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Synthesis of the C10–C24 fragment of (+)-cannabisativine

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ABSTRACT

The stereoselective synthesis of the C10–C24 fragment of (+)-cannabisativine has been achieved. The key steps involved in this strategy are the Sharpless asymmetric dihydroxylation, the diastereoselective allylation of an imine, and the ring closing metathesis (RCM).

1. Introduction

The piperidine ring system is one of the most common motifs found in numerous natural products, drugs, and drug candidates.[1] It was pointed out by Watson et al.[2] that the piperidinic substructure was reported in over 12,000 compounds in clinical or pre-clinical studies from July 1988 to December 1998. 2,6-Disubstituted piperidines represent a subclass of naturally occurring alkaloids that have also been the target of many synthetic efforts due to their wide range of pharmacological activities.[3] Moreover, the 2,6-disubstituted tetrahydropyridine framework can be regarded as a valuable basic unit since the possibility of modification and functionalization of the double bond enables the preparation of polysubstituted piperidines.

(+)-Cannabisativine **1** is a macrocyclic spermidine alkaloid containing a *trans*-2,6-disubstituted-1,2,5,6-tetrahydropyridine ring annulated to a 13-membered lactam ring (Fig. 1). This was the first reported non-quaternary alkaloid possessing the pyrido[1,2-*d*]-[1,5,9]-triazacyclotridecine nucleus isolated from *Cannabis sativa L* and perhaps the most challenging alkaloid of its class.[4] Since then, it has attracted two racemic and two asymmetric syntheses including the one by Hamada et al. for (−)-cannabisativine.[5]

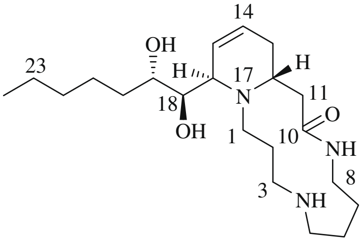

Figure 1. Structure of (+)-cannabisativine.

These unique as well as challenging structural features, along with our interest in synthesizing heterocyclic compounds, especially containing nitrogen[6] and oxygen[7] as the heteroatoms, prompted us to undertake the synthesis of (+)-cannabisativine. Herein, we report the synthesis of *trans*-2,6-disubstituted tetrahydropyridine core, that is, C10–C24 fragment of (+)-cannabisativine.

From a retrosynthetic perspective (Scheme 1), disconnection of **1** at the amide bond and the C1–N17 bond led to the target fragment **2** comprising all the stereocenters of **1**. The fragment **2** was envisaged to be derived from sub target **3** which itself could be realized from fragments **4** and **5**. The aminoalcohol segment **4** could be synthesized from (*R*)-Garner's aldehyde **6**.

2. Results and discussion

The synthesis commenced with the Wittig olefination[8] of (*R*)-Garner's aldehyde **6**[9] using *n*-hexyltriphenylphosphonium bromide and *n*-BuLi to furnish olefin **7** in 72% yield. The acetonide group in **7** was cleaved in the presence of 70% aqueous acetic acid at 60 °C to give aminoalcohol **8** (84%), which was selectively protected as its pivaloyl ester **9** (PivCl, Py, CH_2Cl_2) in 93% yield. The pivaloyl-protected olefin **9** was exposed to Sharpless asymmetric dihydroxylation[10,11] using an AD mix α,-methanesulfonamide in *t*-BuOH/H_2O (1:1) to give diol **10** along with another diastereomer (92:8) in 86% yield (for both diastereomers) (Scheme 2). The two hydroxyl groups in **10** were protected as their MOM-ethers to yield **11** using MOMCl and DIPEA in CH_2Cl_2 in 96% yield. The reductive removal of the pivaloyl group in **11** with DIBAL-H at 0 °C provided the alcohol **12** in 95% yield. Alcohol **12** was subsequently oxidized to the corresponding aldehyde using Dess–Martin periodinane followed by Wittig olefination to furnish the olefinic product **13** in 74% yield over two steps (a separable mixture of *trans*:*cis* = 92:8). Finally, fragment **4** was realized by deprotection of both the MOM and Boc groups in a single step using 5% HCl in MeOH in 89% yield.

