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Tetrahedron 63 (2007) 3000–3005
Tetrahedron

Efficient, asymmetric synthesis of (−)-isooncinotine

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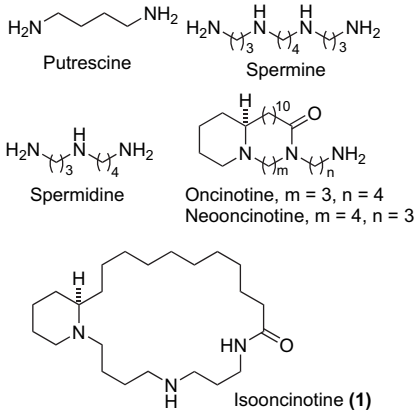
Received 14 December 2006; revised 29 January 2007; accepted 31 January 2007
Available online 2 February 2007

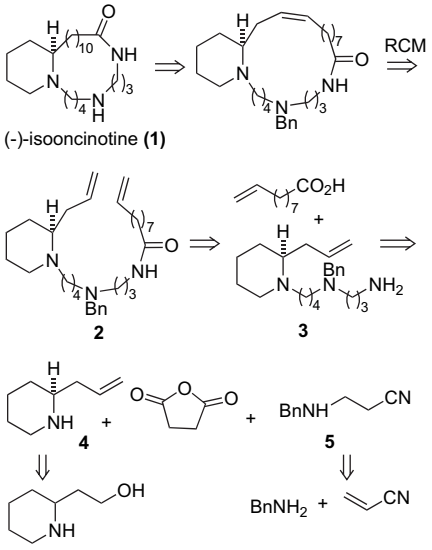
Abstract—Asymmetric synthesis of (−)-isooncinotine, a 22-membered lactam of spermidine alkaloid, starting from resolution of 2-piperidineethanol with (*S*)-10-camphorsulfonic acid is reported. Michael addition, amidations, and aluminum hydride reduction were applied to form the moiety of spermidine. Retro-Michael addition was observed when β-amido- and β-amino-propionitriles were reduced by LAH. The effects of LAH versus AlH_3 were discussed. The synthesis of the skeleton of this macrolide is achieved with ring-closing metathesis of the diene prepared from acylation of the spermidine.

1. Introduction

Polyamines, such as putrescine, spermidine, and spermine, are essential for the growth and function of normal cells.[1] Studies on *N*-alkylated polyamines revealed that these compounds possess antineoplastic activity against a number of murine and human tumor lines in vitro and in vivo.[2] Therefore, polyamines and their inhibitors/analogues have drawn certain attentions in recent years.[3] Isooncinotine, isolated from *Oncinotisnitida* (Apocynaceae),[4] is a member of oncinotines with spermidine skeleton. Recently, Fürstner's group reported the first enantioselective synthesis of this 22-membered lactam.[5] In pursuit of efficient syntheses involving ring-closing metathesis (RCM) and following our previous work on oncinotines,[6] we report our results in preparing isooncinotine here.



As shown in Scheme 1, our synthetic strategy toward (−)-isooncinotine is based on ring-closing metathesis[7] of the diene **2**, which could be obtained from diamidation of succinic anhydride with amines **4** and **5**, reduction to triamine **3**, and acylation of **3** with 9-decenoic acid.



Scheme 1. Retrosynthetic analysis of (−)-isooncinotine.

