A Modified Synthetic Approach to Optically Pure Benzoxazepines from Amino Acid Precursors Using Intramolecular Buchwald–Hartwig C–O Bond-Formation Reaction

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Abstract: Palladium-catalyzed intramolecular aryl etherification reaction using bulky binaphthylphosphane ligand is shown to be a convenient method for the synthesis of seven-membered heterocycles. Application of this methodology to a naturally occurring proteinogenic L-amino acid has led to the synthesis of optically active benzoxazepine ring systems of versatile biological importance.

Key words: amino acids, palladium, ligand, etherification, chiral benzoxazepines

A wide variety of benzo-fused medium ring heterocycles containing nitrogen and oxygen atoms form the core structural motif of common natural products endowed with a broad range of medicinal values.[1] These structures represent a class of molecules, which are capable of binding to multiple receptors with high affinity and acting as good antagonist.[2] Benzannulated seven-membered rings have significant antinociceptive properties[3] and are frequently used as antidepressants.[4] Abundance of a large number of CNS active novel seven-membered oxa-aza heterocycles[5] support their huge potency in neuro diseases and these are of great pharmacological demand due to their properties as enzyme inhibitors, analgesics, and antitussives.[6] Among them, 1,4-benzoxazepines are well known for their enormous antitumor activities in breast cancer cells[7] as well as for excellent anti-inflammatory[8] and antithrombotic[9] activities. Also, 1,4-benzoxazepine derivatives were established for squalene synthase inhibitory and cholesterol biosynthesis inhibitory activities.[10] Hence, the development of a simple and modified route to synthesize seven-membered fused heterocycles has become a challenging area for synthetic organic chemists.

Although several approaches to the synthesis of benzo- and dibenzoxazepines using Pd-mediated intramolecular aryl etherification, aryl amination, carbonylation, or other methods have been reported in the literature,[11] application of these methodologies to the preparation of chiral benzannulated heterocycles are scarce. Recently, Panda et al. reported[12] the synthesis of chiral benzoxazepines from natural amino acids using intramolecular Mitsunobu approach of C–O bond formation reaction. But this method requires a lengthy sequence of reactions and provides only low yields of reaction products. Another synthetic route[13] developed by Vinsova et al. described unexpected and poor formation of benzoxazepine moiety through esterification of biologically active salicylanilides with some N-protected amino acids. Therefore a better procedure for the synthesis of optically pure benzoxazepines remains to be established.

In continuation of our project for the synthesis of chiral medium ring heterocycles from carbohydrate precursors,[14] we designed the synthesis of biologically active optically pure 1,4-benzoxazepines using L-amino acids as cheap and useful chiral synthon. In this article, we report a short and efficient synthetic route of this class of compounds in excellent yield and good purity applying intramolecular aryl etherification[15] strategy.

Initially we planned to protect the NH_2 and CO_2H group of naturally abundant amino acids. Condensation with α-bromobenzyl bromides should then lead successfully to N-benzylation and the esterified CO_2H group was to be smoothly reduced to alcohol. The product was expected to function as a substrate for an intramolecular Buchwald–Hartwig aryl etherification reaction leading to the chiral benzoxazepines. In actual practice different L-amino acids **1** were first reacted with *p*-toluenesulfonyl chloride (**2**) and aqueous NaOH; subsequent acidification with concentrated HCl afforded[16] *N*-tosylamino acids **3** (Scheme 1). These N-protected amino acids were then converted[17] to their methyl esters **4** by treatment with *p*-toluenesulfonic acid in anhydrous MeOH under refluxing condition. N-Alkylation of the products **4** with appropriately substituted 2-bromobenzyl bromides **5** afforded[18] the respective bromobenzyl-*N*-tosylamino acid methyl esters **6a–g** in 70–73% yields (Table 1). There was a choice of reagents for this particular step. Primarily, NaH in anhydrous DMF was employed at 0 °C to room temperature (Table 1, entry 1) furnishing the required product in short time but in low yield. So the reaction condition was changed to K_2CO_3 in anhydrous acetone at room temperature (Table 1, entries 2 and 4) to get a somewhat better yield. But the best result was recorded by changing the solvent to anhydrous acetonitrile. Lithium borohydride ($LiBH_4$) reduction of **6a–g** in anhydrous THF under reflux for 14–20 hours then gave the corresponding alcohols[19] **7a–g** as thick oils in 75–78% yields (Table 2).

In order to develop a facile aryl etherification methodology through intramolecular Pd-induced cyclization, we

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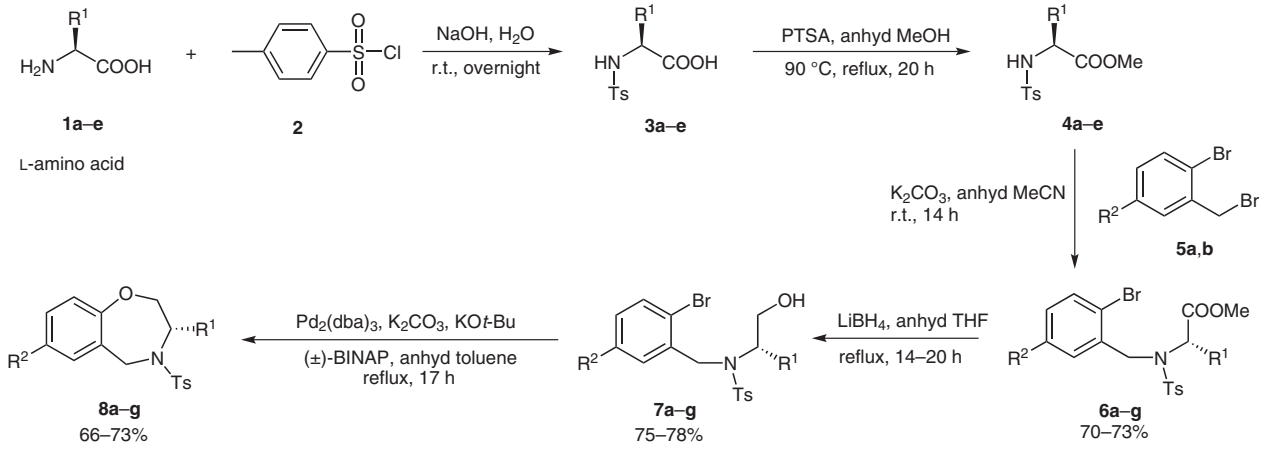


Scheme 1 Synthesis of optically pure 1,4-benzoxazepine moieties

Table 1 Benzylation of N-Protected Amino Acid Ester

4a–e + **5a,b** —(base / solvent)→ **6a–g**

Entry	Substrate	R^1	R^2	Base	Solvent (anhyd)	Product	Yield (%)[a]
1	**4a**	Me	H	NaH	DMF	**6a**	58[b]
2	**4a**	Me	H	K_2CO_3	acetone	**6a**	64
3	**4a**	Me	H	K_2CO_3	MeCN	**6a**	71
4	**4b**	*i*-Pr	H	K_2CO_3	acetone	**6b**	66
5	**4b**	*i*-Pr	H	K_2CO_3	MeCN	**6b**	73
6	**4c**	*i*-Bu	H	K_2CO_3	MeCN	**6c**	72
7	**4d**	*s*-Bu	H	K_2CO_3	MeCN	**6d**	71
8	**4e**	Bn	H	K_2CO_3	MeCN	**6e**	72
9	**4e**	Bn	OMe	K_2CO_3	MeCN	**6f**	71
10	**4b**	*i*-Pr	OMe	K_2CO_3	MeCN	**6g**	70

[a] Isolated yield.
[b] Reaction conditions: 0 °C to r.t., 7 h.

