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Enantiospecific and stereoselective synthesis of (−)-allosedamine

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Abstract—A total synthesis of (−)-allosedamine (>99% ee, de) is described in 14 steps with an overall yield of 29% from benzaldehyde.

(−)-Allosedamine **13** has been isolated from *Lobelia inflata* (also known as Indian tobacco).[1] Although the crude extract is toxic, it has been used for the treatment of respiratory illnesses such asthma, bronchitis and pneumonia.[2] As little is known about the biological properties of **13**, we were interested to develop a novel route to (−)-allosedamine **13** which could also be adapted for the preparation of its analogues in order to investigate structure–activity relationships. To our knowledge, only one enantiomeric[3] synthesis of this alkaloid has been reported.

The synthetic sequence starting from benzaldehyde is depicted in Scheme 1. Brown's asymmetric allylation[4] of benzaldehyde with *B*-allyldiisopinocampheylborane, prepared from (+)-*B*-chlorodiisopinocampheylborane ((+)-Ipc_2BCl) and allylmagnesium bromide, afforded the chiral homoallylic alcohol (*R*)-**2** in 85% yield and 94.8% ee[5] (best value). In our opinion, an improvement of the ee was necessary, so we turned our attention to a synthesis of enantiopure (*R*)-**2**, based on the enantioselective reduction of the carbonyl of **1**. The β,γ-unsaturated ketone **1** was obtained by treatment of benzaldehyde with an excess of allylzinc bromide followed by oxidation with the Dess–Martin periodinane reagent (DMP).[6] In order to save one step, we attempted without success the direct preparation of ketone **1** from benzoyl chloride. Thus, treatment of benzoyl chloride with various allyl reagents afforded mixtures of the desired adduct, recovered starting material and the corresponding tertiary alcohol. The enantioselective reduction of the stable β,γ-unsaturated ketone **1** with (+)-Ipc_2BCl[7] proceeded smoothly in THF at −35°C.[8] The enantiomerically pure (>99% ee[5]) homoallylic alcohol (*R*)-**2** was obtained in good yield (80%) from benzaldehyde, in a multigram sequence requiring no purification of the intermediates. The next step was the stereoselective epoxidation of the C–C double bond of homoallylic alcohol (*R*)-**2**. The initial homoallylic epoxidation of **2** using Sharpless' procotol[9] with *tert*-butyl hydroperoxide in the presence of vanadium acetylacetonate led to the desired epoxyalcohol **5** in moderate yield (73%) with low (<4:1) selectivity. To achieve this transformation with an excellent level of diastereoselectivity, we used a sequence reported by Cardillo and al.[10] Following their procedure, the homoallylic *tert*-butyl carbonate **3** was prepared from the corresponding alcohol **2** via deprotonation with *n*-BuLi followed by treatment with Boc-ON (2-(*tert*-butoxycarbonyl)oxy)-imino)-2-phenylacetonitrile).[11]

Then, diastereoselective iodine-induced electrophilic cyclization of the homoallylic *tert*-butyl carbonate **3** was carried out by simple treatment with IBr at low temperature (−85°C) to furnish the corresponding iodocarbonate **4**,[12] which under basic conditions led to the desired epoxyalcohol **5**,[13] as a single diastereoisomer (as judged by ^1H and ^{13}C NMR spectral analysis of the crude reaction mixture) in 73% overall yield for the three steps.

The epoxyalcohol **5** was protected as its *tert*-butyldimethylsilyl (TBS) ether **6**. Regioselective copper-mediated Grignard allylation of the epoxide **6** afforded the compound **7** in high yield (91%).[14] Replacement of the free hydroxy group of **7** by a *N*-Me functionality to give **9** was carried out in an acceptable overall yield (73%) with total inversion of configuration through the nucleophilic displacement of the corresponding mesylate **8** by methylamine.[15] Other classical methods of introducing the nitrogen functionality with the requisite

