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Convergent, stereoselective syntheses of the glycosidase inhibitors broussonetines C, O and P

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Dedicated to Professor P. Camps, from the University of Barcelona, on the occasion of his 65th birthday

ABSTRACT

The first syntheses of the polyhydroxylated alkaloids (iminosugars) broussonetines O and P, glycosidase inhibitors of the pyrrolidine class, have been performed in a convergent, stereocontrolled way from D-serine as the chiral starting material. The synthesis of broussonetin C, a further member of this compound family, is also reported. 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.

1. 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 some glycosidases.[5] This property, which relies on structural similarities with sugars, is frequently associated to pharmacological utility.[6] This therefore has led to a significant synthetic effort on members of this compound class.[7]

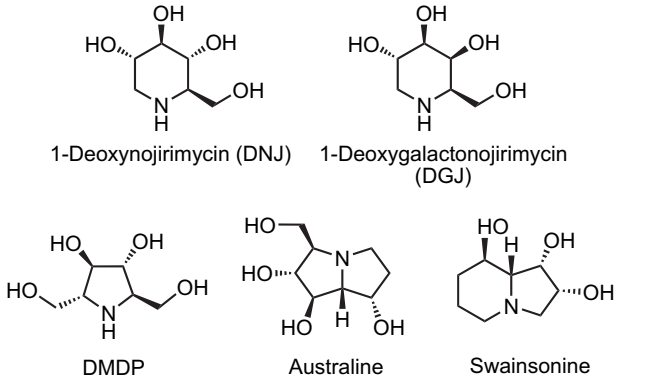

Figure 1. Structures of some representative iminosugars with inhibitory ability on glycosidases.

Within naturally occurring pyrrolidines, the broussonetines constitute a particular subgroup with about 30 reported examples. They all have been isolated in recent years from the terrestrial 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 glycosidase types (the IC_{50} values are situated in the micromolar to nanomolar range). Furthermore, their selectivity has proven both qualitatively and quantitatively different from that of other standard iminosugars such as DNJ (Fig. 1). 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. The iminosugar DGJ, which is structurally related to DNJ, does inhibit this enzyme but at a concentration 4.5 times higher than broussonetine D.

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

Synthetic activity in the field of the broussonetines has been very scarce until now.[10] The first total synthesis of a member of the broussonetine group in enantiopure form was carried out in 1999 by Yoda and co-workers,[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 co-workers, once again with a member of chiral pool, D-arabinose, as

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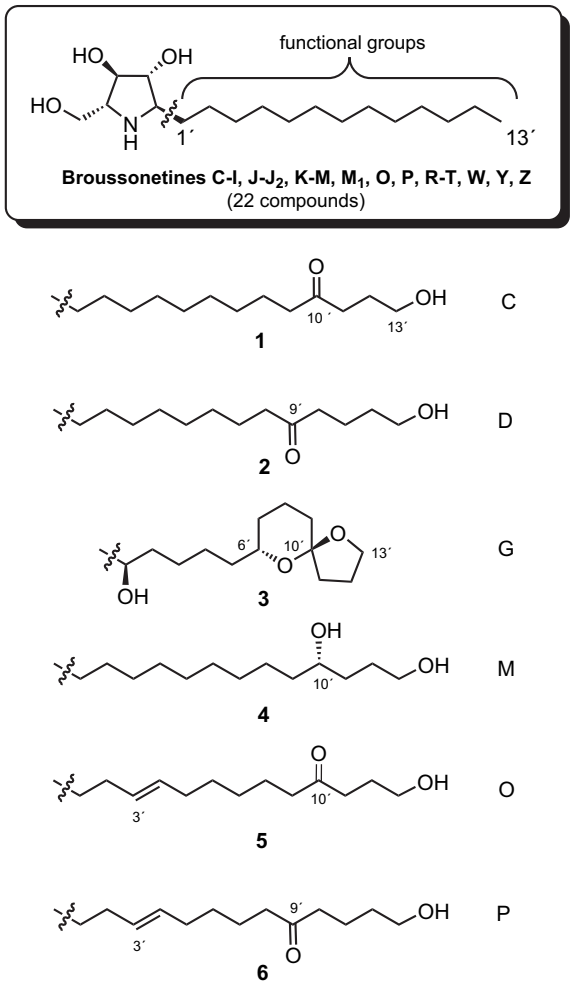


Figure 2. General structure of most broussonetines and some specific examples.

