naphthene (59) as quenchers. These were conducted in a merry-go-round apparatus (Corning glass filter 0.52, medium pressure mercury lamp) with a quencher concentration of 0.06 M and a thione concentration of 0.04 M. A control having 0.04 M thione without quencher was also irradiated. After 25 h of irradiation, the solvent was evaporated under reduced pressure and the products were chromatographed. The thioacetoxy signal was monitored with respect to the internal standard. The reaction was quenched by phenanthrene, naphthalene, and acenaphthene, while fluorene was not effective. Therefore the triplet T_1 is concluded to be the reactive state.

5. Oxidation of Arylalkylcyclopropenethiones. Dye-sensitized oxidation of **1b–e** was conducted by irradiating aerated solutions of **1b–e** (0.01 M in benzene, chloroform, and acetonitrile) in the presence of appropriate dyes (10^{-4} M methylene blue or rose bengal). Selective excitation of the dye was achieved by using Corning glass filter CS-2.58 (transmission above 630 nm). Corresponding cyclopropenones **7** were isolated in 60% yield as the only products in all four cases.

Triphenyl phosphite ozonide was prepared at −78 °C in dichloromethane by following the reported procedure.[16] The above solution was warmed to −10 °C at which time oxygen evolution was visible and at this stage **1b–e** were added. After the reaction mixture was kept at room temperature for about an hour, the solvent was evaporated and the products were separated by column chromatography. Similar to dye-sensitized oxidation, the corresponding cyclopropenones **7** were isolated as the only products.

6. Miscellaneous Experiments. (a) Photolysis of Arylalkylcyclopropenones. Irradiation of arylalkylcyclopropenones (corresponding to **1b–e**) in methanol and benzene with a 450-W medium pressure mercury lamp for 20 h resulted in the formation of the corresponding acetylenes. These were identified by their spectral properties and by comparison with authentic samples.

(b) Acid Hydrolysis of Methyl 3-Methoxy-2-phenylbutenethioate (5b). To 100 mg of **5b** in 20 mL of methanol was added a drop of dilute hydrochloric acid, and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, extracted with ether, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave **6b** (90%). Spectral data of **6b** are provided in Table II.

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Registry No. **1a**, 2570-01-6; **1b**, 56764-07-9; **1c**, 77853-14-6; **1d**, 97703-38-3; **1e**, 97703-39-4; **2**, 35093-32-4; **3**, 82246-85-3; **4**, 97703-40-7; **5b**, 97703-41-8; **5c**, 97703-42-9; **5d**, 97703-43-0; **5e**, 97703-44-1; **6b**, 97703-45-2; **6c**, 97703-46-3; **7a**, 26307-30-2; **7c**, 5909-87-5; **7d**, 97703-47-4; **7e**, 69425-02-1; Michler's ketone, 90-94-8; triphenyl phosphite ozonide, 29833-83-8.

(16) Murray, R. W.; Kaplan, M. L. *J. Am. Chem. Soc.* **1969**, *91*, 5358.

Total Synthesis of Halogenated Monoterpene Marine Natural Products via the Diels–Alder Reaction

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This work represents the first de novo synthetic approach to the halogenated, monocyclic monoterpenes isolated from red algae belonging to the genus *Plocamium*. The total syntheses of two natural products, i.e., *epi*-plocamene D (**2**) and the allylic chloride **3**, are presented along with an approach to the synthesis of violacene (**1**). A key step in the construction of the terpenoid skeleton is the Diels–Alder reaction utilizing a β-halogenated dienophile. The stereochemistry, regiochemistry, yields, and rates are compared for Diels–Alder reactions between the β-halogenated dienophiles *cis*- or *trans*-3-chloro-2-methylpropenal (**5** and **6**) and the dienes butadiene, isoprene, or cyclopentadiene. These results are compared with the corresponding Diels–Alder reactions of nonhalogenated dienophiles. All of the known, halogenated monocyclic *Plocamium* monoterpenes are classified according to a Diels–Alder retrosynthetic analysis.

Introduction

An unusual set of halogenated monoterpenes has been isolated from red algae belonging to the genus, *Plocamium*.[1] Violacene (**1**), isolated by Mynderse and Faulkner in 1974,[2] was the first monocyclic monoterpene in this series to be described. Compound **1** exhibits the most complex pattern of halogenation yet found among the monocyclic *Plocamium* metabolites. The correct structure for **1** was confirmed by X-ray diffraction analysis after some initial confusion about the location of the bromine atom.[3,4] Violacene (**1**) is relatively ubiquitous with respect to other *Plocamium* metabolites, since it was isolated from several sources in combination with other monoterpenes.[5] Its unique pattern of halogenation poses an unprecedented challenge for the stereo- and regiospecific introduction of halogen into organic molecules. Although a total synthesis

(1) An excellent compilation of *Plocamium* metabolites can be found in the following reviews: (a) Sims, J. J.; Allan, F.; Izac, Richard, R. "Applications of ^{13}C NMR to Marine Natural Products" in "Marine Natural Products: Chemical and Biological Perspectives"; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol 2, p 297–378. (b) Naylor, S.; Hanke, F. J.; Manes, L. V.; Crews, P. "Chemical & Biological Aspects of Marine Monoterpenes" in "Prog. in Chem. of Org. Nat. Prods."; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1983; Vol. 44, p 190–241. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, 252–280.

(2) Mynderse, J. S.; Faulkner, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 6771.

(3) Van Engen, D.; Clardy, J.; Kho-Wiseman, E.; Crews, P.; Higgs, M. D.; Faulkner, D. J. *Tetrahedron Lett.* **1978**, 29.

(4) The original structure of violacene (**1**) had the primary bromide and the tertiary chloride interchanged. The incorrect structure apparently was based upon interpretation of mass spectral data. An unprecedented halogen migration seems to have occurred in this experiment. Even now the structural assignment of highly halogenated marine metabolites remains a significant problem. For a recent discussion of this problem see: Crews, P.; Naylor, S.; Hanke, F. J.; Hogue, E. R.; Kho, E.; Braslau, R. *J. Org. Chem.* **1984**, *49*, 1371.

(5) Violacene (**1**) has been reported by several investigators including the following: (a) Crews, P.; Kho, E. *J. Org. Chem.* **1975**, *40*, 2568. (b) Crews, P.; Ng, P.; Kho-Wiseman, E.; Parce, C. *Phytochemistry* **1976**, *15*, 1707. (c) Crews, P.; Campbell, L.; Heron, E. *J. Phycol.* **1977**, *13*, 297. (d) Crews, P.; Kho-Wiseman, E.; Montana, P. *J. Org. Chem.* **1978**, *43*, 116. (e) Mynderse, J. S.; Faulkner, D. J. *Phytochemistry* **1978**, *17*, 237. (f) Higgs, M. D.; Vanderah, D. J.; Faulkner, D. J. *Tetrahedron* **1977**, *33*, 2775. (g) Stierle, D. B.; Sims, J. J. *Tetrahedron* **1979**, *35*, 1261.

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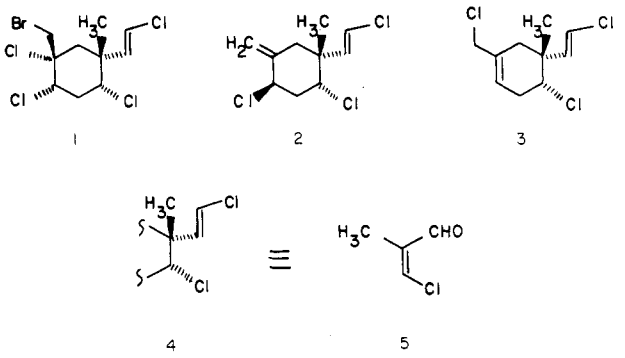


Figure 1.

of **1** remains elusive, we now report our approach to the total synthesis of this compound along with the total syntheses of two related *Plocamium* metabolites shown in Figure 1 as **2** and **3**.[6]

As part of the project whose goal is the synthesis of halogenated marine natural products, we sought new methods for the stereo- and regiospecific introduction of halogen atoms into organic molecules. The time-honored methods of electrophilic addition or nucleophilic substitution have certainly been applied to the total synthesis of halogenated marine metabolites.[7] However, both steric and stereoelectronic effects, i.e., Markovnikov addition rules, impose a well-defined set of limitations on the introduction of halogen by electrophilic addition. Introduction of halogen by nucleophilic substitution reactions is also fraught with limitations.

In an attempt to overcome some of the constraints associated with the reactions noted above, we began to explore the possibility of utilizing a [4 + 2] cycloaddition reaction for the stereo- and regiospecific introduction of halogen atoms into organic molecules. Thus the presentation of results on the use of β-chloroacroleins as dienophiles precedes the presentation of our total syntheses. These results demonstrate that halogen atoms can be introduced with predetermined geometry into organic molecules by the Diels–Alder reaction.

A common structural feature found in all three of the natural products depicted in Figure 1 is the fragment **4**. Use of the (*Z*)-β-chloromethacrolein **5** as a dienophilic precursor of **4** led us to the first total syntheses of monocyclic, halogenated *Plocamium* metabolites. It will be shown that the Diels–Alder reactions with isomeric β-halogenated dienophiles can lead to total syntheses of several halogenated *Plocamium* monoterpenes. This Diels–Alder reaction with β-halogenated dienophiles is also shown to be a useful method for the stereospecific introduction of halogen into organic compounds.

Results

The two β-dienophiles which we studied are *cis*- and *trans*-3-chloro-2-methylpropenals (**5** and **6**). Compound **5** is prepared by a procedure previously described by us and has been utilized in the total synthesis of costatolide and costatone.[8] Compound **6** is obtained by the Vilsmeier–Arnold–Haack reaction of propionaldehyde with a chloromethylene iminium salt.[9] We compared the [4 + 2] cycloaddition reactions of the two aldehydes **5** and **6** with three simple dienes: butadiene (**7**), isoprene (**8**), and cyclopentadiene (**9**). All cycloaddition reactions were carried out in a sealed tube in toluene solution at 150 °C over a period of 24 h. The products obtained for these cycloaddition reactions, the isomer distributions, and the yields are summarized in Figure 2.

Structural assignment for the cyclohexenes **10** and **11** is unambiguous since no regioisomers are possible in the cycloaddition reaction leading to their formation. A conclusion drawn from Figure 2 is that in the reactions of **5** or **6** with the various dienes, consistently higher yields of cycloaddition products were obtained from **5** than were obtained from **6**. This observation was confirmed by monitoring separate small-scale reactions of **5** and **6** with butadiene under identical conditions by NMR. A surprising result obtained from this NMR experiment is that formation of the cycloadduct **10**, by reaction of **5** with butadiene, proceeds at a rate somewhat faster than the formation of the cycloadduct **11** from butadiene (**7**) and the β-haloacrolein **6** (vide infra).

We had noted previously that the cis dienophile **5** is almost quantitatively converted into the trans dienophile **6** by trace acid catalysis.[8a] In the absence of an acid scavenger, the reaction of **5** with butadiene (**7**) yields a mixture of cycloadducts **10** and **11** due to isomerization of **5** to **6** before cycloaddition occurs. In order to avoid this undesirable isomerization by traces of acid liberated by dehydrohalogenation of a cycloadduct or by cyclocondensation of the β-haloacroleins (**5** or **6**) with themselves,[10] propylene oxide was added to each of the cycloaddition reactions as an acid scavenger.

We demonstrated that the cycloadducts **10** and **11** neither interconvert nor decompose significantly when these compounds are isolated and individually resubmitted to the reaction conditions. We also determined that selective destruction of either of the dienophiles **5** or **6** does not occur under the conditions of the reaction. The observation that **5** undergoes a faster cycloaddition reaction than **6** appears to be valid for all cycloaddition reactions of these dienophiles with the dienes **7**–**9**. This difference in the cycloaddition rates of **5** and **6** is great enough to effect kinetic separation of a mixture of these two dienes. Kinetic separation in the cycloaddition reaction proved advantageous because a 1:1 mixture of **5** and **6** is readily available on a large scale.[8a] We utilize the cyclohexene **10** as a starting material for synthesis of natural products **2** and **3**.

Qualitatively, a similar rate difference was observed for the reaction of **5** or **6** with butadiene (**7**) or with isoprene (**8**); i.e., **5** undergoes cycloaddition faster than **6**. A quantitative assessment of the rate difference in the isoprene reactions is difficult because of the additional complication of regioisomeric products.

An accurate isomer ratio of the cycloadducts **12**/**13** and **14**/**15** is obtained by direct integration of the 250-MHz ^{1}H NMR spectra of the two different mixtures of aldehydes, **12**/**13** or **14**/**15**, provided that unambiguous NMR assignments are made for these compounds. In order to

(6) The isolation of natural products **2** and **3** is described: Stierle, D. B.; Sims, J. J. *Tetrahedron* **1979**, *35*, 1261.