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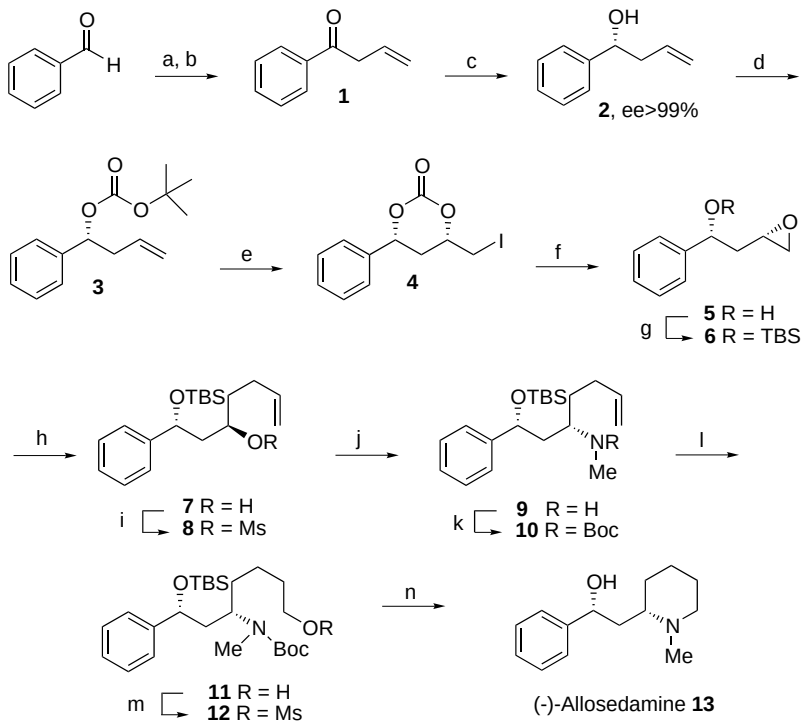

Scheme 1. *Reagents and conditions*: (a) allylbromide, Zn, THF, rt, 1 h, 98%; (b) DMP, CH_2Cl_2, rt, 1 h, 97%; (c) (+)-Ipc_2BCl, THF, −35°C, 12 h, 84%; (d) *n*-BuLi, Et2O, −78°C, 30 min then Boc-ON, THF, 0°C to rt, 2 h, 90%; (e) IBr, toluene, −85°C, 1 h, 85%; (f) K_2CO_3, MeOH, rt, 2 h, 96%; (g) TBDMSCl, Et_3N, DMAP, DMF, rt, 3 h, 96%; (h) AllylMgBr, CuI, Et_2O, −40°C, 30 min, 91%; (i) MsCl, Et_3N, CH_2Cl_2, 0°C, 10 min, 88%; (j) $MeNH_2$, DMF, H_2O, 60°C, 20 h, 83%; (k) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 6 h, 95%; (l) Cy_2BH, CH_2Cl_2, 0°C, to rt, 6 h, then H_2O_2, NaOH, 0°C to rt, 1 h, 90%; (m) MsCl, Et_3N, CH_2Cl_2, 0°C, 40 min, 95%; (n) 1% HCl conc., MeOH, 60°C, 3 h, 94%.

stereochemistry failed. On standard Mitsunobu reaction with alcohol **7**, diethyl azodicarboxylate (DEAD), triphenylphosphine and phthalimide, the expected *N*-phtalimide was obtained in 70% yield, but its hydrolysis to the corresponding amine failed. On the other hand, the same reaction carried on with diphenylphosphoryl azide (DPPA) afford the corresponding azide which spontaneously decomposed via an intramolecular 1,3-dipolar cycloaddition.[16]

At this point of the synthesis, it seemed appropriate to protect the amino function of **9** to avoid its oxidation in the next step. Our synthetic plan required a protecting group prone to be cleaved in acidic conditions, concomitantly with the silylether. Accordingly, *N*-Me amine **9** was treated with di-*tert*-butyl dicarbonate (Boc_2O) employing a standard procedure, to afford the Boc-derivative **10** in high yield (95%). Selective hydroboration of the terminal olefin of **10** was achieved with dicyclohexylborane, and oxidation of the borane intermediate to give alcohol **11** in high yield (90%).[17] This intermediate **11** was converted to the corresponding mesylate **12** under standard conditions.

