dium. Each sample was analyzed twice with HPLC with a maximum error of <1% in the determination of (area of **2**-OMe)/(area of R) and (area of 4)/(area of R) and a maximum error of <10% in the determination of (area of **3**)/(area of R) and (area of **6**)/(area of R).

The rate of disappearance of *h*-**2**-Cl was measured by withdrawing samples of the reaction solution and allowing the unreacted *h*-**2**-Cl to react with 25 vol % acetonitrile/water to form the corresponding allylic alcohols before carrying out the extraction procedure.[7] Analyses were made by HPLC. Plots of ln [(area of alcohols)/(area of R)] vs. time yielded the rate constant.

Measurement of Rearrangement Isotope Effect (k_{12}^H/k_{12}^D). To 100 mL of the buffered base solution was added 0.6 μL of 3-methylindene (R). The same stock solution of base was used in the reactions of both *h*-**1**-Cl and *d*-**1**-Cl. About 0.06 g of the substrate was weighed into a 25-mL flask sealed with a tight TFE septum, and the reaction was initiated by filling the flask with prethermostated base solution. Four samples were withdrawn after 10% reaction and quenched by the extraction procedure described above. Trichloroethane solution (230 μL) was transferred after the second centrifugation and diluted with 500 μL of ethanol. The samples were analyzed 3–8 times with HPLC and the peaks of R and 4 were then greatly enlarged, so that the areas could be integrated with a desk computer equipped with a digitizer.

The isotope effect of the formation of the ether, 4, is also the isotope effect on the rearrangement since the product compositions obtained from *h*-**2**-Cl and *d*-**2**-Cl were found to be constant and equal, within experimental error. In an initial-rate experiment, the concentration of **1**-Cl was approximated with the average concentration at time zero and the sampling time. Accordingly, the formation of 4 will be linear (eq 9). The

$$\frac{\Delta[4]}{\Delta t} \approx k_{14}([\mathbf{1}\text{-Cl}]_0 + [\mathbf{1}\text{-Cl}]_t)/2 \tag{9}$$

$$\frac{k_{12}^H}{k_{12}^D} = \frac{k_{14}^H}{k_{14}^D} = \frac{\left(\frac{\text{area of } (h\text{-}4)}{\text{area of R}}\right)}{\left(\frac{\text{area of } d\text{-}4}{\text{area of R}}\right)} \frac{\Delta t^D}{\Delta t^H} \frac{[d\text{-}\mathbf{1}\text{-Cl}]_0 + [d\text{-}\mathbf{1}\text{-Cl}]_t^D}{[h\text{-}\mathbf{1}\text{-Cl}]_0 + [h\text{-}\mathbf{1}\text{-Cl}]_t^H} \tag{10}$$

isotope effect was calculated by employing eq 10. The error in determining the area ratio of *h*-4 and R was estimated to $2\sigma = 3\%$ and the error in area ratio of *d*-**4** and R to $2\sigma = 10\%$. Evaluation of the error in the rearrangement isotope effect was based on the average of maximum errors from five experiments.

Isotopic-Exchange Experiments. The extent of incorporation of protium into *d*-**1**-Cl was determined by ^{1}H NMR analysis (100 MHz, CCl_4) of a sample from the reaction of *d*-**1**-Cl using the same concentration of substrate, base, and buffer as in the determination of the rearrangement isotope effect. The reaction solution (25 mL) was quenched after 52% reaction by shaking it vigorously with a mixture of 25 mL of 0.5 M aqueous sulfuric acid solution and 5 mL of carbon tetrachloride. The organic phase was washed with water until neutral and once with brine and then evaporated to 1 mL.

Registry No. *h*-**1**-Cl, 64909-94-0; *h*-**2**-Cl, 98800-46-5; deuterium, 7782-39-0.

The Octant Rule. 17. Front Octant Effects: Synthesis and Circular Dichroism of *syn*-(1′*R*)-Spiro[cyclobutan-2-one-1,2′-(4′(a)-methyladamantane)] and *syn*-(1′*S*)-Spiro[cyclobutan-2-one-1,7′-(2′-*exo*-methylnorbornane)][1]

David A. Lightner,* Tsung C. Chang, Daniel T. Hefelfinger, Dennis E. Jackman, W. M. Donald Wijekoon, and John W. Givens, III

Contribution from the Department of Chemistry, University of Nevada, Reno, Nevada 89557-0020. *Received April 19, 1985*

Abstract: Optically active (1*R*,3*S*)-4(*R*)(a)-methyladamantan-2-one (**3**) has been synthesized and converted to the isomeric *syn*- (**1**) and *anti*-(1′*R*)-spiro[cyclobutan-2-one-1,2′-(4′(a)-methyladamantane)] (**2**) by spiroannelation methods. Similarly, (1*S*,4*R*)-*exo*-2(*R*)-methylbicyclo[2.2.1]heptan-7-one (**15**) was converted to *syn*-(1′*S*)-spiro[cyclobutan-2-one-1,7′-(2′-*exo*-methylnorbornane)] (**14**). The ring skeletons of **1** and **14** are essentially symmetric, and all normal back octant (rule) perturbers cancel. The lone dissymmetric methyl group, however, lies in front of the carbonyl oxygen and is observed to control the sign and magnitude of the circular dichroism Cotton effect with a strong front octant contribution.

The octant rule[2,3] for the n → π* transition of saturated alkyl ketones was formulated over 25 years[4] ago and has since become one of the most important chirality rules for extracting stereochemical and conformational information from optically active ketones. The octant rule is derived from the local symmetry (C_{2v}) of the carbonyl group and a consideration of the relevant orbitals of the n → π* transition. The two well-defined carbonyl symmetry planes (*XZ* and *YZ*, Figure 1) divide all space about the C=O (C at origin) group into quadrants (hence a quadrant rule) and a third, ill-defined, non-symmetry-derived nodal surface further divides all space into octants (hence the octant rule). The shape of this third nodal surface was crudely *approximated* as a plane (A, Figure 1) bisecting the C=O bond, and recently it has become more accurately pictured on the basis of theory[3a] and experiment[3b] as a convex surface (B, Figure 1) cutting *behind* the carbonyl carbon and bending outward in the +*Z* direction. The octant occupied by a particular perturber determines the sign of its contribution to the rotatory strength of the n → π* transition. Reflection of the perturber across either of the *XZ* or *YZ* symmetry planes leads to a mirror image molecular fragment and hence one with an oppositely signed rotatory strength contribution. Since the third nodal surface does not follow from symmetry,

(1) For Part 16, see: Lightner, D. A.; Pak, C. S.; Crist, B. V.; Rodgers, S. L.; Givens, J. W., III *Tetrahedron*, in press.

(2) (a) Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013–4018. (b) The octant rule was given earlier in: Djerassi, C. "Optical Rotatory Dispersion"; McGraw-Hill: New York, 1961; Chapter 13. (c) For leading references, see: Deutsche, C. W.; Lightner, D. A.; Woody, R. W.; Moscowitz, A. *Annu. Rev. Phys. Chem.* **1966**, *20*, 407–448.

(3) (a) Bouman, T. D.; Lightner, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 3145–3154. (b) Lightner, D. A.; Crist, B. V.; Kalyanam, N.; May, L. M.; Jackman, D. E. *J. Org. Chem.* **1985**, *50*, 3867–3878.

(4) Moffitt, W.; Moscowitz, A. *Abstrs. Pap.–Am. Chem. Soc.* **1958**, *133rd*, abstract No. 1.

0002-7863/85/1507-7499$01.50/0

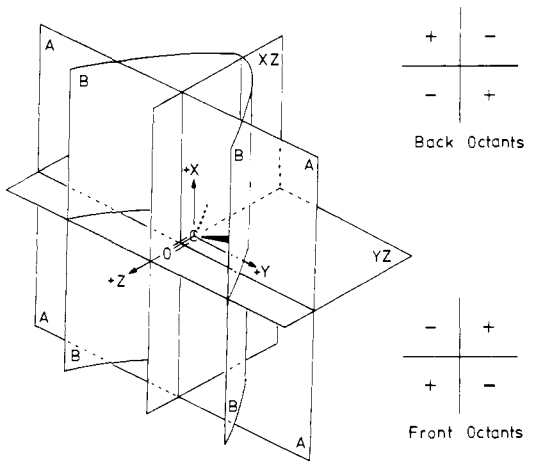

Figure 1. Octant rule diagram for the ketone carbonyl n → π* transition. As originally stated (ref 2), the two carbonyl symmetry planes (*XZ* and *YZ*) divide all space into quadrants, and a third nodal surface, approximated by a plane (A) orthogonal to *XZ* and *YZ* and bisecting the C=O bond, divides the quadrants into octants. The third nodal surface was subsequently determined to be better approximated by a convex surface (B), cutting behind the carbonyl carbon and bending outward in the +*Z* direction (ref 3). Atoms lying in the symmetry planes and nodal surfaces make zero contribution to the circular dichroism; atoms lying in octants make contributions to the Cotton effect whose signs are shown to the right of the octant figure, for back octants (behind B) and front octants (in front of B).

"reflection" across it does not correspond to a mirror image situation; consequently, the weight given to a particular perturber in a front octant is not the same as for a like position in a back octant. The signs, however, are expected to change with reflection across the third nodal surface, and the signs for atoms such as C, H, Cl, Br, and I are given in Figure 1.

Despite the obvious utility of the octant rule, only the back octants had been verified experimentally[2] until recently when the dissignate[5] perturbers of certain anti-octant compounds were found to be just in front of the third nodal surface (B, Figure 1), rather than behind it (A, Figure 1).[3,6] The experimental evidence on which the octant rule rests is largely and convincingly from numerous examples where the dissymmetric elements (the groups perturbing the carbonyl chromophore in a nonsymmetric way, e.g., the methyl group of 3(e)-methylcyclohexanone) are invaraible located behind the carbon of the carbonyl group (*back octants*), as viewed from oxygen toward carbon. There are extremely few examples in which dissymmetric perturbers are located in front of the carbonyl carbon or oxygen, and almost all the known rare compounds having such perturbers in front octants also have other perturbers nonsymmetrically located in back octants. The question of the existence of or need for front octants has not escaped attention, however, for it was quite obvious at an early stage in the development of the octant rule that some atoms would occasionally lie in front octants (e.g., in 1-oxo, 7-oxo-, and 11-oxosteroids), although the effects of atoms lying in back octants always appeared to dominate the sign of the Cotton effect.[2] Examples of contributors entering front octants have been discussed by Djerassi and Klyne,[7] but the cited examples also have back octant as well as front octant contributions and therefore did not clearly test the existence of front octants. More recently, the circular dichroism (CD) data from 7-oxosteroids and de-D-7-oxosteroids were analyzed by difference methods, and the authors concluded in favor of the existence of front octants.[8] At the same time, CD spectra of potentially cleaner examples, *cis*- and *trans*-6-methylspiro[4.4]nonan-1-ones, supported the notion of front octants, but the analysis was complicated by ring conformational changes.[9]

With the lack of unambiguous proof for the existence of front octants, the "octant" rule remained unproven, and a quadrant rule was discussed as an alternative chirality rule.[10] In the quadrant rule, the third nodal surface (A or B, Figure 1) is deleted, and the quadrants are signed the same as for back octants. Subsequently, Bouman and Moscowitz[11] showed, in a theoretical treatment using a limited basis set, that "quadrant" contributions were suppressed by assuming delocalized n orbitals and that the octant set gives larger contributions than the quadrant set. These authors favored an octant rule.

