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A SYNTHESIS OF HEXAHYDRO-*H*-OXAZOLO[3,4-*a*]PYRAZIN-3-ONES FROM FUSED AZIRIDINES

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Abstract – The piperazine ring is a common structural component of a large variety of biologically active small molecules. While a number of methods to prepare simple piperazine rings are known, the methods available for the synthesis of fused-ring piperazines are lacking. We report here a method for the synthesis of novel fused-ring piperazines through reaction with fused-ring aziridines followed by a ring closure to form the fused-ring piperazine system. The dependence of the reaction on the stereochemistry of the system has also been studied.

The piperazine ring is a common structural motif in pharmaceuticals. 8% of the top 100 drugs by retail sales in 2013 contain a piperazine ring.[1] Of these 8 drugs 5 contain an unsubstituted piperazine. Some examples of these include molecules such as quetiapine and eszopiclone. For the remaining 3, the piperazine is part of a fused ring system as seen in sitagliptin. In addition to being found in marketed drugs, the piperazine ring is found in a number of additional pharmacologically active compounds. A search in the Web of Science for piperazines, limited to pharmacology/pharmacy, lists 30,767 citations from 2000-2015. Just two examples are the nootropic **1**[2] and α7 nicotinic modulator **2**.[3]

Methods to prepare piperazine rings typically involve some type of dialkylation reaction with an amine or diamine[4] or an intramolecular coupling of a diimine.[5] More recent routes for piperazine synthesis have involved ring expansion reactions,[6] reduction of pyrazine *N*-oxides,[7] Ugi reactions,[8] and palladium-catalyzed cyclizations.[9]

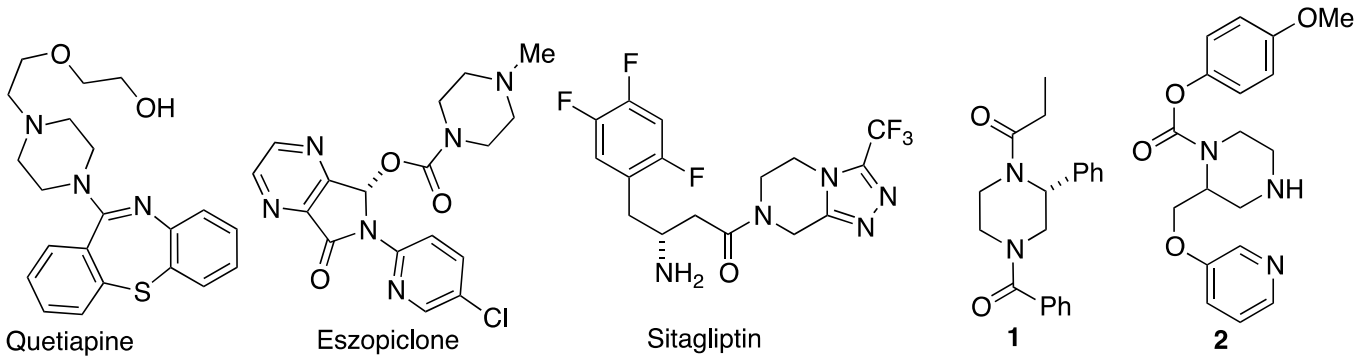
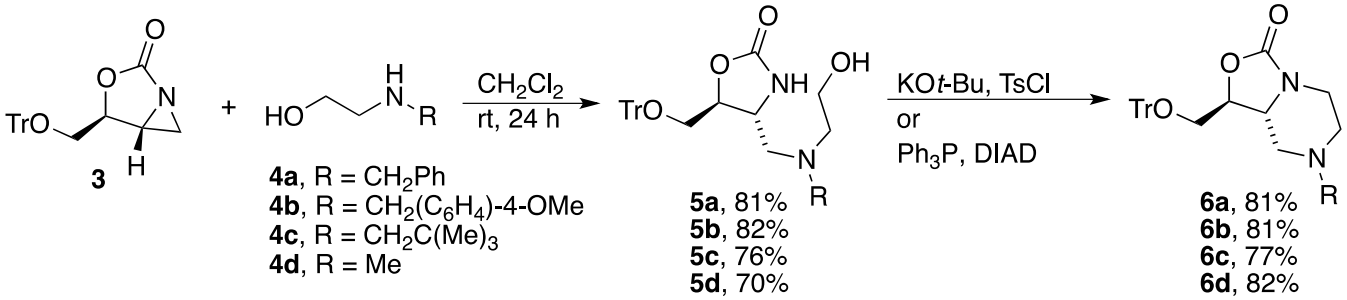


Figure 1. Piperazine rings found in pharmacologically active compounds

However, methods to prepare substituted or fused ring piperazines are lacking. We were interested in preparing piperazines fused to an oxazolidinone ring (hexahydro-*H*-oxazolo[3,4-*a*]pyrazin-3-ones) as part of an ongoing project aimed at optimizing small molecule modulators of the T box riboswitch antiterminator.[10] We have previously reported on the synthesis of fused ring piperazines through an intramolecular azide-alkyne cycloaddition.[10b] This report outlines our initial work on the synthesis of substituted, fused ring piperazines (**6**) from fused ring aziridines.

The planned synthesis of the fused ring piperazine system is outlined Scheme 1. Treatment of fused ring aziridine **3** with an appropriately substituted secondary amine would be expected to provide oxazolidinone **5**. We have previously shown that the reaction of secondary amines with aziridine **3** provide the expected aminomethyl oxazolidinone.[10e] Alternatively, the use of a primary amine can lead to either an aziridinyl urea[11] or an imidazolidinone[12] depending upon the reaction conditions. With the substituted oxazolidinone in hand, cyclization to **6** could be initiated through conversion of the hydroxyl group to a better leaving group (e.g. convert an alcohol to a tosylate, or Mitsunobu reaction).



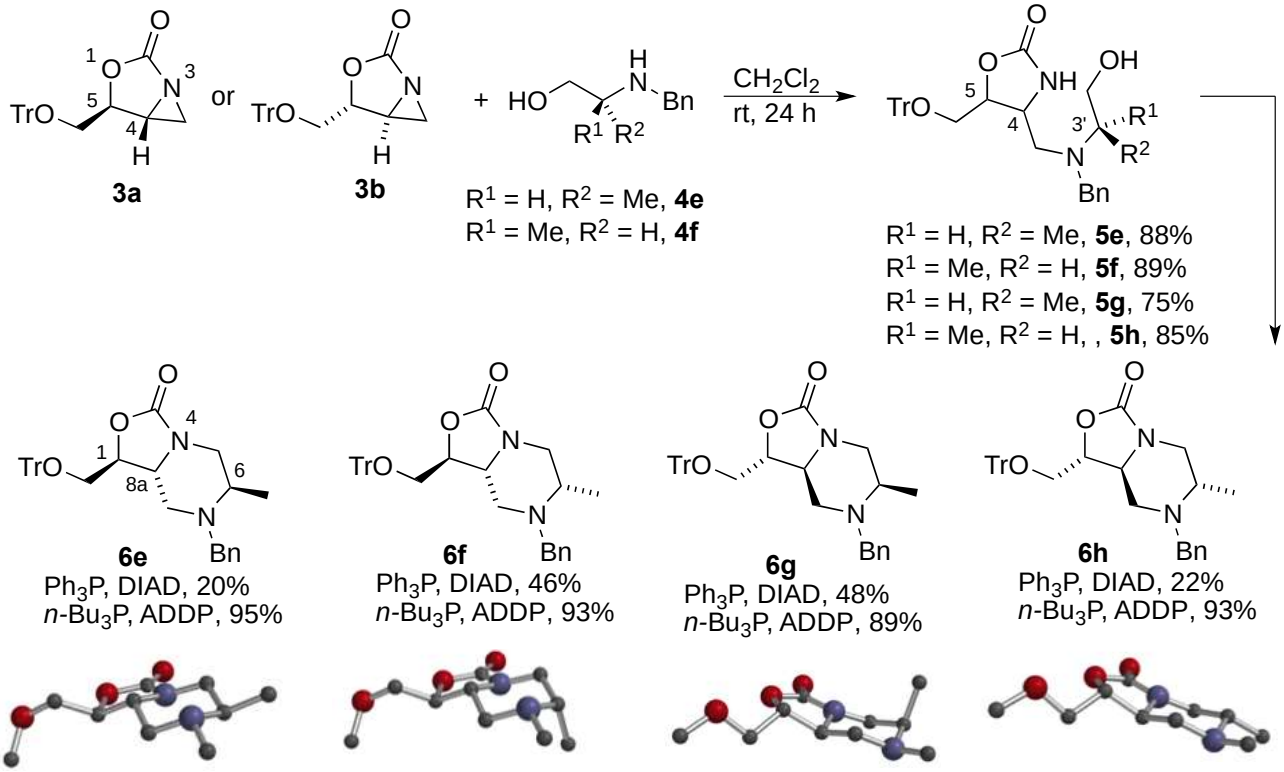
Scheme 1. Synthesis of simple fused ring piperazines

The first attempt at the proposed reaction used commercially available *N*-benzylethanolamine (**4a**) to open the aziridine ring. Oxazolidinone **5a** was obtained in 81% isolated yield. The first cyclization used 200 mol% of KO*t*-Bu and 100 mol% of toluenesulfonyl chloride. This was an attempt to initially prepare the dianion of **5a** which upon tosylation of the alkoxide would rapidly cyclize to provide piperazine **6a**. Unfortunately none of the hoped for cyclization product was obtained, only starting materials and

decomposition products were isolated. Subsequently, treatment of the oxazolidinone **5a** with Ph_3P/DIAD led to isolation of **6a** in excellent yield.

