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Cascade cyclization and intramolecular nitrone dipolar cycloaddition and formal synthesis of 19-hydroxyibogamine

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A cascade or domino sequence of condensation of hydroxylamine and an aldehyde to give an oxime, cyclization to a nitrone, and intramolecular 1,3-dipolar cycloaddition has been successfully employed where there is branching at C-4 as a route to the *iboga* alkaloids. Cyclization occurs with displacement of chloride as a leaving group and intramolecular cycloaddition occurs with an alkene as a dipolarophile. The reaction gives an azabicyclo[2.2.2]octane product containing a fused isoxazolidine as a single stereoisomer and this was converted to an isoquinuclidine that completed a formal synthesis of the alkaloid (±)-19-hydroxyibogamine.

Introduction

Iboga alkaloids have been isolated from plants of the *Tabernanthe* genus, found particularly in West Africa.[1] The *iboga* alkaloids are related by a common pentacyclic structure found in ibogamine **1**, that consists of an isoquinuclidine core with a fused indoloazepine ring and representative examples are shown in Figure 1. Their pharmacological properties have been studied widely and they have attracted attention due to their ability to treat drug addiction.[2] Ibogaine **2** is the most abundant of the alkaloids in *Tabernanthe iboga* and has been used clinically. The alkaloid catharanthine **4** has potent antagonist activity against transient receptor potential melastatin 8 (TRPM8), which is expressed in sensory neurons and involved in thermoregulation and pain.[3] This compound is an important intermediate in the synthesis of vinblastine and analogues.[4]

Many syntheses of the alkaloid ibogamine have been reported.[5,6] In contrast, there is only one report of the preparation of the *iboga* alkaloid (–)-19-hydroxyibogamine **5**,[7] which shows marked antibiotic activity.[8] There is a growing number of *iboga* alkaloids with a hydroxyethyl group or other oxygenated side chain at C-20 of the core ring system.[9] Here we report an efficient synthesis of the isoquinuclidine core with a hydroxyethyl side chain that makes use of a nitrone cycloaddition as part of a cascade process involving simple condensation of hydroxylamine with an aldehyde followed by cyclization on to an alkyl halide and cycloaddition. We have applied this to a formal synthesis of 19-hydroxyibogamine **5**.

We have reported a number of examples of the formation of polycyclic amines by use of a cascade strategy that incorporates a condensation reaction of an amine and an aldehyde (or ketone) followed by in situ cyclization of the imine (or oxime or hydrazone) on to an alkyl halide, followed by in situ dipolar cycloaddition.[10–15] Our efforts have been centred mostly on fused ring systems (Scheme 1a) and this chemistry leads to the synthesis of several natural products (*aspidosperma* alkaloids, myrioxazine A).[10-11] An intermolecular cycloaddition alternatively leads to bicyclic products and has been used to prepare crispine A and macronecine.[12] We have extended the methodology to bridged polycyclic compounds (Scheme 1b),[13] and recently to spirocyclic compounds (Scheme 1c).[14] The research on the bridged compounds located the branch point (between the alkene dipolarophile and the alkyl halide) β- to the aldehyde. This led to compounds with a one-carbon bridge. We were interested to see if the chemistry could be extended to compounds that would give a two-carbon bridge and hence access the isoquinuclidine ring system. Here we report the results of this study in the context of the synthesis of the *iboga* alkaloids.

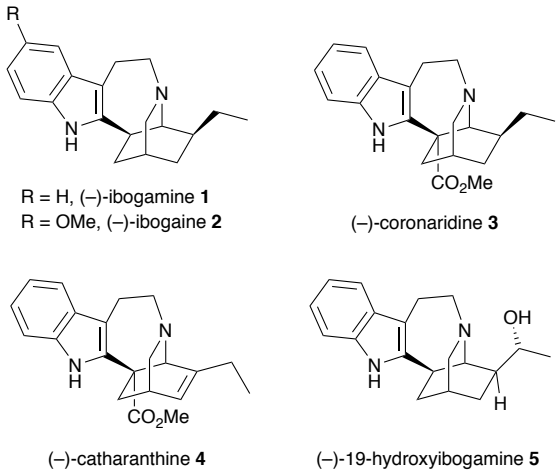

Figure 1 Representative *iboga* alkaloids, **1–5**.

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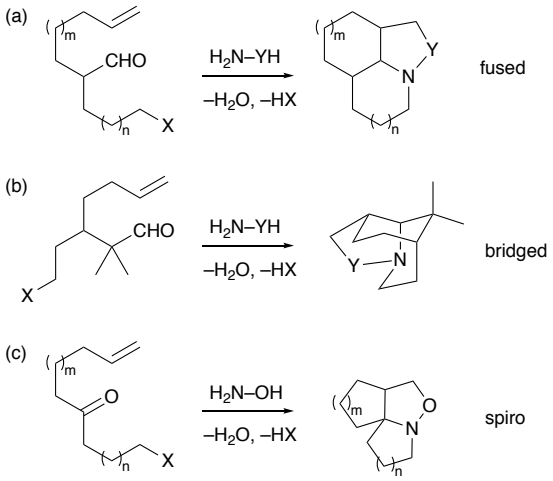
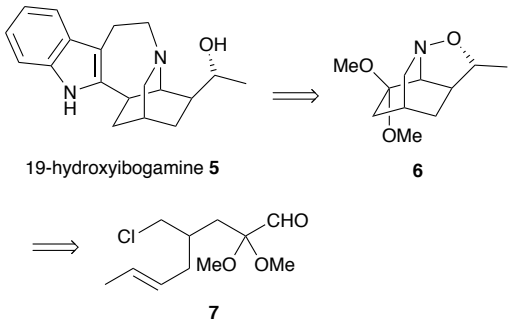


Scheme 1 Cascade chemistry to polycyclic amines (X = Br, Cl; Y = O, NR, CHR).[10–14]

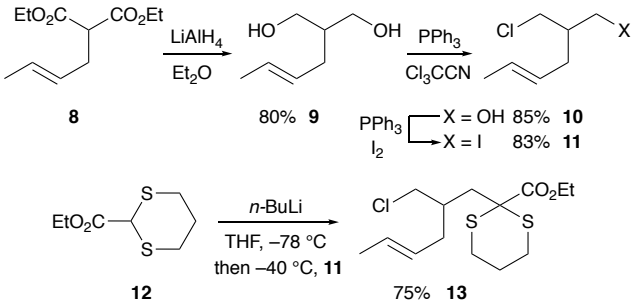
Results and discussion

To explore the ability to conduct the cascade chemistry towards a two-carbon bridged compound that could lead to the *iboga* alkaloids, we needed to prepare an aldehyde such as compound **7** with branching between the alkene and the alkyl halide g- to the aldehyde (Scheme 2). We anticipated that condensation of hydroxylamine with this aldehyde would provide an intermediate oxime that would undergo cyclization with displacement of the chloride and subsequent 1,3-dipolar cycloaddition of the resulting nitrone with the tethered alkene to give the isoquinuclidine core **6**.

