Diversity-Oriented Synthetic Approach to Naturally Abundant *S*-Amino Acid Based Benzannulated Enantiomerically Pure Medium Ring Heterocyclic Scaffolds Employing Inter- and Intramolecular Mitsunobu Reactions†

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The diversity-oriented organic synthesis of enantiomerically pure benzannulated oxazepine, diazepine, thiazepine, oxazocine, and diazocine scaffolds is described from easily accessible naturally occurring *S*-amino acids as chiral synthons. Inter- and intramolecular Mitsunobu reactions for the formation of carbon−nitrogen, carbon−oxygen, and carbon−sulfur bonds have been used as key transformations to construct these biologically important privileged heterocycles. This is the first example where the Mitsunobu approach has been utilized for the construction of *S*-amino acid based seven- and eight-membered ring systems.

Introduction

The diversity-oriented synthesis (DOS) generates chemical space of small molecules with divergent structures. The objective of DOS is to produce efficiently a collection of small molecules capable of perturbing any disease-related biological process, leading ultimately to identification of therapeutic protein targets which is being modulated by small molecules.[1] DOS involves three key elements: building blocks, stereochemistry, and molecular framework. Divergent reaction pathways are efficient means of generating structural diversity particularly through the creation of diverse molecular frameworks and functional groups. Skeletal diversity is generated by the use of different sets of reagents or reaction conditions to convert common substrates into collections of products with wide-ranging molecular skeletons.[2]

Over the past decades, the design and synthesis of medium ring heterocycles having a ring size in the range of 7−11 have received a lot of attention in synthetic organic chemistry as a consequence of a wide variety of applications such as biologically active natural products,[3] drug candidates,[4] materials,[5] and for catalysis.[6] Among them, benzodiazepines are the class of privileged structures having a wide range of biological activities.[7] Benzoxazepines show pharmacological activities such as antipsychotic for the central nervous system along with antibreast cancer.[8] Benzothiazepines are active constituents of an important class of biologically active compounds such as bradykinin agonists.[9] Eight-membered benzannulated heterocycle benzodiazocine, such as Teleocidines, activate protein kinase C (PKC) isozymes.[10] Benzoxazocine, such as Nefopam hydrochloride,[11] is a nonnarcotic analgesic drug with antidepressant properties.[12] The abundance of medium ring heterocycles continues to ensure that they are attractive targets for synthetic organic chemists.[13] Despite their wide occurrence and bioactivity, benzannulated medium ring heterocycles are not sufficiently investigated, one barrier to their access generally being unsatisfactory synthetic procedures. Thus, the development of novel and efficient methods leading to medium size heterocycles is an important area of research.[14]

Few reported approaches for the construction of medium ring heterocycles are available based on cycloaddtions,[15] ring closing metathesis,[16] ring expansion,[17] transannular cyclizations,[18] and metal-mediated ring cyclization.[19a] Recently, Alper et al. reported an excellent method for the synthesis of fused medium ring heterocycles using easily recoverable palladium-complexed dendrimer supported on silica.[19b] The existing procedures require expensive transition metal reagents (Sc, Ti, Ru, Mo, etc.) and severe reaction conditions with long reaction time and often led to products with low yields as described by Broggini et al. (11−42%)[15] and by Buchwald et al. (5−55%).[17]

Synthesis Plan

As part of our research program related to the synthesis and biology of *S*-amino acid based heterocycles,[20] we intended to synthesize seven- and eight-membered rings bearing nitrogen, oxygen, and sulfur atoms. Interest in the use of easily accessible and versatile proteinogenic amino acids as a chiral pool for synthesis of optically active heterocycles has been growing rapidly[21] because of their response to the enantiospecificity shown by most biological systems and the increased demand to market chiral drugs as single enantiomers. In most of the cases, the chirality contained in marketed drugs is derived from the chiral pool, i.e., chirality already present in nature. Toward our objective for the synthesis of naturally occurring *S*-amino acid incorporated medium ring heterocycles, we recognized that

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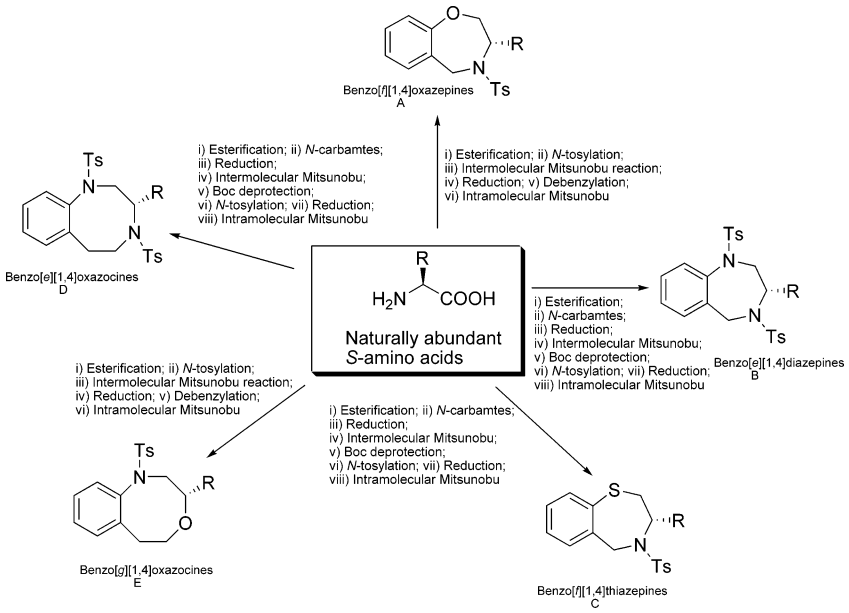
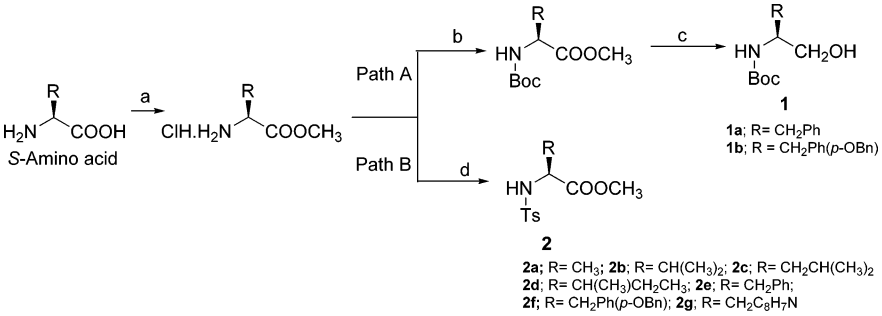
Scheme 1. Synthesis of Diverse Chiral Benzannulated Medium Ring Heterocyclic Scaffolds from Naturally Abundant *S*-Amino Acids



Scheme 2. Synthesis of *S*-Amino Acid Derivatives[a]



[a] Reagents: (a) MeOH, conc HCl, 0 °C−RT 10 h; (b) $(Boc)_2O$, TEA, THF, 0−25 °C, 12 h, quant; (c) $LiAlH_4$, THF, 0 °C, 0.5 h, 68−89%; (d) *p*-toluenesulfonyl Chloride, TEA, DCM, 0−25 °C, 4 h, 70−78%.

the Mitsunobu approach for the formation of the carbon−heteroatom bond offers a better and more convenient route to the synthesis of benzannulated medium ring heterocycles in an optically pure form. While there are very few examples for the formation of achiral seven-membered heterocyles using Mitsunobu reaction,[22] similar strategies were not reported for eight-membered rings. In this article, we report a facile conversion of *S*-amino acid derivatives to bicyclic amino acid-annulated seven- and eight-membered ring heterocycles (benzoxazepines, benzodiazepines, benzothiazepine, benzodiazocines, and benzoxazocines) in chiral form. The scaffolds (**A**−**E**) shown in Scheme 1 are the core structural motifs in a variety of biologically active privileged heterocycles derived from naturally abundant chiral amino acids.

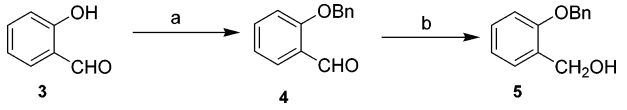
Results and Discussion

Synthesis of seven- and eight-membered chiral heterocycles was undertaken. *S*-amino acid and substituted benzene derivatives were used as building blocks for the construction of benzannulated chiral heterocycles (Scheme 1). For the synthesis of amino alcohols from amino acids, the naturally occurring *S*-amino acids were first converted to their methyl esters which on treatment with $(Boc)_2O$ under basic condition afforded the desired *N*-*tert*-butyl carbamate derivative of amino esters in quantitative yield, which on subsequent reduction with lithium aluminum hydride (LAH) gave the amino alcohols **1a-b** in 68−89% yield (Scheme 2, path A). The tosyl derivatives of amino acids were synthesized by path B as shown in Scheme 2, in which the amino esters of naturally occurring *S*-amino acid derivatives were treated with *p*-toluenesulfonyl chloride in the presence of triethyl amine to afford the *N*-tosyl amino esters **2a-g** in 70−78% yield.

To begin with, salicylaldehyde **3** and *N*-tosyl amino acid methyl esters **2a-g** were used for the synthesis of chiral 3-substituted-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo-[*f*][1,4]oxazepine derivatives. Treatment of salicylaldehyde **3** with benzyl bromide and potassium carbonate in acetone gave the *O*-benzyl salicylaldehyde **4** in quantitative yield. Subsequent reduction of **4** with sodium borohydride in THF yielded benzyl alcohol derivative **5** (Scheme 3).

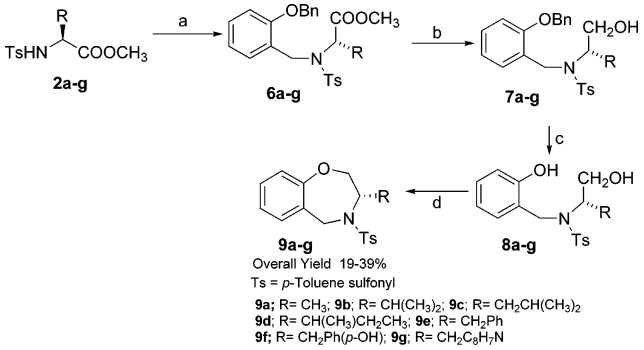
The Mitsunobu reaction of *S*-amino acid derivatives **2a-g** with **5** provided the esters **6a-g** in 57−82% yield. The lithium aluminum hydride (LAH) reduction of **6a-g** afforded the corresponding alcohols **7a-g**, which on subsequent debenzylation by H_2/ Pd (10% on carbon) gave **8a-g** containing free alcoholic and phenolic hydroxyl groups in 62−91% yield.

Scheme 3. Preparation of (2-Benzyloxy-phenyl)-methanol[a]



[a] Reagents: (a) BnBr, K_2CO_3 acetone, RT, 8 h, quantitative; (b) $NaBH_4$, THF, 0 °C, 1 h, quantitative.

Scheme 4. Syntheses of (*S*)-3-Substituted-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine Derivatives[a]



[a] Reagents: (a) **5**, DEAD, PPh_3, THF, 0 °C (2 h) to RT (10 h), N_2, 57−82%; (b) LAH, THF, 0 °C, 1 h, 59−86%; (c) H_2, 10% Pd/C, MeOH, RT, 2 h, 50 psi, 71−91%; (d) DEAD, PPh_3, THF, 0 °C (1 h) to RT (14 h), N_2, 63−76%.

Exposure of **8a-g** to Mitsunobu reaction conditions, i.e., diethylazodicarboxylate (DEAD) and triphenylphosphine (TPP), at 0 °C resulted in the formation of desired enantiomerically pure benzoxazepine derivatives **9a-g** in 63−76% yield (Scheme 4, Table 1).

The structures of all benzoxazepine derivatives were ascertained by their spectroscopic data (H, C NMR, MS) and elemental analyses. In compounds **9a-g** ($CDCl_3$ solutions), the ethereal methylene protons (O*CH*$_2$) appeared between δ 3.70−3.91 ppm as separate multiplets. The proton attached to the chiral carbon (C*H*) appeared between δ 3.92−4.32 ppm as a multiplet. The benzylic methylene protons attached with nitrogen appeared as separate doublets between δ 4.31−4.80 ppm. As a representative, the tosyl group from the benzoxazepine derivatives can be removed by 4% Na−Hg at 70 °C in 65−73% yield (Scheme 5).

The successful syntheses of enantiomerically pure 1,4-benzoxazepines prompted us to initiate further application of this strategy for the synthesis of 1,4-benzodiazepines where 2-nitrobenzaldehyde can be used in place of salicylaldehyde. Unfortunately, reaction of 2-nitrobenzyl alcohol with **2** provided 30% yield and subsequent reaction steps led to products with lower yields perhaps due to hydrogen bonding between the hydrogen of the hydroxyl group and the nitro group at the ortho position. In order to overcome this problem, a modified synthetic approach was explored (Schemes 6 and 7). It is noted that a successful Mitsunobu displacement reaction is depended on the pK_a associated with the incoming nucleophile and independent of the nucleophilicity of the nucleophile.[23] Hence, the amino functionality of commercially available methyl anthranilate **11** was converted to its tosyl derivative **12** (Scheme 6).

The introduction of a tosyl group on the NH_2 function made the proton attached to nitrogen acidic enough to participate in Mitsunobu reaction. The treatment of *S*-amino alcohol derivatives **1a-b** with **12** under DEAD/PPh_3 conditions furnished **13a-b** in 63−70% yield as a mixture of rotamers. The cleavage of Boc in **13a-b** by 6 N HCl in methanol furnished corresponding amine hydrochlorides **14a-b**. The primary amine functionality in **14a-b** was again activated; to participate in the Mitsunobu reaction, through conversion into its tosyl derivative **15a-b** in 55−79% yield. The products **15a-b** were further obtained as a mixture of rotamers in which the CH_3 group of ester functionality, tosyl group, and NH of sulfonamide showed duplicity in their δ values. The CH_3 of tosyl group in **15a-b** showed the peaks at δ 2.29, 2.34, and 2.36 ppm whereas the CH_3 of ester appeared at δ 3.82 and 3.98 ppm. The NH of sulfonamide appeared at δ 5.54 and 6.27 ppm. Exchange spectroscopy and H NMR at elevated temperatures further confirmed the existence of rotamers. The reduction of **15a-b** by LAH at 0 °C afforded the rotameric mixture of alcohols **16a-b** which under Mitsunobu cyclization conditions (DEAD/PPh_3, 0 °C) yielded the desired enantiomerically pure 3-substituted-1,4-benzodiazepines **17a-b** in 62−77% yield (Scheme 7, Table 1).

The assigned structure of **17a-b** was based on spectroscopic data (H, C NMR, MS) and elemental analyses. In H NMR of **17a-b**, the proton associated with the tosyl group appeared at δ 2.24−2.44 ppm. The benzylic protons attached to the chiral center appeared at δ 3.01−3.11 ppm as a multiplet. One of the methylene protons adjacent to *N*-tosyl appeared at δ 3.13−3.25 ppm while the other one appeared at 4.22−4.35 ppm as a multiplet. The proton attached to the chiral carbon appeared at δ 4.06−4.16 ppm as a multiplet. The tosyl group from the benzodiazepine derivatives can be removed by 4% Na−Hg at 70 °C (representative example shown in Scheme 8).

The synthetic approach was further extended for the access of chiral benzo[*f*][1,4]thiazepine scaffold, (*S*)-3-(4-benzyloxy-benzyl)-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*]-[1,4]thiazepine **25**. The thiosalicylic acid **19** on treatment with methanol in the presence of HCl gave methylthiosalicylate **20** in quantitative yield (Scheme 9).

Treatment of Boc protected tyrosinol **1b** with **20** under DEAD/PPh_3 conditions furnished the ester derivative **21** in 66% yield. The deprotection of the Boc group with 6 N HCl afforded the free amine hydrochloride **22**, which was again converted to its tosyl derivative **23** through treatment with tosyl chloride and triethylamine in 79% yield. The reduction of ester group in **23** by LAH gave alcohol **24** in 71% yield. The intramolecular Mitsunobu cyclization between the sulfonamide and benzylic hydroxyl in **24** furnished enantiomerically pure benzothiazepine derivative **25** in 69% yield (Scheme 10, Table 1).

