Synthesis of Brombyins II and III, Cyclostachines A and B, and Cyclopiperstachine, Plant-Derived Octahydronaphthalenes

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Dedicated to Prof. Gerry Pattenden on the occasion of his 70th birthday.

Abstract: In this paper we present a study into the direct formation of five plant-derived natural products via intramolecular Diels–Alder cycloaddition of a series of 1,7,9-decatriene precursors. Methods for the preparation of the trienes are also discussed.

Key words: natural products, Diels–Alder, diene synthesis

Brombyins I–IV and VI (**1**–**5**, Figure 1) have been isolated from *Brombya platynema* F. Muell, a tree found in the wet tropics of Queensland, Australia.[1,2] All of these compounds appear to occur naturally as racemates and this has led to the suggestion that the octahydronaphthalene ring system may have been formed from a (*E*,*E*,*E*)-triene precursor **8** (X = Me) via a spontaneous intramolecular Diels–Alder cycloaddition.[2] Such a process would be expected to lead directly to brombyin II (**2**, *exo*-cycloadduct) and brombyin III (**3**, *endo*-cycloadduct), the remaining structures possibly being formed via autoxidation of **3**.[3] Taking into account the relative amounts of compounds **1**–**5** isolated, it has been proposed that the initial cycloadducts (**2** and **3**) are probably formed in roughly equal amounts.[2] If this is true, it would suggest that brombyins II and III are being produced via a thermal Diels–Alder cycloaddition in a relatively nonpolar environment as a Brønsted acid catalysed process or an aqueous environment would be expected to favour formation of the *endo*-adduct **3**.

A series of related octahydronapthalene natural products, cyclostachines A and B (**6a** and **7a**), and cyclopiperstachine (**7b**) has also been reported.[4] These were isolated from the stem of *Piper trichostachyon* and again were obtained as racemates, suggesting that they may also have arisen via a nonenzymic intramolecular Diels–Alder reaction. In this case the *exo*-adducts **7** seem to be most abundant as **6a** and **7a** were isolated in a 1:5 ratio, and only the *exo*-isomer **7b** was reported. Piperstachine **8** (X = $NHCH_2CHMe_2$) was also isolated from the same source[5] and it was established that this undergoes cycloaddition on heating (xylene, reflux) to give a 33% yield of cyclopiperstachine **7b**, but no details of the *exo*/*endo* selectivity were reported.[4] As far as we are aware trienes **8** (X = Me or 1-pyrrolidinyl) have so far not been isolated from natural sources and their Diels–Alder chemistry has not been reported.

Our research group has had a longstanding interest in the use of intramolecular Diels–Alder reactions to generate octahydronaphthalene ring systems.[6] We were intrigued by the above observations as we had previously found that the thermal cycloaddition of a range of 1,7,9-decatrienes **9** (X = alkyl, OR, NR_2) in nonpolar media (toluene) required temperatures above 100 °C.[6,7] Although the electron-donating 3,4-methylenedioxyphenyl substituent should render diene **8** more reactive, it seemed unlikely that this would be enough to result in reasonable rates of

