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Synthesis of (±)-Aureol by Bioinspired Rearrangements

Antonio Rosales,*[,‡] Juan Muñoz-Bascón,[†] Esther Roldan-Molina,[†] Nazaret Rivas-Bascón,[†] Natalia M. Padial,[†] Roman Rodríguez-Maecker,[⊥] Ignacio Rodríguez-García,[§] and J. Enrique Oltra*[,†]

[†]Department of Organic Chemistry, Faculty of Sciences, University of Granada, 18071 Granada, Spain

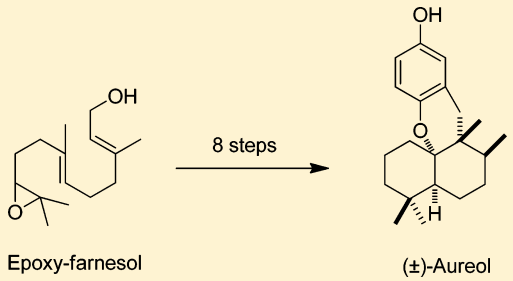
[‡]Department of Chemical and Environmental Engineering, Escuela Politécnica Superior, University of Sevilla, 41011 Sevilla, Spain

[§]Química Orgánica, CeiA3, Universidad de Almería, 04120 Almería, Spain

[⊥]Petrochemical Engineering, Universidad de las Fuerzas Armadas-ESPE, 050150 Latacunga, Ecuador

Supporting Information

ABSTRACT: A bioinspired and sustainable procedure for the straightforward synthesis of (±)-aureol has been achieved in eight steps (14% overall yield) from epoxyfarnesol. The key steps are the titanocene(III)-catalyzed radical cascade cyclization of an epoxyfarnesol derivative and a biosynthetically inspired sequence of 1,2-hydride and methyl shifts.



INTRODUCTION

Many biologically active compounds, some of them having a marine origin, are composed of a sesquiterpene unit linked to a phenolic moiety.[1] Prominent examples include (+)-aureol (**1**),[2,3] (+)-stachyflin (**2**),[4] and (+)-strongylin A (**3**)[5] (Figure 1). (+)-Aureol was originally isolated in 1980 by Faulker et al.[2]

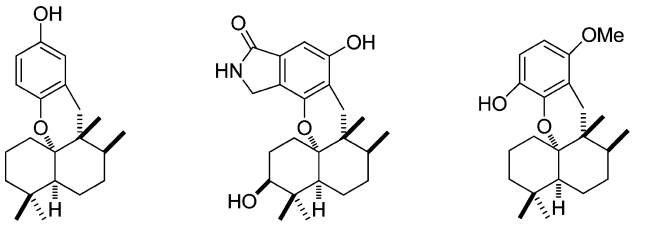


Figure 1. Representative members of the aureol family of sesquiterpenoid natural products.

from the caribbean sponge *Smeonspongia aurea*, and subsequently in 2000 by Fattorusso and his co-workers[3] from another species of caribbean sponge, *Verongula gigantea*. The aureol structure contains a compact tetracyclic ring system, with four contiguous stereocenters and a cis-relationship between the two cyclohexane rings of the decalin fragment. This marine natural product has been shown to exhibit selective cytotoxicity against A549 human nonsmall cell lung cancer cells (IC = 4.3 μg/mL)[6] and anti-influenza-A virus activity (IC = 4.3 μg/mL).[7]

Beside the unique structural features and interesting variety of biological activities of this group of compounds, there is still a need for efficient synthetic methods, as the already described approaches have too many steps or start from natural synthons which are not widely accessible.[8−14]

In recent years, titanocene(III)-catalyzed radical cyclization has become a powerful tool in organic synthesis.[15−18] In fact, this reaction has paved the way to the straightforward synthesis of several terpenes.[19]

RESULTS AND DISCUSSION

As part of our ongoing efforts in the synthesis of biologically active terpenoids of marine origin,[20−23] we were interested in the development of a new concise synthesis of aureol (**1**). It was our intention to use the already proposed biosynthesis of aureol (Scheme 1) as a guideline for our retrosynthetic analysis (Scheme 2).

