

First Total Synthesis of a New Tetrasubstituted Pyrrolidine Alkaloid, Broussonetine C

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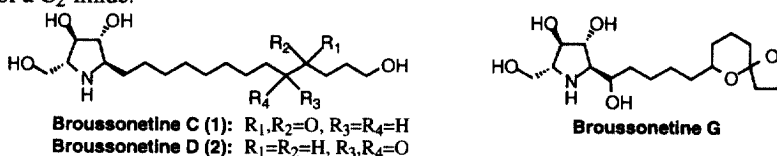
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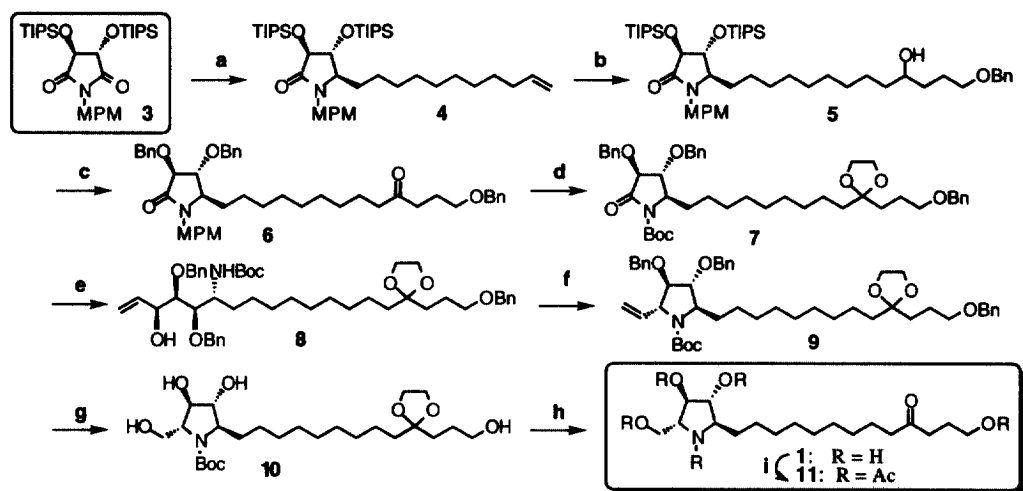
Abstract: An efficient and stereodefined process is described for the first asymmetric synthesis of a tetrasubstituted pyrrolidine alkaloid, broussonetine C, as a potent β -galactosidase and β -mannosidase inhibitor by featuring the elaboration through asymmetric deoxygenation of a homochiral C₂-imide and stereoselective reduction of its derivative. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Broussonetine C, Pyrrolidine Alkaloid, C₂-imide, Deoxygenation, Tartaric Acid.

Broussonetine C (**1**) and D (**2**) together with several structurally related compounds were first isolated in 1997 by Kusano *et al.*¹ from the branch of *Broussonetia kazinoki* SIEB. (Moraceae) (whose branches, leaves, and fruits have been used as a diuretic, a tonic, and a suppressant for edema in Chinese folk medicine.) These compounds exhibit unique β -galactosidase and β -mannosidase inhibitory activities, while their congeners inhibit other glycosidases. After structural characterization by the same group based on spectroscopic and chemical methods, these were revealed to be a new class of tetrahydroxylated pyrrolidine alkaloids possessing a 1,2,3,4-tetrasubstituted structure² situated in all *trans* positions. Since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol, no report concerning the total synthesis of **1** or **2** has been appeared to date despite those pharmacological activities and interesting structural features. With these considerations in mind, we wish to communicate the details of the first asymmetric synthesis of **1** by means of requisite stereoselective reduction of a hydroxypyrrolidine intermediate elaborated through Lewis acid-promoted deoxygenation of a C₂-imide.



