Synthesis of Montelukast (MK-0476) Metabolic Oxidation Products

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We report the chemical synthesis of six oxidized derivatives of MK-0476 (Montelukast, L-706631), which have been key tools in the identification of its metabolites. We have prepared three diastereoisomeric pairs of potential oxidative metabolites of MK-0476, starting from the (*S*)-hydroxy ester **7** in 10 and five steps, and starting from MK-0476 itself in one step. The key benzylic hydroxyl of **1** and **2** was introduced by a bromination and saponification reaction sequence. In the case of the hydroxyl of **3** and **4**, the key step was the addition of a hydroxymethyl carbanion equivalent on ketone **20**. The two sulfoxide **5** and **6** were prepared by a direct oxidation of MK-0476 with *m*-chloroperbenzoic acid.

Introduction

MK-0476 (Montelukast, L-706631) is a potent, orally active cys-LT_1 (leukotriene D_4) receptor antagonist.[1] As this compound progressed through clinical trials,[2] it became important to characterize its metabolism. The preparation of oxidative metabolites of MK-0476 by microsomal oxidation *in vitro* has been described and several metabolites have been tentatively identified.[3] We now report the chemical synthesis of six oxidized derivatives of MK-0476, which have been key tools in the identification of its metabolites.

Results and Discussion

We elected to prepare authentic samples of the compounds which are proposed as metabolites based on the microsomal study on MK-0476[3] and on previously reported metabolism of similar molecules.[4] To help clarify the regiochemistry of metabolic oxidation, the diastereomeric pairs **1** and **2**, and **3** and **4**, as well as the sulfoxides **5** and **6**, were selected and prepared (Scheme 1). A straightforward approach to the synthesis of diastereoisomers **1** and **2** would be a direct benzylic oxidation at the C-21 position from the readily available MK-0476. Oxidants known to perform this type of transformation include ceric ammonium nitrate in acetic acid,[5] selenium dioxide in acetic acid or in xylene,[6] and DDQ.[7] Unfortunately, all attempts to carry out the oxidation using these reagents were unsuccessful due to the presence of the thioether moiety, which underwent rapid oxidation to sulfoxide or sulfone. Another decomposition pathway was also present for the reactions performed in acidic media, namely the dehydration of the tertiary alcohol of MK-0476 to give the styrene analog. A multistep synthesis was then devised starting from the available intermediate (*S*)-hydroxy ester **7**, an intermediate in the synthesis of MK-0476 (Scheme 2).[1]

Protection of the C-19 hydroxyl as an acetate by treatment with Ac_2O in the presence of Et_3N yielded **8** in quantitative yield. The desired oxidation state at C-21 for **1** and **2** was obtained by bromination of the ester **8** with NBS in the presence of a catalytic amount of benzoyl peroxide, providing a 1:1 diastereoisomeric mixture of benzylic bromides **9a**,**b** in 69% yield. All attempts to improve this yield by varying the reaction conditions such as the amount of reactants (NBS, $(BzO)_2$) or running the reaction at higher concentration led to the formation of larger amounts of polybrominated material. The introduction of the hydroxyl functionality was performed on the mixture of bromo esters **9** via a nucleophilic displacement of the bromide by hydroxide, in what is presumably a multiple-step reaction amounting to a saponification and lactonization sequence. The process was carried out as a one-pot procedure, starting by saponification of the methyl ester and of the acetate with 4 equiv of LiOH in a mixture of water, THF, and MeOH. The newly formed carboxylate then displaced the benzylic bromide to generate a mixture of the hydroxylactones **10a**,**b**, which could be transiently observed by TLC. These intermediates were further hydrolyzed to a nonmobile TLC spot, probably the mixture of hydroxycarboxylates. The reaction mixture was then treated with TFA to regenerate **10a**,**b** by lactonization. Interestingly, the basic hydrolysis step led to the formation of side products, which arose from a Grob fragmentation and Cannizzaro dismutation. Under these basic conditions, the hydrolysis of the acetyl protecting group occurred readily, and the resulting alkoxide intermediate underwent fragmention to give **11** and **12** (Scheme 3). The aldehyde **11** reacted further with LiOH to afford Cannizzaro reaction-derived benzylic alcohol **13** and benzoic acid derivative **14**. After careful optimization of the amount of LiOH, the reaction produced a limited amount of aldehyde **11** (<5%) and a trace

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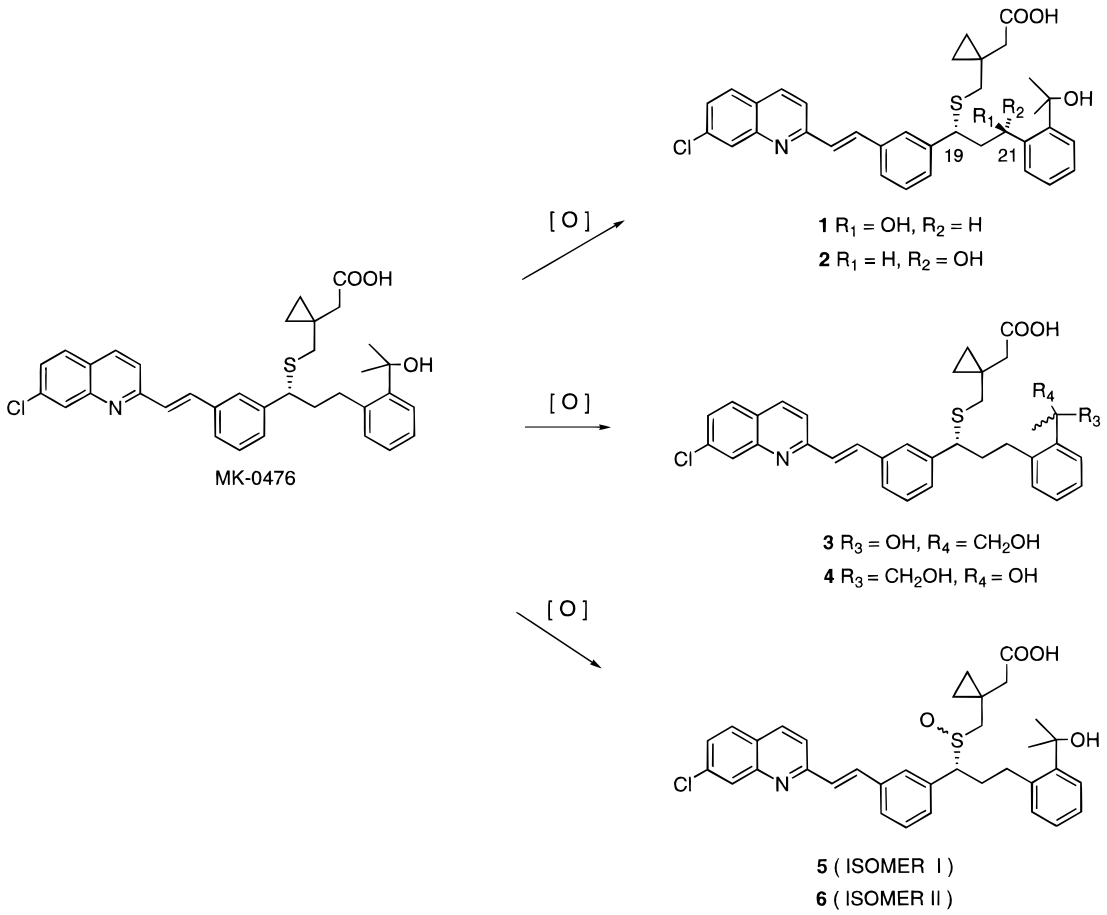
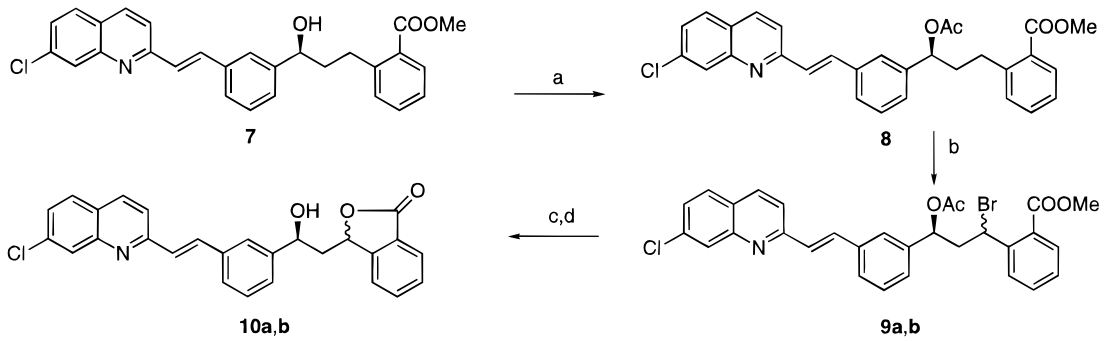
S0022-3263(96)01581-2 CCC: $12.00

Scheme 1



Scheme 2[a]

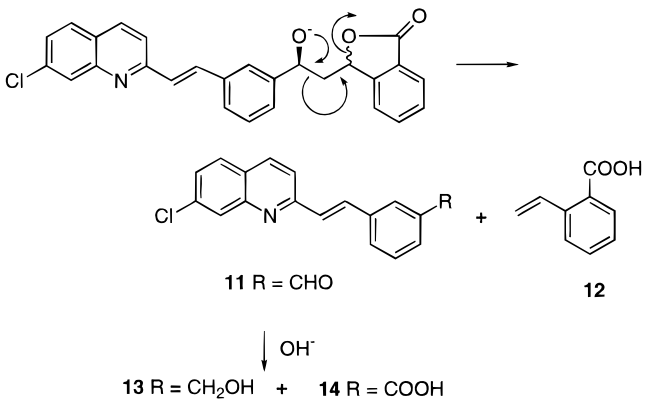


[a] Reaction conditions: (a) Ac_2O, Et_3N; (b) NBS, $(BzO)_2$, CCl_4; (c) LiOH; (d) TFA.