The biosynthesis of aureol (**1**) presumably involves the stereoselective cyclization of polyene **4** to generate the tertiary carbocation **5** (Scheme 1). This carbocation could then undergo a sequence of stereospecific 1,2-hydride and methyl shifts to produce another tertiary carbocation **6**, which could be stabilized by cyclization with the adjacent hydroquinone to give aureol.

Inspired by this biosynthesis, we deemed that the synthesis of aureol (**1**) could be efficiently achieved through a key titanocene(III)-catalyzed cascade cyclization of the epoxyfarnesol derivate **7** and a new biogenetic-type rearrangement as the pivotal step (Scheme 2).

In this way, our synthesis of aureol (**1**) (Scheme 3) started with the epoxidation of farnesyl acetate following a previously described procedure[24] to form the epoxyfarnesol **7**. One-pot

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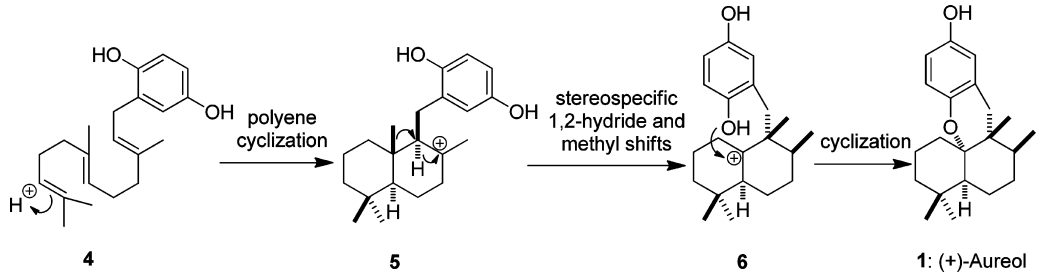
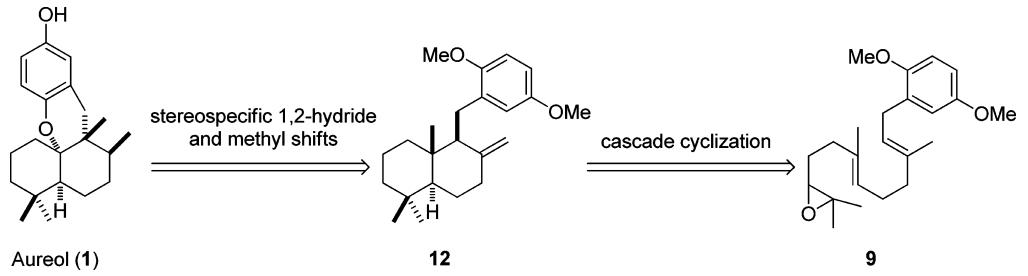
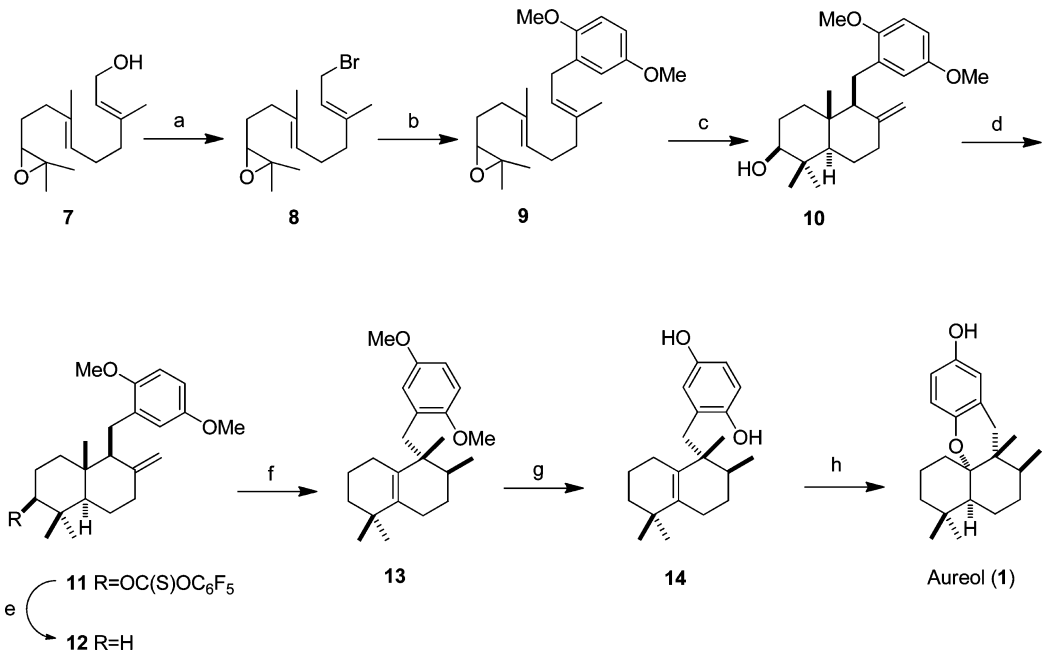
Scheme 1. Proposed Biosynthesis of Aureol



