Total Synthesis of Clavepictines A and B. Diastereoselective Cyclization of δ-Aminoallenes

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Abstract: The stereocontrolled total synthesis of (−)-clavepictine A (**1A**) and (+)-clavepictine B (**1B**) has been accomplished in an enantioselective fashion, which has unequivocally established the absolute configuration of **1A** and **1B**. The pivotal step in the synthesis is diastereoselective silver(I)-promoted cyclization of δ-amino allenes. Another key method includes cross-coupling of enol triflates of *N*-acyl lactams, which allows stereocontrolled functionalization of otherwise unreactive lactams under mild conditions. The utility of Beak's α-lithiation-substitution chemistry of *N*-BOC piperidines involving a functionalized aldehyde as the electrophile is demonstrated in the preparation of highly substituted nitrogen heterocycles. These new synthetic strategies should be of general synthetic utility in the stereoselective syntheses of quinolizidines, indolizidines, and related aza-heterocylces. Also included is the unique conformational preference of the highly substituted *cis*-quinolizidine core of clavepictines; the (superfluous) *m*-(trifluoromethyl)benzoate substituent has a surprisingly significant influence on the relative energies of the two possible chair−chair conformations.

Introduction

Clavepictines A and B (**1A,B**) were isolated in 1991 by Cardellina and co-workers from the tunicate *Clavelina picta*.[1] A lower homologue **1C** of clavepictine A was independently isolated by the Faulkner group and named pictamine.[2] These new quinolizidine alkaloids have been reported to exhibit antimicrobial, antifungal, and antitumor activity, but their thorough biological evaluation was hampered primarily by supply problems. The structures of these alkaloidal homologues were determined on the basis of spectroscopic data and X-ray diffraction analysis, while their absolute configuration remained undefined. Key structural characteristics center around a rare cis-ring fused quinolizidine nucleus bearing axially disposed methyl and acetoxy (or hydroxy) groups (Scheme 1); this cis-ring junction conformation **I** appears to be favored over the alternative cis-conformation **II**, presumably because in the latter isomer the bulky 1,3-dienyl side chain must be axial. Due to severe 1,3-diaxial interactions among the ring junction hydrogen, the methyl group, and the dienyl side chain, the otherwise favorable trans-ring junction conformer **III** is of significantly higher energy than the cis isomers.
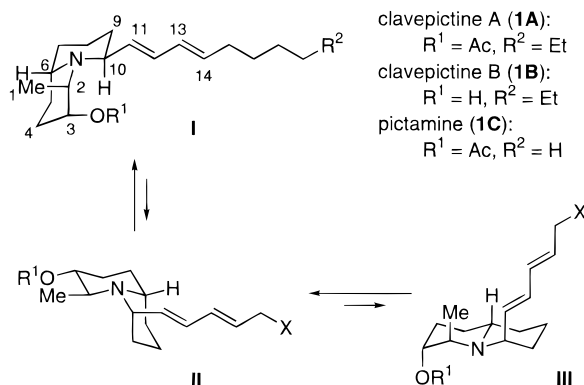
The Hart group first reported a synthetic approach to a 3-desoxyquinolizidine skeleton **3** by reduction of the vinylogous carbamate **2** via an iminium ion (Scheme 2).[3a] The stereochemical outcome of reduction was found to depend on two possible half-chair conformations of the iminium ion intermediate and the effective size of the reducing agent. This approach was based upon the previous syntheses of structurally related *Lythraceae* alkaloids [e.g., Lythrancepine III (**5**)].[3b] Subsequently, two groups have completed enantioselective syntheses of **1A** and **1B**: the first enantioselective total synthesis was reported by Momose and co-workers,[4] followed by our own work.[5] These

Scheme 1

clavepictine A (**1A**):
　R^1 = Ac, R^2 = Et
clavepictine B (**1B**):
　R^1 = H, R^2 = Et
pictamine (**1C**):
　R^1 = Ac, R^2 = H

total syntheses unequivocally established the absolute configuration of **1A** and **1B** as shown in Scheme 1. Herein we report a full account of our first-generation and more convergent, second-generation syntheses of **1A** and **1B**.
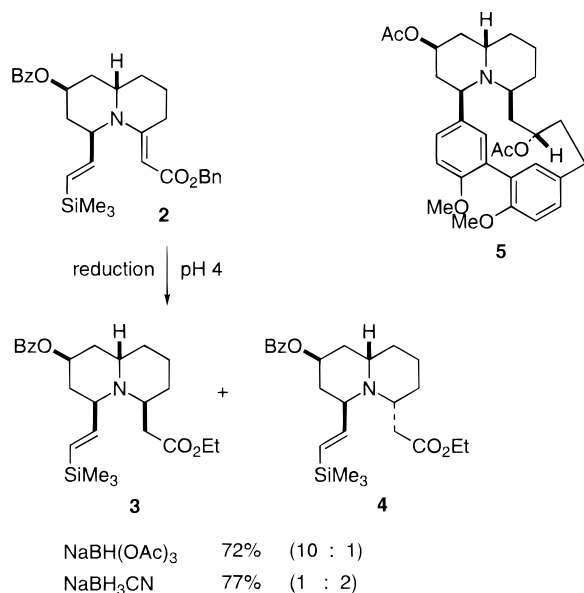
Results and Discussion

Conjugate Addition Approach. The initial synthetic plan was based on an intramolecular conjugate addition[6] of a trisubstituted piperidine **8** to produce the requisite quinolizidine **6** in preference to the C-10 epimer **7** (Scheme 3). Subsequent elaboration of the side chain of **6** would then afford the target alkaloids. The stereochemical course of the intramolecular

(1) Raub, M. F.; Cardellina, J. H., II; Choudhary, M. I.; Ni, C.-Z.; Clardy, J.; Alley, M. C. *J. Am. Chem. Soc.* **1991,** *113,* 3178.

(2) Kong, F.; Faulkner, D. J. *Tetrahedron Lett.* **1991,** *32,* 3667.

(3) (a) Hart, D. J.; Leroy, V. *Tetrahedron* **1995,** *51,* 5757. (b) Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987,** *52,* 4665.

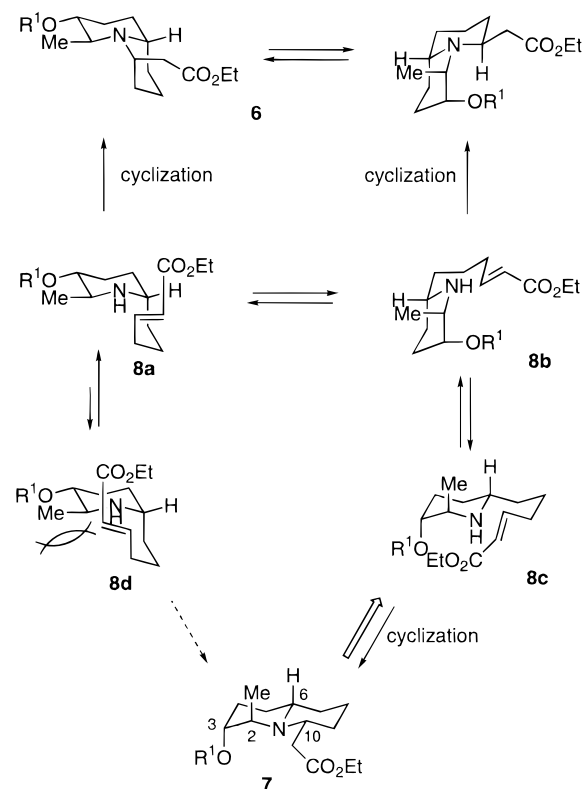(4) Toyooka, N.; Yotsui, Y.; Yoshida, Y.; Momose, T. *J. Org. Chem.* **1996,** *61,* 4882.

(5) For a preliminary account of part of this work, see: Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997,** *62,* 4550.

(6) For recent developments in conjugate additions, see: (a) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1997,** *47,* 315. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992,** *92,* 771. (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1992. (d) Akiyama, E.; Hirama, M. *Synlett* **1996,** 100.

