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Synthesis of Chiral Benzoxa(thia)zepine and Pyridoxazepine Derivatives Using Palladium-Catalyzed Intramolecular Aryl Amination Reaction

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A palladium-catalyzed method employing different bulky biaryl phosphanes as ligands has been developed for the intramolecular amination of aryl bromides and iodides. A variety of aryl halide substrates have been aminated through the intramolecular pathway in good yield using different sugar-derived amines to give furo-benzoxa(thia)zepine and pyridoxazepine derivatives. The method is capable of furnishing chiral, enantiopure benzoxa(thia)zepines and pyridoxazepines of significant biological importance.

Introduction

Benzofused cyclic molecules that incorporate the nitrogen atom into the ring are capable of binding to multiple receptors with a high affinity, and hence, are described as "privileged structures."[1] Among them, medium-sized heterocycles, particularly seven-membered ring heterocycles, receive a great deal of attention, as these structural units are widely found in numerous natural products[2] and are also components of a number of biologically interesting molecules.[3] The abundance of oxygen-, nitrogen-, and sulfur-containing medium rings in pharmaceuticals and agrochemicals continues to ensure that they are important synthetic targets for organic chemists. Derivatives of 1,5-benzoxazepine exhibit a wide range of bioactivities, for example, as antidepressants, anxiolytics,[4] and antioxidant and lipid peroxidation inhibitors,[5] and are used for treating bronchial asthma or allergic bronchitis.[6] Several compounds contain this structural unit such as non-nucleoside HIV-1 reverse transcriptase and human adenosine kinase inhibitors,[7] 5HT2C and nonpeptidic vasopressin V2 receptor agonists, and calcium antagonists.[8] In addition, 1,5-benzothiazepines[9] and pyridoxazepines[10] have attracted attention for many reasons including their biological activities. As seven-membered rings are generally more difficult to prepare, because of enthalpic and entropic reasons, and direct cyclization methods are ineffective unless certain conformational constraints are present in the acyclic precursor,[11] only a few synthetic procedures are known for benzoxa(thia)zepines and pyridoxazepines. These include reductive ring expansion,[12] multicomponent reactions,[13] microwave-assisted synthesis,[5] or catalytic cyclization.[7a,7b,9,14] Most of these are either intermolecular, pertain to achiral substrates, use lengthy reaction sequences, or furnish low yields of products. A palladium-catalyzed sequential intra- and intermolecular aryl amination has been applied to the syntheses of benzazepine and benzoxazepine,[14h] however, these suffer from low yields of product (51–56%). In addition, because of preparation difficulties, the synthesis of benzothiazepine, generally less reported than benzoxazepine, is completely ignored. We were encouraged to apply the palladium-catalyzed aromatic C–N bond-forming reaction which involves the cross coupling of aryl halides (triflates, nonaflates, or mesylates) and amines. There has recently been an upsurge of interest in this method as a useful synthetic tool for this task.[15] A number of studies have reported that an intramolecular version of this aryl amination chemistry has been utilized for the synthesis of benzofused heterocycles.[16] The chiron approach to the synthesis of chiral target molecules involves the use of sugars as starting materials.[17] A key element in this strategy is the ability to form optically active heterocycles from carbohydrate molecules.[18] In a continuation of our research activities related to the synthesis of benzannulated medium-ring heterocycles through C–N/C–O bond formation,[16d,16g,19] we felt that an intramolecular cycloamination strategy leading to the formation of highly functionalized benzoxa(thia)zepine derivatives starting from carbohydrate precursors would be an interesting task.

In this paper, we report an intramolecular aryl amination strategy to furnish chiral tricyclic furo-benzoxa(thia)zepine and pyridoxazepine derivatives. The cleavage of the sugar ring in one of these tricyclic derivatives and appropriate follow-up reactions provide the chiral, functionalized benzoxazepine.

Results and Discussion

The starting material 1,2:5,6-di-*O*-isopropylidene allofuranose (**1**) was converted into the triflate derivative which

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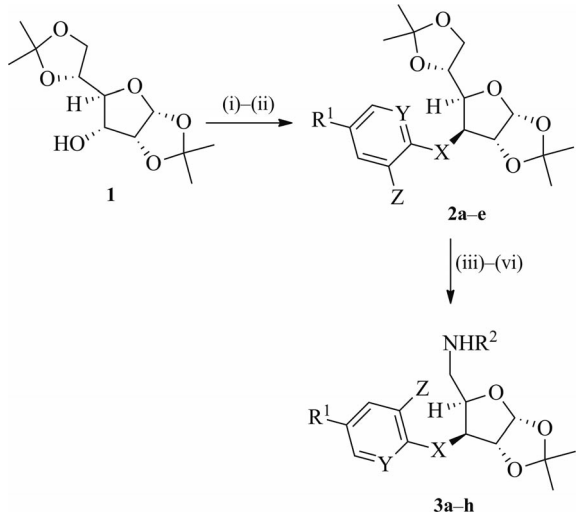
was subsequently treated with the 2-bromo/iodophenol/2-bromothiophenol derivatives to give 3-*O*-(2-bromophenyl) glucofuranosides **2a**–**c**, 3-*O*-(2-iodophenyl) glucofuranoside **2d**, and 3-*S*-(2-bromophenyl) glucofuranoside **2e** (Scheme 1 and Table 1). Selective removal of the 5,6-*O*-isopropylidene moiety from **2a**–**e** was smoothly effected with 70% aqueous HOAc at 25 °C. Oxidation of the resulting diol with $NaIO_4$, followed by imine formation by treatment with aliphatic amines, and subsequent $NaBH_4$ reduction in MeOH afforded the desired amines **3a**–**h** in good yields (Scheme 1 and Table 2). The structures of **3a**–**h** were supported by spectroscopic data and by comparison to data of similar compounds previously prepared by us.[20]



Scheme 1. Synthesis of *o*-bromo/iodophenyl/thiophenyl sugar amines **3a**–**h**. Reagents and conditions: (i) Tf_2O, pyridine, dry DCM (dichloromethane), –10 °C, 1 h, N_2; (ii) 2-bromo/iodophenol/2-bromothiophenol, K_2CO_3, dry CH_3CN, reflux, 6 h; (iii) HOAc (70%, v/v), room temp., overnight; (iv) aqueous $NaIO_4$, MeOH, room temp., 45 min; (v) R^2NH_2, anhydrous CH_2Cl_2, MS (molecular sieves, 4 Å), room temp., 12 h, N_2; (vi) $NaBH_4$, dry MeOH, room temp., 3 h.

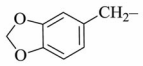
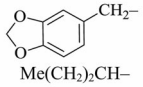
Table 1. Preparation of **2a**–**e** from **1**.

Entry	R^1	X	Y	Z	Product	Yield[a] [%]
1	H	O	CH	Br	**2a**	82
2	CN	O	CH	Br	**2b**	72
3	CH_3	O	N	Br	**2c**	78
4	H	O	CH	I	**2d**	80
5	H	S	CH	Br	**2e**	71

[a] Isolated yield.

Our initial goal was to explore the synthesis of benzoxazepine-annulated furanose derivatives **4** from **3** through a palladium-catalyzed intramolecular cycloamination reaction in the presence of bases and ligands. For this, we applied different reported reagent systems for the aryl amination reaction of substrate **3a**. Evaluation of these showed that the best conditions for this reaction were using $Pd_2(dba)_3$ (10 mol-%) as the palladium source,[16l] (±)-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, 7 mol-%)

Table 2. Preparation of sugar amines **3a**–**h**.

