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Stereochemical Aspects of Substitution Reactions of Stannyl and Germyl Anionoids with Cyclohexyl Derivatives

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The reactions of trimethyltinlithium (in THF) and trimethylgermaniumlithium (in HMPA) with some 4-alkylcyclohexyl bromides and tosylates have been conducted, and product stereochemistry has been established by ^{1}H and ^{13}C NMR spectroscopy. With the cis bromides both the stannyl and the germyl anionoids yield mixtures of *cis*- and *trans*-4-alkylcyclohexylstannanes and -germanes, respectively, whereas the stannyl anionoid reacts cleanly with inversion with *trans*-4-methylcyclohexyl tosylate. Both anionoids react in a straightforward way with cyclohexene oxide to yield the corresponding *trans*-2-hydroxycyclohexyl metalloids. Certain of our results contrast with some of those in a previous report. Variable-temperature ^{13}C NMR examination of *cis*-4-methylcyclohexyltrimethylgermane, and other considerations, yield a $-\Delta G°_{203}[Ge(CH_3)_3]$ of 2.1 ± 0.2 kcal/mol (*A* value), somewhat greater than the *A* value for CH_3 (1.74 kcal/mol).

Introduction

The reactions of organic halides with alkali metal derivatives of organometal anions have been extensively utilized for the formation of carbon–metal bonds as illustrated below:

$$R'_xM^-M_1^+ + RX \rightarrow R'_xMR + M_1X \ldots\ldots \quad (1)$$

This general area has been reviewed.[1]

This approach to carbon–metal bond formation has been particularly useful in group 4B chemistry, and many tetraorganostannanes have been synthesised in this manner.

$$R_3SnM + R'X \rightarrow R_3SnR' + MX \ldots\ldots \quad (2)$$

$$(R_3Sn = (CH_3)_3Sn, (C_6H_5)_3Sn;\ M = Na, K, Li)$$

Derivatives of silicon, germanium, and lead have also been obtained in the same general way.[1]

Stereochemical studies of the reaction (eq 2) have been reported and inversion of configuration at carbon was the general result, in keeping with the suspicion that the reaction was S_N2 in character.[2] Other transformations, however, indicated that other mechanisms must also be possible.[1d,3,4]

Recently, there has been great interest in the fine details of these anionoid substitutions, particularly for the systems in eq 2. In particular, Koermer, Hall, and Traylor[5] reported that whereas the 4-*tert*-butylcyclohexyl Grignard reagent on reaction with trimethyltin chloride provided overwhelmingly trans product, reaction of *cis*-4-*tert*-butylcyclohexyl bromide with $(CH_3)_3SnLi$ (in THF) yielded *cis*-4-*tert*-butylcyclohexyltrimethylstannane. The latter compound also resulted from the displacement of tosylate in the *trans*-4-*tert*-butylcyclohexyl derivative by $(CH_3)_3SnLi$ (in THF). These sequences seemed very attractive as they could provide geometric isomers of cyclohexyltin systems of high isomeric purity for other studies. Kuivila and co-workers[6] have also been conducting systematic studies of the reactions of stannyl anionoids under various conditions and have established that the stereochemistry of the reaction with certain bromonorbornenes (eq 2) is profoundly dependent upon the solvent and alkali metal counterion in $(CH_3)_3SnM$.

For some time we have been pursuing spectroscopic and conformational studies[7,8] of cyclohexyl derivatives of group 4B and have required 4-alkylcyclohexyl derivatives of tin and germanium of established stereochemistry. We have utilized reactions of $(CH_3)_3SnLi$ (in THF) and $(CH_3)_3GeLi$ (in HMPA) with cyclohexyl bromides and tosylates, as well as the Grignard route. In this report, we wish to present our conclusions concerning the stereochemistry of certain of these displacements (formally on carbon).

Results and Discussion

(A) Organotin Systems. The stereochemistry of the displacement of bromide and tosylate by $(CH_3)_3SnLi$ in the following cases (eq 3 and 4) has been examined.

In addition to tetraorganostannane product significant amounts of alkylcyclohexene (elimination) and hexamethyldistannane were also formed in these reactions.[5,6]

^{1}H NMR spectroscopy has been widely employed to determine the stereochemistry of substituted cyclohexyl sys-

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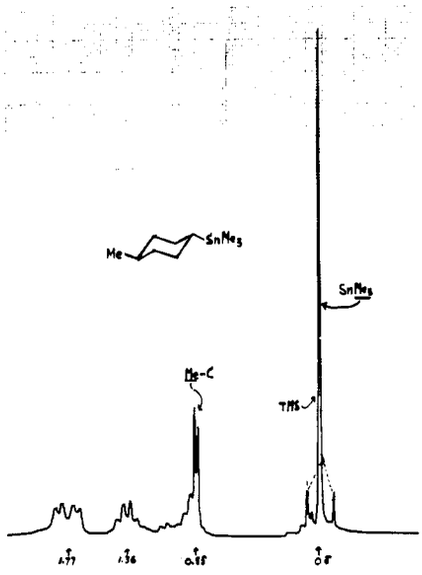
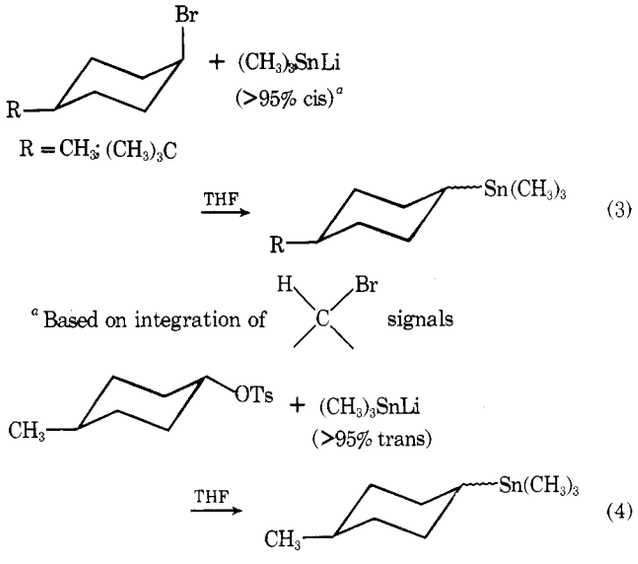


Figure 1. The 270-MHz ^1H NMR spectrum of *trans*-4-methylcyclohexyltrimethylstannane, showing the CH_3Sn resonance to the high field of Me_4Si. (Chemical shifts quoted in the text have been obtained from 100-MHz spectra.) This compound was obtained from the Grignard reaction of 4-methylcyclohexyl bromide with trimethyltin chloride.



tems, particularly when an electronegative group significantly deshields the methine proton from the general cyclohexyl absorption, so that ^1H–^1H coupling constants can be measured.[9] In the tin compounds, there were good reasons for anticipating that the methine proton (>C(H)Sn) would not be strongly deshielded and the ^1H NMR approach would be of rather limited use.[10] We did, nevertheless, expect some differences in the general spectral shape of *cis*- and *trans*-4-alkylcyclohexyltin isomers.[9] Studies of the ^{13}C NMR spectra of cyclohexyl and related organostannanes have provided a bank of data of $^{117,119}Sn$–^{13}C coupling constants and chemical shifts, which would constitute the basis of a definitive approach to isomer determination (vide infra).[8a,11,12] In addition, it would be advantageous to obtain, in essentially pure form, one of the possible isomers. Fortunately there were reports which indicated that *trans*-4-methylcyclohexyltrimethylstannane was accessible.