2. Results and discussion

Commercially available, racemic 2-piperidineethanol was resolved by (*S*)-10-camphorsulfonic acid according to Toy and Price's procedure with some modifications.[8] The optical purity of the resulting (*S,S*)-ammonium salt **6** was further

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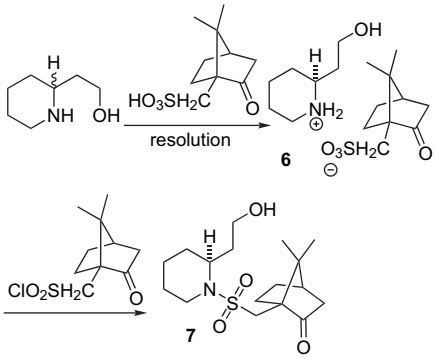
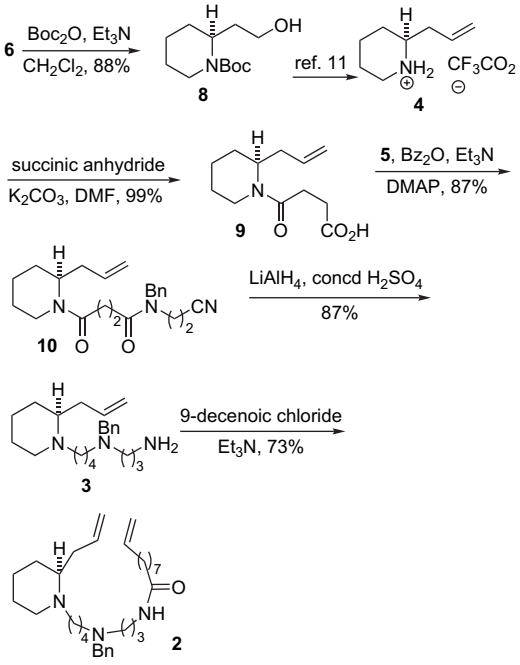
doi:10.1016/j.tet.2007.01.068

confirmed by preparing its camphorsulfonamide derivative **7** (Scheme 2).[9,10] Only one set of diastereotopic hydrogens, assigned to α-methylene of sulfonamide **7**, was observed on ^{1}H NMR (Fig. 1a); on the other hand, the diastereomeric mixtures, prepared directly from racemic 2-piperidineethanol and (*S*)-10-camphorsulfonic chloride, clearly show two sets of those hydrogens (Fig. 1b). Compound **6** was then neutralized and protected as a carbamate **8**, which was converted to 2-allylpiperidine **4** by Swern oxidation, Wittig olefination, and deprotection following a procedure reported by Ikeda's group (Scheme 3).[11]



Scheme 2.

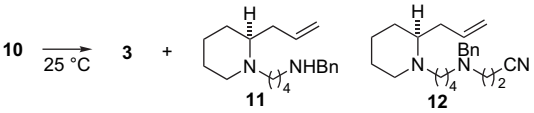


Scheme 3.

The acylation of piperidine **4** with succinic anhydride was achieved in high yield. The resulting carboxylic acid **9**[6] was coupled with amino nitrile **5**[12] to give diamide **10**. Here, we found that benzoic anhydride is a better dehydrating reagent than conventional *N*,*N*′-diisopropylcarbodiimide (DIC) for this coupling reaction. This is mainly due to the product **10**, which was difficult to separate from diisopropyl urea, the byproduct from DIC. On the other hand, the usage of benzoic anhydride greatly simplified the purification step with a good yield.[13]

Reduction of cyanoamide **10** requires more efforts (Eq. 1 and Table 1). We found that reduction using lithium aluminum hydride (LAH) gives a 2:3 mixture of the desired, fully reduced product **3** and diamine **11**, obviously derived from retro-Michael addition of **10** (entry 1).[14] On the other hand, the reductions with aluminum hydride[15,16] are free of the fragmented product **11** (entries 2–4). We also noticed that excess amount of hydride is required to ensure complete

Table 1. Reduction of compound **10**



(1)

Entry	Reagent	Yield[a] (%)	Product ratio[b] (%)		
			3	**11**	**12**
1	$LiAlH_4$ (3 equiv)	82	41	59	0
2	$LiAlH_4/AlCl_3$ (2.7 equiv each)	43	0	0	100
3	$LiAlH_4/H_2SO_4$ (3.8 equiv, 1.9 equiv)	73	71	0	29
4	$LiAlH_4/H_2SO_4$ (7.7 equiv, 3.8 equiv)	87	100	0	0

[a] Isolated yields.
[b] Ratios were determined by 500 MHz ^{1}H NMR of the crude product.

