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 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 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).\(^11,12,13\)
Using double isotopic labelling ($^2$H 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 ($7 \rightarrow 8 \rightarrow 10$) has been described (Scheme III).
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\(_2\)O in DME/CH\(_3\)CN (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).

\[
\text{Scheme IV}
\]

Much slower reaction was observed with (CF\(_3\)CO\(_2\))\(_2\)Hg; (AcO)\(_2\)Hg did not react 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).

\[
\text{Nu:} \quad \text{or} \quad \text{RO}
\]

(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 lithiiums, 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**

\[
\begin{align*}
\text{RCH}_2\text{HgX} & \xrightarrow{\text{ox.}} \text{RCH}_2\text{Y} & (a) \\
& \xrightarrow{\text{red.}} \text{RCH}_3 & (b) \\
& \xrightarrow{[M]} \text{RCH}_2[M] & (c)
\end{align*}
\]

Neither reaction $a$ nor $b$ could satisfy us since they are believed to be radical and,
therefore, non-stereohomogeneous. By contrast, reactions of the type transmetallation has been found as a stereohomogenous. Moreover the fact that these reactions have been carried out in the majority of cases with retention of configuration has given us a useful tool to reach our aim. The intermediate R-CH₂[M] may further react in three possible ways (Scheme VI):  

Scheme VI

```
RCH₂CH₂[M]  
/  
|  
electrophile
/  
|  
nucleophile
|  
β-elimination
|  
RCH₂CH₂El (a)  
|  
RCH₂CH₂Nu (b)  
|  
RCH=CH₂ (c)
```

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 organopalladations has been well established 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. 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).  

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(NO₃)₂.H₂O 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 Li₂PdCl₄ (5 mol%; generated from PdCl₂ and LiCl) and CuCl₂ (5 equiv.) in DME/H₂O, which is assumed to proceed with retention of configuration²⁷,²⁸a-d via 12b, furnished lactol 10b, while in the presence of MeOH, methyl acetal 11b was formed. A stoichiometric reaction, in which only Li₂PdCl₄ (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

\[
\begin{align*}
7a, R &= H \\
7b, R &= \text{²H} \\
8a, M &= \text{TlL}_n, R &= H \\
8b, M &= \text{TlL}_n, R &= \text{²H} \\
9a, M &= \text{HgBr}, R &= H \\
9b, M &= \text{HgBr}, R &= \text{²H} \\
10a, R &= H, R' &= H \\
10b, R &= \text{²H}, R' &= H \\
11a, R &= H, R' &= \text{CH₃} \\
11b, R &= \text{²H}, R' &= \text{CH₃}
\end{align*}
\]
Heumann and Bäckvall have shown that Pd-σ-complexes generated, e.g., from organomercurials by the PdCl₂/CuCl₂ 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)$_2$Pd and CF₃SO₃H. The product (10b) was identical with that formed by the PdCl₂/CuCl₂ method. Apparently, the intramolecular $S_N2$ substitution is highly favoured in 12 by the steric arrangement and suppresses the intervention of Cl⁻. 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.

When the transmetallation of the organomercurial 9 with Li₂PdCl₄ 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. This rather unexpected reaction can be rationalized as follows. Instead of undergoing the $5(O)_{5}$-exo-Tet ring closure to 10, in this instance the transient organopalladium 13 preferred an intramolecular insertion into the C-H bond of the aldehyde group. 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) and formation of Pd(0). In order to verify this mechanism, deuterated aldehyde 9c was prepared from 6β-2H-alcohol 7c (Scheme IX), which in turn was synthesized by a highly stereoselective reduction of 3α,5-cyclo-5α-cholestan-6-one with LiAlH₄.

Transmetallation of 9c under the same conditions as applied to its unlabelled counterpart (i.e. Li₂PdCl₄, CH₂=CHCN, DME, H₂O 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, which is in an excellent agreement with the proposed mechanism.

### Scheme IX

![Scheme IX](image)

**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). The reaction was believed to be initiated by an edge attack of Hg(II). In light of the evidence accumulated by us and by other investigators, 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, presumably via the allylic cation 19. These reactions demonstrate that the presence of the 6\(\alpha\)-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. 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 (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 (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. Authors in this paper have declared stereohomogeneity of the above reaction (retention of configuration of transmetallation).

\[
\text{MeCu} \rightarrow \text{MeHg} \quad \text{eq. 2}
\]

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 Me₃Al (69%) and Me₂Zn (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 Me₂CuLi in an excellent yield (93%). This reaction can be understood in terms of the Lipshutz observation of an equilibrium between a cuprate and alkylithium (2 Me₂CuLi ⇌ MeLi + Me₃Cu₂Li). Similarly, CH₂=MoCl₃, generated in situ from MeLi and MoCl₅, 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 CH-OH upon irradiation of 10β-CH₃, is compatible only with an α-configuration for the hydroxyl. (2) Alcohol 24a was oxidized with Jones' reagent to ketone
25a, whose ν\textsubscript{C=O} = 1750 cm\textsuperscript{-1} was in the range typical for cyclobutanones.\textsuperscript{47} (3) On reduction with LiAlH\textsubscript{4}, ketone 25a furnished alcohol 26,\textsuperscript{49} epimeric with 24a, for which no NOE for CHO\textsubscript{OH} and 10β-CH\textsubscript{3} could be observed.

Scheme XI
When deuterated organomercurial 9b was subjected to the reaction with Me₂CuLi, 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)CH₂CO₂Et and BuLi in refluxing THF (Scheme XIII).

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 Me₃Al 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; Me₂CuLi 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 Me₂CuLi. This behaviour suggests that the actual reactive species 29 involves copper. Although the structure of 29 is speculative, it seems reasonable to assume⁴⁴ that M = CuLiCH₃ or CuHgLiCH₃ and that the more suitably positioned C(4) in the complex 29 adds across the double bond in preference to the CH₃ group. Finally, treatment of 28 (first generated in situ from 27 by means of Me₃Al) with Me₃Al/n-BuLi furnished 30 in 92% isolated yield.⁵⁴
2.1.4. Reaction of organomercurial 9 with MoCl₅. Being encouraged by the results described above, we have sought another possibility to enhance the reactivity of the organomercurial 9. According to the literature, organomercurials are activated by treatment with "highly reactive halogenides". One example of such highly reactive species would be MoCl₅ 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 "iso-steroid" rearrangement. 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. 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 MoCl₅ in Et₂O 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 4p 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.

Interestingly, the reactivity of MoCl₅ proved to be solvent dependent. In THF, chloride 37 was formed as the major product from 9a, rather than cholesteryl chloride (Scheme XIV). Since 37 could not be fully purified and characterized, its structure was determined by the silver(I)-mediated conversion 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

\[ \text{BrHg} \quad \xrightarrow{\text{MoCl}_4} \quad \text{9a, } R = \text{H} \]
\[ \text{Cl} \quad \xrightarrow{\text{MoCl}_5} \quad \text{Et}_2\text{O} \quad \text{-78 } \text{C} \]
\[ \quad \xrightarrow{} \quad \text{[M]} \quad \text{31b, } R = \text{H} \]

\[ \begin{align*}
\text{9a, } R &= \text{H} \\
\text{9b, } R &= \text{H}^{2}
\end{align*} \]

\[ \begin{align*}
\text{31a, } R &= \text{H} \\
\text{31b, } R &= \text{H}^{2}
\end{align*} \]

\[ \begin{align*}
\text{34a, } R &= \text{H} \\
\text{34b, } R &= \text{H}^{2}
\end{align*} \]

\[ \begin{align*}
\text{32a, } R &= \text{H} \\
\text{32b, } R &= \text{H}^{2}
\end{align*} \]

\[ \begin{align*}
\text{35, } R &= \text{H} \\
\text{36, } R &= \text{H}^{2}
\end{align*} \]
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\(^6\) 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).\(^6\)
Reduction of aldehyde 39 with NaB\textsuperscript{2}H\textsubscript{4} afforded the deuterated alcohol 40b as a 70:30 mixture of C(19)-epimers.\textsuperscript{68} Mesylation followed by reaction with LiAlH\textsubscript{4} afforded cyclopropyl alcohol 42b\textsuperscript{69} oxidation of which with Jones' reagent furnished the desired ketone 43b as a 68:32 mixture of C(19)-epimers.\textsuperscript{70}

Treatment of 43a with Hg(NO\textsubscript{3})\textsubscript{2}.H\textsubscript{2}O in DME at 0 °C for 2h led, after KBr workup, to a mixture of three olefinic organomercurials 44a, 46a, and 47a (Scheme XVI).\textsuperscript{71}

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

The reaction of the deuterated cyclopropyl derivative 43b with Hg(NO\textsubscript{3})\textsubscript{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). This outcome corresponds to 96% and 100% diastereoselectivity, respectively, which is within the experimental error of the ratio determination by the $^1$H and $^2$H NMR. Since the configuration at C(19) of these organomercurials could not be safely established from their NMR spectra, we assumed that chemical correlation employing the chemistry described for 9b would be of use for this purpose. To this end we have attempted transmetalation with cuprates, expecting a ring closure reaction in analogy with the previously observed formation of cyclobutane ring (9b $\rightarrow$ 24b and 27 $\rightarrow$ 30). First, the reaction was tested on the unlabelled organomercurial 44a. To our delight, Me$_2$CuLi 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$_2$O 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 $^1$H 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 $\rightarrow$ 24b where no more than 10% scrambling was observed. While retention of configuration at the nucleophilic carbon largely dominated the cyclobutane ring formation, this pathway (44b $\rightarrow$ B $\rightarrow$ 49) was considerably suppressed at the expense of a competing mechanism (44b $\rightarrow$ A $\rightarrow$ 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 $\rightarrow$ 32b.
We reasoned that a Lewis acid-mediated ring closure might proceed with higher stereoselectivity, in analogy with the highly stereoselective reaction of MoCl₅ described above (Scheme VIII). Therefore, the cyclization of 44b by means of AlCl₃ (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 AlCl₃ and found it to proceed with the same stereochemistry as for MoCl₅. This not only further supports the mechanism formulated in Scheme XIV but also lends additional credence to the mechanism of formation of 43 from
44. In view of these mechanistic considerations we can assign a (19S) 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 LiAlH(OBu)₃ (generated in situ from 1 mol of LiAlH₄ and 3 mos of ₁-butyl alcohol) to give 40b as an 85:15 epimeric mixture (in contrast to the 70:30 mixture arising from the NaBH₄ 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(NO₃)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\textsuperscript{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 \textit{exo}-annulated isomers),\textsuperscript{12} as well as for the parent cyclopropane 5\textsuperscript{13} and its methylated counterpart.\textsuperscript{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 \textit{exo}-diastereoisomer (which are known to be corner-opened\textsuperscript{12} with Hg$^{2+}$), has been cleaved by Pt (a transition metal) with exclusive edge selectivity (Scheme XVIII).\textsuperscript{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.\textsuperscript{78}
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 $\rightarrow$ 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 $\rightarrow$ 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$_{N}$2 reaction (12 $\rightarrow$ 10). By contrast, addition of $\pi$-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 $\rightarrow$ 15).

Reactions with MeLi or Me$_2$CuLi (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 $\rightarrow$ 24 and 27 $\rightarrow$ 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 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, the difference in reactivity must originate elsewhere.

**Scheme XIX**

![Diagram showing reaction schemes](image)

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).\(^3\) 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 (\(V \rightarrow VI \rightarrow VII\)).\(^4\) 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 stereospecifically labelled organomercury compounds could help us to understand the mechanism of anticipated transformations.

Thus, the reaction of organomercurial 9a with \(\text{Br}_2\) 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 \(\text{Bu}_3\text{SnH}\) 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 NaBH₄ or Bu₃SnH 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. 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) (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.