Scheme 2. Biosynthetically Inspired Retrosynthesis of Aureol



Scheme 3. Synthesis of Aureol (1) from Epoxyfarnesol (7)[a]



[a]Reagents and conditions: (a) (i) MsCl (1.3 equiv), Et_3N (2.0 equiv), THF, 1 h; (ii) LiBr (5 equiv), 30 min, quantitative; (b) Li_2CuCl_4 (0.1 equiv), $C_8H_9O_2MgBr$ (1.2 equiv), THF, 3 h at 0 °C, over night at rt, 97%; (c) Cp_2TiCl (0.2 equiv), THF, 3 h, 48%; (d) DMAP (3.0 equiv), $C_6F_5OC(S)Cl$ (2.0 equiv), CH_2Cl_2, 5 h 30 min, quantitative; (e) AIBN (0.2 equiv), *n*-Bu_3SnH (3.0 equiv), benzene, 4 h, 86%; (f) $BF_3{\cdot}Et_2O$ (5.0 equiv), CH_2Cl_2, 5 h, 63%; (g) (i) AgO (2.0 equiv), 6 N HNO_3 (3.0 equiv), 1,4-dioxane, rt, 15 min; (ii) Pd/C (0.05 equiv), H_2 (1 atm), $CHCl_3$, 25 min, 82%; (h) $BF_3{\cdot}Et_2O$ (4.5 equiv), CH_2Cl_2, 3 h, 62%.

mesylation of compound **7** with MsCl in Et_3N at −40 °C and subsequent addition to the reaction medium of LiBr at 0 °C afforded a quantitative yield of the bromide **8**. Condensation of **8** with 2,5-dimethoxyphenylmagnesium bromide using substoichiometric amounts of Li_2CuCl_4 gave a 97% yield of the epoxyfarnesol derivate **9**, previously described as the starting material in our synthesis of zonarol.[21]

The first key step was, as proposed, the titanocene(III)-catalyzed cascade cyclization of epoxyfarnesol derivate **9**. This radical reaction gave the trans-fused decalin **10** bearing a crucial exocyclic double bond on C-8, although in a moderate 48% yield. The cyclization proceeds with high regio- and stereoselectivity, and the yield can be regarded as satisfactory, if it is considered that the new compound has four stereocenters with a defined relative configuration. Previous theoretical and experimental evidence suggested that this radical cyclization proceeds through a nonconcerted fashion via discrete carbon-centered radicals.[17] Assuming the nonconcerted nature or this

