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Total Synthesis of (+)-Batzelladine A and (−)-Batzelladine D via [4 + 2]-Annulation of Vinyl Carbodiimides with *N*-Alkyl Imines

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Abstract

A diastereoselective [4 + 2]-annulation of vinyl carbodiimides with chiral *N*-alkyl imines has been developed to access the stereochemically rich polycyclic guanidine cores of the batzelladine alkaloids. Application of this strategy, together with additional key steps such as long-range directed hydrogenation and diastereoselective intramolecular iodo-amination, led to highly convergent total syntheses of (−)-batzelladine D and (+)-batzelladine A with excellent stereocontrol.

Introduction

Polycyclic guanidine natural products comprise an intriguing class of structurally diverse marine alkaloids possessing varied and potent biological activities. In the mid to late 1990s, nine novel tricyclic guanidine marine alkaloids were isolated as metabolites of the *Crambe* genus.[1] This family of batzelladine alkaloids (**1**–**9**, Chart 1) is characterized by at least one stereochemically rich fused tricyclic guanidine core to which are appended additional guanidine fragments (R^1–R^6) of varying complexity. Members of the batzelladine alkaloids have exhibited biological activities that include potential antiviral activity in the inhibition of the binding of HIV gp120 to human CD4 (batzelladines A and B), as well as potential immunosuppressive activity in the induction of dissociation of protein tyrosine kinase $p56^{lck}$ from CD4 (batzelladines F–I).

Over the past decade, considerable effort has been devoted to the synthesis of this class of alkaloids. The first total synthesis of any member of the batzelladine alkaloids was reported by Snider and Chen,[2] involving a biomimetic strategy consisting of the condensation of isourea derivatives with multifunctional bis(enones) in the preparation of (±)-batzelladine E (**5**). A nonracemic synthesis of (−)-batzelladine D (**2**) by Overman and co-workers soon followed employing a versatile tethered Biginelli condensation approach that later served in their enantioselective synthesis and structure revision of (+)-batzelladine F (**7**).[3] A completely distinct strategy involving a nitrone 1,3-dipolar cycloaddition was showcased by Nagasawa and co-workers first in their synthesis of (±)-batzelladine D (**2**) and later in the only report to date of the synthesis of (+)-batzelladine A (**1**) employing the same strategy.[4] Other creative approaches to complex fragments of the batzelladines have included N-acylation,[5] *N*-acyliminium cyclizations,[6] biomimetic guanidine-bis(enone) condensations,[7] formal aza-Diels–Alder reactions,[8] and stereoselective radical cyclizations.[9]

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Within a considerable number of the batzelladine alkaloids, namely batzelladines A, D, F, and G, there exists a common tricyclic tetrahydropyrimidine core (**10**, Scheme 1) incorporating multiple stereogenic centers along its periphery. Consideration of this tetrahydropyrimidine core suggests a potentially expedient route toward its construction, in which simple retrosynthetic oxidation state adjustment of **10** would provide the tricyclic dihydropyrimidine intermediate **11**. A direct [4 + 2]-disconnection along the highlighted C–C and C–N bonds in **11** would yield simple precursors in the form of a vinyl carbodiimide **12** and a chiral imine **13**. Ideally, the lone chiral center in **13** would dictate the entire stereochemical course of the synthesis. Reports on annulations of vinyl carbodiimides with imines in *N*-heterocycle syntheses are rare,[10] in which only achiral PhCH=NPh was used as a coupling partner with generally modest yields. We report herein our establishment of a diastereoselective [4 + 2]-annulation of vinyl carbodiimides with chiral *N*-alkylimines and its application to the nonracemic total syntheses of batzelladines D[11] and A.

Results and Discussion

To assess the feasibility and stereochemical outcome of the diastereoselective [4 + 2]-annulation of vinyl carbodiimides and imines, model investigations commenced with the preparation of electron-deficient vinyl carbodiimides **16** and **17** (Scheme 2). 2-Butynoic acid methyl ester (**14**) was subjected to 1,4-conjugate addition with tetramethylguanidinium azide (TMGA) to afford the *β*-azido acrylate **15** as a mixture of geometrical isomers. The *E*-isomer **15** could be isolated in high purity (44%) and was thus employed in the initial model experiments for carbodiimide formation. Treatment of *E*-**15**[12] with PPh_3 led to conversion to its iminophosphorane derivative (81%), which allowed for its condensation by aza-Wittig reaction with either *p*-methoxyphenyl isocyanate or *p*-methoxybenzyl isocyanate to form the carbodiimides **16** (72%) and **17** (74%), respectively. Notably, both of these vinyl carbodiimides could be purified by silica gel chromatography. The model chiral imine coupling partner was derived from (*S*)-5-(hydroxymethyl)-2-pyrrolidinone (**18**), which, after TBDPS protection of the hydroxyl group (83%), could be directly reduced to the imine **19** with Schwartz's reagent (68%).[13,14]

Exposure of the vinyl carbodiimide **16** or **17** to the imine **19** resulted in successful [4 + 2]-annulation in both cases to provide exclusively the (*S*,*S*)-diastereomer of the bicyclic dihydropyrimidines **20** and **21** (62% and 98%, respectively). Detailed NMR analysis of the dihydropyrimidine products confirmed the anti-stereochemical configuration of the pyrrolidine substructure within both **20** and **21**. The high efficiency and degree of diastereoselectivity in this annulation process highlight the potential for its application to the synthesis of batzelladines D and A, both of which share a common anti-fused tricyclic guanidine core.

