hexanedione (429 mg, 1.70 mmol) was allowed to react with copper (197 mg, 3.10 mmol) activated with 8.6 mg of iodine and 1-(phenylthio)-1-propene (161 mg, 1.07 mmol) in refluxing benzene for 2 h. After the usual workup, flash chromatography (9:1 hexane/ethyl acetate) gave three fractions containing the title compound; (1) 56 mg (*E* isomer), (2) 31 mg (a 1:1 mixture of *E* and *Z* isomers), and (3) 38 mg (*Z* isomer). Total yield was 43% (*E*/*Z* = 56/44).

***E* isomer**: TLC (4:1 hexane/ethyl acetate) R_f 0.22; ^{1}H NMR (60 MHz, CCl_4) δ 1.0–1.3 (m, 3 H), 1.30 (d, *J* = 6 Hz, 3 H), 1.8–2.6 (m, 5 H), 2.8–3.7 (m, 1 H), 5.5 (d, *J* = 5 Hz, 1 H), 7.1–7.6 (m, 5 H), IR (neat) 3050 (w), 2950 (m), 2920 (w), 2860 (w), 1635 (s), 1395 (s), 1205 (s), 1020 (m), 885 (m), 735 (m), 635 (m) cm^{-1}.

***Z* isomer**: TLC (4:1 hexane/ethyl acetate) R_f 0.18; ^{1}H NMR (60 MHz, CCl_4) δ 0.9–1.3 (m, 3 H), 1.35 (d, *J* = 7 Hz, 3 H), 1.7–2.7 (m, 5 H), 3.2–3.8 (m, 1 H), 6.1 (d, *J* = 9 Hz, 1 H), 7.2–7.7 (m, 5 H); IR (neat) 3050 (w), 2950 (m), 2925 (m), 2860 (w), 1640 (s), 1390 (m), 1200 (m), 1020 (m) cm^{-1}.

The spectral data of both isomers of **23** are very similar to those reported in the literature,[17] except for NMR signals of the 6-methyl group. Presumably our compounds are mixtures of stereoisomers as far as the 6-methyl group is concerned, whereas the compounds reported in the literature seem to be isomerically pure.

Registry No. **1**, 92912-81-7; **2**, 92898-22-1; **3**, 92898-23-2; **4**, 13463-61-1; **5**, 92912-82-8; **6**, 97467-11-3; **7**, 97467-12-4; **8**, 97467-13-5; **9**, 92898-24-3; **10**, 97467-14-6; **11**, 92898-18-5; **12**, 97467-15-7; **13**, 97467-16-8; **14**, 92898-19-6; **15**, 92898-20-9; **16**, 97485-96-6; **17**, 97467-17-9; **18**, 18150-87-3; **19**, 97467-18-0; **20**, 92898-21-0; **21a**, 92898-25-4; **21b**, 92898-26-5; **22**, 54023-37-9; **23**, 67808-96-2; $C_6H_5C(CH_3)=CH_2$, 98-83-9; *p*-$CH_3C_6H_4CH=CH_2$, 622-97-9; *p*-$ClC_6H_4CH=CH_2$, 1073-67-2; *m*-$CF_3C_6H_4CH=CH_2$, 402-24-4; (*Z*)-PhCH=$CHCH_3$, 766-90-5; (*E*)-PhCH=$CHCH_3$, 873-66-5; $C_5H_{11}CH=CH_2$, 592-76-7; $CH_3COCH=CH_2$, 78-94-4; $CH_2=C(CH_3)CH=CH_2$, 78-79-5; $CH_2=CHCH=CHCH_3$, 504-60-9; $CH_2=CHC(=CH_2)CH_2CH_2CH=C(CH_3)CH_3$, 123-35-3; $CH_3CH=CHCH=CHCOOMe$, 1515-80-6; PhC≡CH, 536-74-3; PhC≡CCH_3, 673-32-5; $C_6H_{13}C≡CH$, 629-05-0; 3,3-dibromo-2,4-pentanedione, 4111-99-3; acetylacetone, 123-54-6; 2,2-dibromo-1-phenyl-1,3-butanedione, 97467-19-1; 1-phenyl-1,3-butanedione, 93-91-4; copper, 7440-50-8; 2,2-dibromo-1,3-cyclohexanedione, 6648-30-2; styrene, 100-42-5; cuprous bromide, 7787-70-4; cupric bromide, 7789-45-9; ethyl 2,2-dibromoacetoacetate, 89415-67-8; 2,2-dibromo-5-methyl-1,3-cyclohexanedione, 21544-85-4; 1-(phenylthio)-1-propene, 22103-05-5; 2,2-dibromo-5,5-dimethyl-1,3-cyclohexanedione, 21428-65-9; 2,5-norbornadiene, 121-46-0; 2,3-dihydrofuran, 1191-99-7.

Stereochemistry of the Reductive Alkylation of α,β-Epoxy Ketones

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α-Epoxy ketones have been found to be useful intermediates for the regiospecific alkylation of ketones. We have examined the steric course of the alkylation and shown it to be highly stereoselective.

Regio- and stereoselective formation of new carbon–carbon bonds is a fundamental problem in synthetic organic chemistry. One of the more important bond-forming reactions is the alkylation of carbonyl-activated carbons. However, when an unsymmetrical ketone with protons at both the α and α′ positions is treated with a base, two enolates are possible. Usually a mixture of enolates is formed; the composition of the mixture being dependent upon the conditions used in proton abstraction. D'Angelo has reviewed ways in which regiospecific enolates may be prepared.[1] One useful approach is the direct generation of specific enolates by treatment of ketones with dissolving metals in liquid ammonia or with organometallic reagents under appropriate conditions. Many of the applications of this approach have been tabulated.[2] This method is, of course, limited to those cases which involve α,β-unsaturated ketones or ketones with appropriate α-substitution (leaving groups).

With respect to enolate alkylations, there are two main factors which influence the stereochemical outcome of the reaction: (1) stereoelectronic control and (2) steric hindrance to the approach of the alkylating agent. Stereoelectronic control dictates that the alkylating agent approach the plane of the enolate in a perpendicular manner, allowing maximum orbital overlap during bond formation and bond cleavage. Steric hindrance considerations dictate that the alkylating agent approach the enolate from the most accessible face.

House[3] and Jackman and Lange[4] have summarized much of the work on stereochemistry of alkylation. Despite the variance of results, two observations seem generally applicable: first, the presence of an α-substituent such as an alkyl, cyano, or carbalkoxy group enhances the degree to which alkylation at that carbon proceeds via the axial mode. Second, if axial alkylation results in a 1,3-diaxial interaction, the product from equatorial alkylation is frequently favored.

The reaction mechanism which best explains the stereochemical outcome of enolate alkylations has been suggested by Lansbury[5] and House.[6] In this mechanism it is suggested that the enolate oxygen and the α R group do not remain coplanar after enolate formation. Instead, they become staggered (at a dihedral angle of θ) so as to diminish any eclipsing interaction. Approach of the enolate via the path which leads to axial alkylation tends to

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(1) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.
(2) Caine, D. In "Organic Reactions"; Dauben, W. G., Ed.; John Wiley and Sons: New York, 1976; Vol. 23, Chapter 1.
(3) House, H. O. In "Modern Synthetic Reactions", 2nd ed.; Benjamin, Inc.: Menlo Park, CA, 1972; Chapter 9.
(4) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.
(5) Lansbury, P. T., Dubois, G. E. *Tetrahedron Lett.* **1972**, 3305.
(6) House, H. O., Umen, M. J. *J. Org. Chem.* **1973**, *38*, 1000.

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expand θ as the orbital hydridization changes from sp^2 to sp^3. In contrast, approach via the path which leads to equatorial alkylation tends to compress θ. Intuitively, one would expect that when R is large enough to provide a significant steric interaction with the enolate oxygen, axial alkylation (angle expansion) would be favored over equatorial alkylation (angle compression). On the other hand, when R is small, as when R = H, steric interaction is less significant, and thus the effect of compression of θ would be less pronounced. This model is consistent with both the stereoselective and nonstereoselective results reported for R = alkyl and R = H, respectively. In those cases where 1,3-diaxial interaction between the entering alkyl group and one already present in the enolate would result from axial alkylation, this steric hindrance is sufficient to overcome the angle compression energy of equatorial alkylations.

We have reported[7] that α,β-epoxy ketones make excellent substrates for the regioselective generation of enolates by reductive conditions. The intermediate β-alkoxy enolates may be alkylated in high yields to produce β-hydroxy-α-alkyl ketones. If no α-substituent is present in the α,β-epoxy ketone, then the product may be dehydrated very easily to form specifically α-alkylated-α,β-unsaturated ketones. When an α-substituent is present, then β-hydroxy-α,α-disubstituted ketones are formed.

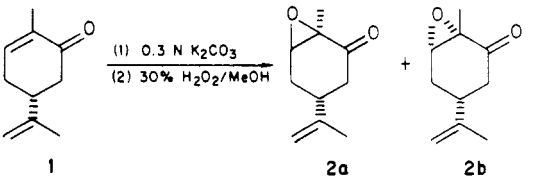
In the present study we wished to establish the stereochemical outcome of the reductive-alkylation sequence and to examine the extension of the reaction to the 4a-methyl-4,4a,9,10-tetrahydro-2(3*H*)-phenanthrone series, a series useful for diterpene natural product synthesis.

