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Formal Synthesis of Manzamine C *via* a Sila-Cope Elimination

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Abstract: Piperidine derivative **7**, prepared in six steps from 2-methylpyridine, afforded by a sila-Cope elimination aminoalcohol **10** which is a direct synthetic precursor of the azaundecene ring of Manzamine C **2**.
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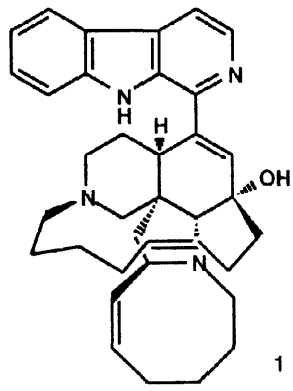
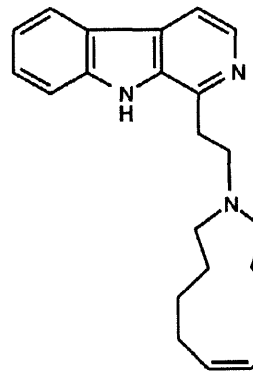
Manzamine alkaloids[1] are a growing family of marine natural products extracted from various species of sponges. Owing to their cytotoxic activity and novel frameworks, these alkaloids and particuliary Manzamine A **1** have recently become the target of a number of synthetic approaches[2]. Manzamine C **2**[1b], the simplest member of this group to retain some cytotoxic activity, has already been synthetized by Hino and Nakagawa in Japan[3] and by Gerlach in Germany[4]. More recently structure-activity studies disclosed further aspect concerning the cytotoxicity of Manzamine C **2** and analogues[5] and confirmed the interest of the simpler member of this family of β-carboline derived alkaloids. In the present paper is described a new formal synthesis of Manzamine C **2** using a strategy based on a sila-Cope elimination previously described by our group[6].



1



2

2-Methylpyridine **3** was deprotonated with LDA and treated with chloro-*tert*-butyldimethylsilane. In a same sequence of reactions, the resulting 2-*tert*-butyldimethylsilylmethylpyridine was deprotonated and alkylated with 1-iodo-4-*tert*-butyldimetylsilyloxybutane[7] to furnish the pyridine derivative **4**. This compound was *N*-alkylated and the methylpyridinium salt intermediate was subjected to sodium borohydride reduction to afford 1,2,5,6-tetrahydropyridine **6** in 71% yield together with small amount of isomeric 1,2,3,6-tetrahydropyridine and of piperidine **7**. Hydrogenation of this mixture of compounds gave quantitatively piperidine derivative **7**.

