ferent time intervals aliquots (4 ml) were withdrawn (under argon) and the resin separated immediately by suction filtration, washed thoroughly with DMF, $CH_2Cl_2$, and MeOH, and then subjected to amino acid analysis. The rate of decrease in amino acid content was taken as the rate of photolysis of the α-methylphenacyl ester anchoring bond. Exactly the same experiments were performed on tetrapeptide resins VII and VIII to determine the rate of photolytic cleavage of the o-nitrobenzyl and benzyl ester linkages. The results are summarized in Figure 1. For the studies of the rates of acidolysis or hydrazinolysis of the resins III, VII, and VIII, 0.5 g each of the samples were stirred individually in 20 volumes each of TFA–$CH_2Cl_2$ (1:1) or 10% $H_2NNH_2$ (DMF) in six separate flasks. Aliquots (1 ml) from each reaction were taken at different times and treated as described above for the photolysis experiments. The results are also shown in Figure 1.

**Acknowledgment.** The author wishes to thank Dr. R. B. Merrifield and Dr. J. Meienhofer for suggestions and discussions; Dr. F. Scheidl, Dr. T. Williams, Dr. V. Toome, Mr. S. Traiman, and their colleagues for physicochemical measurements and determinations; and Dr. C. C. Wei for discussions concerning some of the photochemical techniques.

**Registry No.**—IV, 40099-54-5; copolystyrene divinylbenzene, 9003-70-7; 2-bromopropionyl chloride, 7148-74-5; Boc-Gly-OH, 4530-20-5; Boc-Phe-OH, 13734-34-4; Z-Lys(Z)-OH, 405-39-0.

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# Total Synthesis of Sativene and Copacamphene via a Free Radical Cyclization

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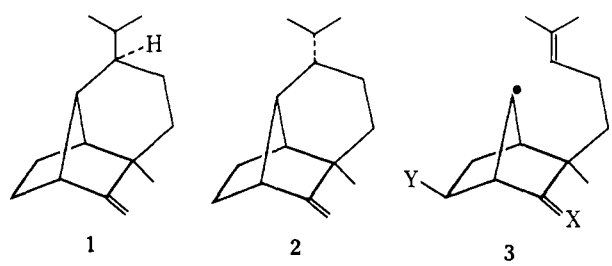
A synthesis of the tricyclic sesquiterpenes sativene (1) and copacamphene (2) is described, the key carbon–carbon bond formation being effected via a free-radical cyclization of the bicyclic compound 3 (X = O; Y = H). A new method for transforming a terminal olefin to an aldehyde via the corresponding alkyl phenyl sulfide followed by oxidation with *N*-chlorosuccinimide and hydrolysis of the resulting chloroalkyl phenyl sulfide is used to prepare the aldehyde precursor of 3.

The tricyclic sesquiterpenes sativene (1) and copacamphene (2) possess five chiral centers and thus offer interesting substrates to test and develop synthetic methodology.[1] While schemes based on heterolytic processes leading to carbon–carbon bond formation have been responsible for all but a handful of synthesis, one can expect[2] that homolytical processes, at least in isolated steps, will become more and more common as traditional prejudices against free-radical intermediates are removed.[3] Accordingly, we sought to develop a synthetic scheme based on free-radical intermediates which might be used to synthetize not only sativene and copacamphene, but also structurally related compounds such as cyclosativene, isosativene, and longifolene.

The key intermediate of our projected synthesis was the free radical 3, which could be expected[4] to cyclize to the tricyclic skeleton found in 1 and 2. Unfortunately, the factors controlling stereoselectivity of free-radical cyclizations are not understood, but because of the strained nature of the 7-norbornyl radical[5] and the expected stability of the tertiary radical produced, the product ratio should reflect kinetic and not thermodynamic factors. However, no clear prediction of the stereoselectivity expected could be made by consulting Dreiding models of radical 3. This steric ambiguity was offset by the choice of the norbornanone skeleton as the starting point of the synthesis, the other four asymmetric centers being controlled by the topological and steric restraints of the bicyclic ring structure.

