Practical Route to a New Class of LTD_4 Receptor Antagonists

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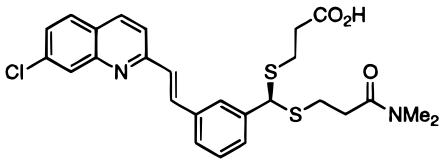
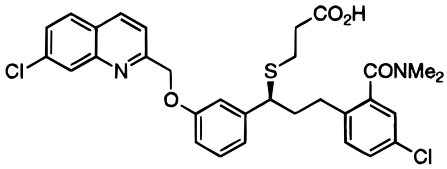
A general approach to the synthesis of a new class of LTD_4 antagonists is presented. The key diarylpropane framework was prepared by Claisen−Schmidt condensation and selective reduction of the enone. Depending on the bridge to the 7-chloroquinaldine moiety, alkylation or Heck coupling methodology was developed. The chiral sulfides were introduced by asymmetric reduction of the diarylpropanone intermediates and subsequent inversion of the chiral center.

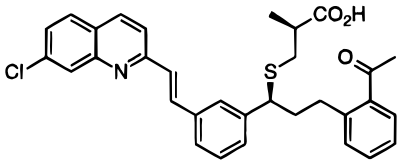
Since the discovery of the role played by the leukotrienes in asthma and associated inflammatory diseases the search for specific antagonists or inhibitors of this portion of the aracadonic acid cascade has been intensive.[1] An early candidate for the control of asthma was the LTD_4 antagonist MK-0571/MK-0679.[2,3] Elaboration of this original structure has advanced a new class of LTD_4 antagonists with the selection of L-691,698 (**1**) and L-699,392 (**2**) as active agents.[4] Here the 3-thiapropionamide side chain has been replaced with an arylethyl group, and in the case of the former, the *trans*-double bond has been changed to a phenyl quinaldine ether.



MK-679



1, L-691,698



2, L-699,392

Our goal was the development of a general approach to this new class of LTD_4 antagonists.[4,5] By incorporating the quinaldine portion of the molecule at the later stages of the synthesis the target became the diarylpropanol **3**. A classical synthesis of a 1,3-diarylpropenone is condensation of an acetophenone and a benzaldehyde, the Claisen−Schmidt reaction, producing an enone known as a chalcone;[6] selective 3,4-reduction then provides the 1,3-diarylpropanone (Scheme 1). In the synthesis of **1** and **2** coupling of the 3′-substituted acetophenone **4** with a 2-carboxybenzaldehyde **5** afforded the backbone of **3**

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

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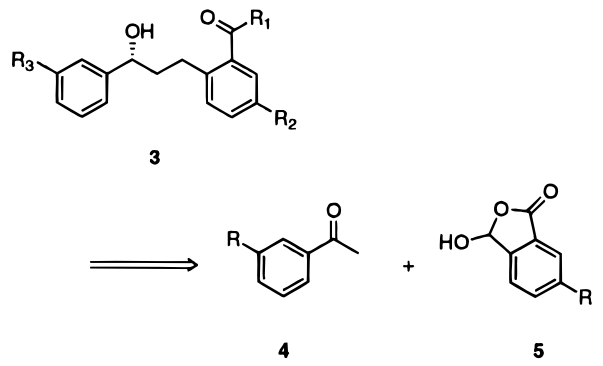
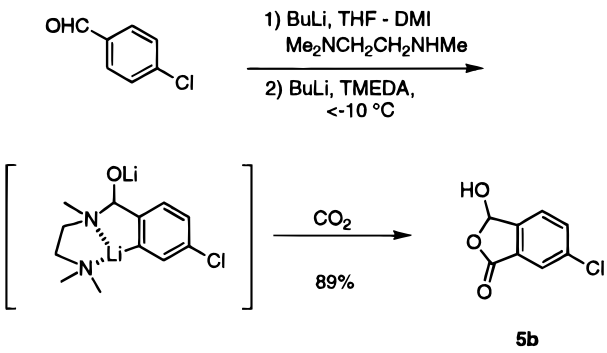
Scheme 1



Scheme 2



in one step. After coupling and hydrogenation of the enone, chiral reduction completed the construction of the diarylpropanol framework. The quinaldine portions of the molecules were now incorporated by alkylation to provide the ether linkage or by Heck coupling to install the ethene bridge. Thiolation with inversion of the chiral alcohol via the mesylate completed the enantioselective syntheses of the LTD_4 antagonists. We now wish to disclose herein the efficient syntheses of these drug candidates that are suitable to the preparation of multigram quantities for testing.

Results and Discussion

The key to the synthesis of diarylpropane-based LTD_4 antagonists was the efficient preparation of the ketoester **9**. The Claisen−Schmidt reaction is a highly effective method to prepare the 1,3-diarylpropane framework from simple starting materials. In order to use this route for construction of the 1,3-diarylpropane intermediate of L-691,698, the hydroxyphthalide **5b** was required. The only reported synthesis of **5b** was carried out in five steps by traditional methods from phthalide.[7] Probably the most suitable method in modern synthetic chemistry for preparing complex aromatic structures is directed ortho metalation (DOM).[8] Such hydroxyphthalides have been prepared by ortho-lithiation of benzamides and alkylation with an aldehyde.[8,9] In our case the problem of formation of regioisomers from a 3-chlorobenzamide caused us to consider metalation of a para-substituted system. Directed ortho metalation of a benzyl alcohol followed by carboxylation and subsequent oxidation of the phthalide has been reported.[10] In order to avoid the oxidation step, the more direct ortho lithiation of a benzaldehyde derivative was explored. With the recent success of Comins the ortho-lithiation of benzaldehydes has become more practical;[11] *N,N,N′*-Trimethylethylenediamine acts as a combined aldehyde-protecting group[11a] and ortho-directing group[11c,d] (Scheme 2).

Ortho-carboxylation of 4-chlorobenzaldehyde would provide a one-step preparation of **5b**.[12] Unfortunately, in order to obtain suitable metalation of the α-aminoalkoxide 3 equiv of BuLi was required.[11c] Because of the excess BuLi, carboxylation gave poor yields of **5b** (<30%). However, smooth metalation of the ortho-position of the α-aminoalkoxide occurred with only 1.1 equiv of *n*-BuLi in combination with 1.1 equiv of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA). Addition of the anion to THF continually saturated with CO_2 provided an 89% yield of **5b**. The combination of the two ethylenediamine reagents was critical: replacement of trimethylethylenediamine with 1-methylpiperazine or morpholine[11b] failed to give efficient metalation, and omission of TMEDA gave incomplete lithiation.

Chalcone coupling of the phenol **4a** with the hydroxyphthalides **5a** and **5b** proceeded in high yield using ethanolic NaOH (Scheme 3).[6a] In the case of the *des*-chloro derivative the enone was not isolated; rather, the lactone species formed.[13] Reduction of this intermediate was not expected to be selective. This problem was overcome after we observed that **6a** exists as the enone **7a** under basic conditions. Addition of 1.05 equiv of

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(8) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

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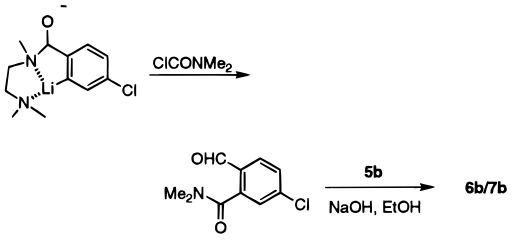
(10) Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835.

