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SYNTHESIS OF 2-PHENYLOXAZOLE DERIVATIVES CONTAINING AMINO ACIDS AS INSULIN SENSITIVITY ENHANCERS FOR TREATMENT OF TYPE II DIABETES

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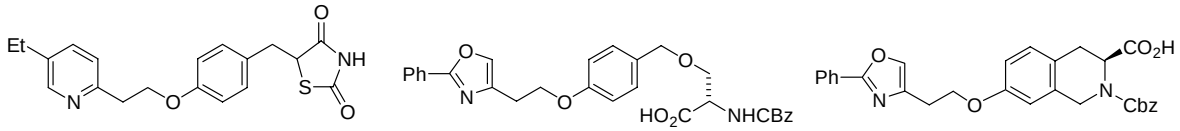
Abstract - The search for Insulin Sensitivity Enhancers (ISE) for use in the treatment of Non-Insulin Dependent Diabetes Mellitus (NIDDM) has led to the preparation of *N*-[(phenylmethoxy)carbonyl]-*O*-[[4-[2-(2-phenyl-4-oxazolyl)-ethoxy]phenyl]methyl]-L-serine (**1**) and 7-[2-(2-phenyl-4-oxazolyl)ethoxyl]-L-1,2,3,4-tetrahydro-*N*-Cbz-isoquinoline-3-carboxylic acid (**2**), that contain a 2-phenyloxazole moiety linked to an amino acid in place of the 2,4-thiazolidinedione pharmacophore. The 2-phenyloxazole was incorporated into **1** and **2** in high yield by alkylation of 4-hydroxybenzaldehyde or methyl 7-1,2,3,4-tetrahydro-*N*-benzyloxycarbonyl-hydroxyisoquinoline-3-carboxylate with 2-(2-phenyl-4-oxazolyl)ethyl *p*-toluenesulfonate (**16**). Successful incorporation of serine into **1** required use of an *N*-trityl protecting group to minimize β-elimination and epimerization at the α-center.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia (high glucose levels) caused by insulin resistance.[1] Only 10% of diabetics have a complete deficiency of insulin (Type I), while 90% exhibit reduced response to insulin and are classified as non-insulin dependent (Type II).[2] Currently the national cost of diabetes treatment is greater than $92 billion. The majority of the cost is due to treatment

of the long term complications of the disease, namely hospitalization, cardiovascular disease, retinopathy, neuropathy and nephropathy.[3] Recently a Diabetes Control and Complications Trial demonstrated that better insulin control can significantly reduce the appearance of these complications. Although this study was performed with Type I diabetic patients, most experts anticipate that these results can be extrapolated to the more common Type II diabetic. However, an undesirable side effect of this study was an increase in hypoglycemia (low blood glucose). Therefore, there is renewed interest in finding a new anti-diabetic drug that would provide the appropriate sensitivity to insulin but avoid the onset of complications and hypoglycemia.

Figure 1



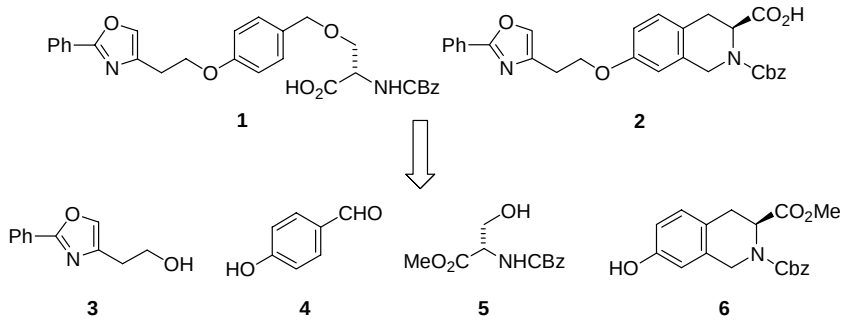
Pioglitazone HCl (Actos®) **1** **2**

The primary compounds being pursued for the treatment of NIDDM are the thiazolidinediones (TZDs) or glitazones, insulin sensitizing agents that reduce insulin resistance in patients with type 2 diabetes. The success of the TZDs was recently demonstrated by the launch of pioglitazone HCl (Actos®), distributed by Takeda Pharmaceuticals America and co-promoted by Eli Lilly and Company (Figure 1).[4] Pioglitazone HCl, the leading TZD for new prescriptions written by endocrinologists since February 2000, has been shown to increase the mean HDL ("good") cholesterol levels by as much as 19% from baseline. Although the TZD's have been very successful in the treatment of Type II diabetes, a number of studies have been preformed to evaluate compounds in which the TZD moiety has been replaced.[5,6] Our work in this area has identified chiral 2-phenyloxazoles (**1**) and (**2**) as potential insulin sensitivity enhancers for treatment of Type II diabetes (Figure 1). To support preliminary pharmacology and toxicology studies multi-gram quantities of **1** and **2** were required. This paper describes our work that has resulted in an efficient stereoselective synthesis of this class of compounds.

RESULTS AND DISCUSSION

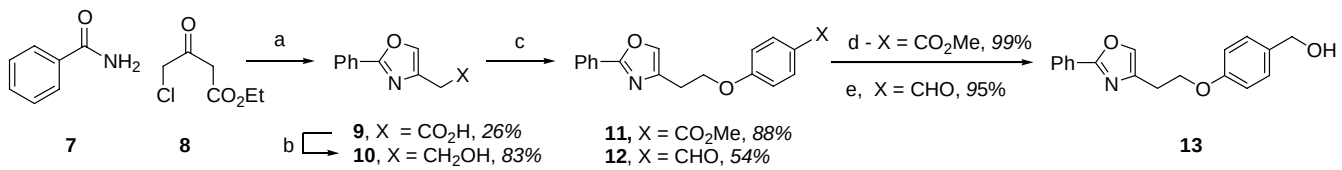
Our primary approach to an efficient construction of **1** was through the convergent combination of fragments (**3**), (**4**) and (**5**). Once a synthesis of **1** had been identified, construction of **2** by alkylation of **6** with **3** containing an appropriate leaving group was explored (Scheme 1).