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

\[
\begin{align*}
\text{Mo(CO)}_6 & \quad \text{R}_4\text{N}^+\text{X}^- \\
\xrightarrow{- \text{CO}} & \quad \text{R}_4\text{N}^+\text{[Mo(CO)}_5\text{X}]^- \\
\xrightarrow{\text{Br}_2} & \quad \text{R}_4\text{N}^+\text{[Mo(CO)}_4\text{Br}_3]^- \\
\text{CF}_3\text{SO}_3\text{Ag} & \quad (-\text{AgX}) \\
\xrightarrow{\text{heat}} & \quad \text{R}_4\text{N}^+\text{[Mo(CO)}_4\text{OTf}]^- \\
\xrightarrow{- \text{CO}} & \quad '' \text{R}_4\text{N}^+\text{[Mo(CO)}_4\text{OTf}]''^-
\end{align*}
\]

On treatment with Br₂, A gives away another molecule of CO, to generate complex B.⁹⁰ Thus we have prepared the complex Me₄N⁺[Mo(CO)₄Br₃]⁻, 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 CF₃SO₃⁻ group on treatment with silver triflate⁹⁶ 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

\[
\text{Me}_4\text{N}^+\text{Br}^- + \text{Mo(CO)}_6 + \text{Br}_2 \longrightarrow \text{Me}_4\text{N}^+\text{[Mo(CO)}_4\text{Br}_3]^- + 2\text{CO} \quad (\text{eq. 3})
\]

Using complex B, transmetallation of 9a was apparently accomplished again (with extrusion of HgBr₂) 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 fragmentation⁹² (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.\textsuperscript{94} Hence, the reactive conformation of the intermediate 56b should be that discussed above (assuming retention of configuration in the transmetallation step\textsuperscript{3}) and the fragmentation can be viewed as occurring accordingly to Scheme XXIV.\textsuperscript{95} The methylated counterpart 22 under the same conditions, however, turned out to be inert.

\textbf{Scheme XXIV}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\textbf{9a, }R = H \hspace{1cm} \textbf{56a, }R = H \hspace{1cm} \textbf{57a, }R = H \hspace{1cm} \textbf{58a, }R = H};
\node (B) at (2,0) {\textbf{9b, }R = 2H \hspace{1cm} \textbf{56b, }R = 2H \hspace{1cm} \textbf{57b, }R = 2H \hspace{1cm} \textbf{58b, }R = 2H};
\node (C) at (0,-2) {\textbf{9a, }R = H \hspace{1cm} \textbf{56a, }R = H \hspace{1cm} \textbf{57a, }R = H \hspace{1cm} \textbf{58a, }R = H};
\node (D) at (2,-2) {\textbf{9b, }R = 2H \hspace{1cm} \textbf{56b, }R = 2H \hspace{1cm} \textbf{57b, }R = 2H \hspace{1cm} \textbf{58b, }R = 2H};

\draw[->, thick] (A) -- node[above] {\textbf{Me}_4\text{N}^+[\text{Mo(CO)}_4\text{Br}_3]^\cdot} (B);
\draw[->, thick] (B) -- node[above] {DME, r.t., 12 h} (C);
\draw[->, thick] (D) -- node[below] {\textbf{H}_3\text{O}^+} (E);
\end{tikzpicture}
\end{center}

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\%).
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.
By contrast, with 22, the complex C may find the best stabilization by coordination to the carbonyl group followed by transmetalation (IX); the initial coordination will thus direct the regiochemistry of transmetallation in favour of the Hg-CH₂ bond (rather than Hg-CH₃). 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 (\(M = L_n Mo^+\)).

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.

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 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 NaB²H₄ 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 by \(\alpha\)-elimination from the initially formed alkyl molybdenum complex (\(L_n M = CHR_2 \leq L_n HM = CR_2\)). Once generated, the metallocarbene X is likely to be capable of hydride transfer from the CH₂-O.
group with concomitant departure of the triflate group. This would produce aldehyde 54b that may be further oxidized to acid 15b. Blank experiment showed that 54a (prepared by an independent method) is, indeed, oxidized to acid 15a by the in situ generated complex C in several minutes which is consistent with the proposed mechanism.

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, CH₃SO₃⁻ 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 MoCl₅ 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 XXVI).
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).
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 = HgCH₃) to occur. It is pertinent to note that for 18 (M = HgOAc), nucleophilic substitution is preferred, furnishing 20 (Scheme X). In this case, 18 (M = HgCH₃) behaves differently which can be associated with the different substituent on Hg; alternatively, transmetallation to 18 (M = MoL₄) 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 MoCl₅ readily converted the substituted [3.3.0]bicyclooctane system into a [4.4.0] skeleton (9 → 33), the [MoLₙ]⁻ 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 framework¹¹³ and can also be viewed as a retro-Conia reaction.

\[
\begin{align*}
\text{YHC} & \quad + \quad \text{C≡C} & \quad + \quad X^− \\
\text{LₙM} & \quad + \quad \text{C≡C} & \quad + \quad \text{C≡C}^−
\end{align*}
\]  
\hspace{1cm} (eq. 4)

\[
\begin{align*}
\text{LₙM} & \quad + \quad \text{C≡C} & \quad + \quad \text{C≡C}^−
\end{align*}
\]  
\hspace{1cm} (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)₄Br₃]⁻ 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 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 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 TF 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).
Abbreviations

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
NMNO 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 Tetramethyilsilan
Ts Toluensulfonyl
$[\alpha]_D$ Optical rotation
v Waven lenght
4. Experimental Section

General Methods. Melting points were determined on a Kofler block and are uncorrected. The optical rotations were measured in CHCl₃ with a Perkin Elmer 141 polarimeter at 22 °C with an error of < ±1°. The NMR spectra were recorded for CDCl₃ solutions at 25 °C on a Varian Unity 400 (operating at 400 MHz for ¹H, 100.6 MHz for ¹³C, 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 ¹³C). The ¹⁹⁹Hg NMR spectra were recorded on a Varian XL-300 instrument (at 53.7 MHz) and referenced to external Ph₂Hg (d₆-DMSO solution) at -808.5 ppm. Diastereoisomeric ratios for 52b and 53b were determined by ²H NMR (61.4 MHz); spectra were recorded for CHCl₃ 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-H values were determined from f₂ traces of HMQC spectra. Standard software supplied by the manufacturer was used throughout. The IR spectra were recorded in CHCl₃ 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% KHCO₃ (aqueous) and drying with MgSO₄. 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 KHCO₃ (2 x 10 mL) and water (1 x 20 mL), dried with MgSO₄, and evaporated. The residue contained pure product 9a (325 mg; 97%), showing one spot on TLC: mp 149-151 °C; [α]D -9.9° (c, 3.9 in CHCl₃/EtOH 3:2); IR (CHCl₃) v(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, Jgem = 11.7 Hz, J3α-H,4-H = 8.5 Hz, pro-S-4-H), 2.05 (m, 2 H, 12-H and pro-R-4-H); Jgem = 11.7 Hz, J4-H,3α-H = 8.1 Hz), 2.37 (m, 1 H, 3α-H), 2.47 (dd, J7α-H,7β-H = 12.0 Hz, J7β-H,8β-H = 6.9 Hz, 7β-H), 9.72 (s, 1 H, CHO); ¹³C 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); ¹⁹⁹Hg NMR (53.6 MHz) δ -1063. NOE difference experiments: Irradiation of CHO 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 CHO (4%) and 7α-H (22%). Irradiation of 3α-H gave increase of CHO (1%), 4-H (4%) and 4-H' (4%). Anal. Calcd for C₂₇H₄₅BrHgO: 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-cholestan-5-carbaldehyde (9a). Method B: To a solution of 22a (100 mg, 0.167 mmol) in DME (25 ml) was added HgBr₂ (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.

[6²H]-3β-[(Bromomercurio)methyl]-A,B-bisnor-5β-cholestan-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 LiAlH₄ (75 mg, 1.54 mmol). After 10 min, reaction mixture was checked using TLC and then 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 KHCO₃ (4 x 10 mL) and water (2 x 20 mL), dried with MgSO₄, and evaporated. The residue contained pure product 9c (310 mg, 93%): mp 151-154°C; IR (CHCl₃) ν(CHO) 1703 cm⁻¹; ¹³C 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);

[4²H]-3β-[Bromomercurio)methyl]-A,B-bisnor-5β-cholestan-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); ¹³C 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. KHCO₃ (1 x 10 mL), and water (1 x 10 mL) and dried with MgSO₄. 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\(_3\)) \(v(\text{OH})\) 3395, 3620 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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, \(J_{\text{gem}} = 8.6\) Hz, \(J_{3\alpha-\text{H}, 4\beta-\text{H}} = 4.9\) Hz, 4β-H), 4.17 (dd, 1 H, \(J_{\text{gem}} = 8.6\) 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\(_3\)) \(\delta\) 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, \(M^+ - \text{OH}\)), 384 (21, \(M^+ - \text{H}_2\text{O}\)), 358 (21, \(M^+ - \text{CO}_2\)), 356 (58, C\(_{26}H_{44}\)). The configuration of hydroxyl was established by \(^1\)H NMR, as an appreciable NOE (ca. 8%) can be seen for the acetal proton upon irradiation of the angular methyl. Anal. Calcd for C\(_{27}H_{46}O_2\): C, 80.54; H, 11.51. Found C, 80.21; H, 11.72.

**Method B:** To a solution of 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)\(_3\)Br (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 petrol ether-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, $J_{3\alpha-H,4\alpha-H}=9.2$ Hz, 4-α-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), 65.58 (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, 3 H, 18-H), 0.87 (s, 3 H, 19-H), 3.40 (d, 0.5 H, $J_{gem} = 8.6$ Hz, $J_{3\alpha-H,4\beta-H} = 4.9$ Hz, 4β-H) 4.16 (d, 0.5 H, $J_{3\alpha-H,4\alpha-H} = 9.2$ 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$=12.5$ Hz, J$_{11\alpha-H,12\beta-H} = 6.5$, and J$_{11\beta-H,12\beta-H} = 6.5$ Hz, 12β-H), 2.24 (dd, 1 H, $J_{gem} = 12.9$ Hz, J$_{7\beta-H,8\beta-H} = 6.0$, 7β-H), 2.31 (m, 1 H, 3α-H), 3.32 (s, 3 H, CH$_3$O), 3.37 (dd, 1 H, $J_{gem} = 8.5$ Hz, J$_{3\alpha-H,4\beta-H} = 4.4$ Hz, 4β-H), 3.98 (dd, $J_{gem} = 8.5$ Hz, J$_{3\alpha-H,4\alpha-H} = 9.1$ 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$_3$O), 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\textsubscript{3}O), 356 (100, C\textsubscript{26}H\textsubscript{44}). Anal. Calcd for C\textsubscript{28}H\textsubscript{48}O\textsubscript{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 monoxide 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.); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 0.63 (s, 3 H, 18-H), 0.88 (s, 3 H, 19-H), 4.15 (d, 1 H, J\textsubscript{3α-H,4α-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); \textsuperscript{13}C NMR (75.4 MHz, CDCl\textsubscript{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-cholestone-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\textsubscript{2} (2 x 20 mL) and water (3 x 20 mL). The solution was dried with MgSO\textsubscript{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); [α]_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_γem = 12.8 Hz, J_7βH,8βH = 7.2 Hz, 7β-H), 11.8 (1 H, CO_2H); ^13C 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_{45}O_2: C, 80.54; H, 11.51. Found: C, 80.19; H, 11.84.

3β-Methyl-A,B'-bisnor-5β-cholestan-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-cholestan-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; ¹³C NMR δ 12.31 (C-18), 13.85 (CH₂⁻H-C-4), 18.75 (C-21), 19.47 (C-19), 21.55 (CH₂), 22.43 (C-26 or C-27), 22.72 (C-26 or C-27), 23.54 (CH₂), 24.20 (CH₂), 27.72 (C-25), 28.31 (CH₂), 34.88 (CH₂), 35.52 (CH), 36.01 (CH₂), 37.92 (C-1), 38.85 (C-7), 39.02 (C-24), 39.45 (CH₂), 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).

