Supporting Information for:

The Resolution of Important Pharmaceutical Building Blocks by Palladium Catalyzed Aerobic Oxidation of Secondary Alcohols

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Materials and Methods.

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized using a combination of UV, anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral HPLC was performed on a Chiralcel OJ, AD, or OB-H column (each is 4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical achiral GC was performed using an Agilent DB-WAX (30.0 m x 0.25 m) column. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-1010 polarimeter. High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI.

Table SI1. Methods for Determination of Enantiomeric Excess.

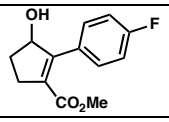
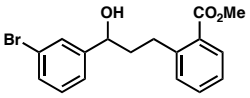
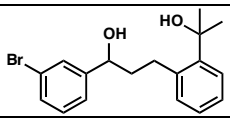
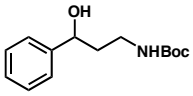
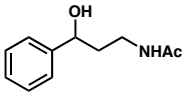
Entry	Substrate	HPLC Assay	Conditions	Retention Time (min)	
				(*R*)-isomer	(*S*)-isomer
1.		Chiralcel OB-H	5% EtOH/hexanes 1.0 mL/min 254 nm	22.3	18.2
2.		Chiralcel AD	5% EtOH/hexanes 1.0 mL/min 254 nm	15.8	17.1
3.		Chiralcel OJ	5% EtOH/hexanes 1.0 mL/min 210 nm	17.8	15.0
4.		Chiralcel OJ	8% 2-propanol/hexanes 1.0 mL/min 210 nm	10.5	20.1
5.		Chiralcel AD	6% 2-propanol/hexanes 1.0 mL/min 210 nm	27.9	23.8

Table SI2. Methods for Determination of % Conversion.

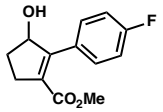
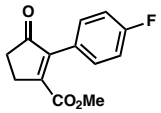
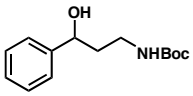
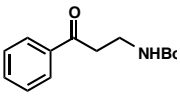
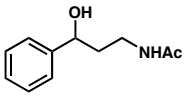
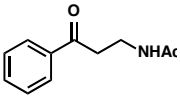
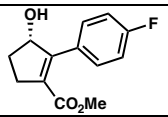
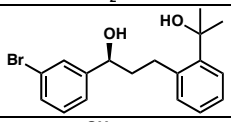
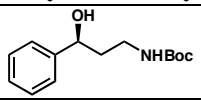
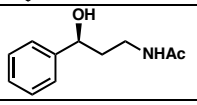
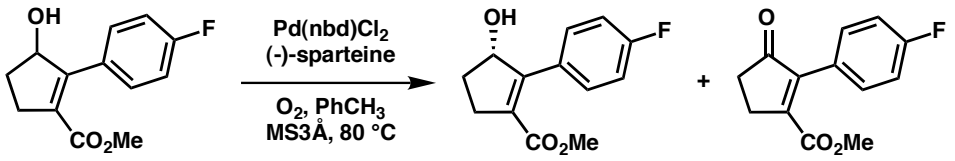
Entry	Substrate	Ketone	GC Conditions	Retention Time (min)	
				Alcohol	Ketone
1.			70 °C, 15 min; 7 °C/min to 240 °C; hold 20 min 1.0 mL/min carrier gas flow	44.4	42.0
2.			70 °C, 15 min; 7 °C/min to 240 °C; hold 20 min 1.0 mL/min carrier gas flow	48.1	42.2
3.			70 °C, 15 min; 7 °C/min to 240 °C; hold 20 min 1.0 mL/min carrier gas flow	53.5	45.1

Table SI3. Optical Rotations for New Compounds.

Entry	Substrate	Rotation
1.		$[\alpha]^{22}_{D}$ = -37.2° (c 0.1, MeOH) lit[4]: $[\alpha]_{D}$ = -186.6° (c 0.01, MeOH)
2.		$[\alpha]^{26}_{D}$ = -31.7° (*c* 1.0, benzene)*
3.		$[\alpha]^{25}_{D}$ = -15.4° (*c* 1.0, $CHCl_3$)*
4.		$[\alpha]^{25}_{D}$ = -23.6° (*c* 1.3, $CHCl_3$)**

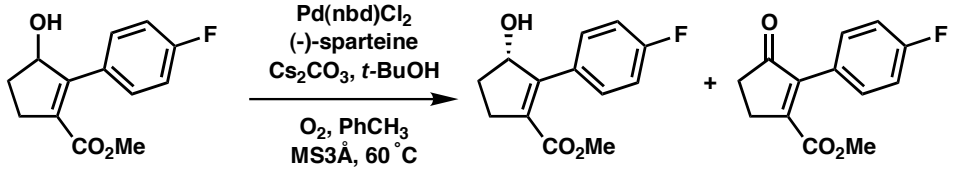
* absolute configuration assigned by conversion to known compounds
** absolute configuration assigned by analogy

