A small sample (5 mg) of **21**, isolated by preparative GLC, was dissolved in hexane (3 mL) and hydrogenated over 10% Pd/C at 40 lb. After 2 h the solution was filtered through Celite, concentrated, and analyzed by GLC. Only one component was detected, which was identified as methyl *cis*-decalin-9-carboxylate by comparison with authentic specimens of the cis and trans compounds.

Cyclization of 23 (X = I). Heating of 58 mg of **23** (X = I) with 1.1 molar equiv of Bu_3SnH (0.05 M) gave a mixture of methyl *p*-hydroxybenzoate (4%) and methyl 2-keto-*cis*-decahydronaphthalene-4a-carboxylate (**24**; 76%) as a clear oil: ^1H NMR (C_6D_6) δ 1.3-1.8 (m, 7 H), 2.0-2.3 (m, 2 H), 2.4-2.6 (m, 2 H), 3.22 (s, 3 H), 5.95 (d, 1 H, J = 10.3 Hz), 6.15 (dd, 1 H, J = 10.3, 1.2 Hz). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.48; H, 7.95.

Kinetic Experiments: General Procedure. A solution was prepared which contained the halide, about 10 molar equiv of tributylstannane of known molarity, and about 0.05 molar equiv of azobis(isobutyronitrile) in purified benzene. Where possible, the concentration of stannane was chosen so as to give comparable amounts of cyclized and direct reduction products. Small aliquots of the solution were then placed in vials and degassed by freeze/thawing. The vials were sealed under vacuum and heated in constant temperature baths until the reaction was complete. The mixtures were then analyzed by GLC on a capillary column. For experiments conducted at low temperatures the reaction was initiated by UV irradiation. For those carried out at temperatures above 100 °C di-*tert*-butyl peroxide was used as initiator instead of azobis(isobutyronitrile). In some cases deuteriobenzene was used as solvent, and the reaction mixtures were directly analyzed by ^1H NMR spectroscopy as well as GLC.

From the relative yields of cyclized and uncyclized products and the mean value of the stannane concentration, the value of k_c/k_H was determined by means of the appropriate pseudo first-order integrated rate equation (see text).

In the case of compounds containing an unsaturated ketone group a slight deficiency of stannane was employed. In these cases the final concentration of cyclized product was determined from the analytical results, and values of k_c/k_H were obtained from the appropriate integrated rate equation by an iterative technique as previously described.[10] Values of k_H were calculated from the appropriate Arrhenius equation[8] and used to determine k_c. Arrhenius parameters for the cyclization reactions were obtained in the usual way from the straight line of best fit obtained by plotting log k_c against $1/T$ (K).

In a typical experiment 20.0 mg (0.077 mmol) of **3a** and 1.0 mg (0.006 mmol) of AIBN were added to 1.25 mL of 0.671 M tributylstannane solution (0.84 mmol), and the mixture was divided between four vials. The aliquots were then degassed, sealed, irradiated with UV light or heated, and analyzed as described above. A second mixture prepared from 18.3 mg (0.071 mmol) of **3a**, 0.5 mg (0.004 mmol) of di-*tert*-butyl peroxide, and 1.25 mL of 0.0667 M tributylstannane solution (0.83 mmol) was similarly treated. The results obtained and the values of rate constants calculated from the expression $k_c/k_H = S_n(CH/UH)$, where S_n is the mean concentration of stannane and CH/UH is the ratio of yields of cyclized and uncyclized products, were as follows: (temperature, S_n, CH/UH, k_c/k_H) (I) 0 °C, 0.640 M, 0.8947, 0.573; (II) 40 °C, 0.640 M, 1.808, 0.157; (III) 75 °C, 0.640 M, 2.706, 1.732; (IV) 110 °C, 0.639 M, 3.271, 2.090; (V) 150 °C, 0.639 M, 4.875, 3.115. The reaction was carried out similarly at other concentrations of stannane. The values of k_c/k_H so obtained together with those listed above were used to obtain values of k_c by multiplying each by appropriate values of k_H.[8] Some typical values of k_c are 7.87×10^5 s^{-1} at 0 °C, 3.76×10^6 s^{-1} at 40 °C, 1.02×10^7 s^{-1} at 75 °C, 1.89×10^7 s^{-1} at 110 °C, and 4.76×10^7 at 150 °C. An Arrhenius plot gave log $A = 10.82 \pm 0.27$ (s^{-1}) and $E = 6.12 \pm 0.38$ kcal·mol^{-1}.

Synthesis, Bromination, and Photoelectron Spectra of Meso-Bridgehead Dienes[1]

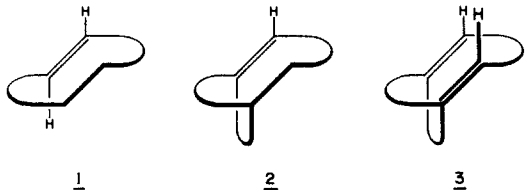
K. J. Shea,*[†] A. C. Greeley,[†] S. Nguyen,[†] P. D. Beauchamp,[†] D. H. Aue,[‡] and J. S. Witzeman[‡]

Contribution from the Departments of Chemistry, University of California, Irvine, California 92717, and University of California, Santa Barbara, California.
Received September 23, 1985

Abstract: The Cope rearrangement of 1,*n*-divinylbicycloalkanes has been employed for the synthesis of a series of meso-bridgehead dienes, molecules that contain two torsionally distorted carbon-carbon double bonds held in proximate relationship. The rate of Cope rearrangement does not correlate with reaction exothermicity or release of strain energy. A frontier molecular orbital explanation is one of several considerations offered to account for these observations. Spectroscopic (UV and photoelectron spectra) and chemical studies have permitted documentation of the progressive transannular interactions of the two bridgehead double bonds.

Reactivity of carbon-carbon double bonds can be modified in a predictable manner by direct attachment of substituents to the olefinic linkage. Considerably less is understood regarding the chemical and spectroscopic response of alkenes to a torsional distortion of the double bond. Indeed a consideration of these factors can provide new insight into subtle yet important chemical behavior of the carbon-carbon double bond.[2]

Torsionally distorted carbon-carbon double bonds are embodied in such compounds as *trans*-cycloalkenes **1**[3] and bridgehead alkenes **2**.[4] Incorporation of two distorted bridgehead olefinic linkages in the same molecule results in compounds that have been termed bridgehead dienes.[4a,5] Bridgehead dienes include such topologically interesting species as meso-bridgehead diene **3**, a molecule that contains two torsionally distorted carbon-carbon double bonds "locked" in close proximate relationship. Not only would the availability of molecules of this type allow for the study of distorted double bonds but it would also permit evaluation of the chemical



1 2 3

[†] University of California, Irvine.
[‡] University of California, Santa Barbara.

(1) For a preliminary account of this work see: Shea, K. J.; Greely, A. C.; Nguyen, S.; Beauchamp, P. S.; and Wise, S. *Tetrahedron Lett.* **1983**, 4173.

(2) The chemical response to a distortion (i.e., change in facial or regioselectivity) may originate from electronic factors that arise from changes in the energy levels and coefficients of the orbitals and/or from steric factors that stem from a concentration of substituents on one face of the olefin plane. For leading references to these matters see: *Stereochemistry and Reactivity of Systems Containing π Electrons*; Watson, W., Ed.; Verlag Chemie International: Deerfield Beach, FL, 1983.

(3) Greenberg, A.; Liebman, J. F., *Strained Organic Molecules*; Academic Press: New York, 1978; p 112.

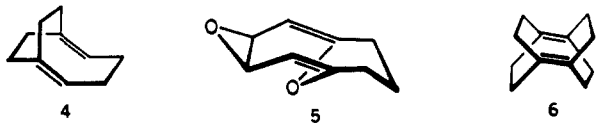
(4) Reviews: (a) Shea, K. J., *Tetrahedron Lett.* **1982**, *36*, 1683. (b) Szeimies, G. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1983; p 299.

(5) Warner, P. M.; Peacock, S. *Tetrahedron Lett.* **1983**, 4169.

0002-7863/86/1508-5901$01.50/0

and spectroscopic consequences of close proximate relationships of double bonds in molecules, a topic of considerable current interest.[6] In particular, the ultraviolet and photoelectron spectra of such dienes should be especially sensitive to electronic interaction between the π bonds.

Selected representatives of meso-bridgehead dienes are now known. Wiseman and Vanderbilt generated bicyclo[4.2.2]deca-1,5-diene (**4**), a reactive bridgehead diene that undergoes sigmatropic rearrangement at room temperature.[7] Rastetter and Richard synthesized oxepin **5**



4 5 6

and examined several of its chemical reactions[8] while Wiberg and co-workers have recently described diene **6**.[9]

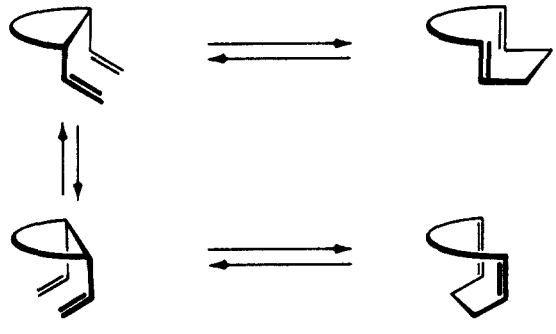
The two related derivatives, shown in the structures below, have been prepared by Paquette and co-workers.[9c,d] They constitute some of the first examples of these molecules. Our objective was

to develop a general synthetic entry into meso-bridgehead dienes that would afford an opportunity to survey the properties of compounds with progressively shorter nonbonded π-bond distances.

