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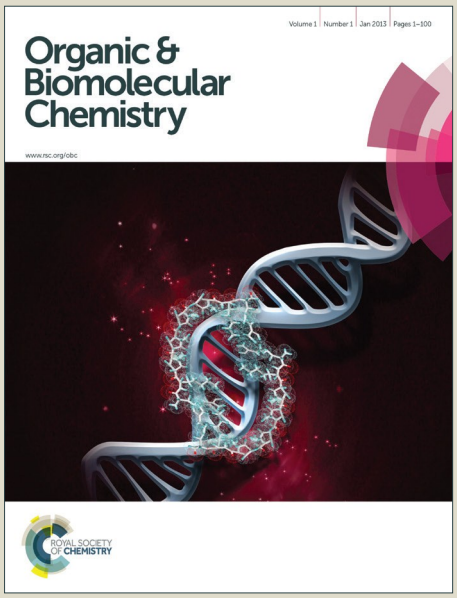

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ARTICLE

Total synthesis of a piperidine alkaloid, Microcosamine A

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The first asymmetric total synthesis of a new natural piperidine alkaloid, microcosamine A, has been accomplished from *D*-Serine and *D*-methyl lactate as chiral pool starting materials. Key features of the strategy include the utility of Horner-Wadsworth-Emmons reaction, Luche reduction, intramolecular carbamate *N*-alkylation to form the piperidine framework and Julia-Kocienski olefination to install the triene side-chain.

Introduction

2-Methyl-3-hydroxy-6-alkylated piperidines constitute an important class of natural alkaloids due to their interesting biological and pharmacological properties (anaesthetic, analgesic, antitumor, antibiotic, CNS stimulating biological properties, antihypertensive and antifungal activities etc.).[1-6] These molecules possess in different stereochemical pattern and C6 side chain with either saturated or unsaturated alkyl group. Up to date three types of 2-methyl-3-hydroxy natural piperidines having different unsaturated side chain at C6 carbon, such as corydendramines A & B (**1a, 1b**),[4] microgrewiapine A (**1c**)[5] and microcosamines A & B (**2a**, **2b**)[6] have been isolated. However, there is no synthesis reported for any of these molecules. The interesting structural feature of these molecules is the presence of a chiral hydroxy group at C3-position of piperidine ring with *trans* stereochemistry with respect to the C2 and C6 carbons, which is a rare substructure in piperidine alkaloids. Structurally, these compounds possess a polar head group with hydroxyl and amine functionalities and a hydrophobic aliphatic tail, which can be considered as cyclic analogues of the lipid sphingosine membrane.[7] The above observations combined with our interest in the synthesis of alkaloids[8] have driven us for the synthesis of microcosamine A (**2a**).

Microcosamine A (**2a**), was first isolated by Lin and co-workers in 2008, from the chloroform extraction of the leaves of *Microcos paniculata* along with microcosamine B (**2b**) and found their insecticidal activity against the larvae of *Culex quinquefasciatus* with LC_{50} value of 5.2 and 17.0 µg/mL, respectively.[6] *Microcos paniculata*, a large shrub or small tree that grows in South and Southeast Asia countries, is found to be a rich source of bio-active compounds and several parts such as roots, stem bark, leaves and fruits are being used traditionally to treat diarrhea and fever, as herbal tea to treat cold, enteritis, and skin rash and as insecticides.[9] There is a good number of 2,3,6-trisubstituted piperidine alkaloids which have been isolated from this species.[10] Later, in 2013, it was again isolated from the same plant along with some other piperidine alkaloids by Kinghorn *et al* and examined for their effects on neuronal nicotinic acetylcholine receptors (nAChRs).[5] Microcosamine A (**2a**) exhibited approximately 53.7% and 59% h$\alpha3\beta4$ and h$\alpha3\beta2$ nAChR activity, respectively Herein, we presented the first total synthesis of microcosamine A (**2a**).

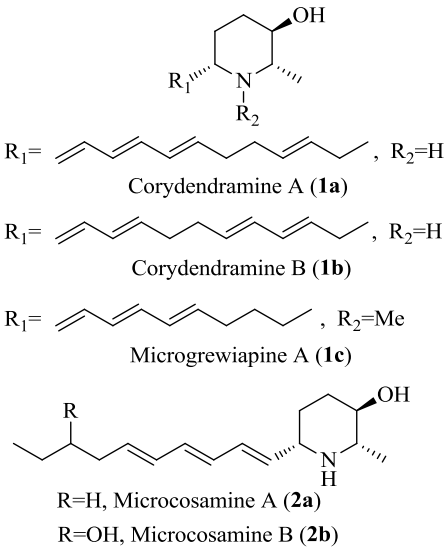
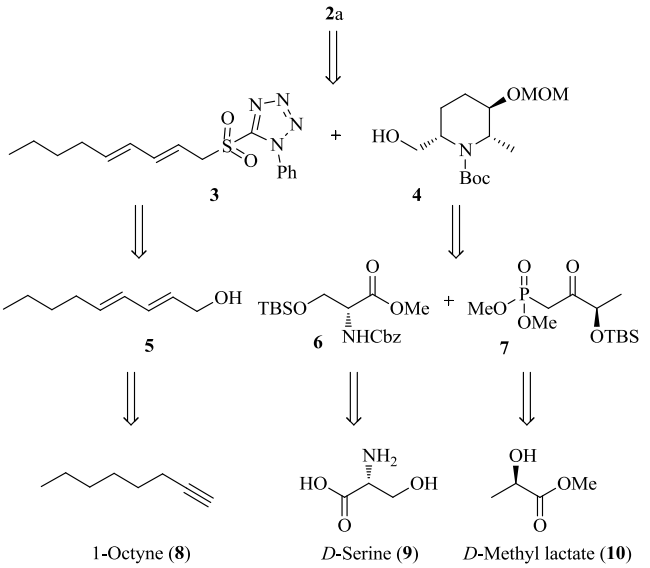


Figure 1. Structures of corydendramines A & B, microgrewiapine A and microcosamines A & B

