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

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Alkaloids, secondary metabolites that contain basic nitrogen atoms, are some of the most well-known biologically active natural products in chemistry and medicine. Although efficient laboratory synthesis of alkaloids would enable the study and optimization of their biological properties, their preparation is often complicated by 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. Efforts to address these issues have led to the invention of a large number of protecting groups that temper the reactivity of nitrogen; however, the use of protecting groups typically introduces 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. Here 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 uses several key transformations that would be challenging or impossible to implement using saturated nitrogen heterocycles and highlights some of the advantages of beginning with aromatic reagents.

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 ($pK_a = 3.1$) than the corresponding aromatic heterocycle pyridine ($pK_a = 10.6$, DMSO, ref. 7). Moreover, functionalized heteroaromatics are readily elaborated by well-established carbon–carbon bond-forming reactions, such as cross-couplings.

In the strategy we pursue here, simple pyrrole-based precursors serve as sources of partially or fully saturated nitrogen heterocycles and are 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.

We applied this strategy towards a synthesis of the guanidinium alkaloid (+)-batzelladine B (1, Fig. 1a). Structurally, I contains a [3.1.0]tricyclic guanidine (vessel) connected to a bicyclic guanidine (anchor) via an alkyl ester. At least 15 batzelladine alkaloids have been isolated and several members of this family inhibit the binding of HIV glycoprotein gp120 to human CD4 receptor cells (half-maximal inhibitory concentration of 1 is 31 μM), thereby preventing viral induction. The absolute stereochemistries of the vessel and anchor of 1 were established in refs 13 and 14, respectively, and syntheses and synthetic studies of other batzelladines have been reported (for selected examples, see refs 15–22). Notably, in ref. 13, a tethered Biginelli condensation strategy was developed and this has provided access to several batzelladines and related alkaloids.

In refs 16 and 17, enantioselective synthetic routes to (+)-batzelladine A (2) are reported, 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-catalysed formal [4 + 3] cycloaddition between 3 and a donor-acceptor carbene was proposed to provide entry to the dehydroptaline 4, which contains all of the functional group handles required for synthesis of the vessel fragment. We posited that the pyrrole 6 could serve as a precursor to the anchor of 1 by a Mannich addition to form 7 (ref. 25), followed by cyclization and controlled adjustment of oxidation state, with concomitant isomerization.

The N-amidinopyrrole 3 (Fig. 2a) was prepared in two steps and 75% yield from commercial reagents (see Supplementary 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 (ref. 26) and dirhodium(II) tetrakis[N-phthaloyl-(S)-tert-leucinate] (Rh$_2$(S-ptttl)$_4$) as catalyst (0.5 mol%) provided the dehydroptalan 10 in 93% yield and >95:5 diastereoselectivity. Formal cycloaddition between 3 and

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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 used produces the vessel and anchor substructures of 1 (5 and 8, respectively) from the pyrrole-based starting materials 3 and 6, via the intermediates 4 and 7.
Figure 2 | Synthesis of the vessel fragment of (+)-batzelladine B (1) and
determination of its stereochemistry. a, Synthesis of the vessel precursor
17. Reagents and conditions: (1) Rh$_2$[(S)-pplt]$\lambda_1$ (0.5 mol%), pentane, 36°C,
93%, >95.5 d.r.; or Rh$_2$[(S)-pplt]$\lambda_1$ (0.1 mol%), pentane, 36°C, 87%, >95.5 d.r.; or 
(2) H$_2$ (30 atm), ClRh(PPh$_3$)$_2$ (2.0 mol%), i-PrOH, 23°C; (3) tetra-n-
butylammonium fluoride (TBAF), TMS-EBX, THF-CH$_2$Cl$_2$ (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); and (6) LiOH, THF–H$_2$O (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$_2$Cl$_2$, 24°C, >99% and (8) 
TFA, CH$_2$Cl$_2$, 0–23°C, >99%.

ent-9 using the same catalyst provided 10 with 76:24 diastereoselec-
tivity (81% yield), demonstrating that the former substrate–catalyst
pair is stereochemically matched (an example of double asymmetric synthesis$^{25}$). Formal cycloaddition between 3 and achiral diazoesters
afforded the corresponding adducts in 45%–93% yield and 60%–86%
enantionic excess (Supplementary Table 1). The yield of 10 was
essentially unaffected (87%) when the catalyst loading was reduced
to 0.1 mol%. With this key step accomplished, the pyrrole ring was
selectively reduced by treatment with chlorotris(triphenylphosphi-
ni)rhodium under dihydrogen ($^{10}$). With this key step accomplished, the pyrrole ring was
selectively reduced by treatment with chlorotris(triphenylphosphine-
ni)rhodium under dihydrogen ($^{10}$).