Representative Procedures for Oxidative Kinetic Resolutions



8 ***8*** ***14***

Kinetic Resolution Conditions A: "Original Conditions".[1] To an oven dried reaction tube with stir bar was added oven dried powdered 3Å molecular sieves (250 mg). After cooling, $Pd(nbd)Cl_2$ (6.7 mg, 0.025 mmol) followed by toluene (2.5 mL) and then (-)-sparteine (23.4 mg, 23 μL, 0.10 mmol) were added. The reaction tube was then vacuum evacuated and purged with O_2 (3x), and the tube was heated to 80 °C with vigorous stirring under O_2 atmosphere (1 atm) for 20 min. A solution of allylic alcohol **8** (118.1 mg, 0.50 mmol) in toluene (2.5 mL) was added, and the reaction was allowed to proceed under O_2 atmosphere (1 atm) at 80 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **14** and enantioenriched alcohol **8** was accomplished by direct chromatography of the crude reaction mixture.

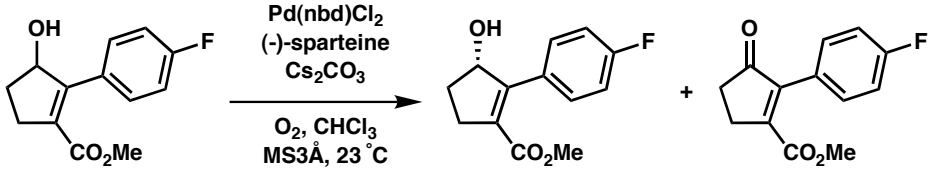


8 ***8*** ***14***

Kinetic Resolution Conditions B: "Rate Accelerated Conditions".[2] To an oven dried reaction tube with stir bar was added oven dried powdered 3Å molecular sieves (500 mg). After cooling, $Pd(nbd)Cl_2$ (13.5 mg, 0.05 mmol), followed by toluene (2 mL) and then (-)-sparteine (46.9 mg, 46 μL, 0.20 mmol) were added. The reaction tube was then vacuum evacuated and purged with

[1] Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725.

O_2 (3x), and the tube was heated (60 °C) with vigorous stirring under O_2 atmosphere (1 atm) for 20 min. Finely powdered anhydrous Cs_2CO_3 (162.9 mg, 0.50 mmol) was added, followed by a solution of allylic alcohol **8** (236.3 mg, 1.0 mmol), *t*-butanol (111.2 mg, 143 μL, 1.5 mmol) and toluene (2 mL). The reaction was allowed to proceed under O_2 atmosphere (1 atm) at 60 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **14** and enantioenriched alcohol **8** was accomplished by direct chromatography of the crude reaction mixture.



8 ***8*** ***14***

Kinetic Resolution Conditions C: "Chloroform Conditions".[3] To an oven dried reaction tube with stir bar was added oven dried powdered 3Å molecular sieves (500 mg). After cooling, $Pd(nbd)Cl_2$ (13.5 mg, 0.05 mmol), followed by chloroform (2 mL, stabilized with amylenes) and then (-)-sparteine (28.1 mg, 27.6 μL, 0.12 mmol) were added. The reaction tube was then vacuum evacuated and purged with O_2 (3x), and the reaction was stirred vigorously at 23 °C under O_2 atmosphere (1 atm) for 15 min. Finely powdered anhydrous Cs_2CO_3 (130.3 mg, 0.40 mmol) was added, followed by a solution of allylic alcohol **8** (236.3 mg, 1.0 mmol) in chloroform (2 mL). The reaction was allowed to proceed under O_2 atmosphere (1 atm) at 23 °C. Aliquots were filtered through a small plug of silica gel (Et_2O eluent), evaporated, and analyzed. Purification of ketone **14** and enantioenriched alcohol **8** was accomplished by direct chromatography of the crude reaction mixture.

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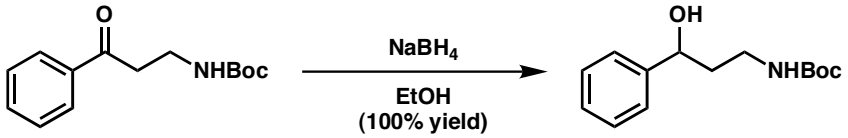
[2] Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835.
[3] Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2003**, *42*, *In Press*.

