Tetrahedron Vol. 42, No. 6, pp. 1703 to 1709, 1986
Printed in Great Britain.

0040–4020/86 $3.00+.00

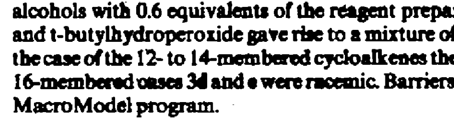
JUMP ROPE ROTATION IN *TRANS*-CYCLOALKENES

James A. Marshall, Vicki H. Audia, Todd M. Jenson and Wayne C. Guida*
Department of Chemistry, University of South Carolina, Columbia, SC 29208, U.S.A.

(*Received in USA* 16 *April* 1985)

Abstract—A series of 1,2-*bis*-methylenecycloalkane monoepoxides (**2a–e**) was prepared from the related 12- to 16-membered cyclic ketones. Reduction with lithium in ammonia afforded the corresponding *trans*- and *cis*-2-methylcycloalkenylmethanols (**3a**/**4a**–**3e**/**4e**) in ratios of 92 : 8–78 : 22. Sharpless epoxidation of these allylic alcohols with 0.6 equivalents of the reagent prepared from titanium isopropoxide, (+)-diisopropyl tartrate, and t-butylhydroperoxide gave rise to a mixture of the epoxy alcohols **6a–e** and recovered allylic alcohols. In the case of the 12- to 14-membered cycloalkenes the recovered alcohols **3a–c** were optically active. The 15- and 16-membered cases **3d** and **e** were racemic. Barriers to jump rope rotation were calculated by means of the Still MacroModel program.

The configurational stability of *trans*-cycloalkenes has been a matter of interest to chemists since 1952 when Blomquist pointed out the chiral nature of these olefins and described his unsuccessful attempts to resolve *trans*-6-cyclononenone.[1,2] Some ten years later Cope found that *trans*-cyclooctene (I; R = H, $n = 6$) maintains full optical activity for extended periods at room temperature while *trans*-cyclononene racemizes rapidly even at low temperature.[3] Binsch and Roberts subsequently studied the rotational barrier to racemization (I ⇆ III) using variable temperature NMR measurements and calculated room temperature half-lives of 10^5 years and 10 s for *trans*-cyclooctene and *trans*-cyclononene.[4]



I II III

Fig. 1. Jump rope rotation in cycloalkenes.

The preparation of optically active *trans*-cycloalkenes poses an interesting synthetic challenge. Cope resolved *trans*-cyclooctene and *trans*-cyclononene via conversion to diastereomeric platinum complexes which could be separated by fractional crystallization.[3] Enantiomerically enriched *trans*-cyclononene could be liberated from the complex at low temperature, but it was found to racemize upon warming to room temperature. While similar complexes of *trans*-cyclodecene could be prepared and separated, the derived olefin showed no rotation, even at low temperature. Syntheses of enantiomerically enriched 1-methyl *trans*-cyclodecenes from resolved precursors via fragmentation routes have been attempted by several workers but none have succeeded.[5] Evidently jump rope rotation of the bridging carbon chain past the vinylic hydrogen is facile in these systems. Replacing the hydrogen by a more sterically demanding group should increase the barrier to such rotation, thereby extending the ring size for observable optical activity. In fact, we were able to prepare optically active *trans*-1,2-dimethylcyclodecene via asymmetric synthesis from a resolved bicyclo[5.3.1]-camphorsulfonate.[6] The dimethyl cycloundecene homolog was similarly secured from the analogous bicyclo[6.3.1]camphorsulfonate. Attempts to prepare the corresponding bicyclo[7.3.1]precursor of *trans*-1,2-dimethylcyclododecene were unsuccessful.

We were also able to partially resolve *trans*-1,2-dimethylcycloundecene by enantioselective hydroboration with isopinocampheylborane.[6] The method did not afford optically active *trans*-1,2-dimethylcyclododecene and we therefore concluded that racemization of this olefin must be favorable. Subsequent reexamination of these hydroboration experiments revealed that only a small fraction of the olefin was consumed. Substantial rearrangement and decomposition of the hydroboration product may have occurred so the conclusion must now be considered doubtful.[7]

A simple and direct route to optically active *trans*-cycloalkenes of defined absolute configuration was recently developed in connection with our work on optically active betweenanenes.[8] We found that various *trans*-cyclododecenylmethanols (e.g. I/III; $n = 10$, R = 4-pentenyl, R' = CH_2OH) are readily resolved via Sharpless enantioselective epoxidation. The (+)-tartrate-derived reagent cleanly epoxidizes the (*R*)-enantiomer III and the unreacted (*S*)-enantiomer I of 90% optical purity can be recovered in high yield.[9]

In view of the uncertainties surrounding our hydroboration results we decided to apply the Sharpless methodology to the *trans*-cyclododecenylmethanol **3a** as a probe for jump rope rotation in methyl substituted *trans*-cyclododecenes. It is presumed that the CH_3 substituent of alcohol **3a** has the smaller steric requirement so the rotational barrier would approximate that of the dimethyl cycloalkene. Alcohol **3a** could be prepared via Birch reduction of the epoxy olefin **2a**[9] with lithium/ammonia followed by quenching with ammonium chloride. A 9 : 1 mixture of the *trans* and *cis* isomers **3a** and **4a** was thereby obtained along with varying amounts of the related hydrogenolysis products, *trans*- and *cis*-1,2-dimethylcyclododecene. The formation of these latter by-products was dependent upon reaction time,

---

* On sabbatical leave from Eckerd College, St. Petersburg, Florida, 1983–84 academic year. Present address: Department of Chemistry, Columbia University, New York, NY 10027, U.S.A.

stoichiometry, concentration, and ring size. Lesser amounts of lithium or shorter reaction times resulted in recovery of starting material. The *cis* product **4a** gave rise to a singlet at 4.1 ppm in the ^{1}H-NMR spectrum of the mixture arising from the carbinyl CH_2. The corresponding signal for the carbinyl protons of the *trans* isomer appeared as an AB quartet at approximately the same chemical shift. We were unable to separate these isomers so resolutions were therefore carried out on the mixture.