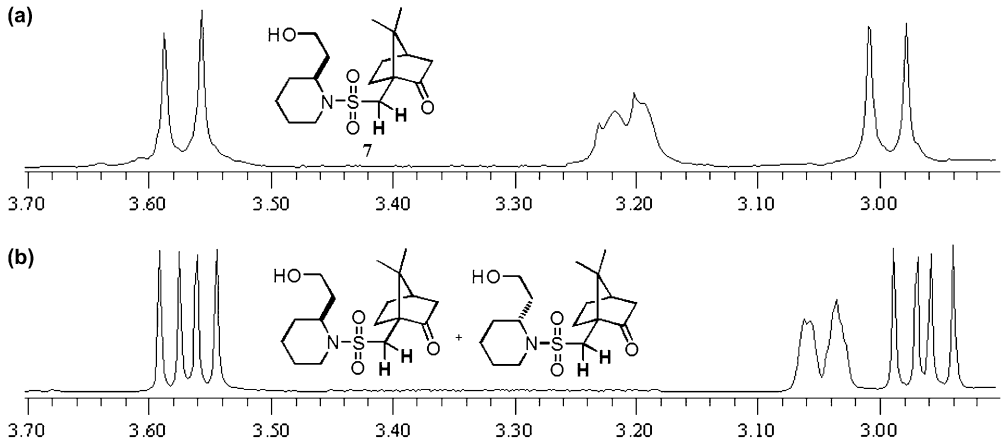


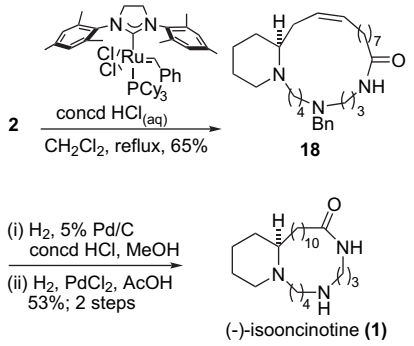
Figure 1. (a) ^{1}H NMR (500 MHz) of **7** prepared from **6**; (b) ^{1}H NMR (500 MHz) of two diastereomers prepared from racemic 2-piperidineethanol.

reduction to give pure triamine **3** with 87% yield (entry 4). The two byproducts **11** and **12** were independently synthesized and confirmed by spectroscopic data (see Section 3). Further studies on the reductions of β-amino- or β-amidopropionitriles using model compounds **13** and **14** are summarized in Table 2.[17] All the products **15**–**17** are known and have distinct absorptions on ^{1}H NMR.[18–20] When LAH was applied, the fragmented product **16** was observed in both substrates in spite of different ratios (entries 1, 2, and 5). The fact that β-aminonitriles (**12** and **14**) were not found in the LAH reduction of β-amidonitriles (**10** and **14**) and different product ratios derived from **13** and **14** imply that **12** and **14** as the reaction intermediates are unlikely. Thus, LAH preferentially reacts with the cyano group and has two reaction pathways: reduction and retro-Michael addition. In contrast, only amide reduced **12** and **15** as the byproducts/intermediates in AlH_3 reductions suggests that this reduction occurs at amides first and free of retro-Michael addition.

Acylation of triamine **3** with 9-decenoic chloride[6,21] provided the diene **2**, the essential synthetic intermediate for RCM.