The synthesis of aldehyde **5** was accomplished using a well-documented procedure in the literature from 1,3-propane diol (Scheme 3).[12]

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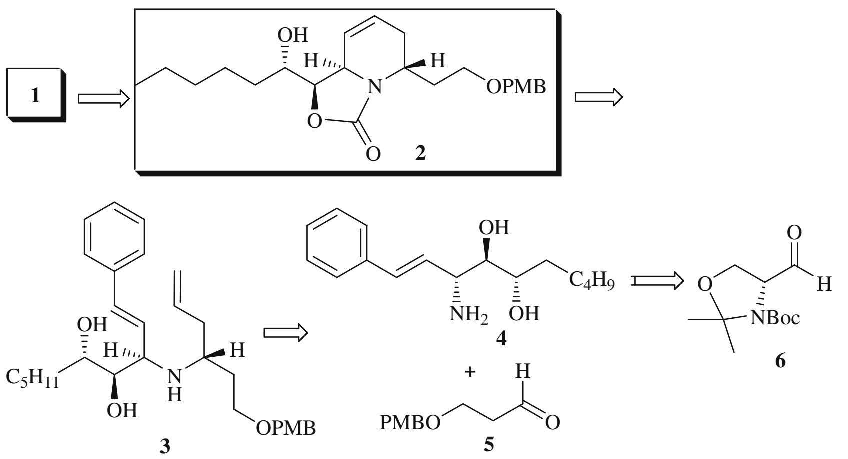
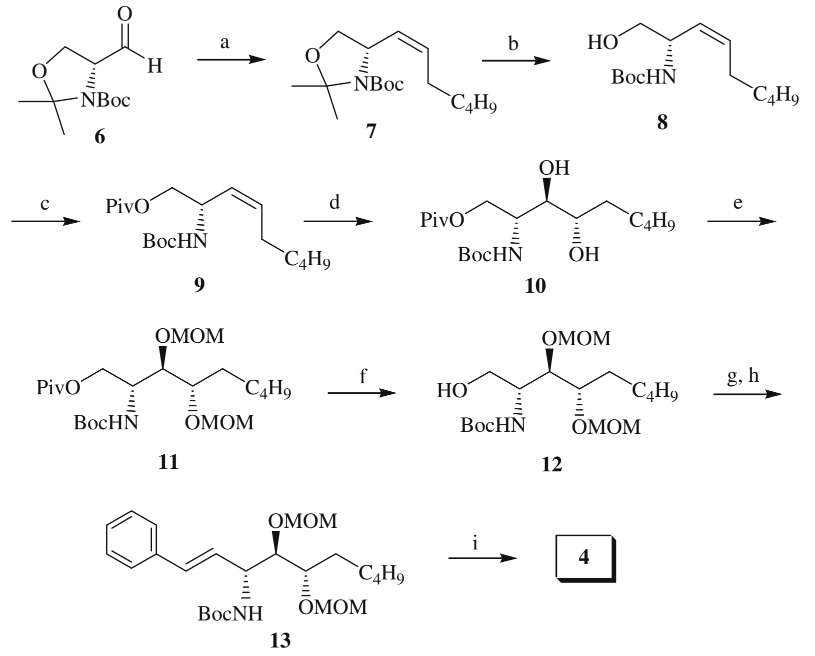
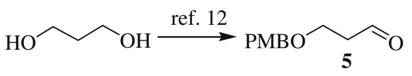


Scheme 1. Retro synthesis of (+)-cannabisativine.



Scheme 2. Reagents and conditions: (a) $C_6H_{13}Ph_3P^+Br^-$, *n*-BuLi, −78 °C-rt, 3 h, 72%; (b) 70% CH_3CO_2H (aq), 60 °C, 1 h, 84%; (c) $(CH_3)_3CCOCl$, Py, CH_2Cl_2, 93%; (d) AD-mix-α, *t*-BuOH/H_2O (1:1) 0 °C, 24 h, 86%; (e) MOMCl, DIPEA, CH_2Cl_2, 2 h, 96%; (f) DIBALH, CH_2Cl_2, −30-0 °C, 30 min, 95%; (g) DMP, CH_2Cl_2; (h) $PhCH_2Ph_3P^+Br^-$, KHMDS, 0 °C-rt, 6 h, 74%; (i) 5% HCl in MeOH, 0 °C-rt, 89%.



Scheme 3.

