Efficient construction of the securine A carbon skeleton

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Securamine A is a structurally intriguing alkaloid possessing a pyrroloindole core joined via a modified isoprene subunit to a functionalized imidazole ring. Recent synthetic efforts in this laboratory have resulted in the efficient construction of key lactone 36, which undergoes tandem azide reduction/ring expansion to macrolactam 37. Macrolactam 37 possesses the complete macrocyclic core of securamine A.

The bryozoans *Flustra foliacea* and *Chartella papyracea* have proven to be a rich source of structurally unprecedented halogenated indole-alkaloids. A series of investigations resulted in the isolation of a host of novel natural products, including the flustramines (1–3), chartellines (4–6), and chartellamides (7). Additionally, two reports describe the securamines (8, 9), which are characterized by a central tricyclic pyrroloindole core and a highly substituted imidazole ring linked via a modified isoprene subunit and a macrocyclic *cis*-enamide (Fig. 1). Interestingly, pyrroloindole securamine A (**1**) exists in a synthetically exploitable solvent-dependent equilibrium with ring-opened isomer securine A (**2**) (8, 9).

Despite synthetic work toward both the flustramines (10–12) and chartellines/chartellamides (13, 14), no efforts toward the construction of the securamine/securine skeleton have yet been reported (15, 16). Intrigued by the densely functionalized heterocycles characterizing the securamines, in addition to reports that securine A serves as a biogenic precursor for a variety of other natural products (8, 9), we have focused our efforts on the efficient construction of **1** and **2**.

Retrosynthetically, securine A was visualized as the union of two heterocyclic subunits (pyrroloindole and imidazole) joined into a macrocycle via two tethers (the isoprene and enamide) (Fig. 2). We envisioned that the elimination-prone C(10) neopentyl chloride moiety (13, 14) could be installed at a late stage via direct chlorination of the corresponding alcohol, whereas the sensitive enamide-moiety could be generated from a C(2)-C(3) amido-alcohol (**5**). Orthogonal diol **5** would arise via macrocyclization of the corresponding amino alcohol, which could be accessed directly from a C(2)-C(3) olefin (17, 18). Key indole **6** could be accessed from internal alkyne **7**, which would be generated from elaboration of **8**. Imidazole **8** could be derived from the condensation of two equivalents of formamide with α-bromo ketone **9** (19).

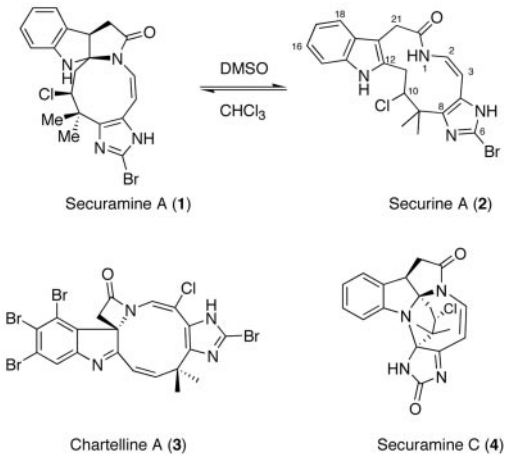

Fig. 1. Representative akaloids from *C. papyracea*.

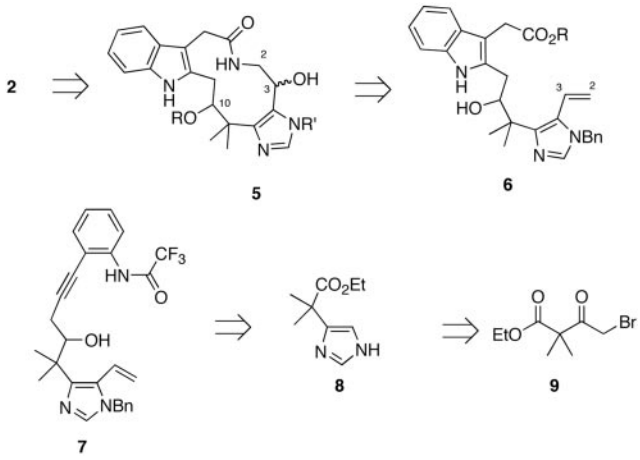

Fig. 2. Securine A retrosynthetic analysis.

Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere by using freshly distilled solvents. Experimental and spectral data pertaining to compounds **7**, **11**–**15**, **18**–**20**, **22**, and **25**–**40** can be found in *Supporting Text*, which is published as supporting information on the PNAS web site.

Results

Exposure of **10** to bromine and acetic acid gave smooth conversion to the corresponding α-bromoketone. Subsequent dissolution in neat formamide and prolonged heating gave imidazole **8** in 80% overall yield after two recrystallizations (19). Benzylation at N(5) and bromination at C(4) proceeded in a highly regioselective manner to afford versatile bromide **11**. Subsequent installation of the requisite C(2)-C(3) terminal olefin, two-step adjustment of the C(10) oxidation state, and addition of propargyl magnesium bromide furnished key neopentyl alcohol **13** in excellent overall yield (27% yield, eight steps) from **10** (Scheme 1).

With **13** in hand we explored chlorination under a variety of conditions. In most cases, the desired neopentyl chloride was accompanied by variable amounts of **15**, arising via an imidazole-assisted elimination pathway (Scheme 2). Similar participation via intermediate cyclpropanes has been reported in other homobenzyllic systems (20, 21). Interestingly, phosphine cone

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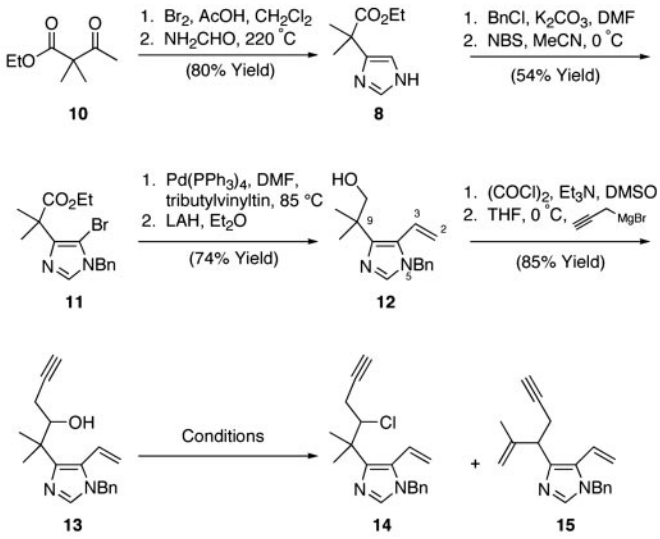
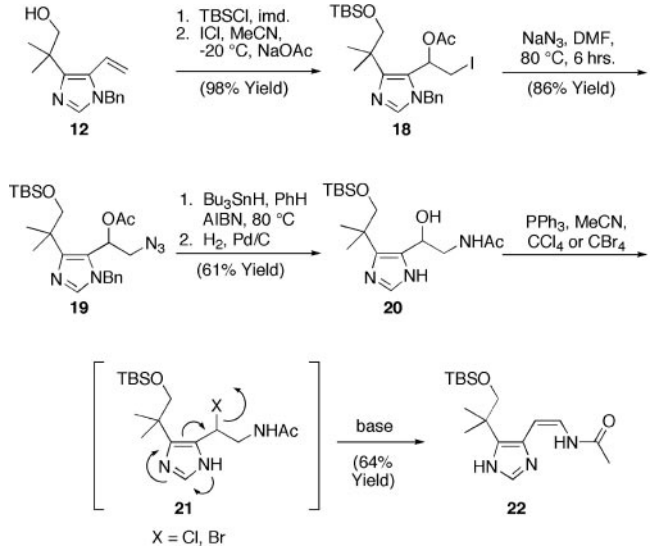


Conditions	Cone Angle	Ratio 14:15	
$P(Ph)_2Cy$, CCl_4, MeCN	162°	1:5	65% Yield
PPh_3, CCl_4, MeCN	145°	1:1	70% Yield
$P(Bu)_3$, CCl_4, MeCN	135°	2:1	80% Yield
MsCl, py, CH_2Cl_2		1:1	55% Yield

Scheme 1. Imidazole construction and model chlorine installation. DMF, *N*,*N*-dimethylformamide; LAH, lithium aluminum hydride; NBS, *N*-bromosuccinimide; THF, tetrahydrofuran.

angle seemed to correlate directly with the ratio of **14** to **15**, and we found **14** could be accessed in reasonable yield by using tributylphosphine and carbon tetrachloride (Scheme 1). Although **14** proved relatively uncooperative toward further advancement to **1**, we were pleased to find that a variety of related hindered alcohols, including those possessing fully elaborated indoles (Scheme 9, which is published as supporting information on the PNAS web site), also proved suitable for direct phosphine-mediated introduction of the neopentyl chlorine. Resolved to install the C(10) chlorine at a later stage, we proceeded to test our plans for dehydrative enamide installation.

