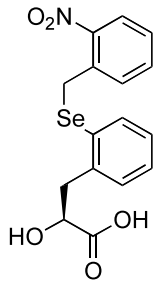
# APPENDIX 3: Synthetic Routes Considered for the Preparation of the Key Aryl Selenide α-Hydroxy Acid in Chapter 6

## A3.1 RESULTS AND DISCUSSION

This appendix describes three synthetic routes for the preparation of α-hydroxy acid **1**, which was an important structure in Chapter 6. The first route was proposed by Dr. Amy L. Eastwood (Dougherty lab) and is illustrated in the retro-synthetic pathway shown in **Figure A3.1**.[1] The key step in this route is the insertion of elemental selenium into an aryl-lithium compound that is generated *in situ* by lithium-halogen exchange of a protected aryl bromide. The aryl bromide is derived from the commercially available starting material *L*-2-bromo-Phe. There is extensive precedent for selenium insertion into aryl-lithium compounds, but a search of the literature revealed no examples of this methodology applied to highly functionalized starting materials. As such, installation of suitable protecting groups was considered a significant requirement for the success of this route. Eastwood encountered substantial difficulty when identifying a protecting group for the carboxylic acid that is compatible with *t*-butyllithium (*t*-BuLi) or alternative Grignard reagents. Eastwood's efforts to prepare an oxazolidine-protected acid were successful, but the oxazolidine ring had a tendency to open by *t*-BuLi or Grignard reagents.[1] By the time I began work on this project, there was a general consensus that the acid should be left unprotected.




**1**
**(a key structure from Chapter 6)**

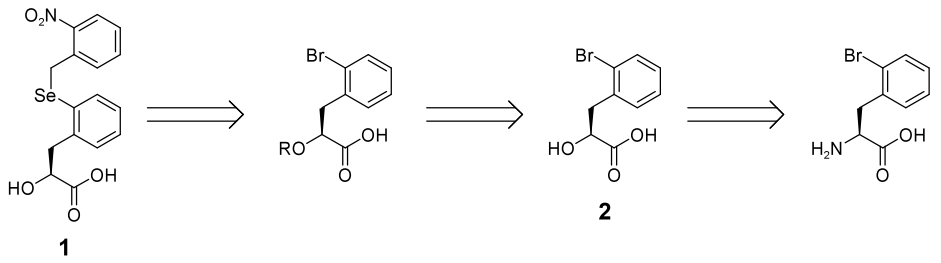
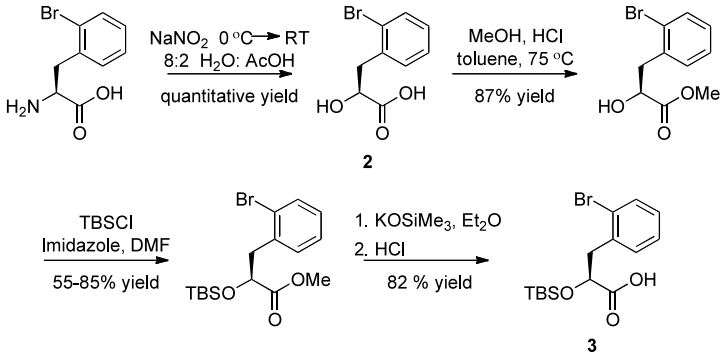



**Figure A3.1.** Original retro-synthetic pathway proposed by Eastwood.

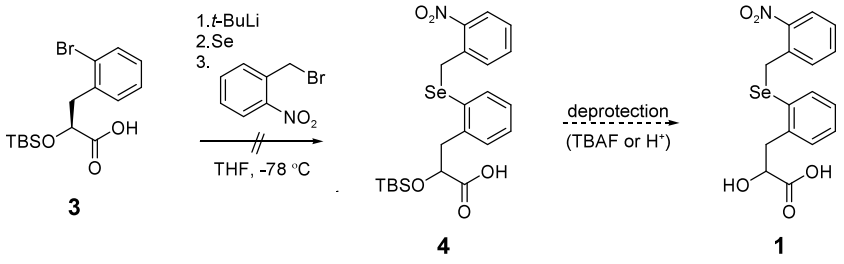
The α-hydroxy acid **2** was stereo-selectivity prepared from *L*-2-bromo-Phe by Eastwood in quantitative yields via a published procedure.[2] I began work on this route by testing several alcohol protecting groups including *t*-butyldimethylsilyl (TBS), *t*-butyldiphenylsilyl (TBDPS) and methoxyethoxymethyl (MEM) ethers. These groups were selected for their perceived orthogonality with subsequent reaction conditions of the planned synthesis and for the ease with which they can be removed.[3] Unfortunately, all protection reactions gave poor yields, which probably resulted from steric hindrance at the secondary alcohol or competing esterification reactions. To improve these yields, the free acid was esterified by Fischer esterification in methanol. This reaction gave a high yield (87%) and provided a convenient handle for flash column chromatography purification of subsequent products. A TBS group could then be readily installed by standard methods as shown in **Scheme A3.1**. The methyl group of the ester was removed by potassium trimethylsilanolate. This high-yielding reaction gave the potassium carboxylate salt, which was insoluble in organic solvents. Protonation of this salt during aqueous work-up gave TBS-protected aryl bromide **3**. Alternative methods of de-methylation (including hydrolysis by 0.2 M LiOH) gave lower yields of **3**.