Sharpless epoxidation of allylic alcohol **3a** was effected in methylene chloride at −20° with 0.6 equivalents of t-butyl hydroperoxide using (+)-diisopropyl tartrate as the chiral ligand.[9] Both the epoxy alcohol product **6a** and the recovered allylic alcohol (*S*)-**3a** were found to be optically active. The latter showed no loss of optical activity upon prolonged storage or heating to 100°. The recovered allylic alcohol was enriched in the *cis* isomer **4a** indicating preferential epoxidation of the *trans*-cycloalkene **3a**. The optical purities of the recovered alcohol (*S*)-**3a** and the epoxy alcohol **6a** were found to be 73 and 59%, respectively, through ^{19}F-NMR analysis of the Mosher ester derivatives (*S*)-**5a** and **7a**.[10] The configurational assignments are based on the known enantioselectivity of the Sharpless reagent for allylic alcohols.[9,11]

The apparent optical stability of the methyl-substituted *trans*-cyclododecene **3a** prompted our examination of larger ring homologs of **3** in our search for the cross-over point for jump rope rotation in such systems. Molecular mechanics calculations pointed to the 16-membered system **3e** as the most likely candidate, but we decided to examine the lower homologs **3b–d** as well for the sake of completeness. These alcohols could be prepared by Birch reduction of the vinyloxiranes **2b–e** as described for **2a** (Table 1).[†] In each case, the *trans*-carbinol product **3** predominates but to a lesser degree for the larger ring sizes. Addition of butylcuprates to **2a–e**, on the other hand, favors the *trans*-carbinol products by 9 : 1 or better.[12] The *cis*-*trans* ratios were easily determined from the ^{1}H-NMR spectra by comparison of the carbinyl singlet of the *cis* isomer **4** at ~ 4.1 ppm with the AB quartet shown by the *trans* isomer **3** at nearly the same chemical shift. None of these mixtures could be separated so resolutions were carried out on mixtures of the compositions shown.

Sharpless epoxidation of the 13-membered *trans*-cycloalkenylcarbinol **3b** with 0.6 equivalents of the (+)-diisopropyl tartrate reagent afforded the optically active epoxy alcohol **6b** in 46% yield (77% of theory). The recovered allylic alcohol (*S*)-**3b** showed an ee in excess of 90% according to ^{19}F-NMR analysis of the Mosher ester (*S*)-**5b**. Similarly, the 14-membered *trans*-cycloalkenylcarbinol **3c** gave rise to epoxy alcohol **6c** of 51% ee and recovered allylic alcohol (*S*)-**3c** of 77% ee. The optical rotation of this alcohol was unchanged after prolonged heating at 80°. It should be noted that control experiments with racemic alcohols showed apparent optical enrichment of 2–3% in the formation of ester **7**. Enrichments of the allylic alcohol esters **5** were less than 2%. We did not attempt to correct for this slight stereochemical bias in our ee determinations.

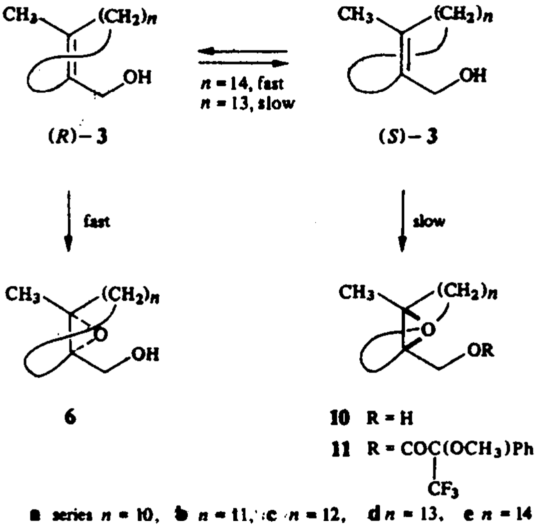
Table 1. Reductions of epoxides **2** with Li/NH_3

2	*n*	Time (h)	Yield (%)	**3** (%)	**4** (%)
a	10	4.0	49	92	8
b	11	11	70	96	4
c	12	11	55	88	12
d	13	1.8	72	83	17
e	14	1.5	83	78	22

Epoxidation of the 15-membered allylic alcohol **3d** afforded an optically active epoxy alcohol **6d** of 40% enantiomeric excess. The recovered alcohol, however, was racemic. As a check on the methodology, Sharpless resolution of allylic alcohol **3d** was effected with (−)-diisopropyl tartrate as the chiral ligand. As expected, the enantiomeric epoxy alcohol was obtained and the recovered allylic alcohol **3d** was again racemic.

Treatment of allylic alcohol **3d** with an excess of the epoxidation reagent afforded epoxy alcohol **6d** of negligible optical rotation. The 14-membered allylic alcohol **3d** behaved analogously. The ^{19}F-NMR spectrum of the Mosher esters of the former epoxy alcohol mixture showed resonances of nearly equal intensity for the *trans* diastereoisomers **7d** and **11d** (Scheme 1). Two additional peaks arising from the *cis* isomer were present in the ratio 9 : 1 (mainly **9d**). Unlike the 14- and 15-membered homologs, the 16-membered allylic alcohol **3e** gave optically active epoxy alcohol **6e** of 55% ee in 80% yield upon epoxidation with excess reagent.

The foregoing experiments reveal an interesting interplay of reagent and substrate steric control (Scheme 1). The (+)-tartrate derived Sharpless reagent is known to preferentially epoxidize the *re* face of allylic alcohols such as **3**.[9,11] This is the open face of (*R*)-**3** and epoxidation therefore proceeds in concert with both substrate and reagent preferences to afford epoxy alcohol **6**. With (*S*)-**3**, on the other hand, the bridging methylene chain blocks the reagent



Scheme 1.

