believe that both species can serve as intramolecular nucleophiles to trap the C(5)-electron-defficient centre. If, however, transmetallation had occurred, retention of configuration at C(4) is assumed.[60-62]

Interestingly, the reactivity of $MoCl_5$ proved to be solvent dependent. In THF, chloride **37** was formed as the major product from **9a**, rather than cholesteryl chloride (Scheme XIV).[64] Since **37** could not be fully purified and characterized, its structure was determined by the silver(I)-mediated conversion[65] to lactol **10a**. The same reaction carried out with **9b** showed that **38** was formed non-stereospecifically, as a ~2:1 mixture of **10b** and its C(4)-epimer.

Scheme XIII



9a, R = H
9b, R = ^{2}H

31a, R = H
31b, R = ^{2}H

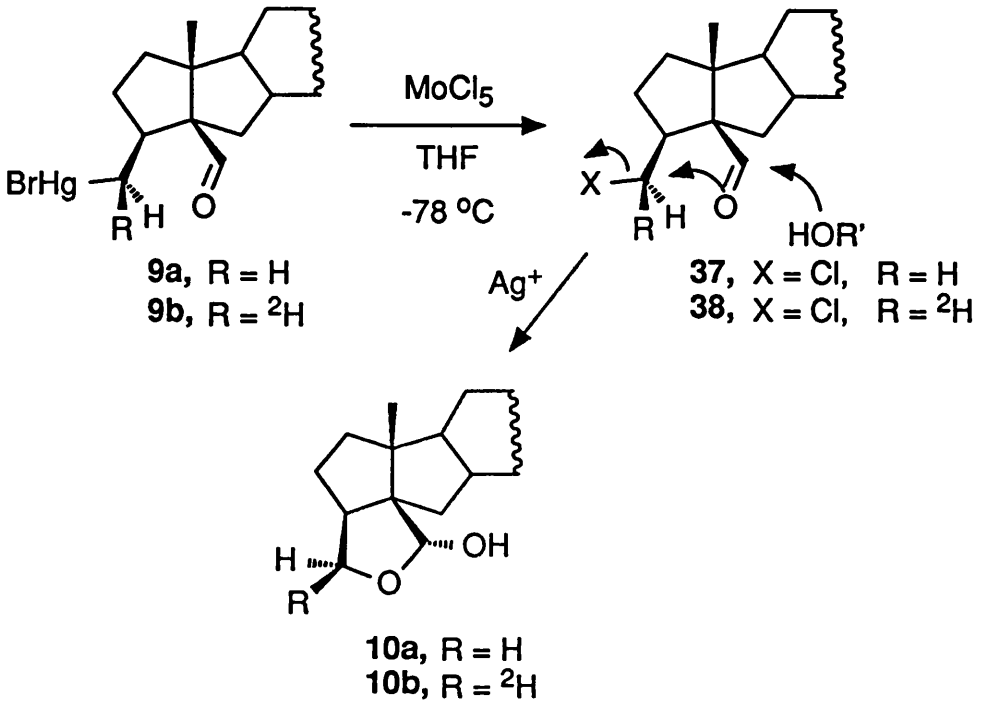
34a, R = H
34b, R = ^{2}H

32a, R = H
32b, R = ^{2}H

35, R = H
36, R = ^{2}H

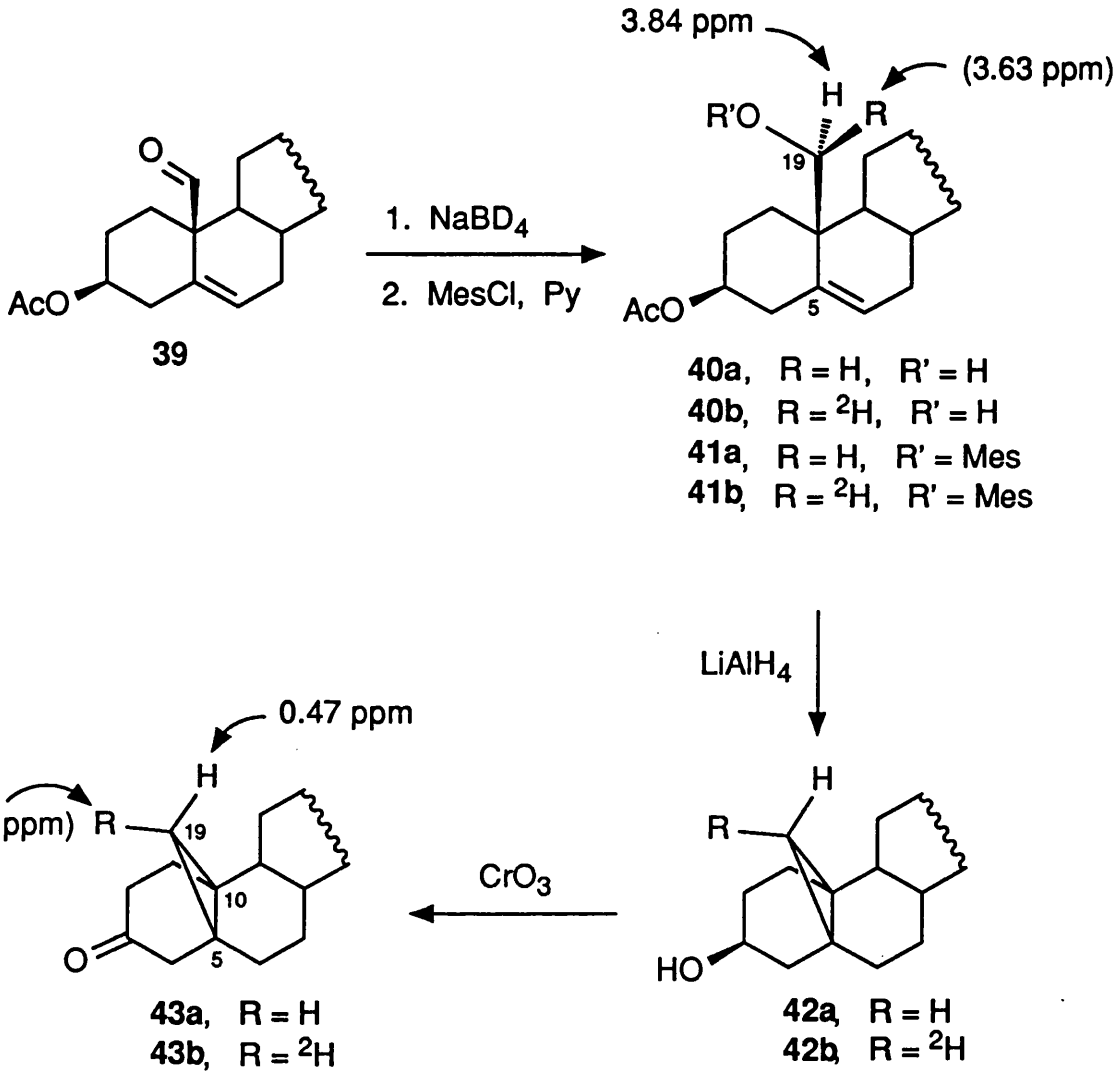
33a, R = H
33b, R = ^{2}H

Scheme XIV



2.2. Mercury(II)-mediated ring opening in 51 and reactivity of the resulting organomercurials. Seeking further generalization of the stereochemistry of cyclopropane scission, we decided to synthesize **43** as another model compound for it seemed to be particularly suitable to our goals. In this case, preferential cleavage of C(5)-C(19) and/or C(10)-C(19) bond was anticipated[66] in accordance with the apparently general regioselectivity observed, e.g., with **7** (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 **43a** because in this instance, the C(5)-cation should produce only a conjugated ketone. The deuterated derivative **43b** was prepared from the aldehyde **39** employing a literature procedure (Scheme XV).[67,68]

Scheme XV : Mes = CH_3SO_2



Reduction of aldehyde **39** with NaB^2H_4 afforded the deuterated alcohol **40b** as a 70:30 mixture of C(19)-epimers.[68] Mesylation followed by reaction with $LiAlH_4$ afforded cyclopropyl alcohol **42b**[69] oxidation of which with Jones' reagent furnished the desired ketone **43b** as a 68:32 mixture of C(19)-epimers.[70]

Treatment of **43a** with $Hg(NO_3)_2.H_2O$ in DME at 0 °C for 2h led, after KBr workup, to a mixture of three olefinic organomercurials **44a**, **46a**, and **47a** (Scheme XVI).[71]

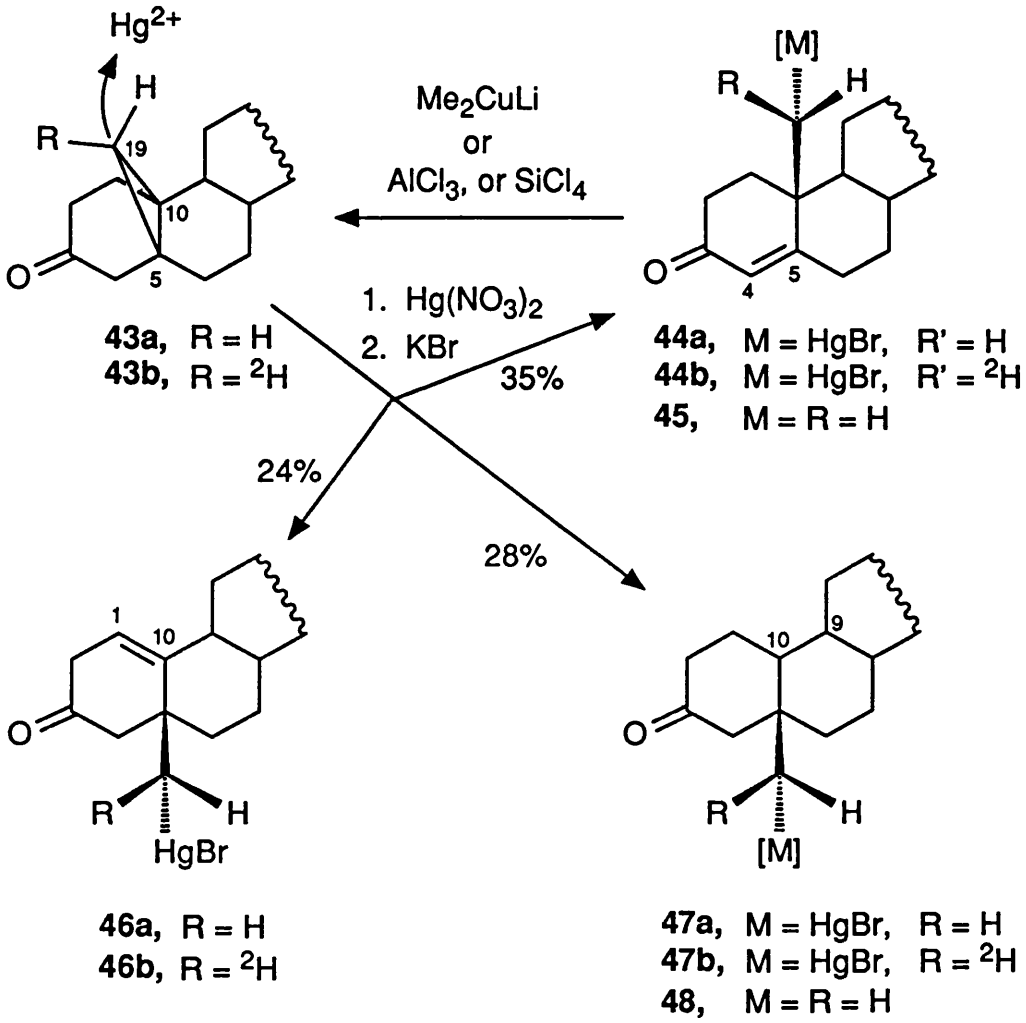
The structures of **44a** and **47a** were corroborated by chemical correlation: upon Bu_3SnH reduction, **44a** furnished the known cholest-4-en-3-one (**45**), while **47a** afforded the Westphalen-type ketone **48**, identical with an authentic sample.[72,73] The structure of **46a** was deduced from spectral data.[74]

The reaction of the deuterated cyclopropyl derivative **43b** with $Hg(NO_3)_3$ proceeded

analogously giving **44b**, **47b**, and **46b**. The reaction was highly stereospecific: starting from a 68:32 mixture of **43** and its C(19)-epimer, **44b** turned out to be a 65:35 mixture of C(19)-epimers; a similar composition was detected for **46b** (68:32).[75] This outcome corresponds to 96% and 100% diastereoselectivity, respectively, which is within the experimental error of the ratio determination by the ^1H and ^2H NMR. Since the configuration at C(19) of these organomercurials could not be safely established from their NMR spectra, we assumed that chemical correlation employing the chemistry described for **9b** would be of use for this purpose. To this end we have attempted transmetallation with cuprates, expecting a ring closure reaction in analogy with the previously observed formation of cyclobutane ring (**9b** → **24b** and **27** → **30**). First, the reaction was tested on the unlabelled organomercurial **44a**. To our delight, Me_2CuLi was found to induce cyclization resulting in the formation of **43a** (86%). This highly efficient ring closure represents a novel way for the construction of cyclopropyl derivatives and was also accomplished with $AlCl_3$ and $SiCl_4$ in good yields (93% and 80%, respectively); $MoCl_5$ and $BF_3.Et_2O$ gave complex mixtures of products.

Unfortunately, the promising cuprate-mediated cyclization of **44b** turned out to be nonstereospecific. Thus, starting from the 65:35 mixture of **44b** and its C(19)-epimer, a mixture of **43b** and **49** in 53:47 ratio was formed (Scheme XVII) as revealed by integration of the signals of cyclopropane protons in the ^1H NMR spectrum (singlets at 0.47 for **43b** and 0.51 for **49**). This is in sharp contrast with the highly stereohomogeneous cyclobutane ring closure **9b** → **24b** where no more than 10% scrambling was observed.[76] While retention of configuration at the nucleophilic carbon largely dominated the cyclobutane ring formation, this pathway (**44b** → **B** → **49**) was considerably suppressed at the expense of a competing mechanism (**44b** → **A** → **43b**). The latter mechanism would be in line with the inversion of configuration at C(4) in the $MoCl_5$-mediated cyclopropane ring closure **31b** → **32b**.

Scheme XVI



43a, R = H
43b, R = ^{2}H

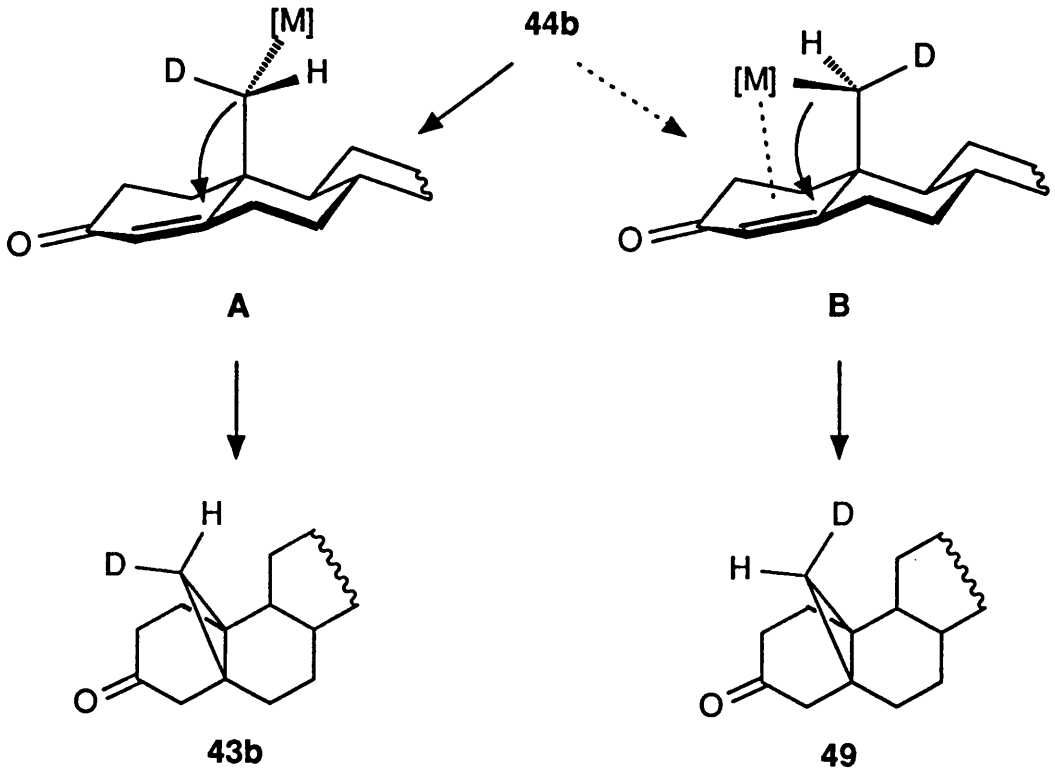
44a, M = HgBr, R' = H
44b, M = HgBr, R' = ^{2}H
45, M = R = H

46a, R = H
46b, R = ^{2}H

47a, M = HgBr, R = H
47b, M = HgBr, R = ^{2}H
48, M = R = H

We reasoned that a Lewis acid-mediated ring closure might proceed with higher stereoselectivity, in analogy with the highly stereoselective reaction of $MoCl_5$ described above (Scheme VIII). Therefore, the cyclization of **44b** 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 cyclopropyl derivative obtained turned out to be a 62:38 mixture of **43b** and **49** which corresponds to 95% d.e. for the ring closure and 91% d.e. overall for the two-step sequence (**43b** → **44b** → **43b**). Since transmetallation of Hg for Al is unlikely, we can conclude that the crucial ring closure occurred predominantly with inversion at C-19 (**44b** → **A** → **43b**; M = HgBr). To gain further support for this mechanism, we have explored the reaction of **9b** (Scheme XIV) with $AlCl_3$ and found it to proceed with the same stereochemistry as for $MoCl_5$. This not only further supports the mechanism formulated in Scheme XIV but also lends additional credence to the mechanism of formation of **43** from

Scheme XVII



44. In view of these mechanistic considerations we can assign a (19*S*) configuration to the organomercurial **44b** (major epimer) which is consistent with a stereospecific corner opening of the cyclopropane ring in **43b** (Scheme XVI).

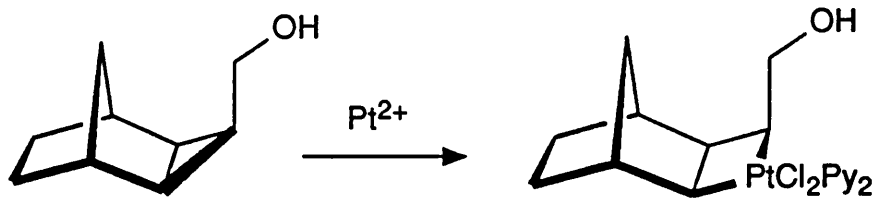
Since **43b** was recovered (after the opening and ring-closure) as a 62:38 mixture of C-19 epimers, one can possibly argue that this ratio reflects some sort of thermodynamic equilibration rather than a stereodefined transformation. To rule out this possibility, we endeavored to synthesize the starting cyclopropane derivative **43a** of a different (preferably higher) epimeric purity. Carrying out the sequence of ring-opening and ring-closure again should show whether or not the stereoselectivity of the process was the same as in the previous case. We have found that the aldehyde **39** can be reduced with $LiAl^2H(OBu^t)_3$ (generated in situ from 1 mol of $LiAl^2H_4$ and 3 mols of *t*-butyl alcohol) to give **40b** as an 85:15 epimeric mixture (in contrast to the 70:30 mixture arising from the NaB^2H_4 reduction). The alcohol **40b** thus obtained was converted to the cyclopropyl ketone **43b** (84:16) via the mesylate **41b**, using the same procedure as before (Scheme XV). The new derivative **43b** was then treated with $Hg(NO_3)_2$ to give **44b** and its isomers (Scheme XVI). Organomercurial **44b**

was converted back to **43b** on reaction with aluminium chloride. ^{1}H 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 an excellent agreement with the overall stereoselectivity obtained for the lower isomeric ratio (91% d.e.; 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.

2.3. Discussion

The observed behaviour 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 favour *stereospecific corner opening*[77] 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 **7** and **43** (this report) and **1** and **2** (and their *exo*-annulated isomers),[12] as well as for the parent cyclopropane **5**[13] and its methylated counterpart.[14] Unfortunately, direct comparison of the reactivity of Hg and Tl vs transition metals (Pd, Pt, etc.) and with Br_2 cannot be made with our model compounds as they are either inert to these reagents or undergo different transformations (namely the conversion to cholesterol or its derivatives; see above). Nevertheless, e.g. the cyclopropyl derivative **50**, very closely related to **1** and its *exo*-diastereoisomer (which are known to be corner-opened[12] with Hg^{2+}), has been cleaved by Pt (a transition metal) with exclusive edge selectivity (Scheme XVIII).[8e] Therefore, we believe that the mechanism of opening (corner or edge) is dictated by the nature of the reagent rather than by the substrate structure.[78]

Scheme XVIII



50 **51**

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 (**7** → **8** or **9**). The difference between Tl and Hg is only seen in the fate of the organometallics generated in this way. While the organomercurial **9** is fairly stable, can be isolated in pure state, and used for subsequent transformations, its thalliated counterpart is more reactive and undergoes the nucleophilic ring closure (**8** → **10**). This divergence in behaviour serves as a clear example of how a choice of metal can be used for delicate control of the reactivity.

The organopalladium intermediate **12** offers further opportunities for tuning: here, it is the ligands attached to the same metal that have a decisive influence. In the absence of acceptor ligands or in the presence of $CuCl_2$, the Pd(II) intermediate **12** undergoes a clean, intramolecular S_N2 reaction (**12** → **10**). By contrast, addition of π-acids promotes Pd-insertion into the C-H bond, thus generating a Pd(IV) species and triggering an intramolecular, redox reaction involving a cascade hydride transfer (**13** → **14** → **15**).

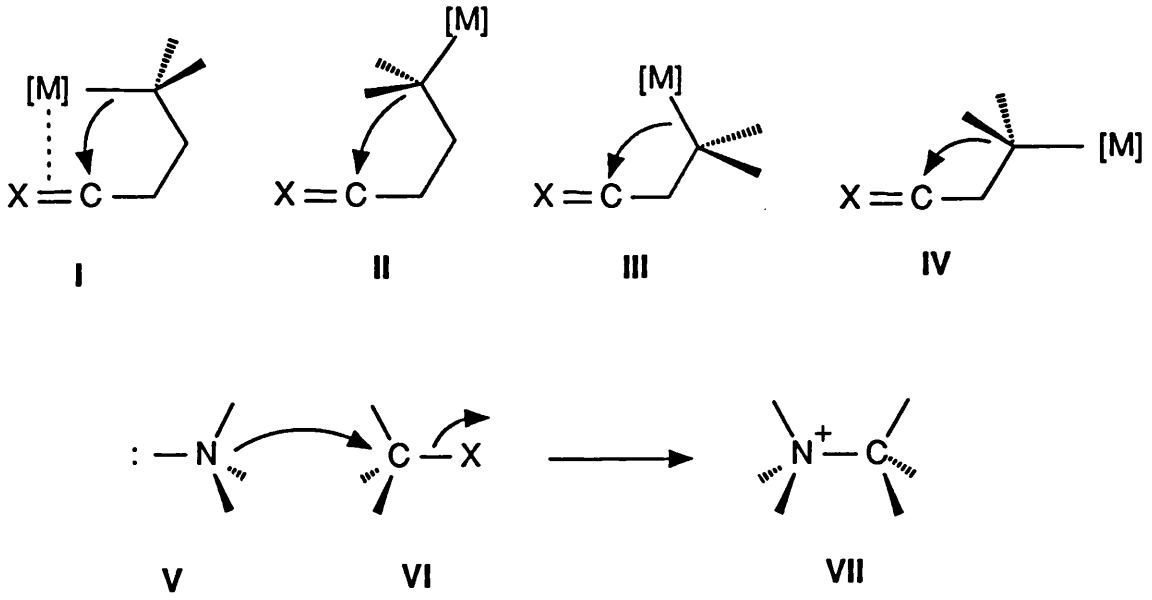
Reactions with MeLi or Me_2CuLi (presumably occurring via transmetallation) have effected a highly stereoselective, intramolecular addition to a carbonyl group and/or across a conjugated double bond, and so construct a "5,5,4" tricyclic system (**9** → **24** and **27** → **30**). These transformations represent a novel methodology for cyclobutane annulation that may be of general use in view of the rather limited number of alternative approaches[79,80] and of the failure of radical reactions. Alternatively, we believe that the strategy employing organomercurials, which can be generated by a number of stereoselective routes,[22] may result in the development of a general method for the stereoselective construction of rings of various size, and for intermolecular coupling as well.

The high configurational stability of the organometallic species such as **23** is remarkable

and contrasts, e.g., with the recently reported[81] 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 cyclobutane ring induced by cuprates (Scheme XI) and a non-stereospecific reaction or predominant retention of configuration in cyclopropane formation when cuprates or Lewis acids are used, respectively (Scheme XIII and XVII). Since no difference in hybridization at the carbon atom adjacent to mercury has been observed for **9a** and **44a**,[82] the difference in reactivity must originate elsewhere.

Scheme XIX



In the cyclobutane ring formation, one can assume frontal interaction of the σ-orbital of the C-[M] bond 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 XIX). 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 favoured 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 disfavours the formation of cyclopropane ring (where ~60° angle is required).[83] For the inversion mechanism (**IV**), at least the bonding angle is much more favourable (~ 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**).[84] 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 favoured for the formation of four-membered ring (**I**), whereas both retention and inversion mechanisms (**III** and **IV**) apparently operate when three-membered ring is to be closed up. With Lewis acids as activators, no transmetallation 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**).

3. Further Utilization of the Organomercurials.

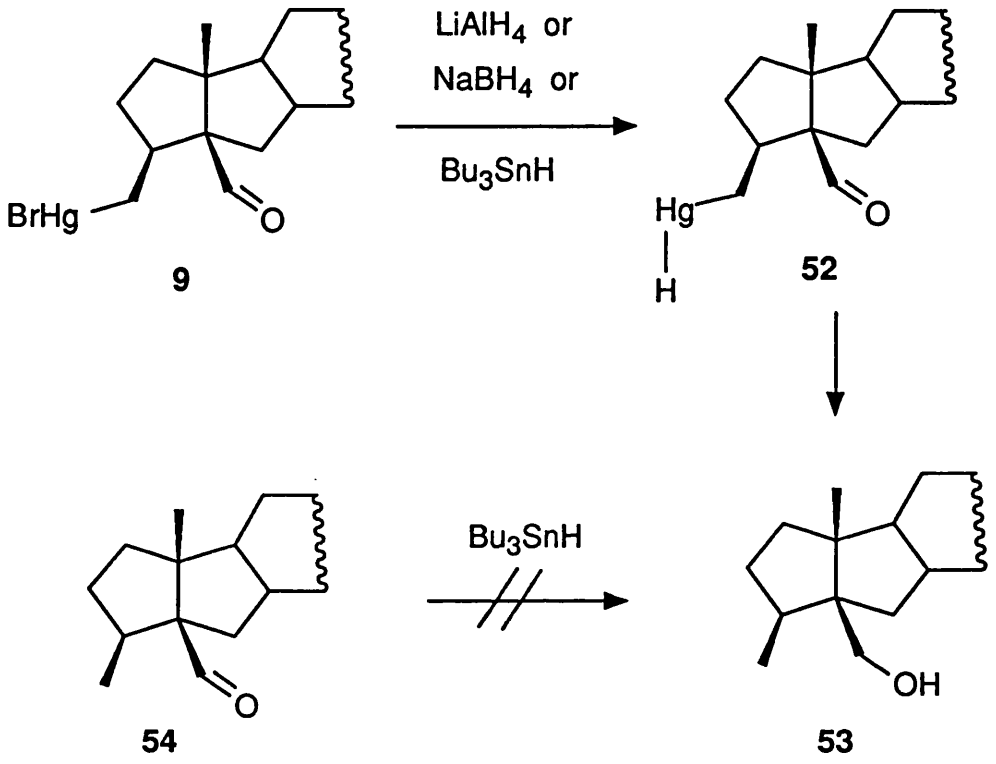
3.1. Transformation of the organomercurials with demercuration. Having established stereochemistry of the cyclopropane scission, we have kept our attention on further utilization of organomercurials for organic synthesis. It was assumed, that stereospecificaly labelled organomercury compounds could help us to understand the mechanism of anticipated transformations.

