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Syntheses of marine molecules

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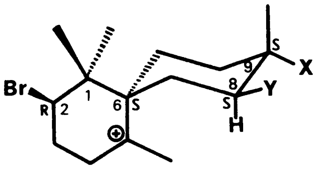
Abstract - The enantioselective total syntheses of (-)(E)γ-bisabolene-8,9-epoxide, (+)(2S,6R)-2-bromo-β-chamigrene, and (+)β-chamigrene, important intermediates in the biosynthesis of natural sesquiterpenoids isolated from algae of the genus Laurencia, are described. The compounds are synthesized with regio and stereocontrol by using simple forms of bridged intermediates. This represents a general strategy for the enantioselective construction of spiro|5.5|undecane systems containing a chiral quaternary center. Our recent current progress towards the synthesis of the biologically active C_{25} tetronic acids isolated from sponges of the genus Ircinia is also described.

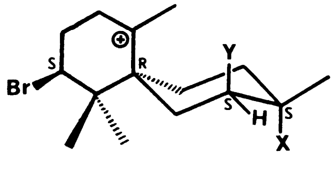
INTRODUCTION

Among the halogenated marine natural products, the largest and most varied group is the spirobicarbocyclic chamigrenes obtained from the red algae of the genus Laurencia and their associated herbivores (Ref. 1). It has also been repeatedly postulated, and chemically proven in some cases or simply hypothesized in others, that the variety of carbon skeletons isolated from these algae owe their origin to particular rearrangements of common chamigrene precursors (Ref. 2).

Most of the halogenated chamigranes described up to now from marine algae are derived (Ref. 2) from one of the two chamigrane ions represented by structures I and II. Both types of precursors possess an (8S,9S)-trans-heterosubstituted moiety and a bromine atom at C2 in opposite absolute configuration to that of the quaternary chiral center at C6.



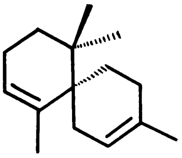
(I)



(II)

X ; Y = Br;Cl ; OH

Spirocycles represent challenging targets in both natural products and theoretical chemistry, and the construction of the quaternary carbon-center remains a fundamental test of synthetic methodology (Ref. 3). Although several successful racemic syntheses (Ref. 4) of the terrestrially found (-)α-chamigrene (1) (Ref. 5), a sesquiterpene that has the spiro|5.5|undecane system as the basic skeleton, have been reported, little is known about the synthesis of the more complex chamigrenes found in marine sources. The reported racemic syntheses (Ref. 6) of the naturally found (2R,6S)-2-bromo-α-chamigrene (2) (Ref. 7) gave a diastereoisomeric mixture (Ref. 6a,b) with apparent spectroscopic and chromatographic identity. As a part of our program on the synthesis of intermediates in terpene biogenesis and constituents of marine organisms, we have developed and record herein the first enantioselective synthesis of the L. pacifica (Ref. 8) metabolite (2S,6R)-2-bromo-β-chamigrene (3b), a discussion of which is part of this communication.



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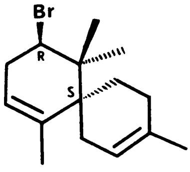

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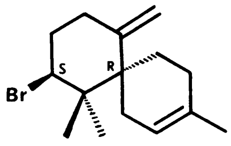


3b

RESULTS AND DISCUSSION

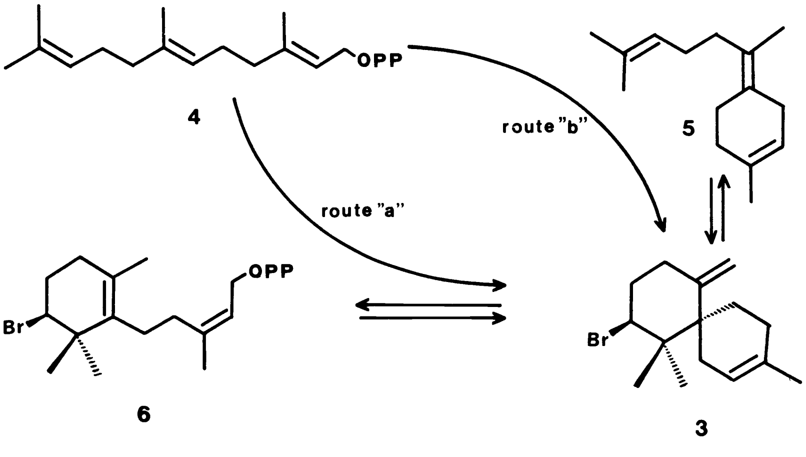
The approach to the synthesis of polycyclic systems with terpenoid stereochemistry and substitution, by acid-catalyzed cyclization of appropriate polyolefinic substrates, provides not only non-enzymic analogies that mimic biosynthetic processes but also practical synthetic procedures for the stereoselective generation of fused carbocyclic systems. The elegant work undertaken at Stanford (Ref. 9, 10) and Harvard (Ref. 11) has allowed the syntheses of steroids and terpenes following the "biochemically patterned" routes. The so-called "biomimetic synthesis" appears to be a reasonable synthetic alternative for polycyclic terpenoids (Ref. 12), although careful choice of starting polyenes and some "non-biomimetic" modifications may be required.