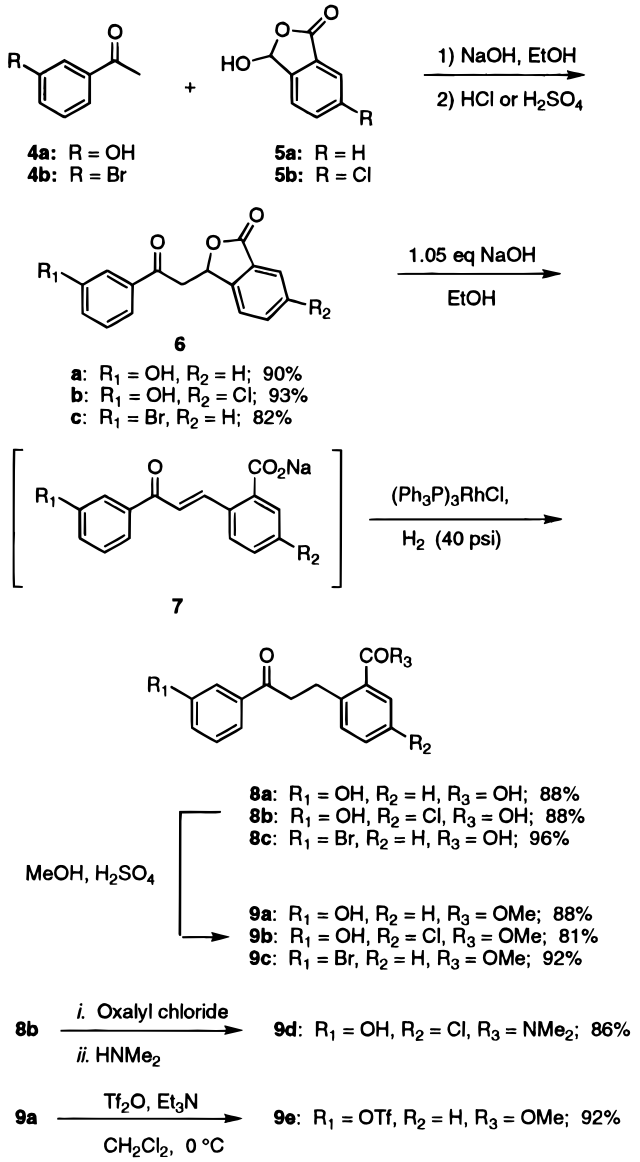
(11) (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213. (b) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. (c) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078. (d) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104. (e) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1989**, *54*, 3730. (f) Tamao, K.; Yao, H.; Tsutsumi, Y.; Abe, H.; Hayashi, T.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 2925. (g) Comins, D. L. *Synthesis Lett.* **1992**, 615.

(12) Directed ortho metalation of the cyclohexylimine of 4-chlorobenzaldehdye only provided BuLi attack at the imine and no detectable ortho lithiation. Ortho lithiation of the cyclohexylimines is reported to work only with aryl groups with electron-donating groups present; see: Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564. For a list of other benzaldehyde-related ortho directing groups see ref 8.

(13) Since the dimethylamide was ultimately desired, the metalation−carboxylation of 4-chlorobenzaldehyde was carried out with dimethylcarbamoyl chloride. The dimethylcarbamide derivative was obtained cleanly; however, upon subjecting the material to the coupling reaction the amide was easily hydrolyzed in situ to provide only **7b**.

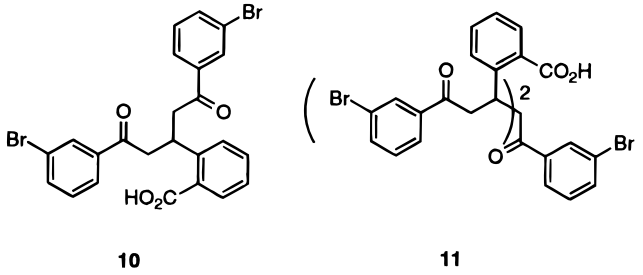


Scheme 3



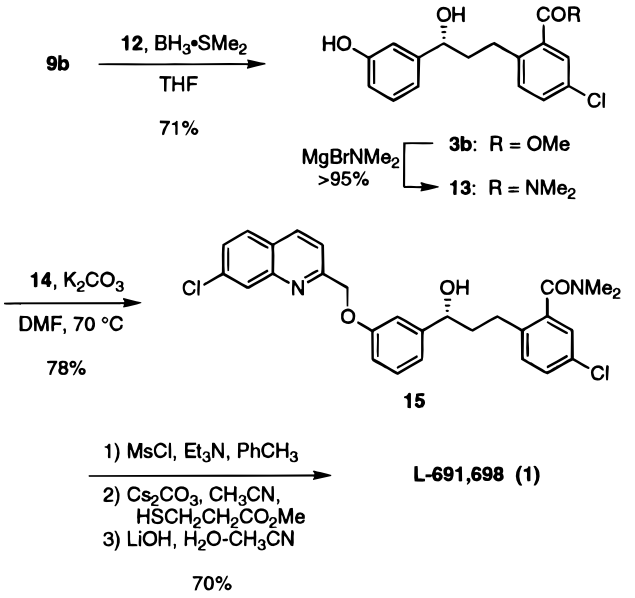
NaOH to an ethanol slurry of **6a** converted the lactone completely to the enone **7a** as evidenced by NMR. Hydrogenation of this mixture with Wilkinson's catalyst[14] provided the diarylpropanone **8a** in 88% isolated yield. Interestingly, with the chloro compound the isolated product from the coupling of hydroxyacetophenone **4a** and **5b** existed as a 16:84 mixture of the lactone **6b** and the enone **7b**. The enone form could be completely converted to the lactone by acidification and heating of the mixture. Instead, the addition of base to the reduction mixture was obviated by modifying the workup of the coupling: adjustment of the pH to 6.0−6.5 provided the enone as the sodium salt **7b** in 93% yield. Reduction of this enone with Wilkinson's catalyst at 40 psi gave the diarylpropanone **8b** in 88% isolated yield.

The bromo derivative **4b**, however, gave a mixture of products under the same conditions. This conversion was plagued by the propensity of the resultant enone **7c** to undergo Michael reactions forming the acetophenone adducts **10** and **11** as byproducts. Presumably, the increased electron density of the phenolate moiety of **7a**



and **7b** under the basic conditions suppressed the Michael reaction. By adding 1.2 equiv of NaOH and aging the reaction mixture at 0 °C for ∼10 h the formation of adduct **11** was prevented and **10** was kept to ∼5%. The lactone was then closed by the addition of sulfuric acid and heating the mixture at 60 °C for 0.5 h. The resultant lactone **6c** was isolated in 82% yield. This material reduced in the same fashion as the phenol analogues to provide the 3′-bromo keto acid **8c** in 96% isolated yield. The acids **8a**−**c** were then converted to the methyl esters **9a**−**c**, respectively, by refluxing in a mixture of methanol and sulfuric acid.

Scheme 4



The introduction of the chiral center of L-691,698 (Scheme 4) proceeded via asymmetric reduction of the keto ester **9b** rather than the dimethylamide **9d**. The diphenylprolinol-based reducing agents[15] have profoundly improved the enantioselective reduction of acetophenone derivatives. Because of the potential reduction of the amide group with borane the keto ester was chosen. Treatment of the ketone **9b** with borane in the presence of 10 mol % of (*S*)-tetrahydro-1-methyl-3,3-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole−borane (**12**) gave the hydroxy ester **3b** in 90% enantiomeric excess. An increased benefit of using the methyl ester was its crystallinity

(14) (a) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390. (b) Nakamura, K.; Fujii, M.; Ohno, A.; Oka, S. *Chem. Lett.* **1984**, 925. (c) Malek, J. *Org. React.* **1985**, *34*, 1.