The first objective was to be met in two ways. First, the alkylation of carvone epoxide with trideuteriomethyl iodide was to be carried out. The stereochemistry of this reaction could then be studied by the ^1H NMR properties of the labeled product by use of aromatic solvent-induced shift (ASIS) techniques.

Second, the reductive alkylation of carvone epoxide with methyl bromoacetate as the alkylating agent was to be examined. It was thought that the resultant β-keto-γ-hydroxy esters could be hydrolyzed to a γ-hydroxy acid and subsequently lactonized. The stereochemistry of the alkylation could then be deduced from the structure of the lactone and compared to the results from the study of reductive methylation.

l-Carvone epoxide (**2**) was selected as the model epoxy ketone because it was readily available from the natural product *l*-carvone (**1**) and because previous work had shown that the base-catalyzed epoxidation of *l*-carvone is stereoselective, and that the major product is the epoxide **2a** with the oxirane ring trans to the isopropenyl group.[8] When **1** was treated with 0.3 N K_2CO_3 and 30% H_2O_2 in methanol, carvone epoxide was isolated in 85–95% yield. Gas chromatographic analysis of the product revealed two peaks in ca. 19 to 1 ratio. When analyzed by GC/MS both peaks exhibited molecular ions of 166 and similar fragmentation patterns. In accordance with the earlier work, the major peak was assigned structure **2a**. The minor peak was presumed to be isomer **2b**. No attempt was made to separate the isomers and all subsequent reactions were carried out on the mixture.

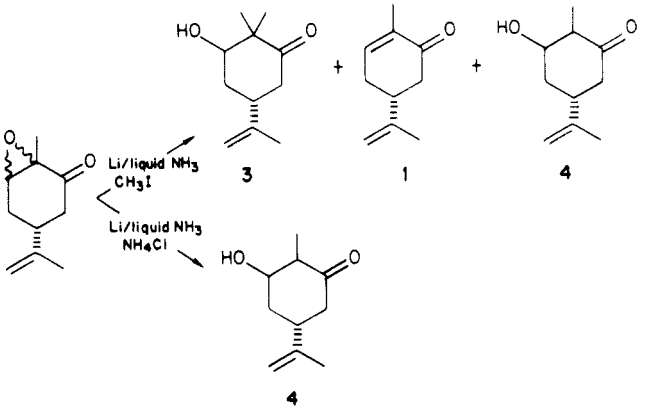
With the epoxide **2** in hand, attention was turned to the reductive alkylation. Initial efforts were devoted to an



1 **2a** **2b**

attempt to optimize the yield of the alkylated hydroxy ketone. Various modifications of our basic procedure[7] for reductive alkylation were systematically examined. Lithium was retained as the reducing metal because of its superior solubility and reducing capacity and because lithium enolates are less prone to equilibrate or give *O*-alkylation than are enolates of other alkali-earth-metal cations.[3] Three equivalents of lithium were used instead of the stoichiometric requirement of two because in the latter case ca. 10–15% of the starting epoxide remained unreacted. Little difference was noted when the cosolvent was varied from ether to tetrahydrofuran or dimethoxyethane or when the ammonia was replaced by the cosolvent prior to alkylation. A four- to fivefold excess of methyl iodide was found to give the best result. Other reaction parameters such as time and temperature of enolate formation, time and temperature of alkylation, and choice of quenching agent were also examined. The optimal reaction conditions are described in detail in the Experimental Section.

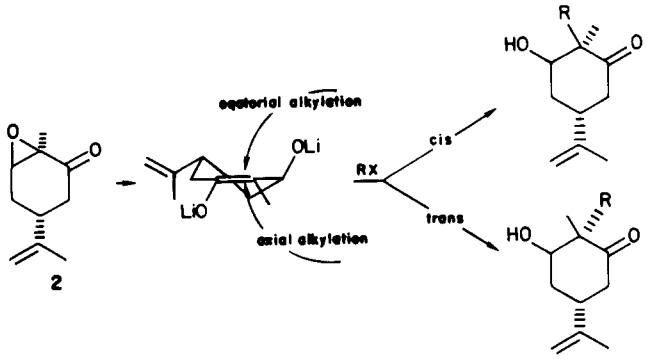
When epoxide **2** was treated under the optimal reaction conditions, the desired alkylation product **3** was obtained in 65–70% yield, as determined by quantitative GC analysis of the crude mixture. Alternately, the product could be isolated on a preparative scale in 60–65% yield by chromatography of the reaction mixture on silica gel. Other components of the crude reaction mixture which were isolated and characterized include carvone **1** (ca. 10%) and the unalkylated reduction product **4** (less than 1%). Ketone **4** could also be obtained by reductive protonation of epoxide **2**. No oxygen alkylation was observed as determined by the ^1H NMR analysis of the crude reaction mixture.



Once a satisfactory procedure for the reductive methylation of carvone epoxide had been worked out, the stereochemistry of the alkylation was studied. Reduction of **2** gives an enolate which can be approached by the alkylating agent from two directions, cis or trans, to the alkoxy group at position 3. The result is either equatorial or axial alkylation, respectively. Note that carbons 3 and 5 are not directly involved in the alkylations, so the configuration at these centers remains unchanged from the configuration present in the epoxide **2**.

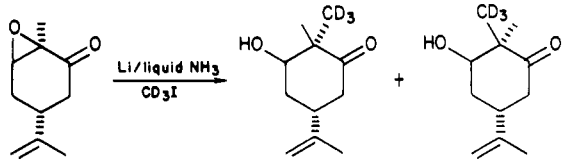
When R = CH_3, it is not possible to distinguish between the original α-methyl group and the one added by alkylation. Previous workers have found it convenient to study

(7) McChesney, J. D.; Wycpalek, A. F. *J. Chem. Soc., Chem. Commun.* **1971**, 542.
(8) (a) Klein, E.; Ohloff, G. *Tetrahedron* **1963**, *19*, 1091. (b) Djerassi, C.; Klyne, W.; Norin, T.; Ohloff, G.; Klein, E. *Tetrahedron* **1965**, *21*, 163. (c) Katsuhara, J. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2391.



the methylation of α-methyl ketones with the use of trideuteriomethyl iodide (CD_3I) as the alkylating agent.[9] This reagent has more or less the same reactivity and steric requirements as methyl iodide and is, therefore, assumed to cause minimal change in the steric course of the alkylation. Moreover, it renders the two methyl groups distinguishable by ^1H NMR since the trideuteriomethyl group does not exhibit a signal. The strategy, then, was to prepare the trideuteriomethylated ketone **5** under the same conditions as before and compare its ^1H NMR properties to those of **3**.

Accordingly, epoxide **2** was treated with lithium in ammonia as before and alkylated with CD_3I. The major product was isolated from this alkylation in ca. 65% yield. Analysis of the IR, ^1H NMR, ^{13}C NMR, mass spectral, and elemental analysis data suggested that the desired ketone **5** had been obtained. With ketones **3** and **5** both in hand,



their NMR properties were compared. The ^1H NMR spectrum of ketone **3** in $CDCl_3$ has 3 H singlets at 1.91, 1.30, and 1.23 ppm. The ^{13}C NMR spectrum of **3** also has three signals that correspond to methyl groups which occur at 24.5, 20.6, and 20.4 ppm. When the ^1H NMR spectrum of **5** was obtained, it was found to be virtually identical with that of **3** with one exception: the 3-H singlet at 1.30 ppm was completely absent. Likewise, the ^{13}C NMR spectra of **3** and **5** were identical except that the signal at 24.5 ppm was absent in the spectrum of **5**.

These results were interpreted to mean that the methylation was completely stereoselective within the limits of detection by NMR (i.e., 95% ± 5% stereoselective) to give either **5a** or **5b** (as yet indistinguishable). Were this not the case, the ^1H NMR of the product would be expected to show two peaks for α-methyl groups. The ratio of the peaks would reflect the relative proportion of **5a** to **5b**, and the sum of the integration of both peaks would equal 3 H.

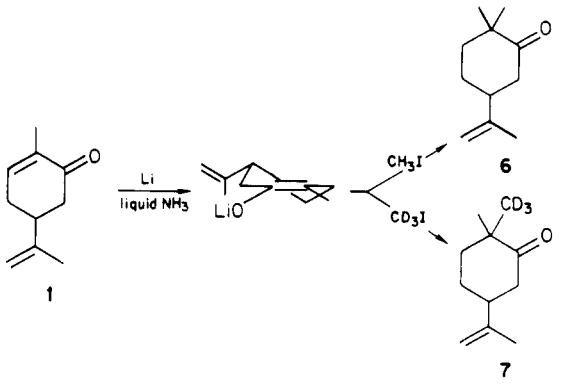
In order to distinguish whether the structure of the product was **5a** (axial alkylation) or **5b** (equatorial alkylation), it was necessary to be able to assign the three methyl signals in the ^1H NMR spectrum of **3**. The broad singlet at 1.91 ppm could clearly be assigned to the allylic methyl group of the side chain. The two remaining signals, 1.30 and 1.23 ppm, correspond to the two methyl groups α to the carbonyl.