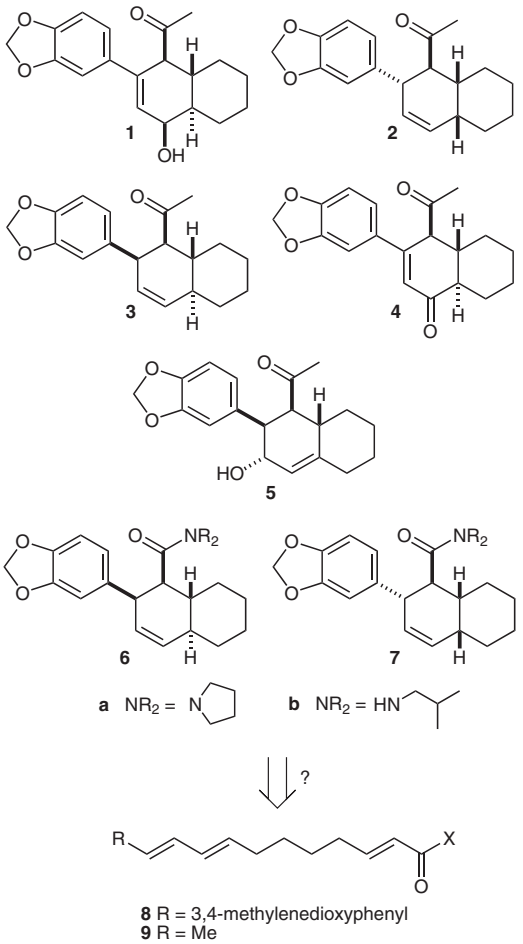

Figure 1

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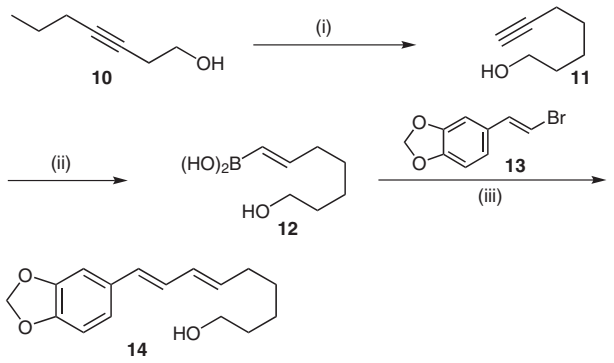
reaction at ambient temperature without additional catalysis. This makes the biogenesis of these natural products puzzling and so we decided to investigate the synthesis and cycloaddition chemistry of trienes **8**.

For the purposes of this study we first opted to prepare diene **14** as this could serve as common intermediate for all the Diels–Alder substrates. Two approaches to this compound were investigated.



Scheme 1 *Reagents and conditions*: (i) 1,3-diaminopropane, Li, KO*t*-Bu (80%); (ii) catechol borane; H_2O (69%); (iii) $Pd(PPh_3)_4$, $Ba(OH)_2$, THF, MeOH (50%).

The first (Scheme 1) started with commercially available 3-heptyn-1-ol (**10**). This was subjected to an 'alkyne-zipper' reaction[8] to provide the terminal alkyne **11**, which was subsequently converted into boronic acid **12** via hydroboration with catechol borane. Suzuki coupling with bromide **13** then provided the target diene **14**.[9] This sequence proceeded in adequate overall yield and required no protecting-group chemistry, but it was difficult to purify the product **14** due to the presence of small amounts of homocoupled diene byproducts generated in the Suzuki reaction. This limited the quantities of **14** that could be produced and so we also considered an alternative approach.

In this context, our attention was drawn to a report that treatment of a mixture of cyclohexanone **15** and aldehyde **16** with 1,3-propanediol and boron trifluoride led to diene **20** in ca. 14% yield.[10] This transformation is thought to proceed via an aldol reaction followed by Grob fragmentation as outlined in Scheme 2. Clearly reduction of ester **20** would provide access to diene intermediate **14** and so we decided to investigate this approach in more detail.

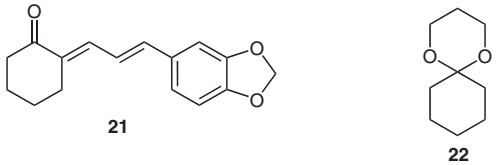
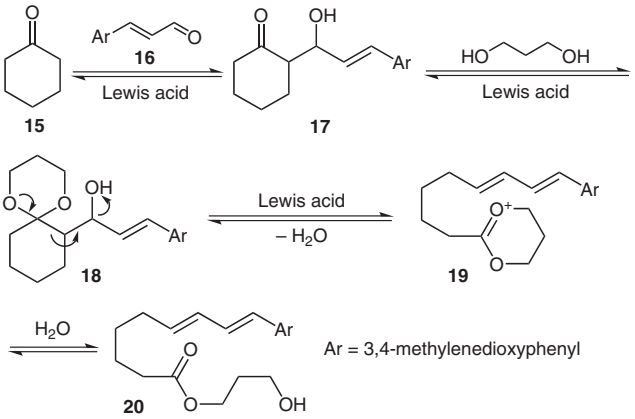