The mechanism by which the formation of the bicyclic dihydropyrimidines **20** and **21** occurs is unclear. Be it a concerted or stepwise process, the anti-stereochemical outcome could be rationalized primarily on the basis of steric factors. For example, in the case of an asynchronous concerted [4 + 2]-cycloaddition (Scheme 3), the inverse electron-demand hetero-Diels–Alder (IED-HDA) may proceed through an endo (**22**) or exo (**23**) transition state. In either case, approach of the diene should preferentially occur on the imine dienophile face opposite to that of the alkyl ether side chain, thereby committing to the anti-cycloadduct **24** following tautomerization. Alternatively, a stepwise process could entail initial nucleophilic addition of the imine to form the guanidine zwitterion **25**, followed by an intramolecular Mannich closure in which the *π*-nucleophile approaches from the less sterically encumbered face of the iminium group. An additional stepwise process invokes the zwitterionic resonance structure of the initial adduct **25** in the form of **26**, which incorporates a conjugated 1,3,5-triene substructure, thereby setting the stage for a 6*π*-electrocyclic rearrangement. If such a process were thermally induced, disrotatory closure would likely be torquo-selective wherein the sterically demanding alkyl

ether substituent adopts an "out-orientation" to again secure formation of the anti-cycloadduct **24** after tautomerization.

Despite the different mechanistic pathways by which the annulation process can proceed, the outcome nonetheless appeared ideally suited for a stereoselective synthesis of the batzelladine core **10**, especially with the presence of the *β*-oriented alkyl ether side chain within **21** (Scheme 4). Previous approaches at employing hydrogenation protocols to establish the C7 and C15 stereochemistry[15] within the tetrahydropyrimidine core of the batzelladine alkaloids were met with significant difficulties.[3] However, the presence of the Lewis basic oxygen functionality in the C11 side chain of **21** offered unique opportunities to explore a long-range directed hydrogenation process to secure these two C-stereocenters. Thus, the TBDPS ether within **21** was removed (TBAF, 97%), and the vinylogous carbamate **27** was subjected to hydrogenation with Crabtree's catalyst[16] under 400 psi H_2. The *β*-guanidino dihydropyrimidine product **28** was formed as a single stereoisomer (81%), whose structure was verified through X-ray analysis. The free hydroxyl functionality in **27** was found to be critical in this stereoselective reduction, as attempts at Crabtree hydrogenation of the silyl ether **21** under otherwise identical conditions led to no reaction, and Rh/Al_2O_3-catalyzed hydrogenation of **27** led to 2:1 dr, favoring the undesired C7/C15 configurations in addition to reduction of the PMB group.

Synthesis of (−)-Batzelladine D

The promising results of these initial annulation investigations prompted efforts to apply this approach to the total synthesis of the simplest of the batzelladine alkaloids, namely batzelladine D (**2**, Chart 2). Although the stereoselective production of tetrahydropyrimidine **28** (Scheme 4) suggested the direct use of this intermediate in the total synthesis efforts, advancement of **28** to the tricyclic core of batzelladine D was not possible owing to functional group incompatibilities during its late-stage elaboration to close the third ring. As a result, a new imine coupling partner was prepared to overcome these difficulties (Scheme 5). In this sequence, the chiral imine was again derived from (*S*)-5-(hydroxymethyl)-2-pyrrolidinone (**18**), in which the primary hydroxyl was activated (TsCl, Et_3N, 85%) and displaced with cyanide to form nitrile **29** (91%). Ethanolysis of the nitrile (89%) and reduction to the primary alcohol ($LiBH_4$, 91%) allowed for its subsequent conversion to the TBDPS ether **30** (88%), which then underwent amide reduction with Cp_2ZrHCl[13] to afford the chiral imine **31** (66%), an intermediate corresponding to the single carbon homologation derivative of the original imine **19**.

Preparation of an appropriately protected vinyl carbodiimide employed 1,4-but-2-ynoic acid benzyl ester (**32**, Scheme 6), which was subjected to 1,4-conjugate addition with TMGA to afford the *β*-azido acrylate **33** as a mixture of geometrical isomers (84%; 2:1 *E:Z*). In the earlier model investigations into the key [4 + 2]-annulation reaction (Scheme 2), only the *E*-isomers of the vinyl carbodiimides **16**/**17** were employed in the successful study. Since the formation of the alkenyl azide **33** was nearly nonstereoselective, it was prudent to determine the suitability of both isomers in the key annulation for the efficient synthesis of batzelladine D (**2**). Thus, both the *E*- and *Z*-isomers of **33** (Scheme 6) were separated by silica gel chromatography and subjected to Staudinger-aza-Wittig condensation with *p*-methoxybenzyl isocyanate to form the vinyl carbodiimides *E*-**34** and *Z*-**34** with comparable efficiency (73% and 67%, respectively). Treatment of either *E*-**34** or *Z*-**34** with 2-(2-*O*-TBDPS-ethyl)-3,4-dihydro-2*H*-pyrrole (**31**) led to the formation of a single diastereomer of the dihydropyrimidine **35** (86% from *E*-**34** and 88% from *Z*-**34**), incorporating the expected anti-stereochemistry. It is worth noting that the formation of **35** may arise from either (1) both *E*- and *Z*-isomers of **34** undergoing the annulation or (2) in situ interconversion of the *E/Z* isomers of **34** wherein one preferentially undergoes dihydropyrimidine formation. Nevertheless, this sequence does illustrate that the low

stereoselectivity in the conversion of **32** → **33** is not a liability given that both isomers comparably converge to the bicylic guanidine **35**.