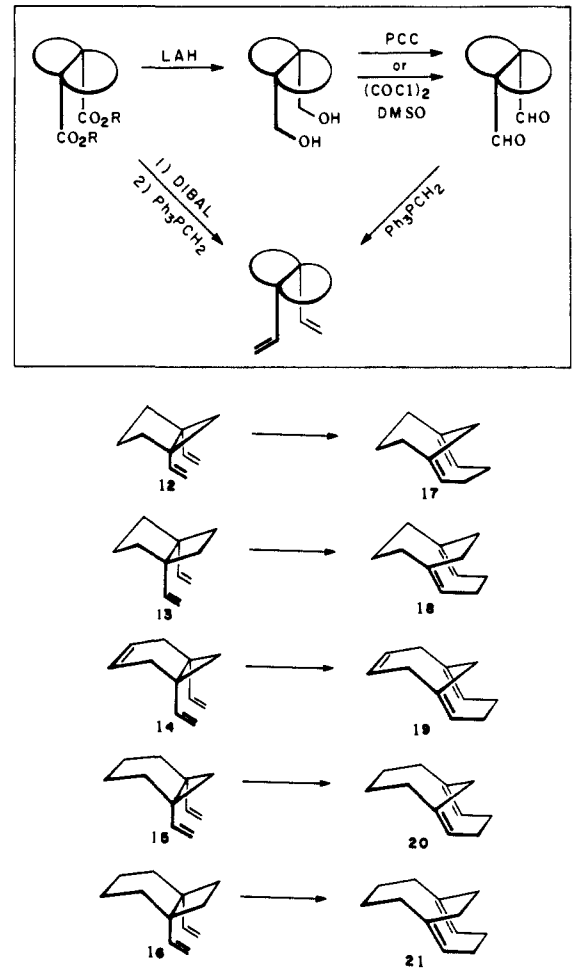
Results and Discussion

The key substructural feature of meso-bridgehead dienes represented by structure **3** is a *trans,trans*-1,5-cycloalkadiene unit. The second carbocyclic bridge "locks" the two double bonds into a parallel orientation.

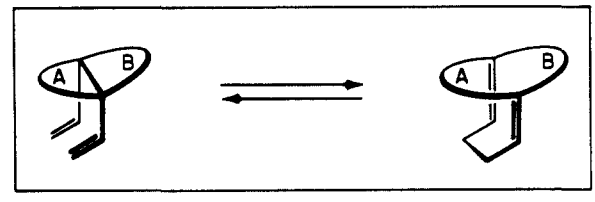
Our analysis of the synthesis of meso-bridgehead dienes recognizes the *trans,trans*-1,5-cycloalkadiene substructural feature. [3.3]Sigmatropic rearrangement of *cis*-1,2-divinylcycloalkanes can arise from one of two boat-like conformations.[10] The endo conformation results in formation of *cis,cis*-1,5-cycloalkadiene while rearrangement from the exo conformation produces a *trans,trans*-1,5-cycloalkadiene. In small- and medium-ring 1,5-cycloalkadienes, the cis,cis isomer is more stable[10b,c] and thermal rearrangement proceeds via the endo conformation.



Scheme I



If *cis*-divinyl groups occupy the bridgehead positions of bicyclo[*n.m.*0]alkanes, sigmatropic rearrangement will result in formation of a bicyclic *trans,trans*-1,5-cycloalkadiene, i.e., meso-bridgehead diene **3**. In the equation below the diene product is trans,trans in the B ring and cis,cis in the A ring. We anticipated that the *trans,trans*-1,5-diene component would be favored to reside in the largest ring. The overall position of equilibrium would dictate the success of the synthetic entry.



Synthesis of the required divinyl derivatives was accomplished by elaboration of the known bridgehead diesters. The choice of the reaction sequence was dictated by the propensity of the bridgehead functional groups toward undesirable propellane-forming side reactions. For example, PCC oxidation of diol **7**, prepared by LAH reduction of dimethyl bicyclo[3.2.0]heptane-1,5-dicarboxylate, afforded an 80:20 mixture of an unstable dialdehyde **8** and lactone **9**. This mixture was immediately carried through to the divinylbicycloalkane by the Wittig olefination procedure. This sequence was unsuitable for diester **10** since lactone **11** was the major product from the oxidation. Lactone formation presumably results from oxidation of a lactol that is produced in situ from the intermediate aldehyde alcohol.[11] In this situation, the oxidation could be accomplished by oxalyl

(6) (a) Hoffman, R. *Acc. Chem. Res.* **1971**, *4*, 1. (b) Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 696. (c) Martin, H.-D.; Mayer, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 283.

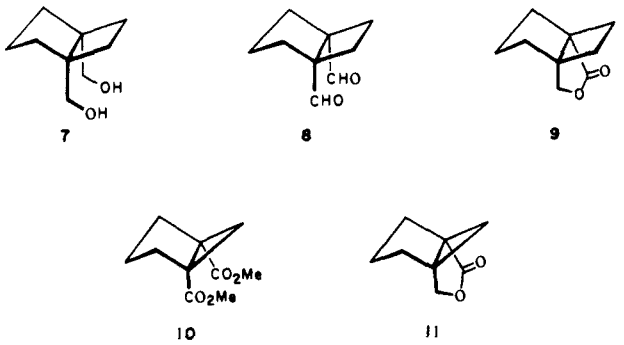
(7) Wiseman, J. R.; Vanderbilt, J. J. *J. Am. Chem. Soc.* **1978**, *100*, 7730.

(8) Rastetter, W. H.; Richard, T. J. *J. Am. Chem. Soc.* **1979**, *101*, 3893.

(9) (a) Wiberg, K. B.; Matturro, M. G.; Okarma, P. J.; Jason, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 2194. (b) Wiberg, K. B.; Adams, R. D.; Okarma, P. J.; Matturo, M. G.; Segmuller, B. *J. Am. Chem. Soc.* **1984**, *106*, 2200. (c) Wingard, R. E. Jr.; Russell, R. K.; Paquette, L. A. *J. Am. Chem. Soc.* **1974**, *96*, 7474. (d) Paquette, L. A.; Philips, J. C.; Wingard, R. E., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4516.

(10) Cope rearrangement from a chair transition state results in formation of a *cis,trans*-1,5-cycloalkadiene. Except in very large ring 1,5-dienes, the cis,trans geometry is at significantly higher energies than the corresponding *cis,cis*- or *trans,trans*-dienes. See for example: (a) Vogel, E.; Grimme, W. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 739. (b) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734. (c) Zuccarello, F.; Buemi, G.; and Favini, G. *J. Mol. Structure* **1971**, *8*, 459.

(11) (a) Jones, P. R. *Chem. Rev.* **1963**, *63*, 461. (b) Kayser, M. M.; Salvador, J.; Morano, P.; Kishamamurty, H. G. *Can. J. Chem.* **1982**, *60*, 1199.

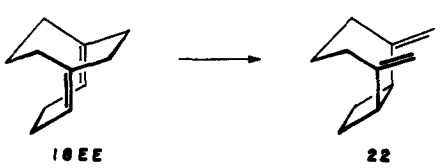


chloride/Me_2SO (−60 °C) or by an alternative procedure that involved a one-pot reduction of the diester to the dialdehyde (DIBAL) followed by Wittig olefination. An outline of the synthetic approaches is given in Scheme I.

Divinylbicycloalkanes **12–16** undergo smooth rearrangement to the corresponding bridgehead dienes **17–21**. The position of equilibrium lies exclusively on the side of bridgehead diene. Interestingly, the divinyl compounds exhibit a broad spectrum of reactivity. For example, diene **16** undergoes rearrangement at 60 °C ($t_{1/2}$ = 30 min), permitting isolation and complete spectral characterization. Diene **12**, on the other hand, has not as yet been detected in the Wittig olefination reaction—it spontaneously rearranges at temperatures <−10 °C to bridgehead diene **17**.[12]

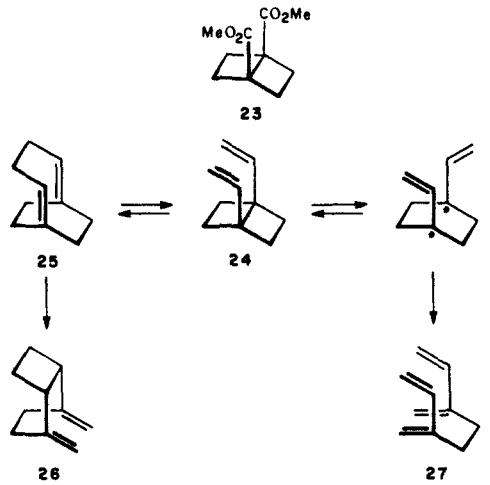
Bridgehead dienes **17–21** are all isolatable compounds that have been completely characterized. The dienes vary in reactivity and sensitivity to oxygen; the most reactive, diene **17**, does not persist at room temperature in air. Their spectroscopic properties are summarized in the experimental section.