[†] The synthesis of vinyloxiranes **2a–c** and **e** was effected via treatment of the α-methylene cycloalkanone with dimethylsulfonium methylide; **2d** was obtained by Wittig methylenation of the epoxy ketone.[12]

Table 2. Sharpless resolution of *trans*-cycloalkenylcarbinols

		Recovered 3			6		
3	*n*	$[\alpha]_D$[a] (°)	ee[b,c] (%)	Yield (%)	$[\alpha]_D$[a] (°)	ee[b] (%)	Yield (%)
a	10	29.8	73	41	−44.5	59	34
b	11	101.4	>90	28	−56.5	—	46
c	12	83.3	77[d]	20	−27.0	51	51
c	12	—	—	—	−0.6	—	63[f]
d	13	0	—	29	−22.6	40	47
d	13	0	—	33	24.9[e]	—	49
d	13	0	—	8	−7.0	15	51[g]
d	13	—	—	—	−0.7	—	65[f]
e	14	0	—	34	−23.1	55[h]	37
e	14	—	—	—	−23.0	—	80[f]

[a] (+)-Diisopropyl tartrate.

[b] ^{19}F-NMR analysis of the Mosher ester.

[c] These olefins contain over 10% of the *cis*-olefin **4**. The ee is calculated by integration of the ^{19}F signals of the *trans* diastereoisomers.

[d] Analysis of the (−)-α-naphthylethylurethane derivatives by gas chromatography.

[e] (−)-Diisopropyl tartrate. The product is **10d**.

[f] Excess reagent.

[g] 0.9 equivalents of reagent.

[h] ^{1}H-NMR analysis of the Mosher ester at 400 MHz.

preferred mode of epoxidation and reaction is thus substrate directed to the less preferred *si* face. The relative rates of these two reactions reflect the enantioselectivity of the epoxidation, as is the case for acyclic allylic alcohols. However in **3**, unlike acyclic allylic alcohols, the bridging chain effectively shields the double bond and only one enantiomer can undergo reagent preferred epoxidation. Consequently, none of the diastereomeric epoxy alcohol would be expected to form. With excess reagent the disfavored (but substrate directed) *si* face epoxidation of (*S*)-**3** should eventually proceed to completion and the enantiomeric epoxy alcohols **6** and **10** would then be produced in equal amount. By stopping short of this point it is possible to effect kinetic resolution of **3**.

The 14-membered allylic alcohol **3c** behaves precisely in this way. When Sharpless epoxidation is carried out with 0.6 equivalents of the reagent, allyl alcohol (*S*)-**3c** of *ca* 77% ee is recovered along with epoxy alcohol of 51% ee. Epoxidation with excess reagent results in a nearly racemic mixture of epoxy alcohols **6c** and **10c**.

Epoxidation of the 16-membered allylic alcohol **3e** with a full equivalent of Sharpless reagent leads not to a racemic mixture of epoxy alcohols, as in the 14-membered ring system, but gives instead resolved epoxy alcohol **6e** of 55% ee in high chemical yield. Evidently, jump rope rotation is possible under the Sharpless conditions in this larger ring olefin, thus allowing for constant replenishment of the more reactive (*R*) enantiomer. Allylic alcohol **3e** thus approximates an acyclic achiral alcohol with regard to Sharpless epoxidation.

The 15-membered allylic alcohol **3d** behaves somewhat differently in that partial epoxidation leads to optically enriched epoxide **6d** but the recovered alcohol is racemic. Thus jump rope rotation must occur. However, unlike the 16-membered homolog, complete epoxidation affords nearly racemic epoxy alcohol **6d**/**10d**. Apparently the (*R*) and (*S*) enantiomers of **3d** do not interconvert under the Sharpless conditions (−20°) since such interconversion would allow preferential epoxidation of the (*R*) enantiomer as was observed for **3e**. Therefore, racemization of **3d** must take place during product isolation. Interestingly, alcohol **3d** recovered from epoxidations employing 0.6 equivalents of reagent was enriched in the *cis* contaminant **4d** whereas **3d** recovered from epoxidations using 0.9 equivalents was completely devoid of **4d**. The 14-membered allylic alcohol **3c** behaved similarly. Thus the *cis*-allylic alcohols **4c** and **d** must epoxidize more slowly than (*R*)-**3c** and **d** but more rapidly than (*S*)-**3c** and **d**. It is of further interest that the *trans* allylic alcohol **3d** was epoxidized with only modest enantioselectivity whereas the *cis* contaminant **4d** gave epoxy alcohol **8d** of 80% ee according to ^{19}F-NMR analysis of the Mosher ester **9d**. A similar observation was made for the 14-membered system.

As noted above, preliminary to some of the foregoing experimental work we carried out molecular mechanics calculations in an attempt to predict the jump rope barrier in several *trans*-dimethylcycloalkenes (I, R = CH_3). Ground state conformational energies were calculated via the Still "Ringmaker/Bakmod" program.[13] For the transition state energy computation we constructed a Dreiding model of the crown conformer with the double bond oriented in the mean plane of the ring.† The Cartesian coordinates of this model were generated graphically and MM2 energy minimization was performed using the restricted motion option of the program to maintain coplanarity of the double bond and the most remote sp^3 ring carbon center.‡

