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An Efficient Synthesis of LTD$_4$ Antagonist L-699,392

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The asymmetric synthesis of L-699,392 (1) [3-[[(1*S*)-[3(*E*)-[2-(7-chloroquinolinyl)ethenyl]phenyl]-3-(acetylphenyl)propyl]thio]-2(*S*)-methylpropanoic acid], a leukotriene antagonist, is accomplished in six steps starting from the monoaldehyde **2**. The main framework of the molecule is formed via a Pd-catalyzed Heck reaction. The asymmetric center is introduced via the chiral reduction of the ketone **4** using optically active *B*-chlorodiisopinocampheylborane (**10**) derived directly from chloroborane and (−)-α-pinene. A very high asymmetric amplification is observed in which 95% ee product can be obtained from 70% optically pure α-pinene. Reagent **17**, which is prepared *in situ* from methylmagnesium chloride and 2 equiv of lithium hexamethyldisilazide, is used to convert the methyl ester **5** to the methyl ketone **6** in one step with essentially no impurities formed under the reaction conditions. The thio side chain is finally incorporated by the displacement of the chiral mesylate **7** with complete inversion at the chiral center. The overall yield for the sequence is 42%.

Introduction

With the discovery of the biological activity of the slow-reacting substance of anaphylaxis (SRS-A) and its relation to the leukotrienes (LTC$_4$, LTD$_4$, and LTE$_4$) and asthma, the search for leukotriene antagonists has been intensive.[1] As part of an ongoing program for the development of specific LTD$_4$ antagonists for the treatment of asthma and other associated diseases, L-699,392 (1) [3-[(1*S*)-[3(*E*)-[2-(7-chloroquinolinyl)ethenyl]phenyl]-3-(acetylphenyl)propylthio]-2(*S*)-methylpropanoic acid] was identified as a potent, orally active agent. This new structural class is an extension of the dithioacetal series best exemplified by MK-0571/MK-0679 (formerly known as L-660,711).[2] Here, the 3-thiapropionamide side chain has been replaced with a 2-arylethyl group. In order to prepare multikilogram quantities of materials for further testing, an efficient synthesis of **1** was developed (Scheme I).

The synthesis was carried out in six steps. We chose as our starting material the monoaldehyde **2**, since this is an existing intermediate in the synthesis of MK-0571 and is available in large quantities. The material was prepared in one step from 7-chloroquinaldine and 1,3-benzenedicarboxaldehyde.[3] The diarylpropanone building block of L-699,392 was prepared using the Heck coupling[4] of the allylic alcohol **3**, derived from the monoaldehyde **2**, and methyl 2-iodobenzoate. The ketone and ester functionalities were then converted, respectively, to the hydroxy and methyl ketone groups by a simplified adaptation of chlorodiisopinocampheylborane[5] to produce the chiral alcohol **4**, followed by conversion of the benzoate to the acetophenone **5** using a novel reagent prepared from lithium hexamethyldisilazide and methylmagnesium chloride. The synthesis was completed by the introduction of the chiral mercapto side chain with inversion of the benzyl center via the mesylate.

Results and Discussion

Recently, a number of new applications of the Heck coupling have appeared in the literature.[4] In particular is the palladium-catalyzed coupling of an allylic alcohol and aryl halide to prepare a 3-arylpropanone derivative. The structure of L-699,392 lent itself well to this methodology. As mentioned, the monoaldehyde **2** is a readily available intermediate previously prepared in the synthesis of L-660,711. By addition of commerically available