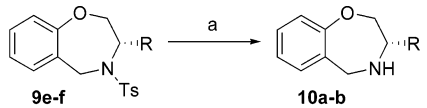
The structure of benzothiazepine derivative **25** was ascertained by spectroscopic data (H, C NMR, MS) and elemental analyses. In the H NMR of **25**, the proton of tosyl CH_3 appears at δ 2.33 ppm. The benzylic proton attached to a chiral carbon appears at δ 2.56−2.68 ppm as a multiplet. The methylene proton attached to the sulfur appears separately in the form of multiplets at δ 2.86−2.91 ppm and 3.28−3.35 ppm. The proton of chiral center appears at δ 4.25−4.27 ppm as a multiplet. The benzylic protons attached

Table 1. Representative Compounds of the 1,4-Benzoxazepines (**9a-g**), 1,4-Benzodiazepines (**17a-b**), Benzo[*f*][1,4]thiazepines **25**, Benzo[*e*][1,4]diazocine (**35a-b**), and Benzo[*g*][1,4]oxazocine (**41a-d**) Series

entry no.	product	R	yield[a]/HPLC purity[b] (%)	$[\alpha]_D^{20}$	t_R[c] (min)	ee
1	**9a**	CH_3	76/97	−28 (c 1, $CHCl_3$)	29.12	>99
2	**9b**	$CH(CH_3)_2$	70/95	−24 (c 1, $CHCl_3$)	22.80	>99
3	**9c**	$CH_2CH(CH_3)_2$	63/97	+22 (c 1, $CHCl_3$)	18.16	>99
4	**9d**	$CH(CH_3)(C_2H_5)$	68/96		20.99	>99
5	**9e**	$CH_2C_6H_5$	64/97	+32 (c 1, $CHCl_3$)	25.17	>99
6	**9f**	$CH_2C_6H_4$(*p*-OH)	65/93	+16 (c 1, $CHCl_3$)	25.23	>99
7	**9g**	$CH_2C_7H_6N$	74/97	+22 (c 1, $CHCl_3$)	22.08	>99
8	**17a**	$CH_2C_6H_5$	77/91	+30 (c 1, $CHCl_3$)	19.49	>99
9	**17b**	$CH_2C_6H_4$(*p*-OBn)	62/94	+28 (c 1, $CHCl_3$)	20.80	>99
10	**25**	$CH_2C_6H_4$(*p*-OBn)	69/96	+39 (c 1, $CHCl_3$)	26.96	>99
11	**35a**	$CH_2C_6H_5$	86/97	−29(c 1, $CHCl_3$)	21.33	>99
12	**35b**	$CH_2C_6H_4$(*p*-OBn)	77/97	−33 (c 1, $CHCl_3$)	25.09	>99
13	**41a**	CH_3	66/96	+45 (c 1, $CHCl_3$)	27.20	>99
14	**41b**	$CH_2C_6H_5$	63/97	−65 (c 1, $CHCl_3$)	18.69	>99
15	**41c**	$CH_2C_6H_4$(*p*-OH)	71/94	−44 (c 1, $CHCl_3$)	30.03	>99
16	**41d**	$CH_2C_7H_6N$	63/98	−14 (c 1, $CHCl_3$)	23.39	>99

[a] Compounds (**9a-g**, **17a-b**, **25**, **35a-b**, and **41a-d**) obtained after purification from silica gel chromatography from their corresponding precursors (**8a-g**, **16a-b**, **24**, **34a-b**, and **40a-d**). [b] Purity of products evaluated from the HPLC column. [c] Retention time on HPLC LichroCART Chiradex column (250 mm × 4 mm, 5 μm) with a linear gradient of 0−100% CH_3OH in water over 30 min, a flow rate of 0.75 mL/min, and UV detection at 254 nm.

Scheme 5. Representative Examples of Tosyl Removal from Benzoxazepine Derivatives **9e** and **9f**[a]



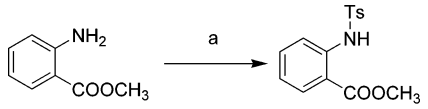
9e-f **10a-b**

9e; R= CH_2Ph
9f; R= CH_2Ph(*p*-OH)

10a; R= CH_2Ph
10b; R= CH_2Ph(*p*-OH)

[a] Reagents: (a) 4% Na−Hg, Na_2HPO_4, MeOH, 70 °C, 12 h (65−73%).

Scheme 6. Preparation of *N*-Tosyl Derivative of Methyl Anthranilate **12**[a]



11 **12**

[a] Reagents: (a) *p*-toluenesulfonyl chloride, pyridine, RT, 6 h, N_2, 85%.

to NTs appear as separate doublets at δ 4.67 and 4.76 ppm. The benzylic proton attached to oxygen appears at δ 5.04 ppm. As a representative, the tosyl group from the benzothiazepine derivative can be removed by 4% Na−Hg at 70 °C in 64% yield (Scheme 11).

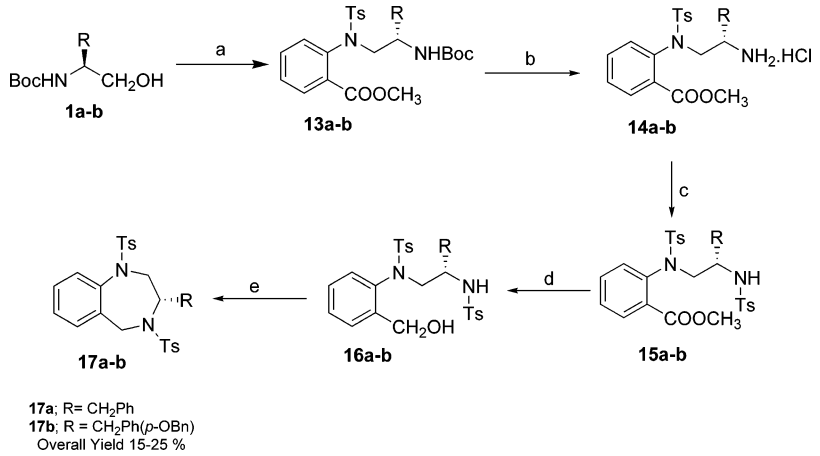
After successful application of an inter- and intramolecular Mitsunobu reaction strategy for chiral seven-membered heterocycles, we elaborated this strategy for the synthesis of eight-membered ring systems. However, the entropic factor for the formation of eight-membered rings is disfavored as the carbon chain becomes too long and thus the probability of a cyclization reaction taking place between the two chain termini decreases. The enthalpic factor is mainly created by steric interactions, i.e., torsional effects in single bonds (Pitzer strain), deformation of bond angles from their optimal values (Baeyer strain), and transannular strain.[24] For the synthesis of chiral diazocines, the 2-nitrophenylacetic acid **27** was taken as a precursor in which the acid and nitro groups were converted into their ester derivative **28** and amine **29**, respectively, by methanol/HCl followed by 10% Pd/C−H_2. The activated sulfonamide **30** was prepared by treatment of **29** with TsCl in pyridine (at 0 °C to room temperature) to make its proton acidic for Mitsunobu reaction (Scheme 12).

The synthesis of (*S*)-3-substituted-1,4-bis-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-benzo[*e*][1,4]diazocines was outlined in Scheme 13. Treatment of amino alcohol **1a-b** with **30** in the presence of DEAD/PPh_3 gave **31a-b** in 61−68% yield in the form of a mixture of rotamers. Deprotecteion of Boc by 6 N HCl in MeOH gave the hydrochloride salt **32a-b**. The reaction of **32a-b** with tosyl chloride in the presence of triethylamine yielded the rotameric mixture of **33a-b** in 64−73% yield, which on further reduction by LAH gave the rotameric mixture of alcohols **34a-b**. Finally under intramolecular Mitsunobu cyclization conditions (DEAD, TPP, 0 °C), **34a-b** furnished benzo[*e*][1,4]diazocines **35a-b** (Scheme 13, Table 1). Because of the presence of a number of possible conformers of the diazocine ring system, the H NMR of **35a-b** showed broad peaks. The structure was fully confirmed on the incisive analysis of MS and the elemental analysis.

For the synthesis of chiral 3-substituted-4-(toluene-4-sulfonyl)-3,4,5,6-tetrahydro-2*H*-benzo[*g*][1,4]oxazocine derivatives, 2-hydroxyphenethyl alcohol **36** was examined as a potential synthetic precursor. The phenolic hydroxyl of **36** was selectively protected as benzyl group by treatment with benzyl bromide in the presence of K_2CO_3 to give **37** in quantitative yield (Scheme 14).

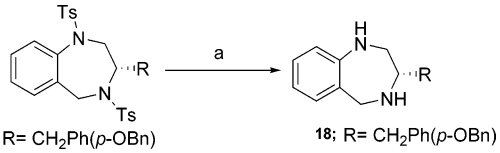
The previously synthesized sulfonamide derivatives of *S*-amino acid methyl esters **2** were used as activated nucleophiles for Mitsunobu reaction. The treatment of **2** with **37** under Mitsunobu conditions furnished **38a-d** in 56−59% yield, which were reduced to their alcoholic derivatives **39a-d** by treatment with LAH at 0 °C under the atmosphere of nitrogen in 63−75% yield. The benzyl group of **39a-d** was removed by hydrogenation in the presence of 10% Pd/C to furnish the compound **40a-d**. The intramolecular Mitsunobu reaction between a phenolic hydroxyl and primary hydroxy of **40a-d** furnished the desired benzoxazocine derivatives **41a-d** in 63−71% yield, (Scheme 15, Table 1).

Scheme 7. Syntheses of (*S*)-3-Substituted-1,4-bis-(toluene-4-sulfonyl-2,3,4,5-tetrahydro-1*H*-benzo[*e*]-1,4-diazepines[a]



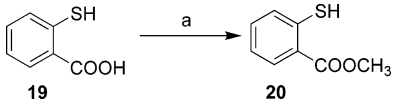
[a] Reagents: (a) **12**, DEAD, PPh_3, THF, 0 °C (2 h) to RT (11 h), N_2, 63−70%; (b) 6 N HCl, MeOH, 0 °C−RT, 45 min; (c) *p*-toluenesulfonyl chloride, triethylamine, DCM, 0 °C−RT, 1 h, N_2, 55−79%; (d) LAH, THF, 0 °C, 1 h, 67−75%; (e) DEAD, PPh_3, THF, 0 °C (1 h) to RT (14 h), N_2, 62−77%.

Scheme 8. Representative Example of Tosyl Removal from Benzodiazepine Derivatives[a]



[a] Reagents: (a) 4% Na−Hg, Na_2HPO_4, MeOH, 70 °C, 18 h, 62%.

Scheme 9. Preparation of Methyl Thiosalicylate[a]



[a] Reagents: (a) MeOH, conc HCl, 0 °C−RT, 6 h, quantitative.

The assigned structures of products **41a-d** were based on spectroscopic data (H, C NMR, MS) and elemental analyses. The methylene protons at numbering position 6 of **41a-d** appeared separately as multiplets at δ 2.59−2.71 and 3.14−3.24 ppm. The methylene protons at position 5 of **41a-d** appeared at δ 3.43−3.55 ppm. The proton of chiral center (i.e., position 3) appeared at δ 3.73−3.93 ppm as a multiplet. The methylene proton (position 2) attached to the oxygen of an eight-membered ring appeared at different δ values 3.87−3.95 and 4.23−4.32 ppm in the form of multiplets.

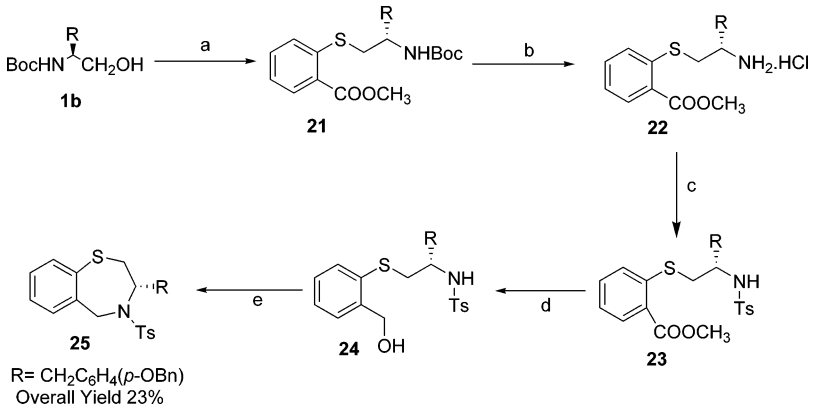
In summary, we have demonstrated a diversity-oriented approach to a variety of enantiomerically pure bicyclic 3-substituted benzoxazepines, benzodiazepines, benzothiazepine, benzoxazocines, and benzodiazocines from naturally occurring natural *S*-amino acids and benchtop-substituted benzene derivatives through the use of inter- and intramolecular Mitsunobu reactions. This simple protocol is capable of being extended to other amino acid (unnatural *R*-amino acids, etc.) derived chiral heterocycles, leading to a unity of structural prototypes having two to three points of diversity. The synthesized chiral heterocycles might possess useful biological properties and efforts to highlight these are currently underway.

Experimental Section

General Remarks. Amino acids, salicylaldehyde, *p*-toluenesulfonyl chloride, methyl anthranilate, 2-mercaptobenzoic acid, 2-hydroxyphenethyl alcohol, LAH, and 10% Pd/C were purchased from Aldrich Milwaukee, WI. Diethylazodicarboxylate and triphenyl phosphine were purchased from Lancaster (England), and benzyl bromide was purchased from Spectrochem (India). All other reagents were purchased from commercial sources and were used without further purification. Melting points were determined on a COMPLAB melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Fourier transform infrared (FT-IR) RXI spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker DPX-200 (operating at 200 MHz for ^{1}H and 50 MHz for ^{13}C) or DPX-300 (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometers using $CDCl_3$ as solvent. Tetramethylsilane (0.00 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). Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded using electron spray ionization (ESMS) or fast atom bombardment spectra (FAB-MS) on a JEOL SX 102 spectrometer using argon/xenon as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Elemental analyses were done on a Varian EL-III C H N analyzer (Germany). Reactions were monitored on silica gel thin layer chromatography (TLC) plates (coated with TLC-grade silica gel, obtained from Merck). Detecting agents used (for TLC) were iodine vapors and/or spraying with an aqueous solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatography was performed over silica gel (60−120 mesh) procured from Qualigens (India) using freshly distilled solvents. Anhydrous tetrahydrofuran used in Mitsunobu reactions was obtained from Spectrochem and refluxed over sodium prior to use. Anhydrous methanol used for detosylation was obtained from Specrochem and refluxed over calcium oxide followed by on magnesium cake and kept over molecular sieves. The enantiomeric excess was determined by a LichroCART Chiradex column (250 mm × 4 mm, 5 μm) using water and methanol as eluents at 25 °C.

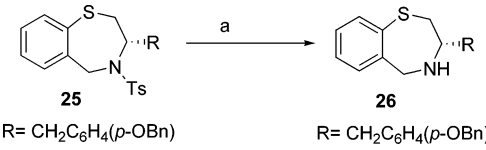
General Experimental Procedure for *N*-Boc Amino Alcohols 1a-b Starting from Amino Acids. To a solution of *S*-amino acid (1 g) in methanol (30 mL) was added conc

Scheme 10. Syntheses of (*S*)-3-(4-Benzyloxy-benzyl)-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]thiazepine[a]



[a] Reagents: (a) **20**, DEAD, PPh_3, THF, 0 °C (1 h) to RT (11 h), N_2, 66%; (b) 6 N HCl, MeOH, 0 °C−RT, 45 min, 84%; (c) *p*-toluenesulfonyl chloride, DCM, 0 °C−RT, 1 h, N_2,79%; (d) LAH, THF, 0 °C, 1 h, 71%; (e) DEAD, PPh_3, THF, 0 °C (1 h) to RT (13 h), N_2, 69%.

Scheme 11. Removal of Tosyl from Benzothiazepine Derivative[a]



[a] Reagents: (a) 4% Na−Hg, Na_2HPO_4, MeOH, 70 °C, 12 h, 64%.

HCl (2.5 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred at the same temperature for 10 h. The solvent was removed under vacuum, and the hydrochloride salt was directly used for next step.

To a stirred solution of amino acid methyl esters (1 equiv) in THF (30 mL) was added triethylamine (3 equiv) and $(Boc)_2O$ (1.2 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred at the same temperature for 12 h. After the usual workup and column chromatography over silica gel using AcOEt−hexane as eluent, the mixture furnished *N*-Boc amino acid methyl esters in quantitative yield. To a solution of LAH (2 equiv), in THF (15 mL) at 0 °C was added *N*-Boc amino acid methyl esters (1 equiv) in THF (30 mL), and the mixture was stirred for 0.5 h at 0 °C. The reaction was quenched by addition of 25 mL of ethylacetate. After the usual workup, the organic layer was dried over anhydrous Na_2SO_4, the solvent was removed in vacuum, and the crude product was purified by column chromatography using AcOEt−hexane as eluent to furnish *N*-Boc amino alcohols in 68−89% yield.

General Procedure for *N*-Tosyl Amino Acid Methyl Esters 2a-g. A solution of amino acid methyl ester hydrochloride (1 equiv) and triethylamine (3 equiv) in anhydrous dichloromethane (30 mL) was stirred at 0 °C for 5 min followed by addition of *p*-toluenesulfonyl chloride (1.5 equiv). The mixture was stirred at 0 °C for 1 h followed by stirring at 25 °C for 3 h. The reaction mixture was washed successively with water (3 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to obtain crude product, which was purified by column chromatography over silica gel to furnish *N*-tosyl amino acid methyl esters **2a-g** in 70−78% yield.

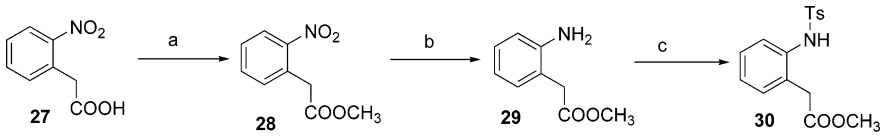
(2-Benzyloxy-phenyl)-methanol 5: To a solution of salicylaldehyde **3** (2 g, 16.37 mmol) in 30 mL of anhydrous acetone was added K_2CO_3 (4.52 g, 32.74 mmol) at 25 °C followed by benzyl bromide (2.9 mL, 24.56 mmol). The mixture was stirred for 8 h at room temperature, K_2CO_3 was filtered off, acetone was removed under vacuum, and water was added (50 mL). The aqueous layer was extracted with ethylacetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the product was chromatographed on silica gel (eluent = hexane/ethylacetate, 9.5/0.5) to give **4** in quantitative yield.