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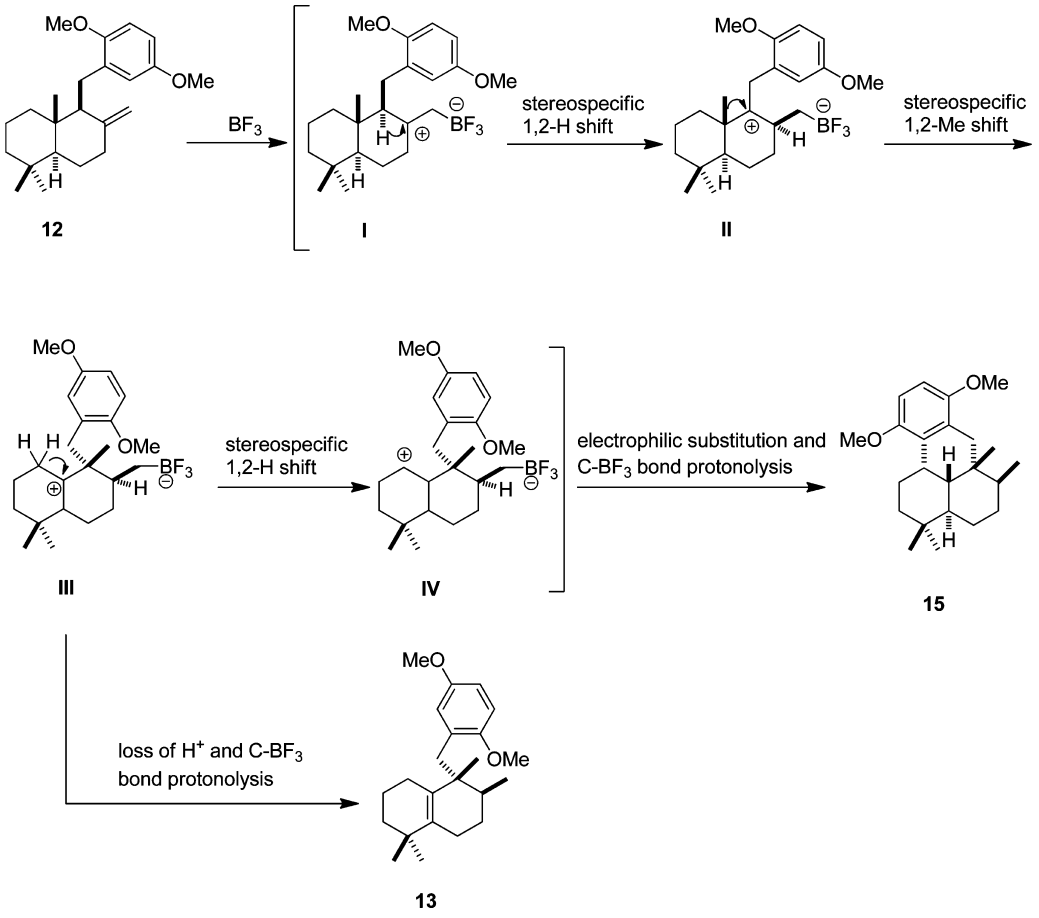
Scheme 4. Proposed Reaction Mechanism for the BF_3·Et_2O-Mediated Rearrangement of 12 to 13 and 15



radical cyclization, the stereoselectivity observed can be explained in terms of Beckwith–Houk rules described elsewhere.[25] Deoxygenation of alcohol **10** was achieved by means of the reduction of its thiocarbonate derivate.[26] Thus, treatment of alcohol **10** with DMAP and $C_6F_5OC(S)Cl$ in CH_2Cl_2 yielded quantitatively the thiocarbonate **11**. Subsequent reduction with *n*-Bu_3SnH and AIBN in benzene gave the deoxygenated derivate **12** in 86% yield.

The second key step in our synthesis of aureol (**1**) was the BF_3·Et_2O-mediated rearrangement of **12** to the tetrasubstituted olefin **13** which proceeded via stereospecific 1,2-hydride and methyl shifts. The reaction afforded the desired compound **13** in 63% yield, together with a minor compound **15** in 30% yield. Formation of **13** was confirmed by the presence of three singlets at 1.02, 0.99, and 0.93 ppm characteristic of methyl groups and one doublet at 0.79 due to the methyl group on C-8 in the ^{1}H NMR spectrum. The ^{13}C NMR of this compound showed two quaternary signals at 132.6 and 129.6 ppm characteristic of the $\Delta^{5,10}$ internal carbon–carbon double bond. The ^{1}H and ^{13}C NMR spectra of the synthetic **15** were identical to those reported.[27] The exocyclic double bond on C-8 of the compound **10** again has been of paramount importance to complete the synthesis of aureol (**1**). A similar exocyclic olefin was functionalized with formation of a C–O bond in the synthesis of puupehedione and its epimer, as reported by Gansäuer et al.[20]

