Enantioselective Ring Construction: Synthesis of Halogenated Marine Natural Spiro[5.5]undecane Sesquiterpenes†

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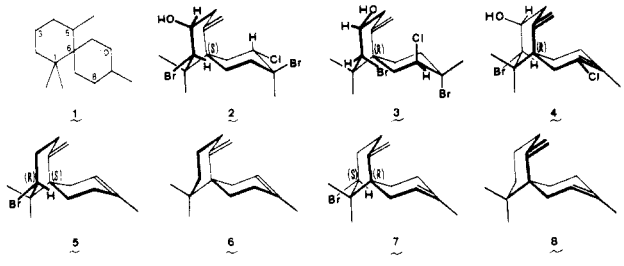
Abstract: The primary objective in this investigation was to develop a general method to achieve a significant amount of asymmetric induction in the bromonium initiated intramolecular carbocyclization reaction. This goal has been achieved by generation of exocyclic alkylidienes containing two stereogenic atoms located on the cyclohexene ring. The stereochemistry of the process has been investigated in some detail, and the total synthesis of (−)-(2*R*,6*S*,8*S*,9*S*)-2,8-dibromo-9-hydroxy-α-chamigrene (**9**), (−)-(2*R*,6*S*,8*S*,9*S*)-2,8-dibromo-9-hydroxy-β-chamigrene (**10**), (−)-(2*R*,6*S*)-2-bromo-β-chamigrene (**5**), (−)-β-chamigrene (**6**), and their corresponding (+)-**11**, -**12**, -**7**, and -**8** enantiomers is described for the first time. These compounds were prepared from (8*S*,9*S*)-8-bromo-9-hydroxy-(*E*)-γ-bisabolene, (−)-**33**, and (8*R*,9*R*)-8-bromo-9-hydroxy-(*E*)-γ-bisabolene, (+)-**33**, as the basic building blocks. This asymmetric methodology represents a general strategy for the enantioselective construction of spiro[5.5]undecane systems containing a chiral quaternary center. This approach should be generally useful for the preparation of a wide variety of six-membered spirocycle-containing natural compounds.

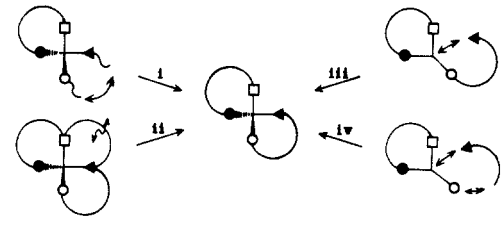
The compounds obtusol,[1] (2*S*,3*R*,6*S*,8*S*,9*S*)-2,9-dibromo-8-chloro-3-hydroxy-β-chamigrene (**2**), isoobtusol,[2] (2*R*,3*S*,6*R*,8*S*,9*S*)-2,9-dibromo-8-chloro-3-hydroxy-β-chamigrene (**3**), and (+)-elatol,[3] (2*R*,3*S*,6*R*)-2-bromo-8-chloro-3-hydroxy-β-chamigrene (**4**), are three examples of the more than 40 polyhalogenated sesquiterpenes with a chamigrane[4] skeleton **1** isolated



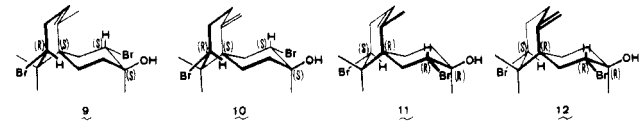
from red algae of the genus *Laurencia*. The structures of these three compounds as well as the absolute configuration of their stereogenic atoms were determined by X-ray diffraction studies, and the enantiomeric relationship of the carbon skeleton of **2** with that of **3** (or **4**) was confirmed[5] by CD studies. The acid-catalyzed rearrangement products of obtusol[6] (**2**) and isoobtusol[7] (**3**) were studied, and the conclusions reached allowed a better knowledge of the genesis of some of the sesquiterpene skaleta specifically isolated from this prolific genus of algae as well as their dependence on the position and orientation of the heteroatoms in the chamigrane precursor. In all, the most notable difference between obtusol (**2**) and isoobtusol (**3**) is to be found in the observed pharmacological activity. Compound **3** presents a moderate cytostatic[8] activity and a remarkable antimicrobial[9] activity on both Gram + and Gram − bacteria, which bioactivity is not observed in isomer **2**. The antimicrobial activity is, however, maintained in (+)-elatol (**4**), a natural compound readily prepared[5] from **3** by HBr elimination, which occurs with concomitant chair–chair interconversion of the ring having the exocyclic methylene, in such a manner that the differences in bioactivity must be related above all with the enantiomeric relationship of their carbon skeleta.

These reasons and the intrinsic synthetic interest of the preparation of spirocycles and quaternary carbon centers prompted us to undergo the enantioselective synthesis of the more simple chamigrenes: (−)-(2*R*,6*S*)-2-bromo-β-chamigrene (**5**) and (+)-(2*S*,6*R*)-2-bromo-β-chamigrene[10] (**7**) having respectively the basic skeleta: (−)-β-chamigrene[11] (**6**) and (+)-β-chamigrene (**8**)

Scheme I



of obtusol (**2**) and isoobtusol (**3**). In this study,[12] a series of optically active chamigrenes **9**–**12** having four stereogenic atoms,



which include the natural[13] (−)-(2*R*,6*S*,8*S*,9*S*)-2,8-dibromo-9-

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† We dedicate this article to Professor Antonio González on the occassion of his 68th birthday.

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(9) With use of the standard disk assay, isoobtusol (**3**) inhibited the growth of *Staphylococcus aureus*, *Escherichia coli*, *Proteus vulgaris*, and *Klebsiella pneumoniae* at 5 μg/disk; elatol (**4**) inhibited the growth of *S. aureus* and *M. ranae* at 20 μg/disk; obtusol (**2**) was inactive showing only slight inhibitory activity against *S. aureus* at 100 μg/disk.

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(12) The numbering scheme in this discussion section is intended to simplify discourse by maintaining a fixed designation for a particular carbon throughout a series of structures. Proper IUPAC names are provided for each compound in the Experimental Section.

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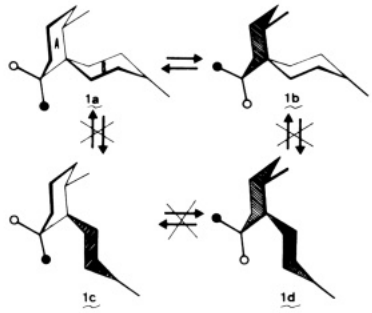
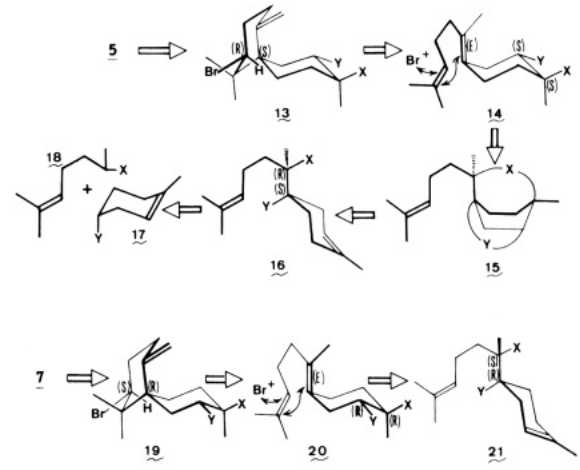
Scheme II



Scheme III



hydroxy-α-chamigrene (**9**) and the recently[14] reported 8*R*,9*R*-heterosubstituted chamigrenes **11**–**12** were synthesized. In spite of the numerous racemic total synthesis[15] of sesquiterpenes possessing the chamigrane skeleton, there is yet to be described in the literature a true asymmetric[16] approach to these substances. In addition, and probably more important in regard to laying a solid foundation for future synthetic efforts, we focused our attention in refining our view of the factors that are responsible for the control of selectivity.[17]

Background. Spirocycles[18] represent challenging targets in both natural products or theoretical chemistry. Especially the construction of spiro[4.5]decane and spiro[5.5]undecane systems has attracted the attention of many synthetic chemists, as they constitute the basic carbon framework found in sesquiterpenes[19] of the spirovetivane, acorane, or chamigrane classes. The strategies used for construction of spirosystems might be grouped in two conceptually different approaches (Scheme I): (a) The strategy involves the synthesis of an adequate quaternary carbon center on a mono- or tricarbocyclic system, and the spirocompounds are reached by intramolecular cyclization (*path i*) or via a specific bond cleavage (*path ii*). (b) The spirosystem is constructed simultaneously with the quaternary carbon spirocenter via intramolecular (*path iii*) or intermolecular (*path iv*) processes. Although quaternary carbon centers[20] are pivotal and synthetically structural components of many complex intermediates and natural components, only a few methods have been available for stereocontrolled formation of molecules containing such quaternary centers in high enantiomeric purity.[21] Apart from the problem of the quaternary carbon center one has also to cope with the relative stereochemistry of substituents on the same ring; the major stereochemical problem, however, is establishing the correct sense of the chirality of the spirocarbon relative to the centers present in both rings. The great amount of chemical work, both synthetic[15] and structural,[4] carried out with many different substitutions on compounds having a carbon chamigrane skeleton, proved to be of interest when planning our enantioselective syntheses. In the absence of bonding interactions, of the four possible ground-state *all-chair* conformations of chamigrane (Scheme II), only the interconversion **1a** $\rightleftarrows$ **1b** is possible, since the conformations **1c** and **1d** are submitted to strong steric repulsion due to the presence of the *gem*-dimethyl substituents at C_1. The conformations **1a** and **1b** can be "frozen" under nonbonding interaction, as occurs with isoobtusol (**3**), where the axially bonded chlorine atom at C_8 controls the orientation of the substituents on ring A [$C_2(Br)_a$ and $C_3(OH)_e$], when the said interaction disappears; e.g., by conversion into (+)-elatol (**4**), the chair–chair interconversion occurs on ring A, the substituents adopting a more energetically favored orientation [$C_2(Br)_e$ and $C_3(OH)_a$]. It is therefore possible, with an appropriate substitution on ring B and in a rigid controlled conformation of the ring, to construct the spirosystem of chamigrane simultaneously with the quaternary carbon spirocenter by intramolecular or intermolecular processes, following *path iii* or *iv* shown in Scheme I. The fact that conformations **1a** and **1b** may be generated to very different transition states, with no possibility of equilibrium among them, makes the enantioselective construction of the system feasible.

Synthetic Rationale. The syntheses were planned following the retrograde pathways shown in Scheme III. Our interest[22] in the

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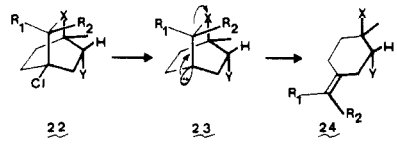
asymmetric syntheses of compounds containing on *E* or *Z* exocyclic tetrasubstituted olefin with specific stereochemistry on the ring substituents has led us to consider the enantioselective synthesis of the chamigrane skeleton as a viable target via X,Y-*trans*-disubstituted exocyclic cyclohexenes such as **14** or **20**, which could be derived from the chiral compounds **16** or **21**. We report here that it was feasible to prepare the *E* exocyclic tetrasubstituted olefins **14** (or **20**) and sequentially alkylate them intramolecularly to the key intermediates **13** (or **19**) which led after X,Y-elimination to an efficient synthesis of (−)-**5** or (+)-**7** in 18% overall yield and in >97% enantiomeric excess.

Our interest in such total syntheses arose from a perception that the stereogenic quaternary carbon center of the spirocyclic system could be assembled by asymmetric carbocyclization on the exocyclic tetrasubstituted dienes induced stereospecifically by the stereocontrol elements X and Y. Though for the moment we leave the precise nature of X and Y unspecified, it was anticipated that they are utilized for coupling the synthons **17** and **18**, thus to induce chirality by control bridging to C_8 and C_9 carbons as shown in **15**. The control elements X and Y are inherent to the molecular organization of the starting material and converted to *vicinal* groupings having defined chirality in the dienic intermediates **14** or **20**. The *E* stereochemistry of the tetrasubstituted olefinic bonds is controlled by bridging delivery from C_5 and C_6 positions.

We view the intramolecular bromonium induced carbocyclization on the exocyclic olefins **14** and **20** as a kinetically controlled process. Thus, the product distribution is determined by the activation barriers leading to each of the products, with the major product being formed from the lowest energy pathway. Therefore, the requirement to induce asymmetry is to generate diastereomeric transition states with different energies. The approach to inducing asymmetry was to incorporate stereogenic atoms on the cyclohexane ring. The nature and localization of these atoms were chosen to allow access to the naturally occurring, biologically active chamigrenes. Of the several functional groups and stereogenic atoms found in chamigranes, the ring B heteroatom-bearing carbons appeared well-suited to be built into the (*E*)-γ-bisabolene intermediate. Thus, our initial target became the independent syntheses of the enantiomeric X,Y-disubstituted γ-bisabolenes **14** and **20**.

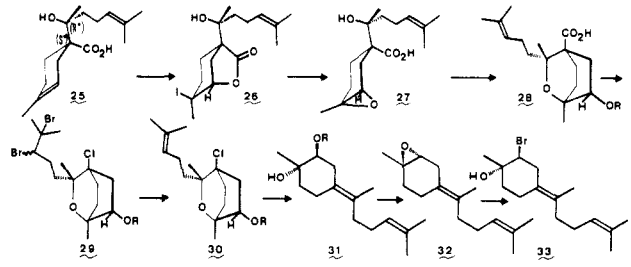
Discussion of Results

Synthesis of C_8 and C_9 Stereogenic Atoms. Our decision was, therefore, made to postpone the need for optically resolved intermediates until many of the uncertainties implicit in the retrosynthesis approach could be experimentally evaluated. The first subgoal became the stereocontrolled synthesis of racemic 8,9-heterosubstituted (*E*)-γ-biosabolene **14**. The difficulties in the synthesis of these substances in a steroecontrolled way arise mainly because of the lack of methodology[23] which can generate specifically either an *E* or *Z* exocyclic tetrasubstituted olefin. We have recently reported[22] a method in which stereocontrolled tetrasubstituted olefins are formed by using bridgehead intermediates[24] created on small bicyclic ring systems, such as the bicyclo[2.2.2]octane framework **22**. The fragmentation to give **24** is enforced by the structure of the bicyclic intermediate **23** whose rigid nature allows the whole process to occur without stereochemical ambiguity.

