Convergent, stereoselective syntheses of the glycosidase inhibitors broussonetines D and M†‡

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The first syntheses of the polyhydroxylated alkaloids (iminosugars) broussonetines D and M, glycosidase inhibitors of the pyrrolidine class, have been performed in a convergent, stereocontrolled way from D-serine as the chiral starting material. A cross metathesis step was one key feature of the synthesis. The versatility of the synthetic concept chosen permits the access to many members of this compound family, both natural ones and analogues thereof.

Introduction

Pyrrolidine alkaloids have been isolated from species of many plant families,[1] as well as from some animal organisms.[2] Members of this compound class are known to exhibit a broad range of biological activities.[1d,3] Those bearing several hydroxyl functions display a structural similarity to monosaccharides and are thus included into the general group of the iminosugars.[4] These compounds display various types of heterocyclic systems (Fig. 1) and often exhibit inhibitory activity on diverse glycosidases.[5] This property, which relies on structural similarities with sugars, is frequently associated with valuable pharmacological utility.[6] This therefore has led to a significant synthetic effort on members of this compound class.[7]

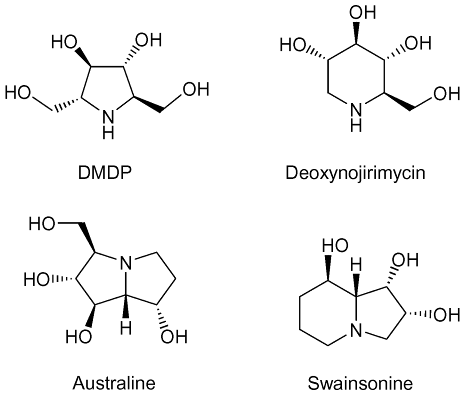

Fig. 1 Structures of some representative iminosugars with inhibitory ability on glycosidases.

Within the pyrrolidine class of iminosugars, the broussonetines constitute a particular subgroup with about 30 representatives. They all have been isolated in recent years from the plant species *Broussonetia kazinoki* Siebold (Moraceae), a deciduous tree growing in several Far East countries, mainly China and Japan, where it is used in folk medicine.[8,9]

Most broussonetines have been found to display marked inhibitory activities on various glycosidases (IC_{50} values in the micromolar to nanomolar range). Furthermore, their selectivity has proven to be different from that of other standard iminosugars such as deoxynojirimycin (DNJ). Broussonetine D, for instance, was found to display a strong inhibitory activity (IC_{50}, 29 nmol) against bovine liver β-galactosidase, an enzyme not inhibited by DNJ.[8]

The majority of the reported broussonetines show the general structure depicted in Fig. 2. A common, polyhydroxylated pyrrolidine core is bound to a variable 13-carbon chain that displays various types and degrees of functionalization. Fig. 2 shows five selected examples.

Synthetic activity in the field of the broussonetines has been very scarce until now. The first total synthesis of a member of the broussonetine group in enantiopure form was carried out in 1999 by Yoda and coworkers,[10a] who prepared broussonetine C (**1**) from D-tartaric acid as the chiral starting material. Four years later, a second total synthesis of **1** was reported by Perlmutter and coworkers, once again with a member of chiral pool, D-arabinose, as the starting material.[10b] The third and to date last total synthesis has been reported by Trost and coworkers, who synthesized broussonetine G (**3**) by means of a palladium-based, asymmetric catalytic procedure.[10c]

In the present communication, we report on the first total syntheses of broussonetines D (**2**) and M (**4**). The fact that the broussonetines depicted above show a common pyrrolidine core and a variable side chain led us to conceive the general retrosynthetic analysis depicted in Scheme 1. Thus, the olefinic bond of a side chain as in **5** may be hydrogenated to the saturated side chains of the type present in **2** or **4** and, at the same time, allows for a cleavage *via* retro-cross-metathesis (retro-CRM) to a common building block and a variable side chain fragment. The common building block was then retrosynthetically cleaved in a way which relied on that used in our recent synthesis of radicamine B,[11] and led to the commercially available amino acid D-serine as

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‡ Electronic supplementary information (ESI) available: Additional experimental procedures and tabulated spectral data of compounds **7**, **8**, **9a**, **10**, **11**, **13**, **14**, **16–19** and **21**. CCDC reference number 711630. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b821431j