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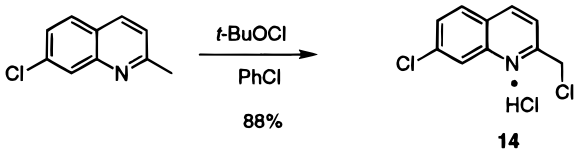
Scheme 5

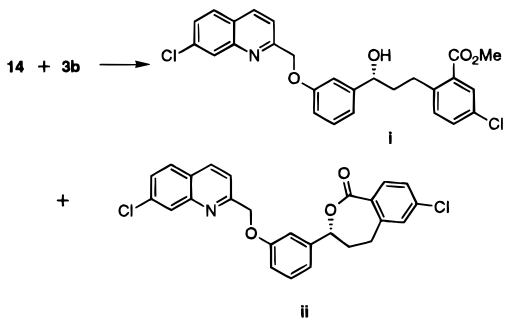


which facilitated optical enrichment; as was later learned the hydroxyamide **13** would not crystallize. The crude hydroxy ester was dissolved in CH_2Cl_2 by heating. The precipitated solid from the cooled solution was filtered, which proved to be a 33:67 mixture of the *R*/*S* enantiomers. Only a 4.7% loss of the available *R*-enantiomer resulted with an 86% removal of the undesired *S*-enantiomer. By concentration of the filtrate, addition of hexanes to the slurry and filtration of the solid the (*R*)-hydroxy ester **3b** was obtained 98% optically pure and in 83% yield. The methyl ester was then converted to the amide by treatment with magnesium dimethylamide in THF to provide the key intermediate **12** in 49% overall yield in five steps from 4-chlorobenzaldehyde.

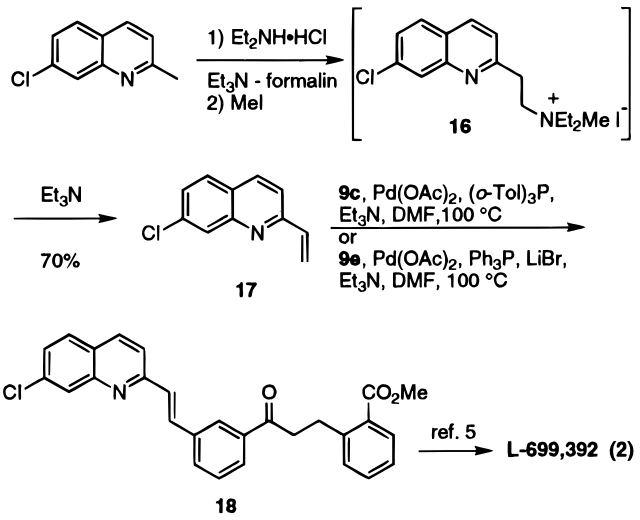
To complete the synthesis of L-691,698 alkylation of the phenol and inversion at the chiral center with the mercaptan were run successively. To introduce the quinaldine moiety 7-chloroquinaldine was functionalized as the α-chloro derivative **14** with *tert*-butyl hypochlorite in chlorobenzene (Scheme 5). This reagent offered the benefit of not requiring photochemical or free-radical generation of the active chlorinating agent. To the best of our knowledge this is the first use of *tert*-butyl hypochlorite for this purpose. The monochlorinated material was separated from the α,α-dichloro byproduct and starting material by crystallization from chlorobenzene as the HCl salt in 88% yield. The phenol **12** was then alkylated with **14** in DMF at 70 °C with K_2CO_3 as base.[16] The amorphous quinaldine phenyl ether **15** was purified by crystallization as the HCl salt from CH_2Cl_2 in 78% yield by addition of 1 M HCl in ethyl ether.

The thia side chain was then introduced with inversion of the stereochemistry by a three-step nonisolation process: First, the alcohol was activated as the mesylate in toluene at −20 °C with methanesulfonyl chloride and triethylamine as base. The reaction was followed by the downfield shift of the methine proton from 4.5 to 5.45 ppm. The solvent was changed to CH_3CN, and methyl 3-mercaptopropionate and cesium carbonate were added. After 2 h the displacement was complete. The salts were removed by filtration, and the ester was then hydrolyzed directly by addition of aqueous LiOH. The amorphous parent compound L-691,698 was converted to the crystalline hydrochloride salt in 70% overall yield from **15**.

(16) The alkylation of the hydroxy ester **3b** gave the crystalline product **i**. However, a major byproduct in the alkylation was the lactone **ii** (38%) formed by intramolecular esterification. Although the mixture of **i** and **ii** could be converted to **13**, purification and isolation of the reaction intermediate was compromised.



Scheme 6



The synthesis of L-699,392 required a carbon−carbon bond formation[17] rather than the etherification. The Heck reaction is an extremely efficient method for mixed couplings of aryl and alkenyl carbon bonds.[18] Either the bromide **9c** or phenol **9a** could be used; the latter was converted to the triflate **9e**. For incorporation of the ethenyl bridge preparation of a 2-ethenylquinoline was required. The best approach to prepare **17** was through a Mannich reaction of 7-chloroquinaldine followed by Hofmann elimination of **16** via the quaternary salt (Scheme 6).[19]

Palladium-catalyzed coupling of the vinyl group with the bromide **9c** or triflate **9e** was run in DMF at 100 °C using 3 mol % palladium(II) acetate. To couple the bromide substrate **9c** the addition of tri-*o*-tolylphosphine was necessary. The reaction was complete in 1 h, providing a 98% conversion to the keto ester **18**. With triphenylphosphine a more sluggish reaction resulted, requiring 20 h to reach 78% conversion. The optimized coupling was run with 3 mol % of $Pd(OAc)_2$, 9 mol % of (tri-*o*-tolylphosphine), and 1.5 equiv of triethylamine in DMF at 100 °C for 1.5 h to provide the keto ester in 91% isolated yield (>95% conversion). The product was formed as >99% *trans*-isomer.

Similarly, the triflate **9e** gave effective coupling. In contrast to **9c**, the addition of LiBr was necessary. Without the LiBr the coupling only reached 63% conversion after 18 h. Also, triphenylphosphine (9 mol %) provided superior results to tri-*o*-tolylphosphine. Even with the optimization the coupling reaction of the triflate was slower, requiring 6 h to complete. The product mixture was not as clean as with **9c**, providing only a 66% isolated yield. Again, only the *trans*-isomer of the keto ester **18** was detected.

The resultant ketoester **18** has been previously converted to L-699,392 in 53% overall yield over three steps.[5]

(17) For the preparation of the ethene bridge via the Wittig olefination, see: Lau, C. K.; Dufresne, C.; Gareau, Y.; Zamboni, R.; Labelle, M.; Young, R. N.; Metters, K. M.; Rochette, C.; Sawyer, N.; Slipetz, D. M.; Charette, L.; Jones, T.; McAuliffe, M.; McFarlane, C.; Ford-Hutchinson, A. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1615.

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Summary

A practical approach to synthesis of the LTD_4 antagonists L-691,698 and L-699,392 has been developed, which hinges on the straightforward coupling and selective enone reduction to prepare the key diarylpropane intermediate. Subsequently, the quinoline heterocycle can be joined to this framework by either alkylation or Heck coupling, appropriately, providing a general approach to this important new class of drug candidates.

Experimental Section

General. The reactions were assayed by high-pressure liquid chromatography (HPLC) on a Microsorb C-8 column (4.6 mm × 15 cm) using CH_3CN/H_2O as eluents containing 0.1% TFA with detection at 230 nm unless otherwise indicated. Reactions were carried out under an atmosphere of nitrogen. As necessary, CH_2Cl_2, THF, CH_3CN, DMF, toluene, and DMI were dried over 3 Å molecular sieves.