(7) Syntheses of halogenated marine terpenoids which utilize electrophilic addition reactions include the following: (a) Gonzalez, A. G.; Martin, J. D.; Perez, C.; Ramierz, M. A.; Rauclo, P. *Tetrahedron Lett.* **1980**, 187. (b) Murai, A.; Kato, K.; Masamune, T. *Tetrahedron Lett.* **1982**, 2887. (c) Hoye, T. R.; Kurth, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5065. (d) White, J. D.; Nishiguchi, T.; Skeear, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 3923. (e) Hoye, T. R.; Caruso, A. J.; Dellaria, J. F.; Kurth, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 6704. (f) Goscelin, P.; Rouessac, F. *Tetrahedron Lett.* **1983**, 3351. (g) Kato, T.; Ichinose, I.; Kamoshida, A.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 518. (f) Faulkner, D. J. *Pure and Appl. Chem.* **1976**, *48*, 25 and references therein.

(8) (a) Williard, P. G.; Grab, L. A.; de Laszlo, S. E. *J. Org. Chem.* **1983**, *48*, 1123. (b) Williard, P. G.; Grab, L. A. *Tetrahedron Lett.* **1984**, 5009.

(9) Arnold, A.; Zemlicka, Z. *J. Collect. Chem. Comm.* **1959**, *24*, 2385.

(10) See: Jutz, C. In "Advances in Organic Chemistry: Methods and Results"; Boehme, H., Viehe, H. G., Eds.; Wiley: New York, 1976; Vol. 9, p 324–333.

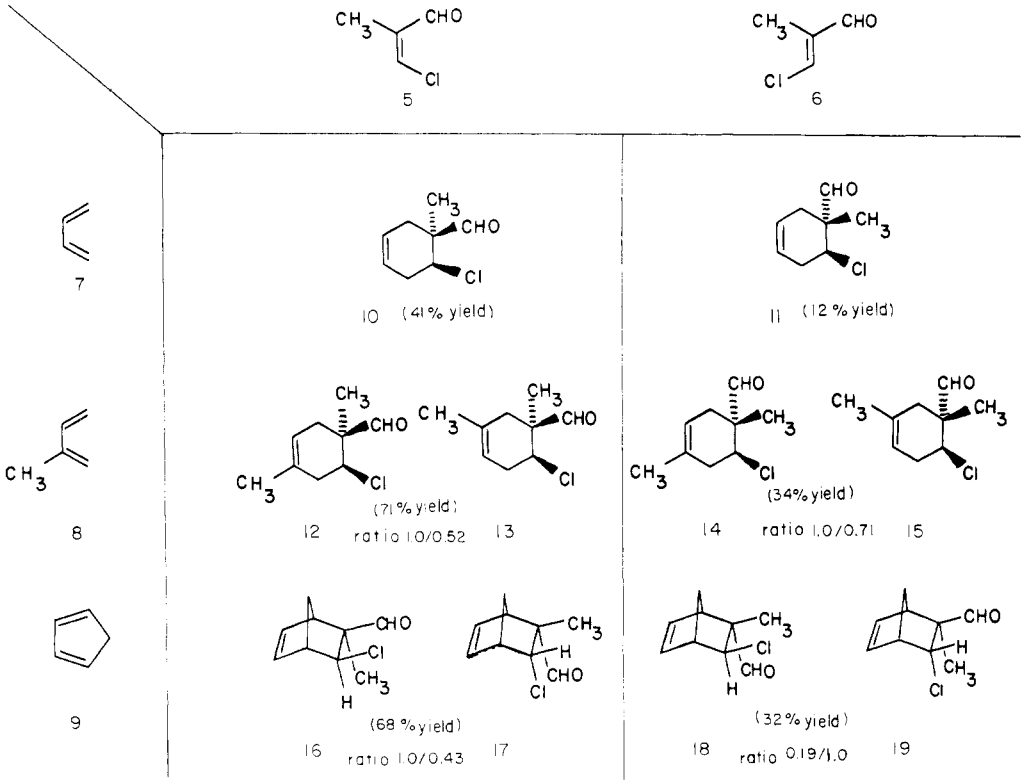
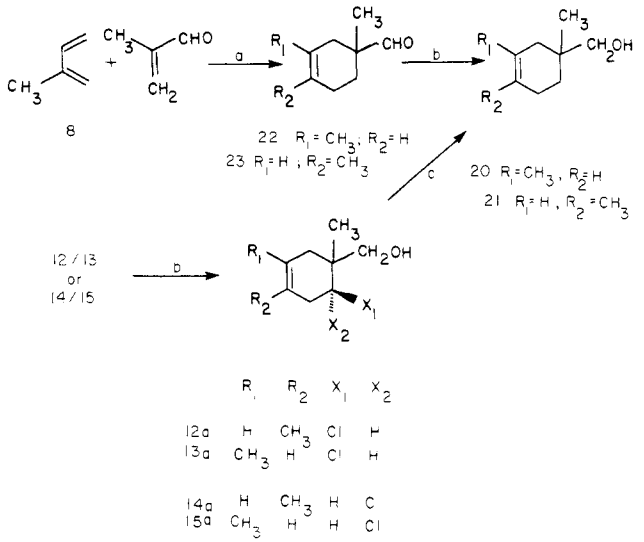


Figure 2. Yields and products ratios for the reaction of **5** or **6** with the dienes **7–9**.

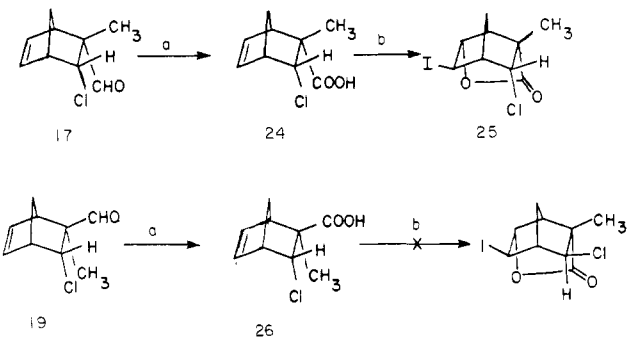
Scheme I[a]



	R_1	R_2	X_1	X_2
12a	H	CH_3	Cl	H
13a	CH_3	H	Cl	H
14a	H	CH_3	H	Cl
15a	CH_3	H	H	Cl

[a] a, 150 °C, toluene; b, lithium aluminum hydride; c, Li^0, *t*-BuOH.

Scheme II[a]



[a] a, PDC, DMF; b, I^-, I_2, $NaHCO_3$.

assign structures to the cycloadducts **12–15** the chemical correlations shown in Scheme I were performed. The two mixtures of regioisomers **12/13** and **14/15** were first reduced with LAH to a corresponding mixture of primary alcohols **12a/13a** and **14a/15a**. Each of the two mixtures of alcohols was separately treated with Li metal in the presence of 2-methyl-2-propanol to reduce the secondary chlorine atom.[11] These tandem reductions produce two separate mixtures of primary alcohols, **20/21**, whose ratio is approximately equivalent to the ratio of regioisomers **12/13** or **14/15** obtained in the Diels–Alder reaction.

An authentic sample of the mixture of alcohols **20/21** was prepared by LAH reduction of the mixture of cycloadducts **22/23**. The mixture of **22/23** is obtained by reaction of isoprene (**8**) with methacrolein. Since the 1,4-adduct, **23**, is known to be the major product of the methacrolein cycloaddition,[12] the resolved peaks in the high-field ^{1}H NMR spectrum of the mixture of alcohols **20/21** prepared from methacrolein are assigned unambiguously on this basis. Correlation of the three different mixtures of alcohols **20/21** obtained from the three different sources shown in Scheme I permits unambiguous assignment of major and minor isomers and, by analogy, of the ratio of aldehydes **12/13** or **14/15** obtained directly from the Diels–Alder reaction.

This assignment is valid if the isomer ratios **12/13** and **14/15** remain relatively constant throughout the series of two reductions which convert these cycloadducts into the alcohols **20/21**. This assumption is verified in the Experimental Section. We are unable to separate the mix-

(11) Bruck, P.; Thomson, D.; Winstein, S. *Chem. Ind. (London)* **1960**, 405.

(12) Kochel, G. N.; Farberov, M. I. *Izv. Vysshikh. Vchebn, Zavedenii, Khim. i Khim. Teknol.* **1964**, *7*, 639.

tures of aldehydes **12/13** or **14/15** (or the corresponding mixture of alcohols **12a/13a** or **14a/15a**) into pure components in order to characterize the individual compounds satisfactorily other than as a mixture of two components as described.

Structures of the exo/endo adducts **16–19** obtained from reaction of **5** or **6** with cyclopentadiene (**9**) (see Figure 2) are assigned according to the reactions depicted in Scheme II. The mixture of aldehydes **16/17**, obtained from the cycloaddition reaction of **5** with **9**, is separable by flash chromatography. The minor isomer is assigned structure **17** because oxidation with PDC[13] produces the carboxylic acid **24**, which when treated with potassium iodide/iodine in sodium bicarbonate solution[14] is transformed into a bicyclic lactone **25**. Lactonization confirms the endo orientation of the carbonyl moiety. Once compound **17** was unambiguously identified, the ratio of exo/endo adducts **16/17** could be assigned by direct integration of the 250-MHz ^{1}H NMR spectrum of the reaction mixture itself.

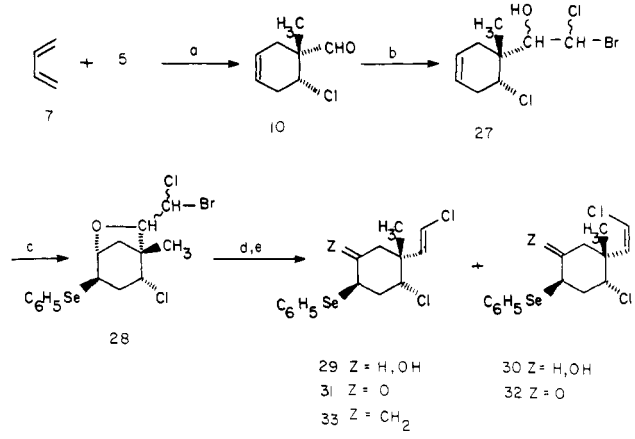
Separation of the mixture of Diels–Alder adducts **18/19** is achieved by small-scale distillation. However, we find it to be more expedient to oxidize the mixture of cycloadducts **18/19** with PDC (pyridinium dichromate) in dimethylformamide. Oxidation produces a crude oil in 66% yield. This oil consists of only one compound by high-field ^{1}H NMR. The single carboxylic acid produced from the oxidation of a mixture of **18/19** is identical with the oxidation product derived from the major Diels–Alder adduct after purification from the minor isomer by distillation. This single carboxylic acid was obtained as a crystalline, white solid which resisted all attempts to form a tricyclic iodolactone. Hence, this acid is assigned as the exo acid, structure **26**. It follows that the major Diels–Alder adduct from cycloaddition of **6** with cyclopentadiene (**9**) is the exo-cyclic carboxaldehyde **19**.

Presumably, the minor Diels–Alder adduct **18**, which is present to the extent of approximately 15%, undergoes a selective decomposition during the PDC oxidation reaction. This would explain why oxidation of the mixture of **18/19** yielded only the single carboxylic acid **26**. It is not inconceivable that the chromium oxidation could induce an oxidative decarboxylation via radical intermediates of the minor β-halo carboxylic acid derived from **19** and that this decarboxylation product is lost in the subsequent acid–base extraction.[15]

Since cycloaddition reaction between **5** and monosubstituted dienes such as isoprene gives a mixture of regioisomers, a straightforward construction of the terpenoid skeleton found in 1–3 was not feasible by cycloaddition of **5** with a 2-substituted diene. Thus, we selected cycloadduct **10** as the starting point for the synthetic work. Compound **10** is a convenient starting material for total synthesis because no regioisomers are possible in the cycloaddition reaction leading to its formation.

A mixture of diastereomeric secondary alcohols, **27**, is obtained by addition of the bromochloromethylide anion to the aldehyde **10**. We find it most convenient to employ the lithium salt of this anion, formed in situ from bromochloromethane and lithium dicyclohexylamide, as the nucleophile for this addition.[16] The mixture of alcohols, **27**, consists of up to four diastereomers.[17] Since the diastereomeric alcohols **27** are not readily separable, the entire mixture of diastereomers is immediately cyclized to a mixture of diastereomeric bicyclic ethers **28** by treatment with phenylselenenyl chloride.[18] Reductive elimination of the bicyclic ethers **28** with activated zinc in ether produces an approximately 1:1 mixture of only two products, i.e., the *E* and *Z* chloro olefins **29** and **30**.[19] The olefinic isomers **29** and **30** are easily separable by column chromatography on silica gel after oxidation to the ketones **31** and **32** with Me_2SO/trifluoroacetic anhydride.[20] Stereochemistry of the two olefinic isomers **31/32** was deduced from the three-bond (^{1}HC=C^{1}H) coupling constants of the olefinic protons (J_{cis} = 7.5 Hz) and (J_{trans} = 13.5 Hz).