Table 2 Reduction of Substituted Bromobenzyl Ester

6a–g —($LiBH_4$, anhyd THF, reflux)→ **7a–g**

Entry	Substrate	R^1	R^2	Time (h)	Product	Yield (%)[a]
1	**6a**	Me	H	20	**7a**	76
2	**6b**	*i*-Pr	H	18	**7b**	77
3	**6c**	*i*-Bu	H	17	**7c**	78
4	**6d**	*s*-Bu	H	17	**7d**	78
5	**6e**	Bn	H	16	**7e**	77
6	**6f**	Bn	OMe	14	**7f**	75
7	**6g**	*i*-Pr	OMe	14	**7g**	78

[a] Isolated yield.

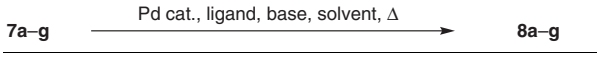
tested the reagent system – $Pd_2(dba)_3$/(±)-BINAP/*t*-BuOK + K_2CO_3 – in toluene as reported by Rogers et al.[11c,15] However, as no reaction took place (based on TLC) even after 18 hours of heating at 90 °C, the reaction mixture was allowed to reflux gently for 17 hours when the reactant was entirely consumed. Usual workup followed by column chromatographic purification gave the desired cyclic products **8** in 66–73% yields. Deprotection of tosyl group can easily be performed in different ways.[12,20]

In order to optimize the reaction condition, we have explored other reported reagent systems. By screening a variety of bases we found the combination of K_2CO_3 and *t*-BuOK as the most efficient base for cyclization including Cs_2CO_3 and *t*-BuONa (Table 3, entries 2 and 3). $Pd(OAc)_2$ as an alternative source of Pd also furnished the desired cyclic ether but less efficiently (Table 3, entry 2) and $Pd(PPh_3)_4$ was not at all a good choice. The most versatile ligand was found to be (±)-BINAP and toluene was more effective as solvent than DMF. Therefore, the appropriate reaction condition includes 10 mol% $Pd_2(dba)_3$ as catalyst, 7 mol% (±)-BINAP as ligand, 2 equivalents each of K_2CO_3 and *t*-BuOK, and toluene (10 L/mol) as solvent under reflux.

The assigned structures of the benzoxazepine derivatives **8a–g** were rationalized by ^{1}H NMR as well as ^{13}C NMR, mass, and IR spectroscopy. The benzylic methylene protons attached to N resonated between δ = 4.47–4.79 as doublets. The only proton on the chiral center was detected as a multiplet between δ = 4.02–4.26. The signals for OCH_2 protons adjacent to the chiral center appeared at δ = 3.68–3.92. For compounds **8f** and **8g**, the methoxy protons signal showed up as a singlet at δ = 3.76. The cyclic structure was also confirmed by a single crystal X-ray analysis[21–23] of **8g** (Figure 1).

The present strategy thus establishes transition-metal-catalyzed cycloetherification as a suitable synthetic tool for the preparation of optically active benzoxazepines by exploiting the supremacy of L-amino acids as chiral synthon. A probable mechanism of intramolecular aryl

Table 3 Optimization of the Intramolecular Palladium-Catalyzed Cycloetherification Reaction



Entry	Substrate	Base	Catalyst	Ligand	Solvent	Product[a]	Yield (%)[b]
1	**7a**	K_2CO_3	$Pd(PPh_3)_4$	–	THF	**8a**	NR[c]
2	**7a**	Cs_2CO_3	$Pd(OAc)_2$	(±)-BINAP	toluene	**8a**	55[d]
3	**7a**	*t*-BuONa	$Pd_2(dba)_3$	DPPF	toluene	**8a**	51[e]
4	**7a**	K_2CO_3 + *t*-BuOK	$Pd_2(dba)_3$	(±)-BINAP	toluene	**8a**	69[f]
5	**7b**	*t*-BuOK	$Pd_2(dba)_3$	xantphos	toluene	**8b**	59[g]
6	**7b**	K_2CO_3 + *t*-BuOK	$Pd_2(dba)_3$	(±)-BINAP	DMF	**8b**	48[h]
7	**7b**	K_2CO_3 + *t*-BuOK	$Pd_2(dba)_3$	(±)-BINAP	toluene	**8b**	73[i]
8	**7c**	K_2CO_3 + *t*-BuOK	$Pd_2(dba)_3$	(±)-BINAP	toluene	**8c**	72[i]
9	**7d**	K_2CO_3 + *t*-BuOK	$Pd_2(dba)_3$	(±)-BINAP	toluene	**8d**	73[i]
10	**7e**	K_2CO_3 + *t*-BuOK	$Pd_2(dba)_3$	(±)-BINAP	toluene	**8e**	72[i]
11	**7f**	K_2CO_3 + *t*-BuOK	$Pd_2(dba)_3$	(±)-BINAP	toluene	**8f**	66[i]
12	**7g**	K_2CO_3 + *t*-BuOK	$Pd_2(dba)_3$	(±)-BINAP	toluene	**8g**	73[i]

[a] β-Elimination products (5–10%) were detected in all cases.
[b] Isolated yield.
[c] Reaction conditions: $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3 equiv), toluene (10 L/mol), reflux, overnight.
[d] Reaction conditions: $Pd(OAc)_2$ (10 mol%), (±)-BINAP (7 mol%), Cs_2CO_3 (5 equiv), toluene (10 L/mol), reflux, 16 h.
[e] Reaction conditions: $Pd_2(dba)_3$ (10 mol%), DPPF (7 mol%), *t*-BuONa (4 equiv), toluene (10 L/mol), reflux, 17 h.
[f] Reaction conditions: $Pd_2(dba)_3$ (10 mol%), (±)-BINAP (7 mol%), K_2CO_3 (2 equiv), *t*-BuOK (2 equiv), toluene (10 L/mol), reflux, 18 h.
[g] Reaction conditions: $Pd_2(dba)_3$ (10 mol%), xantphos (7 mol%), *t*-BuOK (4 equiv), toluene (10 L/mol), reflux, 19 h.
[h] Reaction conditions: $Pd_2(dba)_3$ (10 mol%), (±)-BINAP (7 mol%), K_2CO_3 (2 equiv), *t*-BuOK (2 equiv), DMF (10 L/mol), 110 °C, 14 h.
[i] Reaction conditions: $Pd_2(dba)_3$ (10 mol%), (±)-BINAP (7 mol%), K_2CO_3 (2 equiv), *t*-BuOK (2 equiv), toluene (10 L/mol), reflux, 17 h.