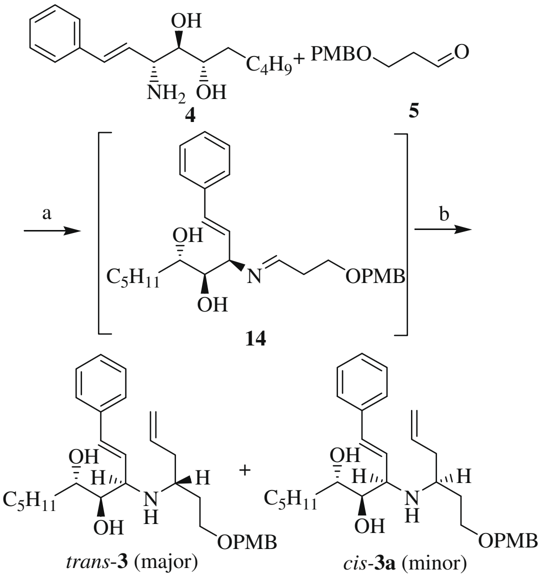
The synthesis of target fragment **2** began with the coupling of fragments **4** and **5** subsequently followed by diastereoselective allylation,[13] which was the crucial step in the synthetic strategy. The aminoalcohol **4** and the aldehyde **5** were condensed in anhydrous Et_2O in the presence of anhydrous $MgSO_4$ to generate the imine **14**. This reaction mixture containing **14** was filtered under an argon atmosphere and without any concentration or purification, was added to a freshly prepared solution of allylmagnesium bromide in Et_2O at −78 °C to obtain two diastereomers, the *trans*-**3** (major) and the *cis*-**3a** (minor) in a ratio of 82:18 (separated by column chromatography) in 73% yield over two steps (Scheme 4).

It is believed that this diastereoselective allylation reaction of the imine proceeded through any one of the following proposed transition states shown in Figure 2. The attack of the incumbent allyl group was more facile from the side opposite to the orientation of bulky phenyl group leading to the observed diastereoselectivity in favor of the *trans* configuration at the 2,6-position of the piperidine ring.

The amine group, along with the adjacent hydroxyl group in **3** was protected as a cyclic carbamate using $(Im)_2CO$ and Et_3N in CH_2Cl_2 to give **15** with 98% conversion. Finally, the ring closing metathesis[14] on **15** proceeded smoothly with a 2nd generation Grubbs catalyst to furnish the required C10–C24 fragment **2** in 88% yield (Scheme 5). The stereochemistry at the centers adjacent to the nitrogen (2,6-position) of the piperidine ring was confirmed by a 2D NOE study and found to be *trans* as predicted.

3. Conclusions

In conclusion, we have achieved the stereoselective synthesis of a functionalized C10–C24 fragment of (+)-cannabisativine using



Scheme 4. Reagents and conditions: (a) $MgSO_4$, Et_2O, 2 h; (b) AllylMgBr, Et_2O, −78 to −40 °C, 6 h, 73%.

the Sharpless asymmetric dihydroxylation, the diastereoselective allylation of an imine, and the ring closing metathesis (RCM) reactions as the key reaction steps.

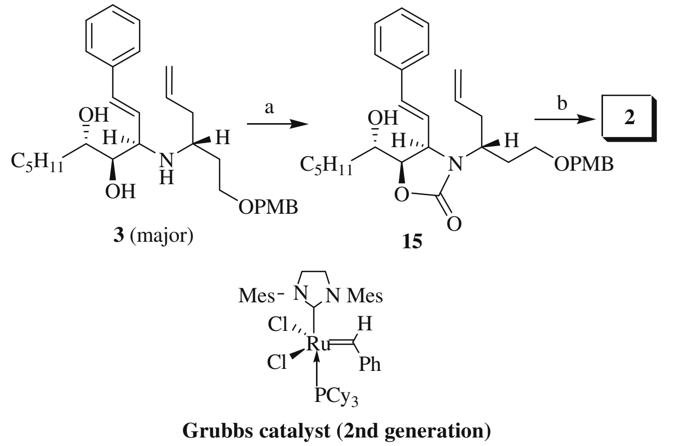
4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Brucker Avance 300. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in hertz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL.

4.1.1. (*S,Z*)-*tert*-Butyl 4-(hept-1-enyl)-2,2-dimethyloxazolidine-3-carboxylate 7