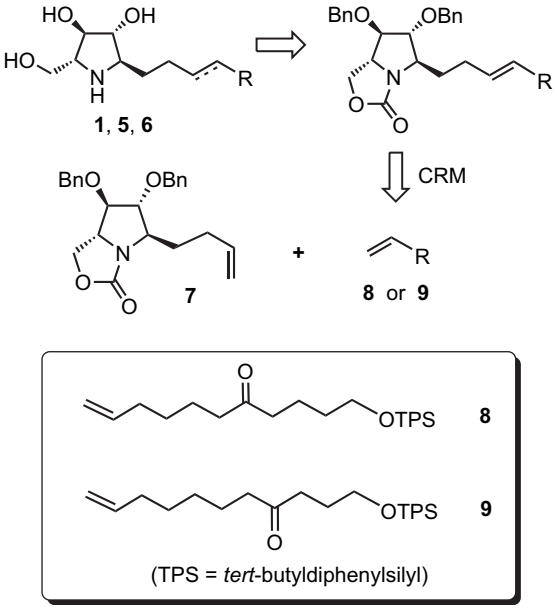
the starting material.[10b] Almost simultaneously, the third total synthesis was reported by Trost and co-workers, who synthesized broussonetine G (**3**) by means of a palladium-based, asymmetric catalytic procedure.[10c] Finally, we have recently published the first syntheses of broussonetines D (**2**) and M (**4**). The commercial amino acid D-serine was the chiral starting material.[11]

In the present article, we describe the first total syntheses of broussonetines O (**5**) and P (**6**). In addition, we also report a further synthesis of broussonetine C (**1**). For that purpose, we have followed the same retrosynthetic analysis of our previous syntheses of **2** and **4**.[11] Thus, the olefinic bond of the side chain in **5** may be hydrogenated to the saturated side chain of **1** and, at the same time, allows for a cleavage via retro-cross-metathesis (retro-CRM) to the common building block **7**[11] and the appropriate side chain fragment (Scheme 1). In the present case, the side chain fragment is one of the two unsaturated ketones **8**[11] (for the synthesis of **6**) or **9** (for the synthesis of **1** and **5**).

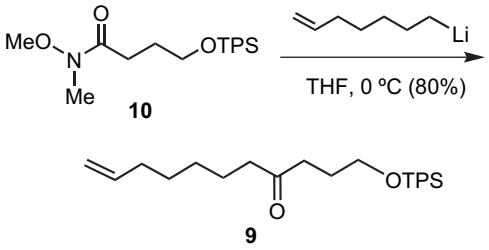
2. Results and discussion

The synthesis of ketone **9**, depicted in Scheme 2, followed the same methodology used in our previous preparation of the structurally close **8**.[11] Thus, the known Weinreb amide **10**, prepared as reported[12] from γ-butyrolactone, was treated with 6-heptenyllithium, obtained by means of halogen–lithium exchange in the corresponding bromide, to yield **9**.

In the same manner as in our previous synthesis of **2** and **4**,[11] a 1:2 mixture of **7** and **9** was heated at reflux in CH_2Cl_2 for 24 h in



Scheme 1. Retrosynthetic analysis of **1**, **5** and **6**.



Scheme 2. Synthesis of ketone **9**.