With a method for the synthesis of the desired piperazine, several additional examples were prepared. Both the PMB-protected ethanolamine derivative **4b**,[4b] the commercially available methylamine (**4d**), and the neopentylamine (**4c**) provided the corresponding oxazolidinone (**5**) and piperazine derivatives (**6**) in excellent yield.

With the general method understood, a study of the substitution of the linking carbon chain was undertaken. As the starting aziridine **3** initially used in this study was a single diastereomer (albeit racemic) the introduction of a new stereoisomer on the linking carbon chain would provide a mixture of diastereomers. Consequently all further work was carried out with homochiral versions of **3** (**3a** and **3b**).[10e]



Scheme 2. Stereospecific formation of piperazines. 3D drawings of diastereomers of **6e** - **6h** (aromatic rings removed for clarity)

We first questioned whether different diastereomers would cyclize at different rates or perhaps not at all. Thus both **3a** and **3b** were treated with commercially available enantiomeric amines **4e** and **4f**. The reaction of **3a** with **4e** provided oxazolidinone **5e** while the reaction of **3a** with **4f** provided **5f**. Similarly the reaction of **3b** with **4e** provided oxazolidinone **5g** while the reaction of **3b** with **4f** provided **5h**. As expected, all four diastereomers of **5** were obtained in very good yield (75-89%). Cyclization of all four compounds using the Ph_3P/DIAD method gave the expected products in low to moderate yields. As might

be expected, the cyclization of both **5e** and **5f** provided piperazines **6e** and **6f** in differing yields. We had anticipated that formation of **6f** with the methyl group at C6 in an axial orientation would be the least favored and obtained in a poorer yield than **6e** in which the C6-methyl ended up in an equatorial orientation. The opposite proved to be the case with **6e** (equatorial C6-methyl) obtained in only 20% yield while **6f** (axial C6-methyl) was obtained in 46% yield. The cyclization of both **5g** and **5h** provided a similar product yield ratio with **6h** (equatorial C6-methyl) obtained in a 22% yield while **6g** (axial C6-methyl) was obtained in a 48% yield.

A possible rationale for the difference in yield is outlined in Figure 2. An eclipsed conformation of the C5-C6 bond is necessary for the cyclization of the oxazolidinone with the oxophosphonium substituted position. In such a conformation, the reaction of **5f** puts the C6-methyl group in an apical position with the large oxophosphonium in a gauche position. The alternate reactant **5e** puts the C6-methyl group in an eclipsed position relative to the oxophosphonium group. Based on this analysis, diastereomer **6f** would be expected to more readily cyclize than diastereomer **6e**.

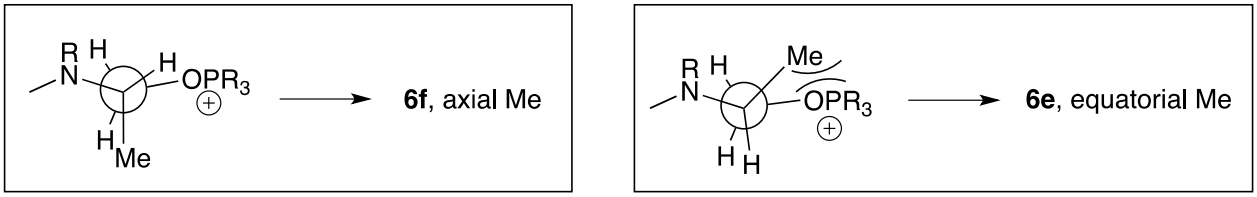
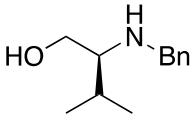
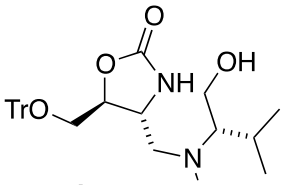
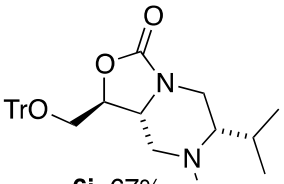
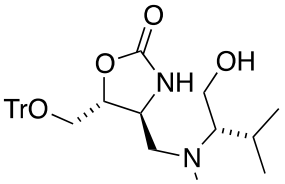
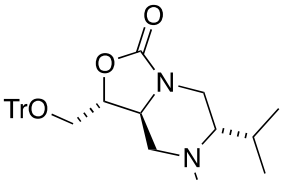
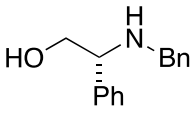
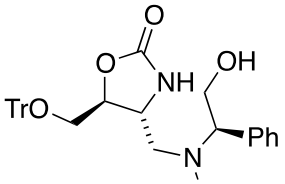
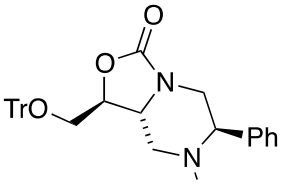
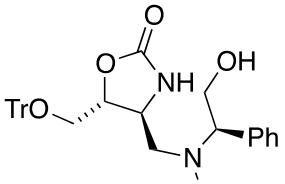
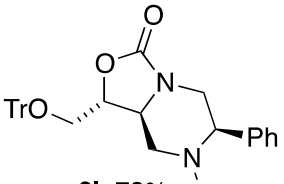
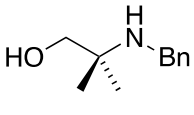
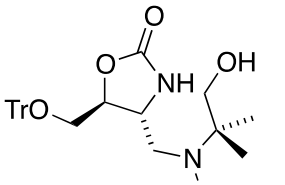
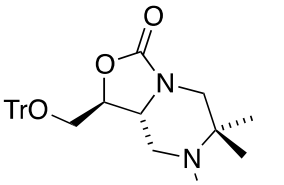


Figure 2. Newman projections of reaction intermediates leading to **6e** and **6f**

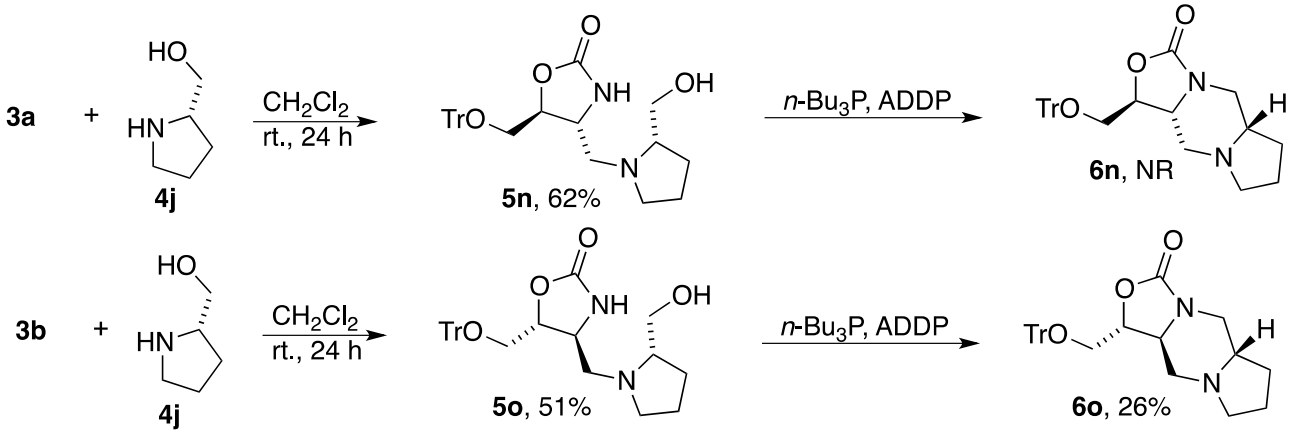
Given the low yields of the cyclization, several variants of the Mitsunobu reaction[13] were examined in order to improve the yield. The use of ADDP/*n*-Bu_3P[14] proved to be an excellent reagent system providing all four diastereomers in excellent yield (89-95% yield). Given that we had ready access to both **3a** and **3b**,[10e] while obtaining both enantiomers of different ethanolamines was sometimes difficult, further studies used **3a** and **3b** with a single enantiomeric ethanolamine.

