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Enantioselective Synthesis of 2,3-Disubstituted Benzomorpholines: Analogues of Lignan Natural Products

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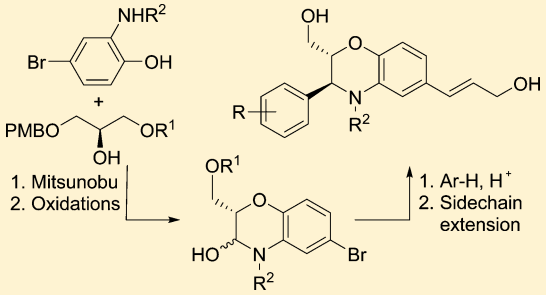
Supporting Information

ABSTRACT: The enantioselective synthesis of 2,3-disubstituted benzomorpholines, analogues of 1,4-benzodioxane natural products, has been achieved via addition of electron-rich aromatic donors to acyl-iminium ions derived from benzomorpholine aminols. Subsequent modification of the benzomorpholine scaffold allows side chains mimicking those found in 1,4-benzodioxane lignans to be added. Antiproliferative testing of the prepared analogues showed promising results against MDA-MB-231 and HCT116 cancer cell lines.



1,4-Benzodioxane neolignans are a subclass within the lignan family of natural products that exhibit potent biological effects, including antimicrobial, hepaprotective, and antiproliferative activities.[1−5] Naturally occurring compounds all contain a 2-aryl-1,4-benzodioxane core structure with various oxygenated substituents.[6] The eusiderin family is the largest group of 1,4-benzodioxane lignans (e.g., eusiderin A **1**) while isoamericanol A **2**, the well-known lignan-hybrid silybin A, and lignan **3** are other examples that have a hydroxymethyl group at C-9 (Figure 1).[1,2]

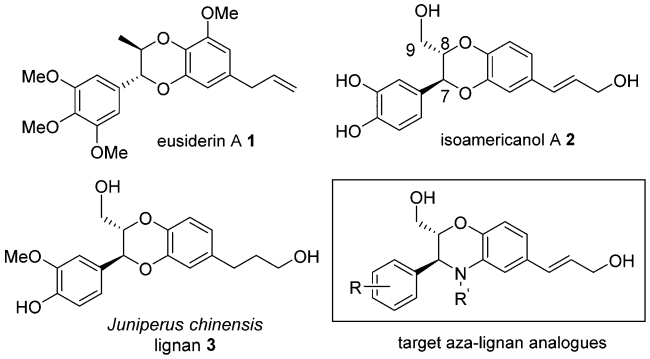


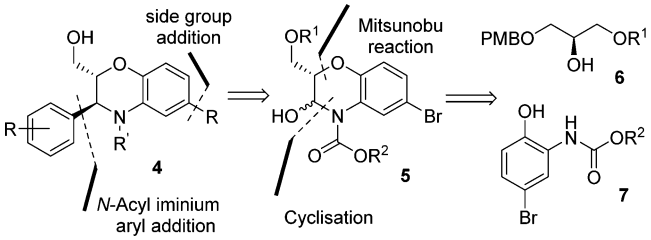
Figure 1. Natural products and target aza-lignan.

In particular, silybin A, one of the components of silymarin (milk thistle extract), has shown inhibitory activity against hepatotoxicants.[7,8] Biosynthetically, 1,4-benzodioxane neolignans are formed by the oxidative dimerization of two phenylpropanoid units through phenoxy radical coupling.[9]

Previously, we have developed an enantioselective and flexible synthetic method to produce 1,4-benzodioxane lignans such as eusiderin A **1**, isoamericanol A **2**, and the rodgersinines.[1−3] Unfortunately, naturally occurring 1,4-benzodioxane lignans are known to have poor aqueous solubility which limits their therapeutic application.[10−12]

We wished to prepare 3-aryl benzomorpholine analogues **4** of these natural products to explore the solubility of these compounds and the effect of exchanging an oxygen with a substituted amino group. There are limited examples of the preparation of 2,3-disubstituted benzomorpholines,[13−16] and few of these are diastereo- or enantioselective.[17−20] Our approach was designed around the addition of various electron-rich aromatic nucleophiles to an acyl-iminium ion derived from benzomorpholine aminol **5**. To date there are very few examples of morpholine[21,22] and benzomorpholine[23] ring systems participating in acyl-iminium chemistry.[24] Aminol **5** would be prepared from chiral-pool derived, suitably protected, glycerol **6** and aminophenol **7** derivatives (Scheme 1).

Scheme 1. Retrosynthetic Analysis



The synthesis began with an enantiopure glycerol derivative, which was prepared by selective protection of diol **8** to give either benzyl ether **9** or Si^iPr_3 (TIPS) **10** over three high yielding steps (Scheme 2). Mitsunobu reaction of alcohols **9** and **10**, which have previously been shown to undergo inversion with high enantiospecificity,[2] with *N*-Cbz **11**[25] or *N*-Boc **12**[26] protected aminophenols gave highly enantioentriched aryl ethers **13**, **14**,

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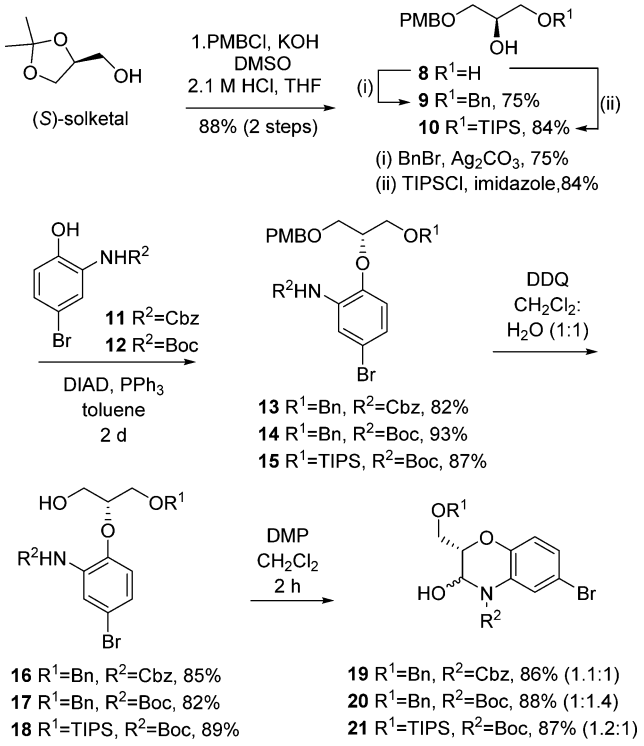
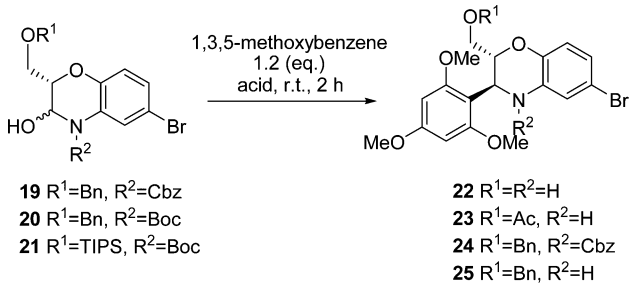
Scheme 2. Synthesis of Benzomorpholine Aminol



and **15** all in high yields. Deprotection of the PMB group in ethers **13**–**15** gave primary alcohols **16**–**18**, which were oxidized using Dess-Martin periodinane (DMP) to give cyclic benzomorpholine aminols **19**–**21** as a separable mixture of diastereomers.

Having prepared aminols **19**–**21**, we then wished to add a range of electron-rich aromatics that mimic the aryl groups found in natural lignans. *N*-Acyl iminium ions are commonly formed using either Lewis acids or Brønsted acids. We began with benzomorpholine aminol **21** containing *N*-Boc and *O*-TIPS groups to find optimized conditions using 1,3,5-trimethoxybenzene (Table 1). Using $BF_3{\cdot}OEt_2$[27] induced decomposition of starting materials while 10 mol % AuOTf[28] resulted in successful aryl addition; however, the Boc and TIPS groups were removed, giving amino alcohol **22** in low yield. The use of Brønsted acids methanesulfonic acid and sulfuric acid improved the yield, especially when acetic acid was used as solvent.[29,30] When catalytic sulfuric acid was used, in spite of the better yield compared to the use of AuOTf, deprotection of both the TIPS and BOC group occurred with acetate **23** and alcohol **22** being obtained in 17% and 7% yield, respectively. Increasing the amount of sulfuric acid (8 equiv) gave acetate **23** and alcohol **22** in improved yields of 69% and 30%, respectively. It is assumed that the acetate is formed due to the acidic deprotection of the TIPS group and the resultant formation of an acetylating agent TIPS acetate which then reacts with the free primary alcohol. We then applied these conditions to *N*-Cbz, *O*-Bn aminol **19** and *N*-Boc and *O*-Bn aminol **20**. Both aminols **19** and **20** gave aryl addition products **24** and **25**, respectively, in near-quantitative yield with cleavage of the *N*-Boc in **25** observed. Conveniently, the deprotected Boc group allowed functionalization of the benzomorpholine nitrogen position at a later stage.

Table 1. Optimization of Aryl Addition Conditions



aminol	acid	solvent	products	yield (%)
21	$BF_3{\cdot}OEt_2$ (2 equiv)	CH_2Cl_2	–	NR
21	AuOTf (10 mol %)	CH_2Cl_2	**22**	11
21	H_2SO_4 (30 mol %)	AcOH	**22**/**23**	17/7
21	H_2SO_4 (8 equiv)	AcOH	**22**/**23**	69/30
19	H_2SO_4 (8 equiv)	AcOH	**24**	97
20	H_2SO_4 (8 equiv)	AcOH	**25**	97

Having found optimized conditions, the nucleophile scope was investigated with various electron-rich aromatic donors (Table 2). Benzomorpholine aminols **19**, **20**, and **21** gave a variety of 3-aryl-benzomorpholines **26**–**32** as single diastereoisomers all with the more stable 2,3-*trans* configuration. This was determined by analysis of the $J_{2,3}$ coupling constant; all compounds with a *N*-Cbz group had J = ∼2 Hz which indicates a *trans*-diaxial configuration. In cases where the aryl group was a 2,4,6-trimethoxyphenyl then additional steric interactions between the Cbz and aryl substituents led the compound to adopt a *trans*-diequatorial conformation (J = ∼8 Hz). After removal of the *N*-Cbz group (see below) all compounds adopted the more favored *trans*-diequatorial conformation (J = ∼8 Hz). When investigating the nucleophilic scope of the reaction the only unsuccessful example was when using syringol (2,6-dimethoxyphenol), which upon reaction with aminols **19**–**21** gave a complex mixture of 3-aryl-benzomorpholines, most likely due to competing directing effects.

With an adaptable route to *N*-acyl iminium addition determined, addition of side chains to benzomorpholines was explored. The first aim was to add an allylic alcohol which found in a number of benzodioxane lignans, such as isoamericanol A **2**. Attempted formylation of *N*-Cbz/*O*-Bn aryl benzomorpholines **24**, using lithiation, was unsuccessful. Further studies with *N*-Cbz/*O*-Bn benzomorpholine **24** concluded that selective reduction or deprotection of the Cbz group were similarly unsuccessful. To obtain a deprotected amine, the *N*-Boc-*O*-Bn aminol **20** was chosen due to removal of the Boc group under optimized acidic conditions. After methylation of benzomorpholine **25** the bromide was successfully converted to aldehyde **32** in 93% yield, via lithiation and addition of DMF. A Wittig reaction with aldehyde **32** gave the unsaturated ester, which was reduced to give allylic alcohol **33** (Scheme 3).

Exhaustive hydrogenation of **33** using hydrogen and Pd/C removed the benzyl ether and reduced the alkene, giving compound **34** in 51% yield, which is an aza-analogue of lignan **3**.[31] Attempted selective removal of the *O*-benzyl group in the presence of the allylic alcohol under various conditions was unfortunately unsuccessful. In an attempt to successfully obtain the natural allylic alcohol side chain, we revised our strategy to use the previously prepared acetate **23**. Compound **23** was subjected to a four-step procedure (*N*-methylation, ester hydrolysis, TIPS protection, and formylation) to obtain aldehyde **35** which was then converted to allylic alcohol **36** (Scheme 3).

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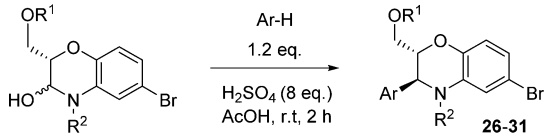
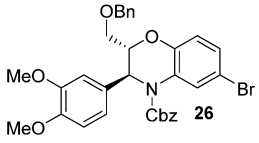
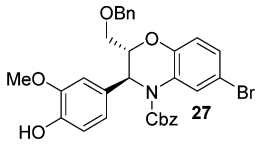
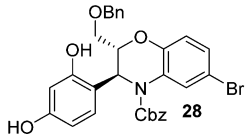
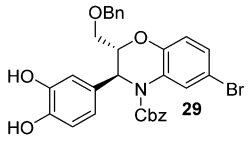
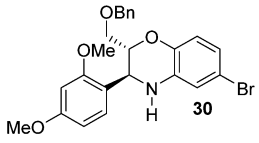
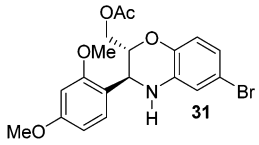
Table 2. Nucleophile Scope of Reaction



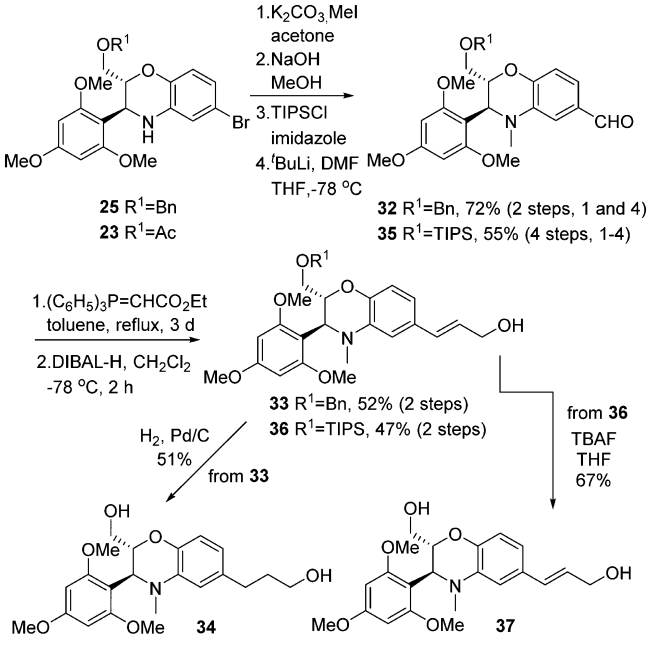
R^1	R^2	product	yield (%)
Bn	Cbz	 **26**	61
Bn	Cbz	 **27**	56
Bn	Cbz	 **28**	39
Bn	Cbz	 **29**	36
Bn	Boc	 **30**	94
TIPS	Boc	 **31**	50

Finally, removal of the TIPS group from **36** gave the desired compound **37**, an analogue of lignans such as isoamericanol A **2**.

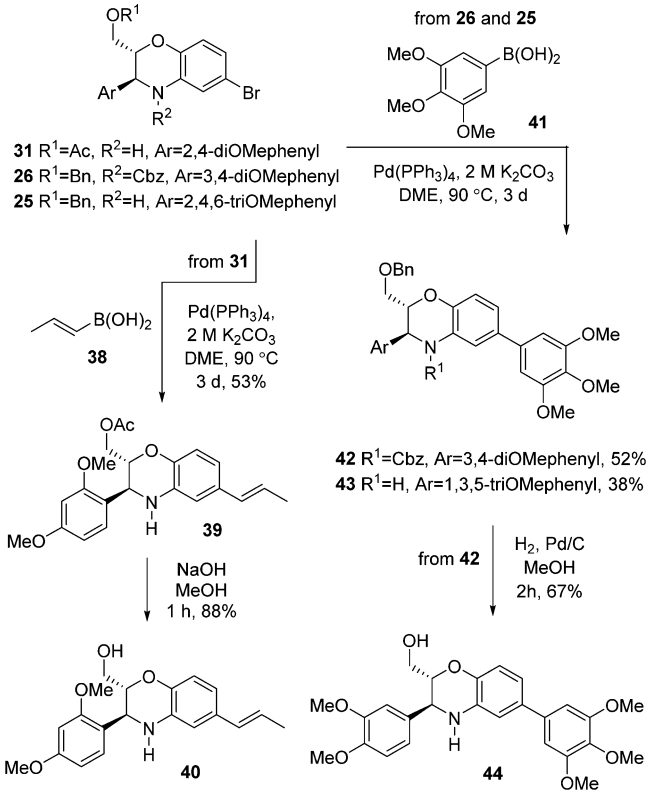
We then explored alternative side chain additions using Suzuki reactions on benzomorpholine bromides. The Suzuki coupling reaction between **31** and *trans*-prop-1-enylboronic acid **38** gave alkene **39**, from which the acetyl protecting group was hydrolyzed to give analogue **40** (Scheme 4). Additionally, a Suzuki coupling reaction between **25** and **26** with boronic acid **41** gave biaryls **42** and **43**, respectively. Hydrogenolysis of benzyl and Cbz protecting groups in **42** gave alcohol **44** in 67% yield.