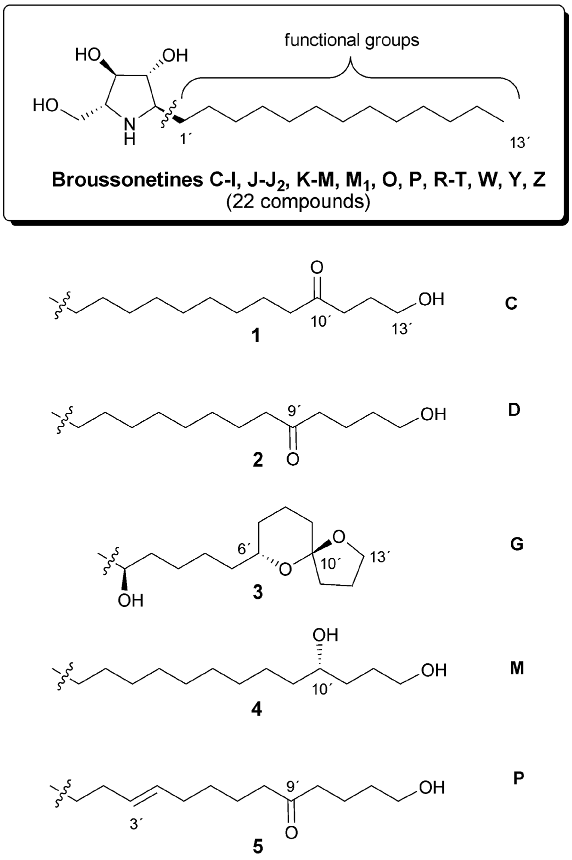
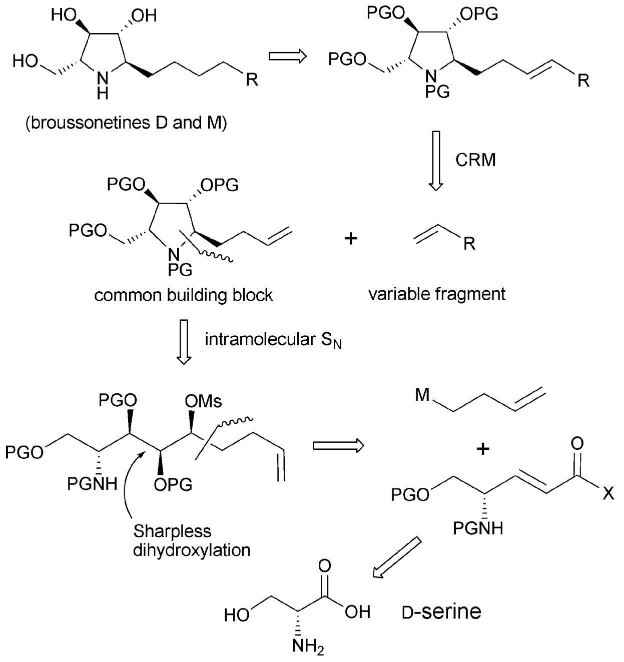


Fig. 2 General structure of most broussonetines and some specific examples.

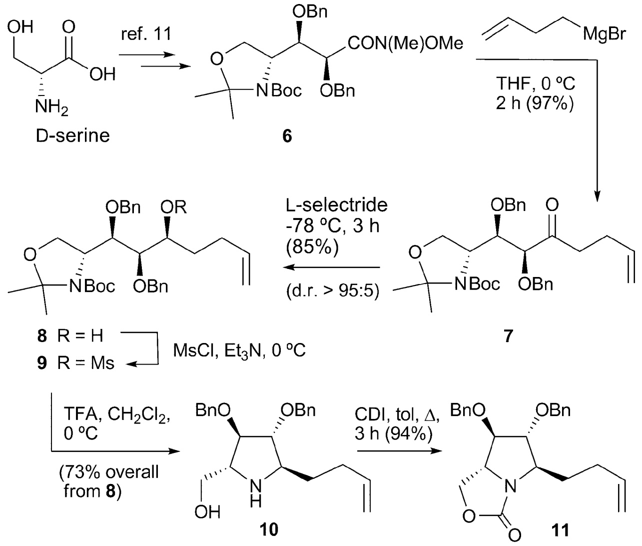


Scheme 1 Retrosynthetic analysis of broussonetines D and M (PG = protecting groups).

the chiral starting material. This retrosynthetic concept permits an access not only to most of the natural broussonetines but also to non-natural analogues thereof.

