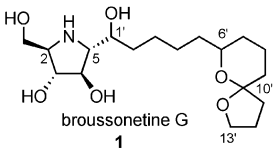
Natural Product Synthesis

Palladium-Catalyzed DYKAT of Vinyl Epoxides: Enantioselective Total Synthesis and Assignment of the Configuration of (+)-Broussonetine G**

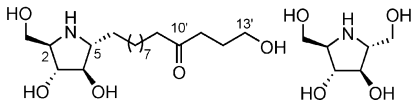
Barry M. Trost, Daniel B. Horne, and Michael J. Woltering*

The ability of polyhydroxylated pyrrolidines and pyrrolizidines to inhibit numerous glycosidases continues to draw attention to such structural types.[1] The broussonetines are a class of polyhydroxylated alkaloids that were isolated from the branches of the deciduous tree *Broussontia kazinoki*. Thus far, G. Kusano and co-workers have isolated and characterized 29 unique compounds from this family of natural products.[2] These compounds show striking glycosidase-inhibitory properties, and as such have enormous therapeutic potential as antitumor and anti-HIV agents.[3] The members of the broussonetine family all share a polyhydroxylated pyrrolidine core and a 13-carbon-atom side chain that contains various functional groups.

(+)-Broussonetine G (**1**), one of the most active inhibitors of this class ($IC_{50} = 3$ nM, β-galactosidase; 24 nM, β-glucosidase), contains a structurally interesting 5,6-spiroketal in the side chain.[4] The synthesis of **1** presents an additional



broussonetine G
1



broussonetine C
2

DMDP
3

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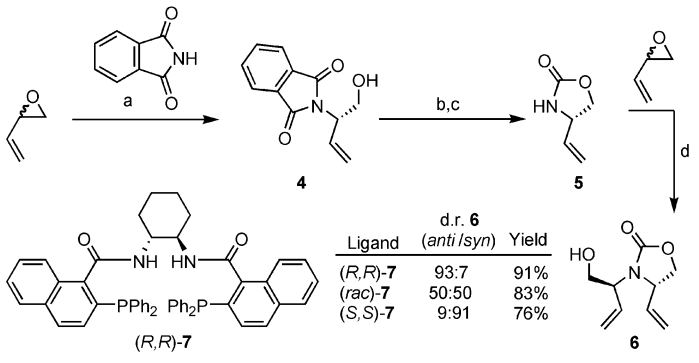
challenge in that the assignment of the relative stereochemistry of the spiroketal and the 1′-hydroxy group has not been reported.

Despite the interesting structural features and biological activity of these compounds, only one synthesis has been reported: Yoda et al. described the chiral-pool-based synthesis of broussonetine C (**2**).[5] Herein we describe an enantioselective synthesis that involves a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT)[6] process, which potentially allows access to all members of the broussonetine family as well as many other pyrrolidine-containing glycosidase inhibitors, including pyrrolizidine and indolizidine types.

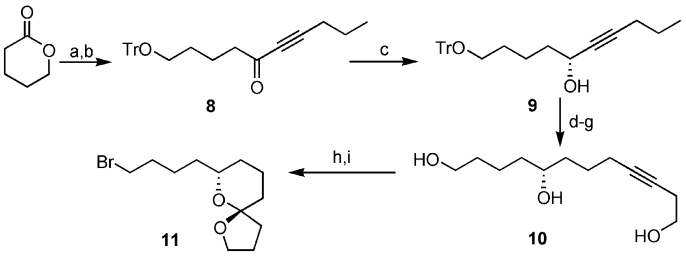
We envisioned that two successive palladium-catalyzed asymmetric allylic alkylations of butadiene monoxide with a suitable nitrogen nucleophile followed by ring-closing metathesis (RCM) could provide a unique access to chiral, substituted pyrrolidines. This strategy could potentially be used to provide all diastereomers of the proposed structure, a key feature for us since the full stereochemistry of our target was not known. Furthermore, we hoped that this strategy could also be used to access many other important polysubstituted pyrrolidine alkaloid natural products, such as (2*R*,3*R*,4*R*,5*R*)-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP; **3**).[7]

The synthesis began with the addition of phthalimide to butadiene monoxide to give **4**[8] in a highly regio- and enantioselective fashion (94% yield, 98% *ee*) (Scheme 1). After deprotection of the diimide to give a vinylglycinol, formation of the cyclic carbamate with triphosgene gave vinyloxazolidinone **5**, the substrate for the second palladium-catalyzed DYKAT reaction. Despite our attempts with various other vinylglycinol surrogates in this reaction, we found the best results were obtained with oxazolidinone **5**, which gave the desired product **6** in 91% yield with excellent diastereoselectivity (d.r. 93:7). We observed that the diastereoselectivity of the product is completely dependent on the choice of ligand (see Table in Scheme 1).