Jensen and Nakamaye[13] reported that reaction of 4-methylcyclohexyl Grignard yielded predominantly (>80%) trans mercurial, and this has been confirmed by ^1H and ^{13}C

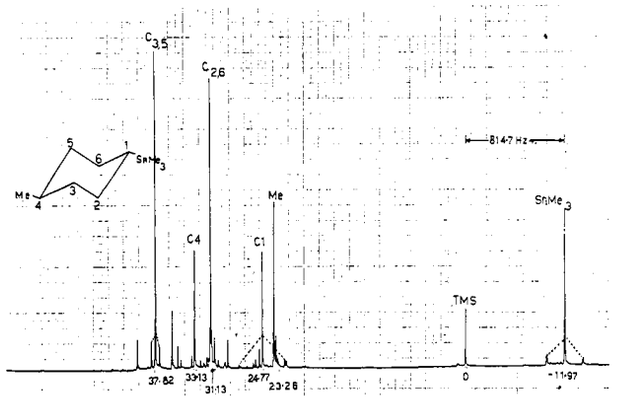


Figure 2. The proton-decoupled PFT 67.89-MHz ^{13}C spectrum of *trans*-4-methylcyclohexyltrimethylstannane obtained by the Grignard route. Assignments are indicated, and the lone $Sn(CH_3)_3$ signal indicates high isomeric purity. The vicinal ^{119}Sn–^{13}C coupling (about $C_{3,5}$) is consistent with the trans description. (A number of low-intensity signals may be associated with bicyclohexyl formation.)

NMR spectroscopy.[14] We anticipated that use of $(CH_3)_3SnCl$ as an electrophile would not seriously alter this stereochemical pattern. The Grignard reagent from >95% *cis*-4-methylcyclohexyl bromide on reaction with $(CH_3)_3SnCl$ yielded a 4-methylcyclohexyltrimethylstannane which exhibited a single $(CH_3)_3Sn$ ^1H resonance (Figure 1) at δ −0.045 ($J_{^{119}Sn-^1H}$ = 52 Hz), and a doublet (δ 0.84, $J \simeq 7$ Hz) for CH_3C. The proton-decoupled PFT ^{13}C spectrum (Figure 2) confirmed the presence of one isomer (six signals excluding ^{119}Sn satellites) with δ CH_3Sn at −12.00 ppm and CCH_3 at +23.26 ppm. These chemical shifts agree nicely with those for equatorial $Sn(CH_3)_3$[7] and CCH_3[15] in cyclohexyl systems. The ring carbon chemical shifts were in good agreement with those calculated (on the basis of additivity) from equatorial $Sn(CH_3)_3$ and CH_3 induced shifts.[16] The value of the vicinal ^{13}C–^{119}Sn coupling constant (^3J) was 67.5 Hz, absolutely consistent[11] with a dihedral angle of 180° as present in the trans isomer. There is therefore no doubt that this stannane is the *trans*-4-methylcyclohexyl derivative.

Reaction of *trans*-4-Methylcyclohexyl Tosylate with $(CH_3)_3SnLi$. *trans*-4-Methylcyclohexyl tosylate (>95% trans) was prepared and reacted with $(CH_3)_3SnLi$, and on workup and distillation yielded an essentially pure isomer of 4-methylcyclohexyltrimethylstannane, as judged by the lone $(CH_3)_3Sn$ signal at δ 0.05 ($J_{^{119}Sn-^1H} \sim 52$ Hz) in the ^1H spectrum (Figure 3), with the CCH_3 doublet ($J \sim 7$ Hz) at δ +0.90. The distinct differences between the above $Sn(CH_3)_3$ and CCH_3 chemical shifts, and those for the trans isomer discussed previously, indicated possession of the pure *cis*-4-methylcyclohexyl derivative. The ^{13}C spectrum (Figure 4) confirmed the presence of one isomer, as a total of six signals (neglecting $^{117,119}Sn$ satellites) was observed, and the chemical shift pattern was different from that for the trans compound but completely consistent with that anticipated for the cis isomer.

Before discussing these ^{13}C parameters it is important to remember that while the *trans*-4-methylcyclohexyl derivative could be discussed in terms of a homogeneous (e,e) conformation the cis isomer must be treated as a two-component mobile (e,a) system, with comparable populations of A and B as shown in eq 5.

Employing the conformational free energies (A values) for CH_3 (1.74 kcal/mol)[15] and $Sn(CH_3)_3$ (1.06 kcal/mol),[7] it is possible to calculate that at ~300 K, [A]/[B] ~ 3:1. This deduction for the cis isomer allows a calculated "average" vicinal ^{119}Sn–^{13}C coupling constant of ~24 Hz, utilizing the Karplus-type dependence previously established[11] for this cou-

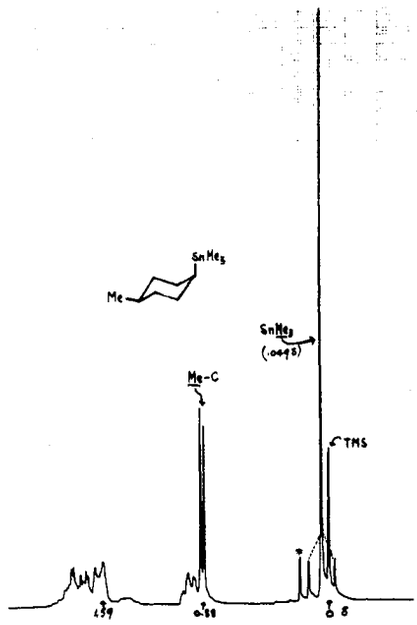
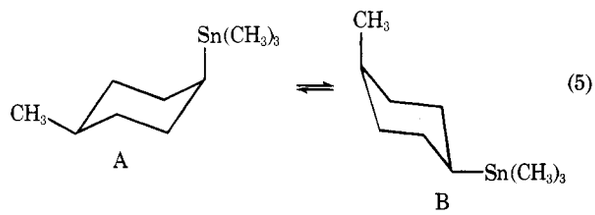


Figure 3. The 270-MHz ^1H NMR spectrum of *cis*-4-methylcyclohexyltrimethylstannane showing the CH_3Sn resonance to the low field of Me_4Si. The general cyclohexyl absorption is dissimilar to that of the trans isomer (Figure 1). This compound was obtained from the reaction of *trans*-4-methylcyclohexyl tosylate with $(CH_3)_3SnLi$. (Chemical shifts quoted in the text were measured from 100-MHz spectra.)



(5)

pling [~10 Hz for $\theta = 60°$ in A; ~67 Hz for $\theta = 180°$ in B]. The observed $^3J_{vic}$ of 23.1 Hz is in satisfying agreement with this analysis. The other ^{13}C parameters also must be analyzed on this basis, and the observed shift of −9.85 ppm for $Sn(CH_3)_3$ is appropriate for this ~3:1 mixture of A and B, given that $\delta_{Sn(CH_3)}$(equatorial) ~−12.00 ppm and $\delta_{Sn(CH_3)_3}$(axial) is ~−9.20 ppm[7] (i.e., $\frac{1}{4}[(3 \times 9.20) + 12.00]$). Similarly, the observed chemical shift for CCH_3 of 22.00 ppm is in close agreement with the computed value of 21.96 ppm based on the established shifts for axial (17.43 ppm) and equatorial (23.47 ppm) methyl groups in methylcyclohexane.[15] Comparison of predicted and observed chemical shifts for ring carbons in A ⇄ B strictly is not possible, as only the γ carbon shifts, where strong compressional effects operate, are available for the axial forms of methylcyclohexane[16] and cyclohexyltrimethylstannane.[7] Even in their absence, however, the above correspondences of calculated and observed ^{13}C NMR properties leave no doubt that reaction of the *trans*-4-methylcyclohexyl tosylate yields only the *cis*-tin compound (along with some olefin and hexamethylditin).[5]

It is instructive also to compare the ^1H NMR spectra of the *trans*- and *cis*-4-methylcyclohexyltrimethylstannanes. In the cis isomer, both the CH_3Sn and CH_3C resonances (+0.05 and +0.90 ppm, respectively) are downfield from the corresponding resonances (−0.045 and 0.84 ppm, respectively) in the trans compound. These differences are expected, as the axial CH_3 group in methylcyclohexane is known to resonate at lower field than the equatorial.[17] It is very reasonable that an axial $Sn(CH_3)_3$ will behave similarly, as "steric deshielding" would be operative for both axial CH_3 and $Sn(CH_3)_3$ groups.

