EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Synthesis of tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxides

Authors: Hemi Borgohain, Runjun Devi, Divya Dheer, Biraj Jyoti Borah, Ravi Kumar, and Sajal Kumar Das

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701152

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701152

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201701152

WILEY-VCH

Synthesis of tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxides

Hemi Borgohain,[a] Runjun Devi,[a] Divya Dheer,[b] Biraj Jyoti Borah,[a] Ravi Shankar,[b,c] and Sajal Kumar Das*[a]

Abstract: A diastereoselective synthesis of previously unknown tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxides is presented. The three-step protocol utilizes readily available *N*-aryl-2-fluorobenzenesulfonamides and *trans*-2,3-epoxy cinnamyl alcohol-derived tosylates as the starting materials, involves *N*-alkylation of sulfonamides, intramolecular epoxide ring-opening and S_NAr reactions as the reaction steps, and requires only one chromatographic purification to access the desired products in good overall yields.

Introduction

To explore broad swaths of the chemical space, diversity-oriented synthesis of privileged scaffold-based small organic molecules has been an important goal in modern drug discovery and chemical biology.[1] In this context, developments of efficient, scalable and rapid but mild synthetic methods for the stereoselective construction of highly valuable heterocyclic scaffolds have attracted a great deal of interest over the years. The privileged tetrahydroquinoline scaffold is a part of the molecular frameworks of a wide range of natural products and synthetic molecules that exhibit a broad spectrum of bioactivities.[2] Among several types of tetrahydroquinoline scaffolds, 4-arenesulfonyl-tetrahydroquinoline (Figure 1) represents the core structure of a number of medicinally important molecules including farnesyltransferase inhibitors,[2a] antiparasitic agent,[2c] 11β-hydroxylase inhibitors,[2e] histone deacetylase inhibitors,[2f] RORc inverse agonists,[2h] myeloid cell leukemia-1 inhibitors[2i], etc. On the other hand, sultam is another privileged heterocyclic unit that is ubiquitously distributed in a large family of synthetic compounds, including some clinical drugs, exhibiting versatile bioactivities.[3] Benzothiaoxazepine-1,1-dioxides (Figure 1), a particular group of benzosultams, have shown biological activities as modulators of histamine H3-receptor,[4] positive allosteric modulators,[5] and KEAP1/NRF2 protein–protein interaction inhibitors.[6] Owing to their enormous synthetic and pharmacological utilities, 4-arenesulfonyltetrahydroquinolines and benzothiaoxazepine-1,1-dioxides have become important synthetic targets for organic and medicinal chemists.[7,8] However, combination of these two privileged scaffolds in one single molecule, which may provide a source of new lead compounds,[9] remains unreported, and is therefore highly desirable.

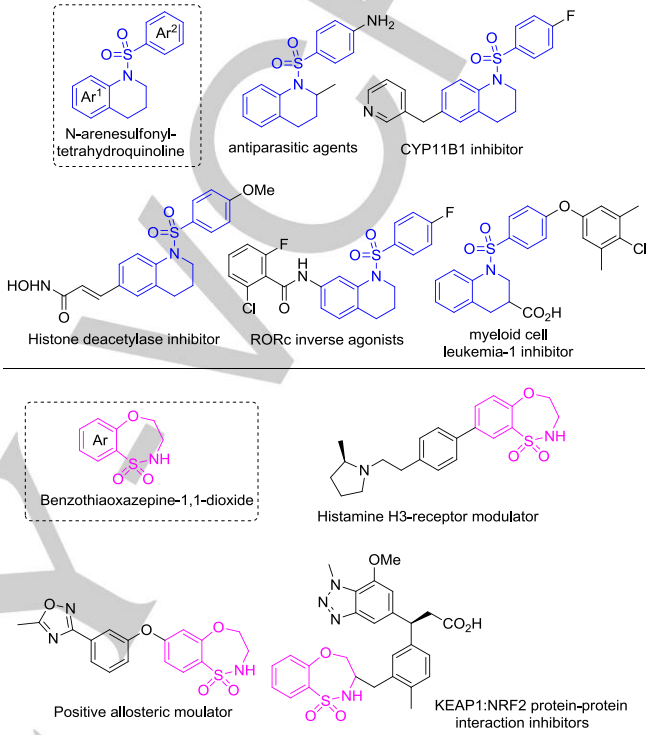


Figure 1. *N*-arenesulfonyl-tetrahydroquinoline (upper panel) and benzothiaoxazepine-1,1-dioxide (lower panel) in the core structures of selected biologically important molecules.

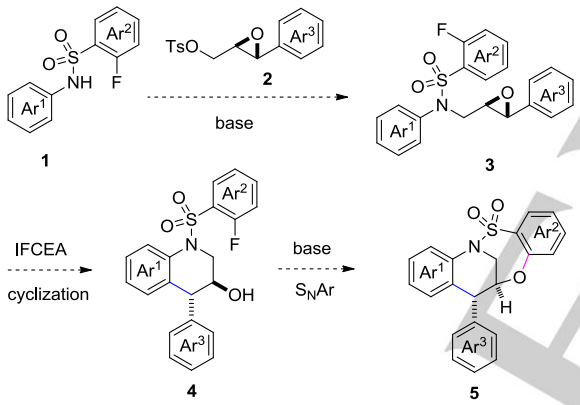
Intramolecular Friedel-Crafts epoxide-arene (IFCEA) cyclization of aryl-substituted epoxides tethered with arenes/heteroarenes has been an efficient and powerful tool for constructing diverse benzo-fused carba- and heterocycles, largely because of the ready accessibility of aryl-substituted epoxides in both racemic and single-enantiomeric forms, and their capability to undergo this cyclization reaction in highly chemo-, regio-, and stereoselective fashions.[10] Specifically, notable achievements have been registered in applying IFCEA reaction as a key step to synthesize diverse chromans, tetrahydro-1-benzazepines and tetrahydro-2-benzazepines.[10c] Despite these accomplishments, we believe that IFCEA reaction is underutilized in synthetic organic chemistry and there are still many opportunities to exploit it to access benzo-fused carba- and heterocycles with rich structural complexity and stereochemical diversity. In continuation of our previous work in synthesizing structurally diverse benzo-fused heterocycles,[11] herein, we wish to report the synthesis of tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxides. Examples of bridged sultams with nitrogen at the bridgehead are scarce although they have potential applications in medicinal chemistry.[12]

[a] Department of Chemical Sciences, Tezpur University, Napaam, Tezpur, Assam, India-784028
[b] Bio-Organic Chemistry Division, Indian Institute of Integrative Medicine (CSIR), Jammu, India-180001
[c] Academy of Scientific and Innovative Research (AcSIR), Jammu Campus, India

Supporting information for this article is given via a link at the end of the document.

Results and Discussion

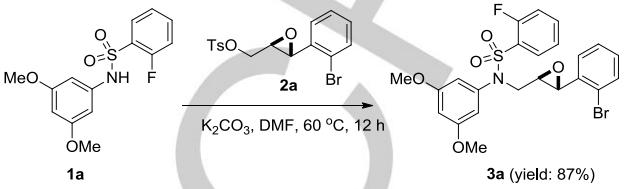
We envisaged that *N*-alkylation of *N*-aryl-2-fluorobenzenesulfonamides **1** with readily available *trans*-2,3-epoxy cinnamyl alcohol-derived tosylates **2** would provide compounds **3** which, in turn, would furnish *trans*-4-aryl-3-hydroxy-*N*-(*o*-fluoroarene)sulfonyl-tetrahydroquinolines **4** via IFCEA reaction (Scheme 1). Our interest in applying IFCEA reaction to prepare **4** was motivated by their structural similarity to *trans*-4-arylchroman-3-ols that have already been synthesized by us using similar strategy.[11a-c] In contrast to these previously reported synthesis of chroman derivatives, however, we suspected that synthesis of **4** would be more challenging owing to the lower nucleophilicity of the aryl group of a *N*-tosylaniline moiety; but the process would be more versatile with additional diversification positions with three aromatic rings, thus creating the possibility of synthesizing a wide variety of compounds. Nevertheless, compounds **4** on treatment with a base should furnish tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxides **5** via an intramolecular S_NAr cycloetherification.[8]



Scheme 1. Proposed synthesis of tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxides.

