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Stereoselective synthesis of (−)-allosedamine and (1*R*,3*R*)-HPA-12 from β-*p*-toluenesulfonamido-γ,δ-unsaturated sulfoxide☆

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Abstract—A stereoselective synthesis of (−)-allosedamine and HPA-12 is disclosed. The key steps of the synthesis include the diastereoselective synthesis of a β-sulfonamido unsaturated sulfoxide, elaboration of a bromohydrin via intramolecular sulfinyl group participation and a ring-closing metathesis reaction for the construction of the piperidine ring of allosedamine.

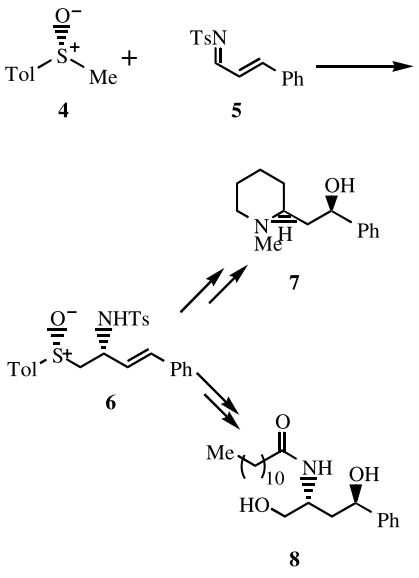
1. Introduction

1,3-Aminoalcohols are constituents of many synthetic[1] and natural products[2] possessing potent physiological activity. They are useful as ligands and as chiral auxiliaries in asymmetric synthesis.[3] We recently disclosed the preparation of protected β-amino γ,δ-unsaturated sulfoxides **2** and their regio- and stereoselective elaboration into 1,3-aminoalcohol derivatives **3**.[4] The unsaturated sulfoxides **2** were prepared from the Garner aldehyde **1** using a multistep sequence of straightforward reactions (Scheme 1). This study demonstrated the potential of the sulfinyl group as an intramolecular nucleophile to regio- and stereoselectively functionalize an olefin and the importance of the relative configurations of the sulfinyl group and the carbon bearing the amino substituent on the stereoselectivity of bromohydrin formation.

However, for protected β-amino γ,δ-unsaturated sulfoxides **2** to be useful synthons, it is important that they be accessible in one or two steps from readily available starting materials.

An attractive route to synthon **2** would be the direct addition of sulfoxide stabilized anions to *N*-substituted imines. The use of chiral sulfoxide stabilized carbanions for asymmetric C–C bond formation, via alkylation or addition to C=O and activated C=C bonds has been studied extensively.[5] However, the addition of sulfoxide stabilized carbanions to imines has received less attention.[6] Most of the literature reports are concerned with the addition of sulfoxide anions to imines derived from aromatic aldehydes[7] and to the best of our knowledge there is only one report on the addition of the carbanion derived from (*S*)-*tert*-butyl phenylmethyl-sulfoxide to imines derived from α,β-unsaturated aldehydes.[8]

We disclose herein the diastereoselective addition of the anion of methyl *p*-tolyl sulfoxide **4** with *N*-Ts imine **5**, derived from cinnamaldehyde, to yield the protected β-amino γ,δ-unsaturated sulfoxide **6** and its elaboration to (−)-allosedamine **7** and (1*R*,3*R*)-HPA-12, **8** (Eq. (1)).



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Keywords: (−)-Allosedamine; (1*R*,3*R*)-HPA-12; Protected β-amino sulfoxide; Bromohydrin; Pummerer reaction; Ring-closing metathesis reaction.

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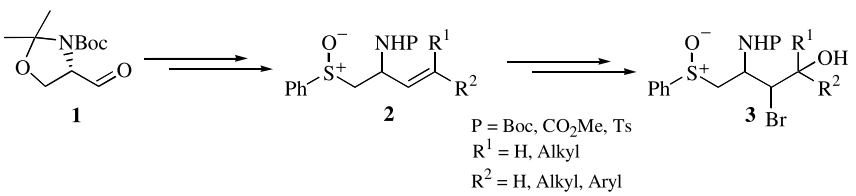
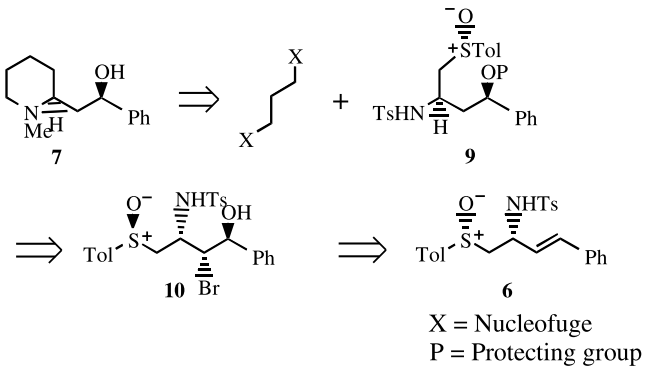


Scheme 1.



Scheme 2.

Table 1. Reaction of lithium anion of (*R*)-methyl *p*-tolyl sulfoxide **4** and imine **5**

Entry	T_1[a] (°C)	T_2[b] (°C)	Time (min)	Yield (%)	Ratio[c]	
					6s	**6a**
1	−30	−78	15	82	70	30
2	−78	−78	15	81	75	25
3	−78	−78	90	71	60	40
4	−30	−78–80	120	53	53	47
5	−42	−42	30	62	58	42

[a] Temperature at which lithium anion of (*R*)-methyl *p*-tolyl sulfoxide was generated.
[b] Temperature at which the reaction was carried out.
[c] Ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