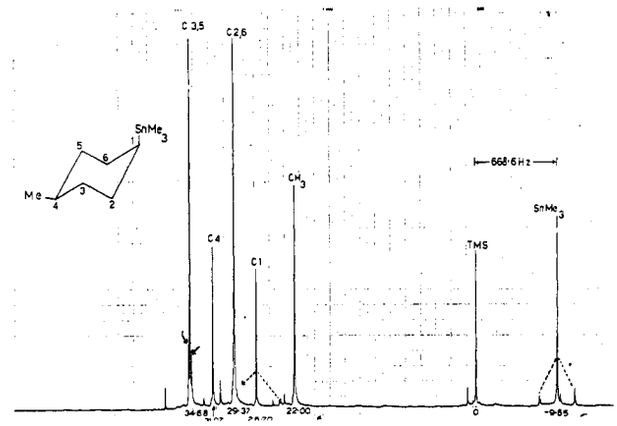


Figure 4. The proton-decoupled PFT 67.89-MHz ^{13}C spectrum of *cis*-4-methylcyclohexyltrimethylstannane. The chemical shifts and the magnitude of the vicinal ^{119}Sn–^{13}C coupling constant confirm the cis structure.

Another anticipated difference in the ^1H spectra of the isomers concerns the position and multiplicity of the methine proton $>C(H)SnMe_3$.[9]

In the trans isomer, this proton (axial) should be at higher field (by ~0.5 ppm) and appear as a broadened triplet (two trans diaxial couplings), whereas this proton in the cis isomer (now predominantly an equatorial proton) should be narrower and to lower field.[9] In the ^1H spectrum of the trans isomer, a broadened triplet ($J \sim 12$ Hz) at δ 1.24 is superimposed on the general absorption, whereas in the cis isomer this absorption is absent, and there has been a shift of intensity to lower field in the δ 1.5–1.9 region. In the low-temperature (−80 °C) 270-MHz ^1H spectrum of cyclohexyltrimethylstannane two components of what appears to be a triplet ($J \sim 11$–12 Hz) at δ 1.28 are clearly visible and are tentatively assigned to the methine proton in this compound.[36] Differences of this type should be visible also in the spectra of the pure *cis*- and *trans*-4-*tert*-butyl derivatives, and we were surprised at the report that these isomers (other than for the $Sn(CH_3)_3$ resonances) provided "identical" spectra.[5,18]

The above data demonstrate that reaction of *trans*-4-methylcyclohexyl tosylate with $(CH_3)_3SnLi$ proceeds with inversion at carbon to yield the *cis*-tin compound. The same conclusion has been reached for the *tert*-butylcyclohexyl system by Koermer, Hall, and Traylor.[5] With the availability of the spectroscopic data for the authentic cis and trans isomers above, we are now in a position to assign the isomers formed from the 4-alkyl cyclohexyl bromides.

***cis*-4-Methylcyclohexyl Bromide with Trimethyltinlithium.** The reaction of predominantly (>95%) *cis*-4-methylcyclohexyl bromide with $(CH_3)_3SnLi$ yielded an oil, the analysis of which corresponds to 4-methylcyclohexyltrimethylstannane. The 100-MHz ^1H NMR spectrum exhibited two $(CH_3)_3Sn$ signals at −0.04 and +0.05 ppm in the ratio of ~2:1, such resonance positions corresponding nicely with those for trans and cis isomers, respectively (vid supra) (see Figure 5). The CCH_3 doublets half overlapped as expected ("three" lines instead of four), and other features were consistent with a cis,trans mixture. The PFT ^{13}C spectrum (Figure 6) establishes the presence of both isomers, with resonances present essentially identical in position with those alluded to above for the authentic trans and cis isomers. The isomer ratio is trans/cis ~2.3:1, based on the $(CH_3)_3Sn$ signal intensities.

***cis*-4-*tert*-Butylcyclohexyl Bromide with Trimethyltinlithium.** This reaction (employing >95% *cis*-bromide) yielded the expected tetraorganostannane which was clearly an isomeric mixture. A duality of $(CH_3)_3Sn$ signals (~2:1) appeared in the ^1H (Figure 7) (+0.07 and −0.03 ppm)

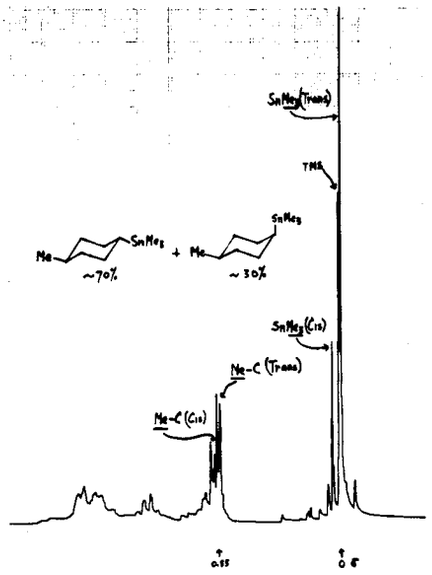


Figure 5. The 270-MHz ^1H spectrum of the isomeric mixture of stannanes obtained from (>93%) *cis*-4-methylcyclohexyl bromide and $(CH_3)_3SnLi$. Comparison with the ^1H spectra of the authentic cis and trans isomers confirms the predominance of the trans isomer.

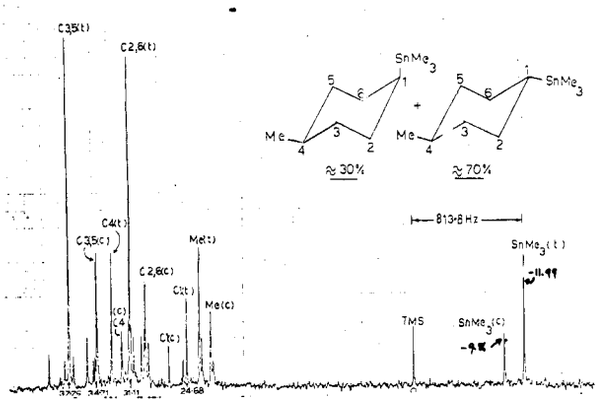


Figure 6. The proton-decoupled PFT 67.89-MHz ^{13}C spectrum of the stannane mixture obtained from (>95%) *cis*-4-methylcyclohexyl bromide and $(CH_3)_3SnLi$. The trans isomer clearly predominates, as deduced from the ^1H spectrum (Figure 5).

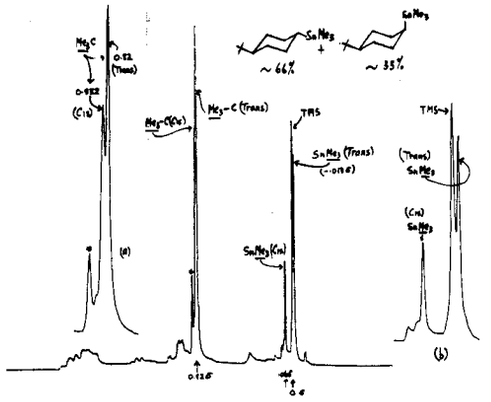


Figure 7. The 270-MHz ^1H NMR spectrum of the stannane mixture obtained from (>95%) *cis*-4-*tert*-butylcyclohexyl bromide and $(CH_3)_3SnLi$. Chemical shift considerations strongly suggest the predominance of the trans isomer.

