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Explorations on the Asymmetric Total Synthesis of Isoschizogamine

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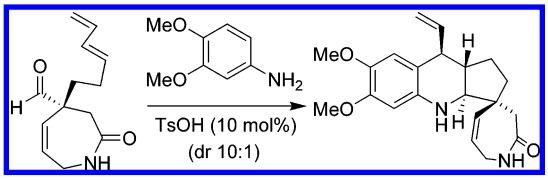

Two approaches to the synthesis of isoschizogamine were reported. Both routes utilized an efficient aza-Claisen rearrangement to establish the absolute stereochemistry of the all-carbon quaternary center in the natural product. In the first approach, a highly diastereoselective (10:1) hetero-Diels−Alder reaction was utilized to reach a densely functionalized tetrahydroquinoline derivative as an advanced intermediate to the targeted alkaloid. An acylamidine intermediate was prepared and studied in the intramolecular cyclization reaction under acidic conditions in our second approach.

Introduction

Isoschizozygane alkaloids were isolated from the monotypic shrub *Schizozygia caffaeoides* (Boj.) Baill growing in East Africa.[1] Isoschizogamine (**1a**) and isoschizogaline (**1b**) are the two members of the isoschizozygane family (Figure 1). Both were isolated in the 1960s; however, the correct structures of **1a** and **1b** containing the aminal functionality were reported in 1998[2] and 2002,[3] respectively, as a result of extensive NMR experiments. Although there were no reports regarding the biological activities of isoschizogamine (**1a**), bioassay-guided isolation of isoschizogaline (**1b**) showed that it had weak antibacterial activities, with an MIC of 62.5 μg/mL for *Bacillus subtilis* and 125 μg/mL for *Staphylococcus aureas*.[3]

The unusual structures of the isoschizozyganes as compared to those of the more abundant schizozygane alkaloids (i.e., schizozygine **2** in Figure 1)[4,5] made them challenging targets for total synthesis. Heathcock and Hubbs[6] reported a concise total synthesis of (±)-isoschizogamine (**1a**) based on a partial biosynthesis proposed by Hajicek.[2] In their synthesis, the key step to forming the aminal functionality was realized through the attack of an aniline nitrogen onto a transient iminium ion embedded in a 6−6−5 fused ring system. The same kind of transformation was also employed by Padwa and co-workers[7] in their model studies toward a total synthesis, but their approach to the 6−6−5 fused ring system, a precursor to the iminium ion, was based on a 1,4-dipolar cycloaddition reaction. During the context of our own interest in this area, we developed an alternative strategy to construct the cyclopenta[*b*]quinoline core of these alkaloids via a highly diastereoselective intramolecular formal hetero-Diels−Alder reaction.[8] In this Article, we describe our continuing endeavors toward this total synthesis.

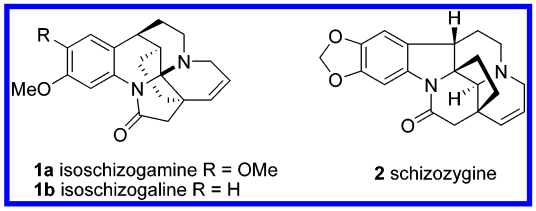

FIGURE 1. The isoschizozygane alkaloids and schizozygine.

We considered the ambitious goal of making our synthesis asymmetric. Thus, we proposed a plan shown in Scheme 1 for the synthesis of the specific enantiomer of isoschizogamine **1a**, the absolute stereochemistry of which is still unknown. We envisioned that the synthesis of isoschizogaline **1b** would probably follow a similar route if this were successful for **1a**. In this plan, we imagined the formation of the *N*-acyl aminal in **3** by the attack of the allylic amine on the imine (dihydroquinoline) in **4** followed by lactam formation. The imine group was originally envisioned to be generated by the oxidation of a suitable tetrahydroquinoline intermediate derived from **5**. On

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‡ Passed away on Feb 7, 2006.

(1) Renner, U. *Lloydia* **1964**, *27*, 406.
(2) Hajicek, J.; Taimr, J.; Budesinsky, M. *Tetrahedron Lett.* **1998**, *39*, 505.
(3) Kariba, R. M.; Houghton, P. J.; Yenesew, A. *J. Nat. Prod.* **2002**, *65*, 566.
(4) Renner, U.; Kernweisz, P. *Experientia* **1963**, *19*, 244.
(5) Renner, U.; Fritz, H. *Helv. Chim. Acta* **1965**, *48*, 308.
(6) Hubbs, J. L.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1315.
(7) Padwa, A.; Flick, A. C.; Lee, H. I. *Org. Lett.* **2005**, *7*, 2925.
(8) Magomedov, N. A. *Org. Lett.* **2003**, *5*, 2509.

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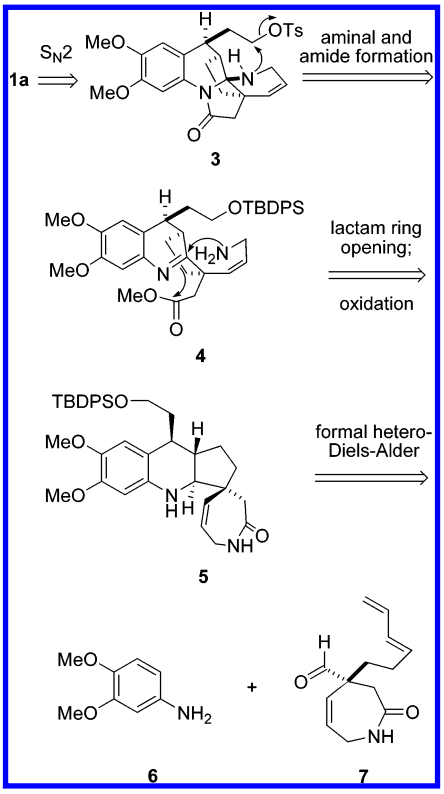
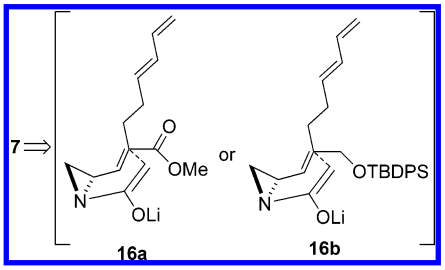
SCHEME 1. Retrosynthetic Analysis of Isoschizogamine 1a