Results and discussion

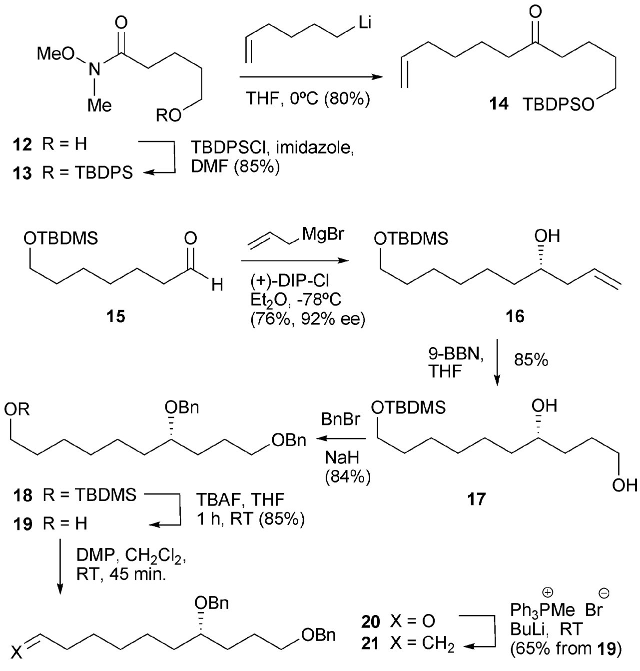
The known Weinreb amide **6** was first prepared from D-serine as previously reported.[11] Reaction of **6** with 3-butenyl-magnesium bromide afforded in excellent yield ketone **7**, which was then stereoselectively reduced with L-selectride to secondary alcohol **8** (Scheme 2).[12] Mesylation of **8** and acid treatment of mesylate **9** provided pyrrolidine **10** in a one-pot transformation which encompasses three consecutive steps: successive cleavage of the Boc and acetonide groups, followed by intramolecular nucleophilic substitution with formation of the C–N bond. Compound **10** was then converted into oxazolidinone **11** for reasons to be explained below.



Scheme 2 Synthesis of the pyrrolidine core (**10**/**11**).

The side chain fragments were prepared *via* standard methods as shown in Scheme 3. Thus, Weinreb amide **12**, prepared as reported from δ-valerolactone,[13] was silylated to **13** and then allowed to react with 5-hexenyllithium, obtained in turn *via* halogen-lithium exchange in the corresponding bromide. This gave ketone **14**, suitable for cross metathesis with the pyrrolidine moiety. As for the side chain fragment of broussonetine M, Brown's asymmetric allylation[14] of the known aldehyde **15**[15] furnished homoallyl alcohol **16** in 92% optical purity and 76% overall yield from the alcohol precursor of **15**. Hydroboration-oxidation of the olefinic bond, benzylation of the two hydroxyl groups and desilylation provided primary alcohol **19**, which was then oxidized to aldehyde **20**. Wittig olefination of the latter afforded terminal alkene **21**. With the two necessary olefins **14** and **21** now in hand, we investigated their CRM reactions[16] with pyrrolidine **10** (Scheme 4).

All attempts at CRM of **10** with olefin **14** in the presence of 10% Grubbs' second-generation catalyst **22**[17] and one equivalent of acid (*p*-toluenesulfonic acid, trifluoroacetic acid or titanium tetraisopropoxide) in refluxing CH_2Cl_2 gave disappointing results.[18] Assuming that this was due to the presence of residual, unprotonated amine, we replaced **10** by its N,O-protected derivative **11**. When a 1 : 2 mixture of **11** and **14** was heated at reflux in CH_2Cl_2 for 24 h in the presence of **22**,[19] the desired CRM product **23** was obtained as an inseparable 4 : 1 *E*/*Z* mixture in 63% yield. The



Scheme 3 Synthesis of the side chain fragments **14** and **21**.

remaining products identified were the homodimers **24** and **25**, likewise formed as *E*/*Z* mixtures.[20]

