Syntheses of the Insect Antifeedant (±)-Cinnamodial and the Drimane Sesquiterpenoids (±)-Isodrimenin and (±)-Fragrolide[1,2]

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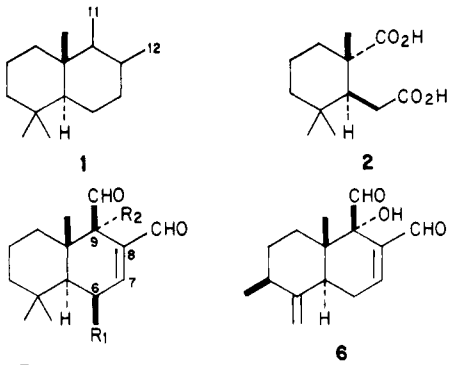
Total syntheses of (±)-cinnamodial (**5**), (±)-isodrimenin (**24**), and (±)-fragrolide (**29**) are described beginning from the diene **7**. Hydroboration–oxidation of **7** gave the trans-fused alcohol **18**, and elimination of mesylate **21**, followed by selective reduction at the more accessible ester function, led to γ-lactone **23**, which afforded **24** upon hydrogenation. A different route from **18** produced triol **27**, which was selectively oxidized at the more exposed primary alcohol to yield γ-lactone **28**. The latter, upon oxidation, furnished **29**. The synthesis of **5** hinged upon the construction of furan **38**, which was obtained from lactone **26** via **37** or, directly, by oxidation of **27**. Oxidation of **38** with lead tetraacetate gave **41**, which underwent elimination with DBU to provide **43**. Regio- and stereoselective epoxidation of this dienone gave **45** which, upon acidic methanolysis, led to **50**. Reduction of this ketone resulted in the 6β alcohol **51**, and exposure of this bis acetal to acid released the dialdehyde array of **52**. Finally, acetylation of **52** gave **5**.

Sesquiterpenes of the drimane family, named for their widespread occurrence in the stem bark of South American *Drimys* species,[3] contain the bicyclofarnesol nucleus **1**,



which is invariably oxidized at C-11 or C-12 and often at other sites as well.[4] A study by Wenkert and Strike explored a synthetic entry to this class via drimic acid (**2**), obtained from degradation of abietic or podocarpic acids.[5] Subsequently, others developed more versatile approaches which have led to syntheses of numerous members of the drimane group.[6]

Recently, interest in this family has been heightened with the discovery of drimanes, e.g., polygodial (**3**),[7] warburganal (**4**),[8] and cinnamodial (ugandensidial, **5**),[9] which

Scheme I

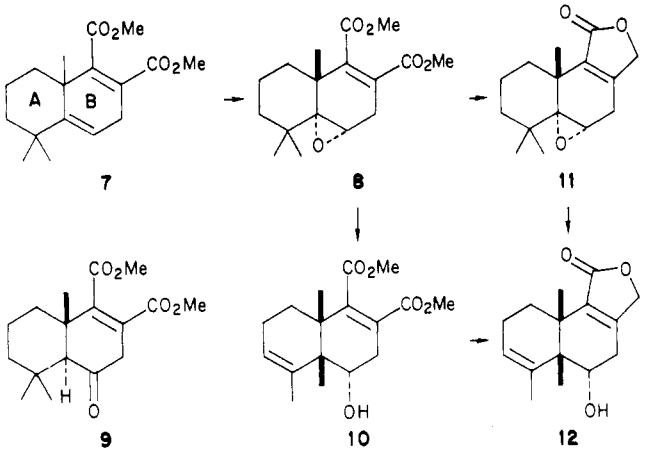


exhibit remarkable insect antifeedant activity.[10] A structural feature common to these antifeedants is the presence of a $\Delta^{7,8}$-ene-11,12-dialdehyde functionality which, in the more potent substances **4** and **5**, is further elaborated with a 9α-hydroxyl substituent. An analogous array is found in the rearranged drimane antifeedant muzigadial (**6**).[11]

Syntheses of **4**[12] have exploited a variety of methods for introducing the sensitive hydroxy ene–dialdehyde function; however, most of these do not readily lend themselves to inclusion of the 6β-acetoxy group required for **5**. In fact, only one synthesis, that of Oishi,[12c] has been extended from **4** to **5**, and this required a lengthy sequence for masking the 9-hydroxy 11,12-dial substructure while oxygen functionality was introduced at C-6.[13] Herein, we describe a

(1) This work is abstracted from the doctoral dissertation of L.P.J.B., Oregon State University, 1981.

(2) A preliminary account of this work has been published: Burton, L. P. J.; White, J. D. *J. Am. Chem. Soc.* **1983**, *103*, 3226.

(3) Overton, K. H.; Appel, H. H.; Bond, R. P. M. *Tetrahedron* **1963**, *19*, 635 and references cited.

(4) For a compendium of structures, see: Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds"; Academic Press: New York, 1973; Vol. 2, pp 154–156.

(5) Wenkert, E.; Strike, D. P. *J. Am. Chem. Soc.* **1964**, *86*, 2044.

(6) Heathcock, C. H. "The Total Synthesis of Natural Products"; ApSimon, J. W., Ed.; Wiley-Interscience: New York, 1973; Vol. 2, pp 338–333. Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. "The Total Synthesis of Natural Products"; ApSimon, J. W., Ed.; Wiley: New York, 1983; Vol. 5, pp 169–179.

(7) Ishiwatari, K.; Kawaguchi, R. *Yakugaku Zasshi* **1944**, *64*, 76. Ishikawa, S. *Sci. Rep. Soc. Res. Phys.-Chem.* **1962**, *8*, 567. Ohsuka, A. *J. Chem. Soc. Jpn.* **1962**, *83*, 757. Barnes, C. S.; Loder, J. W. *Aust. J. Chem.* **1962**, *15*, 322.

(8) Kubo, I.; Lee, Y.-W.; Pettei, M. J.; Pilkiewicz, F.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1976**, 1013.

(9) (a) Canonica, L.; Corbella, A.; Jommi, G.; Krepinsky, J. *Tetrahedron Lett.* **1967**, 2137. (b) Brooks, C. J. W.; Draffan, G. H. *Tetrahedron* **1969**, *25*, 2887. The latter authors, apparently unaware that **5** had been isolated previously from the Madagascar tree *Cinnamosa fragrans* Baillon, renamed the compound.

(10) Nakanishi, K.; Kubo, I. *Isr. J. Chem.* **1977**, *16*, 28. Ma, W.-C.; Kubo, I. *Entomol. Exp. Appl.* **1977**, *22*, 107.

(11) Kubo, I.; Miura, I.; Pettei, M. J.; Lee, Y.-W.; Pilkiewicz, F.; Nakanishi, K. *Tetrahedron Lett.* **1977**, 4553.

(12) (a) Ohsuka, A.; Matsukawa, A. *Chem. Lett.* **1979**, 635. (b) Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1979**, *101*, 4398. (c) Nakata, T.; Akita, H.; Naito, T.; Oishi, T. *J. Am. Chem. Soc.* **1979**, *101*, 4400. (d) Kende, A. S.; Blacklock, T. J. *Tetrahedron Lett.* **1980**, 3119. (e) Goldsmith, D. J.; Kezar, H. S. *Tetrahedron Lett.* **1980**, 3543. (f) Ley, S. V.; Mahon, M. *Tetrahedron Lett.* **1981**, 3909. (g) Wender, P. A.; Eck, S. L. *Tetrahedron Lett.* **1982**, *23*, 1871.

(13) Naito, T.; Nakata, T.; Akita, H.; Oishi, T. *Chem. Lett.* **1980**, 445.

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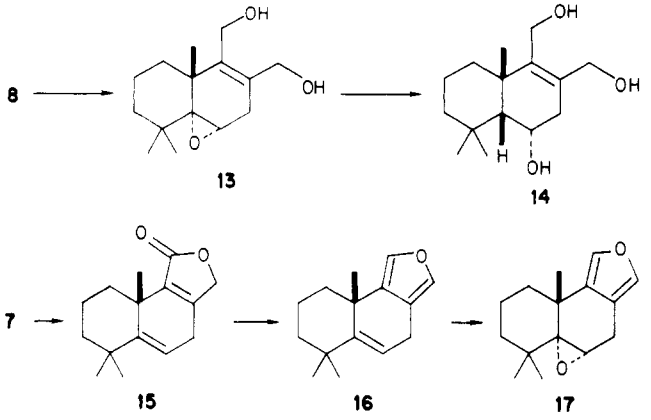
Scheme II



strategy for the synthesis of (±)-cinnamodial (**5**) which incorporates functionality at C-6 of the bicyclofarnesyl skeleton from the outset. A second, important element of our plan involves the use of a furan as a latent 1,4-dialdehyde function, which is unveiled near the termination of the sequence in conjunction with stereoselective introduction of the 9α-hydroxyl group. The flexibility inherent in this design is further expressed in syntheses of the natural drimanes fragrolide (**29**) and isodrimenin (**24**).