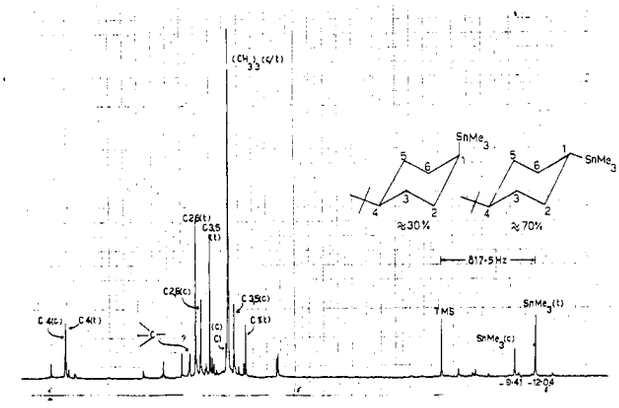


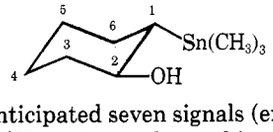
Figure 8. The proton-decoupled PFT 67.89-MHz ^{13}C spectrum of the stannane mixture obtained from (>95%) *cis*-4-*tert*-butylcyclohexyl bromide and $(CH_3)_3SnLi$. Consideration of $Sn(CH_3)_3$ resonances and vicinal ^{119}Sn–^{13}C couplings confirm the predominance of the trans isomer.

and ^{13}C (Figure 8) (−9.41 and −12.04 ppm) NMR spectra (with the higher field signals more intense) with the $C(CH_3)_3$ resonance at +0.85 ppm (^1H). We did conduct a reaction between *trans*-4-*tert*-butylcyclohexyl tosylate and $(CH_3)_3SnLi$ and obtained an impure product whose ^1H spectrum nevertheless was appropriate for a 4-*tert*-butylcyclohexyltrimethylstannane and was isomerically homogeneous. The $Sn(CH_3)_3$ resonance at +0.07 ppm characterized an axial $Sn(CH_3)_3$ group, assuming an inversion mechanism established in the case of the 4-CH_3 counterpart. There was no "broad triplet" absorption in the δ ~1.2 region, previously ascribed to an axial methine proton $>C(^1H)SnMe_3$.

Consideration of the above data establishes the predominance of the trans isomer. In particular, −12.04 ppm in the ^{13}C spectrum agrees very well with shifts established for equatorial $Sn(CH_3)_3$.[7] Note that the shift of −9.41 ppm for $Sn(CH_3)_3$ in the cis isomer is somewhat to lower field than the corresponding signal (at −9.85 ppm) for *cis*-4-methylcyclohexyltrimethylstannane. This is because the 4-*tert*-butyl group is more effective than a 4-CH_3 group in controlling the position of the (a,e) conformational equilibrium in the *cis*-4-alkylcyclohexyltin compounds, and the shift of −9.41 ppm agrees reasonably well with that for axial $Sn(CH_3)_3$ in cyclohexyltrimethylstannane (−9.27 ppm).[7] Further compelling evidence that the trans isomer predominates follows from the values of vicinal (^3J) ^{119}Sn–^{13}C couplings. A value of 67.1 Hz is associated with the more intense carbon resonance vicinal to tin and corresponds to a trans (θ = 180°) arrangement. The other vicinal coupling (12 Hz) agrees well with a predicted value[11] of ~10 Hz for θ = 60°, as present in the cis isomer. It is also interesting to note that in the ^1H spectrum of this product mixture there is significant absorption in the δ 1.2 region, as expected for an axial methine proton, $>C(^1H)$-$SnMe_3$, in the trans isomer.

These results on the 4-*tert*-butyl system contrast markedly with those of Traylor et al.[5] who reported formation of exclusively cis isomer.[18]

Cyclohexene Oxide with Trimethyltinlithium. Cyclohexene oxide reacted smoothly and a hydroxycyclohexyltrimethylstannane was obtained and shown to be isomerically pure by its ^1H and (particularly) its ^{13}C spectrum, the latter



exhibiting the anticipated seven signals (excluding $^{117,119}Sn$ satellites). In the ^1H spectrum, the methine proton >C(H)OH at δ 3.54 was quite broad ($W_{1/2}$ ~ 24 Hz), indicating two adjacent trans diaxial protons. Thus, the trans diequatorial structure is implicated and supported by the ^{13}C spectrum,

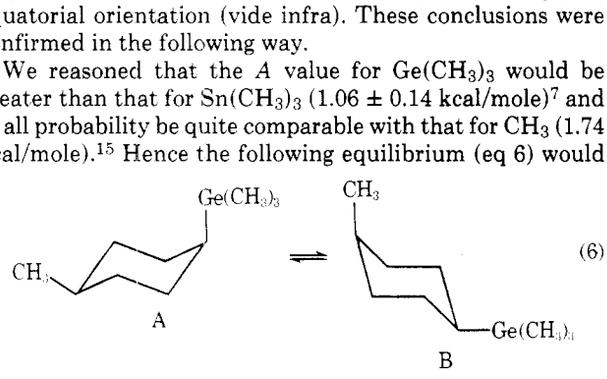
particularly the values of the two different vicinal $^{119}Sn-^{11}C$ couplings of 52 and 50 Hz. The calculated chemical shifts, based on the known substitutent effects of equatorial $Sn(CH_3)_3$[7] and OH[19] in cyclohexanes agree quite well with those observed. The largest discrepancies occur for C_1 and C_3. The vicinal couplings are slightly smaller than in alkyl-substituted cyclohexylstannanes, but the effect of oxygen functionality on vicinal $M^{13}C$ couplings has been noted before in organomercury systems.[14]

Thus the above reaction proceeds with inversion at carbon to yield *trans*-2-hydroxycyclohexyltrimethylstannane. Recently Fish and Broline reported the same stereochemical outcome for the reaction of triphenyltinsodium with cyclohexene oxide.[20]

(B) Organogermanium Systems. In view of the results obtained with $(CH_3)_3SnLi$, we decided to examine similar reactions with $(CH_3)_3GeLi$, now routinely prepared from $(CH_3)_3GeBr$ using hexamethylphosphoric triamide as solvent.[21] Our feeling was that electron-transfer and/or -displacement reactions at bromine in the 4-alkylcyclohexyl bromides may be more important with this reagent,[22] leading to a greater degree of overall retention at carbon.

***cis*-4-Methylcyclohexyl Bromide with $(CH_3)_3GeLi$.** In the ^1H NMR spectrum of the product 4-methylcyclohexyltrimethylgermane, $(CH_3)_3Ge$ resonances at δ 0.035 and 0.08 are observed, with the lower field resonance more intense (~2.5:1). As explained previously for the tin systems, this lower field resonance is more likely to be $Ge(CH_3)_3$ in the cis isomer, as this group will, to a significant degree, be axial, depending on the equilibrium constant for (a,e) interconversion. This constant in turn is dependent on the *A* values of the CH_3 and $Ge(CH_3)_3$ groups. Two overlapping CCH_3 doublets are discernible in the ^1H spectrum, at 0.86 and 0.94 ppm, with the lower field one more intense, again consistent with a predominance of cis isomer. In the ^{13}C spectrum, $(CH_3)_3Ge$ signals at −4.48 and −3.18 ppm are recorded, again with the lower field resonance more intense. Reasonable extrapolation from the NMR data for the analogous isomeric tin compounds indicates the predominant formation of *cis*-4-methylcyclohexyltrimethylgermane. In addition, cyclohexyltrimethylgermane itself[8a] (from cyclohexyl bromide and $(CH_3)_3GeLi$) shows ^1H and ^{13}C shifts (for $Ge(CH_3)_3$) at δ 0.05 and −4.49, respectively, and $Ge(CH_3)_3$ is certain to prefer strongly an equatorial orientation (vide infra). These conclusions were confirmed in the following way.