Thus, the reaction of organomercurial **9a** with Br_2 or NBA was found to produce the lactol **10a**. However, labelled compound **9b** under the same conditions afforded a 1:1 mixture of the corresponding diastereoisomers in accordance with literature.[22]

Reaction of organomercurial **9a** with a variety of hydride reagents has furnished demercurated alcohol **53** in a good yield. Since Bu_3SnH also gave **53** we assume the generation of mercury hydride as an intermediate followed by an intramolecular reduction of

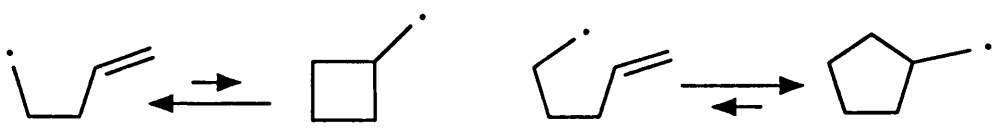
the aldehyde group. No cyclobutane ring closure was observed (Scheme XX).

Scheme XX



Attempted radical cyclization of **27** using $NaBH_4$ or Bu_3SnH gave only the demercurated product (in 81% and 87% respectively), although analogous radical cyclization of an organomercurial intermediate has been successfully employed to construct a five membered ring.[85] Radicals of the type **i** does not cyclize to **ii** as the equilibrium is shifted towards the open species. In contrast, five membered rings can readily be formed by the intramolecular radical addition (**iii** → **iv**)[86,87] (Scheme XXI).

Scheme XXI

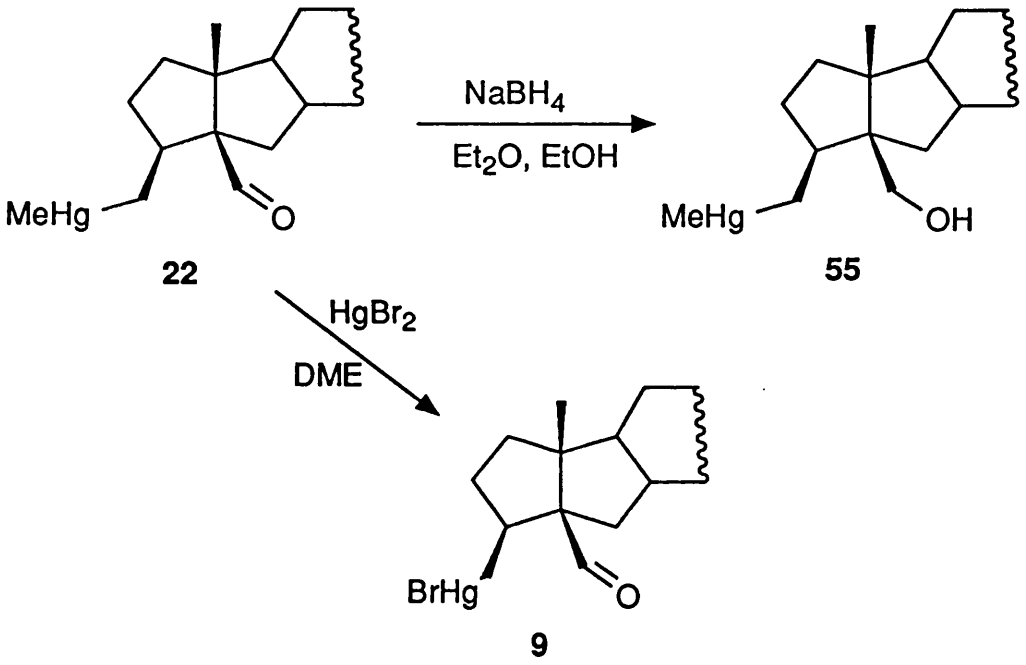


3.2. Transformation of the organomercurials without the loss of mercury. Rather surprisingly, we have found that the methylmercurio derivative **22** behaved differently: while

$LiAlH_4$ still effected the total reduction to the demercurated alcohol **53**, $NaBH_4$ turned out to be milder, producing the alcohol **55** in good yield without side-products (Scheme XXII).

Since we have found that treatment of the methylmercurioaldehyde **22** with $HgBr_2$ produced desired bromomercurioaldehyde **9a** quantitatively (Scheme XXII), methylation can be viewed as a protection of C-Hg group.

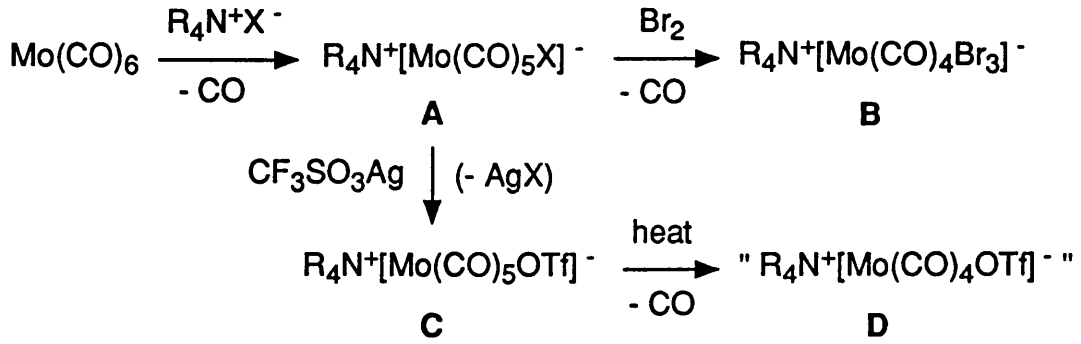
Scheme XXII



3.3. Transmetallation of the organomercurials with molybdenum carbonyl reagents. Finally we turned our attention to the transition metal complexes, namely lower oxidation state molybdenum reagents, and have explored further possibility how to transmetalate organomercury compounds.

Molybdenum hexacarbonyl can readily be converted into several interesting complexes that have not attracted much attention among organic community to date.[88,89] Thus, on reaction with quaternary ammonium halides ($R_4N^+X^-$), $Mo(CO)_6$ looses one molecule of CO to afford a relatively stable complex **A** that can be isolated and stored (Scheme XXIII).[90]

Scheme XXIII



On treatment with Br_2, **A** gives away another molecule of CO, to generate complex **B**.[90] Thus we have prepared the complex $Me_4N^+[Mo(CO)_4Br_3]^-$, that can also be generated in situ, via a known procedure (eq.3).[91,90] We have now found that Br^- or Cl^- in **A** can be replaced by $CF_3SO_3^-$ group on treatment with silver triflate[96] to presumably generate the novel complex **C** which spontaneously looses CO at rt, producing a highly reactive species, for which we tentatively suggest structure **D**.[97]

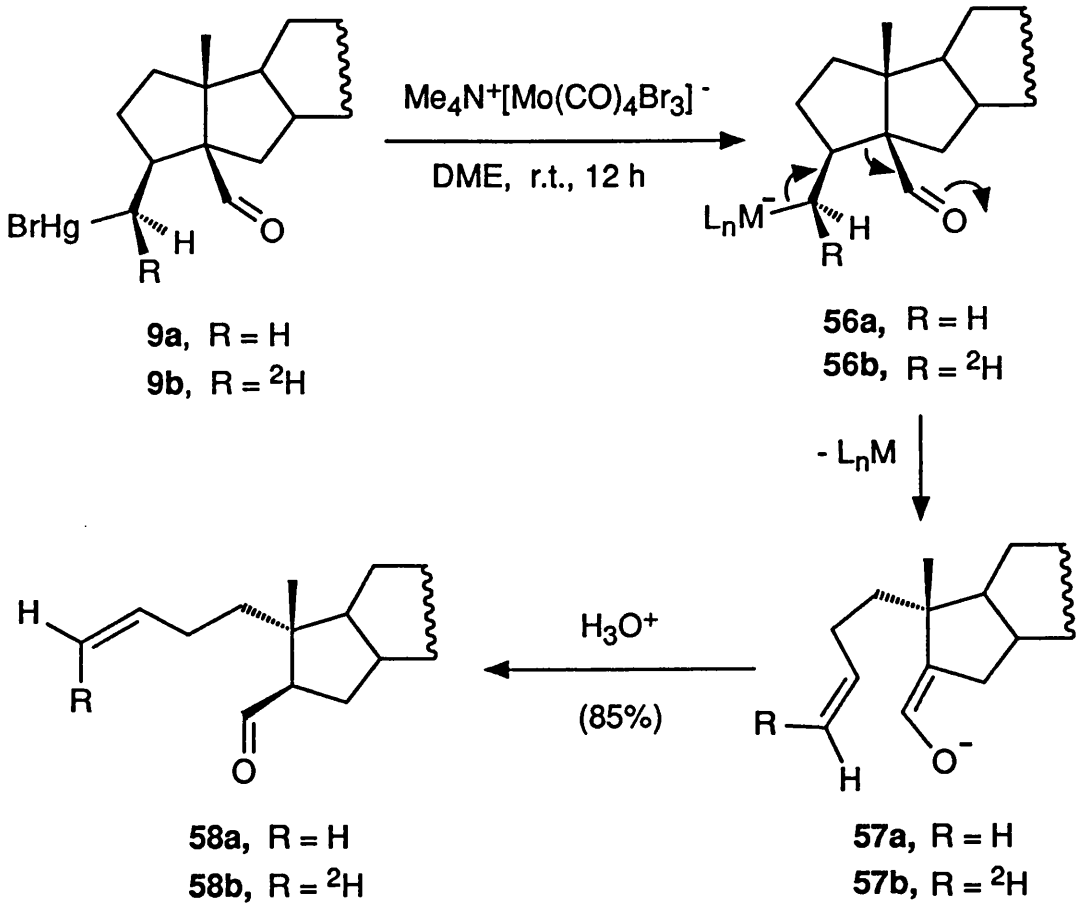
$$Me_4N^+Br^- + Mo(CO)_6 + Br_2 \longrightarrow Me_4N^+[Mo(CO)_4Br_3]^- + 2\,CO \quad \text{(eq. 3)}$$

Using complex **B**, transmetallation of **9a** was apparently accomplished again (with extrusion of $HgBr_2$) but, owing to the negative charge on the metal, the resulting organomolybdenum intermediate **56a** displayed a completely different behaviour compared to other related organometallics (Scheme XXIV). In this case, the molecular structure favoured a stereoelectronically controlled Grob-type fragmentation[92] (or retro-Conia reaction) which eventually gave rise to the olefinic aldehyde **58a** (85%), presumably via the enolate **57a**.[93]

The fragmentation reaction presumably requires an antiperiplanar conformation of C(4)-[M] and C(3)-(5) bonds to allow the stereoelectronically controlled process to occur.[92f] To provide support for this hypothesis, the fragmentation was carried out with deuterated **9b** under the same conditions as those used for its unlabelled counterpart. Analysis of the ^1H NMR spectrum of the product **58b** revealed a (*Z*)-configuration for the terminal,

monodeuterated double bond.[94] Hence, the reactive conformation of the intermediate **56b** should be that discussed above (assuming retention of configuration in the transmetallation step[3]) and the fragmentation can be viewed as occurring accordingly to Scheme XXIV.[95] The methylated counterpart **22** under the same conditions, however, turned out to be inert.

Scheme XXIV



9a, R = H
9b, R = ^{2}H

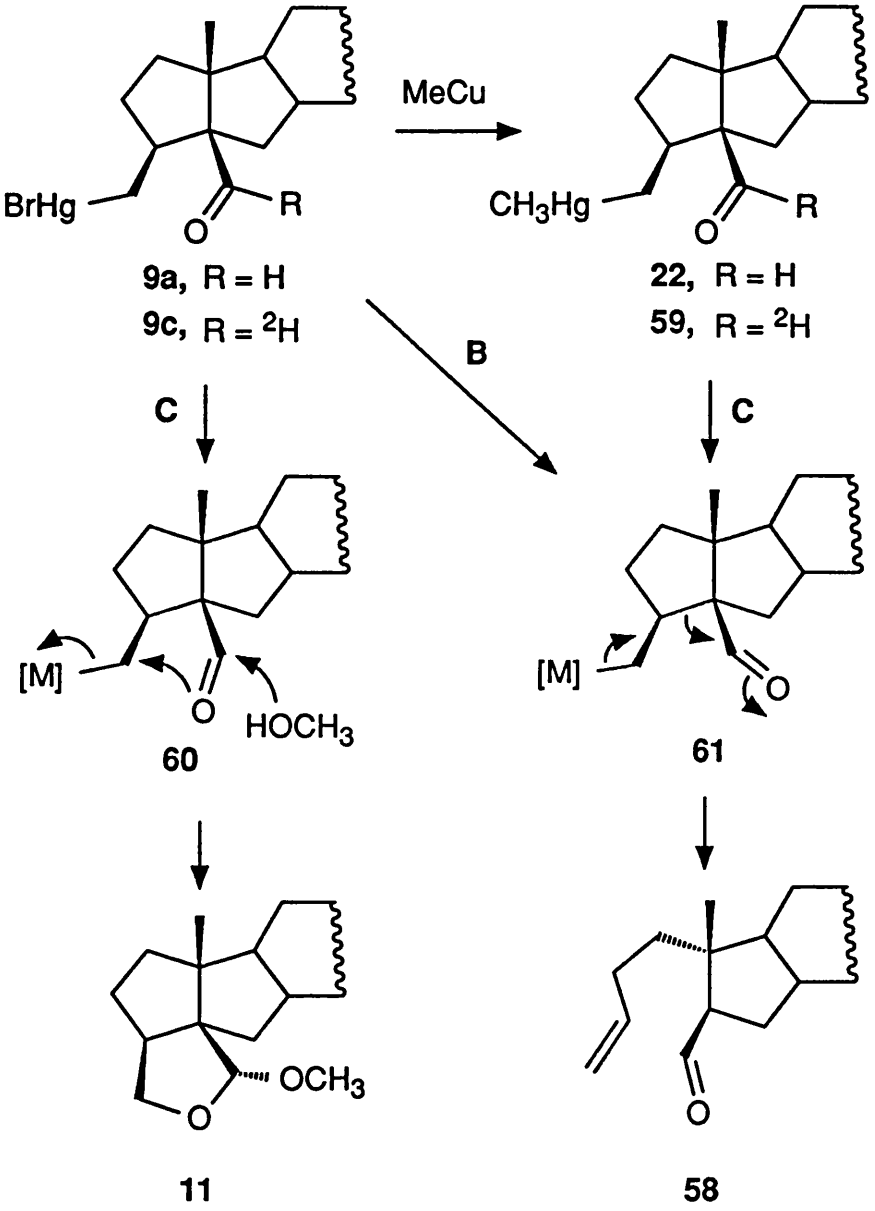
56a, R = H
56b, R = ^{2}H

58a, R = H
58b, R = ^{2}H

57a, R = H
57b, R = ^{2}H

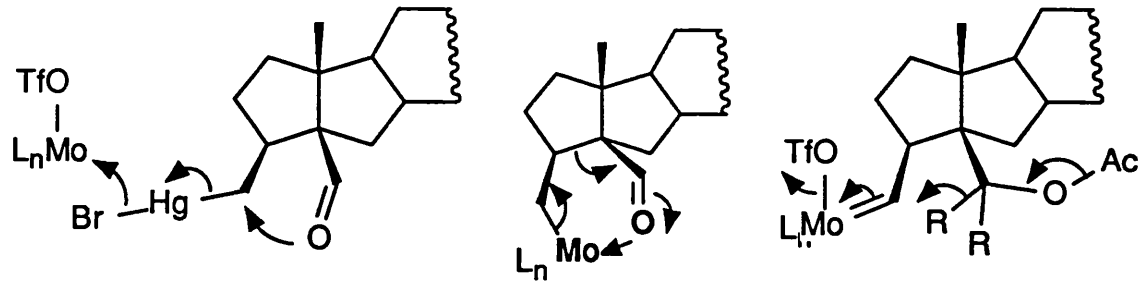
While **9a** undergoes a Grob-type fragmentation (or retro-Conia reaction) on treatment with **B** to produce **58** in 85% yield (Scheme XXV), the complex **C** was found to induce a ring closure resulting in the formation of acetal **11** (50 °C, 4 h; 86%). In contrast to **9a**, methylmercurioderivative **22** is inert to **A** and **B**. However, with **C**, fragmentation was observed, giving rise to **58** (50 °C, 10 min; 95%).

Scheme XXV



To rationalize this intriguing behaviour, we have to take into account the coordinative unsaturation of **C** (or **D**). Such a complex will seek the highest electron density in the substrate molecule. As a consequence, the Hg-Br group in **9a** can be assumed to become the primary target for attack. Pulling Br^- from the molecule (**VIII**) will then induce the cyclization reaction (Chart I) to afford **11**.

Chart I



VIII **IX** **X**

By contrast, with **22**, the complex **C** may find the best stabilization by coordination to the carbonyl group followed by transmetalation[98] (**IX**); the initial coordination will thus direct the regiochemistry of transmetallation in favour of the Hg-CH_2 bond (rather than Hg-CH_3). Subsequent fragmentation of the cyclic intermediate **IX** seems to be the likely pathway to **58**. Finally, reaction of **9a** with **B** has been previously ascribed to transmetallation followed by fragmentation of **59** (M = L_nMo^-).

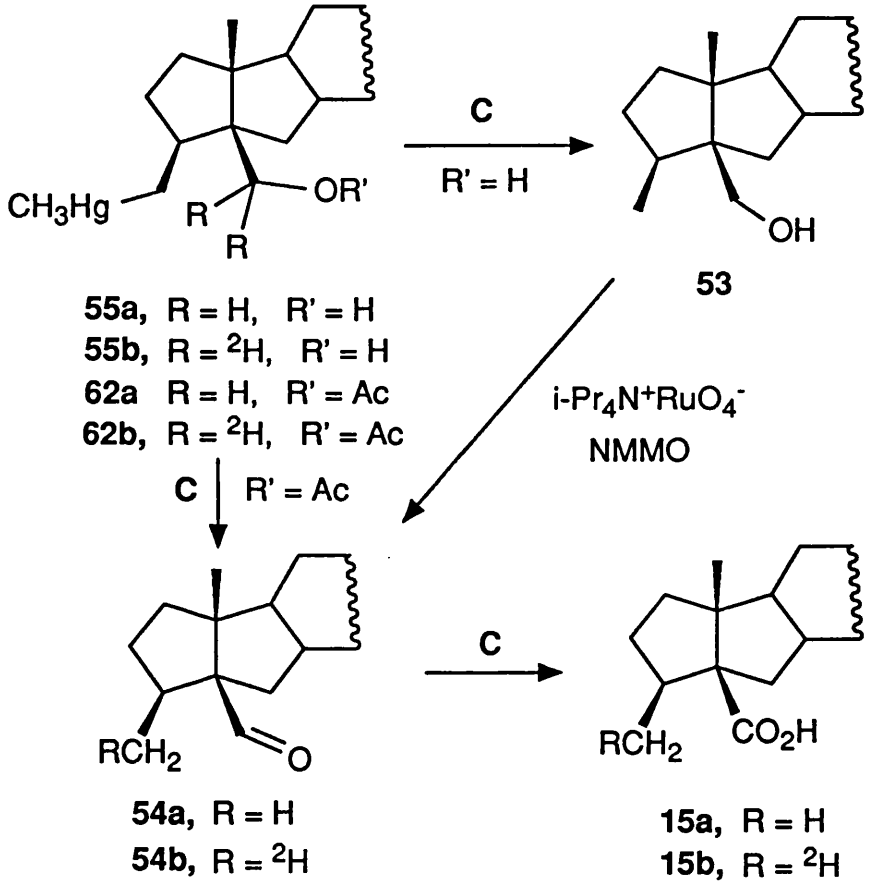
This unexpected diversity prompted us to elucidate the lower oxidation state of the starting organomercurial, i.e. the corresponding alcohol **55** (Scheme XXVI).

The alcohol **55a** turned out to be inert to **A** or **B**. However, complex **C** effected the conversion of **55a** into **53** (50 °C, 20 min; 90%). Although this is formally a reduction reaction, a more likely explanation can be suggested, namely transmetallation followed by protonolysis.[101]

The most striking behaviour was observed for acetate **62a**: while inert to **A** and **B**, it was converted into acid **15a** (94%) on reaction with **C** (50°C, 1 h). Since oxidation of protected alcohols is rare[102] it was of interest to elucidate the mechanism. To this end, we have prepared the deuterated substrate **62b**: the deuterated aldehyde **9c** was first methylated with MeCu and the resulting methylmercurio derivative **59** was reduced with NaB^2H_4 to give deuterated alcohol **55b**, acetylation of which furnished the desired acetate **62b**. The acetate **62b** was then reacted with **C** and the mass spectrum of the product (**15b**) revealed that ≥95% of deuterium was transferred to the methyl. This outcome can be rationalized assuming that a Schrock-type metallocarbene **X** is generated as an intermediate[103] by α-elimination from the initially formed alkyl molybdenum complex (L_nM-CHR_2 ⇄ $L_nHM{=}CR_2$).[104] Once generated, the metallocarbene **X** is likely to be capable of hydride transfer from the CH_2-O

group with concomitant departure of the triflate group.[109] This would produce aldehyde **54b** that may be further oxidized to acid **15b.** Blank experiment showed that **54a** (prepared by an independent method)[111,112] is, indeed, oxidized to acid **15a** by the in situ generated complex **C** in several minutes which is consistent with the proposed mechanism.

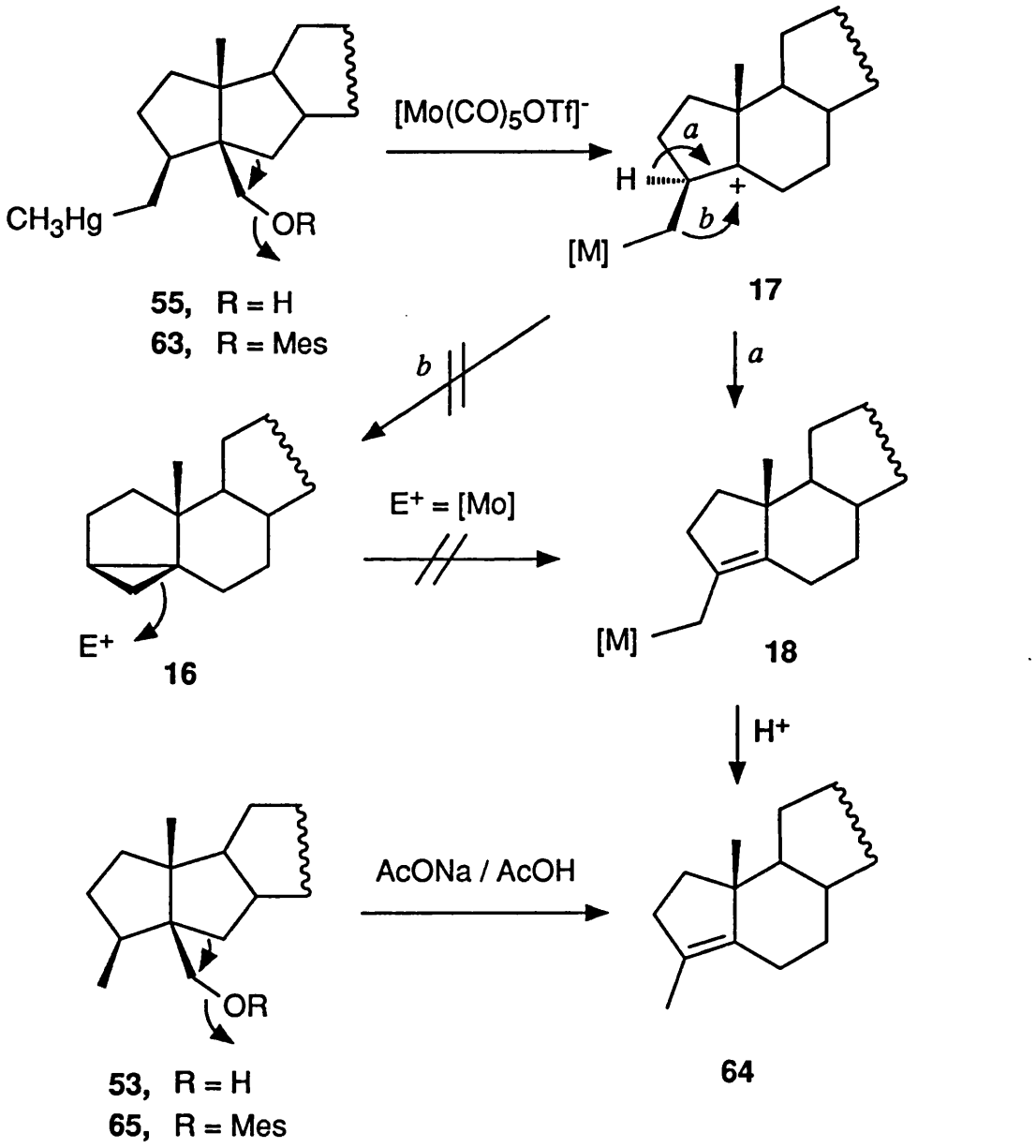
Scheme XXVI



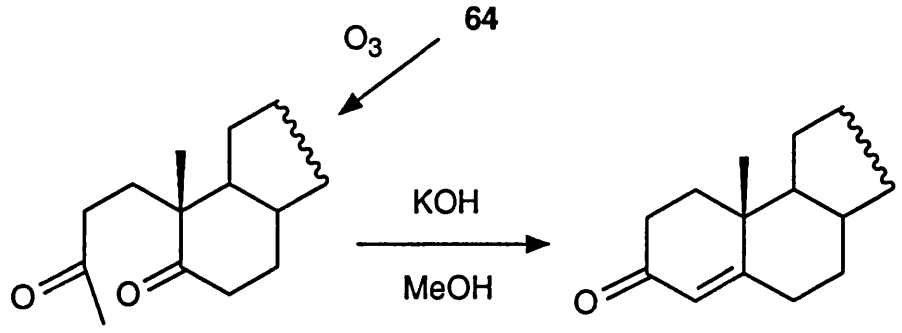
In order to gain further insight into the chemistry of the molybdenum-mediated rearrangements and transformations, we intended to investigate the reactivity of a mesylate corresponding to mercurioaldehyde **9**. In particular, being a good leaving group, CH_3SO_3 in place of the aldehyde oxygen should be even more prone to induce a skeletal rearrangement and provide further mechanistic support to the conclusions concerning $MoCl_5$ mediated rearrangement of bromomercurioaldehyde **9** (see Scheme XIII). Thus, by mesylation of alcohol **55** we prepared desired mesylate **63**. The mesylate **63** was then treated at 45 °C with complex C mentioned above, to give the rearranged olefin **64** as a single product (Scheme

XXVII). The structure of **64** was deduced from spectral data and confirmed by chemical correlation (Scheme XXVIII): ozonolysis resulted in the formation of diketone **66** which readily underwent a base-catalyzed aldol condensation to afford cholestenone (**45**).

