Mechanistic Studies of the Palladium(II)–Copper(II)-mediated Demercuriation of Cycloalkyl and Cycloalkylmethyl Systems

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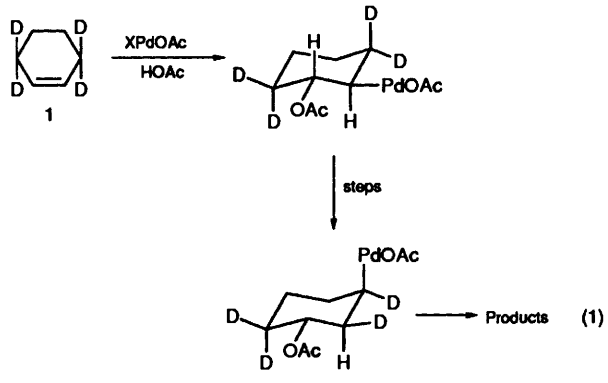
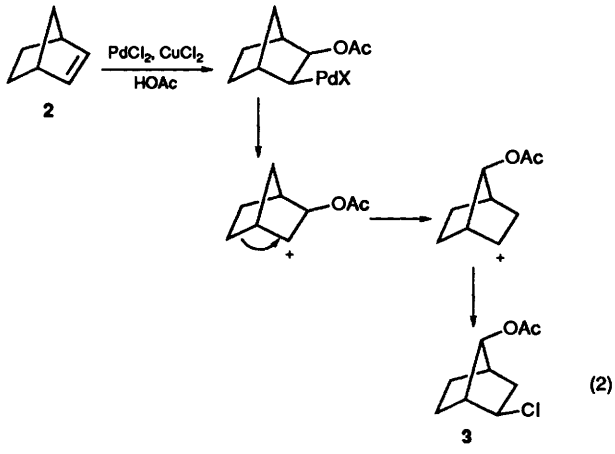
The likely events involved in the conversion of cyclohexylmethylmercuric chloride into predominantly *trans*-4-methylcyclohexyl chloride, on treatment with $PdCl_2$–$CuCl_2$ in acetic acid, have been identified by product and deuterium-labelling studies, as well as by the behaviour of probable intermediates. Extension to related cycloalkyl- and cycloalkylmethyl-mercuric chlorides is reported, and mechanistic changes occur as a function of ring size, with elimination–re-addition of [HPdX] being important in cyclohexyl systems, but carbocation formation dominating in cyclooctyl cases.

Palladium-mediated organic transformations are now of major importance in synthetic organic chemistry, and palladium–carbon bond formation and subsequent cleavage are often central to these processes.[1,2] Oxidative cleavage is one of the methods commonly employed for Pd–C bonds,[3] which are generally sluggish in hydrolyses, and the oxidant presumably functions by converting the palladium moiety into a leaving group for nucleophilic attack at the palladium-bearing carbon.[4] Cupric chloride has been extensively used in the role of oxidant, particularly in some palladium-catalysed oxidations of alkenes,[5] described mainly by Henry.[5,6] Oxidant systems other than Cu^{II} have also been employed, and oxidation of alkenes by salts other than Pd^{II}, in the presence of Cu^{II}, has also been examined

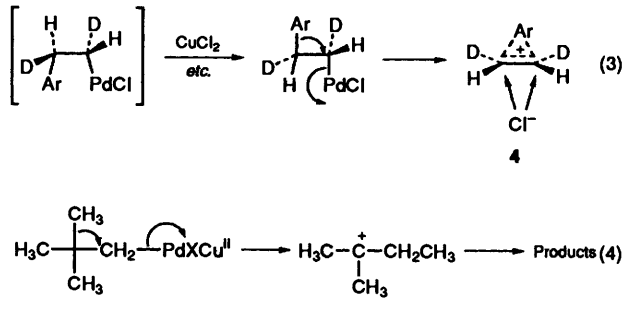
The manner in which Cu^{II} transforms the C–Pd bond, so that 'Pd' is now a better leaving group, is not certain, but the suggestion by Henry that electron transfer from the Pd^{II}–C bond to a Cu^{II}–Pd^{II} polynuclear complex occurs, is very reasonable.[6,7] The use of Cu^{II}–Cl_2 diverts the normal production of vinyl and allylic acetates from Pd^{II} and alkenes alone, to saturated acetate esters of glycols and chloro alcohols[5,6] and stereochemical features among the product types have been identified in the oxidation of the cyclohexene **1**.[8] *trans* Acetoxypalladiation was concluded to be followed by a stepwise movement of Pd^{II} around the ring, by *cis*-[HPdX] eliminations and re-additions, prior to substitution by chloride or acetate[7] [eqn. (1)]. There appears to be no information concerning similar oxidations of higher cycloalkenes.



Evidence for carbocation involvement in the oxidative cleavage of [RPdCl] by Cu^{II} has also been provided. Treatment of norbornene **2** in glacial acetic acid, with palladium chloride and copper chloride, led to the formation of *exo*-2-chloro-*syn*-7-acetoxynorbornene **3**[9] a useful precursor of *syn*-norbornen-7-ol. The suggested pathway involved acetoxypalladiation followed by C–Pd heterolysis and rearrangement, prior to *exo*-capture by chloride [eqn. (2)]. Bäckvall[10] has provided evidence for

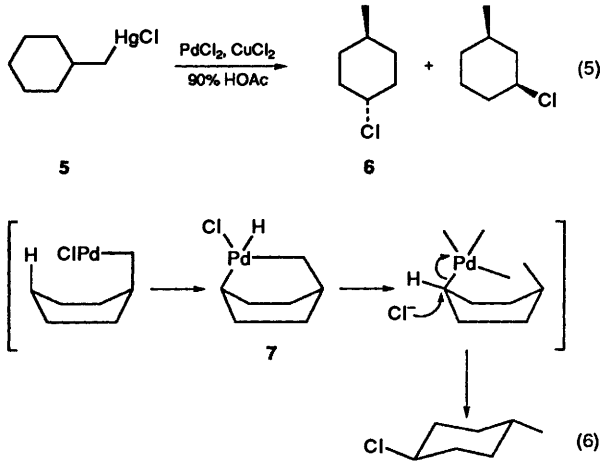


cation involvement in the Cu^{II}-mediated cleavage of phenethylpalladium bonds, in which phenyl participation is invoked, and a symmetrical phenonium ion suggested **4**, largely on the basis of deuterium-labelling results and *threo*-product formation [eqn. (3)].



Phenyl participation in the solvolytic demercuriation (C–Hg heterolysis) of various phenethylmercuric perchlorates has also been suggested on the basis of significant solvolysis rate enhancements.[11] There is also strong evidence for cation intermediacy in the Pd^{II}–$CuCl_2$ promoted demercuriation of neopentylmercuric chloride with rearranged tertiary acetate and chloride, and methylbutenes being formed[12] [eqn. (4)]. However, Heumann and Bäckvall invoked a fundamentally different process to account for the product profile when cyclohexylmethylmercuric chloride **5** was treated with $PdCl_2$–$CuCl_2$ in 90% acetic acid in the absence of chloride ion. The major product, *trans*-4-methylcyclohexyl chloride **6** (74%) was

accompanied by a low-level of the *cis*-3-isomer and some unidentified products [eqn. (5)]. Although Heumann and Bäckvall considered the operation of a series of eliminations and readditions of [HPdX], followed by chloride substitution, as proposed by Henry,[6,13] the absence of elimination products and the stereoselectivity were considered to argue against such a route. The favoured pathway[12] involved a *trans*-annular 1,5-H migration *via* a cyclic seven-membered transition state and a 'palladabicyclooctane' intermediate **7**, as shown in eqn. (6).

