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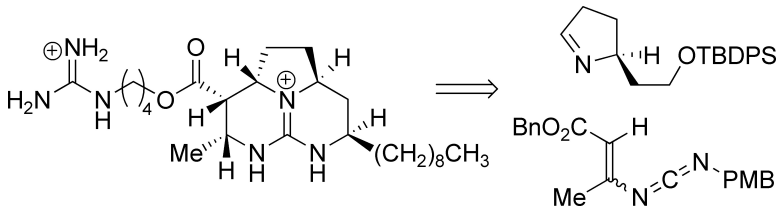

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Diastereoselective [4+2] Annulation of Vinyl Carbodiimides with *N*-Alkyl Imines. Asymmetric Synthetic Access to the Batzelladine Alkaloids

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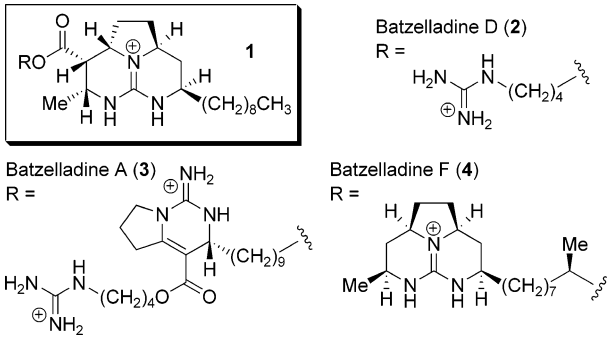
The stereoselective construction of complex polycyclic guanidine structures is of paramount importance given the abundance of biologically active complex guanidine natural products. This is exemplified by members of the batzelladine family of polycyclic guanidine marine alkaloids (Chart 1),[1] several of which exhibit notable biological activity, including inhibition of binding of HIV gp120 to human CD4, as well as the induction of protein tyrosine kinase p56^{lck} dissociation from CD4. Consequently, this family of alkaloids has been the focus of extensive synthetic studies in which stereoselective construction of the tricyclic guanidine core **1** presents the principal challenge. Elegant synthetic strategies directed toward this goal have included multiple N-acylation,[2] N-acyliminium cyclization,[3] aza-Diels−Alder reaction,[4] stereoselective acyl radical cyclization,[5] condensation of isoureas and guanidines with bis-(enones),[6] tethered Biginelli condensation,[7] and nitrone 1,3-dipolar cycloaddition,[8] with the latter three approaches culminating in racemic[6b,8b] and asymmetric[7b,c,8c] total syntheses. We report herein a new strategy to the batzelladine alkaloids employing a diastereoselective [4+2] annulation reaction of chiral *N*-alkyl imines and vinyl carbodiimides, illustrated in a concise asymmetric synthesis of batzelladine D (**2**).

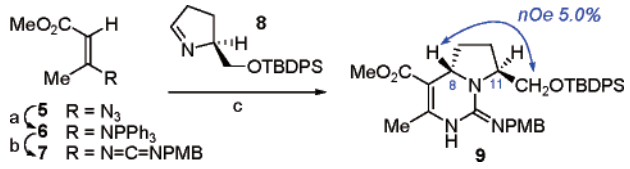
Chart 1



Although vinyl carbodiimides have been employed in N-heterocycle syntheses,[9] their annulation reactions with imines have been limited to the use of only PhCH═NPh in a modest-yielding nonstereoselective process.[9b] Nevertheless, the prospect of developing an efficient [4+2] annulation of *chiral N-alkyl imines* with vinyl carbodiimides seemed to be ideally suited for the preparation of the tricyclic batzelladine skeleton **1**, both in terms of convergent strategic bond construction as well as providing an attractive means for stereocontrol.