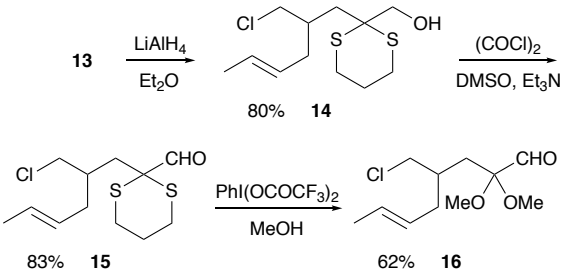
To test the chemistry and to access the required aldehyde rapidly, we prepared the racemic iodide **11** by reduction of the known diester **8**[16] followed by two separate mono-halogenations (Scheme 3). The diester **8** was formed by allylation with crotyl bromide as a mixture of stereoisomers *E*:*Z* 5.5:1 and could be reduced without purification. Treatment of iodide **11** with the anion formed from $(EtO)_2CHCN$ and LDA or NaH failed to give any alkylated product.[17] We therefore turned to a dithiane anion. Deprotonation of dithiane **12** with *n*-BuLi followed by addition of the iodide **11** gave the desired alkylated product **13**. As expected, this occurred by displacement of the iodide not the chloride and best conditions involved addition of the iodide **11** at –40 °C followed by warming to room temperature.



Scheme 2 Retrosynthesis for 19-hydroxyibogamine **5**.



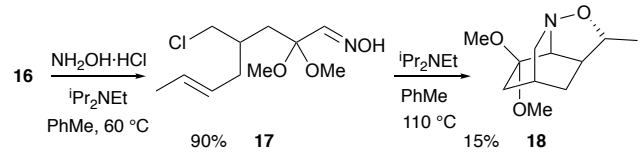
Scheme 3 Synthesis of the dithiane **13**. Ratio *E*:*Z* 5.5:1 for **8**–**11**, **13**.



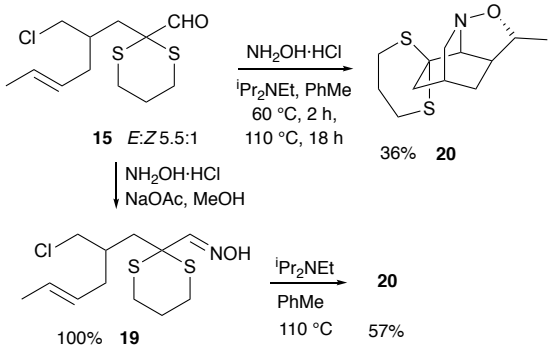
Scheme 4 Synthesis of the aldehydes **15** and **16**. Ratio *E*:*Z* 5.5:1 for **13**–**16**.

The ester **13** was reduced with $LiAlH_4$ to give the alcohol **14** (Scheme 4). The presence of a dimethyl acetal (rather than a dithiane) adjacent to the required aldehyde has previously been found to be beneficial in an intramolecular dipolar cycloaddition reaction.[18] Therefore, initially, alcohol **14** was treated with methanol, silver nitrate and *N*-chlorosuccinimde to promote transacetalation from the dithiane to the corresponding dimethyl acetal, although this new acetal proved to be unstable to subsequent Swern oxidation. Therefore, alcohol **14** was oxidised to give aldehyde **15**. The aldehyde **15** could be converted to the dimethyl acetal **16**.

We now had in-hand two aldehydes to test the cascade chemistry. Taking the aldehyde **16** (which was still an inseparable mixture of *E*:*Z* stereoisomers in a ratio of 5.5:1) and heating with hydroxylamine at 60 °C gave the expected oxime **17** (Scheme 5). This oxime could be isolated or, alternatively, directly raising the temperature to heat under reflux gave a low yield (15%) of a single stereoisomer of the cycloadduct **18**. No other isolable compounds could be obtained and it appeared that decomposition was taking place predominantly. Heating the purified oxime **17** in toluene in the presence of $^{i}Pr_2NEt$ gave the same result, with cycloadduct **18** being isolated in only 15% yield. Carrying out this cascade reaction in the presence of Bu_4NI or by using xylene instead of toluene failed to provide any cycloadduct **18**. The stereochemistry of the cycloadduct **18** was assigned on the basis of similar coupling constants in its ^1H NMR spectrum in comparison with the cycloadduct **20** (and on the basis of the single crystal X-ray analysis of ketone **21**, see below).



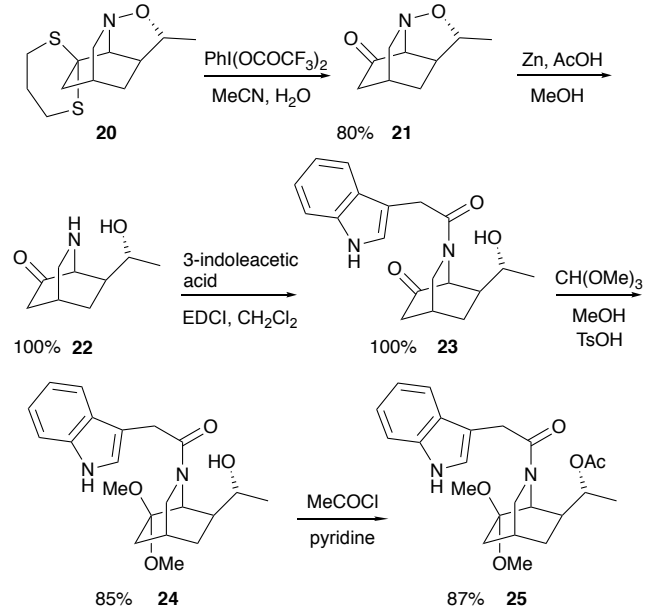
Scheme 5 Cycloaddition from the aldehyde **16** to give (±)-**18**.



