

An efficient strategy for the construction of X-azatricyclo[m.n.0.0^{a,b}]alkanes by intramolecular [3 + 2] cycloaddition of nonstabilized cyclic azomethine ylides[†]

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Dedicated to Prof. T. R. Govindachari on the occasion of his 85th birthday

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Abstract

Various new structural entities related to X-azatricyclo[m.n.0.0^{a,b}]alkanes **15a-d** are constructed employing the intramolecular [3+2]-dipolar cycloaddition of nonstabilized cyclic azomethine ylides. The ylides are generated by the sequential double desilylation of *N*-alkyl- α,α' -bis(trimethylsilyl)cyclic amines **14a-d** using Ag(I)F as a one-electron oxidant. More rigid azatetracyclo compounds of type **23**, in which benzene ring is attached as a tether unit in the *N*-alkyl chain moiety, are also synthesized by the cyclization of **22**. These rigid azatricyclo compounds **15** and **23** possess structural resemblance to the rigid azatricyclo analogues **8-10**, which are reported to exhibit selective and high binding affinity at dopamine transporter (DAT).

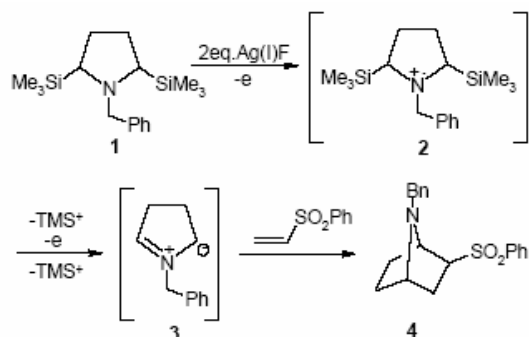
Keywords: X-Azatricyclo[m.n.0.0.]alkanes, intramolecular cycloaddition reactions, azomethine ylides, one electron oxidants, dopamine transporter (DAT)

Introduction

The fused pyrrolidine ring systems are frequently encountered structural unit in many synthetically challenging and biologically active alkaloids.¹ As a consequence, the construction of polycyclic fused pyrrolidine ring system has emerged as an important and challenging synthetic endeavor. The 1,3-dipolar cycloaddition of azomethine ylides with olefinic dipolarophile is identified as one of the most attractive strategy for the construction of isolated as well as fused pyrrolidine ring systems.^{2,3} Taking the advantage of the regio- and stereoselectivity of such cycloadditions, compounds possessing complex molecular framework such as eserethole,⁴ erythramine,⁵ α -lycorane,⁶ allokainic acid,⁷ acromelic acid,⁸ (-)-kainic acid,⁹ sceletium alkaloid A4,¹⁰ menzamine alkaloids,¹¹ martinelline alkaloids¹² and various other bicyclic¹³⁻¹⁶ and polycyclic¹⁷⁻¹⁹ fused pyrrolidine ring systems such as 2-azatricyclo[5.2.1.0^{4,10}]decanes,²⁰ and 2,5-diazatricyclo[5.2.1.0^{4,10}]decane²⁰ have been synthesized utilizing intramolecular [3+2]-

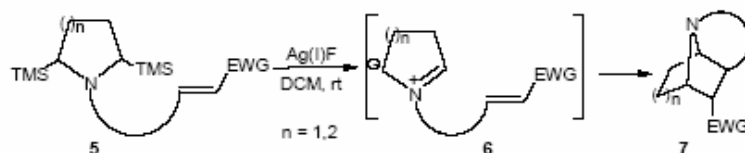
cycloaddition of appropriate stabilized acyclic azomethine ylides with tethered dipolarophiles.

Recently, our group has developed a versatile strategy of generating non-stabilized cyclic azomethine ylides **3** by the sequential double desilylation of N-alkyl- α,α' -bis(trimethylsilyl)cyclic amines **1** using Ag(I)F as one-electron oxidant (Scheme 1).²¹⁻²³ We have also explored its application for the regio- and stereoselective construction of X-azabicyclo[m.2.1]alkane skeletons.²⁴ Synthetic application of this strategy have also been demonstrated for the synthesis of biologically important alkaloids epibatidine²⁵ and epiboxidine.²⁶



Scheme 1

Our continuing interest and the desire to explore the versatility of such ylides in the construction of complex polycyclic fused pyrrolidine ring systems led us to consider the intramolecular cycloaddition variant. We envisaged the construction of X-azatricyclo[m.n.0.0^{a,b}]alkanes **7**, a new azatricyclic structural entities, by the intramolecular [3+2]-dipolar cycloaddition reaction of a nonstabilized cyclic azomethine ylide **6** (Scheme 2). The interest of constructing skeletons of type **7** was further enlightened by the recent disclosure of Smith *et al.*^{27,28} that the rigid cocaine analogues (**8-10**) having azatricyclo ring systems show high binding affinity to the site of the monoamine transporters. The enhanced selectivity of these rigid tropane analogues for the monoamine transporter inhibitors is understood to be influenced by the fixed orientation of the nitrogen lone pair due to the tethered carbon bridge of the tropane moiety.



Scheme 2

In this article we delineate the full details²⁹ of our effort and the success on the construction of various X-azatricyclo[m.n.0.0^{a,b}]alkanes skeleton **7** through the strategy as shown in Scheme 2.

