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Palladium-Catalyzed DYKAT of Butadiene Monoepoxide: Enantioselective Total Synthesis of (+)-DMDP, (−)-Bulgecinine, and (+)-Broussonetine G

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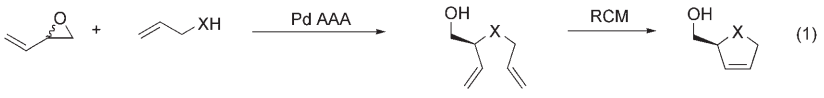
Abstract: Palladium catalyzed asymmetric allylic alkylation reaction of an amine with two equivalents of butadiene monoxide allows for the expedient synthesis of *trans*- and *cis*-2,5-dihydropyrroles. The versatility of these chiral synthons towards the synthesis of a wide variety of iminosugar natural products was demonstrated with the short and high yielding asymmetric syntheses of (+)-DMDP, and (−)-bulgecinine. In addition, the first total synthesis of (+)-broussonetine G, a potent glycosidase inhibitor, is described along with the assignment of its relative and absolute stereochemical configuration.

Keywords: asymmetric catalysis · asymmetric synthesis · natural products · palladium · total synthesis

Introduction

Pyrrolidine-, pyrrolizidine-, and indolizidine-based natural products are widely present in nature (Figure 1). The ability of this class of compounds to inhibit numerous glycosidases draws attention to such structural types. Since enzyme-catalyzed carbohydrate hydrolysis is such a biologically widespread process, it is not particularly surprising that molecules which bind to glycosidases and inhibit their function, glycosidase inhibitors, exhibit potent biological activity. The resulting potential applications of glycosidase inhibitors as antiviral, antibacterial, antimetastatic, antidiabetic, and agrochemical agents has been the subject of copious research throughout the scientific community worldwide.[1]

In approaching chiral five-membered ring heterocycles, we have been investigating a strategy represented in Equation (1) and demonstrated its effectiveness towards the synthesis of the corresponding oxygen heterocycles (X = O), most notably towards nucleosides and their analogues. Such a strategy should be equally applicable towards nitrogen heterocycles which can then serve as the basis to some pyrrolidine and pyrrolizidine alkaloids (e.g. castanospermine and swainsonine). On the other hand, alkaloids bearing carbon substituents in the 2,5-position as illustrated in Figure 2 raises a new question regarding the Pd AAA, the ability to effect a catalyst controlled regio- and diastereoselective second alkylation with butadiene monoepoxide as shown in Equation (2). This strategy should be quite versatile because of the nature of the juxtaposition of functionality as well as providing access to both the *cis* and *trans* targets enantiomerically pure. Obtaining the former enantiomerically enriched is particularly noteworthy since the diol related to **B** is, of course, *meso*.



(1)

Palladium-catalyzed DYKAT: Asymmetric allylic alkylation (AAA) reactions utilizing palladium have proven to be extremely useful and versatile synthetic transformations.[2] A general mechanism for palladium allylic alkylation is shown below (Scheme 1). The cycle involves olefin complexation, ionization of the leaving group, then nucleophilic addition followed by decomplexation. The ability to utilize each of the first four steps, with the appropriate conditions, as an enantiodescriminating event is a key feature of this process and allows facile preparation of chiral compounds from achiral starting materials.

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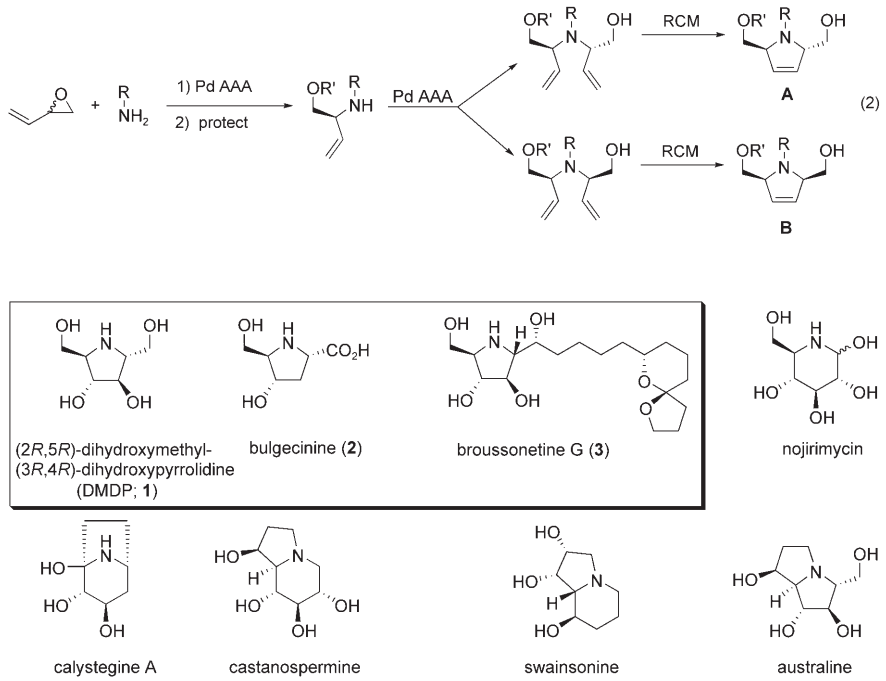


Figure 1. Representative pyrrolidine, pyrrolizidine and indolizidine natural products.

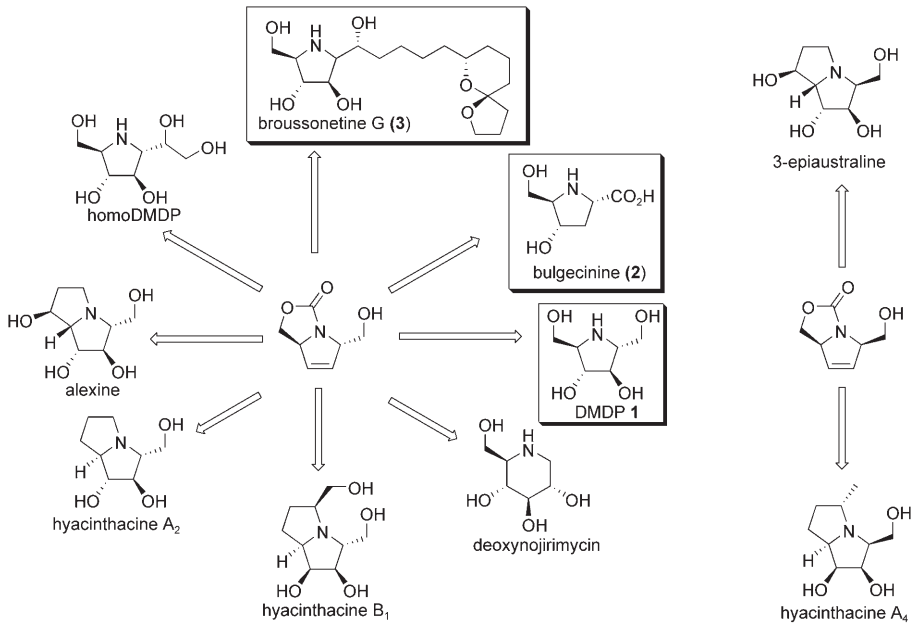


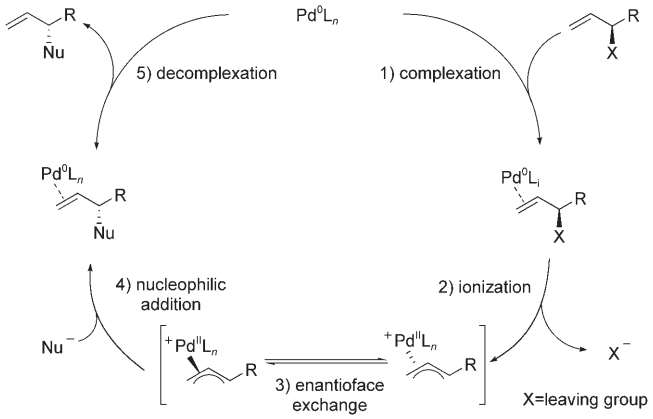
Figure 2. Some potential natural products accessible from *trans*- or *cis*-2,5-dihydropyrroles.

Allylic alkylation is known to be catalyzed by a variety of transition-metal complexes, including iron,[3] cobalt,[4] nickel,[5] molybdenum,[6] ruthenium,[7] rhodium,[8] palladium,[2] iridium,[9] tungsten,[10] and platinum.[11] Palladium has thus far proven to be the most versatile metal catalyst for AAA transformations.

A particularly worthwhile process that has emerged from transition metal asymmetric allylic alkylation is the ability to transform a racemic compound into a single enantiomer of product. This deracemization constitutes a dynamic kinetic asymmetric transformation (DYKAT), also referred to as a dynamic kinetic resolution. In most cases, the resultant enantiomerically enriched product is structurally different than the starting material and, thus is more properly termed an asymmetric transformation rather than a resolution. DYKAT reactions differ from traditional kinetic asymmetric reactions in that *both* enantiomers of the racemic starting material are converted into a single chiral product. This transformation thus allows potential yields of 100% of a particular enantiomer as opposed to only 50% for a traditional kinetic resolution process.

Previous research has shown that vinyl epoxides are excellent electrophiles for Pd catalyzed DYKAT with oxygen,[12] carbon,[13] and some nitrogen nucleophiles.[14] While there has been some research into the use of nitrogen nucleophiles in AAA chemistry, nitrogen nucleophiles have generally presented challenges in several respects. First, with primary amines, double alkylation frequently occurs since the product, a secondary amine, is more nucleophilic than the starting material, leading to mixtures of products. Second, regioselectivity of the alkylation with unsymmetrical allyl systems can be a significant problem and frequently mixtures of products are obtained. Third, the pK_a of nitrogen nucleophiles spans a wide range, from ~8 (e.g. imide) to ~35 (e.g. amine), and this makes the choice of nitrogen nucleophile difficult as each potentially shows different reactivity and selectivity.