Freshly prepared *n*-hexyl triphenylphosphonium bromide (22.3 g, 52.4 mmol) was suspended in dry THF (60 mL) in a round-bottomed flask under N_2, was cooled to −78 °C, and *n*-BuLi (17.6 mL, 44.2 mmol, 2.5 M in hexanes) was added dropwise over a period of 10 min. The resulting dark red solution was allowed to warm to 0 °C and stirred for 30 min at the same temperature. The solution was then cooled to −78 °C and a solution of Garner's aldehyde **6** (6.0 g, 26.2 mmol) in dry THF (20 mL) was added dropwise over a period of 30 min. After being stirred for 3 h at room temperature, the reaction mixture was diluted with saturated aqueous NH_4Cl (30 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. Purification by flash chromatography on silica gel (petroleum ether/EtOAc, 19:1) provided the olefinic product **7** as a pale yellow oil (5.6 g, 72%): $[\alpha]_D^{25} = -75.5$ (*c* 1.0, $CHCl_3$); IR (Neat): *v* 2960, 2928, 1689, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.46–5.39 (m, 2H), 4.70–4.65 (m, 1H), 4.06 (dd, 1H, *J* = 8.5, 14.5 Hz), 3.65 (dd, 1H, *J* = 8.5, 3.0 Hz), 2.09 (br s, 2H), 1.60–1.26 (m, 21H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.2, 132.0, 131.0, 79.9, 69.3, 54.8, 31.7, 29.9, 29.6, 28.7, 27.7, 22.8, 14.3; ESIMS: *m/z* 298 $[M+H]^+$; HRMS calcd for $C_{17}H_{32}NO_3$: 298.2363, found: 298.2366.



Scheme 5. Reagents and conditions: (a) $(Im)_2CO$, Et_3N, CH_2Cl_2, rt, 98%; (b) Grubbs catalyst (2nd generation), CH_2Cl_2, reflux, 6 h, 88%.

4.1.2. (*S,Z*)-*tert*-Butyl-1-hydroxynon-3-en-2-ylcarbamate 8

A solution of olefin **7** (5.50 g, 18.5 mmol) in 70% aqueous acetic acid (25 mL) was stirred at 60 °C for 1 h. After the complete disappearance of the starting material, the reaction mixture was cooled to 0 °C, diluted with $CHCl_3$ (50 mL), and neutralized with saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL) and combined organic extracts were washed with water, brine (50 mL), and dried over Na_2SO_4. After removal of the solvent under vacuo, the crude residue was chromatographed using hexanes/EtOAc (8:2) to furnish the alcohol **8** (4.0 g) in 84% yield as a white solid: mp 99 °C;

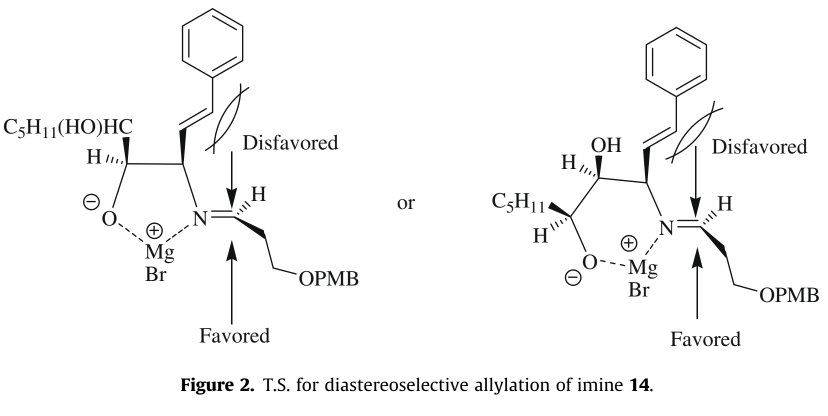


Figure 2. T.S. for diastereoselective allylation of imine **14**.

$[\alpha]_D^{25} = -27.2$ (*c* 1.0, $CHCl_3$); IR (Neat): *ν* 3361, 2964, 2861, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): *δ* 5.59 (dd, 1H, *J* = 7.5, 17.5 Hz), 5.25 (t, 1H, *J* = 9.4 Hz), 4.71 (br s, 1H), 4.49 (br s, 1H), 3.59 (m, 2H) 2.90 (br s, 1H), 2.13 (m, 2H) 1.44 (s, 9H), 1.41–1.25 (m, 6H), 0.89 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 156.2, 134.7, 125.9, 79.8, 66.4, 50.6, 31.4, 29.1, 28.3, 27.8, 22.4, 14.2; ESIMS: *m/z* 280 $[M+Na]^+$; HRMS calcd for $C_{14}H_{27}NNaO_3$: 280.1883, found: 280.1884.