Noteworthy is that synthesis of tetrahydroquinolines and their derivatives by epoxide-arene cyclization have rarely been reported in the literature. Kobayashi and Harayama in 2009 reported the synthesis of 3-hydroxy-4-arylquinolin-2(1*H*)-ones by leaving group-assisted IFCEA cyclization.[13] Gansäuer, Flowers II and co-workers recently reported the synthesis of *N*-alkyl tetrahydroquinolines via epoxide-arene cyclization involving homolytic aromatic substitution.[14] However, an operationally simple method to access compounds of type **4** using the strategy as outlined in Scheme 1 has not been investigated. Furthermore, the conception that products from such a method could be used to prepare the bridged tetrahydroquinolines **5** has not been apprehended so far.

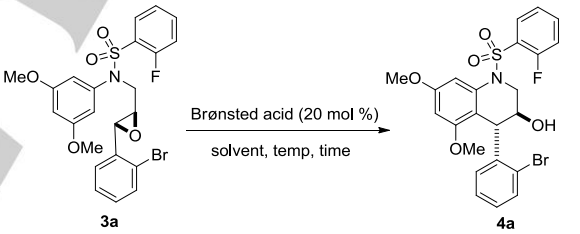
To examine the feasibility of the strategy outlined above, we first carried out the *N*-alkylation of 2-fluorobenzene sulfonamide derivative **1a** (1 equiv) with epoxy tosylate **2a** (1 equiv) in the presence of K_2CO_3 in DMF at 60 °C (Scheme 2). The reaction showed virtually one spot on TLC, furnishing the desired product **3a** in 87% isolated yield. It is important to mention that Mitsunobu reaction of **1a** and *trans*-((3-(2-bromophenyl)oxiran-2-yl)methanol also afforded **3a** (not shown here); but the chromatographic purification was problematic.



Scheme 2. Synthesis of **3a** by base-mediated *N*-alkylation of **1a** with **2a**.

Nevertheless, with compound **3a** in hand, we decided to screen the reaction conditions for the crucial IFCEA reaction by systematic variations of Brønsted acid, solvent, and reaction temperature (Table 1). Catalyzed by 20 mol% of $TsOH{\cdot}H_2O$ in 1,2-dichloroethane (DCE) at 80 °C, compound **3a** gave tetrahydroquinoline derivative **4a** in 78 % yield (Table 1, entry 1) without generating even trace amount of the corresponding *cis*-isomer.

Table 1. Optimization of the reaction conditions for the IFCEA reaction of **3a**[a]



entry	catalyst (20 mol%)	solvent	temp (^oC)	time (min)	Yield[b] (%)
1	$TsOH{\cdot}H_2O$	DCE	50	45	78
2	H_2SO_4	DCE	50	60	65
3	TFA	DCE	DCE	45	74
4	TfOH	DCE	rt	45	79
5	MsOH	DCE	50	45	78
6	$TsOH{\cdot}H_2O$	MeCN	70	45	88
7	**$TsOH{\cdot}H_2O$**	**toluene**	**70**	**45**	**90**
8	$TsOH{\cdot}H_2O$	benzene	70	60	85
9	$TsOH{\cdot}H_2O$	THF	50	60	40
10	$TsOH{\cdot}H_2O$	toluene	rt	60	75
11	$TsOH{\cdot}H_2O$	toluene	85	60	85

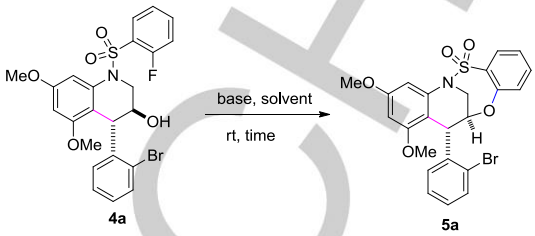
[a]Reaction conditions: **3a** (0.4 mmol) in 8 mL solvent. [b]Isolated yields

Delighted by this result, we screened the reaction conditions by systematic variations of Brønsted acid, solvent, and reaction temperature (Table 1, entries 2-11). With DCE as the reaction medium, catalysis of this reaction with other well-known Brønsted acids such as H_2SO_4, TFA, TfOH and MsOH also led to the formation of **4a**, albeit in varying yields (entries 2–5). Notably, yields of the TsOH- and MsOH- catalyzed reaction were identical (entries 1 and 5). However, given the low cost and practical advantage of handling of $TsOH{\cdot}H_2O$, we settled on this reagent as the preferred catalyst. Furthermore, with $TsOH{\cdot}H_2O$ as catalyst, the optimal solvent was screened to be toluene among others, such as MeCN, benzene and THF (entries 1 and 6−9). Finally, the optimal reaction temperature was determined to be 70 °C (Table 1, entries 7, 10 and 11) with $TsOH{\cdot}H_2O$ in toluene. The optimized reaction conditions were thus identified as the treatment of the substrate in toluene at 70 °C for 45 min in the presence of 20 mol% of $TsOH{\cdot}H_2O$ under which this cyclization reaction exhibited essentially one spot on TLC (with traces of polar and nonpolar impurities), and delivered the desired tetrahydroquinoline derivative **4a** in 90% isolated yield.

After gaining efficient access to compound **4a**, we decided to explore its potential in the preparation of tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxide **5a** (Table 2). We carried out the crucial S_NAr-based cycloetherification reaction first with 2.0 equiv of DBU as the base in DMF at 80 °C for 2 h (Table 2, entry 1). The desired product **5a** was isolated, albiet in lower yield. When the base was switched to KO^{t}Bu, **5a** was furnished in higher yields in THF and DMSO (entries 2 and 3) but lower yields were observed in DMF and toluene (entries 4 and 5). Use of Cs_2CO_3 in DMF at 110 °C for 2 h also gave inferior result (entry 6). Finally, we employed NaH in different solvents (entries 7−10) for this transformation. The best result was obtained when the reaction was performed in DMF in the presence of NaH at rt for 15 min (entry 9). Interestingly and surprisingly, this cyclization conditions appeared to be much milder than that involved in Hanson's synthesis of benzothiaoxazepine-1,1-dioxides wherein microwave irradiation at higher temperature (140-150 °C) was employed.[8b,d]

At this point, the viability of the method to access a tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxide skeleton had clearly been demonstrated; however, we wanted to further simplify this three-step synthetic protocol via process intensification. Given the very clean nature of the first two steps, we believed that there was the opportunity to avoid the chromatographic isolation of the intermediate compounds **3a** and **4a**, and so we began investigating a modified approach that would involve a sole chromatographic purification after the final step (Table 3). Thus, after the completion of the first step, the reaction mixture was subjected to usual workup to obtain crude **3a** which was then exposed for the second step involving an IFCEA reaction under the optimized conditions. After the completion of this step, two aspects regarding process intensification came to our mind. While the first one was performing the second and final steps in a highly ambitious one-pot fashion, telescoping these two steps appeared as the second one. However, ineffectiveness of the cycloetherification reaction in toluene (entry 10, Table 2) removed the first possibility.