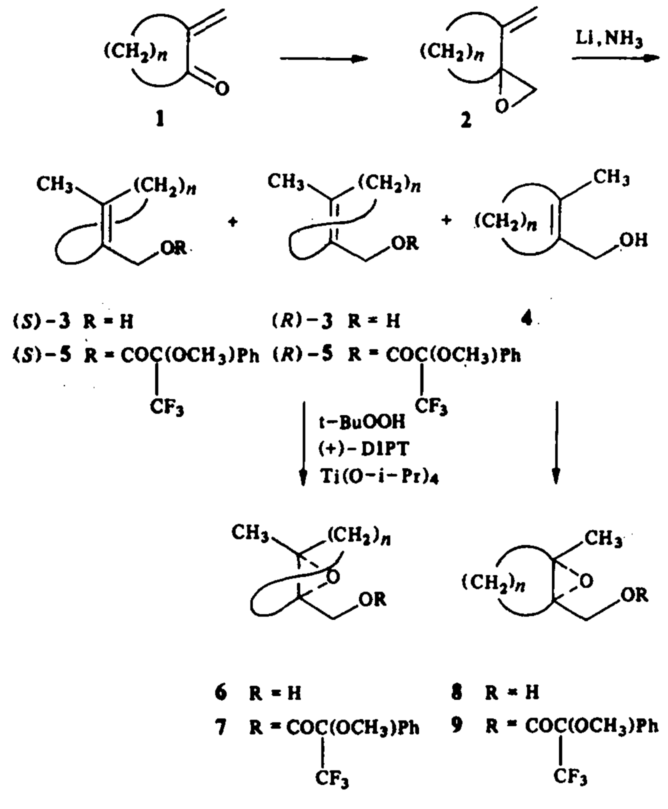
---

† For medium ring cycloalkanes the crown conformation is not the lowest energy form but it was selected here because it offers the largest cavity for the CH_3 substituent. The results of our MacroModel calculations indicate that jump rope rotation can proceed through other lower energy conformers.[14]

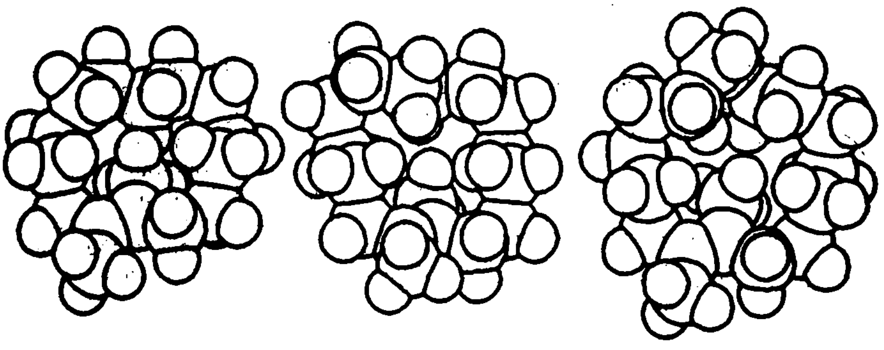
‡ The MM2 program is available from Indiana University's Quantum Chemistry Program Exchange.[15]

The barriers for *trans*-cyclononene and -cyclodecene calculated in this way were 4–6 kcal higher than the experimental values. We were subsequently able to perform these calculations on a prototype version of Still's second generation modeling program, "MacroModel", with significantly better agreement (Table 3).† Accordingly, ground state conformational energies of *trans*-1,2-dimethylcyclotetradecene, -cyclopentadecene, and -cyclohexadecene and, for calibration, *trans*-cyclononene and -cyclodecene were calculated via the "multiconformer submode". The technique here is similar to that used by the Ringmaker program[13] in that numerous trial conformations are produced from an acyclic "precursor" of the macrocycle by preselected incremental rotation about all sigma bonds. From this large set of acyclic conformers a smaller subset is chosen whose termini are within preselected criteria of bonding distance and angle. Each member of this subset is converted to a cyclic structure which is then minimized by using the MM2 force field. The resulting conformers are ordered according to energy content. The ground state energy values thus obtained were close to those calculated earlier via the Ringmaker/Bakmod program.[13]

The lowest energy conformer of each *trans*-cycloalkene was used as the starting structure for determining rotational barriers using the "orient" submode of MacroModel. This submode permits rotation or translation of atoms about a definable axis. Jump rope



a series $n = 10$, b $n = 11$, c $n = 12$, d $n = 13$, e $n = 14$



trans-1,2-dimethylcyclotetradecene *trans*-1,2-dimethylcyclopentadecene *trans*-1,2-dimethylcyclohexadecene

Fig. 2. Transition state conformations for jump rope rotation of *trans*-1,2-dimethylcycloalkenes.

---

† The calculations were carried out by W. C. G. at Columbia University. We are grateful to Professor Clark Still for his generous cooperation.

Table 3. Calculated conformational energies of *trans*-cycloalkenes (I)[a]

		Energy		Activation	
R	*n*	Ground state (kcal mol^{-1})	Transition state (kcal mol^{-1})	Calc (kcal mol^{-1})	Found (kcal mol^{-1})
CH_3	12	18.7	49.4	30.7	—
CH_3	13	21.1	47.7	26.6	—
CH_3	14	20.8	40.2	19.4	—
H	7	21.8	41.1	19.3	20.0[4]
H	8	17.9	31.6	13.7	10.7[4]

[a] The Still "MacroModel" program was used.

rotation was simulated by rotation of the double bond in preselected increments about an axis containing the two allylic methylene groups of the *trans*-cycloalkene. The approximate energy resulting from each incremental rotation is displayed in the form of an energy bar graph. The structure corresponding to the highest bar of this graph was minimized via the MM2 force field after constraining the distance between the internal methyl substituent (H in the case of *trans*-cyclononene and -cyclodecene) and the nearest transannular carbon (see Fig. 2). In this way the bridging methylenes are allowed to rotate but the double bond is forced to remain coplanar with the ring.