A special technique to distinguish between axial and equatorial methyl groups which are α to a carbonyl has been described by Bhacca and Williams[10] and has seen frequent use in stereochemical assignments of α-methyl ketones.[6,9,11] It has been empirically observed that when the solvent is changed from $CDCl_3$ or CCl_4 to benzene-d_6, the ^1H NMR signal for an axial α-methyl group typically undergoes an upfield shift of 0.06–0.27 ppm while the signal of an equatorial α-methyl group undergoes a downfield shift of 0.0–0.15 ppm.[10]

The ^1H NMR spectra of **3** and **5** were obtained in both CCl_4 and benzene-d_6 and then compared. The two 3-H singlets of **3** corresponding to the α-methyl groups resonate at 1.18 and 1.10 ppm in CCl_4. When the solvent is changed to benzene-d_6, the two signals appear at 0.93 and 1.22 ppm, an apparent aromatic solvent-induced shift (ASIS) of +0.25 and −0.12 ppm, respectively. When the ^1H NMR spectrum of trideuteriomethyl ketone **5** is obtained in CCl_4, the lone α-methyl signal appears at 1.10 ppm. When the solvent is changed to benzene-d_6, the signals shift downfield to 1.22 ppm, an ASIS of −0.12 ppm. While it could be argued that in the case of **3** it was the upfield signal at 1.10 ppm that shifted further upfield to 0.93 and the downfield signal at 1.18 ppm shifted further downfield, by analogy to the literature and the ASIS results of ketone **5**, this does not seem likely.

On the basis of this ASIS data and literature analogy,[6,12] the 1.18 ppm signal of **3** (CCl_4) was assigned to the axial methyl group and the 1.10 ppm signal was assigned to the equatorial methyl group. Therefore, since the only α-methyl resonance of **5** occurred at 1.10 ppm and underwent a downfield shift of −0.12 ppm to 1.22 ppm, the methyl group was assigned an equatorial orientation. It can therefore be deduced that the alkylation had been stereoselective (95% ± 5%) axial alkylation.

In order to assess any role that the β-alkoxy group might play in directing the alkylation of the enolate derived from **2**, the preparation of ketones **6** and **7** was undertaken. It was reasoned that the enolate formed by the reduction of *l*-carvone (**1**) would only differ from the enolate generated by the reduction of carvone epoxide **2** by the absence of the β-alkoxy group.



l-Carvone (**1**) was treated with 3 equiv of lithium and alkylated with 4 equiv of either CH_3I or CD_3I under the same conditions as used in the preparation of ketones **3** and **5**. The methylated ketones **6** and **7** were isolated by

(9) (a) Huff, B. J. L.; Tuller, F. N.; Caine, D. *J. Org. Chem.* **1969**, *34*, 3070. (b) Matthews, R. S.; Hyer, P. K.; Folkers, E. A. *J. Chem. Soc., Chem. Commun.* **1970**, 38.

(10) Bhacca, N. S.; Williams, D. H. In "Applications of NMR Spectroscopy in Organic Chemistry", 1st ed.; Holden-Day, Inc.: San Francisco, 1964; Chapter 7.

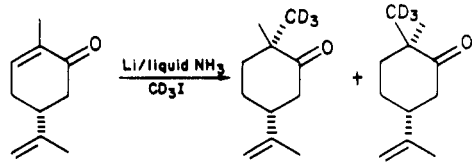
(11) Matthews, R. S.; Girgenti, S. J.; Folkers, E. A. *J. Chem. Soc., Chem. Commun.* **1979**, 708.

(12) Huff, B. J. L.; Tuller, F. N.; Caine, D. *J. Org. Chem.* **1969**, *34*, 3070.

column chromatography in 30% and 32% yields, respectively. No attempt was made to optimize these yields.

An ASIS study was performed on the two ketones **6** and **7** by obtaining their ^1H NMR spectra in CCl_4, $CDCl_3$, and benzene-d_6. In CCl_4, the dimethyl ketone **6** exhibited two 3-H singlets which corresponded to α-methyl groups at 1.17 and 1.05 ppm. When the solvent was changed to benzene-d_6, the downfield peak shifted +0.20 ppm to 0.97 ppm while the upfield peak shifted −0.07 to 1.12 ppm. In CCl_4, trideuteriomethyl ketone **7** exhibited a small peak at 1.13 ppm and a larger peak at 1.03 ppm in a ratio of 1:2.75, respectively; the two peaks together integrated for 3 H. When the solvent was changed to benzene-d_6, the small peak shifted upfield by 0.23 to 0.90 ppm while the large peak shifted downfield by 0.07 to 1.10 ppm.

The observation that the total integration of the small and large peaks together is equal to 3 H suggests that ketone **7** is a mixture of stereoisomers. the upfield ASIS for the small peak suggests that it arises from a ketone with an axial methyl. Likewise, the downfield shift of the larger peak suggests that it arises from a ketone with an equatorial methyl. These data were therefore interpreted to mean that the trideuteriomethylation occurred to give a mixture of stereoisomers **7a** and **7e** in a ratio of 73:27, respectively. The ASIS data for compounds **3**, **5**, **6**, and **7** are summarized in Table I.

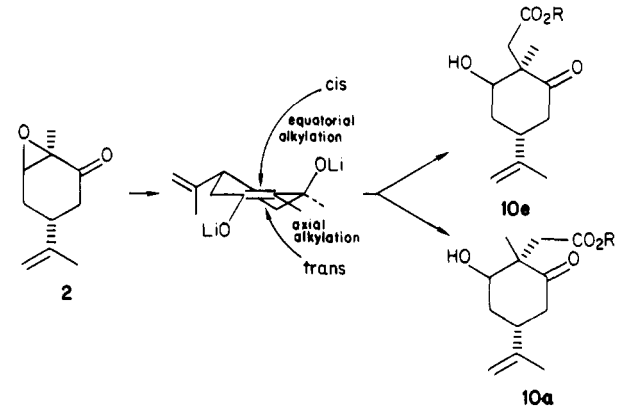


The stereochemical outcome of the reductive methylation of carvone is in general agreement with those which have been reported for the methylation of similar α-methylcyclohexanone systems and reflects the usual preference for axial methylation of cyclohexanones when the α-group is a non-hydrogen group such as methyl, cyano, or carbomethoxy.

The degree of stereoselectivity observed in the methylation of carvone epoxide (≥95% axial alkylation) is somewhat higher. Examination of the enolates generated by reduction of carvone epoxide **2** suggests that the β-alkoxy group should be a significant steric factor which enhances the natural preferences for axial approach of the alkylating agent.

When carvone epoxide was treated with methyl bromoacetate under the same conditions as those used for reductive methylation, a polar material was isolated in modest yield which was shown to have a hydroxyl group, a ketone carbonyl group, and a carbomethoxy group. Additional spectral data and elemental analysis confirmed that the desired alkylated material, **10**, had been obtained. As before, careful attention was then given to the selection of reaction conditions which would optimize the yield of **10**. There was a systematic alteration of the following reaction variables: the amount of lithium used, the temperature and time of enolate formation, the choice of amine solvent, the choice of ether cosolvent, the amount of alkylation agent, the temperature and time of alkylation, the choice of quenching agents, replacement of amine solvent by cosolvent before alkylation.

The optimal reaction conditions, which are detailed in the Experimental Section, consisted of reduction with 3 equiv of lithium and alkylation with 2.5 equiv of methyl bromoacetate. Under these conditions, keto ester **10** could be isolated in 31% yield (based on consumed epoxy ketone). Several other compounds could be isolated from the crude reaction mixture: unreacted carvone epoxide (ca. 10% by weight), carvone (ca. 5%), the unalkylated reduction product (trace), and two side products, A (ca. 5%) and B (ca. 16%), which were not fully characterized.



Attention was then turned to the determination of the stereochemical course of alkylation. Spectral and chromatographic properties of **10** suggest that, within the experimental limits of detection, it is one or the other of its diastereomeric forms **10a** or **10e**, but *not* a mixture of both. In both the ^1H and ^{13}C NMR spectra of the product, only *one* alkyl methyl, *one* vinyl methyl, and *one* methoxy methyl (all of equal intensity) peak is observed. Thin-layer chromatography (TLC) of the product in different systems shows one spot. GC analyses on different columns at varying temperatures all show one peak. The same result is observed in the GC analysis of the heptafluorobutyrate ester derivative. The absence of any evidence for a second product by any of these techniques suggests that the product is one diastereomer.

In order to distinguish between **10a** and **10e**, we exposed the product to base with the expectation that the β-hydroxy ketone would undergo a reversible retroaldol, thereby forming all possible isomers. Basic hydrolysis of the keto ester **10** (KOH/EtOH), acidification, and extraction afforded in high yield an oil which exhibited three spots on TLC (EtOAc/hexane, 2:3) with R_f's of 0.40, 0.29, and 0.20. Upon standing, a fourth spot of R_f 0.49 appeared. All four compounds were isolated, and spectral data were obtained for each one.