The synthesis of (−)-batzelladine D (**2**) continued with removal of the TBDPS ether in **35** to expose the primary hydroxyl group (TBAF, 99%) in **36** for directed hydrogenation of the vinylogous carbamate functionality. Even with the further extended hydroxyl group in **36**, the Ir^{+}-catalyzed reduction[16] proceeded with complete stereocontrol to provide the corresponding tetrahydropyrimidine (80%), which efficiently underwent IBX oxidation to provide the tricyclic guanidine hemiaminal **37** (98%). At this juncture, advancement of **37** through the direct attachment of the C7–C25[15] fragment via selective Wittig fragment coupling proved troublesome. For example, treatment of hemiaminal **37** with the ylide derived from nonyltriphenylphosphonium bromide led to stereoselective formation of the *cis*-alkene **38**, although with unavoidable C7 epimerization of the pseudo-axial ester substituent. To remedy this situation, the benzyl ester in **37** was first subjected to hydrogenolysis (99%), allowing for cis-selective Wittig olefination[17] with excess ylide (thereby generating the carboxylate anion in situ) to afford the alkene acid **39** after acidification (72%). Attachment of the guanidine-containing side chain of batzelladine D (**2**) was then accomplished by carboxylate O-alkylation with $(BocHN)_2C{=}N(CH_2)_4OSO_2Me$[18] to form **41** in 93% yield.

Closure of the remaining ring in (−)-batzelladine D was effected by intramolecular iodo-amination of the alkene in **41** (Scheme 7), employing I_2 in the presence of K_2CO_3. Preferential 6-exo-cyclization (70%) proceeded with complete regio- and stereocontrol to establish the desired C13-(*R*)-configuration[15] in **42** after reductive deiodination[19] (89%). The high stereoselectivity of this final ring closure can be rationalized by the preferential formation and reaction of the iodonium diastereomer **43** (Chart 3), directly derived from oxidation of the *cis*-alkene. Cyclization in this manifold would place the alkyl group in a pseudo-equatorial orientation. Conversely, cyclization to form the undesired C13-(*S*)-diastereomer would arise from formation and reaction of the iodonium diastereomer **44**, which places the alkyl group in a pseudo-axial orientation to experience pronounced $A^{1,3}$-like strain. It is worth noting that the current data does not discount the possibility of iodine-induced alkene *E/Z* isomerization prior to cyclization. Unfortunately, further elucidation of the stereocontrol elements in the cyclization was hampered by difficulties both in the determination of the configuration of the newly formed iodine-bearing stereocenter in the immediate iodo-amination product and in the independent synthesis of the *trans*-alkene isomer of **41** to probe its oxidative cyclization. Nevertheless, the favorable outcome of this final cyclization event permitted the global deprotection of **42** (Scheme 7) with aqueous TFA to conclude the synthesis of (−)-batzelladine D (**2**, 82%).

Synthesis of (+)-Batzelladine A

The successful application of the carbodiimide annulation strategy in the synthesis of the simplest member of batzelladine alkaloids (**2**) prompted investigation of this approach to more complex members of the family, namely the small-molecule binder to CD4,[20] batzelladine A (**1**, Scheme 8). Unfortunately, the highlighted [4 + 2]-annulation approach does not immediately map onto the bicylic guanidine substructure **45** within **1**. However, retrosynthetic rupture of the pyrrolidine at C11–N[21] in **45** would generate a dihydropyrimidine intermediate **46**, which should be amenable to the key [4 + 2]-disconnection wherein the absolute configuration of the lone C13-chiral center[21] would be established.[22]

The preparation of a suitable vinyl carbodiimide substrate for the synthesis of the bicyclic guanidine substructure **45** within (+)-**1** commenced (Scheme 9) with sequential O-benzylation (NaH, BnBr, 80%) and C-acylation (MeOC(O)Cl, 85%) of pent-4-yn-1-ol to afford the propargyllic ester **48**. Treatment of alkyne **48** with TMGA led to conjugate 1,4-addition of azide to afford a 2:1 (*E:Z*) mixture of vinyl azides **49**, which was then converted to vinyl

carbodiimide **50** via Staudinger-aza-Wittig condensation with *p*-methoxybenzyl isocyanate (63%). The mixture of both geometrical isomers of **50** was exposed to chiral imine (*R*)-**19**, prepared similarly to that of its *S*-enantiomer (see Scheme 2). The annulation process proceeded at 23 °C to provide the dihydropyrimidine **51** (89%) as a single diastereomer. While it remains unclear whether the cyclization proceeded via a concerted or stepwise mechanism, the anti-stereochemistry of the product emerged as expected based on our previous experience with this reaction. Thus, annulation of chiral imine *R*-**19** with vinyl carbodiimide **50** secured the required C13-*R*-configuration in **51** via relay of stereochemical information from the sacrificial stereogenic center originally obtained from chiral pyrrolidinone (*R*)-**18**.

