Application of the Nickel-Mediated Neopentyl Coupling in the Total Synthesis of the Marine Natural Product Arenarol

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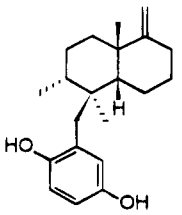
Racemic arenarol (**1**) has been synthesized from the known decalin 5β-carbethoxy-1,1-(1,2-ethylenedioxy)-5α,8aβ-dimethyl-1,2,3,5,6,7,8,8a-octahydro-6-oxonaphthalene (**9**) via a short, efficient, and highly stereocontrolled sequence. Key steps in this synthesis are the directed hydrogenation of an unsaturated neopentyl alcohol to provide stereocontrolled formation of the two adjacent tertiary centers and subsequent elaboration of the arenarol skeleton via a nickel-mediated coupling of the corresponding neopentyl iodide. This sequence demonstrates the value of nickel-mediated cross-coupling reactions for carbon–carbon bond formation at neopentyl centers.

The formation of carbon–carbon bonds at neopentyl centers is a difficult transformation, at least through most classical reactions, because of the relatively high energy associated with both the S_N1 and S_N2 transition states.[1] At the same time, groups such as neopentyl alcohols can be employed to direct the stereochemistry of reactions at nearby sites[2] and might be much more commonly employed for such tasks if there were more facile procedures for following such a sequence with elaboration of the carbon skeleton at the neopentyl position.[3] One solution to this conflict was suggested by previous studies of metal-mediated neopentyl coupling reactions from this laboratory. We initially reported that some neopentyl iodides undergo efficient reduction when treated with ethylmagnesium bromide in Pd-catalyzed reactions[4] and subsequently found that use of dichloro-(1,1,'-bis(diphenylphosphino)ferrocene)nickel(II), (dppf)-$NiCl_2$, resulted in efficient coupling of neopentyl iodides with aromatic Grignard reagents in the presence of $ZnCl_2$·dioxane.[5] On the basis of these results, it appeared reasonable to contemplate the design of total syntheses wherein a neopentyl alcohol is used to direct the stereochemical formation of a nearby center and the hydroxyl group is subsequently converted to a neopentyl iodide for use in extending the carbon skeleton.

The marine natural product arenarol (**1**) appeared to be an attractive initial target for exploration of this strategy. Arenarol was first reported from the marine



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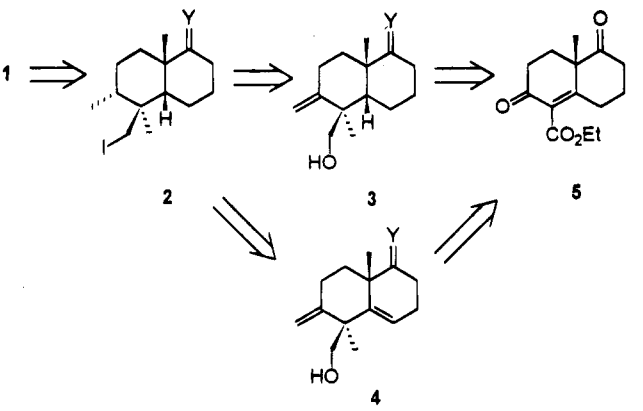
sponge *Dysidea arenaria* in 1984,[6] subsequently from a *Fenestraspongia* species,[7] and most recently from a *Dysidea* species.[8] This compound has not been prepared by chemical synthesis, and issues of stereocontrol are significant because of the *cis*-fused decalin[9] and the necessity for stereocontrol at two tertiary and two quaternary carbons.

Scheme 1



Retrosynthetic analysis as summarized in Scheme 1 readily dissects arenarol to a neopentyl iodide (**2**) and 2,5-dimethoxyphenylmagnesium bromide. The neopentyl iodide in turn could be derived from the corresponding alcohol (**3**), assuming that the hydroxyl group could be employed to control the stereochemistry of reduction at an adjacent exocyclic olefin, or the diene alcohol **4**, if the hydroxyl group could be employed to fix both adjacent

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(2) For a review, see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190–203.
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(4) Yuan, K.; Scott, W. J. *J. Org. Chem.* **1990**, *55*, 6188–6194.
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(7) Carte, B.; Rose, C. B.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 2785–2787.
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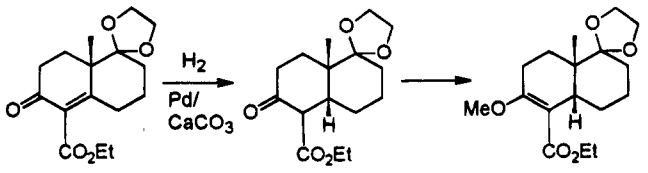
stereocenters. Either olefin in turn could be viewed as a derivative of the known decalin **5**,[10] depending on the sequence employed to accomplish methylation, introduction of the exocyclic olefin, and, for compound **3**, reduction of the endocyclic olefin. We now report the first total synthesis of (±)-arenarol via a synthetic sequence based on this approach, one that includes both directed introduction of two key stereogenic centers and a (dppf)$NiCl_2$-mediated coupling at a neopentyl center.