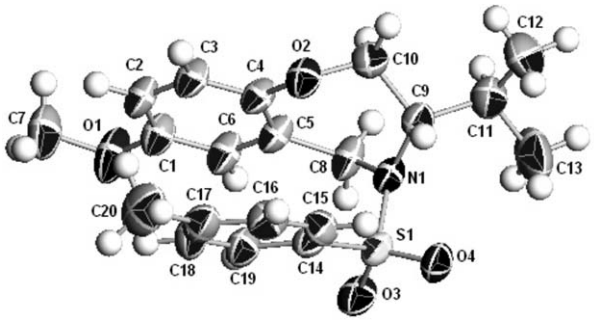
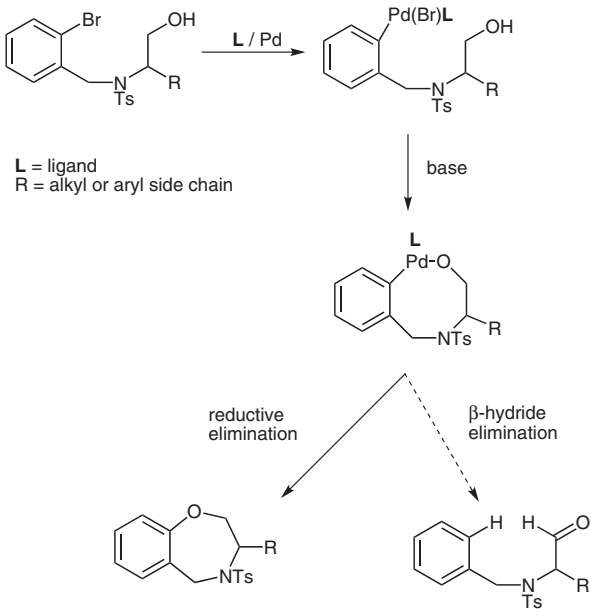


Figure 1 ORTEP diagram of compound **8g**



Scheme 2 Proposed mechanism of intramolecular aryl etherification in the synthesis of seven-membered ring

etherification[15,24] for the synthesis of benzoxazepines has been outlined in Scheme 2.

In conclusion, we have demonstrated an easy and improved synthesis of enantiomerically pure 1,4-benzoxazepines from naturally abundant L-amino acids using intramolecular C–O bond formation reaction as a key step. This is a unique approach of aryl etherification extending the feasibility of the Buchwald–Hartwig strategy using suitably designed starting materials. The fairly smooth and short reaction procedures, ease of purification, and good yield of reaction products open more opportunities for further development.

Reactions at r.t. or ambient temperature generally imply a temperature of 25 °C. Some reagents were obtained from commercial sources and used without purification. The solvents used were of technical grade, and freshly distilled prior to use. ^{1}H (300 MHz, 600 MHz) and ^{13}C (75 MHz, 150 MHz) NMR spectra were recorded using $CDCl_3$ as solvent and TMS as internal standard on Bruker DPX 300 MHz and Bruker DRX 600 MHz NMR instruments at ambient temperature. Chemical shifts are stated in parts per million in δ scales. Optical rotations were measured on a Jasco P-1020 Polarimeter. IR spectra were recorded on a Jasco FTIR Model-410, using KBr pellets or in neat condition. Mass spectra were measured mostly in ESIMS (+) and some in EIMS mode. DI-EIMS were recorded on a GCMS-Shimadzu-QP5050A and ESIMS were done on a Waters Micromass Q-TOF micro™ Mass Spectrometer. X-ray crystallographic data of single crystals were collected on Bruker Kappa Apex II with Mo-Kα radiation (λ = 0.71073Å). TLC was performed on precoated plates (0.25 nm, silica gel 60 F_{254}). Organic extracts were dried over anhyd Na_2SO_4. Column chromatography and flash chromatography were carried out using commercial grade silica gel (100–200 mesh). Petroleum ether (PE) used refers to the fraction boiling in the range 60–80 °C.

Bromobenzyl(toluene-4-sulfonyl)amino Acid Methyl Esters 6a–g; General Procedure

To a magnetically stirred solution of compound **4a–e** (5.26 mmol) in anhyd MeCN (30 mL) at r.t. was added K_2CO_3 (1.45 g, 10.52 mmol) and sonicated for 20 min. The suspension was stirred for 10 min at r.t. and the respective 2-bromobenzyl bromide **5a**,**b** (0.98 mL, 6.31 mmol) was added and again sonicated for 10 min. The mixture was then stirred for 14 h at r.t. under dry condition and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried (Na_2SO_4) and evaporated. The residue was washed with PE (2–3 × 20 mL) to remove excess 2-bromobenzyl bromide and subjected to column chromatography over silica gel (eluent: PE–EtOAc, 7:1) to afford pure solid product.

2-[(2-Bromobenzyl)(toluene-4-sulfonyl)amino]propionic Acid Methyl Ester (6a)

White crystalline solid; mp 115–118 °C; R_f = 0.53 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –28.15 (*c* 0.50, $CHCl_3$).

IR (KBr): 3064, 2976, 1740, 1596, 1450, 1342, 1198, 1161, 1029, 902, 846, 816 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 7.2 Hz, 3 H), 2.43 (s, 3 H), 3.43 (s, 3 H), 4.55–4.72 (m, 3 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 7.2 Hz, 3 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.68–7.74 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.6 (CH_3), 21.5 (CH_3), 49.0 (CH_2), 52.0 (CH_3), 55.4 (CH), 122.1 (C), 127.5 (3 CH), 128.7 (CH), 129.6 (2 CH), 129.6 (CH), 132.4 (CH), 136.5 (C), 137.0 (C), 143.7 (C), 171.4 (C).

MS (ESI): *m*/*z* = 448, 450 [M + Na]$^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{18}H_{20}BrNO_4S$: C, 50.71; H, 4.73; N, 3.29. Found: C, 50.94; H, 4.99; N, 3.05.

