A Practical and Stereoselective Synthesis of (+/−)-*trans*-4-Benzyloctahydropyrrolo[3,4-*b*][1,4]oxazine

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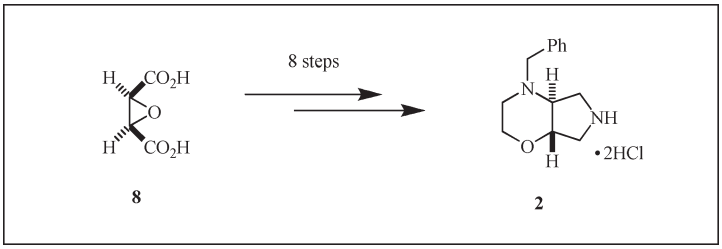

8 **2**

trans-Octahydropyrrolo[3,4-*b*][1,4]oxazine is an important heterocycle within the pharmaceutical industry for the preparation of biologically active analogs, including the phase III drug, finafloxacin. A practical synthesis of the title compound (**2**) is described in eight steps and ca. 10% overall yield. The key synthetic step is the formation of the pyrrolo[3,4-*b*][1,4]oxazine core **20** *via* a one pot double *N*-alkylation of the corresponding bis-tosylate **18** with 4-nitrobenzenesulfonamide. Subsequent removal of the nosyl group occurred under mild conditions.

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INTRODUCTION

The morpholine ring is utilized extensively in drug discovery research. Due to its hydrophilic nature, medicinal chemists will often look for opportunities to incorporate morpholine into their analogs as a means to increase solubility. Within a chemical series, morpholine, with its lower pKa compared to isosteric piperidine (8.3 *vs*. 11.1), has been shown to reduce hERG activity [1], which is an early indicator of cardiovascular risk. Numerous drugs incorporating the morpholine ring have been approved for the treatment of human diseases; a snapshot of some recent examples is shown in Chart 1, including linezolid (Zyvox®) [2], gifitinib (Iressa®) [3], and reboxetine [4]. Finafloxacin, which is currently undergoing clinical trials for the treatment of *Helicobacter pylori (H. pylori)* infections [5], possesses a morpholine ring fused onto a pyrrolidine ring, giving rise to the *trans*-pyrrolo[3,4-*b*][1,4]oxazine heterocycle. The ring fusion restricts the spatial orientation of the morpholine ring compared to the unfused analog; this restriction is presumably important for optimal binding to the biological receptor. In addition, the pyrrolidine nitrogen provides a chemical handle for attaching the heterocycle to the analog of interest.

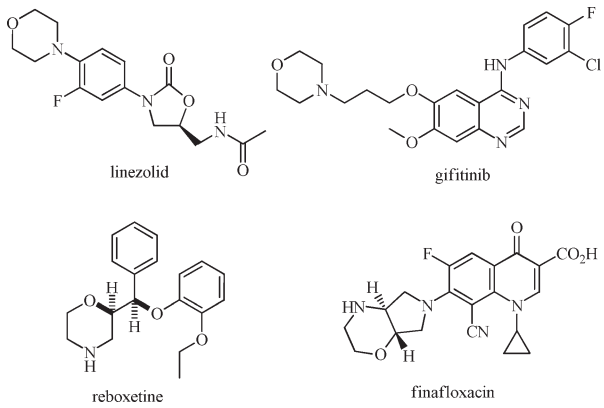
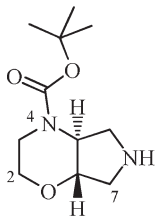
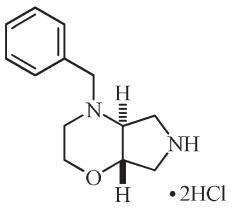


Chart 1.

Recently, Hong *et al*. [6] have disclosed a synthesis of enantiomerically pure (4a*S*,7a*S*)-*tert*-butyl hexahydro pyrrolo [3,4-*b*][1,4]oxazine-4(4a*H*)-carboxylate [(4a*S*,7a*S*)-**1**], wherein the morpholine nitrogen is differentially protected with respect to the pyrrolidine nitrogen. In connection with our own medicinal chemistry efforts, we were also interested in preparing this novel heterocycle wherein the morpholine nitrogen was selectively protected. We detail below a stereoselective synthesis of (+/−)-*trans*-4-benzyloctahydropyrrolo[3,4-*b*][1,4]oxazine (**2**).



(*4aS, 7aS*)-**1**



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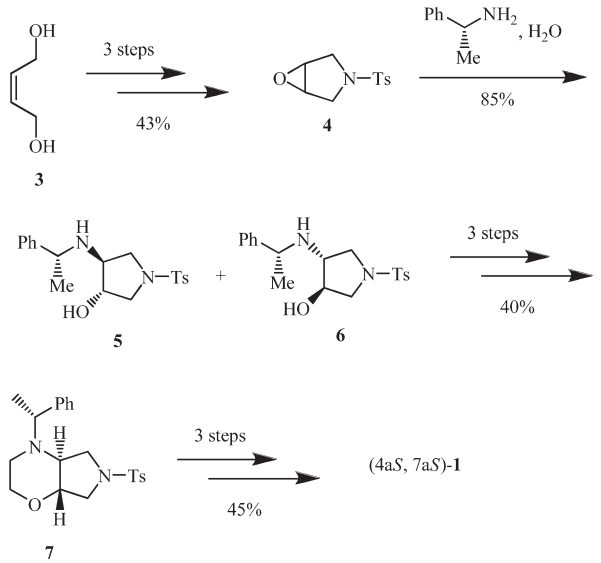
RESULTS AND DISCUSSION

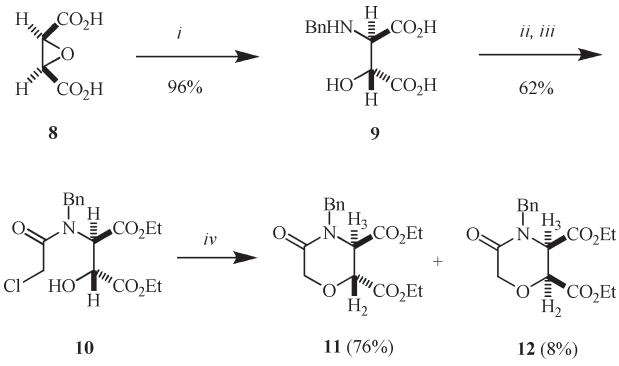
Hong prepared enantiomerically pure pyrrolo[3,4-*b*][1,4]oxazine (4a*S*,7a*S*)-**1** by a ten step synthesis outlined in Scheme 1 [6]. Thus, epoxypyrrolidine **4** was prepared in three steps from commercial (*Z*)-but-2-ene-1,4-diol (**3**). Opening epoxide **4** with (*R*)-α-methylbenzylamine led to diastereomers **5** and **6**, which were readily separated by solvent extraction and crystallization techniques. Treatment of diastereomer **5** with chloroacetyl chloride, followed by exposure to base effected ring closure, and subsequent reduction of the lactam carbonyl afforded the intact pyrrolo[3,4-*b*][1,4]oxazine heterocycle **7**. Exchanging the α-methylbenzyl protecting group on N(4) for a *tert*-butoxycarbonyl (BOC) group and deprotection of the pyrrolidine nitrogen led to pyrrolo[3,4-*b*][1,4]oxazine (4a*S*,7a*S*)-**1**.