SCHEME 2. Synthetic Plan To Prepare Aldehyde 7 through an Aza-Claisen Rearrangement



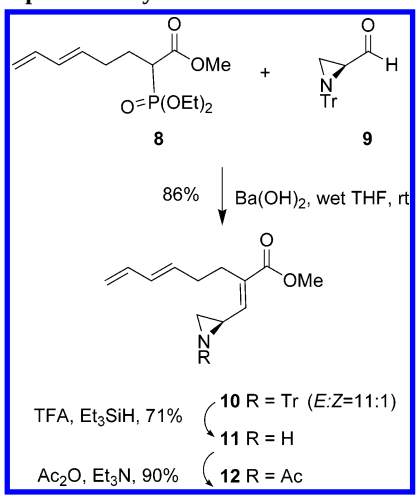
the basis of our previous studies,[8] we decided to synthesize the densely functionalized tetrahydroquinoline **5** by a reaction between aniline **6** and aldehyde **7**. However, at this point, we could not predict the diastereoselectivity of this transformation. Further, we were faced with a question of finding an efficient way to prepare the seven-membered lactam **7**.

Results and Discussion

Synthesis of Aldehyde 7. After inspection of the structure features of aldehyde **7**, we decided to devise an aza-Claisen rearrangement strategy.[9] As shown in Scheme 2, amide enolate **16a** or **16b** would adopt a boat-like transition state during the rearrangement so that the chirality of the aziridine would be transferred to the quaternary center. The release of the aziridine ring-strain would then facilitate the formation of a seven-membered lactam. We expected at this point that the rearrangement of **16a** would be less facile than **16b** due to disruption of conjugation of the α,β-unsaturated ester in the transition state, so the synthesis of **16b** seems more attractive at first sight.

(9) Lindstrom, U. M.; Somfai, P. *Chem.-Eur. J.* **2001**, *7*, 94.

SCHEME 3. Synthesis of *N*-Actetyl Aziridine 12 Beginning with Enantiopure Aldehyde 9

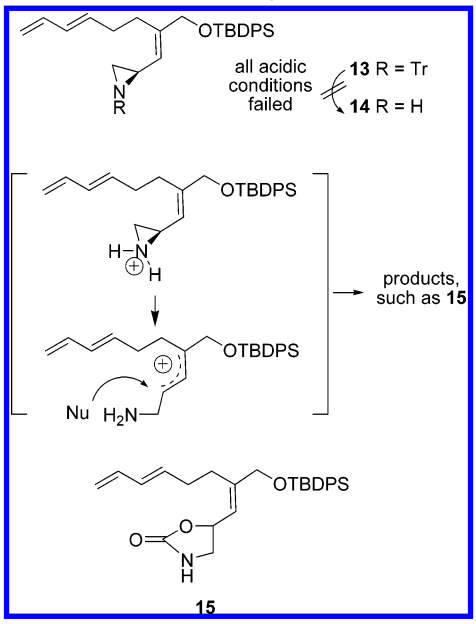


In the event, efforts to synthesize both the *N*-acetyl aziridine intermediates leading to **16a** and **16b** were undertaken. Toward this goal, α,β-unsaturated ester **10** was readily synthesized through Horner−Wadsworth−Emmons olefination[10] between phosphonate **8**[11] and enantiomerically pure aldehyde **9**[12,13] to provide an inseparable mixture of *E*/*Z* isomers (11:1). A number of acidic conditions were attempted for the deprotection of the trityl group in **10**, and finally the conditions of TFA, Et_3SiH, 0 °C were observed to give the best results.[14] After detritylation, the *Z*-isomer was readily removed during separation, and geometrically pure aziridine **11** was obtained. *N*-Acetylation of **11** (Ac_2O, Et_3N, CH_2Cl_2) gave compound **12**, the precursor of enolate **16a** (Scheme 3). At the same time, the synthesis of a silyl ether analogue of **12** was attempted to generate the more attractive enolate **16b**. Thus, compound **13**, derived from ester **10** via reduction (LAH, THF, 0 °C) and protection (TBDPSCl, Et_3N, CH_2Cl_2), was chosen as a starting material. The deprotection of the trityl group on this substrate, however, proved to be problematic. Under all of the conditions we tried, no aziridine product **14** could be isolated. The failure may result from the sensitivity of **14** toward acidic conditions, in which protonated aziridine would easily open to form a stable carbocation, which could then be trapped by nucleophiles in the solution. For example, the formation of compound **15** was observed under the conditions of TFA, Et_3SiH. The success of the detritylation of **10** demonstrates that the electron-withdrawing methyl ester played an important role in the prevention of aziridine ring from opening by destabilizing a carbocation analogue (Scheme 4).

We therefore decided to study the aza-Claisen rearrangement of *N*-acetyl aziridine **12**. Under the Somfai conditions (LHMDS, THF, −78 to 0 °C),[9] the rearrangement did not occur at all. The failure was presumably due to a much higher activation energy for this reaction as compared to those reported by Somfai. We speculated that heating of enolate **16a** would overcome this higher energy barrier for the rearrangement to

(10) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.
(11) Synthesized by the alkylation of methyl diethylphosphonoacetate with *trans*-1-iodo-3,5-hexadiene.
(12) Kato, S.; Harada, H.; Morie, T. J. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 3219.
(13) Nakajima, K.; Tanaka, T.; Meya, M.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3237.
(14) Vedejs, E.; Klapars, A.; Warner, D. L.; Weiss, A. H. *J. Org. Chem.* **2001**, *66*, 7542.