We reasoned that the *A* value for $Ge(CH_3)_3$ would be greater than that for $Sn(CH_3)_3$ (1.06 ± 0.14 kcal/mole)[7] and in all probability be quite comparable with that for CH_3 (1.74 kcal/mole).[15] Hence the following equilibrium (eq 6) would



(6)

obtain with $K \sim 1$ at low temperatures. Therefore, if the −3.18-ppm carbon signal ($Ge(CH_3)_3$) at ambient temperature were ascribable to the above mobile cis system, the signal should collapse with reducing temperature and, at the slow interconversion limit, be replaced by two signals, one for axial $Ge(CH_3)_3$ (A) and another for equatorial $Ge(CH_3)_3$ (B). However, the −4.48-ppm signal, alleged above to represent $Ge(CH_3)_3$ in the *trans*-4-methyl isomer, should be essentially nondependent on temperature. On cooling from 302 K through 253 K, the 3.18-ppm signal broadens and at 203 K has disappeared to be replaced by new signals at ~−1.2 ppm and another more intense signal, unfortunately but not unexpectedly, overlapping with the signal ascribed to $Ge(CH_3)_3$ in the trans compound. In addition the CH_3C signal at 19.75 ppm (302 K) resolves into signals at 17.45 (axial CH_3C in B)[15] and 23.17 ppm (equatorial CH_3 in A) at 203 K, with the former representing B clearly more intense. K_{203} [B]/[A] is calculated to be ~3. This temperature dependence and chemical shift correlations establish the dominant isomer to be cis.

Concordant data is obtained from the 4-*tert*-butylcyclohexyl system described below.

***cis*-4-*tert*-Butylcyclohexyl Bromide with $(CH_3)_3GeLi$.** 4-*tert*-Butylcyclohexyltrimethylgermane was isolated from this reaction and exhibited $(CH_3)_3Ge$ ^1H resonances at δ 0.05 and 0.16 and ^{13}C signals for $(CH_3)_3Ge$ at −1.17 and −4.49 ppm, with the lower field resonance in each case more intense (~2.5:1). Note the remarkably good agreement between the shift of −1.17 ppm for axial $Ge(CH_3)_3$ here and that for the axial $Ge(CH_3)_3$ in the "frozen" (a,e) form of the *cis*-4-methylcyclohexyl derivative. This is because in the *cis*-4-*tert*-butyl derivative the *tert*-butyl group will greatly favor the equatorial orientation, necessitating an axial $Ge(CH_3)_3$. Also noteworthy is the correspondence between the equatorial $Ge(CH_3)_3$ shift in the *trans*-4-methyl (−4.48 ppm), *trans*-4-*tert*-butyl (−4.49 ppm), and cyclohexyltrimethylgermane itself (−4.49 ppm).

We did attempt to synthesize pure *trans*-4-methylcyclohexyltrimethylgermane via the Grignard route which provided access to the tin compound, but the reaction yielded virtually none of the desired compound. Additionally, we reacted *trans*-4-methylcyclohexyl tosylate with $(CH_3)_3GeLi$, hoping to produce the cis isomer. None of the desired compound was isolated.

In any event, the ^1H and ^{13}C NMR data establish the formation of isomeric mixtures in these $(CH_3)_3GeLi$ reactions with *cis*-4-alkylcyclohexyl bromides, with the cis isomers predominating.

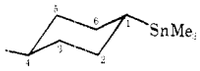
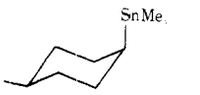
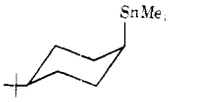
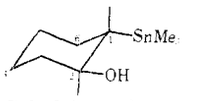
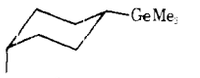
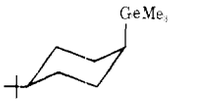
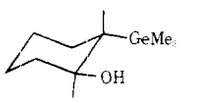
Reaction of Cyclohexene Oxide with $(CH_3)_3GeLi$. This reaction proceeded smoothly and in high yield to provide a colorless oil which solidified at room temperature. The microanalysis and ^1H and ^{13}C spectra establish its constitution as *trans*-2-hydroxycyclohexyltrimethylgermane. The methine proton (>C(**H**)OH) with $W_{1/2} \sim 24$ Hz for its ^1H signal (δ 3.4) requires two trans diaxial vicinal couplings. In a related compound, the methine proton (>C(**H**)OH) in *cis*-2-hydroxycyclohexyltrimethylsilane[23] (δ 4.15) has $W_{1/2} \sim 11$ Hz, consistent with an equatorial orientation. The PFT ^{13}C spectrum established the presence of one isomer (total of seven signals; also one $(CH_3)_3Ge$ signal in the ^1H spectrum) and the observed shifts agreed nicely with those calculated for the trans isomer, assuming additive substituent effects on the ^{13}C shifts by OH and $Ge(CH_3)_3$ groups, both equatorial.[16,19] As in the case of $(CH_3)_3SnLi$, epoxide ring opening proceeds with anti stereochemistry. A full listing of ^{13}C NMR parameters is in Table I.

Substitution Mechanisms. $(CH_3)_3SnLi$ Reactions. The formation of pure *cis*-4-methylcyclohexyltrimethylstannane from *trans*-4-methylcyclohexyl tosylate and *trans*-2-hydroxycyclohexyltrimethylstannane from cyclohexene oxide require inversion of configuration at carbon. There seems no justification in postulating other than an S_N2 mechanism for these transformations, which is consistent with the displacement of "hard" oxy-type leaving groups. Traylor et al.[5] reported inversion of configuration for $(CH_3)_3Sn$ displacement on *trans*-4-*tert*-butylcyclohexyl tosylate.

The nonstereospecific nature of the reactions with *cis*-4-methyl- and *cis*-4-*tert*-butylcyclohexyl bromides requires other mechanistic considerations, but it is possible or even probable that the trans (inverted) product also results from simple S_N2 displacements. Kinetic evidence supporting an S_N2 description is not available for any of these systems.

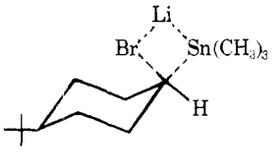
There are a number of possible mechanisms that could

Table I. Carbon-13 NMR Chemical Shifts[a] of Cyclohexyl Compounds

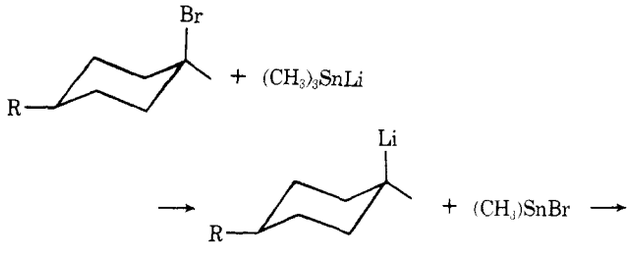
Registry no.	Compd	Carbon 1	2	3	4	5	6	$M(CH_3)_3$	CH_3	CH_3C
64871-26-7		24.77 (~390)	31.13 (nr)	37.82 (67.5)	33.13	37.82 (67.5)	31.13 (nr)	−11.97 (305; 289)	23.26	
	Calcd	24.45	30.87	37.88	32.53	37.88	30.87			
64871-27-8		26.70 (403.2; 384.7)	29.37 (nr)	34.68 (23.1)	31.97	34.68 (23.1)	29.37 (nr)	−9.85 (~292)	22.00	
64871-28-9		25.26	31.72	29.91 (67.1)	48.53	29.91 (67.1)	31.72	−12.04	27.46	32.49?
	Calcd	24.26	31.67	30.18	48.83	30.18	31.67			
38630-14-7		27.80	31.06	26.78 (12.0)	48.57	26.78 (12.0)	31.06	−9.41	27.53	nl
	Calcd			26.33		26.33				
		35.39 (~300)	74.34 (nr)	38.30 (52)	25.14	27.40 (50)	29.24 (nr)	−10.57		
64871-29-0	Calcd (trans)	32.65	74.07	36.88	25.83	27.38	29.77			
64871-30-3	Calcd (cis, axial OH)	30.25	68.67	34.5	20.13	28.28	24.07			
58992-27-1		27.90	28.74	28.31	27.06	28.31	28.74	−4.48		
64871-31-4		27.03	28.85	36.94	32.28	36.94	28.85	−4.49	23.18	
	Calcd	27.6	28.74	37.3	32.66	37.3	28.74			
64871-32-5		27.35	24.71	33.43	29.56	33.43	24.71	−3.24	19.59	
64871-33-6		27.22?	28.9	28.9	48.08	28.9	28.9	−4.49	27.5	32.61
	Calcd	27.51	28.83	28.75	48.07	28.75	28.83		27.5	32.26
64871-34-7		27.5	27.5?	25.39	48.36	25.39	27.5?	−1.17	27.5	33.42
		36.72	73.51	37.97	25.15	27.37	26.8	−2.74		
64871-08-5	Calcd (trans)	35.8	71.94	36.21	25.96	~28.00	27.64			
64871-10-9	Calcd (cis, axial OH)	33.4	66.54	33.81	20.26	27.6	21.94			