Scheme XXVII



Scheme XXVIII



66 **45**

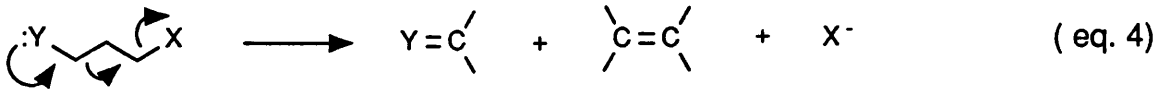
The formation of **64** is apparently triggered off by the departure of the MesO group from **64** followed by the Wagner-Meerwein skeletal rearrangement to generate carbocation **17**. For the stabilization of the latter species, two mechanistic pathways can be proposed: (*a*) proton elimination giving rise to **18**, protonolysis of which gives the final product; (*b*) ring-closure generating the cyclopropyl derivative **16** which might be reopened to **18**. However, it turned out that the cyclopropyl derivative **16** is stable under the reaction conditions, so that path *b* can be ruled out. Since the mesylate **63** was stable (at 45 °C) in the absence of the molybdenum complex, it must be the reagent, rather than the propensity of the skeleton itself to rearrange, that initiates the reaction. The Mo-complex may activate the molecule of **63** in two ways: (1) by lowering the activation energy required for the dissociation of the C-OMes bond, and (2) by enabling the protonolysis of **18** (M = $HgCH_3$) to occur. It is pertinent to note that for **18** (M = HgOAc), nucleophilic substitution is preferred,[39] furnishing **20** (Scheme X). In this case, **18** (M = $HgCH_3$) behaves differently which can be associated with the different substituent on Hg; alternatively, transmetallation to **18** (M = MoL_n) can also be considered. Although it is not possible to differentiate between these two pathways at the present time, it is clear that [M] in **18** in this case (Scheme XXVII) is different from that of Scheme X, as reflected by their different behaviour.

The natural tendency of the skeleton to rearrange, was tested with mesylate **65**. While the molybdenum complex turned out to be inert in this case (at 45 °C), standard solvolytic conditions (AcONa, AcOH, reflux) led to the formation of **64**. This suggests that the Mo-complex activates **63** in two ways, as described above. Moreover, the behaviour of **63**

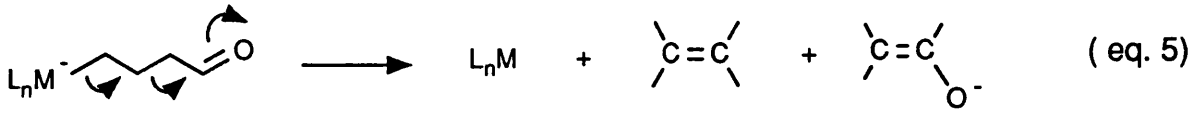
has also provided further support for the mechanistic considerations concerning the Lewis acid-catalyzed rearrangement of the aldehyde **9**, summarized in Scheme XIII.

3.4. Discussion

Similarly to palladium, reactions of the organomercurials with molybdenum complexes can also allow access to different pathways. In this case, the reactivity appears to be controlled by the oxidation state of molybdenum, its ligands, stereoelectronic effects, and the solvent. The remarkable oxophilicity of Mo(V) seems to play decisive role. Thus, while $MoCl_5$ readily converted the substituted [3.3.0]bicyclooctane system into a [4.4.0] skeleton (**9** → **33**), the $[MoL_n]^-$ anion effected a fragmentation reaction (**9** → **56** → **58**). It is pertinent to note, however, the difference between the classical Grob reaction and our Mo-mediated fragmentation: according to the Grob protocol, TsO^- typically serves as a leaving group and the negative species (e.g. O^-) forms a double bond (eq. 4). By contrast, our Mo-complex suffers a different series of events: the negative charge on molybdenum is transduced to the enolate, while Mo leaves as a neutral species (eq. 5). Moreover, whereas the classical Grob fragmentation requires a three-carbon unit with the reacting substituents at 1,3-positions, our fragmentation has occurred on a 1,4-disubstituted, four-carbon framework[113] and can also be viewed as a retro-Conia reaction.



(eq. 4)

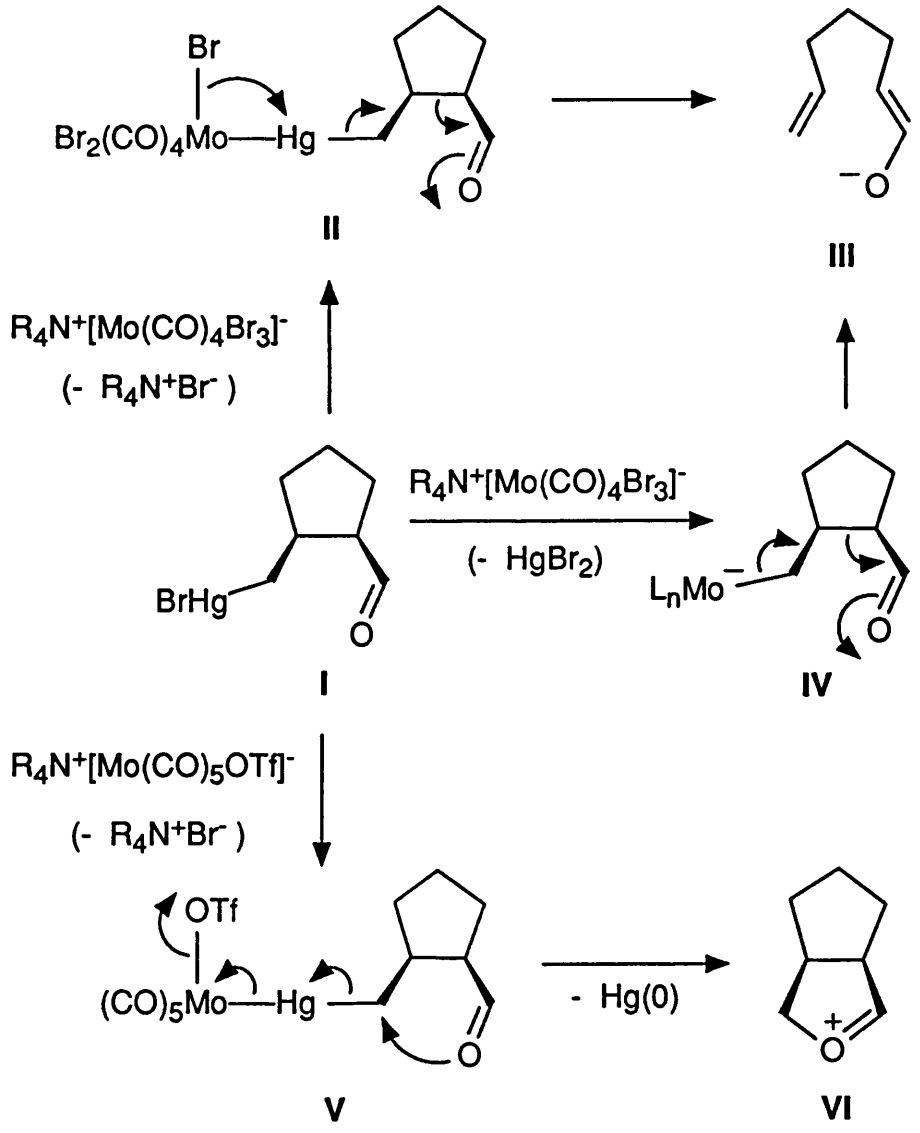


(eq. 5)

Variation of the ligands attached to molybdenum appears to have a dramatic effect on the course of reaction with **9**; whereas $[Mo(CO)_4Br_3]^-$ triggers the fragmentation (Scheme XIV and eq. 4), $[Mo(CO)_5Br]^-$ is inert. In contrast, $[Mo(CO)_5OTf]^-$ has been found to induce a fast intramolecular S_N2 reaction with the aldehyde oxygen (Scheme XXV), mimicking the

reactivity of Pd^{2+} (Scheme VII). This raises the question as to what is the nature of "M" in these reactions and what causes the dramatic difference in reactivity. In the fragmentation reaction, transmetallation[98] would generate species **56** where M = Mo; being negatively charged, the metal can be expected to give off its excessive electrons and push the fragmentation forward (**I** → **IV** → **III** in Scheme XXIX). An alternative explanation assumes that the anionic Mo-complex may replace Br^- at mercury[100] in **I** (Scheme XXIX).

Scheme XXIX



The resulting species **II** would then undergo a shift of Br^- from Mo to the highly halophilic Hg atom with a concomitant dissociation of the Hg-C bond resulting in the fragmentation (**II** → **III**). However, our present experimental data do not allow to

differentiate between these two alternatives.

When halogene is replaced by TfO group in the Mo-complex, a similar anion exchange at mercury can be assumed (**I** → **V**). It is reasonable to anticipate that the reactivity of the resulting intermediate **V** will be different from that of its counterpart **II**. Lacking halogen and having an excellent leaving group (OTf) on Mo, the complex **V** could react via dissociation of the Mo-OTf bond and extrusion of Hg(0). This sequence would simultaneously generate electron deficiency at the carbon atom which is to be quenched by the neighbouring nucleophile (**V** → **VI**).

Abbrevations

aq.	Aqueous
c	Concentration
d	Doublet
dd	Doublet of doublets
DME	Dimethoxyethane
J	Coupling constant
L_n	Ligand(s)
m	Multiplet
[M]	General metal
Ms	Methansulphonyl
NBA	N-bromoacetamide
NMMO	N-methylmorpholiniumoxide
NMR	Nuclear Magnetic Radiation
NOE	Nuclear Overhauser Enhancement
ppm	$1/10^6$
q	Quartet
s	Singlet
sat.	Saturated
sol.	Solution
t	Triplet
Tf	Trifluoromethansulphonyl
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMS	Tetramethylsilan
Ts	Toluensulfonyl
$[\alpha]_D$	Optical rotation
ν	Waven lenght

4. 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 (d_6-DMSO solution) at -808.5 ppm. Diastereoisomeric ratios for **52b** and **53b** were determined by ^2H NMR (61.4 MHz); spectra were recorded for $CHCl_3$ solutions (no lock, ^1H broadband 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 $^1J_{C\text{-}H}$ 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 were 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-bisnor-5β-cholestane-5-carbaldehyde (9a). Method A: To a solution of cyclopropyl alcohol **7a** (200 mg; 0.52 mmol) in DME (8 mL) was 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 aq. KBr, diluted with ether (40 mL) and the solution was washed with 5% aq $KHCO_3$ (2 x 10 mL) and water (1 x 20 mL), dried with $MgSO_4$, and evaporated. The residue contained pure product **9a** (325 mg; 97%), showing one spot on TLC: mp 149-151 °C; $[\alpha]_D$ -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 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 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.

3β-[(Bromomercurio)methyl]-A,B-bisnor-5β-cholestane-5-carbaldehyde (9a). Method B: To a solution of **22a** (100 mg, 0,167 mmol) in DME (25 ml) was added $HgBr_2$ (120 mg, 0,33 mmol). The resulting mixture was stirred at a room temperature for 15 min. Than diethylether (40 ml) was added and the mixture was worked up. The residue contained pure (according to TLC) compound **9a** (106 mg, 0,16 mmol, 96%), identical with that prepared under Method A.

[6^{2}H]-3β-[(Bromomercurio)methyl]-A,B-bisnor-5β-cholestane-5-carbaldehyde (9c): To a precooled solution (-78°C) of 3α,5-cyclo-5α-cholestan-6-one (200 mg, 0.5 mmol) in

diethylether (50 ml) was added $LiAl^2H_4$ (75 mg, 1.54 mmol). After 10 min. reaction mixture was checked using TLC and than decomposed by sat.sol. of ammonium chloride. The mixture was worked up and residues **7c** after evaporation of diethylether (200 mg, pure on TLC) were immediately used for next reaction. Thus to a solution of crude **7c** (200 mg, 0.51) in DME (10 ml) was 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 aq. KBr, diluted with ether (40 mL) and the solution was washed with 5% aq $KHCO_3$ (4 x 10 mL) and water (2 x 20 mL), dried with $MgSO_4$, and evaporated. The residue contained pure product **9c** (310 mg, 93%): mp 151-154°C; IR ($CHCl_3$) ν(CHO) 1703 cm^{-1}; ^{13}C NMR (75.4 MHz) δ 12.21 (C-18), 18.76 (C-21), 19.71 (C-19), 21.11 (t), 22.55 (C-26 or C-27), 22.82 (C-26 C-27), 23.85 (t), 24.38 (t), 28.01 (C-25), 28.47 (C-11), 34.76 (C-4), 35.64 (C-20), 36.22 (C-22), 36.95 (C-7), 38.89 (C-2), 39.40 (C-1), 39.47 (C-12 and C-24), 43.74 (C-13), 44.41 (C-8), 53.05 (C-3), 55.73 (C-17), 56.77 (C-14), 58.31 (C-10), 59.22 (C-9), 70.60 (C-5), 206.27 (C-6);

[4^{2}H]-3β-[(Bromomercurio)methyl]-A,B-bisnor-5β-cholestane-5-carbaldehyde (9b): mp 148-150 °C; ^1H NMR δ 0.63 (s, 3 H, 18-H), 1.96 (d, J = 8.7 Hz, 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 x 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).

Lactol (10a). Method A: 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 **9a** (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) and washed water (6 x 10 mL), 5% aq. $KHCO_3$ (1 x 10 mL), and water (1 x 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 **10a** (56 mg; 93%), identical with an authentic sample:[11] mp 156-158 °C (aqueous acetone); IR ($CHCl_3$) ν(OH) 3395, 3620 cm^{-1}; ^1H 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 ^1H 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 chloroaldehyde **38a** (80 mg; 0.19 mmol) in DME (5 mL) was added water (0.2 mL) and silver nitrate (50 mg; 0.29 mmol). The mixture was stirred at rt overnight, then filtered and the filtrate diluted with ether and washed with water and dried with $MgSO_4$. The crude product was chromatographed on silica gel (5 g) with a petrol ether-ether mixture (8:2) to furnish lactol **10a** (71 mg; 91%), identical with the product obtained under A.

Method C: To a solution of **9a** (120 mg; 0.18 mmol) in THF (30 mL) was added $CpMo(CO)_3Br$ (325 mg, 1.00 mmol; prepared freshly before use from 264 mg of molybdenum hexacarbonyl[102]) in THF (20 mL). The mixture was stirred at rt for 8 h, then diluted with ether and the ethereal solution was worked up. The crude product was chromatographed on silica gel (5 g) with a petrol ether-ether (7:3) to afford **10a** (51 mg; 71%), identical with the product obtained under A.

Method D: To a solution of **9a** (200 mg, 0.3 mmol) in DME (20 ml) was added NBS (135 mg, 0.76mmol, 2.5 eq.) at -20 °C. The mixture was stirred at the same temperature for 6 hours . The excess of the reagent was then decomposed by sat.aq. sol. of sodium thiosulphate, diethylether (40 ml) was added and the mixture was worked up. Solvent was evaporated and the residue was chromatographed on a column of silica with a petrolether-ether mixture (8:2)

to give **10a** (98mg, 0.25 mmol, 81%), identical to the product obtained under A.

Deuterated lactol (10b): (prepared under A) 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^+).

Deuterated lactol (10 b): (prepared under D) mp 153-154 °C (aqueous acetone); ^{1}H NMR δ 0.64 (s, 3H, 18-H), 0.87 (s, 3 H, 19H),3.40 (d, 0.5 H, J_{gem} = 8.6 Hz, $J_{3\alpha\text{-H},4\beta\text{-H}}$ = 4.9 Hz, 4β-H) 4,16 (d, 0.5 H, $J_{3\alpha\text{-H},4\alpha\text{-H}}$ = 9.2 Hz, 4α-H), 5.19 (s, 1 H, 6β-H)

Methyl acetal (11a). Method A: Prepared from **9a** in the same way as lactol **10a**, using $PdCl_2$, $CuCl_2$, and LiCl 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, and $J_{11\beta\text{-H},12\beta\text{-H}}$ = 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.

Method B: Benzyltriethylammonium chloride (142 mg; 0.625 mmol; 1.1 equiv.) was added to a solution of molybdenum hexacarbonyl (150 mg; 0.568 mmol; 1 equiv.) in DME (30 mL) and methanol (3 mL) and the mixture was refluxed for 30 min. When the evolution of carbon monooxide ceased, the mixture was cooled to rt and a solution of silver(I) trifluorosulfonate (120 mg; 0.454 mmol; 0.8 equiv.) was added and the mixture was stirred at rt for 20 min. Then a solution of **9a** (100 mg; 0.150 mmol) in DME (5 mL) was added and the mixture was stirred at 45 °C for 4 h. The mixture was filtered through a pad of silica gel, the filtrate was diluted with ether (30 mL) and worked up. The crude product was chromatographed on silica gel (5 g) with a petroleum ether-ether mixture (9:1) to give acetal **11a** (54 mg; 86%) identical with the compound prepared under A.

Deuterated Acetal (11b): 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 (3β-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.

3β-Methyl-A,B-bisnor-5β-cholestane-5-carboxylic acid (15a). Method A: To a solution of organomercurial **9a** (360 mg; 0.54 mmol) in DME (10 mL) was added maleic anhydride (260 mg; 2.6 mmol), followed by lithium chloride (100 mg) and palladium(II) chloride (120 mg; 0.67 mmol)and the mixture was stirred at rt overnight. The mixture was then diluted with ether and washed with saturated aq. $CuCl_2$ (2 x 20 mL) and water (3 x 20 mL). The solution was dried with $MgSO_4$ and evaporated. The residue was chromatographed

on a column of silica gel, using a petroleum ether-ether mixture (9:1) as eluent to afford acid **15a** (210 mg; 97%): mp 89-92 °C (acetone); $[\alpha]_D$ +52° (c, 4.7); IR ($CHCl_3$) ν(C=O) 1683, ν(CO_2H) 2500-3100 cm^{-1}; ^1H NMR δ 0.63 (s, 3 H, 18-H), 0.99 (s, 3 H, 19-H), 1.01 (d, 3 H, J = 6.5 Hz, 4-H), 1.05 (m, 1 H, 7α-H), 1.74 (m, 1 H, 8β-H), 2.08 (m, 1 H, 3α-H), 2.51 (dd, 1 H, J_{gem} = 12.8 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 7.2 Hz, 7β-H), 11.8 (1 H, CO_2H); ^{13}C NMR δ 12.39 (C-18), 13.94 (C-4), 18.75 (C-21), 19.54 (C-19), 21.66 (CH_2), 22.55 (C-26 or C-27), 22.81 (C-26 or C-27), 23.86 (CH_2), 24.35 (CH_2), 27.99 (C-25), 28.56 (CH_2), 34.92 (CH_2), 35.66 (CH), 36.22 (CH_2), 38.05 (C-1), 39.03 (C-7), 39.47 (C-24), 39.73 (CH_2), 43.27 (C-8), 43.85 (C-13), 49.48 (C-3), 55.70 (C-17), 57.11 (C-14), 58.22 (C-9), 58.28 (C-10), 68.14 (C-5), 181.56 (C-6). Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.19; H, 11.84.

3β-Methyl-A,B-bisnor-5β-cholestane-5-carboxylic acid (15a). Method B: To a solution of acetate **62a** (200 mg; 0.31 mmol) and the molybdenum complex A (290 mg; 0.62 mmol) in DME (40 mL) was added silver(I) trifluoromethyl sulfonate (150 mg; 0.62 mmol) at -10 °C. The mixture was first stirred at rt for 30 min (evolution of CO was observed) and then at 45 °C for 30 min. The mixture was then cooled to rt, diluted with ether (60 mL) and worked up. The crude product was chromatographed on silica gel (8 g) with a petroleum ether-ether mixture (9:1) to give pure acid **15a** (104 mg; 84%) identical with the compound prepared under A.

3β-Methyl-A,B-bisnor-5β-cholestane-5-carboxylic acid (15b).Authentic sample: To a solution of **9a** (120 mg; 1.80 mmol) in ether (20 mL) and methanol (2 mL) was added sodium borodeuteride (160 mg; 3.82 mmol) and the mixture was stirred at 0 °C for 10 min. The excess of reagent was then decomposed with 5% aqueous HCl at -78 °C, the mixture was diluted with ether and worked up to give deuterated alcohol (44 mg; 0.113 mmol; 83%). Above alcohol was than dissolved in acetone (15 ml) and Jones' reagent was added dropwise at -20°C. Reaction was monitored by TLC. After 30 min. reaction was complete and reaction mixture was worked up as usual. Solvent was than evaporated to give TLC pure **15b** (42 mg, 0.104 mmol, 92%): mp 93-94°C (acetone); IR ($CHCl_3$) ν(C=O) 1685, ν(CO_2H) 2500-3100

cm^{-1}; ^{13}C NMR δ 12.31 (C-18), 13.85 ($CH_2{}^2H$,C-4), 18.75 (C-21), 19.47 (C-19), 21.55 (CH_2), 22.43 (C-26 or C-27), 22.72 (C-26 or C-27), 23.54 (CH_2), 24.20 (CH_2), 27.72 (C-25), 28.31 (CH_2), 34.88 (CH_2), 35.52 (CH), 36.01 (CH_2), 37.92 (C-1), 38.85 (C-7), 39.02 (C-24), 39.45 (CH_2), 43.14 (C-8), 43.63 (C-13), 49.25 (C-3), 55.55 (C-17), 57.01 (C-14), 57.99 (C-9), 58.12 (C-10), 68.11 (C-5), 181.35 (C-6).

[4-^{2}H]-3β-Methyl-A,B-bisnor-5β-cholestane-5-carboxylic acid (15b): Prepared using **Methode A** and/or **Methode B:** ^{13}C NMR δ 13.69 ($CH_2{}^2H$) or 13.76 ($CH_2{}^2H$) respectively and compared with autentic sample **15b**.

3-(Hydroxymethyl)-A-nor-choleste-3-ene (20). After isolation of **21**, chromatography was continued with hexane-ether (95:5) to afford **20** (98 mg; 66%): mp 119-120 °C (aqueous acetone; lit.[39] gives 116-117 °C); ^1H 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-Methyliden-A-nor-5β-cholestan-5-ol (21). A mixture of **16** (140 mg; 0.38 mmol), thallium nitrate trihydrate (230 mg, 0.52mmol) 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 **21** (38 mg; 26%): mp 56-58 °C (aqueous acetone; lit.[41] gives 58 °C); $[\alpha]_D$ +21° (c = 2.0; lit.[41] gives +20°); ^1H 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, 1 H, 2-H), 2.45 (m, 1 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).

3β-[(Methylmercurio)methyl]-A,B-bisnor-5β-cholestane-5-carbaldehyde (22). Method A: To a stirred suspension of copper(I) iodide (266 mg; 1.40 mmol) in dry THF (10 mL) was added dropwise a 1.4M solution of methyl lithium 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 pre-cooled (-20 °C) solution of organomercurial **9a** (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 aq. 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 **22** (225 mg; 94%) showing one spot on TLC: $[\alpha]_D$ -6° (c 6.3); IR 1712, 2698 cm^{-1}; ^1H 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-16 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 **9a** (150 mg; 0.23 mmol) in ether (50 mL) was added a 2M solution of trimethyl aluminum 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 filtered through a pad of silica gel. The filtrate was evaporated to give **22** (121 mg; 69%) identical with the product prepared under method A.

Method C: A 1.4M solution of methyl lithium 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 **9a** (100 mg; 1.50 mmol) was then added, the

mixture was stirred at -30 °C, then cooled to -78 °C and decomposed with sat. NH_4Cl (aqueous). The mixture was then diluted with ether and worked up to give pure **22** (82 mg; 91%), identical with the product obtained under A.

A-Homo-B-nor-3,5-cyclo-5α-cholestan-6α-ol (24a). Method A: To a stirred suspension of copper(I) iodide (260 mg; 1.40 mmol) in dry THF (20 mL) was added dropwise a 1.4M solution of methyl lithium 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 pre-cooled (-20 °C) solution of the organomercurial **9a** (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 aq. solution of NH_4Cl, the product was extracted with ether and the organic phase was worked up. The solvent was evaporated to give cyclobutanol **24a** (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}; ^1H 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); in NOE difference experiments, irradiation at 0.94 (19-H) gave 9% enhancement of the signal at 4.19 (C*H*OH), while irradiation at 4.19 resulted in 4% enhancement of the signal at 0.94 (19-H); ^{13}H 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 (s, C-10), 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.

Method B: The mercurioaldehyde **22** (200 mg; 0.33 mmol) was dissolved in diethylether (50 ml) and cooled down to -78°C. Then solution of MeLi (1.5 ml of 1.4M sol.) was added dropwise via syringe to the reaction mixture. Reaction was stirred under nitrogen for 10 min. and then excess of reagent decomposed by water and aqueous sol. NH_4Cl. After working up (brine-ether, sat. sol. $KHCO_3$, $MgSO_4$) solvent was evaporated and residues were separated by collumn chromatografy (petrolether- ether; 9:1) to obtain pure alcohol **24a** (94 mg; 73%) identical with the compound prepared under A.

Method C: Molybdenum reagent (2 mmol) was prepared according to the Kauffmann

protocol[46] and stirred at -10°C and then solution of **22** (150 mg; 0.247 mmol) in THF (7 ml) was added. Mixture was then stirred at r.t. for 5 hrs. under nitrogen. Reaction was monitored by TLC. After reaction was completed mixture was cooled down and excess of reagent was decomposed by aqueous sat. NH_4CL. Product was extracted in ether and organic layer was worked up as usual and evaporated. After column chromatografy (petrolether-ether; 9:1) of the reaction residues alcohol **24a** was obtained (62 mg; 65%) identical with the compond prepared under A.

[4α^{2}H]-A-Homo-B-nor-3,5-cyclo-5α-cholestan-6α-ol (24b): 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 CHOH); ^{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 (25a). Method A: The alcohol **24a** (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, the mixture was diluted by ether and water and worked up. The solvent was worked up and the residue was crystallized from aq. acetone to give ketone **25a** (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; 1H; 7β-H), 2.35 (m, 1 H, 3α-H), 2.61 (dd, 1 H, $J_{gem} = 17.6$ Hz, $J_{4\beta\text{-H},3\alpha\text{-H}} = 6.8$ Hz, 4β-H), 2.90 (dd, 1 H $J_{gem} = 17.6$, $J_{4\alpha\text{-H},3\alpha\text{-H}} = 8.6$ 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 x 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.

Method B: Alcohol **26** (100 mg; 0.26 mmol) was dissolved in acetone (15 ml) and treated with Jones' reagent for 30 min at - 20 °C. The excess of reagent was decomposed by methanol, the mixture was diluted by ether and water and worked up. The solvent was worked up and the residue was crystallized from aq. acetone to give ketone **25a** (92 mg; 93%) identical with the sample prepared under A.

[4α^{2}H]-A-Homo-B-nor-3,5-cyclo-5α-cholestan-6-one (25b): mp 112-114 °C; ^{1}H NMR δ 0.67 (s, 3 H, 18-H), 2.64 (br d, 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 x 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).

6-methylidene-[4αH]-A-Homo-B-nor-3,5-cyclo-5α-cholestan: Tebbe reagent (2 mmol) was prepared according to the literature[48]. Then ketone **25a** (190 mg, 0.5 mmol) was dissolved in very dry THF (15 ml) and stirred at -30°C. Pre-cooled solution of Tebbe reagent was then added dropwise to the reaction mixture. After 12 hours excess of the reagent was decomposed by 10% aq. sol. HCl and organic phase worked up to give 6-methylidene-[4αH]-A-Homo-B-nor-3,5-cyclo-5α-cholestan (141 mg; 75%): $[\alpha]_D$+17° (c 0.7); ^{1}H NMR δ 0.68 (s, 3H, 18-H), 1.29 (s, 3H, 19-H), 2.59 (m, 1H, 3β-H), 2.34 (m, 1H, 3α-H), 4.73 (s, 1H, C=*H*H), 4.78 (s, 1H, C=H*H*); ^{13}C NMR δ 12.37 (q), 18.80 (q), 19.21 (q), 20.25 (t), 22.58 (q), 22.84 (q), 23.89 (t), 24.52 (t), 28.04 (d), 28.60 (t), 29.40 (t), 32.02 (t), 35.63 (t), 35.71 (d), 36.28 (t), 39.53 (t), 39.88 (t), 41.55 (d), 41.92 (t), 44.02 (s), 46.40 (d), 53.40 (d), 54.73 (s), 55.76 (d), 57.04 (d), 68.05 (s), 103.93 (t), 154.57 (s).