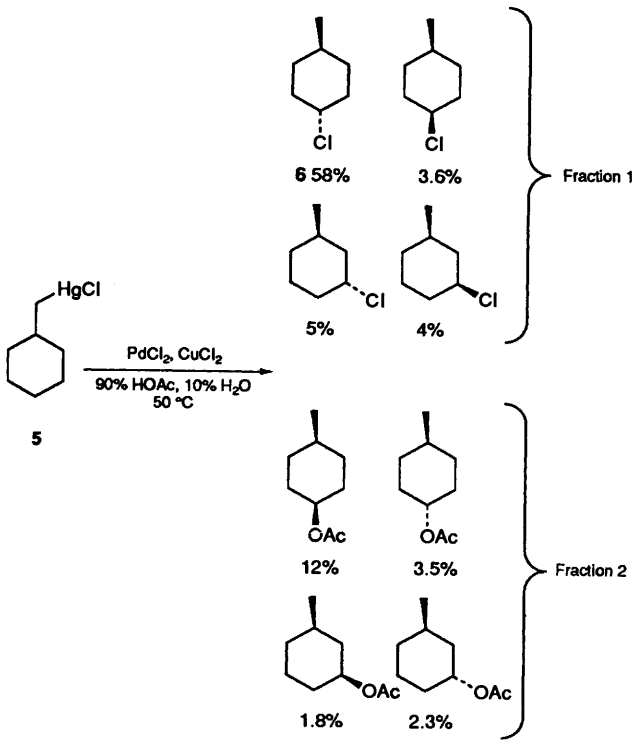


This course of events would explain the *trans*-annular functionalisation resulting in formation of *trans*-4-methylcyclohexyl chloride **6**. The implications of these suggestions for C–H activation were recognised[12] and in view of the established propensity of medium-ring carbocycles to exhibit *trans*-annular reactivity, and in this case of possible direct *trans*-annular insertion of palladium into a C–H bond, we decided a detailed study of this system was required. We now report the results of this study, in which a variety of cycloalkyl and cycloalkylmethyl systems have been examined, some by ^{2}H-labelling methods.[14]

Results and Discussion

(a) *Reaction of Cyclohexylmethylmercuric Chloride* (**5**) *with* Pd^{II}–Cu^{II}.—Cyclohexylmethylmercuric chloride was treated with $PdCl_2$ and $CuCl_2$ in the solvent system 90% CH_3CO_2H–10% H_2O, as previously described.[12] The crude reaction product was analysed by capillary gas chromatography, and two groups of compounds were evident, with very similar retention times for components within each group. Combined gas chromatography–mass spectrometry established the earlier eluting group consisted of chlorides, and the later eluting group of acetates. This separation permitted the collection of each group by preparative gas chromatography on a non-polar column. Subsequent examination of each of the two separated groups showed the components within each group to be unaltered by the separation and collection procedures. High-field (400 MHz) ^{1}H and ^{13}C NMR spectra were obtained for each fraction, and the individual components were identified by comparing the ^{1}H and ^{13}C NMR spectra obtained with those of authentic compounds, which were synthesised from the corresponding alcohols. The outcome of this reaction is shown in Scheme 1, with six minor components constituting the unidentified fraction (10%).

This product profile is similar to that reported[12] in that the major product is *trans*-4-methylcyclohexyl chloride **6** but the acetates were not previously identified. All diastereoisomers of the 3- and 4-methylcyclohexyl chlorides and acetates are present (Scheme 1), but the 2-isomers are absent. The configuration of the major acetate is opposite to that of the major chloride, but

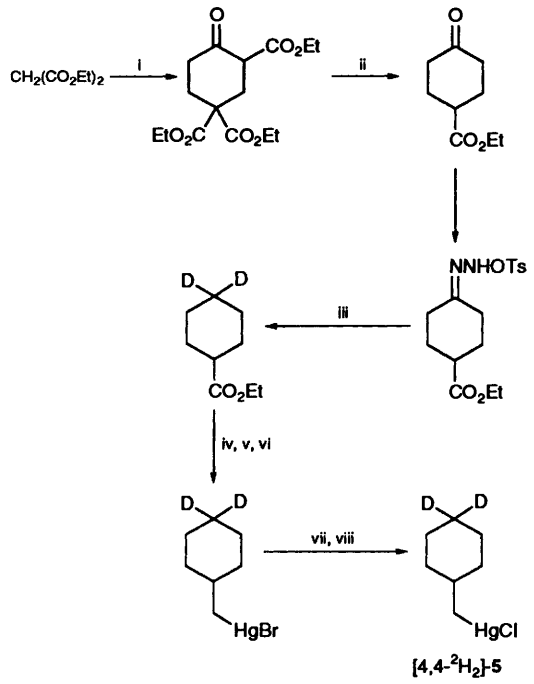


Scheme 1

we are disinclined to comment in detail on the significance of the stereochemistry of the minor chlorides and acetates. Use of 90% CD_3COOD–10% D_2O resulted in no ^{2}H incorporation into the products, as judged by careful ^{2}H and ^{13}C NMR studies, and there was no loss of ^{2}H (when the various labelled starting materials were utilised) to the protio solvent system.

The palladabicyclooctane route [eqn. (6)] envisages the transfer of a hydrogen atom at C-4 ultimately into the CH_3 group. To investigate this feature, ^{2}H labelling at C-4 was undertaken, and we were hopeful that direct ^{2}H NMR spectroscopy would provide a sufficiently sensitive analytical tool for determining the initial and final ^{2}H locations, and relative amounts. Fortunately, this was indeed the case. The procedure shown in Scheme 2 was developed to provide the [4,4-$^2H_2$]cyclohexylmethylmercuric chloride, and is based on the work of Sanches[15] who described the double Michael addition of diethyl malonate to ethyl acrylate. The ketonic ester was converted into the 4,4[$^2H_2$] derivative predominantly, by [$^2H_4$]borodeuteride–acetic acid reduction of the tosylhydrazone.[16] Full details are in the Experimental section.

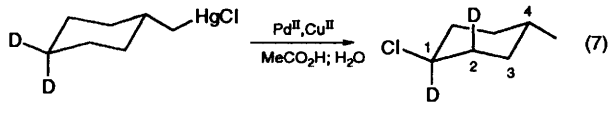
The product mercurial was identical with unlabelled **5**, except for ^{2}H effects, and the ^{2}H NMR spectrum was compared with that of the fully assigned ^{1}H NMR spectrum of **5**, in which 4ax-H (δ 1.07) and 4eq-H (δ 1.60) were readily assigned. The ^{2}H NMR spectrum showed major signals at δ 1.05 and 1.62 of equal intensity, confirming that deuterium predominantly was attached to C-4. Minor signals at δ 1.22 and 1.7 were also present and correspond to 3,5ax-H and 3,5eq-H, indicating some ^{2}H incorporation α to the tosylhydrazone or an intermediate in the reduction step. Labelled mercurial, 4,4[$^2H_2$]-**5** was treated under the described conditions, and the product mixture separated into two fractions as described previously. The chloride fraction was analysed by ^{1}H, ^{2}H and ^{13}C NMR spectroscopy, with the ^{2}H NMR spectra of this fraction defining the location of deuterium, as we had already assigned the ^{1}H spectrum of *trans*-4-methylcyclohexyl chloride by 2D-techniques. It was immediately clear that one deuterium was still resident in its original position, but that the other had re-



