Stereoselective Asymmetric Synthesis of (+)-Sedamine and (+)-Allosedamine

STÉPHANE LEBRUN,[1,2] AXEL COUTURE,[1,2]* ERIC DENIAU,[1,2] AND PIERRE GRANDCLAUDON[1,2]
[1]*Université des Sciences et Technologies de Lille 1, LCOP, Bâtiment C3(2), 59655 Villeneuve d'Ascq, France*
[2]*CNRS, UMR 8009 "Chimie Organique et Macromoléculaire", 59655 Villeneuve d'Ascq, France*

ABSTRACT A convenient method for the generation of (+)-sedamine and (+)-allosedamine in high optical purity has been elaborated. The key steps are the highly stereoselective 1,2-nucleophilic addition to SAMP hydrazones allowing the installation of the stereogenic center at C2 and ring closing metathesis. *Chirality 22:212–216, 2010.* © 2009 Wiley-Liss, Inc.

KEY WORDS: alkaloids; diastereoselective nucleophilic addition; hydrazones ring closing metathesis

INTRODUCTION

The 1,3-aminoalcohol moiety is found in many synthetic and natural products possessing physiological activities and is an integral part of a variety of potent drugs.[1,2] It is also the most distinctive structural feature of 2-(2-hydroxyalkylsubstituted)piperidine-based alkaloids which display a wide range of biological activities.[3] Consequently these bifunctional compounds have been the subject of considerable synthetic efforts, prompting an exceptional development of methodologies for the asymmetric approaches.[4]

Sedamine, allosedamine, and their stereoisomers, **1a,b** and **2a,b** respectively, (see Fig. 1) fall into this category. Sedamine (**1a**) was the first alkaloid isolated from *Sedum acre*[5,6] and the enantiomeric forms **1a,b** have been obtained later from a number of *Sedum* species.[7–11] This type of alkaloid has been shown to display memory-enhancing properties and may be effective for the treatment of cognitive disorders.[12,13] (+)-Allosedamine (**2a**) and its levorotary enantiomer **2b** are lipophilic alkaloidal constituents of *Lobelia inflata* L INN which has a long history of therapeutic activities[14] ranging from respiratory stimulant to tobacco smoking cessation agent.[14,15] As these alkaloids are only available in trace amounts from natural sources, the last decade has witnessed a strong incentive in the development of asymmetric synthetic approaches to these naturally occurring substances.

While numerous and elegant synthetic routes have been reported for the synthesis of (+)-sedamine (**1a**)[16–24] and (−)-sedamine (**1b**)[18,23,25-34] in optically active forms, facile and direct application of these approaches to the synthesis of (+)-allosedamine (**2a**)[21,23,24] and (−)-allosedamine (**2b**)[23,35–40] turned out to be difficult in most cases and in particular, the synthesis of (+)-allosedamine has received only minor attention.[41]

We were then interested in developing a feasible and highly stereoselective route giving rise equally to the piperidine-based alkaloids (+)-sedamine and (+)-allosedamine featuring the 1,3-aminoalcohol moiety. The salient features of the synthetic strategy are (i) the early creation of the C2 stereogenic center of the piperidine unit relying on the highly diasteroselective nucleophilic 1,2-addition to chiral SAMP hydrazones[42]; (ii) the creation of the piperidine ring template by ring closing metathesis which ranks highly in the hierarchy of synthetic tactics for the elaboration of nitrogen containing ring systems[43–46]; and (iii) the installation of the hydroxylated benzylic stereogenic center at C8 by chirality transfer to a ketyl functionality while retaining the configuration at C2.

MATERIALS AND METHODS

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were predried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. Methanol (MeOH) and ethanol (EtOH) were distilled from magnesium turnings and dichloromethane (CH_2Cl_2) from CaH_2, before storage on 4 Å molecular sieves. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μm; 230–400 mesh ASTM) was used. Petroleum ether (PE, boiling range 40–60°C), ethyl acetate (AcOEt), acetone, and methanol were used as eluents. The melting points were obtained on a Reichert-Thermopan apparatus and are not corrected. Optical rotations were measured on a Perkin Elmer P 241 polarimeter. NMR spectra: Bruker AM 300 (300 MHz and 75 MHz, for ^1H, and ^{13}C), $CDCl_3$ as solvent, TMS as internal standard. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment.

