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Practical Syntheses of (2*S*)-R207910 and (2*R*)-R207910

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Concise and practical syntheses of (2*S*)-R207910 (**3a**) and (2*R*)-R207910 (**3b**) have been achieved in high overall yield of 12% in 10 steps for each isomer starting from a known intermediate following Sharpless asymmetric epoxidation, regioselective epoxide opening, modified allylzinc bromide addition as key reactions.

Introduction

Tuberculosis (TB) is a deadly infectious disease caused by *Mycobacterium tuberculosis*. It is primarily an infirmity of the respiratory system and is spread through air via coughing and sneezing of the infected person. In conjunction with the spread of HIV infection,[1] tuberculosis is today amongst the worldwide health intimidations.[2–8] As a result, TB has become a major health and socioeconomic problem in most of the countries. Currently, a major problem in TB treatment is the development of multidrug-resistant tuberculosis strains (MDR-TB), which can be defined as strains that show resistance towards at least isoniazid (**1**)[9] and rifampicin (**2**),[10] two important first-line drugs used in TB treatment. Another serious problem, in the context of MDR-TB, is the emergence of extensively drug-resistant tuberculosis (XDR-TB), which are strains resistant to first- and second-line *anti*-TB drugs.[11]

In this context, a search for new entities led to the quinoline nucleus, which constitutes an important class of heterocyclic compounds found in many synthetic and natural products with a wide variety of important pharmacological activities. R207910 (TMC 207) (Figure 1) is one such compound structurally dissimilar to isoniazid and rifampicin and consisting of diarylquinoline scaffold. This compound was developed at Johnson & Johnson Pharmaceutical Research and Development,[12] and possess a new mechanism of action based on the interaction with the enzyme adenosine triphosphate (ATP) synthase. It is active against both drug-resistant and drug-susceptible *M. tuberculosis*, as well as other mycobacterial species. It has a relatively longer half life in plasma and tissues, of nearly 24 h. The compound stops the energy production by acting on the proton pump of adenosine triphosphate (ATP) synthase of *M. tuberculosis* but not on other bacterial ATP systems, which explains its high specificity for mycobacteria.[13–15] In the mouse model, 2-month treatment regimes containing R207910 and PZA led to sterilization, which shows the potential for reduction of treatment time to two months.[16]

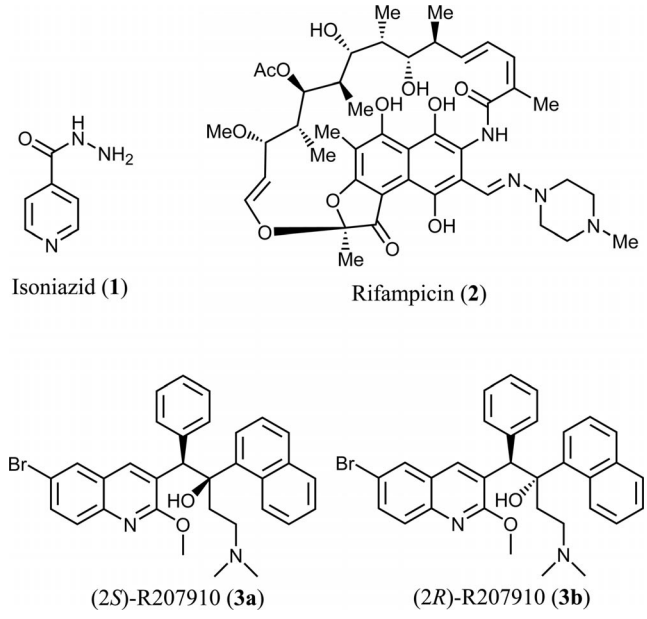

Figure 1. Structures of isoniazid (**1**), rifampicin (**2**), (2*S*)-R207910 (**3a**) and (2*R*)-R207910 (**3b**).

It's fascinating biological activity interested us to develop an asymmetric and practical synthesis of R207910. There is no asymmetric synthesis reported on R207910 except a recent publication by Shibasaki et al. which appeared during the completion of our work.[17] Herein, we report an efficient synthesis of (2*S*)-R207910 (**3a**) and (2*R*)-R207910 (**3b**) in 10 linear steps starting from a known compound with 12% overall yield for each.

