STEREOSELECTIVE SOLID-STATE NaBH₄ REDUCTION OF 1-METHYL-PENTACYCLO[5.4.0.0²,6.0³,10.0⁵,9]UNDECANE-8,11-DIONE, SYNTHESIS AND CHEMISTRY OF STRAINED ALKENES, AND CHEMICAL AND MICROBIAL SYNTHESIS OF RACEMIC AND OPTICALLY ACTIVE (S)-4-HYDROXY-2-CYCLOHEXENONE

Dissertation

Presented to the Graduate Council of the University of North Texas in Partial Fulfillment of the Requirements For the Degree of

Doctor of Philosophy

By

Dongxia Xing, B.S., M.S.
Denton, Texas
August, 1995
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DISSERTATION

Presented to the Graduate Council of the University of North Texas in Partial Fulfillment of the Requirements For the Degree of DOCTOR OF PHILOSOPHY

By

Dongxia Xing, B. S., M.S.
Denton, Texas
August, 1995
Xing, Dongxia, Stereoselective Solid-State Sodium Borohydride Reduction of 1-Methylpentacyclo[5.4.0.0^2.6-.0^3.10.0^5.9]undecane-8,11-dione, Synthesis and Chemistry of strained alkenes, and Chemical and Microbial Synthesis of Racemic and Optically Active (S)-4-Hydroxy-2-cyclohexenon.

Doctor of Philosophy (Chemistry), August, 1995, 224 pp., 5 tables, 88 illustrations, references, 102 titles.

Part I. Reduction of the 1-methylpentacyclo[5.4.0.0^2.6-.0^3.10.0^5.9]undecane-8,11-dione (9) with solid NaBH₄ resulted in highly stereoselective reduction of both C=O groups in the substrate, thereby affording the corresponding endo-8,endo-11-diol (11a). The configuration of 11a was established unequivocally by converting 11a into the corresponding cyclic thiocarbonate ester, 12.

Part II. Z-1,2-Di(1'-adamantyl)ethene (14) was synthesized with a high degree of stereoselectively in four steps (Scheme 9 in Chapter 2). E-1,2-di(1'-adamantyl)ethene (15) was synthesized by iodine promoted isomerization of 14. Both structures were established unequivocally via single-crystal X-ray structural analysis. E-1-(exo-8'-Pentacyclo[5.4.0.0^2.6.0^3.10.0^5.9]undecyl)-2-phenylethylene (16a) was synthesized, and its structure was established via analysis of its ^1H, ^13C, and 2D COSY NMR spectra.

Part III. Reactions of electrophiles, i.e., :CCl₂, PhSCL, and Br₂, to Z- and E-1,2-di(1'-adamantyl)ethenes (14
and 15, respectively) are described (Scheme 5, 8, 10, and 13 in Chapter 3). Structures of the corresponding products were established unequivocally via analysis of their respective one- and two-dimensional NMR spectra and/or single-crystal X-ray structural analysis.

Part IV. An improved asymmetric synthesis of optically active (S)-4-hydroxy-2-cyclohexenone 1 (64% ee, determined via Mosher's method) has been developed (Scheme 5 in Chapter 4). The key step in this synthesis involves the baker's yeast reduction of 13. The absolute configuration of the major product, (S)-1, was established unequivocally via single-crystal X-ray structural analysis of a precursor. The optical purity of the major product 14a (80% de, 67% ee) was established via careful integration of relevant gated-decoupled $^{13}$C NMR spectra.
I thank my major professor, Dr. Alan P. Marchand, who introduced me into these interesting fields and advised me throughout my research. My thanks also go to Dr. Simon G. Bott and Dr. K. Venkatesan for providing single-crystal X-ray structures of my compounds. The calculation of vicinal coupling constants of Z- and E-alkenes, 14 and 15, and the corresponding figures done by Dr. Michael Barfield are highly appreciated. Finally, I would like to thank the members of Dr. Alan P. Marchand’s group for help and discussion.
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## Chapter

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CHAPTER I

STEREOSELECTIVE SOLID-STATE NaBH₄ REDUCTION of 1-METHYL-PENTACYCLO[5.4.0.0²,6.0³,10.0⁵,9]UNDECANE-8,11-DIONE

Introduction

Organic solid-state chemistry is a field which lies at the crossroads of solid-state science, organic chemistry, and X-ray crystallography. In general, it is concerned with the ways in which organic molecules pack in crystals. Since molecules are arranged tightly and regularly in crystals, any chemical reaction of a crystalline material in the solid state is expected to proceed efficiently and with a high degree of regio- and/or stereoselectivity.

A variety of reactions occur in the solid state, e.g., decomposition, oxidation and dehydration of solids are typical reactions which have been investigated in detail. Applications of solid-state reactions in organic synthesis have received increasing attention in recent years. Some ordinary organic reactions, e.g., oxidative coupling reactions and pinacol rearrangements, which proceed with only modest stereoselectivity in solution, have been reported to proceed efficiently and with high stereoselectivity when performed in the solid state.

Toda and co-workers have performed extensive studies of
several solid state organic reactions. An example in this regard is their study of oxidative coupling reactions of phenols. These reactions were carried out in the solid state using FeCl₃ as the oxidant. Such reactions, when performed in solution, usually require a molar excess of oxidant. Interestingly, the Toda group⁴ found that some coupling reactions of phenols with FeCl₃ proceed much more rapidly and efficiently in the solid state than do those in solution. Thus, a mixture of finely powered 2-hydroxynaphthalene (1) and FeCl₃·6H₂O reacts to form the corresponding dimer (2) in 95% yield (Scheme 1).

Scheme 1

Pinacol rearrangements are often performed in solution under extreme experimental conditions (e.g., in concentrated acid solution at relatively high temperature). However, the pinacol rearrangement has been reported to occur smoothly when an intimate mixture of solid pinacol 3 and solid p-
toluenesulfonic acid is heated at 60 °C for 40 minutes; the corresponding pinacolone, 4a, is obtained stereospecifically in 89% yield (Scheme 2). It should be noted that instead of phenyl anion migration, only the hydride migrates in this reaction. In solution, however, the corresponding reaction gave a mixture of two isomers (ratio 4a:4b = 4:1).5

Scheme 2

Recently, two groups6,7 have reported examples of solid-state NaBH4 reductions of ketone C=O groups, all of which afforded the corresponding alcohols with a high degree of regio- and stereoselectivity. Thus, Toda and co-workers6 have reported that treatment of a solid 1:1 inclusion complex
composed of \((-\)-5 and \((-\)-6 with solid NaBH$_4$ for 3 days afforded \((-\)-7 (100% ee, 54% yield; Scheme 3). These investigators suggested that the observed selective reduction of the nonconjugated carbonyl group in \((-\)-5 results from the fact that the enone moiety becomes "masked" via specific hydrogen bonding with the hydroxyl group of \((-\)-6 in the inclusion complex (see mode a).

Marchand and Reddy$^7$ have reported that solid-state NaBH$_4$ reductions of pentacyclo[5.4.0.0$^{2,6}.0^{3,10}.0^{5,9}$]undecane-8,11-diones, 8a and 8b, afford the corresponding alcohols with a
high degree of stereoselectivity. In each case, the solid-state reduction proceeds via exclusive attack of the exo face of the C=O group in the substrate. In contrast, the corresponding homogeneous (solution phase) reductions display only moderate stereoselectivity (Scheme 4).

Scheme 4

![Scheme 4 Diagram]

We now report the results obtained from a study of the solid-state NaBH₄ reduction of 1-methylpentacyclo[5.4.0.0²,⁶.0³,¹⁰.0⁵,⁹]undecane-8,11-dione (9).

Results and Discussion

Synthesis of 1-Methylpentacyclo[5.4.0.0²,⁶.0³,¹⁰-
undecane-8,11-dione (9). The substrate, 9, was synthesized in two steps by using the method shown in Scheme 5. Diels-Alder cycloaddition of freshly cracked monomeric cyclopentadiene to toluquinone afforded the corresponding endo [4 + 2] cycloadduct, 10. Subsequent intramolecular [2 + 2] photocyclization of 10 produced 9 in good overall yield.

**Scheme 5**

 Sodium Borohydride Reduction of 1-Methylpentacyclo[5.4.0.0²,6.0³,10.0⁵,9]undecane-8,11-dione (9). In agreement with the results obtained by Marchand and Reddy, it was found that the solid-state NaBH₄ reduction of 9 is more highly stereoselective than is the corresponding reaction when performed in solution. Theoretically, four possible isomeric diols could be formed in the reduction of 9 (Scheme 6). Thus, an intimate mixture of finely powdered 9 and NaBH₄ under argon was agitated mechanically at room temperature for 7 days. Workup of the reaction mixture
afforded the corresponding endo,endo-diol, **11a**, high stereoselectively (Scheme 7, product ratio **11a** : other isomers)
= 9:1, which was determined via analysis of the $^1$H NMR spectrum). The corresponding reaction when performed in solution (EtOH solvent) afforded a mixture of isomers. The ratio was endo,endo-diol:other isomers = 3:1, which was determined via analysis of the $^1$H NMR spectrum.

The infrared (FT-IR) spectra of the starting diketone (9) and the product diol (11a) are shown in Figures 1-1 and 1-2, respectively. The IR spectrum of 9 displays two very intense absorptions at 1750 and 1728 cm$^{-1}$ (C=O stretching vibrations). These peaks are absent in the corresponding IR spectrum of 11a, but a new absorption peak is evident at 3200 cm$^{-1}$ (due to the O-H stretching vibrations in the product diol). The corresponding $^1$H and $^{13}$C NMR spectra of 9 and 11a are shown in Figures 1-3 to 1-6. Analysis of these spectra confirms the fact that solid-state NaBH$_4$ reduction of 9 affords the endo,endo-diol with a high degree of stereoselectivity. Thus, the $^{13}$C NMR spectrum of the product (11a) contains ten aliphatic carbons in the region $\delta$ 21.87-46.27. In addition, there are two lowfield absorptions at $\delta$ 72.51 and 75.64 (due to the two nonequivalent CHOH carbon atoms in the product diol). The lowfield absorptions due to the C=O carbon atoms in 9 are absent in the $^{13}$C NMR spectrum of 11a (see Figure 1-4), thereby confirming that the desired reduction has indeed occurred.

Determination of the Stereochemistry of the Two C-OH Bonds in the Reduction Product (11). It should be
noted that reduction of the two C=O groups in 9 could give rise to any of four possible isomeric diols: endo,endo-diol (11a), endo,exo-diol (11b), exo,endo-diol (11c), and/or exo,exo-diol (11d) (see Scheme 6). Analysis of the $^1$H and $^{13}$C NMR spectra (Figures 1-7 and 1-8, respectively) of the product suggests that endo,endo-diol is formed via stereoselective solid-state NaBH$_4$ reduction of 9.

The identity of the reduction product was established by converting this material into the corresponding cyclic thiocarbonate ester, 12 (Scheme 8). Of the four possible cage diols which might result via reduction of 9, only 11a contains C-OH bonds in a configuration which is appropriate for conversion into a cyclic thiocarbonate ester derivative.$^{10}$ Thus, the successful conversion of the reduction product into 12 in 80% yield via its reaction with 1,1'-thiocarbonyl-diimidazole (Scheme 8) unequivocally establishes the endo, endo-diol configuration of the C-OH bonds in the reduction

Scheme 8

\[
\begin{array}{c}
\text{11a} \\
toluene, reflux under argon 2 h \rightarrow \\
\text{12 (80%)}
\end{array}
\]
product.

Compound 12 was further characterized via analysis of its $^1$H and $^{13}$C NMR spectra which are shown in Figures 1-7 and 1-8, respectively. Thus, the $^{13}$C NMR spectrum of 12 (Figure 1-8) displays ten resonances in the aliphatic region ($\delta$ 20.71-46.06) along with two downfield peaks at $\delta$ 75.65 and 88.32, which correspond to the two nonequivalent C=O carbon atoms. In addition, this spectrum contains a lowfield resonance at $\delta$ 192.8, which is assigned to the C=S carbon atom in 12. The $^1$H NMR spectrum of 12 (Figure 1-7) displays a clear triplet at $\delta$ 4.5, which can be assigned to proton H-8 (coupled both to H-7 and to H-9, Scheme 9). In addition, this spectrum contains a doublet at $\delta$ 4.1, due to H-11 (coupled only to H-10).

Scheme 9

![Diagram of Compound 12]

The fact that the solid-state NaBH$_4$ reduction of 9...
affords the corresponding endo,endo-diol (11a) attests to the strong preference for hydride transfer from the reducing agent to the exo face of each carbonyl group in the substrate under these conditions. The reason for the observed stereoselectivity may be due in part to the nature of the crystal packing in solid 9 and also the rigid structure of this substrate.

A structure drawing and crystal packing diagram for solid 9 are shown in Figures 1-9 and 1-10, respectively. The asymmetric unit contains four molecules that are packed together regularly, with individual molecules in the unit cell mutually separated by a network of channels. Reduction of the carbonyl functionalities in 9 is likely to occur in the crystal lattice when solid NaBH₄ passes through these channels and encounters the exo face of each of the C=O groups. Due to the nature of crystal packing in 9, it seems likely that the nonbonded intramolecular distance between the two carbonyl oxygen atoms in 9 is smaller than the intermolecular distance in the crystal lattice. Thus, NaBH₄ is transported through the channels between neighboring substrate molecules, thereby increasing the likelihood of reaction at the exo face of each C=O group in 9.

In solution, the endo face of each C=O group in 9, although certainly less open to attack by NaBH₄ than the corresponding exo face, nevertheless is somewhat accessible.
The ratio of the endo,endo-diol to the other three isomers is 3:1. In this way, the increased level of stereoselectivity which is observed for the solid-state reduction vis-à-vis the corresponding process in solution can be rationalized.

In order for reduction to occur, diffusion of either the substrate (9) into the NaBH₄ lattice or the reverse process must occur. Since NaBH₄ is a nonvolatile inorganic salt and is stable in dry air, diffusion of the dione into NaBH₄ is the more likely of these two diffusion processes. In order to examine the role of solid-solid diffusion in this reaction, finely powdered dione 9 was mixed with finely powdered NaBH₄ under argon at room temperature, and the resulting intimate mixture was allowed to stand undisturbed (i.e., without agitation) for 50 days. The IR spectrum of the reaction mixture revealed that some reduction had occurred, but a considerable amount of 9 remained unreacted after 50 days.

In a separate control experiment, finely powdered solid 9 and solid NaBH₄ were placed in a flask under argon in such a manner that the two solids did not come into mutual contact. After standing in this manner for 50 days, the IR spectrum of each material was obtained. IR spectral analysis revealed that no change had occurred in either material. We therefore conclude that the observed reduction is indeed a solid-solid reaction phenomenon and that the primary reaction site occurs at or very near the surface of both solid
reactants. Thus, effective agitation during the reaction is required to assure continuous renewal of fresh reacting surfaces. The manner in which the crystal lattice in 9 is broken during the reduction process and the exact orientation of the reactive C=O groups in the substrate molecule at the surface of the crystal is likely to dramatically affect the stereochemistry and rate of the solid-state reduction process.

The rate of the solid-state reduction is slow at ambient temperature. It seems likely that the reaction rate depends not only upon the inherent rate of the reduction process itself but also upon the rate of transport of the reducing agent in the solid phase to the reaction site in the substrate.\(^{14}\)

Chemical reactions which occur entirely within the solid state are less commonly observed than the corresponding reactions when performed in the vapor and/or liquid phase. This situation probably reflects limitations imposed by rate-determining material transport phenomena in the solid state.

Summary and Conclusions

The foregoing analysis leads to the conclusion that the solid-state NaBH\(_4\) reduction of 9 affords the corresponding endo,endo-diol (11a). The high degree of stereoselectivity which is observed for this reaction attests to the strong preference for hydride transfer from the reducing agent to
the exo face of each carbonyl group in the substrate under
the reaction conditions employed. The reason for the
observed stereoselectivity may be due in part to the nature
of crystal packing in solid 9 and also the rigid structure of
this substrate.

Experimental Section

Melting points are uncorrected.

6-Methyl-1α, 4α, 4αα, 5α, 8β, 8αα-hexahydro-1, 4-
methanonaphthalene-5, 8-dione (10). To a solution of 2-
methyl-p-benzoquinone ("toluquinone", 20 g, 0.16 mol) in MeOH
(40 mL) at 0 °C was added a solution of freshly cracked
cyclopentadiene (11 g, 0.166 mmol). The resulting mixture
was stirred magnetically at 0 °C until the stirring bar
became immobilized, at which time the cold bath was removed,
and the reaction mixture was allowed to warm gradually to
room temperature overnight. The reaction mixture then was
filtered, and the residue was recrystallized from hexane.

Pure 10 (27.71 g, 92%) was thereby obtained as a bright
yellow microcrystalline solid: mp 59.9-60.2 °C (lit.8 mp 61-
63 °C); IR (KBr) 2993 (m), 2965 (m), 2930 (m), 2866 (w), 1654
(s), 1625 (s), 1443 (m), 1323 (m), 1272 (m), 1225 (m), 1168
(m), 1119 (m), 1055 cm\(^{-1}\) (m); \(^1\)H NMR (CDC\(_3\)) \(\delta\) 1.41 (AB, \(J_{AB} =
8.70\) Hz, 1 H), 1.52 (AB, \(J_{AB} = 8.60\) Hz, 1 H), 1.90 (d, \(J =
1.42\) Hz, 3 H), 3.18 (d, \(J = 0.90\) Hz, 1 H), 3.19 (d, \(J = 0.40\)
Hz, 1 H), 3.49-3.60 (m, 2 H), 5.97-6.06 (m, 2 H), 6.45 (q, \(J\)
= 1.42 Hz, 1 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 16.28 (q), 48.20 (d), 48.57 (d), 48.80 (t), 48.88 (d), 49.03 (d), 134.8 (d), 135.4 (d), 139.6 (d), 151.6 (s), 199.0 (s), 199.5 (s).

1-Methylpentacyclo[5.4.0.0$^2$.6.0$^3$.10.0$^5$.9]undecane-8,11-dione (9). A solution of 10 (23 g, 0.12 mol) in acetone (400 mL) under argon was irradiated by using a Hanovia medium-pressure Hg lamp (Pyrex filter) for 4 h. The reaction mixture was concentrated in vacuo, thereby affording 9 (19.3 g, 84%) as a colorless microcrystalline solid: mp 60-61 °C (lit. mp 64-65 °C); IR (KBr) 2982 (w), 2962 (w), 2929 (w), 2916 (w), 2862 (w), 1750 (s), 1728 (s), 1079 (m), 1052 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.15 (d, $J$ = 3.8 Hz, 3 H), 1.93 (dd, $J$ = 30, 12 Hz, 2 H), 2.28-2.38 (m, 1 H), 2.54-2.94 (m, 5 H), 3.11 (dd, $J$ = 14, 7.6 Hz, 1 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 15.70 (t), 36.18 (d), 40.79 (s), 43.59 (d), 44.23 (d), 44.97 (d), 48.37 (d), 50.27 (d), 54.47 (d), 54.63 (d), 212.2 (s), 212.8 (s).

