DOI: 10.1002/ejoc.200901472

Palladium-Catalyzed Intramolecular Aryl Amination Reaction: An Expeditious Approach to the Synthesis of Chiral Benzodiazocine Derivatives

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Keywords: Palladium / Catalysts / Ligands / Amination / Diazocine

A palladium-catalyzed method for intramolecular amination of aryl bromides and iodides has been developed employing different bulky biaryl phosphanes as ligands and toluene as solvent. A variety of electron-rich aryl halide substrates have been aminated by the intramolecular pathway in good yield using different sugar-derived amines as well as benzylamine. The method is capable of furnishing benzodiazocines in chiral form besides dibenzodiazocine derivatives of potential biological interest.

Introduction

Heterocyclic compounds attract attention for many reasons including their biological activities. Benzo-fused cyclic molecules incorporating nitrogen atom in the structure are often referred to as "privileged structures" owing to their capability of binding to multiple receptors with high affinity.[1] Benzodiazocines, containing two nitrogen atoms, exhibit important pharmacological properties.[2] For example, 9-decyl benzolactam-V8 is known to be a potent PKC activator similar to the teleocidines[3] and buflavine has been shown to possess interesting adrenolytic and anti-serotonin activities.[4] Moreover, 1,5-benzodiazocines have attracted much interest as homologues of 1,4-benzodiazepine drugs.[5] As eight-membered rings are generally more difficult to prepare due to enthalpic and entropic reasons, and direct cyclization methods are ineffective unless certain conformational constraints are present in the acyclic precursor,[6] only a few synthetic procedures are known for benzodiazocines. Most of these are either intermolecular or deal with achiral substrates.[7] We were encouraged to apply the palladium catalyzed aromatic carbon–nitrogen bond forming reaction involving the cross coupling of aryl halides (or triflates, nonaflates, mesitylates) and amines which has recently seen an upsurge in interest as a useful synthetic tool.[8] Amination of aryl bromides under tin free conditions, initially achieved both by Buchwald[9a] and Hartwig[9b] groups, mainly focused on the intermolecular amination of aryl bromides or iodides to give substituted anilines.[10] However, recently a number of studies have been reported where an intramolecular version of this aryl amination chemistry has been utilized for the synthesis of benzofused five, six and seven membered heterocycles,[11] though only a few approaches have been made to synthesize benzofused eight membered heterocycles.[12] In continuation of our research activities related to the synthesis of benzannulated medium-ring heterocycles by C–N/C–O bond formation[12b,13] we therefore felt that an intramolecular cycloamination strategy leading to the formation of highly functionalized benzodiazocine derivatives offers a solution to this problem. Applied to chiral furanose derivatives, the strategy could furnish chiral products, while extension to synthesize dibenzodiazocine derivatives was attractive as these serve as precursors of different Tröger's bases.[14]

In this paper, we report an intramolecular aryl amination strategy which, when applied to D-glucose-derived sugar amines, furnished chiral tricyclic furo-benzodiazocine derivatives. Cleavage of the sugar ring of one of these tricyclic derivatives provided an optically active, functionalized benzodiazocine. The strategy has also been extended to synthesize a dibenzodiazocine derivative.

Results and Discussion

The starting material 1,2:5,6-di-*O*-isopropylidene glucofuranose was converted to amino derivatives **1a** and **1b** according to the reported procedure (Scheme 1).[15] *N*-Alkylation of the corresponding tosyl amides **2a**, **2c** and Boc amide (**2b**, derived from **1a**) with appropriately substituted 2-bromo/iodobenzyl bromides afforded the respective 3-*N*-(2-bromobenzyl)tosyl-glucofuranoses **3a**–**d** and 3-*N*-(2-bromo/iodobenzyl)-*N*-*tert*-butoxycarbonyl-glucofuranoses **3e**–**f** in good yields (Scheme 1; Table 1). Selective removal of the 5,6-*O*-isopropylidene moiety from **3a**–**f** was smoothly effected with 80% aqueous HOAc at 25 °C, and the resulting diol on $NaIO_4$ oxidation, imine formation with aliphatic amines, and subsequent $NaBH_4$ reduction in MeOH

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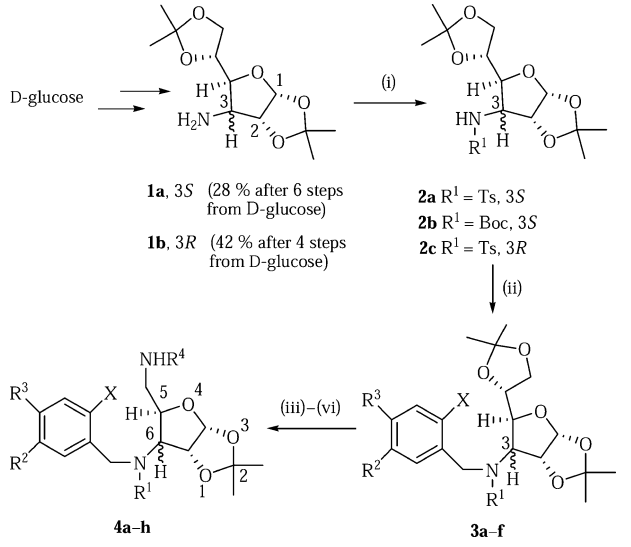
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901472.

afforded the desired amines **4a**–**h** in good yields (Scheme 1; Table 2). The structures of **4a**–**h** were derived from the spectroscopic data and comparison with data for similar compounds prepared by us.[16]



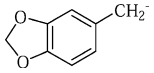
Scheme 1. Synthesis of *o*-bromo/iodo benzylated sugar amines **4a**–**h**. Reaction conditions: (i) TsCl, Py, room temp., 16 h (when R^1 = Ts, crude yield 88% for **2a**, 85% for **2c**) or Boc_2O, dry DCM, room temp., 1 h (when R^1 = Boc, crude yield 92% for **2b**); (ii) 2-bromo/iodobenzyl bromide derivative, K_2CO_3, acetone, room temp., 6 h; (iii) 80% AcOH (v/v), room temp., overnight; (iv) aq. $NaIO_4$, MeOH, room temp., 45 min; (v) RNH_2, anhydrous CH_2Cl_2, MS (4 Å), room temp., 12 h, N_2; (vi) $NaBH_4$, dry MeOH, room temp., 3 h.

Table 1. Preparation of **3a**–**f**.

Entry	Substrate	R^2	R^3	X	Product	Yield[a] (%)
1	**2a**	H	H	Br	**3a**	74
2	**2a**	OMe	H	Br	**3b**	78
3	**2a**	–O–CH_2–O–		Br	**3c**	68
4	**2c**	H	H	Br	**3d**	61
5	**2b**	H	H	Br	**3e**	77
6	**2b**	H	H	I	**3f**	74

[a] Isolated yield.

Table 2. Preparation of sugar amines **4a**–**h**.

Entry	Substrate	R^4	C-6 config.	Product	Yield[a] (%)
1	**3a**	$PhCH_2$–	*S*	**4a**	70
2	**3b**	$PhCH_2$–	*S*	**4b**	73
3	**3c**	$PhCH_2$–	*S*	**4c**	78
4	**3a**	$(CH_3)_2CH$–	*S*	**4d**	72
5	**3d**	$PhCH_2$–	*R*	**4e**	75
6	**3d**		*R*	**4f**	83
7	**3e**	$PhCH_2$–	*S*	**4g**	68
8	**3f**	$PhCH_2$–	*S*	**4h**	78

[a] Isolated yield.

Our initial goal was to explore the synthesis of benzodiazocine-annulated furanose derivatives **5** from **4** through Pd-catalyzed intramolecular cycloamination reactions in the presence of bases and ligands. For this, we tested the reagent system [$Pd_2(dba)_3$/±BINAP/*t*BuOK + K_2CO_3] reported by Rogers et al.[11d] on substrate **4a**. However, as no reaction took place (TLC) even after 20 h of heating at 90 °C, the reaction mixture was allowed to reflux gently. To our satisfaction, the reactant was fully consumed after 17 h

Table 3. Optimization of the intramolecular palladium catalyzed cycloamination reactions.

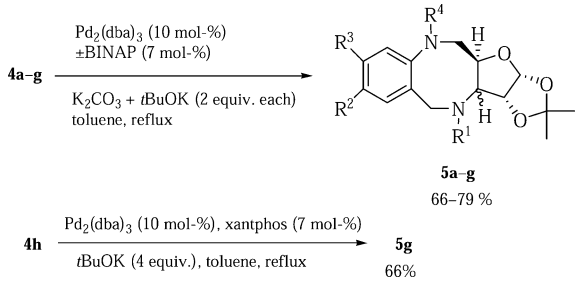
4a–h —Pd cat, ligand, base, solvent, Δ→ **5a–g**

Entry	Substrate	Base	Catalyst	Ligand	Solvent	Product	Yield[a] (%)
1	**4a**	K_2CO_3 + *t*BuOK	$Pd_2(dba)_3$	±BINAP	toluene	**5a**	72[b]
2	**4a**	*t*BuONa	$Pd_2(dba)_3$	DPPF	toluene	**5a**	62[c]
3	**4a**	Cs_2CO_3	$Pd(OAc)_2$	±BINAP	toluene	**5a**	55[d]
4	**4a**	*t*BuOK	$Pd_2(dba)_3$	xantphos	toluene	**5a**	58[e]
5	**4a**	K_2CO_3 + *t*BuOK	$Pd_2(dba)_3$	±BINAP	DMF	**5a**	32[f]
6	**4a**	K_2CO_3 + *t*BuOK	$Pd_2(dba)_3$	±BINAP	toluene	**5a**	51[g]
7	**4b**	K_2CO_3 + *t*BuOK	$Pd_2(dba)_3$	±BINAP	toluene	**5b**	66[b]
8	**4c**	K_2CO_3 + *t*BuOK	$Pd_2(dba)_3$	±BINAP	toluene	**5c**	68[b]
9	**4d**	K_2CO_3 + *t*BuOK	$Pd_2(dba)_3$	±BINAP	toluene	**5d**	79[b]
10	**4e**	K_2CO_3 + *t*BuOK	$Pd_2(dba)_3$	±BINAP	toluene	**5e**	68[b]
11	**4f**	K_2CO_3 + *t*BuOK	$Pd_2(dba)_3$	±BINAP	toluene	**5f**	71[b]
12	**4g**	K_2CO_3 + *t*BuOK	$Pd_2(dba)_3$	±BINAP	toluene	**5g**	75[b]
13	**4h**	*t*BuOK	$Pd_2(dba)_3$	xantphos	toluene	**5g**	66[e]