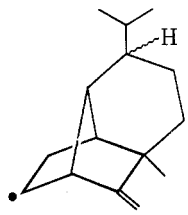



1 2 3

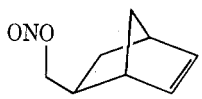
Of the variety of methods that could be used to synthesize the desired radical 3, the Barton reaction appeared to have several advantages since the desired precursors should be

readily prepared and, additionally, the cyclized product from **3** (Y = $CH_2OH$) should be convertible into the tetracyclic sesquiterpenoids cyclosativine and cyclocopacamphene by an additional free-radical cyclization of radical **4**.

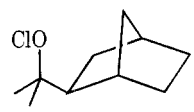
As a model system, we examined the Barton reaction on compound **5**, but found no evidence of functionalization at



**4**



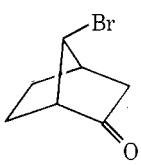

**5**



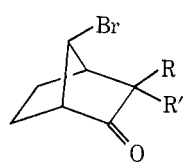

**6**

C-7. This result is consistent with that obtained with compound **6**,[6] although the alkoxy radical derived from the latter system is expected to be more prone to fragmentation reactions. Accordingly, we decided to prepare the desired radical in a less ambigouous manner from the corresponding 7-bromo compound.

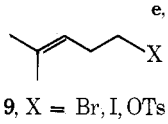
The readily available[7] *syn*-7-bromonorbornanone (**7**) was methylated in DME using the conditions developed by House[8] to give a 3:1 mixture of **8a** and **8b**, the stereochemistry being assigned on the basis of H NMR data as follows. The chemical shifts of the methyl groups in *exo*- and *endo*-3-methylbicyclo[2.2.1]heptan-2-one are nearly identical[9] and substitution



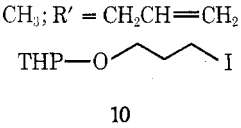
**7**



**8a**, R = $CH_3$; R′ = H
**b**, R = H; R′ = $CH_3$
**c**, R = $CH_2CH_2CH{=}C(CH_3)_2$; R′ = $CH_3$
**d**, R = $CH_2CH{=}CH_2$; R′ = $CH_3$
**e**, R = $CH_3$; R′ = $CH_2CH{=}CH_2$




**9**, X = Br, I, OTs




**10**

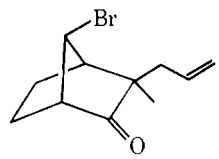
of the syn hydrogen at C-7 by a bromine atom would be expected[10] to deshield an exo methyl group more than the endo methyl substituent. The observed difference, 0.31 ppm, of the chemical shifts of the methyl groups in compounds **8a** and **8b** permits assignment of the stereochemistry. Collaboration for this assignment comes from the multiplicies of the bromomethine peaks, compound **8a**, capable of a "W"-type coupling between the hydrogens at C-3 and C-7, presenting a multiplet while in **8b** the peak appears as an apparent triplet.[11]

The relatively low stereoselectivity in the alkylation step is in contrast to the stereospecific methylation of norbornanone,[9] although we cannot be certain that our ratio does not reflect some postalkylation equilibration.[12] In the event, while the isomers could be separated, this is not necessary since the synthetically important stereoselectivity is determined in the subsequent alkylation step.

