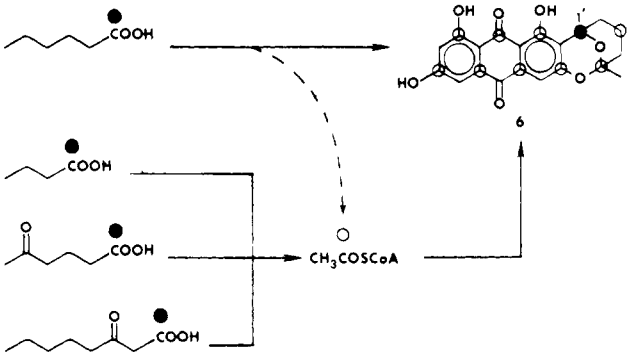
In the first of these (expt 1), 12 g of 48-h old mycelial pellets of the averufin-accumulating mutant ATCC 24551 were suspended in a low-sugar replacement medium[18] (100 mL) in each of 12 500-mL Erlenmeyer flasks. Labeled acid (12 mg) was administered to each flask under sterile conditions, and they were shaken at 28 °C for 24 h. The averufin produced was isolated by extraction of the filtered pellets and purified by chromatography on silica gel. In the second experiment (expt 2), a 100-mL 48-h-old standing culture of the same mutant grown on a low-salts medium[19] was treated with [1-^{13}C]hexanoic acid (25 mg) and again at 72 and 96 h. At 120 h the fermentation was terminated and the averufin was isolated.

When compared to a $^{13}C\{^1H\}$ NMR spectrum of averufin at natural abundance (normalization to C-5, an unlabeled center derived from C-2 of acetate), the corresponding spectra of the ^{13}C-enriched averufin from both expt 1 and 2 showed the resonance for C-1′ at δ 66.2 to be enhanced more than 3 times the natural abundance (solid circle in **6**). Some degradation of the labeled



hexanoate to [1-^{13}C]acetate and secondary incorporation (open circles in **6**) were observed, being about 0.5%/site in expt 1 and 1%/site in expt 2.

The implications of these findings were further examined by testing the incorporation of *equimolar* amounts of [1-^{13}C]acetate, [1-^{13}C]butyrate, [1-^{13}C]-5-oxohexanoate,[20] and [1-^{13}C]-3-oxooctanoate[21] under the suspended-cell conditions above. For each of these substrates the pattern of ^{13}C enrichment in averufin, while varying somewhat in overall magnitude from experiment to experiment, was the same as that for the uniform incorporation of [1-^{13}C]acetate (about 0.5%/site for the latter). Therefore, all of these experiments to a first approximation label the acetate pool to roughly the same extent as reflected in the incorporation of C-1 throughout averufin (**6**) but [1-^{13}C]hexanoate alone shows a significant level of intact incorporation.

These data suggest an intact hexanoate starter unit arising from a separate synthetase or from β-oxidation. Alternatively, a single polyketide synthetase may produce the initially reduced segment which is able to exchange with free hexanoyl CoA at the C_6 stage. This process would have to be quite efficient given the 3% specific incorporation of label from hexanoate compared with about 0.5% from acetate. Butyrate and 3-oxooctanoate, which might be expected to show analogous exchange, fail detectably to do so or at best with significantly reduced efficiency. Lastly, it is possible that acylation of a preformed anthraquinone may take place. 1,3,6,8-Tetrahydroxyanthraquinone has been isolated from *A. versicolor*,[22] and while structurally symmetrical, its labeling pattern from [1,2-$^{13}C_2$]acetate is not. Such a process would require acylation to occur in the enzyme-bound state. Parallel formation of averufin from 5-oxohexanoate is not supported experimentally.

Of these interpretations we prefer, but cannot strictly prove, the first for its simplicity and direct relation to precedents noted at the outset. It is of interest at this point to recall the observation of Holker and Mulheirn[23] that the bisfuran carbons of sterigmatocystin, from *A. versicolor*, bore about 10% lower specific activity from [1-^{14}C]acetate than did nuclear carbons. In contrast Büchi's extensive degradations of aflatoxin B_1 (**5**) from the corresponding incorporation experiment in *A. flavus* revealed no differential labeling.[14] In the event, it is now clear that the seemingly elaborate formation of averufin (**4**) is necessary given the constraint of an hexanoate primer (Scheme I) and equally necessary one might assume to ultimately construct the singular bisfuran that characterizes this family of mycotoxins.[24,25]

Acknowledgment. Professor J. M. Schwab (Catholic University of America) is thanked for recording the [1-^{13}C]hexanoate incorporation spectra. We are pleased to note helpful conversations with Dr. U. Weiss (NIH) and Professor J. C. Vederas (University of Alberta). Financial support of the National Institutes of Health (ES 01670) and the Alfred P. Sloan Foundation is gratefully acknowledged.