According to our retrosynthetic analysis, **3a** could be obtained from **4a** in two steps (Scheme 1). The stereocenter at the tetrasubstituted C atom was introduced by chelation-

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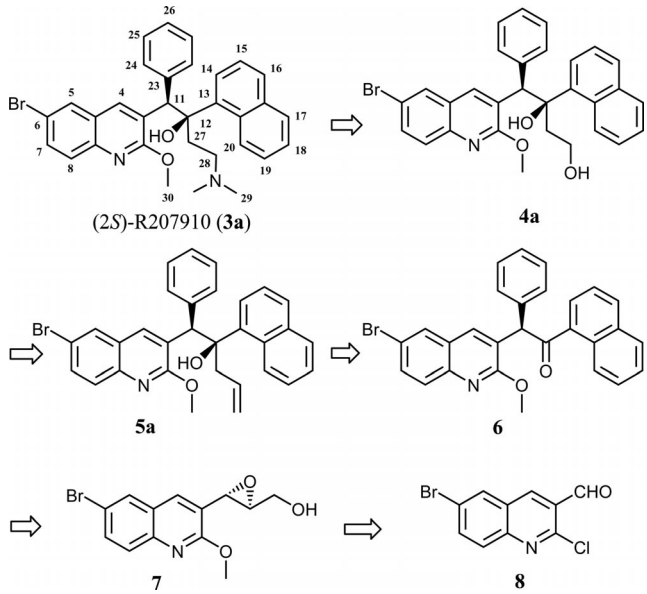
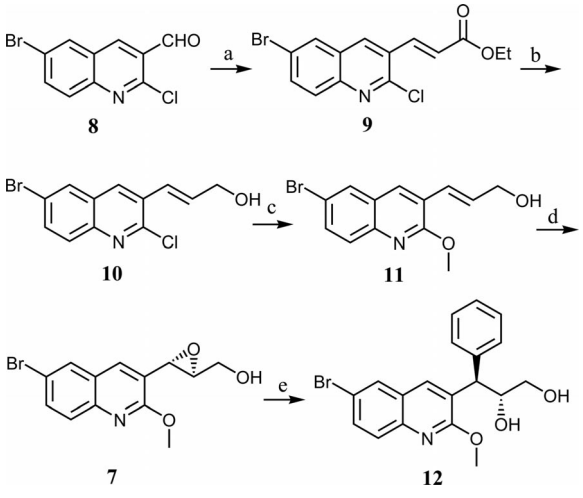
controlled Barbier-type reaction. The enantiomerically enriched ketone **6** could be obtained by Sharpless epoxidation followed by ring opening with PhMgBr.



Scheme 1. Retrosynthetic analysis of (2*S*)-R207910 (**3**).

Results and Discussion

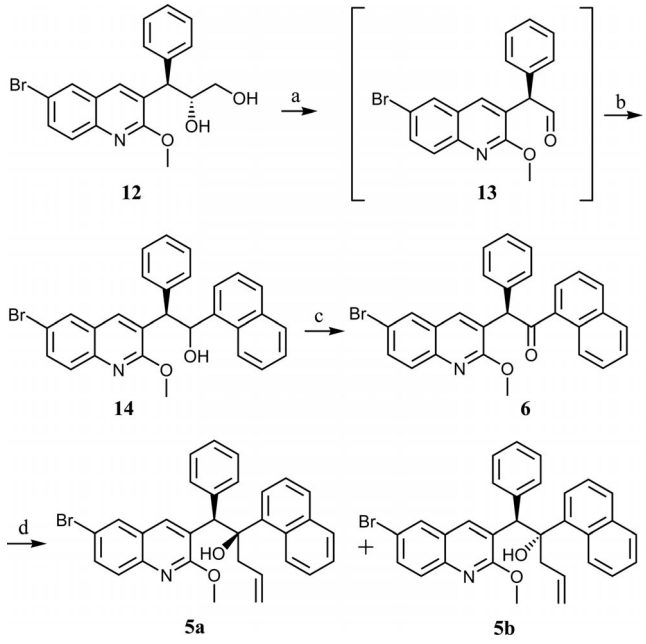
The synthesis commenced with a known intermediate 6-bromo-2-chloroquinoline-3-carbaldehyde **8**,[18a] prepared from 4-bromo-acetanilide following Vilsmeier–Haack modified protocol (Scheme 2). It was subjected to Horner–Wadsworth–Emmons olefination using lithium enolate of the phosphonate [$(OEt)_2P(O)CH_2CO_2Et$] to afford α,β-unsaturated ester **9** in 89% yield with complete *E*-selectivity.