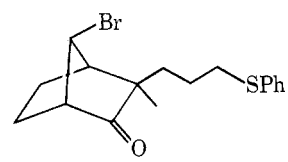
Unfortunately, the alkylation of **8a** and **8b** with **9** (X = Br, I, or OTS) failed under a great variety of conditions, in sharp contrast to the success in the debromo case.[9] Conditions that were examined included bases such as potassium *tert*-butoxide and *tert*-amyl oxide, in various solvents, NaH in benzene, DMF, or $Me_2SO$, lithium diisopropylamide in DME, and butylmagnesium bromide in HMPA. In all cases, only the endo starting material **8b**, or products that indicated ring cleavage and elimination, were isolated. Equally disappointing were attempts to alkylate **8a** and **8b** with the three-carbon synthon **10** or effect Michael reaction with acrolein.[13]

Successful alkylation was affected by allylation of the magnesium enolate[15] of **8a** and **8b** in HMPA at 60 °C. $^1H$ NMR analysis of the crude product mixture indicated a ca. 3:5 ratio of O- and C-alkylated products, the alkylated compounds **8d** and **8e** being formed in a 4:1 ratio, respectively. Use of higher temperatures to effect a postalkylation Claisen rearrangement increased the amount of C-alkylated product, but the exo to endo ratio decreased and with prolonged reaction times, the syn bromo substituent suffered SN2 attack by magnesium bromide (see Experimental Section).

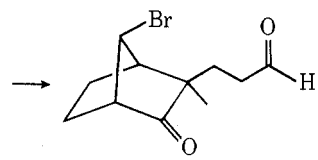
Hydroboration followed by oxidation of the exo allyl compound **8d** and subsequent oxidation of the resulting alcohol by $CrO_3$–pyridine in $CH_2Cl_2$[16] gave the unstable aldehyde **12**



**8d**




**11**

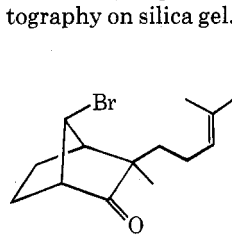


**12**

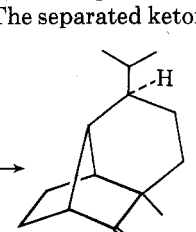
in 35% overall yield. The yield for the hydroboration–oxidation steps was not improved by use of other hydroboration reagents such as 9-BBN or diborane in dimethyl sulfide. Equally disappointing were other olefin to aldehyde transformations via the corresponding epoxides,[17] thus forcing us to develop an alternate sequence of reactions.[18]

Treatment of **8d** with thiophenol at 80 °C in the presence of AIBN (azobisisobutyronitrile) led to sulfide **11**, which was oxidized with *N*-chlorosuccinimide by refluxing in carbon tetrachloride for 20 min. The crude chloro sulfide was hydrolized in the presence of $Cu^{II}$ (to oxidize the thiophenol formed)[19] to give the aldehyde **12** in 60% isolated yield (87% yield by NMR).[20] Treatment of the crude aldehyde **12** with $Ph_3P{=}C(CH_3)_2$ in $Me_2SO$ at 60 °C led to a nearly quantitative retro-Michael reaction, the major product being **8b**. However, reaction of the Wittig reagent at −65 °C and in ether as solvent gave the desired isopropylidene compound **8c** in 64% yield, shown to be free of its epimer at C-3 by the absence of a low-field methyl group.

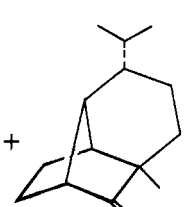
The key carbon–carbon bond formation reaction, cyclization via the intermediate **3** (X = O; Y = H), was conveniently carried out in 62% yield by the catalyzed reaction of **8c** and tributyl stannane in benzene at 36 °C. The resulting products, norsativone (**13**)[21] and copacamphenilone (**14**),[22] formed in a 3:2 ratio, respectively, were separated by careful chromatography on silica gel. The separated ketones **13** and **14** were



**8c**



**13**



**14**

transformed into sativene (**1**) and copacamphene (**2**) by published[21,22] procedures and found to be identical in all respects examined with the authentic natural products.