Our approach toward synthesizing the *trans*-fused pyrrolo[3,4-*b*][1,4]oxazine heterocycle focused on stereoselectively preparing a 2,3-disubstituted morpholine wherein the sustituents at C(2) and C(3) are *trans* with respect to each other. Thus, the known dicarboxylic acid **9** [7], prepared in near quantitative yield from commercial *cis*-epoxysuccinic acid (**8**), served as the logical starting point (Scheme 2). Esterification of **9** with absolute ethanol and hydrogen chloride, generated *in situ*

Scheme 1



Scheme 2. Reagents and conditions: (i) $BnNH_2$ (excess), H_2O, reflux, 3 h; (ii) AcCl, EtOH, 0°C, 1h; add substrate, reflux, 72 h; (iii) chloroacetyl chloride, CH_2Cl_2-aq. 1 *N* NaOH, 0°C, 15 min; (iv) NaH (1.8 eq.), THF-CH_3CN-DMF (90:5:5), 0°C, 1 h.



from ethanol and acetyl chloride, provided the corresponding diester in good yield. Esterification with ethanol in the presence of thionyl chloride was also effective; however, the yield was significantly lower, and chromatography was necessary to remove the impurities formed during the reaction. Treatment of the diester with chloroacetyl chloride under Shotten-Baumann conditions afforded α-chloroacetamide **10**. Under these conditions, 5–10% of the corresponding *o*-acylated product was formed along with 1–2% of di-acylated product. However, the *o*-acylated product could be easily removed by extracting the crude reaction mixture with aqueous hydrochloric acid. Subjection of chloroalcohol **10** to sodium hydride gave rise, after purification, to a 9:1 mixture [8] of morpholinones **11** and **12**, respectively. Fortuitously, whereas the desired *trans*-diester **11** was a solid (mp 117–118°C), the undesired *cis*-diester **12** was an oil. Thus, a simple trituration of the product mixture efficiently removed the undesired **12**, affording a 76% yield of pure **11**.

The structural assignments of **11** and **12** were based on a combination of 1D and 2D NMR experiments. For *trans*-diester **11**, the vicinal coupling constant between H_2 and H_3 was 1.7 Hz, which suggested that the ester groups adopt a pseudo *trans*-diaxial orientation to avoid $A^{1,2}$ strain between the C(3) ester moiety and the benzylic hydrogens (Fig. 1). This interpretation is consistent

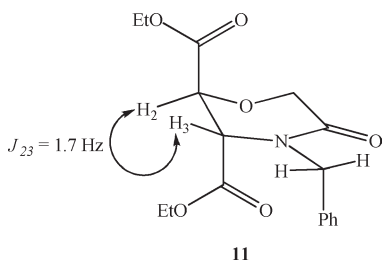
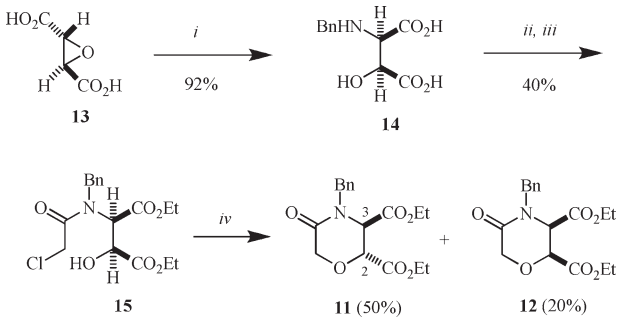


Figure 1. 3D representation of diester **11.** Arrow shows vicinal coupling relationship.

Scheme 3. Reagents and conditions: (i) $BnNH_2$ (excess), H_2O, reflux, 3 h; (ii) AcCl, EtOH, 0°C; add substrate, reflux, 72 h; (iii) chloroacetyl chloride, CH_2Cl_2-aq. 1.0 *N* NaOH, 0°C, 15 min; (iv) NaH (1.8 eq.), THF-CH_3CN-DMF (90:5:5), 0°C, 1 h.



with observations made by others on similar ring systems [9]. Also, once the pyrrolidine ring was fused onto **11** (*vide infra*), the H_2–H_3 vicinal coupling constant changed to ca. 9 Hz, which is consistent with a *trans*-diaxial orientation of the two vicinal hydrogens. The H_2–H_3 vicinal coupling constant for *cis*-diester **12** was 2.7 Hz, which is consistent with an axial-equitorial orientation of the two ester moieties.

Unexpectedly, subjection of alcohol **15**, prepared according to Scheme 3, to identical cyclization conditions [NaH (1.8 eq.), THF-CH_3CN-DMF (90:5:5), 0°C, 30 min] afforded a 2.5:1 mixture of **11** and **12**, respectively [8]. Clearly, equilibration of one of the esters is taking place during the reaction. Furthermore, it is likely that equilibration is occurring after ring closure based on the following observations: (1) resubmitting pure *trans*-diester **11** to the cyclization conditions for 30 min led to a 10:1 mixture of **11** and **12**, respectively. Likewise, resubmitting pure *cis*-diester **12** to the cyclization conditions for 30 min led to a 6:1 ratio of **11** and **12**, respectively; (2) stopping the cyclization reaction of **10** prior to completion (Scheme 2) and analysis of the reaction mixture found no evidence of diastereomer **15**.

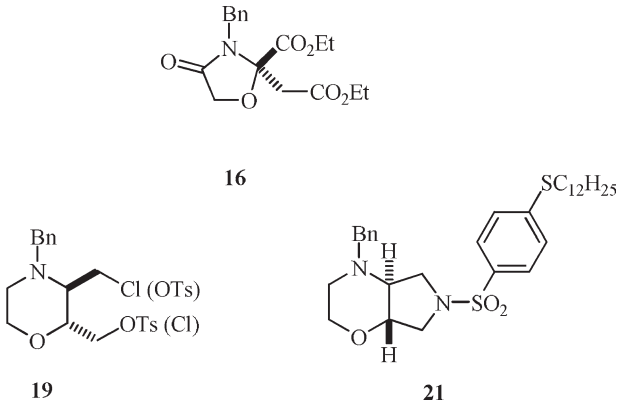
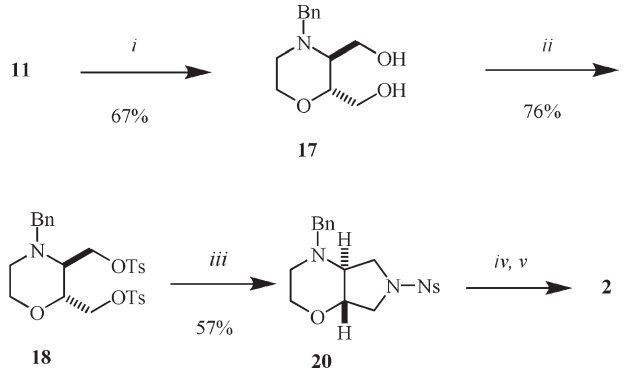


Chart 2.

Scheme 4. Reagents and conditions: (i) $LiAlH_4$ (5.0 eq.), THF, 0° → room temperature, 30 min, room temperature → reflux, 30 min; (ii) Ts_2O (3.0 eq.), pyridine (3.0 eq.), CH_2Cl_2, 0°C, 30 min; (iii) 4-nitrobenzenesulfonamide (3.0 eq.), DBU (2.0 eq.), CH_3CN, 70°C, 2 h; (iv) $C_{12}H_{25}SH$ (2.0 eq.), $LiOH•H_2O$ (2.0 eq.), DMF, room temperature, 2 h, 77%; (v) 4 *M* HCl-dioxane, MeOH, room temperature→40°C, 60%.