[4-²H]-3β-Methyl-A,B-bisnor-5β-cholestan-5-carboxylic acid (15b): Prepared using Methode A and/or Methode B: ¹³C NMR δ 13.69 (CH₂⁻H) or 13.76 (CH₂⁻H) 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.⁹ 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); ¹³C 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 (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); [α]₀ +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, 4E-H), 5.07 (dd, J = 2.5 and 2.5 Hz, 1 H, 4Z-H); ¹³C 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), 31.21 (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).
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 NH₄Cl, 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: [α]D -6° (c 6.3); IR 1712, 2698 cm⁻¹; ¹H NMR δ 0.32 (s, 3 H, CH₃Hg), 0.64 (s, 3 H, 18-H), 0.96 (s, 3 H, 19-H), 9.81 (s, 1 H, CH=O); ¹³C NMR δ 12.19 (C-18), 18.72 (C-21), 19.57 (C-19), 20.94 (CH₃Hg), 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); ¹⁹⁹Hg 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 C₂₈H₄₈HgO: 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. NH₄Cl (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 NH₄Cl, 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 (Me₂CO); [α]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, CF/OH); in NOE difference experiments, irradiation at 0.94 (19-H) gave 9% enhancement of the signal at 4.19 (CHOH), while irradiation at 4.19 resulted in 4% enhancement of the signal at 0.94 (19-H); ¹³C 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 mercurialdehyde 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. NH₄Cl. After working up (brine-ether, sat. sol. KHCO₃, MgSO₄) solvent was evaporated and residues were separated by column chromatography (petroleum-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\textsuperscript{46} and stirred at \(-10^\circ\text{C}\) 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\textsubscript{4}CL. Product was extracted in ether and organic layer was worked up as usual and evaporated. After column chromatography (petrolether-ether; 9:1) of the reaction residues alcohol 24a was obtained (62 mg; 65\%) identical with the compound prepared under A.

\[4\alpha^2\text{H}]\text{-A-Homo-B-nor-3,5-cyclo-5\alpha-cholestan-6\alpha-ol (24b): mp 98-99 \text{o}\text{C}; } ^1\text{H NMR } \delta \\
\text{0.67 (s, 3 H, 18-H), 0.91 (s, 3 H, 19-H), 2.42 (dd, 1 H, } J \equiv 2 \times 6.5 \text{ Hz, 3\alpha-H), 4.18 (d, } J = 6.8 \text{ Hz CHOH); } ^{13}\text{C NMR } \delta 12.31 (q), 17.17 (q), 18.78 (q), 21.85 (t), 22.56 (q), 22.81 (q), 23.83 (t), 24.49 (t), 28.00 (d), 28.56 (t), 28.96 (t), 32.50 (dt, CH\textsuperscript{2}H), 34.93 (t), 35.66 (d), 36.24 (t), 36.31 (t), 39.50 (t), 39.82 (t), 40.96 (d), 43.98 (s), 45.42 (d), 53.49 (d), 53.61 (s) 55.72 (d), 57.08 (d), 63.80 (s), 68.45 (d).\]

\text{A-Homo-B-nor-3,5-cyclo-5\alpha-cholestan-6-one (25a). Method A: The alcohol 24a (150 mg; 0.39 mmol) in acetone (10 mL) was treated with Jones’ reagent at \(-20 \text{o}\text{C}\) 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 \text{o}\text{C}; [\alpha]_D ^{-9^\circ} (c 2.4); IR v(C=O) 1750 cm\textsuperscript{-1}; ^1\text{H NMR } \delta 0.66 (s, 3 H, 18-H), 0.96 (s, 3 H, 19-H), 1.09 (t, 1 H, } J = 13 \text{ Hz, 7\alpha-H), 1.68 (m, 1 H, 8\beta-H), 2.29 (dd, } J_{\text{gem}} = 13.4 \text{ Hz, } J_{7\beta-H, 8\beta-H} = 7.4 \text{ Hz; } 1\text{H; 7\beta-H), 2.35 (m, 1 H, 3\alpha-H), 2.61 (dd, 1 H, } J_{\text{gem}} = 17.6 \text{ Hz, } J_{4\beta-H, 3\alpha-H} = 6.8 \text{ Hz, 4\beta-H), 2.90 (dd, 1 H } J_{\text{gem}} = 17.6, J_{4\alpha-H, 3\alpha-H} = 8.6 \text{ Hz, 4\alpha-H); } ^{13}\text{C NMR } \delta 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 4\alpha-H (at } \delta 2.90) resulted in the increase of 4\beta-H (19.6\%) and 3\alpha-H (8.6\%); irradiation of 4\beta-H (at } \delta 2.61) resulted in the increase of 4\alpha-H (21.6\%); irradiation of 3\alpha-H (at } \delta 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^2H]-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 \( \geq 95\% \) \(^2\)H (d1).

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\%): \([\alpha]_D+17^\circ\) (c 0.7); \(^1\)H NMR δ 0.68 (s, 3 H, 18-H), 1.29 (s, 3 H, 19-H), 2.59 (m, 1 H, 3β-H), 2.34 (m, 1 H, 3α-H), 4.73 (s, 1 H, C=HH), 4.78 (s, 1 H, C=HHz; \(^13\)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 LiAlH₄ (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); [α]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); ¹³C 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 C₂₇H₄₅O: 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-cholestan (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. KHCO₃ (2 x 20 mL), sat. aq. KBr (1 x 20 mL) and water (2 x 20 mL) and dried with Na₂SO₄. 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 (Me₂CO, H₂O); [α]D -3° (c 2.6); IR v(C=C) 1631, v(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, CH₂CH₂), 4.26 (q, 2 H, J = 7.1 Hz, CH₂CH₂O), 5.92 (d, J = 16.0 Hz, 1 H, CH=CHCO₂Et), 7.06 (d, 1 H, J = 16.0 Hz, CH=CHCO₂Et); ¹³C 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 C₃₁H₃₁BrHgO₂: 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-cholestane (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%): [α]D -5° (c 3.7); IR ν(C=C) 1640, ν(C=O) 1710 cm⁻¹; ¹H NMR δ 0.25 (s, 3 H, CH₃Hg), 0.65 (s, 3 H, 18-H), 0.79 (s, 3 H, 19-H), 1.35 (d, 3 H, J = 7.1 Hz, CH₃CH₂O), 4.25 (d, 2 H, J = 7.1 Hz, CH₃CH₂O), 5.84 (d, 1 H, J = 16.0 Hz, CH=CHCO₂Et), 7.15 (d, 1 H, J = 16.0 Hz, CH=CHCO₂Et); ¹³C 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 C₃₂H₅₄HgO₂: 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. NH₄Cl, 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. NaBH₄ (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 column 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, CH₃CH₂), 4.23 (q, 2 H, J = 7.1 Hz, CH₃CH₂O), 5.87 (d, J = 16.0 Hz, 1 H, CH=CHCO₂Et), 7.04 (d, 1 H, J = 16.0 Hz, CH=CHCO₂Et); ¹³C 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 Bu₃SnH (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.

6a-[(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%): [α]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, CH₃CH₂O), 4.15 (q, 2 H, J = 7.1 Hz,
CH$_3$CH$_2$O); $^{13}$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$_4$Cl, 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$_4$Cl, 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.

$3\beta$-Chloro-5-cholesten (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 (dd, $J_{gem} = 13.5$, $J_{4\alpha-H,3\alpha-H} = 5.1$, $J_{4\alpha-H,6-H} = 2.1$ 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 +) / 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 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, $J_{7\beta-H,8\beta-H} = 6.5$ 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.

(19S)-[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 mixture was stirred at -78 °C for 20 min while monitored by TLC. The excess of reagent was decomposed by sat. NH\(_4\)Cl (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\(_3\)CO\(_2\)), 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; 0.57 mmol) 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).

(19S)-[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); this product was directly use in the next without further purification.

(19R)-[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. NH₄Cl (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 counterpart (42a).

5,19-Cyclo-5β-cholestan-3-one (43a). Method A: The alcohol 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 KHCO₃ (3 x 30 mL) and water, and dried with MgSO₄. 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); [α]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); ¹³C 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 C₂₇H₄₄O: 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 lithiu 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, 0.15 mmol) 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 SiCl₄ (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.

\[(19R)-[19^2H]-5,19-Cyclo-5\beta-cholestan-3-one (43b)\]: 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.\(^6\)

(The same as mentioned above in case of 43a Method A.)

\[(19R)-[19^2H]-5,19-Cyclo-5\beta-cholestan-3-one (43b)\] and \[(19R)-[19^2H]-5,19-Cyclo-5\beta-cholestan-3-one (49) mixture:\]

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, 19-H).

**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
\(\nu(C=O)\) cm\(^{-1}\); \(^1\)H NMR \(\delta\) 0.75 (s, 3 H, 18-H), 2.20 and 2.51 (AB system, two d, \(J_{\text{gem}} = 12.1\) Hz, 2 x 1 H, 19-H), 5.78 (s, 1 H, 4-H); \(^{13}\)C NMR \(\delta\) 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.

\((19\text{S})\)-\([19^2\text{H}]\)-19-Bromomercurio-cholest-4-en-3-one (44b): \(^1\)H NMR \(\delta\) 0.71 (s, 3 H, 18-H), 2.15 (s, <1 H, 19-H), 5.74 (s, 1 H, 4-H); \(^2\)H NMR \(\delta\) 2.53 (\(W/2 = 13.8\) Hz);\(^75\) \(^{13}\)C NMR \(\delta\) 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, \(J_{\text{CD}} = 21.5\) 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 \(\delta\) -1011; MS 95±3% \(^2\)H (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]-5\(\beta\)-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 KHCO₃, 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; [α]D -30° (c 8.8); IR 1709 v(C=O) cm⁻¹; ¹H NMR δ 0.68 (s, 3 H, 18-H), 2.21 and 2.47 (AB system, J₆₉ = 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); ¹³C 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 (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 C₂₇H₄₃BrHgO: C, 48.83; H, 6.53. Found: C, 48.61; H, 6.74.

(19R)-(19²H)-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); ¹³C 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 (CH²H, J₆₉ = 22.5 Hz), 56.0 (d), 57.5 (t), 57.9 (d), 115.4 (d), 149.2 (s), 210.0 (s). ¹⁹⁹Hg NMR δ 739.16;

19-Nor-5-[(bromomercurio)methyl]-5β-cholest-9-en-3-one (47a). The second chromatographic fraction after isolation of 46a (435 mg; 28%): mp 174-178 °C (acetone); [α]D +36° (c 12.6); IR 1705 v(C=O) cm⁻¹; ¹H NMR δ 0.83 (s, 3 H, 18-H), 2.23 and 2.27 (AB system, two d, J₆₉ = 11.6 Hz, 2 x 1 H, 19-H), 2.70 (d, J₆₉ = 14.00 Hz, 1 H, 4β-H), 3.00 (dd, J₆₉ = 12.5 Hz, J₁₉-H₂₈-H = 6.7 Hz, 1 H, 2β-H); ¹³C 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 C₂₇H₄₃BrHgO: 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$_2$SO$_4$, 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: $^\circ\mathrm{D} +18^\circ$ (c 2.0; lit. gives +20$^\circ$); IR $\nu$ 1713 (C =0) cm$^{-1}$; $^1$H NMR $\delta$ 0.82 (s, 3 H, 18-H), 1.03 (s, 3 H, 5g-methyl).

3β-Methyl-5-(hydroxyoxymethyI)-A,B-bisnor-5β-cholestan (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%): $^\circ\mathrm{D} +15^\circ$ (c 1.2); IR $\nu$(OH) 3420, 3595 cm$^{-1}$; $^1$H NMR $\delta$ 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$_2$OH), 3.70 (dd, J = 10.7 and 1.0 Hz, 1 H, CH$_2$OH); $^{13}$C NMR $\delta$ 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$_2$Cl$_2$ (20 mL), the insoluble material was filtered off and the solution was worked up. The crude product was dissolved in petroleum ether and the solution was filtered through a pad of silica gel to afford aldehyde 54a (93 mg;
94%) which is slowly oxidized by air to the corresponding acid: \[ ^1H \text{NMR} \delta 0.62 \text{ (s, 3 H, 18-H), 0.92 (s, 3 H, 19-H), 2.50 (dd, } J_{\text{gem}} = 12.3 \text{ Hz, } J_{\text{7p-H,8p-H}} = 6.7 \text{ Hz, 1 H, 7p-H) and 12.97 (s, 1 H, CH=O);} \]
\[ ^{13}C \text{NMR} \delta 12.07 \text{ (q), 14.40 (q), 18.62 (q), 19.56 (q), 21.18 (t), 22.41 (q), 22.66 (q), 23.73 (t), 24.24 (t), 27.85 (d), 28.38 (t), 35.05 (t), 35.50 (d), 36.09 (t), 36.55 (t), 39.19 (t), 39.34 (t), 39.47 (t), 43.13 (d), 43.55 (s), 47.28 (d), 55.59 (d), 56.99 (d), 57.99 (s), 58.67 (d), 66.93 (s), 206.72 (d).} \]

3β-[(MethyImercurio)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%): \[ [\alpha]_D^{+14°} \text{ (c 2.5);} \]
\[ ^1H \text{NMR} \delta 0.25 \text{ (s, 3 H, } \text{CH}_2\text{Hg), 0.62 \text{ (s, 18-H), 0.89 (s, 3 H, 19-H), 3.52 and 3.73 (AB system, } J = 10.8 \text{ Hz, 2 H, 6-H);} \]
\[ ^{13}H \text{NMR} \delta 12.27 \text{ (q), 18.76 (q), 19.06 (q), 21.55 (q), 21.82 (t) 22.55 (q), 22.80 (q), 23.84 (t), 24.52 (t), 27.98 (d), 28.38 (t) 35.66 (d), 35.81 (d) 36.23 (t), 38.70 (t), 39.48 (t), 39.90 (t), 40.86 (t), 41.27 (d), 43.40 (t), 43.78 (s), 49.58 (d), 52.19 (s), 55.74 (d), 56.45 (d), 58.27 (d), 59.97 (s), 64.97 (t). Anal. Calcd for C_{28}H_{50}HgO: C, 55.75; H, 8.35; Hg, 33.25. Found, C, 56.03; H, 8.59. \]

[6-\(^2\text{H}_2\)]-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-Seo-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%): [α]D +14° (c 2.4); 1H NMR
δ 0.69 (s, 3 H, 18-H), 0.90 (s, 3 H, 19-H), 4.98 (m, 1 H, (4E)-H), 5.07 (m, 1 H, (4Z)-H), 5.83
(m, 1 H, 3-H), 9.70 (d, J = 3.2 Hz, CH=O); 13C 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 C27H46O: 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
PhCH2(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; [α]D
+13° (c 2.0).