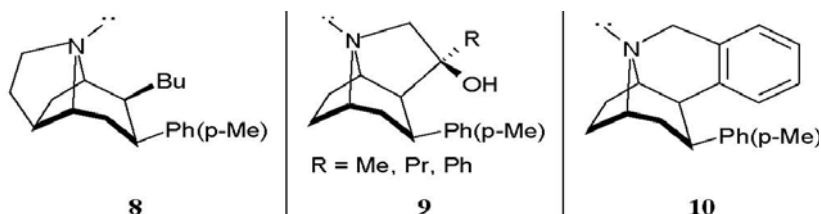
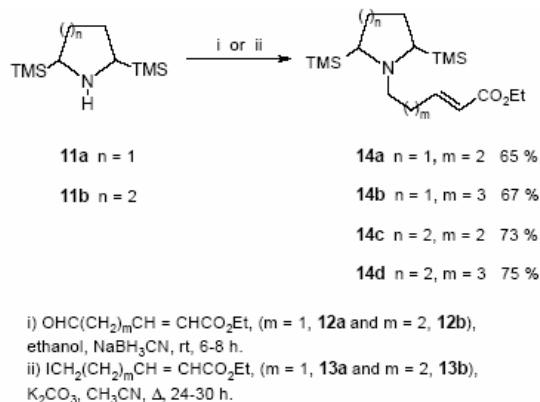


Figure 1

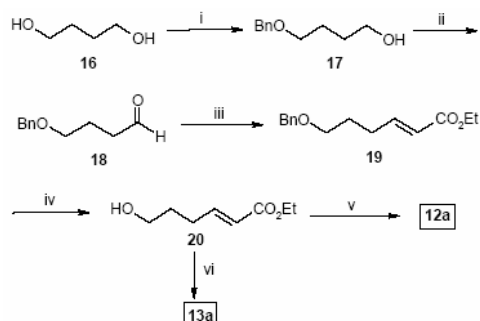
Results and Discussions

As per the synthetic strategy as depicted in Scheme 2, we initially envisaged possible construction of ethyl-2-azatricyclo[4.4.0.0^{2,8}]decane-7-carboxylate (15a) through the intramolecular [3+2]-dipolar cycloaddition of the azomethine ylide generated from the precursor ethyl-6-[2,5-di(trimethylsilyl)tetrahydro-1*H*-1-pyrrolyl]-(*E*)-2-hexenoate (14a). To obtain 14a, we initially tried the reductive amination of 2,5-di(trimethylsilyl)pyrrolidine (**11a**)²⁵ with 6-oxo-(*E*)-2-hexenoate (**12a**) in the presence of NaBH₃CN in ethanol, however, this approach failed due to the formation of many uncharacterized products. Ultimately, the *N*-alkylation of **11a** by refluxing with 6-iodo-(*E*)-2-hexenoate (**13a**) in dry acetonitrile in the presence of K₂CO₃ afforded **14a** in 65 % yield as a pale yellow liquid (Scheme 3). Similarly, precursor **14b** was prepared in 67 % yield as a viscous yellow liquid by heating **11a** with 7-iodo-(*E*)-2-heptenoate (**13b**)³⁰ in dry acetonitrile in the presence of K₂CO₃. The substrates **14c** and **14d** were synthesized by the reductive amination of 2,6-di(trimethylsilyl)piperidine (**11b**)²⁵ with 6-oxo-(*E*)-2-hexenoate (**12a**) (73 % yield) and 7-oxo-(*E*)-2-heptenoate (**12b**)³¹ (75 % yield) as a viscous yellow liquids, respectively.



Scheme 3

Although synthesis of ethyl-6-hydroxy-(*E*)-2-hexenoate **20** was reported in literature³² starting from γ -butyrolactone, we synthesized it from commercially available 1,4-butanediol **16** as shown in Scheme 4.^{33,34} Compound **12a** was prepared in 93 % yield by the Swern oxidation³⁵ of **20** whereas **13a** was synthesized in 91 % yield from **20** by stirring with triphenylphosphine, iodine and imidazole³⁰ in DCM at room temperature.

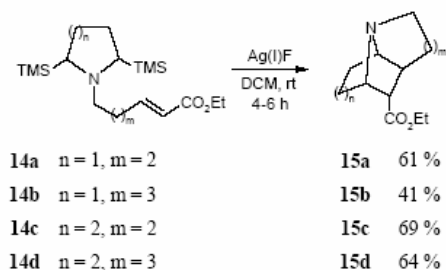


Reagents and conditions: i) BnCl, KOH, rt, 5 h, 87 %; ii) PCC/Celite, DCM, rt, 3 h, 83 %; iii) Ph₃PCHCO₂Et, DCM, rt, 24 h, 92 %; iv) TMSCl, NaI, CH₃CN, rt, 4 h, 66 %; v) (COCl)₂, DMSO, Et₃N, -78° C, 93 %; vi) Ph₃P, I₂, imidazole, DCM, rt, 6 h, 91 %.

Scheme 4

The intramolecular [3 + 2]-dipolar cycloaddition reaction was first carried out with the key precursor **14a**, by essentially following the experimental protocol as reported earlier.²⁶ A solution of **14a** (1.0 g, 2.82 mmol) in dry DCM was added slowly to a stirred suspension of vacuum dried Ag(I)F (0.89 g, 7.02 mmol) at room temperature. The color of the reaction mixture gradually turned dark brown and the reaction was completed within 46 h with the concomitant formation of silver mirror on the surface of the reaction flask. The reaction mixture was passed through a Celite pad and the residue was purified by silica gel column chromatography using chloroform / methanol (7:3) to afford a single product **15a** in 61 % yield, characterized by ¹H NMR, ¹³C NMR and mass spectral data (Scheme 5).

The generality of the cycloaddition reaction was established by constructing a number of X-azatricyclo[m.n.0.^{a,b}]alkanes **15b-d** through the intramolecular cycloaddition reaction of substrates **14b-d** as illustrated in Scheme 5.