2-[(2-Bromobenzyl)(toluene-4-sulfonyl)amino]-3-methylbutyric Acid Methyl Ester (6b)

White crystalline solid; mp 132–133 °C; R_f = 0.52 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –34.46 (*c* 0.46, $CHCl_3$).

IR (KBr): 3067, 2970, 1737, 1595, 1468, 1439, 1347, 1295, 1203, 1158, 1112, 1022 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.3 Hz, 6 H), 1.88–1.96 (m, 1 H), 2.43 (s, 3 H), 3.32 (s, 3 H), 4.16 (d, *J* = 9.6 Hz, 1 H), 4.61 (d, *J* = 17.7 Hz, 1 H), 5.04 (d, *J* = 18.0 Hz, 1 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 7.29 (d, *J* = 7.2 Hz, 3 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.70–7.74 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 (CH_3), 20.1 (CH_3), 21.5 (CH_3), 28.7 (CH), 48.8 (CH_2), 51.2 (CH_3), 65.9 (CH), 122.3 (C), 127.2 (CH), 127.7 (2 CH), 128.5 (CH), 129.4 (2 CH), 130.2 (CH), 132.3 (CH), 136.2 (C), 137.0 (C), 143.7 (C), 170.7 (C).

MS (ESI): *m*/*z* = 476, 478 [M + Na]$^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{20}H_{24}BrNO_4S$: C, 52.87; H, 5.32; N, 3.08. Found: C, 53.09; H, 5.53; N, 3.29.

2-[(2-Bromobenzyl)(toluene-4-sulfonyl)amino]-4-methylpentanoic Acid Methyl Ester (6c)

White crystalline solid; mp 118–120 °C; R_f = 0.52 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –20.49 (*c* 0.30, $CHCl_3$).

IR (KBr): 3059, 2958, 2921, 2868, 1942, 1737, 1593, 1440, 1346, 1201, 1160, 1028 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.58 (d, *J* = 5.7 Hz, 3 H), 0.87 (d, *J* = 5.4 Hz, 3 H), 1.26–1.38 (m, 1 H), 1.46–1.50 (m, 1 H), 2.44 (s, 3 H), 3.38 (s, 3 H), 4.57–4.62 (m, 2 H), 4.68–4.79 (m, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.31–7.36 (m, 3 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.72–7.79 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 21.7 (CH_3), 22.2 (CH_3), 24.7 (CH), 39.2 (CH_2), 48.9 (CH_2), 51.8 (CH_3), 58.2 (CH), 122.3 (C), 127.5 (CH), 127.6 (2 CH), 128.7 (CH), 129.5 (2 CH), 130.2 (CH), 132.4 (CH), 136.4 (C), 137.1 (C), 143.7 (C), 171.4 (C).

MS (ESI): *m*/*z* = 490, 492 [M + Na]$^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{21}H_{26}BrNO_4S$: C, 53.85; H, 5.59; N, 2.99. Found: C, 53.66; H, 5.38; N, 3.20.

2-[(2-Bromobenzyl)(toluene-4-sulfonyl)amino]-3-methylpentanoic Acid Methyl Ester (6d)

White crystalline solid; mp 136–137 °C; R_f = 0.50 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –28.58 (*c* 0.50, $CHCl_3$).

IR (KBr): 3071, 2961, 2873, 1734, 1595, 1440, 1340, 1199, 1157, 1110, 1018 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.47 (br s, 3 H), 0.75 (d, *J* = 4.2 Hz, 3 H), 0.91–0.96 (m, 1 H), 1.52–1.59 (m, 2 H), 2.43 (s, 3 H), 3.31 (s, 3 H), 4.21 (d, *J* = 9.3 Hz, 1 H), 4.65 (d, *J* = 17.7 Hz, 1 H), 5.14 (d, *J* = 17.7 Hz, 1 H), 7.11–7.13 (m, 1 H), 7.29–7.31 (m, 3 H), 7.49 (d, *J* = 6.9 Hz, 1 H), 7.71 (d, *J* = 6.3 Hz, 2 H), 7.82 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.5 (CH_3), 15.4 (CH_3), 21.5 (CH_3), 26.4 (CH_2), 35.0 (CH), 48.7 (CH_2), 51.2 (CH_3), 64.5 (CH), 122.3 (C), 127.4 (CH), 127.7 (2 CH), 128.6 (CH), 129.5 (2 CH), 130.4 (CH), 132.4 (CH), 136.1 (C), 137.3 (C), 143.7 (C), 171.0 (C).

MS (ESI): *m*/*z* = 490, 492 [M + Na]$^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{21}H_{26}BrNO_4S$: C, 53.85; H, 5.59; N, 2.99. Found: C, 54.07; H, 5.80; N, 3.18.

2-[(2-Bromobenzyl)(toluene-4-sulfonyl)amino]-3-phenylpropionic Acid Methyl Ester (6e)

White crystalline solid; mp 130–133 °C; R_f = 0.49 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –14.08 (*c* 0.24, $CHCl_3$).

IR (KBr): 3062, 3034, 2948, 2926, 1734, 1440, 1346, 1160, 1091, 1021 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.79 (dd, *J* = 6.2, 13.6 Hz, 1 H), 3.06 (dd-like, 1 H), 3.28 (s, 3 H), 4.65 (d, *J* = 17.4 Hz, 1 H), 4.79–4.85 (m, 2 H), 7.02–7.11 (m, 3 H), 7.18–7.23 (m, 4 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 7.52 (dd, *J* = 8.1, 12.3 Hz, 2 H), 7.72 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 36.7 (CH_2), 49.0 (CH_2), 51.7 (CH_3), 60.8 (CH), 122.2 (C), 126.8 (CH), 127.4 (CH), 127.6 (2 CH), 128.4 (2 CH), 128.7 (CH), 129.0 (2 CH), 129.6 (2

CH), 129.9 (CH), 132.3 (CH), 136.0 (C), 136.3 (C), 136.4 (C), 143.8 (C), 170.3 (C).

MS (ESI): *m*/*z* = 524, 526 $[M + Na]^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{24}H_{24}BrNO_4S$: C, 57.37; H, 4.81; N, 2.79. Found: C, 57.11; H, 5.08; N, 2.55.

2-[(2-Bromo-5-methoxybenzyl)(toluene-4-sulfonyl)amino]-3-phenylpropionic Acid Methyl Ester (6f)

White crystalline solid; mp 126–128 °C; R_f = 0.47 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –34.46 (*c* 0.50, $CHCl_3$).