Sodiumborohydride (2.85 g, 75.74 mmol) was added to the stirred solution of **4** (8 g, 37.73 mmol) in 60 mL of THF at 0 °C. The reaction mixture was stirred vigorously for 1 h. The reaction was quenched by dropwise addition of water at 0 °C. The aqueous layer was extracted with ethylacetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane/ethylacetate, 9/1) to give **5** in quantitative yield: colorless oil, R_f: 0.45 (hexane/ethylacetate, 9/1).

General Procedure for the Synthesis of 6. To a stirred solution of **5** (100 mg, 0.47 mmol), **2** (0.47 mmol), and triphenylphosphine (122 mg, 0.47 mmol) in anhydrous THF (5 mL) under an atmosphere of N_2 was added DEAD (0.07 mL, 0.47 mmol, in THF) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for an additional 2 h. It was allowed to warm to room temperature and was stirred for an additional 10 h. The mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The solvent was removed in vacuum; 50 mL of water was added and then extracted with ethylacetate (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum, and the column chromatography of the crude product over silica gel furnished **6**.

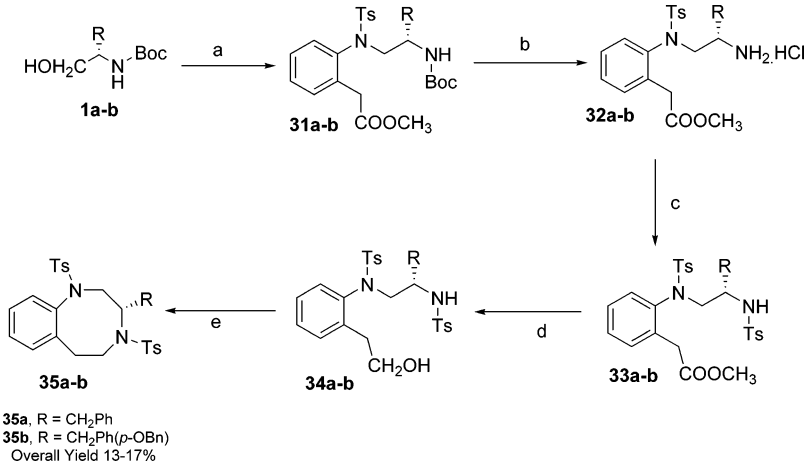
2-[(2-Benzyloxy-benzyl)-(toluene-4-sulfonyl)-amino]-propionic Acid Methyl Ester 6a: Colorless semisolid; yield 81%; R_f, 0.6 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1341, 1742, 2362, 3071, 3422; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (d, 3H, J = 7.3, CHCH_3), 2.40 (s, 3H, $SO_2C_6H_4$-CH_3), 3.37 (s, 3H, COOCH_3), 4.56−4.62 (m, 3H, CH_2-NC*H*COOCH$_3$), 5.04 (s, 2H, OC$H_2C_6H_5$), 6.83−7.38 (m, 10H, Ar*H*), 7.53 (d, 2H, J = 7.5, Ar*H*), 7.71 (d, 2H, J = 8.3, Ar*H*); ESI-MS (*m/z*) 476 $[M+Na]^+$. Anal. calcd for

Scheme 12. Preparation of *N*-Tosyl Derivative of 2-Nitrophenylacetic Acid Methyl Ester[a]



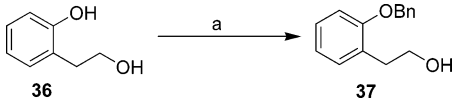
[a] Reagents: (a) MeOH, HCl, 0 °C−RT, 6 h, quantitative; (b) 10% Pd/C, MeOH, 2 h, 50 psi, quantitative; (c) *p*-TsCl, Py, 0 °C−RT, N_2, 6 h, 78%.

Scheme 13. Syntheses of (*S*)-3-Substituted-1,4-bis-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-benzo[*e*][1,4]diazocines[a]



[a] Reagents: (a) **30**, DEAD, PPh_3, THF, 0 °C−RT, 12 h, N_2, 61−68%; (b) 6 N HCl, MeOH, 0 °C−RT, 45 min, 86−88%; (c) *p*-TsCl, TEA, DCM, 0 °C−RT, 1 h, N_2, 64−73%; (d) LAH, THF, 0 °C, 1 h, 49−54%; (e) DEAD, PPh_3, THF, 0 °C−RT, 14 h, N_2, 77−86%.

Scheme 14. Preparation of 2-Benzyloxyphenethyl Alcohol[a]



[a] Reagents: (a) BnBr, K_2CO_3, acetone, RT, 6 h, quantitative.

$C_{25}H_{27}NO_5S$: C 66.20%, H 6.00%, N 3.09%. Found: C 66.31%, H 6.09%, N 3.19%.

2-[(2-Benzyloxy-benzyl)-(toluene-4-sulfonyl)-amino]-3-methyl-butyric Acid Methyl Ester 6b: Colorless semisolid; yield, 57%; R_f,0.6 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1345, 1746, 2359, 3076, 3423; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.77 (d, 3H, J = 2.7, C*H*$_3$CHCH$_3$), 0.80 (d, 3H, J = 2.6, CH$_3$CHC*H*$_3$), 2.12 (m, 1H, CH$_3$C*H*CH$_3$), 2.39 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 3.26 (s, 3H, COOC*H*$_3$), 4.14 (d, 1H, J = 10.2, NC*H*COOCH$_3$), 4.55 (d, 1H, J = 16.9, NC*H*HC), 4.94 (d, 1H, J = 16.9, NCH*H*C), 5.07 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.83−7.53 (m, 10H, Ar*H*), 7.55 (d, 1H, J = 6.37, Ar*H*), 7.68 (d, 2H, J = 8.27, Ar*H*); FAB-MS (*m*/*z*) 482 [M+H]$^+$. Anal. calcd for $C_{27}H_{31}NO_5S$: C 67.34%, H 6.49%, N 2.91%. Found: C 67.26%, H 6.62%, N 3.09%.

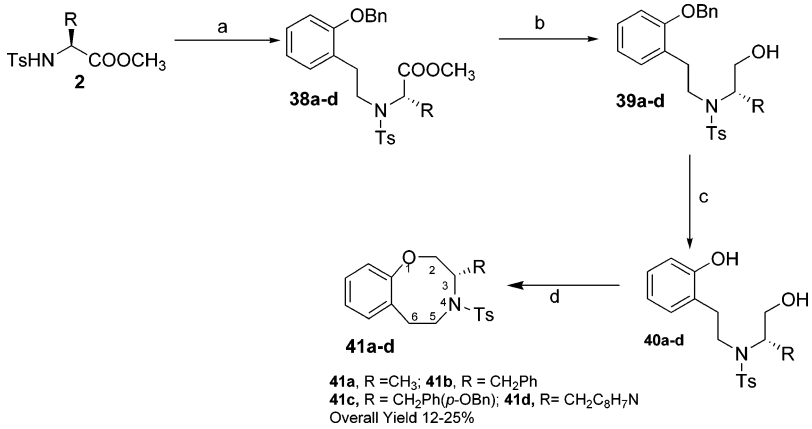
2-[(2-Benzyloxy-benzyl)-(toluene-4-sulfonyl)-amino]-4-methyl-pentanoic Acid Methyl Ester 6c: Colorless semisolid; yield, 82%; R_f,0.6 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1341, 1752, 2350, 3062, 3422; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.53 (d, 3H, J = 5.9, C*H*$_3$CHCH$_3$), 0.81 (d, 3H, J = 5.9, CH$_3$CHC*H*$_3$), 1.39−1.48 (m, 3H, CHC*H*$_2$C*H*), 2.41 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 3.30 (s, 3H, COOC*H*$_3$), 4.52−4.54 (m, 1H, NC*H*COOCH$_3$), 4.71 (d, 1H, J = 16.8, ArC*H*HN), 4.63 (d, 1H, J = 16.8, ArCH*H*N), 5.04 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.87 (d, 1H, J = 8.2, Ar*H*), 6.96−7.60 (m, 8H, Ar*H*), 7.63 (d, 1H, J = 6.3, Ar*H*), 7.72 (d, 2H, J = 8.2, Ar*H*); ESI-MS (*m*/*z*) 518 [M+Na]$^+$. Anal. calcd for $C_{28}H_{33}NO_5S$: C 67.85%, H 6.71%, N 2.83%. Found: C 67.88%, H 6.69%, N 2.91.

2-[(2-Benzyloxy-benzyl)-(toluene-4-sulfonyl)-amino]-3-methyl-pentanoic Acid Methyl Ester 6d: Colorless semisolid; yield, 74%; R_f,0.5 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1346, 1597, 1741, 2965, 3431; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.34 (t, 3H, J = 7.3, CHCH$_2$C*H*$_3$), 0.64 (d, 3H, J = 6.6, CHC*H*$_3$), 0.77−0.82 (m, 1H, C*H*CH$_2$CH$_3$), 1.21−1.61 (m, 2H, CHC*H*$_2$CH$_3$), 2.31 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 3.16 (s, 3H, COOC*H*$_3$), 4.10 (d, 1H, J = 10.1, NC*H*COOCH$_3$), 4.48 (d, 1H, J = 17.0, NCH*H*C), 5.06 (d, 1H, J = 17.0, NCH*H*C), 5.05 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.80−7.63 (m, 13H, Ar*H*); ESI-MS (*m*/*z*) 518 [M+Na]$^+$. Anal. calcd for $C_{28}H_{33}NO_5S$: C 67.85%, H 6.71%, N 2.83%. Found: C 67.94%, H 6.89%, N 2.89%.

2-[(2-Benzyloxy-benzyl)-(toluene-4-sulfonyl)-amino]-3-phenyl-propionic Acid Methyl Ester 6e: Colorless semisolid; yield, 81%; R_f,0.4 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1349, 1595, 2373, 2926, 3426; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.29 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.68−2.78 (m, 1H, CHCH*H*C$_6$H$_5$), 3.01−3.12 (m, 1H, CHC*H*HC$_6$H$_5$), 3.16 (s, 3H, COOC*H*$_3$), 4.53−4.55 (m, 2H, NC*H*$_2$C), 4.63−4.71 (m, 1H, NC*H*COOCH$_3$), 5.17 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.77−7.38 (m, 16H, Ar*H*), 7.55 (d, 2H, J = 8.2, Ar*H*); FAB-MS (*m*/*z*) 530 [M+H]$^+$.

2-[(2-Benzyloxy-benzyl)-(toluene-4-sulfonyl)-amino]-3-(4-benzyloxy-phenyl)-propionic Acid Methyl Ester 6f: Colorless semisolid; yield, 64%; R_f,0.4 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1351, 1596, 2371, 2820, 3401; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.74−2.77 (m, 1H, CHCH*H*C$_6$H$_5$), 2.99−3.17 (m, 1H, CHC*H*HC$_6$H$_5$), 3.22 (s, 3H, COOC*H*$_3$), 4.57−4.70 (m, 3H, C*H*$_2$NC*H*COOCH$_3$), 4.98−5.11 (m, 4H, OC*H*$_2$C$_6$H$_5$, OC*H*$_2$C$_6$H$_5$),

Scheme 15. Synthesis of (*S*)-3-Substituted-4-(toluene-4-sulfonyl)-3,4,5,6-tetrahydro-2*H*-benzo[*g*][1,4]oxazocines[a]



[a] Reagents: (a) **37**, DEAD, PPh_3, THF, 0 °C (2 h) to RT (10 h), N_2, 56−59%; (b) LAH, THF, 0 °C, 1 h, 63−75%; (c) 10% Pd/C, MeOH, RT, 2 h, 50 psi, 45−77%; (d) DEAD, PPh_3, THF, 0 °C−RT, 14 h, N_2, 63−71%.

6.74−7.41 (m, 20H, Ar*H*), 7.62 (d, 2H, *J* = 8.2, Ar*H*); ESI-MS (*m/z*) 658 $[M+Na]^+$.

2-[(2-Benzyloxy-benzyl)-(toluene-4-sulfonyl)-amino]-3-(1*H*-indol-3-yl)-propionic Acid Methyl Ester 6g: Brown semisolid; yield, 59%; R_f,0.3 (7.5/2.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1342, 1572, 2371, 2828, 3398; ^1H NMR (200 MHz, $CDCl_3$) δ 2.37 (s, 3H, $SO_2C_6H_4CH_3$), 2.69−2.80 (m, 2H, $CHCH_2C_8H_6N$), 3.31 (s, 3H, $COOCH_3$), 4.02−4.10 (m, 1H, CH_2CHN), 4.61−4.65 (m, 2H, NCH_2C), 5.02 (s, 2H, $OCH_2C_6H_5$), 6.55 (s, 1H, Ar*H*), 6.58−7.62 (m, 18H, Ar*H*), 8.01 (bs, 1H, N*H*); ESI-MS (*m/z*) 591 $[M+Na]^+$.

General Procedure for the Synthesis of 7. Compound **6** (1 equiv) in anhydrous THF (15 mL) was added to a suspension of LAH (1.5 equiv) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by dropwise addition of ethylacetate (50 mL) followed by water (50 mL) at 0 °C. The aqueous layer was extracted with ethylacetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel with hexane/ethylacetate as eluent to furnish **7**.

***N*-(2-Benzyloxy-benzyl)-*N*-(2-hydroxy-1-methyl-ethyl)-4-methyl-benzenesulfonamide 7a:** Colorless semisolid; yield, 86%; R_f,0.4 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1349, 1594, 2341, 2369, 3424: ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (d, 3H, *J* = 6.9, $CHCH_3$), 1.82 (bs, CH_2OH), 2.40 (s, 3H, $SO_2C_6H_4CH_3$), 3.24−3.30 (m, 2H, CH_2OH), 3.99−4.09 (m, 1H, $NCHCH_2OH$), 4.40 (d, 1H, *J* = 16.1, NCHHC), 4.54 (d, 1H, *J* = 16.1, NCHHC), 5.05 (s, 2H, $OCH_2C_6H_5$), 6.88 (d, 1H, *J* = 8.14, Ar*H*), 6.99 (m, 1H, Ar*H*), 7.18−7.71 (m, 11H, Ar*H*); FAB-MS (*m/z*) 426 $[M+H]^+$. Anal. calcd for $C_{24}H_{27}NO_4S$: C 67.74%, H 6.40%, N 3.29%. Found: C 67.79%, H 6.54%, N 3.12%.

***N*-(2-Benzyloxy-benzyl)-*N*-(1-hydroxymethyl-2-methyl-propyl)-4-methyl-benzenesulfonamide 7b:** Colorless semisolid; yield, 75%; R_f,0.5 (7.5/2.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1348, 1596, 2340, 2964, 3449; ^1H NMR (200 MHz, $CDCl_3$) δ 0.61 (d, 3H, *J* = 6.6, CH_3CHCH_3), 0.80 (d, 3H, *J* = 6.5, CH_3CHCH_3), 1.84 (bs, CH_2OH), 2.08−2.15 (m, 1H, CH_3CHCH_3), 2.37 (s, 3H, $SO_2C_6H_4CH_3$), 3.37−3.44 (m, 1H, OH CH_2CHN), 3.50−3.59 (m, 2H, $OHCH_2$), 4.45 (d, 1H, *J* = 16.1, NCHHC), 4.48 (d, 1H, *J* = 16.1, NCHHC), 4.98 (s, 2H, $OCH_2C_6H_5$), 6.79 (d, 1H, *J* = 8.2, Ar*H*), 6.96 (m, 1H, Ar*H*), 7.20−7.64 (m, 11H, Ar*H*); FAB-MS (*m/z*) 454 $[M+H]^+$. Anal. calcd for $C_{26}H_{31}NO_4S$: C 68.85%, H 6.89%, N 3.09%. Found: C 68.97%, H 6.93%, N 3.11%.

***N*-(2-Benzyloxy-benzyl)-*N*-(1-hydroxymethyl-3-methyl-butyl)-4-methyl-benzenesulfonamide 7c:** Colorless semisolid; yield, 62%; R_f,0.5 (8/2, hexane/ethylacetate); ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (d, 3H, *J* = 6.5, CH_3CHCH_3), 0.67 (d, 3H, *J* = 6.4, CH_3CHCH_3), 1.11−1.19 (m, 3H, $CH_2CH\ CH_3CH_3$), 1.32 (bs, CH_2OH), 2.42 (s, 3H, $SO_2C_6H_4CH_3$), 3.32−3.37 (m, 2H, CH_2OH), 3.80−3.92 (m, 1H, OH $CH_2CH\ CH_2$), 4.45−4.54 (m, 2H, NCH_2C), 5.06 (s, 2H, $OCH_2C_6H_5$), 6.89 (d, 1H, *J* = 7.8, Ar*H*), 6.99−7.02 (m, 1H, Ar*H*), 7.02−7.73 (m, 11H, Ar*H*); ESI-MS (*m/z*) 490 $[M+Na]^+$. Anal. calcd for $C_{27}H_{33}NO_4S$: C 69.35%, H 7.11%, N 3.00%. Found: C 69.44%, H 7.18%, N 3.04%.