[4,4-$^2H_2$]-5

Scheme 2 *Reagents:* i, NaH, CH_2=$CHCO_2Et$; ii, DMSO–H_2O, LiCl, pyridine, 180 °C; iii, $NaBD_4$, CD_3CO_2D; iv, $LiAlH_4$; v, Ph_3P, Br_2; vi, Mg, $HgBr_2$; vii, AgOAc; viii, NaCl

located, in a quite specific way, to the 2-*axial* position of the major product **8** as shown in eqn. (7). (A significant minor signal



(7)

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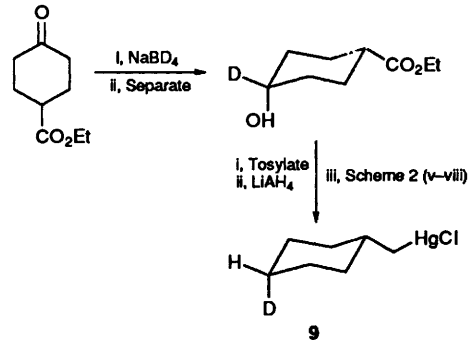
corresponds to 3eq-H.) There was no signal at δ 0.85, the resonance position of the methyl group, and consequently the 'palladabicyclooctane' route [eqn. (6)] cannot be important. Although the deuterium at C-1 is *axial*, it is not clear which deuterium in the starting compound has migrated, because this would depend on whether the chloride was introduced with inversion or retention. In order to clarify this point, a 4-[$^2H_1$]-cyclohexylmethylmercuric chloride **9** of known relative stereochemistry *viz cis*, was synthesised as shown in Scheme 3. This mercurial **9** showed a ^2H NMR signal at δ 1.1, confirming its *axial* orientation.



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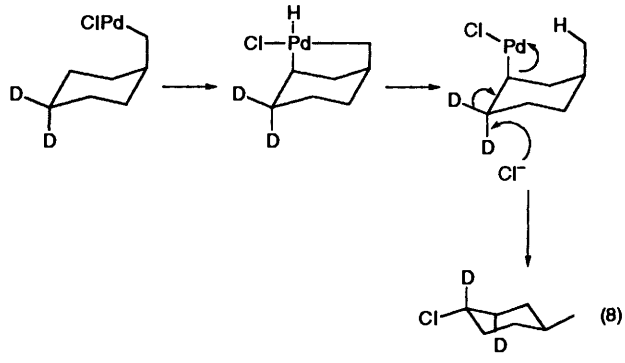
Scheme 3

Reaction of the mercurial **9** and analysis of the chloride fraction showed a ^2H NMR signal at δ 3.79, identical with the ^1H shift for 1-H in authentic *trans*-4-methylcyclohexyl chloride and therefore this *axial*-^2H has not migrated, whereas the *equatorial*-^2H has experienced the stereospecific *cis*-1,2-movement.

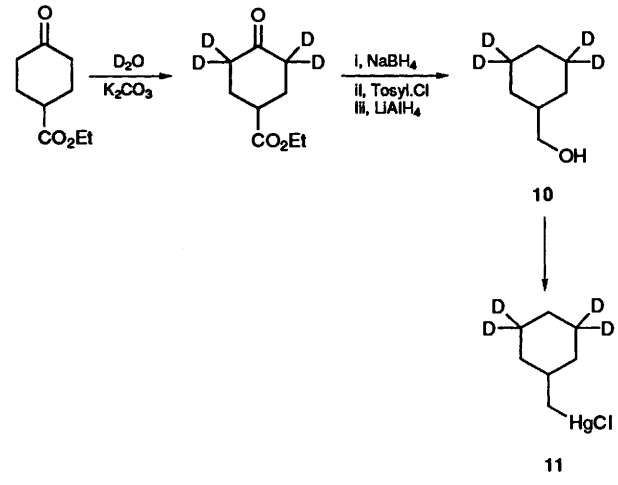
With these results eliminating the route originally suggested,[12] but confirming the stereospecific 1→2 ^2H-shift, consideration was then given to the intermediacy of a 2-palladabicyclo[3.2.1]octane as shown below in eqn. (8). This



(8)

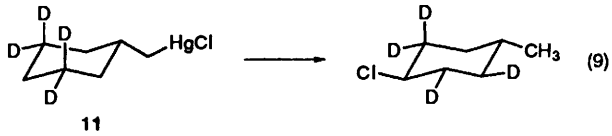
intermediate has more attraction than the 'palladabicyclooctane', which required access to a boat-conformation for the crucial *trans*-annular palladium insertion into the C–(4)H bond [see eqn. (6)].

The events shown in eqn. (8) are unattractive also, in that a *trans*-1,2-shift of ^2H would be required, with inverting displacement of palladium, to provide the correct distribution of ^2H labels in the product *trans*-chloride. The methyl group, according to this proposal, would be created by re-locating a hydrogen atom, originally at C-3. A suitably labelled derivative **10** that would test this proposal was prepared as shown in Scheme 4.



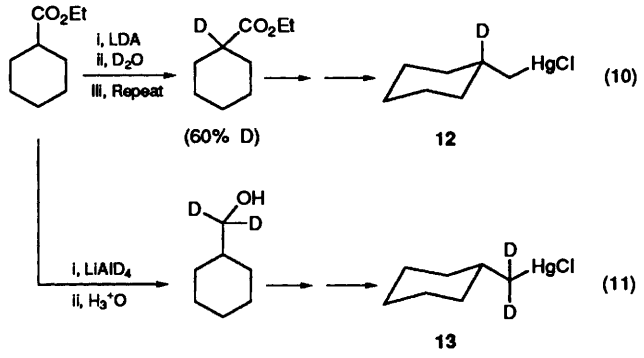
Scheme 4

The ^2H NMR spectrum of the labelled cyclohexylmethanol **10** confirmed that ^2H is located very predominantly at C-3,5, with chemical shifts of δ 1.20 (*ax*) and 1.70 (*eq*). Reaction of the mercurial **11** in the normal way, and ^2H NMR examination showed no incorporation of ^2H into the methyl group. This excludes the route shown in eqn. (8), but did confirm a stereospecific *cis*-1,2-relocation of ^2H from C-3 to C-2, as shown below [eqn. (9)] and in harmony with the results embodied in eqn. (7).