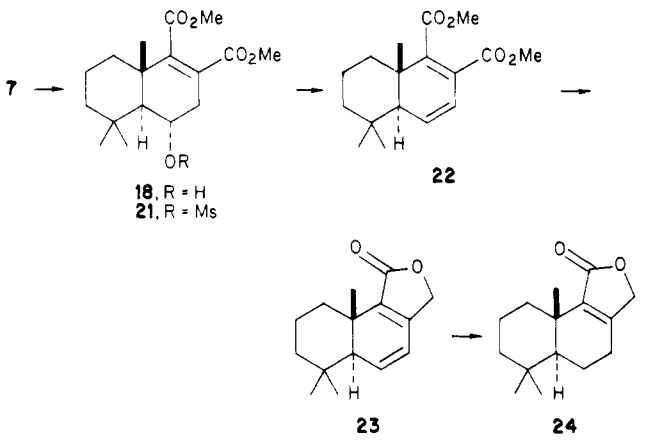
Results

The diene diester **7**[14] was selected as the starting point in our approach to the drimanes, since this readily available substance permits a high degree of variation in planning the oxidation level of the B ring. Our initial scheme for deploying an oxygen function at C-6 envisioned epoxidation of **7**, followed by an acid-catalyzed rearrangement to a ketone. However, although **7** reacted smoothly with *m*-chloroperbenzoic acid to give a single epoxide **8**, an exceptionally facile 1,2-methyl shift foiled the intended transformation of **8** to ketone **9** (Scheme I). Thus, the reaction of **8** with boron trifluoride etherate or with lithium perchlorate led in high yield to the alcohol **10**. An analogous skeletal reorganization, affording **12**, was observed with the epoxy lactone **11**, obtained from reduction of **8** with lithium aluminum hydride. The readiness with which this Wagner–Meerwein rearrangement occurs can be reconciled with a conformation for **8** and **11** which permits axial methyl migration in concert with opening of the oxirane.

In an attempt to suppress this rearrangement, **8** was reduced with aluminum hydride with the hope that this reagent would lead to a secondary α alcohol possessing a cis ring fusion;[15] subsequent epimerization to a trans decalin could be envisioned via a C-6 ketone. Unfortunately, the action of aluminum hydride on **8** resulted only in reduction of the ester functions to yield diol **13** (Scheme II). With a large excess of aluminum hydride and prolonged reaction times a very polar product, assumed to be triol **14**, could be seen, but this substance proved quite intractable when oxidation of the pair of allylic alcohol functions was attempted.

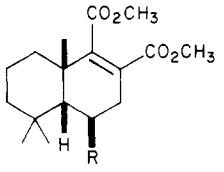
Modification of the ester groups in a more deliberate fashion was possible by careful reduction of **7** with either lithium aluminum hydride or diisobutylaluminum hydride. These reagents effected clean reduction of the less hindered ester function giving **15** (5,6-dehydroisodrimenin) in good yield after lactonization.[16] Further reduction of

Scheme III



the γ-lactone with diisobutylaluminum hydride produced the furan **16** in 86% yield.[17] Unfortunately, epoxidation of this olefin was accomplished in only 10% yield, and, to make matters worse, the resulting epoxide **17** could not be reduced to the desired 6-hydroxydrimane system.

At this point an alternative gambit for introducing oxygen functionality at C-6 via a hydroboration–oxidation sequence was considered (Scheme III). Our expectation, based upon examination of a Dreiding model of **7**, was that hydroboration at the C-5,6 double bond should take place preferentially from the α side, leading to a trans ring fusion. In fact, the reaction of **7** with diborane, followed by oxidation with basic hydrogen peroxide, yielded two alcohols in the ratio 95:5. However, our assumption that **18** was the major alcohol was confounded when Tanis and Nakanishi reported, in the course of their synthesis of **4**,[12b] that hydroboration–oxidation of **7** yielded **19**. No proof was offered for their assignment, but a plausible analogy was drawn between hydroboration and hydrogenation of **7**. The latter reaction is reported to give the cis-fused decalin **20**, a fact that we have confirmed. In view of this



19, R = OH
20, R = H

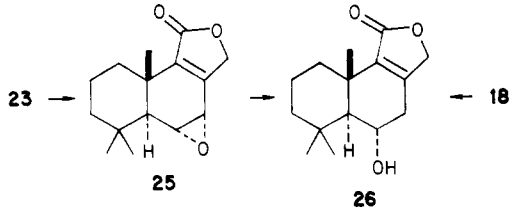
ambiguity, it was decided to establish the configuration of **18** beyond question by correlation with a substance of known stereochemistry, and, to this end, (±)-isodrimenin (**24**)[5] was selected as the point of reference.

The major alcohol **18** from hydroboration–oxidation of **7** was converted to its mesylate **21** which, upon exposure to 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), underwent elimination to give diene **22** in 79% yield. Reduction of **22** with diisobutylaluminum hydride, as in the case of **7**, produced a γ-lactone **23** (80%), which was hydrogenated over palladium-on-carbon to give a material **24** identical in all respects with an authentic sample of (±)-isodrimenin (**24**).[18] Our surmise that hydrogenation and hydroboration of **7** take place from opposite sides of the C-5,6 double bond was confirmed by hydrogenation of **15**, which did not yield **24** but rather its cis-fused stereoisomer.

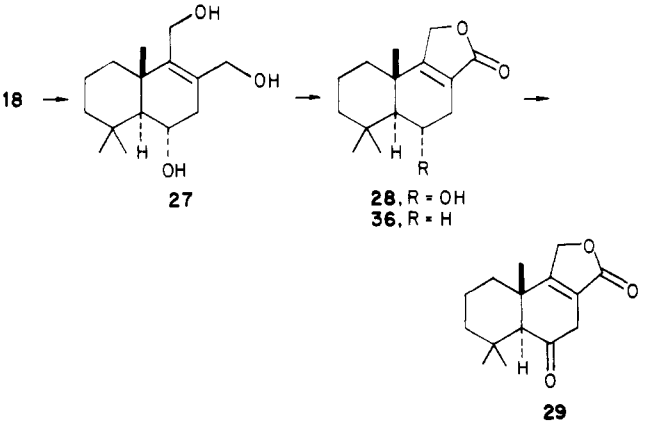
Although the correlation of **18** with isodrimenin appeared to remove any stereochemical doubt regarding the

(14) Loperfido, J. C. *J. Org. Chem.* **1973**, *38*, 399.
(15) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1968**, *90*, 2686.
(16) Gensler, W. J.; Bruno, J. J. *J. Org. Chem.* **1963**, *28*, 1254.
(17) Minato, H.; Nagasaki, T. *J. Chem. Soc. C* **1966**, 377.
(18) Akita, H.; Naito, T.; Oishi, T. *Chem. Lett.* **1979**, 1365.

Scheme IV



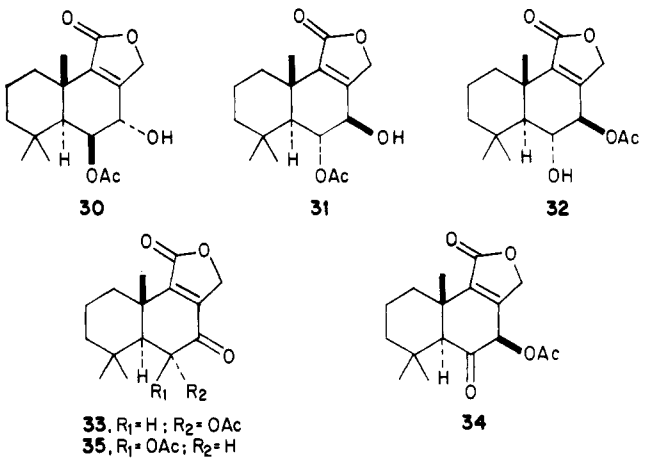
Scheme V



hydroboration of 7, there remained a remote chance that epimerization at the ring fusion might have occurred in the course of the transformation 21 → 23 with DBU. No trace of a second epimer (or nonconjugated diene isomer) of either 22 or 23 could be seen when these were subjected to DBU but, nevertheless, to remove the nagging possibility of an epimerization at C-5, a reverse correlation of 23 with 18 was carried out (Scheme IV). Epoxidation of 23 with *m*-chloroperbenzoic acid afforded a single product in 72% yield, and, based upon steric considerations again derived from examination of a Dreiding model, we presumed this epoxide to be 25. In any case, the configuration at C-6 was now independent of the ring fusion, which must be trans, since 23 had given isodrimenin upon reduction. When 25 was reduced with sodium borohydride in the presence of diphenyl diselenide,[19] the hydroxy lactone 26 was produced in quantitative yield. This same lactone was obtained in 85% yield upon reduction of 18 with diisobutylaluminum hydride, an identity which confirms the stereochemical integrity at C-5 throughout the correlation between 18 and isodrimenin. Thus, it is now clear that hydroboration of 7, in contrast to hydrogenation, takes place from the α side to give 18 after oxidation. These divergent stereochemical pathways probably reflect the fundamentally different constraints which steric effects impose upon hydroboration and hydrogenation. Protruding substituents, particularly axial methyl groups, generate severe compressional strain when highly branched ligands are packed around a relatively small boron atom, and the stereochemistry of hydroboration is therefore influenced to a greater extent by the orientation and bulk of substituents than by the overall molecular contour. For hydrogenation, however, the shape of the molecule plays a major role in determining the disposition of the substrate at the catalyst surface. The relatively flat diene ring of 7, fused to a chair cyclohexane, gives this molecule a convex surface on the upper side which favors attachment to the catalyst from this direction, axial methyl groups notwithstanding.