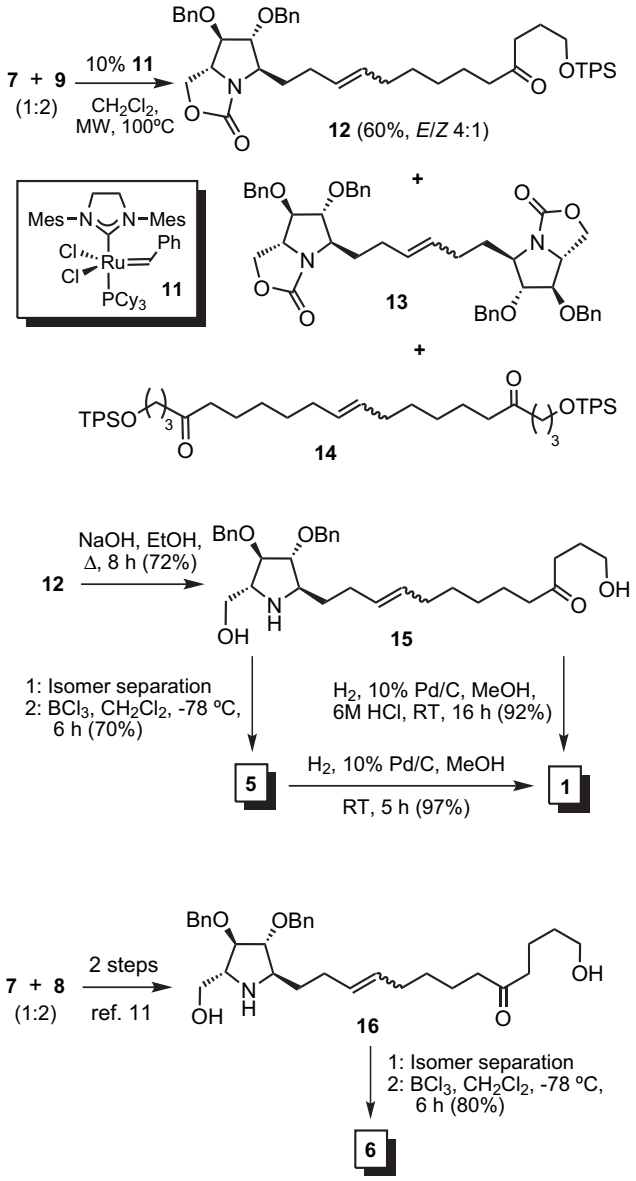
the presence of ruthenium catalyst **11**.[13] This gave the desired CRM product **12** in 61% overall yield as a 4:1 *E*/*Z* mixture. Other products obtained in the same reaction were the two expected homodimers **13** and **14**.[11,14] As observed in our previous synthesis, the reaction could be also conducted under microwave (MW) irradiation with practically unchanged yields but much shorter reaction times.

For the preparation of **1**, separation of the *E*/*Z* mixture is not necessary. Thus, treatment of (*E*+*Z*)-**12** with ethanolic NaOH caused sequential cleavage of the silyl and cyclic carbamate groups.[15] The resulting product **15**, still as an *E*/*Z* mixture, was then subjected to hydrogenation in an acidic medium[16] to yield a product identical in its physical and spectral properties to broussonetine C (**1**).

The preparation of broussonetine O (**5**) proved laborious. Only after repeated column chromatography on silica gel of (*E*+*Z*)-**15** we were able to obtain reasonably pure (*E*)-**15**. Cleavage of the two benzyl groups in the latter compound was achieved through treatment with BCl_3 in CH_2Cl_2 at low temperature[17] and afforded **5** in 70% yield. As expected, hydrogenation of **5** in a neutral medium yielded **1**.

In our previous paper,[11] we reported the cross-metathesis reaction between oxazolidinone **7** and ketone **8** catalyzed by ruthenium complex **11**. After cleavage of the silyl and cyclic carbamate groups in the resulting compound with ethanolic NaOH, compound **16** (*E*+*Z*) was obtained. Hydrogenation of the mixture furnished broussonetine D (**2**).[11] For the preparation of broussonetine P (**6**), the isolation of pure (*E*)-**16** was necessary. As in the previous case, this required a lengthy chromatographic separation. Finally, treatment of (*E*)-**16** with BCl_3 in CH_2Cl_2 at low temperature[17] gave **6** in 80% yield.

In summary, the three bioactive pyrrolidine alkaloids broussonetine C (**1**), broussonetine O (**5**) and broussonetine P (**6**) have been prepared in enantiopure form from the commercially available amino acid D-serine as the ultimate chirality source (Scheme 3).[11] This is the first synthesis of both **5** and **6**, as well as the third synthesis of **1**.