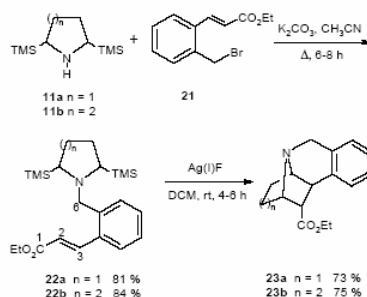


Scheme 5

Detailed ¹H NMR decoupling and ¹H COSY experiments determined the stereochemistry of the cycloadducts. For illustration in the ¹H COSY of **15a**, the H₆ at δ2.53 (m, 1H) couples with H₇ at δ 2.95 (d, J = 5.7 Hz), H_{5endo} at δ1.51-1.64 (m) and H_{5exo} at δ1.65-1.78 (m), but not with H₁ at δ 3.05-3.17 (m). This observation is in conformity with the ¹H NMR patterns of the 7-azabicyclo[m.2.1]alkane skeletons^{36,37} where no coupling is observed between bridgehead bowsprit and the adjacent *endo*-hydrogen due to the dihedral angle of 90° between them. Therefore, H₆ is assigned with an *endo*-orientation. In contrast, H₇ coupled with H₆ and H₈ at δ

3.73 (t, $J = 4.6$ Hz) confirming the *endo* orientation of the carboethoxy moiety. The stereochemistry of other cycloadducts **15b-d** was ascertained similarly and it is confirmed that in all the cycloadducts the carboethoxy moiety is *endo*-oriented.

Considering the reported²⁷ high binding affinity at the dopamine transporter of the azatricyclo analogue **10** (Fig. 1), we extended our effort towards the synthesis of a more rigid azatetracyclo compounds of type **23** by the intramolecular [3+2] cycloaddition of the substrate **22**. Precursor **22** was easily obtained by the *N*-Alkylation of **11** with ethyl-3-(2-bromomethylphenyl)-(E)-2-propenoate **21**³⁸ by refluxing in acetonitrile in the presence of K_2CO_3 (Scheme 6). Cycloaddition reaction of **22** with $Ag(I)F$, utilizing the exact experimental protocol as described above for the substrate **14a**, gave cycloadducts **23a,b** in 73-75 % yield. The stereochemical assignments of **23a,b** was established on the similar logic as described for **15a**.



Scheme 6

In summary, we have successfully demonstrated the synthesis of a number of polycyclic X-azatricyclo[m.n.0.0^{a,b}]alkanes by employing the intramolecular [3+2]-dipolar cycloaddition of nonstabilized cyclic azomethine ylides. We believe that these rigid polycyclic structures may be of interest in natural product synthesis and medicinal chemistry. Studies related to the biological activities of these products are in progress and will be reported appropriately.

Experimental Section

General Procedures. All the yields reported refer to isolated material but are not optimized. Temperatures above and below ambient temperature refer to bath temperature unless otherwise stated. Solvents and anhydrous liquid reagents were dried according to the established procedures by distillation under argon atmosphere from an appropriate drying agent. Chemicals and reagents were procured from Aldrich, U. S. A. and SD Fine Chemicals, India. Analytical TLC was performed using precoated silica gel plates (0.25 mm). Column chromatography was performed using Silica gel by standard chromatographic techniques.

IR spectra were recorded on a Perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR. All nuclear magnetic resonance spectra were recorded on either Bruker AC-200, Bruker MSL-300 and Bruker DRX-500 instruments using $CDCl_3$ as solvent. All chemical shifts are reported in parts per million down field from TMS; coupling constants are given in Hertz. Mass (m/z , relative intensity) spectra were recorded at a voltage of 70 eV on Finnigan-Mat 1020B instrument.

Preparation of 4-benzyloxy-1-butanol (17). Powdered KOH (19.91 g, 355.5 mmol) and benzyl chloride (25.0 g, 197.48 mmol) were added in four equal portions over 1 h to 1,4-butanediol **16** (44.5 g, 493.7 mmol) at rt with stirring. After stirring for an additional 4-5 h at rt, 100 mL of water was added and the reaction mixture was extracted with diethyl ether (3 × 50 mL). The combined extracts were washed with water (2 × 30 mL), brine (30 mL), dried over Na₂SO₄ and concentrated under vacuum. The crude residue was purified by fractional distillation (bp 80 °C / 1 mm) to afford 30.9 g (87 %) of **17** as a colorless liquid. IR (neat): 3393, 2864, 1363 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 1.60-1.85 (m, 4H), 2.55 (s, -OH), 3.55 (t, *J* = 7.9 Hz, 2H), 3.65 (t, *J* = 7.9 Hz, 2H), 4.55 (s, 2H), 7.25-7.45 (m, 5H). ¹³C NMR (CDCl₃, 50.3 MHz): δ 25.6 (-CH₂-), 28.9 (-CH₂-), 61.3 (-CH₂-), 69.6 (-CH₂-), 72.1 (-CH₂-), 126.8 (-CH-), 126.9 (-CH-), 127.6 (-CH-), 137.8 (-C-). MS (*m/z*): 180 (*M*⁺, 3), 107 (45), 91 (100), 77 (31).

Preparation of 4-Benzyloxy-1-butanal (18). Into a stirring mixture of pyridinium chlorochromate (18 g, 83.5 mmol) and Celite (9 g) in 100 mL of dry CH₂Cl₂ at 0 °C was added dropwise a solution of **17** (10 g, 55.55 mmol) in dry CH₂Cl₂ (20 mL). The resulting black slurry was stirred for an additional 2.5 h at rt and diluted with dry ether (100 mL). The supernatant solution was filtered from the black residue and washed with dry ether (2 × 30 mL). The combined filtrate was evaporated under vacuum and the brown residue was chromatographed on silica gel, eluting with hexane/EtOAc (8:2), to afford 8.21 g (83%) of **18** as a colorless liquid. IR (neat): 2935, 1711, 1364 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 1.85-2.05 (m, 2H), 2.55 (t, *J* = 8.1 Hz, 2H), 3.55 (t, *J* = 7.9 Hz, 2H), 4.50 (s, 2H), 7.25-7.45 (m, 5H), 9.80 (s, 1H). ¹³C NMR (CDCl₃, 50.3 MHz): δ 21.8 (-CH₂-), 39.8 (-CH₂-), 68.4 (CH₂-), 71.8 (-CH₂-), 126.6 (-CH-), 127.4 (-CH-), 137.9 (-C-), 200.6 (-CH-). MS (*m/z*): 178 (*M*⁺, 1), 107 (78), 91 (100).