**Scheme A3.1.** Synthesis of TBS-protected aryl bromide **3**.




Compound **3** was put through several variations of the key first step shown in **Scheme A3.2**, but no conditions resulted in the desired *o*-nitrobenzyl-caged aryl selenide product **4**. Although it was apparent that all of the elemental selenium dissolved, no indication of selenium incorporation was ever observed. Many variables including temperature, reagent purities, reaction times and lithium sources (*n*-BuLi or *sec*-butyl instead of *t*-BuLi) were adjusted, but no conditions yielded the desired product or even selenium addition. These complications as well as Eastwood's inability to produce **1** through the oxazolidine-protected material inspired the design of an alternative synthetic route as depicted in the retro-synthetic pathway shown in **Figure A3.2**.

**Scheme A3.2.** Failed synthesis of the desired α-hydroxy acid, **1**.




It should be noted that TBS was originally chosen as the alcohol protecting group (for route 1, **Figure A3.1**) because it could be readily removed (by TBAF or acidic

media) and was noted as being compatible with Grignard and BuLi reagents.[3] Contradictory reports on the compatibility of *t*-BuLi and TBS-protected alcohols were later found through subsequent literature searches. In these reports, lithiation of the TBS methyl groups was observed as a substantial side-reaction.[4] While it is unlikely that this was the only cause of the reaction failures described above (especially given that reactions with other alcohol protecting groups by Eastwood also did not produce **1**), this side-reaction probably contributed.

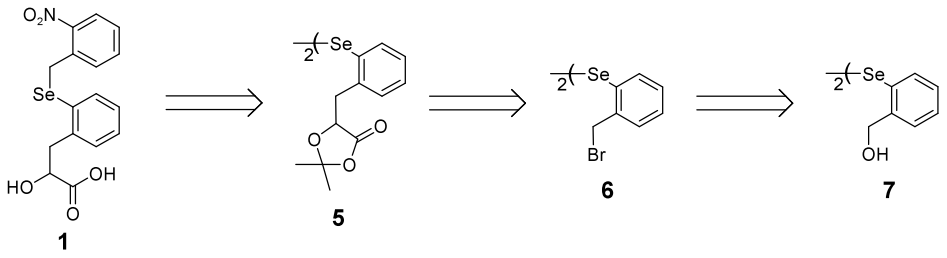



**Figure A3.2.** Second retro-synthetic pathway.

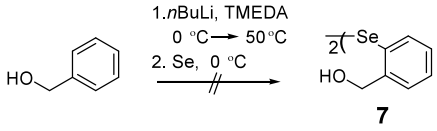
Because functional groups were suspected to be major players in the failure of the original route, selenium is introduced in the second route before the installment of the carboxylic acid and secondary alcohol (**Figure A3.2**). In this route, the desired product **1** is derived from a diselenide that was anticipated to be accessible via nucleophilic displacement of a benzyl bromide by the enolate of a Seebach-type ester.[5-7] The conversion of aryl diselenides to phenylalkyl selenides is well-precedented and generally involves the reduction of an aryl diselenide in the presence of an alkyl halide.[8-10]

The nucleophilic attack of alkyl bromides by enolates of Seebach-type esters is also well-documented. Generally, chiral Seebach-type esters are employed to control the stereochemistry of the products.[5-7] This was viewed as an advantage given that an enantio-enriched version of **1** was ultimately desired for model peptide or *in vivo* studies.

Unfortunately, no appropriate chiral Seebach-type esters are commercially available. As such, the initial goal of this route was to produce **1** racemically by the commercially available Seebach-type ester, 2,2-dimethyl-1,3-dioxolan-4-one. Had the overall route been successful, alternative chiral Seebach-type esters would have been synthesized by known methods.[11]

Compounds **6** and **7** are both known compounds whose syntheses have been reported previously.[12, 13] Two procedures are reported for the synthesis of the benzyl alcohol **7**. The first route is a one-step synthesis that involves the *ortho*-lithiation of benzyl alcohol as shown in **Scheme A3.3**. While the product is reported in 60% yield,[13] all attempts to reproduce this procedure were unsuccessful. Compound **7** was never produced by this strategy despite efforts to optimize several variables including reaction temperature, reaction time, work-up procedures and reagent purities. Undissolved elemental selenium was seen throughout these reactions, and no sign of selenium incorporation was ever obtained by MS or NMR.

**Scheme A3.3.** Failed synthesis of benzyl alcohol **7** by *ortho*-lithiation of benzyl alcohol.

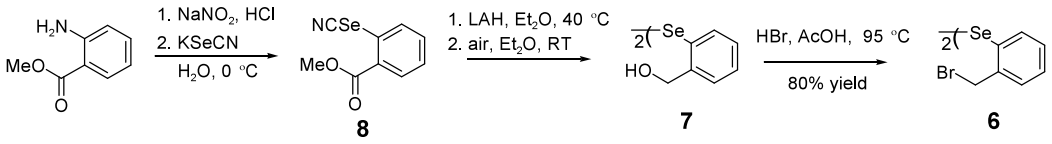



**7**

The second published procedure for the preparation of **7** consists of two high-yielding steps.[12] The first step in this route produces selenocyanate **8** through nucleophilic attack on a diazonium intermediate (formed *in situ* from the commercially available starting material, methyl anthranilate) by potassium selenocyanate. The methyl ester of **8** is reduced by lithium aluminum hydride, and the selenocyanate is then oxidized

