

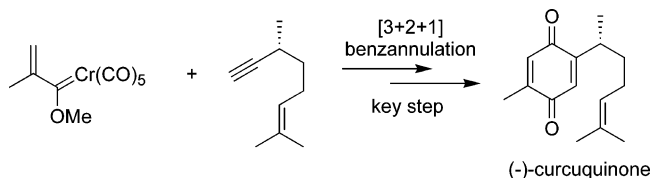
Enantioselective Total Synthesis of (-)-Curcuquinone via Regioselective Chromium-Mediated Benzannulation

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A short and efficient, high-yielding enantioselective total synthesis of the marine natural product (-)-curcuquinone **1** is reported involving a regioselective [3 + 2 + 1]-benzannulation reaction as the key step. Additionally, this strategy allows the isolation of curcuhydroquinone monomethyl ether **9** as an intermediate of the benzannulation reaction and its subsequent further protection toward diversified hydroquinones.

(-)-Curcuquinone **1**, (-)-curcuhydroquinone, and (-)-curcuphenol are aromatic bisabolene sesquiterpenoids isolated from the Caribbean gorgonian sea plume *Pseudotergorgia rigida*.¹ Apart from displaying antibacterial activity themselves, curcuquinone and curcuhydroquinone have proven to be versatile chiral building blocks for the synthesis of related important natural products, such as heliannuols, which represent a group of allelochemical phenolic sesquiterpenes.²

Due to the common difficulty of introducing defined absolute stereochemistry at the nonfunctionalized benzylic position, only two reports on the synthesis of optically active curcuquinone are available.^{3,4} However, both routes require an enzymatic resolution as the key step, and 50% of the synthetic material is lost at an earlier or later stage of synthesis.

Herein, we report on the first enantioselective total synthesis of the naturally occurring (-)-curcuquinone **1**. It represents a first convergent synthetic approach which directly generates the quinonid core. Thus, this strategy contrasts the customary routes starting from aromatic precursors. From a retrosynthetic perspective, the chromium-mediated benzannulation reaction was envisaged as an efficient key-step to afford both the hydroquinone

and quinone moiety of curcuquinone in a completely regioselective way, as outlined in Figure 1.⁵

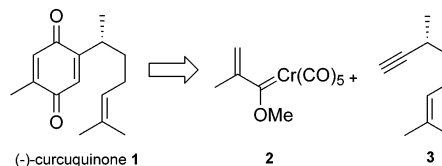
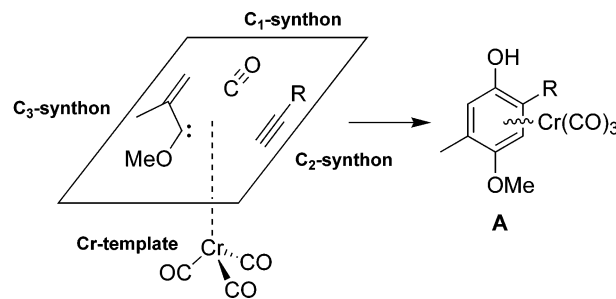


FIGURE 1. Retrosynthetic analysis of (-)-curcuquinone **1**.

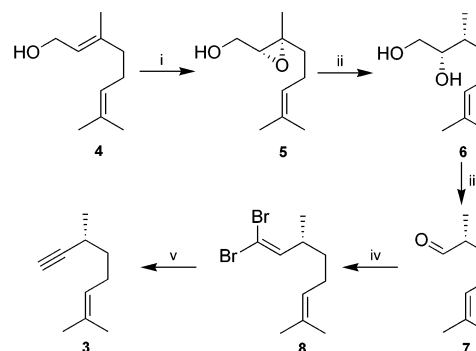
The key substrates for the benzannulation reaction are the propenyl methoxy chromium carbene complex **2**⁶ and the chiral terminal acetylene **3**. This unique type of metal carbene reaction provides one of the most powerful tools to generate densely substituted benzenoid compounds.⁷ It proceeds via a formal [3 + 2 + 1]-cycloaddition, which involves an α,β -unsaturated carbene ligand (C_3 -synthon), an alkyne (C_2 -synthon), and a carbonyl ligand (C_1 -synthon) and takes place within the coordination sphere of the chromium(0) metal center which acts as a template (Scheme 1).