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Scheme 2

NaBH(OAc)₃   72%   (10 : 1)
NaBH₃CN   77%   (1 : 2)

Scheme 3

conjugate addition should be governed by the relative energies of the respective conformers of **8** and also the rates of their cyclization reactions. Predominant formation of **6** is expected from conjugate addition via the chair conformer **8a**, as the diastereomeric transition state derived from **8d** suffers from the severe repulsive interaction shown. In contrast, cyclization of the alternative chair piperidine (i.e, **8b** and **8c**) could proceed with poor selectivity or possibly favor the undesired epimer **7**. Thus, the stereochemistry of the intramolecular Michael reaction would depend primarily on conformational energies of the two ring-inverted chair conformations of the trisubstituted piperidine. On the basis of cursory consideration of *A* values for the three substituents, we surmised that **8a** might be the most stable

Scheme 4
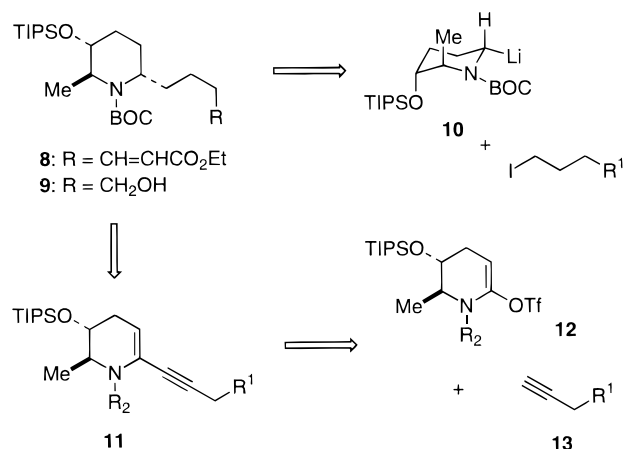
conformer. At the same time, however, we were concerned that the ring conformation of **1A−1C** is identical with that of **8b** (and **8c**), rather than that of **8a**.

Two different approaches to piperidine **8** via alcohol **9** were envisaged starting from a disubstituted piperidine derivative (Scheme 4). Beak's elegant diastereoselective deprotonation−substitution sequence would provide a direct method for introducing the required side chain.[7] However, the known sluggish reactivity of an α-carbamoylamino carbanion (e.g., **10**) toward S_N2 alkylation with aliphatic halides prompted us to explore another approach: reduction of **11** via the iminium ion should be highly diastereoselective due to the $A^{(1,2)}$ strain and axial addition of hydride should occur.[8] The *N*-acyl enamine **11**, in turn, could be available by cross-coupling of an enamide triflate (e.g., **12**) derived from an *N*-acyl lactam with a suitable reaction partner (e.g., **13**). In marked contrast to the widely utilized enol triflates from ketone or ester enolates, the corresponding triflates of lactams have received surprisingly little attention. Prior to our own work, the literature had dealt only with the preparation and coupling of triflates of heteroaromatics.[9] While our synthetic studies were in progress, Comins and Foti first reported the preparation and reactions of *N*-acylaminoene triflates from alicyclic *N*-acyl lactams.[10a] Subsequently, Hiemstra and Speckamp described syntheses and applications of pyrrolidinone- and piperidinone-derived triflates.[10b−e]

Toward this end, our first task was to prepare the enantiopure lactam **17**. Our synthesis began with the known, enantiopure diol **14**, which was conveniently prepared by the Sharpless asymmetric dihydroxylation of ethyl sorbate in excellent ee (Scheme 5).[11] As the absolute configuration of the target

(7) (a) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109. (c) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. (d) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(8) Cf.: (a) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831. (b) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373. (c) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983. (d) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575.

(9) (a) Okita, T.; Isobe, M. *Synlett* **1994**, *26*, 589. (b) Okita, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 3737. See also: (c) Thomas, E. W. *Synthesis* **1993**, 767.

(10) (a) Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656. (b) Bernabé, P.; Rutjes, F. P. J. T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *37*, 3561 (c) Luker, T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1996**, *37*, 8257. (d) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592. (e) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131. Cf.: (f) Jacobi, P. A.; Liu, H. *J. Am. Chem. Soc.* **1999**, *121*, 1958.
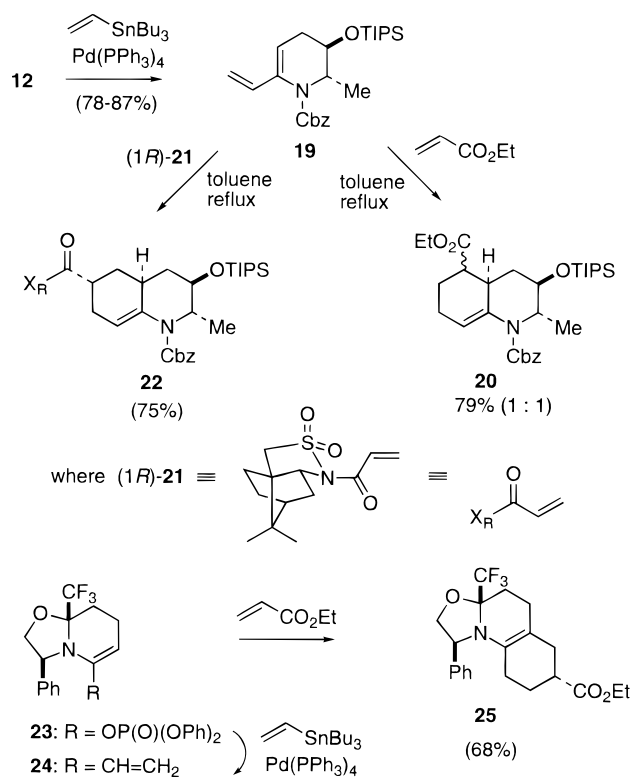
Scheme 5

Scheme 6
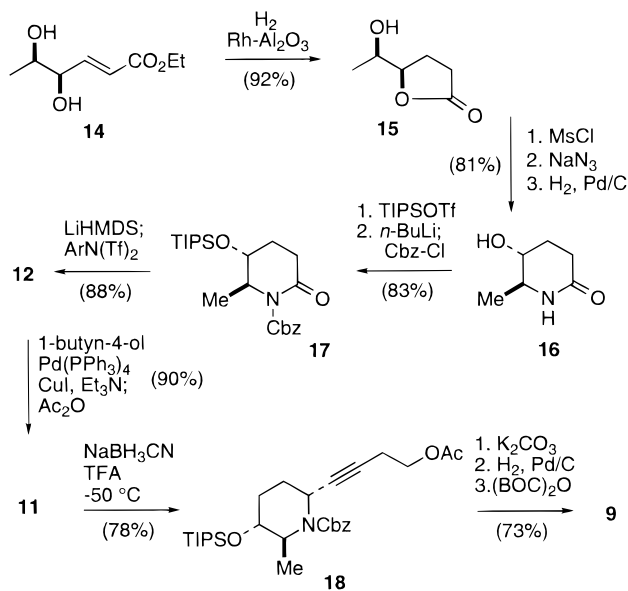
alkaloids was unknown at the outset, we arbitrarily chose (DHQD)$_2$-PHAL for asymmetric dihydroxylation. Hydrogenation of **14** afforded (92% yield) γ-lactone **15**, which allowed the regioselective introduction of the amino group at C-2 (clavepictine numbering system). By means of the azide intermediate, lactam **16** was then prepared in 81% overall yield. Following protection (83%), sequential treatment of **17** with LiHMDS and Comins' reagent[12] furnished the aminovinyl triflate **12** (R^2 = Cbz) in excellent (88%) yield. Sonogashira-type coupling[13] with 1-butyn-4-ol (**13**: R^1 = CH$_2$OH), followed by acetylation (to facilitate isolation and characterization), afforded the cross-coupling product **11** (R^1 = CH$_2$OAc; R^2 = Cbz) in 90% yield. Subsequent reduction with NaBH$_3$CN−TFA resulted in the stereoselective construction of the desired piperidine **18** in 78% yield. Finally, removal of the acetate group, followed by catalytic hydrogenation and reprotection of the amine, gave the desired alcohol **9** in good yield.