1-Methylpentacyclo[5.4.0.0$^2$.6.0$^3$.10.0$^5$.9]-undecane-endo-8,endo-11-diol (11a) via solid state NaBH$_4$ reduction of 9. An intimate mixture of reactants was prepared by grinding 9 (87 mg, 0.45 mmol) together with NaBH$_4$ (360 mg, 9.5 mmol, excess) in a mortar until the mixture became a fine powder. The resulting mixture was stirred magnetically under an argon atmosphere at room temperature for 7 days. Water (15 mL) then was added, and
the resulting mixture was extracted with CHCl₃ (3 x 20 mL). The combined extracts were washed with water (30 mL), dried (Na₂SO₄), and filtered. The filtrate was concentrated in vacuo. The residue, a mixture of the isomers of 11, was purified via column chromatography on silica gel by eluting with 5% EtOAc in Hexane, thereby affording the corresponding pure endo,endo-diol (11a, 74 mg, 85%) as a colorless, waxy solid: mp 147-148 °C; IR (KBr) 3195 (br, s), 2943 (s), 2856 (m), 1478 (w), 1445 (w), 1259 (w), 1102 (m), 1059 cm⁻¹ (m); ¹H NMR (CDCl₃) δ 0.98-1.04 (m, 1 H), 1.18 (s, 3 H), 1.57 (d, J = 10.7 Hz, 1 H), 2.03-2.52 (m, 7 H), 3.36 (d, J = 3.0 Hz, 1 H), 3.82 (dd, J = 4.1 Hz, 2.7 Hz, 1 H), 5.76 (s, 2 H); ¹³C NMR (CDCl₃) δ 21.87 (q), 34.72 (t), 36.61 (d), 41.50 (d), 42.82 (d), 43.19 (s), 44.58 (d), 45.00 (d), 46.09 (d), 46.27 (d), 72.51 (d), 75.64 (d). Anal. Calcd for C₁₂H₁₆O₂: C, 75.15; H, 8.33; Found: C, 74.97; H, 8.39.

1-Methylpentacyclo[5.4.0.0²,6,0³,10,0⁵,9]-undecane-endo-8,endo-11-diol (11) via reduction of 9 with NaBH₄ in solution. To a solution of 9 (40 mg, 0.21 mmol) in EtOH (10 mL) was added NaBH₄ (40 mg, 1.06 mmol), and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo, and water (10 mL) was added to the residue. The resulting mixture was extracted with CHCl₃ (3 x 20 mL). The combined extracts were washed with water (20 mL), dried (Na₂SO₄), and filtered, and
the filtrate was concentrated in vacuo. A mixture of the isomers of 11 (41 mg, 100%) was thereby obtained. The major product is 11a (ratio 11a:other isomers = 3:1, which is determined by the integration of hydrogens in the proton NMR spectra); $^{13}$C NMR (CDCl$_3$) δ 19.62 (q), 21.04 (q), 21.44 (q), 21.86 (q), 34.71 (t), 35.32 (t), 35.42 (t), 35.57 (t), 36.35 (d), 36.56 (d), 37.23 (d), 41.23 (d), 41.25 (d), 41.44 (d), 41.83 (d), 42.56 (d), 42.76 (d), 43.14 (s), 43.21 (d), 43.46 (s), 44.20 (d), 44.50 (d), 44.91 (d), 45.35 (d), 45.55 (d), 45.93 (d), 46.00 (d), 46.02 (d), 47.92 (d), 48.79 (d), 48.80 (d), 49.36 (d), 72.36 (d), 73.17 (d), 73.78 (d), 73.79 (d), 74.74 (d), 75.50 (d), 75.72 (d), 78.11 (d).

1-Methylpentacyclo[5.4.0.0$^2$6.0$^3$10.0$^5$9]undecane-endo-8,endo-11-diol Cyclic Thiocarbonate (12). A solution of 11a (97 mg, 0.50 mmol) and 1,1-thiocarbonyldiimidazole (90 mg, 0.50 mmol), in dry toluene (15 mL) was refluxed under argon for 2 h. The reaction mixture was allowed to cool to room temperature and then was concentrated in vacuo. The residue was dissolved in CHCl$_3$ (50 mL), and the resulting solution was washed successively with water (30 mL), 10% aqueous HCl (2 x 30 mL), water (30 mL), saturated aqueous NaHCO$_3$ (2 x 30 mL), and water (30 mL). The organic layer was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 20% CHCl$_3$-
hexane. Pure 12 was thereby obtained as a colorless microcrystalline solid (94 mg, 80%): mp 223.0-224.5 °C; IR (KBr) 2942 (m), 2849 (w), 1717 (w), 1398 (m), 1265 (s), 1232 (s), 1205 (s), 1006 (m), 973 cm\(^{-1}\) (m); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.20-1.30 (m, 1 H), 1.37 (s, 3 H), 1.78 (d, \(J = 12.0\) Hz, 1 H), 2.28-2.38 (m, 1 H), 2.40-2.49 (m, 2 H), 2.58-2.71 (m, 1 H), 2.72-2.82 (m, 1H), 2.85-3.05 (m, 2 H), 4.11 (d, \(J = 3.4\) Hz, 1 H), 4.50 (dd, \(J = 5.0\) Hz, 3.6 Hz, 1 H); \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 20.71 (q), 36.30 (t), 36.75 (d), 41.31 (d), 42.76 (d), 44.05 (d), 44.35 (s), 44.74 (d), 45.66 (d), 46.06 (d), 84.58 (d), 88.31 (d), 192.8 (s). Anal. Calcd for C\(_{13}\)H\(_{14}\)O\(_2\)S: C, 66.77; H, 6.15. Found: C, 66.64; H, 6.02.
REFERENCES


12. The single-crystal X-ray structure and the crystal packing diagram of 9 (Figures 1-9 and 1-10, respectively) were provided by Dr. K. Venkatesan and Mr. J. Narasaimha Moorthy. We thank Professor Venkatesan and Mr. Moorthy for having kindly provided these data.


Figure 1-2. FT-IR Spectrum of 11a.
Figure 1.3. 1H NMR Spectrum of 9.
Figure 1-5. 1H NMR Spectrum of 11a.
Figure 1-6. $^{13}$C and APT NMR Spectra of 11a.
Figure 1-9. Drawing of X-ray crystal structure of 9.
SYNTHESIS OF Z- AND E-1,2-DI(1'-ADAMANTYL)ETHENE AND OF E-1-
(EXO-8'-PENTACYCLO[5.4.0.0^2,6.0^3,10.0^5,9]UNDECYL-2-PHENYLETHENE

Introduction

Alkenes are an important class of organic compounds whose synthesis and chemistry have received considerable attention. Among alkenes, strained alkenes are significant because the structural deformation of the carbon-carbon double bonds is related to instability and enhanced reactivity.

A important feature of alkenes is that all atoms adjacent to the C=C moiety, as well as the doubly bonded carbon atoms themselves, prefer to be coplanar. This situation reflects the stereochemical requirements of the sp^2 hybridized carbon atoms which comprise the C=C double bond.

An unstrained carbon-carbon double bond in the ground state is described by six atoms lying in a plane with bond angles near 120° and bond lengths of double bonds about 1.30 Å. In the case of strained alkenes, Greenberg and Liebman have described four modes by which strain can be introduced into a C=C double bond (Scheme 1). Mode a involves a torsionally strained double-bond as in, e.g., tetra-tert-
butylethene 1, for which the torsion angle ($\phi$) was calculated to be $75^\circ$.\textsuperscript{4} Mode \textbf{b} represents a normal (i.e., planar) $\pi$ system which contains a bond angle ($\theta$) distortion ($\theta$ is increased or decreased in the strained alkenes of this type compared with $\theta = 120^\circ$ in an unstrained alkene).

Cyclopropene (2) possesses this kind of strain.\textsuperscript{3} Modes \textbf{c} and \textbf{d} illustrate "syn-bent" and "anti-bent" alkenes, respectively. 1,2-Dehydrocubene ("cubene", 3), the most
highly pyramidalized alkene yet synthesized, contains a "syn-bent" C=C double bond. No purely carbon-containing examples of "anti-bent" organic molecules which include mode d strain are known. However, a main-group organometallic compound, 4, does contain this feature. Generally, distortions of alkene linkages result to form combinations of the various modes shown above.

Ogawa and coworkers have studied intramolecular motion in the crystal lattices of solid E-stilbenes. They observed that E-stilbenes possess unusually short C=C bond lengths (vis-à-vis that of an isolated ethylene C=C bond). In addition, they observed that the molecular structures of E-stilbenes are markedly temperature-dependent. In order to understand the observed low isomerization barrier for rotation about the C=C double bond in compounds of this type, Gano and coworkers investigated the structure of Z-2,2,5,5-
tetramethyl-3,4-diphenyl-3-hexene, (5). They found that this compound possesses an unusual, cofacial structure. X-ray structural analysis of this compound revealed that the planes of the phenyl groups are perpendicular to the plane of the central C=C bond, and the π-systems of the phenyl rings are mutually cofacial (e.g., "face-to-face" and orthogonal to the central π-bond). The dominant distortion is caused by mutual repulsion of the tert-butyl groups, with the result that the t-Bu-C=C angle is increased to 132.7° and the phenyl rings become compressed so that the Ph-C=C angle is 116.0°.

Borden and coworkers have studied the synthesis and properties of a homologous series of highly strained pyramidalized alkenes. Much of the classical π bonding that exists between parallel p orbitals of adjacent sp² hybridized carbons in "normal" alkenes is lost in such systems. The rehybridization that is required to accommodate the geometric demands of the carbocyclic skeleton in such systems results in the introduction of substantial s-character into the C=C double bond. Borden and Hrovat calculated the strain energies for alkenes 6-9 (shown below) and found that the olefin pyramidalization strain energies (OPSEs) for 6-9 are the same as the olefin strain energies (OSEs) for the corresponding alkenes. Accordingly, they concluded that the unusual physical and chemical properties of these alkenes can be attributed entirely to strain effects brought about via alkene pyramidalization.
Wiberg and coworkers synthesized the strained alkene, tricyclo[4.2.2.2\(^2\).5]dodeca-1,5-diene (10) (as showed below), and investigated its chemical and physical properties.\(^{10}\)

They found that the strain energy in 10 is 44 kcal/mol. The inherent strain in 10 appears primarily in the form of two molecular distortions: (1) the elongation of the C-C single bonds (C\(_3\)-C\(_4\) = 1.595 Å) in the bridging CH\(_2\)CH\(_2\) groups which is caused by the repulsive interaction between two pairs of \(\pi\) orbitals; and (2) the nonplanarity of the double bond and their substituents which can be seen through the distortion of the dihedral angle \(\theta = 76.4^\circ\). This dihedral angle would
be $0.0^\circ$ in a planar alkene. The diene 10 has very high chemical reactivity. An increase in strain energy caused by molecular distortion frequently leads to high reactivity in a Diels-Alder reaction, whereas simple alkenes are normally relatively unreactive. The reaction between 10 and cyclopentadiene proceeded rapidly at room temperature and gave a bis adduct, 12 (Scheme 2), which was a mixture of syn and anti isomers. When a limited amount of cyclopentadiene was used, a mixture of 12 and mono adduct, 11, was obtained.

**Scheme 2**

(a). Diels-Alder reaction of 10.

(b). Bromination of 10.
The diene 10 rapidly reacted with 1 equivalent of bromine to give a dibromide 13 (Scheme 2).

In order to study the structural properties of alkenes, especially those which possess bulky groups, alkenes 14-16 were synthesized (structures are shown below).

![Diagrams of alkenes 14, 15, and 16a](image)

Numerous methods exist for the synthesis of alkenes. In general, compounds of this type are prepared via elimination reactions (loss of water, hydrogen halides, acids, etc.) and by condensation reactions. Methods which employ oxidation, reduction, reductive dimerizations of aldehydes and ketones, isomerization/rearrangement, free radicals, photolysis, and/or enzymatic reactions have also been used for this purpose. The strained alkene, \(E-3,4\)-diethyl-2,2,5,5-tetramethylhexane-3-ene (18a), was synthesized by using McMurray's method (Scheme 3), i.e., via titanium promoted reductive dimerization of tert-butyl ethyl ketone (17).
reaction was found to proceed with a high degree of stereoselectivity to afford the corresponding alkenes 18a and 18b (ratio E:Z = 12:1).

1,1-Diphenyl-2,2-di-tert-butylethylene (19), a highly...
congested alkene, was prepared by using the method which is outlined in Scheme 4.\textsuperscript{14b}

Borden and coworkers have successfully synthesized highly strained alkenes 7 and 8 via the gas-phase pyrolysis of \( \beta \)-lactones 20 and 21 (Scheme 5).\textsuperscript{7b,7c}

\begin{center}
\textbf{Scheme 5}
\end{center}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme5.png}
\end{center}

Reductive bis-dehydroxylation of vicinal diols is another useful method for preparing strained alkenes. Here, syn elimination proceeds via cyclic derivatives of the type 22 (Scheme 6). This methodology is particularly useful for synthesizing alkenes which possess unusual structural features, e.g., strained and/or twisted C=C double bonds.\textsuperscript{15,16}

In addition, the formation of cyclic derivatives provides a useful means of establishing the stereochemistry of vic-diols (see Chapter 1).

Carbonyl condensation (Wittig-type) reactions have also
been utilized extensively to prepare alkenes. These reactions proceed under relatively mild conditions via initial attack of a nucleophilic carbanion upon the (electrophilic) carbonyl carbon atom. Nucleophilic addition occurs with concomitant formation of an intermediate betaine which is subsequently converted to the corresponding oxaphosphetane. Finally, cycloelimination of Ph₃P=O occurs, thereby affording the corresponding alkene (Scheme 7). The Wittig reaction lends itself readily to the synthesis of heat-sensitive alkenes. In addition, it often is possible to predict the stereochemistry of the resulting alkenes. It is generally found that ylides which contain stabilizing electron-donating groups or ylides which are formed from trialkyl phosphines undergo Wittig reactions to afford trans olefins. Ylides formed from triarylphosphines that do not contain other stabilizing groups usually afford mainly cis (or a mixture of cis and trans) olefins.
Based upon the foregoing considerations, it was designed to employ bis-dehydroxylation of vic-diols as a means to synthesize alkene 14. A Wittig reaction was used to synthesize alkene 16a.

Synthesis of E-1,2-di(1'-adamantyl)ethene (15) has been reported by Adam and coworkers. They found that β-lactones can serve as convenient precursors to sterically congested E-alkenes (Scheme 8). Thus, they condensed an α-lithiocarboxylate with a carbonyl containing substrate to afford predominantly the desired threo-β-hydroxy acid 23. Dehydration of 23 to produce the corresponding β-lactone (24) and subsequent thermal extrusion of CO₂ from 24 provided a generally useful route for preparing the corresponding E-alkenes (25).

Capozzi and coworkers have reported a one-step
Scheme 8

Scheme 9

Me$_3$SiC≡CSiMe$_3$ + RX $\xrightarrow{L}$ Me$_3$SiC≡CR + Me$_3$SiX + L
(L = Lewis Acid)

synthesis of tertiary alkyl-substituted acetylenes from silylacetylenes (Scheme 9). Thus, reactions of silylacetylenes with tertiary alkyl halides, when performed in the presence of a Lewis acid catalyst, afforded tertiary alkyl-substituted alkynes in high yields. This procedure has been used to synthesize bis(1'-adamantyl)acetylene in 84% yield. Subsequently, E-1,2-di(1'-adamantyl)ethene could be prepared via catalytic hydrogenation (PtO$_2$ catalyst) of this acetylene.
In the present study, the synthesis of Z-1,2-di(1'-adamantyl)ethene, 14, a sterically congested Z-alkene, and its subsequent isomerization to the corresponding E-alkene (15) are reported. In addition, alkene 16a was synthesized as a part of this study (vide infra).

Results and Discussion

Z- and E-1,2-Di(1'-adamantyl)ethene (14 and 15, respectively). The route shown in Scheme 10 has been utilized in the present study. This route has proved to be a convenient method for the stereoselective synthesis of highly congested Z-alkenes. Thus, sodium promoted acyloin condensation of methyl 1-adamantanecarboxylate (26) afforded the corresponding hydroxyketone, 27, whose $^1$H and $^{13}$C NMR spectra are shown in Figures 2-1 and 2-2, respectively. Interestingly, reduction of 27 with NaBH$_4$ in EtOH proceeded with high stereoselectivity to afford the corresponding meso-diol, 28a, (ratio meso:d,l = 15:1, as determined via $^1$H NMR). The $^1$H and $^{13}$C NMR spectra are shown in Figures 2-3 and 2-4, respectively. Reduction of 27 by LiAlH$_4$ produced a mixture of meso- and d,l-isomers (ratio meso:d,l = 2:1, as determined via $^1$H NMR). The results are contrary to expectations based upon consideration of Cram’s rule as modified by the Felkin-Anh model (Scheme 11).\textsuperscript{22} By considering the "effective size" of the substituents and the influence of the steric bulk of
Scheme 10

\[ \text{Cram's Rule (Felkin-Anh model)} \]

**Scheme 10**

\[ \text{Na, xylene reflux} \quad \text{EtOH-CH}_2\text{Cl}_2 \]

26

\[ \text{NaBH}_4 \]

27

28a: \( W = Z = \text{OH}; X = Y = \text{H} \)

28b: \( W = Y = \text{OH}; X = Z = \text{H} \)

29 (mixture of diastereoisomers)

Scheme 11

Cram's Rule (Felkin-Anh model)

major

minor
substituents which influences the direction of nucleophilic attack, the substituents are simply classified as being "large" (L), "medium" (M), or "small" (S). The large group (L) generally is that substituent which possesses the greater repulsive effect, which may be either steric or dipolar (e.g. OR, NR₂) in origin. In the case of BH₄⁻ reduction of 27, the hydroxy group is considered to be the "large group", and BH₄⁻ attacks the carbonyl carbon atom from a direction which is antiperiplanar with respect to the substituent hydroxy group. As a result, the major product of the NaBH₄ promoted reduction of 27 is predicted to be d,l-diol, 28b (Scheme 12).

Scheme 12

Since the experimental result is contrary to this prediction, we conclude that some other factors must control the stereochemistry of the NaBH₄ promoted reduction of 27.

The following explanation is offered to account for
these results. Hydrogen bonding between the hydroxyl hydrogen atom and the carbonyl oxygen atom may occur. Based on this assumption, a scenario which may account for the observed stereospecificity of the NaBH$_4$ reduction of 27 is summarized in Scheme 13. Thus, it is suggested that BH$_4^-$ attacks the reaction center via the least sterically hindered and least electrically repulsive pathway (i.e., via the face furthest from the oxygens). By way of contrast, LiAlH$_4$, which is a much more reactive reducing agent than NaBH$_4$, reacts preferentially with the (acidic) hydroxyl hydrogen atom in 27, thereby removing the possibility of intramolecular hydrogen bonding in the resulting lithium alkoxide. As a consequence, the stereoselectivity of the LiAlH$_4$ reduction of 27 is reduced dramatically compared with that which results via the corresponding NaBH$_4$ promoted reduction.
In order to gain further insight into the mechanism of the NaBH₄ reduction of 27, the reaction sequence shown in Scheme 14 was studied. The possibility of intramolecular hydrogen bonding was eliminated from consideration by converting 27 to the corresponding acetate derivative, i.e., 2-oxo-1,2-di(1'-adamantyl)ethyl acetate (30). The ¹H and ¹³C NMR spectra of 30 are shown in Figures 2-5 and 2-6, respectively. The structure of 30 was established unequivocally via single-crystal X-ray structural analysis (see Figure 2-7).²³

Subsequent NaBH₄ promoted reduction of 30 afforded a
mixture of meso-31a and d,l-31b (ratio 1:1.5, as determined via $^1$H NMR). The $^1$H and $^{13}$C NMR spectra of the mixture of 31a and 31b thereby obtained are shown in Figures 2-8 and 2-9, respectively. The lack of stereoselectivity in the NaBH$_4$ promoted reduction of 30 may be considered to indicate that hydrogen bonding between the hydroxyl hydrogen and the carbonyl oxygen in 27 is the dominant factor that determines the stereoselectivity of the NaBH$_4$ promoted reduction of 27.