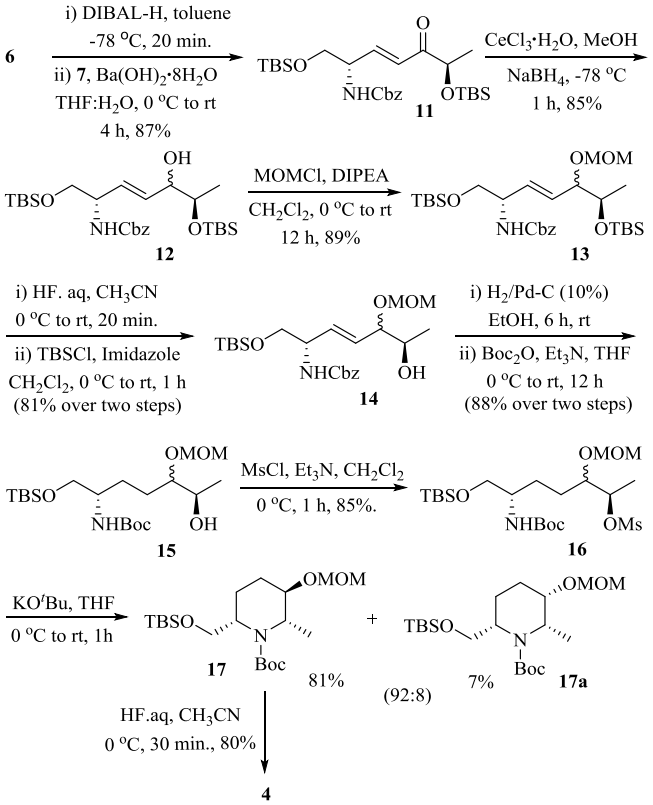
Results and discussion

Scheme 1 outlines the retrosynthetic strategy of **2a**. We planned the installation of triene-side chain at C6 position of hydroxy piperidine ring **4** by using **3** *via* oxidation followed by Julia-Kocienski olefination.[11] Synthesis of the sulfone fragment **3** was projected from 1-octyne (**8**) by way of a known conjugated alcohol **5**.[12] The construction of piperidine **4** was designed through the intramolecular carbamate *N*-alkylation of its precursor which could be obtained from *N*,*O*-protected *D*-serine ester **6** and *β*-keto phosphonate **7** using Horner-Wadsworth-Emmons (HWE) olefination[13] as the key reaction. Ester **6** and phosphonate **7** inturn could be prepared from the chiral starting materials, *D*-serine (**9**) and *D*-methyl lactate (**10**), respectively. The C2 and C6 stereochemistry is expected to arise from **9** and C3-hydroxyl stereochemistry envisaged from **10** using diastereoselective Luche reduction[14] of keto functionality.



Scheme 1. Retrosynthetic analysis of **2a**

The ester intermediate **6** was prepared in three steps from *D*-serine (**9**) following the reported procedure.[15] The desired *β*-keto phosphonate **7** was also smoothly obtained in two steps from *D*-methyl lactate (**10**) using literature protocol.[16] The synthesis of piperidine fragment is outlined in scheme 2. Initially, the ester **6** was subjected to DIBAL-H reduction to aldehyde followed by HWE olefination with *β*-keto phosphonate **7** under $Ba(OH)_2 \bullet 8H_2O$ in THF/H_2O condition to afford the enone **11** in 87% yield, a precursor for diastereoselective Luche reduction. Exposure of **11** to $NaBH_4$ in MeOH in the presence of $CeCl_3 \bullet H_2O$ at -78 °C provided the allylic alcohol **12** along with its minor diastereomer in 85% yield [dr >9:1, based on the diastereomers **17** & **17a**, seperated in the cyclization step]. At this stage, we were unable to separate these diastereomers either by column or by HPLC (In ^1H NMR spectra, the signals were not seperated to verify the diasrereomeric ratio) and hence, moved for further transformations as a mixture. Thus, the hydroxyl group of **12** was protected as methoxy methyl (MOM) ether **13** using MOMCl/diisopropylethyl amine in CH_2Cl_2 (89%). To obtain



Scheme 2. Synthesis of **4** from **6** and **7**

free secondary hydroxyl group, a two-step protecting group manipulation was chosen. Deprotection of both the *tert*-butyldimethyl silyl groups of **13** under HF (40% in water) in CH_3CN followed by selective protection of the resulting primary hydroxyl group as a TBS ether produced the required alcohol **14** in 81% yield over two steps. After the oxidation of alcohol **14** to the corresponding ketone **14-I**, the attempt to form the piperidine ring **14-II** through hydrogenation was unsuccessful.[17]

Thus, an alternative sequence was followed. Hydrogenation reaction of **14** using 10% Pd/C in EtOH involves the olefin reduction as well as Cbz-deprotection to free amine, which was subsequently treated with di-*tert*-butyl-dicarbonate (Boc_2O)/Et_3N to get Boc-protected amino alcohol **15** in 88% yield. Treatment of **15** with methanesulfonyl chloride in presence of triethyl amine in CH_2Cl_2 gave the mesylate **16** in 85% yield. Compound **16** was successfully converted into 2,3,6-trisubstituted piperidine *via* intramolecular carbamate *N*-alkylation (SN reaction) using potassium *tert*-butoxide in THF (88%).[18] At this point, the diastereomers formed during the Luche reduction of **11** were seperated by column chromatography (dr 92:8). The major isomer **17** was found to the desired one and the minor isomer **17a** was undesired, which were characterized by 2D COSY and NOESY experiments.[19] The nOe cross correlations between H8(Me)/H7(H7'), H2/H9 and H3/H8(Me) for **17** (Figure 2) support the desired

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diastereomer. In case of **17a** the nOe cross correlations observed between H8(Me)/H7(H7'), H7/H9, H8/H9, H2/H3 support the undesired diastereomer (Figure 2). Next, TBS group of **17** was deprotected using HF (40% in water) in CH_3CN to give the piperidinol **4** in 80% yield.

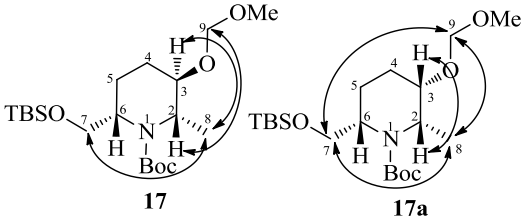
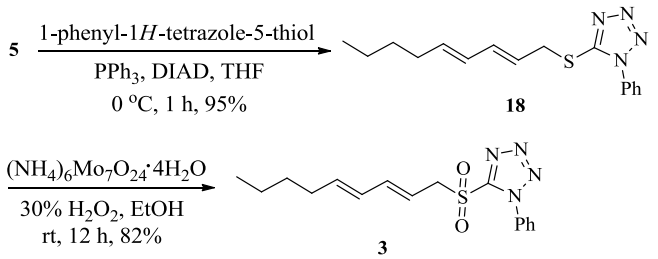


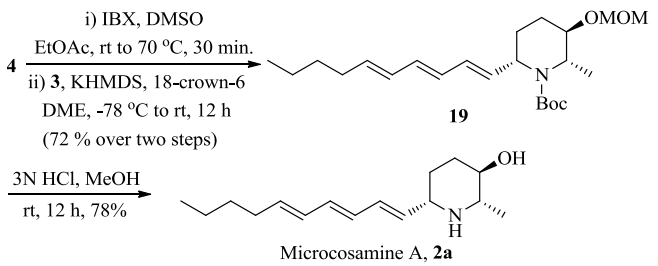
Figure 2: The characteristic nOe cross correlations of compound **17** and **17a**.

The sulfone **3** required for Julia olefination was synthesised from dienol **5**, obtained from 1-octyne (**8**).[12] Mitsunobu reaction[20] of the alcohol **5** with 1-phenyl-1*H*-tetrazole-5-thiol to thio-tetrazole **18** (95% yield) followed by ammonium molybdate catalyzed oxidation[21] using hydrogen peroxide in EtOH provided the sulfone **3** in 82% yield (Scheme 3).



Scheme 3. Synthesis of sulfone **3**

The stage was set for the conversion of **4** to microcosamine A (**2a**) by connecting the side chain (Scheme 4). Accordingly, the alcohol **4** was oxidized with IBX (2-iodoxybenzoic acid) to the corresponding aldehyde followed by Julia-Kocienski olefination with the trienyl sulfone **3** by treating with KHDMS in the presence of 18-crown-6 in DME provided the trienyl-piperidine **19** exclusively as *Z*-isomer in 72% yield over two steps.[22] Removal of MOM and Boc groups was accomplished in one step by the treatment of **19** with 3N HCl in MeOH to give the desired microcosamine A (**2a**) in 78% yield.



Scheme 4. Synthesis of **2a** from **4**

The spectral data (^1H, ^{13}C NMR and mass) of our synthetic microcosamine A (**2a**) were in full agreement to those reported for natural product (see Table S1 in supplementary information). The specific rotation of synthetic **2a** $\{[\alpha]_D^{20}$: +5.6 (*c* 1.00, CH_3OH)} was also comparable to the natural product $\{[\alpha]_D^{20}$: +4.0 (*c* 1.00, CH_3OH)}. These results confirm the structure and absolute configuration of the natural product **2a**.