As illustrated by the preparation of the piperidine **9** from the piperidinone **16**, coupling of enol triflates derived from *N*-acyl lactams represents a new, convenient method for reductive alkylation of lactams to prepare amines with the stereocontrolled attachment of a functionalized alkyl group and complements other currently available methods such as Eschenmoser sulfide contraction of thiolactams[14] or addition of organometallic reagents to lactams, thiolactams, or iminoethers.[15] As an aside, enol triflates of *N*-acyl lactams should have wide applicability in alkaloid synthesis. For example, triflate **12** smoothly underwent Stille coupling with tributyl(vinyl)tin in the presence of catalytic Pd(PPh$_3$)$_4$ to afford diene **19** in excellent yield (Scheme 6).[16] Diels−Alder reaction with ethyl acrylate gave the abnormal 1,3-regioisomer **20** as a 1:1 mixture of endo and exo diastere-

omers (79% yield). Exo preference was amplified by use of the dienophile **21** bearing (1*R*)-(+)-2,10-camphorsultam to afford the exo cycloaddict **22**, as a single isomer, with complete reversal of regioselectivity.[17]

Returning to the clavepictine project, the alcohol **9** was converted by standard methods (1. Swern oxidation; 2. Ph$_3$P=CHCO$_2$Et) to the requisite α,β-unsaturated ester **8** in 88% overall yield to set the stage for the pivotal intramolecular Michael addition (Scheme 7). Removal of the BOC group, followed by treatment with triethylamine, induced facile cyclization to give nearly exclusive formation of the undesired epimer **7** (R^1 = TIPS) in 82% yield. The initial stereochemical assignment rested upon diagnostic ^{1}H NMR coupling constants: the proton H$_6$ appears as a triplet of triplets with coupling constants 11.0 and 2.8 Hz at δ 2.26, which indicate the trans-ring junction. The stereochemistry of **7** was further supported by analysis of other protons [H$_2$: δ 3.31 (dq, J = 2.7, 6.8 Hz); H$_3$: δ 3.79 (q, J = 2.7 Hz); H$_{10}$: δ 3.09 (dddd, J = 2.8, 4.8, 7.8, 10.6 Hz where $J_{9ax,10}$ = 10.6 Hz)]. This disappointing stereochemical outcome was attributed to the preponderance of the conformer depicted as **8c** (in Scheme 3). As judged from the ^{1}H NMR spectrum, the free amine **26**, as well as related 2,3,6-trisubstituted piperidine derivatives bearing a different side chain, was indeed found to exhibit the preference for the conformation **26a,a,e** over **26e,e,a**.[18]

(11) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) For regioselective osmylation of dienoates, see also: Whang, K.; Cooke, R. J.; Okay, G.; Cha, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 8985.

(12) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

(13) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(14) (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710. (b) Shiosaki, K. In *The Eschenmoser Coupling Reaction*; Trost, B. M., Fleming, I., Eds.; Heathcock, C. H., Vol. Ed.; *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 2, Chapter 3.7. (c) Gugelchuk, M. M.; Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1981**, *46*, 3671. (d) For a recent modification, see: Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30.

(15) See inter alia: (a) LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664. (b) Hwang, Y. C.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 3885. (c) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 1719. (d) Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682. (e) Tominaga, Y.; Kohra, S.; Hosomi, A. *Tetrahedron Lett.* **1987**, *28*, 1529. (f) Takahata, H.; Takahashi, K.; Wang, E.-C.; Yamazaki, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1211. (g) Zezza, C. A.; Smith, M. B.; Ross, B. A.; Arhin, A.; Cronin, P. L. E. *J. Org. Chem.* **1984**, *49*, 4397.
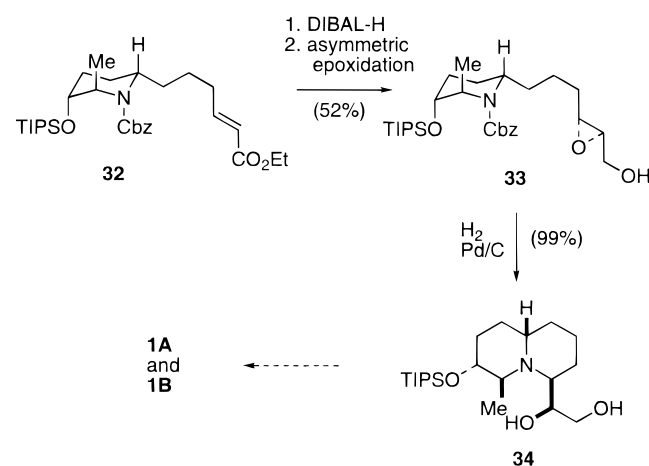
(16) Ha, J. D.; Kang, C. H.; Belmore, K. A.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 3810.

(17) For a recent example (**24** → **25**), see: Jiang, J.; DeVita, R. J.; Doss, G. A.; Goulet, M. T.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593.
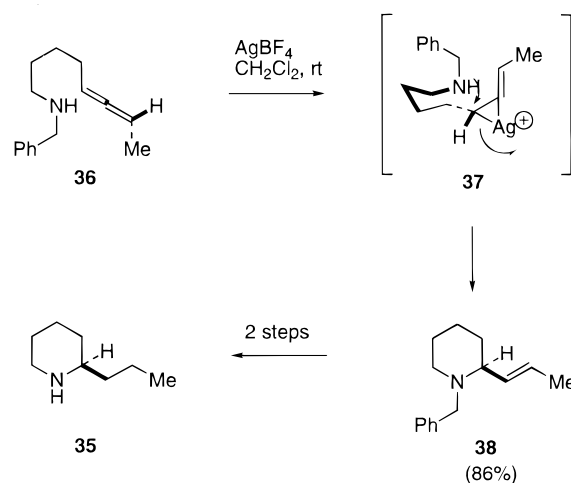
Scheme 7
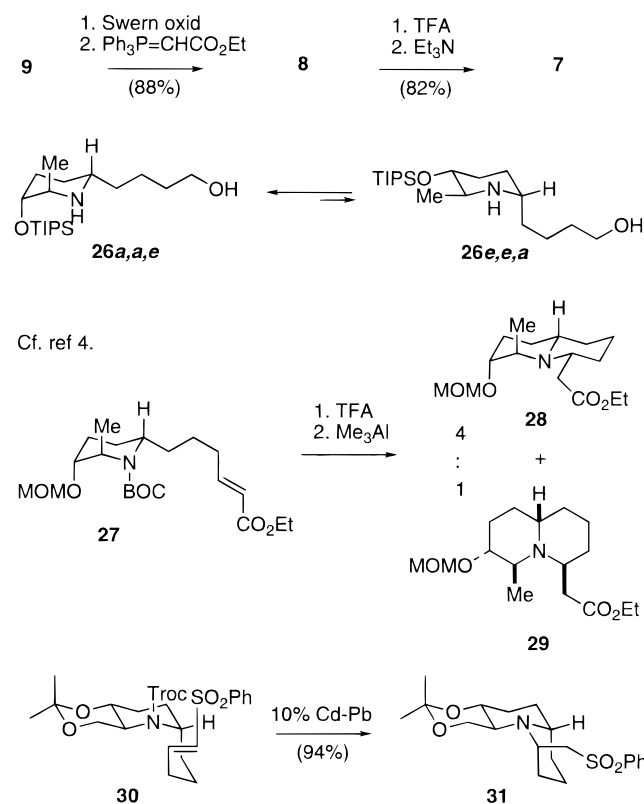
Scheme 8

Similar results were also documented by Momose and co-workers: cyclization of **27** resulted in formation of a ca. 4:1 mixture of *trans*- and *cis*-quinolizidines **28** and **29**.[4] An ingenious solution was devised by use of the acetonide group as an anchor, which locks the conformation of the piperidine ring into the framework **30** of the *trans*-decalin type. As expected, upon removal (with 10% Cd−Pb) of the 2,2,2-trichloroethyl carbamate protecting group, cyclization afforded the desired quinolizidine **31** as the sole product, which was ultimately converted to the target alkaloids, **1A** and **1B**.