[a] Referenced to internal Me_4Si for $CDCl_3$ solvent. Low-temperature spectra for CD_2Cl_2 solvent. Numbers in parentheses refer to ^{13}C–^{119}Sn coupling constants. Calculated chemical shifts assume additivity of substituent effects on chemical shifts. [b] In the spectrum of the *cis*- and *trans*-4-*tert*-butylcyclohexyltrimethylgermanes there is considerable signal overlap at 27.5 and 28.9 ppm, and some assignments are therefore uncertain.

explain the retention (i.e., cis) product. The simplest would be a four-center process, but this cannot operate exclusively, as other products, e.g., hexamethylditin, cycloalkene, and almost certainly bicyclohexyls, need to be explained. The cycloalkene may arise mainly from β elimination, and decomposition of the resulting $(CH_3)_3SnH$ would yield hexamethylditin.



A strong possibility as a first step is a displacement formally on bromine to yield (via bromo–lithium exchange) a 4-alkylcyclohexyllithium and $(CH_3)_3SnBr$.[5,6] (Subsequent reaction of $(CH_3)_3SnBr$ and $(CH_3)_3SnLi$ would produce hexamethylditin.) The above reaction is indicated to yield *cis*-4-alkylcyclohexyllithium, which seems very plausible when mechanisms for this bromo–lithium exchange are considered. Rapid capture by $(CH_3)_3SnBr$ would then yield the tetraorganostannane, and Traylor[5] considered this sequence would produce pure *cis*-tin compound. However, the stereochemistry of electrophilic substitution at the carbon–lithium bond is by no means settled, and variable results have been reported.



Glaze[24] has reported that deuteriolysis of 4-*tert*-butylcyclohexyllithium proceeds with predominant retention at carbon, whereas bromination (with molecular bromine in pentane) yields predominantly inverted product, with temperature effects on the cis/trans ratio being unexplained.[25] Radicals may be implicated in these reactions. More polar brominating agents, e.g., pyridine–Br_2, were reported to proceed with predominant retention.[26] Most pertinent perhaps was the finding[26] that trimethylsilyl chloride reacted with 4-*tert*-butylcyclohexyllithium with predominant retention, and a similar outcome is reasonable for $(CH_3)_3SnBr$. A further aspect concerns the configurational stability of the C–Li bond in an ether solvent (THF) at 25–30 °C. There is evidence that ethers promote C–Li bond dissociation so that carbanion-triggered inversion may occur and hence lead to some trans product.[27] Bicyclohexyl formation might be explained in part by coupling of the cyclohexyllithium with unreacted cyclohexyl bromide.

Electron transfer from $(CH_3)_3SnLi$ to bromine must also be considered and would proceed as shown in eq 7. Tetraorganostannane, alkylbicyclohexyls, and hexamethylditin would be anticipated products, and almost certainly some *trans*-4-alkylcyclohexyltrimethylstannane would result, when the component radical stabilities are considered. At the moment, we have no evidence that this explanation is superior to one involving a combination of S_N2 at carbon (to yield the trans compound) and the two-step halogen–lithium‖ coupling reaction to yield the cis compound. Also no evidence is available to indicate stereochemistry at the tin center during these reactions. Very recently[28] ESR studies of certain metalate ion reactions with alkyl halides were reported,and in the case of $(CH_3)_3SnLi$ and cyclopropylcarbinyl halides it was concluded that a free-radical pathway was operative to extents regulated by the halide, solvent, etc.

$(CH_3)_3GeLi$ Reactions. The $(CH_3)_3GeLi$ reactions differ in that cis product clearly predominates (~2.5:1) for 4-CH_3 and 4-*tert*-butyl systems. Previously Bulten and Noltes[29] had investigated the reactions of $(CH_3)_3GeLi$ (in HMPA) with a variety of substrates, but no mechanistic conclusions could be drawn. Subsequently Eaborn, Hill, and Simpson[30] investigated reactions of optically active ethyl(1-naphthyl)phenylgermyllithium (R'_3Ge^*Li) with alkyl halides (RX) to yield optically active (R'_3GeR) compounds. Processes proceeding with both predominant retention (e.g., CH_3Br, $PhCH_2Cl$, $CH_2{=}CHCH_2Cl$) and inversion (e.g., CH_3I, $CH_2{=}CHCH_2I$, $PhCH_2I$) at germanium were identified. Suggestions were that the retention process involved direct coupling between R'_3Ge^*Li and RX in a four-center process, whereas the inversion process resulted from halogen–lithium exchange to give R'_3GeX and RLi (four-center retention) followed by coupling between R'_3GeX and RLi with inversion at germanium. Clearly a mechanistic duality was demonstrated for these reactions.

In the cases reported herein, it is clear that the mechanisms outlined for the $(CH_3)_3Sn$ reactions may also be operative to varying degrees. The most appealing suggestions are that the ~30% *trans*-4-alkylcyclohexyltrimethylgermane results from straightforward S_N2 displacement, while the cis compound is the result of halogen–lithium exchange (retention) followed by capture (with retention) of the cyclohexyllithium by $(CH_3)_3GeBr$. Eaborn's results indicate that alkyl bromides (e.g., isopropyl) react with predominant retention at germanium, a result consistent with an S_N2 description, although stereochemistry at carbon was not established. We would anticipate that electron-transfer mechanisms would be more important for R_3GeLi than R_3SnLi, but definite evidence along these lines is still being sought. Ring opening of cyclohexene oxide by $(CH_3)_3GeLi$ almost certainly requires the S_N2 description.

It is worthwhile emphasizing that bridgehead chlorides are unreactive toward $(CH_3)_3SnLi$, whereas bridgehead bromides are reactive[5,18] and provide a straightforward route to bridgehead tin derivatives. In view of this reactivity of bridgehead bromides which must proceed with retention, the variable stereochemistry in certain 7-norbornyl systems,[6] and the mixed stereochemistry for simple cyclic bromides reported here, it is clear that both stereochemical outcomes are possible and regulated by factors as yet incompletely defined.