Scheme 6 Cycloaddition from the aldehyde **15** to give (±)-**20**.

With the disappointing result in the formation of the cycloadduct **18**, our attention turned to the corresponding dithiane **15**. Heating aldehyde **15** with the hydrochloride salt of hydroxylamine in toluene and $^{i}Pr_2NEt$ resulted in a low yield (18%) of the cycloadduct **20** (Scheme 6). Addition of Bu_4NI or heating in xylene did not change the outcome significantly (22% of **20** isolated). However, addition of $MgSO_4$ did improve the yield, particularly if the oxime was allowed to form at 60 °C prior to heating at 110 °C. In this case the cycloadduct **20** was isolated in 36% yield. The difficulty appeared to be the poor formation of the oxime intermediate (**19**). Therefore an alternative strategy was adopted, whereby the oxime **19** was formed (in quantitative yield) under modified conditions (with sodium acetate as the base in methanol). The oxime was then heated in toluene with $^{i}Pr_2NEt$ and $MgSO_4$ to give the desired cycloadduct **20** in more acceptable yield (57%). In the absence of either $^{i}Pr_2NEt$ or $MgSO_4$, the yields were lower. A single stereoisomer of the cycloadduct **20** was formed; the stereochemistry was confirmed as discussed below and this fits with a concerted cycloaddition across the *E*-alkene.

With a successful synthesis of the cycloadduct **20**, we sought to carry out further transformations towards the *iboga* alkaloid structures. Attempts to reduce the N–O bond in the cycloadduct **20** with zinc in aqueous acetic acid gave only recovered starting material. Alternatively, hydrolysis of the dithiane was carried out and we found that [bis(trifluoroacetoxy)iodo]benzene in aqueous acetonitrile resulted in the desired ketone **21** (Scheme 7). The relative stereochemistry of the ketone **21** was confirmed by single crystal X-ray analysis (see SI). At this point it was possible to reduce the N–O bond with activated zinc in acetic acid and methanol to give the isoquinuclidine **22**. The crude material was coupled with 3-indoleacetic acid to give the isoquinuclidine **23** in quantitative yield from the isoquinuclidine **21**. Finally, we were able to convert in high yield the ketone functional group to the dimethyl acetal **24** and the alcohol to the acetate so as to prepare racemic isoquinuclidine **25**. The NMR spectroscopic data of the isoquinuclidine **25** matched those reported by Höck and Borschberg.[7b] Therefore this chemistry provides a formal synthesis of the alkaloid 19-hydroxyibogamine **5**.



Scheme 7 Completion of the formal synthesis of 19-hydroxyibogamine **5** by preparation of (±)-**25**.

Experimental

Reactions were carried out under nitrogen or argon using oven-dried glassware. Petrol refers to petroleum ether (b.p. 40–60 °C). Thin layer chromatography was carried out using silica plates, visualising by UV irradiation at 254 nm or by staining with an alkaline aqueous $KMnO_4$ dip. The silica gel used for column chromatography was 40–63 micron mesh. The chemical shifts in the ^{1}H NMR spectra are reported in ppm with respect to residual solvent peaks, with multiplicities s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Coupling constants, *J*, are quoted to the nearest 0.5 Hz. High resolution (accurate mass) mass spectra (HRMS) used electrospray ionisation (ESI) with a time-of-flight (TOF) mass analyzer.

2-[But-2-en-1-yl]propane-1,3-diol **9**. Diethyl malonate (24.0 g, 100 mmol) was added to sodium hydride (1.44 g, 60 mmol) in THF (40 mL) at room temperature. After 15 min, the suspension was added dropwise to crotyl bromide (6.69 g, 50 mmol, *E*:*Z* 5.5:1) in THF (100 mL). After 3 h, saturated aqueous ammonium chloride (100 mL) and H_2O (100 mL) were added. The aqueous layer was extracted with Et_2O (3 × 75 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated. The crude product was added dropwise to a suspension of Et_2O (50 mL) and $LiAlH_4$ (3.7 g, 100 mmol) at 0 °C. After 10 min, the mixture was warmed to room

temperature. After 3 h, aqueous sodium hydroxide (25 mL, 1 M) was added until a white precipitate was observed. The mixture was filtered through Celite®, washed with CH_2Cl_2–MeOH (9:1) (200 mL) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (3:2), gave the diol **9** (5.2 g, 80%) as an oil as a 5.5:1 *E*:*Z* mixture; R_f 0.2 [petrol–EtOAc (1:1)]; IR ν_{max}(film)/cm^{-1} 3315, 2915, 2885; ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.57–5.37 (2H, m), 3.80 (2H, dd, *J* 10.5, 4 Hz), 3.66 (2H, dd, *J* 10.5, 7.5 Hz), 2.55 (2H, br s), 1.98 (2H, t, *J* 7 Hz), 1.87–1.79 (1H, m, CH), 1.67 (3H, dd, *J* 6, 1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 128.5, 127.2, 65.8, 42.2, 31.2, 17.9; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_7H_{15}O_2$ 131.1070; Found: 131.1072.

