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CYCLIZATION OF POLYENES XXVII[1]
SYNTHESIS OF OXOCRINOL, dl-CAULERPOL, AND dl-CRINITOL

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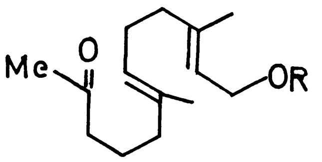
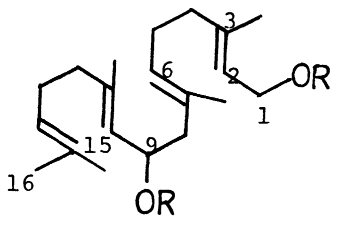
Novel terpene alcohols, oxocrinol (1a), caulerpol (3a), and crinitol (2a), isolated from marine algae, were synthesized by the alkylation of lithium salt of benzenesulfonyl derivatives, 5, 6, and 11 (R = THP; X = SO_2Ph) followed by reductive cleavage of SO_2Ph and the protecting groups. The present study confirms unequivocally the proposed structures of oxocrinol, caulerpol, and crinitol, respectively.

Recent papers have described the elaboration of several new terpene alcohols from marine algae. These are oxocrinol (1a) and crinitol (2a) from Cystoseira crinita Bory[2] and caulerpol (3a) from Caulerpa brownii[3], respectively.

From a synthetic point of view, these terpenoids are characterized by the presence of a geranyl moiety as their common partial structure. In conjunction with another project, we needed acquirement of a method for carbon carbon bond formation accompanying an introduction of 3,7-dimethyl-2,6-octadien-1-ol unit. For this purpose, we undertook the synthesis of these terpenoids as our model experiment.



(1a) R = H
(1b) R = Ac



(2a) R = H
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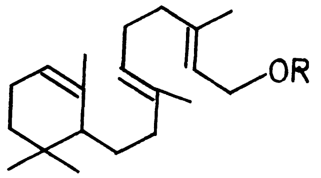
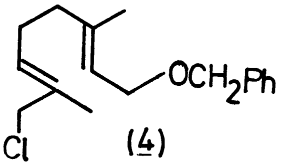


(3a) R = H
(3b) R = Ac

SYNTHESIS OF OXOCRINOL (1a) AND dl-CAULERPOL (3a)

Oxocrinol (1a) and dl-caulerpol (3a) were synthesized effectively starting from trans,trans-8-chloro-3,7-dimethyl-2,6-octadienyl benzyl ether (4)[4]. 1-Benzenesulfonyl-3-ethylenedioxybutane (5)[5] was lithiated with 1 mol equivalent of BuLi in a mixed solvent of anhydrous tetrahydrofuran (THF)-hexamethylphosphoramide (HMPA) (4:1) at -76°C under argon atmosphere for 1 h. A THF solution of freshly prepared allyl chloride (4) was dropped to the anion under the same conditions. After 1 h at -76°C, the mixture was quenched successively with MeOH-ether at -76°C and then water at ambient temperature. After usual work up, the coupled product (7) was isolated in 85% yield. 7: PMR (CCl_4), 1.15 (s, Me), 1.47 and 1.60 (C=C-Me x 2), 3.95 (2H, d, 6.5 Hz, $OCH_2C=C$), 4.42 (2H, s, OCH_2Ph), 5.12 (1H, m, C=C-H), and 5.33 ppm (1H, t, 6.5 Hz, $C=CH-CH_2O-$). Similarly, metalation of α-cyclocitryl phenyl sulfone (6)[6] with BuLi in THF-HMPA (4:1) at -76°C and addition of 4 resulted in formation of the coupled product (8) in 91% yield. Simultaneous reductive removal of both benzenesulfonyl and benzyl groups from the coupled products, 7 and 8, was achieved by treatment with excess Li in ethylamine[8] at -76°C, affording 9 and 3a in 41 and 52% yields, respectively. Treatment of 9 with HCl in refluxing acetone yielded 1a quantitatively. IR (CCl_4) and PMR spectra of 1a and 3a were identical with those of natural oxocrinol (1a) and caulerpol (3a), respectively. The structures of the synthesized materials were further confirmed by the physical data (IR and PMR) of the corresponding acetates, 1b and 3b.