Scheme III[a]



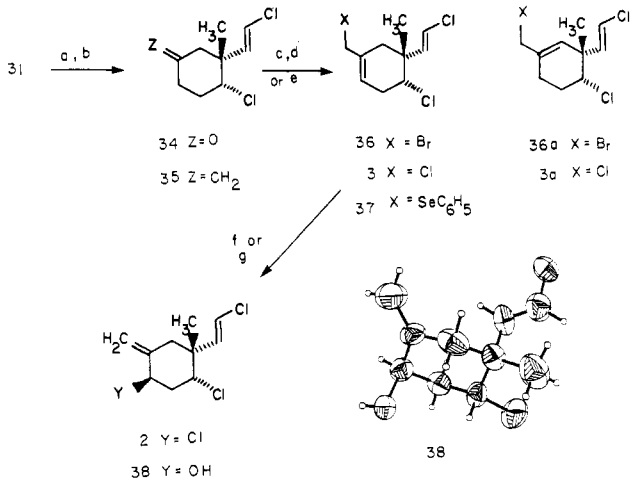
[a] a, 170–180 °C; toluene; b, Li$^+$ CHClBr$^-$, THF; c, C_6H_5SeCl, CH_2Cl_2; d, Zn^0, CH_2Cl_2, HOAc; e, $(CF_3CO)_2O$, Me_2SO, CH_2Cl_2.

It is possible to obtain several hundred milligrams of the pure *E* chloro olefin **31** in about 10% yield from the Diels–Alder adduct **10** in a preparative-scale run as outlined in Scheme III. The stereochemistry of cyclohexanone **31** is confirmed by ^{1}H NMR decoupling experiments. The ketone **31** is the keystone for our synthesis of the natural products 1–3.

Several functional group interconversions failed to transform the ketone **31** into a natural product easily. At first we attempted to convert the ketone of cyclohexanone **31** into the exocyclic methylenecyclohexane **33** by utilizing phosphorous or sulfur ylides without success. Although we could methylenate α-(phenylselenenyl)cyclohexanone with $Zn/CH_2Br_2/TiCl_4$[21] in moderate yield, this same re-

(13) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(14) (a) van Tamelen, E. E.; Shamma, M. *J. Am. Chem. Soc.* **1954**, *76*, 2315. (b) Kline, J. *J. Am. Chem. Soc.* **1959**, *81*, 3611.
(15) For evidence of radical intermediates in Cr(IV) oxidations of organic substrates see: Wiberg, K. B.; Szeimies, G. *J. Am. Chem. Soc.* **1974**, *96*, 1889 and references therein.
(16) Taguchi, H.; Tamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 3010.
(17) We have observed some interesting diastereoselectivity in the addition of the bromochloromethylide anion **6**. Depending upon the reaction conditions, the alcohols **7** can be obtained as an approximately 1:1:1:1 mixture of the four possible diastereomers or simply as a 1:1 mixture of only two major diastereomers. We have not been able to separate and purify these diastereomers satisfactorily. However, the diastereoselectivity of the addition of the bromochloromethylide anion to aldehydes and unsymmetrical ketones is noteworthy and will be investigated in further detail.
(18) Nicolaou, K. C.; Lysenko, Z. *Tetrahedron Lett.* **1977**, 1257.
(19) A similar reductive elimination to form bromo olefins was recently described, c.f. Williams, D. R.; Nishitani, K.; Bennett, Ward; Sit, S. Y. *Tetrahedron Lett.* **1981**, 3745.
(20) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
(21) Lombardo, L. *Tetrahedron Lett.* **1982**, 4293.
(22) Corey, E. J.; Petrzilka, M.; Veda, Y. *Tetrahedron Lett.* **1975**, 4343.
(23) Barton, D. H. R.; Miller, E. *J. Am. Chem. Soc.* **1950**, 72, 370. Lucas, H. J.; Kennedy, E. R. "Organic Syntheses"; Wiley: New York; Vol. III, 1955, p 482.
(24) Compound **38** was assigned to the rhombohedral space group, $R\bar{3}$. The unit cell parameters were determined to be $a = b = c = 15.737$ (4) Å and $\alpha = \beta = \gamma = 116.93$ (1)°. The unit cell contained six asymmetric units of molecular formula $C_{10}H_{14}Cl_2O$ in a volume of 1739.0 Å^3. The final agreement factors for this structure were $R = 0.0366$ and $R_w = 0.0468$. A set of crystallographic parameters can be found in the supplementary material.

Scheme IV[a]



[a] a, Zn^0, CH_2Cl_2, HOAc; b, Ti^4, Zn, CH_2Br_2; c, NBS, DME, H_2O; d, $NaBH_4$, $C_6H_5SeSeC_6H_5$; e, NaOCl, CH_2Cl_2; f, $C_6H_5ICl_2$, $CHCl_3$; g, H_2O_2, THF.

action fails to produce the corresponding exocyclic methylene derivative **33** from **31** (Scheme III). Another reaction sequence that is successful on the model compound, α-(phenylselenenyl)cyclohexanone, but that fails with compound **31** is alkylation at selenium (with triethyloxonium tetrafluoroborate) followed by nucleophilic substitution of ethyl phenyl selenoether with nucleophilic chloride ion.

The lack of success of these functional group transformations on compound **31** is attributed to the steric bulk associated with having a quaternary carbon atom in **31**. This steric inhibition is absent in the simple model ketone, α-(phenylselenenyl)cyclohexanone, where the selenium to chloride substitution reactions were successful. We thank a reviewer for noting that a conformational difference (i.e., α-phenylselenyl group axial in compound **31** and equatorial in cyclohexanone) may explain the differing reactivity between these two compounds.

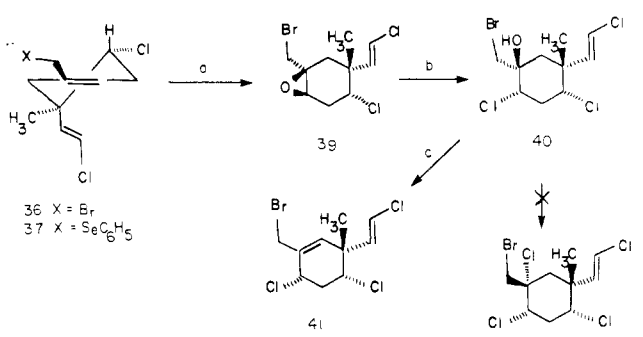
It is unfortunate that the α-phenylselenyl group in compound **31** could not be utilized in the synthesis of **1**–**3** and therefore had to be discarded. The α-phenylselenyl group was removed from **31** by reduction to the cyclohexanone **34** with activated zinc (Scheme IV). This reductive elimination proceeds in 89% yield. Methylenation of cyclohexanone **34** following the Lombardo procedure[21] provides **35** in 69% yield. Although **35** is not a natural product, it is reported as a degradation product from **1**.[5d] Favorable comparison of the spectra of our synthetic material with the literature was made at this stage.

Bromination of **35** with *N*-bromosuccinimide under conditions which were expected to produce a bromohydrin[22] affords the rearranged allylic bromide **36** along with a trace of an isomeric olefin **37a** in over 62% yield in a ratio of 2:1. These two olefins are separable on silica gel. The allylic bromide **36** is not naturally occurring but has been characterized as a rearrangement product from another natural product.[5g] The spectra of our synthetic **36** are identical with those reported in the literature for this material.

The natural product *epi*-plocamene **2** is obtained quite readily from allylic bromide **36** in the following manner. Treatment of **36** with phenyldichloroiodine[23] in carbon tetrachloride leads directly to *epi*-plocamene (**2**) in 23% yield. The spectra of our synthetic material exactly matched those reported in the literature.

We prepared the naturally occurring, endocyclic allylic chloride **3** by allylic chlorination of **34** with a dilute solution

Scheme V[a]



[a] a, MCPBA, $ClCH_2CH_2Cl$; b, anhydrous HCl, Et_2O; c, $SOCl_2$, K_2CO_3.

of sodium hypochlorite (Chlorox) as shown in Scheme IV. This chlorination reaction proceeds in 75% yield. No traces of the rearranged olefin, **3a**, were observed in this chlorination reaction.

Allylic rearrangement of the primary bromide **36** was effected by nucleophilic substitution of bromide with sodium phenylselenide to produce the selenoether **37**. When the selenenyl ether **37** is treated with H_2O_2, a [2.3]-sigmatropic rearrangement ensues. This sequence of reactions proceeds cleanly and in high yield to a single, crystalline secondary allylic alcohol **38**, whose structure was confirmed by X-ray diffraction analysis.[24] A computer-generated plot of the results of this structure determination are given in Scheme IV.

Conversion of **36** into violacene (**1**) was attempted as shown in Scheme V. Epoxidation of **36** with *m*-chloroperoxybenzoic acid for 4 h at 90 °C following the Kishi protocol[25] produced a single epibromohydrin in 83% yield. We assume that the reactive conformation of **36** is that shown in Scheme V. The peracid attacks the olefin in this molecule from the top face. The half-chair conformation depicted is favored because a similar conformation of the selenide **37** is responsible for stereospecific rearrangement of **37** to the single alcohol **38** whose structure was assigned by crystallography (see Scheme IV). Anhydrous hydrogen chloride in diethyl ether opens the epoxide **39** regiospecifically to the tertiary alcohol **40** in 87% yield. The regiochemistry of the epoxide opening is unambiguous because oxidation failed to convert the alcohol **40** into a ketone.

The regiochemistry and stereochemistry of **40** are confirmed by comparing the ^1H NMR of the $-CHCl-CH_2-CHCl-$ portion of the spectrum with that reported for violacene (**1**). Violacene (**1**) has a four-signal pattern at δ 4.29 (dd, J = 4, 12 Hz, 1 H, (-CHCl-)), 3.64 (dd, J = 4 and 12 Hz, 1 H, (-CHCl-)), 2.64 (ddd, J = 12, 12, 14 Hz, 1 H ($-CH_2-$)), and 2.44 (ddd, J = 4, 4, 14 Hz, 1 H ($-CH_2-$)). Our alcohol **40** has similar spectral characteristics indicative of the same regio and stereochemical assignments as those for violacene, i.e., δ 4.16 (dd, J = 4.3, 12.7 Hz, 1 H, (-CHCl-)), 3.76 (dd, 1 H, J = 3.8, 12.0 Hz, 1 H, (-CHCl-)), 2.22 (ddd, J = 12.4, 12.7, 12.0 Hz, 1 H, ($-CH_2-$)), and 2.57 (ddd, J = 4.3, 3.8, 12.4 Hz, 1 H, ($-CH_2-$)).

Total synthesis of violacene (**1**) from **40** requires only one step. This step is nucleophilic substitution with inversion of the tertiary alcohol in **40** and introduction of tertiary chloride. We felt confident that the tertiary chloride could be introduced with the proper stereochemistry because the X-ray crystal structure of **1** clearly shows

(25) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goro, T.; Inove, S.; Sugiura, S. Kakoi, H. *J. Chem. Soc., Chem. Commun* **1972**, 64.

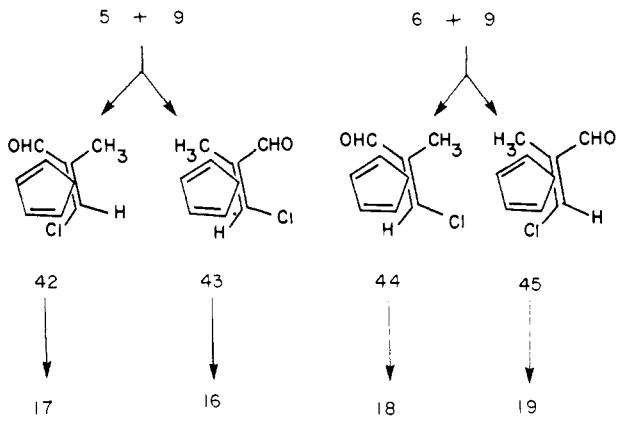


Figure 3. Transition states for the reactions of **5** and **6** with cyclopentadiene (**9**).

the tertiary chloride to be axial.[3] *Numerous* attempts were made to cleanly convert **40** into **1** including those conditions specifically recommended for the conversion of tertiary alcohols into tertiary chlorides.[26] We are unable to effect this conversion. The only product which could be characterized spectroscopically was the elimination product **41** shown in Scheme V. At present we feel that compound **40** is not a viable precursor to violacene (**1**) and that another route for synthesis of **1** must be designed.