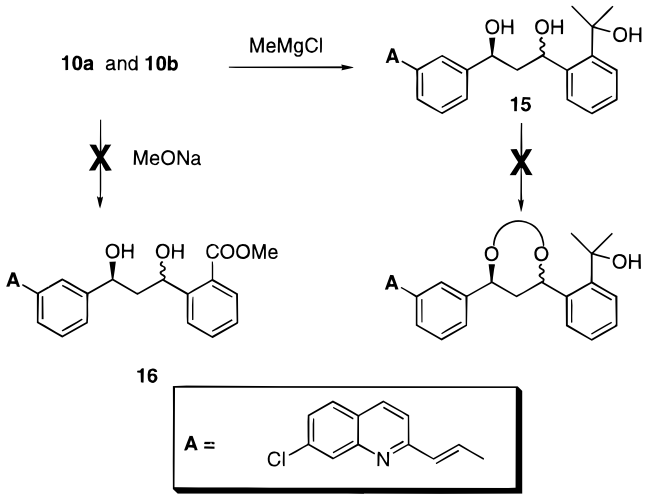
of Cannizaro products (**13** and **14**), while giving the desired material **10** in 64% overall yield as a mixture of diastereoisomers.

We next proceeded to assign the relative configuration of the two hydroxylactones **10a**,**b**. We elected to prepare a cyclic structure generated from a 1,3-diol derivative of **10**. The initial attempts at the preparation of the 1,3-diol intermediate involved a nucleophilic ring opening of lactones **10** with methylmagnesium chloride to give the mixture of triols **15** (Scheme 4). Unfortunately, all attempts to generate the corresponding cyclic acetonide or benzylidene failed, giving mostly cyclic ethers. Alternatively, the preparation of a 1,3-diol methyl benzoate derivative (**16**) from acidic or basic methanolysis also failed, as only starting material was recovered. This observation demonstrated the need for a different nucleophile in the lactone ring opening, which would give a 1,3-diol derivative with less propensity to return to the lactone. Thus, treatment of a mixture of hydroxylactones **10** with magnesium piperidide (Scheme 5) gave the desired diastereoisomeric 1,3-dihydroxyamide compounds **17**, isolated in 90% yield. The diols **17** were treated with benzaldehyde dimethyl acetal and phosphorus oxychloride in CH_2Cl_2 to provide the mixture of diastereoisomeric benzylidene amides **18**, accompanied by only a trace amount of lactonization. The diastereoisomers **18** were easily separated by flash chromatography. The relative stereochemistry of the benzylidenes was determined by analysis of coupling constants and NOE measurements. For benzylidene **18b**, strong NOE's were observed between all three of the benzylidene methine protons, indicating that these were all axial and on the same side of the ring. The large three-bond coupling constants of 10.9 Hz for $^3J_{19,20ax}$ and $^3J_{21,20ax}$ also indicated a *syn* stereochemistry. In the case of **18a**, a strong NOE was observed between the acetal methine and only one of the

Scheme 3



Scheme 4



other two benzylidene methines. This same benzylidene methine had a large three-bond coupling constant of 11.0 Hz to the axial proton at H-20, whereas the remaining benzylidene methine had a coupling constant of 5.3 Hz with the axial proton at H-20. These results are consistent with an *anti* configuration for **18a**. The *anti*-benzylidene **18a** and *syn*-benzylidene **18b** were respectively hydrolyzed to *anti*-hydroxylactone **10a** and *syn*-hydroxylactone **10b** using TFA in aqueous THF.

With the pure diastereoisomers **10** in hand, the synthesis of **1** and **2** could be continued. The secondary alcohols were mesylated,[1] but these mesylates were insoluble and, therefore, unreactive under the conditions of the thiol displacement. However, the butanesulfonates **19** prepared from butanesulfonyl chloride were more soluble and reacted cleanly with the dianion of 1-(mercaptomethyl)-1-cyclopropaneacetic acid to give the respective compounds (Scheme 6).

In the final step of the sequence, organocerium addition on **20a**,**b** using 5 equiv of methylmagnesium chloride and 1.5 equiv of $CeCl_3$[8] at 40 °C for 10 min generated the desired materials **1** and **2**, respectively. Longer reaction times or excess reagent gave lower yields. Isomers **1** and **2** were found to have fairly different retention times on HPLC and flash chromatography. Therefore, while benzylidenes **18** were key in the assignment of the configuration of hydroxylactones **10** and, therefore, of **1** and **2**, scaling-up the synthesis of **1** and **2** only required a three-step sequence from the mixtures of isomers **10a**,**b** and separation of **1** and **2** in the last step for an overall yield of 16%.

The synthesis of the other diastereomeric 1,2-diols **3** and **4** was also studied. The straightforward dihydroxylation of the styryl analog of MK-0476 with OsO_4/NMO[9] or AD-mix mixtures[10] failed to give any desired material (Scheme 7). The thioether moiety once again underwent rapid oxidation to sulfoxide and sulfone. Given this intrinsic sensitivity of MK-476 toward oxidants, a multistep preparation of the diastereoisomeric metabolites **3** and **4** was devised (Scheme 8). The (*S*)-hydroxy ester **7** was converted to ketone **22** via the organomagnesium compound prepared in THF from lithium hexamethyldisilazide and methylmagnesium chloride.[11] The addition of a hydroxymethyl carbanion equivalent generated from [(methoxymethoxy)methyl]tributylstannane[12] and *n*-BuLi to the ketone **22** gave a 1:1 mixture of diastereoisomers **23a**,**b** in 32% yield, along with 44% recovered starting material. The thiol acid side chain of **3** and **4** was introduced by selective mesylation of the secondary alcohol, giving mesylates **24a**,**b**, followed by displacement with the dianion of 1-(mercaptomethyl)-1-cyclopropaneacetic acid to provide the acids **25**. Esterification using diazomethane and removal of the MOM protecting group using pyridinium *p*-toluenesulfonate in *tert*-butyl alcohol afforded a 1:1 diastereoisomeric mixture of **26a**,**b**. These compounds were best separated on a Chiralpak AD HPLC column to afford **3** and **4** in a 8% overall yield from **7**. The absolute stereochemistry of the newly created chiral center in **3** and **4** has not yet been assigned.

The two diastereomeric MK-0476 sulfoxides **5** and **6** were readily prepared by oxidation of the TFA salt of MK-0476 with *m*-chloroperbenzoic acid at −20 °C (Scheme 9). The two isomers were separated by flash chromatography. The absolute configuration at the sulfur atom is unknown at this time.

Conclusion

We have described the synthesis of the three diastereoisomeric pairs of potential oxidative metabolites of MK-0476, starting from the (*S*)-hydroxy ester **7** in 10 and five steps, and starting from MK-0476 itself in one step. The key benzylic hydroxyl of **1** and **2** was introduced by a bromination and saponification reaction sequence. In the case of the hydroxyl of **3** and **4**, the key step was the addition of a hydroxymethyl carbanion equivalent on ketone **20**. The two sulfoxides **5** and **6** were prepared by a direct oxidation of MK-0476 with *m*-chloroperbenzoic acid. Comparison of these compounds with metabolites observed in humans and animals will be reported in a future article.

Experimental Section

General. Melting points (uncorrected) were determined in an open capillary tube. ^1H and ^{13}C NMR spectra were recorded in deuterated acetone unless otherwise noted. All reactions were performed in the dark to avoid olefin isomerization in flame-dried glassware under nitrogen.