Entry	Substrate	R^2	Product	Yield[a] [%]
1	**2a**	$PhCH_2$–	**3a**	71
2	**2a**		**3b**	68
3	**2b**	$PhCH_2$–	**3c**	62
4	**2c**	$PhCH_2$–	**3d**	69
5	**2d**	Me_2CH–	**3e**	70
6	**2e**	$PhCH_2$–	**3f**	65
7	**2e**		**3g**	66
8	**2e**	$Me(CH_2)_2CH$–	**3h**	69

[a] Isolated yield.

as the ligand, a combination of K_2CO_3 (2.0 equiv.) with *t*BuOK (2.0 equiv.) as the base, and toluene (10 mL/mmol substrate) as the solvent (Table 3, Entry 3). Using a less or excess amount of catalyst as well as ligand gave a low yield of product **4a** (Table 3, Entries 2 and 4). Other catalytic systems like $Pd(PPh_3)_4$,[16p] $Pd_2(dba)_3$-dppf,[15d] or $Pd_2(dba)_3$-Xantphos[15c] were less effective (Table 3, Entries 1, 6, and 7). As an alternative palladium source, $Pd(OAc)_2$[15d] also gave the desired cyclized product, but did it less efficiently (Table 3, Entry 5). Changing the solvent to DMF (dimethylformamide)[16o] in place of toluene was also ineffective (Table 3, Entry 8).

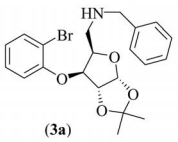
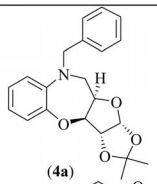
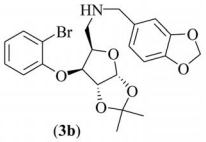
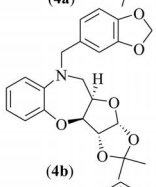
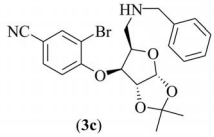
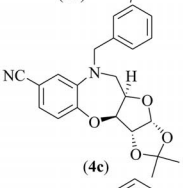
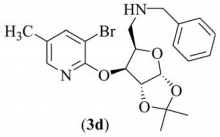
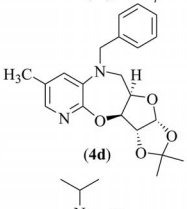
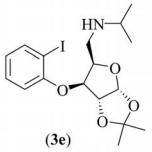
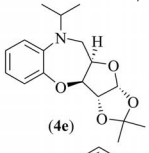
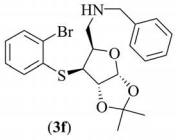
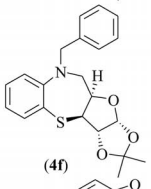
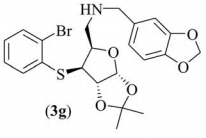
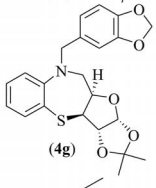
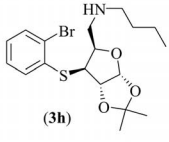
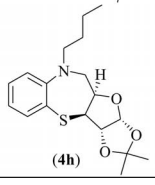
Table 3. Optimization of the intramolecular palladium-catalyzed cycloamination reaction of **3a**.

Entry	Reaction conditions[a]	Yield [%]
1	$Pd(PPh_3)_4$, K_2CO_3 + *t*BuONa, toluene, reflux, 24 h	n.r.[b]
2	$Pd_2(dba)_3$, (±)-BINAP, K_2CO_3 + *t*BuOK, toluene, reflux, 15 h	56[c]
3	$Pd_2(dba)_3$, (±)-BINAP, K_2CO_3 + *t*BuOK, toluene, reflux, 15 h	77
4	$Pd_2(dba)_3$, (±)-BINAP, K_2CO_3 + *t*BuOK, toluene, reflux, 18 h	74[d]
5	$Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, toluene, reflux, 16 h	53
6	$Pd_2(dba)_3$, dppf, *t*BuONa, toluene, reflux, 17 h	62
7	$Pd_2(dba)_3$, Xantphos, *t*BuOK, toluene, reflux, 19 h	58
8	$Pd_2(dba)_3$, (±)-BINAP, K_2CO_3 + *t*BuOK, DMF, 110 °C, 15 h	32

[a] Catalyst (10 mol-%), ligand (7 mol-%), for base pair (2 equiv. each) or a single base (4 equiv. each), solvent (10 mL/mmol). [b] NR = no reaction. [c] Catalyst (5 mol-%), ligand (3 mol-%). [d] Catalyst (15 mol-%), ligand (10 mol-%).

We then applied our standardized reagent system (conditions A) to the cycloamination reaction of synthesized haloamines **3b**–**h**. Although the yields of cyclized product for bromo substrates **3b**–**d** and **3f**–**h** were satisfactory (Table 4), that of iodo substrate **3e** was significantly lower (48%, see Table 4, Entry 5). We then applied different rea-

Table 4. Synthesis of benzoxa(thia)zepine and pyridoxazepine derivatives **4a**–**f**.[a]

Entry	Starting materials (sugar amines)	Reaction conditions	Time	Product	Yield[b] [%]
1	 (**3a**)	A	15 h	 (**4a**)	77
2	 (**3b**)	A	15 h	 (**4b**)	79
3	 (**3c**)	A	17 h	 (**4c**)	62
4	 (**3d**)	A	16 h	 (**4d**)	73
5	 (**3e**)	B	19 h	 (**4e**)	69[c]
6	 (**3f**)	A	19h	 (**4f**)	75
7	 (**3g**)	A	15 h	 (**4g**)	76
8	 (**3h**)	A	18 h	 (**4h**)	73

[a] Reagents and conditions: (A) $Pd_2(dba)_3$ (10 mol-%), (±)-BINAP (7 mol-%), K_2CO_3 (2.0 equiv.), *t*BuOK (2.0 equiv.), toluene (10 mL/mmol), reflux. (B) $Pd_2(dba)_3$ (10 mol-%), Xantphos (7 mol-%), *t*BuOK (4.0 equiv.), toluene (10 mL/mmol), reflux. [b] Isolated yield. [c] 48% for conditions A.

gent systems for the cyclization of **3e** and finally observed that our previously standardized reaction conditions required modification entailing the use of Xantphos[21] (7 mol-%) as the ligand and *t*BuOK (4.0 equiv.) as the base (conditions B, see Table 4, Entry 5). The structures of the cyclized products **4a**–**h** were supported by spectroscopic data and determined by single-crystal X-ray analysis[22] of **4a** (Figure 1).

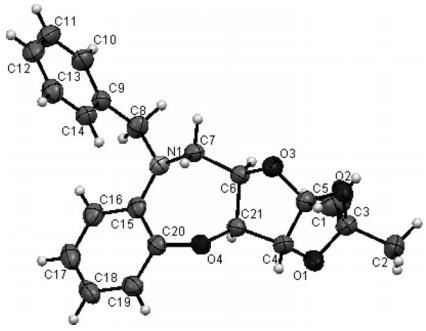
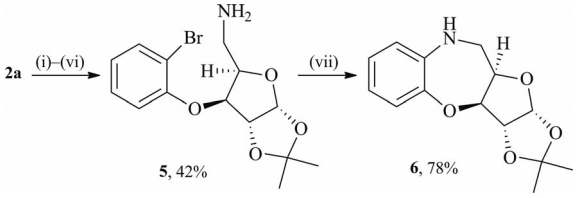


Figure 1. ORTEP diagram of **4a**.

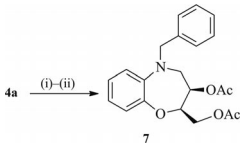
After successful tests with secondary amines, we focused on extending our methodology to the aryl amination of primary amines, realizing that the resulting secondary amine would be amenable to functionalization and give varying substituted products. For this purpose, we synthesized compound **5** from **2a** in 42% yield through a sequence of reactions beginning with the selective removal of the 5,6-*O*-isopropylidine moiety with 70% aqueous HOAc. Oxidation of the resulting diol with $NaIO_4$ and $NaBH_4$ reduction to the alcohol was followed by mesylation and azidation with NaN_3. Reduction with LAH (lithium aluminum hydride) afforded **5** which was heated to reflux under the standard conditions A described for the bromo derivatives to afford the desired cyclized product **6** in 78% yield (Scheme 2). The spectroscopic data of **6** were in agreement with the assigned structure.