2-(Chloromethyl)hex-4-en-1-ol **10**. Triphenylphosphine (7.25 g, 27.6 mmol) was added to the diol **9** (3.0 g, 23 mmol) in CH_2Cl_2 (230 mL) at 0 °C. After 10 min, trichloroacetonitrile (2.31 mL, 23.0 mmol) was added dropwise and the mixture was allowed to warm to room temperature. After 4 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), gave the chloroalcohol **10** (2.89 g, 85%) as an oil as a 5.5:1 *E*:*Z* mixture; R_f 0.27 [petrol–EtOAc (4:1)]; IR ν_{max}(film)/cm^{-1} 3330, 2935, 2915, 1435, 725; ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.57–5.50 (1H, m), 5.43–5.35 (1H, m), 3.72–3.68 (2H, m), 3.67–3.60 (2H, m), 2.13–2.08 (2H, m), 1.97–1.90 (1H, m), 1.68 (3H, dd, *J* 6, 1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 128.0, 127.7, 62.8, 45.6, 42.8, 31.8, 18.0; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_7H_{14}{}^{35}ClO$ 148.0655; Found: 148.0655; LRMS *m/z* (ES) 150 (60%), 148 (100).

6-Chloro-5-(iodomethyl)hex-2-ene **11**. Imidazole (1.64 g, 25.9 mmol) and triphenylphosphine (6.80 g, 25.9 mmol) were added to 2-(chloromethyl)hex-4-en-1-ol **10** (3.20 g, 21.6 mmol) in THF (75 mL) at room temperature. After 15 min, ground iodine (6.00 g, 23.8 mmol) was added portionwise. After 3 h, CH_2Cl_2 (50 mL) was added, the suspension was filtered through Celite® and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol, gave the iodide **11** (4.62 g, 83%) as an oil as a 5.5:1 *E*:*Z* mixture; R_f 0.5 (petrol); IR ν_{max}(film)/cm^{-1} 2960, 1435; ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.62–5.54 (1H, m), 5.38–5.29 (1H, m), 3.66 (1H, dd, *J* 11, 4.5 Hz), 3.52 (1H, dd, *J* 11, 6.5 Hz), 3.40 (1H, dd, *J* 10, 4.5 Hz), 3.30 (1H, dd, *J* 10, 6 Hz), 2.16–2.06 (2H, m), 1.80–1.72 (1H, m), 1.69 (3H, dd, *J* 6.5, 1.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 128.9, 126.7, 47.9, 41.8, 35.1, 18.0, 10.5; HRMS (ESI-TOF) *m/z*: [M]$^+$ Calcd for $C_7H_{12}{}^{35}ClI$ 257.9672; Found: 257.9669; LRMS *m/z* (EI) 260 (2%), 258 (6), 55 (100).

Ethyl 2-[2-(Chloromethyl)hex-4-en-1-yl]-1,3-dithiane-2-carboxylate **13**. *n*-BuLi (6.2 mL, 15.6 mmol, 2.5 M in hexanes) was added to ethyl 1,3-dithiane-2-carboxylate **12** (2.0 mL, 13 mmol) in THF (35 mL) at –78 °C. After 15 min, the iodide **11** (4.0 g, 15.6 mmol) in THF (5 mL) was added at –40 °C and the mixture was allowed to warm to room temperature. After 16 h, H_2O (40 mL) was added and the aqueous layer was extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), gave the ester **13** (3.2 g, 75%) as an oil as a 5.5:1 *E*:*Z* mixture; R_f 0.3 [petrol–EtOAc (98:2)]; IR ν_{max}(film)/cm^{-1} 2980, 2920, 1720; ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.60–5.51 (1H, m), 5.40–5.32 (1H, m), 4.31–4.24 (2H, m), 3.68–3.61 (2H, m), 3.33–3.25 (2H, m), 2.73–2.67 (2H, m), 2.27–2.11 (5H, m), 2.05 (1H, dd, *J* 14, 4 Hz), 1.93–1.82 (1H, m), 1.68 (3H, dd, *J* 6, 1 Hz), 1.36 (3H, t, *J* 7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 171.0, 128.4, 127.5, 62.1, 52.9, 49.1, 39.8, 36.8, 35.9, 27.95, 27.9, 24.4, 18.0, 14.2; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{24}O_2S_2{}^{35}Cl$ 323.0906; Found: 323.0909; LRMS *m/z* (ES) 325 (45%), 323 (100).

2-[2-(Chloromethyl)hex-4-en-1-yl]-1,3-dithian-2-ylmethanol **14**. The ester **13** (3.17 g, 9.8 mmol) in Et_2O (5 mL) was added to a suspension of $LiAlH_4$ (0.56 g, 14.7 mmol) in Et_2O (25 mL) at room temperature. After 2.5 h, aqueous NaOH (30 mL, 1 M) was added until a white precipitate was observed. The mixture was filtered through Celite® washing with CH_2Cl_2–MeOH (9:1) (100 mL) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), gave the alcohol **14** (2.2 g, 80%) as an oil as a 5.5:1 *E*:*Z* mixture; R_f 0.5 [petrol–EtOAc (4:1)]; IR ν_{max}(film)/cm^{-1} 3275, 2935, 2910; ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 5.59–5.50 (1H, m), 5.42–5.34 (1H, m), 3.77–3.74 (2H, m), 3.72–3.66 (2H, m), 2.99–2.90 (2H, m), 2.64–2.59 (2H, m), 2.28–2.19 (3H, m), 2.15–2.06 (2H, m), 1.93–1.78 (2H, m), 1.73 (1H, dd, 14, 3 Hz), 1.68 (3H, dd, *J* 6, 1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 128.3, 127.7, 64.0, 54.8, 49.6, 39.0, 36.4, 35.9, 25.9, 25.8, 24.6, 18.0; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{22}OS_2{}^{35}Cl$ 281.0801; Found: 281.0796; LRMS *m/z* (ES) 283 (3%), 281 (8), 265 (45), 263 (100).