As a method to gauge the steric tolerance of the cyclization reaction, amino alcohols with isopropyl substitution (**4g**),[15] phenyl substitution (**4h**) and dimethyl substitution (**4i**)[16] were evaluated in the reaction with both **3a** and **3b**. As shown in Table 1, amine **4g** provided the corresponding oxazolidinones **5i** and **5j** in poor yield however both diastereomers of the final piperazine **6i** and **6j** were obtained in good to moderate yield. Amine **4h** provided one diastereomer of the oxazolidinone (**5k**) in excellent yield while the other diastereomer (**5l**) was obtained in poor yield. Both diastereomers of the piperazine were obtained in excellent isolated yields. The dimethyl substituted amine provided the oxazolidinone **5m** in excellent yield however the piperazine **6m** was obtained in only 5% yield. This low yield for this reaction is not unexpected as both possible conformers of the reaction intermediate will have detrimental steric interactions.

Table 1. C2-Substituted ethanolamines

 **4g**	 **5i**, 25%	 **6i**, 67%
	 **5j**, 31%	 **6j**, 85%
 **4h**	 **5k**, 86%	 **6k**, 96%
	 **5l**, 38%	 **6l**, 78%
 **4i**	 **5m**, 89%	 **6m**, 5%

An alternate type of C2 substituted amine would be a cyclic amine. Such an amine would be expected to be more sterically congested than the simple C2 substituted amines examined in Table 1. Commercially available prolinol was chosen as a readily available non-racemic cyclic amine. The reaction of prolinol (**4j**) with aziridines **3a** and **3b** provided oxazolidinones **5n** and **5o** in moderate yields. Cyclization of **5n** provided none of the expected piperazine while cyclization of **5o** provided a poor yield of piperazine **6o**. The steric effects as outlined in Figure 2 are clearly more pronounced in this system. The lack of flexibility in the C2 substitution makes the cyclization of **5n** untenable.



Scheme 3. Prolinol substituted derivatives.

Substitution adjacent to the alcohol (C1 substitution) was next examined. It was suspected that this reaction would be more sterically demanding. Reaction of both enantiomers of aziridine **3** with aminoalcohols **4k**[17] and **4l** provided reasonable yields of oxazolidinones **5p** – **5s**.

Table 2. C1-Substituted ethanolamines

4k	**5p**, 95%	**6p**, 28%
	5q, 83%	**6q**, 46%
4l	**5r**, 70%	**6r**, 50%
	5s, 82%	**6s**, NR

Use of the *n*-Bu_3P/ADDP reagent provided neither of the expected piperazine products **6p** or **6q**. These results were not completely surprising as the original work on the *n*-Bu_3P/ADDP system showed that it

was much less reactive with secondary alcohols than primary alcohols. However reverting to the Ph_3P/DIAD method provided 28% and 46% yields of piperazines **6p** and **6q** respectively. Use of the *n*-Bu_3P/ADDP reagent with oxazolidinone **5r** provided piperazine **6r** in 50% yield. Cyclization of oxazolidinone **5s** with either reagent provided no product. The difference in yield is likely due to differences in the conformation of the reaction intermediates. The intermediate required for formation of **6s** is a much more sterically congested folded conformation relative to the somewhat flat conformation of the intermediate leading to **6r**.

Additional ethanolamines were also unsuccessfully examined in this reaction sequence. These include epinephrine, 3-hydroxypiperidine, and 3-hydroxymethylpiperidine. In all cases the formation of the initial adduct (**5**) proceeded with typical yields (70-90%) but none of the piperazine product (**6**) was obtained with either Ph_3P/DIAD or *n*-Bu_3P/ADDP.

The general method of ring opening of the fused ring aziridine with an aminoalcohol followed by a ring closure has proven to be a general and useful method for the synthesis of fused-ring piperazines. While this reaction has been shown to be very sensitive to the stereochemistry of both the aminoalcohol as well as the starting aziridine, it should prove to be useful for the synthesis of a variety of piperazine derivatives.

EXPERIMENTAL

^1H NMR (300 MHz) and ^{13}C NMR spectra were measured on Bruker Avance 300 MHz NMR spectrometer and referenced to TMS as an internal standard. High Resolution Mass Spectrometry measurements were performed at the Old Dominion University COSMIC Lab through positive electrospray ionization on a Bruker 12 Tesla APEX –Qe FTICR-MS with and Apollo II ion source. High Performance Liquid Chromatography was conducted on Shimadzu LC-10AT liquid chromatograph coupled with a SIL-HT autosampler equipped with a SPD-10A UV-vis detector with Supelco discovery C8 column (15 cm x 4.6 cm, 5 μm). Method 1: eluting at 1.0 mL/min with a gradient elution starting at 50% of MeOH-H_2O for 5 minutes going to 70% over 20 minutes. Method 2: eluting at 1.0 mL/min with a gradient elution starting at 70% of MeOH-H_2O for 5 minutes going to 80% over 20 minutes. Method 3: eluting at 1.0 mL/min with a gradient elution starting at 50% of MeCN-H_2O for 5 minutes going to 70% over 20 minutes. Method 4: eluting at 1.0 mL/min with a gradient elution starting at 60% of MeCN-H_2O for 2 minutes going to 80% over 20 minutes. Method 5: eluting at 1.0 mL/min with a gradient elution starting at 60% of MeOH-H_2O for 5 minutes going to 80% over 20 minutes. Method 6: eluting at 1.0 mL/min with a gradient elution starting at 10% of MeCN-H_2O for 5 minutes going to 30% over 19 minutes. IR data were recorded on a Shimadzu FTIR-8400. All reagents were purchased from commercial suppliers and used without further purification unless noted. Amines **4a**, **4c**, **4d**, **4e**, **4f**, **4h**, **4j**, and **4l** were

obtained from commercial vendors. All other amines were prepared using the method of James et.al.[4b] CH_2Cl_2 and THF were dried with a SOLVTEK column purification system. Toluene was distilled from and stored over molecular sieves. All reactions were conducted under an atmosphere of argon. The products were purified with flash chromatography on silica gel (230-400 mesh).[18]

General procedure for aziridine ring opening: To a solution of aziridine **3** (100 mol%) in CH_2Cl_2 (0.5-0.1 M) was added the appropriate aminoalcohol (180 mol%) The reaction mixture was stirred at room temperature until complete by TLC (18-36 h). The solvent was removed and the residue was purified by column chromatography.

(4*R,5*S**)-4-((Benzyl(2-hydroxyethyl)amino)methyl)-5-((trityloxy)methyl)oxazolidin-2-one (5a):** (The *R**/*S** notation is used to indicate relative stereochemistry not absolute stereochemistry) Prepared by the general method using 300 mg (0.81 mmol) of racemic aziridine **3** and 220 mg (1.45 mmol) of amine **4a** to provide 275 mg (65%) of **5a** as a clear oil: R_f = 0.25 (hexanes-EtOAc, 1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38.7.32 (m. 6H), 7.25-7.11 (m, 14H), 6.69 (s, 1H), 4.05 (m, 1H), 3.61-3.46 (m, 1H), 3.53 (AB d, J_{AB} = 27.9, J = 13.8, 2H), 3.17 (AB dd, J_{AB} = 17.5, J = 10.2, 5.0, 2H), 2.68-2.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 143.6, 138.4, 129.1, 128.8, 128.2, 127.7, 127.4, 87.2, 79.0, 64.3, 60.0, 59.9, 59.5, 57.3, 53.9; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{33}H_{34}N_2O_4Na^+$: 546.2416; Found: 546.2390; HPLC (214 nm, Method 2): 12.670 min, 95.7%.

(4*R,5*S**)-4-(((2-Hydroxyethyl)(4-methoxybenzyl)amino)methyl)-5-((trityloxy)methyl)oxazolidin-2-one (5b):** Prepared by the general procedure using 370 mg (1 mmol) of racemic aziridine **3** and 330 mg (1.8 mmol) of amine **4b** to provide 450 mg (82%) of **5b**: R_f = 0.1 (hexanes-EtOAc, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.40 (m, 6H), 7.31-7.20 (m, 9 H), 7.10 (d, J = 8.5, 2H), 6.74 (d, J = 8.5, 2H), 6.81 (bs, 1H), 4.13 (m, 1H), 3.70 (s, 3H), 3.72-3.48 (m, 5H), 3.24 (ABdd, J_{AB} = 19.8, J = 10.1, 5.0, 2H), 2.73-2.63 (m, 2H), 2.60-2.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 130.3, 128.8, 128.2, 127.4, 114.1, 87.2, 79.1, 64.6, 59.9, 59.4, 57.2, 55.4, 53.9; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{36}N_2O_5Na^+$: 575.2552; Found: 575.2565; HPLC (214 nm, Method 2): 12.812 min, 96.3%.