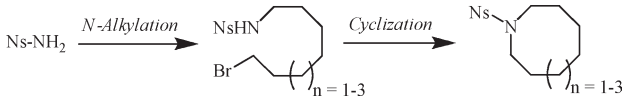


Interestingly, prolonged exposure of either **11** or **12** to sodium hydride in tetrahydrofuran at 0°C resulted, in addition to decomposition, in the formation of a new product, which, based on spectral data, we have assigned as ethyl 3-benzyl-2-(2-ethoxy-2-oxoethyl)-4-oxooxazolidine-2-carboxylate (**16**, Chart 2) [10].

With the stereochemistry at C(2) and C(3) secure, efforts were directed toward installing the remaining pyrrolidine ring. Toward this end, reduction of **11** with lithium aluminum hydride afforded diol **17** (Scheme 4). Bis-tosylate **18** was realized in 76% yield by treating diol **17** with tosic anhydride. The use of tosyl chloride in pyridine led, in addition to bis-tosylate **18**, a significant amount of monotosylate-monochloride products **19** (Chart 2).

Fukuyama has popularized the use of 2-nitro- and 4-nitrobenzenesulfonamide (2-Ns-NH_2, Ns-NH_2, respectively) as useful starting materials for the efficient construction of cyclic secondary amines [11]. The protocol involves a two-step alkylation-cyclization sequence (Scheme 5). Since this two-step protocol was primarily developed for the preparation of medium-sized rings, we were curious as to whether a pyrrolidine ring could be formed in a single pot *via* a double *N*-alkylation with Ns-NH_2. While we could find no examples of pyrrolidine ring formation *via* a double *N*-alkylation with Ns-NH_2, pyrrolidine ring formation *via* double *N*-alkylation with *para*-toluenesulfonamide (Ts-NH_2) is well precedented [12], including one example by Hong *et al*. [6] to prepare (4a*S*,7a*S*)-**1**. However, Ts-NH_2 was a less

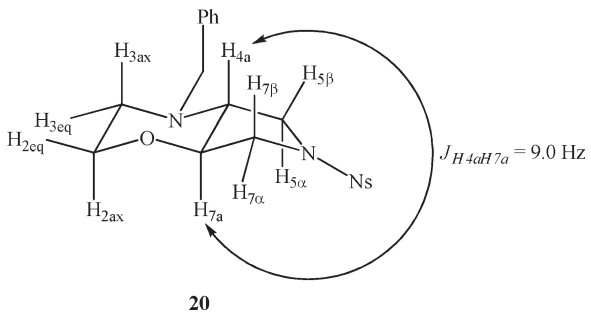
Scheme 5. Fukuyama's nitrobenzenesulfonamide methodology for the construction of secondary cyclic amines.



attractive nucleophile to us in that subsequent removal of the tosyl group typically requires either strongly reducing conditions, such as sodium naphthalide, or strongly acidic conditions. On the contrary, the nosyl group is typically removed under mild conditions [11]. We were pleased to find that heating an acetonitrile solution of bis-tosylate **18** with 4-nitrobenzenesulfonamide in the presence of DBU gave rise (57%) to pyrrolo[3,4-*b*][1,4]oxazine **20** (Scheme 4). While other bases, such as sodium hydride, potassium carbonate, or diisopropylethylamine, did effect ring closure, the reactions did not go to completion, even when additional base was added. No other organic-soluble product could be isolated from this reaction. Given the presence of DBU and the ease of bis-tosylate **18** forming an anti-periplanar relationship between the carbon-oxygen bond of one of the tosylates and the axial carbon-hydrogen bond at C(2) or C(3), it is possible that the elimination pathway was competing with substitution. However, no elimination byproducts could be isolated upon workup. That pyrrolo[3,4-*b*][1,4]oxazine **20** possessed a *trans*-ring fusion was readily confirmed based on the large coupling constant (9.0 Hz) between the bridgehead protons, H_{4a} and H_{7a} in the ^{1}H-NMR spectrum (Fig. 2). Additional 2D NMR experiments on **20** were also in support of the proposed structure (data not shown).

Cleavage of the nosyl group to afford pyrrolo[3,4-*b*][1,4]oxazine **2** was realized in 77% yield *via* treatment of sulfonamide **20** with dodecanethiol in the presence of lithium hydroxide [13] (Scheme 4). Under these conditions, ca. 15% of aryl thioether **21** was formed (Chart 2). This was not surprising given others have also observed this byproduct during thiol-mediated deprotection of nosyl-protected cyclic amines [14]. Wuts *et al*. [14a] has further observed that 2-nitrobenzenesulfonamide (2-Ns-NH_2) was less likely to produce the corresponding byproduct. Unfortunately, the use of 2-Ns-NH_2 in the pyrrolidine cyclization reaction led to inferior yields (20% *vs*. 57%).

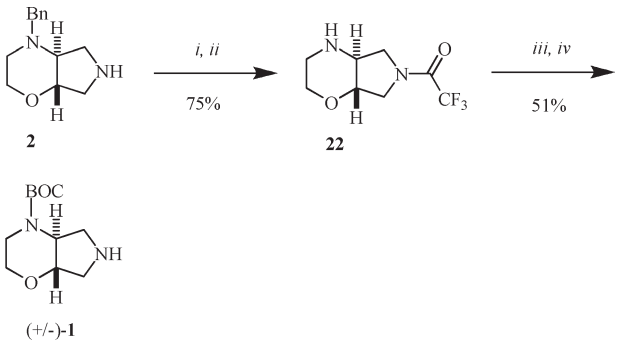
As a final proof of structure, we have converted benzyl-protected pyrrolo[3,4-*b*][1,4]oxazine **2** into



20

Figure 2. 3D Representation of compound **20**. Arrow shows vicinal coupling relationship.

Scheme 6. Reagents and conditions: (i) $(CF_3CO)_2O$ (2.0 eq.), Et_3N (4.0 eq.), CH_2Cl_2, 0°C → room temperature, 1.5 h; (ii) H_2, 10% Pd/C, MeOH, 42 psi, room temperature, 48 h; (iii) $(BOC)_2O$, CH_2Cl_2, room temperature, 24 h; (iv) K_2CO_3 (2.0 eq.), MeOH-water (5:1), room temperature, 1 h.



Hong's BOC-protected pyrrolo[3,4-*b*][1,4]oxazine **1** by the sequence outlined in Scheme 6. Thus, trifluoroacetylation of **2** and subsequent hydrogenolysis of the benzyl group led to amine **22**, which should serve as a useful intermediate for the preparation of pyrrolo[3,4-*b*][1,4]oxazine analogs connected through N(4). BOC protection of N(4) and hydrolysis of the trifluoroacetamide group afforded (+/−)-**1**. The spectral properties of our racemic (+/−)-**1** were consistent with those of (4a*S*,7a*S*)-**1** [6,15].

CONCLUSIONS

In summary, we have reported a practical and stereoselective eight-step synthesis of (+/−)-*trans*-4-benzyloctahydropyrrolo[3,4-*b*][1,4]oxazine (**2**) from inexpensive starting materials and reagents. Only two intermediates required chromatographic purification; otherwise, the remaining compounds were purified by precipitation or trituration. The conditions developed for the one pot double *N*-alkylation-pyrrolidine ring formation using 4-nitrobenzenesulfonamide and DBU will likely be of general interest to the synthetic community.

EXPERIMENTAL

Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). Assignments of key NMR signals were made by a combination of gHSQC, gHMBC, and ROESY experiments. Stereochemical assignments for compounds **11**, **12**, **20** and (+/−)-**1** were made based on a combination of ROESY and non-overlapping *J* coupling constants. Infrared (IR) spectra were recorded on a Bruker Vector 33 FTIR. High resolution mass spectra (MS) were acquired on an Agilent 1200 series LCMS TOF with UV detection. Combustion analyses were performed by QTI Intertek, Whitehouse, NJ. Melting points were recorded on an ®Electrothermal Mel-Temp 3.0 device and are uncorrected.

