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A SIMPLE CHIRAL TEMPLATE FOR THE SYNTHESIS OF FUNCTIONALIZED α-ARYLGLYCINE DERIVATIVES

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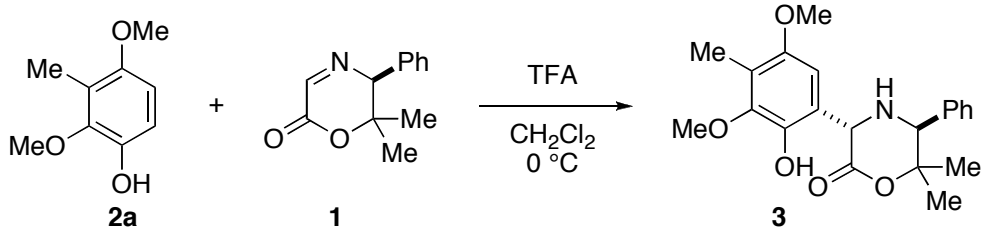
Abstract – A simple chiral template for the synthesis of arylglycine derivatives has been developed. The chiral template, which is derived from valinol in three steps, reacts with electron rich aromatic compounds to afford adducts in good yield with moderate to high diastereoselectivities.

INTRODUCTION

α-Arylglycines are important components of biologically active compounds, including vancomycin and amoxicillin. Their growing importance has prompted the exploration of a variety of synthetic methods for α-arylglycine, such as the asymmetric Strecker reaction, the Sharpless asymmetric aminohydroxylation, a catalytic enantioselective hydrogenation, and an asymmetric N-H insertion reaction.[1,2] However, development of efficient methods for the synthesis of poly-functionalized arylglycines including *o*-substituted ones, has been hampered because electron-donating substituents adjacent to the reaction site tend to lower both the reactivity and the selectivity. During the course of our synthetic studies on ecteinascidin 743,[3] preparation of a functionalized arylglycine derivative was a critical task. Thus, we have developed an original synthetic method for optically active α-arylglycine derivatives using the iminolactone **1** as a chiral template.[4] Nucleophilic addition of electron-rich aromatic compounds to iminolactone **1** proceeded stereoselectively to provide a range of arylglycine derivatives (Scheme 1). However, one problem with our synthesis is that the chiral template is derived from phenylglycine

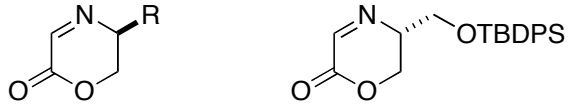


Scheme 1

through a seven-step procedure, which includes oxidation with $Pb(OAc)_4$. Herein, we report the more readily available iminolactone as a chiral template, which is applicable to the synthesis of a variety of arylglycines.

RESULTS AND DISCUSSION

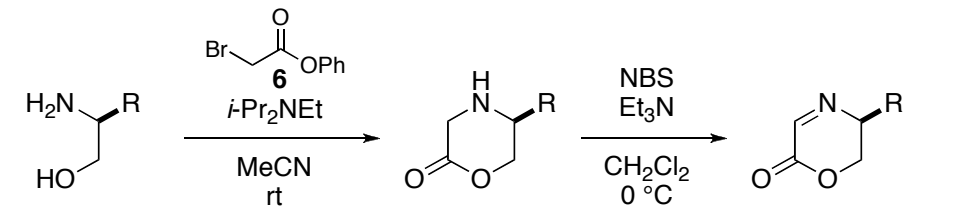
We designed an iminolactone without a gem-dimethyl moiety as a simple chiral template. In this regard, Wang and coworkers have attempted nucleophilic additions of aromatic compounds to iminolactone **4p** (Figure 1).[5] Zhu and coworkers have reported the same type of reaction using iminolactone **4t** derived from D-serine.[6] On the other hand, Harwood and coworkers have reported that iminolactone **4s** reacts with Grignard reagents to furnish adducts in a stereoselective manner.[7] To screen the potential of this type of iminolactones as a chiral template for α-arylglycine synthesis, we prepared iminolactones **4p**-**r** according to the Harwood's procedure (Scheme 2). Reaction of readily available aminoalcohols **5p**-**r** with phenyl bromoacetate (**6**) furnished lactones **7p**-**r**, which, upon oxidation with NBS, gave iminolactones **4p**-**r**.[8]



4p : R = *i*-Pr
4s : R = Ph

4t

Figure 1. Iminolactones



5p : R = *i*-Pr
5q : R = *s*-Bu
5r : R = Bn

7p : R = *i*-Pr (62%)
7q : R = *s*-Bu (49%)
7r : R = Bn (79%)

