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Stereoselective synthesis of (−)-allosedamine ☆

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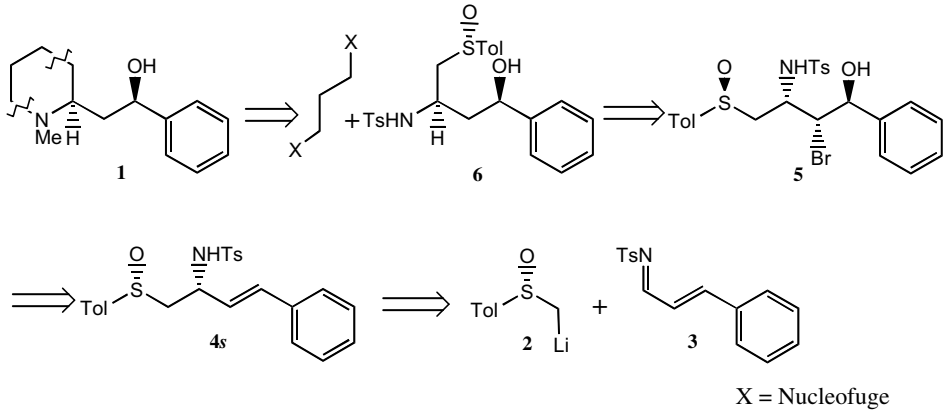
Abstract—A stereoselective synthesis of (−)-allosedamine is disclosed. β-Aminosulfoxide **4** was generated stereoselectively by condensation of the sulfinyl anion **2** with *N*-Ts imine **3**. The bromohydrin **5** was obtained by intramolecular sulfinyl group participation and the piperidine ring of allosedamine was elaborated using the ring-closing metathesis (RCM) reaction.

The alkaloid (−)-allosedamine **1**, was isolated[1] from *Lobelia inflata*, the crude extract of which has been used for the treatment of respiratory disorders such as asthma, bronchitis and pneumonia. Although several syntheses of the racemic alkaloid have been reported,[2] stereoselective asymmetric syntheses are few in number.[3] We report herein a stereoselective route to (−)-allosedamine, the key steps of which include, the diastereoselective condensation of the anion **2**, derived from (*R*)-methyl *p*-tolyl sulfoxide with an imine **3** and stereo- and regioselective preparation of the bromohydrin **5** from the resulting β-aminosulfoxide **4** (Scheme 1).

In contrast to the numerous reports on the addition of α-sulfinyl carbanions to aldehydes,[4] the addition of these carbanions to imines has received less attention.[5] Except for one report on the addition of the carbanion derived from (*S*)-*tert*-butyl phenyl methyl sulfoxide to an imine derived from an unsaturated aldehyde,[6] most of the literature reports are concerned with the addition of sulfoxide anions to imines derived from aromatic aldehydes.[7]

The addition of the anion **2** with imine **3**[8] afforded a mixture of adducts **4**. Kagan has noted the importance



Scheme 1.