The seemingly unrelated problem of "anti-octant" effects emerged about this time. It focused on, but was not limited to,[12] the 3-axial position of chair cyclohexanone. In 1966, Pao and Santry[13] used a Gaussian orbital calculation to derive the octant rule for various methyl-substituted chair cyclohexanones. Their results agreed with the predictions of Moscowitz' original theoretical derivation of the octant rule[14] for *all* methyl configurations except 3-axial,[15] as did later calculations using an extended Hückel treatment.[16] At nearly the same time, Snatzke and co-workers[17] published the first experimental verification that the 3-axial position of chair cyclohexanone did not follow the classical octant rule.[2] In particular, (1*R*,3*S*)-4(*R*)(a)-methyladamantan-2-one (**3**) gave a weak, *positive* CD Cotton effect (CE) in ethanol or dioxane solvent,[17a] in opposition to the octant rule prediction: a *negative* CE for the methyl perturber in a lower left or upper right back octant (Figure 1). The significance of this surprising observation was clouded somewhat by the fact that a weak (−)-CE was observed for the same ketone in isooctane.[18] However, adamantanones with other β-axial perturbers, e.g., Cl, Br, I, N_3,[17a,b] and SCN, ONO_2, OAc, OCO_2CH_3,[17c] exhibited "anti-octant" CD CEs which did not change sign. Other apparent "anti-octant" effects have been reported,[3b,6,12] but in many of these examples, the controlling dissymmetric perturber(s) apparently lies just in front of the third nodal surface (B, Figure 1),[3] viz., in front octants and not back octants. A prime example of this is ketone **15**, which shows a moderately strong (+)-CE in both hydrocarbon and polar solvents.[3b,6]

In this work, we present unequivocal evidence for front octants, where the lone dissymmetric perturber lies in front of the carbonyl oxygen—and thus in front of the third nodal surface of both the revised[3] (B, Figure 1) and original[2] (A, Figure 1) octant rule. These conditions are satisfied by *syn*-(1′*R*)-spiro[cyclobutan-2-one-1,2′-(4′(a)-methyladamantane)] (**1**)[19] and *syn*-(1′*S*)-spiro-[cyclobutan-2-one-1,7′-(2′-*exo*-methylnorbornane)] (**14**),[20] whose preparations and properties are discussed in the following.

Results and Discussion

Synthesis, Stereochemistry, and ^{13}C NMR. The key synthetic intermediate in the preparation of spiroadamantyl ketones **1** and

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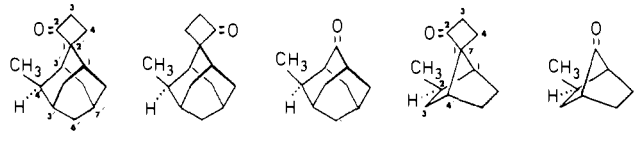
(9) Lightner, D. A.; Christiansen, G. D. *Tetrahedron Lett.* **1972**, 883–886.
(10) (a) Schellman, J. A. *J. Chem. Phys.* **1966**, *44*, 55–63. (b) Schellman, J. A. *Accounts Chem. Res.* **1968**, *1*, 144–151. (c) Wagnière, G. *J. Am. Chem. Soc.* **1966**, *88*, 3937–3940.
(11) Bouman, T. D.; Moscowitz, A. *J. Chem. Phys.* **1968**, *48*, 3115–3120.
(12) Coulombeau, C.; Rassat, A. *Bull. Soc. Chim. Fr.* **1971**, *71*, 516–526.
(13) Pao, Y. H.; Santry, D. P. *J. Am. Chem. Soc.* **1966**, *88*, 4157–4163.
(14) Moscowitz, A. *Adv. Chem. Phys.* **1962**, *4*, 67–112. See also ref 11.
(15) The 3-axial methyl configuration of chair cyclohexanone was not included in the original theoretical derivation of the octant rule: Moscowitz, A., personal communication. See also ref 14.
(16) Gould, R. R.; Hoffmann, R. *J. Am. Chem. Soc.* **1970**, *92*, 1813–1818.
(17) (a) Snatzke, G.; Eckhardt, G. *Tetrahedron* **1968**, *24*, 4543–4558. (b) Snatzke, G.; Ehrig, B.; Klein, *Tetrahedron* **1969**, *25*, 5601–5609 and references therein. (c) Snatzke, G.; Eckhardt, G. *Tetrahedron* **1970**, *26*, 1143–1155. (d) Snatzke, G.; Marquarding, D. *Chem. Ber.* **1967**, *100*, 1710–1724.
(18) However, ketone **3** has recently been shown to give moderately strong (+) CEs at low temperatures in methylcyclohexane–isopentane, 4:1, v/v, and ether–isopentane–ethanol, 5:5:2, v/v/v. Lightner, D. A.; Wijekoon, W. M. D. *J. Org. Chem.* **1982**, *47*, 306–310.
(19) Lightner, D. A.; Chang, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 3015–3016.
(20) Lightner, D. A.; Jackman, D. E. *J. Chem. Soc., Chem. Commun.* **1974**, 344–345.

2 was (1*R*,3*S*)-4(*R*)(a)-methyladamantan-2-one (**3**). To obtain



1 2 3 14 15

ketone **3**, we modified the previously published stereospecific synthesis[17b] beginning with the preparation (Scheme I) of Meerwein's ester,[21] an easily obtained bicyclo[3.3.1]nonane derivative which was recently shown to be in the completely enolized form.[22] Meerwein's ester was smoothly hydrolyzed and decarboxylated to yield bicyclo[3.3.1]nonan-2,6-dione, from which the functionalized racemic adamantane-2,8-dione-2-carboxylic acid (**4**) was prepared via reaction of the bis-enamine with methyl dibromoacetate. Resolution of **4** to ~100% enantiomeric excess (ee) of **4b** was achieved in three crystallizations of its cinchonidine salt. Stereoselective thioketalization of the less sterically hindered ketone group of the methyl ester (**5b**) gave **6b**, which was smoothly desulfurized with Ni(R) followed by oxidation to give **7**. Conversion of **7** to **3** involved protection of the ketone group as the dimethyl ketal followed by $LiAlH_4$ reduction of the carbomethoxy group and deketalization to give **8** and then conversion of the hydroxymethyl group (of **8**) to a bromomethyl group (**9**) using Br_2 + triphenylphosphine followed by Ni(R) reduction.

We attempted to determine the enantiomeric excess (ee) of ketone **3** and its precursors **8** and **9** by use of ^1H NMR spectroscopy and the chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III), $Eu(tfc)_3$. However, we could not separate the methyl doublets of racemic **3** or the hydroxymethyl and bromomethyl doublets of **8** and **9**. The ee of **3** was, nevertheless, determined in two ways, both involving the derived alcohol **10** produced stereospecifically by $LiAlH_4$ reduction. (1) Whereas the CH_3 signal of racemic alcohol (**10a** + **10b**) in the ^1H NMR spectrum moved and split into two signals (1.00:1.00 ratio) upon addition of the chiral shift reagent, $Eu(tfc)_3$, the alcohol (**10b**) derived from **3** exhibited only one CH_3 signal under the same conditions. (2) Mosher esters (from (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, (*R*)-(+)-MTPA)[23] of both racemic alcohol (**10a** + **10b**) and that (**10b**) derived from **3** were prepared and examined by ^1H NMR (for OCH_3) and ^{19}F NMR (for CF_3). In the ^1H NMR, the Mosher ester of racemic alcohol showed only one OCH_3 signal which moved and split into two lines of equal intensity upon addition of $Eu(fod)_3$. In the ^{19}F NMR spectrum, the diastereomeric CF_3 groups were split into two equal intensity lines (δ 35.12 and 34.92 relative to $CFCl_3$) without addition of shift reagent. The Mosher ester of **10b**, derived from **3**, showed only one line (corresponding to the more deshielded signal of the Mosher ester of racemic alcohol) in the ^{19}F NMR spectrum and one OCH_3 signal in the ^1H NMR spectrum upon addition of $Eu(fod)_3$. These data are in agreement with **3**, being optically pure (>99% ee).

The absolute configuration of **3** was determined by using the LIS-NMR method[23] on the Mosher ester of the alcohol (**10b**) derived from **3**. With the Mosher ester of racemic alcohol for reference, we found that the more *shielded* CF_3 resonance was faster moving upon addition of $Eu(fod)_3$—corresponding to the ester of **10a**. Since the more deshielded CF_3 signal corresponds to the (*R*)-(+)-MTPA ester of **10b**, the absolute configuration of **10b** and its precursor (**3**) is assigned the 1*R*,3*S* configuration. This LIS-NMR determination of absolute configuration is in full agreement with the absolute configuration assigned by circular dichroism.[17]

Before attempted transformation of **3** to **1** and **2**, we explored Trost's spiroannelation methods[25a] with the parent, adamantanone. Adamantanone was smoothly and essentially completely converted to the crystalline spirocyclobutanone **11** by reaction during 24 h with diphenylsulfonium cyclopropylide[25a] generated at room temperature in situ in Me_2SO by reaction of KOH with cyclopropyldiphenylsulfonium tetrafluoroborate,[25b] followed by acidic workup. The mechanism[25a] proceeds via acid-catalyzed rearrangement of the reactive oxaspiropentane intermediate **16**. Reaction at higher temperatures led to destruction of the desired product, **11**. Ketone **11** could also be prepared by an alternative two-step route involving (1) conversion of adamantanone to cyclopropylidene–adamantane (**12**) in high yield with triphenylphosphonium cyclopropylide and then (2) reaction of **12** with *m*-chloroperbenzoic acid. The unstable oxaspiropentane (**16**) formed in (2) rearranges under mild acid catalysis to **11**, in quantitative yield.

Spiroannelation of β(a)-methyladamantanone (**3**) presented an important stereochemical consideration because the product spirocyclobutanone can have its carbonyl group oriented syn (**1**) or anti (**2**) with respect to the β-axial methyl group. The methyl group should, in fact, be expected to control the product stereochemistry, depending upon the choice of spiroannelation method.[25c] In the direct spiroannelation procedure with diphenylsulfonium cyclopropylide, we expected predominant attack of the ylide on the least hindered face of **3**, i.e., opposite to that bearing the β-axial CH_3, to give first the unstable oxaspiropentane **17** (with oxygen syn to CH_3). Since the oxaspiropentane is expected to rearrange stereoselectivity with retention of oxygen and methyl relative stereochemistry,[25a] the major product of **17** is expected to be the *syn*-spiro ketone **1**. Less likely attack of sulfonium ylide on the *more* hindered carbonyl face should proceed via oxaspiropentane **18** (with oxygen anti to CH_3) to give mainly the *anti*-spiro ketone **2**. In the indirect spiroannelation reaction sequence, the cyclopropylidene derivative **17** is prepared, isolated, and treated with *m*-chloroperbenzoic acid. In the epoxidation step, attack of the oxygen-delivering peracid should be sterically hindered on one face of the C=C by the CH_3 group, leading to preferential formation of oxaspiropentane **18**, which has its oxygen anti to CH_3. Again, stereoselective oxaspiropentane rearrangement with retention of the oxygen and CH_3 relative stereochemistry[25a] should lead to the *anti*-spiro ketone **2** as the predominant product from **18**.