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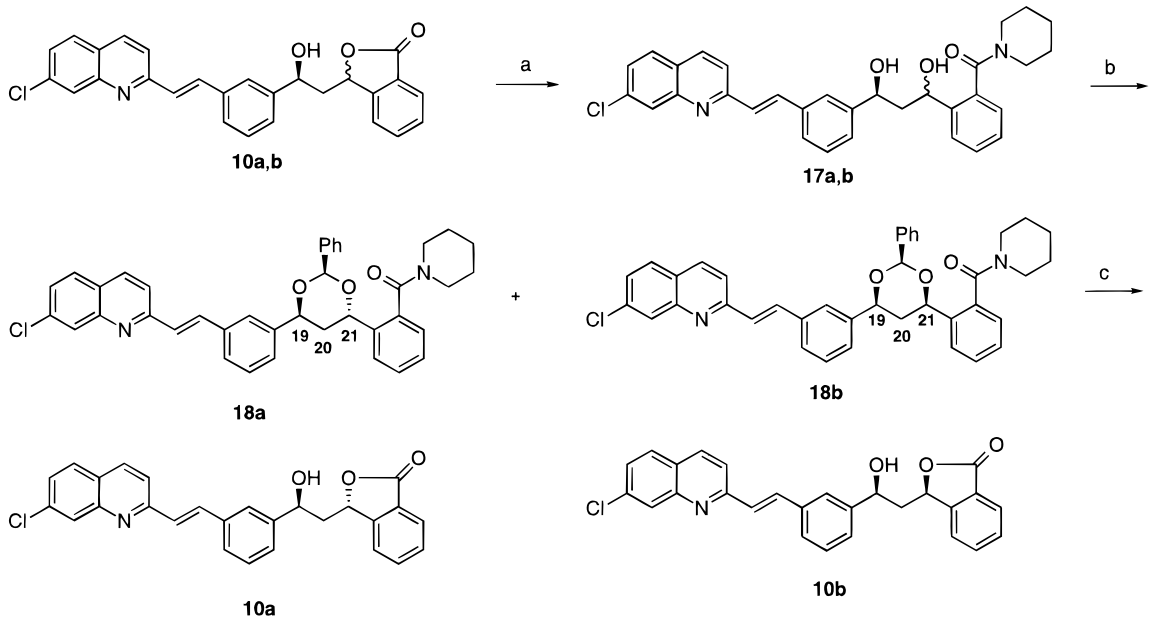
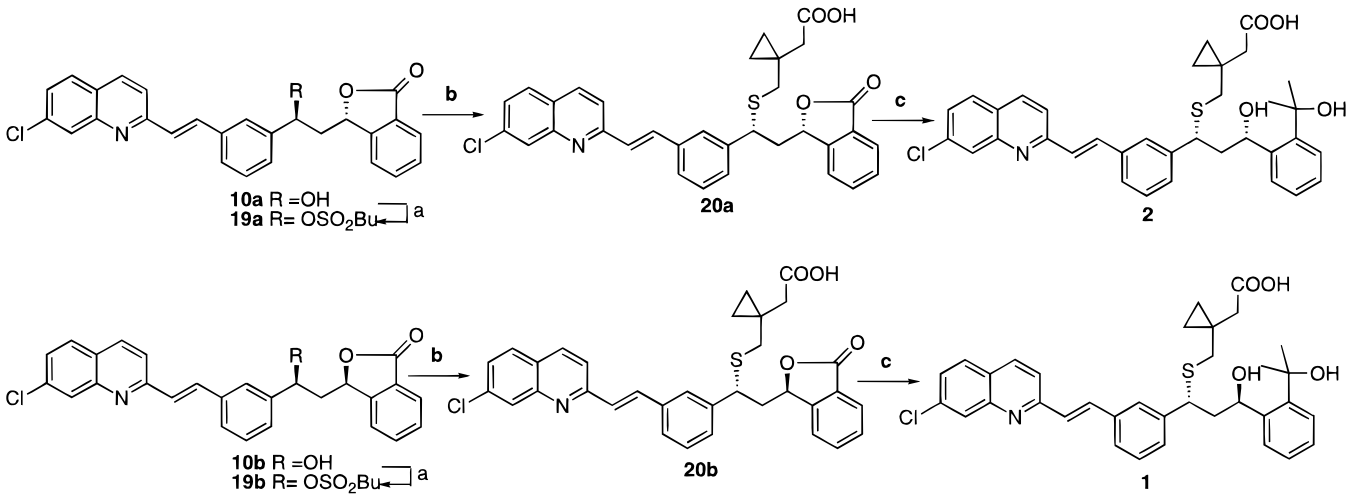
Scheme 5[a]



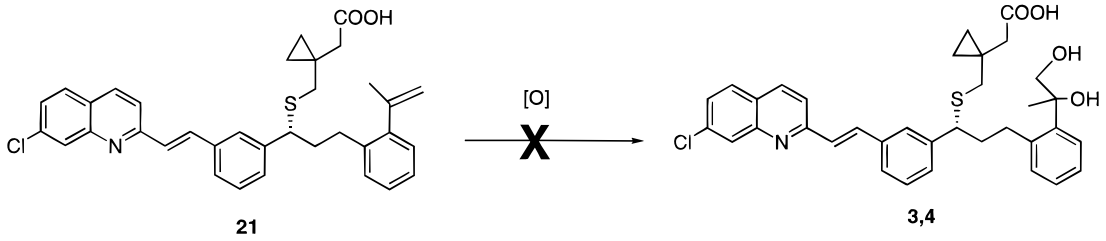
[a] Reaction conditions: (a) piperidine, MeMgCl; (b) $PhCH(OMe)_2$, $POCl_3$; (c) TFA, H_2O.

Scheme 6[a]



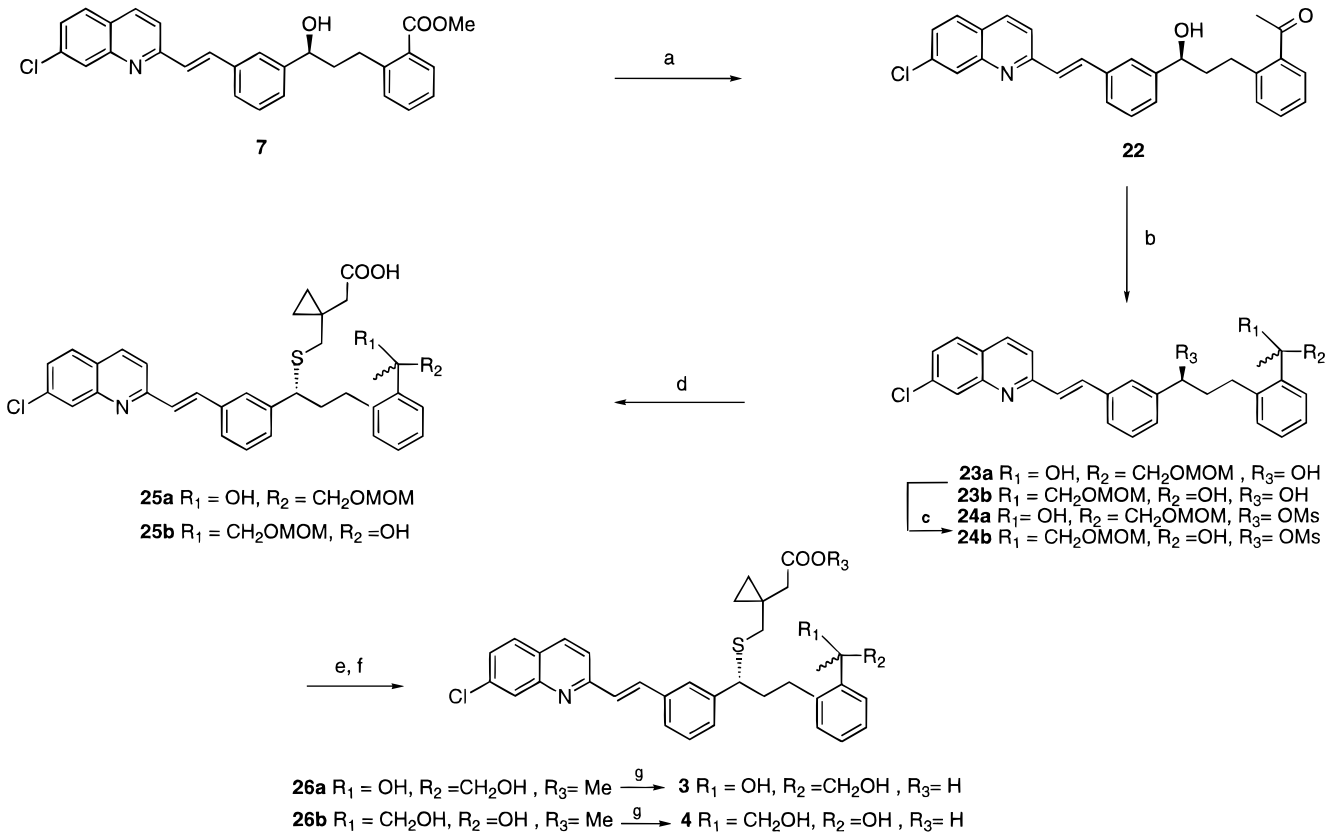
[a] Reaction conditions: (a) $CH_3(CH_2)_3SO_2Cl$, Et_3N; (b) *n*-BuLi, 1-(mercaptomethyl)-1-cyclopropaneacetic acid; (c) MeMgCl, $CeCl_3$.