## Experimental Section

***syn*-7-Bromo-3-methylbicyclo[2.2.1]heptan-2-ones (8a and 8b).** To a solution of excess lithium diisopropylamide in 350 ml of dry DME[8] at 0 °C, under $N_2$, containing 200 mg of triphenylmethane as indicator, was added 8.9 g of *syn*-7-bromobicyclo[2.2.1]heptan-2-one (7) in 15 ml of DME over a 15-min period. To the resulting pink solution was added 15 ml of methyl iodide and the mixture allowed to come to room temperature. After standing overnight, the mixture was poured into water, extracted with ether, dried over $Na_2SO_4$, and filtered, and solvent was removed to give 7.6 g of crude product, shown by GLC (DC 550 column at 170 °C) to be a mixture of starting material and exo and endo methylated ketones **8a** and **8b** (3:1 exo:endo ratio). Chromatography on 250 g of silica with 1:5 benzene–petroleum ether gave 4.37 g of monomethylated ketones **8a** and **8b** (56% yield based on unrecovered starting material) and 1.60 g of starting material. Rechromatography of the methylated ketones separated the two isomers, the endo isomer **8b** eluting first. Analytical samples of **8a** and **8b** were prepared by bulb to bulb distillation at 0.05 mm (75 °C bath temperature). **8a:** ir (neat) 5.70 $\mu$; $^1$H NMR ($CCl_4$) $\delta$ 4.04 (m, 1 H, CHBr), 2.67 (m, 2 H, C-1 and C-4 methines), 1.38 (d, $J$ = 7 Hz, $CH_3$). **8b:** ir (neat) 5.70 $\mu$; $^1$H NMR ($CCl_4$) $\delta$ 4.25 (t, 1 H, $J$ = 1.5 Hz, CHBr), 2.68 (m, 2 H, C-1 and C-4 methines), 1.07 (d, 3 H, $J$ = 7 Hz, $CH_3$).

Anal. Calcd for $C_8H_{11}BrO$ (**8a**): C, 47.31; H, 5.46. Found: C, 47.43; H, 5.55.

Anal. Calcd for $C_8H_{11}BrO$ (**8b**): C, 47.31; H, 5.46. Found: C, 47.35; H, 5.45.

**Allylation of *syn*-7-Bromo-3-methylbicyclo[2.2.1]heptan-2-ones (8a and 8b).** A solution of 6.25 g of butyl bromide in 50 ml of ether was added to 1.13 g of Mg, under $N_2$. Ether was removed from the resulting Grignard solution at 60 °C, under vacuum, replaced with 50 ml of freshly distilled (from Na) HMPA, and stirred at 80 °C for 10 min. To this solution was added 8.66 g of ketone **8a** or **8b** in 10 ml of HMPA, dropwise, over 5 min. After stirring for an additional 30 min, the mixture was cooled to 60 °C; to it was added 11 ml of allyl bromide and the mixture was stirred overnight at 60 °C. The cooled mixture was diluted with water and extracted with ether; the extract was washed several times with water and dried over $Na_2SO_4$ and solvent was removed to give 9.00 g of crude product, shown by $^1$H NMR to be a mixture of C- and O-allylated compounds. Chromatography on 250 g of silica gel with 2:1 petroleum ether–benzene gave 1.50 g of starting material and 4.85 g of a 4:1 mixture of exo and endo allylated product (57% yield, based on unrecovered starting material). The isomers were separated upon careful rechromatography, the endo allyl compound **8e** eluting first. Analytical samples were prepared by bulb to bulb distillation. Exo allyl compound **8d:** ir (neat) 5.72, 6.09 $\mu$; $^1$H NMR ($CCl_4$) $\delta$ 4.15 (t, 1 H, $J$ = 1.0 Hz, CHBr), 1.07 (s, 3 H, $CH_3$). Endo allyl compound **8e:** ir (neat) 5.72, 6.09 $\mu$; $^1$H NMR ($CCl_4$) $\delta$ 4.14 (t, 1 H, $J$ = 1.0 Hz, CHBr), 1.44 (s, 3 H, $CH_3$).