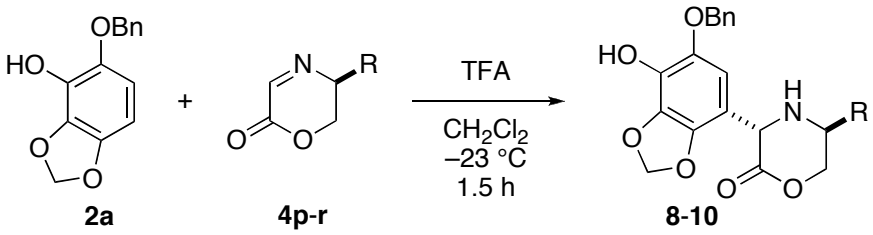
4p : R = *i*-Pr (73%)
4q : R = *s*-Bu (71%)
4r : R = Bn (93%)

Scheme 2. Synthesis of Iminolactones

We next tried nucleophilic addition of the iminolactones thus prepared. Addition of phenol **2a** to iminolactones **4p**-**r** proceeded in the presence of TFA to furnish the desired products **8**-**10** (Table 1). While Wang and coworkers have reported that nucleophilic addition reactions of **4p** resulted in formation of the products with low diastereoselectivities,[5] slow addition of TFA substantially improved the selectivity to give the adduct **8** in good yield with high diastereoselectivity. The selectivity of the reaction appeared to depend on the bulk of the side chain. That is, a branched alkyl chain had a superior stereoselectivity compared to a benzyl group. In consideration of the availability of each enantiomer, **4p**

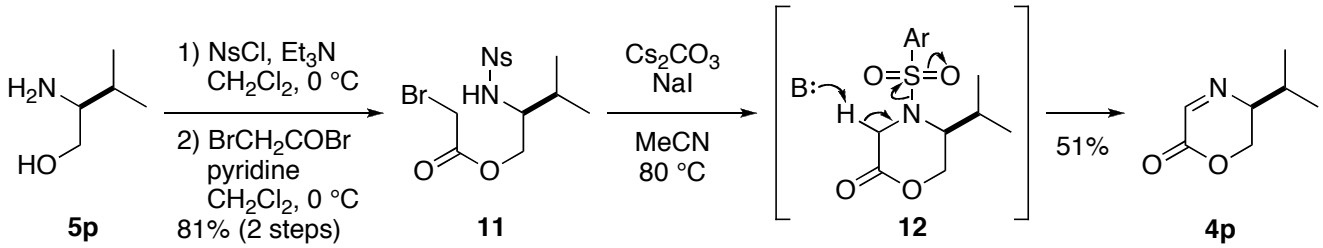
was chosen as the chiral template.

Table 1. Screening of iminolactones



entry	R	product	yield (%)	dr (*R* : *S*)
1	*i*-Pr (**4p**)	**8**	98	20 : 1
2	*s*-Bu (**4q**)	**9**	73	20 : 1
3	Bn (**4r**)	**10**	99	10 : 1

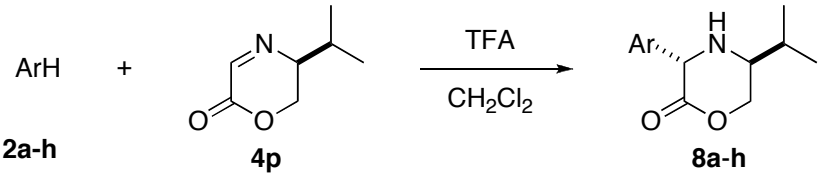
At this stage we developed an alternative route to iminolactone **4p** without using any oxidant (Scheme 4). Introduction of a nosyl group onto the amino group of valinol (**5p**), followed by a bromoacetylation of the hydroxy group afforded **11**. Upon treatment of **11** with Cs_2CO_3 in the presence of NaI, a cyclization and a subsequent elimination of the Ns group occurred to afford iminolactotne **4p** in moderate yield.[9]