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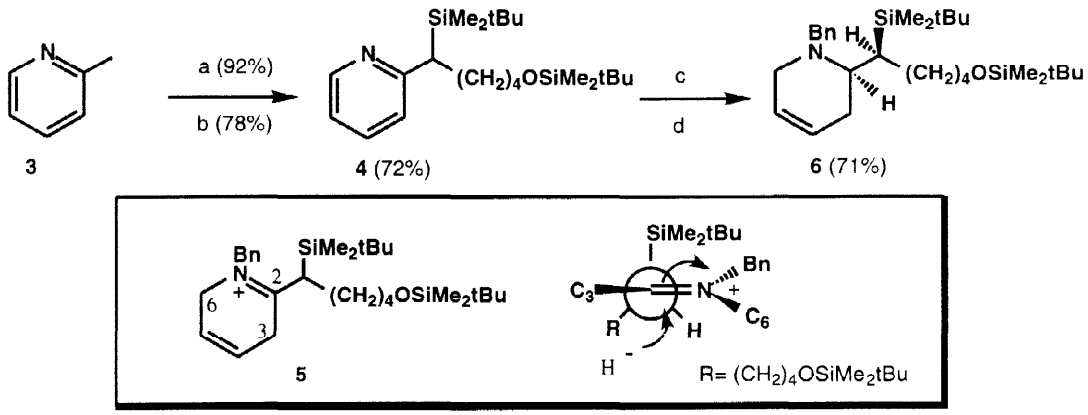
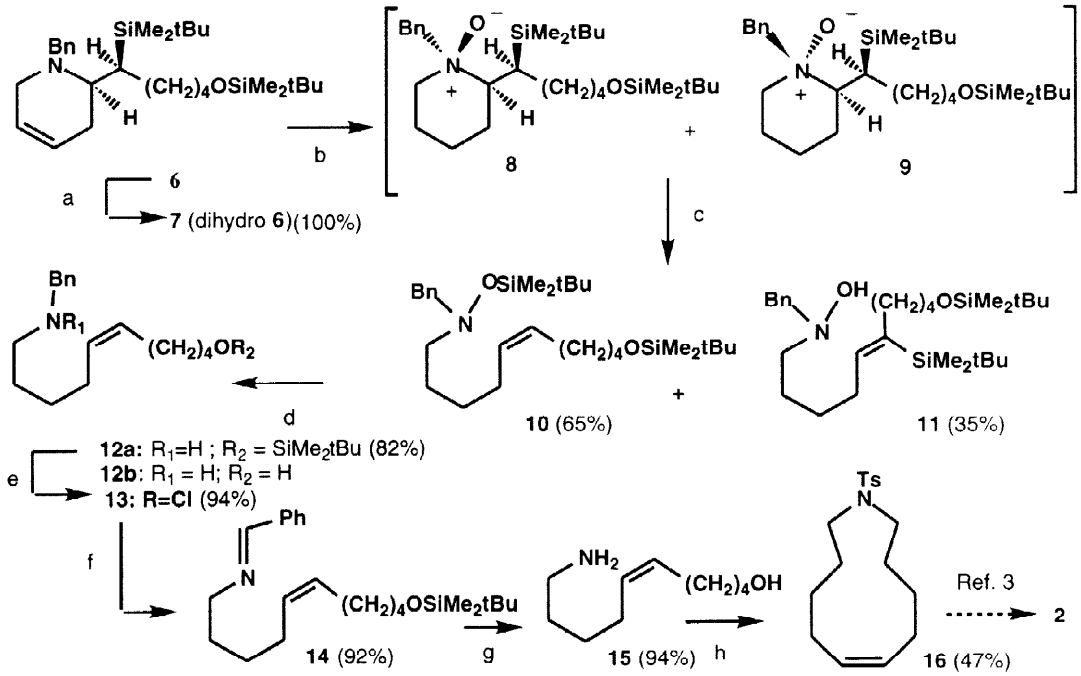
The diastereoselectivity of the reduction of the imminium intermediate **5** can be rationalized by a molecular modelling study. The more stable conformation shown in Newman projection (Scheme 1) led to the observed stereoselective hydride attack. This parallels the diastereoselectivity observed in the alkylation of α-alkoxyiminium ions with Grignard reagents[8].



Scheme 1 : a : 1) LDA, 1.3eq, THF, -78°C, 30min. 2) $ClSiMe_2tBu$, 0.5eq, -78°C, 2h. b : 1) LDA, 2.1eq, THF, -78°C, 30min. 2) $I(CH_2)_4OSiMe_2tBu$, 0.6eq, -78°C, 2h. c : BnBr, 1.4eq, MeCN, 20°C, 2d. d : $NaBH_4$, 5eq, MeOH, 0°C, (51% overall yield from **3**).

*m*CPBA Oxidation piperidine derivative **7** afforded a mixture of diastereomeric *N*-oxides **8** and **9** which was thermolyzed without purification and afforded respectively alkene derivatives **10** and **11**. The instability of these *N*-oxides precluded their isolation, however, the ratio of *N*-oxides **8** and **9** can be estimated by ^1H NMR spectroscopy. This ratio is temperature dependent : -78°C: 30/70; -20°C: 50/50; 0°C: 65/35. As previously observed[9,10], *N*-oxide **8** led to compound **10** *via* sila-Cope elimination whereas *N*-oxide **9** afforded compound **11** as the result of a Cope elimination. Configurations at nitrogen in the isomeric *N*-oxides **8** and **9** were deduced from our previous work[9,10]. Reductive cleavage of the N-O bond in **10** was performed with sodium naphthalenide to afford secondary amine **12a** in good yield. Irradiation of allylic protons C_4H_2 and C_7H_2 in aminoalcohol **12b** resulting from desilylation of **12a** allowed measurement of the coupling constant C_5H-C_6H, J= 9Hz, characteristic of a *Z* double bond (400 MHz, C_6D_6).