Discussion

The Diels–Alder reaction of (*Z*)- and (*E*)-3-chloro-2-methylpropenal **5** and **6** gives moderate yields of adducts with conventional 1,3-dienes **7–9**. The preponderance of exo adducts in the reaction with both **5** and **6** with cyclopentadiene (**9**) is noteworthy since the Diels–Alder reaction is generally thought to proceed via a transition state with maximum overlap of π orbitals to give largely an endo product.[27] However, the Diels–Alder reactions of α-methylacroleins, -acrylates, and -acrylonitriles have been shown to give the exo isomer as the major product with cyclopentadiene.[28] Two arguments are given for this observation.[29–31] One argument states that the methyl group of the dienophile sterically interacts with the incipient bridging methylene and that this interaction destabilizes the endo transition state. The other argument invokes a van der Waals interaction between the methyl group and the π orbitals of the diene which stabilizes the exo transition state. Interpretations favoring the van der Waals theory over the steric argument have been given.[30] A combination of both arguments can be used to rationalize our results in Figure 2.

Four transition states, i.e., TS **42–45**, are drawn in Figure 3, two for each dienophile, **5** and **6**. It is clear that the steric interaction between the diene methylene and the substituents on the dienophile is greater than the interaction between the diene vinyl protons and the dienophile's substituents. As a rough estimate, we consider the steric interaction between the diene and either the β-chlorine atom or the α-methyl on the dienophile to be roughly equivalent. Thus, when comparing the exo and endo transition states for the *Z* diene (**5**), i.e., TS **42** and **43**, are compared on steric grounds, TS **42** and **43** are equally favored; but when the van der Waals argument discussed above and in ref 30, is utilized, TS **43** is favored. This comparison explains the fact that the exo TS, **43**, gives rise to the major product of cycloaddition of **5** with **9**.

The arguments given above also can be used to explain the fact that the reaction of **6** with **9** shows more selectivity than that of **5** with **9**. This greater selectivity is interpretable by comparing TS **44** with TS **45**. Since TS **45** exhibits little of the steric congestion seen in **42** or **43** and since TS **45** is also electronically favored by the van der Waals attraction of the diene for the α-methyl group on the dienophile, one expects greater selectivity in favor of the exo product from TS **45**. This is what is observed.

The difference in the rates at which (*Z*)- and (*E*)-3-chloro-2-methylpropenal, **5** and **6**, react with all of the dienes is harder to explain. In the case of the reaction of **5** and **6** with butadiene, a difference in rate of approximately 4:1 is observed. This corresponds to a difference in free energy of activation of approximately 0.82 kcal/mole. This small difference in energy may be attributed to either steric or electronic factors in the transition state. Since the *Z*-aldehyde (**5**) was shown to be thermodynamically less stable (vide supra), it is possible that the small but discernible rate difference is simply a manifestation of the difference in ground-state energy of the two aldehydes. Small differences in the energies of the LUMO orbitals of **5** and **6** could also readily explain the observed difference in reactivity.[31]

In Figure 4 we have categorized all of the known *Plocamium* monoterpenes along with several closely related degradation products described in the literature, i.e., compounds **1–3, 35, 36, 46–57**.[1–6] This classification scheme is based upon the relative stereochemistry of two vicinal asymmetric centers marked with dots in all of the structures. The compounds in Figure 4 are subdivided into seven groups according to a retrosynthetic dissection of the molecules. We wish to emphasize that the relative stereochemistry of the dotted vicinal stereogenic centers in the compounds in Figure 4 corresponds to the stereochemistry of the simple β-haloacroleins also depicted in Figure 4. We suggest that the β-halo aldehydes may be utilized as dienophilic precursors to each of the natural products depicted in Figure 4 since we have demonstrated the feasibility of this Diels–Alder approach to the *Plocamium* monoterpenes by our syntheses of compounds **2** and **3** from the aldehyde **5**.

Conclusion

It is clear that α-halogenated dienophiles impart synthetically useful characteristics to both the rates and the regiochemistry of certain cycloaddition reactions.[32,33] The Diels–Alder reactions of α-halogenated dienophiles stand in marked contrast to the β-halogenated dienophiles re-

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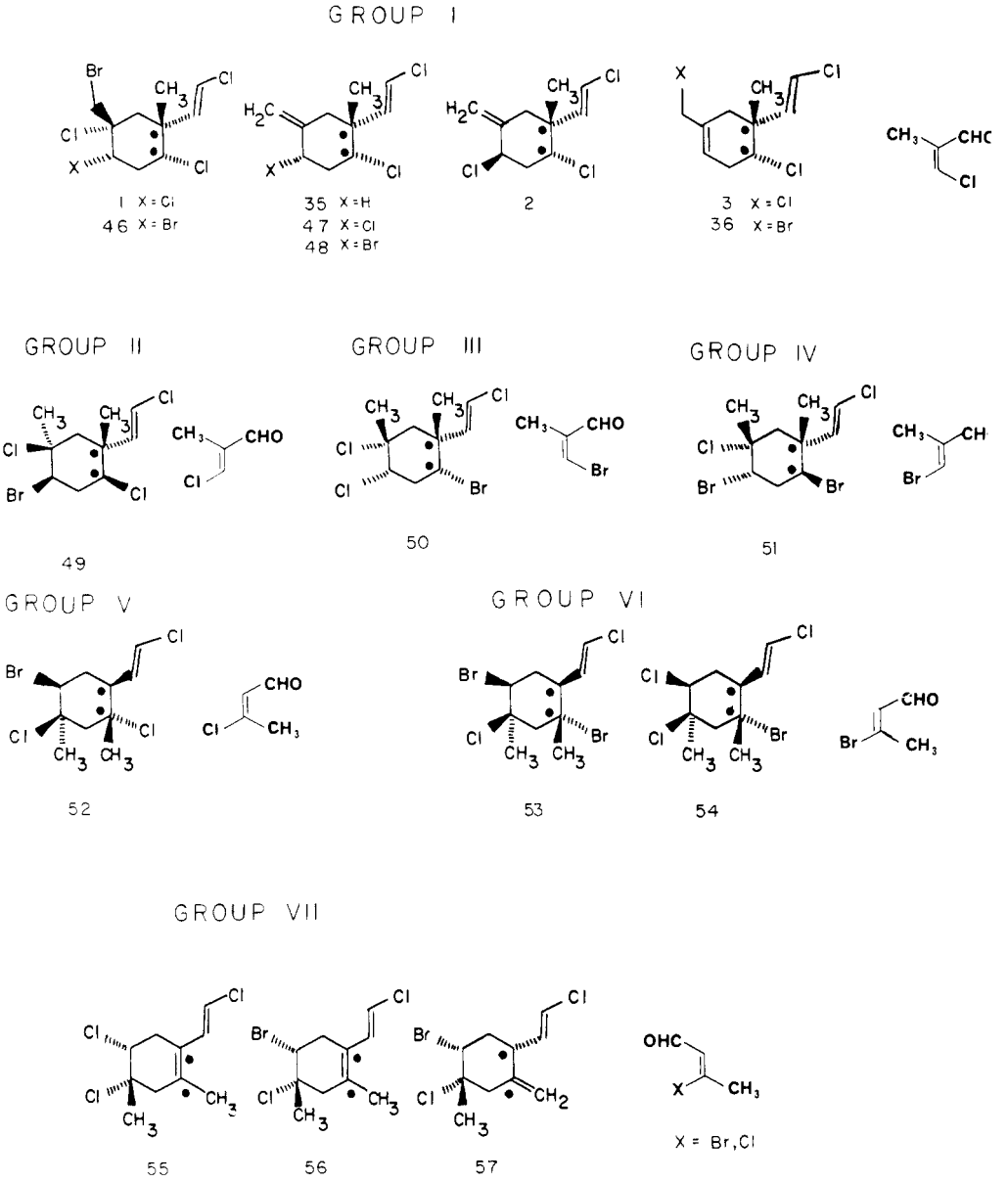

Figure 4. Classification of the monocyclic, *Plocamium* monoterpenes according to a Diels–Alder retrosynthetic analysis.

ported herein. A search for Diels–Alder reactions of β-halogenated dienophiles revealed that virtually nothing was known apart from the sole example appearing in Corey's gibberelic acid synthesis.[34] In this latter case, an intramolecular cycloaddition was performed, and the regiochemistry was restricted by the intramolecular nature of the reaction, so little could be inferred about the controlling influence exerted by the β-halogen substituent.

This work reported here demonstrates that α-methyl-β-chloroacroleins may be used in Diels–Alder reactions to produce moderate yields of synthetically useful adducts. These adducts have been utilized by us for the total synthesis of some halogenated marine monoterpenes. The dienophiles **5** and **6** may be useful synthons for other applications in organic synthesis. The conclusion of this work is that a β-halogen atom exerts little influence on either the regio- or the stereochemistry of the cycloaddition reaction relative to a nonhalogenated dienophile. However, a small difference in the rate of cycloaddition relative to olefin geometry was noticed.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus. The following spectrometers were used to record spectral data: IR, Perkin-Elmer 681; ^{13}C NMR, Bruker WM-250; ^{1}H NMR, Bruker WM-250 or Varian EM-360 (chemical shifts are reported in ppm δ downfield from an internal standard (Me_4Si)). Elemental analyses were performed by the Schwartzkopf Microanalytical Labs, Woodside, NY. X-ray crystallography was carried out on a Nicolet R3m/E crystallographic system. Mass spectra were recorded by electron impact (EI) or chemical ionization (CI) with a Kratos MS80 mass spectrometer.

General Procedure for the Cycloaddition Reactions. To a dry, thick walled glass tube was added 0.05 mol of the appropriate diene **7–9** (in the case of butadiene (**7**) the tube was cooled and 2.7 g (0.05 mol) of butadiene was condensed directly into the tube), 1.04 g (0.01 mol) of the dienophile **5**[8] or **6**,[8] 0.23 g (0.001 mol) of propylene oxide, and 0.22 g (0.001 mol) of butylated hydroxytoluene (BHT).[35] The mixture was made up to 10 mL with dry toluene. The tube was cooled to −78 °C and sealed under a vacuum of 30 mmHg. The apparatus was heated at 150 °C for 24 h in an oven. After cooling, the tube was opened and the contents evaporated in vacuo with warming to 50 °C, 30 mmHg

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(35) This compound was purchased from Sigma Chemical Co. and used without further purification.

to remove any diene dimer. The residue was flash chromatographed over silica gel, eluting with the appropriate solvent as described for each of the individual adducts **10–19** described below. These experiments were repeated at least twice to verify the reproducibility of the results.

***cis*-6-Chloro-1-methyl-3-cyclohexenecarboxaldehyde (10).** Flash chromatography with 20% CH_2Cl_2/hexanes gave a colorless oil: average yield 41%; bp 55–60 °C (2 mmHg); ^1H NMR ($CDCl_3$ 250 MHz) δ 1.16 (s, 3 H), 1.96 (b, d, 1 H, J = 16 Hz, many fine couplings), 2.46–2.77 (m, 3 H), 4.25 (t, 1 H, J = 5 Hz), 5.56–5.75 (m, 2 H), 9.65 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.07, 31.58, 32.58, 49.92, 59.19, 123.87, 124.24, 202.94; IR ($CHCl_3$) 3020, 2970, 2920, 2880, 2700, 1725, 1450, 1440, 1370, 1335, 1320, 1290, 1250, 1160, 1118, 1082, 1070, 1040, 1000, 940, 900, 855, 680 cm^{-1}.

