Preliminary Communication

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Synthesis of tricyclic indolizidines from ethyl isocyanoacetate

Abstract: Tricyclic indolizidines were synthesized in good yields from commercially available ethyl isocyanoacetate by a novel sequential alkylation, thiol-mediated radical cyclization, *N*-alkylation, and microwave-assisted Pauson-Khand reaction.

Keywords: indolizidine; isocyanide; isocyanoacetate; Pauson-Khand reaction; radical cyclization.

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In this communication, we present a novel strategy for the synthesis of tricyclic indolizidines starting from a simple isocyanoacetate and using a radical cyclization/*N*-alkylation/Pauson-Khand [1–6] cycloaddition strategy. Recently, the synthesis of functionalized indolizidines *via* Pauson-Khand reaction using a stoichiometric amount of $Co_2(CO)_8$, in the presence of various promoters (CO, DMSO, NMO, and TMANO) has been reported [7–9]. Isocyanoacetates [10] have been widely used in many different areas of chemistry as efficient building blocks in the total synthesis of natural products and biologically active molecules. It was envisaged that ethyl isocyanoacetate could be used as the starting building block to access tricyclic indolizidines, useful substrates for the synthesis of indolizidine alkaloids such as asperparaline, and its derivatives (Figure 1), which exhibit potent paralytic, fungicidal, insecticidal, and antifeedant activity [11–13].

Ethyl isocyanoacetate was first alkylated with excess allyl bromide to give isocyanide **1** in 83% yield [14]. Subsequent microwave-assisted thiol-mediated radical cyclization using 2-mercaptoethanol [15] gave pyroglutamates **2** and **3** in 88% yield (Scheme 1) as a 1:1 inseparable mixture of *cis*/*trans* diastereomers. The diastereomeric ratio was determined by ^{1}H NMR.

The next step in our strategy was the *N*-alkylation of these substrates with a variety of propargyl bromides that would give access to substrates that could then be subjected to the Pauson-Khand cyclization reaction. Although NaH and NaOH, under phase transfer conditions, are the bases employed for *N*-alkylation of either proline or pyroglutamates in the literature [16], better yields were obtained using *tert*-butyliminotri(pyrrolidino)phosphorane (BTPP). Alkylation of pyroglutamates **2, 3** was then performed using BTPP and three different propargyl bromides (RX) in refluxing acetonitrile (Scheme 2). Compounds **4, 5** and **8, 9** were obtained as inseparable mixtures of diastereomers in 72% yield (1.4:1 *cis*/*trans* ratio by ^{1}H NMR) and 99% yield (1.7:1 *cis*/*trans* ratio by ^{1}H NMR), respectively. Pyroglutamates **6** and **7**, with a terminal Trimrthylsilyl (TMS) group, were obtained in 30% yield only as an inseparable mixture of diastereomers (1.9:1 *cis*/*trans* ratio by ^{1}H NMR), due to loss of the TMS group and consequent formation of **8** and **9** (isolated in 31% yield) as a by-product. With these substrates in hand, it was possible to perform the final step in our synthetic strategy, the Pauson-Khand cycloaddition. Substrates **4–9** were first allowed to react with $Co_2(CO)_8$, under standard Pauson-Khand reaction conditions (Table 1). Reaction of substrates **8, 9** with an equimolar amount of $Co_2(CO)_8$ at room temperature, using NMO as promoter,

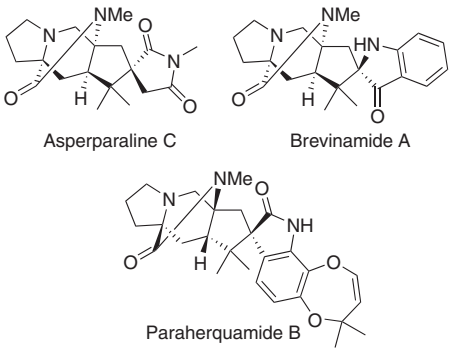

Figure 1 Asperparaline and its derivatives.