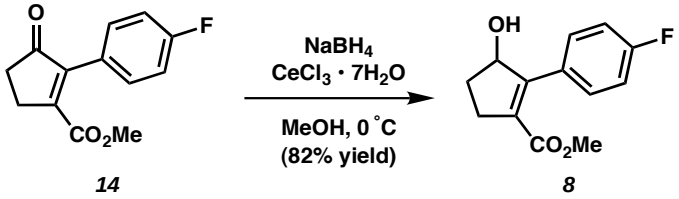
Representative Procedure for Ketone Recycling



11a *6a*

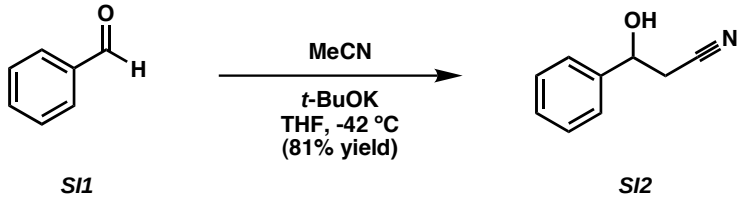
Carbamate 6a. To keto-carbamate **11a** (113.3 mg, 0.45 mmol) in EtOH (2.0 mL) was added $NaBH_4$ (40.0 mg, 1.0 mmol) at 0 °C. After stirring for 3 hr and allowing the reaction to warm to 23 °C, saturated aq. NH_4Cl was added dropwise at 0 °C. The mixture was diluted with EtOAc (1 mL) and H_2O (1 mL) and the phases were partitioned. The aqueous phase was extracted with EtOAc (3 x 1 mL). The organic extracts were combined and passed over a small plug of silica gel (EtOAc eluent). The solvent was removed *in vacuo* to afford carbamate **6a** (113.8 mg, 100% yield).

Substrate Synthesis



14 *8*

Methyl 2-(4-Fluorophenyl)-3-hydroxycyclopent-1-enecarboxylate 8. To a cooled (0 °C) solution of enone **14**[4] (125 mg, 0.53 mmol) in methanol (10.6 mL) was added $CeCl_3 \bullet 7H_2O$ (218 mg, 0.59 mmol). The solution was allowed to stir for 10 min, after which $NaBH_4$ (40.3 mg, 1.06 mmol) was added in small portions over 5 min. After warming to 23 °C, the solvent was removed under reduced pressure to give a white solid. The solid was treated with H_2O (20 mL), and after stirring the slurry for 30 min, the mixture was extracted with EtOAc (4 x 25 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography (4:1 hexanes:EtOAc) afforded allylic alcohol **8** (103 mg, 82% yield) as a pale yellow oil. R_f 0.11 (4:1 hexanes:EtOAc); characterization data for this compound have been previously reported.[4]

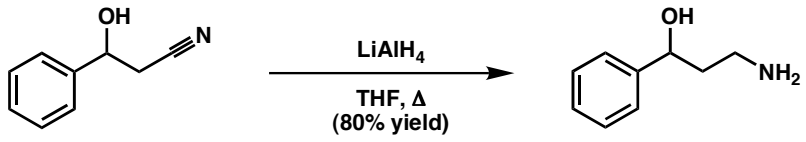


SI1 *SI2*

Nitrile SI2.[5] A flask charged with THF (100 mL) and acetonitrile (3.2 mL, 57.1 mmol) was cooled to –42 °C and treated dropwise with a solution of *t*-BuOK (7.1 g, 63.3 mmol) in THF (25 mL). After stirring for 45 min, freshly distilled benzaldehyde (**SI1,** 5.7 mL, 56.4 mmol) was added dropwise. The reaction was allowed to warm to –15 °C over a 4 hr period, and then was quenched

[4] Kuethe, J. T.; Wong, A.; Wu, J.; Davies, I.W.; Dormer, P.G.; Welch, C.J.; Hillier, M.C.; Hughes, D.L.; Reider, P.J. *J. Org. Chem.* **2002**, *67*, 5993-6000.

by slow addition of saturated aq. NH_4Cl (35 mL). The layers were partitioned, and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organics were washed with H_2O (2 x 20 mL) and saturated aq. NaCl (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was flash chromatographed (1:1 Et_2O:hexanes eluent) to give nitrile **SI2** (6.69 g, 81% yield) as a colorless oil. R_f 0.16 (1:1 Et_2O:hexanes); characterization data for this compound have been previously reported.[6]



SI2 *10*

Amino alcohol 10. A flask was charged with a suspension of $LiAlH_4$ (2.92 g, 77.0 mmol) in THF (100 mL). After cooling to 0 °C, the suspension was treated with nitrile **SI2** (4.54 g, 30.9 mmol) dropwise, and the resulting brown mixture was heated to reflux for 5 hr. The reaction was cooled to 0 °C, and quenched by slow addition of H_2O (3 mL), followed by 15% *w/v* aq. NaOH (3 mL), and finally by H_2O (9 mL). The crude green sludge was vacuum filtered and washed well with Et_2O. The filtrate was concentrated under reduced pressure to a green oil, and partitioned between EtOAc (100 mL) and 15% *w/v* aq. NaOH (30 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated *in vacuo* to afford amino alcohol **10** (3.74 g, 80% yield) as a dark orange oil, which was used without further purification. R_f 0.0 (1:1 EtOAc:hexanes); characterization data for this compound have been previously reported.[6]

