Synthesis of dehydroindolizidine-type poison-frog alkaloids *via* Michael-type conjugate addition

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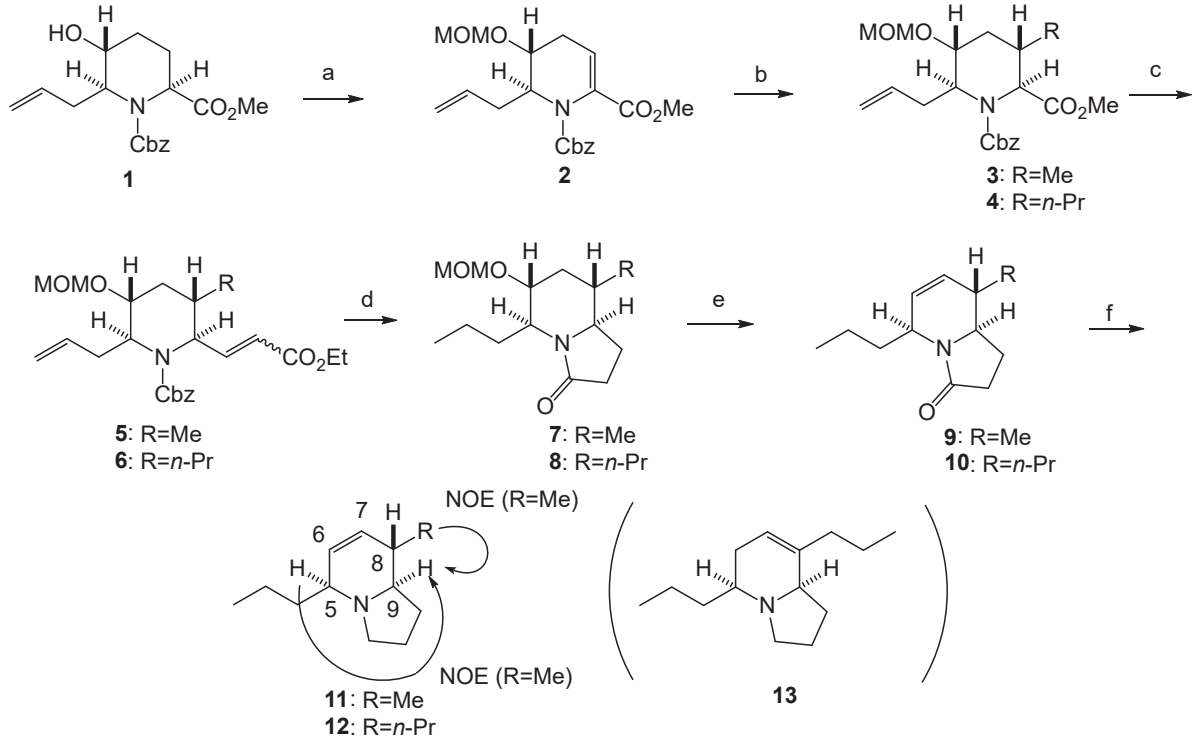
A concise stereoselective synthesis of proposed dehydroindolizidine-alkaloids of types **179** and **207E**[1] was accomplished *via* Michael-type conjugate addition. A comparison of natural **207E** and synthesised compound **207E** on GC–FTIR revealed the double bond of natural **207E** is most likely at the 7,8-position.

Keywords: dehydroindolizidine, Michael-type conjugate addition

GC–MS and GC–FTIR spectral data showed more than 800 alkaloids in the amphibian skin, among them, a subclass of dehydro-5,8-disubstituted indolizidine. Most alkaloids appeared as minor or trace alkaloids typical of dendrobatid, mantellid and bufonid anurans. Dietary source was unknown, but ants were the likely food source.[1,2] Several methods for the synthesis of dehydroindolizidine alkaloids have been established.[3–5] We have reported previously[6] the flexible synthesis of poison frog alkaloids of the 5,8-disubstituted indolizidine class. In the present study, the efficient chiral syntheses of the compounds **207E** and **179** are addressed.

Results and discussion

Chiral piperidinol **1**[7] was gradually converted to the MOM (methoxymethyl) ether. Next, the MOM ether was transformed into enaminoester **2** following Rubio's procedure.[8] Dimethylcuprate and dipropylcuprate were used for the Michael-type conjugate additions to **2** in order to transform compounds **3** and **4** each into single stereoisomers. The ester moieties of **3** and **4** were treated with superhydride reduction, Swern oxidation and Horner–Emmons reaction to obtain the α,β-unsaturated esters **5** and **6**. The esters were hydrogenated to obtain an amino ester under Weinreb's reaction conditions,[9] as well as to form lactams **7** and **8**. Next, by eliminating mesylates, the lactams were converted into dehydropiperidines **9** and **10**. Reducing the lactam moiety with LAH (lithium aluminum hydride) produced the compounds **11** and **12** with 91% and 70% yields, respectively. The compounds **11** and **12** are alkaloids **179** and **207E**[1] respectively. The stereochemistry of the compound **11** was determined by conducting an NOE NMR experiment. The GC–FTIR spectrum and GC retention time of the compound **12** differed from those of the natural **207E**.[1]



Scheme 1 Syntheses of the proposed **179** and **207E**. Reagents and conditions: (a) i) MOMCl, $(i\text{-Pr})_2$EtN, CH_2Cl_2 (98%); ii) LiHMDS, PhSeCl (2 equiv.), THF, −78 °C to r.t. (79%); (b) **3**: Et_2O, **4**: THF, R_2CuX [**3**: R = Me, X = Li, (78%); **4**: R = *n*-Pr, X = MgBr (83%)]; (c) i) Super-Hydride, THF, 0 °C; ii) Swern oxidation; iii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C to r.t. (**5**: 73%; **6**: 76%); (d) i) 20% $Pd(OH)_2$, H_2, MeOH, 1 atm; ii) Et_3Al, DCE, reflux (**7**: 86%); **8**: 98%); (e) i) conc. HCl MeOH, reflux; ii) MsCl, Et_3N, CH_2Cl_2, 0 °C; iii) DBU, toluene, reflux (**9**: 62% in 3 steps; **10**: 64% in 3 steps); (f) LAH, THF (**11**: 91%; **12**: 70%).