Scheme 3. Alternative synthesis of the chiral template

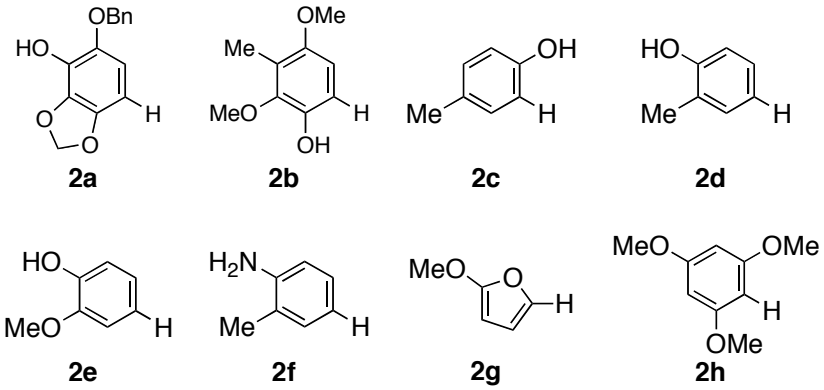
Having developed a synthetic route to iminolactone **4p**, we next studied the addition of a variety of nucleophiles to the chiral template. Table 2 summarizes the reaction conditions, yield, and diastereoselectivity. We found that highly substituted phenols such as **2a**-**e** were suitable substrates for this transformation. The reaction occurred preferentially at the *para* position of the phenol unless it was substituted. Aniline **2f** was also a good nucleophile, giving the product with high diastereoselectivity. While the reactions with highly electron rich aromatic rings such as **2g**-**h** furnished the corresponding products with relatively low diastereoselectivities, lowering the temperature improved the selectivity (entry 8). The stereochemistry of the major product was determined by a NOESY analysis of **8e** (Figure 2).

Table 2. Nucleophilic addition into the chiral template

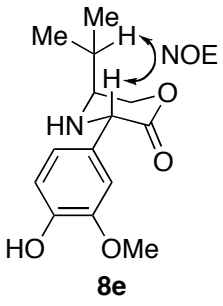


2a-h **4p** **8a-h**

entry	ArH	temperature (°C)	product	time (h)	yield (%)	dr (*R* : *S*)
1	**2a**	–23	**8a**	1.5	98	20 : 1
2	**2b**	–23 to –10	**8b**	2.5	72	10 : 1
3	**2c**	–23 to –10	**8c**	5.5	76	13 : 1
4	**2d**	–23	**8d**	1.5	86	10 : 1
5	**2e**	–23 to rt	**8e**	6	78	8 : 1
6	**2f**	–23 to –10	**8f**	90	70	10 : 1
7	**2g**	–23	**8g**	0.25	43	3 : 1
8	**2h**	–23	**8h**	0.25	>99	2 : 1
9	**2h**	–78	**8h**	0.75	92	5 : 1



2a **2b** **2c** **2d** **2e** **2f** **2g** **2h**

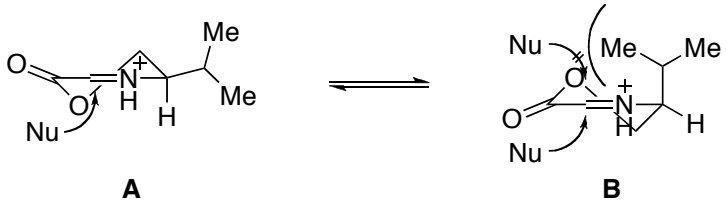


8e

Figure 2. Observed NOE

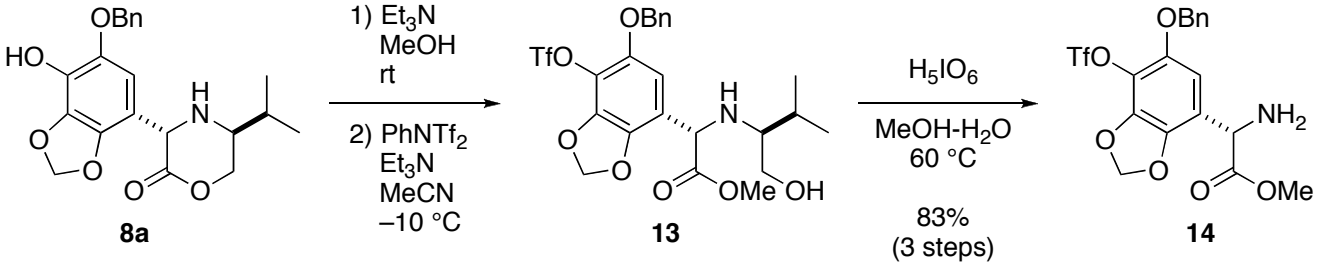
Zhu and coworkers have reported the same type of a nucleophilic addition reaction, and discussed that the reaction proceeds via an axial attack onto a more stable conformer **A** (Scheme 5). However, DFT calculation (B3LYP/6-31G*) revealed that the protonated iminolactone exists as a 3 : 2 mixture of the conformer **A** and **B** at –23 °C (the energy gap between **A** and **B** is 0.29 kcal/mol), suggesting that an axial attack onto the conformer **A** is not an exclusive route to the product. A nucleophilic addition onto the conformer **B** may also occur from the less hindered side to provide the product with the same

stereochemistry.