Conclusions

In summary, The first asymmetric total synthesis of natural piperidine alkaloid, microcosamine A, was accomplished using commercially available *D*-serine, *D*-methyl lactate (for piperidine unit) and 1-octyne (for triene-side chain) as starting materials. The key features of the strategy are the successful utilization of HWE-olefination and intramolecular carbamate *N*-cyclization for piperidine ring construction and Julia-Kocienski olefination for the installation of side chain in the natural product synthesis. The approach is handy for the synthesis of other natural products and their analogues having different side chains.

Experimental

General

Melting points were determined on a POLMON melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ on 300 MHz, 400 MHz or 500 MHz spectrometers at ambient temperature. Chemical shifts δ were denoted with reference to TMS or solvent residual ($CDCl_3$: δ 7.26 ppm for ^1H and 77.0 ppm for ^{13}C) peak given in ppm (parts per million) and coupling constants *J* are measured in Hz (hertz). FTIR spectra were recorded on a Perkin-Elmer 683 infrared spectrophotometer in KBr or as neat. Optical rotations were measured on an Anton Paar MLP 200 modular circular digital polarimeter by using a 2 mL cell with a path length of 1 dm with MeOH or $CHCl_3$ as solvent. Low-resolution MS were collected on an Agilent Technologies LC-MSD trap SL spectrometer in positive ion mode. Technical-grade EtOAc and hexanes used for column chromatography were distilled before use. All the reagents and solvents were of reagent grade and used without further purification unless otherwise stated. THF, when used as solvent for reactions, was freshly distilled from sodium benzophenone ketyl radical. Progress of the reactions was monitored by thin-layer chromatography using silica plates (UV_{254}, glass backed; Merk KGaA) and the spots were visualized under UV-light and/or after charring with nihydrin or potassium permanganate or β-naphthol stain solutions. Column chromatography was performed over silica gel (60–120 mesh) or on alumina (aluminium oxide activated, neutral, 150 mesh) packed in glass columns, eluted with gradients of petroleum ether and ethyl acetate. Column fractions were concentrated under reduced pressure at temperatures not more than 40 °C. All the reactions were performed under N_2 in ovendried glassware with magnetic stirring.

Benzyl (6*S*,10*R*,*E*)-2,2,3,3,10,12,12,13,13-nonamethyl-9-oxo-4,11-dioxa-3,12-disilatetradec-7-en-6-ylcarbamate (11):

Methyl *N*-((benzyloxy)carbonyl)-*O*-(tert-butyldimethylsilyl)-*D*-serinate.[15] **6** (2.2 g, 5.99 mmol) was taken in a round bottemed flask and added anhydrous toluene (20 mL). The mixture was cooled to -78 °C before adding DIBAL-H (25% w/v in toluene, 5.1 mL, 7.18 mmol) drop wise under N_2 and stirred at the same temperature for 10 min. The mixture was quenched with aqueous saturated sodium potassium tartrate (20 mL), diluted with DCM (20 mL), stirred for 3 h at rt for the separation of two layers. The organic layers were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The aldehyde was used for the next step without further purification. To a stirred solution of (*R*)-dimethyl (3-((*tert*-butyldimethylsilyl)oxy)-2-oxobutyl)phosphonate[16] **7** (2.2 g, 7.19 mmol) in THF (30 mL), was added $Ba(OH)_2 \bullet 8H_2O$ (2.8 g, 8.99 mmol) at rt and stirred vigorously for 45 min. The reaction mixture was cooled to 0 °C before adding above crude aldehyde in 15 mL of THF/H_2O (20:1) and the mixture was allowed to warm to rt. After completion of reaction (4 h), the reaction mixture was diluted with EtOAc (30 mL), organic layer was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (neutral alumina, hexanes/EtOAc 9:1) to afford enone **11** (2.7 g, 87%) as a colorless oil. R_f = 0.4 (petroleum ether : EtOAc = 9:1); $[\alpha]_D^{20}$ = + 9.5 (*c* 1.50, $CHCl_3$); IR (neat): ν_{max} 3446, 2954, 2931, 2858, 1705, 1631, 1255, 1116, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.28 (m, 5H, Ph), 6.93 (dd, *J* = 15.8, 4.7 Hz, 1H, CH=C*H*), 6.73 (d, *J* = 15.8 Hz, 1H, C*H*=CH), 5.22-5.06 (m, 3H, CH_2−Ph, -N*H*), 4.52-4.43 (br m, 1H, C*H*−N), 4.25 (q, *J* = 13.6, 6.8 Hz, 1H, C*H*−CH_3), 3.76 (d, *J* = 3.7 Hz, 2H, CH_2−O), 1.29 (d, *J* = 6.8 Hz, 3H, CH−CH_3), 0.90 (s, 9H, ^{t}Bu-Si), 0.85 (s, 9H, ^{t}Bu-Si), 0.06 (s, 3H, Si(CH_3)$_2$), 0.05 (s, 3H, Si(CH_3)$_2$), 0.03 (s, 3H, Si(CH_3)$_2$), 0.02 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.0, 155.7, 145.2, 136.3, 128.5, 128.1, 128.0, 124.2, 74.3, 66.9, 64.6, 53.7, 25.7, 25.7, 20.8, 18.2, 18.0, -4.8, -4.9, -5.5, -5.5; MS (ESI): *m/z* 544 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{47}NO_5Si_2Na$ $(M+Na)^+$, 544.2885; found 544.2890.

Benzyl (6*S*,9*R*,10*R*,*E*)-9-hydroxy-2,2,3,3,10,12,12,13,13-nonamethyl-4,11-dioxa-3,12-disilatetradec-7-en-6-ylcarbamate (12): To a stirred solution of **11** (2.5 g, 4.79 mmol) in MeOH (30 mL) was added $CeCl_3 \cdot 7H_2O$ (3.5 g, 9.59 mmol) and was allowed to stir for 45 min at room temperature. It was cooled to -78 °C and $NaBH_4$ (265 mg, 7.18 mmol) was added portion wise for over 10 min and stirred for an additional 1 h at the same temperature. After completion of the reaction (10 min), it was quenched by addition of ice pieces/ice cold water (2 mL) at -78 °C and slowly allowed to warm to room temperature. After stirring at room temperature for further 30 min, it was poured into water (20 mL) and extracted with diethyl ether (3 x 25 mL). Combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (neutral alumina, hexanes/EtOAc 8:2) to furnish **12** (2.1 g, 85%) as a colorless oil. R_f = 0.2 (petroleum ether : EtOAc = 9:1); $[\alpha]_D^{20}$ = −6.6 (*c* 1.10, $CHCl_3$); IR (neat): ν_{max} 3446, 2953, 2930, 1714, 1253, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41-7.28 (m, 5H, Ph), 5.79 (dd, *J* = 15.6, 5.7 Hz, 1H, CH=C*H*), 5.65 (dd, *J* = 15.6, 5.9 Hz, 1H, C*H*=CH), 5.15-5.04 (m, 1H, -N*H*), 5.11 (s, 2H, CH_2−Ph), 4.32-4.20 (br m, 1H, C*H*−N), 3.84-3.76 (m, 1H, C*H*−OH), 3.72 (dd, *J* = 10.1, 4.1 Hz, 1H, CH_2−OTBS), 3.67-3.58 (m, 2H, CH_2−OTBS, C*H*−OTBS), 1.10 (d, *J* = 5.8 Hz, 3H, CH_3), 0.91 (s, 9H, ^{t}Bu-Si), 0.89 (s, 9H, ^{t}Bu-Si), 0.09 (s, 3H, Si(CH_3)$_2$), 0.08 (s, 3H, Si(CH_3)$_2$), 0.05 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 136.5, 131.2, 130.9, 130.4, 128.4, 128.0, 76.5, 71.9, 66.6, 65.2, 53.7, 25.7, 25.8, 19.8, 18.2, 17.9, -4.2, -4.8, -5.4; MS (ESI): *m/z* 524 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{50}NO_5Si_2$ $(M+H)^+$, 524.3222; found 524.3228.