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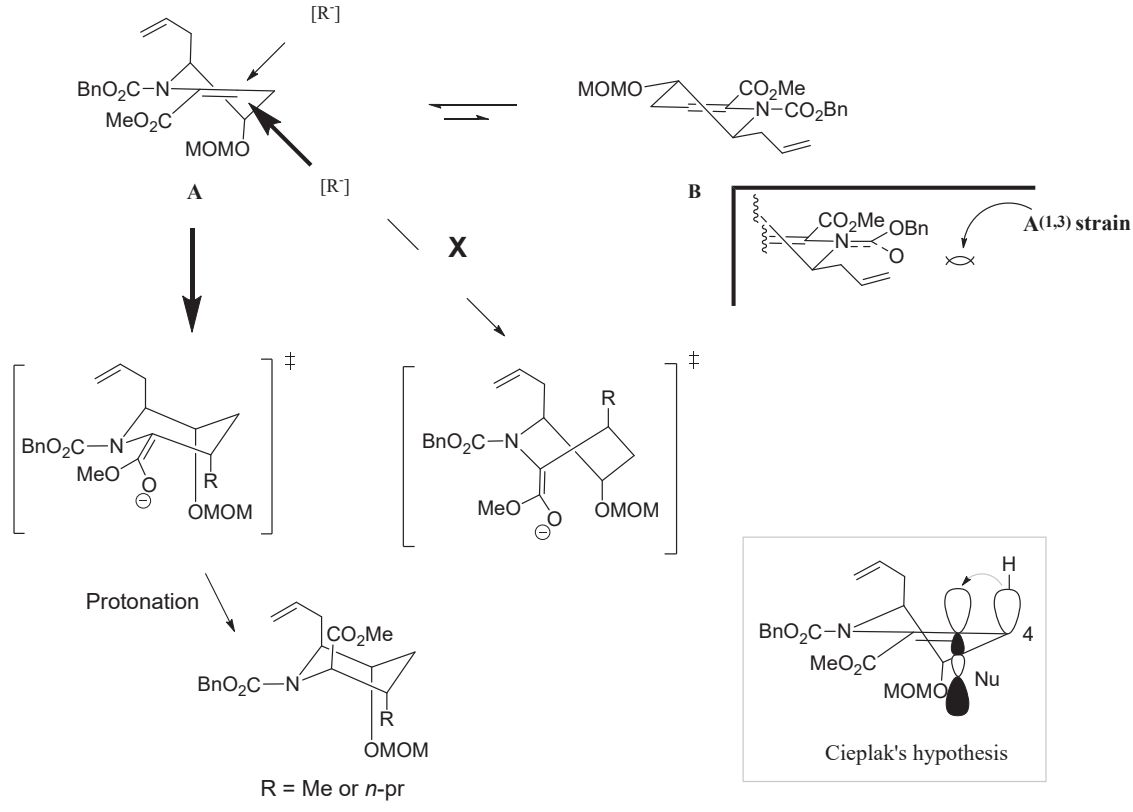

Scheme 2 Stereoselectivity of the key Michael-type conjugate addition.

Table 1 Study the conditions for synthesis of the compound **3** from the compound **2**[a]

Entry	Me_2CuX (equiv.)	Solvent	Time (h)	Yield (%)
1	Me_2CuLi (5)	Et_2O	1	78
2	Me_2Cu MgBr (5)	Et_2O	1.5	70
3	Me_2Cu MgCl (5)	Et_2O	2.0	61
4	Me_2CuLi (5)	THF	1	75
5	Me_2Cu MgBr (5)	THF	1.5	69
6	Me_2Cu MgCl (5)	THF	2.0	59

[a]All the reactions were performed with 100 mg of the substrate **2** and the reactions stopped once the substrate disappeared.

Table 2 Study the conditions for synthesis of the compound **4** from the compound **2**[a]

Entry	*n*-Pr_2CuX (equiv.)	Solvent	Time (h)	Yield (%)
1	*n*-Pr_2CuLi (5)	Et_2O	1	60
2	*n*-Pr_2Cu MgBr (5)	Et_2O	1.5	75
3	*n*-Pr_2Cu MgCl (5)	Et_2O	2.0	63
4	*n*-Pr_2CuLi (5)	THF	1	61
5	*n*-Pr_2Cu MgBr (5)	THF	1.5	83
6	*n*-Pr_2Cu MgCl (5)	THF	2.0	71

[a]All the reactions were performed with 100 mg of the substrate **2** and the reactions stopped once the substrate disappeared.

In the GC–FTIR spectra, both compound **12** and natural **207E** were sharp and intense Bohlmann band appeared near 2790 cm^{-1}, which suggest 5,8a-*cis* in both compounds. Compound **12** developed an absorption band at 3030 cm^{-1}, which is typical of vinyl C–H stretching. In contrast, the natural **207E** showed only weak vinyl C–H stretching and no enamine absorption was observed.[1] Results suggest that the natural alkaloid **207E** might have developed a 7,8-double bond similar to that of compound **13**. (Scheme 1) In order to prove this hypothesis the synthesis of compound **13** is now in progress.

The stereoselectivity of the main Michael-type conjugate addition is shown in Scheme 2. An $A^{(1,3)}$ strain[10] was observed between the *N*-Cbz group and the allyl substituent at the α position. The anion attacks from the α-axial orientation were caused by stereoelectronic effects,[11] after which the enolate protonation produced a single isomer from the trisubstituted piperidine. The remarkable stereoselectivity can also be explained by Cieplak's hypothesis.[12] The desired conformation of **A** was obtained. The σ* at the transition state developed and stabilised because of the antiperiplanar donor σ_{C-H} at the C-4 position.

The reaction conditions required to synthesise compound **3** from compound **2** are shown in Table 1. Et_2O was used as the reaction solvent in the experiment (entries 1–3). The nucleophilic reagents Me_2CuLi, $Me_2CuMgBr$ and $Me_2CuMgCl$ obtained 78%, 70% and 61% yields, respectively. When THF was used as the reaction solvent, the corresponding yields were 75%, 69% and 59% yields (entries 4–6).