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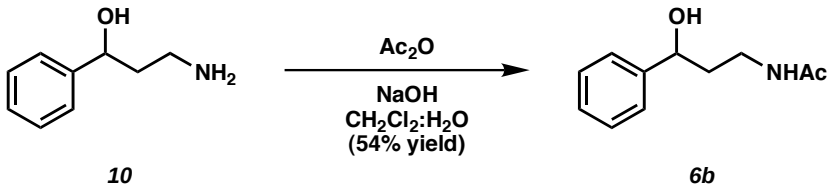
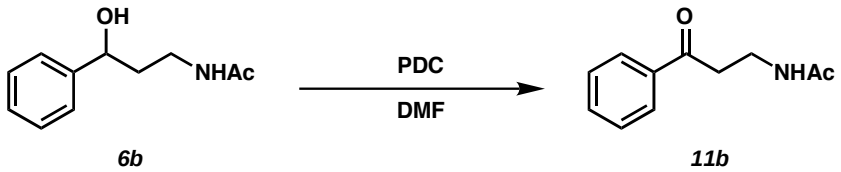
[5] Koenig, T.M.; Mitchell, D. *Tetrahedron Lett*. **1994**, *35(9)*, 1339-1342.
[6] Mitchell, D.; Koenig, T.M. *Synthetic Comm.* **1995**, *25(8)*, 1231-1238.



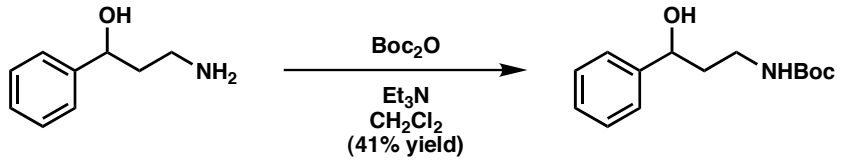
10 ***6b***

Acetamide 6b. To amino alcohol **10** (1.61 g, 10.6 mmol) in CH_2Cl_2 (17 mL) and aq. 1.4 N NaOH (17 mL, 23.8 mmol) was added acetic anhydride (1.3 mL, 13.8 mmol) at 23 °C. After the biphasic reaction was stirred for 5 hr, the layers were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were washed with H_2O (15 mL) and saturated aq. NaCl (15 mL), then dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude material was passed over a short plug of silica gel (20:1 CH_2Cl_2:MeOH eluent). After concentrating to a yellow oil, the crude product was precipitated with hexanes:Et_2O (10:1, 10 mL), and evaporated *in vacuo* to yield a yellow solid. The solid was triturated with pentane:Et_2O (12:1), and collected by suction filtration to afford acetamide **6b** (1.10 g, 54% yield) as a pale yellow solid. R_f 0.50 (9:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 5.96 (br s, 1H), 4.72 (dd, J = 7.4 Hz, 5.8 Hz, 1H), 3.73-3.59 (m, 1H), 3.28-3.14 (m, 1H), 3.19 (br s, 1H), 1.97 (s, 3H), 1.90-1.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 144.4, 128.6, 127.5, 125.8, 72.0, 39.0, 37.0, 23.3; IR (film): 3295 (br), 1651, 1556 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{11}H_{16}NO_2$, 194.1181; found, 194.1190.



6b ***11b***

Keto-Acetamide 11b. Compound **11b** was prepared in an analogous manner to keto-carbamate **11a**. The characterization data for this compound have been previously reported by Knochel.[7]