*Correspondence to: Axel Couture, Université des Sciences et Technologies de Lille 1, LCOP, Bâtiment C3(2), 59655 Villeneuve d'Ascq, France. E-mail: axel.couture@univ-lille1.fr
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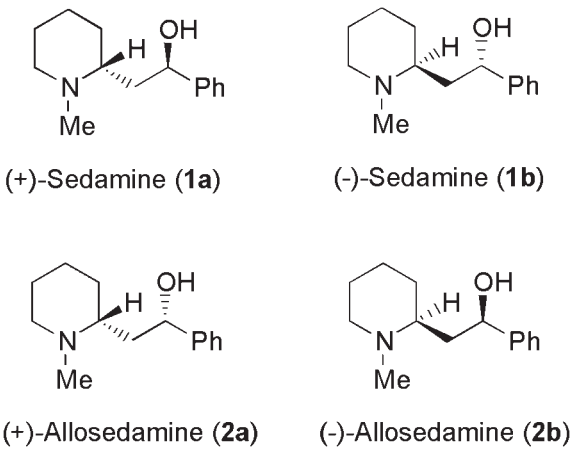


Fig. 1. Stereoisomers of sedamine and allosedamine.

The masked oxocarboxaldehyde **5** was synthesized according to literature methods.[47]

Experiment

((*S*)-2-Methoxymethylpyrrolidin-1-yl)-[2-(2-phenyl-1,3-dioxolan-2-yl)-ethylidene]-amine (3). SAMP (**4**, 2.20 g, 0.017 mol) and $MgSO_4$ (0.40 g) were added to a solution of aldehyde **5** (2.69 g, 0.014 mol) in CH_2Cl_2 (25 ml). The mixture was stirred at r.t. for 12 h. Filtration of $MgSO_4$ and evaporation of the solvent left a residue which was purified by flash column chromatography on silica gel using AcOEt/PE (15:85) as eluent to afford the hydrazone **3** (3.32 g, 78%) as colorless oil. $[\alpha]_D^{20}$ −74.6 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.73–1.96 (m, 4H), 2.68–2.79 (m, 1H), 2.85 (d, *J* = 4.8 Hz, 2H), 3.36–3.55 (m, 7H), 3.73–3.81 (m, 2H, OCH_2); 3.96–4.04 (m, 2H, OCH_2), 6.52 (brs, 1H, CH=N), 7.25–7.36 (m, 3H, H_{arom}), 7.43–7.49 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.2, 26.6, 44.1, 50.2, 59.2, 63.1, 64.7, 74.6, 109.5, 125.7, 127.9, 128.1, 132.5, 142.1; Anal. Calcd. for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.29, H, 7.81, N, 9.02%.

***N*-((*S*)-2-Methoxymethylpyrrolidin-1-yl)-*N*-[(*R*)-1-(2-phenyl-1,3-dioxolan-2-ylmethyl)-but-3-enyl]-acrylamide (6).** Phenyllithium (1.8 M in dibutyl ether, 3.65 ml, 6.58 mmol) was added dropwise to a solution of allyltriphenyltin (2.57 g, 6.58 mmol) in Et_2O (20 ml). After stirring at r.t. for 30 min the suspension was cooled at −78°C and a solution of hydrazone **3** (1 g, 3.29 mmol) in Et_2O (5 ml) was added dropwise by syringe. The reaction mixture was stirred at −78°C for 40 min then allowed to warm to r.t. and stirred for an additional 12 h. The reaction mixture was then recooled to −78°C and acryloyl chloride (9.87 mmol, 0.8 ml) was added dropwise. After stirring at this temperature for 30 min, the reaction mixture was allowed to warm to r.t. over 3 h. Water (15 ml) was added and the mixture was filtered and extracted with CH_2Cl_2 (3×30 ml). The combined organic extracts were dried ($MgSO_4$), the solvent was removed under vacuum, and the product was purified by flash column chromatography on silica gel using AcOEt/PE (20:80) as eluent to afford dienehydrazide **6** (618 mg, 47%) as yellow oil. $[\alpha]_D^{20}$ −32.7 (*c* 0.64, $CHCl_3$); ^{1}H NMR: δ = 1.62–1.83 (m, 4H), 2.33 (d, *J* = 15.3 Hz, 1H), 2.51–2.62 (m, 1H), 2.74–2.78 (m, 2H), 2.82 (d, *J* = 15.3 Hz, 1H), 2.95–3.06 (m, 1H), 3.14–3.28 (m, 6H), 3.35–3.47 (m, 1H), 3.68–3.76 (m, 2H, CH_2O), 3.96–4.04 (m, 2H, CH_2O), 4.92–5.03 (m, 2H, H_{vinyl}), 5.51 (dd, *J* = 10.4, 2.2, 1H, H_{vinyl}), 5.64–5.82 (m, 1H, H_{vinyl}), 6.22 (dd, *J* = 17.2, 2.2 Hz, 1H, H_{vinyl}), 7.03 (dd, *J* = 17.2, 10.4, 1H, H_{vinyl}), 7.23–7.41 (m, 5H, H_{arom}); ^{13}C NMR: δ = 21.1, 26.2, 37.7, 45.8, 51.8, 52.2, 55.7, 58.7, 64.1, 64.4, 73.9, 110.1, 116.6, 125.7, 125.8, 127.9, 128.1, 129.4, 136.9, 142.4, 169.0; Anal. Calcd. for $C_{23}H_{32}N_2O_4$: C, 69.97; H, 8.05; N, 6.99. Found: C, 70.11, H, 8.10, N, 7.15%.