[a] Isolated yield. [b] Reaction conditions: 10 mol-% $Pd_2(dba)_3$, 7 mol-% ±BINAP, 2.0 equiv. K_2CO_3, 2.0 equiv. *t*BuOK, toluene (10 L/mol), reflux (17 h). [c] Reaction conditions: 10 mol-% $Pd_2(dba)_3$, 7 mol-% DPPF, 4.0 equiv. *t*BuONa, toluene (10 L/mol), reflux (17 h). [d] Reaction conditions: 10 mol-% $Pd(OAc)_2$, 7 mol-% ±BINAP, 5.0 equiv. Cs_2CO_3, toluene (10 L/mol), reflux (16 h). [e] Reaction conditions: 10 mol-% $Pd_2(dba)_3$, 7 mol-% xantphos, 4.0 equiv. *t*BuOK, toluene (10 L/mol), reflux (19 h). [f] Reaction conditions: 10 mol-% $Pd_2(dba)_3$, 7 mol-% ±BINAP, 2.0 equiv. K_2CO_3, 2.0 equiv. *t*BuOK, DMF (10 L/mol), 110 °C (15 h). [g] Reaction conditions: 15 mol-% $Pd_2(dba)_3$, 10 mol-% ±BINAP, 2.0 equiv. K_2CO_3, 2.0 equiv. *t*BuOK, toluene (10 L/mol), reflux (18 h).

of reflux. Usual work-up followed by chromatographic purification gave the desired cyclized product **5a** in 72% yield (entry 1, Table 3). The spectroscopic data of **5a** was in excellent agreement with the assigned structure.

We then applied other reported reagent systems[17] in an effort to improve the yield. Evaluation of these systems showed that use of DPPF/*t*BuONa or xantphos/*t*BuOK was less effective (entry 2, 4, Table 3). As an alternative palladium source, $Pd(OAc)_2$ also gave the desired cyclized product but less efficiently (entry 3, Table 3). The best conditions for the reaction were $Pd_2(dba)_3$ (10 mol-%) as the palladium source, ±BINAP (7 mol-%) as the ligand, a combination of K_2CO_3 (2.0 equiv.) with *t*BuOK (2.0 equiv.) as the base, and toluene (10 L/mol substrate) as the solvent when the bromo substrates were used (reactants **4a**–**g**, products **5a**–**g**, Scheme 2). For the iodo substrate (reactant **4h**, product **5g**, Scheme 2) the applied condition was that recommended by Guari et al.,[17b] i.e, $Pd_2(dba)_3$ (10 mol-%) as the palladium source, xantphos (7 mol-%) as the ligand, *t*BuOK (4.0 equiv.) as the base and toluene (10 L/mol substrate) as the solvent (entry 13, Table 3). The structures of **5a**–**g** were determined by spectroscopic data and supported by single-crystal X-ray analysis[18] of **5e** (Figure 1).



Scheme 2. Synthesis of fused furo-benzodiazocines.

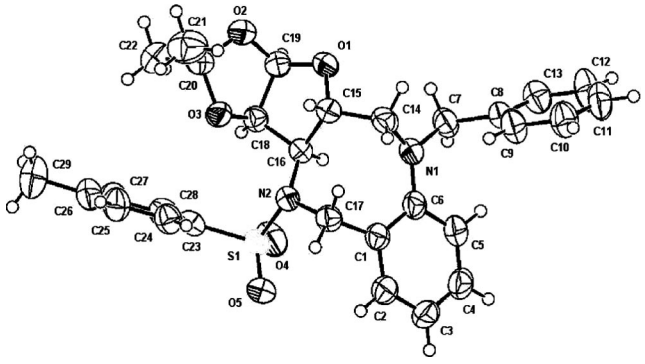
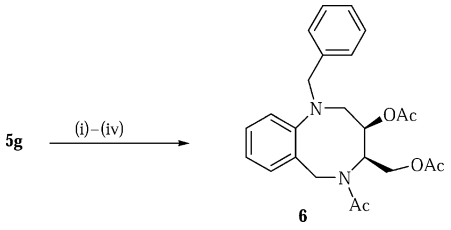


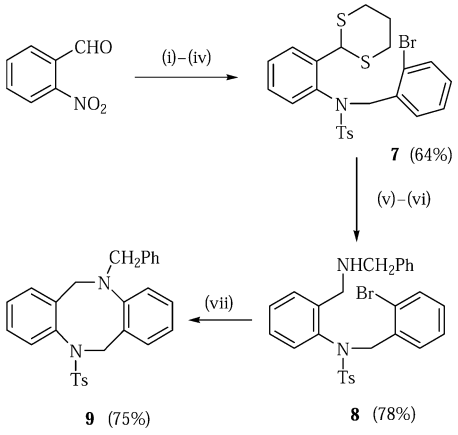
Figure 1. ORTEP diagram of **5e**.

As an application of our methodology, the feasibility of synthesizing chiral functionalized benzodiazocines from the annulated sugar derivatives thus obtained could be demonstrated using **5g**. Thus, subjecting **5g** to a sequence of reactions involving removal of the 1,2-*O*-isopropylidine group as well as *tert*-butoxycarbonyl group with H_2SO_4 in MeCN/H_2O (2:18:5), $NaIO_4$ cleavage of the diol, $NaBH_4$ reduction of the generated carbonyl group, and acetylation of the resulting diol with acetic anhydride and pyridine furnished the benzodiazocine derivative **6** (Scheme 3).



Scheme 3. Conversion of **5g** to benzodiazocine derivative **6**. Reaction conditions: (i) $CH_3CN/H_2O/H_2SO_4$ (18:5:2), room temp., 36 h; (ii) aq. $NaIO_4$, MeOH, room temp., 45 min; (iii) $NaBH_4$, MeOH, room temp., 3 h; (iv) Ac_2O, pyridine, room temp., 12 h, overall yield, 62%.

We next focused our attention on extending our methodology to the synthesis of dibenzodiazocine derivatives. For this, we synthesized compound **7** through a sequence of reactions involving thioacetalization of *o*-nitrobenzaldehyde using propanedithiol,[19] reduction of the nitro group with Pd/C and hydrazine hydrate, tosylation of the resulting amino group and benzylation of the tosyl amide with 2-bromobenzyl bromide. Compound **7** was converted into the cyclization substrate **8** by dethioketalization in the presence of MeI/aq. MeCN,[20] imine formation with benzyl amine in EtOH, and subsequent $NaBH_4$ reduction. Refluxing of **8** under the standard conditions for bromo derivatives afforded the desired cyclized product **9** in 72% yield (Scheme 4). The spectroscopic data and single-crystal X-ray analysis[21] (Figure 2) of **9** are in excellent agreement with the assigned structure. A probable mechanism of intramolecular aryl amination[8a,10d] for the synthesis of benzodiazocines and dibenzodiazocines has been outlined (Scheme 5).



Scheme 4. Synthesis of dibenzodiazocine derivative. Reaction conditions: (i) 1,3-propanedithiol, I_2, dry DCM, 0 °C; (ii) hydrazine hydrate, Pd/C (10%), EtOH, reflux; (iii) TsCl, Py, room temp., 16 h; (iv) 2-bromobenzyl bromide, K_2CO_3, acetone, room temp., 6 h; (v) CH_3I, CH_3CN/H_2O (90:1), room temp., 24 h; (vi) benzylamine, EtOH, room temp., 12 h, then $NaBH_4$, 0 °C, 3 h; (vii) $Pd_2(dba)_3$ (10 mol-%), ±BINAP (7 mol-%), K_2CO_3 + *t*BuOK (2 equiv. each), toluene, reflux.

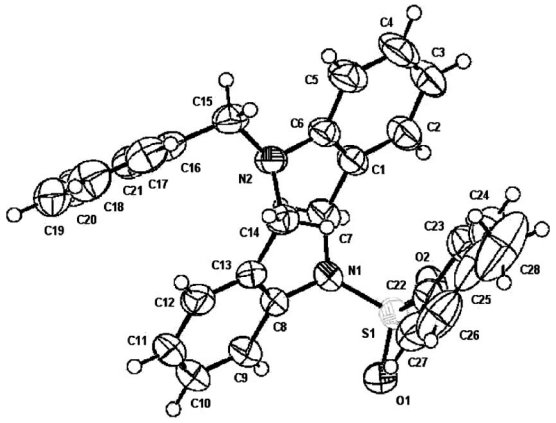
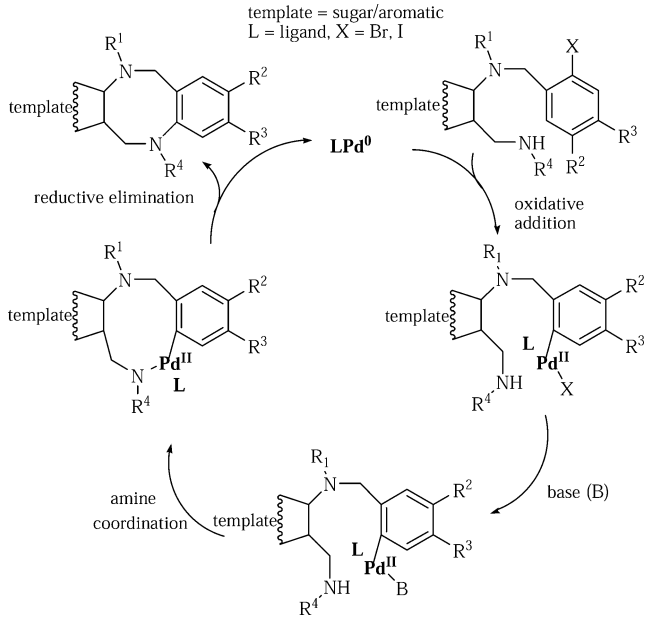


Figure 2. ORTEP diagram of **9**.