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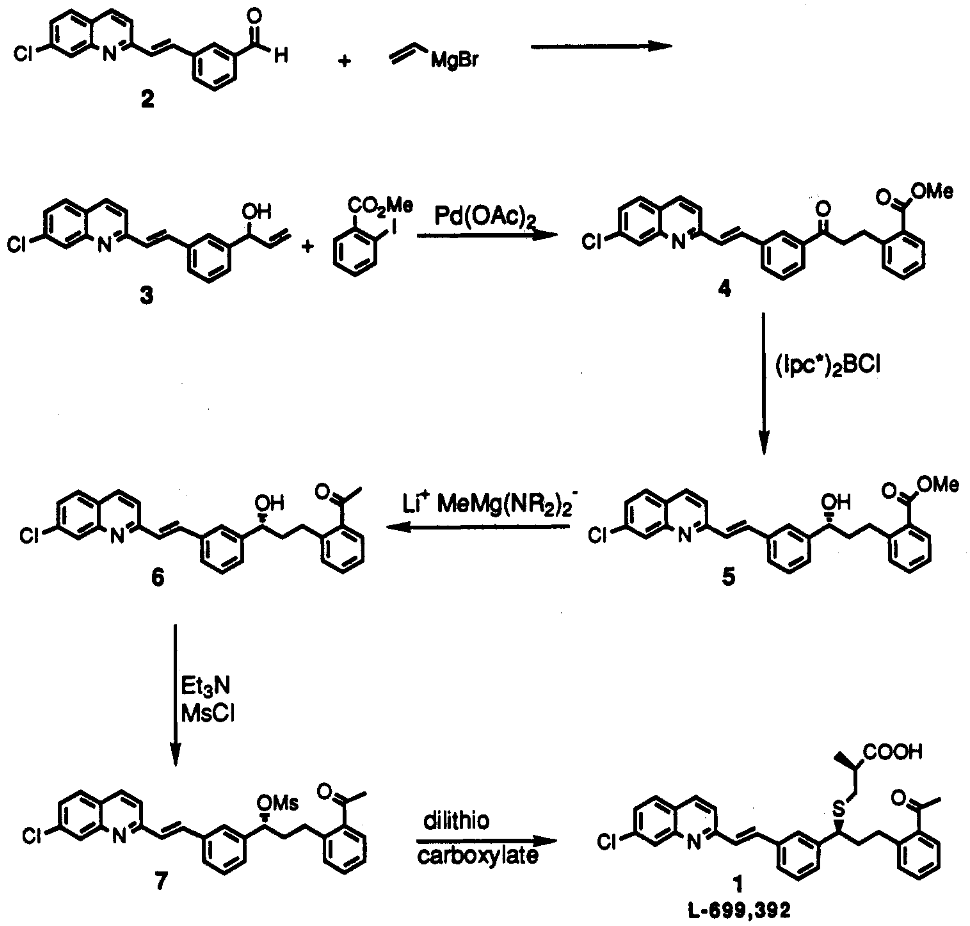
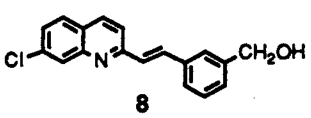
Scheme I



vinylmagnesium bromide to the aldehyde the requisite allylic alcohol 3 was obtained. Under the reaction conditions in THF 30–40% of the benzyl alcohol 8 was produced by reduction. The use of toluene as the reaction solvent has been reported to minimize the amount of reduction;[5] indeed, the amount of 8 was lowered to <3% in this manner. The quality of the reagent also affected the yield and purity of the product. Even in toluene the amount of reduction was greatly increased sometimes. On these occasions the reagent's color was observed to be a deep red; the material gave the best results when it was amber. The problem is probably due to the decomposition of the vinylmagnesium bromide to a mixture of magnesium hydride and polymeric alkenyl- or alkynylmagnesium bromides. The poorer quality reagent resulted in the formation of a number of unidentified nonpolar impurities from the polymeric metalated species, and the benzyl alcohol 8 from reduction by the magnesium hydride and other electron transfer reduction pathways.

Although the allylic alcohol was obtained in 92% yield, isolation was not necessary. The THF–toluene solvent mixture, after aqueous workup, was removed from the crude product by evaporation and replaced with acetonitrile. The product mixture was used directly in the next reaction; the small amount of benzyl alcohol 8 did not interfere with the palladium-catalyzed coupling and was easily separated from the ketoester 4.