The first approach to the terpenoid portion of the arenarol skeleton required preparation of *cis*-fused decalin **7**. This sequence began with the known decalin **6**,[11,12]

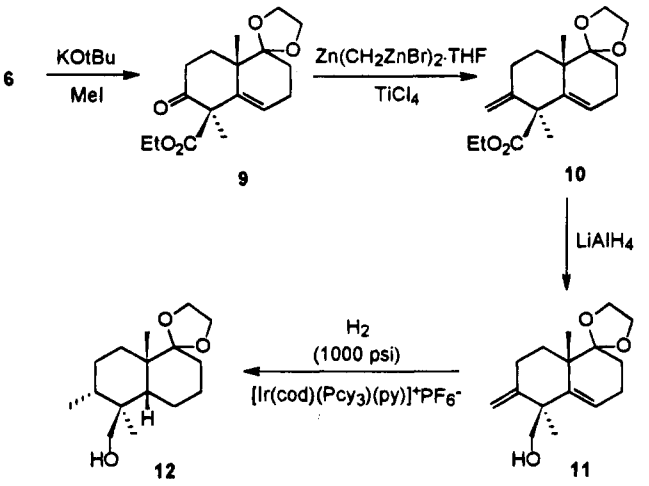


prepared by reaction of 2-methyl-1,3-cyclohexanedione and Nazarov's reagent[13] to give decalin **5**, and subsequent protection of the isolated ketone through TsOH-catalyzed reaction with ethylene glycol. Catalytic hydrogenation of compound **6** over $Pd/CaCO_3$ gave the desired *cis*-fused system (**7**) in excellent yield.[9] Unfortunately, attempted methylation of β-keto ester **7** under standard conditions gave only the *O*-methyl compound **8** or complex reaction mixtures,[14] prompting exploration of an alternate route.

Pelletier et al.[12] have reported that methylation of the methyl ester corresponding to decalin **6** through reaction with MeI/KOtBu affords the α-methyl β-carbomethoxy derivative. The ethyl ester **6** undergoes a parallel reaction under these conditions, yielding olefin **9**.[11] Unfortunately, olefin **9** proved resistant to hydrogenation over $Pd/CaCO_3$ at 60 psi, as Pelletier observed for the corresponding methyl ester derivative.

Given the difficulty with standard Pd-catalyzed hydrogenation of compound **9**, it became attractive to explore directed hydrogenations to obtain the cis-fused decalin system. There are a number of reports describing directed hydrogenations where stereocontrol is obtained through coordination of the catalyst to a nearby hydroxyl group.[2,15] While conversion of the carbethoxy group to the corresponding alcohol appeared straightforward, the most attractive sequence to arenarol suggested postponing these transformations until after introduction of the exocyclic methylene. With this diene, it might be possible to accomplish directed reduction of both olefins at the same time, setting the stereochemistry as needed at both flanking positions in a single reaction.

Compound **9** proved unreactive with the Tebbe reagent,[16] but reaction with Nysted's reagent ($Zn(CH_2ZnBr)_2$·THF)[17] and $TiCl_4$ afforded the exocyclic methylene compound **10** in variable yields (35–57%). Treatment of ester **10** with $LiAlH_4$ provided the desired neopentyl alcohol **11** in high yield (93%).



Several catalysts are known to participate in hydrogenations directed by hydroxyl groups, but an iridium complex reported by Crabtree appeared to offer the best precedent.[15b] Hydrogenation of diene **11** over $[Ir(cod)(PCy_3)(py)]PF_6$ under 1000 psi of H_2 for 6 days gave a single diastereomer (**12**) in virtually quantitative yield. Given the difficulty noted above for Pd-catalyzed hydrogenations of the trisubstituted olefin of keto ester **6**, and the observation that a single diastereomer was formed, it was reasonable to assume that hydrogenation of diene **11** involved complexation with the neopentyl alcohol, affording the desired stereocontrol. However, while the ^1H NMR and mass spectra of this product were consistent with the desired reduction, a rigorous assignment of stereochemistry based on spectral data was not possible, given the extensive overlap of resonances in the ^1H NMR spectrum and the lack of appropriate model compounds. Therefore, we decided to pursue completion of the arenarol synthesis and ultimately confirm this stereochemical assignment by comparison with the natural product.