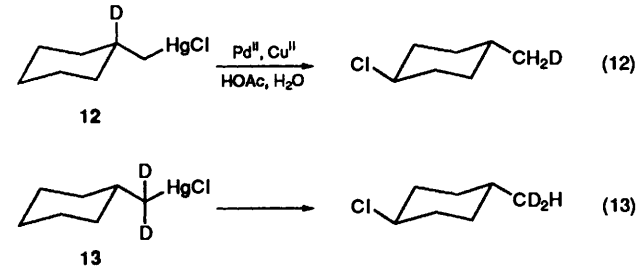


(9)

The foregoing results greatly reduced the possibilities as to the origin of the H-atom that ultimately becomes part of the methyl group, and further labelling was conducted to produce the mercurials **12** and **13** shown in eqns. (10) and (11) and these



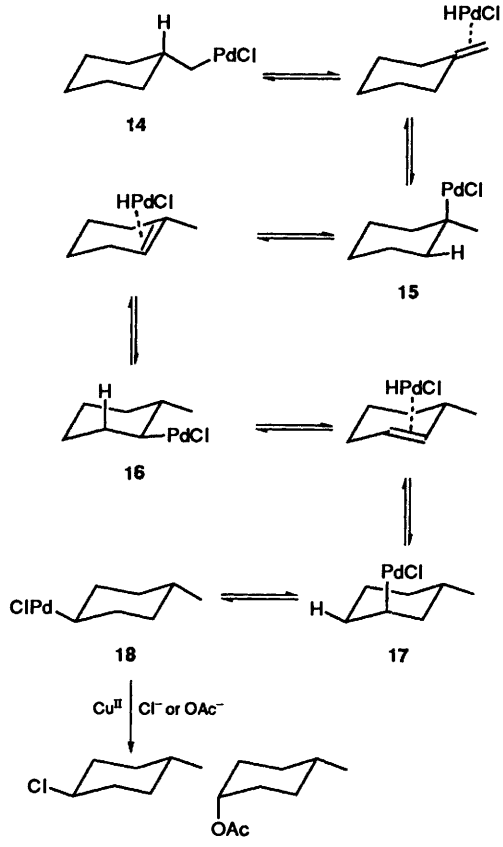
exhibited ^2H NMR signals at δ 1.75 and 2.07 respectively, with essentially no other site of deuteriation. Both mercurials were treated in the standard way, and ^2H NMR spectroscopy shows that the ^2H-label in **12** moves only to create the methyl group [eqn. (12)] and that the CD_2 label in **13** does not migrate to ring sites [eqn. (13)].



The series of *cis*-1,2-hydrogen transfers and lack of solvent involvement (no H-D exchange) suggested a sequence initiated by Pd-for-Hg exchange to provide an alkyl palladium chloride. There is evidence that this exchange proceeds with *retention* of configuration at carbon, although the systems examined are not ideal and free of co-ordinative or special structural features. For example, Stille and Wong[17] determined that the methoxycarbonylation of several oxymercurials, mediated by Pd^{II}, proceeded with predominant retention, and on the basis that conversion of the intermediate organopalladium compound into ester proceeds with retention at the metal-bearing carbon, then so does the triggering Pd-for-Hg substitution. At about the same time, Bäckvall examined the transfer of aminoalkyl groups form Hg to Pd and concluded that retention was again favoured, although this was dependent on an assumption that $LiAlD_4$ reduction of C–Pd bonds proceeded with retention, but the evidence for this traces to special systems.[18] However, it should be emphasised that substitution of alkyl C–Hg bonds with electrophiles, into which class Pd^{II} would reside, proceeds with retention of configuration.[19]

The cyclohexylmethylpalladium chloride is now postulated to undergo a series of reversible eliminations and readditions of [HPdX], without solvent involvement, to provide rearranged alkylpalladium species, which experience displacement by either chloride or acetate, to provide the two product types. Elimination, to form alkene, is not a major pathway in this system, whereas it is in the absence of $CuCl_2$, and loss of [HPdOAc] from acetoxypalladiation adducts of simple olefins can lead to either enol acetates or allylic acetates.

However Henry[5] has shown that treatment of cyclohexenes with Pd^{II} in the *presence* of $CuCl_2$, introduces a new mode of alkylpalladium cleavage, with palladium, now transformed by Cu^{II} in some way to be a better leaving group, suffering displacement by either chloride or acetate. In important contributions, Henry provided strong evidence for *cis*-palladium hydride (or deuteride) eliminations and *cis*-readditions in cyclohexenes, and these processes were faster than exchange of [HPdX] with solvent.[8,13] The processes shown in Scheme 5 are consistent with this chemistry and account for the ^2H-labelling results.



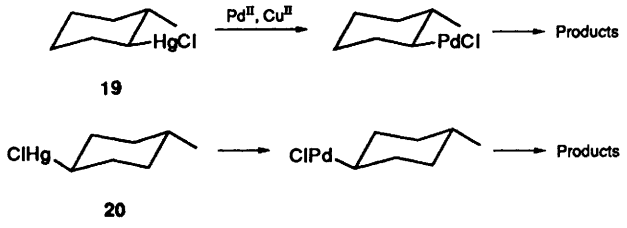
Scheme 5

Before commenting on the conversion of the organopalladium compounds into chloro and acetate products, it is of interest to consider the likely relative free energies of each palladium compound in the equilibria portrayed in Scheme 5, and their reactivity towards nucleophiles, although this latter aspect is difficult to assess. Efficient conversion of **14** into **15** and then **16** may be associated with the 'hydridic' nature of the tertiary hydrogen in **14**, followed by the extra stability of the internal olefin complex on the way to **16**. The conformational preference of **15** is probably as drawn, with 'PdCl' rather than the methyl group, being located *axially*. The absence of significant products derived directly from **14**, **15** and **16** may indicate low equilibrium concentrations of these species, and while this may be true for **14** and **15**, there is no obvious reason why **16** should, for example, be of much higher energy than **18** although the detailed structure and therefore effective size of the Pd-containing group is uncertain. However, depalladiation of **16** may be hindered by the adjacent methyl group. Consequently, it would be reasonable that *trans*-4-methylcyclohexylpalladium chloride **18** would predominate in the equilibria of Scheme 5.

The displacement of the 'Pd–Cu' group by the available nucleophiles, chloride and acetate, may proceed by several routes, but it is important to note that acetate is not appreciably bound to palladium(II) in the presence of an excess of chloride,

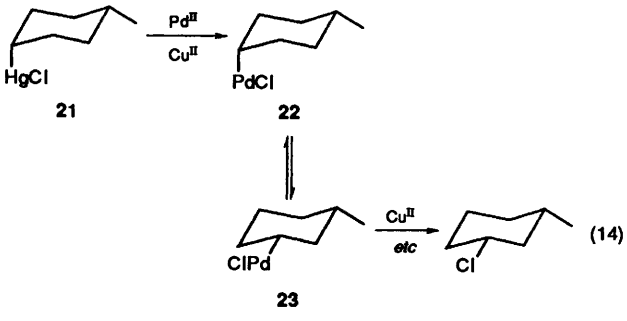
and it is likely, as suggested by Henry,[20] that Cu^{II}-assisted ionisation of the C–Pd bond, may be associated with internal retentive capture by chloride delivered from the halogeno-complexed palladium. However, displacement of the Pd group by acetate is likely to be S_N2 in nature, and when in competition with 'S_Ni–S_N1' attack by chloride at the same carbon, would furnish acetate of opposite configuration to the chloride. However, in certain cases, direct S_N2 displacement by chloride could also occur. The relatively low levels of products at the 3-position (*i.e.* from **17**) suggest **17** to be unimportant, but the similar amounts of *cis* and *trans* chlorides and acetates may reflect subtleties of the *axially* disposed leaving group at this position. However, we suggest that the dominant products, *trans*-4-methylcyclohexyl chloride **6** and *cis*-4-methylcyclohexyl acetate are formed largely by retentive capture by palladium-bound chloride, and S_N2 displacement by acetate, respectively.

Support for the intermediacy of the cyclohexylpalladium compounds in Scheme 5 could be provided if they were generated independently, and their fate established. Fortunately, *trans*-2- and *trans*-4-methylcyclohexylmercuric chlorides **19** and **20** respectively, are known and therefore would provide access to the corresponding palladium derivatives (Scheme 6).