Attempts to deprotect the methoxy groups in **13** with CAN/Na_2SO_4 proved to be ineffective, as only a disappointing 25% product could be recovered. The reported sodium ethanethiolate deprotection of **13** was also unfruitful, as only the monodeprotected product was formed. A significant improvement was made through a two-step oxidative (AgO, HNO_3)/reductive (Pd/C, H_2) sequence, following the procedure reported by Wright et al.[28] in the synthesis of (+)-frondosin A. Under these reaction conditions, the dihydroquinone **14** was obtained in 82% yield. The ^{1}H NMR data of this synthetic compound **14** was identical to those reported by Faulkner et al.[2] Finally, the phenolic compound **14** was treated with BF_3·Et_2O using the same reaction conditions as described by George et al. for the synthesis of (+)-aureol.[14] In our hands, this cyclization afforded aureol (**1**) in a gratifying 62% yield. Spectroscopic data for synthetic aureol (**1**) were identical to those of the natural compound.[2]

The remarkable stereocontrolled BF_3·Et_2O rearrangement of **12** to give **13** can be rationalized by the mechanistic route shown in Scheme 4. The process is, to the best of our knowledge, the first example of an acid-mediated rearrangement of a labdane derivate bearing an exo-olefin at C-8. The reaction process would involve four possible carbocationic intermediates such as **I**, **II**, **III**, and **IV**. Thus, the first coordination–activation between the Lewis acid and the C-8 exo-olefin moiety in **12** would lead to the formation of the intermediate **I**, which would suffer a 1,2-hydride shift from the C-9 position to the C-8 carbocation to provide the intermediate **II**. This carbocationic species **II** would lead to the intermediate **III** via migration of the C-9 methyl group to the C-8 carbocation center. Stabilization of the intermediate **III** by proton loss gives the tetrasubstituted alkene **14**. On the other

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hand, this intermediate **III** could suffer a 1,2-hydride shift from the C-1 position to the C-10 carbocation to provide the intermediate **IV**, which can react with the aromatic ring to form the tetracyclic compound **15**.

CONCLUSIONS

In summary, we have described a novel procedure for the straightforward synthesis of bioactive aureol (**1**). The key steps are the titanocene(III)-catalyzed radical cascade cyclization of epoxyfarnesol (**7**) and a new biomimetic sequence of 1,2-hydride and methyl shifts. Further applications of the cyclization/rearrangement strategy to the synthesis of biologically important natural products possessing monocyclic, bicyclic, tricyclic, and tetracyclic skeletons and the nonracemic synthesis or aureol (**1**) using a chiral epoxyfarnesol **7** are currently under investigation and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All chemicals used were purchased from commercial suppliers and used as received. All organic extracts were dried over anhydrous sodium sulfate. Products were purified by flash chromatography on Merck silica gel 50.Visualization was aided by viewing under a UV lamp and staining with CAM stain followed by heating. Infrared spectra were recorded using a FT-IR system spectrometer as the neat compounds. ^{1}H and ^{13}C NMR spectra were recorded on 600, 500, and 300 MHz spectrometers. The NMR solvent used was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to chloroform (δ 7.26), and ^{13}C NMR are reported in ppm relative to chloroform (δ 77.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (qnt) quintet, (sxt) sextet, and (m) multiplet. All J values were rounded to the nearest 0.5 Hz. Mass spectra were recorded by LC-QTof-MS by electrospray ionization.

Preparation of Bromide 8. Et_3N (0.29 mL, 2.0 mmol) and MsCl (0.1 mL, 1.3 mmol) were added to a cooled solution of **7** (238.4 mg, 1.0 mmol) in dry THF (6.5 mL) in a nitrogen atmosphere at −40 °C. The reaction mixture was stirred a −40 °C for 1 h. To the resulting mesylate solution was added LiBr (400 mg, 5.0 mmol) in dry THF (2.5 mL) at −40 °C. The reaction mixture was stirred at 0 °C for 30 min. After adding aq NH_4Cl and EtOAc, the reaction mixture was extracted with EtOAc (40 mL). The combined organic extract was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford 298.3 mg of the crude product **8** (99%), isolated as a colorless oil. IR, NMR, and HRMS of compound **8** were consistent with that of the original isolation literature.[29]