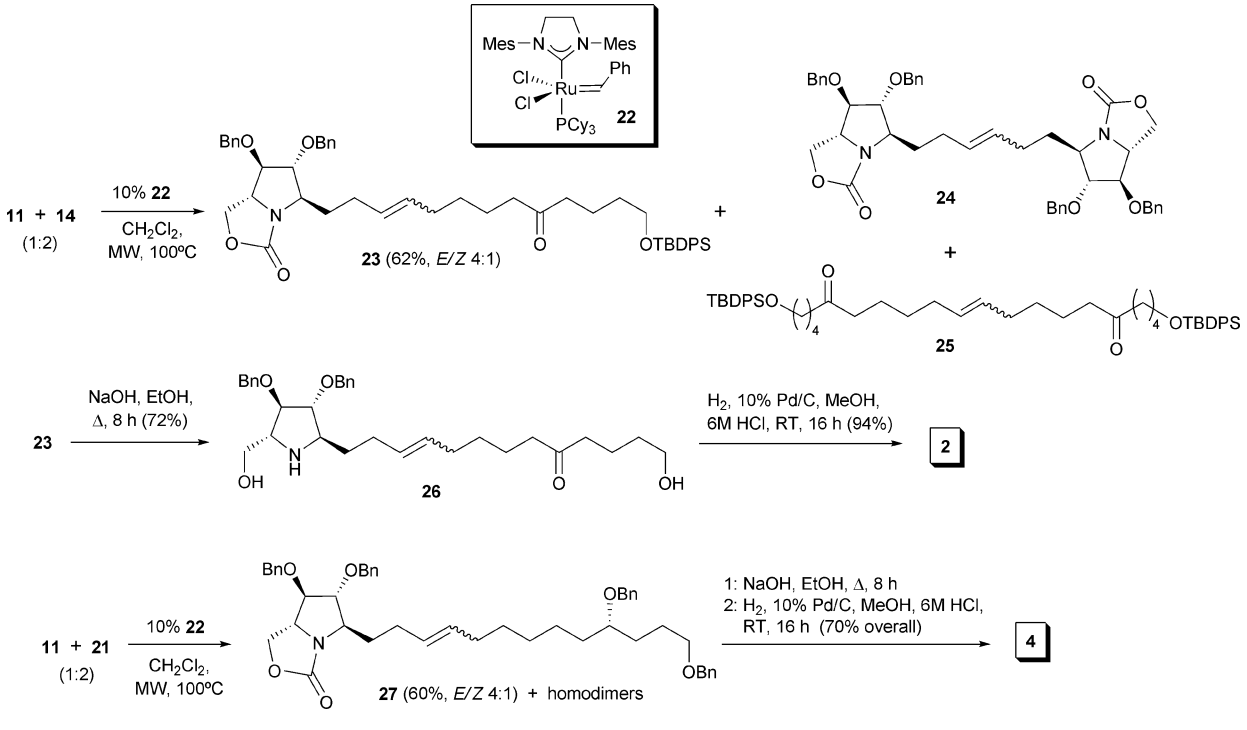
We then discovered that the reaction could be better carried out under microwave (MW) irradiation.[21] In fact, while yields and products remained essentially unchanged (62% of **23**), the reaction time was much shorter (1 h). Compound **23** was then subjected to alkaline hydrolytic conditions, which caused cleavage of both the oxazolidinone and TBDPS groups.[22] The crude *E*/*Z* mixture was stirred under a H_2 atmosphere in an acidic medium to yield broussonetine D (**2**) in good yield.[23]

A similar reaction sequence led to broussonetine M (**4**). CRM of a 1 : 2 mixture of **11** and alkene **21** (Scheme 4) gave the coupling product **27** as a 4 : 1 *E*/*Z* mixture in 60% yield, together with the expected homodimers. Without separation of geometrical isomers, **27** was subjected to the same alkaline hydrolysis conditions as above, followed by catalytic hydrogenation/hydrogenolysis in acidic medium. This caused saturation of the olefinic bond and cleavage of the four benzyl groups to yield **4**.