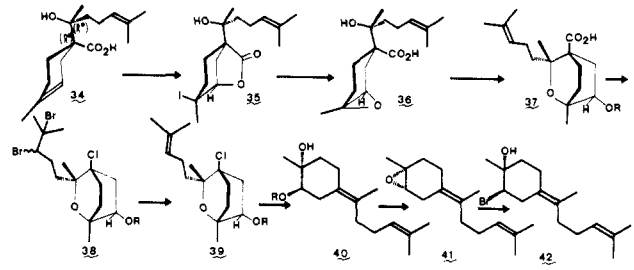


22 **23** **24**

Scheme IV



Scheme V



The starting material was the readily available[25] (±)-β-hydroxy acid **25** (Scheme IV), which can be obtained on a large scale from 4-methyl-3-cyclohexanecarboxylic acid, **17** (Y = CO_2H), and 6-methyl-5-hepten-2-one, **18** (X = =O), in 85% yield, followed by fractional recrystallization of the diastereomers **25** and **34** (Scheme V). Both of these compounds were independently carried on in the remainder of the synthesis in the same manner. For the sake of simplicity, the following discussion of the preparation of the chiral 8,9-disubstituted γ-bisabolenes will focus mainly upon the *E* isomer. Complete experimental details and spectral data of both series of compounds, **25**–**33** and **34**–**42**, are given in the Experimental Section. The extra functionalized carbon of compound **25** (C_{16}) was specifically introduced following a homologative approach[26] to make the molecule consonant and to further control stereoselectivities by a bridging process. The extra carboxylic atom was used for racemate resolution.

Reaction of the diisopropylamine salt of **25** with iodine in dichloromethane gave the iodolactone **26** which was treated with aqueous KOH to give the epoxy acid **27** which without any further purification was treated with a catalytic amount of *p*-toluenesulfonic acid to produce **28** (R = Ac) followed by decarboxylation[27] (reverse to homologation) to give, after reductive elimination of bromine, the chloro ether **30** (R = H). The reductive fission of the β-chloro ether bonds with powdered sodium metal gave 8,9-dihydroxy-(*E*)-γ-bisabolene **31** (R = H) in 80% overall yield from **27** (R = H). Epoxide **32** was obtained in 96% yield through the monotosyl derivative of **31** (R = Ts), followed by base treatment with aqueous KOH in methanol. 8-Bromo-9-hydroxy-(*E*)-γ-bisabolene (**33**) was obtained in 94% yield by treatment[28] of epoxide **32** with excess of dilithium tetrabromonickelate(II) in tetrahydrofuran.

The synthesis of racemic 8-bromo-9-hydroxy-(*Z*)-γ-bisabolene (**42**) was accomplished starting from the diastereoisomeric β-hydroxy acid (±)-**34** following an identical sequence of reactions in 60% overall yield.

Starting from (−)-acetoxy acid **28** (R = Ac) or its corresponding (+)-enantiomer, (8*R*,9*R*)-8-bromo-9-hydroxy-(*E*)-γ-bisabolene (**33**) and the (8*S*,9*S*)-antipodal were respectively synthesized following the reaction sequence indicated in Scheme IV. The

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(−)-acid, **28** (R = Ac), directs stereoselective decarboxylation to give 8*R*,9*R*-disubstituted *E*-γ-bisabolenes. From (+)-**28** (R = Ac), the synthesis of 8*S*,9*S*-disubstituted *E*-γ-bisabolene was achieved.

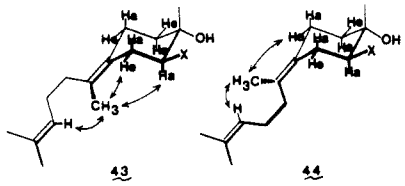
For enantiomeric purification of racemic **28** (R = Ac), we previously reported[17] the optical resolution with quinine to give the (−)-acid; the (+)-acid was easily obtainable by resolution with L(−)-α-methylbenzylamine by recrystallization of the salt from *n*-hexane.[29] The enantiomeric excesses[30] of the optically pure compounds were established as >97% by proton NMR spectroscopy by using chiral LISR for the acetates **28**, **30**, and **31**.

The critical conformational and stereochemical assignments to **31** (R = Ac) and **33** rest upon detailed proton NMR examination of both dienes (see **43**). Identification of C_7H_e as the multiplet centered at δ 2.66 (dd, *J* = 14, 4 Hz) in **43** (X = OAc) or at δ 3.08 (ddd, *J* = 14, 4, 1.5 Hz) for **43** (X = Br) was achieved by irradiation of the methine proton at C_8, δ 4.64 (dd, *J* = 9, 4 Hz) or at δ 4.08 (dd, *J* = 11, 4 Hz), in the NMR spectra of **43**, X = OAc and X = Br, respectively. Simplification of the absorption pattern to a doublet resulted. Complementary double resonance experiments involving C_7H_e result*ed* in the collapse of the C_8H_a to a doublet. The proton homonuclear correlation spectrum COSY-90 displayed correlations for practically all the protons of both compounds, and besides the normal couplings, other long-range couplings (e.g., C_7H_e–$C_{11}H_e$, $C_{11}H_a$–C_9Me, C_9Me–C_7H_a, C_9Me–C_8H_a) could be easily detected. Additionally, a NOE difference experiment revealed the existence of nuclear Overhauser enhancements between C_5Me and C_7H_e; when C_5Me was examined, strong through-space interactions with C_7H_e, C_2H, and C_8H_a were detected on both **43**, X = OAc and X = Br.

Similarly, structural assignments for **40** (R = Ac) and **42** were also based upon extensive proton NMR experiments (see **44**). Thus, proton–proton decoupling and proton homonuclear correlation spectrum COSY-90 experiments allowed assignment of nearly every proton according to **44**, X = OAc and X = Br. Having assigned the resonance corresponding to C_7H_e and $C_{11}H_e$, we next carried out a series of NOEDS experiments to determine the geometric relationship with C_5Me. The most significant observation was the absence of signal enhancement of C_7H_e upon presaturation of C_5Me and the strong enhancement of $C_{11}H_e$.

On this basis, we assigned to **31** (R = OAc) and **33** and to **40** (R = OAc) and **42** the conformations shown, respectively, in **43** and **44**, upon which the observed through-space interactions are overlaid.

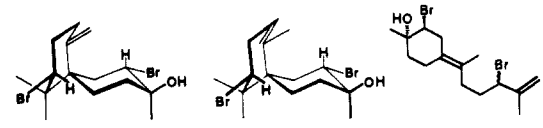
With elucidation of the conformation of **33**, though not fully conclusive, evidence is obtained that the induced bromocarbocyclization and the creation of the tetrasubstituted carbon center via the chair conformation are shown in **43** (X = Br). Presumably, this conclusion can be generalized to include the related molecules studied herein.



43 **44**

Synthesis of C_2 and C_6 Stereogenic Atoms. With the availability of racemic **33** in quantity, an electrophilic induced diene carbocyclization was initiated by using equivalents[31-33] to bromonium ion as cationic inductors. The ensuing cyclization, especially its stereochemical outcome, has extensive precedent[34] in the studies of Lewis acid catalyzed polyolefin cyclizations. The indirect incorporation of bromine through a mercuriation–bromination tandem has been reported[32-33] to be somewhat superior to direct[31] brominative carbocyclization and has the advantage of permitting stereospecific synthesis of either an equatorial or axial bromide.[32a] Unexpectedly, when **33** was treated with both mercuric trifluoroacetate[32] or mercuric trifluoromethane–sulfonate–amine complex[33] in acetonitrile or nitromethane, no bicarboxylic products were formed; instead a mixture of nonstudied monocarbocyclized mercuric complexes was always obtained.

Brominative carbocyclization of (±)-**33** was effected by using 1.5–2.0 equiv of 2,4,4,6-tetrabromocyclohexa-2,5-dienone[35] (TBCD) in dry nitromethane at 0–25 °C for 3 h to give[36] racemic **45** (17%), **46** (6%), and **47** (32%) following chromatographic



45 **46** **47**

separation. This stereoselective cyclization was only successful when performed by using freshly distilled dry nitromethane. Bicarbocyclic compounds are readily distinguished from other reaction products in the crude reaction mixture by the presence of methyl singlets shifted to a lower field in the proton NMR spectrum, due to the newly created quaternary carbons.

The model system (±)-**33** is therefore capable of delivering a product, i.e., (±)-**45** having a carbocyclic framework comparable to that found in obtusol (**2**) or isoobtusol (**3**). The approach undertaken so far is responsible for the question of the stereochemistry and nicely installs the stereogenic quaternary and ternary carbons. However, loss of product for competitive formation of **47** remains an attractive feature that demands further attention.

(29) The resolution of racemic **37** (R = Ac) was readily achieved by a similar process as the above described: recrystallization of the salt with quinine from acetone yield (−)-**37** (R = Ac), while the antipodal (+)-**37** (R = Ac) was prepared by recrystallization of the salt with L-(−)-α-methylbenzylamine from *n*-hexane (see Experimental Section).

(30) The enantiomeric excesses were stablished by ^1H NMR examination of the methyl acetate signals obtained in the presence of Eu(tfc)$_3$, tris[((trifluoromethyl)hydroxymethylene)-(−)-camphorato]europium(III).

(31) (a) van Tamelen, E. E.; Hessler, E. J. *J. Chem. Soc., Chem. Commun.* **1966**, 411–412. (b) Grenwood, J. M.; Salomon, M. D.; Sutherland, J. K.; Torre, A. *J. Am. Soc. C* **1968**, 3004–3008. (c) González, A. G.; Martín, J. D.; Pérez, C.; Ramírez, M. A. *Tetrahedron Lett.* **1976**, 137–138. (d) Hoye, T. R.; Kurth, M. A. *J. Org. Chem.* **1978**, *43*, 3693–3697. (e) Kato, T.; Ichinose, I.; Kumazawa, S.; Kitahara, Y. *Bioorg. Chem.* **1975**, *4*, 188–190. (f) Kato, T.; Ichinose, I.; Kamoshida, A.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 518–519. (g) Ichinose, I.; Kato, T. *Chem. Lett.* **1978**, 61–62. (h) Shieh, H. M.; Preswich, G. *Tetrahedron Lett.* **1982**, 4643–4646. (i) Yamaguchi, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1985**, 343–346. (j) Murai, A.; Abiko, A.; Kato, K.; Masamune, T. *Chem. Lett.* **1981**, 1125–1128. (k) Murai, A.; Kato, K.; Masamune, T. *Tetrahedron Lett.* **1982**, 2887–2890. (l) Murai, A.; Abiko, A.; Masamune, T. *Tetrahedron Lett.* **1984**, 4955–4958.

(32) (a) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461–3467. (b) Hoye, T. R.; Kurth, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5065–5067. (c) White, J. D.; Nishiguchi, T.; Skeen, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 3923–3928. (d) Hoye, T. R.; Caruso, A. J.; Dellaria, J. F., Jr.; Kurth, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 6704–6709.

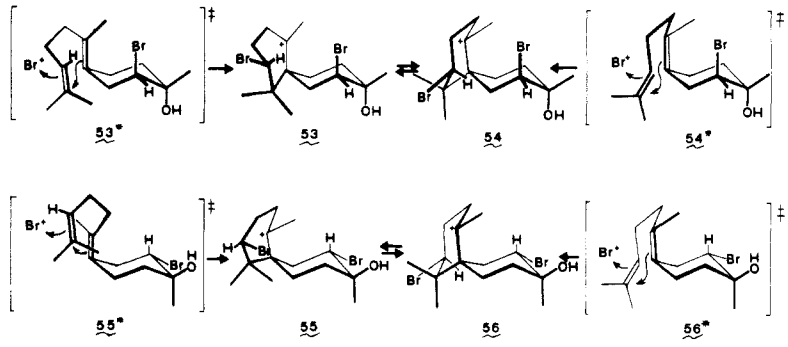
(33) (a) Nishizawa, M.; Takenaka, H.; Hirotsu, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1984**, *106*, 4290–4291. (b) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522–523. (c) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806–813.

(34) For more recent reviews, see: (a) Sutherland, J. K. In *Stereoselective Synthesis of Natural Products*; Proceeding of the Seventh Workshop Conference, Hoechst, Schloss Reisenburg, September, 1978; Bartmann, W., Winterfeldt, E., Eds.; Excerpta Media: Amsterdam-Oxford, 1979; pp 142–150. (b) Matsuki, M.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1979**, 2901–2904. (c) Yamada, Y.; Nakamura, S.; Iguchi, K.; Hosaka, K. *Tetrahedron Lett.* **1981**, 1355–1356. (d) Kametani, T. *Tetrahedron Lett.* **1981**, 3633–3656. (e) van Tamelen, E. E. *J. Am. Chem. Soc.* **1982**, *104*, 6480–6481. (f) Saito, A.; Matsushita, H.; Kaneko, H. *Chem. Lett.* **1983**, 729–723. (g) Nishizawa, M.; Takanaka, H.; Nishide, H.; Hayashi, Y. *Tetrahedron Lett.* **1983**, 2581–2584. (h) Dewar, M. J. S.; Reynolds, C. H. *J. Am. Chem. Soc.* **1984**, *106*, 1744–1750. (i) Erion, M. D.; McMurry, J. E. *Tetrahedron Lett.* **1985**, 559–562.

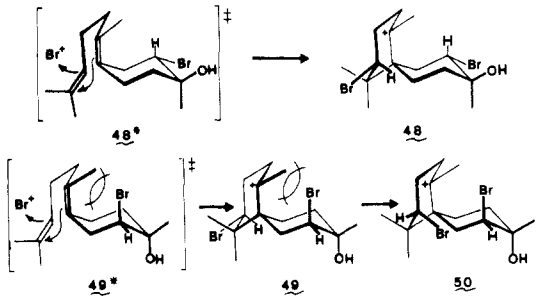
(35) (a) Kato, T.; Ichinose, I.; Kamashida, A.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 518–519. (b) Kitahara, Y.; Kato, T.; Ichinose, I. *Chem. Lett.* **1976**, 283–286.