Scheme 1



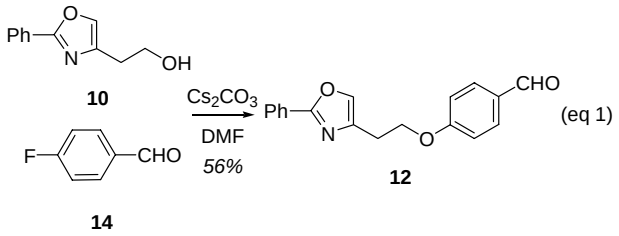
2-Phenyloxazole (**10**) was prepared by reaction of benzamide (**7**) with ethyl 4-chloroacetoacetate (**8**) followed by hydrolysis of the ester to generate **9** in 26% yield, from readily available starting materials.[7] Reduction of **9** with BH_3·THF gave **10** 83% yield. Mitsunobu reaction of **10** with methyl 4-hydroxybenzoate or 4-hydroxybenzaldehyde using diethyl azodicarboxylate (DEAD) and PPh_3 in THF provided **11** and **12** in 88 and 54% yields. Reduction of ester (**11**) with $LiAlH_4$/THF or aldehyde (**12**) with $NaBH_4$/*i*-PrOH afforded alcohol (**13**) in 87% or 52% yields respectively (Scheme 2). Although both of these routes yielded an efficient synthesis of **13**, removal of the Ph_3PO and urea by-products from the Mitsunobu reaction required multiple chromatographic purification's that were difficult to perform on large scale. To eliminate this problem alternative approaches to the synthesis of **13** were examined.

Scheme 2



(a) (i) 125 ºC; (ii) 5*N* NaOH, 50 ºC; (b) BH_3·THF, THF; (c) methyl 4-hydroxybenzoate, PPh_3, DEAD, THF; or 4-hydroxybenzaldehyde, PPh_3, DEAD, THF; (d) $LiAlH_4$, THF; (e) $NaBH_4$, *i*-PrOH.

The first approach was based upon direct nucleophilic aromatic substitution of the alkoxide derived from **10** with 4-fluorobenzaldehyde (**14**) in DMF. A variety of bases (NaH, *tert*-BuOK and Cs_2CO_3) were examined. Cs_2CO_3 proved optimal affording a 56% yield of **12** (eq 1). However attempts to improve the yield of this reaction were unsuccessful.

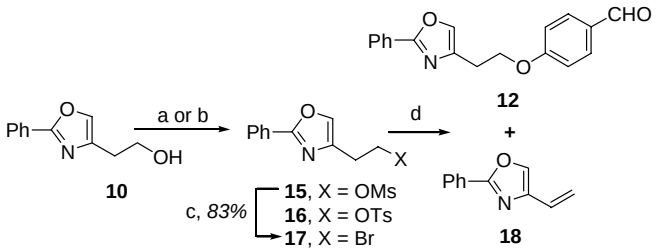


The second approach examined was based upon alcohol activation. Conversion of alcohol (**10**) into mesylate (**15**), tosylate (**16**) and bromide (**17**) was performed under standard conditions. Alkylation of 4-hydroxybenzaldehyde with **15** using Cs_2CO_3 in DMF at 55 ºC afforded aldehyde (**12**) in 78% yield, after recrystallization from hexanes/ethyl acetate. Although bromide (**17**) afforded **12** in only 21% yield together with **18** (60%), the tosylate (**16**) proved optimal affording **12** in 81% yield with minimal (6%) yield of the olefin (**18**) (Scheme 3).

Reduction of aldehyde (**12**) to alcohol (**13**) using $NaBH_4$/*i*-PrOH, followed by treatment with PBr_3 in CH_2Cl_2 afforded an 88% yield of bromide (**19**). Bromide (**19**) was unstable at room temperature and was typically prepared and used directly (Scheme 4). Attempts to prepare the mesylate or tosylate of **13** were unsuccessful. Using bromide (**19**) the final steps for the synthesis of **1**, which required incorporation of the amino acids, were examined.

It has been reported in the literature that alkylation of a benzyloxycarbonyl (Cbz)-protected serine affords only didehydroalanine due to β-elimination. In fact, Wojciechowska et al. reported this reaction as an efficient method for producing didehydroalanine derivatives from **5** using DEAD and PPh_3.[8] Therefore upon alkylation of **5** with bromide (**19**) under Mitsunobu conditions only didehydroalanine was obtained. However, Cherney who reported that by using bulky protecting groups on nitrogen e.g. N-trityl or N-

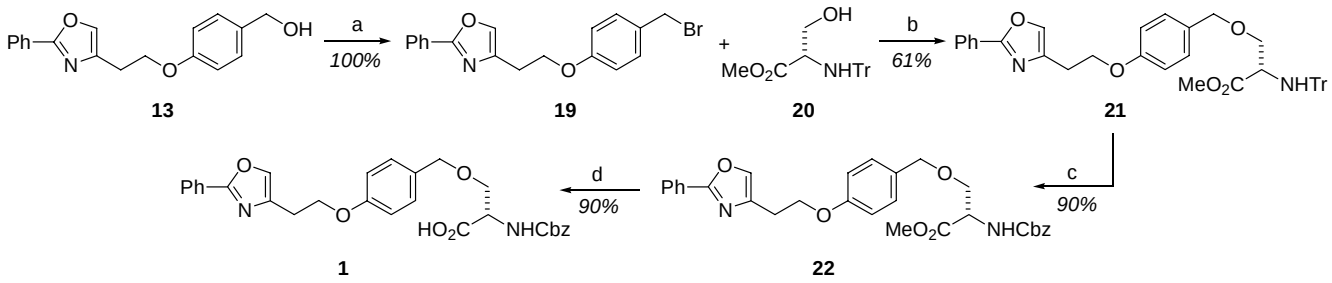
Scheme 3



(a) MsCl, Et_3N, CH_2Cl_2 – *96%*; (b) *p*-Ts_2O, pyridine, CH_2Cl_2, reflux – *98%*; (c) NaBr, DMF, 50 ºC; (d) 4-hydroxybenzaldehyde, Cs_2CO_3, DMF, 55 ºC – *81%* from **16**.

