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THE STEREOSELECTIVE TOTAL SYNTHESIS OF RACEMIC COSTOL AND COSTIC ACID

James A. Marshall and Ronnie D Carroll

Department of Chemistry, Northwestern University
Evanston, Illinois 60201

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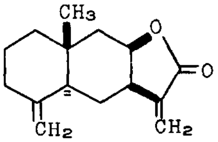
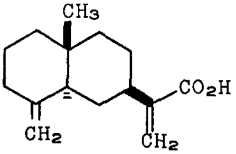
The sesquiterpenes costol (7)[1] and costic acid (10)[2] possess C-7 side chains which are unique among the eudesmane group. However, a similar type of oxygenated isopropenyl substituent commonly occurs in the form of an α-methylene-γ-butyrolactone moiety. Isoalantolactone,[3] for example, bears a strong resemblance to costic acid. Our interest in potential synthetic routes to the alantolactone family[4] prompted a consideration of methods which might also apply to the construction of costol (7) and the closely related costic acid (10).



isoalantolactone

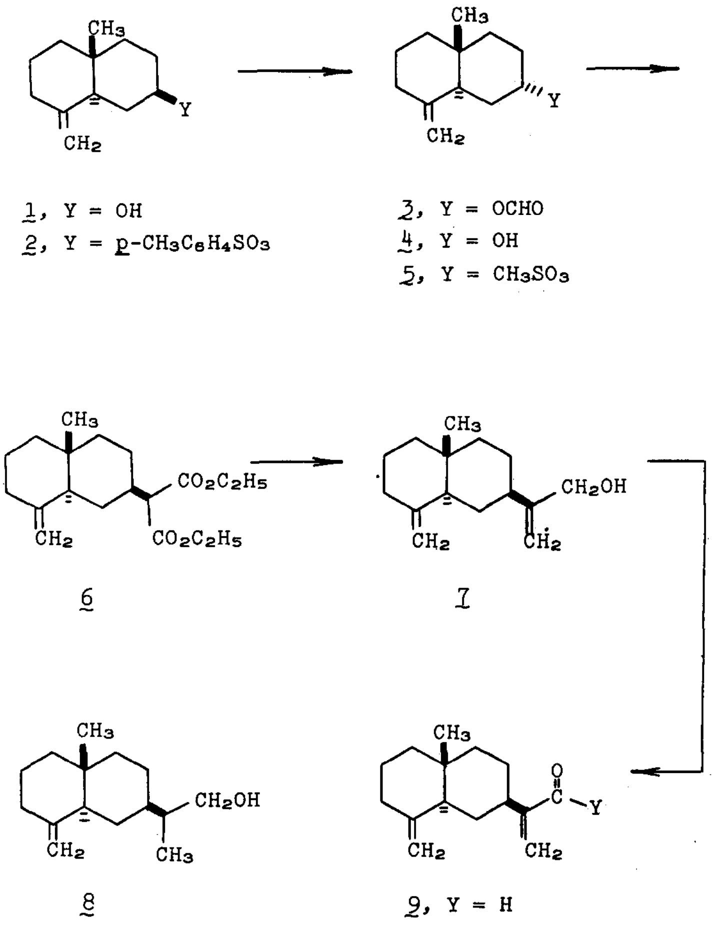


costic acid

From our viewpoint, the principal synthetic problem relative to costol involved the aforementioned propenol side chain. We required for the attainment of this objective a stereoselective method which would be compatible with an existing olefinic linkage.[5] The total synthesis presented below delineates a satisfactory solution to this problem and confirms the structures assigned to costol (7) and costic acid (10).

The previously described decalyl p-toluenesulfonate 2 (m.p. 81-82°)[6] upon treatment with N,N-dimethylformamide (95°, 29 hr.)[7] afforded the decalyl formate 3 which was subjected to alkaline hydrolysis without purification. The resulting axial alcohol 4 [m.p. 66.5-67°; λ_{max}^{KBr} 3.02(OH), 3.27 (vinyl H), 6.08 ($C=CH_2$), 10.00, 10.22, 10.94, 11.28, 11.60, 11.94 μ] differed from the known equatorial isomer 1[6] according to gas chromatographic retention time, infrared spectrum, and mixture melting point. The methanesulfonate derivative 5 (93% yield, m.p. 57-58°) smoothly yielded the decalylmalonate 6 [80% yield; b.p. 125° (bath temperature) at 0.3 mm.; λ_{max}^{film} 3.27 (vinyl H), 5.78 (ester CO), 6.09 ($C=CH_2$), 8.71, 9.66, 11.26 μ] through the action of diethyl malonate and sodium hydride in refluxing 1,2-dimethoxyethane.

The sodio derivative of decalylmalonate 6, prepared *in situ* using sodium hydride in refluxing 1,2-dimethoxyethane (64 hr.), after reduction with lithium aluminum hydride in the same refluxing solvent (3 hr.) afforded a 3:1 mixture (analyzed by gas chromatography) of racemic costol



1, Y = OH

2, Y = p-$CH_3C_6H_4SO_3$

3, Y = OCHO

4, Y = OH

5, Y = CH_3SO_3

6

7

8

9, Y = H

10, Y = OH

(7) and 11,12-dihydrocostol (8) in 82% yield. Previous enolate reduction studies using diethyl cyclohexylmalonate gave a comparable ratio of the analogous products.[8] The mixture of alcohols yielded a mixture of costal (9) and unchanged dihydrocostol 8 after treatment with manganese dioxide in chloroform (12 g. of MnO_2 per 1 g. of alcohol mixture) for 2.5 hr.[9] The costal component of this mixture was eluted from Florisil[10] with benzene [63% yield of 9 based on the mixture of 7 and 8; b.p. 110° (bath temperature) at 0.3 mm.; λ_{max}^{film} 3.27 (vinyl H), 3.72 (aldehyde H), 5.92 (conj. CO), 6.08 ($C=CH_2$), 6.16 (conj. $C=CH_2$), 8.00, 8.26, 8.48, 10.60, 10.91, 11.26 μ] and treated with ethereal lithium aluminum hydride whereupon racemic costol (7) [b.p. 90° (bath temperature) at 0.2 mm.; λ_{max}^{film} 2.99 (OH), 3.27 (vinyl H), 6.08 ($C=CH_2$), 7.23, 8.48, 8.76, 9.05, 9.42, 9.45, 9.71, 10.09, 10.59, 10.68, 11.25, 11.60 μ] was formed in 95% yield. Racemic costic acid (10) [m.p. 113-115°; λ_{max}^{KBr} 3.0-4.0 (acid OH), 5.94 (conj. CO), 6.10 ($C=CH_2$), 6.18 (conj. $C=CH_2$), 7.69, 7.96, 8.19, 8.66, 9.16, 10.52, 11.30, 11.67 μ] was secured upon oxidation of racemic costal (9) with silver oxide.[11]

Both racemic costol and costic acid were identified by comparison of their infrared and n.m.r. spectra with the published spectra of the natural products.[2]

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