Benzyl (6*S*,9*R*,10*R*,*E*)-9-(methoxymethoxy)-2,2,3,3,10,12,12,13,13-nonamethyl-4,11-dioxa-3,12-disilatetradec-7-en-6-ylcarbamate (13): To the compound **12** (2 g, 3.82 mmol) in dry dichloromethane (40 mL) was added *i*Pr_2EtN (1.98 mL, 11.47 mmol) and methoxymethyl chloride chloride (MOMCl) (0.92 mL, 11.47 mmol) at 0 °C. The solution was stirred at rt for 12 h and quenched by the addition of saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous layer was separated and extracted with DCM (2 x 25 mL). The combined organic layers were dried over Na_2SO_4 and volatiles were removed under reduced pressure. The crude product was purified by column chromatography (neutral alumina, hexanes/EtOAc 9:1) to get compound **13** as a colourless liquid (1.9 g, 89%). R_f = 0.4 (petroleum ether : EtOAc = 9:1); $[\alpha]_D^{20}$ = −15.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3446, 2954, 2857, 1725, 1254, 1106, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43-7.27 (m, 5H, Ph), 5.71 (dd, *J* = 15.8, 5.6 Hz, 1H, CH=C*H*), 5.57 (dd, *J* = 15.7, 6.9 Hz, 1H, C*H*=CH), 5.16-5.03 (m, 3H, CH_2−Ph, -N*H*), 4.64 (A of AB q, *J* = 6.5 Hz, 1H, OCH_2O), 4.57 (B of AB q, *J* = 6.6 Hz, 1H, OCH_2O), 4.35-4.21 (m, 1H, C*H*−N), 3.89 (t, *J* = 6.4 Hz, 1H, C*H*OMOM), 3.85-3.76 (m, 1H, C*H*−OTBS), 3.70 (dd, *J* = 10.0, 4.3 Hz, 1H, CH_2−OTBS), 3.64 (dd, *J* = 9.6, 3.5 Hz, 1H, CH_2−OTBS), 3.34 (s, 3H, OCH_3), 1.06 (d, *J* = 6.1 Hz, 3H, CH_3), 0.89 (s, 9H, ^{t}Bu-Si), 0.87 (s, 9H, ^{t}Bu-Si), 0.06 (s, 6H, Si(CH_3)$_2$), 0.03 (s, 3H, Si(CH_3)$_2$), 0.03 (s, 3H, Si(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 136.5, 131.8, 128.5, 128.4, 128.0, 94.4, 80.3, 70.4, 66.6, 65.2, 55.3, 53.7, 25.8, 25.8, 19.4, 18.2, 18.1, -4.6, -4.7, -5.5, -5.5; MS (ESI): *m/z* 590 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{29}H_{53}NO_6Si_2Na$ $(M+Na)^+$, 590.3303; found 590.3304.

Benzyl (5*R*,8*S*,*E*)-5-((*R*)-1-hydroxyethyl)-11,11,12,12-tetramethyl-2,4,10-trioxa-11-silatridec-6-en-8-ylcarbamate (14): To a stirred solution of **13** (1.9 g, 3.35 mmol) in CH_3CN (20 mL) at 0 °C was added HF (40% in water, 0.29 mL, 6.70 mmol) drop wise and allowed to rt over 30 min. After completion of the reaction, saturated aqueous $NaHCO_3$ (20 mL) was added dropwise and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. To the residue in DCM (30 mL) was

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added imidazole (296 mg, 4.35 mmol) and *t*-BuMe$_2$SiCl (502 mg, 3.35 mmol) at 0 °C and warmed to rt. The reaction mixture was diluted with water (20 mL) at the point all the starting materials consumed and extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and evaporated. Flash chromatography of the residue over neutral alumina (hexanes/EtOAc 7:3), gave **14** (1.23 g, 81%) as a colorless oil. R_f = 0.3 (petroleum ether : EtOAc = 7:3); $[\alpha]_D^{20}$ = −46.2 (*c* 1.70, $CHCl_3$); IR (neat): ν_{max} 3445, 3332, 2953, 2931, 1716, 1255, 1102, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H, Ph), 5.75 (dd, *J* = 15.7, 5.5 Hz, 1H, CH=C*H*), 5.49 (dd, *J* = 15.6, 8.0 Hz, 1H, C*H*=CH), 5.11 (s, 2H, CH_2−Ph), 4.70 (d, *J* = 6.1 Hz, 1H, OCH_2O), 4.55 (d, *J* = 6.4 Hz, 1H, OCH_2O), 4.28 (m, 1H, C*H*−N), 3.79 (t, *J* = 7.6 Hz, 1H, C*H*OMOM), 3.74-3.62 (m, 3H, CH_2−OTBS, C*H*−OH), 3.38 (s, 3H, OCH_3), 2.03 (br s, 1H, O*H*), 1.12 (d, *J* = 6.0 Hz, 3H, CH_3), 0.88 (s, 9H, ^{t}Bu-Si), 0.04 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 136.4, 134.0, 128.5, 128.1, 93.9, 81.7, 69.5, 66.7, 65.0, 55.6, 53.7, 25.8, 18.4, 18.2, -5.5, -5.5; MS (ESI): *m/z* 476 (M+Na)$^+$; HRMS (ESI): *m/z* calcd for $C_{23}H_{39}NO_6SiNa$ (M+Na)$^+$, 476.2438; found 476.2445.

Benzyl ((5*R*,8*S*,*E*)-5-acetyl-11,11,12,12-tetramethyl-2,4,10-trioxa-11-silatridec-6-en-8-yl)carbamate (14-I): 2-Iodoxybenzoic acid (IBX) (185 mg, 0.66 mmol) was taken in a round bottomed flask, added DMSO (0.5 mL) and stirred at rt under nitrogen atmosphere for 10 min to get a clear solution. To the clear solution, at the same temperature, added compound **14** (200 mg, 0.44 mmol) in EtOAc (2 mL) dropwise. The reaction mixture was heated to 70 °C and stirred for 30 min. After completion of reaction, the mixture was diluted with EtOAc (10 mL). The precipitate was filtered and washed with EtOAc (10 mL). The filtrate was washed with aqueous saturated $NaHCO_3$ solution (15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (neutral alumina, hexanes/EtOAc 8:2) to yield ketone **14-I** as the product (175 mg, 88%). R_f = 0.7 (petroleum ether : EtOAc = 7:3); $[\alpha]_D^{20}$ = −28.8 (*c* 1.57, $CHCl_3$); IR (neat): ν_{max} 3441, 2940, 1716, 766 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.29 (m, 5H, Ph), 5.91 (dd, *J* = 15.6, 5.5 Hz, 1H,CH=C*H*), 5.61 (dd, *J* = 15.6, 6.6 Hz, 1H, C*H*=CH), 5.15-5.07 (m, 1H, -N*H*), 5.09 (s, 2H, CH_2−Ph), 4.68 (d, *J* = 6.4 Hz, 1H, OCH_2O), 4.61 (d, *J* = 6.6 Hz, 1H, OCH_2O), 4.52 (d, *J* = 6.6 Hz, 1H, C*H*OMOM), 4.34-4.26 (br m, 1H, C*H*−N), 3.70 (dd, *J* = 10.0, 4.3 Hz, 1H, CH_2−OTBS), 3.65 (d, *J* = 7.2 Hz, 1H, CH_2−OTBS), 3.35 (s, 3H, OCH_3), 2.15 (s, 3H, CO*CH*$_3$), 0.86 (s, 9H, ^{t}Bu-Si), 0.03 (s, 3H, Si(CH_3)$_2$), 0.02 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 155.7, 136.3, 133.9, 128.4, 128.1, 125.7, 94.7, 82.0, 66.8, 64.9, 55.8, 53.6, 25.7, 18.2, -5.5; MS (ESI): *m/z* 452 (M+H)$^+$; HRMS (ESI): *m/z* calcd for $C_{23}H_{37}NO_6SiNa$ (M+Na)$^+$, 474.2282; found 474.2286.