Following the synthesis of the 3-aryl benzomorpholine analogues, their antiproliferative activity was investigated against two human cell lines, MDA-MB-231, a breast cancer cell line and HCT116, a human colon cancer cell line, and their IC_{50} values were determined. In particular, biaryl-benzomorpholine **44** showed promising activity, with IC_{50} values of 0.65 μM and 0.82 μM against MDA-MB-231 and HCT116 cell lines,

Scheme 3. Synthesis of Allylic and Saturated Side Chains



Scheme 4. Synthesis of Alternative Analogues



respectively. Biaryl-benzomorpholine **44** is a novel scaffold which could be further explored for its antiproliferative activity. Further studies to compare the solubility and bioactivity of these biaryl compounds to their oxygen counterparts are currently being investigated.

In conclusion, we report methods to enantioselectively synthesize functionalized 2,3-disubstituted benzomorpholines. Aryl addition to benzomorpholine aminols via an *N*-acyl iminium intermediate was promoted under Brønsted acid conditions to

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generate a variety of 3-aryl-benzomorpholines as single diastereomers. We then utilized these compounds to the synthesis of a number of aza-lignan analogues. The route used to prepare these analogues is adaptable to the preparation of numerous other compounds, with modification of the aryl groups and side chain easily achievable.

EXPERIMENTAL SECTION

General Procedures. All reactions were carried out with oven-dried glassware and under a nitrogen atmosphere in dry, freshly distilled solvents unless otherwise noted. Diisopropylethylamine was distilled from CaH_2 and stored over activated 4 Å molecular sieves. NMR spectra were recorded on a 300 or 400 MHz spectrometer. Chemical shifts are reported relative to the solvent peak of chloroform (δ 7.26 for ^{1}H and δ 77.16 ± 0.06 for ^{13}C). ^{1}H NMR data are reported as position (δ), relative integral, multiplicity (s, singletl; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; t, triplet; td, triplet of doublets; tt, triplet of triplets; m, multiplet), coupling constant (*J*, Hz), and the assignment of the atom. ^{13}C NMR data are reported as position (δ) and assignment of the atom. NMR assignments were performed using COSY, HSQC, and HMBC experiments. High-resolution mass spectroscopy (HRMS) was carried out by either chemical ionization (CI) or electrospray ionization (ESI) on a MicroTOF-Q mass spectrometer. Unless noted, chemical reagents were used as purchased. Compounds **8** and **10** were prepared using previously reported methods.[2]

(R)-1-(Benzyloxy)-3-((4′-methoxybenzyl)oxy)propan-2-ol ***9***. To a solution of diol **8** (1.0 g, 4.71 mmol) and Ag_2CO_3 (2.60 g, 9.42 mmol) in toluene (35 mL) under an atmosphere of nitrogen, in the absence of light at room temperature, was added BnBr (0.84 mL, 7.07 mmol) slowly, and the mixture was stirred for 20 h. The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (3:1 hexanes, ethyl acetate) to give the *title compound* **9** (1.07 g, 75%) as a pale yellow oil. R_f = 0.43 (2:1 hexane, ethyl acetate); $[\alpha]_D$ +2.34 (*c* = 1.19, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.52 (1H, d, *J* = 4.2 Hz, OH), 3.47−3.56 (4H, m, 1-CH_2, 3-CH_2), 3.79 (3H, s, OMe), 3.97−4.02 (1H, m, 2-H), 4.47 (2H, s, OCH_2Ar), 4.54 (2H, s, OCH_2Ph), 6.86 (3H, d, *J* = 8.6 Hz, 3′-H), 7.24 (1H, d, *J* = 8.6 Hz, 2′-H), 7.28−7.35 (5H, Ar−H, Bn); δ_C (125 MHz; $CDCl_3$) 55.4 (4′-OCH_3), 69.6 (C-2), 71.0 (C-1), 71.4 (C-3), 73.1 (OCH_2Ar), 73.5 (OCH_2Ph), 114.0 (C-3′), 127.8, 128.4 (Ar−CH), 129.4 (C-2′), 130.1 (C-1′), 138.0 (Ar−C), 159.3 (C-4′); IR (film)/cm^{-1}: 3448, 2861, 1708, 1610, 1490, 1454, 1417, 1388, 1364, 1326, 1301, 1245, 1205, 1174, 1088, 1028, 952, 815, 735; HRMS (ESI+) Found (MNa^+): 325.1418; $C_{18}H_{22}NaO_4$ requires 325.1410.

Benzyl (5-Bromo-2-hydroxyphenyl)carbamate ***11***. To a solution of 2-amino-4-bromophenol (4.0 g, 21 mmol) and Amberlyst 15 (1.6 g, 40% w/w) in CH_3CN (60 mL) under an atmosphere of nitrogen at room temperature was added benzyl chloroformate (3.64 mL, 26 mmol) slowly, and the mixture was stirred for 4 h. The solution was filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 hexanes, ethyl acetate) to give the *title compound* **11** (3.5 g, 51%) as a brown solid. R_f = 0.65 (2:1 hexane, ethyl acetate); mp 164−166 °C; δ_H (500 MHz; $CDCl_3$; Me_4Si) 5.23 (2H, s, OCH_2Ph), 6.79 (1H, d, *J* = 8.6 Hz, 3-H), 6.93 (1H, br s, OH), 7.05 (1H, br s, NH), 7.11 (1H, dd, *J* = 8.6, 2.4 Hz, 4-H), 7.35−7.42 (5 H, Ar−H), 7.56 (1H, d, *J* = 2.4 Hz, 6-H); δ_C (125 MHz; $CDCl_3$) 68.1 (OCH_2Ph), 112.8 (C-5), 119.2 (C-3), 123.5 (C-6), 126.8 (C-1), 127.8 (C-4), 128.5, 128.6, 128.7 (Ar−CH), 135.4 (Ar−C), 145.6 (C-2), 154.6 (C═O); IR (film)/cm^{-1}: 3431, 3203, 3031, 1703, 1611, 1593, 1538, 1454, 1423, 1381, 1349, 1299, 1272, 1215, 1189, 1121, 1078, 1054, 1025, 969, 882, 866, 800, 736; HRMS (ESI+) Found (MNa^+): 345.9859; $C_{14}H_{12}{}^{81}BrNNaO_3$ requires 345.9874. Found (MNa^+): 343.9881; $C_{14}H_{12}{}^{79}BrNNaO_3$ requires 343.9893.

tert-Butyl (5-Bromo-2-hydroxyphenyl)carbamate ***12***. To a solution of 2-amino-4-bromophenol (2.0 g, 11 mmol) and Amberlyst 15 (0.8 g, 40% w/w) in EtOH (30 mL) under an atmosphere of nitrogen was added di-*tert*-butyl dicarbonate (4.89 mL, 21 mmol). The mixture was heated to 45 °C and stirred for 2 h. The solution was filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 hexanes, ethyl acetate) to give the *title compound* **12** (2.5 g, 83%) as a brown solid. R_f = 0.62 (2:1 hexane, ethyl acetate); mp 143−145 °C; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.52 (9H, s, $(CH_3)_3$), 6.77 (1H, d, *J* = 8.6 Hz, 3-H), 6.86 (1H, br s, OH), 7.06 (1H, dd, *J* = 8.6, 2.4 Hz, 4-H), 7.51 (1H, d, *J* = 2.4 Hz, 6-H), 7.97 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 28.3 ($C(CH_3)_3$), 82.4 ($C(CH_3)_3$),112.6 (C-5), 118.9 (C-3), 123.4 (C-6), 127.3 (C-1), 127.4 (C-4), 145.6 (C-2), 154.4 (C═O); IR (film)/cm^{-1}: 3388, 3257, 2978, 1689, 1594, 1522, 1455, 1419, 1392, 1366, 1352, 1306, 1277, 1252, 1227, 1193, 1151, 1123, 1056, 1028, 883, 857, 808, 766. 747; HRMS (ESI+) Found (MNa^+): 312.0023; $C_{11}H_{14}{}^{81}BrNNaO_3$ requires 312.0030. Found (MNa^+): 310.0040; $C_{11}H_{14}{}^{79}BrNNaO_3$ requires 310.0049.

General Procedure for the Mitsunobu Synthesis of Aryl Ethers. To a solution of alcohol **9** or **10** (3.54 mmol) in toluene (30 mL), under an atmosphere of nitrogen, was added PPh_3 (5.59 mmol), and resultant mixture was stirred for 10 min. A solution of phenol **11** or **12** (2.79 mmol) in toluene (15 mL) was then added dropwise, and the mixture was stirred at 0 °C for 20 min. DIAD (5.59 mmol) was added, and the solution was allowed to warm to room temperature and stirred for 3 days. Following this, the solvent was removed *in vacuo*. The crude product was purified by flash chromatography to give the aryl ether **13**−**15**.

(S)-Benzyl (2′-(1-(Benzyloxy)-3-((4″-methoxybenzyl)oxy)propan-2-yl)oxy)-5′-bromophenyl)carbamate ***13***. Using the general procedure, alcohol **9** gave the *title product* **13** (1.48 g, 82%) as a brown oil: R_f = 0.66 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +0.47 (*c* = 0.21, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.56−3.66 (4H, m, 1-CH_2, 3-CH_2), 3.79 (3H, s, OMe), 4.18−4.21 (1H, m, 2-H), 4.44 (2H, s, OCH_2Ar), 4.51 (2H, s, OCH_2Ph), 5.15 (2H, s, OCH_2Ph), 6.81−6.83 (3H, m, 3″-H, 3′-H), 7.01 (1H, dd, *J* = 8.6, 2.4 Hz, 4′-H), 7.16 (1H, d, *J* = 8.6 Hz, 2″-H), 7.28−7.44 (10 H, Ar−H), 8.29 (1H, br s, NH), 8.36 (1H, br, s, 6′-H); δ_C (125 MHz; $CDCl_3$) 55.3 (4″-OCH_3), 67.2 (OCH_2Ph), 68.7 (C-3), 69.2 (C-1), 73.1 (OCH_2Ar), 73.5 (OCH_2Ph), 81.0 (C-2), 113.8 (C-3″), 116.3 (C-5′), 119.9 (C-3′), 121.5 (C-6′), 125.2 (C-4′), 127.7 (Ar−CH), 127.8 (Ar−CH), 128.3 (Ar−CH), 128.4 (Ar−CH), 128.5 (Ar−CH), 128.6 (Ar−CH), 129.4 (C-2″), 129.5 (C-1″), 132.3 (C-2′), 136.2 (Ar−C), 137.4 (Ar−C), 145.2 (C-2′), 152.5 (C═O), 159.4 (C-4″); IR (film)/cm^{-1}: 3262, 3032, 2863, 1732, 1594, 1515, 1470, 1454, 1417, 1366, 1295, 1248, 1217, 1082, 1046, 906, 877, 821, 737, 697; HRMS (ESI+) Found (MNa^+): 630.1297; $C_{32}H_{32}{}^{81}BrNNaO_6$ requires 630.1291. Found (MNa^+): 628.1312; $C_{32}H_{32}{}^{79}BrNNaO_6$ requires 628.1305.

tert-Butyl (S)-(2′-((1-(Benzyloxy)-3-((4″-methoxybenzyl)oxy)-propan-2-yl)oxy)-5′-bromophenyl)carbamate ***14***. Using the general procedure, alcohol **9** gave the *title product* **14** (1.27 g, 93%) as a brown oil: R_f = 0.60 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +0.51 (*c* = 0.19, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.49 (9H, s, $(CH_3)_3$), 3.58−3.69 (4H, m, 1-CH_2, 3-CH_2), 3.80 (3H, s, OMe), 4.20−4.23 (1H, m, 2-H), 4.51 (2H, s, OCH_2Ar), 4.58 (2H, s, OCH_2Ph), 6.81 (1H, d, *J* = 8.6 Hz, 3′-H), 6.86 (2H, d, *J* = 8.6 Hz, 3″-H), 6.98 (1H, dd, *J* = 8.6, 2.4 Hz, 4′-H), 7.22 (2H, d, *J* = 8.6 Hz, 2″-H), 7.28−7.34 (5 H, Ar−H), 8.01 (1H, br s, NH), 8.36 (1H, br, s, 6′-H); δ_C (125 MHz; $CDCl_3$) 28.4 ($C(CH_3)_3$), 55.3 (4″-OCH_3), 68.6 (C-3), 69.1 (C-1), 73.1 (OCH_2Ar), 73.5 (OCH_2Ph), 80.6 ($C(CH_3)_3$), 80.8 (C-2), 113.9 (C-3″), 116.2 (C-5′), 119.7 (C-3′), 121.5 (C-6′), 124.9 (C-4′), 127.7 (Ar−CH), 127.8 (Ar−CH), 128.5 (Ar−CH), 129.4 (C-2″), 129.6 (C-1″), 132.7 (C-1′), 137.6 (Ar−C), 145.3 (C-2′), 152.8 (C═O), 159.4 (C-4″); IR (film)/cm^{-1}: 3020, 2970, 1743, 1593, 1515, 1454, 1366, 1231, 1217, 1156, 906, 732; HRMS (ESI+) Found (MNa^+): 596.1423; $C_{29}H_{34}{}^{81}BrNNaO_6$ requires 596.1446. Found (MNa^+): 594.1440; $C_{29}H_{34}{}^{79}BrNNaO_6$ requires 594.1462.

tert-Butyl (R)-(5′-Bromo-2′-((3-((4″-methoxybenzyl)oxy)-1-((triisopropylsilyl)oxy)propan-2-yl)oxy)phenyl)carbamate ***15***. Using the general procedure, alcohol **10** gave the *title compound* **15** (2.71 g, 87%) as a brown oil: R_f = 0.78 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +1.72 (*c* = 0.29, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.02 (18H, d, *J* = 6.0 Hz, $Si(CH(CH_3)_2)_3$, 1.03−1.07 (3H, m, $Si(CH(CH_3)_2)_3$, 1.50 (9H, s, $(CH_3)_3$), 3.63 (1H, dd, *J* = 10.4, 5.6 Hz, 3-H_a), 3.67 (1H, dd, *J* = 10.4, 4.4 Hz, 3-H_b), 3.79 (3H, s, OMe), 3.87 (1H, dd, *J* = 10.4, 4.8 Hz, 1-H_a), 3.92 (1H, dd, *J* = 10.4, 4.8 Hz, 1-H_b), 4.21−4.25 (1H, m, 2-H), 4.52 (2H, s, OCH_2Ar), 6.84 (1H, d, *J* = 8.4 Hz, 3′-H), 6.86 (2H, d, *J* = 8.8 Hz, 3″-H), 6.99 (1H, dd, *J* = 8.4, 2.4 Hz, 4′-H), 7.23 (2H, d, *J* = 8.8 Hz, 2″-H), 7.66

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(1H, br s, NH), 8.34 (1H, br, s, 6′-H); δ_C (125 MHz; $CDCl_3$) 11.9 ($Si(CH(CH_3)_2)_3$), 17.9 ($Si(CH(CH_3)_2)_3$, 28.3 ($C(CH_3)_3$), 55.4 (4″-OCH_3), 62.5 (C-1), 68.3 (C-3), 73.1 (OCH_2Ar), 80.5 ($C(CH_3)_3$), 81.3 (C-2), 113.9 (C-3″), 115.2 (C-5′), 117.6 (C-3′), 121.1 (C-6′), 124.9 (C-4′), 129.4 (C-2″), 129.7 (C-1″), 131.8 (C-1′), 145.3 (C-2′), 152.5 (C═O), 159.9 (C-4″); IR (film)/cm^{-1}: 3434, 2941, 2866, 1729, 1592, 1513, 1462, 1416, 1391, 1367, 1302, 1230, 1154, 1126, 1049, 996, 954, 919, 881, 849, 803, 772, 751; HRMS (ESI+) Found (MNa^+): 662.2295; $C_{31}H_{48}{}^{81}BrNNaO_6Si$ requires 662.2312. Found (MNa^+): 660.2312; $C_{31}H_{48}{}^{79}BrNNaO_6Si$ requires 660.2326.