***N*-(2-Benzyloxy-benzyl)-*N*-(1-hydroxymethyl-2-methyl-butyl)-4-methyl-benzenesulfonamide 7d:** Colorless semisolid; yield, 59%; R_f,0.5 (7.5/2.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1347, 1597, 2372, 2964, 3429; ^1H NMR (300 MHz, $CDCl_3$) δ 0.56 (t, 3H, *J* = 7.3, $CHCH_2CH_3$), 0.77 (d, 3H, *J* = 6.6, $CHCH_3$), 1.28−1.62 (m, 3H, $NCHCHCH_2$), 1.83 (bs, 1H, CH_2OH), 2.43 (s, 3H, $SO_2C_6H_4CH_3$), 3.44−3.65 (m, 3H, $CHCH_2OH$), 4.48 (s, 2H, NCH_2C), 5.28 (s, 2H, $OCH_2C_6H_5$), 6.84 (d, 1H, *J* = 8.1, Ar*H*), 6.97−7.00 (m, 1H, Ar*H*), 7.02−7.67 (m, 11H, Ar*H*); ESI-MS (*m/z*) 490 $[M+Na]^+$. Anal. calcd for $C_{27}H_{33}NO_4S$: C 69.35%, H 7.11%, N 3.00%. Found: C 69.45%, H 7.26%, N 3.02%.

***N*-(2-Benzyloxy-benzyl)-*N*-(1-hydroxymethyl-2-phenyl-ethyl)-4-methyl-benzenesulfonamide 7e:** Colorless semisolid; yield, 66%; R_f,0.5 (7/3, hexane/ethylacetate); IR (KBr, cm^{-1}) 1350, 1595, 2372, 2928, 3447; ^1H NMR (200 MHz, $CDCl_3$) δ 1.85 (bs, 1H, CH_2OH), 2.38 (s, 3H, $SO_2C_6H_4CH_3$), 2.58−2.64 (m, 2H, $CHCH_2C_6H_5$), 3.34−3.38 (m, 2H, CH_2OH), 4.02−4.09 (m, 1H, $CH_2CHCH_2C_6H_5$), 4.64−4.66 (m, 2H, NCH_2C), 5.07 (s, 2H, $OCH_2C_6H_5$), 6.82−7.66 (m, 18H, Ar*H*); FAB-MS (*m/z*) 502 $[M+H]^+$.

***N*-(2-Benzyloxy-benzyl)-*N*-[2-(4-benzyloxy-phenyl)-1-hydroxymethyl-ethyl]-4-methyl-benzenesulfonamide 7f:** Colorless semisolid; yield, 66%; R_f,0.4 (7/3, hexane/ethylacetate); IR (KBr, cm^{-1}) 1357, 1585, 2380, 2922, 3432; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H, $SO_2C_6H_4CH_3$),

2.57−2.63 (m, 2H, CHC*H*$_2$C$_6$H$_4$OBn), 3.37−3.41 (m, 2H, C*H*$_2$OH), 4.02−4.03 (m, 1H, NC*H*CH$_2$OH), 4.62 (s, 2H, NC*H*$_2$C), 5.02 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.10 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.73−6.79 (m, 5H, Ar*H*), 6.95 (d, 1H, J = 8.2, Ar*H*), 7.01−7.71 (m, 16H, Ar*H*); ESI-MS (*m/z*) 630 [M+Na]$^+$. Anal. calcd for $C_{37}H_{37}NO_5S$: C 73.12%, H 6.14%, N 2.30%. Found: C 73.25%, H 6.29%, N 2.28%.

***N*-(2-Benzyloxy-benzyl)-*N*-[1-hydroxymethyl-2-(1*H*-indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide 7g:** Pale yellow semisolid; yield, 59%; R_f,0.3 (3/7, hexane/ethylacetate); IR (KBr, cm^{-1}) 1350, 1596, 2340, 2369, 2817, 3408; ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.22 (bs, 1H, CH$_2$O*H*), 2.31 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.77−2.82 (m, 2H, CHC*H*$_2$C$_8$H$_6$N), 3.39 (d, 2H, J = 6.4, C*H*$_2$OH), 4.08−4.16 (m, 1H, CH$_2$C*H*N), 4.64−4.65 (m, 2H, NC*H*$_2$C), 5.02 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.59 (s, 1H, Ar*H*), 6.60−7.66 (m, 18H, Ar*H*), 8.01 (bs, 1H, N*H*); ESI-MS (*m/z*) 541 [M+H]$^+$.

General Experimental Procedure for the Synthesis of 8. Compound **7** was dissolved in MeOH and Pd (10% on carbon) was added in a bottle under atmosphere of nitrogen. Then, nitrogen was completely replaced by hydrogen in a parr assembly. The reaction was allowed to run for 2 h under a pressure of 50 psi. After completion of the reaction (TLC monitoring), the catalyst was removed by filteration through celite, solvent was removed under vacuum, the reaction mixture was diluted with water, and an aqueous layer was extracted with ethylacetate (3 × 50 mL). Removal of solvent under vacuum and column chromatography of the crude product on silica gel with hexane/ethylacetate as eluent yielded the desired compond **8**.

***N*-(2-Hydroxy-benzyl)-*N*-(2-hydroxy-1-methyl-ethyl)-4-methyl-benzenesulfonamide 8a:** Colorless semisolid; yield, 74%; R_f,0.4 (7.5/2.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1338, 1597, 2367, 3189, 3445; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.98 (d, 3H, J = 1.6, CHC*H*$_3$), 1.76 (bs, CH$_2$OH), 2.41 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 3.34−3.37 (m, 2H, C*H*$_2$OH), 4.07−4.14 (m, 1H, NC*H*CH$_2$OH), 4.17−4.57 (m, 2H, NC*H*$_2$C), 6.78−7.70 (m, 8H, Ar*H*), 7.39 (bs, 1H, -OH); ESI-MS (*m/z*) 358 [M+Na]$^+$. Anal. calcd for $C_{17}H_{21}NO_4S$: C 60.87%, H 6.31%, N 4.18%. Found: C 60.95%, H 6.33%, N 4.29%.

***N*-(2-Hydroxy-benzyl)-*N*-(1-hydroxymethyl-2-methyl-propyl)-4-methyl-benzenesulfonamide 8b:** Colorless semisolid; yield, 71%; R_f,0.5 (7/3, hexane/ethylacetate); IR (KBr, cm^{-1}) 1352, 1594, 2365, 2966, 3396; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.81 (d, 3H, J = 6.6, C*H*$_3$CHCH$_3$), 0.87 (d, 3H, J = 6.5, CH$_3$CHC*H*$_3$), 1.77−1.79 (m, 1H, CH$_3$C*H*CH$_3$), 2.36 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.51 (bs, CH$_2$O*H*), 3.61−3.76 (m, 3H, C*H*C*H*$_2$OH), 4.35−4.37 (m, 2H, NC*H*$_2$C), 6.65 (d, 1H, J = 8.1, Ar*H*), 6.79 (m, 1H, Ar*H*), 6.86−7.26 (m, 4H, Ar*H*), 7.54 (d, 2H, J = 8.1, Ar*H*), 8.01 (bs, 1H, ArO*H*); ESI-MS (*m/z*) 386 [M+Na]$^+$.

***N*-(2-Hydroxy-benzyl)-*N*-(1-hydroxymethyl-3-methyl-butyl)-4-methyl-benzenesulfonamide 8c:** Colorless semisolid; yield, 78%; R_f,0.3 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1326, 1460, 1597, 2956, 3397; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.66 (d, 3H, J = 6.4, C*H*$_3$CHCH$_3$), 0.71 (d, 3H, J = 6.33, CH$_3$CHC*H*$_3$), 1.06−1.36 (m, 3H, CHC*H*$_2$C*H*CH$_3$-CH$_3$), 2.33 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 3.40 (d, 2H, J = 6.8, C*H*$_2$-OH), 3.94−4.00 (m, 1H, CH$_2$C*H*N), 4.27 (s, 2H, NC*H*$_2$C), 6.62−7.53 (m, 6H, Ar*H*), 7.56 (d, 2H, J = 7.3, Ar*H*); ESI-MS (*m/z*) 378 [M+H]$^+$. Anal. calcd for $C_{20}H_{27}NO_4S$: C 63.63%, H 7.21%, N 3.71%. Found: C 63.76%, H 7.29%, N 3.89%.

***N*-(2-Hydroxy-benzyl)-*N*-(1-hydroxymethyl-2-methyl-butyl)-4-methyl-benzenesulfonamide 8d:** Colorless semisolid; yield, 72%; R_f,0.4 (7/3, hexane/ethylacetate); IR (KBr, cm^{-1}) 1351, 1595, 2368, 2817, 3426; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.61 (t, 3H, J = 7.3, CHCH$_2$C*H*$_3$), 0.81 (d, 3H, J = 6.6, C*H*$_3$CHCH$_2$), 1.24−1,27 (m, 1H, CH$_3$CH$_2$C*H*), 1.42−1.50 (m, 2H, CH$_3$C*H*$_2$CH), 2.00 (bs, 1H, CH$_2$O*H*), 2.42 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 3.66−3.74 (m, 3H, C*H*C*H*$_2$OH), 4.34 (d, 1H, J = 15.1, ArC*H*HN), 4.54 (d, 1H, J = 15.0, ArCH*H*N), 6.80−6.87 (m, 2H, Ar*H*), 7.17−7.28 (m, 4H, Ar*H*), 7.65−7.70 (m, 2H, Ar*H*); ESI-MS (*m/z*) 400 [M+Na]$^+$.

***N*-(2-Hydroxy-benzyl)-*N*-(1-hydroxymethyl-2-phenyl-ethyl)-4-methyl-benzenesulfonamide 8e:** Colorless semisolid; yield, 91%; R_f,0.4 (6.5/3.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1365, 1589, 2362, 2832, 3432; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.91 (bs, 1H, CH$_2$O*H*), 2.37 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.68 (bs,1H, O*H*), 2.73−2.77 (m, 2H, CHC*H*$_2$C$_6$H$_5$), 3.47−3.57 (m, 2H, C*H*$_2$OH), 4.17−4.22 (m, 1H, CH$_2$C*H*CH$_2$C$_6$H$_5$), 4.41 (d, 1H, J =14.8, NCH*H*C), 4.41 (d, 1H, J =14.8, NC*H*HC), 6.75 (d, 1H, J = 8.0, Ar*H*), 6.86−7.25 (m, 10H, Ar*H*), 7.58 (d, 2H, J = 8.24, Ar*H*); ESI-MS (*m/z*) 434 [M+Na]$^+$. Anal. calcd for $C_{23}H_{25}NO_4S$: C 67.13%, H 6.12%, N 3.40%. Found: C 67.09%, H 6.26%, N 3.49%.

***N*-(2-Hydroxy-benzyl)-*N*-[1-hydroxymethyl-2-(4-hydroxy-phenyl)-ethyl]-4-methyl-benzenesulfonamide 8f:** Colorless semisolid; yield, 71%; R_f,0.3 (6/4, hexane/ethylacetate); IR (KBr, cm^{-1}) 1370, 1581, 2365, 2821, 3426; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.12 (bs, 1H, CH$_2$O*H*), 2.42 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.58−2.75 (m, 2H, CHC*H*$_2$C$_6$H$_4$OH), 3.49−3.57 (m, 2H, CHC*H*$_2$OH), 4.11−4.15 (m, 1H, NC*H*CH$_2$OH), 4.42 (d, 1H, J = 15.1, NC*H*HC), 4.54 (d, 1H, J = 15.1, NCH*H*C), 5.37 (bs, 1H, ArO*H*), 6.63−7.28 (m, 10H, Ar*H*), 7.64 (d, 2H, J = 8.3, Ar*H*); ESI-MS (*m/z*) 428 [M+H]$^+$. Anal. calcd for $C_{23}H_{25}NO_5S$: C 64.62%, H 5.89%, N 3.28%. Found: C 64.86%, H 5.91%, N 3.43%.

***N*-(2-Hydroxy-benzyl)-*N*-[1-hydroxymethyl-2-(1*H*-indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide 8g:** Colorless semisolid; yield, 62%; R_f,0.3 (5.5/4.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1362, 1590, 2376, 2828, 3428; ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.29 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.80−2.86 (m, 2H, CHC*H*$_2$C$_8$H$_6$N), 3.41−3.54 (m, 2H, C*H*$_2$OH), 4.08−4.23 (m, 1H, CH$_2$C*H*N), 4.43 (s, 2H, NC*H*$_2$C), 6.67−7.24 (m, 11H, Ar*H*), 7.48 (d, 2H, J = 8.18, Ar*H*), 8.05 (bs, 1H, N*H*); ESI-MS (*m/z*) 451 [M+H]$^+$.

General Experimental Procedure for the Synthesis of 9. To a stirred solution of **8** (1 equiv) and triphenylphosphine (1 equiv) in anhydrous THF under atmosphere of nitrogen was added DEAD (1 equiv, in THF) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional h. It was then allowed to warm to room temperature and was stirred for an additional 14 h. The reaction mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum; the mixture

was diluted with 30 mL of water, then extracted with ethylacetate (3 × 50 mL), and dried over anhydrous Na_2SO_4. Concentration under vacuum and column chromatography of the crude product over silica gel furnished the title product **9**.

(*S*)-3-Methyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine 9a: White solid; mp 109 °C; yield, 76%; R_f0.5 (9/1, hexane/ethylacetate); IR (KBr, cm^{-1}) 1493, 1594, 2365, 2972, 3438; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, 3H, J =3.8, CHC*H*$_3$), 2.29 (s, 3H, $SO_2C_6H_4CH_3$), 3.84−3.96 (m, 2H, CHC*H*$_2$O), 4.27−4.32 (m, 1H, NC*H*CH$_2$O), 4.63 (d, 1H, J = 15.0, NCH*H*C), 4.69 (d, 1H, J = 15.0, NC*H*HC), 6.53 (d, 1H, J = 7.8, Ar*H*), 6.87−7.11 (m, 5H, Ar*H*), 7.37 (d, 2H, J = 8.2, Ar*H*); ^{13}C NMR (50 MHz, CDCl3) 16.2, 21.7, 45.0, 54.4, 74.4, 120.0, 123.0, 126.5, 127.4, 128.9, 129.3, 129.9, 137.5, 143.0, 158.6; FAB-MS (*m/z*) 318 $[M+H]^+$. Anal. calcd for $C_{17}H_{19}NO_3S$: C 64.33%, H 6.03%, N 4.41%. Found: C 64.36%, H 6.17%, N 4.49%.

(*S*)-3-Isopropyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine 9b: White solid; mp 134 °C; yield, 70%; R_f0.5 (8.7/1.3, hexane/ethylacetate); IR (KBr, cm^{-1}) 1350, 1595, 2367, 2966, 3429; ^{1}H NMR (200 MHz, CDCl3) δ 1.03 (d, 3H, J = 3.7, C*H*$_3$CHCH$_3$), 1.07 (d, 3H, J = 3.9, CH$_3$CHC*H*$_3$), 2.10−2.15 (m, 1H, CH$_3$C*H*CH$_3$), 2.26 (s, 3H, $SO_2C_6H_4CH_3$), 3.80−3.89 (m, 2H, CHC*H*$_2$O), 4.08−4.14 (m, 1H, NC*H*CH$_2$O), 4.54 (d, 1H, J = 17.0, NC*H*HC), 4.75 (d, 1H, J = 17.0, NCH*H*C), 6.48 (d, 1H, J = 8.9, Ar*H*), 6.90−7.10 (m, 5H, Ar*H*), 7.36 (d, 2H, J = 8.3, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) 19.8, 20.4, 21.7, 28.4, 46.2, 64.4, 71.9, 120.1, 123.1, 126.9, 127.7, 128.8, 129.1, 129.9, 137.6, 142.9, 158.8; ESI-MS (*m/z*) 346 $[M+H]^+$. Anal. calcd for $C_{19}H_{23}NO_3S$: C, 66.06%; H, 6.71%; N, 4.05%. Found: C, 66.40%; H, 6.93%; N, 4.29%.

(*S*)-3-Isobutyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine 9c: White solid; mp 145 °C; yield, 63%; R_f0.6 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1338, 1594, 2369, 2965, 3428; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, 6H, J = 6.5, C*H*$_3$C*H*$_3$CH), 1.28−1.76 (m, 1H, CH$_3$CH$_3$C*H*), 1.59−1.76 (m, 2H, CHC*H*$_2$CH), 2.28 (s, 3H, $SO_2C_6H_4CH_3$), 3.70−3.94 (m, 2H, CHC*H*$_2$O), 4.15−4.17 (m, 1H, NC*H*CH$_2$O), 4.52 (d, 1H, J = 16.9, NC*H*HC), 4.68 (d, 1H, J = 16.9, NCH*H*C), 6.47 (d, 1H, J = 7.8, Ar*H*), 6.87−7.09 (m, 5H, Ar*H*), 7.33 (d, 2H, J = 8.2, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) 21.8, 22.8, 23.6, 24.7, 30.1, 39.2, 45.4, 56.6, 73.7, 96.6, 120.2, 123.1, 127.2, 127.8, 128.8, 129.1, 130.0, 137.9, 142.6, 158.9; ESI-MS (*m/z*) 360 $[M+H]^+$. Anal. calcd for $C_{20}H_{25}NO_3S$: C 66.82%, H 7.01%, N 3.90%. Found: C 66.95%, H 7.09%, N 3.99%.