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The Heck coupling of the allylic alcohol 3 and methyl iodobenzoate was carried out in refluxing CH$_3$CN in the presence of 1.5 equiv of triethylamine (to neturalize the generated hydrogen iodide) and 1 mol % palladium acetate.[4a] No phase-transfer catalysts or other salts were required. The level of palladium acetate was lowered to 0.5–1.0 mol % as compared to the 2.5–5.0 mol % normally indicated in the literature.[4] At 1 mol % catalyst charge the reaction required only 1 h with the isolated allylic alcohol. Slightly longer reaction times were observed with the nonisolation process; at 0.5 mol % catalyst charge a 12 h reaction age was required. On cooling to 22 °C the keto ester 4 crystallized cleanly from the solution in 83% yield (76% overall yield from the aldehyde 2). The minor byproduct resulting from addition of the arylpalladium to the C-2 carbon of the allylic alcohol, as well as the benzyl alcohol 8 from the previous reaction, remained in solution.

Two reagents for the chiral reduction of the ketone to the desired (*R*)-hydroxy ester 5 were used: the oxazaborolidine(OAB)–borane complex 9 derived from (*S*)-α,α-diphenyl-2-pyrrolidinemethanol[5] and *B*-chlorodiisopinocampheylborane (10).[6] Although the former reagent provided exceptional enantioselectivity in the reduction (98.5% ee), the overreduction to the ethane-bridged analogue 11 (3–10%) was a problem. This was due mainly to the remaining traces of palladium in 4 from the coupling

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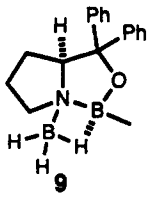

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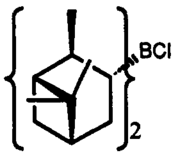

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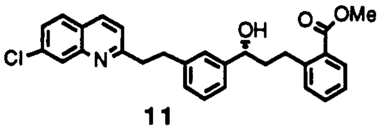

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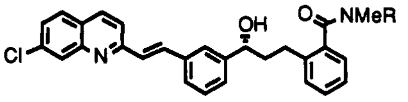
reaction. The byproduct could be kept to a minimum by increasing the catalyst load from 20% to 55%; however, the advantage of this reagent was now overshadowed. The five-step synthesis[5d] to prepare enough catalyst for a 55% charge also became a burden. The borane reducing agent **10**, although used stoichiometrically, can be prepared cheaply and easily from α-pinene and borane. With the report from these same laboratories[6d] of an in situ preparation of **10**, the reagent was more practical for our purposes. In addition, the reagent showed no propensity for reduction of the ethene bridge (<1%) and gave only a slightly lower enantiomeric excess (97.8%).

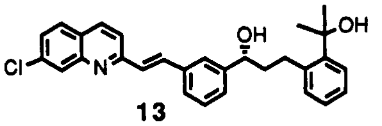
In the development of this reduction we have further improved on the use and simplicity of this reagent. In order to bypass the use of HCl, as described in the literature, the use of chloroborane for the direct preparation of the reducing agent was examined. In fact, active chiral reducing agent can be prepared from 98% optically pure (−)-α-pinene and commercially available chloroborane-methylsulfide complex or, alternatively, a 2:1 mixture of borane and boron trichloride-methyl sulfide.[7] Although dihaloboranes or alkylhaloboranes have been used before to prepare dialkylhaloboranes,[8] this is the first application of this method to **10**. The reduction of **4** with this reagent at −20 °C gave the hydroxy ester **5** in 97% ee. A tremendous asymmetric amplification resulting from this reagent was evidenced by its generation of 95% ee product from 70% optically pure α-pinene. To obtain both completion and the high enantioselectivity, 1.8 equiv of the reagent was necessary. Under these conditions the reaction was complete in <4 h. The isolation yield of the product was 80% with >99.5% ee. Identical results were obtained with (+)-α-pinene providing the (*S*)-enantiomer.

The nature of the selectivity of this reagent, considering that 95% ee can be obtained with 70% optically pure α-pinene, can be understood. The reactivity of (±)-*B*-chlorodiisopinocampheylborane derived from racemic α-pinene was informative. By using 1 equiv of (±)-*B*-chlorodiisopinocampheylborane, 47% conversion of **4** to **5** was observed in 3 h. The reaction became quite sluggish at this point only reaching 52% conversion after 6 h. Apparently, the (±)-**10** is composed of a statistical mixture of the (+,+), (−,−), and (+,−) species. The first two reagents are very reactive toward ketone reduction, whereas, the last species, formally a mixture of two diastereomers, are inactive or very slow reacting. According to this scenario and assuming a statistical mixture of the reagents was formed, the maximum asymmetric induction that one can obtain with 70% optically pure α-pinene is 94%. The results match this predicted value closely. Using an excess of the reagent and assuming that the rate of reduction by (+,+) and (−,−) far exceeds that of (+,−) this effectively prepares a 97 (+,+):3 (−,−) reagent mixture.[9]