Construction of the bicyclic guanidine skeleton in batzelladine A continued as the guanidine group in **51** was fully protected by acylation with Boc_2O (86%), allowing for conversion of the primary alkyl silyl ether to its iodo-counterpart **52** via sequential treatment with TBAF and I_2/PPh_3 (88%, two steps). Low-temperature lithium–halogen exchange of **52** occurred rapidly with concomitant *β*-elimination of the acylated guanidine functionality to cleave the pyrrolidine ring (93%). The resultant α-olefin in **53** served as a convenient handle with which to attach the C17–C22[21] oligomethylene linker present in batzelladine A; thus, alkene **53** was exposed to the TBDPS ether of hept-6-en-1-ol (**54**) in the presence of Grubbs-G2 ruthenium catalyst[23] to effect olefin cross-metathesis to provide a mixture of *E*- and *Z*-disubstituted alkene isomers (73%). Subsequent treatment with H_2 and $Pd(OH)_2$ led to benzyl ether hydrogenolysis, *p*-methoxybenzyl removal from the guanidine, and alkene hydrogenation in a single pot procedure to yield the primary alcohol **55** (90%). Closure of the pyrrolidine ring was accomplished by intramolecular aza-Mitsunobu (DIAD, PPh_3, 93%),[24] followed by acylation of the guanidine core with Boc_2O to provide the bicyclic vinylogous carbamate **56** (85%). The remaining steps for elaboration of the bicyclic guanidine fragment of batzelladine A involved thiolate-induced removal of the vinylogous methyl carbamate followed by BOPCl-mediated esterification[25] of $(BocHN)_2C{=}N(CH_2)_4OH$ (**57**) to provide the vinylogous carbamate **58** (55%, two steps). Subsequent conversion of the silyl ether in **58** to its methanesulfonate ester derivative (TBAF; MsCl, 84%, two steps) provided **59**, an appropriately derivatized bicyclic guanidine core of batzelladine A.

The convergent final sequence in the assembly of both polycyclic guanidine fragments employed the advanced bicyclic guanidine construct **39**, originally prepared (Scheme 6) for the synthesis of batzelladine D. The cesium carboxylate of **39** (Scheme 10) was generated to undergo O-alkylation with the alkyl methanesulfonate **59** to provide the C23 ester **60** (68%). The third ring within the tricyclic core of batzelladine A was then closed by way of a stereoselective intramolecular iodoamination (I_2, Cs_2CO_3, 72%) to establish the desired C30-*R*-stereocenter, followed by reductive de-iodination (Et_3N, H_2, Pd/C, 71%) to afford **61**, a fully protected form of batzelladine A. Global deprotection of **61** (TFA) completed the total synthesis of batzelladine A (75%), whose analytical data were found to be identical in all respects to that reported for the natural product.

Conclusions

Through the use of a unified strategy involving the diastereoselective [4 + 2]-annulation of chiral imines with vinyl carbodiimides, the total syntheses of (+)-batzelladine A (**1**) and (−)-batzelladine D (**2**) were accomplished in highly convergent and stereoselective sequences. The successful application of this approach to dihydropyrimidine construction in the synthesis of **1** and **2** illustrates its potential for the synthesis of other related alkaloids such as the crambescidin family of natural products, as well as for the construction of complex non-natural *N*-heterocycles of potential biological utility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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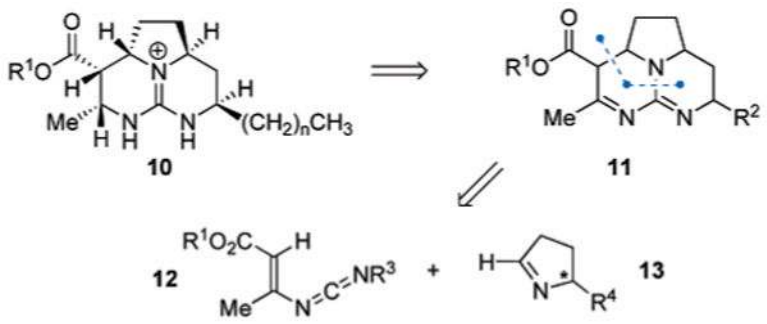
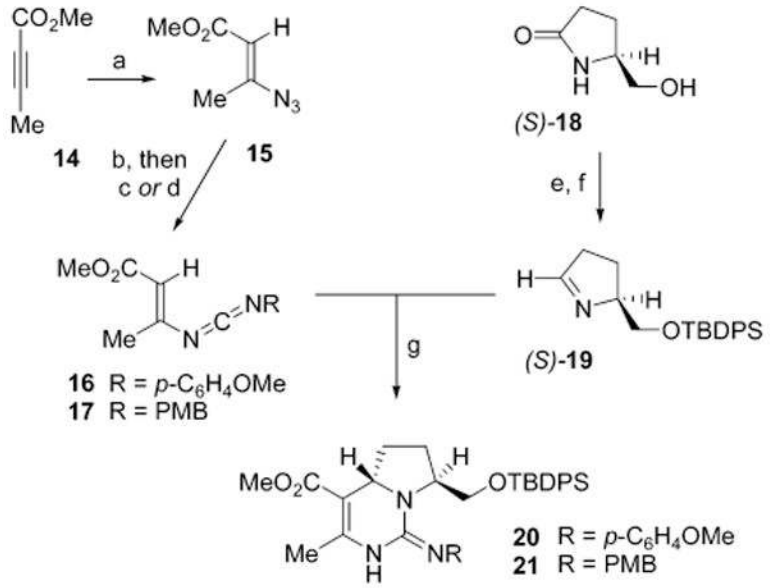
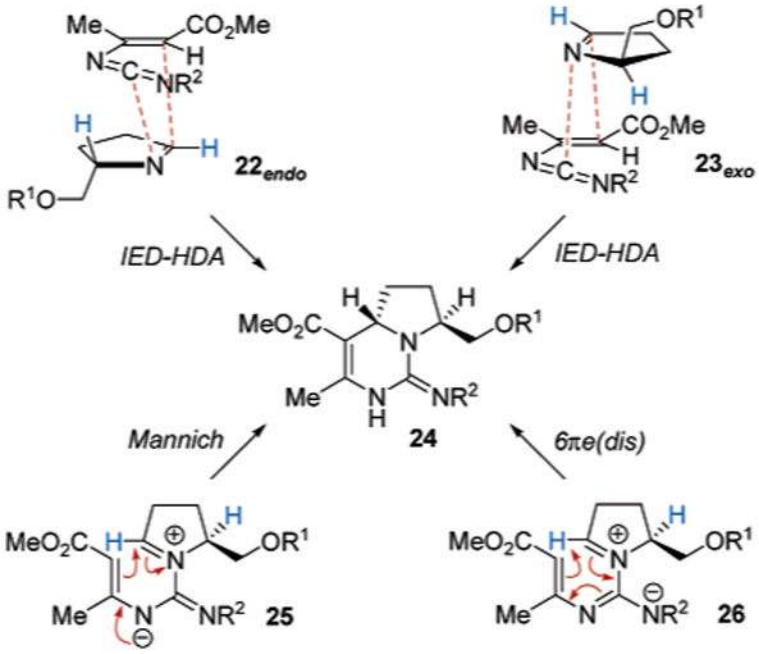