Experimental

General

NMR spectra were recorded at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR) in $CDCl_3$ solution at 25 °C, if not otherwise indicated, with the solvent signals as internal reference. The spectra of compounds with N-Boc residues were measured at higher temperatures in order to have sharper signals. ^{13}C NMR signal multiplicities were determined with the DEPT pulse sequence. Mass spectra were run in the EI (70 eV) or the FAB (*m*-nitrobenzyl alcohol matrix) mode. IR data were measured as films on NaCl plates (oils) or as KBr pellets (solids), and are given only when relevant functions (C=O, OH) are present. Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere were carried out under dry N_2 with flame-dried glassware. Commercial reagents were used as received. THF and Et_2O were freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Toluene was freshly distilled from sodium wire. Tertiary amines were freshly distilled from KOH. Where organic solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings



Scheme 4 Final steps of the synthesis of broussonetines D (**2**) and M (**4**).

incorporated to the main organic layer. The latter was dried over anhydrous Na_2SO_4 and the solvent was eliminated under reduced pressure. Column chromatography was performed on a silica gel column (60–200 μm) and elution with the indicated solvent mixture.

(5*R*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-(13-*tert*-butyldiphenylsilyloxy-9-oxotridec-3*E*,*Z*-enyl)tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one (23)

Procedure A): Compounds **11** (197 mg, 0.5 mmol), **14** (422 mg, 1 mmol) and Grubbs' catalyst **22** (42 mg, 0.05 mmol) were dissolved in dry, deoxygenated CH_2Cl_2 (8 mL). The mixture was heated at reflux under N_2 for 24 h. Solvent removal under reduced pressure gave a residue which was dissolved in Et_2O (25 mL). The organic layer was washed three times with water and then dried on Na_2SO_4. After this, charcoal (1 g) was added and the suspension stirred for 24 h at room temperature. Solvent removal under reduced pressure and column chromatography on silica gel (elution with hexanes-EtOAc, 8 : 2) yielded compound **23** (248 mg, 63% as a 4 : 1 *E*/*Z* mixture). In addition, homodimers **24** (57 mg, 30% based on **11**) and **25** (269 mg, 66% based on **14**) were isolated, likewise as ~ 4 : 1 *E*/*Z* mixtures. *Procedure B*): Compounds **11** (197 mg, 0.5 mmol), **14** (422 mg, 1 mmol) and Grubbs' catalyst **22** (42 mg, 0.05 mmol) were dissolved in dry, deoxygenated CH_2Cl_2 (8 mL). The reaction mixture was placed in a CEM Discover microwave oven and heated for 1 h at 100 °C (100 W power). Work-up as above gave **23** (240 mg, 62%) together with **24** and **25** in yields similar to those of procedure A). Homodimer **25** could be recycled to **23** through reaction with **11** under the same metathesis conditions. It gave compound **23** in 57% yield, together with excess **25** and homodimer **24**. *Title compound* (*E* + *Z mixture*): colourless oil; IR ν_{max} 1760, 1712 (C=O) cm^{-1}; ^1H NMR (signals from the major *E* isomer) δ 7.70 (4H, br d, *J* ~ 7.5 Hz), 7.45–7.25 (16H, br m), 5.50–5.45 (2H, m), 4.61 (2H, br d, *J* = 11.6 Hz), 4.50–4.40 (3H, m), 4.10 (1H, dd, *J* = 9, 4 Hz), 4.05 (1H, m), 4.00–3.90 (2H, m), 3.87 (1H, m), 3.68 (2H, t, *J* = 6 Hz), 2.40–2.35 (4H, m), 2.20–2.10 (2H, m), 2.05–2.00 (2H, m), 1.70–1.60 (4H, m), 1.60–1.55 (4H, m), 1.38 (2H, br quint, *J* ~ 7.5 Hz), 1.07 (9H, s); ^{13}C NMR (signals from the major *E* isomer) δ 211.1, 161.2, 137.3, 137.2, 134.0 (× 2), 19.2 (C), 135.5 (× 4), 131.1, 129.5 (× 2), 129.0, 128.6 (× 2), 128.5 (× 2), 128.2, 127.9, 127.7 (× 4), 127.6 (×4), 88.8, 87.8, 62.8, 62.3 (CH), 72.7, 71.6, 67.2, 63.5, 42.5, 42.4, 32.3, 32.1, 32.0, 29.2, 29.1, 23.3, 20.3 (CH_2), 26.9 (× 3) (CH_3); HR FABMS *m*/*z* 788.4377 (M + H^+), calcd. for $C_{49}H_{62}NO_6Si$, 788.4346.