4.1.3. (*S*,*Z*)-2-(*tert*-Butoxycarbonylamino)non-3-enyl pivalate 9

To a solution of amino alcohol **8** (4.20 g, 16.3 mmol) in dry CH_2Cl_2 (45 mL) was added pyridine (2.6 mL, 32.6 mmol) at 0 °C and stirred for 15 min under the inert atmosphere of nitrogen. Pivaloyl chloride (2.35 g, 19.6 mmol) was added at the same temperature and stirring was continued for the next 3 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (70 mL), washed with 1 M HCl (2 × 20 mL), water, brine (40 mL), and dried over Na_2SO_4. After removal of the solvent under vacuum, the crude residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 88:12) to furnish the protected alcohol **9** (5.18 g) as a pale yellow oil in 93% yield: $[\alpha]_D^{25} = -8.4$ (*c* 0.7, $CHCl_3$); IR (Neat): *ν* 3379, 2927, 1722, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.61–5.49 (m, 1H), 5.20 (t, 1H, *J* = 9.0 Hz), 4.73–4.60 (m, 1H), 4.50 (br s, 1H), 4.06–3.96 (m, 2H), 2.24–2.05 (m, 2H), 1.43 (s, 9H), 1.39–1.23 (m, 6H), 1.20 (s, 9H), 0.90 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 178.6, 155.2, 134.9, 133.6, 126.1, 79.7, 66.1, 47.5, 39.0, 31.6, 29.3, 28.5, 28.0, 27.3, 26.6, 22.7, 14.1; ESIMS: *m/z* 364 $[M+Na]^+$; HRMS calcd for $C_{19}H_{35}NNaO_4$: 364.2458, found: 364.2469.

4.1.4. (2*R*,3*R*,4*S*)-2-(*tert*-Butoxycarbonylamino)-3,4-dihydroxynonyl pivalate 10

AD mix-α (8.12 g, 1.4 g for 1.0 mmol of olefin) was dissolved in ^{t}BuOH (10 mL) and H_2O (10 mL). Methanesulfonamide (0.55 g, 5.8 mmol) and alkene **9** (2.00 g, 5.8 mmol) were then added at 0 °C and the reaction mixture was stirred vigorously for 24 h at the same temperature. After complete consumption of the starting material, Na_2SO_3 (8.00 g) was added and the solution was stirred for 1 h after which the reaction mixture was poured into water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine (30 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield the crude diol which was purified by silica gel column chromatography using EtOAc/hexanes (35:65) to yield pure diol **10** (1.73 g, 80%) as a colorless thick oil: $[\alpha]_D^{25} = -19.2$ (*c* 1.35, $CHCl_3$); IR (Neat): *ν* 3372, 2962, 1713, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 4.96 (d, 1H, *J* = 8.8 Hz), 4.43 (dd, 1H, *J* = 6.9, 14.7 Hz), 4.24 (dd, 1H, *J* = 3.5, 15.2 Hz), 4.06–3.95 (m, 1H), 3.72–3.62 (m, 1H), 3.54 (q, 1H, *J* = 6.0 Hz), 3.08 (d, 1H, *J* = 4.5 Hz), 2.47 (d, 1H, *J* = 4.1 Hz), 1.73–1.60 (m, 1H), 1.58–1.25 (m, 17H), 1.22 (s, 9H), 0.89 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 179.0, 155.8, 79.6, 75.1, 72.6, 63.8, 51.3, 38.7, 32.3, 31.6, 28.2, 27.0, 25.4, 22.4, 13.9; ESIMS: *m/z* 398 $[M+Na]^+$; HRMS calcd for $C_{19}H_{37}NNaO_6$: 398.2513, found: 398.2526.

4.1.5. (2*R*,3*R*,4*S*)-2-(*tert*-Butoxycarbonylamino)-3,4-bis(methoxymethoxy)nonyl pivalate 11

To a stirred solution of the diol **10** (3.60 g, 9.6 mmol) and diisopropylethyl amine (6.2 mL, 48.0 mmol) in dry CH_2Cl_2 (30 mL) was added MOMCl (3.84 g, 48.0 mmol) under a nitrogen atmosphere over 5 min at 0 °C and the mixture was allowed to warm to room temperature and stirred for 2 h. After cooling to 0 °C, the reaction mixture was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with water, brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (93:7) gave **11** (4.48 g, 96% yield) as a pale yellow liquid: $[\alpha]_D^{25} = +24.1$ (*c* 1.0, $CHCl_3$); IR (Neat): 3373, 2960, 1720, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.07 (d, 1H, *J* = 9.4 Hz), 4.69 (td, 4H, *J* = 6.7, 6.9 Hz), 4.24 (d, 2H, *J* = 5.8 Hz), 4.13–4.02 (m, 1H), 3.71–3.62 (m, 2H), 3.40 (s, 3H), 3.39 (s, 3H), 1.63–1.53 (m, 2H), 1.43 (s, 9H), 1.38–1.23 (m, 6H), 1.20 (s, 9H), 0.90 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 178.5, 155.2, 97.1, 96.4, 80.3, 79.2, 77.9, 63.5, 56.1, 55.8, 50.1, 31.7, 30.4, 28.3, 27.0, 25.1, 22.5, 13.9; ESIMS: *m/z* 464 $[M+H]^+$; HRMS calcd for $C_{23}H_{46}NO_8$: 464.3218, found: 464.3231.