Anal. Calcd for $C_{11}H_{15}BrO$ (**8d**): C, 54.33; H, 6.22. Found: C, 54.48; H, 6.25.

Anal. Calcd for $C_{11}H_{15}BrO$ (**8e**): C, 54.33; H, 6.22. Found: C, 54.23; H, 6.15.

The alkylation could be forced to completion by heating the crude reaction mixture at 130–150 °C for 3–6 h. However, the exo to endo allylation ratio decreased to about 2:1, and after prolonged reaction times *anti*-7-bromo-*exo*-3-allyl-*endo*-3-methylbicyclo-[2.2.1]heptan-2-one became an important by-product. It was isolated and purified as above, bulb to bulb distillation providing an analytical sample: ir (neat) 5.70, 6.08 $\mu$; $^1$H NMR ($CCl_4$) $\delta$ 4.58 (m, 1 H, CHBr), 1.06 (s, 3 H, $CH_3$).

Anal. Calcd for $C_{11}H_{15}BrO$: C, 54.33; H, 6.22. Found: C, 54.49; H, 6.26.

**Addition of Thiophenol to *syn*-7-Bromo-*exo*-3-allyl-*endo*-3-methylbicyclo[2.2.1]heptan-2-one (8d).** A mixture of 750 mg of olefin **8d**, 225 mg of AIBN, and 5 ml of thiophenol was stirred at 77 °C under $N_2$ for 2.5 h, cooled, poured into 10% KOH solution, and extracted with ether. The extract was washed three times with water and dried over $Na_2SO_4$, and solvent was removed to give 1.275 g of crude product. Two chromatographies on 65 g of alumina neutral, activity 2–3, elution with 2:1 petroleum ether–benzene to 1:1 petroleum ether–benzene separated, in order of elution, 210 mg of diphenyl disulfide, 120 mg of starting material **8d**, and 783 mg of sulfide **11** (86% yield, based on unrecovered starting material). An analytical sample was prepared by bulb to bulb distillation at 0.1 mm (165 °C pot temperature): ir (neat) 5.70, 6.27, 13.5, and 14.45 $\mu$; $^1$H NMR ($CCl_4$) $\delta$ 7.22 (m, 6 H, aromatic), 4.06 (t, 1 H, $J$ = 1.5 Hz, CHBr), 2.84 (t, 2 H, $J$ = 7 Hz, $CH_2SPh$), 1.03 (s, 3 H, $CH_3$).

Anal. Calcd for $C_{17}H_{21}BrOS$: C, 57.79; H, 5.99. Found: C, 57.67; H, 5.91.

**Preparation of *syn*-7-Bromo-*endo*-3-methyl-*exo*-3-(4-methyl-3-pentenyl)bicyclo[2.2.1]heptan-2-one (8c).** A mixture of 164 mg of sulfide **11**, 70 mg of *N*-chlorosuccinimide, and 5 ml of $CCl_4$ was refluxed under $N_2$ for 20 min, cooled and filtered and solvent was removed. To the residue was added 170 mg of CuO, 170 mg of $CuCl_2 \cdot 2H_2O$, 5 ml of acetone, and 0.1 ml of $H_2O$ and the mixture was refluxed under $N_2$ for 15 min, cooled, poured into water, and extracted with ether. The extract was washed with 10% KOH, three times with water, and dried over $Na_2SO_4$ and solvent was removed to give 146 mg of crude aldehyde **12** (see below), used without purification in the next step.