IR (KBr): 3064, 3029, 2997, 2951, 2833, 1938, 1735, 1593, 1468, 1436, 1345, 1295, 1265, 1215, 1165, 1117, 1090, 1047, 1017 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.83 (dd, *J* = 7.0, 14.0 Hz, 1 H), 3.13 (dd, *J* = 8.1, 14.1 Hz, 1 H), 3.35 (s, 3 H), 3.63 (s, 3 H), 4.59 (d, *J* = 17.4 Hz, 1 H), 4.75 (d, *J* = 17.4 Hz, 1 H), 4.83 (t-like, *J* = 7.7 Hz, 1 H), 6.65 (dd, *J* = 3.0, 8.7 Hz, 1 H), 7.02–7.04 (m, 3 H), 7.19–7.21 (m, 3 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 7.36 (d, *J* = 8.7 Hz, 1 H), 7.72 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 36.6 (CH_2), 49.2 (CH_2), 51.8 (CH_3), 55.2 (CH_3), 60.8 (CH), 112.5 (C), 114.7 (CH), 115.6 (CH), 126.7 (CH), 127.6 (2 × CH), 128.4 (2 × CH), 128.8 (2 × CH), 129.6 (2 × CH), 132.9 (CH), 136.1 (C), 136.4 (C), 137.2 (C), 143.8 (C), 159.0 (C), 170.4 (C).

MS (ESI): *m*/*z* = 554, 556 $[M + Na]^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{25}H_{26}BrNO_5S$: C, 56.39; H, 4.92; N, 2.63. Found: C, 56.14; H, 5.11; N, 2.39.

2-[(2-Bromo-5-methoxybenzyl)(toluene-4-sulfonyl)amino]-3-methylbutyric Acid Methyl Ester (6g)

White crystalline solid; mp 137 °C; R_f = 0.50 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +9.88 (*c* 0.20, $CHCl_3$).

IR (KBr): 2969, 1736, 1594, 1438, 1347, 1158, 1022 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (dd, *J* = 6.8, 9.4 Hz, 6 H), 1.92–2.00 (m, 1 H), 2.43 (s, 3 H), 3.34 (s, 3 H), 3.76 (s, 3 H), 4.18 (d, *J* = 9.9 Hz, 1 H), 4.55 (d, *J* = 17.4 Hz, 1 H), 5.00 (d, *J* = 17.7 Hz, 1 H), 6.67 (dd, *J* = 2.8, 8.6 Hz, 1 H), 7.29 (d, *J* = 8.1 Hz, 3 H), 7.36 (d, *J* = 8.7 Hz, 1 H), 7.72 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 (CH_3), 20.1 (CH_3), 21.5 (CH_3), 28.6 (CH), 48.8 (CH_2), 51.3 (CH_3), 55.3 (CH_3), 66.0 (CH), 112.6 (C), 115.0 (CH), 115.2 (CH), 127.6 (2 × CH), 129.4 (2 × CH), 132.9 (CH), 136.2 (C), 137.8 (C), 143.7 (C), 158.8 (C), 170.7 (C).

MS (ESI): *m*/*z* = 506, 508 $[M + Na]^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{21}H_{26}BrNO_5S$: C, 52.07; H, 5.41; N, 2.89. Found: C, 51.88; H, 5.18; N, 3.12.

Benzenesulfonamides 7a–g; General Procedure

To a magnetically stirred solution of compound **6a–g** (1.545 mmol) in anhyd THF (20 mL) was added $LiBH_4$ (67 mg, 3.09 mmol) and refluxed for 14–20 h at 90 °C under dry conditions. The reaction was monitored by TLC and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford the crude product. The purification of the crude material was performed by column chromatography over silica gel (eluent: PE–EtOAc, 5:1) to furnish the pure compound as a sticky oil.

***N*-(2-Bromobenzyl)-*N*-(2-hydroxy-1-methylethyl)-4-methylbenzenesulfonamide (7a)**

Thick oil; R_f = 0.30 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +21.47 (*c* 0.16, MeOH).

IR (neat): 3527, 2926, 1730, 1597, 1441, 1335, 1156, 1091, 1019, 907, 848, 815, 751 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.9 Hz, 3 H), 2.44 (s, 3 H), 3.30 (d, *J* = 6.3 Hz, 2 H), 4.06 (q, *J* = 6.6 Hz, 1 H), 4.43 (d, *J* = 16.8 Hz, 1 H), 4.63 (d, *J* = 16.8 Hz, 1 H), 7.13 (t, *J* = 7.0 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 3 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.76 (d, *J* = 8.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1 (CH_3), 21.5 (CH_3), 46.9 (CH_2), 56.0 (CH), 64.6 (CH_2), 122.2 (C), 127.1 (2 CH), 127.9 (CH), 129.0 (CH), 129.8 (CH), 129.9 (2 CH), 132.6 (CH), 137.2 (C), 137.4 (C), 143.6 (C).

MS (ESI): *m*/*z* = 420, 422 $[M + Na]^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{17}H_{20}BrNO_3S$: C, 51.26; H, 5.06; N, 3.52. Found: C, 51.46; H, 4.89; N, 3.30.

***N*-(2-Bromobenzyl)-*N*-(1-hydroxymethyl-2-methylpropyl)-4-methylbenzenesulfonamide (7b)**

Thick oil; R_f = 0.31 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –4.08 (*c* 0.6, $CHCl_3$).

IR (neat): 3537, 2962, 1598, 1466, 1440, 1334, 1155, 1092, 1021, 884, 814, 754 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.56 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 6.3 Hz, 3 H), 1.79–1.81 (m, 1 H), 2.45 (s, 3 H), 3.40–3.47 (m, 2 H), 3.71 (d, *J* = 9.6 Hz, 1 H), 4.52 (d, *J* = 16.8 Hz, 1 H), 4.70 (d, *J* = 16.8 Hz, 1 H), 7.15 (t, *J* = 7.2 Hz, 1 H), 7.28–7.38 (m, 3 H), 7.51 (d, *J* = 7.8 Hz, 1 H), 7.82 (dd, *J* = 7.5, 20.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.1 (CH_3), 20.4 (CH_3), 21.4 (CH_3), 28.0 (CH), 48.2 (CH_2), 62.0 (CH_2), 66.8 (CH), 122.5 (C), 127.4 (2 × CH), 127.6 (CH), 129.0 (CH), 129.6 (2 × CH), 130.3 (CH), 132.5 (CH), 136.8 (C), 137.4 (C), 143.5 (C).

MS (ESI): *m*/*z* = 448, 450 $[M^+ + Na]$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{19}H_{24}BrNO_3S$: C, 53.52; H, 5.67; N, 3.29. Found: C, 53.29; H, 5.42; N, 3.48.

***N*-(2-Bromobenzyl)-*N*-(1-hydroxymethyl-3-methylbutyl)-4-methylbenzenesulfonamide (7c)**

Sticky oil; R_f = 0.28 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +10.22 (*c* 0.50, $CHCl_3$).