Rotational barriers obtained through MacroModel were significantly better than those calculated earlier for *trans*-cyclononene and -cyclodecene. In addition, the calculations were more easily performed, particularly those relating to transition state energies. Although excellent agreement with experimental results was found for *trans*-cyclononene (Table 3), the barrier calculated for *trans*-cyclodecene was 3 kcal too high. *trans*-1,2-Dimethylcyclopentadecene and *trans*-cyclononene both racemize between −20° and room temperature so the jump rope barrier should be similar for each.[3,4] Here again our calculation overstates the energy. Most likely these errors result from exaggerated values for the van der Waals repulsion term at close interatomic distance in the MM2 force field.[16]

EXPERIMENTAL

2-Methyl-1-cyclotridecenylmethanol (**3b**). To 20 ml of ammonia in a 100 ml round bottom flask equipped with a mechanical stirrer, dry ice condenser and stopper was added 25.9 mm (114 mg, 16.06 mmol) of Li wire in small pieces. To this soln was added 1.190 g (5.35 mmol) of **2b** in 1.5 ml of THF followed by an additional 25.9 mm (114 mg, 16.06 mmol) of Li wire. The soln was stirred for 11 h, carefully quenched with solid NH_4Cl and diluted with hexane. The ammonia was allowed to evaporate and the residue was diluted with water and extracted with ether. The combined ether layers were washed with water, brine and dried over K_2CO_3. Filtration and removal of solvent at reduced pressure gave 1.189 g (99%) of a yellow oil. Purification on silica gel with 10:1 hexane–EtOAc yielded 0.857 g (70%) of the alcohol as a 96:4 mixture of *trans* and *cis* isomers, **3b** and **4b**. IR (film) ν 3350, 2910, 2850, 1470, 1460, 1390, 1000, 900 cm^{-1}. ^{1}H-NMR (90 MHz) δ 1.06–1.60 (env, ring CH_2), 1.76 (s, CH_3), 1.83–2.76 (m), 4.18 (ABq, J = 10.8 Hz, Δν = 52.9 Hz, *trans* CH_2O), 4.11 (s, CH_2O) ppm. (Found: C, 80.26; H, 12.36. Calc for $C_{15}H_{28}O$: C, 80.29; H, 12.58%.)

2-Methyl-1-cyclododecenylmethanol (**3a**). The vinyloxirane **2a** (1.00 g, 4.8 mmol), in 164 ml of ammonia was treated with 23.9 mm (102.8 mg, 14.8 mmol) of Li wire over 4 h. Purification gave **3a**, m.p. 45.5–47.5°, as a 92:8 mixture of *trans* and *cis* isomers, **3a** and **4a**. IR (film) ν 3350, 2900, 2850, 1640, 1465, 1445, 1000, 900 cm^{-1}. ^{1}H-NMR (90 MHz) δ 1.06–1.60 (env, ring CH_2), 1.78 (s, CH_3), 1.83–2.75 (m), 4.21 (ABq, J = 10.8 Hz, Δν = 52.9 Hz, *trans* CH_2O), 4.12 (s, *cis* CH_2O) ppm. (Found: C, 80.07; H, 12.49. Calc for $C_{14}H_{26}O$: C, 79.94; H, 12.46%.)

2-Methyl-1-cyclotetradecenylmethanol (**3c**). The vinyloxirane **2c** (1.245 g, 5.27 mmol), in 21.0 ml of ammonia was treated with 68.0 mm (294 mg, 42.2 mmol) of Li wire for 11 h. Purification afforded 0.688 g (55%) of the allylic alcohol as a 88:12 mixture of *trans* and *cis* isomers, **3c** and **4c**. IR (film) ν 3300, 2900, 2850, 1650, 1460, 1380, 1030, 1000 cm^{-1}. ^{1}H-NMR (90 MHz) δ 0.93–1.56 (env, ring CH_2), 1.66 (s, *trans* CH_3), 1.73 (s, *cis* CH_3), 1.80–2.76 (m), 4.12 (ABq, J = 10.8 Hz, Δν = 43.7 Hz, *trans* CH_2OH), 4.10 (s, *cis* CH_2O) ppm. (Found: C, 80.89; H, 12.34. Calc for $C_{16}H_{30}O$: C, 80.61; H, 12.68%.)

2-Methyl-1-cyclopentadecenylmethanol (**3d**). The vinyloxirane **2d** (0.410 g, 1.6 mmol), in 7 ml of ammonia was treated with 6.44 mm (27.7 mg, 3.99 mmol) of Li wire for 1.8 h. Purification gave 0.298 g (72%) of the allylic alcohol as an 83:17 mixture of *trans* and *cis* isomers, **3d** and **4d**. IR (film) ν 3300, 2900, 2850, 1460, 1010 cm^{-1}. ^{1}H-NMR (90 MHz) δ 1.10–1.60 (env, ring CH_2), 1.73 (s, CH_3), 1.83–2.80 (m), 4.11 (ABq, J = 10.8 Hz, Δν = 48.30 Hz, *trans* CH_2O), 4.11 (s, *cis* CH_2O) ppm. (Found: C, 80.67; H, 12.80. Calc for $C_{17}H_{32}O$: C, 80.88; H, 12.78%.)

2-Methyl-1-cyclohexadecenylmethanol (**3e**). The vinyloxirane **2e** (0.501 g, 1.89 mmol), in 8 ml of ammonia was treated with 7.65 mm (32.9 mg, 4.7 mmol) of Li wire for 1.5 h. Purification gave 0.418 g (83%) of the alcohol as a 78:22 mixture of *trans* and *cis* isomers, **3e** and **4e**. IR (film) ν 3300, 2900, 2840, 1650, 1460, 1380, 1010 cm^{-1}. ^{1}H-NMR (400 MHz) δ 1.10–1.57 (env, ring CH_2), 1.69 (s, *trans* CH_3), 1.75 (s, *cis* CH_3), 1.83–1.93 (m), 2.03–2.10 (m), 2.11–2.19 (m), 2.33–2.43 (m), 2.53–2.63 (m), 4.15 (ABq, J = 12.0 Hz, Δν = 14.2 Hz, *trans* CH_2O), 4.14 (s, *cis* CH_2O) ppm. (Found: C, 80.98; H, 12.88. Calc for $C_{18}H_{34}O$: C, 81.13; H, 12.86%.)