The above aldehyde, in 3 ml of ether, was added over 6.5 min to a Wittig solution at −65 °C (prepared at room tmperature by treating a suspension of 430 mg of triphenylisopropylphosphonium iodide in 10 ml of $Et_2O$, under $N_2$, with 490 $\mu$l of 1.9 M *n*-BuLi in hexane). After the mixture was stirred at −65 °C for an additional 0.5 h, it was allowed to come to room temperature over 1 h and then poured into water and extracted with ether. The extract was washed with water and dried over $Na_2SO_4$ and solvent was removed to give 187 mg of crude product, purified by chromatography on 15 g of silica gel by eluting with 1:1 petroleum ether–benzene to 1:2 petroleum ether–benzene. The resulting oil, 64 mg (48% overall yield from **11**), was distilled at 0.2 mm (100 °C pot temperature) to give an analytical sample of **8c**: ir (neat) 5.71 $\mu$; $^1$H NMR ($CCl_4$) $\delta$ 5.08 (m, 1 H, vinyl), 4.13 (t, 1 H, $J$ = 1.6 Hz, CHBr), 1.67 and 1.61 (s, 6 H, isopropylidine), 1.07 (s, 3 H, $CH_3$).

Anal. Calcd for $C_{14}H_{21}BrO$: C, 58.95; H, 7.42. Found: C, 58.85; H, 7.44.

Purification of the aldehyde **12** used above resulted in lower overall yields for the three steps, presumably because of the instability of the aldehyde for which acceptable C, H analyses were not obtained. $^1$H NMR analysis of the products of the oxidation and hydrolysis steps indicated yields of aldehyde up to 87% but isolated yields never exceeded 60%, while the maximum yield for the Wittig reaction on purified aldehyde was 64%. For **12**: ir (neat) 3.65, 5.72, 5.78 $\mu$; $^1$H NMR ($CCl_4$) $\delta$ 9.71 (broad s, 1 H, aldehyde), 4.19 (t, 1 H, $J$ = 1.5 Hz, CHBr), 1.07 (s, 3 H, $CH_3$).

**Free-Radical Cyclization of 8c to Norsativone (13) and Copacamphenenilone (14).** A mixture of 235 mg of the olefin **8c**, 220 mg of freshly distilled tributylstannane, and 10 mg of *tert*-butyl perbenzoate in 20 ml of benzene was irradiated at 36 °C in a Merry-Go-Round apparatus with the 257-mm source for 1.5 h (quartz tube). Removal of solvent left 530 mg of residue, which was chromatographed on 60 g of silica gel using 1:1 petroleum ether–benzene as eluent to give, in order of elution, 340 mg of tributyltin bromide, 9 mg of starting olefin **8c**, 47 mg of a mixture of norsativone and copacamphenilone enriched in norsativone, and 53 mg of a mixture favoring copacamphenilone (62% yield of cyclized material). Chromatography of the latter fraction on 45 g of silica gel gave 20 mg of a mixture of **13** and **14** and 29 mg of copacamphenilone[1b] (**14**). The above two mixtures were combined and rechromatographed on 45 g of silica gel to give 58 mg of norsativone[1a] (**13**) and 5 mg of copacamphenilone (**14**). The separated ketones **13** and **14** were transformed into sativene and copacamphene, respectively, by published procedures.[1a,1c] Sativene was identified by comparison of ir, $^1$H NMR, mass spectrum, and TLC behavior with an authentic sample, while copacamphene was identified by spectral comparison (ir, $^1$H NMR, mass spectrum).

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**Registry No.**—**3**, 59796-80-4; **7**, 7176-91-2; **8a**, 59796-81-5; **8b**, 59796-82-6; **8c**, 59796-83-7; **8d**, 59796-84-8; **8e**, 59796-85-9; **11**, 59796-86-0; **12**, 59796-87-1; allyl bromide, 106-95-6; *anti*-7-bromo-*exo*-3-allyl-*endo*-3-methylbicyclo[2.2.1]heptan-2-one, 59796-88-2; thiophenol, 108-98-5; sativene, 6813-05-4; copacamphene, 16641-59-1.

## References and Notes

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(13) The simplest rationale to explain the failures of these alkylations is the steric hindrance offered by the syn bromo substituent. This would presumably increase O-alkylation, but should also have resulted in endo alkylation, which was not observed. The anti bromo compound corresponding to **8a** or **8b** is not expected to be more useful, since it could be expected[14] to undergo intramolecular alkylation.
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(22) References 1b–d.