A distinction between the *E,E* or *Z,Z* isomeric bridgehead dienes is not readily established on the basis of spectroscopic data alone. Our working assumption is that thermodynamics will dictate the configurational isomer formed. In all cases, this corresponds to the *Z,Z* isomer. The *E,E* isomer of dienes **17**, **19**, and **20** would correspond to derivatives of *trans,trans*-1,5-heptadiene, molecules that are not expected to be isolatable. The *E,E* isomer of **18**, on the other hand, is expected to be isolatable, albeit reactive. Evidence in support of the assigned structure stems from the thermal stability of diene **18**; it was recovered unchanged after heating at 160 °C for 24 h. The failure to detect the bismethylene derivative **22** under these conditions constitutes persuasive evidence for the *Z,Z* configuration in view of the strong thermodynamic driving force for formation of **22**.[13]

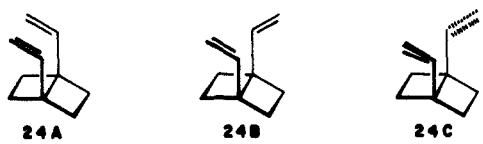


Extension of this methodology to include synthesis of bridgehead dienes **25** and **30** was not successful. These results are discussed below.

The synthesis of 1,4-divinylbicyclo[2.2.0]hexane (**24**) was attempted starting from diester **23**.[14] A one-pot sequence of reduction to dialdehyde followed by Wittig olefinition did not produce detectable quantities of **24**, **25**, or **26** a thermal rearrangement product of **25**.[7] The sole organic product isolated from the reaction is tetraene **27** (25%), which arises from a formal retro 2 + 2 cycloaddition of the bicyclo[2.2.0]hexane ring. This is a common thermal reaction pathway of bicyclo[2.2.0]hexanes.[15] Formation of tetraene **27** rather than bridgehead diene **25** or its thermal rearrangement product **26** suggests the activation energy



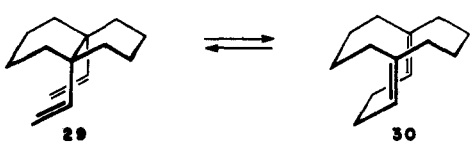
of the Cope rearrangement of **24** is *higher* than the zero bond dissociation energy in **24**. Compound **24** is an interesting species



in that the bond dissociation energy of the central bond is a function of the conformation of the vinyl groups. In conformation A or B the vinyl groups are in position for optimum overlap with the zero bond. In either conformation the bond dissociation energy is expected to be lowered by two allylic resonance stabilization energies.[16] This analysis leads to a BDE of (36 − 24) = 12 kcal/mol for **24A** or **24B**. In conformation C, on the other hand, the BDE is expected to be closer to the normal bond dissociation energy of bicyclo[2.2.0]hexane (36 kcal/mol).[17] Although our experimental observations do not permit an estimate of this value, the appearance of tetraene is consistent with a homolytic cleavage of the bicyclohexane at temperatures below 0 °C, corresponding to a very weak carbon–carbon bond.[18] It is most informative to compare this result with the thermal stability of tricyclic diene **28**, an ethano bridged derivative of **24**. Wiberg has reported that

this compound is stable to temperatures up to 150 °C, at which point rearrangement to **6** takes place.[19] The ethano bridge locks the double bonds in an orthogonal relationship to the zero bond of the [2.2.0] ring (i.e., conformation **24C**).

A thermodynamic limitation to the use of the Cope rearrangement for the synthesis of large ring bridgehead dienes was encountered with *cis*-1,6-divinyldecalin (**29**). A combination of



force-field calculations and thermodynamic group equivalents

(12) For an independent synthesis of diene **17** see: Warner, P.; Chu, I-S; Boulanger, W. *Tetrahedron Lett.* **1983**, 4165.
(13) Calculated H_{RXN}^0 = −17.0 kcal/mol (ref 5 and unpublished results).
(14) Owsley, D. C.; Bloomfield, J. J. *J. Am. Chem. Soc.* **1971**, *93*, 782.
(15) Cain, E. N.; Solly, R. K. *J. Am. Chem. Soc.* **1973**, *95*, 4791 and references cited therein.
(16) Rossi, M.; King, K. D.; Golden, D. M. *J. Am. Chem. Soc.* **1979**, *101*, 1223 and references cited therein.
(17) Steel, C.; Zand, R.; Hurwitz; Cohen, S. G. *J. Am. Chem. Soc.* **1964**, *86*, 679.
(18) Evidence for the independent generation of the diyl derived from **24** has been offered by Engel and co-workers: (a) Engel, P. S.; Allgren, R.; Chae, W. K.; Leckonby, R. A.; Marron, N. A. *J. Org. Chem.* **1979**, *44*, 4233. (b) Engel, P. S.; Nelepa, C. J.; Leckonby, R. A.; Chae, W. K. *J. Am. Chem. Soc.* **1979**, *101*, 6435.
(19) Wiberg, K. B.; Matturro, M. G.; Adams, R. *J. Am. Chem. Soc.* **1981**, *103*, 1600.

Table I. Activation Parameters for the Conformational Inversion of Cis-9,10-Disubstituted Decalins

compd	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, kcal/mol	ref
$R_1 = R_2 = H$	12.9	0.2	12.3	*a*, *b*
$R_1 = R_2 = CH_3$	16.2	1.4	15.2	*a*
$R_1 = CH_3$, $R_2 = OH$	16.7	2.9		*c*
$R_1 = R_2 = CH_2CO_2CH_3$	20.6	13.3	13.3	*c*
$R_1 = R_2 = CH_2CN$	18.5	9.3	15.1	*c*
$R_1 = R_2 = CHCH_2$	15.3	0.8	14.4	this work

[a] Brown, L. M.; Klinck, R. E.; Stothers, J. B. *Can. J. Chem.* **1979**, *57*, 803. [b] Dalling, D. K.; Grant, D. M.; Johnson, L. F. *J. Am. Chem. Soc.* **1971**, *93*, 3678. [c] Altman, J.; Gilboa, H.; Ginsburg, D.; Lowenstein, A. *Tetrahedron Lett.* **1967**, 1329.

permits evaluation of the enthalpy change for the reaction **29** ⇄ **30**. The estimates suggest equilibrium lies to the left by 5 kcal/mol.[20] Compound **29** was prepared and its NMR spectrum examined as a function of temperature. Substantial spectral changes were noted in both ^1H and ^{13}C NMR spectra as the temperature increased from 0 °C to 100 °C. In particular, the proton-decoupled ^{13}C NMR spectra exhibited seven signals at 0 °C, while at temperatures above 70 °C a five-line pattern was observed. These results are consistent either with a facile [3.3]sigmatropic rearrangement (**29** ⇄ **30**) *or* with the conformational isomerization shown in eq 1. We believe the spectral

28 **28** (1)

changes are consistent with the *cis*-decalin chair–chair interconversion. In support of this we used DNMR line-shape analysis to measure the activation energy parameters for the isomerization. These are given in Table I together with activation energy parameters for conformational inversion of a variety of 1,6-disubstituted *cis*-decalins. The similarity of these values lends support to our analysis that the dominant kinetic process at 70 °C is the conformational interconversion of two chair forms of *cis*-decalin and not [3.3]sigmatropic rearrangement. Efforts to populate the bridgehead diene manifold utilizing flash vacuum pyrolysis have so far proven unsuccessful.

Rates of [3.3]Sigmatropic Rearrangement

Our initial experimental observations revealed a substantial difference in the rates of [3.3]sigmatropic rearrangement of divinylbicycloalkanes **12–16**. The reactivity *increases* as the total number of atoms in the bicycloalkane *decreases*. A summary of the rate data is given in Table II. Rough estimates of the half-life of compounds **13** and **15** were obtained by monitoring the disappearance of starting material (or appearance of bridgehead diene) at the indicated temperature. As mentioned previously compound **12** was in fact *not* observed. All efforts to observe the initial Wittig olefination product afforded the NMR spectra of bridgehead diene **17**. The reported half-life ($t_{1/2}$ = 2 min, 0 °C) therefore represents a conservative upper limit for the rearrangement. Compound **16**, on the other hand, was sufficiently stable to permit isolation and measurement of its rate of isomerization to bridgehead diene **21**. Rate data were gathered over a 35 °C range. Derived Arrhenius activation energy parameters together with the activation energy parameters for related Cope rearrangements are included in Table II. Extrapolation of the rate data for diene **16** to 0 °C permits a crude comparison of the reactivities of **12** and **16**. The ratio of half-lives at 0 °C is in excess of 10^4. The origin of the rate difference between compound **12** and **16** is of considerable interest as a result of the similarities between these two compounds including the substitution pattern on the 1,5-diene, a required boatlike transition state, and the

(20) Alder, R. W., Arrowsmith, R. J.; Bryce, M. R.; Eastment, P.; Orpen, A. G. *J. Chem. Soc., Perkin Tran. 2* **1983**, 1519, and unpublished results from this laboratory.

Table II. Kinetic and Thermodynamic Data for the Cope Rearrangement (Boat Conformation) of Selected 1,5-Dienes

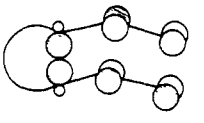
compd	$\Delta H^{\ddagger}$, kcal/mol	$t_{1/2}$, 50 °C	$\Delta H°$, kcal/mol[a]
1,5-hexadiene	44.7[b]	$\sim 10^{16}$ min	0
cis-1,2-divinylcyclobutane	23.1[c]	$\sim 2.5 \times 10^3$ min	−30
cis-1,2-divinylcyclopropane	19.4[d]	0.3 min	−29
16	20.4	1.2×10^2 min	−15
15		5 min	−20
13		5 min	−9
12		<1 min	−15
28	24.0[9]	$\sim 3 \times 10^6$ min	−5

[a] Estimated from heats of formation derived from known strain energies and group additives or by force-field calculations. See also ref 5. [b] Doering, W. Von E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299. Shea, K. J.; Phillips, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 3156. [c] Hammond, G. S.; De Boer, C. D. *J. Am. Chem. Soc.* **1964**, *86*, 899.

geometrical constraints imposed by the bicyclic framework. These factors eliminate conformational effects as important contributions to the rate difference. The origin of the kinetic differences therefore will be common to the transition state of al boatlike [3.3]sigmatropic rearrangements.