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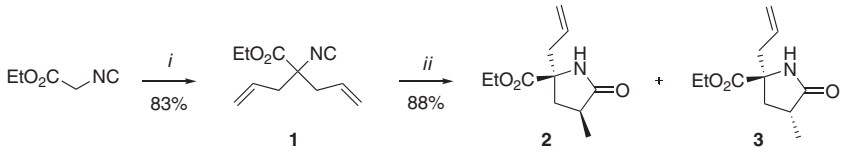
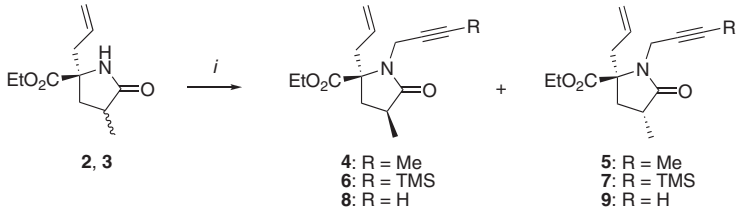
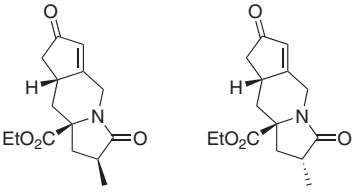
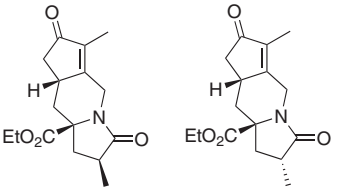
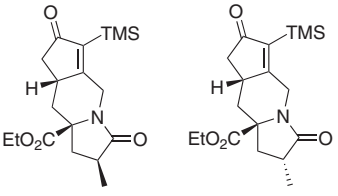


Scheme 1 Synthesis of pyroglutamates.
Reagents and conditions: (i) allyl bromide (2.5 equiv), K_2CO_3, TBAB, CH_3CN, reflux 20 h; (ii) 2-mercaptoethanol (3.0 equiv), AIBN (0.2 equiv) in toluene, MW 130°C 2×5 min.



Scheme 2 Synthesis of alkylated pyroglutamates 4–9.
Reagents and conditions: (i) RX (1.5 eq), BTPP (1.5 eq), 12 h at reflux in CH_3CN.

Table 1 Synthesis of tricyclic indolizidines.

Substrate	Conditions	Product	Yield
8, 9	$Co_2(CO)_8$ (1.0 eq), NMO (3.0 eq), 2d rt; $Co_2(CO)_8$ (1.0 eq), μω 10 min at 100°C	 **10 (42%)** **11 (23%)**	Trace, 65%
4, 5	$Co_2(CO)_8$ (1.0 eq), μω 10 min at 100°C	 **12** **13** (1.2 : 1 ratio by ^{1}H NMR)	56%
6, 7	$Co_2(CO)_8$ (1.0 eq), μω 10 min at 100°C	 **14** **15** (2.1 : 1 ratio by ^{1}H NMR)	87%

gave only traces of the tricyclic indolizidines **10** and **11**, even after a few days. Use of different promoters and even increasing the reaction temperature did not improve the reaction yield. It was then decided to perform the reaction under microwave irradiation [17]. We were delighted to obtain the desired compounds **10** (42%) and **11** (23%) in an overall yield of 65%, in 10 min only and in the absence of promoters. Microwave irradiation was then used to test other substrates. Compounds **12–15** bearing a functionalized terminal alkyne were cyclized in good to excellent

yields under microwave irradiation. These indolizidines **12, 13** and **14, 15** were obtained as inseparable mixtures of two diastereoisomers, 1.2:1 and 2.1:1 *cis*/*trans* ratio by ^{1}H NMR, respectively (Table 1).

In conclusion, tricyclic indolizidines **10–15** were successfully synthesized from a simple and commercially available isocyanide *via* sequential alkylation/radical cyclization/*N*-alkylation/microwave-assisted Pauson-Khand cyclization in good yields. The synthesized substrates could be used to access asperparaline and its derivatives.