Scheme 2. Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, LiHMDS, THF, 0 °C to room temp., 2 h, 89%; (b) DIBAL-*H*, CH_2Cl_2, 0 °C to room temp., 2 h, 84%; (c) NaOMe, MeOH, reflux, 8 h, 92%; (d) (+)-DIPT, Ti(O*i*Pr)$_4$, TBHP, CH_2Cl_2, –20 °C, 4 h, 86%; (e) PhMgBr, CuCN, THF, –40 °C, 4 h, 86%. LiHMDS = lithium hexamethyldisilazide, THF = tetrahydrofuran, DIBAL = diisobutylaluminum hydride, DIPT = diisopropyl tartrate, TBHP = *tert*-butyl hydroperoxide.

Reduction of compound **9** with DIBAL-*H* at 0 °C furnished allyl alcohol **10**. Reaction of **10** with sodium methoxide gave 2-methoxy derivative **11**.[19]

The next operation was the Sharpless asymmetric epoxidation[20] which was carried out with (+)-DIPT, Ti(O*i*Pr)$_4$, TBHP at –20 °C to afford epoxy alcohol **7** in 86% yield (95% *ee*). Subsequent exposure of the epoxide to PhMgBr in the presence of CuCN furnished diol **12** in 86% yield.[21] Diol **12** was oxidatively cleaved with $NaIO_4$ impregnated over silica gel[22] to furnish aldehyde **13**. The crude aldehyde was treated with 1-naphthylmagnesium bromide[23] to obtain secondary alcohol **14** as a mixture of isomers which on oxidation with Dess–Martin periodinane[24] afforded the keto derivative **6** in 81% yield with high enantiomeric purity (95% *ee*). Our next concern was to construct the tetrasubstituted carbon center through allylation of carbonyl group present in **6**. In accordance with Shibasaki et al. observation, our attempts to introduce the tetrasubstituted carbon through conventional nucleophiles like allylmagnesium, allylaluminium, allylindium, allylboronate, and allylstannane derivatives were not successful. In all the attempts, the starting material was recovered from the reaction mixture. A recent development of solvent free addition reaction of allylzinc bromide to carbonyl compound developed by Wang et al. attracted our attention in this regard.[25] Thus, addition of allylzinc bromide by a modified protocol, in which compound **6** in THF was added to allylzinc bromide to afford the required homoallyl alcohol **5a** and **5b** as an inseparable mixture in 2:3 ratio in favor of unwanted diastereomer (Scheme 3). To improve the ratio towards the desired isomer, different chelating agents like CuBr, CuCN, CuI, CuBr·Me_2S were tried. Only in the case of CuBr·Me_2S,

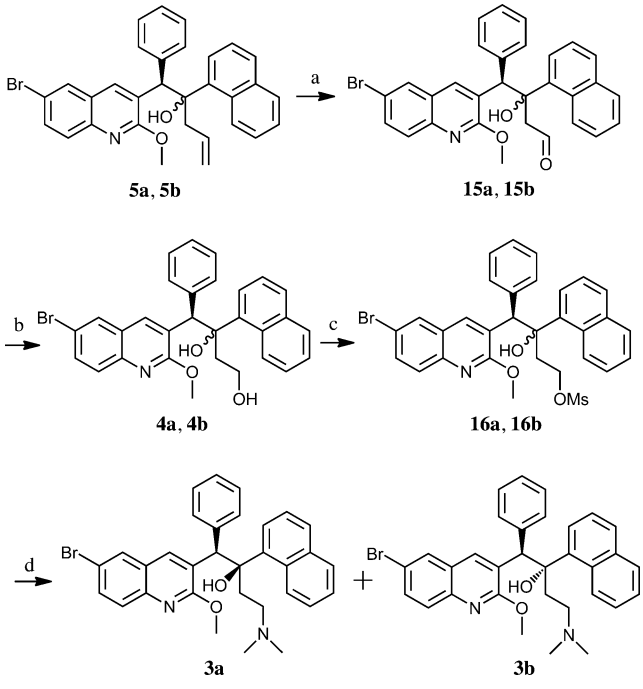


Scheme 3. Reagents and conditions: (a) $NaIO_4$, CH_2Cl_2, 0 °C to room temp., 1 h, 98%; (b) 1-naphthylmagnesium bromide, Et_2O, 0 °C, 1 h, 92%; (c) DMP, CH_2Cl_2, 3 h, 87%; (d) allylzinc bromide, neat, room temp., 1 h, 90%. DMP: Dess–Martin periodinane.

the ratio changed to almost equal amounts of diastereomers (by HPLC).