A-Homo-B-nor-3,5-cyclo-5α-cholestan-6β-ol (26). Ketone **25a** (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% aq. HCl at -78 °C and worked up. The solvent was evaporated and to give alcohol **26** (201 mg; 96%) showing one spot on TLC: mp 125-127 °C (aq. acetone); $[\alpha]_D$ +20° (c 5.3); ^1H 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-bisnor-5β--cholestane (27). To a stirred solution of triethyl phosphonoacetate (1.27 g; 1.5 equiv.) in dry THF (100 mL) was slowly added a 1.6M solution of butyl lithium 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 **9a** (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, diluted with ether and water and the organic layer was washed with water (1 x 20 mL), 5% aq. HCl (2 x 20 mL), 5% aq. $KHCO_3$ (2 x 20 mL), sat. aq. KBr (1 x 20 mL) and water (2 x 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 petrol ether-ether mixture (9:1) and then with a petrol ether-ether-acetone mixture (7:1:2) to give **27** (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}; ^1H 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, CH_3CH_2), 4.26 (q, 2 H, *J* = 7.1 Hz, CH_3CH_2O), 5.92 (d, *J* = 16.0 Hz, 1 H, CH=C*H*CO_2Et), 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-bisnor-5β-choles tane (28). Method A: To a solution of **27** (120 mg; 0.16 mmol) in dry ether (10 mL) was added a 2M 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 the reagent was decomposed by 10% aq. HCl and the mixture was worked up. The solvent was evaporated, the residue was dissolved in petroleum ether-ether mixture (9:1) and the solution was filtered through a pad of aluminum oxide. The filtrate was evaporated to afford pure, oily **28** (107 mg; 95%): $[\alpha]_D$ -5° (c 3.7); IR ν(C=C) 1640, ν(C=O) 1710 cm^{-1}; ^1H NMR δ 0.25 (s, 3 H, CH_3Hg), 0.65 (s, 3 H, 18-H), 0.79 (s, 3 H, 19-H), 1.35 (d, 3 H, J = 7.1 Hz, CH_3CH_2O), 4.25 (d, 2 H, J = 7.1 Hz, CH_3CH_2O), 5.84 (d, 1 H, J = 16.0 Hz, CH=C*H*CO_2Et), 7.15 (d, 1 H, J = 16.0 Hz, C*H*=$CHCO_2Et$); ^{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.

Method B: To a stirred suspension of copper(I) iodide (266 mg; 1.40 mmol) in dry THF (10 mL) was added dropwise a 1.4M solution of methyl lithium 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 pre-cooled (-20 °C) solution of organomercurial **27** (100 mg; 0.133 mmol) in dry ether (7 ml) was added. Mixture was stirred under nitrogen at the same temperature for 20 min. The excess of reagent was then decomposed by sat. aq. NH_4CL,the product was extracted with ether and the organic phase was worked up. Solvent was evaporated to give methylmercury **28** (83 mg; 91%), identical with the sample prepared under A.

3β-methyl-5-[(*E*)-2'-(Ethoxycarbonyl)ethenyl]- A,B-bisnor-5β-cholestane. Method A: The ester **27** (120 mg, 0.16 mmol) was dissolved in ether (12 ml) and methanol (2 ml) and stirred at -10°C. $NaBH_4$ (200 mg) was added and formation of black mercury precipitate

followed immediately. After 10 min. excess of hydride was decomposed by 10% sol. of HCl. Mixture was worked up and resulting organic phase was filtered through short collumn of celite. After evaporation **3β-methyl-5-[(*E*)-2'-(Ethoxycarbonyl)ethenyl]-A,B-bisnor-5β-cholestane** was obtained (60 mg; 81%): IR ν(C=C) 1635, ν(C=O) 1700 cm^{-1}; ^1H NMR δ 0.61 (s, 3 H, 18-H), 0.77 (s, 3 H, 19-H), 1.32 (t, 3 H, J = 7.1 Hz, CH_3CH_2), 4.23 (q, 2 H, J = 7.1 Hz, CH_3CH_2O), 5.87 (d, J = 16.0 Hz, 1 H, CH=C$H$$CO_2Et$), 7.04 (d, 1 H, J = 16.0 Hz, CH=$CHCO_2Et$); ^{13}C NMR δ 12.27 (q), 14.32 (q), 18.77 (q), 20.76 (q), 21.74 (q), 22.57 (q), 22.82 (q), 23.88 (t), 24.48 (t), 28.00 (d), 28.51 (t), 35.65 (d), 36.22 (t), 37.09 (t), 38.55 (t), 39.47 (t), 39.64 (t), 39.76 (t), 41.22 (t), 43.57 (d), 43.77 (s), 54.72 (d), 55.72 (d), 56.75 (d), 57.17 (s), 58.94 (d), 60.41 (t), 62.77 (s), 119.50 (d), 152.23 (d), 166.46 (s).

Method B: The ester **27** (120 mg, 0.16 mmol) was dissolved in DME and stirred at -40°C. Then Bu_3SnH (186 mg; 4 eq.) was added dropwise via syringe. Mixture was kept at the same temperature under nitrogen for 4 hrs. After then excess of hydride was decomposed by 10% sol. of HCl. Mixture was worked up and resulting organic phase was filtered through short column of celite. Solvent was evaporated and after chromatography (petrolether, petrolether- ether 9:1) **3β-methyl-5-[(*E*)-2'-(Ethoxycarbonyl)ethenyl]-A,B-bisnor-5β-cholestane** was obtained (65 mg; 87%), identical with the sample prepared under A.

6α-[(Ethoxycarbonyl)methyl]-A-homo-B-nor-3,5-cyclo-5α-cholestane (30). Method A: To a solution of **27** (120 mg; 0.16 mmol) in dry THF (10 mL) was added a 2M 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 1.6M solution of butyllithium in hexane (0.3 mL; 3 equiv.) was added, the mixture was stirred at -78 °C for 1 h and allowed to warm up to rt. The excess of reagent was decomposed by 10% aq. 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 **30** (68 mg; 92%): $[\alpha]_D$ +18° (c 6.8); IR 1728 cm^{-1}; ^1H NMR δ 0.65 (s, 3 H, 18-H), 0.96 (s, 3 H, 19-H), 1.28 (t, J = 7.1 Hz, 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 1.4M solution of methyl lithium 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 pre-cooled (-20 °C) solution of **27** (78 mg; 0.11 mmol) in THF (5 mL) was added. The mixture was stirred at -78 °C for 15 min and then let gradually to warm to rt. The excess of reagent was decomposed by aq. NH_4Cl, the product was taken up into ether and the etheral 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 **30** (35 mg; 75%), identical with the product obtained by method A.

Method C: To a stirred suspension of copper(I) iodide (260 mg; 1.40 mmol) in dry THF (20 mL) was added dropwise a 1.4M solution of methyl lithium 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 pre-cooled (-20 °C) solution of the organomercurial **28** (0.140 mg; 0.20 mmol) in THF (8 mL) was added. Since TLC indicated an instantaneous reaction, the mixture was then poured into an ice-cold aq. solution of NH_4Cl, the product was extracted with ether and the organic phase was worked up. After chromatography (petrolether- ether; 95:5) **30** was obtained (38 mg; 40%) identical with the compound prepared under A.

3β-Chloro-5-cholestene (33a). Method A: Molybdenum(V) chloride (50 mg; 1.2 equiv.) was added in small portions to a solution of organomercurial **9a** (100 mg; 0.15 mmol) in ether (10 mL) at -78 °C over a period of 1 h. The mixture was then stirred at the same temperature for 4 h. The mixture was then gradually warmed up to rt, diluted with ether (20 mL), and washed with water (5 x 5 mL), 5% aq. $KHCO_3$ (5 x 5 mL), water (5 mL) and dried

with $MgSO_4$. The solvent was evaporated and the residue was chromatographed on a column of silica gel with petrol ether to yield **33a** (47 mg; 79%), identical with an authentic sample: mp 95-97 °C (ethyl acetate) (Fluka catalogue 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 (br d, 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 (d), 60.33 (d), 122.46 (d), 140.77 (s); MS *m/z*, 406 (34,$M^{\cdot+}$) / 404 (91%).

Method B: a mixture of **9a** (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 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 **33a** (48 mg; 79%): mp 94-96 °C.

[4β^{2}H]-3β-Chloro-5-cholestene (33b): 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).

3β-Chloromethyl-A,B-bisnor-5β-cholestane-5-carbaldehyde (38a). Molybdenum(V) chloride (200 mg) was introduced in small portions to a solution of organomercurial **9a** (245 mg; 0.68 mmol) in THF (10 mL) at -78 °C over a period of 2 h. After this time, TLC indicated a completion of the reaction and, along the main product **38a** (ca. 90%), identified lactol **10a** (ca. 5-10%). The TLC analysis also revealed a slow conversion of **38a** to **10a** on silica gel, e.g. during the attempted flash chromatography. Therefore the chloride **38a** could not be isolated in pure state and fully characterized: ^{1}H NMR δ 0.66 (s, 3 H, 18-H), 0.97 (s, 3 H, 19-H), 2.50 (dd, J_{gem} = 12.9 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.5 Hz, 1 H, 7β-H), 3.68 (t, J = 7.5 Hz, 2 H, 4-H), 9.68 (s, 1 H, CH=O). Treatment of the crude product with silver nitrate (120 mg; 0.7 mmol) in wet DME (10 mL) at rt for 5 h, resulted in the deposition of AgCl and formation of

10a (119 mg; 80%), identical with an authentic sample, which was purified by flash chromatography.

(19*S*)-[19^{2}H]-Cholest-5-ene-3β,19-diol 3-Monoacetate (40b). Method A: To a solution of lithium aluminum deuteride (280 mg; 7.38 mmol) in ether (70 mL) was added drop-wise *t*-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 down to -78 °C. A solution of aldehyde **39** (300 mg; 0.68 mmol) in ether (10 mL) was added and the mixure was stirred at -78 °C for 20 min while monitored by TLC. The excess of reagent was decomposed by sat. NH_4Cl (aqueous), the mixture was diluted by ether and worked up to afford **40b** (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).

Method B: To the solution of the aldehyde **39** (250 mg; 0.57mmol) was dissolved in ether (10 ml) and methanol (1 ml). Reaction mixture was kept at -20°C and then $NaBH_4$ (100 mg) was added. Mixture was stirred for 12 hrs. and monitored by TLC. After reaction was completed, excess of deuteride was decomposed by 10% aq. sol. of HCl and mixture was worked up to give **40b** (242 mg, 95%): ^{1}H NMR δ 3.56 (s, 0.30 H, 19H), 3.78 (s, 0.70 H, 19-H).

(19*S*)-[19^{2}H]-Cholest-5-ene-3β,19-diol 3-Acetate 19-Mesylate (41b). To a solution of the alcohol **40b** (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 **41b** (330 mg; 97%), identical (TLC) with its unlabeled counterpart (**41a**);[68] this product was directly use in the next without further purification.

(19*R*)-[19^{2}H]-5,19-Cyclo-5β-cholestan-3β-ol (42b). The mesylate **41b** (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 sat. NH_4Cl (aqueous), and 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 **42b** (176 mg; 88%), identical (TLC) with its unlabeled couterpart (**42a**).[68]

5,19-Cyclo-5β-cholestan-3-one (43a). Method A: The alcohol[68] **42a** (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 sat. aqueous $KHCO_3$ (3 x 30 mL) and water, and dried with $MgSO_4$. Ether was evaporated and the residue was chromatographed on silica (30 g) using a petrol ether-ether mixture (95:5) as eluent to yield **43a** (710 mg; 95%): mp 96-98 °C (acetone); $[\alpha]_D$ +47° (c 1.7); IR 1705 ν(C=O) cm^{-1}; ^1H 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 1.4M solution of methyl lithium 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 pre-cooled (-20 °C) solution of the organomercurial **44a** (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 petrol ether-ether mixture (95:5) as eluent to give pure **43a** (40 mg; 86%): mp 98-99 °C.

Method C: The organomercurial **44a** (100 mg, 0.15mmol) 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 **43a** (54 mg; 93%): mp 95-96 °C.

Method D: The organomercurial **44a** (50 mg, 0.075 mmol) was treated with $SiCl_4$ (25 mg) in dry DME (5 ml) at 40 °C for 48 hours. Reaction was monitored by TLC. The mixture was then cooled down and decomposed with water, worked up and organic layer filtered through short column of celite. After evaporation was obtained **43a** (23 mg; 81%) identical with the sample prepared under A.

(19*R*)-[19^{2}H]-5,19-Cyclo-5β-cholestan-3-one (43b): mp 86-87 °C; ^{1}H NMR δ 0.47 (s, 0.84 H, 19-H), 0.71 (s, 3 H, 18-H). Prepared from the alcohol **42b** via known procedure.[68] (The same as mentioned above in case of **43a Method A.**)

(19*R*)-[19^{2}H]-5,19-Cyclo-5β-cholestan-3-one (43b) and (19*R*)-[19^{2}H]-5,19-Cyclo-5β-cholestan-3-one (49) mixture:

To a stirred suspension of copper(I) iodide (270 mg; 1.42 mmol) in dry DME (5 mL) was added dropwise a 1.4M solution of methyl lithium 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 pre-cooled (-20 °C) solution of the organomercurial **44b** (50 mg; 0.075 mmol) in DME (0.75 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 (3 g) using a petrol ether-ether mixture (95:5) as eluent to give mixture **43b** and **49** (26 mg; 90%) in 53:47 ratio. ^{1}H NMR δ 0.47 (s, 0.53 H, 19-H), 0.51 (s, 0.47 H, 19H).

19-Bromomercurio-cholest-4-en-3-one (44a). The third fraction after isolation of **46a** and **47a** contained **44a** (543 mg; 35%): mp 117-120°C (DME); $[\alpha]_D$ +67° (c 5.5); IR 1672

ν(C=O) cm^{-1}; ^1H NMR δ 0.75 (s, 3 H, 18-H), 2.20 and 2.51 (AB system, two d, J_{gem} = 12.1 Hz, 2 x 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 (44b): ^1H NMR δ 0.71 (s, 3 H, 18-H), 2.15 (s, <1 H, 19-H), 5.74 (s, 1 H, 4-H); ^2H NMR δ 2.53 (*W*/2 = 13.8 Hz);[75] ^{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% ^2H (d_1).

Cholest-4-en-3-one (45). (A) From 66: To a solution of **66** (70 mg; 0.174 mmol) in methanol (10 mL) was added a 10% solution of NaOH in water (0.2 mL) and the mixture was stirred at rt for 1 h. The mixture was then diluted with ether and the ethereal solution was worked up to afford **45** (60 mg; 90%), identical with an authentic sample: mp 75-78 °C (acetone; Aldrich catalogue gives 79-81 °C).

(B) From 44a: To a solution of organomercurial **44a** (120 mg; 0.18 mmol) in toluene (20 mL) was added with tributyltin hydride (0.2 mL; 0.74 mmol) in toluene (2 mL). The mixture was stirred at rt for 10 min, then diluted with ether and the ethereal solution was worked up. The crude product was chromatographed on silica gel (5g) first with petrol ether, then with a petrol ether-ether mixture (8:2) to furnish **45** (52 mg; 75%), identical with an authentic sample: mp 74-77 °C.

19-Nor-5-[(bromomercurio)methyl]-5β-cholest-1(10)-en-3-one (46a). To a solution of **43a** (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, saturated aqueous solution of KBr (30 mL) was added and the mixture was stirred for 5 min. The product was extracted with ether (4 x 50 mL) and the ethereal solution was washed successively with aq KBr, 5% aq $KHCO_3$, and water, and dried with sodium sulfate. The solvent was evaporated to give crude mixture of isomeric organomercurials. The mixture was chromatographed on silica (52 g) using a petrol ether-ether mixture (7:3 to 1:1). The first fraction contained **46a** (372 mg; 24%): mp 93-95 °C; $[\alpha]_D$ -30° (c 8.8); IR 1709 ν(C=O) cm^{-1}; ^1H NMR δ 0.68 (s, 3 H, 18-H), 2.21 and 2.47 (AB system, J_{gem} = 13.8 Hz, 2 x 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-^2H]-19-Nor-5-[(bromomercurio)methyl]-5β-cholest-1(10)-en-3-one (46b): ^1H 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); ^2H NMR δ 2.12 ($W/2$ = 13.8 Hz);[75] ^{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^2H, $J_{C,D}$ = 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 (47a). The second chromatographic fraction after isolation of **46a** contained **47a** (435 mg; 28%): mp 174-178 °C (acetone); $[\alpha]_D$ +36° (c 12.6); IR 1705 ν(C=O) cm^{-1}; ^1H NMR δ 0.83 (s, 3 H, 18-H), 2.23 and 2.27 (AB system, two d, J_{gem} = 11.6 Hz, 2 x 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 (48). A solution of **47a** (40 mg; 0.060 mmol) in benzene (5 mL) was refluxed with a 1M 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 **48** (23 mg; 69%), identical with an authentic sample:[72] $[\alpha]_D$ +18° (c 2.0; lit.[72] gives +20°); IR ν 1713 (C=O) cm^{-1}; ^1H NMR δ 0.82 (s, 3 H, 18-H), 1.03 (s, 3 H, 5β-methyl).

3β-Methyl-5-(hydroxyoxymethyl)-A,B-bisnor-5β-cholestane (53). To a solution of **9a** (120 mg; 1.80 mmol) in ether (20 mL) and methanol (2 mL) was added sodium borohydride (321 mg; 8.48 mmol) and the mixture was stirred at 0 °C for 10 min. The excess of reagent was then decomposed with 5% aqueous HCl at -78 °C, the mixture was diluted with ether and worked up to give alcohol **53** (44 mg; 0.113 mmol; 83%): $[\alpha]_D$ +15° (c 1.2); IR ν(OH) 3420, 3595 cm^{-1}; ^1H NMR δ 0.66 (s, 3 H, 18-H), 0.88 (s, 3 H, 19-H), 1.02 (d, 3 H, J = 7.1 Hz, 3β-CH_3), 3.46 (d, J = 10.7 Hz, 1 H, CH_2OH), 3.70 (dd, J = 10.7 and 1.0 Hz, CH_2OH); ^{13}C NMR δ 12.27 (q), 15.98 (q), 18.79 (q), 18.93 (q), 22.10 (t), 22.57 (q), 22.83 (q), 23.88 (t), 24.57 (t), 28.02 (d), 28.61 (d), 31.05 (t), 35.70 (d), 36.26 (t), 38.57 (t), 39.51 (t), 39.92 (t), 40.40 (d), 41.17 (t), 42.85 (d), 43.77 (s), 51.67 (s), 55.76 (d), 56.37 (d), 57.75 (d), 64.72 (t). Anal. Calcd for $C_{27}H_{48}O$: C, 83.44; H, 12.45. Found: C, 83.17; H, 12.66.

3β-Methyl-A,B-bisnor-5β-cholestane-5-carbaldehyde (54a). To a stirred mixture of alcohol **53** (100 mg; 2.6 mmol) and a molecular sive 4 Å in dichloromethane (50 mL) were successively added tetraispropylammonium perruthenate (610 mg; 0.02 mmol) and *N*-methylmorpholin-*N*-oxide 75 mg; 9 mmol) in three portions. and the mixture was stirred at rt for 8 h. Then the mixture was diluted with CH_2Cl_2 (20 mL), the insoluble material was filterred off and the solution was worked up. The crude product was dissolved in petroleum ether and the solution was filterred through a pad of silica gel to afford aldehyde **54a** (93 mg;

94%) which is slowly oxidized by air to the corresponding acid: ^{1}H NMR δ 0.62 (s, 3 H, 18-H), 0.92 (s, 3 H, 19-H), 2.50 (dd, J_{gem} = 12.3 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.7 Hz, 1 H, 7β-H) and 12. 9.77 (s, 1 H, CH=O); ^{13}C NMR δ 12.07 (q), 14.40 (q), 18.62 (q), 19.56 (q), 21.18 (t), 22.41 (q), 22.66 (q), 23.73 (t), 24.24 (t), 27.85 (d), 28.38 (t), 35.05 (t), 35.50 (d), 36.09 (t), 36.55 (t), 39.19 (t), 39.34 (t), 39.47 (t), 43.13 (d), 43.55 (s), 47.28 (d), 55.59 (d), 56.99 (d), 57.99 (s), 58.67 (d), 66.93 (s), 206.72 (d).

3β-[(Methylmercurio)methyl]-5-(hydroxymethyl)-A,B-bisnor-5β-cholestane (55). To a solution of aldehyde **22** (200 mg; 0.33 mmol) in ether (45 mL) and ethanol (5 mL), cooled at -30 °C, was added sodium borohydride (300 mg, 7.93 mmol). The mixture was stirred at -30 °C and monitored by TLC. After 5 h, the excess of reagent was decomposed with 5% aqueous HCl and the mixture was worked up to afford **55** (185 mg; 92%): $[\alpha]_D$ +14° (c 2.5); IR 3628 ν(OH) cm^{-1}; ^{1}H NMR δ 0.25 (s, 3 H, CH_3Hg), 0.62 (s, 18-H), 0.89 (s, 3 H, 19-H), 3.52 and 3.73 (AB system, J = 10.8 Hz, 2 H, 6-H); ^{13}H NMR δ 12.27 (q), 18.76 (q), 19.06 (q), 21.55 (q), 21.82 (t) 22.55 (q), 22.80 (q), 23.84 (t), 24.52 (t), 27.98 (d), 28.57 (t), 35.66 (d), 35.81 (d) 36.23 (t), 38.70 (t), 39.48 (t), 39.90 (t), 40.86 (t), 41.27 (d), 43.40 (t), 43.78 (s), 49.58 (d), 52.19 (s), 55.74 (d), 56.45 (d), 58.27 (d), 59.97 (s), 64.97 (t). Anal. Calcd for $C_{28}H_{50}HgO$: C, 55.75; H, 8.35; Hg, 33.25. Found, C, 56.03; H, 8.59.

[6-$^2H_2$]-3β-[(Methylmercurio)methyl]-5-(hydroxymethyl)-A,B-bisnor-5β-cholestane (55b). To a solution of **59** (100 mg; 0.16 mmol) in ether (20 mL) and methanol (0.5 mL) was added sodium borodeuteride (80 mg; 1.9 mmol) at -20 °C and the mixture was stirred at 0 °C for 4 h. The excess of reagent was then decomposed with 5% aqueous HCl at -78 °C, the mixture was diluted with ether and worked up to give crude alcohol **55b** (51 mg) which was directly converted to acetate **62b** and purified at that stage by chromatography.

4,5-Seco-B-nor-5β-cholest-3-ene-5-carbaldehyde (58a). Tetramethylammonium bromide (160 mg; 1 mmol; 2 equiv.) was added to a solution of molybdenum hexacarbonyl (140 mg; 0.53 mmol) in dry DME (5 mL) and the mixture was refluxed until the evolution of

carbon monooxide had ceased (ca. 20 min). The resulting yellow-brown mixture was cooled to 0 °C and titrated with a solution of bromine (85 mg; 1 equiv.) in DME (2 mL), which was accompanied by a vigorous evolution of CO. The mixture was stirred for at 0 °C additional 10 min and then a solution of organomercurial **9a** (140 mg; 0.21 mmol) in dry DME (2 mL); evolution of CO was observed again and the color of the solution turned to yellow. The mixture was then stirred at rt for 12 h, then diluted with ether (20 mL) and worked up. The solvent was evaporated and the residue was chromatographed on a column of silica gel with a petroleum ether-ether mixture (95:5) to yield **58a** (69 mg; 85%): $[\alpha]_D$ +14° (c 2.4); ^{1}H NMR δ 0.69 (s, 3 H, 18-H), 0.90 (s, 3 H, 19-H), 4.98 (m, 1 H, (4*E*)-H), 5.07 (m, 1 H, (4*Z*)-H), 5.83 (m, 1 H, 3-H), 9.70 (d, J = 3.2 Hz, CH=O); ^{13}C NMR δ 12.32 (q), 17.78 (q), 18.76 (q), 21.36 (t), 22.57 (q), 22.82 (q), 23.86 (t), 24.40 (t), 28.01 (d), 28.48 (t), 29.35 (t), 35.66 (d), 36.23 (t), 39.44 (t), 39.50 (2 x t), 40.48 (d), 41.92 (t), 43.88 (s), 47.40 (s), 55.69 (d), 56.63 (d), 57.43 (d), 58.27 (d), 114.32 (t), 138.85 (d), 204.96 (d). Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.55; H, 12.68.

From 22a: To a mixture of aldehyde **22a** (200 mg; 0.33 mmol) and $PhCH_2(Et)_3N[Mo(CO)_5Cl]$ (300 mg; 0.66 mmol; 2 equiv.) in DME (30 mL) was added a solution of silver(I) trifluorosulfonate (171 mg; 0,66 mmol; 2 equiv.) in DME (2 mL) at -20 °C. The mixture was stirred and allowed to warm to rt and then heated at 40 °C for 5 min to complete the reaction. The mixture was then diluted with ether and worked up. The product was purified by filtration through a pad of aluminum oxide using a petrolether ether-ether mixture (1:1) to afford **58a** (122 mg; 95%) identical with the product obtained above; $[\alpha]_D$ +13° (c 2.0).

(*Z*)-[4^{2}H]-4,5-Seco-B-nor-5β-cholest-3-ene-5-carbaldehyde (58b): $[\alpha]_D$ +13° (c 2.0); ^{1}H NMR δ 0.69 (s, 3 H, 18-H), 0.90 (s, 3 H, 19-H), 4.97 (m, 1 H, (4*E*)-H), 5.85 (m, 1 H, 3-H); MS > 95% ^{2}H (d_1).

3β-Methyl-5-(acetoxymethyl)-A,B-bisnor-5β-cholestane (62a). To a solution of

alcohol **55a** (100 mg; 0.16 mmol) and triethyl amine (2 mL) in THF (30 mL) was was added drop-wise acetyl chloride (26 mg; 0.33 mmol) in THF (1 mL) at -5 °C and the mixture was kept at -5 °C for 2 h. The mixture was then decomposed by ice and water, the product was extracted into ether and the ethereal solution was worked up. The crude product was chromatographed on silica gel (5 g) with a petroleum ether-ether mixture (95:5) to give acetate **62a** (95 mg; 89%): $[\alpha]_D$ +8° (c 1.0); ^{1}H NMR δ 0.30 (s, 3 H, CH_3-Hg), 0.66 (s, 3 H, 18-H), 0.92 (s, 3 H, 19-H), 2.10 (s, 3 H, CH_3CO_2), 4.05 and 4.09 (AB system, J = 11.4 Hz, 2 H, CH_2-OAc); ^{13}C NMR δ 12.28 (q), 18.78 (q), 19.17 (q), 21.33 (q), 21.78 (t), 21.95 (q), 22.57 (q), 22.82 (q), 23.86 (t), 24.50 (t), 28.00 (d), 28.56 (t), 35.66 (d), 36.16 (t), 36.25 (t), 38.57 (t), 39.50 (t), 39.86 (t), 41.46 (t), 41.51 (d), 43.13 (t), 43.81 (s), 50.46 (d), 52.87 (s), 55.74 (d), 56.68 (d), 57.92 (s), 58.34 (d), 67.13 (t), 171.34 (s); MS *m/z* 631 ($M^{\cdot+}$).