Scheme 3. Stereoselective synthesis of **1**, **5** and **6**.

3. Experimental

3.1. General

$^1H/^{13}C$ NMR spectra were recorded at 500/125 MHz in the indicated solvent at 30 °C. Signals of the deuterated solvent were taken as the reference (for $CDCl_3$, δ 7.25 and 77.0 ppm for ^1H and ^{13}C NMR, respectively; for pyridine-d_5, the signals at δ 7.20 and 123.5 ppm for ^1H and ^{13}C NMR, respectively). Carbon atom types (C, CH, CH_2, CH_3) were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact mode (EIMS) or by the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix). IR data are given only for compounds with significant functions (OH, C=O) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions, which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O and THF were freshly distilled from sodium/benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parenthesis. If the reaction medium was acidic, an additional washing with 5% aq $NaHCO_3$ was performed. If the reaction medium was basic, an additional washing with aq NH_4Cl was performed. New washing with brine, drying over anhydrous Na_2SO_4 and elimination of the solvent under reduced pressure were followed by chromatography on a silica gel column (60–200 μm) and elution with the indicated solvent mixture. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer.

*3.1.1. 1-(tert-Butyldiphenylsilyloxy)undec-10-en-4-one (**9**).* A 1.7 M pentane solution of *tert*-butyllithium (11.8 mL, ca. 20 mmol) was added under N_2 to THF (10 mL) cooled to −78 °C. Subsequently, a solution of 7-bromo-1-heptene (1.53 mL, ca. 10 mmol) in dry THF (6 mL) was added dropwise. The mixture was stirred for 3 h at the same temperature. Weinreb amide **10** (1.93 g, 5 mmol) was then dissolved in dry THF (8 mL) and added dropwise during 10 min. The cooling bath was then removed and the solution was left to reach room temperature and stirred for further 30 min. Work-up (extraction with EtOAc, 3×25 mL) and column chromatography on silica gel (elution with hexanes/EtOAc, 95:5) gave ketone **9** (1.69 g, 80%): oil; ^1H NMR ($CDCl_3$) δ 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 5.81 (1H, ddt, J=17, 10.3, 6.5 Hz), 5.02 (1H, br dd, J=17, 1.5 Hz), 4.96 (1H, br d, J=10.3 Hz), 3.69 (2H, t, J=6 Hz), 2.53 (2H, t, J=7.3 Hz), 2.40 (2H, t, J=7.4 Hz), 2.07 (2H, br q, $J\sim$7 Hz), 1.85 (2H, br quint, $J\sim$6.7 Hz), 1.60 (2H, br quint, $J\sim$7.5 Hz), 1.42 (2H, br quint, $J\sim$7.5 Hz), 1.32 (2H, br quint, $J\sim$7.5 Hz), 1.05 (9H, s); ^{13}C NMR ($CDCl_3$) δ 211.0, 133.9 (×2), 19.2 (C), 138.9, 135.6 (×4), 129.6 (×2), 127.7 (×4) (CH), 114.4, 63.1, 42.8, 39.1, 33.6, 28.7 (×2), 26.7, 23.7 (CH_2), 26.9 (×3) (CH_3); IR ν_{max} 1715 (C=O) cm^{-1}; HR EIMS *m/z* (rel int.) 365.1935 ($M^+-{}^t$Bu, 100), 199 (64), calcd for $C_{27}H_{38}O_2Si-{}^t$Bu 365.1936.