(*S*)-3-*sec*-Butyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine 9d: White solid; mp 96 °C; yield, 68%; R_f0.5 (8.7/1.3, hexane/ethylacetate); IR (KBr, cm^{-1}) 1341, 1598, 2369, 2876, 2966, 3429; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91−1.00 (m, 6H, C*H*$_3$CHCH$_2$C*H*$_3$), 1.19−1.26 (m, 1H, CH$_3$C*H*CH$_2$CH$_3$), 1.68−1.87 (m, 2H, CH$_3$CHC*H*$_2$-CH$_3$), 2.25 (s, 3H, $SO_2C_6H_4CH_3$), 3.75−3.88 (m, 2H, CHC*H*$_2$O), 4.04−4.11 (m, 1H, NC*H*CH$_2$O), 4.52 (d, 1H, J = 17.0, NC*H*HC), 4.72 (d, 1H, J = 17.1, NCH*H*C), 6.42 (d, 1H, J = 7.8, Ar*H*), 6.81−7.05 (5H, Ar*H*), 7.30 (d, 2H, J = 8.0, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) 11.8, 15.7, 21.7, 26.1, 30.1, 35.1, 46.3, 63.0, 71.6, 96.5, 120.0, 122.8, 126.6, 127.7, 128.7, 128.9, 129.9, 137.7, 142.2, 158.8; ESI-MS (*m/z*) 360 $[M+H]^+$. Anal. calcd for $C_{20}H_{25}NO_3S$: C, 66.82%; H, 7.01%; N, 3.90%. Found: C, 67.01%; H, 6.85%; N, 4.11%.

(*S*)-3-Benzyl-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine 9e: White solid; mp 98 °C; yield, 64%; R_f0.5 (8.5/1.5, hexane/ethylacetate) IR (KBr, cm^{-1}) 1338, 1599, 2373, 3029, 3424; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.27 (s, 3H, $SO_2C_6H_4CH_3$), 3.03−3.10 (m, 2H, NCHC*H*$_2$-C$_6$H$_5$), 3.74−3.76 (m, 1H, NCHC*H*HO), 3.80−3.82 (m, 1H, NCHCH*H*O), 4.00−4.10 (m, 1H, NC*H*CH$_2$O), 4.48 (d, 1H, J = 16.9, NC*H*HC), 4.68 (d, 1H, J = 16.9, NCH*H*C), 6.57 (d, 1H, J = 6.9, Ar*H*), 6.59−7.37 (m, 12H, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) 21.8, 37.6, 46.1, 59.7, 72.2, 120.1, 123.1, 127.0, 127.2, 127.5, 129.1, 129.3, 129.8, 130.0, 137.3, 137.4, 143.2, 158.8; FAB-MS (*m/z*) 394 $[M+H]^+$. Anal. calcd for $C_{23}H_{23}NO_3S$: C 70.20%, H 5.89%, N 3.56%. Found: C 70.31%, H 5.99%, N 3.58%.

(*S*)-4-[4-(Toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo-[*f*][1,4]oxazepin-3-ylmethyl]-phenol 9f: White solid; mp 115 °C; yield, 65%; R_f0.5 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1332, 1572, 2369, 3029, 3464; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H, $SO_2C_6H_4CH_3$), 2.90−3.06 (m, 2H, CHC*H*$_2$C$_6$H$_4$OH), 3.76−3.81 (m, 1H, NCHC*H*HO), 4.01−4.08 (m, 1H, NCHCH*H*O), 4.26−4.27 (m, 1H, NC*H*CH$_2$O), 4.36 (d, 1H, J = 17.0, NC*H*HC), 4.55 (d, 1H, J = 17.0, NCH*H*C), 6.31 (bs, 1H, ArO*H*), 6.56 (d, 1H, J = 5.2, Ar*H*), 6.77 (d, 2H, J =8.1, Ar*H*), 6.86−7.07 (m, 7H, Ar*H*), 7.33 (d, 2H, J = 8.1, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) 21.8, 36.7, 46.1, 59.7, 72.1, 96.6, 115.9, 120.1, 123.1, 126.9, 127.6, 128.9, 129.3, 129.9, 130.9, 137.5, 142.9, 155.3, 158.8; ESI-MS (*m/z*) 432 $[M+Na]^+$. Anal. calcd for $C_{23}H_{23}NO_4S$: C, 67.46%; H, 5.66%; N, 3.42%. Found: C, 67.66%; H, 5.82%; N, 3.58%.

(*S*)-3-(1*H*-Indol-3-ylmethyl)-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine 9g: Brown semisolid; yield, 74%; R_f0.4 (7.5/2.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1351, 1595, 2369, 2817, 3429; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H, $SO_2C_6H_4CH_3$), 3.07−3.19 (m, 2H, CHC*H*$_2$C$_8$H$_6$), 3.64−3.92 (m, 2H, CHC*H*$_2$O), 3.92−4.02 (m, 1H, CH$_2$C*H*N), 4.43 (d, 1H, J = 16.9, NC*H*HC), 4.60 (d, 1H, J = 16.9, NCH*H*C), 6.43 (d, 1H, J = 7.9, Ar*H*), 6.40−7.50 (m, 12H, Ar*H*), 8.24 (bs, 1H, N*H*); ^{13}C NMR (50 MHz, $CDCl_3$) 14.8, 21.8, 27.4, 46.1, 58.6, 72.3, 111.4, 111.6, 119.3, 120.1, 122.6, 123.0, 123.4, 126.9, 127.5, 127.8, 129.0, 129.3, 130.4, 136.6, 137.2, 143.1, 158.7; ESI-MS (*m/z*) 433 $[M+H]^+$. Anal. calcd for $C_{25}H_{24}N_2O_3S$: C, 69.42%; H, 5.59%; N, 6.48%. Found: C, 69.58%, H, 5.79%; N, 6.77%.

Experimental Procedure of Tosyl Removal from Benzoxazepine Derivatives. (a) Synthesis of (*S*)-3-Benzyl-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepine 10a. To a mixture of compound **9e** (0.14 mmol) and disodiumhydrogen phosphate (1.4 mmol) in dry methanol (15 mL) was added 4% Na−Hg (1.4 mmol). The resulting solution was stirred at 70 °C for 12 h. The reaction mixture was then diluted with an additional 10 mL of methanol and filtered. The residue was washed with methanol (2 × 5 mL) and DCM (2 × 10 mL) successively. The solvent was removed under

vacuum, water was added, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with water (2 × 20 mL) and brine (2 × 20 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the crude product was chromatographed over silica gel (eluent = chloroform/methanol, 9.5/0.5) to afford the desired compound **10a**: Brown oil; yield, 73%; R_f, 0.4 (chloroform/methanol, 9.5/0.5); IR (KBr, cm^{-1}) 1351, 1593, 2367, 2930; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (bs, N*H*), 2.65−2.76 (m, 2H, CHCH_2-Ph), 3.38−3.50 (m, 1H, C*H*CH_2Ph), 3.56−3.63 (m, 1H, NCHC*H*HO), 3.87 (d, 1H, J = 14.4, C*H*HNHCH), 4.01 (d, 1H, J = 14.4, CH*H*NHCH), 4.33−4.37 (m, 1H, NCHCH*H*O), 6.97−7.03 (m, 2H, Ar*H*), 7.12−7.40 (m, 7H, Ar*H*); ESI-MS (*m/z*) 240 $[M+H]^+$.

(b) Synthesis of (*S*)-4-(2,3,4,5-Tetrahydro-benzo[*f*]-[1,4]oxazepin-3-ylmethyl)-phenol 10b. To a mixture of compound **9f** (0.24 mmol) and disodiumhydrogen phosphate (2.4 mmol) in dry methanol (25 mL) was added 4% Na−Hg (2.4 mmol). The resulting solution was stirred at 70 °C for 12 h. The reaction mixture was then diluted with an additional 10 mL of methanol and filtered. The residue was washed with methanol (2 × 5 mL) and DCM (2 × 10 mL) successively. The solvent was removed under vacuum, water was added, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with water (2 × 20 mL) and brine (2 × 20 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the crude product was chromatographed over silica gel (eluent = chloroform/methanol, 9/1) to afford the desired compound **10b**: Brown semisolid, yield, 65%; R_f, 0.5 (chloroform/methanol, 9/1); IR (KBr, cm^{-1}) 1351, 1593, 2364, 3439; ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (brs, N*H*), 2.60−2.75 [m, 2H, CHCH_2Ph (*p*-OH)], 3.34−3.42 [m, 1H, C*H*CH_2Ph(*p*-OH)], 3.56−3.63 (m, 1H, NCHC*H*HO), 3.90 (d, 1H, J = 14.4, C*H*HNHCH), 4.02 (d, 1H, J = 14.4, CH*H*NHCH), 4.32−4.37 (m, 1H, NCHCH*H*O), 6.75−6.78 (m, 2H, Ar*H*), 6.97−7.03 (m, 2H, Ar*H*), 7.08−7.22 (m, 4H, Ar*H*); ESI-MS (*m/z*) 256 $[M+H]^+$.

Experimental Procedure for the Synthesis of 12. To the stirred solution of methyl anthranilate **11** (1 g, 6.62 mmol) in anhydrous pyridine (20 mL) was added *p*-toluenesulfonyl chloride (1.5 g, 7.95 mmol) under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 6 h and was quenched by addition of water. The aqueous layer was extracted with ethylacetate (3 × 50 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the crude product was then chromatographed over silica gel (eluent = hexane/ethylacetae, 9/1) to afford the title compound **12** (1.71 g, 85%): Brown semisolid, R_f 0.5 (hexane/ethylacetae, 9/1).

General Experimental Procedure for the Synthesis of 13. To a solution *N*-tosylmethyl anthranilate **12** (1.64 mmol), amino alcohol **1** (1.64 mmol) and triphenyl phosphine (1.64 mmol) in anhydrous THF, under an atmosphere of nitrogen, was added DEAD (1.64 mmol, in THF) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. It was then allowed to warm to room temperature and was stirred for an additional 11 h. The mixture was stirred with a 1:1 mixture of hexane:diethylether, the triphenylphosphine oxide precipitated was filtered off. The solvent was removed in vacuum, diluted with 20 mL of water, extracted with ethylacetate (3 × 50 mL), and dried over anhydrous Na_2SO_4. Concentration under vacuum and column chromatography of the crude product over silica gel furnished the title product **13**.

2-[(2-*tert*-Butoxycarbonylamino-3-phenyl-propyl)-(toluene-4-sulfonyl)-amino]-benzoic Acid Methyl Ester 13a: Brown semisolid; yield, 70%; R_f,0.4 (9/1, hexane/ethylacetate); IR (KBr, cm^{-1}) 1352, 1597, 2371, 2816, 3430; ^1H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 1.14 {s, 3H, OCCH_3(CH_3)$_2$}, 1.29 {s, 6H, OCCH_3(CH_3)$_2$}, 2.36 (s, 3H, ArCH_3), 2.73−2.78 (m, 1H, ArC*H*HCH), 2.90−3.10 (m, 1H, ArCH*H*CH), 3.57−3.62 (m, 1H, SO_2NC*H*H), 3.85 (s, 3H, $COOCH_3$), 3.83−3.93 (m, 2H, SO_2NCH*H*, NHC*H*CH_2), 5.80 (bs, 1H, NH), 6.59−6.58 (m, 1H), 6.85−6.82 (m, 1H, Ar*H*), 6.96−6.94 (m, 1H, Ar*H*), 7.16−7.11 (m, 6H, Ar*H*), 7.38−7.20 (m, 4H, Ar*H*), 7.85−7.77 (m, 1H, Ar*H*); ESI-MS (*m/z*) 561 $[M+Na]^+$. Anal. calcd for $C_{29}H_{34}N_2O_6S$: C 64.66%, H 6.36%, N 5.20%. Found: C 64.69%, H 6.51%, N 5.29%.

2-[[3-(4-Benzyloxy-phenyl)-2-*tert*-butoxycarbonylamino-propyl]-(toluene-4-sulfonyl)-amino]-benzoic Acid Methyl Ester 13b: Colorless semisolid; yield, 63%; R_f,0.5 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1352, 1600, 2372, 2930, 3428; ^1H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 1.17 {s, 3H, OCCH_3(CH_3)$_2$}, 1.37 {s, 6H, OCCH_3(CH_3)$_2$}, 2.39 (s, 3H, ArCH_3), 2.69−2.77 (m, 1H, ArC*H*HCH), 2.96−3.00 (m, 1H, ArCH*H*CH), 3.55−3.62 (m, 1H, SO_2NC*H*H), 3.83 (s, 3H, $COOCH_3$), 3.83−3.97 (m, 2H, SO_2NCH*H*, NHC*H*CH_2), 5.00 (s, 2H, OCH_2Ph), 5.53−5.54 (bs, 1H, NH), 6.61 (m, 2H, ArH), 6.75−6.90 (m, 12H, ArH), 7.16−7.50 (m, 2H, ArH), 7.79−7.87 (m, 1H, ArH); ESI-MS (*m/z*) 667 $[M+Na]^+$. Anal. calcd for $C_{36}H_{40}N_2O_7S$: C 67.06%, H 6.25%, N 4.34%. Found: C 67.03%, H 6.30%, N 4.23%.

General Experimental Procedure for the Synthesis of 14. To a solution of **13** (400 mg) in methanol (10 mL) was added 6 N HCl (15 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 45 min, and the solvent was removed under vacuum to afford crude **14** which was directly used for the next step.

General Experimental Procedure for the Synthesis of 15. To the solution of **14** (0.52 mmol) and triethylamine (1.56 mmol) in anhydrous DCM (10 mL) was added *p*-toluenesulfonyl chloride (0.62 mmol) under an atmosphere of nitrogen at 0 °C. The reaction mixture was warmed to room temperature and stirred for about 1 h. The reaction mixture was quenched by slow addition of water (30 mL). The aqueous layer was extracted with DCM (3 × 50 mL). The organic layer was dried over Na_2SO_4. The removal of solvent under vacuum and column chromatography of crude product on silica furnished **15**.

2-[[3-Phenyl-2-(toluene-4-sulfonylamino)-propyl]-(toluene-4-sulfonyl)-amino]-benzoic Acid Methyl Ester 15a: White solid; mp 86 °C; yield, 79%; R_f,0.5 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1349, 1610, 2378, 2922, 3436; ^1H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 2.29 (s,

ArC*H*$_3$), 2.36 (s, ArC*H*$_3$), 2.40−2.43 (m), 2.70−2.78 (m), 3.00−3.14 (m), 3.35−3.40 (m), 3.52−3.64 (m), 3.71−3.78 (m), 3.82 (s), 3.89 (s),3.91 (s), 3.98 (s), 4.02−4.05 (m), 5.54 (d), 6.27 (d), 6.48 (d), 6.60−6.63 (m), 6.91−6.94 (m), 7.04−7.41 (m), 7.72−7.75 9 (m), 7.83−7.84 (m); ESI-MS (*m/z*) 593 $[M+H]^+$. Anal. calcd for $C_{31}H_{32}N_2O_6S_2$: C 62.82%, H 5.44%, N 4.73%. Found: C 62.93%, H 5.50%, N 4.86%.

2-[[3-(4-Benzyloxy-phenyl)-2-(toluene-4-sulfonylamino)-propyl]-(toluene-4-sulfonyl)-amino]-benzoic Acid Methyl Ester 15b: Pale yellow semisolid; yield, 55%; R_f,0.4 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1352, 1610, 2372, 2936, 3440; ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 2.32 (s), 2.36 (s), 2.40 (s), 2.50−2.70 (m), 3.01−3.06 (m), 3.50−3.60 (m), 3.85 (s), 4.01 (s), 4.20−4.50 (m), 5.01 (d), 5.47 (d), 6.29 (d), 6.68−7.43 (m), 7.75−8.01 (m); ESI-MS (*m/z*) 721 $[M+Na]^+$. Anal. calcd for $C_{38}H_{38}N_2O_7S_2$: C, 65.31%; H, 5.48%; N, 4.01%. Found: C, 65.53; H, 5.70; N, 4.22.

General Experimental Procedure for the Synthesis of 16. Compound **6** (1 equiv) in anhydrous THF (15 mL) was added to a suspension of LAH (1.5 equiv) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of ethylacetate (50 mL) followed by water (50 mL) at 0 °C. The aqueous layer was extracted with ethylacetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel with hexane/ethylacetate as eluent to furnish **16**.

Compound 16a: Colorless semisolid; yield, 67%; R_f,0.4 (7.5/2.5, hexane/ethylacetate); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 2.30 (brs, O*H*), 2.32−2.38 (m), 2.41 (s), 2.45−2.48 (m), 2.59−2.66 (m), 2.69−2.74 (m), 2.94−3.13 (m), 3.34−3.39 (m), 3.55−3.64 (m), 3.81−3.99 (m), 4.01−4.05 (m), 4.6−4.66 (m), 4.77−5.06 (m), 6.42−6.59 (m), 6.71−6.73 (m), 6.82−6.84 (m), 6.97−7.20 (m), 7.23−7.31 (m), 7.31−7.51 (m), 7.62−7.71 (m); ESI-MS (*m/z*) 565 $[M+H]^+$.

Compound 16b: Colorless semisolid; yield, 75%; R_f,0.4 (7/3, hexane/ethylacetate); ^{1}H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 2.29−2.31 (m), 2.35 (s), 2.40 (s), 2.47 (d), 2.51−2.76 (m), 2.88−3.07 (m), 3.30−3.37 (m), 3.53−3.66 (m), 3.76−3.88 (m), 4.00 (d), 4.05 (d), 4.22 (q), 4.61−4.66 (m), 4.75−4.83 (m), 4.87 (bs), 4.95−5.04 (m), 5.28 (d), 6.42 (d), 6.56−6.80 (m), 6.94−7.16 (m), 7.27−7.51 (m), 7.63 (d), 7.66 (d), 7.69 (d), 7.71 (d); ESI-MS (*m/z*) 559 $[M+H]^+$. Anal. calcd for $C_{24}H_{27}NO_4S$: C 67.74%, H 6.40%, N 3.29%. Found: C 67.80%, H 6.54%, N 3.22%.