Table 2. Optimization of the reaction conditions for the S_NAr reaction of **4a**[a]



4a **5a**

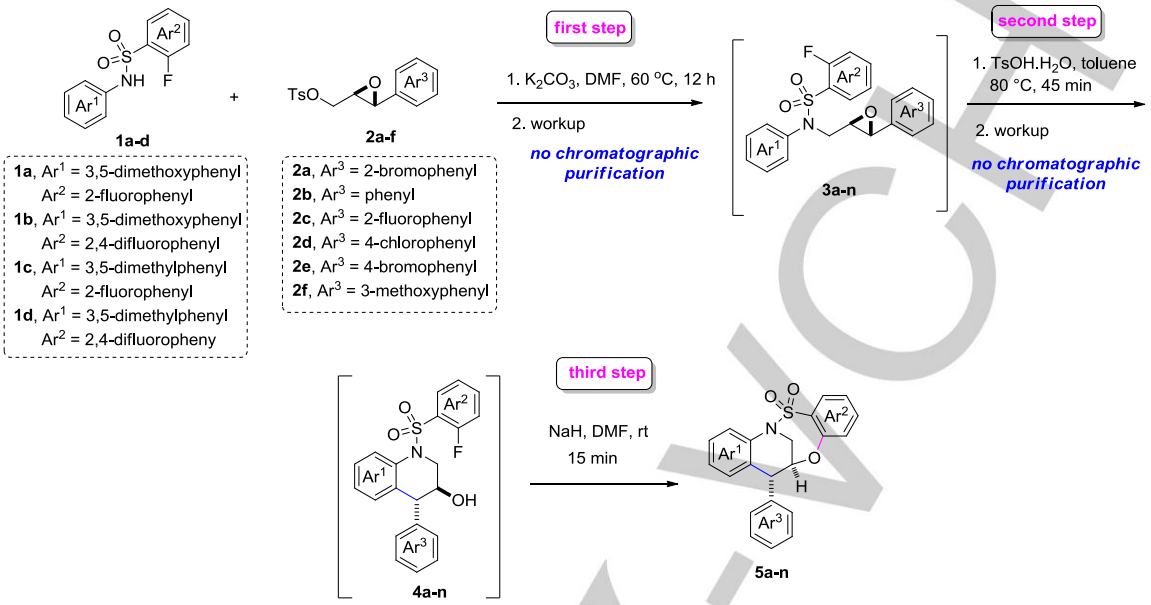
entry	catalyst (mol%)	solvent	temp (^{o}C)	time (min)	yield[b] (%)
1	DBU	DMF	80	120	60
2	KO^{t}Bu	THF	rt	30	75
3	KO^{t}Bu	DMSO	rt	15	80
4	KO^{t}Bu	DMF	rt	15	50
5	KO^{t}Bu	PhMe	110	120	40
6	Cs_2CO_3	DMF	110	120	45
7	NaH	THF	50	45	65
8	NaH	1,4-dioxane	50	45	60
9	**NaH**	**DMF**	**rt**	**15**	**87**
10	NaH	toluene	110	120	20

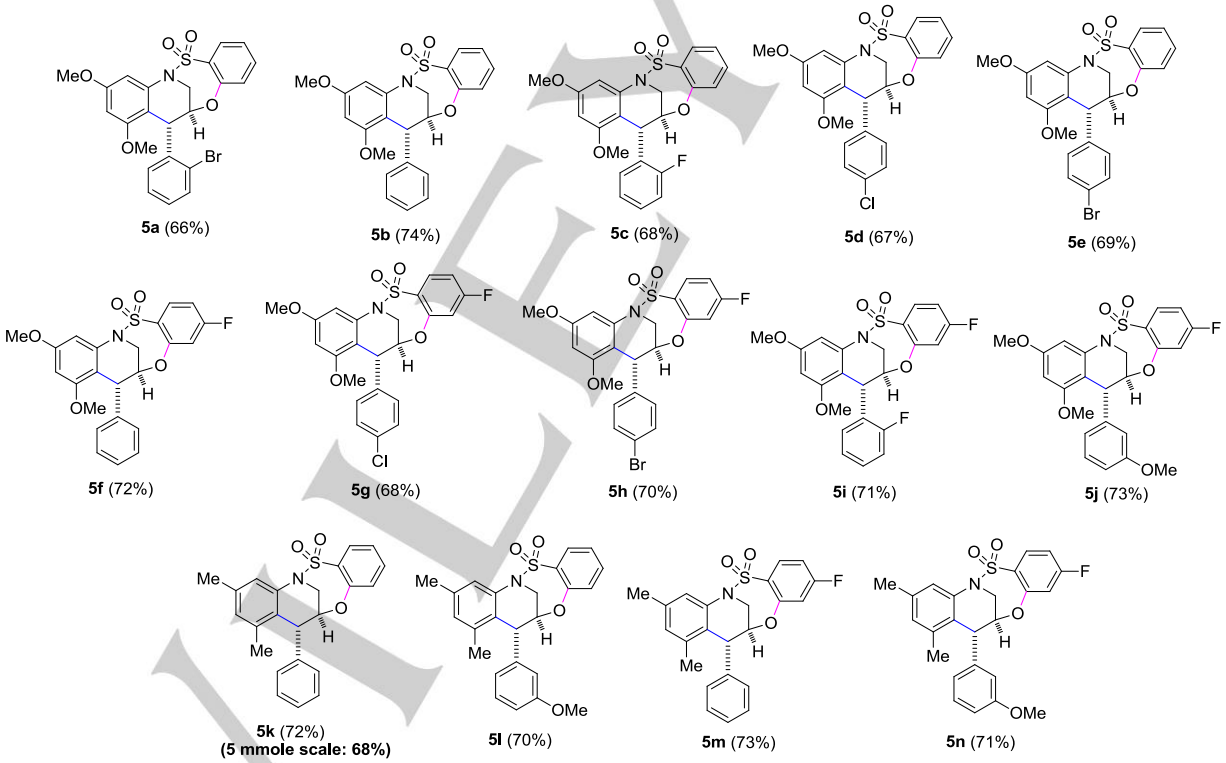
[a]Reaction conditions: **4a** (0.2 mmol) and base (0.4 mmol) in solvent (3 mL) under an argon atmosphere. [b]Isolated yields.

Having been unable to investigate the one-pot protocol, we briefly investigated the alternative option of telescoping these two steps by swapping the solvent from toluene to DMF. Thus, after the completion of the second step, toluene was removed and a solution of the resulting crude **4a** in DMF was treated with NaH. Unfortunately, this modification resulted in the incomplete conversion of **4a** even with using excess equivalent of NaH. We were, however, delighted to find that a basic workup ($NaHCO_3$) after the first step followed by the S_NAr reaction with NaH in DMF afforded **5a** in a good 66% overall isolated yield (Table 3, product **5a**).

With these findings, we then turned our attention to explore the three-step transformation with different substrates under the optimized conditions, without chromatographic purification of the intermediate compounds. Towards that objective, additional *N*-aryl-2-fluorobenzenesulfonamides **1** and *trans*-2,3-epoxy cinnamyl alcohol-derived tosylates **2** were prepared (see Supporting Information for full details). The scope of the optimized protocol was then screened with these substrates. As summarized in Table 3, all the corresponding tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxide **5b−n** were obtained in good 65−74% overall yields.

Table 3. Three-step synthesis of tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxides[a,b]



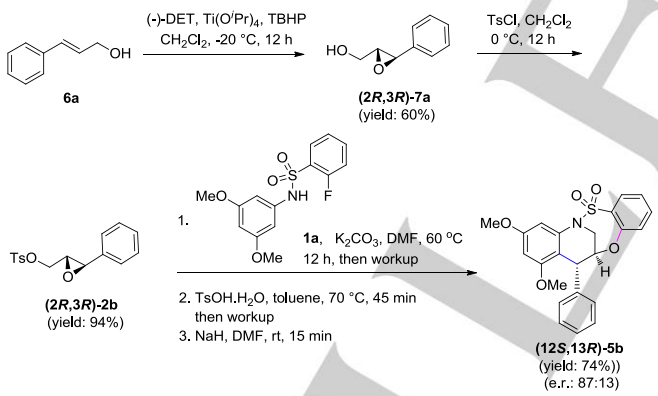


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol) and K_2CO_3 (0.3 mmol) in 5 mL DMF for the first step; $TsOH{\cdot}H_2O$ (20 mol%) in 5 mL toluene for the second step; NaH (0.4 mmol), DMF (3 mL) under an argon atmosphere for the third step. [b]The percentage values indicate overall isolated yields.