(5*R*,5′*R*,6*R*,6′*R*,7*R*,7a*R*,7′*R*,7a′*R*)-5,5′-(Hex-3*E*,*Z*-ene-1,6-diyl)-bis(6,7-bis(benzyloxy)tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one) (24)

Obtained as described above as an *E*/*Z* mixture: colourless oil; ^1H NMR (signals from the major *E* isomer) δ 7.45–7.20 (20H, br m), 5.50–5.40 (2H, m), 4.60 (4H, br d, *J* = 11.8 Hz), 4.50–4.40 (6H, br m), 4.10–4.00 (4H, m), 3.95–3.80 (6H, br m), 2.20–2.00 (4H, br m), 1.70–1.50 (4H, br m); ^{13}C NMR (signals from the major *E* isomer) δ 161.2 (× 2), 137.5 (× 2), 137.3 (× 2) (C), 130.0 (× 2), 128.7 (× 5), 128.5 (× 5), 128.2 (× 2), 127.9 (× 2), 127.8 (× 6), 88.8 (× 2), 87.9 (× 2), 62.8 (× 2), 62.3 (× 2) (CH), 72.7 (× 2), 71.6 (× 2), 67.2 (× 2), 32.0 (× 2), 29.3 (× 2) (CH_2).

1,20-Bis(*tert*-butyldiphenylsilyloxy)eicos-10*E*,*Z*-ene-5,16-dione (25)

Obtained as described above as an *E*/*Z* mixture: colourless oil; ^1H NMR (signals from the major *E* isomer) δ 7.70 (8H, br d, *J* ~ 7.5 Hz), 7.45–7.25 (12H, br m), 5.40–5.35 (2H, m), 3.67 (4H, t, *J* = 6.5 Hz), 2.37 (8H, br q, *J* ~ 7.5 Hz), 2.00 (4H, m), 1.65 (4H, br quint, *J* ~ 7 Hz), 1.57 (8H, m), 1.35 (4H, br quint, *J* ~ 7 Hz), 1.06 (18H, s); ^{13}C NMR (signals from the major *E* isomer) δ 211.0 (× 2), 133.9 (× 4), 19.2 (× 2) (C), 135.5 (× 8), 130.2 (× 2), 129.5 (× 4), 127.6 (× 8) (CH), 63.5 (× 2), 42.5 (× 2), 42.4 (× 2), 37.3 (× 2), 32.0 (× 2), 29.2 (× 2), 23.3 (× 2), 20.3 (× 2) (CH_2), 26.9 (× 6) (CH_3).

13-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-(hydroxymethyl)-pyrrolidin-2-yl]-1-hydroxytridec-10*E*-en-5-one (26)

A solution of compound **23** (315 mg, 0.4 mmol) in EtOH–H_2O 3 : 1 (10 mL) was treated with NaOH (400 mg, 10 mmol). The reaction mixture was stirred at reflux for 8 h. After this, all volatiles were removed under reduced pressure and the residue was taken into brine, followed by extraction with EtOAc (3 × 10 mL). The organic layer was then dried on anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (elution with $CHCl_3$–MeOH, from 95 : 5 to 90 : 10) to furnish compound **26** (150 mg, 72%) as a 4 : 1 *E*/*Z* mixture. For the synthesis of broussonetine D, the *E*/*Z* mixture was used as such in the hydrogenation step (see below). *Title compound* (*E* + *Z mixture*): colourless oil; IR ν_{max} 3390 (br, OH), 1709 (C=O) cm^{-1}; ^1H NMR (signals from the major *E* isomer) δ 7.40–7.30 (10H, br m), 5.40–5.30 (2H, m), 4.60–4.50 (4H, m), 3.85 (1H, m), 3.75–3.70 (1H, m), 3.65–3.55 (4H, br m), 3.45 (1H, m), 3.25–3.20 (1H, m), 3.15 (3H, br s, NH, 2 OH), 2.43 (2H, t, *J* = 7 Hz), 2.38 (2H, t, *J* = 7 Hz), 2.20–1.95 (4H, br m), 1.75–1.50 (8H, br m), 1.35 (2H, br quint, *J* ~ 7.5 Hz); ^{13}C NMR (signals from the major *E* isomer) δ 211.2, 138.0, 137.9 (C), 131.0, 129.5, 129.0, 128.5 (× 2), 128.4 (× 2), 127.9 (× 2), 127.7 (× 3), 88.8, 85.5, 62.3, 61.6 (CH), 72.1 (× 2), 63.7, 61.5, 42.6, 42.3, 33.1, 32.2, 32.0, 29.5, 29.1, 23.3, 20.0 (CH_2); HR FABMS *m*/*z* 524.3390 (M + H^+), calcd. for $C_{32}H_{46}NO_5$, 524.3376.