2-[2-(Chloromethyl)hex-4-en-1-yl]-1,3-dithiane-2-carbaldehyde **15**. DMSO (0.80 mL, 11 mmol) in CH_2Cl_2 (1 mL) was added dropwise to oxalyl chloride (0.50 mL, 5.5 mmol) in CH_2Cl_2 (15 mL) at –60 °C. After 5 min, alcohol **14** (1.4 g, 5.0 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After 10 min, *N,N*-diisopropylethylamine (4.5 mL, 25 mmol) was added. After 15 min at –60 °C the mixture was allowed to warm to room temperature, then water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were washed successively with aqueous HCl (2 × 15 mL, 1 M), H_2O (15 mL), aqueous Na_2CO_3 (15 mL, 5%), and H_2O (20 mL), then dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting

with petrol–EtOAc (9:1) gave the aldehyde **15** (1.15 g, 83%) as an oil as a 5.5:1 *E*:*Z* mixture; R_f 0.5 [petrol–EtOAc (9:1)]; IR ν_{max}(film)/cm^{-1} 2930, 2855, 1705; ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 9.03 (1H, s), 5.57–5.50 (1H, m), 5.36–5.28 (1H, m), 3.61 (1H, dd, *J* 11.5, 4 Hz), 3.56 (1H, dd, *J* 11.5, 4 Hz), 3.17–3.10 (1H, m), 3.01–2.93 (1H, m), 2.65–2.58 (2H, m), 2.24–2.17 (1H, m), 2.13–2.02 (4H, m), 1.87–1.75 (2H, m), 1.68 (3H, dd, *J* 6, 1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 188.7, 128.9, 127.1, 57.7, 48.2, 37.0, 35.9, 30.1, 26.8, 26.7, 24.3, 18.0; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{20}OS_2{}^{35}Cl$ 279.0644; Found: 279.0646; LRMS *m/z* (ES) 281 (45%), 279 (100).

4-(Chloromethyl)-2,2-dimethoxyoct-6-enal **16**. Bis(trifluoroacetoxy)iodobenzene (3.00 g, 6.85 mmol) was added to aldehyde **15** (1.12 g, 4.04 mmol) in anhydrous methanol (5 mL) at room temperature. After 15 min, saturated aqueous sodium bicarbonate (5 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–Et_2O (9:1), gave the aldehyde **16** (580 mg, 62%) as an oil as a 5.5:1 *E*:*Z* mixture; R_f 0.3 [petrol–Et_2O (9:1)]; IR ν_{max}(film)/cm^{-1} 2945, 2840, 1750, 1440; ^{1}H NMR (400 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 9.46 (1H, s), 5.56–5.47 (1H, m), 5.34–5.25 (1H, m), 3.60–3.55 (2H, m), 3.31 (3H, s), 3.30 (3H, s), 2.17–2.05 (3H, m), 1.87–1.80 (1H, m), 1.75 (1H, dd, *J* 15, 5 Hz), 1.67 (3H, dd, *J* 6, 1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for the major *E* isomer) δ = 199.5, 128.7, 127.3, 102.1, 49.9, 49.7, 48.4, 35.6, 34.9, 32.6, 18.0; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{11}H_{20}O_3{}^{35}Cl$ 235.1101; Found: 235.1097; LRMS *m/z* (ES) 237 (35%), 235 (100).

4-(Chloromethyl)-2,2-dimethoxyoct-6-enal oxime **17**. Aldehyde **16** (100 mg, 0.43 mmol), hydroxylamine hydrochloride (0.04 g, 0.64 mmol), *N*,*N*-diisopropylethylamine (0.18 mL, 1.06 mmol) and $MgSO_4$ in toluene (4 mL) were heated at 60 °C. After 30 min, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (96:4), gave the oxime **17** (96 mg, 90%) as an oil as a mixture of *E* and *Z* alkene and oxime isomers; R_f 0.3 [CH_2Cl_2–MeOH (96:4)]; IR ν_{max}(film)/cm^{-1} 3340, 2935, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (1H, s), 7.31 (1H, s), 5.62–5.49 (1H, m), 5.37–5.29 (1H, m), 3.63–3.60 (2H, m), 3.28 (3H, s), 3.26 (3H, s), 2.19–2.10 (2H, m), 2.08 (1H, dd, *J* 15, 7.5 Hz), 1.95–1.88 (1H, m), 1.75 (1H, dd, *J* 15, 5 Hz), 1.68 (3H, dd, *J* 6, 1.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for the major isomer) δ = 151.0, 128.4, 127.6, 100.7, 49.3, 49.2, 48.6, 35.6, 35.5, 35.4, 18.0. HRMS and LRMS could not be obtained.

8,8-Dimethoxy-5-methyl-4-oxa-3-azatricyclo[4.3.1.0^{3,7}]decane **18.** The oxime **17** (*E*:*Z* 5.5:1) (100 mg, 0.43 mmol), *N*,*N*-diisopropylethylamine (0.18 mL, 1.07 mmol), hydroxylamine hydrochloride (40 mg, 0.64 mmol) and $MgSO_4$ (50 mg) in toluene (4 mL) were heated under reflux. After 16 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97:3), gave the cycloadduct **18** (14 mg, 15%) as an oil as a single stereoisomer; R_f 0.36 [CH_2Cl_2–MeOH (9.7:0.3)]; IR ν_{max}(film)/cm^{-1} 2950, 2900, 1460; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.10 (1H, q, *J* 6 Hz), 3.49 (1H, d, *J* 3.5 Hz), 3.37–3.01 (4H, m), 3.26 (3H, s), 2.97 (1H, dt, *J* 14.5, 3 Hz), 2.18 (1H, dd, *J* 9.5, 3.5 Hz), 1.96–1.89 (1H, m), 1.82–1.80 (1H, m), 1.68–1.65 (2H, m), 1.52 (1H, dd, *J* 13, 4 Hz), 1.21 (3H, d, *J* 6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 100.0, 85.6, 60.6, 60.3, 48.7, 47.8, 40.6, 39.0, 34.1, 22.8, 20.9; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{11}H_{20}NO_3$ 214.1438; Found: 214.1433; LRMS *m/z* (ES) 214 (100%), 182 (50).

2-(2-(Chloromethyl)hex-4-en-1-yl)-1,3-dithiane-2-carbaldehyde oxime **19**. Hydroxylamine hydrochloride (135 mg, 2.0 mmol) and sodium acetate (365 mg, 4.5 mmol) were added to aldehyde **15** (500 mg, 1.8 mmol) in dry methanol (25 mL) at room temperature. After 5 h, the solvent was evaporated. The residue was washed with CH_2Cl_2 and then concentrated to give the oxime **19** (527 mg, 100%) which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (1H, s), 5.62–5.50 (1H, m), 5.38–5.30 (1H, m), 3.67–3.60 (2H, m), 3.16–3.04 (2H, m), 2.73–2.66 (2H, m), 2.27–2.07 (5H, m), 1.94–1.83 (2H, m), 1.69 (3H, dd, *J* 6, 1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, peaks for the major isomer) δ = 153.2, 128.7, 127.4, 51.5, 48.9, 41.0, 36.2, 35.9, 27.3, 27.2, 24.8, 18.0; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{21}NOS_2{}^{35}Cl$ 294.0753; Found: 294.0746; LRMS *m/z* (ES) 296 (48%), 294 (100).