The reaction conditions for synthesis of the compound **4** from the compound **2** are shown in Table 2. Et_2O was used as the reaction solvent in the initial experiment (entries 1–3) The nucleophilic reagents *n*-Pr_2CuLi, *n*-Pr_2Cu MgBr and *n*-Pr_2Cu MgCl obtained 60%, 75% and 63% yields, respectively. When THF was used as a reaction solvent, results compared with the Et_2O at 61%, 83% and 71% yields for *n*-Pr_2CuLi, *n*-Pr_2Cu MgBr and *n*-Pr_2Cu MgCl, respectively (entries 4–6).

Conclusion

The proposed dehydroindolizidine frog alkaloids **179** and **207E** were synthesised. A comparison of natural **207E** with synthesised compound **207E** on GC and FTIR showed they were different and suggests that the double bond of natural **207E** is at the 7,8-position (compound **13**).

Experimental

All chemical reagents were obtained from commercial suppliers (Aldrich, Kanto Chemical, Tokyo Chemical Industry (TCI), Aladdin, Wako Pure Chemical Industries) and used without further purification. Anhydrous solvents were obtained from commercial protocols. All non-aqueous reactions were carried out under Ar atmosphere. Thin layer chromatography (TCL) was performed on silica gel 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel (Merck). Column chromatography was carried out on Cica Silica Gel 60*N* (spherical, neutral, 40–50 μm or 63–210 μm). ^{1}H and ^{13}C NMR spectra were obtained on a Varian UNITY plus 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) instrument in $CDCl_3$, CD_3OD or DMSO-d_6. IR spectra were measured on a JNM FT/IR-460Plus spectrometer. Mass spectra were recorded on a JEOL D-200, JEOL JMS-GCmate II, SHIMAZU GC-MS-QP 500, or JEOL AX 505 spectrometer.

*Synthesis of 1-benzyl 2-methyl (5*R*,6*S*)-6-allyl-5-(methoxymethoxy) piperidine-1,2-dicarboxylate* (**2A**)

To a stirred solution of **1** (5.1 g, 9.4 mmol) in $CHCl_3$ (50 mL), was added MOMCl (1.42 mL, 18.8 mmol) and (*i*-Pr)$_2$EtN (3.56 mL, 20.6 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 15 h. Then the reaction was quenched with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 × 30 mL) and the organic extracts were combined, dried ($MgSO_4$) and evaporated to give pale yellow oil, which was purified by column chromatography (silica gel, hexane/acetone, 10:1) to afford **2A**: Pale yellow oil; yield 5.4 g, 98%; IR (ν_{max}, cm^{-1}) neat: 2930, 1735, 1698, 1413, 1295, 1211, 1036; ^{1}H NMR (300 MHz) δ 1.71-1.73 (2H, m), 2.06-2.11 (3H, m), 2.16-2.47 (1H, br. m), 3.28 (3H), 3.34 (3H), 3.65-3.80 (4H, m), 4.29-4.32 (1H, br. m), 4.60-4.64 (2H, m), 4.85-5.25 (5H, m), 5.74-5.79 (1H,br. m), 7.30-7.36 (5H, m); ^{13}C NMR (75 MHz) δ19.03 (t), 20.70 (t), 35.79 (t), 36.36 (t), 51.97 (q), 52.16 (d), 55.22 (q), 55.58 (d), 67.28 (t), 69.35 (d), 70.08 (d), 94.38 (t), 94.55 (t), 117.17 (t), 127.42 (d), 127.63 (d), 128.10 (d), 134.65 (d), 136.27 (s), 155.71 (s), 156.33 (s), 172.65 (s); MS: 377; HRMS calcd for $C_{20}H_{27}NO_6$: 377.1838; found: 377.1839; $[\alpha]_D^{25}$ –64.27 (c 1.28, $CHCl_3$).

*Synthesis of 1-benzyl 2-methyl (5*R*,6*S*)-6-allyl-5-(methoxymethoxy)-5,6-dihydropyridine-1,2(4*H*)-dicarboxylate* (**2**)

To a stirred solution of **2A** (3.2 g, 8.49 mmol) in THF at –78 °C was added a solution of LiHMDS [prepared from 1,1,1,3,3,3-hexamethyldisilazane (2.37 mL, 10.3 mmol) and BuLi (1.6M in hexane, 6.4 mL, 10.3 mmol) in THF (20 mL) at 0 °C for 30 min] and the reaction stirred for 30 min. To the reaction mixture was added dropwise a solution of PhSeCl (3.25g, 17 mmol) in THF (9 mL) *via* a double-tipped stainless steel needle at –78 ℃ and the resulting mixture was stirred at –78 ℃ – 0 °C for 1h. The reaction mixture was evaporated to give pale yellow oil, which was purified by column chromatography (silica gel, hexane/acetone, 20:1–6:1) to afford **2**: Pale yellow oil; yield 2.52 g, 79%; IR (ν_{max}, cm^{-1}) neat: 3075, 3026, 2950, 2353, 1715, 1652, 1437, 1396, 1270, 1033, 752, 697; ^{1}H NMR (300 MHz) δ 1.92–2.03 (1H, m), 2,16–2.23 (1H, m), 2.33 (2H, br. s), 3.15–3.91 (7H, br. m), 4.34–4.71 (3H, br. m), 5.02–5.17 (2H, m), 5.26 (2H, br. s), 5.82–5.90 (1H, m), 6.07 (1H, br. s), 7.27–7.47 (5H, m); ^{13}C NMR (75 MHz) δ 26.67 (t), 33.14 (t), 51.78 (q), 54.61 (d), 55.43 (q), 67.91 (t), 69.30 (d), 93.96 (t), 117.61 (t), 119.55 (d), 127.90 (d), 127.98 (d), 128.18 (d), 129.08 (d), 132.95 (d), 133.21 (d), 135.64 (s), 144.29 (s), 154.84 (s), 164.73 (s); HRMS calcd for $C_{20}H_{25}NO_6$: 375.1682; found: 375.1680; $[\alpha]_D^{25}$ +74.76 (c 0.70, $CHCl_3$).