(±)-*cis*-6-Chloro-1-methyl-3-cyclohexenecarboxaldehyde (10). On a preparative scale the aldehyde **6** is prepared as follows. To 40 g of activated, base washed manganese dioxide[36] was added enough dry CH_2Cl_2 to form a slurry. To this was added 6 g (0.056 mol) of a 50:50 mixture of *cis*- and *trans*-3-chloro-2-methylpropenol.[8a] The mixture was stirred for 6 h and then filtered through a Celite pad. After evaporation in vacuo the filtrate gave an average of 3.5–4.0 g (0.033–0.038 mol) in a yield of 59–68% as a 50:50 mixture of *cis*-3-chloro-2-methylpropenal (**5**) and the corresponding trans isomer **6**. The aldehyde mixture was immediately sealed under vacuum in a thick walled glass tube in the presence of 11.0 g (0.2 mol) of butadiene, 0.88 g (0.004 mol) of BHT,[35] and 0.23 g (0.004 mol) of propylene oxide made up to 40-mL total volume with dry toluene. The tube was then heated for 24 h at 170–180 °C. After cooling, the reaction mixture was evaporated in vacuo to give a pale yellow oil that was distilled in a Kugelrohr apparatus at 2 mmHg, the fraction boiling at 50–65 °C being collected. On average 2.4 g (0.015 mol) of a mixture of **6** and the undesired aldehyde **11** arising from the *trans*-3-chloro-2-methylpropionaldehyde (**6**) was obtained in a ratio of 3:1 in a total yield of 36%. The product was not purified or analyzed further in the preparative scale reactions but was used directly in the preparation of compound **27**. For analytical purposes a pure sample of the *Z*-aldehyde **5** was prepared as described in ref 8a and utilized in the preparation of adduct **10**. Spectral data for the pure aldehyde **10** are reported as follows: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.16 (s, 3 H), 1.96 (bd, 1 H, J = 16 Hz + fine coupling) 2.46–2.77 (m, 3 H), 4.25 (t, 1 H, J = 5 Hz), 5.56–5.75 (m, 2 H), 9.65 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.07, 31.58, 32.58, 49.92, 59.19, 123.87, 124.24, 202.94; IR ($CHCl_3$) 3020, 2970, 2920, 2880, 2700, 1725, 1450, 1440, 1370, 1325, 1320, 1290, 1250, 1160, 1118, 1082, 1070, 1040, 1000, 940, 900, 855, 680 cm^{-1}.

***trans*-6-Chloro-1-methyl-3-cyclohexenecarboxaldehyde (11).** Flash chromatography with 20% CH_2Cl_2/hexanes gave a colorless oil: average yield 12.5%; bp 55–60 °C, 2 mmHg; ^1H NMR ($CDCl_3$ 250 MHz) δ 1.21 (s, 3 H), 2.05 (bd, 1 H), 2.3–2.7 (m, 3 H), 4.38 (dd; 1 H, J = 5.54, 7.58 Hz), 5.55–5.75 (m, 2 H); 9.51 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.02, 31.63, 32.66, 49.84, 59.16, 123.80, 124.14, 202.63. IR (film): 3020, 2965, 2920, 2840, 2700, 1725, 1650, 1450, 1430, 1370, 1180, 1080, 988, 845 cm^{-1}. Anal. Calcd for $C_8H_{11}ClO$: C, 60.57; H, 6.99. Found: C, 59.87; H, 7.13.

***cis*-6-Chloro-1,4-dimethyl-3-cyclohexenecarboxaldehyde (12) and *cis*-6-Chloro-1,3-dimethyl-3-cyclohexenecarboxaldehyde (13).** Flash chromatography with 25% CH_2Cl_2/hexanes gave an oil in an average yield of 71%: ratio of isomers **12**/**13** = 1.0/0.52. The isomers could not be separated by HPLC. ^1H NMR ($CDCl_3$ 250 MHz): Characteristic signals of two isomers, vinyl protons, δ 5.42 (bs, 1 H), major isomer; 5.30 (bs, 1 H), minor isomer; Allylic methyl groups, δ 1.70 (bs, 3 H), major isomer; 1.73 (bs, 3 H), minor isomer. ^{13}C NMR ($CDCl_3$): major isomer, δ 19.98, 22.79, 30.45, 37.39, 48.26, 60.38, 118.46, 130.08, 203.02; minor isomer, 20.05, 23.25, 32.76, 34.82, 49.08, 59.87, 116.61, 131.89, 202.95. Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.59. Found: C, 62.67; H, 7.57.

***trans*-6-Chloro-1,4-dimethyl-3-cyclohexenecarboxaldehyde (14) and *trans*-6-Chloro-1,3-dimethyl-3-cyclohexenecarboxaldehyde (15).** Flash chromatography with 25% CH_2Cl_2/hexanes gave a colorless oil: average yield 34%; ratio of isomers **14**/**15** = 1.0/0.71. The isomers could not be separated by HPLC. ^1H NMR ($CDCl_3$ 250 MHz): Characteristic peaks of two isomers, quaternary methyl group, δ 1.18 (s, 3 H), major isomer; 1.20 (s, 3 H), minor isomer. Allylic methyl group: δ 1.67 (bs, 3 H), major isomer; 1.70 (bs, 3 H), minor isomer. Vinyl proton: δ 5.38 (bs, 1 H), major isomer; 5.31 (bs, 1 H), minor isomer. Aldehyde proton: δ 9.48 (s, 1 H), major isomer; 9.49 (s, 1 H), minor isomer. ^{13}C NMR ($CDCl_3$): major isomer, δ 15.05, 22.71, 31.67, 37.36, 49.72, 59.58, 117.73, 131.71, 203.12; minor isomer, δ 15.23, 23.16, 32.75, 36.33, 50.31, 59.34, 118.16, 131.32, 202.79. Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.59. Found: C, 62.60, H, 7.61.

***exo*- and *endo*-*cis*-3-Chloro-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (16 and 17).** Flash chromatography with 20% CH_2Cl_2/hexanes gave two fractions in an average yield of 72%; ratio of **16**/**17** = 1.0/0.43. Both fractions were thick oils that were distilled: exo adduct **16** bp 50–60 °C (2 mmHg); endo adduct **17** bp 60–65 °C (2 mmHg).

Exo adduct (**16**) ^1H NMR ($CDCl_3$ 250 MHz): δ 1.10 (s, 3 H), 1.75 and 2.15 (ABq with fine splitting, 2 H, J = 9.44 Hz), 2.93 (bs, 1 H), 3.01 (bs, 1 H), 3.61 (d, 1 H, J = 2 Hz), 6.22–6.30 (m, 2 H), 9.77 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 20.32, 46.61, 48.45, 53.42, 54.48, 66.72, 135.79, 138.29, 201.93. IR ($CHCl_3$) 3060, 3005, 2970, 2860, 2820, 2720, 1718, 1445, 1390, 1365, 1320, 1270, 1250, 1230, 1220, 1182, 1160, 1145, 1090, 1080, 1010, 982, 973, 960, 940, 900, 850, 830, 700 cm^{-1}.

Endo adduct (**17**) ^1H NMR ($CDCl_3$ 250 MHz): δ 1.34 (s, 3 H), 1.70 and 1.74 (ABq, 2 H, J = 1.7 Hz), 2.73 (bs, 1 H), 3.24 (bs, 1 H), 4.25 (d, 1 H, J = 3.5 Hz), 6.23–6.26 (m, 1 H), 6.51–6.54 (m, 1 H), 9.49 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 21.25, 45.97, 50.36, 52.10, 55.87, 67.59, 132.51, 138.01, 204.25. IR ($CHCl_3$): 3060, 2970, 2860, 2730, 1710, 1460, 1445, 1388, 1330, 1300, 1270, 1250, 1155, 1080, 1040, 940, 912, 892, 870, 850, 795 cm^{-1}.

***endo*-*cis*-3-Chloro-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (18) and *exo*-*trans*-3-Chloro-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (19).** Flash chromatography with 20% CH_2Cl_2/hexanes gave a colorless oil that thickened on standing. This oil consisted of a mixture of isomers: average yield 32%; ratio of endo (**18**) and exo (**19**) = 0.19/1.0. The isomers were separated by Kugelrohr distillation. The major isomer **19** boiling at 55–60 °C (2 mmHg) gave a crystalline solid (mp 25–30 °C). The minor isomer **18** could not be isolated from the remaining residue. Spectral data for the major isomer **19** are as follows: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.10 (s, 3 H), 1.37 and 1.51 (ABq with fine splitting, 2 H, J = 9.5, many smaller couplings), 2.93 (bm, 1 H), 3.20 (bm, 1 H), 4.89 (d, 1 H, J = 3.67 Hz), 6.33 (m, 2 H), 9.59 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 44.56, 48.94, 50.55, 57.70, 61.75, 135.05, 137.32, 202.15; IR ($CHCl_3$) 3060, 3020, 2960, 2870, 2800, 2705, 1715, 1450, 1365, 1330, 1300, 1275, 1250, 1222, 1080, 1040, 1020, 990, 932, 918, 850, 825 cm^{-1}.

***endo*-*cis*-3-Chloro-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (24).** To 0.15 g (0.89 mmol) of the aldehyde **17** dissolved in 1.5 mL of dry DMF was added 0.699 g (1.85 mmol) of PDC. The solution was stirred at room temperature for 60 h and then diluted with 2 mL of ether. The solution was then washed into a separatory funnel with 5 mL of water and extracted with ether (3 × 10 mL). The combined ethereal extracts were washed with water (1 × 5 mL) followed by 5% $NaHCO_3$ (3 × 5 mL). The combined $NaHCO_3$ extracts were acidified and subsequently extracted with ether (3 × 10 mL). The ethereal extracts were dried over $MgSO_4$ as were the ethereal extracts from the neutral extraction. On evaporation in vacuo 0.055 g of unreacted aldehyde **17** was recovered, and 0.057 g (0.31 mmol) of acid **24** was obtained: yield 54% with respect to aldehyde used. The oil obtained was crystallized from ether/pentane to give colorless crystals, mp 156–157: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.58 (s, 3 H), 1.71 and 1.57 (ABq, 2 H, J = 9.65 Hz), 2.81 (bs, 1 H), 3.12 (bs, 1 H), 4.16 (d, 1 H, J = 3.5 Hz), 6.11–6.14 (m, 1 H), 6.59–6.62 (m, 1 H); ^{13}C NMR ($CHCl_3$) δ 26.63, 44.98, 50.04, 51.34, 56.24, 67.84, 132.67, 140.18, 178.79; IR ($CHCl_3$) 3500–2500, 2975, 2920, 1698, 1460, 1448, 1400, 1328, 1300, 1275, 1250, 1168, 1130, 1120, 1068, 1030, 940, 910, 890, 838 cm^{-1}. Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.91, H, 5.94. Found: C, 57.89, H, 6.06.

Iodo Lactone of *endo*-*cis*-3-Chloro-2-methylbicyclo-[2.2.1]hept-5-ene-2-carboxylic Acid (25). To a solution of 57 mg (0.3 mmol) of the acid **24** dissolved in 2.0 mL of 0.5 N $NaHCO_3$ was added a solution of 0.3 g (1.84 mmol) of KI in 1 mL of water

(36) Attenboro, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.

and 76 mg (0.3 mmol) of iodine. The solution was stirred in the dark overnight. The reaction mixture, which contained a precipitate, was extracted with ether (3 × 10 mL) after dilution with 5 mL of water. The combined ethereal extracts were washed with saturated $NaHSO_3$ solution (1 × 5 mL) and saturated $NaHCO_3$ solution (2 × 5 mL), dried over $MgSO_4$, and evaporated in vacuo to give a thick pale yellow oil (94 mg) in 98% yield. The oil was crystallized from ether/pentane to give colorless needles: mp 110–111 °C; ^1H NMR ($CDCl_3$ 250 MHz) δ 1.29 (s, 1 H), 2.02 and 2.48 (ABq, 2 H, J = 12.2 Hz), 2.87–2.91 (bm, 2 H), 3.89 (d, 1 H, J = 3.63 Hz), 4.42 (d, 1 H, J = 2.55 Hz), 5.13 (d, 1 H, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$) δ 18.31, 23.10, 34.33, 42.12, 52.86, 54.67, 65.79, 86.62, 175.59; IR ($CHCl_3$) 3020, 2970, 2925, 1780, 1460, 1380, 1342, 1283, 1270, 1255, 1230, 1178, 1155, 1130, 1112, 1080, 1052, 1005, 960, 910, 892, 875, 848, 800 cm^{-1}. Anal. Calcd for $C_9H_{10}ClIO_2$: C, 34.58; H, 3.22. Found: C, 34.62; H, 3.25.

***exo-trans*-3-Chloro-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (26).** To 0.15 g (0.88 mmol) of the aldehyde mixture (**18** and **19**) was added 1.5 mL of dry DMF. To this solution was added 0.7 g (1.85 mmol) of PDC.[13] The red solution was stirred under N_2 overnight. To the dark solution was added 5 mL of ether, and the mixture was poured into 5 mL of water. The aqueous phase was extracted with ether (3 × 5 mL), and the combined ethereal extracts were subsequently washed with 5% $NaHCO_3$ solution (3 × 5 mL). The combined basic extracts were acidified and extracted with ether (4 × 5 mL), and the resulting ethereal phase was dried over $MgSO_4$ and evaporated in vacuo to give 0.11 g (0.58 mmol) of a colorless oil: yield 66%. The oil showed the presence of only one compound by NMR. The oil was purified in a sublimation apparatus at 110 °C (2 mmHg) to give a white solid: mp 89–91 °C; ^1H NMR ($CDCl_3$ 250 MHz) δ 1.21 (s, 3 H), 1.50 and 1.59 (ABq, 2 H, J = 9.5 Hz and other fine coupling), 3.16 (bs, 2 H), 5.02 (d, 1 H, J = 3.6 Hz), 6.25–6.35 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.17, 45.95, 50.51, 51.44, 53.58, 64.33, 135.96, 136.26, 183.25; IR ($CHCl_3$) 3600–2400, 3050, 2970, 2860, 1690, 1450, 1400, 1330, 1305, 1280, 1270, 1250, 1165, 1110, 1036, 1020, 936, 910, 900, 888, 860, 840 cm^{-1}. Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.91; H, 5.94. Found: C, 57.84, H, 5.93.