phenylfluorenyl the elimination reaction to dehydroalanine is disfavored recently accomplished successful alkylation of serine.[9] In addition, these groups were found to protect the α-center from base promoted epimerization. We therefore chose to complete our synthesis of **1** using commercially available *N*-trityl-L-serine methyl ester (**20**). In addition, due to problems with scale-up of the Mitsunobu reaction, we decided to examine the use of phase transfer catalysis for alkylation of **20**, due to the success of Palmer who has reported that reaction of *N*-trityl-L-serine ethyl ester with a variety of activated electrophiles efficiently provides the *O*-alkylated products in 49-84% yield.[10]

Scheme 4



(a) PBr_3, CH_2Cl_2; (b) NaOH, tetrabutylammonium bromide, CH_2Cl_2, reflux; (c) (i) HCl, Et_2O:MeOH; (ii) $NaHCO_3$, CbzCl, EtOAc:H_2O; (d) LiOH (2 equiv.), THF:H_2O (3:1).

Thus reaction of **20** with bromide (**19**) using tetrabutylammonium bromide (TBAB) and 50% aqueous NaOH in refluxing CH_2Cl_2 for 24 h afforded **21** in 61% yield (Scheme 4). For comparison use of the *N*-Cbz-L-serine methyl ester (**5**), under identical conditions, yielded only didehydroalanine. Detritylation of **21** using 1 *M* HCl in Et_2O:MeOH at 0 °C, followed by acylation under Schotten-Baumann conditions using $NaHCO_3$ and benzyl chloroformate in EtOAc afforded **22** in 90% yield.

The final step of the synthesis required hydrolysis of **22** to **1** (Table 1). Thus, treatment of **22** with 4 equiv. of 50% aqueous NaOH in MeOH at 0 °C afforded the sodium salt in 90% yield as a white crystalline solid. Acidification with 1 *N* HCl in acetonitrile/water afforded **1** in 80% yield and >97% purity (Entry 1). However analysis by chiral HPLC indicated that the enantiomeric purity of **1** was only 5%. Reducing the equivalent of NaOH failed to improve the enantioselectivity (Entry 2). Potassium trimethylsilanolate in THF, a non-aqueous hydrolysis procedure, produced **1** in only 11% ee (Entry 3). However, using 2.0 equiv. of lithium hydrogen peroxide (LiOOH) **1** was obtained in 68% yield and 100% ee (Entry 4). Although, at room temperature this reaction was very slow, yielding only **1** (68%) after 24 h, the reaction rate could be increased to 6 h using 4 equiv. of LiOOH to afford **1** in 84% yield and 97% ee (Entry 5). Further development identified the optimum conditions that employed 2.0 equiv. of LiOH in THF:H_2O (3:1) at 0 ºC to afford **1** in >98% ee and 90% yield after recrystallization from acetonitrile (Entry 6). This work completed a new 8 step synthesis of **1** that proceeds in 37% overall yield and >98% enantioselectivity from 2-phenyloxazole (**10**).

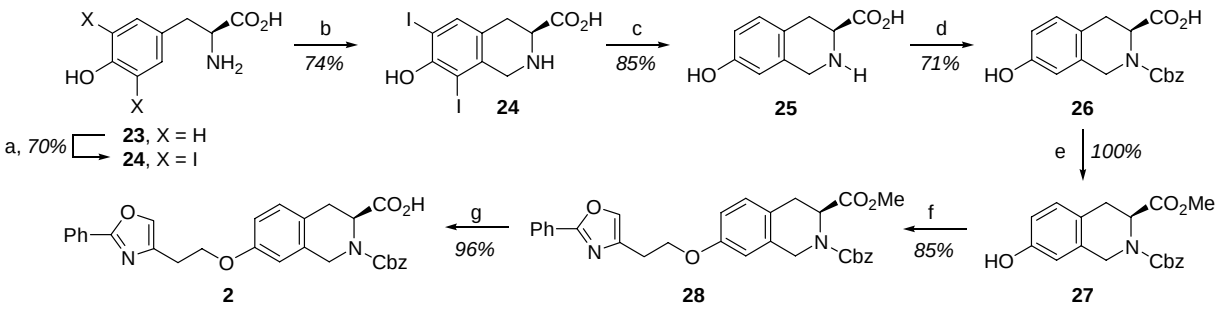
Table 1: Effect of Base on Enantioselectivity of **1** by Hydrolysis of **22**.

Entry	Base	Equivalents	Solvent	Yield, %	ee, %[b]
1	NaOH	4.0	MeOH	80	5
2	NaOH	2.0	MeOH	62[a]	7
3	$KOSiMe_3$	1.7	THF	42	11
4	LiOOH	2.0	THF:H_2O (3:1)	68[a]	100
5	LiOOH	4.0	THF: H_2O (3:1)	84	97
6	LiOH	2.0	THF: H_2O (3:1)	90	>98

[a] Reactions did not go to completion, yields based upon HPLC area percent. [b] Determined by Chiral HPLC

Using the experience gained during the synthesis of **1** a synthesis of **2** was developed. The tetrahydroisoquinolinecarboxylic acid (**25**) was prepared in 63% yield using the procedure of Tourwé and Hruby, by Pictet-Spingler reaction of a diiodotyrosine (**24**) followed by catalytic dehalogenation.[11] Acylation of **25** with benzyl chloroformate in H_2O/dioxane followed by esterification afforded a 70% yield of the protected tryosine derivative (**27**). Etherification of **27** with tosylate (**16**), under the conditions developed for **1** (Cs_2CO_3, DMF) afforded an 83% yield of ester (**28**), accompanied by 8% yield of olefin (**18**). Hydrolysis of the ester provided 2-phenyloxazole (**2**) in 25% overall yield from tyrosine (**23**) (Scheme 5).