Scheme 2. Synthesis of a 1,5-benzoxazepine from the primary amine. Reagents and conditions: (i) HOAc (70%, v/v), room temp., overnight; (ii) aqueous $NaIO_4$, MeOH, room temp., 45 min; (iii) $NaBH_4$, dry MeOH, room temp., 2 h; (iv) MsCl, Et_3N, dry DCM, room temp., 1 h, N_2; (v) NaN_3, dry DMF, 80 °C, 5 h, N_2; (vi) LAH, dry Et_2O, room temp., 3 h, N_2. (vii) $Pd_2(dba)_3$ (10 mol-%), (±)-BINAP (7 mol-%), K_2CO_3 and *t*BuOK (2 equiv. each), toluene, reflux, 14 h, N_2.

As an application of our methodology, we investigated the feasibility of synthesizing chiral functionalized benzoxazepines from the obtained annulated sugar derivatives. Thus, subjecting **4a** to a sequence of reactions involving removal of the 1,2-*O*-isopropylidine group with H_2SO_4 in $MeCN/H_2O$, cleavage of the diol with $NaIO_4$, reduction of

the generated carbonyl group with $NaBH_4$, and then acetylation with acetic anhydride and pyridine furnished benzoxazepine derivative **7** (Scheme 3).



Scheme 3. Conversion of **4a** to benzoxazepine derivative. Reagents and conditions: (i) $CH_3CN/H_2O/H_2SO_4$ (18:5:2), room temp., 24 h; (ii) aqueous $NaIO_4$, MeOH, room temp., 45 min; (iii) $NaBH_4$, MeOH, room temp., 3 h; (iv) Ac_2O, pyridine, room temp., 12 h, overall yield 63%.

Conclusions

In conclusion, we have developed a straightforward, efficient synthetic strategy for the palladium-catalyzed intramolecular C–N bond formation and demonstrated its applicability in the syntheses of benzoxa(thia)zepines and pyridoxazepines fused to a sugar template. The reaction was successful with a variety of D-glucose-derived secondary amines, and the products were smoothly converted to chiral benzoxazepines. These findings reveal the possibility of obtaining functionalized benzoxa(thia)zepines and pyridoxazepines in the chiral form.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectroscopic data were recorded with a Bruker AM 300L or Avance 600 MHz spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra were obtained with either a JEOL AX-500 or Micromass Q-Tof micro mass spectrometer. X-ray diffraction data were collected with a Bruker Kappa Apex II diffractometer. IR spectra were obtained employing a JASCO FTIR Model 410. Elemental analyses were carried out with a CHN analyzer. Specific rotations were measured at 589 nm with a JASCO P-1020 polarimeter. TLC was performed on precoated plates (0.25 mm, silica gel $60F_{254}$). Column chromatography and flash chromatography were carried out using commercial-grade silica gel (100–200 mesh or 230–400 mesh). PS and EA are abbreviations for petroleum ether (boiling range 60–80 °C) and ethyl acetate, respectively.

General Procedure for the Synthesis of Compounds 2a–e: To a magnetically stirred solution of 1,2:5,6-di-*O*-isopropylidine-α-D-allofuranose (**1**, 1.04 g, 4 mmol) in dry CH_2Cl_2 (10 mL) at –10 °C was added pyridine (1 mL) followed by trifluoromethanesulfonic anhydride (1.7 g, 1 mL, 6 mmol). The solution was stirred for 1 h under a N_2 atmosphere, and then it was poured onto crushed ice. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated to afford a gummy material that was dissolved in dry CH_3CN (25 mL). Anhydrous K_2CO_3 (1.4 g, 10 mmol) and an appropriately substituted 2-bromophenol/thiophenol (4.8 mmol) were added to the mixture which was then heated to reflux for 6 h until completion of reaction (indicated by TLC). The mixture was then filtered, and the filtrate was concentrated. The residue was diluted with H_2O, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated. Column chromatography over silica gel yielded the corresponding 3-*O*-bromophenyl derivatives.

(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromophenoxy)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (2a): Oil (1.36 g, 3.28 mmol, 82%); R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 11:1). $[\alpha]_D^{25}$ = –24.6 (*c* = 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.33 (s, 3 H), 1.44 (s, 3 H), 1.55 (s, 3 H), 4.13 (dd, *J* = 8.7, 5.4 Hz, 1 H), 4.22 (dd, *J* = 8.7, 6.3 Hz, 1 H), 4.33 (dd, *J* = 7.5, 3.0 Hz, 1 H), 4.57–4.63 (m, 2 H), 4.75 (d, *J* = 3.0 Hz, 1 H), 5.99 (d, *J* = 3.0 Hz, 1 H), 6.87–7.56 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 67.3 (CH_2), 72.3 (CH), 80.6 (CH), 81.4 (CH), 82.1 (CH), 105.4 (CH), 109.1 (C), 112.1 (C), 113.2 (C), 114.6 (CH), 122.9 (CH), 128.5 (CH), 133.7 (CH), 153.5 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2986, 2934, 2229, 1594, 1487 cm^{-1}. $C_{18}H_{23}BrO_6$ (415.28): calcd. C 52.06, H 5.58; found C 51.88, H 5.45. MS (ESI): *m*/*z* = 437 [M + Na]$^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-4-cyanophenoxy)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (2b): Foamy solid (1.268 g, 2.88 mmol, 72%). R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 11:1). $[\alpha]_D^{25}$ = –31.5 (*c* = 0.65, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.32 (s, 3 H), 1.42 (s, 3 H), 1.56 (s, 3 H), 4.09 (dd, *J* = 8.4, 5.1 Hz, 1 H), 4.20 (apparent dd, 1 H), 4.28 (dd, *J* = 8.1, 2.7 Hz, 1 H), 4.50–4.56 (m, 2 H), 4.80 (d, *J* = 2.4 Hz, 1 H), 5.99 (d, *J* = 3.6 Hz, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 7.85 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0 (CH_3), 26.1 (CH_3), 26.5 (CH_3), 26.7 (CH_3), 67.3 (CH_2), 71.9 (CH), 80.4 (CH), 81.6 (CH), 82.0 (CH), 105.2 (CH), 106.2 (C), 109.3 (C), 112.4 (C), 113.4 (C), 113.9 (CH), 117.3 (C), 132.9 (CH), 137.0 (CH), 157.0 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2986, 2934, 2229, 1594, 1487 cm^{-1}. $C_{19}H_{22}BrNO_6$ (440.29): calcd. C 51.83, H 5.04, N 3.18; found C 51.70, H 4.95, N 3.07. MS (ESI): *m*/*z* = 462 [M + Na]$^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-6-(3-Bromo-5-methylpyridine-2-yloxy)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]-dioxole (2c): Foamy solid (1.34 g, 3.12 mmol, 78%). R_f = 0.65 (PS/EA, 2:1), column eluent (PS/EA, 10:1). $[\alpha]_D^{25}$ = –21.4 (*c* = 0.22, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 6 H), 1.42 (s, 3 H), 1.56 (s, 3 H), 2.25 (s, 3 H), 4.11–4.21 (m, 2 H), 4.39 (dd, *J* = 6.9, 3.3 Hz, 1 H), 4.54 (dd, *J* = 12.6, 6.0 Hz, 1 H), 4.63 (d, *J* = 3.6 Hz, 1 H), 5.44 (d, *J* = 3.0 Hz, 1 H), 5.95 (d, *J* = 3.6 Hz, 1 H), 7.66 (d, *J* = 1.5 Hz, 1 H), 7.94 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9 (CH_3), 25.1 (CH_3), 26.2 (CH_3), 26.67 (CH_3), 26.69 (CH_3), 66.9 (CH_2), 72.6 (CH), 78.5 (CH), 79.9 (CH), 82.9 (CH), 105.0 (CH), 106.6 (C), 108.8 (C), 111.9 (C), 128.1 (C), 142.6 (CH), 145.0 (CH), 156.5 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2986, 2936, 2896, 1596, 1454 cm^{-1}. $C_{18}H_{24}BrNO_6$ (430.29): calcd. C 50.24, H 5.62, N 3.26; found C 50.08, H 5.48, N 3.18. MS (ESI): *m*/*z* = 452 [M + Na]$^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Iodophenoxy)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (2d): Thick oil (1.48 g, 3.2 mmol, 80%). R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 11:1). $[\alpha]_D^{25}$ = –28.8 (*c* = 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.34 (s, 3 H), 1.44 (s, 3 H), 1.55 (s, 3 H), 4.10–4.15 (m, 1 H), 4.23 (dd, *J* = 7.8, 6.3 Hz, 1 H), 4.29 (dd, *J* = 8.1, 3.0 Hz, 1 H), 4.58 (d, *J* = 3.9 Hz, 1 H), 4.63–4.69 (m, 1 H), 4.77 (d, *J* = 3.0 Hz, 1 H), 6.00 (d, *J* = 3.9 Hz, 1 H), 6.74–7.80 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 67.5 (CH_2), 72.3 (CH), 80.7 (CH), 81.3 (CH), 82.0 (CH), 87.3 (C), 105.3 (CH), 109.2 (C), 112.1 (C), 113.4 (CH), 123.5 (CH), 129.5 (CH), 139.8 (CH), 155.5 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3397, 2985, 2936, 1577, 1468, 1376, 1240 cm^{-1}.