IR (neat): 3533, 3062, 2956, 2872, 1921, 1597, 1465, 1441, 1333, 1156, 1091, 1026 cm^{-1}.

1H NMR (300 MHz, $CDCl_3$): δ = 0.69 (dd, *J* = 6.4, 11.8 Hz, 6 H), 1.16–1.45 (m, 2 H), 1.84 (s, 1 H), 2.46 (s, 3 H), 3.28–3.34 (m, 1 H), 3.43 (br s, 1 H), 3.88 (br s, 1 H), 4.64 (dd, *J* = 16.8, 45.9 Hz, 2 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 7.34–7.45 (m, 3 H), 7.52 (d, *J* = 7.8 Hz, 1 H), 7.78–7.85 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 22.3 (CH_3), 22.6 (CH_3), 24.7 (CH), 38.2 (CH_2), 47.4 (CH_2), 58.7 (CH), 63.4 (CH_2), 122.3 (C), 127.4 (2 CH), 127.9 (CH), 129.1 (CH), 129.8 (2 CH), 130.1 (CH), 132.6 (CH), 137.2 (C), 137.5 (C), 143.7 (C).

MS (ESI): *m*/*z* = 462, 464 $[M^+ + Na]$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{20}H_{26}BrNO_3S$: C, 54.55; H, 5.95; N, 3.18. Found: C, 54.31; H, 6.16; N, 3.34.

***N*-(2-Bromobenzyl)-*N*-(1-hydroxymethyl-2-methylbutyl)-4-methylbenzenesulfonamide (7d)**

Thick oil; R_f = 0.29 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ – 5.81 (*c* 0.50, $CHCl_3$).

IR (neat): 3536, 2963, 2926, 1596, 1464, 1326, 1156, 1091, 1018 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.60 (d, *J* = 3.9 Hz, 3 H), 0.77 (d, *J* = 6.6 Hz, 3 H), 0.88–0.99 (m, 1 H), 1.26 (br s, 1 H), 1.43 (br s, 1 H), 2.44 (s, 3 H), 3.41–3.58 (m, 2 H), 3.69 (d, *J* = 10.0 Hz, 1 H), 4.59 (dd, *J* = 16.8, 27.6 Hz, 2 H), 7.13 (t, *J* = 6.9 Hz, 1 H), 7.32 (d,

J = 7.8 Hz, 3 H), 7.50 (d, J = 7.8 Hz, 2 H), 7.76 (d, J = 8.1 Hz, 2 H), 7.84 (d, J = 7.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2 (CH_3), 15.8 (CH_3), 21.5 (CH_3), 26.3 (CH_2), 34.8 (CH), 48.4 (CH_2), 62.0 (CH_2), 65.6 (CH), 122.6 (C), 127.5 (2 CH), 127.8 (CH), 129.0 (CH), 129.7 (2 CH), 130.5 (CH), 132.6 (CH), 136.9 (C), 137.6 (C), 143.6 (C).

MS (ESI): m/z = 462, 464 $[M + Na]^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{20}H_{26}BrNO_3S$: C, 54.55; H, 5.95; N, 3.18. Found: C, 54.28; H, 5.77; N, 2.93.

_N_-(1-Benzyl-2-hydroxyethyl)-_N_-(2-bromobenzyl)-4-methylbenzenesulfonamide (7e)

Sticky oil; R_f = 0.28 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –25.02 (c 0.9, $CHCl_3$).

IR (neat): 3529, 3064, 3029, 2926, 1598, 1494, 1443, 1334, 1156, 1093, 1027, 888, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 2.57–2.72 (m, 2 H), 3.33–3.42 (m, 2 H), 4.02–4.06 (m, 1 H), 4.63 (d, J = 17.1 Hz, 1 H), 4.76 (d, J = 17.1 Hz, 1 H), 6.96 (d, J = 5.4 Hz, 2 H), 7.17 (br s, 4 H), 7.29–7.38 (m, 4 H), 7.54 (d, J = 8.1 Hz, 1 H), 7.74–7.81 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 36.0 (CH_2), 48.2 (CH_2), 62.1 (CH_2), 62.2 (CH), 122.4 (C), 126.6 (CH), 127.3 (2 CH), 128.0 (CH), 128.6 (2 CH), 128.9 (2 CH), 129.2 (CH), 129.9 (2 CH), 130.1 (CH), 132.7 (CH), 137.1 (C), 137.3 (C), 137.4 (C), 143.7 (C).

MS (ESI): m/z = 496, 498 $[M + Na]^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{23}H_{24}BrNO_3S$: C, 58.23; H, 5.10; N, 2.95. Found: C, 57.98; H, 4.89; N, 3.11.

_N_-(2-Bromo-5-methoxybenzyl)-_N_-(1-hydroxymethyl-2-phenylethyl)-4-methylbenzenesulfonamide (7f)

Sticky liquid; R_f = 0.26 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +6.05 (c 0.20, $CHCl_3$).

IR (neat): 3535, 3024, 2924, 1597, 1469, 1333, 1238, 1157, 1094, 1020, 894, 812 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 2.58–2.73 (m, 2 H), 3.36–3.48 (m, 2 H), 3.77 (s, 3 H), 4.04–4.09 (m, 1 H), 4.57 (d, J = 17.1 Hz, 1 H), 4.70 (d, J = 17.1 Hz, 1 H), 6.72 (dd, J = 3.0, 8.7 Hz, 1 H), 6.97 (d, J = 5.4 Hz, 2 H), 7.18 (br s, 3 H), 7.29–7.34 (m, 3 H), 7.41 (d, J = 8.7 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 36.0 (CH_2), 48.2 (CH_2), 55.4 (CH_3), 62.1 (CH_2), 62.3 (CH), 112.5 (C), 114.6 (CH), 116.0 (CH), 126.6 (CH), 127.3 (2 × CH), 128.6 (2 × CH), 128.9 (2 × CH), 129.8 (2 × CH), 133.2 (CH), 137.3 (C), 137.4 (C), 137.9 (C), 143.7 (C), 159.3 (C).

MS (ESI): m/z = 526, 528 $[M + Na]^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{24}H_{26}BrNO_4S$: C, 57.14; H, 5.20; N, 2.78. Found: C, 56.93; H, 5.42; N, 2.55.

_N_-(2-Bromo-5-methoxybenzyl)-_N_-(1-hydroxymethyl-2-methylpropyl)-4-methylbenzenesulfonamide (7g)

Thick oil; R_f = 0.29 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +7.14 (c 0.20, $CHCl_3$).