SCHEME 1. Atom Connectivity in the Regioselective [3 + 2 + 1]-Benzannulation Reaction toward **1** (R = (*R*)-2-methylhept-2-enyl)



To perform the total synthesis in an enantioselective manner, a stereoselective synthesis of the enyne **3** in optically pure form was required (Scheme 2).

SCHEME 2. Stereoselective Synthesis of Enyne **3**^a



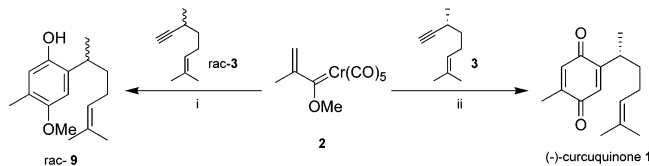
^a Reagents and conditions: (i) (*D*)-(-)-DIPT, Ti(*O*-*i*-Pr)₄, TBHP, CH₂Cl₂, MS 4 Å, -20 °C, 1 h, 87%; (ii) NaBH₃CN, BF₃·OEt₂, THF, rt, 4 h, 86%; (iii) NaIO₄, Bu₄NIO₄, H₂O, CH₂Cl₂, 0 °C, 1 h, 95%; (iv) CBr₄, PPh₃, Zn, CH₂Cl₂, rt, 12 h, 60%; (v) *n*-BuLi, THF, -78 °C, 1 h, rt, 1 h, 99%.

(1) (a) McEnroe, F. J.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661–1664. (b) (+)-Curcuphenol has been isolated from the Jamaican sponge, *Didiscus oxeata*.

(2) (a) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807–1808. (b) Vyvyan, J. R.; Looper, R. E. *Tetrahedron Lett.* **2000**, *41*, 1151–1154.

Our synthesis of the prerequisite acetylene commenced with commercially available geraniol **4**, which was epoxidized asymmetrically according to Sharpless AE to yield epoxide **5** $\{[\alpha]_{\text{D}}^{25} = +5.0^\circ (c = 3.0, \text{CHCl}_3, \text{lit.}^{5b} [\alpha]_{\text{D}}^{25} = -5.3^\circ (c = 3.0, \text{CHCl}_3) \text{ for the } (-)\text{-enantiomer}\}$ in 95% ee (Scheme 2).⁸ Lewis acid-mediated reductive ring opening of this compound with NaBH_3CN occurred at the higher substituted center to furnish diol **6**,⁹ which was subjected to oxidative glycol cleavage to afford the desired aldehyde **7**.^{10,11} Severe difficulties were encountered in cleaving the diol with NaIO_4 in dioxane/ H_2O following the procedure of Kibayashi et al., as this reaction failed on scales bigger than 5 mmol and the removal of dioxane turned out to be deleterious.¹¹ Therefore, the oxidative cleavage with NaIO_4 was performed in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ in the presence of catalytic amounts of Bu_4NIO_4 .¹² This procedure worked nicely even on larger scale-ups. The racemization-free conversion of aldehyde **7** into the terminal acetylene **3** via the dibromo olefin **8** was achieved according to the Corey–Fuchs protocol.¹³ Finally, the synthesis of **1** was accomplished in 80% yield in a benzannulation reaction of chromium carbene complex **2** with properly functionalized chiral terminal acetylene **3** (Scheme 3). The reaction occurred with complete regioselectivity; no potential regioisomer could be detected in the crude NMR.

SCHEME 3. Synthesis of (–)-**1** and rac-**9**^a



^a Reagents and conditions: (i) CH_2Cl_2 , 55 °C, 2.5 h, MeCN, O_2 , rt, 1 h, 80%; (ii) CH_2Cl_2 , 55 °C, 2.5 h, CAN, H_2O , 0 °C, 30 min, 80%.