Scheme 4. Stereochemical issue

We then focused on the transformation of the product **8a** into an arylglycine derivative (Scheme 6). Methanolysis of the lactone followed by triflation of the phenolic hydroxy group afforded **13**, which was subsequently treated with H_5IO_6 to furnish arylglycine **14**.



Scheme 5. Transformation into an arylglycine derivative

In summary, we have developed a simple chiral template to synthesize arylglycine derivatives. The chiral template can be easily derived from valinol in three steps without using an oxidant. Nucleophilic additions of electron rich aromatic rings proceeded in good yield with moderate to high diastereoselectivities.

EXPERIMENTAL

(*S*)-5-isopropylmorpholin-2-one (7p).

To a solution of 819 mg (7.94 mmol) of **5p** in 25 mL of MeCN was added a solution of phenyl bromoacetate (**6**, 1.9 g, 8.73 mmol) and diisopropylethylamine (2 mL, 11.9 mmol) in 25 mL of MeCN dropwise over 30 min at rt. After stirring for 16 h, the solvent was removed under reduced pressure. A neutral silica gel separation employing a solvent gradient to 50-100% EtOAc in *n*-hexane afforded 701 mg (4.89 mmol, 62%) of **7p** as a yellow oil, which was in full agreement with the reported data. $[\alpha]_D^{21}$ –10.3 ° (*c* 2.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 4.43 (dd, *J* = 11.0, 3.7 Hz, 1 H), 4.16 (dd, *J* = 11.2, 11.0 Hz, 1 H), 3.79 (d, *J* = 18.1 Hz, 1 H), 3.64 (d, *J* = 18.1 Hz, 1 H), 2.76 (ddd, *J* = 11.0, 6.9, 3.7 Hz, 1 H), 1.68 (octet, *J* = 6.9 Hz, 1 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 168.5, 72.6, 56.8, 47.8, 29.7, 18.8, 18.7.

(*S*)-5-isopropyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (4p)

To a solution of 682 mg (4.76 mmol) of **7p** and 1 mL (7.21 mmol) of triethylamine in 50 mL of CH_2Cl_2 was added 848 mg (4.76 mmol) of *N*-bromosuccimide at 0 °C. After stirring for 5 min, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extracts were washed with brine, dried over Na_sSO_4, filtered, and evaporated under reduced pressure. A neutral silica gel separation employing a solvent gradient to 20% EtOAc in *n*-hexane afforded 493 mg (3.49 mmol, 73%) of **4p** as a colorless oil, which was in full agreement with the reported data. $[\alpha]_D^{21}$ +56.9 ° (c 1.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.90 (d, *J* = 2.7 Hz, 1 H), 4.75 (dd, *J* = 11.7, 4.3 Hz, 1 H), 4.26 (dd, *J* = 11.7, 9.6 Hz, 1 H), 3.50 (dddd, *J* = 9.6, 6.9, 4.3, 2.7 Hz, 1 H), 1.95 (octet, *J* = 6.9 Hz, 1 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.06 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 154.5, 152.2, 68.3, 61.4, 30.3, 19.2, 18.6.

(*S*)-3-methyl-2-(2-nitrophenylsulfonamido)butyl 2-bromoacetate (11)

To a solution of 5.28 g (51.2 mmol) of **5p** and 10.7 mL (76.8 mmol) of triethylamine in 100 mL of CH_2Cl_2 was added 11.4 g (51.2 mmol) of *o*-nitrobenzenesulfonyl chloride at 0 °C. After stirring 5 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extracts were washed with 1 N HCl solution and brine, dried over Na_sSO_4, filtered, and evaporated under reduced pressure to afford 13.7 g (47.5 mmol, 92.7%) of nosyl amide. ^{1}H NMR ($CDCl_3$) 8.10-8.15 (m, 1 H) 7.85-7.90 (m, 1 H), 7.70-7.75 (m, 2 H), 5.50-5.55 (m, 1 H), 3.60-3.65 (m, 2 H), 3.25-3.35 (m, 1 H), 1.88 (octet, *J* = 7.3 Hz, 1 H), 1.85 (br s, 1 H), 0.89 (d, *J* = 7.3 Hz, 3 H), 0.87 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 134.8, 133.4, 132.9, 130.6, 125.3, 63.2, 62.2, 30.9, 29.5, 19.3, 18.3.