Reaction of **3** with diphenylsulfonium cyclopropylide during 5 days at room temperature afforded a 29% yield of spiroannelated product, along with unreacted starting ketone. Shorter reaction times led to poorer conversion, and longer reaction times, e.g., 35 days, led to greater conversion of **3** but also rearrangement of product to uncharacterized substances. Elevated reaction temperatures at short reaction times led to consumption of **3** and destruction of spiroannelated products. The reaction is apparently slowed (relative to adamantanone itself) by steric hindrance of the β-axial methyl group, which generally limits attack of the ylide to only one carbonyl face and introduces an incipient 1,3-diaxial methyl–oxygen interaction as attack of the ylide leads to rehybridization from sp^2 to sp^3 at the carbonyl carbon.[26] Insofar as we could determine, the product spirobutanone was homogeneous and was tentatively assigned structure **1**. This assignment was conclusively proved by reactions that converted **3** to both **1** and

(21) Meerwein, H.; Schürmann, W. *Liebigs Ann. Chem.* **1913**, *398*, 196–242.

(22) Radcliffe, M. D.; Gutierrez, A.; Blount, J. F.; Mislow, K. *J. Am. Chem. Soc.* **1984**, *106*, 682–687.

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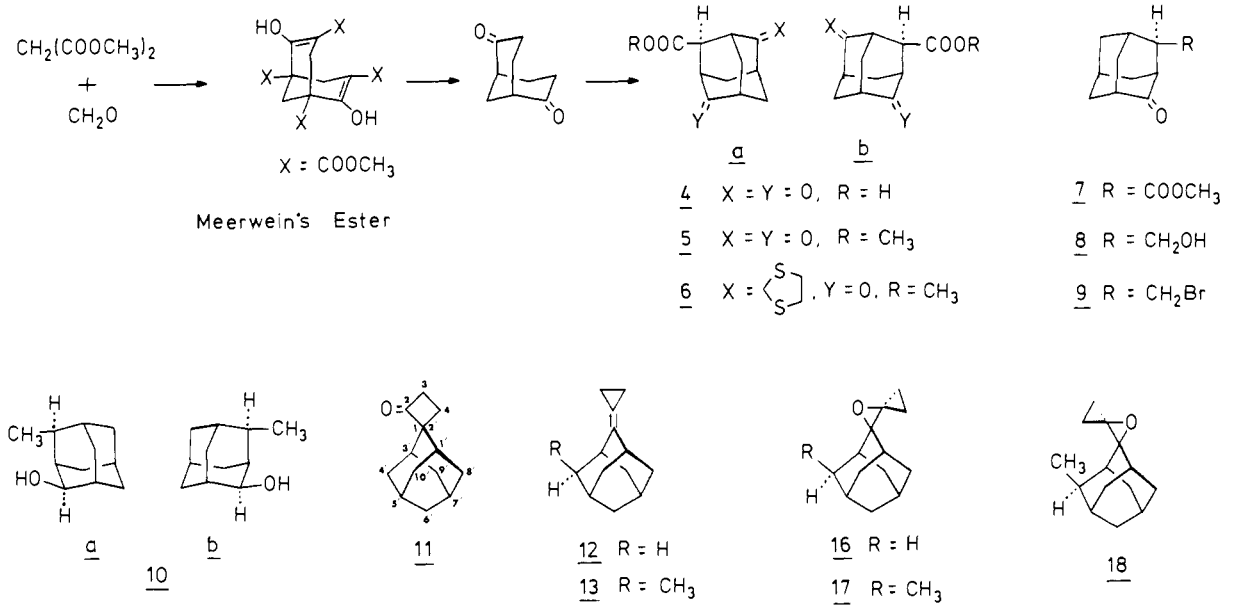
(24) Kalyanam, N.; Lightner, D. A. *Tetrahedron Lett.* **1979**, 415–418 and references therein.

(25) (a) Trost, B. M.; Bogdanowicz, M. A. *J. Am. Chem. Soc.* **1973**, *95*, 5321–5334. (b) Trost, B. M.; Bogdanowicz, M. A. *J. Am. Chem. Soc.* **1973**, *95*, 5298–5307. (c) Spiroannelation of the stereochemically related 14β-methyl-1,2,3,4,5,6-hexahydrophenanthren-4-one using diphenylsulfonium cyclopropylide gave a 93:7 ratio of syn/anti ketones using HBF_4 to catalyze the rearrangement of the isolated oxaspiropentane intermediate. The stereochemical assignments of the spiro ketones were made by LIS-NMR: the *syn*-CH_3 showed a greater downfield shift with added Eu(III) shift reagent than did the *anti*-CH_3 (ref 25a).

(26) For another example of steric hindrance in rehybridization, see: Lightner, D. A.; Wijekoon, W. M. D.; Crist, B. V. *Spectrosc.: An. Intl. J.* **1983**, *2*, 255–259.

Scheme I



2. Thus, reaction of **3** with triphenylphosphonium cyclopropylide gave the cyclopropylidene derivative **17**, which was treated with *m*-chloroperbenzoic acid to afford a high yield of spiroannelated product. This proved to be a 3:1 mixture of spirocyclobutanones, with the minor product corresponding in GC retention time to that of the single spirocyclobutanone obtained (above) from the reaction of **3** with diphenylsulfonium cyclopropylide. According to the expected reaction stereochemistry,[25a,c] the minor product is assigned the syn stereochemistry (**1**) and the major product the anti stereochemistry (**2**). These assignments were confirmed by ^{1}H NMR spectroscopy: the CH_3 doublet of the minor isomer was more deshielded[27] (δ 1.10) than that (δ 1.07) of the major isomer and also exhibited a larger LIS-NMR with Eu(dpm)$_3$.[25c] Consequently, we believe that reaction of **3** with diphenylsulfonium cyclopropylide gave only oxaspiropentane **17**, which rearranged stereospecifically to give only **1**. Epoxidation of **13**, however, probably gave predominantly **18**, but it is unclear whether **18** rearranges stereospecifically to **2**. In light of these findings, the stereospecific synthesis of **14** (the analogue of **1**) was accomplished via reaction of diphenylsulfonium cyclopropylide with ketone **15**[3b,6] (the analogue of **3**).

The ^{13}C NMR assignments for spiro ketones **1**, **2**, and **11** are given in Table I. The syn-CH_3 group of **1** shows no unusual effects due to the close promixity of the C=O oxygen. Both **1** and **2** show the expected γ-gauche effect[28] on C-10′ due to introduction of the axial CH_3 group as well as the deshielding of C-3′, C-4′, and C-5′. Adamantyl carbons farther removed expectedly show minimal changes. The carbons of cyclobutanone have been assigned previously:[29] C_1, 208.2; C_2, 47.8; C_3, 9.9 ppm downfield from $(CH_3)_4Si$ with the C_3 resonance showing unusually large shielding. The effect of spirofusing the adamantane ring to the α-carbon (C_1) shifts C_3 strongly downfield: δ for this carbon (C_4) in **11** is ~24. However, only a small deshielding effect on the carbonyl carbon can be seen.

Circular Dichroism and Molecular Geometry. The adamantane and norbornane skeletal systems are symmetric and are fairly rigid, with well-defined molecular geometry. Cyclobutanone is only moderately flexible. Microwave studies indicate a broad double minimum potential well for two (equivalent) slightly bent (4.6 ± 0.8° out of planarity) conformers in the gas phase with an interconversion barrier of only 0.02 kcal/mol through the planar conformation.[30] NMR measurements favor a planar cyclobutanone ring in a liquid crystal matrix.[31] And recent circular dichroism (CD) studies have shown that 2,2-dimethylcyclobutanone, which is a better model for the cyclobutanone of **1**, **2**, **11**, and **14**, exists in interconverting puckered (enantiomeric) conformations in solution.[32] Consequently, spiro ketone **11** may be viewed as having a time-average plane of symmetry passing through carbons 1(2′), 2, 3, 4, 5′, 6′, and 7′. Molecular mechanics (MM2)[33] computations on **11** give a total steric energy of the energy-minimized conformation (with a 3.2° puckered cyclobutanone ring, as determined by ϕ(1-4-3-2)) only 0.03 kcal/mol lower in energy than that of the conformation with a planar cyclobutanone. Further cyclobutanone puckering (to 6°) in **11** increases the total steric energy by only 0.01 kcal/mol above the energy-minimized geometry. Even larger amplitude puckering (13°) affords only small increases (0.2 kcal/mol) in total steric

Table I. Carbon-13 NMR Chemical Shift[a] Assignments for Spiro Ketones

carbon	11	1	2
1	71.32 (s)	70.21 (s)	70.45 (s)
2	214.89 (s)	213.02 (s)	215.07 (s)
3	40.79 (t)	42.28 (t)	42.60 (t)
4	24.23 (t)	25.52 (t)	25.81 (t)
1′	33.18 (d)	32.54 (d)	32.77 (d)
2′	71.32 (s)	70.21 (s)	70.45 (s)
3′	33.18 (d)	40.11 (d)	40.38 (d)
4′	33.59 (t)	38.72 (d)	39.97 (d)
5′	26.86 (d)	33.88 (d)	34.12 (d)
6′	37.10 (t)	38.42 (t)	38.68 (t)
7′	26.63 (d)	26.33 (d)	26.63 (d)
8′	33.47 (t)	34.69 (t)[b]	35.00 (t)[b]
9′	33.47 (t)	34.18 (t)[b]	34.67 (t)[b]
10′	33.59 (t)	27.57 (t)	27.86 (t)
CH_3		19.41 (q)	19.73 (q)

[a] Determined in $CDCl_3$ at 25.1 MHz and expressed in ppm downfield from Me_4Si. The multiplicities are given in parentheses. [b] These sets of values may be interchanged within the same column.

(27) The CH_3 group of **3**, however, lies in a *shielding* region of the C=O group and exhibits a CH_3 doublet at δ 0.95. The equatorial CH_3 epimer of **3** shows a CH_3 doublet at δ 1.07, but the axial CH_3 shows a greater LIS-NMR with Eu(dpm)$_3$.

(28) See, for example: Breitmaier, E. "^{13}C NMR Spectroscopy"; Verlag Chemie: New York, 1978; pp 74–75.

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Table II. Coordinates[a] of Methyl Carbons in Spiro Ketones **1**, **2**, and **14** and in Ketones **3** and **15** from MM2[b] Molecular Mechanics Calculations

ketone	torsion angle ϕ(1-4-3-2)	cyclobutanone conformation	methyl carbon coordinates, Å[a]			total steric energy, kcal/mol
			X	*Y*	*Z*	
1	−13°	puckered	−0.881 02	2.885 80	1.554 15	53.3335
	0°	planar	−1.694 50	2.487 92	1.468 72	53.0566
	+13°	puckered[c]	−2.573 88	1.898 92	0.789 34	52.5789
14	0°	planar	−1.565 81	2.870 75	1.368 97	58.1552
	+7°	puckered[c]	−2.080 74	2.572 71	1.070 74	57.9738
3			2.543 34	1.466 56	−0.904 71	
15			2.527 17	1.397 51	−1.249 20	
2	−10°	puckered	1.342 23	2.135 77	−3.843 80	52.2805
	0°	planar	1.564 17	2.398 83	−3.576 29	51.9542
	+10°	puckered[c]	1.693 93	2.587 93	−3.345 50	51.4523

[a] Uncertainty in the calculated values begins with the fourth significant figure. [b] MM2 calculations (ref 33) with carbonyl carbon at origin and oxygen in the +*Z* direction. [c] Energy-minimized structure.

