A SYNTHESIS OF THE ABIEANE DITERPENOID QUINONE (±)-ROYLEANONE VIA MALEOYLCOBALT TECHNOLOGY.

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Abstract. (±)-Royleanone has been synthesized by rapid construction of a highly substituted quinone using maleoylcobalt complex technology followed by acid induced cyclization of the corresponding hydroquinone methyl ether onto a tethered enone. The synthesis was completed by straightforward functional group manipulations.

Royleanone, 1, is an abietane diterpenoid quinone first isolated from the roots of Inula Royeana D. C. by Edwards.2 During the course of a search for tumor inhibitors of plant origin, Kupchan also isolated royleanone from Taxodium distichum Rich and reported its modest cytotoxicity against human carcinoma of the nasopharynx.3 More recently royleanone has been found as a main constituent of the root of several Salvia species.4-7 In order to probe further the scope and limitations of our previously developed maleoylcobalt route to highly substituted quinones (Eqn. 1),8-17 (±)-royleanone was chosen as a target for total synthesis. Royleanone has been the object of a number of previous total synthesis efforts.18-21

A very direct approach to a precursor of the royleanone carbon skeleton utilizing the mild and regioselective nature of the maleoylcobalt quinone formation is shown in equation 2. Based on previous experience,16 reaction of isopropyl methoxy maleoylcobalt complex 2 (Ln = dimethylglyoxime-pyridine-chloride) with enediyne 3 would be expected to occur most rapidly at the less hindered terminal alkyne and with a regiochemistry that selectively places the terminal alkyne hydrogen and the methoxy substituent of the cobalt complex in a 1,3-relationship on the quinone product. To test this thesis, cobalt complex 2a, readily prepared in 46% from CICo(PPH3)3 and 3-isopropyl4-methoxycyclobutene-1,2-dione,22 was converted into the more reactive dimethylglyoxime ligated complex 2b15 in 86% yield and was treated with one equivalent of AgBF4.23 Then, addition of 1.6 equivalents of endiyne 324 in dichloroethane at room temperature followed by reaction for 24 hr provided advanced intermediate 4 in 77% yield after oxidation of the crude reaction product with Ag2O. Quinone 4 contained all the carbon atoms necessary to complete the royleanone synthesis. Analysis by 1H NMR indicated a 7:1 mixture of regioisomers; chemical shift differences suggesting that the isomer depicted by structure 4 predominated in this reaction.25 Compound 4 was best handled as the hydroquinone, reduction with sodium hydrosulphite followed by trituration of the crude product with cold petroleum ether providing the crystalline hydroquinone 5, devoid of the minor regioisomer component, in 67% yield.
Hydroquinone 5 was converted into the hydroquinone diene 6a (H₂/Pd on BaSO₄ - quinoline, 86%), the trimethoxyaryl ether 6b (NaH, Mel in THF on 6a, 74%), and the sensitive dienyl quinone 7 (Ag₂O in ether on 6a, 96%), none of which could be induced to cyclize to a species bearing the tricyclic skeleton of royleanone via thermal or photochemical [2+2+2] electrocyclization. A similar strategy was successfully applied by Liotta and Ott to a total synthesis of pallescensin A using a furanoid precursor instead of the quinoid systems under consideration here.²⁶

The failure of electrocyclization protocols to establish the abietanoid skeleton of royleanone led to consideration of Friedel-Crafts-type conditions for construction of the crucial trans-fused B ring, a tactic that has proven valuable in the construction of the B-ring of other abietanoids.²⁷-³¹ After a number of unsuccessful attempts to prepare intermediate 8 by hydration of the alkyne of 5 or its corresponding trimethyl ether, a successful reaction was accomplished by treatment of 5 with BH₃·THF followed by H₂O₂/NaOH workup. However, upon analysis of spectroscopic data, the product of this reaction was identified as the isomeric ketone 9, evidently formed by a hydroxyl-directed hydroboration³²-³³ of the alkylnylhydroquinone.