Classical debenzylation of **12a** (H_2, Pd-C) was precluded by the presence of the double bond. Thus, compound **12a** was oxidized with *N*-chlorosuccinimide and the chloramine intermediate **13** was subjected to an elimination by treatment with potassium *tert*-butoxide. This afforded in high overall yield the corresponding imine **14** which was in turn hydrolyzed to aminoalcohol **15**. Ditosylation of **15** followed by a basic treatment of the ditosylate intermediate afforded the anticipated cyclic sulfonamide **16** in 47% yield together with small amount of dimeric compound (3%) and starting material (5%). Sulfonamide **16** is a direct synthetic precursor of manzamine C **2**[3] (Scheme 2).



Scheme 2 : a : H_2, PtO_2, EtOH, 20°C, 3h. b : *m*CPBA, 1.5eq, CH_2Cl_2, 0°C, 2h. c : MeCN, 80°C, 2h. d: **10**, Na-naphtalene, 3eq, THF, 2h. e : NCS, 1.5eq, CH_2Cl_2, 20°C, 30min. f : *t*BuOK, 1.6eq, THF, 0°C, 30min. g : HCl (1N, 60eq), MeOH, 20°C, 16h. h : 1) TsCl, 3eq, C_5H_5N, 0°C, 5h. 2) Bu_4NI, 1.5eq, NaOH (10N, 230eq), C_6H_5Me, 100°C, 4h.

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Experimental

^1H NMR spectra were taken in $CDCl_3$ on 200, 250 and 400 MHz NMR instruments and are reported as follows: d, ppm, TMS=0. Chemical shift, integration [multiplicity (s=singulet, d=doublet, dd=doublets of doublet, t=triplet, q=quartet, m=multiplet), coupling constants in hertz]. ^{13}C NMR were taken at 50 and 62.5 MHz. Solvents and reagents were dried and purified prior to use when deemed necessary. THF and diethyl ether were distilled from sodium metal-benzophenone; dichloromethane, pyridine and diisopropylamine were distilled from calcium hydride. Usual work up means that organic layers were dried over magnesium sulfate, filtered and evaporated *in vacuo*.

2-((*tert*-butyldimethylsilyl)methyl)pyridine.

To a solution of LDA (*n*BuLi (1.4M in hexane) 154 mmol, di*iso*-propylamine (137 mmol), THF, 200 mL, 0°C) was added dropwise at -78°C a solution of 2-methylpyridine (15.9mL, 107 mmol) in THF (30 mL). Reaction mixture was stirred for 30 min and chloro-*tert*-butyldimethylsilane (12.75g, 57 mmol) in solution in THF (65 mL) was introduced. After stirring at -78°C for additional 2 hours, the reaction medium was hydolyzed with a cold (0°C) aqueous solution of NH_4Cl. After usual work up, purification by flash chromatography (SiO_2, cyclohexane/ether : 8: 2) afforded pyridine derivative (16.3 g, 92%).

MS (IE 70eV) : m/z = 207(MH+). HRMS: Calcd: 206.1365. Found: 206.1357. ^{1}H NMR (200 MHz) : -0.01 (6H, s, Si(Me)$_2$), 0.88 (9H, s, Si*t*Bu), 2.32 (2H, s, C7-H), 6.93 (2H, m, C5-H et C3-H), 7.45 (1H, td, C4-H, J_{4-5} = J4-3 = 8 et J_{4-6} = 2), 8.4 (1H, dd, C6-H, J_{6-5} = 8 et J_{6-4} = 2).^{13}C NMR (50 MHz): -6.6 (Si-(Me)$_2$), 16.4 (Si-C(Me)$_3$), 25.7 (C7), 26.1, 26.6 (Si-C(Me)$_3$), 118.7 (C5), 122.0 (C3), 135.3 (C4), 148.6 (C6), 161.2 (C2).