The compounds with the two higher R_f spots (0.49 and 0.40) both exhibited two carbonyls (1795–1800 and 1725 cm^{-1}) in their IR spectra and were neutral based on their partition properties. On this basis, the two compounds were thought to be lactones and will herein be referred to as the upper lactone (R_f 0.49) **11** and the lower lactone (R_f 0.40) **12**.

The two compounds with the lower R_f spots (0.29 and 0.20) were both base-soluble and had D_2O exchangeable signals in their ^1H NMR spectra. They were thought to be carboxylic acids and will herein be referred to as the upper acid (R_f 0.28) **13** and the lower acid (R_f 0.20) **14**. Infrared analysis of these two compounds supported their presumed acidic nature.

When the upper lactone was refluxed with KOH and ethanol, the TLC of the product showed both upper and lower acids to be present, as well as the lower lactone and a trace of the upper lactone. It appears, therefore, that epimerization is occurring at both C-2 and C-3. The retroaldol mechanism is a plausible explanation of the observed results.

Once it was established that the four hydrolysis products represented the four orientations possible from two asym-

Table I[a]

compd		CCl_4	$CDCl_3$	benzene-d_6	ΔCCl_4–benzene	$\Delta CDCl_3$–benzene
3	axial	1.18 (71)	1.30 (78)	0.93 (56)	+0.25 (15)	+0.37 (22)
	equatorial	1.10 (66)	1.23 (74)	1.22 (73)	−0.12 (7)	+0.01 (1)
5	axial					
	equatorial	1.10 (66)	1.13 (68)	1.22 (73)	−0.12 (7)	−0.09 (5)
6	axial	1.17 (70)	1.18 (71)	0.97 (58)	+0.20 (12)	+0.21 (13)
	equatorial	1.05 (63)	1.12 (67)	1.12 (67)	−0.07 (4)	−0.0 (0)
7	axial	1.13 (68)	1.17 (70)	0.90 (54)	+0.23 (14)	+0.27 (16)
	equatorial	1.06 (62)	1.10 (66)	1.10 (66)	−0.07 (4)	±0.0 (0)

[a] Values are expressed in ppm ± 0.016 ppm downfield from Me_4Si. Values in parentheses are expressed in Hz ± 1 Hz (at 60 MHz) downfield from Me_4Si.

metric centers, a way to determine the configuration of each compound was needed.

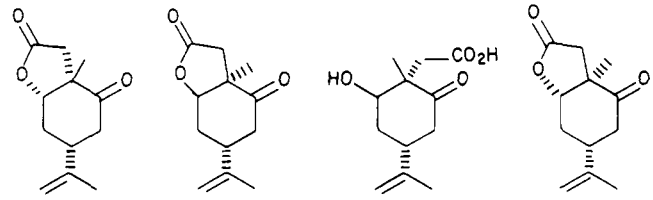
Conversion of all four compounds into the corresponding methyl esters would allow comparison among the four compounds as well as *direct* comparison to the original alkylation product **10**, allowing the assignment of its structure. As expected, both acids **13** and **14** reacted with diazomethane in ether to give neutral compounds whose spectral data suggested that they were methyl esters **16** and **17**, respectively (i.e., 1740 and 1720 carbonyls in IR, and a 3-H singlet at 3.7 ppm in the NMR). The two esters could easily be distinguished from one another by their quite different NMR, TLC, and GC properties. The NMR of the upper acid methyl ester (**16**) exhibited a pair of doublets (J_{AX} = 5 Hz, J_{BX} = 9 Hz) for the methine proton on the hydroxyl carbon and a broad 2-H singlet for the vinyl protons. In contrast, the lower acid methyl ester (**17**) exhibited a triplet for the vinyl region. Compound **16** was less polar (R_f 0.28) than **17** (R_f 0.23) when analyzed by TLC (ethyl acetate/hexane, 1:4) and had a shorter retention time in the GC analysis (8 min 50 s vs. 11 min 10 s on Carbowax 20M at 185 °C and a flow rate of 30 cc/min). Comparison of the spectral and physical properties of these two methyl esters to the original methyl ester **10** revealed that **17** was *identical* with **10** with respect to its IR, NMR, TLC, and GC properties.

Attempts to convert the two lactones **11** and **12** to their corresponding methyl esters proved fruitless. It had already been shown that base treatment of one of the lactones resulted in epimerization at C-3. Epimerization also resulted from treatment of 10 with $NaOCH_3$ in methanol at 0 °C. Treatment of lactones **11** and **12** with anhydrous MeOH saturated with dry HCl afforded only unreacted lactone.

Since two of the compounds were already lactones, the next strategy was to convert the two acids to lactones. Mild acid treatment failed to convert either acid to its lactone. Treatment of **13** with *N,N'*-dicyclohexylcarbodiimide (DCC) in dioxane resulted in the formation of a new neutral compound with different TLC properties (R_f 0.55) than any of the previously isolated compounds. The IR of this material showed two carbonyls (1797 and 1710 cm^{-1}). The NMR was significantly different than the other two lactones, especially the signal for the methine proton, which occurred as a pair of doublets (J_{AX} = 5 Hz, J_{BX} = 11 Hz) centered at 4.0 ppm. These data then suggested that a third lactone (**15**) had been prepared. Unfortunately, treatment of the lower acid under identical conditions failed to give any lactone.

On the basis of the data obtained and by analogy to work done by Johnson et al.,[13] we felt a reliable assignment of the structure of the four hydrolysis products and the original alkylation product **10** could be made. We assumed that in each of the hydrolysis products, as in ketone **10**, the isopropenyl group at C-5 is in the equatorial position of the chair and that the configuration at this carbon is unchanged from epoxide **2**.

In the case of lower lactone **12**, the appearance of a triplet in the ^1H NMR spectrum for the methine proton adjacent to the lactone oxygen indicates that oxygen must be axial, suggesting that the cis-equatorial acid is the parent hydroxy acid.



11 12 14 15

Of the two remaining lactones, both exhibited a pair of doublets for the methine proton adjacent to the lactone oxygen in their ^1H NMR spectra, an indication that the proton is axial and the oxygen is equatorial. Therefore, in one of the parent γ-hydroxy acids the hydroxy and acetoxy groups are oriented trans-diequatorial, while in the other the groups are cis-axial–equatorial.

In Johnson's study, the lactonization of all four diastereomers of 3-hydroxy-trans-decalin-2-acetic acids were studied. It was observed that the trans-diequatorial diastereomer lactonized upon heating in benzene in the presence of *p*-toluenesulfonic acid as catalyst while the cis(equatorial)-hydroxy-(axial)-acetoxy diastereomer lactonized partially spontaneously and completely upon gentle warming in benzene with no catalyst.

One might expect then that the upper lactone **11**, which formed spontaneously from its parent hydroxy acid upon hydrolysis of **10**, has the cis-equatorial–axial orientation. Lactone **15**, which required DCC catalysis for formation, therefore, has the trans-diequatorial orientation.

It is interesting to note that Johnson and co-workers also observed spontaneous lactonization from their other cis diastereomer, just as in the case of the lower lactone **12** of this study. Furthermore, as would be expected, the trans-diaxial hydroxy acid in their study was quite resistant to lactonization. With DCC catalysis, they obtained low, erratic yields of the desired lactone; catalysis by *p*-toluenesulfonic acid was necessary to obtain the desired lactone in good yield. In this study, treatment of the lower acid **14** with DCC afforded none of the desired keto lactone; treatment with *p*-toluenesulfonic acid in refluxing benzene led to formation of a complex mixture of products. On the basis of this evidence it seems reasonable to assign the diaxial orientation to the lower acid.

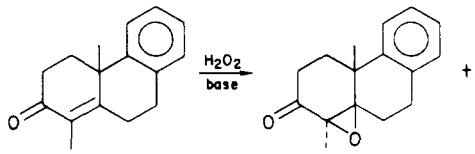
Since esterification of this acid gives a methyl ester which is identical with the original product of the alkyla-

(13) Johnson, W. S.; Bauer, V. J.; Margrove, J. L.; Frisch, M. A.; Dreger, L. H.; Hubbard, W. N. *J. Am. Chem. Soc.* **1961**, *83*, 606.

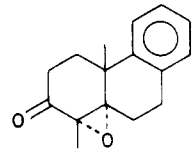
tion, **10**, it follows that the structure of **10** is that resulting from axial alkylation in agreement with the methylation result.

Having established that the reductive alkylation proceeds with a high degree of stereoselectivity as well as regioselectivity, we wished to extend the sequence to the hydrophenanthrene ring system, a ring system of interest because of its extensive occurrence in many natural products such as the diterpene resin acids. The epoxy derivatives of well-known[14] ketone **18** was the logical choice since successful reductive alkylation would provide both regioselective and stereoselective introduction of alkyl groups at the C-1 position, particularly useful in diterpene synthesis.