The final functionalization pattern of the product depends on the workup conditions of the benzannulation

(3) (a) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758–3764. (b) Yoshimura, T.; Kisyuku, H.; Kamei, T.; Takabatake, K.; Shindo, M.; Shishido, K. *Arkiivoh* **2003**, 247–255.

(4) For total syntheses of racemic curcuquinone, see: (a) Sánchez, I. H.; Lemini, C.; Joseph-Nathan, P. *J. Org. Chem.* **1981**, *46*, 4666–4667. (b) Ono, M.; Yamamoto, Y.; Todoriki, R.; Akita, H. *Heterocycles* **1994**, *37*, 181–185. (c) Ono, M.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1995**, *43*, 553. (d) Vyryan, J. R.; Loitz, C.; Looper, R. E.; Mattingly, C. S.; Peterson, E. A.; Staben, S. T. *J. Org. Chem.* **2004**, *6*, 2461–2468.

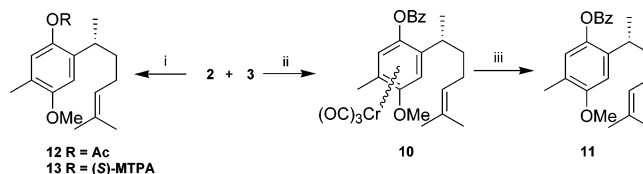
(5) For recent examples on the application of the benzannulation reaction in the total synthesis of natural products, see: (a) Rawat, M.; Wulff, W. D. *Org. Lett.* **2004**, *6*, 329–332. (b) Roush, W. R.; Neitz, R. J. *J. Org. Chem.* **2004**, *69*, 4906–4912. (c) Pulley, S. R.; Czakó, B. *Tetrahedron Lett.* **2004**, *45*, 5511–5514. (d) White, J. D.; Smits, H. *Org. Lett.* **2005**, *7*, 235–238.

(6) (a) Dötz, K. H.; Kuhn, W.; Ackermann, K. Z. *Naturforsch.* **1983**, *38b*, 1351–1356. (b) Fogel, L.; Hsung, R. P.; Wulff, W. D. *J. Am. Chem. Soc.* **2001**, *123*, 5580–5581.

(7) (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644–645. For a recent review, see: (b) Minatti, A.; Dötz, K. H. In *Topics in Organometallic Chemistry*; Dötz, K. H., Ed.; Springer: Heidelberg, Germany, 2004; pp 123–157. (c) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964–4002. (d) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187–198. For mechanistic details, see: (e) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102–126. (f) Barluenga, J.; Aznar, F.; Gutiérrez, I.; Martín, A.; García-Granda, S.; Llorca-Baragano, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 1314–1342.

reaction. Direct oxidative workup of the reaction mixture with CAN in aqueous dichloromethane at 0 °C yielded (–)-curcuquinone **1** $\{[\alpha]_{578}^{23} = -4.9^\circ (c = 1.09, \text{CHCl}_3)$, lit.^{3b} $[\alpha]_{577}^{20} = +4.32^\circ (c = 2.8, \text{CHCl}_3)$ for the (+)-enantiomer} (Scheme 3).¹⁴ The spectroscopic data for the synthetic material were in excellent agreement with those reported for the natural product.¹ Taking advantage of the inherent character of the benzannulation reaction, the present approach allows the synthesis of further valuable congeners. Within this context, mild oxidation of the crude reaction mixture afforded curcuhydroquinone monomethyl ether **9** with an intact hydroquinone core as a colorless, viscous oil (Scheme 3). The elusive primary benzannulation reaction product **A** bearing the chromium-coordinated hydroquinone monomethyl ether functionality could only be isolated after an in situ benzoylation under standard conditions (Scheme 4).