(Z)-[42H]-4,5-Seco-B-nor-5β-cholest-3-ene-5-carbaldehyde (58b): [α]D +13° (c 2.0);
1H NMR δ 0.69 (s, 3 H, 18-H), 0.90 (s, 3 H, 19-H), 4.97 (m, 1 H, (4E)-H), 5.85 (m, 1 H,
3-H); MS > 95% 2H (d1).

3β-Methyl-5-(acetoxymethyl)-A,B-bisnor-5β-cholestan (62a). To a solution of
alcohol 55a (100 mg; 0.16 mmol) and triethyl amine (2 mL) in THF (30 mL) 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%): \([\alpha]_D +8^{o} \text{ (c 1.0)}; \) \(^1\text{H} \text{ NMR } \delta \text{ 0.30 (s, 3 H, CH}_3\text{-Hg), 0.66 (s, 3 H, 18-H), 0.92 (s, 3 H, 19-H), 2.10 (s, 3 H, CH}_3\text{CO}_2\text{), 4.05 and 4.09 (AB system, } J = 11.4 \text{ Hz, 2 H, CH}_2\text{-OAc);} \) \(^{13}\text{C} \text{ NMR } \delta \text{ 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\(^+\)).

\[6-^2\text{H}_2\]3β-Methyl-5-(acetoxymethyl)-A,B-bisnor-5β-cholestan (62b). \(^1\text{H} \text{ NMR } \delta \text{ 0.29 (s, 3 H, CH}_3\text{-Hg), 0.65 (s, 3 H, 18-H), 0.91 (s, 3 H, 19-H), 2.09 (s, 3 H, CH}_3\text{CO}_2\text{); MS m/z 633 (M\(^+\)).}

3β-[(Methylmercurio)methyl]-5-(methanesulfonyloxy)methyl)-A,B-bisnor-5β-cholestan (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\text{H} \text{ NMR } \delta \text{ 0.32 (s, 3 H, CH}_3\text{Hg), 0.65 (s, 3 H, 18-H), 0.95 (s, 3 H, 19-H), 3.04 (s, 3 H, CH}_3\text{SO}_3\text{), 4.15 and 4.27 (AB system, } J = 9.3 \text{ 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); \([\alpha]_D^{+} +54^\circ\) (c 5.3; lit.\(^{41,82}\) gives +59°); ¹H 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-CH₃), 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); ¹³C 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⁺), 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), KHCO₃ (aqueous; 5 x 10 mL), and water and dried with MgSO₄. 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 at this temperature for 1 h. The mixture was then poured onto ice and water, the product was extracted with ether and the
eternal solution was worked up to furnish sufficiently pure mesylate 65 (117 mg; 97%): $^1$H NMR $\delta$ 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$_3$SO$_3$), 4.14 and 4.30 (AB system, $J_{gem} = 9.3$ Hz, 2 H, CH$_2$OMes); $^{13}$C NMR $\delta$ 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%): [α]$_D$ +29° (c 5.8); $^1$H NMR $\delta$ 0.74 (s, 3 H, 18-H), 1.13 (s, 3 H, 19-H), 2.17 (s, 3 H, 4-H); $^{13}$C NMR $\delta$ 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


(6) (a) Aratani, T. *Pure Appl. Chem.* 1985, 57, 1839 and references cited therein. (b)


(16) The structure was determined by NMR spectra using H,H-COSY, P.E. COSY, and NOESY,† HMQC, HSQC, and multiple bond HSQC, and DEPT and selective INEPT. 1H NMR: 9.72 (s, 1 H, CHO); 13C NMR: 34.78 (-CH2HgBr), 206.22 (-CHO); 199Hg NMR: -1063 ppm. The full assignment of carbon signals in the 13C NMR spectrum has been achieved.


For typical NMR Hg-shifts of organomercurials, see, e.g.: Reischl, W.; Kalchhauser, H. Tetrahedron Lett. 1992, 33, 2451.


Deuterated 7b was prepared in four steps\textsuperscript{11} from 4β-\textsuperscript{2}H-cholesterol.\textsuperscript{24,25}


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.


In the \textsuperscript{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-sterospecific, producing a 1:1 mixture of the C(4) epimers.


(32) Nucleophilic $S_N^2$-type displacement of the palladium appears to be a common reaction and is well documented. 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 although for his intermediate i coordination by acetate carbonyl (ii) cannot be excluded; this species preferred to react via an $S_N^2$ reaction; no reductive elimination was observed.

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


The reversed sequence may also be considered. However, this would first generate a nucleophilic CO\(_2\)H group which may be capable of S\(_{N}\)2 replacing of Pd(II) at C(4) and forming a \(γ\)-lactone, in analogy with the conversion of \(12\) to \(10\).

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\(_2\)H\(_4\) followed by Jones' oxidation.


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.\(^{39,41}\)


(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.


(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 Cp₂Ti=CH₂ (Tebbe reagent) was reactive enough to convert this carbonyl into an exo-methylene group.


(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 8.6 Hz) 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 Ph₃P=CHR (R = H, Me, or OMe) or with Ph₃As=CH₂, 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 NaBH₄ or Bu₃SnH, 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


(54) We believe that in this instance, the Lewis acid (Me₃Al) accelerates the conjugate addition, as in its absence only a complex mixture was obtained.


(57) Model experiments demonstrated that both 3α,5-cyclo-5α-cholestan-6β-ol and cholesterol are readily converted to 33a on treatment with MoCl₅ in Et₂O at rt. 5α-Cholesterol-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.


(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-²H 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 $^1$H 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-deficient center (iv → v), even in preference to a nucleophilic ester group. Hence, transmetalation of Hg for Mo may not be required in our case.

\[ \text{SAr} \rightarrow \text{SAr} \]


(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.


In the \(^1\text{H}\) NMR spectrum of 43a the \textit{pro-R-H} appears at $\delta$ 0.51 (d, $J = 5.7$ Hz), while \textit{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 $\rightarrow$ 42b).\(^{58,69}\)

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. \textit{Chem. Listy} \textbf{1979}, \textit{73}, 583.

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.

Both \(^1\text{H}\) and \(^{13}\text{C}\) 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.

The ratio was determined by integration of the signals of \textit{19-2H} in the \(^2\text{H}\) NMR spectrum for each pair of \textit{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.

Racemization has also been observed with another Hg $\rightarrow$ Cu transmetallation.\(^{44a}\)

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.\(^\text{13}\)

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.

\[
\text{vi} \quad \text{PdCl}_2 \quad \text{MeOH} \quad \text{vii}
\]


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


In open chain systems, the 4-exo-Trig process via a radical mechanism is shifted towards the open species. 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. In contrast, five- and six-membered rings can readily be formed by the intramolecular radical addition across a C=C or C=O bond. For a recent report on the ring-opening of a radical generated from cyclobutanone, see: Zhang, W.; Dowd, P. *Tetrahedron Lett.* 1992, 33, 3285.


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


(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 RCO₂Tl and RCO₂Ag: (a) Doyle, G. J.
Evolving CO partly reduces precipitated AgCl to Ag(0). The complex D presumably exists as a dimer.

Precedents for transmetalation are known, e.g., from tungsten and iron chemistry.\(^9^7\)\(^9^8\) Thus, for instance, \(\text{Et}_4\text{N}^+[\text{W}(\text{CO})_5\text{Br}]^\cdot\) reacts instantaneously with \(\text{RLi}\) to furnish \(\text{LiBr}\) and \(\text{Et}_4\text{N}^+\text{[W(CO)_5R]}^\cdot\).\(^9^9\) 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, \(\text{Et}_3\text{HN}^+[\text{Fe}_2(\text{CO})_7\text{SR}]^\cdot\) reacts with various vinylic organomercurials \(\text{RHgCl}\) to give \(\text{Et}_3\text{NHCl}\) and transient \(\text{L}^\cdot\text{Fe-HgR}\) species which extrude \(\text{Hg}(0)\) and yield stable Fe-complexes.\(^1^0^0\)

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 \(\beta\)-elimination rather than protonolysis. For \(\beta\)-elimination of organomercurials, see, e.g.: Jerkunica, J. M.; Traylor, T. G. \textit{J. Am. Chem. Soc.} \textit{1971}, \textit{93}, 6278.

For a direct conversion of a triphenylmethyl ether into a ketone by means of \(\text{Ph}_3\text{C}^+\text{BF}_4^-\), via a hydride abstraction, see: Jung, M. E.; Speltz, L. M. \textit{J. Am. Chem. Soc.} \textit{1976}, \textit{98}, 7882.

An alternative mechanism that would involve insertion of molybdenum into the C-H bond of the \(\text{CH}_2\text{-O}\) group is very unlikely.

Schrock complexes arising by \(\alpha\)-elimination, have been described for various metals\(^3\) (e.g. \(\text{M} = \text{W}^{10^5}, \text{Ta}^{10^6}, \text{and Ti}^{10^7}\)); calculations are also available.\(^1^0^8\) In our case, the \(\alpha\)-elimination to generate III may be further assisted by the release of steric...
hindrance.³


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)$_5$Cr=CH$_2$ seems to be fairly electrophilic.¹¹⁰ Hence, the intramolecular hydride abstraction in III is conceivable.


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 oxidation¹¹² was found to give satisfactory yield of pure aldehyde.


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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.

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.

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 Intermediates.

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.

5. Jiří Šrogl, Adolf Gogoll and Pavel Kočovský:
Molybdenum (V)-Mediated Skeletal Rearrangement of an Organomercury Steroid. Stereoelectronic Control and Mechanism.
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(II) occurs with a skeletal rearrangement to afford a stable organomercurial 3 which on treatment with Me₂CuLi gives cyclobutanol 9; analogous conjugate addition is also reported (10—15).

Stereo- and regioselective cleavage of cyclopropanes 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 stereoselective, thallium-mediated cleavage of steroidal cyclopropane derivative 1 which triggered a unique skeletal rearrangement affording lactol 4 via the thalliated intermediate 2 (Scheme I).⁴ Mercury(II) ion, isoelectronic with TI(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(NO₃)₂·2H₂O 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.³ The mixture was worked up to afford organomercurial 3α,5-cyclo-5α-cholestan-6α-ol 3α,5-cyclo-5α-cholestan-6α-ol 3α,5-cyclo-5α-cholestan-6α-ol 3α,5-cyclo-5α-cholestan-6α-ol 3α,5-cyclo-5α-cholestan-6α-ol.

Samarium (II) seems to be an excellent promoter of this type of reaction:


Iwata, C. Shaded toward the open species 1. In contrast, five-membered rings can readily be formed by the intramolecular radical addition \(^{(15)}\). Formations of carbon-carbon bonds were found either to be inert or to convert 1 to cholesterol or its esters (acetate, nitrate, etc.).

Reduction of 3 with a variety of hydride reagents furnished demercurized alcohol 6 in a quantitative yield (Scheme II). Since Bu₂SnH 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.

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%).\(^{(21)}\) Treatment of 7 with MeLi at low temperature resulted in the formation of the desired cyclobutanol.\(^{(22)}\) Alternatively, we have found that 9 can be obtained in one pot on reaction of 3 with Me₂CuLi.\(^{(24)}\)

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 on Horner-Emmons


\(^{(21)}\) This result itself may represent a new method for the preparation of dialkyl mercury derivatives RHgR\(^{1}\) from the readily available organomercurial halides RHgX. Other reagents that also gave high yields of 7 were Me₂Al, Me₂Zn, and Me₂Sn.