Reduction of Isoprene Adducts 12/13 and 14/15 with Lithium Aluminum Hydride. To a solution of 0.2 g (1.16 mmol) of the aldehyde mixture **12/13** or **14/15** dissolved in 3 mL of dry ether was added 0.044 g (1.16 mmol) of lithium aluminum hydride. The resulting mixture was stirred for 2 h, at which time 5 mL of ether followed by 2 mL of 1 N HCl was added. The aqueous layer was extracted with ether (2 × 1 mL), and the combined ethereal extracts were dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil 0.18 g (1.04 mmol): yield 87%. The products were further purified by Kugelrohr distillation, 70–80 °C (2 mmHg), to give two separate mixtures of alcohols **12a/13a** and **14a/15a**. These mixtures were analyzed by ^1H NMR ($CDCl_3$ 250 MHz) for the chemical shift and relative ratio of the vinyl protons. Compounds **12a/13a** δ 5.41–5.32 and 5.32–5.24, integral ratio = 1.0:0.53. Compounds **14a/15a** δ 5.35–5.27 and 5.27–5.19 integral ratio = 1.0:0.68. Anal. Calcd for $C_9H_{15}ClO$: C, 61.88; H, 8.66. Found: for **12a/13a** C, 61.77; H, 8.74 and for **14a/15a** C, 61.74; H, 8.82.

Reduction of the Alcohols 12a/13a or 14a/15a to 1,3- and 1,4-Dimethylcyclohex-3-enemethanol (20/21). To a solution of 50 mg (0.29 mmol) of the alcohol mixture **12a/13a** or **14a/15a** dissolved in 2 mL of dry THF was added 32 mg of a 25% lithium dispersion in oil (1.15 mmol) followed by 42 mg (0.57 mmol) of dry tert-butyl alcohol. The mixture was refluxed for 4 h under N_2, cooled to room temperature, and quenched by addition of 2 mL of ether and 1 mL of water. The aqueous layer was extracted with ether (2 × 1 mL), and the combined ethereal extracts were dried over $MgSO_4$ and evaporated in vacuo. The resulting oil was distilled in a Kugelrohr apparatus at 75–80 °C (30 mmHg) to give 30 mg (0.22 mmol) of a colorless oil consisting of a mixture of two compounds, **20/21**, in an average yield of 75%. The products were analyzed by ^1H NMR ($CDCl_3$ 250 MHz) for the chemical shift and relative ratio of the vinyl protons. The product from **12a/13a**: δ 5.33–5.25 and 5.41–5.33, integral ratio = 1.0:0.52. The product from **14a/15a**: δ 5.33–5.25 and 5.44–5.33, integral ratio = 1.0:0.82.

1,3- and 1,4-Dimethylcyclohex-3-enemethanol (20, 21). A solution of 3.5 g (0.05 mol) of methacrolein, 10.2 g (0.15 mol) of isoprene, and 200 mg (0.9 mmol) of BHT[35] in 20 mL of dry benzene was heated at 130 °C for 24 h in a sealed tube. The resulting colorless liquid was evaporated in vacuo and the residue distilled collecting the fraction boiling at 70–75 °C (30 mmHg) (lit. 52.5–57 °C (5.6 mmHg)).[12] A total of 6.5 g (0.047 mol) of the aldehyde mixture consisting of compounds **22/23** was obtained in a yield of 94%. The mixture of aldehydes **22/23** was immediately reduced to the alcohols **20/21** with LAH as follows. To a suspension of 0.0387 g (0.99 mmol) of LAH in 10 mL dry ether at 0 °C was added a solution of 0.5 g (3.6 mmol) of the aldehyde mixture **22/23** dissolved in 5 mL of dry ether. The mixture was stirred for $^1/_2$ h and quenched by addition of 1 mL of water. The resulting suspension was dried over $MgSO_4$, evaporated in vacuo, and distilled at 75–80 °C (30 mmHg) to give 0.47 g (3 Mol) of a colorless oil containing the authentic mixture of **20/21** in 94% yield: ^1H NMR ($CDCl_3$ 250 MHz) δ 0.91 (s, 3 H), 1.24–1.56 (m, 2 H), 1.65 (bs, 3 H), 1.63–2.05 (m, 4 H), 3.31–3.41 (m, 2 H), 5.29–5.38 (bm, 1 H). Ratio of isomers **16/17** by integration of vinyl protons: δ 5.33–5.25 and 5.44–5.33 integral ratio = 1.0:0.49.

Competitive Reactivity of 5 and 6 with Butadiene. A solution of 4 g (0.038 mol) of a 50:50 mixture of **5** and **6**, 11.2 g (0.2 mol) of butadiene, 0.88 g (0.004 mol) of BHT,[35] and 0.23 g (0.004 mol) of propylene oxide made up to 40 mL with dry toluene was heated to 170 °C in a sealed tube for 24 h. Prior to heating, an aliquot of the solution was analyzed by ^1H NMR ($CDCl_3$ 250 MHz). The ratios for the aldehyde protons were found by integration to be *Z*-**1** δ 10.95, integral = 2.03, *E*-**2** δ 9.32, integral = 2.19. After further heating, another aliquot was similarly analyzed for the relative integral ratios for the aldehyde protons of the remaining starting materials **5** and **6** and the products **10** and **11**. After 24 h, the spectrum and the integral were as follows: *Z*-aldehyde (**5**) δ 10.95, integral = 0.62, *Z* adduct (**10**) δ 9.60, integral = 1.45; combined integral = 2.07 and *E*-aldehyde (**6**) δ 9.32, integral = 1.49, *E* adduct (**11**) δ 9.45, integral = 0.61; combined integral = 2.10. Since the total integral of **5** + **10** vs. **6** + **11** remained constant throughout the monitoring period, it must be concluded that both the dienophiles were cleanly converted into adducts. Selective destruction of one adduct over the other or of one dienophile over the other would have resulted in a change in the total integral. Also since starting materials were present at the time the reaction was concluded, these results confirm a kinetic preference for the Diels–Alder reaction of butadiene with dienophile **5**.

***cis*-1-(2-Bromo-2-chloro-1-(hydroxyethyl))-6-chloro-1-methyl-3-cyclohexene (27).** To a solution of 9.14 g (0.05 mol) of dicyclohexylamine in 50 mL of dry THF at 0 °C under N_2 was added dropwise a solution of 20.8 mL of 2.4 M (0.05 mol) of *n*-butyllithium in hexanes. After stirring for $^1/_2$ h the solution was added dropwise via a cannula to a stirred solution of 4 g (0.025 mol) of the aldehyde mixture **10/11** obtained as described in the preparative scale reaction and 12.95 g (0.1 mol) of dry bromochloromethane in 50 mL of dry THF at −78 °C. After the solution was stirred for 3.5 h at −78 °C, 50 mL of water was added and the resulting mixture allowed to warm to room temperature. The solution was extracted with ether (3 × 50 mL), and the combined ethereal extracts were washed with saturated citric acid solution (3 × 30 mL) to remove dicyclohexylamine. The ethereal solution was washed with water (1 × 30 mL) followed by saturated NaCl solution (1 × 30 mL) and dried over $MgSO_4$. After evaporation in vacuo the resulting oil was flash chromatographed over silica gel, eluting with 50% CH_2Cl_2/hexanes to produce 2.2 g (0.0076 mol), 30%, of an oil which was not purified further but was directly utilized in the next step in preparative scale reactions.

When this reaction was carried out by utilizing an analytically pure sample of the *Z*-aldehyde **10** on a small scale, the product **27** consisted of four diastereomers in proportions that varied only slightly from reaction to reaction provided that the reaction was carried out as described above. The isomers could be distinguished by the dihalomethine proton resonance which appeared as four separate doublets even at 60 MHz. The chemical shift of the dihalomethine proton for these four diastereomers are given as follows: ^1H NMR ($CDCl_3$ 60 MHz): δ 5.88 (d), 6.05 (d), 6.15 (d), 6.26 (d). Signals due to the four diastereomers were resolved for the most part in the ^{13}C NMR with the exception of a few overlapping peaks and are given as follows: ^{13}C NMR ($CDCl_3$) methyl groups, of 15.4, 15.8, 16.3, 16.6; methylene groups, of 30.2, 30.7, 31.6, 32.2, 32.7, 33.3; quaternary carbon, δ 41.6, 41.9, 42.1,

42.4; secondary hydroxyl and secondary chlorine bearing carbons, δ 61.4, 61.7, 61.8, 61.9, 62.2, 63.0; bromochloromethyl carbon, δ 79.2, 79.5, 79.9, 80.6; olefinic carbons, δ 121.0, 121.3, 121.6, 123.7, 123.9, 124.9. These four diastereomers were not individually characterized further.

(±)-(1*RS*,2*RS*,4*RS*,5*RS*)-7-(Bromochloromethyl)-2-chloro-1-methyl-4-(phenylselenenyl)-6-oxabicyclo[3.2.1]octane (28). To a solution of 2.2 g (7.6 mmol) of the mixture of four alcohols **27** obtained as described above dissolved in 15 mL of dry CH_2Cl_2 at −78 °C was added dropwise a solution of 1.6 g (8.4 mmol) of phenylselenenyl chloride dissolved in 15 mL of dry CH_2Cl_2 under N_2. After 2 h TLC (50% CH_2Cl_2/hexanes) indicated all starting material (R_f 0.3) had reacted to give a more polar product (R_f 0.5). The resulting orange reaction mixture was evaporated in vacuo to give an oil which was flash chromatographed over silica gel eluting with 25% CH_2Cl_2/hexanes. This crude purification gave 2.3 g (5.2 mmol), 68% yield, of an orange oil. It was clear from the 250 MHz ^1H NMR spectrum of the crude material that the desired transformation had occurred. Since the mixture of bicyclic ethers were virtually inseparable, the material was not characterized further but was used directly in the next reaction.

***cis*-4-Chloro-*cis*-5-[(*E*)-2-chloroethenyl]-*trans*-5-methyl-*trans*-2-(phenylselenenyl)cyclohexanol (29) and *cis*-4-Chloro-*cis*-5-[(*Z*)-2-chloroethenyl]-*trans*-5-methyl-*trans*-2-(phenylselenenyl)cyclohexanol (30).** To a dry 2-neck 100-mL round bottom flask fitted with a condenser was added 6.54 g (0.1 mol) of dry activated zinc. To this was added 40 mL of dry CH_2Cl_2 followed by 4.5 g (0.01 mol) of a chromatographed mixture of the bicyclic ethers **28**, prepared as described above, dissolved in 10 mL of dry CH_2Cl_2. The suspension was rapidly stirred, and 1.22 g (0.02 m) of glacial acetic acid was gradually added. On warming to reflux an exothermic reaction occurred. The mixture was stirred under reflux until all the starting material had been converted to the more polar alcohols as indicated by TLC. To this suspension was added 10 mL of water and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (2 × 10 mL) and dried over $MgSO_4$. On evaporation in vacuo 3.68 g (0.01 mol) of a yellow oil was isolated, yield = 100%. The cis chloro olefin **29** could not be separated readily from the trans isomer **30** by chromatography. Hence this separation was postponed until the next step when the separation was easier. Characteristic ^1H NMR ($CDCl_3$ 250 MHz): δ 5.94 and 5.96 (ABq, J = 3 Hz) and 5.71 and 6.00 (ABq, J = 8.0 Hz) due to vinyl groups of the cis and trans isomers respectively and δ 1.01 and (s), 1.22 (s) due to methyl groups of the two isomers. The ratio of trans/cis isomers was variable with the desired trans isomer predominating slightly. The ^{13}C NMR spectrum of the mixture of isomers was well resolved with the exception of a few overlapping peaks. Of course the peaks corresponding to the two individual compounds were unassignable, however the spectrum of the mixture was recorded as follows: ^{13}C NMR overlapping methyl, δ 24.1; overlapping methylenes, δ 36.4, 36.8, 37.0, 38.6; quaternary carbon, δ 42.8, 43.1; selenium substituted methine, δ 46.1, 46.0; secondary chloride, δ 65.3, 65.9; overlapping carbinol, δ 67.9; terminal chloro olefin, δ 117.5, 112.1; aromatic and nonterminal olefin, δ 125.7, 125.9, 128.5, 128.6, 129.2, 136.0, 136.1, 137.1, 140.6.