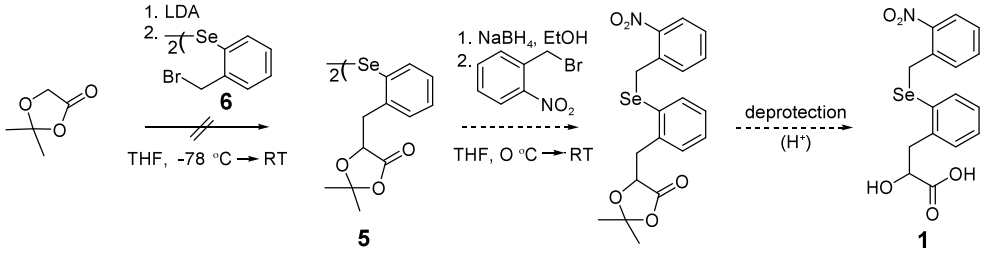
by air to yield **7**.[12] This procedure was successfully reproduced to prepare **7** in high yield as shown in **Scheme A3.4**. Compound **7** was then brominated in 80% yield by another published procedure to give benzyl bromide **6**.[14]

**Scheme A3.4.** Synthesis of benzyl bromide **6** from benzyl alcohol **7**.

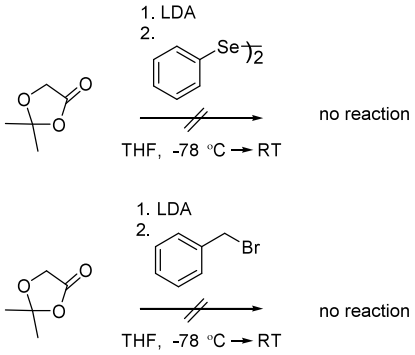



With the benzyl bromide **6** in hand the key step in the synthesis, nucleophilic attack of benzyl bromide **6** by the enolate of a Seebach-type ester, could be attempted (**Scheme A3.5**). This reaction was tried many times but never yielded the desired product of this reaction (Compound **5**). The same reaction also failed with benzyl bromide and diphenyldiselenide (**Scheme A3.6**), suggesting that the presence of the diselenide functionality was not the cause for the failure of the above reaction.

**Scheme A3.5.** Another failed synthesis of the desired α-hydroxy acid, **1.**



**Scheme A3.6.** Model enolate reactions.




Several variables were also changed in this reaction including reaction time and reaction temperature. Other bases including *t*-BuLi, sodium hydride and potassium tert-butoxide were also tried, but none gave any product when tested with benzyl bromide. In fact, the starting materials were recovered quantitatively from each reaction. Lithium diisopropyl amine (LDA) was the most common base used in literature examples involving enolate chemistry with Seebach-type esters.[5-7] It is possible that the LDA used in our reactions was of poor quality despite the fact that it was freshly prepared prior to each reaction. It is still unclear why our reactions (particularly those with benzyl bromide) failed. Had this route been pursued further, alternative Seebach-type esters would have been tested and the purity of the LDA would have been assessed.

A third synthetic route (**Figure A3.3**) was designed and tested soon after work began on the second route. This third route was inspired by the success of the seleoncyanate formation reaction of the second route. All previous attempts to incorporate selenium through BuLi reactions (**Schemes A3.2**, **A3.3** and **A3.4**) were unsuccessful, and so it was thought that preparation of the selenocyanate would be easier.

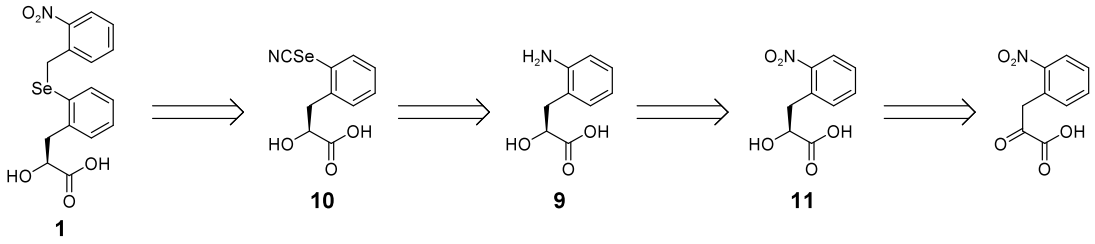
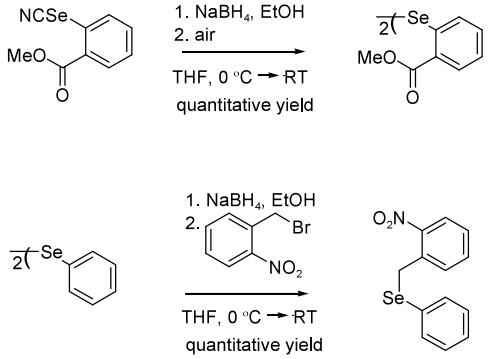



**Figure A3.3**. Third retro-synthetic pathway.

When this route was designed, it appeared that there were two potentially challenging steps, the conversion of the aniline **9** to the selenocyanate **10** and the transformation of this selenocyanate to the desired α-hydroxy acid, **1**. The successful conversion of methyl anthranilate to **8** (**Scheme A3.4**) provided precedent for the former transformation while the latter was precedented by the reported syntheses of other phenylalkyl selenides via reduction of aryl diselenides in the presence of alkyl halides.[15-17] The model studies shown in **Scheme A3.7** confirm that nitrobenzyl groups can be added in this manner.

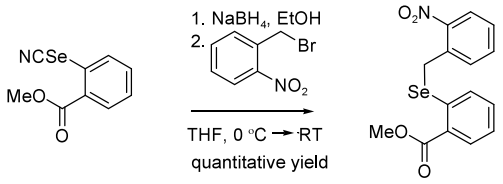
**Scheme A3.7.** Model reactions providing precedent for key steps in route 3.