*3.1.2. (5R,6R,7R,7aR)-6,7-Bis(benzyloxy)-5-(13-tert-butyldiphenylsilyloxy-10-oxotridec-3E,Z-enyl)tetrahydro-pyrrolo[1,2-c]oxazol-3(1H)-one (**12**). Procedure A*: compounds **7** (197 mg, 0.5 mmol), **9** (422 mg, 1 mmol) and Grubbs catalyst **11** (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 sodium sulfate. 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 **12** (240 mg, 61% as a 4:1 *E*/*Z* mixture). In addition, homodimers **13**[11] (57 mg, 30% based on **7**) and **14** (265 mg, 65% based on **9**) were isolated, both as *E*/*Z* mixtures. *Procedure B*: compounds **7** (197 mg, 0.5 mmol), **9** (422 mg, 1 mmol) and Grubbs catalyst **11** (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 **12** (236 mg, 60%) together with **13** and **14** in yields similar to those of procedure A. Homodimer **14** could be recycled to **12** through reaction with **7** under the same metathesis conditions. It gave compound **12** in 56% yield, together with excess **14** and homodimer **13**.

*3.1.2.1. Compound **12**.* Oil; ^1H NMR ($CDCl_3$) (signals from the major *E* isomer) δ 7.65 (4H, br d, $J\sim$7.5 Hz), 7.45–7.25 (16H, br m),

5.50–5.40 (2H, m), 4.62 (2H, br d, J=11.6 Hz), 4.50–4.40 (3H, m), 4.10–4.00 (2H, m), 4.00–3.90 (2H, m), 3.85 (1H, m), 3.68 (2H, t, J=6 Hz), 2.50 (2H, t, J=7.3 Hz), 2.39 (2H, t, J=7.3 Hz), 2.20–2.10 (2H, m), 2.05–2.00 (2H, m), 1.85 (2H, br quint, $J\sim$7 Hz), 1.70–1.50 (4H, m), 1.40–1.25 (4H, m), 1.08 (9H, s); ^{13}C NMR ($CDCl_3$) (signals from the major *E* isomer) δ 211.0, 161.2, 137.3, 137.2, 133.9 (×2), 19.2 (C), 135.5 (×4), 129.6 (×2), 128.7, 128.5 (×2), 128.2, 128.0, 127.9, 127.7 (×4), 127.6 (×4), 88.8, 87.8, 62.8, 62.3 (CH), 72.7, 71.6, 67.2, 63.1, 42.7, 42.6, 39.0 (×2), 35.2, 32.3, 32.1, 29.2, 28.8, 23.7, 23.3 (CH_2), 26.9 (×3) (CH_3); IR ν_{max} 1761, 1714 (C=O) cm^{-1}; HR FABMS m/z 788.4323 (M+H$^+$), calcd for $C_{49}H_{62}NO_6Si$ 788.4346.

*3.1.3. 1,20-Bis(tert-butyldiphenylsilyloxy)eicos-10E,Z-ene-4,17-dione (**14**).* Obtained as described above as an *E*/*Z* mixture: oil; ^{1}H NMR ($CDCl_3$, signals from the major *E* isomer) δ 7.65 (8H, br d, $J\sim$7.5 Hz), 7.45–7.30 (12H, br m), 5.40–5.35 (2H, m), 3.69 (4H, t, J=6.5 Hz), 2.54 (4H, t, J=7.3 Hz), 2.40 (4H, t, J=7.3 Hz), 2.00 (4H, m), 1.86 (4H, br quint, $J\sim$7 Hz), 1.60 (4H, br quint, $J\sim$7 Hz), 1.40–1.30 (8H, m), 1.06 (18H, s).

*3.1.4. 13-[(2R,3R,4R,5R)-3,4-Bis(benzyloxy)-5-(hydroxy-methyl)-pyrrolidin-2-yl]-1-hydroxytridec-10E-en-4-one (**15**).* A solution of compound **12** (315 mg, 0.4 mmol) in 3:1 EtOH/H_2O (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 over anhydrous $MgSO_4$ 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 **15** (150 mg, 72%) as a 4:1 *E*/*Z* mixture. For the synthesis of broussonetine C, the *E*/*Z* mixture was used as such in the hydrogenation step (see below). For the synthesis of broussonetine O, the *E*/*Z* mixture was subjected to repeated column chromatography on silica gel. In this way, a fraction containing almost pure (*E*)-**15** was obtained.