Scheme 5



(a) (i) HOAc, ICl; (ii) NH_3(g); (b) c. HCl, formaldehyde, dimethoxyethane, 65 ºC; (c) 10% Pd/C, H_2O/EtOH, Et_3N; (d) CbzCl, H_2O:dioxane, 5 ºC; (e) MeCOCl, MeOH; (f) **16**, Cs_2CO_3, DMF; (g) 1*N* NaOH.

CONCLUSION

A short stereoselective synthesis of **1** and **2** has been developed from commerically available starting materials. The key step of the synthesis involved alkylation of 4-hydroxybenzaldehyde and 7-hydroxy isoquinoline imtermediate (**27**) with tosylate (**16**) in >80% yield. Successful alkylation of serine required use of the bulky trityl protecting group to minimize β-elimination and epimerization. LiOH was found to be the optimal base for preparation of **1** in high enantioselectivity.

EXPERIMENTAL

General: Infrared spectra were recorded on a Perkin Elmer 781 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C (75 MHz) spectra were recorded on a Varian 300 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm and DMSO-d_6 at 39.5 ppm). Combustion analyses were performed by Eli Lilly & Company Microanalytical Laboratory. High resolution MS were obtained on VG ZAB 3F or VG 70 SE spectrometers. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light.

2-(2-Phenyl-4-oxazolyl)ethyl methanesulfonate (15): To a solution of **10** (5.00 g, 0.03 mol) in CH_2Cl_2 (50 mL) at -5 °C under nitrogen was added triethylamine (3.71 g, 0.04 mol). Methanesulfonyl chloride (3.78 g, 0.03 mol) was added dropwise to the solution keeping the temperature of the reaction mixture at < 15°C and the reaction mixture stirred for 1 h at 0 °C to 5 °C until complete.[12] The reaction was quenched with 10% aqueous NH_4Cl (2 x 50 mL), dried ($MgSO_4$), and filtered. The solvent was removed *in vacuo* to give 7.30 g of **15** as an oil that was purified by silica gel column chromatography, using hexanes:EtOAc (3:1), to afford 6.77 g (96%) of **15** as a light yellow oil. ^{1}H NMR (DMSO-d_6) 8.03-8.00 (m, 2H), 7.58 (s, 1H), 7.47-7.45 (m, 3H), 4.56 (t, 2H, *J* = 6.55 Hz), 3.06 (t, 2H, *J* = 6.55 Hz), 2.98 (s, 3H). ^{13}C NMR (DMSO-d_6) 181.9, 160.5, 137.3, 136.5, 130.5, 129.1, 126.8, 125.8, 124.9, 68.2, 36.7, 26.0. IR (KBr) *v* 1597, 1554, 1361, 1346, 1174 cm^{-1}. MS (FD) *m/z* 268 (M^+, 100%). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 53.92; H, 4.90; N, 5.24. Found C, 54.16; H, 4.80; N, 5.14.

2-(2-Phenyl-4-oxazolyl)ethyl *p*-toluenesulfonate (16). To a solution of **10** (2.00 g, 10.5 mmol) in CH_2Cl_2 (25 mL) under nitrogen was added *p*-toluenesulfonic anhydride (10.3 g, 31.5 mmol) and pyridine (3.32 g, 42.0 mmol). The reaction mixture was stirred for 2.5 h at reflux until complete.[13] The reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with 1 *N* HCl. The organic layer was washed with saturated aqueous NaCl (2 x 50 mL), dried ($MgSO_4$), and filtered. The solvent was removed *in vacuo* and the product was purified by silica gel column chromatography using EtOAc. The solvent was removed *in vacuo* to afford 3.55 g (98%) of pure **16** as a white solid. ^{1}H NMR (DMSO-d_6) 7.92-7.89 (m, 2H), 7.69 (d, 2H, *J* = 8.24 Hz), 7.46-7.42 (m, 4H), 7.20 (d, 2H, *J* = 8.24 Hz), 4.33 (t, 2H, *J* = 6.25 Hz), 2.91 (t, 2H, *J* = 6.25 Hz), 2.23 (s, 3H). ^{13}C NMR (DMSO-d_6) 179.0, 160.4, 144.7, 137.0, 136.4, 132.1, 130.4, 129.9, 129.9, 129.0, 127.4, 126.8, 125.8, 124.9, 68.7, 25.6, 20.8. IR (KBr) *v* 1599, 1554, 1362, 1175 cm^{-1}. MS (FD) *m/z* 344 (M^+, 100%). Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found C, 63.22; H, 5.04; N, 4.09.

1-Bromo-2-(2-phenyl-4-oxazolyl)ethane (17). To a solution of **15** (1.00 g, 2.91 mmol) in DMF (20 mL) under nitrogen was added sodium bromide (3.00 g, 0.03 mol) and the reaction mixture heated to 50 °C for

36 h until complete,[14] then cooled to rt. The reaction mixture was quenched with 10% aqueous NH_4Cl and washed with 5% aqueous LiCl. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford 0.58 g (83%) of **17** as a yellow solid that required no additional purification. ^{1}H NMR (DMSO-d_6) 8.04-8.00 (m, 2H), 7.56 (s, 1H), 7.47-7.42 (m, 3H), 3.69 (t, 2H, *J* = 6.85 Hz), 3.15 (t, 2H, *J* = 6.85 Hz). ^{13}C NMR (DMSO-d_6) 179.0, 160.5, 138.9, 136.3, 130.5, 129.1, 126.9, 125.8, 124.9, 31.9, 29.5. IR (KBr) *v* 1606, 1553, 1349, 1253, 1287, 1063 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{11}H_{11}NOBr$ 252.0024, found 252.0025.