(*R*)-1-((*S*)-2-Methoxymethylpyrrolidin-1-yl)-6-(2-phenyl-1,3-dioxolan-2-ylmethyl)-5,6-dihydro-1H-pyridin-2-one (8). A solution of the dienehydrazide 6 (500 mg, 1.25 mmol) and the first generation Grubbs catalyst (0.067 mmol, 5 mol %) in anhydrous CH_2Cl_2 (15 ml) was refluxed for 12 h under Ar. The reaction mixture was concentrated and the resulting residue was purified by column chromatography on silica gel using AcOEt/PE (40:60) as eluent to give enehydrazide 8 (377 mg, 81%) as yellow oil. $[\alpha]_D^{20}$ −24.9 (*c* 0.51, $CHCl_3$); ^{1}H NMR: δ = 1.31–1.50 (m, 4H), 1.55–1.71 (m, 1H), 1.91–2.03 (m, 1H), 2.29–2.34 (m, 1H), 2.58–2.63 (m, 1H), 3.05–3.22 (m, 6H), 3.47–3.53 (m, 1H), 3.65–3.74 (m, 2H), 3.76–3.83 (m, 2H, CH_2O), 3.91–4.04 (m, 2H, OCH_2), 5.77 (d, *J* = 9.8 Hz, 1H, H_{vinyl}), 6.30–6.39 (m, 1H, H_{vinyl}), 7.22–7.41 (m, 5H, H_{arom}); ^{13}C NMR: δ = 23.3, 27.6, 29.1, 40.9, 52.6, 58.2, 58.7, 60.6, 63.6, 64.7, 76.8, 109.4, 125.6, 126.0, 128.1, 128.3, 137.6, 142.0, 162.9; Anal. Calcd. for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.90, H, 7.33, N, 7.41%.

(*R*)-1-((*S*)-2-Methoxymethylpyrrolidin-1-yl)-6-(2-oxo-2-phenylethyl)-piperidin-2-one (9). A solution of enehydrazide **8** (1.2 g, 3.2 mmol) in EtOH (15 ml) was stirred with Pd/C (10%, 15 mg) under H_2 (1 atm) for 12 h at r.t. The mixture was filtered on a pad of Celite® that was further eluted with EtOH (30 ml), then CH_2Cl_2 (30 m). The filtrate was concentrated under vacuum and the residue dissolved in acetone (20 ml). Water (1 ml) and APTS (100 mg) were added and the mixture was refluxed for 6 h. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel using AcOEt as eluent to give ketone **9** (0.9 g, 85%) as yellow oil. $[\alpha]_D^{20}$ −20.5 (*c* 0.81, $CHCl_3$); ^{1}H NMR: δ = 1.61–1.83 (m, 5H), 1.88–2.05 (m, 3H), 2.36 (t, *J* = 6.5 Hz, 2H, CH_2CO), 2.91–3.03 (m, 2H, CH_2COPh), 3.19–3.25 (m, 5H), 3.51–3.70 (m, 2H), 3.80–3.89 (m, 1H), 4.28–4.36 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 2H, H_{arom}), 7.57 (t, *J* = 7.7 Hz, 1H, H_{arom}), 7.90 (t, *J* = 7.7 Hz, 2H, H_{arom}); ^{13}C NMR: δ = 17.9, 22.7, 27.4, 28.9, 34.2, 43.0, 53.0, 58.7, 59.8, 62.3, 76.5, 128.2, 128.6, 133.1, 137.0, 169.3, 198.3; Anal. Calcd. for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 14.53. Found: C, 68.88, H, 7.81, N, 14.76%.