4.1.6. *tert*-Butyl (2*R*,3*R*,4*S*)-1-hydroxy-3,4-bis(methoxymethoxy)nonan-2-yl carbamate 12

To a stirred solution of the pivaloyl ester **11** (2.20 g, 4.7 mmol) in dry CH_2Cl_2 (20 mL) was added DIBAL-H (5.0 mL, 7.1 mmol, 20% solution in toluene) under nitrogen atmosphere over 5 min at −20 °C and the mixture was allowed to warm to room temperature and stirred for 10 min. After completion of the reaction, the reaction mixture was cooled to 0 °C, quenched with saturated sodium potassium tartrate solution, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with water, brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated. Silica gel column chromatography of the crude product using EtOAc/hexanes (17:83) gave **12** (1.71 g, 95% yield) as a colorless oil: $[\alpha]_D^{25} = +30.3$ (*c* 1.0, $CHCl_3$); IR (Neat): *ν* 3444, 2930, 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.26 (br s, 1H), 4.80–4.57 (m, 4H), 3.94 (d, 1H, *J* = 9.8 Hz), 3.74–3.66 (m, 2H), 3.59 (t, 1H, *J* = 9.0 Hz), 3.42 (s, 3H), 3.38 (s, 3H), 3.00–2.89 (m, 1H), 1.64–1.51 (m, 2H), 1.43 (s, 9H), 1.38–1.25 (m, 6H), 0.90 (t, 3H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 155.5, 97.7, 96.5, 80.7, 79.4, 78.2, 62.5, 56.1, 55.8, 51.7, 31.7, 30.2, 28.3, 25.4, 22.5, 13.9; ESIMS: *m/z* 402 $[M+Na]^+$; HRMS calcd for $C_{18}H_{37}NO_7Na$: 402.2462, found: 402.2467.

4.1.7. *tert*-Butyl (3*R*,4*R*,5*S*,*E*)-4,5-bis(methoxymethoxy)-1-phenyldec-1-en-3-ylcarbamate 13

To a solution of alcohol **12** (1.60 g, 4.2 mmol) in CH_2Cl_2 (15 mL) was added Dess–Martin periodinane (2.69 g, 6.3 mmol) at room temperature and stirred for 30 min at the same temperature. After complete consumption of the starting material, the reaction mixture was diluted with Et_2O (20 mL) and filtered through a Celite bed. The filtrate was washed with $NaHCO_3$ (20 mL), water, brine (20 mL), and concentrated in vacuo. The crude aldehyde thus obtained was utilized for the next step without further purification.

To a stirred suspension of the $PhCH_2Ph_3P^+Br^-$ (3.44 g, 7.9 mmol) in dry THF (20 mL) was added KHMDS (12.3 mL, 6.2 mmol, 0.5 M solution in toluene) dropwise over a period of 5 min at 0 °C under N_2. The bright red solution was stirred for another 30 min at rt. The reaction mixture was cooled to 0 °C, and a solution of the crude aldehyde (1.6 g) in dry THF (10 mL) was slowly added over a period of 30 min. The light yellow mixture was stirred at room temperature for 3 h. Then, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with water, brine (30 mL), and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by column chromatography using a mixture of EtOAc/hexanes (1:9) as eluent to furnish the alkene **13** as a colorless oil (1.40 g, 74% yield over the two steps): $[\alpha]_D^{25} = -18.5$ (*c* 1.3, $CHCl_3$); IR (Neat): *ν* 3366, 3018, 2930, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.39–7.14 (m, 5H), 6.55 (d, 1H, *J* = 15.8 Hz), 6.22 (dd, 1H, *J* = 6.7, 15.3 Hz), 5.61 (d, 1H, *J* = 8.3 Hz), 4.60–4.50 (m, 5H), 3.69–3.58 (m, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 1.64–1.23 (m, 17H), 0.88 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 155.2, 136.9, 131.7, 128.4, 127.3, 126.6, 126.3, 97.9, 96.4, 83.8, 78.0, 56.0, 55.9, 53.0, 31.9, 30.5, 28.3, 24.5, 22.5, 13.9; ESIMS: *m/z* 474 [M+Na]$^+$; HRMS calcd for $C_{25}H_{41}NNaO_6$: 474.2826, found: 474.2815.