Efforts to regioselectively functionalize the C(2)-C(3) olefin of a variety of model imidazoles (**12**–**14**) with standard aminohydroxylation conditions proved problematic (17, 18). However, in a reaction sequence inspired by Khuong-Huu and coworkers (22), we found that addition of the silyl ether derived from **12** to a premixed solution of ICl and sodium acetate in cold acetonitrile furnished primary iodide **18** in excellent overall yield. Subsequent iodide displacement with sodium azide affords azido acetate **19**, possessing the proper C(2)/C(3) functionalization for advancement to **1**. Tandem tributyltinhydride-mediated azide reduction-acetate migration followed by hydrogenation afforded model amido alcohol **20**. We were pleased to find that the

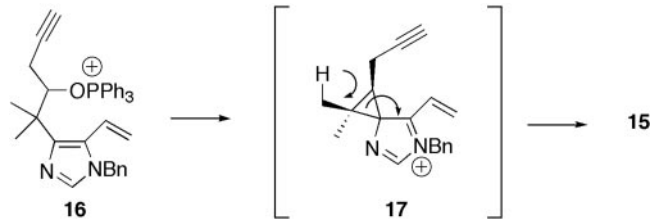


Scheme 3. C2-C3 functionalization and model enamide installation. TBSO, $Me_2{}^tBuSiO-$; DMF, *N*,*N*-dimethylformamide.

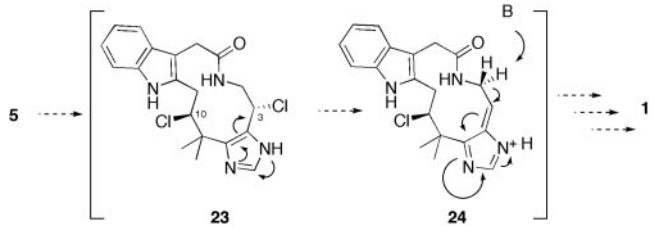
bromide and chloride derived from **20** underwent smooth elimination exclusively to the desired cis-enamide **22** upon treatment with a variety of bases (K_2CO_3, 1,8-diazabicyclo[5.4.0]-undec-7-ene, basic amberlist, Et_3N, Ag_2CO_3) at low temperatures (0°C to room temperature) (23, 24). The mild conditions suitable for elimination are consistent with participation of the pendant imidazole functionality (Scheme 3).

With working model systems for the introduction of the most sensitive functionality in place, we turned toward the completion of the securamine carbocyclic skeleton. In contemplating a suitable end-game scenario, we considered the enticing possibility of simultaneous installation of the C(10) chlorine and enamide functionalities (Scheme 4). In our hands neopentyl chloride **14** (in addition to **42** and **43**, see Scheme 9) proved resistant to elimination upon exposure to a variety of bases [K_2CO_3, 1,8-diazabicyclo[5.4.0]-undec-7-ene, $NH_4OH_{(aq)}$] suitable for the conversion of **20** to **22**; we hoped that the imidazole functionality could be used to effect the low temperature selective elimination of a C(3) chloride in the presence of a C(10) chloride (Scheme 4).

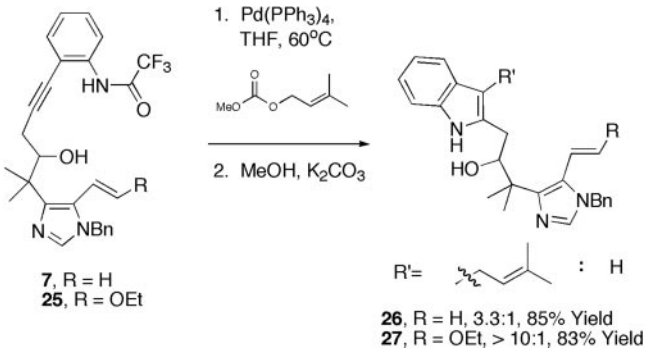
Turning toward the advancement of **13**, Sonagashira coupling with iodoaniline **28** in the presence of catalytic palladium (II) afforded **7** (Scheme 6). A variety of methods aimed at simultaneous palladium-mediated indole formation/(C20) alkylation were explored initially. Optimization of a tandem three-component coupling based on the Cacchi indole synthesis proved quite promising. Unfortunately, attempted oxidations of **26**/**27** proved problematic (see ref. 15) (Scheme 5). However, we ultimately found that the most practical synthetic access to **31** was routed through the C(13) unsubstituted indole **29**, obtained via prolonged exposure of **7** to $Pd(PPh_3)_4$ (25) (Scheme 6).