6-Chloro-3-hydroxy-1(3*H*)-isobenzofuranone (5b). A solution of TMEDA (101.6 mL, 0.78 mol) in THF (1 L) was cooled to −25 °C, and *n*-BuLi (75 mL, 10 M in hexanes, 0.75 mol) was added over 15 min at <−20 °C. The mixture was aged for 15 min at −20 °C. 4-Chlorobenzaldehyde (100 g, 0.71 mol) in THF (1 L) was added over 20 min at −20 °C, and this mixture was aged for 30 min. TMEDA (118 mL, 0.824 mol) was added, followed by *n*-BuLi (78.4 mL, 10 M in hexanes, 0.78 mol) at −25 to −20 °C, and the mixture was stirred for 2 h. The reaction mixture was transferred via cannula to a solution of 1,3-dimethylimidazolidinone (100 mL) in THF (1 L) at −30 °C over 30 min while carbon dioxide gas was simultaneously bubbled through the solution at 0.32 mol/min (15−20 equiv; 7213 mL/min using a Manostate flow meter). The carbon dioxide addition was continued for 5 min. After the mixture was stirred for 1 h at −20 °C, it was quenched with 6 N HCl (860 mL), and the temperature was allowed to warm to 5 °C. **Caution! Foaming occurs due to the release of carbon dioxide.** The mixture was stirred at rt for 30 min, and water (860 mL) was added. The product was extracted with isopropyl acetate (1 × 2 L; 1 × 1 L). The product was extracted from the combined organic layers with 5% $NaHCO_3$ (1 × 2 L; 2 × 1 L). The combined aqueous layers were acidified with 6 N HCl (400 mL), and the product was extracted with isopropyl acetate (1 × 1 L; 3 × 400 mL). The combined organic layers were washed with brine (400 mL) and dried (Na_2SO_4). The filtered solution was concentrated to 1 L. Cyclohexane (1 L) was added, and the mixture was concentrated to 800 mL; the procedure was repeated once again. To the resultant slurry was added cyclohexane (500 mL), and the mixture was cooled at 10 °C for 1 h. The solid was filtered, washed with cold cyclohexane, and dried: 117.4 g, 89% yield. An analytical sample was obtained by recrystallization (cyclohexane/ethyl acetate): mp 135.5−137 °C; ^{1}H NMR (DMSO-d_6) δ 8.3 (br s, 1 H), 7.9 (d, J = 1.85 Hz, 1 H), 7.85 (dd, J = 1.85, 7.86 Hz, 1 H), 7.1 (d, J = 7.86 Hz, 2 H), 6.7 (br s, 1 H). Anal. Calcd for $C_8H_5O_3Cl$: C, 52.05; H, 2.73. Found: C, 52.12; H, 2.75.

3-[2-(3-Hydroxyphenyl)-2-oxoethyl]-1(3*H*)-isobenzofuranone (6a). To a mixture of 3′-hydroxyacetophenone (**4a**) (13.62 g, 100 mmol) and 2-carboxybenzaldehyde (**5a**) (15.01 g, 100 mmol) in 95% ethanol (400 mL) was added 5 N NaOH (140 mL, 700 mmol) at 5−10 °C over 30 min. The mixture was stirred at rt for 20 h. Water (400 mL) was added followed by 6 N HCl (140 mL) at <10 °C whereupon a solid precipitated. The mixture was aged at 5 °C for 5 h. The solid was filtered, washed with 3:1 water−ethanol (150 mL) and water (200 mL), and suction dried. The product was isolated as the lactone (24.3 g, 90% yield). An analytical sample was obtained by recrystallization from ethyl acetate: mp 174−175.5 °C; ^{1}H NMR of **6a** (DMSO-d_6) δ 9.85 (s, 1 H), 7.9−7.3 (m, 7 H), 7.05 (m, 1 H), 6.1 (dd, J = 7.9, 4.2 Hz, 1 H), 3.8 (dd, J = 18.0, 4.2 Hz, 1 H), 3.68 (dd, J = 18.0, 7.9 Hz, 1 H); ^{13}C NMR of **6a** (DMSO-d_6) δ 196.2, 169.7, 157.6, 149.8, 137.5, 134.2, 129.8, 129.2, 125.4, 124.8, 122.8, 120.6, 119.1, 114.0, 77.0, 42.7; ^{1}H NMR of **7a** (DMSO-d_6) δ 8.6 (d, J = 15.7 Hz, 1 H), 7.8 (d, J = 7.4 Hz, 1 H), 7.6−7.2 (m, 7 H), 7.0 (dd, J = 8.3, 1.85 Hz, 1 H); ^{13}C NMR of **7a** (DMSO-d_6) δ 189.8, 172.0, 159.7, 145.0, 143.7, 139.2, 132.4, 129.5, 129.3, 128.8, 127.5, 126.2, 121.7, 120.6, 117.7, 115.3. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.52. Found: C, 71.75; H, 4.45.

3-[2-(3-Hydroxyphenyl)-2-oxoethyl]-5-chloro-1(3*H*)-isobenzofuranone (6b). To a mixture of the chlorohydroxyphthalide **5b** (23.9 g, 129.4 mmol) and 3′-hydroxyacetophenone (**4a**) (20.0 g, 142.3 mmol) in 95% ethanol (490 mL) cooled to 5−10 °C was added 5 N NaOH (181 mL, 0.906 mol) over 6 min. The mixture was then allowed to warm to rt and was stirred for 18 h. The reaction mixture was diluted with water (480 mL) and cooled to 5 °C. At 5−10 °C 6 N HCl (~140 mL) was added to bring the pH to 6.0−6.5. The yellow solid was filtered, washed with ethanol−water (1:2; 200 mL) and water (200 mL), and suction dried: 39 g, 93%; yield mp > 300 °C (ethanol−water). The solid proved to be the sodium carboxylate of **7b**. An analytical sample was obtained by treatment of the salt with 2 N HCl in ethyl acetate−ethanol−water. The organic layer was washed with water (2×) and concentrated to a light-yellow solid. The solid was recrystallized from ethyl acetate−cyclohexane. The solid was found to be the lactone derivative **6b** by ^{1}H NMR: mp 195−197 °C; ^{1}H NMR of **6b** (DMSO-d_6) δ 9.85 (br s, 1 H), 7.9 (d, J = 1.9 Hz, 1 H), 7.85 (dd, J = 8.3, 1.9 Hz, 1 H), 7.75 (d, J = 8.3 Hz, 1 H), 7.48−7.28 (m, 2 H), 7.31 (s, 1 H), 7.05 (dd, J = 7.9, 1.9 Hz, 1 H), 6.1 (dd, J = 7.9, 4.2 Hz, 1 H), 3.84 (dd, J = 18.0, 4.2 Hz, 1 H), 3.7 (dd, J = 18.0, 7.9 Hz, 1 H); ^{13}C NMR of **6b** (DMSO-d_6) δ 196.1, 168.4, 157.6, 148.5, 137.4, 134.2, 133.9, 129.8, 127.7, 124.7, 124.4, 120.7, 119.1, 114.1, 77.1, 42.3; ^{1}H NMR of **7b** (DMSO-d_6) δ 8.6 (d, J = 15.7 Hz, 1 H), 7.93 (d, J = 8.3 Hz, 1 H), 7.6 (d, J = 15.7 Hz, 1 H), 7.55 (m, 1 H), 7.45 (m, 1 H), 7.47 (m, 1 H), 7.34 (s, 1 H), 7.05 (dd, J = 7.9, 2.3 Hz); ^{13}C NMR of **7b** (DMSO-d_6) δ 189.4, 169.8, 158.0, 145.6, 143.6, 139.1, 133.8, 131.2, 129.6, 128.5, 128.4, 127.3, 122.2, 120.1, 119.1, 114.9. Anal. Calcd for $C_{16}H_{11}O_4Cl$: C, 63.48; H, 3.67. Found: C, 63.41; H, 3.60.