Registry No. 4, 14016-29-6; hexanoic acid, 142-62-1.

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Total Synthesis of (±)-Poitediol and (±)-4-Epipoitediol

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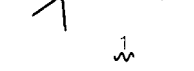
Received January 9, 1984
Revised Manuscript Received April 23, 1984

Poitediol (**1**) is an unusual sesquiterpene diol isolated from the red seaweed *Laurencia Poitei*.[1] It is one of the less complex



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members of a growing family of cyclooctane-containing natural products, many of which have interesting biological activities. We wish to report the total synthesis of racemic poitediol and 4-epipoitediol.[2]

Our earlier work[3] had shown that the anionic oxy-Cope rearrangement of dialkenyl cyclobutoxides was an efficient method for the synthesis of substituted cyclooctenones, and our strategy for the synthesis of poitediol is based upon this approach. In order to construct the bicyclo[6.3.0]undecane system of poitediol, we required the bicyclo[3.2.0]heptanone **9** whose synthesis is outlined in Scheme I.[4]

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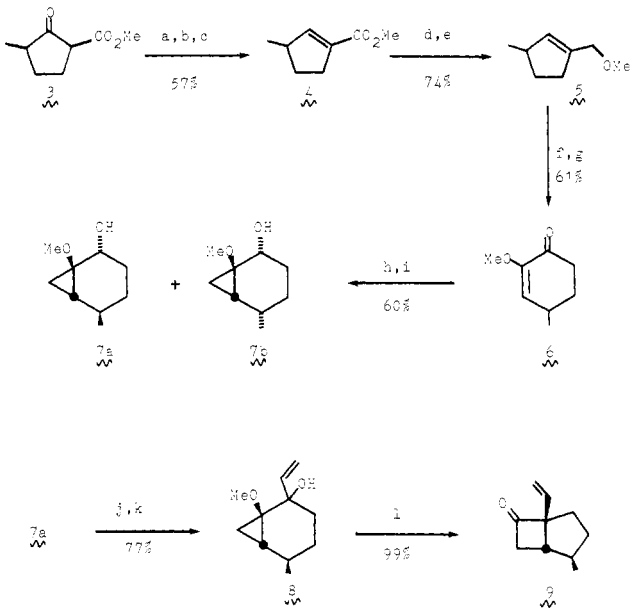
Scheme I[a]



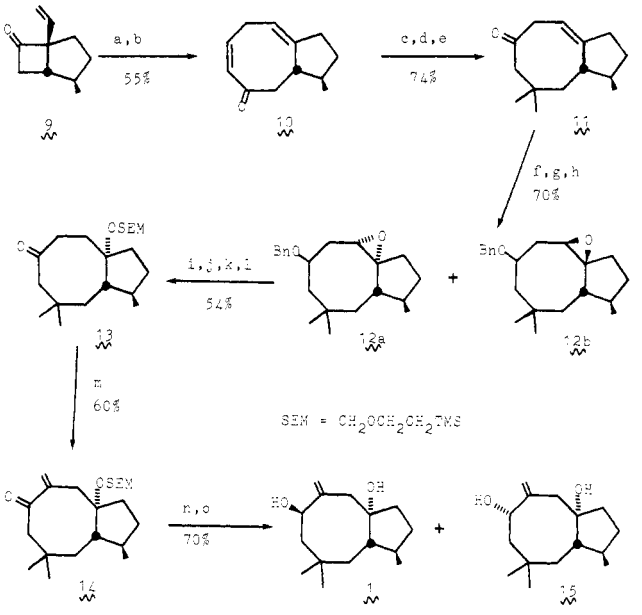
[a] (a) $NaBH_4$, MeOH, 0 °C, (b) Ac_2O, catalytic H_2SO_4, Et_2O, (c) KO-*t*-Bu, THF, (d) DIBAH, toluene, −78 °C; (e) MeI, NaH, THF, 0 °C; (f) (1) O_3, CH_2Cl_2, −78 °C (2) Me_2S, reflux; (g) NaOH, MeOH, reflux; (h) DIBAH, Et_2O, −100 °C; (i) Et_2Zn, CH_2I_2, toluene, 60 °C; (j) PCC, CH_2Cl_2; (k) CH_2=CHMgBr, THF; (l) $BF_3 \cdot Et_2O$, Et_2O.