To our knowledge, direct conversion of a selenocyanate to a disubstituted selenide has not been previously reported in the literature. All published procedures break this transformation into two steps as described above.[15-17] Since reduction to the selenide is required for both steps, we tried to consolidate this protocol into a single step in the

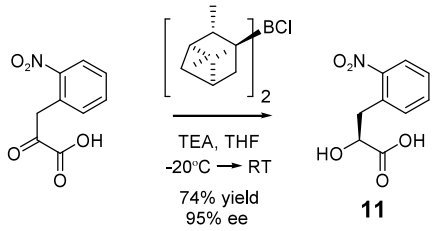
model study shown in **Scheme A3.8**. This route successfully afforded the desired model compound in quantitative yield.

**Scheme A3.8.** Model reaction that condense the two steps of Scheme A3.7 into one.




The remaining transformations in this retro-synthetic pathway (**Figure A3.3**) were thought to be more straightforward. The aniline could be prepared from the selective reduction of the nitro group of **11** and the asymmetric conversion of a commercially available starting material, 2-nitrophenylpyruvic acid, to **11** was previously reported by Wang *et al.*[18] In this report **11** was prepared in high enantiomeric excess (95%) via reduction of 2-nitrophenylpyruvic acid by an asymmetric borane reducing agent, β-chlorodiisopinocampheylborane (DIP-Cl) as shown in **Scheme A3.9**.[18]

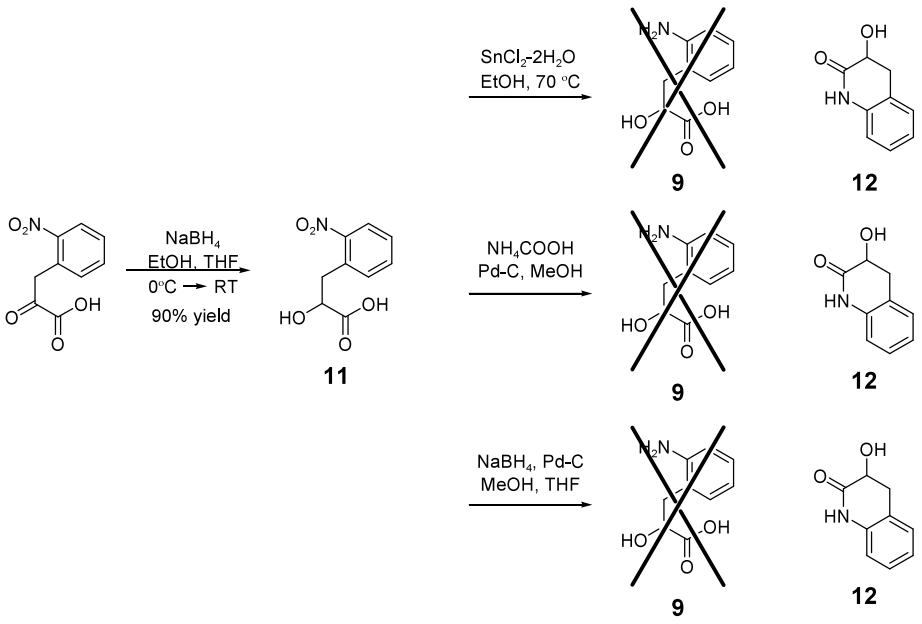
**Scheme A3.9.** Literature procedure for the enantio-enriched synthesis of **11** from 2-nitrophenylpyruvic acid.[18]




While DIP-Cl is commercially available, it was back-ordered for several weeks while the third route was first investigated. As such 2-nitrophenylpyruvic acid was reduced with sodium borohydride to yield the racemic α-hydroxy acid **11** in 90% yield. The reduction of the nitro group of **11** was expected to be facile as an assortment of

reagents are reported to selectively reduce aryl nitro groups in the presence of other reducible groups (including carboxylic acids).[19-21] Several reagents were employed to reduce **11** to **9** as shown in **Scheme A3.10**. Unfortunately, none of the conditions tested resulted in the desired product **9**. Instead, each afforded the ring-closed product **12**. Analysis of the structure of this product suggests that the aniline had formed, but had immediately undergone intramolecular cyclization to afford the δ-lactam **12**.

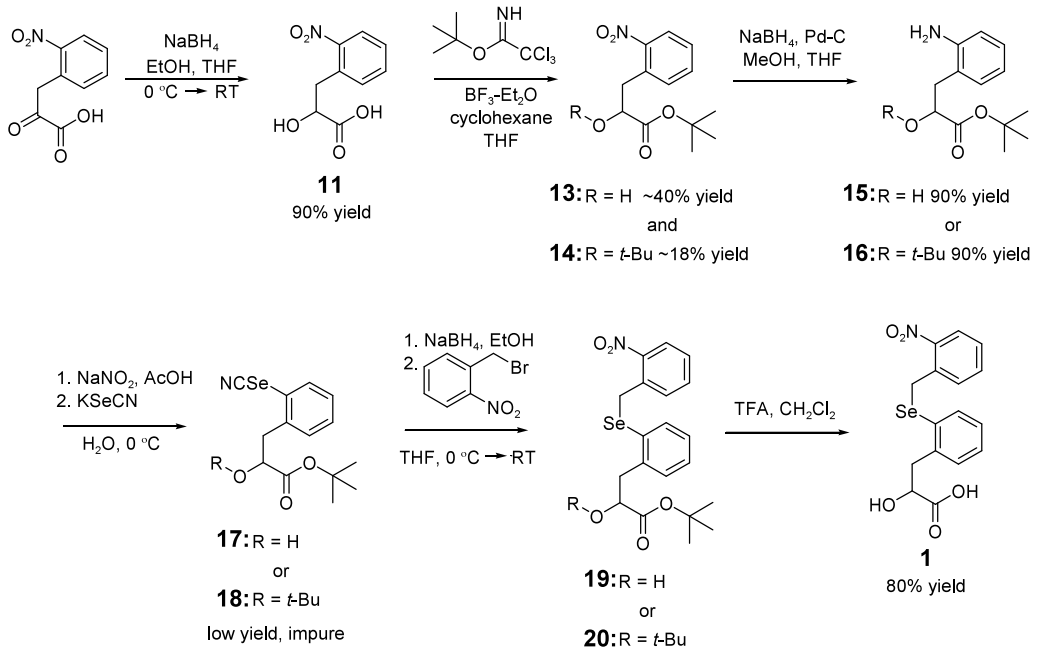
**Scheme A3.10.** Racemic reduction of 2-nitrophenylpyruvic acid and attempted reduction of α-hydroxy acid **11**.