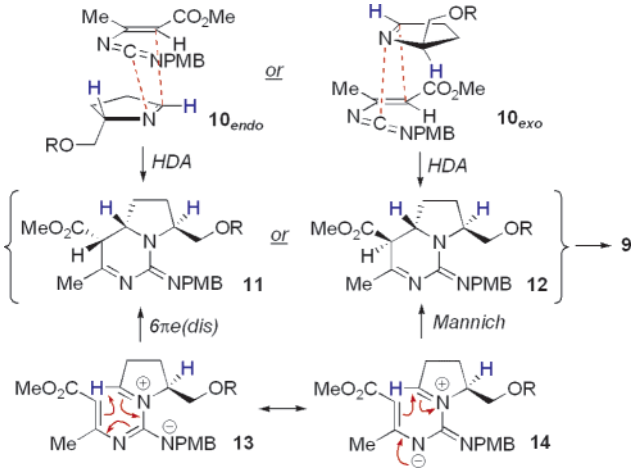
Assessing the feasibility of the process in a model investigation commenced with the preparation of the electron-deficient vinyl carbodiimide **7** (Scheme 1). Thus, (*E*)-3-azidobut-2-enoic acid methyl ester (**5**)[10] was readily converted to its iminophosphorane **6** with PPh_3 (71%) followed by aza-Wittig condensation with *p*-methoxybenzyl isocyanate to form **7** (71%). Exposure of the vinyl carbodiimide **7** to readily available (*S*)-2-*O*-TBDPS-methyl-3,4-

Scheme 1 [a]



[a] Reagents and conditions: (a) PPh_3, CH_2Cl_2, 71%; (b) *p*-$MeOC_6H_4CH_2NCO$, PhMe, 85 °C, 71%; (c) $(ClCH_2)_2$, 23 °C, 98%.

Scheme 2



dihydro-2*H*-pyrrole (**8**)[11] resulted in efficient [4+2] annulation to provide exclusively the *S*,*S*-diastereomer of the bicyclic dihydropyrimidine **9** (98%), a substructure that maps onto the batzelladine skeleton **1** with the requisite anti relationship of its C8 and C11 hydrogens.[12]

Despite the diverse mechanistic pathways through which the annulation process can proceed (Scheme 2), the stereochemical preference can be rationalized based on steric influences arising from the lone stereocenter of the chiral imine. Reasonable pathways include: (1) a hetero-Diels−Alder (HDA) cycloaddition in a sterically minimized *endo* (**10**$_{endo}$ → **11**) or *exo* (**10**$_{exo}$ → **12**) mode; (2) generation of the transient 2,4-diaza-1,3,5-hexatriene **13**, followed by sterically governed torquo-selective disrotatory 6π-electrocyclic ring closure (**13** → **11**); or (3) generation of iminium **14** followed by intramolecular Mannich cyclization (i.e., **14** → **12**) onto the less hindered face of the electrophile. Irrespective of the possible annulation pathways, the formation of either of the guanidine diastereomers **11** or **12** would ultimately result in convergence to the vinylogous carbamate **9** upon tautomerization.

This stereoselective approach to the bicyclic guanidine **9** also provides a superb opportunity for establishing the C7 and C15 stereochemistry (Scheme 3)[12] present in the alkaloids, a formidable challenge highlighted in previous synthetic efforts. Thus, the TBDPS ether within **9** was removed, and the vinylogous carbamate

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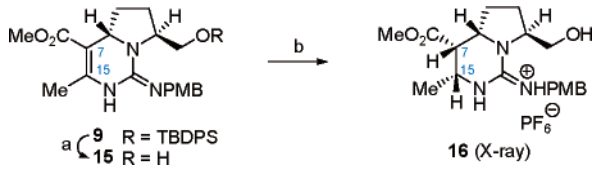
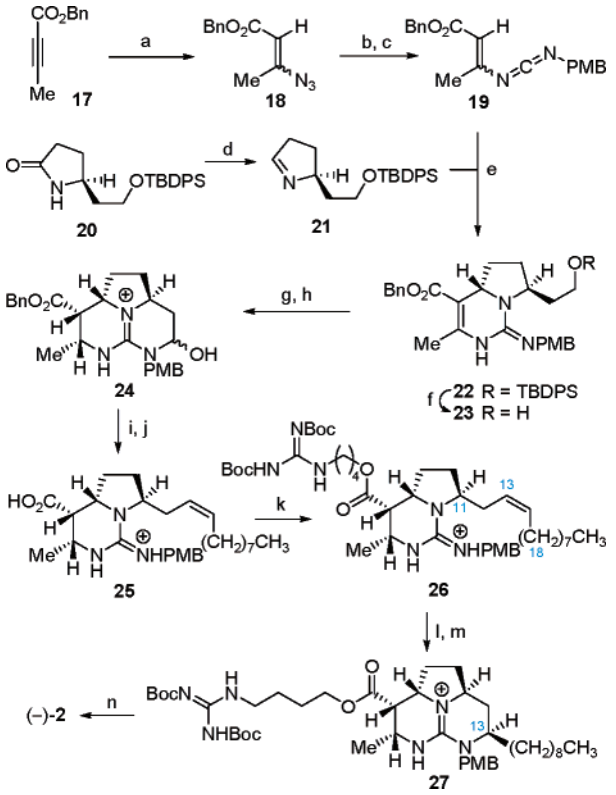
Scheme 3 [a]