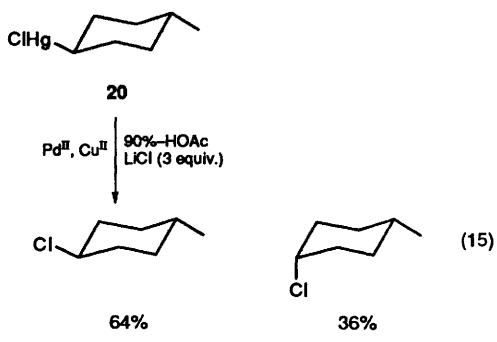
Scheme 6

Treatment of these mercurials with Pd^{II}–Cu^{II} under the same reaction conditions as before provided product profiles essentially identical with those obtained from **5**. These concordances are best considered in terms of *cis*-elimination–*cis*-readdition of [HPdX] and retentive Pd-for-Hg substitution. By way of contrast, reaction of *cis*-4-methylcyclohexylmercuric chloride **21** (containing *ca.* 9% **20**) which should provide the *cis* palladium derivative **22**, yielded mainly *cis*-3-methylcyclohexyl chloride **24**, and other minor products that were present in the reaction of **5**. This result [eqn. (14)] indicates a significant

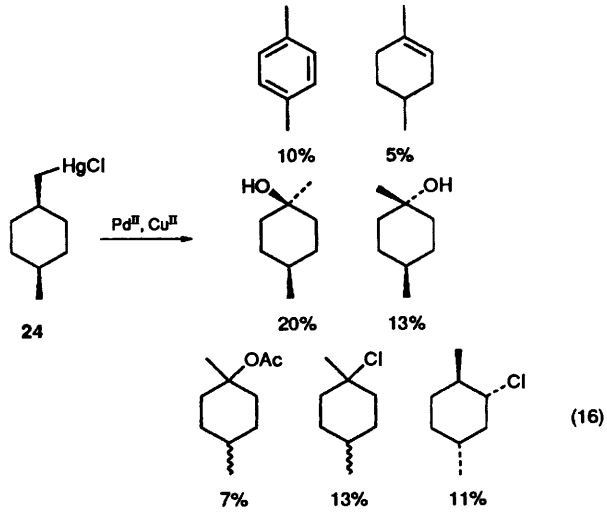


driving force for migration to the di-*equatorial* system **23**, prior to retentive collapse by chloride.

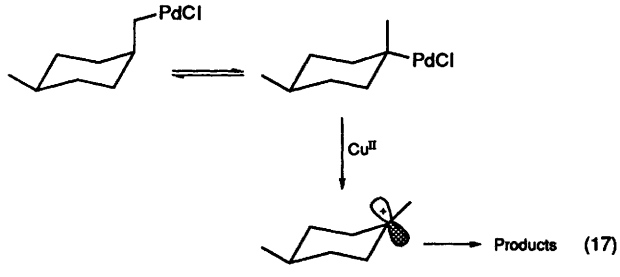
As expected, the product profile changed markedly when palladiation of the mercurial **20** was conducted in the presence of lithium chloride (3 mol equiv.), and *cis*- and *trans*-4-methylcyclohexyl chloride (36:64) were the only products. There was no evidence of Pd migration, and also no acetate product, and presumably external chloride is now competing well in the substitution [eqn. (15)].



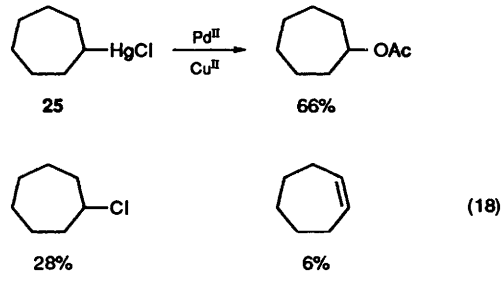
cis-4-Methylcyclohexylmethylmercuric chloride **24** was also investigated and more than 10 products formed, with the major ones shown below in eqn. (16). The first six products are

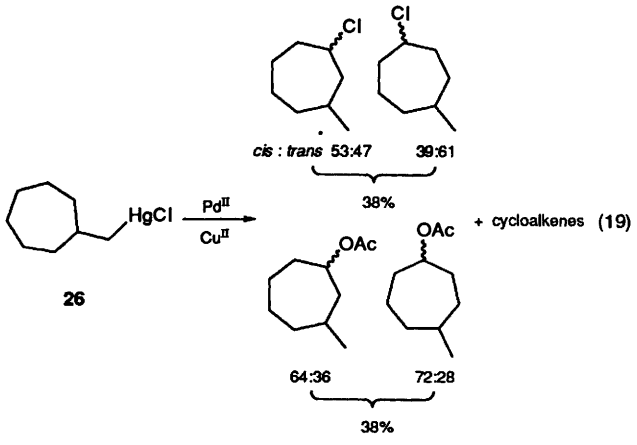


strongly indicative of tertiary carbocation formation, following migration of palladium, as shown below [eqn. (17)].



Demercuriation in the Cycloheptyl System.—The above reaction conditions were applied to both cycloheptyl- and cycloheptyl-methylmercuric chlorides **25** and **26**, respectively, and in the former case a mixture of acetate, chloride and olefin was formed [eqn. (18)]. In the absence of a ^2H marker, it is

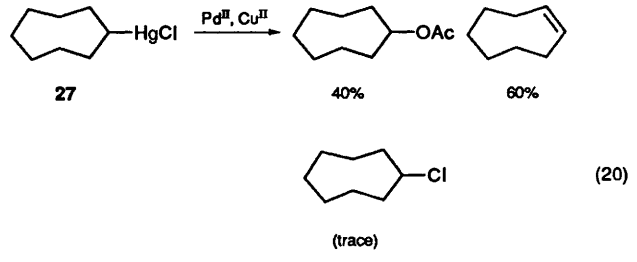




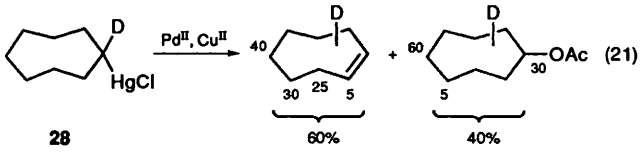
difficult to determine the importance of [HPdX] migrations, but the product mix is again indicative of carbocation involvement.

The situation is different in the cycloheptylmethyl system **26**, and extensive [HPdX] migrations appear to be the best explanation for the formation of 3- and 4-methylcycloheptyl chlorides (38%) and acetates (38%). Again no 2-methyl derivatives were identified, but elimination product (14%) does form [eqn. (19)]. There is a much lower degree of stereo- and regio-selectivity in this reaction compared with the cyclohexylmethyl case, and a greater proportion of acetate product. This may reflect better competition by external (S_N2) displacement in this ring system, or carbocation formation (by Cu^{II} oxidation) after [HPdX] migration.