Scheme 2. Imidazole-assisted rearrangement.



Scheme 4. Tandem chloride installation/enamide formation.

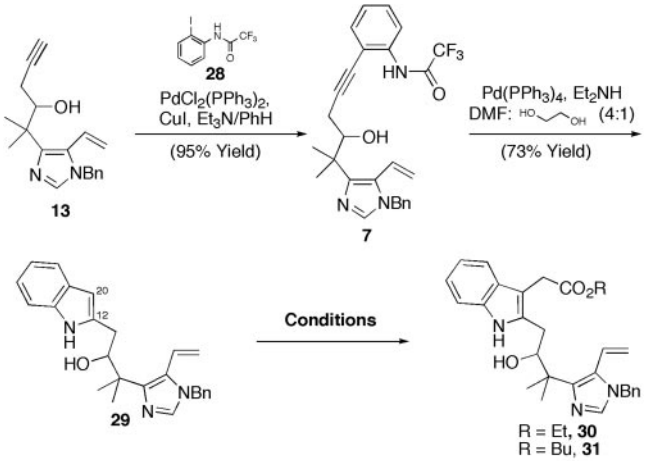


Scheme 5. Tandem indole formation/C20 alkylation.

Installation of the requisite C(21)-C(22) chain via alkylation of **29** initially proved problematic, with a variety of well-documented protocols giving low recovered yields of alkylated indole **30** (Scheme 6). Extensive optimization with regard to base, solvent, and electrophile revealed that *n*-butyl α-iodoacetate proved unique in its ability to function as a suitable electrophile, giving rise to an excellent yield of **31** (26).

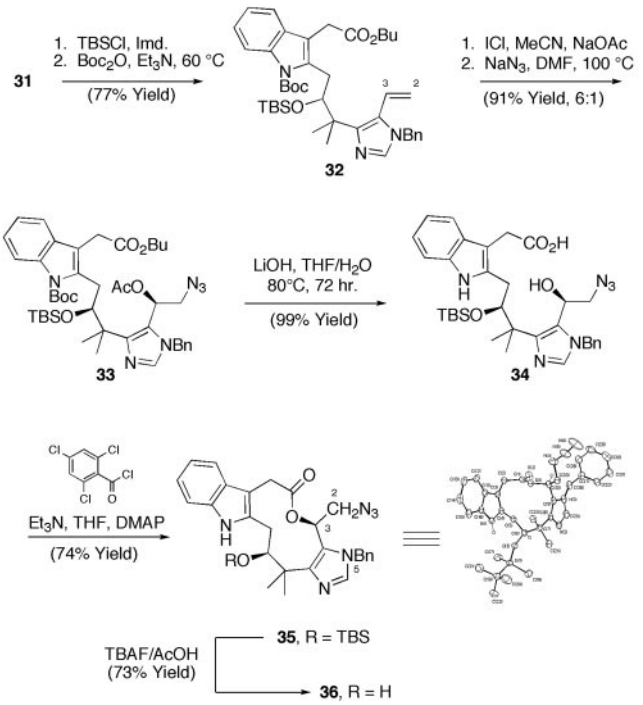
With **31** in hand we turned toward the functionalization of the C(2)-C(3) olefin in analogy with model olefin **12** (Scheme 3). The C(10) hydroxyl and indole were necessarily protected as a silyl ether and carbamate, respectively (Scheme 7). Subsequent exposure to iodine monochloride/sodium acetate followed by sodium azide afforded azido acetate **33** in excellent overall yield from **32** as a roughly 6:1 mixture of diastereomers. Simultaneous hydrolysis of the C(2) acetate, C(22) butyl ester, and indole carbamate was effected upon prolonged exposure to dilute lithium hydroxide to afford acid **34** in quantitative yield.

