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

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Dedicated to Prof. T. R. Govindachari on the occasion of his 85\textsuperscript{th} birthday
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Abstract
Various new structural entities related to $X$-azatricyclo[m.n.0.0\textsuperscript{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-$\alpha,\alpha'$-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.\textsuperscript{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.\textsuperscript{2,3} Taking the advantage of the regio- and stereoselectivity of such cycloadditions, compounds possessing complex molecular framework such as eserethole,\textsuperscript{4} erythramine,\textsuperscript{5} $\alpha$-lycorane,\textsuperscript{6} allokainic acid,\textsuperscript{7} acromelic acid,\textsuperscript{8} (-)-kainic acid,\textsuperscript{9} sceletium alkaloid A4,\textsuperscript{10} menzamine alkaloids,\textsuperscript{11} martinelline alkaloids\textsuperscript{12} and various other bicyclic\textsuperscript{13-16} and polycyclic\textsuperscript{17-19} fused pyrrolidine ring systems such as 2-azatricyclo[5.2.1.0\textsuperscript{4,10}]decanes,\textsuperscript{20} and 2,5-diazatricyclo[5.2.1.0\textsuperscript{4,10}]decane\textsuperscript{20} 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.0.0a,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.0.0a,b]alkanes skeleton 7 through the strategy as shown in Scheme 2.
Results and Discussions

As per the synthetic strategy as depicted in Scheme 2, we initially envisaged possible construction of ethyl-2-azatricyclo[4.4.0.0²,8]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-1H-1-pyrrolyl]-(E)-2-hexenoate (14a). To obtain 14a, we initially tried the reductive amination of 2,5-di(trimethylsilyl)pyrrolidine (11a) 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) 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) with 6-oxo-(E)-2-hexenoate (12a) (73 % yield) and 7-oxo-(E)-2-heptenoate (12b) (75 % yield) as a viscous yellow liquids, respectively.

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

Scheme 3

Although synthesis of ethyl-6-hydroxy-(E)-2-hexenoate 20 was reported in literature starting from γ-butyrolactone, we synthesized it from commercially available 1,4-butanediol 16 as shown in Scheme 4. Compound 12a was prepared in 93 % yield by the Swern oxidation of 20 whereas 13a was synthesized in 91 % yield from 20 by stirring with triphenylphosphine, iodine and imidazole 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. 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 χ-azatricyclo[m.n.0.0ab]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 δ 2.95 (d, J = 5.7 Hz), H₇endo at δ 1.51-1.64 (m) and H₅exo at δ 1.65-1.78 (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 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 \textit{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 \textit{endo}-oriented.

Considering the reported\textsuperscript{27} 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 \textsuperscript{21}\textsuperscript{38} by refluxing in acetonitrile in the presence of K\textsubscript{2}CO\textsubscript{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.

\textbf{Scheme 6}

In summary, we have successfully demonstrated the synthesis of a number of polycyclic X-azatricyclo[[m.n.0.0\textsuperscript{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.

\textbf{Experimental Section}

\textbf{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\textsubscript{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 (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 / 1mm) 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): 2935, 1711, 1364 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). 13C NMR (CDCl3, 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 CH2Cl2, charged into 100 mL two neck argon-flushed flask, was cooled to −78 °C. DMSO (3.34 g, 42.75 mmol) in 10 mL CH2Cl2, followed by 20 (2.7 g, 17.1 mmol) in 10 mL CH2Cl2 was introduced dropwise into the flask over 5 min. The mixture was allowed to stir for 1.5 h at −78 °C and then Et3N (6.92 g, 68.51 mmol) in 10 mL CH2Cl2 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 CH2Cl2 (2 × 20 mL), the combined extracts were washed with water (4 × 20 mL), brine, dried over Na2SO4, 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 (CDCl3, 200 MHz): δ 1.27 (t, J = 7.1 Hz, 3H), 2.45-2.75 (m, 4H), 4.15 (q, J = 7.3 Hz, 3H), 5.85 (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). 13C NMR (CDCl3, 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): 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 CH2Cl2 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 CH2Cl2 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 CH2Cl2, washed with 20 % sodium thiosulphate solution, water, brine, and dried over Na2SO4. 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 (CDCl3, 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). 13C NMR (CDCl3, 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 K2CO3 (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 Na2SO4. 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\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 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). \(^1\)C NMR (CDCl\(_3\), 50.3 MHz): \(\delta\) -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\(_2\)), 59.5 (-CH\(_2\)), 121.1 (CH\(_2\)), 148.7 (-CH\(_2\)), 165.9 (-C). MS (m/ z): 355(M\(^+\), 1), 340 (9), 282 (100), 73 (53).