SCHEME 4. Unsuccessful Detritylation of 13

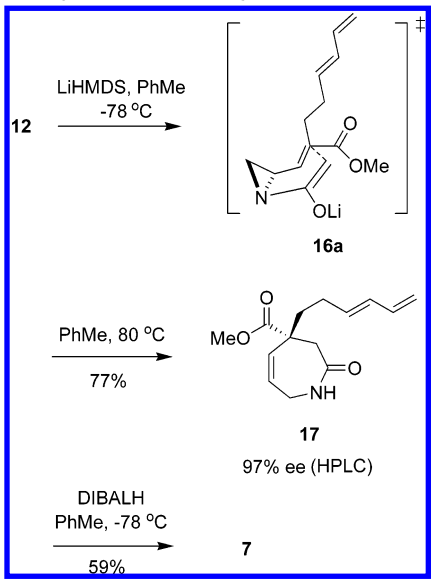


occur. Indeed, after **12** was deprotonated (LHMDS, PhMe, −78 °C, 30 min) and then heated to 80 °C, the starting material disappeared, and the rearranged product **17** was produced cleanly within 10 min. This reaction was also tried in refluxing THF after enolate generation in the same solvent, but the product was obtained in lower yield. Analysis of **17** via chiral HPLC showed an optical purity of 97% ee. This confirmed that the stereochemistry of the aziridine was transferred to the quaternary center with high fidelity. The subsequent transformation of the methyl ester in **17** to an aldehyde group required some optimization to avoid interference with other functional groups in the same molecule. Although superhydride ($LiBHEt_3$)[15] reduced the methyl ester to an alcohol, the diene was also reduced. Lithium aluminum hydride reduction followed by Swern oxidation gave the desired aldehyde **7**, but in a low yield (31%). Using the conditions of DIBALH reduction, a higher and acceptable yield (59%) of aldehyde **7** was obtained, albeit with some over-reduction to the alcohol. It should be noted that aldehyde **7** was not stable and had to be used in the next step immediately after isolation.

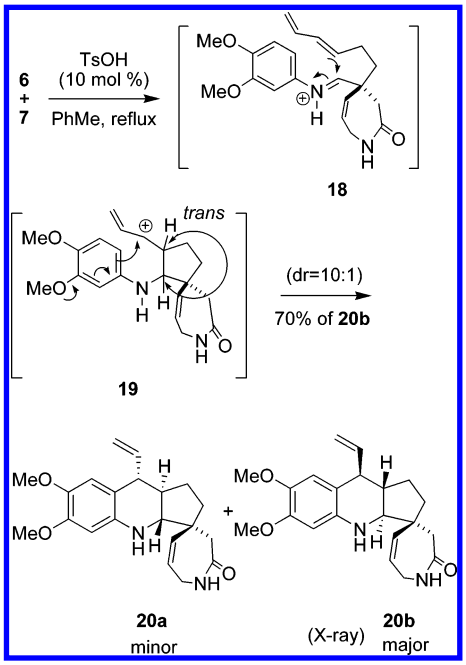
Toward the Synthesis of Imine 24. To continue the synthesis, aldehyde **7** and 3,4-dimethoxyaniline **6** were refluxed in toluene (0.03 M) under the catalysis of *p*-toluenesulfonic acid (10 mol %). To our delight, the highly functionalized tetrahydroquinoline product **20** was produced with a 10:1 diastereoselectivity. The major diastereomer was unequivocally shown to be the desired one through NOE experiments, followed by X-ray crystallographic analysis. Consistent with our previous studies,[8] nucleophilic attack of the diene on the protonated imine (**18**) gave exclusively the *trans*-cyclopentane in **19**. The facial selectivity of this attack then determines the ratio of diastereomers **20a** and **20b** after the electrophilic aromatic substitution (Scheme 6).

With the requisite tetracyclic compound **20b** in hand, we began to investigate further functional group transformations to generate the imine intermediate **4** in our retrosynthetic plan (Scheme 1). Toward this goal, the vinyl group in **20b** was first

SCHEME 5. Synthesis of Aldehyde 7



SCHEME 6. Diastereoselective Synthesis of Tetrahydroquinoline 20b

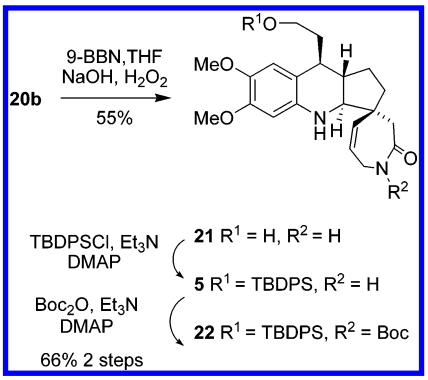


selectively transformed to the primary alcohol **21** (9-BBN, THF; H_2O_2, NaOH) and then protected (TBDPSCl, Et_3N) as silyl ether **5** (Scheme 7). The lactam nitrogen in **5** can be selectively Boc protected in the presence of the tetrahydroquinoline nitrogen (Boc_2O, Et_3N, DMAP) to give **22**. This selectivity is probably due to the steric hindrance around the latter nitrogen. Lactam **22** underwent nucleophilic ring-opening conditions (NaOMe, MeOH)[16] to afford methyl ester **23**. This intermediate combined all of the necessary functionalities except an imine group for the aminal formation. Thus, we were in a position to establish such an imine functionality starting with compound **23**. Unfortunately, all of our efforts to generate imine **24** by oxidation of **23** were not successful (Scheme 8). The oxidation conditions

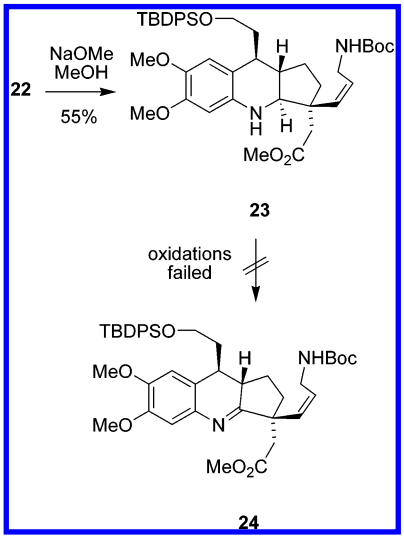
(15) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