Biogenetic reasoning suggests that most of the brominated terpenoids found in marine sources arise in nature by means of "brominative cyclization" of a polyenic precursor, in which the bromonium ion (or a biological equivalent) serves as the initiating electrophile. The ensuing cyclization, especially its stereochemical outcome, has extensive precedent in the studies of Lewis acid-catalyzed polyolefin cyclizations. Methods based on in vitro polyenic cyclization by direct carbon-bromine bond formation with concomitant ring closure, or the alternative indirect incorporation of bromine to cyclized intermediates, have been employed for the stereospecific synthesis of brominated marine terpenoids. Reagent systems that have been used successfully in this endeavor include N-bromosuccinimide (Ref. 13a,c), bromine in the presence of Lewis acids such as $AlBr_3$, $SnBr_4$ or silver (I) ion (Ref. 13d,e), 2,4,4,6-tetrabromocyclohexa-2,5-diene (TBC) in acidic medium (Ref. 14), and acid--catalyzed cyclization of terminal bromohydrins of polyenes (Ref. 15). Mercuric trifluoroacetate (Ref. 16a-d) or the mercuric trifluoro-methanesulfonate/amine complex (Ref. 16e-f) have also been successfully used in the syntheses of brominated terpenoids.

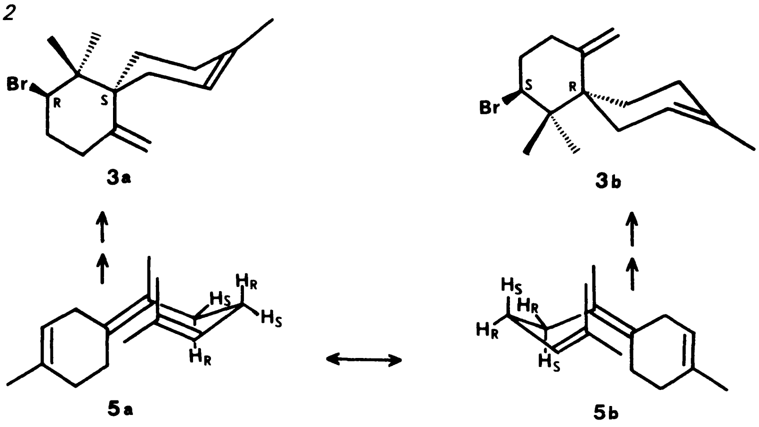
There are two possible biosynthetic routes from farnesyl pyrophosphate (4) to 2-bromo-β-chamigrene (3), depending on the order in which the rings are formed (Scheme 1). Cyclization with loss of pyrophosphate gives γ-bisabolene (5) as an intermediate (route b), while bromonium ion-initiated cyclization gives a brominated monocyclofarnesol pyrophosphate 6 as the intermediate (route a, Scheme 1).

Even if it were possible to check the chemical viability of one of the pathways (a or b) of Scheme 1, the sense in which the biological transformation occurs could not be affirmed with absolute certainty, and those compounds having a monocyclofarnesane (6) or γ-bisabolane skeleton (5) isolated from marine algae (Ref. 1) may well occur by fragmentation of a chamigrene precursor.