Another solution of bypassing the unfavorable conformational preference of the 2,3,6-trisubstituted piperidine derivatives was found in ring opening of the epoxide **33** by the deprotected amine function (Scheme 8). Related cyclizations of epoxy amines have been used previously in alkaloid synthesis by other

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(18) The carbamates **8** and **9** and related compounds all adopt a conformation in which the methyl group is axial to avoid allylic strain.

Scheme 9

research groups and us.[19] By a minor modification of the procedure outlined in Scheme 5 for the preparation of **9**, the benzyl carbamate **32** was readily prepared. DIBAL-H reduction and subsequent Sharpless asymmetric epoxidation[20] with diethyl D-tartrate afforded the requisite epoxy alcohol **33** in 52% (unoptimized) yield. Stereoselective ring closure was then accomplished by catalytic hydrogenation to give the desired *cis*-quinolizidine **34**. Although elaboration of **34** (or structurally related diols) to clavepictines (**1A** and **1B**) would appear to be straightforward, we chose to develop a new synthetic strategy: electrophilic cyclization of chiral δ-amino allenes appeared well-suited for the stereoselective construction of the requisite quinolizidine system.

δ-Amino Allene Electrophilic Cyclization Approach. In contrast to the oxygen-containing heterocycles, the intramolecular cyclization of ω-amino allenes has been limited to a handful of monocyclic ring formations;[21] to our knowledge, only a single application was reported for the stereocontrolled synthesis of nitrogen-containing bicyclic rings.[21a] Particularly relevant is Gallagher's enantioselective synthesis of (*R*)-(−)-coniine (**35**) (Scheme 9), in which silver(I)-catalyzed cyclization of chiral allene **36** was demonstrated to take place with little racemization (<4−10%) to produce **38**.[21d] Exceptional chirality transfer was rationalized in terms of the intermediacy of a dissymmetric silver−allene complex **37**. Surprisingly, no examples have appeared on similar exploitation of chirality of the allene unit in electrophilic cyclization reactions to diastereoselectively form more highly substituted, enantiopure nitrogen heterocycles. Attachment of the chiral allene unit in the correct absolute (i.e, *S*) configuration to the side chain, as shown in **39** (Scheme 10), was predicted to impose an overriding influence to direct the selective formation of the desired *cis*-quinolizidine derivative. Among possible transition states, for example, the transition structure **41**, leading to the *trans*-quinolizidine **43**, is disfavored due to severe nonbonded interactions, and the cis-

(19) (a) Gutawiller, J.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576. (b) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420. (c) Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977 and references therein. (d) Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 7096.

(20) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(21) For cyclization of allenes bearing a proximate nitrogen nucleophile, see: (a) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4253. (b) Arseniyadis, S.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 3997. (c) Arseniyadis, S.; Sartoretti, J. *Tetrahedron Lett.* **1985**, *26*, 729. (d) Lathbury, D.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1986**, 114. (e) Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 243. (f) Shaw, R. W.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3549.

Scheme 10

Scheme 11

TIPS-protected clavepictine B (**46**)

Scheme 12

(R = TIPS)
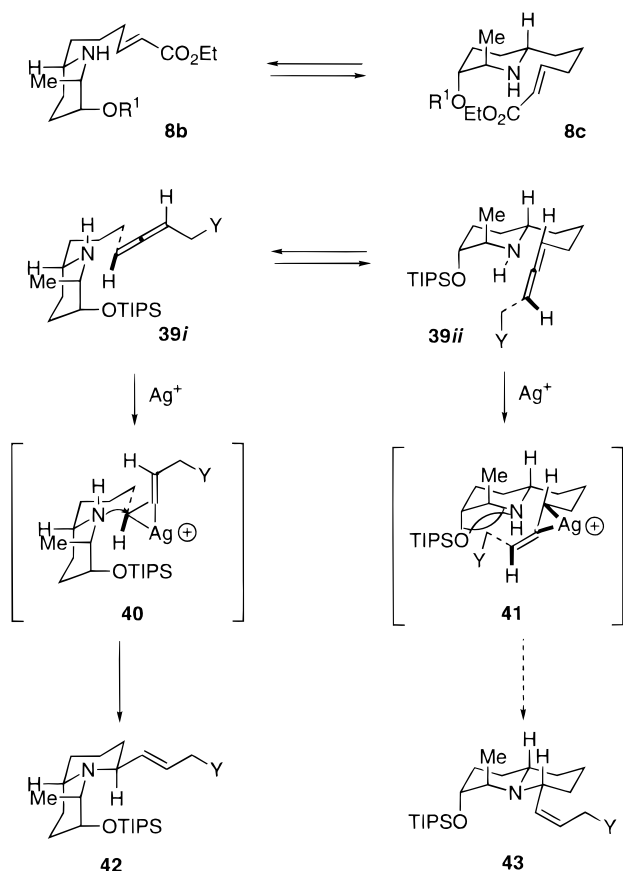
product **42** is expected to form predominantly via the transition structure **40**. Although the olefin geometry of **43** is depicted as *Z* for clarity, it might equally well adopt the *E* configuration as a result of equilibration prior to protonolysis. While not shown in Scheme 10, the identical analysis on the ring-inverted chair conformers of **39** also predicts diastereoselective formation of **42**.

At the outset, we decided to eschew use of a vinyl allene side chain: although the successful cyclization of a δ-amino vinyl allene would directly establish the requisite (*E,E*)-1,3-diene side chain, we were concerned about the likelihood that the known cyclopentenone-type annulation[22] would take place more rapidly than the desired electrophilic cyclization of the aminoallene function (Scheme 11).[23] Instead, our plan called for the late construction of the (*E,E*)-1,3-decadiene moiety by means of dehydration of the homoallyl alcohol.