(16) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

SCHEME 7. Functional Group Transformations from 20b to 22



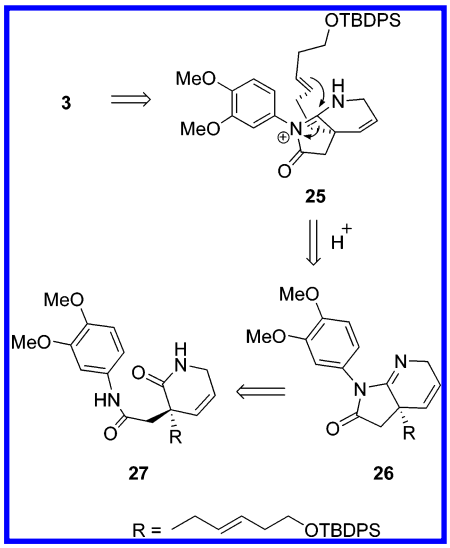
SCHEME 8. Attempted Oxidations To Generate Imine 24



used include TPAP, NMO;[17] Swern oxidation;[18] MnO_2;[19] $Hg(OAc)_2$;[20] $(NH_4)_2Ce(NO_3)_6$;[21] trichloroisocyanuric acid;[22] and H_2O_2, Na_2WO_4.[23] Among these, TPAP, NMO were the only conditions reported that partially oxidize the simple tetrahydroquinoline to dihydroquinoline. These conditions did not produce any imine product from the more sophisticated tetrahydroquinoline **23**. The main problem of this transformation resulted from the very sensitive nature of the dihydroquinoline (imine) intermediate toward aromatization to quinoline derivatives by both over-oxidation and disproportionation. The lesson we learned from this prompted us to revise our original synthetic plan to avoid this nontrivial oxidation step.

An Acylamidine Cyclization Strategy. We therefore designed an alternative synthetic plan shown in Scheme 9. In this approach, the protonated amidine group in **25** would be a precursor to an aminal after intramolecular nucleophic attack

SCHEME 9. An Alternative Plan To Avoid Imine Formation



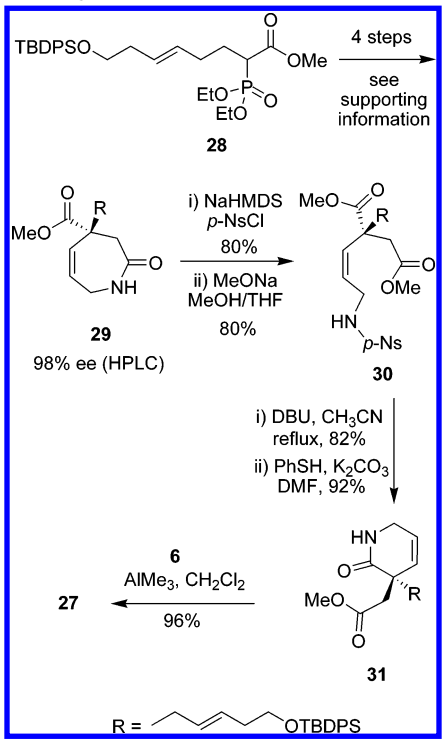
by the appended alkene chain. The carbocation thus formed was to be trapped by the aromatic ring to afford pentacyclic compound **3**, an immediate precursor to the natural product **1**. This plan obviously avoided the tricky oxidation state manipulation of our previous route. The *N*-acylamidine compound **26** was envisioned to be derived from diamide **27** via dehydration. A homoallylic silyl ether in the R group of **27** was installed at an early stage to make this synthetic sequence more convergent (Scheme 9).

En route to the synthesis of diamide **27**, synthetic sequences similar to those shown in Schemes 3 and 5 were applied to the preparation of the seven-membered lactam **29** (98% ee) beginning with the new phosphonate **28**.[24] Lactam **29** was then converted to open chain intermediate **30** after *N*-nosyl protection (*p*-NsCl, NaHMDS)[25] and lactam ring opening (NaOMe, MeOH). It was necessary to use elevated temperatures (DBU, CH_3CN, reflux) on **30** to promote the formation of a six-membered lactam, which was then converted to lactam **31** after nosyl deprotection (PhSH, K_2CO_3, DMF). Reaction of secondary lactam **31** with 3,4-dimethoxyaniline **6** ($AlMe_3$, CH_2Cl_2)[26] gave diamide **27** in 96% yield (Scheme 10).

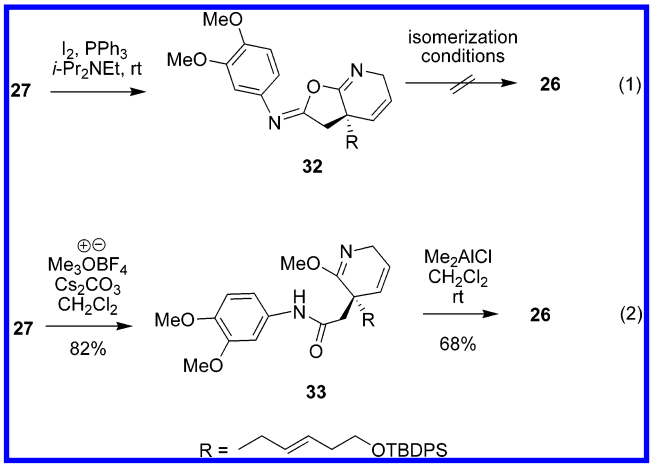
Next, we turned our attention to the formation of amidine **26** from diamide **27**. Dehydration conditions (I_2, PPh_3, *i*-Pr_2NEt)[27] were first attempted, and a new compound was cleanly generated whose in situ NMR and MS data were consistent with structure **32**. Not surprisingly, this imidate-like intermediate was very unstable and could not be isolated. The attempted in situ isomerization of **32** ($LiAlMe_3SPh$[27] or piperidine[28]) only led to decomposition (sequence 1 in Scheme 11). After much experimentation, it was discovered that the lactam in **27** could be selectively *O*-methylated (Meerwein reagent, Cs_2CO_3, CH_2Cl_2) to afford stable compound **33** in 82% yield. The observed selectivity should result from the stronger Lewis basicity of the lactam oxygen as compared to the phenyl amide oxygen. Bases other than Cs_2CO_3 gave considerable amounts of lactam *N*-methylated product for this transformation, although the

(17) Goti, A.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6567.
(18) Jinbo, Y.; Kondo, H.; Taguchi, H.; Sakamoto, F.; Tsukamoto, G. *J. Org. Chem.* **1994**, *59*, 6057.
(19) Kashdan, D. S.; Schwartz, J. A.; Rapoport, H. *J. Org. Chem.* **1982**, 2638.
(20) Leonarda, N.; Hay, L.; Fulmer, R. W.; Gash, V. W. *J. Am. Chem. Soc.* **1955**, *77*, 439.
(21) White, J. D.; Yager, K. M.; Yakura, T. *J. Am. Chem. Soc.* **1994**, 1831.
(22) Tilstam, U.; Harre, M.; Heckrodt, T.; Weinmann, H. *Tetrahedron Lett.* **2001**, *42*, 5385.
(23) Murahashi, S.; Oda, T.; Sugahara, T.; Masui, Y. *J. Org. Chem.* **1990**, *55*, 1744.
(24) Details of the syntheses were included in the Supporting Information.
(25) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 1338.
(26) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.
(27) Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892.
(28) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397.