Ring-closing metathesis of **2** was carried out with the Grubbs' second-generation catalyst under an acidic condition to afford the cyclized lactam **18** in 65% yield. Hydrogenation and then debenzylation of lactam **18** gave isooncinotine (Scheme 4). We found that our previous debenzylation method for oncinotines, using Pearlman's catalyst (palladium hydroxide in charcoal) and ammonium formate did not complete the deprotection and the amount of impurities gradually raised as the reaction time increased.[6,22] However, the procedure reported by Bergeron et al., $H_2/PdCl_2$ in acetic acid, proves to be effective and gives clean product **1**.[23] One-pot reduction and deprotection of **18** using Bergeron's condition led to incomplete deprotection (50%) even when the reaction time was prolonged to 24 h. The optical rotation of our synthetic (−)-isooncinotine is consistent with that previously reported.[4c,5]

In summary, we have developed an efficient method to prepare (−)-isooncinotine. Starting from resolution of



Scheme 4.

2-piperidineethanol, the title compound was prepared in 11 steps with 9% total yield. There are several advantages in this synthesis. All the chemical reagents used here are commercially available and inexpensive. Only two protective groups (Boc and Bn) were applied; therefore, the whole synthesis is straightforward and concise. It should provide an easy access to (−)-isooncinotine and opportunity for further studying its functions in biological systems.

3. Experimental section

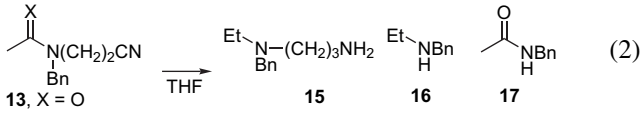
3.1. Resolution of 2-piperidineethanol

A solution of (1*S*)-(+)-10-camphorsulfonic acid (31.0 g, 0.13 mmol) in ethanol (45 mL) was added dropwise to a solution of 2-piperidineethanol (33.0 g, 0.25 mmol) in ethanol (50 mL) with stirring. The reaction mixture was cooled in a refrigerator overnight and the needle- to lath-like crystals (compound **6**, 17.7 g, mp 130–151 °C) were collected by filtration, washed with ether, and dried under vacuum. The first crop crystals were redissolved in warm ethanol (20 mL) and cooled in a refrigerator. The formed crystals (15.2 g, mp 162–165 °C) were collected, and the recrystallization procedure was repeated with warm ethanol (15 mL) to have the lath-like crystal (11.3 g, mp 165–167 °C, 24%). This product was used for the following synthesis.

3.2. Sulfonamide 7

(1*S*)-(+)-10-Camphorsulfonyl chloride (36 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added to the solution of (*S*,*S*)-ammonium salt **6** (40 mg, 0.10 mmol) and triethylamine (46 μL, 0.33 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. After stirring at room temperature for 24 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water (5 mL×2) and saturated $NaCl_{(aq)}$ (10 mL), dried over sodium sulfate, filtered, and concentrated to give **7** as a yellow oil (20 mg, 0.058 mmol, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (1H, m), 4.43 (1H, m), 3.57 (1H, d, J=15.1 Hz), 3.20 (1H, m), 2.99 (1H, d, J=15.1 Hz), 2.90 (1H, m), 2.71 (1H, dt, J=12.2, 2.3 Hz), 2.45–2.39 (2H, m), 2.12 (1H, m), 2.10–1.98 (2H, m), 1.97–1.89 (2H, m), 1.88–1.72 (2H, m), 1.70–1.50 (4H, m), 1.49–1.29 (4H, m), 1.06 (3H, s), 0.85 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ (rotamers) 216.8, 214.6, 66.8, 58.3, 57.9, 53.6, 48.1, 47.9, 47.4, 46.7, 45.3, 42.8, 42.7, 42.6, 42.5, 33.5, 29.0, 26.9, 26.8, 24.9, 24.5, 22.8, 22.7, 21.3, 19.7, 19.6; HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{30}O_4NS$): 344.1896, found: 344.1894.