General Procedure for Removal of PMB Group. To a stirred solution of ethers **13**−**15** (0.59 mmol) in a mixture of CH_2Cl_2 (20 mL) and water (20 mL) was added DDQ (0.71 mmol), and the mixture was stirred at room temperature for 18 h. The resulting solution was washed with portions of sat. aq. $NaHCO_3$ (40 mL) until the washings were colorless. The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography to yield the primary alcohols **16**−**18**.

Benzyl (R)-(2′-((1-(Benzyloxy)-3-hydroxypropan-2-yl)oxy)-5′-bromophenyl)carbamate ***16***. Using the general procedure, ether **13** gave the *title compound* **16** (0.21 g, 85%) as a brown oil: R_f = 0.47 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −5.26 (*c* = 0.27, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.01 (1H, br s, OH), 3.63 (1H, dd, *J* = 10.6, 5.4 Hz, 1-H_a), 3.67 (1H, dd, *J* = 10.2, 4.4 Hz, 1-H_b), 3.85 (2H, d, *J* = 4.4 Hz, 3-CH_2), 4.19−4.25 (1H, m, 2-H), 4.49 (1H, d, *J* = 12.2 Hz, OCH_aH_bPh), 4.55 (1H, d, *J* = 12.2 Hz, OCH_aH_bPh), 5.16 (1H, d, *J* = 12.0 Hz, OCH_aH_bPh), 5.19 (1H, d, *J* = 12.0 Hz, OCH_aH_bPh), 6.85 (1H, d, *J* = 8.6 Hz, 3′-H), 7.06 (1H, dd, *J* = 8.6, 2.4 Hz, 4′-H), 7.28−7.39 (10 H, Ar−H), 8.04 (1H, br s, NH), 8.35 (1H, s, 6′-H); δ_C (125 MHz; $CDCl_3$) 62.4 (C-3), 67.2 (OCH_2Ph), 68.9 (C-1), 73.7 (OCH_2Ph), 81.2 (C-2), 116.3 (C-5′), 118.9 (C-3′), 122.0 (C-6′), 125.5 (C-4′), 127.8 (Ar−CH), 127.9 (Ar−CH), 128.4 (Ar−CH), 128.5 (Ar−CH), 128.6 (Ar−CH), 128.7 (Ar−CH), 131.7 (C-1′), 136.2 (Ar−C), 137.4 (Ar−C), 145.2 (C-2′), 152.3 (C═O); IR (film)/cm^{-1}: 3427, 3032, 2931, 1728, 1594, 1520, 1472, 1454, 1415, 1368, 1293, 1252, 1214, 1043, 1027, 873, 799, 738. HRMS (ESI+) Found (MNa^+): 510.0733; $C_{24}H_{24}{}^{81}BrNNaO_5$ requires 510.0713. Found (MNa^+): 508.0750; $C_{24}H_{24}{}^{79}BrNNaO_5$ requires 508.0730.

tert-Butyl (R)-(2′-((1-(Benzyloxy)-3-hydroxypropan-2-yl)oxy)-5′-bromophenyl)carbamate ***17***. Using the general procedure, ether **14** gave the *title compound* **17** (0.26 g, 82%) as a brown oil: R_f = 0.45 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +0.51 (*c* = 0.20, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.50 (9H, s, $(CH_3)_3$), 2.39 (1H, br s, OH), 3.64 (1H, dd, *J* = 10.6, 4.2 Hz, 1-H_a), 3.68 (1H, dd, *J* = 10.2, 5.4 Hz, 1-H_b), 3.87 (2H, d, *J* = 4.4 Hz, 3-CH_2), 4.22−4.25 (1H, m, 2-H), 4.56 (1H, d, *J* = 12.2 Hz, OCH_aH_bPh), 4.62 (1H, d, *J* = 12.2 Hz, OCH_aH_bPh), 6.83 (1H, d, *J* = 8.6 Hz, 3′-H), 7.02 (1H, dd, *J* = 8.6, 2.4 Hz, 4′-H), 7.30−7.36 (5 H, Ar−H), 7.77 (1H, br s, NH), 8.31 (1H, br, s, 6′-H); δ_C (125 MHz; $CDCl_3$) 28.3 ($C(CH_3)_3$), 62.4 (C-3), 69.0 (C-1), 73.6 (OCH_2Ph), 80.9 ($C(CH_3)_3$), 81.2 (C-2), 115.8 (C-5′), 118.4 (C-3′), 121.9 (C-6′), 125.1 (C-4′), 127.8 (Ar−CH), 128.0 (Ar−CH), 128.6 (Ar−CH), 132.2 (C-1′), 137.7 (Ar−C), 145.2 (C-2′), 152.8 (C═O); IR (film)/cm^{-1}: 3433, 2978, 2932, 1724, 1592, 1516, 1454, 1414, 1392, 1367, 1295, 1232, 1201, 1152, 1102, 1048, 1026, 917, 848, 735; HRMS (ESI+) Found (MNa^+): 476.0867; $C_{21}H_{26}{}^{81}BrNNaO_5$ requires 476.0869. Found (MNa^+): 474.0884; $C_{21}H_{26}{}^{79}BrNNaO_5$ requires 474.0887.

tert-Butyl (R)-(5′-Bromo-2′-((3-hydroxy-1-((triisopropylsilyl)oxy)-propan-2-yl)oxy)phenyl)carbamate ***18***. Using the general procedure, ether **15** gave the *title compound* **18** (0.39 g, 89%) as a brown oil: R_f = 0.67 (2:1hexanes, ethyl acetate); $[\alpha]_D$ +0.33 (*c* = 0.30, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.04 (18 H, d, *J* = 6.0 Hz, $Si(CH(CH_3)_2)_3$, 1.07−1.13 (3H, m, $Si(CH(CH_3)_2)_3$, 1.50 (9H, s, $(CH_3)_3$), 2.37 (1H, t, *J* = 6.4 Hz, OH), 3.91 (1H, dd, *J* = 10.4, 4.4 Hz, 1-H_a), 3.94 (1H, dd, *J* = 10.4, 5.8 Hz, 1-H_b), 3.96 (2H, d, *J* = 6.4 Hz, 3-CH_2), 4.29−4.33 (1H, m, 2-H), 6.83 (1H, d, *J* = 8.6 Hz, 3′-H), 7.04 (1H, dd, *J* = 8.6, 2.4 Hz, 4′-H), 7.33 (1H, br s, NH), 8.28 (1H, br, s, 6′-H); δ_C (125 MHz; $CDCl_3$) 11.9 ($Si(CH(CH_3)_2)_3$), 17.9 ($Si(CH(CH_3)_2)_3$, 28.4 ($C(CH_3)_3$), 62.5 (C-3), 63.2 (C-1), 80.5 ($C(CH_3)_3$), 80.7 (C-2), 114.9 (C-5′), 116.0 (C-3′), 121.8 (C-6′), 124.9 (C-4′), 131.3 (C-1′), 145.0 (C-2′), 152.5 (C═O); IR (film)/cm^{-1}: 3426, 2942, 2866, 1731, 1593, 1518, 1464, 1461, 1392, 1367, 1232, 1203, 1156, 1050, 919, 881, 850, 733; HRMS (ESI+) Found (MNa^+): 542.1716; $C_{23}H_{40}{}^{81}BrNNaO_5Si$ requires 542.1734. Found (MNa^+): 540.1734; $C_{23}H_{40}{}^{79}BrNNaO_5Si$ requires 540.1751.

General Procedure for the Synthesis of Benzomorpholine Aminols. To a stirred solution of alcohol **16**−**18** (0.18 mmol) in CH_2Cl_2 (15 mL) was added DMP (0.28 mmol) with subsequent stirring at room temperature for 2 h. Sat. aq. $Na_2S_2O_5$ solution (10 mL) was added followed by sat. aq. $NaHCO_3$ solution (10 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography to yield the aminols **19**−**21** as separate, but undefined, diastereomers.

Benzyl (2S)-2-((Benzyloxy)methyl)-6-bromo-3-hydroxy-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate ***19a*** *and* ***19b***. Using the general procedure, alcohol **16** gave the *title products* **19a** (0.039 g, 45%) as a white solid and **19b** (0.037 g, 41%) as a yellow oil. **19a**: R_f = 0.72 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −5.39 (*c* = 0.46, $CHCl_3$); mp 130−133 °C; δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.28 (1H, d, *J* = 4.4 Hz, OH), 3.85 (2H, d, *J* = 5.4 Hz, 9-CH_2), 4.11 (1H, td, *J* = 5.4, 1.2 Hz, 2-H), 4.63 (2H, s, OCH_2Ph), 5.28 (1H, d, *J* = 12.2 Hz, OCH_aH_bPh), 5.32 (1H, d, *J* = 12.2 Hz, OCH_aH_bPh), 6.04 (1H, d, *J* = 4.4, 1.2 Hz, 3-H), 6.82 (1H, d, *J* = 8.6 Hz, 8-H), 7.10 (1H, dd, *J* = 8.6, 2.4 Hz, 7-H), 7.27−7.43 (10 H, Ar−H), 8.24 (1H, br, s, 5-H); δ_C (125 MHz; $CDCl_3$) 68.6 (OCH_2Ph), 68.8 (C-9), 73.8 (C-3), 73.9 (OCH_2Ph), 74.9 (C-2), 113.8 (C-6), 118.4 (C-8), 124.7 (C-5), 125.4 (C-4a), 127.3 (C-7), 127.9 (Ar−CH), 128.1 (Ar−CH), 128.3 (Ar−CH), 128.5 (Ar−CH), 128.6 (Ar−CH), 128.8 (Ar−CH), 135.1 (Ar−C), 137.3 (Ar−C), 144.1 (C-8a), 151.7 (C═O); IR (film)/cm^{-1}; 3431, 2926, 1935, 1711, 1599, 1489, 1391, 1302, 1257, 1211, 1144, 1050, 1026, 910, 871, 809, 739; HRMS (ESI+) Found (MNa^+): 508.0559; $C_{24}H_{22}{}^{81}BrNNaO_5$ requires 508.0557. Found (MNa^+): 506.0577; $C_{24}H_{22}{}^{79}BrNNaO_5$ requires 506.0574. **19b**: R_f = 0.66 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −21.13 (*c* = 1.11, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.25 (1H, d, *J* = 4.6 Hz, OH), 3.55 (1H, dd, *J* = 10.4, 5.2 Hz, 9-H_a), 3.65 (1H, dd, *J* = 10.4, 5.2 Hz, 9-H_b), 4.28 (1H, q, *J* = 5.2 Hz, 2-H), 4.49 (2H, s, OCH_2Ph), 5.24 (1H, d, *J* = 12.2 Hz, OCH_aH_bPh), 5.30 (1H, d, *J* = 12.2 Hz, OCH_aH_bPh), 5.97 (1H, t, *J* = 4.6 Hz, 3-H), 6.83 (1H, d, *J* = 8.6 Hz, 8-H), 7.11 (1H, dd, *J* = 8.6, 2.4 Hz, 7-H), 7.27−7.41 (10 H, Ar−H), 8.03 (1H, br, s, 5-H); δ_C (125 MHz; $CDCl_3$) 68.2 (C-9), 68.6 (OCH_2Ph), 73.7 (OCH_2Ph), 75.0 (C-3), 76.8 (C-2), 113.7 (C-6), 118.9 (C-8), 125.4 (C-5), 125.7 (C-4a), 127.6 (C-7), 127.7 (Ar−CH), 127.9 (Ar−CH), 128.3 (Ar−CH), 128.5 (Ar−CH), 128.7 (Ar−CH), 128.8 (Ar−CH), 135.3 (Ar−C), 137.5 (Ar−C), 144.5 (C-8a), 151.9 (C═O); IR (film)/cm^{-1}: 3431, 2926, 1935, 1711, 1599, 1489, 1391, 1302, 1257, 1211, 1144, 1050, 1026, 910, 871, 809, 739; HRMS (ESI+) Found (MNa^+): 508.0563; $C_{24}H_{22}{}^{81}BrNNaO_5$ requires 508.0557. Found (MNa^+): 506.0583; $C_{24}H_{22}{}^{79}BrNNaO_5$ requires 506.0574.

tert-Butyl (2S)-2-((Benzyloxy)methyl)-6-bromo-3-hydroxy-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate ***20a*** *and* ***20b***. Using the general procedure, alcohol **17** gave the *title products* **20a** (0.12 g, 42%) as a white solid and **20b** (0.16 g, 58%) as a yellow oil. **20a**: R_f = 0.77 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +3.79 (*c* = 0.58, $CHCl_3$); mp 133−135 °C; δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.58 (9H, s, $(CH_3)_3$), 3.20 (1H, d, *J* = 4.8 Hz, OH), 3.86 (2H, d, *J* = 5.2 Hz, 9-CH_2), 4.11 (1H, td, *J* = 5.2, 1.2 Hz, 2-H), 4.64 (2H, s, OCH_2Ph), 5.97 (1H, dd, *J* = 4.8, 1.2 Hz, 3-H), 6.82 (1H, d, *J* = 8.6 Hz, 8-H), 7.08 (1H, dd, *J* = 8.6, 2.2 Hz, 7-H), 7.30−7.37 (5 H, Ar−H), 8.17 (1H, br, s, 5-H); δ_C (125 MHz; $CDCl_3$) 28.3 ($C(CH_3)_3$), 69.0 (C-9), 73.5 (C-3), 73.9 (OCH_2Ph), 75.0 (C-2), 83.4 ($C(CH_3)_3$), 113.4 (C-6), 118.4 (C-8), 124.8 (C-5), 125.2 (C-4a), 126.8 (C-7), 127.9 (Ar−CH), 128.0 (Ar−CH), 128.6 (Ar−CH), 137.4 (Ar−C), 144.0 (C-8a), 151.5 (C═O); IR (film)/cm^{-1}; 3460, 2977, 2933, 1702, 1598, 1486, 1454, 1369, 1326, 1255, 1156, 1121, 1018, 855, 811, 740; HRMS (ESI+) Found (MNa^+): 474.0704; $C_{21}H_{24}{}^{81}BrNNaO_5$ requires 474.0712. Found (MNa^+): 472.0719; $C_{21}H_{24}{}^{79}BrNNaO_5$ requires 472.0730. **20b**: R_f = 0.60 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −34.16 (*c* = 0.52, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.54 (9H, s, $(CH_3)_3$), 3.34 (1H, br, s, OH), 3.58 (1H, dd, *J* = 10.4, 5.4 Hz, 9-H_a), 3.67 (1H, dd, *J* = 10.4, 5.4 Hz, 9-H_b), 4.26 (1H, m, 2-H), 4.55 (2H, s, OCH_2, Bn), 5.89 (1H, t, *J* = 3.6 Hz, 3-H), 6.83 (1H, d, *J* = 8.6 Hz, 8-H), 7.08

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(1H, dd, J = 8.6, 2.4 Hz, 7-H), 7.28−7.37 (5 H, Ar−H, Bn), 7.93 (1H, d, J = 2.4 Hz, 5-H); δ_C (125 MHz; $CDCl_3$) 28.2 ($C(CH_3)_3$), 68.5 (C-9), 73.7 (OCH_2, Bn), 74.9 (C-3), 77.1 (C-2), 83.3 ($C(CH_3)_3$), 113.6 (C-6), 118.7 (C-8), 125.6 (C-5), 126.4 (C-4a), 127.1 (C-7), 127.7 (Ar−C, Bn), 127.9 (Ar−C, Bn), 128.5 (Ar−C, Bn), 137.5 (Ar−C, Bn), 144.7 (C-8a), 152.5 (C═O); IR (film)/cm^{-1}: 3460, 2977, 2933, 1702, 1598, 1486, 1454, 1369, 1326, 1255, 1156, 1121, 1018, 855, 811, 740; HRMS (ESI+) Found (MNa^+): 474.0707; $C_{21}H_{24}{}^{81}BrNNaO_5$ requires 474.0712. Found (MNa^+): 472.0725; $C_{21}H_{24}{}^{79}BrNNaO_5$ requires 472.0730.