Reduction of 5-methyl-2-carbomethoxycyclopentanone[5] followed by acetylation and elimination afforded cyclopentene **4**. Further reduction and methylation of the resulting alcohol produced **5**. Ozonolysis (Me_2S workup) and cyclization of the resulting keto aldehyde led to cyclohexenone **6**. Stereoselective reduction of **6** with DIBAH in Et_2O at −100 °C[6] gave a diastereomeric mixture, which was cyclopropanated[7] to afford a separable mixture of norcaranols **7a** and **7b** (8:1 ratio).[8]

Oxidation of **7a** and addition of vinylmagnesium bromide gave norcaranol **8**. Attempted rearrangement of **8** using aqueous HBF_4[10] led to formation of two products, apparently due to competitive migration of both cyclopropyl carbon–carbon bonds. However, treatment with 1 equiv of $BF_3 \cdot Et_2O$ afforded bicyclo[3.2.0]heptanone **9** in essentially quantitative yield.

Ring expansion of **9** via sequential addition of 1-lithiovinyl phenyl sulfide (or selenide) and anionic oxy-Cope rearrangement was successful, as was the subsequent oxidative elimination. However, this sequence proceeded in disappointingly low overall yield. In contrast, as shown in Scheme II,[4] the more direct procedure of lithium acetylide addition[11] followed by neutral oxy-Cope rearrangement[12,13] was more successful, leading to **10** in overall yields of 50–60%. The oxy-Cope rearrangement of a 1-alkynyl-2-alkenylcyclobutanol is unprecedented and should open up new avenues for the synthesis of functionalized cyclooctanes.

Scheme II[a]



[a] (a) LiC≡CH, THF, −30 °C, 5 min; (b) hexane, 50 °C, 4 h; (c) MeLi, Et_2O, −78 °C; (d) PCC, CH_2Cl_2; (e) $LiMe_2Cu$, Me_2S, Et_2O; (f) DIBAH, Et_2O, −78 °C; (g) (1) KH, THF, (2) $PhCH_2Br$; (h) MCPBA, $CHCl_3$; (i) $LiEt_3BH$, THF; (j) SEMCl, *i*-Pr_2NEt, THF, 50 °C; (k) Na, NH_3; (l) (1) oxalyl chloride, Me_2SO, −78 °C; (2) *i*-Pr_2NEt; (m) (1) LDA, THF; (2) CH_2O, (3) MsCl, *i*-Pr_2NEt; (n) DIBAH, hexane, −78 °C; (o) 0.1 M HCl in MeOH.

Geminal dimethylation and carbonyl transposition of **10** were accomplished by addition of methyllithium, oxidative rearrangement with PCC,[14] and reaction with lithium dimethyl cuprate[15] to afford enone **11**. Reduction and benzylation followed by epoxidation afforded an inseparable 3:2 mixture of epoxides **12a** and **12b**. Treatment of this mixture with $LiEt_3BH$ produced a mixture of alcohols, from which the desired diastereomer could be easily separated. Protection of this alcohol as a SEM ether[16] followed by debenzylation and Swern oxidation[17] produced ketone **13**. Introduction of the α-methylene group to produce **14** was accomplished by enolate formation with LDA, quenching with formaldehyde, and elimination of the intermediate alcohol. Reduction with DIBAH produced a separable 1:1 mixture of alcohols, which were deprotected to afford poitediol and 4-epipoitediol. The synthetic pitoediol gave spectral data identical with an authentic sample.[18]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to NSF for support of this work. We are also grateful to NSF for funds used to purchase a 270-MHz NMR spectrometer.

(4) All new compounds gave satisfactory NMR, IR, and mass spectral or analytical data.

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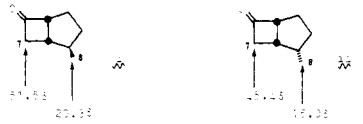
(8) The relative stereochemistries of the major and minor norcaranols were determined by acid-catalyzed rearrangement to the bicyclo[3.2.0]heptanones



i and ii, respectively, which gave the ^{13}C NMR data shown below. Both C7 and C8 of the ketone **ii** from the minor norcaranol are clearly shifted upfield due to the steric shielding effect of the endo methyl group.[9]

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