\(^{(22)}\) \(^{1}\)H NMR: 0.32 (s, CH₃Hg), 9.81 (s, CH—O) ppm, \(^{13}\)C NMR: 14.74 (CH₃Hg), 207.27 (CH=O) ppm. \(^{198}\)Hg NMR: -161.6 ppm; m/z 600 (M⁺).
olefination. Attempted radical cyclization of 10, using NaBH₄ or Bu₃SnH (Scheme III), gave only the reduced product 12 (in 81% and 87% yield, respectively). However, as with the aldehyde 3, copper reagents proved more rewarding. First, organomercurial 10 was methylated with MeCu or Me₃Al to give 13 (in 91% and 95% yield, respectively). Although in this instance MeLi produced a complex mixture on reaction with 13, Me₃CuLi afforded the desired cyclobutane derivative 15 (40%). Alternatively, 15 was obtained in much higher isolated yield (75%) in one pot from 10 on reaction with Me₃CuLi. This behavior suggests that the actual reactive species involves copper. Although the structure of 14 is unknown, it seems reasonable to assume that M = CuLiCH₃ or CuHgLiCH₃ and that the more suitably positioned C(4) in the complex 14 adds across the double bond in preference to the CH₃ 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 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, may result in the development of a general method for the stereoselective construction of rings of various size, and for intermolecular coupling as well.

Acknowledgment. We thank Profs. M. Nilsson and J.-E. Bäckvall, and Dr. T. Olsson for stimulating discussions and Dra. G. Griffith and A. Gogoll for obtaining the NMR spectra. We also thank Merck Sharp and Dohme and the University of Leicester for financial support to J.A.

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.


(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. Recently, we have described a stereospecific, Tl(III)-mediated cleavage of the steroidal cyclopropane derivative, followed by a unique skeletal rearrangement that afforded lactone 4 via the thalliated intermediate 2 (Scheme 1). Mercury(II) ion, isoelectronic with thallium(III), is also known to be capable of cleavage of cyclopropane. Herein, we report the reaction of 1 with Hg(ii), isolation of the organomercurial product, and its transmetallation with Pd.

Treatment of 3a,5-cyclo-5a-cholestan-6a-ol I* with Li2PdCl4 (5 mol %; generated in situ from PdCl2 and LiCl) and CuCl2 (3 equiv.) in DME–H2O, presumably proceeding via the organopalladium(II) species 6, furnished lactol 4; in the presence of MeOH, the corresponding methyl acetal 5 was formed.

Catalytic reaction of 3 with Li2PdCl4 (5 mol %; generated in situ from PdCl2 and LiCl) and CuCl2 (3 equiv.) in DME–H2O, 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 CuCl2, when a stoichiometric amount of Li2PdCl4 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 Li2PdCl4 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 proximity to a π-acid dramatically changed the reactivity of Pd. § This rather unexpected reaction can be rationalized as follows. Instead of undergoing the 5(0)π-exo-tet ring closure to 4, in this instance the transient organopalladium 6 preferred an intramolecular insertion into the C–H bond of the aldehyde group. 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 hydride elimination of the acyl–Pd bond (presumably via an chloro) and formation of Pd(II). ¶ In order to verify this mechanism, deuteriated aldehyde 10 was prepared from [6DCH2]–alcohol 9 (Scheme 2), which in turn was synthesized by a highly stereoselective reduction of 3a,5-cyclo-5a-cholestan-6-one with LiAlH4. Transmetallation of 10 under the same conditions as applied to its unlabeled counterpart (i.e., Li2PdCl4, CH2=CHCN, DME, H2O room temp.) resulted in the formation of acid 11 labelled in the methyl group. The mass and 13C NMR spectra revealed an almost quantitatively transfer of deuterium from the aldehyde group to the methyl,|| which is in an excellent agreement with the proposed mechanism.

The observed behaviour of Hg2+ parallels the reactivity of Tl3+ in the cyclopropane ring-opening. The difference

† IR: ν=O 1683, νCOH 2500–3100 cm−1; 13C NMR: δ 181.87.
‡ This transformation occurs with a stoichiometric amount of Pd(II). When attempted as a catalytic process with added CuCl2 to reoxidize Pd0, no reaction was observed. It was also found that addition of CuCl2 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 CO2H group which may be capable of Sn2 replacing of Pd0 at C(4) and forming a γ-lactone, in analogy to the conversion of 6 into 4.

¶ The observed behaviour of Hg2+ parallels the reactivity of Tl3+ in the cyclopropane ring-opening. The difference

|| In the proton-decoupled 13C 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 LiAlH4 followed by Jones' oxidation.

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† 1H NMR: δ 9.72 (s, 1 H, CHO); 13C NMR: δ 34.78 (CH3HgBr) and 206.22 (CHO); 199Hg NMR: δ –1063 (indirectly referenced to HgCl2 at δ –1501.6 and Ph2Hg at δ –808.5). The full assignment of carbon signals in the 13C NMR spectrum has been achieved.
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 Sn² 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 Pd¹¹ intermediate 6 undergoes a clean Sn² reaction, while addition of n acids promotes its conversion into the Pd¹⁻¹ 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 Cannizzaro or Tishchenko reaction) of potential synthetic applicability.

We thank Dr R. D. W. Kemmitt and Professor J.-E. Backvall 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 Me₂CuLi (−78 °C, 5 min) led to a ring closure producing the corresponding cyclobutanol in high yield.⁹

References
8 For general discussion and other examples of the conversion of acylpalladium(II) species to acids and Pd⁻¹, see e.g., ref. 1, p. 727.
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

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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. 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). 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. Herein, we report on the transmetalation of 2 with molybdenum in two different forms.

Scheme I

1. Hg(NO₃)₂·H₂O
   DME, MeCN
   r.t., 1.5 h

2. KBr, H₂O
   BrHg
   (97%)

3. MoCl₅
   Et₂O
   r.t., 2 h

4. -Cl⁻

5. -Cl⁻

6. O=MoCl₃
   (78%)

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Reaction of 2 with MoCl₅ afforded cholesteryl chloride (6), 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-deficiency at C₅ (4) which was then saturated by forming a bond to C₆ (4 → 5). The resulting cyclopropyl intermediate 5 subsequently collapsed to cholesteryl chloride (6) via the well-known “iso-steroid” rearrangement. The whole reaction sequence is apparently controlled by the combination of high oxophilicity 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):

\[
\text{Me}_4\text{N}^+\text{Br}^- + \text{Mo(CO)}_6 + \text{Br}_2 \rightarrow \text{Me}_4\text{N}^+\text{[Mo(CO)}_2\text{Br}_2]^+ + 2 \text{CO} \quad (\text{eq. 1})
\]

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 which eventually gave rise to the olefinic aldehyde 9 (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), 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 MoCl₅ readily converted the substituted [3.3.0]bicyclooctane system into a [4.4.0] skeleton (2 → 3 → 6), the [MoL₃]⁻ 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, \( \text{TsO}^- \) typically serves as a leaving group and the negative species (e.g., \( \text{O}^- \)) 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.\(^\text{17}\)

\[
\begin{align*}
\text{Y} & \quad \xrightarrow{\Delta} \quad \text{Y} &= \text{C} &= \text{C}^- + \text{X}^- \\
\text{L}_n\text{Mo} & \quad \xrightarrow{\Delta} \quad \text{L}_n\text{Mo} + \text{C} &= \text{C}^- + \text{C} &= \text{C}^- (\text{eq. 2})
\end{align*}
\]

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 state 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.\(^\text{16}\)

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.

References and Notes

1. Dedicated to Dr. Václav Černý on the occasion of his 70th birthday.


Identical with an authentic sample.

This process may be concerted.


Model experiments demonstrated that both the 3α,5-cyclo-5α-cholestan-6β-ol and cholesterol are readily converted into 6 on treatment with MoCl₅ in E₂O at r.t.

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 S₅₁ mechanism.


9: [α]D +14° (c 2.4, CHCl₃); IR (CHCl₃): 1637, 1710, and 2704 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): 0.69 (s, 3 H, 18-H), 0.90 (s, 3 H, 19-H), 4.90-5.10 (m, 2 H, CH=CH₂), 5.70-5.95 (m, 1 H, CH=CH₂), 9.70 (d, 1 H, J = 3.2 Hz, CH=O) ppm; ¹³C NMR: 12.32 (q), 17.78 (q), 18.76 (q), 21.36 (t), 22.57 (q), 22.82 (q), 23.86 (q), 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.

For general methods of synthesis of organomercurials, see ref. 6.


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

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Abstract: The reactivity of the two isoelectronic cations (Hg²⁺ and Tl³⁺) toward the cyclopropane ring is compared, and further evidence for the exclusive corner selectivity for Hg²⁺ is provided by isotope labeling. Cleavage of cyclopropyl derivative 1 with Hg(NO₃)₂, followed by KBr quenching, afforded the stable, rearranged organomercurial 3, whose transmetallation has been studied. Whereas reaction of 3 with Pd(II) afforded lactol 4, treatment with Me₃CuLi 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 Me₃CuLi or AICl₃ 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 metals¹ 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,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 catalyzed by various metals,⁵ followed by ring-opening,⁶ is an attractive strategy for construction of up to three contiguous chiral centers.⁷ However, the mechanism of cleavage of the cyclopropane ring was only little understood until very recently,⁸ 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.⁹ Thus, electrophilic opening by reagents capable of back-donation, such as transition metals,¹° followed by ring-opening,¹¹ is an attractive strategy 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.

Scheme 1

of this mechanism and this issue has been a subject of controversy. Using double isotope labeling (¹H and ²H₂O) we have recently shown, for the first time, that thallium(III) is capable of stereospecific "corner" activation and has described a unique skeletal rearrangement (Scheme 2) of 3,5-cyclo-5a-cholestan-6-ol (1 → 2 → 11).¹² While this project was in progress, exclusive "corner" opening was also observed with other poor back-donors, namely, with a proton¹³ and with mercury(II).¹⁴

Cyclopropane Ring-Opening by Hg(II) and Ti(IV) in Steroidal Derivative 1. Treatment of steroidal cyclopropyl alcohol\(^{15}\) 1a with \(\text{Hg(NO}){\text{H}_{2}}\) in \(\text{DMF-CH}_{3}\text{CN} (2:5)\) at room temperature

Herein we compare the reactivity of the two isoelectronic cations (Ti(IV) and Hg(II)) in cyclopropane ring-opening, offering further evidence for the preferential corner selectivity for \(\text{Hg}^{2+}\), 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 Ti(IV) in Steroidal Derivative 1.**

**Treatment of steroidal cyclopropyl alcohol**\(^{15}\) 1a with \(\text{Hg(NO}){\text{H}_{2}}\) in \(\text{DMF-CH}_{3}\text{CN} (2:5)\) at room temperature

for 1.5 h led, after KBr workup, to a single product 3a in 97% isolated yield (Scheme 2). In contrast to the Ti(III)-mediated reaction, 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 \(\text{Hg}^{2+}\) and Ti(IV) (soft, strong Lewis acids). Other isoelectronic cations (Au(III) and Pb(II)) and those of high redox potential as well as other ions (Ce(IV), Cu(II), Ag(I), Mn(II), Al(III), In(III), and Ti(IV)) 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 \(\text{Ph(OH}){\text{OTS}}\). 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 \(\text{PdCl}_{2}\)) at higher temperature and prolonged reaction time. The latter reaction can be ascribed to the inherent acidity of \(\text{PdCl}_{2}\).

**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 cyclopropanol fission could be established in a way analogous to that which we have employed for thallium,\(^{11}\) i.e., by using sterosepecifically deuterated cyclopropyl alcohol 1b.\(^{22}\) 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 (\(d_{1} = 8.7 \text{ Hz}\) and \(J = 11.7 \text{ Hz}\)) and 2.05 ppm (\(d_{1} = 8.1 \text{ Hz}\) and \(J = 11.7 \text{ Hz}\)), 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.\(^{23}\) 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 4a-H and 6-H were easily identified.\(^{27}\) Similarly, excess of Br(II) 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. Stereosepecifically labeled cyclopropyl derivative 1b was treated with \(\text{Hg(NO}){\text{H}_{2}}\) and quenched with aqueous KBr in the same way as was the unlabeled analogue 1a. Analysis of the \(\text{H}^1\) NMR spectrum of the product 3b revealed the presence of the lower field resonance (3a to the corresponding lactone).