In order to identify structures of 31a and 31b, a solid derivative of each compound was made (i.e., 32a and 32b, Scheme 15). The corresponding $^1$H and $^{13}$C NMR spectra of these derivatives are shown in Figures 2-10, 2-11, 2-12, and 2-13. The structure of 32a was identified via single-crystal x-ray structural analysis (see Figure 2-14).

Reaction of meso-diol 28a with ethyl orthoformate afforded the corresponding cyclic orthoformate ester, 29, as a mixture of diastereoisomers. The $^1$H NMR spectrum of 29 is shown in Figure 2-15. When 29 was heated in the presence of benzoic acid at 200 °C for 4 h, highly stereoselective syn cycloelimination occurred (ratio Z:E alkenes = 42:1, as determined via integration of the vinyl protons in 14 and 15 in their respective $^1$H NMR spectra). In this way, Z-1,2-di(1'-adamantyl)ethene (14) was obtained in 90% yield. The $^1$H and $^{13}$C NMR spectra of 14 are shown in Figures 2-16 and 2-17, respectively. Unequivocal verification of the structure
Scheme 15

of 14 was obtained via single-crystal X-ray structural analysis;\textsuperscript{23} a structure drawing of 14 thereby obtained is shown in Figure 2-18.\textsuperscript{23}

A plausible mechanism to account for the course of acid promoted thermal cycloelimination of 29 is shown in Scheme 16.\textsuperscript{15,25} Under acidic conditions, the carbocation 33 is trapped by PhCO\textsubscript{2}H, and the resulting intermediate 34
subsequently undergoes cycloelimination to afford Z-alkene 14.

Isomerization of 14 to the corresponding E-isomer, 15, was performed by heating 14 in the presence of elemental iodine. The $^1$H and $^{13}$C NMR spectra of 15 thereby obtained are shown in Figures 2-19 and 2-20, respectively.
Unequivocal verification of the structure of 15 was obtained via single-crystal X-ray structural analysis;\textsuperscript{23} a structure drawing of 15 thereby obtained is shown in Figure 2-21.\textsuperscript{23} An unusual feature of the $^1$H NMR spectrum of 14 can be discerned by comparing the $^{13}$C satellite peaks in the vinyl proton region in the $^1$H NMR spectra of 14 and 15 (cf. inset in Figures 2-16 and 2-19, respectively). The (vicinal) vinyl proton-proton coupling constants ($^3J_{HH}$) of 14 and 15 are 13.9 and 16.1 Hz, respectively, which were obtained via the analysis of $^{13}$C satellite peaks in their $^1$H NMR spectra. For alkenes of the type RCH=CHR' (R and R' are alkyl groups), the coupling constants of Z-alkenes are generally ca. 10 Hz and the coupling constants of E-alkenes are ca. 16 Hz.\textsuperscript{27} In the case of 14, the $^3J_{HH}$ coupling constant appears to be unusually large for a Z-$^3J_{HH}$ coupling between vinyl protons in a Z-alkene. For 15, the $^3J_{HH}$ coupling constant is in normal range.

On the basis of molecular orbital theoretical considerations, Barfield and Smith\textsuperscript{28} have formulated an explicit expression for vicinal $H-H$ coupling constants ($^3J_{HH}$) in systems of the type RCH=CHR' in terms of the two internal $H-C-C$ angles, $\theta_1$ and $\theta_2$, and the torsion angle $\varphi$ (see Scheme 17). By using eq.1 and the data contained in Figures 2-22\textsuperscript{29} and 23,\textsuperscript{29} the calculated $^3J_{HH}$ values for the Z- and E-isomer are 13.4 and 15.9 Hz,\textsuperscript{29} which are consistent with the experimentally observed values: 13.9 and 16.1 Hz,
Scheme 17

\[ R_1 = R_2, R_3 = R_4 = H \]

\[ R_1 = R_4, R_2 = R_3 = H \]

\[ 3J_{HH}(\theta_1, \theta_2, \phi) = 41.1a(\theta_1, \theta_2)\cos^2\phi + [752.8 b_1(\theta_1, \theta_2) - 406.0 b_2(\theta_1, \theta_2) - 541.6 b_3(\theta_1, \theta_2)]\cos\phi + 1.9 \text{ Hz} \quad \text{eq.1} \]

Table 2-1. Structural Data Based on Calculated MMX and Experimental Data for Vicinal H-H Coupling in Ethylenic (CH=CH) Fragments of alkenes.

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \theta_1 = \theta_2 ) deg</th>
<th>( 3J_{HH}(\theta_1, \theta_2, \phi) ) (calc. values) Hz</th>
<th>( J_{expt} ) Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-1,2-di(1'-adamantyl)ethene (14)</td>
<td>112.7(^a)</td>
<td>13.4(^a)</td>
<td>13.9</td>
</tr>
<tr>
<td>Z-di-tert-butylethene(^b)</td>
<td>111.0</td>
<td>14.2</td>
<td>14.2</td>
</tr>
<tr>
<td>E-1,2-di(1'-adamantyl)-ethene (15)</td>
<td>118.6(^a)</td>
<td>15.9(^a)</td>
<td>16.1</td>
</tr>
<tr>
<td>E-di-tert-butylethene(^b)</td>
<td>118.6</td>
<td>15.9</td>
<td>16.1</td>
</tr>
</tbody>
</table>

\(^a\) Calculated\(^{29}\) by the method described in ref. 28. \(^b\) Data taken from ref. 28.

respectively (see Table 2-1).

The magnitude of \( 3J_{HH} \) depends upon the internal angles \( \theta_1 \).
and $\theta_2$, the torsion angle $\varphi$, the $C=C$ internuclear distance, and the effective nuclear charges on the $C=C$.\textsuperscript{27} In this case, since there is no torsion on the double bond in $14$,\textsuperscript{23} it is possible that nonbonded repulsion between the two bulky adamantyl groups produces changes in the internal angles, the $C=C$ internuclear distances, and the effective nuclear charges on the $C=C$, with the result that the magnitude of $^3J_{HH}$ is larger than expected. The X-ray structural data for $14$ and $15$ are shown in Scheme 18 and 19.\textsuperscript{23} The data for $14$ shows that the internal $C-C-C$ angles are widened. For $15$, all data are in normal range.

The foregoing results can be compared with the corresponding $^3J_{HH}$ coupling constants in $Z$- and $E$-di-tert-

\begin{Scheme} 18

Single-Crystal X-Ray Structural Analysis Data of $14$ at Room Temperature

![Diagram](attachment:image.png)

14

Torsion angle of $C_{11}$-$C_1$=$C_2$-$C_{21}$ is equal to $0^\circ$.
butylethenes. These isomeric alkenes contain bulky tert-butyl groups and possess alkyl substituents in which quaternary carbons are attached to each of the doubly bonded \( sp^2 \) carbon atoms. Both 15 and \( E \)-di-\( \text{tert} \)-butylethylene contain the same internal angles and vicinal \( H-H \) coupling constants \( ^3J_{HH} \) (see Table 2-1). In the case of two \( Z \)-alkenes, \( Z \)-1,2-di(1'-'adamantyl)ethene (14) contains a larger internal angle (\( \theta_1 \) and \( \theta_2 \)) than \( Z \)-di-\( \text{tert} \)-butylethene and also displays a smaller \( ^3J_{HH} \) value. Therefore, we conclude that the large \( ^3J_{HH} \) value for 14 is due to electronic distributions about the \( ^1H \) and \( ^13C \) nuclei are a consequence of the nonbonded repulsion that occurs between the two bulky adamantyl groups.

\[ E-1-(ex \text{-} 8'-' \text{pentacyclo} \{5.4.0.0^{2'},6',0^{3}10',0^{5}9'\}' \text{-} \text{undecyl}) \text{-} 2 \text{-} \text{phenylethene} \ (16a) \]. Isomerically pure 16a was
synthesized in two steps: (i) Wittig olefination of pentacyclo[5.4.0.0²,6,0³,10,0⁵,9]undecane-8-one (36) followed by (ii) base promoted thermodynamic isomerization of the resulting alkenes, 37a and 37b (Scheme 20). The ¹H, ¹³C and 2D COSY NMR spectra of 16a are shown in Figures 2-24, 2-25, and 2-26, respectively.

Scheme 20

\[
\begin{align*}
\text{PhCH}_2\text{CH}_2\text{Br} + \text{Ph}_3\text{P} & \xrightarrow{\text{xylene, reflux for 24 h}} \text{PhCH}_2\text{CH}_2\text{PPh}_3^+\text{Br}^- \\
\text{35}
\end{align*}
\]

\[
\begin{align*}
\text{36} & \xrightarrow{\text{35, KOt-Bu, THF}} \text{37} \\
37a & \text{X} = \text{H}, \text{Y} = \text{CH}_2\text{Ph} \\
37b & \text{X} = \text{CH}_2\text{Ph}, \text{Y} = \text{H}
\end{align*}
\]

Theoretically, as many as four isomeric alkenes could result from the second (isomerization) step, i.e., exo-\(E\) (16a), exo-\(Z\) (16b), endo-\(E\) (16c), and endo-\(Z\) (16d) (Scheme 21). However, in practice, only one alkene was formed via base-promoted thermal isomerization of a mixture of 36a and 36b. In order to determine the configuration of 16, its ¹H,
The $^{13}$C NMR spectrum of 16 contains eleven peaks in the aliphatic region ($\delta$ 27-48) which correspond to the aliphatic cage carbon atoms. In addition, there are six downfield peaks which correspond to the phenyl and vinyl carbon atoms. The peak integrations in the $^1$H NMR spectrum of 16 are consistent with the assigned gross structure of 16. The chemical shifts of the two vinyl hydrogens $H_{12}$ and $H_{13}$ fall in the range $\delta$ 5.95-6.35. These two hydrogens are mutually coupled (AB pattern). The peaks at $\delta$ 6.23 and 6.31 (downfield half of the AB pattern) correspond to $H_{13}$. Since
H$_{13}$ is situated on a vinyl carbon adjacent to the phenyl group, it is expected to be deshielded relative to H$_{12}$. Since H$_{12}$ is coupled with both H$_8$ and H$_{13}$, the peak which corresponds to H$_{12}$ appears as the upfield half of the AB pattern which is further doubled (via H$_8$-H$_{12}$ coupling). The coupling constant between H$_{12}$ and H$_{13}$ is 16.0 Hz. For alkenes of the type PhCH=CHR, cis isomers generally display coupling constants of ca. 12 Hz, while trans isomers show coupling constants of ca. 16 Hz (see Table 2-2). The magnitude of

<table>
<thead>
<tr>
<th>Compound</th>
<th>Coupling constants (Hz)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZPHCH=CH-1-Ad</td>
<td>12.7 16.5</td>
<td>30</td>
</tr>
<tr>
<td>ZPhCH=CH(CH$_3$)$_2$OH</td>
<td>12.0 16.0</td>
<td>31</td>
</tr>
<tr>
<td>ZPhCH=CHCH$_3$</td>
<td>11.56 15.7</td>
<td>32</td>
</tr>
<tr>
<td>ZPhCH=CH-3,5-(MeO)$_2$C$_6$H$_3$</td>
<td>12.0 17.0</td>
<td>33</td>
</tr>
</tbody>
</table>

J$_{12,13}$ in 12 suggests that this alkene possesses the E-configuration, i.e., that it possesses either structure 12a or 16c. The coupling constant between H$_{12}$ and H$_8$ is 7.0 Hz. In order to determine the chemical shift of H$_8$, the 2D COSY NMR spectrum of 16 was obtained. In this spectrum, H$_8$
appears as a half of the AB pattern in the range $\delta$ 2.50-2.55. In general, the magnitudes of vicinal coupling constants depend mainly on the dihedral angle, $\phi$ (eq. 2 and eq. 3). Therefore, the MMX energies and dihedral angles of 16a and 

$$J = J^0 \cos^2 \phi - 0.3 \quad 0^\circ < \phi < 90^\circ \quad \text{eq. 2}$$

$$J = J^{180} \cos^2 \phi - 0.3 \quad 90^\circ < \phi < 180^\circ \quad \text{eq. 3}$$

16c were calculated by using PCMODEL$^{34}$ (see Figures 2-27 to 2-32); the results of these calculations are summarized in Table 3. MOPAC$^{35}$ and Chem3D Plus$^{37}$, also were employed in order to find the energy differences between 16a and 16c. The results are summarized in Table 4. From these data, we can see that even through the different calculation methods give different absolute energy values, the magnitude of the minimized energy value of 16a is always slightly larger than that of 16c. Both computational methods, MOPAC and Chem3D Plus$^{TM}$, show that the magnitudes of the C=C bond lengths in 16a and 16c are about the same and in the range of that of a "normal" (i.e., unstrained) alkene. Therefore, the computational results do not permit a clear distinction to be made between 16a and 16c. However, if 16 possesses configuration 16c (see Scheme 22), then the calculated dihedral angles of 16c, H8-C8-C7-H7 and H8-C8-C9-H9, are 50.18$^\circ$ and -57.81$^\circ$, respectively and the calculated coupling
Table 3. The Calculated MMXEs (E), Dihedral Angles and Coupling Constants of 16a and 16c via PCMODEL.\textsuperscript{35}

<table>
<thead>
<tr>
<th></th>
<th>16a</th>
<th>16c</th>
</tr>
</thead>
<tbody>
<tr>
<td>E (Kcal/mol)</td>
<td>76.21</td>
<td>77.14</td>
</tr>
<tr>
<td>H\textsubscript{12}-C\textsubscript{12}-C\textsubscript{13}-H\textsubscript{13} (Deg)</td>
<td>177.33</td>
<td>176.45</td>
</tr>
<tr>
<td>H\textsubscript{12}-C\textsubscript{12}-C\textsubscript{8}-H\textsubscript{8} (Deg)</td>
<td>138.16</td>
<td>-95.39</td>
</tr>
<tr>
<td>H\textsubscript{8}-C\textsubscript{8}-C\textsubscript{7}-H\textsubscript{7} (Deg)</td>
<td>-75.46</td>
<td>50.18</td>
</tr>
<tr>
<td>H\textsubscript{9}-C\textsubscript{9}-C\textsubscript{9}-H\textsubscript{9} (Deg)</td>
<td>68.85</td>
<td>-57.81</td>
</tr>
<tr>
<td>J\textsubscript{7,8} (Hz)</td>
<td>1.01</td>
<td>4.38</td>
</tr>
<tr>
<td>J\textsubscript{9,9} (Hz)</td>
<td>1.63</td>
<td>3.13</td>
</tr>
</tbody>
</table>

Table 4. The Calculated Heats of Formation (\(\Delta H_f\)) and Vicinal Doubled Bond Length (L) of 16a and 16c via MOPAC and Chemdraw 3D plus.\textsuperscript{35}

<table>
<thead>
<tr>
<th></th>
<th>16a</th>
<th>16c</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOPAC</td>
<td>(\Delta H_f) (kcal/mol)</td>
<td>66.91</td>
</tr>
<tr>
<td></td>
<td>L (Å)</td>
<td>1.339</td>
</tr>
<tr>
<td>Chem3D</td>
<td>(\Delta H_f) (kcal/mol)</td>
<td>59.16</td>
</tr>
<tr>
<td>Plus\textsuperscript{TX}</td>
<td>L (Å)</td>
<td>1.348</td>
</tr>
</tbody>
</table>

constants \(J_{7,8}\) and \(J_{9,9}\) are 4.38 and 3.13 Hz, respectively. Therefore, we would expect exo-H\textsubscript{9} to be coupled with H\textsubscript{7}, H\textsubscript{9} and H\textsubscript{12} to afford a maximum of eight peaks (dddd), a result which is not consistent with the \(^1\text{H} NMR\) spectral data. If 16 instead possesses configuration 16a, endo-H\textsubscript{9} should couple very weakly to H\textsubscript{7} and H\textsubscript{9} because the calculated coupling
For Scheme 22:

In fact, only one doublet peak is seen in the $^1$H NMR spectrum of 16. Therefore, the large differences in the calculated coupling constants $J_{7,8}$ and $J_{8,9}$ between 16a and 16c suggest that the product may be 16a rather than 16c. The coupling constant between H$_8$ and H$_{12}$ is equal to 7.0 Hz which is in the expected range for coupling to an exo H$_8$ proton. We therefore conclude that 16 most likely possesses structure 16a (see Scheme 21).

It should be noted that the driving force for thermodynamic isomerization of the C=C double bond in 36 is provided by the fact that this process brings the C=C group into conjugation with the phenyl group in the product (Scheme 23). Nevertheless, only one of four isomeric alkenes was
obtained, i.e., the exo-\( E \) isomer (16a). The results of MOPAC AMI calculations show the difference of heats of formation between 16a and 16c is only 1.09 kcal/mol (see Table 4), but the magnitude of heat of formation for 16a is larger than that for 16c. It is likely that this result reflects the fact that 16a is the most stable of the four possible \( C=C \) isomerization products.

**Summary and Conclusion**

A convenient route shown in Scheme 10, has been developed to synthesize \( Z \)-1,2-di(1'-adamantyl)ethene (14) with high stereoselectivity. This route consists of four steps: (i) acyloin condensation of methyl 1-adamantanecarboxylate (26) to afford \( 1,2\)-di(1'-adamantyl)-2-hydroxyethanone (27); (ii) \( \text{NaBH}_4 \) promoted reduction of 27 to afford \( \text{meso-1,2-di(1'-adamantyl)ethane-1,2-diol} \) (28); (iii) reaction of 28 with triethyl orthoformate to produce a
mixture of isomeric cyclic orthofomates, 2-ethoxy-1,2-di(1'-adamantyl)-1,3-dioxolanes (29); (iv) acid promoted thermal cycloelimination of 29 to afford 14. Iodine promoted isomerization of 14 quantitatively generated E-1,2-di-(1'- adamantyl)ethene (15). Both Z- and E-alkenes, 14 and 15, have been characterized unequivocally via single-crystal X-ray structural analysis. E-1-(exo-8'-pentacyclo-
[5.4.0.0²,6.0³,10.0⁵,9]undecyl)-2-phenylethene (16a) has been synthesized stereospecifically (Scheme 13) via a Wittig reaction of 36 with the phosphonium ylide (PhCH2CH=PPh3) to form 37 (mixture of isomers) followed by a base promoted isomerization of 37 to afford 16a. The configuration of 16a was determined via analysis of its ¹H, ¹³C, and 2D COSY NMR spectra.

**Experimental Section**

Melting points are uncorrected and uncalibrated.

Elemental microanalysis were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

**Methyl 1-adamantanecarboxylate (26)** To a solution of 1-adamantanecarboxylic acid (5.0 mg, 27.7 mmol) in MeOH (25 mL, excess) under argon was added concentrated H₂SO₄ (1.5 mL, catalytic amount), and the resulting mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature, and water (30 mL) was added. The resulting mixture was extracted with Et₂O (3 x 40 mL), and washed
sequentially with saturated aqueous NaHCO₃ (30 mL) and water (2 x 30 mL). The organic layer was dried (MgSO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 5% EtOAc in hexane. Pure 26 (5.1 mg, 95%) was thereby obtained as a colorless microcrystalline solid: mp 34.8-35.3 °C (lit. 35 mp 38-39 °C); IR (KBr) 2922 (s), 2894 (s), 2849 (s), 1724 (s), 1445 (m), 1418 (w), 1244 (s), 1172 (m), 1007 (s), 959 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.60 (s, 6 H), 1.75 (d, J = 3.6 Hz, 6 H), 1.82-1.94 (m, 3 H), 3.52 (br s, 3 H); ¹³C NMR (CDCl₃) δ 27.72 (d), 36.25 (t), 38.58 (t), 40.38 (s), 177.6 (s).