(36) The product ratios were obtained from the observed GC integrations and thus assume equal response factors for the diastereomers. Isolated ratios were somewhat lower, but, due to the small scale of the reactions, only a few milligrams of the minor products were formed making accurate isolated ratios difficult to determine.

Chart I



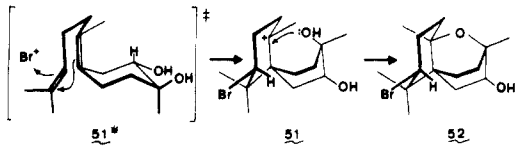
The substantial preference observed[32] for six-membered ring formation suggested a highly ordered transition-state in which the two methylenes of the chain have adopted a staggered conformation, leading to a chairlike six-membered ring. In the present study, the relevant options are given by **48*** and **49***. Of the pair



transition-state represented, **48*** would be expected to be of lower energy due to the existence of the energy-raising nonbonded interactions which are present in **49*** but not in **48***. Inasmuch as these expectations represent accurate descriptions of fact, one can reasonably anticipate the achievement of asymmetric induction to an extent that is related to the energy difference between **48*** and **49***.

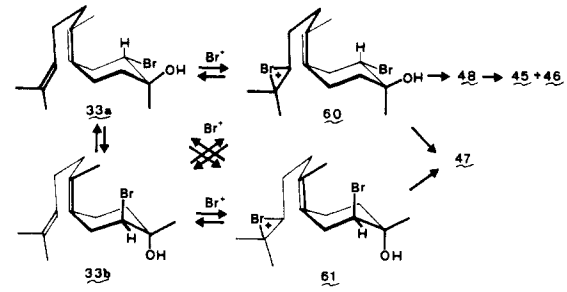
It is to be specifically noted that adoption of one or other transition state leads ultimately to diastereochemically distinctive products. The latter pathway is further distinguished by requirement for kinetic formation of the more sterically congested **49**, subsequent chair–chair interconversion in the newly created ring which delivers **50**, as occurs in the natural isoobtusol (**3**). Although the latter possibility was viewed less likely, we sought to clarify this question as well.

Brominative carbocyclization of the racemic diol **31** (R = H) with TBCD under the above described conditions was followed by chromatography on silica gel to give the tricyclic ether **52** in



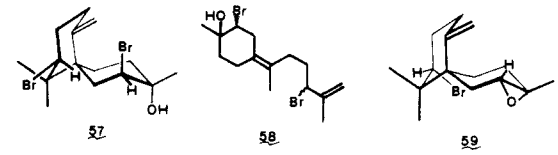
15% yield as the only bicarbocyclic product. The cyclization to **52** must occur by internal trapping in the carbocationic intermediate **51** by the tertiary hydroxyl group, which exclude any alternative transition-state different to **51*** in which the C_5–C_6 bond and the *t*-OH were not syn oriented. Studies on the mechanism of cationic induced carbocyclization have shown a chairlike transition state to be favored over a boatlike transition state.[31-34,37] However, some 1,5-diene carbocyclizations forced

Scheme VI



to proceed via boatlike transition states do so readily.[33a,38] Being rigorous, this less likely possibility cannot strictly be ruled out, and the boatlike transition states also need to be studied. In the present work, these two options are given by the transition states **53*** and **55***, to afford, respectively, **53** and **55** which after boat–chair conformational interconversions would reach the ground-state *all*-chair **54** and **56**, identical with those obtained directly from 8-bromo-9-hydroxy-(*Z*)-γ-bisabolene (**42**) through the chairlike transition-state options given by **54*** and **56***.

Bromocarbocyclization of racemic diene **42** with TBCD under the previously described conditions proceeded with full regio- and stereoselectivity to give the bicarbocyclic dibromide **57** (23% yield)



after chromatographic purification. The allylic dibromide **58** was the major reaction product (38% yield). Compound **57** showed the bromomethine proton at δ 4.51 (dd, *J* = 12.5, 4.5 Hz), C_2H_a, and δ 4.13 (dd, *J* = 4.5, 4.0 Hz), C_8H_e, in its proton NMR spectrum. The trans diaxial relationship of the *vic*-bromohydroxyl in **57** was chemically proved by its easy conversion to the epoxide **59**, a reaction that occurs, as expected, with concomitant chair–chair interconversion as is shown in the proton NMR spectrum of **59** where the bromomethine proton appears at δ 4.30 as a triplet (*J* = 5 Hz), C_2H_e.

The electrophilic bromination of 1,5-dienes formally involves a two-step process which is initiated by the interaction of Br^+ with a double bond followed by an irreversible (a) loss of a proton to give a brominated diene or (b) intramolecular attack by a second olefinic bond to give the desired bromocarbocyclized alkene after proton elimination. In practice, attempts to bring about carbocyclizations have led to disappointing results,[31] with optimized yields no better than ca. 20%. The bromonium ion intermediate, represented by a three-membered cyclic structure[39] in which all bonds are of the two-electron two-center type,[40] are generated

(37) Ireland, R. E.; Dawson, M. I.; Bordner, J.; Dickerson, R. E. *J. Am. Chem. Soc.* **1970**, *92*, 2568–2570. Ireland, R. E.; Dawson, M. I.; Kowalski, C. J.; Lipinski, C. A.; Marshall, D. R.; Tilley, J. W.; Bordner, J.; Trus, B. L. *J. Org. Chem.* **1975**, *40*, 973–1000. Ireland, R. E.; Bey, P.; Cheng, K.-F.; Czarny, R. J.; Moser, J.-F.; Trust, R. I. *J. Org. Chem.* **1975**, *40*, 1000–1007. Ireland, R. E.; McKenzie, T. C.; Trust, R. I. *J. Org. Chem.* **1975**, *40*, 1007–1017.

(38) van Tamelen, E. E.; Anderson, R. *J. Am. Chem. Soc.* **1972**, *94*, 8225–8228.

(39) Slevocka-Tilt, H.; Ball, R. G.; Brown, R. S. *J. Am. Chem. Soc.* **1985**, *10m*, 4504–4508.

(40) Servis, K. L.; Domenick, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 7186–7187.

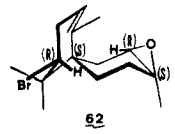
reversibly[41] during the course of the Br^+ addition to the double bond.

In the present study, these options are given by the intermediates **60** and **61**, which are equilibrated through their diene precursors, **33a** and **33b**, and by direct crossing capture[41] of Br^+ (Scheme VI). In accordance with Scheme VI, propensity to reverse the equilibrium and form irreversibly the carbocationic intermediate **48** could account by slow addition of the bromination agent in polar aprotic solvents, thus allowing the equilibration to take place, before proton elimination occurs to give the undesired brominated diene **47**. This was in fact observed, and the combined yield of the racemic **45**, **46** mixture was succesfully improved up to 28% by slow addition (over 1.5 h) of 0.8–1.0 equiv of TBCD in dry and freshly distilled nitromethane over 1.0 equiv of **33** in the same solvent, quenching the reaction after further stirring at 0 °C for 1.5 h (12% of **33** was recovered). Although the formation of two cyclized products arising from a common intermediate was an inconvenience from the standpoint of synthetic practicality, the fact that both compounds share the backbone and stereochemical arrangements identical with those observed in natural chamigranes made the synthesis useful.

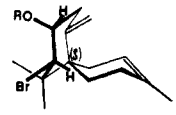
Both the proton NMR spectrum and the capillary column gas chromatogram reveal, after chromatographic separation of monocarbocyclic dienes **33** and **47**, that the reaction was highly stereoselective; the two racemic diastereomers **45** and **46** were formed, respectively, in a 12:1 ratio. Thus, in this first critical experimental test, we attained a synthetically useful amount of diastereoselectivity.

Reaction of (8*S*,9*S*)-8-bromo-9-hydroxy-*E*-γ-bisabolene (**33**) with TBCD under the now standard conditions described above[42] was followed by chromatography on silica gel. A 26% yield was obtained of the 3:1 mixture of **(−)-45** and **(−)-46** and was separated by liquid chromatography. The absolute stereodisposition of the four stereogenic carbon atoms in **(−)-46** was determined as 2*R*,6*S*,8*S*,9*S* by correlation with naturally occurring (2*R*,6*S*,8*S*,9*S*)-2,8-dibromo-9-hydroxy-α-chamigrene (**9**) isolated from *Laurencia nipponica*,[13] whose structure including the absolute configuration has been clairified by relating it[43] to the *L. glandulifera* epoxychamigrene **62**, the absolute configuration of which[44] was determined by X-ray diffraction analysis. That is, *not only does the bicyclic product possess the same relative stereochemistry as the naturally occurring halogenated chamigrenes but the same absolute stereochemistry as well.*

The four stereogenic atoms in **(−)-45** were determined as 2*R*,6*S*,8*S*,9*S*, and their structure identified as (2*R*,6*S*,8*S*,9*S*)-2,8-dibromo-9-hydroxy-β-chamigrene (**10**) by the following sequence of reactions: treatment of **(−)-45** with Zn dust in acetic acid afforded in 80% yield the monobrominated diene (2*R*,6*S*)-2-bromo-β-chamigrene (**5**)[45] and (−)-β-chamigrene (**6**).[11] To assure ourselves of the absolute configuration of **5** and **6**, we carried out their synthesis starting from the natural *L. obtusa* metabolite obtusol (**2**),[1] reduction of which with Zn–AcOH in either yielded the partially dehalogenated **63** (R = H) which was further transformed into **5** through the mesyl derivative **63** (R = Ms) by treatment[46] with lithium triethylborohydride in refluxing tetrahydrofuran.



62



63

Brominated chamigranes possessing 2*S*,6*R* stereogenic carbons are prepared starting from (8*R*,9*R*)-8-bromo-9-hydroxy-(*E*)-γ-bisabolene, **(+)-33**. These two differentiated functional groups provide potential access to numerous optically active synthons from this readily available precursor; thus, **(+)-45** and **(+)-46** were obtained from **(+)-33** and identified respectively with (2*S*,6*R*,8*R*,9*R*)-2,8-dibromo-9-hydroxy-α-chamigrene (**11**) and (2*S*,6*R*,8*R*,9*R*)-2,8-dibromo-9-hydroxy-β-chamigrene (**12**). The compound **(+)-45** was readily converted by Zn–AcOH treatment into a mixture of the natural[10] (2*S*,6*R*)-2-bromo-β-chamigrene (**7**) and (+)-β-chamigrene (**8**), which was separated by chromatography on silica gel. This method has allowed us to prepare also several enantiomerically homogeneous 2-bromochamigrenes starting from (+)- and (−)-(*Z*)-γ-bisabolene (**42**).

The interesting biological activity of these substances as well as that of the *vic*-dihydroxylated chamigrenes derived from (+) and (−) **31** (R = H) and **40** (R = H) will be reported elsewhere.

Conclusions

In summary, the total synthesis of natural chamigrenes of both (2*R*,6*S*,8*S*,9*S*) and (2*S*,6*R*,8*R*,9*R*) and chamigradienes of both (2*R*,6*S*) and 2*S*,6*R*) configurations, uncontainated by diastereoisomers, have been prepared for the first time. Since our methodology is generally applicable and enantioconservative, we feel confident that the principles governing the stereochemistry of the process presented in this work will find applications in other systems. Future studies involving applications of other sorts of systems containing multiple stereogenic atoms to various problems in organic synthesis are planned. It is also hoped that suitable modifications in the designs described above should provide access to a wide variety of optically pure chamigrane derivatives, which is important for exploring their pharmacological potential.

Experimental Section

Preparations of Racemic (1*S,1*R**)- and (1*R**,1*R**)-1-(1,5-Dimethyl-1-hydroxy-4-hexene)-4-methyl-3-cyclohexenecarboxylic Acid (25 and 34).** A solution of lithium diisopropylamide was prepared by dissolving diisopropylamine (4.14 g, 40 mmol) in 60 mL of anhydrous tetrahydrofuran, cooling to −40 °C in dry ice–acetone bath, and adding *n*-butyllithium in hexane (40 mmol, 36.4 mL, 1.1 M) under an atmosphere of argon. A solution of 4-methyl-3-cyclohexenecarboxylic acid (2.84 g, 20 mmol) in cold (−40 °C) tetrahydrofuran (20 mL) was injected via cannula and reacted for 30 min at −40 °C. The reaction mixture was heated to 50 °C for an additional 2 h. The resulting bright yellow solution was cooled to −40 °C, and 6-methyl-5-hepten-2-one (2.52 g, 20 mmol) was added dropwise (via a syringe pump) and over 65 min. After complexion of the addition, the reaction mixture was stirred for 1.5 h at −40 °C. The quenched reaction mixture was worked up as usual and purified on silica gel (MPLC, elution with 30% ethyl acetate in petroleum ether). The eluted solid was found to be a 1:1 mixture of **(±)-25** and **(±)-34** (3.69 g, 85%) which was separated by repeated fractional recrystallization from chloroform: **(±)-25**, mp 122–124 °C; **(±)-34**, 150–151 °C (lit.[25] mp 149–150 °C).

Spectral data for **(±)-25**: IR (KBr) 3500, 1700, 1440, 1380, 940 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.20 (s, 3 H), 1.62 (s, 6 H), 1.68 (s, 3 H), 5.11 (dd, *J* = 7, 6 Hz, 1 H), 5.38 (br s, 1 H, D_2O-exchangeable); ^{13}C NMR ($CDCl_3$) δ 15.4 (q), 17.8 (q), 22.4 (t), 23.3 (q), 25.4 (t), 25.8 (q), 28.4 (t), 37.1 (t), 54.0 (s), 64.2 (t), 75.8 (s), 104.4 (d), 124.5 (d), 136.6 (s), 179.8 (s). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.11; H, 9.84.