Scheme 7



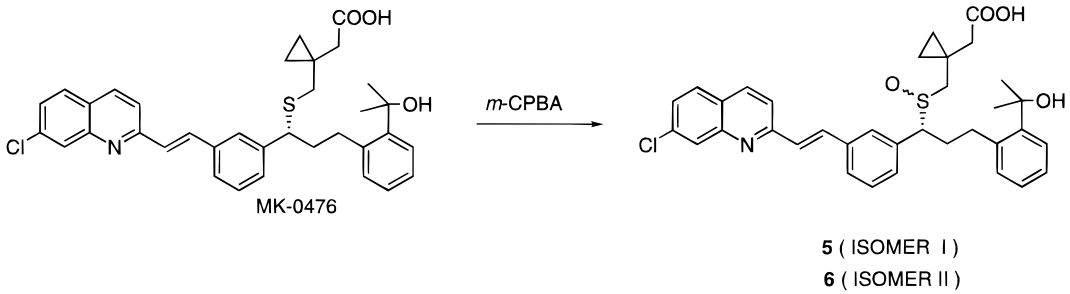
Methyl (*S*)-2-(3-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-3-acetoxypropyl)benzoate (8). Methyl (*S*)-2-(3-[3-(2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-3-hydroxypropyl)benzoate·H_2O[3] (25.10 g, 52.7 mmol) was dehydrated by codistillation with 2 × 250 mL of toluene. To the residue, suspended in 100 mL of CH_2Cl_2, were added Ac_2O (8.50 mL, 116 mmol), triethylamine (8.80 mL, 63.5 mmol), and 4-DMAP (321 mg, 2.60 mmol). The reaction mixture was stirred for 15 min and then poured into 200 mL of saturated aqueous $NaHCO_3$ and finally extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with 25% aqueous NH_4Cl (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* at 60 °C for 1 h to give 26.40 g (99%) of the desired material, which was used without further purification. An analytical sample was obtained by flash chromatography (SiO_2, toluene/EtOAc 95:5): IR (neat) 3000, 1740 and 1600 cm^{-1}; $[\alpha]_D = -19.2°$ ($c = 1.55$, $CHCl_3$); ^1H NMR (400 MHz) δ 2.11 (s, 3H), 2.12−2.30 (m, 2H), 2.96−3.09 (m, 2H), 3.83 (s, 3H), 5.87 (dd, $J = 7.9$ and 5.5 Hz, 1H), 7.27 (dd, $J = 7.5$ and 1.3 Hz, 1H), 7.29 (d, $J = 7.3$ Hz, 1H), 7.35−7.47 (m, 5H), 7.62 (dt, $J = 7.4$ and 1.59, 1.56 Hz, 1H), 7.73 (d, $J = 1.5$ Hz, 1H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.83−7.88 (m, 3H), 7.99 (d, $J = 2.2$ Hz, 1H), and 8.21 (d, 1H); ^{13}C NMR (100 MHz) δ 21.1, 31.1, 38.7, 52.1, 75.9, 121.0, 126.2, 126.6, 126.9, 127.3, 127.4, 127.6, 128.5, 129.5, 129.7, 130.1, 130.4, 131.3, 131.7, 132.7, 135.4, 135.5, 136.9, 137.4, 142.4, 143.7, 149.3, 157.6, 168.1, and 170.3.

Scheme 8[a]



[a] Reaction conditions: (a) MeMgCl, $(Me_3Si)_2NLi$; (b) $MeOCH_2OCH_2Sn(Bu)_3$, *n*-BuLi, −78 °C; (c) MsCl, Et_3N; (d) *n*-BuLi; 1-(mercaptomethyl)-1-cyclopropaneacetic acid; (e) CH_2N_2; (f) (i) PPTs, *tert*-butyl alcohol, (ii) HPLC, Chiralpak AD; (g) NaOH, MeOH.

Scheme 9



Anal. Calcd for $C_{30}H_{26}ClNO_4$: C, 72.07; H, 5.24; N, 2.80. Found: C, 72.38; H, 5.29; N, 2.84.

Methyl 2-(3-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)-phenyl]-(1*R*/*S*,*S*)-3-acetoxy-1-bromopropyl)benzoate (9a,b). To a solution of the ester **8** (26.3 g, 52.6 mmol) in CCl_4 (1.3 L) was added *N*-bromosuccinimide (9.90 g, 55.8 mmol), followed by benzoyl peroxide (923 mg, 3.80 mmol). After 3 h of reflux, the mixture was cooled to room temperature and poured into 200 mL of saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, toluene/Et_2O 95:5) afforded 21.00 g (69%) of a mixture of the desired diastereoisomers (1:1), contaminated with 4.10 g (16%) of starting material. This mixture was used as such in the next step. An analytical sample of the mixture of diastereoisomers was obtained by a second flash chromatography (SiO_2, toluene/Et_2O 95:5): IR (KBr) 1730, 1600, and 1250 cm^{-1}; ^1H NMR (400 MHz) δ 2.06 (s, 3H), 2.08 (s, 3H), 2.78−2.87 (m, 3H), 2.96−3.04 (m, 1H), 3.78 (s, 3H), 3.90 (s, 3H), 5.72 (dd, J = 8.3 and 5.7 Hz, 1H), 6.08 (dd, J = 8.1 and 5.2 Hz, 1H), 6.30 (t, J = 7.8 and 7.5 Hz, 1H), 6.43 (dd, J = 8.3 and 6.1 Hz, 1H), 7.32−7.47 (m, 10H), 7.51−7.66 (m, 4H), 7.70−7.73 (m, 4H), 7.82−7.93 (m, 8H), 8.00 (s, 1H), and 8.18−8.21 (m, 2H); ^{13}C NMR (100 MHz) δ 20.9, 21.0, 45.9, 46.4, 46.7, 47.4, 52.5, 52.6, 74.4, 74.4, 120.9, 121.0, 126.1, 126.3, 126.6, 127.4, 127.4, 127.7, 127.8, 128.5, 128.9, 129.0, 129.1, 129.4, 129.7, 129.7, 129.8, 129.9, 130.0, 130.1, 130.2, 131.0, 131.0, 133.3, 133.5, 135.2, 135.2, 135.5, 136.9, 137.6, 141.0, 141.6, 142.6, 143.2, 149.3, 157.5, 167.6, 170.0, and 171.1. Anal. Calcd for $C_{30}H_{25}BrClNO_4$: C, 62.25; H, 4.35; N, 2.42; found: C, 62.26; H, 4.58; N, 2.46.

3-(2-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-(*S*)-2-hydroxyethyl)-(*R*/*S*)-3*H*-isobenzofuran-1-one (10a,b). To a solution of the previous mixture (19.90 g, 34.4 mmol) in 280 mL of THF and 140 mL of MeOH was added 140 mL of a 1 N LiOH. The mixture was stirred at 23 °C for 24 h. The mixture was neutralized using 11.0 mL (143 mol) of TFA and stirred for an additional 2 h. The solvents were removed under vacuum and the residue poured into saturated aqueous $NaHCO_3$ (1.0 L). The aqueous phase was extracted with EtOAc (3 × 500 mL), and the combined organic fractions were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, toluene/EtOAc/AcOH 95:5:1 to 50:50:1) afforded 9.69 g (64%) of the desired lactones **10**: ^1H NMR (400 MHz) δ 1.89−1.96 (m, 1H), 2.33−2.52 (m, 3H), 4.65 (d, J = 4.1 Hz, 1H), 4.90 (d, J = 3.4 Hz, 1H), 5.13−5.17 (m, 2H), 5.51 (dd, J = 8.1 and 5.3 Hz, 1H),

5.95 (dd, J = 10.4 and 2.5 Hz, 1H), 7.37−7.52 (m, 8H), 7.56−7.65 (m, 4H), 7.67−7.77 (m, 4H), 7.79−7.93 (m, 10H), 7.98−8.00 (m, 2H), and 8.28−8.31 (m, 2H); ^{13}C NMR (100 MHz) δ 45.0, 45.9, 70.4, 71.3, 79.1, 79.6, 121.0, 123.1, 123.5, 125.3, 125.8, 125.8, 126.0, 126.6, 126.7, 126.7, 127.0, 127.1, 127.3, 127.4, 127.6, 128.4, 128.5, 129.2, 129.3, 129.6, 129.7, 129.8, 129.8, 130.2, 134.7, 134.8, 135.6, 135.8, 137.1, 137.3, 137.4, 146.1, 147.1, 149.4, 151.1, 151.4, 157.8, 170.3, and 170.5. Anal. Calcd for $C_{27}H_{20}ClNO_3$: C, 73.38; H, 4.56; N, 3.16. Found: C, 73.21; H, 4.51; N, 3.14.