General Experimental Procedure for the Synthesis of 17. To a stirred solution of **16** (1 equiv) and triphenylphosphine (1 equiv) in anhydrous THF under an atmosphere of nitrogen, was added DEAD (1 equiv), in THF, dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional h. It was then allowed to warm to room temperature and was stirred for an additional 14 h. The reaction mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The solvent was removed in vacuum, the mixture was diluted with 30 mL of water, and the aqueous layer was extracted with ethylacetate (3 × 50 mL) and dried over anhydrous Na_2SO_4. Concentration under vacuum and column chromatography of the crude product over silica gel furnished the title product **17**.

(*S*)-3-Benzyl-1,4-bis-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine 17a: White solid; mp 176 °C; yield, 77%; R_f,0.5 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1360, 1625, 2352, 2912, 3460; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H, $SO_2C_6H_4CH_3$), 2.36 (s, 3H, $SO_2C_6H_4CH_3$), 3.01−3.09 (m, 2H, $CHCH_2C_6H_5$), 3.13−3.16 (m, 1H, NCHCH*H*N), 4.06−4.08 (m, 1H, $NCHCH_2N$), 4.22−4.29 (m, 1H, NCHC*H*HN), 4.48 (s, 2H, $NCH_2C_6H_4$), 6.87−7.33 (m, 15H, Ar*H*), 7.55 (d, 2H, J = 8.0, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.60, 21.74, 37.34, 45.59, 52.45, 58.13, 126.45, 126.55, 127.23, 127.37, 127.47, 127.75, 128.59, 129.74, 129.87, 130.61, 136.76, 137.05, 137.96, 138.41, 140.44, 142.92, 143.84; ESI-MS (*m/z*) 569 $[M+Na]^+$. Anal. calcd for $C_{30}H_{30}N_2O_4S_2$: C 65.91%, H 5.53%, N 5.12%. Found: C 65.99%, H 5.64%, N 5.09%.

(*S*)-3-(4-Benzyloxy-benzyl)-1,4-bis-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine 17b: White solid; mp 156 °; yield, 62%; R_f,0.6 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1323, 1597, 2367, 2927, 3409; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, $SO_2C_6H_4CH_3$), 2.45 (s, 3H, $SO_2C_6H_4CH_3$), 2.98−3.20 (m, 2H, $CHCH_2C_6H_4OBn$), 3.21−3.26 (m, 1H, CHCH*H*N), 4.09−4.16 (m, 1H, $CHCH_2NSO_2$), 4.32−4.35 (m, 1H, CHC*H*HN), 4.44 (d, 2H, J = 3.1), 5.07 (s, 2H, $OCH_2C_6H_5$), 6.82−7.63 (m, 19H, Ar*H*), 7.67 (d, 2H, J = 11.6, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.46, 21.58, 36.31, 45.51, 52.24, 58.20, 70.01, 114.80, 126.33, 127.20, 127.31, 127.51, 127.66, 128.00, 128.55, 128.63, 129.29, 129.79, 130.30, 130.48; ESI-MS (*m/z*) 675 $[M+Na]^+$.

Experimental Procedure of Tosyl Removal from Benzodiazepine Derivatives: Synthesis of (*S*)-3-(4-Benzyloxy-benzyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine 18. To a mixture of compound **17** (0.15 mmol) and disodium-hydrogen phosphate (1.5 mmol) in dry methanol (25 mL) was added 4% Na−Hg (1.5 mmol). The resulting solution was stirred at 70 °C for 18 h. The reaction mixture was then diluted with an additional 10 mL of methanol and filtered. The residue was washed with methanol (2 × 5 mL) and DCM (2 × 10 mL) successively. The solvent was removed under vacuum, water was added, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with water (2 × 20 mL) and brine (2 × 20 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the crude product was chromatographed over silica gel (eluent = chloroform/methanol, 9/1) to afford the desired compound **18:** White solid; mp 115 °C; yield, 62%; R_f, 0.5 (chloroform/methanol, 8.5/1.5); IR (KBr, cm^{-1}) 1350, 1595, 2366, 2930; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64−2.75 [m, 3H, $CHCH_2Ph$(*p*-OBn), CHC*H*HNH], 3.14−3.16 [m, 1H, NHC*H*CH_2Ph(*p*-OBn)], 3.86 (d, 1H, J = 14.4, C*H*HNHCH), 3.96 (d, 1H, J = 14.4, CH*H*NHCH), 5.07 (s, 2H, OCH_2Ph), 6.73−6.86 (m, 2H, Ar*H*), 6.94−6.96 (m, 2H, Ar*H*), 7.07−7.18 (m, 4H, Ar*H*), 7.32−7.47 (m, 5H, Ar*H*); ESI-MS (*m/z*) 355 $[M+H]^+$.

2-[3-(4-Benzyloxy-phenyl)-2-*tert*-butoxycarbonylamino-propylsulfanyl]-benzoic Acid Methyl Ester 21. To a

solution of compound **1b** (0.59 mmol), **20** (0.59 mmol) and triphenyl phosphine (0.59 mmol) in THF (10 mL) was added DEAD (0.59 mmol, 0.093 mL, in THF) at 0 °C. The reaction mixture was stirred at the same temperature for 1h, and then, the reaction mixture was warmed to room temperature and stirred for 11 h. The reaction mixture was treated with a 1:1 solution of hexane:diethylether. The triphenylphospine oxide that precipitated was filtered off, the solvent was removed under vacuum and diluted with water (20 mL), and the aqueous layer was extracted with ethylacetate (3 × 50 mL), washed by water (2 × 50 mL) and brine (2 × 50 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the crude was purified by column chromatography using ethylacetate/hexane as eluent: Colorless semisolid; yield, 66%; R_f,0.5 (9/1, hexane/ethylacetate); IR (KBr, cm^{-1}) 1349, 1594, 2374, 2928, 3447; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 {s, 9H, C(C*H*$_3$)$_3$}, 2.83−2.91 (m, 2H, CHC*H*$_2$C$_6$H$_4$OBn), 3.91 (s, 3H, COOC*H*$_3$), 4.23−4.26 (m, 2H, CHC*H*$_2$S), 4.80−4.84 (m, 1H, CH$_2$C*H*NHBoc), 4.94 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.81 (d, 2H, J = 8.5, Ar*H*), 7.04−7.33 (m, 7H, Ar*H*), 7.67 (d, 2H, J = 8.1, Ar*H*), 7.97 (d, 2H, J = 8.8, Ar*H*); FAB-MS (*m*/*z* %) 416 (20, [M−CH$_2$C$_6$H$_5$] $^+$, 341 (40, [M−OCH$_2$C$_6$H$_5$−COOCH$_3$] $^+$. Anal. calcd for $C_{29}H_{33}NO_5S$: C 68.61%, H 6.55%, N 2.76%. Found: C 68.77%, H 5.99%, N 2.81%.

Removal of Boc Group from Compound 21: Synthesis of Compound 23. To a solution of **21** (500 mg) in 10 mL of methanol was added 6 N HCl (5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 45 min. After completion of reaction (TLC monitoring), the solvent was removed in vacuum and the resulting crude hydrochloride **22** was directly used for the next step.

2-[3-(4-Benzyloxy-phenyl)-2-(toluene-4-sulfonylamino)-propylsulfanyl]-benzoic Acid Methyl Ester 23. To the solution of **22** (1.12 mmol) and triethylamine (3.36 mmol) in anhydrous DCM (15 mL) was added *p*-toluenesulfonyl chloride (1.35 mmol) under an atmosphere of nitrogen at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched by slow addition of water (30 mL). The aqueous layer was extracted with DCM (3 × 50 mL). The organic layer was dried over Na_2SO_4. The removal of solvent under vacuum and column chromatography of crude product on silica furnished **23:** Colorless semisolid; yield, 79%; R_f,0.4 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1326, 1582, 2374, 2929, 3460; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.29 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.83−2.86 (m, 2H, CHC*H*$_2$C$_6$H$_4$OBn), 3.77−3.90 (m, 1H, C*H*CH$_2$S) 3.98 (s, 3H, COOC*H*$_3$), 4.20−4.22 (m, 2H, CHC*H*$_2$S), 4.97 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.44 (bs, 1H, NH), 6.76 (d, 2H, J = 1.34, Ar*H*), 6.79−8.01 (m, 15H, Ar*H*); ESI-MS (*m*/*z*) 562 [M+H]$^+$.

***N*-[1-(4-Benzyloxy-benzyl)-2-(2-hydroxymethyl-phenylsulfanyl)-ethyl]-4-methyl-benzenesulfonamide 24.** Compound **23** (800 mg, 1.51 mmol) in anhydrous THF (20 mL) was added to a suspension of LAH (86 mg, 2.26 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of ethylacetate (50 mL) followed by water (50 mL) at 0 °C. The aqueous layer was extracted with ethylacetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel with hexane/ethylacetate as eluent to furnish **24:** Colorless semisolid; yield, 71%; R_f,0.4 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1324, 1576, 2352, 2929, 3484; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.68 (bs, 1H, CH$_2$O*H*), 2.36 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.70−2.83 (m, 2H, CHC*H*$_2$C$_6$H$_4$OBn), 2.86−2.89 (m, 1H, CHC*H*HS), 3.06−3.15 (m, 1H, CHCH*H*S), 3.33−3.45 (m, 1H, C*H*CH$_2$S), 4.73−4.80 (m, 2H, C*H*$_2$OH), 5.02 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.25 (d, 1H, NH, J = 7.3), 6.75−7.42 (m, 17H, Ar*H*); ESI-MS (*m*/*z*) 534 [M+H]$^+$. Anal. calcd for $C_{30}H_{31}NO_4S_2$: C 67.51%, H 5.85%, N 2.62%. Found: C 67.47%, H 5.89%, N 2.63%.

(*S*)-3-(4-Benzyloxy-benzyl)-4-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]thiazepine 25. To a stirred solution of **24** (100 mg, 0.18 mmol) and triphenylphosphine (49 mg, 0.18 mmol) in anhydrous THF under an atmosphere of nitrogen was added DEAD (0.03 mL, 0.18 mmol, in THF) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional h. It was then allowed to warm to room temperature and was stirred for an additional 13 h. The reaction mixture was stirred with a 1:1 mixture of hexane: diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The solvent was removed in vaccuo, the mixture was diluted with 30 mL of water, and the aqueous layer was extracted with ethylacetate (3 × 50 mL) and dried over anhydrous Na_2SO_4. Concentration under vacuum and column chromatography of the crude product over silica gel furnished the title product **25:** Colorless semisolid; yield, 69%; R_f,0.5 (9/1, hexane/ethylacetate); IR (KBr, cm^{-1}) 1331, 1576, 2354, 2936, 3494; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.53−2.68 (m, 2H, CHC*H*$_2$C$_6$H$_4$OBn), 2.86−2.91 (m, 1H, CHC*H*HS), 3.28−3.36 (m, 1H, CHC*H*HS), 4.25−4.27 (m, 1H, SCH$_2$C*H*N), 4.67 (d, 1H, J = 10.4, NC*H*HC), 4.76 (d, 1H, J = 10.4, NCH*H*C), 5.04 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.88 (d, 2H, J = 8.4, Ar*H*), 7.05−7.41 (m, 15H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.45, 35.81, 36.30, 47.13, 57.73, 70.07, 115.11, 127.22, 127.48, 127.75, 127.93, 128.00, 128.62, 129.32, 130.44, 130.61, 132.00. FAB-MS (*m*/*z*) 516 [M+H]$^+$. Anal. calcd for $C_{30}H_{29}NO_3S_2$: C 69.87%, H 5.67%, N 2.72%. Found: C 69.96%, H 5.62%, N 2.80%.

Experimental Procedure of Tosyl Removal from Benzothiazepine Derivatives: Synthesis of (*S*)-3-(4-Benzyloxy-benzyl)-2,3,4,5-tetrahydro-benzo[*f*][1,4]thiazepine 26. To a mixture of compound **25** (0.19 mmol) and disodiumhydrogen phosphate (1.9 mmol) in dry methanol (25 mL) was added 4% Na−Hg (1.9 mmol). The resulting solution was stirred at 70 °C for 12 h. The reaction mixture was then diluted with an additional 10 mL of methanol and filtered. The residue was washed with methanol (2 × 5 mL) and DCM (2 × 10 mL) successively. The solvent was removed under vacuum, water was added, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with water (2 × 20 mL) and brine (2 × 20 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the crude product was chromatographed over silica gel (eluent = ethylacetate/hexane, 7.5/2.5) to afford the desired compound **26**: White solid; mp 96 °C; yield, 64%; R_f, 0.4 (ethylacetate/hexane,

7.5/2.5); IR (KBr, cm^{-1}) 1351, 1594, 2151, 2365, 2821; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (brs, NH), 2.52−2.60 [m, 1H, CHC*H*HPh(*p*-OBn)], 2.72 (d, 2H, J = 6.9, CHCH_2S), 2.87−2.92 (m, 1H, CHCH*H*Ph(*p*-OBn)], 3.33 (m, 1H, NHC*H*CH_2S), 4.02 (d, 1H, J = 14.2, C*H*HNCH), 4.17 (d, 1H, J = 14.2, CH*H*NCH), 5.08 (s, 2H, OCH_2Ph), 6.90−6.99 (m, 2H, Ar*H*), 7.09−7.25 (m, 5H, Ar*H*), 7.29−7.52 (m, 5H, Ar*H*), 7.57−7.60 (m, 1H, Ar*H*); ESI-MS (*m/z*) 362 $[M+H]^+$.

Experimental Procedure for the Synthesis of 30. The procedure was carried out as described for **12** to yield **30**: Brown semisolid; yield, 78%; R_f,0.5 (9/1, hexane/ethylacetate); ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, 3H, $SO_2C_6H_4C_6H_4CH_3$), 3.86 (s, 3H, COOCH_3), 6.97−7.89 (m, 6H, Ar*H*), 7.92 (d, 2H, J = 1.5, Ar*H*).

General Experimental Procedure for the Synthesis of 31. To a stirred solution of **1a-b** (500 mg, 1.56 mmol), **30** (1.56 mmol) and triphenylphosphine (409 mg, 1.56 mmol) in anhydrous THF (10 mL) under an atmosphere of N_2, was added DEAD (0.24 mL, 1.56 mmol, in THF) dropwise at 0 °C. The reaction mixture was warmed to the room temperature and stirred for 12 h. The mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The solvent was removed in vacuum, 50 mL of water was added and then extracted with ethylacetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. Concentration under vacuum and column chromatography of the crude product over silica gel furnished **31**.

{**2-[(2-*tert*-Butoxycarbonylamino-3-phenyl-propyl)-(toluene-4-sulfonyl)-amino]-phenyl**}**-acetic Acid Methyl Ester 31a:** Colorless semisolid; yield, 61%; R_f,0.4 (9/1, hexane/ethylacetate); IR (KBr, cm^{-1}) 1354, 1562, 2327, 2972, 3496; ^1H NMR (200 MHz, $CDCl_3$) mixture of rotamers, δ 1.31 (s), 2.39 (s), 2.54−2.50 (m), 3.29 (s), 3.64−3.69 (m), 3.69 (s), 3.88−4.20 (m), 5.01 (bs), 6.20 (d, Ar*H*), 7.42−7.64 (m, Ar*H*); ESI-MS (*m/z*) 575 $[M+Na]^+$. Anal. calcd for $C_{30}H_{36}N_2O_6S$: C 65.19%, H 6.57%, N 5.07%. Found: C 65.28%, H 6.60%, N 5.19%.

{**2-[[3-(4-Benzyloxy-phenyl)-2-*tert*-butoxycarbonylamino-propyl]-(toluene-4-sulfonyl)-amino]-phenyl**}**-acetic Acid Methyl Ester 31b:** Brown semisolid; yield, 68%; R_f,0.5 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1352, 1557, 2332, 2976, 3496; ^1H NMR (200 MHz, $CDCl_3$) mixture of rotamers, δ 1.33 {s, C(CH_3)$_3$}, 2.39 (s, ArCH_3), 2.46−2.50 (m, 2H), 2.80−2.90 (m), 3.31 (s), 3.64−3.68 (m), 3.70 (s), 5.02 (s), 5.40 (bs, NH), 6.50 (d, ArH), 6.80−7.45 (m, Ar*H*); ESI-MS (*m/z*) 681 $[M+Na]^+$.

General Experimental Procedure for the Synthesis of 32. To a solution of **31** in methanol was added 6 N HCl (15 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 45 min, and the solvent was removed under vacuum to afford crude **32** which was directly used for next step.

General Experimental Procedure for the Synthesis of 33. To the solution of **32** (1 equiv) and triethylamine (3 equiv) in anhydrous DCM (20 mL) was added *p*-toluenesulfonyl chloride (1.2 equiv) under atmosphere of nitrogen at 0 °C. The reaction mixture was warmed to room temperature and stirred for about 1 h. The reaction mixture was quenched by the slow addition of water (30 mL). The aqueous layer was extracted with DCM (3 × 50 mL). The organic layer was dried over Na_2SO_4. The removal of solvent under vacuum and column chromatography of crude product on silica furnished **33**.