SCHEME 4. Synthesis of Curcuhydroquinone Derivatives **10**, (–)-**11**, (–)-**12**, and (+)-**13**^a



^a Reagents and conditions: (i) CH_2Cl_2 , 55 °C, 2.5 h, AcBr or (S)-MTPA-Cl, DMAP, NEt_3 , –20 °C to rt, 2 h, 40 or 33%, respectively; (ii) CH_2Cl_2 , 55 °C, 2.5 h, BzCl, DMAP, NEt_3 , –20 °C to rt, 2 h, 60%; (iii) CH_2Cl_2 , MeCN, O_2 , rt, 5 h, 95%.

Arenechromium complex **10** was isolated as an equimolar mixture of the two diastereomeric planar–chiral metal complexes, which are direct precursors of (–)-curcuquinone obtained by subsequent CAN oxidation. Mild decomplexation released the free hydroquinone (–)-**11** as a colorless, viscous oil with the two phenolic groups differentiated as methyl ether and benzoyl ester, respectively. In a similar protocol, the methyl acetyl-bisprotected hydroquinone (–)-**12** could be synthesized. Likewise, upon reaction with Mosher's chloride, the corresponding Mosher ester **13** was generated as a single stereoisomer. Comparison of the respective set of ^1H , ^{13}C , and ^{19}F NMR signals with those of a 1:1 diastereomeric mixture proved the overall sequence to be enantioselective. This overall ease of phenoxy group differentiation in **9**, (–)-**11**, and (–)-**12** is of major synthetic importance

(8) (a) The enantiomeric excess was determined by ^1H NMR for the corresponding epoxy acetate in the presence of $\text{Eu}(\text{hfc})_3$. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780. (c) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299–2311.

(9) (a) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437–475. (b) Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004–4006.

(10) Racemic aldehyde **7** is commercially available.

(11) Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett.* **2001**, *3*, 193–196.

(12) Corey, E. J.; Wright, S. W. *J. Org. Chem.* **1990**, *55*, 1670–1673.

(13) For the synthesis of racemic 3,7-dimethyl-6-octene-1-yne **3**, starting from racemic aldehyde **7**, see: (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772. (b) Snider, B. B.; Killinger, T. A. *J. Org. Chem.* **1978**, *43*, 2161–2164.

(14) Attempts to determine the enantiomeric excess of the natural product **1** did not meet with success as enantiomers of curcuquinone could not be separated on HPLC employing standard Chiralcel OD, OG, OB, Chiralpak AD, AS columns.

since related protection in synthetic approaches to he-liannuol A and D required multistep synthesis, including resolution.^{2a} Moreover, within the current general aim-toward biological diversity, such structures might poten-tially show complementary pharmaceutical and biological activity.

In summary, we have described the first enantio-selective total synthesis of (–)-curcuquinone **1** in 7 steps and 20% overall yield starting from commercially avail-able geraniol. The key features are the enantiose-lective synthesis of the enyne **3** and the regioselective [3 + 2 + 1]-benzannulation reaction to construct the fully substituted aromatic core. Taking advantage of the benzannulation key step, complementary protection pat-terns further allow straightforward access to molecu-les of higher diversity.

Experimental Section

(–)-Curcuquinone (**1**).^{1,3} A solution of **2** (276 mg, 1 mmol) and **3** (204 mg, 1.5 mmol) in dichloromethane (5 mL) was degassed by three freeze–pump–thaw cycles and warmed to 55 °C for 2.5 h under inert atmosphere. The benzannulation reaction mixture was cooled to room temperature and slowly added to a solution of (NO₃)₆Ce(NH₄)₂ (3.84 g, 7 mmol) in H₂O (20 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and extracted with dichloromethane. The organic layer was washed with aqueous sodium bicarbonate and brine. The residue was purified by column chromatography [*n*-hexane/dichloromethane, 1/1 (v/v)] to yield the title compound **1** (0.19 g, 80%) as a yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 1.03 (3H, d, *J* = 6.8 Hz), 1.35–1.53 (5H, m), 1.58 (3H, d, *J* = 1.1 Hz), 1.89 (2H, m), 1.96 (3H, d, *J* = 1.7 Hz), 2.83 (1H, m), 4.97 (1H, t, *J* = 6.9 Hz), 6.42 (1H, d, *J* = 0.9 Hz), 6.50 (1H, d, *J* = 1.7 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 188.3, 187.2, 154.0, 144.9, 133.7, 131.9, 131.0, 123.8, 35.7, 31.2, 25.7, 25.5, 19.4, 17.5, 15.2; IR (neat) ν 3272, 2966, 2926, 1657, 1610, 1452, 1241 cm^{–1}; MS (EI) *m/z* = 232 (M⁺), 164, 151, 122, 69; HRMS (EI) calcd for C₁₅H₂₀O₂ 232.1463, found 232.1471; [α]_D²³₇₈ = –4.9° (*c* = 1.09, CHCl₃).¹⁴