(±)-(2-*RS*,4-*RS*,5-*RS*)-4-Chloro-5-[(*E*)-2-chloroethenyl]-5-methyl-2-(phenylselenenyl)cyclohexanone (31) and (±)-(2-*RS*,4-*RS*,5-*RS*)-4-Chloro-5-[(*Z*)-2-chloroethenyl]-5-methyl-2-(phenylselenenyl)cyclohexanone (32). To a solution of 1.56 g (20 mmol) of dry Me_2SO in 25 mL of dry CH_2Cl_2 at −78 °C under N_2 was added a solution of 3.21 g (15.3 mmol) of trifluoroacetic anhydride in 7 mL of dry CH_2Cl_2. After the mixture was stirred for $^1/_2$ h, a solution of 3.68 g (10.1 mmol) of the mixture of alcohols **29** and **30** dissolved in 10 mL of dry CH_2Cl_2 was added dropwise to the white suspension. After an additional $^1/_2$ h, 2.86 g (28.0 mmol) of dry triethylamine was added dropwise and the solution allowed to warm to room temperature. The reaction mixture was then washed with 1 N HCl (3 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL), and saturated NaCl solution (1 × 10 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo to give a yellow oil. The oil consisted of two olefinic isomers which were separated by flash chromatography over silica gel eluting with 30% methylene chloride/hexanes. The more polar fraction contained the cis isomer **31**, 0.69 g; the less polar fraction is the trans isomer **32**, 1.61 g, along with an intermediate mixed fraction, 0.3 g. The overall yield for all fractions was 71%. The fractions containing the cis isomer and mixed isomers also contained other minor isomers which had been carried along through the sequence of reactions but which were finally removed at this point. The cis fraction was rechromatographed to isolate a pure sample of **31** for analysis.

E chloro olefin **31**: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.25 (s, 3 H), 2.46–2.52 (m, 2 H), 2.57 (dd, 1 H, J = 15.12, 1.92 Hz), 3.02 (d, 1 H, J = 15.12 Hz), 3.97 (ddd, 1 H, J = 4.68, 4.68, 1.92 Hz), 4.29 (dd, 1 H, J = 9.5, 5.0 Hz), 6.03 and 6.05 (AB q, 2 H, J = 14.0 Hz), 7.25–7.34 (m, 3 H), 7.50–7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.2 (q), 38.25 (t), 45.94 (t), 46.32 (s), 48.09 (d), 63.52 (d), 120.82 (d), 127.47 (s), 129.41 (d), 128.82 (d), 134.32 (d), 134.90 (d), 203.2 (s); IR ($CHCl_3$) 3080, 3002, 2965, 2930, 1700, 1615, 1578, 1475, 1438, 1300, 1020, 1000, 978, 950, 855, 830 cm^{-1}. Anal. Calcd for $C_{15}H_{16}Cl_2OSe$: C, 49.74; H, 4.45. Found: C, 49.51; H, 4.45.

Z chloro olefin **32**: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.40 (s, 3 H), 2.51–2.57 (m, 2 H), 2.94 (A of AB, 1 H, J = 14.4, 0.61 Hz), 3.24 (B of AB, 1 H, J = 14.4, 1.7 Hz), 4.15 (m, 1 H), 4.45 (dd, 1 H, J = 7.4, 4.7 Hz), 5.78 and 6.12 (AB q, 2 H, J = 8.2 Hz), 7.26–7.34 (m, 3 H), 7.51–7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.57, 38.48, 46.10, 46.20, 47.58, 64.40, 120.35, 127.40, 128.52, 129.30, 131.58, 134.99, 203.07; IR ($CHCl_3$): 3085, 3020, 3000, 2960, 2925, 2865, 1705, 1620, 1575, 1470, 1430, 1378, 1345, 1298, 1290, 1200, 1110, 1060, 1018, 995, 973, 864, 845 cm^{-1}. Anal. Calcd for $C_{15}H_{16}Cl_2OSe$: C, 49.74; H, 4.45. Found: C, 49.86; H, 4.58.

(±)-*cis*-4-Chloro-3-[(*E*)-2-chloroethenyl]-3-methylcyclohexanone (34). To 0.81 g (12.4 mmol) of activated zinc in 10 mL of dry CH_2Cl_2 was added a solution of 0.45 g (1.24 mmol) of the phenylseleno ketone **31** dissolved in 15 mL of dry CH_2Cl_2. To this mixture was added 0.15 g (2.48 mmol) of glacial acetic acid. The mixture was then refluxed for 1.5 h at which time the solution was decanted from the unreacted zinc into a 100-mL separatory funnel. The zinc was washed with 10 mL of CH_2Cl_2, and the combined organic layers were washed with 1 N HCl (1 × 15 mL) followed by saturated $NaHCO_3$ solution (1 × 5 mL). After drying over $MgSO_4$, the solution was evaporated in vacuo to give a pale yellow oil which was flash chromatographed over silica gel eluting with 60% CH_2Cl_2/hexanes to give a colorless oil 0.23 g (1.1 mmol) in a yield of 89%: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.23 (s, 3 H), 2.11–2.46 (m, 4 H), 2.55–2.65 (m, 1 H), 2.74 (dd, 1 H, J = 14.5, 1.9 Hz), 4.13 (dd, 1 H, J = 3.5, 8.4 Hz), 6.02 and 6.08 (AB q, 2 H, J = 13.7 Hz); ^{13}C NMR ($CDCl_3$) δ 26.39 (q), 31.27 (t), 38.24 (t), 45.62 (s), 48.89 (t), 65.22 (d), 119.82 (d), 136.04 (d), 207.03 (s); IR ($CHCl_3$) 3078, 3015, 2962, 2920, 2865, 1715, 1610, 1450, 1445, 1442, 1425, 1415, 1380, 1348, 1328, 1315, 1308, 1290, 1278, 1245, 1232, 1230, 1202, 1120, 1080, 1038, 960, 945, 935, 905, 882, 850, 825 cm^{-1}.

***cis*-1-Chloro-2-[(*E*)-2-chloroethenyl]-2-methyl-5-methylenecyclohexane (35).** To a solution of 0.2 g (1 mmol) of the ketone **34** dissolved in 15 mL of dry CH_2Cl_2 under a $CaSO_4$ drying tube was added aliquots of the $CH_2Br_2/Zn/TiCl_4$ methylenation reagent.[21] The reaction progress was monitored by TLC for the disappearance of the starting material (R_f 0.3, 50% CH_2Cl_2/hexanes) and the formation of the product (R_f 0.9). After enough reagent had been added for complete reaction, the mixture was poured into 50 mL of 1:1 ether/saturated $NaHCO_3$ solution. The aqueous phase was extracted with ether (2 × 10 mL) and the combined organic phase dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil. Flash chromatography over silica gel eluting with hexanes gave 0.14 g (0.68 mmol) of the colorless oil **35** in a total yield of 69%: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.18 (s, 3 H), 1.82–1.93 (m, 1 H), 2.04 and 2.46 (AB q, 2 H, J = 13.6 Hz); 2.01–2.19 (m, 1 H), 3.90 (dd, 1 H, J = 9.7 and 3.6 Hz), 4.69 (bs, 1 H), 4.81 (bs, 1 H), 6.05 and 6.07 (AB q, 2 H, J = 13.6 Hz); ^{13}C NMR ($CDCl_3$) δ 26.08, 32.71, 32.94, 43.44, 44.58, 67.85, 111.39, 119.14, 136.25, 143.15; IR ($CHCl_3$) 3060, 2975, 2935, 2825, 1650, 1608, 1445, 1370, 1230, 1010, 993, 978, 938, 890, 820, 800, 770, 722 cm^{-1}. Anal. Calcd for $C_{10}H_{14}Cl_2$: C, 58.55; H, 6.88. Found: C, 58.92, H, 6.98.

(±)-[4*R*-[4α,5α(*E*)]]-1-(Bromomethyl)-4-chloro-5-(2-chloroethenyl)-5-methylcyclohexene (36) and (±)-[4*R*-[4α,3α(*E*)]]-1-(Bromomethyl)-4-chloro-3-(2-chloroethenyl)-3-methylcyclohexene (36a). To a solution of 0.51 g

(2.88 mmol) recrystallized NBS in 78 mL of 2:1 DME/H_2O at −20 °C was added a solution of 0.39 g (1.9 mmol) of the alkene **35** dissolved in 3 mL of DME. The reaction mixture was stirred at −20 °C for 5 h at which time TLC indicated the formation of 2 products (R_f 0.37 and 0.31 in hexanes). The solution was extracted with ether (3 × 10 mL), dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography of the resulting oil over silica gel eluting with hexanes gave two fractions: less polar material **36a**, 0.09 g, and more polar **36**, 0.247 g, in an overall yield of 62% and a ratio of 27:63.

36a: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.28 (s, 3 H), 1.94–2.15 (m, 2 H), 2.27–2.34 (m, 2 H), 3.85 (dd, 1 H, J = 11.9, 3.6 Hz), 3.87 and 3.93 (AB q, 2 H, J = 10.3 Hz), 5.54 (bs, 1 H), 5.87 and 6.05 (AB q, 2 H, J = 13.5 Hz); ^{13}C NMR ($CDCl_3$) δ 26.13, 27.09, 29.30, 36.24, 43.68, 65.89, 120.43, 131.58, 135.45, 136.36; IR ($CHCl_3$) 2960, 2920, 1600, 1450, 1428, 1367, 1305, 1240, 1180, 942, 878, 825, 805 cm^{-1}. Anal. Calcd for $C_{10}H_{13}BrCl_2$: C, 42.28; H, 4.61. Found: C, 42.29; H, 4.74.

36: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.22 (s, 3 H), 2.10–2.67 (m, 4 H), 3.93 (bs, 2 H), 3.92 (dd, 1 H, J = 5.4, 8.4 Hz), 5.77 (bs, 1 H), 6.06 and 6.12 (AB q, 2 H, J = 13.6 Hz); ^{13}C NMR ($CDCl_3$) δ 25.6, 33.9, 37.2, 37.2, 40.7, 64.1, 119.1, 124.7, 133.0, 135.3; IR ($CHCl_3$) 2955, 2920, 1445, 1428, 1375, 1320, 1240, 1180, 940, 872, 820 cm^{-1}. Anal. Calcd for $C_{10}H_{13}BrCl_2$: C, 42.28; H, 4.61. Found: C, 42.63; H, 4.78.

(±)-[1*R*-[1α(*E*),2α]]-1-(2-Chloroethenyl)-2,4-dichloro-1-methyl-5-methylenecyclohexane (2).[6] To a solution of the allylic bromide **36**, 33.8 mg (0.12 mmol), in 1.5 mL of $CHCl_3$ under a reflux condenser and drying tube was added 29.0 mg (0.13 mmol) of phenyldichloroiodine.[23] The solution was refluxed for a period of 1 hour, and TLC indicated the formation of 3 or 4 different products along with complete reaction of the starting material. The solution was evaporated in vacuo and the residue examined by NMR for formation of any compounds giving rise to signals characteristic of natural products. Subsequently, the residue was flash chromatographed over silica gel by eluting with hexanes to give a colorless oil **2** as the least polar product 6.7 mg (0.027 mmol) in a yield of 23%. The other inseparable fractions were reexamined by NMR and shown to have no compounds present corresponding to natural product spectra. The fractions were not purified further. ^1H NMR ($CDCl_3$ 250 MHz): δ 1.26 (s, 3 H), 2.21–2.45 (m, 3 H), 2.63 (bd, 1 H, J = 14.4 Hz), 4.32 (dd, 1 H, J = 11.3, 4.2 Hz), 4.74 (bt, 1 H, J = 3.4 Hz), 4.92 (bs, 1 H), 5.17 (bs, 1 H), 6.01 and 6.08 (AB q, 2 H, J = 13.6 Hz). ^{13}C NMR ($CDCl_3$): δ 26.5, 40.96, 41.39, 43.48, 61.54, 63.13, 115.44, 120.25, 133.9, 142.12. IR ($CHCl_3$): 2980, 2935, 1600, 1450, 1432, 1312, 1290, 1230, 970, 940, 915, 855, 830, 810 cm^{-1}. Anal. Calcd for $C_{10}H_{13}Cl_3$: C, 50.13; H, 5.47. Found: C, 50.06; H, 6.75.