Scheme 1



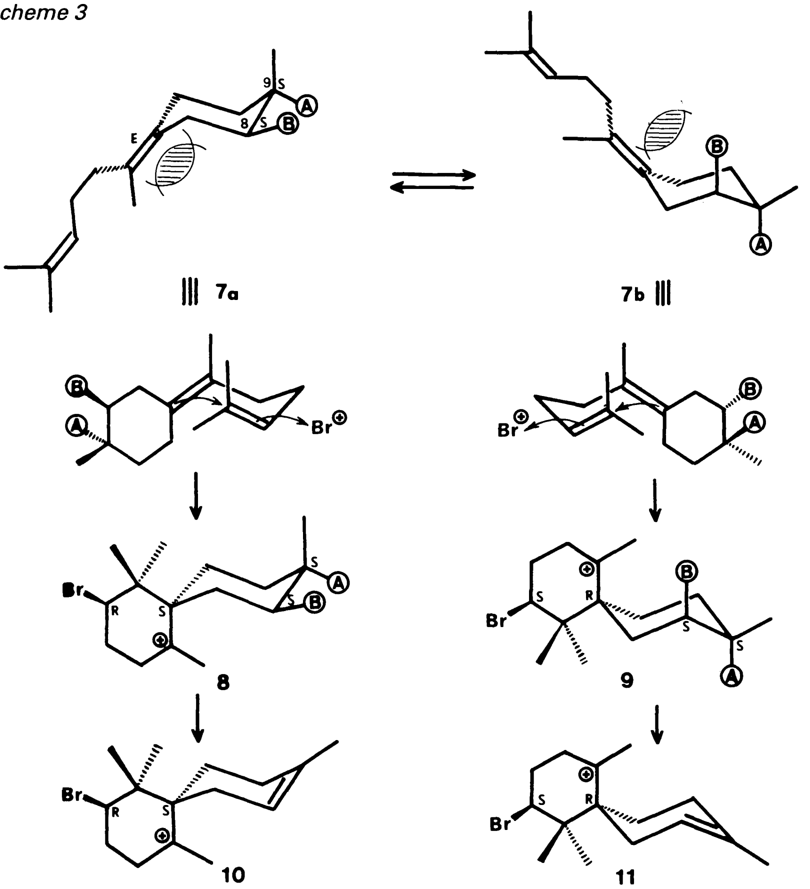
Scheme 2



It is not our intention to enter into a discussion as to which of the two possible biogenetic pathways is the one that probably occurs in the marine environment, nor do we wish the results of the synthesis reported here to be interpreted in favour of either. Our synthesis was inspired by the biogenetic option shown in pathway b, for the purely synthetic reason that we would be carrying out an enantioselective synthesis through enantiocontrolled bromination, in accordance with Scheme 2, which would allow differentiated syntheses to be carried out on bromochamigrenes with the absolute configuration of their chiral centers identical with that of those isolated from the natural marine medium.

The structures of I and II suggested to us a synthesis in which all four chiral centers could be introduced stereospecifically by cyclization of the common diene 7 (Scheme 3), in which the absolute configuration at C8 and C9 would uniquely determine the remaining two stereocenters. The conformations of 7 required for synchronous brominative cyclization *via* diastereomeric transition states to give 8 and 9 are shown in Scheme 3, and the cyclization

Scheme 3



preference will depend on the conformational 7a-7b interconversion and their coiled transition states. The substantial preference observed ((Ref. 17) 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 chair-like six-membered ring. It should be noted that the diastereomeric transition state to 7a is 7b, in which the dienic chain is swung across the front face of the cyclohexane ring, rather than the back face. It would be necessary to control the folding of the rapidly coiling side chain in such a way that the desired site was particularly available for reaction. To achieve enantioselectivity, it is necessary to selectively destabilize one of these two transition states.

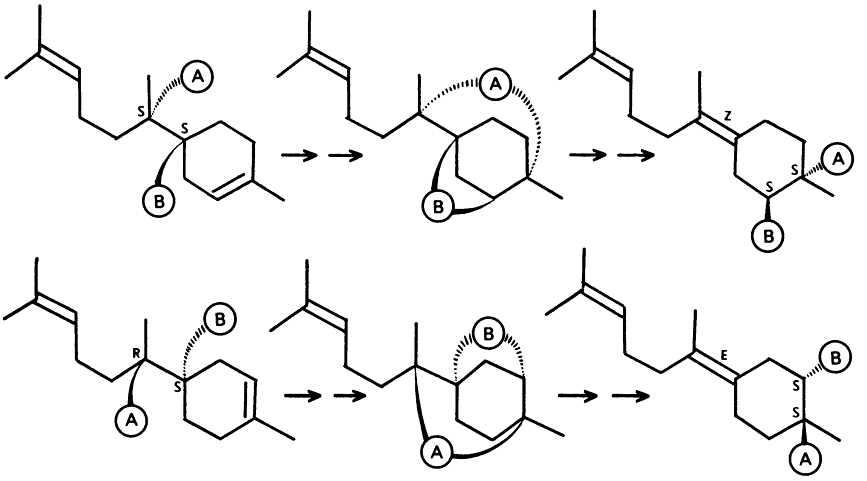
In the absence of overriding competing steric hindrance, access to closure should be largely restricted to the more convex sides which control the stereochemistry of ring junction. Following a parallel sequence, the (Z)-diastereoisomer of 7 would give the non-naturally found chamigrane intermediates possessing identical absolute configuration at C2 and C6 : (2S,6S) or (2R,6R). The olefinic intermediates 10 and 11 may be formed by trans-elimination of the control elements Ⓐ and Ⓑ. Due to the enantiomeric 10 and 11 relationship, identical results would be reached starting from the (8R,9R)-enantiomer of 7.

We have now shown that such is indeed the case. By combining this enantioselective cyclization with our reported method (Ref. 18) for stereocontrolled synthesis of (±)(E)-γ-bisabolene-8,9-epoxide (20) it should be possible to create a variety of diversely substituted chamigrenes of high enantiomeric purity.