When **18** was treated with 4 N NaOH and 30% H_2O_2 for 24–48 h,[15] a yellow solid was obtained in ca. 80–85% yield. NMR and IR analyses of this crude product were consistent with those expected for **19**. GC (6 ft, 6% SE-30, 240 °C) analysis of this material indicated the presence of two peaks in a 2:3 ratio at 7.0 and 7.5 min, respectively, as well as a small amount (ca. 5%) of unreacted **18**.



18 **19a**



19b

Recrystallization of the crude solid **19** from methanol afforded a crystalline material of mp 116 °C. GC analysis of this product showed one peak with a retention time of 7.5 min. The mother liquors from this recrystallization proved to be enriched with the other product with the 7.0 min retention time.

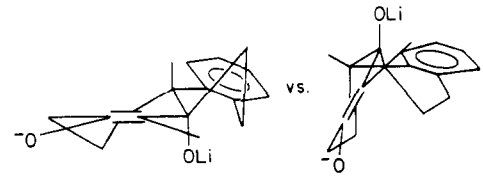
The mother liquors were concentrated to an oil which was purified by pressure-assisted liquid chromatography to afford, as expected, the other isomer as a crystalline solid, mp 82 °C. The mass spectra of both isomers gave molecular ions of 242 and similar fragmentation patterns. The stereochemistry of these isomers was deduced from an analysis of their ^{1}H NMR spectra and particularly the chemical shifts of their methyl resonances. We have observed in a related series of 4a-methyloctahydrophenanthrenes that in the case of the cis-A–B ring junction and in the presence of 1,3-diaxial interactions the 4a-methyl resonates at a lower field.[16] The major isomer showed two methyl resonances in its spectrum at 1.48 and 1.30 ppm, while the minor isomer showed two methyl peaks at 1.50 and 1.45 ppm. Molecular models of structures **19a** and **19b** revealed that the methyl group next to the carbonyl in both isomers was in more or less the same quasi-equatorial position with respect to the carbonyl group and as such would be expected to exhibit a nearly equal chemical shift in the ^{1}H NMR spectrum of each isomer. On this basis, the 1.30 ppm peak of the major isomer was assigned to its 4a-methyl, while the 1.45 ppm peak, which is roughly equal to either of the two peaks of the minor isomer, was assigned to the C-1 methyl group. The two chemical shifts of the methyl groups in the minor isomer are nearly equal, and an unambiguous assignment to the angular methyl or the methyl group at C-1 could not be made without additional data. However, it was clear that whichever peak was assigned to the angular methyl group of the minor isomer, it had a ^{1}H NMR signal which was downfield relative to the corresponding resonance of the major isomer by 0.15 to 0.20 ppm. Accordingly, the minor isomer was thus assigned the cis configuration **19a**. With both epoxides in hand and their structures assigned, attention was turned to their reductive alkylation.

Initially the reactions were run on a 1:2 mixture of *cis*-**19a** to *trans*-**19b** under the optimal reaction conditions for the reductive methylation of carvone epoxide. Under these conditions, the isolated product was comprised of unsaturated ketone **18** and a material whose NMR and IR suggested that it was the protonated reduction product. None of the desired β-hydroxy-α-dimethyl ketone was detected.

Several additional attempts with modified reaction conditions failed to afford any of the alkylated product, as did the use of either pure cis epoxide **19a** or pure trans epoxide **19b** as starting materials. It should be noted that when cis epoxide **19a** was used as the starting material, unreacted epoxide could be recovered along with **18** and protonated reduction product. In contrast, when the trans epoxide, **19b**, was used a smooth reduction takes place and the unalkylated reduction product and enone are isolated.

The isolation of a protonated reduction product and **18** (which is presumably derived by dehydration of the reduction product) suggested that reduction of the epoxy ketone had occurred but that alkylation of the resultant β-alkoxy enolate was not proceeding as in the case of the enolate from carvone epoxide.

The increased susceptability of the trans epoxide to reduction may reflect a product-like transition state for the reductive opening of the epoxy ketone to the alkoxy enolate. In such a case, the trans epoxide would be expected to react faster than the cis isomer, since transition-state destabilization due to the steric interaction between the angular methyl group and a trans alkoxy group is less severe than that with a cis alkoxy group.



If the trans alkoxy enolate is indeed the major reduction product, it is not altogether surprising that alkylation failed to occur. The stereochemical outcome of carvone epoxide alkylation indicated that a lithium alkoxy group is a significant steric factor and tends to direct alkylation to the opposite face of the molecule. However, in the trans alkoxy enolate case, approach to the other face is hindered by the presence of an angular methyl group, whose influence on the direction of alkylation has been amply documented.[17] Further, the gauche interactions within the cis alkoxy enolate would cause ring B to assume a conformation which sterically hinders approach from the face opposite

(14) Ghatak, U. R.; Datta, D. K.; Ray, S. C. *J. Am. Chem. Soc.* **1960**, *82*, 1728.
(15) Plattner, P. A.; Heusser, H.; Kulkarni, A. B. *Helv. Chim. Acta* **1948**, *31*, 1822.
(16) Campbell, A. L.; Leader, H. N.; Gonzalez-Sierra, M.; Spencer, C. L.; McChesney, J. D. *J. Org. Chem.* **1979**, *44*, 2755.
(17) Wenkert, E.; Afonso, A.; Bredenberg, J. B-son; Kaneko, C.; Tahara, A. *J. Am. Chem. Soc.* **1964**, *86*, 2038.

the 4a-methyl and the alkoxy. Since approach to both faces of the molecule is hindered, the alkylation does not take place to any appreciable extent.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained with a Beckman IR-33, Perkin-Elmer 257, or Perkin-Elmer 281B spectrometer in a 2% $CHCl_3$ solution, as a 1% KBr pellet, or as a thin film between NaCl plates. ^1H NMR spectra were obtained with a Varian EM-360 or a JEOL C-60HL. FT ^1H NMR spectra and ^{13}C NMR spectra were obtained with a JEOL FX60. All NMR spectra were obtained in a $CDCl_3$ solution unless otherwise indicated and are reported in δ units (ppm) relative to tetramethylsilane (Me_4Si). Mass spectra were recorded with a Varian Associates CH-5 mass spectrometer, a DuPont Model 21-492 GC/MS, a Hewlett-Packard 5985 GC/MS/DS, or a Finnigan 3200 F GC/MS/DS. Microanalyses were performed on a Hewlett-Packard 185B CHN Analyzer, Department of Medicinal Chemistry, University of Kansas. Gas chromatographic analyses (GC) were obtained with a Varian Associates Model 3700 (10 ft × $^1/_8$ in. 6% SE-30 on Chromasorb W, 100 mesh), a Perkin-Elmer 900 (6 ft × $^1/_8$ in. 3% OV-17 on Anachrom 100–120 mesh), Beckman GC-65 (6 ft × $^1/_8$ in. Carbowax 20M on Chromasorb W 100–120 mesh DMCS-AW, or 6 ft × $^1/_8$ in. 3% OV-17 on Chromasorb W 100–120 mesh) equipped with flame ionization detectors with helium or nitrogen as the carrier gas at a flow rate of ca. 30 mL/min. Quantitative GC analyses were made by the method of internal standards as described by McNair and Bonelli.[18] Liquid chromatography was performed with Brinkman silica gel 60 (70–235 mesh). Preparative and thin-layer chromatography (TLC) were performed on Brinkman precoated plates. Preparative-scale pressure-assisted liquid chromatography was performed with Merck silica gel 60 (230–400 mesh) at ca. 70 psi on 1 m × 2 cm glass columns and a solvent flow rate of 20 mL/min.

Solvents used for chromatography were distilled prior to use. Ether, tetrahydrofuran (THF), and dimethoxyethane (DME) used as cosolvents in the reductive alkylations were distilled from lithium aluminum hydride (LAH) immediately prior to use. All other solvents used were of analytical reagent grade or purified according to literature methods. *l*-Carvone, methyl iodide, trideuteriomethyl iodide, methyl bromoacetate, β-tetralone, methyl vinyl ketone, and ethyl vinyl ketone were purchased from the Aldrich Chemical Company.

All reactions using dry solvents were run in flame-dried apparatus under a positive pressure of argon. All transfers of reagents were made under anhydrous conditions with a syringe or cannula. Usual workup of a reaction involved extraction with a solvent, a wash with saturated NaCl solution (brine), drying with anhydrous granular $MgSO_4$, Na_2SO_4 or K_2CO_3, and concentration in vacuo (rotary evaporator).

***l*-Carvone Epoxide (2).** A solution of *l*-carvone (50 g, 0.332 M) in methanol (120 mL) was added to a three-necked round bottomed flask (1 L) fitted with a pressure equalizing addition funnel. An aqueous solution of 30% H_2O_2 (100 mL) was added, and the reaction mixture was cooled to 5 °C. A solution of 0.289 N K_2CO_3 (100 mL) was then added in a dropwise manner over a 45-min period with the temperature maintained below 10 °C. When addition was complete, the reaction was allowed to warm to 25 °C and stirred until GC analysis (OV-17) showed the reaction to be complete (ca. 5 h). The reaction mixture was then poured into ice water (400 mL), salted (NaCl), and extracted with ether (5 × 150 mL). The extracts were combined, dried (Na_2SO_4), and concentrated in vacuo to afford a colorless oil (55.0 g) which was distilled (70 °C/0.6 mmHg) to yield a distillate (47.5 g, 86%) whose physical and spectral properties were identical with those reported by Wycpalek[7] for **2**. GC analysis (6 ft 3% OV-17, 100 °C 4 min to 180 °C at 7.5° per min) of the product showed two peaks in ca. a 19 to 1 ratio.[18] GC/MS analysis (6 ft, 5% FFAP, 145 °C) showed both peaks had M^+ = 166 and similar fragmentation patterns.