Sharpless epoxidation of (±) - (*Z*) - 2 - *methyl* - 1 - *cyclotetradecenylmethanol* (**3c**)

(a) *Using* 0.6 *equivs of* t-*butyl hydroperoxide*. The procedure of Sharpless and Katsuki was followed.[11] To a cooled soln of 6.5 ml of CH_2Cl_2 was added dropwise 0.262 ml (0.88 mmol) of titanium tetraisopropoxide followed by 0.212 ml (1.01 mmol) of (+)-diisopropyl tartrate at −23° under Ar. The mixture was stirred for 5 min and 0.200 g (0.84 mmol) of **3c** in 4.0 ml of CH_2Cl_2 was added followed by 0.144 ml (0.504 mmol) of 3.5 M anhyd t-butyl hydroperoxide in dichloroethane. After 35 min, the mixture was poured into a cooled soln of 16.0 ml of acetone and 1.0 ml of water. After stirring for 4 h, the mixture was filtered through a pad of Celite, concentrated, and extracted with CH_2Cl_2. The combined extracts were dried over K_2CO_3, filtered, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (10:1 hexane–EtOAc) afforded 0.040 g (20%) of **3c**, $[\alpha]_D^{23}$ +83.3 (*c*, 3.94, $CHCl_3$) whose spectral properties matched those of the racemic alcohol described above.

The isocyanate derivative, prepared according to Pirkle and co-workers,[17] was analyzed by high pressure liquid chromatography. The derivative of the racemic alcohol showed peaks of relative areas 1.00 : 1.04 : 0.34 compared to 1.00 : 7.75 : 0.55 for the resolved material.

Continued elution of the above column with 10 : 1 hexane–EtOAc afforded 0.110 g (52%) of **6c**, $[\alpha]_D^{24}$ $-27.0°$ (*c*, 11.0, $CHCl_3$). IR (film) ν 3400, 2900, 2845, 1470, 1390, 920 cm^{-1}. ^1H-NMR (90 MHz) δ 1.1–1.63 (env, ring CH_2), 1.73–2.43 (m), 2.7–2.86 (m), 3.53–4.0 (m) ppm. (Found: C, 75.31; H, 11.95. Calc for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89%.)

The Mosher derivative **7c**, prepared according to Sharpless and Katsuki,[11] exhibited resonances at 4.625 and 4.550 ppm in the ratio 1.0 : 2.4 in the ^{19}F-NMR spectrum. The corresponding spectrum of the Mosher ester derived from the racemic epoxy alcohol mixture showed peaks at 4.627, 4.625 and 4.550 ppm in the ratio 0.31 : 1.08 : 1.00.

(b) *Using excess t-butyl hydroperoxide*. The racemic **3c** (1.06 g, 4.4 mmol), in 4.0 ml of CH_2Cl_2 was added to a cooled soln of 2.0 ml (6.7 mmol) of titanium tetraisopropoxide and 1.9 ml (9.0 mmol) of (+)-diisopropyl tartrate in 40 ml of CH_2Cl_2 as above. Addition of 1.8 ml (6.3 mmol) of 3.5 M t-butyl hydroperoxide in CH_2Cl_2 followed by workup after 30 min gave upon purification no **3c** and 0.712 g (63%) of **6c** $[\alpha]_D^{25}$ $-0.56°$ (*c*, 8.0, $CHCl_3$) whose spectral properties matched those of **6c** obtained in Part a above.

(+)-(S)-(Z)-2-Methyl-1-cyclododecenylmethanol [(*S*)-**3a**]. The racemic **3a** (0.243 g, 1.15 mmol), in 4 ml of CH_2Cl_2 was added to a cooled soln of 0.36 ml (1.2 mmol) of titanium tetraisopropoxide and 0.29 ml (1.4 mmol) of (+)-diisopropyl tartrate in 7.5 ml of CH_2Cl_2 as above. Addition of 0.20 ml (0.69 mmol) of 3.5 M t-butyl hydroperoxide in CH_2Cl_2 followed by workup after 26 min gave upon purification 0.10 g (41%) of (*S*)-**3a**, $[\alpha]_D^{26}$ $+29.82°$ (*c*, 5.0, $CHCl_3$) whose spectral properties matched those of the racemic **3a** described above.

Continued elution of the column gave 0.090 g (35%) of **6a**, $[\alpha]_D^{26}$ $-44.5°$ (*c*, 4.5, $CHCl_3$). IR (film) ν 3450, 2930, 2870, 1480, 1040, 760 cm^{-1}. ^1H-NMR (90 MHz) 1.33 (env, ring CH_2), 1.42 (s, CH_3), 2.0–2.4 (env), 3.65 (d, J = 12 Hz, downfield half of ABq), and 3.9 ppm (env, upfield half of ABq).

(+)-(S)-(Z)-2-Methyl-1-cyclotridecenylmethanol (*S*)-**3b**. The racemic **3b** (0.348 g, 1.55 mmol), in 4.5 ml of CH_2Cl_2 was added to a cooled soln of 0.485 ml (1.63 mmol) of titanium tetraisopropoxide and 0.391 ml (1.86 mmol) of (+)-diisopropyl tartrate in 15.0 ml of CH_2Cl_2 as above. Addition of 0.199 ml (0.93 mmol) of 4.68 M t-butyl hydroperoxide in dichloroethane followed by workup after 41 min gave upon purification, 0.0983 g (28%) of (*S*)-**3b**, $[\alpha]_D^{27}$ $+101.4°$ (*c*, 4.47, $CHCl_3$) whose spectral properties matched those of the racemic **3b** described above. The Mosher ester derivative (*S*)-**5b** exhibited resonances at 5 114 and 4.406 ppm in the ^{19}F-NMR spectrum in the ratio 1 : 10.

Continued elution of the column gave 0.1723 g (46%) of **6b**. $[\alpha]_D^{27}$ $-56.46°$ (*c*, 5.01, $CHCl_3$). IR (film) ν 3400, 2930, 2860, 1470, 1390, 1060 cm^{-1}. ^1H-NMR (90 MHz) δ 1.2–1.53 (env, ring CH_2), 1.53–2.43 (m), 2.5–2.8 (m), 3.52–4.10 (m) ppm. (Found: C, 74.80; H, 11.76. Calc for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74%.)