In principle, the hydroxy diester 18 affords a convenient means of access to a variety of drimane structures. Exemplifying this strategy, (±)-fragrolide (29) a drimane isolated from *Cinnamosma fragrans* possessing a γ-lactone orientation reversed from that of isodrimenin (24),[20] was synthesized in three steps from 18 (Scheme V). Reduction of the latter with an excess of diisobutylaluminum hydride gave triol 27 which, without purification, was subjected to manganese dioxide. As with the regioselective reduction of 18, the more exposed allylic alcohol of 27 was oxidized preferentially, resulting in lactone 28. This substance was further oxidized with pyridinium chlorochromate[21] to give 29 in an overall 47% yield from 18. Although we were unable to secure a sample of natural fragrolide, (±)-29 possessed physical and spectroscopic properties in agreement with those reported by Canonica et al. for this compound.[20,22]

The drimane ugandensolide, isolated along with 5 from *Warburgia ugandensis*,[9b] has been shown to possess stereostructure 30 which, we believed, should be accessible from epoxide 25. However, when 25 was treated with acetic acid containing sodium acetate, two hydroxy acetates were obtained, neither of which corresponded to 30. The structures of these materials were deduced as 31 and 32 from their oxidation with pyridinium chlorochromate to 33 and 34, respectively. Also, 33 was clearly stereoisomeric with a keto acetate 35 reported previously.[9b] From these results, it is clear that the epoxide function in 25 undergoes fission of the allylic C–O bond rather than the desired trans, (pseudo)diaxial opening.

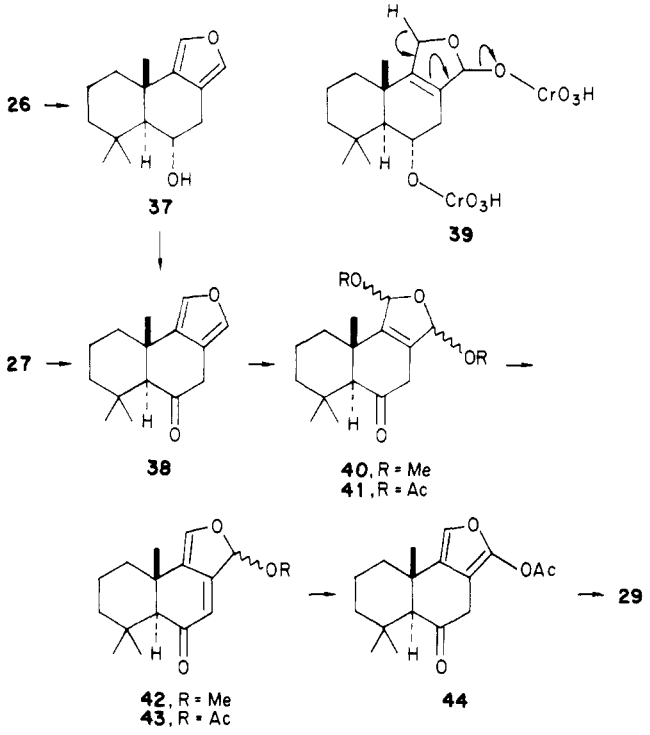


Although Oishi et al.,[18] in the course of their syntheses of isodrimenin (24) and confertifolin (36), had demonstrated that a furan ring can provide a latent version of the γ-lactone moieties in these drimanes, extrapolation of this approach to construction of the dialdehyde functions of 3–5 had not been explored. The possibility of employing a furanoid precursor for elaborating the B ring functionality of cinnamodial was especially appealing in that an oxygen substituent (ketone) at C-6 could assist placement of the 7,8 double bond as well as installation of the 9α-hydroxyl group.

Accordingly, the lactone 26, from reduction of 18, was further reduced with a limited quantity of diisobutylaluminum hydride, giving the furan 37 in 43% yield, along with recovered starting material. The alcohol 37 was readily oxidized to 38, but the relative inefficiency of the conversion 26 → 37 (which required *less* than the stoichiometric quantity of diisobutylaluminum hydride),

(19) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
(20) Canonica, L.; Corbella, A.; Gariboldi, P.; Jommi, G.; Krepinsky, J.; Ferrari, G.; Casagrande, C. *Tetrahedron* **1969**, *25*, 3903.
(21) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(22) For a different synthesis of 29, see: Akita, H.; Oishi, T. *Tetrahedron Lett.* **1978**, 3733.

Scheme VI

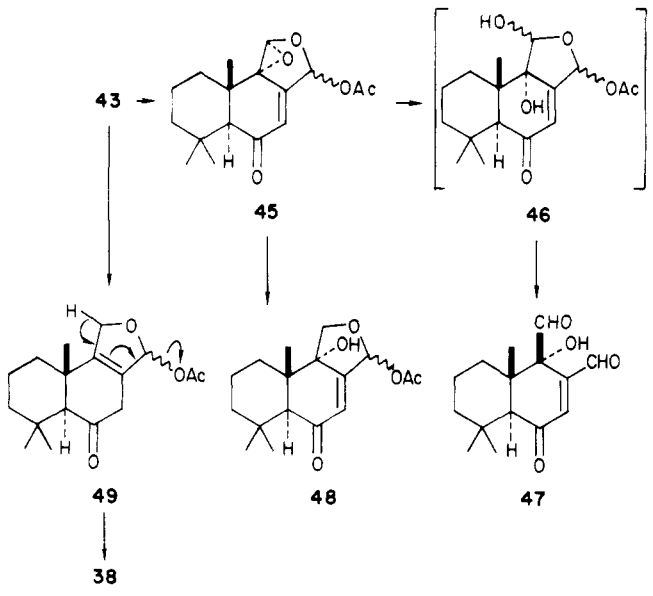


prompted us to search for an alternative route to **38**. This was forthcoming from the triol **27**, which was found to undergo a pleasing transformation directly to **38** (68%) upon oxidation with pyridinium chlorochromate. Although the precise sequence of events in this multiple oxidation has not been elucidated, a plausible pathway proceeds via 1,4-elimination from the chromium(VI) ester **39**.

Our plan at this juncture called for oxidation of furan **38** to a 1,4-dialkoxydihydrofuran and then a conjugate elimination to generate a dienone, in which the 9α-hydroxyl group could be sited. Treatment of **38** with bromine–methanol gave the expected dimethoxy derivative **40** (as an epimeric mixture)[23] in 94% yield, but, to our disappointment, this system failed to yield a trace of the dienone **42** upon exposure to a variety of bases. Fortunately, this difficulty was circumvented with the diacetate **41**, which was obtained in 90% yield by oxidation of **38** with lead tetraacetate and which underwent a smooth transformation to **43** (70%) upon brief treatment with 1 equiv of DBU. The elimination of acetic acid from **41** proved to be critically dependent on reaction conditions since longer contact with base produced very little **43** but, instead, yielded (±)-fragrolide (**29**) as the major product (ca. 72%). The probable precursor of **29** in this sequence is the acetoxyfuran **44**, which would result from a base-promoted double-bond isomerization in **43**; hydrolysis of the labile acetoxyfuran during acidic workup of the mixture would lead directly to the α,β-unsaturated γ-lactone of **29**. This serendipitous synthesis of fragrolide, although longer than that shown in Scheme V, is of comparable overall efficiency (ca. 45% from **27**).

With **43** in hand, it was anticipated that epoxidation would occur preferentially at the more nucleophilic γ,δ-unsaturation[24] and from the less obstructed α face of the π system, as shown in Scheme VII. In practice, the sensitive dienone **43** was epoxidized promptly with *m*-chloroperbenzoic acid in the presence of sodium carbonate, resulting in 91% yield of **45** which, from its NMR spectrum, was clearly an epimeric mixture *only at the center bearing the acetoxy substituent*. The stability of this epoxide towards silica gel chromatography—the two epimers could be cleanly separated by this means–is somewhat puzzling, given the known propensity of alkoxy epoxides toward ring opening.[25] Whether this is due to the presence of the α,β-unsaturated ketone diminishing the reactivity of the oxirane toward electrophilic attack, or to some other factor, is not known. In any event, acidification of **45** with 5% hydrochloric acid resulted in epoxide hydrolysis and concomitant unmasking of the dialdehyde to furnish a single product **47** (6-oxowarburganal), via elimination of acetic acid from the transient tetrahydrofuran **46**.