Demercuriation in the Cyclooctyl System.—Extension of this work to cyclooctylmercurials reveals that [HPdX]-mediated processes are now supplanted by direct C–Pd heterolysis and carbocation formation. Treatment of cyclooctylmercuric chloride **27** under the standard conditions provided predominantly acetate and olefins, with a mere trace of cyclooctyl chloride [eqn. (20)], such product profile being very suggestive of

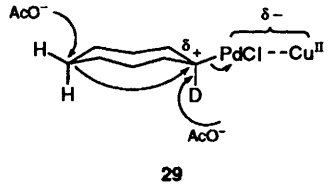


carbocation involvement. This is not too surprising as it is known that among cycloalkyl cations, the cyclooctyl is easily reached [eqn. (20)]. Cyclooctyl cation generation is well known[21–24] to be associated with *trans*-annular hydride shifts, and this possibility was tested with respect to **27**, by utilising the 1-[$^2H_1$] analogue **28**. Careful ^{13}C NMR spectral examination of the product cyclooctene and cyclooctyl acetate revealed the ^2H distribution shown below [eqn. (21)] based on a report[25] of



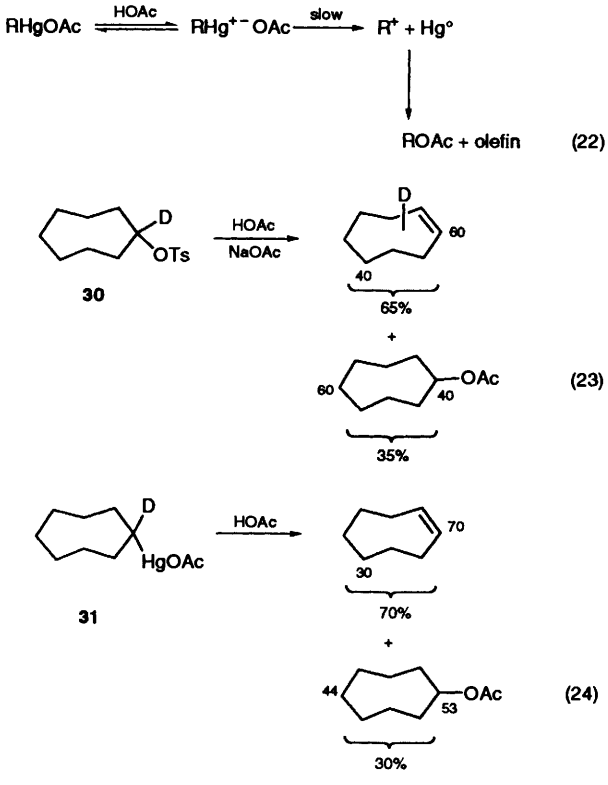
^2H-isotope effects on the ^{13}C NMR spectra of various cyclooctyl derivatives.

With respect to the acetate, the ^2H label is divided between C-1 and C-5, which is not consistent with stepwise [HPdX] intervention, but it is consistent with *trans*-annular response to carbocation generation, as shown below in structure **29**. The



wide distribution of ^2H in cyclooctene is not amenable to useful analyses, since undoubtedly, subsequent palladium-induced hydrogen shifts have occurred.

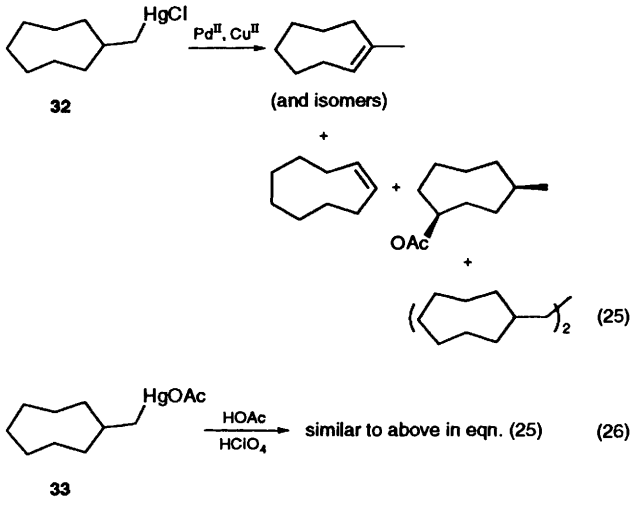
For comparative purposes, two reactions that involve carbocation-like intermediates were applied to the cyclooctyl system, labelled at C-1. These were acetolysis of the tosylate **30** and acetolysis of the mercurial **31**, a reaction clarified by Jensen and Ouellette,[36] and shown to proceed as in eqn. (22). The results with compounds **30** and **31** are shown in eqns. (23) and (24)



respectively, and are again based on analysis of ^{13}C NMR spectra.

There is a strong resemblance between the product ratios (olefin : ester) in all three systems [eqns. (21), (23), (24)], given that the actual details of ion-pairing and related phenomena are bound to be slightly different with such diverse leaving groups. The ^2H distributions are likewise impressively similar in the acetate product. As pointed out, the ^2H labelling in the cyclooctene in eqn. (21) has no counterpart in the model reactions [eqns. (23), (24)] as the tosylate solvolysis was buffered (NaOAc), and strong acid is not generated in the solvolytic demercuriation, since $HClO_4$ catalysis[26] was not employed. In the acetolysis of cyclooctyl tosylate about equal amounts of acetate and cyclooctene were reported to be formed.[21–24]

Cyclooctylmethylmercuric chloride **32** was also examined [eqn. (25)] and cyclooctylmethylmercuric acetate **33** [eqn. (26)]



was subjected to $HClO_4$-catalysed demercuriation in acetic acid. The major products were methylcyclooctenes (> 70%) with a small proportion of cyclononene indicative of carbocation involvement. In both reactions, a significant amount of 1,2-dicyclooctylethane was formed, and may result from decomposition of the palladium or mercury compounds under the reaction conditions. This dimer of 'cyclooctylmethyl' was also formed in the $NaBH_4$ reduction of cyclooctylmethylmercuric acetate, a procedure known to involve free alkyl radicals.

Conclusion.—These studies confirm that the Pd^{II}–Cu^{II} promoted demercuriation of various cycloalkyl and cycloalkylmethylmercuric chlorides may proceed by several mechanisms, with [HPdX]-mediation dominating in the cyclohexyl system, whereas the relatively easily reached cyclooctyl cation results from oxidation of the C–Pd bond, a process indicated by Bäckvall[10,12] to operate in other systems as well. It remains to be seen whether manipulation of the conformational profile of medium rings, *e.g.* by methyl group attachment, may allow [HPdX]-mediation to compete more favourably with direct cation formation. This study confirms many of the earlier suggestions in this general area made by Henry and Bäckvall.

Experimental

^1H NMR spectra were recorded at 400 MHz in the FT mode on a JEOL JNM-GX400 or at 500 MHz with a Bruker AMX-500 spectrometer. The chemical shifts were referenced to residual chloroform at 7.24 ppm. ^2H NMR spectra were recorded on either a JEOL JNM-GX400 spectrometer, Bruker AC200 spectrometer or Bruker AMX-500 spectrometer, normally using $CHCl_3$ solutions spiked with 1 mm^3 of $CDCl_3$ for reference at 7.24 ppm. ^{13}C NMR spectra were recorded on either a JEOL JNM-GX400 spectrometer, Bruker AC200 spectrometer or Bruker AMX-500 spectrometer at 100, 25 or 125 MHz respectively. The chemical shifts were referenced to the central peak of the $CDCl_3$ triplet at 77.00 ppm. Gas chromatographic analyses were conducted using either a Hewlett-Packard 5710A gas chromatograph or a Shimadzu Model GC-14A gas chromatograph fitted with either OV101 or BP5 capillary columns. Preparative gas chromatography was performed on a Shimadzu Model GC-9A gas chromatograph equipped with OV101 or C-20M packed columns. GC–MS analyses were conducted on either a Hewlett-Packard Model 5992B instrument or a Hewlett-Packard 5970 Series MSD instrument, both of which were fitted with OV101 or BP5 columns. Accurate mass measurements were performed on a Kratos MS25 instrument, with an ionising potential of 70 eV. FAB mass spectra measurements were conducted on a ZAB 2HF Mass Spectrometer in FAB mode with 7 kV accelerating voltage, argon as the FAB gas, and 3-nitrobenzyl alcohol as the matrix. HPLC separations were carried out using a Dynamax-60A preparative silica column.