1,2-Di(1'-adamantyl)-2-hydroxyethanone (27) To a suspension of Na (1.26 g, 6.49 mg-atom) in dry xylene (50 mL) under argon was added dropwise with stirring a solution of 26 (4.90 g, 25.6 mmol) in dry xylene (10 mL). The reaction mixture was refluxed for 1 h and then allowed to cool to room temperature. An external ice-water bath then was applied, and the reaction mixture was further cooled to 0 °C. To the cooled reaction mixture was added with stirring a solution of concentrated H₂SO₄ (2.4 mL) in water (12 mL). Water (100 mL) then was added, and the resulting mixture was extracted with xylene (3 x 80 mL). The combined extracts were washed with H₂O (50 mL), dried (MgSO₄), and filtered, and the filtrate was concentrated in vacuo. Compound 27 was thereby obtained as a colorless microcrystalline solid (726 mg, 85%): mp 224-225 °C.
meso-1,2-Di(1'-adamantyl)ethane-1,2-diol (28a) A solution of 27 (2.00 g, 6.09 mmol) in EtOH (30 mL) under argon was cooled via application of an external ice bath. To this cooled solution was added with stirring NaBH₄ (345.6 mg, 9.14 mmol). After all of the reducing agent had been added, the reaction mixture was allowed to warm gradually to room temperature with continuous stirring for 4 h. The reaction mixture then was quenched via sequential addition of water (50 mL) and 10% aqueous HCl (5 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 150 mL), and the combined organic layers were washed with water until the aqueous layer became slightly acidic (ca. pH 6). The organic layer was dried (MgSO₄) and filtered, and the filtrate was concentrated in vacuo to afford a mixture of 28a and 28b (ratio 28a:28b = 15:1). The mixture was purified via column chromatography on silica gel by eluting with 2% EtOAc in hexane to afford 28a as a colorless microcrystalline solid (1.88 g, 93%): mp 273.5-274.0 °C; IR (KBr) 3528 (w), 3455 (br, m), 2899 (s), 2846 (m), 1438 (w), 1212 (br, w), 992 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.40-1.46 (m, 3 H), 1.60-1.78 (m, 14 H), 1.78-1.92 (m, 6 H), 1.92-2.12 (m, 7 H), 2.20 (d, J = 11.6 Hz, 1 H), 4.05 (d, J = 11.6 Hz, 1 H); ¹³C NMR (CDCl₃) δ 27.84 (d), 28.19 (d), 36.45 (t), 36.96 (t), 37.38 (s), 37.91 (t), 38.11 (t), 46.37 (s), 76.93 (d), 218.7 (s).
δ 1.64-1.80 (m, 24 H), 1.92-2.05 (m, 6 H), 3.10-3.15 (m, 2 H); $^{13}$C NMR (CDCl$_3$) δ 28.53 (d), 37.33 (t), 37.67 (s), 38.24 (t), 79.73 (d). Anal. Calcd for C$_{22}$H$_{34}$O$_2$: C, 79.95; H, 10.37. Found: C, 80.02; H, 10.16.

1,2-Di(1'-adamantyl)ethane-1,2-diol (28a and 28b)
A solution of 27 (50 mg, 0.15 mmol) in dry THF (2 mL) was added to a suspension of LiAlH$_4$ (excess, 35 mg, 0.92 mmol) in THF (5 mL) under argon, and the resulting mixture was refluxed for 0.5 h. The reaction mixture was cooled to room temperature and then quenched via addition of saturated aqueous NH$_4$Cl (20 mL). The resulting mixture was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were washed with water (2 x 30 mL), dried (MgSO$_4$) and filtered, and the filtrate was concentrated in vacuo to afford a mixture of 28a and 28b as a colorless microcrystalline solid (47 mg, 93%): mp 257-265 °C (lit. 257-265°C); $^{13}$C NMR (CDCl$_3$) δ 28.25 (d), 28.56 (d), 37.18 (t) 37.35 (t), 37.68 (s), 38.05 (t), 38.26 (t), 77.50 (d), 79.59 (d).

2-Oxo-1,2-di(1'-adamantyl)ethyl acetate (30)
A solution of 27 (76 mg, 0.21 mmol) in pyridine (1.5 mL) and CH$_2$Cl$_2$ (3 mL) under argon was cooled to 0 °C by application of an external ice bath. Acetic anhydride (1.5 mL) and dimethylaminopyridine (DMAP, 10 mg) then were added. The external cold bath was removed, and the reaction mixture was allowed to warm to room temperature and then was stirred at that temperature for 1 h. The reaction mixture was diluted
with CH₂Cl₂ (80 mL), and the resulting mixture was washed sequentially with cold 3% aqueous HCl (20 mL), saturated aqueous CuSO₄ (20 mL), saturated aqueous NaHCO₃ (20 mL), H₂O (2 x 30), and brine (30 mL). The organic layer was dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo to afford 30 (72 mg, 85%) as a colorless micro-crystalline solid: mp 129-130 °C; IR (KBr) 2930 (s), 2901 (s), 2894 (s), 2845 (m), 1732 (m), 1690 (m), 1443 (w), 1366 (w), 1337 (w), 1304 (w), 1147 (w), 999 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.48-1.54 (m, 1 H), 1.58 (br-s, 2 H), 1.62-1.82 (m, 15 H), 1.86 (br s, 6 H), 1.90-2.06 (m, 6 H), 2.07 (s, 3 H), 5.26 (s, 1 H); ¹³C NMR (CDCl₃) δ 20.70 (q), 27.95 (d), 28.07 (d), 36.42 (t), 36.79 (t), 36.93 (s), 37.84 (t), 38.25 (t), 46.92 (s), 76.67 (d), 170.3 (s), 212.5 (s). Anal. Calcd for C₂₄H₃₄O₃: C, 77.80; H, 9.25. Found: C, 77.70; H, 9.30.

2-Hydroxy-1,2-di(1'-adamantyl)ethyl acetate (31a, 31b) A solution of 30 (20 mg, 0.054 mmol) in EtOH (5 mL) under argon was cooled via application of an external ice-water bath. To this cooled solution was added with stirring NaBH₄ (50 mg, large excess). After all of the reducing agent had been added, the external cooling bath was removed, and the reaction mixture was allowed to warm gradually to room temperature with continuous stirring during 12 h. The reaction mixture then was quenched via addition of water (20 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 20
mL), and the combined organic layers were washed with water (2 x 30 mL). The organic layer was dried (MgSO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 5% EtOAc-hexane, thereby affording a mixture of 31a and 31b (ratio 1:1.5, 16 mg, 80%) as a colorless microcrystalline solid. Further separation of 31a and 31b was accomplished via column chromatography on silica gel (400 mesh) by eluting with 3% EtOAc-hexane. A single pure isomer, (6.4 mg, 32%), 31a, was thereby obtained as a colorless microcrystalline solid: mp 187.0-187.5 °C; IR (KBr) 3587 (w), 2896 (s), 2844 (m), 1734 (m), 1443 (w), 1359 (w), 1230 (m), 1211 (m), 1017 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.45-1.85 (m, 24 H), 1.90-2.04 (m, 6 H), 2.09 (s, 3 H), 3.26 (d, J = 10.0 Hz, 1 H), 4.75 (s, 1 H); ¹³C NMR (CDCl₃) δ 21.27 (q), 28.13 (d), 28.19 (d), 36.90 (t), 37.02 (t), 37.62 (t), 38.27 (t), 74.91 (d), 75.71 (d), 169.85 (s). Anal. Calcd for C₂₄H₃₆O₃: C, 77.38; H, 9.57. Found: C, 77.21; H, 9.57.

Isomerically pure isomer, (9.6 mg, 48%), 31b, was obtained subsequently as a colorless microcrystalline solid: mp 195.5-196.5 °C; IR (KBr) 3548 (br m), 3464 (br m), 2896 (s), 2838 (m), 1734 (m), 1714 (m), 1437 (w), 1359 (w), 1230 (m), 1010 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.47-1.75 (m, 24 H), 1.90-2.02 (m, 6 H), 2.07 (s, 3 H), 3.32 (d, J = 7.2 Hz, 1 H), 4.62 (d, J = 7.1 Hz, 1 H); ¹³C NMR (CDCl₃) δ 21.60 (q), 28.34 (d), 37.06 (t), 37.20 (t), 37.80 (t), 38.17 (t), 77.57 (d),
80.76 (d), 170.5 (s); Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.57. Found: C, 77.54; H, 9.72.

1-({3',5'-dinitrobenzoyloxy})-2-acetoxy-1,2-di(1'-adamantyl)ethane (32a, 32b) To a solution of the mixture of 31a and 31b (50 mg, 0.13 mmol) in $CH_2Cl_2$ (3 mL) was added Et$_3$N (0.8 mL), 3,5-dinitrobenzyl chloride (80 mg, 0.41 mmol) and 1,4-dimethylaminopyridine (10 mg, catalytic amount) under argon at room temperature. The reaction mixture was stirred continuously for 20 h. After the reaction, $CH_2Cl_2$ (80 mL) was added, and the resulting mixture was washed sequentially with cold 3% aqueous HCl (20 mL) and water (2 x 30 mL). The organic layer was dried (MgSO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 2% EtOAc-hexanes, thereby affording isomerically pure 32a, (21 mg, 28%) as a colorless microcrystalline solid: mp 195.0-196 °C; IR (KBr) 3099 (w), 2908 (s), 2845 (m), 1733 (m), 1724 (m), 1621 (w), 1542 (s), 1455 (w), 1339 (m), 1276 (m), 1258 (m), 1239 (m), 1164 (m), 716 cm$^{-1}$ (m); $^1$H NMR ($CDCl_3$) $\delta$ 1.30-1.45 (m, 3 H), 1.45-1.74 (m, 11 H), 1.85-2.02 (m, 6 H), 2.26 (s, 3 H), 5.01 (s, 1 H), 5.08 (s, 1 H), 9.20-9.27 (m, 3 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.18 (q), 27.91 (d), 36.60 (t), 37.27 (s), 37.56 (s), 37.72 (t), 37.78 (t), 74.85 (d), 77.84 (d), 122.4 (d), 129.6 (d), 134.4 (s), 148.8 (s), 161.9 (s), 170.4 (s). Anal. Calcd for $C_{31}H_{38}N_2O_8$: C, 65.71; H, 6.76. Found: C, 65.75; H, 6.59.
Subsequently, isomerically pure 32b (30 mg, 40%) was obtained as a colorless microcrystalline solid; mp 170-171 °C; IR (KBr) 3101 (w), 2980 (w), 2906 (s), 2845 (m), 1733 (m), 1720 (s), 1625 (w), 1544 (m), 1450 (w), 1335 (s), 1268 (m), 1255 (m), 1228 (m), 1153 (m), 722 (w), 709 cm⁻¹ (m); ¹H NMR (CDCl₃) δ 1.40-1.86 (m, 24 H), 1.86-2.02 (m, 6 H), 2.16 (s, 3 H), 5.01 (AB, J_AB = 5.6 Hz, 1 H), 5.20 (AB, J_AB = 5.5 Hz, 1 H), 9.15-9.20 (m, 2 H), 9.22-9.27 (m, 1 H); ¹³C NMR (CDCl₃) δ 21.46 (q), 28.04 (d), 36.76 (t), 36.81 (t), 37.89 (t), 38.05 (t), 38.53 (s), 79.08 (d), 81.57 (d), 122.6 (d), 129.5 (d), 133.9 (s), 148.8 (s), 161.8 (s), 170.1 (s). Anal. Calcd for C₃₁H₅₈N₂O₈: C, 65.71; H, 6.76. Found: C, 65.79; H, 6.69.

Z-1,2-Di(1'-adamantyl)ethene (14) A mixture of diol (28a) (164 mg, 0.50 mmol), triethyl orthoformate (5 mL, excess) and benzoic acid (5 mg, catalytic amount) was heated at 165 °C for 3 h and then was allowed to cool gradually to room temperature. The reaction mixture was stirred with 10% aqueous Na₂CO₃ (10 mL) and then was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed sequentially with H₂O (20 mL) and brine (20 mL), dried (MgSO₄), and filtered. The filtrate was concentrated in vacuo, thereby affording 29 which is not stable (mixture of isomers, 179 mg, 94%); IR (Neat) 2896 (s), 2844 (m), 1172 (w), 1127 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.30 (t, J = 6.6 Hz, 3 H), 1.69 (br s, 12 H), 1.82 (br s, 12 H), 1.93-2.06 (m, 6 H), 3.98 (s, 2 H),
3.74 (q, \( J = 14.0, 6.6 \text{ Hz}, 2 \text{ H} \)), 5.60 (s, 1 H). This material was used as obtained in the next synthetic step without further purification.

The crude product was concentrated in vacuo to remove any remaining triethyl orthoformate, and the residue was heated under argon at 200 °C for 4 h. The reaction mixture was cooled to room temperature, and then was quenched by addition of 10% aqueous Na\(_2\)CO\(_3\) (30 mL). The resulting aqueous suspension was extracted with CH\(_2\)Cl\(_2\) (3 x 30 mL). The combined organic extracts were washed sequentially with H\(_2\)O (2 x 30 mL) and brine (30 mL), dried (MgSO\(_4\)), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with hexane. Pure 14 (133 mg, 90%) was thereby obtained as a colorless microcrystalline solid: mp 139.5-140.0 °C; IR (KBr) 2902 (s), 2894 (s), 2890 (s), 2843 (m), 1442 (w), 1335 cm\(^{-1}\) (w); \(^1^H\) NMR (CDCl\(_3\)) \( \delta \): 1.62-1.72 (m, 12 H), 1.75-1.82 (m, 12 H), 1.95 (br s, 6 H), 4.95 (s, \( 3J_{HH} = 13.9 \text{ Hz}, 2 \text{ H} \)); \(^1^3^C\) NMR (CDCl\(_3\)) \( \delta \): 28.92 (d), 35.11 (s), 36.74 (t), 44.00 (t), 140.4 (d). Anal. Calcd for C\(_{22}\)H\(_{32}\): C, 89.12; H, 10.88. Found: C, 88.88; H, 10.86.

E-1,2-Di(1'-adamantyl)ethene (15)\(^{26}\) To a solution of 14 (120 mg, 0.40 mmol) in xylene (8 mL) was added a few crystals of I\(_2\) (catalytic amount), and the resulting mixture was refluxed for 24 h. The reaction mixture was cooled and concentrated in vacuo. Hexane (50 mL) was added to the
residue, and the resulting mixture was washed sequentially with saturated Na$_2$S$_2$O$_3$ (3 x 30 mL) and H$_2$O (2 x 30 mL), dried (MgSO$_4$), and filtered. The filtrate was concentrated in vacuo, thereby affording 15 (120 mg, 100%) as a colorless microcrystalline solid: mp >278 °C dec. (lit. mp: >260 °C sublimed); IR (KBr) 2906 (s), 2844 (m), 1448 (w), 1342 (w), 1305 (w), 1092 (w), 969 cm$^{-1}$ (w); $^1$H NMR (CDCl$_3$) $\delta$ 1.49-1.55 (m, 13 H), 1.58 (t, $J = 3.2$ Hz, 1 H), 1.62-1.72 (m, 9 H), 1.74 (t, $J = 3.2$ Hz, 1 H), 1.96 (br s, 6 H), 5.10 (s, $^3J_{HH'} = 16.1$ Hz, 2 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 28.68 (d), 34.12 (s), 37.03 (t), 42.73 (t), 136.3 (d). Anal. Calcd for C$_{22}$H$_{32}$: C, 89.12; H, 10.88. Found: C, 89.08; H, 10.63.

(2-Phenylethyl)triphenylphosphonium Bromide (35)

A mixture of 1-bromo-2-phenylethane (10 g, 54 mmol) and triphenylphosphine (19.8 g, 75.6 mmol) in xylene (150 mL) was refluxed under argon for 24 h. The reaction mixture was cooled to ca. 60 °C and then was concentrated in vacuo, thereby affording PhCH$_2$CH$_2$PPh$_3^+$Br$^-$ (35) (23.7 g, 98.1%) as a colorless microcrystalline solid: mp >300 °C. This material was used as obtained in the next synthetic step.

Z- and E-Benzylmethylenepentacyclo[5.4.0.2,6.0$^3$,10.0$^5$,9]undecanes (37a, 37b)

A mixture of phosphonium salt 35 (12 g, 5.88 mmol) in dry THF (200 mL) under argon was cooled to 0°C via application of an external ice bath. To the cooled mixture was added n-BuLi (10 mL of a
2.5 M solution in hexane, 25 mmol) slowly with stirring; a deep red color appeared slowly thereafter. The reaction mixture was stirred at 0 °C for 30 minutes after all of the n-BuLi had been added, at which time a solution of pentacyclo[5.4.0.02,6.03,10.05,9]undecane-8-one (36) (3.2 g, 20 mmol) in dry THF (30 mL) was added dropwise. After stirring for 1 h at 0 °C, the extra cold bath was removed, and the reaction mixture was allowed to warm gradually to room temperature with continuous stirring during 1 h. The reaction mixture was concentrated in vacuo, and CH₂Cl₂ (150 mL) was added to the residue. The resulting mixture was washed with water (3 x 50 mL), dried (MgSO₄), filtered, and the filtrate was concentrated in vacuo. The oily residue (2.3 g, 46.8%) was purified via column chromatography on silica gel by eluting with hexane. A mixture of 37a and 37b (ratio 1:2.5 or 2.5:1 which was calculated by the integration of benzylic hydrogens of 37a and 37b) was thereby obtained. This material was used as obtained in the next synthetic step.

**E-1-(exo-8'-pentacyclo[5.4.0.02,6.03,10.05,9]undecyl)-2-phenylethylene (16a)** To a solution of 37a and 37b (980 mg, 3.94 mmol) in dimethyl sulfoxide (DMSO, 10 mL) was added freshly sublimed KOT-Bu (500 mg, 4.46 mmol), and the resulting mixture was stirred under argon at 60 °C for 4 days. The reaction mixture was quenched via addition of H₂O.
(40 mL). The resulting suspension was extracted with CH$_2$Cl$_2$ (3 x 80 mL), and the combined organic layers were dried (MgSO$_4$), and filtered. The filtrate was concentrated in vacuo to afford 16a as a colorless waxy solid (705 mg, 72%): mp 56-57 °C; IR (film) 2942 (s), 2856 (m), 1304 (w), 1276 (w), 745 (w), 694 cm$^{-1}$ (w); $^1$H NMR (CDCl$_3$) $\delta$ 1.08 (dt, $J =$ 10.0, 3.4 Hz, 1 H), 1.24-1.36 (m, 1 H), 1.57-1.73 (m, 2 H), 2.16-2.40 (m, 3 H), 2.42-2.46 (m, 1 H), 2.52 (AB, $J_{AB} =$ 7.0 Hz, 1 H), 2.54-2.70 (m, 4 H), 6.02 (AB, $J_{AB} =$ 16.0, 7.0 Hz, 1 H), 6.28 (AB, $J_{AB} =$ 16.0, 1 H), 7.14-7.45 (m, 5 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 27.09 (t), 33.47 (t), 35.99 (d), 40.69 (d), 41.6 (d), 42.19 (d), 42.72 (d), 42.93 (d), 43.98 (d), 45.50 (d), 47.61 (d), 125.8 (d), 126.6 (d), 128.4 (d), 133.7 (d), 138.0 (s). Anal. Calcd for C$_{19}$H$_{20}$: C, 91.88; H, 8.12. Found: C, 91.56; H, 7.78.
REFERENCES


23. All single-crystal X-ray structures presented here were provided by Professor Simon G. Bott. We thank Professor Bott for having kindly provided this information.


29. These data and figures were kindly provided by Professor Michael Barfield (University of Arizona). We thank Professor Barfield for having provided this information.