SCHEME 10. Synthesis of Diamide 27



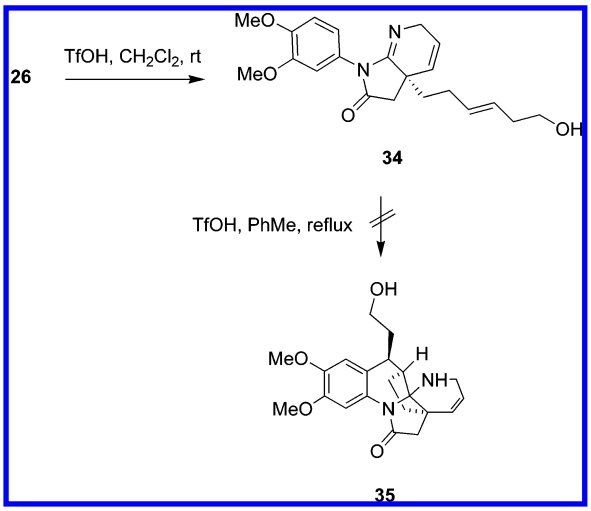
SCHEME 11. Efforts Leading to the Synthesis of Amidine 26



phenyl amide was still unreactive. Further efforts to activate the phenyl amide of **33** (NaH, DBU, LHMDS, or KHMDS in different solvents at rt or elevated temperatures) toward the formation of amidine **26** were not successful. Finally, this transformation could be effected using the conditions of $AlMe_2Cl$, CH_2Cl_2 at room temperature. In contrast, the use of $AlMe_3$ gave no trace of product **26** (sequence 2 in Scheme 11).

After establishing a viable way for the preparation of *N*-acylamidine **26**, we were encouraged to investigate its intramolecular cyclization behavior (Scheme 12). It was then discovered that, under acidic conditions of triflic acid in CH_2Cl_2 at room temperature, no cyclization reactions occurred even when up to 5 equiv of triflic acid was added. Instead, desilylation product **34** was identified after basic workup ($NaHCO_3$). The crude material was then subjected to the forcing conditions of triflic acid in refluxing toluene, which led to complete consumption of the starting material within 1 h. After isolation, a compound was identified as a single diastereomer. Aminal formation was clearly shown in ^{13}C NMR, with chemical shift

SCHEME 12. Reactions of Amidine 26 under Acidic Conditions



of the aminal carbon to be 79 ppm as compared to 166 ppm for the amindine carbon in **26**. However, we were disappointed that the desired cyclization product **35** was not obtained, as evidenced in the ^1H NMR spectrum that the three hydrogens on the phenyl ring remained.

Summary

Although our synthetic investigations did not result in a completed total synthesis of isoschizogamine, an efficient aza-Claisen rearrangement for the installation of the quaternary center, and a highly diastereoselective hetero-Diels−Alder reaction for the preparation of an advanced intermediate, the densely functionalized tetrahydroquinoline **23** was developed. Our synthesis of lactam **31** with high optical purity may be useful for the enantioselective synthesis of this alkaloid via the route previously described by Padwa and co-workers.[7] With an alternate R group installed, this could also be a useful intermediate for the synthesis of other alkaloids such as Eburnamonine and Rhazinilam.[29,30]

Experimental Section

(2*E*)-2-(1-Tritylaziridin(2*R*)-2-ylmethylene)octa(5*E*)-5,7-dienoic Acid Methyl Ester (10). To a suspension of $Ba(OH)_2$ (8.8 g, 27.9 mmol, activated by heating at 140 °C for 2 h) in wet THF (50 mL, THF:H_2O/40:1) at rt was added dropwise a solution of phosphonate **8** (8.12 g, 27.9 mmol) in THF (50 mL) via cannula. After 30 min at rt, aldehyde **9** (8.7 g, 27.9 mmol) was added in one portion, and stirring was continued for 5 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with saturated aqueous solution of $NaHCO_3$ (40 mL) followed by brine (50 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (gradient from 5% to 20%), gave α,β-unsaturated methyl ester **10** (11.1 g, 88%) as a colorless oil: $[\alpha]^{23}_D$ −109.6 (*c* 3.05, $CHCl_3$); IR (neat) 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.45 (m, 6H), 7.32−7.22 (m, 9H), 6.73 (d, *J* = 9.5 Hz, 1H), 6.06 (td, *J* = 10.5, 17.0 Hz, 1H), 5.85 (dd, *J* = 10.5, 15.0 Hz, 1H), 5.48 (td, *J* = 7.0, 15.0 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.93 (d, *J* = 10.5 Hz, 1H), 3.80 (s, 3H), 2.29−

(29) Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Kieczykowski, G. R.; Normandin, S. N.; Quesada, M. L.; Semmelhack, C. L.; Poss, A. J.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1540.
(30) Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647.

2.24 (m, 2H), 2.08−1.99 (m, 2H), 1.97 (d, J = 3.5 Hz, 1H), 1.90 (ddd, J = 3.5, 6.0, 9.5 Hz, 1H), 1.52 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 144.0, 143.6, 137.0, 133.7, 133.2, 131.4, 129.3, 127.4, 126.8, 115.0, 74.3, 51.7, 32.1, 31.0. HRMS (ESI): exact mass calcd for $C_{31}H_{31}NNaO^2$ $[M + Na]^+$, 472.2252. Found: 472.2256.