*Synthesis of 1-benzyl 2-methyl (2*S*,3*S*,5*R*,6*S*)-6-allyl-5-(methoxymethoxy)-3-methylpiperidine-1,2-dicarboxylate* (**3**)

To a stirred suspension of CuI (2.6 g, 13.6 mmol) in Et_2O (5 mL) was added a solution of MeLi (26.2 mL, 27.2 mmol) at –78 ℃ and the resulting suspension was stirred at –78 °C to –35 °C for 20 min. The resulting solution was cooled to –78 °C and a solution of **2** (1.02 g, 2.72 mmol) in Et_2O (9 mL) was added dropwise *via* a double-tipped stainless steel needle to at –78 ℃. The temperature was gradually raised to 0 °C and then the reaction mixture was quenched with saturated NH_4Cl solution. The aqueous mixture was diluted with $CHCl_3$ (50 mL) and the insoluble material was removed through a celite pad. The filtrate was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined, dried and evaporated to give pale yellow oil, which was purified by column chromatography to afford **3**: Colourless oil; yield 0.83 g, 78%; IR (ν_{max}, cm^{-1}) neat: 2950, 1747, 1700, 1408, 1294, 1039; ^{1}H NMR (300 MHz) δ 1.15 (3H, d, *J* = 6.41 Hz), 1.35–1.41 (1H, m), 1.58 (1H, br. s), 2.00–2.05 (1H, m), 2.13–2.19 (2H, m), 2.51 (1H, br. d, *J* = 13.70 Hz), 3.31 (3H, s), 3.63–3.76 (4H, br. m), 4.26–4.58 (1H, br. m), 4.60 (2H, s), 5.05–5.21 (4H, m), 5.80–5.82 (1H, br. d, *J* = 8.54 Hz), 7.28–7.40 (5H, m); ^{13}C NMR (75 MHz) δ 20.18 (q), 27.59 (d), 32.09 (t), 39.12 (t), 51.92 (q), 55.40 (q), 56.39 (d), 60.69 (d), 67.44 (t), 73.38 (d), 94.59 (t), 117.38 (t), 127.61 (d), 127.79 (d), 128.24 (d), 134.83 (d), 136.30 (s), 156.23 (s), 172.95 (s); HRMS calcd for $C_{21}H_{29}NO_6$: 391.1995; found: 391.1997; $[\alpha]_D^{25}$ –48.11 (c 2.65, $CHCl_3$).

*Synthesis of 1-benzyl 2-methyl (2*S*,3*S*,5*R*,6*S*)-6-allyl-5-(methoxymethoxy)-3-propylpiperidine-1,2- dicarboxylate* (**4**)

To a stirred suspension of CuI (4.2 g) in THF (10 mL) was added a solution of *n*-PrMgBr (44.3 mL, 44.4 mmol) at –78 ℃ and the resulting suspension was stirred at –78 ℃ to –35 °C for 20 min. The resulting solution was cooled to –78 ℃ and a solution of **2** (1.66g, 4.43 mmol) in THF (9 mL) was added dropwise *via* a double-tipped stainless steel needle at –78 ℃. The temperature was gradually raised to 0 °C and then the reaction mixture was quenched with saturated NH_4Cl solution. The aqueous mixture was diluted with $CHCl_3$ (50 mL), stirring continued at room temperature for 20 min. The insoluble material was removed by filtration through a celite pad. The filtrate was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined, dried and evaporated to give pale yellow oil, which was purified by column chromatography (silica gel, hexane/acetone, 20:1–15:1) to afford **4**: Colourless oil; yield 1.54 g, 83%; IR (ν_{max}, cm^{-1}) neat: 2954, 1737, 1701, 1639, 1438, 1411, 1295, 1208, 1150, 1097, 1040, 917, 739, 698; ^{1}H NMR (300 MHz) δ 0.91 (3H, t, *J* = 7.26 Hz), 1.30 (1H, br. s), 1.33–1.46 (4H, m), 1.59 (1H, sep-like, *J* = 2.09), 2.01 (1H, dt-like, *J* = 14.01, 5.13), 2.09–2.17 (1H, m), 2.45 (1H, br. d-like *J* = 14.10 Hz), 3.31 (3H, s), 3.59–3.75 (4H, m), 4.33 (1H, br. s), 4.57 (1H, br. s), 4.59 (2H, t-like, *J* = 6.84 Hz), 5.06 (2H, br. d-like, *J* = 17.09 Hz), 5.18 (2H, br. d-like, *J* = 2.99 Hz), 5.78 (1H, br. s), 7.29–7.38 (5H, m); ^{13}C NMR (75 MHz) δ 13.73 (q), 19.88 (t), 27.65 (t), 31.83 (d), 35.49 (t), 37.78 (t), 51.54 (q), 54.96 (q), 56.13 (d), 57.45 (d), 67.07 (t), 72.80 (d), 94.31 (t), 116.96 (t), 127.36 (d), 127.56 (d), 128.02 (d), 128.10 (d), 134.76 (d), 136.23 (s), 156.25 (s), 172.86 (s); HRMS calcd for $C_{23}H_{33}NO_6$: 419.2308; found: 419.2340; $[\alpha]_D^{25}$ –42.52 (c 1.06, $CHCl_3$).