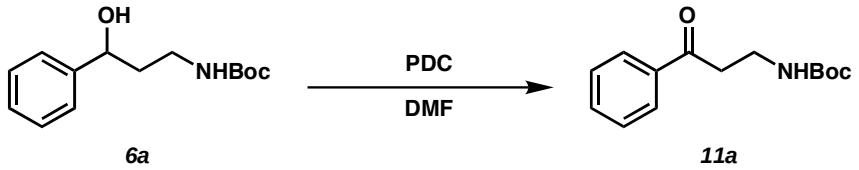


10 ***6a***

Carbamate 6a. To amino alcohol **10** (2.14 g, 14.1 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (2.8 mL, 20.1 mmol) over 1-2 min at 23 °C, followed by Boc_2O (3.09 g, 14.2 mmol). The reaction was stirred for 2 hr, then quenched by addition of saturated aq. NH_4Cl (15 mL). The phases were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The organic extracts were combined, washed with saturated aq. $NaHCO_3$ (15 mL), H_2O (15 mL), and saturated aq. NaCl (15 mL), and dried over $MgSO_4$. The crude product was evaporated *in vacuo*, and passed over a short plug of silica gel (20:1 CH_2Cl_2:MeOH eluent). A solid was precipitated from the residue by treatment with hexanes:Et_2O (10:1, 10 mL), and then resulting suspension was taken to dryness *in vacuo*. This material was then recrystallized from hexanes:Et_2O (10:1, 10 mL), filtered, and rinsed with ice-cold pentane (3 x 5 mL) to afford carbamate **6a** (1.44 g, 41% yield) as a white solid. R_f 0.60 (7:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H), 4.84 (br s, 1H), 4.77-4.69 (m, 1H), 3.55-3.36 (m, 1H), 3.22-3.09 (m, 1H), 2.94 (br s, 1H), 1.88-1.80 (m, 2H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 144.5, 128.6, 127.6, 125.8, 79.8, 71.9, 39.8, 37.8,

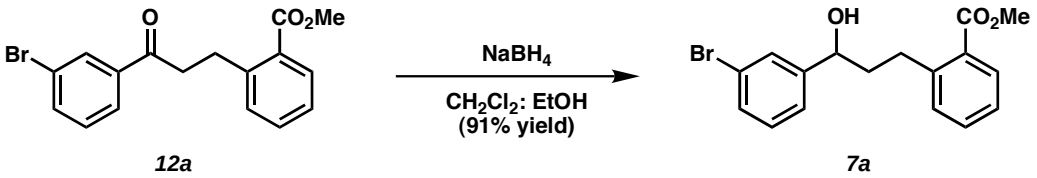
[7] Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H.P.; Berger, S.; Knochel, P. *Tetrahedron*. **1994**, *50(8)*, 2415-2432.

28.6; IR (film) 3360 (br), 1688, 1515, 1281, 1252, 1170 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ calc'd for $C_{14}H_{22}NO_3$, 252.1600; found, 252.1600.



6a ***11a***

Keto-Carbamate 11a. To carbamate **6a** (27.5 mg, 0.11 mmol) in DMF (2 mL) was added pyridinium dichromate (237 mg, 0.63 mmol) at 23 °C. After 10 hr, the reaction mixture was diluted in Et_2O (5 mL) and brine (5 mL), and the phases were partitioned. The aqueous phase was extracted with Et_2O (2 x 5 mL), and the organic extracts were combined, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed (20:1 hexanes:EtOAc → 10:1 hexanes:EtOAc eluent) to afford keto-carbamate **11a** as a solid, which was used as an authentic standard to confirm the oxidative kinetic resolution product of carbamate **6a**. R_f 0.50 (1:1 EtOAc:hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-7.90 (m, 2H), 7.61-7.51 (m, 1H), 7.49-7.39 (m, 2H), 5.13 (br s, 1H), 3.53 (q, *J* = 5.9 Hz, 2H), 3.19 (t, *J* = 5.5 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 156.1, 136.7, 133.6, 128.8, 128.1, 79.3, 38.8, 35.6, 28.5; IR (film) 1682, 1506, 1172 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ calc'd for $C_{14}H_{20}NO_3$, 250.1443; found, 250.1441.

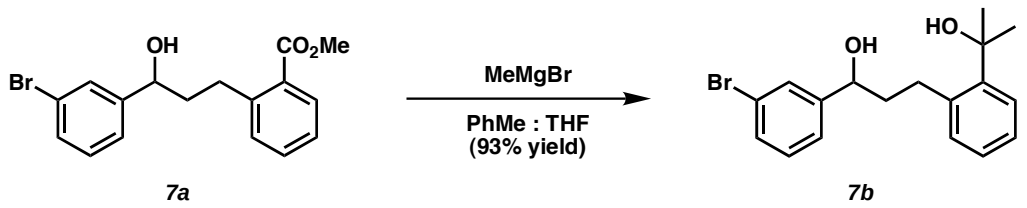


12a *7a*

Bromo Methyl Ester 7a. To 2-[3-(3-Bromophenyl)-3-oxoproyl]benzoic Acid Methyl Ester[8] (**12a**, 1.763 g, 5.08 mmol), previously described by Larsen, et al.,[9] in EtOH (12 mL) and CH_2Cl_2 (12 mL), was added $NaBH_4$ (208.8 mg, 5.52 mmol) portionwise over a 5 min period at 0° C. The reaction was stirred for 3.5 hr at °C, then quenched by slow addition of 0.1 N HCl (45 mL). After stirring 30 min, the mixture was poured over CH_2Cl_2 (75 mL) and the phases were partitioned. The aqueous phase was extracted with CH_2Cl_2 (75 mL), and the organic extracts were combined, washed with H_2O (15 mL) and brine (15 mL), and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the crude product was chromatographed (7:1 hexanes:EtOAc eluent) to provide the product as a viscous oil. The residual solvent was removed by lyophilization from benzene to afford bromo methyl ester **7a** (1.61 g, 91% yield) as a white to off-white solid. R_f 0.44 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (app. dd, J = 8.1 Hz, 1.5 Hz, 1H), 7.50 (app. t, J = 1.7 Hz, 1H), 7.46-7.33 (m, 2H), 7.28-7.14 (m, 4H), 4.64 (app. t, J = 6.2 Hz), 3.87 (s, 3H), 3.16-2.97 (m, 3H), 2.06-1.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 147.2, 143.7, 132.4, 131.2, 130.9, 130.3, 130.0, 129.2, 129.0, 126.2, 124.5, 122.6, 72.6, 52.5, 41.6, 30.4; IR (film) 3460 (br), 1722, 1263, 1083 cm^{-1}; HRMS-EI *m/z*: $[M - H]^+$ calc'd for $C_{17}H_{16}BrO_3$, 347.0283; found, 347.0274.