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**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 cyclopropanol fission could be established in a way analogous to that which we have employed for thallium,\(^{11}\) i.e., by using sterosepecifically deuterated cyclopropyl alcohol 1b.\(^{22}\) 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 (\(d_{1} = 8.7 \text{ Hz}\) and \(J = 11.7 \text{ Hz}\)) and 2.05 ppm (\(d_{1} = 8.1 \text{ Hz}\) and \(J = 11.7 \text{ Hz}\)), 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.\(^{23}\) 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 4a-H and 6-H were easily identified.\(^{27}\) Similarly, excess of Br(II) 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. Stereosepecifically labeled cyclopropyl derivative 1b was treated with \(\text{Hg(NO}){\text{H}_{2}}\) and quenched with aqueous KBr in the same way as was the unlabeled analogue 1a. Analysis of the \(\text{H}^1\) NMR spectrum of the product 3b revealed the presence of the lower field resonance (3a to the corresponding lactone).
configuration via 6b, furnished lactol 4b, while in the presence of MeOH, methyl acetal 5b was formed. A stoichiometric reaction, in which only Li₂PdCl₄ (1.1 equiv) was added, gave the same result. The configuration of deuterium as being 4δ was inferred from the 1H NMR spectra of the respective products: in the labeled compounds, the absence of the higher field signal (3.4 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-H configuration; the other stereoisomer could not be detected.

Heumann and Bäckvall have shown that Pdα-complexes generated, for example, from organomercurials by the PdCl₄/CuCl₂ method undergo Sn₂ 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 CF₃SO₂H. The product (4b) was identical with that formed by the PdCl₄/CuCl₂ method.

Apparently, the intramolecular Sn₂ substitution is highly favored in in situ the steric arrangement which suppresses the intervention of Cl⁻. These experiments thus provided conclusive evidence for the mechanism of the whole sequence and showed that opening of the cyclopropyl ring in 1 by Hg(II) occurred solely in a corner fashion.

Cyclopropane Ring-Opening by Hg(II) and Ti(III) in Steroidal Hydrocarbon 7. In the absence of the 6α-hydroxy group, as in the hydrocarbon 7, the reaction with (AcO)₂Pd has been reported to proceed via a simple ring-opening followed by elimination to give the acetoxy of the corresponding allylic alcohol 11 (Scheme 3). The reaction was believed to be initiated by an edge attack of Hg(II). In light of the evidence accumulated by us and by other investigators, this interpretation seems doubtful. Now, we have found that Ti(III) reacts in a similar way, giving a 72:28 mixture of allylic alcohols 11 and 12, presumably via allylic cation 10. 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.

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). Thus, on treatment with (CH₃CN)₂PdCl₂ in methanol at room temperature for 20 h, 13 was converted into the α-complex 15 (53%). The structure of 15 was corroborated by comparison of spectral methods (namely NMR) and chemical correlation: reduction of 15 with LiAPHz (which is assumed to proceed stereospecifically via a syn-delivery of hydride from Pd) afforded deuterated olefin 16, for which the 7α-2H configuration was confirmed by the coupling constant Jδ,7α-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.

21. In order to further explore the reactivity of the cyclopropane

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.


(30) The bromine-mediated conversion of 3b to the corresponding lactone 6, which would involve the carbonyl oxygen coordination to Pd followed by reductive elimination, is extremely unlikely in light of the results of Bäckvall and others.

(31) Nucleophilic Sn₂-type displacement of the palladium appears to be a common reaction and is well documented. 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 and others.

(32) (a) Wicher, O. M.; Hegedus, L. S.; Akermark, B.; Michalson, E.T.


(34) In the presence of a δ-acid (maleic anhydride, p-benzoquinone, acrylonitrile, or 2-cyclohexene-1,4-dione), this reaction takes a different course.


(36) The structure of the products was deduced from their NMR spectra and verified by comparison with authentic samples of 11δ and 11β prepared by the known methods.


Corner Opening of Cyclopropanes

Scheme 5

**Scheme 6**

BuSnH 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(NO₃)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 ¹H 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 ¹³C NMR.


- 5.7 Hz), while the proton at 3.63 ppm (J = 5.3 Hz), while the proton at 3.63 ppm (J = 5.3 Hz), while the proton at 3.63 ppm (J = 5.3 Hz), while the proton at 3.63 ppm (J = 5.3 Hz), while the proton at 3.63 ppm (J = 5.3 Hz)
softer metals might be more promising, and after several unsuccessful attempts using various transition metals, we turned our attention to copper
(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 Me3Al (69%) and Me2Zn (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 Me2CuLi, in an excellent yield (93%). This reaction can be understood in terms of the Lipshutz equilibrium between a cuprate and alkylolithium (2Me2CuLi = MeLi + Me2CuLiLi). The stereostructure of cyclobutanol 29a was corroborated by combination of NMR spectroscopy and chemical transformations:

1. Upon irradiation of 10^-CHj, an NOE (5.7%) was observed for CHOH which is compatible only with an α-configuration for the hydroxyl.

2. Alcohol 29a was oxidized with Jones' reagent to ketone 30a, whose ν(CO) = 1750 cm^{-1} was in the range typical for cyclobutanones.

3. On reduction with LiAlH4, ketone 30a furnished alcohol 31, epimeric with 29a, for which no NOE for CHOH and 10^-CHj could be observed.

When deuterated organomercurial 3b was subjected to the reaction with Me2CuLi, a steroselectively deuterated cyclobutanol 29b was obtained. In this case, the 4α-configuration of deuterium was determined in ketone 30b, which was prepared from 29b by Jones' oxidation. The 1H NMR spectrum of 30b also revealed a ca. 86% diastereoisomeric purity, which in view of the label content, indicates ≥90% overall retention of configuration at C(4). This result is compatible with double retention of configuration at C(4) through the whole sequence and with a mechanism for the cyclization step comprising intramolecular coordination of the metal to the carbonyl oxygen.

Having thus successfully accomplished intramolecular addition to the C=C 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)CH2CO2Et 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. The organomercurial 32 was first methylated with MeCu or Me2Al 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; Me2CuLi 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 Me2CuLi. This behavior suggests that the actual reactive species 34 involves copper. Although the structure of 34 is speculative, it seems reasonable to assume that M = CuLiCH3 or CuHgLICuHg-CH3, and that the more suitably positioned C(4) in the complex 34 adds across the double bond in preference to the CH3 group.

(53) (a) For transmetalation R-HgX — R-Cu, see: Bergbreiter, D. E.; Whitenedes, 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: Wigo, P. Synthesis 1993, 537.


(55) Similarly, CH==MoCl2 generated in situ from Meli and MoCl4 also converted 27 to 29a in good yield.


(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 Cp2Ti==CH2 (Tebbe reagent) was reactive enough to convert this carbonyl into an exo-methylene group.


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

(60) The signals of C(4)-protons were much better resolved in ketone 30a than in the parent alcohol 29a. Thus, in the 1H NMR spectrum of 30a, 4α-H appears at 2.90 ppm (dd, J = 17.6 and 8.6 Hz), while 4β-H gives a signal at 2.61 ppm (dd, J = 17.6 and 6.8 Hz). In the spectrum of 30b, the signal of 4α-H was reduced to ca. 14% relative to the 4β-H signal. In view of the total deuterium content (2.94%, as evidenced by MS) in ketone 30b, the corrected integration of the relative intensities of 4α- and 4β-H is indicative of a ca. 2:1 ratio of 30b to its 4α-epimer.

(61) No reaction of aldehyde 3a was observed with Ph2P==CHR (R = H, Me, or OMe) or with Ph3As==CH2, presumably due to the lower reactivity of these reagents and/or preferential coordination of P or As to Hg.
Finally, treatment of 33 (first generated in situ from 32 by means of Me$_2$Al) with Me$_2$Al/n-BuLi furnished 35 in 92% isolated yield.

Steroselective Skeletal Rearrangement of Organomercurial 3 by Means of Lewis Acids. In the previous paragraph, we have described a 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$_2$Al (a weak Lewis acid) only effected methylation on mercury (3a → 27a and 32 → 33). By contrast, we have now found that the reaction of 3a with AlCl$_3$ (a strong Lewis acid) takes a completely different course, producing 38a (Scheme 9). Similar reaction was also observed with MoCl$_5$ 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(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 "iso-steroid" rearrangement.

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

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 electron-rich center (C=O, C—CC=O, or C*), which worked remarkably well for 3 and 32, we set out to explore the reactivity of the unlabeled organomercurial 22a with the aim to close up a cyclopropane ring. To our delight, Me$_2$CuLi was found to induce cyclization, resulting in the formation of 21a (86%). This highly efficient ring-closure represents a novel way for the construction of cyclopropyl derivatives and was also accompanied with AlCl$_3$ and/or SiCl$_4$ in good yields (93% and 80%, respectively).

Unfortunately, the cuprate-mediated cyclization of 22b turned out to be nonstereospecific. Thus, starting from the 65:35 mixture of 22b and its C(19)-epimer, which originated from the ring-opening of 21b (68:32 mixture; Scheme 6), a mixture of 21b and 21c in a 53:47 ratio was formed (Scheme 10), as revealed by integration of the signals of cyclopropane protons in the $^1$H NMR spectrum (singlets at 0.47 for 21b and 0.51 for 21c). This is in sharp contrast with the highly stereohomogeneous cyclobutane ring-closure 3b → 29b (Scheme 7), where no more than 10% scrambling was observed, 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 product obtained was cyclodervative and was accompanied with AlCl$_3$ and/or SiCl$_4$ in good yields (93% and 80%, respectively).

Al is unlikely, we can conclude that the crucial ring-closure occurred predominantly with inversion at C(19) (22b → A → 21b; M = HgBr2), which is in line with the previously observed stereochemistry (36 → 37; Scheme 9). In view of these mechanistic considerations we can assign a (1S)-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 cyclopropyl derivative 21b of higher epimeric purity (such as 84:16; see above). Treatment of the enriched derivative 21b (84:16) with Hg(NO3)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 stereochemistry obtained for the lower isomeric ratio (91% d.e. see above). Hence, it can be concluded that the originally observed ratio reflected the diastereoselectivity 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 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 3913 and its methylated counterpart14 (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 Br2 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 43 with Pd(II) demonstrates that edge opening is indeed possible with our type of compounds, i.e. that the polycyclic structure itself does not originate elsewhere. In the cyclobutane ring formation, one can consider the transition 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 cyclopropanation when cuprates or Lewis acids are used, respectively (compare Schemes 3 and 9). Since no difference in hybridization at the carbon atom adjacent to mercury has been observed for 3a and 22a,27 the difference in lability must originate elsewhere. In the cyclobutane ring formation, one can assume frontier interaction of the σ-orbital of the C-[M] bond with the 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 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 3913 and its methylated counterpart14 (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 Br2 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 43 with Pd(II) demonstrates that edge opening is indeed possible with our type of compounds, i.e. that the polycyclic structure itself does not originate elsewhere. In the cyclobutane ring formation, one can consider the transition 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 cyclopropanation when cuprates or Lewis acids are used, respectively (compare Schemes 3 and 9). Since no difference in hybridization at the carbon atom adjacent to mercury has been observed for 3a and 22a,27 the difference in lability must originate elsewhere. In the cyclobutane ring formation, one can assume frontier interaction of the σ-orbital of the C-[M] bond

**Scheme 11**

![Scheme 11](image)

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

The two isoelectronic cations (Tl+ and Hg2+) 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 Me2CuLi, 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 approaches68 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 reported12 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 cyclopropanation when cuprates or Lewis acids are used, respectively (compare Schemes 3 and 9). Since no difference in hybridization at the carbon atom adjacent to mercury has been observed for 3a and 22a,27 the difference in lability must originate elsewhere. In the cyclobutane ring formation, one can assume frontier interaction of the σ-orbital of the C-[M] bond

**Discussion**

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The preferential edge opening by transition metals and halogens has been attributed to the back-donation from the electrone of the LUMO Walsh orbitals, which stabilizes the transition state.11,12 By contrast, electrophiles incapable of back-donation (H+, Hg2+, and Tl+) 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 Sn2-like reaction with an external nucleophile.33 (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 intermediates very closely stereosemate to the corner-metalated species via a trigonal bipyramidal.
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 organomercury.

Experimental Section

General Methods. Melting points were determined on a Kofler block and are uncorrected. The optical rotations were measured in CHCl₃ with a Perkin-Elmer 141 polarimeter at 22 °C with an error of ±1°.