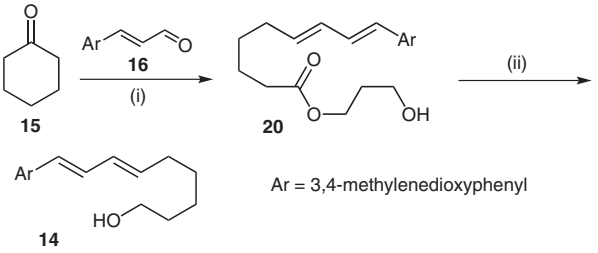
Figure 2

A known problem with this aldol–Grob fragmentation is competing aldol condensation. This is particularly significant with aldehyde **16**, presumably because the electron-rich aryl group assists the dehydration of intermediate **17**. Preliminary studies in our group confirmed that the aldol condensation product **21** (Figure 2) was a major byproduct in the reaction and that it was not converted into diene **20** under the reaction conditions.



Scheme 2

In an effort to improve on this we investigated replacement of cyclohexanone with acetal **22**. Although this led to diene **20**, overall yields were not significantly improved. After extensive investigation we found the yield of the desired diene could be increased to 35% simply by modifying the workup of the original procedure.[10,11] Although we have been unable to improve this further, this adjustment did allow rapid access to large quantities of target alcohol **14** (Scheme 3).



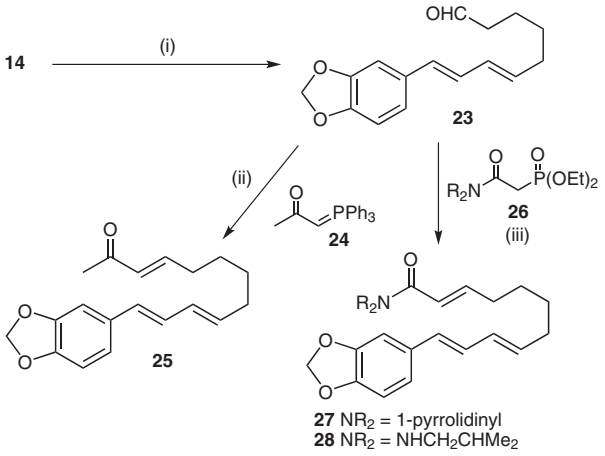
Scheme 3 *Reagents and conditions*: (i) 1,3-propanediol, $BF_3 \cdot OEt_2$ (35%); (ii) DIBAL-H, PhMe, –78 °C (68%).

With alcohol **14** in hand, conversion to the Diels–Alder precursors simply required oxidation to the corresponding aldehyde **23**, followed by olefination reaction to install the requisite dieneophile (Scheme 4).

Attempted oxidation of alcohol **14** with PCC led to oxidative cleavage of the diene, giving aldehyde **16** as the major product. Fortunately this could be avoided by using a Swern oxidation which delivered the desired aldehyde **23** in high yield. Synthesis of the brombyin precursor **25** was then achieved by reacting aldehyde **23** with ylid **24** at 60 °C in toluene. At this temperature the Wittig reaction was relatively slow, but these conditions were chosen so as to avoid Diels–Alder cycloaddition of the product **25** as we were keen to study this process in isolation. If re-

quired, the Wittig–Diels–Alder sequence could be carried out in one pot simply by heating the mixture at higher temperatures.

For preparation of Diels–Alder precursors **27** and **28**, we found it advantageous to use a Horner–Wadsworth–Emmons olefination as the corresponding Wittig reaction gave low overall yields. The resulting dienes **27** and **28** proved to be unstable to chromatography on silica gel, rapidly degrading to give a mixture of compounds of which the major component was again identified as aldehyde **16**. Interestingly, the corresponding oxidative cleavage of 1-phenylbutadiene on silica gel in the presence of oxygen is known to be promoted by light and has also been reported to occur slowly in the dark (25% conversion after 72 h).[12] A similar process looks to be occurring here, but with dienes **27** and **28** the decomposition is rapid (minutes) and is not hampered by attempts to exclude light or oxygen. It is unlikely that this is simply a feature of the electron-rich diene fragment, as **25** could be purified by chromatography on silica gel without significant decomposition. Fortunately the Horner–Wadsworth–Emmons olefination generated **27** and piperstachine **28** with sufficient purity for the subsequent Diels–Alder studies.