Scheme 5. Proposed mechanism of intramolecular aryl amination for the synthesis of benzodiazocines and dibenzodiazocines.

Conclusions

In summary, we have developed a straightforward, efficient synthetic route to benzannulated eight-membered diazacycles by using the Buchwald–Hartwig aryl amination for appropriate furanose derivatives. The reaction worked on a variety of D-glucose-derived substrates and the products could be smoothly converted to chiral, optically active benzodiazocines. The strategy could be extended to synthesize dibenzannulated eight-membered diazacycles also. The findings open up the possibility of obtaining functionalized benzodiazocines in chiral form and also dibenzodiazocine derivatives.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded in a Bruker AM 300L or AVANCE 600 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were obtained using either JEOL AX-500 or Micromass Q-Tofmicro™ spectrometers. X-ray diffraction data were collected in Bruker Kappa Apex II diffractometer. IR spectra were obtained employing JASCO FT/IR Model 410. Elemental analyses were carried out with a C,H,N analyzer. Specific rotations were measured at 589 nm on a JASCO P-1020 polarimeter. TLC was performed on pre-coated plates (0.25 mm, silica gel $60F_{254}$). Column chromatography and flash chromatography were carried out using commercial-grade silica gel (60–120 mesh or 230–400 mesh). PS and EA are abbreviated for petroleum ether (boiling range 60–80 °C) and ethyl acetate, respectively.

General Procedure for the Synthesis of Compounds 3a–b,[16c] 3c and 3d:[16c] To a magnetically stirred solution of 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**1a**) or α-D-allofuranoside (**1b**) (4 mmol) in pyridine (12 mL) was added TsCl (4.8 mmol) in pyridine (12 mL), and the stirring was continued at room temp. for 16 h. The mixture was then poured into crushed ice and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with H_2O and dried. Removal of solvent under reduced pressure gave a syrupy liquid, which was dissolved in 25 mL of dry acetone. Anhydrous K_2CO_3 (4 g) and appropriately substituted 2-bromobenzyl bromide (4.4 mmol) were added to it. The mixture was sonicated for 15 min and stirred for 6 h at room temp. until completion of reaction (indicated by TLC). The reaction mixture was then filtered; the filtrate was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 extract was washed with H_2O, dried and concentrated to afford a syrup which on column chromatography (silica gel) yielded the corresponding 3-*N*-(2-bromobenzyl)tosyl derivatives.

3-{[(6-Bromo-1,3-benzodioxol-5-yl)methyl](*p*-tolylsulfonyl)amino}-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (3c): Foamy solid; yield 1.704 g (2.72 mmol, 68%). R_f = 0.55 (PS/EA, 2:1), eluent PS/EA (5:1). $[\alpha]_D^{25}$ = –36.2 (*c* = 0.92, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (s, 3 H), 1.28 (s, 3 H), 1.32 (s, 3 H), 1.45 (s, 3 H), 2.44 (s, 3 H), 3.52–3.54 (m, 1 H), 3.78 (d, *J* = 4.8 Hz, 2 H), 3.93–3.97 (m, 2 H), 4.43 (d, *J* = 16.8 Hz, 1 H), 4.56 (d, *J* = 17.1 Hz, 1 H), 4.97 (br. s, 1 H), 5.97 (s, 2 H), 5.97–5.99 (d-like, 1 H), 6.96 (s, 1 H), 7.21 (s, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.78–7.80 (d-like, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.5 (CH_3), 25.0 (CH_3), 25.8 (CH_3), 26.4 (CH_3), 26.5 (CH_3), 52.6 (CH_2), 67.0 (CH), 68.1 (CH_2), 71.7 (CH), 80.8 (CH), 84.3 (CH), 101.8 (CH_2), 105.3 (CH), 108.9 (CH), 109.5 (C), 111.0 (C), 112.5 (CH), 112.9 (C), 128.0 (2 CH), 128.8 (C), 129.5 (2 CH), 136.9 (C), 143.9 (C), 147.74 (C), 147.76 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3535), 2986, 2936, 1703, 1595 cm^{-1}. $C_{27}H_{32}BrNO_9S$ (626.51): calcd. C 51.76, H 5.15, N, 2.24; found C 51.57, H 5.08, N 2.16. MS (ESI): *m*/*z* = 648 (M^+ + Na for Br^{79}).

General Procedure for the Synthesis of Compounds 3e–f: To a magnetically stirred solution of **1a** (4 mmol) in 30 mL of CH_2Cl_2, Boc_2O (4 mmol) was added drop wise and the solution was stirred for 1 h. Then it was treated with 20 mL of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with H_2O and dried. Removal of solvent under reduced pressure gave a syrupy liquid, which was dissolved in 25 mL of dry acetone. Anhydrous K_2CO_3 (4 g) and appropriately substituted 2-bromobenzyl bromide (4.4 mmol) were added to it. The mixture was sonicated for 15 min and stirred for 6 h at room temp. until completion of reaction (indicated by TLC). The reaction mixture was then filtered; the filtrate was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 extract was washed with H_2O, dried and concentrated to afford a syrup which

on column chromatography (silica gel) yielded the corresponding 3-*N*-(2-bromo/iodobenzyl) Boc derivatives.

3-Deoxy-3-[(2-bromobenzyl)(*tert*-butoxycarbonyl)amino]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (3e): Syrup; yield 1.625 g (3.08 mmol, 77%) (eluent PS/EA, 5:1). $[\alpha]_D^{25}$ = –31.4 (*c* = 0.76, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 3 H), 1.38–1.52 (m, 15 H), 1.56 (s, 3 H), 4.03–4.18 (m, 4 H), 4.23 (br. s, 1 H), 4.48 (br. s, 1 H), 4.63 (br. s, 1 H), 5.02 (br. s, 1 H), 6.08 (br. s, 1 H), 7.11–7.37 (m, 3 H), 7.55 (d, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 25.4 (CH_3), 26.1 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 28.2 (3 CH_3), 64.0 (CH_2), 66.5 (CH), 67.9 (CH_2), 73.5 (CH), 80.6 (CH), 81.8 (CH), 85.1 (C), 106.3 (CH), 109.4 (C), 110.7 (C), 127.5 (CH), 128.3 (C), 128.4 (CH), 132.8 (2 CH), 138.5 (C), 155.3 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 2984), 2936, 2887, 1701, 1568 cm^{-1}. $C_{24}H_{34}BrNO_7$ (528.43): calcd. C 54.55, H 6.49, N 2.65; found C 54.32, H 6.26, N 2.45. MS (ESI): *m*/*z* = 550 (M^+ + Na for Br^{79}).

3-Deoxy-3-[(2-iodobenzyl)(*tert*-butoxycarbonyl)amino]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (3f): Syrup; yield 1.705 g (2.96 mmol, 74%) (eluent PS/EA, 5:1). $[\alpha]_D^{25}$ = –34.8 (*c* = 0.82, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 3 H), 1.39–1.52 (m, 15 H), 1.57 (s, 3 H), 4.03–4.23 (m, 5 H), 4.38 (br. s, 1 H), 4.57 (br. s, 1 H), 5.04 (br. s, 1 H), 6.09 (br. s, 1 H), 6.97 (t, *J* = 7.2 Hz 1 H), 7.20 (br. s, 1 H), 7.38 (t, *J* = 7.2 Hz 1 H), 7.30 (d, *J* = 7.5 Hz 1 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 25.5 (CH_3), 26.1 (CH_3), 27.0 (CH_3), 27.4 (CH_3), 28.2 (3 CH_3), 63.9 (CH_2), 66.9 (CH), 67.9 (CH_2), 73.5 (CH), 80.5 (CH), 81.9 (CH), 85.1 (C), 106.5 (CH), 109.4 (C), 110.7 (C), 128.0 (CH), 128.4 (C), 128.6 (CH), 139.4 (CH), 139.5 (CH), 140.1 (C), 155.3 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 2983), 2935, 1700, 1582, 1564 cm^{-1}. $C_{24}H_{34}INO_7$ (575.43): calcd. C 50.09, H 5.96, N 2.43; found C 50.21, H 5.76, N 2.35. MS (ESI): *m*/*z* 576, (M^+ + H).

General Procedure for the Synthesis of Compounds 4a–h: Each of the compounds **3a**–**f** (2 mmol) was dissolved in 80% aq. HOAc (v/v, 60 mL) and the solution was stirred overnight at room temperature (monitored by TLC until the disappearance of starting material). Removal of HOAc on 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 treated with aq. $NaIO_4$ (513 mg, 2.4 mmol, dissolved in 5 mL of water) slowly with stirring (45 min). The reaction mixture was filtered (using sintered funnel), evaporated under reduced pressure and extracted with $CHCl_3$ (4 × 30 mL). The combined organic layer was washed with water, dried and evaporated to afford the crude aldehyde. This aldehyde was dissolved in dry CH_2Cl_2 (35 mL) and treated with activated molecular sieves (4 Å) and appropriate amine (2.4 mmol) at 0 °C. Then the mixture was stirred at room temperature for 12 h under N_2 atmosphere. Dry MeOH (15 mL) was added to the reaction mixture and $NaBH_4$ (151 mg, 4 mmol) was added to it (in small portions) over a period of 1 h at 0 °C. The 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 layer was washed with water, dried, evaporated, and chromatographed on silica gel to afford the amine **4a**–**h**.