(4*R,5*S**)-4-(((2-Hydroxyethyl)(neopentyl)amino)methyl)-5-((trityloxy)methyl)oxazolidin-2-one (5c):** Prepared by the general procedure using 370 mg (1 mmol) of racemic aziridine **3** and 236 mg (1.8 mmol) of amine **4c** to provide 390 mg (76%) of **5c**: R_f = 0.30 (hexanes-EtOAc, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.42 (m, 6H), 7.33-7.21 (m, 9H), 6.98 (bs, 1H), 4.15 (m, 1H), 3.83-3.77 (m, 1H), 3.64-3.48 (m, 2H), 3.30 (AB dd, J_{AB} = 15.0, J = 10.2, 5.2, 2H), 2.79 (m, 1H), 2.77-2.58 (m, 2H), 2.54-2.46 (m, 2H), 2.22 (AB d, J_{AB} = 26.8, J = 14.0, 2H), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 143.6, 128.8, 128.2, 127.5, 87.2, 78.7, 69.6, 64.1, 62.6, 60.5, 60.0, 54.6, 32.9, 28.6; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{31}H_{38}N_2O_4Na^+$: 525.2729; Found: 525.2755; HPLC (214 nm, Method 2): 11.432 min, 94.4%.

(4*R,5*S**)-4-(((2-Hydroxyethyl)(methyl)amino)methyl)-5-((trityloxy)methyl)oxazolidin-2-one (5d):** Prepared by the general procedure using 100 mg (0.27 mmol) of racemic aziridine **3** and 36 mg (0.49 mmol) of amine **4d** to provide 72 mg (60%) of **5d** as a clear oil: R_f = 0.1 (hexanes-EtOAc, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.43 (m, 6H), 7.36-7.24 (m, 9H), 5.98 (s, 1H), 4.28 (m, 1H), 3.81 (m, 1H), 3.60 (m, 2H), 3.34 (AB dd J_{AB} = 38.9, J = 10.2, 2H), 2.63-2.44 (m, 4H), 2.34 (bs, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 127.5, 128.2, 143.6, 87.2, 79.1, 64.2, 62.8, 60.0, 59.2, 53.2, 42.6; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{27}H_{30}N_2O_4Na^+$: 469.2103; Found: 469.2200; HPLC (214 nm, Method 2): 10.900 min, 95.6%.

(4*R*,5*S*)4-((Benzyl((*R*)-1-hydroxypropan-2-yl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (5e): Prepared by the general procedure using 80 mg (0.22 mmol) of **3a** and 66 mg (0.4 mmol) of amine **4e** which provided 100 mg (86%) of the product **5e** as a white solid: mp 69.4 – 71.3 °C; R_f = 0.32 (hexanes-EtOAc, 1:2); $[\alpha]_D^{25.7}$ +20.3 (*c* 1.02, $CHCl_3$); IR (KBr): 3425, 1751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.38 (d, J = 7.1 Hz, 6H), 7.29 – 7.12 (m, 14H), 6.93 (s, 1H), 4.11 (d, J = 4.2 Hz, 1H), 3.72 (d, J = 13.4 Hz, 1H), 3.46 – 3.35 (m, 3H), 3.27 (d, J = 13.5 Hz, 1H), 3.22 – 3.17 (m, 1H), 3.06 (dd, J = 10.2, 4.4 Hz, 1H), 2.90 – 2.86 (m, 1H), 2.70 – 2.54 (m, 2H), 0.91 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ159.6, 143.5, 139.3, 128.8, 128.6, 128.0, 127.4, 127.2, 86.8, 79.4, 64.4, 63.9, 59.3, 56.9, 54.2, 54.2, 10.1; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{36}N_2O_4Na^+$: 559.2567; Found: 559.2558; HPLC (214 nm, Method 2): 12.900 min, 92.4%.

(4*R*,5*S*)4-((Benzyl((*S*)-1-hydroxypropan-2-yl)amino)methyl)-5-(trityloxymethyl)oxa-zolidin-2-one (5f): Prepared by the general procedure using 80 mg (0.22 mmol) of **3a** and 67 mg (0.4 mmol) of amine **4f** which provided 103 mg (89%) of the product **5f** as a white solid: mp 58.9 – 59.7 °C; R_f = 0.30 (hexanes-EtOAc, 1:2); $[\alpha]_D^{24.4}$ +79.3° (*c* 1.01, $CHCl_3$); IR (KBr): 3425, 1751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.31 (d, J = 7.7 Hz, 6H), 7.22 – 7.07 (m, 15H), 4.04 – 3.99 (m, 1H), 3.62 (d, J = 13.5 Hz, 1H), 3.47 – 3.34 (m, 3H), 3.28 – 3.23 (m, 1H), 3.17 – 3.06 (m, 2H), 2.89 – 2.82 (m, 1H), 2.59 – 2.51 (m, 1H), 2.37 – 2.32 (m, 1H), 0.77 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ159.5, 143.5, 139.1, 128.9, 128.6, 128.6, 128.0, 127.4, 127.3, 87.0, 78.5, 64.2, 63.6, 57.3, 56.1, 54.0, 53.9, 9.4; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{36}N_2O_4Na^+$: 559.2567; Found: 559.2557; HPLC (254 nm, Method 2): 13.517 min, 90.9%.

(4*S*,5*R*)4-((Benzyl((*R*)-1-hydroxypropan-2-yl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (5g): Prepared by the general procedure using 80 mg (0.22 mmol) of **3a** and 65 mg (0.4 mmol) of amine **4e** which provided 87 mg (75%) of the product **5g** as a white solid: mp 58.9 – 59.7 °C; R_f = 0.28 (hexanes-EtOAc, 1:2); $[\alpha]_D^{25.3}$ -75.2º (*c* 1.00, $CHCl_3$); IR (KBr): 3425, 1751 cm^{-1}; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{36}N_2O_4Na^+$: 559.2567; Found: 559.2550; HPLC (214 nm, Method 2): 13.508 min, 90.7%. Identical ^{1}H and ^{13}C-NMR to it's enantiomer **5f**.

(4*S*,5*R*)4-((Benzyl((*S*)-1-hydroxypropan-2-yl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5h)**: Prepared by the general procedure using 80 mg (0.22 mmol) of **3b** and 66 mg (0.4 mmol) of amine **4f** which provided 99 mg (85%) of the product **5h** as a white solid: mp 69.4 – 71.3 °C; R_f = 0.34 (hexanes-EtOAc, 1:2); $[\alpha]_D^{24.8}$ -20.9 (*c* 1.01, $CHCl_3$); IR (KBr): 3425, 1751 cm^{-1}; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{36}N_2O_4Na^+$: 559.2567; Found: 559.2557; HPLC (254 nm, Method 2): 12.900 min, 92.4%. Identical ^1H and ^{13}C-NMR to it's enantiomer **5e**.

(4*R*,5*S*)-4-((Benzyl((*S*)-1-hydroxy-3-methylbutan-2-yl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5i)**: Prepared by the general procedure using 117 mg (0.32 mmol) of **3a** and 111 mg (0.58 mmol) of amine **4g** which provided 45 mg (25%) of the product **5i** as a white solid: mp 69.3-69.9 °C; R_f = 0.41 (CH_2Cl_2-EtOAc, 3:2); $[\alpha]_D^{25.5}$ 42.0 (*c* 1.075, $CHCl_3$); IR (KBr): 3426, 3284, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.3 Hz, 6H), 7.33 – 6.98 (m, 14H), 6.07 (s, 1H), 4.05 (q, *J* = 4.9 Hz, 1H), 3.78 (s, 2H), 3.72 (dd, *J* = 11.1, 4.0 Hz, 1H), 3.50 – 3.31 (m, 2H), 3.15 (d, *J* = 4.9 Hz, 2H), 2.90 – 2.73 (m, 2H), 2.68 (s, 1H), 2.48 (td, *J* = 9.2, 4.0 Hz, 1H), 1.86 (tt, *J* = 13.8, 6.7 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 143.4, 140.1, 128.8, 128.7, 128.6, 128.0, 127.6, 127.2, 86.9, 78.5, 69.5, 64.1, 60.8, 57.6, 56.5, 54.3, 28.6, 22.2, 20.4; HRMS-ESI: *m/z* $[M + Na^+]$ calcd for $C_{36}H_{40}N_2O_4Na^+$: 587.2880; Found: 587.2866; HPLC (214 nm, Method 2): 15.517 min, 93.2%.