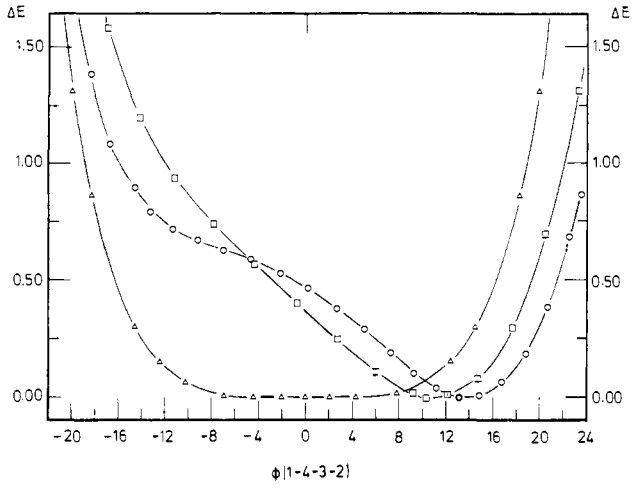

Figure 2. Increase in total steric energy (ΔE, vertical axis) vs. cyclobutanone ring puckering (ϕ(1-4-3-2), horizontal axis) as determined by MM2 molecular mechanics calculations for **11** (△), **1** (⊙), and **2** (⊡). The increase in total steric energy (ΔE, kcal/mol) is calculated as the energy increase above the energy of the energy-minimized structure for each ketone (see Table II).

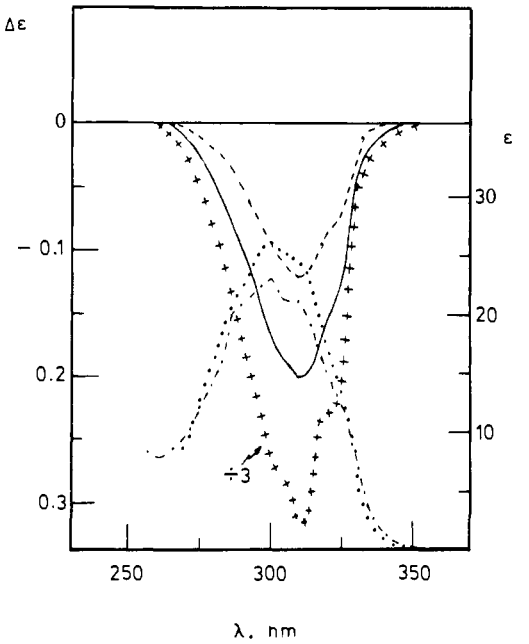

Figure 3. Circular dichroism (CD) spectra of 5 × 10^{-3} M *syn*-(1′*R*)-spiro[cyclobutan-2-one-1,2′-(4′(a)-methyladamantane)] (**1**) in MI (methylcyclohexane–isopentane, 4:1 (v/v) (- - -) and EPA (ether–isopentane–ethanol, 5:5:2, v/v/v) (—) and UV spectra in EPA (···) and MI (-·-·-) at 25 °C. CD (+) spectrum of 7 × 10^{-3} M *syn*-(1′*S*)-spiro-[cyclobutanone-1,7′-(2′-*exo*-methylnorbornane)] (**14**) in isopentane at 20 °C, corrected to 100% ee and scaled to one-third value.

energy. Taken collectively, the data indicate a very shallow double minimum potential energy well that tolerates moderately large amplitudes of cyclobutanone ring puckering in spiro ketone **11** (see Figure 2).

Introduction of a *syn*-methyl group at C-4′ of **11** (to give **1**) or an *anti*-methyl group at C-8′ of **11** (to give **2**), destroys the symmetry of the spiroappended adamantane and is expected to destabilize one of the two (enantiomeric) puckered cyclobutanone conformations (available in **11**). MM2 calculations on **1** indicate that one puckered conformation, that with the *syn*-CH_3 and cyclobutanone C=O farther apart (as represented by positive torsion angles, ϕ(1-4-3-2), Figure 2), possesses the energy-minimized stereochemistry. The energy well is fairly broad and rises shallowly as ϕ changes from +13° to −13° and steeply as ϕ assumes increasingly larger magnitudes. As ϕ changes from +13° to −13° the C=O and *syn*-CH_3 groups move closer together, with only modest increases in total steric energy at the planar cyclobutanone conformation [ϕ = 0°, $\Delta E \simeq$ 0.5 kcal/mol] and the ϕ = −13° puckered conformation ($\Delta E \simeq$ 0.8 kcal/mol). With increased ring puckering to move the *syn*-CH_3 farther away from the C=O, e.g., ϕ moving from +13° to +23°, the total steric energy rises steeply due to increased bending strain. A somewhat similar situation is obtained for **2**, where the 1,3-diaxial steric repulsion between the *anti*-CH_3 and the CH_2 at C_4 of the cyclobutanone ring becomes minimized in one of the cyclobutanone ring-puckered conformations—the one with ϕ(1-4-3-2) = +10°. As the cyclobutanone ring puckering is increased in the same direction, e.g., to ϕ = +23°, the total steric energy rises steeply. But as the cyclobutanone ring conformation moves through the planar form to the "enantiomeric" ring-puckered form, the energy increases only modestly: for ϕ = 0°, $\Delta E \simeq$ 0.3 kcal/mol; for ϕ = −10°, $\Delta E \simeq$ 0.8 kcal/mol (Figure 2).

The molecular geometries are of particular interest in assessing the relative importance of octant contributions from ring atom perturbers vs. the lone CH_3 perturber. In the planar cyclobutanone conformation, a symmetry plane passes through C-1(2′), -2, -3, -4, -5′, -6′, and -7′ of spiro ketones **1** and **2**, and through C-1(7′), -2, -3, and -4 of spiro ketone **14**. Consequently, in these conformations, ring atoms make no contributions to the ketone $n \rightarrow \pi^*$ circular dichroism (CD) Cotton effect (CE), whose sign and magnitude are determined in each case by the lone disymmetric CH_3 perturber. The CH_3 groups of **1** and **14** lie well in front of the carbonyl carbon and oxygen, whereas the CH_3 group of **2** lies far behind (Table II). Accordingly, if a quadrant chirality rule[10] obtains, the CH_3 perturbers of **1** and **14** should make a (+) contribution to the CE, and a net (+) $n \rightarrow \pi^*$ CD CE should be seen. On the other hand, if the octant rule[2,3] is obeyed, the CH_3 perturbers of **1** and **14** should make a (−) contribution to the CE and lead to net (−) $n \rightarrow \pi^*$ CD CEs. The CD spectra of **1** and **14** are shown in Figure 3, and their (−) $n \rightarrow \pi^*$ CEs[34] are in full

(34) As noted for (*R*)-2-methylcyclobutanone, the UV λ_{max} (293 nm) is normal (λ_{max} 22.1), whereas, the CD CE is markedly red-shifted, λ_{max} 306 nm, λ_{max} −0.2 (64% ee). See: van Leusen, D.; Rouwette, P. H. F. M.; Van Leusen, A. M. *J. Org. Chem.* **1981**, *46*, 5159–5163.

Table III. Reduced Rotatory Strengths[a] of Spiro Ketones **1** and **2**

ketone	solvent[b]	$[R]^{25}$	$[R]^{0}$	$[R]^{-50}$	$[R]^{-100}$	$[R]^{-150}$	$[R]^{-175}$
1	EPA	-0.6112	-0.6139	-0.5904	-0.5351	-0.5427	-0.5609
	MI	-0.3083	-0.3952	-0.3797	-0.3697	-0.4210	-0.4224
2	EPA	+0.1306	+0.2528	+0.4239	+0.6088	+0.7195	+0.8421
	MI	-0.0908	+0.1462	+0.4213	+0.6192	+0.7796	+1.0076

[a] Reduced rotatory strength $[R]^T$ = rotatory strength, R, 1.08×10^{40}. Superscripted numbers are temperature (°C). Data are corrected for solvent contraction and ee. [b] EPA is ether–isopentane–ethanol 5:5:2, v/v/v; MI is methylcyclohexane–isopentane 4:1, v/v.

accord with octant behavior; viz., the CH_3 perturbers make *strong front octant* contributions. The locations of the front octant CH_3 perturbers of **1** and **14** may be compared (Table II) with those of their precursor ketones **3** and **15**, respectively, which have their lone dissymmetric CH_3 perturbers lying behind the C=O carbon but just in front of the third nodal surface, B of Figure 1. Previously only weak and sometimes ambiguous front octant contributions had been observed for, e.g., (1*S*,3*R*)-4(*S*)(a)-methyladamantan-2-one (enantiomer of **3**) [$\Delta\epsilon_{306}^{max} = -0.046$ (EPA); $\Delta\epsilon_{313}^{max} = +0.025$ (MI)].[35] But the strong (-) CEs of **1** and **14** are in full accord with their CH_3 perturbers, lying unambiguously in front octants, i.e., in front of A and B of Figure 1 (Table II).

When the cyclobutanone ring assumes a puckered conformation, the CH_3 perturbers of **1** and **14** still lie in front of the C=O carbon or oxygen, and the CH_3 perturber of **2** still lies far behind the C=O group. Here, however, the adamantane and norbornane ring atoms do not all fall on nor are they symmetrically disposed about an extended local symmetry plane of the C=O group, and they would be expected to contribute to the n → π* CD CE. In **1** and **14**, a puckered cyclobutanone conformer, with the C=O moved slightly away from the *syn*-CH_3, is predicted by MM2 calculations to be favored by 0.2–0.5 kcal/mol over the planar conformation. Although these predictions do not take solvation effects into consideration, they suggest the importance of a conformation in which the adamantane and norbornane ring atoms make a weak (+) contribution to the CE. thus, in the energy-minimized conformer of **1** and **14**, with the cyclobutanone ring puckered to move the C=O away from the CH_3 group [**1**, ϕ(1-4-3-2) = +13°; **14**, ϕ(1-4-3-2) = +7°], adamantane and norbornane ring atoms 1′ assume a ψ-axial configuration on the cyclobutanone ring and are expected therefore to make a more positive octant contribution than the negative contribution of their counterpart ψ-equatorial atoms (3′ of **1** and 4′ of **14**).[33] However, even these (+) back octant contributions are dominated by the intense (-) contribution of the front octant CH_3 perturber, and the net CD CE is negative even at -175 °C (Table III).

In the *anti*-spiro ketone **2**, the situation is different. Its CH_3 perturber lies well to the rear in a back octant, and both the octant and quadrant rules predict it should make a (-) contribution to the n → π* CD CE. However, the CD spectra of **2** (Figure 4) are unusual in that the CE sign is found to be solvent dependent at 25 °C. The (-) CE observed in the hydrocarbon solvent is characteristic of back octant (consignate) behavior for the CH_3 perturber, but the (+) CE in the more polar solvent, EPA, is not. Upon lowering the temperature, the CD CEs are all (+), and the magnitudes increase (Table III). Although asymmetric solvation[35-37] may play a role in determining the CE sign at room temperature, we assume that a nonplanar cyclobutanone conformer becomes important—a conformation in which the inherently (-) back octant contribution of the CH_3 perturber is dominated by (+) contributions from the adamantane skeleton, especially from ring atoms lying close to the C=O group. In particular, as the cyclobutanone ring bends away from planar conformation, the α-carbons (1′ and 3′ of the adamantane) are no longer equidistant above and below the *YZ* octant symmetry plane and begin to take on more axial and equatorial-like positions, depending on which bent conformation is assumed.[33] In the MM2 energy-minimized

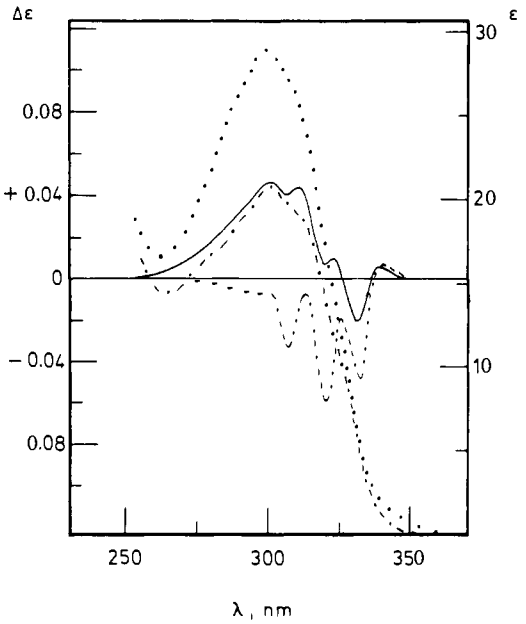

Figure 4. Circular dichroism (CD) spectra of 4×10^{-3} M *anti*-(1′*R*)-spiro[cyclobutan-2-one-1,2′-(4-(a)-methyladamantane)] (**2**) in MI (---) and EPA (—) and UV spectra in EPA (···) and MI (-·-·-) at 25 °C.

conformation, adamantanone carbon 1′ assumes a ψ-axial configuration on the cyclobutanone ring, and this conformation is expected to have a (+) CE. As the temperatures are lowered and more of the energy-minimum conformer becomes present, the net CE is increasingly dominated by contributions from this puckered cyclobutanone structure.