2-[5-(*tert*-Butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyl)]-1-pentyl)pyridine **4**

To a solution of LDA (*n*BuLi (1.4 in hexane) 168 mmol, di*iso*-propylamine (122 mmol), THF (170 mL), 0°C) was added dropwise at -78°C, 2-(*tert*-butyl-dimethylsilylmethyl)-pyridine.(16.3g, 78.7 mmol) in THF (50 mL). The resulting mixture was stirred at this temperature for 30 min before addition of a solution of 4-iodo-1-*tert*-butyldimethylsilyloxybutane (16g, 50,9 mmol) in THF (70mL). After stirring for additional 2 hours, reaction mixture was hydrolyzed with an aqueous solution of NH_4Cl cooled at 0°C. After usual work up, the crude residue was purified by flash chromatography (SiO_2, heptane/ether : 9: 1) affording pyridine derivative **4** (16.5g, 78%).

MS : m/z = 394 (MH+), 264. HRMS: Calcd:393.2883 Found: 393.2872. ^{1}H NMR (200 MHz) : -0.25 (3H, s, Si-Me), -0.05 (6H, s, Si(Me)$_2$), 0.02 (3H, s, Si-Me), 0.77 (9H, s, Si*t*Bu), 0.81 (9H, s, Si*t*Bu), 1.15 (2H, m), 1.6 (2H, m), 2.02 (2H ,m), 2.40 (1H, dd, C1-H, J = 11 and 3), 3.74 (2H, t, C5-H, J = 8), 6.93 (2H, m, C5-H et C3-H), 7.45 (1H, td, C4-H, J_{4-5} = J_{4-3} = 8 and J_{4-6} = 2), 8.4 (1H, dd, C6-H, J_{6-5} = 8 and J_{6-4} = 2).^{13}C NMR (50 MHz) : -7.1, -6.9, -5.4 (4 x Si-Me), 17.5, 18.2 (2 x Si-C(Me)$_3$), 25.8, 26.7 (2 x Si-C(Me)$_3$), 30.1, 32.6 (C2 et C3), 37.0 (C1), 53.3 (C4), 63.0 (C5), 119.3 (C5), 122.7 (C3), 135.4 (C4), 148.9 (C6), 164.9 (C2).

N-Benzyl-2-[5-(*tert*-butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyl))-1-pentyl]-1,2,3,6-tetrahydropyridine **6.**

A solution of benzyl bromide (7 mL, 58.8 mmol), pyridine derivative **4** (16.5g, 42 mmol) in acetonitrile (110 mL) was stirred at 20°C for 2 days. After evaporation in vacuo, the residue was dissolved in MeOH (450 mL) and treated portionwise at 0°C with an excess of sodium borohydride (210 mmol). After 4 hours, the reaction medium was hydrolysed with brine and extracted with CH_2Cl_2. After chromatography (SiO_2, cyclohexane/ether : 93:7) tetrahydropyridine **6** was isolated with small amounts of tetrahydro-1,2,5,6 isomer and of piperidine derivative **7** (14.5g, 71%). Starting material **4** was also recovered (25%).
7: MS: m:z= 487(M+), 91. ^{1}H NMR (200MHz) : -0.05 (9H, s, 3 x Si-Me), 0.07 (3H, s, SiMe), 0.88 (18H, s, 2 x Si*t*Bu), 1.57(7H, m, C8-H, C9-H, C10-H, C7-H), 2.2 (2H, m, C3-H) 2.86 (2H, m, C6-H),3.06 (1H,broad d , C2-H), 3.48 (1H, d, N-CHa-Ph, J = 14), 3.60 (2H, t, C11-H, 8), 3.76 (1H, d, N-CHb-Ph, J = 14), 5.52 (1H, m, C4-H or C5-H), 5.74 (1H, m, C4-H or C5-H), 7.25 (5H, m, aromatics). ^{13}C NMR: -5.2, -4.5, -4.0, -3.2 (4 x Si-Me), 17.8, 18.3 (2 x Si-C(Me)$_3$), 25.9, 27.5 (2 x Si-C(Me)$_3$), 28.0,28.5, 33.7 (C3, C8, C9),48.8 (Ph-CH$_2$-N), 53.8 (C6), 58.2 (C2), 58.5 (C10), 63.3 (C11), 64.9 (C7), 126.3, 126.5 (C4 and C5), 127.6, 128.1, 128.3, 140.4 (C aromatics).