34. Calculation of MMX-minimized structures of 16a and 16c: PCMODEL, version 4.51, Serena Software, Box 3076, Bloomington, IN 47402-3076.34

35. All calculations presented here were performed on a Macintosh IIci personal computer provided by Professor Alan P., Marchand. I thank Professor Marchand for having kindly provided this information.

36. MOPAC, version 6.0 Quantum Chemistry Program Exchange (QCPE), Program Number 455, 1990.34

37. Chem3D Plus™, version 3.0, 1991; Cambridge Scientific Computing, 875 Massachusetts Avenue, Suite 61, Cambridge, MA 02139.34

Figure 2-1. $^1$H NMR Spectrum of 27.
Figure 2.3. IH NMR Spectrum of 28a.
Figure 2-4. $^{13}$C and APT NMR Spectra of 28a.
Figure 2.5. 1H NMR Spectrum of 30.
Figure 2.7: Drawing of X-ray crystal structure of 30.
Figure 2.8. $^1$H NMR Spectrum of 31a and 31b.
Figure 2-9. $^{13}$C and APT NMR Spectra of 31a and 31b.
Figure 2-10. $^1$H NMR Spectrum of 32a.
Figure 2-12. $^1$H NMR Spectrum of 32b.
Figure 2-14, Drawing of X-ray crystal structure of 32a.
Figure 2.15. $^1$H NMR Spectrum of 29.
Figure 2-16. $^1$H NMR Spectrum of 14.
Figure 2.19. $^1$H NMR Spectrum of 15.
Figure 2-22. Corresponding drawing of the $\theta_1$ & $\theta_2$ calculation for 14.
Figure 2-24. $^1$H NMR Spectrum of 16a.
Figure 2-27. Corresponding drawing of the MMXE calculation for 16a.
Figure 2-28. Corresponding drawing of the MMXE calculation for 16c.
Figure 2-30. Corresponding drawing of the dihedral angle calculation for 16c.
Figure 2-31. Corresponding drawing of the coupling constant calculation for 16a.
Figure 2-32. Corresponding drawing of the coupling constant calculation for 16c.
CHAPTER III

ELECTROPHILIC ADDITION REACTIONS OF Z- AND E-1,2-DI(1'-ADAMANTYL)ETHENES

Introduction

As mentioned in Chapter II, sterically crowded alkenes have attracted considerable interest because of the possibility that significant nonbonded interactions among bulky substituent groups may produce structural distortions about the double bond. Such "distorted" alkenes frequently display unusual chemical and physical properties when compared with 'normal' alkenes.

Electrophilic additions to strained alkenes are very useful tools with which the effects of structure on chemical properties can be investigated. The nature of the intermediate complexes that results via electrophilic additions to alkenes is of substantial interest. In general, it is believed that the electron donor π bond first interacts with electrophiles, thereby forming a two-electron three-center bonded alkonium ion (π complex) which subsequently opens to the corresponding σ complex (alkenium ion).

Much work has been done in this field. Brooks and co-workers investigated the chemistry and structure of anti-(Z)- and syn-(E)-bis(fenchylidene), 1a and 1b, respectively.
They found that the chemical behavior of 1a and 1b was affected by steric strain. Bromination of 1a afforded 3 (15%) along with 50% recovered 1a. The corresponding bromine addition product was not formed. It was suggested that intermediate 2 was formed and then subsequently rearranged to form 3, since backside attack by a nucleophile upon a C-Br bond in bromonium ion 2 is extremely hindered. In comparison, the C=C double bond in 1b is even more highly sterically hindered; no product could be isolated from the reaction of 1b with bromine.

Brown and co-workers investigated electrophilic bromination of adamantylideneadamantane (4), whose carbon-
carbon double bond is also highly sterically congested (Scheme 2).³ X-ray crystallographic data were obtained for bromonium ion 5, which established for the first time the detailed structure of a three-membered bromonium ion. The X-ray structure of 5 indicates that it is severely sterically hindered at the side opposite to the C-Br bonds, thereby effectively impeding access by a nucleophile. Admittedly, 5 is derived from a unique olefin; thus, electrophilic addition of Br₂ to the carbon-carbon double bond in 4 proceeds only partway along the "normal" reaction pathway which is accessible to unhindered olefins.

Several groups have been involved in stereochemical studies of electrophilic homoallylic chlorinations of sterically congested alkene 4 with PhSCl,⁴ PhSeCl,⁵ and NCS (N-chlorosuccinimide).⁶ These reactions yielded homoallylic chlorination product, 9, instead of the normal addition products (see Scheme 3). Bennet and co-workers investigated
the mechanism of electrophilic homoallylic chlorinations of 4 with PhSCl. They isolated an intermediate sulfonium ion, 6, and suggested a possible reaction pathway which leads to the homoallylic substitution product 9 (Scheme 3). They further investigated the corresponding reaction by using the sterically congested (1R', 4R')-4-methyl-2-(tricyclo-[3.3.1.1^3,7;decylidene]tricyclo[3.3.1.1^3,7]decane (10) as substrate. This reaction also proceeds stereospecifically; chlorine substitution occurs on the face of the alkene.
opposite to that at which the initial electrophilic attack took place (Scheme 4). The regioselectivity of this reaction is controlled by the sterically-driven ring opening of the intermediate thiiranium ion.

Scheme 4

In order to study the effects of the structures of 2- and E-1,2-di(1'-adamantyl)ethenes (i.e., 14 and 15, respectively) on their chemical reactivities, several electrophilic addition reactions were carried out by using dichlorocarbene (\(:\text{CCl}_2\) ), phenylsulfenyl chloride (PhSCl), and bromine (Br\(_2\)) as the electrophilic reagents.
Results and Discussion

Dichlorocarbene Additions to Z- and E-1,2-di(1'-adamantyl)ethenes (14 and 15) Dichlorocarbene is highly reactive and generally adds smoothly to the carbon-carbon double bond in alkenes. In the present study, Z- and E-1,2-di(1'-adamantyl)ethene (14 and 15) were treated with dichlorocarbene which was generated via reaction of chloroform with base in the presence of benzyltriethylammonium chloride (TEBAC, a phase transfer catalyst). In both reactions, the starting materials (14 and 15) were recovered along with products that resulted via C-H insertion by :CCl₂ and/or skeletal rearrangement (see Scheme 5). These results are very unusual, since no carbon-carbon double bond addition products were found to have been formed directly.

In the case of the Z-alkene (14), the resulting products are Z-1-[1'-{(3'-dichloromethyl)adamantyl}]2-(1'-adamantyl)-ethene (16a), Z-1,3-di(1'-adamantyl)-2,3-dichloro-1-propene (16b), 1-(1'-adamantyl)-2,2,3-trichloro-3-[(1'-adamantyl)-chloromethyl]cyclopropane (16c). Compound 16a resulted via direct insertion of :CCl₂ into a tertiary C-H in one of the adamantyl moieties in 14. The ¹H and ¹³C NMR spectra of 16a are shown in Figures 3-1 and 3-2, respectively. Integration of the proton NMR spectrum of 16a indicates the presence of 29 protons in the aliphatic range. The singlet peak at δ 4.99 corresponds to two vinyl protons. The singlet at δ 5.43 corresponds to the CHCl₂ proton in the insertion
Scheme 5

14 (20%)

\[ \text{CHCl}_3, 50 \text{ % aq. NaOH} \]

TEBACl, 45 °C, 8 h

16a (27%)

16b (20%)

16c (21%)

15 (60.8%)

\[ \text{CHCl}_2 + \]

\[ \text{CHCl}_2 \]

17a (33.6%)

17b (5.1%)

\[ \text{CHCl}_2 \]
product. In the $^{13}$C NMR spectrum, there are 11 peaks which appear in the aliphatic range, and a peak at δ 83.73 which corresponds to the CHCl$_2$ carbon atom in the insertion product. The peaks at δ 138.6 and 141.4 correspond to the vinyl C=C carbon atoms in 16a. Both the $^1$H and $^{13}$C NMR spectra are consistent with the suggested structure of 16a. The structure of 16a was further confirmed via single crystal X-ray structural analysis (see figure 4-3).

Typically, :CCl$_2$ adds to the carbon-carbon double bond in alkenes to form the corresponding gem-dichlorocyclopropenes. Although :CCl$_2$ has previously been reported to insert into C-H bonds, this nevertheless is an unusual reaction, particularly when there is a carbon-carbon double bond present in the substrate.

Compound 16b, a rearrangement product, was identified via analysis of its $^1$H and $^{13}$C NMR spectra (Figures 3-4 and 3-5, respectively). Integration of the proton NMR spectrum of 16b indicates the presence of 30 protons in the aliphatic range. The singlet at δ 4.07 corresponds to a CHCl proton. The singlet at δ 5.50 corresponds to one vinyl proton in 16b. The $^{13}$C NMR spectrum of 16b contains 8 aliphatic carbons. The peak at δ 77.78 corresponds to the CHCl carbon atom. The peaks at δ 128.9 and 139.9 corresponds to vinyl carbon atoms. Both $^1$H and $^{13}$C NMR spectra correspond to the assigned structure for 16b. This structure received unequivocal
conformation via single-crystal X-ray structural analysis of 16b (see Figure 3-6). A reasonable mechanism which accounts for the formation of 16b in this reaction is shown in Scheme 6. First, it is suggested that the expected product, 18, was formed via addition of :CCl₂ to the carbon-carbon double bond in 14. Subsequent solvolytic ring opening of 18, a two-electron disrotatory electrocyclic process, afforded intermediate 19 as an ion pair. Finally, ion pair 19 recombines rapidly to afford the final product, 16b. The fact that 16a and 16b are formed in this reaction indicates
that carbene C-H insertion competing effectively with electrophilic addition of :CCl₂ to 14. The latter reaction occurs faster than does the former one.

Compound 16c results via reaction of two equivalents of :CCl₂ with 14. Its structure was determined via analysis of its one- and two-dimensional ¹H and ¹³C NMR spectra (Figures 3-3, 3-6, and 3-3). Integration of the proton NMR spectrum of 16c indicates the presence of 31 aliphatic protons. One of these peaks is a singlet at δ 1.55, which corresponds to the cyclopropyl proton in 16c. The peak at δ 3.58 corresponds to the CHCl proton in 16c. The proton noise-decoupled ¹³C NMR spectrum of 16c indicates the presence of 12 nonequivalent carbon atoms. No vinyl carbon resonances appear therein. The doublet at δ 51.93 in the APT ¹³C NMR spectrum of 16c corresponds to the C-1 carbon atom. The singlet at δ 57.68 corresponds to carbon atom C-3, while that which occurs at δ 66.93 corresponds to carbon atom C-2. The doublet at δ 78.72 corresponds to carbon atom C-4. Both the ¹H and ¹³C NMR spectra are consistent with the assigned structure of 16c. Some ¹³C chemical shift data of chloro- and alkyl-substituted cyclopropanes are listed in Table 3-1. These data indicate that the chemical shifts of carbon atoms in the cyclopropane derivatives vary with different substituents. For -CCl₂ carbon atoms in the cycloproparyl ring in compounds a - c, the chemical shifts vary from δ 67.75 to 72.50; the corresponding chemical shift (δ 66.93)
<table>
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<th>Compound</th>
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<th>data about carbon atom</th>
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<td></td>
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<td>26.95 67.75 32.90</td>
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<td>-t-Bu -Cl -CH₃</td>
<td>49.50 72.00 29.80</td>
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<tr>
<td>d</td>
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</tr>
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</tr>
<tr>
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<td>8.90 8.90 27.30</td>
</tr>
<tr>
<td></td>
<td>-H -H -H</td>
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</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>-H -Cl -CHCl-1-Ad</td>
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</tr>
</tbody>
</table>

a. All data presented here except 16c were obtained from ref.11.

for the -CCl₂ carbon atom in the cyclopropane ring in 16c lies in this range. For -CCl carbon atoms in the cyclopropane ring in compounds d and e, the chemical shifts vary from δ 27.30 to 44.75 due to the different environment
of these carbon atoms. The corresponding chemical shift for the -CCl carbon atom in the cyclopropane ring in 16c is δ 57.68. It seems likely that the -CCl carbon atom in the cyclopropane ring in 16c has two neighboring chlorines and also has a bulky Ad group nearby, so that the 13C resonance of the CCl group is shifted downfield (see data for compounds b and c). For -CHR carbon atoms in the cyclopropane ring in compounds b and c, the chemical shifts vary from δ 33.10 to 49.50; the corresponding chemical shift (δ 51.91) for the -CHR carbon atom in the cyclopropane ring in 16c lies approximately in this range. Thus, the 13C chemical shifts of the cyclopropane carbon atoms in 16c appear to be consistent with the data shown in Table 3-1.

In order to confirm the assigned structure of 16c, an inverse gated-decoupled 13C NMR spectrum12 of 16c was obtained (Figure 3-10). The 1JCH coupling constant between C-1 and H-1 in 16c is 152 Hz. The range of 1JCH coupling constants of carbon atoms in cyclopropanes lies between 155 and 163 Hz for pure hydrocarbons.11 This value differs significantly from those of normal sp3 hybridized carbon atoms (which display coupling constants between 124 and 129 Hz).11 Therefore, we conclude that the 1JCH value between C-1 and H-1 in 16c consistent with the assigned structure for 16c.

The structure of 16c was further confirmed via the results of a two-dimensional NMR study (see Figure 3-9). For
the protons H-1 and H-2 in 16c, the 2D HETCOR\textsuperscript{11} NMR spectrum shows a existence of a correlation between C-1 and H-1, thereby confirming that the chemical shift at $\delta$ 51.93 corresponds to carbon atom C-1. Similarly, the observed correlation between C-4 and H-4 confirms that the chemical shift at $\delta$ 78.72 corresponds to carbon atom C-4.

A plausible mechanism which accounts for the formation of 16c in this reaction is shown in Scheme 7. It seems likely that the C=C double bond in 16b is much less hindered than that in 14 (see the single-crystal X-ray structures of 14 and 16b in Figures 2-18 and 3-6, respectively). Therefore, reaction of 16b with :CCl\textsubscript{2} can proceed in the manner shown in Scheme 7 to afford 16c.

For the corresponding E-alkene (15), reaction with :CCl\textsubscript{2} afforded mainly unreacted starting material along with two products, E-1-[1'-{(3')-dichloromethyl}adamantyl]-2-(1'- adamantyl)ethene (17a) and E-1,2-di[1'-{(3')-dichloromethyl}- adamantyl]ethene (17b) (see Scheme 5).

Compound 17a results via C-H insertion of :CCl\textsubscript{2} with 15. Its structure was determined via analysis of its one- and two-dimensional $^1$H and $^{13}$C NMR spectra (Figures 3-11, 3-12, and 3-13). Integration of the proton NMR spectrum of 17a indicates the presence of 29 aliphatic protons. There are two singlets which appear in the olefinic range. One of them occurs at $\delta$ 5.13, which correspond to two olefinic hydrogens, H-1 and H-2, in 17a. The remaining vinyl proton resonance at
Scheme 7

$\delta$ 5.42 corresponds to the CHCl$_2$ proton in 17a.

The proton noise-decoupled $^{13}$C NMR spectrum contains 11 peaks in the aliphatic region, as expected. The doublet at $\delta$ 83.76 correspond to carbon atom C-3; the remaining two doublets at $\delta$ 134.8 and 137.3 correspond to the vinyl carbon atoms, C-1 and C-2. Both $^1$H and $^{13}$C NMR spectra are consistent with the assigned structure for 17a.

The structure of 17a was further confirmed via analysis of its 2D HETCOR NMR spectrum (see Figure 3-13). The 2D HETCOR NMR spectrum shows the existence of correlations between C-1 and H-1 and between C-2 and H-2. This observation confirms that the proton signal at $\delta$ 5.13
corresponds to the vinyl proton in 17a. Similarly, the existence of the correlation between C-3 and H-3 confirms that the proton signal at 6 5.42 corresponds to the CHCl₂ proton in 17a.

Compound 17b arises via direct insertion of :CCl₂ into a tertiary C-H in each of the two adamantyl moieties in 15. The ¹H and ¹³C NMR spectra of 17b are shown in Figures 3-14 and 3-15, respectively. Integration of the proton NMR spectrum shows 28 protons in the aliphatic region. There are two singlets in the olefinic region. The signal at 6 5.19 corresponds to the two vinyl protons in 17b. The remaining signal at 6 5.43 corresponds to the two CHCl₂ protons in 17a.

In the ¹³C NMR spectrum, there are seven peaks which appear in the aliphatic region. The peak at 6 83.73 corresponds to the CHCl₂ carbon atom in 17b, while the signal at 6 135.8 corresponds to the vinyl carbon atoms in this product. Both ¹H and ¹³C NMR spectra are consistent with the assigned structure for 17b. The structure of 17b was confirmed unequivocally via single-crystal X-ray structural analysis (see Figure 3-16).⁸

Products 17a and 17b resulted via insertion of :CCl₂ into a tertiary C-H bond in one or both of the adamantyl moieties in 15. Interestingly, no products were obtained that might have been derived via addition of :CCl₂ to the carbon-carbon double bond in 15. It seems likely that the adamantyl groups sterically hinder approach by an
electrophile, thereby limiting accessibility and effectively shielding the C=C double bond in 15 from attack by :CCl₂.

Compared with the corresponding Z-isomer (14), the double bond in E-isomer 15 is clearly less reactive. This appears to result from the decreased steric accessibility toward electrophiles of the C=C double bond in 15 as compared with the corresponding situation in 14.

Phenylsulfinyl Chloride (PhSCl) Additions to Z- and E-1,2-di(1'-adamantyl)ethenes (14 and 15) The reactions of 14 and 15 with PhSCl proceeded in strikingly different fashion. Thus, 14 reacted with PhSCl which was generated in situ via the reaction of PhSSPh with SO₂Cl₂ in CH₂Cl₂ under argon at -78 °C. This reaction produced the corresponding trans-addition product, 20, with high stereoselectivity (see Scheme 8). The structure of 20 was identified via analysis of its ¹H and ¹³C NMR spectra (see Figures 3-17 and 3-18.

Scheme 8
respectively). Integration of the $^1$H NMR spectrum of 20 revealed the presence of 30 aliphatic protons. The two singlets at $\delta$ 3.51 and 4.08 correspond to the CH$_2$Ph and CHCl protons, respectively. The aromatic region of the $^1$H NMR spectrum of 20 contains signals that correspond to the five phenyl group protons. The corresponding proton noise-decoupled $^{13}$C NMR spectrum contains eight signals which correspond to the carbon atoms in two adamantyl groups in 20. The peak at $\delta$ 56.91 corresponds to the CH$_2$Ph carbon atom, and the signal at $\delta$ 71.01 corresponds to the CHCl carbon atom in 20. There are four peaks in aromatic region which corresponds to the phenyl group carbon atoms in 20. The structure of 20 was confirmed unequivocally via single crystal X-ray structural analysis (Figure 3-19).