$C_{18}H_{23}IO_6$ (462.28): calcd. C 46.77, H 5.01; found C 46.60, H 4.88. MS (ESI): m/z = 485 $[M + Na]^+$.

(3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromophenylsulfanyl)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (2e): Thick oil (1.224 g, 2.84 mmol, 71%). R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 11:1). $[\alpha]_D^{25}$ = –36.2 (c = 0.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 3 H), 1.35 (s, 3 H), 1.44 (s, 3 H), 1.54 (s, 3 H), 3.93 (d, J = 3.0 Hz, 1 H), 4.03–4.07 (m, 1 H), 4.15–4.19 (m, 1 H), 4.36–4.45 (m, 2 H), 4.59 (d, J = 3.3 Hz, 1 H), 5.94 (d, J = 3.3 Hz, 1 H), 7.07–7.59 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1 (CH_3), 26.2 (CH_3), 26.5 (CH_3), 26.8 (CH_3), 52.5 (CH), 67.6 (CH_2), 73.6 (CH), 79.9 (CH), 84.9 (CH), 105.0 (CH), 109.6 (C), 112.0 (C), 124.5 (C), 127.3 (CH), 127.9 (CH), 129.0 (CH), 133.2 (CH), 135.4 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2985, 2935, 2885, 1580, 1449, 1376 cm^{-1}. $C_{18}H_{23}BrO_5S$ (431.34): calcd. C 50.12, H 5.37; found C 49.94, H 5.24. MS (ESI): m/z = 453 $[M + Na]^+$ for ^{79}Br.

General Procedure for the Synthesis of Compounds 3a–h: Each compound **2a**–**e** (2 mmol) was dissolved in aqueous HOAc (70%, v/v, 60 mL), and the solution was stirred overnight at room temperature (monitored by TLC until the starting material disappeared). Removal of the HOAc with a rotary evaporator (40 °C) using anhydrous toluene (3 × 50 mL) afforded the intermediate diol as a highly viscous syrup. A solution of the diol in methanol (10 mL) was cooled to 0 °C and slowly treated with a solution of $NaIO_4$ (513 mg, 2.4 mmol) dissolved in water (5 mL). The reaction mixture was stirred for 45 min and then was filtered (using a sintered funnel). The filtrate was evaporated under reduced pressure, and the residue was extracted with $CHCl_3$ (4 × 30 mL). The combined organic layers were washed with water, dried, and evaporated to afford the crude aldehyde. This aldehyde was dissolved in dry CH_2Cl_2 (35 mL), and the resulting solution was treated with activated molecular sieves (4 Å) and the appropriate amine (2.4 mmol) at 0 °C. The mixture was then stirred at room temperature for 12 h under a N_2 atmosphere. Dry MeOH (15 mL) was added followed by the addition in small portions of $NaBH_4$ (151 mg, 4 mmol) over a period of 1 h at 0 °C. Stirring was continued for another 2 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were washed with water, dried, and evaporated. Chromatography over silica gel afforded amine **3a**–**h**.