The completion of the synthesis of the main framework of the LTD$_4$ antagonist involved selective conversion of the ester to the methyl ketone **6**. Methods for the clean transformation of esters to ketones usually require the preparation of some intermediate esters or amides.[10] Initially, Weinreb's procedure[10a] provided adequate results. Isolation of the intermediate *N*,*O*-dimethylhydroxamide **12** was not necessary; the methyl ketone **6** was subsequently obtained in 71% overall yield from the ester by addition of methylmagnesium bromide. Several impurities were formed (0.5–1%) in this process which were not easily removed without a yield penalty. The impurities, besides unreacted *N*,*O*-dimethylhydroxamide, were identified as the tertiary alcohol **13** and the dimethylamide **14**. The latter was formed by nucleophilic displacement of the methoxyl group of the amide with methylmagnesium bromide.



12 R = OMe
14 R = Me



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A one-step method for a similar transformation has been recently developed at these laboratories.[11] This procedure when applied to the ester **5** provided a very clean product. The reagent was prepared from lithium hexamethyldisilazide and methylmagnesium chloride (2:1) in THF. Addition of 3.2 equiv of the reagent to a toluene solution of the ester at −10 to −5 °C afforded a 75% isolated yield (88% reaction yield) of the methyl ketone **6**. The suppression of tertiary alcohol formation was complete. This occurs by enolization of the methyl ketone with the lithium amide. The reagent mixture is optimal: adjustment of the stoichiometry to a 1:1 mixture of the lithium hexamethydisilazide and methylmagnesium chloride or substitution of the amide with LDA was ineffective. In both cases a substantial amount of the tertiary alcohol

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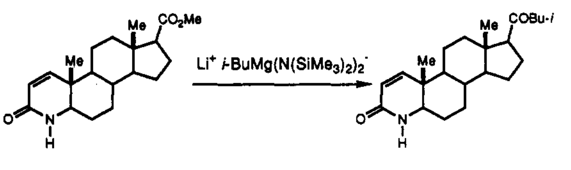
[7] ^{11}B NMR of commercial monochloroborane-methyl sulfide complex showed the reagent to be a mixture of borane/monochloroborane/dichloroborane in a 12:76:12 ratio. Only one boron species was observed after the hydroboration of pinene (see ref 6b).

[8] (a) Brown, H. C.; Ravindran, N. *J. Am. Chem. Soc.* **1976**, *98*, 1785. (b) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 2417. (c) Brown, H. C.; Srebnik, M.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 1577.

[9] A related observation was published recently in the literature. Joshi, N. N.; Pyun, C.; Mahindroo, V. K.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 504.

[10] (a) Weinreb, S. M.; Nahm, S. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5320.

[11] Conversion of the methyl ester directly to the isobutyl ketone was carried out by Micheal Williams, Ulf Dolling, and George Marchesini. Further studies with this reagent have shown it to be compatable with only nonenolizable or hindered esters. The results of this work are forthcoming.



was formed, similar to the results observed with methylmagnesium chloride alone. Not unexpectedly, no racemization was observed at the hydroxy carbon. The quality of the product was sufficient for use in the next step.

The activation of the hydroxy group for displacement by the mercaptan was best accomplished with methanesulfonyl chloride and triethylamine in toluene at <0 °C; tosylation failed. Other solvents, such as CH_2Cl_2, THF, and *tert*-butyl methyl ether, gave incomplete conversion to the mesylate **7**. The mesylation was followed by the change in the NMR signal of the methine proton: 4.72 and 5.65 ppm for the alcohol and mesylate, respectively. The toluene solution of the mesylate was washed with water, dried, and used directly in the next step.