In the present instance, the second DYKAT probes the effect of a pre-existing stereocenter on the selectivities of the process. The proximity of the stereogenic center might be anticipated to exert a strong influence on the selectivity of the second alkylation. Our initial studies describing the synthesis of broussonetine G (**3**) utilizing this method have



Scheme 1. Mechanism of palladium catalyzed allylic alkylation.

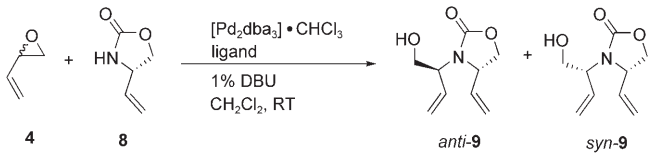
been published in preliminary form previously.[15] This paper provides a full description of that work and, much more broadly, the nature of the methodology and synthetic applications.

Results and Discussion

Synthesis of *trans*- and *cis*-2,5-dihydropyrrole synthons: For the initial allylic alkylation the palladium catalyzed DYKAT reaction of phthalimide **5** and butadiene monoxide **4**, a process which proceeds in excellent yield and selectivity, was utilized (Scheme 2). This reaction was reported previously by our group and led to the asymmetric syntheses of vinylglycinol, (+)-ethambutol and (*R*)-vigabatrin.[14] In our studies of this reaction, further optimization from previously published results allows scale up to >50 g and lower catalyst (0.4 mol %) and ligand (1.2 mol %) loadings and higher yields (99.6 %) than previously realized. The reaction is fairly sensitive to concentration effects and enantiomeric purity is decreased by minor concentration changes (0.09 M = 98 % *ee*, 0.26 M = 94 % *ee*). This concentration effect is likely due to the increased rate of nucleophilic attack in more concentrated media, which occurs before π–σ–π equilibration of the π-allyl intermediate can occur. In any case the enantiopurity of the product **7** can be easily improved by one recrystallization from ethanol to give product with >99 % *ee*. Unmasking of the amino group by aminolysis of **7** followed by cyclization with triphosgene affords oxazolidinone **8**, the substrate for the second palladium catalyzed DYKAT reaction.

Numerous reactions were performed with the oxazolidinone nucleophile **8** to eventually arrive at the optimized conditions shown below (Table 1, entry 4). It was observed

Table 1. Pd catalyzed DYKAT reactions, second equivalent of butadiene monoxide.[a]



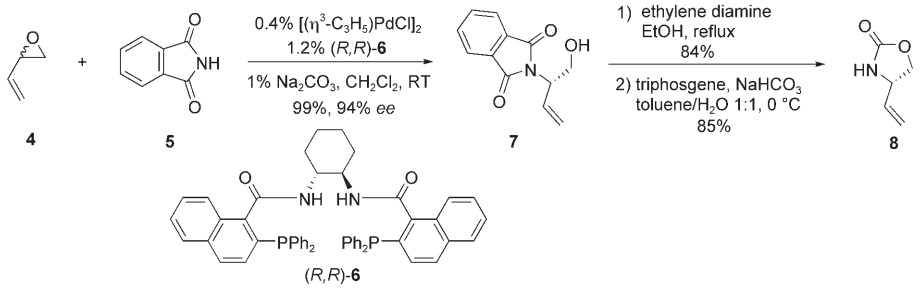
4 8 *anti*-**9** *syn*-**9**

Entry	Ligand[a]	Pd [mol %]	*t* [h]	Yield [%]	d.r. **9** [*anti*/*syn*]
1	(*R*,*R*)-**6**	1	1.5	91	93:7
2	racemic-**6**	1	3	83	50:50
3	(*S*,*S*)-**6**	1	6	83	9:91
4	(*R*,*R*)-**6**	0.25	8	94	90:10

[a] 1.5:1 mol % ligand to Pd ratios were used in all reactions.

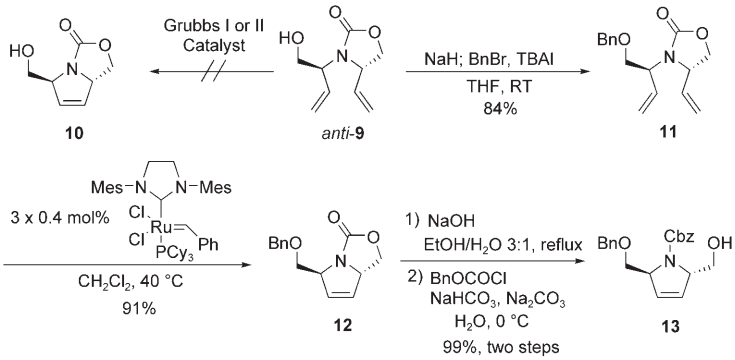
that, depending on the chirality of the ligand, the reaction rate decreases according to the following order: (*R*,*R*)-**6** > racemic-**6** > (*S*,*S*)-**6**, the result of matched and mismatched pairs of the chiral nucleophile and diastereomeric π-allyl complexes. The slower reactions are lower yielding even though the conversion is complete in the specified reaction times; presumably oligomeric products form over longer reaction times. Nevertheless, the diastereoselectivity depended mostly on the chirality of the catalyst as equal but opposite ratios for the *anti* and *syn* products were obtained (Table 1, entry 1 vs. 3). Because the product and starting material are not conveniently separable by silica gel chromatography, it is imperative to obtain full product conversion. However, the *syn*-**9** and *anti*-**9** diastereomers were separable at this stage. Lowering the catalyst loading to 0.25 mol % had a very small effect on the selectivity (Table 1, entry 1 vs. 4).

Attempts to perform the ring-closing metathesis (RCM) reaction on the unprotected homoallylic alcohol *anti*-**9** with Grubbs first- or second-generation catalyst failed to yield any product **10**. This is likely the result of coordination of the pendant free alcohol to the intermediate ruthenium carbene which shuts down the catalytic cycle. In addition, this reaction is slowed by the formation of a slightly strained bicyclic system. Protection of the free alcohol as the benzyl ether **11** disfavors ruthenium coordination and the RCM reaction, although sluggish, occurs with portionwise addition of Grubbs second-generation catalyst over 8 h intervals. The TBS ether analogue of **11**, prepared in 93 %



Scheme 2. Preparation of oxazolidinone **8**.

yield by standard procedures, also underwent metathesis under similar conditions but still extremely sluggishly giving an 83% yield (99% BRSM) after 4.75 days and four additions of catalyst. Elevated temperatures utilizing higher boiling solvents in the metathesis reaction (1,2-dichloroethane or toluene) resulted in better reaction rates, but the yield of the reactions were lower at the higher temperatures. At this stage, the 2,5-dihydropyrrole **12** may be purified either by silica gel chromatography or by recrystallization from hexanes/diethyl ether. Basic hydrolysis of the oxazolidinone and protection of the secondary amine as the benzylcarbamate affords 2,5-dihydropyrrole **13** (Scheme 3).



Scheme 3. Diene ring closing metathesis formation of 2,5-dihydropyrrole **13**.

Single crystal X-ray analysis of oxazolidinone **12** confirmed the relative stereochemistry of the 2,5-hydroxymethyl substituents as *trans* (Figure 3).[16]

We also prepared the *cis*-2,5-dihydropyrrole (**15**) by the same reaction sequence used in the synthesis of the *trans* isomer (Scheme 4). We hoped this substrate would show the generality of the reactions and that access to all four possible stereoisomers of the 2,5-dihydropyrroles is available using our protocol simply by using the appropriate ligand. This intermediate is an optically active derivative of the *meso*,*cis*-diol which would allow the asymmetric synthesis of targets having the *cis*-relative stereochemistry. The yields for these transformations are comparable to those described previously for the *trans*-isomer.

This sequence demonstrates the potential access of all four diastereomeric 2,5-dihydropyrrole stereoisomers by choice of the appropriate ligand in the successive AAA reactions (Scheme 5).

Synthesis of (+)-DMDP (2,5-dideoxy-2,5-imino-D-mannitol); One of the most important and frequently synthesized iminosugar glycosidase inhibitors is DMDP **1**. The previous syntheses of DMDP and its biological activity have been recently reviewed.[17] Our synthesis of this natural product is shown below (Scheme 6).

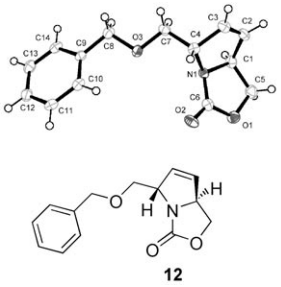
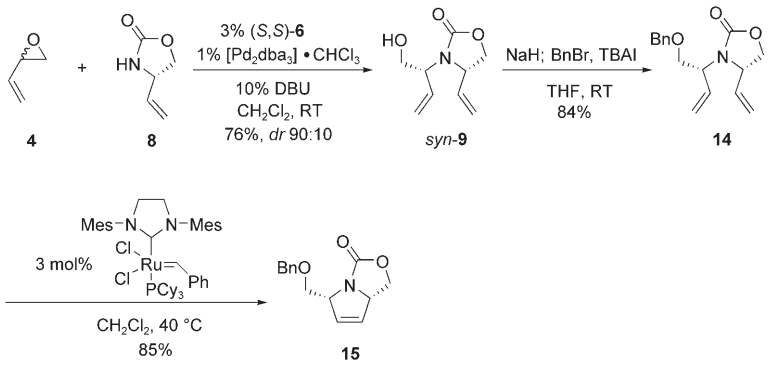


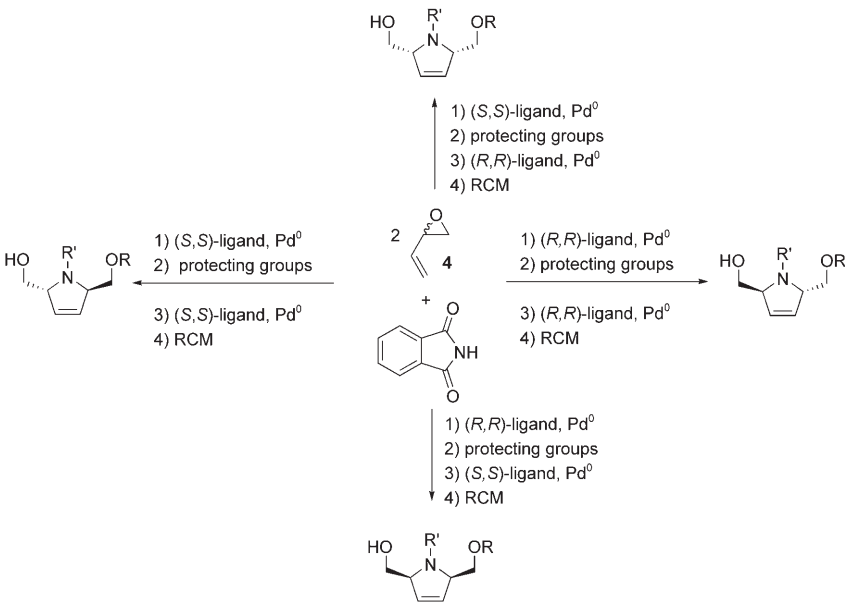
Figure 3. X-ray structure of oxazolidinone **12**.