SYNTHESIS OF (−) (E)-γ-BISABOLENE-8,9-EPOXIDE

We have recently (Ref. 18) published how racemic 8,9-trans-disubstituted (E)- and (Z)-γ-bisabolenes are synthesized with regio- and stereocontrol by using simple forms of bridged intermediates (Scheme 4). The control elements Ⓐ and Ⓑ are inherent to the molecular organization of the starting material and are converted to vicinal groupings having defined stereochemistry in the final products. The stereochemistry of the tetrasubstituted olefinic bonds is controlled by bridging delivery from C5 and C6 positions.

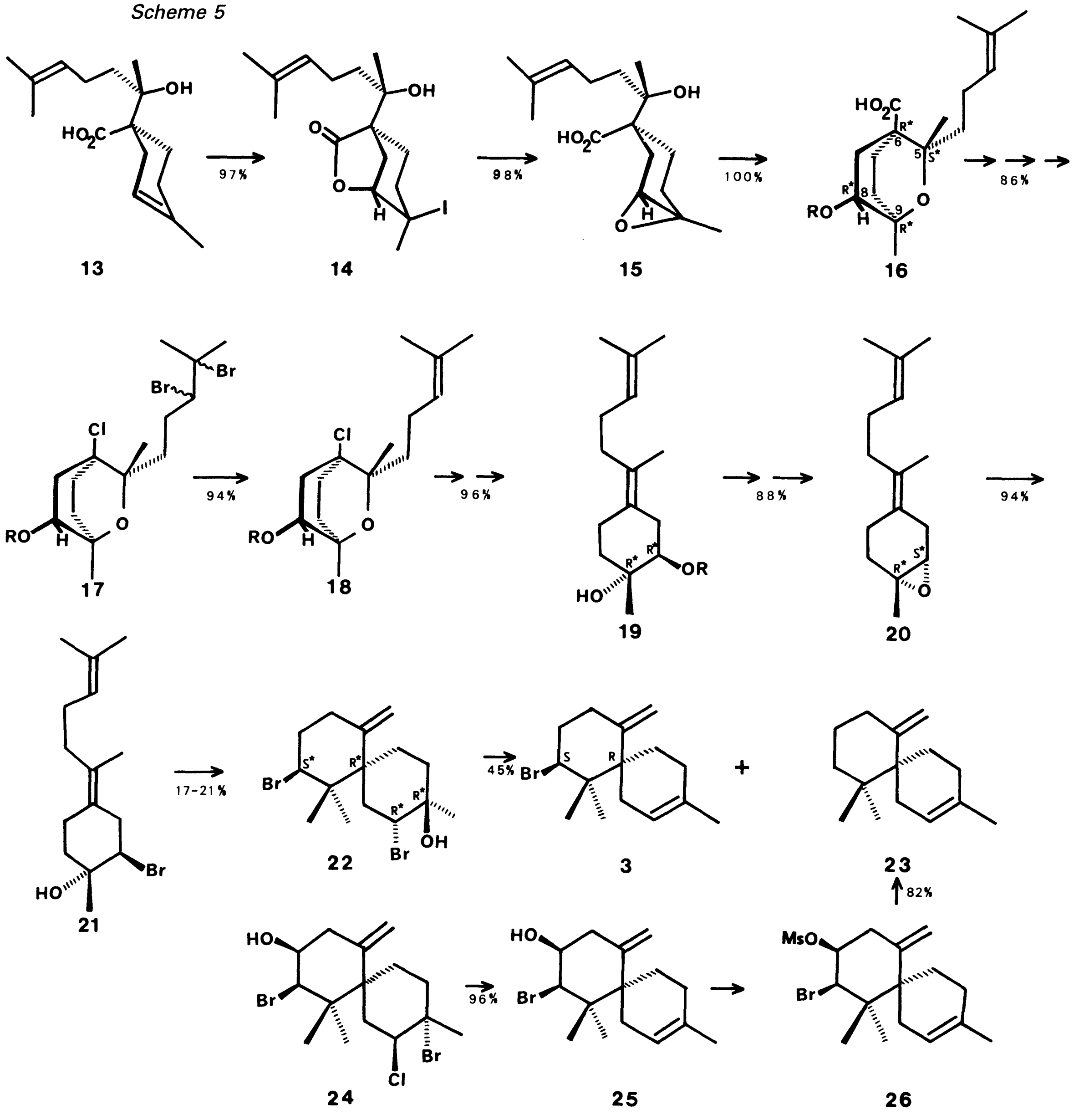
Scheme 4



The synthesis (Scheme 5) was initiated from the (±)β-hydroxy acid 13, available (Ref. 19) on a large scale from 4-methyl-3-cyclohexene carboxylic acid and 6-methyl-5-hepten-2-one in 85% yield, followed by fractional recrystallization of the diastereoisomeric mixture. Reaction of the diisopropylamine salt of 13 with iodine in dichloromethane produced the iodolactone 14 (Ref. 20) in 97% yield. Treatment of 14 in THF with 1.5 equiv of aqueous potassium hydroxide at 0°C for 2 h and isolation of the acidic product provided the unstable epoxy acid 15 in 98% yield, which without further purification was treated with a catalytic amount of p-toluenesulfonic acid in methylene chloride to produce 16 (R=H) in 100% yield. The sequence 13 to 16 (R=H) can be carried out easily in the laboratory on a 1-mole scale, and the intermediates 14 and 15 need not be purified. The $(5S^*,6R^*,8R^*,9R^*)$ enantiomer 16 (R=Ac), $\{\alpha\}_D$ −32.3° ($CHCl_3$) could be obtained readily from the racemic acetoxy-acid by resolution involving recrystallization of the salt with quinine from acetone (Ref. 21). Bromination (Br_2, CCl_4) of the crystalline acetate 16 (R=Ac) gave the dibromo-derivative which was decarboxylated (Ref. 22) by reaction with lead tetraacetate and N-chlorosuccinimide in DMF--HOAc (5:1) to give 17 (R=H) in 86% yield (10% of 16 (R=H) was recovered). The dibromide 17 (R=H) was then subjected to reductive elimination of bromine by zinc dust (ether-HOAc) to form the chloro ether 18 (R=H), $\{\alpha\}_D$-31.9° (c 0.94, $CHCl_3$), which was purified by acetylation to give 18 (R=Ac), $\{\alpha\}_D$-24.5° (c 1.3, $CHCl_3$).