*Synthesis of benzyl (2*S*,3*R*,5*S*,6*S*)-2-allyl-6-(hydroxymethyl)-3-(methoxymethoxy)-5-methylpiperidine-1-carboxylate* (**5A**)

To a stirred solution of **3** (367 mg, 0.94 mmol) in THF (10 mL) was added a solution of lithium triethylborohydride (Super-Hydride®, 1 M in THF, 2.06 mL, 2.06 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 2h. The reaction was quenched with small pieces of ice and the mixture was diluted with CH_2Cl_2 (30 mL). The organic layer was dried and evaporated to give colourless oil, which was purified by column chromatography (silica gel, hexane/acetone, 10:1–5:1) to afford **5A**: Colourless oil; yield 300 mg, 88%; IR (ν_{max}, cm^{-1}) neat: 3444, 2932, 1683, 1417, 1313, 1095, 1038, 916, 769, 698; ^{1}H NMR (300 MHz) δ 1.13 (3H, d, *J* = 8.84 Hz), 1.29–1.36 (1H, m), 1.60 (1H, br. s), 1.91–1.96 (1H, m), 2.33 (2H, t-like, *J* = 7.26 Hz), 3.32 (3H, s), 3.60 (2H, d-like, *J* = 7.69 Hz), 3.74 (1H, br. d, *J* = 8.97 Hz), 3.91 (1H, sxt-like, *J* = 3.73 Hz), 4.39 (1H, br. s), 4.63 (2H, q-like, *J* = 6.74 Hz), 5.04–5.21 (4H, m), 5.78 (1H, br. d, *J* = 7.69 Hz), 7.28–7.39 (5H, m); ^{13}C NMR (75 MHz) δ 20.97 (q), 27.02 (d), 31.84 (t) 40.40 (t), 55.16 (q), 56.48 (d), 58.49 (d), 60.58 (d), 66.89 (t), 67.21 (t), 94.65 (t), 116.79 (t), 117.22 (t), 127.29 (d), 127.38 (d), 127.46 (d), 127.59 (d), 128.01 (d), 128.08 (d), 134.73 (d), 134.84 (d), 136.17 (s),136.40 (s), 157.36 (s); HRMS calcd for $C_{20}H_{29}NO_5$: 363.2046; found: 363.2048; $[\alpha]_D^{25}$ –61.67 (c 1.51, $CHCl_3$)

Synthesis of benzyl (2S,3R,5S,6S)-2-allyl-6-(hydroxymethyl)-3-(methoxymethoxy)-5-propylpiperidine-1-carboxylate (**6A**)

To a stirred solution of **4** (650 mg, 1.55 mmol) in THF (20 mL) was added a solution of lithium triethylborohydride (Super-Hydride®, 1 M in THF, 3.41 mL, 3.41 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 2h. The reaction was quenched with small pieces of ice and the mixture was diluted with CH_2Cl_2 (30 mL). The organic layer was dried and evaporated to give colourless oil, which was purified by column chromatography (silica gel, hexane/acetone, 10:1–8:1) to afford **6A**: Colourless oil; yield 507 mg, 84%; IR (ν_{max}, cm^{-1}) neat: 3467, 3100, 2954, 1688, 1417, 1313, 1217, 1038, 919, 744, 691; ^1H NMR (300 MHz) δ 0.90 (3H, t, *J* = 6.84 Hz), 1.28–1.41 (5H, m), 1.52 (1H, br. s), 1.96 (1H, dt, *J* = 12.82 Hz, 4.27 Hz), 2.34 (2H, t, *J* = 7.26 Hz), 3.32 (3H, s), 3.58 (2H, t-like, *J* = 8.54 Hz), 3.67 (1H, br. s), 4.08 (2H, dt-like, *J* = 8.12 Hz, 5.55 Hz), 4.32 (1H, br. s), 4.61 (2H, dd-like, *J* = 19.65 Hz, 6.84 Hz), 5.02–5.23 (4H, m), 5.79 (1H, br. s), 7.30–7.37 (5H, m); ^{13}C NMR (75 MHz) δ 13.94 (q), 20.15 (t), 28.72 (t), 32.35 (d), 36.98 (t), 40.00 (t), 55.32 (q), 56.68 (d), 58.27 (d), 65.54 (t), 67.27 (t), 75.02 (d), 94.80 (t), 117.20 (t), 127.57 (d), 127.75 (d), 128.17 (d), 128.22 (d), 134.91 (d), 136.32 (s), 156.72 (s); MS: 391; HRMS calcd for $C_{22}H_{33}NO_5$: 391.2359; found: 391.2361; $[\alpha]_D^{25}$ 0.64 (c 1.395, $CHCl_3$).

Synthesis of benzyl (2S,3R,5S,6S)-2-allyl-6-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(methoxymethoxy)-5-methylpiperidine-1-carboxylate (**5**)

To a stirred solution of $(COCl)_2$ (0.17 mL, 1.9 mmol) in CH_2Cl_2 (10 mL) was added DMSO (0.27 mL, 3.8 mmol) at –78 °C and the resulting mixture was stirred for 5 min. To the reaction mixture was added dropwise a solution of **5A** (345 mg, 0.95 mmol) in CH_2Cl_2 (6 mL) *via* a double-tipped stainless steel needle at –78 °C. The resulting solution was stirred at –78 °C for 30 min followed by the addition of triethylamine (0.79 mL, 5.7 mmol) to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h and quenched with H_2O (15 mL). The aqueous mixture was extracted with Et_2O (3 × 30 mL) and the organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 46 mg, 1.14 mmol) in THF (15 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.24 mL, 1.14 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 30 min. To the resulting mixture was added dropwise a solution of the above aldehyde in THF (6 mL) *via* a double-tipped stainless steel needle at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The reaction was quenched with H_2O (15 mL) and the aqueous mixture was extracted with CH_2Cl_2 (4 × 40 mL). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was purified by column chromatography (silica gel, hexane/acetone, 20:1–10:1) to afford **5** as a 2:1 mixture of the *E*- and *Z*-isomers: Pale yellow oil; yield 339 mg, 83%; ^1H NMR (300 MHz) δ 1.05 (3H, d, *J* = 8.84 Hz), 1.29 (3H, t, *J* = 7.10 Hz), 1.70–1.75 (2H, br. m), 1.98–2.05 (1H, m), 2.24–2.42 (2H, m), 3.32 (3H, s), 3.69 (1H, t–like *J* = 7.26 Hz), 4.16–4.20 (2H, d, *J* = 7.10 Hz), 4.22 (1H, br. s), 4.47 (1H, t-like, *J* = 6.91 Hz), 4.60–4.64 (2H, m), 5.07–5.16 (4H, m), 5.71–5.98 (3H, m), 6.78 (1H, q, *J* = 7.26 Hz), 7.28–7.37 (5H, m).