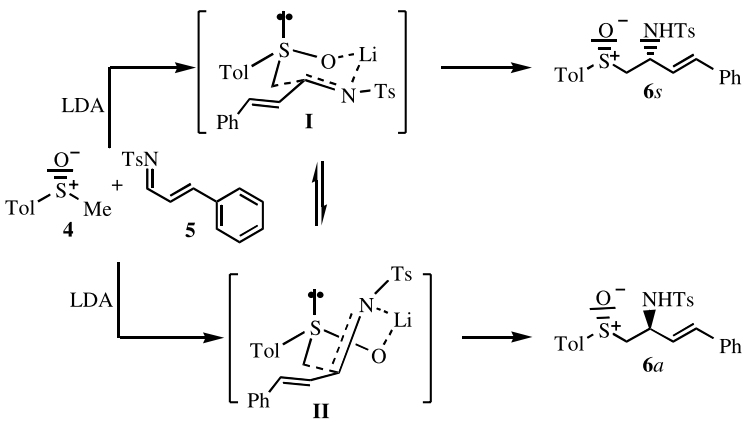
2. Results and discussion

2.1. Synthesis of (−)-allosedamine

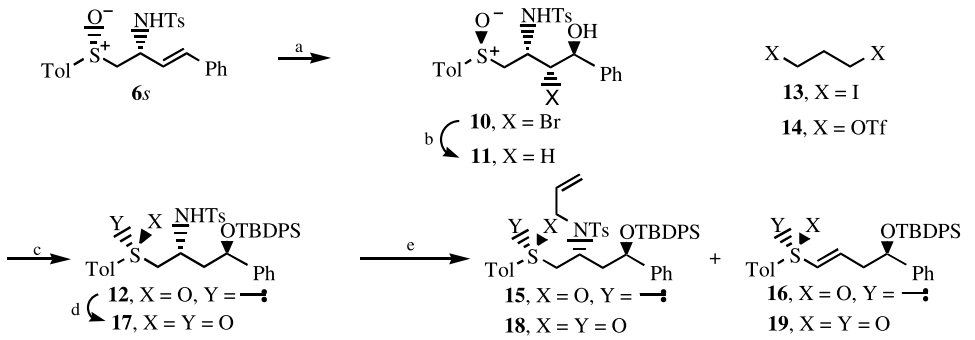
Allosedamine **7**, was isolated from *Lobelia inflata*,[9] the crude extract of which has been utilized for the treatment of asthma, bronchitis and pneumonia.[10] Though several routes to racemic allosedamine have been disclosed,[11] stereoselective asymmetric syntheses are few in number.[12,13] We describe herein a stereoselective synthesis of (−)-allosedamine taking advantage of the potential of the sulfinyl group as an intramolecular nucleophile to regio- and stereoselectively functionalize an olefin[4,14] (Scheme 2, retrosynthetic analysis). The piperidine ring of allosedamine was envisaged to be elaborated via dialkylation of the dianion derived from **9** using a suitable 1,3-dielectrophile.

The first step of the synthesis required the stereoselective preparation of the unsaturated sulfoxide **6**. Kagan and co-workers[6b] have pointed out the influence of temperature, both during anion generation from the chiral sulfoxide and addition of the anion with the imine, on the diastereoselectivity of β-amino sulfoxide formation. Thus anion generation from **4** and subsequent addition of the anion with the imine **5**[15] were conducted at different temperatures and the results are tabulated in Table 1. Not surprisingly, the best diastereoselectivity (ca. 3:1 of **6*s*/6*a***) was observed when the anion was generated at −78 °C and subsequently reacted with the imine at −78 °C over a period of 15 min (entry 2). The diastereoselectivity eroded when the reaction was allowed to proceed for longer periods of time at −78 °C (entry 3) or when the reaction was carried out at higher temperatures (entries 4 and 5). The temperature at which the anion was generated did not profoundly influence the diastereoselectivity (entry 1). The observed results can be rationalized by invoking intermediates **I** and **II** which are in equilibrium, higher temperatures favour more rapid equilibration to give the thermodynamic isomer **II** (Scheme 3).

The diastereomers **6*s*** and **6*a*** were readily separated by column chromatography and the structures assigned to them by comparison of their ^{1}H NMR data with that of related compounds previously synthesized by us.[4,16] The



Scheme 3.



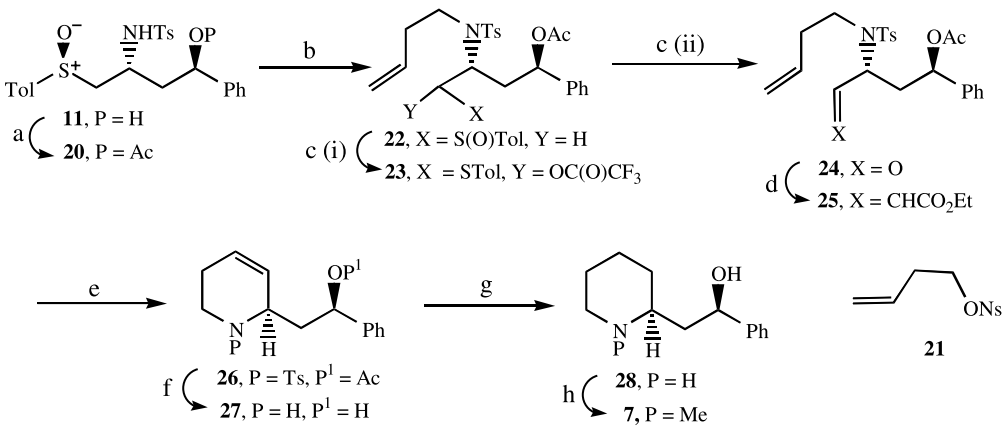
Scheme 4. Reagents and conditions: (a) NBS, H_2O, toluene, rt, 1 h, 84%; (b) *n*-Bu_3SnH, AIBN, benzene, reflux, 1.5 h, 76%; (c) TBDPS-Cl, imidazole, DCM, rt, 2 h, 80%; (d) *m*-CPBA, $CHCl_3$, 0 °C, 10 min, 93%; (e) LDA, HMPA, $I(CH_2)_3I$ **13** or $TfO(CH_2)_3OTf$ **14**, THF, −78 to −20 °C, 2 h.

unsaturated sulfoxide **6*s*** on treatment with NBS afforded regio- and stereospecifically the bromohydrin **10**. The structure was assigned to **10** based on our studies on the related unsaturated sulfoxide prepared from methyl phenyl-sulfoxide.[4] The bromine atom in **10** was removed by treatment with *n*-tributyltin hydride to afford the amino-alcohol **11**. Protection of the hydroxy group in **11** by treatment with *t*-butyldiphenylchlorosilane in dichloro-methane as the solvent afforded the silyl ether **12**. Generation of the dianion of **12** using excess LDA and subsequent treatment with 1,3-diiodopropane **13**, with the intention of elaborating the piperidine ring did not bear fruit. The products isolated were the *N*-allylation product **15** and the eliminated product **16**. The use of 1,3-propane di triflate **14**, HMPA as the co-solvent and bases such as LiHMDS, NaHMDS or KHMDS also gave the same result (Scheme 4). Attempted elaboration of the piperidine ring on sulfone **17**, obtained from **12** by *m*-CPBA oxidation, using a variety of bases and dielectrophiles **13/14** proved disappointing. The *N*-allylated product **18** and the elimination product **19** were the only products obtained. Similar results have been observed by Najera and co-workers in the attempted dialkylation of protected β-amino sulfones.[17]

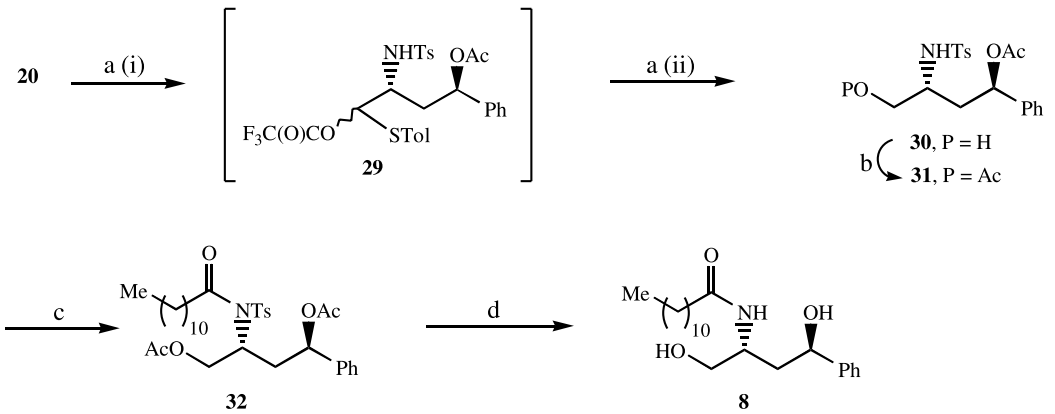
In the search for an alternative route for the construction of the piperidine ring on **11**, we zeroed in on the ring-closing metathesis (RCM) reaction.[18] The aminoalcohol **11**, on treatment with acetic anhydride yielded the acetate **20**. *N*-Alkylation of **20** with homoallyl nosylate **21**, yielded the compound **22** which on treatment with trifluoroacetic anhydride in the presence of Et_3N yielded the Pummerer intermediate **23**.[19] Hydrolysis of **23** with saturated aq. $NaHCO_3$ and treatment of the resulting aldehyde **24** with ethyl (triphenylphosphoranylidene)acetate yielded the (*E*)-ester **25** as the sole product. RCM reaction of **25** in the presence of 5 mol% of Grubbs' catalyst (first generation) proceeded uneventfully to yield **26** which was elaborated to allosedamine **7** using a straightforward sequence of reactions. It is noteworthy that an electron deficient olefin participates in the RCM reaction to afford the product cleanly.[20] Deprotection of the *p*-toluenesulfonyl group in **26** with Na–Hg[21] yielded alcohol **27** by concomitant deacetyl-ation. Subsequent reduction of the double bond by treatment with Pt/C under an atmosphere of hydrogen followed by reductive alkylation with aq. formaldehyde in the presence of sodium cyanoborohydride[22] yielded (−)-allosedamine **7**, with physical characteristics that were in good agreement to those reported in the literature[12d] (Scheme 5).

