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Synthesis of Callicarpone, a Fish-killing Diterpene

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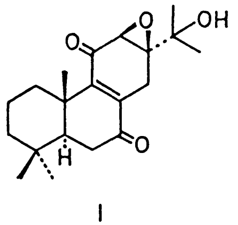
Callicarpone, a fish-killing diterpene, has been synthesized from (+)-11-acetoxy-12-benzoyloxy-8,11,13-abietatrien-7-one via an intermediate, 11,11-ethylenedioxy-9βH-abieta-13(15)-en-12-one.

Callicarpone, a fish-killing diterpene, has been isolated from the leaves of *Callicarpa candicans* by Kawazu et al.[1] On the basis of chemical and spectroscopic studies, they deduced the structure of callicarpone to be 12β,13β-epoxy-15-hydroxy-8-abietene-7,11-dione (1),[1,2] possessing some unique functional features in B and C rings of abietane skeleton. We have now attempted the synthesis of this unique toxin and herein wish to report a successful synthesis of callicarpone (1). For the present purpose, (+)-11-acetoxy-12-benzoyloxy-8,11,13-abietatrien-7-one (2)[3] was chosen as a convenient relay intermediate, because the synthetic route of 2 starting from (R)-(-)-α-cyclocitral via (+)-ferruginol[4] has already been established in our laboratory.