Then, Boc and TBS protecting groups of **12** were cleaved in a single step under acidic conditions, and the resulting amino derivative spontaneously cyclized by displacing the mesylate to afford (−)-allosedamine **13** in 94% yield after purification. Spectral data (IR, ^1H, ^{13}C NMR) for **13** were in excellent agreement with those recorded for the natural material, including specific optical rotation, $[\alpha]_D^{20} = -28.6$ (*c* 0.84, MeOH), lit.[3] $[\alpha]_D^{20} = -29.8$ (*c* 0.2, MeOH).

In summary, we have achieved an enantiocontrolled synthesis of (−)-allosedamine **13** via the epoxyalcohol **5**, using a strategy that could be applied to the preparation of piperidine alkaloids, such as (−)-lobeline. In addition, this synthetic scheme is adaptable to the preparation of a range of substituted analogues.

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12. Representative procedure for compound **4**. To a solution of carbonate **3** (4.7 g, 18.95 mmol) in toluene (150 mL) at −85°C, was slowly added a solution of IBr (1 M in CH_2Cl_2, 30.3 mL, 30.3 mmol). After stirring at −85°C for 1 h, the resulting mixture was quenched with (1:1) 20% aqueous $Na_2S_2O_3$: 5% aqueous $NaHCO_3$ solution and diluted with ether (120 mL). The aqueous phase was extracted with ether (2×). The organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate–hexane) to give the cyclic cabonate **4** (5.12 g, 85%) as a white solid which was quickly used in the next step due to its extensive decomposition. $[\alpha]_D^{20}=+23.1$ (*c* 1.08, CH_2Cl_2). IR (KBr), *v* 1722, 3024 cm^{-1}. ^1H NMR δ (ppm) 2.01 (dt, 1H, $J=11.7$ Hz, $J=14.3$ Hz), 2.59 (dt, 1H, $J=3$ Hz, $J=14.3$ Hz), 3.27–3.46 (m, 2H), 4.55–5.68 (m, 1H), 5.44–5.51 (dd, 1H, $J=2.9$ Hz, $J=11.9$ Hz), 7.38 (s broad, 5H); ^{13}C NMR δ (ppm) 5.6, 35.6, 77.2, 79.5, 125.9, 129.0, 129.3, 137.2, 148.4.
13. Representative procedure for compound **5**. To a solution of cyclic carbonate **4** (4.14 g, 13.02 mmol) in anhydrous MeOH (52 mL) at room temperature, was added K_2CO_3 (5.57 g, 40.36 mmol) and the reaction was stirred for 2 h. The mixture was diluted with ether (200 mL) and was quenched with (1:1) saturated aqueous $Na_2S_2O_3$: saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with ether (3×). The organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and filtered. Removal of solvent left an oil which was purified by flash chromatography (30% ethyl acetate–hexane), affording the epoxyalcohol **5** (2.05 g, 96%) as a colorless oil. $[\alpha]_D^{20}=+30.7$ (*c* 1, CH_2Cl_2). IR (KBr), *v* 1410, 1454, 1494, 2921, 3061, 3418 cm^{-1}. ^1H NMR δ (ppm) 1.80–2.07 (m, 2H), 2.47 (dd, 1H, $J=2.7$ Hz, $J=4.9$ Hz), 2.72 (dd, 1H, $J=4.4$ Hz, $J=4.9$ Hz), 2.77 (s broad, 1H), 2.92–3.02 (m, 1H), 4.89 (dd, 1H, $J=5.5$ Hz, $J=7.8$ Hz), 7.27–7.37 (m, 5H); ^{13}C NMR δ (ppm) 41.9, 46.9, 50.3, 72.8, 125.9, 127.9, 128.6, 144.0. HRMS (CI/NH_3) calcd for $C_{10}H_{16}N_1O_2$ ($M+NH_4^+$) 182.1181, found 182.1177.
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