Reactions were monitored by thin layer chromatography (TLC) using Analtech silica gel GF 250 micron plates. The plates were visualized either by UV inspection or by staining with an ammonium molybdate/ ceric sulfate mixture. Flash chromatography was performed as described by Still *et al*. [16] using Aldrich column chromatography grade silica gel (200–400 mesh). All reagents were purchased from either the Aldrich Chemical Co. or TCI America Chemical Co. and used without further purification. All solvents were HPLC grade unless otherwise stated. Anhydrous solvents were purchased from EMD Chemical Co. and used as supplied.

***N*-Benzyl-*threo*-β-hydroxy-DL-aspartic acid (9).** This compound was prepared according to the procedure of Liwscitz [7] with slight modification:

To a stirred solution of *cis*-epoxysuccinic acid (8, 30 g, 227 mmol) in water (50 mL), benzylamine (84 mL, 770 mmol) was added. The mixture was heated to reflux for 3 h. The mixture was cooled to room temperature, followed by the addition of 15% aqueous sodium hydroxide until pH = 13. The aqueous layer was extracted with ether (3×) to remove the benzylamine. The ethereal layer was discarded. The aqueous layer was acidified with concentrated hydrochloric acid to pH = 4, which caused a white precipitate to form. The precipitate was filtered and washed with water. The pH of the mother liquor was re-adjusted to 4 with concentrated hydrochloric acid and additional precipitation occurred. The precipitate was filtered, washed with water. The combined precipitates were dried *in vacuo* to afford 52 g (96%) of 9 as a white solid: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.0–10.0 (br s, 2H), 7.35–7.22 (m, 5H), 4.25 (d, 1H, J = 5.5 Hz), 3.92 (ABq, 2H, J_{AB} = 12.9 Hz, $\Delta\nu_{AB}$ = 61.6 Hz), 3.58 (d, 1H, J = 5.9 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 173.5, 171.0, 137.1, 129.2, 128.9, 128.1, 69.79, 61.55, 50.75; high resolution MS (ESI) Calcd. for $C_{11}H_{14}NO_5$ [M + H] *m*/*e* 240.0892. Found: 240.0866. An analytical sample was prepared *via* recrystallization from water: mp 224–225°C (dec.) (Ref. [7] 225–226°C).

Diethyl *N*-benzyl-*threo*-β-hydroxy-DL-aspartate. To a stirred solution of dry ethyl alcohol (550 mL) at 0°C, acetyl chloride (54 mL, 760 mmol) was added. After complete addition, the solution was stirred at 0°C for 1 h. To this solution, diacid **9** (45.0 g, 190 mmol) was added, and the whole mixture was heated to reflux for 72 h. The mixture was cooled to room temperature, and the ethanol was removed *in vacuo* to afford a clear oil. The oil was partitioned between ether and saturated aqueous potassium carbonate solution. The ethereal layer was washed with aqueous potassium carbonate solution and brine. The ethereal layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford 43 g (77%) of diethyl *N*-Benzyl-*threo*-β-hydroxy-DL-aspartate as a white solid: R_f 0.31 (hexanes-ethyl acetate, 3:1), IR (CH_2Cl_2) 3490, 3347, 3028, 2982, 2906, 2872, 1741, 1465, 1454, 1258, 1190, 1107, 740, 700 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 4.46 (d, 1H, J = 2.7 Hz), 4.22 (q, 2H, J = 7.0 Hz), 4.25–4.16 (m, 1H), 4.13–4.05 (m, 1H), 3.74 (ABq, 2H, J_{AB} = 13.3 Hz, $\Delta\nu_{AB}$ = 124 Hz), 3.59 (d, 1H, J = 2.8 Hz), 1.26 (t, 3H, J = 6.8 Hz), 1.16 (t, 3H, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.4, 171.7, 139.5, 128.3, 128.2, 127.1, 72.10, 62.03, 61.93, 61.43, 52.15, 14.17, 14.00; high resolution MS (ESI) Calcd. for $C_{15}H_{22}NO_5$ [M + H] *m*/*e* 296.1529. Found: 296.1492. An analytical sample was prepared *via* recrystallization from hexanes-ethyl acetate: mp 40–41°C. Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.06; H, 7.13; N, 4.67.

Diethyl 2-(*N*-benzyl-2-chloroacetamido)-*threo*-3-hydroxysuccinate (10). To a rapidly stirred solution of diethyl *N*-Benzyl-*threo*-β-hydroxy-DL-aspartate (20.0 g, 67.7 mmol) in dichloromethane (160 mL) at 0°C, ice cold sodium hydroxide (102 mL of a 1.0 *M* aqueous solution) was added, followed by dropwise addition of a solution of chloroacetyl chloride (8.1 mL, 102 mmol) in dichloromethane (8.0 mL). After complete addition, the mixture was stirred at 0°C for 15 min. Sodium hydroxide (20 mL of a 1.0 *M* aqueous solution) was added, followed by separation of the layers. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The remaining oil was dissolved in ether and extracted three times with 3.0 *M* aqueous hydrochloric acid (to remove *o*-acylated byproduct). The ethereal layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford an oil. Trituration of the oil in hexanes-ether (9:1) gave 20.2 g (80%) of **10** as a white solid: mp 69–71°C; R_f 0.20 (hexanes-acetone, 85:15); IR (CH_2Cl_2) 3427, 2984, 1738, 1660, 1452, 1267, 1026, 737 cm^{-1}; 1H-NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H), 4.95–4.83 (m, 2H), 4.69 (ABq, 2H, J_{AB} = 17.2 Hz, $\Delta\nu_{AB}$ = 85.6 Hz), 4.25–4.10 (m, 4H), 4.00–3.85 (m, 2H), 1.51 (br s, 1H), 1.25 (t, 3H, J = 7.0 Hz), 1.18 (t, 1H, J = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.5, 169.2, 167.4, 135.4, 128.9, 128.1, 126.9, 70.94, 62.26, 62.13, 62.03, 53.58, 41.43, 13.99, 13.91; high resolution MS (ESI) Calcd. for $C_{17}H_{23}ClNO_6$ [M + H] *m*/*e* 372.1247. Found: 372.1208. Anal. Calcd. for $C_{17}H_{22}ClNO_6$: C, 54.92; H, 5.96; N, 3.77. Found: C, 54.87; H, 5.73; N, 3.70.

Diethyl *trans*-4-benzyl-5-oxomorpholine-2,3-dicarboxylate (11) and diethyl *cis*-4-benzyl-5-oxomorpholine-2,3-dicarboxylate (12). To a stirred suspension of sodium hydride (60% oil dispersion, 1.98 g, 49.4 mmol) in dry tetrahydrofuran (150 mL) at 0°C under nitrogen atmosphere, a solution of alcohol **10** (10.2 g, 27.4 mmol) in tetrahydrofuran-acetonitrile (50 mL, 4:1) *via* canula was added. After complete addition, DMF (10 mL) was added, and the mixtue was stirred at 0°C for 1 h. Once the reaction was complete (TLC monitoring), it was poured over a rapidly stirred solution of 10% aqueous acetic acid (100 mL). Note: once the cyclization was complete, the mixture becomes dark orange in color. If the reaction was not quenced shortly after the orange color appeared, 4-oxooxazolidine **16** began to form. In latter runs, we found that adding solid alcohol **10** directly to a 0°C suspension of 1.4 equivalents of sodium hydride in tetrahydrofuran-acetonitrile-DMF (9:0.5:0.5) for 1 h minimized the formation of **16**. The mixture was concentrated *in vacuo* to a volume of ca. 80 mL. The remaining liquid was extracted with ethyl acetate. The organic layer was extracted with saturated aqueous potassium carbonate solution (to remove carboxylic acid byproducts). The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The organic layer was passed through a short plug of silica gel to remove base-line impurities. The organic layer was concentrated *in vacuo* to a tan solid. Trituration of the remaining solid in hexanes-ether (9:1) gave 5.9 g (64%) of **11** as a fluffy white solid. The mother liquor was concentrated *in vacuo* and purified by flash chromatography on silica gel. Elution with hexanes-ethyl acetate (70:30) afforded

an additional 1.1 g of **11** as a fluffy white solid (76% combined yield of **11**). Further elution afforded 0.70 g (8%) of *cis*-diester **12** as a clear oil.