Scheme 1. Synthesis of the chiral core subunit. Reagents and conditions: a) $[\{(C_3H_5)PdCl\}_2]$ (0.4 mol%), (*R*,*R*)-**7** (1.2 mol%), Na_2CO_3, CH_2Cl_2, room temperature, 94%, 98% *ee*; b) ethylenediamine, EtOH, reflux, 84%; c) triphosgene, $NaHCO_3$, toluene/H_2O, 0°C, 85%; d) $[Pd_2(dba)_3]\cdot CHCl_3$ (0.25 mol%), (*R*,*R*)-**7** (0.75 mol%), DBU (1 mol%), CH_2Cl_2, room temperature, 91%, 93:7 d.r. dba = *trans*,*trans*-dibenzylideneacetone, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

The synthesis of the side chain began with the addition of 1-pentyne to δ-valerolactone, followed by protection of the primary alcohol with trityl chloride to give alkynone **8** (Scheme 2). Reduction of **8** by using Noyori's enantioselective transfer hydrogenation protocol[9] gave propargyl alcohol

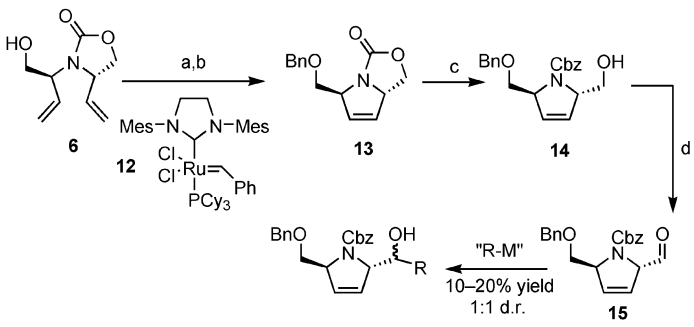


Scheme 2. Synthesis of the spiroketal side chain **11**. Reagents and conditions: a) *n*BuLi, 1-pentyne, THF, −78°C→RT, 94%; b) TrCl, NEt_3, DMAP, DMF, room temperature, 77%; c) [(η^6-*p*-cymene)Ru{(1*R*,2*R*)-*p*-TsNCH(Ph)CH(Ph)NH}] (3 mol%), *i*PrOH, room temperature, 95%, 97% *ee*; d) KH (10 equiv), 1,3-diaminopropane, THF, 79%; e) 3,4-dihydro-2*H*-pyran, PPTS, CH_2Cl_2, room temperature, 76%; f) *n*BuLi, $AlMe_3$, $BF_3\cdot OEt_2$, Et_2O, −78°C; then ethylene oxide, −78°C→RT, 76%; g) HCl/MeOH (1%), 95%; h) $[PdCl_2(PhCN)_2]$ (2 mol%), CH_3CN/THF (3:2), 85%, 97:3 d.r.; i) PPh_3Br_2, imidazole, THF, 91%. Tr = trityl = triphenylmethyl, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylylformamide, Ts = *p*-toluenesulfonyl, PPTS = pyridinium *p*-toluenesulfonate.

9 (97% *ee*). The alkyne zipper reaction[10] (KH, 1,3-diaminopropane) was performed to give the desired terminal alkyne. Protection of the secondary alcohol followed by alkylation of the terminal alkyne with ethylene oxide provided the desired homopropargyl alcohol. After acid-catalyzed global deprotection, the resulting triol **10** underwent the requisite regioselective palladium-catalyzed spiroketalization reaction[11] to give the desired 5,6-spiroketal with excellent diastereoselectivity (d.r. 97:3). The high stereoselectivity of this cyclization reaction is attributed to the anomeric affect.[12] Subsequent bromination of the primary alcohol gave bromide **11**.

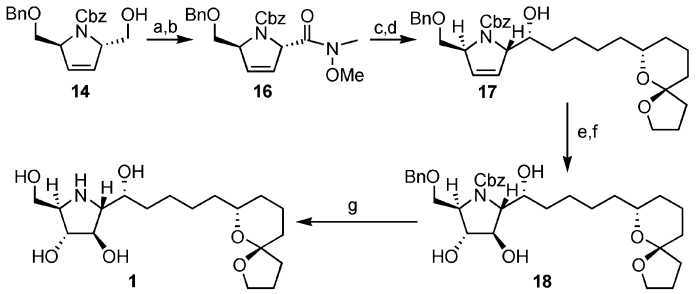
The synthesis of the pyrrolidine core continued with the protection of the homoallylic alcohol with benzyl bromide, followed by RCM with a Grubbs second-generation catalyst[13] **12** to give 2,5-dihydropyrrole **13** (Scheme 3). The absolute stereochemistry was assigned based on the stereochemical assignment of vinylglycinol performed previously[8] and single-crystal X-ray analysis of oxazolidinone **13**.[14] Unfortunately, oxidation of the primary alcohol derived from **13** after deprotection of the benzyl group led only to decomposition products. We surmised that the oxazolidinone moiety was probably responsible for the lability of the aldehyde intermediate and therefore adopted an alternative pathway. Saponification of the oxazolidinone and protection of the resulting amine with BnOCOCl gave alcohol **14**. Subsequent oxidation with Dess–Martin periodinane delivered the aldehyde **15**. Our attempts to add various alkyl nucleophiles to aldehyde **15** resulted in very poor yields of the desired products and always produced a 1:1 diastereomeric ratio of alcohols.