***N*,*N*-Pentamethylene-2-(3-[3-(2-(7-chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-(1*R*/*S*,3*S*)-1,3-dihydroxy-1,3-*O*-benzylidene)propyl)benzamide (18a,b).** To a solution of piperidine (5.60 mL, 57.0 mmol) in THF (30 mL) was slowly added a solution of methylmagnesium chloride in THF (10.9 mL, 3.0 M, 32.8 mmol). The mixture was stirred at room temperature until the evolution of methane ceased (15 min) A solution of diastereomeric hydroxylactones **10a**,**b** (6.30 g, 14.3 mmol) in THF (30 mL) was then added over 20 min. The final mixture was stirred at room temperature for 4 h and then quenched with 25% aqueous NH_4OAc (50 mL). The organic layer was separated and the aqueous layer further extracted with ethyl acetate (4 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, hexanes/EtOAc 40:60 to 0:100) provided 5.82 g (77%) of a diastereomeric mixture of diol amide **17a**,**b** as a 1:1 mixture. To 2.50 g of this mixture and benzaldehyde dimethylacetal (3.90 mL, 25.5 mmol) in CH_2Cl_2 (50 mL) was added a 5% solution of phosphorus oxychloride (21 mL) in CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 18 h and neutralized to pH 7 using saturated aqueous $NaHCO_3$. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, hexanes/EtOAc 30:70 to 50:50) afforded 0.89 g (28%) of **18a** (*anti*-benzylidene), along with 1.26 g (40%) of **18b** (*syn*-benzylidene). **18a** : $[\alpha]_D = -89.3°$ (c = 1, $CHCl_3$); IR (neat) 2915, 1620, 1600, and 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17−1.60 (m, 6H), 2.50 (m, 1H), 2.94 (br d, J = 14.2 Hz, 1H), 3.09 (m, 2H), 3.51 (m, 1H), 3.79 (m, 1H), 5.09 (br d, J = 10.9 Hz, 1H), 5.48 (br d, J = 5.1 Hz, 1H), 5.73 (s, 1H), 7.19 (dd, J = 7.6 and 1.2 Hz, 1H), 7.31−7.74 (m, 14H), 7.80 (d, J = 7.8 Hz, 1H), 7.91 (m, 2H), 8.08 (s, 1H), and 8.09 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 25.4, 26.2, 34.1, 42.4, 48.0, 72.7, 73.6, 95.6, 120.0, 124.9, 125.5, 126.0, 126.1, 126.6, 126.8, 127.7, 128.0, 128.1, 128.5, 128.6, 128.7, 129.1, 129.2, 134.5, 134.9, 135.2, 135.9, 136.9, 138.5, 138.6, 139.5, 148.5, and 156.8; MS (FAB) m/z (relative intensity) 615 (100), 509 (28), 491 (48), 292 (86). Anal. Calcd for $C_{39}H_{35}ClN_2O_3 \cdot {}^1/_2H_2O$: C, 75.05; H, 5.81; N, 4.49. Found: C, 75.11; H, 5.98; N, 4.49. **18b**: $[\alpha]_D = +4.2°$ (c = 1.4, $CHCl_3$); IR (neat) 2915, 1615, 1600, and 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39−1.67 (m, 6H), 2.10 (m, 1H), 2.37 (br d, J = 13.2 Hz, 1H), 3.07−3.81 (m, 4H), 5.08 (br d, J = 10.4 Hz, 1H), 5.19 (br d, J = 10.1 Hz, 1H), 5.89 (s, 1H), 7.17 (br d, J = 7.4 Hz, 1H), 7.29−7.72 (m, 17H) and 8.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 25.6, 26.0, 39.6, 42.4, 48.2, 76.1, 78.5, 101.8, 119.4, 124.7, 125.4, 125.5, 126.3, 126.4, 126.5, 126.8, 126.9, 127.8, 128.0, 128.1, 128.5, 128.7, 128.8, 129.0, 134.8, 135.2, 135.3, 135.9, 136.3, 137.6, 138.4, 141.8, 148.4, 156.6, and 169.2. Anal. Calcd for $C_{39}H_{35}ClN_2O_3 \cdot {}^1/_2H_2O$: C, 75.05; H, 5.81; N, 4.49. Found: C, 74.87; H, 5.81; N, 4.43.

3-(2-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-(*S*)-2-hydroxyethyl)-(*R*)-3*H*-isobenzofuran-1-one (10a). To a solution of *anti*-benzylidene **18a** (1.91 g, 2.60 mmol) in tetrahydrofuran (60 mL) was added at room temperature an aqueous solution of trifluoroacetic acid (50%, 40 mL). The mixture was stirred at room temperature for 18 h and then neutralized to pH = 7 by addition of saturated aqueous $NaHCO_3$. The separated aqueous layer was extracted with EtOAc (4 × 75 mL), and the combined organic layers were washed wtih water (2 × 100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, hexanes/EtOAc 30:70 to 50:50) provided 980 mg (83%) of hydroxylactone **10a** as a light yellow solid. Recrystallization in CH_2Cl_2/EtOAc/hexane 50:50:5 afforded 380 mg (first crop), along with 420 mg (second crop): mp = 154 °C; $[\alpha]_D = +25.7°$ (c = 1.0, $CHCl_3$); IR (KBr) 3400, 1705, 1600, and 750 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.94 (m, 1H), 2.49 (m, 1H), 4.86 (dd, J = 4.6 and 1.2 Hz, 1H), 5.14 (m, 1H), 5.95 (dd, J = 10.4 and 2.3 Hz, 1H), 7.39−8.00 (m, 14H), and 8.32 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 50.1, 74.6, 83.3, 125.3, 127.3, 129.5, 130.0, 130.9, 131.2, 131.3, 131.6, 132.7, 133.5, 133.8, 134.0, 134.4, 139.0, 139.8, 140.0, 141.3, 141.6, 151.4, 153.7, 155.7, 162.1, and 174.6. Anal. Calcd for $C_{27}H_{20}ClNO_3 \cdot {}^1/_2H_2O$: C, 71.94; H, 4.69; N, 3.11. Found: C, 72.34; H, 4.72; N, 3.34.

3-(2-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-(*S*)-2-hydroxyethyl)-(*S*)-3*H*-isobenzofuran-1-one (10b). Starting from the *syn*-benzylidene **18b** (3.00 g, 4.20 mmol), the same procedure afforded 1.22 g (68%) of *syn*-hydroxylactone **10b**: mp = 149−150 °C; IR (KBr) 3410, 1710, 1600, and 750 cm^{-1}; $[\alpha]_D = +51.7°$ (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz) δ 2.36 (m, 2H), 4.65 (dd, J = 4.1 and 1.8 Hz, 1H), 5.15 (m, 1H), 5.52 (dd, J = 8.1 and 5.5 Hz, 1H), 7.42−8.00 (m, 14H), and 8.31 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 49.2, 75.6, 83.9, 125.2, 127.7, 130.1, 130.3, 130.8, 130.9, 131.5, 131.6, 131.8, 132.7, 133.2, 133.5, 133.8, 133.9, 134.1, 134.4, 139.0, 139.8, 140.0, 141.3, 141.6, 150.2, 153.6, 155.3, 162.0, and 174.7. Anal. Calcd for $C_{27}H_{20}ClNO_3 \cdot {}^1/_2H_2O$: C, 71.94; H, 4.69; N, 3.11. Found: C, 72.10; H, 4.62; N, 3.21.

1-[((1-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-(*R*)-2-(*S*)-(3-oxo-1,3-dihydroisobenzofuran-1-yl)ethyl)-thio)methyl]cyclopropaneacetic Acid (20a). To a suspension of the hydroxylactone **10a** (859 mg, 1.94 mmol) in 10 mL of CH_2Cl_2 at −20 °C was added triethylamine (400 μL, 2.89 mmol), followed by butanesulfonyl chloride (300 μL, 2.32 mmol). The mixture was stirred at 0 °C for 1 h and then poured into 50 mL of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated to afforded 1.091 g (99%) of the desired butanesulfonate **19a**, which was used as such in the next step: ^{1}H NMR (400 MHz) δ 0.78 (t, J = 7.4 Hz, 3H), 1.22−1.34 (m, 2H), 1.64−1.75 (m, 2H), 2.09−2.27 (m, 1H), 2.98−3.08 (m, 2H), 3.11−3.19 (m, 1H), 5.86 (dd, J = 2.3 and 10.3 Hz, 1H), 5.99 (dd, J = 2.9 and 10.5 Hz, 1H), 7.44−7.49 (m, 3H), 7.52 (d, J = 7.8 Hz, 1H), 7.55−7.59 (m, 1H), 7.67 (d, J = 7.63 Hz, 1H), 7.71−7.76 (m, 3H), 7.82−7.86 (m, 3H), 7.90 (s, 1H), 7.96 (d, J = 2.1 Hz, 1H) and 8.24 (d, J = 8.6 Hz, 1H). To a degassed solution of 1-(mercaptomethyl)-1-cyclopropaneacetic acid (320 mg, 2.20 mmol) in 3 mL of dry THF at −20 °C was added dropwise *n*-BuLi (2.48 M, 1.70 mL, 4.22 mmol). The mixture was stirred at 0 °C for 15 min and then cooled back to −20 °C. The butanesulfonate **19a** in 5 mL of THF was then cannulated into the thiolate suspension and the final mixture was stirred at 4 °C for 16 h. The solution was exposed to air at 0 °C for 1 h and then was poured into a mixture of 20 mL of water and 1.0 mL of AcOH. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, hexanes/EtOAc/AcOH 90:10:1) afforded 825 mg (74%) the desired acid **20a**: $[\alpha]_D = -12.1°$ (c = 1.0, $CHCl_3$); IR (KBr) 1765, 1710, 1600, and 1495 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.40−0.56 (m, 4H), 2.23−2.30 (m, 1H), 2.44 (s, 2H), 2.63 (d, J = 13.1 Hz, 1H), 2.70 (d, J = 13.1 Hz, 1H), 2.70−2.77 (m, 1H), 4.36 (dd, J = 4.4 and 11.2 Hz, 1H), 5.22 (dd, J = 10.3 and 2.8 Hz, 1H), 7.42−7.58 (m, 5H), 7.62−7.65 (m, 2H), 7.71 (t, J = 7.4 Hz, 1H), 7.80 (s, 1H), 7.82 (s, 1H), 7.86−7.90 (m, 3H), 8.00 (d, J = 1.9 Hz, 1H), and 8.28 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 12.7, 12.8, 17.4, 30.0, 39.9, 39.9, 42.7, 46.8, 79.4, 121.0, 123.2, 125.9, 126.6, 126.7, 127.2, 127.5, 128.1, 128.5, 129.6, 130.0, 130.1, 130.3, 134.9, 135.7, 135.8, 137.2, 137.8, 143.0, 149.4, 150.6, 157.9, 170.1, and 173.4. Anal. Calcd for $C_{33}H_{28}ClNO_4S$: C, 69.52; H, 4.95; N, 2.46. Found: C, 69.26; H, 5.19; N, 2.44.