(*R*)-6-((*R/S*:25/75)-2-Hydroxy-2-phenylethyl)-1-((*S*)-2-methoxymethylpyrrolidin-1-yl)-piperidin-2-one (10 and 11). A solution of K-Selectride® (1 M in THF, 2.3 ml) was added to a solution of ketone **9** (500 mg,

1.51 mmol) in THF (10 ml) at −78°C under Ar. After stirring for 3 h, water (15 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 40 ml). Combined extracts were dried ($MgSO_4$) and the solvent was evaporated under vacuum to afford the alcohol **10**, **11** as a mixture of unseparable diastereoisomers (1:3, 448 mg, 89%). ^{1}H NMR (mixture of diastereoisomers): δ = 1.42–1.86 (m, 8H), 1.93–2.08 (m, 2H), 2.26–2.34 (m, 2H), 3.22–3.36 (m, 7H), 3.55–3.66 (m, 1H, **11**), 3.74–3.86 (m, 2H, **10**), 3.87–3.95 (m, 1H, **11**), 4.68–4.73 (m, 1H, **11**), 4.76–4.82 (br. s, 1H, **10**), 4.93–4.99 (m, 1H, **10**), 5.31–5.36 (brs, 1H, **11**), 7.19–7.38 (m, 5H); ^{13}C NMR (mixture of diastereoisomers): δ 17.7 (**11**), 17.8 (**10**), 23.0 (**10**), 23.05 (**11**), 27.2 (**10**), 27.25 (**11**), 30.6 (**10**), 30.8 (**11**), 34.0 (**10**), 34.2 (**11**), 45.2 (**10**), 46.4 (**11**), 53.0 (**10**), 53.2 (**11**), 58.4 (**10**), 58.7 (**11**), 58.8 (**10**), 60.6 (**11**), 60.7 (10), 61.1 (**11**), 70.8 (**10**), 72.6 (**11**), 75.1 (**10**), 75.9 (**11**), 125.6 (**10**), 125.7 (**11**), 127.1 (**10**), 127.3 (**11**), 128.3 (**10**), 128.35 (**11**), 144.5 (10), 145.0 (**11**), 168.8 (**11**), 169.3 (**10**).

(*R*)-2-((*R*)-2-Hydroxy-2-phenylethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (12) and (*R*)-2-((*S*)-2-hydroxy-2-phenylethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (13). BH_3-THF (1 M in THF, 30 ml) was added slowly to a solution of alcohols **10, 11** (500 mg, 1.51 mmol) in dry THF (5 ml) at 0°C. After refluxing for 48 h, the reaction mixture was cooled to r.t. and quenched with aq NaOH (10%, 15 ml). The mixture was concentrated to one-third in volume and refluxed for 5 h. After separation of the organic layer, the aqueous layer was extracted with Et_2O (3 × 30 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to afford a mixture of aminoalcohols which were used directly in the next step. Di-*tert*-butyl dicarbonate (446 mg, 2.04 mmol) was added to a solution of crude amino alcohols (280 mg, 1.36 mmol) in toluene (10 ml) and refluxed for 5 h. The solvent was evaporated, the diastereomeric ratio (1:3) was then evaluated from ^{1}H NMR spectrum and the products were separated by flash column chromatography on silica gel with AcOEt/PE (30:70) as eluent to afford the pure diastereoisomers 12 (115 mg, 25%); $[\alpha]_D^{20}$ +65.8 (*c* 0.71, EtOH), Ref. 21 $[\alpha]_D^{20}$ +44.8 (*c* 0.6, EtOH, *ee* 87%) and 13 (230 mg, 50%); $[\alpha]_D^{20}$ +43.8 (*c* 0.65, EtOH), Ref. 21 $[\alpha]_D^{20}$ +26.5 (*c* 0.60, EtOH, *ee* 89%), as colorless oil.