Preparation of ethyl-6-benzyloxy-(E)-2-hexenoate (19). To a solution of ethoxycarbonylmethylene triphenylphosphorane (19.27 g, 55.34 mmol) in 50 mL CH₂Cl₂ was added a solution of **18** (8.21 g, 46.12 mmol) in 15 mL of dry CH₂Cl₂ at rt. The reaction mixture was further allowed to stir for another 24 h at rt. The solvent was removed under vacuum and the residue was chromatographed on silica gel, eluting with hexane/EtOAc (9:1) to afford 10.52 g (92 %) of **19** as a colorless liquid. IR (neat): 2928, 1718, 1366, 1168 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 1.30 (t, *J* = 7.1 Hz, 3H), 1.70-1.90 (m, 2H), 2.32 (dt, *J* = 7.9, 1.4 Hz 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.52 (s, 2H), 5.85 (dt, *J* = 15.6, 1.4 Hz, 1H), 6.97 (dt, *J* = 15.6, 6.9 Hz 1H), 7.20-7.45 (m, 5H). ¹³C NMR (CDCl₃, 50.3 MHz): δ 13.9 (-CH₃), 27.9 (-CH₂-), 28.5 (-CH₂-), 59.6 (-CH₂-), 68.9 (-CH₂-), 72.6 (-CH₂-), 121.5 (-CH-), 127.2 (-CH-), 128.0 (-CH-), 138.3 (-C-), 147.9 (-CH-), 165.2 (-C-). MS (*m/z*): 248 (*M*⁺, 1), 202 (9), 114 (39), 91 (100).

Preparation of ethyl-6-hydroxy-(E)-2-hexenoate (20). To a solution of **19** (10 g, 40.32 mmol) and sodium iodide (6.05 g, 40.32 mmol) in 45 mL of acetonitrile was added dropwise trimethylsilyl chloride (4.38 g, 40.32 mmol) at 0 °C. The resulting reaction mixture was allowed to stir at rt for 5-6 h until the completion of reaction as monitored by TLC. The reaction mixture was quenched with water (25 mL) and extracted with diethyl ether (2 × 30 mL), washed with sodium thiosulphate, brine and dried over Na₂SO₄. The ether layer was concentrated and the crude residue was chromatographed on silica gel, eluting with hexane/EtOAc (7:3) to afford 4.2 g, (66 %) of **20** as a colorless liquid. IR (neat): 3421, 2876, 1717, 1370 cm⁻¹. ¹H NMR (CDCl₃,

200 MHz): δ 1.27 (t, J = 7.1 Hz, 3H), 1.60-1.80 (m, 2H), 2.28 (q, J = 6.3, Hz, 2H and -OH, 1H), 3.65 (q, J = 6.3 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 5.83 (dt, J = 15.6, 1.4 Hz, 1H), 6.94 (dt, J = 15.6, 6.9 Hz, 1H). ^{13}C NMR (CDCl_3 , 50.3 MHz): δ 13.4 (-CH₃), 27.8 (-CH₂), 30.2 (-CH₂-), 59.4 (-CH₂-), 60.6 (CH₂-), 120.8 (-CH-), 148.1 (-CH-), 166.0 (-C-). MS (m/z): 158 (M^+ , 2), 127 (20), 112 (100), 99 (55), 84 (84).

Preparation of ethyl-6-oxo-(E)-2-hexenoate (12a). A solution of oxalyl chloride (3.25 g, 25.6 mmol) in 30 mL dry CH_2Cl_2 , charged into 100 mL two neck argon-flushed flask, was cooled to -78°C . DMSO (3.34 g, 42.75 mmol) in 10 mL CH_2Cl_2 , followed by **20** (2.7 g, 17.1 mmol) in 10 mL CH_2Cl_2 was introduced dropwise into the flask over 5 min. The mixture was allowed to stir for 1.5 h at -78°C and then Et_3N (6.92 g, 68.51 mmol) in 10 mL CH_2Cl_2 was introduced dropwise. The reaction mixture was allowed to warm to rt and quenched with 30 mL of water. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL), the combined extracts were washed with water (4×20 mL), brine, dried over Na_2SO_4 , and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography, eluting with hexane/EtOAc (8:2) to afford 2.48 g (93 %) of **12a** as a colorless liquid. IR (neat): 3446, 1719, 1401 cm^{-1} . ^1H NMR (CDCl_3 , 200 MHz): δ 1.27 (t, J = 7.1 Hz, 3H), 2.45-2.75 (m, 4H), 4.15 (q, J = 7.1 Hz, 2H), 5.83 (dt, J = 15.6, 1.4 Hz, 1H), 6.93 (dt, J = 15.6, 6.9 Hz, 1H), 9.75 (t, J = 1.4 Hz, 1H). ^{13}C NMR (CDCl_3 , 50.3 MHz): δ 13.7 (-CH₃), 23.9 (-CH₂-), 41.2 (-CH₂-), 59.6 (-CH₂-), 121.9 (-CH-), 145.9 (-CH), 165.5 (-C-), 199.8 (-C-). MS (m/z): 156 (M^+ , 1), 126 (39), 108 (100), 99 (71).