Scheme 1.

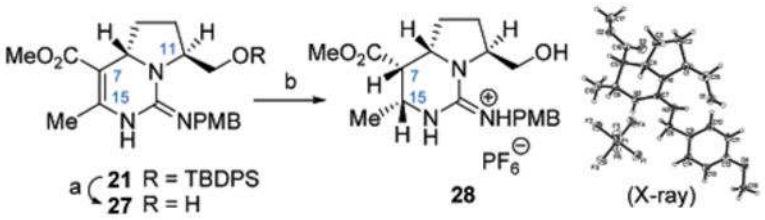


Scheme 2 a.

[a] Reagents and conditions: (a) $(MeHN)_2CNMe_2N_3$, $CHCl_3$, 44% (*E*); (b) PPh_3, CH_2Cl_2, 81%; (c) *p*-$MeOC_6H_4NCO$, PhMe, 72%; (d) *p*-$MeOC_6H_4$-CH_2NCO, PhMe, 85 °C, 74%; (e) TBDPSCl, imidazole, DMF, 83%; (f) Cp_2ZrHCl, THF, −20 °C, 68%; (g) $(ClCH_2)_2$, 62% (R = PMP), 98% (R = PMB).

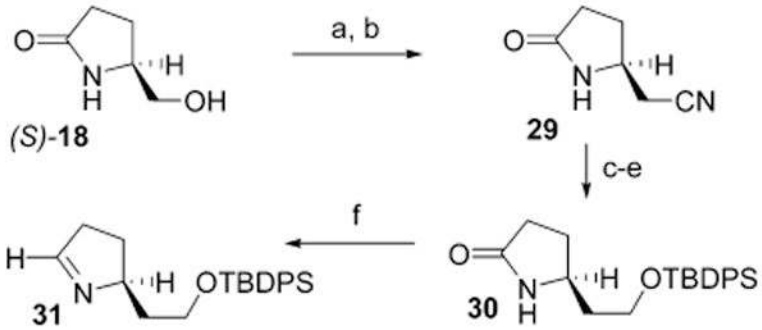


Scheme 3.



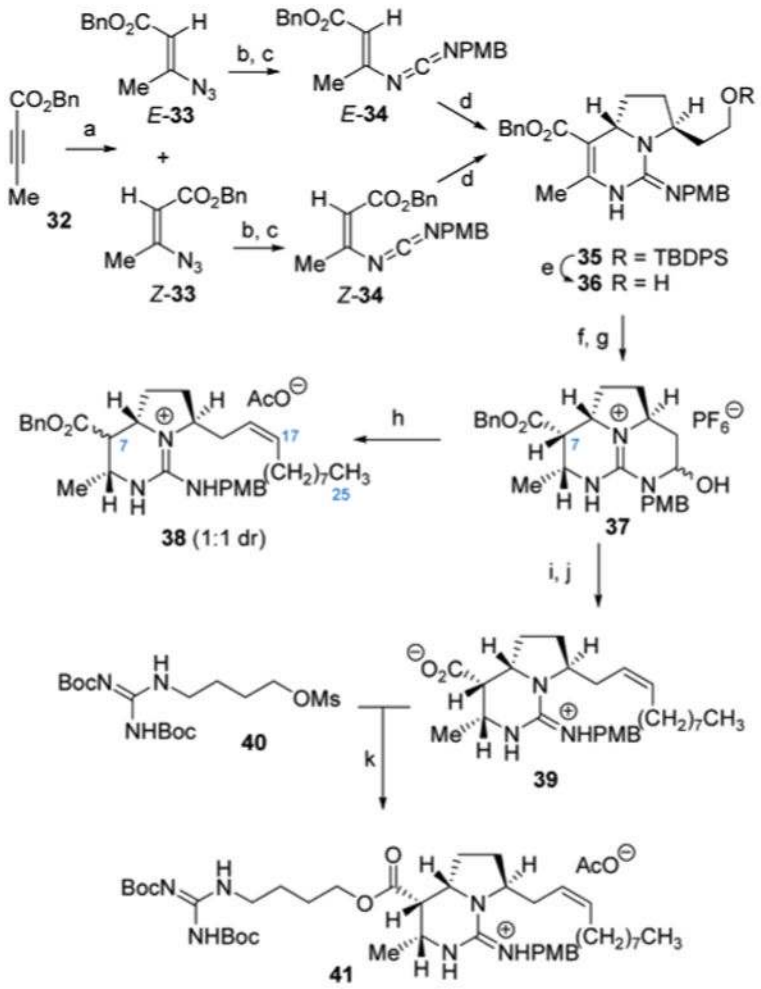
Scheme 4 a.