(4*S*,5*R*)-4-((Benzyl((*S*)-1-hydroxy-3-methylbutan-2-yl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5j)**: Prepared by the general procedure using 100 mg (0.27 mmol) of **3b** and 95 mg (0.49 mmol) of amine **4g** which provided 47 mg (31%) of the product **5j** as a white solid: mp 68.7-70.4 °C; R_f = 0.35 (CH_2Cl_2-EtOAc, 3:2); $[\alpha]_D^{25.4}$ -60.6 (*c* 1.1, $CHCl_3$); IR (KBr): 3437, 1747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.00 (m, 20H), 6.62 (s, 1H), 3.97 (q, *J* = 4.9 Hz, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.79 (d, *J* = 3.7 Hz, 1H), 3.59 (d, *J* = 13.6 Hz, 1H), 3.52 (t, *J* = 10.4 Hz, 1H), 3.21 (dt, *J* = 9.1, 4.5 Hz, 1H), 3.02 (d, *J* = 4.8 Hz, 3H), 2.90 (dd, *J* = 13.9, 4.0 Hz, 1H), 2.78 (dd, *J* = 13.9, 9.4 Hz, 1H), 2.52 (td, *J* = 9.5, 3.7 Hz, 1H), 1.80 (td, *J* = 13.3, 6.6 Hz, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 143.5, 140.3, 128.8, 128.7, 128.6, 127.9, 127.4, 127.2, 86.8, 78.3, 71.9, 64.0, 61.6, 60.3, 55.6, 54.2, 29.1, 21.8, 20.4; HRMS-ESI: *m/z* $[M + Na^+]$ calcd for $C_{36}H_{40}N_2O_4Na^+$: 587.2880; Found: 587.2863; HPLC (214 nm, Method 2): 15.142 min, 85.7%.

(4*R*,5*S*)-4-((Benzyl((*R*)-2-hydroxy-1-phenylethyl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5k)**: Prepared by the general procedure using 150 mg (0.40 mmol) of **3a** and 160 mg (0.72 mmol) of amine **4h** which provided 208 mg (86%) of the product **5k** as a white solid: mp 78.8-80.1 °C; R_f = 0.33 (CH_2Cl_2-EtOAc, 3:1); $[\alpha]_D^{25.3}$ +16.1 (*c* 1.17, $CHCl_3$); IR (KBr): 3426, 1749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.04 (m, 25H), 6.23 (s, 1H), 4.12 (q, *J* = 4.3 Hz, 1H), 4.07 – 3.94 (m, 1H), 3.87 (d, *J* = 4.4 Hz, 1H), 3.83 (d, *J* = 4.4 Hz, 1H), 3.77 (dd, *J* = 10.7, 4.7 Hz, 1H), 3.41 (dd, *J* = 11.8, 6.1 Hz, 1H), 3.26 – 3.19 (m, 1H), 3.16 (d, *J* = 13.9 Hz, 1H), 3.06 (dd, *J* = 10.3, 4.4 Hz, 1H), 2.67 (ddd, *J* = 21.3, 13.6,

6.8 Hz, 2H), 2.57 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 142.1, 137.7, 135.1, 127.4, 127.3, 127.2, 127.2, 126.7, 126.6, 126.2, 125.8, 85.5, 77.9, 66.5, 62.8, 60.6, 56.2, 54.2, 52.7; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{39}H_{38}N_2O_4Na^+$: 621.2724; Found: 621.2708; HPLC (254 nm, Method 2): 13.825 min, 81.2%.

(4*S*,5*R*)-4-((Benzyl((*R*)-2-hydroxy-1-phenylethyl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5l**): Prepared by the general procedure using 150 mg (0.40 mmol) of **3b** and 160 mg (0.72 mmol) of amine **4h** which provided 93 mg (38%) of the product **5l** as a white solid: mp 78.4-79.8 °C; R_f = 0.32 (CH_2Cl_2-EtOAc, 3:1); $[\alpha]_D^{25.3}$ -69.5 (*c* 0.905, $CHCl_3$); IR (KBr): 3431, 1750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.17 (m, 23H), 7.17 – 7.00 (m, 2H), 6.73 (s, 1H), 4.13 – 4.04 (m, 2H), 3.91 (dd, *J* = 9.9, 4.4 Hz, 1H), 3.77 – 3.70 (m, 2H), 3.68 – 3.55 (m, 1H), 3.40 (d, *J* = 13.7 Hz, 1H), 3.22 (d, *J* = 4.9 Hz, 2H), 2.92 (br s, 1H), 2.83 (dd, *J* = 13.1, 10.4 Hz, 1H), 2.28 (dd, *J* = 13.2, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 142.5, 137.9, 135.0, 127.9, 127.8, 127.7, 127.7, 127.1, 126.7, 126.4, 86.1, 77.5, 64.5, 63.1, 60.6, 55.5, 53.9, 52.7; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{39}H_{38}N_2O_4Na^+$: 621.2724; Found: 621.2711; HPLC (214 nm, Method 2): 14.533 min, 82.5%.

4-((Benzyl(1-hydroxy-2-methylpropan-2-yl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (*rac*-**5m**): Prepared by the general procedure using 200 mg (0.54 mmol) of *rac*-**3** and 170 mg (0.97 mmol) of amine **4i** which provided 264 mg (89%) of *rac*-**5m** as a white solid: mp 158.9 – 160.1 °C; R_f = 0.38 (CH_2Cl_2-EtOAc, 1:1); IR (KBr): 3418, 3279, 1744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 17H), 7.12 – 7.11 (m, 3H), 6.72 (s, 1H), 4.01 – 3.93 (m, 2H), 3.51 – 3.34 (m, 3H), 3.22 – 2.92 (m, 4H), 2.85 (dd, *J* = 13.5, 9.8 Hz, 1H), 2.50 (dd, *J* = 13.7, 3.4 Hz, 1H), 1.06 (d, *J* = 18.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.21, 143.37, 141.10, 128.61, 128.55, 128.11, 127.85, 127.11, 86.70, 78.70, 68.61, 64.08, 58.91, 55.91, 55.16, 55.00, 22.67, 21.15; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{35}H_{38}N_2O_4Na^+$: 573.2724; Found: 573.2720; HPLC (254 nm, Method 3): 13.008 min, 93.3%.

(4*R*,5*S*)-4-(((*S*)-2-(Hydroxymethyl)pyrrolidin-1-yl)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5n**): Prepared by the general procedure using 100 mg (0.27 mmol) of **3a** and 50 mg (0.49 mmol) of amine **4j** which provided 79 mg (62%) of the product **5n** as a white solid: mp 68.9 – 69.4 °C; R_f = 0.25 (CH_2Cl_2-MeOH, 20:1); $[\alpha]_D^{24.4}$ 19.7 (*c* 0.995, $CHCl_3$); IR (KBr): 3417, 1749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 6H), 7.31 – 7.19 (m, 9H), 4.37 (dd, *J* = 9.0, 4.3 Hz, 1H), 3.79 (td, *J* = 8.0, 5.4 Hz, 1H), 3.49 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.43 – 3.33 (m, 2H), 3.17 (dd, *J* = 10.3, 4.3 Hz, 1H), 2.84 – 2.73 (m, 2H), 2.58 – 2.49 (m, 2H), 2.34 (br s, 1H), 2.20 (dd, *J* = 15.7, 8.8 Hz, 1H), 1.86 – 1.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 143.4, 128.6, 128.0, 127.2, 86.9, 80.2, 65.4, 64.1, 63.0, 59.4, 55.2, 53.6, 27.2, 23.9; HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{29}H_{32}N_2O_4Na^+$: 495.2254; Found: 495.2247; HPLC (214 nm, Method 2): 7.075 min, 97.6%.

(4*S*,5*R*)-4-(((*S*)-2-(Hydroxymethyl)pyrrolidin-1-yl)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5o**): Prepared by the general procedure using 75 mg (0.20 mmol) of **3b** and 36 mg (0.36 mmol) of amine **4j** which provided 48 mg (51%) of the product **5o** as a white solid: mp 62.4 – 63.7 °C; R_f = 0.30 (EtOAc-MeOH, 10:1); $[\alpha]_D^{24.7}$ -44.1 (*c* 0.95, $CHCl_3$); IR (KBr): 3419, 1749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.42 (m, 6H), 7.33 – 7.22 (m, 9H), 7.19 (d, *J* = 16.0 Hz, 1H), 4.21 (q, *J* = 5.1 Hz, 1H), 3.81 – 3.75 (m, 1H), 3.60 (dd, *J* = 11.3, 2.8 Hz, 1H), 3.34 – 3.28 (m, 3H), 3.16 – 3.12 (m, 1H), 2.82 (t, *J* = 11.0 Hz, 1H), 2.61 - 2.58 (m, 1H), 2.40 (dd, *J* = 12.2, 2.8 Hz, 1H), 2.19 (dd, *J* = 15.8, 8.3 Hz, 1H), 1.87 – 1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 143.4, 128.6, 128.0, 127.3, 87.0, 78.7, 65.4, 64.0, 62.6, 59.8, 54.6, 54.5, 26.9, 24.0; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{29}H_{32}N_2O_4Na^+$: 495.2254; Found: 495.2247; HPLC (214 nm, Method 2): 7.658 min, 94.8%.

