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A concise synthesis of (+)-batzelladine B from simple pyrrole-based starting materials

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Abstract

Alkaloids, secondary metabolites that contain basic nitrogen atoms, are some of the most well-known biologically active natural products in chemistry and medicine[1]. Although the efficient laboratory syntheses of alkaloids would enable researchers to study and optimize their biological properties,[2] the basicity and nucleophilicity of nitrogen, its susceptibility to oxidation, and its ability to alter reaction outcomes in unexpected ways – for example, through stereochemical instability and neighboring group participation – complicates their preparation in the laboratory. Efforts to address these issues have led to the invention of a large number of protecting groups that temper the reactivity of nitrogen[3]; however, the use of protecting groups typically introduce additional steps and obstacles into the synthetic route. Alternatively, the use of aromatic nitrogen heterocycles as synthetic precursors can attenuate the reactivity of nitrogen and streamline synthetic strategies[4]. In this manuscript, we use such an approach to achieve a synthesis of the complex anti-HIV alkaloid (+)-batzelladine B in nine steps (longest-linear sequence) from simple pyrrole-based starting materials. The route employs several key transformations that would be challenging or impossible to implement using saturated nitrogen heterocycles and highlights some of the advantages conferred by the use of aromatic starting materials.

The retrosynthetic conversion of a saturated nitrogen heterocycle to a heteroaromatic exchanges a reactive, basic functional group with one that is lower in energy, non-basic, non-nucleophilic, and more easily-manipulated. For example, analysis of well-appreciated physical organic scales of basicity and nucleophilicity shows that the six-membered heterocycle piperidine is much more basic (pK_b = 3.1, DMSO)[5] and nucleophilic (N = 18.1, H_2O)[6] than the corresponding aromatic heterocycle pyridine (pK_b = 10.6, DMSO[7]; N = 11.0, H_2O[6]). Moreover, functionalized heteroaromatics are readily elaborated by well-established C–C bond-forming reactions, such as cross-couplings. In the strategy we pursued herein,

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Supplementary Information including detailed experimental procedures and characterization of all new compounds (^1H and ^{13}C NMR, IR, HRMS) are available in the online version of this manuscript.

simple pyrrole-based precursors would serve as sources of partially- or fully-saturated nitrogen heterocycles and would be advanced by carbon–carbon bond-forming and reductive transformations. This approach complements terpene synthesis and biosynthesis, which typically proceeds by oxidation of a complex hydrocarbon template[8].

We applied this strategy toward a synthesis of the guanidinium alkaloid (+)-batzelladine B (**1**, Fig. 1a)[9]. Structurally, **1** contains a *syn*-tricyclic guanidine (vessel) connected to a bicyclic guanidine (anchor) via an alkyl ester. At least 15 batzelladine alkaloids have been isolated[9–12] and several members of this family inhibit the binding of HIV glycoprotein gp120 to human CD4 receptor cells (IC_{50} of **1** = 31 μM)[9], thereby preventing viral induction. The absolute stereochemistries of the vessel and anchor of **1** were established by Overman[13] and Gin[14], respectively, and syntheses and synthetic studies of other batzelladines have been reported (for selected examples, see refs. 15–22). Notably, Overman has developed a tethered Biginelli condensation strategy that has provided access to several batzelladines and related alkaloids[23]. Gin[17] and Nagasawa[16] have reported enantioselective synthetic routes to (+)-batzelladine A (**2**), but a route to **1** has not been described.

We envisioned that the vessel and anchor fragments of **1** (Fig. 1b) could be derived from the pyrrole-based precursors **3** and **6**, respectively, if suitable methods for carbon–carbon bond formation and controlled reduction in oxidation state could be achieved. A rhodium-catalyzed formal [4+3] cycloaddition between **3** and a donor–acceptor carbene[24] was envisioned to provide entry to the dehydrotropane **4**, which contains all of the functional group handles required for synthesis of the vessel fragment. We envisioned that the pyrrole **6** could serve as a precursor to the anchor of **1** by a Mannich addition[25], followed by cyclization and controlled adjustment of oxidation state, with concomitant isomerization.