Preparation of ethyl-6-iodo-(E)-2-hexenoate (13). To a stirring solution of triphenylphosphine (4.97 g, 18.95 mmol) and imidazole (1.29 g, 18.95 mmol) in 40 mL of dry CH_2Cl_2 at 0°C , was added iodine (4.81 g, 18.95 mmol) portion wise over a period of 30 min. A solution of **20** (2.3 g, 14.56 mmol) in 10 mL of CH_2Cl_2 was introduced dropwise at 0°C and the reaction was further allowed to stir for 6 h at rt. The reaction mixture was diluted with 50 mL of CH_2Cl_2 , washed with 20 % sodium thiosulphate solution, water, brine, and dried over Na_2SO_4 . The organic layer was concentrated and the crude residue was chromatographed on silica gel, eluting with hexane/EtOAc (9:1) to afford 3.55 g (91 %) of **13a** as a colorless liquid which changed slowly to a brownish color on keeping for a longer time at room temperature. IR (neat): 2979, 1720, 1367 cm^{-1} . ^1H NMR (CDCl_3 , 200 MHz): δ 1.28 (t, J = 7.3 Hz, 3H), 1.85-2.05 (m, 2H), 2.32 (q, J = 6.6 Hz, 2H), 3.18 (t, J = 6.6 Hz, 2H), 4.17 (q, J = 7.3 Hz, 2H), 5.85 (dt, J = 15.4, 1.4 Hz, 1H), 6.88 (dt, J = 15.4, 6.9 Hz, 1H). ^{13}C NMR (CDCl_3 , 50.3 MHz): δ 5.1 (-CH₂-), 13.8 (-CH₃), 31.0 (-CH₂-), 32.2 (CH₂-), 59.7 (-CH₂-), 122.1 (-CH-), 146.0 (-CH-), 165.6 (-C-). MS (m/z): 268 (M^+ , 6), 223 (32), 155 (39), 141 (100), 113 (57).

Preparation of ethyl-6-[2,5-di(trimethylsilyl)tetrahydro-1H-1-pyrrolyl]-(E)-2-hexenoate (14a). To a suspension of **11a** (1.9 g, 8.83 mmol) and K_2CO_3 (2.47 g, 17.9 mmol) in 30 mL of acetonitrile was added a solution of **13a** (1.6 g, 5.97 mmol) in 10 mL of acetonitrile under argon atmosphere at rt. The resultant suspension was refluxed for 24-30 h. The reaction mixture was cooled, filtered, diluted with EtOAc, washed with water, brine and dried over Na_2SO_4 . The organic layer was evaporated under vacuum and the brownish oily residue was purified over silica gel column chromatography using hexane/EtOAc (8:2) to give 1.38 g (65 %) of **14a** as a

pale yellow liquid. IR (neat): 3381, 2952, 1722, 1367, 1249 cm^{-1} . ^1H NMR (CDCl_3 , 200 MHz): δ 0.05 (s, 18H), 1.27 (t, $J = 7.3$ Hz, 3H), 1.35-2.03 (m, 6H), 2.05-2.62 (m, 6H), 4.18 (q, $J = 7.3$ Hz, 2H), 5.83 (dt, $J = 15.2, 1.4$ Hz, 1H), 6.97 (dt, $J = 15.2, 6.9$ Hz, 1H). ^{13}C NMR (CDCl_3 , 50.3 MHz): δ - 2.1 (- CH_3), 14.0 (- CH_3), 25.6 (- CH_2 -), 26.6 (- CH_2 -), 32.7 (- CH_2 -), 55.5 (- CH_2 -), 55.8 (- CH -), 59.5 (- CH_2 -), 121.1 (CH-), 148.7 (-CH-), 165.9 (-C-). MS (m/z): 355 (M^+ , 1), 340 (9), 282 (100), 73 (53).

Preparation of ethyl-7-[2,5-di(trimethylsilyl)tetrahydro-1H-1-pyrrolyl]-(E)-2-heptenoate (14b). The N-alkylation reaction of **11a** (1.5 g, 6.97 mmol) with **13b** (1.31 g, 4.65 mmol) was carried out, by adopting the procedure as described above for the preparation **14a**, to obtain 1.15 g (67 %) of **14b** as a viscous yellow liquid. IR (neat): 3429, 2952, 1717, 1654, 1368, 1254, 1042 cm^{-1} . ^1H NMR (CDCl_3 , 200 MHz): δ 0.05 (s, 18H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.35-1.73 (m, 5H), 1.76-1.98 (m, 3H), 2.11-2.59 (m, 6H), 4.18 (q, $J = 7.2$ Hz, 2H), 5.83 (dt, $J = 15.6, 1.4$ Hz, 1H), 6.95 (dt, $J = 15.6, 6.9$ Hz, 1H). ^{13}C NMR (CDCl_3 , 50.3 MHz): δ - 2.1 (- CH_3), 13.9 (- CH_3), 25.6 (- CH_2 -), 26.4 (- CH_2 -), 29.7 (- CH_2 -), 31.9 (- CH_2 -), 55.3 (- CH_2 -), 55.6 (-CH-), 59.4 (- CH_2 -), 121.2 (-CH-), 148.3 (-CH-), 165.8 (C-). MS (m/z): 369 (M^+ , 1), 354 (6), 296 (100), 73 (53).