2.2. Synthesis of (1*R*,3*R*)-HPA-12

(1*R*,3*R*)-*N*-(3-Hydroxy-1-hydroxymethyl-3-phenylpropyl)-dodecanamide (HPA-12), **8** is an inhibitor of ceramide movement from the endoplasmic reticulum to the site of sphingomyelin synthesis and is a specific inhibitor of sphingomyelin synthesis in mammalian cells.[23] Kobayashi and co-workers have reported three routes to HPA-12, all of them exploiting the enantioselective Mannich reaction as



Scheme 5. Reagents and conditions: (a) Ac_2O, pyridine, DCM, rt, 4 h, 96%; (b) **21**, K_2CO_3, CH_3CN, reflux, 2 h, 90%; (c) (i) TFAA, Et_3N, CH_3CN, 0 °C, 50 min; (ii) aq. $NaHCO_3$, 0 °C, 20 min; (d) Ph_3PCHCO_2Et, PhH, rt, 30 min, 75% for two steps; (e) Grubbs' catalyst, toluene, reflux, 16 h, 80%; (f) Na–Hg, Na_2HPO_4, MeOH, reflux, 6 h, 78%; (g) H_2, Pt/C, AcOEt, rt, 3 h, 90%; (h) 37% aq. HCHO, $NaCNBH_3$, AcOH, CH_3CN, rt 4 h, 70%.



Scheme 6. Reagents and conditions: (a) (i) TFAA, 2,6-Lutidine, CH_3CN, 0 °C, 5 min; (ii) 20% aq. K_2CO_3, $NaBH_4$, 0 °C to rt, 15 min, 78%; (b) Ac_2O, pyridine, rt, 2 h, 97%; (c) Et_3N, DMAP, $C_{11}H_{23}COCl$, 0 °C to rt, 4 h, 91%; (d) Na-naphthalenide, DME, −20 °C, 2 min, K_2CO_3, 24 h, 55%.

the key step.[24] While the C–N bond was introduced with high selectivity, the diastereoselectivity of C–OH bond formation was modest. We describe herein a highly stereoselective route to HPA-12 using the acetate **20** as the key intermediate (Scheme 6). The Pummerer intermediate **29** without isolation was subjected to treatment with aq. K_2CO_3 and $NaBH_4$ to yield the alcohol **30**, which was protected as its acetate **31**. Treatment of **31** with dodecanoyl chloride in the presence of Et_3N and catalytic amounts of DMAP afforded the compound **32**. Reductive removal of the *p*-toluenesulfonyl group using freshly prepared sodium naphthalenide[25] led to the removal of the acetyl group during workup to yield (1*R*,3*R*)-HPA-12, which had physical characteristics in excellent agreement to that reported in the literature.[24a]

In conclusion, we have described a stereoselective route to (−)-allosedamine and (1*R*,3*R*)-HPA-12 using the bromosulfonamide **10** as the key intermediate. Efforts are in progress to prepare diastereomerically pure protected β-amino sulfoxide **2** and the results will be disclosed in the future.

3. Experimental

3.1. General

All air or moisture sensitive reactions were carried out under nitrogen atmosphere. Solvents were freshly distilled, THF over Na/benzophenone ketyl, DCM over P_2O_5 followed by CaH_2 and toluene over P_2O_5. Commercially available reagents were used without further purification except NBS, which was freshly recrystallized from hot water before use. Thin layer chromatography was performed with precoated silica gel plates. Column chromatography was carried out using silica gel (60–120 mesh). NMR spectra were recorded on a 200, 300 or 400 MHz spectrometer. ^1H NMR and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Melting points are uncorrected.

3.1.1. *N*-[3-Phenyl-(2*E*)-2-propenylidene]-4-methyl-1-benzenesulfonamide, 5. To a solution of cinnamaldehyde (1.32 g, 10 mmol) and *p*-toluenesulfonamide (1.71 g, 10 mmol) in benzene (60 mL) under reflux in a Dean and Stark apparatus was added $BF_3{\cdot}Et_2O$ (50 mg, 0.4 mmol). The reflux was continued for 2 h and the solution was cooled to 0 °C. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with cold 1 N NaOH (2×50 mL) solution. The organic layer was washed with water (75 mL), brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a solid that was crystallized from chloroform–petroleum ether to afford the imine **5**[15] (2.08 g, 7.3 mmol) as colorless crystals in 73% yield. Mp 202–204 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, J=9.4 Hz, 1H), 7.82 (d, J=8.3 Hz, 2H), 7.57–7.38 (m, 6H), 7.32 (d, J=8.3 Hz, 2H), 6.97 (dd, J=15.9, 9.4 Hz, 1H), 2.45 (s, 3H).

3.2. Experimental procedure for the reaction of anion generated from 4 with imine 5

Diisopropylamine (2.4 mL, 18 mmol) in THF (27 mL) was cooled at 0 °C and *n*-BuLi (9 mL, 2.0 M, 18 mmol) was added dropwise over 10 min. The reaction mixture was allowed to stir for 10 min at 0 °C and then cooled to −78 °C. (*R*)-Methyl *p*-tolylsulfoxide **4**, (1.85 g, 12 mmol) in THF (18 mL) was added dropwise via a syringe and stirred for 20 min at this temperature. A solution of the imine **5** (2.65 g, 12 mmol) in THF (12 mL) was added dropwise over a period of 5 min. After 15 min of stirring at −78 °C, the reaction mixture was quenched by the addition of aq. saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with ethyl acetate (75 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The diastereomeric sulfonamides **6*s*** and **6*a*** were separated by column chromatography using AcOEt/chloroform (23:2, v/v) as the eluent. The diastereomer **6*a*** eluted first followed by **6*s*** in 20 and 61% yields, respectively (combined yield 81%).