The reductive fission of the β-chloro ether bonds with powdered sodium metal in the presence of ethylamine and THF afforded the crystalline ($8R^*$,$9R^*$)-diol 19 (R=H), $\{\alpha\}_D$+10.3° (c 0.8, $CHCl_3$) in 96% yield (Ref. 23). Other reagents such as the zinc-silver couple (Ref. 24) or magnesium (ether, THF) were ineffective. The overall yield of 19 (R=H) from 16 (R=H) was 74%. The enantiomeric excesses of the new chiral compounds were established as >95% by ^{1}H-NMR spectroscopy using chiral LISR |for the acetates 16 (R=Ac), 18 (R=Ac) and 19 (R=Ac)|. Completion of the synthesis of (E)-γ-bisabolene-8(S^*),9(R^*)-epoxide (20), which showed $\{\alpha\}_D$-68.8° (c 2.18, $CHCl_3$) |lit (Ref. 25) $\{\alpha\}_D$+37.3° (c 2.20, $CHCl_3$) for the natural enantiomer| proceeded by tosylation (p.TsCl, C_5H_5N) of the diol 19 (R=H) to yield the oily monotosyl--derivative 19 (R=Ts) which was converted to 20 in 96% yield by treatment with aqueous potassium hydroxide in methanol.

Scheme 5



SYNTHESES OF (+) β-CHAMIGRENE AND (2S, 6R)-2-BROMO-β-CHAMIGRENE

Bromohydrin (**21**), $\{\alpha\}_D^{22}$+42.8 (c 1.16, $CHCl_3$), was obtained in 94% yield by treatment (Ref. 26) of **20** in THF with excess of dilithium tetrabromonickelate (II). The stereochemistry of **21** is clear from the ^1H NMR spectrum which unambiguously indicates that the bromomethine proton is axial: δ 4.05 (*dd*, *J*= 11, 4Hz, 1H). Brominative cyclization (Ref. 27) of **21** was effected using 1.5 equiv of 2,4,4,6-tetrabromocyclohexa-2,5-diene in dry nitromethane at ambient temperature for 3 h. The pure enantiomer **22**, $\{\alpha\}_D$+44.2 (c 1.12, $CHCl_3$) was isolated as a non-crystalline solid from the crude reaction mixture by flash chromatography (Ref. 28). Treatment of **22** with Zn-dust in acetic acid afforded in 83% yield the monobrominated diene (2S,6R)-2-bromo-β-chamigrene (**3**), {α}+13.5 (c 1.12, $CHCl_3$) |lit. (Ref. 8a) $\{\alpha\}_D$+14 (c 2.46, $CHCl_3$) for the natural enantiomer| and (+)β-chamigrene (**23**), $\{\alpha\}_D$+59.2 (c 0.91, $CHCl_3$) |lit. (Ref. 29) $\{\alpha\}_D$-52.7 (c 0.71, $CHCl_3$) for the natural opposite enantiomer|. To assure ourselves of the absolute configuration and optical rotation of **3**, we carried out its synthesis starting from the L. obtusa metabolite isoobtusol (**24**) (Ref. 30). Reduction of **24** with Zn-AcOH in ether at 0°C yielded the partially dehalogenated **25**, $\{\alpha\}_D^{22}$+82.1 (c 0.84, $CHCl_3$), which was further transformed into **3**, $\{\alpha\}_D^{22}$+14.4 (c 1.18, $CHCl_3$) through the mesyl derivative **26** by treatment (Ref. 31) with lithium triethylborohydride in refluxing THF.