Synthesis of Compounds

Organomercurials were acquired by quenching the corresponding organomagnesium bromide with $HgBr_2$ (1 equiv.) in the following general way. Magnesium turnings (365 mg, 15 mmol) were introduced into a flame-dried flask, containing a N_2 atmosphere. The bromide (500 mg) was then added slowly while Grignard formation proceeded, and stirred for 1 h after bromide addition was complete. The cooled Grignard solution was then poured onto a cold solution of $HgBr_2$ (6.0 g, 16 mmol) in THF (200 cm^3). After 2 h, the mixture was poured onto ice, and acidified with HBr to dissolve any excess of Hg salts. This mixture was extracted with ether, and the combined ether extracts were washed with 10% HBr, separated and dried ($MgSO_4$). Solvent evaporation left an oily product consisting mainly of the organomercuric bromide. This material dissolved in acetone, was stirred in the dark with an excess of AgOAc for 4 h, after which filtration provided a solution of the organomercuric acetate. Sodium chloride (*ca.* 3 g, 50 mmol) in water (20 cm^3) was then added to the solution, and the acetone was evaporated to leave a precipitate of the organomercuric chloride in water, which was filtered off and recrystallised from ethanol or benzene. In this way the following mercurials were obtained. (Although the %C figures for several of the organomercury chlorides are outside the ±0.3% range, high quality NMR spectra, particularly ^{13}C spectra, were free of impurity signals.)

Cyclohexylmethylmercuric chloride **5**. δ_H 0.9 (q of d, 2 H, 2-, 6ax-H), 1.07 (q of t, 1 H, 4ax-H), 1.25 (q of t, 2 H, 3,5ax-H), 1.57–1.85 (m, 6 H, 1-, 2,6eq-, 3,5eq-, 4eq-H) and 2.08 (d, 2 H, CH_2Hg, $J_{^{199}Hg,1H}$ 200 Hz); δ_C 25.69 (C-4), 26.16 (C-3, -5), 37.67 (C-1, $J_{^{13}C-^{199}Hg}$ 85), 38.43 (C-2, -6, *J* 145) and 42.74 (C-7, *J* 1400) (Found: C, 24.0; H, 3.9. Calc. for $C_7H_{13}ClHg$: C, 25.23; H, 3.93%) [Found (HRMS): 334.0392. Calc. for $C_7H_{13}{}^{202}Hg\,{}^{35}Cl$: 334.0411].

Cyclohexylmethylmercuric Chloride [4,4-$^2H_2$]-**5** (see Scheme 2).—Diethyl malonate (15 g, 93 mmol) in THF (20 cm^3) was added to a stirred and cooled (0 °C) suspension of NaH in THF (100 cm^3). After being stirred at 45 °C for 30 min, the mixture was again cooled and ethyl acrylate (22 cm^3, 197 mmol) in THF (20 cm^3) was added to it. After 15 min, the reaction mixture was poured into ice–water (200 cm^3) and the pH adjusted to *ca.* 3. The mixture was then extracted with ethyl acetate and the combined and dried extracts were evaporated and distilled (160 °C, 1 mmHg) to provide the keto triester (22 g, 75%); δ_C 13.81, 14.06, 25.89, 26.47, 27.70, 52.82, 60.35, 61.41, 95.05, 170.04, 170.62 and 171.76. This ester (22 g, 72 mmol), LiCl (7.6 g, 20 mmol), water (3.3 cm^3), pyridine (5 cm^3) and degassed DMSO was heated to 180 °C (N_2 atmosphere) with vigorous stirring. The cooled light brown solution was poured into ice-cold saturated brine, and then extracted with ether. The combined ether extracts were washed with 10% aqueous HCl and brine and then separated, dried and evaporated to give 4-(ethoxycarbonyl)cyclohexanone[15] (4.6 g, 45%). This ketone (4.6 g, 27 mmol) and tosylhydrazide (5.2 g, 30 mmol) were dissolved in 1% HCl in ethanol (20 cm^3), and the mixture was refluxed for 2 h, after which it was cooled and the solid tosylhydrazone filtered off and recrystallised from ethanol (6.3 g, 68%). This tosylhydrazone (5.0 g, 15 mmol) was added to a reagent solution prepared by

adding $NaBD_4$ (1.6 g, 40 mmol) suspended in ether (20 cm^3) to CH_3COOD (3 cm^3), and this resulting mixture was refluxed for 30 min. The solution was poured onto an ice-cold solution of NaOH (5 g) in water (10 cm^3) and extracted with ether. The extract was dried ($MgSO_4$) and then flash distilled to give ethyl 4[$^2H_2$]cyclohexanecarboxylate (1.4 g, 60%); δ_C 14.00, 25.00, 25.17, 28.82, 43.05, 59.80 and 175.91. Reduction of this ester with $LiAlH_4$ in the standard way provided the alcohol which was then converted into the bromide and the mercurial by the general procedures outlined above. The ^1H and ^{13}C NMR spectra of the mercurial, [4,4-$^2H_2$]-**5** matched that of **5** except for ^2H effects on the spectra. The ^2H NMR spectra confirmed that ^2H was located at the 4-position, with signals at δ 1.1 and 1.65 of approximately equal intensity corresponding to the *axial* and *equatorial* deuterons respectively, with minor signals at δ 1.25 and 1.72 associated with some deuterium incorporation at H_{3ax} and H_{3eq}.

[cis-4-$^2H_1$]*Cyclohexylmethylmercuric Chloride* **9** (Scheme 3).—To a suspension of $NaBD_4$ (650 mg, 16 mmol) in dry ether (20 cm^3) was added 4-ethoxycarbonylcyclohexanone (~ 5 g, 30 mm^3) in ether (10 cm^3). The mixture was stirred for 3 h and then quenched with water and extracted with ether. Standard work-up gave a mixture of isomeric alcohols (3.0 g) which were separated by HPLC (60–40, ethyl acetate, hexane on silica) to provide pure *cis*-4-hydroxy ester (800 mg) and pure *trans*-4-hydroxy ester (1.7 g), which were characterised by ^1H and ^{13}C NMR spectroscopy. The *cis*-ester was tosylated in the standard way and the tosylate (700 mg, 8 mmol) added to a cold slurry of $LiAlH_4$ in THF (200 mg, 17 mmol). The reaction mixture was stirred for 4 h, after which the excess of hydride was carefully decomposed with water. The aqueous solution was extracted with ether, *etc.* and work-up followed by flash distillation provided [*cis*-4-$^2H_1$]cyclohexylmethanol. This was converted *via* the bromide into the mercurial **9** (500 mg, 30%) for which a single ^2H NMR signal was observed at δ 1.1; this corresponded to an *axial* orientation.

[3,3,5,5-$^2H_4$]*Cyclohexylmethylmercuric Chloride* **11** (*Scheme* 4).—The keto ester described above was exchanged with D_2O and K_2CO_3 under N_2, in a standard way. The recovered exchanged material (^2H NMR) (6.5 g, 38 mmol) was reduced with $NaBH_4$ (900 mg, 22 mmol) in THF (50 cm^3) and the recovered hydroxy ester (2.8 g) was tosylated with tosyl chloride in pyridine in a standard way. The isolated crude tosylate was reduced with $LiAlH_4$ as described above to provide predominantly [3,3,5,5-$^2H_4$]-cyclohexylmethanol (1.3 g) which exhibited ^2H NMR signals at δ 1.20 and 1.70 corresponding to *axial* and *equatorial* deuterium, respectively. This alcohol was converted as described above into the mercuric bromide and then into the mercuric chloride **11** (500 mg, 30%).