Keywords: Allosedamine; β-Aminosulfoxide; Bromohydrin; Pummerer reaction; Ring-closing metathesis reaction.
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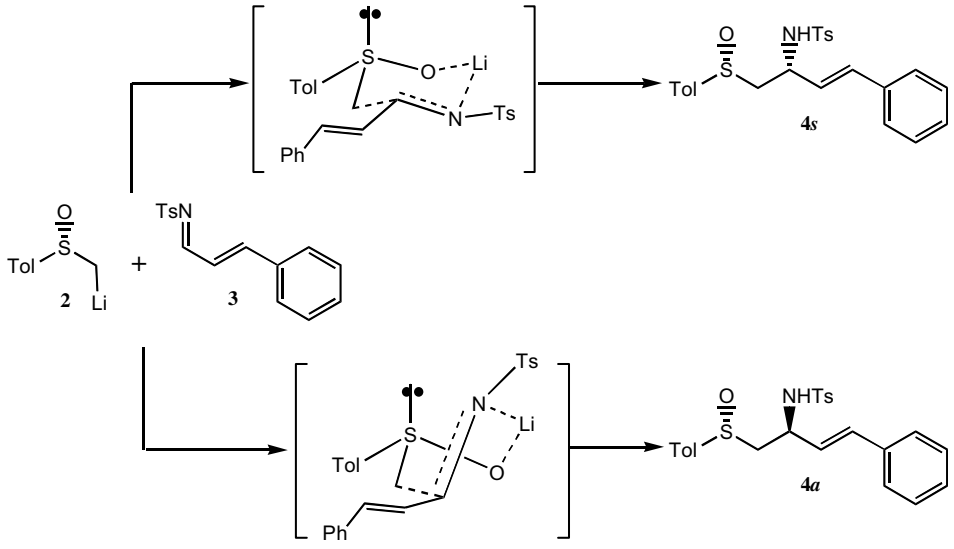
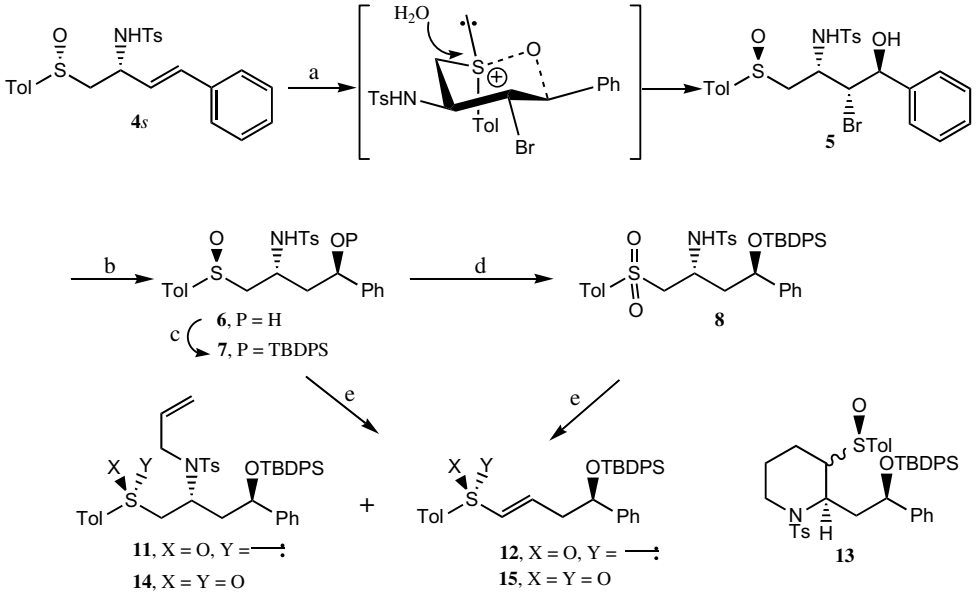


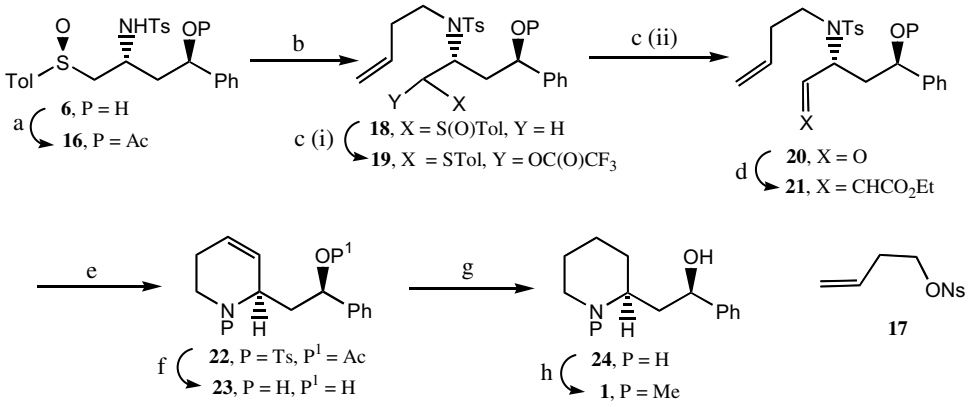
Scheme 2. Reagents and conditions: LDA, THF, −78 °C, add **2**, 20 min, then add **3**, 15 min, 81%.