The dioxolane protecting group of compound **12** was removed in nearly quantitative yield by treatment with aqueous acid. Reaction of the resulting ketone (**13**) with Nysted's reagent gave the desired olefin **14** in good yield (74%). Conversion of the hydroxyl group of compound **14** to the corresponding iodide (**16**) was accomplished by initial formation of the mesylate (**15**) and subsequent reaction with NaI.[18] Thus, neopentyl iodide **16** was obtained in 7 steps (21–34% yield) from the known decalin **9**.

(10) (a) Spencer, T. A.; Weaver, T. D.; Greco, W. J., Jr. *J. Org. Chem.* **1965**, *30*, 3333–3336. (b) Sánchez, I. H.; Larraza, M. I.; Breña, F. K.; Crúz, A.; Sotelo, O.; Flores, H. J. *Synth. Commun.* **1986**, *16*, 299–308. (c) Ellis, J. E.; Dutcher, J. S.; Heathcock, C. H. *Synth. Commun.* **1974**, *4*, 71–77.

(11) Peterse, A. J. G. M.; de Groot, Ae. *Rec. Trav. Chim. Pays-Bas* **1977**, *96*, 219–221.

(12) For preparation of the methyl esters corresponding to compounds **5**, **6**, and **9**, see: Pelletier, S. W.; Chappell, R. L.; Prabhakar, S. *J. Am. Chem. Soc.* **1968**, *90*, 2889–2895.

(13) Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717–4719.

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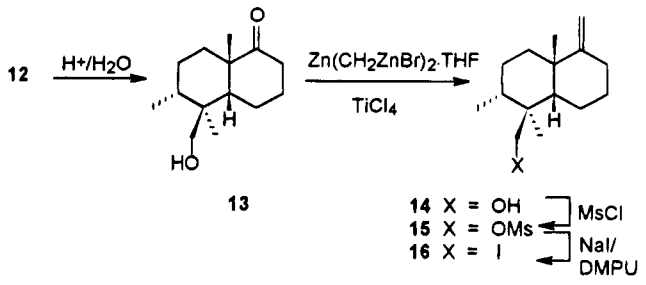
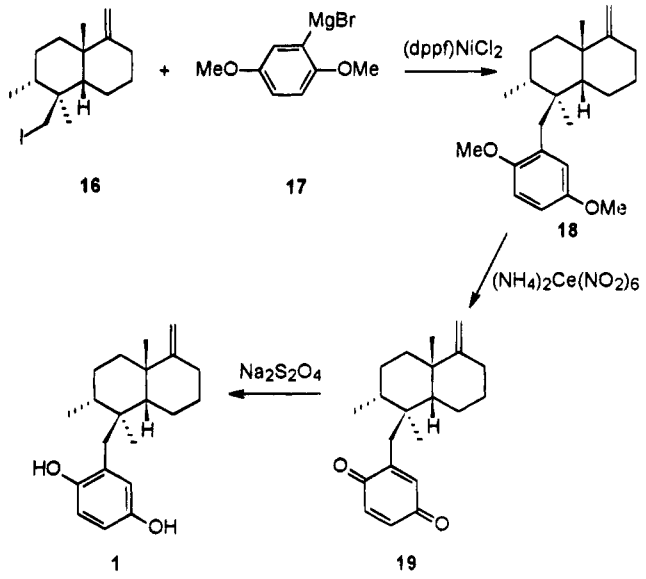
(16) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613. (b) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H. Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212–1216. (c) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394. (d) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165–167.

(17) (a) Nysted, L. N. US Patent 3 865 848, 1975; *Chem. Abstr.* **1975**, *83*, 10406q. (b) Nysted, L. N. US Patent 3 960 904, 1976; *Chem. Abstr.* **1976**, *85*, 94618n. (c) *Aldrichim. Acta* **1993**, *26*, 14.

(18) Gilbert, J. C.; Selliah, R. D. *J. Org. Chem.* **1993**, *58*, 6255–6265.