Table 2. Reduction of compounds **13** and **14**



(2)

Entry	Substrate	Reagent	Yield[a] (%)	Product ratio[b] (%)		
				15	**16**	**17**
1	**13**	$LiAlH_4$ (1.9 equiv)[c]	71	34	14	49
2	**13**	$LiAlH_4$ (1.9 equiv)[d]	85	37	63	0
3	**13**	AlH_3 (2.5 equiv)[c,e]	87	41[f]	0	0
4	**13**	AlH_3 (5 equiv)[c,e]	72	100	0	0
5	**14**	$LiAlH_4$ (1 equiv)[c]	56	83	17	—

[a] Isolated yields.
[b] Ratios were determined by 500 MHz ^{1}H NMR of the crude product.
[c] 25 °C.
[d] 65 °C.
[e] Generated from $LiAlH_4/H_2SO_4$ (2:1).
[f] With 59% of **14**.

3.3. 4-((*S*)-2-Allyl-piperidin-1-yl)-*N*-benzyl-*N*-(2-cyano-ethyl)-4-oxo-butyramide (10)

To a solution of triethylamine (210 μL, 1.5 mmol), DMAP (6 mg, 0.04 mmol), and benzoic anhydride (116 mg, 0.44 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of acid **9** (100 mg, 0.44 mmol) in dry dichloromethane (1.5 mL). After stirring at room temperature for 10 min, the resulting mixture was added with amino nitrile **5** (60 mg, 0.37 mmol) in dry CH_2Cl_2 (3.5 mL) and stirred for another 25 h at room temperature. The reaction mixture was washed with saturated $NH_4Cl_{(aq)}$ (4 mL×2), and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: EtOAc/hexane 1:1; R_f 0.67) to provide the compound **10** (120 mg, 0.33 mmol, 87%) as a yellow oil. $[\alpha]_D^{20}$ −28.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (rotamer) 1.38 (br, 1H), 1.48–1.71 (m, 5H), 2.18–2.40 (m) and 2.40–2.52 (m, 2H), 2.54–2.60 (m, 3H), 2.60–2.72 (m, 3H), 2.62–2.72 (m) and 3.07 (dt, *J*=13.3 Hz, *J*=2.7 Hz, 1H), 3.53 (m, 1H), 3.53 (m) and 4.45 (d, *J*=13.5 Hz, 1H), 3.66 (m, 1H), 4.15 (br) and 4.80 (dd, *J*=13.0 Hz, *J*=7.1 Hz, 1H), 4.63 (s) and 4.69 (s, 2H), 4.88–5.10 (m, 2H), 5.67 (m, 1H), 7.17–7.34 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (rotamer) 16.0, 18.7, 25.2, 25.8, 27.0, 27.8, 28.1, 28.2, 28.4, 28.7, 34.0, 34.4, 36.6, 40.7, 42.7, 43.0, 47.5, 52.2, 52.3, 116.5, 116.6, 117.3, 117.8, 118.1, 126.5, 127.5, 127.7, 128.6, 128.9, 129.7, 134.2, 135.1, 135.2, 135.9, 170.0, 169.9, 170.0, 172.3, 173.0; IR (neat) 704, 735, 918, 1009, 1434, 1636, 2247, 2936, 3067, 3480 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ ($C_{22}H_{30}N_3O_2$): 368.2338, found: 368.2342.