(±)-[4*R*-[4α,5α(*E*)]]-4-Chloro-5-(2-chloroethenyl)-1-(chloromethyl)-5-methylcyclohexene (3).[6] To a stirred solution of 9 mg (0.044 mmol) of alkene **35** in 1 mL of CH_2Cl_2 was added one drop of water and 60 μL of a 5% NaOCl solution (Chlorox). The mixture was stirred for 1 h. TLC indicated the formation of a single compound (R_f 0.18 in hexanes); 5 mL of ether was added. The solution was dried over $MgSO_4$ and evaporated in vacuo. Flash chromatography of the resulting oil over silica gel eluting with hexanes gave a colorless oil, 8 mg (0.033 mmol), in 75% yield: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.22 (s, 3 H), 2.14 (bd, 1 H, J = 17 Hz), 2.32–2.48 (m, 2 H), 2.61 (bd, 1 H, J = 17 Hz), 3.93 (dd, 1 H, J = 8.5, 5.3 Hz), 3.99 (bs, 2 H), 5.68 (bs, 1 H), 6.06–6.08 (AB q, 2 H, J = 13.6 Hz); ^{13}C NMR ($CDCl_3$) δ 25.65, 33.78, 36.80, 40.75, 48.90, 64.19, 119.1, 124.34, 132.50, 135.29; IR ($CHCl_3$) 2920, 1610, 1432, 1375, 1320, 1255, 940, 875, 820, 680 cm^{-1}.

***trans*-5-Chloro-*trans*-4-[(*E*)-2-chloroethenyl]-*cis*-4-methyl-2-methylenecyclohexanol (38).** To a solution of 56 mg (0.18 mmol) of diphenyl diselenide dissolved in 1 mL of dry ethanol in a 10 mL round bottom flask was added enough sodium borohydride to render the yellow solution colorless. To this solution was added 93 mg (0.33 mmol) of the allylic bromide 36 dissolved in 0.5 mL of dry ethanol. The solution was stirred for $^1/_2$ h at which time $^1/_2$ of the ethanol was evaporated under a stream of N_2 gas, and 1 mL of THF was added followed by 0.19 mL of 30% H_2O_2 solution (1.6 mmol). The resulting mixture was stirred at room temperature for 3 h, diluted with 10 mL ether and washed successively with saturated $NaHCO_3$ (2 × 3 mL), water (1 × 3 mL), and saturated NaCl (1 × 3 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil. Flash chromatography over silica gel eluting with 80% CH_2Cl_2/hexanes gave rise to an oil 62.6 mg (0.28 mmol) in a yield of 86%. The oil was crystallized from cold pentane to give colorless cubic shaped crystals, mp 75–76 °C, which were subjected to X-ray analysis.[24] ^1H NMR ($CDCl_3$ 250 MHz): δ 1.22 (s, 3 H), 2.0–2.27 (m, 2 H), 2.34–2.48 (AB q, 2 H, J = 14.0 Hz), 4.25 (dd, 1 H, J = 4.1, 9.9 Hz), 4.40 (bd, 1 H, J = 4.3, 4.3 Hz), 4.87 (bs, 1 H); 5.08 bs, 1 H), 6.05 (bs, 2 H). ^{13}C NMR ($CDCl_3$): δ 25.97, 40.04, 40.81, 43.49, 64.61, 71.26, 112.64, 119.29, 135.47, 145.22. IR ($CHCl_3$): 3600, 3080, 2960, 2920, 1650, 1608, 1430, 1372, 1312, 1228, 1035, 1000, 940, 910, 870, 850, 820 cm^{-1}. Anal. Calcd for $C_{10}H_{14}Cl_2O$: C, 54.31; H, 6.38. Found: C, 54.32; H, 6.39.

1-(Bromomethyl)-4-chloro-3-[(*E*)-2-chloroethenyl]-3-methyloxabicyclo[4.1.0]heptane (39). To a solution of 0.28 g (1 mmol) of the allylic bromide **36** in 5 mL of ethylene dichloride was added 20 mg (0.05 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide.[37] This was followed by 0.207 g (1.2 mmol) of recrystallized *m*-chloroperbenzoic acid. The solution was refluxed for 4 h at which time TLC indicated complete reaction of the starting material. The solution was diluted with 10 mL of ether and washed with saturated $NaHSO_3$ (1 × 5 mL) followed by saturated $NaHCO_3$ (1 × 5 mL) and dried over $MgSO_4$. After evaporating in vacuo, the residue was flash chromatographed over silica gel by eluting with 20% CH_2Cl_2/hexanes to give 0.25 g (0.83 mmol) of a colorless oil **39** in a yield of 83%: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.18 (s, 3 H), 2.0 and 2.31 (AB q, 2 H, J = 15.8 Hz), 2.17 (ddd, 1 H, J = 10.1, 15.3, 2.4 Hz), 2.56 (ddd, 1 H, J = 15.3, 4.7, 1.8 Hz), 3.26 (bs, 1 H), 3.34 (s, 2 H), 3.86 (dd, 1 H, J = 10.8, 4.9 Hz), 6.10 and 6.16 (AB q, 2 H, J = 13.7 Hz); ^{13}C NMR ($CDCl_3$) δ 26.23, 33.25, 37.78, 38.93, 40.06, 57.64, 60.79, 62.09, 120.01, 134.81; IR ($CHCl_3$) 3080, 2980, 2920, 2880, 1610, 1450, 1430, 1375, 1333, 1300, 1230, 1105, 1070, 1000, 972, 960, 950, 902, 875, 822 cm^{-1}.

1-(Bromomethyl)-*trans*-5-[(*E*)-2-chloroethenyl]-*trans*,-*trans*-2,4-dichloro-*cis*-5-methylcyclohexanol (40). To a solution of 30 mg (0.1 mmol) of the epoxide **39** dissolved in 10 mL of dry ether was added dry HCl gas until the ether was saturated. Th solution was stirred overnight, diluted with a further 10 mL of ether, and washed with 3 × 5 mL saturated $NaHCO_3$ solution followed by 1 × 5 mL saturated NaCl solution. The organic phase was then dried over $MgSO_4$ and evaporated in vacuo. The residue flash chromatographed over silica gel eluting with 80% CH_2Cl_2/hexanes to give 29 mg (0.087 mmol) of a colorless oil **40** in a yield of 87%: ^1H NMR ($CDCl_3$ 250 MHz) δ 1.25 (s, 3 H), 1.50 (dd, 1 H, J = 14.6, 2.0 Hz), 2.22 (ddd, 1 H, J = 12.4, 12.7, 12.0 Hz), 2.57 (ddd, 1 H, J = 12.4, 4.3, 3.8 Hz), 2.59 (d, 1 H, J = 14.6 Hz), 3.57 (d, 1 H, J = 11.4 Hz), 3.76 (dd, 1 H, J = 12.0, 3.8 Hz), 4.0 (dd, 1 H, J = 11.2, 2.0 Hz), 4.16 (dd, 1 H, J = 12.7, 4.3 Hz), 6.15 and 6.35 (AB q, 2 H, J = 13.7 Hz); ^{13}C NMR ($CDCl_3$) δ 29.50 (q), 40.05 (t), 40.04 (d), 42.61 (s), 46.67 (t), 63.28 (d), 64.65 (d), 72.52 (s), 121.33 (d), 133.41 (d); IR ($CHCl_3$) 3610, 3550, 3400 (broad), 3000, 2975, 2920, 2890, 1610, 1450, 1435, 1423, 1380, 1350, 1322, 1300, 1270, 1235, 1170, 1130, 1040, 1025, 1018, 975, 925, 875, 865, 820 cm^{-1}.

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Registry No. (±)-**2**, 97858-40-7; (±)-**3**, 97805-62-4; **5**, 84895-35-2; **6**, 84895-36-3; **7**, 106-99-0; **8**, 78-79-5; **9**, 542-92-7; (±)-**10**, 97733-27-2; (±)-**11**, 97733-28-3; (±)-**12**, 97733-29-4; (±)-**12a**, 97733-45-4; (±)-**13**, 97733-30-7; (±)-**13a**, 97733-46-5; (±)-**14**, 97733-31-8; (±)-**14a**, 97733-47-6; (±)-**15**, 97733-32-9; (±)-**15a**,

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97733-48-7; (±)-**16**, 97733-33-0; (±)-**17**, 97733-34-1; (±)-**18**, 97805-63-5; (±)-**19**, 97805-64-6; (±)-**20**, 97733-35-2; (±)-**21**, 95760-46-6; (±)-**22**, 97733-36-3; (±)-**23**, 97733-37-4; (±)-**24**, 97733-38-5; (±)-**25**, 97733-39-6; (±)-**26**, 97805-65-7; (±)-**27** (isomer 1), 97733-40-9; (±)-**27** (isomer 2), 97805-68-0; (±)-**27** (isomer 3), 97805-69-1; (±)-**27** (isomer 4), 97805-70-4; (±)-**28** (isomer 1), 97749-49-0; (±)-**28** (isomer 2), 97859-23-9; (±)-**28** (isomer 3), 97859-24-0; (±)-**28** (isomer 4), 97859-25-1; **29**, 97733-41-0; (±)-**31**, 97749-28-5; (±)-**32**, 97733-42-1; (±)-**34**, 97733-43-2; (±)-**35**, 97805-66-8; (±)-**36**, 97805-67-9; (±)-**36a**, 97733-49-8; (±)-**38**, 97749-29-6; (±)-**39**, 97733-44-3; (±)-**40**, 97749-50-3; CH_2=CHC-(CH_3)=CH_2, 78-79-5; CH_2BrCl, 74-97-5.

Supplementary Material Available: Details of the X-ray analysis of compound **38**, an ORTEP plot, and tables of final positional parameters, atomic thermal parameters, and bond distances and angles (6 pages). Ordering information is given on any current masthead page.

Conversion of Resin Acids into a Steroid Skeleton. Formation of the D Ring[1]

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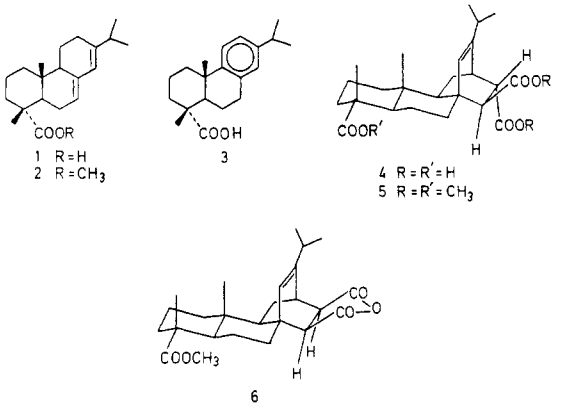
The conversion of abietic acid (**1**) to a 15-hydroxy-17-keto steroid is reported. This route uses the 13-isopropyl group of **1** as a building block for the D ring of the steroid skeleton. The diene system of the resin acid is protected by a Diels–Alder reaction with maleic or fumaric acid. No oxygen function is introduced in the B ring during the whole procedure.

The conversion of tricyclic diterpenoids into steroid compounds has attracted considerable effort and ingenuity. Several synthetic approaches to a steroid skeleton using resin acids as starting material have been reported in the literature.[2-11]

The most abundant resin acid, abietic acid (**1**), is unfortunately not a good starting material due to isomerization and autoxidation. Therefore the more stable dehydroabietic acid (**3**) has been used mostly for such synthetic conversions.



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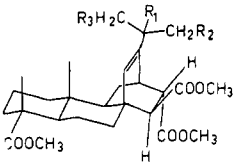
We have developed a synthetic route from **1** to a *C*-aryl 18-norsteroid skeleton using the isopropyl group as a building block for the D ring. The main synthetic problem in this approach was to attack the isopropyl group selectively, avoiding any reactions at the ring system. Selective bromination of this group could be achieved on compounds **4** and **6**, the Diels–Alder adducts of fumaric or maleic acid with **1**, using a similar procedure as described earlier.[12,15] The most important advantage of **4** is that it is stable and can be conveniently prepared directly from rosin without previous isolation of **1** or **2**.[13,14] Avoiding temperatures above 0 °C, bromination of the ester **5** (irradiating with a 1000-W light bulb) yielded **7** quantitatively.[15] Further



7 R_1=Br R_2=R_3=H
8 R_1=R_2=Br R_3=H
9 R_1=R_2=R_3=Br

bromination of **7** gave the di- and tribromo products **8** and **9**; no other products, obtained earlier from bromination reactions have been detected.[16-18] By addition of dry pyridine to the reaction mixture after the bromination, the olefin (**10**) could be obtained directly from **5** by a one-step procedure.[12]

Selective cleavage of the terminal double bond in **10** is possible by two procedures. With OsO_4/$NaIO_4$ **11** is obtained quantitatively. Reaction with ozone is better suited for large-scale preparations although the yield is lower (77%). Ozonolysis of **12** gave other products probably due

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