N-Benzyl-2-[5-(*tert*-butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyl)-1-pentyl]piperidine **7**

A solution of the crude mixture of tetrahydropyridine **6** (7g, 14.3 mmol) in ethanol (240mL) was stirred under hydrogen in the presence of catalytic amount of PtO_2 (70mg). The reaction was monitored by ^1H NMR. After 3 hours, the reaction medium was filtered off on Celite and evaporated in vacuo affording quantitatively piperidine derivative **7** (overall yield 71% from **4**)

MS : m/z = 490(MH+). HRMS : Calcd : 490.3904 Found : 490.3900. ^1H NMR (200 MHz) : -0.08 (3H, s, Si-Me), 0.04 (6H, s, Si(Me)$_2$), 0.3 (3H, s, Si-Me), 0.86 (9H, s, SitBu), 0.9 (9H, s, SitBu), 1.41 (15H, m, H aliphatics and C6-Ha), 2.26 (1H, broad d, C6-Hb, JHa-Hb = 10), 2.80 (1H, d, N-CH_2-Ph, J_{AB} = 12), 3.60 (2H, t, C11-H, 6), 4.30 (1H, d, N-CH_2-Ph, J_{AB} = 12), 7.22 (5H, m, Ph). ^{13}C NMR (50 MHz) : -5.2, -3.2 (4 x Si-Me), 17.8, 18.3 (2 x Si-C(Me)$_3$), 24.4 (C7), 26.0, 27.4 (2 x Si-C(Me)$_3$), 25.4, 25.5, 26.3, 29.7, 30.9, 34.4 (C3, C4, C5, C8, C9, C10), 53.9 (N-CH_2-Ph), 58.5 (C6), 63.1 (C11), 64.9 (C2), 126.3, 128.1, 128.6, 140.4 (C aromatics).

(*Z*)-(*N*-Benzyl-*N*-(*tert*-butyldimethylsilyloxy)-10-(*tert*-butyldimethylsilyloxy)dec-5-ene-1-amine **10**

To a solution of piperidine derivative **7** (7.7g, 15.8 mmol) in anhydrous dichloromethane (150 mL) was added at 0°C *m*CPBA (4.1g, 23.8 mmol). The resulting mixture was stirred for 2 hours while the temperature raised to 20°C. After treatment with an aqueous solution saturated with sodium carbonate, followed by usual work up, a solution of the resulting residue in acetonitrile (160 mL) was refluxed for 2 hours. After evaporation to dryness, the crude residue was chromatographed on silica gel (eluant: cyclohexane/ether : 98: 2) affording compound **10** (5.18 g, 65%) and compound **11** (2.5 g, 35%).

Compound **10**: MS (CI/NH_3) : m/z = 506(MH+). ^1H NMR (200 MHz, $CDCl_3$) : 0.05 (12H, s, 2 x Si(Me_2), 0.87 (18H, s, 2 x SitBu), 1.35 (8H, m, C2-H, C3-H, C8-H, C9-H), 1.95 (4H, m, C4-H, C7-H), 2.60 (2H, t, C1-H, J = 7.8), 3.58 (2H, t, C10-H, 8), 3.8 (2H, broad s , N-CH_2-Ph), 5.31 (2H, m, C5-H, C6-H), 7.25 (5H, m, aromatics).^{13}C NMR (50 MHz) : -7.1, -6.9, -5.4 (4 x Si-Me), 17.5, 18.2 (2 x Si-C(Me)$_3$), 25.9, 26.1 (2 x Si-C(Me)$_3$), 26.4, 26.9, 27.1, 27.5, 29.7, 32.5 (C2, C3, C4, C7, C8, C9), 59.8 (NCH_2Ph), 63.1 (C1), 64.8 (C10), 127.1, 127.7, 128.0, 128.3 (aromatics), 129.6, 129.8 (C5, C6), 137.5 (aromatics).