Scheme VII

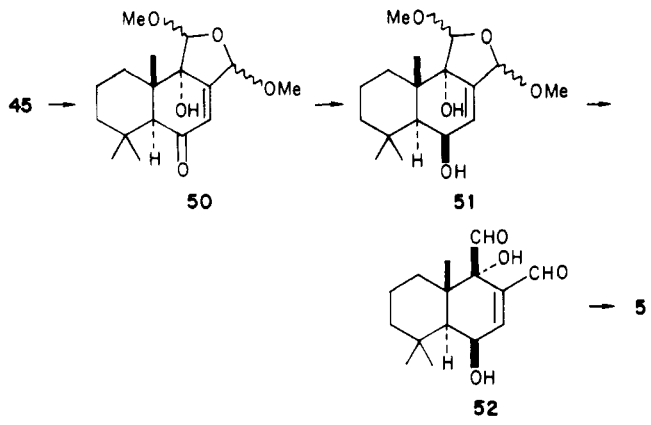


Although the successful outcome of our construction of the hydroxy dialdehyde array of **47** was encouraging, it was recognized that a modification to this scheme would be needed for synthesis of **5**, since we foresaw no means of converting the C-6 ketone into the desired β-acetoxy substituent without masking the aldehyde functions. The simple expedient employed for reduction of ketones in the presence of aldehydes, which hinges on the more facile hydration of the latter in the presence of cerium(III) chloride,[26] failed completely with **47** and attempts to reduce the 6-keto group at an earlier stage in the sequence went equally unrewarded. The sole product from **45** and lithium tri-*tert*-butoxyhydridoaluminate was **48**, derived from reduction of the epoxide, while the action of L-Selectride on **43** produced the furan **38**, presumably via 1,6-hydride addition followed by elimination of acetic acid from **49**.

The fact that both of these deviant pathways originated from hydride attack at C-11 indicated that, for the desired reduction at C-6 to be successful, the vulnerability of C-11 toward hydride must be removed. This was conveniently accomplished, as shown in Scheme VIII, by opening the epoxide of **45** with methanol in the presence of an acidic catalyst, which simultaneously replaced the acetoxy function to give **50**. With the dialdehyde moiety now

(23) Elming, N. "Advances in Organic Chemistry. Methods and Results"; Raphael, R. A., Taylor, E. C., Wynberg, H., Eds.; Interscience: New York, 1960; Vol. 2, p 67.
(24) Fukuyama, Y.; Kirkemo, C. L.; White, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 646.
(25) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972; p 314.
(26) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

Scheme VIII



suitably protected, **50** was reduced with diisobutylaluminum hydride to furnish a single alcohol **51** in quantitative yield. The high stereoselectivity associated with reduction of the keto function here is readily explained by steric obstruction of the β face of this ketone by the axial methyl substituents, forcing hydride delivery from the equatorial direction. However, it is also possible that the 9α-hydroxyl appendage serves to direct hydride attack by coordination with the reducing reagent. In any event, **51** underwent clean hydrolysis with dilute hydrochloric acid to give **52** (92% based on **50**). As expected, the sterically encumbered, axial alcohol of **52** was slow to undergo acetylation but, with acetic anhydride in the presence of a catalytic quantity of 4-(dimethylamino)pyridine, (±)-cinnamodial (**5**) was produced in 81% yield. This material was identical in all respects with a sample of (±)-**5** kindly provided by Dr. T. Oishi.

Experimental Section

Melting points are uncorrected. Infrared spectra (IR) were obtained with a Perkin-Elmer 727B infrared spectrometer. Nuclear magnetic resonance spectra (NMR) were obtained with either a Varian EM-360A, HA-100, or FT-80A spectrometer and are reported in δ units with tetramethylsilane (Me_4Si) as the internal standard; the abbreviations s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b s = broad singlet are used throughout. Mass spectra (MS) were obtained on a Varian MAT CH-7 spectrometer. Exact mass determinations were performed on a CEC-110C spectrometer at an ionization potential of 70 eV. Column chromatography was performed by using neutral silica gel (Activity II–III). Analytical and preparative thin-layer chromatography (TLC) plates were obtained from Analtech. Dry tetrahydrofuran (THF) and dry ether were obtained by distillation over sodium benzophenone ketyl. Other solvents were purified by using standard procedures. All organic solutions were dried over magnesium sulfate and filtered prior to rotary evaporation at water aspirator pressure. Residual solvent was removed under vacuum, usually at less than 0.2 torr. All reactions were routinely carried out under an inert atmosphere of argon or nitrogen.

(1aα,4aβ,8aα)-2,4a,5,6,7,8-Hexahydro-3,4-bis(methoxycarbonyl)-4a,8,8-trimethyl-1a*H*-naphth[8a,1-*b*]oxirane (8). A 40-mg (0.20-mmol) portion of 85% *m*-chloroperbenzoic acid was added to a stirred solution of **7** (40 mg, 0.14 mmol) in 5 mL of methylene chloride. After 4 h, the solution was diluted with ether (10 mL), washed with 10% aqueous sodium sulfite and with saturated sodium bicarbonate, then dried, and concentrated. Purification by column chromatograpy (10% ethyl acetate/*n*-hexane) provided 42 mg (99%) of **8** as a colorless solid: mp 111–114 °C; IR (Nujol) 1710, 1260 cm^{-1}; NMR (CCl_4) δ 3.66 (s, 6 H), 3.20 (b s, 1 H), 3.09 (dd, 1 H, J = 20, 3 Hz), 2.43 (dd, 1 H, J = 20, 2.5 Hz), 1.41 (s, 3 H), 1.18 (s, 3 H), 0.78 (s, 3 H); MS, *m/e* (relative intensity) 308 (9.6, M$^+$), 277 (25), 221 (51), 161 (67), 123 (100); exact mass 308.162 (calcd for $C_{17}H_{24}O_5$, 308.162).

Dimethyl (4aα,4aβ,8aβ)-4a,5,8a-Trimethyl-4-hydroxy-3,4,4a,7,8,8a-hexahydronaphthalene-1,2-dicarboxylate (10). In a thick-walled tube, 1 mL of benzene, 20 mg (0.065 mmol) of **8**, and a catalytic amount of lithium perchlorate were combined, sealed under reduced pressure, and heated in an oil bath to 150 °C for 44 h. After being cooled, the contents were combined with 10 mL of ether, washed with water and with saturated aqueous sodium chloride, dried, and concentrated. Purification by TLC yielded 19 mg (95%) of **10** as an oil: IR (neat) 3500, 1708, 1615 cm^{-1}; NMR (CCl_4) δ 5.72 (m, 1 H), 3.80 (b d, 1 H, J = 3.5 Hz, collapses to singlet on irradiation at δ 2.54), 3.70 (s, 3 H), 3.68 (s, 3 H), 2.54 (d, 2 H, J = 3.5 Hz, collapses to a singlet on irradiation at δ 3.82), 1.72 (b s, 3 H), 0.96 (s, 3 H), 0.93 (s, 3 H); MS, *m/e* (relative intensity) 308 (13, M$^+$), 258 (25), 244 (61), 253 (70), 215 (40), 199 (53), 122 (84), 107 (86), 91 (97), 59 (87), 43 (95), 41 (100); exact mass 308.165 (calcd for $C_{17}H_{24}O_5$, 308.162).

(5aα,6aα,10β)-(±)-5,6-Oxyisodrimen (11). A 25-mg (0.62-mmol) portion of 95% lithium tetrahydridoaluminate was added to a stirred solution of 195 mg (0.63 mmol) of **8** in 10 mL of dry ether. After being refluxed for 1 h, the solution was cooled, quenched with 25 mL of water, and acidified with sufficient 5% hydrochloric acid to disperse the emulsion before extraction with ether. The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried, and concentrated to yield 147 mg of a residue which gave 87 mg (55%) of **11** as an oil after column chromatography (ethyl acetate): IR (Nujol) 1730, 1240 cm^{-1}; NMR ($CDCl_3$) δ 4.63 (s, 2 H), 3.49 (m, 1 H), 2.84 (m, 2 H), 2.63 (m, 1 H), 1.40 (s, 3 H), 1.28 (s, 3 H), 0.88 (s, 3 H); MS, *m/e* (relative intensity) 248 (69, M$^+$), 220 (61), 192 (58), 177 (59), 162 (67), 119 (63), 105 (68), 91 (100), 77 (63); exact mass 248.141 (calcd for $C_{15}H_{20}O_3$, 248.141).