At this point, a strategy was needed to prevent the formation of the δ-lactam. It was believed that the introduction of steric hindrance near the electrophilic carbon might impede cyclization. To test this theory, *t*-butyl groups were introduced by the synthetic procedure shown in **Scheme A3.11**. This reaction yielded two major products, **13** and **14**. Both products were isolated and run through subsequent reactions independently. It should be noted that the yields for this reaction are dramatically dependent upon the

reaction time. When the reaction was run for 12 hours, the total yield was <15%. A reaction time of 45 minutes, however, gave a total yield of ~60%. This yield is comparable to the yields reported for other methods of *t*-butyl esterification.[3]

**Scheme A3.11.** Successful racemic preparation of the desired α-hydroxy acid, **1**.




The sodium borohydride reduction of compounds **13** and **14** to compounds **15** and **16** was catalyzed by 10% palladium on activated carbon. No cyclization of **15** or **16** was ever observed under these conditions. It should be noted that the pH of the aqueous work-ups of the reactions was carefully monitored as acidic conditions could lead to the hydrolysis of the *t*-butyl protecting group and/or the catalysis of the intramolecular cyclization reaction. The anilines **15** and **16** were converted to their corresponding selenocyanates (**17** and **18**) by a slight modification of the standard procedure in which AcOH was used instead of a stronger acid to prevent loss of the *t*-butyl groups. These reactions gave low yields, but were optimized in the final synthetic route described in

Chapter 6. Using the protocol derived in the model studies of **Scheme A3.8**, compounds **17** and **18** were converted to the protected selenides **19** and **20**. Removal of the *t*-butyl protecting groups by TFA triumphantly afforded the α-hydroxy acid **1**.

After the racemic synthesis of **1** had been completed, DIP-Cl was no longer on back-order and an enantio-enriched version of the desired compound was prepared and optimized as described in Chapter 6.

## A3.2 EXPERIMENTAL SECTION

All reactions involving potentially air-sensitive compounds were conducted under nitrogen or argon atmospheres using standard glove box or Schlenk techniques. Solvents were purified by passage through alumina.[22] Resonances for NMR spectra are reported relative to $Me_4Si$ (δ 0.0). NMR Spectra are reported as follows: chemical shift (δ ppm), integration, multiplicity and coupling constant (Hz). All reagents were purchased from Aldrich and used without prior purification.

**Synthesis of α-hydroxy acid 2.** The α-hydroxy acid **2** was prepared from L-2-bromo-Phe by the published procedure.[2] Quantitative Yield. $^1$H NMR (300 MHz, $CD_3OD$, 298 K) δ 7.55 (1H, d, $J$ = 6.88 Hz), 7.31 (2H, m), 7.14 (1H, m), 4.41 (1H, dd, $J$ = 9.35, 4.40 Hz), 3.35 (1H, dd, $J$ = 8.38, 5.50 Hz) 3.08 (1H, dd, $J$ = 9.35, 3.85 Hz). High-resolution MS analysis (FAB+) m/z; calcd 244.9813 ([M+H]), found 244.9818 ([M+H]) and calcd 266.9633 ([M+Na]), found 266.9750 ([M+Na]).

**Synthesis of the methyl ester of 2.** Compound **2** (2.00g, 8.18 mmol) was added to a 3-neck, 100 mL round-bottom flask equipped with a reflux condenser under Ar(g) and

dissolved in 66 mL of MeOH, 33 mL of toluene and 1 mL of HCl and the solution stirred for 16 hours at 75 $^{o}$C. The solution was cooled to room temperature and the pH was increased to ~pH 7.0 by addition of 5% $NaHCO_3$ (aq). The solvent was removed by rotavap until only ~20% remained. Water was added (~50mL) and the organics were extracted with $Et_2O$, washed with brine, dried over $Na_2SO_4$ and concentrated to afford a yellow oil. Yield: 87%. $^{1}$H NMR (300 MHz, $CDCl_3$, 298 K) δ 7.56 (1H, d, *J* = 7.98 Hz), 7.28 (2H, m), 7.13 (1H, dd, *J* = 7.98, 5.78 Hz), 4.52 (1H, dd, *J* = 8.53, 4.68 Hz), 3.80 (3H, s), 3.34 (1H, dd, *J* = 14.03, 4.78 Hz), 3.02 (1H, dd, *J* = 14.03, 5.50 Hz), 2.75 (1H, b). $^{13}$C NMR (75 MHz, $CDCl_3$, 298 K) δ 174.9, 136.3, 133.0, 132.0, 128.7, 127.5, 124.9, 70.1, 51.8, 41.0. MS analysis (ESI) m/z; calcd 281.0 ($[M+Na]^+$), found 280.8 ($[M+Na]^+$).