To diastereoselectively install the requisite allene functionality, we decided to rely on the orthoester-Claisen rearrangement of a propargyl alcohol (Scheme 12). Toward this end, the enantiopure propargyl alcohol **47** was first prepared from commercially available (*S*)-(−)-glycidol by standard methods (1. *t*-BuCOCl, pyridine; 2. LiC≡CTMS, BF₃·OEt; 3. *n*-Bu₄-NF). Application of the previously developed sequential reaction sequence involving cross-coupling of **47** and **12** and reduction
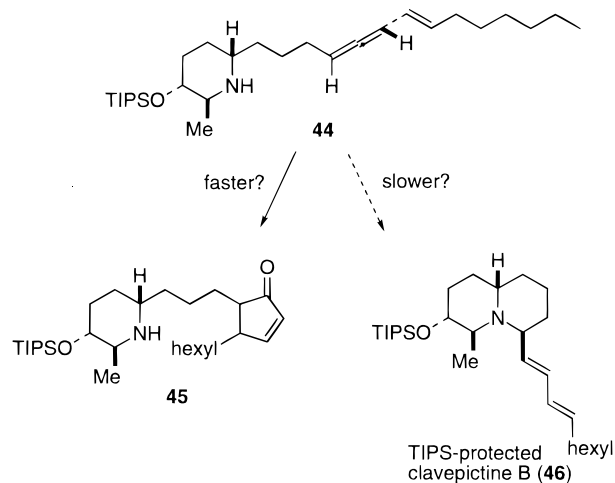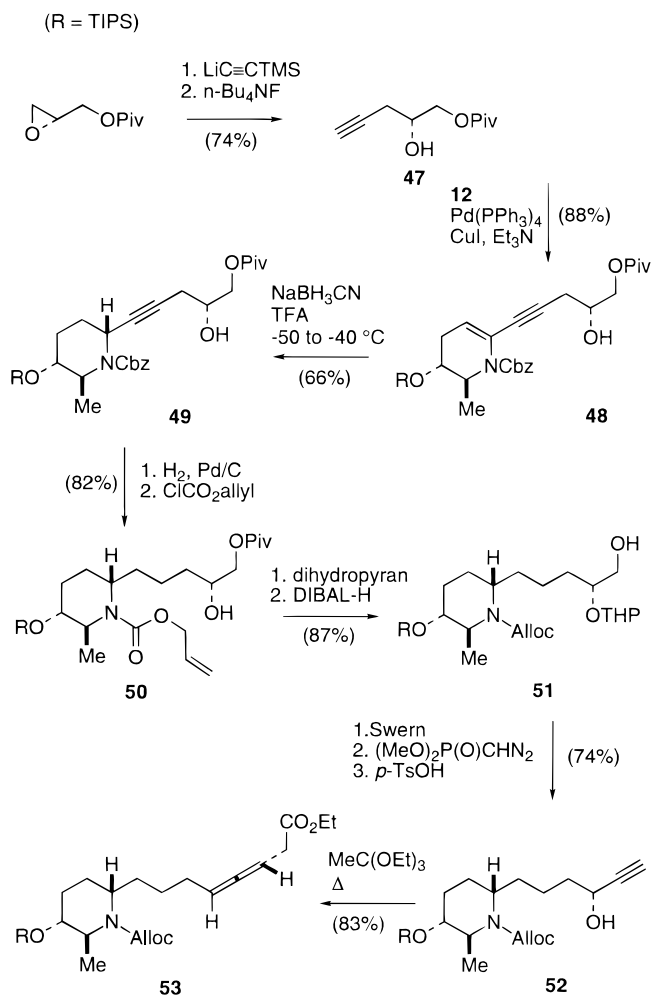
(22) Formation of cyclopentenones from vinyl allenes has been achieved by acetoxymercuration or acetoxythallation, as well as peracid oxidation, although there exists no example of Ag⁺-mediated cyclopentenone annulation: (a) Balme, G.; Malacria, M.; Goré, J. *Tetrahedron Lett.* **1979**, 7. (b) Malacria, M.; Goré, J. *J. Org. Chem.* **1979**, *44*, 885. (c) Dulcere, J. P.; Grimaldi, J.; Santelli, M. *Tetrahedron Lett.* **1981**, *22*, 3179. (d) Kim, S. J.; Cha, J. K. *Tetrahedron Lett.* **1988**, *29*, 5613 and references therein.

(23) In a model study with a piperidine bearing an allenyne pendant at C-2, however, it was found that, upon treatment with AgNO₃ (0.3 equiv) in aqueous acetone, a δ-amino allenyl alkyne underwent cyclization without complication.

with NaBH₃CN−TFA resulted in the stereoselective construction of the trisubstituted piperidine **49** in 52% yield, along with the corresponding desilylated diol in 14% yield. Hydrogenation of the alkyne group, followed by straightforward functional group manipulation of the carbamate and alcohol protecting groups, furnished the allyl carbamate **51** via **50**. To introduce the allene group, the propargyl alcohol **52** was then prepared in 74% overall yield. Subsequent diastereoselective orthoester-Claisen rearrangement afforded the allenic ester **53** (83%).

Prior to the key cyclization, the rest of the side chain was

Scheme 13

(R = TIPS)
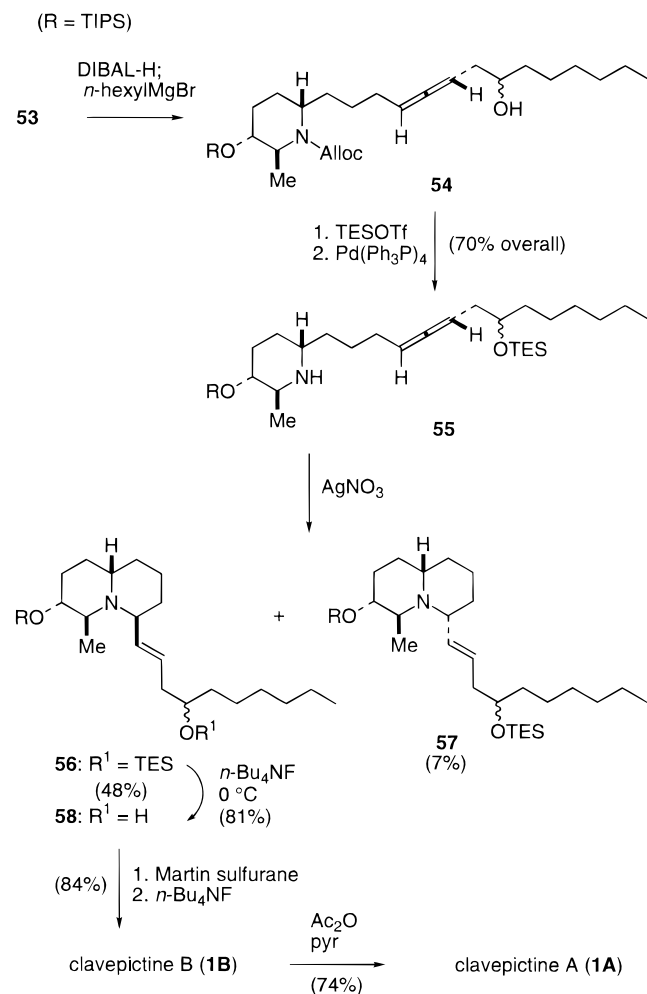
then introduced (86%) in a one-pot operation by sequential treatment of **53** with DIBAL-H and *n*-hexylmagnesium bromide to afford alcohol **54** (Scheme 13). Not surprisingly, **54** was obtained as an inseparable 1:1 diastereomeric mixture of the C-14 alcohols, but since the alcohol was destined to undergo dehydration, lack of stereocontrol here was inconsequential. Subsequent alcohol protection and removal of the allyl carbamate group by standard methods provided the δ-allenic amine **55** (70% overall). Silver nitrate-mediated cyclization of **55** produced a 7:1 mixture of the desired *cis*-quinolizidine **56** and its C-10 epimer **57** in 54% yield. Selective removal of the triethylsilyl group, followed by treatment with the Martin sulfurane,[25] gave a 10:1 mixture of TIPS-protected clavepictine and the corresponding *E,Z*-isomer. Finally, separation and treatment with *n*-Bu4NF afforded (+)-clavepictine B (**1B**). (−)-Clavepictine A (**1A**) was then prepared by acetylation of **1B**. The spectroscopic and physical properties of **1A** and **1B** were in excellent agreement with literature data;[1] the ¹H and ¹³C NMR spectra of **1A** and **1B** were found to be identical with those of authentic samples which were kindly provided by Professor Momose.[4] For additional characterization, the *trans*-quinolizidine **57** was converted to epi-clavepictine B, which exhibits drastically different spectra from **1B**.

(24) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837. (c) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (d) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540.
(25) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604.

To probe the origin of the observed diastereocontrol in the key cyclization, the 1:1 diastereomeric allenes were also prepared starting from the racemic alcohol **47**. The otherwise identical cyclization of these diastereomeric allenes in place of **55** produced a ca. 1:2 mixture of **56** and **57** in 48% yield. In additional studies, poor selectivity was also observed in the cyclization of several piperidines bearing structurally related, racemic (i.e., 1:1 diastereomeric) allenes. It is, therefore, clear that diastereofacial control generated by the allene functionality is exceptionally high and overrides the inherent conformational bias of the substituted piperidine ring.

Having demonstrated the utility of electrophilic cyclizations of ω-amino allenes in the synthesis of multi-substituted quinolizidines, our next goal was to optimize the yield and diastereoselectivity of the cyclization reaction. At the same time, we sought to reduce the overall number of steps used in our first-generation synthesis of clavepictines, most of which involved diastereocontrolled installation of the allene function after the cross-coupling reaction. Utilization of a prefabricated allene would lend itself to a convergent, efficient synthesis, but is not compatible (i.e., see **49** → **50** in Scheme 12) with the alkyne group employed for Sonogashira coupling. In lieu of the operationally simple Sonogashira reaction, cross-coupling of the vinyl triflate **12** and a primary alkyl group was required: the more challenging coupling reaction of this type has been achieved by the Suzuki procedure involving use of alkylboranes derived from hydroboration with 9-BBN or by action of organozinc reagents.[26] As summarized in Scheme 14,[27] β-hydride elimination proved to be the major pathway under several reaction conditions. This unsatisfactory result prompted us to explore Beak's deprotonation−substitution chemistry for the second-generation synthesis of **1A** and **1B**.