To a solution of 2.97 g (10.3 mmol) of nosyl amide and 1.00 mL (12.3 mmol) of pyridine dissolved in 30 mL of CH_2Cl_2 was added 0.97 mL (11.3 mmol) of bromoacetyl bromide at 0 °C. After stirring for 15 min, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extracts were washed with 1 N HCl solution and brine, dried over Na_sSO_4, filtered, and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 25% EtOAc in hexane to afford 3.66 g (8.94 mmol, 87% yield) of **11**. ^{1}H NMR ($CDCl_3$) 8.10-8.15 (m, 1 H) 7.85-7.90 (m, 1 H), 7.75-7.80 (m, 2 H), 5.51-5.55 (m, 1 H), 4.10-4.20 (m, 2 H), 3.67 (s, 2 H), 3.50-3.60 (m, 1 H), 1.90 (octet, *J* = 6.6 Hz, 1 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 166.9, 147.6, 133.5, 133.0, 130.3, 125.4, 65.8, 60.3, 58.8, 29.9, 25.3, 19.1, 18.1.

(*S*)-5-isopropyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (4p)

To a solution of 2.23 g (5.44 mmol) of **11** in 27 mL of MeCN were added 162 mg (1.09 mmol) of sodium iodide and 3.63 g (11.1 mmol) of cesium carbamate. The resulting mixture was heated to 80 °C for 1 h. After cooling to rt, the reaction mixture was diluted with EtOAc, and filtrated through a pad of Celite. The filtrate was concentrated *in vacuo*, and the residue was purified with a neutral silica gel column chromatography eluting with EtOAc to afford 392 mg (2.78 mmol, 51%) of **4p** as a pale yellow oil.

General Procedure for Nucleophilic Addition

To a solution of ArH (0.50 mmol) and iminolactone (0.75 mmol) in 5 mL of CH_2Cl_2 was cooled to –23 °C and added 1.44 mL (20.0 mmol) of trifluoroacetic acid dropwise over 1.5 h. After the starting material was consumed, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The extracts were washed with brine, dried over Na_sSO_4, filtered, and evaporated under reduced pressure. A neutral silica gel separation eluting EtOAc in *n*-hexane afforded the Mannich-adduct.

(3*S*,5*S*)-5-benzyl-3-(6-(benzyloxy)-7-hydroxybenzo[*d*][1,3]dioxol-4-yl)morpholin-2-one (10)

$[\alpha]_D^{21}$ –29.2 ° (c 0.42, $CHCl_3$); IR (film, cm^{-1}) 3309, 2895, 1741, 1510, 1458, 1215, 1072, 912; ^1H NMR ($CDCl_3$) 7.10-7.40 (m, 10 H), 6.28 (s, 1 H), 5.83 (d, *J* = 1.6 Hz, 1 H), 5.63 (d, *J* = 1.6 Hz, 1 H), 4.99 (s, 2 H), 4.92 (s, 1 H), 4.38 (dd, *J* = 10.8, 3.9 Hz, 1 H), 4.22 (dd, *J* = 10.8, 9.2 Hz, 1 H), 3.33 (dddd, *J* = 9.2, 8.5, 5.3, 3.9 Hz, 1 H), 2.79 (dd, *J* = 13.7, 5.3 Hz, 1 H), 2.66 (dd, *J* = 13.7, 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 168.1, 142.3, 140.7, 136.6, 136.1, 134.1, 131.0, 129.0, 128.8, 128.7, 128.4, 128.0, 126.9, 109.9, 104.8, 101.8, 73.3, 72.2, 56.3, 49.1, 37.4; HRMS (FAB) Calculated for $C_{25}H_{23}NO_6$ 433.1525; Found 433.1535.

(3*S*,5*S*)-3-(6-(benzyloxy)-7-hydroxybenzo[*d*][1,3]dioxol-4-yl)-5-isopropylmorpholin-2-one (8a)

$[\alpha]_D^{22}$ –43.3 ° (c 0.40, $CHCl_3$); IR (film, cm^{-1}) 3319, 2964, 2897, 1743, 1510, 1460, 1219, 1072, 912; ^1H NMR ($CDCl_3$) 7.35-7.40 (m, 5 H), 6.32 (s, 1 H), 5.94 (s, 2 H), 4.99 (s, 2 H), 4.83 (s, 1 H), 4.41 (dd, *J* = 11.0, 3.9 Hz, 1 H), 4.25 (dd, *J* = 11.0, 9.4 Hz, 1 H), 2.78 (ddd, *J* = 9.4, 6.9, 3.9 Hz, 1 H), 1.72 (octet, *J* = 6.9 Hz, 1 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 169.0, 142.6, 141.0, 137.7, 136.2, 134.3, 128.7, 128.4, 128.0, 109.7, 105.1, 101.9, 72.2, 71.6, 55.7, 54.0, 29.3, 18.8, 18.7; HRMS (FAB) Calculated for $C_{21}H_{24}NO_6$ ($[M+H]^+$) 386.1603; Found 386.1590.