The Conformational Preference of the Trimethylgermyl Group $(CH_3)_3Ge$. Previously we determined conformational free-energy differences for $Sn(CH_3)_3$ and $Pb(CH_3)_3$ in cyclohexane by direct observation.[7] Data accumulated in this work allow an indirect, but nevertheless useful, estimate of $\Delta G°(Ge(CH_3)_3)$. We have already discussed the variable-temperature ^{13}C spectra of *cis*-4-methylcyclohexyltrimethylgermane, and deduced that $K([B]/[A]) \sim 3$. Using the recently determined[15] $-\Delta G°(CH_3)$ of 1.74 kcal/mol, a $-\Delta G°_{203}[Ge(CH_3)_3]$ of 2.1–2.2 kcal/mol can be calculated. This assumes additivity of conformational energies. Alternatively, we can employ the chemical shift of CCH_3 in the mobile cis form (at 302 K) (19.75 ppm) in conjunction with those for equatorial CCH_3 (23.47 ppm) and axial CCH_3 (17.43 ppm)[15] to calculate another value of [B]/[A]. This procedure leads to $-\Delta G°[Ge(CH_3)_3]$ of 2.0 kcal/mol. The same method applied to $Ge(CH_3)_3$ chemical shifts gives a virtually identical result. That these "additivity" procedures are reasonable follows from calculations on the closely related cyclohexyltin systems. The directly determined $-\Delta G°_{204}[Sn(CH_3)_3]$ is 1.06 ± 0.14 kcal/mol,[7] whereas a value of 1.03 kcal/mol is obtained by utilizing the chemical shifts of either CCH_3 or $Sn(CH_3)_3$ in the mobile *cis*-4-methylcyclohexyltrimethylstannane, together with the appropriate reference values for equatorial and axial groups. There is no doubt the *A* value ($A = -\Delta G° = RT \ln K$) for $Ge(CH_3)_3$ is greater than that for CH_3, and the $Ge(CH_3)_3$ (~2.0 kcal/mol), $Sn(CH_3)_3$ (~1.1 kcal/mol), and $Pb(CH_3)_3$ (~0.7 kcal/mol) sequence reflects increasing C–M bond lengths, which apparently in part offset increasing atom size.

Experimental Section

Compounds. ***cis*-4-Methylcyclohexyl bromide** was prepared from commercial (predominantly trans ~65–70%) 4-methylcyclohexanol by reaction with triphenylphosphine dibromide in dry acetonitrile: yields were of the order of 55–60%; bp 75–78 °C (18 mm) [lit. 64–65 °C at (14 mm)];[32] the ^1H NMR spectrum showed the bromide to be >95% cis, H_{eq} at δ 4.45 (narrow m) and H_{ax} (~5%) at 3.9 (br).

***cis*-4-*tert*-Butylcyclohexyl bromide** was obtained in the same way from the alcohol (~80% trans): bp 38–40 °C (0.3 mm); mp 20–23 °C [lit. bp 70 °C (2 mm); mp 23–25 °C];[31] ^1H NMR H_{eq} at δ 4.7, $(CH_3)_3C$ at 0.9.

***trans*-4-Methylcyclohexyl tosylate** was prepared from trans alcohol, obtained by the method of Stork and White:[32] bp 101–102 °C (56 mm) [lit. 100.5–101 °C (56 mm)].[32] This alcohol showed >C(**H**)OH (axial) at 3.5 ppm (>95%) and >C(**H**)OH (equatorial) at 3.9 ppm. The tosylate was prepared in the standard way from tosyl chloride in pyridine: mp 70.5–71 °C (lit. 70.8–71.8 °C);[33] ^1H NMR H_{ax} at 4.3 ppm (br m).

Cyclohexene oxide was prepared, via the bromohydrin, in the manner outlined by Read and Hurst:[33] bp 66 °C (60 mm) [lit. 129–130 °C (760 mm)]; ^1H NMR δ 1.4 (4 H), 1.9 (4 H), 3.15 (2 H). Another identical sample was obtained by treating cyclohexene with *m*-chloroperbenzoic acid in the usual way.

***trans*-4-Methylcyclohexyltrimethylstannane** was obtained from the reaction of the Grignard reagent (prepared from (>95% *cis*-4-methylcyclohexyl bromide in the normal way) with $(CH_3)_3SnCl$. Standard workup and distillation yielded a clear oil with bp 68–72 °C (3–5 mm). VPC analysis indicated slight contamination with another component, suspected to be bis(4-methylcyclohexyl).

Anal. Calcd for $C_{10}H_{22}Sn$: C, 46.00; H, 8.4. Found: C, 48.1; H, 8.7. Although the carbon analysis is slightly high, the ^1H and ^{13}C NMR confirm the consitution. The yield of distilled material was about 30%.

Preparation of Trimethyltinlithium. This reagent was prepared basically in the manner described by Tamborski and co-workers.[34] Lithium metal (3.36 g, 0.48 mol) was cut into small pieces which were then protected and flattened with a hammer. The flattened Li pieces (now about the size of a cent) were then cut into smaller pieces (~2-mm wide) and placed in the reaction vessel containing anhydrous THF. The vessel (250-mL round-bottom flask) was fitted with a condenser, drying tube, N_2 inlet, and pressure equalizing dropping funnel. $(CH_3)_3SnCl$ (9.58 g, 0.048 mol) was dissolved in dry THF (~30 mL) and placed in the dropping funnel. The reaction vessel was cooled (0 to ~−5 °C) and blanketed with N_2, and the Li/THF was stirred vigorously. The $(CH_3)_3SnCl$ solution was added dropwise, and a color change to dark olive green usually appeared after about 15 min. Stirring was continued for about 2 h. The unreacted Li metal was removed by filtering the solution (under N_2 pressure) through a fitted bent side arm into an attached 250-mL three-neck round-bottom flask. The $(CH_3)_3SnLi$ solution is then available for reaction.

***cis*-4-Methylcyclohexyltrimethylstannane.** *trans*-4-Methylcyclohexyl tosylate (11.5 g, 0.043 mol) in dry THF (~30 mL) was added dropwise to the preformed $(CH_3)_3SnLi$ solution cooled to 0 °C under N_2. Reaction proceeded for a total of 5 h, and then the system was quenched with 20% NH_4Cl solution (~20 mL). The ethereal layer was separated and the aqueous layer extracted with ether. The combined organic layers were dried ($MgSO_4$) and ether was removed under reduced pressure. A ^1H NMR spectrum of the crude product was obtained, and $(CH_3)_3Sn$ resonances were observed for the desired product, as well as for hexamethyldistannane, which occurs to lower field and has two sets of $^{117,119}Sn$ satellites. Distillation yielded an oil: bp 95–100 °C (20 mm).

Anal. Calcd for $C_{10}H_{22}Sn$: C, 46.00; H, 8.4. Found: C, 44.17, H, 8.46. The ^1H and ^{13}C NMR spectra establish its constitution. (The yield was 40%.) Significant amounts of alkene and hexamethylditin were identified by ^1H NMR analysis.

***cis*- and *trans*-4-Methylcyclohexyltrimethylstannane.** The *cis*-4-methylcyclohexyl bromide (~10 g, 0.057 mol) was added to $(CH_3)_3SnLi$ in THF (~0.058 mol) and allowed to react for about 3 h. Workup in the standard way provided a crude oil which was found to have a trans/cis ratio of ~2:1, which was unchanged by our distillation procedure. The purified stannane had bp 57–59 °C (3 mm) (yield ~35%).

Anal. Calcd for $C_{10}H_{22}Sn$: C, 46.00; H, 8.44. Found: C, 46.06; H, 8.63. Concordant ^1H and ^{13}C spectra were obtained and described in the text. Hexamethylditin and probably bicyclohexyls were also found.

***cis*- and *trans*-4-*tert*-Butylcyclohexyltrimethylstannane** were prepared as described above for the 4-CH_3 isomer, and the crude oil obtained was examined by ^1H NMR to determine the cis/trans ratio. Substantial amounts of hexamethylditin were found and slightly contaminated the desired product on distillation, which had no effect on the cis/trans ratio. The yield was again poor (30–35%): bp 104–108 °C (4 mm).

Anal. Calcd for $C_{13}H_{28}Sn$: C, 51.48; H, 9.24. Found: C, 50.92; H, 9.24.

***trans*-2-Hydroxycyclohexyltrimethylstannane.** Cyclohexene oxide (4.5 g, 0.046 mol) was reacted with $(CH_3)_3SnLi$ (0.046 mol) in the manner described for the bromides, and the product was obtained in quite pure form in good yield (80%): bp 90 °C (3–4 mm); ^1H NMR δ 0.06 (9 H, $(CH_3)_3Sn$, $J \sim 52$ Hz), 1.0–2.2 (10 H, ring protons including –OH), 3.54 (m, 1 H, >C(**H**)OH).

Anal. Calcd for $C_9H_{20}SnO$: C, 41.11; H, 7.61. Found: C, 40.33; H, 7.81.