Spectral data for **(±)-34**: IR (KBr) 3500, 1690, 1440, 1240 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.22 (s, 3 H), 1.68 (s, 9 H), 5.18 (t, *J* = 7 Hz, 1 H), 5.30 (br s, 1 H), 6.69 (br s, 1 H, D_2O-exchangeable); ^{13}C NMR ($CDCl_3$) δ 15.4 (q), 18.1 (q), 21.9 (q), 22.4 (t), 25.4 (q), 25.8 (t), 28.8 (t), 37.1 (t), 54.0 (s), 64.2 (t), 75.8 (s), 104.4 (d), 119.4 (d), 133.6 (s), 179.8 (s). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.16; H, 9.63.

Preparations of Racemic Iodolactones 26 and 35. Lactones **(±)-26** and **(±)-35** were obtained in 98% yields by treatment of the diisopropylamine salt of the hydroxy acids **(±)-25** and **(±)-34** with iodine in dichloromethane. **(±)-26**: diisopropylamine (4.6 mL, 30.0 mmol) was added

(41) Brown, R. S.; Gedye, R.; Slevocka-Tilt, H.; Buschek, J. M.; Kopecky, K. R. *J. Am. Chem. Soc.* **1984**, *106*, 4515–4521, and references quoted therein. See also ref 6.

(42) Although several instances of bromo-induced carbocyclization have been demonstrated, the combined yields of the cyclization products were all in the range of only 22–28%. It was of interest to learn something more about the origin of the yield problem. Unfortunately, aside from the deprotonation products previous to carbocyclization already discussed, the remaining materials seemed to be polymeric, and their spectral properties were uninformative.

(43) Suzuki, M.; Kurosawa, E.; Irie, T. *Tetrahedron Lett.* **1974**, 821–824.

(44) Suzuki, M.; Furusaki, A.; Kurosawa, E. *Tetrahedron* **1979**, *35*, 823–831.

(45) For the natural opposite enantiomer, see: ref 10.

(46) Krishnamurphy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064–3066.

dropwise to a solution of **(±)-25** (8.14 g, 30.0 mmol) in 125 mL of acetone. The formed diisopropylamine salt was concentrated in vacuo and dissolved in anhydrous dichloromethane (150 mL). Iodine (7.80 g, 30 mmol) in dichloromethane (130 mL) was injected under argon and reacted for 48 h at room temperature. The quenched reaction mixture was shaken with 10% aqueous sodium thiosulphate (20 mL), dried, and evaporated in vacuo. The residue was chromatographed on silica gel to afford an unstable bright yellow solid, 11.41 g, 29.1 mmol (97%), identified as the iodolactone **(±)-26**: IR ($CHCl_3$) 3500, 2960, 1760, 1450, 1375, 1100, 850 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.23, 1.67, 1.71, 2.13 (s, 3 H each), 3.30 (s, 1 H, D_2O-exchangeable), 4.63 (d, J = 9 Hz, 1 H), 5.18 (t, J = 7 Hz, 1 H); MS (EI), *m/e* (relative intensity) 390 (2, M^+), 247 (100), 179 (40), 139 (97), 121 (80).

(±)-35 was prepared: I_2 (8.22 g, 32.4 mmol) in methylene chloride (150 mL); add diisopropylamine salt formed from 8.54 g, 32.1 mmol, of **(±)-34**, to give in 98% yield the iodolactone **(±)-35** (12.42 g, 31.7 mmol): IR ($CHCl_3$) 3500, 2960, 1760, 1450, 1375, 1100, 850 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.28, 1.70, 1.75, 2.18 (s, 3 H each), 4.68 (d, J = 9 Hz, 1 H), 5.19 (t, J = 7 Hz, 1 H); MS (EI), *m/e* (relative intensity) 390 (1, M^+), 247 (43), 219 (3), 201 (5), 179 (13), 165 (7), 139 (34), 125 (14), 121 (26), 109 (60), 93 (50).

Preparations of Racemic (1*S,3*S**,4*R**,1′*R**)- and (1*R**,3*R**,4*S**,1′*R**)-3,4-epoxy-1-(1,5-dimethyl-1-hydroxy-4-hexene)-4-methyl-3-cyclohexenecarboxylic Acid (27 and 36).** Epoxy acids **(±)-27** and **(±)-36** were obtained in 98% yields by treatment of iodolactones **(±)-26** and **(±)-35** in tetrahydrofuran with 1.5 equiv of aqueous potassium hydroxyde at 0 °C. **(±)-27**: the racemic iodolactone **26** (12.5 g, 31.8 mmol) was dissolved in 100 mL of tetrahydrofuran under argon. To the cold solution was added 1.96 g, 35.0 mmol, of potassium hydroxide dissolved in 125 mL of water. After completion of the addition, the mixture was stirred at room temperature. When monitoring of the reaction by TLC indicated that all starting material has been consumed (ca. 12 h), the quenched reaction mixture was taken with 5% aqueous HCl solution (50 mL), and the separated aqueous phase was extracted with ether (2 × 25 mL). The combined organic layers were washed with 5% sodium bicarbonate solution (150 mL) and water (150 mL). The organic phase was dried over $MgSO_4$ and concentrated to give 8.79 g, 31.2 mmol, of the very unstable epoxide **(±)-27.** The white solid so obtained was dried by passing argon through and transferred under anhydrous atmosphere. A solution of this solid in 100 mL of methylene chloride and cooled under argon to −78 °C was used in the next experiment. **(±)-36**: this was prepared from **(±)-35** (11.8 g, 30.1 mmol) and KOH (1.86 g, 33.11 mmol), in 98% (8.32 g, 29.5 mmol) yield. The compound was dissolved in 100 mL of CH_2Cl_2, cooled under argon at −78 °C, and used in the next experiment.

Preparations of Racemic (1*S,3*R**,4*S**,6*S**)- and (1*R**,3*R**,4*R**,6*R**)-3-(4-methyl-3-pentene)-1,3-dimethyl-6-hydroxy-2-oxabicyclo[2.2.2]octane-4-carboxylic Acid (28 (R = H) and 37 (R = H)).** The ethers **(±)-28** (R = H) and **(±)-37** (R = H) were synthesized from **(±)-27** and **(±)-36** by catalytic treatment with *p*-toluenesulfonic acid in methylene chloride. **(±)-28** (R = H): *p*-toluenesulfonic acid (2 mg) was dissolved in 60 mL of dichloromethane and cooled under argon. This solution was stirred at −78 °C for 10 min and cannulated into the solution of the epoxy acid **(±)-27** (8.79 g, 31.2 mmol). The bath was removed, and the reaction was stirred for 30 min. The quenched reaction was washed with water (3 × 20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (15% ethyl acetatre in *n*-hexane) to give the ether **(±)-28** (R = H) (8.75 g, 31.0 mmol), 98% overall yield based on iodolactone **(±)-26**: IR (KBr) 3500, 1700, 1370, 1050 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.19, 1.21, 1.62, 1.68 (s, 3 H each), 3.83 (d, J = 7 Hz, 1 H), 5.18 (t, J = 7 Hz, 1 H); MS (EI), *m/e* (relative intensity) 282 (0.8, M^+), 264 (1.5), 246 (2), 199 (41), 181 (27), 153 (28), 139 (41), 135 (17), 121 (55), 109 (100); HRMS $C_{16}H_{26}O_4$ (*m/e* 282.1842, −1.1 mass error); $C_{16}H_{24}O_3$ (*m/e* 264.1696, +3.0 mass error); $C_9H_{13}O_2$ (*m/e* 153.0924, −0.9 mass error); C_9H_{13} (*m/e* 121.1018, −0.1 mass error). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.09; H, 9.22. Found: C, 67.93; H, 9.12. **Acetate 28** (R = OAc): mp 81–83 °C; IR (KBr) 3550, 1700, 1460, 1225, 1060 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20, 1.47, 1.62, 1.69, 2.01 (s, 3 H each), 4.51 (d, J = 7 Hz, 1 H), 5.20 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.6 (q), 22.2 (q), 22.7 (q), 23.0 (t), 24.2 (q), 25.7 (q), 27.9 (t), 31.0 (t), 33.7 (t), 34.8 (t), 54.0 (s), 78.1 (d), 81.9 (s), 84.7 (s), 124.6 (d), 131.7 (s), 170.5 (s), 179.2 (s); MS (EI), *m/e* (relative intensity) 324 (3, M^+), 264 (4), 199 (14), 181 (11), 139 (27), 121 (42), 109 (100), 93 (38); HRMS $C_{18}H_{28}O_5$ (*m/e* 324.1969, −3.4 mass error); $C_{16}H_{22}O_2$ (*m/e* 246.1626, −0.8 mass error); $C_{14}H_{14}O$ (*m/e* 199.1081, −0.4 mass error). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.67; H, 8.64. Found: C, 66.83; H, 8.89.

(±)-37 (R = H): this was prepared in similar manner from **(±)-36** (8.32 g, 29.5 mmol) in 99% (8.29 g, 29.4 mmol) yield (98% based of iodolactone **(±)-35**): IR (KBr) 3480, 1700, 1380, 1050, 975 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.22, 1.40, 1.60, 1.65 (s, 3 H each), 3.75 (br s, 1 H), 5.18 (t, J 6.5 Hz, 1 H), 6.01 (br s, 2 H, D_2O-exchangeable); MS (EI), *m/e* (relative intensity) 282 (0.5), 246 (5), 199 (45), 181 (30), 153 (37), 139 (44), 135 (36), 121 (70), 109 (100). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.09; H, 9.22. Found: C, 68.27; H, 9.12. **Acetate 37** (R = Ac) mp 96–98 °C; IR (KBr) 3550, 1700, 1465, 1220, 1035, 980 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.40, 1.46, 1.60, 1.67, 2.00 (s, 3 H each), 4.50 (d, J = 7 Hz, 1 H), 5.10 (t, J = 6.5 Hz, 1 H), 8.80 (br s, 1 H, D_2O-exchangeable); ^{13}C NMR ($CDCl_3$) δ 17.7 (q), 18.7 (q), 22.2 (t), 22.3 (q), 22.7 (q), 25.8 (q), 28.5 (t), 33.4 (t), 39.6 (t), 54.1 (s), 78.2 (d), 82.3 (s), 84.6 (s), 124.5 (d), 131.7 (s), 170.6 (s), 179.2 (s); MS (EI), *m/e* (relative intensity) 324 (2, M^+), 264 (2), 199 (15), 181 (18), 139 (35), 121 (50), 109 (100), 93 (40). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.67; H, 8.64. Found: C, 66.70; H, 8.61.

(1*R*,3*S*,4*R*,6*R*)-6-Acetoxy-3-(4-methyl-3-pentene)-1,3-dimethyl-2-oxabicyclo[2.2.2]octane-4-carboxylic Acid ((−)-28) (R = Ac). To a hot solution of quinine (4.10 g, 10.0 mmol) in acetone (50 mL) was added a solution of racemic **28** (R = Ac), 3.24 g, 10.0 mmol, in acetone (50 mL). The solution was left to stand overnight in a refrigerator to give less soluble crystals which were collected and recrystallized 4 times from hot acetone. This less soluble salt (2.94 g) was shaken for 15 min with 5 mL of 6 N hydrochloric acid, and the solid was collected and washed with 6 N HCl solutions (2 × 10 mL) and thoroughly extracted with ether. The ether solution was washed with NaCl solution, dried on $MgSO_4$, and concentrated in vacuo to give 1.28 g of crystalline acid, **(−)-28** (R = Ac), mp 81–83 °C, $[\alpha]_D$ −32.3 (*c* 1.3, $CHCl_3$), ee > 97%. The spectroscopic data were identical with that of racemic **28** (R = Ac).

(1*S*,3*R*,4*S*,6*S*)-6-Acetoxy-3-(4-methyl-3-pentene)-1,3-dimethyl-2-oxabicyclo[2.2.2]octane-4-carboxylic Acid ((+)-28) (R = Ac). The slightly dextrorotatory acetoxy ether (1.94 g) was obtained by acidifying the mother liquor recovered after removal of the quinone salt. This solid and L(−)-α-methylbenzylamine (0.7. mL, 6.0 mmol) were dissolved in acetone (100 mL) by stirring and heating at 50 °C for 1 h. The solution was left to stand in a refrigerator for 2–3 days. The separated crystals were recrystallized 4 times from *n*-hexane. Thus obtained salt was dissolved in 2 N HCl (to pH 2–3). The mixture was extracted with ether (3 × 10 mL), and the organic layer was washed with water and saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to give 864 mg of the crystalline acid **(+)-28** (R = Ac), mp 81–83 °C, $[\alpha]_D$ +32 (*c* 2.1, $CHCl_3$), ee > 97%. The spectroscopic data were identical with that of racemic compound.

(1*R*,3*R*,4*R*,6*R*)-6-Acetoxy-3-(4-methyl-3-pentene)-1,3-dimethyl-2-oxabicyclo[2.2.2]octane-4-carboxylic Acid ((−)-37) (R = Ac). Quinine (4.10 g, 10.0 mmol) and **(±)-37** (R = Ac) (3.24 g, 10.0 mmol) were dissolved in hot 95% ethanol (75 mL). After cooling, the separated crystals were collected and recrystallized 5 times from acetone. The less soluble salt thus obtained was dissolved in 6 N HCl (50 mL), and the solution was thoroughly extracted with ether. The ether solution was washed with NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to give 1.15 g of crystalline acid **(−)-37** (R = Ac), mp 97–98 °C, $[\alpha]_D$ −47.3 (*c* 1.12, $CHCl_3$), ee > 97%. The spectroscopic data were identical with that of racemic compound.

(1*S*,3*S*,4*S*,6*S*)-6-Acetoxy-3-(4-methyl-3-pentene)-1,3-dimethyl-2-oxabicyclo[2.2.2]octane-4-carboxylic Acid ((+)-37) (R = Ac). L(−)-α-Methylbenzylamine (0.60 mL, 4.6 mmol) and **(±)-37** (R = Ac) (1.50 g, 4.6 mmol) were dissolved in hot acetone (30 mL). After cooling, the separated crystals were collected and recrystallized 3 times from *n*-hexane. This salt was dissolved in 2 N HCl, and the solution was dried ($MgSO_4$) and concentrated in vacuo to give the crystalline acid **(+)-37** (R = Ac), 815 mg, mp 97–98 °C, $[\alpha]_D$ +47.4 (*c* 0.87, $CHCl_3$), ee > 97%. The spectroscopic data were identical with that of racemic compound.