(18) McNair, H. M.; Bonelli, E. J. In "Basic Gas Chromatography", 5th ed.; Varian: Palo Alto, CA, 1965; Chapter 7.

General Procedure for Reductive Alkylation. The reactions were carried out under anhydrous conditions with dry cosolvents and dry ammonia freshly distilled from Na or Li. Lithium wire (Foote) was rinsed in hexane prior to use. Method A: This procedure was a modification of the method of Wycpalek.[7] Ammonia was distilled into the reaction vessel, and lithium was added which produced a deep blue color. After 10–15 min, a solution of *l*-carvone or **2** in cosolvent was added. The resultant mixture stirred at −33 °C for 60–70 min. A solution of alkylating agent in cosolvent was then added which discharged the blue color. The reaction mixture stirred another 15 min at −33 °C and was then quenched by addition of saturated NH_4Cl solution. The ammonia was then allowed to evaporate under nitrogen or argon. The reaction was worked up by addition of brine and extraction of the aqueous layer with ether. The ether extracts were dried and concentrated in vacuo. Alternately, solid NH_4Cl was used to quench the reaction, in which case after evaporation of ammonia the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with brine and 0.1 N HCl. The aqueous phases were combined and extracted with $CHCl_3$. The $CHCl_3$ phases were combined, dried, and evaporated in vacuo. Method B: Same as method A except as follows. When addition of **1** or **2** was complete, the dry ice condenser was removed, and the reaction flask was gradually warmed to 0 °C while a continuous stream of argon swept through. As the ammonia distilled away, it was replaced by dry cosolvent. When the ammonia had been removed, a solution of alkylating agent in cosolvent was added and allowed to stir for 15–30 min at 0 °C before addition of solid NH_4Cl and workup as described in method A.

2,2-Dimethyl-3(*R*)-hydroxy-5(*R*)-isopropenylcyclohexanone (3). Method A: *l*-Carvone epoxide (**2**) (0.491 g, 2.95 mM) in ether (10 mL) was added to a solution of lithium (0.0621 g, 8.95 mM) in ammonia (50 mL) and stirred 70 min before a solution of methyl iodide (1.72 g, 12.1 mM) in ether (10 mL) was added. After ca. 15 min, the reaction was quenched by addition of saturated NH_4Cl solution (2.5 mL). The ammonia was allowed to evaporate and the reaction was worked up by addition of brine (10 mL) and 0.1 N HCl (10 mL). The aqueous phase was separated and extracted with ether (5 × 10 mL). The ether extracts were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil (0.520 g). Quantitative GC analysis[18] indicated a 68% yield of **3**. Pure **3** could be isolated (65%) by silica gel chromatography (100 to 1) with ethyl acetate/hexane (15:85) as the eluent: IR (film) 3490, 2960, 1715, 890 cm^{-1}; ^1H NMR, δ 5.0 (d, 2 H, vinyl H), 4.2 (t, 1 H, J = 3.5 Hz, C*H*OH), 3.2–2.0 (m, 5 H), 2.7 (s, 1 H, D_2O exchangeable, OH), 1.9 (br s, 3 H, vinyl CH_3), 1.30 (s, 3 H, axial C-2 CH_3), 1.23 (s, 3 H, equatorial C-2 CH_3); ^{13}C NMR δ 215.1 (s, C=O), 147.3 (s, —*C*=CH_2), 110.0 (t, C=*C*H_2), 49.5 (s, C-2), 42.3 (t, C-6), 39.2 (d, C-5), 33.2 (t, C-4), 24.5 (q, axial C-2 CH_3), 20.6 (q), 20.4 (q); MS, m/z 182 (M^+), 164, 69 (base).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.48; H, 9.95. Found: C, 72.36; H, 10.20.

Method B: A solution of *l*-carvone epoxide (0.490 g, 2.95 mM) in ether (10 mL) was added to a solution of lithium (0.0616 g, 8.8 mM) in ammonia (50 mL). Upon completion of the addition (ca. 2 min), the dry ice condenser was removed and the ammonia was swept away by a stream of argon and replaced by ether (50 mL). A solution of methyl iodide (2.5 g, 17.6 mM) in ether (10 mL) was added and stirred at 0 °C for 30 min before solid NH_4Cl was added. The reaction mixture evaporated to dryness, and then the residue was dissolved in $CHCl_3$ (50 mL). The $CHCl_3$ was washed with brine (10 mL) and 0.1 N HCl (10 mL). The aqueous phase was extracted with $CHCl_3$ (5 × 10 mL). The $CHCl_3$ phases were combined, dried (K_2CO_3), and concentrated to give a yellow oil (0.489 g) which, by quantitative GC analysis (3% OV-17), contained 70% by weight of **3** for an overall yield of 64%.

2-Methyl-3(*R*)-hydroxy-5(*R*)-isopropenylcyclohexanone (4). Method A was used. A solution of epoxide **2** (0.650 g, 3.9 mM) in ether (10 mL) was added to a solution of lithium (0.0602 g, 8.7 mM) in ammonia (50 mL), and the solution was stirred for 60 min at −33 °C. A solution of saturated NH_4Cl (4 mL) was added, and the ammonia was allowed to evaporate. The residue was dissolved in ether (50 mL) and washed with brine (2 × 10 mL). The aqueous phase was extracted with ether (5 × 10 mL). The ether extracts were combined, dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil (0.507 g). A portion of this

material (0.235 g) was separated by silica gel chromatography (100 to 1) with ethyl acetate/hexane (1:9) as the eluent to afford **4** as a clear oil (0.112 g, 35% calcd overall yield): IR (film) 3460, 2920, 1700, 890 cm^{-1}; ^1H NMR, δ 4.75 (br s, 2 H, vinyl H), 4.30 (q, J = 3.0 Hz, 1 H, -C*H*OH), 3.16–1.98 (m, 7 H), 2.61 (s, D_2O exchangeable, 1 H, OH), 1.80 (br s, 3 H, vinyl CH_3), 1.12 (d, J = 7 Hz, 3 H, α-CH_3); ^{13}C NMR, δ 211.3 (s, C=O), 147.4 (s, —*C*=CH_2), 109.9 (t, —C=*C*H_2), 73.4 (d, *C*HOH), 49.4 (d, C-5), 46.6 (t, C-6), 40.0 (d, C-2), 37.9 (t, C-4), 20.5 (q, vinyl CH_3), 10.65 (q, α-CH_3); MS, m/z 168 (M^+), 150 (base), 93.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.10; H, 9.70.

2-Methyl-2-(trideuteriomethyl)-3(*R*)-hydroxy-5(*R*)-isopropenylcyclohexanone (5). Method A was used. A solution of *l*-carvone epoxide (2.90 g, 17.3 mM) in ether (20 mL) was added to a solution of lithium (0.363 g, 52.0 mM) in ammonia (100 mL), and the resulting solution was allowed to stir at −33 °C for 1 h. A solution of trideuteriomethyl iodide (10 g, 69 mM) in ether (10 mL) was added, and the mixture was stirred for 10 min at −33 °C before addition of saturated NH_4Cl solution (3 mL). The ammonia was allowed to evaporate, and brine (20 mL) and 0.1 N HCl (20 mL) were added. The aqueous phase was separated and extracted with ether (5 × 20 mL). The ether extracts were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil (2.66 g). Pure **5** could be isolated in 65% yield by silica gel chromatography (100 to 1) of the crude product with ethyl acetate/hexane (15:85) as the eluent: IR (film) 3490, 2960, 2210 (weak), 1715, 890 cm^{-1}; ^1H NMR, δ 4.8 (br s, 2 H, vinyl H), 3.9 (t, J = 3.5 Hz, 1 H, -C*H*OH), 3.0–1.9 (m, 5 H), 2.9 (br s, D_2O exchangeable, 1 H, OH), 1.8 (s, 3 H, vinyl CH_3), 1.13 (s, 3 H, equatorial C-2 CH_3); ^{13}C NMR, δ 215.1 (s, C=O), 147.3 (s, —C=CH_2), 110.0 (t, C=*C*H_2), 77.1 (d, -*C*HOH), 49.6 (s, C-2), 42.3 (t, C-6), 39.2 (d, C-5), 33.2 (t, C-4), 20.7 (q), 20.3 (q); MS, m/z 185 (M^+), 167 (M − 18), 69 (base).

Anal. Calcd for $C_{11}H_{15}D_3O_2$: C, 71.31; H, 9.80. Found: C, 71.13; H, 10.2.