Epoxidation of *trans*-2,5-dihydropyrrole **13** was very sluggish and required catalytic methyltrioxorhenium (MTO) to obtain appreciable conversions. *m*CPBA, vanadium/*t*BuOOH, or Mo/*t*BuOOH did not react at sufficient rates to afford product or led to decomposition. Epoxide **17** was isolated as a single diastereomer, evidently resulting from hydroxyl direction. The product was assigned based upon coupling constants and COSY spectra. Acid-catalyzed hydrolysis of the epoxide **16** gives exclusively the *trans*-diol which upon palladium-catalyzed hydrogenolysis affords synthetic (+)-DMDP (**1**), identical in all respects to the natural product. The synthesis is only 11 steps and proceeds in 22% overall yield. This result is comparable in steps to previous syntheses, but represents the first catalytic asymmetric synthesis of this important natural product.

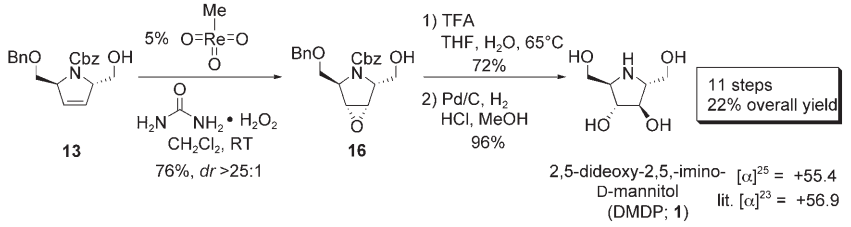
Total synthesis of (−)-bulgecinine; (−)-Bulgecinine (**2**), an unnatural amino acid, is the aglycon constituent of O-sulfonated glycopeptides of the bulgecin class (Figure 4). β-Lactam antibiotics function by binding to transpeptidase penicillin-binding proteins (PBP 2 & 3) which are responsible for crosslinking of peptidoglycan chains. The binding to the PBP's disrupts the synthesis of peptidoglycan, resulting in the release of autolysins, an enzyme that degrades the cell wall to form spheroplasts. Thus, the bacterial cells lyse and are killed by β-lactam antibiotics. The bulgecins in concert



Scheme 4. Preparation of *cis*-2,5-dihydropyrrole **15**.



Scheme 5. The possible access to all four 2,5-dihydropyrrole stereoisomers using palladium catalyzed DYKAT reactions and choice of ligand chirality.



Scheme 6. Total synthesis of (+)-DMDP (**1**).

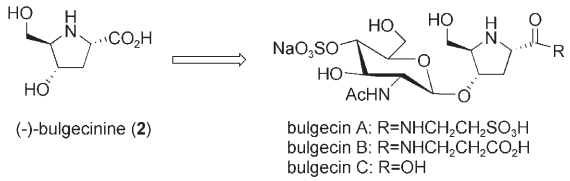


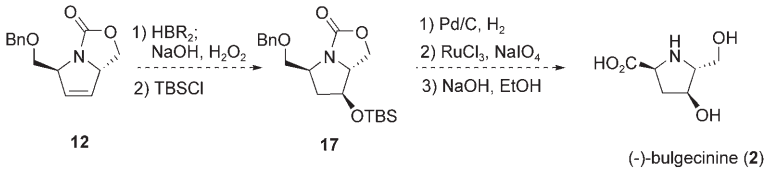
Figure 4. The aglycon, bulgecinine **2**, of the bulgecin family of natural products.

with β-lactam antibiotics induce bulge formation in the cell wall of Gram-negative bacteria by interaction with two penicillin-binding proteins (PBP 2 & 3). Although bulgecins by themselves show no antibiotic activity, the morphological changes brought about by their cooperation with β-lactam antibiotics work to greatly enhance the antibiotics' lytic activity.[18]

The bulgecins were isolated from the bacterial cultures of *Pseudomonas acidophila*, and *Pseudomonas mesoacidophila*,[19] also isolated in these cultures are the N-sulfonated β-lactam antibiotics sulfazecin and isosulfazecin. Thus, it appears the *Pseudomonas* bacteria produce both compounds to increase their synergistic antibiotic activity so they can kill other competing bacterial strains. In addition, (−)-bulgecinine (**2**) was latter found to be the amino acid constituent of SQ-28504 and SQ-28546, O-sulfonated glycopeptides isolated from cultures of *Chromobacterium violaceum*.[20]

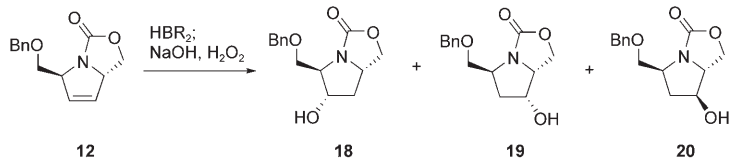
Our original synthetic plan for the synthesis is shown below (Scheme 7). The synthesis begins with the versatile *trans*-2,5-dihydropyrrole intermediate **12** synthesized from phthalimide and butadiene monoxide in six steps by palladium catalyzed DYKAT. We initially proposed that hydroboration of **12** should occur from the convex face of the bicyclic system, and distal to the bulky benzyloxymethyl group, which after silyl ether formation would give **17**. Subsequent deprotection of the benzyl ether, oxidation to the carboxylic acid, and deprotection should yield the desired product **2** in only 11 steps and would constitute the first asymmetric synthesis of this natural product from achiral starting materials.

As stated above, we originally thought that hydroboration would occur from the convex face of the bicyclic system. However, it appears from the experimental results shown below that the bulky benzyloxymethyl group determines the facial selectivity of hydroboration and gives **18** as the major product in all cases instead of the expected product **20** (Table 2). The more bulky the hydroborating reagent, the better the **18**:(**19** + **20**) ratio. Apparently, the more bulky reagent prefers reaction on the olefin face opposite the adjacent benzyloxymethyl substituent.

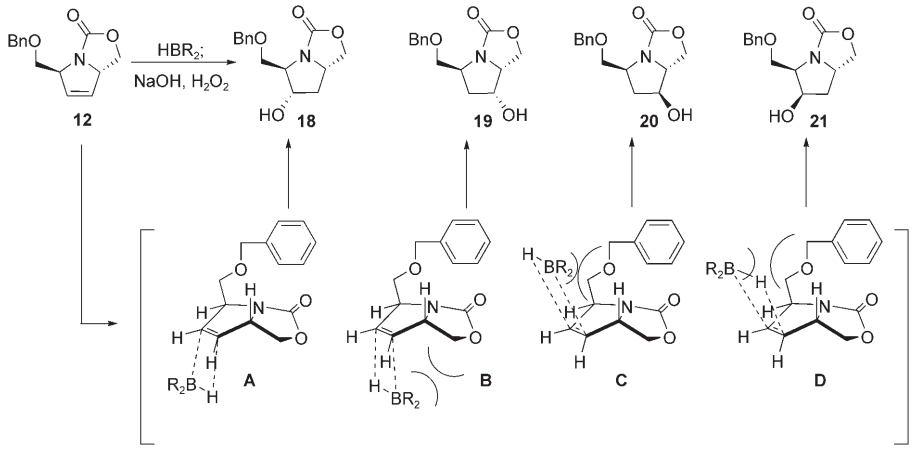


Scheme 7. Original synthetic plan for synthesis of bulgecinine **2**.

Table 2. Hydroboration of *trans*-2,5-dihydropyrrole **12**.



Entry	HBR_2	Yield [%]	Product ratio (**18**/**19**/**20**)[a]
1	9-BBN	75	100:0:0
2	$BH_3{\cdot}SMe_2$	72	45:40:15
3	catecholborane/ 5% $[RhCl(PPh_3)_3]$	89	63:25:12

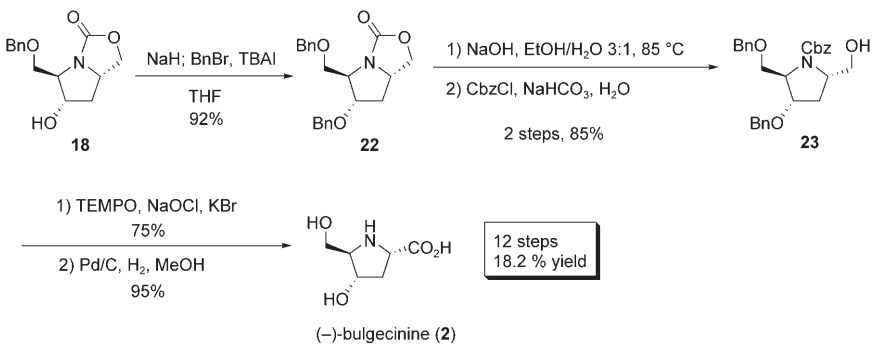


Scheme 8. Transition states of diastereoselective hydroboration of oxazolidinone **12**.