**Preparation of ethyl-7-[2,5-di(trimethylsilyl)tetrahydro-1\(\H\)-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\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 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). \(^1\)C NMR (CDCl\(_3\), 50.3 MHz): \(\delta\) -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\(_2\)), 59.4 (-CH\(_2\)), 121.2 (-CH\(_2\)), 148.3 (-CH\(_2\)), 165.8 (C\(_2\)). 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\(_3\)CN (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\(_4\)OH solution. The reaction mixture was diluted with water (10 mL), extracted with chloroform (3 × 25 mL), washed with brine and dried over Na\(_2\)SO\(_4\). 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\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 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). \(^1\)C NMR (CDCl\(_3\), 50.3 MHz): \(\delta\) -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\(_2\)), 59.8 (-CH\(_2\)), 121.3 (CH\(_3\)), 149.1 (-CH\(_2\)), 166.4 (-C\(_2\)). MS (m/ z): 369 (M\(^+\),1), 354 (6), 296 (100), 73 (53).

**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\(_3\)CN (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\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 200 MHz): \(\delta\) 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). \(^1\)C NMR (CDCl\(_3\), 50.3 MHz): \(\delta\) -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\(_2\)), 59.8 (-CH\(_2\)), 121.3 (CH\(_2\)), 149.1 (-CH\(_2\)), 166.4 (-C\(_2\)). 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[4.4.0.0²,8]decane-7-carboxylate 15a.

**Ethyl-2-azatricyclo[4.4.0.0²,8]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, H₁₀endo), 1.27 (t, J = 7.3 Hz, 3H), 1.31-1.43 (m, 2H, H₄endo, H₉endo), 1.51-1.64 (m, 3H, H₅endo, H₉exo, H₁₀exo), 1.65-1.78 (m, 2H, H₄exo, H₅exo), 2.53 (m, 1H, H₆endo), 2.95 (d, J = 5.7 Hz, 1H, H₇exo), 3.05-3.17 (m, 3H, H₃exo, H₃endo, 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[5.4.0.0²,9]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, H₇endo), 2.62-2.68 (m, 1H, H₃endo), 2.88 (t, J = 5.1 Hz, 1H, H₁), 3.23-3.37 (m, 1H, H₃exo), 3.40 (d, J = 3.6 Hz, 1H, H₁), 3.55 (d, J = 4.3 Hz, 1H, H₁), 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[5.4.0.0³,8]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), 2.62-2.68 (m, 1H, H₃exo), 2.88 (t, J = 5.1 Hz, 1H, H₁), 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), 25.5 (-CH₂), 27.5 (-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-). 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[5.5.0.0²,9]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, H₇endo), 2.81-2.94 (m, 1H, H₇endo), 3.01 (t, J = 7.2 Hz, 1H, H₇exo), 3.06-3.16 (m, 1H, H₈exo), 3.22 (bs, 1H, H₁), 3.32-3.45 (m, 1H, H₁), 4.04-4.31 (m, 2H). ¹³C NMR (CDCl₃, 75.3 MHz): δ 14.1 (CH₃), 16.8 (-CH₂), 18.5 (-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.
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-benzylation 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 = 7.3Hz, 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-), 131.3 (-C-), 134.7 (-C-), 142.4 (-CH-), 166.6 (-C-). MS (m/z): 417 (M+, 2), 330 (100), 117 (35), 73 (39). HRMS: calcd for C23H39NO2Si2 417.2284, found 417.2298.

Synthesis of ethyl-8-azatetracyclo[8.4.0.0 2,7.04,8]tetradeca-1(10),11,13-trine-3-carboxylate (23a). Viscous yellow liquid. Yield 73 %. IR (neat): 2975, 1716, 1500, 1441, 1312, 1244 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, H3exo), 3.18 (d, J = 5.4 Hz, 1H, H7), 3.36 (d, J = 1.8 Hz, 1H, Hendo), 3.74 (t, J = 4.9 Hz, 1H, H4), 4.04 (d, J = 18.5 Hz, 1H, Hendo), 4.14 (q, J = 7.3 Hz, 2H), 4.42 (d, J = 18.5 Hz, 1H, H9exo), 6.95- 7.20 (m, 4H). 13C NMR (CDCl 3, 75.3 MHz): δ13.9 (-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 2,7.09,14]pentadeca-2(7),3,5-triene-15-carboxylate (23b). Viscous yellow liquid. Yield 75 %. IR (neat): 2975, 1730, 1581, 1457, 1190 cm−1 . 1H NMR (CDCl3, 300 MHz): δ1.27 (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, H15exo), 3.16 (bs, 1H, H10), 3.59 (d, J = 2.0 Hz, 1H, Hendo), 3.68 (t, J = 3.9 Hz, 1H, H14), 3.77 (d, J = 18.0 Hz, 1H, Hendo), 4.05-4.31 (m, 2H), 4.55 (d, J = 18.0 Hz, 1H, H8exo), 6.82-7.20 (m, 4H). 13C NMR (CDCl3, 75.3 MHz): δ14.0 (-CH3), 15.8 (-CH2–), 29.2 (-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.
CH$_2$-), 43.8 (-CH-), 58.4 (-CH-), 58.7 (-CH$_2$-), 60.2 (-CH$_2$-), 65.3 (-CH-), 67.7 (-CH-), 123.8 (-CH-), 125.2 (-CH-), 125.9 (-CH-), 126.2 (-C-), 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 C$_{17}$H$_{21}$NO$_2$ 271.1572 found 271.1567.

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References

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