[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 4 [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) Cp_2ZrHCl, THF, −20 °C, 66%; (e) $(ClCH_2)_2$, 23 °C, 86% from (*E*)-**19**, 88% from (*Z*)-**19**; (f) TBAF, THF, 99%; (g) [Ir(cod)pyr(PCy_3)]PF_6, H_2 (400 psi), CH_2Cl_2, 80%; (h) IBX, DMSO, CH_3CN, 98%; (i) 10% $Pd(OH)_2$/C, AcOH, H_2 (1 atm), MeOH, 99%; (j) $Me(CH_2)_8PPh_3$, THF, 50 °C, 72%; (k) $(BocHN)_2C{=}N(CH_2)_4OMs$, Cs_2CO_3, DMF, 40 °C, 93%; (l) I_2, K_2CO_3, DME, 70%; (m) 10% Pd/C, Et_3N, H_2 (1 atm), EtOAc, 89%; (n) TFA, 82%.

15 was subjected to long-range, hydroxy-directed hydrogenation with Crabtree's catalyst[13,14] to provide the *β*-guanidino ester **16** as a single stereoisomer (81%), whose structure was verified through X-ray analysis.

Having secured the feasibility and favorable stereochemical consequences of the heteroannulation, the strategy was validated in a short asymmetric synthesis of batzelladine D (**2**, Scheme 4). 1,4-But-2-ynoic acid benzyl ester (**17**) was treated with tetramethylguanidinium azide to afford the *β*-azido acrylate **18** (84%; 2:1 *E*:*Z*). Both the *E* and *Z* isomers of **18** separately underwent Staudinger−aza-Witting condensation with *p*-methoxybenzyl isocyanate to form the vinyl carbodiimides (*E*)-**19** and (*Z*)-**19** with comparable efficiency. Treatment of either (*E*)- or (*Z*)-**19** with 2-(2-*O*-TBDPS-ethyl)-3,4-dihydro-2*H*-pyrrole (**21**), derived from Cp_2ZrHCl-mediated reduction[15] of its lactam precursor **20**,[16] provided the bicyclic dihydropyrimidine **22** with complete diastereoselectivity (86 and 88%, respectively). Removal of the TBDPS ether in **22** allowed for directed hydrogenation of its vinylogous carbamate (80%) with complete stereocontrol, even with the further-removed homologated hydroxyl directing group in **23** (cf. **15**). Subsequent IBX oxidation afforded the tricyclic guanidine hemiaminal **24** (98%), which underwent sequential benzyl ester hydrogenolysis (99%) and cis-selective Wittig olefination[17] with the ylide derived from nonyltriphenylphosphonium bromide to form **25** (72%). Introduction of the guanidine-containing side chain of batzelladine D (**2**) was then effected by carboxylate O-alkylation with $(BocHN)_2C{=}N(CH_2)_4OSO_2Me$[18] to form **26** in 93% yield. Closure of the remaining ring was accomplished via intramolecular regio- and stereoselective iodoamination (70%) of the alkene in **26**, relying on minimization of $A^{1,3}$-like strain between C11 and C18 of the reacting *cis*-alkene hydrocarbon chain to establish the desired C13 configuration.[12] Subsequent reductive deiodination[19] provided **27** (89%), whose protective groups were removed with TFA to provide (−)-**2** (82%) as its bis(trifluoroacetate) salt.

A diastereoselective [4+2] annulation of vinyl carbodiimides with chiral *N*-alkyl imines has been developed to access the stereochemically rich tricyclic core of the batzelladine alkaloids. Its application to the asymmetric synthesis of batzelladine D (**2**) permitted the use of long-range, directed hydrogenation and stereoselective intramolecular iodoamination as additional key steps to establish the remaining stereocenters within **2** with excellent stereocontrol. Efforts are underway to apply this novel approach to other members of the batzelladine alkaloids.

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Supporting Information Available: Complete ref 1a, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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