4.1.8. (3*R*,4*R*,5*S*,*E*)-3-Amino-1-phenyldec-1-ene-4,5-diol 4

A solution of **13** (1.20 g, 2.6 mmol) in MeOH (15 mL) was treated with concentrated HCl (0.7 mL, 5% v/v) at 0 °C. After stirring at reflux for 4 h, the volatiles were evaporated under reduced pressure. The residue was taken up with CH_2Cl_2 and H_2O and the resulting mixture was basified with solid NaOH. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined extracts were dried over anhydrous Na_2SO_4. Removal of the solvent left a light yellow solid, which on silica gel column chromatography eluted with $CHCl_3$/MeOH (94:6) furnished the pure free amino alcohol **4** as a white solid (0.7 g) in 89% yield: $[\alpha]_D^{25} = +14.0$ (*c* 0.9, $CHCl_3$); IR (Neat): *ν* 3363, 3299, 2924, 2861 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.42–7.21 (m, 5H), 6.56 (d, 1H, *J* = 15.8 Hz), 6.28 (dd, 1H, *J* = 7.7, 12.4 Hz), 3.74–3.59 (m, 2H), 3.39 (dd, 1H, *J* = 5.8, 14.3 Hz), 2.56 (br s, 4H), 1.81–1.70 (m, 1H), 1.59–1.23 (m, 7H), 0.88 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 136.3, 131.9, 130.1, 128.6, 127.8, 126.4, 75.8, 74.3, 57.6, 33.7, 31.9, 25.0, 22.6, 14.0; ESIMS: *m/z* 264 [M+H]$^+$; HRMS calcd for $C_{16}H_{26}NO_2$: 264.1958, found: 264.1957.

4.1.9. (3*R*,4*R*,5*S*,*E*)-3-((*R*)-1-(4-Methoxybenzyloxy)hex-5-en-3-ylamino)-1-phenyldec-1-ene-4,5-diol 3

The aldehyde **5** (0.51 g, 2.6 mmol) and $MgSO_4$ (1.5 g) were added to a solution of amino alcohol **4** (0.70 g, 2.6 mmol) in Et_2O (10 mL) at room temperature to generate the imine **14**. The mixture was stirred for 2 h and filtered through a Celite pad under the inert atmosphere of argon. The filtrate containing the imine **14** was slowly added over 30 min to a solution of allylmagnesium bromide (26.5 mL, 26.0 mmol, 1 M solution in Et_2O) in freshly distilled Et_2O (10 mL) cooled to −78 °C. After addition, the mixture was stirred at −78 °C for 1 h and slowly warmed up to −40 °C over 5 h. Then, the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water, brine (20 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes/EtOAc, 65:35) affording the amino alcohol **3** and **3a** (0.93 g, 82:18) in 73% yield as a colorless oil: $[\alpha]_D^{25} = -5.5$ (*c* 1.5, $CHCl_3$); IR (Neat): *ν* 3436, 2925, 2868 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.35–7.18 (m, 7H), 6.84 (d, 2H, *J* = 8.4 Hz), 6.53 (dd, 1H, *J* = 11.3, 18.6 Hz), 5.99–5.84 (m, 1H), 5.83–5.56 (m, 1H), 5.14–5.03 (m, 2H), 4.43 (dd, 2H, *J* = 2.8, 6.6 Hz), 3.78 (s, 3H), 3.66–3.39 (m, 4H), 3.22 (q, 1H, *J* = 3.3 Hz), 2.91–2.80 (m, 1H), 2.35–2.25 (m, 1H), 2.22–1.96 (m, 1H), 1.84–1.62 (m, 3H), 1.59–1.23 (m, 8H), 0.89 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 159.0, 136.0, 134.9, 134.5, 130.3, 129.2, 128.5, 127.9, 126.4, 118.5, 117.7, 113.6, 74.9, 73.9, 72.6, 66.7, 63.5, 55.1, 50.5, 39.2, 38.3, 34.1, 31.9, 24.7, 22.6, 14.0; ESIMS: *m/z* 482 [M+H]$^+$; HRMS calcd for $C_{30}H_{44}NO_4$: 482.3265, found: 482.3274.