(2*E*)-2-Aziridin(2*R*)-2-ylmethyleneocta(5*E*)-5,7-dienoic Acid Methyl Ester (11). To a solution of compound **10** (5.0 g, 11.1 mmol) in CH_2Cl_2 (37 mL) cooled to 0 °C were added triethylsilane (7.1 mL, 44.5 mmol) followed by dropwise addition of trifluroacetic acid (3.4 mL, 44.5 mmol). The reaction mixture became slightly yellow and turned colorless upon the addition of each drop of TFA. The yellow color persisted at the end of the addition. Stirring was then continued for 20 min, and the reaction was quenched with *N*,*N*-diisopropylethylamine (9.7 mL, 55.5 mmol) followed by diethyl ether (100 mL). The resulting mixture was washed with brine (30 mL), and the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography on silica gel (deactivated with Et_3N), using EtOAc/hexanes as an eluent (gradient from 30% to 50%), gave the deprotected aziridine **11** (1.63 g, 71%) as a colorless oil: $[\alpha]^{23}_D$ +30.0 (*c* 1.19, $CHCl_3$); IR (neat) 3292, 1711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (td, J = 10.5, 17.0 Hz, 1H), 6.14 (d, J = 9.6 Hz, 1H), 6.09 (dd, J = 10.5, 15.0 Hz, 1H), 5.74 (td, J = 7.0, 15.0 Hz, 1H), 5.12 (d, J = 17.0 Hz, 1H), 5.00 (d, J = 10.5 Hz, 1H), 3.73 (s, 3H), 2.68−2.66 (m, 1H), 2.57−2.54 (m, 2H), 2.34−2.24 (m, 2H), 2.11 (d, J = 5.2 Hz, 1H), 1.80 (d, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 143.3, 136.9, 133.6, 133.4, 131.7, 115.3, 51.7, 32.2, 28.9, 28.0, 26.8. HRMS (ESI): exact mass calcd for $C_{12}H_{18}NO_2$ $[M + H]^+$, 208.1332. Found: 208.1334.

(2*E*)-2-(1-Acetylaziridin(2*R*)-2-ylmethylene)octa(5*E*)-5,7-dienoic Acid Methyl Ester (12). To a solution of aziridine **11** (3.69 g, 17.8 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C were added triethylamine (5.0 mL, 35.6 mmol) and DMAP (108 mg, 0.89 mmol) followed by dropwise addition of acetic anhydride (1.85 mL, 19.6 mmol). After 5 min, the reaction mixture was diluted with Et_2O (150 mL) and washed successively with water (20 mL), a saturated aqueous solution of $NaHCO_3$ (25 mL), and brine (20 mL). The organic extract was dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (30%), gave compound **12** (4.0 g, 90%) as a colorless oil: $[\alpha]^{23}_D$ −2.30 (*c* 1.14, $CHCl_3$); IR (neat) 1707, 1651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (td, J = 10.5, 17.0 Hz, 1H), 6.26 (d, J = 9.0 Hz, 1H), 6.09 (dd, J = 10.5, 15.0 Hz, 1H), 5.71 (td, J = 7.0, 15.0 Hz, 1H), 5.13 (d, J = 17.0 Hz, 1H), 5.01 (d, J = 10.5 Hz, 1H), 3.77 (s, 3H), 3.22 (ddd, J = 3.0, 6.0, 9.0 Hz, 1H), 2.63 (d on top of m, J = 6.0 Hz, 1H), 2.67−2.56 (m, 2H), 2.39−2.23 (m, 2H), 2.30 (d on top of m, J = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 166.9, 138.4, 136.7, 135.6, 133.1, 132.1, 115.7, 51.9, 34.4, 32.0, 26.9, 23.7. HRMS (ESI): exact mass calcd for $C_{14}H_{20}NO_3$ $[M + H]^+$, 250.1432. Found: 250.1438.

(4*R*)-4-Hexa(3*E*)-3,5-dienyl-2-oxo-2,3,4,7-tetrahydro-1*H*-azepine-4-carboxylic Acid Methyl Ester (17). To a solution of compound **12** (1.0 g, 4.01 mmol) in toluene (20 mL) cooled to −78 °C was added LHMDS (8 mL, 1 M in hexanes, 8 mmol) dropwise within a 5-min period of time. The reaction mixture turned slightly yellow. After 20 min, the reaction mixture was placed in a preheated (100 °C) oil bath. After 10 min at this temperature, the reaction turned orange, and disappearance of starting material was indicated by TLC analysis. Next, the reaction mixture was allowed to cool to rt. Diethyl ether (50 mL) was added followed by saturated aqueous solution of NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (50%), gave the seven-membered lactam **17** (770 mg, 77%) as a colorless oil: $[\alpha]^{23}_D$ +3.70 (*c* 2.71, $CHCl_3$); IR (neat) 3238, 1730, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (td, J = 10.5, 17.0 Hz, 1H), 6.07 (dd, J = 10.5, 15.0 Hz, 1H), 5.92 (s, br, 1H), 5.86−5.76 (m, 2H), 5.63 (td, J = 7.0, 15.0 Hz, 1H), 5.10 (d, J = 17.0 Hz, 1H), 4.98 (d, J = 10.5 Hz, 1H), 3.96−3.89 (m, 1H), 3.72 (s, 3H), 3.60 (td, J = 6.5, 18.0 Hz, 1H), 3.10 (d, J = 13.0 Hz, 1H), 2.81 (d, J = 13.0 Hz, 1H), 2.32−2.22 (m, 1H), 2.06−1.96 (m, 1H), 1.89 (dt, J = 5.0, 14.0 Hz, 1H), 1.79 (dt, J = 5.0, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 173.9, 136.9, 133.6, 133.4, 131.6, 125.5, 115.3, 52.5, 48.0, 39.3, 19.0, 37.9, 27.4. HRMS (ESI): exact mass calcd for $C_{14}H_{20}NO_3$ $[M + H]^+$, 250.1437. Found: 250.1443. Optical purity determination: HPLC analysis of the purified product **17** (Chiralpak AD-H, hexane/2-propanol = 80:20, flow rate: 0.4 mL/min, λ = 240 nm) showed a 98.5:1.5 mixture of enantiomers ($t_{R(R)}$ = 12.52 min, $t_{R(S)}$ = 13.74 min). For comparison purpose, *rac*-**17** was prepared starting with *rac*-**9**.