Our initial speculation regarding these rate differences focused on the reaction enthalpy; that is, we anticipated that the pattern of reactivity paralled reaction exothermicity. To our surprise, this turned out to be *not* the case. The reaction enthalpy for the two rearrangements, **12** → **17** and **16** → **21**, is very similar (Table II).[21] Furthermore there is little difference in the net change in strain energy between reactant and product for *both reactions*. It is not likely, therefore, that the origin of the rate difference stems from differential relief of strain. Indeed the most exothermic reaction, **15** ⇄ **20**, is one of the slowest reactions in the series.

One possible explanation for the rate difference involves the energy of orbitals associated with the central carbon–carbon bond. In the boat transition state there is optimum overlap between the two π orbitals and the zero bond of the bicyclic alkane structure (structure **31**). It is believed that for strained bicyclic [*n*.



31

m.0]alkanes, the zero bond makes a substantial bonding contribution to the highest occupied molecular orbital.[23] There is also ample precedent to establish the trend that the energy of the HOMO increases as function of decreasing ring size. If we view the Cope rearrangement as ($\pi + \sigma\pi$) exchange,[24] involving a HOMO fragment ($\sigma\pi$) and LUMO fragment (π), structure **31**, the increased energy of the HOMO fragment is expected to result in a greater rate for the Cope rearrangement. More quantitative rate studies will be necessary to confirm this relationship for the Cope rearrangement. Interestingly, similar parallels in reactivity have recently been noted in the reactions of electrophiles with bicycloalkanes.[25]

Transannular Interactions of Bridgehead Double Bonds

The proximate relationship of the two bridgehead double bonds is expected to influence both chemical and spectroscopic properties

(21) Reaction enthalpies were established from calculated strain energies and heats of formation (kcal/mol) of the parent bicyclic alkanes and bridgehead dienes using the Allinger MM2 force field.[5,22]

(22) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(23) (a) Gleiter, R. *Top. Curr. Chem.* **1979**, *86*, 196. (b) Heilbronner, E.; Prinzbach, H.; Martin, H. D. *Helv. Chem. Acta* **1971**, *54*, 1072.

(24) Klopman, G. *Chemical Reactivity and Reaction Paths*; Klopman, G., Ed.; Wiley: New York, 1974; p 156.

(25) (a) Wiberg, K. B.; Kass, S. R. *J. Am. Chem. Soc.*, **1985**, *107*, 988. (b) Wiberg, K. B.; Kass, S. R.; Bishop, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 996. (c) Wiberg, K. B., Kass, S. R.; deMeijere, A.; Bishop, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1003. (d) Gassman, P.; Yamaguchi, R. *Tetrahedron*, **1982**, *38*, 1113.

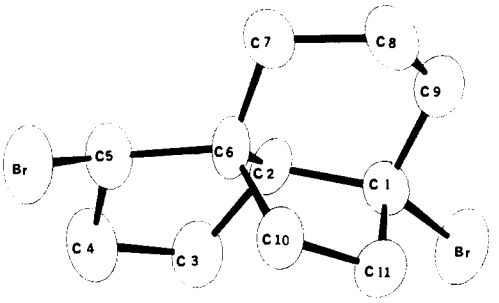
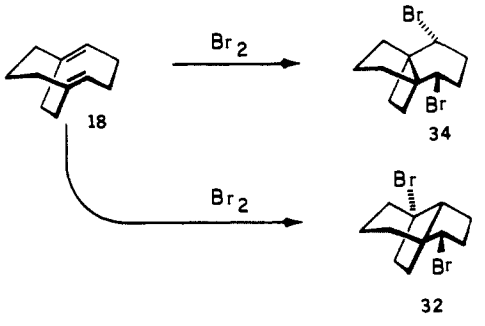


Figure 1. An Ortep drawing of dibromide **32** showing the atomic numbering scheme.

of dienes **17–21**. The magnitude of through-space interaction of the two bridgehead double bonds should correlate with their separation. This distance decreases from **21** to **17**. Several diagnostics have been chosen to evaluate the "communication" between the two double bonds, electrophilic addition and a combination of ultraviolet and photoelectron spectroscopy. In the bromination reactions below, the interaction between the π-bonds is evident in the formation of σ-bonds across the ring. In the ultraviolet and photoelectron spectra, remarkable spectral changes are also attributable to the effects of such nonbonded interactions.

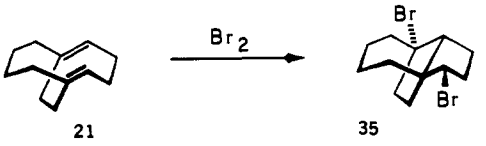
Bromination. When dilute solutions of bridgehead diene **18** were titrated with Br_2, the bromine color ceased to be discharged after addition of only 1 equiv of reagent. A single dibromide product was isolated in greater than 90% yield.

Uptake of a single equivalent of bromine suggests transannular participation of the second double bond. Two modes of addition may be anticipated, resulting in either a symmetrical propellane dibromide adduct **34** or an unsymmetrical adduct **32**. The



crystalline adduct isolated from bromination of bicyclo[4.3.2]-undeca-1,5-diene (*Z,Z*) exhibits spectral properties consistent with the unsymmetrical tricyclo[4.3.2.$0^{2,6}$]undecane carbocyclic skeleton (**32**). In particular, the 11 unique carbon atoms in the dibromide adduct support the assignment of the unsymmetrical carboxylic skeleton. An X-ray crystal structure of the dibromide confirms this assignment (Figure 1).[26] Force-field calculations reveal a slight twisting of the two bridgehead double bonds (4.6°) about the axis through the two π-bond centers which may predispose the transannular participation of the "back" double bond toward the observed cycloadduct.[28] The chemical behavior of bridgehead diene **18** is perhaps best understood in terms of its *cis,cis*-1,5-cyclooctadiene substructure. Electrophilic additions to these dienes exhibit a strong tendency to form derivatives of bicyclo[3.3.0]-octane.[29] Although the brominations proceed in the absence of light, there is insufficient evidence at present to unambiguously establish the ionic or free radical nature of these reactions.

In a similar reaction, bromination of diene **21** yields a single crystalline dibromide with 12 unique carbon atoms as shown by ^{13}C NMR. The spectral properties are consistent with adduct **35**.



21 35

Ultraviolet and Photoelectron Spectra

The ultraviolet spectrum of **17** shows an anomalous long wavelength band at 251 nm that apparently results from interaction between the two π-bonds. The dienes **18**, **20**, and **21** in which the π-bonds are further apart show ultraviolet abssorption only below 205 nm. The triene **19** also shows an anomalous band at 230 nm, apparently as a result of interaction among all three π-bonds, since no such band is seen in **20**.

The photoelectron spectral data in Table III show a general increase in the $\pi-\pi$ splitting with increasing proximity of the bridgehead π-bonds, as might have been expected from a simple through-space interaction model. The splitting ranges from 0.33 eV in **21** to 1.13 eV in **17**. That such a naive analysis could potentially be misleading is apparent from the fact that the two π-bonds in **6** are nearly degenerate because of compensatory through-space interactions.[30] Nevertheless it is clear that the P–π interactions are quite large in these dienes. A theoretical analysis of these photoelectron spectral data that allows approximate separation of the through-space and through-bond components of the interaction will be published separately.[31]

Experimental Section[32]

1,5-Bis(hydroxymethyl)bicyclo[3.1.0]hexane. LAH (0.421 g, 11.1 mmol) was placed in an oven-dried 250-mL flask fitted with a reflux condenser, an addition funnel, a mechanical stirrer, and a N_2 source. Et_2O (100 mL) was added via double needle. The reaction flask was cooled to −78 °C and then treated dropwise with dimethyl bicyclo-[3.1.0]hexane-1,5-dicarboxylate (**10**)[33] (1.0 g, 5.05 mmol) in Et_2O (50 mL) over 20 min. Stirring was continued for 2 h at −78 °C, at which

(26) Crystal data for dibromide: $C_{11}H_{16}Br_2$, orthorhombic, space group $P2_1cn$ (nonstandard setting of $Pna2_1$, No. 33), a = 6.813 Å, b = 8.34 Å, c = 19.890 Å, z = 2. Intensity measurements were made on a Syntex $P2_1$ diffractometer, Mo Kα radiation, λ = 0.71073 Å, graphite monochromator. Intensities of 1206 reflections with $2\theta \leq 50°$ were measured; of these 656 had intensities $I > 3\sigma(I)$. The two bromine atoms were located by diret methods;[27] the remaining non-hydrogen atoms were found by Fourier techniques and refined by full-matrix least-squares calculations to R = 0.077, R_w = 0.088 (anisotropic thermal parameters for carbon and bromine atoms, hydrogen atoms in calculated positions). Tables of positional parameters, anisotropic temperature factors, bond angles, interatomic distances, and structure factors are included as supplemental information.