(4aα,4aβ,8aβ)-3,4,4a,7,8,8a-Hexahydro-4a,5,8a-trimethyl-4-hydroxy-2-(hydroxymethyl)-1-naphthoic Acid γ-Lactone (12). To a stirred solution of 21 mg (0.085 mmol) of **11** in 1 mL of methylene chloride, cooled in an ice bath, was added 0.1 mL of boron trifluoride etherate. After 20 min, the reaction mixture was diluted with 10 mL of ether, washed with saturated aqueous sodium bicarbonate, dried, and concentrated. The residue was purified by preparative TLC (100% ethyl acetate) to yield 14 mg (67%) of **12** as an oil: IR (neat) 3450, 1740, 1660 cm^{-1}; NMR ($CDCl_3$) δ 5.83 (m, 1 H), 4.67 (b s, 2 H), 4.06 (m, 2 H), 2.56 (b s, 2 H), 1.75 (b s, 3 H), 1.24 (s, 3 H), 0.91 (s, 3 H); exact mass 248.140 (calcd for $C_{15}H_{20}O_3$, 248.141).

(1aα,4aβ,8aβ)-2,4a,5,6,7,8-Hexahydro-3,4-bis(hydroxymethyl)-4a,8,8-trimethyl-1a*H*-naphth[8a,1-*b*]oxirane (13). To a stirred solution of 325 mg (1.06 mmol) of **8** in 3 mL of dry ether was added 60 mg (1.5 mmol) of 95% lithium tetrahydroaluminate, and the mixture was refluxed for 1 h. To the cooled slurry were added 30 mL of ether and 25 mL of water, together with a few drops of 10% hydrochloric acid (to break emulsion). The aqueous layer was separated and extracted with ether. The combined organic layers were dried and concentrated to give 250 mg (94%) of fairly pure **13**. A small sample was purified by preparative TLC (ethyl acetate): IR (neat) 3350, 970 cm^{-1}; NMR ($CDCl_3$) δ 3.84–4.44 (m, 4 H), 3.35 (m, 1 H), 3.15 (b s, 2 H, exchangeable with D_2O), 2.7 (dd, 1 H, J = 2.5, 20 Hz), 2.55 (b d, 1 H, J = 20 Hz), 1.19 (s, 3 H), 1.18 (s, 3 H), 0.80 (s, 3 H); exact mass 252.173 (calcd for $C_{15}H_{24}O_3$, 252.173).

5,6-Dehydroisodrimenin (15). To a stirred solution of 230 mg (0.79 mmol) of **7** in 5 mL of dry ether, cooled to 0 °C, was added 19 mg (0.48 mmol) of 95% lithium tetrahydridoaluminate. The slurry was warmed and refluxed for 45 min. After being cooled, the mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ether. The organic layers were dried and concentrated, and the residue was purified by column chromatography (15% ether/*n*-hexane) to afford 84 mg (60%) of **15** as a colorless solid: mp 112–114 °C: IR (Nujol) 1740 cm^{-1}; NMR (CCl_4) δ 6.54 (b t, 1 H, J = 3.5 Hz), 4.55 (s, 2 H), 2.93 (d, 2 H, J = 3.5 Hz), 2.61 (dm, 1 H, J = 14 Hz, collapses to a m on irradiation at δ 1.26), 1.38 (s, 3 H), 1.20 (s, 3 H), 1.10 (s, 3 H); MS, *m/e* (relative intensity) 232 (11, M$^+$), 217 (77), 175 (31), 161 (69), 147 (20); exact mass 232.147 (calcd for $C_{15}H_{20}O_3$, 232.146).

4,6,7,8,9,9a-Hexahydro-6,6,9a-trimethylnaphtho[1,2-*c*]furan (16). To a stirred solution of 50 mg (0.22 mmol) of **15** in 5 mL of dry toluene, cooled in a dry ice/acetone bath, was added 0.23 mL of a 1 M solution of DIBAL in *n*-hexane. After 3 h, the reaction was quenched with 10 mL of saturated sodium bicarbonate and extracted with ether. The organic layer was washed with saturated aqueous sodium chloride, dried, and concentrated

to give a yellow oil which was chromatographed (hexane) to yield 40 mg (86%) of **16** as a colorless oil: IR (neat) 2900, 1450 cm^{-1}; NMR (CCl_4) δ 7.03 (s, 2 H), 5.76 (m, 1 H), 3.11 (m, 2 H), 1.32 (s, 3 H), 1.20 (s, 3 H), 1.12 (s, 3 H); MS, *m/e* (relative intensity) 216 (65, M^+), 202 (14), 201 (100), 184 (16), 183 (99), 159 (19), 155 (45), 145 (62), 131 (67).

(5α,5aα,9aβ)-4,5,5a,6,7,8,9,9a-Octahydro-6,6,9a-trimethyl-5,5a-epoxynaphtho[1,2-*c*]furan (17). To a stirred solution of 120 mg (0.79 mmol) of **16** in 5 mL of methylene chloride was added 190 mg (20% excess) of 85% *m*-chloroperbenzoic acid. After 1 h, 1 mL of 10% aqueous sodium sulfite was added, and the mixture was extracted with ether. The combined ether extracts were dried and concentrated to a residue which was chromatographed (10% ether/*n*-hexane ether) to yield 24 mg (10%) of **17** as an oil: IR (neat) 2900, 1460 cm^{-1}; NMR (CCl_4) δ 6.99 (b s, 1 H), 6.95 (s, 1 H), 3.21 (m, 1 H), 3.15 (dd, 1 H, J = 18, 3.5 Hz), 2.76 (dm, 1 H, J = 18 Hz), 1.34 (s, 3 H), 1.21 (s, 3 H), 0.80 (s, 3 H); MS, *m/e* (relative intensity) 232 (100, M^+), 217 (31), 199 (25), 189 (34), 176 (20), 163 (24), 161 (22), 147 (24), 133 (25), 119 (26), 91 (37); exact mass 232.146 (calcd for $C_{15}H_{20}O_2$, 232.146).

Dimethyl (4α,4aα,8aβ)-5,5,8a-Trimethyl-4-hydroxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylate (18). To a stirred solution of 1.00 g (3.4 mmol) of **7** in 0.5 mL of dry THF, cooled in an ice bath, was added 4.5 mL of 1 M diborane/THF (4.5 mmol) over 0.5 h. The solution was allowed to warm to room temperature and stirred for 1.5 h. Carefully, 0.2 mL of water was added. When the effervescence had subsided, the solution was again cooled in an ice bath. A 0.6-mL portion of 3 M sodium hydroxide was added rapidly, followed by dropwise addition of 0.4 mL of 30% hydrogen peroxide. Again the solution was allowed to warm to room temperature and stirred. When 3 h had elapsed, the solution was diluted with distilled water and extracted with ether. The combined organic layers were dried, concentrated, and chromatographed (15% ethyl acetate/*n*-hexane) to yield 660 mg (62%) of **18** as an oil: IR (neat) 3500, 1710 cm^{-1}; NMR ($CDCl_3$) δ 4.24 (m, 1 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 2.90 (dd, 1 H, J = 6.5, 18 Hz), 2.38 (dd, 1 H, J = 8, 18 Hz), 1.28 (s, 3 H), 1.18 (s, 3 H), 1.08 (s, 3 H); MS, *m/e* (relative intensity) 310 (0.9, M^+), 41 (100); exact mass 292.168 ($M^+ - H_2O$, calcd for $C_{17}H_{24}O_4$, 292.167).

Dimethyl *trans*-5,5,8a-Trimethyl-4a,5,6,7,8,8a-hexahydronaphthalene-1,2-dicarboxylate (22). To a stirred solution of 550 mg (1.77 mmol) of **18** in 9 mL of pyridine was added dropwise 405 mg (3.5 mmol) of mesyl chloride. After 4.5 h, the solution was poured into 100 mL of ether, washed with 100 mL of saturated aqueous copper sulfate and with 50 mL of saturated aqueous sodium chloride, then dried, and concentrated to an oil. This was chromatographed (8% ethyl acetate/benzene) on silica gel to yield 550 mg (80%) of **21** as an oil: IR (neat) 1710, 1325, 1160 cm^{-1}; NMR ($CDCl_3$) δ 5.23 (m, 1 H), 3.82 (s, 3 H), 3.75 (s, 3 H), 1.30 (s, 3 H), 1.10 (s, 6 H); MS, *m/e* (relative intensity) 388 (0.5, M^+), 357 (6.6), 233 (100).

A solution of the crude mesylate **21** and 229 mg (1.50 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 20 mL of dry benzene was refluxed for 22 h. The solution was combined with 50 mL of ether, washed with water and with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated to yield 413 mg (98%) of a mixture of **22** and **7** in a ratio of 8:2, respectively. These isomers were separated by chromatography (10% ethyl acetate/benzene) to give pure **22**: IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 6.45 (dd, 1 H, J = 3, 10 Hz, collapses to a d on irradiation at δ 2.18), 6.04 (dd, 1 H, J = 2.5, 10 Hz, collapses to a d on irradiation at δ 2.18), 3.82 (s, 3 H), 3.75 (s, 3 H), 2.18 (m, 3 H), 1.13 (s, 3 H), 0.99 (s, 3 H), 0.96 (s, 3 H); MS, *m/e* (relative intensity) 292 (6.8, M^+), 2.61 (15), 233 (70), 162 (100); exact mass 292.170 (calcd for $C_{17}H_{24}O_4$, 292.167).