Different bis-salts (Li, Na, and K) of the mercaptan were screened for displacement of the mesylate; the dilithio salt proved to be the most effective. The mercaptan can be obtained by saponification of the commercially available *S*-acetyl ester. The dilithio salt is then prepared by addition of butyllithium to a THF solution of the mercapto acid at <−50 °C. The dried toluene solution of the mesylate was then added at 0 °C and the mixture was aged at rt for 2–3 h. L-699,392 (**1**) was isolated in 88% yield from *i*-PrOAc. Chiral HPLC assay[12] showed complete inversion of configuration at the reaction center; no racemization was observed at either of the two chiral centers.

Conclusion

An effective approach to this new class of LTD_4 antagonists has been developed that provides L-699,392 (**1**) in six steps in 40% overall yield. Application of the Heck reaction to the synthesis of the diarylpropanone sets up the main framework of the molecule. Adaptation of Brown's reagent has provided a simple, highly effective chiral reduction of the ketone. Further application of a new reagent for conversion of an ester to a methyl ketone improved on the moderate yield obtained via the *N*,*O*-dimethylhydroxamide and avoided impurity formation. This scheme provides an overall effective and efficient approach to this important class of pharmaceuticals.

Experimental Section

General. Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus in an open capillary tube. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brucker AM-300 spectrometer. ^{1}H chemical shifts are reported in ppm referenced to the residual $CHCl_3$ (7.27 ppm). ^{13}C chemical shifts are reported in ppm referenced to the center peak of $CDCl_3$ (77.0 ppm).

All chemicals were used as received without further purification, and all operations must be performed in the dark to avoid olefin isomerization.

(*E*)-3-[2-(7-Chloro-2-quinolinyl)ethenyl]-α-ethenylphenylmethanol (3). Isolation Procedure. A suspension of monoaldehyde **2** (200 g, 0.681 mol) in toluene (1600 mL) at 0 °C was degassed by purging three times with vacuum and nitrogen. Vinylmagnesium bromide (1.0 M in THF, 720 mL, 0.72 mol) was added dropwise over 35 min while the internal temperature was maintained at <10 °C. The reaction mixture was stirred at 0–5 °C for 1 h and quenched by slowly adding 10% aqueous ammonium acetate (1600 L). This two-phase mixture was stirred for 1 h to ensure the solvolysis of the magnesium salts. The separated organic layer was washed with water (2 × 1500 mL) and concentrated in vacuo to ~300 mL. Addition of hexanes (300 mL) followed by filtration gave 204 g (93% yield) of allylic alcohol **3** contaminated with 3% of benzyl alcohol **8**. An analytical sample was obtained by silica gel chromatography (toluene/EtOAc/AcOH (9:1:0.5)) followed by recrystallization from toluene: mp 116–117.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.65 (d, J = 3.6 Hz, 1H), 5.21–5.27 (m, 2H), 5.37–5.43 (dt, J = 17.0, 1.3 Hz, 1H), 6.03–6.14 (ddd, J = 17.0, 5.9, 10.3 Hz, 1H), 7.31–7.45 (m, 4H), 7.50–7.54 (dt, J = 7.1, 1.7 Hz, 1H), 7.58–7.7 (m, 4H), 8.05–8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 75.2, 115.5, 119.5, 125.2, 125.7, 126.8, 127.0, 127.2, 128.1, 128.68, 128.72, 129.1, 135.1, 135.6, 136.2, 136.6, 140.2, 143.3, 148.6, and 156.9. Anal. Calcd for $C_{20}H_{16}ClNO$: C, 74.65; H, 5.01; N, 4.35. Found: C, 74.68; H, 5.07; N, 4.28.

(*E*)-3-[2-(7-Chloro-2-quinolinyl)ethenyl]-α-ethenylphenylmethanol (3). Nonisolation Procedure. The reaction was carried out as above and worked up in the same manner except that CH_3CN (300 mL) was added in place of hexanes. The mixture was again concentrated in vacuo to 300 mL. A second charge of CH_3CN was added and the mixture again concentrated to 350 mL. The resulting slurry was used directly in the next step.