These results can be interpreted by looking closely at the conformation of oxazolidinone **12**, which is known from our X-ray structure of this compound (Figure 3 and Scheme 8). It appears that the olefin prefers attack on the concave face of the bicyclic system, distal to the oxazolidinone ring, via transition state **A**, to give alcohol **18** as the major product. The alternative regioselectivity via transition state B is disfavored by a vicinal eclipsing interaction between the boron and the oxazolidinone ring. Presumably, the steric hindrance of the benzyloxymethyl group overrides the inherent convex/concave facial selectivity, and intermediates **C** and **D** are disfavored from unfavorable 1,2- and 1,3-steric interactions. Meyers et al. have described similar results in the alkylation from the concave face of a bicyclic lactam.[21]

The synthesis of (−)-bulgecinine (**2**) was completed by protection of the secondary hydroxy group to give benzyl ether **22**, hydrolysis of the oxazolidinone, and protection of the amine affords benzyl carbamate **23** (Scheme 9). TEMPO oxidation of the primary alcohol to the carboxylic acid followed by global deprotection by palladium-catalyzed hydrogenolysis gave the natural product, (−)-bulgecinine (**2**) in 12 steps and 18% overall yield. Of the four asymmetric syntheses of this natural product,[22] ours is one of the shortest and has the highest overall yield.

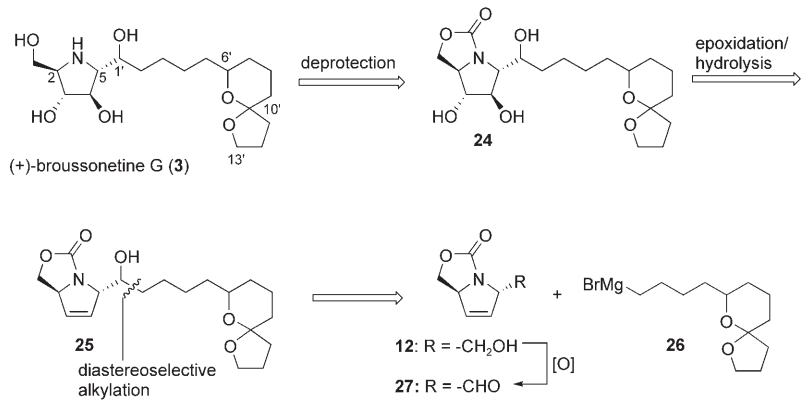
Total synthesis of (+)-broussonetine G: The broussonetines, A–X, which were only recently discovered, are isolated from the branches of the Asian paper mulberry tree *Broussontia kazinoki*, and comprise a new class of glycosidase inhibitor.[23] Each broussonetine contains a polyhydroxylated pyrrolidine and a 13 carbon side chain with differing functionality. The 29 unique broussonetines isolated thus far show very potent and selective glycosidase inhibitory properties. It is particularly interesting that the variation of the 13 carbon side chain functionality plays a key role in influencing the potency and enzyme specificity of glycosidase inhibitory activity. In addition, this lipophilic side chain could potentially be useful in drug development as lipophilic moieties are known to facilitate drug bioavailability. As our target, we chose broussonetine G (**3**) due to its very high β-glucosidase ($IC_{50}=3$ nM) and β-galactosidase ($IC_{50}=24$ nM) inhibitory properties as well as the interesting functionality, a 5,6-spiroketal, incorporated in the side chain. Since the relative stereochemistry of the natural product at the spiroketal and the 1′-hydroxyl was not reported; we envisioned a flexible, concise, and atom-economic approach to broussonetine G that



Scheme 9. Completion of the total synthesis of bulgecinine **2**.

would allow easy manipulation of these centers during the course of the synthesis.[15] Broussonetine A–X's striking glycosidase inhibiting properties let them appear as potentially interesting lead structures for the drug development targeting a medical treatment of diabetes, cancer or AIDS.[24]

The retrosynthetic analysis of broussonetine G (Scheme 10) again takes advantage of the *trans*-2,5-dihydropyrrole core **12** described previously. Thus, the natural product could be obtained by simple oxazolidinone hydrolysis to give triol **24**. The *trans*-diol at C-3 and C-4 of **24** would be installed by diastereoselective epoxidation and regioselective epoxide opening of 2,5-dihydropyrrole **25**. Finally, the addition product is derived from a diastereoselective nucleophilic addition of an organometallic bearing side chain **26** to an aldehyde **27** derived from **12**.



Scheme 10. Retrosynthesis of broussonetine G (**3**).

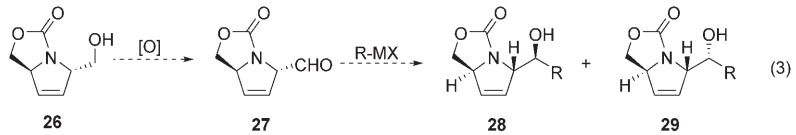
Utilizing the chiral *trans*-2,5-dihydropyrrole **12** we first turned our attention to the oxidation to an aldehyde **27** [Eq. (3)]. We hoped the resulting aldehyde would allow diastereoselective addition of organometallic reagents to yield chiral secondary alcohols **28** or **29**. This strategy would allow synthesis of many of the members of the broussonetine family simply by selecting the appropriate organometallic side chain equivalent. Unfortunately numerous attempts to oxidize alcohol **12** led either to decomposition of the starting material to unrecognizable byproducts, or no reaction. In addition, when we attempted to add nucleophiles to the crude reaction mixture of the resulting aldehyde none of the desired addition products were obtained.

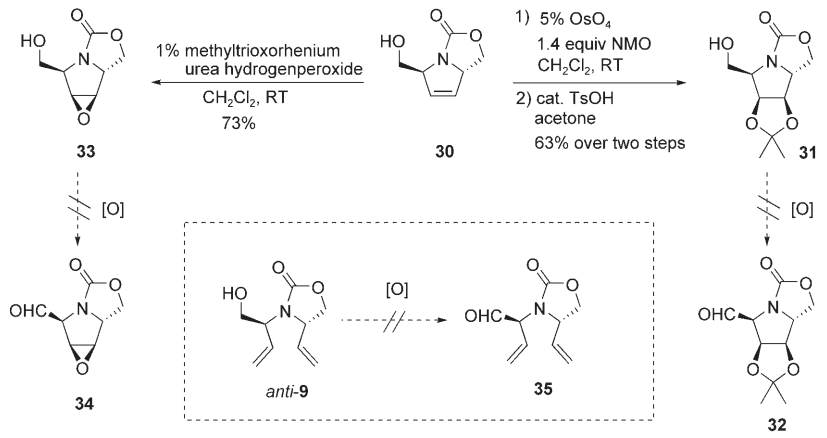
Eventually, it became apparent that the cause for the decomposition of the aldehyde was due to the strain inherent in the bicyclic system containing an oxazolidinone. Dihydroxylation of 2,5-dihydropyrrole **30**, obtained in 98% yield by TBAF desilylation of the corresponding silyl ether, followed by protection of the *cis*-diol as the acetonide yielded **31** (Scheme 11). Attempts to oxidize acetonide **31** to aldehyde **32** also failed. Since the Moffatt–Swern oxidation of a similar hydroxymethyl substrate was reported to give good yields by Ikota in his synthesis of swainsonine,[25] and also by others with similar substrates, we surmised that the oxazolidinone was the most likely cause of the instability of the aldehyde. Further evidence for the role of the oxazolidinone moiety in the decomposition of the aldehyde product was obtained by attempting oxidation of both the substrate containing an epoxide **33**, and also the diene substrate *anti*-**9** (see Table 1). These reactions also led only to complete decomposition of the starting materials.

At first, we had planned to carry out our synthesis via the N-Boc protected aldehyde **38** (cf. Scheme 12). However, the formation of the *tert*-butyl carbamate was difficult due to the steric demands of the amine, and a two-step procedure was required to first form the bis-Boc protected compound, followed by basic hydrolysis to selectively cleave the Boc-carbonate and afford alcohol **37**. We anticipated that both the Cbz and benzyl protecting groups could be removed in the same step at the completion of the synthesis, therefore the Boc protected substrate was used only to determine the diastereoselectivity of organometallic additions to aldehyde **38**.

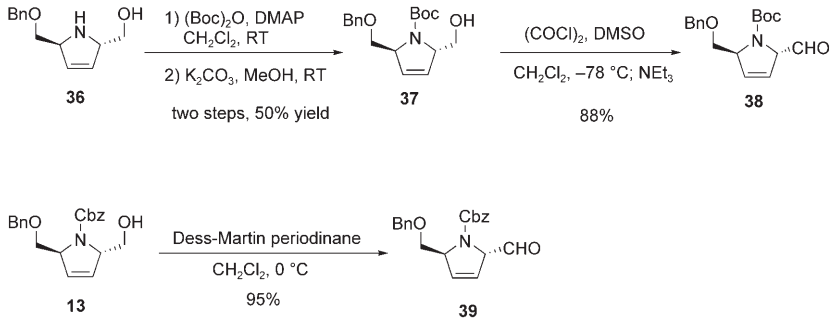
Regrettably, our various attempts to add organometallic species to aldehyde **38** resulted in very low yields of product and always afforded a 1:1 diastereomeric mixture of products regardless of conditions. The non-selective addition of a sterically undemanding organometallic reagent to an α-aminoaldehyde has been reported in the literature on several occasions.[26] However, appreciable levels of diastereoselectivity from the alkylation of α-aminoaldehydes requires either allylation protocols[27] or Reformatsky-type reagents.[28]

Therefore, we next turned our attention to changing the nature of the electrophile. Oxidation of alcohol **13** to the carboxylic acid with catalytic TEMPO and hypochlorite gives carboxylic acid **40**. Amide formation was best accomplished using PyBOP (benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate) as coupling reagent; other amide forming conditions resulted in significantly decreased yields. We hoped the Weinreb amide **41** would allow higher yields to be obtained with the addition of the organometallic reagent and also that

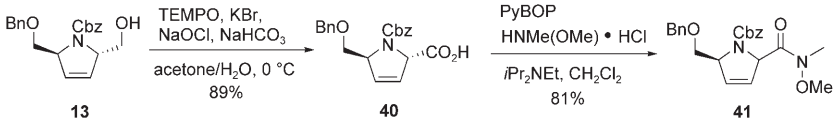




Scheme 11. Attempted oxidation of diene *anti*-**9**, acetonide **31**, and epoxide **33**.