***tert*-Butyl (5*R*,8*S*)-5-((*R*)-1-hydroxyethyl)-11,11,12,12-tetramethyl-2,4,10-trioxa-11-silatridecan-8-ylcarbamate (15)**: 10% Pd on C (5 mol %) was added to a degassed solution of the compound **14** (1.0 g, 2.20 mmol) in EtOH (0.5 M) and the heterogeneous mixture was stirred for 12 h under hydrogen atmosphere at rt. The reaction mixture was filtered over celite, the volatiles removed under reduced pressure. To the residue and triethyl amine (0.62 ml, 4.41 mmol) in THF (20 ml), di-*tert*-butyl-dicarbonate (Boc_2O) (0.5 mL, 2.20 mmol) was added at 0 °C. The reaction mixture was warmed to rt and stirred for 4 h. The reaction mixture was diluted with water after the completion of reaction and extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the residue over neutral alumina (hexanes/EtOAc 7:3), gave **15** (817 mg, 88%) as a colorless oil. R_f = 0.5 (petroleum ether : EtOAc = 7:3); $[\alpha]_D^{20}$ = −19.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3451, 2955, 2932, 1709, 1103, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71-4.66 (m, 2H, OCH_2O), 3.71-3.63 (m, 1H, C*H*−OH), 3.59-3.52 (m, 2H, CH_2−OTBS), 3.40 (s, 3H, OCH_3), 3.29-3.22 (m, 1H, C*H*−N), 3.05-3.14 (m, 1H, C*H*OMOM), 1.70-1.57 (m, 2H, CH_2−CH_2), 1.50-1.38 (m, 11H, ^{t}Bu in Boc, CH$_2$−CH_2), 1.13 (d, *J* = 6.4 Hz, 3H, CH_3), 0.87 (s, 9H, ^{t}Bu-Si), 0.03 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 97.4, 85.4, 79.0, 69.1, 64.6, 55.7, 52.0, 28.3, 27.7, 27.1, 25.8, 18.8, 18.2, -5.4; MS (ESI): *m/z* 444 (M+Na)$^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{44}NO_6Si$ (M+H)$^+$, 422.2751; found 422.2761.

(2*R*,3*R*,6*S*)-6-(*tert*-Butoxycarbonylamino)-7-(*tert*-butyldimethylsilyloxy)-3-(methoxymethoxy)heptan-2-yl methanesulfonate (16): To a stirred solution of compound **13** (1.0 g, 2.37 mmol), triethyl amine (0.66 mL, 4.75 mmol) in dichloromethane (20 mL) at 0 °C, was added methane sulfonyl chloride (0.27 mL, 3.56 mmol) dropwise. The mixture was allowed to warm to rt and stirred for a further 1 hour. After completion of reaction, it was diluted with water (20 mL) and the aqueous layer was extracted with DCM (2 x 15 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4. Volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (neutral alumina, hexanes/EtOAc 7:3) to yield pale yellow oil **16** as the product (1 g, 85%). R_f = 0.6 (petroleum ether : EtOAc = 7:3); $[\alpha]_D^{20}$ = −6.9 (*c* 1.20, $CHCl_3$); IR (neat): ν_{max} 3392, 2933, 1712, 1361, 1176, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87-4.59 (m, 3H, OCH_2O, C*H*OMs), 3.69-3.49 (m, 4H, CH_2−OTBS, C*H*−N, C*H*OMOM), 3.39 (s, 3H, OCH_3), 3.02 (s, 3H, CH_3 in Ms), 1.80-1.60 (m, 2H, CH_2−CH_2), 1.56-1.47 (m, 2H, CH$_2$−CH_2), 1.47-1.38 (m, 12H, *t*Bu in Boc, CH_3), 0.88 (s, 9H, *t*Bu-Si), 0.04 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 96.9, 79.6, 79.2, 79.1, 64.8, 55.9, 51.9, 38.4, 28.3, 26.9, 26.6, 25.8, 18.2, 16.8, -5.4; MS (ESI): *m/z* 522 (M+Na)$^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{45}NO_8SSiNa$ (M+Na)$^+$, 522.2527; found 522.2560.

(2*S*,3*R*,6*S*)-*tert*-Butyl 6-((*tert*-butyldimethylsilyloxy)methyl)-3-(methoxymethoxy)-2-methylpiperidine-1-carboxylate (17): The mesylated compound **16** (650 mg, 1.30 mmol) was dissolved in dry THF (20 mL) under nitrogen atmosphere and added potassium *tert*-butoxide (1.16 g, 10.4 mmol) dropwise as a solution in dry THF (10 mL). The reaction was stirred at rt for 2 h then quenched with water (30 mL) and extracted with

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EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (neutral alumina, 2% EtOAc in hexanes) to give **17** (425 mg, 81%) and **17a** (37 mg, 7%) as a separable mixture (92:8) of diastereomers. R_f = 0.4 (petroleum ether : EtOAc = 9:1); **17:** $[\alpha]_D^{20}$ = −8.7 (*c* 0.90, $CHCl_3$); IR (neat): ν_{max} 2954, 2932, 1691, 1367, 1099, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70-4.61 (m, 2H, OCH_2O), 4.25 (q, *J* = 6.8 Hz, 1H, 2-C*H*−N), 4.17-4.06 (m, 1H, 6-C*H*−N), 3.61-3.50 (m, 2H, CH_2−OTBS, C*H*OMOM), 3.46 (dd, *J* = 9.3, 4.7 Hz, 1H, CH_2−OTBS), 3.36 (s, 3H, OCH_3), 1.97-1.56 (m, 4H, CH_2−CH_2), 1.45 (s, 9H, ^{t}Bu in Boc), 1.07 (d, *J* = 7.1 Hz, 3H, CH_3), 0.89 (s, 9H, *t*Bu-Si), 0.06 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 94.7, 79.3, 73.5, 63.1, 55.3, 51.2, 50.0, 28.4, 25.8, 19.6, 19.3, 18.2, 17.3, -5.2, -5.4; MS (ESI): *m/z* 426 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{42}NO_5Si$ $(M+H)^+$, 404.2827; found 404.2858.