IR (neat): 3534, 2962, 1597, 1470, 1332, 1239, 1155, 1092, 1046, 1014, 890, 814 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.58 (d, J = 6.3 Hz, 3 H), 0.85 (d, J = 6.3 Hz, 3 H), 1.76–1.81 (m, 1 H), 2.43 (s, 3 H), 3.38–3.51 (m, 2 H), 3.71 (d, J = 12.0 Hz, 1 H), 3.78 (s, 3 H), 4.43 (d, J = 16.8 Hz, 1 H), 4.64 (d, J = 17.1 Hz, 1 H), 6.70 (dd, J = 2.5, 8.6 Hz, 1 H), 7.30–7.37 (m, 4 H), 7.76 (d, J = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2 (CH_3), 20.6 (CH_3), 21.5 (CH_3), 28.1 (CH), 48.4 (CH_2), 55.5 (CH_3), 62.0 (CH_2), 67.0 (CH), 112.6 (C), 114.6 (CH), 116.1 (CH), 127.5 (2 CH), 129.6 (2 CH), 133.1 (CH), 137.6 (C), 137.8 (C), 143.6 (C), 159.2 (C).

MS (ESI): m/z = 478, 480 $[M + Na]^+$ for ^{79}Br, ^{81}Br.

Anal. Calcd for $C_{20}H_{26}BrNO_4S$: C, 52.63; H, 5.74; N, 3.07. Found: C, 52.87; H, 5.58; N, 2.87.

Benzoxazepines 8a–g; General Procedure

To a magnetically stirred solution of compound **7a–g** (0.8 mmol) in anhyd toluene (10 mL/mol substrate) were added $Pd_2(dba)_3$ (0.073 g, 10 mol%), (±)-BINAP (0.035 g, 7 mol%), t-BuOK (0.179 g, 1.6 mmol), and K_2CO_3 (0.221 g, 1.6 mmol) and the reaction mixture was heated at 90 °C for 16–18 h under N_2. 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 × 50 mL). The combined organic layers were washed with H_2O (4 × 50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography over silica gel (eluent: PE–EtOAc, 8:1) to furnish the pure cyclized product.

3-Methyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydrobenzo[_f_][1,4]oxazepine (8a)

White solid; mp 111 °C; R_f = 0.58 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +14.6 (c 0.10, $CHCl_3$).

IR (neat): 2923, 2853, 1601, 1491, 1457, 1334, 1262, 1156, 1092, 757 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.28 (d, J = 3.0 Hz, 3 H), 2.31 (s, 3 H), 3.87 (dd, J = 4.2, 13.2 Hz, 1 H), 3.97 (dd, J = 8.4, 13.2 Hz, 1 H), 4.30–4.34 (m, 1 H), 4.64 (d, J = 17.4 Hz, 1 H), 4.73 (d, J = 16.8 Hz, 1 H), 6.53 (d, J = 7.2 Hz, 1 H), 6.92 (t, J = 7.3 Hz, 1 H), 6.99 (d, J = 7.8 Hz, 2 H), 7.03–7.05 (m, 1 H), 7.10 (d, J = 7.2 Hz, 1 H), 7.37 (d, J = 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 16.2 (CH_3), 21.2 (CH_3), 44.3 (CH_2), 54.7 (CH), 74.5 (CH_2), 119.6 (CH), 122.7 (CH), 126.5 (C), 127.3 (CH), 128.2 (CH), 128.5 (CH), 129.6 (CH), 137.2 (C), 142.7 (C), 158.5 (C).

MS (ESI): m/z = 340 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.11; H, 6.27; N, 4.19.

3-Isopropyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydrobenzo[_f_][1,4]oxazepine (8b)

Crystalline white solid; mp 145–148 °C; R_f = 0.58 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –11.16 (c 0.20, $CHCl_3$).

IR (KBr): 3060, 2966, 1581, 1492, 1452, 1399, 1334, 1297, 1263, 1226, 1153 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.04 (d, J = 6.0 Hz, 3 H), 1.06 (d, J = 6.0 Hz, 3 H), 2.10–2.17 (m, 1 H), 2.27 (s, 3 H), 3.79–3.88 (m, 2 H), 4.13 (dd, J = 7.0, 12.8 Hz, 1 H), 4.56 (d, J = 17.1 Hz, 1 H), 4.76 (d, J = 16.8 Hz, 1 H), 6.48 (d, J = 7.8 Hz, 1 H), 6.88–7.03 (m, 4 H), 7.09 (d, J = 6.9 Hz, 1 H), 7.36 (d, J = 7.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.4 (CH_3), 20.0 (CH_3), 21.3 (CH_3), 28.0 (CH), 45.8 (CH_2), 64.0 (CH), 71.6 (CH_2), 119.7 (CH), 122.7 (CH), 126.4 (C), 127.3 (CH), 128.4 (CH), 128.6 (CH), 129.5 (CH), 137.1 (C), 142.5 (C), 158.4 (C).

MS (ESI): m/z = 368 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.05. Found: C, 65.89; H, 6.97; N, 4.27.

3-Isobutyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydrobenzo[_f_][1,4]oxazepine (8c)

Crystalline white solid; mp 148–149 °C; R_f = 0.61 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +9.38 (c 0.20, $CHCl_3$).

IR (KBr): 2925, 2857, 1579, 1487, 1454, 1333, 1152, 1090, 1047 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d-like, *J* = 5.4 Hz, 6 H), 1.31–1.40 (m, 1 H), 1.61–1.71 (m, 1 H), 1.76–1.82 (m, 1 H), 2.29 (s, 3 H), 3.80 (dd-like, *J* = 4.0, 13.0 Hz, 1 H), 3.93 (dd-like, *J* = 7.2, 12.9 Hz, 1 H), 4.21 (br s, 1 H), 4.64 (dd, *J* = 16.8, 41.1 Hz, 2 H), 6.51 (d, *J* = 7.8 Hz, 1 H), 6.90–7.05 (m, 4 H), 7.11 (d, *J* = 6.9 Hz, 1 H), 7.37 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 22.4 (CH_3), 23.0 (CH_3), 24.3 (CH), 38.8 (CH_2), 45.0 (CH_2), 56.3 (CH), 73.4 (CH_2), 119.7 (CH), 122.7 (CH), 126.6 (C), 127.3 (2 CH), 128.5 (CH), 128.7 (2 CH), 129.6 (CH), 137.1 (C), 142.6 (C), 158.4 (C).

MS (ESI): *m*/*z* = 360 [M + H], 382 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90. Found: C, 67.04; H, 6.78; N, 4.13.

3-*sec*-Butyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (8d)

Crystalline white solid; mp 143 °C; R_f = 0.60 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +7.04 (*c* 0.20, $CHCl_3$).