***trans*-Diester 11.** R_f 0.32 (hexanes-acetone, 85:15); IR (CH_2Cl_2) 2987, 2941, 1738, 1657, 1454, 1426, 1296, 1137, 737, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30–7.10 (m, 5H), 4.68 (m, 1H), 4.57 (ABq, 2H, J_{AB} = 14.8 Hz, $\Delta\nu_{AB}$ 676 Hz), 4.50 (ABq, 2H, J_{AB} = *13.2 Hz*, $\Delta\nu_{AB}$ = 184 Hz), 4.23 (d, 1H, J = 1.8 Hz), 4.20 (dq, 2H, J = 7.4, 2.3 Hz), 4.05 (m, 1H), 3.75 (m, 1H), 1.23 (t, 3H, J = 7.4 Hz), 1.00 (t, 3H, J = 7.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.5, 168.0, 166.3, 135.1, 128.9, 128.6, 128.0, 72.88, 64.80, 62.51, 61.93, 58.61, 48.79, 14.05, 13.73; high resolution MS (ESI) Calcd. for $C_{17}H_{22}NO_6$ [M + H] *m*/*e* 336.1478. Found: 336.1441. An analytical sample was prepared *via* recrystallization from hexanes-ethyl acetate: mp 117–118°C. Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.95; H, 6.23; N, 4.12.

***cis*-Diester 12.** R_f 0.15 (hexanes-acetone, 85:15); IR ($CDCl_3$) 2984, 1750, 1669, 1453, 1209, 1140, 1028, 704 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H), 4.65 (ABq, 2H, J_{AB} = 14.9 Hz, $\Delta\nu_{AB}$ = 576 Hz), 4.47 (ABq, 2H, J_{AB} = 17.2 Hz, $\Delta\nu_{AB}$ = 62.5 Hz), 4.42 (d, 1H, J = 2.7 Hz), 4.23–4.03 (m, 5H), 1.24 (t, 3H, J = 7.0 Hz), 1.18 (t, 3H, J = 7.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.2, 166.1, 166.1, 135.1, 128.9, 128.6, 128.1, 74.67, 67.75, 62.51, 62.05, 59.09, 49.35, 14.06, 14.01; high resolution MS (ESI) Calcd. for $C_{17}H_{22}NO_6$ [M + H] *m*/*e* 336.1478. Found: 336.1441. Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.64; H, 6.24; N, 4.12.

4-Oxooxazolidine 16. R_f 0.34 (hexanes-acetone, 85:15); IR ($CHCl_3$) 2983, 1735, 1717, 1404, 1266, 1182, 1057, 1028, 704 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 5H), 4.54 (ABq, 2H, J_{AB} = 16 Hz, $\Delta\nu_{AB}$ = 45 Hz); 4.47 (ABq, 2H, J_{AB} = 14 Hz, $\Delta\nu_{AB}$ = 38 Hz); 4.06–3.87 (m, 4H), 2.90 (ABq, 2H, J_{AB} = 15 Hz, $\Delta\nu_{AB}$ = 108 Hz); 1.15 (t, 6H, J = 7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4, 167.9, 167.6, 135.4, 128.5, 128.1, 127.7, 93.1, 67.3, 62.1, 60.9, 43.72, 39.3, 13.80, 13.65; high resolution MS (ESI) Calcd. for $C_{17}H_{22}NO_6$ [M + H] *m*/*e* 336.1478. Found: 336.1441. Anal. Calcd. for $C_{17}H_{21}NO_6 \bullet 0.25H_2O$: C, 60.07; H, 6.38; N, 4.12. Found: C, 59.94; H, 6.15; N, 4.02.

***trans*-(4-Benzylmorpholine-2,3-diyl)dimethanol (17).** To a stirred suspension of lithium aluminum hydride (3.71 g, 97.7 mmol) in dry tetrahydrofuran (250 mL) at 0°C, a solution of diester **11** (6.55 g, 19.5 mmol) in tetrahydrofuran (50 mL) *via* canula was added. After complete addition, the mixture was warmed to room temperature for 30 min, followed by heating to reflux for 30 min. The mixture was cooled to 0°C, and 3.7 mL of water was added dropwise, followed by sodium hydroxide (3.7 mL of a 3.0 *M* aqueous solution), followed by 11 mL of water. The mixture was stirred at room temperature for 15 min, followed by the addition of ethyl acetate and anhydrous potassium carbonate. After further stirring for 15 min, the mixture was filtered, and the precipitate was washed with ethyl acetate. The filtrate was concentrated *in vacuo* to afford an oil. The crude product was purified by flash chromatography on silica gel. Elution with ethyl acetate gave 3.1 g (67%) of **17** as a clear oil: R_f 0.23 EtOAc; IR (CH_2Cl_2) 3650, 3550, 30390, 3005, 1450, 1400, 1275, 1130, 1075, 925 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5H), 4.00 (dd, 1H, J = 12.1, 3.5 Hz), 3.82, (m, 1H), 3.78 (ddd, 1H, J = 11.7, 3.5, 1.9 Hz), 3.71–3.65 (m, 2H), 3.64 (ABq, 2H, J_{AB} = 13.3 Hz, $\Delta\nu_{AB}$ = 392 Hz), 3.58 (td, 1H, J = 11.3, 1.9 Hz), 3.55 (m, 1H), 2.73, (br s, 1H), 2.67 (dm, 1H, J = 11.8 Hz), 2.45 (m, 1H), 2.33 (td, 1H, J = 11.3, 3.5 Hz), 2.07 (br s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.9, 128.1, 127.8, 126.7, 77.31, 64.99, 62.64, 62.19, 58.02, 50.54; high resolution MS (ESI) Calcd. for $C_{13}H_{20}NO_3$ [M + H] *m*/*e* 238.1472. Found: 238.1437. %Water (KF): 2.07. Anal. Calcd. for $C_{13}H_{19}NO_3 \bullet 2.07\%$ H_2O: C, 64.48; H, 8.13; N, 5.78. Found: C, 64.15; H, 8.17; N, 5.74.