17a: $[\alpha]_D^{20}$ = −26.2 (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (q, *J* = 7.0 Hz, 2H, OCH_2O), 4.11 (qd, *J* = 7.0, 3.1 Hz, 1H, 2-C*H*−N), 3.87 (t, *J* = 9.5 Hz, 1H, CH_2−OTBS), 3.75 (dd, *J* = 9.6, 4.2 Hz, 1H, CH_2−OTBS), 3.69-3.55 (m, 2H, 6-C*H*−N, C*H*OMOM), 3.34 (s, 3H, OCH_3), 2.00-1.83 (m, 2H, CH_2−CH_2), 1.81-1.69 (m, 2H, CH_2−CH_2), 1.44 (s, 9H, *t*Bu in Boc), 1.22 (d, *J* = 7.1 Hz, 3H, CH_3), 0.88 (s, 9H, ^{t}Bu-Si), 0.04 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 94.5, 79.2, 73.9, 62.9, 55.3, 53.3, 51.3, 28.4, 25.9, 22.9, 20.2, 18.2, 17.9, -5.2, -5.3.

(2*S*,3*R*,6*S*)-*tert*-Butyl 6-(hydroxymethyl)-3-(methoxymethoxy)-2-methylpiperidine-1-carboxylate (4): HF (40% in water, 0.04 mL, 0.99 mmol) was added to a stirred solution of **17** (400 mg, 0.99 mmol) in CH_3CN (10 mL) at 0 °C. The reaction mixture was allowed to warm to rt slowly over 30 min and added saturated aqueous $NaHCO_3$ (10 mL) dropwise. The reaction mixture was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the residue over neutral alumina (hexanes/EtOAc 1:1) gave **4** (229 mg, 80%) as a colorless oil. R_f = 0.2 (petroleum ether : EtOAc = 6:4); $[\alpha]_D^{20}$ = −5.4 (*c* 1.10, $CHCl_3$); IR (neat): ν_{max} 3444, 2973, 2936, 1667, 1686, 1369, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (s, 2H, OCH_2O), 4.29 (q, *J* = 6.9 Hz, 2H, C*H*−N), 3.68-3.52 (m, 3H, CH_2−OH, C*H*OMOM), 3.37 (s, 3H, OCH_3), 2.06-1.94 (m, 1H, CH_2−CH_2), 1.84-1.49 (m, 3H, CH_2−CH_2), 1.46 (s, 9H, *t*Bu in Boc), 1.15 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 94.9, 80.0, 73.5, 65.6, 55.4, 51.1, 50.5, 28.4, 19.7, 19.5, 18.4; MS (ESI): *m/z* 312 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{27}NO_5Na$ $(M+Na)^+$, 312.1781; found 312.1808.

5-((2*E*,4*E*)-Nona-2,4-dien-1-ylthio)-1-phenyl-1*H*-tetrazole (18): To a solution of (2*E*,4*E*)-nona-2,4-dien-1-ol[12] **5** (500 mg, 3.57 mmol) in THF (30 mL) was added PPh_3 (1.12 g, 4.28 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (762 mg, 4.28 mmol). The reaction mixture was cooled to 0 °C, DIAD (0.9 mL, 4.64 mmol) was slowly added and stirred at room temperature for 1 h. After completion of the reaction, solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, hexanes/EtOAc 9:1) to give **18** (1.01 g, 94%) as a colorless oil. R_f = 0.4 (petroleum ether : EtOAc = 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.68-7.43 (m, 5H, Ar), 6.31 (dd, *J* = 15.0, 10.4 Hz, 1H, 3-C*H*), 5.97 (dd, *J* = 15.2, 10.4 Hz, 1H, 4-C*H*), 5.81-5.55 (m, 2H, 2-C*H*, 5-C*H*), 4.06 (d, *J* = 7.6 Hz, 2H, 1-CH_2), 2.05 (q, *J* = 6.7 Hz, 2H, 6-CH_2), 1.43-1.20 (m, 4H, CH_2−CH_2), 0.87 (t, *J* = 7.0 Hz, 3H, −CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 137.0, 135.8, 133.6, 130.0, 129.6, 128.7, 123.7, 122.8, 35.7, 32.2, 31.1, 22.1, 13.8; MS (ESI): *m/z* 323 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{21}N_4S$ $(M+H)^+$, 301.1481; found 301.1482.

5-((2*E*,4*E*)-Nona-2,4-dien-1-ylsulfonyl)-1-phenyl-1*H*-tetrazole (3): To the solid $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.03 g, 0.834 mmol) in a round bottemed flask at 0 °C was added aq. H_2O_2 (30% w/w, 4 mL) and stirred for 15 min at 0 °C before it was added to a solution of **18** (0.5 g, 1.66 mmol) in EtOH (17 mL) at 0°C. The mixture was allowed to warm up to room temperature and stirred overnight. After completion of the reaction, it was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography of the residue (silica gel, hexanes/EtOAc 9:1) gave **3** (453 mg, 82 %) as a colorless oil. R_f = 0.4 (petroleum ether : EtOAc = 9:1); IR (neat): ν_{max} 2958, 2930, 2871, 1723, 1498, 1349, 1153, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.50 (m, 5H, Ar), 6.35 (dd, *J* = 15.2, 10.5 Hz, 1H, 3-C*H*), 6.01 (dd, *J* = 15.2, 10.5 Hz, 1H, 4-C*H*), 5.86-5.78 (m, 1H, 2-C*H*), 5.48 (dt, *J* = 15.3, 7.6 Hz, 1H, 5-C*H*), 4.41 (d, *J* = 7.6 Hz, 2H, 1-CH_2), 2.09 (q, *J* = 7.0 Hz, 2H, 6-CH_2), 1.40-1.24 (m, 4H, CH_2−CH_2), 0.89 (t, *J* = 7.2 Hz, 3H, −CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 142.4, 139.9, 132.9, 131.3, 129.5, 128.3, 125.2, 111.8, 60.0, 32.2, 30.9, 22.1, 13.8; MS (ESI): *m/z* 355 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{21}N_4O_2S$ $(M+H)^+$, 333.1380; found 333.1404.

(2*S*,3*R*,6*S*)-*tert*-Butyl 6-((1*E*,3*E*,5*E*)-deca-1,3,5-trienyl)-3-(methoxymethoxy)-2-methylpiperidine-1-carboxylate (19): A round bottomed flask charged with 2-iodoxybenzoic acid (IBX) (116 mg, 0.41 mmol), DMSO (0.2 mL) was stirred under nitrogen atmosphere for 10 min at rt to get a clear solution. To this solution was then added compound **4** (60 mg, 0.20 mmol) in EtOAc (1 mL) dropwise at room temperature. The reaction mixture was heated to 70 °C and stirred for 30 min. After completion of the reaction, the reaction mixture was cooled to room temperature and diluting with EtOAc (5 mL). The precipitate was filtered and washed with EtOAc (5 mL). The filtrate was washed with aqueous saturated $NaHCO_3$ solution (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get aldehyde which was used for the next step without further purification.