The *N*-amidinylpyrrole **3** (Fig. 2a) was prepared in two steps and 75% yield from commercial reagents (see Supporting Information). Extensive experimentation was required to realize the formal [4+3] cycloaddition with high yield and stereoselectivity. Ultimately, we found that use of the (*S*)-pantolactonyl α-diazo ester **9**[26] and dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate] as catalyst (0.5 mol%) provided the dehydrotropane **10** in 93% yield and >95:5 diastereoselectivity. Formal cycloaddition between **3** and ***ent*-9** using the same catalyst provided **10** with 76:24 diastereoselectivity (81% yield), demonstrating that the former substrate–catalyst pair is stereochemically-matched (an example of double asymmetric synthesis[27]). Formal cycloaddition between **3** and achiral diazoesters afforded the corresponding adducts in 45–93% yield and 60–86% ee (Table S1). The yield of **10** was essentially unaffected (87%) when the catalyst loading was reduced to 0.1 mol%. With this key step accomplished, the pyrroline ring was selectively reduced by treatment with chlorotris(triphenylphosphine)rhodium under dihydrogen (**10**→**11**). Exposure of the reduction product **11** to *n*-tetrabutylammonium fluoride and 1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TMS-EBX)[28] at −78 °C provided the α-alkynyl-β-ketoester **12** as a single diastereomer (^{1}H NMR analysis). The first three steps of this sequence were readily telescoped to provide **12** in 80% overall yield after one purification. The relative stereochemistry of **12** was unequivocally established by 7-*endo*-dig hydroguanylation[29] (**12**→**18**, Fig. 2b) followed by carbamate cleavage (**18**→**19**) and X-ray analysis.

We then investigated the ring-opening of the bicyclic skeleton of **12** by cleavage of the β-ketoester. As **12** presents four acidic sites, a careful balance between the protonation state of the substrate and the basicity of the incoming nucleophile was essential to achieving the desired mode of reactivity. After intensive experimentation and optimization, we found that deprotonation of **12** with *n*-butyllithium (1.0 equiv) followed by addition of lithium benzyl octanoate (1.8 equiv) afforded the bicyclic pyrrolidine **15**. This cascade sequence is thought to proceed by 1,2-addition to the β-ketoester, retro-aldol ring-opening, and proton transfer to provide the enolyne **13**. Isomerization of **13** to the acylallene **14** followed by Michael addition of the guanidinyl anion and neutralization of the resulting enolate may then provide **15**. The addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) was necessary to promote the retro-aldol ring-opening. Other nucleophiles, such as sodium methoxide, morpholine, ethanethiol, and Grignard or organozinc reagents, were also investigated, but in most instances complex mixtures of products were obtained. The addition–rearrangement product **15** exists as a mixture of diastereomers and tautomers; consequently we cleaved the β-ketoester of the unpurified product with palladium on carbon under dihydrogen, to form the ketone **16** (49% from **12**). Saponification of the pantolactonyl ester (lithium hydroxide) afforded the keto acid **17** (75%; 29% overall from **3**).

The anchor fragment was assembled by the sequence shown in Fig. 3 and begins with a highly-diastereoselective Mannich addition[25] to form the β-aminoester of the target. Treatment of **6** with lithium diisopropylamide and chloro tris(isopropoxy)titanium, followed by addition of the sulfinimine **20**, provided the product **21** in 99% yield. The addition product **21** was formed as a single detectable C-2 stereoisomer and an inconsequential (~94:6) mixture of C-1 stereoisomers (^{1}H NMR analysis). The C-1 and C-2 stereocenters were assigned by analogy to related products[25] and the C-2 stereochemistry was confirmed by derivatization (see Supporting Information). Notably, attempts to functionalize saturated analogs of **6** by a Mannich addition would be complicated by issues of diastereoselectivity and β-elimination. Owing to the presence of the alkyne and the difficulties associated with handling the vinylogous carbamate of the target[17], reduction of the pyrrole ring was postponed until later in the sequence. The *tert*-butanesulfinyl substituent of **21** was cleaved by treatment with hydrochloric acid in methanol, and the resulting product was cyclized in the presence of bis(chlorodibutyltin)oxide, to provide the urea **22** (78%, two steps). *O*-Selective ethylation formed an *iso*-urea (90%, not shown) that was treated with 2,4-(dimethoxy)benzyl (DMB) amine hydrogen chloride to provide the guanidine **23** (71%). The ester was then cleaved (trimethylsilyl trifluoromethanesulfonate, 2,6-lutidine) and the resulting carboxylic acid was coupled with the alcohol **24**, to provide **25**, which contains the complete carbon framework of the anchor (75%). Anti-Markovnikov reductive hydration[30] of the terminal alkyne of **25** mediated by the ruthenium catalyst **26** (15 mol%) formed the alcohol **27** (71%; 26% overall from **6**). The addition of *p*-toluenesulfonic acid (PTSA) to quantitatively protonate the guanidine was essential in this step.