Synthesis of benzyl (2S,3R,5S,6S)-2-allyl-6-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-(methoxymethoxy)-5-propylpiperidine-1-carboxylate (**6**)

To a stirred solution of $(COCl)_2$ (0.24 mL, 2.74 mmol) in CH_2Cl_2 (15 mL) was added DMSO (0.39 mL, 5.48 mmol) at –78 °C and the resulting mixture was stirred for 5 min. To the reaction mixture was added dropwise a solution of **6A** (536 mg, 1.37 mmol) in CH_2Cl_2 (3 × 3 mL) *via* a double-tipped stainless steel needle at –78 °C. The resulting solution was stirred at –78 °C for 30 min and then triethylamine (1.37 mL, 8.22 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h. and quenched with H_2O (10 mL). The aqueous mixture was extracted with Et_2O (3 × 30 mL) and the organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 66 mg, 1.64 mmol) in THF (10 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.35 mL, 1.64 mmol) at 0 °C and the reaction mixture was stirred for 30 min. To the resulting mixture was added dropwise a solution of the above aldehyde in THF (6 mL) *via* a double-tipped stainless steel needle at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The reaction was quenched with H_2O (10 mL) and the aqueous mixture was extracted with CH_2Cl_2 (4 × 30 mL). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was purified by column chromatography (silica gel, hexane/acetone, 20:1–10:1) to afford **6** as a 2:1 mixture of the *E*- and *Z*-isomers: Pale yellow oil; yield 565 mg, 90%.

Synthesis of (5S,6R,8S,8aR)-6-(methoxymethoxy)-8-methyl-5-propyl-hexahydroindolizin-3(2H)-one (**7**)

To a stirred solution of **5** (300 mg, 0.7 mmol) in MeOH (15 mL) was added 20% $Pd(OH)_2/C$ (50 mg) and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 44 h. The catalyst was filtered off and the filtrate was evaporated to give pale yellow oil. The oil was dissolved in $ClCH_2CH_2Cl$ (10 mL) and Et_3Al (0.92M in hexane, 2.3 mL, 2.1 mmol) was added at 0 °C and the resulting solution was refluxed for 15 h. After cooling, the reaction was quenched with 10% HCl (aq) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the organic portions were combined, dried and evaporated to give pale yellow oil, which was purified by column chromatography (silica gel, hexane/acetone, 20:1–5:1) to afford **7**: Colourless oil; yield 153 mg, 86%; IR (ν_{max}, cm^{-1}) neat: 2958, 2886, 1691, 1418, 1150, 1103, 1039, 917; ^1H NMR (300 MHz) δ 0.91 (3H, t, *J* = 7.26 Hz), 0.94 (3H, d, *J* = 6.41 Hz), 1.23–1.30 (1H, m), 1.31–1.38 (1H, m), 1.44–1.62 (4H, m), 2.06–2.15 (2H, m), 2.16–2.22 (1H, m), 2.34 (2H, t-like, *J* = 6.41 Hz), 3.20 (1H, q-like, *J* = 6.84 Hz), 3.35 (3H, s), 3.42 (1H, q-like, *J* = 6.92 Hz), 3.71 (1H, q-like, *J* = 5.54 Hz), 4.66 (2H, dd-like, *J* = 16.66 Hz, 6.84 Hz); ^{13}C NMR (75 MHz) δ 14.02 (q), 17.79 (q), 19.89 (t), 24.28 (t), 31.65 (t), 31.73 (t), 34.66 (d), 36.32 (t), 55.39 (q), 57.98 (d), 62.62 (d), 73.33 (d), 94.88 (t), 174.45 (s); HRMS calcd for $C_{14}H_{25}NO_3$: 255.1834; found: 255.1836; $[\alpha]_D^{25}$ +146.90 (c 0.62, $CHCl_3$).

Synthesis of (5S,6R,8S,8aR)-6-(methoxymethoxy)-5,8-dipropylhexa-hydroindolizin-3(2H)-one (**8**)

To a stirred solution of **6** (500 mg, 1.09 mmol) in MeOH (20 mL) was added 20% $Pd(OH)_2/C$ (100 mg) and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 44 h. The catalyst was filtered off and the filtrate was evaporated to give pale yellow oil. The oil was dissolved in $ClCH_2CH_2Cl$ (15 mL) and Et_3Al (0.92M in hexane, 3.55 mL, 3.27 mmol) was added at 0 °C and the resulting solution was refluxed for 15 h. After cooling, the reaction was quenched with 10% HCl (aq) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the organic portions were combined, dried and evaporated to give pale yellow oil, which was purified by column chromatography (silica gel, hexane/acetone, 10:1–5:1) to afford **8**: Colourless oil; yield 302 mg, 98%; IR (ν_{max}, cm^{-1}) neat: 2957, 2360, 1688, 1458, 1415, 1377, 1278, 1215, 1149, 1097, 1039, 917, 861, 740; ^1H NMR (300 MHz) δ 0.87–0.93 (6H, m), 1.04–1.11 (1H, m), 1.21–1.40 (3H, m), 1.40–1.55 (6H, m), 1.98–2.05 (1H, m), 2.09–2.21 (2H, m), 2.30–2.33 (2H, m), 3.33–3.35 (1H, m), 3.34 (3H, s), 3.53 (1H, q-like, *J* = 5.98 Hz), 3.78 (1H, q-like, *J* = 4.13 Hz), 4.60–4.65 (2H, m); ^{13}C NMR (75 MHz) δ 13.85 (q), 14.06 (q), 19.07 (t), 19.72 (t), 24.99 (t), 31.43 (t), 32.29 (t), 32.57 (t), 34.51 (t), 39.13 (d), 55.16 (q), 56.68 (d), 60.41 (d), 72.78 (d), 94.50 (t), 174.29 (s); HRMS calcd for $C_{16}H_{29}NO_3$: 283.2147; found: 283.2145; $[\alpha]_D^{25}$ +21.41 (c 1.67, $CHCl_3$).