5'-Methyl-4'-oxa-3'-azaspiro-1,3-dithiane-2,8'-tricyclo[4.3.1.0^{3,7}]decane **20**. Oxime **19** (527 mg, 1.8 mmol), *N*,*N*-diisopropylethylamine (0.32 mL, 1.8 mmol) and $MgSO_4$ (100 mg) in toluene (15 mL) were heated under reflux. After 16 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97:3), gave the cycloadduct **20** (263 mg, 57%) as an oil as a single stereoisomer; R_f 0.3 [CH_2Cl_2–MeOH (97:3)]; IR ν_{max}(film)/cm^{-1} 2925, 2900, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.19 (1H, q, *J* 6 Hz), 3.87 (1H, d, *J* 3.5 Hz), 3.46 (1H, dd, *J* 14.5, 2 Hz), 3.20–3.13 (1H, m), 3.09–3.00 (2H, m), 2.86–2.76 (2H, m), 2.42 (1H, dd, *J* 9.5, 3.5 Hz), 2.13–2.00 (3H, m), 1.91–1.88 (2H, m), 1.79–1.77 (1H, m), 1.55 (1H, dd, *J* 13.5, 4.5 Hz), 1.26 (3H, d, *J* 6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 86.6, 61.8, 59.4, 44.7, 44.5, 41.9, 33.2, 27.5, 27.2, 24.7, 23.0, 21.1; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{20}NOS_2$ 258.0986; Found: 258.0994; LRMS *m/z* (ES) 258 (100%).

5-Methyl-4-oxa-3-azatricyclo[4.3.1.0^{3,7}]decan-8-one **21**. Bis(trifluoroacetoxy)iodobenzene (500 mg, 1.16 mmol), and trifluoroacetic acid (10 equiv.) was added to dithiane **20** (300

mg, 1.16 mmol) in acetonitrile/water (1:1) (44 mL) at room temperature. Additional bis(trifluoroacetoxy)iodobenzene (1.9 g, 4.4 mmol) was added over a 1 h period, and the mixture was stirred for 2.5 h, before being neutralised with saturated aqueous sodium bicarbonate (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97:3), gave the ketone **21** (155 mg, 80%) as needles, m.p. 62–63.5 °C; R_f 0.32 [CH_2Cl_2–MeOH (97:3)]; IR ν_{max}(film)/cm^{-1} 2965, 1730, 1450; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.26 (1H, q, *J* 6 Hz), 3.62 (1H, d, *J* 3.5 Hz), 3.51 (1H, dd, *J* 14.5, 2.5 Hz), 3.30–3.20 (1H, m), 2.45 (1H, dd, *J* 9, 3.5 Hz), 2.25–2.23 (2H, m), 2.20–2.18 (1H, m), 2.03–1.96 (1H, m), 1.79 (1H, dd, *J* 13.5, 4.5 Hz), 1.21 (3H, d, *J* 6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.1, 85.6, 68.9, 61.5, 44.8, 44.5, 34.1, 23.3, 20.5; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_9H_{14}NO_2$ 168.1019; Found: 168.1020; LRMS *m/z* (ES) 168 (100%).

7-[(1RS)-1-Hydroxyethyl]-2-[2-(1H-indol-3-yl)acetyl]-2-azabicyclo[2.2.2]octan-6-one **23**. Activated Zn powder (168 mg, 2.6 mmol) [washed with freshly prepared aqueous HCl (1.0 M), EtOH, then Et_2O] was added to the cycloadduct **21** (85 mg, 0.51 mmol) in AcOH–MeOH (5 mL, 4:1) at room temperature. After 4 h, the mixture was filtered through Celite® and the solvent was evaporated. The residue was dissolved in MeOH (5 mL) and poured onto aqueous sodium hydroxide (5 mL, 2 M). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the organic layers were dried ($MgSO_4$) and evaporated to give the crude aminoalcohol **22** (86 mg, 100%). Indole acetic acid (89 mg, 0.51 mmol) and EDCI (97 mg, 0.51 mmol) were added to the crude amino alcohol (86 mg, 0.51 mmol) in CH_2Cl_2 (6 mL) at room temperature. After 1.5 h, the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and were washed with aqueous HCl (1.5 mL, 0.01 M) and with saturated aqueous K_2CO_3 (1.5 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (9:1), gave the amide **23** (165 mg, 100%) as a foam; R_f 0.39 [CH_2Cl_2–MeOH (9:1)]; IR ν_{max}(film)/cm^{-1} 3320, 2970, 1730, 1625, 1460; ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers 64:36, data for major rotamer) δ = 8.50 (1H, br s), 7.59 (1H, d, *J* 7.5 Hz), 7.38 (1H, d, *J* 7.5 Hz), 7.24–7.11 (3H, m), 5.01 (1H, d, *J* 1.5 Hz), 3.96–3.93 (2H, m), 3.59–3.52 (2H, m), 3.32–3.28 (1H, m), 2.49–2.33 (3H, m), 1.89–1.81 (2H, m), 1.16 (3H, d, *J* 6 Hz), 1.07–1.03 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$, as a mixture of rotamers, data for major rotamer) δ = 206.6, 173.3, 136.1, 127.1, 122.9, 122.3, 119.8, 118.3, 111.5, 107.7, 68.7, 54.7, 50.3, 43.7, 42.5, 30.7, 28.4, 27.7, 19.6; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{22}N_2O_3$ 327.1703; Found: 327.1703; LRMS *m/z* (ES) 327 (100%).