The failure of the coupling reaction led us to consider an alternate strategy. Oxidation of alcohol **14** (TEMPO/bleach/



Scheme 3. Synthesis and attempted coupling of aldehyde **15**. Reagents and conditions: a) NaH; BnBr, TBAI, THF, room temperature, 84%; b) **12** (1.2 mol%), CH_2Cl_2, reflux, 87%; c) 1) NaOH, EtOH/H_2O (3:1), reflux; 2) BnOCOCl, $NaHCO_3$, Na_2CO_3, H_2O, 0°C→RT, 99% from **13**; d) Dess–Martin periodinane, CH_2Cl_2, 0°C, 95%; TBAI = tetrabutylammonium iodide; Cbz = benzyloxycarbonyl.

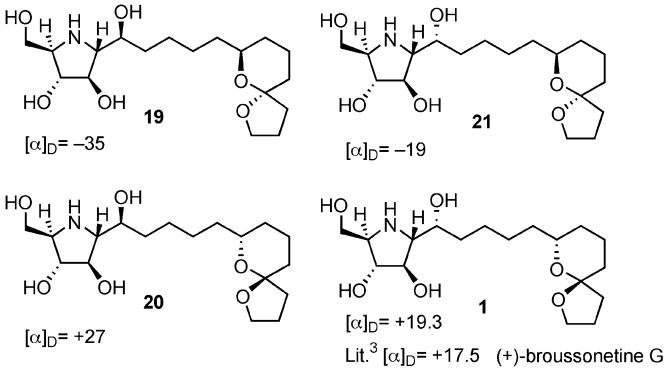
KBr) led to a carboxylic acid, which was converted into Weinreb amide **16** (Scheme 4). Gratifyingly, the subsequent coupling of the two fragments via the alkyl magnesium reagent derived from alkyl bromide **11** led to a ketone.



Scheme 4. Completion of the synthesis of **1**. Reagents and conditions: a) TEMPO, KBr, NaOCl, $NaHCO_3$, acetone/H_2O, 0°C, 89%; b) HNMe(OMe)·HCl, pybop, *i*Pr_2NEt, CH_2Cl_2, 81%; c) 1) **11** (1.2 equiv), Mg, THF, reflux→RT; **16**, room temperature, 65%; d) DIBAL-H, Et_2O, 0°C, 76%, 4.3:1 d.r.; e) $F_3CC(O)CH_3$, oxone, Na_2CO_3, CH_3CN/H_2O, 0°C, 68%; f) TFA, THF/H_2O, 65°C, 73%; g) Pd/C, MeOH, HCl, H_2 (1 atm), room temperature, 95%; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical, pybop = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, DIBAL-H = diisobutylaluminum hydride, TFA = trifluoroacetic acid.

Subsequent diastereoselective reduction of the ketone with DIBAL-H gave a 4.3:1 (*R*/*S*) diastereomeric mixture of secondary alcohols. The major diastereomer, alcohol **17**, presumably results from a four-centered transition state.[15] In contrast, reduction of the ketone with $NaBH_4$ led to a diastereomeric mixture of alcohols (*R*/*S* 1:2.6, 83%), the major product of which was the expected Cram product. The stereochemistry of the secondary alcohol was established by ^{1}H NMR analysis of the (*R*)- and (*S*)-*O*-methylmandelates.[16] The assignment of the stereochemistry of the C1′ center as *R* also agrees with the assignment of several other broussonetines that contain an hydroxy group at C1′ whose configurations were determined by Kusano et al. by using the Mosher method.[2] Epoxidation of dihydropyrrole **17** led to a mixture of epoxides, both of which gave the same triol **18** as a single diastereomer upon hydrolysis with aqueous TFA. To complete the synthesis, removal of the protecting groups by hydrogenolysis gave **1**, whose spectra and optical rotation matched those of an authentic sample of the natural product in all respects. This constitutes the first synthesis of (+)-broussonetine G.

In addition to the natural product, the remaining three possible diastereomers of broussonetine G were synthesized during the course of our investigations by using the procedures outlined above (Schemes 1–4). Diastereomers **19** and **20** did not correlate with the spectroscopic data of the natural product (Scheme 5). However, the ^{1}H and ^{13}C NMR spectra



Scheme 5. $[\alpha]_D$ Values of diastereomers **1**, **19**, **20**, and **21**.

of **21** were nearly identical to that of **1** and the natural product.[17] Fortunately, the optical rotation was significantly different and led to our assignment of the structure of broussonetine G as shown (Scheme 5).

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Keywords: asymmetric synthesis · inhibitors · natural products · structure elucidation · total synthesis

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