

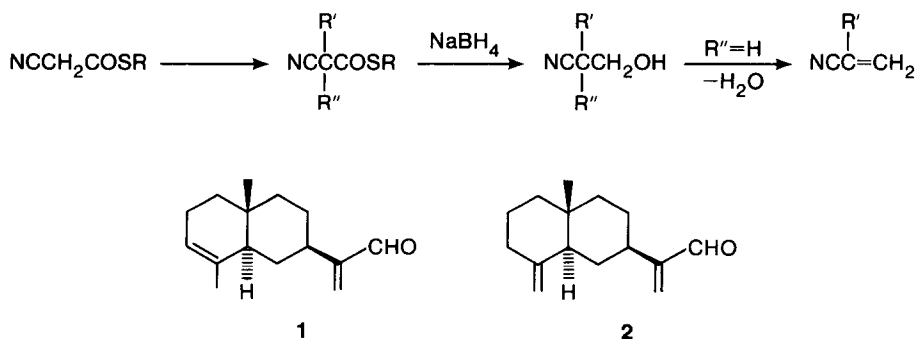
THE TOTAL SYNTHESIS OF (±)- α -COSTAL

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Abstract: The structure of α -costal (**1**) has been confirmed by an unequivocal total synthesis which makes use of S-t-butyl cyanthiolacetate to facilitate the incorporation of the labile acrolein unit present in the naturally occurring aldehyde.

Recently, we have developed a convenient method for the preparation of acrylonitrile derivatives¹ using cyanthiolacetate as a masked β -hydroxypropionitrile carbanion according to Scheme 1. The method, which in essence facilitates the introduction of a highly functionalized isopropyl unit, is expected to have broad utility in the synthesis of natural products, especially those of isoprene origin. This is illustrated, in this communication, with the total synthesis of α -costal (**1**) in racemic form. The sesquiterpene aldehyde was isolated two decades ago along with the β -isomer (**2**) as an inseparable mixture from the leaf oil of *Thujopsis dolabrata* Sieb. et Zucc. by Ito and co-workers.² Its structure was tentatively deduced² solely on the basis of the information gathered on the mixture. This assignment is now confirmed by the unequivocal synthesis reported herein.