Conclusions

We have shown experimentally that an octant rule rather than a quadrant rule governs the behavior of certain saturated alkyl ketones, **1** and **14**, whose dissymmetric CH_3 perturbers lie well in front of the third nodal surface. The CD CEs of these substances are dominated by strong (-) front octant contributions of the CH_3 groups, as opposed to the (+) contributions produced by a quadrant rule. Although the locations of the CH_3 perturbers are not the same for **1** and **14** (Table II), the CD spectra are complementary and show that the front octant contributions found in this work are not associated with a unique and specific location of the CH_3 group but rather with the fact that these perturbers lie well in front of the octant rule third nodal surface.

Experimental Section

General. Circular dichroism (CD) spectra were recorded on a JASCO J-40 instrument equipped with a photoelastic modulator and a J-DPY data processor. Ultraviolet (UV) spectra were recorded on a Cary 219 spectrophotometer, and specific rotations were determined in chloroform, unless otherwise indicated, on a Perkin-Elmer 141 polarimeter. All nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$ and reported in δ (parts per million) downfield from tetramethylsilane unless otherwise indicated on a Perkin-Elmer R-24B, Varian A-60, Varian XL-100, or JEOL FX-100 instrument. Mass spectra (MS) were recorded at 70-, 20-, or 14-eV ionizing voltage on a JEOL JMS-07, AEI MS-9, or Varian MAT-311 mass spectrometer. Infrared (IR) spectra were measured on a Perkin-Elmer Model 599 or 457 instrument. All melting points are uncorrected and were determined on a Thomas-Hoover or Mel-Temp cappillary apparatus. Combustion analyses were performed by Micro-Analytical Lab, Mountain View, CA. Analytical gas chro-

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matography (GC) was carried out on a Varian-Aerograph Model 2400 F/1 instrument using a 6ft × $^1/_8$ in. diameter column with 12% QF-1 stationary phases absorbed on 80/100 Chromosorb W AW, DMCS. Preparative gas chromatography (GC) was achieved on a 6 ft × $^3/_8$ in. diameter column (12% of QF-1 on 60/80 Chromosorb W AW-DMCS) by using a Varian Aerograph Model 1720 T/C instrument.

Spectral data were obtained by using spectral grade solvents (MCB): isopentane, methylcyclohexane–isopentane, 4:1, v/v (MI), and ether–isopentane–ethanol, 5:5:2, v/v/v (EPA). Other solvents were distilled and dried before use: benzene, petroleum ether (30/60), hexane, chloroform, and dichloromethane all from P_2O_5; acetone from $KMnO_4$, and diethyl ether and tetrahydrofuran from $LiAlH_4$ under N_2. The solvents were used freshly distilled or stored under 4A molecular sieves (Linde). Dimethyl sulfoxide (Me_2SO) was distilled from CaH_2 and stored over 4A molecular seives (Linde). Column chromatography was accomplished on Florisil (Floridin Co.) or (0.05–0.20 mm) Merck silica gel. Analytical thin-layer chromatography (TLC) was carried out on a 125-μm layer of silica gel F (M. Woelm, Eschwege), preparative layer chromatography with a 1000-μm layer.

Synthesis of (+)-2-Carboxyadamantan-4,8-dione (4a + 4b). Dione acid 4 was prepared by procedure used earlier[17,21,38b] and is presented here as a large-scale synthesis with improvements.

(a) 1,3,5,7-Tetracarbomethoxybicyclo[3.3.1]nona-2,6-diene-2,6-diol (Meerwein's Ester). In a 3-L three-neck round-bottom flask equipped with a Dean-Stark water separator were added 528 g (4.00 mol) of dimethyl malonate (Aldrich), 96.0 g (3.20 mol) of paraformaldehyde (Eastman), piperidine (8 mL), and benzene (750 mL). This mixture was stirred at room temperature for 2 h and then brought to reflux (very gentle reflux at first so as not to distill the azeotrope during the first 8 h). After 8 h at reflux, the azeotrope was allowed to distill out of the pot into the Dean-Stark water separator. The azeotrope was removed at the end of 6–8 h (ca. 53 mL of water was removed). At this time, the refluxing was ended (the second azeotrope was ignored and not removed), and the solvent was removed on a rotary evaporator to give 625 g of an oil.

To a refluxing solution of 132 g (5.68 g-atoms) of sodium dissolved in 1600 mL of absolute methanol in a 3-L three-neck flask equipped with a mechanical stirrer, reflux condenser, and a drying tube there was added rapidly, in one portion, the combined oils (above) from two preparations, 1230 g. Only a small amount of heat was liberated. After stirring 7 h at reflux, the clear solution had become yellow, and a precipitate had formed. After the solution was stirred a total of 8 h, a distillation head was placed on the flask and methanol was distilled at reduced pressure, using a water aspirator, until the volume was reduced from one-half to one-third of the original volume. The reaction mixture, kept dry at all times with drying tubes, was then cooled in ice–water. Two liters of ice water was then added to dissolve the syrupy precipitate. The aqueous solution was extracted 2 times with 500 mL of ether. The ether layers were washed once with water, and all the aqueous layers were combined. Carbon dioxide was bubbled into the aqueous solution until the pH was 7–8. The precipitate which formed was filtered, washed well with water, and air-dried to give 390 g (51%) of Meerwein's ester. The melting point was usually about 161–163 °C but also varied between 153 and 164 °C [lit.[21] mp 163–164 °C (crystallized from methanol)].

(b) Bicyclo[3.3.1]nona-2,6-dione. Meerwein's ester (110 g, 0.724 mol) and 300 mL of glacial acetic acid were brought to reflux in a 1-L one-neck round-bottom flask equipped with a condenser and dropping funnel placed atop the condenser. There was added slowly over 12 h 200 mL of 6 N aqueous HCl, and the mixture was heated at reflux for 12 h. The water—hydrochloric acid—acetic acid mixture was removed by distillation under reduced pressure (using a plastic water aspirator). The semisolid pot residue was transferred to a smaller flask by using benzene as the transfer solvent and distilled at reduced pressure by using a vacuum pump. The solid diketone distills at 125–150 °C (1–4 mm) and melts at 139–147 °C. Recrystallization from ethanol (50 g of diketone dissolves in 70 mL of hot ethanol) gave a pure sample, 31.5 g (72%), mp 145–148.5 °C [lit.[21,38a] mp 138–140, 141 °C].

(c) (±)-2-Carbomethoxyadamantane-4,8-dione (5a + 5b). The bisenamine of bicyclo[3.3.1]nona-2,6-dione was formed in a 1-L one-neck round-bottom flask equipped with a Dean-Stark water separator by combining the following reagents: 40 g (0.263 mol) of dione, 60 g (0.845 mol, 70.5 mL) of pyrrolidine (Matheson, undistilled), 100 mg of *p*-toluenesulfonic acid, and 320 mL of reagent-grade benzene. This mixture was heated at reflux for 2–3 h during which time 10.2 mL of H_2O was removed (theoretical yield of H_2O is 9.46 g). At this time, the benzene and excess pyrrolidone were removed on a rotary evaporator by using a 70–80 °C hot-water bath. The flask was then evacuated at 1 mm for a few minutes with heating from a hot air gun to remove as much of the pyrrolidine as possible. Nitrogen was admitted to the flask, and 240 mL of chloroform (previously stored over 3A and 4A molecular sieves) was added.

The bis-enamine solution was kept under nitrogen, and a condenser and dropping funnel were attached to the flask using a 2-for-1 adapter. While still under nitrogen, the chloroform solution of the bis-enamine was brought to reflux, and a solution of 30.2 g (14.6 mL, 0.130 mol) of methyl dibromoacetate [K&K Laboratories] in 80 mL of chloroform was added over a period of 2 h. The nitrogen blanket and reflux were maintained throughout. The deep-red, almost black solution was heated at reflux for an additional 0.5 h after the addition was complete; then, the reaction mixture was allowed to stand at room temperature overnight. One hundred and sixty milliliters of 10% aqueous HCl were added, and the mixture was heated to reflux. Reflux was maintained for 45 min. The reaction was cooled, and the chloroform layer was separated. The aqueous layer was extracted with chloroform (3 × 50 mL), and the combined extracts were washed with water (3 × 100 mL), dried ($MgSO_4$), and concentrated on a rotary evaporator. The residue after chloroform removal was distilled under vacuum (0.2 mm) to give fraction 1 (12 g of liquid (25–100 °C plus solid (110–145 °C) and fraction 2 (solid 8.6 g, bp 145–170 °C). Fraction 1 yielded mostly dione by crystallization, although the ^1H NMR showed the mother liquors to contain some dione ester **5**. Fraction 2 yielded the desired dione ester (**5a + 5b**), 6.0 g, 10.3%, mp 124–125 °C, after recrystallization from 2-propanol with small amounts of added pentane or from ethanol [lit.[38b,c] mp 115–120, 120–121 °C].

(d) (±)-2-Carboxyadamantane-4,8-dione (4a + 4b). The preparation may be accomplished on either pure dione ester **5a** and **5b** or dione ester contaminated with dione from the previous step. The acid can be extracted into aqueous bicarbonate, and this aqueous solution can be extracted with dichloromethane, acidified with dilute aqueous hydrochloric acid, and dried by using a benzene–water azeotrope. The dione acid thus obtained can be further purified by crystallization from acetone or acetone–petroleum ether.

There were combined 16.5 g of a mixture of dione ester (**5a + 5b**) and dione [70% dione ester and 30% dione by ^1H NMR] and 75 mL of concentrated HCl. The mixture was heated at reflux for 9 h and distilled to dryness (at aspirator pressure, bp 35–50 °C) to give a beige solid. The dione acid product was dissolved in 5% aqueous $NaHCO_3$ from which dione and other impurities could be extracted into dichloromethane. The aqueous layer was then acidified with aqueous HCl, and the water was removed by adding benzene then distilling a benzene–water azeotrope. This procedure gave 11.7 g, 75% yield, of a beige solid, mp 228–331 °C lit.[17d] mp 222–224, 228–230 °C]. Thin-layer chromatography of the acid showed no dione (silica gel, 8:2 dichloromethane–ethyl acetate; R_f of acid, 0–0.1, R_f of dione, 0.38). The suggested recrystallization solvent, 1,4-dichlorobutane[17d] at 120–130 °C, offered no advantage. Acetone or acetone–petroleum ether was at least an equally good recrystallization solvent.