*tert-Butyl (2S)-6-Bromo-3-hydroxy-2-(((triisopropylsilyl)oxy)-methyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate **21a** and **21b**.* Using the general procedure, alcohol **18** gave the *title products* **21a** (0.82 g, 55%) as a colorless oil and **21b** (0.15 g, 45%) as a pale yellow oil. **21a**: R_f = 0.84 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +7.03 (c = 0.24, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.09 (18 H, d, J = 4.8 Hz, $Si(CH(CH_3)_2)_3$, 1.12−1.14 (3H, m, $Si(CH(CH_3)_2)_3$, 1.58 (9H, s, $(CH_3)_3$), 3.45 (1H, br, s, OH), 3.99 (1H, ddd, J = 5.6, 4.2, 1.4 Hz, 2-H), 4.08 (1H, dd, J = 10.4, 4.2 Hz, 9-H_a), 4.12 (1H, dd, J = 10.4, 5.6 Hz, 9-H_b), 6.06 (1H, dd, J = 4.4, 1.4 Hz, 3-H), 6.78 (1H, d, J = 8.6 Hz, 8-H), 7.08 (1H, dd, J = 8.6, 2.4 Hz, 7-H), 8.20 (1H, br, s, 5-H); δ_C (125 MHz; $CDCl_3$) 11.8 ($Si(CH(CH_3)_2)_3$), 17.9 ($Si(CH(CH_3)_2)_3$, 28.3 ($C(CH_3)_3$), 62.7 (C-9), 73.4 (C-3), 75.6 (C-2), 83.0 ($C(CH_3)_3$), 113.2 (C-6), 118.2 (C-8), 125.1 (C-5), 125.2 (C-4a), 126.8 (C-7), 144.2 (C-8a), 151.3 (C═O); IR (film)/cm^{-1}; 3447, 2943, 2867, 1719, 1486, 1465, 1369, 1255, 1155, 1123, 1058, 908, 882, 806, 735; HRMS (ESI+) Found (MNa^+): 540.1567; $C_{23}H_{38}{}^{81}BrNNaO_5Si$ requires 540.1578. Found (MNa^+): 538.1577; $C_{23}H_{38}{}^{79}BrNNaO_5Si$ requires 538.1595. **21b**: R_f = 0.83 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −28.95 (c = 0.23, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.04 (18 H, d, J = 4.8 Hz, $Si(CH(CH_3)_2)_3$, 1.07−1.10 (3H, m, $Si(CH(CH_3)_2)_3$, 1.57 (9H, s, $(CH_3)_3$), 3.30 (1H, d, J = 4.4 Hz, OH), 3.74 (1H, dd, J = 10.4, 6.8 Hz, 9-H_a), 3.88 (1H, dd, J = 10.4, 4.4 Hz, 9-H_b), 4.18−4.23 (1H, ddd, J = 6.8, 4.4, 1.0 Hz, 2-H), 5.96 (1H, dd, J = 4.4, 1.0 Hz, 3-H), 6.79 (1H, d, J = 8.6 Hz, 8-H), 7.07 (1H, dd, J = 8.6, 2.4 Hz, 7-H), 8.03 (1H, br, s, 5-H); δ_C (125 MHz; $CDCl_3$) 11.8 ($Si(CH(CH_3)_2)_3$), 17.9 ($Si(CH(CH_3)_2)_3$, 28.2 ($C(CH_3)_3$), 62.1 (C-9), 74.1 (C-3), 78.1 (C-2), 83.2 ($C(CH_3)_3$), 113.3 (C-6), 118.5 (C-8), 125.0 (C-5), 126.1 (C-4a), 126.8 (C-7), 144.3 (C-8a), 152.2 (C═O); IR (film)/cm^{-1}: 3447, 2943, 2867, 1719, 1486, 1465, 1369, 1255, 1155, 1123, 1058, 908, 882, 806, 735; HRMS (ESI+) Found (MNa^+): 540.1566; $C_{23}H_{38}{}^{81}BrNNaO_5Si$ requires 540.1578. Found (MNa^+): 538.1582; $C_{23}H_{38}{}^{79}BrNNaO_5Si$ requires 538.1595.

General Procedure for the Aryl Addition to Benzomorpholine Aminols. To a stirred solution of aminol **19**−**21** (0.050 mmol) in AcOH (5 mL) was added conc. H_2SO_4 (8 equiv), and the resultant solution was stirred at room temperature for 5 min. An aromatic nucleophile (1.2 equiv) was added, and the solution was stirred for 2 h. Sat. aq. $NaHCO_3$ solution (3 mL) was added. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography to yield the 3-arylbenzomorpholines **22**−**32**.

*((2R,3S)-6-Bromo-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol 22 and ((2R,3S)-6-Bromo-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methyl Acetate **23**.* Using the general procedure, aminol **21** gave the *title products* **22** (0.043 g, 31%) as a yellow oil and **23** (0.10 g, 69%) as a yellow oil. **22**: R_f = 0.52 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −32.33 (c = 0.16, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.58 (1H, dd, J = 12.6, 5.4 Hz, 9-H_a), 3.67 (1H, dd, J = 12.6, 3.0 Hz, 9-H_b), 3.79 (6H, s, 2′, 6′-MeO), 3.83 (3H, s, 4′-MeO), 4.41 (1H, ddd, J = 8.6, 5.4, 3.0 Hz, 2-H), 4.82 (1H, d, J = 8.6 Hz, 3-H), 6.16 (2H, s, 3′, 5′-H), 6.77 (1H, d, J = 2.2 Hz, 5-H), 6.80 (1H, d, J = 8.6 Hz, 8-H), 6.81 (1H, dd, J = 8.6, 2.2 Hz, 7-H); δ_C (125 MHz; $CDCl_3$) 48.2 (C-3), 55.4 (4′-MeO), 55.9 (2′, 6′-MeO), 63.2 (C-9), 75.6 (C-2), 91.3 (C-3′, C-5′), 105.6 (C-1′), 113.3 (C-6), 118.3 (C-5), 119.6 (C-8), 121.6 (C-7), 135.2 (C-4a), 143.9 (C-8a), 159.7 (C-2′, C-6′), 161.6 (C-4′); IR (film)/cm^{-1}; 3374, 2925, 2856, 1737, 1593, 1496, 1457, 1364, 1228, 1153, 1123, 1203, 1034, 814, 739; HRMS (ESI+) Found (MNa^+): 434.0407; $C_{18}H_{20}{}^{81}BrNNaO_5$ requires 434.0399. Found (MNa^+): 432.0420; $C_{18}H_{20}{}^{79}BrNNaO_5$ requires 432.0417. **23**: R_f = 0.79 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −22.18 (c = 0.73, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.02 (3H, s, OAc), 3.77 (6H, s, 2′, 6′-MeO), 3.82 (3H, s, 4′-MeO), 4.09 (1H, dd, J = 10.4, 5.2 Hz, 9-H_a), 4.13 (1H, dd, J = 10.4, 3.2 Hz, 9-H_b), 4.64 (1H, ddd, J = 8.6, 5.2, 3.2 Hz, 2-H), 4.84 (1H, d, J = 8.6 Hz, 3-H), 6.13 (2H, s, 3′-H and 5′-H), 6.78 (1H, d, J = 2.2 Hz, 5-H), 6.79 (1H, d, J = 8.6 Hz, 8-H), 6.80 (1H, dd, J = 8.6, 2.2 Hz, 7-H); δ_C (125 MHz; $CDCl_3$) 20.9 (OCH_3, OAc), 48.2 (C-3), 55.4 (4′-MeO), 55.8 (2′, 6′-MeO), 64.2 (C-9), 73.3 (C-2), 91.2 (C-3′, C-5′), 105.3 (C-1′), 113.5 (C-6), 118.3 (C-5), 119.5 (C-8), 121.6 (C-7), 135.2 (C-4a), 143.9 (C-8a), 159.8 (C-2′, C-6′), 161.7 (C-4′), 170.8 (CO, OAc); IR (film)/cm^{-1}: 3370, 2939, 1740, 1592, 1495, 1457, 1367, 1227, 1208, 1153, 1125, 1037, 952, 900, 813; HRMS (ESI+) Found (MNa^+): 476.0500; $C_{20}H_{22}{}^{81}BrNNaO_6$ requires 476.0505. Found (MNa^+): 474.0516; $C_{20}H_{22}{}^{79}BrNNaO_6$ requires 474.0523.

*Benzyl (2R,3S)-2-((Benzyloxy)methyl)-6-bromo-3-(2′,4′,6′-trimethoxyphenyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate **24**.* Using the general procedure, aminol **19** gave *title product* **24** (0.031 g, 97%) as a yellow oil. R_f = 0.66 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +29.36 (c = 0.53, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.44 (6H, s, 2′, 6′-MeO), 3.59 (1H, dd, J = 11.6, 3.0 Hz, 9-H_a), 3.63 (1H, dd, J = 11.6, 6.0 Hz, 9-H_b), 3.79 (3H, s, 4′-MeO), 4.22 (1H, ddd, J = 9.6, 6.0, 3.0 Hz, 2-H), 4.51 (1H, d, J = 12.0 Hz, OCH_aH_bPh), 4.58 (1H, d, J = 12.0 Hz, OCH_aH_bPh), 5.04 (1H, d, J = 12.2 Hz, OCH_aH_bPh), 5.06 (1H, d, J = 12.2 Hz, OCH_aH_bPh), 5.70 (1H, d, J = 9.6 Hz, 3-H), 6.00 (2H, s, 3′-H, 5′-H), 6.88 (1H, d, J = 8.6 Hz, 8-H), 7.10−7.12 (3H, m, 7-H and Ar−H), 7.26−7.31 (8 H, Ar−H), 7.96 (1H, d, J = 2.2 Hz, 5-H); δ_C (125 MHz; $CDCl_3$) 52.8 (C-3), 55.2 (2′, 6′-MeO), 55.3 (4′-MeO), 67.6 (OCH_2Ph), 69.9 (C-9), 73.5 (OCH_2Ph), 79.8 (C-2), 90.5 (C-3′, C-5′), 107.1 (C-1′), 113.9 (C-6), 118.7 (C-8), 126.3 (C-5), 127.6 (C-7), 127.7, 127.9, 128.0, 128.3, 128.4 (Ar−CH), 132.9 (C-4a), 136.0 (Ar−C), 138.0 (Ar−C), 148.6 (C-8a), 153.5 (C═O), 159.1 (C-2′, C-6′), 161.0 (C-4′); IR (film)/cm^{-1}: 2936, 1706, 1591, 1488, 1454, 1416, 1388, 1326, 1299, 1253, 1223, 1204, 1150, 1057, 1026, 951, 907, 866, 811, 735; HRMS (ESI+) Found (MNa^+): 658.1242; $C_{33}H_{32}{}^{81}BrNNaO_7$ requires 658.1240. Found (MNa^+): 656.1262; $C_{33}H_{32}{}^{79}BrNNaO_7$ requires 656.1254.

*(2R,3S)-2-((Benzyloxy)methyl)-6-bromo-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine **25**.* Using the general procedure, aminol **20** gave the *title product* **25** (0.026 g, 97%) as a yellow oil. R_f = 0.62 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −70.36 (c = 0.39, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.53 (1H, dd, J = 10.4, 5.0 Hz, 9-H_a), 3.56 (1H, dd, J = 10.4, 3.2 Hz, 9-H_b), 3.72 (6H, s, 2′, 6′-MeO), 3.82 (3H, s, 4′-MeO), 4.46 (1H, d, J = 12.2 Hz, OCH_aH_bPh), 4.49 (1H, d, J = 12.2 Hz, OCH_aH_bPh), 4.65 (1H, ddd, J = 8.4, 5.0, 3.2 Hz, 2-H), 4.85 (1H, d, J = 8.4 Hz, 3-H), 6.11 (2H, s, 3′, 5′-H), 6.77 (1H, dd, J = 8.8, 2.2 Hz, 7-H).6.78 (1H, d, J = 2.0 Hz, 5-H), 6.80 (1H, d, J = 8.8 Hz, 8-H), 7.21−7.29 (5H, Ar−H); δ_C (125 MHz; $CDCl_3$) 48.4 (C-3), 55.4 (4′-MeO), 55.7 (2′-MeO and 6′-MeO), 70.4 (C-9), 73.4 (OCH_2Ph), 75.1 (C-2), 91.0 (C-3′, C-5′), 106.2 (C-1′), 113.0 (C-6), 118.4 (C-5), 119.2 (C-8), 121.4 (C-7), 127.4, 127.5, 128.2 (Ar−CH), 135.4 (C-4a), 138.3 (Ar−C), 144.1 (C-8a), 159.8 (C-2′, C-6′), 161.4 (C-4′); IR (film)/cm^{-1}: 3397, 2936, 2835, 1591, 1494, 1454, 1419, 1333, 1274, 1225, 1204, 1152, 1126, 1060, 1037, 953, 906, 813, 735; HRMS (ESI+) Found (MNa^+): 524.0865; $C_{25}H_{26}{}^{81}BrNNaO_5$ requires 524.0870. Found (MNa^+): 522.0881; $C_{25}H_{26}{}^{79}BrNNaO_5$ requires 522.0887.

*Benzyl (2R,3S)-2-((Benzyloxy)methyl)-6-bromo-3-(3′,4′-dimethoxyphenyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate **26**.* Using the general procedure, aminol **19** gave *title product* **26** (0.022 g, 61%) as a yellow oil. R_f = 0.77 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +19.33 (c = 0.15, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.50 (1H, dd, J = 10.2, 7.3 Hz, 9-H_a), 3.64 (1H, dd, J = 10.2, 5.6 Hz, 9-H_b), 3.68 (3H, s, 3′-MeO), 3.81 (3H, s, 4′-MeO), 4.45 (1H, d, J = 12.2 Hz, OCH_aH_bPh), 4.49 (1H, d, J = 12.2 Hz, OCH_aH_bPh), 4.74 (1H, ddd, J = 7.3, 5.6, 2.4 Hz, 2-H), 5.24 (1H, d, J = 12.0 Hz, OCH_aH_bPh), 5.26 (1H, d, J = 12.0 Hz, OCH_aH_bPh), 5.75 (1H, d, J = 2.4 Hz, 3-H), 6.71 (1H, d, J = 8.4 Hz, 5′-H), 6.72 (1H, d, J = 2.0 Hz, 2′-H), 6.75 (1H, d, J = 8.8 Hz, 8-H), 6.77 (1H, dd, J = 8.4, 2.0 Hz, 6′-H), 7.07 (1H, dd, J = 8.8, 2.2 Hz, 7-H), 7.27−7.34 (10 H, Ar−H), 8.11 (1H, br, s, 5-H); δ_C (125 MHz; $CDCl_3$) 53.6 (C-3), 55.7 (4′-MeO), 55.8 (3′-MeO), 68.3 (OCH_2Ph), 69.0 (C-9), 73.7 (OCH_2Ph), 76.0 (C-2), 110.1 (C-5′), 111.1 (C-2′),

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113.3 (C-6), 118.6 (C-8), 119.0 (C-6′), 125.7 (C-5), 127.5 (C-7), 127.8, 127.9, 128.1, 128.4, 128.5, 128.6 (Ar−CH), 130.3 (C-1′), 130.4 (C-4a), 135.0 (Ar−C), 137.5 (Ar−C), 144.1 (C-8a), 148.5 (C-4′), 148.9 (C-3′), 153.6 (C═O); IR (film)/cm^{-1}: 2929, 2860, 1714, 1596, 1517, 1489, 1454, 1417, 1389, 1208, 1142, 1027, 862, 807, 751; HRMS (ESI+) Found (MNa$^+$): 628.1104; $C_{32}H_{30}{}^{81}BrNNaO_6$ requires 628.1134. Found (MNa$^+$): 626.1128; $C_{32}H_{30}{}^{79}BrNNaO_6$ requires 626.1149.