(3a*R*,5*R*,6*S*,6a*R*)-5-(Benzylaminomethyl)-6-[(2-bromobenzyl)(*p*-tolylsulfonyl)amino]-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole (4a): Syrup; yield 0.84 g (1.4 mmol, 70%). R_f = 0.36 (PS/EA, 2:1), eluent PS/EA (4:1). $[\alpha]_D^{25}$ = –28.2 (*c* = 1.42, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.13 (s, 3 H), 1.43 (s, 3 H), 1.98 (br. s, 1 H), 2.26 (dd, *J* = 12.3, 4.2 Hz, 1 H), 2.43 (s, 3 H), 2.54 (dd, *J* = 16.8, 7.5 Hz, 1 H), 3.57 (d, *J* = 13.2 Hz, 1 H), 3.64 (d, *J* = 13.2 Hz, 1 H), 4.33 (dd, *J* = 13.5, 4.8 Hz, 2 H), 4.40–4.43 (m, 2 H), 4.55 (d, *J* = 17.7 Hz, 1 H), 5.58 (d, *J* = 3.4 Hz, 1 H), 7.12 (t, *J* = 7.2 Hz, 1 H), 7.21–7.42 (m, 8 H), 7.48–7.51 (m, 1 H), 7.62 (d, *J* = 7.5 Hz, 1 H), 7.73–7.76 (d-like, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4 (CH_3), 25.7 (CH_3), 26.2 (CH_3), 47.4 (CH_2), 50.9 (CH_2), 53.7 (CH_2), 65.3 (CH), 78.9 (CH), 83.3 (CH), 104 (CH), 111 (C), 122.1 (C), 126.9 (CH), 127.5 (2 CH), 127.8 (2 CH), 128.3 (2 CH), 128.5 (CH), 128.8 (CH), 129.1 (CH), 129.8 (2 CH), 132.5 (CH), 135.9 (C), 136.4 (C), 139.6 (C), 144 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 2985), 2931, 1665, 1597, 1449 cm^{-1}. $C_{29}H_{33}BrN_2O_5S$ (601.55): calcd. C 57.90, H 5.53, N 4.66; found C 57.78, H 5.47, N 4.58. MS (ESI): *m*/*z* = 601 (M^+ + H for Br^{79}).

(3a*R*,5*R*,6*S*,6a*R*)-5-(Benzylaminomethyl)-6-[(2-bromo-5-methoxybenzyl)(*p*-tolylsulfonyl)amino]-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole (4b): Gummy material; yield 0.92 g (1.46 mmol, 73%) (eluent PS/EA, 4:1). $[\alpha]_D^{25}$ = –27.6 (*c* = 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (s, 3 H), 1.44 (s, 3 H), 1.60 (br. s, 1 H), 2.30–2.35 (dd-like, 1 H), 2.42 (s, 3 H), 2.57 (dd, *J* = 12.3, 7.5 Hz, 1 H), 3.58 (d, *J* = 13.5 Hz, 1 H), 3.65 (d, *J* = 13.5 Hz, 1 H), 3.76 (s, 3 H), 3.81 (br. s, 1 H), 4.32–4.34 (d-like, 1 H), 4.35 (d, *J* = 18 Hz, 1 H), 4.48–4.50 (d-like, 1 H), 4.53 (d, *J* = 18 Hz, 1 H), 5.63 (d, *J* = 3 Hz, 1 H), 6.69 (dd, *J* = 6.9, 2.7 Hz, 1 H), 7.17–7.39 (m, 9 H), 7.73–7.75 (d-like, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 21.5 (CH_3), 25.8 (CH_3), 26.4 (CH_3), 47.7 (CH_2), 53.1 (CH_2), 53.8 (CH_2), 55.4 (CH_3), 65.5 (CH), 79.1 (CH), 83.4 (CH), 104.1 (CH), 111.1 (C), 112.4 (C), 114.8 (CH), 114.9 (CH), 126.9 (CH), 127.6 (CH), 127.9 (2 CH), 128.1 (CH), 128.3 (3 CH), 129.8 (CH), 133.1 (CH), 136.5 (C), 136.9 (C), 139.7 (C), 144.0 (C), 158.9 (C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3330, 2986, 2934, 2837, 1671, 1596 cm^{-1}. $C_{30}H_{35}BrN_2O_6S$ (631.58): calcd. C 57.05, H 5.59, N 4.44; found C 57.18, H 5.42, N 4.36. MS (ESI): *m*/*z* = 631 (M^+ + H for Br^{79}).

(3a*R*,5*R*,6*S*,6a*R*)-5-(Benzylaminomethyl)-6-{[(6-bromo-1,3-benzodioxol-5-yl)methyl](*p*-tolylsulfonyl)amino}-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole (4c): Gummy material; yield 1.006 g (1.56 mmol, 78%) (eluent PS/EA, 4:1). $[\alpha]_D^{25}$ = –29.7 (*c* = 0.94, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (s, 3 H), 1.44 (s, 3 H), 1.57 (br. s, 1 H), 2.24–2.29 (dd-like, 1 H), 2.43 (s, 3 H), 2.49–2.55 (dd-like, 1 H), 3.56 (d, *J* = 13.2 Hz, 1 H), 3.64 (d, *J* = 13.2 Hz, 1 H), 4.26 (m, 3 H), 4.45 (m, 2 H), 5.66 (br. s, 1 H), 5.98 (s, 2 H), 6.94 (s, 1 H), 7.15 (s, 1 H), 7.21–7.32 (m, 7 H), 7.72–7.75 (d-like, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4 (CH_3), 25.8 (CH_3), 26.3 (CH_3), 47.4 (CH_2), 50.8 (CH_2), 53.7 (CH_2), 65.3 (CH), 78.9 (CH), 83.4 (CH), 101.7 (CH_2), 104 (CH), 109.1 (CH), 111.0 (C), 112.3 (CH), 112.4 (C), 126.8 (CH), 127.5 (2 CH), 127.8 (2 CH), 128.2 (2 CH), 129.0 (C), 129.7 (2 CH), 136.4 (C), 139.5 (C), 144.0 (C), 147.5 (2 C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 2924), 1593, 1479, 1378, 1345 cm^{-1}. $C_{30}H_{33}BrN_2O_7S$ (645.56): calcd. C 55.82, H 5.15, N 4.34; found C 55.68, H 5.06, N 4.25. MS (ESI): *m*/*z* = 645 (M^+ + H for Br^{79}).

(3a*R*,5*R*,6*S*,6a*R*)-5-(Isopropylaminomethyl)-6-[(2-bromobenzyl)(*p*-tolylsulfonyl)amino]-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole (4d): Syrup; yield 0.795 g (1.44 mmol, 72%) (eluent PS/EA, 4:1). $[\alpha]_D^{25}$ = –32.4 (*c* = 1.36, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6 Hz, 3 H), 1.39–1.18 (m, 6 H), 1.42 (s, 3 H), 1.49 (br. s, 1 H), 2.46 (s, 3 H), 2.64–2.65 (d-like, 2 H), 3.01 (br. s, 1 H), 4.19–4.35 (m, 2 H), 4.42–4.46 (m, 1 H), 5.58 (dd, *J* = 17.7, 8.3 Hz, 2 H), 5.72 (br. s, 1 H), 7.12–7.19 (m, 1 H), 7.33–7.39 (m, 3 H), 7.50–7.55 (m, 1 H), 7.63–7.65 (d-like, 1 H), 7.76–7.82 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.9 (CH_3), 22.6 (CH_3), 23.1 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 46.3 (CH_2), 49.2 (CH_2), 51.5 (CH_2), 65.8 (CH), 79.6 (CH), 83.8 (CH), 104.5 (CH), 111.6 (C), 122.6 (C), 127.8 (CH), 128.0 (2 CH), 129.2 (CH), 129.7 (CH), 130.3 (2 CH), 133.0 (CH), 136.5 (C), 137.1 (C), 144.5 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ =

2964), 1595, 1442, 1378, 1345 cm^{-1}. $C_{25}H_{33}BrN_2O_5S$ (553.51): calcd. C 54.25, H 6.01, N 5.06; found C 54.12, H 5.88, N 4.92. MS (ESI): m/z = 553 (M^+ + H for Br^{79}).

(3a*R*,5*R*,6*R*,6a*R*)-5-(Benzylaminomethyl)-6-[(2-bromobenzyl)(*p*-tolylsulfonyl)amino]-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole (4e): Gummy material; yield 0.9 g (1.5 mmol, 75%) (eluent PS/EA, 4:1). $[\alpha]_D^{25}$ = +66.3 (c = 0.26, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 3 H), 1.45 (s, 3 H), 1.54 (br. s, 1 H), 2.32 (dd, J = 13.1, 5.2 Hz, 1 H), 2.44 (s, 3 H), 2.56–2.61 (dd-like, 1 H), 3.51 (d, J = 13.4 Hz, 1 H), 3.66 (d, J = 13.4 Hz, 1 H), 4.01–4.03 (m, 1 H), 4.19 (t, J = 3.9 Hz, 1 H), 4.27 (dd, J = 9.7, 4.2 Hz, 1 H), 4.73 (d, J = 18 Hz, 1 H), 5.13 (d, J = 18 Hz, 1 H), 5.58 (d, J = 3.6 Hz, 1 H); 7.04–7.12 (m, 3 H), 7.24–7.32 (m, 6 H), 7.44–7.47 (dd-like, 1 H), 7.56 (d, J = 7.5 Hz, 1 H), 7.81–7.84 (d-like, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 21.6 (CH_3), 26.0 (CH_3), 26.6 (CH_3), 49.5 (CH_2), 50.1 (CH_2), 54.1 (CH_2), 59.6 (CH), 74.3 (CH), 80.6 (CH), 103.7 (CH), 112.7 (C), 126.3 (CH), 126.9 (CH), 128.0 (4× CH), 128.3 (2 CH), 128.7 (CH), 129.1 (CH), 129.2 (CH), 130.0 (CH), 130.3 (CH), 134.0 (C), 134.4 (C), 139.5 (C), 139.9 (C), 143.8 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3024), 2985, 2930, 1674, 1599 cm^{-1}. $C_{29}H_{33}BrN_2O_5S$ (601.55): calcd. C 57.90, H 5.53, N 4.66; found C 57.74, H 5.48, N, 4.52. MS (ESI): m/z = 601 (M^+ + H for Br^{79}).