4.1.10. (4*R*,5*R*)-5-((*S*)-1-Hydroxyhexyl)-3-((*R*)-1-(4-methoxybenzyloxy)hex-5-en-3-yl)-4-((*E*)-styryl)oxazolidin-2-one 15

To a solution of amino alcohol **3** (0.50 g, 1.0 mmol) in CH_2Cl_2 (5 mL) were successively added Et_3N (0.3 mL, 2.0 mmol) and carbonyl diimidazole (0.17 g, 1.0 mmol) and stirred for 1 h at room temperature. After completion of reaction, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with 0.5 M HCl (2 × 10 mL), water, and brine (20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of this residue by silica gel chromatography using petroleum ether/EtOAc (89:11) afforded cyclic carbamate **15** (0.51 g) in 98% yield as a colorless oil: $[\alpha]_D^{25} = +14.8$ (*c* 1.0, $CHCl_3$); IR (Neat): *ν* 3449, 2927, 2859, 1800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.28–7.14 (m, 7H), 6.78 (d, 2H, *J* = 8.6 Hz), 6.42 (d, 1H, *J* = 15.8 Hz), 5.81(dd, 1H, *J* = 8.6, 15.8 Hz), 5.64–5.49 (m, 1H), 5.06–4.95 (m, 2H), 4.58 (q, 1H, *J* = 7.3 Hz), 4.48 (t, 1H, *J* = 5.8 Hz), 4.35 (d, 2H, *J* = 1.5 Hz), 3.72 (s, 3H), 3.53–3.36 (m, 3H), 2.81–2.72 (m, 1H), 2.25–2.15 (m, 1H), 2.0–1.87 (m, 1H), 1.69 (quin, 2H, *J* = 7.1 Hz), 1.60–1.42 (m, 3H), 1.31–1.17 (m, 5H), 0.82 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 159.4, 154.6, 136.1, 135.2, 134.4, 130.3, 129.1, 128.5, 127.9, 126.5, 125.9, 118.2, 113.7, 81.8, 80.2, 72.6, 66.8, 57.0, 55.2, 50.4, 39.5, 33.9, 31.4, 28.3, 25.4, 22.4, 13.9; ESIMS: *m/z* 508 [M+H]$^+$; HRMS calcd for $C_{31}H_{42}NO_5$: 508.3057, found: 508.3059.

4.1.11. (1*R*,5*R*,8a*R*)-1-((*S*)-1-Hydroxyhexyl)-5-(2-(4-methoxybenzyloxy)ethyl)-5,6-dihydro-1*H*-oxazolo[3,4-a]pyridin-3(8a*H*)-one 2

A flame-dried round-bottomed flask was charged with olefin **15** (0.11 g, 0.2 mmol) and CH_2Cl_2 (100 mL). Grubbs catalyst (2nd generation) (9 mg, 0.01 mmol) was subsequently added as a solid. The reaction mixture was refluxed for 6 h. After completion of the reaction (by TLC), the mixture was concentrated in vacuo to dark brown oil. Purification of this residue by silica gel chromatography using petroleum ether/EtOAc (75:25) afforded exclusively the tetrahydropyridine derivative **2** (76 mg) in 88% yield as a brownish oil: $[\alpha]_D^{25} = +32.1$ (*c* 1.1, $CHCl_3$); IR (Neat): *ν* 3452, 3019, 2923, 2855, 1800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): *δ* 7.24 (d, 2H, *J* = 8.6 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 5.97–5.89 (m, 1H), 5.78–5.72 (m, 1H), 4.69–4.61 (m, 1H), 4.49–4.35 (m, 3H), 3.81 (s, 3H), 3.75–3.68 (m, 1H), 3.64–3.47 (m, 2H), 2.99–2.88 (m, 1H), 2.08–1.96 (m, 1H), 1.92–1.60 (m, 7H), 1.37–1.18 (m, 5H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 159.2, 154.3, 130.0, 129.4, 129.3, 129.1, 113.7, 79.8, 77.2, 72.7, 67.6, 55.2, 53.8, 51.5, 35.4, 31.6, 29.6, 28.4, 25.3, 22.4, 13.9; ESIMS: *m/z* 404 [M+H]$^+$; HRMS calcd for $C_{23}H_{34}NO_5$: 404.2431, found: 404.2417.

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