***trans*-(4-Benzylmorpholine-2,3-diyl)bis(methylene) bis(4-methylbenzenesulfonate) (18).** To a stirred solution of diol **17** (1.00 g, 4.21 mmol) in dichloromethane (40 mL) at 0°C, pyridine (1.0 mL, 12.6 mmol), followed by *p*-toluenesulfonic anhydride (4.13 g, 12.6 mmol) was added. The mixture was stirred at 0°C for 30 min. The mixture was diluted with ether and water. The organic layer was washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to an amber oil. The crude product was purified by flash chromatography on silica gel. Elution with hexanes-ethyl acetate (80:20 → 70:30), followed by further elution with hexanes-ethyl acetate-triethylamine (58:40:2) afforded 1.75 g (76%) of **18** as a clear oil: R_f 0.25 (hexanes-ethyl acetate, 3:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 2H, J = 8.2 Hz), 7.72 (d, 2H, J = 8.6 Hz), 7.30 (d, 2H, J = 8.2 Hz, 7.28 (d, 2H, J = 8.4 hz), 7.25–7.10 (m, 5H), 4.26 (dd, 1H, J = 10.9, 5.4 Hz), 4.23–4.18 (m, 2H), 4.15 (td, 1H, J = 10.5, 3.9 Hz), 3.69–3.65 (m , 1H), 3.63–3.54 (m, 1H), 3.51 (ABq, 2H, J_{AB} = 13.3 Hz, $\Delta\nu_{AB}$ = 188 Hz), 3.47–3.38 (m, 1H), 2.66–2.60 (m, 1H), 2.56–2.48 (m, 1H), 2.39 (s, 6H), 2.21–2.13 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.1, 144.9, 137.6, 132.7, 132.4, 130.0, 129.8, 128.6, 128.3, 128.0, 127.9, 127.2, 72.55, 68.32, 65.29, 63.13, 58.43, 57.81, 48.29, 21.61; low resolution MS (ESI) *m*/*e* 546 [M + H]. Note: In our hands, bis-tosylate **18** decomposed at room temperature under nitrogen atmosphere by ca. 20% (based on the ^{1}H-NMR spectrum) over a two week period. In latter runs, bis-tosylate **18** was stored at 0°C and used in the next reaction within a 24 h period, which minimized decomposition.

***trans*-4-Benzyl-6-(4-nitrophenylsulfonyl)octahydro- pyrrolo[3,4-b][1,4]oxazine (20).** To a stirred solution of 4-nitrobenzenesulfonamide (1.44 g, 7.15 mmol) and DBU (0.71 mL, 4.76 mmol) in dry acetonitrile (10 mL) at 70°C, a solution of bis-tosylate **18** (1.30 g, 2.38 mmol) in acetonitrile (5.0 mL) *via* canula was added. After complete addition, the mixture was stirred at 70°C and monitored by TLC. Once the starting material had been consumed (ca. 2 h), the mixture was diluted with ether-ethyl acetate (1:1) and water. The organic layer was washed five times with 1.0 *M* aqueous sodium hydroxide solution (to remove excess 4-nitrobenzenesulfonamide). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered through a short pad of silica gel (to remove baseline impurities), and concentrated *in vacuo* to an orange solid. Trituration of the crude product in hexanes-ether afforded 560 mg (58%) of **20** as a tan solid: R_f 0.23 (hexanes-ethyl acetate, 3:1); IR (CH_2Cl_2) 3104, 3060, 2988, 2871, 2822, 1532, 1351, 1266, 1172, 1140, 740 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3CN) δ 8.45 (d, 2H, J = 8.2 Hz), 8.06 (d, 2H, J = 8.2 Hz), 7.38–7.33 (m, 5H), 3.85 (dd, 1H, J = 11.7, 3.7 Hz), 3.69 (dd, 1H, J = 8.0, 8.0 Hz), 3.65 (dd, 1H, J = 9.2, 6.8 Hz), 3.57 (td, 1H, J = 11.8, 2.67), 3.43 (ABq, 2H, J_{AB} = 13.3 Hz, $\Delta\nu_{AB}$ = 160 Hz), 3.11 (dd, 1H, J = 10.4, 9.2 Hz), 2.95 (dd,

1H, J = 10.8, 9.7 Hz), 2.63 (ddd, 1H, J = 12.1, 2.67, 1.24 Hz), 2.12 (ddd, 1H, J = 10.8, 9.0, 7.1 Hz); ^{13}C-NMR (125 MHz, CD_3CN) δ 156.6, 142.5, 137.7, 129.1, 128.6, 128.3, 127.4, 124.7, 77.9, 67.7, 65.2, 60.6, 52.0, 49.4, 48.6; high resolution MS (ESI) Calcd. for $C_{19}H_{22}N_3O_5S$ [M + H] *m*/*e* 404.1312. Found: 404.1274. An analytical sample was prepared *via* recrystallization from hexanes-ethyl acetate: mp 155–157°C. Anal. Calcd. for $C_{19}H_{21}N_3O_5S$: C, 56.56; H, 5.25; N, 10.41. Found: C, 56.21; H, 4.89; N, 10.21.

***trans*-4-Benzyloctahydropyrrolo[3,4-*b*][1,4]oxazine dihydrochloride (2).** To a stirred solution of sulfonamide **20** (600 mg, 1.49 mmol) in DMF (2.0 mL), dodecanethiol (0.71 mL, 2.97 mmol) and lithium hydroxide hydrate (125 mg, 2.97 mmol) were added. The mixture was stirred at room temperature for 2 h. The mixture was diluted with hexanes-ethyl acetate (1:1) and 1.0 *M* aqueous hydrochloric acid, and the layers were separated. The organic layer was extracted with aqueous hydrochloric acid, and the combined aqueous layers were back extracted with 1:1 hexanes-ethyl acetate. The organic layers were discarded, and the aqueous layer was basified with 50% aqueous sodium hydroxide to pH = 13. The aqueous layer was extracted twice with dichloromethane-methanol (9:1). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 250 mg (77%) of the free base of **2** as a brown semi-solid: R_f 0.40 (chloroform-methanol-ammonium hydroxide, 90:9:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27–7.18 (m, 5H), 3.85 (dd, 1H, J = 11.7, 3.5 Hz), 3.67 (m, 1H), 3.57 (ddd, 1H, J = 10.1, 9.0, 7.0 Hz), 3.46 (ABq, 2H, J_{AB} = 12.9 Hz, $\Delta\nu_{AB}$ = 168 Hz), 3.43–3.25 (br s, 1H), 3.22–3.11 (m, 2H), 2.85 (t, 1H, J = 10.1 Hz), 2.71 (t, 1H, J = 10.1 Hz), 2.63, dm, 1H, J = 12.1 Hz), 2.27 (ddd, 1H, J = 11.0, 9.0, 6.7 Hz), 2.09 (td, 1H, J = 12.2, 3.6 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 137.5, 129.1, 128.2, 127.3, 80.34, 68.08, 66.97, 61.42, 52.60, 46.75, 46.29; low resolution MS (ESI) *m*/*e* 219 [M + H].

To a solution of the above semi-solid (250 mg) in methanol (3 mL), a 4.0 *M* solution of hydrogen chloride in dioxane (1.0 mL) was added. The solution was warmed to 40°C in a water bath for 10 min, followed by concentration *in vacuo*. Trituration of the remaining residue in ethyl acetate afforded 200 mg (60%) of **2** as a white solid: mp 253–255°C; ^{1}H-NMR (400 MHz, D_2O) δ 7.41–7.34 (m, 5H), 4.26 (ABq, 2H, J_{AB} = 12.9 Hz, $\Delta\nu_{AB}$ = 48.31 Hz), 4.11 (dd, 1H, J = 13.3, 3.9 Hz), 4.00 (ddd, 1H, J = 11.0, 10.2, 7.5 Hz), 3.76 (td, 1H, J = 12.5, 2.4 Hz), 3.64–3.56 (m, 2H), 3.47 (ddd, 1H, J =11.4, 10.1, 7.4 Hz), 3.33 (dm, 1H, J = 10.5 Hz), 3.14–3.05 (m, 3H); ^{13}C-NMR (100 MHz, D_2O) δ 130.5, 130.0, 128.9, 127.7, 74.27, 64.87, 61.46, 59.82, 50.94, 43.05, 41.61; high resolution MS (ESI) $C_{13}H_{19}N_2O$ [M + H] *m*/*e* 219.1525. Found: 219.1491. %Water (KF): 0.47. Anal. Calcd. for $C_{13}H_{18}N_2O\bullet 2HCl\bullet 0.47\%\ H_2O$: C, 53.35; H, 6.94; N, 9.57. Found: C, 52.97; H, 6.81; N, 9.35.