Sharpless epoxidation of (±)-(Z)-2-Methyl-1-cyclopentadecenylmethanol 3d

(a) *Using (+)-diisopropyl tartrate*. The racemic **3d** (0.161 g, 0.64 mmol), in 3.0 ml of CH_2Cl_2 was added to a cooled soln of 0.200 ml (0.67 mmol) of titanium tetraisopropoxide and 0.161 ml (0.77 mmol) of (+)-diisopropyl tartrate in 3.5 ml of CH_2Cl_2 as above. Addition of 0.110 ml (0.384 mmol) of 3.5 M anhyd t-butyl hydroperoxide in dichloroethane followed by workup after 25 min gave upon purification, 0.0458 g (29%) of **3d**, $[\alpha]_D^{24}$ 0° (*c*, 2.27, $CHCl_3$) whose spectral properties matched those of the racemic **3d** described above. The Mosher derivative **5d** exhibited resonances at 5.035, 5.006, and 4.985 ppm in the ^{19}F-NMR spectrum in the ratio 1.00 : 0.97 : 0.21. The resonance at 4.985 ppm can be attributed to the *cis* isomer.

Continued elution of the column gave 0.0812 g (47%) of **6d**, $[\alpha]_D^{24}$ $-22.59°$ (*c*, 4.0, $CHCl_3$) IR (film) ν 3400, 3000, 2910, 2840, 1460, 1380, 1220, 1040, 760 cm^{-1}. ^1H-NMR (60 MHz) δ 1.1–1.66 (env, ring CH_2), 1.76–2.46 (m), 3.40–4.03 (m) ppm. (Found: C, 75.80; H, 12.03. Calc for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02%.) The Mosher ester derivative of **7d** exhibited resonances at 5.110, 5.081, 4.920, and 4.861 ppm in the ratio 1.0 : 8.8 : 18.0 : 7.6 in the ^{19}F spectrum. The corresponding spectrum of the racemic epoxy alcohol mixture contained these four peaks in the ratio 1.0 : 1.0 : 3.3 : 3.0. The resonances at 5.110 and 5.081 ppm can be attributed to the *cis* isomer **9d**.

(b) *Using (−)-diisopropyl tartrate*. The racemic **3d** (0.105 g, 0.41 mmol), in 2.0 ml of CH_2Cl_2 was added to a cooled soln of 0.130 ml (0.43 mmol) of titanium tetraisopropoxide and 0.10 ml (0.49 mmol) of (−)-diisopropyl tartrate in 3.0 ml of CH_2Cl_2 as above. Addition of 0.07 ml (0.25 mmol) of 3.5 M anhyd t-butyl hydroperoxide in dichloroethane followed by workup after 17 min gave upon purification, 0.0350 g (33%) of **3d**, $[\alpha]_D^{24}$ 0° (*c*, 3.5, $CHCl_3$) whose spectral properties matched those of the racemic **3d** described above.

Continued elution of the column gave 0.0543 g (49%) of **6d**, $[\alpha]_D^{25}$ $+24.93°$ (*c*, 5.43, $CHCl_3$). The IR spectrum corresponded to that of the (−)-isomer. ^1H-NMR (90 MHz) δ 1.10–1.66 (env, ring CH_2), 1.70–2.40 (m), 3.52–3.98 (m) ppm.

(c) *Using excess t-butyl hydroperoxide*. The racemic **3a** (0.110 g, 0.44 mmol), in 1.5 ml of CH_2Cl_2 was added to a cooled soln of 0.195 g (0.65 mmol) of titanium tetraisopropoxide and 0.167 ml (0.79 mmol) of (+)-diisopropyl tartrate in 3.5 ml of CH_2Cl_2 as above. Addition of 0.138 ml (0.48 mmol) of 3.5 M anhyd t-butyl hydroperoxide in dichloroethane followed by workup after 1.2 h gave upon purification, 0.0706 g (65%) of **6d**, $[\alpha]_D^{25}$ $-0.69°$ (*c*, 7.0, $CHCl_3$) whose spectral properties matched those of the material prepared in Part a. ^1H-NMR (400 MHz) δ 1.17–1.57 (env, ring CH_2), 1.65 (s, CH_3), 1.76–1.97 (m), 2.18 (m), 3.76 (ABq, J = 11.2 Hz, $\Delta\nu = 98.7$ Hz, *trans* CH_2O), 3.67 (ABq, J = 11.2 Hz, $\Delta\nu = 34.6$ Hz, *cis* CH_2O) ppm.

(d) *Using 0.9 equivalents of t-butyl hydroperoxide*. The racemic **3d** (0.209 g, 0.82 mmol), in 2.0 ml of CH_2Cl_2 was added to a cooled soln of 0.390 ml (1.31 mmol) of titanium tetraisopropoxide and 0.310 ml (1.48 mmol) of (+)-diisopropyl tartrate in 6.0 ml of CH_2Cl_2 as above. Addition of 0.220 ml (0.78 mmol) of 3.5 M anhyd t-butyl hydroperoxide in dichloroethane, followed by workup after 1.2 h, gave upon purification, 0.0166 g (8%) of **3d**, $[\alpha]_D^{25}$ 0° (*c*, 1.6, $CHCl_3$) whose spectral properties matched those of the allylic alcohol above except for the absence of peaks attributed to the *cis* isomer **4d** in the ^1H-NMR spectrum.

Continued elution of the above column gave 0.1135 g (51%) of **6d**, $[\alpha]_D^{24}$ $-7.0°$ (*c*, 3.0, $CHCl_3$), whose spectral properties matched those of the (−)-isomer, **6d**. ^1H-NMR (90 MHz) δ 1.1–1.6 (env, ring CH_2), 1.7–2.34 (m), 3.76 (ABq, J = 12.6 Hz, $\Delta\nu = 21.3$ Hz, CH_2O) ppm.