Having **5a** and **5b** in hand, the next task was to achieve chromatographic separation of the mixture obtained from further reactions of **5a** and **5b** which was not practical at this stage. Thus, we proceeded further without separation of diastereomers.

Oxidative cleavage[26] of olefin using $OsO_4/NaIO_4$ in presence of 2,6-lutidine afforded aldehyde **15a** and **15b**. The mixture of aldehydes was treated with $NaBH_4$ in methanol at 0 °C to obtain the diol **4a** and **4b** in 82% yield over two steps. Finally, *O*-mesylation followed by displacement of the mesylate group in **16a** and **16b** with dimethylamine furnished (2*S*)-R207910 (**3a**) and (2*R*)-R207910 (**3b**) in 79% yield over two steps (Scheme 4).[27] The products were separated easily by silica gel column chromatography (ethyl acetate:hexane = 1:6). The spectral and analytical data of **3a** $[\alpha]_D^{25}$ = –165.2 (*c* = 0.8, DMF); ref.[12] $[\alpha]_D^{25}$ = –166.98 (*c* = 0.5, DMF) was in good agreement with the reported data.



Scheme 4. Reagents and conditions: (a) $NaIO_4$, 2,6-lutidine, OsO_4, dioxane/H_2O (3:1), room temp., 2 h; (b) $NaBH_4$, MeOH, 0 °C to room temp., 82% over two steps; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C to room temp., 3 h, 88%; (d) Me_2NH, THF, 45 °C, 24 h, 90%. Ms = methylsulfonyl, THF = tetrahydrofuran.

Conclusions

In conclusion, we have achieved the synthesis of (2*S*)-R207910 (**3a**) and (2*R*)-R207910 (**3b**) in overall yield of 12% each in 10 steps. The key steps involved are Sharpless asymmetric epoxidation, regioselective epoxide opening and modified allylzinc bromide addition. Optimization of the allylation reaction would enable the approach amenable for scale up at affordable cost as Sharpless asymmetric epoxidation is a commercially viable process and our attempt is first in this area. There is no report till date of creating crowded asymmetric centers using Sharpless asymmetric epoxidation strategy. Furthermore, our protocol has great potential for the generation of R207910 analogues. The process described herein is in the (unpatented) public domain and can be utilized for bulk scale production.

Experimental Section

General Remarks: Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in an oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene and diethyl ether from Na and benzophenone; CH_2Cl_2, quinoline, Et_3N from CaH_2; MeOH, EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^{2}g^{-1}. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) and coupling constants (*J*) are repo rted in Hertz [Hz]. The following abbreviations are used to designate signal multiplicity: s singlet, d doublet, t triplet, q quartet, m multiplet, br. broad.

Ethyl (*E*)-3-(6-Bromo-2-chloroquinolin-3-yl)acrylate (9): To a stirred solution of phosphonate $(EtO)_2P(O)CH_2CO_2Et$ (32.2 g, 140 mmol) in THF (200 mL) was added LiHMDS (138.0 mL, 38.0 mmol, 1.0 M) at 0 °C slowly for 30 min and stirred further for 30 min at room temperature. The above solution was cannulated to a solution of **8** (30.0 g, 11 mmol) in THF (50 mL) dropwise and stirred for 2 h. The reaction was quenched with water (100 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was silica gel chromatographed (eluent: ethyl acetate/hexane = 1:19) to give **9** as a white solid (33.2 g, 89%); m.p. 175 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.98 (s, 1 H, H4), 8.28 (d, *J* = 1.5 Hz, 1 H, H8), 8.03–7.86 (m, 3 H, H7, H5, H11), 6.83 (d, *J* = 16.0 Hz, 1 H, H12), 4.26 (q, *J* = 7.1 Hz, 2 H, H13), 1.29 (t, *J* = 7.1 Hz, 3 H, H14) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 165.2, 148.1, 145.6, 137.9, 136.6, 134.7, 130.3, 129.7, 128.0, 127.3, 123.4, 120.6, 60.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 1701 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{12}BrClNO_2$ [M + H]$^+$ 339.9734; found 339.9739.