(5*R*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-[(10*S*)-10,13-bis(benzyloxy)tridec-3*E*,*Z*-enyl]tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one (27)

The metathesis reaction was carried out with compounds **11** (197 mg, 0.5 mmol), **21** (366 mg, 1 mmol) and Grubbs' catalyst **22** (42 mg, 0.05 mmol) in dry, deoxygenated CH_2Cl_2 (8 mL) under the same conditions as in the previous case. Work-up as above afforded **27** (220 mg, 60%, as a 4 : 1 *E*/*Z* mixture), together with the expected homodimers. *Title compound* (*E* + *Z mixture*): colourless oil; IR ν_{max} 1760 (C=O) cm^{-1}; ^1H NMR (signals from the major *E* isomer) δ 7.45–7.30 (20H, br m), 5.55–5.45 (2H, m), 4.65–4.60 (2H, m), 4.55–4.40 (7H, br m), 4.12 (1H, dd, *J* = 9, 4 Hz), 4.08 (1H, m), 3.94 (2H, m), 3.88 (1H, dd, *J* = 5, 2.6 Hz), 3.52 (2H, br t, *J* ~ 6.5 Hz), 3.45 (1H, br quint, *J* ~ 5.5 Hz), 2.20–2.10 (2H, m), 2.10–2.00 (2H, m), 1.80–1.50 (8H, br m), 1.50–1.30 (6H, br m); ^{13}C NMR (signals from the major *E* isomer) δ 161.2, 139.0, 138.6, 137.3, 137.2 (C), 131.5, 128.5 (× 2), 128.4 (× 2), 128.3 (× 2), 128.2 (× 2), 128.1, 127.9, 127.8 (× 2), 127.7 (× 3), 127.6 (× 2), 127.5 (× 2), 127.4, 127.3, 88.8, 87.7, 78.7, 62.7, 62.2 (CH), 72.7, 72.6, 71.5, 70.7, 70.5, 67.1, 33.7, 32.5, 32.2, 30.3, 29.5, 29.3, 29.2, 25.6, 25.2 (CH_2); HR FABMS *m*/*z* 732.4249 ($M + H^+$), calcd. for $C_{47}H_{58}NO_6$, 732.4264.

Broussonetine D (2)

Compound **26** (26 mg, 0.05 mmol) as an *E*/*Z* mixture (see above) was dissolved in MeOH (5 mL) and treated with 6M HCl (0.5 mL). After addition of 10% Degussa-type Pd/C catalyst (30 mg), the mixture was placed under a H_2 atmosphere and stirred for 16 h at room temperature. The mixture was then filtered through Celite (washing with MeOH). Removal of all volatiles under reduced pressure gave a residue which was dissolved in MeOH (2 mL) and treated dropwise with 33% aq ammonia until basic pH. Removal of all volatiles under reduced pressure gave a residue which was chromatographed on silica gel (elution with $CHCl_3$:MeOH:NH_4OH, from 95 : 4 : 1 to 70 : 29 : 1). The eluted material was subsequently purified in a ion-exchange column (Dowex 5Wx4-400 Aldrich, acidified with 0.5M HCl). Elution was performed first with distilled water (50 mL) and then with 1M aq ammonia (until elution of the product). This provided broussonetine D (16 mg, 94%). The identity of the synthetic sample was confirmed by direct comparison with an authentic sample by means of co-chromatography in an HPLC-MS system. *Title compound*: amorphous solid; $[\alpha]_D$ +23.6 (*c* 0.4; MeOH), lit.[24] $[\alpha]_D$ +22.9 (*c* 0.31; MeOH); IR ν_{max} 3330 (br, OH), 1706 (C=O) cm^{-1}; ^1H NMR (pyridine-d_5) δ 4.70 (1H, t, $J = 6.5$ Hz), 4.41 (1H, t, $J = 6.5$ Hz), 4.25 (1H, dd, $J = 11.2$. 4.5 Hz), 4.20 (1H, dd, $J = 11.2$. 5.5 Hz), 3.86 (2H, t, $J = 6.5$ Hz), 3.82 (1H, m), 3.53 (1H, m), 2.48 (2H, t, $J = 7.5$ Hz), 2.36 (2H, t, $J = 7.5$ Hz), 2.05–2.00 (2H, m), 1.90–1.85 (2H, m), 1.80–1.70 (4H, br m), 1.65–1.50 (4H, br m), 1.40–1.15 (11H, br m); ^{13}C NMR (pyridine-d_5) δ 210.5 (C), 84.2, 80.2, 65.2, 63.1 (CH), 63.4, 61.8, 42.7, 42.6, 35.2, 33.2, 30.2, 29.8 (several overlapped signals), 27.3, 24.2, 21.0 (CH_2); HR FABMS *m*/*z* 346.2585 ($M + H^+$), calcd. for $C_{18}H_{36}NO_5$, 346.2593.