4-[2-(2-Phenyl-4-oxazolyl)ethoxy]benzaldehyde (12): A suspension of **15** (0.31 g, 1.16 mmol), 4-hydroxybenzaldehyde (0.17 g, 1.39 mmol) and Cs_2CO_3 (0.47 g, 1.45 mmol) in DMF (20 mL) was heated to 60 °C for 5 h under nitrogen. Analysis by HPLC[15] indicated the formation of a 78:14 mixture of **12**:**18**. The reaction was diluted with EtOAc (50 mL), quenched with water, and washed with 10% aqueous NH_4Cl. The organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a yellow solid that was purified by silica gel column chromatography, using 98% CH_2Cl_2-2% MeOH, to afford 0.02 g (11%) of **18** as a brown oil**.** ^{1}H NMR (DMSO-d_6) 8.09-8.06 (m, 2H), 7.62 (s, 1H), 7.48-7.44 (m, 3H), 6.60 (dd, 1H, *J* = 17.4, 10.7 Hz), 6.05 (dd, 1H, *J* = 17.1, 2.10), 5.35 (dd, 1H, *J* = 10.9, 1.80 Hz); ^{13}C NMR (DMSO-d_6) 161.0, 140.1, 137.3, 131.2, 129.5, 127.0, 126.5, 126.0, 116.2, 67.4, 23.5. IR (KBr) *v* 1706, 1604, 1451, 1063, 923 cm^{-1}. Aldehyde (**12**) 0.26 g (78%) was also obtained as a white solid. ^{1}H NMR (DMSO-d_6) 9.81 (s, 1H), 8.01 (s, 1H), 7.92-7.89 (m, 2H), 7.81 (d, 2H, *J* = 8.72 Hz), 7.49-7.45 (m, 3H), 7.11 (d, 2H, *J* = 8.72 Hz), 4.34 (t, 2H, *J* = 6.55 Hz), 2.99 (t, 2H, *J* = 6.55 Hz); ^{13}C NMR (DMSO-d_6) 191.2, 163.3, 160.4, 138.2, 136.3, 131.7, 130.4, 129.9, 129.7, 129.0, 128.7, 126.9, 125.8, 124.9, 124.9, 114.9, 66.2, 25.9. IR (KBr) *v* 1693, 1600, 1164, 1114, 814, 690 cm^{-1}. MS (FD) *m/z* 293 (M^+, 100%). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.77. Found C, 73.75; H, 5.12; N, 4.77.

4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylmethanol (13): To a suspension of **12** (23.0 g, 0.08 mol) in isopropanol (1 L) was added a solution of sodium borohydride (2.95 g, 0.08 mol) diluted in 0.1 *N* NaOH (70 mL) . The reaction mixture was stirred vigorously under nitrogen and allowed to slowly exotherm to

32 °C. After stirring at rt for 3 h the reaction was complete.[16] The pH of the reaction was adjusted to 7.0 with 1 *N* HCl, and then the reaction mixture was diluted in EtOAc (250 mL) and washed with 10% aqueous NH_4Cl using additional EtOAc to back-wash the aqueous layers. The organic layers were combined and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford 22.0 g (95%) of **13** as a white solid after drying in a vacuum oven at 50 °C. HPLC analysis indicated >98% purity. ^{1}H NMR (DMSO-d_6) 7.98 (s, 1H), 7.92-7.89 (m, 2H), 7.48-7.44 (m 3H), 7.17 (d, 2H, *J* = 8.54 Hz), 6.86 (d, 2H *J* = 8.54 Hz), 5.00 (t, 1H, *J* = 5.74 Hz), 4.36 (d, 2H, *J* = 5.74 Hz), 4.20 (t, 2H, *J* = 6.63 Hz), 2.95 (t, 2H, *J* = 6.63 Hz); ^{13}C NMR (DMSO-d_6) 160.3, 157.2, 141.1, 138.5, 136.1, 134.7, 130.4, 129.0, 127.9, 126.9, 126.6, 125.8, 124.9, 114.1, 65.7, 62.5, 26.2. IR (KBr) *v* 1599, 1510, 1243, 812, 690 cm^{-1}. MS (FD) *m/z* 295 (M^+, 100%). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found C, 72.95; H, 5.59; N, 4.65.

4-[2-[4-(Bromomethyl)phenoxy]ethyl]-2-phenyloxazole (19): To a suspension of **13** (15.0 g, 0.05 mol) in CH_2Cl_2 (150 mL) at 5 °C under nitrogen was added phosphorous tribromide (14.5 g, 0.05 mol) dropwise at < 20 °C. The resultant yellow solution was stirred for 2 h at rt until complete by TLC (hexanes:EtOAc (2:1)). The reaction mixture was then cooled to 10 °C, quenched with MeOH (10 mL), and stirred for 5 min. The solvent was removed *in vacuo* to give a yellow solid that was diluted in EtOAc (100 mL) and cold (0 ° to 5°C) 5% aqueous $NaHCO_3$ (75 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ (2 x 50 mL), dried ($MgSO_4$), and filtered. The solvent was removed *in vacuo* to give 18.3 g (100%) of **19** as a white solid that was immediately used.[17] ^{1}H NMR (DMSO-d_6) 8.14-8.11 (m, 2H), 7.62 (s, 1H), 7.49-7.47 (m 3H), 7.30 (d, 2H, *J* = 8.55 Hz), 6.87 (d, 2H *J* = 8.55 Hz), 4.47 (s, 2H), 4.30 (t, 2H, *J* = 6.25 Hz), 3.17 (t, 2H, *J* = 6.25), ^{13}C NMR (DMSO-d_6) 161.4, 158.4, 137.1, 135.8, 135.7, 131.5, 130.5, 130.3, 130.2, 128.9, 126.8, 125.5, 114.6, 65.9, 34.2, 34.0, 26.1.