[6-$^2H_2$]-3β-Methyl-5-(acetoxymethyl)-A,B-bisnor-5β-cholestane (62b). ^{1}H NMR δ 0.29 (s, 3 H, CH_3-Hg), 0.65 (s, 3 H, 18-H), 0.91 (s, 3 H, 19-H), 2.09 (s, 3 H, CH_3CO_2); MS *m/z* 633 ($M^{\cdot+}$).

3β-[(Methylmercurio)methyl]-5-(methanesulfonyloxymethyl)-A,B-bisnor-5β-cholestane (63). To a solution of alcohol **55** (80 mg; 0.133 mmol) and triethyl amine (1 mL; 726 mg; 7.17 mmol) in tetrahydrofuran (10 mL) at -20 °C was added a solution of methanesulfonyl chloride (22 mg; 0.199 mmol; 1.5 equiv.) in THF (2 mL) and the mixture was stirred at -20 °C for 3 h. The reaction was then quenched by pouring on ice, the product was taken up into ether and the ethereal phase was worked up to furnish **63** (86 mg; 95%): ^{1}H NMR δ 0.32 (s, 3 H, CH_3Hg), 0.65 (s, 3 H, 18-H), 0.95 (s, 3 H, 19-H), 3.04 (s, 3 H, CH_3SO_3), 4.15 and 4.27 (AB system, J = 9.3 Hz, 2 H, 6-H).

3-Methyl-A-norcholest-3(5)-ene (64). (A) From 63: Benzyltriethylammonium chloride (142 mg; 0.625 mmol; 1.1 equiv.) was added to a solution of molybdenum hexacarbonyl (150 mg; 0.568 mmol; 1 equiv.) in DME (30 mL) and the mixture was refluxed for 30 min. When

the evolution of carbon monooxide ceased, the mixture was cooled to rt and a solution of silver(I) trifluorosulfonate (146 mg; 0.568 mmol; 1 equiv.) was added, followed by addition of mesylate **63** (86 mg; 0.127 mmol) in DME (2 mL). The mixture was then heated at 45 °C and monitored by TLC. After 1 h the mixture was cooled to rt, diluted with ether and worked up. The crude product was chromatographed on silica gel (5 g) with petroleum ether to give pure olefin **64** (35 mg; 75%): mp 62-64 °C (acetone; lit.[41] gives 64-65 °C); $[\alpha]_D$ +54° (c 5.3; lit.[41,82] gives +59°); ^{1}H NMR δ 0.68 (s, 3 H, 18-H), 0.76 (m, 1 H, 9α-H), 0.87 (two d, *J* = 6.6 Hz, 6 H, 26-H and 27-H), 0.90 (s, 3 H, 19-H), 0.91 (d, *J* = 6.6 Hz, 3 H, 21-H), 1.11 (m, 1 H, 12 α-H), 1.47 (m, 1 H, 1β-H), 1.57 (br s, 3 H, =C-CH_3), 1.64 (ddd, *J* = 12.4, 8.2, and 1.1 Hz, 1 H, 1α-H), 1.71 (m, 1 H, 7α-H), 1.81 (m, 1 H, 6β-H), 1.97 (ddd, *J* = 12.5, 3.6, and 3.0 Hz, 1H, 12β-H), 2.08 (ddm, *J* = 15.7 and 9.6 Hz, 1 H, 2β-H), 2.27 (m, 1 H, 2α-H), 2.33 (ddd, *J* = 14.1, 4.5, and 2.4 Hz, 1 H, 6α-H); ^{13}C NMR δ 11.90 (q, C-18), 13.46 (q, C-4), 17.93 (q, C-19), 18.59 (q, C-21), 22.43 (q, C-26/27), 22.61 (two t, C-6 and C-11), 22.69 (q, C-26/27), 23.71 (t, C-23), 24.30 (t, C-15), 27.88 (d, C-25), 28.08 (t, C-12), 31.96 (t, C-7), 35.37 (t, C-2), 35.65 (d, C-20), 35.96 (d, C-8), 36.05 (t, C-16), 38.00 (t, C-1), 39.38 (t, C-24), 39.83 (t, C-22), 42.73 (s, C-13), 49.62 (s, C-10), 55.00 (d, C-9), 55.93 (d, C-17), 56.07 (d, C-14), 125.60 (s, C-3), 141.62 (s, C-5); MS *m/z* (%) 370 (34, $M^{\cdot+}$), 355 (69), 147 (47), 135 (26), 122 (39), 109 (42), 93 (90), 57 (100).

(B) From 65: A mixture of the mesylate **65** (100 mg; 0.21 mmol) and sodium acetate (200 mg; 2.44 mmol) in acetic acid (30 mL) was refluxed for 30 min. The mixture was then cooled to rt, diluted with ether and the ethereal solution was washed successively with water (10 x 10 mL), $KHCO_3$ (aqueous; 5 x 10 mL), and water and dried with $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel (5 g) with petroleum ether as eluent to yield **64** (65 mg; 82%) identical with the product obtained under A: mp 62-64 °C.

3β-Methyl-5-(methanesulfonyloxymethyl)-A,B-bisnor-5β-cholestane (65). To a solution of the alcohol **53** (100 mg 0.026 mmol) and triethyl amine (0.4 mL) in THF (20 mL) was added mesyl chloride (0.2 mL) at -10 °C and the mixture was kept et this temperature for 1 h. The mixture was then poured onto ice and water, the product was extracted with ether and the

ethereal solution was worked up to furnish sufficiently pure mesylate **65** (117 mg; 97%): ^{1}H NMR δ 0.74 (s, 3 H, 18-H), 0.99 (s, 3 H, 19-H), 1.08 (d, J = 7.1 Hz, 3 H, 3β-CH_3), 3.12 (s, 3 H, CH_3SO_3), 4.14 and 4.30 (AB system, J_{gem} = 9.3 Hz, 2 H, CH_2OMes); ^{13}C NMR δ 12.16 (q), 15.42 (q), 18.62 (q), 18.83 (q), 21.85 (t), 22.43 (q), 22.68 (q), 23.71 (t), 24.35 (t), 27.86 (d), 28.41 (t), 31.07 (t) 35.50 (d), 36.09 (t), 37.03 (q), 38.19 (t), 39.35 (t), 39.60 (t), 40.32 (d), 41.36 (t), 43.01 (d), 43.62 (s), 52.56 (s), 55.56 (d), 55.77 (s), 56.05 (d), 57.52 (d), 72.04 (t).

4,5-Seco-cholestane-3,5-dione (66): Ozone was bubbled to a solution of olefin **64** (70 mg; 0.189 mmol) in dichloromethane (20 mL) at -48 °C and the progress of ozonization was monitored by TLC. When the reaction was complete, acetic acid (1 mL) and powdered zinc (500 mg) were added and the mixture was stirred at rt for 8 h. The inorganic solid was then filtered off and the filtrate was washed with water, 5% aqueous potassium hydrogen carbonate, and water, and dried with anhydrous $MgSO_4$. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel (5 g) with a petroleum ether-ether mixture (9:1) to yield diketone **66** (70 mg; 92%): $[\alpha]_D$ +29° (c 5.8); ^{1}H NMR δ 0.74 (s, 3 H, 18-H), 1.13 (s, 3 H, 19-H), 2.17 (s, 3 H, 4-H); ^{13}C NMR δ 11.97 (q), 18.58 (q), 20.50 (q), 21.40 (t), 22.54 (q), 22.79 (q), 23.78 (t), 24.22 (t), 27.99 (d), 28.06 (t), 28.37 (t), 29.88 (q), 31.44 (t), 34.87 (d), 35.69 (d), 36.09 (t), 38.19 (t), 38.80 (t), 39.36 (t), 39.47 (t), 42.51 (s), 48.05 (d), 50.31 (s), 55.79 (d), 56.01 (d), 209.18 (s), 215.20 (s). Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.26; H, 11.75.

5. References and Notes

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(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, e.g.: Reischl, W.; Kalchhauser, H. *Tetrahedron Lett.* **1992**, *33*, 2451.

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(22) (a) Larock, R. C. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 27. (b) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985. (c) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic Synthesis*; Springer, Berlin 1986.

(23) Deuterated **7b** was prepared in four steps[11] from 4β-^{2}H-cholesterol.[24,25]

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

(25) For recent synthesis of 4α-^{2}H-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 up-field resonance to *pro*-(*S*)-H, and the down-field signal to *pro*-(*R*)-H.

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

(28) (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 and *ibid* **1985**, *107*, 7265. (e) Wieber, G. M.; Hegedus, L. S.; Åkermark, B.; Michalson, E. T. *J. Org. Chem.* **1989**, *54*, 4649. (f)Åkermark, B.; Zetterberg, K. *J. Am. Chem. Soc.* **1984**, *106*, 5560. (g) Hegedus, L. S.; Åkermark, B.; Zetterberg, K.; Olsson, L. F. *J. Am. Chem. Soc.* **1984**, *106*, 7122. (h)Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474. (i) Brown, J. M.; James, A. P. *J. Chem. Soc., Chem. Commun.* **1987**, 181. (j) Brown, J. M.; Maddox, P. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1277.

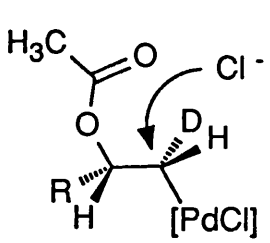
(29) In the ^{1}H NMR spectrum of unlabeled **10a** the 4α-H appears at 4.17 ppm (dd, J = 8.6 Hz and 9.1 Hz) and 4β-H at 3.40 ppm (dd, J = 8.6 and 4.9 Hz); the up-field signal exhibits an NOE (0.2 %) with the acetal proton (δ 5.17), while the down-field signal

shows an NOE (15 %) with 3α-H.

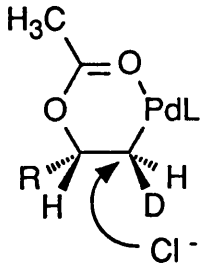
(30) The bromine-mediated conversion of **9b** to the corresponding lactol turned out to be non-stereospecific, producing a 1:1 mixture of the C(4) epimers.

(31) For assessment of the intramolecular nucleophilicities of various functional groups, see, e.g.: Kočovský, P.; Stieborová, I. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1969.

(32) Nucleophilic S_N2-type displacement of the palladium appears to be a common reaction and is well documented.[27,28] Another mechanism for the formation of **10** from **12**, which would involve the carbonyl oxygen coordination to Pd followed by reductive elimination, is extremely unlikely in light of Bäckvall's results:[27,28] although for his intermediate **i** coordination by acetate carbonyl (**ii**) cannot be excluded,[33] this species preferred to react via an S_N2 reaction; no reductive elimination was observed.

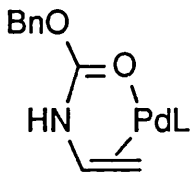


i



ii

(33) Cyclic structure **iii** was suggested as an intermediate in the Pd-mediated carbonylation of enamides.[28e] Other palladacycles have been reported for Pd-mediated amination,[28f,g] and other reactions.[28h] Coordination of various transition metals (e.g. Ir and Rh) by carbonyl oxygen has also been observed, but did not result in reductive elimination.[28i,j]



iii

(34) This transformation occurs with a stoichiometric amount of Pd^{2+}. When attempted as a catalytic process with added $CuCl_2$ to reoxidize Pd(0), no reaction was observed. It was also found that addition of $CuCl_2$ to the stoichiometric experiment (still in the presence of a π-acid) dramatically slowed down the rate; a 1:1 mixture of **10** and **15** was now obtained. Hence, a different type of oxidant has to be sought in order to make this process catalytic. Preliminary experiments suggest that *p*-benzoquinone (itself a π-acid) might be the reagent of choice, but the conditions need to be optimized.

(35) (a) For examples of intermolecular insertion of Pd into the C-H bond of aldehydes, see: Trost, B. M.; Verhoeven T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G.; Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, p. 909. (b) Recently, the transannular insertion of Pd into a non-activated C-H bond has been observed on transmetalation Hg → Pd: Wells, A. P.; Kitching, W. *J. Org. Chem.* **1992**, *57*, 2518.

(36) The reversed sequence may also be considered. However, this would first generate a nucleophilic CO_2H group which may be capable of S_N2 replacing of Pd(II) at C(4) and forming a γ-lactone, in analogy with the conversion of **12** to **10**.

(37) In the proton decoupled ^{13}C NMR spectrum of **15a**, the C(4) (methyl) appeared at 13.97 ppm as a singlet. This resonance was replaced by a triplet at 13.73 ppm in the spectrum of deuterated **15b**. No trace of the signal corresponding to the unlabelled methyl was detected in the latter spectrum. Mass spectrum of **15b** confirmed that ≥ 95% of deuterium has migrated to the methyl group. An authentic sample of **15b** was prepared from **9a** by reduction with $LiAl^2H_4$ followed by Jones' oxidation.

(38) Kočovský, P.; Šrogl, J.; Gogoll, A.; Hanuš, V.; Polášek, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1086.

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

(40) The structure of the products was deduced from their NMR spectra and verified by comparison with authentic samples of **20**[39] and **21**[41] prepared by the known methods.[39,41]

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

(42) 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.

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

(44) (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 e.g.: Wittig, G.; Bickelhaupt, F. *Chem. Ber.* **1958**, *91*, 883. (c) For a review on transmetalations in organocopper chemistry, see: Wipf, P. *Synthesis* **1993**, 537.

(45) Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197.

(46) Kauffmann, T.; Fiegenbaum, P.; Wiescholek, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 531.

(47) It is pertinent to note that the carbonyl group of ketone **25a** proved extremely hindered. Thus for instance, attempts at Wittig or Peterson olefination were unsuccessful; only $Cp_2Ti{=}CH_2$ (Tebbe reagent)[48] was reactive enough to convert this carbonyl into an *exo*-methylene group.

(48) (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.

(49) This reduction can be easily understood as occurring from the convex side of the molecule. The resulting alcohol **26** was also reoxidized to ketone **25a** to make sure that no skeletal rearrangement had occurred on reduction.

(50) The signals of C(4)-protons were much better resolved in ketone **25a** than in the parent alcohol **24a.** Thus, in the ^1H NMR spectrum of **25a**, 4α-H appears at 2.90 ppm (dd, J = 17.6 and 8.6Hz) while 4β-H gives a signal at 2.61 ppm (dd, J = 17.6 and 6.8 Hz). In the spectrum of **25b**, 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 mass spectroscopy) in ketone **25b**, the corrected integration of the relative intensities of

4α-H and 4β-H is indicative of ca. 90:10 ratio of **25b** to its 4-epimer.

(51) No reaction of aldehyde **9a** 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.

(52) Attempted radical cyclization of **27**, using $NaBH_4$ or Bu_3SnH, 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.[53]

(53) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986, p. 143. (b) Imanishi, T.; Ohra, T.; Sugiyama, K.; Ueda, Y.; Takemoto, Y.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 269.

(54) We believe that in this instance, the Lewis acid (Me_3Al) accelerates the conjugate addition, as in its absence only a complex mixture was obtained.

(55) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry* Fifth edition; John Wiley: New York, 1988.

(56) Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: Amsterdam, 1968.

(57) Model experiments demonstrated that both 3α,5-cyclo-5α-cholestan-6β-ol and cholesterol are readily converted to **33a** on treatment with $MoCl_5$ in Et_2O at rt. 5α-Cholestan-3β-ol was converted by the same reagent to a ca. 1:1 mixture of the corresponding 3α- and 3β-chlorides, which indicates S_N1 mechanism, in contrast to the former, stereoelectronically controlled substitutions.

(58) Šrogl, J.; Kočovský, P. *Tetrahedron Lett.* **1992**, *33*, 5991.

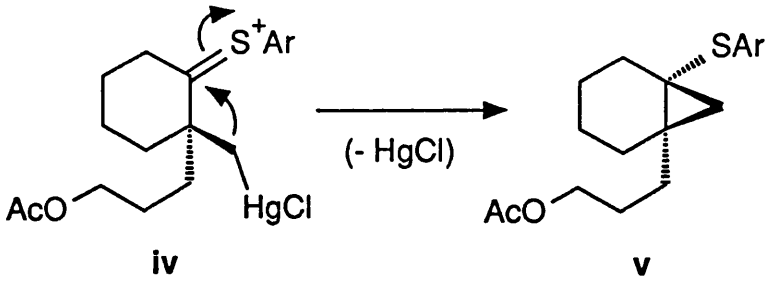
(59) Diagnostic was the signal of 3α-H (at 3.77 ppm). While the width of this multiplet was 32.7 Hz for **33a**, in the spectrum of the deuterated compound **33b** (in which ≥ 95% of deuterium was revealed by HRMS) it was only 19.7 Hz, which indicated that one large (i.e. axial) coupling was missing. This is only compatible with the 4β-^{2}H configuration. Compared to the spectrum of **33a**, 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 **33b**,

and the former has lost its geminal coupling (13.6 Hz). For a detailed description of the ^1H NMR patterns in 4α-^2H- and 4β-^2H-cholesterol, see ref 25.

(60) Alternative explanation that would encompass transmetallation with inversion followed by the C(4)-C(5) bond formation with retention at C(4) (**35** → **32**), is unlikely in view of the generally accepted mechanism of transmetalations.

(61) It is noteworthy that $MoCl_5$ is far more reactive than other Lewis acids, such as $AlCl_3$ or $TiCl_4$. Thus, while the reaction of **9a** with $MoCl_5$ is complete in 5 h at -78 °C, only 50% conversion has been observed with $AlCl_3$ at rt over 5 days(!) and complete conversion has been achieved (with $AlCl_3$) at 45 °C over 12 h.

(62) A recent precedent[63] suggests that the carbon atom adjacent to HgX can serve as an effective nucleophile to quench an electron-defficient center (**iv** → **v**), even in preference to a nucleophilic ester group. Hence, transmetalation of Hg for Mo may not be required in our case.



iv **v**

(63) Takemoto, Y.; Ohra, T.; Yonetoku, Y.; Imanishi, T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 192.

(64) Since $MoCl_5$ is known to react with THF to give $THF_2.MoOCl_3$, the latter is likely to be the actual reagent in this case: McAuliffe, C. A.; Werfali, A. *Inorg. Chim. Acta* **1980**, *60*, 87.

(65) (a) Kočovský, P. *J. Org. Chem.* **1988**, *53*, 5816. (b) Kočovský, P.; Pour, M. *J. Org. Chem.* **1990**, *55*, 5580 and references cited therein.

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

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

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

(69) This reaction employs π-electrons of the double bond as an internal nucleophile and has been shown to proceed via an S_N2-like inversion at C(19).[67,68] For nucleophiles other than H^-, see: (a) Tadanier, 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.

(70) In the ^1H NMR spectrum of **43a** the *pro-R*-H appears at δ 0.51 (d, J = 5.7 Hz), while *pro-S*-H at 0.47 (d). In the spectrum of **43b**, two signals appeared as singlets at 0.51 and 0.47, respectively, in 32:68 ratio. This assignment is based on the stereochemistry of the reduction of aldehyde **39** assuming S_N2 inversion at C(19) in the cyclopropane formation (**41b** → **42b**).[68,69]

(71) In contrast to **7a**, carrying the reaction in a DME/MeCN mixture resulted in the formation of a complex mixture of olefinic products, indicating that C(10)-cation has further migrated along the back bone of the skeleton. For reviews on back bone rearrangement, see ref 56 and: Kočovský, P. *Chem. Listy* **1979**, *73*, 583.

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

(73) The $LiAlH_4$ reduction of **44a** produced cholest-4-en-3β-ol as the major product, while **47a** afforded 19-nor-5-methyl-5β-cholest-9-en-3β-ol (ca. 60%) identical with an authentic sample,[72] along with its C(3)-epimer.

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

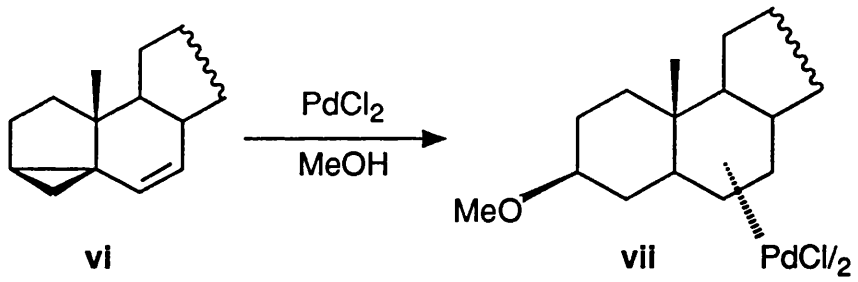
(75) The ratio was determined by integration of the signals of 19-^2H in the ^2H NMR spectrum for each pair of 19-epimers. For **44b** the ratio of 2.53 ($W/2$ = 13.8 Hz) to 2.23 ($W/2$ = 12.0) was 65:35; for **44b**, the signals at 2.42 ($W/2$ = 18.0 Hz) to 2.12 ($W/2$ = 13.8 Hz) were in 32:68 ratio.

(76) Racemization has also been observed with another Hg → Cu transmetallation.[44a]

(77) 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]

(78) On the other hand, activation of the cyclopropane by a neighbouring double bond, as in **vi**, resulted in a clean reaction with Pd(II) furnishing the complex **vii**. Here, the reaction can be rationalized by initial coordination of Pd to the double bond followed by edge opening of the cyclopropyl ring (Kočovský, P.; Pour, M. unpublished results; see: Pour, M. *Thesis*, Charles University, Prague, 1988.) For similar examples, see refs 8c-8e.



vi **vii**

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

(80) (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.

(81) Krief, A.; Hobe, M.; Dumont, W.; Badaoui, E.; Guittet, E.; Evrard, G. *Tetrahedron Lett.* **1992**, *33*, 3381.

(82) This is evidenced by almost identical ^{13}C-H coupling constants at the carbon adjacent to mercury: $^{1}J_{C\text{-}H}$ = 135.3 Hz for **9a** and $^{1}J_{C\text{-}H}$ = 135.6 Hz for **44a**.

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

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

(85) In open chain systems, the *4-exo-Trig* process via a radical mechanism is shifted towards the open species.[53] The seemingly favorable distance and orientation of the two potential partners, imposed by the rigid skeleton of **9**, does not compensate for the thermodynamic factors.[86] In contrast, five- and six-membered rings can readily be formed by the intramolecular radical addition across a C=C or C=O bond.[86,87] For a recent report on the ring-opening of a radical generated from cyclobutanone, see: Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1992**, *33*, 3285.

(86) For occasional reports on cyclobutane or cyclopropane formation via a radical addition, see: (a) Picardi, P.; Modena, M.; Cavalli, L. *J. Chem. Soc. (C)* **1971**, 3935. (b) Piccardi, P.; Massardo. P.; Modena, M.; Santoro, E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 982. (c) Araki, Y.; Endo, T.; Arai, Y.; Tanji, M.; Ishio, Y. *Tetrahedron Lett.* **1989**, *30*, 2829. (d) Gill, G. B.; Pattenden, G.; Reynolds, S. J. *Tetrahedron Lett.* **1989**, *30*, 3229. (e) Park, S. U.; Varick, T. R.; Newcomb, M. *Tetrahedron Lett.* **1990**, *31*, 2975. (f) Pattenden, G.; Reynolds, S. J. *Tetrahedron Lett.* **1991**, *32*, 259. (g) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725. (h) Fremont, S. L.; Belletire, J. L.; Ho, D. M. *Tetrahedron Lett.* **1991**, *32*, 2335. (i) Srikrishna, A.; Hemamalini, P.; Sharma, G. V. R. *Tetrahedron Lett.***1991**, *32*, 6609. (j) Jung, M.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719.

(87) Although C=O is not particularly prone to radical addition, successful cyclization producing 5- and 6-membered rings via an intramolecular radical addition have been described: (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116 and 8102. (b) Tsang, R.; Dickson, J. K.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484. (c) Mori, M.; Isono, N.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 2972. Samarium(II) seems to be an excellent promoter of this type of reaction: (d) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (e) Molander, G. A.;

McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.

(88) Murdoch, D. *J. Organomet. Chem.* **1965**, *4*, 114.

(89) Brisdon, B. J.; Edwards, D. A.; White, J. W. *J. Organomet. Chem.* **1978**, *156*, 427.

(90) (a) Ganorkar, M. C.; Stiddard, M. H. B. *J. Chem. Soc.* **1965**, 3494. (b) Abel, E. W.; Butler, I. S.; Red, J. G. *J. Chem. Soc.* **1963**, 2068. (c) Durrant, M. C.; Hughes, D. L.; Richards, R. L.; Baker, P. K.; Harris, S. D. *J. Chem. Soc., Dalton Trans.* **1992**, 3399.

(91) King, R. B.; *Inorg. chem.*, **1964**, *3*, 1039.

(92) For the classical, "organic" Grob fragmentation, see: (a) Grob, C. A.; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 535. (b) Grob, C. A.; Schwarz, W. *Helv. Chim. Acta* **1964**, *47*, 1870. (c) Bottini, A. T.; Grob, C. A.; Schumacher, E.; Zergenyi, J. *Helv. Chim. Acta* **1966**, *49*, 2516. (d) Grob, C. A.; Kunz, W.; Marbet, P. R. *Tetrahedron Lett.* **1975**, 2613. (e) Grob, C. A.; Bolleter, M.; Kunz, W. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 708. For general discussion and synthetic applications, see: ref 2a and (f) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.

(93) The CH=O proton (at 9.70 ppm) shows NOE (1.4%) upon irradiation of the angular methyl (19-H at 0.90 ppm), indicating their *cis* relationship.

(94) The signal for the (Z)-proton of **58a** (at 5.07 ppm) was reduced to ca. ≤ 20% in the spectrum of **58b** and the signals of the remaining two olefinic protons were accordingly changed. In view of the total deuterium content (≥ 85%, as evidenced by mass spectroscopy), the corrected integration of the relative intensities of 4(Z)-H and 4*(E)*-H is indicative of ≥90:10 ratio of **58b** to its isomer.

(95) Another conformation of **56** which might induce this stereoelectronically controlled fragmentation is that with a syn-periplanar arrangement of the C(4)-[M] and C(3)-C(5) bonds. However, we believe that in this conformation, the negatively charged molybdenum and the electropositive carbonyl carbon would interact in preference to other events. Apparently, this was not the case, since no product of such a reaction was isolated.

(96) Analogous reactions have been reported for RCO_2Tl and RCO_2Ag: (a) Doyle, G. *J.*

Organomet. Chem. **1975**, *84*, 323. (b) Cotton, F. A.; Darensbourg, D. J.; Kolthammer, B. W. S. *J. Am. Chem. Soc.* **1981**, *103*, 398.

(97) Evolving CO partly reduces precipitated AgCl to Ag(0). The complex **D** presumably exists as a dimer.

(98) Precedents for transmetalation are known, e.g., from tungsten and iron chemistry.[99,100] Thus, for instance, $Et_4N^+[W(CO)_5Br]^-$ reacts instantaneously with RLi to furnish LiBr and $Et_4N^+[W(CO)_5R]^-$.[99] Although organomercurials are generally less reactive than their organolithium analogues, this can be compensated by higher reactivity of Mo-complexes (as compared to W-complexes). Furthermore, $Et_3HN^+[Fe_2(CO)_7SR]^-$ reacts with various vinylic organomercurials R-HgCl to give Et_3NHCl and transient L_nFe-HgR species which extrude Hg(0) and yield stable Fe-complexes.[100]

(99) Casey, C. P.; Polichnowski, S. W.; Anderson, R. L. *J. Am. Chem. Soc.* **1975**, *97*, 7375.