3.4. N^1-[4-((*S*)-2-Allyl-piperidin-1-yl)-butyl]-N^1-benzyl-propane-1,3-diamine (3)

To a solution of $LiAlH_4$ (43 mg, 1.13 mmol) in dry THF (1 mL) was added concentrated H_2SO_4 (30 μL, 0.56 mmol) under N_2 at 0 °C and stirred for 10 min. A solution of amide **10** (50 mg, 0.14 mmol) in dry THF (1 mL) was added to the solution of aluminum hydride by syringe and stirred at room temperature for another 3 h. The reaction mixture was diluted with ether (10 mL) and quenched with $NaOH_{(aq)}$ (1 N, 2 mL×2). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to give triamine **3** (41 mg, 0.12 mmol, 87%) as a yellow oil. $[\alpha]_D^{20}$ −25.5 (*c* 2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15–1.38 (m, 2H), 1.38–1.50 (m, 6H), 1.50–1.68 (m, 5H), 2.20–2.09 (m, 2H), 2.30–2.20 (m, 2H), 2.44–2.30 (m, 5H), 2.60 (m, 1H), 2.82–2.69 (m, 2H), 2.77 (br, 1H), 3.50 (s, 2H), 4.98–5.02 (m, 2H), 5.76 (m, 1H), 7.19 (m, 1H), 7.24–7.29 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.3, 24.8, 25.1, 25.5, 30.2, 30.9, 35.6, 40.4, 51.2, 51.7, 53.5, 53.7, 58.6, 59.4, 116.1, 126.6, 128.0, 128.6, 136.0, 139.9; IR (neat) 737, 910, 995, 1452, 1494, 1638, 2857, 2933, 3026, 3062, 3417 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ ($C_{22}H_{38}N_3$): 344.3066, found: 344.3063.

3.5. Diamine 11

To a solution of acid **9** (350 mg, 1.55 mmol) in dry CH_2Cl_2 (10 mL) was added triethylamine (0.6 mL, 4.3 mmol), DMAP (8 mg, 0.07 mmol), benzoic anhydride (407 mg, 1.55 mmol), and benzylamine (138 mg, 1.29 mmol), sequentially. The reaction mixture was stirred for 20 h at room temperature, diluted with CH_2Cl_2 (20 mL), washed with saturated $NH_4Cl_{(aq)}$ (10 mL×2), $NaHCO_{3(aq)}$ (10 mL×3), and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: EtOAc/hexane 1:1; R_f 0.26) to provide the diamide (46 mg, 0.15 mmol, 10%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (rotamer) 1.31 (m, 1H), 1.40–1.59 (m, 4H), 1.65 (m, 2H), 2.15–2.20 (m), 2.24–2.32 (m) and 2.39–2.45 (m, 2H), 2.52–2.61 (m, 3H), 2.62–2.72 (m, 1H), 2.52–2.61 (m) and 3.01 (m, 1H), 3.64 (d, *J*=13.3 Hz) and 4.44 (br, 1H), 3.97 (m) and 4.69–4.73 (m, 1H), 4.38 (d, *J*=5.7 Hz, 2H), 4.90–5.06 (m, 2H), 5.62 (m, 1H), 6.88 (br, 1H), 7.18–7.27 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (rotamer) 18.7, 25.2, 25.8, 27.1, 28.2, 28.9, 29.2, 31.5, 34.0, 34.4, 36.6, 40.7, 43.3, 47.6, 52.4, 116.6, 117.9, 127.0, 127.4, 128.4, 134.1, 135.0, 138.5, 170.4, 172.5. The diamide (30 mg, 0.1 mmol) in THF (1 mL) was added with LAH (18 mg, 0.48 mmol) and refluxed for 1 h. The reaction mixture was diluted with ether (5 mL), quenched with saturated $NaHCO_{3(aq)}$ (0.3 mL), filtered, and concentrated to have diamine **11** (25 mg, 0.09 mmol, 93%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (m, 1H), 1.30 (m, 1H), 1.35–1.50 (m, 5H), 1.50–1.67 (m, 4H), 2.17 (m, 1H), 2.27 (m, 1H), 2.35 (m, 1H), 2.61 (m, 3H), 2.76 (m, 1H), 3.75 (s, 2H), 4.98–5.02 (m, 2H), 5.72–5.77 (m, 1H), 7.20–7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.2, 25.6, 28.1, 30.2, 35.6, 49.2, 51.7, 53.4, 53.9, 59.4, 116.2, 126.7, 128.0, 128.2, 135.9, 140.3; HRMS (FAB) calcd for $[M+H]^+$ ($C_{19}H_{31}N_2$): 287.2482, found: 287.2491.