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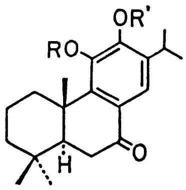
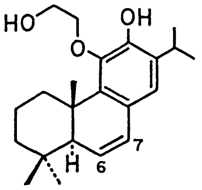
Hydrolysis of 2 with sodium hydrogencarbonate in refluxing aqueous methanol afforded the corresponding 11,12-diol which was partially methoxymethylated with a mixture of chloromethyl methyl ether, anhydrous potassium carbonate, and 18-crown-6 in tetrahydrofuran-dichloromethane (1:1) to give 12-methoxymethyl ether (3), mp 131-132 $^{\circ}$C, in 78% yield. The ether 3 was further converted into 11-(ethoxycarbonylmethyl) ether (4: 97%) by treatment with a mixture of ethyl bromoacetate, anhydrous potassium carbonate, and 18-crown-6 in acetone. Lithium aluminum hydride reduction of 4 in refluxing tetrahydrofuran followed by dehydration with refluxing dilute hydrochloric acid afforded a tetraene compound (5), mp 167.5-168 $^{\circ}$C. The tetraene 5 was submitted to catalytic hydrogenation over Pd-C in acetic acid to give 12-hydroxy-11-(2-hydroxyethoxy)-8,11,13-abietatriene (6), mp 180.5-181.5 $^{\circ}$C, in 93% yield from 4. Oxidation of 6 with thallium nitrate trihydrate and calcium carbonate[5] in tetrahydrofuran yielded an o-quinone acetal (7), mp 125.5-126.5 $^{\circ}$C, in 85% yield. Catalytic hydrogenation of 7 over Rh-Al_2O_3 in dioxane in the presence of aqueous potassium hydroxide produced three tetrahydro ketones (8, 9, 10) and a dihydro ketone (11) in 41, 5, 12, and 10% yields, respectively. Treatments of 8 (mp 77-77.5 $^{\circ}$C) and 11 (mp 91.5-92.5 $^{\circ}$C) with sodium methoxide in refluxing methanol afforded the corresponding C-13 epimers, 9 (93%) and 12 (46%), respectively. On the other hand, when the ketone 10 was refluxed with sodium methoxide in methanol, the starting 10 was recovered. These results indicate that 8 and 11 possess an axial isopropyl group whereas an isopropyl group in 9, 10, and 12 must be in an equatorial configuration. The ^{1}H NMR spectra[6)] of 8, 9, 10, 11, and 12 showed a singlet signal due to the C-10 angular methyl group at δ 1.06, 1.06, 0.81, 1.16, and 1.17, respectively. The appearance of the angular methyl group of 10 in very high field (δ 0.81) is attributable to the shielding effect of the C-12 carbonyl group. This suggested that the ketone 10 possesses a trans-anti-cis geometry as shown in a perspective drawing B of Fig. 1. Reduction of 10 with lithium aluminum hydride in ether afforded an alcohol (13: 98 %). The ^{1}H NMR spectrum of 13 showed a singlet signal due to the C-10 angular methyl group in very low field (δ 1.28), indicating that the angular methyl group was deshielded by a newly formed hydroxyl group. Thus, the structure of 10 was assigned to be 11,11-ethylenedioxy-8αH,13αH-abietan-12-one. The structures of the C-13 epimeric ketones 8 and 9 were also assigned, respectively, to be 11,11-ethylenedioxy-9βH-abietan-12-one and 11,11-ethylenedioxy-9βH,13αH-abietan-12-one, possessing the same trans-syn-cis geometry as shown in a perspective drawing A of Fig. 1. The structural confirmation of 8 and 9 is described later. The comparisons of the ^{1}H NMR spectra of 11 (C_{10}-CH_3: δ 1.16) and 12 (C_{10}-CH_3: δ 1.17) with 13αH-abieta-8-en-18-ol (14) (C_{10}-CH_3: δ 0.98)[7)] indicated that the C-10 methyl groups in 11 and 12 were each deshielded by their C-11 acetal group. The spectrum of 12 also showed a double triplet signal due to the C-13 methine proton in very low field (δ 2.83, J=11 and 7.5 Hz). This suggested a cis relationship between the C-13 proton and an acetalic oxygen as shown in a perspective drawing C in Fig. 1. Thus, the structure of the ketone 11 was assigned to be 11,11-ethylenedioxy-13αH-abieta-8-en-12-one. Oxidation of 8 with benzeneseleninic anhydride and sodium hydride[8)] in refluxing toluene produced a mixture of the C-13 epimeric alcohols (15: ca. 3:2) which was dehydrated with thionyl chloride in pyridine to give 11,11-ethylenedioxy-9βH-abieta-13(15)-en-12-one (16: 20%), mp 139-140 °C, and 11,11-ethylenedioxy-9βH-abieta-13-en-12-one (17: 68%), mp 71.5-72 °C. In the ^{1}H NMR spectrum of 17, a broad doublet signal due to an olefinic proton was observed at δ 6.64 with a coupling constant ($J_{8,14}$) of 6 Hz. This coupling constant suggested that the enone 17 possesses a trans-syn-cis geometry.[9)] The ketone 9 was similarly oxidized with benzeneseleninic anhydride and the resulting mixture of the C-13 epimeric alcohols (15) was dehydrated with thionyl chloride to give 16 (11%) and 17 (35%) together with the recovered 9 (41%). Reduction of 17 with potassium tri-sec-butylborohydride[10)] in tetrahydrofuran followed by treatment with alkaline hydrogen peroxide afforded the ketones, 8 (67%) and 9 (23%). The exo-enone 16 was reduced with lithium aluminum hydride in ether and the resulting alcohol (18) (^{1}H NMR: δ 4.22, 1H, bs, $C_{12\beta}$-H) was further heated with dilute sulfuric acid in dioxane at 90 °C to give 15-hydroxy-12-abieten-11-one (19)[11)] in 70% yield from 16. Oxidation of 19 with alkaline hydrogen peroxide in methanol afforded an epoxide (20), mp 89-89.5 °C, in 56% yield. It is well known[12)] that the epoxydation of cyclic ketones containing α,β-endocyclic double bonds with alkaline hydrogen peroxide proceeds in a stereospecific manner to give a single epoxide. The nucleophilic attack of hydroperoxide anion to the polarized double bond in 19 would produce two conceivable transition state carbanions, D and E in Fig. 2. Of these two transition states, only D having an axial hydroperoxy group can fulfill the



2 R=Ac, R'=COPh
3 R=H, R'=CH_2OMe
4 R=CH_2CO_2Et, R'=CH_2OMe



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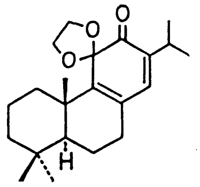
6 6,7-dihydro



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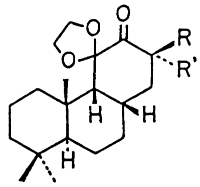
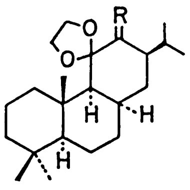
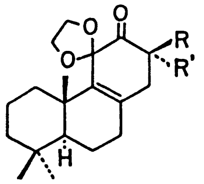


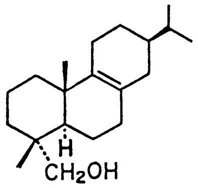
8 R=H, R'=i-Pr
9 R=i-Pr, R'=H
15 R,R'=i-Pr,OH