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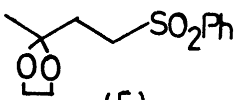

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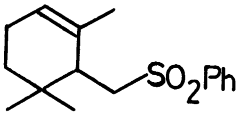

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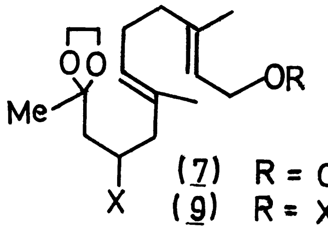
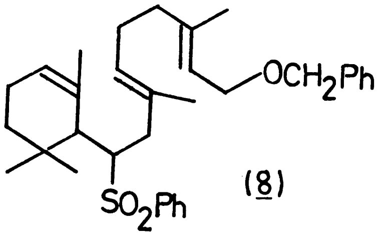


(7) $R = CH_2Ph$, $X = SO_2Ph$
(9) R = X = H



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SYNTHESIS OF CRINITOL (2a)

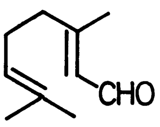
Coupling reaction of the formyl carbon of trans citral (10) with C_8-carbanion of geraniol derivative (11) was designed for the construction of crinitol skeleton. It has been observed that lithium salt of allyl phenyl sulfide reacts with aldehyde and ketone at α and γ-positions of the allylic moiety[9]. In fact, our model experiment demonstrated that when lithiated geranyl phenyl sulfide was allowed to react with acetone in anhydrous THF at -76°C under argon atmosphere, 2:3 mixture of α and γ-alkylated products, 13 and 14 (X = SPh) was formed in 81% yield[10]. PMR; 13 (X = SPh), 1.19 and 1.24 (s, Me_2COH), 1.33 (d, 1.2 Hz, C=CMe), 1.58 and 1.67 ($C=CMe_2$), 3.80 and 5.18 (each 1H, d, 11 Hz, $PhSO_2CHCH=C$), and 5.0 ppm (m, C=C-H). 14 (X = SPh), 1.05 (s, Me), 1.15 (Me_2COH), 1.58 and 1.66 ($C=CMe_2$), 5.05 (m, C=CH), 5.98 and 6.05 ppm (each 1H, d, 16 Hz, -CH=CH-). When SPh of 12 was converted to the corresponding SO_2Ph group, however, we found that the addition occurred regioselectively at α-position to give 13 ($X = SO_2Ph$) in 71% yield. Our present finding was applied to the coupling reaction of trans citral (10) with the lithium salt of benzenesulfonyl derivative (11, R = THP; $X = SO_2Ph$), which was prepared from the known alcohol (11, R =

Ac; X = OH)[11] in 75% overall yield. The alcohol was submitted to the successive treatments with PPh_3 in refluxing CCl_4 to the allylic chloride (11, R = Ac; X = Cl) followed with $PhSO_2Na$ in DMF[12] to afford the benzenesulfonyl derivative (11, R = Ac; X = SO_2Ph). The corresponding tetrahydropyranyl ether was obtained by hydrolysis with methanolic KOH at -20°C and subsequent etherification with dihydropyran under acidic conditions[13].