Experimental details

Flash column chromatography was performed using Sorbsil C60, 40–60-mesh silica gel. Dichloromethane and toluene were distilled from calcium hydride and diethyl ether from sodium wire. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were obtained in $CDCl_3$ on a Brucker AVANCE III spectrometer. IR spectra were recorded on a Nicolet Impact 400 using a neat film on a Bio-Rad Golden Gate ATR FT-IR and a FTIR Perkin-Elmer 2000 spectrometers coupled with an AutoIMAGE FTIR microscope. Mass spectrometry data were obtained on a ThermoQuest TraceMS gas chromatograph-mass spectrometer configured for open access and on an LC-MS. Microwave reactions were performed on a CEM Microwave Synthesizer.

2-Allyl-1-(but-2-yn-1-yl)-*cis*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (4) and 2-allyl-1-(but-2-yn-1-yl)-*trans*-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (5) A homogeneous mixture of pyroglutamates **2, 3** (554 mg, 2.63 mmol, 1.0 eq), 1-bromobut-2-yne (348 µL, 3.93 mmol, 1.5 eq), BTPP (1.24 mL, 3.93 mmol, 1.5 eq) in dry acetonitrile (30 mL) was heated under reflux with stirring for 12 h. The mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate, 3:1) gave the title compounds **4** and **5** as a yellowish oil (494 mg, 72% yield); inseparable mixture of diastereoisomers (1.4:1); R_f = 0.43. Compound **4**: ^{1}H NMR: δ 1.17 (3H, d, *J* = 7.5 Hz, C*H*$_3$CH), 1.25 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.64 (1H, dd, *J* = 13.0, 10.5 Hz, CH$_3$CHC*H*H), 1.73 (3H, t, *J* = 2.5 Hz, C*H*$_3$C≡C), 2.33 (1H, dd, *J* = 13.5, 9.0 Hz, CH$_3$CHCH*H*), 2.56–2.69 (1H, m, CH$_3$C*H*CHH), 2.67–2.83 (1H, m, CH$_2$=CHC*H*$_2$), 3.96 (1H, d, *J* = 18.0 Hz, NC*H*H), 4.09–4.21 (3H, m, CH$_2$O and NCH*H*), 5.15–5.22 (2H, m, CH$_2$CH=C*H*$_2$), 5.65–5.79 (1H, m, CH$_2$C*H*=CH$_2$); ^{13}C NMR ($CDCl_3$): δ 3.8, 14.4, 16.4, 30.8, 35.2, 37.2, 38.9, 61.9, 66.4, 73.8, 79.8, 120.6, 132.1, 173.4, 178.0. Compound **5**: ^{1}H NMR: δ 1.18 (3H, d, *J* = 7.5 Hz, C*H*$_3$CH), 1.26 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.73 (3H, t, *J* = 2.5 Hz, C*H*$_3$C,1.4:1, C≡C), 1.84 (1H, dd, *J* = 13.0, 7.0 Hz, CH$_3$CHC*H*H), 2.32 (1H, dd, *J* = 13.5, 10.0 Hz, CH$_3$CHCH*H*), 2.45–2.54 (1H, m, CH$_3$C*H*CHH), 2.67–2.83 (1H, m, CH$_2$=CHC*H*$_2$), 3.95 (1H, d, *J* = 18.0 Hz, NC*H*H), 4.09–4.21 (3H, m, CH$_2$O and NCH*H*), 5.15–5.22 (2H, m, CH$_2$CH=C*H*$_2$), 5.65–5.79 (1H, m, CH$_2$C*H*=CH$_2$); ^{13}C NMR: δ 3.8, 14.4, 17.3, 31.3, 35.4, 36.6, 39.6, 62.0, 67.4, 74.1, 80.0, 120.6, 132.2, 173.6, 177.9; IR: ν_{max} 1736, 1711, 1368, 1305, 1251, 1204, 1140 cm^{-1}: GC/CI-MS: *m*/*z* 322 (92%), [M+H]$^+$; retention time 13.87 min. HRMS (ESI$^+$). Calcd for $C_{15}H_{21}NO_3Na$ [M+Na]$^+$: *m*/*z* 344.1652. Found: *m*/*z* 344.1654.