Pentacarbonyl[methoxy(2-propenyl)carbene]chromi-um (**2**).⁶ The known synthesis of **2** was slightly modified with regard to the methylation. A solution of 1.81 g (15 mmol) of 2-bromopropene in 30 mL of diethyl ether was cooled to –78 °C, and 17.6 mL (30 mmol) of a 1.7 M solution of *t*-BuLi in *n*-hexane was added dropwise over 10 min. The resulting light-yellow solution was stirred for 3 h at –78 °C before it was slowly transferred via cannula to a slurry of 3.29 (15 mmol) Cr(CO)₆ and 225 mL of diethyl ether kept at –60 °C. After the resulting brown solution was stirred at –60 °C for 30 min, it was warmed to room temperature and the solvent was evaporated under reduced pressure. The remaining residue was dissolved in 150 mL of dichloromethane, and 3.33 g (22.5 mmol) of Me₃OBF₄ was added at 0 °C. The solution was warmed to room temper-ature and stirred for 1 h. The crude reaction mixture was filtered through a cooled pad of silica gel, and the solvent was evaporated under reduced pressure. The known title compound **2** (2.83 g, 68%) was obtained by column chromatography (*n*-hexane) at –25 °C as a red, viscous oil, which has to be stored rigorously under argon at –78 °C: ¹H NMR (300 MHz, acetone-*d*₆) δ 1.92 (3H, m), 4.56 (3H, s), 4.82 (1H, m), 5.07 (1H, m); ¹³C NMR (75 MHz, acetone-*d*₆) δ 356.5, 225.1, 216.9, 160.0, 119.6, 68.6, 19.7; IR (*n*-hexane) ν 2065, 1988, 1951 cm^{–1}.

(*R*)-3,7-Dimethyl-6-octen-1-yne (**3**).¹³ Compound **3** was synthesized in an analogous manner as reported. Purification was carried out by distillation: bp 55 °C (15 mbar); ¹H NMR (300 MHz, C₆D₆) δ 1.01 (3H, d, *J* = 7 Hz), 1.21–1.46 (2H, m), 1.52 (3H, s), 1.60 (3H, s), 1.83 (1H, d, *J* = 2 Hz), 2.12 (2H, m), 2.25 (1H, m), 5.06 (1H, t, *J* = 7 Hz); ¹³C NMR (75 MHz, C₆D₆) δ 131.8, 124.4, 88.8, 68.9, 37.2, 26.2, 25.8, 25.6, 21.1, 17.7; IR (neat) ν 3311, 2970, 2927, 2856, 2114, 1452, 1377 cm^{–1}; [α]_D²³ = –47.5°

(*c* = 1.0, CHCl₃); GC analysis [Chirasil-Dex CB column, N₂ carrier gas, 40 °C, retention times 63.6 min (*S*), 72.2 min (*R*)].