(3*S*,5*S*)-3-(2-hydroxy-3,5-dimethoxy-4-methylphenyl)-5-isopropylmorpholin-2-one (8b)

$[\alpha]_D^{22}$ –72.4 ° (c 1.00, $CHCl_3$); IR (film, cm^{-1}) 3293, 2963, 2838, 1741, 1468, 1190, 1130; ^1H NMR ($CDCl_3$) 6.51 (s, 1 H), 4.76 (s, 1 H), 4.47 (dd, *J* = 11.0, 3.2 Hz, 1 H), 4.35 (dd, *J* = 11.0, 10.8 Hz, 1 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.00 (ddd, *J* = 10.8, 6.9, 3.2 Hz, 1 H), 2.14, (s, 3 H), 1.76 (octet, *J* = 6.9 Hz, 1 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 168.2, 151.3, 147.1, 142.4, 121.2, 119.7, 107.0, 72.3, 61.6, 60.6, 57.5, 55.9, 29.9, 18.8, 18.7, 9.11; HRMS (FAB) Calculated for $C_{16}H_{24}NO_5$ ($[M+H]^+$) 310.1654; Found 310.1644.

(3S,5S)-3-(2-hydroxy-5-methylphenyl)-5-isopropylmorpholin-2-one (8c)

$[\alpha]_D^{25}$ –11.0 ° (c 0.30, $CHCl_3$); IR (film, cm^{-1}) 3288, 2964, 1741, 1500, 1263, 1219; ^1H NMR ($CDCl_3$) 7.04 (d, *J* = 8.3 Hz, 1 H), 6.90 (s, 1 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 5.08 (s, 1 H), 4.51 (dd, *J* = 11.7, 4.6 Hz, 1 H), 4.29 (dd, *J* = 11.7, 8.2 Hz, 1 H), 2.90 (ddd, *J* = 8.2, 6.9, 4.6 Hz, 1 H), 2.25 (s, 3 H), 1.80 (octet, *J* = 6.9 Hz, 1 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 167.4, 154.6, 130.4, 129.0, 128.1, 119.0, 117.3, 71.7, 58.2, 52.7, 29.3, 20.5, 18.9, 18.8; HRMS (FAB) Calculated for

$C_{14}H_{20}NO_3$ 249.1365; Found 249.1375.

(3*S*,5*S*)-3-(4-hydroxy-3-methylphenyl)-5-isopropylmorpholin-2-one (8d)

$[\alpha]_D^{25}$ –41.5 ° (c 0.17, $CHCl_3$); IR (film, cm^{-1}) 3340, 2964, 1730, 1512, 1267, 1120; ^1H NMR ($CDCl_3$) 7.13 (s, 1 H), 7.05 (d, *J* = 8.2 Hz, 1 H), 6.69 (d, *J* = 8.2 Hz, 1 H), 4.75 (s, 1 H), 4.45 (dd, *J* = 11.0, 4.1 Hz, 1 H), 4.26 (dd, *J* = 11.0, 9.2 Hz, 1 H), 2.88 (ddd, *J* = 9.2, 6.9, 4.1 Hz, 1 H), 2.22 (s, 3 H), 1.72 (octet, *J* = 6.9 Hz, 1 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 170.7, 154.2, 129.9, 129.0, 125.8, 124.6, 114.9, 71.9, 59.1, 53.1, 29.6, 18.8, 18 7, 15.9; HRMS (FAB) Calculated for $C_{14}H_{20}NO_3$ 249.1365; Found 249.1377.

(3*S*,5*S*)-3-(4-hydroxy-3-methoxyphenyl)-5-isopropylmorpholin-2-one (8e)

$[\alpha]_D^{25}$ –19.1 ° (c 0.37, $CHCl_3$); IR (film, cm^{-1}) 3321, 2964, 1736, 1516, 1468, 1273, 1213, 1034; ^1H NMR ($CDCl_3$) 7.01 (s, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 6.89 (d, *J* = 8.3 Hz, 1 H), 4.80 (s, 1 H), 4.43 (dd, *J* = 11.2, 4.1 Hz, 1 H), 4.26 (dd, *J* = 11.2, 9.2 Hz, 1 H), 3.87 (s, 3 H), 2.87 (ddd, *J* = 9.2, 6.9, 4.1 Hz, 1 H), 1.73 (octet, *J* = 6.9 Hz, 1 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 169.8, 146.7, 145.4, 129.0, 120.0, 114.4, 109.9, 72.0, 58.9, 55.9, 53.1, 29.7, 18.9, 18.8; HRMS (FAB) Calculated for $C_{14}H_{20}NO_4$ 265.1314; Found 265.1305.