Compound **11**: MS (CI/NH_3): m/z = 506(MH+), 505 (M+). ^1H NMR (200 MHz) : 0.02 (6H, s, Si(Me)$_2$), 0.07 (6H, s, Si(Me)$_2$), 0.85 (18H, s, 2 x SitBu), 1.40 (8H, m, C2-H, C3-H, C8-H, C9-H), 2.01 (4H, m, C4-H, C7-H), 2.67 (2H, t, C1-H, J = 7.8), 3.57 (2H, t, C10-H,J = 8), 3.76 (2H, broad s, N-CH_2-Ph), 5.98 (1H, t, C6-H, J = 7), 7.30 (5H, m, Ph). ^{13}C NMR (50 MHz) : -5.2, -3.4 (4 x Si-Me), 18.2 (2 x Si-C(Me)$_3$), 26.0, 27.0 (2 x Si-C(Me)$_3$), 27.1, 27.7, 27.9, 32.7, 32.8, 37.9 (C2, C3, C4, C7, C8, C9), 59.9 NCH_2Ph, 63.2 (C1), 65.0 (C10), 127.3, 128.3, 128.5, 129.5, 143.9 (aromatics), 136.5 (C5), 137.5 (C6).

(*Z*)-*N*-Benzyl-10-*tert*-butyldimethylsilyloxy-dec-5-ene-1-amine **12**

To a dark green solution of sodium naphtalide (naphtalene, 4g, 30.6 mmol), sodium (1.4g, 61.2 mmol) in THF (400mL) under argon was added at room temperature a solution of compound **10** (5.18g, 10.2 mmol) in THF (50mL). After 2 hours, excess of sodium naphtalide was quenched with MeOH and the resuting mixture

was hydrolyzed with a saturated solution of sodium carbonate. After extraction with CH_2Cl_2 and usual workup the crude product was purified by chromatography on silica gel (eluant: dichloromethane:methanol: 9 :1) affording **12** (3.15g, 82%).

MS (CI/NH_3) : m/z = 376(MH+), 375(M+). HRMS: Calcd: 374.2879, Found: 374.2873. NMR ^{1}H (200 MHz) : 0.03 (6H, s, Si(Me)$_2$), 0.87 (9H, s, SitBu), 1.43 (8H, m, C2-H, C3-H, C8-H, C9-H), 1.96 (4H, m, C4-H, C7-H), 2.61 (2H, t, C1-H, J = 7.8), 3.55 (2H, t, C10-H,), 3.75 (2H, broad s, N-CH_2-Ph), 3.98 (1H, s, NH), 5.31 (2H, m, C5-H, C6-H), 7.25 (5H, m, aromatics). NMR ^{13}C (50 MHz) : -5.6, -4.0 (2 x Si-Me), 18.1 (Si-C(Me)$_3$), 25.6 (Si-C(Me)$_3$), 26.3, 26.6, 26.9, 28.4, 29.0, 32.1 (C2, C3, C4, C7, C8, C9), 53.1 (N-CH_2-Ph), 62.4, 62.9 (C1, C10), 127.2, 128.2, 129.1, 129.6 (aromatics), 129.8, 130.1 (C5, C6), 137.9 (aromatic).

(*Z*)-*N*-Benzyl-*N*-chloro-10-(*tert*-butyldimethylsilyloxy)dec-5-ene-1-amine **13**

To a stirred solution of **12** (200mg, 536mmol) in dichloromethane (30 mL) was added *N*-chlorosuccinimide (107 mg, 804 mmol). After being stirred for 30 min., the reaction medium was treated with a saturated aqueous solution of sodium carbonate. After extraction with dichloromethane and usual work up, compound **13** (206 mg, 94%) was isolated.

MS (CI/NH_3) : m/z = 410(MH+), 376(M+-Cl). ^{1}H NMR : (200 MHz) : 0.05 (6H, s, Si(Me)$_2$), 0.90 (9H, s, SitBu), 1.60 (8H, m, C2-H, C3-H, C8-H, C9-H), 1.98 (4H, m, C4-H, C7-H), 2.85 (2H, t, C1-H, J = 7.8), 3.60 (2H, t, C10-H, J = 8), 4.13 (2H, broad s , N-CH_2-Ph), 5.35 (2H, m, C5-H, C6-H), 7.25 (5H, m, aromatics). ^{13}C NMR (50 MHz) : -5.3 (2 x Si-Me), 18.3 (Si-C(Me)$_3$), 25.9 (Si-C(Me)$_3$), 26.7, 26.9, 27.4, 27.8, 29.3, 32.4 (C2, C3, C4, C7, C8, C9), 53.4 (N-CH_2-Ph), 63.1 (C10), 68.3 (C1), 127.7, 128.3, 129.1, 137.1 (aromatics), 129.5, 130.1 (C5, C6).