(*E*)-2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-oxopropyl]benzoic Acid Methyl Ester (4). The crude slurry of **3** in CH_3CN was treated with methyl 2-iodobenzoate (178.4 g, 0.681 mol), triethylamine (142.3 mL, 1.02 mol), and palladium acetate (0.77 g, 3.4 mmol). The mixture was heated at reflux under nitrogen for ~12 h. The hot reaction mixture was diluted with CH_3CN (1090 mL) and warmed to 75 °C. The solution was filtered, hot through Solka Floc to remove any precipitated palladium. Keto ester **4** crystallized from solution as the filtrate cooled to ambient temperature. After a 1-h age at 20 °C the solids were filtered. The filter cake was washed consecutively with CH_3CN (500 mL), CH_3CN/water (1:1 mixture, 400 mL), water (400 mL), and finally CH_3CN (700 mL) and suction dried. (**Note**: the aqueous washes were necessary to remove triethylammonium hydroiodide which partially precipitated with the product). The product was obtained as a white solid (235 g, 76% from aldehyde **2**). An analytical sample was prepared by recrystallization from isopropyl acetate: mp 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 4H), 3.91 (s, 3H), 7.30–7.49 (m, 6H), 7.59–7.78 (m, 4H), 7.92–7.97 (m, 2H), 8.04–8.09 (m, 2H), 8.26 (t, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.6, 40.9, 52.2, 119.8, 125.8, 126.5, 126.9, 127.3, 128.2, 128.3, 128.8, 129.1, 129.4, 129.6, 131.0, 131.6, 131.7, 132.4, 134.1, 135.6, 136.3, 136.8, 137.4, 143.4, 148.6, 156.5, 167.8, and 199.2. Anal. Calcd for $C_{28}H_{22}ClNO_3$: C, 73.76; H, 4.86; N, 3.07. Found: C, 73.73; H, 4.98; N, 3.02.

[*R*-(*E*)]-2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-hydroxypropyl]benzoic Acid Methyl Ester (5). A solution of (−)-α-pinene (4.25 L, 26.77 mol) in 2.5 L of hexanes was cooled to −5 °C under an atmosphere of nitrogen, and chloroborane-methyl sulfide complex (1.25 L, 12.0 mol) was added slowly while the temperature was maintained below 25 °C. The mixture was aged at 30 °C for 2 h and then added slowly to a THF solution of **4** (3.025 kg, 6.63 mol in 24 L THF) and diisopropylethylamine (288 mL, 1.65 mol) at −25 to −20 °C. The reaction mixture was aged at −20 °C for 3.5 h and warmed to 0 °C over 1 h. Chiral HPLC analysis for **5** was as follows: Chiralcel OD 4.6-mm × 25-cm column, hexanes/*i*-PrOH (90:10), 2.0 mL/min, at 238 nm; keto ester **4**, 11.6 min; (*S*)-hydroxy ester **5**, 17.0 min; (*R*)-hydroxy ester **5**, 18.8 min. When the reaction was complete, it was quenched with acetone (900 mL), and the solution was stirred at room temperature for 12 h. A 20% aqueous solution of potassium sodium tartrate (35 L) was added at ≤15 °C, the mixture was stirred for 30 min, and the layers were separated. The organic phase was further washed with 90% saturated brine (15 L). The aqueous layer was removed, and the volume of the organic solution was reduced in vacuo to ~25 L. *i*-PrOAc (30 L) was added, and the volume was again reduced in vacuo to 25 L. Water (450 mL) was added to the mixture, and the slurry formed was aged fro 30 min before dilution with hexanes (30 L). After aging for another 30 min, the crystallized product was collected by filtration. The cake was washed with *i*-PrOAc/hexanes (30:70 mixture; 10 L) followed with hexanes (16 L) and dried. The hydroxy ester **5** (2.75 kg, 87.1%, 99.5% ee) was obtained as the monohydrate: mp 100–102 °C; $[\alpha]^{22}_{D}$ 28.3° (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.03 (m, 2 H), 3.04–3.22 (m, 2 H),

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3.32 (s, 1 H), 3.89 (s, 3 H), 4.75 (t, J = 6.2 Hz, 1 H), 7.21–7.57 (m, 8 H), 7.57–7.75 (m, 4 H), 7.91 (d, J = 7.5 Hz, 1 H), 8.03–8.12 (m, 2 H); ^{13}C NMR (CDCl$_3$) δ 30.3, 41.3, 52.1, 73.1, 119.5, 124.7, 125.6, 126.0, 126.3, 126.4, 127.0, 128.1, 128.4, 128.6, 128.8, 129.2, 130.8, 131.1, 132.2, 135.2, 135.5, 136.1, 136.3, 143.8, 145.4, 148.6, 156.9, and 168.4. Anal. Calcd for $C_{28}H_{24}ClNO_3 \cdot H_2O$: C, 70.66; H, 5.51; N, 2.94. Found: C, 70.52; H, 5.55; N, 2.98.