2,2-Dimethyl-5(*R*)-isopropenylcyclohexanone (6). Method A was used. *l*-Carvone (0.596 g, 3.96 mM) in ether (10 mL) was added to a solution of lithium (0.068 g, 9.8 mM) in ammonia (50 mL), and the mixture was stirred at −33 °C for 1 h. A solution of methyl iodide (2.2 g, 15.5 mM) in ether (10 mL) was added, and the mixture was stirred for 15 min before addition of a saturated NH_4Cl solution (2 mL). The ammonia was allowed to evaporate, and the reaction was worked up by addition of brine (10 mL) and 0.1 N HCl (10 mL). The aqueous phase was separated and extracted with ether (5 × 10 mL). The ether extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give a yellow oil (0.535 g). Pure **6** (0.197 g, 30%) was isolated by silica gel chromatography (100 to 1) with ethyl acetate/hexane (1:19) as the eluent: IR ($CHCl_3$) 2950, 1715, 890 cm^{-1}; ^1H NMR, δ 4.9 (br s, 2 H, vinyl H), 2.45 (s, 2 H, -$COCH_2$-), 1.8 (br s, 8 H, vinyl C*H*$_3$, -CH_2CH_2C*H*-), 1.18 (s, 3 H, axial C-2 CH_3), 1.12 (s, 3 H, equatorial C-2 CH_3); ^{13}C NMR, δ 214.8 (s, C=O), 147.5 (s, —*C*=CH_2), 109.9 (t, —C=*C*H_2), 46.3 (d, C-5), 44.5 (s, C-2), 43.0 (t, C-6), 39.6 (t), 26.6 (t), 25.2 (q, C-2 CH_3), 25.1 (q, C-2 CH_3), 20.6 (q, vinyl *C*H_3); MS, m/z 166 (M^+), 69 (base).

2-Methyl-2-(trideuteriomethyl)-5(*R*)-isopropenylcyclohexanone (7). Method B was used. *l*-Carvone (0.489 g, 3.2 mM) in DME (10 mL) was added to a solution of lithium (0.0663 g, 9.5 mM) in ammonia (50 mL). The ammonia was replaced by DME (50 mL) over a 1-h period and brought to 0 °C. Trideuteriomethyl iodide (2.28 g, 15.7 mM) was added next, and the reaction mixture stirred for 30 min at 0 °C. NH_4Cl (ca. 0.500 g) was added, and the DME was removed in vacuo. The residue was dissolved in $CHCl_3$ (50 mL) and then washed with brine (2 × 15 mL), 0.1 N HCl (15 mL), and again with brine (15 mL). The aqueous phases were extracted with $CHCl_3$ (5 × 10 mL). The organic phases were combined, washed with brine (15 mL), dried (Na_2SO_4), and concentrated to give a clear oil (0.427 g). Pure **7** (0.171 g, 32%) was isolated by silica gel chromatography (90:1) with ethyl acetate/hexane (1:19) as the eluent: IR (film) 2950, 2220 (weak), 1710, 890 cm^{-1}; ^1H NMR, δ 4.9 (br s, 2 H, vinyl H), 2.45 (br s, 2 H, -$COCH_2$), 1.8 (br s, 8 H, vinyl C*H*$_3$, -CH_2CH_2C*H*), 1.17 (s, 0.61 H, axial C-2 CH_3), 1.10 (s, 2.39 H, equatorial C-2 CH_3); ^{13}C NMR, δ 215.1 (s, C=O), 147.6 (s, —*C*=CH_2), 109.9 (s, —C=CH_2), 46.3 (d, C-5), 44.3 (s, C-2), 43.0 (t, C-6), 39.5 (t), 26.6 (t), 25.1 (q, C-2 CH_3), 20.6 (q, vinyl CH_3); MS, m/z 169 (M^+), 85, 72 (base).

2-(Carbomethoxymethyl)-2-methyl-3(*R*)-hydroxy-5(*R*)-isopropenylcyclohexanone (10). Method A was used. A solution of carvone epoxide **2** (2.25 g, 13.5 mM) in ether (20 mL) was added to a solution of lithium (0.287 g, 41.3 mM) in ammonia (200 mL), and the resulting mixture was stirred for 70 min at −33 °C. A solution of methyl bromoacetate (5.47 g, 35.0 mM) in ether (20 mL) was cooled to −40 °C and added as a steady stream (caution: reaction is exothermic!). This stirred for 15 min before solid NH_4Cl (ca. 1.5 g) was added. The ammonia was allowed to evaporate, and the residue was dissolved in $CHCl_3$ (200 mL) and washed with brine (5 × 20 mL). The aqueous phase was extracted with $CHCl_3$ (5 × 40 mL), and the organic layers were combined, washed with 0.1 N HCl (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil (2.42 g). Quantitative GC analysis showed that the crude product consisted of unreacted **2** (10%), ketone **10** (25%), and various side products. The overall yield of **10** was calculated to be 31%, based on consumed starting material. Pure **10** was obtained as a solid by silica gel chromatography (100:1) with ethyl acetate/hexane (1:4) as the eluent. Recrystallization (ether/hexane) afforded white plates, mp 83 °C. Thin-layer chromatography of **10** in several ethyl acetate/hexane mixtures (1:9, 1:4, 3:7, 2:3, 1:1) showed one spot. GC analysis on (s, OV-17 at 140 °C (5 min) to 180 °C at 13°/min, 100 °C (5 min) to 220 °C at 13°/min, 220 °C and 200 °C (isothermal) showed one peak, while on 3% Carbowax 20M at 185 °C, a major peak (94%) and a minor peak (6%) were evident: IR (KBr) 2980, 1740, 1710, 890 cm^{-1}; ^1H NMR, δ 4.93 (br s, 1. H, vinyl H), 4.83 (s, 1 H, vinyl H), 4.23 (t, J = 5 Hz, 1 H, -C*H*OH), 3.73 (s, 3 H, OCH_3), 3.2–2.0 (m, 7 H), 2.76 (br s, D_2O exchangeable, 1 H, OH), 1.83 ns, 3 H, vinyl CH_3), 1.23 (s, 3 H, C-2 CH_3); ^{13}C NMR δ 211.8 (s, C=O of C-1), 171.7 (s, CH_2OC=O), 146.8 (s, —C=CH_3), 110.8 (t, —C=*C*H_2), 73.7 (q, OCH_3), 52.4 (s, C-2), 51.7 (d, C-5), 42.0 (t, C-6), 38.9 (t), 32.7 (t), 21.1 (q, vinyl CH_3), 17.4 (q, C-2 CH_3); MS, m/z 208 (M − 32), 95, 69 (base); the heptafluorobutyrate ester ($C_{17}H_{19}F_7O_5$) was prepared for GC/MS analysis. GC analysis (6 ft 3% OV-17, 100–220 °C at 13 °C/min) showed one peak; MS, m/z 436 (M^+), 95 base.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.18; H, 8.56.

Base Treatment of Keto Ester 10. Keto ester **10** (0.254 g, 1.06 mM) was dissolved in 95% ethanol (4 mL). Solid KOH (0.111 g, 2.0 mequiv) was added, and the reaction mixture was refluxed under argon for $3^1/_4$ h. The reaction mixture was cooled, concentrated in vacuo to a brown oil, and dissolved in water at 0 °C (4 mL). The pH of the solution was adjusted to ca. pH 2 with ice-cold (0 °C) 6 N H_2SO_4 and then extracted with ether (5 × 5 mL). The ether extracts were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil (0.250 g) which was immediately dissolved in ether (25 mL) and washed with an aqueous solution of 10% K_2CO_3 (2 × 5 mL). The ether solution was dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil (0.022 g) which, by GC (3% OV-17, 100 °C (5 min) to 220 °C at 13 °C/min), was a mixture of lactones **11** (minor) and **12** (major). The basic aqueous phase was cooled to 0 °C, its pH adjusted to ca. pH 2 with cold (0 °C) 6 N H_2SO_4, and the solution then extracted with ether (7 × 7 mL). The ether extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a pale yellow oil (0.198 g) which by TLC (ethyl acetate/hexane, 2:3) was a mixture of lactone **11** (R_f 0.49), lactone **12** (R_f 0.40), acid **13** (R_f 0.29) and acid **14** (R_f 0.20). Silica gel chromatography (110:1) of a portion of this oil (0.182 g) with ethyl acetate/hexane (1:4) as the eluent afforded pure **11** (0.0273 g), **12** (0.0265 g), **13** (0.0448 g), and **14** (0.048 g).

Lactone 11: IR ($CHCl_3$) 3000, 1790, 1720, 1200, 900 cm^{-1}; ^1H NMR, δ 4.9 (m, 2 H, vinyl H), 4.57 (d of d, J_{AX} = 6 Hz, J_{YX} = 10 Hz, 1 H, -CHO-), 3.07 (d, J = 18 Hz, 1 H, -C*H*$_2$COOCH-), 2.4–2.1 (m, 5 H), 2.27 (d, J = 18 Hz, 1 H, -C*H*$_2$COOCH-), 1.80 (s, 3 H, vinyl CH_3), 1.37 (s, 3 H, CH_3); MS, m/z 208 (M^+), 164 (base), 98, 69.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.99; H, 7.70.