***O*-[4-[2-(2-Phenyl-4-oxazolyl)ethoxy]phenylmethyl]-*N*-triphenylmethyl-L-serine methyl ester (21).** To a solution of *N*-trityl-L-serine methyl ester (**20**) (16.3 g, 0.05 mol), freshly prepared **19** (18.0 g), and tetrabutylammonium bromide (14.5 g, 0.05 mol) in CH_2Cl_2 (500 mL) was added a 50% aqueous solution of NaOH (36.0 g, 0.05 mol) and the reaction mixture was heated to a gentle reflux for 24 h.[18] The

reaction mixture was cooled, diluted with CH_2Cl_2 (250 mL), and washed with water (3 x 500 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford a yellow oil that was purified by silica gel column chromatography, using hexanes:EtOAc (8:1), to afford 19.2 g (61%) of **21** as a colorless oil. ^{1}H NMR (DMSO-d_6) 8.02 (s, 1H), 7.96-7.93 (m, 2H), 7.51-7.49 (m, 3H), 7.37 (d, 6H, *J* = 8.8 Hz), 7.25 (t, 6H, *J* = 7.48 Hz), 7.16 (t, 5H, *J* = 8.40 Hz), 6.91 (d, 2H, *J* = 8.8 Hz), 4.39-4.20 (m, 4H), 3.58-3.48 (m, 1H), 3.44-3.27 (m, 2H), 3.15 (s, 3H), 3.03-2.94 (t, 2H, *J* = 6.40 Hz), 2.87-2.84 (d, 1H, *J* = 9.40 Hz); ^{13}C NMR (DMSO-d_6) 173.2, 160.3, 157.8, 145.6, 138.5, 136.2, 130.4, 130.1, 129.1, 129.0, 128.3, 127.8, 126.9, 126.3, 125.8, 124.9, 124.8, 114.2, 72.6, 70.9, 66.3, 56.5, 51.8, 27.0. IR (KBr) *v* 3008, 1732, 1246, 1174, 1106, 1034 cm^{-1}. Anal. Calcd for $C_{41}H_{38}N_2O_5$: C, 77.09, H, 6.00, O, 4.39. Found C, 76.85, H, 5.81, O, 4.09.

***N*-(Benzyloxycarbonyl(Cbz)-*O*-[4-[2-(2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl)-L-serine methyl ester (22).** To a solution of **21** (1.40 g, 0.02 mol) in Et_2O-MeOH (1:1) (50 mL) was added dropwise 1 *M* anhydrous hydrogen chloride in Et_2O (4.2 mL, 0.05 mol) at 0° to 5°C over 20 min. The reaction mixture was stirred in an ice bath for 1 h until (**21**) was completely consumed.[19] The solvent was removed *in vacuo*, and the resultant residue was taken up in Et_2O (200 mL) and the extract was washed with water (4 x 50 mL). The combined aqueous layers were re-extracted with Et_2O (100 mL). The pH of the aqueous layer was adjusted to pH~8 by slowly adding $NaHCO_3$ (solid). To the resulting aqueous layer was added EtOAc (100 mL) and benzyl chloroformate (0.41 g, 0.02 mol) with vigorous stirring. The reaction mixture was stirred for 1 h at rt, the organic layer isolated, and the aqueous layer extracted with EtOAc (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to give **22** as a yellow oil, that was purified by silica gel column chromatography, using hexanes:EtOAc (2:1) to afford 1.05 g (90%) of **22**. ^{1}H NMR (DMSO-d_6) 7.98 (s, 1H), 7.92-7.89 (m, 2H), 7.74 (d, 1H, *J* = 8.00 Hz), 7.49-7.45 (m, 3H), 7.31-7.25 (m, 5H), 7.17 (d, 2H, *J* = 8.55 Hz), 6.88 (d, 2H, *J* = 8.55 Hz), 4.99 (s, 2H), 4.34 (d, 2H, *J* = 1.64 Hz), 4.31-4.29 (m, 1H), 4.21 (t, 2H, *J* = 6.58 Hz), 3.29-3.60 (m, 5H), 2.95 (t, 2H, *J* = 6.58 Hz); ^{13}C NMR (DMSO-d_6) 170.7, 160.3, 157.8, 156.0, 138.4, 136.8, 136.2, 130.4, 129.9, 129.2, 129.0,

128.3, 127.8, 127.6, 126.9, 125.8, 124.9, 114.2, 92.5, 71.7, 68.5, 65.7, 65.5, 54.1, 51.9, 26.2. IR (KBr) *v* 3311, 1735, 1248, 1177, 1036 cm^{-1}. MS (FD) *m/z* 530 (M^+, 100%). Anal. Calcd for $C_{30}H_{30}N_2O_7$: C, 67.91; H, 5.70; N, 5.28. Found C, 67.92; H, 5.70; N, 5.19.