(*E*)-3-(6-Bromo-2-chloroquinolin-3-yl)prop-2-en-1-ol (10): DIBAL-*H* (125.0 mL, 170.0 mmol, 1.4 M in hexane) was added slowly to α,β-unsaturated ester **9** (30.0 g, 88.0 mmol) in CH_2Cl_2 (150 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was carefully quenched with saturated aqueous Rochelle's salt (150 mL) at 0 °C and the resulting suspension was stirred vigorously for 4 h. The reaction mixture was filtered and the two layers separated. The aqueous layer was further extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was silica gel chromatographed (eluent: AcOEt/hexane = 1:5) to afford **10** as a pale yellow solid (22.0 g, 84%); m.p. 130 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.62 (s, 1 H, H4), 8.30–8.24 (m, 1 H, H8), 7.89–7.83 (m, 2 H, H7, H5), 6.94 (td, *J* = 15.6, 1.9 Hz, 1 H, H11), 6.64 (td, *J* = 15.6, 3.9 Hz, 1 H, H12), 5.16 (t, *J* = 4.8 Hz, 1 H, OH), 4.26 (br. s, 2 H, H13) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 149.4, 144.4, 137.5, 133.7, 133.2, 130.4, 129.8, 129.6, 128.5, 122.0, 120.2, 61.0 ppm. IR (KBr): $\tilde{\nu}$ = 3285 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{10}BrClNO$ [M + H]$^+$ 297.9629; found 297.9616.

(*E*)-3-(6-Bromo-2-methoxyquinolin-3-yl)prop-2-en-1-ol (11): To a solution of **10** (39.4 g, 130 mmol) in MeOH (150 mL), was added NaOMe (35.6 g, 650 mmol) and the resulting suspension was refluxed at 80 °C for 8 h. The solvent was evaporated under reduced pressure to give a crude solid which was quenched with water (100 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried with Na_2SO_4 and rotary evaporated. The crude product was silica gel chromatographed (eluent: AcOEt/hexane = 1:5) to furnish **11** as a pale yellow solid (35.1 g, 92%); m.p. 134 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.32 (s, 1 H, H4), 8.10 (d, J = 1.7 Hz, 1 H, H8), 7.75–7.64 (m, 2 H, H7, H5), 6.8 (d, J = 16.0 Hz, 1 H, H11), 6.63 (td, J = 16.0, 4.5 Hz, 1 H, H12), 5.04 (br. s, 1 H, OH), 4.21 (br. s, 2 H, H13), 4.04 (s, 3 H, H14) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 159.5, 143.4, 135.4, 133.0, 131.9, 129.3, 128.4, 126.6, 122.7, 121.1, 116.5, 61.4, 53.5 ppm. IR (KBr): $\tilde{\nu}$ = 3258 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{13}BrNO_2$ [M + H]$^+$ 294.0124; found 294.0120.