1-[((1-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-(*R*)-2-(*R*)-(3-oxo-1,3-dihydroisobenzofuran-1-yl)ethyl)-thio)methyl]cyclopropaneacetic Acid (20b). The title compound was prepared from hydroxylactone **10b** (630 mg, 1.43 mmol) using triethylamine (300 μL, 2.16 mmol), butane-

sulfonyl chloride (220 μL, 1.70 mmol), 1-(mercaptomethyl)-1-cyclopropaneacetic acid (230 mg, 1.57 mmol), and *n*-BuLi (1.20 mL, 2.98 mmol), which afforded the butanesulfonate intermediate **19b** (810 mg, 99%): ^{1}H NMR (400 MHz) δ 0.77 (t, J = 7.4 Hz, 3H), 1.18−1.32 (m, 2H), 1.59−1.72 (m, 2H), 2.55−2.63 (m, 1H), 2.86−2.91 (m, 1H), 2.92−3.02 (m, 1H), 3.06−3.13 (m, 1H), 5.37 (dd, J = 3.5 and 9.5 Hz, 1H), 5.99 (dd, J = 6.7 and 8.1 Hz, 1H), 7.44−7.60 (m, 5H), 7.69−7.77 (m, 4H), 7.82−7.91 (m, 3H), 7.96 (s, 1H), 7.97 (s, 1H) and 8.24 (d, J = 8.6 Hz, 1H). The desired material **20b** was also obtained (570 mg, 70%): $[\alpha]_D$ = +64.5° (c = 1.0, $CHCl_3$); IR (KBr) 1760, 1710, 1600, and 1495 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.43−0.55 (m, 4H), 2.17−2.25 (m, 1H), 2.39 (d, J = 16.0 Hz, 1H), 2.50 (d, J = 16.0 Hz, 1H), 2.63 (d, J = 13.0 Hz, 1H), 2.68−2.75 (m, 1H), 2.71 (d, J = 13.2 Hz, 1H), 4.30 (dd, J = 4.9 and 10.1 Hz, 1H), 5.93 (dd, J = 3.1 and 9.3 Hz, 1H), 7.31−7.39 (m, 2H), 7.43−7.56 (m, 4H), 7.67−7.69 (m, 2H), 7.73 (s, 1H), 7.77−7.83 (m, 3H), 7.89 (d, J = 8.7 Hz, 1H), 7.99 (d, J = 2.0 Hz, 1H), and 8.27 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 12.7, 13.7, 17.5, 39.5, 40.0, 42.6, 47.0, 79.8, 121.0, 123.3, 124.8, 126.7, 126.8, 127.0, 127.4, 127.5, 128.4, 129.0, 129.4, 129.9, 130.0, 130.3, 134.8, 135.7, 135.8, 137.2, 137.6, 144.6, 149.3, 150.7, 157.9, 170.3, and 173.5. Anal. Calcd for $C_{33}H_{28}ClNO_4S\cdot{}^1/_2H_2O$: C, 68.44; H, 5.04; N, 2.41. Found: C, 68.51; H, 5.00; N, 2.40.

1-[[(-1-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-(1*R*,3*R*)-3-(2-(1-hydroxy-1-methylethyl)phenyl)-3-hydroxypropyl)thio)methyl]cyclopropaneacetic Acid (2). A suspension of cerium chloride (1.49 g, 6.00 mmol) in 15 mL of THF was refluxed for 10 h. Methylmagnesium chloride (7.80 mL, 23.5 mmol, 3 M in THF) was then added to the suspension at 0 °C, and the mixture was stirred for 40 min. The suspension was warmed to 40 °C, and a solution of a mixture of lactones **20a**,**b** (2.68 g, 4.70 mmol) in THF (15 mL) was added dropwise. The reaction mixture was stirred for 10 min and then poured into 25% aqueous NH_4OAc (60 mL) containing a few drops of AcOH. The aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, toluene/EtOAc/AcOH 67:33:1) afforded 780 mg (50%) of the desired acid **1**: $[\alpha]_D$ = +185.5° (c = 0.87, $CHCl_3$); IR (neat) 3400, 2990, 1600, and 1560 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.16−0.60 (m, 4H), 1.67 (s, 6H), 2.08−2.13 (m, 2H), 2.27−2.33 (m, 1H), 2.46 (d, J = 12.7 Hz, 1H), 2.59 (d, J = 14.3 Hz, 1H), 2.79 (d, J = 12.7 Hz, 1H), 4.51 (dd, J = 11.5 and 2.7 Hz, 1H), 6.18 (d, J = 9.3 Hz, 1H), 7.06−7.13 (m, 2H), 7.25−7.54 (m, 7H), 7.69−7.85 (m, 4H), 7.95 (s, 1H), and 8.19 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 12.4, 13.9, 18.6, 33.0, 33.3, 41.5, 44.8, 47.6, 48.4, 68.4, 73.7, 121.1,126.2, 126.7, 127.2, 127.3, 127.5, 127.6, 128.6, 128.6,129.1, 129.2, 129.4, 129.7, 130.2, 135.5, 136.0, 137.0, 137.3, 144.9, 146.4, 147.1, 149.4, 157.9, and 180.8; HRMS (FAB) m/z calcd for $C_{35}H_{35}ClNO_4SNa + Na^+$ 646.1770, found 646.1768. Anal. Calcd for $C_{35}H_{35}ClNO_4S\cdot H_2O$: C, 65.46; H, 5.80; N, 2.18. found: C, 65.29; H, 5.82; N, 2.04. Further elution afforded 570 mg (36%) of the diastereoisomer **2**: $[\alpha]_D$ = +83.3° (c = 0.79, $CHCl_3$); IR (neat) 3400, 2990, 1600, and 1570 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.28−0.52 (m, 4H), 1.30 (s, 3H), 1.34 (s, 3H), 2.14−2.17 (m, 1H), 2.33 (s, 2H), 2.55−2.66 (m, 1H), 2.69 (m, 2H), 4.45−4.48 (dd, J = 10.5 and 4.03 Hz, 1H), 5.46 (d, J = 8.6 Hz, 1H), 7.04−7.16 (m, 2H), 7.28−7.59 (m, 7H), 7.73−7.84 (m, 4H), 7.95 (s, 1H), and 8.19 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 12.9, 13.5, 18.9, 32.7,40.8, 44.8, 46.8, 47.6, 68.7, 73.2, 121.1,126.0, 126.5,126.7,127.2, 127.3, 127.5 , 128.3, 128.6,129.0, 129.3, 129.6, 130.0, 130.2, 135.5, 136.2, 137.0, 137.2, 144.5, 144.9, 146.4, 149.4, 158.0, 157.9, and 180.5; HRMS (FAB) m/z calcd for $C_{35}H_{35}ClNO_4SNa + Na^+$ 646.1770, found 646.1768. Anal. Calcd for $C_{35}H_{35}ClNO_4S\cdot{}^1/_2H_2O$: C, 66.39; H, 5.73; N, 2.21. Found: C, 66.24; H, 5.32; N, 2.11.

(*S*)-1-[2-(3-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)-phenyl]-3-hydroxypropyl)phenyl]ethanone (22). To a solution of lithium bis(trimethylsilyl)amide (355 mL, 352 mmol, 1 M in THF) at −15 °C was added dropwise methylmagnesium chloride (59.3 mL, 178 mmol, 3M in THF). The reaction mixture was warmed to 0 °C and stirred for 1 h. The Grignard reagent was then added over 1 h to a solution of ester **7** (25.00 g, 54.6 mmol) in toluene (150 mL) at −20 °C. The reaction mixture was warmed to 0 °C and stirred for 3 h. The mixture was poured into aqueous NH_4Cl (2.4 M solution with 5% HOAc, 1.2 L) and extracted with EtOAc (2 × 500 mL). The combined organic fractions were dried over anhydrous $MgSO_4$. Flash chromatography (SiO_2, toluene/EtOAc 80:20) gave 19.01 g (80%) of the title compound **22**: mp 98−100 °C; $[\alpha]_D$ = −25° (c = 1.0, $CHCl_3$); IR (neat) 3400, 3150, 2900, and 1680 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.04 (m, 2H), 2.56 (s, 3H), 2.89−2.96 (m, 1H), 3.00−3.07 (m, 1H), 4.40 (d, J = 4.2 Hz, 1H), 4.75 (m, 1H), 7.28−7.60 (m, 8H), 7.75 (s, 2H), 7.83−8.00 (m, 4H), and 8.33 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 30.5, 30.9, 42.3, 73.6, 121.0, 125.6, 126.6, 126.7, 127.3, 127.4, 128.5, 128.5, 129.1, 129.4, 129.9, 130.2, 131.8, 132.0, 135.5, 136.0, 137.0, 137.1, 139.2, 142.6,147.6, 149.4, 157.9, and 202.5; HRMS (FAB) m/z calcd for $C_{28}H_{24}ClNO_2$ 442.1574, found 442.1575. Anal. Calcd for $C_{28}H_{24}ClNO_2$: C, 76.09; H, 5.47; N, 3.16. Found: C, 76.12; H, 5.37 N, 3.25.