The NMR spectra were recorded for CDCl₃ solutions at 25 °C on a Varian Unity 400 (operating at 400 MHz for 1H, 100.6 MHz for 13C, and 61.4 MHz for 19F), Varian XL-300, or Bruker AM 300 spectrometer. Chemical shifts were initially referenced to TMS via the solvent signals (7.26 ppm for 1H and 77.0 ppm for 13C). The 19F NMR spectra were recorded on a Varian XL-300 instrument (at 57.7 MHz) and referenced to external PhF (CDCl₃-solution) at -80.5 ppm. Diastereomeric ratios for 22b and 24b were determined by 1H NMR (61.4 MHz); spectra were recorded for CHCl₃ 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 each diastereomer were used for calculation (primitive line-shape). The Vc-H values were determined from 1H traces of HMQC spectra. Standard software supplied by the manufacturer was used throughout. The IR spectra were recorded on a Perkin-Elmer 621 instrument. The mass spectra was measured on a JEOL JMS-D100 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(aq), water, and 5% KHC₂O₃ (aqueous) and drying with MgSO₄.

Conclusions

In conclusion, we have achieved a unique regio- and stereo-selective 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). Stereoselective deuteration (1b and 2b) provided further evidence to support the concept of preferred corner opening of the cyclopropane ring by poor back-donors (H⁺, Hg²⁺, and Tl⁺ 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 Hg²⁺, 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 S₂2 displacement (3 → 6 → 4); (2) the unprecedented Cu-facilitated construction of the cyclobutane ring via the


Lactol (4a). Method A. To a solution of 1a (410 mg; 1.06 mmol) in dioxane (12 mL) and water (2 mL) were added 10% aqueous HClO4 (2 mL) and thallium nitrate trihydrate (570 mg; 1.28 mmol), and the mixture was stirred 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 (1:1) as a solvent; mp 155-157 °C (aqueous acetone); IR (CHCl3) 1640, 1540, 1450, 1300, 1210 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 6.03 (s, 3 H, 18-H), 1.08 (s, 3 H, 19-H), 4.15 (d, 1 H, J = 9.2 Hz, 4a-H), 9.24 (s, 1 H, 3-H); 13C NMR (75.4 MHz, CDCl3) δ 122.41 (d), 18.53 (d), 18.75 (q), 24.26 (t), 27.94 (d), 28.11 (t), 28.19 (d), 28.24 (t), 28.29 (d), 28.31 (t), 29.39 (d), 31.07 (q), 31.75 (t), 35.56 (d), 35.66 (dd), 36.10 (t), 36.22, 37.89, 39.48, 39.74, 40.94, 43.68, 49.15, 53.04, 55.09, 55.68, 56.58, 64.99, 101.20.

3-Hydroxymethyl)A-nor-cholesta-3,5-diene (5a). To a solution of 12 (80 mg; 0.38 mmol) in dioxane (230 mL) and aqueous 10% perchloric acid (0.4 mL) in dioxane (8 mL) was stirred at rt for 4 h. The mixture was then diluted with ether, the precipitate was filtered off, and the organic phase was worked up as usual. The crude product was chromatographed on silica gel (10 g) using hexane, which eluted lipophilic impurities, followed by hexane-ether (1:1) mixture to yield 12 (36 mg; 26%); mp 56-58 °C (aqueous acetone; lit.27 gives 58 °C; [α]25 +20°; 27. Ch: 81.44 (s), 107.33 (s), 127.42 (s), 128.00 (d), 132.52 (t), 135.70 (d), 136.07 (d), 136.12 (t), 139.48 (t), 140.04 (d), 143.68 (d), 49.15 (d), 53.04 (s), 55.09 (d), 55.68 (d), 56.58 (d), 64.99 (s), 101.20 (d); LRMS m/z 403 (M*).

Methyl acetal (5a). To a solution of 1a (61 mg; 0.17 mmol) in methanol (10 mL) and water (1 mL) was added 20% aqueous KOH (1 mL) and MgO (0.05 mL). The solution was stirred for 15 min. The excess of reagent was decomposed with water, the mixture was then diluted with ether, the precipitate was filtered off, and the organic phase was worked up as usual. The crude product was chromatographed on silica gel (10 g) using hexane, which eluted lipophilic impurities, followed by hexane-ether (1:1) mixture to yield 12 (38 mg; 25%); mp 56-58 °C (aqueous acetone; lit.27 gives 58 °C; [α]25 +20°; 27. Ch: 81.44 (s), 107.33 (s), 127.42 (s), 128.00 (d), 132.52 (t), 135.70 (d), 136.07 (d), 136.12 (t), 139.48 (t), 140.04 (d), 143.68 (d), 49.15 (d), 53.04 (s), 55.09 (d), 55.68 (d), 56.58 (d), 64.99 (s), 101.20 (d); LRMS m/z 403 (M*).
compound: mp 83-84 °C (lit.4 gives 83.7-84.4 °C); [α]D +40° (c 1.9); 1H NMR 0.86 (s, 3 H, 18-H), 1.18 (m, W = 29 Hz, 1 H, 18-H), 2.39 (m, W = 9 Hz, 2 H, 19-H), 3.06 (m, W = 11 Hz, 3 H, 19-H); 13C NMR 31.4, 39.3, 50.6, 50.8, 120.7, 126.8, 128.0, 128.4, 137.1. HRMS: m/z 401 (M+Na+) C21H34O2S2. Anal. Calcd for C % 83.59; H, 12.19; S, 4.22. Found: C, 83.45; H, 12.15; S, 4.17.

(9S)-[19H]-Cholest-5-ene-3,19-diol-3-Monoacetate (18b). To a solution of aluminium chloride (40 mg) in dry DME (5 mL) at rt for 12 h and stirred at -78 °C for 5 min and then quenched with water. The product was extracted with ether and then with saturated aqueous NaHCO3, and the solvent was evaporated. The residue was chromatographed on silica gel (30 g) using a petroleum ether-10%98% ethyl acetate (9:1) as eluent to give 26 (23 mg; 69%), identical with an authentic sample: mp 95-96 °C. 

(19S)-[19H]-19-(Bromomercurio)methyl)-5^-cholestan-3-one (23). To a solution of organomercurial 24a (200 mg, 0.56 mmol) in THF (10 mL) at rt for 30 min under argon and then cooled to -78 °C. A precooled (-20 °C) solution of the organomercurial 

(DME); [α]D +67° (c 5.5); IR ν(C=O) 1705 cm-1; 1H NMR 0.75 (s, 3 H, 18-H), 2.20 and 2.51 (AB system, two d, J = 13.8 Hz, 2 H, 19-H). 

(19R)-[19H]-5^-Cholest-5-en-3-one (21a). Method A. To a stirred suspension of copper(I) iodide (266 mg; 0.060 mmol) in benzene (5 mL) was added dropwise tert-butyllithium (1.64 g; 22.13 mmol) in ether (2 mL) at -78 °C. The mixture was then poured on to ice and water, and the product was extracted with ether, and the ethereal solution was worked up to yield a crude mixture of isomeric organomercurials. The mixture was chromatographed on silica (30 g) using an ethyl acetate-10%98% petroleum ether (4:1) as eluent to give 27 (23 mg; 69%), identical with an authentic sample: mp 117-120 °C. 

5-Methyl-19-norcholesterol-9-en-3-one (26a). A solution of 25a (40 mg; 0.060 mmol) in benzene (5 mL) was refluxed with triethylsilane (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% KClO3 (aqueous), and dried with Na2SO4, and the solvent was evaporated. The residue was chromatographed on silica gel (2g) with a petroleum ether-ether mixture (9:1) as eluent to give 28 (23 mg; 69%), identical with an authentic sample: [α]D +18° (c 2.0); lit.4 gives +20°; IR ν(C=O) 1713 cm-1; 1H NMR 0.82 (s, 3 H, 18-H), 1.03 (s, 3 H, 5^-methyl).

35-(Methylmercury(methyl))-25^-cholestan-5-carboxaldehyde (27). Method A. To a stirred suspension of copper(I) iodide (266 mg; 0.060 mmol) in THF (10 mL) at -78 °C was added dropwise tert-butyllithium (1.64 g; 22.13 mmol) in ether (2 mL) at -78 °C. The mixture was then poured on to ice and water, and the product was extracted with ether, and the ethereal solution was worked up to yield mesylate 19b (330 mg, 88% yield).
A-Homo-B-nor-3,5-cyclo-5a-cholestan-6-one (30a). The alcohol 29a
was crystallized from aqueous acetone to give ketone 30a (135 mg; 78%); showing
one spot on TLC: mp 100-105 °C (Me2CO, H2O); [4a*S]-A-Homo-B-nor-3,5-cyclo-5a-cholestan-6-one (30b): mp 260-263 °C (20 mL), 5% aqueous
HCl (2 x 20 mL), saturated KHCO3 (2 x 20 mL), saturated aqueous KBr (1 x 20 mL), and water (2 x 20 mL) and dried with 
Na2SO4. 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 (2:1:1) to give 32 (2.02 g; 73%), showing one spot on TLC: mp 100-105 °C (Me2CO, H2O); [4a*S]-A-Homo-B-nor-3,5-cyclo-5a-cholestan-6-one (30b): mp 98-99 °C; 1HNMR δ 0.67 (s, 3 H, 18-H), 0.91 (s, 3 H, 19-H), 1.24 (d, 6H, J = 6.8 Hz, 4-6H); 2.50 (dd, 1H, J1 = 17.6 Hz, J2 = 7.0 Hz, 18-Ha); 2.85 (s, 3H, 19-OCH3); 4.25 (d, 2H, J = 10.6 Hz, C8-H); 5.92 (d, 1H, J = 6.8 Hz, 4-6H); 5.92 (s, 3H, 18-H); 0.25 (s, 3H, C6H3N); 16.0 Hz C(=O)CH2Et); 212.97 (s); MS m/z 497 (20%); 479 (10%); 461 (100); 443 (30); 425 (30); 407 (20); 399 (20); 381 (20); 363 (20); 345 (20); 327 (20); 309 (20); 291 (20); 273 (20); 255 (20); 237 (20); 219 (20); 201 (20); 183 (20); 165 (20); 147 (20); 129 (20); 111 (20); 93 (20); 75 (20). NOE difference experiments: irradiation of 4a-H (at δ 2.90) resulted in the increase of 4b-H (19.6%) and 2b-H (8.6%); irradiation of 4b-H (at δ 2.61) resulted in the increase of 2b-H (17.8%) and 2a-H (13.2%). Anal. Calcd for C29H48O2: C, 83.87; H, 11.9%. Found: C, 83.89; H, 11.80.

A-Homo-B-nor-3,5-cyclo-5a-cholestan-6-ol (31). Ketone 30a (210 mg; 0.56 mmol) in dry ether (20 mL) was treated with LiAlH4 (50 mg) at -10 °C for 5 min. The excess of reagent was decomposed with 10% aqueous HCl at -78 °C and the mixture was 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). [4b*S]-A-Homo-B-nor-3,5-cyclo-5a-cholestan-6-one (30b). Method A. To a solution of 32 (120 mg; 0.16 mmol) in dry THF (5 mL) was added a 2 M solution of trimethylaluminum in hexane (0.5 mL; 2.5 equiv) at -78 °C. The mixture was stirred at this temperature for 1 h, then 1.6 M solution of butyllithium in hexane (2.8 mL; 4.5 equiv) was added and the mixture was stirred at -78 °C for 2 min. 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 stirred at the same temperature for 1 h. The excess of reagent was decomposed by methanol, 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 stirred at rt for 30 min. The progress of the 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 x 20 mL), 5% aqueous HCl (2 x 20 mL), saturated KHCO3 (2 x 20 mL), saturated aqueous KBr (1 x 20 mL), and water (2 x 20 mL) and dried with 
Na2SO4. 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 (Me2CO, H2O); [4b*S]-A-Homo-B-nor-3,5-cyclo-5a-cholestan-6-one (30b): mp 98-99 °C; 1HNMR δ 0.67 (s, 3 H, 18-H), 0.91 (s, 3 H, 19-H), 1.24 (d, 6H, J = 6.8 Hz, 4-6H); 2.50 (dd, 1H, J1 = 17.6 Hz, J2 = 7.0 Hz, 18-Ha); 2.85 (s, 3H, 19-OCH3); 4.25 (d, 2H, J = 10.6 Hz, C8-H); 5.92 (d, 1H, J = 6.8 Hz, 4-6H); 5.92 (s, 3H, 18-H); 0.25 (s, 3H, C6H3N); 16.0 Hz C(=O)CH2Et); 212.97 (s); MS m/z 497 (20%); 479 (10%); 461 (100); 443 (30); 425 (30); 407 (20); 399 (20); 381 (20); 363 (20); 345 (20); 327 (20); 309 (20); 291 (20); 273 (20); 255 (20); 237 (20); 219 (20); 201 (20); 183 (20); 165 (20); 147 (20); 129 (20); 111 (20); 93 (20); 75 (20). NOE difference experiments: irradiation of 4a-H (at δ 2.90) resulted in the increase of 4b-H (19.6%) and 2b-H (8.6%); irradiation of 4b-H (at δ 2.61) resulted in the increase of 2b-H (17.8%) and 2a-H (13.2%). Anal. Calcd for C29H48O2: C, 83.87; H, 11.9%. Found: C, 83.89; H, 11.80.
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 etheral 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%): \( \delta_{\text{d}} = 18^\circ \) (c 6.8); IR \( 1728 \text{ cm}^{-1} \); 'H NMR \( 0.65 \) (s, 3 H, 18-H), 0.96 (s, 3 H, 19-H), 1.28 (t, J = 7.1 Hz, 3 H, CH\(_3\)CH\(_2\)O), 2.26 (q, 2 H, J = 7.1 Hz, CH\(_2\)CH\(_3\)O); 13C NMR \( 12.18 \) (q), 14.17 (q), 17.28 (q), 18.64 (q), 21.93 (t), 22.42 (q), 22.67 (q), 23.69 (q), 24.37 (q), 26.95 (q), 27.86 (q), 28.43 (q), 29.06 (q), 30.68 (q), 35.22 (q), 36.02 (q), 36.11 (q), 37.46 (q), 39.36 (two t), 39.76 (q), 40.90 (q), 43.82 (q), 46.53 (q), 52.84 (q), 55.57 (q), 56.90 (q), 59.93 (q), 60.21 (q), 173.20 (q). Anal. Calcd for C\(_{17}\)H\(_{34}\)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 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 precooled (-20 °C) solution of 32 (78 mg; 0.1 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\(_4\)Cl, 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.