3.6. Nitrile 12

Diamine **11** (25 mg, 0.087 mmol) in acrylonitrile (1 mL, 15 mmol) was refluxed for 48 h. The excess acrylonitrile was removed under vacuum to give nitrile **12** as a light yellow oil (24 mg, 0.07 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (m, 1H), 1.36 (m, 1H), 1.39–1.58 (m, 5H), 1.58–1.71 (m, 3H), 2.19–2.21 (m, 2H), 2.21–2.33 (m, 2H), 2.33–2.42 (m, 3H), 2.42–2.55 (m, 2H), 2.65 (m, 1H), 2.74–2.77 (m, 3H), 3.60 (s, 2H), 4.99–5.02 (m, 2H), 5.72–5.80 (m, 1H), 7.21–7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 23.2, 25.3, 25.5, 30.2, 35.6, 49.2, 51.7, 53.4, 53.7, 58.4, 59.5, 116.34, 118.9, 127.1, 128.3, 128.6, 136.0, 138.8; HRMS (FAB) calcd for $[M+H]^+$ ($C_{22}H_{34}N_3$): 340.2747, found: 340.2756.

3.7. Nitrile 13

Acetyl chloride (0.6 mL, 0.84 mmol) was added to the solution of nitrile **5** (0.9 g, 5.6 mmol), triethylamine (2.5 mL, 17.9 mmol), and CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, washed with water (5 mL×2), saturated $NaCl_{(aq)}$ (10 mL), and the organic layer was dried over Na_2SO_4, filtered, and concentrated to give nitrile **13** (0.91 g, 4.5 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.63 (t, *J*=6.6 Hz), 3.56 (t, *J*=6.6 Hz), 4.66 (s, 2H), 7.15 (d, *J*=7.3 Hz), 7.30–7.36 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 21.5, 42.6, 53.2, 118.2, 126.2, 127.9, 128.7, 135.8, 171.4.

3.8. Diene 2

A mixture of 9-decenoic acid (155 mg, 0.91 mmol) and thionyl chloride (0.5 mL) was heated at 60 °C for 30 min.

Excess thionyl chloride was removed under vacuum and CH_2Cl_2 (1 mL) was added. The resulting solution of 9-decenoyl chloride was added to a solution of triamine **3** and triethylamine (0.5 mL) in dry CH_2Cl_2 (10 mL) by syringe at 0 °C and stirred for another 2 h. The reaction mixture was washed with water (5 mL×2), saturated $NaCl_{(aq)}$ (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: MeOH/CH_3Cl 1:9; R_f 0.5) to give diene **2** (276 mg, 0.56 mmol, 73%) as a yellow oil. $[\alpha]_D^{20}$ −13.7 (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (rotamer) 1.15–1.30 (br, 8H), 1.30–1.38 (m, 2H), 1.38–1.45 (br, 4H), 1.45–1.50 (m, 3H), 1.50–1.60 (5H), 3.46, 4.86–4.91 (m, 2H), 4.95–5.00 (m, 2H), 5.71–5.75 (m, 2H), 6.24 and 6.29 (br, 1H), 7.20 (m, 1H), 7.23–7.26 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (rotamer) 22.9, 23.2, 24.7, 24.9, 25.1, 25.6, 25.9, 26.1, 28.7, 28.8, 29.0, 29.1, 29.7, 33.6, 35.3, 36.6, 38.1, 51.4, 51.6, 51.7, 53.2, 53.6, 58.7, 59.5, 114.0, 116.4, 126.9, 128.1, 128.8, 135.5, 138.9, 139.4, 172.7, 172.8; IR (neat) 699, 734, 909, 995, 1452, 1465, 1494, 1551, 1643, 2928, 3028, 3076, 3303, 3424 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ ($C_{32}H_{54}N_3O$): 496.4267, found: 496.4271.