[a] Reagents and conditions: (a) TBAF, THF, 97%; (b) [Ir(cod)pyr(PCy_3)]PF_6, H_2 (400 psi), CH_2Cl_2, 81%.



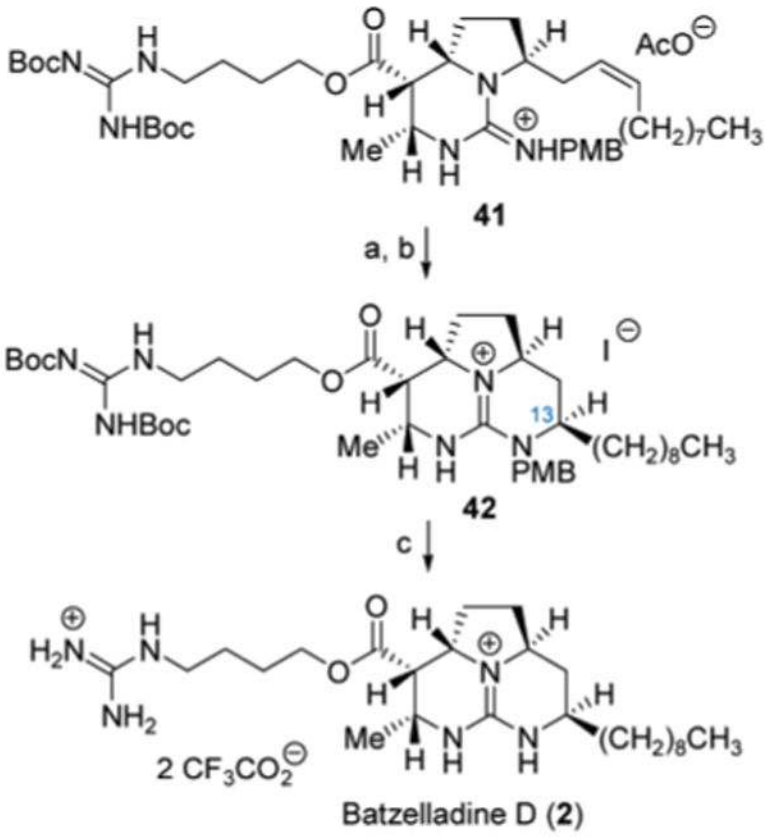
Scheme 5 a.

[a] Reagents and conditions: (a) TsCl, TEA, DMAP, CH_2Cl_2, 85%; (b) KCN, CH_3CN, 85 °C, 91%; (c) $HCl_{(g)}$, EtOH, 65 °C, 89%; (d) $LiBH_4$, MeOH, THF, 0 °C, 91%; (e) TBDPSCl, imidazole, DMF, 88%; (f) Cp_2ZrHCl, THF, −20 °C, 66%.



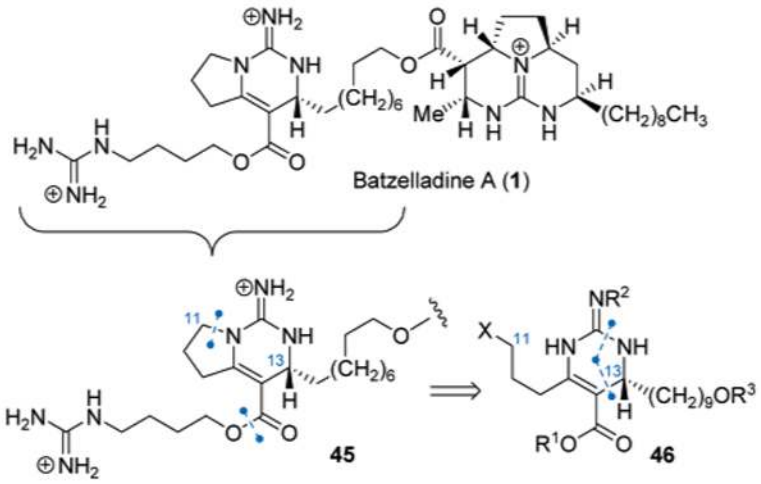
Scheme 6 a.