3.2.1. 4-Methyl-1-[2-(S_R)(4-methylphenylsulfonamido)-4-phenyl-(2*R*,3*E*)-3-butenylsulfinyl]benzene, 6*s*. Pale yellow solid. Mp 187–188 °C. 61% (2.6 g). ^1H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, J=8.2 Hz, 2H), 7.49 (d, J=8.2 Hz, 2H), 7.36–7.04 (m, 9H), 6.30 (d, J=15.6 Hz, 1H), 6.09 (d, J=5.9 Hz, NH), 5.88 (dd, J=15.6, 7.4 Hz, 1H), 4.43–4.26 (m, 1H), 3.11 (dd, J=13.4, 7.4 Hz, 1H), 2.89 (dd, J=13.4, 6.7 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 141.8, 141.4, 141.1, 131.9, 129.8, 129.2, 128.4, 127.8, 126.7, 126.5, 126.3, 125.6,

124.0, 62.2, 51.7, 20.9, 20.8. $[\alpha]_D^{25}=+75.0$ (*c* 0.7, $CHCl_3$). *m/z* LSIMS 440 $[M^+ +H]$. IR (neat) 3453, 1597, 1493, 1365, 1338, 1158 cm^{-1}. Anal. calcd For $C_{24}H_{25}NO_3S_2$: C, 65.58; H, 5.73; N, 3.19; S, 14.59. Found: C, 65.43; H, 5.65; N, 3.12; S, 14.51.

3.2.2. 4-Methyl-1-[2-(S_R)(4-methylphenylsulfonamido)-4-phenyl-(2*S*,3*E*)-3-butenylsulfinyl]benzene, 6*a*. Colorless solid. Mp 208–209 °C. 20% (853 mg). ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.2 Hz, 2H), 7.44 (d, *J*=8.2 Hz, 2H), 7.36–7.10 (m, 9H), 6.48 (d, *J*=6.7 Hz, NH), 6.41 (d, *J*=15.6 Hz, 1H), 6.03 (dd, *J*=15.6, 6.7 Hz, 1H), 4.58–4.42 (m, 1H), 2.94–2.85 (m, 2H), 2.43 (s, 3H), 2.33 (s, 3H). $[\alpha]_D^{25}=+91.8$ (*c* 1.5, $CHCl_3$). *m/z* LSIMS 440 $[M^+ +H]$. IR (neat) 3340, 1593, 1488, 1363, 1340, 1157 cm^{-1}.

3.2.3. *N*-[2-Bromo-3-hydroxy-1-(S_S)(4-methylphenylsulfinylmethyl)-3-phenyl-(1*S*,2*R*,3*S*)-propyl]-4-methyl-1-benzenesulfonamide, 10. To a solution of sulfoxide **6*s*** (3.07 g, 7 mmol) in toluene/chloroform (2:1, 35 mL) was added water (210 μL, 11.7 mmol) followed by *N*-bromosuccinimide (1.58 g, 8.4 mmol) and the reaction mixture stirred at room temperature for 1 h. Then the reaction mixture was quenched by the addition of aqueous saturated $NaHCO_3$ (10 mL) solution. The mixture was diluted with chloroform (40 mL) and the organic layer was washed with water (25 mL), brine (25 mL) and dried over Na_2SO_4. Evaporation of the solvent afforded the crude bromohydrin, which was purified by column chromatography using AcOEt/petroleum ether (7:13, v/v) as the eluent to yield bromohydrin **10** (3.15 g, 5.88 mmol) in 84% yield. Colorless solid. Mp 180–182 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.2 Hz, 2H), 7.48–7.24 (m, 11H), 5.32 (d, *J*=10.4 Hz, NH), 4.85 (dd, *J*=9.7, 5.2 Hz, 1H), 4.70–4.56 (m, 1H), 4.06 (d, *J*=9.7 Hz, 1H), 3.84 (d, *J*=5.2 Hz, OH), 3.01 (dd, *J*=13.4, 6.0 Hz, H), 2.68 (dd, *J*=13.4, 7.4 Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 143.2, 142.6, 141.4, 140.8, 138.6, 130.1, 129.8, 128.1, 127.9, 127.5, 127.0, 123.8, 73.6, 62.6, 61.9, 49.9, 21.2, 21.0. $[\alpha]_D^{25}=-38.8$ (*c* 1, acetone). *m/z* LSIMS 536 $[M+H]^+$. IR (neat) 3405, 3221, 1589, 1370, 1341, 1159 cm^{-1}. Anal. calcd for $C_{24}H_{26}BrNO_4S_2C$, 53.73; H, 4.88; N, 2.61; S, 11.95. Found: C, 53.69; H, 4.84; N, 2.62; S, 11.95.

3.2.4. *N*-[3-Hydroxy-1-(S_S)(4-methylphenylsulfinylmethyl)-3-phenyl-(1*R*,3*R*)-propyl]-4-methyl-1-benzenesulfonamide, 11. To a stirred solution of bromohydrin **10** (2.68 g, 5 mmol) in benzene (30 mL) were added successively at room temperature *n*-Bu_3SnH (1.53 g, 5.25 mmol) and AIBN (41 mg, 0.25 mmol). The solution was refluxed for 90 min when TLC examination revealed complete consumption of starting material. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using AcOEt/petroleum ether (2:3, v/v) as the eluent to afford the product **11** (1.73 g, 3.8 mmol) in 76% yield. Colorless solid. Mp 55–56 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, *J*=8.2 Hz, 2H), 7.32 (d, *J*=8.2 Hz, 2H), 7.26–7.11 (m, 9H), 6.86 (d, *J*=8.9 Hz, NH), 4.87 (d, *J*=8.9 Hz, 1H), 4.58–4.52 (m, 1H), 3.75 (bs, OH), 2.79–2.67 (m, 2H), 2.39 (s, 6H), 2.12–1.96 (m, 1H), 1.91–1.75 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 143.4, 142.0, 139.8, 137.6, 130.2, 129.7, 128.3, 127.3, 127.2, 125.5, 123.9, 70.0, 60.9, 49.0, 43.4, 21.4, 21.3. $[\alpha]_D^{25}=-63.7$ (*c* 1, acetone). *m/z* LSIMS 458 $[M+H]^+$. IR (neat) 3540, 3272, 1598, 1494, 1398, 1327, 1159 cm^{-1}. Anal. calcd for $C_{24}H_{27}NO_4S_2C$, 62.99; H, 5.95; N, 3.06; S, 14.07. Found: C, 63.03; H, 5.91; N, 3.05; S, 14.06.

3.2.5. 1-[4-*tert*-Butyldiphenylsilyloxy-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*,4*R*)-butyl-(S_S)-sulfinyl]-4-methylbenzene, 12. To a solution of the sulfoxide **11** (457 mg, 1 mmol) in dichloromethane (4 mL) was added imidazole (136 mg, 2 mmol) and TBDPS-Cl (275 mg, 1 mmol) at ambient temperature. The reaction mixture was stirred for 2 h at room temperature and solvent was removed under reduced pressure. The residue was diluted with ether (15 mL) and washed with water (2×10 mL), brine (10 mL), dried over Na_2SO_4 and evaporated to afford the crude product mixture. Purification on silica gel column using AcOEt/petroleum ether (3:17, v/v) as the eluent afforded the silyl ether **12** (557 mg, 0.8 mmol) in 80% yield. Viscous oil. ^1H NMR (200 MHz, $CDCl_3$) δ 7.72–7.60 (m, 4H), 7.57–6.97 (m, 17H), 6.79 (d, *J*=8.2 Hz, 2H), 5.94 (bs, NH), 4.70 (t, *J*=4.7 Hz, 1H), 3.32–3.26 (m, 1H), 2.92–2.85 (m, 2H), 2.47 (s, 3H), 2.45–2.42 (m, 4H), 2.25–2.18 (m, 1H), 1.06 (s, 9H). *m/z* LSIMS 696 $[M+H]^+$. IR (neat) 3522, 1585, 1491, 1398, 1335, 1155 cm^{-1}. Anal. calcd for $C_{40}H_{45}NO_4S_2Si$: C, 69.03; H, 6.52; N, 2.01; S, 9.21. Found: C, 68.83; H, 6.61; N, 2.08; S, 9.02.