2-Allyl-*cis*-4-methyl-5-oxo-1-(3-trimethylsilanyl-prop-2-yn-1-yl)-pyrrolidine-2-carboxylic acid ethyl ester (6) and 2-allyl-*trans*-4-methyl-5-oxo-1-(3-trimethylsilanyl-prop-2-yn-1-yl)-pyrrolidine-2-carboxylic acid ethyl ester (7) A homogeneous mixture of pyroglutamates **2**, **3** (560 mg, 2.65 mmol, 1.0 eq), (3-bromoprop-1-ynyl)trimethylsilane (636 µL, 3.98 mmol, 1.5 eq), BTPP (1.25 mL, 3.98 mmol, 1.5 eq) in dry acetonitrile (30 mL) was heated under reflux with stirring for 12 h. The mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate, 3:1) gave the title compounds **6** and **7** as a yellowish oil (249 mg, 30% yield); inseparable mixture of diastereoisomers (1.9:1); R_f = 0.5. Compound **6**: ^{1}H NMR: δ 0.09 (9H, s, (CH$_3$)$_3$Si), 1.16 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.23 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.64 (1H, dd, *J* = 13.0, 10.5 Hz, CH$_3$CHC*H*H), 2.33 (1H, dd, *J* = 13.0, 8.5 Hz, CH$_3$CHCH*H*), 2.46–2.57 (1H, m, CH$_3$C*H*CHH), 2.61–2.90 (1H, m, CH$_2$=CHC*H*$_2$), 3.93 (1H, d, *J* = 18.0 Hz, NC*H*H), 4.12 (2H, q, *J* = 7.0 Hz, CH$_2$O), 4.36 (1H, d, *J* = 18.0 Hz, NCH*H*), 5.12–5.22 (2H, m, CH$_2$CH=C*H*$_2$), 5.67–5.82 (1H, m, CH$_2$C*H*=CH$_2$); ^{13}C NMR: δ 0.0, 14.3, 16.3, 31.4, 35.1, 37.1, 38.8, 61.7, 66.6, 88.7, 100.4, 120.4, 132.2, 173.1, 177.8; GC/CI-MS: *m*/*z* 264 (30%), [M+H]$^+$, 190 (100%), [M-TMS]$^+$; retention time 13.49 min. Compound **7**: ^{1}H NMR: δ 0.08 (9H, s, (CH$_3$)$_3$Si), 1.15 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.25 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.79 (1H, dd, *J* = 13.5, 7.5 Hz, CH$_3$CHC*H*H), 2.33 (1H, dd, *J* = 13.0, 8.5 Hz, CH$_3$CHCH*H*), 2.46–2.57 (1H, m, CH$_3$C*H*-CHH), 2.61–2.90 (1H, m, CH$_2$=CHC*H*$_2$), 3.92 (1H, d, *J* = 18.0 Hz, NC*H*H), 4.16 (2H, q, *J* = 7.0 Hz, CH$_2$O), 4.35 (1H, d, *J* = 18.0 Hz, NCH*H*), 5.12–5.22 (2H, m, CH$_2$CH=C*H*$_2$), 5.67–5.82 (1H, m, CH$_2$C*H*=CH$_2$); ^{13}C NMR: δ 0.0, 14.4, 17.2, 31.7, 35.0, 36.8, 39.6, 61.9, 67.4, 88.9, 100.7, 120.4, 132.3, 173.4, 177.6; IR: ν_{max} 1733, 1697, 1456, 1394, 1304, 1256, 1199 cm^{-1}; GC/MS: *m*/*z* 264 (30%), [M+H]$^+$, 190 (100%), [M-TMS]$^+$; retention time 13.53 min. HRMS (ES$^+$). Calcd for $C_{17}H_{28}NO_3Si$, [M+H]$^+$: *m*/*z* 264.1594. Found: *m*/*z* 264.1597.