Benzyl (2R,3S)-2-((Benzyloxy)methyl)-6-bromo-3-(4′-hydroxy-3′-methoxyphenyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate ***27***. Using the general procedure, aminol **19** gave the *title product* **27** (0.023 g, 56%) as a yellow oil. R_f = 0.48 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +23.68 (c = 0.46, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.49 (1H, dd, J = 10.2, 7.4 Hz, 9-H$_a$), 3.64 (1H, dd, J = 10.2, 5.4 Hz, 9-H$_b$), 3.67 (3H, s, 3′-MeO), 4.45 (1H, d, J = 12.0 Hz, OCH_aH$_b$Ph), 4.47 (1H, d, J = 12.0 Hz, OCH$_a$H$_b$Ph), 4.72 (1H, ddd, J = 7.4, 5.4, 2.0 Hz, 2-H), 5.23 (1H, d, J = 12.2 Hz, OCH_aH$_b$Ph), 5.26 (1H, d, J = 12.2 Hz, OCH$_a$H$_b$Ph), 5.52(1H, br s, OH), 5.72 (1H, d, J = 2.0 Hz, 3-H), 6.68 (1H, dd, J = 8.4, 2.0 Hz, 6′-H), 6.73 (1H, d, J = 2.0 Hz, 2′-H), 6.74 (1H, d, J = 8.6 Hz, 8-H), 6.76 (1H, d, J = 8.4 Hz, 5′-H), 7.07 (1H, dd, J = 8.6, 2.4 Hz, 7-H), 7.26−7.33 (10 H, Ar−H), 8.10 (1H, s, 5-H); δ_C (125 MHz; $CDCl_3$) 53.6 (C-3), 55.8 (3′-MeO), 68.3 (OCH_2Ph), 69.0 (C-9), 73.8 (OCH_2Ph), 76.1 (C-2), 109.5 (C-6′), 113.0 (C-6), 114.5 (C-2′), 118.6 (C-8), 119.8 (C-5′), 125.8 (C-5), 127.6 (C-7), 127.8, 127.9, 128.1, 128.4, 128.5, 128.6 (Ar−CH), 129.8 (C-1′), 129.8 (C-4a), 135.9 (Ar−C), 137.3 (Ar−C), 144.2 (C-8a), 145.2 (C-4′), 146.5 (C-3′), 153.6 (C═O); IR (film)/cm^{-1}: 3451, 2979, 2916, 1736, 1722, 1514, 1484, 1366, 1299, 1256, 1229, 1216, 1140, 1090, 1042, 906, 807, 740; HRMS (ESI+) Found (MNa$^+$): 614.0971; $C_{31}H_{28}{}^{81}BrNNaO_6$ requires 614.0977. Found (MNa$^+$): 612.0988; $C_{31}H_{28}{}^{79}BrNNaO_6$ requires 612.0992.

Benzyl (2R,3S)-2-((Benzyloxy)methyl)-6-bromo-3-(2′,4′-dihydroxyphenyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate ***28***. Using the general procedure, aminol **19** gave the *title product* **28** (0.018 g, 39%) as a yellow oil. R_f = 0.37 (2:1 *n*-hexanes, ethyl acetate); $[\alpha]_D$ −0.53 (c = 0.19, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.43 (1H, dd, J = 10.2, 7.6 Hz, 9-H$_a$), 3.65 (1H, dd, J = 10.2, 5.4 Hz, 9-H$_b$), 4.42 (1H, d, J = 11.8 Hz, OCH_aH$_b$Ph), 4.46 (1H, d, J = 11.8 Hz, OCH$_a$H$_b$Ph), 4.84 (1H, ddd, J = 7.6, 5.4, 1.8 Hz, 2-H), 5.02 (2H, br s, OH), 5.22 (1H, d, J = 12.0 Hz, OCH_aH$_b$Ph), 5.34 (1H, d, J = 12.0 Hz, OCH$_a$H$_b$Ph), 5.75 (1H, d, J = 1.8 Hz, 3-H), 6.21 (1H, dd, J = 8.6, 2.4 Hz, 5′-H), 6.38 (1H, d, J = 2.4 Hz, 3′-H), 6.81 (1H, d, J = 8.8 Hz, 8-H), 7.06 (1H, d, J = 8.6 Hz, 6′-H), 7.09 (1H, dd, J = 8.8, 2.4 Hz, 7-H), 7.26−7.36 (10 H, Ar−H), 7.56 (1H, s, 5-H); δ_C (125 MHz; $CDCl_3$) 47.8 (C-3), 69.2 (C-9), 69.4 (OCH_2Ph), 73.7 (OCH_2Ph), 75.6 (C-2), 104.2 (C-3′), 107.6 (C-5′), 112.6 (C-6), 115.9 (C-1′), 118.6 (C-8), 126.7 (C-5), 127.8 (Ar−CH), 127.9 (C-6′), 128.3 (C-7), 128.4, 128.5, 128.7, 128.8 (Ar−CH), 130.4 (C-4a), 134.8 (Ar−C), 137.8 (Ar−C), 144.0 (C-8a), 152.8 (C═O), 156.9 (C-4′), 157.0 (C-3′); IR (film)/cm^{-1}: 3352, 2924, 2849, 1685, 1604, 1489, 1396, 1303, 1259, 1147, 960, 740, 697. HRMS (ESI+) Found (MNa$^+$): 600.0817; $C_{30}H_{26}{}^{81}BrNNaO_6$ requires 600.0820. Found (MNa$^+$): 598.0834; $C_{30}H_{26}{}^{79}BrNNaO_6$ requires 598.0836.

Benzyl (2R,3S)-2-((Benzyloxy)methyl)-6-bromo-3-(3′,4′-dihydroxyphenyl)-2,3-dihydro-4H-benzo[b][1,4]oxazine-4-carboxylate ***29***. Using the general procedure, aminol **19** gave the *title product* **29** (0.013 g, 36%) as a yellow oil. R_f = 0.34 (2:1 *n*-hexanes, ethyl acetate); $[\alpha]_D$ +19.36 (c = 0.25, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.48 (1H, dd, J = 9.8, 7.4 Hz, 9-H$_a$), 3.61 (1H, dd, J = 9.8, 5.4 Hz, 9-H$_b$), 4.43 (1H, d, J = 12.0 Hz, OCH_aH$_b$Ph), 4.47 (1H, d, J = 12.0 Hz, OCH$_a$H$_b$Ph), 4.67 (1H, ddd, J = 7.4, 5.4, 2.2 Hz, 2-H), 5.20 (1H, d, J = 12.4 Hz, OCH_aH$_b$Ph), 5.26 (1H, d, J = 12.4 Hz, OCH$_a$H$_b$Ph), 5.29 (2H, br s, OH), 5.67 (1H, d, J = 2.2 Hz, 3-H), 6.66 (1H, dd, J = 8.6, 2.0 Hz, 6′-H), 6.68 (1H, d, J = 2.0 Hz, 2′-H), 6.71 (1H, d, J = 8.6 Hz, 5′-H), 6.73 (1H, d, J = 8.8 Hz, 8-H), 7.09 (1H, dd, J = 8.8, 2.0 Hz, 7-H), 7.27−7.33 (10 H, Ar−H), 8.11 (1H, s, 5-H); δ_C (125 MHz; $CDCl_3$) 53.6 (C-3), 68.3 (OCH_2Ph), 68.9 (C-9), 73.7 (OCH_2Ph), 76.0 (C-2), 113.0 (C-6), 113.9 (C-2′), 115.6 (C-5′), 118.6 (C-8), 119.5 (C-6′), 125.7 (C-5), 127.5 (C-7), 127.8, 127.9, 128.1, 128.4, 128.5, and 128.6 (Ar−CH), 130.8 (C-4a), 130.8 (C-1′), 135.6 (Ar−C), 137.5 (Ar−C), 143.2 (C-4′), 143.5 (C-3′), 144.1 (C-8a), 153.6 (C═O); IR (film)/cm^{-1}: 3351, 2923, 1712, 1598, 1521, 1490, 1454, 1390, 1256, 1207, 1144, 1045, 908, 869, 810, 744; HRMS (ESI+) Found (MNa$^+$): 600.0813; $C_{30}H_{26}{}^{81}BrNNaO_6$ requires 600.0820. Found (MNa$^+$): 598.0827; $C_{30}H_{26}{}^{79}BrNNaO_6$ requires 598.0836.

(2R,3S)-2-((Benzyloxy)methyl)-6-bromo-3-(2′,4′-dimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine ***30***. Using the general procedure, aminol **20** gave the *title product* **30** (0.012 g, 94%) as a yellow oil; R_f = 0.65 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −14.19 (c = 0.16, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.57 (1H, dd, J = 10.4, 4.2 Hz, 9-H$_a$), 3.60 (1H, dd, J = 10.4, 5.6 Hz, 9-H$_b$), 3.77 (6H, s, 2′, 6′-MeO), 3.80 (3H, s, 4′-MeO), 4.34−4.38 (1H, m, 2-H), 4.50 (1H, d, J = 12.2 Hz, OCH_aH$_b$Ph), 4.53 (1H, d, J = 12.2 Hz, OCH$_a$H$_b$Ph), 4.69 (1H, d, J = 6.6 Hz, 3-H), 6.44 (1H, d, J = 2.2 Hz, 3′-H), 6.46 (1H, dd, J = 8.2, 2.2 Hz, 5′-H), 6.71 (1H, d, J = 2.4 Hz, 5-H), 6.73 (1H, d, J = 8.8, 2.4 Hz, 7-H), 6.75 (1H, d, J = 8.8 Hz, 8-H), 7.22 (1H, dd, J = 8.2 Hz, 6′-H); δ_C (125 MHz; $CDCl_3$) 48.1 (C-3), 55.4 (4′-MeO), 55.5 (2′-MeO), 70.0 (C-9), 77.0 (C-2), 98.6 (C-3′), 104.6 (C-5′), 113.2 (C-6), 117.1 (C-5), 118.2 (C-8), 120.1 (C-1′), 121.0 (C-7), 128.3 (C-6′), 134.9 (C-4a), 142.0 (C-8a), 158.1 (C-2′), 160.2 (C-4′), 127.6, 128.1, 128.3 (Ar−CH); IR (film)/cm^{-1}: 3374, 2923, 1738, 1604, 1495, 1454, 1417, 1366, 1259, 1231, 1206, 1090, 1069, 1019, 795, 736; HRMS (ESI+) Found (MNa$^+$): 494.0780; $C_{24}H_{24}{}^{81}BrNNaO_4$ requires 494.0764. Found (MNa$^+$): 492.0793; $C_{24}H_{24}{}^{79}BrNNaO_4$ requires 492.0781.

((2R,3S)-6-Bromo-3-(2′,4′-dimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methyl Acetate ***31***. Using the general procedure, aminol **21** gave the *title product* **31** (0.027 g, 50%) as a yellow oil. R_f = 0.44 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −12.40 (c = 0.52, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.04 (3H, s, OAc), 3.80 (3H, s, 2′-MeO), 3.81 (3H, s, 4′-MeO), 4.11 (1H, dd, J = 12.0, 3.6 Hz, 9-H$_a$), 4.16 (1H, dd, J = 12.0, 6.0 Hz, 9-H$_b$), 4.27 (1H, ddd, J = 6.8, 6.0, 3.6 Hz, 2-H), 4.68 (1H, d, J = 6.8 Hz, 3-H), 6.46 (1H, d, J = 2.2 Hz, 3′-H), 6.49 (1H, dd, J = 8.2, 2.2 Hz, 5′-H), 6.74 (1H, d, J = 2.4 Hz, 5-H). 6.76 (1H, d, J = 8.8 Hz, 8-H), 6.76 (1H, d, J = 8.8, 2.4 Hz, 7-H), 7.22 (1H, dd, J = 8.2 Hz, 6′-H); δ_C (125 MHz; $CDCl_3$) 20.8 (OCH_3, OAc), 47.9 (C-3), 55.4 (4′-MeO), 55.5 (2′-MeO), 63.8 (C-9), 76.3 (C-2), 98.6 (C-3′), 104.9 (C-5′), 113.4 (C-6), 117.2 (C-5), 118.1 (C-8), 119.1 (C-1′), 121.2 (C-7), 128.7 (C-6′), 135.0 (C-4a), 142.0 (C-8a), 158.1 (C-2′), 160.9 (C-4′), 170.8 (*C*O, OAc); IR (film)/cm^{-1}: 3377, 2965, 2835, 1741, 1607, 1496, 1465, 1234, 1207, 1159, 1125, 1039, 907, 797, 731; HRMS (ESI+) Found (MNa$^+$): 446.0399; $C_{19}H_{20}{}^{81}BrNNaO_5$ requires 446.0399. Found (MNa$^+$): 444.0416; $C_{19}H_{20}{}^{79}BrNNaO_5$ requires 444.0417.

(2R,3S)-2-((Benzyloxy)methyl)-6-bromo-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine. To a stirred solution of aryl benzomorpholine **25** (0.04 g, 0.080 mmol) in acetone (12 mL) was added K_2CO_3 (0.11 g, 0.80 mmol), and the resultant solution was stirred at room temperature for 10 min. Methyl iodide (0.05 mL, 0.80 mmol) was added, and the resultant mixture was stirred vigorously at 40 °C for 3 days. Water (10 mL) was added, the layers were separated, and the aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (9:1 hexanes, ethyl acetate) to yield the *title product* (0.03 g, 73%) as a yellow oil. R_f = 0.71 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +5.38 (c = 0.37, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.55 (3H, s, N−CH_3), 3.53 (1H, dd, J = 10.4, 5.0 Hz, 9-H$_a$), 3.56 (1H, dd, J = 10.4, 3.2 Hz, 9-H$_b$), 3.65 (6H, s, 2′-MeO, 6′-MeO), 3.82 (3H, s, 4′-MeO), 4.48 (1H, d, J = 12.2 Hz, OCH_aH$_b$Ph), 4.52 (1H, d, J = 12.2 Hz, OCH$_a$H$_b$Ph), 4.60 (1H, ddd, J = 8.4, 5.0, 3.2 Hz, 2-H), 4.94 (1H, d, J = 8.4 Hz, 3-H), 6.10 (2H, s, 3′, 5′-H), 6.66 (1H, dd, J = 8.8, 2.2 Hz, 7-H), 6.67 (1H, d, J = 2.2 Hz, 5-H), 6.73 (1H, d, J = 8.8 Hz, 8-H), 7.23−7.29 (5H, Ar−H); δ_C (125 MHz; $CDCl_3$) 34.2 (*N*-CH_3), 53.4 (C-3), 55.3 (4′-MeO), 55.7 (2′-MeO and 6′-MeO), 70.8 (C-9), 73.3 (OCH_2Ph), 75.8 (C-2), 90.8 (C-3′ and C-5′), 105.7 (C-1′), 113.5 (C-5), 114.1 (C-6), 117.0 (C-8), 118.3 (C-7), 127.4, 127.8, 128.2 (Ar−CH), 138.3 (Ar−C), 139.2 (C-4a), 144.3 (C-8a), 160.1 (C-2′, C-6′), 161.2 (C-4′); IR (film)/cm^{-1}: 2936, 2846, 1731, 1592, 1508, 1454, 1436, 1418, 1364, 1325, 1229, 1204, 1152, 1119, 1062, 1037, 992, 953, 815, 737; HRMS (ESI+) Found (MNa$^+$): 538.1004; $C_{26}H_{28}{}^{81}BrNNaO_5$ requires 538.1027. Found (MNa$^+$): 536.1023; $C_{26}H_{28}{}^{79}BrNNaO_5$ requires 536.1043.