3.2.6. 3-Trifluoromethanesulfonyloxypropyl trifluoromethanesulfonate, 14. To a solution of Tf_2O (5.64 g, 20 mmol) in dry dichloromethane (20 mL) cooled at 0 °C under nitrogen atmosphere was added 1,3-propanediol (760 mg, 10 mmol) via a syringe and stirred for 40 min. A solution of pyridine (1.58 g, 20 mmol) in dry dichloromethane (4 mL) was added to the above stirred solution over a period of 5 min and stirred further for a period of 1 h. The reaction mixture was allowed to attain room temperature over a period of 30 min and the solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate (20 mL) and washed successively with aq. $CuSO_4$ solution (2×20 mL), water (2×10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford **14** (2.71 g, 8 mmol) in 80% yield which was used in the next step without further purification. Liquid. ^1H NMR (200 MHz, $CDCl_3$) δ 4.67 (t, *J*=6.8 Hz, 4H), 2.33 (quintet, *J*=6.8 Hz, 2H).

3.3. General procedure for the dialkylation of 12 and 17

To a solution of sulfoxide **12** (35 mg, 0.05 mmol) in THF (0.5 mL) was added LDA (0.1 mL, 0.1 mmol, 1 M) dropwise at −78 °C. After stirring for 30 min at this temperature, a solution of diiodopropane (33 mg, 0.11 mmol) in THF (0.1 mL) was added dropwise, and stirring was continued. As the TLC revealed no reaction at −78 °C, the reaction mixture was warmed to −20 °C and stirred for 3 h. The reaction mixture was quenched by addition of saturated aq. NH_4Cl solution (0.2 mL) and extracted with ether (2×10 mL). The ether extracts were washed with brine (10 mL), dried and evaporated. Column chromatography on silica gel eluting with AcOEt/petroleum ether (1:9, v/v) afforded the products.

3.3.1. 1-[2-Allyl(4-methylphenyl)sulfonamido-4-(*tert*-butyldiphenylsilyloxy)-4-phenyl-(2*R*,4*R*)-butyl-(S_S)-sulfinyl]-4-methylbenzene, 15. 32% (12 mg). Low melting solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H), 7.46 (d, J=8.1 Hz, 2H), 7.40–7.08 (m, 19H), 5.56–5.42 (m, 1H), 4.82 (d, J=9.8 Hz, 1H), 4.57 (d, J=16.9 Hz, 1H), 4.27 (dd, J=9.8, 3.7 Hz, 1H), 3.86–3.73 (m, 1H), 3.58 (dd, J=15.4, 6.4 Hz, 1H), 3.51 (dd, J=15.4, 6.4 Hz, 1H), 3.32 (dd, J=15.1, 6.4 Hz, 1H), 2.78 (dd, J=15.1, 11.7 Hz, 1H), 2.49 (s, 3H), 2.43 (s, 3H), 2.12–1.96 (m, 2H), 0.98 (s, 9H). *m*/*z* LSIMS 758 $[M+Na]^+$. IR (neat) 2945, 2826, 1598, 1490, 1393, 1329, 1157 cm^{-1}. Anal. calcd for $C_{43}H_{49}NO_4S_2Si$: C, 70.17; H, 6.71; N, 1.90; S, 8.71. Found: C, 69.78; H, 6.33; N, 1.75; S, 8.56.

3.3.2. 4-(*tert*-Butyldiphenylsilyloxy)-1-(S_S)(4-methylphenylsulfinyl)-4-phenyl-(*E*)-1-(4*R*)-butene, 16. 16% (4 mg). Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73–7.62 (m, 2H), 7.47–7.18 (m, 17H), 6.27 (dt, J=15.8, 8.2 Hz, 1H), 5.93 (d, J=15.8 Hz, 1H), 4.71 (dd, J=7.6, 3.8 Hz, 1H), 2.40 (s, 3H), 2.12–1.96 (m, 2H), 0.98 (s, 9H). *m*/*z* LSIMS 524 $[M+H]^+$. IR (neat) 2848, 1595, 1498, 1357 cm^{-1}.

3.3.3. 1-[4-(*tert*-Butyldiphenylsilyloxy)-2-(4-methylphenylsulfonamido)-4-phenyl-(2*R*,4*R*)-butylsulfonyl]-4-methylbenzene, 17. To a solution of sulfoxide **12** (350 mg, 0.5 mmol) in chloroform (2 mL), *m*-CPBA (123 mg, 0.5 mmol, 60%) was added at 0 °C and the reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was diluted with chloroform (15 mL) and washed successively with 10% aq. sodium bisulfite solution (2×10 mL), 10% aq. sodium bicarbonate solution (2×10 mL), water (10 mL) and brine (10 mL). The reaction mixture was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford crude product. Column chromatography using AcOEt/petroleum ether (1:4, v/v) afforded sulfone **17** (330 mg, 0.47 mmol) in 93% yield. Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77–7.65 (m, 2H), 7.54–7.28 (m, 9H), 7.27–6.97 (m, 10H), 6.76 (d, J=8.2 Hz, 2H), 5.72 (d, J=5.9 Hz, NH), 4.80 (t, J=4.6 Hz, 1H), 3.63 (dd, J=13.4, 3.1 Hz, 1H), 3.24–3.13 (m, 1H), 2.77 (dd, J=13.4, 8.9 Hz, 1H), 2.48 (s, 6H), 2.46–2.40 (m, 1H), 2.14–2.07 (m, 1H), 0.97 (s, 9H). *m*/*z* LSIMS 712 $[M+H]^+$. IR (neat) 3522, 1597, 1498, 1398, 1347, 1171 cm^{-1}. Anal. calcd for $C_{40}H_{45}NO_5S_2Si$: C, 67.48; H, 6.37; N, 1.97; S, 9.01. Found: C, 67.03; H, 6.11; N, 2.05; S, 9.26.

3.3.4. 1-[2-Allyl(4-methylphenyl)sulfonamido-4-(*tert*-butyldiphenylsilyloxy)-4-phenyl-(2*R*,4*R*)-butylsulfonyl]-4-methylbenzene, 18. 30% (11 mg). Low melting solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78–7.60 (m, 4H), 7.54–7.13 (m, 19H), 5.49–5.28 (m, 1H), 4.75 (d, J=10.2 Hz, 1H), 4.59 (d, J=16.5 Hz, 1H), 4.24 (dd, J=7.9, 4.9 Hz, 1H), 3.90–3.72 (m, 1H), 3.56–3.50 (m, 1H), 3.42 (dd, J=15.4, 6.8 Hz, 1H), 3.21 (dd, J=15.1, 6.8 Hz, 1H), 2.62 (dd, J=15.1, 4.5 Hz, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.35–2.26 (m, 1H), 2.10–2.01 (m, 1H), 0.97 (s, 9H). *m*/*z* LSIMS 775 $[M+Na]^+$. IR (neat) 2956, 2843, 1591, 1398, 1333, 1171 cm^{-1}. Anal. calcd for $C_{43}H_{49}NO_5S_2Si$: C, 68.67; H, 6.57; N, 1.86; S, 8.53. Found: C, 68.43; H, 6.33; N, 1.75; S, 8.56.