(3a*R*,5*R*,6*S*,6a*R*)-*N*-Benzyl-[6-(2-bromophenoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]amine (3a): Thick oil (0.616 g, 1.42 mmol, 71%). R_f = 0.3 (PS/EA, 2:1), column eluent (PS/EA, 4:1). $[\alpha]_D^{25}$ = –48.2 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.53 (s, 3 H), 1.64 (s, 1 H), 3.08 (dd, J = 12.3, 5.4 Hz, 1 H), 3.21 (dd, J = 12.3, 7.2 Hz, 1 H), 3.84 (s, 2 H), 4.51–4.57 (m, 1 H), 4.60 (d, J = 3.9 Hz, 1 H), 4.65 (d, J = 3.3 Hz, 1 H), 6.00 (d, J = 3.3 Hz, 1 H), 6.86–6.91 (m, 1 H), 7.01 (d, J = 8.1 Hz, 1 H), 7.22–7.56 (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3 (CH_3), 26.6 (CH_3), 47.4 (CH_2), 54.2 (CH_2), 79.5 (CH), 81.8 (CH), 82.3 (CH), 105.0 (CH), 111.8 (C), 112.9 (C), 113.9 (CH), 122.7 (CH), 126.9 (CH), 128.17 (2 CH), 128.19 (2 CH), 128.3 (CH), 133.7 (CH), 140.0 (C), 153.4 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3328, 3062, 2984, 2929, 2854, 1663, 1581 cm^{-1}. $C_{21}H_{24}BrNO_4$ (434.32): calcd. C 58.07, H 5.57, N 3.22; found C 57.88, H 5.43, N 3.08. MS (ESI): m/z = 456 $[M + Na]^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-*N*-(1,3-Benzodioxol-5-ylmethyl)-[6-(2-bromophenoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]-amine (3b): Gummy material (0.65 g, 1.36 mmol, 68%). R_f = 0.3 (PS/EA, 2:1), column eluent (PS/EA, 4:1). $[\alpha]_D^{25}$ = –39.3 (c = 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.53 (s, 3 H), 3.05 (dd, J = 12.3, 5.4 Hz, 1 H), 3.17 (dd, J = 12.3, 7.2 Hz, 1 H), 3.74 (s, 2 H), 4.49–4.55 (m, 1 H), 4.59 (d, J = 3.9 Hz, 1 H), 4.64 (d, J = 3.3 Hz, 1 H), 5.92 (s, 2 H), 5.99 (d, J = 3.9 Hz, 1 H), 6.70–6.77 (m, 2 H), 6.81 (s, 1 H), 6.89 (t, J = 7.5 Hz, 1 H), 7.01 (d, J = 8.1 Hz, 1 H), 7.26–7.56 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_3), 26.6 (CH_3), 47.1 (CH_2), 53.9 (CH_2), 79.4 (CH), 81.7 (CH), 82.2 (CH), 100.7 (CH_2), 104.9 (CH), 107.9 (CH), 108.6 (CH), 111.7 (C), 112.8 (C), 113.8 (CH), 121.2 (CH), 122.7 (CH), 128.4 (CH), 133.6 (CH), 133.9 (C), 146.3 (C), 147.5 (C), 153.3 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3341, 2984, 2931, 1581, 1482 cm^{-1}. $C_{22}H_{24}BrNO_6$ (478.33): calcd. C 55.24, H 5.06, N 2.93; found C 55.02, H 4.93, N 2.78. MS (ESI): m/z = 478 $[M + Na]^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-*N*-Benzyl-[6-(2-bromo-4-cyanophenoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]amine (3c): Gummy material (0.57 g, 1.24 mmol, 62%). R_f = 0.3 (PS/EA, 2:1), column eluent (PS/EA, 4:1). $[\alpha]_D^{25}$ = –51.2 (c = 1.12, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.53 (s, 3 H), 1.61 (s, 1 H), 3.03 (dd, J = 12.3, 6.0 Hz, 1 H), 3.19 (dd, J = 12.3, 7.2 Hz, 1 H), 3.82 (s, 2 H), 4.51–4.56 (m, 2 H), 4.69 (d, J = 3.3 Hz, 1 H), 5.99 (d, J = 3.9 Hz, 1 H), 7.08 (d, J = 8.7 Hz, 1 H), 7.21–7.32 (m, 5 H), 7.61 (dd, J = 8.4, 1.8 Hz, 1 H) 7.84 (d, J = 2.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_3), 26.5 (CH_3), 47.0 (CH_2), 54.1 (CH_2), 79.2 (CH), 82.1 (CH), 82.2 (CH), 104.8 (CH), 106.1 (C), 112.1 (C), 113.3 (C), 113.5 (CH), 117.3 (C), 127.0 (CH), 128.0 (2 CH), 128.3 (2 CH), 133.0 (CH), 137.0 (CH), 139.8 (C), 157.0 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3340, 2985, 2931, 2228, 1594, 1487, 1378 cm^{-1}. $C_{22}H_{23}BrN_2O_4$ (459.33): calcd. C 57.53, H 5.05, N 6.10; found C 57.31, H 4.95, N 5.98. MS (ESI): m/z = 459 $[M + H]^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-*N*-Benzyl-[6-(3-bromo-5-methylpyridine-2-yloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]amine (3d): Gummy material (0.62 g, 1.38 mmol, 69%). R_f = 0.25 (PS/EA, 2:1), column eluent (PS/EA, 3:1). $[\alpha]_D^{25}$ = –38.7 (c = 0.36, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.54 (s, 3 H), 2.24 (s, 3 H), 2.95 (dd, J = 12.3, 5.4 Hz, 1 H), 3.10 (dd, J = 12.3, 7.5 Hz, 1 H), 3.79 (dd, J = 18.0, 13.2 Hz, 2 H), 4.54–4.59 (m, 1 H), 4.67 (d, J = 3.6 Hz, 1 H), 5.39 (d, J = 3.0 Hz, 1 H), 5.98 (d, J = 3.9 Hz, 1 H), 7.18–7.31 (m, 5 H), 7.65 (d, J = 1.5 Hz, 1 H) 7.89 (d, J = 1.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$,0): δ = 16.9 (CH_3), 26.3 (CH_3), 26.7 (CH_3), 47.5 (CH_2), 54.1 (CH_2), 79.0 (2 CH), 83.5 (CH), 104.7 (CH), 106.8 (C), 111.7 (C), 126.8 (CH), 128.10 (2 CH), 128.19 (C), 128.2 (2 CH), 140.1 (C), 142.7 (CH), 145.0 (CH), 156.7 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3343, 2983, 2930, 1596, 1454, 1380, 1290 cm^{-1}. $C_{21}H_{25}BrN_2O_4$ (449.34): calcd. C 56.13, H 5.61, N 6.23; found C 55.92, H 5.46, N 6.07. MS (ESI): m/z = 449 $[M + H]^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-*N*-[6-(2-Iodophenoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]isopropylamine (3e): Gummy material (0.606 g, 1.4 mmol, 70%). R_f = 0.3 (PS/EA, 2:1), column eluent (PS/EA, 4:1). $[\alpha]_D^{25}$ = –31.2 (c = 0.45, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.10 (m, 6 H), 1.31 (s, 3 H), 1.54 (s, 3 H), 1.62 (s, 1 H), 2.85–2.89 (m, 1 H), 3.09–3.23 (m, 2 H), 4.53–4.67 (m, 3 H), 6.00 (s, 1 H), 6.77 (s, 1 H), 6.95 (d, J = 7.8 Hz, 1 H), 7.32 (d, J = 6.6 Hz, 1 H), 7.79 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 (CH_3), 22.9 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 45.9 (CH_2), 49.0 (CH), 79.6 (CH), 81.8 (CH), 82.2 (CH), 86.9 (C), 104.9 (CH), 111.8 (C), 112.7 (CH), 123.3 (CH), 129.5 (CH), 139.8 (CH), 155.4 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3403, 2963, 1577, 1467, 1375, 1240, 1164 cm^{-1}. $C_{17}H_{24}INO_4$ (433.28): calcd. C 47.12, H 5.58, N 3.23; found C 46.93, H 5.41, N 3.03. MS (ESI): m/z = 434 $[M + H]^+$.

(3a*R*,5*R*,6*S*,6a*R*)-*N*-Benzyl-[6-(2-bromophenylsulfanyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]amine (3f): Thick oil (0.585 g, 1.3 mmol, 65%). R_f = 0.3 (PS/EA, 2:1), column eluent (PS/EA, 4:1). $[\alpha]_D^{25}$ = –43.7 (*c* = 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3 H), 1.52 (s, 3 H), 1.65 (s, 1 H), 2.99 (dd, *J* = 12.3, 5.4 Hz, 1 H), 3.09 (dd, *J* = 10.8, 7.5 Hz, 1 H), 3.80 (d, *J* = 3.9 Hz, 1 H), 3.86 (d, *J* = 3.6 Hz, 2 H), 4.57 (d, *J* = 3.6 Hz, 1 H), 4.66–4.71 (m, 1 H), 5.97 (d, *J* = 3.6 Hz, 1 H), 7.08–7.35 (m, 6 H), 7.41 (dd, *J* = 7.8, 1.5 Hz, 2 H), 7.58–7.61 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_3), 26.4 (CH_3), 49.2 (CH_2), 54.0 (CH_2), 78.2 (CH), 85.0 (CH), 104.7 (CH), 111.7 (C), 125.2 (C), 126.8 (CH), 127.7 (CH), 128.0 (3 CH), 128.2 (2 CH), 129.7 (CH), 133.3 (CH), 135.1 (C), 139.7 (C), 160.2 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3330, 2985, 2934, 2834, 1950, 1662, 1577 cm^{-1}. $C_{21}H_{24}BrNO_3S$ (450.39): calcd. C 56.00, H 5.37, N 3.11; found C 55.76, H 5.23, N 2.95. MS (ESI): *m*/*z* = 450 $[M + H]^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-*N*-(1,3-Benzodioxol-5-ylmethyl)-[6-(2-bromophenylsulfanyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]amine (3g): Oil (0.65 g, 1.32 mmol, 66%). R_f = 0.3 (PS/EA, 2:1), column eluent (PS/EA, 4:1). $[\alpha]_D^{25}$ = –36.8 (*c* = 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 3 H), 1.47 (s, 3 H), 1.59 (s, 1 H), 2.95 (dd, *J* = 12.3, 5.4 Hz, 1 H), 3.05 (dd, *J* = 12.3, 7.2 Hz, 1 H), 3.69 (d, *J* = 5.4 Hz, 2 H), 4.63–4.69 (m, 1 H), 5.11 (apparent d, 1 H), 5.29 (d, *J* = 3.3 Hz, 1 H), 5.93 (s, 2 H), 5.96 (d, *J* = 3.6 Hz, 1 H), 6.75 (s, 1 H), 6.79–6.85 (m, 2 H), 7.08–7.61 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.7 (CH_3), 28.1 (CH_3), 45.6 (CH_2), 52.8 (CH_2), 78.3 (CH), 83.6 (CH), 85.1 (CH), 100.8 (CH_2), 104.8 (CH), 106.0 (CH), 108.0 (CH), 111.9 (C), 121.2 (CH), 125.4 (C), 127.8 (CH), 128.1 (CH), 130.0 (CH), 133.4 (CH), 133.9 (C), 135.2 (C), 146.5 (C), 147.6 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3327, 2965, 2618, 1663, 1451, 1376, 1322 cm^{-1}. $C_{22}H_{24}BrNO_5S$ (494.39): calcd. C 53.45, H 4.89, N 2.83; found C 53.23, H 4.63, N 2.71. MS (ESI): *m*/*z* = 494 $[M + H]^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-*N*-[6-(2-Bromophenylsulfanyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-ylmethyl]butylamine (3h): Oil (0.575 g, 1.38 mmol, 69%). R_f = 0.3 (PS/EA, 2:1), column eluent (PS/EA, 4:1). $[\alpha]_D^{25}$ = –38.5 (*c* = 0.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H), 1.32–1.39 (m, 2 H), 1.44 (s, 3 H), 1.46 (s, 3 H), 1.49–1.51 (m, 2 H), 1.53 (s, 1 H), 2.58–2.69 (m, 2 H), 2.96 (dd, *J* = 12.3, 5.1 Hz, 1 H), 3.05 (dd, *J* = 12.3, 7.8 Hz, 1 H), 4.65–4.71 (m, 1 H), 5.09 (apparent d, 1 H), 5.28 (d, *J* = 3.3 Hz, 1 H), 6.05 (d, *J* = 5.4 Hz, 1 H), 7.10–7.62 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 20.2 (CH_2), 27.7 (CH_3), 28.0 (CH_3), 32.0 (CH_2), 46.6 (CH_2), 49.0 (CH_2), 78.2 (CH), 83.6 (CH), 98.4 (CH), 106.0 (CH), 111.8 (C), 125.4 (C), 127.7 (CH), 128.0 (CH), 129.9 (CH), 133.4 (CH), 135.1 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3404, 2931, 2864, 1661, 1455, 1376, 1321 cm^{-1}. $C_{18}H_{26}BrNO_3S$ (416.37): calcd. C 51.92, H 6.29, N 3.36; found C 51.78, H 6.11, N 3.18. MS (ESI): *m*/*z* = 416 $[M + H]^+$ for ^{79}Br.