***N*-Cbz-*O*-[[4-[2-(2-phenyl-4-oxazolyl)ethoxy]benzyl-L-serine (1).** A solution of **22** (1.00 g, 1.90 mmol) in THF (30 mL) and deionized water (10 mL) was cooled to 2 °C. A solution of lithium hydroxide (0.10 g, 3.80 mmol) dissolved in deionized water (10 mL) was slowly added to this solution over 5 min while keeping the reaction temperature < 4 °C. The reaction mixture was stirred in an ice bath for 2.5 h until complete.[19] The reaction mixture was acidified with 6 *N* HCl (3 mL) to pH ~ 1, then diluted with deionized water (100 mL) and extracted with EtOAc (2 x 50 mL), using saturated aqueous NaCl (50 mL) to improve layer separations. The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a residue that was taken up in MeCN (50 mL). 2-Phenyloxazole **1** crystallized from the MeCN to give a slurry that was stirred for 1 h in an ice bath, then filtered using the cold filtrate as an initial rinse and then cold (5°C) MeCN (50 mL) as a final rinse to give 0.87 g (90%) of (**1**) after drying in a vacuum oven at 50°C that was >95% pure (by HPLC) and had 98.7% ee (by chiral HPLC analysis). 2-Phenyloxazole (**1**) could be further purified by a second recrystallization from MeCN. ^{1}H NMR (DMSO-d_6) 12.71 (s, 1H), 7.99 (s, 1H) 7.92-7.89 (m, 2H), 7.54 (d, 1H, *J* = 8.22 Hz), 7.48-7.46 (m, 3H), 7.31-7.25 (m, 5H), 7.18 (d, 2H, *J* = 8.47 Hz), 6.87 (d, 2H, *J* = 8.47 Hz), 4.98 (s, 2H), 4.34 (s, 2H), 4.23-4.16 (m, 3H), 3.59 (d, 2H, *J* = 4.51 Hz), 2.95 (t, 2H, *J* = 6.52 Hz); ^{13}C NMR (DMSO-d_6) 171.6, 160.3, 157.8, 156.0, 138.5, 136.9, 136.2, 130.4, 130.1, 129.2, 129.1, 128.3, 127.7, 127.6, 126.9, 125.8, 114.2, 92.6, 71.7, 68.9, 65.7, 65.4, 54.2, 26.2. IR (KBr) *v* 3313, 1690, 1609, 1532, 1513, 1277, 1264, 1250, 1077, 1061, 1031, 688 cm^{-1}. MS (FD) *m/z* 517 (M^+, 100%). Anal. Calcd for $C_{29}H_{28}N_2O_7$: C, 67.43; H, 5.46; N, 5.42. Found C, 67.31; H, 5.26; N, 5.35.

(3S)-*N*-Cbz-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid (26): A solution of **25** (5.00 g, 0.03 mol) in dioxane:H_2O (1:1) (100 mL) was treated with 50% aqueous solution of NaOH (1.04 g, 0.03 mol) and the reaction cooled to -5 ^{o}C in an ice-acetone bath. The pH was adjusted to 9.0 with 1.0 *N* HCl.

Upon reaching -5 ^{o}C, benzyl chloroformate (4.90 g, 0.03 mol) was added over 20 min, maintaining the temperature at -5 ^{o}C and the pH at 9-9.5 using 1.0 *N* NaOH. After addition of benzyl chloroformate was complete the reaction mixture was stirred for 1 h. Completion of the reaction was checked by HPLC.[20] The ice-acetone bath was removed and the pH adjusted to 12.5 using 50% NaOH. The solution was stirred at high pH for approximately 2 h.[21] The pH was adjusted to 8 with conc. HCl. The solution was concentrated to give an oil, that was diluted with 100 mL of water, and the pH was adjusted up to 12.5 with 50% NaOH. The aqueous layer was washed with methyl *t*-butyl ether (2 x 100 mL) and adjusted to a pH of 2.0 with conc. HCl. The product was extracted into EtOAc (100 mL). The extract was washed with water (3 x 100 mL) and saturated aqueous NaCl (3 x 100 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford 6.00 g of **26** as a foam. ^{1}H NMR (DMSO-d_6) 12.65 (s, 1H), 9.27 (d, 1H, *J* = 3.30 Hz), 7.35 (m, 5H), 6.96 (dd, 1H, *J* = 3.00 Hz, 8.00 Hz), 6.56 (d, 2H, *J* = 11.0 Hz), 5.16 (s, 1H), 5.10 (d, 1H, *J* = 5.70 Hz), 4.85 (dd, 0.5H, *J* = 3.00 Hz, 5.00 Hz), 4.80 (t, 0.5H, *J* = 5.00 Hz), 4.47 (dd, 1H, *J* = 17.00 Hz, 76.0 Hz), 4.45 (app.dd, 1H, *J* = 16.00 Hz, 24.00 Hz), 3.0 (s, 1H): ^{13}C NMR (DMSO-d_6) 172.4, 155.9, 136.8, 133.9 133.3, 129.1, 128.9, 128.4, 127.5, 121.9, 114.0, 112.5, 66.5, 53.5, 44.4, 44.1, 29.8. IR (KBr) *v* 3028, 1694, 1419, 1312, 1122 cm^{-1}. HRMS (FD) *m/z* calcd for $C_{18}H_{17}NO_5$: 327.1107, found *m/z* (M+1) 328.1052.

Methyl (3S)-*N*-Cbz-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylate (27): A solution of **26** (3.00 g, 9.20 mmol) in MeOH (60 mL) was stirred under nitrogen atmosphere, cooled to 2 ^{o}C, and treated with acetyl chloride (1.00 g, 0.01 mol) added over 1 min. During addition the reaction warmed to 7 ^{o}C. The solution was stirred at ambient overnight (18 h) and checked for completion by HPLC. The reaction mixture was evaporated *in vacuo* to an oil, diluted with a 3:1 mixture of EtOAc-deionized water (120 mL), and washed with 3% $NaHCO_3$ solution (2 x 50 mL) and saturated aqueous NaCl (2 x 50 mL). The organic layer was then dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to afford a yellow oil that was purified by silica gel column chromatography using hexanes:EtOAc (5:1) to afford 3.60 g (100%) of **27**. ^{1}H NMR (DMSO-d_6) 9.29 (d, 1H, *J* = 2.40 Hz), 7.34 (m, 5H), 6.96 (d, 1H, *J* = 7.50 Hz), 6.57 (m, 2H),

5.17 (s, 1H), 5.09 (d, 1H, *J* = 16.00 Hz), 4.93 (t, 0.5H, *J* = 4.50 Hz), 4.86 (dd, 0.5H, *J* = 4.20 Hz, 6.00 Hz), 4.47 (dd, 1H, *J* = 16.00 Hz, 82.00 Hz), 4.46 (dd, 1H, *J* = 16.00 Hz, 30.00 Hz), 3.52 (s, 1.5H), 3.48 (s, 1.5H), 3.01 (m, 2H): ^{13}C NMR (DMSO-d_6) 171.7, 156.0, 136.6, 134.0, 133.3, 129.0, 128.7, 128.4, 127.5, 121.7, 114.0, 112.5, 66.5, 53.8, 53.3, 52.0, 44.3, 44.1, 29.7. IR (KBr) *v* 1739, 1696, 1417, 1312, 1121 cm^{-1}. HRMS (FD) *m/z* calcd for $C_{19}H_{19}NO_5$: 341.1263, found *m/z* (M+1) 342.1384.