3.3.5. 4-(*tert*-Butyldiphenylsilyloxy)-1-(4-methylphenylsulfonyl)-4-phenyl-(*E*)-1-(4*R*)-butene, 19. 14% (4 mg). Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73–7.62 (m, 2H), 7.47–7.18 (m, 17H), 6.27 (dt, J=15.7, 7.9 Hz, 1H), 5.93 (d, J=15.7 Hz, 1H), 4.79 (t, J=6.3 Hz, 1H), 2.47 (s, 3H), 2.37–2.04 (m, 2H), 0.98 (s, 9H). *m*/*z* LSIMS 541 $[M+H]^+$. IR (neat) 2867, 1592, 1334, 1167 cm^{-1}.

3.3.6. 3-Butenyl 4-nitro-1-benzenesulfonate, 21. To a solution of 3-buten-1-ol (360 mg, 5 mmol) in dry dichloromethane (20 mL) was added successively Et_3N (1.01 g, 10 mmol) and *p*-nitrobenzenesulfonyl chloride (1.11 g, 5 mmol) at room temperature under N_2. The reaction mixture was stirred for a period of 4 h. The reaction mixture was washed with water (10 mL), brine (10 mL) and evaporated to dryness under reduced pressure. The crude product mixture was chromatographed on silica gel using AcOEt/petroleum ether (1:4, v/v) as the eluent to afford the nosylate **21** (4 mmol) as a pale yellow solid in 80% yield. Mp 122 °C. ^{1}H NMR (200 MHz, $CDCl_3$) 8.42 (d, J=8.8 Hz, 2H), 8.19 (d, J=8.8 Hz, 2H), 5.78–5.55 (m, 1H), 5.18–5.05 (m, 2H), 4.21–4.11 (m, 2H), 2.51–2.36 (m, 2H). *m*/*z* LSIMS 258 $[M^+ + H]$.

3.3.7. 4-(S_S)(4-Methylphenylsulfinyl)-3-(4-methylphenylsulfonamido)-1-phenyl-(1*R*,3*R*)-butyl acetate, 20. To a stirred solution of **11** (1.37 g, 3 mmol) in dichloromethane (12 mL) were added successively pyridine (474 mg, 6 mmol) and acetic anhydride (331 mg, 3.25 mmol). The reaction mixture was stirred for 4 h and then diluted with dichloromethane (20 mL). The organic layer was washed successively with aqueous saturated $CuSO_4$ solution (2×15 mL), water (15 mL), 5% aq. $NaHCO_3$ solution (2×10 mL), water (10 mL), brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by column chromatography using AcOEt/petroleum ether (1:1, v/v) as the eluent afforded the acetate **20** (1.44 g, 2.88 mmol) in 96% yield. White solid. Mp 70–72 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, J=8.2 Hz, 2H), 7.36–7.13 (m, 11H), 6.16 (d, J=8.2 Hz, NH), 5.71 (dd, J=8.9, 4.5 Hz, 1H), 3.98–3.81 (m, 1H), 2.78 (d, J=5.2 Hz, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.41–2.14 (m, 2H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 143.3, 142.0, 139.9, 139.8, 137.9, 130.0, 129.7, 128.5, 128.0, 127.2, 126.1, 123.9, 72.4, 60.1, 48.3, 41.2, 21.4, 21.3, 21.0. $[\alpha]_D^{25}=-71.8$ (*c* 0.75, $CHCl_3$). *m*/*z* LSIMS 500 $[M+H]^+$. IR (neat) 3249, 1741, 1596, 1493, 1371, 1327, 1152 cm^{-1}. Anal. calcd for $C_{26}H_{29}NO_5S_2$: C, 62.50; H, 5.85; N, 2.80; S, 12.83. Found: C, 62.43; H, 5.91; N, 2.84; S, 12.80.

3.3.8. 3-[3-Butenyl(4-methylphenyl)sulfonamido)-4-(S_S)(4-methylphenylsulfinyl)-1-phenyl-(1*R*,3*R*)-butyl acetate, 22. Homoallyl nosylate **21** (566 mg, 2.2 mmol) was added to a stirred mixture of acetate **20** (1.1 g, 2.2 mmol) and K_2CO_3 (456 mg, 3.3 mmol) in dry acetonitrile (8.8 mL) and the reaction mixture was allowed to reflux for 2 h. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2×15 mL) followed by brine (15 mL) solution. After drying over Na_2SO_4, evaporation of the solvent under reduced pressure afforded the crude compound which on column chromatography using AcOEt/petroleum ether (3:7, v/v) as the eluent afforded the *N*-alkylated product **22** (1.1 g, 1.98 mmol) in 90% yield. Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67 (d,

J=8.2 Hz, 2H), 7.45 (d, J=8.2 Hz, 2H), 7.36–7.11 (m, 9H), 5.68–5.48 (m, 2H), 5.04–4.90 (m, 2H), 4.21–4.04 (m, 1H), 3.32–3.24 (m, 1H), 3.19–3.11 (m, 1H), 2.94 (dd, J=13.4, 7.4 Hz, 1H), 2.79 (dd, J=13.4, 6.7 Hz, 1H), 2.42 (s, 6H), 2.36–2.10 (m, 4H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 143.7, 141.7, 140.4, 139.8, 137.5, 134.2, 130.0, 129.8, 128.5, 128.1, 127.5, 126.3, 123.9, 117.2, 72.8, 62.5, 52.1, 47.1, 40.9, 34.1, 21.5, 21.4, 21.0. $[\alpha]_D^{25}=-45.5$ (c 2.2, $CHCl_3$). m/z LSIMS 554 [M^++H]. IR (neat) 2977, 1752, 1595, 1488, 1449, 1337, 1142, 1083 cm^{-1}. Anal. calcd for $C_{30}H_{35}NO_5S_2$: C, 65.07; H, 6.37; N, 2.53; S, 11.58. Found: C, 65.43; H, 5.75; N, 2.21; S, 12.01.