**Synthesis of the TBS-protected methyl ester (of 2).** The methyl ester of **2** (0.0811g, 0.313 mmol) was added to a 20 mL scintillation vial and dissolved in 1.4 mL of DMF. To this was added imidazole (0.128 g, 1.88 mmol) followed by *t*-butyldimethylsilyl chloride (0.189g, 1.25 mmol). The solution then stirred for 23 hours. The solution was suspended/diluted in brine (20 mL) and the organics were extracted with $Et_2O$, washed with brine, dried over $Na_2SO_4$ and concentrated to afford a yellow oil. This oil was purified by flash column chromatography on silica gel (3% EtOAc: Hex) to yield a clear oil. Yield: 85%. $^{1}$H NMR (300 MHz, $CDCl_3$, 298 K) δ 7.53 (1H, d, *J* = 6.88 Hz), 7.23 (2H, m), 7.09 (1H, dd, *J* = 7.98, 4.68 Hz), 4.52 (1H, dd, *J* = 9.09, 5.78 Hz), 3.74 (3H, s), 3.31 (1H, dd, *J* = 9.35, 4.13 Hz), 2.96 (1H, dd, *J* = 9.63, 3.85 Hz), 0.77 (9H, s), –0.13 (3H, s), –0.27 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3$, 298 K) δ 173.7, 136.9, 133.3, 132.8, 128.7, 127.4, 124.8, 71.5, 52.2, 42.0, 25.8, 18.4, –5.4, –5.5. High-resolution MS analysis (FAB+) m/z; calcd 373.0835, found 373.0844.

**Synthesis of TBS-protected acid 3**. The TBS-protected methyl ester of **2** (0.128g, 0.343 mmol) was added to a 2-neck, 10 mL round-bottom flask under Ar (g) and dissolved in 3.4 mL $Et_2O$. To this was added potassium trimethylsilanolate (0.048g, 0.377 mmol). Within five minutes after this addition, a white precipitate appeared in the yellow solution. The solution stirred for a total of 2 hours. The yellow liquid was removed and the white solid was scintillated with cold ether (3 × 30 mL) to afford a white powder. To protonate the carboxylate, the powder was suspended/diluted in water (20 mL) and the pH was lowered to pH 4.5 by the addition of 3N HCl. The organics were extracted with $CH_2Cl_2$, washed with brine, dried over $Na_2SO_4$ and concentrated to afford a white crystalline solid. Yield: 82%. $^1$H NMR (300 MHz, $CDCl_3$, 298 K) δ 10.94 (1H, b), 7.55 (1H, d, *J* = 7.70 Hz), 7.26 (2H, m), 7.12 (1H, dd, *J* = 7.43, 4.95 Hz), 4.59 (1H, dd, *J* = 10.18, 3.58 Hz), 3.43 (1H, dd, *J* = 13.48, 3.58 Hz), 2.99 (1H, dd, *J* = 10.18, 3.30 Hz), 0.795 (9H, s), –0.10 (3H, s), –0.28 (3H,s). $^{13}$C NMR (75 MHz, $CDCl_3$, 298 K) δ 179.3, 136.9, 133.7, 133.4, 129.3, 127.8, 125.7, 71.6, 42.3, 26.2, 18.7, –5.1, –5.2. High-resolution MS analysis (FAB+) m/z; calcd 359.0678 ([M+H]), found 359.0683 ([M+H]).

**Synthesis of α-hydroxy acid 11.** 2-nitrophenyl pyruvic acid (0.50g, 2.39 mmol) was dissolved in 20 mL of THF in a 100 mL, 3-neck round-bottom flask under Ar (g) at 0 °C. Sodium borohydride (0.181g, 4.78 mmol) in 12 mL EtOH was added to the reaction vessel dropwise via syringe. During this addition, the solution turned from yellow to orange and bubbling was observed. After fifteen minutes of stirring, the solution was slowly warmed to room temperature. Stirring was continued for a total of 3.5 hrs until the solution was quenched by the addition of 50 mL 3 N HCl. The pH of the solution was increased to pH 7 by addition of saturated $NaHCO_3$ (aq). After extraction with $Et_2O$

(2 × 30 mL), the pH of the aqueous layer was decreased to pH 1.6 by addition of 3 N HCl. The organics were extracted with $Et_2O$, washed with brine, dried over $Na_2SO_4$ and concentrated to yield a pale brown solid. Yield: 90%. $^1$H NMR (300 MHz, $CD_3OD$, 298 K) δ 7.85 (1H, d, *J* = 6.88 Hz), 7.47 (3H, m), 4.44 (1H, b), 3.48 (1H, dd, *J* = 9.35, 3.48 Hz), 3.14 (1H, dd, *J* = 8.80, 5.23 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$, 298 K) δ 175.3, 151.1, 134.4, 133.8, 132.9, 129.0, 125.5, 71.6, 38.0. High-resolution MS analysis (FAB+) m/z; calcd 212.0559 ([M+H]), found 212.0558 ([M+H]).

**Synthesis of an enantio-enriched version of 11.** The enantio-enriched version of **11** was prepared according to published procedures.[19-21] The resulting solid was dry-loaded with MeOH onto a silica column in preparation for purification by flash column chromatography (1:1:0.016 ratio of EtOAc: Hex: formic acid) After purification, a yellow solid was obtained. Yield: 85%.