The Grignard reagent needed for preparation of arenarol, (2,5-dimethoxyphenyl)magnesium bromide (**17**), has been shown to undergo a cross-coupling reaction with neopentyl iodide itself if heated at reflux in ether in the presence of (dppf)$NiCl_2$ and $ZnCl_2$·dioxane.[5b] Iodide **16**



also proved to be reactive under these conditions, or even at room temperature, forming the desired coupling product **18** in yields of 45–50%. Initially, several isomeric byproducts were observed in variable amounts, resulting from rearrangement of the desired product under the mildly acidic conditions of the standard workup and parallel to known rearrangements of arenarol (**1**) itself.[19] When the $ZnCl_2$·dioxane was omitted from the reaction mixture,[5a] to minimize the potential for Lewis acid catalyzed rearrangements, and the coupling reaction was quenched by addition of aqueous $NaHCO_3$, the coupling proceeds less efficiently. However, because formation of the rearrangement products is suppressed, it is easier to isolate the desired product and yields of 45% are readily attained.

Conversion of the coupled product **18** to the target compounds required cleavage of the methyl protecting groups. While analogous deprotections have been accomplished by reaction with thiolates in HMPA,[20] similar treatment of compound **18** resulted in the formation of many highly-colored products. However, treatment of compound **18** with ceric ammonium nitrate (CAN)[21] resulted in oxidation to the natural product arenarone (**19**). Under standard conditions this oxidation proceeds very rapidly, but the reaction is complicated by acid-catalyzed rearrangements. If this reaction is conducted in a mixture of saturated aqueous $NaHCO_3$ and CH_3CN, complete conversion requires 2 days but arenarone is obtained in good yield (73%) without rearrangement. Finally, mild reduction of arenarone (**19**) with $Na_2S_2O_4$ gave the final target, arenarol (**1**). Comparison of the synthetic material with an authentic sample of the natural product by TLC and ^1H and ^{13}C NMR established its identity, thus confirming that hydrogenation of diene **11** had in fact given the expected diastereomer **12**.

In conclusion, the first total synthesis of (±)-arenarol (**1**) has been completed through a short, efficient, and stereocontrolled sequence. This synthesis demonstrates the first application of a (dppf)$NiCl_2$-mediated neopentyl coupling in a natural product synthesis and emphasizes the attractive combination of hydroxyl-directed hydrogenation to control stereochemistry followed by a neopentyl coupling to elaborate the carbon skeleton. Further applications of this strategy and preparation of related compounds will be reported in due course.

Experimental Section

All reaction solvents were distilled immediately prior to use. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were distilled from potassium or sodium/benzophenone, while ether was distilled from sodium/benzophenone. Benzene, CH_2Cl_2, triethylamine, and diisopropylamine were distilled from CaH_2. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) was distilled from CaH_2 at 20 Torr and stored over 4 Å molecular sieve. Iodomethane was percolated through activated alumina and stored over copper. Unless water was used as a reagent, all reactions were conducted in oven-dried glassware, under an atmosphere of dry nitrogen, and with magnetic stirring. Organic extracts were dried by swirling over anhydrous $MgSO_4$, filtered through a fritted-glass funnel, and concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Flash chromatography was carried out on Baker silica gel with 40 μm average particle diameter. Melting points are uncorrected. IR spectra were recorded with an FT spectrophotometer. NMR spectra (^1H at 300 MHz and ^{13}C at 75 MHz) were recorded with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards. Low resolution GC–mass spectra were obtained at an ionization potential of 70 eV. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA), or in the University of Iowa Chemistry Department.

Ketone 5. A variation[14] on a literature procedure employed for preparation of the corresponding methyl ester[12] was used to prepare the desired decalin. Thus, to a solution of 2-methylcyclohexane-1,3-dione (10.4 g, 82.5 mmol) and anhydrous potassium fluoride (11.0 g, 189 mmol) in anhydrous methanol (330 mL) at rt was added a solution of ethyl 3-oxo-4-pentenoate[13] (13.1 g, 92.3 mmol) in methanol (30 mL) dropwise over 20 min. After 15 h, the solvent was removed in vacuo. The residue was dissolved in ether and washed with 10% aqueous sodium carbonate until colorless washings were obtained. The ethereal layer was washed with saturated aqueous NaCl, dried, and concentrated in vacuo to give the Nazarov product **5** (13.4 g, 58%) as a white solid. This material gave a ^1H NMR spectrum identical to a partial spectrum:[10a] mp 66–68 °C (lit.[10b] mp 68–69 °C); IR ($CHCl_3$) 1719, 1675 cm^{-1}; ^1H NMR δ 4.31 (q, J = 7.1 Hz, 2H), 2.77–2.61 (m, 3H), 2.59–2.43 (m, 3H), 2.24–2.07 (m, 3H), 1.87–1.67 (m, 1H), 1.49

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(21) For a recent example of the use of CAN in demethylation of hydroquinones, see: Yoon, T.; Danishefsky, S. J.; de Gala, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 853–855.