Generally, the mechanism proposed for the addition of arenesulfonyl chloride to alkenes is believed to involve rate-determining formation (eq. 1) of an episulfonium ion which is subsequently attacked by chloride ion in the product-determining step, thereby affording the corresponding trans addition product (eq. 2). A plausible mechanism for the formation of 20 which accounts for the observed trans stereoselectivity of PhSCl addition to 14 is shown in Scheme 9. An episulfonium ion 21 is formed initially via reaction of PhSCl with 14, followed by backside nucleophilic attack on the episulfonium ion ring in 21 by chloride ion to afford the
Scheme 9

Scheme 10
The corresponding reaction of PhSCl with 15 afforded the corresponding meso dichloride, 22 (see Scheme 10), which was characterized via analysis of its $^1$H and $^{13}$C NMR spectra (see Figures 3-20 and 3-21, respectively). Integration of the $^1$H NMR spectrum of 22 revealed the presence of 30 aliphatic protons which correspond to the protons of adamantyl groups in 22. The singlet at $\delta$ 4.03 corresponds to the CHCl protons. The corresponding proton noise-decoupled $^{13}$C NMR spectrum contains four signals which correspond to the carbon atoms in two adamantyl groups in 22. The peak at $\delta$ 74.23 corresponds to the CHCl carbon atoms. The structure of 22 was confirmed unequivocally via single-crystal X-ray structural analysis (Figure 3-22).§

Interestingly, no products were obtained that might have been derived via addition of PhSCl to the carbon-carbon double bond in 15. The reason may be due to the fact that bulky adamantyl groups block access of PhSCl to the C=C double bond, thereby inhibiting approach by PhS$.\text{^+}$. In contrast to this result, PhSCl can readily access the C=C double bond in 14 from the less hindered face (see Scheme 11). However, in the case of the Z-alkene (15), both faces of the C=C double bond are sterically blocked by the bulky adamantyl groups. By analogy to the results of a closely related study,4-7 a mechanism which accounts for the formation of 22 via the reaction of 15 with PhSCl is suggested in
Scheme 11

PhSCl (less hindered face) → \(-X^-\) PhSCl (highly hindered face)

14

PhSCl → \(-X^-\) PhSCl (highly hindered face)

15

Scheme 12

\[ \text{Cl}^- + \text{PhSSPh} \rightarrow \text{PhSSPh}^- \]

15

Cl-SPh

PhS-Cl

22

23

Scheme 12. Since Cl\(^+\) is smaller than PhS\(^+\), it seems reasonable to suggest that two equivalents of PhSCl can react with the C=\(\text{C}\) moiety in 15 in the manner shown in Scheme 12. A chlonium ion, 23, is thereby obtained, which subsequently suffers backside nucleophilic attack by Cl\(^-\) to afford the
Brominations of Z- and E-1,2-di(1'-adamantyl)ethenes (14 and 15). Bromination of 14 in CCl₄ at -15 °C occurred very rapidly (Scheme 13), as judged by the fact that bromine was
decolorized immediately upon addition to the substrate. The structure of the resulting product, 24, was determined via analysis of its ¹H and ¹³C NMR spectra (see Figures 3-23 and 3-24, respectively). Integration of the ¹H NMR spectrum of 24 revealed the presence of 30 aliphatic protons. The
singlet at $\delta$ 4.16 corresponds to the CHBr protons. The corresponding proton noise-decoupled $^{13}$C NMR spectrum displays only five signals, four of which correspond to the adamantyl carbon atoms in 24. The peak at $\delta$ 77.21 is assigned to the CHBr carbon atoms in 24. Both the $^1$H and $^{13}$C NMR spectra are consistent with the assigned structure for 24.

Bromination of 15 was carried out under the same conditions as described above for the corresponding bromination of 14 (Scheme 9). The structure of the product, 26, was determined via analysis of its $^1$H and $^{13}$C NMR spectra (see Figures 3-25 and 3-26, respectively). Integration of the $^1$H NMR spectrum of 26 revealed the presence of 30 aliphatic protons. The singlet at $\delta$ 4.43 corresponds to the CHBr protons. The corresponding proton noise-decoupled $^{13}$C NMR spectrum displays only five signals, four of which correspond to the adamantyl carbon atoms in 26. The signal at $\delta$ 69.65 is assigned to the CHBr carbon atoms in 26.

The mechanism and theory of bromination of olefins appear to be well-understood. As early as 1937, Roberts and Kimball explained the anti selectivity of bromination of olefins by invoking a bridged bromonium ion as intermediate. More recently, the bromonium ion which results via addition of bromine to adamantylideneadamantane has been isolated as a stable perbromide salt and its structure was established via X-ray crystal structural analysis. Here, subsequent nucleophilic attack of the counter ion is prevented by steric
hindrance in the bromonium ion.\textsuperscript{3} It is generally accepted that a \( \pi \) complex precedes formation of such halonium ions, and it is supposed that cation-stabilizing substituents (e.g., phenyl) at the olefin lead to distorted or even nonbridged cations (Scheme 14).\textsuperscript{15}

\textbf{Scheme 14}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\( + \)};
\node (b) at (1,0) {\( X_2 \)};
\node (c) at (2,0) {\( \Rightarrow \)};
\node (d) at (3,0) {\( \pi \text{ complex} \)};
\node (e) at (4,0) {\( \Rightarrow \)};
\node (f) at (5,0) {\( X^- \)};
\node (g) at (6,0) {\( + \)};
\node (h) at (7,0) {\( X_2 \)};
\node (i) at (8,0) {\( \Rightarrow \)};
\node (j) at (9,0) {\( \text{halonium ion} \)};
\node (k) at (10,0) {\( \Rightarrow \)};
\node (l) at (11,0) {\( \text{nonbridged cation} \)};
\end{tikzpicture}
\end{center}

In the present case, when comparing the \( ^1H \) and \( ^{13}C \) NMR spectra of the dibromides, 24 and 26, it should be noted that they have the same number of peaks in their respective \( ^{13}C \) NMR spectra; however, the chemical shifts for the CHBr protons are different. A plausible mechanism that accounts for the formation of 24 and 26 from 14 and 15, respectively, is shown in Scheme 15. Bromine reacts with 14 and 15 to afford the corresponding bromonium ions, i.e., 25 and 27, respectively.
Subsequent nucleophilic attack by Br⁻ on these intermediate bromonium ions occurs, thereby affording d,l- and meso-dibromide compounds, 25 and 27, respectively.

Scheme 15

The reaction of 15 with bromine occurs more slowly than does the corresponding reaction of 14. After the bromine was added, the color persisted for more than 1 h. This result can be explained by the same steric effect which was discussed earlier (see Scheme 11). The C=C double bond in 14 is less hindered than is that in 15. In addition, enhanced steric repulsion in the intermediate 25 which is formed via
reaction of 14 with Br⁺ will force the strained three-membered ring in 25 to open rapidly, thereby releasing steric strain in the intermediate 25. For these reactions, bromination of 14 occurs more rapidly than does the corresponding process in 15.

Summary and Conclusion

Electrophilic additions of :CCl₂, PhSCl, and Br₂ to Z- and E-1,2-di(1'-adamantyl)ethenes (14 and 15, respectively) have been investigated. (i) The reaction of :CCl₂ with 14 affords products (16a, 16b, and 16c) that result either via insertion of :CCl₂ into a tertiary C-H bond in one of the adamantyl moieties in the substrate or via addition of :CCl₂ to the C=C double bond in the substrate followed by skeletal rearrangement of the intermediate adduct (a substituted gem-dichlorocyclopropane). Addition of :CCl₂ to the C=C double bond in 16b afford a saturated product, 16c. The corresponding reaction of 15 affords only C-H insertion products (17a and 17b). The structures of 16a, 16b, and 17b were identified unequivocally via single-crystal X-ray structural analysis. The structures of 16c and 17a were determined via analysis of their respective one- or two-dimensional ²H and ¹³C NMR spectra. (ii) The reaction of PhSCl with 14 afforded the corresponding trans addition product 20 stereospecifically. The structure of 20 was established unequivocally via single crystal X-ray structural analysis.
Reaction of PhSCl with 15 afforded meso-1,2-dichloro-1,2-di(1′-adamantyl)ethane 22. The structure of 22 also was established unequivocally via single crystal X-ray structural analysis. (iii) Brominations of 14 and 15 afforded d,l- and meso-dibromo-1,2-di(1′-adamantyl)ethanes, 24 and 26, respectively. The structures of 24 and 26 were determined via analysis of their respective ¹H and ¹³C NMR spectra.

Experimental Section

Melting points are uncorrected and uncalibrated. Elemental microanalysis were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

Dichlorocarbene Addition of Z-1,2-Di(1′-adamantyl)-ethene (14) To a stirred solution of 14 (200 mg, 0.67 mmol) in CHCl₃ (40 mL) was added sequentially benzyltriethylammonium chloride (80 mg, 0.35 mmol) and 50% aqueous NaOH (16 mL, large excess) was added. The reaction mixture was heated to 45 °C in an oil bath for 8 h. The reaction mixture then was allowed to cool to ambient temperature. Water (200 mL) was added, and the aqueous layer was washed with CHCl₃ (3 x 60 mL). The combined organic layers were washed sequentially with 1% aqueous HCl (50 mL), water (2 x 200 mL), and brine (200 mL), dried (MgSO₄), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with pentane, thereby
affording starting material (14) (40 mg, 20.0%), followed by
16a (70 mg, 27%) as a colorless microcrystalline solid: mp
100.5-101.5 °C; IR (nujol) 2942 (vs), 2896 (s), 2856 (vs),
1458 (m), 1452 (m), 1378; ^H NMR (CDCl3) δ 1.50-1.82 (m, 25
H), 1.90-2.00 (3 H), 2.08-2.18 (m, 2 H), 4.98 (s, 2 H), 5.43
(s, 1 H); ^13C NMR (CDCl3) δ 28.75 (d), 28.89 (d), 35.25 (s),
35.56 (s), 35.62 (t), 36.70 (t), 41.89 (s), 43.02 (t), 43.54
(t), 44.00 (t), 83.73 (d), 138.6 (d), 141.4 (d). Anal. Calcd
for C23H32Cl2: C, 72.81; H, 8.50. Found: C, 72.61; H, 8.38.
The structure of 16a was characterized unequivocally via
single-crystal X-ray structural analysis.8

Continued elution of the chromatography column with
pentane afforded 16b (50 mg, 20%) as a colorless
microcrystalline solid: mp 138-139 °C; IR (nujol) 2929 (vs),
2856 (s), 1458 (m), 1452 (m), 1378 cm⁻¹ (w); ^H NMR (CDCl3) δ
1.50-1.74 (m, 16 H), 1.74-1.88 (m, 3 H), 1.88-2.07 (m, 11 H),
4.03 (s, 1 H), 5.48 (s, 1 H); ^13C NMR (CDCl3) δ 28.50 (d),
28.55 (d), 35.48 (s), 36.75 (t), 38.24 (s), 39.46 (t), 40.98
(t), 77.76 (d), 128.9 (s), 139.9 (d). Anal. Calcd for
C23H32Cl2: C, 72.81; H, 8.50. Found: C, 72.79; H, 8.35. The
structure of 16b was characterized unequivocally via single-
crystal X-ray structural analysis.8

Finally, 16c (64 mg, 21%) was eluted from the column as
a colorless microcrystalline solid: mp 196-197 °C; IR (nujol)
2922 (vs), 2856 (s), 1458 (m), 1452 (m), 1378 cm⁻¹ (w); ^H NMR
(CDCl3) δ 1.51 (s, 1 H), 1.64-1.74 (m, 13 H), 1.74-1.82 (m, 2
H), 1.91-2.08 (m, 15 H), 3.58 (s, 1 H); $^{13}$C NMR (CDCl$_3$) $\delta$
28.38 (d), 28.57 (d), 36.68 (t), 38.47 (s), 39.94 (s), 40.25 (t), 41.39 (t), 51.91 (d), 57.68 (s), 66.93 (s), 78.72 (d).

Anal. Calcd for C$_{24}$H$_{32}$Cl$_4$: C, 62.35; H, 6.98. Found: C, 62.35; H, 6.97. The structure of 16c was determined via analysis of its $^1$H, $^{13}$C, and 2D HETCOR NMR spectra.

Dichlorocarbene Addition of E-1,2-Di(1'-adamantyl)-ethene (15) To a stirred solution of 15 (150 mg, 0.51 mmol) in CHCl$_3$ (30 mL) was added sequentially benzyltriethylammonium chloride (TEBAC, 60 mg, 0.26 mmol) and 50% NaOH solution (12 mL, large excess). The reaction mixture was heated to 45 °C in an oil bath for 8 h. The reaction mixture was allowed to cool to ambient temperature. Water (150 mL) was added, and the aqueous layer was washed with CHCl$_3$ (3 x 40 mL). The combined organic layers were washed sequentially with 1% HCl (30 mL), water (2 x 150 mL) and brine (150 mL), dried (MgSO$_4$), and filtered. The filtrate was concentrated in vacuo; the residue thereby obtained was purified via column chromatography on silica gel by eluting with pentane. Starting material (15, 92 mg, 60.8%) was collected, followed by 17a (65 mg, 33.6%) as a colorless microcrystalline solid: mp 122-122.5 °C; IR (nujol) 2929 (vs), 2856 (s), 1458 (m), 1451 (m), 1378 cm$^{-1}$ (w); $^1$H NMR (CDCl$_3$) $\delta$ 1.43-1.76 (m, 25 H), 1.88-2.01 (m, 3 H), 2.08-2.20 (m, 2 H), 5.13 (s, 1 H), 5.42 (s, 1 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 28.53 (d), 28.62 (d), 34.27 (s), 34.81 (s), 35.87 (t), 36.99 (t), 37.23 (t), 41.70 (t),
41.77 (s), 42.64 (t), 42.69 (t), 83.76 (d), 134.8 (d), 137.3 (d). Anal. Calcd for C_{23}H_{32}Cl_{2}: C, 72.81; H, 8.50. Found: C, 72.92; H, 8.44. The structure of 17a was determined via analysis of its ^1H, ^13C, and 2D HETCOR NMR spectra.

Continued elution of the chromatography column with pentane afforded 17b (12 mg, 5.1%) as a colorless microcrystalline solid: mp 172-173 °C; IR (nujol) 2929 (vs), 2856 (s), 1458 (m), 1452 (m), 1378 cm^{-1} (w); ^1H NMR (CDCl_{3}) \delta 1.43-1.52 (m, 11 H), 1.53-1.69 (15 H), 2.09-2.18 (m, 4 H), 5.18 (s, 2 H), 5.42 (s, 2 H); ^13C NMR (CDCl_{3}) \delta 28.94 (d), 35.39 (s), 36.28 (t), 37.69 (t), 42.07 (t), 42.20 (s), 42.97 (t), 84.16 (d), 136.3 (d). Anal. Calcd for C_{24}H_{32}Cl_{4}: C, 62.35; H, 6.98. Found: C, 62.10; H, 6.85. The structure of 17b was characterized unequivocally via single-crystal X-ray structural analysis.\(^8\)

1,2-Di(1'-adamantyl)-1-chloro-2-(phenyl)sulphonuyl-ethane (20) A solution of 14 (30 mg, 0.10 mmol) in CH_{2}Cl_{2} (1.5 mL) was cooled under argon to -78 °C. Phenylsulffenyl chloride (150 mg, large excess) was added, and the resulting mixture was allowed to warm gradually to room temperature. The reaction mixture was stirred continuously overnight, and then quenched with water (20 mL). The resulting aqueous suspension was extracted with CH_{2}Cl_{2} (3 x 20 mL), and the combined organic extracts were washed with water (3 x 20 mL), dried (MgSO_{4}), and filtered. The filtrate was concentrated in vacuo, and the residue thereby obtained was purified via
column chromatography on silica gel by eluting with hexane. Pure 20 (38 mg, 86%) thereby obtained as a colorless microcrystalline solid: mp 194-195 °C; IR (KBr) 2900 (s), 2886 (s), 2839 (s), 1576 (w), 1468 (m), 1333 (m), 1306 (m), 1090 (w), 725 (m), 685 cm$^{-1}$ (w); $^1$H NMR (CDCl$_3$) $\delta$ 1.52-1.90 (m, 24 H), 1.90-2.07 (m, 6 H), 3.51 (s, 1 H), 4.08 (s, 1 H), 7.04-7.15 (m, 1 H), 7.19-7.30 (2 H), 7.32-7.42 (m, 2 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 28.50 (d), 28.62 (d), 36.79 (t), 36.85 (t), 38.74 (s), 39.71 (t), 40.03 (t), 56.90 (d), 71.01 (d), 124.9 (d), 127.7 (d), 128.9 (d), 139.7 (s). Anal. Calcd for C$_{28}$H$_{37}$ClS: C, 76.24; H, 8.45. Found: C, 76.12; H, 8.55. The structure of 20 was characterized unequivocally via single-crystal X-ray structural analysis.$^3$

meso-1,2-Di(1'-adamantyl)-1,2-dichloroethane (22) A solution of 15 (30 mg, 0.10 mmol) in CH$_2$Cl$_2$ (1.5 mL) was cooled under argon to -78 °C. Phenylsulfenyl chloride (150 mg, large excess) was added, and the resulting mixture was allowed to warm gradually to room temperature. The reaction mixture was stirred continuously overnight and then quenched with water (20 mL). The resulting aqueous suspension was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL), dried (MgSO$_4$), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with hexane, thereby affording 22 (36 mg, 98%) as a colorless microcrystalline solid: mp 165.5-166.0 °C; IR
(KBr) 2901 (s), 2845 (m), 1443 (w), 1337 (w), 682 cm\(^{-1}\) (w); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.62-1.70 (m, 12 H), 1.70-1.76 (m, 2 H), 1.76-1.83 (m, 4 H), 1.83-1.89 (m, 4 H), 1.89-1.95 (m, 2 H), 1.95-2.07 (m, 6 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 28.57 (d), 36.85 (t), 39.21 (t), 39.68 (s), 74.03 (d). Anal. Calcd for C\(_{22}\)H\(_{32}\)Cl\(_2\): C, 71.92; H, 8.78. Found: C, 72.17; H, 8.78. The structure of 22 was characterized unequivocally via the single crystal X-ray structural analysis.\(^6\)

\(d,1,2\)-Di(1'-adamantyl)-1,2-dibromoethane (24) A stirred solution of 14 (15 mg, 0.05 mmol) in CCl\(_4\) (1.5 mL) was cooled to -15 °C under argon. A solution of bromine in CCl\(_4\) (0.5 M, 0.11 mL, 0.055 mmol) was added dropwise. Bromine was decolorized immediately upon addition. The reaction mixture was continuously stirred for 5 minutes after the addition of Br\(_2\) had been completed. The reaction mixture was concentrated in vacuo, and the residue was washed with CH\(_2\)Cl\(_2\), thereby affording 24 (23 mg, 100%) as a colorless microcrystalline solid: mp 292.5-293.5 °C (dec.); IR (nujol): 2922 (vs), 2856 (s), 1458 (m), 1452 (m), 1378 cm\(^{-1}\) (w); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.52-1.74 (m, 19 H), 1.74-1.82 (m, 3 H), 1.82-1.88 (m, 2 H), 1.93-2.03 (m, 6 H), 4.16 (s, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 28.63 (d), 36.70 (t), 38.20 (s), 40.53 (t), 77.21 (d). Anal. Calcd for C\(_{22}\)H\(_{22}\)Br\(_2\): C, 57.91; H, 7.07. Found: C, 57.79; H, 6.89.

\(meso\)-1,2-Di(1'-adamantyl)-1,2-dibromoethane (26) A stirred solution of 15 (15 mg, 0.05 mmol) in CCl\(_4\) (1.5 mL)
under argon was cooled externally to -15 °C. A solution of bromine in CCl₄ (0.5 M, 0.11 mL, 0.055 mmol) was added dropwise. After the addition had been completed, the external cold bath was removed, and the reaction mixture was allowed to warm gradually to room temperature during 1 h. The reaction mixture was concentrated in vacuo, thereby affording 26 (23 mg, 100%) as a colorless microcrystalline solid: mp > 296 °C (dec.); IR (nujol): 2929 (vs), 2856 (s), 1458 (m), 1452 (m), 1378 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.58-1.68 (m, 12 H), 1.71-1.78 (m, 2 H), 1.78-1.87 (m, 3 H), 1.88-2.05 (m, 12 H), 4.43 (s, 2 H); ¹³C NMR (CDCl₃) δ 28.76 (d), 36.75 (t), 40.31 (s), 40.37 (t), 69.65 (d). Anal. Calcd for C₂₂H₂₂Br₂: C, 57.91; H, 7.07. Found: C, 57.99; H, 7.02.
REFERENCES


8. All single-crystal X-ray structures presented herein were obtained by Professor Simon G. Bott. We thank Professor Bott for having kindly provided this information.