The vessel and anchor fragments **17** and **27** were coupled using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl) to provide the penultimate intermediate **28** (77%), and the synthesis was completed by the carefully-optimized sequence shown in Fig. 4. First, a dry mixture of palladium on carbon and the coupling

product **28** was suspended in trifluoroacetic acid under argon for 2 h at 24 °C. Under these conditions, the four *tert*-butoxycarbonyl protecting groups were cleaved, the liberated vessel domain underwent cyclodehydration, and the 1,1-disubstituted enamide was isomerized into conjugation with the ester (**28**→**29**). Upon completion of this step (as judged by UPLC/MS analysis), the atmosphere within the reaction vessel was replaced with dihydrogen. Stirring the resulting mixture for 18 h at 24 °C effected stereoselective reduction of the trisubstituted eneguanidine of the vessel (>20:1 dr, see Supporting Information)[15], controlled semireduction of the anchor pyrrole with tandem isomerization of the resulting dihydropyrrole, and cleavage of the DMB substituent, to provide **1** in 40% isolated yield (45% by NMR).

Prior approaches to batzelladine alkaloids and related natural products have employed non-aromatic (aliphatic) nitrogen precursors, followed by stepwise adjustments (typically, increases) of oxidation state. The approach we have presented proceeds in the opposite direction and begins with oxidized nitrogen heteroaromatics, followed by C–C bond-forming reactions and controlled reduction to achieve the saturation patterns of the target. This approach brings to light additional synthetic pathways not apparent or viable when starting from aliphatic nitrogen building blocks, and tempers nitrogen's promiscuous and often problematic reactivity. An added virtue of this strategy derives from its dependence on late-stage C–H bond-forming reactions, which are among the most reliable classes of transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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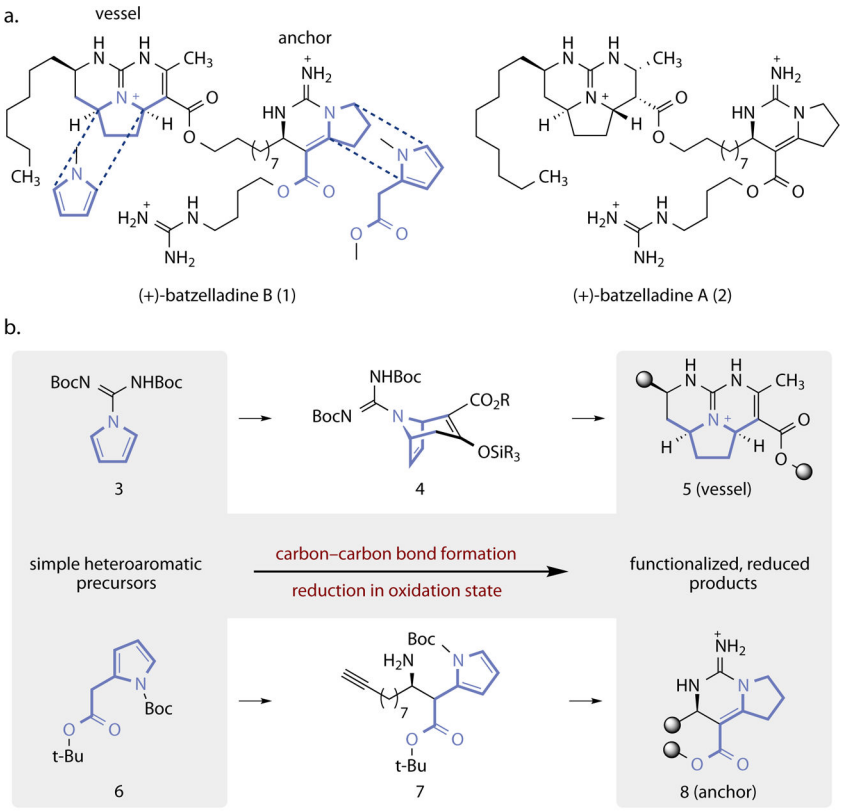