(3a*R*,5*R*,6*R*,6a*R*)-5-{[(6-Bromo-1,3-benzodioxol-5-yl)methyl]-aminomethyl}-6-[(2-bromobenzyl)(*p*-tolylsulfonyl)amino]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (4f): Gummy material; yield 1.07 g (1.66 mmol, 83%) (eluent PS/EA, 4:1). $[\alpha]_D^{25}$ = +64.8 (c = 0.24, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 3 H), 1.45 (s, 3 H), 1.51 (br. s, 1 H), 2.30 (dd, J = 12.9, 4.8 Hz, 1 H), 2.44 (s, 3 H), 2.54–2.59 (dd-like, 1 H), 3.42 (d, J = 13.2 Hz, 1 H), 3.54 (d, J = 13.2 Hz, 1 H), 3.99 (d, J = 7.8 Hz 1 H), 4.18–4.25 (m, 2 H), 4.73 (d, J = 18 Hz, 1 H), 5.14 (d, J = 18 Hz, 1 H), 5.57 (d, J = 2.7 Hz, 1 H), 5.95 (s, 2 H), 6.67 (d, J = 7.8 Hz, 1 H), 6.76 (d, J = 8.1 Hz, 2 H), 7.07 (t, J = 7.5 Hz, 1 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.32 (d, J = 7.8 Hz, 2 H), 7.46 (d, J = 7.8 Hz, 1 H), 7.60 (d, J = 7.5 Hz, 1 H), 7.81–7.83 (d-like, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.5 (CH_3), 25.6 (CH_3), 26.5 (CH_3), 48.8 (CH_2), 50.2 (CH_2), 53.2 (CH_2), 59.0 (CH), 75.8 (CH), 79.0 (CH), 100.8 (CH_2), 103.5 (CH), 107.9 (CH), 108.5 (CH), 112.5 (C), 120.9 (CH), 121.7 (C), 127.2 (CH), 127.5 (2 CH), 128.5 (CH), 129.6 (2 CH), 129.7 (CH), 132.2 (CH), 134.1 (C), 137.1 (C), 137.4 (C), 143.9 (C), 146.3 (C), 147.5 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3395), 2924, 1645, 1597, 1488 cm^{-1}. $C_{30}H_{33}BrN_2O_7S$ (645.56): calcd. C 55.82, H 5.15, N 4.34; found C 55.67, H 5.03, N 4.21. MS (ESI): m/z = 645 (M^+ + H for Br^{79}).

(3a*R*,5*R*,6*S*,6a*R*)-5-(Benzylaminomethyl)-6-[(2-bromobenzyl)(*tert*-butoxycarbonyl)amino]-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole (4g): Syrup; yield 0.745 g (1.36 mmol, 68%) (eluent PS/EA, 4:1). $[\alpha]_D^{25}$ = –30.8 (c = 1.36, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 3 H), 1.25–1.42 (m, 9 H), 1.47 (s, 3 H), 1.68 (br. s, 1 H), 2.85 (br. s, 2 H), 3.82 (d, J = 5.1 Hz, 2 H), 4.13–4.18 (d-like, 1 H), 4.46–4.75 (m, 4 H), 5.84 (br. s, 1 H), 7.10–7.33 (m, 8 H), 7.53 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 26.0 (CH_3), 26.6 (CH_3), 28.0 (3 CH_3), 48.2 (CH_2), 53.0 (CH_2), 54.2 (CH_2), 63.5 (CH), 80.2 (CH), 83.4 (CH), 97.9 (C), 104.4 (CH), 110.9 (C), 126.9 (CH), 127.5 (C), 128.1 (4× CH), 128.3 (3 CH), 128.8 (C), 132.7 (CH), 137.9 (C), 140.1 (C), 155.2 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3327), 3062, 2978, 2934, 1697, 1599 cm^{-1}. $C_{27}H_{35}BrN_2O_5$ (547.48): calcd. C 59.23, H 6.44, N 5.12; found C 59.12, H 6.34, N 5.04. MS (ESI): m/z = 547 (M^+ + H for Br^{79}).

(3a*R*,5*R*,6*S*,6a*R*)-5-(Benzylaminomethyl)-6-[(2-iodobenzyl)(*tert*-butoxycarbonyl)amino]-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxole (4h): Syrup; yield 0.925 g (1.56 mmol, 78%) (eluent PS/EA, 4:1). $[\alpha]_D^{25}$ = –29.4 (c = 1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 3 H), 1.25–1.42 (m, 9 H), 1.47 (s, 3 H), 1.61 (br. s, 1 H), 2.86 (br. s, 2 H), 3.83 (d, J = 8.7 Hz, 3 H), 4.48–4.58 (m, 4 H), 5.84 (br. s, 1 H), 6.94–6.99 (m, 1 H), 7.15 (br. s, 1 H), 7.26–7.38 (m, 6 H), 7.81 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 26.0 (CH_3), 26.6 (CH_3), 28.0 (3 CH_3), 48.2 (CH_2), 53.1 (CH_2), 54.2 (CH_2), 63.8 (CH), 80.2 (CH), 83.5 (CH), 96.7 (C), 104.8 (CH), 111.0 (C), 126.7 (CH), 126.9 (CH), 127.8 (C), 128.1 (2 CH), 128.3 (3 CH), 128.6 (CH), 137.5 (C), 139.4 (CH), 139.9 (C) 155.4 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 2978), 2930, 1696, 1452 cm^{-1}. $C_{27}H_{35}IN_2O_5$ (594.48): calcd. C 54.55, H 5.93, N 4.71; found C 59.12, H 6.34, N 5.04. MS (ESI): m/z = 595 (M^+ + H).

General Procedure for the Cycloamination Reactions: To a solution of each of the amines **4a**–**g** (1 mmol) in dry toluene (10 mL/mmol substrate) were added *t*BuOK (224 mg, 2 equiv.) and K_2CO_3 (276 mg, 2 equiv.) [only *t*BuOK (448 mg, 4 equiv.) for **4h**], $Pd_2(dba)_3$ (10 mol-%) and ±BINAP (7 mol-%) (for **4a**–**g**) or xantphos (7 mol-%) (for **4h**), and the reaction mixture was heated at reflux for 17 h under argon atmosphere. After completion of the reaction (monitored by TLC), the crude mixture was passed through a bed of silica gel. The solvent was evaporated and the residue was extracted with CH_2Cl_2 (4×25 mL). The organic layer was washed with water and dried. The solvent was evaporated under reduced pressure to give the crude product which was purified by column chromatography over silica gel to furnish the pure cyclized product.

(2*R*,3*R*,3a*S*,11a*R*)-10-Benzyl-2,3-(isopropylidenedioxy)-4-(*p*-tolylsulfonyl)-3a,4,5,10,11,11a-hexahydrofuro[3,2-*b*][1,5]benzodiazocine (5a): Gummy material; yield 0.375 g (0.72 mmol, 72%). R_f = 0.64 (PS/EA, 2:1), eluent PS/EA (6:1). $[\alpha]_D^{25}$ = +69.4 (c = 1.56, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 6 H), 2.31 (s, 3 H), 3.10 (dd, J = 15.6, 8.5 Hz, 1 H), 3.49 (dd, J = 15.3, 7.3 Hz, 1 H), 3.71–3.87 (m, 4 H), 4.67 (d, J = 16.8 Hz, 1 H), 4.74 (d, J = 17.1 Hz, 1 H), 4.94 (br. s, 1 H), 5.90 (br. s, 1 H), 6.69 (d, J = 7.8 Hz, 1 H), 6.86–6.96 (m, 3 H), 7.06–7.45 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.3 (CH_3), 26.3 (CH_3), 26.4 (CH_3), 47.2 (CH_2), 51.8 (CH_2), 56.1 (CH_2), 65.8 (CH), 76.7 (CH), 86.8 (CH), 104.5 (CH), 111.4 (C), 116.0 (CH), 120.5 (CH), 127.0 (C), 127.5 (CH), 127.8 (2 CH), 128.5 (3 CH), 128.8 (2 CH), 129.1 (2 CH), 132.8 (CH), 136.1 (C), 137.6 (C), 142.8 (C), 151.8 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 2924), 1651, 1597, 1496 cm^{-1}. $C_{29}H_{32}N_2O_5S$ (520.63): calcd. C 66.90, H 6.20, N 5.38; found C 66.78, H 6.08, N 5.25. MS (ESI): m/z = 543 (M^+ + Na).

(2*R*,3*R*,3a*S*,11a*R*)-10-Benzyl-2,3-(isopropylidenedioxy)-7-methoxy-4-(*p*-tolylsulfonyl)-3a,4,5,10,11,11a-hexahydrofuro[3,2-*b*][1,5]benzodiazocine (5b): Gummy material; yield 0.365 g (0.66 mmol, 66%) (eluent PS/EA, 6:1). $[\alpha]_D^{25}$ = +63.7 (c = 1.48, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3 H), 1.30 (s, 3 H), 2.33 (s, 3 H), 3.01 (dd, J = 11.4, 8.2 Hz, 1 H), 3.35 (d, J = 9.3 Hz, 1 H), 3.74–3.95 (m, 4 H) overlapped with 3.80 (s, 3 H), 4.58 (br. s, 2 H), 4.96 (br. s, 1 H), 5.93 (d, J = 3.3 Hz, 1 H), 6.73–6.80 (m, 2 H), 6.86 (s, 1 H), 6.94 (d, J = 4.5 Hz, 2 H), 7.10 (d, J = 7.8 Hz, 2 H), 7.16–7.32 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4 (CH_3), 26.3 (CH_3), 26.5 (CH_3), 47.2 (CH_2), 55.1 (CH), 55.6 (CH_3), 57.2 (CH_2), 61.3 (CH_2), 77.2 (CH), 86.1 (CH), 104.8 (CH), 111.4 (C), 113.6 (CH), 117.8 (CH), 120.1 (C), 127.4 (CH), 127.8 (3 CH), 128.4 (3 CH), 128.9 (3 CH), 129.7 (CH), 136.5 (C), 138.2 (C), 143.0 (C), 145.8 (C) 153.9 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3431), 2916, 1691, 1596 cm^{-1}. $C_{30}H_{34}N_2O_6S$ (550.67): calcd. C 65.43, H 6.22, N 5.09; found C 65.04, H 6.11, N 4.95. MS (ESI): m/z = 573 (M^+ + Na).