6,7-Dehydroisodrimenin (23). To a stirred solution of 111 mg (0.38 mmol) of **22** in 5 mL of dry THF was added 76 mg of 95% lithium tetrahydridoaluminate. After 2 h, the reaction was quenched with water and extracted with ethyl acetate. The organic layers were dried and concentrated to a residue which was chromatographed (10% ethyl acetate/*n*-hexane) to give 71 mg (80%) of **23** as a colorless solid: mp 102–104 °C; IR (Nujol) 1740 cm^{-1}; NMR ($CDCl_3$) δ 6.92 (dd, 1 H, J = 2.5, 10 Hz), 6.24 (dd, 1 H, J = 3, 10 Hz), 4.73 (s, 2 H), 2.52 (dm, 1 H, J = 10 Hz, collapses to a m on irradiation at δ 1.48), 2.24 (dd, 1 H, J = 3, 2.5 Hz), 1.04 (s, 3 H), 0.99 (s, 6 H); MS, *m/e* (relative intensity) 232 (15, M^+), 161 (18), 149 (35), 91 (16), 61 (25), 59 (21), 43 (100), 29 (77); exact mass 232.145 (calcd for $C_{15}H_{20}O_2$, 232.146).

(±)-Isodrimenin (24). To a stirred slurry of 4.0 mg of prehydrogenated 5% palladium on carbon in 5 mL of ethyl acetate under a hydrogen atmosphere was added 20 mg (0.086 mmol) of **23**. After 1 h, the slurry was filtered (Celite). Concentration of the filtrate yielded an oil which crystallized upon addition of *n*-hexane to give 20 mg (100%) of **24**: mp 89–90 °C (sublimed sample mp 91–92 °C); IR (Nujol) 1740 cm^{-1}; NMR ($CDCl_3$) δ 4.57 (s, 2 H), 2.57 (dm, 1 H), 2.37 (m, 2 H), 1.15 (s, 3 H), 0.93 (s, 3 H), 0.90 (s, 3 H); MS, *m/e* (relative intensity) 234 (38, M^+), 220 (15), 219 (100), 153 (19), 151 (48), 123 (26); exact mass 234.161 (calcd for $C_{15}H_{22}O_2$, 234.162).

6,7α-Epoxyisodrimenin (25). A stirred solution of 340 mg (1.5 mmol) of **23** in 15 mL of methylene chloride containing 500 mg (2.5 mmol) of 85% *m*-chloroperbenzoic acid and 4 mg of 4-methyl-2,6-di-*tert*-butylphenol was heated to 90 °C. After 2 h, 100 mL of ether was added to the cooled solution. The organic layer was washed with 10% aqueous sodium sulfite and saturated aqueous sodium bicarbonate and was dried and concentrated to an oil. This was chromatographed (40% *n*-hexane/ether) to yield 260 mg (72%) of **25**: IR (neat) 1750 cm^{-1}; NMR ($CDCl_3$) δ 4.85 (s, 2 H), 3.46 (m, 2 H), 2.48 (dm, 1 H), 1.20 (s, 3 H), 1.11 (s, 6 H); MS, *m/e* (relative intensity) 248 (11, M^+), 233 (10), 91 (36), 41 (66), 28 (41), 18 (100), 17 (55); exact mass 248.141 (calcd for $C_{15}H_{20}O_3$, 248.141).

6α-Hydroxyisodrimenin (26). (a) From 18. To a stirred solution of 1.0 g (3.2 mmol) of **18** in 19 mL of dry toluene, cooled in a dry ice–acetone bath, was added dropwise 9.6 mL of 1 N DIBAL in *n*-hexane. After 1.5 h, the reaction was quenched with water and allowed to warm to room temperature before adding 50 mL of 30% aqueous potassium sodium tartrate. The mixture was extracted with ethyl acetate, and the organic layers were dried and concentrated to a residue which was chromatographed (15% ethyl acetate/benzene) to yield 680 mg (85%) of **26** as an oil: IR (neat) 3300, 1730 cm^{-1}; NMR ($CDCl_3$) δ 4.58 (s, 2 H), 4.32 (m, 1 H), 2.78 (dd, 1 H, J = 18, 5 Hz), 2.36 (dd, 1 H, J = 18, 8 Hz), 1.95 (b s, 1 H), 1.20 (s, 6 H), 1.10 (s, 3 H); exact mass 250.156 (calcd for $C_{15}H_{20}O_3$, 250.157).

(b) From 25. To a stirred solution (yellow) of 37 mg (0.12 mmol) of diphenyl diselenide in 0.5 mL of absolute ethanol was added carefully 9.5 mg (0.25 mmol) of sodium borohydride. To this now colorless solution was added 50 mg (0.2 mmol) of **25** in 0.5 mL of ethanol. After 3 h, the solution was treated with 0.5 mL of THF and 0.2 mL of 30% hydrogen peroxide, which caused a colorless precipitate to form. After 6.5 h, 15 mL water was added and the mixture was extracted with ether. The organic layers were washed with saturated aqueous sodium bicarbonate, dried, and concentrated to give 50 mg of **26**, identical with material isolated from **18**.

(±)-Fragrolide (29). (a) From 18. To a stirred solution of 600 mg (2.4 mmol) of **18** in 15 mL of dry THF, cooled in a salt–ice bath, was added dropwise 15 mL of 1 N DIBAL in *n*-hexane. After 2 h, the mixture was quenched with water, and 50 mL of 10% aqueous potassium sodium tartrate was added. Extraction with ethyl acetate, followed by drying and concentration of the organic layers, gave 440 mg of triol **27**. Without purification, a 315-mg portion of this material was redissolved in 15 mL of ether and stirred with 2.5 g of activated manganese dioxide over 4 days. The slurry was filtered (Celite) and concentrated to give 170 mg of **28** which, without purification, was redissolved in 2.5 mL of methylene chloride and added to a stirred slurry of 1.0 g of pyridinium chlorochromate in 25 mL of methylene chloride. After 1 h, the slurry was poured into 50 mL of ether and filtered (Florisil). The filtrate was concentrated to a residue which was chromatographed (25% ether/*n*-hexane) to provide 163 mg (47%) of **29**: mp 136–138 °C; IR (Nujol) 1760, 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 5.84 (t, 2 H, J = 2 Hz), 3.06 (m, 2 H), 2.44 (s, 1 H), 1.30 (s, 3 H), 1.18 (s, 3 H), 1.03 (s, 3 H); MS, *m/e* (relative intensity) 248 (M^+, 100), 233 (64), 205 (23), 165 (32), 123 (24), 121 (32), 105 (26), 91 (32), 83 (48), 55 (34), 41 (50); exact mass 248.140 (calcd for $C_{15}H_{20}O_3$, 248.141).

(b) From 41. To a stirred solution of 50 mg (0.14 mmol) of **41** in 1 mL of THF was added 85 mg (4 equiv) of 1,5-diazabicyclo[5.4.0]undec-5-ene. After 3 h, the solution was filtered through

silica gel, and the filtrate was concentrated to give 30 mg (72%) of **41**, identical with material prepared from **18**.

6-Acetoxy-7-oxoisodrimenin (33) and 6-Oxo-7-acetoxyisodrimenin (34). A 30-mg (0.12 mmol) sample of **25** was stirred in 1 mL of glacial acetic acid at 80 °C for 24 h. The cooled solution was neutralized with satured aqueous sodium bicarbonate and extracted with ethyl acetate. The extract was dried and concentrated to an oil. Preparative layer chromatography (25% ethyl acetate/*n*-hexane) of this residue provided 20 mg of a mixture of products. The mixture was treated with a slurry of 100 mg of pyridinium chlorochromate in 2 mL of methylene chloride for 3 h. The slurry was poured into 21 mL of ether, filtered (Celite), and concentrated. The resulting oil was chromatographed (25% ethyl acetate/benzene) to yield 6 mg each of **33** and **34**. **33**: R_f 0.37 in 10% ethyl acetate/benzene; IR (neat) 1750 cm^{-1}; NMR ($CDCl_3$) δ 5.78 (d, 1 H, J = 13 Hz), 4.86 (s, 2 H), 2.27 (d, 1 H, J = 13 Hz), 2.12 (b s, 3 H), 1.45 (s, 3 H), 1.08 (s, 3 H), 1.03 (s, 3 H); MS, m/e (relative intensity) 306 (9.4, M^+), 264 (28), 247 (34), 43 (100), 41 (28); exact mass 306.146 (calcd for $C_{17}H_{22}O_5$, 306.147). **34**: R_f 0.24 in 10% ethyl acetate/benzene; IR (neat) 1750 cm^{-1}; NMR ($CDCl_3$) δ 5.78 (d, 1 H, J = 1 Hz), 4.71 (b s, 2 H), 2.63 (s, 1 H), 2.22 (s, 3 H), 1.32 (s, 3 H), 1.20 (s, 1 H), 0.96 (s, 3 H); MS, m/e (relative intensity) 306 (42, M^+), 264 (46), 235 (13), 96 (13), 91 (13), 83 (19), 69 (15), 55 (19), 43 (100), 41 (25); exact mass 306.149 (calcd for $C_{17}H_{22}O_5$, 306.147).