We then investigated the ring-opening of the bicyclic skeleton of 12
by cleavage of the β-ketoester. Because 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 optim-
ization, we found that deprotonation of 12 with n-butyllithium
(1.0 equiv.) followed by the addition of lithium benzyl octanoate
(1.8 equiv.) afforded the cyclic 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 enyne 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,
ethanol, and organometallic reagents (for example, Grignard,
organocerium, organotinanium, 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
diastereomers and tautomers; consequently, the β-ketoester of the
unpurified product was cleaved with palladium on carbon under dihy-
drogen, to form the ketone 16 (49% from 12). Saponification of the
pantactolly 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, beginning with a highly-diastereoselective Mannich addition$^{25}$
to form the β-aminooester of the target. Treatment of 6 with lithium
diisopropylamidine (LDA) and chloro tris(isopropoxy)titanium, fol-
lowed by addition of the sulfinimine 20, provided the product 21 in
99% yield. The addition product 21 was formed as a single detectable
C2 stereoisomer and an inconsequential (approximately 94:6) mixture
of C1 stereoisomers ($^{1}$H NMR analysis). The C1 and C2 stereocentres
were assigned by analogy to related products 25 and the C2 stereochem-
istry was confirmed by derivatization (see Supplementary Infor-
matuion). Notably, attempts to functionalize saturated analogues of
6 by a Mannich addition would be complicated by issues of diaster-
eselectivity and β-elimination. Owing to the presence of the alkylne
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-Selectiv ethylation formed an
iso-urea (90%, not shown) that was treated with 2,4-(dimethoxy)benzyl
Figure 3 | Synthesis of the anchor fragment of (+)-batzelladine B (1). Reagents and conditions: (1) LDA, Ti(Oi-Pr)3Cl, THF, −78°C, 99%, >20:1 mixture of C1 stereoisomers; (2) HCl, CH3OH–H2O–1,4-dioxane (4.4:1), 0°C; (3) (ClSnBu2)2O, toluene, 100°C, 78% (two steps); (4) EtOTf, 2,4,6-tri-tert-butyl-pyrimidine, (DMB) amine hydrogen chloride to afford the guanidine 23 (71%). The ester was then cleaved (trimethylsilyl trifluoromethanesulfonate, 2,6-lutidine) and the resultant carboxylic acid was coupled with the alcohol 24 to provide 25, which contains the complete carbon framework of the vessel (75%). Anti-Markovnikov reductive hydration30 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; in its absence, the conversion of 25 was low.

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. 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, CH3Cl, 23°C, 90%; (5) DMBNH3Cl, 3 Å molecular sieves, EtOH, 70°C, 71%; (6) TMSOTf, 2,6-lutidine, CH3Cl, 0–23°C, then 24, 4-(dimethylamino)-pyridine (DMAP), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)·HCl, CH3Cl, 0–23°C, 75%; and (7) 26 (15 mol%), PTSA (1.0 equiv.), HCO2H, N-methyl-2-pyrrolidinone (NMP)–H2O (4:1), 23°C, 71%.

and the 1,1-disubstituted enamide was isomerized into conjugation with the ester (28 → 29). Upon completion of this step (as judged by ultra-high-performance liquid chromatography/mass spectrometry analysis), the atmosphere within the reaction vessel was replaced with dihydrogen. Stirring the resultant mixture for 18 h at 24°C effected stereoselective reduction of the trisubstituted eneguanidine of the vessel (20:1 diastereometric ratio (d.r.); see Supplementary Information)15, controlled semireduction of the anchor pyrrole with tandem isomerization of the resultant dihydropyrrole, and cleavage of the DMB substituent, to provide 1 in 40% isolated yield (45% by NMR).

Previous approaches to synthesizing batzelladine alkaloids and related natural products have used 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 carbon–carbon bond-forming reactions and controlled reduction to achieve the saturation patterns of the target. This

Figure 4 | Coupling of 17 and 27 and completion of the synthesis of (+)-batzelladine B (1). Reagents and conditions: (1) EDC·HCl, DMAP, CH3Cl2, 24°C, 77% and (2) TFA, Pd/C, argon, 0°C, then H2, 24°C, 45% (NMR), 40% (isolated).
approach demonstrates additional synthetic pathways that are 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 is its dependence on late-stage carbon–hydrogen bond-forming reactions, which are among the most reliable classes of transformations.

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Supplementary information is available in the online version of the paper.

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Author Information Crystallographic data for 19 have been deposited at the Cambridge Crystallographic Data Centre as CCDC 1400311. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to S.B.H. (seth.herzon@yale.edu).