(s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 209.9, 193.8, 166.2, 161.8, 132.3, 61.3, 50.1, 37.1, 33.1, 29.0, 28.5, 23.2, 21.7, 14.0.

Ketal 6. Reaction of the Nazarov product **5** (8.38 g, 33.4 mmol) with TsOH (0.16 g, 0.84 mmol) and ethylene glycol (19.0 mL, 341 mmol) in benzene was conducted under standard conditions for azeotropic removal of water.[12,14] The product was purified by flash column chromatography (2:1 hexanes:ethyl acetate) to afford ketal **6** (8.65 g, 88%) as a colorless oil with IR and ^{1}H NMR spectra identical to partial data:[11] IR ($CHCl_3$) 1723, 1670 cm^{-1}; ^{1}H NMR δ 4.28 (q, J = 7.1 Hz, 2H), 4.02–3.90 (m, 4H), 2.56–2.26 (m, 5H), 1.95–1.59 (m, 5H), 1.39 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 194.9, 166.9, 164.0, 132.1, 112.3, 65.3, 65.0, 61.0, 44.7, 33.5, 29.7, 28.3, 26.2, 21.3, 20.8, 14.1.

Keto Ester 9. According to the procedure of Pelletier for the corresponding methyl ester,[12] a solution of the ethyl ester **6** (3.00 g, 10.2 mmol) in anhydrous benzene (10 mL) was added dropwise to a suspension of potassium *tert*-butoxide (95%, 1.26 g, 10.7 mmol) in anhydrous benzene (40 mL) at rt over 15 min. Subsequent reaction with methyl iodide (16.1 mL, 242 mmol), and an aqueous workup, gave keto ester **9** (2.1 g, 70%) as a colorless oil with IR and ^{1}H NMR spectra identical to partial data:[11] IR ($CHCl_3$) 1728, 1712 cm^{-1}; ^{1}H NMR δ 5.59 (t, J = 3.8 Hz, 1H), 4.17 (dq, J = 10.8, 7.1 Hz, 1H), 4.14 (dq, J = 10.8, 7.1 Hz, 1H), 4.05–3.88 (m, 4H), 2.64 (ddd, J = 18.0, 11.2, 6.6 Hz, 1H), 2.55 (ddd, J = 18.0, 6.4, 4.6 Hz, 1H), 2.30–2.22 (m, 2H), 2.14 (ddd, J = 13.8, 11.2, 6.4 Hz, 1H), 1.96 (ddd, J = 13.5, 10.2, 8.0 Hz, 1H), 1.78–1.64 (m, 2H), 1.49 (s, 3H), 1.26 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 208.6, 172.7, 141.2, 123.2, 111.8, 65.0, 64.8, 61.3, 60.4, 42.2, 34.9, 25.9, 25.4, 23.9, 23.6, 22.9, 13.8; EIMS m/z (rel abundance) 308 (19), 290 (3), 235 (8), 217 (7), 194 (17), 166 (36), 86 (100).

Diene 10. To a slurry of Nysted reagent (20% suspension in THF, 40.0 mL, 20.8 mmol) and ketone **9** (1.80 g, 5.84 mmol) at −78 °C was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (18.0 mL, 18 mmol) dropwise over 5 min. The reaction mixture was allowed to warm to rt. After 20 h, the mixture was cooled to 0 °C, and triethylamine (18.0 mL, 0.129 mol) was added in one portion, followed by the rapid addition of 63–200 mesh silica gel (1.8 g). The resulting brown sludge was allowed to warm to rt, filtered through a plug of 63–200 mesh silica gel with ethyl acetate, and concentrated. The residue was purified by flash chromatography (5:1 hexanes:ethyl acetate) to afford compound **10** (0.806 g, 45%) as a white crystalline solid: mp 80–83 °C; IR ($CHCl_3$) 1718 cm^{-1}; ^{1}H NMR δ 5.69 (t, J = 3.8 Hz, 1H), 4.91–4.88 (m, 1H), 4.80 (s, 1H), 4.16 (dq, J = 10.8, 7.1 Hz, 1H), 4.08 (dq, J = 10.8, 7.1 Hz, 1H), 4.01–3.85 (m, 4H), 2.67–2.54 (m, 1H), 2.41–2.22 (m, 3H), 1.92 (ddd, J = 13.1, 10.8, 7.4 Hz, 1H), 1.87–1.74 (m, 1H), 1.67–1.50 (m, 2H), 1.51 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.20 (s, 3H); ^{13}C NMR δ 176.0, 149.9, 142.7, 121.7, 112.2, 108.9, 65.3, 64.7, 60.9, 52.7, 44.0, 30.5, 29.8, 26.2, 24.2, 24.1, 23.3, 14.0; EIMS m/z (rel abundance) 306 (4), 244 (1), 233 (2), 205 (10), 147 (100), 87 (54). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.60; H, 8.75.

