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

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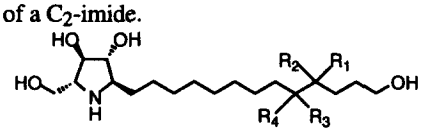
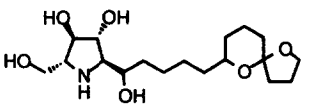
Abstract: An efficient and stereodefined process is described for the first asymmetric synthesis of a tetrasubstituted pyrrolidine alkaloid, broussoneitne C, as a potent β-galactosidase and β-mannosidase inhibitor by featuring the elaboration through asymmetric deoxgenation of a homochiral C_2-imide and stereoselective reduction of its derivative.

Keywords: Broussonetine C, Pyrrolidine Alkaloid, C_2-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 structure[2] 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 C_2-imide.



Broussonetine C (1): R_1,R_2=O, R_3=R_4=H
Broussonetine D (2): R_1=R_2=H, R_3,R_4=O



Broussonetine G

TIPS-protected C_2-imide (**3**) obtained from D-tartaric acid[3] was treated with undecenylmagnesium bromide at ambient temperature to give the quaternary α-hydroxylactam intermediate, which underwent subsequently $BF_3 \cdot OEt_2$-promoted reductive deoxgenation with Et_3SiH,[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 C_3-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

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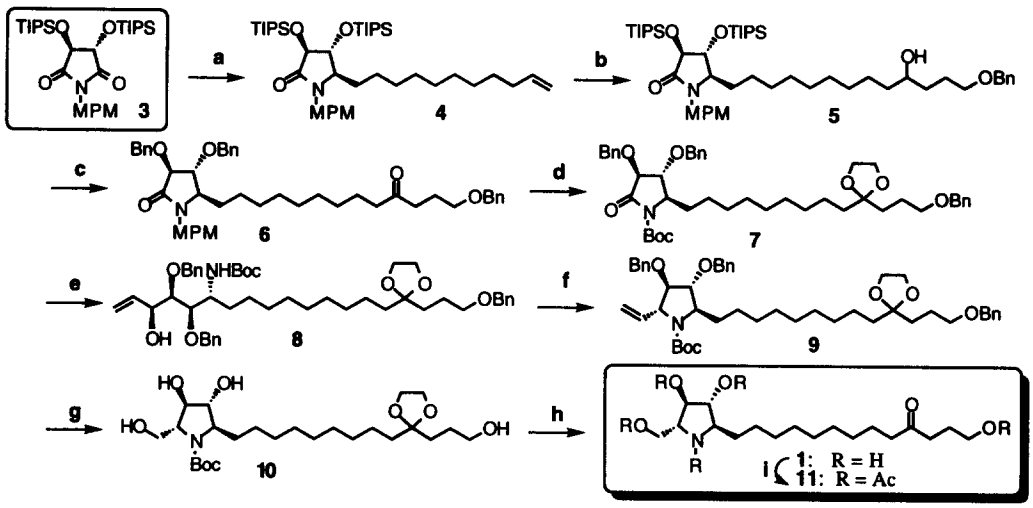

Scheme 1. Reagents and conditions: (**a**) **1**, undecenylmagnesium bromide, THF, rt; **2**, Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78~-50 °C; 83% (2 steps); (**b**) **1**, OsO_4, NMO, acetone-H_2O (1:1); 99%; **2**, $NaIO_4$, Et_2O-H_2O (1:1); **3**, benzyloxypropylmagnesium bromide, THF, 0 °C; 85% (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**, $HOCH_2CH_2OH$, cat. *p*-TsOH, benzene, reflux; 96%; **3**, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; 100%; (**e**) **1**, vinylmagnesium bromide, THF, -78 °C; **2**, $NaBH_4$-$CeCl_3$, 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**, $NaIO_4$, Et_2O-H_2O (1:1); **3**, $NaBH_4$, MeOH; 92% (2 steps); **4**, Pd (black), 4.4% HCOOH-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 cleavaged *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 derivarization to the pentaacetate **11**, $[\alpha]_D^{24}$-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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6. The absolute configuration of the generated stereogenic centre in **8** was easily assigned to be *S* based on our previous results.[5]
7. HRMS calcd for $C_{28}H_{46}NO_{10}$ (M^++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 penaresidins[8] based on its spectra. Further details of these results will be reported and discussed elsewhere.
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