3.9. Lactam 18

Concentrated $HCl_{(aq)}$ (10 drops) was added to a solution of diene **2** (20 mg, 0.04 mmol) in CH_2Cl_2 (10 mL) and stirred for 5 min. The solvent was removed under vacuum and a solution of Grubbs' second-generation catalyst (4 mg, 0.0047 mmol) in CH_2Cl_2 (30 mL) was added to the flask. The reaction mixture was heated to reflux for 14 h. The solution was poured into a separation funnel, washed with saturated $NaHCO_{3(aq)}$ (10 mL×2), saturated $NaCl_{(aq)}$ (10 mL), dried over $NaSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2: MeOH/CH_3Cl, 1:9; R_f 0.23 and then SiO_2: MeOH/CH_3Cl/Et_3N, 1:10:0.5; R_f 0.71) to give lactam **18** (12 mg, 0.026 mmol, 65%) as a yellow oil. $[\alpha]_D^{20}$ −23.5 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.34–1.14 (m, 10H), 1.49–1.34 (br, 5H), 1.60–1.49 (m, 4H), 1.70–1.60 (m, 3H), 2.14–1.88 (m, 5H), 2.30–2.14 (m, 2H), 2.48–2.30 (m, 4H), 2.60–2.48 (m, 2H), 2.75–2.60 (br, 1H), 2.88–2.75 (br, 1H), 3.15–3.32 (m, 2H), 3.51–3.46 (m, 2H), 5.39–5.35 (m, 2H), 6.92 (br, 1H), 7.30–7.21 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.2, 23.3, 24.8, 25.1, 25.4, 25.5, 27.4, 27.9, 28.0, 28.6, 30.6, 31.5, 34.3, 36.8, 39.2, 51.7, 53.0, 53.2, 53.7, 58.8, 60.0, 127.0, 127.4, 128.2, 128.9, 131.8, 138.9, 172.8; IR (neat) 699, 734, 969, 1452, 1644, 2854, 2928, 3025, 3434 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ ($C_{30}H_{50}N_3O$): 468.3954, found: 468.3947.

3.10. (−)-Isooncinotine (1)

Concentrated $HCl_{(aq)}$ (two drops) was added to the solution of lactam **18** (19 mg, 0.04 mmol) and Pd/C (7 mg, 5% w/w) in MeOH (0.5 mL). The reaction flask was placed into an autoclave, filled with H_2 (20 atm), and stirred for 2 h. The reaction mixture was filtered, concentrated, and redissolved in acetic acid (0.5 mL). The resulting solution was added with palladium chloride (4 mg) and stirred under H_2 (1 atm) at room temperature for another 20 h. The reaction mixture was filtered, neutralized with $NaOH_{(aq)}$ (1 N, 1 mL) and MeOH (1 mL), and concentrated. The crude product was further purified by column chromatography (SiO_2: MeOH/CH_3Cl 1:10 and then MeOH/CH_3Cl/Et_3N 1:4:0.5; R_f 0.5) to give isooncinotine (8 mg, 0.021 mmol, 53%) as a yellow oil. $[\alpha]_D^{20}$ −32.3 (*c* 0.07, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.18–1.39 (m, 17H), 1.39–1.50 (m, 6H), 1.50–1.69 (m, 8H), 2.13 (t, 4H), 2.32 (br, 1H), 2.50–2.68 (m, 3H), 2.75 (br, 2H), 2.86 (m, 1H), 3.33–3.35 (m, 2H), 7.55 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 23.8, 24.0, 25.7, 27.6, 28.0, 28.4, 28.5, 28.7, 28.9, 30.5, 30.8, 36.9, 39.8, 49.4, 50.3, 52.4, 53.4, 60.0, 173.0; IR (neat) 729, 1461, 1549, 1643, 2853, 2926, 3078, 3284 cm^{-1}; HRMS (FAB) calcd for $[M+H]^+$ ($C_{23}H_{46}N_3O$): 380.3641, found: 380.3655.

Acknowledgements

This research was supported by National Central University and the National Science Council (NSC 94-2113-M-008-007), Taiwan.

Supplementary data

^1H and ^{13}C NMR spectra of all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.01.068.

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