Resolution of 2-Carboxyadamantane-4,8-dione (4a + 4b). The cinchonidine salt of the dione acid was prepared by mixing 14.4 g (0.069 mol) of racemic **4** and 20.4 g (0.069 mol) of cinchonidine (Matheson) and heating in chloroform to effect dissolution. Evaporation of the chloroform gave a salt which was recrystallized 5 times from 2-butanone. Each successive recrystallization gave material with (1) $[\alpha]^{22}_{589}$ −96.7°, (2) $[\alpha]^{22}_{589}$ −101.6°, (3) $[\alpha]^{22}_{589}$ −103.5°, (4) $[\alpha]^{22}_{589}$ −103.6°, and (5) $[\alpha]^{22}_{589}$ −103.4°. The (−)-(1*S*)-dione acid **5b** was regenerated from its cinchonidine salt [fifth crystallization 4.15 g, $[\alpha]^{22}_{589}$ −103.4°] by stirring overnight with 38 g of Dowex 50W-X2[39] ion-exchange resin in 1 mL of water. The resin was removed by filtration, and the aqueous solution was extracted for 24 h with $CHCl_3$ by using a continuous extractor. The $CHCl_3$ layer was separated, dried ($MgSO_4$), and evaporated at reduced pressure to yield a grey-white solid: 1.68 g, 97.6% recovery, mp 234–238 °C [lit.[17a] mp 235–240°C], $[\alpha]^{22}_{589}$ −13.3° (*c* 0.97). This corresponds to >99% ee as determined from chiral shift reagent studies. The mother liquor from the fifth crystallization gave 0.7 g of (−)-(1*S*)-dione acid **4b**, $[\alpha]^{22}_{589}$ −12.8° (*c* 1.1).

(+)-(1*S*)-2-Carbomethoxyadamantan-4-one 8-Ethylene Dithioketal (6). To 1.38 g (6.64 mol) of (1)-(1*S*)-diketo acid **4b**, $[\alpha]^{22}_{589}$ −13.3° (*c* 1.0), 100% ee, was added 35 mL of glacial acetic acid, 0.46 mL (7.7 mmol) of ethanedithiol dissolved in 16 mL of acetic acid, and 3.5 mL of BF_3 etherate. After 6 h of stirring at room temperature, an additional 1.8 mL of BF_3 etherate was added, and the reaction mixture was stirred an additional 14 h at room temperature. The reaction mixture was then concentrated by distillation at reduced pressure (water aspirator) until

(38) (a) Stetter, H.; Held, H.; Schulte-Oestrich, A. *Chem. Ber.* **1962**, *95*, 1687–1691. (b) Stetter, H.; Held, H.; Mayer, J. *Liebigs Ann. Chem.* **1962**, *658*, 151–155. (c) Stetter, H.; Thomas, H. G. *Chem. Ber.* **1966**, *99*, 920–924.

(39) We thank Dow Chemical Co., Midland, MI, for a generous gift of Dowex 50W-X2.

about 7–9 mL of liquid remained in the flask. About 40 mL of CH_2Cl_2 was added, the solution was washed 3 times with water, and the combined CH_2Cl_2 extracts were dried ($MgSO_4$). After evaporation of the solvent, a solid mixture of mono and bis(ethylene dithioketals) was obtained, 1.63 g. The solid was dissolved in CH_2Cl_2–ether (the acid is only slightly soluble in ether) and esterified with excess diazomethane (about 0.5 g of CH_2N_2 was generated from 3.6 of Diazald (Aldrich) and 0.85 g of KOH). The yellow solution was allowed to stand overnight and gave an oil after removal of the solvent. The oily product was chromatographed on a silica gel column packed in CH_2Cl_2. Elution with 10% ethyl acetate in CH_2Cl_2 gave a satisfactory separation of **6** from the bis(thioketal) (crude yield 6%). The pure monothioketal **6** solidified on standing, mp 150–152 °C [lit.[17a] mp 150–151 °C], 72% yield. It was used directly in the next step.

(+)-(1*S*)-2(*R*)(a)-Carbomethoxyadamantan-4-one (7). Monothioketal **6** (2.41 g, 8.1 mmol, 100% ee) was dissolved in 300 mL of absolute ethanol, and 6 teaspoonsful of W-2 Ni(R)[40] were added. The solution was stirred mechanically for 11 h at room temperature, at which time the desulfurization was complete. After the black nickel powder had settled to the bottom of the flask, the clear ethanolic solution was decanted through a filter. The residual nickel was washed several times with absolute ethanol. The combined ethanolic fractions were evaporated to yield an oil. The oily product was dissolved in 35 mL of acetone and cooled to 5 °C in an ice bath. Cold Jones Reagent[41] (about 2 mL), was added until an orange–brown color remained, and the mixture was stirred for an additional 20 min at 5 °C. Aqueous $NaHSO_3$ was added until the mixture turned green; then, water was added to dissolve the salts. The mixture was extracted 3 or 4 times with ether, and the ether solution was dried ($MgSO_4$) and evaporated to give 1.02 g of an oil, which exhibited only one spot on TLC (20% ethyl acetate–CH_2Cl_2). It was used directly in the next step.

(+)-(1*R*,3*S*)-4(*R*)(a)-Hydroxymethyladamantan-2-one (8). Step 1. Ketalization. In a 50-mL round-bottom flask, a mixture of ethanolic (12.5 mL), 2,2-dimethoxypropane (ca. 2 mL), *p*-toluenesulfonic acid (30 mg), and the keto ester **7** (0.930 g, 4.61 mmol, 100% ee) was allowed to reflux overnight. After cooling, 12 mL of water containing 0.14 g of sodium carbonate were added to basify, and the mixture was extracted 5 times with dichloromethane. The combined dichloromethane extracts were dried ($MgSO_4$) and evaporated to give 1.14 g of an oily ketal: ^1H NMR δ 1.5–2.8 (13 H), 3.06 (s, 3 H, OCH_3), 3.18 (s, 3 H, OCH_3), and 3.68 (s, 3 H, $COOCH_3$).

Step 2. Reduction. The oily ketal obtained above (1.14 g, 4.49 mmol, 100% ee) was dissolved in 59 mL of anhydrous ether, and 0.53 g (13.9 mmol) of lithium aluminum hydride was carefully added. The mixture was stirred magnetically for 8 h and then an additional 0.52 g 91.37 mmol) of lithium aluminum hydride was added. The mixture was stirred overnight at room temperature. The reaction mixture was worked up by successive dropwise addition (with cooling) of 0.6 mL of water, 0.6 mL of 15% aqueous NaOH, and 1.6 mL of water. The resulting granular precipitate was filtered and washed thoroughly with ether. The combined filtrates were dried, and the ether was evaporated to yield hydroxymethyl ketal, an oil, 920 mg, 91% yield.

Step 3. Hydrolysis. The hydroxymethyl ketal (920 mg, 4.07 mmol, 100% ee) was dissolved in 20 mL of acetone, 10% aqueous HCl (20 mL) was added, and the mixture was heated at reflux for 2 h. On cooling, the mixture was neutralized with solid Na_2CO_3 and was extracted 4 times with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated to give 880 mg of an oil. The oil was chromatographed on 50 g of Florisil. The column was packed with 50:50 petroleum ether–CH_2Cl_2 and gradually changed to 100% CH_2Cl_2 and then to 96:4 CH_2Cl_2–ether eluent. The yield of the hydroxymethyl ketone **8** was 680 mg (3.87 mmol, 93%). The overall yield was 82% from (+)-(1*S*,3*R*)-2(*R*)(a)-carbomethoxyadamantan-4-one (**7**), and the material was used directly in the next step.

(+)-(1*R*,3*S*)-4(*R*)(a)-(Bromomethyl)adamantan-2-one (9). Under a nitrogen atmosphere, a solution of 2 mL (ca. 6.3 g, 39.1 mmol) of bromine in 45 mL of dimethylformamide was added dropwise into a solution of 9.7 g (37 mmol) of triphenylphosphine and 680 mg (3.77 mmol) of (1*R*,3*S*)-4(*R*)(a)-hydroxymethyladamantan-2-one (**8**) (100% ee) in 60 mL of dimethylformamide contained in a 200-mL round-bottom flask at room temperature. A yellow–orange color persisted at the end of the bromine addition. The mixture was then heated in an oil bath at 90 °C for 24 h. On cooling, it was poured into cold water to yield a flocculent precipitate. Solid Na_2CO_3 was added until the mixture was pH neutral, and it was then extracted 4 times with CH_2Cl_2 (ca. 250-mL total was used). Removal of the CH_2Cl_2 left 40–50 mL of a liquid which was mostly dimethylformamide. Water was added, and the aqueous solution was extracted several times with ether. A solid containing some triphenylphosphine oxide was obtained after removal of the ether. The solid was dissolved in benzene and chromatographed on a silica gel column (2.5 cm i.d. × 34 cm) packed in 70:30 CH_2Cl_2–petroleum ether. The eluent was gradually changed to 90:10 CH_2Cl_2–petroleum ether, and about 20 mL was collected for each fraction. The 4(a)-(bromomethyl)adamantan-2-one (**9**), 748 mg (82%), was collected in fractions 10–30 and identified by its ^1H NMR spectrum: δ 3.24 (2 H, d, J = 7 Hz, $-CH_2Br$). It was used directly in the next step.

(−)-(1*R*,3*S*)-4(*R*)(a)-Methyladamantan-2-one (3). W-4 Raney nickel[40] (15 g, freshly prepared) was added to a solution of (+)-(1*R*,3*S*)-4(*R*)(a)-(bromomethyl)adamantan-2-one (**9**) (0.736 mg, 3.03 mmol) in 100 mL of an ethanol–acetone mixture, and the heterogeneous mixture was heated at reflux for 10 h and maintained an additional 10 h at room temperature. TLC analysis showed only one spot corresponding to the desired product. The clear solution was decanted. The nickel catalyst was washed several times with acetone followed by decantation. The combined solutions were filtered and evaporated to give a solid which was treated with Jones reagent as in the earlier desulfurization reaction. The product was column-chromatographed on silica gel using 10% ether in CH_2Cl_2 to give 0.454 g (91%) of a white solid: $[\alpha]^{22}_{589}$ −20.5° (*c* 0.976), mp 187–189 °C [lit.[17b] mp 185–187 °C), TLC (10% ethyl acetate in CH_2Cl_2) showed only one spot, R_f = 0.62: IR (CCl_4) ν 1715 cm^{-1}; MS, *m/z* 164.1199 [$M^{+\cdot}$, $C_{11}H_{16}O$, 164.1201]; UV and CD.[35]

Determination of Enantiomeric Excess (ee) and Absolute Configuration of (−)-(1*R*,3*S*)-4(*R*)(a)-Methyladamantan-2-one (3). LIS-NMR techniques were used. Racemic 4(a)-methyladamantan-2-one, which had been prepared from racemic **4** exactly as **3** was prepared from **4a** (above) in a procedure that involved no crystallization steps (15 mg, 0.093 mol), was reduced stereospecifically with excess $LiAlH_4$ in ether at room temperature during 2 h to afford a nearly quantitative yield of the *syn*-4-(a)-methyladamantan-2(a)-ol (**10a** + **10b**). We could detect no epimeric alcohol impurity either by GC or by ^1H NMR. Addition of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III), Eu(tfc)$_3$ (Aldrich), to the alcohol in $CDCl_3$ shifted its *H*–C–O hydrogen downfield and resolved it into a 1.00:1.00 integrated ratio of *two* broadened singlets. Similarly, the CH_3 doublet resolved into two doublets. When the *syn*-alcohol **10b** from (−)-**3**, $[\alpha]^{22}_{589}$ −20.5° (*c* 0.976), again prepared with no intervening crystallization steps, was examined by LIS-NMR when using Eu(tfc)$_3$, only *one* *H*–C–O singlet (br) appeared. It integrated to >99% of the combined region where both diastereotopic *H*–C–O signals would have appeared. This alcohol, and hence its parent ketone, has >99% ee. Since no crystallization steps intervened between the ketone and its precursor (−)-(1*S*)-2-carboxyadamantan-4,8-dione (**4b**), we conclude that the dione with $[\alpha]^{22}_{589}$ −13.3° (*c* 0.97) is >99% enantionerically pure. This means that the acid resolved with cinchonidine to >99% ee in three crystallizations.