2-Allyl-*cis*-4-methyl-5-oxo-1-prop-2-yn-1-yl-pyrrolidine-2-carboxylic acid ethyl ester (8) and 2-allyl-*trans*-4-methyl-5-oxo-1-prop-2-yn-1-yl-pyrrolidine-2-carboxylic acid ethyl ester (9) A homogeneous mixture of pyroglutamates **2**/**3** (208 mg, 0.99 mmol, 1.0 eq), 3-Bromopropyne (165 µL, 1.48 mmol, 1.5 eq), BEMP (436 µL, 1.48 mmol, 1.5 eq) in dry acetonitrile (10 mL) was heated under reflux with stirring for 12 h. The reaction mixture was then cooled, and the solvent removed *in vacuo*. Purification by flash chromatography eluting with hexane/ethyl acetate (4:1) gave the title compounds **8** and **9** as a yellowish oil (200 mg, 82% yield); 1.7:1 inseparable mixture of diastereoisomes (1.7:1); R_f = 0.35. Compound **8**: ^{1}H NMR: δ 1.19 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.26 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.66 (1H, dd, *J* = 13.0, 10.5 Hz, CH$_3$CHC*H*H), 2.15 (1H, t, *J* = 2.5 Hz, C*H*≡CCH$_2$N), 2.41 (1H, dd, *J* = 12.5, 8.5 Hz, CH$_3$CHCH*H*), 2.48–2.62 (1H, m, CH$_3$C*H*CHH), 2.65–2.82 (1H, m, CH$_2$=CHC*H*$_2$), 3.99–4.28 (2H, m, NCH$_2$), 4.10–4.16 (2H, m, CH$_2$O), 5.21 (2H, m, CH$_2$CH=C*H*$_2$), 5.74 (1H, m, CH$_2$C*H*=CH$_2$); ^{13}C NMR: δ 14.4, 16.3, 30.5, 35.2, 37.4, 39.3, 62.0, 66.6, 72.0, 78.8, 120.8, 131.8, 173.1, 178.0; GC/CI-MS: *m*/*z* 250 (100%), [M+H]$^+$; retention time 11.79 min. Compound **9**: ^{1}H NMR: δ 1.25 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.29 (3H, t, *J* = 7.0 Hz, C*H*$_3$CH$_2$O), 1.89 (1H, dd, *J* = 13.0, 7.0 Hz, CH$_3$CHC*H*H), 2.16 (1H, t, *J* = 2.5 Hz, C*H*≡CCH$_2$N), 2.34 (1H, dd, *J* = 13.5, 10.0 Hz, CH$_3$CHCH*H*), 2.48–2.62 (1H, m, CH$_3$C*H*CHH), 2.65–2.82 (1H, m, CH$_2$=CHC*H*$_2$), 3.99–4.28 (2H, m, NCH$_2$), 4.10–4.16 (2H, m, CH$_2$O), 5.21 (2H, m, CH$_2$CH=C*H*$_2$), 5.74 (1H, m, CH$_2$C*H*=CH$_2$); ^{13}C NMR: δ 14.4, 17.2, 30.9, 35.1, 36.7, 39.7, 62.1, 67.4, 71.8, 79.1, 120.8, 132.0, 173.4, 177.8; IR: ν_{max} 1728, 1693, 1455, 1390, 1302, 1212, 1154 cm^{-1}; GC/CI-MS: *m*/*z* 250 (1000%), [M+H]$^+$; retention time 11.94 min. HRMS (ESI$^+$). Calcd for $C_{14}H_{19}NO_3Na$ [M+Na]$^+$: *m*/*z* 272.1257. Found: *m*/*z* 272.1258.