*3.1.4.1. Compound (E)-**15**.* Oil; $[\alpha]_D$ +8.2 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40–7.25 (10H, br m), 5.40–5.30 (2H, m), 4.60–4.50 (4H, m), 3.85 (1H, m), 3.80–3.70 (4H, m), 3.65–3.55 (4H, br m), 3.44 (1H, m), 3.25–3.20 (1H, m), 2.50 (2H, t, J=7 Hz), 2.40 (2H, t, J=7 Hz), 2.20–1.95 (4H, br m), 1.80 (2H, br quint, $J\sim$7 Hz), 1.75–1.60 (2H, m), 1.55 (2H, br quint, $J\sim$7 Hz), 1.40–1.20 (4H, br m); ^{13}C NMR ($CDCl_3$) δ 212.2, 137.8, 137.7 (C), 131.1, 129.2, 128.5 (×2), 128.4 (×2), 127.8 (×3), 127.7 (×3), 88.4, 85.3, 61.9, 61.4 (CH), 72.0 (×2), 63.7, 61.5, 42.7, 39.4, 33.0, 32.2, 29.5, 29.1, 28.5, 26.5, 23.6 (CH_2); IR ν_{max} 3380 (br, OH), 1709 (C=O) cm^{-1}; HR FABMS m/z 524.3379 (M+H$^+$), calcd for $C_{32}H_{46}NO_5$ 524.3376.

*3.1.5. Broussonetine O (**5**).* A solution of (*E*)-**15** (26 mg, 0.05 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −78 °C under N_2 and treated with BCl_3 (0.4 mL of a 1 M solution in CH_2Cl_2, 0.4 mmol). The reaction mixture was stirred at −78 °C for 5 h and then at −30 °C for 1 h. The reaction was quenched through addition of MeOH (1 mL) followed by stirring at room temp for 1 h. After removal of all volatiles under reduced pressure, the crude residue was dissolved in MeOH (1 mL) and evaporated again to dryness. The yellowish oily residue was then subjected to column chromatography 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 0.5 M HCl). Elution was performed first with distilled water (50 mL) and then with 1 M aq ammonia (until elution of the product). This provided **5** (14 mg, 80%): amorphous solid; $[\alpha]_D$ +24.8 (*c* 0.35, MeOH), lit.[8d] $[\alpha]_D$ +22.7 (*c* 0.37, MeOH); ^{1}H NMR (pyridine-d_5) δ 5.55–5.45 (2H, m), 4.73 (1H, br t, J=6.3 Hz), 4.46 (1H, m), 4.30–4.20 (2H, m), 3.90–3.85 (3H, m), 3.68 (1H, m), 2.65 (2H, br t, J=7.3 Hz), 2.40 (3H, m), 2.20 (1H, m), 2.08 (3H, m), 1.94 (3H, m), 1.60–1.50 (2H, m), 1.40–1.20 (4H, br m), five exchangeable protons (4OH, NH) were not detected under these conditions; ^{13}C NMR (pyridine-d_5) δ 209.3 (C), 131.5, 129.2, 81.5, 77.4, 65.2 (×2), 62.3 (CH), 60.5, 45.0, 42.6, 39.4, 32.5, 29.8 (×2), 28.0, 26.9, 23.9 (CH_2). Hydrogenation of **5** under standard conditions (Pd/C, H_2) gave **1**.

Even though no natural sample of broussonetine O was available for direct comparison with synthetic compound **5**, the hydrogenation of the latter to **1** (broussonetine C), for which an authentic sample was available, gives support to our structural assignment. Besides, the reaction sequence, which leads to **5** is almost identical to that giving **6**, the structure of which could be secured (see below).