IR (KBr): 2966, 2927, 2874, 1917, 1600, 1492, 1453, 1384, 1342, 1222, 1155, 1091, 1045, 1007 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (dd, *J* = 7.1, 16.0 Hz, 6 H), 1.15–1.25 (m, 1 H), 1.71–1.79 (m, 1 H), 1.89–1.91 (m, 1 H), 2.27 (s, 3 H), 3.84–3.92 (m, 2 H), 4.10–4.17 (m, 1 H), 4.58 (d, *J* = 17.1 Hz, 1 H), 4.77 (d, *J* = 17.1 Hz, 1 H), 6.45 (d, *J* = 7.8 Hz, 1 H), 6.87–7.02 (m, 4 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4 (CH_3), 15.3 (CH_3), 21.3 (CH_3), 25.8 (CH_2), 35.0 (CH), 46.1 (CH_2), 62.8 (CH), 71.3 (CH_2), 119.6 (CH), 122.6 (CH), 126.0 (C), 127.3 (2 CH), 128.4 (CH), 128.6 (2 CH), 129.5 (CH), 137.0 (C), 142.5 (C), 158.3 (C).

MS (ESI): *m*/*z* = 382 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90. Found: C, 67.06; H, 7.23; N, 3.74.

3-Benzyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (8e)

Crystalline colorless solid; mp 153–154 °C; R_f = 0.59 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +11.60 (*c* 0.60, $CHCl_3$).

IR (neat): 3439, 3029, 2924, 1656, 1602, 1492, 1451, 1335, 1156, 1110, 1049 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 3.03 (dd, *J* = 4.8, 13.2 Hz, 1 H), 3.11 (dd, *J* = 9.0, 13.2 Hz, 1 H), 3.79 (dd, *J* = 3.6, 13.2 Hz, 1 H), 4.06 (dd, *J* = 7.2, 13.2 Hz, 1 H), 4.33–4.35 (m, 1 H), 4.49 (d, *J* = 16.8 Hz, 1 H), 4.68 (d, *J* = 16.8 Hz, 1 H), 6.57 (d, *J* = 7.8 Hz, 1 H), 6.91 (t, *J* = 7.2 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 2 H), 7.04 (t, *J* = 7.2 Hz, 1 H), 7.08 (d, *J* = 7.2 Hz, 1 H), 7.23–7.25 (m, 3 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 37.2 (CH_2), 45.7 (CH_2), 59.2 (CH), 71.8 (CH_2), 119.7 (CH), 122.7 (CH), 126.6 (C), 126.8(CH), 127.1 (2 CH), 128.6 (CH), 128.7 (2 CH), 129.0 (2 CH), 129.4 (2 CH), 129.6 (CH), 136.9 (C), 137.0 (C), 142.8 (C), 158.3 (C).

MS (ESI): *m*/*z* = 416 $[M + Na]^+$.

Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56. Found: C, 69.97; H, 6.07; N, 3.34.

3-Benzyl-7-methoxy-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (8f)

Yellowish white solid; mp 159–160 °C; R_f = 0.55 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ +5.20 (*c* 0.15, $CHCl_3$).

IR (KBr): 2948, 1667, 1623, 1506, 1432, 1355, 1121, 1034 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.99 (dd, *J* = 4.6, 13.0 Hz, 1 H), 3.12–3.20 (m, 1 H), 3.67–3.71 (m, 1 H), 3.77 (s, 3 H), 4.00 (dd, *J* = 5.8, 12.8 Hz, 1 H), 4.27–4.28 (m, 1 H), 4.49 (d, *J* = 16.8 Hz, 1 H), 4.63 (d, *J* = 17.1 Hz, 1 H), 6.63 (d, *J* = 15.9 Hz, 3 H), 7.03 (d, *J* = 8.1 Hz, 3 H), 7.30–7.41 (m, 6 H).

MS (ESI): *m*/*z* = 424 $[M + H]^+$, 446 $[M + Na]^+$.

Anal. Calcd for $C_{24}H_{25}NO_4S$: C, 68.06; H, 5.95; N, 3.31. Found: C, 68.29; H, 6.14; N, 3.05.

3-Isopropyl-7-methoxy-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (8g)

Crystalline white solid; mp 157–158 °C; R_f = 0.56 (PE–EtOAc, 4:1); $[\alpha]_D^{25}$ –8.08 (*c* 0.20, $CHCl_3$).

IR (KBr): 2966, 1591, 1500, 1336, 1275, 1211, 1151, 1051, 899, 814 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.02–1.05 (m, 6 H), 2.18–2.20 (m, 1 H), 2.30 (s, 3 H), 3.70 (d, *J* = 10.8 Hz, 2 H), 3.76 (s, 3 H), 4.10 (t-like, *J* = 6.9 Hz, 1 H), 4.50 (d, *J* = 16.8 Hz, 1 H), 4.68 (d, *J* = 16.8 Hz, 1 H), 6.49 (d, *J* = 8.7 Hz, 1 H), 6.57 (dd, *J* = 2.4, 8.7 Hz, 1 H), 6.64 (s, 1 H), 7.00 (d, *J* = 7.8 Hz, 2 H), 7.41 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5 (CH_3), 20.0 (CH_3), 21.4 (CH_3), 27.4 (CH), 45.7 (CH_2), 55.7 (CH_3), 64.0 (CH), 71.8 (CH_2), 113.7 (CH), 114.2 (CH), 120.6 (CH), 127.4 (2 CH), 128.2 (C), 128.8 (2 CH), 137.3 (C), 142.7 (C), 152.7 (C), 155.0 (C).

MS (ESI): *m*/*z* = 376 $[M + H]^+$, 398 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.73. Found: C, 64.14; H, 6.54; N, 3.98.

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(21) Crystal data of compound **8g**: $C_{20}H_{25}NO_4S$, FW = 375.47, triclinic, space group *P*1, a = 6.687(4) Å, b = 7.508(5) Å, c = 10.114(6) Å, α = 75.93(4)°, β = 88.29(4)°, γ = 80.28(4)°, V = 485.4(5) Å^3, Z = 1, T = 296(2) K, d_{calcd} = 1.284 g cm^{-3}, F(000) = 200. Diffraction data were measured with Mo-Kα (λ = 0.71073 Å) radiation at 296 K using a Bruker Kappa Apex 2 CCD system. A total of 2595 unique reflections were measured (θ_{max} = 28.18°). Data analyses were carried out with the Fast Fourier Transform program. The structures were solved by direct methods using the SHELXS-97[22] program. Refinements were carried out with a full matrix least squares method against $F2$ using SHELXL-97.[23] Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R value was $R1$ = 0.0479 and w$R2$ = 0.1255 with $I > 2\sigma(I)$. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre with reference numbers CCDC 776221. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033, E-mail: deposit@ccdc.cam.ac.uk].

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