(*R*)-2,6-Dimethyl-5-heptenal (**7**).^{10,11} A solution of 1.72 g (10 mmol) of **6** in 40 mL of dichloromethane was cooled to 0 °C; 0.2 g (0.46 mmol) of tetra-*n*-butylammonium periodate and a solution of 4.28 g (20 mmol) of sodium periodate in 40 mL of water cooled to 0 °C were added sequentially. After 1 h, 100 mL of pentane was added, the layers were separated, and the organic layer was washed with water and brine. The solvent was evaporated under ambient pressure to yield the known title compound **7** as a colorless liquid (1.33 g, 95%): ¹H NMR (300 MHz, CDCl₃) δ 1.03 (3H, d, *J* = 7 Hz), 1.35 (1H, m), 1.54 (3H, s), 1.63 (3H, s), 1.72 (1H, m), 1.97 (2H, m), 2.27 (1H, m), 5.03 (1H, t, *J* = 7 Hz), 9.56 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 205.0, 132.6, 123.4, 45.8, 30.6, 25.6, 25.3, 17.6 13.2.

(*R*)-1,1-Dibromo-3,7-dimethyl-1,6-octadiene (**8**).¹³ Com-pound **8** was synthesized in an analogous manner as reported: bp 50 °C (2.5–3 × 10^{–2} mbar); ¹H NMR (300 MHz, C₆D₆) δ 0.78 (3H, d, *J* = 7 Hz), 1.17 (2H, m), 1.55 (3H, s), 1.69 (3H, s), 1.90 (2H, m), 2.40 (1H, m), 5.08 (1H, t, *J* = 7 Hz), 6.00 (1H, d, *J* = 9 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 144.2, 131.9, 124.0, 87.5, 38.0, 36.3, 25.9, 25.8, 19.3, 17.8; IR (neat) ν 2964, 2927, 2852, 1616, 1454, 1377, 1117, 847, 781 cm^{–1}; [α]_D²³ = –7.8° (*c* = 3.0, CHCl₃), GCMS *m/z* = 296 (M⁺), 215, 135.

Curcuhydroquinone Monomethyl Ether (**9**). A solution of **2** (276 mg, 1 mmol) and racemic **3** (204 mg, 1.5 mmol) in dichloromethane (5 mL) was degassed by three freeze–pump–thaw cycles and warmed to 55 °C for 2.5 h under inert atmosphere. The benzannulation reaction mixture was cooled to room temperature, diluted with acetonitrile (10 mL), and stirred for 1 h with exposure to air. After filtration of the crude reaction mixture through a pad of Celite, the solvent was evaporated under reduced pressure. The pure product **9** (0.2 g, 80%) was obtained by column chromatography [*n*-hexane/dichloromethane, 1/1 (v/v)] as a colorless, viscous oil: ¹H NMR (300 MHz, CDCl₃) δ 1.21 (3H, d, *J* = 7.0 Hz), 1.53 (3H, s) 1.54–1.67 (5H, m), 1.93 (2H, m), 2.13 (3H, s), 2.96 (1H, m), 3.76 (3H, s), 4.32 (1H, s), 5.11 (1H, t, *J* = 7.0 Hz), 6.56 (1H, s), 6.60 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 152.2, 146.5, 132.0, 130.7, 124.9, 124.6, 118.2, 109.4, 56.2, 37.4, 31.9, 26.1, 25.7, 21.2, 17.7, 15.7; IR (neat) ν 3423, 2962, 2927, 1685, 1502, 1452, 1411, 1200 cm^{–1}; MS (EI) *m/z* = 248 (M⁺), 165, 151, 122, 109, 67, 55; HRMS (EI) calcd for C₁₆H₂₄O₂ 248.1776, found 248.1769.