(5α,5aα,9aβ)-4,5,5a,6,7,8,9,9a-Octahydro-5-hydroxy-6,6,9a-trimethylnaphtho[1,2-*c*]furan (37). To a stirred solution of 650 mg (2.6 mmol) of **26** in 60 mL of dry toluene, cooled in a dry ice–acetone bath, was added 6 mL of 1 N DIBAL in *n*-hexane. The reaction mixture was allowed to warm to −20 °C. After 1 h, the solution was quenched with 100 mL of 15% aqueous potassium sodium tartrate and extracted with ethyl acetate. The organic layer was dried and concentrated to an oil which was chromatographed (70% ether/*n*-hexane) to yield 306 mg (43%) of **37** as a pale yellow oil: IR (neat) 3350 cm^{-1}; NMR (CCl_4) δ 7.01 (d, 1 H, J = 1.5 Hz, collapses to a s on irradiation at δ 2.48), 6.95 (s, 1 H), 4.25 (m, 1 H), 3.04 (dd, 1 H, J = 16, 7 Hz), 2.48 (dd, 1 H, J = 16, 7 Hz), 1.18 (s, 3 H), 1.11 (s, 3 H), 1.09 (s, 3 H); MS, m/e (relative intensity) 234 (80, M^+), 219 (43), 206 (14), 201 (100), 183 (21); exact mass 234.161 (calcd for $C_{15}H_{22}O_2$, 234.162).

***trans*-4,5,5a,6,7,8,9,9a-Octahydro-5-oxo-6,6,9a-trimethylnaphtho[1,2-*c*]furan (38). (a) From 18.** To a stirred solution of 8.40 g (27 mmol) of **18** in 10 mL of dry THF and 200 mL of toluene, cooled to −30 °C, was added 140 mL of 1 N DIBAL in *n*-hexane. The reaction mixture was allowed to warm to 0 °C and was stirred for 1 h before quenching with 300 mL of 10% aqueous sodium potassium tartrate. The mixture was extracted with ethyl acetate, and the organic layer was dried and concentrated to a residue, which was redissolved in 200 mL of methylene chloride and treated with 25 g of pyridinium chlorochromate for 1.5 h. The filtrate was concentrated, and the residue was chromatographed (5% ether/*n*-hexane) to afford 4.01 g (63%) of **38** as an oil: IR (neat) 1705 cm^{-1}; NMR (CCl_4) δ 7.09 (s, 2 H), 3.21 (s, 2 H), 2.27 (s, 1 H), 1.26 (s, 3 H), 1.16 (s, 3 H), 1.01 (s, 3 H); MS, m/e (relative intensity) 232 (62, M^+), 218 (14), 217 (100), 189 (17), 161 (14), 149 (19), 105 (16), 91 (27), 77 (18); exact mass 232.145 (calcd for $C_{15}H_{20}O_2$, 232.146).

(b) From 43. To a stirred solution of 70 mg (0.24 mmol) of **43** in 1.5 mL of dry THF, cooled in a dry ice–acetone bath, was added 0.25 mL of 1 N L-Selectride (Aldrich) in THF. After 1 h, the reaction was quenched with saturated, aqueous sodium chloride and extracted with ether. The organic layer was dried and concentrated to a residue which was chromatographed (30% ethyl acetate/benzene) to yield 30 mg (54%) of **38**, identical with material prepared from **18**.

***trans*-1,3,4,5,5a,6,7,8,9,9a-Decahydro-5-oxo-6,6,9a-trimethyl-1,3-dimethoxynaphtho[1,2-*c*]furan (40).** To a stirred solution of 140 mg (0.60 mmol) of **38** and 20 mg of sodium carbonate in 6 mL of dry methanol cooled to −25 °C was added 31 (1.16 mmol) of bromine. The solution was allowed to warm to 0 °C, held at this temperature for 1 h, and then allowed to warm to room temperature, at which point 20 mL of benzene and 20 mg of $MgSO_4$ were added. After 0.5 h, the slurry was filtered and concentrated to a residue which was redissolved in ether, refiltered, and concentrated to give 167 mg (94%) of **40** as a mixture of methoxy epimers. A small sample was purified by preparative TLC (50% ether/*n*-hexane): IR (neat) 1708 cm^{-1}; NMR (CCl_4) δ 5.15–5.66 (m, 2 H), 3.22 (m, 6 H), 2.76 (b s, 2 H), 2.22–3.02 (m, 1 H); MS, m/e (relative intensity) 294 (100, M^+), 263 (45), 262 (24), 247 (14), 231 (13); exact mass 294.184 (calcd for $C_{17}H_{26}O_4$, 294.183).

***trans*-1,3,4,5,5a,6,7,8,9,9a-Decahydro-5-oxo-6,6,9a-trimethyl-1,3-diacetoxynaphtho[1,2-*c*]furan (41).** Lead tetraacetate was prepared in situ by warming to 50 °C a stirred slurry of 150 mg (0.21 mmol) of red lead oxide in 0.31 mL of acetic acid and 0.12 mL of acetic anhydride for 1 h. To the cooled slurry was added a solution of 50 mg (0.21 mmol) of **38** in 1 mL of benzene, and the mixture was stirred for 2 h and filtered. The filtrate was treated with saturated aqueous sodium bicarbonate, dried, and concentrated to a residue, which was chromatographed (10% ethyl acetate/benzene) to yield 68 mg (90%) of **41** as a viscous oil (mixture of epimers): IR 1765, 1755, 1715 cm^{-1}; NMR ($CDCl_3$) δ 6.5–6.9 (m, 2 H), 2.85–3.00 (m, 2 H), 2.3–2.6 (m, 1 H), 2.12 (b s, 6 H); MS, m/e (relative intensity) 350 (1.7, M^+), 290 (73), 248 (49), 83 (14), 55 (13), 43 (100), 41 (15); exact mass 290.151 (M^+ − AcOH; calcd for $C_{17}H_{22}O_4$, 290.152).

***trans*-3,5,5a,6,7,8,9,9a-Octahydro-3-acetoxy-5-oxo-6,6,9a-trimethylnaphtho[1,2-*c*]furan (43).** To a stirred solution of 120 mg (0.34 mmol) of **41** in 2 mL of THF was added 50 μL (0.33 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene. After 15 min, the solution was poured into 20 mL of ether and filtered through a short column of silica gel. The filtrate was concentrated to a residue which was chromatographed (10% ethyl acetate/benzene) to afford 70 mg (70%) of **43** as an oily mixture of acetoxy epimers: IR (neat) 1780, 1660, 1600 cm^{-1}; NMR ($CDCl_3$) δ 7.00 (d, 0.5 H, J = 2 Hz, collapses to a s on irradiation at δ 5.81), 6.87 (d, 0.5 H, J = 2 Hz, collapses to a s on irradiation at δ 5.81), 6.67 (b s, 1 H, collapses to a sharp s on irradiation at δ 5.81), 5.81 (m, 1 H), 2.30 and 2.32 (both s, 1 H), 2.16 and 2.14 (both s, 3 H), 1.21 (s, 6 H), 1.10 (s, 3 H); MS, m/e (relative intensity) 290 (8.1, M^+), 248 (26), 165 (13), 149 (15), 91 (11), 77 (11), 55 (13), 43 (100), 41 (23); exact mass 290.148 (calcd for $C_{17}H_{22}O_4$, 290.152).

(1α,5aα,9aβ,9bα)-1,3,5,5a,6,7,8,9,9a,9b-Decahydro-3-acetoxy-5-oxo-6,6,9a-trimethyl-1,9b-oxirenonaphtho[1,2-*c*]furan (45). A mixture of 103 mg (0.35 mmol) of **43**, 75 mg (0.7 mmol) of sodium carbonate, and 123 mg (0.65 mmol) of 85% *m*-chloroperbenzoic acid in 15 mL of methylene chloride was stirred at room temperature for 18 h. To this mixture was added 40 mL of ether, and the whole was washed with 10% aqueous sodium sulfite and concentrated to a residue. This was chromatographed (10% ethyl acetate/benzene) to yield 99 mg (91%) of **45** as an oily mixture of acetoxy epimers: NMR ($CDCl_3$) δ 6.92 (b s, 0.5 H), 6.48 (b s, 0.5 H), 6.30 (b s, 0.5 H), 6.28 (b s, 0.5 H), 5.47 (s, 1 H), 2.61 (s, 1 H), 2.13 (s, 3 H). The isomer of lower R_f was isolated by chromatography (35% ether/cyclohexane) to obtain the following data: IR (neat) 1750, 1670 cm^{-1}; NMR ($CDCl_3$) δ 6.92 (d, 1 H, J = 1.5 Hz), 6.28 (d, 1 H, J = 1.5 Hz), 5.47 (s, 1 H), 2.61 (s, 1 H), 2.13 (s, 3 H), 1.23 (s, 3 H), 1.19 (s, 3 H), 1.14 (s, 3 H); MS, m/e (relative intensity) 306 (2.5, M^+), 264 (20), 236 (100), 43 (84), 41 (20).