Alcohol 11. To a slurry of $LiAlH_4$ (95%, 0.210 g, 5.26 mmol) in ether (5.0 mL) at 0 °C was added a solution of ester **10** (0.800 g, 2.61 mmol) in ether (4.0 mL) dropwise via cannula over 2 min. The cannula was rinsed into the reaction mixture with an additional portion of ether (4.0 mL), and the mixture was allowed to warm to rt. After 1 h, the mixture was cooled to 0 °C and quenched by sequential addition of water (0.21 mL), 15% aqueous NaOH (0.21 mL), and water (0.63 mL) and allowed to warm to rt over 1 h. The white slurry was filtered and concentrated. The product was purified by flash chromatography (2:1 hexanes:ethyl acetate) to afford compound **11** (0.639 g, 93%) as a white amorphous solid: mp 111–112 °C; IR ($CHCl_3$) 3560, 1652, 1638 cm^{-1}; ^{1}H NMR δ 5.66 (t, J = 3.8 Hz, 1H), 4.91 (d, J = 1.1 Hz, 1H), 4.90 (d, J = 1.1 Hz, 1H), 4.02–3.90 (m, 4H), 3.55 (dd, J = 10.7, 5.4 Hz, 1H), 3.48 (dd, J = 10.7, 7.0 Hz, 1H), 2.52–2.18 (m, 4H), 2.00–1.80 (m, 2H), 1.66 (dddd, J = 13.4, 6.4, 2.4, 0.5 Hz, 1H), 1.52 (dt, J = 13.0, 4.7 Hz, 1H), 1.38 (br t, J = 6.2 Hz, 1H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR δ 151.3, 144.1, 122.2, 112.6, 109.1, 69.2, 65.3, 64.8, 48.1, 42.9, 29.3, 29.1, 25.9, 25.4, 24.2, 23.7. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.97; H, 9.43.

Alcohol 12. A solution of diene **11** (45.0 mg, 17.0 mmol) and (tricyclohexylphosphine)(1,5-cyclooctadiene)(pyridine)iridium(I) hexafluorophosphate[15b] (15.8 mg, 0.0196 mmol) in CH_2Cl_2 (40 mL) was placed in a Parr high-pressure bomb. The apparatus was filled and purged with 1000 psi of H_2 (5×), and the reaction mixture was stirred under 1000 psi of H_2 at rt. After 6 d, the mixture was concentrated. The residue was purified by flash chromatography (4:1 hexanes:ethyl acetate) to afford alcohol **12** (44.2 mg, 97%) as a colorless oil: IR ($CHCl_3$) 3628 cm^{-1}; ^{1}H NMR δ 3.98–3.86 (m, 4H), 3.42 (d, J = 11.7 Hz, 1H), 3.40 (d, J = 11.7 Hz, 1H), 2.00 (dt, J = 14.1, 3.7 Hz, 1H), 1.83–1.36 (m, 10H), 1.29–1.20 (m, 1H), 1.16 (s, 3H), 1.00 (ddd, J = 14.2, 12.2, 4.7 Hz, 1H), 0.86 (s, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 113.7, 67.2, 64.6, 64.2, 43.8, 41.7, 40.6, 34.3, 33.2, 30.7, 30.0, 28.5, 22.2, 21.0, 16.4, 13.9; EIMS m/z (rel abundance) 268 (0.6), 253 (0.1), 237 (16), 176 (11), 155 (2), 99 (100). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.23; H, 10.61.

Ketone 13. To a solution of ketal **12** (0.475 g, 1.77 mmol) in THF (9.0 mL) at rt was added 2% aqueous HCl (4.5 mL). After 17 h, the reaction mixture was concentrated by azeotropic distillation with ethanol. The resulting product was purified by flash chromatography (2:1 hexanes:ethyl acetate) to afford ketone **13** (0.383 g, 97%) as a white amorphous solid: mp 77–79 °C; IR ($CHCl_3$) 3628, 1701 cm^{-1}; ^{1}H NMR δ 3.52 (d, J = 11.7 Hz, 1H), 3.43 (d, J = 11.7 Hz, 1H), 2.68 (ddd, J = 15.5, 10.8, 9.0 Hz, 1H), 2.33 (dt, J = 13.4, 3.2 Hz, 1H), 2.28–1.96 (m, 5H), 1.95–1.86 (m, 1H), 1.66–1.44 (m, 2H), 1.41 (ddd, J = 13.3, 12.2, 3.5 Hz, 1H), 1.34–1.24 (m, 1H), 1.30 (s, 3H), 0.97 (td, J = 13.3, 4.5 Hz, 1H), 0.81 (d, J = 6.8 Hz, 3H), 0.57 (s, 3H); ^{13}C NMR δ 217.1, 65.6, 47.8, 47.5, 42.1, 36.2, 35.5, 34.6, 30.4, 27.2, 23.8, 19.4, 15.7, 13.6. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.85; H, 10.78.