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(2R,3S)-2-((Benzyloxy)methyl)-4-methyl-3-(2,4,6-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbaldehyde ***32***. To a solution of (2*R*,3*S*)-2-((benzyloxy)methyl)-6-bromo-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (0.027 g, 0.052 mmol) in THF (3 mL) at −78 °C under an atmosphere of nitrogen was added *tert*-butyllithium (1.6 M in pentane, 0.23 mL, 0.31 mmol). After 30 s, dry DMF (0.08 mL, 1.04 mmol) was added, and the mixture was stirred at −78 °C for 30 min, allowed to warm to room temperature, and stirred for a further 1 h. Sat. aq. NH_4Cl (3 mL) was added, and the aqueous mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 hexanes, ethyl acetate) to yield the *title product* **33** (0.024 g, 99%) as a yellow oil. R_f = 0.39 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +1.58 (*c* = 0.57, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.65 (3H, s, N−CH_3), 3.56 (1H, dd, *J* = 10.4, 5.4 Hz, 9-H_a), 3.60 (1H, dd, *J* = 10.4, 3.2 Hz, 9-H_b), 3.65 (6H, s, 2′-MeO, 6′-MeO), 3.82 (3H, s, 4′-MeO), 4.49 (1H, d, *J* = 12.2 Hz, OC$H_a$$H_b$Ph), 4.52 (1H, d, *J* = 12.2 Hz, OCH$_a$$H_b$Ph), 4.75 (1H, ddd, *J* = 8.4, 5.4, 3.2 Hz, 2-H), 4.97 (1H, d, *J* = 8.4 Hz, 3-H), 6.11 (2H, s, 3′, 5′-H), 6.98 (1H, d, *J* = 8.2 Hz, 8-H), 7.12 (1H, d, *J* = 2.0 Hz, 5-H), 7.14 (1H, dd, *J* = 8.2, 2.0 Hz, 7-H). 7.24−7.29 (5H, Ar−H), 9.81 (1H, CHO); δ_C (125 MHz; $CDCl_3$) 34.5 (*N*-CH_3), 53.0 (C-3), 55.3 (4′-MeO), 55.7 (2′, 6′-MeO), 70.7 (C-9), 73.4 (OCH_2Ph), 76.2 (C-2), 90.9 (C-3′, C-5′), 105.4 (C-1′), 109.6 (C-5), 115.9 (C-8), 122.0 (C-7), 127.5, 127.8, 128.2 (Ar−CH), 131.0 (C-6), 138.1 (C-4a), 138.2 (Ar−C), 150.1 (C-8a), 160.1 (C-2′, C-6′), 161.2 (C-4′), 191.9 (CHO); IR (film)/cm^{-1}: 2937, 2860, 1736, 1592, 1509, 1455, 1365, 1229, 1203, 1154, 1120, 1032, 812, 736; HRMS (ESI+) Found (MNa^+): 486.1879; $C_{27}H_{29}NNaO_6$ requires 486.1887.

Ethyl (E)-3″-((2R,3S)-2-((Benzyloxy)methyl)-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-acrylate. To a solution of aldehyde **32** (0.028 g, 0.060 mmol) in dry toluene (6 mL) under an atmosphere of nitrogen at room temperature was added triphenylcarbethoxymethylenephosphorane (0.032 g, 0.091 mmol). The solution was heated at reflux for 4 days, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 hexanes, ethyl acetate) to yield the *title product* (0.018 g, 57%) as a yellow oil. R_f = 0.5 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +3.13 (*c* = 0.16, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.33 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 2.60 (3H, s, N−CH_3), 3.55 (1H, dd, *J* = 10.4, 5.2 Hz, 9-H_a), 3.58 (1H, dd, *J* = 10.4, 3.2 Hz, 9-H_b), 3.65 (6H, s, 2′-MeO, 6′-MeO), 3.82 (3H, s, 4′-MeO), 4.24 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.48 (1H, d, *J* = 12.2 Hz, OC$H_a$$H_b$Ph), 4.52 (1H, d, *J* = 12.2 Hz, OCH$_a$$H_b$Ph), 4.73 (1H, ddd, *J* = 8.4, 5.2, 3.2 Hz, 2-H), 4.93 (1H, d, *J* = 8.4 Hz, 3-H), 6.11 (2H, s, 3′, 5′-H), 6.28 (1H, d, *J* = 15.8 Hz, 2″-H), 6.76 (1H, d, *J* = 2.0 Hz, 5-H), 6.81 (1H, dd, *J* = 8.2, 2.0 Hz, 7-H). 6.87 (1H, d, *J* = 8.2 Hz, 8-H), 7.22−7.30 (5H, Ar−H), 7.63 (1H, d, *J* = 15.8 Hz, 3″-H); δ_C (125 MHz; $CDCl_3$) 14.4 (OCH_2CH_3), 34.4 (N−CH_3), 53.4 (C-3), 55.3 (4′-MeO), 55.7 (2′, 6′-MeO), 70.7 (C-9), 73.3 (OCH_2Ph), 76.0 (C-2), 90.9 (C-3′, C-5′), 106.5 (C-1′), 110.1 (C-5), 114.7 (C-2″), 116.1 (C-8), 117.9 (C-7), 127.4 (C-6), 127.5, 128.0, 128.2 (Ar−CH), 138.0 (C-4a), 138.3 (Ar−C), 145.6 (C-3″), 146.7 (C-8a), 160.1 (C-2′, C-6′), 161.2 (C-4′), 167.8 (CO); IR (film)/cm^{-1}: 2970, 2919, 1741, 1600, 1453, 1365, 1231, 1217, 1203, 1121, 906, 800. HRMS (ESI+) Found (MNa^+): 556.2319; $C_{31}H_{35}NNaO_7$ requires 556.2306.

(E)-3″-((2R,3S)-2-((Benzyloxy)methyl)-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)prop-2″-en-1″-ol ***33***. To a solution of ethyl (*E*)-3″-((2*R*,3*S*)-2-((benzyloxy)-methyl)-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)acrylate (0.018 g, 0.034 mmol) in CH_2Cl_2 (4 mL) at −78 °C, under an atmosphere of nitrogen, was added DIBAL-H (1.0 M in cyclohexane, 0.11 mL, 0.10 mmol), and the resultant solution was stirred at −78 °C for 1 h. A saturated solution of Rochelle salt (3 mL) was added, and the aqueous mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (3 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (1:1 hexanes, ethyl acetate) to yield the *title product* **33** (0.015 g, 91%) as a yellow oil. R_f = 0.16 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +2.27 (*c* = 0.26, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.60 (3H, s, N−CH_3), 3.54 (1H, dd, *J* = 10.4, 5.0 Hz, 9-H_a), 3.58 (1H, dd, *J* = 10.4, 3.4 Hz, 9-H_b), 3.65 (6H, s, 2′, 6′-MeO), 3.82 (3H, s, 4′-MeO), 4.29 (2H, dd, *J* = 6.0, 1.2 Hz, 1″-H), 4.48 (1H, d, *J* = 12.0 Hz, OC$H_a$$H_b$Ph), 4.52 (1H, d, *J* = 12.0 Hz, OCH$_a$$H_b$Ph), 4.72 (1H, ddd, *J* = 8.0, 5.0, 3.4 Hz, 2-H), 4.92 (1H, d, *J* = 8.0 Hz, 3-H), 6.11 (2H, s, 3′, 5′-H), 6.22 (1H, dt, *J* = 15.8, 6.0 Hz, 2″-H), 6.54 (1H, d, *J* = 15.8 Hz, 3″-H), 6.66 (1H, dd, *J* = 8.2, 2.0 Hz, 7-H), 6.67 (1H, d, *J* = 2.0 Hz, 5-H), 6.84 (1H, d, *J* = 8.2 Hz, 8-H), 7.23−7.30 (5H, Ar−H); δ_C (125 MHz; $CDCl_3$) 34.5 (N−CH_3), 53.6 (C-3), 55.3 (4′-MeO), 55.7 (2′, 6′-MeO), 64.2 (C-1″), 70.9 (C-9), 73.3 (OCH_2Ph), 76.0 (C-2), 90.9 (C-3′, C-5′), 106.1 (C-1′), 109.2 (C-5), 115.3 (C-7), 116.0 (C-8), 125.3 (C-2″), 127.3, 127.5, 128.2 (Ar−CH), 130.2 (C-6), 132.7 (C-3″), 136.0 (C-4a), 138.5 (Ar−C), 144.6 (C-8a), 160.1 (C-2′, C-6′), 161.0 (C-4′); IR (film)/cm^{-1}: 3419, 2928, 2856, 1727, 1605, 1512, 1420, 1322, 1228, 1205, 1152, 1118, 955, 814, 735; HRMS (ESI+) Found (MNa^+): 514.2189; $C_{29}H_{33}NNaO_6$ requires 514.2200.

3″-((2R,3S)-2-(Hydroxymethyl)-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)propan-1″-ol ***34***. To a solution of alcohol **33** (0.013 g, 0.027 mmol) in MeOH (3 mL) was added 10% Pd/C (0.003 g, 20% w/w), and the mixture was stirred under an atmosphere of hydrogen for 1 h. The mixture was filtered through Celite and washed with methanol (3 × 3 mL), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (1:1 hexanes, ethyl acetate) to yield the *title product* **34** (0.005 g, 51%) as a yellow oil. R_f = 0.13 (1:2 hexanes, ethyl acetate); $[\alpha]_D$ +4.55 (*c* = 0.02, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.87−1.93 (2H, m, 2″-H), 2.57 (3H, s, *N*-CH_3), 2.63 (2H, t, *J* = 7.6 Hz, 3″-H), 3.56 (1H, dd, *J* = 12.2, 5.6 Hz, 9-H_a), 3.63 (1H, dd, *J* = 12.2, 3.2 Hz, 9-H_b), 3.70 (2H, t, *J* = 6.4 Hz, 1″-H), 3.73 (6H, s, 2′, 6′-MeO), 3.83 (3H, s, 4′-MeO), 4.54 (1H, ddd, *J* = 8.6, 5.6, 3.2 Hz, 2-H), 4.86 (1H, d, *J* = 8.6 Hz, 3-H), 6.15 (2H, s, 3′, 5′-H), 6.44 (1H, dd, *J* = 8.2, 2.0 Hz, 7-H), 6.48 (1H, d, *J* = 2.0 Hz, 5-H), 6.78 (1H, d, *J* = 8.2 Hz, 8-H); δ_C (125 MHz; $CDCl_3$) 32.2 (C-3″), 34.3 (*N*-CH_3), 34.6 (C-2″), 53.4 (C-3), 55.3 (4′-MeO), 55.9 (2′, 6′-MeO), 62.6 (C-1″), 63.7 (C-9), 76.1 (C-2), 91.1 (C-3′, C-5′), 105.5 (C-1′), 111.8 (C-5), 115.5 (C-8), 116.0 (C-7), 135.2 (C-6), 137.6 (C-4a), 142.5 (C-8a), 160.1 (C-2′, C-6′), 161.3 (C-4′); IR (film)/cm^{-1}: 3405, 2929, 2846, 1736, 1603, 1591, 1514, 1457, 1416, 1362, 1229, 1152, 1122, 1041, 908, 815, 733; HRMS (ESI+) Found (MNa^+): 426.1880; $C_{22}H_{29}NNaO_6$ requires 426.1887.

((2R,3S)-6-Bromo-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methyl Acetate. To a stirred solution of aryl benzomorpholine **23** (0.041 g, 0.091 mmol) in acetone (15 mL) was added K_2CO_3 (0.13 g, 0.91 mmol), and the resultant solution was stirred at room temperature for 10 min. Methyl iodide (0.06 mL, 0.91 mmol) was added, and the resultant mixture was stirred vigorously at 40 °C for 4 days. Water (10 mL) was added. The layers were separated, and the aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (9:1 hexanes, ethyl acetate) to yield the *title product* (0.033 g, 79%) as a yellow oil: R_f = 0.68 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +13.46 (*c* = 0.05, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.05 (3H, s, OAc), 2.56 (3H, s, N−CH_3), 3.71 (6H, s, 2′, 6′-MeO), 3.82 (3H, s, 4′-MeO), 4.08 (1H, dd, *J* = 12.0, 3.4 Hz, 9-H_a), 4.12 (1H, dd, *J* = 12.0, 5.2 Hz, 9-H_b), 4.63 (1H, ddd, *J* = 8.6, 5.2, 3.4 Hz, 2-H), 4.94 (1H, d, *J* = 8.6 Hz, 3-H), 6.12 (2H, s, 3′, 5′-H), 6.68 (1H, dd, *J* = 8.4, 2.4 Hz, 7-H), 6.69 (1H, d, *J* = 2.4 Hz, 5-H), 6.72 (1H, d, *J* = 8.4 Hz, 8-H); δ_C (125 MHz; $CDCl_3$) 20.7 (OCH_3, OAc), 34.1 (N−CH_3), 53.1 (C-3), 55.3 (4′-MeO), 55.7 (2′, 6′-MeO), 64.7 (C-9), 73.8 (C-2), 90.9 (C-3′, C-5′), 104.8 (C-1′), 113.7 (C-5), 114.4 (C-6), 117.1 (C-7), 118.4 (C-8), 138.9 (C-4a), 143.1 (C-8a), 160.1 (C-2′, C-6′), 161.5 (C-4′), 170.8 (CO); IR (film)/cm^{-1}: 3013, 2907, 1736, 1594, 1442, 1366, 1229, 1217, 1205, 1107, 897; HRMS (ESI+) Found (MNa^+): 490.0668; $C_{21}H_{24}{}^{81}BrNNaO_6$ requires 490.0668. Found (MNa^+): 488.0684; $C_{21}H_{24}{}^{79}BrNNaO_6$ requires 488.0679.

((2R,3S)-6-Bromo-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol. To a stirred solution of ((2*R*,3*S*)-6-bromo-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methyl acetate (0.032 g, 0.069 mmol) in MeOH (7 mL) was added NaOH (0.022 g, 0.55 mmol), and the resultant solution was stirred at room temperature for 2 h. The

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resulting solution was added to water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (9:1 hexanes, ethyl acetate) to yield the *title product* (0.027 g, 93%) as a yellow oil: R_f = 0.17 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +24.81 (c = 0.26, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.55 (3H, s, N−CH_3), 3.58 (1H, dd, J = 12.0, 5.6 Hz, 9-H_a), 3.65 (1H, dd, J = 12.0, 3.4 Hz, 9-H_b), 3.73 (6H, s, 2′, 6′-MeO), 3.83 (3H, s, 4′-MeO), 4.41 (1H, ddd, J = 8.6, 5.6, 3.4 Hz, 2-H), 4.92 (1H, d, J = 8.6 Hz, 3-H), 6.14 (2H, s, 3′, 5′-H), 6.67 (1H, dd, J = 8.4, 2.4 Hz, 7-H), 6.68 (1H, d, J = 2.4 Hz, 5-H), 6.71 (1H, d, J = 8.4 Hz, 8-H); δ_C (125 MHz; $CDCl_3$) 34.0 (N−CH_3), 53.1 (C-3), 55.3 (4′-MeO), 55.9 (2′, 6′-MeO), 63.5 (C-9), 76.2 (C-2), 91.0 (C-3′, C-5′), 104.9 (C-1′), 113.6 (C-5), 114.4 (C-6), 116.9 (C-8), 118.3 (C-7), 138.9 (C-4a), 143.3 (C-8a), 160.0 (C-2′, C-6′), 161.7 (C-4′); IR (film)/cm^{-1}: 3437, 2931, 2860, 1738, 1601, 1509, 1456, 1365, 1228, 1205, 1153, 1123, 1037, 814; HRMS (ESI+) Found (MNa^+): 448.0538; $C_{19}H_{22}{}^{81}BrNNaO_5$ requires 448.0555. Found (MNa^+): 446.0559; $C_{19}H_{22}{}^{79}BrNNaO_5$ requires 446.0574.

(2R,3S)-6-Bromo-4-methyl-2-(((triisopropylsilyl)oxy)methyl)-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine. To a solution of ((2*R*,3*S*)-6-bromo-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-yl)methanol (0.025 g, 0.058 mmol) and 1*H*-imidazole (0.01 g, 0.12 mmol) in DMF (5 mL) under an atmosphere of nitrogen at room temperature was added TIPSCl (0.015 mL, 0.071 mmol) dropwise, and the mixture was stirred for 2 days. Water (5 mL) was added, and the aqueous mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with water (3 × 5 mL) and brine (5 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (19:1 hexanes, ethyl acetate) to yield the *title product* (0.031 g, 91%) as a yellow oil: R_f = 0.86 (2:1 *n*-hexanes, ethyl acetate); $[\alpha]_D$ +1.40 (c = 0.43, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.01 (18 H, d, J = 6.0 Hz, Si(CH(CH_3)$_2$)$_3$, 1.02−1.04 (3H, m, Si(CH(CH_3)$_2$)$_3$, 2.58 (3H, s, N−CH_3), 3.64 (6H, s, 2′, 6′-MeO), 3.72 (1H, dd, J = 10.6, 5.6 Hz, 9-H_a), 3.75 (1H, dd, J = 10.6, 3.2 Hz, 9-H_b), 3.81 (3H, s, 4′-MeO), 4.38 (1H, ddd, J = 6.8, 5.6, 3.2 Hz, 2-H), 4.97 (1H, d, J = 6.8 Hz, 3-H), 6.11 (2H, s, 3′, 5′-H), 6.64 (1H, d, J = 1.8 Hz, 5-H), 6.64 (1H, dd, J = 8.0, 1.8 Hz, 7-H), 6.65 (1H, d, J = 8.0 Hz, 8-H); δ_C (125 MHz; $CDCl_3$) 12.0 (Si(CH(CH_3)$_2$)$_3$), 17.9 (Si(CH(CH_3)$_2$)$_3$, 34.6 (N−CH_3), 52.9 (C-3), 55.3 (4′-MeO), 55.5 (2′, 6′-MeO), 64.1 (C-9), 77.1 (C-2), 90.7 (C-3′, C-5′), 106.6 (C-1′), 113.0 (C-5), 113.7 (C-6), 116.6 (C-8), 118.0 (C-7), 139.3 (C-4a), 143.5 (C-8a), 160.0 (C-2′, C-6′), 160.9 (C-4′); IR (film)/cm^{-1}: 2925, 2856, 1739, 1601, 1509, 1464, 1418, 1367, 1230, 1203, 1154, 1123, 1060, 988, 880, 815; HRMS (ESI+) Found (MNa^+): 604.1862; $C_{28}H_{42}{}^{81}BrNNaO_5Si$ requires 604.1892. Found (MNa^+): 602.1889; $C_{28}H_{42}{}^{79}BrNNaO_5Si$ requires 602.1908.