(4*R*,5*S*)-4-((Benzyl((*R*)-2-hydroxypropyl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5p**): Prepared by the general procedure using 80 mg (0.22 mmol) of **3a** and 65 mg (0.4 mmol) of amine **4k** which provided 110 mg (95%) of the product **5p** as a white solid: mp 54.7 – 56.7 °C; R_f = 0.32 (hexanes-EtOAc, 1:2); $[\alpha]_D^{25.8}$ +19.8 (*c* 0.97, $CHCl_3$); IR (KBr): 3425, 1751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ7.41 (d, *J* = 7.4 Hz, 6H), 7.30 – 7.16 (m, 15H), 4.14 – 4.13 (m, 1H), 3.80 – 3.59 (m, 3H), 3.46 (d, *J* = 13.6 Hz, 1H), 3.28 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.17 (dd, *J* = 10.2, 4.4 Hz, 1H), 3.10 (br s, 1H), 2.68 – 2.48 (m, 3H), 2.38 – 2.31 (m, 1H), 1.05 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ159.6, 143.5, 138.1, 129.0, 128.6, 128.0, 127.5, 127.3, 86.9, 79.2, 64.8, 64.3, 64.2, 60.5, 59.9, 53.9, 20.4; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{36}N_2O_4Na^+$: 559.2567; Found: 559.2558; HPLC (214 nm, Method 2): 13.017 min, 95.1%.

(4*S*,5*R*)-4-((Benzyl((*R*)-2-hydroxypropyl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5q**): Prepared by the general procedure using 80 mg (0.22 mmol) of **3b** and 66 mg (0.4 mmol) of amine **4k** which provided 96 mg (83%) of the product **5q** as a white solid: mp 56.7 – 57.8 °C; R_f = 0.37 (hexanes-EtOAc, 1:2); $[\alpha]_D^{25.7}$ -74.9 (*c* 1.13, $CHCl_3$); IR (KBr): 3410, 1751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ7.42 – 7.31 (m, 7H), 7.31 – 7.20 (m, 14H), 4.09 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.83 – 3.68 (m, 3H), 3.46 (d, *J* = 13.6 Hz, 1H), 3.30 – 3.20 (m, 2H), 2.66 – 2.58 (m, 1H), 2.47 – 2.32 (m, 3H), 1.06 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ159.6, 143.4, 137.9, 129.1, 128.6, 128.5, 128.0, 127.4, 127.3, 87.0, 78.6, 64.2, 63.9, 63.0, 60.2, 59.1, 53.4, 20.3; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{36}N_2O_4Na^+$: 559.2567; Found: 559.2558; HPLC (214 nm, Method 2): 13.242 min, 94.1%.

(4*R*,5*S*)-4-((Benzyl((*R*)-2-hydroxy-2-phenylethyl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5r**): Prepared by the general procedure using 100 mg (0.27 mmol) of **3a** and 110 mg (0.49 mmol) of amine **4l** which provided 113 mg (70%) of the product **5r** as a white solid: mp 76.4-77.5 °C; R_f = 0.37 (hexanes-EtOAc, 1:1); $[\alpha]_D^{27.5}$ +10.8 (*c* 1.00, $CHCl_3$); IR (KBr): 3425, 1751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 6H), 7.36 – 7.09 (m, 19H), 6.67 (s, 1H), 4.63 (dd, *J* = 8.9, 3.5 Hz, 1H), 4.12

(q, *J* = 4.3 Hz, 1H), 3.73 (d, *J* = 13.6 Hz, 1H), 3.65 (dd, *J* = 12.5, 5.9 Hz, 1H), 3.58 (d, *J* = 13.6 Hz, 1H), 3.31 (dd, *J* = 10.0, 4.5 Hz, 2H), 3.17 (dd, *J* = 10.2, 4.3 Hz, 1H), 2.76 – 2.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 143.5, 142.2, 137.9, 129.0, 128.7, 128.6, 128.5, 128.0, 127.7, 127.6, 127.3, 126.0, 86.9, 79.0, 71.6, 64.2, 60.2, 59.9, 53.7; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{39}H_{38}N_2O_4Na^+$: 621.2724; Found: 621.2711; HPLC (254 nm, Method 2): 13.700 min, 92.3%.

(4*S*,5*R*)-4-((Benzyl((*R*)-2-hydroxy-2-phenylethyl)amino)methyl)-5-(trityloxymethyl)oxazolidin-2-one (**5s**): Prepared by the general procedure using 100 mg (0.27 mmol) of **3b** and 111 mg (0.49 mmol) of amine **4l** which provided 132 mg (82%) of the product **5s** as a white solid: mp 77.0-78.0 °C; R_f = 0.55 (hexanes-EtOAc, 2:3); $[\alpha]_D^{28.8}$ -92.2 (*c* 1.005, $CHCl_3$); IR (KBr): 3433, 1751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.2 Hz, 6H), 7.35 – 7.09 (m, 19H), 4.69 (dd, *J* = 9.2, 2.6 Hz, 1H), 4.13 (q, *J* = 5.0 Hz, 1H), 3.83 (d, *J* = 13.6 Hz, 1H), 3.74 – 3.73 (m, 2H), 3.54 (d, *J* = 13.5 Hz, 1H), 3.26 (d, *J* = 4.9 Hz, 2H), 2.77 – 2.47 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 143.4, 142.1, 137.8, 129.1, 128.6, 128.4, 128.0, 127.6, 127.5, 127.3, 126.0, 87.0, 78.6, 70.6, 64.1, 63.6, 60.2, 59.0, 53.4; HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{39}H_{38}N_2O_4Na^+$: 621.2724; Found: 621.2723; HPLC (254 nm, Method 2): 14.467 min, 90.9%.

General procedure for the Mitsunobu reaction.

Method 1: Use of DIAD/PPh_3. PPh_3 (200 mol%) was added to a solution of DIAD (200 mol%) in MeCN (0.1 M). The reaction mixture was stirred at room temperature for 30 min, a solution of the requisite oxazolidinone **5** (100 mol%) in MeCN (0.05 M) was then added. The reaction was stirred for 18 h, concentrated and the residue purified via chromatography to afford the product.

Method 2: Use of ADDP/*n*-Bu_3P. ADDP (300 mol%) was added to a solution of the requisite oxazolidinone **5** in toluene (0.01 M). The solution was degassed three times and then *n*Bu_3P (300 mol%) was added. The reaction mixture was stirred at rt for 2 h, concentrated and chromatographed to provide the product.

(1*S,8a*R**)-7-Benzyl-1-((trityloxy)methyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6a)**: Prepared by Method 1 using 105 mg (0.2 mmol) of **5a** to provide 80 mg (81%) of **6a**: R_f = 0.4 (hexanes-EtOAc, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.42 (m, 14H), 4.13 (m, 1H), 3.82 (dd, *J* = 13.1, 2.6, 1H), 3.71-3.66 (m, 1H), 3.57 (AB d, JAB = 23.0, *J* = 13.2, 3.5, 2H), 3.33 (d, *J* = 5.0, 2H), 3.12 (dt, *J* = 12.7, 3.7, 1H), 2.85 (dt, *J* = 11.1, 3.7, 2H), 2.11 (dt, *J* = 11.7, 3.6, 1H), 1.94 (t, *J* = 10.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 143.6, 137.4, 129.2, 128.7, 87.1, 76.4, 64.1, 63.0, 57.1, 55.7, 52.1, 41.0; HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{33}H_{32}N_2O_3Na^+$: 527.2311; Found: 527.2275; HPLC (214 nm, Method 2): 13.900 min, 96.3%.

(1*S,8a*R**)-7-(4-Methoxybenzyl)-1-((trityloxy)methyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6b)**: Prepared by Method 1 using 111 mg (0.2 mmol) of **5b** to provide 87 mg (81%) of **6b**: R_f =

0.4 (hexanes-EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 6H), 7.30-7.18 (m 11H), 6.84 (d, *J* = 8.6, 2H), 4.08 (m, 1H), 3.77, s, 3H), 3.79-3.74 (m, 1H), 3.60 (m, 1H), 3.46 (AB d, JAB = 25.8, *J* = 12.9, 2H), 3.28 (d, *J* = 5.0, 2H), 3.06 (dt, *J* = 12.5, 3.7, 1H), 2.80 (dt, *J* = 11.3, 3.6, 2H), 2.04 (dt, *J* = 11.7, 3.7, 1H), 1.85 (t, *J* = 10.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 156.4, 143.5, 130.4, 129.3, 128.7, 128.1, 127.4, 87.1, 76.4, 64.1, 62.3, 57.0, 55.7, 55.4, 51.9, 41.0; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{34}N_2O_4Na^+$: 557.2416; Found: 557.2389; HPLC (214 nm, Method 2): 14.020 min, 94.5%.

(1*S,8a*R**)-7-Neopentyl-1-((trityloxy)methyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6c)**: Prepared by Method 1 using 100 mg (0.2 mmol) of **5c** to provide 74 mg (77%) of **6c**: R_f = 0.4 (hexanes-EtOAc, 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.40 (m, 6H), 7.33-7.21 (m, 9H), 4.08, (m, 1H, 3.70 (dd, *J* = 12.9, 2.4, 1H), 3.66-3.58 (m, 1H), 3.33 (ABdd, JAB = 27.0, J = 10.0, 5.0, 2H), 3.04 (dt, *J* = 12.0, 3.7, 1H), 2.82, dd, *J* = 10.9, 3.3, 1H), 2.71-2.66 (m, 1H), 2.30 (dt, *J* = 11.7, 3.5, 1H), 2.16 (t, *J* = 10.9, 1H), d.10 (AB d, JAB = 14.2, *J* = 20.3, 2.1, 2H), 0.87 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 143.6, 128.7, 128.1, 127.4, 87.1, 76.0, 70m.1, 64.1, 60.2, 56.3, 54.6, 41.4, 33.4, 27.8; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{31}H_{36}N_2O_3Na^+$: 507.2624; Found: 507.2610; HPLC (214 nm, Method 2): 13.510 min, 97.4%.