# Celorbicol, Isocelorbicol, and Their Esters: New Sesquiterpenoids from *Celastrus orbiculatus*

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Esters of two new sesquiterpenoid polyalcohols—celorbicol (**1a**) and isocelorbicol (**2a**)—have been isolated from *Celastrus orbiculatus*. Structures of the parent alcohols have been established by x-ray crystallography, and those of the derived esters have been assigned by NMR spectroscopy. These compounds are structurally related to other polyesters and ester alkaloids from the Celastraceae, all of which are based on the dihydroagarofuran ring system.

In a previous paper,[1a] we reported the isolation of a series of sesquiterpenoid polyol esters from seeds of *Celastrus orbiculatus* (Celastraceae). In this present paper, we report the complete structural elucidation of the parent alcohols and present evidence for the structures of three of their naturally occurring esters.

The occurrence of sesquiterpenoid esters in the seed oil of *Celastrus paniculatus* was first suggested by Gunde and Hilditch in 1938.[2] Recently, several esters of this sesquiterpenoid group from various celastraceous genera have been characterized, including examples from *Celastrus*,[3,4] *Euonymus*,[5-10] *Maytenus*,[11] and *Catha*.[12,13] The parent alcohols of several of these esters have been characterized, including malkanguniol,[3,4] celapanol,[4] euonyminol,[5] isoeuonyminol,[5] evoninol,[5,7-9] alatol,[5e] maytol,[11] deoxymaytol,[11a] 8-epideoxymaytol,[8] 3,4-dideoxy-7$\beta$-hydroxymaytol,[8] and cathol.[12,13] Apparently, all of these alcohols have the same ring system, but they vary in the number, position, and configuration of hydroxyl substituents. This ring system[14] has been considered to be identical with that of $\beta$-dihydroagarofuran; however, the widely accepted stereochemistry of $\beta$-dihydroagarofuran has been questioned recently.[15] As isolated from their natural sources, the hydroxyl groups of these polyalcohols are acylated with acetic acid and various other carboxylic acids.[3-13] Since certain of these acyl groups contain nitrogen, some of the esters of this series are classed as alkaloids.[4-13]

**Isolation of Polyalcohols.** After alkaline hydrolysis of *Celastrus orbiculatus* seed oil, a neutral fraction was isolated which provided two isomeric polyalcohols—celorbicol (**1a**) and isocelorbicol (**2a**)[16]—when subjected to preparative TLC. Alcohols **1a** and **2a** are high-melting, crystalline solids with the empirical formula $C_{15}H_{26}O_4$, as shown by high-resolution mass spectra. Their ir spectra showed strong hydroxyl absorptions, but none for carbonyl groups. General features of the NMR and mass spectra of **1a, 2a,** and their various esters (vide infra) led us to infer that **1a** and **2a** are closely related to malkanguniol,[3] and that **1a** is a 1,6,9-trihydroxy derivative of the dihydroagarofuran system.[1a] The complete structure and stereochemistry of **1a** and **2a** were established subsequently by single crystal x-ray crystallography.

**X-Ray Crystallographic Analysis.** Celorbicol was converted to a mono-*p*-bromobenzoate derivative (**1f**) which was used to elucidate its absolute stereostructure by x-ray diffraction experiments. A computer-generated drawing of the final x-ray model is presented in Figure 1. Table I lists fractional coordinates for **1f**. Figure 1 clearly shows both of the cyclohexane rings in the chair conformation. The hydroxyl at C-1 is equatorial while the one at C-9 is axial. The C-14 and C-15 methyl groups are both axial. The absolute configuration we assign to this structure is the same as that previously reported by Sasaki and Hirata[6,17] for neoevonine. Bond distances and angles agree with generally accepted values and