3.3.9. Ethyl 4-[3-butenyl(4-methylphenyl)sulfonamido]-6-acetoxy-6-phenyl-(*E*,4*R*,6*R*)-2-hexenoate, 25. To a solution of the *N*-homoallyl compound **22**, (664 mg, 1.2 mmol) in acetonitrile (6 mL) cooled at 0 °C was added triethylamine (364 mg, 3.6 mmol) followed by trifluoroacetic anhydride (1.26 g, 6 mmol) and the mixture stirred for 50 min. An aq. 5% $NaHCO_3$ solution (2 mL) was added at 0 °C and stirred for another 20 min. The reaction mixture was then extracted into benzene (10 mL) and washed successively with water (5 mL), brine (5 mL) and dried over Na_2SO_4. The benzene solution of the aldehyde was directly taken ahead to the next step and reacted with ethyl (triphenylphosphoranylidene)acetate (498 mg, 1.2 mmol). The reaction was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford a residue which was purified by column chromatography using EtOAc/petroleum ether (1:9) as the eluent to afford the α,β-unsaturated ester **25** (449 mg, 0.9 mmol) in 75% yield (for the two steps). Pale yellow solid. Mp 59–61 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63 (d, J=8.2 Hz, 2H), 7.39–7.20 (m, 7H), 6.54 (dd, J=15.6, 5.2 Hz, 1H), 5.76–5.56 (m, 3H), 5.08–4.93 (m, 2H), 4.64–4.47 (m, 1H), 4.12 (q, J=6.7 Hz, 2H), 3.18 (ddd, J=15.6, 11.1, 5.9 Hz, 1H), 2.92 (ddd, J=15.6, 10.4, 5.9 Hz, 1H), 2.56–2.16 (m, 6H), 2.06–1.91 (m, 4H), 1.24 (t, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 165.9, 144.7, 144.0, 140.1, 137.5, 134.8, 130.2, 129.1, 128.7, 127.7, 126.8, 124.3, 117.7, 73.0, 61.0, 55.8, 45.2, 39.5, 36.0, 21.9, 21.5, 14.6. $[\alpha]_D^{25}=+58.7$ (c 2.25, $CHCl_3$). m/z LSIMS 500 [M^++H]. IR (neat) 2957, 2887, 1745, 1590, 1498, 1450, 1343, 1140, 1078 cm^{-1}. Anal. calcd for $C_{27}H_{36}NO_6S$: C, 64.91; H, 6.66; N, 2.80; S, 6.42. Found: C, 65.08; H, 6.85; N, 2.71; S, 6.46.

3.3.10. 2-[1-(4-Methylphenylsulfonyl)-(2*R*)-1,2,5,6-tetrahydropyridin-2-yl]-1-phenyl-(1*R*)-ethyl acetate, 26. Bis-(tricyclohexylphosphine)benzylideneruthenium(IV)dichloride $\mathbf{G_1}$ (25 mg, 0.032 mmol) was added to a solution of diene **25** (324 mg, 0.65 mmol) in toluene and refluxed for 16 h, when TLC revealed the complete consumption of the starting material. The solvent was removed under reduced pressure. Column chromatography using EtOAc/petroleum ether (1:4, v/v) as the eluent afforded the product **26** (207 mg, 0.52 mmol) in 80% yield. Pale yellow solid. Mp 75–76 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67 (d, J=8.9 Hz, 2H), 7.36–7.16 (m, 7H), 5.74 (dd, J=9.7, 4.5 Hz, 1H), 5.66–5.54 (m, 2H), 4.54–4.41 (m, 1H), 3.77 (dd, J=14.9, 5.2 Hz, 1H), 3.08 (ddd, J=14.9, 11.9, 5.2 Hz, 1H), 2.42 (s, 3H), 2.20–1.60 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 143.2, 140.5, 138.1, 129.5, 128.5, 128.0, 127.3, 127.2, 126.5, 125.5, 72.7, 50.2, 41.4, 38.0, 29.7, 21.5, 21.2. $[\alpha]_D^{25}=-119.0$ (c 0.75, $CHCl_3$). m/z LSIMS 400 [M+H]$^+$. IR (neat) 3032, 2925, 2853, 1744, 1598, 1494, 1374, 1345, 1159, 1096 cm^{-1}. Anal. calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51; S, 8.02. Found: C, 66.03; H, 6.55; N, 3.41; S, 8.07.

3.3.11. 2-[(2*R*)-1,2,5,6-Tetrahydropyridin-2-yl]-1-phenyl-(1*R*)-ethan-1-ol, 27. Freshly prepared Na–Hg (6%, 150 mg) was added to a well-stirred mixture of **26** (179 mg, 0.45 mmol) and anhydrous Na_2HPO_4 (319 mg, 2.25 mmol) in methanol (9 mL) at room temperature and allowed to reflux for 6 h. The reaction mixture was quenched with water (3 mL) and extracted into ethyl acetate (2×15 mL). The organic layer was washed with brine (15 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was chromatographed on a small pad of silica gel using CH_2Cl_2: MeOH (50:1 then 1:10, v/v) as the eluent to afford **27** (71 mg, 0.35 mmol) in 78% yield. Viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.12 (m, 5H), 5.97–5.82 (m, 1H), 5.58–5.44 (m, 1H), 5.12–4.96 (m, 1H), 4.04–3.88 (m, 1H), 3.43–3.24 (m, 1H), 3.03–2.83 (m, 1H), 2.56–1.85 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 128.3, 127.1, 126.3, 125.4, 69.4, 51.1, 41.3, 40.3, 29.6. $[\alpha]_D^{25}=-39.1$ (c 0.8, $CHCl_3$). m/z LSIMS 204 [M^++H]. IR (neat) cm^{-1} 3331, 2972, 2845, 1591, 1494. Anal. calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.57; H, 8.15; N, 6.66.

3.3.12. 1-Phenyl-2-[(6*S*)-tetrahydro-6-piperidin-2-yl]-(1*R*)-ethan-1-ol, 28. To a solution of **27** (15 mg, 0.075 mmol) in ethyl acetate (1.5 mL) was added Pt/C (5 mg, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere for 3 h. The reaction mixture was filtered through celite and evaporated to dryness under reduced pressure to afford **28** (14 mg, 0.068 mmol) in 90% yield. Viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.18 (m, 5H), 5.22 (bd, J=7.4 Hz, 1H), 3.44 (bd, J=11.7 Hz, 1H), 3.36–3.21 (m, 1H), 2.91–2.71 (m, 1H), 2.42–2.22 (m, 1H), 2.04–1.66 (m, 6H), 1.51–1.32 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 22.5, 29.6, 42.1, 44.9, 54.4, 68.4, 125.5, 127.2, 128.4, 143.6. $[\alpha]_D^{25}=-28.1$ (c 0.2, methanol). m/z EI 206 [M^++H]. Anal. calcd for $C_{13}H_{19}NO$, C, 76.06; H, 9.33; N, 6.82. Found: C, 76.57; H, 9.15; N, 6.66.

3.3.13. 2-[1-Methyl-(6*S*)-tetrahydro-6-piperidin-2-yl]-1-phenyl-(1*R*)-ethan-1-ol, 7. To a solution of the substrate **28** (12 mg, 0.06 mmol) in acetonitrile (0.9 mL) was added 37% aq. HCHO (0.28 mL, 3.43 mmol), AcOH (20 μL) and $NaCNBH_3$ (19 mg, 0.33 mmol). The resulting reaction mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. The residue was extracted into dichloromethane (2×10 mL) and the solvent was evaporated under reduced pressure. Column chromatography using MeOH/DCM (first with 1:10 v/v then methanol alone) as the eluent afforded the product **7** in 70% yield as a solid. Mp 78–80 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.21 (m, 5H), 5.10 (dd, J=10.4, 3.4 Hz, 1H), 3.02 (d, J=10.4 Hz, 1H), 2.46 (s, 3H), 2.45–3.32 (m, 1H), 2.17 (ddd, J=14.9, 10.9, 4.3 Hz, 1H), 1.96–1.53 (m, 6H), 1.32–1.20 (m, 2H). $[\alpha]_D^{25}=-28.8$ (c 0.4, MeOH) [lit.[12d] $[\alpha]_D^{25}=-29.8$ (c 0.2, MeOH)]. m/z LSIMS 220 [M+H]$^+$.