7-[(1RS)-1-Hydroxyethyl]-6,6-dimethoxy-2-azabicyclo [2.2.2]octan-2-yl]-2-(1H-indol-3-yl)ethanone **24**. *p*-Toluenesulfonic acid (7.5 mg, 0.04 mmol) was added to crude **23** (100 mg, 0.31 mmol), trimethylorthoformate (1.21 mL, 11 mmol) and MeOH (1.2 mL) at room temperature. After 7 h, saturated aqueous $NaHCO_3$ (1.5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97:3), gave amide **24** (98 mg, 85%) as a foam; R_f 0.35 [CH_2Cl_2–MeOH (95:5)]; IR ν_{max}(film)/cm^{-1} 3320, 2970, 1625, 1460; ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers ~9:1, data for major rotamer) δ = 8.33 (1H, br s), 7.61 (1H, d, *J* 8 Hz), 7.38 (1H, d, *J* 8 Hz), 7.23–7.15 (3H, m, ArH), 4.78 (1H, d, *J* 1 Hz), 4.17–4.10 (1H, m), 3.83–3.80 (2H, m), 3.53–3.49 (1H, m), 3.36 (1H, dd, *J* 10, 3 Hz), 3.23 (3H, s), 3.14 (3H, s), 2.09–2.05 (1H, m), 1.96–1.88 (1H, m), 1.76–1.69 (3H, m), 1.15 (3H, d, *J* 6 Hz), 0.84–0.79 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.7, 136.1, 127.2, 122.7, 122.2, 119.6, 118.5, 111.3, 108.6, 101.4, 69.6, 49.2, 48.6, 48.1, 47.1, 40.9, 37.2, 30.4, 28.7, 27.6, 19.6; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{21}H_{28}N_2O_4$ 373.2122; Found: 373.2122; LRMS *m/z* (ES) 373 (100%).

2-[2-(1H-Indol-3-yl)acetyl]-7,7-dimethoxy-2-azabicyclo[2.2.2]octan-6-yl]ethyl acetate **25**.[7b] Acetyl chloride (0.02 mL, 0.3 mmol) and pyridine (0.024 mL, 0.3 mmol) were added to the alcohol **24** (100 mg, 0.28 mmol) in CH_2Cl_2 (6 mL) at room temperature. After 30 min, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (97.5:2.5), gave the ester **25** (98 mg, 87%) as a foam; R_f 0.26 CH_2Cl_2–MeOH (97.5:2.5)]; IR ν_{max}(film)/cm^{-1} 3280, 2940, 1730, 1640, 1450; ^{1}H NMR (400 MHz, $CDCl_3$, as a mixture of rotamers ~8:1, data for major rotamer) δ = 8.30 (1H, br s), 7.57 (1H, dd, *J* 8, 1 Hz), 7.36 (1H, dd, *J* 8, 1 Hz), 7.23–7.22 (1H, m), 7.19 (1H, ddd, *J* 8, 7, 1 Hz), 7.13 (1H, ddd, *J* 8, 7, 1 Hz), 4.91 (1H, d, *J* 1.5 Hz), 4.52 (1H, dq, *J* 10.5, 6 Hz), 3.77–3.74 (2H, m), 3.39 (1H, dt, *J* 10, 2.5 Hz), 3.29 (1H, dt, *J* 10, 2.5 Hz), 3.26 (3H, s), 3.20 (3H, s), 2.29–2.20 (1H, m), 2.13 (3H, s), 2.05–2.02 (1H, m), 1.78 (1H, dt, *J* 13.5, 2.5 Hz), 1.74–1.69 (1H, m), 1.66 (1H, dt, *J* 13.5, 2.5 Hz), 1.22 (3H, d, *J* 6 Hz), 0.92 (1H, ddt, 13.5, 5.5, 2.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, as a mixture of rotamers, data for major rotamer) δ = 171.2, 171.1, 136.1, 127.4, 122.9, 121.9, 119.3, 118.4, 111.2, 108.9, 101.7, 71.4, 49.0, 48.9, 48.1, 45.8, 38.1, 36.9, 30.7, 28.2, 27.5, 21.5, 17.8; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{23}H_{31}N_2O_5$ 415.2227; Found: 415.2227; LRMS *m/z* (ES) 415 (100%). Data match the literature.[7b]

Conclusions

We have demonstrated that cascade chemistry involving condensation of hydroxylamine and an aldehyde to give an oxime, cyclization on to an alkyl halide to give a nitrone, and intramolecular dipolar cycloaddition is successful in which the branch point for the alkyl halide and alkene tethers is at C-4. This leads to bridged compounds with the

azabicyclo[2.2.2]octane framework and thereby extends the methodology described previously (Scheme 1) to a new class of ring system. In addition, the chemistry has been applied to a formal synthesis of the alkaloid 19-hydroxyibogamine. The cascade sequence has potential for the formation of a variety of *iboga* alkaloid frameworks.

Conflicts of interest

There are no conflicts of interest to declare.

