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

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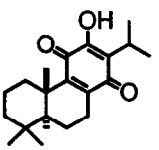
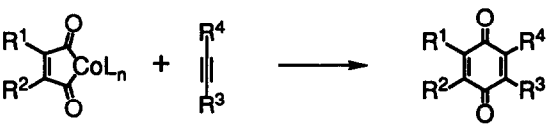
Abstract. (±)-Royleanone has been synthesized by rapid construction of a highly substituted quinone using maleoylcobalt complex technology followed by acid induced cyclization of the corresponding hydroquinone methyl ether onto a tethered enone. The synthesis was completed by straightforward functional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

Royleanone, **1**, is an abietane diterpenoid quinone first isolated from the roots of *Innula Royleana* 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]



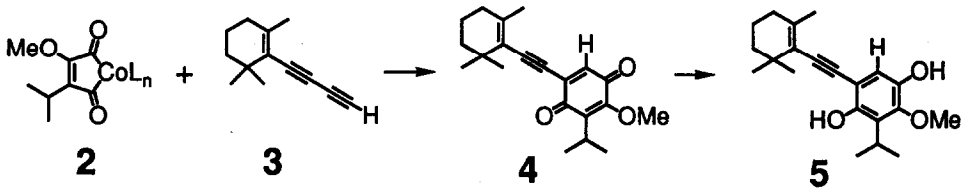
1

Eqn. 1



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** (L_n = 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 $ClCo(PPh_3)_3$ and 3-isopropyl-4-methoxycyclobutene-1,2-dione,[22] was converted into the more reactive dimethylglyoxime ligated complex **2b**[15] in 86% yield and was treated with one equivalent of $AgBF_4$.[23] Then, addition of 1.6 equivalents of endiyne **3**[24] 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 Ag_2O. 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.

Eqn. 2

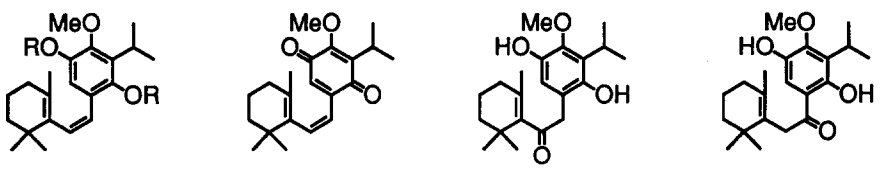


2 **3** **4** **5**

a, L_n = $(PPh_3)_2Cl$
b, L_n = (dimethylglyoxime)(pyridine)chloride

Hydroquinone **5** was converted into the hydroquinone diene **6a** (H_2/Pd on $BaSO_4$ - quinoline, 86%), the trimethoxyaryl ether **6b** (NaH, MeI in THF on **6a**, 74%), and the sensitive dienyl quinone **7** (Ag_2O 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 BH_3•THF followed by H_2O_2/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 hydroboration[32, 33] of the alkynylhydroquinone.

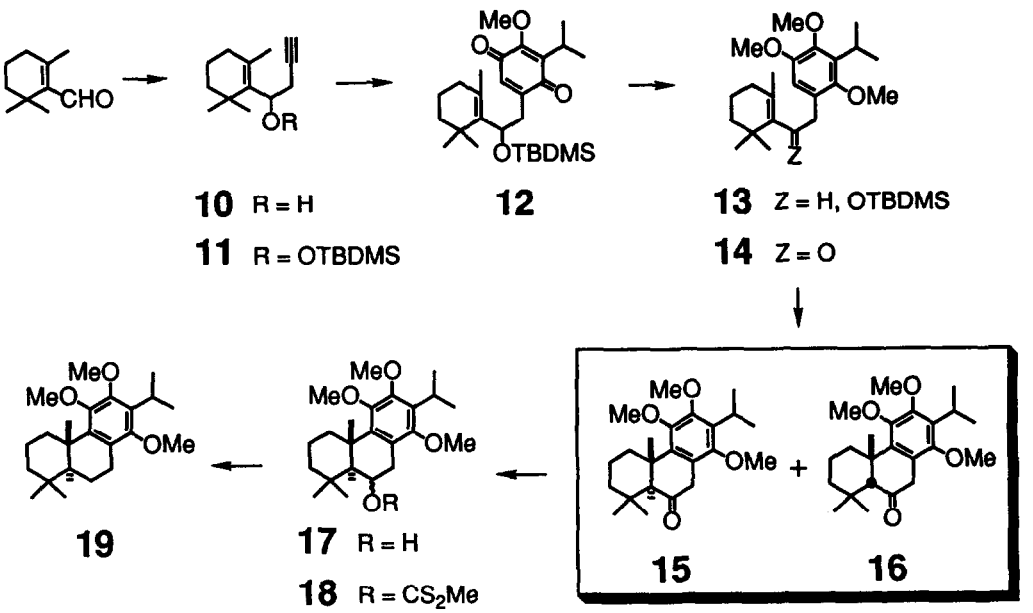


6a R = H **7** **8** **9**

6b R = Me

The trimethyl ether, **14**, of the sought after tricyclic precursor **8**, was efficiently synthesized by an alternative route (Scheme). β-Cyclocitral[34, 35] was treated with propargyl magnesium bromide[36] 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 Fuchs[37] 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 ($SnCl_4$, $AgBF_4$, $Zn(OSO_2CF_3)_2$) 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. $CoCl_2$•$6H_2O$)[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/MeI) gave a mixture of aryltrimethyl ether regioisomers (94%, 5:1 ratio), from which the major isomer, **13**, was easily isolated by column chromatography (SiO_2/hexanes). Silyl ether deprotection (*n*-Bu_4NF/THF, 89%) and oxidation (CrO_3/pyridine, 62%) gave the crucial royleanone precursor, **14**.

Scheme



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.[27–29, 31] Following the lead established by Stevens,[31] 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.[31] Interestingly, when the same reaction was terminated after 12 h, *trans* isomer **15** (characteristic[19] ^{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**.[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] (*n*-Bu_3SnH/AIBN) 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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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), $SnCl_4$ was used to catalyze formation of the quinone from the dimethylglyoxime ligated maleoylcobalt complex and an alkyne at room temperature. Unfortunately, endiyne **3** was decomposed by $SnCl_4$; however, pretreatment of cobalt complex **2b** with $AgBF_4$ to remove chloride provided a species of sufficient reactivity to allow quinone synthesis from endiyne **3**.
24. 2,2,6-Trimethylcyclohexanone, prepared in 75% yield from 2,6-dimethylcyclohexanone by methylation (LDA, MeI), 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 $BF_3 \cdot Et_2O$ 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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