(3a*R*,5*R*,6*S*,6a*R*)-[6-(2-Bromophenoxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]methylamine (5): To an ice-cold, stirred solution of the aldehyde derived from compound **2a** (3 mmol), prepared by the above procedure, dissolved in dry MeOH (30 mL) was added $NaBH_4$ (220 mg, 6 mmol) in small portions over 1 h. The stirring was continued for another 1 h at room temperature to complete the reaction. The solvent was evaporated under reduced pressure, and the residue was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were washed with water and dried with Na_2SO_4. Evaporation of the solvent afforded the alcohol as a crude oil. To an ice-cold, stirred solution of this alcohol in CH_2Cl_2 (25 mL) was added Et_3N (5 mL). The reaction mixture was stirred for 15 min under a N_2 atmosphere. Methanesulfonyl chloride (0.6 mL) was added dropwise. After 1 h, the mixture was poured onto crushed ice, and the resulting solution was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with water and dried with Na_2SO_4. Evaporation of the solvent afforded the mesylate as a brown, gummy material which was dissolved in dry DMF (20 mL). NaN_3 (1.95 g, 30 mmol) was added, and the mixture was heated to 80 °C for 5 h under a N_2 atmosphere and then filtered. The filtrate was extracted with ethyl acetate (3 × 25 mL), and the combined organic layers were washed with water and dried with Na_2SO_4. Evaporation of the solvent afforded the azide as a syrupy liquid which was dissolved in dry Et_2O (20 mL). This solution was added dropwise to a stirred suspension of LAH (275 mg, 7 mmol) in dry Et_2O (20 mL) at 0 °C under a N_2 atmosphere. After 3 h of stirring, a saturated solution of Na_2SO_4 (2 mL) was added dropwise. The mixture was filtered, washed, and evaporated. Column chromatography over neutral alumina afforded the desired amine as a colorless, thick oil (0.435 g, 1.26 mmol, 42%). R_f = 0.4 (PS/EA, 1:1), column eluent (PS/EA, 2:1). $[\alpha]_D^{25}$ = –53.7 (*c* = 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.47 (s, 2 H), 1.55 (s, 3 H), 3.16 (dd, *J* = 13.2, 6.0 Hz, 1 H), 3.26 (dd, *J* = 13.2, 6.6 Hz, 1 H), 4.39–4.44 (m, 1 H), 4.60 (d, *J* = 3.9 Hz, 1 H), 4.69 (d, *J* = 3.3 Hz, 1 H), 6.02 (d, *J* = 4.2 Hz, 1 H), 6.87–7.57 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_3), 26.6 (CH_3), 40.5 (CH_2), 81.2 (CH), 81.8 (CH), 82.3 (CH), 104.9 (CH), 111.8 (C), 112.8 (C), 113.8 (CH), 122.8 (CH), 128.5 (CH), 133.7 (CH), 153.3 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3382, 2983, 2935, 2102, 1590, 1477 cm^{-1}. $C_{14}H_{18}BrNO_4$ (344.20): calcd. C 48.85, H 5.27, N 4.07; found C 48.61, H 5.11, N 3.85. MS (ESI): *m*/*z* = 344 $[M + H]^+$ for ^{79}Br.

General Procedure for the Cycloamination Reaction of 3a–h, and 5: To a solution of each amine **3a**–**d**, **f**–**h**, and **5** (1 mmol) in dry toluene (10 mL/mmol substrate) were added *t*BuOK (224 mg, 2 equiv.), K_2CO_3 (276 mg, 2 equiv.), $Pd_2(dba)_3$ (10 mol-%), and (±)-BINAP (7 mol-%). To a solution of amine **3e** (1 mmol) in dry toluene (10 mL/mmol substrate) were added *t*BuOK (448 mg, 4 equiv.), $Pd_2(dba)_3$ (10 mol-%), and Xantphos (7 mol-%). The reaction mixtures were heated at reflux for 15 h under an argon atmosphere. After completion of each reaction (monitored by TLC), the crude mixtures were passed through a bed of silica gel. The solvents were evaporated, and the residues were extracted with CH_2Cl_2 (4 × 25 mL). The organic layers were washed with water and then dried. The solvents were evaporated under reduced pressure to give the crude products which were purified by column chromatography over silica gel to furnish each pure cyclized product **4a**–**h**, and **6**.

(2*R*,3*R*,3a*S*,10a*R*)-9-Benzyl-2,3-isopropylidenedioxy-2,3,3a,9,10,10a-hexahydro-2*H*-furo[3,2-*c*][1,5]benzoxazepine (4a): Crystalline solid (0.27 g, 0.77 mmol, 77%); m.p. 162 °C. R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 11:1). $[\alpha]_D^{25}$ = +36.9 (*c* = 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.48 (s, 3 H), 3.39 (dd, *J* = 13.8, 6.3 Hz, 1 H), 3.78 (dd, *J* = 13.8, 9.9 Hz, 1 H), 4.36 (d, *J* = 15.6 Hz, 1 H), 4.50–4.57 (m, 2 H), 4.62 (d, *J* = 3.0 Hz, 1 H), 4.76 (d, *J* = 3.6 Hz, 1 H), 6.02 (d, *J* = 3.6 Hz, 1 H), 6.65–7.36 (m, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 26.4 (CH_3), 27.0 (CH_3), 51.8 (CH_2), 56.4 (CH_2), 77.9 (CH), 84.5 (CH), 85.3 (CH), 105.9 (CH), 111.8 (C), 116.3 (CH), 119.4 (CH), 121.0 (CH), 123.8 (CH), 127.2 (3 CH), 128.6 (2 CH), 138.1 (C), 141.2 (C), 147.0 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2990, 2938, 1598, 1498, 1449 cm^{-1}. $C_{21}H_{23}NO_4$ (353.41): calcd. C 71.37, H 6.56, N 3.96; found C 71.13, H 6.40, N 3.82. MS (ESI): *m*/*z* = 376 $[M + Na]^+$.