TIPS-protected C₂-imide (**3**) obtained from D-tartaric acid³ was treated with undecenylmagnesium bromide at ambient temperature to give the quaternary α -hydroxylactam intermediate, which underwent subsequently BF₃·OEt₂-promoted reductive deoxygenation with Et₃SiH,⁴ leading to the *trans*-substituted lactam **4** exclusively (96% d.e., determined by HPLC using Daicel Chiralpak AS) in 83% yield. After oxidative cleavage of the olefinic part in **4** followed by the coupling reaction with the C₃-unit containing a hydroxyl function, **5** thus obtained was subjected to oxidation with PCC and then exchange of the TIPS-protecting groups to benzylethers to resist changes in pH resulted in the preparation of **6** in high yield. This was deprotected and transformed into the *N*-Boc lactam **7** by 2 steps to enhance the nucleophilicity. The second



Scheme 1. Reagents and conditions: (a) 1, undecenylmagnesium bromide, THF, rt; 2, Et_3SiH , $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , $-78 \sim -50^\circ\text{C}$; 83% (2 steps); (b) 1, OsO_4 , NMO, acetone- H_2O (1:1); 99%; 2, NaIO_4 , $\text{Et}_2\text{O}-\text{H}_2\text{O}$ (1:1); 3, benzyloxypropylmagnesium bromide, THF, 0°C ; 85% (2 steps); (c) 1, PCC, CH_2Cl_2 , MS 4A; 90%; 2, Bu_4NF , THF; 92%; 3, BnBr , Ag_2O , CH_3COOEt ; 100%; (d) 1, CAN, CH_3CN ; 70%; 2, $\text{HOCH}_2\text{CH}_2\text{OH}$, cat. *p*-TsOH, benzene, reflux; 96%; 3, $(\text{Boc})_2\text{O}$, Et_3N , DMAP, CH_2Cl_2 ; 100%; (e) 1, vinylmagnesium bromide, THF, -78°C ; 2, $\text{NaBH}_4-\text{CeCl}_3$, MeOH, -45°C ; 78% (2 steps); (f) 1, MsCl, Et_3N , CH_2Cl_2 ; 2, *t*-BuOK, THF; 92% (2 steps); (g) 1, OsO_4 , NMO, acetone- H_2O (1:1); 100%; 2, NaIO_4 , $\text{Et}_2\text{O}-\text{H}_2\text{O}$ (1:1); 3, NaBH_4 , MeOH; 92% (2 steps); 4, Pd (black), 4.4% $\text{HCOOH}-\text{MeOH}$; 83%; (h) conc. HCl, CH_3COOEt ; (i) Ac_2O , pyridine, DMAP; 67% (2 steps).

Grignard addition to **7** easily afforded the labile quaternary α -hydroxypyrrolidine,⁵ which was successively subjected to reduction with NaBH_4 in the presence of CeCl_3 to provide the desired stereoisomer **8**⁶ as a sole product fortunately (determined by C^{13} NMR and chiral HPLC analysis). Then, **8** was effected by the reactions of mesylation and cyclization, leading to the homochiral tetrasubstituted pyrrolidine **9** with the desired configurations. The double bond in **9** was cleaved *via* dihydroxylation and reduced to the primary alcohol. Finally, deprotection of the obtained product was at first performed with Pd (black) due to avoid the acetal formation, affording the debenzylated *N*-Boc ketal derivative **10** of broussonetine C (**1**). Then, removal of the resulted protecting groups in **10** was conducted under acidic conditions to complete the total synthesis of **1**, whose structure was characterized after derivatization to the pentaacetate **11**, $[\alpha]_{\text{D}}^{24} -21.5$ (c 1.21, MeOH).⁷

In summary, the first asymmetric synthesis of natural broussonetine C was achieved in 21% overall yield from C_2 -imide. This process will be widely applicable to the synthesis of other broussonetine congeners.

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References and notes

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- The absolute configuration of the generated stereogenic centre in **8** was easily assigned to be *S* based on our previous results.⁵
- HRMS calcd for $\text{C}_{22}\text{H}_{46}\text{NO}_{10}$ ($\text{M}^+ + \text{H}^+$) 556.3121, found 556.3110. It seems that the compound **11** exists as a mixture of two rotational isomers concerning to the *N*-Ac bond in analogy with the case of acetylated penaresidins⁸ based on its spectra. Further details of these results will be reported and discussed elsewhere.
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