of reaction temperature in determining the product diastereoselection.[5b] Thus anion generation at −78 °C and condensation at −78 °C afforded the best diastereoselection (3:1 of **4***s*:**4***a*) in 81% yield. The diastereomeric β-aminosulfoxides could be readily separated by column chromatography and the structure was assigned to them based on their ^{1}H NMR spectra (Scheme 2).[9]

The hydroxy group of allosedamine was introduced stereo- and regioselectively via bromohydration of **4***s* using the sulfinyl group as the intramolecular nucleophile to yield **5**.[10] The relative disposition of the heteroatoms at C2–C4 in **5** was unambiguously proven by tetrahydrofuran ring formation by a Pummerer type reaction promoted by *t*-butyldiphenylchlorosilane in anhydrous DMF.[11] The bromine atom in **5** was removed using *n*-Bu_3SnH to yield the 1,3-aminoalcohol **6**. The piperidine ring was envisaged to be elaborated by dialkylation at C_1 and N using a suitable dielectrophile.[12] Thus **6** was protected as its silyl ether **7** by treatment with *t*-butyldiphenylchlorosilane and imidazole in dichloromethane as the solvent. Subjecting the dianion (1,3-dinucleophile), derived from compound **7** by treatment with LDA in THF, to treatment with 1,3-diiodopropane **9** or 1,3-propanediol ditriflate **10** in the presence/absence of HMPA afforded varying amounts of *N*-allylated **11** and β-elimination product **12**[12] with no traces of the piperidine derivative **13** to be detected. Attempted alkylation of the dianion from sulfone **8**, derived from sulfoxide **7** by treatment with *m*-CPBA, with 1,3-diiodopropane or 1,3-propanediol ditriflate afforded varying amounts of the *N*-allylated sulfone **14** and β-elimination product **15** (Scheme 3).



Scheme 3. 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, 1 h, 78%. (d) *m*-CPBA, $CHCl_3$, 0 °C, 10 min, 89%. (e) *n*-BuLi, HMPA, $I(CH_2)_3$ **9** or $TfO(CH_2)_3OTf$ **10**, THF, −78 to −20 °C, 2 h.



Scheme 4. Reagents and conditions: (a) Ac_2O, pyridine, DCM, rt, 4 h, 96%. (b) **17**, 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) $\mathbf{G_I}$, toluene, reflux, 16 h, 80%. (f) Na–Hg, Na_2HPO_4, MeOH, reflux, 6 h, 78%. (g) H_2, Pt/C, AcOEt, rt, 4 h, 95%. (h) 37% aq HCHO, $NaCNBH_3$, AcOH, CH_3CN, rt, 4 h, 70%.

The piperidine ring was successfully elaborated by a ring-closing metathesis reaction.[13] *N*-Alkylation of **16**, derived from alcohol **6**, with the nosylate **17**, afforded compound **18**. Sulfoxide **18** on treatment with trifluoroacetic anhydride in the presence of Et_3N, underwent Pummerer rearrangement[14] to yield the intermediate **19**, which on hydrolysis by treatment with aq saturated sodium bicarbonate yielded the aldehyde **20**. The aldehyde **20**, without purification was subjected to Wittig olefination with ethyl(triphenylphosphoranylidene)acetate to yield the *trans* ester **21** exclusively.[15] Ester **21** was subjected to RCM reaction[16] using 5 mol% of Grubbs' catalyst ($\mathbf{G_I}$) to yield compound **22**.[17] Deprotection of the *N*-Ts group by treatment of **22** with Na–Hg[18] afforded alcohol **23** by concomitant deacetylation. Reduction of double bond by treatment of **23** with Pt/C under an atmosphere of hydrogen afforded nor-allosedamine **24**, which was transformed into (−)-allosedamine **1**, by reductive alkylation with formaldehyde in the presence of sodium cyanoborohydride (Scheme 4).[19] The synthetic allosedamine prepared as detailed above had physical characteristics that were in good agreement with those reported in the literature[3d] ($[\alpha]_D^{25}$ −28.8° (*c* 0.4, MeOH), lit.[3d] $[\alpha]_D^{20}$ −29.8° (*c* 0.2, MeOH)).