To a solution of sulfone **3** (82 mg, 0.24 mmol) and 18-crown-6 (64 mg, 0.24 mmol) in dry DME (5 mL) was added dropwise KHMDS (1 M in THF, 0.2 mL, 0.2 mmol) at -78 °C under nitrogen atmosphere. After being stirred for 30 min, a solution

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of above prepared aldehyde in dry DME (3 mL) was added slowly to the reaction mixture and stirred for 2 h at -78 °C before warming to rt and stirred over night. The reaction mixture was poured into aqueous saturated NH_4Cl solution (5 mL) and extracted with ethyl acetate (2 x 5 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and solvent was removed under reduced pressure. Flash chromatography of the crude over neutral alumina (5% EtOAc in hexanes) gave **19** (58 mg, 72%) as a colorless oil. R_f = 0.3 (petroleum ether : EtOAc = 9:1); $[\alpha]_D^{20}$ = −18.6 (*c* =1.30, $CHCl_3$); IR (neat): ν_{max} 2930, 1688, 1365, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20-5.98 (m, 4H, =C*H*−C*H*=C*H*−C*H*=), 5.76-5.62 (m, 2H, −CH_2−C*H*=, =C*H*−CHN), 4.77 (br t, *J* = 5.1 Hz, 1H, 6-C*H*−N), 4.66 (q, *J* = 7.0 Hz, 2H, OCH_2O), 4.31 (q, *J* = 7.0 Hz, 1H, 2-C*H*−N), 3.64-3.55 (m, 1H, C*H*OMOM), 3.36 (s, 3H, OCH_3), 2.19-2.00 (m, 2H, =CH−CH_2), 1.90-1.54 (m, 3H, CH_2−CH_2), 1.45 (s, 9H, ^{t}Bu in Boc), 1.50-1.22 (m, 5H, CH_2−CH_2), 1.11 (d, *J* = 7.2 Hz, 3H, CH−CH_3), 0.88 (t, *J* = 7.0 Hz, 3H, CH_2−CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 135.4, 134.7, 132.5, 130.3, 130.1, 130.1, 94.7, 79.4, 73.3, 55.3, 50.5, 50.4, 32.4, 31.4, 28.4, 22.1, 21.6, 19.8, 19.3, 13.8; MS (ESI): *m/z* 416 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{23}H_{40}NO_4$ $(M+H)^+$, 394.2952; found 394.2976.

Microcosamine A (2a): To the compound **19** (100 mg, 2.18 mmol) was added 3N HCl in methanol (2 mL) and stirred for 12 h at rt. After completion of the reaction, methanol was evaporated to dryness under reduced pressure and 6N HCl (5 mL) was added. The aqueous layer was washed with diethyl ether (2 x 10 mL), basified with 2 N NaOH solution and extracted with diethyl ether (3 x 15 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish the desired compound **2a** (49 mg, 78%) as a pale yellow solid. . Mp: 107-109 °C; R_f = 0.2 (EtOAc : MeOH = 95:5); $[\alpha]_D^{20}$ = +5.6 (*c* 1.00, CH_3OH); IR (neat): ν_{max} 3445, 2924, 2854, 1660, 1127, 473 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.22-6.11 (m, 2H, =CH−C*H*=C*H*−CH=), 6.11-5.98 (m, 2H, =C*H*−CH=CH−C*H*=), 5.73-5.66 (m, 1H, −CH_2−C*H*=), 5.60 (dd, *J* = 15.2, 7.1 Hz, 1H, =C*H*−CHN), 3.23-3.14 (m, 2H, 6-C*H*−N, C*H*OH), 2.57-2.50 (m, 1H, 2-C*H*−N), 2.25 (br s, 1H, O*H*), 2.11-2.04 (m, 3H, =CH−CH_2, CH_2−CH_2), 1.77-1.71 (m, 1H, CH_2−CH_2), 1.40-1.28 (m, 6H, CH_2−CH_2), 1.20 (d, *J* = 6.1 Hz, 3H, CH−CH_3), 0.89 (t, *J* = 7.1 Hz, 3H, CH_2−CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 135.0, 132.9, 130.4, 130.1, 129.8, 73.6, 58.6, 58.3, 33.9, 32.4, 31.9, 31.4, 22.2, 18.9, 13.9; MS (ESI): *m/z* 250 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{28}NO$ $(M+H)^+$, 250.2165; found 250.2180.

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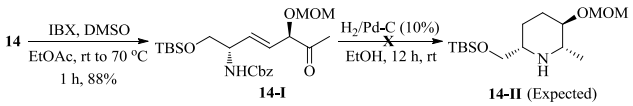
1. For selected reviews of piperidine alkaloids, see; (a) Makabe, H. *Stud. Nat. Prod. Chem*. **2014**, *42*, 353−371; (b) Ojima, I.; Iula, D. M. *Alkaloids: Chemical and Biological Perspectives*; Elsevier: Oxford, UK, **1999**; Vol. *13*, p 371−412; (c) Plunkett, O.; Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Sainsbury, M., Ed.; Elsevier: Amsterdam, **1998**, Part F/Part G (partial), pp 365−421; (d) Schneider, M. J. *Alkaloids: Chemical and Biological Perspectives*; Elsevier: Oxford, UK, **1996**; Vol. *10*, p 155−299; (e) Angle, S. R.; Breitenbucher, J. G. *Stud. Nat. Prod. Chem*. **1995**, *16*, 453−502; (f) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, **1985**, Vol. *26*, pp 89−183; (g) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, NY, **1985**, Vol. *3*, pp 1−90; (h) Jones, T. H.; Blum, M. S. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, **1983**; Vol. *1*, Chapter 2, pp. 33−84.
2. Representative references, for isolation, see: (a) Viegas Jr., C.; Bolzani, V. da S.; Furlan, M.; Barreiro, E. J.; Young, M. C. M.; Tomazela, D.; Eberlin, M. N. *J. Nat. Prod.* **2004**, *67*, 908−910; (b) Kusano, G.; Orihara, S.; Tsukamoto, D.; Shibano, M.; Coskun, M.; Guvenc, A.; Erdurak, C. S. *Chem. Pharm. Bull.* **2002**, *50*, 185−192; (c) Highet, R. J. *J. Org. Chem.* **1964**, *29*, 471−474; (d) Rice, W. Y.; Coke, J. L. *J. Org. Chem*. **1966**, *31*, 1010−1012; For activity, see: (e) Sansores-Peraza, P.; Rosado-allado, M.; Brito-Loeza, W.; Mena-Rejon, G. J.; Quijano, L. *Fitoterapia* **2000**, *71*, 690−692; (f) Astudillo, S. L.; Jurgens, S. K.; SchmedaHirschmann, G.; Griffith, G. A.; Holt, D. H.; Jenkins, P. R. *Planta Med.* **1999**, *65*, 161−162; (g) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem*. **1994**, *59*, 3575−3584; (h) Aguinaldo, A. M.; Read, R. W. *Phytochemistry* **1990**, *29*, 2309−2313; (i) Ahmad, A.; Khan, K. A.; Ahmad, V. U.; Qazi, S. *Planta Med.* **1986**, *4*, 285−288; (j) Fodor, G. B.; Colasanti, B. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, **1985**; Vol. *3*, Chapter 1, pp. 1−90; (k) Fodor, G.; Fumeaux, J.-P.; Sankaran, V. *Synthesis* **1972**, 464−472; (l) Bourinet, P.; Quevauviller, A. *Compt. Rend. Soc. Biol.* **1968**, *162*, 1138−1140; (m) Bourinet, P.; Quevauviller, A. *Ann. Pharm. Fr.* **1968**, *26*, 787−796.
3. Selected recent references for synthesis, see: (a) Pijl, F. V. D.; Delft, F. L. V.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2015**, 4811−4829; (b) Xiao, K.-J.; Wang, Y.; Huang, Y.-H.; Wang, X.-G.; Huang, P.-Q. *J. Org. Chem.* **2013**, *78*, 8305−8311; (c) Wijdeven, M. A.; Willemsen, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2010**, 2831−2844; (d)

Koulocheri, S. D.; Pitsinos, E. N.; Haroutounian, S. A. *Curr. Org. Chem.* **2008**, *12*, 1454−1467; (e) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001; (f) Maa, D.; Ma, N. *Tetrahedron Lett.* **2003**, *44*, 3963–3965; (g) Singh, R.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 7711–7715; (h) Zhai, H.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2007**, *72*, 3853−3858; (i) Kim, G.; Kim, N. *Tetrahedron Lett.* **2007**, *48*, 4481−4483; (j) Yu, S.; Pu, X.; Cheng, T.; Wang, R.; Ma, D. *Org. Lett.* **2006**, *8*, 3179−3182; (k) Pu, X.; Ma, D. *J. Org. Chem.* **2006**, *71*, 6562−6572; (l) Snider, B. B.; Neubert, B. J. *Org. Lett.* **2005**, *7*, 2715−2718; (m) Lofstedt, J.; Pettersson-Fasth, H.; Backvall, J.-E. *Tetrahedron* **2000**, *56*, 2225–2230; (n) Toyooka, N.; Yoshida, Y.; Yotsui, Y.; Momose, T. *J. Org. Chem.* **1999**, *64*, 4914−4919.