(3*S*,5*S*)-3-(4-amino-3-methylphenyl)-5-isopropylmorpholin-2-one (8f)

$[\alpha]_D^{25}$ –16.0 ° (c 4.45, $CHCl_3$); IR (film, cm^{-1}) 3447, 3367, 2962, 1733, 1628, 1508, 1471, 1287, 1210, 1159; ^1H NMR ($CDCl_3$) 7.07 (s, 1 H), 7.05 (d, *J* = 7.8 Hz, 1 H), 6.64 (d, *J* = 7.8 Hz, 1 H), 4.72 (s, 1 H), 4.41 (dd, *J* = 11.0, 4.1 Hz, 1 H), 4.23 (dd, *J* = 11.0, 9.4 Hz, 1 H), 3.87 (s, 3 H), 2.87 (ddd, *J* = 9.4, 6.9, 4.1 Hz, 1 H), 2.14 (s, 3 H), 1.69 (octet, *J* = 6.9 Hz, 1 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 170.3, 144.4, 129.3, 127.4, 125.8, 122.3, 114.9, 71.8, 59.1, 53.1, 29.6, 18.8, 18.7, 17.4; HRMS (FAB) Calculated for $C_{14}H_{20}N_2O_2$ 249.1603; Found 249.1594.

(3*S*,5*S*)-5-isopropyl-3-(5-methoxyfuran-2-yl)morpholin-2-one (8g)

$[\alpha]_D^{25}$ –89.9 ° (c 1.85, $CHCl_3$); IR (film, cm^{-1}) 3336, 2964, 2876, 1746, 1615, 1586, 1260, 1212, 1018; ^1H NMR ($CDCl_3$) 6.19 (d, *J* = 3.2 Hz, 1 H), 5.11 (d, *J* = 3.2 Hz, 1 H), 4.83 (s, 1 H), 4.42 (dd, *J* = 10.8, 3.6 Hz, 1 H), 4.21 (dd, *J* = 10.8, 10.5 Hz, 1 H), 3.83 (s, 3 H), 2.97 (ddd, *J* = 10.5, 6.9, 3.6 Hz, 1 H), 1.69 (octet, *J* = 6.9 Hz, 1 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 161.4, 140.3, 110.0, 80.1, 72.5, 57.8, 57.5, 55.1, 53.2, 29.6, 18.7, 18.6; HRMS (FAB) Calculated for $C_{12}H_{17}NO_4$ ($[M+H]^+$) 240.1236; Found 240.1244.

(3*S*,5*S*)-5-isopropyl-3-(2,4,6-trimethoxyphenyl)morpholin-2-one (8h)

$[\alpha]_D^{23}$ –17.7 ° (c 0.95, $CHCl_3$); IR (film, cm^{-1}) 2960, 2841, 1734, 1611, 1595, 1506, 1457, 1419, 1227, 1205, 1151, 1119; ^1H NMR ($CDCl_3$) 6.14 (s, 2 H), 5.15 (s, 1 H), 4.52 (dd, *J* = 11.2, 3.9 Hz, 1 H), 4.40 (dd, *J* = 11.2, 6.2 Hz, 1 H), 3.81 (s, 6 H), 3.80 (s, 3 H), 2.78 (ddd, *J* = 6.6, 6.2, 3.9 Hz, 1 H), 1.92 (octet, *J* = 6.6 Hz, 1 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 171.7, 161.3, 158.6,

108.4, 91.2, 70.8, 55.9, 55.8, 55.4, 49.2, 28.0, 19.4, 19.2; HRMS (FAB) Calculated for $C_{16}H_{24}NO_5$ ([M+H]$^+$) 310.1654; Found 310.1649.

methyl (*S*)-2-amino-2-(6-(benzyloxy)-7-(trifluoromethylsulfonyloxy)benzo[*d*][1,3]dioxol-4-yl)acetate (14)