***cis*-2-Methyl-3,6-dioxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-*s*-indacene-8a-carboxylic acid ethyl ester (10) and *trans*-2-methyl-3,6-dioxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-*s*-indacene-8a-carboxylic acid ethyl ester (11)** To a heavy-walled Pyrex tube were added pyroglutamates **8, 9** (113 mg, 0.45 mmol, 1.0 eq) and dicobaltoctacarbonyl (155 mg, 0.45 mmol, 1.0 eq) in 3 mL of dry toluene. The Pyrex tube was then capped, and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (100°C) for 10 min. The tube was then allowed to cool for a couple of minutes, and mixture was then filtered on celite, and the solvent removed under reduced pressure. Purification by flash chromatography eluting with ethyl acetate afforded the title compounds **10** (52 mg, 42%, R_f = 0.64) and **11** (29 mg, 23%, R_f = 0.58) as colorless liquids. Compound **10**: ^{1}H NMR: δ 1.17 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.23–1.30 (1H, m, C*H*HCO), 1.28 (3H, t, *J* = 7.0 Hz, CH$_3$CH$_2$O), 1.56 (1H, dd, *J* = 12.5, 10.0 Hz, CH$_3$CHC*H*H), 2.00 (1H, dd, *J* = 18.5, 2.5 Hz, C*H*HCHCH$_2$), 2.50–2.56 (1H, m, CH$_3$C*H*), 2.61 (1H, dd, *J* = 12.5, 8.5 Hz, CH$_3$CHCH*H*), 2.62 (1H, dd, *J* = 18.5, 6.5 Hz, CH*H*CHCH$_2$), 2.78–2.84 (1H, m, CH$_2$C*H*CH$_2$), 2.86 (1H, dd, *J* = 12.5, 5.0 Hz, CH*H*CO), 3.80 (1H, d, *J* = 16 Hz, NC*H*H), 4.24 (2H, q, *J* = 7.0 Hz, CH$_2$O), 4.97 (1H, d, *J* = 16 Hz, NCH*H*), 6.01 (1H, s, C=CH); ^{13}C NMR: δ 14.6, 16.1, 35.8, 37.7, 40.9, 41.4, 41.5, 42.0, 62.6, 64.9, 129.3, 172.3, 172.9, 176.5, 207.1; IR: ν_{max} 1707, 1455, 1384, 1302, 1274, 1195, 1021 cm^{-1}; GC/CI-MS: *m*/*z* 278 (60%), [M+H]$^+$. HRMS (EI). Calcd for $C_{15}H_{19}NO_4$ (M)$^+$: *m*/*z* 277.13141. Found: *m*/*z* 277.13061. Compound **11**: ^{1}H NMR: δ 1.21 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.31–1.37 (1H, m, C*H*HCO), 1.32 (3H, t, *J* = 7.0 Hz, CH$_3$CH$_2$O), 1.97–2.02 (2H, m, CH$_3$CHC*H*H and C*H*HCHCH$_2$), 2.26 (1H, dd, *J* = 13.5, 9.5 Hz, CH$_3$CHCH*H*), 2.52–2.58 (1H, m, CH$_3$C*H*), 2.63 (1H, dd, *J* = 18.5, 6.5 Hz, CH*H*CHCH$_2$), 2.78 (1H, dd, *J* = 12.5, 5.0 Hz, CH*H*CO), 2.79–2.87 (1H, m, CH$_2$C*H*CH$_2$), 3.92 (1H, d, *J* = 16.0 Hz, NC*H*H), 4.28 (2H, q, *J* = 7.0 Hz, CH$_2$O), 5.05 (1H, d, *J* = 16.0 Hz, NCH*H*), 6.01 (1H, s, C=CH); ^{13}C NMR: δ 14.6, 17.5, 35.9, 37.8, 38.7, 41.4, 41.6, 41.9, 62.5, 65.3, 129.2, 172.3, 173.5, 176.7, 206.9; IR: ν_{max} 1705, 1455, 1388, 1278, 1195, 1022 cm^{-1}; GC/CI-MS: *m*/*z* 278 (45%), [M+H]$^+$.

