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SYNTHESIS OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION IX.

TOTAL SYNTHESIS OF (±)-OBSCURONATIN AND (±)-BIFLORA-4,10(19),15-TRIENE.

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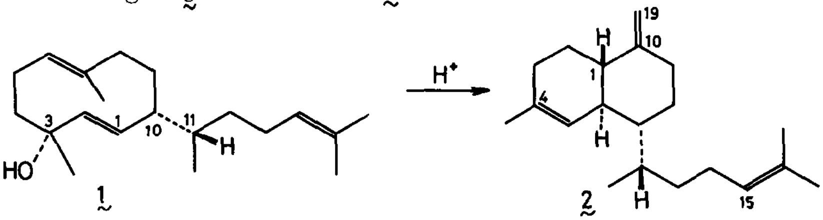
Abstract: Stereoselective total synthesis of (±)-obscuronatin, a marine diterpene with a 10-membered ring, has been achieved utilizing the anion-induced cyclization of an acyclic epoxy sulfide. The synthesis confirmed the stereostructure of the natural product.

Obscuronatin (1) is a novel 10-membered ring diterpene isolated from a soft coral Xenia obscuronata[1)]. Although planar structure and configurations at C-10 and C-11 have been determined on the basis of spectral data and correlation with biflora-4,10(19),15-triene (2), a diterpene isolated from termite soldiers[2)], stereochemistry at C-3 has not been established. We have previously proposed cis relationship between the hydroxyl group and the long side chain based on the stereochemical requirement in acid-catalyzed transannular reaction of its sesquiterpenic analogue 3 to cadinane 4[3)].



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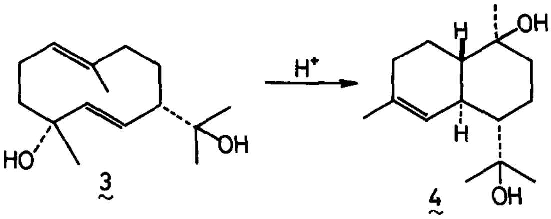

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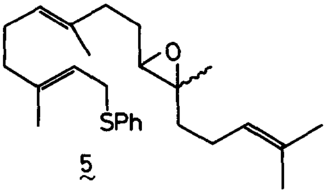

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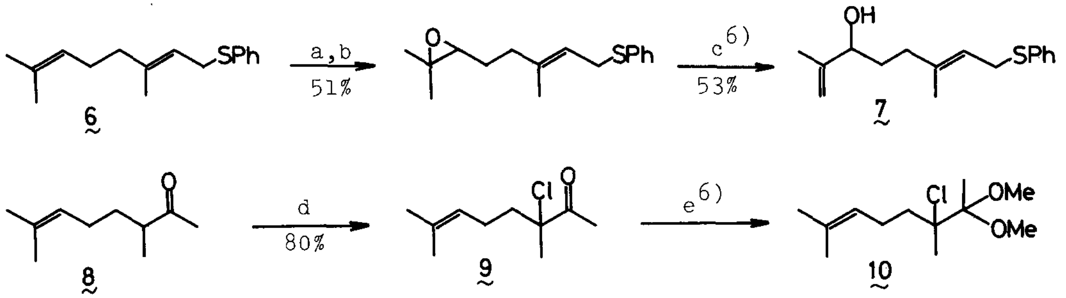
We describe herein the total synthesis of 1 utilizing the anion-induced biomimetic cyclization of an acyclic epoxy sulfide 5 which in turn was prepared using sigmatropic rearrangement. The synthesis not only confirmed the proposed structure of 1, but also illustrated the versatility of our cyclization reaction[4)], since this is its first application to acyclic precursor with epoxy group at the central part of carbon chain.