(+)-Sedamine (1a) and (+)-allosedamine (2a). A solution of **12** (50 mg, 0.16 mmol) in THF (2 ml) wasadded dropwise to a stirred suspension of $LiAlH_4$ (30.4 mg, 0.8 mmol) in THF (5 ml) under Ar. The mixture was refluxed for 6 h then cooled to 0°C. Aq NaOH solution (15%, 0.5 ml) was carefully added followed by water (5ml). The mixture was extracted with CH_2Cl_2 (3 × 30 ml) and the combined organic layers were dried (Na_2SO_4). Evaporation of the solvent under vacuum left an oily residue (32 mg, 91%) which was purified by TLC (Merck precoated neutral aluminum oxide $150F_{254}$-Typ T; CH_2Cl_2-MeOH, 90:10, as eluent) to afford (+)-Sedamine (**1a**) as a colorless oil (22 mg, 62%); $[\alpha]_D^{20}$ +85.3 (*c* 0.8, EtOH), Ref. 20 $[\alpha]_D^{20}$ +87.0 (*c* 1.1, EtOH). Crude (+)-allosedamine **2a** (100 mg, 93%) was obtained from **13** (150 mg, 0.48 mmol) according to the same procedure. TLC purification afforded **2a** as a colorless oil (72 mg, 67%); $[\alpha]_D^{20}$ +26.0 (*c* 0.73, MeOH), Ref. 16 {$[\alpha]_D^{20}$ +28.8 (*c* 0.16, MeOH).

RESULTS AND DISCUSSION

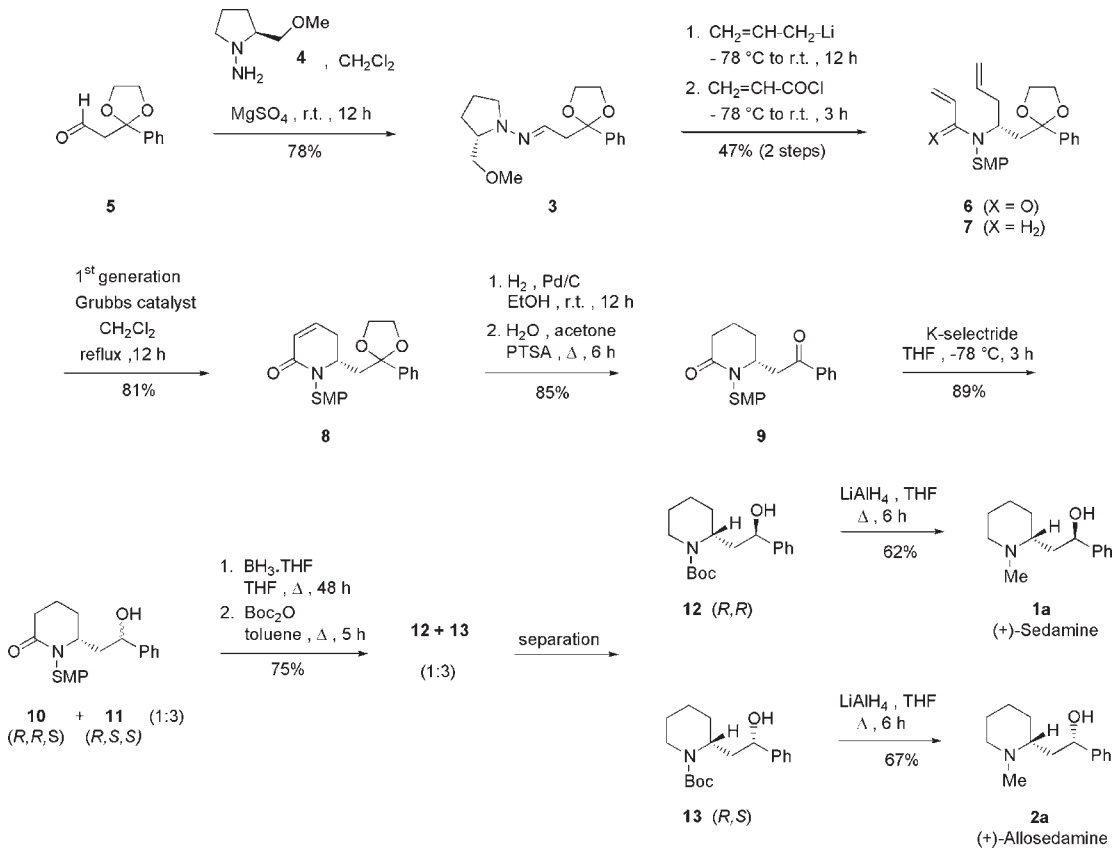
The first facet of the synthesis which is depicted in Scheme 1 was the elaboration of the protected parent hydrazone **3**. This compound was easily obtained by simply mixing the enantiomerically pure hydrazine (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP, **4**) with the aromatic masked oxocarboxaldehyde **5**.