Preparation of ethyl-6-[2,6-di(trimethylsilyl)hexahydro-1-pyridinyl]-(E)-2-hexenoate (14c). To a stirred solution of **11b** (1.5 g, 6.55 mmol) in 50 mL of ethanol was added a solution of **12a** (0.72 g, 4.61 mmol) in 10 mL of ethanol at rt. After stirring for 3 h, NaBH_3CN (0.29 g, 4.61 mmol) followed by glacial acetic acid (1.0 mL) was added and contents were further allowed to stir for another 3 h at rt. The reaction mixture was basified by slow addition of concentrated NH_4OH solution. The reaction mixture was diluted with water (10 mL), extracted with chloroform (3×25 mL), washed with brine and dried over Na_2SO_4 . The organic layer was concentrated and the crude residue was purified by silica gel chromatography using hexane/EtOAc (9:1) to afford 1.24 g (73 %) of **14c** as a pale yellow liquid. IR (neat): 2951, 1723, 1655, 1402, 1248, 1044 cm^{-1} . ^1H NMR (CDCl_3 , 200 MHz): δ 0.05 (s, 18H), 1.30 (t, $J = 7.3$ Hz, 3H), 1.35-1.70 (m, 8H), 2.03-2.42 (m, 5H), 2.83-2.95 (m, 1H), 4.17 (q, $J = 7.3$ Hz, 2H), 5.78 (dt, $J = 15.4, 1.4$ Hz, 1H), 6.97 (dt, $J = 15.4, 6.9$ Hz, 1H). ^{13}C NMR (CDCl_3 , 50.3 MHz): δ -1.5 (- CH_3), 14.1 (- CH_3), 19.7 (- CH_2 -), 25.1 (- CH_2 -), 28.3 (- CH_2 -), 29.9 (- CH_2 -), 50.3 (- CH_2 -), 51.5 (-CH-), 59.8 (- CH_2 -), 121.3 (CH-), 149.1 (-CH-), 166.4 (-C-). MS (m/z): 369 (M^+ , 1), 354 (4), 296 (100), 73 (81).

Preparation of ethyl-7-[2,6-di(trimethylsilyl)hexahydro-1-pyridinyl]-(E)-2-heptenoate (14d). The reductive amination of **11b** (1.5 g, 6.55 mmol) with **12b** (0.79 g, 4.65 mmol) in the presence of NaBH_3CN (0.29 g, 4.62 mmol) gave **14d** (1.34 g, 75 %) as a viscous yellow liquid. IR (neat): 3442, 2949, 1723, 1655, 1445, 1368, 1248, 1044 cm^{-1} . ^1H NMR (CDCl_3 , 200 MHz): δ 0.05 (s, 18H), 1.29 (t, $J = 7.3$ Hz, 3H), 1.33-1.72 (m, 10H), 2.12-2.43 (m, 5H), 2.76-2.95 (m, 1H), 4.19 (q, $J = 7.3$ Hz, 2H), 5.83 (dt, $J = 15.2, 1.4$ Hz, 1H), 6.97 (dt, $J = 15.2, 6.9$ Hz, 1H). ^{13}C NMR (CDCl_3 , 50.3 MHz): δ -1.5 (- CH_3), 14.1 (CH₃), 19.6 (- CH_2 -), 25.1 (- CH_2 -), 25.7 (- CH_2 -), 29.3 (- CH_2 -), 32.1 (- CH_2 -), 50.6 (- CH_2 -), 51.5 (-CH-), 59.7 (- CH_2 -), 121.3 (-CH-), 148.7 (-CH-), 166.2 (-C-). MS (m/z): 383 (M^+ , 1), 310 (58), 156 (49), 73 (100).

General Intramolecular [3 + 2]-cycloaddition procedure

This is illustrated by taking the example of the synthesis of ethyl-2-azatricyclo[4.4.0.0^{2,8}]decane-7-carboxylate **15a**.

Ethyl-2-azatricyclo[4.4.0.0^{2,8}]decane-7-carboxylate (15a). A solution of **14a** (1.0 g, 2.82 mmol) in 10 mL of dry CH₂Cl₂ was introduced dropwise to an argon flushed 50 mL two neck flask containing a suspension of vacuum dried Ag(I)F (0.89 g, 7.02 mmol) in CH₂Cl₂ (30 mL). The color of the reaction mixture gradually turned to dark brown with concomitant deposition of silver on the surface of the flask in the form of a mirror. The reaction mixture was periodically monitored through TLC. After stirring for another 4-6 h, the reaction mixture was filtered through a small plug of Celite and the solvent was evaporated to give a brown residue. The crude residue was purified by silica gel column chromatography using (CHCl₃: MeOH: NH₃ = 97: 2: 1) to afford **15a** (0.36 g) in 61 % yield as a thick yellow liquid. IR (neat): 3145, 2927, 1723, 1395 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ 1.22-1.25 (m, 1H, H_{10endo}), 1.27 (t, *J* = 7.3 Hz, 3H), 1.31-1.43 (m, 2H, H_{4endo}, H_{9endo}), 1.51-1.64 (m, 3H, H_{5endo}, H_{9exo}, H_{10exo}), 1.65-1.78 (m, 2H, H_{4exo}, H_{5exo}), 2.53 (m, 1H, H_{6endo}), 2.95 (d, *J* = 5.7 Hz, 1H, H_{7exo}), 3.05-3.17 (m, 3H, H_{3exo}, H_{3endo}, H₁), 3.73 (t, *J* = 4.6 Hz, 1H, H₈), 4.15 (m, 2H). ¹³C NMR (CDCl₃, 125.3 MHz): δ 14.1 (-CH₃), 17.5 (-CH₂-), 25.5 (-CH₂-), 26.7 (-CH₂-), 28.1 (-CH₂-), 39.8 (-CH-), 46.2 (-CH₂-), 48.7 (-CH-), 60.4 (CH₂-), 64.2 (-CH-), 65.3 (-CH-), 172.8 (-C-). MS (*m/z*): 209 (M⁺, 56), 180 (26), 164 (28), 136 (100), 83 (68). HRMS: calcd for C₁₂H₁₉NO₂ 209.1415 found 209.1410.