To a solution of 108 mg (0.28 mmol) of **8a** and 45 μL (0.56 mmol) of pyridine in 3 mL of CH_2Cl_2 was added 47 μL (0.28 mmol) of trifluoromethanesulfonic anhydride at –10 °C. After stirring for 5 min, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The extracts were washed with brine, dried over Na_sSO_4, filtered, and evaporated under reduced pressure. A neutral silica gel separation employing a solvent gradient to 20% EtOAc in *n*-hexane afforded 143 mg (0.276 mmol, 99%) of triflate as a colorless oil. $[\alpha]_D^{26}$ –32.4 ° (c 1.90, $CHCl_3$); IR (film, cm^{-1}) 3338, 2965, 2907, 1740, 1500, 1462, 1426, 1213, 1139, 1094, 832; ^{1}H NMR ($CDCl_3$) 7.30-7.50 (m, 5 H), 6.43 (s, 1 H), 6.07 (d, *J* = 1.4 Hz, 1 H), 6.05 (d, *J* = 1.4 Hz, 1 H), 5.09 (s, 1 H), 5.07 (s, 1 H), 4.86 (s, 1 H), 4.43 (dd, *J* = 11.2, 4.1 Hz, 1 H), 4.27 (dd, *J* = 11.2, 9.2 Hz, 1 H), 2.81 (ddd, *J* = 9.2, 6.8, 4.1 Hz, 1 H), 1.73 (octet, *J* = 6.8 Hz, 1 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 168.3, 146.5, 140.9, 140.5, 135.6, 128.6, 128.5, 128.2, 127.5, 122.8, 118.6, 105.5, 103.3, 71.9, 71.6, 55.5, 54.2, 29.4, 18.8, 18.7; HRMS (FAB) Calculated for $C_{22}H_{22}F_3NO_8S$ ([M+H]$^+$) 518.1096; Found 518.1113.

To a solution of 101 mg (0.20 mmol) of the triflate in 2 mL of MeOH was added a catalytic amount of triethylamine at 0 °C. After stirring for 5 min, the solvent was removed under reduced pressure. A silica gel separation employing a solvent gradient to 20% EtOAc in *n*-hexane afforded 88 mg (0.164 mmol, 82%) of **13** as a yellow oil. $[\alpha]_D^{26}$ +18.4 ° (c 0.88, $CHCl_3$); IR (film, cm^{-1}) 3352, 2960, 2906, 1741, 1498, 1458, 1427, 1214, 1139, 1094, 832; ^{1}H NMR ($CDCl_3$) 7.30-7.50 (m, 5 H), 6.40 (s, 1 H), 6.07 (d, *J* = 1.4 Hz, 1 H), 6.06 (d, *J* = 1.4 Hz, 1 H), 5.08 (s, 2 H), 4.59 (s, 1 H), 3.70 (s, 3 H), 3.54 (dd, *J* = 11.0, 4.4 Hz, 1 H), 3.39 (dd, *J* = 11.0, 6.4 Hz, 1 H), 2.34 (ddd, *J* = 6.8, 6.4, 4.4 Hz, 1 H), 1.82 (octet, *J* = 6.8 Hz, 1 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 172.5, 152.2, 145.2, 142.6, 140.3, 128.5, 128.2, 127.5, 127.4, 122.6, 118.9, 104.2, 103.2, 71.8, 63.0, 61.0, 57.8, 52.7, 29.7, 19.4, 18.3; HRMS (FAB) Calculated for $C_{23}H_{27}F_3NO_9S$ ([M+H]$^+$) 550.1358; Found 550.1348.

To a solution of 13 mg (0.024 mmol) of **13** in 0.24 mL of MeOH and 0.06 mL of H_2O was added 17 mg (0.075 mmol) of orthoperiodic acid at rt, which was subsequently heated at 60 °C for 30 min. After cooling, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The extracts were washed with brine, dried over Na_sSO_4, filtered, and evaporated under reduced pressure. A silica gel separation employing a solvent gradient to 10% MeOH in CH_2Cl_2 afforded 8 mg (0.017 mmol, 71%) of **14** as a yellow oil. $[\alpha]_D^{26}$ +22.8 ° (c 0.35, $CHCl_3$); IR (film, cm^{-1}) 1743, 1505, 1458, 1426, 1217, 1138, 1095, 831; ^{1}H NMR ($CDCl_3$) 7.30-7.50 (m, 5 H), 6.46 (s, 1 H), 6.08 (d, *J* = 1.2 Hz, 1 H), 6.05 (d, *J* = 1.2 Hz, 1 H), 5.08 (s, 2 H), 4.66 (s, 1 H), 3.71 (s, 3 H), 1.86 (br s, 2 H); ^{13}C NMR ($CDCl_3$) 173.1, 146.7, 140.8, 140.4, 135.6, 128.5, 128.2, 127.5, 122.6, 120.1, 116.9, 104.1, 103.2, 71.8,

53.5, 52.7; HRMS (FAB) Calculated for $C_{18}H_{16}F_3NO_8S$ 463.0549; Found 463.0551.

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