6-Oxowarburganal (47). A solution of **45** (68 mg, 0.22 mmol) in 1 mL of THF was acidified with 0.25 mL of 5% hydrochloric acid and stirred for 1.5 h. The solution was poured into aqueous, saturated sodium bicarbonate (5 mL) and extracted with ethyl acetate. The extract was dried and concentrated to a residue, which was chromatographed (15% ethyl acetate/benzene) to yield 10 mg of **45** and 22 mg (35%) of **47**: IR (neat) 3420, 2920, 1960, 1720, 1680 cm^{-1}; NMR ($CDCl_3$) δ 9.81 (s, 1 H), 9.72 (s, 1 H), 6.66 (s, 1 H), 4.72 (b s, 1 H), 2.99 (s, 1 H), 1.27 (s, 3 H), 1.22 (s, 3 H), 1.19 (s, 3 H); MS, m/e (relative intensity) 264 (5.3, M^+), 235 (47), 217 (11), 189 (20), 147 (24), 140 (26), 121 (38), 109 (68), 91 (20), 86 (63), 84 (100), 69 (32), 67 (23), 55 (57), 43 (54), 29 (43).

(5aα,9aβ,9bα)-1,3,5,5a,6,7,8,9,9a,9b-Decahydro-6,6,9a-trimethyl-5-oxo-6b-hydroxy-3-acetoxynaphtho[1,2-*c*]furan (48). To a stirred solution of 53 mg (0.17 mmol) of **45** in 3 mL of dry THF was added 0.8 mL of 0.5 N lithium tri-*tert*-butoxyaluminohydride in THF. After 44 h, 0.2 mL of acetic anhydride was added, and, after a further 5 h, the mixture was quenched with saturated, aqueous sodium bicarbonate and extracted with ether. The organic extract was dried and concentrated to a residue which was purified by preparative TLC (15% ethyl acetate/benzene) to afford 13 mg of **45** and 23 mg (57% based on reacted

starting material) of **48** as an oily mixture of acetoxy epimers: IR ($CHCl_3$) 3450, 1750, 1670 cm^{-1}; NMR ($CDCl_3$) δ 6.36 (s, 1 H), 5.79 (b s, 1 H), 4.81 (d, 1 H, J = 14 Hz), 4.44 (d, 1 H, J = 14 Hz), 2.98 (s, 1 H), 2.20 (s, 3 H), 1.20 (s, 3 H), 1.17 (s, 3 H), 1.08 (s, 3 H); exact mass 308.164 (calcd for $C_{17}H_{24}O_5$, 308.162).

(5aα,9aβ,9bα)-1,3,5,5a,6,7,8,9,9a,9b-Decahydro-5-oxo-6,6,9a-trimethyl-9b-hydroxy-1,3-dimethoxynaphtho[1,2-*c*]-furan (50). A stirred solution of 175 mg (0.57 mmol) of **45** and a catalytic amount of *p*-toluenesulfonic acid in 15 mL of dry methanol was refluxed overnight. The reaction mixture was poured into 25 mL of ether containing 20 mg of anhydrous sodium carbonate and was filtered (Celite). The filtrate was concentrated to a residue which was purified by preparative TLC (12% ethyl acetate/benzene) to yield 129 mg (73%) of **50** as an oily mixture of epimers: IR (neat) 3500, 1670 cm^{-1}; NMR ($CDCl_3$) δ 5.84, 5.77, 5.63, 5.24, 2.14, 4.94 (each a b s, 1 H), 3.35-3.65 (m, 6 H), 3.03, 2.88 (each a b s, 1 H); MS, m/e (relative intensity) 279 (7.4, $M^+ - OCH_3$) 250 (100), 235 (43), 217 (37), 181 (49), 167 (56), 140 (48).

6β-Hydroxywarburganal (52). To a stirred solution of 75 mg (0.24 mmol) of **50** in dry THF, cooled in a salt-ice bath, was added 0.6 mL of 1 N DIBAL in *n*-hexane. After 1 h, the mixture was quenched with 25 mL of 10% hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with saturated, aqueous sodium bicarbonate, dried, and concentrated to yield an oil. The NMR spectrum of the crude mixture revealed partial hydrolysis to an aldehyde ($\simeq$10%, δ 9.52 and 9.80) and a mixture of methyl acetals (s between δ 3.3 and 3.7) which were devoid of signals at δ 2.88 and 3.03 present in **50**. The crude product was redissolved in 1.5 mL of acetone and 0.25 mL of 10% hydrochloric acid. After 15 min, the reaction mixture was poured into 25 mL of ethyl acetate and was washed with saturated, aqueous sodium bicarbonate. The organic layer was dried and concentrated to give 73 mg of an oil which crystallized from ether/*n*-hexane to yield 59 mg (92%) of **52** as a colorless solid: mp 154-155 °C; IR (Nujol) 3400, 1710, 1670 cm^{-1}; NMR ($CDCl_3$) δ 9.82 (s, 1 H), 9.53 (s, 1 H), 7.09 (d, 1 H, J = 4.5 Hz), 4.90 (m, 1 H), 1.35 (s, 6 H), 1.12 (s, 3 H); MS, m/e (relative intensity) 266 (0.9, M^+), 237 (48), 219 (18), 177 (17), 151 (21), 149 (21), 123 (31), 121 (29), 113 (50), 109 (100); exact mass 266.152 (calcd for $C_{15}H_{22}O_4$, 266.152).

(±)-Cinnamodial (5). To a stirred solution of 10.6 mg (0.039 mmol) of **52** in 0.2 mL of benzene was added 1u μL of triethylamine, 11 μL of acetic anhydride, and a catalytic amount of 4-(dimethylamino)pyridine. After 18 h, 25 mL of ethyl acetate was added. The organic solution was washed with 5% hydrochloric acid and saturated, aqueous sodium bicarbonate and was dried and concentrated to a residue. This was chromatographed (25% ether/*n*-hexane) to yield 10.3 mg (81%) of **5**: mp 127-128 °C (lit.[13] 128-130 °C); IR (Nujol) 3450, 1740, 1720, 1690 cm^{-1}; NMR ($CDCl_3$) δ 9.75 (s, 1 H), 9.46 (s, 1 H), 6.98 (d, 1 H, J = 5 Hz), 5.91 (t, 1 H, J = 5 Hz), 4.10 (b s, 1 H), 2.18 (s, 3 H), 2.09 (d, 1 H, J = 5 Hz), 1.38 (s, 3 H), 1.20 (s, 3 H), 1.06 (s, 3 H); MS, m/e (relative intensity) 279 (19, M^+), 148 (13), 237 (33), 343 (27), 219 (22), 109 (29), 105 (21), 69 (28), 55 (26), 43 (100), 41 (35), 29 (16).

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Synthesis and Absolute Configurations of Halogenoallenes

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The highly stereoselective synthesis of 3-methyl-1-halogenoallenes, 3-*tert*-butyl-1-halogenoallenes, and 1,3-di-*tert*-butylallene is described. The *R* absolute configuration is assigned to the levorotatory halogenoallenes by relating them to allenes of known configurations. The configurational assignments are in agreement with (vacuum) circular dichroism data for the *tert*-butylallenes. The obtained results are used to clarify the hitherto existing confusion in the literature concerning absolute configurations of chloro- and bromoallenes. Further, the signs and magnitudes of the ligand specific parameters for the halogens in the chirality functions approach, used to predict optical rotations of allenes, are discussed. The literature parameter for chlorine is revised and adequate numerical values for those of bromine and iodine are proposed.

Recently, a synthetic route to optically active 3-phenyl-1-halogenoallenes 1 and 21-halogeno steroidal allenes **2** of high enantiomeric purity has been described.[2,3] The present investigation demonstrates the utility of the method to obtain optically active 3-alkyl-1-halogenoallenes, viz., 3-*tert*-butyl-1-halogenoallenes **3a-c** and 3-methyl-1-halogenoallenes **4b** and **4c**. These compounds, together with 1,3-di-*tert*-butylallene **3d**, are very interesting from a theoretical point of view, particularly in relation to theoretical treatments of optical rotations of allenes.[4,5] The relatively simple constitution of compounds **3** and **4** (with only rotationally symmetric substituents) renders them extremely useful for spectroscopic investigations such as (vacuum) ultraviolet and circular dichroism spectroscopy. The spectroscopic and chiroptical properties of **3a-d** are discussed elsewhere.[6]

Further, a lot of confusion can be noted in the literature concerning absolute configurations of chloro- and bromoallenes.[4] It has been shown[2] that levorotatory **1a** as well as **1b** possess the *R* configuration. On the other hand, the *S* configuration has been assigned to both levorotatory chloroallene (**5a**) and dextrorotatory bromoallene (**5b**).[7]

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