[a] Reagents and conditions: (a) $(MeHN)_2CNMe_2N_3$, $CHCl_3$, 84% (2:1 *E*:*Z*); (b) PPh_3, CH_2Cl_2, 75% (*E*), 58% (*Z*); (c) *p*-$MeOC_6H_4CH_2NCO$, PhMe, 85 °C, 73% (*E*), 67% (*Z*); (d) **31**, $(ClCH_2)_2$, 23 °C, 86% from *E*-**34**, 88% from *Z*-**34**; (e) TBAF, THF, 99%; (f) [Ir(cod)pyr(PCy_3)]PF_6, H_2 (400 psi), CH_2Cl_2, 80%; (g) IBX, DMSO, CH_3CN, 98%; (h) $Me(CH_2)_7CH{=}PPh_3$, THF; (i) 10% $Pd(OH)_2$/C, AcOH, H_2 (1 atm), MeOH, 99%; (j) $Me(CH_2)_7CH{=}PPh_3$, THF, 50 °C, 72%; (k) $(BocHN)_2C{=}N(CH_2)_4OMs$, Cs_2CO_3, DMF, 40 °C, 93%.

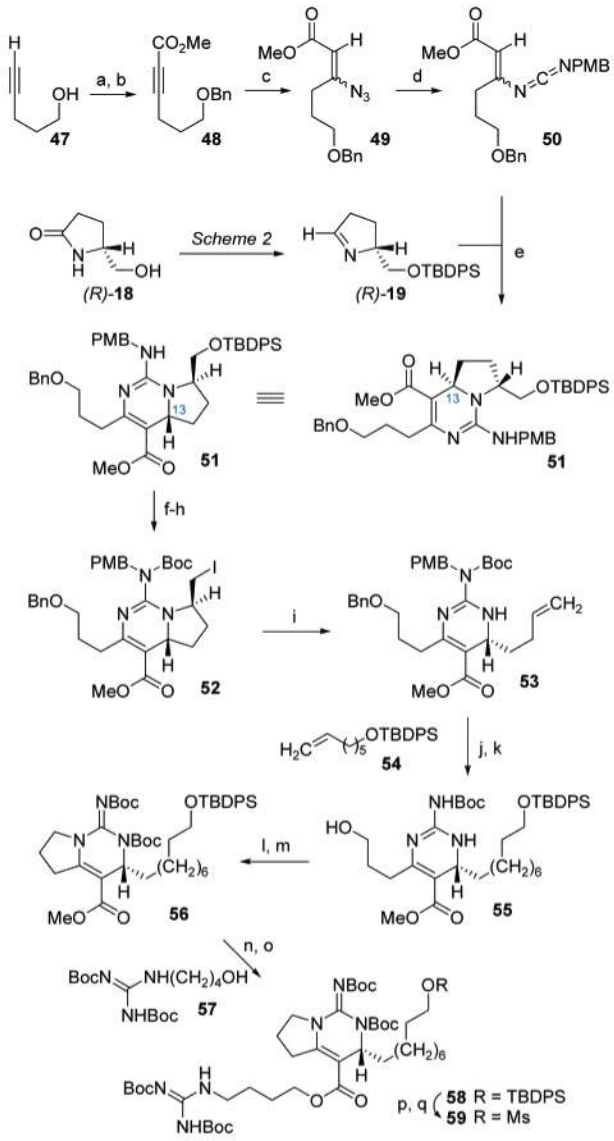


Scheme 7 a.

[a] Reagents and conditions: (a) I_2, K_2CO_3, DME, 70%; (b) 10% Pd/C, Et_3N, H_2 (1 atm), EtOAc, 89%; (c) TFA, 82%.

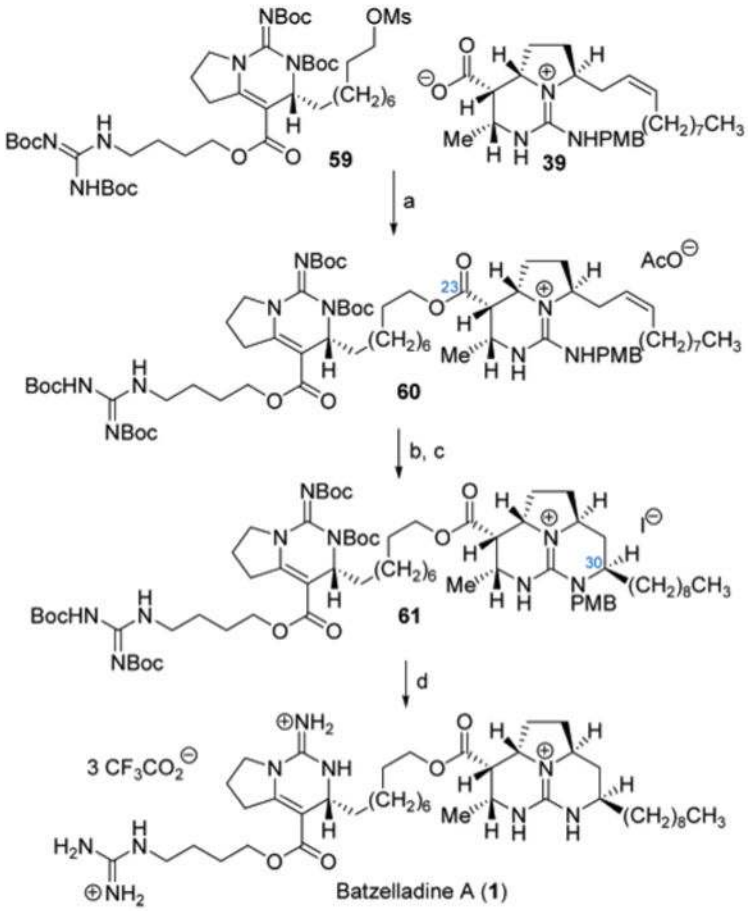


Scheme 8.