{**2-[[3-Phenyl-2-(toluene-4-sulfonylamino)-propyl]-(toluene-4-sulfonyl)-amino]-phenyl**}**-acetic Acid Methyl Ester 33a:** Brown semisolid; yield, 73%; R_f,0.5 (9/1, hexane/ethylacetate); IR (KBr, cm^{-1}) 1360, 1532, 2346, 2981, 3452; ^1H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 2.39 (s), 2.46 (s), 2.48 (s), 2.54−2.73 (m), 3.02 (d), 3.07 (t), 3.13 (d), 3.20−3.30 (m), 3.41 (d), 3.47 (d), 3.54 (d), 3.58 (d), 3.61 (s), 3.66−3.70 (m), 3.93 (s), 3.99 (s), 4.04 (d), 4.09 (d), 4.28 (s), 4.33 (s), 4.67 (d), 5.16 (d), 6.54 9d), 6.57 (d), 6.76−6.78 (m), 6.85−6.91 (m), 7.04−7.52 (m), 7.81 (d); ESI-MS (*m/z*) 607 $[M+H]^+$. Anal. calcd for $C_{32}H_{34}N_2O_6S_2$: C 63.34%, H 5.65%, N 4.62%. Found: C 63.41%, H 5.99%, N 4.66%.

{**2-[[3-(4-Benzyloxy-phenyl)-2-(toluene-4-sulfonylamino)-propyl]-(toluene-4-sulfonyl)-amino]-phenyl**}**-acetic Acid Methyl Ester 33b:** Colorless semisolid; yield, 64%; R_f,0.4 (9/1, hexane/ethylacetate); IR (neat, cm^{-1}) 1341, 1536, 2341, 2981, 3470; ^1H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 2.38 (s), 2.46 (s), 2.48 (s), 2.50−2.65 (m), 2.96 (d), 3.00−3.03 (m), 3.07 (d), 3.16−3.18 (m), 3.39−3.41 (m), 3.45 (d), 3.52 (d), 3.53 (d), 3.61 (s), 3.68 (s), 3.73−3.81 (m), 3.61 (s), 3.68 (s), 3.70−3.85 (m), 4.00 (s), 4.03 (s), 4.08 (s), 4.13 (d), 4.27 (s), 4.32 (s), 4.52 (s), 4.60−4.64 (m), 5.02 (s), 5.03 (s), 5.12 (d), 6.48−6.58 (m), 6.66−6.67 (m), 6.69 (s), 6.76−6.79 (m), 7.02−7.51 (m), 7.80 (s), 7.83 (s); ESI-MS (*m/z*) 735 $[M+Na]^+$.

General Experimental Procedure for the Synthesis of 34: Compound **33a-b** (1 equiv) in anhydrous THF (15 mL) was added to a suspension of LAH (1.5 equiv) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of ethylacetate (50 mL) followed by water (50 mL) at 0 °C. The aqueous layer was extracted with ethylacetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel with hexane/ethylacetate as eluent to furnish **34**.

Compound 34a: Colorless semisolid; yield, 54%; R_f,0.6 (7.5/2.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1346, 1532, 2341, 2962, 3474; ^1H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 2.39 (s), 2.40 (s), 2.46 (s), 2.49 (s), 2.58−2.63 (m), 2.71−2.80 (m), 2.87−2.92 (m), 2.99−3.05 (m), 3.08−3.23 (m), 3.31−3.40 (m), 3.42−3.47 9 m), 3.49−3.56 (m), 3.71−3.84 (m), 3.95−4.01 (m), 4.06−4.10 (m), 4.85 (brd, NH), 5.45 (brd, NH), 6.45−6.52 (m, Ar*H*), 6.71−6.73 (m, Ar*H*), 6.78−6.80 (m, Ar*H*), 6.85−6.90 (m, Ar*H*), 6.99−7.11 (m, Ar*H*), 7.14−7.19 (m, Ar*H*), 7.21−7.33 (m, Ar*H*), 7.36−7.51 (m, Ar*H*), 7.617.75 (m), 7.80−7.85 (m); ESI-MS (*m/z*) 579 $[M+H]^+$.

Compound 34b: Colorless semisolid; yield, 49%; R_f,0.5 (7.5/2.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1341, 1551, 2341, 2972, 3471; ^1H NMR (300 MHz, $CDCl_3$) mixture of rotamers, δ 2.36 (s), 2.38 (s), 2.43 (s), 2.46 (s), 2.58 (s),

2.58−2.68 (m), 2.84−3.02 (m), 3.07−3.16 (m), 3.28−3.43 (m), 3.47 (d), 3.51 (d), 3.50−3.61 (m), 3.69−3.81 (m), 3.90−3.99 (m), 4.03−4.07 (m), 6.49 (d), 6.65 (s), 6.68 (d), 6.71−6.87 (m), 7.00−7.19 (m), 7.23−7.27 (m), 7.30−7.58 (m), 7.77 (s), 7.80 (s); ESI-MS (*m/z*) 685 $[M+H]^+$. Anal. calcd for $C_{38}H_{40}N_2O_6S_2$: C 66.64%, H 5.89%, N 4.09%. Found: C 66.66%, H 5.94%, N 4.14%.

General Experimental Procedure for the Synthesis of 35. To a stirred solution of **34** (1 equiv) and triphenylphosphine (1 equiv) in anhydrous THF under atmosphere of nitrogen was added DEAD (1 equiv, in THF) dropwise at 0 °C. The reaction mixture was stirred at 0 °C. The reaction mixture was warmed to room temperature and stirred for 14 h at the same temperature. The reaction mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The solvent was removed in vaccum, the mixture was diluted with 20 mL of water, and the aqueous layer was extracted with ethylacetate (3 × 50 mL) and dried over anhydrous Na_2SO_4. Concentration under vacuum and column chromatography of the crude product over silica gel furnished the title product **35**.

(*S*)-3-Benzyl-1,4-bis-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-benzo[*e*][1,4]diazocine 35a: White solid; mp 137 °C; yield, 86%; R_f,0.5 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1332, 1569, 2320, 2972, 3490; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, $SO_2C_6H_4CH_3$), 2.47 (s, 3H, $SO_2C_6H_4CH_3$), 2.67−4.52 (m, 9H), 6.59−7.60 (m, 15H, Ar*H*), 7.67−7.79 (m, 2H, Ar*H*); ESI-MS (*m/z*) 561 $[M+H]^+$. Anal. calcd for $C_{31}H_{32}N_2O_4S_2$: C 66.40%, H 5.75%, N 5.00%. Found: C 66.37%, H 5.80%, N 5.03%.

(*S*)-3-(4-Benzyloxy-benzyl)-1,4-bis-(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydro-benzo[*e*][1,4]diazocine 35b: White solid; mp 89 °C; yield, 77%; R_f,0.6 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1336, 1571, 2323, 2972, 3472; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H, $SO_2C_6H_4CH_3$), 2.47 (s, 3H, $SO_2C_6H_4CH_3$), 2.94 (m, 2H), 2.85−3.17 (m, 1H), 3.18−3.42 (m, 1H), 3.44−4.05 (m, 3H), 4.11−4.21 (m, 2H), 5.06 (s, 2H, OCH_2), 6.53−6.83 (m, 3H, Ar*H*), 7.01−7.14 (m, 5H, Ar*H*), 7.21−7.60 (m, 13H, Ar*H*); ESI-MS (*m/z*) 689 $[M+Na]^+$. Anal. calcd for $C_{38}H_{38}N_2O_5S_2$: C 68.44%, H 5.74%, N 4.20%. Found: C 68.55%, H 5.86%, N 4.28%.

General Experimental Procedure for the Synthesis of 38. To a stirred solution of **2** (500 mg, 2.19 mmol), **38a-d** (2.19 mmol), and triphenylphosphine (574 mg, 2.19 mmol) in anhydrous THF (5 mL) under an atmosphere of N_2 was added DEAD (0.34 mL, 2.19 mmol, in THF) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for an additional 2 h. It was allowed to warm to 25 °C and was stirred for an additional 10 h. The mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, 50 mL of water was added then extracted with ethylacetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. Concentration under vacuum and column chromatography of the crude product over silica gel furnished **39a-d**.

2-[[2-(2-Benzyloxy-phenyl)-ethyl]-(toluene-4-sulfonyl)-amino]-propionic acid methyl ester 38a: Colorless semisolid; yield, 57%; R_f,0.5 (9/1, hexane/ethylacetate); IR (KBr, cm^{-1}) 1347, 1596, 1745, 2342, 2370, 3458; ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (d, 3H, $CHCH_3$), 2.32 (s, 3H, $SO_2C_6H_4CH_3$), 2.90−2.94 (m, 2H, NCH_2CH_2), 3.20−3.28 (m, 2H, NCH_2CH_2), 3.35 (s, 3H, $COOCH_3$) 4.46−4.49 (m, 1H, $NCHCOOCH_3$), 4.95 (s, 2H, $OCH_2C_6H_5$), 6.76−7.60 (m, 13H, Ar*H*); ESI-MS (*m/z*) 490 $[M+Na]^+$. Anal. calcd for $C_{26}H_{29}NO_5S$: C 66.79%, H 6.25%, N 3.00%. Found: C 66.63%, H 6.29%, N 2.86%.

2-[[2-(2-Benzyloxy-phenyl)-ethyl]-(toluene-4-sulfonyl)-amino]-3-phenyl-propionicacid methyl ester 38b: Colorless semisolid; yield, 59%; R_f,0.6 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1346, 1590, 1733, 2366, 2970, 3448; ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, 3H, $SO_2C_6H_4CH_3$), 2.91−3.05 (m, 4H, NCH_2CH_2, $CHCH_2C_6H_5$), 3.40 (s, 3H, $COOCH_3$), 3.42−3.47 (m, 2H, NCH_2CH_2), 4.76−4.79 (m, 1H, $NCHCOOCH_3$), 5.06 (s, 2H, $OCH_2C_6H_5$), 6.92−7.52 (m, 18H, Ar*H*); ESI-MS (*m/z*) 566 $[M+Na]^+$.

3-(4-Benzyloxy-phenyl)-2-[[2-(2-benzyloxy-phenyl)-ethyl]-(toluene-4-sulfonyl)-amino]-propionic acid methyl ester 38c: Colorless semisolid; yield, 59%; R_f,0.5 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1351, 1596, 2341, 2368, 2817, 3428; ^1H NMR (200 MHz, $CDCl_3$) δ 2.27 (s, 3H, $SO_2C_6H_4CH_3$), 2.81−2.90 (m, 4H, NCH_2CH_2, $CHCH_2C_6H_5$), 3.31 (s, 3H, $COOCH_3$), 3.34−3.41 (m, 2H, NCH_2CH_2), 4.65−4.94 (m, 1H, $NCHCOOCH_3$), 4.99 (s, 2H, $OCH_2C_6H_5$), 5.00 (s, 2H, $OCH_2C_6H_5$), 6.71−7.46 (m, 22H, Ar*H*); ESI-MS (*m/z*) 672 $[M+Na]^+$. Anal. calcd for $C_{39}H_{39}NO_6S$: C 72.09%, H 6.05%, N 2.16%. Found: C 72.03%, H 6.20%, N 2.19%.

2-[[2-(2-Benzyloxy-phenyl)-ethyl]-(toluene-4-sulfonyl)-amino]-3-(1*H*-indol-3-yl)-propionic Acid Methyl Ester 38d: Colorless semisolid; yield, 56%; R_f,0.5 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1236, 1736, 2365, 3395; ^1H NMR (200 MHz, $CDCl_3$) δ 2.33 (s, 3H, $SO_2C_6H_4CH_3$), 2.92−3.22 (m, 3H, NCH_2CH_2, $CHCHHC_8H_5N$), 3.38 (s, 3H, $COOCH_3$), 3.41−3.51 (m, 1H, NCH_2CH_2), 3.82−3.88 (m, 1H, $CHCHHC_8H_5N$), 4.17 (m, 1H, NCH_2CH_2), 4.90 (m, 1H, $NCHCOOCH_3$), 5.06 (d, 2H, J = 5.9, OCH_2), 6.91−7.50 (m, 18H, Ar*H*), 8.03 (bs, 1H, NH); ESI-MS (*m/z*) 605 $[M+Na]^+$.

General Experimental Procedure for the Synthesis of 39. Compound **38** (1 equiv) in anhydrous THF (15 mL) was added to a suspension of LAH (1.5 equiv) in THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of ethylacetate (50 mL) followed by water (50 mL) at 0 °C. The aqueous layer was extracted with ethylacetate (3 × 50 mL), and the organic layer was dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was chromatographed on silica gel with hexane/ethylacetate as eluent to furnish **39**.

***N*-[2-(2-Benzyloxy-phenyl)-ethyl]-*N*-(2-hydroxy-1-methyl-ethyl)-4-methyl-benzenesulfonamide 39a:** Colorless semisolid; yield, 75%; R_f,0.4 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1246, 1732, 2360, 3395; ^1H NMR (200 MHz, $CDCl_3$) δ 0.65 (d, 3H, $CHCH_3$), 1.65 (bs, 1H, O*H*), 2.39 (s, 3H, $SO_2C_6H_4CH_3$), 2.97 (m, 2H, NCH_2CH_2), 3.03−3.29 (m, 4H, NCH_2CH_2, CH_2OH), 3.80−3.84 (m, 1H, $NCHCH_2OH$), 5.02 (s, 2H, $OCH_2C_6H_5$), 6.76−7.60 (m, 11H, Ar*H*), 7.66

(d, 2H, J = 8.2, Ar*H*). FAB-MS (*m/z*) 440 $[M+H]^+$. Anal. calcd for $C_{25}H_{29}NO_4S$: C 68.31%, H 6.65%, N 3.19%. Found: C 68.24%, H 6.69%, N 3.32%.

***N*-[2-(2-Benzyloxy-phenyl)-ethyl]-*N*-(1-hydroxymethyl-2-phenyl-ethyl)-4-methyl-benzenesulfonamide 39b:** Colorless semisolid; yield, 75%; R_f,0.6 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1232, 1732, 2345, 3376; ^1H NMR (200 MHz, $CDCl_3$) δ 1.64−1.76 (m, 1H, CH_2OH), 2.31 (s, 3H, $SO_2C_6H_4CH_3$), 2.33−2.34 (m, 1H, ArCH*H*CH), 2.86−2.99 (m, 3H, NCH_2CH_2, CHCH*H*C_6H_5), 3.27−3.34 (m, 4H, NCH_2CH_2, CH_2OH), 3.76−3.98 (m, 1H, NC*H*CH_2OH), 4.95 (d, 1H, J = 11.2, OC*H*HC_6H_5), 5.01 (d, 1H, J = 11.2, OCH*H*C_6H_5), 6.92−7.52 (m, 17H, Ar*H*); ESI-MS (*m/z*) 538 $[M+Na]^+$.

***N*-[2-(2-Benzyloxy-phenyl)-ethyl]-*N*-[2-(4-benzyloxy-phenyl)-1-hydroxymethyl-ethyl]-4-methyl-benzenesulfonamide 39c:** Colorless semisolid; yield, 63%; R_f,0.4 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1232, 1748, 2340, 3376; ^1H NMR (200 MHz, $CDCl_3$) δ 1.81 (bs, 1H, O*H*), 2.30−2.32 (m, 2H, CHC$H_2C_6H_4$), 2.36 (s, 3H, $SO_2C_6H_4CH_3$), 3.00−3.08 (m, 2H, NCH_2CH_2), 3.29−3.43 (m, 4H, NCH_2CH_2, CH_2OH), 3.85−3.89 (m, 1H, NC*H*CH_2OH), 5.00 (s, 2H, OC$H_2C_6H_5$), 5.06 (s, 2H, OC$H_2C_6H_5$), 6.72−7.44 (m, 20H, Ar*H*), 7.59 (d, 2H, J = 8.2, Ar*H*); ESI-MS (*m/z*) 644 $[M+Na]^+$. Anal. calcd for $C_{38}H_{39}NO_5S$: C 73.40%, H 6.32%, N 2.25%. Found: C 73.42%, H 6.27%, N 2.29%.

***N*-[2-(2-Benzyloxy-phenyl)-ethyl]-*N*-[1-hydroxymethyl-2-(1*H*-indol-3-yl)-ethyl]-4-methyl-benzenesulfonamide 39d:** White solid; mp 140 °C; yield, 64%; R_f,0.4 (7.5/2.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1212, 1748, 2343, 3376; ^1H NMR (200 MHz, $CDCl_3$) δ 2.33 (s, 3H, $SO_2C_6H_4CH_3$), 2.63 (d, 2H, J = 7.4, CHC$H_2C_8H_6N$), 3.06−3.14 (m, 2H, NCH_2CH_2), 3.45−3.53 (m, 4H, NCH_2CH_2, CH_2OH), 4.05−4.14 (m, 1H, NC*H*CH_2OH), 5.08 (s, 2H, OC$H_2C_6H_5$), 6.68−7.55 (m, 16H, Ar*H*), 7. 59 (d, 2H, J = 8.2, Ar*H*); ESI-MS (*m/z*) 577 $[M+Na]^+$.

General Experimental Procedure for the Synthesis of 40. The procedure was carried out as described for compound **8**.

***N*-(2-Hydroxy-1-methyl-ethyl)-*N*-[2-(2-hydroxy-phenyl)-ethyl]-4-methyl-benzenesulfonamide 40a:** Colorless semisolid; yield, 76%; R_f,0.4 (7.5/2.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1350, 1597, 2340, 2370, 3402; ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (d, 3H, CHCH_3), 1.82 (bs, 1H, O*H*), 2.41 (s, 3H, $SO_2C_6H_4CH_3$), 2.97−3.05 (m, 2H, NCH_2CH_2), 3.14−3.55 (m, 4H, CH_2OH, NCH_2CH_2), 3.92−4.01 (m, 1H, NC*H*CH_2OH), 6.75−7.28 (m, 6H, Ar*H*), 7.71-(d, 2H, J = 8.2, Ar*H*); ESI-MS (*m/z*) 372 $[M+Na]^+$. Anal. calcd for $C_{18}H_{23}NO_4S$: C 61.87%, H 6.63%, N 4.01%. Found: C 61.99%, H 6.59%, N 3.89%.