Alcohol 14. To a slurry of Nysted reagent (20% suspension in THF, 11.0 mL, 5.72 mmol) and ketone **13** (0.365 g, 1.63 mmol) at −78 °C was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (4.90 mL, 4.9 mmol) dropwise over 3 min. The reaction mixture was allowed to warm to rt. After 19 h, triethylamine (5.0 mL, 36 mmol) was added in one portion. The resulting brown sludge was filtered through a plug of 63–200 mesh silica gel with ethyl acetate and concentrated. The product was purified by flash chromatography (7:1 hexanes:ethyl acetate) to afford compound **14** (0.266 g, 74%) as a white amorphous solid: mp 79–82 °C; IR ($CHCl_3$) 3638, 1635 cm^{-1}; ^{1}H NMR δ 4.74 (t, J = 1.9 Hz, 1H), 4.72 (t, J = 2.0 Hz, 1H), 3.52 (d, J = 11.7 Hz, 1H), 3.34 (d, J = 11.7 Hz, 1H), 2.50 (ddddd, J = 14.1, 12.8, 6.9, 2.0, 1.9 Hz, 1H), 2.20–2.08 (m, 2H), 2.01–1.51 (m, 7H), 1.38–1.20 (m, 3H), 1.17 (s, 3H), 0.82 (d, J = 6.4 Hz, 3H), 0.70 (s, 3H); ^{13}C NMR δ 153.7, 105.8, 66.0, 44.4, 42.3, 39.3, 38.1, 36.3, 32.7, 31.8, 27.1, 24.2, 20.9, 15.9, 14.4. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.85; H, 11.78.

Mesylate 15. To a solution of alcohol **14** (37.5 mg, 0.169 mmol) and triethylamine (0.240 mL, 1.72 mmol) in CH_2Cl_2 (0.55 mL) at 0 °C was added methanesulfonyl chloride (65.0 μL, 0.840 mmol) dropwise over 30 s. The reaction mixture was allowed to warm to rt, quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with ether (3 × 5 mL). The ether extracts were combined, dried, and concentrated. The resulting material was purified by flash chromatography (7:1 hexanes:ethyl acetate) to afford mesylate **15** (47.4 mg, 94%) as a colorless oil that crystallized upon standing to a white solid: mp 83–85 °C; IR ($CHCl_3$) 1636, 1356 cm^{-1}; ^{1}H NMR δ 4.77–4.72 (m, 2H), 4.13 (d, J = 10.0 Hz, 1H), 3.91 (d, J = 10.0 Hz, 1H), 3.00 (s, 3H), 2.50 (dddt, J = 14.1, 12.1, 7.7, 2.0 Hz, 1H), 2.21–2.09 (m, 2H), 2.03–1.89 (m, 1H), 1.81–1.50 (m, 6H), 1.38–1.22 (m, 2H), 1.17 (s, 3H), 0.84 (d, J = 6.4 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR δ 153.1, 106.2, 72.1, 44.5, 41.7, 39.2, 37.7, 36.9, 36.6, 32.6, 31.5, 26.8, 23.9, 20.9, 15.7, 13.8. Anal. Calcd for $C_{16}H_{28}O_3S$: C, 63.96; H, 9.39. Found: C, 64.06; H, 9.35.

Iodide 16. To a solution of mesylate **15** (0.275 g, 0.915 mmol) in DMPU (4.6 mL) and DME (4.6 mL) was added NaI (1.10 g, 7.34 mmol) in one portion, and the reaction mixture was heated to 80 °C. After 3.5 d, the mixture was allowed to cool to rt, quenched with 5% aqueous $Na_2S_2O_4$ (20 mL), and extracted with ether (3 × 10 mL). The organic extracts were