(*Z*)-*N*-Benzyliden-10-(*tert*-butyldimethylsilyloxy)dec-5-ene-1-amine **14**

To a solution of chloramine **13** (206 mg, 503mmol) in anhydrous THF, was added at 0°C potassium *tert*-butoxide (90 mg, 804 mmol). After stirring for 30 min. at room temperature, the reaction medium was hydrolyzed and extracted with dichloromethane. After usual work up, imine **14** was isolated (184 mg, 92%).

MS (CI/NH_3) : m/z = 391(M+18), 374(MH+). HRMS : Calcd : 374.2879 Found : 374.2874. ^{1}H NMR (200 MHz) : 0.01 (6H, s, Si(Me)$_2$), 0.86 (9H, s, SitBu), 1.37 (8H, m, C2-H, C3-H, C8-H, C9-H), 2.05 (4H, m, C4-H, C7-H), 3.57 (4H, t, C1-H, C10-H, J = 8), 5.34 (2H, m, C5-H, C6-H), 7.37 (3H, m, H *ortho*, H *para*), 7.69 (2H, m, H *meta*), 8.24 (1H, s, PhC-H). ^{13}C NMR(50 MHz) : -5.3 (2 x Si-Me), 18.3 (Si-C(Me)$_3$), 25.9 (Si-C(Me)$_3$), 26.9, 27.4 , 29.6, 30.4, 30.7, 32.4 (C2, C3, C4, C7, C8, C9), 61.6, 63.1 (C1, C10), 127.9, 128.5, 129.6, 129.8, 136.2 (aromatics), 129.9, 130.4 (C5, C6), 160.8 (PhC-H).

(*Z*)-10-Amino-dec-5-ene-1-ol **15**

To a solution of imine **14** (429 mg, 1.15 mmol) in methanol (50 mL) was added at room temperature, an aqueous solution fo hydrochloric acid (1N, 60 mL). After stirring for sixteen hours, aqueous layer was extracted three times with ether, alkalinized with an aqueous saturated solution of sodium carbonate to pH=11 and extracted three times with dichloromethane. After usual work up, compound **15** was isolated (185.5 mg, 94%). MS (CI/NH_3) : m/z = 172(MH+), 171(M+). HRMS : Cacd : 172.1701 Found : 172.1699. ^{1}H NMR (200 MHz) : 1.36 (8H, m, C2-H, C3-H, C8-H, C9-H), 1.97 (4H, m, C4-H, C7-H), 3.51 (4H, t, C1-H, C10-H, J = 8), 5.31 (2H, m, C5-H, C6-H). ^{13}C NMR (50 MHz) : 25.7, 26.8, 28.7, 29.1, 32.2, 32.3 (C2, C3, C4, C7, C8, C9), 61.6, 61.9 (C1, C10), 129.7, 129.8 (C5, C6).

(*Z*)-*N*- (*p*-Toluenesulfonyl)-10-(*p*-toluenesulfonyloxy)dec-5-en-1-amine. Tosylation of compound **15**.

To aminoalcohol **15** (25 mg, 146mmol) in solution in freshly distillated pyridine (176 mL) was added portionwise at 0°C tosyl chloride (83.2 mg, 438 mmol). The resulting mixture was stirred at the same temperature for five hours. After dilution with water and extraction with dichloromethane and usual work up, the crude mixture was purified by column chromatography (eluant : cyclohexane/ethyl acetate : 7:3) affording the title compound (95%) with minute amount of monotosylate.