Tricarbonylchromiumhydroquinone Complex (**10**). A solution of **2** (276 mg, 1 mmol) and **3** (204 mg, 1.5 mmol) in dichloromethane (5 mL) was degassed by three freeze–pump–thaw cycles and then warmed to 55 °C for 2.5 h under inert atmosphere. The benzannulation reaction mixture was cooled to room temperature and slowly added to a solution of benzoyl chloride (154 mg, 1.1 mmol), DMAP (134 mg, 1.1 mmol), and NEt₃ (0.1 mL, 1.1 mmol) in dichloromethane (10 mL) at –20 °C. The solution was warmed to room temperature and stirred for 2 h. Purification by column chromatography [*n*-hexane/dichloromethane, 2/1 (v/v)] afforded complex **10** (0.29 g, 60%) as a 1:1 diastereomeric mixture as a brownish oil: ¹H NMR (300 MHz, CDCl₃) δ 1.16–1.58 (24H, m), 1.87–2.00 (10H, m), 3.05–3.09 (6H, m), 4.90–5.08 (2H, m), 7.05–7.15 (8H, m), 8.11–8.29 (6H, m); ¹³C NMR (75 MHz, CDCl₃) δ 234.4, 234.3, 165.4, 165.3, 134.3, 134.3, 132.7, 132.3, 131.4, 131.3, 130.4, 130.3, 129.8, 129.1, 129.1, 128.8, 128.8, 128.5, 125.8, 125.7, 125.1, 124.9, 124.1, 123.7, 110.6, 110.2, 98.7, 98.7, 90.5, 90.4, 77.0, 75.6, 56.2, 56.1, 39.4, 36.7, 33.7, 31.8, 26.5, 26.1, 25.7, 25.4, 22.0 19.4, 19.0, 17.7, 17.7, 15.3; IR (CH₂Cl₂) ν 2304, 1961, 1880, 1733, 1645 cm^{–1}; MS (EI) *m/z* = 488 (M⁺), 404, 389, 345, 322, 204, 165, 105, 77; HRMS (EI) calcd for C₂₆H₂₈CrO₆ 488.1291, found 488.1300.

(Methyl, Benzoyl)-Bisprotected Hydroquinone (–)-(11). A solution of the two diastereomers **10** (150 mg, 0.3 mmol) in dichloromethane (4 mL) and acetonitrile (4 mL) was stirred at room temperature for 5 h. After filtration of the crude reaction mixture through a pad of Celite, the solvent was evaporated under reduced pressure. Column chromatography [*n*-hexane/dichloromethane, 2/1 (v/v)] afforded pure **11** (0.1 g, 95%) as a colorless, viscous oil: ¹H NMR (300 MHz, CDCl₃) δ 1.12 (3H, d, *J* = 7.0 Hz), 1.41 (3H, s), 1.48 (3H, s), 1.58 (2H, m), 1.82 (2H,

m), 2.12 (3H, s), 2.82 (1H, m), 3.75 (3H, s), 4.95 (1H, t, $J = 7.0$ Hz), 6.64 (1H, s), 6.81 (1H, s), 7.34–7.56 (3H, m), 8.10 (1H, d, $J = 1.3$ Hz), 8.13 (1H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 165.6, 155.8, 141.5, 137.1, 133.3, 131.5, 130.1, 129.8, 129.5, 128.5, 128.3, 125.1, 124.3, 124.2, 108.3, 55.6, 37.6, 32.4, 26.0, 25.5, 21.2, 17.6, 15.8; IR (neat) ν 3450, 2962, 2927, 1736, 1502, 1265, 1198, 710 cm^{-1} ; MS (EI) $m/z = 352$ (M^+), 269, 247, 230, 215, 187, 165, 105, 77; HRMS (EI) calcd for $\text{C}_{23}\text{H}_{28}\text{O}_3$ 352.2038, found 352.2041; $[\alpha]_{\text{D}}^{23} = -14.9^\circ$ ($c = 1.903$, CHCl_3).