(2*R*,3*R*,3a*S*,11a*R*)-10-Benzyl-2,3-(isopropylidenedioxy)-7,8-(methylenedioxy)-4-(*p*-tolylsulfonyl)-3a,4,5,10,11,11a-hexahydrofuro[3,2-*b*]-[1,5]benzodiazocine (5c): Gummy material; yield 0.384 g

(0.68 mmol, 68%) (eluent PS/EA, 6:1). $[\alpha]_D^{25}$ = +74.3 (*c* = 1.63, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3 H), 1.34 (s, 3 H), 2.36 (s, 3 H), 3.10 (br. s, 1 H), 3.28 (br. s, 1 H), 3.97 (br. s, 4 H), 4.44 (br. s, 2 H), 4.90 (br. s, 1 H), 5.88 (br. s, 1 H), 5.93 (s, 2 H), 6.45 (s, 1 H), 6.80 (s, 1 H), 6.99 (br. s, 2 H), 7.16–7.32 (m, 5 H), 7.38 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 45.2 (CH_2), 54.1 (CH_2), 57.5 (CH_2), 67.9 (CH), 77.9 (CH), 85.5 (CH), 101.0 (CH_2), 104.9 (CH), 111.4 (C), 112.0 (CH), 121.5 (C), 127.3 (CH), 127.7 (3 CH), 128.4 (3 CH), 128.7 (CH), 129.1 (2 CH), 136.5 (C), 138.1 (C), 141.7 (C), 143.2 (C), 147.1 (C), 147.6 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3429), 3059, 3021, 2921, 2805, 1751 cm^{-1}. $C_{30}H_{32}N_2O_7S$ (564.65): calcd. C 63.81, H 5.71, N 4.96; found C 63.67, H 5.59, N 4.88. MS (ESI): *m*/*z* = 587 (M^+ + Na).

(2*R*,3*R*,3a*S*,11a*R*)-10-Isopropyl-2,3-(isopropylidenedioxy)-4-(*p*-tolylsulfonyl)-3a,4,5,10,11,11a-hexahydrofuro[3,2-*b*][1,5]benzodiazocine (5d): Gummy material; yield 0.375 g (0.79 mmol, 79%) (eluent PS/EA, 6:1). $[\alpha]_D^{25}$ = +69.4 (*c* = 1.56, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.0 Hz, 3 H), 1.08 (d, *J* = 6 Hz, 3 H), 1.36 (s, 3 H), 1.53 (s, 3 H), 2.32 (s, 3 H), 2.90 (br. s, 1 H), 3.69 (dd, *J* = 15.0, 8.2 Hz, 1 H), 3.93–4.00 (m, 1 H), 4.59–4.83 (m, 4 H), 5.00 (br. s, 1 H), 6.00 (d, *J* = 2.4 Hz, 1 H), 6.71–7.34 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 16.6 (CH_3), 20.9 (CH_3), 22.7 (CH_3), 25.7 (CH_3), 26.2 (CH_3), 45.0 (CH), 48.0 (CH_2), 50.2 (CH_2), 64.0 (CH), 77.6 (CH), 87.7 (CH), 104.1 (CH), 111.3 (C), 116.7 (CH), 127.4 (2 CH), 127.7 (CH), 128.1 (2 CH), 131.9 (CH), 132.8 (CH), 132.8 (CH), 135.4 (C), 141.8 (C), 150.6 (C), 154.4 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3420), 2975, 2935, 1692 cm^{-1}. $C_{25}H_{32}N_2O_5S$ (472.60): calcd. C 63.54, H 6.82, N 5.93; found C 63.39, H 6.66, N 5.75. MS (ESI): *m*/*z* = 495 (M^+ + Na).

(2*R*,3*R*,3a*R*,11a*R*)-10-Benzyl-2,3-(isopropylidenedioxy)-4-(*p*-tolylsulfonyl)-3a,4,5,10,11,11a-hexahydrofuro[3,2-*b*][1,5]benzodiazocine (5e): Pale yellow solid, m.p. 158 °C; yield 0.355 g (0.68 mmol, 68%) (eluent PS/EA, 6:1). $[\alpha]_D^{25}$ = +34.1 (*c* = 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 3 H), 1.45 (s, 3 H), 2.36 (s, 3 H), 3.23–3.28 (d-like, 1 H), 3.37–3.46 (m, 2 H), 3.97 (d, *J* = 14.8 Hz, 1 H), 4.21 (d, *J* = 15.0 Hz, 1 H), 4.53 (t, *J* = 4.6 Hz, 1 H), 4.65 (d, *J* = 16.3 Hz, 1 H), 4.85 (d, *J* = 16.3 Hz, 1 H), 4.92 (t, *J* = 3.4 Hz, 1 H), 5.56 (d, *J* = 3.6 Hz, 1 H), 6.76–7.48 (m, 13 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4 (CH_3), 26.1 (CH_3), 26.3 (CH_3), 51.4 (CH_2), 54.4 (CH_2), 58.1 (CH_2), 63.0 (CH), 77.8 (CH), 80.0 (CH), 103.0 (CH), 112.0 (C), 118.6 (CH), 121.5 (CH), 127.0 (CH), 127.7 (2 CH), 127.8 (2 CH), 128.4 (2 CH), 128.9 (2 CH), 129.0 (CH), 133.0 (CH), 135.4 (C), 137.9 (C), 141.7 (C), 142.8 (C), 151.1 (C) ppm. IR (KBr): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3431), 2987, 2935, 1599, 1494 cm^{-1}. $C_{29}H_{32}N_2O_5S$ (520.63): calcd. C 66.90, H 6.20, N 5.38; found C 66.75, H 6.09, N 5.22. MS (ESI): *m*/*z* = 543 (M^+ + Na).

(2*R*,3*R*,3a*R*,11a*R*)-10-[(1,3-Benzodioxol-5-yl)methyl]-2,3-(isopropylidenedioxy)-4-(*p*-tolylsulfonyl)-3a,4,5,10,11,11a-hexahydrofuro-[3,2-*b*][1,5]benzodiazocine (5f): Pale yellow solid, m.p. 165 °C; yield 0.4 g (0.71 mmol, 71%) (eluent PS/EA, 6:1), $[\alpha]_D^{25}$ = +32.6 (*c* = 0.26, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 3 H), 1.43 (s, 3 H), 2.37 (s, 3 H), 3.16 (d, *J* = 10.2 Hz, 1 H), 3.33–3.43 (m, 2 H), 3.92 (d, *J* = 14.4 Hz, 1 H), 4.10 (d, *J* = 14.4 Hz, 1 H), 4.48 (t, *J* = 4.5 Hz, 1 H), 4.64 (d, *J* = 16.2 Hz, 1 H), 4.85 (d, *J* = 16.8 Hz, 1 H) overlapped with 4.89 (d, *J* = 3.6 Hz, 1 H), 5.56 (d, *J* = 3.3 Hz, 1 H), 5.93 (d, *J* = 4.2 Hz, 2 H), 6.64 (d, *J* = 7.5 Hz, 2 H), 6.70–6.73 (m, 2 H), 6.83 (d, *J* = 7.5 Hz, 1 H), 6.97 (t, *J* = 7.2 Hz, 1 H), 7.12–7.21 (m, 3 H), 7.42–7.44 (d-like, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.3 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 51.0 (CH_2), 54.9 (CH_2), 58.1 (CH_2), 63.1 (CH), 77.6 (CH), 80.1 (CH), 100.8 (CH_2), 102.9 (CH), 108.0 (CH), 108.2 (CH), 111.9 (C), 118.9 (CH), 121.0 (CH), 121.8 (CH), 127.8 (2 CH), 128.2 (C), 128.9 (3 CH), 131.9 (C), 132.7 (CH), 135.7 (C), 142.8 (C), 146.6 (C), 147.8 (C), 151.1 (C) ppm. IR (KBr): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3429), 2984, 2928, 1599, 1494 cm^{-1}. $C_{30}H_{32}N_2O_7S$ (564.65): calcd. C 63.81, H 5.71, N 4.96; found C 63.65, H 5.59, N 4.83. MS (ESI): *m*/*z* = 587 (M^+ + Na).

(2*R*,3*R*,3a*S*,11a*R*)-10-Benzyl-4-(*tert*-butoxycarbonyl)-2,3-(isopropylidenedioxy)-3a,4,5,10,11,11a-hexahydrofuro[3,2-*b*][1,5]benzodiazocine (5g): Syrup; yield 0.35 g (0.75 mmol, 75%) (eluent PS/EA, 6:1). $[\alpha]_D^{25}$ = +61.3 (*c* = 1.12, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09–1.33 (m, 15 H), 2.79 (d, *J* = 11.5 Hz, 1 H), 3.34–3.38 (m, 1 H), 4.02–4.23 (m, 4 H), 4.46 (d, *J* = 13.5 Hz, 1 H), 5.56 (d, *J* = 14.7 Hz, 1 H), 5.11 (br. s, 1 H), 6.04 (br. s, 1 H), 6.93–7.33 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 26.3 (CH_3), 26.8 (CH_3), 28.3 (3 CH_3), 52.9 (CH_2), 56.0 (CH_2), 58.7 (CH_2), 71.6 (CH), 79.0 (CH), 80.2 (C), 84.5 (CH), 106.7 (CH), 110.3 (C), 127.0 (CH), 127.3 (CH), 128.2 (CH), 128.4 (4× CH), 128.6 (C), 132.6 (CH), 139.2 (C), 139.7 (C), 155.0 (C) ppm. IR (neat): $\tilde{\nu}$ = (ν_{max} = 2925), 2855, 1697, 1599 cm^{-1}. $C_{27}H_{34}N_2O_5$ (466.57): calcd. C 69.50, H 7.35, N 6.00; found C 69.32, H 7.22, N 5.43. MS (ESI): *m*/*z* = 489 (M^+ + Na).