Scheme 12. Formation of N-Boc and N-Cbz protected aldehydes **38** and **39**.

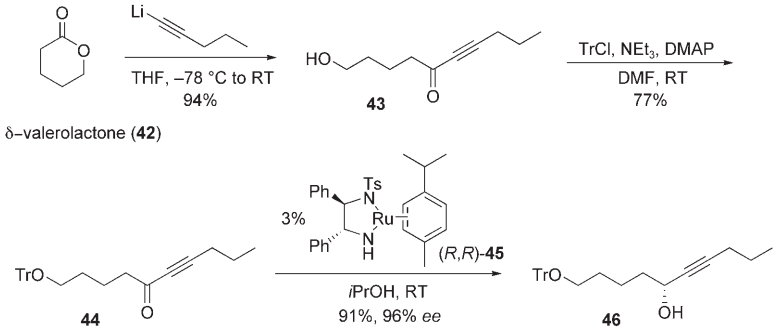


Scheme 13. Formation of Weinreb amide **41**.

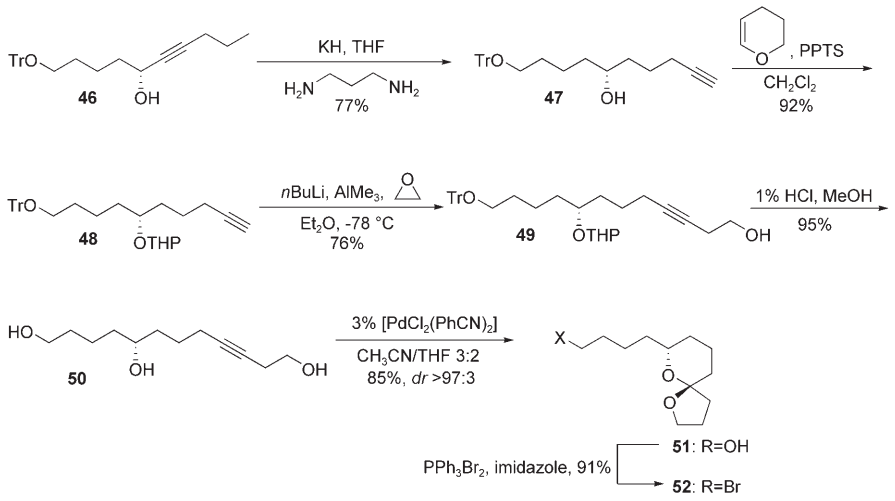
the resulting ketone could be diastereoselectively reduced (Scheme 13).

An innovative strategy was needed for the synthesis of the 5,6-spiroketal side chain. We began with addition of 1-lithio-1-pentyne to δ-valerolactone **42** to yield ynone **43** (Scheme 14).[29] We subsequently attempted two methods to introduce the chiral secondary hydroxyl group by reduction of the ketone using different chiral reducing agents. Catalytic asymmetric Noyori transfer hydrogenation with ruthenium catalyst (*R*,*R*)-**45** proved to be the method of choice for this transformation and afforded chiral propargyl alcohol **46** in 91% yield and 96% *ee*. In another experiment, reduction of the MOM ether analogue of **44** with alpine-borane produced product of only 79–83% *ee*. Regrettably, one shortcoming of the Noyori reduction is the required use of a bulky protecting group, such as triphenylmethyl or triisopropylsilyl ether, to obtain synthetically useful conversions. Attempts at Noyori reduction using benzyl or MOM protected substrates resulted in very low conversions and required the use of very large catalyst loadings (10–20%) to obtain appreciable yields of product. This pendant ether inhibitory effect has been seen by others with a similar ynone substrate containing a THP ether.[30]

An acetylene zipper reaction was next performed with chiral propargyl alcohol **46** to prepare terminal alkyne **47** (Scheme 15).[31] This particular reaction is a very powerful tool to construct terminal acetylenes, but is significantly underutilized in synthetic organic chemistry. Additionally, chiral alcohols are untouched during the reaction and no racemization of the stereogenic center is observed. The acetylene zipper reaction is followed by alkynyllithium addition to ethylene oxide, and global deprotection to give triol **50**. Attempted direct additions of ethylene oxide to the unprotected secondary alcohol **47** by formation of a dianion followed by electrophile addition, resulted in low yields (10–35%) of product.



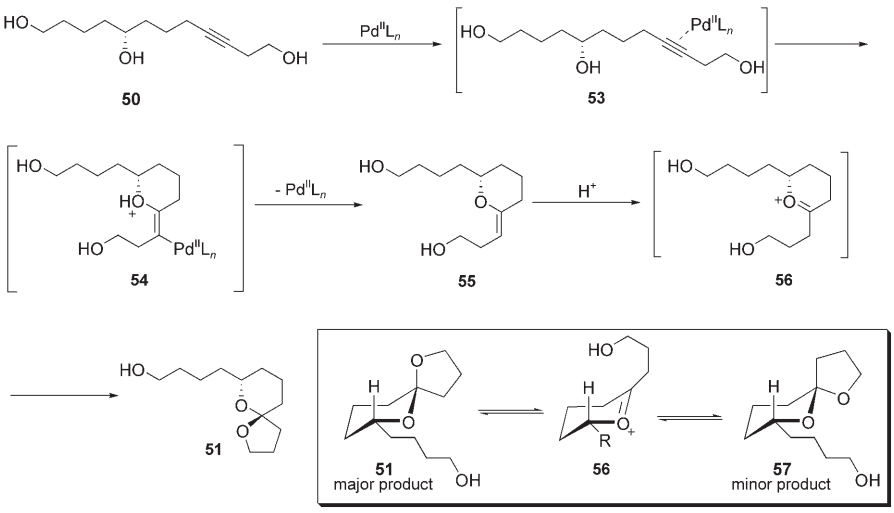
Scheme 14. Formation of chiral propargyl alcohol **46**.



Scheme 15. Acetylene zipper and alkylation with oxirane to form triol **52**.

The stage was now set to perform a Pd-catalyzed spiroketalization reaction. Although the Pd^{II}-catalyzed cyclization of heteroatoms onto alkynes and alkenes is a fairly well studied reaction,[32] the double addition of diols onto alkynes has appeared only in very few papers and only one example is shown to form a 5,6-spiroketal.[33] In this example involving a racemic secondary alcohol, the authors did not report the diastereomeric ratio of products after the cyclization reaction. In our case, the resulting triol **50** underwent the requisite regio- and diastereoselective palladium catalyzed spiroketalization reaction to give the desired 5,6-spiroketal **51** with excellent diastereoselectivity (97:3 d.r.). Primary halide formation was straightforward, and bromide **52** was readily prepared from primary alcohol **51** in good yield.

A likely mechanism of the spiroketalization reaction involves first coordination of the alkyne to the palladium catalyst to give intermediate **53** (Scheme 16). 6-*exo*-dig Attack of the hydroxyl on the coordinated alkyne gives oxonium **54**. Protonation of palladium followed by reductive elimination affords exocyclic olefin **55**. The high stereoselectivity of this cyclization reaction can then be attributed to the second ring forming event. Since the acid-catalyzed addition of the second hydroxyl group onto the oxonium ion is reversible, the thermodynamically most stable product **51** (resulting from the anomeric affect)[34] is isolated as the main product (see inset). An alternate mechanism involves cyclization of the primary alcohol in a 5-*endo*-dig fashion to give a dihydrofuran.

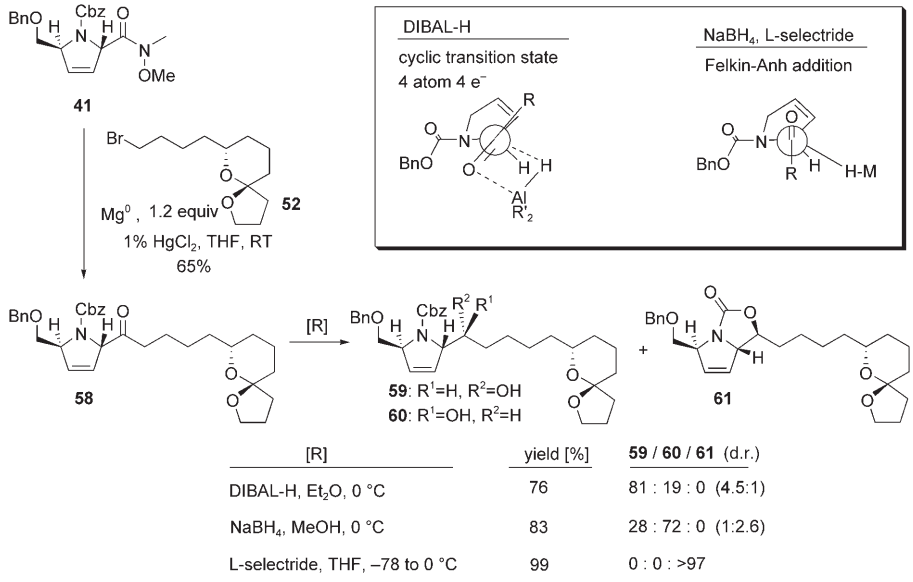


Scheme 16. Mechanism of Pd-catalyzed spiroketal formation.

Although this pathway is not precluded, the 6-*exo*-dig attack should be preferred based upon the trajectory required for the *trans*-attack of the alcohol upon the palladium coordinated alkyne. Utimoto has also observed products resulting from only *exo*-dig attack in the formation of dihydrofurans and -pyrans from palladium catalyzed cyclization of alkynols.[33] While the second ring forming reaction could also be palladium-catalyzed, the absence of olefin products, resulting from β-hydrogen elimination, makes this particular mechanistic pathway less likely.