These conclusions were confirmed with the Mosher esters[23,24] of racemic and optically active *syn*-alcohols prepared above. The Mosher esters were prepared as before[24] by using the acid chloride of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-(+)-MTPA, Aldrich]. The ester of racemic alcohol **10a** + **10b**, in the presence of Eu(fod)$_3$ (Aldrich), gave two signals of equal intensity for the set of diastereomeric OCH_3 groups (^1H NMR δ 6.67 and 6.55). In the ^{19}F NMR, the CF_3 signal was split into two lines (δ 35.12 and 34.92 vs. $CFCl_3$ internal standard) of equal intensity without addition of Eu(fod)$_3$. The ester of the optically active alcohol **10b** gave only one signal at 6.67 ppm (^1H NMR, Eu(fod)$_3$) and one at 35.12 ppm (vs. $CFCl_3$, ^{19}F NMR). Integration over the range of both diastereomeric sets of signals indicated that the optically active ester had >99% ee, in agreement with the previous NMR results.

The absolute configuration of **10b**, and hence **3**, was assigned (1*R*,3*S*) as shown in the following. The more shielded signal of the set of diastereomeric CF_3 groups was faster moving upon addition of Eu(fod)$_3$. As explained earlier,[24] the faster moving signal corresponds to the CF_3 group of enantiomer **10a**. Since the more deshielded signal corresponds to the (*R*)-(+)-MTPA ester of the alcohol **10b** derived from **3**, **3** and its precursor **4b** and derivatives **1** and **2** have the absolute configuration assigned in Scheme I.

Spiro[cyclobutan-2-one-1,2′-adamantane] (11). (1) Sulfonium Ylide Method. Adamantan-2-one (305 mg, 2.03 mmol) (Aldrich) and cyclopropyldiphenylsulfonium tetrafluoroborate[25b] (785 mg, 2.50 mmol) were mixed with 17 mL of Me_2SO in a 50-mL round-bottom flask equipped with a condenser. Potassium hydroxide pellets (520 mg) were added, and the mixture (the pellets do not dissolve) was stirred at room temperature for 24 h. The solution was pipetted into a 60-mL separatory funnel containing a solution of 2 mL of 6 N HCl in 10 mL of water. Twenty

(40) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. I, pp 723–731.

(41) Eisenbraun, E. J. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. 5, pp 310–314.

milliliters of ether were used to wash the original reaction flask which still contained undissolved KOH pellets. The ether washing was added to the separatory funnel to extract the reaction product, and the layers were separated. Three 20-mL portions of ether were used to extract the aqueous layer, and the ether layers were combined. The combined ether fractions were washed twice with water and aqueous NaCl and dried ($MgSO_4$). The ether was evaporated at reduced pressure to yield a mixture of liquid and a solid. TLC showed that the product contained diphenylsulfide, spiro annelated product **11** and a small amount of unreacted adamantan-2-one. The product mixture was dissolved in benzene and separated on a silica gel column (15 cm i.d. × 18 cm). Benzene eluted diphenyl sulfide, and the spiroannelated product **11** was obtained, after removal of the solvent, as a white crystalline solid: 254 mg, 66% yield, mp 87–88 °C (after crystallization from methanol–water); UV (isooctane) $\epsilon_{298}^{max} = 27$; IR ($CCl_4$) ν 1766 cm^{-1}; ^1H NMR δ 1.58–2.30 (16 H), 2.94 (t, 2 H, J = 6 Hz, $-CH_2CO-$); MS, m/z 190.1306 [$M^{+\cdot}$, $C_{13}H_{18}O$, 190.1358].

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.91; H, 9.46.

In a typical small scale reaction, a solution of adamantan-2-one (51 mg, 0.34 mmol) and cyclopropyldiphenylsulfonium tetrafloroborate (136 mg, 0.43 mmol) in 5 mL of Me_2SO was stirred in a 25-mL round-bottom flask for 65 h at room temperature. The solution was then worked up as the manner described in the previous section. The product mixture was dissolved in a few drops of benzene and the components were separated with preparative TLC plates by using benzene. When viewed with the aid of iodine vapor, three bands were seen on the plates: band 1, R_f = 0.65, diphenylsulfide; band 2, R_f = 0.29, spiro ketone **11**; and band 3, R_f = 0.10, adamantan-2-one. Band 2 was scraped from the plates and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated to dryness. There was obtained a crystalline solid (slightly brownish), 62 mg (0.33 mmol, 96%).

A brief study was made on the effect of reaction temperature on the larger-scale spiroannelation of adamantan-2-one by running the reaction at room temperature, 65 and 100 °C for 24 h. The yields of the desired spiroannelated product were compared. It was found that instead of containing three components (as in the case of room temperature reaction), products of the higher temperature reactions, 65 and 100 °C, contained (at least) six components, with the major spiro annelated product decreasing with increasing reaction temperature. The yields of the product **11** at various reaction temperatures were room temperature, 82%, 65 °C, <86%, and 100 °C, <46%. In the latter two runs, the yields represent the sums of two inseparable products.

(2) Cyclopropylidene Method. 2-Cyclopropylideneadamantane (12). In a nitrogen-purged 100-mL two-neck round-bottom flask fitted with a mechanical stirrer was placed cyclopropyltriphenylphosphonium bromide (Aldrich) (4.40 g, 11.5 mmol) in 40 mL of THF (dried over molecular sieves); then, 6 mL of 1.6 M solution of phenyllithium (Alfa) in 70:30 v/v benzene–ether was injected into the suspension during a 10-min period by using a syringe. The mixture became red-brown as the salt dissolved gradually. It was stirred for 1 h and heated at reflux for 20 min. To the red-brown solution was added dropwise over a period of 15 min to a solution of adamantan-2-one (1.60 g, 11.3 mmol) in 8 mL of THF. The mixture turned somewhat cloudy after the addition, and after 10 min it was warmed to 50 °C and stirred for 48 h.

After the THF was evaporated at reduced pressure, a thick brown liquid was obtained. The liquid was dissolved in benzene and purified by silica gel column chromatography using benzene. The first four fractions were collected, and their purities were checked by TLC on silica gel using benzene. TLC showed that only the first fraction was pure 2-cyclopropylideneadamantane (R_f = 0.61). The fourth fraction (R_f = 0.44) did not contain the desired product (**12**) and was discarded. On standing, the first fraction crystallized as a white solid. The second and third fractions, which remained liquid (slightly yellow), were combined and again chromatographed on a silica gel column using hexane solvent. The first five fractions contained pure 2-cyclopropylideneadamantane (R_f = 0.56 in hexane), mp 58–59 °C. The combined yield of the pure product (**12**) was 1.70 g (82%): MS, m/z 174.1413 [$M^{+\cdot}$, calcd for $C_{13}H_{18}$, 174.1408]; ^1H NMR δ 0.98 (s, 4 H, cyclopropyl).

Anal. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.30; H, 10.61.

Epoxidation and Rearrangement of 2-Cyclopropylideneadamantane (12). Into a 100-mL three-neck round-bottom flask equipped with a condenser, thermometer, dropping funnel, and magnetic stirred was added a solution of *m*-chloroperbenzoic acid (85%, Aldrich) (520 mg, 2.55 mmol in 12 mL of $CHCl_3$. The solution was cooled to 10 °C, and a solution of cyclopropropylideneadamantane (**12**) (404 mg, 2.32 mmol) in 12 mL of $CHCl_3$ was added dropwise through the dropping funnel, while keeping the solution temperature at 6–10 °C. The solution was allowed to warm up to room temperature during 2 h, and stirring was continued for an additional 4 h. Although TLC showed a complete disappearance of the starting cyclopropylidene compound, the solution was allowed to stir overnight. No discoloration was observed throughout the reaction. The residual *m*-chloroperbenzoic acid was destroyed by shaking (twice) with 10% aqueous Na_2SO_3 solution. The $CHCl_3$ was then washed 3 times with 5% aqueous $NaHCO_3$, water, and saturated aqueous NaCl and finally dried ($MgSO_4$). TLC showed that the product was nearly pure spiroannelated adamantan-2-one (**11**) (R_f = 0.28) with a small amount of *m*-chlorobenzoic acid at low R_f value. Chromatographic separation gave 437 mg, 99% yield, of **11**.

(–)-*syn*-(1′*R*)-Spiro[cyclobutan-2-one-1,2′-(4′(a)-methyladamantane)] (1). (–)-(1*R*,3*S*)-4(*R*)(a)-Methyladamantan-2-one (**3**) (348 mg, 2.12 mmol, 100% ee), cyclopropyldiphenylsulfonium tetrafluoroborate[25b] (900 mg, 2.82 mmol), and powdered KOH (400 mg, 7.45 mmol) were added to 8 mL of purified, anhydrous Me_2SO in a 50-mL round-bottom flask equipped with a condenser. The condenser was stoppered, and the mixture was stirred at room temperature for 5 days. It was worked up with 10 mL of fluoroboric acid followed by ether extraction as described previously. TLC on silica gel using benzene showed three major spots corresponding to diphenyl sulfide (R_f = 0.66), the spiro ketone **1** (R_f = 0.34), and the unreacted starting (–)-4(a)-methyladamantan-2-one (R_f = 0.11). The products were separated by using eight silica gel preparative TLC plates (1.0 mm). Only the bands centered at R_f = 0.43 and 0.19 corresponding to the desired spiro ketone **1** and starting (–)-4(a)-methyladamantan-2-one were collected. The yield of the spiro ketone was 125 mg (29%). One hundred and ninety milligrams of unreacted (–)-(1*R*)-4(a)-methyladamantan-2-one was recovered. The desired spiro ketone **1**, oil, was >99% pure by analytical GC: $[\alpha]^{25}_{589}$ −16.61°, $[\alpha]^{25}_{578}$ −17.02°, $[\alpha]^{25}_{436}$ −31.38°, $[\alpha]^{25}_{365}$ −47.17° (*c* 0.40); UV (M1) $\epsilon_{299}^{max} = 22$; UV (EPA) $\epsilon_{300}^{max} = 26$; CD (isopentane) $\Delta\epsilon_{312}^{max} = -0.15$,[42] $\Delta\epsilon_{183}^{max} = +3.49$; CD (M1) $\Delta\epsilon_{265}$ 0, $\Delta\epsilon_{250} = -0.02$, $\Delta\epsilon_{310} = -0.12$, $\Delta\epsilon_{320} = -0.093$, $\Delta\epsilon_{338}$ = 0; CD (EPA) $\Delta\epsilon_{260} = 0$, $\Delta\epsilon_{307} = -0.193$, $\Delta\epsilon_{310} = -0.199$, $\Delta\epsilon_{340} = 0$ (CD runs at room temperature); IR (CCl_4) ν 1768 cm^{-1}; ^1H NMR, δ 1.10 (d, 3 H, J = 8 Hz, CH_3), (2.70–3.20 m, 2 H, $-CH_2CO$); MS, m/z 24.1515 [$M^{+\cdot}$, $C_{14}H_{20}O$, 204.1514].