(1*S,8a*R**)-7-Methyl-1-((trityloxy)methyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6d)** : Prepared by Method 1 using 90 mg (0.20 mmol) of **5d** to provide 71 mg (82%) of **6d**: R_f = 0.2 (hexanes-EtOAc, 1:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 6H), 7.25-7.13 (m, 9H), 4.04 (m, 1H), 3.72, (dd, *J* = 13.1, 2.6, 1H), 3.65-3.59 (m, 1H), 3.22 (d, *J* = 5.0, 2H), 3.01 (dt, *J* = 12.1, 3.7, 1H), 2.72 (dd, *J* = 10.9, 3.7, 1H), 2.68-2.63 (m, 1H), 2.23, x, 3H), 1.92 (dt, *J* = 11.7, 3.8, 1H), 1.78 (t, *J* = 10.8, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 143.5, 128.7, 128.1, 127.4, 87.1, 76.3, 64.0, 59.2, 55.6, 53.9, 46.4, 40.9; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{27}H_{28}N_2O_3Na^+$: 451.1998; Found: 451.2002; HPLC (214 nm, Method 2): 13.643 min, 96.1%.

(1*S*,6*R*,8a*R*)-7-Benzyl-6-methyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6e): Prepared by Method 2 using 20 mg (0.037 mmol) of **5e** which provided 18 mg (95%) of the product **6e** as a white solid; mp 64.7-66.1 °C. R_f = 0.47 (hexanes-EtOAc, 3:2). $[\alpha]_D^{24.9}$ -18.7 (*c* 0.665, $CHCl_3$). IR (KBr): 3445, 1762 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.19 (m, 20H), 4.16 (d, *J* = 13.4 Hz, 1H), 4.00 (q, *J* = 4.9 Hz, 1H), 3.76 (dd, *J* = 13.1, 3.5 Hz, 1H) , 3.56 (td, *J* = 11.0, 4.1 Hz, 1H), 3.25 – 3.18 (m, 2H), 3.08 (d, *J* = 13.2 Hz, 1H), 2.82 – 2.72 (m, 2H), 2.42 – 2.31 (m, 1H), 1.88 (t, *J* = 11.1 Hz, 1H), 1.20 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 143.4, 138.1, 129.0, 128.5, 128.4, 128.0, 127.3, 127.2, 86.9, 76.1, 63.9, 58.2, 55.9, 55.5, 55.4, 47.4, 17.4. HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{34}N_2O_3Na^+$: 541.2462; Found: 541.2452. HPLC (254 nm, Method 2): 14.258 min., 91.80%.

(1*S*,6*S*,8a*R*)-7-Benzyl-6-methyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6f): Prepared by Method 2 using 46 mg (0.08 mmol) of **5f** which provided 41 mg (93%) of the product

6f as a white solid; mp 66.1-67.9 °C. R_f = 0.66 (hexanes-EtOAc, 1:1). $[\alpha]_D^{24.7}$ +3.67 (*c* 0.79, $CHCl_3$). IR (KBr): 3487, 1758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 - 7.20 (m, 20H), 4.13 (q, *J* = 5.1 Hz, 1H), 3.69 – 3.50 (m, 4H), 3.33 – 3.19 (m, 3H), 3.07 – 3.02 (m, 1H), 2.57 – 2.43 (m, 2H), 1.04 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 143.4, 138.3, 128.6, 128.6, 128.4, 128.0, 127.3, 127.2, 86.9, 76.4, 64.0, 59.0, 55.6, 51.1, 48.7, 46.2, 7.9. HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{34}N_2O_3Na^+$: 541.2462; Found: 541.2454. HPLC (254 nm, Method 2): 14.642 min, 90.17%.

(1*R*,6*R*,8a*S*)-7-Benzyl-6-methyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6g): Prepared by Method 2 using 19 mg (0.035 mmol) of **5g** which provided 16 mg (89%) of the product **6g** as a white solid; mp 66.1-67.9 °C. R_f = 0.65 (hexanes-EtOAc, 1:1). $[\alpha]_D^{24.7}$ -3.4 (*c* 0.765, $CHCl_3$). HPLC (254 nm, Method 2): 14.475 min., 90.45%. Identical ^1H and ^{13}C-NMR to it's enantiomer **6f**.

(1*R*,6*S*,8a*S*)-7-Benzyl-6-methyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6h): Prepared by Method 2 using 40 mg (0.075 mmol) of **5h** which provided 36 mg (93%) of the product **6h** as a white solid; mp 67.6-68.9 °C. R_f = 0.47 (hexanes-EtOAc, 3:2). $[\alpha]_D^{24.8}$ +18.9 (*c* 0.835, $CHCl_3$). HPLC (254 nm, Method 2) 14.242 min, 91.61%. Identical ^1H and ^{13}C-NMR to it's enantiomer **6e**.

(1*S*,6*S*,8a*R*)-7-Benzyl-6-isopropyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6i): Prepared by Method 2 using 45 mg (0.080 mmol) of **5i** which provided 29 mg (67%) of the product **6i** as a white solid; mp 65.9-67.2 °C. R_f = 0.68 (hexanes-EtOAc, 2:1). $[\alpha]_D^{27.7}$ +2.7 (*c* 0.845, $CHCl_3$). IR (KBr): 3425, 1759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 6.8 Hz, 6H), 7.34 – 7.17 (m, 14H), 4.07 – 3.91 (m, 2H), 3.86 (d, *J* = 13.7 Hz, 1H), 3.80 – 3.64 (m, 2H), 3.39 – 3.17 (m, 3H), 2.87 – 2.73 (m, 1H), 2.66 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.23 (dd, *J* = 10.0, 3.6 Hz, 1H), 2.13 – 1.91 (m, 1H), 0.97 (dd, *J* = 9.0, 6.7 Hz, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.69, 143.36, 139.09, 128.51, 128.43, 128.39, 127.98, 127.29, 127.24, 86.95, 63.75, 62.81, 57.81, 50.40, 47.91, 37.07, 26.12, 20.95, 20.25. HRMS-ESI: *m/z* $[M + Na^+]$ calcd for $C_{36}H_{38}N_2O_3Na^+$: 569.2775; Found: 569.2759. HPLC (254 nm, Method 2): 15.742 min, 95.5%.

(1*R*,6*S*,8a*S*)-7-Benzyl-6-isopropyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6j): Prepared by Method 2 using 36 mg (0.064 mmol) of **5j** which provided 29 mg (85%) of the product **6j** as a white solid; mp 65.4-67.2 °C. R_f = 0.58 (hexanes-EtOAc, 2:1). $[\alpha]_D^{25.8}$ +17.8 (*c* 1.02, $CHCl_3$). IR (KBr): 3429, 1763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.11 (m, 20H), 4.17 (d, *J* = 13.3 Hz, 1H), 3.95 (q, *J* = 5.0 Hz, 1H), 3.78 (dd, *J* = 13.0, 3.3 Hz, 1H), 3.57 – 3.44 (m, 1H), 3.22 (d, *J* = 5.0 Hz, 2H), 3.04 (d, *J* = 13.3 Hz, 1H), 2.95 – 2.83 (m, 1H), 2.79 (dd, *J* = 11.4, 3.6 Hz, 1H), 2.41 – 2.16 (m, 2H), 1.90 (t, *J* = 11.2 Hz, 1H), 1.60 (s, 1H), 1.02 (dd, *J* = 9.3, 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 143.3, 138.3, 128.6, 128.4, 127.9, 127.1, 127.1, 86.8, 76.0, 64.1, 63.7, 55.5, 55.1, 54.2, 39.8, 26.6, 19.4, 15.4. HRMS-ESI: *m/z* $[M + Na^+]$ calcd for $C_{36}H_{38}N_2O_3Na^+$: 569.2775; Found: 569.2758. HPLC (254 nm, Method 2): 18.108 min, 90.4%.