There are differences in the chemical shifts of some signals between the synthetic and the natural sample,[8d] 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.[18]

*3.1.6. Broussonetine C (**1**).* Compound **15** (26 mg, 0.05 mmol) as an *E*/*Z* mixture (see above) was dissolved in MeOH (5 mL) and treated with 6 M 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 subjected to column chromatography 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 0.5 M HCl). Elution was performed first with distilled water (50 mL) and then with 1 M aq ammonia (until elution of the product). This gave **1** (15 mg, 90%). 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: amorphous solid; $[\alpha]_D$ +26.3 (*c* 0.85, MeOH), lit.[8c] $[\alpha]_D$ +25 (*c* 0.96, MeOH); ^{1}H NMR (pyridine-d_5) δ 4.92 (1H, t, J=6.3 Hz), 4.66 (1H, br t, J=6.5 Hz), 4.50–4.40 (2H, m), 4.30 (1H, m), 4.08 (1H, m), 3.88 (2H, t, J=6.5 Hz), 2.67 (2H, t, J=7 Hz), 2.38 (2H, t, J=7 Hz), 2.35–2.25 (2H, m), 2.07 (2H, br quint, $J\sim$7.3 Hz), 1.85–1.60 (4H, br m), 1.60–1.50 (2H, m), 1.40–1.10 (8H, br m), five exchangeable protons (4OH, NH) were not detected under these conditions; ^{13}C NMR (pyridine-d_5) δ 210.6 (C), 80.5, 76.5, 65.1, 61.2 (CH), 63.0, 59.5, 42.7, 39.5, 31.7, 29.5 (five overlapped signals), 27.7, 26.6, 24.0 (CH_2); HR FABMS m/z 346.2581 (M+H$^+$), calcd for $C_{18}H_{36}NO_5$ 346.2593. The identity of the natural and the synthetic sample was secured by comparison with an authentic sample.

As in the previous case, there are differences in the chemical shifts of some signals between the synthetic and the natural sample[8d] and for the same reasons.[18]

*3.1.7. Broussonetine P (**6**).* Compound **16** (*E*+*Z*) was obtained as reported in our previous paper.[11] For the preparation of (*E*)-**16**, the mixture was subjected to a repeated column chromatography on silica gel using the same elution mixtures as for (*E*)-**15**. In this way, a fraction containing almost pure (*E*)-**16** was obtained.

A solution of (*E*)-**16** (26 mg, 0.05 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −78 °C under N_2 and treated with BCl_3 (0.4 mL of a 1 M solution in CH_2Cl_2, 0.4 mmol). The reaction mixture was stirred at −78 °C for 5 h and then at −30 °C for 1 h. The reaction was quenched through addition of MeOH (1 mL) and stirring at room temp for 1 h. After removal of all volatiles under reduced pressure, the crude residue was dissolved in MeOH (1 mL) and evaporated again to dryness. The yellowish oily residue was then

subjected to column chromatography 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 0.5 M HCl). Elution was performed first with distilled water (50 mL) and then with 1 M aq ammonia (until elution of the product). This afforded **6** (13 mg, 75%): amorphous solid; $[\alpha]_D$ +29.7 (*c* 0.3, $CHCl_3$), lit.[8d] $[\alpha]_D$ +28.8 (*c* 0.96, MeOH); ^{1}H NMR (pyridine-d_5) δ 5.55–5.45 (2H, m), 4.90 (1H, br t, $J\sim$6.5 Hz), 4.66 (1H, br t, $J\sim$6.5 Hz), 4.50–4.40 (2H, m), 4.26 (1H, m), 4.10 (1H, m), 3.85 (2H, t, J=6.5 Hz), 2.60–2.50 (2H, m), 2.45 (2H, t, J=7.5 Hz), 2.40 (2H, m), 2.33 (2H, t, J=7.5 Hz), 1.95–1.80 (4H, br m), 1.75 (2H, m), 1.60–1.50 (2H, m), 1.40–1.20 (2H, br m), five exchangeable protons (4OH, NH) were not detected under these conditions; ^{13}C NMR (pyridine-d_5) δ 210.5 (C), 131.7, 129.0, 80.6, 76.4, 65.2, 61.7 (CH), 62.2, 59.5, 42.5, 42.4, 33.0, 32.5, 31.9, 29.7, 29.0, 23.5, 21.0 (CH_2); HR FABMS *m*/*z* 344.2443 ($M+H^+$), calcd for $C_{18}H_{34}NO_5$ 344.2437. The identity of the natural and the synthetic sample was secured by comparison with an authentic sample.

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Supplementary data

Supplementary data contain the graphical NMR spectra. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2009.10.066.

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