3-[2-(3-Bromophenyl)-2-oxoethyl]-1(3*H*)-isobenzofuranone (6c). To a solution of **4b** (10.0 g, 50.0 mmol) and **5a** (8.3 g, 55 mmol) in 95% EtOH (200 mL) cooled to 0 °C was added 5 N NaOH (12.0 mL, 60.0 mmol). The reaction mixture was aged at <5 °C for 10 h and was allowed to warm slowly to 20 °C over another 10 h. Concentrated H_2SO_4 (15 mL) was added while the internal temperature was maintained at <40 °C. The mixture was heated to 60 °C for 30 min to complete the lactonization. After being aged for 30 min at rt, the product was filtered, washed with cold EtOH/H_2O (1:1; 150 mL), and suction dried to provide 17.1 g of 84 wt % lactone **6c** contaminated with sodium sulfate (14.4 g by HPLC assay) in 82% corrected yield. The bis-adduct **10** crystallizes more slowly. In order to prevent its cocrystallization the mixture should not be aged for >2 h at rt. An analytical sample was prepared by filtration/recrystallization from ethyl acetate/cyclohexane: mp 125.5−126 °C; ^{1}H NMR (DMSO-d_6) δ 8.18 (m, 1H), 8.0 (dd, J = 1.16, 2.66 Hz, 1 H), 7.9−7.7 (m, 4 H), 7.6 (m, 1 H), 7.5 (m, 1 H), 6.1 (dd, J = 4.2, 7.8 Hz, 1 H), 3.9 (dd, J = 4.2, 18.2 Hz, 1 H), 3.78 (dd, J = 7.8, 18.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 195.5, 169.8, 149.8, 138.2, 136.2, 134.3, 131.0, 130.8, 129.3, 127.1, 125.5, 124.9, 122.9, 122.2, 76.9, 42.8. Anal. Calcd for $C_{16}H_{11}BrO_3$: C, 58.02; H, 3.35. Found: C, 58.10; H, 3.37.

A General Procedure for the Reduction of the Lactones of 3-(2′-Carboxy)chalcones: 2-[3-(3-Hydroxyphenyl)-3-oxopropyl]benzoic Acid (8a). The keto lactone **6a** (500 mg, 1.86 mmol) was suspended in 100% ethanol (10 mL), and 1 N NaOH (1.96 mL, 1.96 mmol) was added dropwise whereupon the solid dissolved to provide a yellow solution of the enone. The solution was treated with hydrogen at 40 psi, rt in the presence of Wilkinson's catalyst (15 mg). When the reaction was complete 1 N NaOH (25 mL) and isopropyl acetate (25 mL) were added. After the layers were well-mixed and separated the basic layer was acidified with 2 N HCl. The product was extracted into isopropyl acetate (25 mL). The acid was again extracted into 1 N NaOH (20 mL). The basic layer was treated with Darco G-60 (200 mg) and filtered through

Solka-Floc. The filtrate was acidified with 2 N HCl (10 mL), whereupon the product crystallized. The solid was filtered, washed with water, and suction dried to provide 442 mg (88%) of the keto acid **8a** as an off-white solid. An analytical sample was obtained by recrystallization from ethyl acetate−cyclohexane with Darco G-60 decolorization: mp 172−173 °C; ^{1}H NMR (DMSO-d_6) δ 12.9 (br s, 1 H), 9.75 (br s, 1 H), 7.81 (dd, J = 6.5, 1.4 Hz, 1 H), 7.25−7.5 (m, 6H), 7.0 (dd, J = 7.8, 2.3 Hz, 1 H), 3.25 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 198.9, 168.6, 157.5, 142.3, 137.8, 131.7, 130.9, 130.3, 130.2, 129.7, 126.1, 120.1, 118.8, 113.9, 39.9, 28.4. Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.09; H, 5.23. Found: C, 70.83; H, 5.11.

5-Chloro-2-[3-(3-hydroxyphenyl)-3-oxopropyl]benzoic Acid (8b). The crude enone **7b** as the sodium salt (60.5 g, 0.2 mol) was stirred in methanol/DMF (960 mL; 2:1) until most of the solid had dissolved. A small amount of an insoluble solid (1.7 g) was removed by filtration. Wilkinson's catalyst [$(PPh_3)_3RhCl$] (1.6 g) was added, and the mixture was treated with hydrogen under 40 psi pressure at rt until the hydrogen uptake stopped. The reaction mixture was added to a mixture of water (2 L), and the pH was adjusted to 10−11. The mixture was then washed with isopropyl acetate (2 × 500 mL). The aqueous layer was treated with Darco G-60 (5 g) and stirred for 15 min. After the mixture was filtered through Super-Cel the filtrate was acidified with 6 N HCl. The product precipitated as a white solid. The solid was filtered, washed with water (100 mL), and suction dried. Final drying under vacuum at 40 °C provided 53.6 g (88%) of the propanone **8b** as a white solid. An analytical sample was obtained by recrystallization from ethyl acetate: mp 218−221 °C; ^{1}H NMR (DMSO-d_6) δ 13.3 (br s, 1 H), 9.8 (br s, 1 H), 7.79 (d, J = 2.3 Hz, 1 H), 7.55 (dd, J = 8.3, 2.3 Hz, 1 H), 7.42 (dd, J = 8.8, 2.3 Hz, 1 H), 7.32−7.25 (m, 2 H), 7.3 (s, 1 H), 7.0 (dd, J = 8.3, 2.3 Hz, 1 H), 3.2 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 198.6, 167.4, 157.5, 141.2, 137.7, 132.9, 132.4, 131.3, 130.5, 129.7, 129.5, 120.2, 118.8, 113.9, 39.6, 27.7. Anal. Calcd for $C_{16}H_{13}O_4Cl$: C, 63.06; H, 4.31. Found: C, 63.11; H, 4.41.

2-[3-(3-Bromophenyl)-3-oxopropyl]benzoic Acid (8c). A mixture of **6c** (8.7 g, 26.3 mmol), Wilkinson's catalyst (0.3 g), and 5 N NaOH (5.0 mL, 25.0 mmol) in EtOH (200 mL) was hydrogenated at 40 psi and rt for 16 h. The EtOH was removed in vacuo, and the residue was triturated with cyclohexane (50 mL). The slurry was further diluted with hexane (50 mL) and then aged at rt for 1 h. The product was filtered, washed with hexane, and dried to afford 8.44 g of **8c** in 96% yield. An analytical sample was prepared by recrystallization from ethyl acetate/cyclohexanes: mp 120−121 °C; ^{1}H NMR ($CDCl_3$) δ 9.7−8.5 (br s, 1 H), 8.1 (d, J = 2.0 Hz, 1 H), 8.08 (dd, J = 1.5, 3.2 Hz, 1 H), 7.9 (m, 1 H), (ddd, J = 1.0, 2.0, 7.8 Hz, 1 H), 7.5 (m, 1 H), 7.4−6.8 (m, 3 H), 3.5−3.4 (m, 2 H), 3.4-3.3 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 198.1, 172.6, 144.0, 138.5, 135.9, 133.4, 132.0, 131.7, 131.2, 130.2, 128.1, 126.7, 126.6, 123.0, 40.6, 29.3. Anal. Calcd for $C_{16}H_{13}BrO_3$: C, 57.67; H, 3.94. Found: C, 57.66; H, 4.09.