The stage was now set for the coupling of the two halves of the molecule. A potential major detraction of the coupling procedure is the formation of an organometallic species from the nine-step intermediate, bromide **52**. Analysis of the iodine-quenched alkylmagnesium bromide solutions from the reaction of **52** with magnesium indicated that the major byproduct, resulting from Wurtz coupling to form a dimer, could be suppressed with the use of highly purified magnesium. Thus upon optimization of the reaction, only 1.2 equivalents of the precious intermediate **52** was required and afforded 65% of the desired ketone **58** (Scheme 17).

Diastereoselective reduction of ketone **58** with DIBAL-H gave an 81:19 (*R*/*S*) diastereomeric mixture of secondary alcohols **59**/**60** in 76% yield, presumably through a four center transition state (Scheme 17, inset).[35] An alternative mechanism would involve delivery of DIBAL-H by coordination to the carbamate. In contrast, $NaBH_4$ reduction of **58**

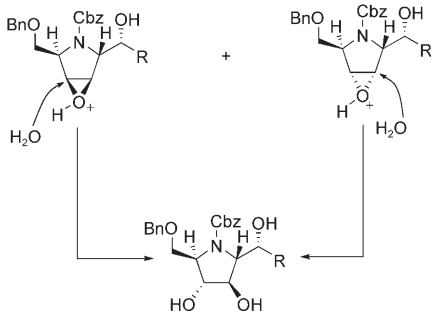


[R]	yield [%]	59 / 60 / 61 (d.r.)
DIBAL-H, Et_2O, 0 °C	76	81 : 19 : 0 (4.5:1)
$NaBH_4$, MeOH, 0 °C	83	28 : 72 : 0 (1:2.6)
L-selectride, THF, –78 to 0 °C	99	0 : 0 : >97

Scheme 17. Diastereoselective reductions of ketone **58**.

led to a 28:72 (*R*/*S*) diastereomeric mixture of alcohols **59**/**61** in 83% yield, the major product which was the expected Felkin–Anh product **60**. L-Selectride on the other hand gave one product, in good yield, but the intermediate lithium alkoxide is trapped by the benzyl carbamate and oxazolidinone **61** is isolated as the sole product. The products **59** and **60** were chromatographically separable, and access to both diastereomers of the 1′-hydroxyl was advantageous since the stereochemistry at this center was unknown. The absolute stereochemistry of the secondary alcohol was determined by formation of the (*R*)- and (*S*)-O-methyl mandelates and analysis of their ^{1}H NMR spectra.[36]

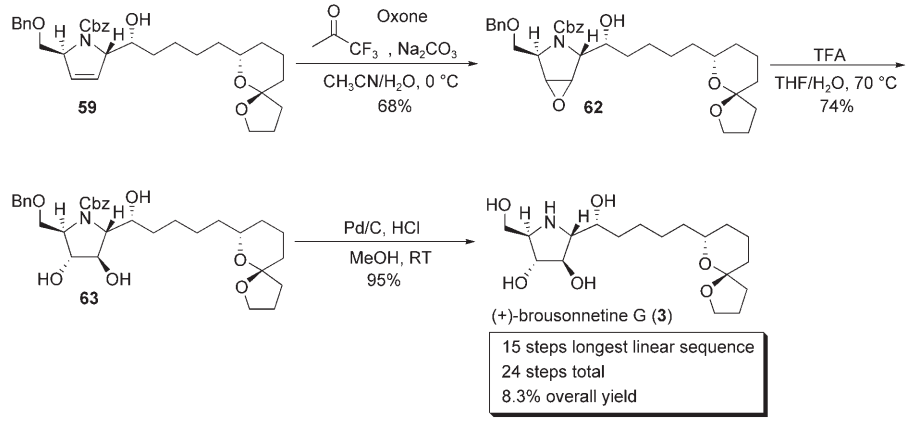
Epoxidation of dihydropyrrole **59** led to a mixture of epoxides **62** (Scheme 18), and attempts to establish the diastereoselectivity of this reaction were unsuccessful. ^{1}H NMR analysis of the isolated product mixture showed a 3:2:2:3 mixture of products. This ratio of four "compounds" is the result of carbamate rotamers along with the diastereomeric mixture of products. Variable temperature ^{1}H NMR was not useful in elucidating the diastereomeric ratios. Attempts to chemically remove the benzyloxycarbonyl protecting group to eliminate the amide rotamers resulted in low yields of a 3:2 diastereomeric mixture of products. In any case, hydrolysis of the mixture of both diastereomers with aqueous TFA or H_2SO_4, gave the same triol **63** as a single diastereomer. Presumably, S_N2 attack of water occurs from the sterically less hindered side of both epoxides to yield the same product (Scheme 19).



Scheme 19. Mechanism of diol formation from mixture of epoxides.

To complete the synthesis, removal of the protecting groups by palladium-catalyzed hydrogenolysis gave **3** whose spectral properties and optical rotation matched in all respects to those of an authentic sample of the natural product. Thus this synthesis constitutes the first synthesis of (+)-broussonetine G (**3**) comprising 24 total steps, with the longest linear sequence being 15 steps, and in 8.2% overall yield.

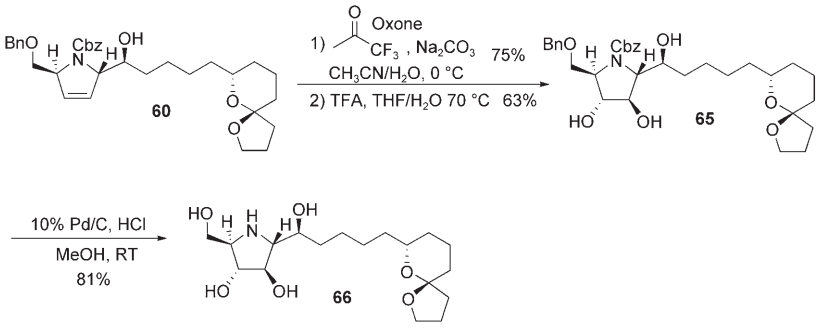
As previously mentioned, another challenge involved in the synthesis of broussonetine G was to assign the stereochemistry of the centers at the spiroketal and the 1′-hydroxyl group. An advantage of our synthetic strategy was its flexibility and convergency which allowed easy modification to provide the various possible stereoisomers to help establish the natural product's configuration. There-



Scheme 18. Completion of the synthesis of (+)-broussonetine G (**3**).

fore, in addition to the natural product, three additional stereoisomers of broussonetine G were synthesized.

The diastereomer with the inverted C1′-hydroxyl group **66** was synthesized using the procedures outlined below (Scheme 20). It should also be noted that oxazolidinone **61**, isolated as a single diastereomer from L-Selectride reduction, could also be used in a more selective synthesis of **66**.



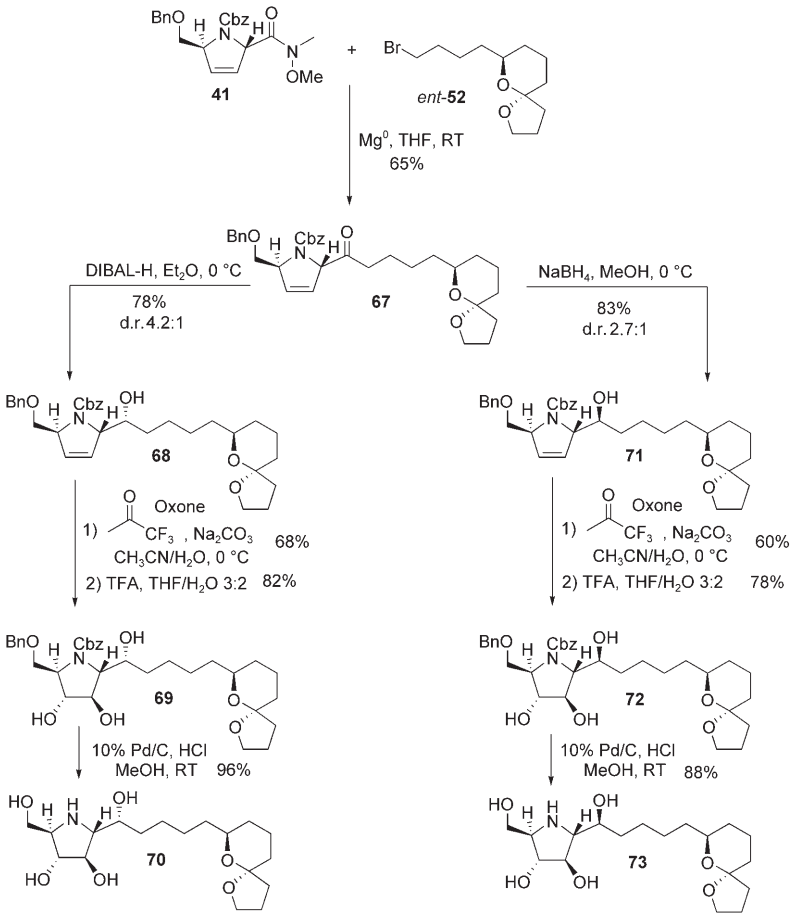
Scheme 20. Synthesis of broussonetine G diastereomer **66**.

Diastereomers **70** and **73** were synthesized by the same procedures outlined above, but using the opposite enantiomer of the side chain, *ent*-**52**, which was obtained through Noyori reduction of ynone **44** with the (*S*,*S*)-diamine ligand (*S*,*S*)-**45** (Schemes 14 and 15). Coupling of the two halves of the molecule and installation of the trans-diol as previously described occurs readily and gives two additional diastereomers of broussonetine G, **70** and **73** (Scheme 21).