(27) Gilmore, C. J. Mithril, University of Glasgow, 1983.

(28) Aue, D.; Shea, K. J., unpublished results.

(29) Vemura, S.; Fukuzawa, S.; Toshimitu, A.; Okano, M.; Tezuka, H.; Sawada, S. *J. Org. Chem.* **1983**, *48*, 270.

(30) Hunneger, E.; Wiberg, K. B. *J. Electron Spectros. Relat. Phenom.* **1983**, *31*, 365.

(31) Aue, D. H.; Witzeman, J. S.; Nakaji, D.; Futel, L. E.; Kirtman, B.; Shea, K. J., to be published.

(32) **General Information**: Melting points were determined in capillary tubes using a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Acculab 2 or Perkin-Elmer 283 spectrophotometer. ^1H NMR spectra were determined with Varian FT 80A (80 MHZ) or Bruker WM250 (250 MHz) spectrometers. Chemical shifts are reported as δ values in ppm relative to internal tetramethylsilane. Coupling constants (J) are reported in Hz. ^{13}C NMR spectra were determined at 22.62 MHz with a Bruker WH-90 spectrometer or a 62.9 MHz with a Bruker WM 250 spectrometer. Chemical shifts are reported as δ values in ppm relative to internal tetramethylsilane. Low-resolution mass spectra were recorded on a Finnigan Model 4000 GC/MS/DS. All chemical ionization (CI) mass spectra were determined at 100 eV. Data are reported as mass/charge (m/e) ratios. UV spectra were obtained on a Cary 219 UV/visible spectrophotometer using quartz cells. A Varian Aerograph Model 920 gas chromatograph equipped with a thermal conductivity detector was used for preparative VPC. Glass inserts were used to line the injection port. The preparative work employed a 5 ft × $^1/_4$ in. glass column packed with 3% SP 2100 on 80/100 Supelcoport or a 10 ft × $^1/_4$ in. glass column packed with 3% Sp-216-PS on 80/100 Supelcort. "In vacuo" refers to evaporation of solvent or volatiles at reduced pressures using a Buchi Rotary Evaporator. Water bath temperature was 25–50 °C unless otherwise noted. Most reagent-grade chemicals solvents were dried and purified by standard methods available. Some common purifications are listed below: Oxalylchloride, distilled fresh under N_2, 63 °C at 1 atm; dimethyl sulfoxide (Me_2SO); distilled twice from CaH_2 under N_2, stored over 3-Å molecular sieves; CCl_4, distilled from P_2O_5 under N_2, stored 3-Å molecular sieves; diethyl ether (Et_2O), distilled fresh from Na/Ph_2CO under N_2; triethylamine (Et_3N), stirred with KOH, decanted, and distilled under N_2; Ph_3PCH_3Br, dried overnight under vacuum at 120 °C.

(33) McDonald, D. N.; and Reitz, R. R. *J. Org. Chem.* **1972**, *37*, 2418.

Table III. Vertical Ionization Potentials of Bridgehead Dienes **17–21**

compd	IP, eV	type
21	8.35	π_a
	8.68	π_s
20	8.03	π_a
	8.96	π_s
19	8.10	π_1
	8.99	π_2
	9.38	π_3
18	8.14	π_a
	8.83	π_s
17	7.92	π_a
	9.05	π_s

time the mixture was refluxed for 5.5 h. The mixture was cooled to 0 °C and quenched by the addition of H_2O (0.4 mL), 10% NaOH (0.4 mL), and then H_2O (1.5 mL). After the mixture had warmed to room temperature, the Et_2O solution was decanted from the white granular precipiate and the precipitate washed well with dry Et_2O. The Et_2O extracts were combined, dried (Na_2SO_4), and concentrated to yield 0.66 g (92%) of viscous light yellow oil. The crude oil was chromatographed on 40 g of silica gel (pentanes–ether, 1:1, R_f 0.12) to yield 0.50 g (70%) of a clear viscous oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.35 (br s, 2 H, O*H*), 4.00, 3.34 (AB, J = 12.41 Hz, 4 H, –C*H*$_2$OH), 2.06 (m, 2 H), 1.66 (m, 2 H), 0.69, 0.33 (AB, J = 5.3 Hz, 2 H, cyclopropane); ^{13}C (62.9 MHz, $CDCl_3$) δ 64.9, 33.7, 29.9, 13.6, 16.7; IR (CCl_4) 3040 (s), 2940 (s), 2870 (s), 1450 (m), 1235 (m), 1040 (s) cm^{-1}; high-resolution mass spectrum, m/e (70 eV, EI) calcd (M^+) 142.0994, obsd (M^+) 142.0984.

Bicyclo[4.3.1]deca-1,5-diene (17). To an oven-dried 3-neck round-bottom flask fitted with two addition funnels, a mechanical stirrer, and a N_2 source was added CH_2Cl_2 (15 mL) and oxalyl chloride (0.6 mL, 6.87 mmol) via syringe. The flask was cooled to –65 °C. One addition funnel was charged with Me_2SO (0.93 mL, 13.11 mmol) in CH_2Cl_2 (5 mL). The second addition funnel was charged with the above diol (0.46 g, 3.24 mmol) in CH_2Cl_2 (5 mL). The Me_2SO/CH_2Cl_2 solution was added over 5 min to the oxalyl chloride in CH_2Cl_2 at –65 °C and stirred an additional 2 min, and then the diol solution was added over 10 min and stirred an additional 15 min at –65 °C. Et_3N (3.63 mL, 26.04 mmol) was added slowly via syringe, and the resulting cloudy white reaction mixture was stirred for 10 min, allowed to warm to room temperature, and poured into 50 mL of cold H_2O. The Me_2SO/H_2O layer was extracted with 2 × 25 mL portions of cold CH_2Cl_2. The combined CH_2Cl_2 layers were washed with cold 1% HCl (50 mL), cold 5% Na_2CO_3 (50 mL), cold brine (50 mL), and cold H_2O (50 mL). The resulting CH_2Cl_2 was dried (Na_2SO_4) and kept at approximately 0 °C. A small sample was removed, CH_2Cl_2 stripped off on the rotovap, and the residue taken up in $CDCl_3$. ^{1}H NMR (80 MHz, $CDCl_3$) revealed aldehyde protons at δ 9.38. The CH_2Cl_2 was decanted from the Na_2SO_4, CH_2Cl_2 removed in vacuo, and the dark red oily residue taken up in Me_2SO (5 mL) and added immediately to a stirred solution of Wittig reagent (Ph_3PCH_2) in Me_2SO under N_2 prepared as follows:[34] To an oven-dried 100-mL round-bottom flask with magnetic stirbar was added 50% NaH oil dispersion (0.6 g, 12.5 mmol). The flask was capped with a septum and connected to a N_2 bubbler. The NaH was washed with dry pentanes. Me_2SO (10 mL) was added and the solution heated to 75 °C with stirring under N_2 until H_2 evolution ceased (approximately 45 min). The resulting blue-green solution of sodium methylsulfinyl carbanion was allowed to cool to room temperature and methyltriphenylphosphonium bromide (3.47 g, 9.72 mmol) in Me_2SO (5 mL) was added via syringe. The yellow solution was stirred at room temperature 30 min before adding the dialdehyde. Addition of the dialdehyde changed the solution of Wittig reagent to a deep red-orange. After the mixture had been stirred under N_2 for 6 h, H_2O (5 mL) was added, and the solution was extracted repeatedly with pentanes. The extracts were combined, dried (Na_2SO_4), and concentrated to approximately 5 mL. Diene **17** was isolated by preparative VPC (5-ft 3% SP 2100, column temperature 90 °C, retention time 5 min): ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.63 (m, 2 H, vinyl), 2.90, 1.90 (AB, J = 10 Hz, 2 H), 2.60–2.00 (m, 10 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 155.4 (bridgehead C), 114.0, 41.5, 40.9, 37.7, 24.4; IR (CCl_4) 2940 (w), 1550 (s), 1250 (m), 1220 (m), 1000 (m), 975 (m) cm^{-1}; mass spectrum, m/e (CI, isobutane, 100 eV) 135 (MH^+); UV (cyclohexane) λ_{max} 251 nm; high-resolution mass spectrum, m/e (70 eV, EI) calcd (M^+) 156.1150, obsd (M^+) 156.1137.

1,5-Bis(hydroxymethyl)bicyclo[3.2.0]heptane. Using the procedure for the preparation of the previous diol, LAH (1.79 g, 47.2 mmol) in Et_2O (250 mL) and dimethyl bicyclo[3.2.0]heptane-1,5-dicarboxylate[35] (5.0 g, 23.6 mmol) in Et_2O (150 mL) gave after workup 3.32 g (90%) of a viscous clear oil containing some crystals. The crude oil was chromatographed on 120 g of silica gel (pentanes–ether, 1:1, R_f 0.2) to yield 3.2 g (87%) of white crystalline **7**: mp 141–150 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.22 (br s, 2 H, O*H*), 3.67, 3.43 (AB, J = 11.8 Hz, 4 H, RC*H*$_2$OH), 2.38–0.76 (m, 10 H); ^{13}C (22.62 MHz, $CDCl_3$) δ 64.8, 50.4, 35.6, 23.6, 23.3; IR (CCl_4) 3300 (s), 2940 (s), 2860 (m), 1550 (m), 1445 (w). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.29; H, 10.33.