Overall, the synthesized products contain the Ar^2-ring as phenyl (Table 3, products **5a−e**, **5k** and **5l**) or 4-fluorophenyl group (products **5f−j**, **5m** and **5n**), and the Ar^3-ring as phenyl (products **5b**, **5f**, **5k** and **5m**), 2-fluorophenyl (products **5c** and **5i**), 2-bromophenyl (product **5a**), 3-methoxyphenyl (products **5j**, **5l** and **5n**), 4-chlorophenyl (products **5d** and **5g**), and 4-bromophenyl (products **5e** and **5h**) groups. As expected, a fluorine or a bromine substituent on the *ortho*-position of the Ar^3-ring did not affect the stereochemical outcome in the first step, and was found to withstand the S_NAr cycloetherification reaction conditions (products **3b**, **3c**, and **3g**); however, in these cases, overall yields were slightly diminished. Among all the synthesized bridged benzosultams, those which contain a halogen atom (F or Br) on the Ar^2 or Ar^3 ring should be potentially useful to introduce additional functionalities via well-established S_NAr or Pd-catalyzed reactions to fit specific biological targets. All these 14 benzosultams are hydrolytically stable crystalline solids (in contrast, bridged lactams are highly prone to hydrolysis) which could be stored.

To evaluate the potential scalability of this approach, gram-scale transformations of **1c** and**d 2b** were carried out under the optimal reaction conditions. The desired product **5k** was obtained in 68% overall isolated yield (Table 3, product **5k**).

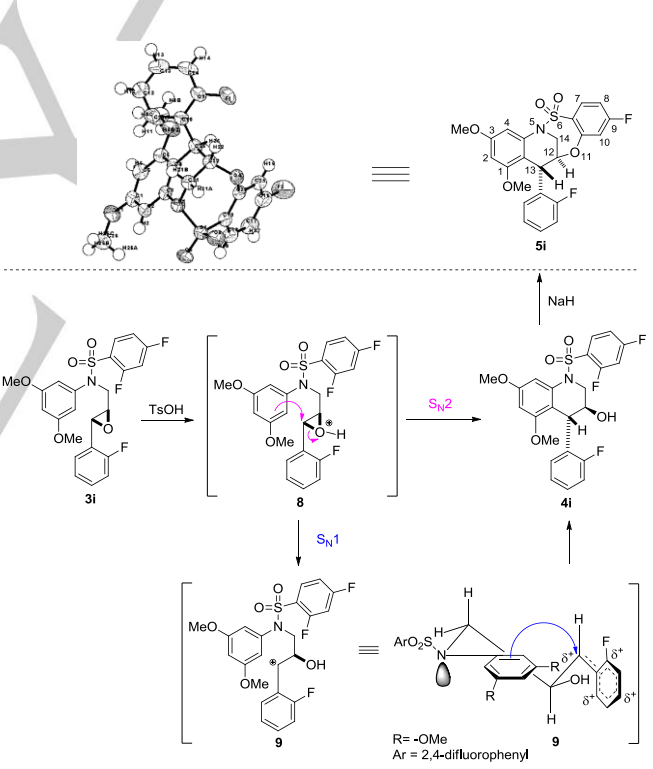
Next, an asymmetric version of this highly diastereocontrolled strategy was also briefly investigated. Thus, enantiomerically enriched epoxy tosylate (2*R*,3*R*)-**2b** was synthesized using Sharpless asymmetric epoxidation as the source of chirality (Scheme 3). Subsequent three-step transformation of (2*R*,3*R*)-**2b** under the optimized reaction conditions furnished (12*R*,13*S*)-**5b** in 87:13 e.r.



Scheme 3. Asymmetric version of the developed methodology; enantiomeric ratio (e.r.) was determined by chiral stationary phase HPLC.

Noteworthy is that that all the tested substrates contain the Ar^1-ring as highly potent 3,5-dimethoxyphenyl or 3,5-dimethylphenyl group only, as our prior studies[11a-c] indicated that Brønsted acid-catalyzed IFCEA cyclization reactions of aryl-substituted epoxides tethered to arenes are highly efficient when the reacting arene group is 3,5-dimethoxyphenyl or 3,5-dimethylphenyl ring. To avoid the purification of the intermediate compounds, such a selection of the Ar^1 group was extremely crucial in the present protocol. However, we believe that, with the Ar^1-ring of moderately electron-rich nature, or bearing more than one reactive sites, this three-step synthetic route might be applicable, although purification of the intermediate compounds would be unavoidable for such cases.

The structures of all the tetracyclic molecules heterocycles **5a−k** were assigned on the basis of ^1H and ^{13}C NMR spectroscopy. In addition, the structures of **5a−k** are further supported by the single-crystal X-ray diffraction analysis of **5i**, which unambiguously confirmed its structure. The structure (Scheme 4, upper panel) clearly shows the relative *trans*-stereochemistry between the 12-H and 13-H atoms on the tetrahydroquinoline ring. Clearly, the stereochemistry observed herein originates from the second step involving IFCEA reaction that is assumed to give rise to the corresponding *trans*-4-aryl-3-hydroxy tetrahydroquinoline derivative **5i** via an S_N2 type epoxide ring opening of protonated epoxide **8** (Scheme 3, lower panel). However, we could not completely ruled out the possibility of an S_N1 pathway. Fortunately, the carbocation **9** generated from such a reaction mechanism also could provide the same product **4i** via the most favorable conformation of **9**.



Scheme 4. X-ray single-crystal structure of **5i** (upper panel) and rational of the stereochemistry (lower panel).

Conclusions

In summary, we have developed a regio- and diastereoselective synthetic route for accessing biologically relevant tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxides via a three-step reaction

sequence. The synthetic route that was used involved three key steps: first the synthesis of epoxide-tethered *N*-aryl-*N*-(2-fluoroarene)sulfonyl anilines via *N*-alkylation of *N*-ary-2-fluorobenzenesulfonamides with *trans*-2,3-epoxy cinnamyl alcohol-derived tosylates, then the intramolecular Friedel-Crafts epoxide-arene reaction to afford *trans*-4-aryl-3-hydroxy tetrahydroquinoline derivatives, and finally the NaH-mediated cycloetherification reaction to afford the target bridged benzosultams. The protocol is experimentally convenient, rapid, and scalable, and requires easily available starting materials, reagents, and catalyst. Further application of this procedure to synthesize analogous polycyclic bridged structures is underway in our laboratory.

Experimental Section

All dry reactions were carried out under nitrogen in oven-dried glassware. Commercial reagents were used without further purification unless otherwise stated. Progress of reactions was monitored by TLC on pre-coated Merck silica gel plates (60F-254). Visualization of reactants and products was accomplished with UV light. Column chromatography was performed over silica gel (60–120 mesh) procured from Merck using freshly distilled solvents. Melting points were determined with a Buchi-535 apparatus and are not corrected. Perkin Elmer 20 analyzer was utilized for elemental analysis of all compounds. Optical rotations were measured by a Rudolph Autopol V polarimeter. HPLC data were recorded using Dionex (Ultimate 3000) HPLC Instruments. ^{1}H NMR and ^{13}C NMR spectra were run on a JEOL 400 MHz spectrometer or Bruker Advance III-400 MHz in $CDCl_3$ as solvent. Chemical shifts are expressed in δ ppm with the abbreviations s, d, t, q, dd, dt and m denoting singlet, doublet, triplet, quartet, doublet of doublets, doublet of triplets, and multiplet, respectively. Tetramethylsilane (δ 0.00 ppm) or residual chloroform (δ 7.27 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. All spectra were recorded at 25 °C. Coupling constants (*J* values) are given in hertz (Hz).

General procedure for the synthesis of bridged benzosultams 5a-n by the three-step (involving only one chromatographic purification) method (Table 3):

First step: A mixture of sulfonamide **1** (0.2 mmol), epoxy tosyalte **2** (0.2 mmol) and anhydrous K_2CO_3 (45 mg, 0.325 mmol) in dry DMF (6 mL) was heated at 60°C under N_2 atmosphere for 12 h. The reaction was terminated by the addition of water (10 mL) and diethyl ether (20 mL) was added. The organic layer was separated, washed by brine (20 mL) and dried over anhyd. Na_2SO_4. After filtration, the solution was evaporated to dryness under reduced pressure. The resulting crude product was further dried by a high vacuum pump, and then subjected to the next step without further purification.