Enantiomeric Excess Determinations. The ee's of the acids **(+)-** and **(−)-28** (R = Ac) and **(+)-** and **(−)-37** (R = Ac) were determined by examining the ^1H NMR spectra in the presence of 0.2–0.3 equiv of $Eu(tfc)_3$,[30] $\Delta\Delta\delta$ separations of 0.25–0.28 ppm were observed for the methyl acetate signal of the reference racemic acids **28** (R = Ac) and **37** (R = Ac). No such peak separations were observable under the same conditions in the spectra of the resolved acids, where only one enantiomer was always detectable within the error limits of the method of ±3%.

Preparation of Racemic (1*S,3*R**,4*S**,6*S**)- and (1*R**,3*R**,4*R**,6*R**)-6-Acetoxy-4-chloro-3-(3,4-dibromo-4-methylpentane)-1,3-dimethyl-2-oxabicyclo[2.2.2]octane (29 (R = Ac) and 38 (R = Ac)).** The chloro ethers **(±)-29** (R = Ac) and **(±)-38** (R = Ac) were obtained by bromination (Br_2, CCl_4) of the crystalline acetates **(±)-28** (R = Ac) and **(±)-37** (R = Ac) followed by decarboxylation with lead tetraacetate and *N*-chlorosuccinimide in DMF–HOAc (5:1) in 86–88% yield. **(±)-29** (R = Ac): bromination of **28** (R = Ac) (2.0 g, 6.2 mmol) in carbon tetrachloride (50 mL) with a solution of bromine (1.0 g, 6.2 mmol) in 25 mL of CCl_4 was performed at −10 °C over 30 min. The reaction mixture was quenched with 50 mL of water and extracted with

ether (2 × 50 mL). The combined organic layers were washed with water and 2 × 25 mL of saturated sodium bicarbonate, dried, and evaporated to yield 2.94 g, 6.07 mmol (98%), of the dibromo derivative of **28** (R = Ac), which was used in the following experiment without any further purification. *N*-Chlorosuccinimide (813 mg, 6.07 mmol) and the dibrominated above prepared compound (2.94 g, 6.07 mmol) were dissolved in a 5:1 mixture of dimethylformamide and glacial acetic acid (10 mL). The solution was freed of oxygen by repeated evacuation and addition of argon. Lead tetraacetate (2.70 g, 6.07 mmol), stabilized with ca. 15% acetic acid, was added, and the reaction mixture was again degassed. Warming at 40–50 °C initiated the exothermic evolution of carbon dioxide which was completed after 5–15 min. The solution was quenched with ice–water and extracted with *n*-hexane (3 × 25 mL). The *n*-hexane fractions were washed with 2% perchloric acid (2 × 25 mL) and 10% aqueous potassium carbonate (3 × 25 mL), dried over $MgSO_4$, and evaporated to yield 2.54 g, 5.34 mmol (88%), of the compound **(±)-29** (R = Ac): IR ($CHCl_3$) 1720, 1455, 1380, 1120, 1100, 990 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.40, 1.51, 1.85, 1.99, 2.01 (s, 3 H each), 4.18 (br d, J = 10 Hz, 1 H), 4.50 (d, J = 8 Hz, 1 H), 7.30 (br s, 1 H, D_2O-exchangeable); MS (EI), m/e (relative intensity) 441/439/437 (5/10/5, M^+ –Cl), 381/379/377 (2/3, 5/2), 231 (5), 217 (6), 190 (20), 153 (20).

(±)-38 (R = Ac) this was obtained from **(±)-37** (R = Ac) (3.24 g, 10.0 mmol) in 88% (4.18 g, 8.8 mmol) yield: IR ($CHCl_3$) 1720, 1450, 1370, 1100, 980 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.42, 1.46, 1.81 (s, 3 H each), 1.98 (s, 6 H), 4.14 (br d, J = 10 Hz, 1 H), 4.52 (d, J = 8 Hz, 1 H), 7.22 (br s, 1 H, D_2O-exchangeable); MS (EI), m/e (relative intensity) 441/439/437 (10/20/10, M^+ – Cl), 381/379/377 (6/12/6), 231 (20), 217 (12), 190 (16), 153 (42).

Preparations of Racemic (1*S,3*R**,4*S**,6*S**)- and (1*R**,3*R**,4*R**,6*R**)-6-Acetoxy-4-chloro-1,3-dimethyl-3-(4-methyl-3-pentene)-2-oxabicyclo[2.2.2]octane (30 (R = Ac) and 39 (R = Ac)).** The chloro ethers **(±)-30** (R = Ac) and **(±)-39** (R = Ac) were prepared from **(±)-29** (R = Ac) and **(±)-38** (R = Ac) by reductive elimination of bromine by zinc dust (ether/acetic acid) in 94–96% yields. **(±)-30** (R = Ac): to a solution of racemic **29** (R = Ac) (4.74 g, 10.0 mmol) in ether–acetic acid (5:1) (15 mL) was added Zn dust (1.30 g, 20.0 mmol), and the mixture was stirred for 12 h at room temperature. After filtering off Zn dust, the mixture was extracted with ether (2 × 50 mL). The ethereal solutions were washed with water (3 × 10 mL), 5% sodium bicarbonate (2 × 20 mL), and finally with water, dried over $MgSO_4$, and evaporated in vacuo. The residual solid was chromatographed on silica gel to give **30** (R = H), mp 60–62 °C (2.95 g, 9.4 mmol) 94% yield: IR (KBr) 3600, 1450, 1370, 1055, 1015, 915, 885 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20, 1.31, 1.62, 1.69 (s, 3 H each), 3.76 (t, J = 3.5 Hz, 1 H), 5.18 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.7 (q), 23.2 (q), 25.1 (q), 25.8 (q), 28.0 (q), 34.6 (t), 35.1 (t), 35.2 (t), 39.7 (t), 71.1 (s), 71.3 (s), 81.0 (d), 85.3 (s), 124.6 (d), 131.9 (s); MS (EI), m/e (relative intensity) 274/272 (0.5/1, M^+), 153 (20), 151 (27), 109 (100); HRMS $C_{15}H_{25}ClO_2$ (m/e 272.1558, –1.5 mass error); $C_{15}H_{24}O_2$ (m/e 236.1792, –1.6 mass error). Anal. Calcd for $C_{15}H_{25}ClO_2$: C, 66.06; H, 9.17; Cl, 13.03. Found: C, 65.82; H, 9.00; Cl, 12.81. **Acetate 30** (R = Ac): IR (neat) 1715, 1640, 1435, 1340, 1090, 890 cm^{-1}; ^1H NMR (60 MHz), $CDCl_3$) δ 1.25, 1.30, 1.60, 1.70, 2.00 (s, 3 H each), 4.48 (t, J = 4 Hz, 1 H), 5.20 (t, J = 7 Hz, 1 H); MS (EI), m/e (relative intensity) 316/314 (0.6/1.2, M^+), 232/230 (2/4), 172 (6), 153 (16), 137 (7), 109 (45), 93 (21), 82 (22); HRMS $C_{17}H_{27}ClO_3$ (m/e 314.1645, +0.3 mass error); $C_{15}H_{22}O$ (m/e 218.1686, –1.5 mass error). Anal. Calcd for $C_{17}H_{27}ClO_3$: C, 64.86; H, 8.59; Cl, 11.29. Found: C, 64.77; H, 8.60; Cl, 11.67.

(±)-39 (R = H): this was prepared from **(±)-38** (R = Ac) (4.74 g, 10.0 mmol) in 96% (3.02 g, 9.6 mmol) yield, mp 73–74 °C; IR (KBr) 3500, 1640, 1380, 1045, 1010, 990 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.25, 1.46, 1.60, 1.68 (s, 3 H each), 3.80 (s, J = 7 Hz, 1 H), 5.20 (t, J = 7 Hz, 1 H); MS (EI), m/e (relative intensity) 274/272 (1.5/3, M^+), 153 (34), 151 (12), 109 (100). Anal. Calcd for $C_{15}H_{25}ClO_2$: C, 66.06; H, 9.17; Cl, 13.03. Found: C, 66.34; H, 9.10; Cl, 13.62.

Acetate 39 (R = Ac): IR (neat) 1720, 1635, 1440, 1360, 1310, 990 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.30, 1.47, 1.62, 1.70, 2.00 (s, 3 H each), 4.50 (d, J = 7 Hz, 1 H), 5.20 (t, J = 7 Hz, 1 H); MS (EI), m/e (relative intensity) 316/314 (2/4, M^+), 232/230 (5/10), 172 (12), 153 (20), 137 (6), 109 (67), 93 (25), 82 (14). Anal. Calcd for $C_{17}H_{27}ClO_3$: C, 64.86; H, 8.59; Cl, 11.29. Found: C, 64.52; H, 8.61; Cl, 11.70.

(1*S*,3*R*,4*S*,6*S*)-6-Acetoxy-4-chloro-1,3-dimethyl-3-(4-methyl-3-pentene)-2-oxabicyclo[2.2.2]octane ((+)-30) (R = Ac). This was obtained from **(+)-28** (R = Ac) (2.72 g, 8.4 mmol) in 81% (2.14 g, 6.8 mmol) yield as a noncrystalline solid, $[\alpha]_D$ + 25.2 (c 1.21, $CHCl_3$). The ee > 97% determined by ^1H NMR spectrum in the presence of $Eu(tfc)_3$[30] (0.2 equiv, $\Delta\Delta\delta$ 0.25 ppm for the methyl acetate racemate signals).

(1*R*,3*S*,4*R*,6*R*)-6-Acetoxy-4-chloro-1,3-dimethyl-3-(4-methyl-3-pentene)-2-oxabicyclo[2.2.2]octane ((–)-30) (R = Ac). This was prepared from **(–)-28** (R = Ac) (2.60 g, 8.02 mmol) in 80.4% (2.03 g, 6.45 mmol) yield as a noncrystalline solid, $[\alpha]_D$ –24.5 (c 1.30, $CHCl_3$), ee > 97%.

(1*S*,3*R*,4*S*,6*S*)-4-Chloro-1,3-dimethyl-3-(4-methyl-3-pentene)-2-oxabicyclo[2.2.2]octan-6-ol ((+)-30) (R = H). This was obtained in quantitative yield from the corresponding acetate, mp 61–62 °C, $[\alpha]_D$ +32.1 (c 0.42, $CHCl_3$).

(1*R*,3*S*,4*R*,6*R*)-4-Chloro-1,3-dimethyl-3-(4-methyl-3-pentene)-2-oxabicyclo[2.2.2]octan-6-ol ((–)-30) (R = H). This was obtained in quantitative yield from the corresponding acetate, mp 61–62 °C, $[\alpha]_D$ –31.9 (c 0.94, $CHCl_3$), ee > 97%. The optically active products showed the same IR and NMR spectra as those of the racemate in every case hereafter described.

Preparation of Racemic (1*S,2*S**)-1-Methyl-4-((*E*)-1,5-dimethylhex-4-enylidene)cyclohexane-1,2-diol (31) (R = H).** To a suspension of granulated sodium (1.46 g, 63.6 mmol) in ether (25 mL) was added a solution of racemic **30** (R = Ac) (2.0 g, 6.36 mmol) in ether (30 mL), and the mixture was refluxed under argon for 12 h. The cooled solution was diluted with methanol (10 mL) followed by water (50 mL), and the basic solution was washed with ether (3 × 25 mL). The organic phase was dried over magnesium sulfate and concentrated to give the dihydroxylated diene **31** (R = H) (1.45 g, 6.11 mmol), 96% yield: mp 41–42 °C; IR (KBr) 3600, 1450, 1375, 1220, 1110, 1050, 890, 880 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.22, 1.60 (s, 3 H each), 1.69 (s, 6 H), 3.46 (dd, J = 10, 5 Hz, 1 H), 5.10 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.7 (q), 18.5 (q), 22.1 (q), 25.9 (q), 26.2 (t), 27.2 (t), 34.4 (t), 34.5 (t), 37.8 (t), 73.3 (s), 76.7 (d), 124.4 (d), 127.6 (s), 129.6 (s), 132.0 (s); MS (EI), m/e (relative intensity) 238 (6, M^+), 151 (70), 133 (16), 123 (15), 109 (36), 107 (58), 95 (16), 93 (35), 81 (20); HRMS $C_{15}H_{26}O_2$ (m/e 238.1918, +1.5 mass error); $C_{15}H_{24}O$ (m/e 220.1838, –1.1 mass error); $C_{10}H_{14}O$ (m/e 151.1088, –1.0 mass error); $C_{10}H_{12}$ (m/e 133.0980, –0.8 mass error). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.63; H, 10.92. Found: C, 75.80; H, 11.01.

(1*S*,2*S*)-1-Methyl-4-((*E*)-1,5-dimethylhex-4-enylidene)cyclohexane-1,2-diol ((–)-31) (*R* = H). This was obtained from **(+)-30** (R = Ac) (2.12 g, 6.67 mmol) in 96% (1.52 g, 6.40 mmol) yield as a crystalline solid, mp 41–42 °C, $[\alpha]_D$ –11.2 (c 1.49, $CHCl_3$). This optically active substance showed identical IR and NMR spectra as those of the racemate. **Acetate (+)-31** (R = Ac): isolated as a noncrystalline substance, $[\alpha]_D$ +10.1 (c 1.05, $CHCl_3$); IR (CCl_4) 3550, 2990, 1715, 1460, 1380, 1250, 1120, 1060, 910, 890 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26, 1.60, 1.65, 1.68, 2.08 (s, 3 H each), 2.38 (ddd, J = 10, 5, 4 Hz, 1 H), 2.66 (dd, J = 14, 4 Hz, 1 H), 4.64 (dd, J = 9, 4 Hz, 1 H), 5.11 (br s, 1 H); the multiplet at δ 4.64 simplifies upon irradiation at 2.66 ppm and at 2.24 ppm; the multiplet at δ 2.38 simplifies upon irradiation at 2.00 ppm and 1.64 ppm. Nuclear Overhauser enhancement difference spectroscopy (NOEDS) gave the following results: presaturation of signal centered at 2.66 ppm resulted in 20% NOE at δ 1.60; presaturation of 1.60 ppm resulted in 22% NOE on δ 2.66, 18% NOE on 5.11, and no NOE on 2.38. MS (EI), m/e (relative intensity) 280 (12, M^+), 262 (18), 238 (20), 220 (10), 151 (65), 133 (12), 123 (18), 109 (40), 107 (66), 93 (40). The ee > 97% as determined by examining the ^1H NMR spectrum in the presence of $Eu(tfc)_3$[30] (0.3 equiv, $\Delta\Delta\delta$ 0.28 ppm for the methyl acetate racemate signals).