(*S*)-1-[2-(3-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)-phenyl]-3-hydroxypropyl)phenyl]-1-(methoxymethoxy)-methyl)ethanol (23a,b). To a solution of ((methoxymethoxy)-methyl)tributylstannane (22.32 g, 61.2 mmol) in THF (100 mL) at −78 °C was added *n*-butyllithium (23.3 mL, 58.2 mmol, 2.5 M in hexane) over 10 min. A solution of the starting ketone **22** (7.20 g, 16.3 mmol) in THF (20 mL) at −78 °C was cannulated slowly, and the mixture was stirred for 1 h at −78 °C. Aqueous NH_4Cl (25%, 200 mL) was added directly into the reaction mixture, extracted with EtOAc (200 mL), and dried over anhydrous $MgSO_4$. Flash chromatography (SiO_2, hexanes/EtOAc 67:33) gave 2.70 g (32%) of the title compounds and 3.21 g of recovered starting materiel: IR (neat) 3405, 2915, 1608, and 1495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (m, 3H), 2.15 (m, 2H), 3.00−3.30 (m, 3H), 3.33 (s, 3H), 3.42−3.48 (m, 1H), 3.62 (d, J = 10 Hz, 1H), 3.98 (d, J = 10 Hz, 1H), 3.73 (d, J = 10 Hz, 1H), 4.05 (d, J = 10 Hz, 1H), 4.69−4.70 (m, 3H), 7.15−7.43 (m, 7H), 7.49 (m, 1H), 7.60−7.71 (m, 5H), and 8.05−8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 26.8, 29.1, 29.45, 41.7, 41.9, 55.2, 72.4, 74.8, 75.2, 75.6, 96.7, 119.1, 124.2, 125.5, 125,.9, 126.2, 126.6, 127.0, 127.2, 127.7, 128.0, 128.2,128.4, 131.2, 134.8, 135.0, 135.7, 135.9, 145.1, and 156.5; HRMS (FAB) m/z calcd for $C_{31}H_{32}ClNO_4$ 518.2096, found 518.2098. Anal. Calcd for $C_{31}H_{32}ClNO_4$: C, 71.87; H, 6.22; N, 2.70. Found: C, 71.82; H, 6.35; N, 2.75.

(*R*,*R* or *S*)-1-[[(1-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-3-(2-(1-((methoxymethoxy)methyl)-1-hydroxyethyl)phenyl)propyl)thio)methyl]cyclopropaneacetic Acid (25a,b). To a solution of the diols **23** (4.61 g, 8.80 mmol) in 30 mL of a 1:1 mixture of toluene/CH_3CN was added diisopropylethylamine (1.61 mL, 9.20 mmol). The reaction mixture was cooled to −48 °C, and methanesulfonyl chloride (0.68 mL, 8.81 mmol) was added slowly. The temperature was raised to −20 °C and maintained for 1 h. The cold solution was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and then concentrated to give **24a**,**b**, which were used as such for the next step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 3H), 2.20−2.32 (m, 1H), 2.38−2.49 (m, 1H), 2.76 (s, 3H), 2.94−3.11 (m, 1H), 3.12−3.20 (m, 2H), 3.30 (s, 3H), 3.59−3.64 (m, 1H), 3.89−3.96 (m, 1H), 4.66 (m, 2H), 5.67 (m, 1H), 7.10−7.49 (m, 8H), 7.61−7.74 (m, 5H), and 8.09−8.15 (m, 2H). To a solution of 1-(mercaptomethyl)-1-cyclopropaneacetic acid (1.31 g, 8.80 mmol) in degassed THF (12 mL) at −20 °C was added slowly *n*-butyllithium (7.10 mL, 17.7 mmol, 2.5 M in hexane) over 10 min. The heterogeneous mixture was stirred at 0 °C for 30 min. The crude mesylate (**24a**,**b**, 5.32 g) in THF (20 mL) was added to the mercapto acid suspension and stirred at −15 °C overnight. Aqueous NH_4Cl (50 mL, 25%) was added, and the mixture was extracted with EtOAc (100 mL) and dried over anhydrous $MgSO_4$. Flash chromatography (SiO_2, hexanes/EtOAc/AcOH 67:33:1) gave 4.10 g (71%) of the title products **25a**,**b**: IR (neat) 3450, 2912, 1708, and 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.46−0.57 (m, 4H), 1.53 (s, 3H), 2.15−2.25 (m, 2H), 2.26−2.36 (m, 2H), 2.57−3.06 (m, 3H), 3.07−3.14 (m, 1H), 3.29 (s, 3H), 3.60−3.64 (m, 1H), 3.93−4.02 (m, 2H), 4.66 (m, 2H), 7.10−7.80 (m, 13H), and 8.03−8.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 12.3, 12.4, 16.6, 26.9, 32.6, 38.6, 38.7, 39.9, 40.0, 40.2, 50.35, 55.6 , 75.1, 75.9, 77.2,

97.0, 119.0, 125.6, ,126.3, 126.4, 126..7, 127.3, 127.4 , 128.6, 128.7, 129.0, 131.6, 131.7, 135.5, 136.5, 136.6, 140.5, 141.6, 143.4, 157.0, and 174.6; HRMS (FAB) *m/z* calcd for $C_{37}H_{40}ClNO_5S$ 646.2394, found 646.2393. Anal. Calcd for $C_{37}H_{40}ClNO_5S$: C, 68.76; H, 6.23; N, 2.16. Found: C, 68.80; H, 6.35; N, 2.14.

Methyl (*R*,*R* or *S*)-1-[((1-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-3-(2-(1,2-dihydroxy-1-methylethyl)-phenyl)propyl)thio)methyl]cyclopropaneacetate (26a,b). To a solution of the acids **25** (1.00 g, 1.55 mmol) in 10 mL of Et_2O was added a solution of diazomethane until total consumption of starting material by TLC. The mixture was evaporated to dryness and was then dissolved in 35 mL of *tert*-butyl alcohol. PPTS (3.89 g, 15.5 mmol) was added and the mixture was refluxed for 12 h. The reaction mixture was poured into 250 mL of aqueous NH_4OAc (25%) and extracted with 100 mL of Et_2O. The organic phase was washed with 100 mL of water, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, toluene/EtOAc 67:33) afforded 550 mg (58%) of the title compounds, along with 302 mg of the methyl ester intermediate. The two diastereoisomers were separated by HPLC on a preparative column (CHIRALPAK AD) using ethanol as the eluent. From 550 mg of the diastereomeric mixture was obtained 191 mg of the title compound **26a**, with a retention time of 14 min: IR (neat) 3450, 2910, 1730, and 1605 cm^{-1}; ^1H NMR (400 MHz) δ 0.38−0.53 (m, 4H), 1.51 (s, 3H), 2.23 (dd, J = 16.3 and 7.6 Hz, 2H), 2.39 (d, J = 15.9 Hz, 1H), 2.46 (d, J = 15.9 Hz, 1H), 2.55 (s, 2H), 2.85−2.92 (m, 1H), 3.05−3.11 (m, 1H), 3.57 (s, 3H), 3.63 (d, J = 10.8 Hz, 1H), 3.89 (d, J = 10.8 Hz, 1H), 4.05 (t, J = 7.4 Hz, 1H), 7.06−7.17 (m, 3H), 7.39−7.44 (m, 3H), 7.52−7.56 (m, 2H), 7.62−7.64 (m, 1H), 7.79 (s, 1H), 7.87−7.96 (m, 3H), 8.04 (s, 1H), and 8.35 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 12.6, 12.8, 17.6, 27.0, 33.6, 39.6, 40.1, 40.9, 50.9, 51.4, 70.6, 76.2, 121.1, 126.1,126.7, 126.8, 127.5, 127.6, 127.8, 128.6, 128.6, 129.4, 129.5, 129.7, 130.3, 132.3, 135.6, 135.9, 137.2, 137.5, 141.5, 144.1, 144.9, 149.5, 158.0, and 172.7; HRMS (FAB) *m/z* calcd for $C_{36}H_{38}ClNO_4S$ 616.2285, found 616.2285. Anal. Calcd for $C_{36}H_{38}ClNO_4S$: C, 70.17; H, 6.21; N, 2.27. Found: C, 70.22; H, 6.25; N, 2.11. The column was further eluted to give 162 mg of diastereoisomer **26b**, with a retention time of 26 min: IR (neat) 3450, 2920, 1730, and 1605 cm^{-1}; ^1H NMR (400 MHz) δ 0.38−0.53 (m, 4H), 1.51 (s, 3H), 2.20−2.29 (m, 2H), 2.39 (d, J = 15.8 Hz, 1H), 2.46 (d, J = 15.8 Hz, 1H), 2.55 (s, 2H), 2.81−2.88 (m, 1H), 3.09−3.12 (m, 1H), 3.57 (s, 3H), 3.63 (d, J = 10.8 Hz, 1H), 3.76 (s, J = 10.8 Hz, 1H), 4.05 (t, J = 6.6 Hz, 1H), 7.06−7.16 (m, 3H), 7.39−7.43 (m, 3H), 7.53−7.57 (m, 2H), 7.62−7.64 (m, 1H), 7.80 (s, 1H), 7.88−7.97 (m, 3H), 8.05 (s, 1H), and 8.35 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 12.6, 12.8, 17.6, 27.0, 33.6, 39.6, 40.1, 40.9, 50.9, 51.4, 70.6, 76.2, 121.1, 126.1,126.7, 126.8, 127.5, 127.6, 127.8, 128.6, 128.6, 129.4, 129.5, 129.7, 130.3, 132.3, 135.6, 135.9, 137.2, 137.5, 141.5, 144.1, 144.9, 149.5, 158.0, and 172.7; HRMS (FAB) *m/z* calcd for $C_{36}H_{38}ClNO_4S$ 616.2285, found 616.2288. Anal. Calcd for $C_{36}H_{38}ClNO_4S$: C, 70.17; H, 6.21; N, 2.27. Found: C, 70.12; H, 6.15; N, 2.37.