Scheme 4 Reagents and conditions: (i) $(COCl)_2$, DMSO, Et_3N (98%); (ii) PhMe, 60 °C (57%); (iii) NaH, PhMe, 60 °C (**27**: 76%, **28**: 59%).

We first investigated the Diels–Alder chemistry of compound **25** (Table 1). It was found that reaction in toluene required heating at 165 °C for 14 hours to drive the reaction to completion. Under these conditions brombyin II (**2**, *exo*-cycloadduct) and brombyin III (**3**, *endo*-cycloadduct) were obtained as a 35:65 mixture. Comparison of this result with that reported for closely related substrates (**9**, X = alkyl)[6] suggests that the electron-rich aryl group results in slightly faster reaction and slightly increased *endo* selectivity. This is fully consistent with the reaction proceeding via an asynchronous intramolecular Diels–Alder cycloaddition.[13]

The corresponding reaction in a polar protic organic solvent (methanol) was much faster, proceeding to completion in 15 hours at 50 °C, and resulted in increased *endo* selectivity. Finally, reaction in water in the presence of sodium dodecylsulfate (SDS)[14,15] gave similar rates of reaction to methanol and again led to high *endo* selectivity. Again, these latter two results are broadly consistent with what would be expected for a Diels–Alder cycloaddition involving an α,β-unsaturated ketone dienophile activated by a polar H-bonding solvent.[16]

Table 1 Intramolecular Diels–Alder Cyclisation of **25**

25 ⟶ *exo*-**2** + *endo*-**3**

Solvent	Temp (°C)	Time (h)	Yield (%)	*exo*:*endo*[b]
PhMe	165	14	86	35:65
MeOH	50	15	67	10:90
H_2O–SDS[a]	40	72	60	5:95

[a] SDS = sodium dodecylsulfate.
[b] Determined by ^1H NMR analysis of crude reaction mixture.

Cycloaddition of trienes **27** and **28** could again be achieved by heating in toluene at 165 °C. As expected these substrates were less reactive, requiring 3 days for the reaction to reach completion. In both cases the *exo*-cycloadducts [cyclostachine B (**7a**) and cyclopiperstachine (**7b**), respectively][17] were favoured (Table 2). Again these results mirror our findings with related trienes (**9**, X = NR_2) which also exhibited *exo* selectivity.[6]

Table 2 Intramolecular Diels–Alder Cyclisation of **27** and **28**

27 or **28** ⟶ (PhMe, 165 °C) *endo*-**6** + *exo*-**7**

Substrate	Time (h)	Yield (%)	*endo*:*exo*[a]
27	72	45	13:87
28	72	55	29:71

[a] Determined by ^1H NMR analysis of crude reaction mixture.

Attempts to promote cycloaddition of trienes **27** and **28** in polar protic media at, or slightly above ambient temperature, were unsuccessful. This is perhaps not surprising given the lower reactivity of the α,β-unsaturated amide dienophile in these structures.

These results confirm that if brombyins II and III (**2** and **3**) are being formed naturally via Diels–Alder cycloaddition of triene **25**, the product distribution best fits with a reaction occurring in a nonpolar environment, at temperatures significantly above ambient. This is not impossible given that these compounds were isolated from a tropical plant species, but at least two other explanations could also account for this product distribution.

They could be artefacts of the isolation procedure (sequential Soxhlet extraction with petrol ether, dichloromethane, and methanol).[1,2] However, this seems unlikely as we have found that both brombyin II and III (**2** and **3**) are stable to storage at ambient temperatures in air

for long periods (weeks), and to heating (50 °C) in deuterobenzene under an oxygen atmosphere for several days. Given the co-isolation of brombyins I (**1**), IV (**4**), and V (**5**) this would seem to rule out the possibility that they are all generated during isolation, unless the latter compounds arise via a different pathway.

It could also be that they are simply formed by Diels–Alder cycloaddition of triene **25** in a polar protic medium at ambient temperatures, and that the *endo*-diastereoisomer [brombyin III (**3**)] is selectively degraded. The isolation of brombyins I (**1**), IV (**4**), and V (**5**) would support this latter hypothesis as they are most likely derived from brombyin III (**3**).