Spectroscopic data (see Tables 3 and 4) for diastereomers **66** and **73** did not correlate with those of the natural product. Although the ^{1}H- and ^{13}C NMR spectra of **70** were nearly identical to that of the natural and synthetic **3**, its optical rotation was of opposite sign. Fortunately, the optical rotation and spectroscopic data of synthetic **3** matched completely with the reported data for the natural product and we assigned the structure of broussonetine G to that shown below (Figure 5).

Conclusion

Herein we have described a palladium catalyzed asymmetric allylic alkylation process whereby a versatile synthetic *trans*-2,5-dihydropyrrole intermediate **12** was prepared. This intermediate was used in short and high yielding asymmetric syntheses of three different natural products (+)-broussonetine G, (+)-DMDP, and (−)-bulgecinine. The *trans*-2,5-dihydropyrrole **12** and *cis*-2,5-dihydropyrrole **15** (Scheme 4) could potentially be used to access a multitude of iminosugar natural products and to prepare synthetic analogues for drug discovery. In addition, the scope of palladium allylic alkylation was expanded to include oxazolidinone nucleophiles. The utility of this chemistry towards the synthesis of pyrrolidine containing natural products is indicated by the potential access to all four possible stereoisomers by a simple choice of chiral ligand in each step of the



Scheme 21. Synthesis of broussonetine G diastereomers **70** and **73**.

Table 3. ^{1}H NMR data of broussonetine G stereoisomers synthesized (see Figure 5).

δ (^{1}H)[a]	Natural product	**3**	**66**	**70**	**73**
2	3.81[b] (m)	3.83[b] (m)	3.91–3.74[b] (m)	3.88–3.77[b] (m)	3.92–3.76[b] (m)
3	4.73 (t, 6.2 Hz)	4.72 (t, 6.4 Hz)	4.66 (t, 6.0 Hz)	4.71[c] (q, 5.7 Hz)	4.65 (t, 5.7 Hz)
4	4.95 (t, 6.2 Hz)	4.95 (t, 6.4 Hz)	4.80 (t, 5.4 Hz)	4.93[c] (q, 6.0 Hz)	4.81 (t, 5.2 Hz)
5	3.65 (t, 6.2 Hz)	3.64 (dd, 6.5, 4.8 Hz)	3.78 (m)[b]	3.62 (t, 5.2 Hz)	3.78 (m)[b]
1′	4.13 (ddd, 6.2, 4.8, 4.8 Hz)	4.11 (ddd, 6.4, 4.8, 4.8 Hz)	4.17 (dd, 9.8, 5.3 Hz)	4.10 (m)	4.15 (dd, 9.8, 5.5 Hz)
2′	1.99[b]	2.00[b]	2.00[b]	2.00[b]	2.00[b]
3′	1.86 (m), 1.57[b]	1.86,[b] 1.57 (m)	1.86,[b] 1.56 m	1.86,[b] 1.57 m	1.86,[b] 1.56 (m)
4′	1.46[b]	1.44,[b]	1.44,[b]	1.44,[b]	1.44,[b]
5′	1.55,[b] 1.41 (m)	1.55,[b] 1.41 (m)	1.55,[b] 1.41[b]	1.55,[b] 1.41 (m)	1.55,[b] 1.41[b]
6′	3.82[b]	3.83[b] (m)	3.93–3.76 (m)	3.88–3.77[b] (m)	3.92–3.76 (m)
7′	1.45,[b] 1.13 (m)	1.42,[b] 1.13 (m)	1.44,[b] 1.10 m	1.42,[b] 1.12 (m)	1.44,[b] 1.10 (m)
8′	1.94,[b] 1.56[b]	1.98,[b] 1.54[b]	2.00–1.55[b]	1.98,[b] 1.54[b]	2.00–1.55[b]
9′	1.66[b]	1.64[b]	1.67[b]	1.66[b]	1.67[b]
10′	–	–	–	–	–
11′	1.96,[b] 1.58[b]	1.96,[b] 1.56[b]	2.00,[b] 1.56[b]	1.98,[b] 1.54[b]	2.00,[b] 1.56[b]
12′	1.95,[b] 1.69[b]	1.95,[b] 1.69[b]	2.00–1.71,[b] 1.67[b]	1.98,[b] 1.66[b]	2.00–1.71,[b] 1.67[b]
13′	3.87[b] (m)	3.83[b] (m)	3.92–3.76[b]	3.88–3.77[b] (m)	3.92–3.76[b]
CH_2OH	4.22 (dd, 10.8, 5.5 Hz) 4.26 (dd, 10.8, 4.3 Hz)	4.24 (dd, 10.8, 5.5 Hz) 4.28 (dd, 10.8, 3.8 Hz)	4.20 (dd, 10.0, 4.8 Hz) 4.33 (dd, 9.8, 5.3 Hz)	4.18[c] (m) 4.21[c] (m)	4.25 (dd, 9.8, 4.8 Hz) 4.29 (dd, 9.8, 4.0 Hz)

[a] All spectra measured at 500 MHz in [D_5]pyridine. [b] Overlapping signals. [c] Additional splitting by coupling to hydroxyl proton.

Table 4. ^{13}C NMR data of broussonetine G stereoisomers synthesized (see Figure 5).

δ (^{13}C)[a]	Natural product	**3**	**66**	**70**	**73**
2	65.88	65.88	66.14	65.94	66.12
3	80.55	80.59	80.93	80.63	81.01
4	80.31	80.31	80.64	80.47	80.84
5	67.53	67.57	67.51	67.60	67.40
1′	74.03	74.04	74.10	74.15	74.13
2′	35.05	35.05	34.98	35.11	35.00
3′	26.85	26.88	26.67	26.87	26.63
4′	26.31	26.28	26.13	26.31	26.17
5′	36.73	36.72	36.82	36.79	36.88
6′	70.31	70.31	70.37	70.30	70.38
7′	31.38	31.40	31.59	31.38	31.51
8′	20.99	20.98	20.99	21.00	21.04
9′	33.39	33.40	33.12	33.38	33.06
10′	105.91	105.91	105.81	105.91	105.83
11′	38.19	38.18	38.40	38.19	38.40
12′	24.17	24.13	24.36	24.16	24.29
13′	66.77	66.82	66.32	66.76	66.31
CH_2OH	63.48	63.50	63.69	63.59	63.74

[a] All spectra measured at 125 MHz in [D_5]pyridine (from residual peak at 125.58 ppm).

palladium catalyzed DYKAT reaction (Scheme 5). The juxtaposition of functionality should also allow these intermediates to be precursors of the pyrrolizidine and indolizidine natural products.

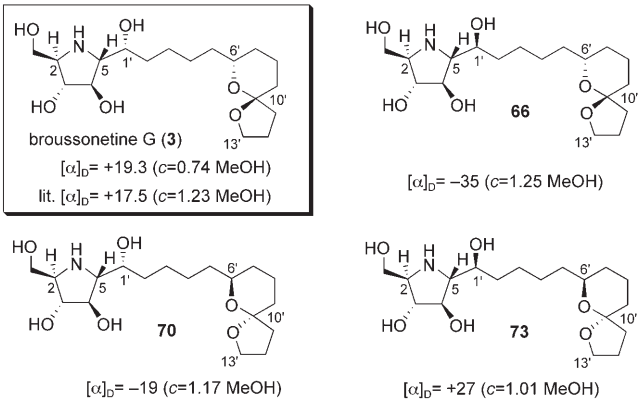


Figure 5.

Experimental Section

Selected experimental procedures for the preparation of **7**, *anti*-**9**, *syn*-**9**, **1**, **51**, and **3** appear below. Full experimental details for all intermediates and natural products reported herein are given in the Supporting Information.

(2*S*)-*N*-Phthalimido-3-buten-1-ol (7); *Large Scale*: Sodium carbonate (1.3 g, 12.3 mmol) was added to a 1 L flask and the flask was flame-dried under vacuum. After cooling under nitrogen, phthalimide **5** (34.0 g, 0.231 mol, recrystallized from hot ethanol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (360 mg, 0.98 mmol), and (*R*,*R*)-**6** (2.32 g, 2.93 mmol) were added and the flask flushed three times with argon. Then dry CH_2Cl_2 (900 mL, degassed with argon for 30 min) was added and the orange/yellow suspension stirred

10 min. Butadiene monoxide **4** (16.5 g, 0.235 mol) was added and the yellow solution stirred at RT for 12 h. The reaction was concentrated and the orange residue purified by flash chromatography (silica gel, Et_2O) to yield **7** (49.79 g, 99.6%) as a white solid. Enantiomeric excess was determined to be 94.4% *ee* by chiral HPLC (Chiralpak OD, heptane/*i*PrOH 90:10, 1.0 mL min^{-1}, t_R[(*R*)-**7**] = 13.75 min and t_R[(*S*)-**7**] = 16.75 min). The spectral data agreed with that previously reported.[14a]

[4*S*,3(1*S*)]-3-(1-Hydroxymethyl-allyl)-4-vinyl-oxazolidin-2-one (*anti*-9); A 1 L flask with $[Pd_2(dba)_3]\cdot CHCl_3$ (357 mg, 0.345 mmol, 0.25 mol%), and (*R*,*R*)-**6** (819 mg, 1.04 mmol, 0.75 mol%) was flushed with argon. Dry CH_2Cl_2 (400 mL, degassed with argon for 30 min) was added followed by **8** (15.5 g, 137 mmol) and DBU (208 mg, 1.37 mmol, 1 mol%) and the suspension stirred 5 min. Butadiene monoxide **4** (9.75 g, 139 mmol) was added and the solution stirred at room temperature for 8 h. The reaction was concentrated in vacuo. The orange residue was purified by flash chromatography (silica gel, Et_2O/MeOH 50:1) to yield *anti*-**9** (22.6 g, 90%, 123 mmol) as a clear, light yellow oil. ^{1}H NMR indicates the product is ≈97% pure with minor contamination by *syn*-**9**. The minor *syn*-diastereomer *syn*-**9** (1.06 g, 4.2%, 5.8 mmol), was also isolated at this stage. The diastereoselectivity of the reaction was determined by GC analysis of the crude reaction mixture (Varian 3600, 100/3-10-250/2; t_R(*syn*-**9**) = 7.19 min t_R(*anti*-**9**) = 7.69 min; *anti*/*syn* 89.4:10.6); $[\alpha]_D^{25} = -68$ (*c* 1.14, CH_2Cl_2); R_f = 0.50 (Et_2O/MeOH 20:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H), 5.74 (ddd, *J* = 17.7, 9.3, 8.7 Hz, 1H), 5.38 (d, *J* = 10.2 Hz, 1H), 5.37 (d, *J* = 16.8 Hz, 1H), 5.29 (d, *J* = 10.2 Hz, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 4.48 (t, *J* = 8.7 Hz, 1H), 4.32 (dd, *J* = 8.7, 8.1 Hz, 1H), 4.02 (dd, *J* = 8.4, 7.8 Hz, 1H), 3.90 (m, 3H), 3.57 (dd, *J* = 8.4, 4.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5, 134.9, 132.3, 121.7, 118.9, 67.6, 62.8, 59.6, 59.2 ppm; IR (thin film): $\tilde{\nu}$ = 3418, 3085, 2985, 2912, 1732, 1644, 1480, 1417, 1336, 1253, 1064, 1030, 992, 936, 764, 706 cm^{-1}; HRMS (EI+): *m*/*z*: calcd for $C_9H_{13}NO_3$: 184.0974, found 184.0969 $[M+H]^+$.