Synthesis of Benzodiazocine Derivative 6: Compound **5g** (0.5 mmol) was dissolved in 25 mL of CH_3CN/H_2O (1:1) containing 5% H_2SO_4 and the solution was kept at room temperature for 36 h. Then the acidic solution was neutralized with solid $NaHCO_3$, filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in minimum volume of MeOH and treated dropwise at 0 °C with an aqueous solution of $NaIO_4$ (128 mg, 0.6 mmol) with stirring for 1 h. Usual work up followed by $NaBH_4$ 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 a crude product, which was purified by silica gel flash chromatography to afford **6**.

(3*R*,4*R*)-3-Acetoxy-4-(acetoxymethyl)-5-acetyl-1-benzyl-1,2,3,4,5,6-hexahydro-benzo[*b*][1,5]diazocine (6): Syrup; yield 0.132 g (0.31 mmol, 62%). R_f = 0.65 (PS/EA, 2:1), eluent PS/EA (6:1). $[\alpha]_D^{25}$ = +73.5 (*c* = 0.98, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3 H), 2.04 (s, 3 H), 2.09 (s, 3 H), 2.81 (dd, *J* = 8.1, 5.1 Hz, 1 H), 3.00–3.07 (dd-like, 1 H), 4.00–4.10 (m, 2 H), 4.16–4.27 (dd-like, 1 H), 4.37 (d, *J* = 15.9 Hz, 1 H), 4.46–4.56 (dd-like, 1 H), 4.68–4.97 (m, 2 H), 5.18 (d, *J* = 13.2 Hz, 1 H),7.00–7.68 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 20.7 (CH_3), 20.9 (2 CH_3), 56.6 (CH_2), 59.0 (CH_2), 59.8 (CH), 61.0 (CH_2), 72.6 (CH), 126.3 (CH), 127.6 (3 CH), 128.4 (CH), 128.6 (3 CH), 130.1 (C), 131.7 (CH), 136.7 (C), 137.7 (C), 169.5 (C), 170.5 (C), 171.1 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3408), 2926, 2855, 1739, 1644 cm^{-1}. $C_{24}H_{28}N_2O_5$ (424.49): calcd. C 67.91, H 6.65, N 6.60; found C 67.79, H 6.53, N 6.46. MS (ESI): *m*/*z* = 447 (M^+ + Na).

Procedure for the Synthesis of the Dibenzodiazocine Derivative: To a stirring solution of *o*-nitrobenzaldehyde (4 mmol) and 1,3-propanedithiol (4.4 mmol) in dry CH_2Cl_2 (30 mL), 0.4 mmol of I_2 was added at 0 °C. After 15 min, the mixture was brought to room temp. and stirred for another half an hour. After complete conversion (indicated by TLC), the reaction mixture was washed with saturated $Na_2S_2O_3$ solution (2× 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford a solid material. It was dissolved in 95% ethanol (50 mL), Pd/C (0.1 g) was added and the mixture was heated to reflux under N_2. Hydrazine hydrate (6 mmol) was then added dropwise. The refluxing was continued for another 4 h. After completion of reaction (indicated by TLC) the reaction mixture was cooled to r. t., filtered through celite to remove the insoluble part, and evaporated in vacuum. The amine was tosylated and the tosylamine was arylated as earlier to afford

7. Compound **7** (2 mmol) was dissolved in 40 mL of CH_3CN/H_2O (90:1), methyl iodide (12 mmol) was added, and the mixture was stirred at room temperature for 24 h. After completion of reaction (indicated by TLC) the solvent was removed under reduced pressure and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The extract was washed with saturated $Na_2S_2O_3$ solution (2 × 30 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford the intermediate benzaldehyde. This was dissolved in 20 mL of dehydrated ethanol, treated with benzylamine (2.4 mmol), and stirred for 12 h. Then it was cooled to 0 °C, $NaBH_4$ (4 mmol) was added, and the mixture was stirred for 6 h. The solvent was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layer was washed with water, dried, and the solvents evaporated. The product was chromatographed on silica gel to afford the amine **8**. It was then subjected to cycloamination reaction as in the earlier procedure.

***N*-(2-Bromobenzyl)-*N*-[2-(1,3-dithian-2-yl)phenyl]-4-methylbenzenesulfonamide (7):** Gummy material. Overall yield 1.37 g (2.56 mmol, 64%). R_f = 0.68 (PS/EA, 2:1), eluent PS/EA (7:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82–1.91 (m, 1 H), 2.08–2.17 (m, 1 H), 2.46 (s, 3 H), 2.69 (d, J = 12.6 Hz, 1 H), 2.88–3.04 (m, 3 H), 4.55 (d, J = 13.5 Hz, 1 H), 5.19 (d, J = 13.8 Hz, 1 H), 5.37 (s, 1 H), 6.77 (d, J = 8.1 Hz, 1 H), 7.03 (t, J = 7.2 Hz, 1 H), 7.13 (br. s, 2 H), 7.20–7.37 (m, 4 H), 7.42 (d, J = 7.2 Hz, 1 H), 7.53–7.61 (m, 1 H), 7.69–7.71 (d-like, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 21.6 (CH_3), 25.1 (CH_2), 32.4 (CH_2), 32.5 (CH_2), 46.7 (CH), 55.5 (CH_2), 124.8 (C), 128.3 (CH), 128.4 (3 CH), 129.0 (CH), 129.2 (CH), 129.4 (CH), 129.6 (2 CH), 130.0 (CH), 131.9 (CH), 133.0 (CH), 134.6 (C), 135.2 (C), 136.1 (C), 1140.4 (C), 143.8 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 2923), 2855, 1659, 1444 cm^{-1}. $C_{24}H_{24}BrNO_2S_3$ (534.55): calcd. C 53.92, H 4.53, N 2.62; found C 53.77, H 4.38, N 2.51. MS (ESI): m/z = 556 (M^+ + Na for Br^{79}).

***N*-[2-(Benzylaminomethyl)phenyl]-*N*-(2-bromobenzyl)-4-methylbenzenesulfonamide (8):** Syrup; yield 0.835 g (1.56 mmol, 78%). R_f = 0.40 (PS/EA, 2:1), eluent PS/EA (4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (br. s, 1 H), 2.45 (s, 3 H), 3.48 (br. s, 1 H), 3.59 (s, 2 H), 3.66 (br. s, 1 H), 4.46 (d, J = 12.9 Hz, 1 H), 5.18 (d, J = 12.9 Hz, 1 H), 6.67 (d, J = 7.8 Hz, 1 H), 6.96–7.00 (m, 1 H), 7.09 (dd, J = 18, 7.8 Hz, 2 H), 7.22–7.36 (m, 10 H), 7.48 (d, J = 7.5 Hz, 1 H), 7.59–7.61 (d-like, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.6 (CH_3), 48.4 (CH_2), 53.7 (CH_2), 55.2 (CH_2), 124.5 (C), 126.7 (CH), 127.0 (CH), 127.3 (CH), 128.1 (2 CH), 128.2 (5 × CH), 128.6 (CH), 129.5 (3 CH), 130.2 (CH), 132.1 (CH), 132.8 (CH), 134.7 (C), 135.2 (C), 136.9 (C), 140.5 (C), 142.1 (C), 143.8 (C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3338), 3061, 3027, 2921, 2856, 1924, 1811, 1596 cm^{-1}. $C_{28}H_{27}BrN_2O_2S$ (535.5): calcd. C 62.80, H 5.08, N 5.23; found C 62.64, H 4.92, N 5.08. MS (ESI): m/z = 557 (M^+ + Na for Br^{79}).

5-Benzyl-11-(*p*-tolylsulfonyl)-5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,5]diazocine (9): Colorless solid, m.p. 132 °C; yield 0.53 g (1.17 mmol, 75%). R_f = 0.62 (PS/EA, 2:1), eluent PS/EA (6:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 3.41 (br. s, 2 H), 4.07 (s, 2 H), 4.83 (br. s, 2 H), 6.60 (br. s, 1 H), 6.82 (br. s, 1 H), 6.92–7.03 (m, 4 H), 7.08–7.14 (m, 5 H), 7.19–7.23 (m, 4 H), 7.40 (br. s, 4 H), 7.61 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4 (CH_3), 55.0 (CH_2), 57.4 (2 CH_2), 119.1 (CH), 121.4 (C), 126.9 (3 CH), 127.0 (CH), 127.3 (CH), 128.1 (2 CH), 128.3 (3 CH), 128.9 (CH), 129.1 (3 CH), 130.4 (CH), 133.0 (CH), 136.4 (2 C), 138.4 (2 C), 142.8 (2 C) ppm. IR (neat): $\tilde{\nu}$ = ($\tilde{\nu}_{max}$ = 3064), 3027, 2929, 1710, 1598 cm^{-1}. $C_{28}H_{26}N_2O_2S$ (454.58): calcd. C 73.98, H 5.76, N 6.16; found C 73.82, H 5.61, N 6.05. MS (ESI): m/z = 477 (M^+ + Na).

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **4a**,**b**, **4f**, **5a**,**b**, **5f**, **6**, **8**, **9**.

Acknowledgments

Financial assistance from Department of Science and Technology (Government of India) is highly acknowledged. N. D. A. thanks the Council of Scientific and Industrial Research for providing a research fellowship. We acknowledge Dr. B. Achari, emeritus scientist, Indian Institute of Chemical Biology, for his interest in this work. We are also grateful to Dr. R. Mukherjee of chemistry division for NMR studies.

[1] a) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930; b) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Berluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953; c) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Carino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springes, J. Hirshfield, *J. Med. Chem.* **1988**, *31*, 2235–2246.

[2] a) E. Vedejs, R. J. Galante, P. G. Goekjian, *J. Am. Chem. Soc.* **1998**, *120*, 3613–3622; b) M. R. Stillings, S. Freeman, P. L. Myers, M. J. Readhead, A. P. Welboum, M. J. Rance, D. C. Atkinson, *J. Med. Chem.* **1985**, *28*, 225–233; c) B. Basil, E. C. J. Coffee, D. L. Gell, D. R. Maxwell, D. J. Sheffield, K. R. H. Wooldridge, *J. Med. Chem.* **1970**, *13*, 403–406.