The relative amounts of cyclostachines A and B (**6a** and **7a**)[18] and cyclopiperstachine (**7b**) isolated from *Piper trichostachyon* also fit best with product ratios arising from a thermal Diels–Alder reaction in a nonpolar medium. In this instance it is difficult to envisage how the temperatures required could be achieved naturally, although this possibility cannot be completely excluded. It is also very unlikely that these are artifacts of isolation (cold percolation with hexane) and so it seems most probable that these natural products are not derived directly from Diels–Alder cycloaddition of trienes **27** and **28**.

Acknowledgment

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(11) A solution of aldehyde **16** (4.00 g, 22.7 mmol) in anhyd THF (100 mL) was placed under an argon atmosphere and cooled to 0 °C. $BF_3{\cdot}OEt_2$ (21.0 mL, 162 mmol) was added dropwise and the mixture stirred for 10 min. A solution of cyclohexanone (2.40 mL, 22.7 mmol) in anhyd THF (50 mL) was then added over 20 min. The mixture was then allowed to warm to r.t. and stirred for a further 30 min. Propan-1,3-diol (8.60 mL, 119 mmol) was then added and the mixture stirred for 12 h before being quenched by pouring onto sat. aq Na_2CO_3 (250 mL). The aqueous layer was extracted with Et_2O (3 × 150 mL), and the combined organics were washed sequentially with sat. aq Na_2CO_3 (2 × 150 mL) and brine (2 × 150 mL). The organic phase was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (2:1 increasing to 1:1 PE–EtOAc) to give diene **20** (2.64 g, 7.95 mmol, 35%) as a pale yellow oil. R_f = 0.16 (2:1 PE–EtOAc). IR (neat): ν_{max} = 3435, 2930, 1731 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.92 (1 H, d, *J* = 1.5 Hz, ArH), 6.80 (1 H, dd, *J* = 8.0, 1.5 Hz, ArH), 6.74 (1 H, d, *J* = 8.0 Hz, ArH), 6.58 (1 H, dd, *J* = 15.5, 10.5 Hz, C*H*=CHAr), 6.36 (1 H, d, *J* = 15.5 Hz, C=CHAr), 6.17 (1 H, dd, *J* = 15.5, 10.5 Hz, C*H*=CHCH_2), 5.94 (2 H, s, OCH_2O), 5.75 (1 H, dt, *J* = 15.5, 7.0 Hz, C=C*H*CH_2), 4.24 (2 H, t, *J* = 6.0 Hz, CH_2OCO), 3.69 (2 H, t, *J* = 6.0 Hz, CH_2OH), 2.34 (2 H, t, *J* = 7.5 Hz, CH_2CO), 2.16 (2 H, dt, *J* = 7.0, 7.0 Hz, CH_2CH=C), 1.87 (2 H, tt, *J* = 6.0, 6.0 Hz, CH_2CH_2OH), 1.66 (2 H, tt, *J* = 7.5, 7.5 Hz, CH_2), 1.46 (2 H, tt, *J* = 7.5, 7.0 Hz, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3 (CO), 148.1 (C), 147.0 (C), 134.3 (CH), 132.2 (C), 131.0 (CH), 130.0 (CH), 127.7 (CH), 121.0 (CH), 108.4 (CH), 105.4 (CH), 101.1 (CH_2), 61.3 (CH_2), 59.3, (CH_2), 34.2 (CH_2), 32.5 (CH_2), 31.8 (CH_2), 28.9 (CH_2), 24.6 (CH_2). MS: (ES$^+$): *m/z* (%) = 355 (100) [M + Na$^+$], 333 (35) [M + H$^+$]. MS (ES$^+$): *m/z* calcd for $C_{19}H_{25}O_5^+$: 333.1697; found: 333.1704 [M + H$^+$].
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(17) **Method 1 (PhMe, 165 °C)**