In summary we have disclosed a stereoselective synthesis of allosedamine. The key steps include (a) diastereoselective condensation of the sulfinyl anion with an imine, (b) regio- and stereoselective bromohydration of an olefin using the sulfinyl moiety as the intramolecular nucleophile, (c) RCM reaction to elaborate the piperidine ring.

Acknowledgements

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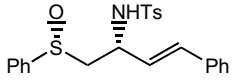
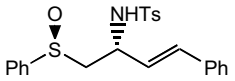
9. The structures were assigned to **4***s* and **4***a* by comparison of their ^{1}H NMR data with sulfoxides **25***s* and **25***a*. The structure of **25***s* was unambiguously assigned by X-ray crystallography of the related *p*-nitrobenzenesulfonamide derivative. Refer: Raghavan, S.; Rajender, A.; Joseph, S. C.; Rasheed, M. A.; Ravikumar, K. *Tetrahedron: Asymmetry* **2004**, *15*, 365.



25*s*



25*a*

Compound	C_2H δ (ppm)	Compound	C_2H δ (ppm)
25*s*	4.38	**4***s*	4.36
25*a*	4.52	**4***a*	4.51

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13. For excellent review, refer to (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036; (b) Schuster, M.; Blechret, S. *Angew. Chem.* **1997**, *109*, 2124; (c) Furstner, A. *Top. Catal.* **1997**, *4*, 285; (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.
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15. Representative procedure for compound **21**. To the solution of **18** (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 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 with benzene (10 mL), washed successively with water, brine, dried over Na_2SO_4 and used directly in the next step. Reaction with ethyl(triphenylphosphoranilidine)acetate (498 mg, 1.2 mmol) at rt for 30 min afforded the unsaturated ester. The solvent was removed under reduced pressure to afford the residue, which was purified by column chromatography using EtOAc/petroleum ether (1:9, v/v) as the eluent to afford the α,β-unsaturated ester **21** (449 mg, 0.9 mmol) in 75% yield (for the two steps). Solid. Mp 59–61 °C. $[\alpha]_D^{25}$ +58.7° (*c* 2.3, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.63 (d, $J = 8.2$ Hz, 2H), 7.39–7.2 (m, 7H), 6.54 (dd, $J = 15.6$, 5.2 Hz, 1H), 5.76–5.56 (m, 3H), 5.08–4.93 (m, 2H), 4.56 (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 (ppm) 14.6, 21.5, 21.9, 36.0, 39.5, 45.2, 55.8, 61.0, 73.0, 117.7, 124.3, 126.8, 127.7, 128.7, 129.1, 130.2, 134.8, 137.5, 140.1, 144.0, 144.7, 165.9. MS (FAB) 500 $[M+H]^+$. 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.
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17. Representative procedure for compound **22**. Bis(tricyclohexylphophine) benzylideneruthenium(IV)dichloride $\mathbf{G_1}$ (25 mg, 0.032 mmol) was added to a solution of diene (324 mg, 0.65 mmol) in toluene (13 mL) and refluxed for 16 h, when TLC revealed the complete consumption of the starting material. The solvent was removed under reduced pressure. Column chromatography of the residue using EtOAc/petroleum ether (1:4, v/v) as the eluent afforded the product (207 mg, 0.52 mmol) in 80% yield. Solid. Mp 75–76 °C. $[\alpha]_D^{25}$ −119.0° (*c* 0.75, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 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), 4.48 (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 (ppm) 21.2, 21.5, 29.7, 38.0, 41.4, 50.2, 72.7, 125.5, 126.5, 127.2, 127.3, 128.0, 128.5, 129.5, 138.1, 140.5, 143.2, 170.1. MS (FAB) 400 $[M+H]^+$. Anal. Calcd for $C_{27}H_{25}NO_4S$: 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.
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