Second-Generation Synthesis. Beak and co-workers have developed an efficient diastereoselective functionalization of BOC-protected pyrrolidines and piperidines by α′-lithiation and subsequent electrophilic substitution.[7] Of particular relevance is the highly diastereoselective preparation of *trans*-2,6-BOC piperidines from *N*-BOC-2-methylpiperidine.[28] However, electrophilic substitution of the dipole stabilized carbanion intermediates is limited to acylation, condensation with aldehydes, or methylation. Indeed, lithiation (*sec*-BuLi/TMEDA) of the *N*-BOC-piperidine **62** and subsequent alkylation with a simple alkyl iodide [e.g., (*E*)-6-iodo-2-hexene] proved to be diastereoselective (∼5:1 ds), but sluggish, affording up to 45% of the correct alkylation product, along with recovered starting material (45%) (Scheme 15). In contrast, use of alkyl iodides bearing an allene gave none of the alkylation product, presumably because of the presence of relatively acidic protons associated with the allene functionality. We subsequently employed an aldehyde bearing an enantiopure allene unit as the electrophile, since the alcohol function of the resulting adduct should be readily reduced at an appropriate stage.

(26) (a) Miyaura, N.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1992**, *33*, 2571. (b) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201. (c) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (d) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221. (e) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (f) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (g) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Y. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157. (h) Stadtmüller, H.; Lentz, R.; Tucker, C. E.; Stüdemann, T.; Dörner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027. (i) *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, UK, 1994.
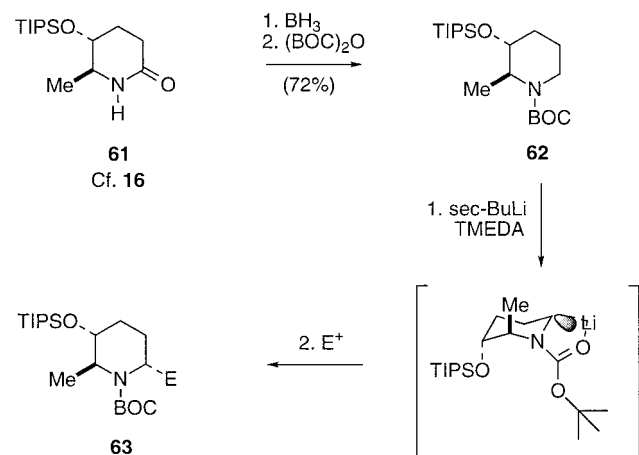(27) Yields given in Scheme 14 are based on recovered starting triflate (13−18%).
(28) (a) Reference 7b. (b) Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. *J. Am. Chem. Soc.* **1996**, *118*, 9812.

Scheme 14
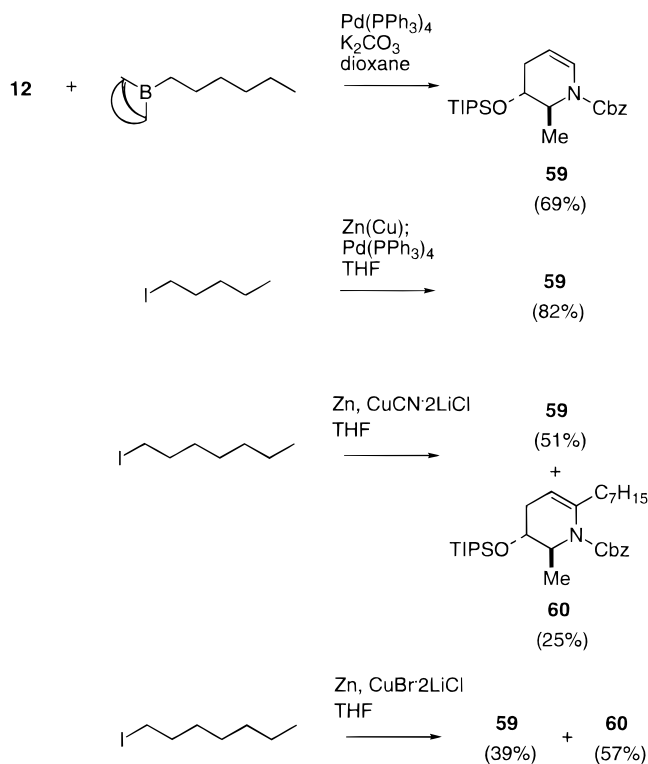
Scheme 15

Moreover, we placed an alkoxy substituent, which was to be eliminated to give the *E*-olefin moiety at C-13 and C-14 of **1A** and **1B**, adjacent to the allene group, rather than at the previously utilized β-position (cf. **55** in the first-generation synthesis): this additional substituent was anticipated to raise the diastereo-selectivity of the key cyclization step. On the basis of inspection of molecular models, the (*S*)-configuration of the alkoxy substituent at C-13 was chosen in an attempt to maximize diastereofacial selectivity.

The enantiopure aldehyde partner **71** was first prepared starting from ethyl (*E*)-2-decenoate (Scheme 16). Sharpless asymmetric dihydroxylation, followed by treatment of the resulting diol **64** with TIPSOTf, resulted in regioselective protection of the β-alcohol to afford **65** in 74% yield. Following protection of the remaining alcohol, the ester functionality was converted by standard methods to the acetylene group, via the dibromoolefin, to provide propargyl alcohol **66** (60% overall). Subsequent orthoester-Claisen rearrangement took place smoothly with excellent diastereocontrol to give allene **67** in 71% yield.
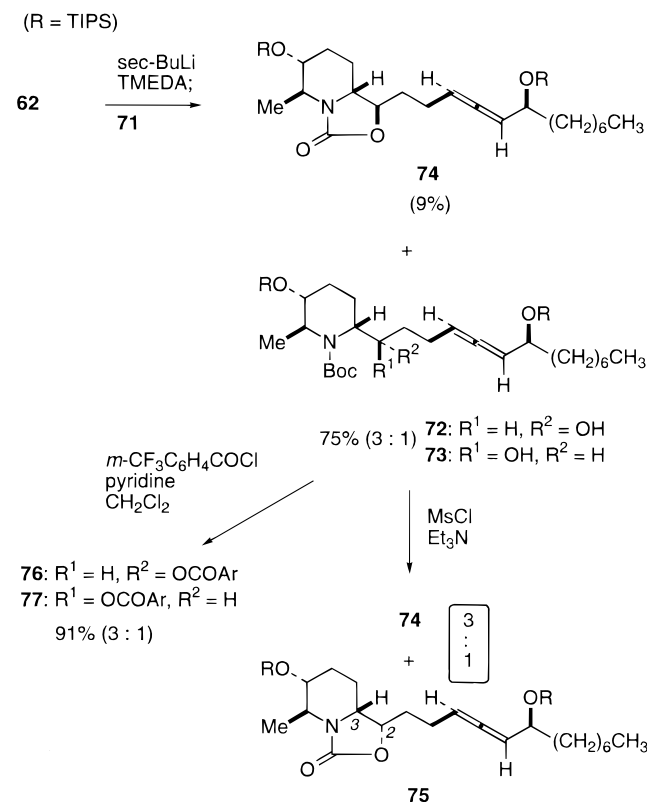
Scheme 16
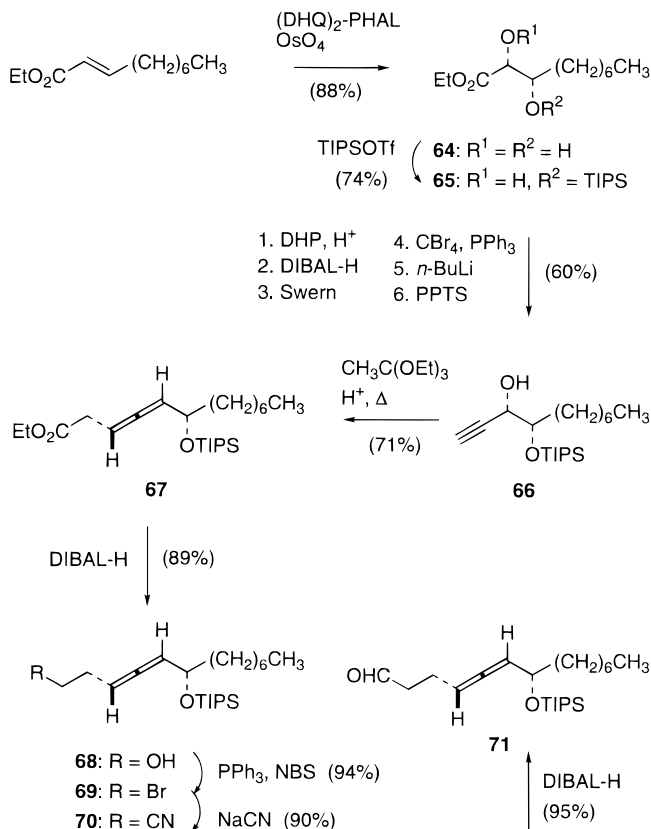
Following reduction with DIBAL-H, the alcohol **68** was subjected to one-carbon chain elongation by displacement of the bromine in **69** with cyanide to produce nitrile **70** in 75% overall yield. The requisite aldehyde **71** was then readily prepared (95%) by reduction with DIBAL-H.