The benzenesulfonyl derivative (11, R = THP; X = SO_2Ph) was lithiated with 1.2 molar equivalents of LDA[14] in anhydrous THF at -76°C under argon atmosphere. Reaction of 10 with the lithium salt at the same temperature proceeded smoothly to result in the exclusive formation of a ca. 1:3 diastereomeric mixture[15] of α-alkylated product (15) in 81% yield, which was closely located on SiO_2 TLC under several solvent systems. Each isomer was easily separated by SiO_2 column chromatography, eluted with hexane-AcOEt (4:1), of the corresponding diacetate (17) derived from the dihydroxy derivative (16)[16]. PMR analysis of each isomer revealed that the coupling had occurred at α-position. PMR; 17a (major), 1.96 (Ac x 2), 3.82 (1H, d, 9.8 Hz, $-C\underline{H}SO_2Ph$), 4.50 (2H, d, 6.5 Hz, $-C\underline{H}_2OAc$), and 6.00 ppm (1H, t, 9.8 Hz, $-C\underline{H}OAc$). 17b (minor), 1.92 and 1.96 (each 3H, Ac x 2), 3.53 (1H, d, 6.0 Hz, $-C\underline{H}SO_2Ph$), 4.48 (2H, d, 6.9 Hz, $C\underline{H}_2OAc$), and 6.03 ppm (1H, dd, 9.0 and 6.0 Hz, $-C\underline{H}OAc$).

The diastereomeric mixture (16) was treated with excess Li in ethylamine containing 2 molar equivalents of BuLi at -76°C to give a reduced product (2a) in 48% yield after purification with SiO_2 column chromatography using hexane-AcOEt (4:1).

IR (CCl_4) and PMR spectra of our synthetic compound (2a) are identical with those of natural crinitol. The geometry of double bonds of 2a was confirmed by CMR spectrum of the corresponding acetate (2b). The chemical shift of each carbon is in accord with the chemical shift rules[17]. CMR ($CDCl_3$) of 2b, 61.5 (C_1), 118.6 (C_2), 140.6 (C_3), 39.5 (C_4), 26.4 (C_5), 127.5 (C_6), 132.0 (C_7), 45.4 (C_8), 70.1 (C_9), 123.8 (C_{10}), 142.3 (C_{11}), 39.6 (C_{12}), 26.4 (C_{13}), 124.2 (C_{14}), 131.5 (C_{15}), 25.8 (C_{16}), and 16.5 ($C=C-\underline{Me}$ x 2), 16.9 ($C=C-\underline{Me}$) and 17.7 ppm ($C=C-\underline{Me}$).



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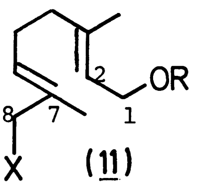

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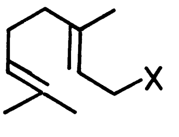

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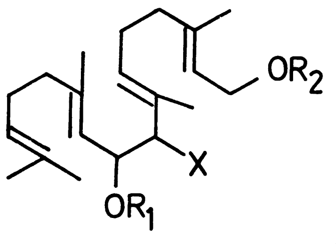
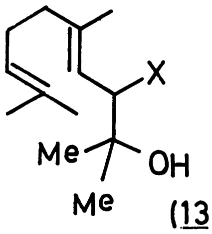


(15) R_1= H, R_2=THP, X =SO_2Ph
(16) R_1= R_2= H, X =SO_2Ph
(17) R_1=R_2= Ac, X = SO_2Ph



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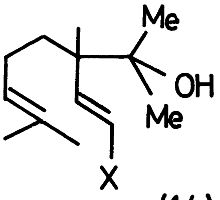

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6. Compound (6) was prepared by the cyclization of geranyl phenyl solfone with 0.5 molar equivalent of $SnCl_4$[7] in CH_2Cl_2 at 40°C followed by SiO_2 column chromatography and then recrystallization from hexane-ether, 6; mp, 65-66°C; PMR (CCl_4), 0.93 (Me x 2), 1.66 (C=CMe), 2.78 and 3.14 (each 1H, $-C\underline{H}_AC\underline{H}_BSO_2Ph$, $J_{AB} = 15$, $J_{AX} = 4$, and $J_{BX} = 5$ Hz, respectively), and 5.31 ppm (C=C-H, m).
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10. These isomers were easily separated by SiO_2 column chromatography using hexane-AcOEt (6:1).
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14. LDA was prepared in situ by treatment of diisopropylamine with 1.2 molar equivalents of BuLi in anhydrous THF at 0°C for 10 min.
15. The formation ratio was estimated by PMR spectrum of diacetate, 17.
16. Compound (15) was hydrolyzed by the action of p-TsOH in MeOH.
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