2-[3-(3-Hydroxyphenyl)-3-oxopropyl]benzoic Acid Methyl Ester (9a). A solution of **8a** (2.5 g, 9.25 mmol) in MeOH (75 mL) and H_2SO_4 (2.5 mL) was heated at reflux for 17 h. The volatiles were removed in vacuo at <30 °C. The residue was diluted with water (10 mL), and the mixture was extracted with EtOAc (2 × 20 mL). The EtOAc layer was dried ($MgSO_4$) and evaporated to dryness to give 2.3 g of **9a** (88% yield). An analytical sample was prepared by recrystallization from ethyl acetate/cyclohexane: mp 88.5−90 °C; ^{1}H NMR ($CDCl_3$) δ 7.92, (dd, J = 1.3, 7.8 Hz, 1 H), 7.55 (m, 1 H), 7.5−7.4 (m, 2 H), 7.35−7.25 (m, 2 H), 7.1 (m, 1 H), 3.9 (s, 3 H), 3.35 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 199.9, 168.0, 156.2, 143.2, 138.1, 132.4, 131.5, 130.9, 129.8, 129.3, 126.4, 120.7, 120.4, 114.6, 52.1, 40.7, 29.4. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.81; H, 5.68. Found: C, 71.73; H, 5.45.

5-Chloro-2-[3-(3-hydroxyphenyl)-3-oxopropyl]benzoic Acid Methyl Ester (9b). The keto acid **8b** (50.0 g, 0.164 mol) was suspended in methanol (800 mL), and sulfuric acid (8.0 mL) was added. The mixture was heated at reflux for 18−24 h. Water (1 L) was added to the cooled reaction mixture, and the pH was adjusted to 8.0−8.5 with saturated $NaHCO_3$. The product was extracted with ethyl acetate (2 × 1 L and then 0.4 L). The combined organic layers were washed with saturated $NaHCO_3$ (500 mL), water (2 × 500 mL), and brine (500 mL). The solution was concentrated to 200 mL. The slurry was warmed to redissolve the solid, and the mixture was filtered to remove particulates. The mixture was then cooled, and hexanes (250 mL) was added whereupon the methyl ester precipitated. The slurry was stirred in an ice bath for 30 min. The solid was filtered, washed with cold 1:1 ethyl acetate/hexanes (50 mL), and suction dried (37.0 g). A second crop was collected (5.6 g) by concentration of the filtrates to 125 mL (81% combined yield). An analytical sample was obtained by recrystallization from CH_2Cl_2−hexanes: mp 105−106.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (d, J = 2.3 Hz, 1 H), 7.56−7.48 (m, 2 H), 7.4 (dd, J = 8.3, 2.3 Hz, 1 H), 7.34−7.25 (m, 1 H), 7.3 (s, 1 H), 7.08 (m, 1 H), 6.4 (br s, 1 H), 3.9 (s, 3 H), 3.3 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 199.7, 166.7, 156.3, 141.7, 138.0, 132.9, 132.3, 132.1, 130.8, 130.6, 129.9, 120.64, 120.6, 114.6, 52.4, 40.4, 28.7. Anal. Calcd for $C_{17}H_{15}O_4Cl$: C, 64.05; H, 4.75. Found: C, 63.94; H, 4.78.

2-[3-(3-Bromophenyl)-3-oxopropyl]benzoic Acid Methyl Ester (9c). A solution of **8c** (8 g, 24.0 mmol) in MeOH (120 mL) and H_2SO_4 (8 mL) was refluxed for 24 h. The volatiles were removed in vacuo at <35 °C, and the partially crystallized residue was slowly diluted with water (50 mL) at rt. After the slurry was aged at rt for 1 h, the product was filtered and dried at 40 °C under vacuum to provide 7.66 g of the ester **9c** in 92% yield. An analytical sample was prepared by recrystallization from ethyl acetate/heptane: mp 83.5−84 °C; ^{1}H NMR ($CDCl_3$) δ 8.1 (m, 1 H), 7.9 (m, 2 H), 7.65 (dd, J = 7.8, 1.0 Hz, 1 H), 7.45 (m, 1H), 7.35−7.25 (m, 3 H), 3.9 (s, 3 H), 3.4−3.3 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 198.0, 167.7, 143.1, 138.7, 135.8, 132.4, 131.5, 131.3, 130.9, 130.2, 129.4, 126.7, 126.5, 122.9, 52.1, 40.7, 29.3. Anal. Calcd for $C_{17}H_{15}BrO_3$: C, 58.80; H, 4.36. Found: C, 58.70; H, 4.39.

***(R)*-5-Chloro-2-[3-hydroxy-3-(3-hydroxyphenyl)propyl]-benzoic Acid Methyl Ester (3b).** The keto ester (20.72 g, 65 mmol) was dissolved in THF (200 mL), and a 0.86 M solution of (8*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (**12**) in toluene (7.6 mL, 6.5 mmol) was added. The mixture was cooled to 0 °C, and 2 M borane·dimethyl sulfide in THF (35.8 mL, 71.5 mmol) was added. The reduction mixture was stirred at 0 °C for 18 h. The reaction was quenched by the addition of 2 N HCl (100 mL). **Caution! Foaming occurs and the temperature increases to 15 °C.** Water (300 mL) was added, and the product was extracted with ethyl acetate (1 × 250 mL; 1 × 125 mL). The combined organic layers were washed with 1 N HCl, water, and brine. After the solution was dried (Na_2SO_4), a sample of the product was assayed for enantiomeric purity by conversion to the bis-acetate derivative: acetic anhydride−DMAP in CH_2Cl_2. Pirkle L-phenylglycine covalent column: 50:3:1 hexanes/CH_2Cl_2/IPA; 2 mL/min; 254 nm; (*S*)-enantiomer, 10.5 min; (*R*)-enantiomer, 11.2 min. The crude product was obtained as a 95:5 *R*/*S* mixture. The filtrate was concentrated, and the residue was treated with CH_2Cl_2 (500 mL). The mixture was heated to reflux, and the solids were filtered: 2.7 g of a 67:33 *S*/*R* mixture of enantiomers. The filtrate was concentrated to 400 mL, and hexanes (300 mL) was added. The mixture was stirred for 10 min, and the solid was filtered: 14.8 g (71%) of a 99.2:0.8 mixture of the *R*/*S*-enantiomers: mp 106−107 °C; $[\alpha]^{25}_D$ +10 (*c* 3, THF). A second crop was collected by concentration of the filtrate to 300 mL: 2.5 g (83% overall yield) of 98:2 mixture: ^{1}H NMR (DMSO-d_6) δ 9.25 (s, 1 H), 7.7 (d, J = 2.3 Hz, 1 H), 7.55 (dd, J = 8.3, 2.3 Hz, 1 H), 7.3 (dd, J = 8.3 Hz, 1 H), 7.1 (m, 1 H), 6.7 (m, 1 H), 6.68 (s, 1 H), 6.6 (ddd, J = 7.9, 2.3, 0.9 Hz, 1 H), 5.2 (d, J = 4.2, 1 H), 4.4 (m, 1 H), 3.8 (s, 3 H), 3.0−2.7 (m, 2 H), 1.85−1.7 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 166.3, 157.1, 147.4, 141.9, 132.6, 131.6, 131.4, 130.3, 129.2, 128.8, 116.3, 113.5, 112.5, 71.8, 52.2, 40.8, 29.5. Anal. Calcd for $C_{17}H_{17}ClO_4$; C, 63.65; H, 5.35. Found: C, 63.74; H, 5.20.