Exhaustive reduction of **34** (H_2, Pd/C, MeOH/EtOAc) served to simultaneously cleave the N(5) benzyl group and reduce the C(2) azide. However, the corresponding amino acid proved exceedingly difficult to handle and could not be coaxed into undergoing smooth macrolactamization under a variety of standard conditions. Recalling the propensity of a C(3) acetate to migrate upon reduction of **19**, we planned to circumvent this problem via construction of the key securamine macrolactam via ring expansion of the corresponding (*n*-2) azido-lactone. Further, we were pleased to find that hydroxy acid **34** proved an excellent substrate for macrolactonization, giving rise to **35** cleanly as a single diastereromic product upon treatment with Yamaguchi's reagent. Desilylation of **35** proceeded without incident to afford **36** in excellent yield.



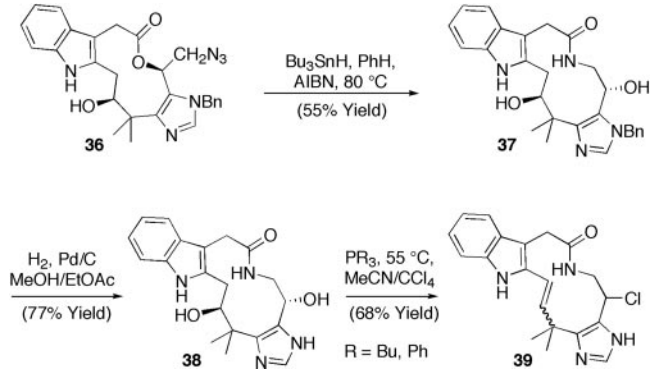
R	Electrophile	Base	% Yield 30	31	Recovered 29
Et	ICH_2CO_2R	EtMgBr	25	--	65
Et	ICH_2CO_2R	*n*-BuLi	48	16	<5
Et	ICH_2CO_2R	*t*-BuLi	35	--	--
n-Bu	ICH_2CO_2R	*n*-BuLi	--	89	<5

Scheme 6. Indole formation/C20 alkylation. DMF, *N*,*N*-dimethylformamide.



Scheme 7. C2/C3 functionalization and macrocyclization. TBSCl, $Me_2{}^tBuSiCl$; TBSO, $Me_2{}^tBuSiO-$; DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran; DMAP, 4-(dimethylamino)pyridine; TBAF, Bu_4NF.

Prolonged exposure of **36** to tributyltinhydride/2,2′-azobisisobutyronitrile in refluxing benzene afforded the corresponding ring-expanded macrolactam **37**. Hydrogenation of **37** gave key diol **38**, primed for attempts at tandem chloride/enamide installation. Screening of a variety of conditions previously suitable for chlorination and/or enamide formation revealed a tendency of **37** and **38** to undergo a tandem chlorination/elimination reaction. However, isomer **39** remains the only isolable product under all of the conditions explored thus far, and the desired regioisomeric enamide remains unde-



Scheme 8. Tandem azide reduction/ring expansion. AIBN, 2,2′-azobisisobutyronitrile.

tectable as a component of the relatively clean reaction mixtures (Scheme 8).

Conclusions

Despite the unanticipated tendency of diol **38** to undergo undesirable reaction pathways, our approach toward the securamine A macrocycle remains quite promising. Key azido lactone **36**, possessing the complete securamine A carbon skeleton in the correct oxidation states, has been accessed in an extremely efficient and high-yielding sequence (17 steps, 6.3% overall yield, 85% average yield per step) from commercially available starting materials. Our approach to **1** includes a highly efficient indole alkylation (**29**→**31**) and a tandem azide reduction-ring expansion of azido-lactone **36** to afford the complete securamine macrocyclic skeleton (**37**).

Model system work has indicated the feasibility of the phosphine-mediated installation of the extremely hindered securamine neopentyl chlorine (**13**→**14**, **40**→**42**, **41**→**43**) as well as a dehydrative approach to the requisite securamine *cis*-enamide (**20**→**22**). Additionally, preliminary data suggest securamine A might arise quite efficiently from selective C(6) bromination of a des-bromo analog (Scheme 10, which is published as supporting information on the PNAS web site). Utilization of our current strategy for the exploration of a variety of end-game scenarios continues, as the C(10) and C(2) hydroxyls remain orthogonal in a variety of our key synthetic intermediates (**33**–**36**, **44**, and **45**).

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