[*R*-(*E*)]-1-[2-[3-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-hydroxypropyl]phenyl]ethanone (6). Methyl magnesiate reagent 17 was prepared by adding methylmagnesium chloride (4.6 L, 13.8 mol, 3 M in THF) to the solution of lithium hexamethyldisilazide (27.6 L, 27.6 mol, 1 M in THF) while the temperature was maintained at ≤0 °C. Monohydrate **5** (2.01 kg, 4.22 mol) was slurried in toluene (18 L), and the mixture was azeotropically dried by the distillation of 6 L of toluene at atmospheric pressure. When the toluene solution was dry (Karl Fisher titration), a homogeneous solution was obtained. The methylmagnesiate reagent prepared above was then added to the toluene solution of **5** at <–10 °C over 5 h. The reaction mixture was aged for 1 h at 0 °C and then quenched with 20 L of water containing AcOH (4 L) and NH$_4$Cl (3.1 kg) at <10 °C. Chiral HPLC analysis for **6** was as follows: Chiralcel OD 4.6-mm × 25-cm column, hexanes/*i*-prOH (90:10), 2.5 mL/min, 238 nm; (*S*)-hydroxy ketone **6**, 16.8 min; (*R*)-hydroxy ketone **6**, 21.3 min. The pH was first adjusted to 6.8 with AcOH (900 mL) before the layers were separated, and the organic layer was further washed with 20 L of water containing NH$_4$Cl (3 kg). The aqueous layer was removed, and the organic layer was washed once more with 20 L of water containing NaHCO$_3$ (1.8 kg). The aqueous layer was removed, and the organic phase was filtered. The filtrate was concentrated to ~20 L at an internal temperature of 5 to 10 °C. The concentrate was diluted with toluene (12 L), and the volume was reduced again to ~15 L. Water (400 mL) was added over 1 h. The mixture was aged for 1 h at rt and 5 h at 0 °C. The crystallized product was filtered, washed with water-saturated toluene (8 L), and then dried in vacuo at room temperature. Hydroxy ketone **6** was obtained as the monohydrate (1.51 kg, 77.7% yield): mp 98–100 °C; ^{1}H NMR (CDCl$_3$) δ 2.07 (q, J = 7.7 Hz, 2H), 2.61 (s, 3 H), 3.01 (t, J = 7.7 Hz, 2 H), 3.65 (s, 1H), 4.72 (t, J = 6.3 Hz, 1 H), 7.00–7.55 (m, 8 H), 7.55–7.84 (m, 5 H), 7.95–8.20 (m, 2 H); ^{13}C NMR (CDCl$_3$) δ 29.7, 30.0, 41.2, 72.9, 119.4, 124.7, 125.5, 125.9, 126.2, 126.4, 126.9, 127.9, 128.2, 128.6, 128.7, 129.6, 131.3, 131.8, 135.3. 135.4, 136.1, 136.2, 137.4, 142.0, 145.4, 148.3, 156.8, 202.7. Anal. Calcd for $C_{28}H_{24}ClNO_2 \cdot H_2O$: C, 73.11; H, 5.70; N, 3.06. Found: C, 72.90; H, 5.55; N, 2.98.