35-Chloro-5-cholestene (38a): A mixture of 3a (100 mg) and aluminium 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 etheral solution was worked up. Chromatography on silica (5 g) with petroleum ether yielded 38a (48 mg; 79%): \( \delta_{\text{d}} = 94-96 \) °C (ethyl acetate; Fluka catalog gives 94-96 °C); \( 1^H \) NMR \( 0.68 \) (s, 3 H, 18-H), 1.04 (s, 3 H, 19-H), 2.49 (ddd, \( J_{2,4,6} = 13.5, J_{2,3,4} = 5.1, J_{3,4,6} = 2.1 \) Hz, 1 H, 4a-H), 3.56 (m, 1 H, 4b-H), 3.77 (m, \( W = 32.7 \) Hz, 1 H, 3a-H), 5.38 (brd, \( J = 5.2 \) Hz, 6-H); \( 1^C \) NMR \( 11.87 \) (q), 18.73 (q), 19.27 (q), 20.97 (q), 22.58 (q), 22.84 (q), 23.83 (q), 24.28 (q), 28.03 (d), 28.23 (t), 31.79 (d), 31.84 (t), 33.39 (t), 35.79 (q), 36.19 (t), 36.38 (s), 39.12 (t), 39.52 (t), 39.71 (t), 42.31 (s), 43.41 (s), 50.07 (d), 56.14 (d), 56.69 (d), 60.33 (d), 122.46 (d), 140.77 (s); MS \( m/z \) 406 (34, \( M^+ \)), 404 (91).

\[ \text{[4\text{d}^3\text{H}]35\text{-Chloro-5-cholestene (38b): mp 94-96 °C; } 1^H \text{ NMR } 0.71 \text{ (s, 3 H, 18-H), 1.06 (s, 3 H, 19-H), 2.50 (m, } W = 6 \text{ Hz, 1 H, 4e-H), 3.80 (m, } W = 19.7 \text{ Hz, 1 H, 3a-H), 5.48 (dd, } J = 5.5 \text{ and } 2.0 \text{ Hz, 1 H, 6-H); MS } \geq 95\% \text{ [d]} \text{ (d).} \]


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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. 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.

We have recently described a stereoelectronically controlled cleavage of 3α,5-cyclo-5α-cholestan-6α-ol (1a) by mercury(II) that afforded the rearranged organomercurial 2a (97%) as a stable compound (Scheme 1).

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.

Herein, we report on the stereospecific rearrangement of the organomercurial 2a 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 MoCl₅ 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 (3a) as a stable compound (Scheme 1).

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 C₃₀ (4a → 5a). The cationic center in 5a is likely to interact with the nucleophilic carbon C₁₈ to generate cyclopentyl intermediate 7a. The latter species should subsequently collapse to cholesteryl chloride (3a) via the well known "iso-steroid" rearrangement.

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

(7) Model experiments demonstrated that both 3α,5-cyclo-5α-cholestan-6β-ol and cholesterol are readily converted to 3a on treatment with MoCl₅ in Et₂O at rt. 5α-Cholesterol-35-ol was converted by the same reagent to a ca. 1:1 mixture of the corresponding 3α- and 3β-chlorides, which indicates Σ₅₂₁ mechanism, in contrast to the former, stereoelectronically controlled substitution.
(8) The (dR)-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 C₂₀ (4a → 5a) was established via chemical correlation. On treatment with Pd(II), the organomercurial 2b was converted into the lactol 14b in which the configuration at C₂₀ (4a → 5a) was established via chemical correlation. On treatment with Pd(II), the organomercurial 2b was converted into the lactol 14b in which the configuration at C₂₀ (4a → 5a) was established via chemical correlation. On treatment with Pd(II), the organomercurial 2b was converted into the lactol 14b in which the configuration at C₂₀ (4a → 5a) was established via chemical correlation.
retention of configuration in the transmetallation step\(^4\) (2b \(\rightarrow\) 4b), the coordination of Mo to the carboxylic oxygen requires rotation about the C\(_{\text{carbonyl}}\)-C\(_{\text{O}}\) bond. Subsequent Wagner–Meerwein migration will generate cationic species 5b in which the C\(_{\text{carbonyl}}\)-C\(_{\text{O}}\) bond formation should occur with the geometry imposed by the cyclic C\(_{\text{O}}\). The resulting cyclopropyl intermediate 7e should then produce 4\(\alpha\)-H1-cholesteryl chloride (8e). Alternatively, MoCl\(_6\) 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 cyclopropene ring-closure is most likely to occur with inversion of configuration at C\(_{\text{O}}\) (6b \(\rightarrow\) 7b) due to the preferred conformation (6b) so that 4\(\alpha\)-H1-cholesteryl chloride (2b) 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\(_6\) was carried out in the same way as for its unlabeled counterpart 2a. Analysis of the \(\text{H}^1\) NMR spectrum of the resulting deuterated cholesteryl chloride established the configuration of deuterium as being \(\text{d} 4\) (i.e. \(\text{d} 3\) rather than \(\text{d} 5\))\(^\#\) and revealed that the whole reaction sequence was remarkably stereoselective, as no other diastereoisomer could be detected by NMR. The 4\(\alpha\)-H1 configuration is compatible with inversion of configuration at C\(_{\text{O}}\) in the C\(_{\text{carbonyl}}\)-C\(_{\text{O}}\) bond-forming step (6b \(\rightarrow\) 7b). The other pathway (5b \(\rightarrow\) 7e) can thus be excluded as it would require retention at C\(_{\text{O}}\).\(^\#\)

The exact structure of 6\(\alpha\) 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\(_{\text{carbonyl}}\)'s electron-deficient center. If, however, transmetallation had occurred, retention of configuration at C\(_{\text{O}}\) is assumed.\(^\#\)

This analysis suggests that MoCl\(_6\) serves as a Lewis acid and that transmetallation 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\(_6\), however, turned out to be superior in terms of the reaction rate and purity of the product.\(^\#\)

The stereochemistry of this transformation was tested for AlCl\(_3\) and found to be identical with that of the MoCl\(_6\) reaction (i.e. 2b \(\rightarrow\) 3b).\(^\#\)

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\(_3\)SO\(_3\)\(_2\) in place of the aldehyde oxygen might also induce the skeletal rearrangements\(^\#\) 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 cholestene (12). In the solvolysis of 9, the departure of the CH\(_3\)SO\(_3\) group is accompanied by Wagner–Meerwein rearrangement to generate the corresponding C\(_{\text{O}}\)-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\(_6\) and other Lewis acids activate 2a 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\(_{\text{O}}\).


Since MoCl\(_6\) is known to react with THF to give THF-MoCl\(_6\), the latter is likely to be the actual reagent in this case.
Reactions in Organic Synthesis; all reactions were carried out under nitrogen. Standard workup: petroleum ether refers to the fraction boiling in the range 40-60 °C. Water, and to RT, diluted with ether (20 mL), washed with water (5 X 5 mL), and no impurities detectable in the NMR spectrum. The solvent was evaporated and the residue was purified and characterized, its structure was determined by the silver(I)-mediated conversion to lactol 14a. The same reaction carried out with 2b showed that 13 was formed nonstereospecifically as a ~2:1 mixture of 13a and its C(18) 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 and stereoelectronic effects. The proposed mechanism is supported by stereospecific labeling and by analogous results in the solvolysis of 9.

**Experimental Section**

General Methods. Melting points were determined on a Kofler block and are uncorrected. The optical rotations were measured in CHCl₃ with a Perkin-Elmer 141 polarimeter at 23 °C with an error of ±1 °C. The NMR spectra were recorded for CDCl₃ solutions at 25 °C on a Varian Unity 400 (operating at 400 MHz for ¹H, 100.6 MHz for ¹³C, and 61.4 MHz for ³¹P). All chemical shifts were 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% KHCO₃ (aqueous) and drying with MgSO₄.

**35-Chloro-5-cholestene (3a).** Molybdenum(V) chloride (50 equiv) was added in small portions to a solution of 5% aqueous K₂CO₃ (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 mL) and methanol (2 mL) and 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%); [α]D +15° (c 1.5). IR ν(OH) 3420, 3595 cm⁻¹; ¹H NMR 0.86 (s, 3 H, 18-H), 0.91 (d, J = 6.5 Hz, 2 H, 16-H), 0.92 (d, J = 2.0 Hz, 1 H, 6-H), MS m/z % 370 (34, M⁺), 355 (69), 147 (100), 119 (26), 109 (29), 93 (90), 79 (43), 57 (100).

**35-Chloro-5-cholestene (3b).** mp 94-96 °C; ¹H NMR 0.71 (s, 3 H, 18-H), 1.06 (s, 3 H, 19-H), 2.50 (m, 2 H, 1 H, 6-H), 3.80 (m, 1 H, 3-H, 19-H), 5.48 (dd, J = 5.3, J = 1.1 Hz), 5.1 ppm (s, 1 H, 5-H). The solvent was evaporated and the residue was purified and characterized, its structure was determined by comparison with an authentic sample. The solvent signals (7.26 ppm for ¹H and 3.89 ppm for ¹³C) were indirectly referenced to TMS in CHCl₃ with a Perkin-Elmer 141 polarimeter at 23 °C. The solvent signals were measured in CHCl₃ with a Perkin-Elmer 141 polarimeter at 23 °C.

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 MgSO₄. 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%): ¹H NMR δ 0.74 (s, 3 H, 18-H), 1.13 (s, 3 H, 19-H), 2.17 (s, 3 H, 4-H); ¹³C NMR δ 11.97 (q), 18.58 (q), 20.50 (q), 21.40 (t), 22.54 (q), 22.79 (q), 23.73 (t), 24.22 (t), 27.99 (d), 28.06 (t), 28.37 (t), 29.58 (q), 31.44 (t), 34.87 (d), 35.69 (d), 36.09 (t), 38.19 (t), 38.80 (t), 39.26 (t), 39.47 (t), 42.51 (s), 48.05 (d), 50.31 (s), 55.79 (d), 56.01 (d), 208.18 (s), 215.20 (s). Anal. Calcd for C₂₀H₂₃O₂: 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).

₃⁻-Chloromethyl-A,B-bisnor-5β-cholestane-5-carbaldehyde (13a). Molybdenum(V) chloride (200 mg) was introduced in small portions to a solution of organomercurial 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, J₉₁₅ = 12.9 Hz, J₂₆₂₆ = 6.5 Hz, 1 H, 7j); ³⁵Cl NMR δ 7.5-8.0 (t, J = 7.5 Hz, 2 H, 4-H), 7.82 (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, 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 MgSO₄. 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.

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