(1*R*,2*R*)-1-Methyl-4-((*E*)-1,5-dimethylhex-4-enylidene)cyclohexane-1,2-diol ((+)-31) (R = H). This was obtained from **(–)-30** (R = Ac) (2.02 g, 6.42 mmol) in 96% (1.47 g, 6.16 mmol) yield as a crystalline solid, mp 41–42 °C, $[\alpha]_D$ +10.3 (c 0.81, $CHCl_3$). This optically active substance showed identical IR and NMR spectra as those of the racemate. **Acetate (–)-31** (R = Ac), noncrystalline, $[\alpha]_D$ –15.2 (c 1.13, $CHCl_3$), showing identical IR and NMR spectra as those of the (+)-enantiomer. The ee > 97% as determined by the ^1H NMR spectra adding $Eu(tfc)_3$ (0.28 equiv, $\Delta\Delta\delta$ 0.27 ppm for the methyl acetate racemic signals).

Preparation of Racemic (1*R,2*R**)-1-Methyl-4-((*Z*)-1,5-dimethylhex-4-enylidene)cyclohexane-1,2-diol (40) (R = H).** To a suspension of granulated sodium (2.32 g, 100.0 mmol) in ether (25 mL) was added a solution of racemic **39** (R = Ac) (3.15 g, 10.0 mmol) in ether (30 mL), and the mixture was refluxed under argon for 12 h. The cooled solution was diluted with methanol (10 mL) followed by water (50 mL), and the basic solution was washed with ether (3 × 25 mL). The organic phase was dried over magnesium sulfate and concentrated to give the dihydroxylated diene **40** (R = H) (2.30 g, 9.7 mmol), 97% yield, mp 53–54 °C: IR (KBr) 3580, 1460, 1375, 1225, 1120, 1080 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20, 1.57 (s, 3 H each), 1.65 (s, 6 H), 2.50 (m, 2 H), 3.40 (dd, J = 10, 5 Hz, 1 H), 5.11 (t, J = 7 Hz, 1 H); MS (EI), m/e (relative intensity) 236 (6, M^+), 151 (78), 133 (18), 123 (19), 109 (40), 107 (56), 95 (18), 93 (48), 81 (30). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.63; H, 10.92. Found: C, 75.49; H, 10.80. **Acetate 40** (R = Ac): IR (CCl_4) 3550, 3450, 1720, 1460, 1385, 1250, 1130, 1080, 940, 920 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25, 1.59 (s, 3 H each), 1.68 (s, 6 H),

2.08 (s, 3 H), 2.38 (ddd, J = 10, 5, 4 Hz, 1 H), 2.68 (dd, J = 14, 4 Hz, 1 H), 4.64 (dd, J = 9, 4 Hz, 1 H), 5.11 (br s, 1 H); the multiplet at δ 4.64 simplifies upon irradiation at 2.68 and at 2.05 ppm, the multiplet at δ 2.38 simplifies upon irradiation at 1.75 ppm. Nuclear Overhauser enhancement difference spectroscopy (NOEDS) gave the following results: presaturation of signal centered at δ 2.68 resulted in no NOE on olefinic methyl signals; presaturation of signal at δ 1.68 resulted in 27% NOE on 2.38 ppm and 20% NOE on 5.11 ppm: MS (EI), m/e (relative intensity) 280 (10, M^+), 2.62 (22), 238 (20), 220 (8), 151 (70), 133 (12), 123 (24), 109 (60), 107 (72), 93 (38).

Preparation of Racemic (1*S,2*R**)-1,2-Epoxy-1-methyl-4-((*E*)-1,5-dimethylhex-4-enylidene)cyclohexane (32).** A cold solution of racemic **31** (R = H) (2.0 g, 8.4 mmol) and methanesulfonyl chloride (0.75 mL, 8.4 mmol) in dry pyridine (15 mL) was stirred overnight under argon. The reaction mixture was quenched with 50 mL of water and extracted with ether (3 × 15 mL). The combined organic layers were washed with 2 × 25 mL of 5% hydrochloric acid and with 25 mL of saturated sodium bicarbonate solution prior to drying. Chromatography of the residue on silica gel (MPLC, elution with 3% ethyl acetate in *n*-hexane) afforded 2.46 g, 8.1 mmol (96.5%), of **31** (R = Ms) which was dissolved in methanol (30 mL). The solution was cooled to 0 °C and treated with 8 mL of 0.5 N potassium hydroxide solution in methanol. The mixture was stirred for 30 min at 0 °C and quenched with 5% hydrochloric acid (50 mL). The aqueous layer was extracted with ether (3 × 50 mL), and the combined ethereal layers were washed with 75 mL of saturated sodium bicarbonate solution, dried ($MgSO_4$), and evaporated to yield, 1.73 g, 7.9 mmol (97%), of racemic **32**, which was isolated, after chromatographic purification as an oil: IR (neat) 3020, 1670, 1380, 1265, 1204, 1100, 975, 840, 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28, 1.55, 1.57, 1.64 (s, 3 H each), 2.60 (br s, 2 H), 2.98 (br s, 1 H), 5.05 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.7 (q), 18.5 (q), 22.8 (q), 23.0 (t), 25.8 (q), 27.2 (t), 28.6 (t), 30.7 (t), 34.2 (t), 57.9 (s), 59.8 (d), 124.5 (d), 125.3 (s), 128.0 (s), 131.6 (s); MS (EI), m/e (relative intensity) 220 (3, M^+), 164 (2), 151 (34), 133 (16), 123 (11), 109 (23), 107 (47), 93 (42), 91 (29); HRMS $C_{15}H_{24}O$ (m/e 220.1910, −8.4 mass error). Anal. Calcd for $C_{15}H_{24}O$: C, 81.82; H, 10.91. Found: C, 81.77; H, 11.00.

(1*S*,2*R*)-1,2-Epoxy-1-methyl-4-((*E*)-1,5-dimethylhex-4-enylidene)cyclohexane ((+)-32). This was obtained from (−)-**31** (R = H) (2.50 g, 10.5 mmol) in 94% (2.17 g, 9.87 mmol) yield as a noncrystalline solid, $[\alpha]_D$ +72 (c 1.29, $CHCl_3$). This optically active substance showed identical IR, NMR, and MS spectra as those of racemate [lit.[47] $[\alpha]_D$ +37.3 (c 2.20, $CHCl_3$) for the natural enantiomer].

(1*R*,2*S*)-1,2-Epoxy-1-methyl-4-((*E*)-1,5-dimethylhex-4-enylidene)cyclohexane ((−)-32). This was obtained from (+)-**31** (R = H) (2.31 g, 9.71 mmol) in 94% (2.01 g, 9.12 mmol) yield as a noncrystalline solid, $[\alpha]_D$ −68.8 (c 2.18, $CHCl_3$). This optically active compound showed identical IR, NMR; MS spectra as those of racemate.

Preparation of Racemic (1*R,2*S**)-1,2-Epoxy-1-methyl-4-((*Z*)-1,5-dimethylhex-4-enylidene)cyclohexane (41).** To a cold (0 °C) solution of racemic diol **40** (R = H) (2.50 g, 10.5 mmol) in dry pyridine was added, dropwise, mesylchloride (0.95 mL, 12.0 mmol). The reaction mixture was stirred at 0 °C for 12 h. To this was added 50 mL of water, and the solution was extracted with ether (3 × 20 mL). The combined organic layers were washed with 2 × 25 mL of 5% HCl and with 25 mL of saturated sodium bicarbonate prior to drying. Chloromatography o the residue on silica gel (MPLC, elution with 3% ethyl acetate in *n*-hexane) afforded 3.25 g, 10.3 mmol (98%) of **40** (R = Ms) which was dissolved in methanol (30 mL). The solution was cooled to 0 °C and treated with 10 mL of 0.5 N potassium hydroxide solution in methanol. The mixture was stirred for 30 min at 0 °C and quenched with 5% HCl (50 mL). The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic layers were washed with 100 mL of saturated sodium bicarbonate solution and water (2 × 50 mL), dried ($MgSO_4$), and evaporated in vacuo to yield 1.901 g, 8.64 mmol (84%), of racemic **41**, which was purified by chromatography on silica gel (MPLC, elution with 2% ethyl acetate in petroleum ether): IR (neat) 3030, 1645, 1375, 1200, 1100, 1050, 970, 880, 840 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.62 (s, 6 H), 1.70 (s, 3 H), 2.70 (br s, 2 H), 3.04 (t, J = 2.5 Hz, 1 H), 5.20 (t, J = 7 Hz, 1 H); MS (EI), m/e (relative intensity), 220 (7, M^+), 164 (6), 151 (40), 133 (21), 123 (18), 109 (32), 107 (52), 93 (59), 91 (27). Anal. Calcd for $C_{15}H_{24}O$: C, 81.82; H, 10.91. Found: C, 81.80; H, 10.97.

Preparation of Racemic (1*S,2*S**)-2-Bromo-1-methyl-4-((*E*)-1,5-dimethylhex-4-enylidene)cyclohexan-1-ol (33).** To a solution of the racemic epoxide **32** (2.20 g, 10.0 mmol) in dried tetrahydrofuran (8 mL) was added under argon an excess of a clear dark blue-green solution of dilithium tetrabromonickelate(II) (40 mL, 16 mmol), prepared by the general procedure described by Turner.[28] The reaction mixture, after being sitrred for 72 h at 30 °C, was treated with phosphate buffer (30 mL, 10% pH 7) and extracted with ether (3 × 25 mL). The combined organic layers were washed with 2 × 25 mL of 2% HCl and with 25 mL of saturated sodium bicarbonate solution and water (2 × 25 mL), prior to drying over $MgSO_4$. Chromatography of the residue on silica gel (MPLC, elution with 3% ethyl acetate in *n*-hexane) afforded 2.89 g, 9.6 mmol (96%), of the bromohydrin (±)-**33**: IR (CCl_4) 3550, 2990, 1460, 1370, 1365, 1240, 1045, 920, 880 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 3 H), 1.59 (d, J = 0.9 Hz, 3 H), 1.68 (s, 6 H), 2.20–2.62 (m, 2 H), 3.08 (ddd, J = 14, 4, 1.5 Hz, 1 H), 4.08 (dd, J = 11, 4 Hz, 1 H), 5.10 (br s, 1 H); the multiplet at δ 4.08 simplifies upon irradiation at 3.08 ppm and at 2.30 ppm; the multiplet at δ 2.50 simplifies upon irradiation at 2.00 ppm and at 1.50 ppm. Nuclear Overhauser enhancement difference spectroscopy (NOEDS) gave the following results: presaturation of the signal centered at 3.08 ppm resulted in 29% NOE on δ 1.59; presaturation of the signals at 1.55 ppm resulted in 32% NOE on δ 3.08 and 21% NOE on δ 5.10. ^{13}C NMR ($CDCl_3$) δ 17.7 (q), 18.5 (q), 23.5 (q), 25.9 (q), 26.1 (t), 27.1 (t), 34.6 (t), 38.0 (t), 38.4 (t), 65.5 (d), 72.6 (s), 124.2 (d), 128.5 (s), 129.4 (s), 131.8 (s); MS (EI), m/e (relative intensity) 302/300 (4/4, M^+), 259/257 (1.5/1.5), 232/230 (6/6), 221 (7), 215/213 (77/77), 203 (68), 151 (54), 147 (64), 134 (100), 119 (58), 109 (70), 105 (98); HRMS $C_{15}H_{25}BrO$ (m/e 300.1099, +1.1 mass error); $C_{15}H_{25}O$ (m/e 221.1902, −0.3 mass error).

(1*S*,2*S*)-2-Bromo-1-methyl-4-((*E*)-1,5-dimethylhex-4-enylidene)cyclohexan-1-ol ((−)-33). This was prepared from (+)-**32** (2.0 g, 9.09 mmol) in 97% (2.65 g, 8.81 mmol) yield as a noncrystaline solid, $[\alpha]_D$ −41.9 (c 1.62, $CHCl_3$). This optically active substance showed identical IR, NMR, and MS spectra as those of racemate.

(1*R*,2*R*)-2-Bromo-1-methyl-4-((*E*)-1,5-dimethylhex-4-enylidene)cyclohexan-1-ol ((+)-33). This was prepared from (−)-**32** (1.98 g, 9.0 mmol) in 96% (2.60 g, 8.64 mmol) yield as a noncrystalline solid, $[\alpha]_D$ +42.8 (c 1.07, $CHCl_3$), showing identical IR, NMR, and MS spectra as those of racemate.