***(R)*-5-Chloro-2-[3-hydroxy-3-(3-hydroxyphenyl)propyl]-*N*,*N*-dimethylbenzamide (13).** To a solution of 2.2 M dimethylamine in THF (50 mL, 100 mmol) was added 2.0 M ethylmagnesium bromide (50 mL, 100 mmol) dropwise over 10 min at 15−25 °C. **Caution! Foaming from released**

ethane occurs. The thick mixture was allowed to stir for 25 min at 10−20 °C. A solution of the methyl ester **3b** (9.62 g, 30 mmol) in THF (40 mL) was added over 12 min at 20−25 °C, maintaining the temperature with an ice bath. The reaction was aged for 4.5 h at room temperature and was then quenched with 2 N HCl (100 mL) with cooling to maintain the temperature <25 °C. The layers were separated, and the aqueous layer was washed with isopropyl acetate (100 mL). The combined organic layers were washed with 2 N HCl (50 mL), water (50 mL), and brine (50 mL) and dried (Na_2SO_4). The filtered solution was concentrated to provide a quantitative yield of the hydroxy amide **13** as a gummy foam, which did not crystallize under many attempts (10.2 g containing 8 mol % isopropyl acetate). The material was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 7.6 (br s, 1 H), 7.3−7.05 (m, 4 H), 6.8 (s, 1 H), 6.8−6.65 (m, 2 H), 4.45 (br m, 1 H), 3.05 (s, 3 H), 2.8 (s, 3 H), 2.7−2.45 (m, 2 H), 2.05−1.9 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.5, 156.5, 145.8, 137.4, 136.8, 131.9, 131.0, 129.4, 125.9, 117.6, 114.5, 112.8, 39.8, 38.8, 34.8, 28.3; high-resolution mass spectrum of $C_{18}H_{20}NO_3Cl$ found 333.1131, calcd 333.1132.

7-Chloro-2-(chloromethyl)quinoline Monohydrochloride (14). A solution of 7-chloroquinaldine (53.17 g, 0.3 mol) in chlorobenzene (530 mL) was treated with *tert*-butyl hypochlorite (53.6 mL, 0.45 mol) at rt over 15 min. The mixture was then heated at 40−45 °C for 20 h. An additional charge of *tert*-butyl hypochlorite (16.1 mL, 0.135 mol) was added carefully, and the reaction was heated for an additional 20 h. The mixture was cooled to rt. The unreacted quinaldine was extracted by vigorously stirring a mixture of the chlorobenzene reaction solution with 2 N HCl (200 mL) for 30 min. The layers were separated, and the organic phase was dried by concentration to 380 mL. A 1.0 M HCl/ethyl ether solution (300 mL) was added, whereupon the hydrochloride salt of 7-chloro-2-(chloromethyl)quinoline precipitated. The mixture was stirred for 1 h. The solid was filtered, washed with chlorobenzene (300 mL) and then ethyl ether (250 mL), and suction dried. The product **14** was obtained as a white solid (65.2 g) in 88% yield. An analytical sample was prepared by recrystallization from 2-propanol−1.6% water: sublimation point (vacuum-nitrogen purged tube) 158 °C. A sample of the hydrochloride salt was broken in isopropyl acetate/concentrated ammonium hydroxide, and the dichloroquinaldine was recrystallized from hexanes: mp 97.5−98.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.175 (d, J = 8.8 Hz, 1H), 8.075 (d, J = 2.3 Hz, 1H)), 7.75 (d, J = 8.8 Hz, 1H), 7.125 (d, J = 8.8 Hz, 1 H), 7.5 (dd, J = 2.3, 8.8 Hz, 1 H), 4.8 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.81, 147.73, 137.06, 135.80, 128.72, 128.28, 128.00, 125.72, 120.62, 47.07. Anal. Calcd for $C_{10}H_7NCl_2$·HCl: C, 48.32; H, 3.25; N, 5.64. Found: C, 48.21; H, 3.01; N, 5.40.

(*R*)-5-Chloro-2-[3-[3-[(7-chloro-2-quinolinyl)methoxy]-phenyl]-3-hydroxypropyl]-*N*,*N*-dimethylbenzamide (15). The crude amide **13** (5.0 g, 15 mmol) was dissolved in DMF (55 mL), and 7-chloro-2-chloromethylquinoline monohydrochloride (**14**) (4.1 g, 16.5 mmol) was added. Finely powdered K_2CO_3 (6.2 g, 45 mmol) was added, and the mixture was heated at 70 °C for 3 h. The mixture was cooled to room temperature and was partitioned between isopropyl acetate (160 mL) and water (160 mL). The organic layer was washed with water (2 × 80 mL) and brine (100 mL) and dried (Na_2SO_4). The solvent was removed under vacuum to give 8.8 g of a crude viscous oil. The oil was dissolved in CH_2Cl_2 (20 mL), and 1 M HCl in ether (20 mL) was added. The resultant slurry was stirred at room temperature for 1 h. The solid was filtered, washed with hexanes/CH_2Cl_2 (3:2; 20 mL), and suction dried under a nitrogen sweep to give 6.4 g (80% overall yield from the hydroxy ester **3b**) of the quinaldine−phenyl ether as an off-white solid. An analytical sample was recrystallized from 2-propanol: mp 170−173 °C (nitrogen-purged sealed tube); $[\alpha]^{25}_D$ +16.2 (*c* 0.93, THF) (as free base); ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8.3 Hz, 1 H), 8.07 (d, J = 2.3 Hz, 1 H), 7.75 (d, J = 8.8 Hz, 1 H), 7.68 (d, J = 8.8 Hz, 1 H), 7.5 (dd, J = 8.8, 1.9 Hz, 1 H), 7.43 (dd, J = 8.3, 1.9 Hz, 1 H), 7.26 (m, 3 H), 7.03 (m, 1 H), 6.95−6.85 (m, 2 H), 5.35 (s, 2 H), 4.5 (br s, 1 H), 3.15 (s, 3 H), 2.85 (s, 3 H), 2.7 (m, 2 H), 2.0 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.4, 159.2, 158.4, 147.9, 146.7, 137.8, 136.8, 136.7, 135.5, 131.9, 131.0, 129.4, 129.3, 128.9, 128.0, 127.5, 125.91, 125.88, 119.3, 118.7, 113.2, 112.4, 71.0, 40.6, 38.8, 34.8, 28.2. Anal. Calcd for $C_{28}H_{26}N_2O_3Cl_2$·HCl: C, 61.60; H, 5.00; N, 5.13. Found: C, 61.88; H, 4.99; N, 4.99.