Triene **25** (330 mg, 1.11 mmol) was dissolved in anhyd toluene (10 mL), the solution degassed (freeze–thaw) and placed in a sealed tube under argon. The solution was heated at 165 °C for 14 h then allowed to cool to r.t. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel (95:5 PE–EtOAc) to give brombyin II(**2**) (100 mg, 0.33 mmol, 30%) and brombyin III (**3**) (185 mg, 0.62 mmol 56%) as colourless low-melting solids.
Method 2 (MeOH, 50 °C)
Triene **25** (39.0 mg, 0.13 mmol) was dissolved in MeOH (2.5 mL) and placed in a sealed tube under argon. The solution was heated at 50 °C for 15 h. The solvent was removed under reduced pressure and the residue passed through a plug of silica gel (9:1 PE–EtOAc) to give a 90:10 mixture of brombyin III (**3**) and brombyin II (**2**) (26 mg, 0.09 mmol, 67%).
Method 2 (H_2O–SDS, 40 °C)
SDS (0.50 g, 1.74 mmol) was dissolved in H_2O (10 mL) and stirred for 5 min. Triene **25** (30 mg, 0.10 mmol) was added and the mixture stirred vigorously at 40 °C for 72 h. The mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was passed through a plug of silica gel (9:1 PE–EtOAc) to provide a 95:5 mixture of brombyin III (**3**) and brombyin II (**2**) (18 mg, 0.06 mmol, 60%).
Brombyin II (**2**):[1] R_f = 0.39 (9:1 PE–EtOAc). IR (neat): ν_{max} = 2925, 1705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.71 (1 H, d, *J* = 8.0 Hz, ArH), 6.64 (1 H, d, *J* = 1.5 Hz, ArH), 6.57 (1 H, dd, *J* = 8.0, 1.5 Hz, ArH), 5.93 (2 H, s, OCH_2O), 5.80 (1 H, ddd, *J* = 10.0, 5.0, 2.5 Hz, CH=C*H*CHAr), 5.49 (1 H, dt, *J* = 10.0, 1.5 Hz, CH=C*H*CHCH$_2$), 3.54 (1 H, ddd, *J* = 10.0, 5.0, 2.0 Hz, CHAr), 3.00 (1 H, dd, *J* = 11.5, 10.5 Hz, CHCO), 2.23 (1 H, m, CH), 2.14 (1 H, m, CH), 1.88 (3 H, s, CH_3), 1.83–0.83 (8 H, m, 4 × CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.0 (CO), 147.9 (C), 146.4 (C), 138.0 (CH), 132.7 (*C*), 128.8 (CH), 121.0 (CH), 108.4 (CH), 108.1 (CH), 101.1 (CH_2), 54.4 (CH), 47.9 (CH), 36.9 (CH), 36.3, (CH), 33.0 (CH_2), 30.2 (CH_2), 28.7 (CH_2), 26.3 (CH_2), 21.4 (CH_3). MS (ES^+): *m/z* (%) = 321 (50) [M + Na^+], 299 (100) [M + H^+]. MS (ES^+): *m/z* calcd for $C_{19}H_{23}O_3^+$: 299.1642; found: 299.1664 [M + H^+].
Brombyin III (**3**):[2] R_f = 0.24 (9:1 PE–EtOAc). IR (neat): ν_{max} = 2920, 1713 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.72 (1 H, d, *J* = 8.0 Hz, ArH), 6.66 (1 H, d, *J* = 1.5 Hz, ArH), 6.56 (1 H, dd, *J* = 8.0, 1.5 Hz, ArH), 5.94 (2 H, s, OCH_2O), 5.68 (1 H, br d, *J* = 10.0 Hz, CH=C*H*CHCH$_2$), 5.58 (1 H, ddd, *J* = 10.0, 4.5, 2.5 Hz, CH=C*H*CHAr), 3.69 (1 H, ddd, *J* = 6.5, 4.5, 2.5 Hz, CHAr), 2.85 (1 H, dd, *J* = 12.0, 6.5 Hz, CHCO), 1.81 (3 H, s, CH_3), 1.89–0.70 (10 H, m, 2 × CH, 4 × CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.8 (CO), 147.6 (C), 146.7 (C), 134.3 (CH), 132.8 (C), 127.4 (CH), 122.7 (CH), 109.9 (CH), 108.1 (CH), 101.1 (CH_2), 58.9 (CH), 43.9 (CH), 42.0 (CH), 36.4 (CH), 33.2 (CH_2), 30.4 (CH_2), 30.3 (CH_3), 26.8 (CH_2), 26.5 (CH_2). MS (ES^+): *m/z* (%) = 321 (70) [M + Na^+], 299 (100) [M + H^+]. MS (ES^+): *m/z* calcd for $C_{19}H_{23}O_3^+$: 299.1642; found: 299.1655 [M + H^+].