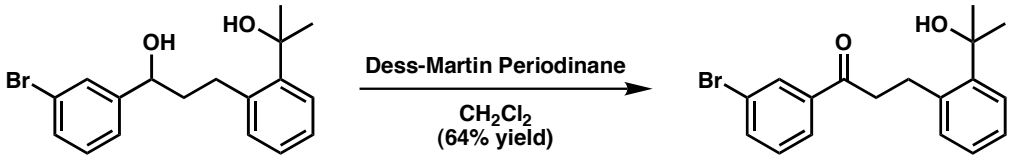
[8] In our hands, the benzofuranone reduction with Wilkinson's catalyst[9] did not proceed as reported unless the starting material was further purified. This could be accomplished by filtering the benzofuranone in boiling EtOAc to remove insoluble impurities. Additionally, the product obtained after the benzofuranone reduction did not match the reported values for the benzoic acid; however, brief exposure to acidic MeOH (conditions for the subsequent reaction) quantitatively converted it to the reported compound.

[9] Larsen, R.D. et al. *J. Org Chem.* **1996**, *61*, 3398-3405.



7a *7b*

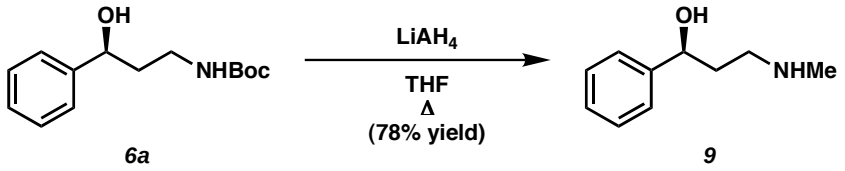
Bromo Diol 7b. To bromo methyl ester **7a** (1.502 g, 4.30 mmol) in THF (9 mL) and toluene (9 mL) was added MeMgBr (2.78 M in Et_2O, 8.5 mL, 23.4 mmol) in a rapid dropwise fashion at 10 °C. The solution was stirred at 23 °C for 3.5 hr after the addition was complete, then quenched by slow addition of saturated aq. NH_4Cl. The resulting mixture was poured over Et_2O (50 mL) and brine (25 mL). The organic phase was dried over $MgSO_4$, and chromatographed (7:1 hexanes:EtOAc → 3:1 hexanes:EtOAc). The fractions containing the methyl ketone (slightly higher R_f than the desired product) were evaporated *in vacuo* and resubjected to the initial reaction conditions. After purification in the same manner described above, all of the product containing fractions were combined and evaporated *in vacuo*. The viscous oil was lyophilized from benzene to provide bromo diol **7b** (1.39 g, 93% combined yield) as a white to off-white solid. R_f 0.33 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (app. s, 1H), 7.37-7.31 (m, 2H), 7.26-7.09 (m, 5H), 4.61 (dd, J = 8.6 Hz, 4.1 Hz, 1H), 3.26-3.14 (m, 1H), 3.12-3.01 (m, 1H), 2.21 (br s, 1H), 2.15-1.95 (m, 3H), 1.67 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 144.9, 140.0, 131.4, 130.3, 130.0, 129.1, 127.4, 125.8, 125.6, 124.5, 122.6, 74.5, 72.5, 42.2, 32.4, 32.3, 29.7; IR (film) 3356 (br), 1069 cm^{-1}; HRMS-EI *m/z*: $[M - H]^+$ calc'd for $C_{18}H_{20}BrO_2$, 349.0628; found, 349.0631.