(Methyl, Acetyl)-Bisprotected Hydroquinone (-)-(12). A solution of **2** (276 mg, 1 mmol) and **3** (204 mg, 1.5 mmol) in dichloromethane (5 mL) was degassed by three freeze–pump–thaw cycles and warmed to 55 °C for 2.5 h under inert atmosphere. The benzannulation reaction mixture was cooled to room temperature and slowly added to a solution of acetyl-bromide (136 mg, 1.1 mmol), DMAP (134 mg, 1.1 mmol), and NEt_3 (0.1 mL, 1.1 mmol) in dichloromethane (10 mL) at –20 °C. The solution was warmed to room temperature and stirred for 2 h. Purification by column chromatography [*n*-hexane/dichloromethane, 1/1 (v/v)] afforded compound **12** (0.12 mmol, 40%) as a colorless, viscous oil: ^1H NMR (300 MHz, CDCl_3) δ 1.14 (3H, d, $J = 7.0$ Hz), 1.50–1.58 (5H, m), 1.63 (3H, s), 1.87 (2H, m), 2.12 (3H, s), 2.23 (3H, s), 2.74 (1H, m), 3.76 (3H, s), 5.04 (1H, t, $J = 7$ Hz), 6.62 (1H, s), 6.71 (1H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 170.0, 155.8, 141.3, 136.9, 131.5, 125.1, 124.3, 124.1, 108.2, 55.6, 37.6, 32.4, 26.1, 25.7, 21.1, 20.8, 17.6, 15.8; IR (neat) ν 3463, 2964, 2929, 1760, 1502, 1369, 1196 cm^{-1} ; MS (EI) $m/z = 290$ (M^+), 248, 165, 151, 138, 82; HRMS (EI) calcd for $\text{C}_{18}\text{H}_{26}\text{O}_3$ 290.1882, found 290.1881; $[\alpha]_{\text{D}}^{25} = -19.4^\circ$ ($c = 1.737$, CHCl_3).

(*R,S*_{Aux})-Mosher Ester (+)-(13). A solution of **2** (276 mg, 1 mmol) and **3** (204 mg, 1.5 mmol) in dichloromethane (5 mL)

was degassed by three freeze–pump–thaw cycles and warmed to 55 °C for 2.5 h under inert atmosphere. The benzannulation reaction mixture was cooled to room temperature and slowly added to a solution of (*S*)-(+)- α -methoxy- α -trifluoromethyl-phenylacetyl chloride (0.2 mL, 1.1 mmol), DMAP (134 mg, 1.1 mmol), and NEt_3 (0.1 mL, 1.1 mmol) in dichloromethane (10 mL) at –20 °C. The solution was warmed to room temperature and stirred for 2 h. Acetonitrile (10 mL) was added, and the reaction mixture was stirred vigorously for 20 h exposed to air. After filtration of the crude reaction mixture through a pad of Celite, the solvent was evaporated under reduced pressure: ^1H NMR (300 MHz, acetone- d_6) δ 1.01 (3H, d, $J = 7$ Hz), 1.43 (3H, s), 1.48–1.64 (5H, m), 1.80 (2H, m), 2.09 (3H, s), 2.69 (1H, m), 3.64 (3H, d, $J = 1.3$ Hz), 3.79 (3H, s), 5.00 (1H, m), 6.82–6.85 (2H, m), 7.46–7.49 (3H, m), 7.65 (2H, m); ^{13}C NMR (75 MHz, acetone- d_6) δ 166.3, 163.3, 157.3, 141.6, 138.0, 132.9, 131.9, 130.8, 130.5, 129.5, 129.3, 128.3, 126.4, 125.9, 125.1, 124.0, 122.6, 109.1, 56.2, 56.1, 37.6, 32.8, 26.8, 25.8, 21.9, 17.7, 15.8; ^{19}F NMR (282 MHz, acetone- d_6) δ –72.7; IR (neat) ν 2962, 2929, 2854, 1761, 1501, 1457, 1398, 1268, 1244, 1200, 1178, 1122, 1020, 885, 715 cm^{-1} ; MS (EI) $m/z = 464$ (M^+), 290, 260, 248, 221, 189; HRMS (EI) calcd for $\text{C}_{26}\text{H}_{31}\text{F}_3\text{O}_4$ 464.2174, found 464.2174; $[\alpha]_{\text{D}}^{25} = +8.2^\circ$ ($c = 1.53$, CHCl_3).

Supporting Information Available: General experimental details and ^1H and ^{13}C NMR spectra of known compounds **1**, **3**, and **5–8** and new compounds **9**, **11**, and **12**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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