combined, dried, filtered, and concentrated. The product was purified by flash chromatography with hexanes to afford iodide **16** (219 mg, 98% based on recovered **15**) as a colorless liquid, followed by 4:1 hexanes:ethyl acetate to give unreacted mesylate **15** (72.2 mg). For iodide **16**: IR ($CHCl_3$) 1636 cm^{-1}; ^1H NMR δ 4.77–4.72 (m, 2H), 3.42 (d, J = 10.7 Hz, 1H), 3.22 (d, J = 10.7 Hz, 1H) 2.49 (dddt, J = 14.3, 12.4, 7.3, 2.0 Hz, 1H), 2.20–2.08 (m, 2H), 1.89 (ddt, J = 14.3, 13.0, 6.4 Hz, 1H), 1.79–1.42 (m, 6H), 1.38–1.21 (m, 2H), 1.17 (s, 3H), 1.01 (s, 3H), 0.73 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 152.9, 106.4, 48.0, 40.0, 39.9, 39.3, 37.7, 32.6, 31.6, 27.2, 24.0, 23.9, 20.7, 15.4, 15.0. Anal. Calcd for $C_{15}H_{25}I$: C, 54.22; H, 7.58. Found: C, 54.62; H, 7.84.

Dimethyl Diether 18. To a solution of iodide **16** (0.200 g, 0.602 mmol) and (dppf)$NiCl_2$ (80.1 mg, 0.117 mmol) in THF (55 mL) at 0 °C was added a solution of (2,5-dimethoxyphenyl)-magnesium bromide[5b] (**17**) in THF (1.3 M, 4.7 mL, 6.1 mmol) in one portion. The reaction mixture was allowed to warm to rt. After 19 h, the mixture was quenched by addition of saturated aqueous $NaHCO_3$ (60 mL) and extracted with ethyl acetate (3 × 20 mL). The organic fractions were combined, dried, filtered, and concentrated. The residue was purified by flash chromatography (2×, 3:1 hexanes:benzene) to afford compound **18** (91.6 mg, 44%) as a colorless oil that crystallized upon standing to a white solid: mp 57–59 °C; IR ($CHCl_3$) 1499, 1464 cm^{-1}; ^1H NMR δ 6.78–6.67 (m, 3H), 4.73–4.67 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 2.76 (d, J = 14.0 Hz, 1H), 2.56 (d, J = 14.0 Hz, 1H), 2.53–2.40 (m, 1H), 2.25–2.08 (m, 2H), 2.00–1.78 (m, 3H), 1.77–1.62 (m, 1H), 1.61–1.45 (m, 1H), 1.41–1.15 (m, 4H), 1.02 (s, 3H), 0.97 (d, J = 6.3 Hz, 3H), 0.90 (s, 3H); ^{13}C NMR δ 153.7, 152.9, 152.7, 128.9, 118.7, 111.2, 111.0, 105.6, 55.6, 55.4, 46.3, 43.5, 39.3, 37.7, 37.4, 37.2, 32.9, 32.0, 27.6, 25.0, 22.3, 19.1, 17.9. Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.51; H, 10.03.

Arenarone (19). To a solution of dimethyl diether **18** (30.5 mg, 0.0890 mmol) in CH_3CN (5.9 mL) at rt was added saturated aqueous $NaHCO_3$ (2.9 mL) followed by ceric ammonium nitrate (0.195 g, 0.356 mmol). After 1.8 d, the reaction mixture was concentrated. The resulting mixture was purified by flash chromatography (2×, 95:5 hexanes:ethyl acetate) to afford arenarone[6] (**19**, 20.3 mg, 73%) as a yellow oil. This material gave ^1H and ^{13}C NMR spectra identical with the partial ^1H NMR data and the ^{13}C NMR spectrum previously reported:[6] ^1H NMR δ 6.79–6.69 (m, 2H), 6.54–6.51 (m, 1H), 4.74–4.69 (m, 2H), 2.66 (d, J = 13.6 Hz, 1H), 2.54–2.35 (m, 1H), 2.41 (dd, J = 13.6, 1.0 Hz, 1H), 2.18–1.92 (m, 3H), 1.91–1.64 (m, 3H), 1.63–1.47 (m, 1H), 1.32–1.19 (m, 3H), 1.17–1.02 (m, 1H), 1.06 (s, 3H), 0.93 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H).

(±)-Arenarol (1). To a solution of arenarone (**19**, 4.6 mg, 0.015 mmol) in THF (0.48 mL) and H_2O (0.24 mL) was added $Na_2S_2O_4$ (50.3 mg, 0.289 mmol). After 5 min, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (1 mL) and extracted with ethyl acetate (3 × 1 mL). The organic extracts were combined, dried, filtered, and concentrated. The residue was purified by flash chromatography (3:1 hexanes:ethyl acetate) to afford arenarol (**1**, 3.8 mg, 82%) as a colorless oil. This material gave ^1H and ^{13}C NMR spectra identical to authentic data[6] and was identical in TLC and ^1H and ^{13}C NMR comparisons with an authentic sample.[7]

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