(18) Cyclostachine B (**7a**):[4] R_f = 0.25 (1:1 PE–EtOAc). IR (neat): ν_{max} = 2923, 1632 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.71–6.64 (3 H, m, 3 × ArH), 5.94 (1 H, ddd, *J* = 10.0, 5.0, 2.0 Hz, CH=C*H*CHCH$_2$), 5.92 (2 H, s, OCH_2O), 5.58 (1 H, dt, *J* = 10.0, 2.0 Hz, CH=C*H*CHAr), 3.68 (1 H, dq, *J* = 10.0, 2.0 Hz, CHAr), 3.39 (2 H, dt, *J* = 7.5, 2.0 Hz, CH_2N), 3.13 (1 H, dt, *J* = 9.5, 7.0, CH=CHC*H*CH$_2$), 2.75 (1 H, dd, *J* = 11.5, 10.0 Hz, CHCO), 2.43–2.13 (3 H, m, CH_2N, C*H*CHCO), 2.04–1.12 (12 H, m, 6 × CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (CO), 147.6 (C), 146.1 (C), 138.7 (CH), 133.3 (C), 128.3 (CH), 122.0 (CH), 108.3 (CH), 108.1 (CH), 100.9 (CH_2), 46.8 (CH), 47.2 (CH), 46.4 (CH_2), 45.5 (CH_2), 36.5 (CH), 35.5 (CH), 30.6 (CH_2), 28.8 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 24.4 (CH_2), 22.1 (CH_2). MS (ES^+): *m/z* (%) = 376 (20) [M + Na^+], 354 (100) [M + H^+]. MS (ES^+): *m/z* calcd for $C_{22}H_{28}NO_3^+$: 354.2064; found: 354.2062 [M + H^+].
Cyclopiperstachine (**7b**):[4] mp 167–168 °C (lit.[4] 220 °C). R_f = 0.20 (1:1 PE–EtOAc). IR (neat): ν_{max} = 3329, 2925, 1641, 1486, 1250 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.75–6.62 (3 H, m, 3 × ArH), 5.93 (1 H, ddd, *J* = 10.0, 5.0, 2.5 Hz, CH=C*H*CHCH$_2$), 5.91 (2 H, s, OCH_2O), 5.52 (1 H, dt, *J* = 10.0, 1.5 Hz, CH=C*H*CHAr), 5.14 (1 H, br t, *J* = 5.5 Hz, NH), 3.68 (1 H, m, CHAr), 2.93 (2 H, dt, *J* = 7.0, 5.5 Hz, CH_2NH), 2.65 (1 H, dd, *J* = 11.5, 6.5 Hz, CHCO) 2.28 (1 H, m, CH), 2.19 (1 H, m, CH), 1.88–1.17 (9 H, m, CH, 4 × CH_2), 0.75, 0.70 (2 × 3 H, d, *J* = 6.5 Hz, 2 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (CO), 147.8 (C), 146.2 (C), 138.7 (CH), 135.1 (C), 128.6 (CH), 121.2 (CH), 110.0 (CH), 108.1 (CH), 101.0 (CH_2), 53.9 (CH), 50.8 (CH), 46.9 (CH_2), 46.8 (CH), 36.5 (CH), 35.3, (CH), 30.3 (CH_2), 28.4 (CH_2), 26.6 (CH_2), 21.6 (CH_2), 20.1 (CH_3). MS (ES^+): *m/z* (%) = 378 (20) [M + Na^+], 356 (100) [M + H^+]. MS (ES^+): *m/z* calcd for $C_{22}H_{30}NO_3^+$: 356.2221; found: 356.2252 [M + H^+].