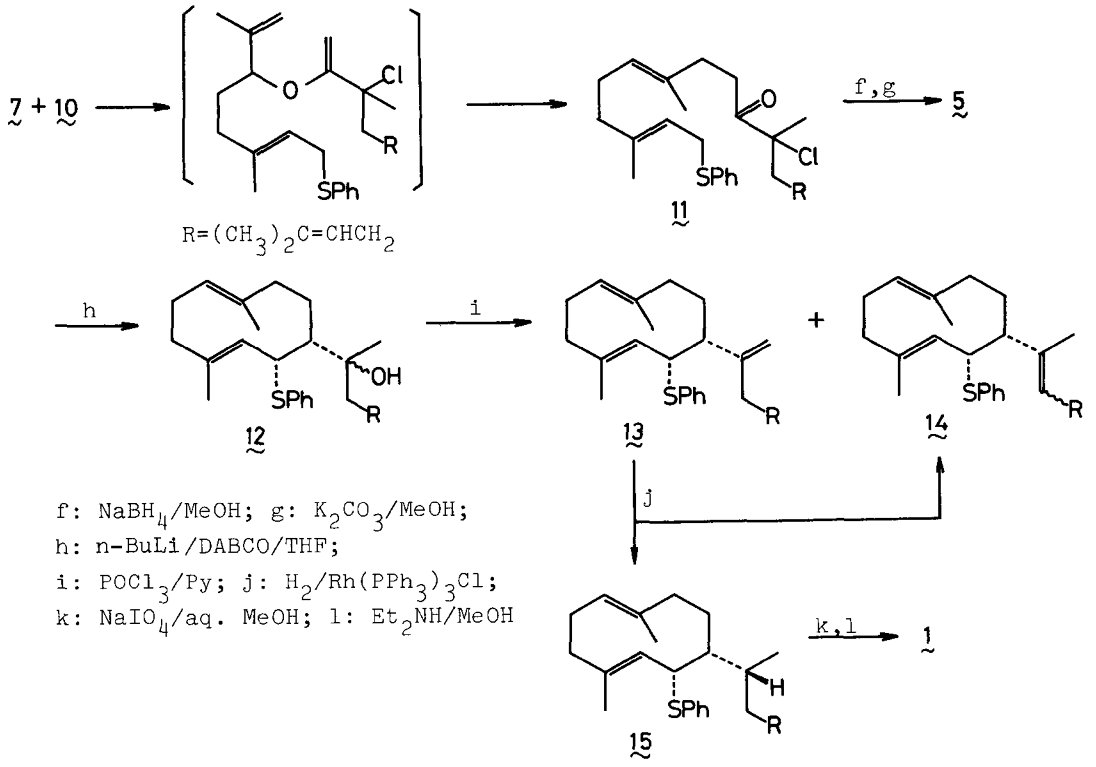
The allylic alcohol 7 and the dimethyl acetal 10, two segments to prepare the acyclic precursor 5, were obtained from geranyl phenyl sulfide 6 and the ketone 8[5], respectively, by the reaction sequences shown below.



a: NBS/THF-H_2O; b: K_2CO_3/MeOH; c: Al_2O_3; d: LiCl/$CuCl_2$/DMF, 90°C;
e: $HC(OMe)_3$/p-TsOH/MeOH, 0°C.

Heating 7 and 10 in toluene at 130°C in the presence of 2,4-dinitrophenol induced a series of reactions, i.e., exchange of alkoxyl group, elimination of methanol and Claisen rearrangement, to give the chloroketone 11[7] in 71% yield. The ketone 11 was further converted to the epoxide 5 (4:3 mixture of diastereomers) in two steps.

The epoxide 5 thus obtained was treated with n-BuLi under the conditions reported previously[4], thereby the cyclization product 12 was obtained in 60%



R=$(CH_3)_2C{=}CHCH_2$

f: $NaBH_4$/MeOH; g: K_2CO_3/MeOH;
h: n-BuLi/DABCO/THF;
i: $POCl_3$/Py; j: H_2/$Rh(PPh_3)_3Cl$;
k: $NaIO_4$/aq. MeOH; l: Et_2NH/MeOH

yield. The relative configuration of **12** was assigned by comparing its PMR spectrum with that of hedycaryol phenyl sulfide (**12**: R=H) of known configuration[8].