In the light of the foregoing effects predicted in Scheme 3, these results suggest that the cyclization of the bromohydrin **21** is not likely to occur from the form of the conformer **7b** due to its exclusive existence in the form of the conformer **7a**.

Neighboring group participation (Ref. 32) is an established tool for reactivity control. It has been used for stereoselective introduction of functional groups (Ref. 33), selective protection (Ref. 34), double-bond transposition (Ref. 35), and to induce molecular conformational changes (Ref. 36). The chamigrene skeleton is synthesized here with regio- and stereocontrol by using simple forms of bridged intermediates.

Although quaternary carbon centers are challenging structural components of many complex natural compounds (Ref. 37), only a few methods for generating this moiety in an efficient enantioselective manner exist to date (Ref. 38). The results described here represent an effective procedure for 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 spirocarbocyclic containing natural compounds, and we are actively pursuing the scope and limitations of this asymmetric methodology.

TETRONIC ACID SESTERTERPENES FROM IRCINIA: SYNTHETHIC APPROACH

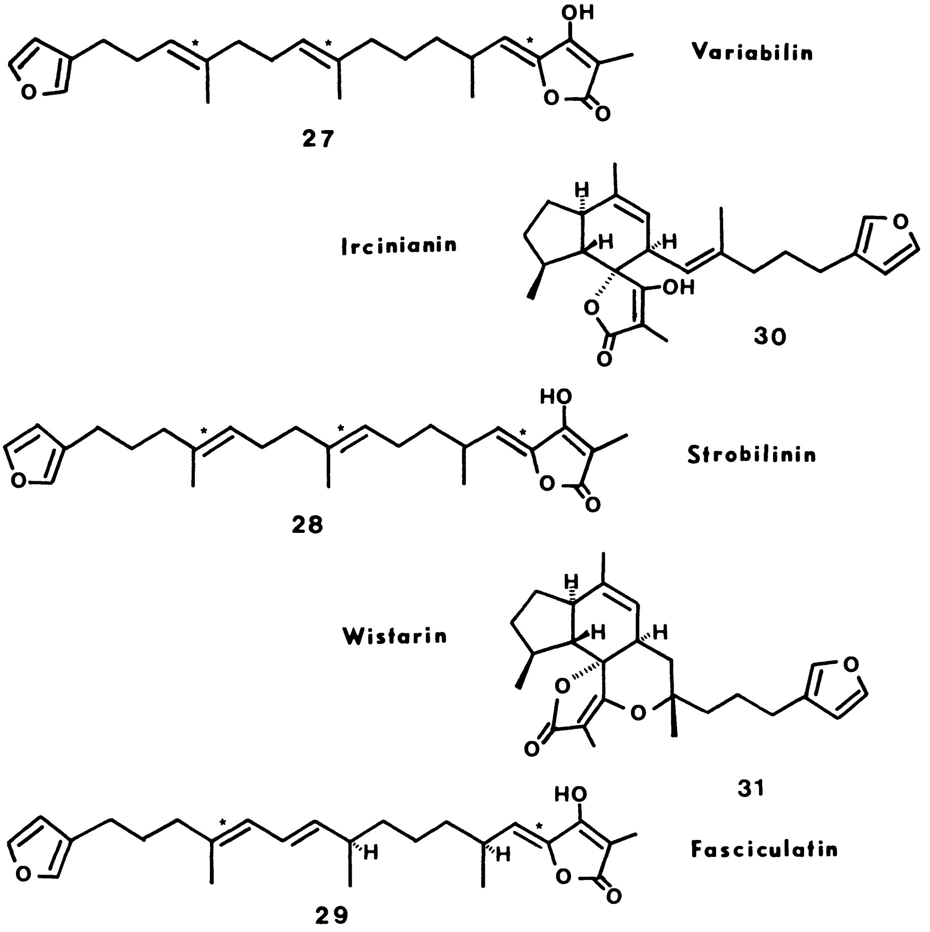
Sesterterpenes are a rare group of natural products, but they are often encountered as secondary metabolites in sponges of the order Dictyoceratida (Ref. 39). The genus Ircinia has yielded a group of closely related linear sesterterpenes characterized by a β-substituted furan and tetronic acid ring as terminal units, the most unusual of which are the bicarbocyclic ircinianin (**30**) (Ref. 40) and wistarin (**31**) (Ref. 41), both isolated from I. wistarii, which appears to be the result of a |4+2|cycloaddition of suitably unsaturated linear precursors (Scheme 6).