(2R,3S)-4-Methyl-2-(((triisopropylsilyl)oxy)methyl)-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carbaldehyde ***35***. To a solution of (2*R*,3*S*)-6-bromo-4-methyl-2-(((triisopropylsilyl)oxy)methyl)-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (0.018 g, 0.031 mmol) in THF (3 mL) at −78 °C under an atmosphere of nitrogen was added *tert*-butyllithium (1.6 M in pentane, 0.14 mL, 0.19 mmol). After 30 s, dry DMF (0.05 mL, 0.62 mmol) was added, and the mixture was stirred at −78 °C for 30 min, allowed to warm to room temperature, and stirred for a further 1 h. Sat. aq. NH_4Cl (3 mL) was added, and the aqueous mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 hexanes, ethyl acetate) to yield the *title product* **35** (0.013 g, 83%) as a yellow oil: R_f = 0.64 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +1.02 (c = 0.39, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.02 (18 H, d, J = 6.0 Hz, Si(CH(CH_3)$_2$)$_3$, 1.04−1.06 (3H, m, Si(CH(CH_3)$_2$)$_3$, 2.68 (3H, s, N−CH_3), 3.63 (6H, s, 2′, 6′-MeO), 3.74 (1H, dd, J = 10.6, 5.2 Hz, 9-H_a), 3.79 (1H, dd, J = 10.6, 3.2 Hz, 9-H_b), 3.81 (3H, s, 4′-MeO), 4.53 (1H, ddd, J = 6.2, 5.2, 3.2 Hz, 2-H), 5.03 (1H, d, J = 6.2 Hz, 3-H), 6.11 (2H, s, 3′, 5′-H), 6.91 (1H, d, J = 8.0 Hz, 7-H), 7.09 (1H, d, J = 1.8 Hz, 7-H), 7.12 (1H, d, J = 8.0, 1.8 Hz, 8-H), 9.81 (1H, CHO); δ_C (125 MHz; $CDCl_3$) 11.9 (Si(CH(CH_3)$_2$)$_3$), 17.9 (Si(CH(CH_3)$_2$)$_3$, 34.8 (N−CH_3), 52.3 (C-3), 55.3 (4′-MeO), 55.5 (2′, 6′-MeO), 63.9 (C-9), 77.8 (C-2), 90.7 (C-3′, C-5′), 106.4 (C-1′), 109.3 (C-5), 115.3 (C-8), 122.0 (C-7), 130.8 (C-6), 138.3 (C-4a), 150.2 (C-8a), 160.0 (C-2′, C-6′), 161.1 (C-4′), 192.0 (CHO); IR (film)/cm^{-1}: 2360, 1741, 1455, 1364, 1215, 904, 735; HRMS (ESI+) Found (MNa^+): 552.2738; $C_{29}H_{43}NNaO_6Si$ requires 552.2752.

Ethyl (E)-3″-((2R,3S)-4-Methyl-2-(((triisopropylsilyl)oxy)methyl)-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)acrylate. To a solution of aldehyde **35** (0.011 g, 0.021 mmol) in dry toluene (5 mL) under an atmosphere of nitrogen at room temperature was added triphenylcarbethoxymethylenephosphorane (0.011 g, 0.032 mmol). The solution was heated at reflux for 4 days, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (4:1 hexanes, ethyl acetate) to yield the *title compound* (9 mg, 73%) as a green oil: R_f = 0.4 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +2.08 (c = 0.22, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.01 (18 H, d, J = 4.4 Hz, Si(CH(CH_3)$_2$)$_3$, 1.02−1.04 (3H, m, Si(CH(CH_3)$_2$)$_3$, 1.33 (3H, t, J = 7.2 Hz, OCH$_2$$CH_3$), 2.63 (3H, s, N−$CH_3$), 3.64 (6H, s, 2′, 6′-MeO), 3.73 (1H, dd, J = 10.6, 5.2 Hz, 9-H_a), 3.78 (1H, dd, J = 10.6, 4.2 Hz, 9-H_b), 3.81 (3H, s, 4′-MeO), 4.24 (2H, q, J = 7.2 Hz, OCH_2CH$_3$), 4.49 (1H, ddd, J = 6.6, 5.2, 4.2 Hz, 2-H), 4.98 (1H, d, J = 6.6 Hz, 3-H), 6.11 (2H, s, 3′, 5′-H), 6.28 (1H, d, J = 15.6 Hz, 2″-H), 6.76 (1H, d, J = 8.0 Hz, 8-H), 6.77 (1H, dd, J = 8.0, 1.2 Hz, 7-H), 6.80 (1H, d, J = 1.2 Hz, 5-H), 7.63 (1H, d, J = 15.6 Hz, 3″-H); δ_C (125 MHz; $CDCl_3$) 11.9 (Si(CH(CH_3)$_2$)$_3$), 14.5 (OCH$_2$$CH_3$), 17.9 (Si(CH($CH_3$)$_2$)$_3$, 34.7 (N−$CH_3$), 52.8 (C-3), 55.3 (4′-MeO), 55.6 (2′, 6′-MeO), 64.1 (C-9), 77.6 (C-2), 90.8 (C-3′, C-5′), 106.5 (C-1′), 109.6 (C-8), 114.4 (C-2″), 115.7 (C-7), 117.9 (C-5), 127.7 (C-6), 138.0 (C-4a), 146.1 (C-3″), 146.9 (C-8a), 160.0 (C-2′, C-6′), 161.0 (C-4′), 167.7 (CO); IR (film)/cm^{-1}: 2919, 2863, 1736, 1631, 1594, 1512, 1463, 1369, 1254, 1221, 1154, 1123, 1200, 1060, 1037, 814; HRMS (ESI+) Found (MNa^+): 622.3152; $C_{33}H_{49}NNaO_7Si$ requires 622.3171.

(E)-3-((2R,3S)-4-Methyl-2-(((triisopropylsilyl)oxy)methyl)-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)prop-2″-en-1″-ol ***36***. To a solution of ethyl (*E*)-3″-((2*R*,3*S*)-4-methyl-2-(((triisopropylsilyl)oxy)methyl)-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)acrylate (8.8 mg, 0.015 mmol) in CH_2Cl_2 (4 mL) at −78 °C under an atmosphere of nitrogen was added DIBAL-H (1.0 M in cyclohexane, 0.05 mL, 0.044 mmol), and the resultant solution was stirred at −78 °C for 1 h. A saturated solution of Rochelle salt (3 mL) was added, and the aqueous mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (3 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (1:1 hexanes, ethyl acetate) to yield the *title product* **36** (5 mg, 65%) as a yellow oil: R_f = 0.21 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +2.08 (c = 0.05, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.01 (18 H, d, J = 4.2 Hz, Si(CH(CH_3)$_2$)$_3$, 1.02−1.04 (3H, m, Si(CH(CH_3)$_2$)$_3$, 2.63 (3H, s, N−CH_3), 3.64 (6H, s, 2′, 6′-MeO), 3.73 (1H, dd, J = 10.4, 5.4 Hz, 9-H_a), 3.77 (1H, dd, J = 10.4, 4.4 Hz, 9-H_b), 3.70 (3H, s, 4′-MeO), 4.28 (2H, dd, J = 6.0, 1.2 Hz, 1″-H), 4.48 (1H, ddd, J = 6.8, 5.4, 4.4 Hz, 2-H), 4.95 (1H, d, J = 6.8 Hz, 3-H), 6.11 (2H, s, 3′, 5′-H), 6.22 (1H, dt, J = 15.8, 6.0 Hz, 2″-H), 6.54 (1H, d, J = 15.8 Hz, 3″-H), 6.63 (1H, dd, J = 8.0, 1.2 Hz, 7-H), 6.64 (1H, d, J = 1.2 Hz, 5-H), 6.76 (1H, d, J = 8.0 Hz, 8-H); δ_C (125 MHz; $CDCl_3$) 11.9 (Si(CH(CH_3)$_2$)$_3$), 17.9 (Si(CH(CH_3)$_2$)$_3$, 34.7 (N−CH_3), 53.0 (C-3), 55.3 (4′-MeO), 55.6 (2′, 6′-MeO), 64.2 (C-9), 64.2 (C-1″), 77.2 (C-2), 90.9 (C-3′, C-5′), 106.8 (C-1′), 108.5 (C-5), 115.0 (C-7), 115.5 (C-8), 125.0 (C-2″), 129.8 (C-6), 132.8 (C-3″), 137.8 (C-4a), 144.8 (C-8a), 160.0 (C-2′, C-6′), 160.8 (C-4′); IR (film)/cm^{-1}: 3370, 2938, 2870, 1591, 1513, 1465, 1418, 1205, 1154, 1126, 911, 812, 730; HRMS (ESI+) Found (MNa^+): 580.3061; $C_{31}H_{47}NNaO_6Si$ requires 580.3065.

(E)-3″-((2R,3S)-2-(Hydroxymethyl)-4-methyl-3-(2′,4′,6′-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)prop-2″-en-1″-ol ***37***. To a stirred solution of the silyl ether **36** (0.005 g, 0.01 mmol) in THF (3 mL), at 0 °C, was added 1 M TBAF in THF (0.047 mL, 0.047 mmol) dropwise, and the mixture was stirred for 3 h. Saturated aqueous $NaHCO_3$ solution (3 mL) was added, and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with brine (3 mL) and dried ($MgSO_4$), and the solvent was

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removed *in vacuo*. The crude product was purified by flash chromatography (1:2 hexanes, ethyl acetate) to give the *title compound* **37** (2 mg, 57%) as a yellow gum, R_f = 0.18 (1:2 hexanes, ethyl acetate); $[\alpha]_D$ +6.25 (*c* = 0.02, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 2.60 (3H, s, N−CH_3), 3.58 (1H, dd, *J* = 11.6, 5.6 Hz, 9-H_a), 3.65 (1H, dd, *J* = 11.6, 3.2 Hz, 9-H_b), 3.73 (6H, s, 2′, 6′-MeO), 3.83 (3H, s, 4′-MeO), 4.29 (2H, dd, *J* = 6.0, 1.2 Hz, 1″-H), 4.54 (1H, ddd, *J* = 8.6, 5.6, 3.2 Hz, 2-H), 4.89 (1H, d, *J* = 8.6 Hz, 3-H), 6.15 (2H, s, 3′, 5′-H), 6.24 (1H, dt, *J* = 15.8, 6.0 Hz, 2″-H), 6.54 (1H, d, *J* = 15.8 Hz, 3″-H), 6.66 (1H, dd, *J* = 8.0, 1.2 Hz, 7-H), 6.68 (1H, d, *J* = 1.2 Hz, 5-H), 6.81 (1H, d, *J* = 8.0 Hz, 8-H); δ_C (125 MHz; $CDCl_3$) 34.2 (N−CH_3), 53.2 (C-3), 55.2 (4′-MeO), 55.9 (2′, 6′-MeO), 63.8 (C-9), 64.3 (C-1″), 76.2 (C-2), 91.1 (C-3′, C-5′), 105.4 (C-1′), 109.4 (C-5), 115.3 (C-7), 115.7 (C-8), 125.6 (C-2″), 130.5 (C-6), 132.5 (C-3″), 137.6 (C-4a), 142.3 (C-8a), 160.1 (C-2′, C-6′), 161.3 (C-4′); IR (film)/cm^{-1}: 3423, 2954, 2922, 2853, 1738, 1603, 1514, 1462, 1366, 1260, 1217, 1228, 1091, 1017, 798; HRMS (ESI+) Found (MNa^+): 424.1719; $C_{22}H_{27}NNaO_6$ requires 424.1719.

((2R,3S)-3-(2′,4′-Dimethoxyphenyl)-6-((E)-prop-1″-en-1″-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methyl Acetate ***39***. To a solution of bromobenzomorpholine **31** (0.023 g, 0.054 mmol) in DME (5 mL) was added 2 M K_2CO_3 (0.18 mL, 0.36 mmol), *trans*-prop-1-enylboronic acid **38** (0.009 g, 0.11 mmol), and $Pd(PPh_3)_4$ (0.013 g, 0.011 mmol). The resultant mixture was stirred vigorously at 90 °C for 24 h. The mixture was cooled, water (5 mL) was added, the organic layer was separated, and the aqueous phase was further extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (3:1 hexanes, ethyl acetate) to give the *title compound* **39** (0.011 g, 51%) as a yellow oil: R_f = 0.45 (2:1 hexanes, ethyl acetate); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.83 (3H, dd, *J* = 6.6, 1.8 Hz, 3″- H), 2.03 (3H, s, OAc), 3.80 (6H, s, 2′, 4′-MeO), 4.13 (1H, dd, *J* = 12.0, 3.6 Hz, 9-H_a), 4.16 (1H, dd, *J* = 12.0, 6.0 Hz, 9-H_b), 4.30 (1H, ddd, *J* = 6.6, 6.0, 3.6 Hz, 2-H), 4.69 (1H, d, *J* = 6.6 Hz, 3-H), 6.04 (1H, dd, *J* = 15.8, 6.6 Hz, 2″- H), 6.26 (1H, dd, *J* = 15.8, 1.8 Hz, 1″- ′H), 6.46 (1H, d, *J* = 2.4 Hz, 3′-H), 6.49 (1H, dd, *J* = 8.2, 2.4 Hz, 5′-H), 6.61 (1H, d, *J* = 2.2 Hz, 5-H). 6.63 (1H, dd, *J* = 8.6, 2.2 Hz, 7-H), 6.80 (1H, d, *J* = 8.6 Hz, 8-H), 7.26 (1H, d, *J* = 8.2 Hz, 6′-H); δ_C (125 MHz; $CDCl_3$) 18.3 (C-3″), 20.9 (OCH_3, OAc), 48.4 (C-3), 55.5 (2′, 4′-MeO), 64.1 (C-9), 76.5 (C-2), 98.6 (C-3′), 104.9 (C-5′), 112.1 (C-5), 116.7 (C-8), 116.8 (C-7), 119.3 (C-1′), 123.5 (C-2″), 128.8 (C-6′), 130.8 (C-1″), 131.7 (C-6), 133.4 (C-4a), 142.2 (C-8a), 158.1 (C-2′), 160.9 (C-4′), 170.8 (CO, OAc); IR (film)/cm^{-1}: 3384, 2933, 2846, 1739, 1607, 1466, 1366, 1229, 1208, 1127, 1041, 905, 803, 729; HRMS (ESI+) Found (MNa^+): 406.1616; $C_{22}H_{25}NNaO_5$ requires 406.1625.