(*S*)-3-[[1-[3-[(7-Chloro-2-quinolinyl)methoxy]phenyl]-3-[4-chloro-2-[(dimethylamino)carbonyl]phenyl]propyl]-thio]propanoic Acid [L-691,698 (1)]. The quinaldine phenyl ether−alcohol **15** as the hydrochloride salt (1.0 g, 1.96 mmol) was slurried in toluene (20 mL), and the mixture was cooled to −25 °C. Triethylamine (0.49 mL, 3.5 mmol) was added followed by the dropwise addition of methanesulfonyl chloride (0.21 mL, 2.7 mmol) at <−25 °C. The mixture was warmed to 0 °C over 2 h and stirred until the mesylation was complete. *An aliquot was removed, and the toluene was evaporated. ^{1}H NMR indicated when the reaction was complete by disappearance of the methine proton of the alcohol (4.5 ppm) and appearance of the methine proton of the mesylate (5.5 ppm).* The reaction was quenched with cold (0 °C) 5% $NaHCO_3$ (20 mL), and the mixture was stirred for 30 min at rt. The layers were separated, and the organic phase was washed with 5% $NaHCO_3$ (20 mL) and brine (10 mL). The organic phase was concentrated to provide the mesylate as an oil. The mesylate was dissolved in CH_3CN (20 mL), and the solution was vacuum purged with nitrogen (3×). 3-Mercaptopropanoic acid methyl ester (0.33 mL, 2.94 mmol) was added at rt followed by Cs_2CO_3 (0.96 g, 2.94 mmol). The reaction mixture was stirred for 2 h. The solids were filtered and washed with CH_3CN (10 mL). Water (20 mL) was added to the filtrate, and this mixture was cooled to <5 °C. Lithium hydroxide (0.25 g, 5.9 mmol) was added, and the saponification mixture was vigorously stirred for 5 h. Acetic acid (1 mL) was added, and the product was extracted with isopropyl acetate (2 × 50 mL). The combined organic layers were washed with brine (25 mL) and dried (Na_2SO_4). The filtered mixture was concentrated to an oil. The crude propionic acid was chromatographed on silica gel (ethyl acetate−toluene; 1:1; followed by ethyl acetate−toluene−acetic acid; 1:1:0.01; R_f = 0.24) to provide L-691,698 (**1**) as a foam in 70% overall yield from the *R*-alcohol **15**: $[\alpha]^{25}_D$ −72.2° (*c* 0.39, THF); ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8.3 Hz, 1 H), 8.08 (d, J = 1.85 Hz, 1 H), 7.74 (d, J = 8.8 Hz, 1 H), 7.68 (d, J = 8.8 Hz, 1 H), 7.48 (dd, J = 8.8, 1.9 Hz, 1 H), 7.25−6.85 (m, 7 H), 5.5 (s, 2 H), 3.8 (m, 1 H), 3.05 (s, 3 H), 3.0−2.8 (m, 2 H), 2.85 (s, 3 H), 2.6−2.4 (m, 4 H), 2.1 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 175.6, 169.7, 158.9, 158.4, 147.4, 143.8, 137.6, 137.1, 136.1, 135.8, 132.0, 130.9, 129.7, 129.0, 128.9, 127.6, 127.5, 126.0, 125.9, 120.9, 119.4, 114.4, 113.6, 70.6, 49.3, 38.6, 37.2, 34.6, 34.4, 30.3, 30.2, 25.9; high-resolution mass spectrum of $C_{31}H_{30}N_2O_4SCl_2$ found 597.1365, calcd 597.1381.

2-[2-(*N*,*N*-Diethylamino)ethyl]-7-chloroquinoline (16). A mixture of 7-chloroquinaldine (53.22 g, 0.297 mol), formalin (23.6 g of 37% by weight formaldehyde, 0.290 mol), triethylamine (1 mL, 7.17 mmol), and ethanol (40 mL) was heated at 60 °C. To this was added a solution of diethylamine hydrochloride (33 g, 0.301 mol), triethylamine (2 mL, 0.0143 mol), ethanol (15 mL), and H_2O (15 mL) from a dropping funnel over 2.5 h. After 3 h the reaction solution was cooled to rt and the ethanol was removed under reduced pressure. The volume was brought to 250 mL with water, and this solution was extracted with methyl *tert*-butyl ether (MTBE) (6 × 50 mL) to remove most of the starting material. The aqueous solution was made basic by adding 5 N NaOH (88 mL), and this product was extracted with MTBE (100 mL; 2 × 50 mL). The combined organic layers were washed with brine (50 mL) and then concentrated *in vacuo* to leave 47.7 g of the crude amine **16**. This material was used as is in the next reaction.

2-Ethenyl-7-chloroquinoline (17). The amine **16** (20.22 g, 0.077 mol) was stirred in ethanol (200 mL) at rt, and methyl iodide (11.6 mL, 0.0186 mol) was added over 5 min. The temperature rose to 40 °C, and a precipitate formed. After 2 h the reaction mixture was concentrated *in vacuo* to remove the ethanol. Water (112 mL), ethanol (24 mL), and triethylamine (10 mL, 7.17 mmol) were added, and this mixture was heated at reflux for 16 h. After being cooled to rt, the mixture was diluted with MTBE (300 mL) and EtOAc (100 mL), and the aqueous layer was adjusted to pH 4.5 with 2 N HCl. After separation of the layers the organic phase was washed with

brine (50 mL) and concentrated to provide 11.89 g of the vinylquinoline **17** as a solid (81% yield from **16**; 45% overall yield from 7-chloroquinaldine). An analytical sample was prepared by Darco treatment in ethanol and crystallization by addition of water (1:1): mp 78−79 °C; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, J = 8.6 Hz, 1 H), 8.05 (d, 0.7 Hz, 1 H), 7.7 (d, J = 8.6 Hz, 1 H), 7.55 (d, J = 8.6 Hz, 1 H), 7.45 (dd, J = 2.0, 8.6 Hz, 1 H), 7.05 (dd, J = 10.9, 17.7 Hz, 1 H), 6.3 (dd, J = 0.7, 17.7 Hz, 1 H), 5.7 (dd, J = 0.7, 10.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 157.0, 148.4, 137.6, 136.1, 135.4, 128.6, 128.4, 127.3, 125.8, 120.6, 118.7. Anal. Calcd for $C_{11}H_8NCl$: C, 69.66; H, 4.26; N, 7.39. Found: C, 69.53; H, 4.49; N, 7.29.

(*E*)-2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-oxopropyl]benzoic Acid Methyl Ester (18). From bromide 9c. A flask was charged with the vinylquinoline **17** (0.536 g, 2.83 mmol), the bromide **9c** (0.889 g, 2.56 mmol), palladium(II) acetate (17.7 mg, 0.079 mmol), tri-*o*-tolylphosphine (72 mg, 0.24 mmol), and DMF (5 mL). The suspension was degassed with three vacuum/nitrogen purges, and then triethylamine (0.54 mL, 3.87 mmol) was added. The mixture was heated at 100 °C for 1 h. The reaction mixture was cooled to rt, and water (1.25 mL) was added slowly while the temperature was maintained at <30 °C. The slurry was aged at rt for 3 h and then filtered. The filtered product was washed with ice-cold 20% aqueous DMF (3 mL) and water (6 mL). After the product was dried under vacuum at 60 °C, 1.06 g of **18** was obtained (91% yield).

From Triflate 9e. The phenol **9a** (0.5 g, 1.76 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to 0 °C. Triethylamine (0.35 mL, 2.5 mmol) was added followed by triflic anhydride (0.43 mL, 2.5 mmol). The mixture was stirred at 0 °C. The product mixture was filtered through a 12-g plug of silica gel and eluted with CH_2Cl_2. The eluent was concentrated to provide 0.67 g of triflate **9e** in 92% yield. A flask was charged with 2-ethenyl-7-chloroquinoline (**17**) (0.34 g, 1.77 mmol), the triflate **9e** (0.67 g, 1.61 mmol), palladium(II) acetate (11 mg, 0.05 mmol), triphenylphosphine (0.026 g, 0.1 mmol), lithium bromide (0.14 g, 1.6 mmol), and DMF (3.5 mL). The suspension was degassed with three vacuum/nitrogen purges, and triethylamine (0.33 mL, 2.4 mmol) was added. The mixture was heated at 100 °C. After 6 h the reaction mixture was cooled to room temperature and was assayed by HPLC to contain 0.71 g (98% yield) of the coupled product **18**. The product could not be isolated directly by the addition of water due to gumming. The reaction mixture was partitioned between isopropyl acetate (10 mL) and water (5 mL). The organic phase was passed through silica gel (10 g) with isopropyl acetate elution. The eluent was treated with Darco (100 mg) and concentrated. The solid was redissolved in DMF (3.5 mL), and water (1.0 mL) was added. The product was collected, washed with 20% water in DMF and water, and vacuum dried under nitrogen to afford 0.48 g of the keto ester (66% overall yield). The product agreed with authentic keto ester[5] by mp, ^{1}H and ^{13}C NMR, and HPLC analysis: mp 124−126 °C (lit.[5] mp 128−130 °C).

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