The remarkable biological activities of tetronic acid sesterterpenes make them attractive targets for synthesis. Our strategy for total syntheses of these compounds envisions completion of the C_{25} skeleton from independent syntheses and connection of the A-D synthons (Scheme 7) permitting a differentiated synthesis of the compounds by means of a common synthetic strategy. The target molecules in these preliminary synthetic studies were the antibiotics variabilin (**27**) (Ref. 42) and strobilinin (**28**) (Ref. 43) that present moreover the unsolved structural problem of the stereochemistry of their double bonds (Scheme 6).

Synthetic approaches to 4-ylidene-tetronic acids

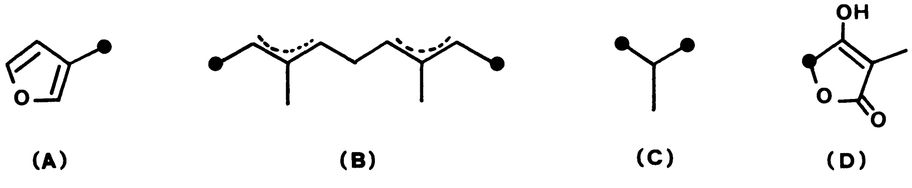
Several methods of preparation of α,β-butenolide and tetronic acid moieties have recently been published (Ref. 44-48). For the synthesis of the target 3-methyl-4-methoxy-5H-furan-2-one (**34**) we have followed the previously described method of rearrangements of the appropriate β-keto esters (Ref. 49) with the modifications and yields indicated in Scheme 8, followed by methylation with dimethyl sulphate in base to give **35** (Ref. 50).

Scheme 6

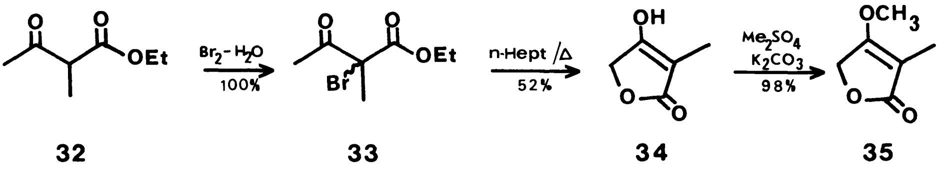


Linear furanoid sesterterpenes in Ircinia. Asterisk indicates that stereochemistry of olefin is unknown.

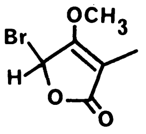
Scheme 7



Despite the fact that the synthesis of α-alkyliden-γ-butyrolactones by means of Wittig olefin syntheses is well documented (Ref. 51-53), bromination of compound 35 by any of the methods described led to an unstable and difficult to separate mixture of bromo-derivatives 36 and 37. Treatment of monobrominated 36 with triphenylphosphine gave the salt 38 that decomposed upon formation. In our hands the conversion 35 → 36 → 38 evolved in a totally different manner, with results that differed from those published (Ref. 54). Other alternatives to the synthesis of 4-ylidene-butenolides and 4-ylidene tetronic acids published recently include condensation of phosphoranes with alkyl-maleic anhydride (Ref. 55), dehydration or dealkoxylation of the



reaction products of ketones with trimethylsilyloxyfuran (Ref. 56) or 2-trimethylsilyloxy-4-methoxyfuran (Ref. 57). Directed metallations of O-alkyl tetronic acids with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by treatment at -78°C with ketones in THF and dehydration proved to be a preparatively useful procedure for the synthesis of the corresponding α-substituted O-methyl tetronic acids (Ref. 58, 59). Reaction of **35** with LDA at -78°C in THF-HMPT followed by addition of D_2O gave O-methyl 5-deuteriotetronate in 82% yield, hence anion **39** was formed and reacted at C-5 in the fashion required. The reaction of **39** with isobutyraldehyde gave **40 (R=H)** as a mixture of *threo*- and *erythro*-isomers in 70% yield, which were separated by fractional crystallization. Both compounds were independently converted into the same elimination product in high yield (∿90%) through their corresponding tosyl-derivatives (**40, R=Ts**) followed by base treatment with 1.5-diazobicyclo |4.3.0|nonene (DBN) at r.t. in ether or THF. The structure **41** for the single elimination product is tentative with respect to the stereochemistry of the double bond introduced, but it seems to be the most probable on the basis of similar previously reported studies (Ref. 60).