**Synthesis of *t*-butyl-protected-nitro compounds 13 and 14.** A 2-neck, 25 mL round-bottom flask under Ar(g) was charged with **11** (0.200g, 0.947 mmol), which was then dissolved in 3 mL THF. To this flask was added 3.5 mL of degassed cyclohexane. *t*-Bu-2,2,2-trichloroacetimidate(0.678 mL, 3.79 mmol) in 3.5 mL of cyclohexane was added simultaneously with 0.041 mL of boron trifluoride-diethyletherate (0.33 mmol). The reaction stirred for 45 min until it was quenched with saturated $NaHCO_3$ (aq). The organics were extracted with $Et_2O$, washed with brine, dried over $MgSO_4$ and concentrated. The resulting white sludge was dissolved in $CH_2Cl_2$ and filtered through a pad of celite to remove a majority of a white salt. The remaining liquid was purified by flash column chromatograpy on silica gel (10% EtOAc: Hex). Two fractions were

collected and identified as **13** ($R_f$ = 0.44 in 30% EtOAc: Hex, yield = 40%) and **14** ($R_f$ = 0.71 in 30% EtOAc: Hex, yield = 18%). The same procedure was used to prepare the enantio-enriched versions **13** and **14**. Analytical chiral HPLC separation of the enantio-enriched version of **13** was performed on a Chiralcel OD-H column (4.6mm × 25 cm) from Daicel Chemical industries, Ltd with 2% isopropyl alcohol: hexanes. $^1$H NMR of **13** (300 MHz, $CDCl_3$, 298 K) δ 7.93 (1H, d, *J* = 7.00 Hz), 7.52 (1H, m), 7.41 (2H, m), 4.36 (1H, dd, *J* = 8.38, 4.26 Hz), 3.51 (1H, dd, *J* = 13.87, 4.26 Hz), 3.15 (1H, dd, *J* = 14.01, 4.26 Hz), 1.46 (9H, s). $^{13}$C NMR of **13** (75 MHz, $CDCl_3$, 298 K) δ 173.5, 150.1, 133.4, 133.0, 132.4, 128.1, 125.0, 83.4, 70.7, 37.6, 28.2. $^1$H NMR of **14** (300 MHz, $CDCl_3$, 298 K) δ 7.93 (1H, d, *J* = 7.98 Hz), 7.49 (1H, m, *J* = 9.8 Hz), 7.39 (2H, m), 4.15 (1H, dd, *J* = 9.08, 4.76 Hz), 3.31 (1H, dd, *J* = 13.2, 4.95 Hz), 3.14 (1H, dd, *J* = 9.08, 4.13 Hz) 1.40 (9H, s), 0.96 (9H, s). $^{13}$C NMR of **14** (75 MHz, $CDCl_3$, 298 K) δ 173.0, 145.0, 134.5, 132.9, 132.7, 128.0, 124.8, 81.2, 75.2, 71.9, 37.7, 28.1, 27.6. High-resolution MS analysis of **13** (FAB+) m/z; calcd 268.1185 ([M+H]), found 268.1194 ([M+H]). High-resolution MS analysis of **14** (FAB+) m/z; calcd 324.1811 ([M+H]), found 324.1827 ([M+H]).

**Synthesis of *t*-butyl-protected-anilines 15 and 16.** Compound **13** or **14** (1 eq) was placed in a 2-neck round-bottom flask and dissolved in THF (0.14 M) under Ar(g) at 0 °C. To this was added 10 wt% palladium on carbon (0.3 eq) followed by the dropwise addition of sodium borohydride (2.5 eq) in MeOH (0.78 M). The reaction bubbled and was followed by TLC using ninhydrin as the stain. The solution was stirred for 30 min until it was quenched with water and filtered through a pad of celite. The filtrate was extracted with $Et_2O$, washed with brine, dried over $MgSO_4$ and concentrated. The resulting liquid was purified by flash column chromatography on silica gel (10−30%

EtOAc: Hex). Yield= 90% (**15**) or 90% (**16**). $^{1}$H NMR of **15** (300 MHz, $CDCl_3$, 298 K) δ 7.26 (1H, m), 7.05 (1H, m), 6.73, (1H, m), 6.69 (1H, dd, *J* = 7.42, 4.49 Hz), 4.37 (1H, dd, *J* = 6.18, 3.98 Hz), 3.10 (1H, dd, J= 10.44, 4.12 Hz), 2.90 (1H, dd, *J* = 8.38, 6.18 Hz), 1.48 (9H, s). $^{13}$C NMR of 1**5** (75 MHz, $CDCl_3$, 298 K) δ 173.6, 146.3, 131.7, 131.1, 128.2, 118.8, 116.7, 83.2, 72.4, 36.5, 28.3. $^{1}$H NMR of **16** (300 MHz, $CDCl_3$, 298 K) δ 7.29 (1H, d, *J* = 7.70 Hz), 7.18 (1H, m), 7.04 (1H, d, *J* = 6.88 Hz), 6.85 (1H, m), 3.99 (1H, m), 2.94 (1H, m), 2.71 (1H, m), 1.47 (9H, s), 0.98 (9H, s). $^{13}$C NMR of **16** (85 MHz, $CDCl_3$, 298 K) δ 173.5, 149.9, 130.5, 128.0, 124.0, 121.2, 114.4, 81.6, 75.8, 74.9, 35.7, 28.2, 27.6. MS analysis for **16** (ESI) m/z; calcd 294.2 ($[M+H]^+$), found 294.3 ($[M+H]^+$) and calcd 332.2 ($[M+K]^+$), found 332.2 ($[M+K]^+$).