Figure 1. Structure and synthetic analysis of (+)-batzelladine B (1)

a, The chemical structures of (+)-batzelladine B (**1**) and (+)-batzelladine A (**2**), with embedded pyrrole substructures shown. **b**, The strategy we pursued calls for elaboration of the pyrrole-based starting materials **3** and **6** to the vessel and anchor substructures of **1** (**5** and **8**, respectively) via the intermediates **4** and **7**.

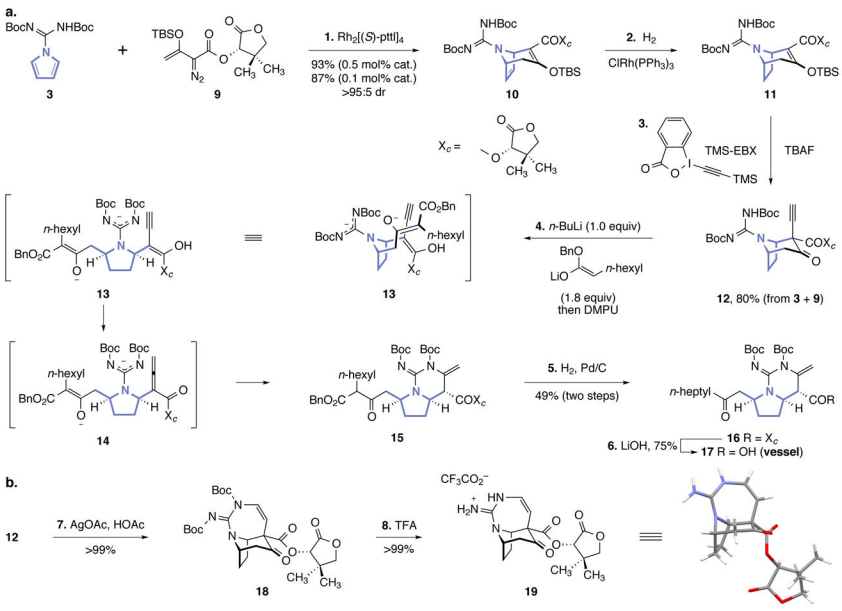

Figure 2. Synthesis of the vessel fragment of (+)-batzelladine B (1) and determination of stereochemistry

a, Synthesis of the vessel precursor **17**. Reagents and conditions: **1.** $Rh_2[(S)\text{-pttl}]_4$ (0.5 mol %), pentane, 36 °C, 93%, >95:5 dr, or $Rh_2[(S)\text{-pttl}]_4$ (0.1 mol%), pentane, 36 °C, 87%, >95:5 dr. **2.** H_2 (30 atm), $ClRh(PPh_3)_3$ (2.0 mol%), *i*-PrOH, 23 °C. **3.** TBAF, TMS-EBX, THF–CH_2Cl_2 (8:1), −78 °C, 80% (from **3** + **9**). **4.** *n*-BuLi, then lithium benzyl octanoate, THF, then DMPU, −78 °C. **5.** H_2 (1 atm), Pd/C (10 mol%), THF, 23 °C, 49% (two steps). **6.** LiOH, THF–H_2O (2:1), 0 °C, 75%. **b**, The relative stereochemistry of **12** was established by cyclization and deprotection, followed by X-ray analysis. Reagents and conditions: **7.** AgOAc, AcOH, CH_2Cl_2, 24 °C, >99%. **8**. TFA, CH_2Cl_2, 0→23 °C, >99%.