Preparation of Trimethylgermyllithium. The procedure described by Bulten and Noltes[21] was followed in essentially all details, and the filtered solution reacted with the bromides as described above.

Cyclohexyltrimethylgermane was prepared from the bromide and had boiling point [75 °C (20 mm)] and NMR spectra in agreement with those obtained previously.[8a]

***cis*- and *trans*-4-Methylcyclohexyltrimethylgermane.** *cis*-4-Methylcyclohexyl bromide (>95% cis) reacted with $(CH_3)_3GeLi$ in the normal way and distillation provided three fractions, which almost certainly contained some 4-cyclohexyl material as judged by ^1H NMR integration and VPC analysis (T = 70 °C, Hipase 3600 column). Fraction 3 [bp 78 °C (19 mm)] contained ~10% dicyclohexyls and 90% of the desired product as a mixture of isomers.

Anal. Calcd for $C_{10}H_{22}Ge$: C, 55.91; H, 10.25. Found: C, 56.7; H, 10.5. This corresponds to 95% germanium compound and 5% of 4,4′-dimethylbicyclohexane.

The mass spectrum exhibited peaks characteristic of the five germanium isotopes, and the cracking pattern observed was consistent with that anticipated for an unsymmetrical A_3GeB type.[35] A molecular ion m/e 216 for ^{74}Ge (36.47%) was observed, with correct isotopic intensities.

***cis*- and *trans*-4-*tert*-Butylcyclohexyltrimethylgermane** was obtained from the reaction of $(CH_3)_3GeLi$ with *cis*-4-*tert*-butylcyclohexyl bromide. The crude product was distilled to give three fractions, the first of which was mainly unreacted *cis*-bromide. Fractions 2 and 3, which were white solids at room temperature, contained no unreacted *cis*-bromide as revealed by the ^1H NMR spectrum. The germane product exhibited two $Ge(CH_3)_3$ peaks at δ 0.05 and 0.16 with the latter more intense [bp 90 °C (5 mm)].

Anal. Calcd for $C_{13}H_{28}Ge$: C, 60.79; H, 10.91. Found: C, 60.8; H, 11.22.

The mass spectrum exhibited a molecular ion at m/e 257 with the correct isotopic intensities. Other germanium-containing ions at m/e 242 (loss of CH_3), 200 (loss of *tert*-butyl), and 118 [$(CH_3)_3Ge$] were observed.

2-Hydroxycyclohexyltrimethylgermane. This product was obtained in satisfactory yield (~60%) as an oil which distilled [bp 96 °C (9 mm)] as a clear oil, but which soon solidified at room temperature (16 °C). The ^1H NMR spectrum exhibited one $(CH_3)_3Ge$ signal at δ 0.12, while >C(**H**)OH resonated at δ 3.4 as a broad band with the ring protons spread from δ 1 to 2; ν_{OH} observed at 3350 cm^{-1}. The mass spectrum did not contain a molecular ion at m/e 217, but a high intensity peak at m/e 199, corresponding to loss of H_2O.

Anal. Calcd for $C_9H_{20}OGe$: C, 49.8; H, 9.2. Found: C, 48.3; H, 9.36.

Solvents. Tetrahydrofuran was dried by distillation from a mixture of lithium aluminium hydride and calcium hydride and stored over 4A molecular sieves.

Hexamethylphosphoric triamide was treated with calcium hydride until bubbling activity stopped. The partly dried solvent was then stirred with sodium until the characteristic blue color persisted. When needed the HMPA was freshly distilled: bp 80–81 °C (3 mm).

NMR Spectra. ^1H NMR spectra were obtained for solutions in either $CDCl_3$ or CCl_4 and referenced to internal Me_4Si on Varian T-60 or Jeol MH100 spectrometers. Some ^1H spectra were obtained at 270 MHz at the National NMR Center in Canberra. ^{13}C spectra were obtained at either 22.625 or 67.89 MHz on Bruker spectrometers for $CDCl_3$ solutions referred to internal Me_4Si. Variable-temperature spectra were obtained for CD_2Cl_2 solutions.

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Registry No.—*cis*-4-Methylcyclohexyl bromide, 28046-90-4; *trans*-methylcyclohexanol, 28046-91-5; triphenylphosphine dibromide, 1034-39-5; *cis*-4-*tert*-butylcyclohexyl bromide, 5009-36-9; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; *trans*-4-methylcyclohexyl tosylate, 7453-05-6; tosyl chloride, 98-59-9; cyclohexene oxide, 286-20-4; $(CH_3)_3SnCl$, 1066-45-1; $(CH_3)_3SnLi$, 17946-71-3; Li, 7439-93-2; $(CH_3)_3GeLi$, 18489-76-4.

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Use of the Thallium Trinitrate Catalyzed Rearrangement of Ketones in the Synthesis of an Acidic Morphinan Derivative

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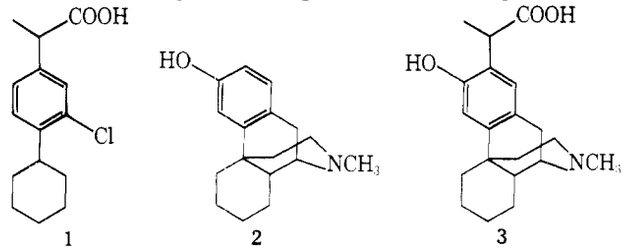
The introduction of the α-methylacetic acid side chain on D,L-*N*-methyl-3-hydroxymorphinan was carried out in an unsuccessful attempt to combine analgesic activity with the antiinflammatory activity associated with 2-arylpropionic acid derivatives. Using D,L-*N*-allyl-3-hydroxymorphinan as starting material, the key steps in the reaction sequence are the thallium trinitrate rearrangement of D,L-2-acetyl-3-methoxy-*N*-carboethoxymorphinan followed by the careful monomethylation of the acetic acid side chain of the rearrangement product using methyl iodide and lithium diisopropylamide. The Taylor–McKillop rearrangement is demonstrated to be useful in complex systems such as the morphinan.

In an attempt to combine both central analgesic and antiinflammatory activity in a single molecule we have developed a synthetic route to **3**, a molecule possessing both the structural features of the antiinflammatory phenylpropionic acids (**1**)[1] and the morphinan analgesics such as levorphanol (**2**).[2]



1 2 3

Results and Discussion

The synthetic plan envisaged introduction of the 2-propionic acid side chain on a suitable morphinan intermediate employing acylation, followed by rearrangement to the acid using the recently developed thallium trinitrate procedure of McKillop and Taylor.[3] Because there was insufficient information available on whether this reaction would proceed well with a propiophenone or with a free phenolic hydroxyl present, some initial model experiments were carried out. Direct rearrangement of propiophenone to methyl α-methylphenylacetate under the conditions of McKillop and Taylor gives poor yields.[3] Thallium trinitrate adsorbed on an insoluble inorganic support such as Florisil[4] or K-10[5] has been utilized to carry out this direct transformation. In our hands TTN adsorbed on Florisil led to none of the desired product and propiophenone was recovered quantitatively. The activity of this reagent was confirmed by reaction with acetophenone, which gave methyl phenylacetate in high yields. Therefore, instead of trying to sort out the reasons for such behavior with adsorbed thallium trinitrate, it proved more efficient to rely on direct methylation of the acetic acid side chain.

An attempted thallium-catalyzed rearrangement of *o*-hydroxyacetophenone (**5a**) at room temperature for 24 h gave no reaction, while the corresponding methyl ether (**5b**) was converted smoothly to the phenylacetate derivative **6b** in 15 min. Thus blocking of phenolic *o*-hydroxy groups is a requirement in the thallium trinitrate reaction.

As this rearrangement has been reported to proceed with difficulty with basic molecules[6] (presumably due to complex formation with the basic center), application of the thallium reaction to the morphinan system would be expected to require prior conversion of the amine to an acyl or carbamate derivative.

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