As outlined in Scheme 17, coupling of the two fragments **62** and **71** was achieved according to Beak's procedure: lithiation (sec-BuLi/TMEDA) of the *N*-BOC-piperidine **62**, followed by addition of the aldehyde **71**, produced, with 80% conversion, an inseparable 3:1 mixture (75%) of alcohol epimers, anti **72** and syn **73**, along with *trans*-oxazolidinone **74** (9%). Preferential cyclization of the syn isomers to the corresponding bicyclic carbamates was also previously noted by Beak.[7b] None of the undesired stereoisomer at the piperidine ring center was found in inspection of the crude reaction mixture. The stereochemical assignments of **72**−**74** rested on analysis of proton coupling constants and was confirmed by conversion to the respective oxazolidinones (vide infra). Upon treatment with methane-sulfonyl chloride, a 3:1 mixture of **72** and **73** underwent facile, stereospecific cyclization to afford the identical ratio of the two bicyclic carbamates, **74** and **75**. Preparation of both oxazolidi-none isomers allowed the unequivocal stereochemical assign-ment: *cis*-oxazolidinone **75** shows a larger coupling constant ($J_{2,3}$) of 8.1 Hz (δ 3.73; ddd, J = 11.8, 8.1, 3.5 Hz) in comparison to a $J_{2,3}$ of 6.4 Hz (δ 3.35; ddd, J = 10.6, 6.4, 3.4 Hz) in *trans*-oxazolidinone **74**. Although the inseparable mixture of **72** and **73** was suitable for subsequent transformations, for ease of characterization we chose to separate them after acylation. For example, anti and syn *m*-(trifluoromethyl)-benzoates, **76** and **77**, were readily obtained in pure form by silica gel column chromatography.

Cleavage of the BOC group of **76** and **77** by TMSOTf-lutidine[29] gave the free amines **78** and **79** in 95% and 90% yields, respectively (Scheme 18). Subsequent treatment of **78**

Total Synthesis of Clavepictines A and B

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Scheme 17

(R = TIPS)

Scheme 18

(R = TIPS)

with silver nitrate in an aqueous acetone solution afforded the desired *cis*-quinolizidine **80**, as a single isomer, in **94**% yield. Similarly, **81** was obtained in **91**% yield as the sole product from **79**. It was gratifying to find that cyclization of both **78** and **79** took place with exceptional selectivity and excellent yield, which represents a significant improvement over that of **55** which proceeded with 7:1 diastereoselectivity in 54% yield (see Scheme 13). Because both C-7 epimers stereoselectively give the respective cyclization product, the presence of an extra (i.e., OTIPS) substituent at the C-13 position must be largely responsible for enhanced selectivity. Particularly noteworthy are the preferred conformations of *cis*-quinolizidines **80** and **81**, in which the epimeric *m*-(trifluoromethyl)benzoate substituent occupies the equatorial position in each compound, as shown in Scheme 18. Interestingly, **82**, which was prepared by DIBAL-H reduction of **80**, adopts the ring-inverted chair, i.e., the framework identical with that of the alcohol **83**, presumably due to intramolecular hydrogen bonding of the alcohol to the ring junction nitrogen.