7b ***12b***

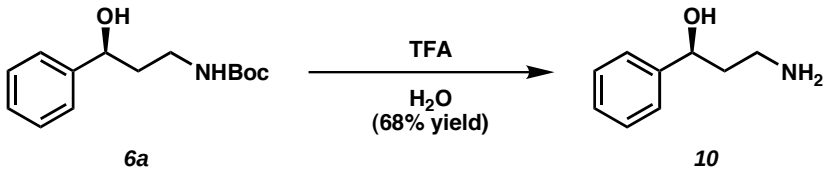
Bromo Hydroxy Propanone 12b. To bromo diol **7b** (51.6 mg, 0.15 mmol) in CH_2Cl_2 (2.5 mL) was added Dess-Martin Periodinane (70.7 mg, 0.17 mmol). The mixture was stirred for 3 hr at 23 °C, and then chromatographed directly (1:1 Et_2O:pentane eluent) to provide bromo hydroxy propanone **12b** (33.0 mg, 64% yield) as a solid. This product was used as an authentic standard to confirm the oxidative kinetic resolution product of bromo diol **7b**. R_f 0.60 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 8.06 (app. t, *J* =1.7 Hz, 1H), 7.86-7.81 (m, 1H), 7.57 (app. ddd, 1H, *J* =7.7 Hz, 1.6 Hz, 1.1 Hz, 1H), 7.25-7.20 (m, 1H), 7.11-6.98 (m, 3H), 6.65 (app. td, *J* = 10.8 Hz, 3.9 Hz), 3.43 (app. t, *J* = 7.7 Hz, 2H), 2.98-2.91 (m, 2H), 1.44-1.41 (m, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.1, 146.4, 140.5, 139.5, 136.0, 132.2, 131.8, 130.6, 127.7, 127.1, 126.4, 126.4, 123.4, 73.8, 42.4, 32.6 (2C), 29.2; IR (film) 3452 (br), 1684, 1198 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ for $C_{18}H_{20}O_2Br$ calc'd, 347.0647; found, 347.0632.

Derivative Synthesis



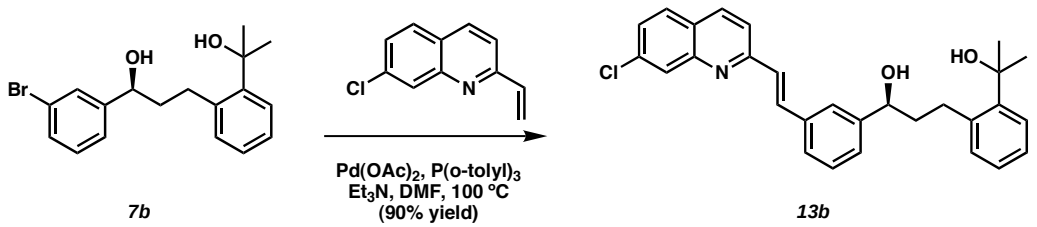
6a *9*

(*S*)-Methyl Amine 9. To a suspension of $LiAlH_4$ (56.8 mg, 1.5 mmol) in THF (1.5 mL) was added enantioenriched carbamate **6a** (47.5 mg, 0.19 mmol). The reaction was heated to reflux for 5.5 hr, and then quenched at 0 °C by slow addition of H_2O (50 μL), followed by 15% *w/v* aq. NaOH (50 μL), and finally by H_2O (150 μL). The mixture was filtered, and the filter cake was rinsed well with Et_2O. The filtrate was evaporated under reduced pressure, diluted in CH_2Cl_2 (1 mL), rinsed with saturated aq. NaCl (0.5 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, which provided methyl amine **9** (24.5 mg, 78% yield) as an oil. $[\alpha]^{26}_D$ = -33.7° (*c* 0.81, $CHCl_3$). lit[10]: $[\alpha]^{23}_D$ = -37.4° (*c* 1%, $CHCl_3$).



6a *10*

(*S*)-Amino Alcohol 10. To enantioenriched carbamate **6a** (25.2 mg, 0.1 mmol) was added a mixture of trifluoroacetic acid (1.0 mL) and H_2O (0.2 mL). The solution was stirred at 23 °C for 48 hr, and then the volatiles were removed *in vacuo*. The aqueous residue was made basic using 5N NaOH (1 mL), and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated *in vacuo* to afford title compound **10** (10.2 mg, 68% yield) as a solid. Characterization data for this compound have been previously reported.[6] $[\alpha]^{25}_D$ = -40.5 ° (*c* 0.5, MeOH). lit[6:] $[\alpha]^{25}_D$ = -43.65° (*c* 1, MeOH).