3.3.14. 4-Hydroxy-3-(4-methylphenylsulfonamido)-1-phenyl-(1*R*,3*R*)-butyl acetate, 30. To a stirred solution of **20** (1.05 g, 2.1 mmol) and dry 2,6-lutidine (674 mg, 6.3 mmol) in acetonitrile (15 mL) under a nitrogen atmosphere at 0 °C, neat trifluoroacetic anhydride (1.5 mL, 10.5 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 5 min. Aq. 20% K_2CO_3 solution was added to adjust pH to 7. Then $NaBH_4$ (400 mg, 10.5 mmol) was added portionwise and the reaction mixture allowed to attain room temperature. After 15 min the reaction was quenched with an aqueous saturated ammonium chloride solution (5 mL). The reaction mixture was extracted with ethylacetate (2×15 mL) and the collected organic layers dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification on a silica gel column using acetone/petroleum ether (1:4, v/v) afforded the β-amino alcohol **29** (617 mg, 1.64 mmol) in 78% yield. Solid. Mp 159–161 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69 (d, J=8.2 Hz, 2H), 7.34–7.12 (m, 7H), 7.01 (d, J=8.2 Hz, NH), 5.60 (dd, J=10.4, 4.4 Hz, 1H), 4.13–4.04 (m, 1H), 3.38–3.16 (m, 2H and 1-OH), 2.44 (s, 3H), 2.09–1.72 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 142.6, 141.6, 138.9, 129.7, 128.5, 127.5, 126.4, 125.6, 72.1, 63.7, 51.7, 38.1, 21.1, 20.8. $[\alpha]_D^{25}$=+13.6 (*c* 0.6, acetone). *m/z* LSIMS 378 $[M+H]^+$. IR (neat) 3421, 3249, 1745, 1598, 1496, 1152 cm^{-1}. Anal. calcd for $C_{19}H_{23}NO_5S$: C, 60.46; H, 6.14; N, 3.71; S, 8.49. Found: C, 60.48; H, 6.03; N, 3.79; S, 8.33.

3.3.15. 4-Acetoxy-3-(4-methylphenylsulfonamido)-1-phenyl-(2*R*,4*R*)-butyl acetate, 31. To a stirred solution of **30** (377 mg, 1 mmol) in dichloromethane (4 mL) was added successively pyridine (158 mg, 2 mmol) and acetic anhydride (122 mg, 1.1 mmol) at room temperature under N_2. The reaction mixture was stirred for a period of 2 h at room temperature. The reaction mixture was then diluted with dichloromethane (16 mL) and washed sequentially with aq. saturated $CuSO_4$ solution (2×10 mL), water (10 mL), aq. 5% $NaHCO_3$ solution (2×10 mL), water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure followed by purification on a silica gel column using AcOEt/petroleum ether (1:3, v/v) as the eluent afforded the diacetate **31** (406 mg, 0.97 mmol) in 97% yield. Viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, J=8.2 Hz, 2H), 7.48–7.12 (m, 7H), 5.68 (dd, J=9.7, 4.5 Hz, 1H), 5.58 (d, J=8.9 Hz, NH), 4.0–3.84 (m, 2H), 3.76–3.52 (m, 1H), 2.44 (s, 3H), 2.12–1.80 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.8, 143.6, 140.0, 137.7, 129.8, 128.6, 128.1, 127.0, 126.2, 72.6, 65.7, 49.8, 39.2, 21.5, 21.0, 20.6. $[\alpha]_D^{25}$=+11.4 (*c* 0.75, $CHCl_3$). *m/z* LSIMS 420 $[M+H]^+$. IR (neat) 3324, 1754, 1590, 1493, 1148 cm^{-1}. Anal. calcd for $C_{21}H_{25}NO_6S$: C, 60.13; H, 6.01; N, 3.34; S, 7.64. Found: C, 60.43; H, 5.91; N, 2.94; S, 7.80.

3.3.16. 2-Dodecanoyl-(4-methylphenyl)sulfonamido-4-acetoxy-4-phenyl-(2*R*,4*R*)-butyl acetate, 32. A solution of dodecanoyl chloride (110 mg, 0.5 mmol) in dichloromethane (0.25 mL) was added dropwise to a mixture of the diacetate **31** (210 mg, 0.5 mmol), Et_3N (101 mg, 1 mmol) and DMAP (cat.) in dichloromethane (1.5 mL) at 0 °C under N_2. The reaction mixture was gradually allowed to attain room temperature and stirred further for a period of 4 h. The reaction mixture was diluted with dichloromethane (10 mL) and washed successively with water (2×5 mL), 10% aq. citric acid solution (5 mL), brine (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel with AcOEt/petroleum ether (1:9, v/v) to afford the amide **31** (274 mg, 0.46 mmol) in 91% yield. Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, J=8.2 Hz, 2H), 7.40–7.22 (m, 7H), 5.57 (dd, J=9.7, 4.5 Hz, 1H), 4.73–4.58 (m, 1H), 4.50–4.32 (m, 2H), 2.60–2.16 (m, 7H), 2.11 (s, 3H), 2.0 (s, 3H), 1.71–1.11 (m, 18H), 0.88 (t, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 170.5, 170.2, 144.9, 140.2, 137.2, 129.9, 128.6, 128.1, 127.7, 126.3, 73.4, 64.2, 56.0, 38.3, 31.9, 29.6, 29.4, 29.2, 29.0, 28.9, 24.7, 22.6, 21.6, 21.2, 20.8, 14.1. $[\alpha]_D^{25}$=+9.66 (*c* 2.0, acetone). *m/z* LSIMS 542 $[M-OAc]^+$. Anal. calcd for $C_{33}H_{47}NO_7S$: C, 65.86; H, 7.87; N, 2.33; S, 5.33. Found: C, 65.66; H, 7.42; N, 2.13; S, 5.47.

3.3.17. *N*-[3-Hydroxy-1-hydroxymethyl-3-phenyl-(1*R*,3*R*)-propyl]dodecanamide, 8. To the substrate **31** (30 mg, 0.05 mmol) in dimethoxyethane (0.5 mL) was added freshly prepared Na-naphthalenide in dimethoxyethane (the solution of sodium naphthalenide in dimethoxyethane was prepared by adding dimethoxyethane (10 mL) to a mixture of Na (300 mg, 13 mmol) and naphthalene (2.05 g, 16 mmol) and stirring the mixture at room temperature for 2 h) at −20 °C under nitrogen atmosphere until light green color persisted (ca 2 min). The reaction mixture was quenched by the addition of water (1 mL). Solid K_2CO_3 (140 mg) was added and the reaction mixture stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was extracted into ethylacetate (2×5 mL). Column chromatography using hexane/isopropylalcohol (4:1, v/v) afforded the product **30** (10 mg, 0.27 mmol) in 55% yield. Solid. Mp 76–78 °C [lit.[24a] mp 75.5–77 °C]. ^{1}H NMR (200 MHz, $CDCl_3$) 7.40–7.12 (m, 5H), 6.19 (d, J=5.9 Hz, NH), 4.62 (bd, J=7.5 Hz, 1H), 4.19–4.08 (m, 1H), 3.77–3.62 (m, 2H), 2.31–2.13 (m, 2H), 1.68–1.45 (m, 2H), 1.42–1.20 (m, 18H), 0.86 (t, J=6.7 Hz, 3H). $[\alpha]_D^{25}$=−36.6 (*c* 0.56, $CHCl_3$) [lit.[24a]=−35.1 (*c* 0.8, $CHCl_3$)].

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