The remaining tasks were deoxygenation of the superfluous alcohol functionality in **82** and **83**, followed by conversion of the allyl alcohol in the side chain to the requisite *E*,*E*-1,3-diene to complete the total syntheses of clavepictines. The *m*-(trifluoromethyl)benzoyl protecting group was originally chosen with an eye toward chemoselective deoxygenation of the secondary alcohol by electron-transfer reaction with *N*-methylcarbazole as the photosensitizer.[30] Unfortunately, this photosensitized deoxygenation by Saito's method resulted only in decomposition under several conditions. This failure might be attributed to the interference of the tertiary amine, even in the
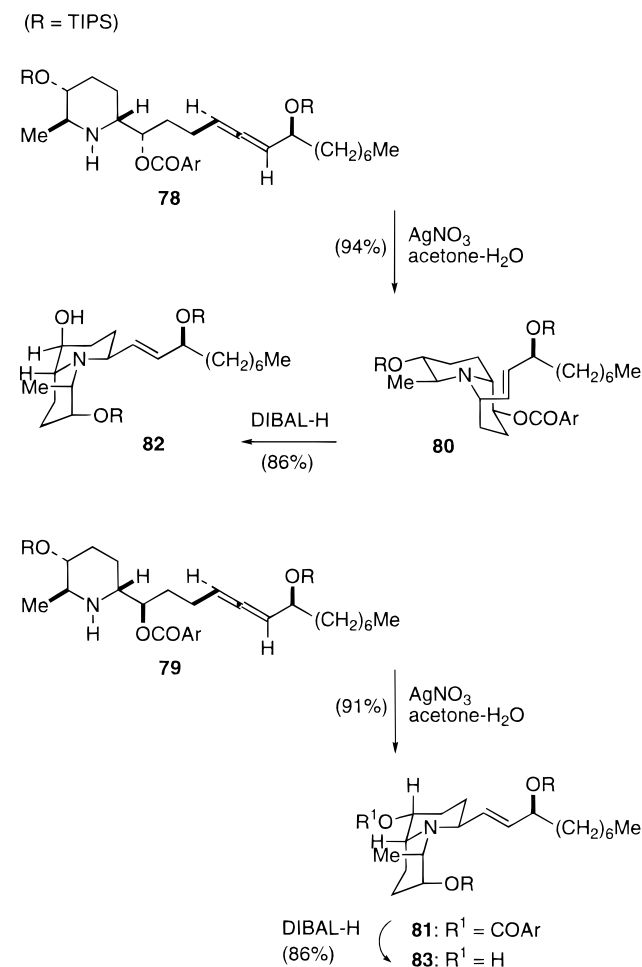
presence of buffer solutions of low pH, with the electron-transfer process. Ultimately, an efficient solution was found using the mesylate **85** (Scheme 19). Treatment of the α-alcohol **83** with methanesulfonyl chloride, followed by LiAlH₄ reduction of the resulting mesylate **85**, resulted in clean deoxygenation and attendant, selective removal of one of the TIPS protecting groups to afford alcohol **86** in 88% overall yield. Acetylation and subsequent desilylation gave the alcohol **88**. In contrast, when the epimeric β-alcohol **82** was subjected to the identical mesylate formation−LiAlH₄ reduction sequence, the rearrangement product **89** (17%), as well as **86** (28%), was obtained. Anchimeric assistance by the tertiary quinolizidine nitrogen atom could account for the unexpected lability of the mesylate **84** and also the formation of **89**. It should be noted that the preferred conformation of the mesylate **84** is conducive for backside attack at the mesylate-bearing carbon by the nitrogen lone pair. Similarly, the desired inversion of configuration of the C-7 alcohol in **82** by the Mitsunobu reaction was foiled due to facile neighboring group participation: exclusive formation (76%) of the ring-rearranged benzoate **90** was obtained instead. The requisite conversion of **82** to **83** was achieved in 86% yield by Swern oxidation, followed by NaBH₄ reduction (MeOH, 0 °C).
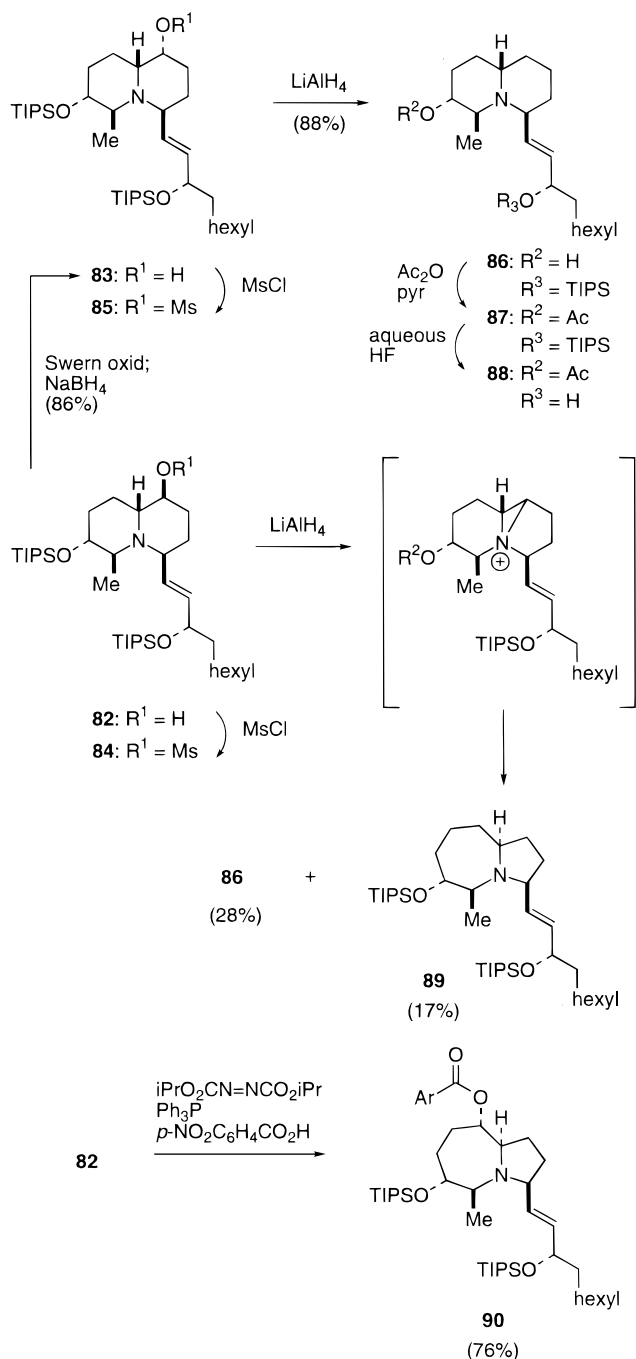
With the stereoselective preparation of **88** achieved, the only remaining task was dehydration to complete the total synthesis of clavepictine A (**1A**) (Scheme 20). It was disappointing to find that dehydration of the allyl alcohol **88** by the Martin sulfurane was nonselective and produced a ca. 1:1 mixture (44%; unoptimized) of **1A** and **91**, which is in sharp contrast to that (10:1) of the corresponding homoallyl alcohol **58** (Scheme 13). Action of the Burgess reagent also resulted in the nonselective

(29) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543. Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870. Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150.

(30) (a) Saito, I.; Ikehira, H.; Kasatani, R.; Watanabe, M.; Matsuura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3115. Cf.: (b) Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1993**, *115*, 7926.
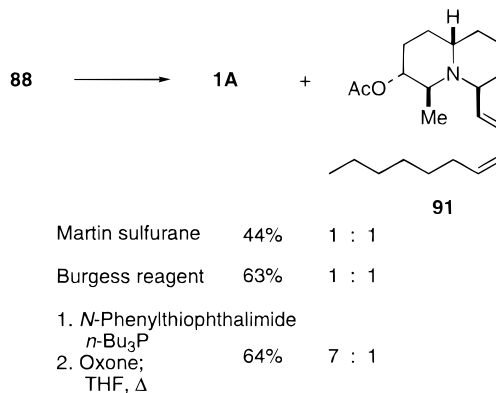
Scheme 19

83: R¹ = H
85: R¹ = Ms } MsCl

Swern oxid;
NaBH₄
(86%)

86: R² = H
         R³ = TIPS
87: R² = Ac
         R³ = TIPS
88: R² = Ac
         R³ = H

Ac₂O
pyr

aqueous
HF

82: R¹ = H
84: R¹ = Ms } MsCl

86   +

(28%)

89

(17%)

82

iPrO₂CN=NCO₂iPr
Ph₃P
p-NO₂C₆H₄CO₂H

90

(76%)

coproduction of **1A** and **91**.[31] However, stereoselective (7:1) formation of **1A** was achieved by way of the allyl sulfide, which was readily prepared (74%) by treatment of **88** with *N*-phenylthiophthalimide and tributylphosphine; subsequent oxida-

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Scheme 20

88 ⟶ **1A**   +   **91**

Martin sulfurane	44%	1 : 1
Burgess reagent	63%	1 : 1

1. *N*-Phenylthiophthalimide
   n-Bu₃P
2. Oxone;
   THF, Δ
	64%	7 : 1

tion with Oxone and thermal syn elimination gave **1A** in 80% yield.[32] Finally, basic hydrolysis (K₂CO₃, MeOH) of **1A** afforded clavepictine B (**1B**) in quantitative yield.

Conclusion

The stereocontrolled total synthesis of (−)-clavepictine A (**1A**) and (+)-clavepictine B (**1B**) was accomplished in an enantioselective fashion, which allowed the unequivocal determination of the absolute configuration of **1A** and **1B**. The pivotal step in the synthesis is diastereoselective cyclization of δ-amino allenes. Another key method includes cross-coupling of enol triflates of *N*-acyl lactams, which allows stereocontrolled functionalization of otherwise unreactive lactams under mild conditions. The utility of Beak's α-lithiation−substitution chemistry of *N*-BOC piperidines involving a functionalized aldehyde as the electrophile is demonstrated in the preparation of highly substituted nitrogen heterocycles. These new synthetic strategies should be of general synthetic utility in the stereoselective syntheses of quinolizidines, indolizidines, and related aza-heterocylces. Also included is the unique conformational preference of the highly substituted *cis*-quinolizidine core of clavepictines, where the *m*-(trifluoromethyl)benzoate substituent plays a surprisingly significant role in determining the relative populations of the two possible chair−chair conformations.

Supporting Information Available: Experimental procedure and the ¹H and ¹³C NMR spectra of synthetic (−)-clavepictine A and (+)-clavepictine B, and also key synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(31) (a) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26. (b) Wipf, P.; Venkatraman, S. *Tetrahedron Lett*. **1996**, *37*, 4659.

(32) (a) Reich, H. J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051. (b) Use of the allylic *o*-nitrobenzeneselenoxide resulted in the [2,3]-sigmatropic rearrangement to provide the 1,3-transposed allylic alcohol. Lability of allylic selenoxides, even in the absence of trapping agents other than adventitious moisture, was previously noted by Reich.