10 R=O
13 R=α-H, β-OH



11 R=i-Pr, R'=H
12 R=H, R'=i-Pr



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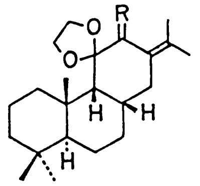
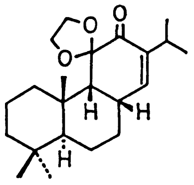


16 R=O
18 R=α-OH,β-H



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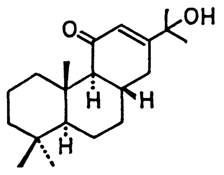

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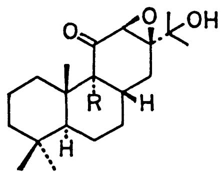
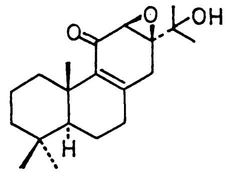


20 R=H
21 R=Br



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stereoelectronic requirement for oxirane ring formation by intramolecular nucleophilic displacement. Thus, the stereochemistry of the oxirane ring in 20 was assigned to be β-configuration. This assignment was supported by the ^1H NMR spectrum of 20. Irradiation of the C-9 proton (δ 2.13, d, J=12 Hz) resulted in a 9.5% enhancement of the C-12 proton signal (δ 3.43), suggesting a cis relationship between these two protons. A sharp singlet signal at δ 3.43 was also suggested no W-configuration coupling between the C-12 proton and the C-14β proton. The epoxide 20 was then treated with bromine in carbon tetrachloride in the presence of silica gel to give a bromide (21: 69%), mp 146-147 °C, which was further converted into 12β,13β-epoxy-15-hydroxy-8-abieten-11-one (22: 91%) by dehydrobromination with

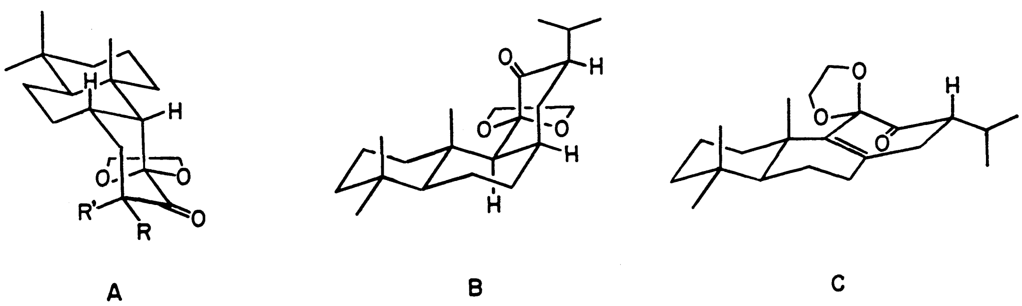
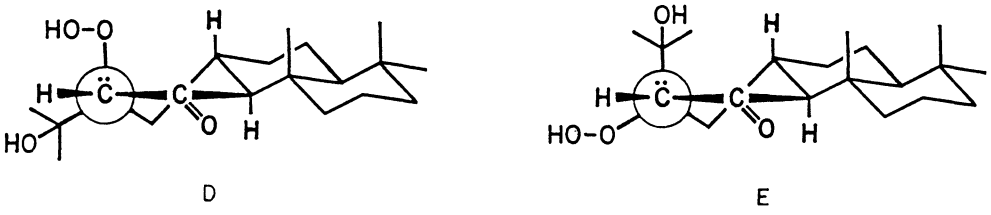


Fig. 1. Conformations of 8, 9, 10, and 12.



D

E

Fig. 2. Transition state carbanions in epoxidation of 19.

lithium carbonate and lithium bromide in N,N-dimethylformamide at 90 $^{\circ}$C. Oxidation of 22 with chromium trioxide in acetic acid at 50 $^{\circ}$C afforded the desired enedione (1: 32%), mp 112.5-113 $^{\circ}$C, $[\alpha]_D$ -194° ($CHCl_3$), IR ($CHCl_3$) 3555 and 1667 cm^{-1}, ^1H NMR δ 0.88, 0.91, 1.17, 1.27, and 1.37 (each 3H and s), 2.42 (1H, d, J=19.5 Hz) and 3.40 (1H, dd, J=19.5 and 1.3 Hz), 3.70 (1H, d, J=1.3 Hz). The physical and spectral data of the synthetic 1 were identical with those of natural callicarpone.

From the present study, the stereochemistry of oxirane ring in natural callicarpone (1) was conclusively assigned as β-configuration.

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