Synthesis of Epoxyfarnesol Derivate 9. A 0.1 M solution of Li_2CuCl_4 in THF (0.4 mL, 0.04 mmol) was added dropwise to a solution of the compound **8** (300.1 mg, 1.0 mmol) in THF (9 mL) at 0 °C. Then a solution of 2,5-dimethoxyphenylmagnesium bromide (2.4 mL, 1.2 mmol) was added dropwise over 20 min. The mixture was stirred at 0 °C for 3 h and then at room temperature overnight. Saturated aq NH_4Cl was added, the mixture was extracted with EtOAc, the extract was dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by flash chromatography (hexane/AcOEt 9:1) to yield 347.5 mg of the coupling product **9** (97%), isolated as a colorless oil.

Data for compound **9**: IR (film) ν_{max} 1588, 1253, 1240 cm^{-1} ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79−6.67 (m, 3H), 5.30 (t, J = 7.1 Hz, 1H), 5.17 (t, J = 7.1 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.31 (d, J = 7.3 Hz, 2H), 2.69 (t, J = 6.3 Hz, 1H), 2.16−2.02 (m, 8H), 1.70 (s, 3H), 1.61 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.6 (C), 151.6 (C), 136.3 (C), 134.1 (C), 131.4 (C), 124.8 (CH), 122.2 (CH), 116.0 (CH), 111.1 (CH), 110.4 (CH), 64.2 (CH), 58.3 (C), 56.0 (CH_3), 55.6 (CH_3), 39.7 (CH_2), 36.3 (CH_2), 28.2 (CH_2), 27.4 (CH_2), 26.6 (CH_2), 24.9 (CH_3), 18.7 (CH_3), 16.1 (CH_3), 16.0 (CH_3); HRMS (ESI): calculated for $C_{23}H_{35}O_3$ [M + H]$^+$: 359.2586; found: 359.2593.

Cp_2TiCl-Catalyzed Cyclization of Epoxyfarnesol Derivate 9. THF (15 mL) was added to a mixture of [$TiCp_2Cl_2$] (50 mg, 0.2 mmol) and Mn dust (440 mg, 8.0 mmol) under Ar, and the suspension was stirred at room temperature until it turned green (about 15 min). Then a solution of 2,4,6-collidine (0.9 mL, 7.0 mmol) and Me_3SiCl (0.5 mL, 4.0 mmol) in THF (5 mL) was added, the mixture was stirred for 5 min, a solution of **9** (358.3 mg, 1 mmol) in THF (5 mL) was added, and the mixture was stirred at room temperature for 3 h. Then 2 N HCl was added, and the mixture was extracted with Et_2O. The combined organic layers were dried with Na_2SO_4 anhydrous, and the solvent was removed. The residue was dissolved in THF, and a 1 M solution of n-Bu_4NF in THF (1.2 mmol) was added. The new mixture was stirred for 30 min, diluted with Et_2O, and washed with brine. The organic layer was dried with Na_2SO_4 anhydrous and the solvent removed. The residue was purified by flash chromatography (hexane/AcOEt 9:1) to yield 172.1 mg of the cyclization compound **10** (48%). IR, NMR, and HRMS of compound **10** were consistent with that of the original isolation literature.[21]

Synthesis of Xanthate 11. *O*-Pentafluorophenyl chlorothioformate (523.2 mg, 2.0 mmol) was added to a stirred solution of **10** (358.5 mg, 1.0 mmol) and DMAP (362.8 mg, 3.0 mmol) in CH_2Cl_2 (7.0 mL) at 0 °C, and the solution was stirred at room temperature for 5 h 30 min. Then AcOEt was added, the mixture was washed with water, the organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed. The residue was purified by flash chromatography (hexane/AcOEt 98:2) to yield 578.8 mg of the xanthate **11** (99%) as a colorless oil. IR, NMR, and HRMS of compound **11** were consistent with that of the original isolation literature.[21]

Synthesis of Compound 12. The xanthate **11** (585 mg, 1.0 mmol) was dissolved in benzene (10 mL), AIBN (33 mg, 0.2 mmol) and n-Bu_3SnH (0.8 mL, 3.0 mmol) were added, and the mixture was stirred at reflux for 4 h. Then the solvent was removed. The residue was purified by flash chromatography (hexane/AcOEt, 99:1) to yield 294.6 mg of the product **12** (86%) as a colorless oil. IR, NMR, and HRMS of compound **12** were consistent with that of the original isolation literature.[21]