(2*R*,3*R*,3a*S*,10a*R*)-9-(1,3-Benzodioxol-5-yl-methyl)-2,3-isopropylidenedioxy-2,3,3a,9,10,10a-hexahydro-2*H*-furo[3,2-*c*][1,5]-benzoxazepine (4b): Foamy solid (0.315 g, 0.79 mmol, 79%). R_f =

0.7 (PS/EA, 2:1), column eluent (PS/EA, 9:1). $[\alpha]_D^{25}$ = +49.3 (*c* = 1.15, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.49 (s, 3 H), 3.37 (dd, *J* = 13.8, 6.0 Hz, 1 H), 3.72 (dd, *J* = 13.8, 9.9 Hz, 1 H), 4.24 (d, *J* = 15.3 Hz, 1 H), 4.43 (d, *J* = 15.3 Hz, 1 H), 4.49–4.55 (m, 1 H), 4.60 (d, *J* = 3.0 Hz, 1 H), 4.76 (d, *J* = 3.6 Hz, 1 H), 5.94 (s, 2 H), 6.02 (d, *J* = 3.9 Hz, 1 H), 6.67–7.33 (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_3), 26.8 (CH_3), 51.3 (CH_2), 56.0 (CH_2), 77.9 (CH), 84.4 (CH), 85.1 (CH), 100.8 (CH_2), 105.8 (CH), 107.6 (CH), 108.1 (CH), 111.6 (C), 116.3 (CH), 119.3 (CH), 120.3 (CH), 120.9 (CH), 123.6 (CH), 131.8 (C), 141.1 (C), 146.6 (C), 146.9 (C), 147.8 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2979, 2934, 1600, 1495, 1444 cm^{-1}. $C_{22}H_{23}NO_6$ (397.42): calcd. C 66.49, H 5.83, N 3.52; found C 66.27, H 5.61, N 3.38. MS (ESI): *m*/*z* = 420 [M + Na]$^+$.

(2*R*,3*R*,3a*S*,10a*R*)-9-Benzyl-2,3-isopropylidenedioxy-7-cyano-2,3,3a,9,10,10a-hexahydro-2*H*-furo[3,2-*c*][1,5]benzoxazepine (4c): Gummy material (0.235 g, 0.62 mmol, 62%). R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 9:1). $[\alpha]_D^{25}$ = +58.4 (*c* = 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.48 (s, 3 H), 3.43 (dd, *J* = 13.8, 6.3 Hz, 1 H), 3.74 (dd, *J* = 13.8, 10.2 Hz, 1 H), 4.32 (d, *J* = 15.8 Hz, 1 H), 4.48–4.57 (m, 2 H), 4.66 (d, *J* = 3.0 Hz, 1 H), 4.76 (d, *J* = 3.6 Hz, 1 H), 6.02 (d, *J* = 3.6 Hz, 1 H), 6.88–7.39 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3 (CH_3), 26.8 (CH_3), 51.7 (CH_2), 56.3 (CH_2), 77.1 (CH), 84.2 (CH), 85.6 (CH), 106.0 (CH), 107.2 (C), 112.1 (C), 119.1 (C), 119.4 (CH), 121.9 (C), 123.6 (CH), 127.1 (2 CH), 127.7 (CH), 128.9 (2 CH), 136.6 (CH), 141.9 (C), 150.3 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2985, 2936, 2225, 1595, 1501, 1428 cm^{-1}. $C_{22}H_{22}N_2O_4$ (378.42): calcd. C 69.83, H 5.86, N 7.40; found C 69.67, H 5.68, N 7.26. MS (ESI): *m*/*z* = 401 [M + Na]$^+$.

(2*R*,3*R*,3a*S*,10a*R*)-9-Benzyl-2,3-isopropylidenedioxy-7-methyl-2,3,3a,9,10,10a-hexahydro-5-aza-2*H*-furo[3,2-*c*][1,5]benzoxazepine (4d): Gummy material (0.27 g, 0.73 mmol, 73%). R_f = 0.65 (PS/EA, 2:1), column eluent (PS/EA, 9:1). $[\alpha]_D^{25}$ = +21.9 (*c* = 0.85, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.48 (s, 3 H), 2.15 (s, 3 H), 3.40 (dd, *J* = 13.8, 6.6 Hz, 1 H), 3.71 (dd, *J* = 13.8, 10.2 Hz, 1 H), 4.28 (d, *J* = 15.6 Hz, 1 H), 4.51–4.56 (m, 2 H), 4.73 (d, *J* = 2.7 Hz, 1 H), 4.87 (d, *J* = 3.3 Hz, 1 H), 6.03 (d, *J* = 3.6 Hz, 1 H), 6.77 (s, 1 H), 7.22–7.38 (m, 5 H), 7.49 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 51.6 (CH_2), 55.8 (CH_2), 77.5 (CH), 84.0 (CH), 84.2 (CH), 106 (CH), 111.9 (C), 124.5 (CH), 127.2 (2 CH), 127.4 (CH), 128.7 (2 CH), 129.6 (C), 135.8 (C), 136.9 (CH), 137.2 (C), 150.9 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2986, 2934, 1590, 1454, 1377, 1246 cm^{-1}. $C_{21}H_{24}N_2O_4$ (368.43): calcd. C 68.46, H 6.57, N 7.60; found C 68.24, H 6.39, N 7.44. MS (ESI): *m*/*z* = 391 [M + Na]$^+$.

(2*R*,3*R*,3a*S*,10a*R*)-9-Isopropyl-2,3-isopropylidenedioxy-2,3,3a,9,10,10a-hexahydro-2*H*-furo[3,2-*c*][1,5]benzoxazepine (4e): Foamy solid (0.21 g, 0.69 mmol, 69%). R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 9:1). $[\alpha]_D^{25}$ = +47.4 (*c* = 1.11, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.6 Hz, 3 H), 1.24 (d, *J* = 6.9 Hz, 3 H), 1.34 (s, 3 H), 1.52 (s, 3 H), 3.36 (dd, *J* = 14.1, 9.9 Hz, 1 H), 3.47 (dd, *J* = 14.1, 6.3 Hz, 1 H), 3.86 (t, *J* = 6.6 Hz, 1 H), 4.48–4.54 (m, 1 H), 4.58 (d, *J* = 3.0 Hz, 1 H), 4.73 (d, *J* = 3.9 Hz, 1 H), 6.05 (d, *J* = 3.6 Hz, 1 H), 6.63–6.73 (m, 2 H), 6.86–6.94 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3 (CH_3), 21.6 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 44.6 (CH_2), 47.8 (CH), 79.6 (CH), 84.4 (CH), 84.5 (CH), 106.1 (CH), 111.8 (C), 115.1 (CH), 118.4 (CH), 121.1 (CH), 123.6 (CH), 141.5 (C), 146.6 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2980, 2941, 2889, 1597, 1496, 1381 cm^{-1}. $C_{17}H_{23}NO_4$ (305.37): calcd. C 66.86, H 7.59, N 4.59; found C 66.58, H 7.41, N 4.39. MS (ESI): *m*/*z* = 328 [M + Na]$^+$.

(2*R*,3*R*,3a*S*,10a*R*)-9-Benzyl-2,3-isopropylidenedioxy-2,3,3a,9,10,10a-hexahydro-2*H*-furo[3,2-*c*][1,5]benzothiazepine (4f): Foamy solid (0.275 g, 0.75 mmol, 75%). R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 9:1). $[\alpha]_D^{25}$ = +29.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.48 (s, 3 H), 3.40 (dd, *J* = 14.4, 4.8 Hz, 1 H), 4.21 (d, *J* = 3.9 Hz, 1 H), 4.36 (dd, *J* = 14.4, 9.6 Hz, 1 H), 4.41 (d, *J* = 6.9 Hz, 1 H), 4.51–4.56 (m, 3 H), 5.91 (d, *J* = 3.6 Hz, 1 H), 6.62–7.52 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.4 (CH_3), 26.8 (CH_3), 51.5 (CH_2), 53.5 (CH), 56.6 (CH_2), 76.8 (CH), 84.5 (CH), 105.7 (CH), 111.8 (C), 116.5 (CH), 119.2 (CH), 119.5 (C), 127.2 (3 CH), 127.5 (CH), 128.6 (2 CH), 131.4 (CH), 137.8 (C), 149.2 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2986 cm^{-1}. HRMS: calcd. for $C_{21}H_{23}NO_3SNa^+$ $[M + Na]^+$ 392.1296; found 392.1302.