[1-$^2H_1$]*Cyclohexylmethylmercuric Chloride* **12** [*Eqn.* (10)].—Ethyl cyclohexanecarboxylate (4.5 g, 30 mmol) in THF (20 cm^3), was treated with lithium diisopropylamide [made from the amine (4.6 cm^3) and 2.55 mol dm^{-3} BuLi (12 cm^3)] followed by quenching with D_2O (3 cm^3). This procedure was repeated on the recovered ester to give a final deuterium incorporation of *ca.* 60%. This ester was reduced to the alcohol and converted in the standard way, into the mercurial **12**, which exhibited a signal at 1.75 ppm.

Cyclohexyl[$^2H_2$]*methylmercuric Chloride* **13** (*Eqn.* (11).—Ethyl cyclohexanecarboxylate was reduced with $LiAlD_4$ in THF in the standard way to provide the deuteriated alcohol, which was converted into the mercurial **13** in the general way; $\delta_{^2H}$ 2.07.

cis- *and* trans-4-*Methylcyclohexylmercuric chlorides* (*Scheme* 6). These compounds were prepared and separated in the manner described by Jensen and Gale.[19] Final separation was achieved by HPLC on silica using 20% ether in hexane, and the separated bromides were converted into the chlorides as described above. *trans*-Mercurial **20**: δ_C 21.83, 32.00, 32.95, 36.95 and 53.10 (Found: C, 24.8; H, 4.0. Calc. for $C_7H_{13}HgCl$: C, 25.23; H, 3.93%) [Found (HRMS): 334.0402. Calc. for $C_7H_{13}{}^{202}Hg^{35}Cl$: 334.0412). *cis*-Mercurial **21**. δ_C 22.65, 32.36, 32.59, 38.01 and 57.80 [Found (HRMS): 334.0402. Calc. for $C_7H_{13}{}^{202}Hg^{35}Cl$, 334.0412].

trans-2-*Methylcyclohexylmercuric chloride* **19**. This compound was obtained from a similar sequence commencing with a mixture of *cis*- and *trans*-2-methylcyclohexyl bromide; δ_C 25.68, 26.38, 28.23, 34.0, 37.5, 38.7 and 64.6 (Found: C, 24.7; H, 3.9. Calc. for $C_7H_{13}HgCl$: C, 25.2; H, 3.93%) [Found (HRMS): 334.0399. Calc. for $C_7H_{13}{}^{202}Hg^{35}Cl$, 334.0412].

cis-4-*Methylcyclohexylmethylmercuric chloride* **24**. This compound was prepared from a sample of the acetate kindly donated by Dr. Henry Olszowy; δ_C 19.20, 28.54, 30.74, 33.10, 36.08 and 40.98 [Found (HRMS for the bromide): 392.0055. Calc. for $C_8H_{15}{}^{79}Br^{202}Hg$, 392.0063].

Cycloheptylmercuric chloride **25**. This compound was obtained from cycloheptyl bromide in the normal way by Grignard formation and reaction with $HgBr_2$ followed by anion exchange; δ_H 1.4–1.75 (m, 8 H), 1.8–2.2 (m, 4 H) and 3.25 (m, 1 H); δ_C 27.03, 30.76, 35.5 and 58.47 (Found: C, 24.5; H, 3.9. Calc. for $C_7H_{13}HgCl$: C, 25.2; H, 3.9%).

Cycloheptylmethylmercuric chloride **26**. δ_H 1.2 (m, 2 H), 1.3–1.9 (m, 11 H) and 2.1 (d, 2 H); δ_C 26.29, 27.94, 39.57, 40.19 and 44.39 (Found: C, 26.1; H, 4.2. Calc. for $C_8H_{15}HgCl$: C, 27.7; H, 4.08%).

Cyclooctylmercuric chloride **27**. This was obtained from cyclooctyl bromide in the normal way; δ_H 1.4–1.7 (m, 10 H), 2.0 (m, 2 H), 2.1 (m, 2 H) and 3.15 (m, 1 H); δ_C 25.23, 27.34, 32.07, 29.35 and 59.54. (Found: C, 25.5; H, 4.05. Calc. for $C_8H_{15}HgCl$: C, 27.75; H, 4.08%).

[1-$^2H_1$]*Cyclooctylmercuric chloride* **28**. This was prepared from [1-$^2H_1$]cyclooctanol, obtained by reducing cyclooctanone with $LiAlD_4$, by employing the standard procedure.

Cyclooctylmethylmercuric chloride **32**. This compound was made from ethyl cyclooctanecarboxylate by reduction with $LiAlH_4$, *etc.*; δ_H 1.3–1.7 (m, 15 H) and 2.1 (d, 2 H); δ_C 25.35, 26.10, 26.93, 37.81, 37.43 and 44.71 (Found: C, 31.1; H, 5.2. Calc. for $C_9H_{17}HgCl$: C, 29.92; H, 4.74%).

Palladiation Procedure.—A mixture of alkylmercuric chloride (1 mmol), $CuCl_2$ (337 mg, 2.5 mmol), $PdCl_2$ (20 mg, cat.), acetic acid (3 cm^3) and water (300 mg) was stirred in the dark at 45 °C for 3 days, during which time the mixture turned very dark brown and formed a dark grey precipitate. The mixture was then cooled, poured into water (20 cm^3) and thoroughly extracted with pentane. The extract was washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated and the resultant oil was dissolved in $CDCl_3$; the ^1H and ^{13}C NMR spectra of the solution were recorded. Subsequently, the compounds were separated, normally into a chloride fraction and an acetate fraction by preparative gas chromatography, and further NMR spectra were then recorded.

Demercuriation Procedures.[11,26]—A solution of the alkylmercuric acetate in dry acetic acid was sealed in an ampoule, and warmed to 130 °C overnight. The reaction was judged complete when no more Hg^0 was deposited. The supernatant liquid was decanted from the mercury which was further washed with ether. The acetic acid and ether fractions were combined, diluted with water and further extracted. The combined organic extracts were washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. ^1H and ^{13}C NMR spectra were recorded for the total product mixture. For 'acidic' solvolysis, the acetic acid used contained 1% $HClO_4$.

Product Identification.—This was conducted by comparing the gas chromatographic and GC–MS behaviour, and high quality, highfield ^{13}C and ^{1}H NMR spectra of the chloride and acetate (and, where applicable, hydrocarbon) fractions with those of separately synthesised, authentic samples. The acetates were made from the authentic alcohols, as were the chlorides by treatment of the alcohols with Ph_3P, CCl_4. The relative configurations of these derivatives were easily established by ^{1}H and ^{13}C NMR spectra. *cis*- and *trans*-4-Methylcycloheptyl acetates and chlorides were made in similar ways from *trans*-4-methylcyclohept-2-enol (kindly donated by Dr. K. Penman) by hydrogenation and hydroxy group conversion. The corresponding 3-methylcycloheptyl derivatives were acquired from 6-methylcyclohept-2-enol (Dr. K. Penman) in a similar way. A full listing of ^{13}C NMR shifts for these unexceptional derivatives is available elsewhere.[27,28]

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