D-(–)-*S*-acetyl-*β*-mercaptoisobutyric Acid. A suspension of K$_2$CO$_3$ (1.81 kg, 13.1 mol) and sodium borohydride (11.4 g, 0.30 mol) in MeOH (16 L) at 0 °C was degassed via vacuum/nitrogen purges (2×), and D-(–)-*S*-acetyl-*β*-mercaptoisobutyric acid (960 g, 5.93 mol) was added. The mixture was aged at room temperature for 18 h and filtered through filter-aid under an atmosphere of nitrogen. The solid cake was washed with MeOH (1 L), and the filtrate was concentrated in vacuo at room temperature to an oil. The residue was diluted with brine (780 g of NaCl in 6 L of water), and the mixture was acidified to pH 8.4 with 6 N HCl. The product was then extracted with EtOAc (1 L). The aqueous phase was further acidified to pH 2 with 6 N HCl and extracted with EtOAc (2 × 2.5 L). The combined EtOAc layers were dried with anhydrous MgSO$_4$ (200 g) and filtered. Most of the solvent was then removed in vacuo (80 mmHg) at <40 °C. The residue was subjected to high vacuum (0.5 mmHg) at rt for 18 h to provide 664 g (93.3%).

3-[[(1(*S*)-[3(*E*)-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-(2-acetylphenyl)propyl]thio]-2(*S*)-methylpropanoic Acid (1). Hydroxy methyl ketone-monohydrate **6** (800 g, 1.74 mol) in toluene (5.6 L) was azeotropically dried by atmospherically distilling 1.6 L of the solvent. After the solution was cooled to –10 °C, triethylamine (448 mL, 3.21 mol) was added followed by the addition of methanesulfonyl chloride (186 mL, 2.40 mol) over 1 h while the internal temperature was maintained at <–5 °C. When the addition was complete the solution was aged at –5 °C for 1 h and then quenched into cold saturated aqueous NaHCO$_3$ (4 L). The organic layer was washed once more with cold saturated aqueous NaHCO$_3$ (4 L) and dried with anhyd Na$_2$CO$_3$ (800 g).

The mercapto acid (250 g, 2.08 mol) in THF (7.8 L) was cooled to –75 °C, and a solution of butyllithium (2.6 L, 4.16 mol, 1.6 M in hexanes) was slowly added while the temperature was kept at <–50 °C. When the addition was over the heterogeneous mixture was warmed to 10 °C over 1 h and the above toluene solution of the mesylate was added over 15 min. The combined mixture was aged at 20 °C for 2 h and then quenched into cold water (8 L). The aqueous layer containing the lithium carboxylate product was separated and washed again with a mixture of toluene/*i*-PrOAc/THF (4 L:4 L:0.4 L). After the layers were separated, the aqueous layer was diluted with *i*-PrOAc (16 L) and then acidified to pH 6.5 with 85% H$_3$PO$_4$ (76 mL). The layers were separated, and the organic solution was filtered. The filtrate was concentrated in vacuo at <20 °C to ~4 L whereupon the product crystallized. The mixture was aged at 0 °C for 10 h and filtered. The product cake was washed with cold *i*-PrOAc (1.4 L) followed with hexanes (3 L). After the product was dried at room temperature, 708 g (74.8% yield) of the product was obtained. A second crop was obtained after concentrating the filtrate to a volume of 3 L and the crystallized product was isolated by filtration. After drying, another 65.5 g of **1** was obtained. The combined yield was 81.7%: mp 134–135 °C; $[\alpha]^{22}_{D}$ –114.0° (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 1.19 (d, J = 6.8 Hz, 3H), 2.18–2.28 (m, 2H), 2.38–2.50 (m, 1H), 2.50–2.67 (m, 1H), 2.54 (s, 3H), 2.67–2.88 (m, 2H), 2.90–3.08 (m, 1H), 3.92 (t, J = 7.4 Hz, 1H), 7.13–7.56 (m, 8H), 7.59–7.77 (m, 5H), 8.05–8.17 (m, 2H), 12.02 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 16.8, 29.6, 32.4, 34.0, 38.0, 39.9, 50.0, 119.2, 125.5, 126.0, 126.3, 126.8, 127.1, 127.6, 128.3, 128.5, 128.6, 129.0, 129.5, 131.4, 131.6, 135.3, 135.6, 136.3, 136.4, 137.4, 141.6, 143.0, 148.1, 156.8, 180.1, and 201.7. Anal. Calcd for $C_{32}H_{30}ClNO_3S$: C, 70.64; H, 5.56; N, 2.57; S, 5.89. Found: C, 70.84; H, 5.60; N, 2.54; S, 5.90.

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