Preparation of Racemic (1*R,2*R**)-2-Bromo-1-methyl-4-((*Z*)-1,5-dimethylhex-4-enylidene)cyclohexan-1-ol (42).** To a solution of the racemic epoxide **41** (1.84 g, 8.4 mmol) in anhydrous tetrahydrofuran (8 mL) was added under argon an excess of clear solution of dilithium tetrabromonickelate(II) (40 mL, 16.0 mmol) prepared by the general procedure of Turner.[28] The reaction mixture was stirred at room temperature for 72 h, after which it was treated with phosphate buffer (27 mL, 10% pH 7) and extracted with ether (3 × 25 mL). The combined organic layers were washed with 2 × 25 mL of 2% HCl, 25 mL of saturated sodium bicarbonate, and water (2 × 30 mL). The ether solution was dried over $MgSO_4$ and concentrated in vacuo to give, after chromatographic purification on silica gel (MPLC, elution with 3% ethyl acetate in *n*-hexane), 2.35 g, 7.8 mmol (93%), of the bromohydrin (±)-**42**: IR ($CHCl_3$) 3545, 3470, 1440, 1435, 1395, 1320, 1215, 1145, 1108, 970 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41, 1.60, 1.68, 1.70 (s, 3 H each), 2.38 (dd, J = 14, 12 Hz, 1 H), 25.6 (m, 1 H), 3.10 (ddd, J = 14, 4, 2 Hz, 1 H), 4.05 (dd, J = 12, 4 Hz, 1 H), 5.11 (br s, 1 H); the multiplet at δ 4.05 simplifies upon irradiation at 3.10 and at 2.38 ppm; the multiplet at δ 2.56 simplifies upon irradiation at 2.02 and at 1.65 ppm. Nuclear Overhauser enhancement difference spectroscopy (NOEDS) gave the following results: presaturation of signal centered at δ 3.10 resulted in no NOE on olefinic methyls; presaturation of methyl singlet at δ 1.60 resulted in 32% NOE on 2.56 ppm and 28% NOE on 5.10 ppm. MS (EI), m/e (relative intensity) 302/300 (3/3, M^+), 259/257 (2/2), 232/230 (10/10), 221 (10), 215/213 (54/54), 203 (64), 151 (52), 147 (63), 134 (80), 119 (42), 109 (80), 105 (100); HRMS $C_{15}H_{25}BrO$ (m/e 300.1073, −1.5 mass error).

Preparations of Racemic (4*R,6*S**,8*S**,9*S**)-4,8-Dibromo-1-methylidene-5,5,9-trimethylspiro[5.5]undecan-9-ol and (4*R**,6*S**,8*S**,9*S**)-4,8-dibromo-1,5,5,9-tetramethylspiro[5.5]undec-1-en-9-ol (45 and 46). Method A.** Brominative carbocyclization was realized following the general procedure described by Prestwich.[31i] To a flame-dried, 200-mL, two-necked flask equipped with a magnetic stirrer and addition funnel and swept with argon was added via cannula a solution of racemic **33** (302 mg, 1.0 mmol) in 100 mL of freshly distilled calcium hydride nitromethane. The solution was cooled by being stirred in an ice bath and a suspension of 533 mg, 1.3 mmol, of the sparingly soluble 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCD) in dry nitromethane (15 min); the mixture was stirred at room temperature for 3 h, diluted with ether (40 mL), and washed with three 20-mL portions of saturated sodium bicarbonate solution and water (3 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 784 mg of a colorless oil. Chromatography of the residue on silica gel (MPLC, elution with 2% ethyl acetate in *n*-hexane) yielded, in ascending order of polarity, the noncrystalline bicarbocyclic derivatives (±)-**45** and

(47) Suzuki, T.; Kikuchi, H.; Kurosawa, E. *Chem. Lett.* **1980**, 1267–1270.

(±)-**46** (72.2 mg, 0.19 mmol), 19% yield, and the diene **47** (122 mg, 0.32 mmol), 32% yield. The above mixture was subjected to preparative TLC, elution with hexane/ether (2:1), to give 48.3 mg of **45** and 6.8 mg of **46**.

Method B. To a stirred solution of racemic **33** (301 mg, 1.0 mmol) in anhydrous freshly distilled nitromethane (20 mL) was very slowly added 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCD) (369 mg, 0.90 mmol) in an argon glovebox. After the addition was complete (2 h), the resulting suspension was further stirred for 1 h at 0 °C. The flask was removed from the glovebox, diluted with ether (20 mL), and poured into ice–water (20 mL). The aqueous portion was washed with ether (2 × 10 mL), and then the combined organic portions were washed with 0.2% HCl (2 × 10 mL), saturated sodium bicarbonate (2 × 10 mL), and water (2 × 10 mL). Drying over $MgSO_4$ and concentration in vacuo afforded 645 mg of a colorless oil which was subjected to chromatography on silica gel. Elution with ethyl acetate/*n*-hexane (1:10) gave the mixture of **45** and **46**, 106.4 mg, 0.28 mmol (28%), which was subjected to a second chromatographic separation on silica gel, 184 mg of **47** (48%) and 62 mg of recovered starting bromohydrin **33**. Compounds **45** and **46** were finally separated by preparative TLC, eluting with *n*-hexane/ether (2:1) to give 68.3 mg of **45** and 27.3 mg of **46**. Spectral data for (±)-**45**: IR (CCl_4) 3550, 2950, 1645, 1375, 1365, 1250, 1230, 1120, 925, 890 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94, 1.13, 1.32 (s, 3 H each), 4.46 (dd, J = 12.5, 4.5 Hz, 1 H), 4.54 (dd, J = 13, 5 Hz, 1 H), 4.84 (s, 1 H), 5.20 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.8 (q), 22.5 (q), 23.8 (q), 25.5 (t), 33.7 (t), 34.4 (t), 36.0 (t), 38.4 (t), 44.18 (s), 51.7 (s), 64.2 (d), 64.6 (d), 73.3 (s), 114.5 (t), 146.1 (s); MS (EI), *m/e* (relative intensity) 382/380/378 (0.9/1.8/0.9, M^+), 301/299 (2.5/2.5) 283/281 (52/52), 201 (48), 159 (24), 146 (17), 133 (15), 132 (20), 119 (26), 109 (35), 107 (45), 95 (23), 81 (25), 79 (27), 43 (100). HRMS $C_{15}H_{24}Br_2O$ (*m/e* 378.0191, –0.2 mass error); $C_{15}H_{22}Br$ (*m/e* 281.0917, +1.2 mass error); $C_{15}H_{21}$ (*m/e* 201.1644, +0.1 mass error).

Spectral data for (±)-**46**: IR ($CHCl_3$) 3570, 1395, 1385, 1340, 1130, 1106, 1095, 1045, 1015, 990, 980, 928, 830 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.95, 1.23, 1.35 (s, 3 H), 4.58 (dd, J = 10.5, 7 Hz, 1 H), 4.77 (dd, J = 10.8, 7.8 Hz, 1 H), 5.21 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.3 (q), 22.2 (q), 24.7 (q), 25.9 (q), 31.6 (t), 35.9 (t), 36.3 (t), 39.1 (t), 42.7 (s), 48.2 (s), 61.3 (d), 66.3 (d), 72.0 (s), 122.3 (d), 140.1 (s); MS (EI), *m/e* (relative intensity) 382/380/378 (0.4/0.6/0.4, M^+), 332/330 (0.4/0.4), 301/299 (8/8), 283/281 (16/16), 219 (32), 203 (16), 201 (37), 175 (42), 173 (11), 164 (14), 159 (49), 147 (43), 145 (49), 135 (23); HRMS $C_{15}H_{24}Br_2O$ (*m/e* 378.0177, –1.8 mass error). Comparison of racemic **46** with a sample provided by Dr. M. Suzuki by means of TLC behavior of the two samples was identical in two solvent systems. In addition, IR, NMR, and MS spectra of the two materials correspond in every detail establishing the correspondence of racemic and natural optically active samples.

Spectral data for (+)-**47**: IR (CCl_4) 3540, 3450, 1645, 1450, 1435, 1380, 1335, 1220, 1190, 1130, 980, 918 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42, 1.68, 1.86 (s, 3 H each), 3.06 (dt, J = 14, 3, 3 Hz, 1 H), 4.10 (ddd, J = 14, 5, 2 Hz, 1 H), 4.50 (dd, J = 7.5, 6 Hz, 1 H), 4.88 (dd, J = 2, 1.5 Hz, 1 H), 5.06 (s, 1 H); MS (EI), *m/e* (relative intensity) 300/298 (12/12, M^+ –Br), 282/280 (4/4), 219 (52), 203 (12), 175 (59), 173 (12), 165 (18), 159 (40), 147 (28), 145 (80), 135 (14).

(1*R,4*R**,6*R**,8*S**,9*S**)-(±)-4-Bromo-1,9-epoxy-1,5,5,9-tetramethylspiro[5.5]undecan-8-ol (52).** Prepared following method A: to a flame-dried, 200-mL, two-necked flask equipped with a magnetic stirrer and addition funnal and swept with argon was added via cannula a solution of racemic **31** (R = H) (119 mg, 0.5 mmol) in 100 mL of nitromethane freshly distilled from CaH_2. The solution was cooled by being stirred in an ice bath, and a suspension of TBCD (287 mg, 0.7 mmol) in dry nitromethane was added (15 min). The mixture was stirred at room temperature for 3 h, diluted with ether (20 mL), and washed with a saturated solution of sodium bicarbonate (3 × 20 mL) and water (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Chromatography of the residue on silica gel (3% ethyl acetate in *n*-hexane) yielded the noncrystalline brominated compound (±)-**52** (23.8 mg, 0.075 mmol) (15%): IR (CCl_4) 3570, 3400, 1450, 1380, 1330, 1315, 1130, 1120, 1070, 920, 900 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08, 1.10, 1.20, 1.36 (s, 3 H each), 3.87 (t, J = 3.8 Hz, 1 H), 4.51 (dd, J = 12, 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.8 (q), 28.3 (q), 28.4 (q), 28.7 (q), 29.0 (q), 30.9 (t), 33.5 (t), 34.3 (t), 34.5 (t), 43.8 (s), 44.9 (s), 63.5 (d), 71.9 (s), 76.5 (s), 82.0 (d); MS (EI), *m/e* (relative intensity) 318/316 (0.5/0.5, M^+), 302/300 (58/58), 258/256 (1/1), 245 (6), 237 (12), 22 (15), 205 (5), 175 (16), 161 (27), 153 (20), 145 (16), 135 (54).

(4*R,6*R**,8*S**,9*S**)-(±)-4,8-Dibromo-1-methylidene-5,5,9-trimethylspiro[5.5]undecan-9-ol (57).** Prepared following method A: to a solution of racemic **42** (302 mg, 1.0 mmol) in dried nitromethane (100 mL) at 0 °C under argon was added a suspension of TBCD (535 mg, 1.3 mmol) in nitromethane (50 mL), and the suspension was stirred at room temperature for 3 h. The mixture was poured into water (150 mL) and extracted with dichloromethane (3 × 50 mL). The extract was evaporated under reduced pressure to leave a residue which, after being washed with a *n*-hexane/dichloromethane (1:1) mixture, gave 640 mg of a colorless solid which was subjected to preparative TLC. Elution with *n*-hexane–ethyl acetate (9:1) gave the bromobicarbocyclic compound (±)-**57** (87.4 mg, 0.23 mmol) (23%) and the allylic dibromide **58** (144.8 mg, 0.38 mmol) (38%). Spectral data for (±)-**57**: IR ($CHCl_3$) 3575, 3400, 1640, 1375, 1330, 1310, 1120, 1080, 940, 905 cm^{-1}; ^1H NMR (20/MHz, $CDCl_3$) δ 0.92, 1.15, 1.38 (s, 3 H), 4.13 (dd, J = 4.5, 4.0 Hz, 1 H), 4.51 (dd, J = 12.5, 4.5 Hz, 1 H), 4.83 (s, 1 H), 5.02 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.2 (q), 22.4 (q), 23.4 (t), 24.3 (q), 32.0 (t), 33.1 (t), 34.8 (t), 36.5 (t), 44.7 (s), 47.0 (s), 58.5 (d), 65.2 (d), 72.4 (s), 112.2 (t), 148.4 (s); MS (EI), *m/e* (relative intensity) 382/380/378 (0.9/1.8/0.8, M^+), 283/281 (52/52), 219/217 (4/4), 201 (50), 189/187 (4/4), 175/173 (6/6), 159 (24), 145 (17), 133 (15), 121 (13), 109/107 (35/35), 105 (46), 95 (23); HRMS $C_{15}H_{24}Br_2O$ (*m/e* 378.0177, –1.8 mass error).

Spectral data for **58**: IR ($CHCl_3$) 3560, 3450, 1640, 1445, 1375, 1335, 1215, 1130, 1115, 970, 920 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42, 1.60, 1.67, 1.82 (s, 3 H), 3.07 (ddd, J = 14, 3.5, 3 Hz, 1 H), 4.12 (ddd, J = 14, 5, 2.5 Hz, 1 H), 4.50 (dd, J = 7, 6.5 Hz, 1 H), 4.90 (dd, J = 2, 1.5 Hz, 1 H), 5.10 (s, 1 H); MS (EI), *m/e* (relative intensity) 300/298 (14/14, M^+ – Br), 282/280 (3/3), 219 (61), 203 (9), 175 (60), 173 (18), 165 (18), 159 (33), 147 (12), 145 (100), 135 (18).

(4*R,6*R**,8*R**,9*R**)-(±)-4-Bromo-8,9-epoxy-1-methylidene-5,5,9-trimethylspiro[5.5]undecane (59).** A solution of racemic **57** (38.0 mg, 0.10 mmol) and potassium carbonate (20.0 mg, 0.20 mmol) in methanol (15 mL) was allowed to stand at room temperature for 5 min. Dichloromethane (20 mL), followed by water (20 mL), was added to the solution, the organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated. The residue was subjected to preparative TLC, eluting with *n*-hexane/ether (1:1), to give the epoxide **59** (28.2 mg, 0.094 mmol) (94%) which was isolated as a noncrystalline solid: IR ($CHCl_3$) 1640, 1390, 1375, 1184, 1160, 1130, 1045, 1035, 970, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.96, 1.12, 1.22 (s, 3 H each), 2.93 (d, J = 4.7 Hz, 1 H), 4.30 (dd, J = 5, 5 Hz, 1 H), 4.63 (s, 1 H), 5.06 (s, 1 H); MS (EI), *m/e* (relative intensity 300/298 (0.5/0.5, M^+), 219 (6), 201 (11), 185 (4), 175 (14), 145 (11), 135 (12), 131 (14), 119 (25), 109 (21), 105 (44).