(1*S*,6*R*,8a*R*)-7-Benzyl-6-phenyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (**6k**): Prepared by Method 2 using 67 mg (0.11 mmol) of **5k** which provided 63 mg (96%) of the product **6k** as a white solid; mp 85.9-88.3 °C. R_f = 0.58 (hexanes-EtOAc, 2:1). $[\alpha]_D^{27.7}$ +9.0 (*c* 1.1, $CHCl_3$). IR (KBr): 3425, 1763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.3 Hz, 2H), 7.42 – 7.03 (m, 23H), 4.08 (q, *J* = 4.6 Hz, 1H), 3.89 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.82 (d, *J* = 13.5 Hz, 1H), 3.67 (dt, *J* = 10.6, 3.8 Hz, 1H), 3.40 – 3.15 (m, 3H), 3.04 (dd, *J* = 13.0, 11.0 Hz, 1H), 2.91 (dd, *J* = 11.2, 3.5 Hz, 1H), 2.83 (d, *J* = 13.5 Hz, 1H), 1.99 (t, *J* = 11.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.94, 143.31, 139.57, 137.94, 128.92, 128.60, 128.48, 128.32, 128.15, 127.93, 127.86, 127.17, 86.81, 76.04, 66.48, 63.88, 58.55, 55.67, 55.28, 48.08. HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{39}H_{36}N_2O_3Na^+$: 603.2618; Found: 603.2611. HPLC (214 nm, Method 2): 19.558 min, 95.3%.

(1*R*,6*R*,8a*S*)-7-Benzyl-6-phenyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (**6l**): Prepared by Method 2 using 62 mg (0.10 mmol) of **5l** which provided 47 mg (78%) of the product **6l** as a white solid; mp 83.8-85.1 °C. R_f = 0.59 (hexanes-EtOAc, 2:1). $[\alpha]_D^{27.7}$ +29.9 (*c* 1.1, $CHCl_3$). IR (KBr): 3406, 1759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.13 (m, 25H), 4.26 – 4.03 (m, 2H), 4.01 – 3.67 (m, 3H), 3.53 (m, 2H), 3.33 (m, 2H), 2.73 – 2.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.16, 143.28, 138.22, 137.53, 128.63, 128.55, 128.49, 128.38, 127.95, 127.62, 127.39, 127.20, 86.97, 63.73, 58.29, 54.40, 48.57, 42.15. HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{39}H_{36}N_2O_3Na^+$: 603.2618; Found: 603.2604. HPLC (214 nm, Method 2): 16.875 min, 97.4%.

7-Benzyl-6,6-dimethyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (*rac*-**6m**): Prepared by Method 2 using 116 mg (0.21 mmol) of *rac*-**5m** which provided 6 mg (5%) of **6m** as a yellow oil. R_f = 0.29 (hexanes-EtOAc, 3:1). IR (KBr): 3479, 1759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.07 (m, 20H), 4.11 – 4.04 (m, 2H), 3.52 – 3.38 (m, 2H), 3.22 (d, *J* = 5.0 Hz, 2H), 3.01 (d, *J* = 13.8 Hz, 1H), 2.89 (d, *J* = 13.0 Hz, 1H), 2.54 (dd, *J* = 11.6, 4.2 Hz, 1H), 2.29 (t, *J* = 11.2 Hz, 1H), 1.25 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.60, 143.36, 139.55, 128.51, 128.40, 128.36, 127.92, 127.16, 127.03, 86.81, 76.26, 63.89, 55.86, 53.49, 53.03, 52.29, 49.70, 26.77, 14.23. HRMS-ESI: *m/z* [M + Na^+] calcd for $C_{35}H_{36}N_2O_3Na^+$: 555.2618; Found: 555.2614. HPLC (214 nm, Method 3): 17.425 min, 91.4%.

(1*R*,5a*S*,10a*S*)-1-(Trityloxymethyl)hexahydro-1*H*-oxazolo[3,4-*a*]pyrrolo[1,2-*d*]pyrazin-3(5*H*)-one (**6o**): Prepared by Method 2 using 33 mg (0.07 mmol) of **5o** which provided 8 mg (26%) of the product **6o** as a white solid; mp 56.1-58.0°C. R_f = 0.41 (CH_2Cl_2-EtOAc, 1:4). $[\alpha]_D^{25.2}$ -35.8 (*c* 0.5, $CHCl_3$). IR (KBr): 3425, 1759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 6H), 7.33 – 7.22 (m, 9H), 4.15 (q, *J* = 5.1 Hz, 1H), 4.01 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.81 – 3.75 (m, 1H), 3.31 (d, *J* = 5.0 Hz, 2H), 3.13 – 3.04 (m, 2H), 2.73 (dd, *J* = 12.5, 10.3 Hz, 1H) 2.17 (q, *J* = 8.8 Hz, 1H), 2.06 – 1.74 (m, 5H), 1.45 – 1.38 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 143.4, 128.6, 128.0, 127.3, 87.0, 76.0, 63.8, 61.6, 56.3,

55.6, 53.5, 46.2, 26.9, 21.1. HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{29}H_{30}N_2O_3Na^+$: 477.2149; Found: 477.2137. HPLC (254 nm, Method 2): 6.975 min, 91.1%.

(1*S*,5*S*,8a*R*)-7-Benzyl-5-methyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6p): Prepared by Method 1 using 84 mg (0.16 mmol) of **5p** which provided 23 mg (28%) of the product **6p** as a white solid; mp 150.0-151.0 °C. R_f = 0.76 (CH_2Cl_2-EtOAc, 10:1). $[\alpha]_D^{24.7}$ +36.4 (*c* 0.72, $CHCl_3$). IR (KBr): 3466, 1744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.40 (m, 6H), 7.31 - 7.21 (m, 14H), 4.09 – 4.02 (m, 2H), 3.82 – 3.76 (m, 1H), 3.50 (s, 2H), 3.34 (dd, *J* = 10.2, 4.7 Hz, 1H) , 3.24 (dd, *J* = 10.2, 4.4 Hz, 1H) , 2.80 (dd, *J* = 10.6, 3.5 Hz, 1H) , 2.63 (d, *J* = 11.3 Hz, 1H), 2.21 (dd, *J* = 11.3, 4.0 Hz, 1H) , 1.89 (t, *J* = 10.7 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 143.4, 137.7, 128.7, 128.6, 128.4, 128.0, 127.4, 127.2, 86.9, 76.3, 63.8, 62.6, 57.5, 56.9, 52.4, 45.9, 16.6. HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{34}N_2O_3Na^+$: 541.2462; Found: 541.2453. HPLC (254 nm, Method 2): 15.275 min, 91.6%.

(1*R*,5*S*,8a*S*)-7-Benzyl-5-methyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6q): Prepared by Method 1 using 73 mg (0.14 mmol) of **5q** which provided 32 mg (46%) of the product **6q** as a white solid; mp 61.8-63.5 °C. R_f = 0.69 (CH_2Cl_2-EtOAc, 10:1). $[\alpha]_D^{24.6}$ -2.6 (*c* 0.69, $CHCl_3$). IR (KBr): 3488, 1760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.37 (m, 6H), 7.28 - 7.20 (m, 14H), 4.02 (dd, *J* = 12.3, 5.0 Hz, 1H), 3.58 – 3.23 (m, 6H), 2.85 (dd, *J* = 10.7, 2.4 Hz, 1H), 2.74 (d, *J* = 9.8 Hz, 1H), 1.92 – 1.83 (m, 2H), 1.53 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 143.4, 137.3, 129.0, 128.6, 128.5, 128.0, 127.5, 127.2, 87.0, 75.4, 63.6, 62.5, 60.3, 58.2, 56.3, 50.7, 15.5. HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{34}H_{34}N_2O_3Na^+$: 541.2462; Found: 541.2452. HPLC (254 nm, Method 2): 14.358 min, 90.1%.

(1*S*,5*S*,8a*R*)-7-Benzyl-5-phenyl-1-(trityloxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (6r): Prepared by Method 2 using 41 mg (0.068 mmol) of **5r** which provided 20 mg (50%) of the product **6r** as a white solid; mp 71.9-73.3 °C. R_f = 0.61 (hexanes-EtOAc, 3:2). $[\alpha]_D^{28.4}$ 34.9 (*c* 0.79, $CHCl_3$). IR (KBr): 3448, 1759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 8H), 7.32 – 7.14 (m, 17H), 5.03 (d, *J* = 3.8 Hz, 1H), 4.13 (q, *J* = 4.5 Hz, 1H), 3.82 – 3.65 (m, 1H), 3.54 (s, 2H), 3.40 (dd, *J* = 10.4, 4.7 Hz, 1H), 3.34 (d, *J* = 12.0 Hz, 1H), 3.16 (dd, *J* = 10.4, 3.9 Hz, 1H), 2.83 (dd, *J* = 10.6, 3.6 Hz, 1H), 2.47 (dd, *J* = 11.9, 4.4 Hz, 1H), 2.02 (t, *J* = 10.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 143.3, 138.8, 137.1, 129.1, 128.6, 128.4, 128.0, 127.5, 127.5, 127.2, 127.2, 87.1, 63.5, 62.8, 57.6, 54.6, 52.6, 52.2. HRMS-ESI: *m/z* $[M + Na^+]$ calcd for $C_{39}H_{36}N_2O_3Na^+$: 603.2618; Found: 603.2610. HPLC (214 nm, Method 2): 16.217 min, 94.1%.

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