[(2*S*,3*S*)-3-(6-Bromo-2-methoxyquinolin-3-yl)oxiran-2-yl]methanol (7): Ti(O*i*Pr)$_4$ (2.0 mL, 0.68 mmol) in CH_2Cl_2 (20 mL) was added to a suspension of molecular sieves (4 Å, 7.0 g, 30% w/w based on substrate) in CH_2Cl_2 (20 mL). The mixture was cooled to –20 °C and L-(+)-diisopropyl tartrate (2.1 mL, 10 mmol) in CH_2Cl_2 (10 mL) was added and stirred for 30 min followed by **11** (20.0 g, 68.0 mmol) in CH_2Cl_2 (200 mL). The resulting suspension was stirred for 40 min at the same temperature. After this time anhydrous *tert*-butyl hydroperoxide in toluene (68.2 mL, 270 mmol, 4.0 M) was added dropwise and stirring continued for 4 h. After warming up to 0 °C, water (100 mL) was added and the mixture was stirred for 1 h. 20% Aqueous NaOH saturated with NaCl (50 mL) was added and stirring continued for 1.5 h. The slurry was filtered through a plug of Celite and rinsed thoroughly with CH_2Cl_2. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, and rotary evaporated. The crude product was silica gel chromatographed (eluent: AcOEt/hexane = 1:5) to obtain **7** as a white solid (18.1 g, 86%); m.p. 153 °C. $[\alpha]_D^{31}$ = –41.8 (c = 0.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3377, 3281 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.16 (d, J = 1.8 Hz, 1 H, H8), 7.99 (s, 1 H, H4), 7.78–7.67 (m, 2 H, H7, H5), 5.09 (t, J = 5.8 Hz, 1 H, OH), 4.11 (d, J = 1.7 Hz, 1 H, H11), 4.06 (s, 3 H, H14), 3.83 (ddd, J = 12.6, 5.4, 2.6 Hz, 1 H, H13), 3.61 (m, 1 H, H13′), 3.21–3.17 (m, 1 H, H12) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 160.1, 143.7, 133.0, 132.3, 129.6, 128.4, 126.1, 123.3, 116.6, 62.8, 60.3, 53.6, 50.3 ppm. HRMS (ESI) calcd. for $C_{13}H_{13}BrNO_3$ [M + H]$^+$ 310.0073; found 310.0088; HPLC [Chiralpak IC (250 × 4.6 mm, 5 μ), IPA/hexane, 1:10, flow 1.0 mL]: t_R = 10.8 min (minor), 15.4 min (major) 95% *ee*.

(2*R*,3*R*)-3-(6-Bromo-2-methoxyquinolin-3-yl)-3-phenylpropane-1,2-diol (12): To a suspension of CuCN (23.0 g, 250 mmol) in THF (150 mL) at –40 °C, PhMgBr (258.2 mL, 510 mmol, 2.0 M in Et_2O) was added. After stirring for 1 h, solution of **7** (16.0 g, 51.0 mmol) in THF (50 mL) was added dropwise via cannula. After 3 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (100 mL), diluted with ethyl acetate (100 mL) and allowed to stir for 3 h. The layers were separated and the aqueous layer extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water, brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude mixture was silica gel chromatographed (eluent: AcOEt/hexane = 1:4) to afford diol **12** as an off white solid (17.1 g, 86%); m.p. 110 °C. $[\alpha]_D^{26}$ = –133.5 (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, H4), 7.86 (d, J = 1.7 Hz, 1 H, H8), 7.67–7.58 (m, 2 H, H7, H5), 7.29–7.14 (m, 5 H, Ph), 4.47 (br. s, 2 H, H11, H12), 3.99 (s, 3 H, H14), 3.57 (m, 1 H, H13), 3.43 (m, 1 H, H13′), 2.82 (br. s, 1 H, OH), 2.50 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 143.8, 139.7, 135.0, 132.1, 129.3, 128.5, 128.4, 126.9, 126.7, 126.4, 117.1, 73.3, 64.8, 53.7, 47.4 ppm. IR (KBr): $\tilde{\nu}$ = 3374, 2924 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{19}BrNO_3$ [M + H]$^+$ 388.0543; found 388.0540.

(2*R*)-3-(6-Bromo-2-methoxyquinolin-3-yl)-1-(naphthalen-1-yl)-2-phenylethanol (14): To a solution of **12** (19.0 g, 49 mmol) in CH_2Cl_2 (400 mL) was added $NaIO_4$ impregnated over silica (20% w/w on silica, 150 g) and stirred for 1 h. The suspension was filtered and washed with CH_2Cl_2 (100 mL). The filtrate was evaporated under reduced pressure to give crude **13** (17.0 g, 98%) which was used immediately for the next reaction.

To a solution of **13** (16.5 g, 46 mmol) in diethyl ether (100 mL) at 0 °C was added freshly prepared naphthyl Grignard reagent (230 mL, 0.6 M in Et_2O, 139.0 mmol) and stirred for 1 h. The reaction was quenched with saturated aqueous solution of NH_4Cl and the aqueous layer extracted with diethyl ether (2 × 150 mL). The combined organic layers were washed with water, brine, dried with Na_2SO_4, and concentrated under reduced pressure. The inseparable mixture of diastereomers were silica gel chromatographed (eluent: ethyl acetate/hexane = 1:10) to give **14** as an off white solid (20.4 g, 92%).