The trimethyl ether, 14, of the sought after tricyclic precursor 8, was efficiently synthesized by an alternative route (Scheme). β-Cyclocitris³⁴,³⁵ was treated with propargyl magnesium bromide³⁶ giving homopropargyl alcohol 10 in 65% yield which was uncontaminated with the allene isomer. Protection of the alcohol as the t-butyldimethylsilyl ether according to the conditions of Fuchs³⁷ provided alkyne 11 in 85% yield. Attempted catalysis of quinone formation at room temperature by treatment of terminal alkyne 11 with cobalt complex 2b in the presence of Lewis acids (SnCl₄, AgBF₄, Zn(O₃SO₂CF₃)₂) led to low yields of quinone, apparently via desilylation. This difficulty was remedied by conducting the quinone formation under the original, although less regioselective, reaction conditions (dichloroethane, 80 °C, 1 equiv. CoCl₂·6H₂O)¹⁵ giving quinone 12 in 81% yield as a 5:1 mixture of regioisomers with the predominate isomer possessing the structure shown.²⁵ Reduction (Zn/HOAc) to the hydroquinone followed by methylation (NaH/Mel) gave a mixture of aryltrimethyl ether regioisomers (94%, 5:1 ratio), from which the major isomer, 13, was easily isolated by column chromatography (SiO₂/hexanes). Silyl ether deprotection (n-Bu₄NF/THF, 89%) and oxidation (CrO₃/pyridine, 62%) gave the crucial royleanone precursor, 14.
Use of Friedel-Crafts-type cyclizations to establish the abietane skeleton have been accomplished under a variety of conditions and produce varying mixtures of cis and trans A/B ring juncture products. Following the lead established by Stevens, enone 14 was treated with 3:1 formic acid:phosphoric acid at reflux for 24 hr and produced exclusively the undesired cis isomer 16 in 42% yield. cis Stereochemistry at the A/B ring junction was assigned based on the characteristic signal for the angular methyl group at 0.37 ppm in the $^1$H NMR spectrum. Interestingly, when the same reaction was terminated after 12 h, trans isomer 15 (characteristic $^1$H NMR signals at 1.36, 1.26, and 1.02) and starting material 14 were present in the reaction mixture. This result suggested that the trans isomer might be formed kinetically, but then equilibrate under the reaction conditions to the more stable cis isomer. Accordingly, cyclization at lower temperature for 24 hr using refluxing trifluoroacetic acid led to a trans-isomer enriched (5:1) ring closed product in 36% yield, from which the desired trans isomer, 15, was readily obtained by silica gel chromatography (29% yield). From this compound, the royleanone synthesis was completed in a straightforward manner, by converging with the Matsui intermediate, 19. Lithium aluminum hydride reduction of 15 gave a 5:1 mixture of alcohols, 17, in 90% yield, which was converted to the corresponding xanthate esters, 18, (NaH/imidazole/CS$_2$/MeI) in 80% yield. Barton deoxygenation$^{38}$ ($t$-Bu$_2$SnH/AlBN) produced 19 in 79% yield. The total synthesis was completed following the route of Matsui by conversion of trimethyl ether 19 into (±)-royleanone, 1, in 58% yield by demethylation (BBr$_3$) followed by oxidation with oxygen.

In summary, maleoylcobalt technology provides a facile means of preparing highly functionalized quinones, regioselectively. Royleanone, 1, a abietanoid diterpene quinone possessing antitumor cytotoxicity, has been constructed via this chemistry.

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References and Footnotes

7. Michavila, A.; Fernández-Gadea, F.; Rodríguez, B. Phytochemistry 1986, 25, 266.
22. Addition of i-PrMgCl to diisopropyl squarate provided 3-isopropyl-4-isopropoxycyclobutene-1,2-dione in 76% yield. Hydrolysis of the isopropyl ester linkage (4N HCl in acetone, 86%) followed by esterification with MeOH in benzene under Dean Stark conditions gave the desired cyclobutenedione in 62% yield.
23. In our previous studies (reference 15), SnCl₄ was used to catalyze formation of the quinone from the dimethylglyoxime ligated maleoylcobalt complex and an alkyne at room temperature. Unfortunately, enediyne 3 was decomposed by SnCl₄; however, pretreatment of cobalt complex 2b with AgBF₄ to remove chloride provided a species of sufficient reactivity to allow quinone synthesis from enediyne 3.
24. 2,2,6-Trimethylcyclohexanone, prepared in 75% yield from 2,6-dimethylcyclohexanone by methylation (LDA, MeLi), was treated with 1-lithio-4-trimethylsilylbutadiyne (from treatment of bis(trimethylsilyl)butadiyne with MeLi in THF at -78 °C) to give an intermediate diynol (81%). Quantitative dehydration with BF₃·Et₂O followed by desilylation (KF in methanol) gave enediyne 3 in 95% yield.
25. An analysis of the chemical shift differences for regioisomeric quinones formed on reaction of methoxy substituted maleoylcobalt complexes can be found in reference 16.

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