Addition of allyllithium followed by interception of the transient hydrazide salt with acryloyl chloride allowed the installation of the mandatory diolefinic system and delivered the opened dienehydrazide **6**, candidate for the planned RCM reaction with a satisfactory yield. It is noteworthy that this synthetic route proved more judicious than that based upon trapping of the hydrazide salt with allyl bromide. Indeed only traces of the diallylated compound **7** were detected in this synthesis. NMR spectroscopic investigation indicated the presence of a single diastereoisomer (de > 95%) making evident the remarkable stereoselectivity of the initial 1,2-nucleophilic addition process securing the absolute stereochemistry at the α-position of the nitrogen atom, i.e., at C2 in the final compound.

The bis olefin **6** obtained after chromatographic treatment was subjected to RCM using 1st generation Grubbs catalyst, $Cl_2Ru(=CHPh)(PCy_3)_2$ (5% mol) in refluxing CH_2Cl_2 to provide a very satisfactory yield of the virtually diastereopure enehydrazide (*S,R*)-**8**. Catalytic hydrogenation of the olefinic double bond was readily achieved with the subsequent retrieval of the carbonyl functionality to afford the cyclic hydrazide (*S,R*)-**9** in high diastereoselectivity (de > 95%).

For the subsequent step—the reduction of the carbonyl functionality—a variety of reducing agents was screened. While standard conditions by making use of $NaBH_4$ furnished an equimolar mixture of diastereoisomers (*R,R,S*)-**10** and (*R,S,S*)-**11** we were pleased to observe that treatment of **9** with K-Selectride® furnished the diastereoisomeric mixture with the diastereoisomeric form **11** predominating by a large margin (**10**/**11**; 1:3). The diastereoisomers could not be chromatographically separated and the diastereoisomeric ratio was evaluated by ^{1}H NMR, namely from integration of the benzylic proton. At this stage the structural assignments of the absolute configuration of alcohols **10** and **11** could not be accessed a priori.

The determination of the absolute configuration of **10** and **11** was achieved by their conversion to the corresponding *N*-Boc protected compounds **12** and **13**. This conversion was secured by sequential treatment of the diastereoisomeric mixture **10**, **11** with BH_3-THF and *tert*-butoxycarbonyl anhydride. This single operation triggered the reduction of the hydrazide carbonyl function with the concomitant release of the chiral appendage and the ultimate installation of the Boc group. Flash chromatography



Scheme 1. Total synthesis of (+)-sedamine and (+)-allosedamine.

allowed the isolation of the diastereochemically enriched carbamates **12** and **13** in the same ratio 1:3, confirming the diastereoisomeric composition of the preceding step.

The structural assignments of the absolute configuration of hydroxycarbamates **12** and **13** were determined by comparison with authentic samples assembled by a conceptually different synthetic approach hinging upon enzymatic resolution of piperidine-2-ethanol as the key step.[21] Ultimate conversion into the targeted piperidine alkaloids sedamine and allosedamine confirmed these structural assignments since reduction of **12** and **13** in refluxing THF for 6 h gave very satisfactory yields of (+)-sedamine and (+)-allosedamine, respectively. The enantiopurity of our synthetic (*R,R*)-(+)-sedamine (**1a**) and (*R,S*)-(+)-allosedamine (**2a**) was clearly established from the optical rotation and spectroscopic data that matched those reported for the natural products: (*R,S*)-**1a** {$[\alpha]_D^{20}$ +85.3 (*c* 0.8, EtOH)}, Ref. 20 {$[\alpha]_D^{20}$ +87.0 (*c* 1.1, EtOH)}; (*R,S*)-**2a** {$[\alpha]_D^{20}$ +26.0 (*c* 0.73, MeOH) }, Ref. 20 {$[\alpha]_D^{20}$ +28.8 (*c* 0.16, MeOH)}.

In summary, we have disclosed a stereoselective synthesis of (+)-sedamine (**1a**) and (+)-allosedamine (**2a**) using a strategy that could be applied to a wide array of 2-hydroxyalkylated piperidine alkaloids. In addition, with the present synthetic approach optically active antipodes of the title compounds could also be readily accessed by the use of RAMP as chiral auxiliary.

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