(*R*)-2-(6-Bromo-2-methoxyquinolin-3-yl)-1-(naphthalen-1-yl)-2-phenylethanone (6): To a solution of **14** (20.3 g, 40.0 mmol) in CH_2Cl_2 (150 mL) was added Dess–Martin periodinane (25.4 g, 60.0 mmol). After being stirred at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine (150 mL), dried with Na_2SO_4 and rotary evaporated. The crude product was silica gel chromatographed (eluent: AcOEt/hexane = 1:10) to furnish **6** as a white solid (17.7 g, 87%); m.p. 168 °C. $[\alpha]_D^{28}$ = +217.9 (c = 0.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, J = 8.4 Hz, 1 H, H20), 8.04 (d, J = 7.2 Hz, 1 H, H8), 7.95 (d, J = 8.3 Hz, 1 H, H7), 7.85 (d, J = 7.6 Hz, 1 H, H17), 7.75 (d, J = 2.1 Hz, 1 H, H5), 7.71 (d, J = 8.9 Hz, 1 H, H16), 7.64 (dd, J = 8.9, 2.1 Hz, 1 H, H14), 7.60–7.33 (m, 9 H, H4, H19, H18, H15, Ph), 6.22 (s, 1 H, H11), 3.97 (s, 3 H, H23) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.9, 160.0, 144.3, 136.8, 136.0, 135.4, 133.9, 132.6, 132.3, 130.5, 129.6, 129.5, 129.3, 128.4, 128.3, 127.9, 127.8, 127.6, 126.8, 126.5, 126.4, 125.7, 124.2, 117.1, 57.2, 53.8 ppm. HRMS (ESI) calcd. for $C_{28}H_{21}BrNO_2$ [M + H]$^+$ 482.0750; found 482.0738; HPLC [Chiralpak IC (250 × 4.6 mm, 5 μ), IPA/hexane, 1:10, flow 1.0 mL]: t_R = 5.0 min (major), 6.2 min (minor) 95% *ee*.

(1*R*)-1-(6-Bromo-2-methoxyquinolin-3-yl)-1-(naphthalen-1-yl)-1-phenylpent-4-en-2-ol (5a and 5b): To a catalytic solution of CuBr·DMS in THF (50 mL) was added freshly prepared allylzinc bromide (14.9 g, 80.0 mmol) at room temperature and stirred for 10 min. Compound **6** (20.0 g, 40.0 mmol) was then added to it. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl solution (100 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and rotary evaporated. The crude product was silica gel chromatographed (eluent: AcOEt/hexane = 1:19) to give **5a** and **5b** as a white solid (19.4 g, 90%) (racemic). IR (KBr): $\tilde{\nu}$ = 3363 cm^{-1}. HRMS (ESI) calcd. for $C_{31}H_{27}BrNO_2$ [M + H]$^+$ 524.1220; found 524.1223.

(4*R*)-4-(6-Bromo-2-methoxyquinolin-3-yl)-3-(naphthalen-1-yl)-4-phenylbutane-1,3-diol (4a and 4b): To a solution of **5a** and **5b** (14.0 g, 26.0 mmol) in dioxane/water (3:1, 100 mL) were added 2,6-

lutidine (6.1 mL, 52.0 mmol), OsO_4 (27.2 mL, 0.4 mmol, 0.5% in toluene) and $NaIO_4$ (22.8 g, 106.0 mmol). After 2 h, water (20 mL) and CH_2Cl_2 (30 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude **15a** and **15b** was used for the next reaction without purification.

To a stirred solution of **15a** and **15b** in MeOH (150 mL) was added $NaBH_4$ (1.2 g, 28.0 mmol) at 0 °C and stirred at room temperature for 2 h. The reaction was quenched with water (50 mL) and methanol was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and rotary evaporated. The crude product was silica gel chromatographed (eluent: AcOEt/hexane = 1:10) to obtain **4a** and **4b** as a white solid (11.2 g, 82% over 2 steps). IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1}. HRMS (ESI) calcd. for $C_{30}H_{27}BrNO_3$ $[M + H]^+$ 528.1169; found 528.1177.