Bicyclo[3.2.0]heptane-1,5-dicarboxaldehyde. The above diol was oxidized by two procedures to the corresponding dialdehyde. Method A involved PCC oxidation while method B used activated Me_2SO. Method B proved to be the best and was used on all subsequent diol oxidations. Method A was attempted in other cases but failed to give satisfactory results.

Method A: To a rapidly stirred suspension of pyridinium chlorochromate[36] (11.04 g, 51.2 mmol) and anhydrous NaOAc (0.84 g, 10.2 mmol) in CH_2Cl_2 (35 mL) at 0 °C under N_2 was added diol **7** (2.0 g, 12.8 mmol) in CH_2Cl_2 (15 mL) via syringe. The mixture changed from yellow-orange to dark black-brown. Stirring was continued for 4.7 h at 0 °C after which the organic layer was decanted into diethyl ether (50 mL) and the tarry residue washed well with Et_2O (7 × 40 mL). The organic layers were combined and passed through Florisil, dried (Na_2SO_4), and concentrated in vacuo, yielding 1.42 g (73%) of a viscous yellow oil. IR (neat) of crude oil showed two C=O stretches at 1770 and 1715 cm^{-1}. TLC showed the oil to be two components with similar R_f's. ^{1}H NMR indicated mixture of unknown component to the dialdehyde of 1:3.

Method B:[37] In an oven-dried 3-neck 50-mL round-bottom flask fitted with two addition funnels and a N_2 source was added oxalyl chloride (0.45 mL, 5.16 mmol) in CH_2Cl_2 (25 mL) via syringe. The flask was cooled to –65 °C. One addition funnel was charged with Me_2SO (0.8 mL, 11.3 mmol) in CH_2Cl_2 (5 mL). The second addition funnel was charged with diol (0.39 g, 2.5 mmol) in CH_2Cl_2 (5 mL). The Me_2SO/CH_2Cl_2 solution was added dropwise over 5 min to the stirred oxalyl chloride/CH_2Cl_2 at –65 °C and the mixture stirred an additional 2 min. The CH_2Cl_2 diol solution was added over 5 min and stirring continued for an additional 15 min at –65 °C. Then Et_3N (1.6 mL, 11.5 mmol) was added via syringe, and the mixture was stirred 5 min and then allowed to warm to room temperature. Cold H_2O (50 mL) was added. The organic layer was separated, and the H_2O layer extracted with CH_2Cl_2 (25 mL). The organic layers were combined and washed with cold 1% HCl (50 mL), cold 5% Na_2CO_3 (50 mL), cold saturated NaCl (50 mL), and cold H_2O (50 mL). The organic layer was dried (Na_2SO_4) and concentrated to yield 0.41 g of green oil which turned crystalline overnight in the refrigerator. The crude product was columned on 20 g of silica gel (pentanes–ether, 1:1, R_f 0.33) to yield after solvent removal 0.18 g (47.4%) of white crystalline bicyclo[3.2.0]heptane-1,5-dicarboxaldehyde, which was a single component by TLC (SiO_2, pentanes–ether, 1:1): ^{1}H NMR (80 MHz, $CDCl_3$) δ 9.65 (s, 2 H, aldehyde), 2.6–1.6 (m, 10 H).

Bicyclo[4.3.2]undeca-1,5-diene (18). Bicyclo[3.2.0]heptane-1,5-dicarboxaldehyde (0.47 g, 3.09 mmol) prepared by method B in Me_2SO (45 mL) was added to a stirred solution of freshly prepared Ph_3PCH_2 (20.6 mmol) in Me_2SO (1.0 g, 20.6 mmol, 50% NaH, Me_2SO (70 mL) and Ph_3PCH_3Br (7.34, 20.6 mmol)) in Me_2SO (45 mL). The yellow-orange solution changed to straw yellow. The solution was stirred 4 h at room temperature, after which pentane (100 mL) and H_2O (20 mL) were added to quench the reaction. The pentane layer was separated and the Me_2SO–H_2O layer diluted with H_2O (100 mL) and extracted with pentane (6 × 75 mL). The combined pentane layers were washed with saturated NaCl solution (3 × 80 mL) and dried (Na_2SO_4). The pentane solution was filtered through silica gel, dried (Na_2SO_4), and concentrated to 45 mL. The yield based on GLC using decane standard was 0.2745 g (60%). The product (**18**) was isolated by preparative VPC (5-ft 3% SP2100, column temperature 95 °C, retention time 14 min): ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.15 (m, 2 H, vinyl), 2.7–1.1 (m, 14 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 144.3 (bridgehead C), 125.2, 38.3, 29.6, 28.0, 25.0; IR (CCl_4) 2940 (s), 1645 (m), 1480 (m), 1455 (m), 1435 (m), 1235 (w), 1000 (w) cm^{-1}; mass spectrum, m/e (CI, isobutane, 100 eV) 149 (MH^+); high-resolution mass spectrum, m/e (70 eV, EI) calcd 148.1252, obsd 148.1241.

1,6-Bis(hydroxymethyl)bicyclo[4.1.0]hept-3-ene. Using the procedure described previously, LAH (0.1074 g, 2.83 mmol) in Et_2O (20 mL) and dimethyl bicyclo[4.1.0]hept-3-ene-1,6-dicarboxylate[38] (0.243 g, 1.16

(34) (a) Corey, E. J.; Chaykovsky, M. J. *J. Am. Chem. Soc.* **1965**, *87*, 1345. (b) Maercker, A., *Org. React.* **1965**, *14*, 270.

(35) (a) Owsley, D. C.; Bloomfield, J. *J. Org. Prep. Proc. Int.* **1971**, *3*, 61. (b) Owsley, D. C.; Bloomfield, J. *J. Org. Chem.* **1971**, *36*, 3768.

(36) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(37) Mancuso, A. J.; Swern, D. *Synthesis*, **1982**, 165.

mmol) in Et_2O (10 mL) gave after workup 0.20 g of crude diol as a viscous yellow oil. This product was chromatographed on 20 g of silica gel (anhydrous Et_2O, R_f 0.82) to yield 0.08 g (45%) of a clear viscous oil: ^1H NMR (80 MHz, $CDCl_3$) δ 5.5 (m, 2 H, vinyl), 4.25 (br s, 2 H, O*H*), 3.88, 3.50 (AB_q, J = 12 Hz, 4 H, RCH_2OH), 3.0–2.0 (m, 4 H), 0.87, 0.37 (AB_q, J = 4 Hz, 2 H); IR (CCl_4) 3420 (m), 3040 (m), 2900 (s), 1440 (w), 1220 (m), 1145 (s), 1020 (s) cm^{-1}; high-resolution mass spectrum, m/e (70 eV, EI) calcd ($M^+ - H_2$, H_2O)) 134.0731, obsd ($M^+ - H_2$, H_2O) 134.0698.

Bicyclo[4.4.1]undeca-1,3,6-triene (19). The above diol (0.10 g, 0.65 mmol) was oxidized to the dialdehyde by use of method B as described above using oxalyl chloride (0.23 mL, 2.64 mmol), Me_2SO (0.35 mL, 4.93 mmol), and Et_3N (1.45 mL, 10.4 mmol). Usual workup and analysis showed aldehyde protons: ^1H NMR (80 MHz, $CDCl_3$) δ 9.55 (s, aldehyde H), 5.75 (m, vinyl), 3.75–2.0 (complex m), 1.75 (d, J = 4 Hz, cyclopropane), 1.0 (m, cyclopropane). The crude dialdehyde was not isolated but subjected to bis-Wittig olefination as described above, using Ph_3PCH_2 (1.46 mmol). After workup the resulting pentane solution containing product had a strong, definite olefin smell. The product was isolated by preparative VPC (10-ft, 3% SP-216-PS, column temperature 135 °C, retention time 9 min): ^1H NMR (250 MHz, $CDCl_3$) δ 5.64 (m, 2 H, vinyl), 4.90 (m, 2 H), 3.3 (d, J = 13 Hz, 1 H), 3.1–2.4 (m, 6 H), 2.10 (m contains d, J = 13 Hz, 3 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 144.4, 126.5, 117.7, 38.5, 34.5, 25.5; IR (CCl_4) 3010 (m), 2966 (m), 2920 (s), 2860 (m), 2820 (m), 1660 (w), 1640 (w), 1480 (m), 1425 (m), 1190 (w), 650 (w) cm^{-1}; mass spectrum, m/e (EI, 70 eV) 146 (M^+); UV (cyclohexane) λ_{max} 230 nm.

Dimethyl Bicyclo[4.1.0]heptane-1,6-dicarboxylate. Dimethyl bicyclo[4.1.0]hept-3-ene-1,6-dicarboxylate[34] (0.90 g, 4.3 mmol) was hydrogenated in ethyl acetate (10 mL) over prereduced PtO_2 (0.115 g) for 5.5 h. The mixture was filtered and dried ($MgSO_4$), and solvent was removed in vacuo to yield 0.621 g of yellow oil. This was chromatographed on 20 g of silica gel (hexanes–ether, 4:1) to yield 0.534 g (59%) of clear liquid: ^1H NMR (250 MHz, $CDCl_3$) δ 3.66 (s, 6 H, OCH_3), 2.35 (m, 2 H), 1.84–1.14 (m, 6 H), 2.94, 1.00 (AB, J = 5.3 Hz, 2 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 173.6, 52.1, 31.7, 25.6, 22.7, 20.3; IR (neat) 2960 (s), 2880 (m), 1740 (vs), 1440 (m), 1255 (m), 1200 (m) cm^{-1}; high-resolution mass spectrum, m/e (70 eV, EI) calcd (M^+) 212.1048, obsd (M^+) 212.1069.