(*R*,*R* or *S*)-1-[((1-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-3-(2-(1,2-dihydroxy-1-methylethyl)phenyl)-propyl)thio)methyl]cyclopropaneacetic acid (3). To a solution of the ester **26a** (191 mg, 0.316 mmol) in 0.50 mL of ethanol was added 0.61 mL of aqueous LiOH (1 N). The mixture was stirred at 60 °C for 4 h and then cooled and acidified with 20 μL of AcOH to pH 5, and finally diluted with 1 mL of H_2O and 2 mL of EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (silicic acid, hexanes/EtOAc 50:50) afforded 0.14 g (73%) of the title compound: $[\alpha]_D$ = +75.2° (c = 0.25, $CHCl_3$); IR (neat) 3450, 2910, 1710, and 1605 cm^{-1}; ^1H NMR (400 MHz) δ 0.38−0.56 (m, 4H), 1.51 (s, 3H), 2.19−2.27 (m, 2H), 2.44 (s, 2H), 2.60 (s, 2H), 2.83−2.97 (m, 1H), 3.08−3.15 (m, 1H), 3.63 (d, J = 10.8 Hz, 1H), 3.76 (d, J = 10.8 Hz, 1H), 4.08 (t, J = 7.35 Hz, 1H), 7.05−7.19 (m, 4H), 7.39−7.62 (m, 5H), 7.80−8.02 (m, 5H), and 8.33 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 12.6, 12.8, 17.6, 27.1, 33.6, 39.6, 40.1, 40.9, 50.9, 51.4, 70.6, 76.2, 121.1, 126.1,126.7, 126.8, 127.5, 127.6, 127.8, 128.6, 129.4, 129.5, 129.7, 130.3, 132.3, 135.6, 135.9, 137.2, 137.5, 141.5, 144.1, 144.9, 149.5, 158.0, and 172.7; HRMS (FAB) *m/z* calcd for $C_{35}H_{36}ClNO_4S$ 602.2131, found 602.2129. Anal. Calcd for $C_{35}H_{36}ClNO_4S$: C, 69.81; H, 6.02; N, 2.32. Found: C, 69.92; H, 5.92; N, 2.40.

(*R*,*S* or *R*)-1-[((1-[3-(2-(7-Chloro-2-quinolinyl)-(*E*)-ethenyl)phenyl]-3-(2-(1,2-dihydroxy-1-methylethyl)phenyl)-propyl)thio)methyl]cyclopropaneacetic acid (4). To a solution of compound **26b** (162 mg, 0.270 mmol) in 0.50 mL of ethanol was added 0.52 mL of aqueous NaOH (1 N). The mixture was stirred at 60 °C for 4 h, and then cooled and acidified with 20 μL of AcOH to pH 5, and finally diluted with 1 mL of H_2O and 2 mL of EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (silicic acid, hexanes/EtOAc 50:50) afforded 110 g (70%) of the title compound **4**: $[\alpha]_D$ = +51.2° (c = 0.25, $CHCl_3$); IR (neat) 3450, 2920, 1710, and 1605 cm^{-1}; NMR (400 MHz) δ 0.39−0.55 (m, 4H), 1.51 (s, 3H), 2.16−2.30 (m, 2H), 2.44 (s, 2H), 2.60 (s, 2H), 2.80−2.88 (m, 1H), 3.10−3.17 (m, 1H), 3.63 (d, J = 10.8 Hz, 1H), 3.76 (d, J = 10.8 Hz, 1H), 4.08 (t, J = 7.8 Hz, 1H), 7.04−7.19 (m, 4H), 7.39−7.60 (m, 5H), 7.80−8.02 (m, 5H), and 8.33 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 12.6, 12.8, 17.6, 27.1, 33.6, 39.6, 40.1, 40.9, 50.9, 51.4, 70.6, 76.2, 121.1, 126.1, 126.7, 126.8, 127.5, 127.6, 127.8, 128.6, 129.4, 129.5, 129.7, 130.3, 132.3, 135.6, 135.9, 137.2, 137.5, 141.5, 144.1, 144.9, 149.5, 158.0, and 172.7; HRMS (FAB) *m/z* calcd for $C_{35}H_{36}ClNO_4S$ 602.2131, found 602.2129. Anal. Calcd for $C_{35}H_{36}ClNO_4S$: C, 69.81; H, 6.02; N, 2.32. Found: C, 69.72; H, 6.10; N, 2.30.

MK-0476 Sulfoxide 5 and 6. To a suspension of the sodium salt of MK-0476 (1.57 g, 2.58 mmol) in 50 mL of dry CH_2Cl_2 at −22 °C was added TFA (400 μL, 5.39 mmol). To the resulting yellow solution was cannulated a solution of *m*-CPBA (543 mg, 3.12 mmol) dropwise, and the resulting mixture was stirred at −22 °C for 2 h. It was poured into 100 mL of citrate buffer (0.5 M) at pH 4.75 and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, toluene/acetone/AcOH 80:20:1) or HPLC using a Prep Nova-Pak® HR C18 columm (CH_3CN/H_2O/AcOH 60:39:1) afforded 192 mg (12%) of the desired diastereomeric sulfoxide **5**: $[\alpha]_D$ = −22.5° (c = 0.10, $CHCl_3$); ^1H NMR (400 MHz) δ 0.51−0.66 (m, 4H), 1.56 (s, 3H), 1.58 (s, 3H), 2.25 (d, J = 15.8 Hz, 1H), 2.34 (d, J = 13.6 Hz, 1H), 2.46−2.54 (m, 2H), 2.67 (d, J = 15.9 Hz, 1H), 2.70 (d, J = 13.8 Hz, 1H), 3.02−3.05 (m, 1H), 3.16−3.19 (m, 1H), 3.94 (dd, J = 9.2 and 6.0 Hz, 1H), 7.10 (td, J = 7.4 and 1.6 Hz, 1H), 7.15 (td, J = 7.4 and 1.5 Hz, 1H), 7.22 (dd, J = 7.5 and 1.6 Hz, 1H), 7.39 (dd, J = 7.8 and 1.5 Hz, 1H), 7.41−7.55 (m, 4H), 7.73 (d, J = 7.6 Hz, 1H), 7.78 (s, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 16.3 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), and 8.35 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 10.7, 12.2, 31.0, 31.4, 31.4, 32.1, 40.0, 56.5, 56.6, 63.9, 71.4, 119.9, 125.0, 125.0, 125.3, 126.1, 126.3, 126.4, 126.9, 128.1, 128.3, 128.4, 129.5, 129.7, 131.0, 134.1, 134.7, 134.8, 135.6, 136.3, 139.3, 146.4, 147.7, 156.6, and 172.4; HRMS (FAB) *m/z* calcd for $C_{35}H_{36}ClNO_4S$ 602.21295, found 602.21295. Further elution afforded 801 mg (50%) of the diastereomeric sulfoxide **6**: $[\alpha]_D$ = +97.9° (c = 0.14, $CHCl_3$); ^1H NMR (400 MHz) δ 0.40−0.68 (m, 4H), 1.52 (s, 6H), 2.22 (d, J = 16.1 Hz, 1H), 2.31−2.36 (m, 1H), 2.58 (d, J = 13.7 Hz, 1H), 2.61−2.67 (m, 1H), 2.72 (d, J = 16.2 Hz, 1H), 2.87 (d, J = 13.9 Hz, 1H), 2.91−2.94 (m, 1H), 3.07−3.13 (m, 1H), 4.07 (dd, J = 11.0 and 4.3 Hz, 1H), 7.12−7.19 (m, 3H), 7.39 (dd, J = 7.7 and 1.5 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.47−7.56 (m, 3H), 7.32 (d, J = 7.7 Hz, 1H), 7.81 (s, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 17.5 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 1.4 Hz, 1H) and 8.35 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 10.5, 12.1, 30.6, 31.1, 31.3, 31.3, 39.8, 56.5, 56.7, 66.2, 71.2, 120.0, 125.0, 125.0, 125.3, 126.1, 126.4, 126.6, 126.9, 127.6, 128.5, 129.0, 129.0, 129.5, 130.9, 134.1, 134.5, 135.7, 136.3, 136.4, 139.3, 146.4, 147.7, 156.5 and 172.4; HRMS (FAB) *m/z* calcd for $C_{35}H_{36}ClNO_4S$ 602.21295, found 602.21295.

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