Ethyl-2-azatricyclo[5.4.0.0^{2,9}]undecane-8-carboxylate (15b). Thick yellow liquid. Yield 41 %. IR (neat): 2937, 1725, 1451, 1385, 1231 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 1.27 (t, *J* = 7.3 Hz, 3H), 1.32-1.87 (m, 10H), 2.53-2.62 (m, 1H, H_{7endo}), 2.62-2.68 (m, 1H, H_{3endo}), 2.88 (t, *J* = 5.1 Hz, 1H, H_{8exo}), 3.23-3.37 (m, 1H, H_{3exo}), 3.40 (d, *J* = 3.6 Hz, 1H, H₁), 3.55 (t, *J* = 4.3 Hz, 1H, H₉), 4.15 (q, *J* = 7.3 Hz, 2H). ¹³C NMR (CDCl₃, 125.3 MHz): δ 14.1 (-CH₃), 24.6 (-CH₂-), 25.8 (-CH₂-), 27.4 (-CH₂-), 29.3 (-CH₂-), 29.5 (-CH₂-), 45.5 (CH-), 49.6 (-CH₂-), 50.3 (-CH-), 60.5 (-CH₂-), 63.7 (-CH-), 66.5 (-CH-), 172.9 (-C-). HRMS calcd for C₁₃H₂₁NO₂ 223.2167 found 223.2175.

Ethyl-7-azatricyclo[5.4.0.0^{3,8}]undecane-2-carboxylate (15c). Thick yellow liquid. Yield 69 %. IR (neat): 3147, 2930, 1723, 1400, 1181, 1048 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 1.27 (t, *J* = 7.3 Hz, 3H), 1.35-1.48 (m, 2H), 1.53-1.84 (m, 6H), 1.85-2.13 (m, 2H), 2.78 (m, 1H, H_{3endo}), 2.87 (bs, 1H, H₈), 2.93-3.07 (m, 2H, H_{6endo}, H_{6exo}), 3.10 (d, *J* = 6.3 Hz, 1H, H_{2exo}), 3.58-3.69 (m, 1H, H₁), 4.04-4.32 (m, 2H). ¹³C NMR (CDCl₃, 75.3 MHz): δ 14.1 (CH₃), 16.0 (-CH₂-), 18.5 (-CH₂-), 9.4 (-CH₂-), 29.7 (-CH₂-), 32.0 (-CH₂-), 39.5 (-CH-), 50.3 (-CH-), 54.0 (-CH₂-), 60.2 (-CH₂-), 64.1 (-CH-), 67.8 (-CH-), 173.5 (-C-). MS (*m/z*): 223 (M⁺, 77), 194 (55), 178 (38), 150 (78), 136 (43), 97 (100). HRMS calcd for C₁₃H₂₁NO₂ 223.1572 found 223.1563.

Ethyl-2-azatricyclo[5.5.0.0^{2,9}]dodecane-8-carboxylate (15d). Thick yellow liquid. Yield 64 %. IR (neat): 2929, 1726, 1453, 1398, 1233, 1180 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.33-1.92 (m, 12H), 2.61 (dt, *J* = 14.8, 5.4 Hz, 1H, H_{3endo}), 2.81-2.94 (m, 1H, H_{7endo}), 3.01 (t, *J* = 7.2 Hz, 1H, H_{8exo}), 3.06-3.16 (m, 1H, H_{3exo}), 3.22 (bs, 1H, H₁), 3.32-3.45 (m, 1H, H₉), 4.04-4.31 (m, 2H). ¹³C NMR (CDCl₃, 75.3 MHz): δ 14.1 (CH₃), 16.8 (-CH₂-), 25.5 (-CH₂-), 27.5 (-CH₂-), 29.5 (-CH₂-), 30.4 (-CH₂-), 32.0 (-CH₂-), 44.0 (-CH-), 55.0 (-CH-), 56.0 (-

CH₂-), 60.0 (-CH₂-), 62.4 (-CH-), 66.1 (-CH-), 173.0 (-C). MS (m/z): 237 (M⁺, 27), 208 (42), 192 (27), 164 (54), 136 (45), 123 (87), 97 (100), 83 (53). HRMS: calcd for C₁₄H₂₃NO₂ 237.1728 found 237.1747.

Preparation of ethyl-3-{2-[2,5-di(trimethylsilyl)tetrahydro-1H-pyrrolylmethyl]-phenyl}-(E)-2-propenoate (22a). To a slurry of **11a** (1.5 g, 6.97 mmol) and K₂CO₃ (1.5 g, 10.87 mmol) in 30 mL of dry acetonitrile was added a solution of ethyl-3-(2-bromomethyl phenyl)-(E)-2-propenoate (**21**) (1.4 g, 5.22 mmol) through syringe under argon atmosphere at rt. The resultant suspension was refluxed for 6-8 h and then allowed to cool to rt. The reaction mixture was filtered, diluted with EtOAc, washed with water, brine, and dried over Na₂SO₄. The organic layer was evaporated and the crude residue was chromatographed using hexane/EtOAc (9:1) to afford 1.7 g (81 %) of **22a** as a viscous yellow liquid. IR (neat): 2935, 1695, 1428 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ -0.1 (s, 18H), 1.35 (t, *J* = 7.3 Hz, 3H), 1.55-1.77 (m, 2H), 1.83-2.04 (m, 2H), 2.33 (t, *J* = 4.8 Hz, 2H), 3.43 (d, *J* = 13.7 Hz, 1H), 3.98 (d, *J* = 13.7 Hz, 1H), 4.14-4.35 (m, 2H), 6.33 (d, *J* = 15.6 Hz, 1H), 7.17-7.36 (m, 3H), 7.48-7.72 (m, 1H), 8.48 (d, *J* = 15.6 Hz, 1H). ¹³C NMR (CDCl₃, 50.3 MHz): δ -2.3 (-CH₃), 14.1 (-CH₃), 26.4 (-CH₂-), 55.4 (-CH-), 57.5 (-CH₂-), 59.8 (-CH₂-), 119.2 (-CH-), 126.2 (-CH-), 127.2 (-CH-), 129.1 (-CH-), 131.2 (-CH-), 134.7 (-C-), 139.0 (-C-), 142.8 (-CH-), 166.4 (-C-). MS (m/z): 403 (M⁺, 2), 330 (100), 117 (35), 73 (39). HRMS: calcd for C₂₂H₃₇NO₂Si₂ 403.2525, found 403.2513.