Dehydration of **12** with $POCl_3$ furnished a 4 : 7 mixture of dehydro compounds **13** and **14** in 93% yield; other methods of dehydration gave less satisfactory ratio of **13** and **14**. The mixture(**13** + **14**) was subjected to catalytic hydrogenation over Wilkinson catalyst, whereby **13** disappeared to give the reduction products but only in 19% along with **14** (ca. 80%), disclosing the extensive isomerization (**13** → **14**) during the hydrogenation. The reduction products consisted of two stereoisomers in the ratio of 10 : 1. That the major product **15** has the desired configuration was demonstrated by its conversion to natural product (vide infra). Oxidation of **15** to a mixture of sulfoxides (80%) and their [2,3]sigmatropic rearrangement[3] afforded a tertialy alcohol in 90% yield, besides the elimination product. IR and PMR spectra of the alcohol were identical with those of natural obscuronatin[1,9]. Since the stereochemistry of the [2,3]sigmatropic rearrangement is well understood[3,10], the synthesis established the stereochemistry of **1** and also completed formal synthesis of **2**[2,11]. In fact, synthetic alcohol gave biflora-4,10(19),15-triene and its Δ^{10}-double bond isomer in 4 : 3 ratio by a trace of acids.

References and Notes

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6) Step c: The corresponding glycol and the isopropyl ketone were formed in 20% and 6% yield, respectively. The former can be converted in three steps (acetylation, dehydration with $SOCl_2$ and alkaline hydrolysis) into **7** in 75% yield. Step e: The reaction is very slow and after 10 days at 0°C, **10** was obtained in only 43% yield with 46% recovery of **9**. At higher temperature, extesive side reactions including the addition of methanol to the double bond take place.
7) The physical properties of the selected intermediates: **10**; Colorless liquid, m/e 434 (M^+), 432 (M^+), 218 (b.p.), ν 1715 cm^{-1}, δ 1.59 (9H,s), 1.63 (3H, s), 1.67 (3H, s), 3.53 (2H, d, J=7.5), 5.12 (2H, m), 5.30 (1H, br.t, J=7.5), 7.25 (5H, m), CMR of methyl groups 16.20, 16.20, 17.72, 25.68, 26.93. **12a**; Colorless liquid, m/e 398 (M^+), 109 (b.p.), ν 3510 cm^{-1}, δ 1.38 (3H, s), 1.52 (3H, s), 1.62 (6H, br.s), 1.68 (3H, s), 4.20 (1H, dd, J=9.4, 2.6), 5.14 (3H, m), 7.25 (5H, m). **12b**: Colorless liquid, m/e 398 (M^+), 73 (b.p.), ν 3510 cm^{-1},

δ 1.16 (3H, s), 1.53 (3H, s), 1.61 (6H, br.s), 1.68 (3H, s), 4.20 (1H, dd, J=9.4, 2.6), 5.11 (3H, m), 7.27 (5H, m). **13**: Colorless liquid, m/e 380 (M^+), 271 (b.p.), ν 1640, 890 cm^{-1}, δ 1.61 (9H, br.s), 1.69 (3H, s), 4.13 (1H, br.d, J=9), 5.01 (iH, br.s), 5.06 (3H, m), 5.08 (1H, br.s), 7.19 (5H, m). **14**: Colorless liquid, m/e 380 (M^+), 271 (b.p.), δ 1.60 (9H, br.s), 1.71 (3H, br.s), 1.76 (3H, s), 2.70 (2H, t, J=7.2), 4.09 (1H, br.d, J=9), 5.05 (3H, m), 5.36 (1H, t, J=7.2), 7.19 (5h, m). **15**; Colorless liquid, m/e 382 (M^+), 271 (b.p.), δ 0.89 (3H, d, J=7), 1.61-1.76 (12H), 4.12 (1H, m), 5.07 (3H, m), 7.22 (5H, m).

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9) We are deeply indebted to Professor Y. Kashman, Tel Aviv University, for IR and PMR spectra of natural obscuronatin.

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11) For the synthesis of biflora-4,10(19),15-triene, see K. Mori and M. Waku, Tetrahedron, **40**, 305 (1984).

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