BF_3·Et_2O-Mediated Rearrangement of 12. Compound **12** (342.5 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (100 mL). The solution was cooled to −50 °C, and BF_3·Et_2O (0.7 mL, 5.0 mmol) was added. Then the solution was gradually warmed up to −5 °C. After 5 h, the stirring was stopped and the solvent removed. The crude product was dissolved in Et_2O and washed with brine. The organic layer was dried, and the solvent was removed in vacuum. The residue was purified by flash chromatography (cyclohexane) to yield 215.8 mg of the product **13** (63%) together with byproduct **15** (98.6 mg, 30%). IR, NMR, and HRMS of compound **15** were consistent with that of the original isolation literature.[26]

Data for compound **13**: mp 58−61 °C; IR (film) ν_{max} 1592, 1490, 1239, 1461 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (d, J = 3.1 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 6.68 (dd, J = 8.8, 3.1 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.93 (d, J = 15.2 Hz, 1H), 2.62 (d, J = 15.2 Hz, 1H), 2.09−2.01 (m, 4H), 1.96−1.90 (m, 1H), 1.69−1.58 (m, 4H), 1.39−1.32 (m, 2H), 1.01 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9 (C), 152.2 (C), 135.6 (C), 132.6 (C), 129.6 (C), 116.4 (CH), 110.8 (CH), 110.7 (CH), 55.7 (CH_3), 55.5 (CH_3), 41.4 (C), 39.7 (CH_2), 34.5 (CH_2), 34.2 (C), 33.3 (CH), 28.2 (CH_3), 28.0 (CH_3), 26.6 (CH_2), 26.2 (CH_2), 23.4 (CH_2), 21.9 (CH_3), 19.8 (CH_2), 15.9 (CH_3); HRMS (ESI): calculated for $C_{23}H_{35}O_2$ [M + H]$^+$: 343.2637; found: 343.2645.

Deprotection of the Methyl Ether Groups in 13. To a flame-dried flask was added alkene **13** (328.2 mg, 1.0 mmol) in dioxane (26 mL). The solution was sequentially treated with AgO (250 mg, 2.0 mmol) and 6 N HNO_3 (0.47 mL, 3.0 mmol). The reaction was stirred for 15 min at room temperature before being quenched by the addition of saturated aq $NaHCO_3$ and diluted with Et_2O. The aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers were washed with H_2O (3 × 20 mL) and brine (2 × 20 mL), dried, over Na_2SO_4, concentrated, and used without further

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purification. The crude quinone obtained above was dissolved in $CHCl_3$ (30 mL). To the solution was added 10% Pd/C (110 mg, 0.05 mmol), and the flask was evacuated and backfilled with H_2 (three cycles). The reaction mixture was stirred under an atmosphere of H_2 (balloon) for 15 min before being filtered through a pad of SiO_2 eluting with Et_2O (3.0 mL). The solvent was removed under vacuum, and the residue was purified by flash chromatography (hexane/AcOEt, 95:5) to give 258 mg of product **14** (82%) as a white foam. IR, NMR, and HRMS of compound **14** were consistent with that of the original isolation literature.[2]

Synthesis of Aureol (1). To a solution of hydroquinone **14** (314.2 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (100 mL) at −60 °C was added $BF_3{\cdot}Et_2O$ (0.56 mL, 4.5 mmol). The reaction mixture was stirred for 3 h at −60 °C, warmed to −20 °C, and then quenched with saturated NH_4Cl solution. The mixture was then extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude material was purified by flash column chromatography (hexane/AcOEt 9:1) to give aureol (**1**) as a white solid (195 mg, 62%). IR, NMR, and HRMS of aureol (**1**) were consistent with that of the original isolation literature.[2]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H NMR spectra for compounds **1** and **8**−**15** and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: arosales@us.es.

*Fax: (+34) 958248437. E-mail: joltra@ugr.es.

Notes

The authors declare no competing financial interest.

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