100) (a) Seyferth, D.; Archer, C. M.; Ruschke, D. P.; Cowie, M.; Hilts, R. W. *Organometallics* **1991**, *10*, 3363. (b) Seyferth, D.; Anderson, L. L.; Villafañe, F.; Cowie, M.; Hilts, R. W. *Organometallics* **1992**, *11*, 3262.

101) In contrast to **22**, there is no driving force for fragmentation in this case, so that the organomolybdenum intermediate reacts differently to give **53**. Direct protonolysis of **22** can be ruled out as on prolonged acid treatment (10% $HClO_4$), **22** undergoes β-elimination rather than protonolysis. For β-elimination of organomercurials, see, e.g.: Jerkunica, J. M.; Traylor, T. G. *J. Am. Chem. Soc.* **1971**, *93*, 6278.

102) For a direct conversion of a triphenylmethyl ether into a ketone by means of $Ph_3C^+BF_4^-$, via a hydride abstraction, see: Jung, M. E.; Speltz, L. M. *J. Am. Chem. Soc.* **1976**, *98*, 7882.

103) An alternative mechanism that would involve insertion of molybdenum into the C-H bond of the CH_2-O group is very unlikely.

104) Schrock complexes arising by α-elimination, have been described for various metals[3] (e.g. M = W[105], Ta[106], and Ti[107]); calculations are also available.[108] In our case, the α-elimination to generate **III** may be further assisted by the release of steric

hindrance.[3]

105) (a) Cooper, N. J.; Green, M. L. H. *J. Chem. Soc., Chem. Soc.* **1974**, 209. (b) Cooper, N. J.; Green, M. L. H. *J. Chem. Soc., Dalton Trans.* **1979**, 1121.

106) (a) Turner, H. W.; Schrock, R. R.; Fellmann, J. D.; Holmes, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 4942. (b) Schrock, R. R. *Acc. Chem. Res.* **1979**, *12*, 98.

107) McDade, C.; Green, J. C.; Bercaw, J. E. *Organometallics* **1982**, *1*, 1629.

108) (a) Berke, H.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 7224. (b) Ziegler, T.; Versluis, L.; Tschinke, V. *J. Am. Chem. Soc.* **1986**, *108*, 612.

109) Although Schrock metallocarbenes are usually regarded as nucleophiles, those having positive charge or coordinatively unsaturated metal (as, presumably, in this instance) tend to react as electrophiles.[3] Thus, for instance, a neutral complex $(CO)_5Cr{=}CH_2$ seems to be fairly electrophilic.[110] Hence, the intramolecular hydride abstraction in **III** is conceivable.

110) Fischer, H.; Weber, L. *Chem. Ber.* **1984**, *117*, 3340.

111) Surprisingly, aldehyde **10a** cannot be prepared from **9** by oxidation with chromium-based reagents (Jones', PCC, or PDC) since the process does not stop at the stage of aldehyde, so that ca. 1:1 mixtures of aldehyde and acid are always isolated. However, perruthenate oxidation[112] was found to give satisfactory yield of pure aldehyde.

112) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

113) (a) A related fragmentation of such a structural pattern employed TsO as a leaving group and boron in place of molybdenum: Marshall, J. A.; Bundy, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 4291. (b) For a recent example of the fragmentation of an acetal with Bu_3Sn group in poition 4, see: Sato, T.; Kawase, A.; Hirose, T. *Synlett* **1992**, 891.

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6. Supplement

1. Pavel Kočovský and Jiří Šrogl:
Regioselective Ring Opening of Cyclopropanes by Mercury(II) and Transmetalation of the Intermediate Organomercurial with Lithium and Copper Reagents. A Novel, Stereoselective Approach to Cyclobutanes.
J.Org.Chem. **1992**, *57*, 4565.

2. Pavel Kočovský, Jiří Šrogl, Adolf Gogoll, Vladimír Hanuš, Miroslav Polášek:
Transmetallation with Palladium(II) of an Organomercurial arising from Mercury-mediated Cyclopropane Cleavage. Tuning of the Palladium Reactivity and a Novel, Intramolecular Redox Reaction.
J.Chem.Soc., Chem.Commun. **1992**, 1086.

3. Jiří Šrogl and Pavel Kočovský:
Regioselective Ring Opening of Cyclopropanes by Mercury(II) and Transmetalation of the Product with Molybdenum. A Novel, Stereoelectronically Controlled, Skeletal Rearrangement and Grob-Type Fragmentation of Organomolybdenum Inermediates.
Tetrahedron Lett. **1992**, *33*, 5991.

4. Pavel Kočovský, Jiří Šrogl, Milan Pour, and Adolf Gogoll:
Corner Opening of Cyclopropanes by Hg(II) and Thallium(III) and Transmetalation of the Intermediate Organomercurials. A Novel, Stereoselective Approach to Cyclobutanes and Cyclopropanes.
J.Am.Chem.Soc., **1994**, *116*, 186.

5. Jiří Šrogl, Adolf Gogoll and Pavel Kočovský:
Molybdenum (V)-Mediated Skeletal Rearrangement of an Organomercury Steroid. Stereoelectronic Control and Mechanism.
J.Org.Chem., in press.

Regioselective Ring Opening of Cyclopropane by Mercury(II) and Transmetalation of the Intermediate Organomercurial with Lithium and Copper Reagents. A Novel, Stereoselective Approach to Cyclobutanes†

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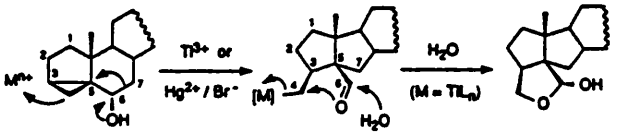
Summary: Cleavage of cyclopropyl derivative 1 by means of Hg^{2+} occurs with a skeletal rearrangement to afford a stable organomercurial 3 which on treatment with Me_2CuLi gives cyclobutanol 9; analogous conjugate addition is also reported (10 → 15).

Stereo- and regioselective cleavage of cyclopropanes[1,2] by means of electrophilic metal complexes can serve as an attractive strategy for the construction of up to three contiguous chiral centers.[3]

Recently, we have described a stereospecific, thallium(III)-mediated cleavage of steroidal cyclopropane derivative 1 which triggered a unique skeletal rearrangement affording lactol 4 via the thalliated intermediate 2 (Scheme I).[6] Mercury(II) ion, isoelectronic with Tl(III), is also known to be capable of cleavage of a cyclopropane.[1,5,7] Since organomercurials are generally more stable than their organothallium counterparts, it was of great interest to explore the reactivity of 1 toward Hg(II), aiming at isolation of the organomercurial product and exploration of its reactivity, including transmetalation.

3α,5-Cyclo-5α-cholestan-6α-ol (1)[8] was treated with $Hg(NO_3)_2 \cdot H_2O$ in DME/MeCN (2:5) at rt. The reaction was monitored by TLC, and when the starting material could no longer be detected (ca. 1.5 h), aqueous KBr was added.[9] The mixture was worked up to afford organo-

Scheme I



† Dedicated to Professor John E. McMurry on the occasion of his 50th birthday.

(1) (a) Rappoport, Z., Ed. *The Chemistry of the Cyclopropyl Group*; J. Wiley and Sons: London, 1987. (b) Crabtree, R. H. *Chem. Rev.* 1985, *85*, 245.

(2) Cyclopropanes themselves can be synthesized with high diastereo- and enantioselectivity.[1]

(3) Two mechanisms can be discerned for the ring opening of cyclopropanes, namely the *edge* (favored by reagents capable of back donation, such as transition metals[1] and halogens[4]) and the *corner* cleavage (typical for electrophiles that are incapable of back donation, e.g., H^+, Hg^{2+}, and Tl^{3+}).[5,6]

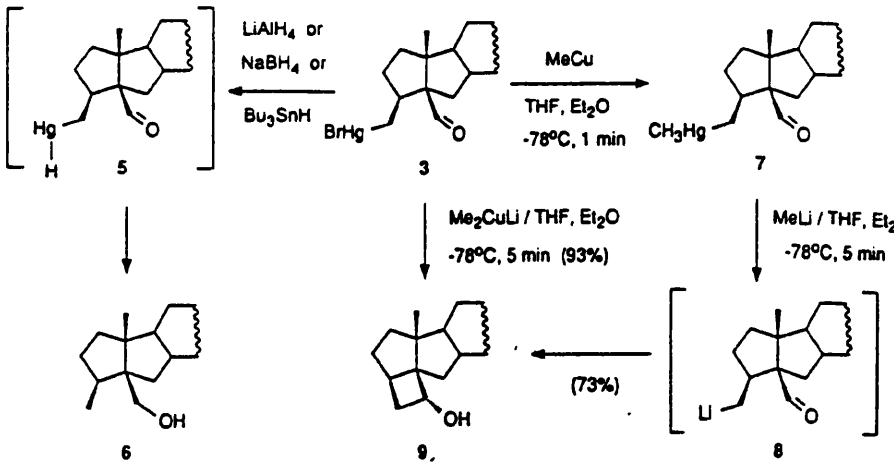
(4) Lambert, J. B.; Chelius, E. C.; Schulz, W. J., Jr.; Carpenter, M. E. *J. Am. Chem. Soc.* 1990, *112*, 3156.

(5) (a) Coxon, J. M.; Steel, P. J.; Whittington, B. L.; 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. L. *J. Org. Chem.* 1990, *55*, 4136. (c) Lambert, J. B.; Chelius, E. C.; Bible, R. H., Jr.; Hajdu, E. *J. Am. Chem. Soc.* 1991, *113*, 1331.

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

0022-3263/92/1957-4565$03.00/0

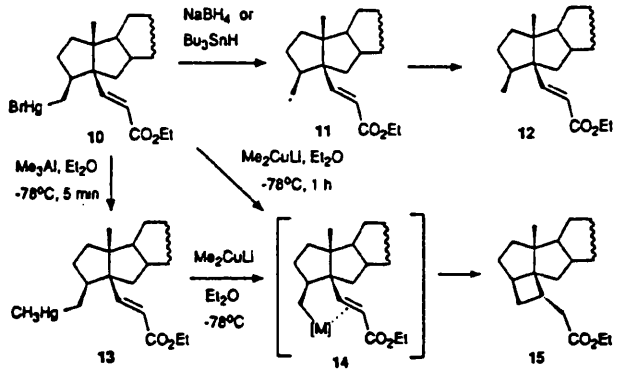
Scheme II



mercurial **3** in 97% isolated yield.[10,14,15] Unlike the thalliated species **2**, compound **3** was fairly stable and could be purified by chromatography and crystallized.

Reduction of **3** with a variety of hydride reagents furnished demercurated alcohol **6** in a quantitative yield (Scheme II). Since Bu_3SnH also gave **6** (1 min at 0 °C), we assume the generation of mercury hydride **5** as an intermediate followed by an intramolecular reduction of the aldehyde group. No cyclobutane ring closure was observed.[16]

Scheme III



In order to achieve an intramolecular addition to the aldehyde group, we have attempted a transmetalation of **1** that would generate a more reactive organometallic species. Since MeLi produced a complex mixture, we turned our attention to intermediates derived from softer metals, such as copper.[20] Rather surprisingly, MeCu (generated by mixing equal parts of CuI and MeLi) effected clean methylation on mercury, providing the MeHg derivative **7** (94%).[21,22] Treatment of **7** with MeLi at low temperature resulted in the formation of the desired cyclobutanol **9**.[23] Alternatively, we have found that **9** can be obtained in one pot on reaction of **3** with Me_2CuLi.[24]

Having successfully accomplished intramolecular addition of an intermediate organometallic species to the C=O bond to produce a 4-membered ring (**3** → **9**), we set out to explore the intramolecular conjugate addition reaction of this or related intermediates to an activated C=C bond. To our delight, aldehyde **3** readily afforded the required α,β-unsaturated ester **10**[25] on Horner–Emmons

(7) (a) Collum, D. B.; Mohamadi, F.; Hallock, J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6882. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094. (c) Rood, L. D. C.; Klump, G. W. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 303. (d) Langbein, G.; Siemann, H.; Gruner, L.; Müller, C. *Tetrahedron* **1986**, *42*, 937. (e) Takemoto, Y.; Ohra, T.; Yonetoku, Y.; Imanishi, T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 192. (f) For review on organomercurials, see: Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985.

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

(9) Much slower reaction was observed with $(CF_3CO_2)_2Hg$; $(AcO)_2Hg$ did not react at rt at all. The DME/MeCN mixture was found out to be superior to dioxane, which, in turn, was the solvent of choice for the Tl(III)-mediated cleavage.[6]

(10) The structure was determined by NMR spectra using H,H-COSY,[11] HMQC,[12] HMBC,[12] and selective INEPT.[13] ^1H NMR: 9.72 (s, 1 H, CHO); ^{13}C NMR: 34.78 ($-CH_2HgBr$), 206.22 (–CHO); ^{199}Hg NMR: −1063 ppm. The full assignment of carbon signals in the ^{13}C NMR spectrum has been achieved.

(11) Bax, A.; Freeman, R.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 164.

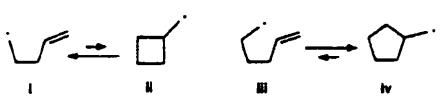
(12) (a) Summers, M. F.; Marzilli, L. G.; Bax, A. *J. Am. Chem. Soc.* **1986**, *108*, 4285. (b) Cavanagh, J.; Hunter, C. A.; Jones, D. N. M.; Keeler, J.; Sanders, J. K. M. *Magn. Reson. Chem.* **1988**, *26*, 867.

(13) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.

(14) In the absence of the 6α-hydroxy group, the reaction with Hg^{2+} occurs via a simple ring-opening followed by elimination to give the corresponding allylic acetate: Blossey, E. C. *Steroids* **1969**, *14*, 725. For review on the chemistry of cyclopropano-steroids, see: Evans, J. M.; Kasal, A. *Acta Cient. Venez.* **1972**, *23*, 95.

(15) Other isoelectronic cations (Au^+ and Pb^{4+}) and those of high redox potential as well as other ions (Ce^{4+}, Cu^+, Cu^{2+}, Ag^+, and Mn^{3+}) were found either to be inert or to convert **1** to cholesterol or its esters (acetate, nitrate, etc.).

(16) Radicals of the type **i** do not cyclize to **ii**, as the equilibrium is shifted toward the open species **i**.[17] In contrast, five-membered rings can readily be formed by the intramolecular radical addition (**iii** → **iv**).[17-19]



i ii iii iv

(17) For discussion, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986; p 143.

(18) Imanishi, T.; Ohra, T.; Sugiyama, K.; Ueda, Y.; Takemoto, Y.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 269.

(19) Although C=O is not particularly prone to radical addition, successful cyclizations producing 6-membered rings via an intramolecular radical addition have been described: (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116 and 8102. (b) Tsang, R.; Dickson, J. K.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484. Samarium(II) seems to be an excellent promoter of this type of reaction: (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(20) Bergbreiter, D. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 4937.

(21) 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 **7** were Me_3Al, Me_2Zn, and Me_2Mn.

(22) ^1H NMR: 0.32 (s, CH_3Hg), 9.81 (s, CH=O) ppm. ^{13}C NMR: 20.94 (CH_3Hg), 207.37 (CH=O) ppm. ^{199}Hg NMR: −161.6 ppm; m/z 600 (M^+).

(23) IR: ν_{OH} = 3430 and 3600 cm^{-1}; ^1H NMR: 4.19 (dd, 1 H, J = 4.6 and 5.4 Hz, CHOH) ppm; ^{13}C NMR 68.59 (d) ppm. The structure of **9** was corroborated by oxidation which afforded the corresponding cyclobutanone which had mp: 112–114 °C. $[\alpha]_D$: −9° (c 2.4). IR: 1750 cm^{-1}. ^1H NMR: 2.61 (dd, 1 H, J = 17.6 and 6.8 Hz, 4β-H), 2.90 (dd, 1 H, J = 17.6 and 8.6 Hz, 4α-H) ppm. ^{13}C NMR 212.93 (C=O) ppm.

(24) This reaction can be understood in terms of the Lipshutz observation of an equilibrium between a cuprate and alkyllithium (2 Me_2CuLi ⇌ MeLi + Me_3Cu_2Li): Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197.

olefination.[26] Attempted radical cyclization of 10, using $NaBH_4$ or Bu_3SnH (Scheme III), gave only the reduced product 12 (in 81% and 87% yield, respectively).[27,28] However, as with the aldehyde 3, copper reagents proved more rewarding. First, organomercurial 10 was methylated with MeCu or Me_3Al to give 13 (in 91% and 95% yield, respectively.)[29] Although in this instance MeLi produced a complex mixture on reaction with 13, Me_2CuLi afforded the desired cyclobutane derivative 15 (40%).[30] Alternatively, 15 was obtained in much higher isolated yield (75%) in one pot from 10 on reaction with Me_2CuLi.[31] This behavior suggests that the actual reactive species 14 involves copper. Although the structure of 14 is unknown, it seems reasonable to assume[20] that M = $CuLiCH_3$ or $CuHgLiCH_3$ and that the more suitably positioned C(4) in the complex 14 adds across the double bond in preference to the CH_3 group.

In conclusion, we have achieved a unique, regio- and stereoselective opening of a cyclopropane ring by Hg(II) followed by a skeletal rearrangement, generating a "5,5" system (1 → 3). As a result of specific transmetalations (with Li or Cu) we have been able to effect a highly stereoselective, intramolecular addition to a carbonyl group and/or across a conjugated double bond, and so construct a "5,5,4" tricyclic system (3 → 9 and 10 → 15). These transformations represent a novel methodology for cyclobutane annulation that may be of general use in view of the rather limited number of alternative approaches[32] and of the failure of radical reactions.[33] Alternatively, we believe that the strategy employing organomercurials, which can be generated by a number of stereoselective routes,[7f] may result in the development of a general method for the stereoselective construction of rings of various size, and for intermolecular coupling as well.

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Supplementary Material Available: Representative experimental procedures and characterization data for new compounds (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(25) IR: $\nu_{C=O}$ = 1702 cm^{-1}. ^1H NMR: 5.92 (d, J = 16.0 Hz, 1 H, CH=C*H*CO_2Et), 7.06 (d, 1 H, J = 16.0 Hz, C*H*=$CHCO_2Et$) ppm. ^{13}C NMR: 119.57 (d), 151.98 (d), 166.46 (s) ppm.

(26) Although the reaction was rather slow [$(EtO)_2P(O)CH_2CO_2Et$, BuLi, THF, reflux for 12 h] due to steric hindrance, the yield of 10 was very good (73%). To our knowledge, this is the first successful Wittig-type olefination in the presence of an HgBr group in the substrate molecule. No reaction of aldehyde 3 was observed with Wittig reagents Ph_3P=CHR or with Ph_3As=CH_2, presumably due to the preferential coordination of Hg to P or As.

(27) Analogous radical cyclization of an organomercurial intermediate has been successfully employed to construct a five-membered ring.[18]

(28) Attempted intramolecular Heck coupling, using various Pd(II)-reagents, resulted solely in β-elimination (to give a product with an endocyclic double bond in 93% yield). This is in sharp contrast to the analogous cyclization that occurs readily to produce five-membered rings.[18]

(29) ^1H NMR: 0.25 (s, 3 H, CH_3Hg), 5.84 (d, 1 H, J = 16.0 Hz, CH=C*H*CO_2Et), 7.15 (d, 1 H, J = 16.0 Hz, C*H*=$CHCO_2Et$) ppm. ^{13}C NMR: 20.92 (CH_3Hg), 118.03 (d), 154.73 (d), 166.89 (s) ppm.

(30) IR: $\nu_{C=O}$ = 1728 cm^{-1}. ^{13}C NMR: 173.20 (s) ppm.

(31) Cyclobutane derivative 15 can also be obtained in high yield (92%) from 13 on reaction with Me_3Al/BuLi. We believe that, in this instance, the Lewis acid (Me_3Al) accelerates the conjugate addition, as in its absence only a complex mixture was produced.

(32) For methods of construction of four-membered rings, see: (a) Trost, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 1, p 843; Vol. 3, pp 588 and 620; Vol. 5, pp 63, 123, and 899. (b) Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC: Boca Raton, FL, 1986; Vol. 1, pp 39, 96, and 145. For a recent enantioselective approach, see: (c) Nemoto, H.; Iahibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem.* 1992, *57*, 1707.

(33) Recently, an ionic, intramolecular addition across a conjugated double bond to form a four-membered ring, has been reported: Cooke, M. P., Jr. *J. Org. Chem.* 1992, *57*, 1495.

Transmetallation with Palladium(II) of an Organomercurial arising from Mercury(II)-mediated Cyclopropane Cleavage. Tuning of the Palladium Reactivity and a Novel, Intramolecular Redox Reaction

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The cleavage of the fused-ring cyclopropane hydroxy derivative **1** by means of Hg^{II} is highly stereoselective and gives a rearranged organomercurial **3**, transmetallation of which with Pd^{II} can be controlled by ligands to afford either lactol **4** or acid **8**; the latter compound is formed *via* an intramolecular insertion of Pd into the C–H bond (**6** → **7**), as evidenced by isotopic labelling.

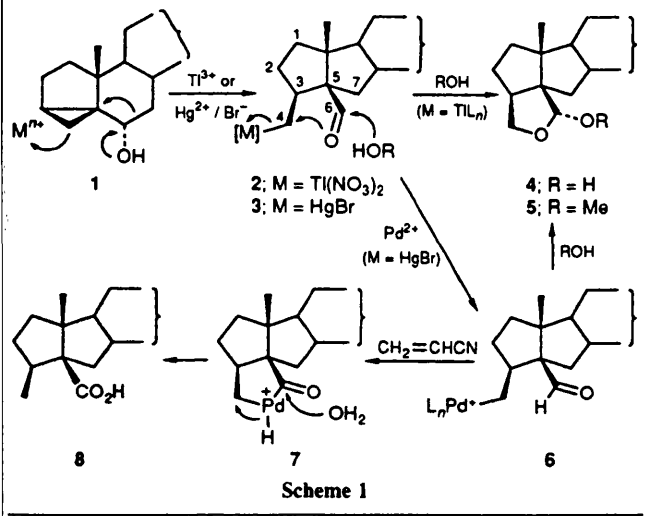
Transmetallation is a promising methodology that takes advantage of combining specific reactivities of different metals.[1] Recently, we have described a stereospecific, Tl^{III}-mediated cleavage of the steroidal cyclopropane derivative **1**, followed by a unique skeletal rearrangement that afforded lactone **4** *via* the thalliated intermediate **2** (Scheme 1).[2] Mercury(II) ion, isoelectronic with thallium(III), is also known to be capable of cleavage of cyclopropane.[3] Herein, we report the reaction of **1** with Hg^{II}, isolation of the organomercurial product, and its transmetallation with Pd.

Treatment of 3α,5-cyclo-5α-cholestan-6α-ol **1**[4] with $Hg(NO_3)_2.H_2O$ in 1,2-dimethoxyethane (DME)–MeCN (3:2) at room temperature for 1.5 h, followed by quenching with aqueous KBr, afforded the organomercurial **3** in 97% isolated yield (Scheme 1),† which, unlike the thalliated species **2**, was fairly stable.

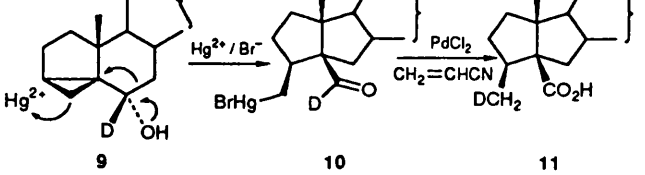
Catalytic reaction of **3** with Li_2PdCl_4 (5 mol %; generated *in situ* from $PdCl_2$ and LiCl) and $CuCl_2$ (3 equiv.) in DME–H_2O,[5] presumably proceeding *via* the organopalladium(II) species **6**, furnished lactol **4**; in the presence of MeOH, the corresponding methyl acetal **5** was formed. The same reaction was observed in the absence of $CuCl_2$, when a stoichiometric amount of Li_2PdCl_4 was used. Thus, similarly to thallium, in this instance palladium served as a good leaving group and enabled the transformation of **3** to **4** to take place employing the same mechanism.

When the transmetallation of the organomercurial **3** with Li_2PdCl_4 was attempted in the presence of a π-acid, such as maleic anhydride, acrylonitrile or cyclohex-2-enone, acid **8** was isolated as the sole or major product,‡ rather than the lactol **4**. Apparently, the coordination to a π-acid dramatically changed the reactivity of Pd.§ This rather unexpected reaction can be rationalized as follows. Instead of undergoing the $5(O)^{\pi,n}$-*exo-tet* ring closure[6] to **4**, in this instance the transient organopalladium **6** preferred an intramolecular insertion into the C–H bond of the aldehyde group.[7] This step generated palladacycle **7** (a highly unstable Pd^{IV} species), which collapsed to the acid **8** *via* a hydrogen transfer from Pd to C(4) (reductive elimination) followed by hydrolysis of the acyl–Pd bond (presumably *via* acyl chloride)[8] and formation of Pd^0.¶ In order to verify this mechanism, deuteriated aldehyde **10** was prepared from [6β-^{2}H]-alcohol **9** (Scheme 2), which in turn was synthesized by a highly stereoselective reduction of 3α,5-cyclo-5α-cholestan-6-one with $LiAl^2H_4$. Transmetallation of **10** under the same conditions as applied to its unlabelled counterpart (*i.e.* Li_2PdCl_4, CH_2=CHCN, DME, H_2O room temp.) resulted in the formation of acid **11** labelled in the methyl group. The mass and ^{13}C NMR spectra revealed an almost quantitative transfer of deuterium from the aldehyde group to the methyl,‖ which is in an excellent agreement with the proposed mechanism.

The observed behaviour of Hg^{2+} parallels the reactivity of Tl^{3+} in the cyclopropane ring-opening. The difference



Scheme 1



Scheme 2

* Correspondence to this author at the University of Leicester (current address).

† ^1H NMR: δ 9.72 (s, 1 H, CHO); ^{13}C NMR: δ 34.78 (CH_2HgBr) and 206.22 (CHO); ^{199}Hg NMR: δ −1063 (indirectly referenced to $HgCl_2$ at δ −1501.6 and Ph_2Hg at δ −808.5). The full assignment of carbon signals in the ^{13}C NMR spectrum has been achieved.

‡ IR: $\nu_{C=O}$ 1683, ν_{COH} 2500–3100 cm^{-1}; ^{13}C NMR: δ 181.87.

§ This transformation occurs with a stoichiometric amount of Pd^{2+}. When attempted as a catalytic process with added $CuCl_2$ to reoxidize Pd^0, no reaction was observed. It was also found that addition of $CuCl_2$ to the stoichiometric experiment (still in the presence of a π-acid) dramatically slowed the rate: a 2:1 mixture of **4** and **8** was obtained. Hence, a different type of oxidant has to be sought in order to make this process catalytic.

¶ The reversed sequence may also be considered. However, this would first generate a nucleophilic CO_2H group which may be capable of S_N2 replacing of Pd^{II} at C(4) and forming a γ-lactone, in analogy to the conversion of **6** into **4**.