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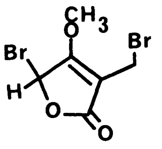

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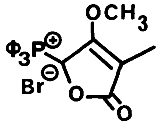

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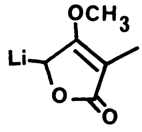

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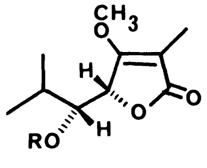

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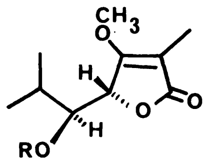

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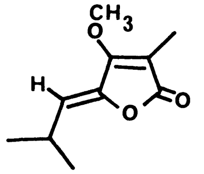

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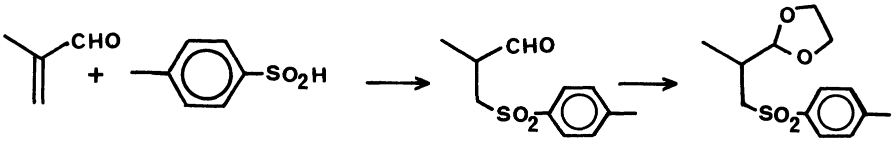
The appropriate aldehyde for our synthetic study (**44**) was prepared from the α-methylacrylaldehyde (**42**) by condensation with p-toluenesulfinic acid (**43**), prepared *in situ* from the sodium salt (Ref. 61).



42 43 44 45

Bifunctional isoprenoid synthesis

The stereoselective synthesis of the polyenic isoprenoid **54** required for the synthesis of both variabilin (**27**) and strobilinin (**28**) was achieved following the classic works of M. Julia (Ref. 62-65) and W. S. Johnson (Ref. 66) (Scheme 9).

Until now only timid attempts have been made to interconnect the prepared intermediates and the yields obtained have not been optimized. Despite the extensive literature available, the final synthetic result put forward here will depend on how the alkylations proposed for the already prepared synthons develop in our hands.

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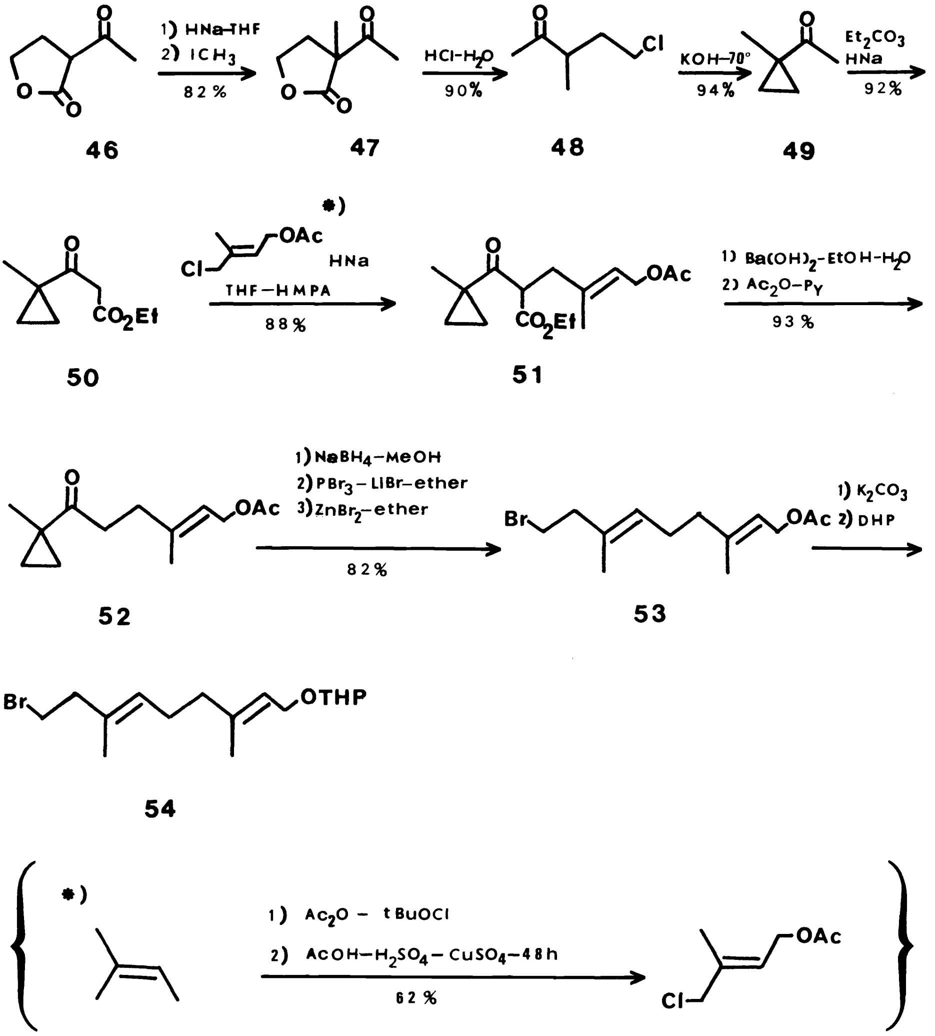
Scheme 9



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