***N*-(1-Hydroxymethyl-2-phenyl-ethyl)-*N*-[2-(2-hydroxy-phenyl)-ethyl]-4-methyl-benzenesulfonamide 40b:** Colorless semisolid; yield, 73%; R_f,0.6 (7/3, hexane/ethylacetate); IR (KBr, cm^{-1}) 1352, 1597, 2332, 2370, 3402; ^1H NMR (200 MHz, $CDCl_3$) δ 1.81 (bs, 1H, O*H*), 2.32 (s, 3H, SO2$C_6H_4CH_3$), 2.36−2.45 (m, 2H, CHC$H_2C_6H_5$), 2.65−2.72 (m, 2H, NCH_2CH_2), 3.27−3.58 (m, 4H, CH_2OH, NCH_2CH_2), 3.85−3.89 (m, 1H, NC*H*CH_2OH), 6.75−7.18 (m, 11H, Ar*H*), 7.60 (d, 2H, J = 8.2, Ar*H*); ESI-MS (*m/z*) 448 $[M+Na]^+$. Anal. calcd for $C_{24}H_{27}NO_4S$: C 67.74%, H 6.40%, N 3.29%. Found: C 67.79%, H 6.46%, N 3.25%.

***N*-[1-Hydroxymethyl-2-(4-hydroxy-phenyl)-ethyl]-*N*-[2-(2-hydroxy-phenyl)-ethyl]-4-methyl-benzenesulfonamide 40c:** Colorless semisolid; yield, 77%; R_f,0.5 (7/3, hexane/ethylacetate); IR (KBr, cm^{-1}) 1352, 1597, 2370, 2947, 3425; ^1H NMR (200 MHz, $CDCl_3$) δ 1.66 (bs, 1H, O*H*), 2.36 (s, 3H, $SO_2C_6H_4CH_3$), 2.40−2.74 (m, 2H, CHC$H_2C_6H_4OH$), 3.04−3.12 (m, 2H, NCH_2CH_2), 3.32−3.65 (m, 4H, CH_2OH, NCH_2CH_2), 3.97−3.99 (m, 1H, NC*H*CH_2-OH), 5.29 (bs, 1H, O*H*), 6.64 (d, 2H, J = 8.4, Ar*H*), 6.82−7.26 (m, 8H, Ar*H*), 7.67 (d, 2H, J = 8.2, Ar*H*); ESI-MS (*m/z*) 442 $[M+H]^+$.

***N*-[1-Hydroxymethyl-2-(1*H*-indol-3-yl)-ethyl]-*N*-[2-(2-hydroxy-phenyl)-ethyl]-4-methyl-benzenesulfonamide 40d:** Brown semisolid; yield, 45%; R_f,0.4 (6.5/3.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1351, 1590, 2390, 2947, 3452; ^1H NMR (200 MHz, $CDCl_3$) δ 2.36 (s, 3H, $SO_2C_6H_4CH_3$), 2.40−2.76 (m, 2H, CHC$H_2C_8H_6$), 3.06−3.16 (m, 2H, NCH_2CH_2), 3.48−3.69 (m, 4H, CH_2OH, NCH_2CH_2), 4.14−4.21 (m, 1H, NC*H*CH_2OH), 6.52 (bs, 1H, O*H*), 6.83−7.31 (m, 11H, Ar*H*), 7. 67 (d, 2H, J = 8.2, Ar*H*); ESI-MS (*m/z*) 487 $[M+Na]^+$. Anal. calcd for $C_{26}H_{28}N_2O_4S$: C 67.22%, H 6.07%, N 6.03%. Found: C 67.37%, H 6.09%, N 6.26%.

General Experimental Procedure for the Synthesis of 41. To a stirred solution of **40** (1 equiv) and triphenylphosphine (1 equiv) in anhydrous THF under atmosphere of nitrogen was added DEAD (1 equiv, in THF) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 additional h. It was then allowed to warm to room temperature and was stirred for an additional 14 h. The reaction mixture was stirred with a 1:1 mixture of hexane:diethylether, and the triphenylphosphine oxide that precipitated was filtered off. The organic solvent was removed in vacuum, the mixture was diluted with 30 mL of water, then extracted with ethylacetate (3 × 50 mL), and dried over anhydrous Na_2SO_4. Concentration under vacuum and column chromatography of the crude product over silica gel furnished the title product **41**.

(*S*)-3-Methyl-4-(toluene-4-sulfonyl)-3,4,5,6-tetrahydro-2*H*-benzo[*g*][1,4]oxazocine 41a: White solid; mp 70 °C; yield, 66%; R_f,0.5 (9/1, hexane/ethylacetate); IR (KBr, cm^{-1}) 1348, 1597, 2376, 2947, 3460; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (d, 3H, J = 7.2. CHCH_3), 2.39 (s, 3H, $SO_2C_6H_4CH_3$), 2.59−2.67 (m, 1H, NCH_2CH), 3.14−3.24 (m, 1H, NCH_2-C*H*H), 3.43−3.50 (m, 2H, NCH_2CH_2), 3.73−3.75 (m, 1H, NC*H*CH_2O), 3.87−3.95 (m, 1H, NCHCH*H*O), 4.23−4.32 (m, 1H, NCHC*H*HO), 6.97−7.24 (m, 6H, Ar*H*). 7.51 (d, 2H, J = 8.1, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$) 15.3, 21.8, 32.4, 47.6, 54.9, 79.7, 122.0, 124.9, 127.2, 128.8, 129.8, 130.3, 133.2, 139.0, 142.8, 159.4; FAB-MS (*m/z*) 332 $[M+H]^+$. Anal. calcd for $C_{18}H_{21}NO_3S$: C 65.23%, H 6.39%, N 4.23%. Found: C 65.29%, H 6.48%, N 4.20%.

(*S*)-3-Benzyl-4-(toluene-4-sulfonyl)-3,4,5,6-tetrahydro-2*H*-benzo[*g*][1,4]oxazocine 41b: White solid; mp 86 °C; yield, 63%; R_f,0.5 (8.5/1.5, hexane/ethylacetate); IR (KBr, cm^{-1}) 1352, 1599, 2370, 2957, 3446; ^1H NMR (200 MHz, $CDCl_3$) δ 2.38 (s, 3H, $SO_2C_6H_4CH_3$), 2.66−2.73 (2H, m, CHC$H_2C_6H_5$), 2.91−3.00 (m, 2H, NCH_2CH_2), 3.24−3.58 (m,

2H, NC*H*$_2$CH$_2$), 3.83−3.85 (m, 1H, NC*H*CH$_2$O), 3.91−3.94 (m, 1H, 4.28−4.36 (m, 1H, NCHCH*H*O), 4.28−4.36 (m, 1H, NCHC*H*HO), 6.97−7.24 (m, 11H, Ar*H*), 7.50 (d, 2H, J = 8.2, Ar*H*); ^{13}C NMR (50 MHz, CDCl$_3$) 21.8, 32.1, 35.8, 47.3, 60.6, 122.1, 125.1, 127.0, 127.3, 129.0, 129.5, 130.0, 130.5, 132.9, 138.1, 143.3, 159.6; ESI-MS (*m/z*) 430 [M+Na]$^+$.

(*S*)-4-[4-(Toluene-4-sulfonyl)-3,4,5,6-tetrahydro-2*H*-benzo[*g*][1,4]oxazocin-3-ylmethyl]-phenol 41c: White solid; mp 81 °C; yield, 71%; R_f,0.5 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1153, 1602, 2363, 2933, 3430; ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.37 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.71−2.73 (2H, m, CHC*H*$_2$C$_6$H$_5$), 2.80−2.83 (m, 2H, NCH$_2$C*H*$_2$), 3.50−3.55 (m, 2H, NC*H*$_2$CH$_2$), 3.82−3.84 (m, 1H, NC*H*CH$_2$O), 3.89−3.93 (m, 1H, NC*H*CH$_2$O), 4.28−4.30 (m, 1H, NCHCH*H*O), 4.31−4.34(m, 1H, NCHC*H*HO), 6.66−7.19 (m, 11H, Ar*H*), 7.48 (d, 2H, J = 8.2, Ar*H*); ^{13}C NMR (50 MHz, CDCl$_3$) 14.5, 14.8, 21.8, 32.0, 35.0, 47.2, 62.8, 115.9, 122.1, 125.1, 127.3, 129.0, 129.7, 130.0, 130.5, 132.8, 137.9, 143.5, 155.1, 159.6; ESI-MS (*m/z*) 446 [M+Na]$^+$. Anal. calcd for C$_{24}$H$_{25}$NO$_4$S: C 68.06%, H 5.95%, N 3.31%. Found: C 68.09%, H 5.81%, N 3.46%.

(*S*)-3-(1*H*-Indol-3-ylmethyl)-4-(toluene-4-sulfonyl)-3,4,5,6-tetrahydro-2*H*-benzo[*g*][1,4]oxazocine 41d: Brown semi-solid; yield, 63%; R_f,0.4 (8/2, hexane/ethylacetate); IR (KBr, cm^{-1}) 1326, 1595, 2246, 2932, 3053, 3422; ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.36 (s, 3H, SO$_2$C$_6$H$_4$C*H*$_3$), 2.75−3.09 (m, 2H, CHC*H*$_2$C$_8$H$_6$N), 3.17−3.29 (m, 2H, NCH$_2$C*H*$_2$), 3.62−3.93 (m, 2H, NC*H*$_2$CH$_2$), 4.14−4.21(m, 1H, CHCH*H*O), 4.33−4.39 (m, 1H, CHC*H*HO), 6.92−7.33 (m, 11H, Ar*H*), 7.47 (d, 2H, J = 8.2, Ar*H*), 8.07 (bs, 1H); ^{13}C NMR (50 MHz, CDCl$_3$) 21.9, 25.5, 32.2, 46.8, 59.2, 111.7, 111.9, 118.8, 119.8, 122.1, 122.5, 123.3, 125.1, 127.3, 129.0, 129.9, 130.4, 132.9, 136.6, 138.2, 143.2, 159.9; ESI-MS (*m/z*) 469 [M+Na]$^+$. Anal. calcd for C$_{26}$H$_{26}$N$_2$O$_3$S: C 69.93%, H 5.87%, N 6.27%. Found: C 69.99%, H 5.90%, N 6.35%.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra and HPLC graph of compounds. This material is available free of charge via the Internet at http://-pubs.acs.org.

References and Notes

(1) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964. (c) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565. (d) Chow, H. F.; Zhang, J. *Chem.—Eur. J.* **2005**, *11*, 5817.

(2) (a) Kotha, S.; Mandal, K.; Tiwari, A.; Mobin, S. M. *Chem.—Eur. J.* **2006**, *12*, 8024. (b) Hotha, S.; Tripathi, A. *J. Comb. Chem.* **2005**, *7*, 968.

(3) Reviews: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125. (b) Maier, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (c) Evans, P. A.; Holmes, B. *Tetrahedron* **1991**, *47*, 9131. (d) Lindström, U. M.; Somfai, P. *Chem.—Eur. J.* **2001**, *7*, 94. (e) Bieräugel, H.; Jansen, T. P.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2002**, *4*, 2673. (f) Derrer, S.; Davies, J. E.; Holmes, A. B *J. Chem. Soc., Perkin Trans. 1* **2000**, 2957. (g) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 44.

(4) (a) Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412. (b) Murray, P. J.; Kranz, M.; Ladlow, M.; Taylor, S.; Berst, F.; Holmes, A. B.; Keavey, K. N.; Jaxa-Chamiec, A.; Seale, P. W.; Stead, P.; Upton, R. J.; Croft, S. L.; Clegg, W.; Elsegood, M. R. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 773.

(5) (a) Sanchez-Quesada, J.; Ghadiri, M. R.; Bayley, H.; Braha, O. *J. Am. Chem. Soc.* **2000**, *122*, 11757. (b) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 988.

(6) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.

(7) (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirscheld, J. *J. Med. Chem.* **1988**, *31*, 2235. (b) Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1. (c) Bock, M. G.; Dipardo, R. M.; Evans, E. B.; Rittle, K. E.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Preidinger, R. M. *J. Med. Chem.* **1989**, *32*, 13. (d) Romer, D.; Buscher, H. H.; Hill, R. C.; Maurer, R.; Petcher, T. J.; Zeugner, H.; Benson, W.; Finnner, E.; Milkowski, W.; Thies, P. W. *Nature* **1982**, *298*, 759. (e) Komecki, E.; Ehrlich, Y. H.; Lenox, R. H. *Science* **1984**, *226*, 1454. (f) Hsu, M.-C.; Schutt, A. D.; Hooly, M.; Slice, L. W.; SherTnan, M. I.; Richman, D. D.; Potash, M. J.; Volsky, D. J. *Science* **1991**, *254*, 1799. (g) Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, J. M.; Breslin, H. J.; Raeymaeckers, A.; Van, Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Janssen, M. A. C.; Clercq, E. D.; Janssen, P. A. J. *Nature* **1990**, *343*, 470.

(8) (a) Liao, Y.; Venhuis, B. J.; Rodenhuis, N.; Timmerman, W.; Wikstrom, H.; Meire, E.; Bartoszyk, G. D.; Bottcher, H.; Seyfried, C. A.; Sundell, S. *J. Med. Chem.* **1999**, *42*, 2235. (b) Toshiyuki, H.; Tokuhiro, I.; Hisao, Y. G. O. 2,-014,223,1969. *Chem. Abstr.* **1970**, *73*, 120697h. (c) Standridge, R. T. U.S. 4,125,538,1978. *Chem. Abstr.* **1979**, *90*, 72246r. (d) James, G. L.; Goldstein, J. L.; Brown, M. S.; Rawson, T. E.; Somers, T. C.; McDowell, R. S.; Crowley, C. W.; Lucas, B. K.; Levinson, A. D.; Marsters, J. C., Jr. *Science* **1993**, *260*, 1937. (e) Díaz-Gavilán, M.; Rodríguez-Serrano, F.; Gómez-Vidal, J. A.; Marchal, J. A.; Aránega, A.; Gallo, M. Á.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2004**, *60*, 11547.

(9) (a) Milligan, G. *Trends Pharmacol. Sci.* **1993**, *14*, 413. (b) Amblard, M.; Daffix, I.; Bedos, P.; Berge, G.; Pruneau, D.; Paquet, J.-L.; Luccarini, J.-M.; Belichard, P.; Dodey, P.; Martinez, J. *J. Med. Chem.* **1999**, *42*, 4185.

(10) Ron, D.; Kazanietz, M. G. *FEBS J.* **1999**, *16*, 1358 (b) Kazanietz, M. G.; Caloca, M. J.; Fujii, T.; Eroles, P.; Garcia-Bermejo, M. L.; Reilly, M.; Wang, H. *Biochem. Pharmacol.* **2000**, *60*, 1417.

(11) *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck: Rahway, NJ, 1996; p 1105 and references cited therein.

(12) Klohs, M. W.; Draper, M. S.; Petracek, F. J.; Ginzel, K. H.; Re', O. N. *Arzneim.-Forsch. (Drug Res.)* **1972**, *22*, 132.

(13) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653 and references cited therein.

(14) For a pertinent discussion of the issues surrounding medium ring synthesis, see: Eliel, E. L. *Stereochemistry of Organic Compounds*; John Wiley: New York, 1994.

(15) Broggini, G.; Bruch, L.; Garanti, L.; Zecchi, G. *J. Chem. Soc., Perkins Trans. 1* **1994**, 433.

(16) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199 and references cited therein.

(17) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529 and references cited therein.
(18) Khlebnikov, A. F.; Novikov, M. S.; Shinkevich, E. U.; Vidovic, D. *Org. Biomol. Chem.* **2005**, *3*, 4040 and references cited therein.
(19) (a) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, *7*, 4781. (b) Lu, S. M.; Alper, H. *J. Am. Chem. Soc.* **2005**, *127*, 14776.
(20) (a) Mishra, J. K.; Panda, G. *Synthesis* **2005**, 1881. (b) Mishra, J. K.; Rao, J. S.; Sastry, G. N.; Panda, G. *Tetrahedron Lett.* **2006**, *47*, 3357. (c) Shagufta; Panda, G. *Org. Biomol. Chem.* **2007**, *5*, 360. (d) Mishra, J. K.; Garg, P.; Dohare, P.; Kumar, A.; Siddiqi, M. I.; Ray, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2007**, in press.
(21) For review of heterocycles from amino acids, see: Sardina, F. J.; Rapport, H. *Chem. Rev.* **1996**, *96*, 1825.
(22) For reviews on Mitsunobu reaction, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335 and references cited therein. (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (d) Anderson, B.; Hansen, M. M.; Viceizi, J. T.; Varie, D. L.; Zmijewski, M. J. Stereoselective process for producing dihydr-2,3-benzodiazepine derivatives. European Patent Application EP699677 A1 19960306, 1996.
(23) Koppel, I.; Kippel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, V. *J. Org. Chem.* **1991**, *56*, 7172.
(24) For strains in medium ring systems, see: (a) Gol'dfarb; Belen'kii *Russ. Chem. Rev.* **1960**, *29*, 214. (b) Raphael *Proc. Chem. Soc.* **1962**, 97. (c) Sicher *Prog. Stereochem.* **1962**, *3*, 202 and references cited therein.

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