‖ In the proton-decoupled ^{13}C NMR spectrum of **8**, the C(4) (methyl) appeared at δ 13.97 as a singlet. This resonance was replaced by a triplet at δ 13.73 in the spectrum of deuteriated **11**. No trace of the signal corresponding to the unlabelled methyl was detected in the latter spectrum. The mass spectrum of **11** confirmed that ≥95% of deuterium had migrated to the methyl group. An authentic sample of **11** was prepared from **3** by reduction with $LiAl^2H_4$ followed by Jones' oxidation.

between Tl and Hg is only seen in the fate of the organometallics generated in this way; the organothallium intermediate **2** is highly unstable and only undergoes the S_N2 ring closure (**2** → **4**) which seriously limits the synthetic applicability. By contrast, the organomercurial **3** is fairly stable, and can be isolated in the pure state and utilized for subsequent transformations.** This divergence of behaviour can serve as a clear example of how a choice of metal can be used to delicately control the reactivity. The organopalladium intermediate **6** offers further opportunities for tuning; here, it is the ligands attached to the same metal that have the decisive influence. In the absence of added ligands, the Pd^{II} intermediate **6** undergoes a clean S_N2 reaction, while addition of π acids promotes its conversion into the Pd^{IV} species **7** *via* insertion into the C–H bond. We are confident that these findings are of a general nature and might be used as the key steps for construction of complex molecules, such as triquinanes. Furthermore, the intramolecular redox reaction of **6**, producing methyl acid **8**, is a novel, mild procedure (related to, *e.g.* the intramolecular Cannizzarro or Tishchenko reaction) of potential synthetic applicability.

We thank Dr R. D. W. Kemmitt and Professor J.-E. Bäckvall for stimulating discussions, and Dr G. Griffith for obtaining some of the NMR spectra. We also thank the Swedish Natural Science Research Council (NFR), Merck Sharp and Dohme, and the University of Leicester for financial support.

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** Aside from the Pd-mediated conversion of **3** into **4**, **5**, or **8**, we have found that, *e.g.*, Wadsworth–Emmons alkenation can be performed with **3** without losing the –HgBr functionality. Furthermore, reaction of **3** with Me_2CuLi (−78 °C, 5 min) led to a ring closure producing the corresponding cyclobutanol in high yield.[9]

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9 P. Kočovský and J. Šrogl, *J. Org. Chem.*, 1992, **57**, in the press.

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Regioselective Opening of a Cyclopropane Ring by Mercury(II) and Transmetalation of the Product with Molybdenum. A Novel, Stereoelectronically Controlled, Skeletal Rearrangement and Grob-Type Fragmentation of Organomolybdenum Intermediates[1]

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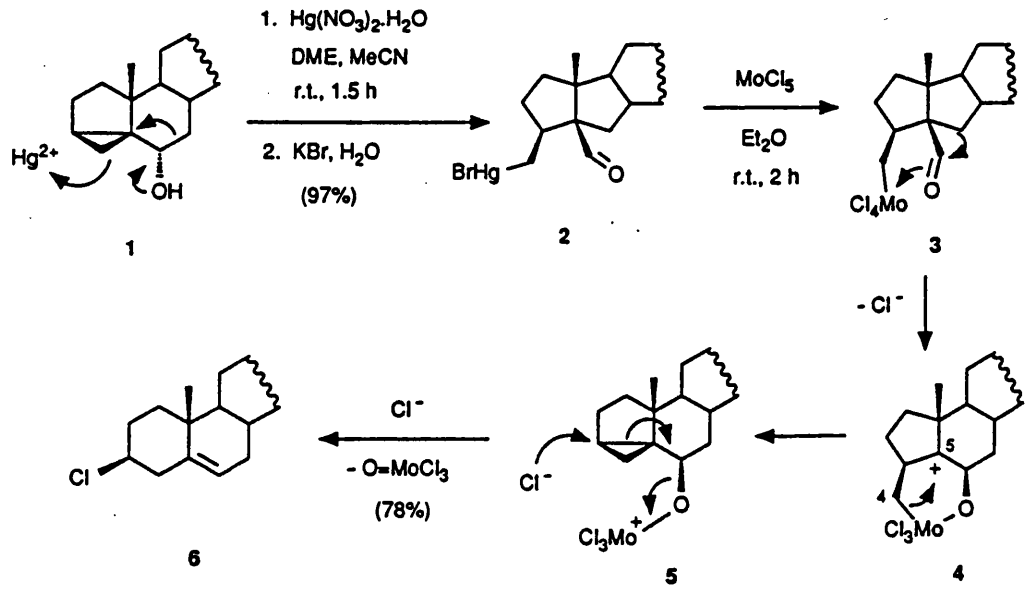
Abstract: Organomercurial **2**, arising by a regioselective ring-opening of cyclopropane derivative **1**, can be transmetalated with Mo-reagents to initially generate complexes **3** and **7**. While **3** reacts further via a stereoelectronically controlled cascade rearrangement to afford **6**, complex **7** favors a Grob-type fragmentation leading to **9**.

Stereoselective cyclopropanation followed by ring-opening is an interesting strategy for building up contiguous chiral centers.[2] We have recently described a stereoelectronically controlled cleavage of 3α,5-cyclo-5α-cholestan-6α-ol (**1**) by mercury(II) that afforded the rearranged organomercurial **2** (97%) as a stable compound (Scheme I).[3-6] We have also shown that transmetalation of **2** with Li, Cu, or Pd can be employed to synthesize various products and that the reactivity of the intermediate organometallics can be further controlled by added ligands.[3] Herein, we report on the transmetalation of **2** with molybdenum in two different forms.

Scheme I



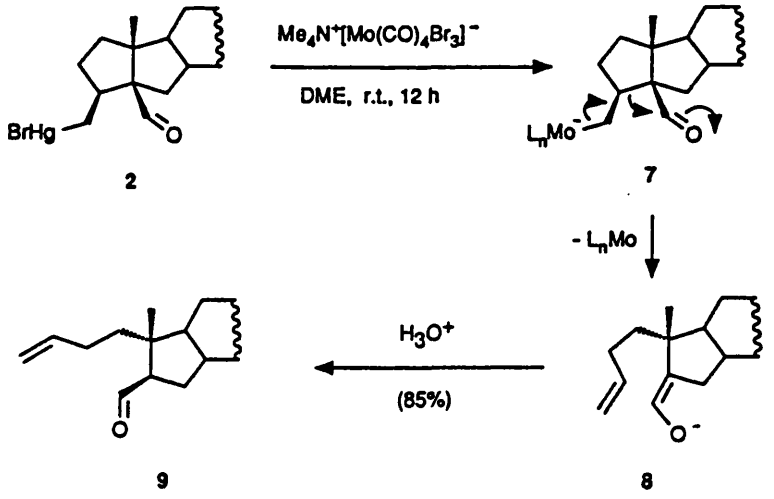
Reaction of 2 with $MoCl_5$ afforded cholesteryl chloride (6),[7] formation of which can be rationalized as follows (Scheme I). Transmetalation of 2 presumably generated molybdenum species 3 (with extrusion of HgBrCl), in which the highly oxophilic Mo can interact with the carbonyl oxygen. This interaction triggered off a stereoelectronically controlled Wagner-Meerwein migration to generate the electron-defficiency at $C_{(5)}$ (4) which was then saturated by forming a bond to $C_{(4)}$ (4 → 5).[8] The resulting cyclopropyl intermediate 5 subsequently collapsed to cholesteryl chloride (6) via the well known[9] "*iso*-steroid" rearrangement.[10,11] The whole reaction sequence is apparently controlled by the combination of high oxophilicity[12] of Mo in 3 with stereoelectronic effects.

Another molybdenum reagent, whose reactivity has been explored, was generated *in situ*, using a known procedure (eq. 1):[13]

$$Me_4N^+Br^- + Mo(CO)_6 + Br_2 \longrightarrow Me_4N^+[Mo(CO)_4Br_3]^- + 2\,CO \qquad \text{(eq. 1)}$$

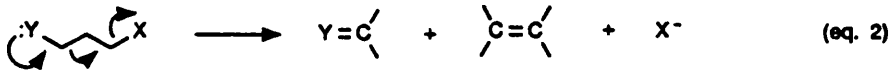
Using this complex, transmetalation of 2 was accomplished again, but the resulting organomolybdenum intermediate 7 displayed a completely different behavior compared to 3. Due to the negative charge on molybdenum, the interaction with the aldehyde oxygen is now precluded so that 7 is compelled to react differently: in this case, the molecular structure favors a novel, stereoelectronically controlled Grob-type fragmentation[14] which eventually gave rise to the olefinic aldehyde 9[15] (via the enolate 8).

Scheme II



In conclusion, we have shown, for the first time, that organomercurials, such as 2 (which in turn are synthesized by a ring-opening of cyclopropane[16]), can be readily transmetalated with various molybdenum reagents. Depending on the nature of the reagent, namely on the oxidation state of Mo, the subsequent reactions of the organomolybdenum intermediates can be directed towards different products. Thus, while $MoCl_5$ readily converted the substituted [3.3.0]bicyclooctane system into a [4.4.0] skeleton (2 → 3 → 6), the $[MoL_n]^-$ anion effected a fragmentation reaction (2 → 7 → 9). It is pertinent to note, however, the difference between the classical Grob reaction and our Mo-mediated fragmentation:

according to the Grob protocol, TsO^- typically serves as a leaving group and the negative species (e.g. O^-) forms a double bond (eq. 2). By contrast, our Mo-complex suffers a different series of events: the negative charge on molybdenum is transduced to the enolate, while Mo leaves as a neutral species (eq. 3). Moreover, whereas the classical Grob fragmentation requires a three-carbon unit with the reacting substituents at 1,3-positions, our fragmentation occurred on a 1,4-disubstituted, four-carbon framework.[17]



(eq. 2)

(eq. 3)

It appears that all these novel transformations (Schemes I and II) are subject to a stringent stereoelectronic control. The unique feature of this chemistry is that the reactivity of the organometallic intermediates can be tuned by a delicate balance of the oxidation sate of the metals involved and the ligands attached. Although the experiments were confined to the steroidal skeleton, we believe that our findings are of general nature and may be used for synthetic purposes, particularly in view of a number of methods for preparation of organomercurials.[16]

Acknowledgment: We thank Drs. G. Griffith and A. Gogoll for obtaining the NMR spectra and Merck Sharp and Dohme, Roche Products Ltd., and the University of Leicester for financial support to J. Š.

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(15) **9**: $[\alpha]_D$ +14° (c 2.4, $CHCl_3$); IR ($CHCl_3$): 1637, 1710, and 2704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.69 (s, 3 H, 18-H), 0.90 (s, 3 H, 19-H), 4.90-5.10 (m, 2 H, CH=C*H*$_2$), 5.70-5.95 (m, 1 H, C*H*=CH$_2$), 9.70 (d, 1 H, J = 3.2 Hz, CH=O) ppm; ^{13}C NMR: 12.32 (q), 17.78 (q), 18.76 (q), 21.36 (t), 22.57 (q), 22.82 (q), 23.86 (t), 24.40 (t), 28.01 (d), 28.48 (t), 29.35 (t), 29.86 (t), 35.66 (d), 36.23 (t), 39.44 (t), 39.50 (t), 40.48 (d), 41.92 (t), 43.88 (s), 47.40 (s), 55.69 (d), 56.63 (d), 57.43 (d), 58.27 (d), 114.32 (t), 138.85 (d), 204.96 (d) ppm. The CH=O proton (at 9.70 ppm) shows NOE (1.4%) upon irradiation of angular methyl (19-H at 0.90 ppm), indicating their *cis* relationship.

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(Received in UK 22 July 1992)

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

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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**.

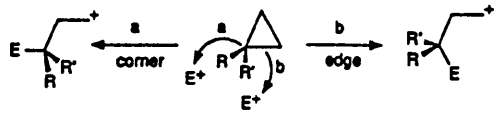
Introduction

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

Scheme 1



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]

† University of Leicester.
‡ Australian National University.
§ University of Uppsala.
• Abstract published in *Advance ACS Abstracts*, December 15, 1993.

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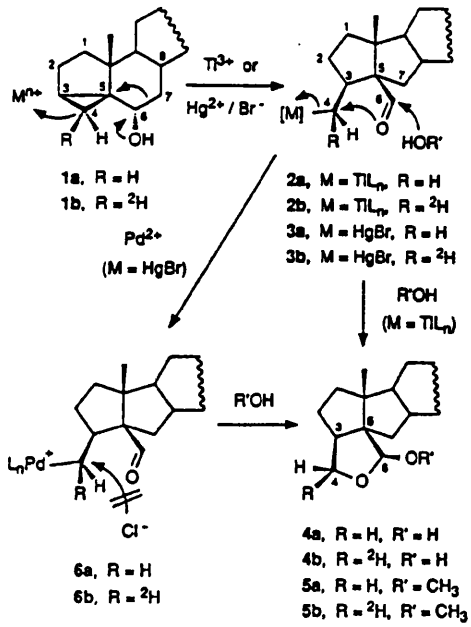
0002-7863/94/1516-0186$04.50/0

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

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(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.

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(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.

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(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-^{2}H-cholesterol.[24,25]

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

(25) For recent synthesis of 4α-^{2}H-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.

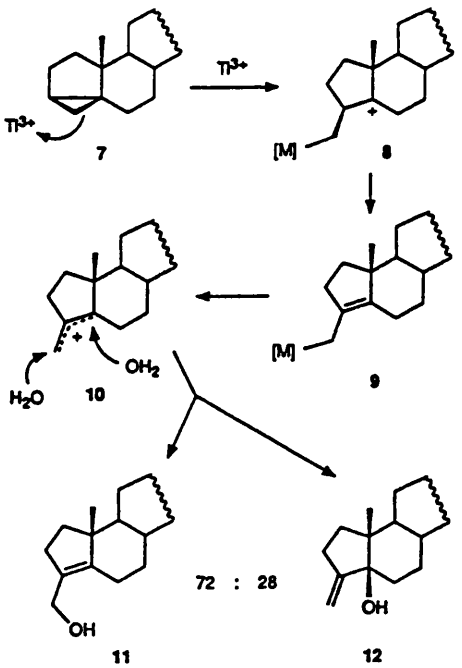
(27) In the ^1H NMR spectrum of unlabeled **4a** the 4α-H appears at 4.17 ppm (dd, J = 8.6 and 9.1 Hz) and 4β-H at 3.40 ppm (dd, J = 8.6 and 4.9 Hz); the upfield signal exhibits an NOE (0.2%) with the acetal proton (δ 5.17), while the downfield signal shows an NOE (15%) with 3α-H.

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 ^1H 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-^2H configuration;[27] the other stereoisomer could not be detected.[30]

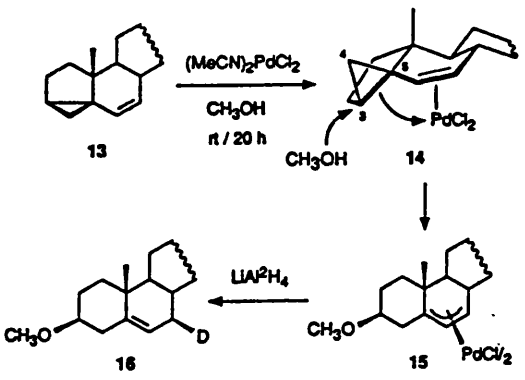
Heumann and Bäckvall have shown[28] that Pd-σ-complexes generated, for example, from organomercurials by the $PdCl_2$/$CuCl_2$ method undergo S_N2 substitution by Cl^- to give alkyl chlorides. Hence, lactol **4b** could be conjectured to arise from the initially formed chloride by a second inversion. 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-^2H 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]

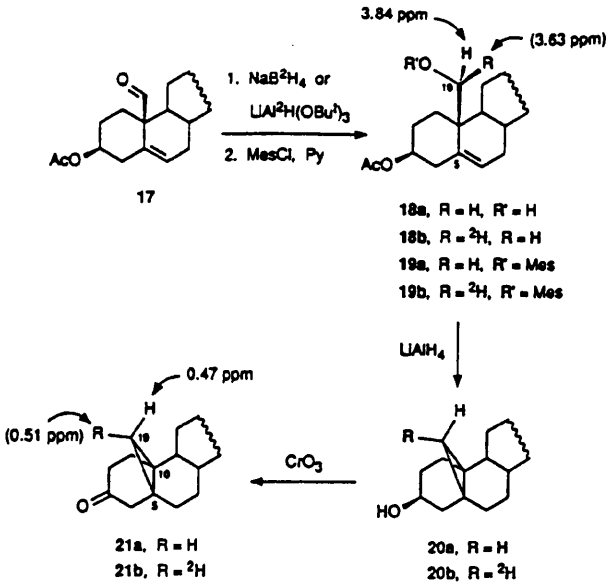
(37) Pradhan, S. K.; Girijarallabhan, V. M. *Steroids* **1969**, *13*, 11.

(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.

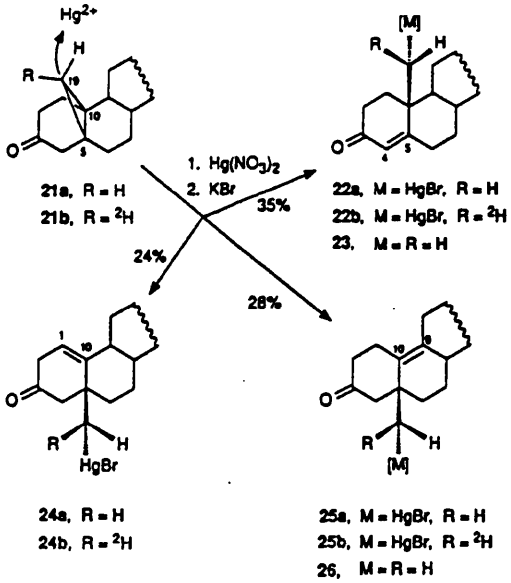
(40) Santaniello, E.; Caspi, E. *J. Steroid Biochem.* **1976**, *7*, 223.

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^2H_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 $LiAl^2H(OBu^t)_3$ (generated *in situ* from 1 mol of $LiAl^2H_4$ 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 $Hg(NO_3)_2{\cdot}H_2O$ 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_3SnH reduction, **22a** furnished the known cholest-4-en-3-one (**23**), while **25a** afforded the Westphalen-type ketone **26**, identical with an authentic sample.[46,47] The structure of **24a** was deduced from spectral data.[48]

The reaction of the deuterated cyclopropyl derivative **21b** with $Hg(NO_3)_2$ 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 ^2H 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 ^1H and ^2H 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_N2-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 ^1H 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_N2 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 ^1H 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.

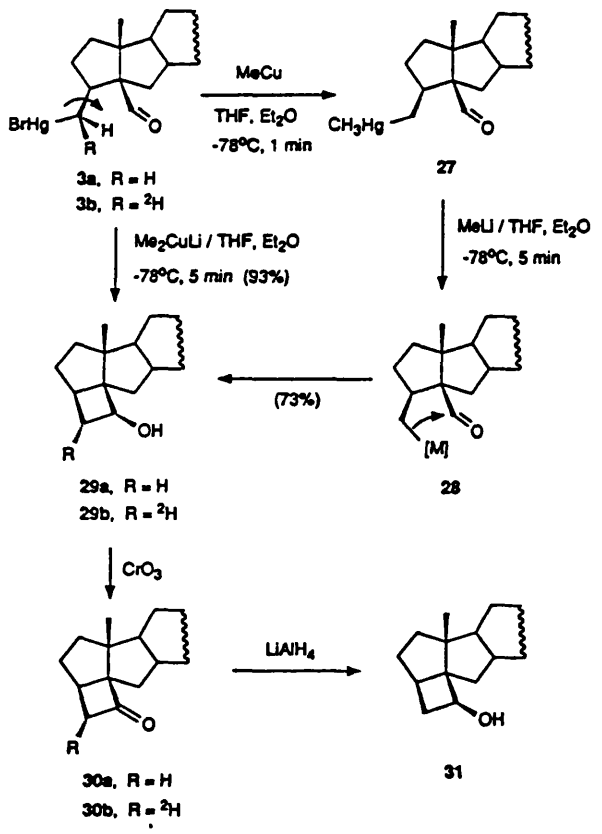
(49) The ratio was determined by integration of the signals of 19-^2H in the ^2H NMR spectrum for each pair of 19-epimers. For **22b** the ratio of 2.53 ($W/2$ = 13.8 Hz) to 2.23 ($W/2$ = 12.0) was 65:35; for **24b**, the signals at 2.42 ($W/2$ = 18.0 Hz) and 2.12 ($W/2$ = 13.8 Hz) were in a 32:68 ratio.

(50) As expected,[51] attempted radical cyclizations failed: reduction of **3a** with $NaBH_4$ or Bu_3SnH 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

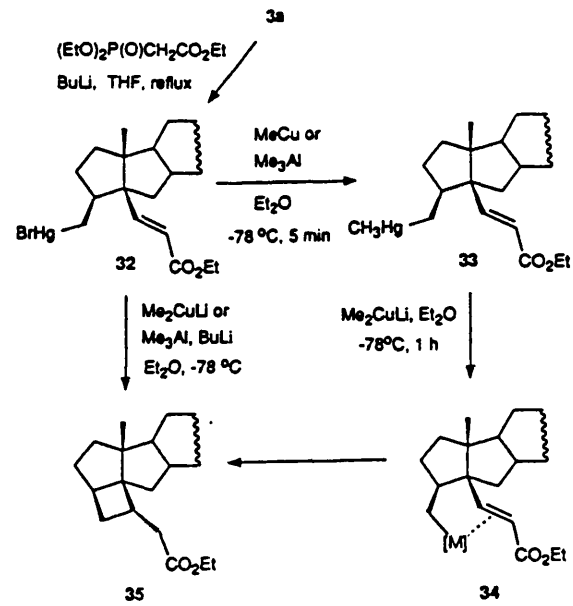


softer metals might be more promising, and after several unsuccessful attempts using various transition metals, we turned our attention to copper[53] (Scheme 7). Rather surprisingly, MeCu effected clean methylation on mercury, providing the MeHg derivative **27** (94%). This result itself may represent 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 ^{1}H 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.; Wiescholek, 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.

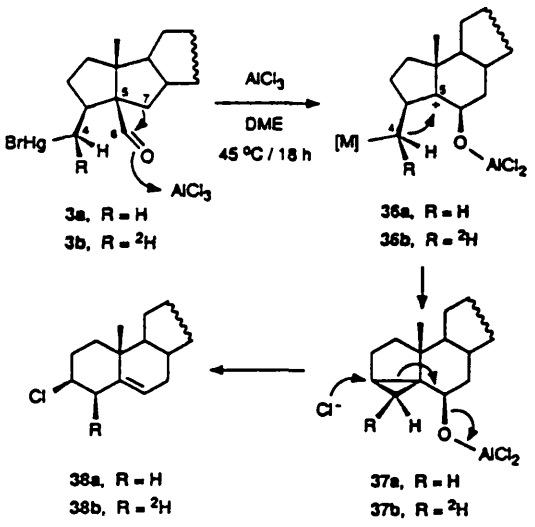
(58) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

(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 ^{1}H 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

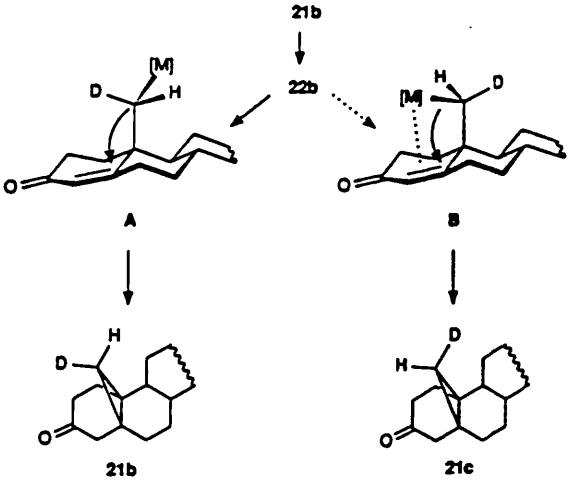


Finally, treatment of **33** (first generated *in situ* from **32** by means of Me_3Al) with Me_3Al/n-BuLi furnished **35** in 92% isolated yield.[62,63]

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_3Al (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_2O as was its unlabeled counterpart. Analysis of the ^1H 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-^2H configuration is compatible with inversion of configuration at C(4) in the C(4)–C(5) bond-forming step (**36b** → **37b**).[67]

Scheme 10



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_2CuLi 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 ^1H 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_3Al) accelerates the conjugate addition, as in its absence only a complex mixture was obtained.

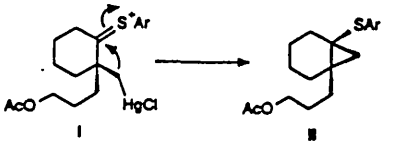
(63) Attempted radical cyclization of **32**, using $NaBH_4$ or Bu_3SnH, gave only the demercurated product. Attempted intramolecular Heck coupling, using various Pd(II) reagents, resulted solely in β-elimination. This is in sharp contrast to the analogous cyclizations that occur readily to produce five-membered rings.[67]

(64) Šrogl, J.; Kočovský, P. *Tetrahedron Lett.* **1992**, *33*, 5991.

(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-^2H 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 ^1H NMR patterns in 4α-^2H- and 4β-^2H-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).

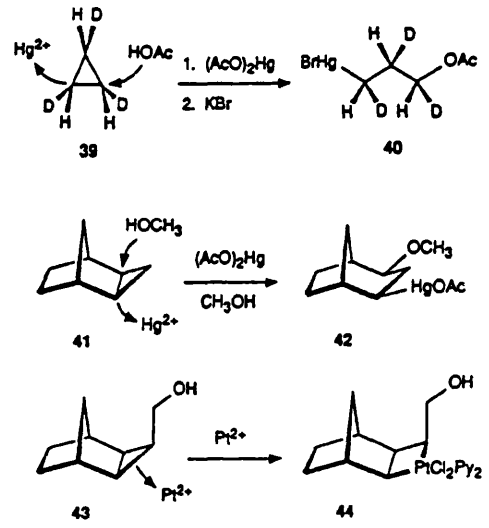
Since **21b** was recovered (after the opening and ring-closure) as a 62:38 mixture of C(19)-epimers (Scheme 10), one can possibly argue that this ratio may reflect some sort of thermodynamic equilibration rather than a stereodefined transformation. We reasoned that this issue can be addressed by carrying 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[8e] (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

Scheme 11



(**39** → **40** or **41** → **42**) or by the Wagner–Meerwein migration (**1** → **2** or **3**).

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]

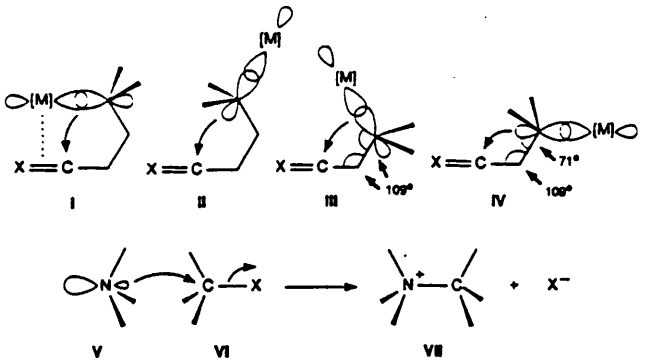
(70) For methods of construction of four-membered rings, see ref 2a (Vol. 1, pp 39, 96, 145) and (a) Trost, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 1, p 843; Vol. 3, pp 588, 620; Vol. 5, pp 63, 123, 899. For a recent enantioselective approach, see: (b) 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.

[4²H]-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.

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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}; ^1H 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 ^1H 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); ^1H 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); ^1H 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); ^1H 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); ^1H 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°); ^1H 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}; ^1H 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); ^1H 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

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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^2H, $J_{C,D}$ = 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^2H, $J_{C,D}$ = 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

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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}; ^1H 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}; ^1H 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; ^1H NMR δ 0.67 (s, 3 H, 18-H), 0.91 (s, 3 H, 19-H), 2.42 (dd, 1 H, *J* ≃ 2 × 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^2H), 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}; ^1H NMR δ 0.66 (s, 3 H, 18-H), 0.96 (s, 3 H, 19-H), 1.09 (t, 1 H, *J* ≈ 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; ^1H 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% ^2H (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); ^1H 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}; ^1H 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, CH_3CH_2), 4.26 (q, 2 H, *J* = 7.1 Hz, CH_3CH_2O), 5.92 (d, *J* = 16.0 Hz, 1 H, CH═C*H*CO_2Et), 7.06 (d, 1 H, *J* = 16.0 Hz, C*H*═CHCO_2Et); ^{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}; ^1H 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, CH_3CH_2O), 4.25 (d, 2 H, *J* = 7.1 Hz, CH_3CH_2O), 5.84 (d, 1 H, *J* = 16.0 Hz, CH═C*H*CO_2Et), 7.15 (d, 1 H, *J* = 16.0 Hz, C*H*═CHCO_2Et); ^{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}; ^1H 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); ^1H 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, $M^{\cdot+}$), 404 (91).