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Notes and references

1 K. R. Alper, *Alkaloids: Chem. Biol.* **2001**, *56*, 1.
2 P. Popik, R. T. Layer and P. Skolnick, *Pharmacol. Rev.*, 1995, **47**, 235.
3 Y. Terada, M. Kitajima, F. Taguchi, H. Takayama, S. Horie and T. Watanabe, *J. Nat. Prod.*, 2014, **77**, 1831.
4 (a) J. E. Sears and D. L. Boger, *Acc. Chem. Res.*, 2015, **48**, 653. (b) Y. Zhang, Y. Xue, G. Li, H. Yuan and T. Luo, *Chem. Sci.*, 2016, **7**, 5530.
5 For reviews, see (a) M. Faisal, D. Shahzad, A. Saeed, B. Lal, S. Saeed, F. A. Larik, P. A. Channar, P. A. Mahesar and J. Mahar, *Tetrahedron: Asym.*, 2017, **28**, 1445. (b) C. Lavaud and G. Massiot, *Progress in the Chemistry of Organic Natural Products*, Eds. Kinghorn, A. D.; Falk, H.; Gibbons, S.; Kobayashi, J.; Springer, Switzerland, 2017, **105**, 89. (c) G. K. Jana, S. Paul and S. Sinha, *Org. Prep. Proced. Int.*, 2011, **43**, 541.
6 For some recent references, see ref. 4b and (a) G. K. Jana and S. Sinha, *Tetrahedron*, 2012, **68**, 7155. (b) A. C. Kruegel, S. Rakshit, X. Li and D. Sames, *J. Org. Chem.*, 2015, **80**, 2062. (c) G. Zhao, X. Xie, H. Sun, Z. Yuan, Z. Zhong, S. Tang and X. She, *Org. Lett.*, 2016, **18**, 2447.
7 (a) S. Höck, F. Koch and H. J. Borschberg, *Tetrahedron: Asym.*, 2004, **15**, 1801. (b) S. Höck and H. J. Borschberg, *Helv. Chim. Acta*, 2006, **89**, 542.
8 H. Achenbach, B. Raffelsberger and G.-U. Brillinger, *Phytochem.*, 1980, **19**, 2185.
9 (a) D.-B. Zhang, D.-G. Yu, M. Sun, X.-X. Zhu, X.-J. Yao, S.-Y. Zhou, J.-J. Chen and K. Gao, *J. Nat. Prod.*, 2015, **78**, 1253. (b) C.-E. Nge, K.-W. Chong, N. F. Thomas, S.-H. Lim, Y.-Y. Low and T.-S. Kam, *J. Nat. Prod.*, 2016, **79**, 1388. (c) C.-E. Nge, K.-S. Sim, S.-H. Lim, N. F. Thomas, Y.-Y. Low and T.-S. Kam *J. Nat. Prod.*, 2016, **79**, 2709.
10 (a) I. Coldham, A. J. M. Burrell, L. E. White, H. Adams and N. Oram, *Angew. Chem. Int. Ed.*, 2007, **46**, 6159. (b) A. J. M. Burrell, I. Coldham, L. Watson, N. Oram, C. D. Pilgram and N. G. Martin, *J. Org. Chem.*, 2009, **74**, 2290.
11 (a) A. J. M. Burrell, I. Coldham and N. Oram, *Org. Lett.*, 2009, **11**, 1515. (b) A. J. M. Burrell, L. Watson, N. G. Martin, N. Oram and I. Coldham, *Org. Biomol. Chem.*, 2010, **8**, 4530. (c) I. Coldham, L. Watson, H. Adams and N. G. Martin, *J. Org. Chem.*, 2011, **76**, 2360. (d) I. Coldham, A. J. M. Burrell, L. Watson, N. Oram and N. G. Martin, *Heterocycles*, 2012, **84**, 597. (e) I. Coldham, A. J. M. Burrell, H. D. S. Guerrand, L. Watson, N. G. Martin, N. Oram, *Beilstein J. Org. Chem.* 2012, **8**, 107.
12 (a) I. Coldham, S. Jana, L. Watson and N. G. Martin, *Org. Biomol. Chem.*, 2009, **7**, 1674. (b) H. D. S. Guerrand, H. Adams and I. Coldham, *Org. Biomol. Chem.*, 2011, **9**, 7921. (c) R. C. Furnival, R. Saruengkhanphasit, H. E. Holberry, J. R. Shewring, H. D. S. Guerrand, H. Adams and I. Coldham, *Org. Biomol. Chem*., 2016, **14**, 10953.
13 I. Coldham, A. J. M. Burrell, H. D. S. Guerrand and N. Oram, *Org. Lett.*, 2011, **13**, 1267.
14 R. Saruengkhanphasit, D. Collier and I. Coldham, *J. Org. Chem.*, 2017, **82**, 6489.
15 For selected reports of other cascade cyclization then dipolar cycloaddition reactions, see (a) H. A. Dondas, R. Grigg, M. Hadjisoteriou, J. Markandu, P. Kennewell and M. Thornton-Pett, *Tetrahedron*, 2001, **57**, 1119. (b) M. S. Karatholuvhu, A. Sinclair, A. F. Newton, M.-L. Alcaraz, R. A. Stockman and P. L. Fuchs, *J. Am. Chem. Soc.*, 2006, **128**, 12656. (c) H. Yuan, J. Gong and Z. Yang, *Org. Lett.*, 2016, **18**, 5500. (d) R. Yamada, Y. Adachi, S. Yokoshima and T. Fukuyama, *Angew. Chem. Int. Ed.*, 2016, **55**, 6067. (e) H.-J. Zhang, L. Hu, Z. Ma, R. Li, Z. Zhang, C. Tao, B. Cheng, Y. Li, H. Wang and H. Zhai, *Angew. Chem. Int. Ed.*, 2016, **55**, 11638. (f) J. Boudreault, F. Lévesque and G. Bélanger, *J. Org. Chem.*, 2016, **81**, 9247. (g) C. Hauduc and G. Bélanger, *J. Org. Chem.*, 2017, **82**, 4703. (h) P. Boissarie and G. Bélanger, *Org. Lett.*, 2017, **19**, 3739. (i) S. Sugita, N. Takeda, N. Tohnai, M. Miyata, O. Miyata and M. Ueda, *Angew. Chem. Int. Ed.*, 2017, **56**, 2469. (j) J. M. E. Hughes and J. L. Gleason, *Angew. Chem. Int. Ed.*, 2017, **56**, 10830. (k) J. M. E. Hughes and J. L. Gleason, *Tetrahedron*, 2018, **74**, 759.
16 R. Berthold, *Chem. Ber.*, 1957, **90**, 793.
17 For alkylation of lithiated 2,2-dimethoxyacetonitrile, see K. Utimoto, Y. Wakabayashi, Y. Shishiyama, M. Inoue and H. Nozaki, *Tetrahedron Lett.*, 1981, **22**, 4279.
18 (a) I. Coldham, K. M. Crapnell, J.-C. Fernàndez, J. D. Moseley and R. Rabot, *J. Org. Chem.*, 2002, **67**, 6181. (b) R. Pathak, B. C. Dobson, N. Ghosh, K. A. Ageel, M. R. Alshawish, R. Saruengkhanphasit and I. Coldham, *Org. Biomol. Chem.*, 2015, **13**, 3331.