There are some differences in the chemical shifts of some signals between the synthetic and the natural sample,[24] even though their identity has been secured as described above. Most likely, these differences are due to the presence of minute amounts of acid and/or metal impurities, which markedly affect the position of some signals, as already reported for basic nitrogen-containing natural products.[25]

Broussonetine M (4)

Alkaline hydrolysis of the protecting oxazolidinone group in **27** was performed in the same manner as for compound **23** (see above). A solution of compound **27** (183 mg, 0.25 mmol) in EtOH–H_2O 3 : 1 (7 mL) was treated with NaOH (280 mg, 7 mmol). The reaction mixture was stirred at reflux for 8 h. Work-up and column chromatography as for **23** → **26** gave a pyrrolidine derivative (as an *E*/*Z* mixture) which was used as such in the next reaction. The pyrrolidine derivative was then dissolved in MeOH (15 mL) and treated with 6M HCl (1.5 mL). After addition of 10% Degussa-type Pd/C catalyst (75 mg), the mixture was placed under a H_2 atmosphere (1 atm) and stirred for 16 h at room temperature The mixture was then filtered through Celite (washing with MeOH). Removal of all volatiles under reduced pressure gave a residue which was dissolved in MeOH (3 mL) and treated dropwise with 33% aq ammonia until basic pH. Removal of all volatiles under reduced pressure gave a residue which was chromatographed on silica gel (elution with $CHCl_3$:MeOH:NH_4OH, from 95 : 4 : 1 to 70 : 29 : 1). The eluted material was subsequently purified in an ion-exchange column (Dowex 5Wx4–400 Aldrich, acidified with 0.5M HCl). Elution was performed first with distilled water (50 mL) and then with 1M aq ammonia (until elution of the product). This provided broussonetine M (61 mg, 70% overall from **27**). *Title compound*: amorphous solid; $[\alpha]_D$ +6 (*c* 0.45; MeOH), lit.[26] $[\alpha]_D$ +5.9 (*c* 0.3; MeOH); IR ν_{max} 3330 (br, OH) cm^{-1}; ^1H NMR (pyridine-d_5) δ 4.90 (1H, t, $J = 7$ Hz), 4.65 (1H, t, $J = 7$ Hz), 4.45 dd (1H, dd, $J = 11.5$. 5.5 Hz), 4.41 dd (1H, dd, $J = 11.5$. 5 Hz), 4.26 (1H, m), 4.05 (1H, br q, $J = 7.5$ Hz), 3.96 (2H, t, $J = 6.5$ Hz), 3.90 (1H, m), 2.30–2.25 (2H, br m), 2.15–2.10 (1H, m), 2.05–2.00 (1H, m), 1.90–1.50 (8H, br m), 1.40–1.15 (16H, br m); ^{13}C NMR (pyridine-d_5) δ 80.7, 76.7, 70.9, 65.2, 63.0 (CH), 62.4, 59.7, 38.5, 35.2, 31.9, 30.3, 29.9, 29.8, 29.6, 29.5, 29.4, 26.7, 26.3 (CH_2); HR FABMS *m*/*z* 348.2763 ($M + H^+$), calcd. for $C_{18}H_{38}NO_5$, 348.2750.

As in the case of **2** and, in all likelihood, for the same reasons, there are also differences in the chemical shifts of several signals between the synthetic and the natural sample.[25,26]

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