(*Z*)-*N*- (*p*-Toluenesulfonyl)-10-(*p*-toluenesulfonyloxy)dec-5-en-1-amine.
MS (CI/NH_3) m/z = 497(M+18), 480(MH+), 479(M+). HRMS: calcd: 479.1800. Found: 479.1796. ^{1}H NMR (200 MHz) : 1.28 (8H, m, C2-H, C3-H, C8-H, C9-H), 1.91 (4H, m, C4-H, C7-H), 2.40 (3H, s, Me-Ar), 2.42(3H, s, Me-Ar), 2.88 (2H, dd, C1-H, J = 6.5), 3.99 (2H, t, , C10-H, J = 6.2), 5.34 (2H, m, C5-H, C6-H), 7.23 (2H, d, ArH, J = 8.3), 7.32 (2H, d, ArH, J = 8.3), 7.71 (2H, d, ArH, J = 8.3), 7.76 (2H, d, ArH, J = 8.3).

(*Z*)-10-(*p*-Toluenesulfonylamino)dec-5-en-1-ol.
MS (CI/NH_3) : m/z = 344(M+19), 343(M+18). ^{1}H NMR (200 MHz) : 1.36 (8H, m, C2-H, C3-H, C8-H, C9-H), 1.93 (4H, m, C4-H, C7-H), 2.40 (3H, s, Me-Ar), 2.88 (2H, dd, C10-H, J = 6.5), 3.49 (2H, t, C1-H, J = 6.2), 4.68 (1H, broad s, NH), 5.28 (2H, m, C5-H, C6-H), 7.27 (2H, d, ArH, J = 8), 7.72 (2H, d, ArH, J = 8).
(*Z*)-*N*-(*p*-Toluenesulfonyl)azacycloundec-6-ene **16**[3]

To the stirred crude mixture of mono and ditosylate (prepared as above from alminoalcohol **15** ,423 mg, 2.48 mmol) in toluene (1.6L) was successively added at room temperature water (40 mL), tetrabutyl ammonium iodide (950 mg, 2.6 mmol) and sodium hydroxide (15.9 g, 397.5 mmol). The resulting mixture was stirred at 100°C under vigourous stirring for four hours. The organic layer was separated and the aqueous layer was extracted three times with ether. The unified organic layers were washed with brine and, after usual work up, afforded a crude residue which was chromatographied on silica gel (eluant: cyclohexane/ethyl acetate: 9 :1). Compound **16** was isolated (253 mg, 47%) along with starting material ditosylate (45 mg, 5%) and dimeric compound (39 mg, 3%).
MS (CI/NH_3) : m/z = 308(MH+). ^{1}H NMR (200 MHz) : 1.50 (4H, m, C3-H or C4-H), 1.64 (4H, m, C3-H or C4-H), 2.27 (4H, q, C5-H), 2.38 (3H, s, Me-Ar), 3.11 (2H, t, , C2-H, J = 6.2), 5.33 (2H, t, C6-H), 7.25 (2H, d, ArH, J = 7.5), 7.62 (2H, d, ArH, J = 7.5). ^{13}C NMR (50 MHz) : 21.4 (Ar-Me), 24.7, 25.7, 26.2 (C3, C4, C5), 50.6 (C2), 127.0, 127.5, 129.5, 130.6 (aromatics), 130.8 (C6), 136.4, 142.7 (aromatics).

Dimeric compound : (*Z,Z*)-*N,N*-bis p-Toluenesulfonyl-1,12-diazadocosa-6,17-diene.

SM (CI/NH_3): m/z = 634(M+18), 615(MH+). ^1H NMR (200 MHz) : 1.23 (8H, m, C3-H, C4-H), 1.54 (8H, m, C3-H, C4-H), 1.98 (8H, q, C5-H), 2.39 (6H, s, Me-Ar), 3.01 (8H, t, C2-H, J = 6.2), 5.32 (4H, t, C6-H), 7.28 (4H, d, ArH, J = 8.3), 7.64 (4H, d, ArH, J = 8.3). ^{13}C NMR: (50 MHz, CDCl3) d (ppm) : 21.5 (Ar-Me), 26.4, 26.8, 28.7 (C3, C4, C5), 48.8 (C2), 127.1, 128.5 (aromatics), 129.5 (C6), 136.4, 142.9 (aromatics).

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10) During a tentative separation of diastereomeric *N*-oxides **8** and **9** by chromatography on silica gel, it was observed that *N*-oxide **9** decomposed spontaneously affording **11**, whereas *N*-oxide **8** was more stable and gave rise to the expected elimination product **10** after heating in acetonitrile.