Scheme 1

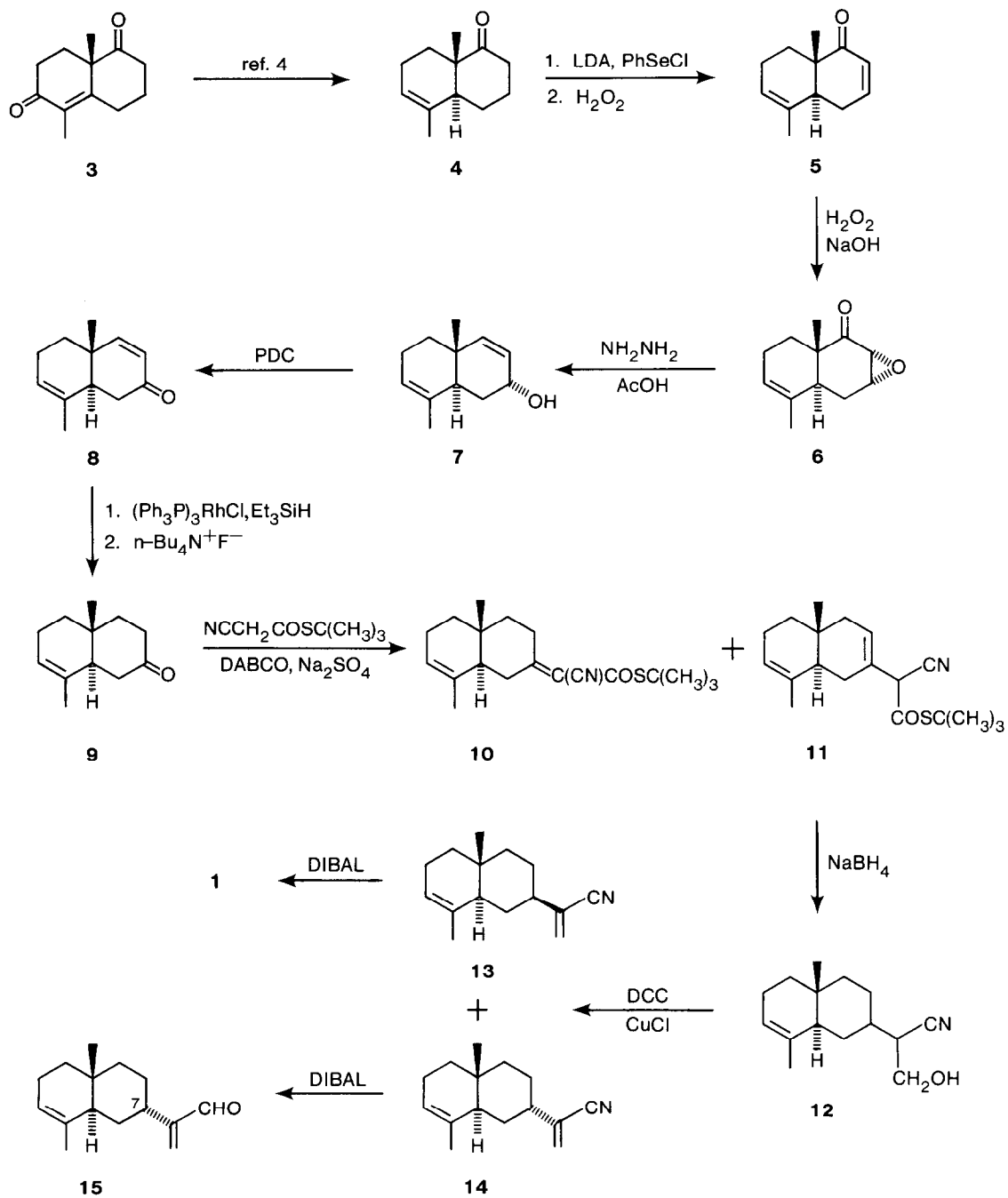


In approaches to the total synthesis of α -costal (**1**), ketone **4** presents itself as an attractive intermediate whose transformation to the target molecule requires the incorporation of an acrolein moiety to the carbon β to the ketone carbonyl. This known compound was readily prepared by modifying the methyl derivative (**3**)³ of Wieland-Miescher ketone according to the described procedure.⁴ In order to activate the β -carbon of its carbonyl, ketone **4** was subjected to treatment with lithium diisopropylamide and phenylselenenyl chloride in tetrahydrofuran at -78°C for 3 hr⁵ (Scheme 2). Oxidative elimination of the resulting selenide using 30% hydrogen peroxide gave dienone **5** in 78% yield. The conjugated carbon-carbon double bond was selectively epoxidized with hydrogen peroxide (30%) in ethanol in the presence of sodium hydroxide to give epoxy ketone **6**, m.p. $54\text{--}55^\circ\text{C}$, as a single stereoisomer in 89% yield. Wharton reaction⁶ of **6** with methanolic hydrazine hydrate and a small amount of acetic acid afforded alcohol **7** (74% yield) which was shown by the nmr analysis to possess an axially disposed hydroxyl group. Alcohol **7** was oxidized with pyridinium dichromate⁷ to give an 89% yield of enone **8**. Hydrosilation of **8** using tris(triphenylphosphine)rhodium chloride and triethylsilane^{8,9} followed by treatment of the silyl enol ether thus formed with tetra-*n*-butylammonium fluoride in tetrahydrofuran effected the selective reduction of the conjugated carbon-carbon double bond to give ketone **9** in 73% yield.

To introduce the acrolein unit, ketone **9** was condensed with *s-t*-butyl cyanthiolacetate at room temperature in tetrahydrofuran using 1,4-diazabicyclo[2.2.2]octane as a base and anhydrous sodium sulfate for the removal of water generated during the reaction. A mixture, consisting of two isomers each of compounds **10** and **11** (4:1), was produced in 73% yield. Sodium borohydride reduction of this mixture in ethanol at -40°C ¹⁰ for 4 hr and at room temperature for 12 hr gave rise to a mixture of diastereomeric alcohols **12**¹¹ (91% yield) which, without separation, was subjected to dehydration with dicyclohexylcarbodiimide in refluxing ether in the presence of a catalytic amount of copper(I) chloride¹² to give cyano olefins **13** and **14** in 2:1 ratio and in 94% total yield. The former showed, in the nmr spectrum, a multiplet at δ 2.28 for the methine proton adjacent to the acrylonitrile moiety. The corresponding proton of the minor isomer was found to be at δ 2.72 also as a multiplet. The fact that the methine proton of the major isomer appeared at a much higher field than that of the minor isomer by 0.44 ppm indicated its axial orientation.^{13,14} Accordingly, the stereochemistry of **13** and **14** was deduced as shown.

Epimeric cyano olefins **13** and **14** were individually treated with diisobutylaluminum hydride at -78°C in toluene for 3 hr. From the former compound, an aldehyde was obtained in 54% yield. This compound showed the following nmr

Scheme 2



(CCl₄) signals identical with those reported² for natural α -costal (**1**): δ 0.83 (s, 3H, -CH₃), 1.58 (s, 3H, =C¹CH₃), 2.53 (m, 1H, C-7 H), 5.28 (m, 1H, =CH-), 5.90, 6.21 (both br.s, 1H each, =CH₂), and 9.52 (s, 1H, -CHO).

Reduction of the minor epimer **14** gave a 48% yield of compound **15**, an epimer of α -costal which showed the following signals in the nmr spectrum: δ 0.85 (s, 3H, -CH₃), 1.54 (br.s, 3H, =C¹CH₃), 3.04 (m, 1H, C-7 H), 5.34 (m, 1H, =CH-), 6.11 (s, 1H, =CHH), 6.48 (d, 1H, J = 1.5 Hz, =CHH), and 9.48 (s, 1H, -CHO). The fact that the C-7 proton of α -costal (**1**) appeared again at a much higher field ($\Delta\delta$ = 0.51 ppm) than the corresponding one of epi- α -costal (**15**) is a further confirmation of the stereochemical assignments.¹⁵

References and Notes

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2. S. Ito, K. Endo, H. Honma, and K. Ota, *Tetrahedron Lett.*, 3777 (1965).
3. Enedione **3** was prepared by an improved procedure as follows. 2-Methyl-1,3-cyclohexanedione was treated with ethyl vinyl ketone and 1,4-diazabicyclo[2.2.2]octane (1.1 equiv. each) in 1,2-dimethoxyethane at room temperature for 12 hr. The Michael adduct thus obtained in 90% yield was then cyclized using benzoic acid (1.1 equiv.) and triethylamine (0.7 equiv.) in refluxing benzene to give compound **3** (89% yield).
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10. At this temperature, only the carbon-carbon double bond was reduced.
11. Apparently, under the reaction conditions compound **11** was isomerized to **10** and then reduced.
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13. L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press Ltd., London, 1969.
14. The predominant formation of the desired epimer **13** resulted apparently from the addition of the hydride ion from the sterically less hindered side of compound **10**.
15. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the University of Alberta for financial support.

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