Second step: To a stirred solution of the crude product (obtained from the first step) in AR grade toluene (5 mL) was added TsOH.H_2O (6.9 mg, 0.04 mmol). The resulting mixture was then heated at 70 °C for 45 min. The mixture was cooled to room temperature, and then poured in beaker containing EtOAc (20 mL) and saturated aq. $NaHCO_3$ solution (15 mL) with vigorous stirring. The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solution was evaporated to dryness under reduced pressure. The resulting crude product was further dried by a high vacuum pump, and then subjected to the next step without further purification.

Third step: Finally, to a stirred solution of the above crude product in freshly dried DMF (4 mL) was added powdered NaH (9.6 mg, 0.4 mmol) at 0 °C under an argon atmosphere. After stirring for 15 min at room temperature, the reaction mixture was quenched with saturated aq. NH_4Cl solution (20 mL), and diluted with EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (5-10% EtOAc/hexanes) afforded the desired bridged benzosultam **5**.

(±)-(12*R*,13*R*/12*S*,13*S*)-13-(2-Bromophenyl)-1,3-dimethoxy-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5] oxathiazonine 6,6-dioxide (5a): Prepared from compounds **1a** and **2a** according to the general procedure; white solid; yield = 66%; mp = 197–199 °C; R_f = 0.45 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.62 (m, 1H), 7.50 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.46-7.41 (m, 1H), 7.37-7.35 (m, 1H), 7.09-7.05 (m, 3H), 6.80 (d, *J* = 2.3 Hz, 1H), 6.45-6.43 (m, 1H), 6.13 (d, *J* = 2.3 Hz, 1H), 4.69-4.64 (m, 1H), 4.60 (s, 1H), 4.53 (d, *J* = 2.3 Hz, 1H), 3.82 (s, 3H), 3.56 (d, J = 15.1 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 157.6, 151.2, 143.5, 138.8, 134.2, 133.1, 132.4, 129.6, 128.2, 128.1, 127.5, 125.4, 124.6, 124.1, 111.5, 103.3, 98.4, 74.7, 55.6, 55.5, 46.7, 41.2; Anal. calcd. for $C_{23}H_{20}BrNO_5S$: C, 54.99; H, 4.01; N, 2.79, found: C, 54.92; H, 4.05; N, 2.84.

(±)-(12*S*,13*R*/12*R*,13*S*)-1,3-Dimethoxy-13-phenyl-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5]oxathiazonine 6,6-dioxide (5b): Prepared from compounds **1a** and **2b** according to the general procedure; white solid; yield = 74%; mp = 186–188 °C; R_f = 0.39 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 7.8 Hz, 1.6 Hz, 1H), 7.41 (td, *J* = 7.9 Hz, 1.8 Hz, 1H), 7.28-7.23 (m, 4H), 7.20-7.17 (m, 1H), 7.07 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 6.97 (d, *J* = 7.1 Hz, 2H), 6.79 (d, *J* = 2.3 Hz, 1H), 4.62-4.58 (m, 2H), 4.21 (s, 1H), 3.81 (s, 3H), 3.62 (d, *J* = 13.7 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 157.9, 151.2, 143.9, 138.5, 134.0, 132.4, 129.6, 128.6, 127.3, 126.6, 125.2, 124.7, 111.7, 103.3, 98.4, 76.8, 55.5, 55.4, 46.2, 42.3; Anal. calcd. for $C_{23}H_{21}NO_5S$: C, 65.23; H, 5.00; N, 3.31, found: C, 65.11; H, 5.07; N, 3.24.

(12*S*,13*R*)-1,3-Dimethoxy-13-phenyl-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5]oxathiazonine 6,6-dioxide {(12*S*,13*R*)-5b}: Prepared from compounds **1a** and **(2*R*,3*R*)-2b** according to the general procedure; $[\alpha]_{20}^{D}$ = +12.34° (c = 0.55, $CHCl_3$); enantiomeric ratio (87:13) was determined by HPLC analysis: (Daicel Chiralpak IA column, *n*-hexane:isopropanol = 85:15, flow rate = 1.0 mL/min, temp. = 25 °C, wavelength = 254 nm, major enantiomer: t_R = 9.7 min, minor enantiomer: t_R = 10.85 min); spectral data and other physical data of **(12*S*,13*R*)-5b** were identical with that of racemic **5b**.

(±)-(12*R*,13*R*/12*S*,13*S*)-13-(2-Fluorophenyl)-1,3-dimethoxy-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5] oxathiazonine 6,6-dioxide (5c): Prepared from compounds **1a** and **2c** according to the general procedure; brown solid; yield = 68%; mp = 180–182 °C; R_f = 0.45 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 7.7 Hz, 1.5 Hz, 1H), 7.44-7.40 (m, 1H), 7.30 (dd, *J* = 8.1 Hz, 1.1 Hz, 1H), 7.22-7.17 (m, 1H), 7.13-7.05 (m, 2H), 6.95-6.91 (m, 1H), 6.80 (d, *J* = 2.6 Hz, 1H), 6.48-6.44 (m, 1H), 6.15 (d, *J* = 2.6 Hz, 1H), 4.67-4.62 (m, 1H), 4.57-4.56 (m, 2H), 3.82 (s, 3H), 3.58 (d, *J* = 14.7 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4 (d, $^1J_{C-F}$ = 246.6 Hz), 159.2, 157.7, 151.2, 138.9, 134.1, 132.6, 130.6 (d, $^2J_{C-F}$ = 13.9 Hz), 129.6, 128.3 (d, $^3J_{C-F}$ = 8.5 Hz), 128.0 (d, $^3J_{C-F}$ = 3.8 Hz), 125.4, 124.7, 124.0 (d, $^4J_{C-F}$ = 3.1 Hz), 115.3 (d, $^2J_{C-F}$ = 22.3 Hz), 110.6, 103.6, 98.4, 75.1, 55.6, 55.4, 46.7, 35.0 (d, $^3J_{C-F}$ = 3.8 Hz); Anal. calcd. for $C_{23}H_{20}FNO_5S$: C, 62.57; H, 4.57; N, 3.17, found: C, 62.62; H, 4.48; N, 3.19.

(±)-(12*S*,13*R*/12*R*,13*S*)-13-(4-Chlorophenyl)-1,3-dimethoxy-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5] oxathiazonine 6,6-dioxide (5d): Prepared from compounds **1a** and **2d** according to the general procedure; white solid; yield = 67%; mp = 198–200 °C; R_f = 0.42 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 7.8 Hz, 1.6 Hz, 1H), 7.42 (td, *J* = 7.8 Hz, 1.6 Hz, 1H), 7.27-7.22 (m, 3H), 7.10-7.06 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 2.3 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 4.64-4.54 (m, 2H), 4.18 (s, 1H), 3.82 (s, 3H), 3.56 (d, J = 15.2 Hz, 1H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 157.8, 151.1, 142.5, 138.5, 134.1, 132.48, 132.45, 129.7, 128.8, 128.6, 125.1, 124.7, 111.1, 103.5, 98.4, 76.6, 55.6, 55.4, 46.1, 41.8; Anal. calcd. for $C_{23}H_{20}ClNO_5S$: C, 60.33; H, 4.40; N, 3.06, found: C, 60.25; H, 4.44; N, 3.00.