Scheme 9 a.

[a] Reagents and conditions: (a) BnCl, NaH, TBAI, THF, 70 °C, 80%; (b) *n*BuLi, methyl chloroformate, THF, −78 °C, 85%; (c) TMGA, $CHCl_3$, 23 °C, 78% (2:1 *E*/*Z*); (d) PPh_3, CH_2Cl_2, 23 °C; PMBNCO, PhMe, 80 °C, 63%; (e) $(ClCH_2)_2$, 23 °C, 89%; (f) NaH, Boc_2O, DMAP, THF, 23 °C, 86%; (g) TBAF, AcOH, THF, 23 °C, 91%; (h) I_2, PPh_3, imidazole, PhMe, 23 °C, 97%; (i) *t*-BuLi, THF, −78 °C, 93%; (j) **54**, Grubbs-G2, CH_2Cl_2, 45 °C, 73%; (k) 10% $Pd(OH)_2$, AcOH, H_2 (1 atm), MeOH, CH_2Cl_2, 23 °C, 90%; (l) DIAD, PPh_3, PhMe, 23 °C, 93%; (m) NaH, Boc_2O, DMAP, THF, 23 °C, 85%; (n) EtSLi, HMPA, 23 °C; (o) **57**, BOPCl, TEA, CH_2Cl_2, 23 °C, 55% (two steps); (p) TBAF, THF, 23 °C, 92%; (q) MsCl, TEA CH_2Cl_2, 0 °C, 91%.



Scheme 10 a.

[a] Reagents and conditions: (a) Cs_2CO_3, DMF, 50 °C, 68%; (b) I_2, Cs_2CO_3, DME, 23 °C, 72%; (c) 10% Pd/C, TEA, H_2 (1 atm), EtOAc, 71%; (d) TFA, 0 °C, 75%.

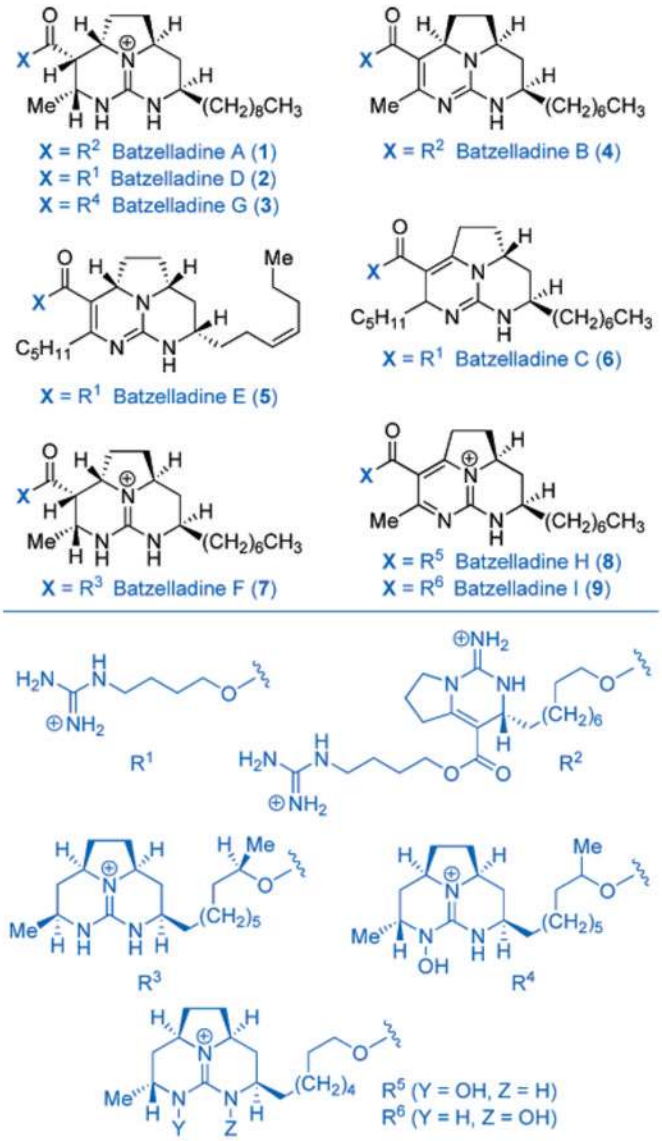


Chart 1.

Chart 2.

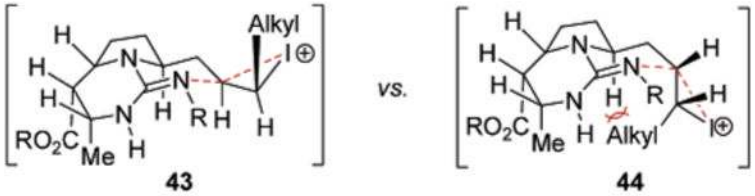


Chart 3.