Figure 3-1. $^1$H NMR Spectrum of 16a.
Figure 3-2. $^{13}$C and APT NMR Spectra of 16a.
Figure 3.3. Drawing of X-ray crystal structure of 16a.
Figure 3-4. $^1$H NMR Spectrum of 16b.
Figure 3.5. 13C and APT NMR Spectra of 16b.
Figure 3.6. Drawing of X-ray crystal structure of 16b.
Figure 3.7. 1H NMR Spectrum of 16c.
Figure 3-8. $^{13}$C and APT NMR Spectra of 16c.
Figure 3-9. 2D HETCOR NMR Spectrum of 16c.
Figure 3-10. Inverse gated-decoupled $^{13}$C NMR spectrum of 16c.
Figure 3-11. $^1$H NMR Spectrum of 17a.
Figure 3-12. $^{13}$C and APT NMR Spectra of 17a.
Figure 3.13. 2D HETCOR NMR Spectrum of 17a.
Figure 3-14. $^1$H NMR Spectrum of 17b.
Figure 3.16. Drawing of crystal X-ray structure of 17b.
Figure 3.19. Drawing of X-ray crystal structure of 20.
Figure 3-20. 1H NMR Spectrum of 22.
Figure 3-25. $^1$H NMR Spectrum of 26.
Figure 3-26. $^{13}$C and APT NMR spectra of 26.
CHAPTER IV
CHEMICAL AND MICROBIAL SYNTHESIS OF RACEMIC AND OPTICALLY
ACTIVE (S)-4-HYDROXY-2-CYCLOHEXENONE

Introduction

The compactin-mevinolin family of natural products consists of a number of highly attractive molecules which have been shown to lower human blood serum cholesterol levels through suppression of HMG-CoA reductase (HMGR).\(^1\) Molecules of this type also have been used as a tool by biochemists in elegant studies which have provided insight into the mechanism by which mammalian cells regulate HMG-CoA reductase.\(^2\) Recently, racemic 4-hydroxy-2-cyclohexenone, 1 (Scheme 1), has been used as the starting material in the

Scheme 1

![Diagram of 4-hydroxy-2-cyclohexenone]

synthesis of ML-236A and compactin.\(^3\) In these syntheses, Danishefsky and co-workers pointed out the importance of the
configuration of the asymmetric center at C(4) in compound 1. All stereochemistry is introduced by communication from this single stereogenic center. Subsequently, several research groups have focused attention upon the preparation of optically active 1. Danishefsky and co-workers developed a route to the (S)-enantiomer of 1, whose derivatives have also been used in the synthesis of the immunosuppressive agent FK-506. This route, shown in Scheme 2, involves a four-step synthesis which utilizes 3,4-O-isopropylidene-1-(hydroxy-methyl)-1(\(R\)), 3(\(R\)), 4(\(R\)), 5(\(R\))-tetrahydroxycyclohexane (2) as

Scheme 2

\[
\begin{align*}
\text{HO—} & \text{PH} \\
\text{HO} & \text{NaO}_4 \\
\text{HO} & \text{MsCl, Et}_3\text{N} \\
\text{HO} & \text{CH}_2\text{Cl}_2 \\
\text{HO} & \text{DBU, PhH} \\
\text{HO} & \text{K}_2\text{CO}_3, \text{aq. THF}
\end{align*}
\]
starting material. Compound 2, in itself, was obtained via an additional two-step synthesis from D(-)-quinic acid.\textsuperscript{5} This is a long and expensive route to 1; also, this route can be used only to synthesize \((S)\)-1. Danishefsky and co-workers\textsuperscript{6} have noted that it would be necessary to devise a different route to prepare the \((R)\)-enantiomer of 1.

In 1990, Solladié and co-workers reported the synthesis of both \((R)\)- and \((S)\)-enantiomers of 1 (Scheme 3).\textsuperscript{7} As shown in Scheme 3, commercially available 1,4-cyclohexanedione mono(ethylene acetal) (6) was reacted with \((S)\)-\((\text{methyl } p\)-toluenesulfinyl) in the presence of \(i\)-Pr\textsubscript{2}NMgBr to afford the corresponding sulfoxide, 7. The reduction of 7, performed by using either diisobutylaluminum hydride (DIBAL) or ZnCl\textsubscript{2}/DIBAL, afforded the corresponding hydroxysulfoxides. Subsequent hydrolysis of each these hydroxysulfoxides gave \((R)\)-1 and \((S)\)-1, respectively. This appears to be a good route; the only drawback is that expensive reagents are required.

Numerous applications of the retro Diels-Alder reaction in organic synthesis have been well-documented.\textsuperscript{8} Winterfeldt and co-workers have utilized the retro Diels-Alder reactions to prepare \((S)\)-1 and its analogs in good yields.\textsuperscript{9} For the synthesis of \((S)\)-1, their route makes use of a configurationally well-defined cyclopentadiene, 9, as a chiral template (Scheme 4).\textsuperscript{10} However, optically active 9 is not a readily available diene, and its subsequent Diels-Alder
reaction with $p$-benzoquinone requires the application of high pressure.

We now report our new route to synthesize racemic and optically active 4-hydroxy-2-cyclohexenone. A key step in this route involves a retro-Diels-Alder reaction. A major advantage to this new route is that it requires the use of inexpensive and readily available starting materials (vide
Results and Discussion

In the present study, (S)-1 was synthesized with high stereo- and enantioselectivity via the four-step route shown in Scheme 5. Each of the required four steps is very simple to perform on relatively large scale, and all materials used in this synthesis are inexpensive and readily available. No chiral reagents or chiral starting materials are required. 1α,4α,4αα,5α,8β,8αα-Hexahydro-1,4-methanonaphthalene-5,8-dione 12 was prepared via Diels-Alder reaction between cyclopentadiene and p-benzoquinone. Subsequent Ultrasound-
promoted Zn/HOAc reduction of **12** afforded 1α4α, 4αα, 5α, 6α, 7α, 8β, 8α-8α-octahydro-1,4-methanoneaphthalene-5,8-dione **13**. It should be noted that **13** was formed via chemoselective reduction of the conjugated enone C=C double bond in **12**.

Subsequently, **13** was subjected to microbial reduction via reaction with baker’s yeast at room temperature for 60 hours. A mixture of optically active diastereoisomeric ketols, i.e., *endo-14* and *exo-14*, was thereby obtained as an oil, 

\[[\alpha]_{D}^{25} +52.4^\circ (c 1.4, \text{CH}_2\text{Cl}_2)\]
consists of a mixture of endo and exo isomers was established via analysis of its $^1$H and $^{13}$C NMR spectra (Figures 4-1 and 4-2, respectively). Integration of the $^1$H NMR spectrum of 14 indicates the presence of 10 aliphatic protons. The multiplet at $\delta$ 4.20-4.32 corresponds to CHOH proton in 14. The multiplet at $\delta$ 5.98-6.20 corresponds to the vinyl protons in 14. The proton noise-decoupled $^{13}$C NMR spectrum of 14 displays 22 signals; the peaks which appear at $\delta$ 213.5 and 214.1 can be assigned to the carbonyl carbon atoms of the endo- and exo-diastereomers, respectively. The peaks at $\delta$ 67.42 and 71.44 can be assigned readily to the CHOH carbon atom in endo-14 and exo-14, respectively. The IR spectrum of endo-14 and exo-14 contains a strong absorption band at 3400 cm$^{-1}$ (OH stretch; see Figure 4-3).

The optically active material obtained via baker's yeast promoted reduction of 13 was pyrolyzed in a Kugelrohr at 250 °C under reduced pressure (~ 80 mmHg) to afford optically active 1 as an oil, [a]$^b_{D}^{25}$ -67.9° (c 0.66, CH$_2$Cl$_2$); [a]$^b_{D}^{25}$ -69.8° (c 0.52, CHCl$_3$). This material was characterized via analysis of its $^1$H and $^{13}$C NMR spectra (Figures 4-4 and 4-5, respectively). Integration of the $^1$H NMR spectrum of 1 indicated the presence of four aliphatic protons; the broad singlet at $\delta$ 3.74 corresponds to the CHOH proton; the multiplet at $\delta$ 4.43-4.56 corresponds to the CHOH proton; the AB patterns at $\delta$ 5.87 and 6.90 correspond to the vinyl
protons. Its proton noise-decoupled $^{13}$C NMR spectrum contains six carbon resonances. The peak at $\delta$ 199.5 corresponds to the C=O carbon atom in 1. The resonances which corresponds to the vinyl carbon atoms in the C=C double bond in 1 appear at $\delta$ 128.7 and 153.7. The peak at $\delta$ 65.94 can be assigned readily to the CHOH carbon atom. The IR spectrum of 1 contains a strong absorption band at 3412 cm$^{-1}$ (Figure 4-6), thereby reconfirming the presence of an OH group.

The reported rotation data for $(S)-1$ are shown in Scheme 6. There is a wide variation among the reported data shown therein.

![Scheme 6](image)

The enantiomeric excess of 1 obtained via baker's yeast reduction of 13 was determined via application of Mosher's method (Scheme 7). The acid chloride prepared from $(R)$-$(+)$-Mosher acid [i.e., $(R)$-$(+)$-MTPACl, prepared from $(R)$-$(+)$-Mosher acid and SOCl$_2$] was allowed to react with 1 (see Scheme 7) to afford the corresponding Mosher esters, $(R,R)$-15.
and (R,S)-15. Integration of the gated decoupled $^{13}$C NMR spectrum of the Mosher esters thereby obtained indicates that (S)-1 prepared via baker's yeast reduction of 13 was formed in 82%ee (Figure 4-7). In comparison with reported procedures, our route is simpler, shorter, and less tedious than other existing routes, and it affords the final product, (S)-1, with high enantioselectivity (64%ee).

The key step in this route is the baker's yeast reduction of 13. Asymmetric microbial reduction of ketones and aldehydes by baker's yeast constitutes one of the most widely applicable methods for preparing optically active
alcohols by kinetic resolution.\textsuperscript{14} Macleod\textsuperscript{15} and Hub\textsuperscript{16} systematically investigated the reductions of substituted ketones, $R(CO)R'$ (where $R, R' = \text{Me, Et, n-Pr, n-Bu, Bz}$), by baker’s yeast. Their results show that the secondary alcohols obtained from these baker’s yeast reductions were predominantly of $S$ configuration. Based on their results, Csuk and Glanzer\textsuperscript{14} suggested that hydrogen transfer takes place via the Re face of the prochiral ketone 16, where $R_L$ represents a large substituent and $R_S$ a small substituent adjacent to the carbonyl group, thereby affording alcohol 17 (Scheme 8). Compound 13 is a prochiral molecule which

\begin{center}
\textbf{Scheme 8}
\end{center}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme8.png}
\end{center}
contains two chemically equivalent carbonyl groups. Theoretically, four possible products can be formed via baker's yeast reduction of 13: (R)-endo-ketoalcohol (14a), (S)-endo-ketoalcohol (14b), (R)-exo-ketoalcohol (14c), (S)-exo-ketoalcohol (14d) (Scheme 9).

Scheme 9

\[
\text{(R)-endo-alcohol 14a} \quad \text{(S)-endo-alcohol 14b} \quad \text{(R)-exo-alcohol 14c} \quad \text{(S)-exo-alcohol 14d}
\]

With regard to baker's yeast reduction of 13, three questions need to be addressed: (i) What is the structure of the major product? (ii) What is the diastereomeric excess of
the major product? (iii) What is the enantiomeric excess of the major product? First, the diastereomeric excess of \( \text{14} \) was determined via a gated-decoupled \( ^{13}\text{C} \) NMR\(^{17} \) study of \( \text{14} \) (Figure 4-8). Integration values for the CHOH carbon atoms and for the C=O carbon atoms indicate a 80% diastereomeric excess of endo-\( \text{14} \). Secondly, in order to identify the structure of the major product obtained via baker's yeast reduction of \( \text{12} \), solid derivatives of \( \text{14} \) were prepared (Scheme 10). The mixture of ketoalcohols \( \text{14} \) was reacted with excess 3,5-dinitrobenzoyl chloride in the presence of base. Column chromatographic purification of the product thereby obtained afforded two fractions: endo-\( \text{18} \) and exo-\( \text{18} \).

![Scheme 10](image)

The derivatives were characterized via analysis of their respective \( ^{1}\text{H} \) and \( ^{13}\text{C} \) NMR spectra (Figures 4-9, 4-10, 4-11, and 4-12). Each fraction shows 16 peaks in its proton noise-
decoupled $^{13}$C NMR spectrum. The absolute configuration of the major product was determined unequivocally to be (S)-endo-$^{18}$ via the single crystal X-ray structural analysis (Figure 4-13).

Finally, the last question concerns the determination of the enantiomeric excess of the major product (endo-$^{18}$). To this end, the reaction sequence shown in Scheme 10 was carried out. Thus, endo-$^{18}$ was hydrolyzed under basic condition to afford a mixture of the corresponding ketoalcohols ($^{14a} + ^{14b}$), $[\alpha]_D^{25} +89.4^\circ$ (c 1.18, CH$_2$Cl$_2$), which was characterized via analysis of its $^1$H and $^{13}$C NMR spectra (Figures 4-14 and 4-15, respectively). The enantiomeric excess of (S)-$^{14}$ was determined via Mosher's method as described previously.$^{13}$ Mosher acid chloride was reacted with ketoalcohols $^{14a} + ^{14b}$ prepared via hydrolysis of endo-$^{18}$ (see Scheme 11). The corresponding Mosher esters, (R,R)-endo-$^{19}$ and (R,S)-endo-$^{19}$ were thereby obtained.$^{13}$ Integration of the gated-decoupled $^{13}$C NMR spectrum of these Mosher esters indicates that (S)-$^{14}$, as prepared via baker's yeast reduction of $^{13}$, was formed in 67%ee (Figure 4-16).

The mixture of ketoalcohols obtained via hydrolysis of the endo-$^{18}$ (see Scheme 12) was pyrolyzed in vacuo (~ 80 mmHg) at 250 °C (Kugelrohr) to afford (S)-$^{1}$, $[\alpha]_D^{25} -69.7^\circ$ (c 0.40, CH$_2$Cl$_2$) $([\alpha]_D^{25} -70.3^\circ$ (c 0.36, CHCl$_3$)) (Scheme 12). The material thereby obtained was characterized via analysis of its $^1$H and $^{13}$C NMR spectra (Figures 4-17 and 4-18,
respectively).

**Scheme 11**

\[
\begin{align*}
\text{KOH, MeOH} & \quad \text{reflux, 6 h} \\
\text{(R)-endo-18} + \text{(S)-endo-18} & \rightarrow \text{(R)-endo-14a} + \text{(S)-endo-14b} \\
\text{(R)-MTPACl} & \rightarrow \text{(R,R)-endo-19} + \text{(R,S)-endo-19}
\end{align*}
\]

**Scheme 12**

\[
\begin{align*}
\text{14a} & \quad \text{and/or} \\
\text{Pyrolysis in vacuo} & \quad \text{at 250 °C, 2 h} \\
\text{14b} & \rightarrow \text{(R)-1} + \text{(S)-1}
\end{align*}
\]
In order to confirm the chemical shift assignments in the diastereoisomeric Mosher's ester derivatives of 1, the corresponding 1:1 mixture of diastereoisomeric Mosher's ester derivatives of rac-endo-14 were synthesized. Thus, NaBH₄ promoted reduction of 13 afforded a diastereomeric mixture of (racemic) 14a-14d in 95% yield (Scheme 13). The diastero-

Scheme 13

isomeric excess of endo-14 and exo-14 was determined via analysis of the gated-decoupled ¹³C NMR spectrum of this
mixture (Figure 19). Integration of the signals which correspond to the CHOH carbon atoms indicates a 94% diastereomeric excess of endo-14. Therefore, we conclude that NaBH₄ promoted reduction of 13 produced endo-14 with high diastereoselectivity. The corresponding Mosher's ester derivatives of 14a and 14b were prepared in same way as was described previously for the corresponding baker's yeast reduction of 13 (vide supra). Integration of the gated-decoupled $^{13}$C NMR spectrum of the racemic Mosher esters, [i.e., (R,R)-endo-19 and (R,S)-endo-19] indicates that the ratio of two enantiomers of endo-14 is 1:1 (Figure 4-20), as expected. Pyrolysis of (racemic) 14a + 14b afforded racemic 1 which was characterized via analysis of its $^1$H and $^{13}$C NMR spectra.

Based upon results obtained via the studies described above, we conclude that baker's yeast reduction of 13 proceeds via selective transfer of hydride to the Re face of the prochiral diketone 13, thereby affording ketoalcohol (S)-14b as the major product. The NaBH₄ promoted reduction of 13 afforded (racemic) endo-14 (i.e., 14a + 14b) as the major product.

Summary and Conclusions

An improved asymmetric synthesis of optically active (S)-4-hydroxy-2-cyclohexenone 1 has been developed by starting with a readily available prochiral tricyclic
diketone (i.e., 13). The procedures are simple and require the use of inexpensive reagents. The key step in this synthesis is the baker's yeast reduction of 13. The absolute configuration of the major product, (S)-1, was established unequivocally via single crystal X-ray structural analysis of a precursor.\(^{13}\) The diastereomeric (80%de) and enantiomeric (67%ee) excesses of the major product observed for the products of baker's yeast reduction of 13 were established via careful integration of the relevant gated-decoupled \(^{13}\)C NMR spectra. The enantiomeric (64%ee) excesses of 1 observed for the products of baker's yeast reduction of 13 was determined via Mosher's method.