(±)-(12*S*,13*R*/12*R*,13*S*)-13-(4-Bromophenyl)-1,3-dimethoxy-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5] oxathiazonine 6,6-dioxide (5e): Prepared from compounds **1a** and **2e** according to the general procedure; brown solid; yield = 70%; mp = 190–192 °C; R_f = 0.44 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 7.8 Hz, 1.6 Hz, 1H), 7.43-7.37 (m, 3H), 7.27-7.24 (m, 1H), 7.08 (td, *J* = 7.4 Hz, 1.2 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 2.3 Hz, 1H), 6.14 (d, *J* = 2.3 Hz, 1H), 4.64-4.53 (m, 2H), 4.16 (s, 1H), 3.82 (s, 3H), 3.56 (d, *J* = 15.2 Hz, 1H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 157.8, 151.0, 143.1, 138.6, 134.1, 132.5, 131.8, 129.7, 129.0, 128.5, 127.7, 125.1, 124.8, 120.5, 111.0, 103.5, 98.4, 76.5, 55.6, 55.4, 46.1, 41.9; Anal. calcd. for $C_{23}H_{20}BrNO_5S$: C, 54.99; H, 4.01; N, 2.79, found: C, 55.12; H, 4.05; N, 2.86.

(±)-(12*S*,13*R*/12*R*,13*S*)-9-Fluoro-1,3-dimethoxy-13-phenyl-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5] oxathiazonine 6,6-dioxide (5f): Prepared from compounds **1b** and **2b** according to the general procedure; white solid; yield = 72%; mp = 174–176 °C; R_f = 0.51 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 8.8 Hz, 6.2 Hz, 1H), 7.27-7.19 (m, 3H), 6.99-6.94 (m, 3H), 6.79-6.75 (m, 2H), 6.15 (d, *J* = 2.6 Hz, 1H), 4.63-4.59 (m, 2H), 4.21 (s, 1H), 3.80 (s, 3H), 3.62 (dd, *J* = 15.7 Hz, 1.5 Hz, 1H), 3.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2 (d, $^1J_{C-F}$ = 255.8 Hz), 159.2, 158.0, 153.2 (d, $^3J_{C-F}$ = 12.3 Hz), 143.7, 138.3, 131.3 (d, $^3J_{C-F}$ = 10.8 Hz), 128.7 (d, $^4J_{C-F}$ = 3.08 Hz), 128.6, 127.2, 126.7, 112.8 (d, $^2J_{C-F}$ = 23.1 Hz), 111.9 (d, $^2J_{C-F}$ = 22.3 Hz), 111.5, 103.4, 98.5, 77.4, 55.5, 55.4, 46.1, 42.3; Anal. calcd. for $C_{23}H_{20}FNO_5S$: C, 62.57; H, 4.57; N, 3.17, found: C, 62.47; H, 4.61; N, 3.19.

(±)-(12*S*,13*R*/12*R*,13*S*)-13-(4-chlorophenyl)-9-fluoro-1,3-dimethoxy-12,13-dihydro-5,12 methanodibenzo[*b*,*f*][1,4,5] oxathiazonine 6,6-dioxide (5g): Prepared from compounds **1b** and **2d** according to the general procedure; white solid; yield = 69%; mp = 187–189 °C; R_f = 0.53 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 8.4 Hz, 6.2 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.98 (dd, *J* = 9.2 Hz, 2.6 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.81-6.76 (m, 2H), 6.16 (d, *J* = 2.6 Hz, 1H), 4.65-4.61 (m, 1H), 4.57-4.56 (m, 1H), 4.18 (s, 1H), 3.82 (s, 3H), 3.57 (dd, *J* = 15.1 Hz, 0.7 Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2 (d, $^1J_{C-F}$ = 255.8 Hz), 159.4, 157.8, 153.1 (d, $^3J_{C-F}$ = 12.3 Hz), 142.3, 138.3, 132.6, 131.4 (d, $^3J_{C-F}$ = 10.8 Hz), 128.9, 128.6, 112.7 (d, $^2J_{C-F}$ = 21.6 Hz), 112.1 (d, $^2J_{C-F}$ = 22.3 Hz), 110.8, 103.5, 98.4, 77.4, 55.6, 55.4, 46.0, 41.8; Anal. calcd. for $C_{23}H_{19}ClFNO_5S$: C, 58.05; H, 4.02; N, 2.94, found: C, 58.09; H, 4.04; N, 2.99.

(±)-(12*S*,13*R*/12*R*,13*S*)-13-(4-Bromophenyl)-9-fluoro-1,3-dimethoxy-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5]oxathiazonine 6,6-dioxide (5h): Prepared from compounds **1b** and **2e** according to the general procedure; brown solid; yield = 70%; mp = 182–184 °C; R_f = 0.51 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 8.8 Hz, 6.2 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.97 (dd, *J* = 9.2 Hz, 2.2 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.81-6.76 (m, 2H), 6.17 (d, *J* = 2.2 Hz, 1H), 4.65-4.60 (m, 1H), 4.57-4.56 (m, 1H), 4.16 (s, 1H), 3.82 (s, 3H), 3.56 (d, *J* = 15.1 Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3 (d, $^1J_{C-F}$ = 256.6 Hz), 159.4, 157.8, 153.1 (d, $^3J_{C-F}$ = 12.3 Hz), 149.7, 142.8, 138.4, 131.8, 131.4 (d, $^3J_{C-F}$ = 10.8 Hz), 128.9, 128.7, (d, $^4J_{C-F}$ = 3.8 Hz), 120.6, 112.7 (d, $^2J_{C-F}$ = 23.1 Hz), 112.1 (d, $^2J_{C-F}$ = 22.3 Hz), 110.8, 103.5, 98.4, 77.1, 55.6, 55.4, 46.0, 41.8; Anal. calcd. for $C_{23}H_{19}BrFNO_5S$: C, 53.09; H, 3.68; N, 2.69, found: C, 52.93; H, 3.74; N, 2.66.

(±)-(12*S*,13*S*/12*R*,13*R*)-9-Fluoro-13-(2-fluorophenyl)-1,3-dimethoxy-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5]oxathiazonine 6,6-dioxide (5i): Prepared from compounds **1b** and **2c** according to the general procedure; brown solid; yield = 71%; mp = 176–178 °C; R_f = 0.44 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 8.8 Hz, 6.2 Hz, 1H), 7.23-7.18 (m, 1H), 7.13-7.08 (m, 1H), 7.02 (dd, *J* = 9.2 Hz, 2.6 Hz, 1H), 6.95-6.91 (m, 1H), 6.81-6.76 (m, 2H), 6.47-6.43 (m, 1H), 6.17 (d, *J* = 2.2 Hz, 1H), 4.67-4.59 (m, 2H), 4.56 (s, 1H), 3.82 (s, 3H), 3.58 (d, *J* = 15.1 Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4 (d, $^1J_{C-F}$ = 256.6 Hz), 159.7 (d, $^1J_{C-F}$ = 246.6 Hz), 159.3, 157.7, 153.2 (d, $^3J_{C-F}$ = 12.3 Hz), 138.7, 131.3 (d, $^3J_{C-F}$ = 10.8 Hz), 130.4 (d, $^2J_{C-F}$ = 13.8 Hz), 128.8 (d, $^4J_{C-F}$ = 3.1 Hz), 128.5 (d, $^3J_{C-F}$ = 8.5 Hz), 127.9 (d, $^3J_{C-F}$ = 3.8 Hz), 124.1 (d, $^4J_{C-F}$ = 3.0 Hz), 115.4 (d, $^2J_{C-F}$ = 22.3 Hz), 112.9 (d, $^2J_{C-F}$ = 23.1 Hz), 112.0 (d, $^2J_{C-F}$ = 22.3 Hz), 110.3, 103.5, 98.4, 75.7, 55.6, 55.4, 46.6, 41.8, 35.0 (d, $^3J_{C-F}$ = 3.8 Hz); Anal. calcd. for $C_{23}H_{19}F_2NO_5S$: C, 60.12; H, 4.17; N, 3.05, found: C, 60.16; H, 4.16; N, 3.07.