2,2,2-Trifluoro-1-(*trans*-hexahydropyrrolo[3,4-*b*][1,4] oxazin-6(2H)-yl)ethanone (22). To a stirred suspension of **2** (100 mg, 0.34 mmol) in dichloromethane (3 mL) at 0°C were added triethylamine (190 μL, 1.37 mmol) and trifluoroacetic anhydride (95 μL, 0.69 mmol). The mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction was diluted with dichloromethane and washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to an oil. The crude product was purified by chromatography on silica gel. Elution with hexanes-ethyl acetate-triethylamine (75:24:1) afforded 85 mg (79%) of 2,2,2-trifluoro-1-(*trans*-hexahydropyrrolo[3,4-*b*][1,4] oxazin-6(2H)-yl)ethanone as an oil: R_f 0.62 (hexanes-ethyl acetate, 1:1); ^{1}H-NMR [400 MHz, $CDCl_3$, two rotomers present (1:1)] δ 7.30–7.18 (m, 5H), 3.98–3.58 (m, 4H), 3.41–3.08 (m, 3H), 2.67 (t, 1H, J = 12.5 Hz), 2.37 (m, 1H), 2.18 (m, 1H); ^{13}C-NMR [100 MHz, $CDCl_3$, two rotomers present (1:1)] δ 156.1 (q, J = 37 Hz), 155.9 (q, J = 37 Hz), 136.7, 136.5, 129. 1, 129.0, 128.4, 128.3, 127. 7, 127.6, 116.0 (q, J = 286 Hz), 115.9 (q, J = 285 Hz), 78.14, 77.01, 67.94, 67. 89, 65.69, 63.85, 61.32, 61.01, 52.34, 52.08, 48.24, 48.15, 47.76, 47.72; ^{19}F-NMR [376 MHz, methanol-d_4, 2 rotomers present (1:1)] δ − 73.68, −73.90; low resolution MS (ESI) *m*/*e* 315 [M + H].

The product from above (85 mg, 0.27 mmol) was dissolved in methanol (15 mL), and 80 mg of 10% palladium on activated carbon was added. The suspension was placed in a Parr hydrogenation bottle and hydrogenated (42 PSI, room temperature) for 48 h. The reaction mixture was filtered through Celite and washed with methanol. The solution was concentrated *in vacuo* to afford 57 mg (95%) of **22** as an oil: R_f 0.40 (hexanes-ethyl acetate, 1:1); ^{1}H-NMR [400 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ 3.90–3.77 (m, 3H), 3.70–3.59 (m, 1H), 3.50–3.39 (m, 1H), 3.34 (t, 0.5H, J = 10.1 Hz), 3.26–3.15 (m, 1H), 3.06 (t, 0.5H, J = 11.3 Hz); 3.00–2.73 (m, 3H), 1.91 (br s, 1H); ^{13}C-NMR [100 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ 156.1 (q, J = 37 Hz), 155.9 (q, J = 37 Hz); 116.0 (q, J = 284 Hz); 78.90, 77.74, 68.05, 67.99, 59.31, 57.68, 48.54, 48.50, 47.80, 47.62, 45.83, 45.72; ^{19}F-NMR [376 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ −72.51, −72.76; low resolution MS (ESI) 225 [M + H].

***tert*-Butyl (+/−)-*trans*-hexahydropyrrolo[3,4-*b*][1,4] oxazine-4(4a*H*)-carboxylate [(+/−)-1].** To a stirred solution of **22** (55 mg, 0.25 mmol) in dichloromethane (1.0 mL), di-*tert*-butyl dicarbonate (60 mg, 0.27 mmol) was added. The mixture was stirred under nitrogen atmosphere for 4 h. The reaction mixture was purified by chromatography on silica gel. Elution with heptane-ethyl acetate (9:1 → 1:1) afforded 55 mg (70%) of *tert*-butyl *trans*-6-(2,2,2-trifluoroacetyl)hexahydropyrrolo[3,4-*b*][1,4]oxazine-4(4a*H*)-carboxylate as an oil: R_f 0.58 (hexanes-ethyl acetate, 1:1); ^{1}H-NMR [400 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ 4.43 (m, 0.5H), 4.35 (m, 0.5H), 4.00–3.94 (m, 1H), 3.93–3.75 (m, 3H), 3.69–3.59 (m, 2H), 3.57–3.42 (m, 1H), 3.34 (t, 0.5H, J = 10.6 Hz), 3.20 (t, 0.5H, J = 10.9 Hz), 3.11–2.87 (m, 2H), 1.40 (s, 9H); ^{13}C-NMR [100 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ 160.0 (q, J = 37 Hz), 159.9 (q, J = 37 Hz), 155.3, 155.2, 116.0 (q, J = 288 Hz), 115.9 (q, J = 288 Hz), 81.50, 78.51, 77.49, 67.40, 67.37, 57.96, 56.59, 49.06, 48.97, 46.67, 46.61, 28.15, 28.09; ^{19}F-NMR [376 MHz, $CDCl_3$, 2 rotomers present (1:1)] δ −72.22, −72.63; high resolution MS (ESI) Calcd. for $C_{13}H_{19}N_2O_4F_3Na$ [M + Na] *m*/*e* 347.1222. Found: 347.1189.

To a stirred solution of *trans*-6-(2,2,2-trifluoroacetyl) hexahydropyrrolo[3,4-*b*][1,4]oxazine-4(4a*H*)-carboxylate (27 mg, 0.83 mmol) in methanol-water (600 μL, 5:1) at room temperature, potassium carbonate (23 mg, 0.17 mmol) was added. The mixture was stirred at room temperature for 1 h. The mixture was diluted with water and ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford 18 mg (95%) of (+/−)-**1** as an oil:

R_f 0.42 (dichloromethane-methanol-ammonium hydroxide, 89:10:1); ^{1}H-NMR (500 MHz, CD_3CN) δ 3.99 (ddd, 1H, J = 11.8, 3.9, 1.56 Hz), 3.81 (ddd, 1H, J = 13.5, 3.06, 1.53 Hz), 3.64 (td, 1H, J = 11.9, 3.1 Hz), 3.6–3.5 (br m, 1H), 3.48 (app. q, 1H, J = 9.6 Hz), 3.15–2.90 (br m, 2H), 2.99–2.94 (m, 1H), 2.91 (ddd, 1H, J = 13.5, 12.0, 3.8 Hz), 2.85–2.68 (br m, 1H), 1.46 (s, 9H); ^{13}C-NMR (125 MHz, CD_3CN) δ 155.9, 81.3, 79.8, 67.2, 59.9, 47.8, 45.0, 44.6, 27.9; high resolution MS (ESI) Calcd. for $C_7H_{13}N_2O_3$ [M – ^{t}Bu + 2H] *m/e* 173.0945. Found: 173.0920.