Preparation of ethyl-3-{2-[2,6-di(trimethylsilyl)hexahydro-1-pyridinylmethyl]-phenyl}-(E)-2-propenoate (22b). The N-benylation of **11b** (1.5 g, 6.55 mmol) with **21** (1.46 g, 5.45 mmol) afforded **22b** in 84 % yield as a thick yellow liquid. IR (neat): 2920, 1716, 1631, 1500, 1441, 1312, 1244 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 0.05 (s, 18H), 1.32 (t, *J* = 7.3 Hz, 3H), 1.47-1.77 (m, 6H), 2.22-2.40 (m, 2H), 3.63 (d, *J* = 13.7 Hz, 1H), 4.28 (q, *J* = 7.3 Hz, 2H), 4.34 (d, *J* = 13.7 Hz, 1H), 6.34 (d, *J* = 15.6 Hz, 1H), 7.21-7.45 (m, 2H), 7.50-7.67 (m, 2H), 8.27 (d, *J* = 15.6 Hz, 1H). ¹³C NMR (CDCl₃, 75.3 MHz): δ -1.2 (CH₃), 14.2 (-CH₃), 19.7 (-CH₂-), 24.8 (-CH₂-), 50.9 (-CH-), 51.6 (-CH₂-), 60.1 (-CH₂-), 119.5 (-CH-), 126.1 (-CH-), 126.9 (-CH-), 129.4 (-CH-), 130.4 (-CH-), 134.1 (-C-), 139.6 (-CH-), 142.4 (-C-), 166.6 (-C-). MS (m/z): 417 (M⁺, 2), 345 (100), 131 (16), 117 (43), 73 (81). HRMS: calcd for C₂₃H₃₉NO₂Si₂ 417.2284, found 417.2298.

Synthesis of ethyl-8-azatetracyclo[8.4.0.0^{2,7}.0^{4,8}]tetradeca-1(10),11,13-triene-3-carboxylate (23a). Viscous yellow liquid. Yield 73 %. IR (neat): 2975, 1729, 1455, 1177 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ 1.27 (t, *J* = 7.3 Hz, 3H), 1.28-1.43 (m, 1H), 1.55-1.97 (m, 3H), 2.77 (d, *J* = 6.3 Hz, 1H, H_{3exo}), 3.18 (d, *J* = 5.4 Hz, 1H, H₇), 3.36 (d, *J* = 1.8 Hz, 1H, H_{2endo}), 3.74 (t, *J* = 4.9 Hz, 1H, H₄), 4.04 (d, *J* = 18.5 Hz, 1H, H_{9endo}), 4.14 (q, *J* = 7.3 Hz, 2H), 4.42 (d, *J* = 18.5 Hz, 1H, H_{9exo}), 6.95-7.20 (m, 4H). ¹³C NMR (CDCl₃, 75.3 MHz): δ 13.9 (-CH₃), 25.4 (-CH₂-), 25.7 (-CH₂-), 45.3 (-CH-), 50.7 (-CH₂-), 56.3 (-CH-), 60.1 (-CH₂-), 62.3 (-CH-), 66.8 (-CH-), 124.6 (-CH-), 125.2 (-CH-), 125.6 (-CH-), 126.0 (CH-), 132.9 (-C-), 144.0 (-C-), 172.0 (-C-). MS (m/z): 257 (M⁺, 42), 184 (100), 169 (47), 115 (77), 91 (40), 68 (76). HRMS: Calcd for C₁₆H₁₉NO₂ 257.1415, found 257.1426.

Synthesis of ethyl-9-azatetracyclo[8.5.0.0^{2,7}.0^{9,14}]pentadeca-2(7),3,5-triene-15-carboxylate (23b). Viscous yellow liquid. Yield 75 %. IR (neat): 2937, 1730, 1581, 1457, 1190 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 1.27 (t, *J* = 7.3 Hz, 3H), 1.37-1.67 (m, 2H), 1.72-2.00 (m, 4H), 3.03 (dd, *J* = 7.8, 2.0 Hz, 1H, H_{15exo}), 3.16 (bs, 1H, H₁₀), 3.59 (d, *J* = 2.0 Hz, 1H, H_{1endo}), 3.68 (t, *J* = 3.9 Hz, 1H, H₁₄), 3.77 (d, *J* = 18.0 Hz, 1H, H_{8endo}), 4.05-4.31 (m, 2H), 4.55 (d, *J* = 18.0 Hz, 1H, H_{8exo}), 6.82-7.20 (m, 4H). ¹³C NMR (CDCl₃, 75.3 MHz): δ 14.0 (-CH₃), 15.8 (-CH₂-), 29.2 (-

CH₂-), 43.8 (-CH-), 58.4 (-CH-), 58.7 (-CH₂-), 60.2 (-CH₂-), 65.3 (-CH-), 67.7 (-CH-), 123.8 (-CH-), 125.2 (-CH-), 125.9 (-CH-), 126.2 (CH-), 132.8 (-C-), 147.9 (-C-), 172.1 (-C-). MS (m/z): 271 (M⁺, 62), 198 (100), 184 (37), 156 (24), 117 (45), 82 (22). HRMS: Calcd for C₁₇H₂₁NO₂ 271.1572 found 271.1567.

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† For part 10 in this series, see the ref. 29.

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