Lactone 12: IR ($CHCl_3$) 3000, 1800, 1720, 1200, 900 cm^{-1}; ^1H NMR, δ 4.9 (m, 2 H, vinyl H), 4.78 (t, J = 3 Hz, 1 H, -CHO-), 3.48 (d, J = 18 Hz, 1 H, -C*H*$_2$COOCH-), 2.83–2.33 (m, 5 H), 2.33 (d, J = 18 Hz, 1 H, -C*H*$_2$COOCH-), 1.83 (s, 3 H, vinyl CH_3), 1.42

(s, 3 H, C-2 CH_3); MS, m/z 208 (M^+), 164 (M – 44), 98 (base), 69.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.98; H, 8.03.

Acid 13: IR (film) 3400 (br), 2950, 1720, 1050, 890 cm^{-1}; ^1H NMR, δ 5.23 (s, D_2O exchangeable, 1 H, COOH), 4.87 (s, 2 H, vinyl H), 4.0 (d of d, J_{AX} = 5 Hz, J_{BX} = 10 Hz, 1 H, -CH_2CHOH-), 3.0–2.0 (m, 7 H), 1.78 (s, 3 H, vinyl CH_3), 1.18 (s, 3 H, C-2 CH_3).

Acid 14: IR (film) 3400 (br), 2950, 1720, 1050, 890 cm^{-1}; ^1H NMR, δ 5.38 (br s, D_2O exchangeable 1 H, COOH), 4.81 (d, 2 H, vinyl H), 4.17 (t, J = 6 Hz, 1 H, -CH_2CHOH-), 3.0–2.0 (m, 7 H), 1.80 (s, 3 H, vinyl CH_3), 1.23 (s, 3 H, C-2 CH_3).

Lactone 15. Acid **13** (0.056 g, 0.25 mM) was dissolved in dioxane (8 mL). Dicyclohexylcarbodiimide (0.049 g, 0.24 mM) was added, and the reaction was stirred at 25 °C for 66 h during which time a white precipitate (dicyclohexylurea) formed. The precipitate was filtered, and the resultant dioxane solution was concentrated to give an oil. The oil was dissolved in acetone (4 mL) and filtered through a short silica gel column. The acetone solution was then dried (Na_2SO_4) and concentrated in vacuo to give an oil (0.040 g). Pure **15** (0.0167 g) was isolated as an oil by preparative TLC on silica gel with ethyl acetate/hexane (1:3) as the eluent: IR ($CHCl_3$) 3000, 1795, 1730, 1190, 910 cm^{-1}; ^1H NMR, δ 4.87 (s, 2 H, vinyl H), 4.0 (d of d, J_{AX} = 5 Hz, J_{BX} = 11 Hz, 1 H, -CHO-), 3.0–2.0 (m, 7 H), 1.81 (s, 3 H, vinyl CH_3), 1.32 (s, 3 H, C-2 CH_3); MS, m/z 208 (M^+), 164 (M – 44), 98, 69 (base).

Keto Ester 16. Acid **13** (0.0161 g, 0.06 mM) was dissolved in ether (5 mL) and cooled to 0 °C. A solution of diazomethane (ca. 0.6 mM) in ether (7 mL) was added and stirred for 2 h as the temperature gradually warmed to 25 °C. The solvent was removed in vacuo to afford **16** (0.0198 g) as an oil. TLC (ethyl acetate/hexane 1:4) showed one spot, R_f 0.28. GC (3% Carbowax 20M, 185 °C) showed one peak with a retention time (flow rate ca. 30 cc/min) of 8 min 50 s: IR ($CHCl_3$) 3000, 1740, 1710, 900 cm^{-1}; ^1H NMR, δ 4.75 (s, 2 H, vinyl H), 4.27 (d of d, J_{AX} = 5 Hz, J_{BX} = 9 Hz, 1 H, -CHOH-), 3.65 (s, 3 H, -OCH_3), 3.0–2.0 (m, 7 H), 1.77 (br s, 3 H, vinyl CH_3), 1.17 (s, 3 H, C-2 CH_3).

Keto Ester 17. The same procedure as for **16** was used. Acid **14** (0.0309 g, 0.13 mM) afforded ester **17** (0.028 g) as an oil. TLC (ethyl acetate/hexane (1:4) showed one spot, R_f 0.20. GC (3% Carbowax 20M, 195 °C) showed one peak with a retention time (flow rate ca. 30 cc/min) of 11 min 10 s. A sample of **10** showed identical TLC and GC and spectral properties.

1α,4aβ-Dimethyl-1β,10aβ-epoxy-1,4,4a,9,10,10a-hexahydro-2(3*H*)-phenanthrone (19a) and 1β,4aβ-Dimethyl-1α,10aα-epoxy-1,4,4a,9,10,10a-hexahydro-2(3*H*)-phenathrone (19b). A modification of the method of Plattner[15] was used. Ketone **18**[14b] (4.82 g, 21.3 mM) was dissolved in methanol (450 mL) along with 4 N NaOH (20 mL). Hydrogen peroxide (37 mL of 30% aqueous) was added, and the reaction mixture was stirred at 30–33 °C for 24 h and then at 25 °C for 4 h until the IR of an aliquot showed no more unsaturated carbonyl. The reaction mixture was extracted with hexane (4 × 100 mL). The methanol phase was concentrated to ca. 100 mL and extracted with hexane (4 × 50 mL). All the hexane layers were combined, dried (Na_2SO_4), and concentrated to give a pale yellow solid (4.24 g, 83%) which GC analysis (10 ft 6% SE-30 240 °C) showed to be a mixture of **19a** (38%), **19b** (59%), and **18** (3%) at 7:00, 7:25, and 8:15, respectively. The yellow solid was recrystallized 2× from methanol to afford pure **19b**: mp 116 °C; IR (KBr) 2980, 2940, 1705, 780 cm^{-1}; ^1H NMR, δ 7.3–7.0 (m, 4 H, Ar), 3.3–1.7 (m, 8 H), 1.48 (s, 3 H, C-1α CH_3), 1.30 (s, 3 H, C-4aβ CH_3); MS, m/z 242 (M^+), 224, 157 (base).

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.29; H, 7.49. Found: C, 79.49; H, 7.60.

Pure **19a** could be obtained by pressure-assisted column chromatography of the mother liquor from above with ethyl acetate (0–5%)/hexane (100–95%) as the eluent: mp 81–82 °C; IR (KBr) 2980, 2940, 1705, 780 cm^{-1}; ^1H NMR, δ 7.3–7.0 (m, 4 H, Ar), 3.0–1.7 (m, 8 H), 1.5 (s, 3 H, C-4aβ CH_3), 1.45 (s, 3 H, C-1α CH_3); MS, m/z 242 (M^+), 224, 157 (base).

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.29; H, 7.49. Found: C, 79.58; H, 7.38.

Registry No. 1, 6485-40-1; **2a**, 36616-60-1; **2b**, 18383-49-8; **3**, 97643-04-4; **4**, 97643-05-5; **5a**, 97570-23-5; **5b**, 97570-28-0; **6**, 69153-92-0; **7a**, 74290-94-1; **7b**, 97643-06-6; **10**, 97570-24-6; **11**, 97570-25-7; **12**, 88580-84-1; **13**, 97591-81-6; **14**, 97591-82-7; **15**, 97570-26-8; **16**, 97591-83-8; **17**, 97570-24-6; (±)-**18**, 97643-07-7; (±)-**19a**, 97570-27-9; (±)-**19b**, 97643-08-8; CD_3I, 865-50-9; $BrCH_2CO_2CH_3$, 96-32-2.

N-(Trifluoroacetyl)-α-amino Acid Chlorides as Chiral Reagents for Friedel–Crafts Synthesis

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Chiral *N*-(trifluoroacetyl)-α-amino acid chlorides undergo Friedel–Crafts reaction with benzene and 1,2-dimethoxybenzene under mild conditions commonly with complete (>99%) preservation of configurational identity. The resultant (trifluoroacetyl)amino ketones may be deoxygenated with Et_3SiH or H_2/Pd–C in acidic media to the corresponding *N*-(trifluoroacetyl)-β-arylalkylamines likewise without loss of configurational purity.

Recently we described the advantageous use of achiral and racemic *N*-(trifluoroacetyl)-α-amino acid chlorides in Friedel–Crafts acylations of benzene, anisole, and veratrole.[2] The resultant ketones could be reduced conveniently to the corresponding *N*-(trifluoroacetyl)-β-hydroxy-β-arylalkylamines or *N*-(trifluoroacetyl)-β-arylalkylamines.[2] Here we report that representative chiral *N*-(trifluoroacetyl)-α-amino acid chlorides can be converted in this manner to aryl α-[(trifluoroacetyl)amino]alkyl ketones and *N*-(trifluoroacetyl)-β-arylalkylamines with complete (>99%) preservation of configurational identity.

Results

Friedel–Crafts Acylations and Configurational Analysis of *N*-(Trifluoroacetyl)amino Ketones. L-

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