(±)-(12*S*,13*R*/12*R*,13*S*)-9-Fluoro-1,3-dimethoxy-13-(3-methoxyphenyl)-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5] oxathiazonine 6,6-dioxide (5j): Prepared from compounds **1b** and **2f** according to the general procedure; off white solid; yield = 73%; mp = 185–187 °C; R_f = 0.42 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 8.7 Hz, 6.4 Hz, 1H), 7.18 (t, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 9.1 Hz, 2.3 Hz, 1H), 6.79-6.72 (m, 3H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.50 (s, 1H), 6.16 (d, *J* = 2.3 Hz, 1H), 4.62-4.58 (m, 2H), 4.18 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.64 (d, *J* = 15.6 Hz, 1.8 Hz, 1H), 3.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3 (d, $^1J_{C-F}$ = 255.9 Hz), 159.8, 159.1, 157.9, 153.1 (d, $^3J_{C-F}$ = 12.4 Hz), 145.4, 138.2, 131.3 (d, $^3J_{C-F}$ = 10.5 Hz), 129.6, 128.9, (d, $^4J_{C-F}$ = 2.8 Hz), 119.6, 113.5, 112.7 (d, $^2J_{C-F}$ = 23.0 Hz), 112.0 (d, $^2J_{C-F}$ = 22.0 Hz), 111.3, 103.3, 98.4, 87.0, 77.3, 55.5, 55.4, 55.2, 46.2, 42.2; Anal. calcd. for $C_{24}H_{22}FNO_6S$: C, 61.14; H, 4.70; N, 2.97, found: C, 61.03; H, 4.74; N, 2.92.

(±)-(12*S*,13*R*/12*R*,13*S*)-1,3-Dimethyl-13-phenyl-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5]oxathiazonine 6,6-dioxide (5k): Prepared from compounds **1c** and **2b** according to the general procedure; brown solid; yield = 72%; mp = 181–183 °C; R_f = 0.59 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.39 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.29-7.25 (m, 4H), 7.23-7.19 (m, 1H), 7.04 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 6.92 (br s, 2H), 6.67 (s, 1H), 4.62-4.56 (m, 2H), 4.18 (s, 1H), 3.65 (d, *J* = 14.7 Hz, 1H), 2.26 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 142.7, 137.3, 136.8, 136.6, 133.8, 132.8, 130.5, 129.7, 129.0, 127.9, 127.1, 125.8, 125.2, 124.82, 124.80, 77.2, 45.5, 45.2, 20.9, 19.3; Anal. calcd. for $C_{23}H_{21}NO_3S$: C, 70.56; H, 5.41; N, 3.58, found: C, 70.48; H, 5.47; N, 3.62.

(±)-(12*S*,13*R*/12*R*,13*S*)-13-(3-Methoxyphenyl)-1,3-dimethyl-12,13-dihydro-5,12 methanodibenzo[*b*,*f*][1,4,5]oxathiazonine 6,6-dioxide (5l): Prepared from compounds **1c** and **2f** according to the general procedure; off white solid; yield = 70%; mp = 172–174 °C; R_f = 0.44 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.39 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.27-7.25 (m, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.75 (dd, *J* = 8.2 Hz, 2.3 Hz, 1H), 6.66 (s, 1H), 6.47 (br s, 2H), 4.62-4.56 (m, 2H), 4.13 (s, 1H),

3.75 (s, 3H), 3.66 (d, *J* = 14.7 Hz, 1H), 2.26 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 151.1, 144.4, 137.3, 136.7, 136.6, 133.8, 132.7, 130.5, 130.1, 129.7, 125.8, 125.1, 124.8, 120.33, 120.30, 114.3, 111.7, 77.1, 55.2, 45.7, 45.1, 20.9, 19.3; Anal. calcd. for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50; N, 3.32, found: C, 68.37; H, 5.58; N, 3.28.

(±)-(12*S*,13*R*/12*R*,13*S*)-9-Fluoro-1,3-dimethyl-13-phenyl-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5] oxathiazonine 6,6-dioxide (5m): Prepared from compounds **1d** and **2b** according to the general procedure; white solid; yield = 73%; mp = 186–188 °C; R_f = 0.59 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 8.7 Hz, 5.9 Hz, 1H), 7.30-7.20 (m, 4H), 6.99 (dd, *J* = 9.1 Hz, 2.7 Hz, 1H), 6.92 (br s, 2H), 6.78-6.74 (m, 1H), 6.71 (s, 1H), 4.66-4.57 (m, 2H), 4.18 (s, 1H), 3.66 (d, *J* = 14.7 Hz, 1H), 2.27 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2 (d, $^1J_{C-F}$ = 255.9 Hz), 153.1 (d, $^3J_{C-F}$ = 12.5 Hz), 142.4, 137.4, 136.8, 136.6, 131.5 (d, $^3J_{C-F}$ = 11.5 Hz), 130.7, 129.1, 128.9 (d, $^4J_{C-F}$ = 3.8 Hz), 127.94, 127.92, 127.2, 125.8, 125.0, 112.4 (d, $^2J_{C-F}$ = 23.9 Hz), 112.1 (d, $^2J_{C-F}$ = 22.0 Hz), 87.1, 77.7, 45.4, 45.1, 20.9, 19.4; Anal. calcd. for $C_{23}H_{20}FNO_3S$: C, 67.46; H, 4.92; N, 3.42, found: C, 67.32; H, 4.89; N, 3.47.

((±)-(12*S*,13*R*/12*R*,13*S*)-9-Fluoro-13-(3-methoxyphenyl)-1,3-dimethyl-12,13-dihydro-5,12-methanodibenzo[*b*,*f*][1,4,5]oxathiazonine 6,6-dioxide (5n): Prepared from compounds **1d** and **2f** according to the general procedure; off white solid; yield = 71%; mp = 179–181 °C; R_f = 0.44 (silica gel, 15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 9.1 Hz, 6.4 Hz, 1H), 7.28-7.27 (m, 1H), 7.23-7.19 (m, 1H), 7.00 (dd, *J* = 9.1 Hz, 2.3 Hz, 1H), 6.79-6.74 (m, 2H), 6.70 (s, 1H), 6.48 (br s, 2H), 4.67-4.66 (m, 2H), 4.63-4.58 (m, 1H), 4.14 (s, 1H), 3.76 (s, 3H), 3.68 (d, *J* = 15.1 Hz, 1H), 2.27 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3 (d, $^1J_{C-F}$ = 255.9 Hz), 160.1, 153.1 (d, $^3J_{C-F}$ = 11.5 Hz), 144.1, 137.5, 131.4 (d, $^3J_{C-F}$ = 10.5 Hz), 130.7, 130.1, 128.9, (d, $^4J_{C-F}$ = 2.9 Hz), 125.8, 124.9, 120.3, 120.2, 119.6, 114.2, 112.3 (d, $^2J_{C-F}$ = 23.9 Hz), 112.1 (d, $^2J_{C-F}$ = 22.0 Hz), 111.8, 77.7, 55.2, 55.4, 45.6, 45.1, 20.9, 19.4; Anal. calcd. for $C_{24}H_{22}FNO_4S$: C, 65.59; H, 5.05; N, 3.19, found: C, 65.47; H, 5.02; N, 3.26.

Acknowledgements

SKD is grateful to the Science and Engineering Research Board, Department of Science and Technology (DST SERB), New Delhi, for financial assistance (Grant No. SB/FT/CS 073/2013). We are thankful to Prof. S. C. Pan, IIT-Guwahati for the HPLC data.

Keywords: Tetrahydroquinolines • benzothiaoxazepine-1,1-dioxides • Intramolecular Friedel-Crafts epoxy arene cyclization • S_NAr reaction • Bridged-benzosultams

References

[1] M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.*, **2010**, *14*, 347–361.