(2*R*,3*R*,3a*S*,10a*R*)-9-(1,3-Benzodioxol-5-yl-methyl)-2,3-isopropylidenedioxy-2,3,3a,9,10,10a-hexahydro-2*H*-furo[3,2-*c*][1,5]benzothiazepine (4g): Gummy material (0.315 g, 0.76 mmol, 76%). R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 9:1). $[\alpha]_D^{25}$ = +32.2 (*c* = 0.68, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.49 (s, 3 H), 3.37 (dd, *J* = 14.7, 4.8 Hz, 1 H), 4.17 (d, *J* = 3.9 Hz, 1 H), 4.29 (d, *J* = 15.6 Hz, 1 H), overlapped with 4.29–4.34 (m, 1 H), 4.43 (d, *J* = 15.6 Hz, 1 H), 4.51–4.55 (m, 2 H), 5.91 (d, *J* = 3.9 Hz, 1 H), 5.94 (d, *J* = 2.1 Hz, 2 H), 6.64–6.78 (m, 4 H), 6.98 (d, *J* = 6.9 Hz, 1 H), 7.18 (dd, *J* = 7.8, 1.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3 (CH_3), 26.7 (CH_3), 51.3 (CH_2), 53.4 (CH), 56.4 (CH_2), 76.7 (CH), 84.4 (CH), 100.9 (CH_2), 105.6 (CH), 107.7 (CH), 108.3 (CH), 111.7 (C), 116.5 (CH), 119.3 (CH), 119.8 (C), 120.3 (CH), 127.5 (CH), 131.4 (CH), 131.6 (C), 147.7 (C), 147.9 (C), 149.2 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3058, 2925, 2857, 2361, 1726, 1671 cm^{-1}. $C_{22}H_{23}NO_5S$ (413.48): calcd. C 63.90, H 5.61, N 3.39; found C 63.68, H 5.49, N 3.27. MS (ESI): *m*/*z* = 436 [M + Na]$^+$.

(2*R*,3*R*,3a*S*,10a*R*)-9-Butyl-2,3-isopropylidenedioxy-2,3,3a,9,10,10a-hexahydro-2*H*-furo[3,2-*c*][1,5]benzothiazepine (4h): Oil (0.245 g, 0.73 mmol, 73%). R_f = 0.7 (PS/EA, 2:1), column eluent (PS/EA, 9:1). $[\alpha]_D^{25}$ = +23.7 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.5 Hz, 3 H), 1.25–1.42 (m, 2 H), overlapped with 1.34 (s, 3 H), 1.55 (s, 3 H), 1.59–1.64 (m, 2 H), 3.07–3.16 (s, 1 H), 3.23 (dd, *J* = 8.7, 6.0 Hz, 1 H), 3.31 (dd, *J* = 14.4, 4.8 Hz, 1 H), 4.11 (d, *J* = 3.9 Hz, 1 H), 4.24 (dd, *J* = 14.4, 9.3 Hz, 1 H), 4.51 (d, *J* = 3.6 Hz, 1 H), 4.68 (dd, *J* = 10.8, 4.8 Hz, 1 H), 5.94 (d, *J* = 3.6 Hz, 1 H), 6.63–7.18 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 20.2 (CH_2), 26.2 (CH_3), 26.8 (CH_3), 29.3 (CH_2), 51.7 (CH_2), 52.6 (CH_2), 53.1 (CH), 77.1 (CH), 84.4 (CH), 105.6 (CH), 111.7 (C), 115.9 (CH), 118.7 (CH), 119.8 (C), 127.4 (CH), 131.7 (CH), 149.4 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2955, 2929, 2868, 1727, 1584, 1481, 1375 cm^{-1}. $C_{18}H_{25}NO_3S$ (335.46): calcd. C 64.45, H 7.51, N 4.18; found C 64.19, H 7.29, N 3.04. MS (ESI): *m*/*z* = 358 [M + Na]$^+$.

(2*R*,3*R*,3a*S*,10a*R*)-2,3-Isopropylidenedioxy-2,3,3a,9,10,10a-hexahydro-2*H*-furo[3,2-*c*][1,5]benzoxazepine (6): Foamy solid (0.205 g, 0.78 mmol, 78%). R_f = 0.5 (PS/EA, 2:1), column eluent (PS/EA, 5:1). $[\alpha]_D^{25}$ = +54.2 (*c* = 1.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.51 (s, 3 H), 3.49–3.53 (m, 1 H), 3.60–3.67 (m, 2 H), 4.59–4.65 (m, 2 H), 4.76 (d, *J* = 3.9 Hz, 1 H), 6.05 (d, *J* = 3.6 Hz, 1 H), 6.56–6.88 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3 (CH_3), 26.9 (CH_3), 46.2 (CH_2), 78.9 (CH), 84.6 (CH), 85.6 (CH), 105.7 (CH), 111.7 (C), 117.7 (CH), 119.6 (CH), 121.2 (CH), 123.7 (CH), 140.0 (C), 146.0 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3396, 2990, 2954, 1601, 1496, 1378 cm^{-1}. $C_{14}H_{17}NO_4$ (263.29): calcd. C 63.87, H 6.51, N 5.32; found C 63.69, H 6.37, N 5.18. MS (ESI): *m*/*z* = 286 [M + Na]$^+$.

(2*R*,3*R*)-3-Acetoxy-2-acetoxymethyl-5-benzyl-2,3,4,5-tetrahydrobenzo[*b*][1,5]oxazepine (7): Compound **4a** (0.5 mmol) was dissolved in 5% H_2SO_4 (25 mL) in CH_3CN/H_2O (3:1), and the solution was kept at room temperature for 24 h. Then the acidic solution was neutralized with solid $NaHCO_3$, and the resulting solution was filtered. The filtrate was evaporated in vacuo. The residue was dissolved in a minimum volume of MeOH, and the solution was treated dropwise with an aqueous solution of $NaIO_4$ (128 mg, 0.6 mmol) at 0 °C and then stirred for 45 min. Usual workup followed by a $NaBH_4$ reduction in MeOH afforded the diol. This was acetylated with Ac_2O (0.3 mL) and pyridine (2 mL) at room temperature for 12 h to furnish the crude product. Purification by silica gel flash chromatography to afforded **7** as a gummy material (0.115 g, 0.315 mmol, 63%). R_f = 0.65 (PS/EA, 2:1), column eluent (PS/EA, 9:1). $[\alpha]_D^{25}$ = –6.2 (*c* = 1.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 2.07 (s, 3 H), 3.40 (dd, *J* = 13.8, 6.0 Hz, 1 H), 3.68 (dd, *J* = 13.8, 9.0 Hz, 1 H), 4.20 (dd, *J* = 11.7, 4.8 Hz, 1 H), 4.33–4.53 (m, 3 H), 4.62–4.65 (m, 1 H), 5.11–5.15 (m, 1 H), 6.74–7.37 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6 (2 CH_3), 52.0 (CH_2), 56.4 (CH_2), 62.7 (CH_2), 69.9 (CH), 78.8 (CH), 116.8 (CH), 120.1 (CH), 120.6 (CH), 123.6 (CH), 127.1 (CH), 127.2 (2 CH), 128.5 (2 CH), 137.9 (C), 141.3 (C), 148.7 (C), 170.0 (C), 170.5 (C) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3450, 3029, 2968, 2910, 2856, 1732, 1599 cm^{-1}. $C_{21}H_{23}NO_5$ (369.41): calcd. C 68.28, H 6.28, N 3.79; found C 68.04, H 6.12, N 3.65. MS (ESI): *m*/*z* = 392 [M + Na]$^+$.

Supporting Information (see footnote on the first page of this article): NMR spectra for **2a**–**e**, **3a**–**f**, **4a**–**h**, **5**, **6**, and **7**.

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