**Synthesis of *t*-butyl-protected-selenocyanates 17 and 18.** Compound **15** or **16** (1.01 eq) was added to a 10 mL round-bottom flask and dissolved in AcOH (0.05 M) at 0 °C. To this was quickly added 3 M sodium nitrite (1.21 eq) via syringe. The solution stirred for 1 hour and was monitored by TLC using ninhydrin as the stain. The pH of the solution was then increased to ~6 by the addition of saturated $CH_3COONa$ (aq). To this was added potassium selenocyanate (1 eq) in water (0.07 M). The solution then stirred for ~30 min. The organics were extracted with $Et_2O$, washed with brine, dried over $MgSO_4$ and concentrated. The resulting brown sludge was used in the subsequent reaction without further purification. Attempts to purify **17** by flash column chromatography (10−30% EtOAc: Hex) gave ~8% yield, but it was apparent that some material was lost in the purification. In any case, the yields for this reaction are low. $^{1}$H NMR of **17** (300 MHz, $CDCl_3$, 298 K) δ 7.85 (1H, d, *J*= 7.83 Hz), 7.29 (3H, m), 4.28 (1H, dd, *J* = 8.52, 4.53 Hz), 3.31 (1H, dd, *J* = 9.48, 4.53 Hz), 3.13 (1H, dd, *J* = 6.18, 3.87 Hz), 1.49 (9H, s). $^{13}$C NMR

of **17** (75 MHz, $CDCl_3$, 298 K) δ 172.7, 137.9, 134.8, 131.5, 129.9, 129.6, 129.2, 105.6, 84.0, 71.3, 39.9, 28.3. MS analysis of **17** (ESI) m/z; calcd 350.0 ($[M+Na]^+$), found 349.9 ($[M+Na]^+$) and calcd 366.0 ($[M+K]^+$), found 365.9 ($[M+K]^+$).

**Synthesis of *t*-butyl-protected-selenides 19 and 20.** Compound **17** or **18** (1 eq) was added to a 2-neck round-bottom flask under Ar(g) and dissolved in THF at 0 °C. To this was added sodium borohydride (1.2 eq) in EtOH (0.5 M) and the solution stirred for 1 hr. 2-nitrobenzylbromide (1.3 eq) in THF (0.1 M) was then added to the now orange solution. After this addition, the solution was allowed to slowly warm to room temperature and was stirred for 3 hours until it was quenched with water. The organics were extracted with $Et_2O$, washed with brine, dried over $MgSO_4$ and concentrated. The resulting solid was purified by flash column chromatography on silica gel with 30% EtOAc: Hex ($R_f$ =0.46 for **19** using 40% EtOAc: Hex and $R_f$ = 0.67 for **20** using 30% EtOAc: Hex) to afford a yellow solid. $^1$H NMR of **19** (300 MHz, $CDCl_3$, 298 K) δ 8.00 (1H, d, *J* = 7.00 Hz), 7.48 (1H, d, *J* = 7.83 Hz), 7.31 (4H, m), 7.12 (1H, m), 6.99 (1H, m), 4.33 (2H, s), 4.15 (1H, m), 3.16 (1H, dd, *J* = 9.90, 4.53 Hz), 2.96 (1H, dd, *J* = 8.24, 5.36 Hz), 1.43 (9H, s). $^1$H NMR of **20** (300 MHz, $CDCl_3$, 298 K) δ 8.01 (1H, d, *J* = 7.70 Hz), 7.45 (1H, d, *J* = 7.70 Hz), 7.37 (2H, m), 7.26 (2H, m), 7.21 (1H, m), 7.07 (1H, m), 4.35 (2H, s), 3.96 (1H, dd, *J* = 8.80, 5.50Hz), 2.97 (1H, dd, *J* = 7.70, 5.23 Hz), 2.85 (1H, dd, *J* = 9.08, 4.13 Hz), 1.37 (9H, s), 0.95 (9H, s). $^{13}$C NMR of **20** (75 MHz, $CDCl_3$, 298 K) δ 173.3, 141.2, 136.2, 135.5, 133.2, 132.2, 131.8, 128.3, 128.1, 127.6, 125.7, 80.9, 74.9, 72.8, 40.9, 30.1, 2807, 27.8. MS analysis of **20** (ESI) m/z; calcd 516.1 ($[M+Na]^+$), found 516.0 ($[M+Na]^+$).

**Synthesis of α-hydroxy acid 1.** Compound **19** or **20** (1 eq) was added to a 2-neck round-bottom flask under Ar(g) and dissolved in $CH_2Cl_2$ (0.2M). To this was added trifluoroacetic acid (140 eq) and the solution stirred for 16 hours. The organics were extracted with $Et_2O$, washed with brine, dried over $MgSO_4$ and concentrated to afford a yellow solid. Yield: 80%. $^1$H NMR (300 MHz, $CDCl_3$, 298 K) δ 7.99 (1H, d, *J* = 7.56 Hz), 7.45 (1H, d, *J* = 7.42 Hz), 7.36 (2H, m), 7.29 (2H, m), 7.13 (1H, m), 7.00 (1H, m), 4.37 (3H, m), 3.31 (1H, dd, J= 14.01, 4.40 Hz), 3.03 (1H, dd, *J* = 8.65, 5.22 Hz). MS analysis (ESI) m/z; calcd 404.0 ($[M+Na]^+$), found 404.1 ($[M+Na]^+$) and calcd 380.0 ($[M+H]^-$), found 379.9 ($[M+H]^-$).

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