4. (a) Lindquist, N.; Shigematsu, N.; Pannell, L. *J. Nat. Prod.* **2000**, *63*, 1290−1291; (b) McCrea-Hendrick, M.; Nichols, C. J. *Synthetic Communications*, **2009**, 39, 3611−3620.
5. Feng, S. X.; Lin, L. D.; Xu, H. H.; Wei, X. Y. *J. Asian Nat. Prod. Res.* **2008**, *10*, 1155−1158.
6. Still, P. C.; Yi, B.; Cestari, T. F. G.; Pan, L.; Pavlovicz, R. E.; Chai, H. B.; Ninh, T. N.; Li, C.; Soejarto, D. D.; McKay, D. B.; Kinghorn, A. D. *J. Nat. Prod.* **2013**, *76*, 243−249.
7. Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488−.
8. (a) Reddy, C. R.; Reddy, M. D.; Dilipkumar, U. *Eur. J. Org. Chem.* **2014**, 6310−6313; (b) Reddy, C. R.; Latha, B.; Rao, N. N. *Tetrahedron* **2012**, *68*, 145−151; (c) Reddy, C. R.; Latha, B. *Tetrahedron: Asymmetry* **2011**, *22*, 1849−1854.
9. (a) L. J. Dorr, In *Flora of China*, Vol. *12*; Z. Y. Wu, P. H. Raven, D. Y. Hong (Eds), Science Press, Beijing, and Missouri Botanical Garden Press: St. Louis, MO, **2007**, 1753, 251−258; (b) T. Ya, M. G. Gilbert, L. J. Dorr, *Tiliaceae*, eFlora China *12*, **2007**; (c) State Administration of Traditional Chinese Medicine, *Chinese Herbal Medicine*, Vol. *5*, (Shanghai Science and Technology Press, Shanghai) **1999**, 324−326.
10. (a) J. Luo, L. Zhang, M. F. Roberts, J. D. Phillipson, *Acta Pharm. Sin.* **2009**, *44*, 150−153; (b) K. A. N. P. Bandara, V. Kumar, U. Jacobsson, L.-P. Molleyres, *Phytochemistry* **2000**, *54*, 29−32; (c) A.M. Aguinaldo, R.W. Read, *Phytochemistry* **1990**, *29*, 2309−2313.
11. (a) Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194−3204; (b) Kocienski, P. J. *Phosphorus and Sulfur* **1985**, *24*, 97−127; (c) Julia, M.; Launay, J.; Verpeaux, S.; Verpeaux, J. *Tetrahedron Lett.* **1982**, *23*, 2465−2472; (d) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829−834; (e) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833−4836.
12. Experimental procedures for preparation of the conjugated alcohol **5** from 1-octyne **8** were described in the supplementary information (Scheme S1). For reference, see: (a) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659−2660; (b) Kazmaier, U. *Tetrahedron* **1998**, *54*, 1491−1496.
13. (a) Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett*, **1993**, 774−776; (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738; (c) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Ber.* **1958**, *91*, 61−63.
14. (a) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459; (b) Luche, J. L. *J. Am. Chem. Soc.* **1978**, 100, 2226−2227.
15. (a) Tamamura, H.; Koh, Y.; Ueda, S.; Sasaki, Y.; Yamasaki, T.; Aoki, M.; Maeda, K.; Watai, Y.; Arikuni, H.; Otaka, A.; Mitsuya, H.; Fujii, N. *J. Med. Chem.* **2003**, *46*, 1764−1768; (b) Jacobsen, E. J. et al., *J. Med. Chem.* **1999**, *42*, 1525−1536; (c) Konradi, A. W. et al., *J. Am. Chem. Soc.* **1994**, *116*, 1316−1323.
16. Rodriquez, M.; Bruno, I.; Cini, E.; Marchetti, M.; Taddei, M.; Gomez-Paloma, L. *J. Org. Chem.* **2006**, *71*, 103−107.
17. Oxidation of compound **14** under IBX condition smoothly gave ketone **14-I** in 88% yield. Further, hydrogenation of compound **14-I** in the presence of H_2/Pd-C (10 wt%) in EtOH gave the complex mixture of diastereomeric products **14-II** along with the starting material.



18. (a) Biela, A.; Oulaïdi, F.; Gallienne, E.; Gorecki, M.; Frelek, J.; Martin, O. R. *Tetrahedron* **2013**, *69*, 3348−3354; (b) Chandrasekhar, B.; Rao, J. P.; Rao, B. V.; Naresh, P. *Tetrahedron Lett.* **2011**, *52*, 5921–5925; (c) Alegret, C.; Ginesta, X.; Riera, A. *Eur. J. Org. Chem.* **2008**, 1789–1796.
19. The 2D COSY and NOESY spectras of compouds **17** and **17a** were included in the supporting information.
20. Mitsunobu, O. *Synthesis* **1981**, 1–28.
21. Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140–1142.
22. (a) Pospisil, J. *Tetrahedron Lett.* **2011**, *52*, 2348−2352; (b) Nakatani, Y.; Oshita, J.; Ishigami, K.; Watandbe, H.; Kitahara, T. *Tetrahedron* **2006**, *62*, 160–165; (c) Blakemore*a*, P. R.; Cole*a*, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26−28.

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Graphical Abstract

Total synthesis of a piperidine alkaloid, Microcosamine A

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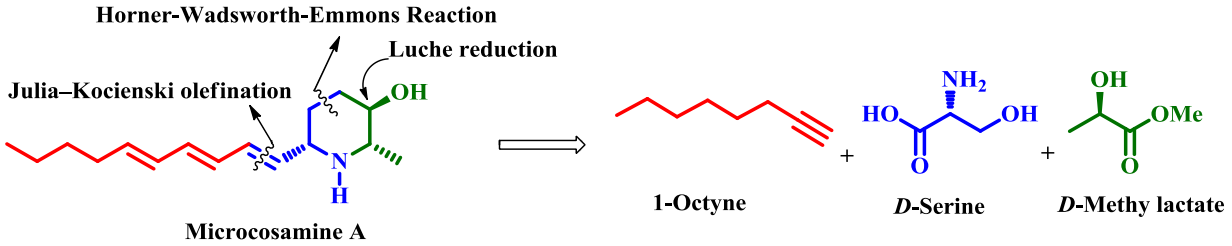

The first total synthesis of a novel piperidine alkaloid, microcosamine A, is achieved from commercially available *D*-serine, *D*-methyl lactate and 1-octyne as starting materials.