[4β-^{2}H]-3β-Chloro-5-cholestene (38b): mp 94–96 °C; ^1H 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% ^2H (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.

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Molybdenum(V)-Mediated Skeletal Rearrangement of an Organomercury Steroid. Stereoelectronic Control and Mechanism

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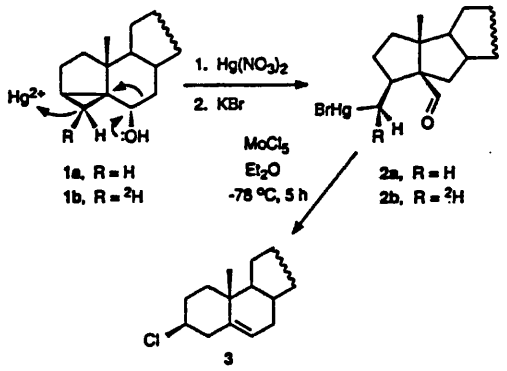
The reactivity of organometallic species has been in the forefront of interest to synthetic organic chemists for a number of years.[1] While alkyllithiums, Grignard reagents, and organocuprates are highly reactive and sensitive, other organometallics, such as those with C–B, C–Sn or C–Hg bonds, are relatively stable and often require activation prior to the reaction.[1]

We have recently described a stereoelectronically controlled cleavage of 3α,5-cyclo-5α-cholestan-6α-ol (1a) by mercury(II)[2,3] that afforded the rearranged organomercurial 2a (97%) as a stable compound (Scheme 1).[2-4] We have also shown that transmetalation of 2a with Pd, Li, Cu, or Mo can be employed to synthesize various products and that the reactivity of the intermediate organometallics can be further controlled by added ligands.[3,5] Herein, we report on the stereospecific rearrangement of the organomercurial 2 initiated by molybdenum(V) chloride and other Lewis acids, discuss the mechanism, and show that, in contrast to other molybdenum reagents, transmetalation Hg → Mo might not occur in this instance.

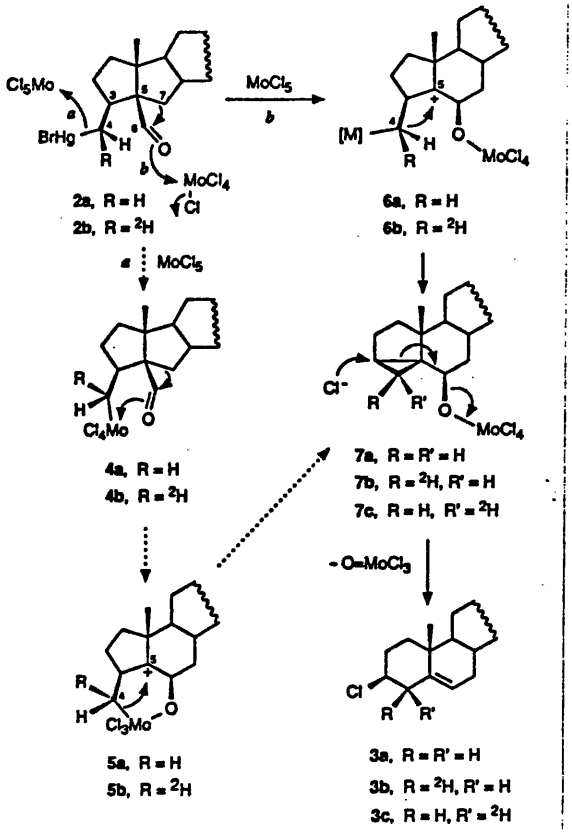
Organomercury steroid 2a was treated with $MoCl_5$ in ether at −78 °C and the reaction was monitored by TLC. When the starting material could no longer be detected (ca. 5 h), the mixture was worked up to afford cholesteryl chloride (3) as a single product (Scheme 1) in 78% isolated yield. This rather surprising outcome was tentatively rationalized in our preliminary communication[5] as follows (Scheme 2). Transmetalation of 2a with Mo was assumed as the initial step (pathway *a*) which would generate molybdenum species 4a (with extrusion of HgBrCl). Interaction of the highly oxophilic Mo(V) with the carbonyl oxygen would then trigger a stereoelectronically controlled Wagner–Meerwein migration to create the electron-deficiency at $C_{(5)}$ (4a → 5a). The cationic center in 5a is likely to interact with the nucleophilic carbon $C_{(4)}$ to generate cyclopropyl intermediate 7a. The latter species should subsequently collapse to cholesteryl chloride (3a) via the well known[6] "*iso*-steroid" rearrangement.[7]

Taking advantage of the accessibility of the stereospecifically deuterated organomercurial 2b,[8] we have now been able to elucidate this mechanism in detail. According to our original mechanism (pathway *a*),[5] and assuming

Scheme 1



Scheme 2



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(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) Colquhoun, H. M.; Holton, J.; Thompson, D. J.; Twigg, M. V. *New Pathways for Organic Synthesis*; Plenum: New York, 1984. (d) Harrington, P. J. *Transition Metals in Total Synthesis*; J. Wiley: New York, 1990. (e) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. (f) Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC Press: Boca Raton, FL, 1986; Vols. I and II.

(2) Kočovský, P.; Šrogl, J.; Pour, M.; Gogoll, A. *J. Am. Chem. Soc.* 1994, *116*, 186.

(3) (a) Kočovský, P.; Šrogl, J. *J. Org. Chem.* 1992, *57*, 4565. (b) Kočovský, P.; Šrogl, J.; Hanuš, V.; Polášek, M. *J. Chem. Soc., Chem. Commun.* 1992, 1086.

(4) For a related reaction with Tl(III), see: Kočovský, P.; Pour, M.; Gogoll, A.; Hanuš, V.; Smrčina, M. *J. Am. Chem. Soc.* 1990, *112*, 6735.

(5) Šrogl, J.; Kočovský, P. *Tetrahedron Lett.* 1992, *33*, 5991.

(6) Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: Amsterdam, 1968.

(7) Model experiments demonstrated that both 3α,5-cyclo-5α-cholestan-6β-ol and cholesterol are readily converted to 3 on treatment with $MoCl_5$ in Et_2O at rt. 5α-Cholestan-3β-ol was converted by the same reagent to a ca. 1:1 mixture of the corresponding 3α- and 3β-chlorides, which indicates S_N1 mechanism, in contrast to the former, stereoelectronically controlled substitutions.

(8) The (*4R*) configuration in 2b was established via chemical correlation. On treatment with Pd(II), the organomercurial 2b was converted into the lactol 14b in which the configuration at $C_{(4)}$ was determined using NOE experiments. For details, see refs 2 and 4.

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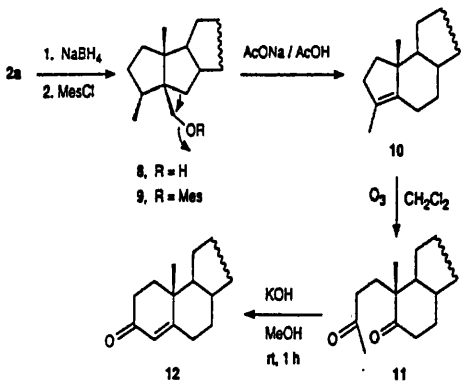
retention of configuration in the transmetalation step[1e] (**2b** → **4b**), the coordination of Mo to the carbonyl oxygen requires rotation about the $C_{(3)}$–$C_{(4)}$ bond. Subsequent Wagner–Meerwein migration will generate cationic species **5b** in which the $C_{(4)}$–$C_{(5)}$ bond formation should occur with *retention* of configuration at $C_{(4)}$ owing to the geometry imposed by the cyclic structure. The resulting cyclopropyl intermediate **7c** should then produce 4α-^{2}H-cholesteryl chloride (**3c**). Alternatively, $MoCl_5$ can be assumed to first coordinate to the aldehyde oxygen (path *b*) which may also trigger the Wagner–Meerwein migration generating carbocation **6b**. The subsequent cyclopropane ring-closure is most likely to occur with *inversion* of configuration at $C_{(4)}$ (**6b** → **7b**) due to the preferred conformation (**6b**) so that 4β-^{2}H-cholesteryl chloride (**3b**) can be expected as the final product. Hence, utilizing the stereospecifically deuterated organomercurial **2b** as the starting material should provide the answer as to which of the two proposed mechanisms does actually operate.

The reaction of deuterated **2b** with $MoCl_5$ was carried out in the same way as for its unlabeled counterpart **2a**. Analysis of the ^{1}H NMR spectrum of the resulting deuterated cholesteryl chloride established the configuration of deuterium as being 4β (i.e. **3b** rather than **3c**)[9] and revealed that the whole reaction sequence was remarkably stereospecific, as no other diastereoisomer could be detected by NMR. The 4β-^{2}H configuration is compatible with inversion of configuration at $C_{(4)}$ in the $C_{(4)}$–$C_{(5)}$ bond-forming step (**6b** → **7b**). The other pathway (**5b** → **7c**) can thus be excluded as it would require retention at $C_{(4)}$.[11] The exact structure of **6** is unknown and it would be premature to make conclusions at this stage as to whether M = Hg or Mo. We believe that both species can serve as intramolecular nucleophiles to trap the $C_{(5)}$-electron-deficient center. If, however, transmetalation had occurred, retention of configuration at $C_{(4)}$ is assumed.[12]

This analysis suggests that $MoCl_5$ serves as a Lewis acid and that transmetalation may not be required. To address this issue, the organomercurial **2a** was treated with other Lewis acids, namely with $AlCl_3$, $SiCl_4$, and $TiCl_4$. In all cases the reaction produced cholesteryl chloride (**3a**) in good yields; $MoCl_5$, however, turned out to be superior in terms of the reaction rate and purity of the product.[14] The stereochemistry of this transformation was tested for $AlCl_3$ and found to be identical with that of the $MoCl_5$ reaction (i.e. **2b** → **3b**).[2]

Scheme 3[a]



[a] Mes = CH_3SO_2

In order to gain further insight into the chemistry of this Lewis acid-mediated rearrangement and to assess the natural tendency of this [3.3.0] skeleton to rearrange, mesylate **9** was prepared from alcohol **8** which, in turn, was obtained by hydride reduction of **2a** (Scheme 3). We reasoned that the presence of a good leaving group, such as CH_3SO_3, in place of the aldehyde oxygen might also induce the skeletal rearrangement[15] and provide further mechanistic support for the above conclusions. Standard solvolytic conditions (AcONa, AcOH, reflux) led to the formation of **10** as a single product, the structure of which was deduced from spectral data and confirmed by chemical correlation; ozonolysis resulted in the formation of diketone **11** which readily underwent a base-catalyzed aldol condensation to afford cholestenone (**12**). In the solvolysis of **9**, the departure of the CH_3SO_3 group is accompanied by Wagner–Meerwein rearrangement to generate the corresponding $C_{(5)}$–cation which, in this instance, undergoes proton elimination to give **10**. The behavior of mesylate **9** lends further credence to the above mechanistic considerations and suggests that $MoCl_5$ and other Lewis acids activate **2** as shown in pathway *b* (Scheme 2). Thus, while proton elimination is the best avenue for stabilizing the rearranged carbocation derived from mesylate **9**, the cation **6** prefers to react with the neighboring nucleophilic center at $C_{(4)}$.

Interestingly, the reactivity of $MoCl_5$ proved to be solvent dependent. In THF, chloro aldehyde **13a** was formed as the major product from **2a** (Scheme 4), rather than cholesteryl chloride.[16] Since **13a** could not be fully

(9) Diagnostic was the signal of 3α-H (at 3.77 ppm). While the width of this multiplet was 32.7 Hz for **3a**, in the spectrum of the deuterated compound **3b** (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 with the spectrum of **3a**, 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 **3b**, 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 10.

(10) Rabinowitz, M. H. *Tetrahedron Lett.* **1991**, *32*, 6081.

(11) Alternative explanation that would encompass transmetalation with inversion followed by the $C_{(4)}$–$C_{(5)}$ bond formation with retention at $C_{(4)}$ (**5** → **7**) is unlikely in view of the generally accepted mechanism of transmetalations.[1e]

(12) (a) A recent precedent[13] suggests that the carbon atom adjacent to HgX can serve as an effective nucleophile to quench an electron-deficient center. Hence, transmetalation of Hg for Mo may not be required in our case. (b) In order to address this issue, we have explored the reaction of $PhCH_2HgCl$ with $MoCl_5$. The only product formed at rt over a period of 2 h was $PhCH_2Cl$; no intermediate could be intercepted (by TLC and NMR). This transformation can be attributed either to the transmetalation followed by reductive elimination or to a disproportionation $MoCl_5$ → $MoCl_3$ + Cl_2 followed by chlorination of $PhCH_2HgCl$. Thus, this experiment did not provide the conclusive evidence; however, transmetalation, if any, can be assumed to be considerably slower than our reaction. For a related transformation RHgX → RCl by means of $CuCl_2$, see: (c) Artamkina, G. A.; Beletskaya, I. P.; Reutov, O. A. *Zh. Org. Khim.* **1973**, *9*, 1769; *J. Org. Chem. USSR* **1973**, *9*, 1795. (d) Beletskaya, I. P.; Artamkina, G. A.; Reutov, O. A. *J. Organomet. Chem.* **1975**, *99*, 343. (e) Budnik, R. A.; Kochi, J. K. *J. Organomet. Chem.* **1976**, *116*, C3. (f) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5538.

(13) (a) Takemoto, Y.; Ohra, T.; Yonetoku, Y.; Imanishi, T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1992**, 192. (b) Takemoto, Y.; Ohra, T.; Yonetoku, Y.; Nishimiré, K.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1994**, 81.

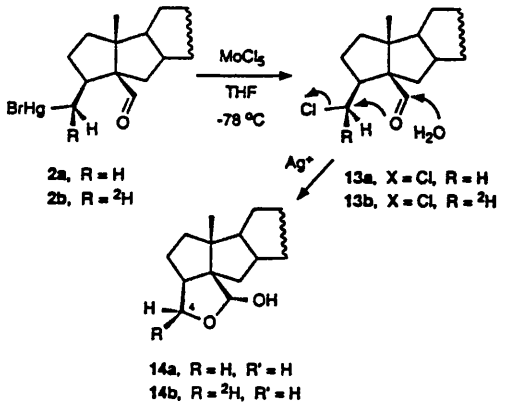
(14) While the reaction of **2a** with $MoCl_5$ is complete in 5 h at −78 °C, only 50% conversion has been observed with $AlCl_3$ at rt over 5 days(!) and complete conversion has been achieved (with $AlCl_3$) at 45 °C over 12 h.

(15) For skeletal rearrangements of a normal steroid skeleton with electron deficiency created at the angular methyl (C-19), see e.g.: (a) Kočovský, P.; Tureček, F. *Tetrahedron Lett.* **1982**, *22*, 2691. (b) Kočovský, P.; Tureček, F.; Langer, V.; Podlahová, J.; Podlaha, J. *J. Org. Chem.* **1986**, *51*, 4888 and references therein.

(16) Since $MoCl_5$ is known to react with THF to give $(THF)_2MoOCl_3$,[17] the latter is likely to be the actual reagent in this case.

(17) McAuliffe, C. A.; Werfali, A. *Inorg. Chim. Acta* **1980**, *60*, 87.

Scheme 4



2a, R = H
2b, R = ^{2}H

13a, X = Cl, R = H
13b, X = Cl, R = ^{2}H

14a, R = H, R' = H
14b, R = ^{2}H, R' = H

purified and characterized, its structure was determined by the silver(I)-mediated conversion[18] to lactol 14a. The same reaction carried out with 2b showed that 13 was formed nonstereospecifically as a ~2:1 mixture of 13b and its C(4)-epimer.

In summary, we have observed interesting, stereoelectronically controlled, skeletal rearrangements. The key reaction 2 → 3 is apparently controlled by the combination of high oxophilicity of $Mo^{(V)}$ and stereoelectronic effects. The proposed mechanism is supported by stereospecific labeling and by analogous results in the solvolysis of 9. Although the experiments were confined to the steroid skeleton, we believe that our findings are general and may be used for synthetic purposes, particularly in view of a number of methods for preparation of organomercurials.[19]

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°C. The NMR spectra were recorded for $CDCl_3$ solutions at 25 °C on a Varian Unity 400 (operating at 400 MHz for ^{1}H, 100.6 MHz for ^{13}C, and 61.4 MHz for ^{2}H), Varian XL-300, or Bruker AM 300 spectrometer. Chemical shifts were indirectly referenced to TMS *via* the solvent signals (7.26 ppm for ^{1}H and ^{2}H, and 77.0 ppm for ^{13}C). The IR spectra were recorded in $CHCl_3$ on a Perkin-Elmer 621 instrument. The mass spectra were 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-Chloro-5-cholestene (3a). Molybdenum(V) chloride (50 mg; 1.2 equiv) was added in small portions to a solution of organomercurial 2a (100 mg; 0.15 mmol) in ether (10 mL) at −78 °C over a period of 1 h. The mixture was then stirred at the same temperature for 4 h. The mixture was then gradually warmed to rt, diluted with ether (20 mL), washed with water (5 × 5 mL), 5% aqueous $KHCO_3$ (5 × 5 mL), and water (5 mL), and dried with $MgSO_4$. The solvent was evaporated and the residue was chromatographed on a column of silica gel with petroleum ether to yield 3a (47 mg; 79%), identical with an authentic sample (Fluka): mp 95–97 °C (ethyl acetate) (Fluka catalogue gives 94–96 °C); ^{1}H NMR δ 0.68 (s, 3H, 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 (br d, 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 (d), 60.33 (d), 122.46 (d), 140.77 (s); MS *m/z* M$^{+\cdot}$ 406 (34%)/404 (91%).

[4β^{2}H]-3β-Chloro-5-cholestene (3b): 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).

3β-Methyl-5-(hydroxymethyl)-A,B-bisnor-5β-cholestane (8). To a solution of 2a (120 mg; 0.18 mmol) in ether (20 mL) and methanol (2 mL) was added sodium borohydride (321 mg; 8.48 mmol) and the mixture was stirred at 0 °C for 10 min. The excess of reagent was then decomposed with 5% aqueous HCl at −78 °C, and the mixture was diluted with ether and worked up to give alcohol 8 (44 mg; 0.113 mmol; 83%): $[\alpha]_D$ +15° (*c* 1.2); IR ν(OH) 3420, 3595 cm^{-1}; ^{1}H NMR δ 0.66 (s, 3 H, 18-H), 0.88 (s, 3 H, 19-H), 1.02 (d, 3 H, J = 7.1 Hz, 3β-CH_3), 3.46 (d, J = 10.7 Hz, 1 H, CH_2OH), 3.70 (dd, J = 10.7 and 1.0 Hz, CH_2OH); ^{13}C NMR δ 12.27 (q), 15.98 (q), 18.79 (q), 18.93 (q), 22.10 (t), 22.57 (q), 22.83 (q), 23.88 (t), 24.57 (t), 28.02 (d), 28.61 (d), 31.05 (t), 35.70 (d), 36.26 (t), 38.57 (t), 39.51 (t), 39.92 (t), 40.40 (d), 41.17 (t), 42.85 (d), 43.77 (s), 51.67 (s), 55.76 (d), 56.37 (d), 57.75 (d), 64.72 (t). Anal. Calcd for $C_{27}H_{48}O$: C, 83.44; H, 12.45. Found: C, 83.17; H, 12.66.

3β-Methyl-5-[[(methanesulfonyl)oxy]methyl]-A,B-bisnor-5β-cholestane (9). To a solution of the alcohol 8 (100 mg; 0.026 mmol) and triethylamine (0.4 mL) in THF (20 mL) was added mesyl chloride (0.2 mL) at −10 °C and the mixture was kept at this temperature for 1 h. The mixture was then poured onto ice and water, the product was extracted with ether, and the ethereal solution was worked up to furnish sufficiently pure mesylate 9 (117 mg; 97%): ^{1}H NMR δ 0.74 (s, 3 H, 18-H), 0.99 (s, 3 H, 19-H), 1.08 (d, J = 7.1 Hz, 3 H, 3β-CH_3), 3.12 (s, 3 H, CH_3SO_3), 4.14 and 4.30 (AB system, J_{gem} = 9.3 Hz, 2 H, CH_2OMes); ^{13}C NMR δ 12.16 (q), 15.42 (q), 18.62 (q), 18.83 (q), 21.85 (t), 22.43 (q), 22.68 (q), 23.71 (t), 24.35 (t), 27.86 (d), 28.41 (t), 31.07 (t), 35.50 (d), 36.09 (t), 37.03 (q), 38.19 (t), 39.35 (t), 39.60 (t), 40.32 (d), 41.36 (t), 43.01 (d), 43.62 (s), 52.56 (s), 55.56 (d), 55.77 (s), 56.05 (d), 57.52 (d), 72.04 (t).

3-Methyl-A-norcholest-3(5)-ene (10). A mixture of the mesylate 9 (100 mg; 0.21 mmol) and sodium acetate (200 mg; 2.44 mmol) in acetic acid (30 mL) was refluxed for 30 min. The mixture was then cooled to rt, diluted with ether and the ethereal solution was washed successively with water (10 × 10 mL), $KHCO_3$ (aqueous; 5 × 10 mL), and water and dried with $MgSO_4$. The solvent was evaporated and the residue was chromatographed on silica gel (5 g) with petroleum ether as eluent to yield 10 (65 mg; 82%): mp 62–64 °C (acetone; lit.[20] gives 64–65 °C); $[\alpha]_D$ +54° (*c* 5.3; lit.[20] gives +59°); ^{1}H NMR δ 0.68 (s, 3 H, 18-H), 0.76 (m, 1 H, 9α-H), 0.87 (two d, J = 6.6 Hz, 6 H, 26-H and 27-H), 0.90 (s, 3 H, 19-H), 0.91 (d, J = 6.6 Hz, 3 H, 21-H), 1.11 (m, 1 H, 12α-H), 1.47 (m, 1 H, 1β-H), 1.57 (br s, 3 H, =C-CH_3), 1.64 (ddd, J = 12.4, 8.2, and 1.1 Hz, 1 H, 1α-H), 1.71 (m, 1 H, 7α-H), 1.81 (m, 1 H, 6β-H), 1.97 (ddd, J = 12.5, 3.6, and 3.0 Hz, 1H, 12β-H), 2.08 (ddm, J = 15.7 and 9.6 Hz, 1 H, 2β-H), 2.27 (m, 1 H, 2α-H), 2.33 (ddd, J = 14.1, 4.5, and 2.4 Hz, 1 H, 6α-H); ^{13}C NMR δ 11.90 (q, C-18), 13.46 (q, C-4), 17.93 (q, C-19), 18.59 (q, C-21), 22.43 (q, C-26/27), 22.61 (two t, C-6 and C-11), 22.69 (q, C-26/27), 23.71 (t, C-23), 24.30 (t, C-15), 27.88 (d, C-25), 28.08 (t, C-12), 31.96 (t, C-7), 35.37 (t, C-2), 35.65 (d, C-20), 35.96 (d, C-8), 36.05 (t, C-16), 38.00 (t, C-1), 39.38 (t, C-24), 39.83 (t, C-22), 42.73 (s, C-13), 49.62 (s, C-10), 55.00 (d, C-9), 55.93 (d, C-17), 56.07 (d, C-14), 125.60 (s, C-3), 141.62 (s, C-5); MS *m/z* (%) 370 (34, M$^{+\cdot}$), 355 (69), 147 (47), 135 (26), 122 (39), 109 (42), 93 (90), 57 (100).

4,5-Secocholestane-3,5-dione (11). Ozone was bubbled to a solution of olefin 10 (70 mg; 0.189 mmol) in dichloromethane (20 mL) at −48 °C and the progress of ozonization was monitored by

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TLC. When the reaction was complete, acetic acid (1 mL) and powdered zinc (500 mg) were added and the mixture was stirred at rt for 8 h. The inorganic solid was then filtered off and the filtrate was washed with water, 5% aqueous potassium hydrogen carbonate, and water, and dried with anhydrous $MgSO_4$. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel (5 g) with a petroleum ether–ether mixture (9:1) to yield diketone 11 (70 mg; 92%): $[\alpha]_D$ +29° (c 5.8); ^1H NMR δ 0.74 (s, 3 H, 18-H), 1.13 (s, 3 H, 19-H), 2.17 (s, 3 H, 4-H); ^{13}C NMR δ 11.97 (q), 18.58 (q), 20.50 (q), 21.40 (t), 22.54 (q), 22.79 (q), 23.78 (t), 24.22 (t), 27.99 (d), 28.06 (t), 28.37 (t), 29.88 (q), 31.44 (t), 34.87 (d), 35.69 (d), 36.09 (t), 38.19 (t), 38.80 (t), 39.36 (t), 39.47 (t), 42.51 (s), 48.05 (d), 50.31 (s), 55.79 (d), 56.01 (d), 209.18 (s), 215.20 (s). Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.26; H, 11.75.

Cholest-4-en-3-one (12). To a solution of 11 (70 mg; 0.174 mmol) in methanol (10 mL) was added a 10% solution of NaOH in water (0.2 mL) and the mixture was stirred at rt for 1 h. The mixture was then diluted with ether and the ethereal solution was worked up to afford 12 (60 mg; 90%), identical with an authentic sample (Aldrich): mp 75–78 °C (acetone; Aldrich catalogue gives 79–81 °C).

3β-Chloromethyl-A,B-bisnor-5β-cholestane-5-carbaldehyde (13a). Molybdenum(V) chloride (200 mg) was introduced in small portions to a solution of organomercurical **2a** (245 mg; 0.68 mmol) in THF (10 mL) at −78 °C over a period of 2 h. After this time, TLC indicated a completion of the reaction and, along with the main product 13a (ca. 90%), lactol 14a (ca. 5–10%) was identified. The TLC analysis also revealed a slow conversion of 13a to 14a on silica gel, e.g. during the attempted flash chromatography. Therefore the chloride 13a could not be isolated in pure state and fully characterized: ^1H NMR δ 0.66 (s, 3 H, 18-H), 0.97 (s, 3 H, 19-H), 2.50 (dd, J_{gem} = 12.9 Hz, $J_{7\beta\text{-H},8\beta\text{-H}}$ = 6.5 Hz, 1 H, 7β-H), 3.68 (t, J = 7.5 Hz, 2 H, 4-H), 9.68 (s, 1 H, CH=O). Treatment of the crude product with silver nitrate (120 mg; 0.7 mmol) in wet DME (10 mL) at rt for 5 h resulted in the deposition of AgCl and formation of 14a (119 mg; 80%), identical with an authentic sample,[2,4] which was purified by flash chromatography.

Lactol (14a). To a solution of chloro aldehyde 13a (80 mg; 0.19 mmol) in DME (5 mL) were added water (0.2 mL) and silver nitrate (50 mg; 0.29 mmol). The mixture was stirred at rt overnight and then filtered, and the filtrate was diluted with ether, washed with water, and dried with $MgSO_4$. The crude product was chromatographed on silica gel (5 g) with a petroleum ether–ether mixture (8:2) to furnish lactol 14a (71 mg; 91%), identical with an authentic sample.[2,4]

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