[4*S*,3(1*S*)]-3-(1-Hydroxymethylallyl)-4-vinyl-oxazolidin-2-one (*syn*-9); A test tube with $[Pd_2(dba)_3]\cdot CHCl_3$ (18.1 mg, 0.018 mmol, 1 mol%), and (*S*,*S*)-**6** (42 mg, 0.053 mmol, 3 mol%) was flushed with argon. Dry CH_2Cl_2, 4.5 mL, (degassed with argon for 10 min) was added followed by **8** (200 mg, 1.77 mmol) and DBU (27 mg, 0.18 mmol, 10 mol%) and the suspension stirred 5 min. Butadiene monoxide **4** (123 mg, 1.77 mmol) was added and the solution stirred at room temperature for 6 h. The reaction was concentrated *in vacuo*. The orange residue was purified by flash chromatography (silica gel, Et_2O/MeOH 50:1) to yield *syn*-**9** (245.8 mg, 76%) as a clear, light yellow oil, the minor *anti*-**9** diastereomer was not isolated, but was determined to be 10% by GC (Agilent 6850 A, 100/5-20-250/5; t_R(*syn*-**9**) = 6.24 min and t_R(*anti*-**9**) = 6.49 min *syn*/*anti* 90:10); $[\alpha]_D^{25} = -19$ (*c* 2.41, $CHCl_3$); R_f = 0.50 (Et_2O/MeOH 20:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.94 (ddd, *J* = 17.6, 10.5, 7.1 Hz, 1H), 5.85 (m, 1H), 5.30 (m, 4H), 4.50–4.44 (m, 2H), 4.14 (m, 1H), 4.00 (m, 1H), 3.94 (m, 1H), 3.74 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.2, 135.7, 132.2, 120.7, 119.2, 67.4, 62.8, 60.2, 58.7 ppm.; IR (thin film): $\tilde{\nu}$ = 3435, 3085, 2984, 2911, 1732, 1644, 1480, 1416, 1337, 1248, 1062, 1030, 994, 936, 764 cm^{-1}; elemental analysis calcd (%) for $C_9H_{13}NO_3$: C 59.00, H 7.15, N 7.65; found: C 59.16, H 7.20, N 7.77.

(2*R*,3*R*,4*R*,5*R*)-2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine [(+)-DMDP] (1); 10% Pd/C (7.5 mg, 0.007 mmol, 5 mol%) was added to a vial with **16a** (54.3 mg, 0.14 mmol). The vial was flushed with N_2, then 1 mL MeOH was added followed by two drops concentrated HCl. A baloon of H_2 was bubbled through the reaction 5 min, then the reaction was stirred under H_2 balloon 2.5 h. The reaction was filtered through a plug of Celite and the plug washed with 2×3 mL MeOH. The filtrates were combined and concentrated to yield the crude HCl salt as yellow oil/solid. ^{1}H NMR (400 MHz, D_2O): δ = 4.07 (dt, *J* = 8.1, 4.4 Hz, 2H), 3.91 (dd, *J* = 12.8, 3.5 Hz, 2H), 3.84 (dd, *J* = 12.8, 5.8 Hz, 2H), 3.57–3.53 (m, 2H) ppm. Purification by ion exchange chromatrography (DOWEX50W-X2) by dissolving in 1 mL H_2O with 1 drop 10% aqueous HCl, and gradient elution with 20 mL H_2O, then 20 mL 1 M NH_4OH. The NH_4OH fractions were collected and concentrated to yield **1** (22 mg, 96%) as a white oily solid. M.p. 112–115 °C (H_2O) [lit. m.p. 115–117 °C];[37] $[\alpha]_D^{28} = +55.4$ (*c* 1.25, H_2O), [lit. $[\alpha]_D^{20} = +53.8$ (*c* 0.32, H_2O)];[37] ^{1}H NMR (400 MHz, D_2O): δ = 3.82 (dt, *J* = 7.3, 2.0 Hz, 2H), 3.70 (dd, *J* = 11.7, 4.1 Hz, 2H), 3.62 (dd, *J* = 11.5, 6.4 Hz, 2H), 3.03–2.89 (m, 2H) ppm; ^{13}C NMR (100 MHz, D_2O): δ = 78.1, 62.3, 61.8 ppm; IR (NaCl, thin film); $\tilde{\nu}$ = 3314, 2924, 1543, 1412 cm^{-1}; elemental analysis calcd (%) for $C_6H_{13}NO_4$: C 44.16, H 8.03, N 8.58; found: C 44.48, H 7.79, N 8.50.

4-[(*R*,7*R*)-1,6-Dioxaspiro[4.5]dec-7-yl]-butan-1-ol (51); A flame-dried 250 mL flask with triol **50** (7.5 g, 35 mmol) in CH_3CN/THF 3:2 (175 mL) was degassed with Ar by bubbling for 5 min. To this solution was quickly added solid $[PdCl_2(PhCN)_2]$ (268 mg, 0.7 mmol, 2 mol%) and the reaction was stirred at RT under Ar balloon 13 h. The resulting yellow/green solution was concentrated and purified by flash column chromatography (silica gel, Et_2O/PE 4:1) to yield **51** (6.37 g, 85%, 29.8 mmol) as a clear, colorless, oil. $[\alpha]_D^{29} = +76$ (*c* 1.24, MeOH); R_f = 0.51 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.88 (m, 2H), 3.71 (m, 1H), 3.65 (t, *J* = 7.0 Hz, 2H), 2.04 (m, 1H), 1.94–1.81 (m, 3H), 1.72–1.35 (m, 12H) 1.20 (ddd, *J* = 16.5, 13.0, 3.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 105.8, 70.1, 66.6, 37.7, 35.7, 32.7, 32.5, 30.8, 23.6, 21.7, 20.3 ppm; IR (thin film); $\tilde{\nu}$ = 3406, 2937, 1457, 1386, 1310, 1271, 1215, 1161, 1115, 1008, 960, 918 cm^{-1}; HRMS (EI+): *m*/*z*: calcd for $C_{12}H_{21}O_3$: 213.1491, found: 213.1491 $[M-H]^+$. Diastereomeric excess determined by GC of crude product (HP 5973 GC/MS, 100/3-10-250/2; t_R(*R*,*R*) = 7.46 min and t_R(*S*,*R*) = 7.69 min; 97:3.

(+)-Broussonetine G (3); 10% Pd/C (15 mg, 0.014 mmol, 25 mol%) was added to a vial with triol **61** (32.1 mg, 0.055 mmol). The flask was flushed with N_2, and MeOH (1 mL) was added via syringe, followed by 3 drops concentrated HCl. A baloon of H_2 was bubbled through the stirring solution 5 min, then the reaction stirred under H_2 at RT for 3 h. The reaction was filtered through a plug of Celite, the plug rinsed with MeOH (10 mL), and the combined filtrates concentrated. Purification of the product by ion exchange chromatography (DOWEX50W-X2 (H^+ form), gradient elution H_2O then 1 M aqueous NH_4OH) provides **3** (18.8 mg, 95%, 0.052 mmol) as a white film. $[\alpha]_D^{25} = +19.3$ (*c* 0.74, MeOH); R_f = 0.80 ($CHCl_3$/MeOH/56% aq. NH_4OH 5:1:1); ^{1}H NMR (500 MHz, [D_5]pyridine): δ = 6.95 (brs, 1H, OH), 6.78 (brs, 1H, OH), 6.30 (brs, 1H, OH), 6.01 (brs, 1H, OH), 4.95 (t, *J* = 6.4 Hz, 1H), 4.72 (t, *J* = 6.4 Hz, 1H), 4.28 (dd, *J* = 10.8, 5.5 Hz, 1H), 4.24 (dd, *J* = 10.8, 3.8 Hz, 1H), 4.11 (ddd, *J* = 6.4, 4.8, 4.8 Hz, 1H), 3.83 (m, 4H), 3.64 (dd, *J* = 6.5, 4.8 Hz, 1H), 2.00–1.71 (m, 6H), 1.71–1.54 (m, 7H), 1.48–1.37 (m, 4H), 1.13 (m, 1H) ppm; ^{13}C NMR (125 MHz, [D_5]pyridine): δ = 105.91, 80.55, 80.31, 74.03, 70.31, 67.53, 66.77, 65.88, 63.48, 38.19, 36.73, 35.05, 33.39, 31.38, 26.85, 26.31, 24.17, 20.99 ppm; IR (thin film): $\tilde{\nu}$ = 3356, 2937, 1683, 1458, 1202 cm^{-1}; HRMS (EI+): *m*/*z*: calcd for $C_{18}H_{33}NO_6$: 359.2308, found: 359.2284 $[M]^+$.

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