Synthesis of (5S,6R,8S,8aR)-8-methyl-3-oxo-5-propyloctahydro-indolizin-6-yl methanesulfonate (**9A**)

To a stirred solution of **7** (185 mg, 0.725 mmol) in MeOH (10 mL), was added dropwise 6 drops HCl (36%). The reaction mixture was reflux for 15 h, allowed to cool and the reaction mixture evaporated to give colourless oil. To a stirred solution of the oil in CH_2Cl_2, was

added MsCl (0.09 mL, 1.1 mmol) and Et_3N (0.18 mL, 1.3 mmol) at 0 °C and the reaction mixture was stirred at the temperature for 1h. the resulting mixture was quenched with $NaHCO_3$, extracted with CH_2Cl_2 (3 × 20 mL), the extracts was combined, dried over $MgSO_4$, evaporated to give **9A** pale yellow oil, which was used directly in the next step.

Synthesis of (5S,8S,8aR)-8-methyl-5-propyl-1,5,8,8a-tetrahydro-indolizin-3(2H)-one (**9**)

To a stirred solution of the above **9A** in toluene, was added DBU (0.4 mL, 2.9 mmol) at room temperature, then was reflux for 15 h, the reaction mixture was diluted with AcOEt (100 mL), then washed with water (2 × 2 mL), 10% HCl (aq) (2 × 2 mL) and saturated NaCl (5 mL), dried over $MgSO_4$, evaporated to give pale yellow oil which was purified by column chromatography (silica gel, hexane/acetone, 30:1–20:1) to afford **9**: Colourless oil; yield 69.4 mg, 62% for three steps; IR (ν_{max}, cm^{-1}) neat: 3038, 2959, 2930, 2871, 1695, 1456, 1406, 1315, 1274, 800, 753; ^{1}H NMR (300 MHz) δ 0.86 (3H, t, *J* = 7.69 Hz), 1.01 (3H, d, *J* = 7.26 Hz), 1.22 (2H, sxt-like, *J* = 7.26 Hz), 1.51 (1H, quint-like, *J* = 9.82 Hz), 1.79–1.84 (1H, m), 2.04–2.11 (2H, m), 2.20–2.27 (2H, m), 2.29–2.40 (3H, m), 3.01 (1H, q-like, *J* = 5.55 Hz), 4.10 (1H, br. d, *J* = 3.42 Hz), 5.60 (1H, d-like, *J* = 9.82 Hz), 5.66 (1H, dt-like, *J* = 10.25 Hz, 2.89 Hz); ^{13}C NMR (75 MHz) δ 14.03 (q), 16.56 (q), 16.82 (t), 25.3 (t), 31.20 (t), 34.62 (t), 36.77 (d), 52.32 (d), 62.20 (d), 128.11 (d), 131.15 (d), 175.54 (s); HRMS calcd for $C_{12}H_{19}NO$: 193.1467; found: 193.1468; $[\alpha]_D^{25}$ +114.63 (c 0.79, $CHCl_3$).

Synthesis of (5S,6R,8S,8aR)-3-oxo-5,8-dipropyloctahydroindolizin-6-yl methanesulfonate (**10A**)

To a stirred solution of **8** (165 mg, 0.58 mmol) in MeOH (10 mL), was added dropwise 10 drops HCl (aq., 36%). The reaction mixture was reflux for 15h, allowed to cool and the reaction mixture evaporated to give a pale yellow residue, which was diluted with $CHCl_3$, dried (K_2CO_3) and evaporated to give a colourless oil. To a stirred solution of the oil in CH_2Cl_2 (10 mL), was added MsCl (0.067 mL, 0.87 mmol) and Et_3N (0.15 mL, 1.04 mmol) at 0 °C and the reaction mixture was stirred for 1 h, the resulting mixture was quenched with $NaHCO_3$, extracted with CH_2Cl_2, the extracts was combined, dried ($MgSO_4$) and evaporated to give **10A** as pale yellow oil, which was used directly in the next step.

Synthesis of (5S,8S,8aR)-5,8-dipropyl-1,5,8,8a-tetrahydroindolizin-3(2H)-one (**10**)

To a stirred solution of **10A** in toluene (7 mL), was added DBU (0.43 mL, 2.9 mmol) at room temperature, the reaction was then stirred at reflux for 15 h, the reaction mixture was diluted with EtOAc (100 mL), then washed with water (2 × 2 mL), 10% HCl (aq., 2 × 2 mL) and saturated NaCl (5 mL), dried ($MgSO_4$) and evaporated to give pale yellow oil. The product was then purified by column chromatography (silica gel, hexane/acetone, 30:1–20:1) to afford **10**: Colourless oil; yield 82.8 mg, 64% for three steps; IR (ν_{max}, cm^{-1}) neat: 3035, 2958, 2871, 2369, 1697, 1646, 1512, 1406, 1319, 1271, 1190, 1125, 875; ^{1}H NMR (300 MHz) δ 0.89 (3H, t, *J* = 7.26 Hz), 0.94 (3H, t, *J* = 7.26 Hz), 1.17–1.27 (2H, m), 1.32–1.38 (1H, m), 1.40–1.47 (1H, m), 1.49–1.59 (2H, m), 1.64 (1H, s), 1.79–1.85 (1H, m), 1.96 (1H, t-like, *J* = 9.40 Hz), 2.02–2.09 (1H, m), 2.19–2.40 (3H, m), 3.12 (1H, sxt-like, *J* = 5.55 Hz), 4.10 (1H, br. d, *J* = 3.85 Hz), 5.68 (1H, t-like, *J* = 3.41 Hz), 5.71 (1H, dd-like, *J* = 18.37 Hz, 3.41 Hz); ^{13}C NMR (75 MHz) δ 14.04 (q), 14.29 (q), 16.91 (t), 19.23 (t), 25.55 (t), 31.25 (t), 32.84 (t), 34.77 (t), 41.71 (d), 52.39 (d), 60.68 (d), 128.44 (d), 129.05 (d), 175.54 (s); HRMS calcd for $C_{14}H_{23}NO$: 221.1780; found: 221.1795; $[\alpha]_D^{25}$ +131.28 (c 2.70, $CHCl_3$).