(4*R*)-4-Hexa(3*E*)-3,5-dienyl-2-oxo-2,3,4,7-tetrahydro-1*H*-azepine-4-carbaldehyde (7). To a solution of compound **17** (662 mg, 2.66 mmol) in toluene (12 mL) cooled to −78 °C was added DIBAL (4 mL, 1 M in hexanes, 4 mmol) dropwise along the flask side over a 10-min period of time. After an additional 20 min, EtOAc (1 mL) was added, and the reaction mixture was immediately poured into a rapidly stirred mixture of saturated aqueous solution of Rochelle's salt (20 mL) and EtOAc (20 mL). After 1 h, the clear biphasic mixture was transferred to a separation funnel, the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (50%), gave aldehyde **7** (342 mg, 59%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 6.54 (s, br, 1H), 6.28 (td, J = 10.5, 17.0 Hz, 1H), 6.08 (dd, J = 10.5, 15.0 Hz, 1H), 5.96 (ddd, J = 4.5, 6.5, 11.0 Hz, 1H), 5.68 (d, J = 11.0 Hz, 1H), 5.62 (td, J = 6.5, 15.0 Hz, 1H), 5.12 (d, J = 17.0 Hz, 1H), 5.00 (d, J = 10.5 Hz, 1H), 3.95−3.88 (m, 1H), 3.65 (td, J = 6.5, 17.4 Hz, 1H), 2.91 (d, J = 13.5 Hz, 1H), 2.71 (d, J = 13.5 Hz, 1H), 2.29−2.20 (m, 1H), 2.08−1.99 (m, 1H), 1.87−1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 173.8, 136.7, 133.0, 131.9, 130.2, 127.8, 115.6, 51.6, 39.5, 36.9, 26.7. HRMS (ESI): exact mass calcd for $C_{29}H_{37}NNaO_3Si$ $[M + Na]^+$, 498.2443. Found: 498.2435.

6,7-Dimethoxy-(3,3,4′,4′)spiro[2-oxo-2,3,4,7-tetrahydro-1*H*-azepine](9*S*)-9-vinyl(3*R*,3*aS*,9*aS*)-2,3,3*a*,4,9,9*a*-hexahydro-1*H*-cyclopenta[*b*]quinoline (20b). Aldehyde **7** (470 mg, 2.14 mmol) was dissolved in toluene (70 mL) at rt. Next, 3,4-dimethoxyaniline **6** (393 mg, 2.57 mmol) and $TsOH\cdot H_2O$ (40 mg, 0.21 mmol) were added, and the reaction flask was placed into a preheated (120 °C) oil bath for 30 min. The resulting mixture was then allowed to cool to rt and partitioned between a saturated aqueous solution of $NaHCO_3$ (30 mL) and EtOAc (30 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc, gave compound **20b** (532 mg, 70%) as a white solid. Recrystallization from CH_2Cl_2 gave a suitable single crystal for X-ray analysis (data in the Supporting Information): $[\alpha]^{23}_D$ +103.4 (*c* 1.70, $CHCl_3$); mp 182−183 °C; IR (neat) 3336, 3306, 1666 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.42 (s, br, 1H), 6.88 (s, 1H), 6.30 (s, 1H), 5.64 (td, J = 9.6, 17.0 Hz, 1H), 5.50 (d, J = 11.8 Hz, 1H), 5.35 (ddd, J = 4.2, 6.4, 11.8 Hz, 1H), 5.18 (dd, J = 2.0, 17.0 Hz, 1H), 5.15 (dd, J = 2.0, 9.6 Hz, 1H), 4.14 (s, br, 1H), 3.60 (s, 3H), 3.44 (s, 3H), 3.30−3.23 (m, 1H), 3.14 (t, J = 9.6 Hz, 1H), 3.07 (d, J = 11.1 Hz, 1H), 2.99 (dt, J = 6.4, 17.4 Hz, 1H), 2.70 (d, J = 12.3 Hz, 1H), 2.41 (d, J = 12.3 Hz, 1H), 1.96 (m, 1H), 1.79−1.71 (m, 1H), 1.64−1.58 (m, 1H), 1.17−1.06 (m, 1H), 1.87−1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 150.1, 143.0, 141.6, 140.2, 136.3, 127.5, 116.1, 115.4, 115.3, 101.8, 67.2, 56.9, 55.2, 50.2, 45.2, 44.9, 44.5, 38.9, 38.6, 25.7. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.13; H, 7.63; N, 7.82.

6,7-Dimethoxy(3,3,4′,4′)spiro[2-oxo-2,3,4,7-tetrahydro-1*H*-aze-pine](9*S*)-9-(2-hydroxyethyl)(3*R*,3*aS*,9*aS*)-2,3,3*a*,4,9,9*a*-hexahydro-1*H*-cyclopenta[*b*]quinoline (21). To a solution of **20b** (532 mg, 1.05mmol) in THF (11 mL) cooled to 0 °C was added dropwise a solution of 9-BBN (10.5 mL, 0.5 M in THF, 5.26 mmol). The resulting mixture was allowed to warm to rt and stirred for 24 h. It was then quenched with water (10 mL) at 0 °C, and H_2O_2 (5.4 mL of a 30% aqueous solution) and NaOH (12 mL of a 2 N aqueous solution) were added. The resulting mixture was stirred for 2 h, and then a saturated aqueous solution of $Na_2S_2O_3$ (2 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with MeOH/EtOAc (10%), gave alcohol **21** (215 mg, 55%) as a white foam: $[\alpha]^{23}_D$ +104.3 (*c* 1.56, $CHCl_3$); IR (neat) 3349, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.44 (t, J = 4.9 Hz, 1H), 6.20 (s, 1H), 5.80−5.70 (m, 2H), 3.89−3.85 (m, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.74−3.69 (m, 1H), 3.70 (t, J = 7.0 Hz, 1H), 3.06 (d, J = 10.7 Hz, 1H), 2.88−2.86 (m, 1H), 2.86 (d, J = 12.5 Hz, 1H), 2.64 (d, J = 12.5 Hz, 1H), 2.15−2.07 (m, 4H), 1.93−1.86 (m, 2H), 1.46−1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 148.2, 142.2, 140.1, 136.1, 123.5, 116.4, 111.8, 101.1, 68.1, 60.1, 56.8, 55.6, 44.9, 44.8, 44.2, 40.5, 39.5, 38.7, 35.5, 26.4. HRMS (ESI): exact mass calcd for $C_{21}H_{29}N_2O_4$ $[M + H]^+$, 373.2122. Found: 373.2125.