[3] Y. Endo, M. Ohno, M. Hirano, A. Itai, K. Shudo, *J. Am. Chem. Soc.* **1996**, *118*, 1841–1855.

[4] F. Viladomat, J. E. Bastida, C. Codina, W. E. Campbell, S. Mathee, *Phytochemistry* **1995**, *40*, 307–311.

[5] a) T. Howard in *Comprehensive Heterocyclic Chemistry II*, vol. 7 (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, New York, **1996**, pp. 151–182; b) K. M. Doxsee, in: *Comprehensive Heterocyclic Chemistry II*, vol. 7 (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, New York, **1996**, pp. 591–649.

[6] a) M. Harmata, W. Ying, C. L. Barnes, *Tetrahedron Lett.* **2009**, *50*, 2326–2328; b) S. M. Lu, H. Alper, *J. Am. Chem. Soc.* **2008**, *130*, 6451–6455; c) E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino, E. Rossi, *Synthesis* **2006**, 2404–2412; d) C. Ferrer, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109; e) H. Bieraügel, T. P. Jansen, H. E. Schoemaker, H. Hiemstra, J. H. van Maarseveen, *Org. Lett.* **2002**, *4*, 2673–2676; f) U. Nubbemeyer, *Top. Curr. Chem.* **2001**, *216*, 125–196; g) U. M. Lindström, P. Somfai, *Chem. Eur. J.* **2001**, *7*, 94–98; h) M. E. Maier, *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077; i) S. Derrer, J. E. Davies, A. B. Holmes, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2957–2967; j) P. A. Evans, B. Holmes, *Tetrahedron* **1991**, *47*, 9131–9166.

[7] a) R. Pflantz, J. Sluiter, M. Krička, W. Saak, C. Hoenke, J. Christoffers, *Eur. J. Org. Chem.* **2009**, 5431–5436; b) J. Rujirawanich, T. Gallagher, *Org. Lett.* **2009**, *11*, 5494–5496; c) I. Stansfield, C. Ercolani, A. Mackay, I. Conte, M. Pompei, U. Koch, N. Gennari, C. Giuliano, M. Rowley, F. Narjes, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 627–632; d) H. Yoshida, E. Shirakawa, Y. Honda, T. Hiyama, *Angew. Chem. Int. Ed.* **2002**, *41*, 3247–3249; e) W. A. L Van Otterlo, G. L. Morgan, S. D. Khanya, B. A. A. Aderibigbe, J. P. Michael, D. G. Billing, *Tetrahedron Lett.* **2004**, *45*, 9171–9175; f) A. Klapars, S. Parris, K. W. Anderson, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 3259–3533; g) G. Cuny, M. Bois-Choussy, J. Zhu, *J. Am. Chem. Soc.* **1998**, *120*, 14475–14484; h) E. C. Taylor, D. M. Sobieray, *Tetrahedron* **1991**, *47*, 9599–9620; i) M. E. Derieg, R. M. Schweininger, R. I. Fryer, *J. Org. Chem.* **1969**, *34*, 179–183; j) M. Denzer, H. Ott, *J. Org. Chem.* **1969**, *34*, 183–187.

[8] a) J. F. Hartwig, *Nature* **2008**, *455*, 314–322; b) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361; c) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125–146; d) J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; e) J. P. Wolfe, S. Wagaw, J. F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805–818.

[9] a) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348–1350; b) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609–3612.

[10] a) M. D. Charles, P. Schultz, S. L. Buchwald, *Org. Lett.* **2005**, *7*, 3965–3968; b) S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402–3415; c) J. F. Hartwig, M. Kawatsura, S. L. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575–5580; d) G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110; e) J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216; f) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.

[11] a) T. P. Majhi, B. Achari, P. Chattopadhyay, *Heterocycles* **2007**, *71*, 1011–1052, and the references cited therein; b) C. Venkatesh, G. S. Sundram, H. Ila, H. Junjappa, *J. Org. Chem.* **2006**, *71*, 1280–1283; c) C. T. Brain, J. T. Steer, *J. Org. Chem.* **2003**, *68*, 6814–6816; d) B. J. Margolis, J. J. Swidorski, B. N. Rogers, *J. Org. Chem.* **2003**, *68*, 644–647; e) Y. M. Zhu, Y. Kiryu, H. Katayama, *Tetrahedron Lett.* **2002**, *43*, 3577–3580; f) K. Yamada, T. Kubo, H. Tokuyama, T. Fukuyama, *Synlett* **2002**, 231–234; g) J. P. Wolfe, R. A. Rennels, S. L. Buchwald, *Tetrahedron* **1996**, *52*, 7525–7546.

[12] a) E. L. Cropper, A.-P. Yuen, A. Ford, A. J. P. White, K. K. Hii, *Tetrahedron* **2009**, *65*, 525–530; b) A. Neogi, T. P. Majhi, R. Mukhopadhyay, P. Chattopadhyay, *J. Org. Chem.* **2006**, *71*, 3291–3294; c) B. E. Fink, A. V. Gavai, G. D. Vite, W.-C. Han, R. N. Misra, H.-Y. Xia, D. J. Norris, J. S. Tokarski, US Patent US2005/0250753.

[13] A. Neogi, T. P. Majhi, B. Achari, P. Chattopadhyay, *Eur. J. Org. Chem.* **2008**, 330–336.

[14] a) Z. Li, X. Xua, Y. Penga, Z. Jianga, C. Dinga, X. Qian, *Synthesis* **2005**, 1228–1230; b) J. Tröger, *J. Prakt. Chem.* **2004**, *36*, 225–245; c) C. Pardo, E. Sesmilo, E. Gutierrez-Puebla, E. Monge, A. Elguero, J. Fruchier, *J. Org. Chem.* **2001**, *66*, 1607–1611; d) S. Ghosh, K. Dasgupta, *J. Org. Chem.* **2000**, *65*, 1907–1914; e) A. Manjula, M. Nagarajan, *Tetrahedron* **1997**, *53*, 11859–11868.

[15] J. S. Brimacombe, J. G. H. Bryan, A. Husain, M. Stacey, M. S. Tolley, *Carbohydr. Res.* **1967**, *3*, 318.

[16] a) T. P. Majhi, A. Neogi, S. Ghosh, A. K. Mukherjee, P. Chattopadhyay, *Tetrahedron* **2006**, *62*, 12003–12010; b) A. Neogi, T. P. Majhi, N. Ghosal, P. Chattopadhyay, *Tetrahedron* **2005**, *61*, 9368–9374; c) T. P. Majhi, A. Nandi, A. Neogi, R. Mukhopadhyay, P. Chattopadhyay, *Synthesis* **2005**, 2307–2314; d) P. Chattopadhyay, M. Mukherjee, S. Ghosh, *Chem. Commun.* **1997**, 2139–2140.

[17] a) J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144–1157; b) Y. Guari, V. E. Es, N. H. Reek, J. Kamer, P. W. N. M. V. Leeuwen, *Tetrahedron Lett.* **1999**, *40*, 3789–3790; c) G. Mann, D. Baralano, J. F. Hartwig, A. L. Rheingold, I. A. J. F. Guzei, *J. Am. Chem. Soc.* **1998**, *120*, 9205–9219.

[18] Crystal data of compound **5e**: $C_{29}H_{32}N_2O_5S$, FW = 520.63, monoclinic, space group $P21$, a = 11.8542 (10) Å, b = 8.0618 (6) Å, c = 14.7356 (13) Å, α = 90.00°, β = 112.119 (6)°, γ = 90.00°, V = 1304.58 (19) Å^3, Z = 2, T = 296(2) K, $d_{calcd.}$ = 1.325 g cm^{-3}, F (000) = 336. Diffraction data were measured with Mo-K_α (λ = 0.71073 Å) radiation at 296 K using a Bruker Kappa Apex 2 CCD system. A total of 1989 unique reflections were measured (θ_{max} = 24.49°). Data analyses were carried out with the Fast Fourier Transform program. The structures were solved by direct methods using the SHELXS-97 program.[22] Refinements were carried out with a full-matrix least-squares method against F^2 using SHELXL-97.[23] Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R value was $R1$ = 0.0291 and $wR2$ = 0.0966 with $I > 2\sigma(I)$. CCDC-755652 contains the supplementary crystallographic data for **5e**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

[19] H. Firouzabadi, N. Iranpoor, H. Hazarkhani, *J. Org. Chem.* **2001**, *66*, 7527–7529.

[20] S. Takano, S. Hatakeyama, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1977**, 68.

[21] Crystal data of compound **9**: $C_{28}H_{26}N_2O_2S$, FW = 454.58, triclinic, space group $P\bar{1}$, a = 9.9082 (11) Å, b = 10.5516 (11) Å, c = 11.7388 (13) Å, α = 99.398 (5)°, β = 91.624 (6)°, γ = 104.646 (4)°, V = 1168.3 (2) Å^3, Z = 2, T = 296(2) K, $d_{calcd.}$ = 1.292 g cm^{-3}, F (000) = 336. Diffraction data were measured with Mo-K_α (λ = 0.71073 Å) radiation at 296 K using a Bruker Kappa Apex 2 CCD system. A total of 4896 unique reflections were measured (θ_{max} = 25.0°). Data analyses were carried out with the Fast Fourier Transform program. The structures were solved by direct methods using the SHELXS-97 program.[22] Refinements were carried out with a full-matrix least-squares method against F^2 using SHELXL-97.[23] Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R value was $R1$ = 0.0436 and $wR2$ = 0.1234 with $I > 2\sigma$ (I). CCDC-756007 contains the supplementary crystallographic data for **9**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

[22] G. M. Sheldrick, *SHELXS-97, Program for solution of crystal structures*, University of Göttingen, Germany, **1997**; G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467.

[23] G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, **1997**.

Received: December 17, 2009
Published Online: February 12, 2010