Methyl 7-[2-(2-phenyl-4-oxazolyl)ethoxyyl]-L-1,2,3,4-tetrahydro-*N*-benzyloxycarbonylisoquinoline-3-carboxylate (28): To a solution of **16** (1.00 g, 3.00 mmol) and **27** (1.00 g, 3.00 mmol) in DMF (25 mL) was added Cs_2CO_3 (1.22 g, 3.75 mmol) and the reaction mixture stirred at 55 ^{o}C for 24 h. Analysis by HPLC indicated the formation of an 80:14 mixture of **28**:**18**. The reaction mixture was diluted with EtOAc (50 mL), quenched with water (2 x 50 mL), and washed with 10% aqueous NH_4Cl (2 x 50 mL). The organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a brown oil that was purified by silica gel column chromatography using hexanes:EtOAc (6:1) to afford 0.04 g (11%) of **18** as a brown oil and 1.26 g (85%) of **28** as a colorless oil, respectively. HRMS (FD) *m/z* calcd for $C_{30}H_{28}N_2O_6$: 512.1947, found *m/z* (M+1) 513.1840.

(3S)-*N*-Cbz-1,2,3,4-tetrahydro-7-[2-(2-phenyl-4-oxazolyl)ethoxy]isoquinoline-3-carboxylic acid (2): To a solution of **28** (30.0 g, 0.06 mol) stirred in MeOH (600 mL) to which was added 1 *N* NaOH (63 mL, 1.05 equiv.). The reaction mixture was stirred at rt for 10 min to give a solution. The pH of the reaction mixture (11.2) was then adjusted to 7.8 using 1 *N* HCl. The sodium salt solution was then load onto a biotage flash 75™ radial compression column pretreated with 1L MeCN and 2L MeCN:H_2O (5:95). The excess base and NaCl were first washed off the column by elution with 1.2L 95:5 H_2O:MeCN. The product was then eluted with 2L 70:30 MeCN:H_2O. The fractions containing the product were combined and the MeCN concentrated *in vacuo* to 150 mL MeCN. The solution was then frozen in dry ice:acetone and freeze dried over 18 h to yield 30.2 g (96%) of **2** as a white amorphous solid. mp 179-182 ºC. ^{1}H NMR (DMSO-d_6) 2.99 (m, 2H), 3.09 (m, 2H), 4.25 (m, 2H), 4.20-4.54 (m, 2H), 4.85-4.95 (m, 1H), 5.13-6.02 (m, 2H), 6.79 (m, 1H), 6.90 (m, 1H), 7.12 (m, 1H), 7.30-7.45 (m, 5H), 7.54 (m, 3H), 7.95 (m, 2H),

8.03 (s, 1H); IR (KBr) *v* 107, 1620 cm^{-1}. Anal. Calcd for $C_{29}H_{26}N_2O_6$ C69.87, H 5.26, N, 6.62. Found C, 69.73, H, 5.48, N. 5.52. MS (FD) *m/z* 499 (M^+, 100%).

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12. HPLC conditions: Zorbax SB-Ph 4.6 mm x 25 cm column with isocratic MeCN:1% TFA (1:1) in water buffer at 1 mL/min and 210 nm. **10** R_t = 4.28 min. **15** R_t = 6.59 min.

13. HPLC conditions: Zorbax SB-Ph 4.6 mm x 25 cm column with isocratic MeCN:1% TFA (1:1) in water buffer at 1 mL/min and 210 nm. **10** R_t = 4.28 min. **16** R_t = 14.71 min.

14. HPLC conditions: Zorbax SB-Ph 4.6 mm x 25 cm column with isocratic MeCN:1% TFA (1:1) in water buffer at 1 mL/min and 210 nm. **10** R_t = 4.28 min. **17** R_t = 14.01 min.

15. HPLC conditions: Zorbax SB-Ph 4.6 mm x 25 cm column with isocratic MeCN:1% TFA (1:1) in water buffer at 1 mL/min and 210 nm. **15** R_t = 6.59 min. 4-Hydroxybenzaldehyde R_t = 3.75 min. **18** R_t = 8.43 min. **12** R_t = 11.72 min.

16. HPLC conditions: Zorbax SB-Ph 4.6 mm x 25 cm column with isocratic MeCN:1% TFA (1:1) in water buffer at 1 mL/min and 210 nm. **12** R_t = 11.72 min. **13** R_t = 6.89 min.

17. Bromide (**19**) begins to decompose within 3 h at rt and within 36 h at 0 ^{o}C

18. HPLC conditions: Zorbax SB-Ph 4.6 mm x 25 cm column with isocratic MeCN:1% TFA (1:1) in water buffer at 1 mL/min and 210 nm. **20** R_t = 7.28 min. **19** R_t = 17.20 min. Reactions generally proceeded to give 59% **21** (*in situ* HPLC area %).

19. TLC conditions: hexanes:EtOAc (2:1)

20. HPLC conditions: Zorbax SB-Ph 4.6 mm x 25 cm column with isocratic MeCN:1% TFA (1:1) in water buffer at 1 mL/min and 210 nm. **25** R_t = 2.43 min. **26** R_t = 5.10 min.

21. The HPLC showed an additional peak that was thought to be the bis-O-carbobenzoxy compound. This was hydrolyzed to the desired monoblocked species with excess base.