1,6-Bis(hydroxymethyl)bicyclo[4.1.0]heptane. Above diester (0.100 g, 0.472 mmol) was reduced to the diol as described above with LAH (0.045 g, 1.18 mmol) in Et_2O to yield after workup 0.086 g of viscous clear oil. Crude diol was chromatographed on 40 g of silica gel (Et_2O, R_f 0.48) to yield 0.0611 g (83%) of white crystalline diol: ^1H NMR (80 MHz, $CDCl_3$) δ 3.77, 3.31 (AB, J = 12 Hz, 4 H, RCH_2OH), 3.06 (br s, 2 H, O*H*), 2.25–1.0 (m, 8 H), 0.50, 0.39 (AB, J = 5.2 Hz, 2 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 69.5, 28.1, 27.3, 22.6, 20.7; IR (CCl_4) 3440 (s), 2936 (s), 1550 (m), 1450 (w), 1020 (m) cm^{-1}; high-resolution mass spectrum, m/e (70 eV, EI) calcd (M^+) 156.1150, obsd (M^+) 156.1132.

Bicyclo[4.4.1]undeca-1,6-diene (20). The above diol (0.1 g, 0.64 mmol) was oxidized by method B with Me_2SO (0.19 mL, 2.7 mmol), oxalyl chloride (0.13 mL, 1.41 mmol), and Et_3N (0.81 mL, 5.8 mmol). ^1H NMR (80 MHz, $CDCl_3$) indicated aldehyde protons at δ 9.42. This crude dialdehyde was subjected to bis-Wittig olefination as described previously with Ph_2PCH_2 (1.4 mmol). The reaction was stirred 8 h. Workup as above gave **20** which was isolated by VPC (5 ft 3% SP2100, column temperature 80 °C, retention time 10.8 min): ^1H NMR (80 MHz, $CDCl_3$) δ 4.75 (m, 2 H, vinyl), 3.16 (d, J = 12 Hz, 1 H), 3.0–1.5 (m, 13 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 147.7, 118.2, 36.8, 32.2, 27.4, 25.4; IR (CCl_4) 2930 (s), 2840 (m), 1650 (mw), 1485 (m), 1440 (m), 1030 (w) cm^{-1}; mass spectrum, m/e (EI, 70 eV) 148 (M^+); high-resolution mass spectrum, m/e (70 eV, EI) calcd (M^+) 148.1252, obsd (M^+) 148.1290.

1,6-Bis(hydroxymethyl)bicyclo[4.2.0]octane. Attempted LAH reduction of 7,9-dioxo-8-oxabicyclo[4.3.2]undecane[31] to the diol using a 2.2:1 molar ratio of LAH to anhydride lead only to lactone formation which gave the following spectral characteristics: ^1H NMR (80 MHz, $CDCl_3$) δ 4.13 (AB, J = 14 Hz, 2 H), 2.25–1.75 (m, 4 H), 1.72–1.50 (m, 8 H); IR (CCl_4) 2940 (s), 1780 (s), 1550 (s), 1255 (m), 1020 (m) cm^{-1}. The anhydride was successfully reduced to the diol using a molar ratio of 6.2:1 LAH:anhydride (ratios of 4:1 resulted in only partial reduction yielding a mixture of products). The following procedure was used:

LAH (1.32 g, 35 mmol) was placed in an oven-dried 50-mL 3-neck flask; Et_2O (20 mL) was added via double needle. The addition funnel was charged with anhydride (1.0 g, 5.6 mmol) in Et_2O (25 mL). The flask was cooled to −78 °C with stirring. The Et_2O solution of anhydride was added over 5 min, and then the mixture was stirred 2 h at −78 °C and refluxed for 6.5 h. The mixture was cooled to 0 °C and quenched by adding H_2O (1.32 mL), 10% NaOH (2.5 mL), and H_2O (3.5 mL). The precipitate was washed with Et_2O. Combined Et_2O was dried (Na_2SO_4) and concentrated to yield 0.82 g (86%) of clear viscous oil which partially crystallized upon standing. Product was recrystallized from pentane–ether, yielding white crystals: mp 149–151 °C; ^1H NMR (80 MHz, $CDCl_3$) δ 3.87, 3.33 (AB, J = 8 Hz, 4 H, 4-CH_2OH), 2.8 (s, 2 H, O*H*), 1.5 (m, 12 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 69.0, 43.0, 32.5, 24.4, 22.5; IR (neat) 3320 (vs), 2920 (vs), 2860 (s), 1460 (m), 1030 (m) cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.28; H, 10.75.

1,6-Divinylbicyclo[4.2.0]octane (16). The above diol (5.0 g, 29.42 mmol) was oxidized by method B with Me_2SO (16 mL, 225.5 mmol), oxalyl chloride (10 mL, 114.6 mmol), and Et_3N (66 mL, 473.5 mmol). After workup a small sample showed aldehyde protons by ^1H NMR (80 MHz, $CDCl_3$), δ 9.6 (s, aldehyde). After the removal of CH_2Cl_2 in vacuo, the crude dialdehyde was subjected to Ph_3PCH_2 (66.5 mmol). The reaction was stirred 9 h at room temperature, then quenched (H_2O), extracted (pentane), and filtered through silica gel to yield 2.61 g (54%) of a viscous clear oil. The product could not be isolated pure by VPC since this caused rearrangement to bicyclo[4.4.2]dodeca-1,6-diene (**21**). Product could be chromatographed on silica gel (pentanes–ether, 1:1, R_f 0.83) yielding a pure compound: ^1H NMR (80 MHz, $CDCl_3$) δ 6.12–5.75 (complex vinyl pattern, 2 H), 5.01–4.75 (complex vinyl pattern, 4 H), 1.75–1.25 (m, 12 H); mass spectrum, m/e (CI; isobutane, 100 eV) 163 (MH^+).

Bicyclo[4.4.2]dodeca-1,6-diene (21). Attempted preparative VPC isolation (5-ft 3% SP 2100, column temperature 150 °C, retention time 3.5 min) of **16** yielded pure bicyclo[4.4.2]dodeca-1,6-diene (**21**): ^1H NMR (250 MHz, $CDCl_3$) δ 5.25 (m, 2 H), 2.66, 2.53 (AB, J = 3.1 Hz, 2 H), 2.30 (m, 2 H), 2.2–1.82 (m, 8 H), 1.80–1.56 (m, 2 H), 1.55–1.20 (m, 2 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 143.1 (bridgehead c), 124.6, 40.3, 31.0, 28.6, 26.6; IR (CCl_4) 2926 (s), 1650 (w), 1478 (m), 1450 (m) cm^{-1}; mass spectrum, m/e (CI, isobutane, 100 eV) 163 (MH^+); high-resolution mass spectrum, m/e (70 eV, EI) calcd (M^+) 162.1409, obsd (M^+) 162.1432.

1,6-Bis(hydroxymethyl)bicyclo[4.4.0]decane. Bicyclo[4.4.0]deca-3-ene-1,6-dicarboxylic anhydride[38] (2.0 g, 9.71 mmol) was hydrogenated over prereduced PtO_2 (0.03 g) at 1 atm in AcOH (25 mL) overnight. Filtration and removal of AcOH in vacuo yielded a viscous residue which was filtered through a plug of silica gel using 4:1 hexanes–ether. Concentration yielded 1.42 g (70.3%) of white solid.

Reduction with LAH (1.13 g, 29.8 mmol) as described previously gave after workup 0.78 g (82%) of the diol which was recrystallized (4:1 hexane–ether): mp 152 °C (lit. 165–167 °C);[38] ^1H NMR (80 MHz, $CDCl_3$) δ 3.65 (br m, 4 H, RCH_2OH), 2.65 (br m, 2 H, O*H*), 1.52 (br s, 16 H); IR (KBr) 3270 (s), 2920 (s), 2860 (s), 1460 (m), 1440 (m), 1280 (w), 1075 (w), 1045 (s), 1020 (vs), 1000 (s), 965 (s) cm^{-1}.

1,6-Divinylbicyclo[4.4.0]decane (29). The above diol (0.13 g, 0.67 mmol) was oxidized by method B with Me_2SO (0.20 mL, 2.8 mmol), oxalyl chloride (0.14 mL, 1.5 mmol), and Et_3N (0.85 mL, 6.05 mmol) and then subjected to Ph_3PCH_2 (1.48 mmol) as described previously to yield **29** isolated by preparative VPC (5-ft 3%, SP2100, column temperature 95 °C, retention time 10.8 min): ^1H NMR (250 MHz, $CDCl_3$) δ 6.28 (dd, J_{cis} = 11.15 Hz, J_{trans} = 17.65 Hz, 2 H, R*H*C=CH$_2$), 5.00 (dd, J_{cis} = 11.1 Hz, J_{gem} = 1.6 Hz) 4.93 (dd, J_{trans} = 17.64 Hz, J_{gem} = 1.55 Hz, total integration for 5.00 and 4.93 = 4H), 1.56 (m, 10 H), 1.28 (d, J = 13.5 Hz), 1.11 (d, J = 13.5 Hz, total integration for 1.28 and 1.11 = 6 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 146.2, 111.9, 41.1, 33.6, 31.9, 22.2, 21.8; IR (CCl_4) 2940 (s), 2860 (m), 1640 (w), 1470 (m), 1050 (w), 910 (m) cm^{-1}; mass spectrum, m/e (CI, isobutane, 100 eV) 191 (MH^+); high-resolution mass spectrum, m/e (70 eV, EI) calcd (M^+) 190.1722, obsd (M^+) 190.1714.