**Experimental Section**

Melting points are uncorrected and uncalibrated. High-resolution mass spectra were obtained by personnel at the Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska, Lincoln, NE. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

1α,4α,4αα,5α,6α,7α,8β,8αα-octahydro-1,4-methano-naphthalene-5,8-dione (13)\(^{12}\) To a solution of 12\(^{11}\) (1 g, 5.74 mmol) in glacial HOAc (15 mL) was added finely powdered Zn (1.5 g, 23.0 mmol). The resulting mixture was sonicated at room temperature for 2 h by using an American Brand ultrasonic cleaner, Model ME 4.6 (input 85 W). The reaction
The mixture was filtered, and the residue was washed with CH₂Cl₂ (3 x 10 mL). The combined filtrates were washed with brine (30 mL), and the aqueous layer was extracted with CH₂Cl₂ (2 x 30 mL). The combined organic layers were washed sequentially with water (50 mL), saturated aqueous NaHCO₃ (3 x 30 mL), and water (30 mL). The organic layer was dried (MgSO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 25% EtOAc-hexane to afford 13 (950 mg, 95%) as a colorless oil; IR (neat) 2989 (m), 2969 (m), 1704 (s), 1418 (m), 1332 (w), 1299 (m), 1259 (m), 1159 (m), 972 (w), 726 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.12 (AB, J_AB = 8.62 Hz, 1 H), 1.30 (AB, J_AB = 8.62 1 H), 1.92-2.14 (centrosymmetric A₂B₂ pattern centered at δ 2.30, 4 H), 3.07 (s, 2 H), 3.25 (t, J = 1.67 Hz, 2 H), 5.98 (t, J = 1.71 Hz, 2 H); ¹³C NMR (CDCl₃) δ 37.34 (t), 46.78 (d), 48.09 (t), 51.26 (d), 136.0 (d), 208.9 (d). The IR spectrum and the ¹H and ¹³C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectra reported previously.¹²

(S)-endo-8-Hydroxy-1α, 4α, 4αα, 5α, 6α, 7α, 8β, 8αα-octahydro-1,4-methanonaphthalene-5-one [(S)-14] To an aqueous solution of sucrose (7.36 g) and Na₂HPO₄ (50 mg) in water (27 mL) at 30-35 °C was added baker's yeast (1.6 g), and the resulting suspension was stirred at 30-35 °C for 30 min. Compound 13 (480 mg, 2.72 mmol) was added to the suspension, and the
resulting mixture was stirred at room temperature for 60 h. Celite (1.6 g) was added, and the resulting mixture was filtered. The residue was washed sequentially with water (30 mL) and Et₂O (2 x 20 mL), and the filtrate was extracted with Et₂O (3 x 30 mL). The combined organic layers were dried (MgSO₄) and filtered, and the filtrate was concentrated in vacuo to afford an oil. The oil was purified via column chromatography on silica gel by eluting with 25% EtOAc-hexane. Workup of the initial chromatography fractions afforded recovered starting material (13, 326 mg, 68%). Subsequent fractions afforded (S)-14 (155 mg, 32%), which was obtained as a pale yellow oil. [α]D⁰₂⁵ +52.4° (c 1.4, CH₂Cl₂); IR (neat) 3430 (s), 2958 (s), 2901 (m), 1690 (s), 1330 (w), 1246 (w), 1182 (w), 1077 (m), 1048 (m), 738 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.25 (AB, J_AB = 8.4 Hz, 1 H), 1.38 (AB, J_AB = 8.3 Hz, 1 H), 1.65-1.94 (m, 2 H), 2.10-2.24 (m, 2 H), 2.27 (s, 1 H), 2.72-2.90 (m, 2 H), 3.03 (s, 1 H), 3.22 (s, 1 H), 4.20-4.34 (m, 1 H), 5.98-6.20 (m, 2 H); ¹³C NMR (CDCl₃) δ 27.59 (t), 30.47 (t), 35.86 (t), 30.06 (t), 44.04 (d), 44.98 (d), 45.57 (d), 45.71 (d), 48.04 (t), 48.91 (d), 49.74 (d), 49.84 (t), 51.35 (d), 51.86 (d), 67.42 (d), 71.14 (d), 134.7 (d), 135.1 (d), 136.5 (d), 137.5 (d), 213.5 (s), 214.1 (s); mass spectrum (70 eV) m/z (relative intensity) 178 (molecular ion, 3.7), 113 (15.0), 95 (14), 91 (15.3), 66 (100). Anal. Calcd for C₁₁H₁₄O₂: Mᵣ⁺, 178.0994. Found (high-resolution mass
spectrometry): $^{19} M_{r}^+$, 178.0990. Integration of the gated-decoupled $^{13}$C NMR spectrum of this material indicates that it contains 80% de of endo-14.

(S)-4-Hydroxy-2-cyclohexenones [(S)-1] Compound (S)-14 (160 mg, 0.90 mmol), produced via baker's yeast reduction of 13, was pyrolyzed in vacuo (~ 80 mmHg) at 250 °C 2.5 h in Kugelrohr. The distillate thereby obtained was purified via flash column chromatography on silica gel by eluting with 40% EtOAc-hexane. Compound (S)-1 was thereby obtained as a pale yellow oil (50 mg, 50%), $[\alpha]_{D}^{25} -67.9^\circ$ (c 0.66, CH$_2$Cl$_2$); $[\alpha]_{D}^{25} -69.0^\circ$ (c 0.52, CHCl$_3$); IR (neat) 3412 (br vs), 2949 (m), 2871 (w), 1670 (s), 1253 (m), 1207 (w), 1063 (m), 972 (w), 861 (w), 757 cm$^{-1}$ (w); $^1$H NMR (CDCl$_3$) $\delta$ 1.80-2.02 (m, 1 H), 2.18-2.58 (m, 3 H), 3.74 (br s, 1 H), 4.43-4.56 (m, 1 H), 5.87 (AB, $J_{AB} = 10.3$ Hz, 1 H), 6.90 (AB, $J_{AB} = 10.3$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 32.15 (t), 35.26 (t), 65.94 (d), 128.7 (d), 153.7 (d), 199.5 (s). The IR spectrum and the $^1$H and $^{13}$C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectra reported previously.4

Preparation and Analysis of Mosher Esters [(R,R)-15 and (R,S)-15] A mixture of 4-N,N-dimethylaminopyridine (DMAP, 15 mg, 0.12 mmol) and Et$_3$N (0.1 mL) in CH$_2$Cl$_2$ (0.5 mL) was treated with (S)-1 (14 mg, 0.12 mmol) which had been obtained previously via baker's yeast reduction of 13. Immediately
thereafter, neat (R)-(+)−α-methoxy−α-(trifluoromethyl)−phenyl acetyl chloride (MTPACl)\textsuperscript{13a} was added, and the resulting mixture was stirred under argon at room temperature for 3 days. The reaction mixture was quenched by addition of NaHCO$_3$ (25 mg), and the quenched reaction mixture then was concentrated in vacuo. The residue was placed on a short pad of silica gel and eluted with 30% EtOAc-hexane in order to remove polar impurities. Integration of the 200 MHz gated-decoupled $^{13}$C NMR spectrum of the material thereby obtained indicates the enantiomeric excess of (S)-1 to be $64\%$ee.

**endo- and exo-8-(3',5'-dinitrobenzoyl)−1\textgreek{a}4\textgreek{a},4\textgreek{a}a,5\textgreek{a},6\textgreek{a}, 7\textgreek{a},8\textgreek{b},8\textgreek{a}−octahydro-1,4-methanonaphthalene-5-one (endo-18 and exo-18)** To a solution of (S)-14 (the mixture of diastereoisomeric, optically active products formed via baker's yeast reduction of 13, 110 mg, 0.61 mmol) in CH$_2$Cl$_2$ (10 mL) under argon was added Et$_3$N (1.5 mL) at room temperature. To the resulting mixture was added 3,5-dinitrobenzoyl chloride (356 mg, 1.54 mmol) and 4-N,N-dimethylaminopyridine (DMAP, 10 mg), and the reaction mixture was stirred continuously overnight. Methylene chloride (100 mL) was added, and the resulting mixture was washed sequentially with cold 3% aqueous HCl (20 mL) and H$_2$O (2 x 40 mL). The organic layer was dried (MgSO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel (400 mesh) by eluting with 20% EtOAc-hexane. Diastereomerically pure
exo-18 (20 mg, 8.8%) was thereby obtained as a colorless microcrystalline solid: mp 168-169 °C, [α]D<sub>25</sub> -69.9° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (nujol) 2922 (vs), 2856 (vs), 1724 (w), 1698 (w), 1538 (w), 1458 (s), 1378 (m), 1272 (w), 1165 (w), 720 cm<sup>-1</sup> (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.35 (AB, J<sub>AB</sub> = 8.6 Hz, 1 H), 1.53 (AB, J<sub>AB</sub> = 8.6 Hz, 1 H), 2.00-2.30 (m, 3 H), 2.38-2.62 (m, 1 H), 2.88-3.10 (m, 3 H), 3.35 (br s, 1 H), 4.70-4.93 (m, 1 H), 6.18 (AB, J<sub>AB</sub> = 5.5 Hz, 1 H), 6.25 (AB, J<sub>AB</sub> = 5.5 Hz, 1 H), 9.15-9.20 (m, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 27.35 (t), 36.96 (t), 44.77 (d), 45.66 (d), 46.11 (d), 48.10 (t), 52.37 (d), 76.72 (d), 122.5 (d), 129.4 (d), 133.9 (s), 135.0 (d), 138.5 (d), 148.7 (s), 211.1 (s); Anal. Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>7</sub>: C, 58.07; H, 4.33. Found: C, 57.89, H, 4.13.

Continued elution of the chromatography column afforded diastereomerically pure endo-18 (130 mg, 57.2%) as a colorless microcrystalline solid: mp 130-131 °C, [α]D<sub>25</sub> -13.8° (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (nujol) 2922 (vs), 2856 (vs), 1724 (w), 1698 (w), 1545 (w), 1458 (s), 1378 (m), 1345 (w), 720 cm<sup>-1</sup> (w); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.35 (AB, J<sub>AB</sub> = 8.6 Hz, 1 H), 1.48 (AB, J<sub>AB</sub> = 8.6 Hz, 1 H), 1.95-2.45 (m, 4 H), 2.98-3.22 (m, 3 H), 3.38 (br s, 1 H), 5.60-5.73 (m, 1 H), 6.06 (AB, J<sub>AB</sub> = 5.5 Hz, 1 H), 6.28 (AB, J<sub>AB</sub> = 5.6 Hz, 1 H), 9.07-9.12 (m, 2 H), 9.20-9.24 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 25.06 (t), 36.23 (t), 43.17 (d), 45.62 (d), 45.96 (d), 49.88 (t), 51.68 (d), 73.57 (d), 122.5 (d), 129.4 (d), 133.8 (s), 135.0 (d), 137.0
(S)-endo-18 was established unequivocally via single-crystal X-ray structural analysis. The absolute configuration of (S)-endo-18 was established via single-crystal X-ray structural analysis. 

(S)-endo-8-Hydroxy-1α,4α,4aa,5α,6α,7α,8β,8aa-octahydro-1,4-methanonaphthalene-5-one [(S)-14] To a solution of endo-15 (400 mg, 1.07 mmol) in MeOH (30 mL) was added KOH (100 mg, 1.78 mmol), and the resulting mixture was refluxed for 6 h. The reaction mixture was concentrated in vacuo, and brine (15 mL) was added to the residue. The resulting mixture was extracted with ether (4 x 30 mL). The combined organic layers were washed with brine (2 x 15 mL), dried (MgSO₄) and filtered, and the filtrate was concentrated in vacuo to afford an oil. The crude product was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexane to afford (S)-14 (160 mg, 83.9%) as a pale yellow oil, [α]D²⁵ +89.4° (c 1.1, CH₂Cl₂); IR (neat) 3427 (br vs), 2966 (s), 2901 (s), 1692 (m), 1328 (m), 1244 (m), 1075 (m), 1075 (m), 1049 (m), 945 (w), 899 (w), 737 cm⁻¹ (m); ¹H NMR (CDCl₃) δ 1.25 (AB, J_AB = 8.4 Hz, 1 H), 1.38 (AB, J_AB = 8.3 Hz, 1 H), 1.65-1.94 (m, 2 H), 2.10-2.24 (m, 2 H), 2.27 (s, 1 H), 2.72-2.90 (m, 2 H), 3.03 (s, 1 H), 3.22 (s, 1 H), 4.25 (m, 1 H), 6.12 (m, 2 H); ¹³C NMR (CDCl₃) δ 27.82 (t), 35.79 (t), 45.10 (d), 45.60 (d), 45.93 (d), 49.95 (t), 51.45 (d), 67.55 (d), 135.0 (d), 136.8 (d), 213.0 (s). The IR spectrum and the ¹H and ¹³C NMR spectra of the material...
thereby obtained are essentially identical with the corresponding spectra described earlier. The enantiomeric excess of (S)-1 thereby obtained was determined by Mosher's method\textsuperscript{13} to be 67%ee.

**Preparation and Analysis of Mosher Esters ((R,R)-endo-19 and (R,S)-endo-19** A mixture of 4-N,N-dimethylaminopyridine (DMAP, 15 mg, 0.12 mmol) and Et\textsubscript{3}N (0.1 mL) in CH\textsubscript{2}Cl\textsubscript{2} (0.5 mL) was treated with (S)-14 (the major product obtained via baker's yeast reduction of 13, 20 mg, 0.11 mmol). Immediately thereafter, neat (R)-(-)-\alpha-methoxy-\alpha- (trifluoromethyl)phenyl acetyl chloride (MTPACl)\textsuperscript{13a} was added. The reaction mixture was stirred under argon at room temperature for 3 days. The reaction was quenched by addition of NaHCO\textsubscript{3} (25 mg), and the reaction mixture then was concentrated in vacuo. The residue was placed on a short pad of silica gel and eluted with 30% EtOAc-hexane in order to remove polar impurities. Integration of the 200 MHz gated-decoupled \textsuperscript{13}C NMR spectrum of the material thereby obtained indicates the enantiomeric excess of (S)-14 to be 67%ee.

**((S)-4-Hydroxy-2-cyclohexenone [(S)-1** Compound (S)-14 (240 mg, 1.35 mmol) was pyrolyzed in vacuo (~ 80 mmHg) at 250 °C for 2.5 h in a Kugelrohr. The distillate was collected and then purified via flash column chromatography on silica gel by eluting with 40% EtOAc-hexane. Compound (S)-1 (150 mg, 50%) was thereby obtained as a pale yellow oil, [\alpha]_D^{25}
-69.7° (c 0.40, CH₂Cl₂); [α]D²⁵ -70.3° (c 0.36, CHCl₃); IR (neat) 3415 (br s), 2955 (m), 1678 (s), 1378 (m), 1205 (m), 1066 (s), 972 (w), 946 (w), 859 cm⁻¹ (w); ¹H NMR (CDCl₃) δ 1.79-2.00 (m, 1 H), 2.17-2.56 (m, 3 H), 3.78 (br s, 1 H), 4.48 (m, 1 H), 5.86 (AB, JAB = 10.2 Hz, 1 H), 6.89 (AB, JAB = 10.3 Hz, 1 H); ¹³C NMR (CDCl₃) δ 32.16 (t), 35.27 (t), 65.93 (d), 128.7 (d), 153.7 (d), 199.5 (s). The IR spectrum and the ¹H and ¹³C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectra reported previously.⁴

rac-endo-8-Hydroxy-1α,4α,4aa,5α,6α,7α,8β,8aa-octahydro-1,4-methanonaphthalene-5-one (endo-14). A solution of 13 (750 mg, 4.3 mmol) in MeOH (12 mL) and water (2 mL) was cooled to 0 °C via application of an external ice-water bath. To this cooled mixture was added NaBH₄ (45 mg, 0.7 mmol). After the addition of NaBH₄ had been completed, the external cold bath was removed. The resulting mixture was allowed to warm to room temperature during 1 h and then was stirred continuously at room temperature for 2 h. Acetic acid (0.1 mL) was added, followed by ice-water (10 mL), and the resulting mixture was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with water (30 mL), dried (MgSO₄) and filtered, and the filtrate was concentrated in vacuo to afford a yellow oil. The crude product was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane to afford endo-14 (730 mg, 97.3%) as a pale
yellow oil; IR (neat) 3428 (br s), 2962 (s), 2902 (s), 1698 (s), 1458 (w), 1418 (w), 1332 (m), 1245 (m), 1179 (m), 1072 (m), 1052 (m), 946 (w), 906 cm$^{-1}$ (w); $^1$H NMR (CDCl$_3$) $\delta$ 1.16 (AB, $J_{AB} =$ 8.4 Hz, 1 H), 1.27 (AB, $J_{AB} =$ 8.4 Hz, 1 H), 1.58-1.78 (m, 2 H), 1.97-2.14 (m, 2 H), 2.73 (s, 2 H), 2.95-3.18 (m, 3 H), 4.11-4.28 (m, 1 H), 5.85-6.12 (m, 2 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 27.30 (t), 35.99 (t), 44.85 (d), 45.39 (d), 45.61 (d), 49.65 (t), 51.21 (d), 67.23 (d), 135.3 (d), 135.9 (d), 213.7 (s). The IR spectrum and the $^1$H and $^{13}$C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectra described earlier. Integration of the gated-decoupled $^{13}$C NMR spectrum of this material indicates that it contains 94% de of endo-14. The enantiomeric excess of endo-14 was determined via Mosher's method$^{13}$ to be 1:1, as expected.

**rac-4-Hydroxy-2-cyclohexen-1-one (1).** Racemic endo-14 (720 mg, 4.04 mmol), the product obtained via NaBH$_4$ reduction of 13, was pyrolyzed in vacuo (-80 mmHg) at 250 °C for 3 h in a Kugelrohr. The distilled product was collected and purified via flash column chromatography on silica gel by eluting with 50% EtOAc-hexane. Racemic endo-1 (226 mg, 50%) was thereby obtained as a pale yellow oil; IR (neat) 3414 (s), 2949 (m), 2862 (w), 1678 (s), 1372 (m), 1059 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.72-1.95 (m, 1 H), 2.10-2.34 (m, 2 H), 2.34-2.50 (m, 1 H), 4.27 (s, 1H), 4.42 (br s, 1 H for OH), 5.79
(AB, $J_{AB} = 9.0$ Hz, 1 H), 6.85 (AB, $J_{AB} = 9.0$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 31.91 (t), 35.11 (t), 65.64 (d), 128.4 (d), 154.0 (d), 199.6 (s). The IR spectrum and the $^1$H and $^{13}$C NMR spectra of the material thereby obtained are essentially identical with the corresponding spectra reported previously. $^4$
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18. The single-crystal X-ray structure of (S)-endo-18 presented herein was obtained by Professor Simon G. Bott. We thank Professor Bott for kindly having provided this information.

19. HRMS data for 14 was kindly provided by Dr. Yanjun Wang.
Figure 4.1. $^1$H NMR Spectrum of 14 (made from baker's yeast reduction of 13).
Figure 4-3. FT-IR Spectrum of 14 (made from baker's yeast reduction of 13).
Figure 4.5: $^{13}$C and APT NMR Spectra of 1 (made from baker's yeast reduction of 13).
Figure 4-6. FT-IR Spectrum of 1 (made from baker’s yeast reduction of 13).
Figure 4-7. Gated-decoupled $^{13}$C NMR spectrum of $(R,R)$-15 and $(R,S)$-15.

(made from baker's yeast reduction of 13).
Figure 4-8. Gated-decoupled $^{13}$C NMR spectrum of $\text{endo-14}$ and $\text{exo-14}$

$14 \quad \text{endo-14} \quad X = \text{OH}, \ Y = H$
$\text{exo-14} \quad X = H, \ Y = \text{OH}$

(made from Baker's yeast reduction of 13).
Figure 4.9. $^1$H NMR Spectrum of endo-18 (prepared from major product in baker's yeast reduction of E3).
Figure 4-10. $^{13}$C and APT NMR Spectra of \textit{endo-18} (prepared from major product in baker's yeast reduction of 13).
Figure 4-11. $^1$H NMR Spectrum of exo-18 (prepared from minor product in baker's yeast reduction of 13).
Figure 4-12. $^{13}$C and APT NMR Spectra of $exo$-18 (minor product in baker's yeast reduction of 13).
Figure 4-13. Drawing of X-ray crystal structure of (S)-endo-18 (prepared from major product in baker's yeast reduction of 13).
Figure 4-14. $^1$H NMR Spectrum of 14a and 14b (made via baker's yeast reduction of 13).
Figure 4-16. Gated-decoupled $^{13}$C NMR spectrum of (R,R)-endo-19 and (R,S)-endo-19 (made from 14a and 14b in baker's yeast reduction of 13).
Figure 4.17. $^1$H NMR Spectrum of (R)-1 and (S)-1 (made from 14a and 14b in baker's yeast reduction of 13).
Figure 4-18. $^{13}$C and APT NMR Spectra of $(R)$-1 and $(S)$-1 (made from the major product in baker's yeast reduction of 13).
Figure 4.19. Gated-decoupled $^{13}$C NMR spectrum of endo-14 and exo-14 (made via NaBH$_4$ reduction of 13).
Figure 4-20. Gated-decoupled $^{13}$C NMR spectrum of (R,R)-endo-19 and (R,S)-endo-19
(made via NaBH$_4$ reduction of 13).
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