(4*R*)-4-(6-Bromo-2-methoxyquinolin-3-yl)-3-hydroxy-3-(naphthalen-1-yl)-4-phenylbutylmethane-Sulfonate (16a and 16b): To a solution of **4a** and **4b** (10.6 g, 20.1 mmol) in CH_2Cl_2 (70 mL) were added Et_3N (5.4 mL, 40.2 mmol) and methanesulfonyl chloride (2.0 mL, 26.1 mmol) sequentially at 0 °C. After stirring for 3 h at room temperature, water (40 mL) was added to quench the reaction. The reaction mixture was diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was silica gel chromatographed (eluent: AcOEt/hexane = 1:5) to afford **16a** and **16b** as a white solid (10.5 g, 88%). IR (KBr): $\tilde{\nu}$ = 3432 cm^{-1}. HRMS (ESI) calcd. for $C_{31}H_{29}BrNO_5S$ $[M + H]^+$ 606.0944; found 606.0955.

(1*R*,2*S*)-1-(6-Bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbut-an-2-ol (3a): A solution of **16a** and **16b** (6.0 g, 10.2 mmol) in Me_2NH (200 mL, 8.0 M in THF) was stirred at 45 °C for 24 h. The solution was filtered and the filtrate concentrated under reduced pressure to afford the crude product which on purification by silica gel column chromatography (eluent: ethyl acetate/hexane = 1:6) furnished **3a** and **3b** as white solids (4.8 g, 90%) (1:1 w/w). **3a**: M.p. 104 °C. $[\alpha]_D^{25}$ = –165.2 (*c* = 0.8, DMF). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.89 (s, 1 H, H4), 8.61 (d, *J* = 8.6 Hz, 1 H, H20), 7.96 (d, *J* = 2.0 Hz, 1 H, H5), 7.92 (d, *J* = 7.4 Hz, 1 H, H14), 7.87 (d, *J* = 8.1 Hz, 1 H, H17), 7.72 (d, *J* = 8.8 Hz, 1 H, H8), 7.68–7.56 (m, 3 H, H7, H16, H19), 7.48 (t, *J* = 7.6 Hz, 1 H, H18), 7.30 (t, *J* = 7.7 Hz, 1 H, H15), 7.17–7.10 (m, 2 H, H24), 6.93–6.83 (m, 3 H, H25, H26), 5.89 (s, 1 H, H11), 4.21 (s, 3 H, H30), 2.60–2.51 (m, 1 H, H27), 2.18–2.02 (m, 2 H, H27′, H28), 1.99 (s, 6 H, H29), 1.95–1.85 (m, 1 H, H28′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3, 143.7, 141.6, 140.5, 138.7, 134.6, 131.9, 129.9, 129.8, 129.7, 128.4, 128.1, 127.8, 127.3, 127.1, 126.8, 125.7, 125.2, 125.1, 125.0, 124.4, 116.9, 82.4, 56.2, 54.1, 49.5, 44.6, 33.4, 29.6 ppm. IR (KBr): $\tilde{\nu}$ = 3441 cm^{-1}. HRMS (ESI) calcd. for $C_{32}H_{32}BrN_2O_2$ $[M + H]^+$ 555.1642; found 555.1671.

(1*R*,2*R*)-1-(6-Bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (3b): M.p. 145 °C. $[\alpha]_D^{25}$ = +41.2 (*c* = 0.31, DMF). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (s, 1 H, H4), 8.48 (d, *J* = 8.7 Hz, 1 H, H20), 7.99 (dd, *J* = 7.4, 0.9 Hz, 1 H, H14), 7.88 (d, *J* = 7.3 Hz, 2 H, H24), 7.82–7.75 (m, 2 H, H17, H5), 7.60–7.50 (m, 2 H, H19, H16), 7.47–7.32 (m, 4 H, H8, H25, H7, H18), 7.30–7.21 (m, 2 H, H26, H15), 5.73 (s, 1 H, H11), 3.25 (s, 3 H, H30), 2.49 (td, *J* = 14.3, 3.0 Hz, 1 H, H27), 2.26 (dt, *J* = 12.2, 3.2 Hz, 1 H, H27′), 2.14–1.90 (m, 9 H, H28, H28′, H29) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 143.2, 141.6, 141.1, 137.8, 134.6, 131.2, 130.0, 129.6, 129.5, 128.1, 128.0, 127.9, 127.6, 127.4, 127.1, 126.5, 126.4, 125.4, 124.9, 124.8, 124.3, 116.2, 81.5, 56.1, 52.7, 50.9, 44.5, 34.1, 29.6 ppm. HRMS (ESI) calcd. for $C_{32}H_{32}BrN_2O_2$ $[M + H]^+$ 555.1642; found 555.1659.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for new compounds.

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