7b *13b*

(*S*)-Chloroquinoline Diol 13b.[11,12] To enantioenriched bromo diol **7b** (41.6 mg, 0.12 mmol) was added $Pd(OAc)_2$ (1.9 mg, 0.008 mmol), $P(o\text{-tolyl})_3$ (10.8 mg, 0.035 mmol), 2-ethenyl-7-chloroquinoline[9] (23.9 mg, 0.12 mmol), and DMF (0.35 mL). The dark mixture was degassed three times using the freeze-pump-thaw technique, and then Et_3N (40 μL, 0.29 mmol) was added. The reaction was heated to 100 °C for 3 hr, then cooled to 23 °C. The crude mixture was chromatographed directly (9:1 hexanes:EtOAc → 3:1 hexanes:EtOAc eluent). The desired chloroquinoline diol **13b** (49.2 mg, 90% yield) was obtained as a solid after evaporation of solvent under reduced pressure and lyophilization from benzene. R_f 0.11 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) 8.32 (app. d, J = 1.6 Hz, 1H), 7.82 (app. d, J = 16.5 Hz, 1H), 7.69 (app. s, 1H), 7.42-7.31 (m, 4H), 7.29-7.00 (m, 8H), 4.68 (dd, 1H, J = 8.2 Hz, 4.4 Hz, 1H), 3.97 (br s, 1H), 3.45-3.32 (m, 1H), 3.21-3.10 (m, 1H), 2.96 (br s, 1H), 2.23-2.09 (m, 2H), 1.50 (s, 1H), 1.48 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6, 28/29 C) 157.5, 149.5, 146.8, 146.1, 141.1, 137.1, 136.2, 136.0, 135.9, 132.2, 129.3, 129.3, 129.0, 129.0, 128.9, 127.8, 127.3, 126.8, 126.3, 126.2, 125.8, 120.4, 74.3, 73.4, 43.0, 32.6, 32.4, 30.4; IR (film) 3361 (br), 1607, 1498 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ calc'd for $C_{29}H_{29}NO_2Cl$, 458.1887; found, 458.1886.

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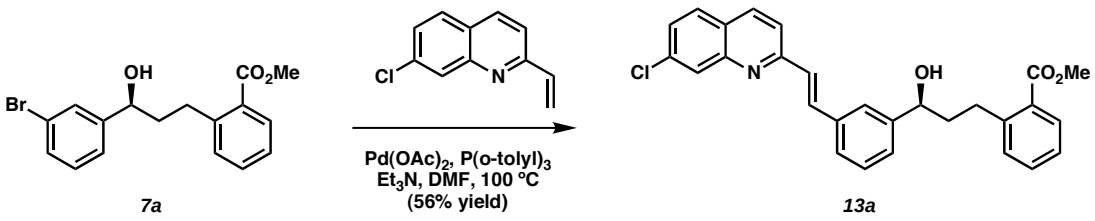
[10] Robertson, D.W.; Krushinski, J.H.; Fuller, R.W.; Leander, J.D. *J. Med. Chem.* **1988,** *31*(7), 1412-1417.
[11] O'Brian, T. et al. *Anal. Chem.* **1997**, *69(11)*, 1999-2007.
[12] The NMR characterization data have been previously reported in $CDCl_3$. In our hands, these compounds slowly decomposed in $CDCl_3$, so we have reported these data in C_6D_6.



(*S*)-Chloroquinoline Methyl Ester 13a.[12,13] To enantioenriched bromo methyl ester **7a** (83.8 mg, 0.24 mmol) was added $Pd(OAc)_2$ (3.0 mg, 0.013 mmol), $P(o\text{-tolyl})_3$ (12.7 mg, 0.042 mmol), 2-ethenyl-7-chloroquinoline[9] (47.0 mg, 0.25 mmol), and DMF (0.7 mL). The dark mixture was degassed three times using the freeze-pump-thaw technique, and then Et_3N (93 μL, 0.67 mmol) was added. The reaction was heated to 100 °C for 3 hr, then cooled to 23 °C. The crude mixture was diluted with EtOAc (2 mL) and H_2O (2 mL). The phases were partitioned, and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried by passage over a short plug of silica gel (EtOAc eluent), and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (5:1 hexanes:EtOAc eluent). The desired chloroquinoline methyl ester **13a** (62.0 mg, 56% yield) was obtained as a solid after evaporation of solvent under reduced pressure, and lyophilization from benzene. R_f 0.21 (3:2 hexanes:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) 8.35 (app. d, J = 1.6 Hz, 1H), 7.92-7.85 (m, 2H), 7.68 (s, 1H), 7.43-7.36 (m, 3H), 7.29-6.89 (m, 8H), 4.67 (t, J = 5.8 Hz, 1H), 3.43 (s, 3H), 3.30-3.10 (m, 2H), 2.65 (br s, 1H), 2.11 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6, 27/28 C) 168.5, 157.5, 149.7, 146.9, 145.1, 137.2, 136.1, 136.0, 132.7, 131.9, 131.5, 130.2, 129.3, 129.3, 129.1, 128.9, 127.3, 127.1, 126.7, 126.5, 126.2, 125.7, 120.6, 73.6, 52.0, 42.5, 31.2; IR (film) 3407 (br), 1719, 1607, 1497, 1258 cm^{-1}; HRMS-FAB *m/z*: $[M + H]^+$ calc'd for $C_{28}H_{25}NO_3Cl$, 458.1523; found, 458.1517.

[13] King, A.O. et al. *J. Org. Chem.* **1993**, *58(14)*, 3731-3735.