***cis*-2,5-Dimethyl-3,6-dioxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-*s*-indacene-8a-carboxylic acid ethyl ester (12) and *trans*-2, 5-dimethyl-3,6-dioxo-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-*s*-indacene-8a-carboxylic acid ethyl ester (13)** To a heavy-walled Pyrex tube were added pyroglutamates **4, 5** (98 mg, 0.37 mmol, 1.0 eq) and dicobaltoctacarbonyl (127 mg, 0.37 mmol, 1.0 eq) in 2.5 mL of dry toluene. The tube was then capped, and the mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (100°C) for 10 min. The tube was then allowed to cool for a couple of minutes; the mixture was then filtered on celite, and the solvent removed under reduced pressure. Purification by flash chromatography eluting with ethyl acetate afforded the title compounds **12** and **13** (61 mg, 56%, R_f = 0.67) as colorless liquid (1.2:1 diastereomeric ratio by NMR). Compound **12**: ^{1}H NMR: δ 1.19 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.24–1.27 (1H, m, C*H*HCO), 1.32 (3H, t, *J* = 7.0 Hz, CH$_3$CH$_2$O), 1.56 (1H, dd, *J* = 12.0, 10.5 Hz, CH$_3$CHC*H*H), 1.74 (3H,s, C=CCH$_3$), 1.93–2.03 (1H, m, C*H*HCHCH$_2$), 2.51–2.57 (1H, m, CH$_3$C*H*), 2.61 (1H, dd, *J* = 12.5, 8.5 Hz, CH$_3$CHCH*H*), 2.61–2.67 (1H, m, CH*H*CHCH$_2$), 2.66–2.73 (1H, m, CH$_2$C*H*CH$_2$), 2.85 (1H, dd, *J* = 12.5, 4.5 Hz, CH*H*CO), 3.74 (1H, d, *J* = 16.0 Hz, NC*H*H), 4.27 (2H, q, *J* = 7.0 Hz, CH$_2$O), 5.00 (1H, d, *J* = 16.0 Hz, NCH*H*); ^{13}C NMR: δ 8.3, 14.7, 16.1, 35.8, 36.1, 38.9, 39.9, 40.7, 42.0, 62.5, 65.2, 136.1, 163.7, 173.1, 176.6, 207.5; GC/CI-MS: *m*/*z* 292 (100%), [M+H]$^+$. Compound **13**: ^{1}H NMR: δ 1.21 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.24–1.27 (1H, m, C*H*HCO), 1.31 (3H, t, *J* = 7.0 Hz, CH$_3$CH$_2$O), 1.73 (3H,s, C=CCH$_3$), 1.93–2.03 (2H, m, CH$_3$CHC*H*H and C*H*HCHCH$_2$), 2.24 (1H, dd, *J* = 13.5, 9.5 Hz, CH$_3$CHCH*H*), 2.51–2.57 (1H, m, CH$_3$C*H*), 2.61–2.73 (2H, m, CH*H*CHCH$_2$ and CH$_2$C*H*CH$_2$), 2.75 (1H, dd, *J* = 12.5, 5.0 Hz, CH*H*CO), 3.84 (1H, d, *J* = 16.0 Hz, NC*H*H), 4.26 (2H, q, *J* = 7.0 Hz, CH$_2$O), 5.06 (1H, d, *J* = 16.0 Hz, NCH*H*); ^{13}C NMR: δ 8.3, 14.6, 17.5, 35.9, 36.0, 38.9, 39.8, 41.0, 41.9, 62.5, 65.6, 136.1, 163.8, 173.7, 176.8, 207.3; IR: ν_{max} 1705, 1456, 1395, 1301, 1199, 1022 cm^{-1}; GC/CI-MS: *m*/*z* 292 (100%), [M+H]$^+$. HRMS (EI). Calcd for $C_{16}H_{20}NO_4$ (M-H)$^-$: *m*/*z* 290.13923. Found: *m*/*z* 290.13892; IR.