(4*R,6*S**)-(±)-4-Bromo-1-methylidene-5,5,9-trimethylspiro[5.5]undec-8-ene (5) and (±)-β-Chamigrene (6).** To a solution of racemic **45** (74 mg, 0.19 mmol) in acetic acid (5 mL) was added Zn dust (150 mg, 2.3 mmol), and the mixture was stirred for 3 h at 60 °C (bath temperature). After cooling and filtrating of Zn dust, the mixture was poured into water (20 mL) and extracted with ether (3 × 10 mL). The ethereal solutions were washed with water (2 × 10 mL), saturated $NaHCO_3$ solution (2 × 10 mL), and water (10 mL), dried over $MgSO_4$, and evaporated. The residual oil (63 mg) was subjected to preparative TLC, eluting with *n*-hexane–ether (5:1), to give (±)-**6** (28 mg, 0.13 mmol) and (±)-**5** (16 mg, 0.06 mmol).

Spectral data for (±)-**5**: IR (CCl_4) 2950, 1650, 1370, 1360, 1230, 1100, 915, 895, 885 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94, 1.10, 1.56 (s, 3 H each), 4.60 (s, 1 H), 4.61 (dd, J = 12, 4 Hz, 1 H), 4.91 (s, 1 H), 5.25 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.7 (q), 23.3 (q), 24.0 (q), 25.8 (t), 27.7 (t), 30.5 (t), 33.2 (t), 35.9 (t), 42.9 (s), 47.2 (s), 66.2 (d), 117.8 (t), 119.9 (d), 132.9 (s), 145.8 (s); MS (EI), *m/e* (relative intensity) 284/282 (2/2 M^+), 269/267 (2/2), 203 (20), 187 (7), 135 (19), 119 (30), 109 (30), 105 (76), 95 (27), 93 (61), 91 (70), 81 (84), 79 (70), 77 (56), 69 (100); HRMS $C_{15}H_{23}Br$ (*m/e* 282.0980, +0.3 mass error); $C_{15}H_{23}$ (*m/e* 203.1800, –0.2 mass error).

Spectral data for (±)-**6**: IR (CCl_4) 2850, 1645, 1380, 1363, 1025, 970, 890 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83, 0.87, 1.58 (s, 3 H each), 4.51 (s, 1 H), 4.86 (s, 1 H), 5.29 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.2 (q), 23.4 (q), 24.0 (q), 25.2 (q), 26.2 (t), 28.1 (t), 29.2 (t), 32.4 (t), 37.2 (t), 37.4 (s), 45.0 (s), 110.7 (t), 120.2 (d), 132.9 (s), 149.2 (s); MS (EI), *m/e* (relative intensity) 204 (29, M^+), 189 (100), 175 (12), 162 (11), 161 (20), 148 (14), 147 (17), 133 (42), 121 (41), 119 (35); HRMS $C_{15}H_{24}$ (*m/e* 204.1799, –7.9 mass error); $C_{14}H_{21}$ (*m/e* 189.1642, +0.1 mass error).

(4*R*,6*S*,8*S*,9*S*)-4,8-Dibromo-1,5,5,9-tetramethylspiro[5.5]undec-1-en-9-ol ((–)-9). This was obtained from (–)-**33** (610 mg, 2.0 mmol) following method B in 8% (62.2 mg, 0.16 mmol) yield as a noncrystalline solid, $[\alpha]_D$ –28.6 (c, 1.15, $CHCl_3$). This optically active substance showed identical IR, NMR, and MS spectra as those of natural enantiomer and synthetic racemate [lit.[13] $[\alpha]_D$ –27.0 (*c* 2.13) and $[\alpha]_D$ –34.2 for the natural enantiomer].

(4*R*,6*S*,8*S*,9*S*)-4,8-Dibromo-1-methylidene-5,5,9-trimethylspiro[5.5]undecan-9-ol ((–)-10). This was obtained from (–)-**33** (610 mg, 2.0 mmol) yield as noncrystalline solid, $[\alpha]_D$ –3.92 (*c* 0.89, $CHCl_3$). This optically active substance was identical in

all respect with the synthetic racemate.

(4*R*,6*S*)-4-Bromo-1-methylidene-5,5,9-trimethylspiro[5.5]undec-8-ene ((−)-5). This was obtained from **10** (130 mg, 0.34 mmol) in 35% (35.2 mg, 0.12 mmol) yield as a noncrystalline solid, $[\alpha]_D$ −14.2 (*c* 0.67, $CHCl_3$). This optically active substance showed identical IR, NMR, and MS spectra as those of racemate and natural opposite enantiomer [lit.[10] $[\alpha]_D$ + 14.0 (*c* 2.46, $CHCl_3$) for the natural enantiomer].

(−)-β-Chamigrene (6). This was obtained from **10** (130 mg, 0.34 mmol) in 60.7% (42.1 mg, 0.21 mmol) yield as a noncrystalline solid, $[\alpha]_D$ −54.1 (*c* 0.35, $CHCl_3$). This optically active substance showed identical IR, NMR, and MS spectra as those of natural enantiomer [lit.[11] $[\alpha]_D$ −52.7 (*c* 0.71, $CHCl_3$)].

(4*S*,6*R*,9*R*,9*R*)-4,8-Dibromo-1,5,5,9-tetramethylspiro[5.5]undec-1-en-9-ol ((+)-11). This was obtained from (+)-**33** (610 mg, 2.0 mmol) following method B in 8.5% (64.3 mg, 0.17 mmol) yield as a noncrystalline solid, $[\alpha]_D$ +25.4 (*c* 0.91, $CHCl_3$). This optically active substance showed identical IR, NMR, and MS spectra as those of natural opposite enantiomer and synthetic racemate [lit.[13] $[\alpha]_D$ −27.0 (*c* 2.13) and $[\alpha]_D$ −34.2 for the natural opposite enantiomer].

(4*S*,6*S*,8*R*,9*R*)-4,8-Dibromo-1-methylidene-5,5,9-trimethylspiro-[5.5]undecan-9-ol ((+)-12). This was obtained for (+)-**33** (610 mg, 2.0 mmol) in 17.5% (133.9 mg, 0.35 mmol) yield as a noncrystalline solid, $[\alpha]_D$ +4.42 (*c* 1.12, $CHCl_3$). This optically active substance showed identical IR, NMR, and MS spectra as those of racemate.

(4*S*,6*R*)-4-Bromo-1-methylidene-5,5,9-trimethylspiro[5.5]undec-8-ene ((+)-7). This was obtained from **12** (130 mg, 0.34 mmol) in 35% (33.6 mg, 0.119 mmol) yield as a noncrystalline solid, +13.5 (*c* 1.13, $CHCl_3$). This optically active substance showed identical IR, NMR, and MS spectra as those of the racemate and natural enantiomer [lit.[10] $[\alpha]_D$ +14.0 (*c* 2.46, $CHCl_3$) for the natural enantiomer].

(+)-β-Chamigrene (8). This was obtained from **12** (130 mg, 0.34 mmol) in 58.8% (40.3 mg, 0.20 mmol) yield as a noncrystalline substance, $[\alpha]_D$ +59.2 (*c* 2.46, $CHCl_3$). This optically active compound showed identical IR, NMR, and MS spectra as those of racemate and natural opposite enantiomer [lit.[11] $[\alpha]_D$ −52.7 (*c* 0.71, $CHCl_3$)].

Preparation of 5 and 6 from Natural Obtusol (2). To a solution of natural[1] obtusol (**2**) (143.7 mg, 0.35 mmol) in 20 mL of ether and acetic acid (0.5 mL) was added Zn dust (65.4 mg, 1.0 mmol), and the mixture was stirred for 10 h at room temperature. After cooling and filtrating off Zn dust, the mixture was extracted with ether (30 mL). The ethereal solution was washed with water (2 × 10 mL), 5% aqueous $NaHCO_3$ and finally (2 × 10 mL) with water, dried over $MgSO_4$, and evaporated. The residual oil was chromatographed on silica gel with ethyl acetate/*n*-hexane (9:1) to give **63** (R = H) (101.7 mg, 0.34 mmol) as a noncrystalline oil, $[\alpha]_D$ +32 (*c* 0.46, $CHCl_3$) [^{1}H NMR (90 MHz, $CDCl_3$) δ 1.08 (s, 6 H), 1.61 (s, 3 H), 4.20 (br s, 1 H), 4.72 (d, *J* = 4 Hz, 1 H), 4.85 (s, 1 H), 5.12 (s, 1 H), 5.32 (br s, 1 H)]. A cold solution of **63** (R = H) (96.2 mg, 0.32 mmol) and methanesulfonyl chloride (0.05 mL, 0.60 mmol) in dry pyridine (3 mL) was stirred overnight under argon. The reaction mixture was quenched with 20 mL of water and extracted with ether (3 × 10 mL). The combined organic layers were washed with 2 × 25 mL of 5% HCl, 2 × 10 mL of saturated $NaHCO_3$, and 2 × 5 mL of water. The ether solution was dried over $MgSO_4$ and concentrated in vacuo to give **63** (R = Ms) (113.2 mg, 0.30 mmol) which was dissolved in 5 mL of dry pyridine under a blanket of argon. After having been cooled in an ice bath, 1 mL of lithium triethylborohydride (1 molar) in tetrahydrofuran was slowly added to the flask from a dry syringe. The solution was stirred with cooling for 30 min and then refluxed for 2 h. After having been cooled to room temperature, excess borane was decomposed by adding 2 mL of water, followed by 0.5 mL of 2 N aqueous NaOH, and 0.5 mL of 30% H_2O_2. The solution was stirred for 1 h and then extracted with 2 × 20 mL of *n*-hexane. After evaporation of the dried ($MgSO_4$) solvent, 76.7 mg of a colorless oil was obtained, which was subjected to chromatographic purification on silica gel (MPLC, *n*-hexane as eluent) to give 16.2 mg of **5**, $[\alpha]_D$ −14.6 (*c* 0.11, $CHCl_3$), and 31.2 mg of **6**, $[\alpha]_D$ −53.8 (*c* 0.09, $CHCl_3$), which were shown to be identical in all respects with synthetic enantiomers.

Preparation of 7 and 8 from Natural Isoobtusol (3). From the natural[2] isoobtusol (**3**) (215.6 mg, 0.52 mmol) and following a similar sequence of reactions as above indicated for obtusol (**2**), the compounds **7** $[\alpha]_D$ +14.4 (*c* 0.23, $CHCl_3$) (21.2 mg), and **8**, $[\alpha]_D$ +54.2 (*c* 0.31, $CHCl_3$) (37.4 mg), were prepared and shown to be identical with their corresponding synthetic enantiomers.

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Registry No. 2, 73494-22-1; **3**, 73494-23-2; (±)-**5**, 104643-42-7; (−)-**5**, 104714-12-7; (±)-**6**, 15401-86-2; (−)-**6**, 87935-44-2; (+)-**7**, 104714-15-0; (+)-**8**, 18431-82-8; (−)-**9**, 89203-65-6; (−)-**10**, 104714-11-6; (+)-**11**, 104714-13-8; (+)-**12**, 104714-14-9; (±)-**25**, 94294-79-8; (±)-**25**·(*i*-Pr)$_2$NH, 94294-80-1; (±)-**26**, 94294-69-6; (±)-**27**, 94294-70-9; (±)-**28** (R = H), 94294-71-0; (±)-**28** (R = Ac), 104643-30-3; (−)-**28** (R = Ac)·quinine, 104757-57-5; (−)-**28** (R = Ac), 104713-96-4; (±)-**28** (R = Ac)·L-(−)-α-methylbenzylamine, 104757-58-6; (+)-**28** (R = Ac), 104713-97-5; **28** (R = Ac) (dibromo derivative), 104643-44-9; **29** (R = Ac), 104643-31-4; (±)-**30** (R = Ac), 94294-74-3; (±)-**30** (R = H), 94294-73-2; (+)-**30** (R = Ac), 104713-99-7; (−)-**30** (R = Ac), 104714-00-3; (+)-**30** (R = H), 104714-01-4; (−)-**30** (R = H), 104714-02-5; (±)-**31** (R = H), 94294-75-4; (−)-**31** (R = H), 104714-03-6; (+)-**31** (R = Ac), 104643-32-5; (+)-**31** (R = H), 104757-61-1; (−)-**31** (R = Ac), 104643-33-6; (±)-**31** (R = Ms), 104643-34-7; (−)-**31** (R = Ms), 104714-05-8; (+)-**31** (R = Ms), 104757-62-2; (±)-**32**, 94347-01-0; (+)-**32**, 75744-73-9; (−)-**32**, 104714-06-9; (±)-**33**, 104643-36-9; (−)-**33**, 104714-07-0; (+)-**33**, 104714-08-1; (±)-**34**, 94294-81-2; (±)-**34**·(*i*-Pr)$_2$NH, 94294-82-3; (±)-**35**, 94347-03-2; (±)-**36**, 94347-04-3; (±)-**37** (R = H), 94347-05-4; (±)-**37** (R = Ac), 104713-95-3; (+)-**37** (R = Ac), 104714-17-2; (−)-**37** (R = Ac)·quinine, 104757-59-7; (−)-**37** (R = Ac), 104713-98-6; (+)-**37** (R = Ac)·L-(−)-α-methylbenzylamine, 104757-60-0; (±)-**39** (R = H), 94347-06-5; (±)-**39** (R = Ac), 94347-07-6; (±)-**40** (R = H), 94294-76-5; (±)-**40** (R = Ac), 104714-04-7; (±)-**40** (R = Ms), 104643-35-8; (±)-**41**, 94347-02-1; (±)-**42**, 104643-37-0; (±)-**45**, 104643-38-1; (±)-**46**, 104714-09-2; **47**, 104643-39-2; (±)-**52**, 104643-40-5; (±)-**57**, 104714-10-5; (±)-**59**, 104643-41-6; **63** (R = H) (isomer 1), 61688-66-2; **63** (R = Ms) (isomer 1), 104643-43-8; **63** (R = H) (isomer 2), 61661-40-3; **63** (R = Ms) (isomer 2), 104714-16-1; (±)-4-methyl-3-cyclohexene-1-carboxylic acid, 98513-87-2; 6-methyl-5-hepten-2-one, 110-93-0.