[2] For selected recent examples of the biological activity of tetrahydroquinoline derivatives, see: a) C. Z. Ding, J. T. Hunt, C. Ricca, V. Manne, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 273–275; b) V. V. Kouznetsov, D. R. M. Arenas, F. Arvelo, J. S. B. Forero, F. Sojo, A. Muñoz, *Lett. Drug Des. Discovery* **2010**, *7*, 632−639; c) R. J. Pagliero, S. Lusvarghi, A. B. Pierini, R. Brun and M. R. Mazzieri, *Bioorg. Med. Chem.* **2010**, *18*, 142−150; d) C. Fonseca-Berzal, A. D. R. Merchan, B. A. R. Romero, J. A. Escario, V. V. Kouznetsov, A. Gomez-Barrio, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4851–4856; e) W. Zhu, Q. Hu, N. Hanke, C. J. van Koppen, R. Hartmann, *J. Med. Chem.* **2014**, *57*, 7811–7817; f) Y. M. Liu, H. Y. Lee, C. H. Chen, C. H. Lee, L. T. Wang, S. L. Pan, M. J. Lai, T. K. Yeh, J. P. Liou, *Eur. J. Med. Chem.* **2015**, *89*, 320–330; g) A. M. Bender, N. W. Griggs, J. P. Anand, J. R. Traynor, E. M. Jutkiewicz, H. I. Mosberg, *ACS Chem. Neurosci.* **2015**, *6*, 1428–1435; h) B. P. Fauber, A. Gobbi, P. Savy, B. Burton, Y. Deng, C. Everett, H. La, A. R. Johnson, P. Lockey, M. Norman, H. Wong, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4109–4113; i) L. Chen, P. T. Wilder, B. Drennen, J. Tran, B. M. Roth, K. Chesko, P. Shapiro, S. Fletcher, *Org. Biomol. Chem.* **2016**, *14*, 5505– 5510; j) A. A. Harland, A. M. Bender, N. W. Griggs, C. Gao, J. P. Anand, I. D. Pogozheva, J. R. Traynor, E. M. Jutkiewicz, H. I. Mosberg, *J. Med. Chem.* **2016**, *59*, 4985–4998.

[3] a) K. C. Majumdar, S. Mondal, *Chem. Rev.* **2011**, *111*, 7749–7773; b) M. D. McReynolds, J. M. Dougherty, P. R. Hanson, *Chem. Rev.* **2004**, *104*, 2239–2258. c) Z. Liu, Y. Takeuchi, *Heterocycles* **2009**, *78*, 1387–1412.

[4] V. J. Santora, J. A. Covel, J. B. Ibarra, G. Semple, B. Smith, J. Smith, M. I. Weinhouse, J. A. Schultz, PCT Int. Appl. WO 2008005338 A1 20080110, 2008.

[5] A. Cordi, P. Desos, P. Lestage, L. Danober, Can. Pat. Appl. CA 2752131 A1 20120316, 2012.

[6] T. G. Davies, W. E, Wixted, J. E. Coyle, C. Griffiths-Jones, K. Hearn, R. McMenamin, D. Norton, S. J. Rich, C. Richardson, G. Saxty, H. M. Willems, A. J. Woolford, J. E. Cottom, J P. Kou, J. G. Yonchuk, H. G. Feldser, Y. Sanchez, J. P. Foley, B. J. Bolognese, G. Logan, P. L. Podolin, H. Yan, J. F. Callahan, T. D. Heighman, J. K. Kerns, *J. Med. Chem.* **2016**, *59*, 3991–4006.

[7] For reviews on the synthesis of tetrahydroquinolines, see: a) B. Nammalwar, R. A. Bunce, *Molecules* **2014**, *19*, 204–232; b) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, *111*, 7157–7259; c) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *52*, 15031–15070.

[8] a) S. Faisal, P. K. Maity, Q. Zang, T. B. Samarakoon, R. L. Sourk, P. R. Hanson, *ACS Comb. Sci.* **2016**, *18*, 387–393; b) T. B. Samarakoon, J. K. Loh, A. Rolfe, L. S. Le, S. Y. Yoon, G. H. Lushington, P. R. Hanson, *Org. Lett.*, **2011**, *13*, 5148–5151; c) A. Rolfe, T. B. Samarakoon, S. V. Klimberg, M. Brzozowski, B. Neuenswander, G. H. Lushington, P. R. Hanson, *J. Comb. Chem.* **2010**, *12*, 850-854; d) A. Rolfe, T. B. Samarakoon, P. R. Hanson, *Org. Lett.* **2010**, *12*, 1216-1219; e) Jeon, K.; Rayabarappu, D. R.; Rolfe, A.; Hanson, P. R. *Tetrahedron* **2009**, *65*, 4992–5000.

[9] Shaveta, S. Mishra, P. Singh, *Eur. J. Med. Chem.* **2016**, *124*, 500–536.

[10] a) S. K. Taylor, *Org. Prep. Proced. Int.* **1992**, *24*, 245–284; b) H. S. Krake, S. C. Bergmeier, *Tetrahedron* **2010**, *66*, 7337–7360; c) S. K. Das, *Asian J. Org. Chem.* **2017**, *6*, 243–256.

[11] a) R. Devi, T. Kalita, S. K. Das, *RSC Advances* **2015**, *5*, 39692–39696; b) R. Devi, D. Gogoi, P. Bora, S. K. Das, *Tetrahedron* **2016**, *72*, 4878–4888; c) D. Gogoi, R. Devi, P. Pahari, B. Sarma, S. K. Das, *Beilstein J. Org. Chem.* **2016**, *12*, 2816–2822; d) R. Devi, S. K. Das, *Beilstein J. Org. Chem.* **2017**, *13*, 571–578.

[12] For reviews on bridged lactams and sultams, see: a) M. Szostak, J. Aubé, *Chem. Rev.* **2013**, *113*, 5701–5765; b) V. A. Rassadin, D. S. Grosheva, A. A. Tomashevskii, V. V. Sokolov, *Chem. Heterocycl. Compd.* **2013**, *49*, 39-65.

[13] Y. Kobayashi, T. Harayama, *Org. Lett.* **2009**, *11*, 1603–1606.

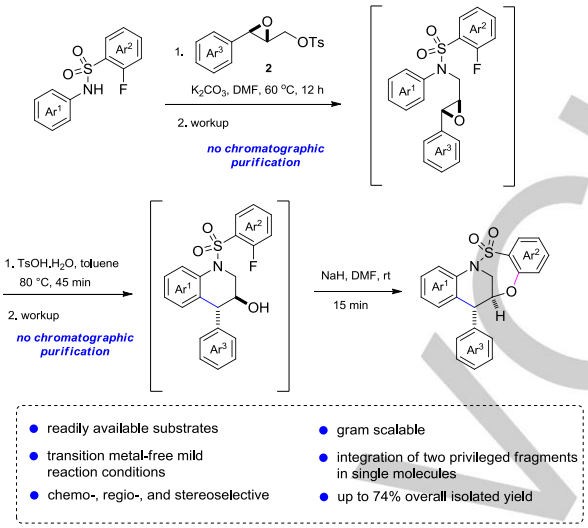
[14] For the synthesis of tetrahydroquinolines and related heterocycles by homolytic aromatic substitution, see: a) S. Hildebrandt, A. Gansäuer, *Angew. Chem., Int. Ed.* **2016**, *55*, 9719–9722; b) A. Gansäuer, S. Hildebrandt, A. Michelmann, T. Dahmen, D. von Laufenberg, C. Kube, G. D. Fianu and R. A. Flowers II, *Angew. Chem., Int. Ed.* **2015**, *54*, 7003–7006. d) Gansäuer, A.; Behlendorf, M.; von Laufenberg, D.; Fleckhaus, A.; Kube, C.; Sadasivam, D. V.; Flowers, R. A., II *Angew. Chem., Int. Ed.* **2012**, *51*, 4739–4742.

10.1002/ejoc.201701152

WILEY-VCH

COMMUNICATION

Synthesis of previously unknown tetrahydroquinoline-implanted bridged benzothiaoxazepine-1,1-dioxides is presented. The three-step protocol utilizes readily available *N*-ary-2-fluorobenzenesulfonamides and *trans*-2,3-epoxy cinnamyl alcohol-derived tosylates as the starting materials, involves *N*-alkylation of sulfonamides, intramolecular epoxide ring-opening and S_NAr reactions as the reaction steps, and requires only one chromatographic purification to access the desired products in good. overall yields



Polycyclic Bridged heterocycles

*Hemi Borgohain, Runjun Devi, Divya Dheer, Biraj Jyoti Borah,Ravi Shankar, and Sajal Kumar Das**

Synthesis of tetrahydroquinoline-embedded bridged benzothiaoxazepine-1,1-dioxides