***cis*-2-Methyl-3,6-dioxo-5-trimethylsilanyl-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-*s*-indacene-8a-carboxylic acid ethyl ester (14) and *trans*-2-methyl-3,6-dioxo-5-trimethylsilanyl-2,3,6,7,7a,8-hexahydro-1*H*,4*H*-3a-aza-*s*-indacene-8a-carboxylic acid ethyl ester (15)** To a heavy-walled Pyrex tube were added pyroglutamates **6, 7** (68 mg, 0.211 mmol, 1.0 eq) and dicobaltoctacarbonyl (72.5 mg, 0.21 mmol, 1.0 eq) in 2.5 mL of dry toluene. The tube was then capped, and the reaction mixture was flushed with nitrogen. Heating was then applied by means of microwave irradiation (100°C) for 10 min. The tube was then allowed to cool for a couple of minutes; the mixture was then filtered on celite, and the solvent removed under reduced pressure. Purification by flash chromatography eluting with ethyl acetate afforded the title compounds **14** and **15** (62 mg, 87%, R_f = 0.73) as colorless liquid (2.1:1 diastereomeric ratio by NMR). Compound **14**: ^{1}H NMR: δ 0.23 (9H, s, (CH$_3$)$_3$Si), 1.19 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.21–1.27 (1H, m, C*H*HCO), 1.29 (3H, t, *J* = 7.0 Hz), 1.56 (1H, t, *J* = 10.0 Hz, CH$_3$CHC*H*H), 1.89–2.01 (1H, m, C*H*H-CHCH$_2$), 2.50–2.62 (3H, m, CH$_3$C*H*CH*H* and CH*H*CHCH$_2$), 2.72–2.77 (1H, m, CH$_2$C*H*CH$_2$), 2.85 (1H, dd, *J* = 12.5, 4.5 Hz, CH*H*CO), 3.75 (1H, d, *J* = 16.0 Hz, NCH*H*), 4.25 (2H, q, *J* = 7.0 Hz, CH$_2$O), 5.17 (1H, d, *J* = 16.0 Hz, NC*H*H); ^{13}C NMR: δ 0.3, 14.4, 16.0, 31.9, 35.8, 38.6, 39.3, 40.8, 41.7, 41.9, 62.4, 64.7, 140.4, 173.0, 178.3, 211.2; GC/CI-MS: *m*/*z* 350 (66%), [M+H]$^+$. Compound **15**: ^{1}H NMR: δ 0.23 (9H, s, (CH$_3$)$_3$Si), 1.20 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH), 1.21–1.27 (1H, m, C*H*HCO), 1.30 (3H, t, *J* = 7.0 Hz), 1.89–2.01 (2H, m, CH$_3$CHC*H*H and C*H*HCHCH$_2$), 2.25 (1H, dd, *J* = 13.5, 10.0 Hz, CH$_3$CHCH*H*), 2.50–2.62 (2H, m, CH$_3$C*H*CH$_2$ and CH*H*CHCH$_2$), 2.72–2.77 (1H, m, CH$_2$C*H*CH$_2$), 2.85 (1H, dd, *J* = 12.5, 4.5 Hz, CH*H*CO), 3.84 (1H, d, *J* = 16.0 Hz, NCH*H*), 4.25 (2H, q, *J* = 7.0 Hz, CH$_2$O), 5.24 (1H, d, *J* = 16.0 Hz, NC*H*H); ^{13}C NMR: δ 0.3, 14.6, 17.4, 31.2, 35.8, 38.6, 39.4, 40.8, 41.8, 42.0, 62.4, 65.0, 140.3, 173.5, 178.4, 211.1; IR: ν_{max} 1731, 1690, 1603, 1454, 1402, 1247, 1193, 1023 cm^{-1}; GC/CI-MS: *m*/*z* 350 (50%), [M+H]$^+$. HRMS (ES$^+$). Calcd for $C_{18}H_{27}NO_4SiNa$ (M+Na)$^+$: *m*/*z* 372.1601. Found: *m*/*z* 372.1607.

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