***N*-Benzyl-*erythro*-β-hydroxy-DL-aspartic acid (14).** This material was prepared according to the established procedure with slight modification:

To a stirred solution of (+/−)-*trans*-epoxysuccinic acid (**13**, 20.0 g, 151 mmol) in deionized water (70 mL), benzylamine (50 mL, 460 mmol) was added. The mixture was heated to reflux under nitrogen atmosphere. A precipitant began to form after ∼15 min at reflux. After 4 h of heating, the reaction was cooled to room temperature and treated with 2.5 N aqueous sodium hydroxide (∼140 mL) to adjust the pH to ∼11. The aqueous layer was extracted with ether (4 × 100 mL) to remove the benzylamine. The aqueous layer was acidified with concentrated hydrochloric acid to pH ∼4 (ca. 19 mL), which caused a white precipitate to form. The precipitate was collected by suction filtration, washed with water (2 × 100 mL) and dried *in vacuo* (vacuum oven, 65°C, house vacuum) to afford 30.4 g (84%) of **14** as a white solid: ^{1}H-NMR (400 MHz, D_2O) δ 7.41 (s, 5H), 4.10–4.34 (m, 3H), 3.81 (d, 1H, J = 4.1 Hz); ^{13}C-NMR (100 MHz, D_2O) δ 175.9, 170.1, 130.6, 129.9, 129.6, 129.2, 70.24, 64.06, 50.60; high resolution MS (ESI) Calcd. for $C_{11}H_{14}NO_5$ [M + H] *m/e* 240.0892. Found: 240.0866. An additional 3.0 g of **20** was obtained from the filtrates upon standing overnight. Combined yield: 92%.

Diethyl *N*-benzyl-*erythro*-β-hydroxy-DL-aspartate. To a stirred solution of dry ethyl alcohol (250 mL) at 0°C under nitrogen atmosphere, acetyl chloride (18 mL, 250 mmol) was added dropwise. After complete addition, the reaction was stirred at 0°C for 30 min. Diacid **14** (12.0 g, 50 mmol) was added in one portion, and the suspension was slowly heated to reflux for 72 h. The reaction mixture was filtered, and the collected precipitate (unreacted **14**) was set aside. The filtrate was concentrated under reduced pressure. The remaining residue was partitioned between ether (100 mL) and half-saturated aqueous potassium carbonate solution (50 mL). The ethereal layer was extracted with potassium carbonate solution. The combined aqueous layers were back-extracted with ether. The combined ethereal layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 6.1 g (41%) of diethyl *N*-Benzyl-*erythro*-β-hydroxy-DL-aspartate as a tan oil: R_f 0.20 (heptane-ethyl acetate, 75:25); IR ($CDCl_3$) 3475, 2983, 1734, 1189, 1116, 1026, 739, 669 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H), 4.51 (d, 1H, J = 3.4 Hz), 4.29–4.15 (m, 4H), 3.98 (d, 1H, J = 13.0 Hz), 3.77 (d, 1H, J = 13.0 Hz), 3.71 (d, 1H, J = 3.1 Hz), 3.43 (br s, 1H), 2.30 (br s, 1H), 1.29 (t, 6H, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.9, 171.0, 139.3, 128.5, 128.3, 127.2, 71.83, 63.23, 61.81, 61.38, 52.60, 14.18, 14.13; high resolution MS (ESI) Calcd. for $C_{15}H_{22}NO_5$ [M + H] *m/e* 296.1529. Found: 296.1492. Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.87; H, 7.23; N, 4.73.

Diethyl 2-(*N*-benzyl-2-chloroacetamido)-*erythro*-3-hydroxysuccinate (15). To a stirred solution of diethyl *N*-benzyl-*erythro*-β-hydroxy-DL-aspartate (5.0 g, 17 mmol) in dichloromethane (40 mL) in an ice-brine bath (−10°C) under nitrogen atmosphere, sodium hydroxide (25 mL of 1.0 N aqueous solution) was added. The mixture was vigorously stirred while a solution of chloroacetyl chloride (2.0 mL, 25 mmol) in dichloromethane (4.0 mL) was added dropwise *via* syringe (addition time ∼10 min). Halfway through the addition, the reaction mixture began to thicken. The ice-brine bath was replaced with an ice bath. After complete addition, the reaction mixture was stirred at 0°C for an additional 15 min. Sodium hydroxide (10 mL of a 1.0 *N* aqueous solution) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The remaining residue was dissolved in ether (100 mL) and extracted with 3 *N* hydrochloric acid (to remove *o*-acylated byproduct). The ethereal layer was washed with brine (2×), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford 6.2 g (99%) of **15** as a viscous tan oil: R_f 0.17 (heptane-ethyl acetate, 75:25); IR ($CDCl_3$) 3462, 2983, 1738, 1163, 1203, 1127, 1203, 1025, 669 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43–7.23 (m, 5H), 5.56 (s, 1H), 4.96–4.81 (m, 2H), 4.44 (br s, 1H), 4.31 (q, 2H, J = 7.2 Hz), 4.26–4.00 (m, 4H), 3.71 (d, 1H, J = 2.4 Hz), 1.34 (t, 3H, J = 7.2 Hz), 1.24 (t, 3H, J = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.4, 168.8, 167.6, 136.6, 129.0, 127.8, 126.1, 70.85, 62.70, 62.02, 61.34, 51.17, 41.61, 14.11, 13.97; high resolution MS (ESI) Calcd. for $C_{17}H_{23}ClNO_6$ [M + H] *m/e* 372.1247. Found: 372.1208. %Water(KF): 0.46. Anal. Calcd. for $C_{17}H_{22}ClNO_6$•0.46% H_2O: C, 54.66; H, 5.98; N, 3.75. Found: C, 54.32; H, 5.98; N, 3.61.

Diethyl *trans*-4-benzyl-5-oxomorpholine-2,3-dicarboxylate (11) and diethyl *cis*-4-benzyl-5-oxomorpholine-2,3-dicarboxylate (12). To a stirred suspension of sodium hydride (60% oil dispersion, 0.22 g, 5.5 mmol) in dry tetrahydrofuran (25 mL) at 0°C under nitrogen atmosphere, a solution of alcohol **15** (0.99 g, 2.7 mmol) in tetrahydrofuran-acetonitrile (5 mL, 4:1) was added dropwise *via* syringe (addition took ∼10 min). During the addition, the reaction turned from a grey suspension to a yellow suspension. After complete addition, the reaction mixture was stirred at 0°C for 30 min. The reaction mixture was poured into a rapidly stirred solution of 10% aqueous acetic acid (20 mL). The mixture was concentrated *in vacuo* to a volume of ca. 15 mL. The remaining residue extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with 1.0 *N* aqueous sodium hydroxide solution (to remove minor carboxylic acid byproducts), brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford an orange solid (0.9 g). The crude product was purified by Biotage® on silica gel. Elution with heptane-ethyl acetate (95:5) afforded 0.45 g (50%) of *trans*-product **11** as a white solid and 0.18 g (20%) of *cis*-product **12** as an oil. The spectral properties of compounds **11** and **12** from this experiment were identical in all respects to compounds **11** and **12** obtained above.

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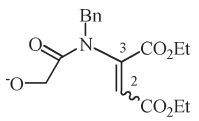
[10] The formation of 4-oxooxazolidine **16** could arise *via* base-catalyzed-elimination of either **11** or **12** to afford ring-opened intermediate **23**, followed by conjugate addition of the alkoxide at C(3),



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[15] Due to severe line broadening of the C(5) and C(7) protons in the ^{1}H NMR spectrum of (+/−)-**1** ($CDCl_3$), exact comparison of our spectra of (+/−)-1 to Hong's reported ^{1}H NMR spectra of (4aS,7aS)-1 was difficult [6]. However, we believe our structure of (+/−)-1 to be correct based on extensive 1D and 2D NMR experiments performed in CD_3CN, where the line broadening was less severe.

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