Synthesis of (5S,8S,8aR)-8-methyl-5-propyl-1,2,3,5,8,8a-hexahydro-indolizine (**11**)

To a stirred solution of **9** (64.9 mg, 0.336 mmol) in THF (7 mL) was added $LiAlH_4$ (25.5 mg, 0.67 mmol) at 0 °C and the resulting suspension was refluxed for 15 h. After cooling, the reaction was quenched with 10% NaOH (aq) and the aqueous mixture was extracted with hot $CHCl_3$ (10 × 15 mL). The organic extracts were combined, dried over K_2CO_3 and evaporated to give the compound **11**: Colourless oil; yield 54.7 mg, 91%; IR (ν_{max}, cm^{-1}) neat: 3025, 2957, 2871, 2781, 1456, 1377, 1326, 1287, 1179, 913, 798, 715; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.5 Hz), 0.94 (3H, d, J = 6.8 Hz), 1.25–1.34 (1H, m), 1.35–1.41 (1H, m), 1.42–1.52 (2H, m), 1.61–1.67 (1H, m), 1.68–1.75 (1H, m), 1.76–1.83 (1H, m), 1.84 (1H, td, J = 9.1, 6.9 Hz), 1.99–2.07 (2H, m), 2.08–2.14 (1H, m), 2.64 (1H, dtd, J = 11.0, 3.6, 1.9 Hz), 3.35 (1H, td, J = 8.4, 1.9 Hz), 5.50 (1H, dt, J = 10.2, 1.9 Hz), 5.57 (1H, dt, J = 10.2, 1.9 Hz); 13C NMR (75 MHz, CDCl3) d 14.39 (q), 18.14 (q), 18.64 (t), 20.77 (t), 29.38 (t), 36.04 (t), 37.61 (d), 52.79 (t), 63.00 (d), 67.83 (d), 128.55 (d), 131.53 (d); MS; HRMS calcd for $C_{12}H_{21}N$: 179.1674; found: 179.1686; $[\alpha]_D^{26}$ +129.3 (c 2.74, $CHCl_3$).

Synthesis of (5S,8S,8aR)-5,8-dipropyl-1,2,3,5,8,8a-hexahydro-indolizine (**12**)

To a stirred solution of **10** (50 mg, 0.23 mmol) in THF (5 mL) was added $LiAlH_4$ (20 mg, 0.46 mmol) at 0 °C and the resulting suspension was refluxed for 15 h. After cooling, the reaction was quenched with 10% NaOH (aq) and the aqueous mixture was extracted with hot $CHCl_3$ (10 × 10 mL). The organic extracts were combined, dried (K_2CO_3) and evaporated to give compound **12**: Colourless oil; IR (ν_{max}, cm^{-1}) neat: 3030, 2957, 2929, 2871, 2790, 1458, 1378, 1329, 1260, 1177, 1105, 929, 803, 713; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.8 Hz), 0.91 (3H, t, *J* = 7.3 Hz), 1.12–1.21 (1H, m), 1.23–1.34 (2H, m), 1.35–1.40 (2H, m), 1.43–1.53 (3H, m), 1.59–1.68 (1H, m), 1.69–1.74 (1H, m), 1.76–1.82 (1H, m), 1.93 (1H, td, *J* = 9.4, 6.8 Hz), 1.99–2.06 (3H, m), 2.63 (1H, dtd, *J* = 11.0, 3.4, 1.7 Hz), 3.34 (1H, td, *J* = 8.5, 2.1 Hz), 5.60 (1H, dt, *J* = 9.8, 1.7 Hz), 5.63 (1H, dt, *J* = 9.8, 1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) d 14.43 (q x 2), 18.64 (t), 19.67 (t), 20.92 (t), 29.69 (t), 34.91 (t), 36.11 (t), 42.54 (d), 52.76 (t), 62.97 (d), 66.13 (d), 129.01 (d), 129.44 (d); HRMS calcd for $C_{14}H_{25}N$: 207.1986; found: 207.1973; $[\alpha]_D^{26}$ +109.1 (*c* 0.32, $CHCl_3$).

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References

1 J.W. Daly, T.F. Spande and H.M. Garraffo, *J. Nat. Prod*., 2005, **68**, 1556.
2 N.R. Andriamaharavo, H.M. Garraffo, R.A. Saporito, J.W. Daly, C.R. Razafindrabe, M. Andriantsiferana and T.F. Spande, *J. Nat. Prod*., 2010, **73**, 322.
3 S.M. Chen, V. Bacauanu, T. Knecht, B.Q. Mercado, R.G. Bergman and J.A. Ellman, *J. Am. Chem. Soc*., 2016, **138**, 12664.
4 F.M. Cordero, C. Vurchio and A. Brandi, *J. Org. Chem*., 2016, **81**, 1661.
5 Y. Park, C.S. Schindler and E.N. Jacobsen, *J. Am. Chem. Soc*., 2016, **138**, 14848.
6 D.J. Zhou, Z.H. Wang, Y.R. Zhang and Z.G. Cui, *J. Chem. Res*., 2017, **41**, 98.
7 M.A. Wijdeven, P.N.M. Botman, R. Wijtmans, H. E. Schoemaker, F.P.J.T. Rutjes and R.H. Blaauw, *Org. Lett*., 2005, **7**, 4005.
8 J. Ezquerra, A. Escribano, A. Rubio, M. J. Remuinan and J.J. Vaquero, *Tetrahedron: Asymmetry*, 1996, **7**, 2613.
9 A. Basha, M. Lipton and S.M. Weinreb, *Tetrahedron Lett*., 1977, **48**, 4171.
10 R.W. Hoffmann, *Chem. Rev*., 1989, **89**, 1841.
11 P. Deslongchamps, *Stereoelectronic effects in organic chemistry*, Pergamon, New York, 1983, 203.
12 A.S. Cieplak, *J. Am. Chem. Soc*., 1981, **103**, 4540.