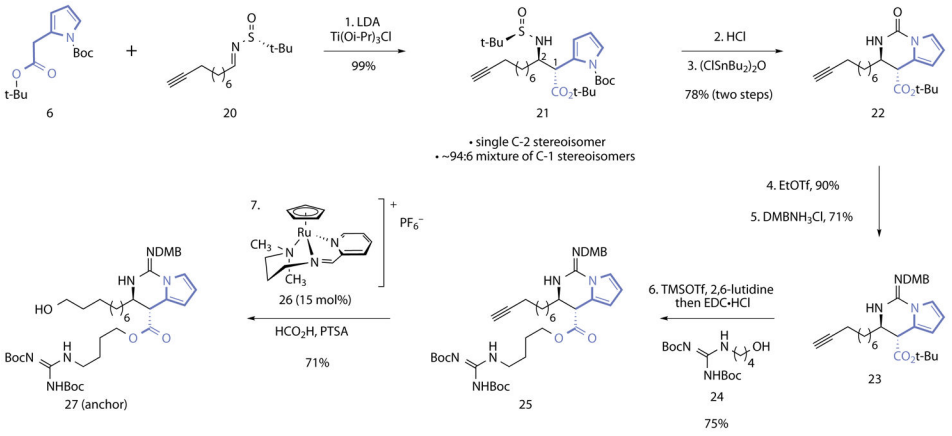

Figure 3. Synthesis of the (+)-batzelladine B (1) anchor

Reagents and conditions: **1.** LDA, $Ti(Oi\text{-}Pr)_3Cl$, THF, −78 °C, 99%, >20:1 mixture of C-1 stereoisomers, ~94:6 mixture of C-2 stereoisomers. **2.** HCl, CH_3OH–1,4-dioxane (4.4:1), 0 °C. **3.** $(ClSnBu_2)_2O$, toluene, 100 °C, 78% (two steps). **4.** EtOTf, 2,4,6-tri-*tert*-butyl-pyrimidine, CH_2Cl_2, 23 °C, 90%. **5.** $DMBNH_3Cl$, 3 Å MS, EtOH, 70 °C, 71%. **6.** TMSOTf, 2,6-lutidine, CH_2Cl_2, 0→23 °C, then **24**, DMAP, EDC•HCl, CH_2Cl_2, 0→23 °C, 75%. **7. 26** (15 mol%), PTSA (1.0 equiv), HCO_2H, NMP–H_2O (4:1), 23 °C, 71%.

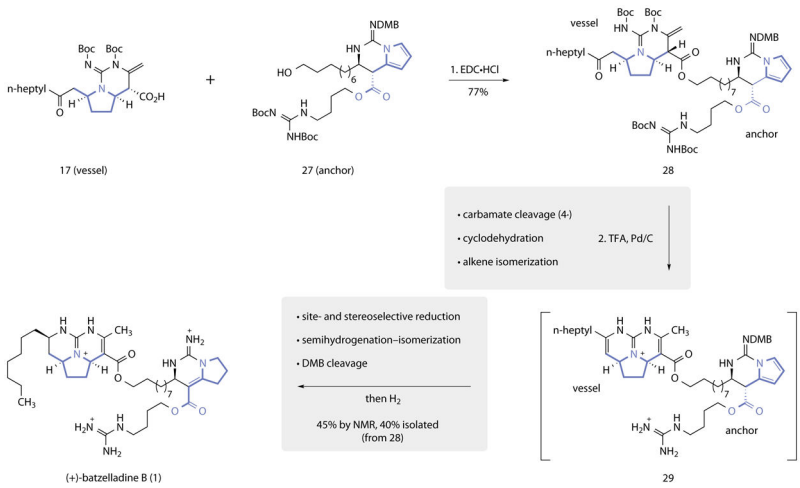

Figure 4. Coupling of 17 and 27 and completion of the synthesis of (+)-batzelladine B (1)

Reagents and conditions: **1.** EDC•HCl, DMAP, CH_2Cl_2, 24 °C, 77%. **2.** TFA, Pd/C, argon, 0 °C, then H_2, 24 °C, 45% (NMR), 40% (isolated).