Addition of Br_2 to Bicyclo[4.3.2]undeca-1,5-diene (18). In an oven-dried 25-mL round-bottom flask was placed **18** (0.023 g; VPC prepped). A magnetic stir bar was added and the flask was capped with a rubber septum. The flask was flushed with N_2 and CH_2Cl_2 (5 mL) syringed in. The solution was cooled to −78 °C, and 5% Br_2/CH_2Cl_2 was added dropwise via syringe until the Br_2 color just persisted. The solution was allowed to warm to room temperature and concentrated, filtered through Florisil (1:1 pentanes–ether), dried (Na_2SO_4), and concentrated in vacuo to yield 0.0187 g of viscous clear oil containing some needle crystals. Recrystallization (EtOH-$CHCl_3$) gave clear needle crystals of dibromide **32**: mp 69–70 °C; ^1H NMR (250 mHz, $CDCl_3$) δ 4.1 (t, J = 10.26 Hz, 1 H), 2.5–0.9 (m, 15 H); ^{13}C (62.9 MHz, $CDCl_3$) δ 64.1, 59.5, 57.2, 44.1, 36.8, 35.9, 33.7, 31.7, 29.5, 25.4, 20.9; mass spectrum, m/e (CI, isobutane, 100 eV) 228 ($M^+ - 80$, M − Br), 229 ($MH^+ - 80$, $MH^+ - Br$); high-resolution mass spectrum, m/e (70 eV, EI) calcd (M^+) 305.9619, obsd (M^+), 305.9642.

(38) Altman, J.; Babad, E.; Itzchaki, J.; Ginsburg, D., *Tetrahedron suppl.* **1966**, *no.* 8, 279.

Addition of Br_2 to Bicyclo[4.4.2]doceda-1,6-diene (21). Diene **21** (9.3 mg) was dissolved in 10 mL of dry CCl_4 in a foil-covered flask. To this was added 5% Br_2/CCl_4 (1.8 mL) via syringe (Br_2 color just persisted). The CCl_4 solution was filtered through Florisil and CCl_4 removed in vacuo to yield 0.030 g of viscous clear oil (**35**): ^1H NMR (80 MHz, $CDCl_3$) δ 4.13 (m, 1 H), 2.80–1.13 (m, 17 H); ^{13}C (62.9, $CDCl_3$) δ 79.5, 77.1, 64.1, 54.7, 49.3, 41.9, 37.9, 35.6, 34.7, 30.8, 25.5, 25.4; mass spectrum, *m/e* (CI, isobutane, 100 eV) 321 (MH^+), 241 ($MH^+ - 80$, $MH^+ - Br$); high-resolution mass spectrum, *m/e* (70 eV, EI) calcd (M^+) 319.9775, obsd (M^+) 319.9744.

Acknowledgment. We wish to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for financial support of this work. We also wish to thank Professor Robert Doedens for assistance with the X-ray crystal structure determination.

Supplementary Material Available: Tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances (4 pages); tables of structure factors for dibromide **32** (3 pages). Ordering information is given on any current masthead page.

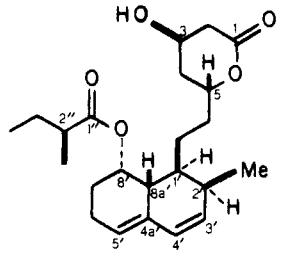
Convergent, Enantiospecific Total Synthesis of the Hypocholesterolemic Agent (+)-Compactin

Paul A. Grieco,* Randall Lis, Robert E. Zelle, and John Finn

Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47405. *Received January 7, 1986*

Abstract: A convergent, enantiospecific total synthesis of (+)-compactin (**1**) is described. The strategy for the construction of (+)-**1** centers around a Diels–Alder reaction between chiral dienophile **23** and chiral diene **62** which provides in a single operation access to allylic sulfide **85** possessing the desired configuration at C(8′), C(8a′), and C(1′). Dienophile **23** is made readily available by resolution of the known racemic β-nitro acid **66**. The synthesis of diene **62** commences with the known epoxide **7** derived from tri-*O*-acetyl-D-glucal. Diels–Alder adduct **85** is transformed into allylic alcohol **87** which sets the stage for incorporation of the C(2′) methyl group. Elaboration of the hexalol portion of compactin with liberation of the C(8′) hydroxyl group is achieved via a Grob-like fragmentation on alcohol **95**. Acylation of **94**, subsequent adjustment of the oxidation state at C(1), and demethylation give way to (+)-compactin.

Compactin (**1**), a fungal metabolite of *Penicillium brevicompactum*, was isolated in 1976 by Brown and co-workers.[1] Concurrently, Endo and co-workers[2] isolated a substance, ML 236B, from strains of *Penicillium citrinum* which proved to be identical with compactin. Compactin was first shown to have antifungal



I

activity[1] but is best known for its hypocholesterolemic activity.[3] Compactin is a potent competitive inhibitor of the microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-determining enzyme in cholesterol biosynthesis.[4]

Compactin's unique structure which possesses a sensitive β-hydroxy lactone moiety and a hexahydronaphthalene unit containing four contiguous chiral centers [C(2′), C(1′), C(8a′), and C(8′)] makes it a synthetically challenging target. Since the disclosure that compactin is a potent competitive inhibitor of HMG-CoA reductase, it has been the object of intense synthetic activity. There have been numerous synthetic approaches to the hexahydronaphthalene fragment[10] and the β-hydroxy lactone portion[10b,11] of compactin. Simple synthetic analogues of compactin have also been described in the literature.[11a,b,12] The first

(1) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.
(2) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.
(3) (a) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. (b) Brown, M. S.; Faust, J. R.; Goldstein, J. L. *J. Biol. Chem.* **1978**, *253*, 1121. (c) Tanzawa, K.; Endo, A. *Eur. J. Biochem.* **1979**, *98*, 195. For a recent review of compactin's activity, see: Endo, A. *Trends Biochem. Sci. (Pers. Ed.)* **1981**, *6*, 10.
(4) The major cause of death in the western hemisphere is coronary artery disease which is attributed in most cases to hypercholesterolemia.[5] The use of compactin has caused a marked decrease in serum cholesterol levels in rabbits, hens, dogs,[6] monkeys,[7] and humans.[8,9] Use of compactin or other hypocholesterolemic drugs may be a way to control or alleviate coronary artery disease.
(5) Kannel, W. B.; Castelli, W. P.; Gordon, T.; McNamara, P. M. *Ann. Med. Interne* **1971**, *74*, 1. Stamler, J. *Arch. Surg. (Chicago)* **1978**, *113*, 21.
(6) Tsujita, Y.; Kuroda, M.; Tanzawa, K.; Kitano, N.; Endo, A. *Atherosclerosis (Shannon, Irel.)* **1978**, *32*, 307.
(7) Kuroda, M.; Tsujita, Y.; Tanzawa, K.; Endo, A. *Lipids* **1979**, *14*, 585.
(8) Yamamoto, A.; Sudo, H.; Endo, A. *Atherosclerosis (Shannon, Irel.)* **1980**, *35*, 259.
(9) Mabuchi, H.; Haba, T.; Tatami, R.; Miyamoto, S.; Sakai, Y.; Wakasugi, T.; Watanabe, A.; Koizumi, J.; Takeda, R. *N. Engl. J. Med.* **1981**, *305*, 478.
(10) (a) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (b) Heathcock, C. H.; Taschner, M. J.; Thomas, J. A. *Abstracts of Papers*, 183rd National Meeting of the American Chemical Society, Las Vegas, NV; American Chemical Society: Washington, DC, 1982; ORGN 13. (c) Deutsch, E. A.; Snider, B. B. *J. Org. Chem.* **1982**, *47*, 2682. (d) Heathcock, C. H.; Taschner, M. J.; Rosen, T.; Thomas, J. A.; Hadley, C. R.; Popjak, G. *Tetrahedron Lett.* **1982**, *23*, 4747. (e) Anderson, P. C.; Clive, D. L. J.; Evans, C. F. *Tetrahedron Lett.* **1983**, *24*, 1373. (f) Funk, R. L.; Mossman, C. J.; Zeller, W. E. *Tetrahedron Lett.* **1984**, *25*, 1655.
(11) (a) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* **1982**, *23*, 281. (b) Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1982**, *23*, 4305. (c) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (d) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981. (e) Rosen, T.; Taschner, M. J.; Heathcock, C. H. *J. Org. Chem.* **1984**, *84*, 4003.
(12) (a) Sato, A.; Ogiso, A.; Noguchi, H.; Mitsui, S.; Kaneko, I.; Shimada, Y. *Chem. Pharm. Bull.* **1980**, *28*, 1509. (b) Lee, T.-J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982**, *47*, 4750. (c) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991. (d) Lee, T.-J. *Tetrahedron Lett.* **1985**, *26*, 4995. (e) Yang, Y.-L.; Manna, S.; Falck, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 3811.

0002-7863/86/1508-5908$01.50/0