((2R,3S)-3-(2′,4′-Dimethoxyphenyl)-6-((E)-prop-1″-en-1″-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)methanol ***40***. To a stirred solution of acetate **39** (0.010 g, 0.026 mmol) in MeOH (4 mL) was added NaOH (0.011 g, 0.26 mmol), and the resultant solution was stirred at room temperature for 2 h. The resulting solution was added to water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (9:1 hexanes, ethyl acetate) to yield the *title product* **40** (7 mg, 78%) as a yellow oil: R_f = 0.28 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +5.68 (*c* = 0.09, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.83 (3H, dd, *J* = 6.6, 1.8 Hz, 3″- H), 3.64 (1H, dd, *J* = 12.0, 5.6 Hz, 9-H_a), 3.68 (1H, dd, *J* = 12.0, 3.2 Hz, 9-H_b), 3.82 (3H, s, 4′-MeO), 3.84 (3H, s, 2′-MeO), 4.04 (1H, ddd, *J* = 8.0, 5.6, 3.2 Hz, 2-H), 4.70 (1H, d, *J* = 8.0 Hz, 3-H), 6.04 (1H, dd, *J* = 15.8, 6.6 Hz, 2″- H), 6.26 (1H, dd, *J* = 15.8, 1.8 Hz, 1″- H), 6.′49 (1H, d, *J* = 2.0 Hz, 3′-H), 6.53 (1H, dd, *J* = 8.6, 2.0 Hz, 5′-H), 6.62 (1H, d, *J* = 2.0 Hz, 5-H). 6.68 (1H, dd, *J* = 8.0, 2.0 Hz, 7-H), 6.82 (1H, d, *J* = 8.0 Hz, 8-H), 7.33 (1H, d, *J* = 8.6 Hz, 6′-H); δ_C (125 MHz; $CDCl_3$) 18.5 (C-3″), 47.7 (C-3), 55.5 (4′-MeO), 55.7 (2′-MeO), 62.7 (C-9), 79.8 (C-2), 98.7 (C-3′), 104.9 (C-1′), 105.2 (C-5′), 112.1 (C-5), 116.6 (C-8), 116.8 (C-7), 123.5 (C-2″), 130.7 (C-1″), 129.1 (C-6′), 131.6 (C-6), 133.7 (C-4a), 142.7 (C-8a), 158.0 (C-2′), 160.7 (C-4′); IR (film)/cm^{-1}: 3370, 2919, 2856, 1737, 1608, 1586, 1503, 1461, 1365, 1258, 1208, 1156, 1120, 1029, 963, 921, 827, 742; HRMS (ESI+) Found (MNa^+): 364.1506; $C_{20}H_{23}NNaO_4$ requires 364.1519.

(2R,3S)-Benzyl 2-((benzyloxy)methyl)-3-(3′,4′-dimethoxyphenyl)-6-(3″,4″,5″-trimethoxyphenyl)-2H-benzo[b][1,4]oxazine-4(3H)-carboxylate ***42***. To a solution of bromobenzomorpholine **26** (0.026 g, 0.044 mmol) in DME (6 mL) were added 2 M K_2CO_3 (0.15 mL, 0.28 mmol), arylboronic acid **41** (0.018 g, 0.086 mmol), and $Pd(PPh_3)_4$ (0.011 g, 0.009 mmol). The resultant mixture was stirred vigorously at 90 °C for 72 h. The mixture was cooled, water (5 mL) was added, the organic layer was separated, and the aqueous phase was further extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (2:1 hexanes, ethyl acetate) to give the *title compound* **42** (0.015 g, 52%) as a yellow oil: R_f = 0.28 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ +42.62 (*c* = 0.30, $CHCl_3$); δ_H (500 MHz; $CD'Cl_3$; Me_4Si) 3.59 (1H, dd, *J* = 9.8, 7.2 Hz, 9-H_a), 3.68 (3H, s, 3′-MeO), 3.71 (1H, dd, *J* = 9.8, 5.5 Hz, 9-H_b), 3.81 (3H, s, 4′-MeO), 3.86 (6H, s, 3″-MeO, 5″-MeO), 3.87 (3H, s, 4″-MeO), 4.51 (2H, s, OCH_2Ph), 4.81 (1H, ddd, *J* = 7.2, 5.5, 1.8 Hz, 2-H), 5.26 (1H, d, *J* = 12.2 Hz, O$CH_a$$H_b$Ph), 5.31 (1H, d, *J* = 12.2 Hz, O$CH_a$$H_b$Ph), 5.82 (1H, d, *J* = 1.8 Hz, 3-H), 6.68 (2H, s, 2″-H and 6″-H), 6.72 (1H, d, *J* = 8.2 Hz, 5′-H), 6.80 (1H, d, *J* = 2.0 Hz, 2′-H), 6.85 (1H, dd, *J* = 8.2, 2.0 Hz, 6′-H), 6.94 (1H, d, *J* = 8.6 Hz, 8-H), 7.18 (1H, dd, *J* = 8.6, 2.4 Hz, 7-H), 7.28−7.34 (10 H, Ar−H), 8.11 (1H, s, 5-H); δ_C (125 MHz; $CDCl_3$) 53.7 (C-3), 55.7 (3′-MeO), 55.8 (4′-MeO), 56.2 (3″, 5″-MeO), 60.9 (4″-MeO), 68.1 (OCH_2Ph), 69.3 (C-9), 73.8 (OCH_2Ph), 76.1 (C-2), 104.3 (C-2″, C-6″), 110.4 (C-2′), 111.1 (C-5′), 117.3 (C-8), 119.2 (C-6′), 121.9 (C-5), 123.4 (C-7), 124.5 (C-4a), 127.8, 127.9, 128.0, 128.3, 128.5, 128.6 (Ar−CH), 130.7 (C-1′), 134.4 (C-6), 135.8 (Ar−C), 136.8 (C-1″), 137.4 (C-4″), 137.6 (Ar−C), 144.5 (C-8a), 148.5 (C-4′), 148.9 (C-3′), 153.4 (C-3″, C-5″), 153.9 (C═O); IR (film)/cm^{-1}: 2923, 2860, 1706, 1577, 1516, 1495, 1456, 1402, 1257, 1127, 1028, 819, 754; HRMS (ESI+) Found (MNa^+): 714.2665; $C_{41}H_{41}NNaO_9$ requires 714.2674.

(2R,3S)-2-((Benzyloxy)methyl)-3-(2′,4′,6′-trimethoxyphenyl)-6-(3″,4″,5″-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine ***43***. To a solution of bromobenzomorpholine **25** (0.029 g, 0.059 mmol) in DME (8 mL) were added 2 M K_2CO_3 (0.2 mL, 0.39 mmol), arylboronic acid **41** (0.025 g, 0.12 mmol), and $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol). The resultant mixture was stirred vigorously at 90 °C for 72 h. The mixture was cooled, water (10 mL) was added, the organic layer was separated, and the aqueous phase was further extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (2:1 hexanes, ethyl acetate) to give the *title compound* **43** (0.013 g, 38%) as a brown oil: R_f = 0.21 (2:1 hexanes, ethyl acetate); $[\alpha]_D$ −63.54 (*c* = 0.19, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.58 (1H, dd, *J* = 10.4, 5.0 Hz, 9-H_a), 3.60 (1H, dd, *J* = 10.4, 3.4 Hz, 9-H_b), 3.74 (6H, s, 2′, 6′-MeO), 3.83 (3H, s, 4′-MeO), 3.87 (3H, s, 4″-MeO), 3.89 (6H, s, 3″, 5″-MeO), 4.49 (1H, d, *J* = 12.2 Hz, O$CH_a$$H_b$Ph), 4.52 (1H, d, *J* = 12.2 Hz, O$CH_a$$H_b$Ph), 4.77 (1H, ddd, *J* = 8.6, 5.0, 3.4 Hz, 2-H), 4.89 (1H, d, *J* = 8.6 Hz, 3-H), 6.13 (2H, s, 3′, 5′-H), 6.73 (2H, s, 2″, 6″-H), 6.93 (1H, d, *J* = 1.8 Hz, 5-H), 6.94 (1H, dd, *J* = 8.4, 1.8 Hz, 7-H), 7.01 (1H, d, *J* = 8.4 Hz, 8-H), 7.22−7.29 (5H, Ar−H); δ_C (125 MHz; $CDCl_3$) 48.9 (C-3), 55.4 (4′-MeO), 55.7 (2′, 6′-MeO), 56.1 (3″, 5″-MeO), 60.9 (4″-MeO), 70.6 (C-9), 73.3 (OCH_2Ph), 75.5 (C-2), 91.0 (C-3′, C-5′), 104.0 (C-2″, C-6″), 106.5 (C-1′), 116.4 (C-5), 117.3 (C-8), 118.4 (C-7), 127.3, 127.5, 128.2 (Ar−CH), 133.7 (C-4a), 134.3 (C-6), 137.0 (C-1″), 137.5 (C-4″), 138.4 (Ar−C), 145.1 (C-8a), 153.3 (C-3″, C-5″), 159.8 (C-2′, C-6′), 161.3 (C-4′); IR (film)/cm^{-1}: 3370, 2937, 2839, 1729, 1603, 1591, 1579, 1496, 1454, 1416, 1275, 1228, 1126, 814, 736; HRMS (ESI+) Found (MNa^+): 610.2404; $C_{34}H_{37}NNaO_8$ requires 610.2411.

((2R,3S)-3-(3,4-Dimethoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4′]oxazin-2-yl)methanol ***44***. To a solution of biaryl-benzomorpholine **42** (0.015 g, 0.022 mmol) in MeOH (3 mL) was added 10% Pd/C (0.003 g, 20% w/w), and the mixture was stirred under an atmosphere of hydrogen for 1 h. The mixture was filtered through Celite and washed with methanol (3 × 3 mL), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (1:1 hexanes, ethyl acetate) to yield the *title product* **44**

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(7 mg, 67%) as a yellow gum: R_f = 0.48 (1:2 hexanes, ethyl acetate); $[\alpha]_D$ +71.02 (c = 0.01, $CHCl_3$); δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.56 (1H, dd, J = 10.4, 5.4 Hz, 9-H_a), 3.75 (1H, dd, J = 10.4, 3.4 Hz, 9-H_b), 3.88 (3H, s, 4″-MeO), 3.90 (6H, s, 3′, 4′-MeO), 3.91 (6H, s, 3″, 5″-MeO), 4.04 (1H, ddd, J = 7.8, 5.4, 3.4 Hz, 2-H), 4.38 (1H, d, J = 7.8 Hz, 3-H), 6.72 (2H, s, 2″, 6″-H), 6.87 (1H, d, J = 2.0 Hz, 5-H), 6.89 (1H, d, J = 8.4 Hz, 5′-H), 6.91 (1H, dd, J = 8.4, 2.0 Hz, 7-H), 6.96 (1H, d, J = 8.4 Hz, 8-H), 6.97 (1H, d, J = 2.0 Hz, 2′-H), 6.99 (1H, dd, J = 8.4, 2.0 Hz, 6′-H); δ_C (125 MHz; $CDCl_3$) 54.9 (C-3), 55.9 (3′-MeO), 56.0 (4′-MeO), 56.2 (3″, 5″-MeO), 60.9 (4″-MeO), 62.2 (C-9), 79.8 (C-2), 104.1 (C-2″, C-6″), 110.5 (C-2′), 111.3 (C-5′), 113.4 (C-5), 116.7 (C-8), 117.7 (C-7), 120.3 (C-6′), 131.0 (C-1′), 133.9 (C-4a), 135.4 (C-6), 137.1 (C-1″), 137.2 (C-4″), 143.1 (C-8a), 149.2 (C-4′), 149.6 (C-3′), 153.4 (C-3″, C-5″); IR (film)/cm^{-1}: 3458, 3349, 2926, 2835, 2342, 1738, 1579, 1497, 1460, 1421, 1371, 1264, 1234, 1128, 1027, 910, 733; HRMS (ESI+) Found (MNa^+): 490.1835; $C_{26}H_{29}NNaO_7$ requires 490.1836.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02265.

NMR spectra for all novel compounds; details of the biological testing (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Pilkington, L. I.; Barker, D. *J. Org. Chem.* **2012**, *77*, 8156.
(2) Pilkington, L. I.; Barker, D. *Eur. J. Org. Chem.* **2014**, *2014*, 1037.
(3) Pilkington, L. I.; Wagoner, J.; Polyak, S. J.; Barker, D. *Org. Lett.* **2015**, *17*, 1046.
(4) Jing, X.; Gu, W.; Bie, P.; Ren, X.; Pan, X. *Synth. Commun.* **2001**, *31*, 861.
(5) Tanaka, H.; Kato, I.; Ito, K. *Chem. Pharm. Bull.* **1987**, *35*, 3603.
(6) Pilkington, L. I.; Barker, D. *Nat. Prod. Rep.* **2015**, *32*, 1369.
(7) Brantley, S. J.; Oberlies, N. H.; Kroll, D. J.; Paine, M. F. *J. Pharmacol. Exp. Ther.* **2010**, *332*, 1081.
(8) Plíšková, M.; Vondráček, J.; Křen, V.; Gažák, R.; Sedmera, P.; Walterová, D.; Psotová, J.; Šimánek, V.; Machala, M. *Toxicology* **2005**, *215*, 80.
(9) Arnoldi, A.; Merlini, L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2555.
(10) Loguercio, C.; Festi, D. *World J. Gastroenterol.* **2011**, *17*, 2288.
(11) Duan, R.; Sun, X.; Liu, J.; Gong, T.; Zhang, Z. *Acta Pharmacol. Sin.* **2011**, *32*, 108.
(12) Yu, J.; Zhu, Y.; Wang, L.; Peng, M.; Tong, S.; Cao, X.; Qiu, H.; Xu, X. *Acta Pharmacol. Sin.* **2010**, *31*, 759.
(13) Saito, I.; Matsugo, S.; Matsuura, T. *J. Am. Chem. Soc.* **1979**, *101*, 7332.
(14) Bunce, R. A.; Herron, D. M.; Hale, L. Y. *J. Heterocycl. Chem.* **2003**, *40*, 1031.
(15) Ilaš, J.; Jakopin, Ž.; Borštnar, T.; Stegnar, M.; Kikelj, D. *J. Med. Chem.* **2008**, *51*, 5617.
(16) Patil, V. P.; Markad, V. L.; Kodam, K. M.; Waghmode, S. B. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6259.
(17) Liu, Z.-T.; Wang, Y.-H.; Zhu, F.-L.; Hu, X.-P. *Org. Lett.* **2016**, *18*, 1190.
(18) Gigant, N.; Gillaizeau, I. *Org. Lett.* **2012**, *14*, 4622.
(19) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283.
(20) Brown, D. W.; Ninan, A.; Sainsbury, M. *Synthesis* **1997**, *1997*, 895.
(21) Saliu, F.; Orlandi, M.; Bruschi, M.; Saliu, F.; Orlandi, M.; Bruschi, M. *ISRN Organic Chemistry* **2012**, *2012*, 281642.
(22) Bonilla-Landa, I.; Viveros-Ceballos, J. L.; Ordóñez, M. *Tetrahedron: Asymmetry* **2014**, *25*, 485.
(23) (a) Bartsch, H.; Kropp, W.; Pailer, M. *Monatsh. Chem.* **1979**, *110*, 267. (b) Bartsch, H.; Schwarz, O. *J. Heterocycl. Chem.* **1983**, *20* (1), 45. (c) Dickson, J. K.; Gungor, T.; Yang, W. US 2003/0195207 A1. (d) Kuo, G.-H.; Wang, A.; Rano, T.; Prouty, C.; Demarest, K. T.; Pelton, P. US 2007/0265252 A1.
(24) (a) Gunawan, S.; Hulme, C. *Tetrahedron Lett.* **2013**, *54*, 4467. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (c) Magnus, P.; Hulme, C.; Weber, W. *J. Am. Chem. Soc.* **1994**, *116*, 4501. (d) Xu, Z.; Martinez-Ariza, G.; Cappelli, A. P.; Roberts, S. A.; Hulme, C. *J. Org. Chem.* **2015**, *80*, 9007. (e) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (f) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.
(25) Bora, P. P.; Vanlaldinpuia, K.; Rokhum, L.; Bez, G. *Synth. Commun.* **2011**, *41*, 2674.
(26) Jahani, F.; Tajbakhsh, M.; Khaksar, S.; Azizi, M. R. *Monatsh. Chem.* **2011**, *142*, 1035.
(27) Lee, Y. S.; Cho, D. J.; Kim, S. N.; Choi, J. H.; Park, H. *J. Org. Chem.* **1999**, *64*, 9727.
(28) Boiaryna, L.; El Mkaddem, M. K.; Taillier, C.; Dalla, V.; Othman, M. *Chem. - Eur. J.* **2012**, *18*, 14192.
(29) Schweitzer-Chaput, B.; Klussmann, M. *Eur. J. Org. Chem.* **2013**, *2013*, 666.
(30) Matsumura, Y.; Terauchi, J.; Yamamoto, T.; Konno, T.; Shono, T. *Tetrahedron* **1993**, *49*, 8503.
(31) Jim-Min, F.; Ching-Kuo, L.; Yu-Shia, C. *Phytochemistry* **1992**, *31*, 3659.

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