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.96; H, 9.70.

***anti*-(1′*R*)-Spiro[cyclobutan-2-one-1,2′-(4′(a)-adamantane)] (2).**[19] The same procedure was used as that for the preparation of 2-cyclopropylideneadamantane (**12**). **(–)-(1*R*,3*S*)-4(*R*)(a)-Methyl-2-cycloproplideneadamantane (13).** The phosphorus ylide was generated from the reaction of a suspension of cyclopropyltriphenylphosphonium bromide (1.50 g, 2.93 mmol) in 15 mL of THF with 2.0 mL of a 1.6 M phenyllithium solution in 70:30 v/v benzene–ether. To this red-brown ylide solution was added dropwise a solution of (–)-4(a)-methyladamantan-2-one (**3**) (613 mg, 3.74 mmol, 100% ee) in 5 mL of THF, and the mixture was stirred at 55 °C for 2 days. The dark-brown, thick liquid which was obtained after evaporation of the THF, was dissolved in benzene, and was purified by column chromatography on silica gel using hexane. The yield of pure product **13** was 468 mg, (67%); ^1H NMR δ 0.85 (d, 3 H, CH_3) and 0.9–1.11 (m, 4 H, cyclopropyl); MS, m/z 188.1578 [M^+; $C_{14}H_{20}$, 188.1565]. It was used directly in the next step.

Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.20; H, 11.06.

Epoxidation of (1*R*,3*S*)-2-Cyclopropylidene-4(*R*)(a)-methyladamantane (13). A solution of *m*-chloroperbenzoic acid (85% pure, Aldrich) (372 mg, 2.15 mmol) in 12 mL of $CHCl_3$ was cooled to 10 °C (with ice water) in a 50-mL three-neck flask equipped with a condenser, a thermometer, dropping funnel, and a magnetic stirrer. (1*R*,3*S*)-2-Cyclopropylidene-4(*R*)(a)-methyladamantane (**13**) (369 mg, 1.96 mmol) from above in 12 mL of $CHCl_3$ was added dropwise from the funnel while controlling the mixture temperature at 10 °C. The mixture was then allowed to stir for 24 h at room temperature, after which time TLC showed complete disappearance of the starting material (**13**). Two 25-mL portions of 10% aqueous Na_2SO_3 solution were used to destroy the residual peracid. The layers were separated. The organic layer was washed 3 times with 5% aqueous $NaHCO_3$ solution, water, and saturated aqueous NaCl and dried ($MgSO_4$). After evaporation of the solvent, a white solid was obtained which exhibited one major spot on TLC (benzene eluent) at the same R_f as **1**. Small amounts of impurities with lower R_f values, including *m*-chlorobenzoic acid, accompanied the major spot. The spiro ketone was purified by silica gel column chromatography using hexane to give a white solid, after evaporation of the solvent, 365 mg, 91%. The spiro ketone, although it showed only one spot on TLC, was a mixture of the syn (**1**) and anti (**2**) isomers as judged from the ^1H NMR spectrum. Two methyl doublets, δ 1.10 (**1**) and 1.07 (**2**) (J = 8 Hz), were found in $CDCl_3$ solvent in the 100-MHz ^1H NMR spectrum. The ratio of the two spiro ketone isomers (**1**/**2**) was 26:74, as determined

(42) The CD data for **1** in ref 19 are scaled a factor of 10 too large.

by ^1H NMR or analytical GC. The melting point of the mixture showed softening at ca. 50 °C with complete melting at 110 °C. The anti isomer **2** was completely separated from the syn isomer **1** by slow and repeated fractional sublimation at atmospheric pressure at 55 °C or by preparative GC. Thus, the more volatile syn isomer **1** was removed by sublimation to leave the less volatile anti isomer **2** behind as a white solid, mp 118-121 °C (racemate mp 120-122 °C), after crystallization from methanol-water. Ketone **2** had the following: $[\alpha]^{25}_{589}$ 0°, $[\alpha]^{25}_{578}$ 0°, $[\alpha]^{25}_{436}$ +23.92°, $[\alpha]^{25}_{365}$ +55.55° (*c* 0.35); UV (MI) $\epsilon^{max}_{300} = 21$; UV (EPA $\epsilon^{max}_{299} = 29$; CD (isopentane) $\Delta\epsilon^{max}_{314} = -0.07$, $\epsilon^{max}_{188} = +3.4$; CD (MI) $\Delta\epsilon_{270} = 0$, $\Delta\epsilon_{306} = -0.034$, $\Delta\epsilon_{320} = -0.056$, $\Delta\epsilon_{332} = -0.046$, $\Delta\epsilon_{339} = 0$; CD (EPA) $\Delta\epsilon_{262} = 0$, $\Delta\epsilon_{302} = +0.045$, $\Delta\epsilon_{312} = +0.040$, $\Delta\epsilon_{324} = +0.007$, $\Delta\epsilon_{327} = 0$, $\Delta\epsilon_{332} = -0.023$, $\Delta\epsilon_{338} = 0$ (CD run at room temperature); IR (CCl_4) ν 1770 cm^{-1}; ^1H NMR δ 1.07 (d, 2 H, J = 8 Hz, CH_3) and 2.72-3.12 (m, 2 H, $-CH_2-CO$); MS, *m/z* 204.1515 [$M^{+\cdot}$; $C_{14}H_{20}O$, 204.1514].

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found C, 82.25; H, 9.78.

***syn*-(1′*S*)-Spiro[cyclobutan-2-one-1,7′-(2′-*exo*-methylnorbornane)] (14).**[20] A solution of diphenylcyclopropylsulfonium tetrafluoroborate[25b] (350 mg, 1.11 mmol), 3 KOH pellets (crushed), and 10 mL of dry Me_2SO were reacted with 124 mg of (1*S*,4*R*)-*exo*-2(*R*)-methylbicyclo-[2.2.1]heptan-7-one (**15**),[3b] $[\alpha]_D$ -11° (*c* 0.7), 42% ee, in a sealed tube for 3 days (with days 1 and 3 at room temperature and day 2 at 48 °C. The reaction was quenched by addition of excess dilute (1:1) hydrochloric acid, poured into 200 mL of cold water, and extracted with petroleum ether (3 × 30 mL). The organic extracts were washed several times with water, dried ($MgSO_4$), evaporated to about 5 mL, and passed through 15 g of neutral alumina (Activity II). The desired sweet smelling product eluted with petroleum ether, following elution of diphenyl sulfide, and the combined fractions gave 45 mg (26%) of a colorless oil. It contained about 15% of an impurity which was removed by repeated preparative GC. The colorless oily ketone **14** (>99% pure) had the following: UV (isopentane) $\epsilon^{max}_{306} = 29$; CD (isopentane) $\Delta\epsilon^{max}_{310} = 0.91$, $\Delta\epsilon^{max}_{190} = 1.17$ (corrected to 100% ee); IR (film) ν 1770, 1460, 1275, 1255, 1100, and 1065 cm^{-1}; ^1H NMR δ 1.04 (d, 3 H, J = 6 Hz, CH_3), 1.10-1.70 (m, 9 H), 1.83 (t, 2 H, J = 8 Hz, cyclobutanone CH_2), 2.80 (t, 2 H, J = 8 Hz, cyclobutanone $COCH_2-$); ^1H NMR (benzene-d_6) δ 1.22 (d, 3 H, J = 6 Hz, CH_3), 2.42 (t, 2 H, J = 8 Hz, $-CH_2CO$); MS, *m/z* 164.1206 [$M^{+\cdot}$, $C_{11}H_{16}O$, 164.1201]. Addition of Eu(thd)$_3$ to the $CDCl_3$ solution gave the following: ^1H NMR shifts δ 1.68 (d, 3 H, J = 6 Hz, CH_3), 3.50 (t, 2 H, J = 8 Hz, α-CH_2-), and 2.28 (t, 2 H, J = 8 Hz, β = CH_2-) with $\Delta\delta(CH_3) = 65$ Hz, $\Delta\delta(\alpha\text{-}CH_2) = 70$ Hz, and $\Delta\epsilon(\alpha\text{-}CH_2-) = 45$ Hz.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.59; H, 9.51.

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[3.3]Metacyclophane: A Novel Synthesis and a Study of the Structure through X-ray Diffraction, Molecular Mechanics, and Solution NMR Analysis

M. F. Semmelhack,*[†,‡] J. J. Harrison,*[†,⊥] D. C. Young,[⊥] A. Gutiérrez,[‡] Shahin Rafii,[†] and Jon Clardy[†]

Contribution from the Department of Chemistry, Cornell University, Ithaca, New York 14852, the Department of Chemistry, Princeton University, Princeton, New Jersey 08544, and the Gulf Research and Development Company, Pittsburgh, Pennsylvania 15116. *Received June 28, 1985*

Abstract: Coordination of 3-phenylpropionitrile with chromium hexacarbonyl followed by treatment of the resulting arene-chromium complex with lithium diisopropylamide and then iodine produced 1,12-dicyano[3.3]metacyclophane in a remarkable 84% yield. The process involves intermolecular nucleophilic addition to the coordinated arene, followed by cyclization of the dimer; iodine completes the addition/oxidation procedure for nucleophilic aromatic substitution for hydrogen. Reductive cleavage of the cyano groups produces the parent hydrocarbon, [3.3]metacyclophane. In the crystals, the molecule assumes a syn geometry with the bridging chains in a chair-chair conformation; however, the arene rings are tilted with respect to one another and slightly twisted. Molecular mechanics calculations find the same conformer as the energy minimum, with a similar tilt of the arene rings, but perfect C_{2v} symmetry (no twist). Two other conformations, syn(chair-boat) and syn(boat-boat), are within 1-2 kcal/mol of the lowest energy structure, while all conformers with the anti geometry are more than 6 kcal/mol higher. In solution, dynamic behavior is observed by variable-temperature ^1H NMR and ^{13}C NMR spectroscopy, attributed to interconversion of two syn conformers via a chair-boat motion of one of the three-carbon bridges. The barrier to isomerization is found to be 10-11 kcal/mol from both ^1H NMR and ^{13}C NMR data sets.

Considerable interest has existed in synthesizing and studying the properties of a class of compounds known as cyclophanes.[1] Of particular interest have been the [*m.n*]metacyclophanes because, in general, two different conformations, syn and anti, can exist (Figure 1). The terms synclinal and anticlinal have recently been used to describe the geometry for higher cyclophanes $n \geq 4$.[2]

In the parent [2.2]metacyclophane (**1**), the anti geometry is observed exclusively. The upfield shift of the aromatic proton H_i in **1** (δ 4.17) is a useful probe for the assignment of the anti geometry since H_i is constrained to lie directly over the π-electron cloud of the aromatic ring.[3] Syn geometries as typified by 2,11-dithia[3.3]metacyclophane (**2**) have H_i positioned downfield, in the usual range for arene hydrogens (e.g., δ 6.82 for **2**).[4] The NMR chemical shift criterion is useful for assigning geometries

[†] Cornell University.
[‡] Princeton University.
[⊥] Gulf Research and Development.

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