The Mosher ester derivative **7d**, prepared according to Sharpless and Katsuki[11] exhibited resonances at 4.801, 4.728, 4.568, and 4.5087 ppm in the ratio 1.0 : 10.0 : 38.0 : 25.6 in the ^{19}F spectrum.

Sharpless epoxidation of (±)-(Z)-2-methyl-1-cyclohexadecenylmethanol (3e).

(a) *Using 0.6 equivalents of t-butyl hydroperoxide*. The procedure described above for **3b** was followed. Addition of 0.130 g (0.49 mmol) of **3e** in 2.6 ml of CH_2Cl_2 to a cooled soln of 0.152 ml (0.512 mmol) of titanium tetraisopropoxide and 0.123 ml (0.585 mmol) of (+)-diisopropyl tartrate in 3.5 ml of CH_2Cl_2 was followed by addition of 0.084 ml (0.293 mmol) of 3.5 M t-butyl hydroperoxide in dichloroethane at −20°. After 20 min, the product was isolated as described above. Flash chromatography on silica gel (10 : 1 hexane–EtOAc) afforded 0.0447 g (34%) of **3e**, $[\alpha]_D^{26}$ $-0.02°$ (*c*, 4.47, $CHCl_3$) whose spectral properties matched those of the racemic **3e** described above.

Continued elution of the above column gave 0.0508 g (37%) of **6e**, $[\alpha]_D^{27}$ $-23.09°$ (*c*, 5.08, $CHCl_3$) whose spectral properties matched those of **6e** described above. The Mosher derivative **7e** gave resonances at 3.58 and 3.55 ppm for the methoxy peak of two isomers in the ratio 1.0 : 3.4 in the 400 MHz ^1H-NMR spectrum.

(b) *Using excess* t-*butyl hydroperoxide*. The racemic **3e** (0.240 g, 0.90 mmol), in 43 ml of CH_2Cl_2 was added to a cooled soln of 0.280 ml (0.94 mmol) of titanium tetraisopropoxide and 0.230 ml (1.08 mmol) of (+)-diisopropyl tartrate in 7.0 ml of CH_2Cl_2 as above. Addition of excess anhyd t-butyl hydroperoxide in dichloroethane followed by workup after 15 min gave upon purification, 0.2039 g (80%) of **6e**, $[\alpha]_D^{27}$ −22.95° (*c*, 3.19, $CHCl_3$). IR (film) ν 3400, 2900, 2850, 1470, 1380, 1060 cm^{-1}. ^1H-NMR (90 MHz) δ 1.06–1.60 (env, ring CH_2), 1.70–2.33 (m), 2.5 (s, OH), 3.76 (ABq, J = 12.6 Hz, $\Delta\nu$ = 21.3 Hz, CH_2OH) ppm. (Found: C, 76.40; H, 12.14. Calc for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13%.)

Acknowledgements—Support for this work through a research grant from the National Science Foundation (CHE-8026013) is gratefully acknowledged. We are indebted to Dr A. R. Garber for his valued expert assistance with the ^{19}F-NMR analyses. A sample of cyclopentadecanone was generously provided by Dr Alan Hochstetler, Givaudan Corporation, Clifton, New Jersey, to whom we are most grateful. We thank Professor Still for access to a prototype version of "MacroModel".

REFERENCES

[1] For a recent review see M. Nakazaki, K. Yamamoto and K. Naemura, *Topics in Current Chemistry* (Edited by F. L. Boschke), pp. 1–25. Springer, Berlin (1984).

[2] A. T. Blomquist, L. H. Liu and J. C. Bohrer, *J. Am. Chem. Soc.* **74**, 3643 (1952).

[3] A. C. Cope, C. R. Genellin and H. W. Johnson Jr., *Ibid.* **84**, 3191 (1962); A. C. Cope, C. R. Genellin, H. W. Johnson Jr., T. V. Van Auken and H. J. S. Winkler, *Ibid.* **85**, 3276 (1963); A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang and H. J. S. Winkler, *Ibid.* **87**, 3644 (1965).

[4] G. Binsch and J. D. Roberts, *Ibid.* **87**, 5157 (1965).

[5] R. K. Hill, M. G. Fracheboud, S. Sawada, R. M. Carlson and S.-J. Yan, *Tetrahedron Lett.* 945 (1978); H. H. Westin, *Helv. Chim. Acta* **47**, 575 (1964).

[6] J. A. Marshall, T. R. Konicek and K. E. Flynn, *J. Am. Chem. Soc.* **102**, 3287 (1980).

[7] K. E. Flynn, Unpublished results.

[8] Cf. J. A. Marshall, *Accts Chem. Res.* **13**, 213 (1980).

[9] J. A. Marshall and K. E. Flynn, *J. Am. Chem. Soc.* **106**, 723 (1984).

[10] J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.* **34**, 2543 (1969).

[11] K. B. Sharpless and T. Katsuki, *J. Am. Chem. Soc.* **102**, 5974 (1980).

[12] J. A. Marshall and V. H. Audia, *J. Org. Chem.* **50**, 1607 (1985).

[13] W. C. Still and I. Galynker, *Tetrahedron* **37**, 3981 (1981); W. C. Still, *IUPAC, Current Trends in Organic Syntheses*, p. 233 (1983).

[14] J. B. Hendrickson, *J. Am. Chem. Soc.* **89**, 7036 (1967).

[15] N. L. Allinger and Y. H. Yuk, *QCPE* **13**, 395 (1981).

[16] N. L. Allinger, Personal communication. We are indebted to Professor Allinger for an enlightening discussion of this point.

[17] W. H. Pirkle and M. S. Hoekstra, *J. Org. Chem.* **39**, 3904 (1974); W. H. Pirkle and J. R. Hauske, *Ibid.* **42**, 2781 (1977); W. H. Pirkle, K. A. Simmons and C. W. Boeder, *Ibid.* **44**, 4891 (1979).