6,7-Dimethoxy(3,3,4′,4′)spiro[1-(carboxylic acid *tert*-butyl ester)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepine](9*S*)-9-[2-(*tert*-butyldiphenylsilanyloxy)ethyl](3*R*,3*aS*,9*aS*)-2,3,3*a*,4,9,9*a*-hexahydro-1*H*-cyclopenta[*b*]quinoline (22). To a solution of alcohol **21** (413 mg, 1.11 mmol) in CH_2Cl_2 (5 mL) at rt were added Et_3N (0.46 mL, 3.3 mmol) and DMAP (149 mg, 1.22 mmol) followed by TBDPSCl (367 mg, 1.34 mmol, rinsed with 0.5 mL of CH_2Cl_2). The reaction mixture was stirred for 3 h, and then diluted with Et_2O (30 mL). The resulting mixture was washed successively with water (5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL), and NH_4Cl (5 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (5 mL) at rt, and to this solution were added Et_3N (0.3 mL, 2.15 mmol) and DMAP (117 mg, 0.95 mmol) followed by di-*tert*-butyldicarbonate (242 mg, 1.1 mmol, rinsed with 0.5 mL of CH_2Cl_2). The reaction mixture was stirred for 30 min, and then was concentrated in vacuo. The resulting yellow residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexanes (50%), to give **22** (517 mg, 66%) as a white foam: $[\alpha]^{23}_D$ +35.7 (*c* 1.15, $CHCl_3$); IR (neat) 3360, 1766, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4H), 7.43−7.36 (m, 6H), 6.64 (s, 1H), 6.16 (s, 1H), 5.85 (td, J = 5.5, 11.5 Hz, 1H), 5.67 (d, J = 11.5 Hz, 1H), 4.39 (dd, J = 5.5, 11.0 Hz, 1H), 4.29 (dd, J = 5.5, 11.0 Hz, 1H), 3.81 (s, 3H), 3.74−3.69 (m, 2H), 3.71 (s, 3H), 3.05 (d, J = 13.0 Hz, 1H), 2.95 (d, J = 10.5 Hz, 1H), 2.81 (td, J = 4.0, 9.5 Hz, 1H), 2.77 (d, J = 13.0 Hz, 1H), 2.12−2.07 (m, 2H), 2.03−1.91 (m, 2H), 1.87−1.74 (m, 2H), 1.57 (s, 9H), 1.43−1.30 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 151.9, 147.9, 142.1, 139.9, 137.4, 135.5, 133.7, 129.5, 127.5, 122.8, 116.6, 111.7, 101.0, 83.3, 67.9, 61.3, 56.6, 55.5, 48.1, 46.5, 44.3, 42.2, 40.2, 38.6, 35.6, 28.0, 26.8, 26.5, 19.1. HRMS (ESI): exact mass calcd for $C_{42}H_{55}N_2O_6Si$ $[M + H]^+$, 711.3824. Found: 711.3839.

{(3*R*)-3-(3-*tert*-Butoxycarbonylaminopropenyl)(9*S*)-9-[2-(*tert*-butyldiphenyl-silanyloxy)ethyl]-6,7-dimethoxy(3*aS*,9*aS*))-2,3,3*a*,4,9,9*a*-hexahydro-1*H*-cyclopenta[*b*]quinolin-3-yl}acetic Acid Methyl Ester (23). To a solution of compound **22** (47.1 mg, 0.0662 mmol) in MeOH (0.5 mL) at 0 °C was added NaOMe (7 mg, 0.132 mmol) in one portion. After 30 min, the reaction mixture was quenched with brine (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (50%), gave **23** (19.4 mg) and **5** (20 mg). Compound **5** was reprotected as the Boc imide **22** and recycled to afford a second batch of **23** (7.2 mg), making the combined yield of **23** to be 55%: $[\alpha]^{23}_D$ −6.7 (*c* 1.51, $CHCl_3$); IR (neat) 3368, 1728, 1700 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.75−7.34 (m, 4H), 7.23−7.21 (m, 6H), 6.86 (s, 1H), 6.26 (d, J = 12.0 Hz, 1H), 6.24 (s, 1H), 5.48 (s, br, 1H), 5.37 (td, J = 7.5, 12.0 Hz, 1H), 4.39 (s, br, 1H), 4.04−3.88 (m, 4H), 3.58 (s, 3H), 3.32 (s, 3H), 3.27 (s, 3H), 2.90 (d on top of m, J = 15.0 Hz, 1H), 2.92−2.87 (m, 1H), 2.75 (d, J = 11.0 Hz, 1H), 2.22 (d on top of m, J = 15.0 Hz, 1H), 2.33−2.11 (m, 3H), 2.06−1.99 (m, 1H), 1.88−1.80 (m, 1H), 1.46 (s, 9H), 1.45−1.38 (m, 1H), 1.17 (s, 9H), 1.13−1.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 155.6, 148.3, 141.5, 140.7, 135.5, 134.7, 134.3, 133.8, 129.5, 127.6, 115.9, 112.3, 100.4, 79.3, 68.5, 61.5, 56.9, 55.7, 51.7, 46.8, 45.5, 45.0, 40.2, 39.2, 38.7, 35.9, 28.4, 27.7, 26.8, 26.7, 19.1. HRMS (ESI): exact mass calcd for $C_{43}H_{59}N_2O_7Si$ $[M + H]^+$, 743.4086. Found: 743.4074.

(2*R*)-2-[6-(*tert*-Butyldiphenylsilanyloxy)hex(3*E*)-3-enyl]-2-[3-(4-nitrobenzenesulfonylamino)propenyl]succinic Acid Dimethyl Ester (30). To a solution of lactam **29** (1.81 g, 3.57 mmol) in THF (20 mL) cooled to −78 °C was added dropwise NaHMDS (4.2 mL, 1 M in THF, 4.2 mmol) over a 10-min period of time. The reaction mixture turned orange at the end of addition. After 20 min, a solution of 4-nitrobenzenesulfonyl chloride (1.06 g, 4.78 mmol) in THF (3 mL and 2 × 1 mL for rinsing) was cannulated into the reaction mixture, which first turned purple and then clear yellow at the end of the addition. After being stirred for 3 h, the reaction mixture was partitioned between Et_2O (35 mL) and water (15 mL), and was allowed to warm to rt. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (gradient from 10% to 50%), gave the *N*-nosyl lactam (1.98 g, 80%) as a light yellow viscous oil: $[\alpha]^{23}_D$ +3.4 (*c* 3.49, $CHCl_3$); IR (neat) 1737, 1709, 1532, 1351, 1310 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42−8.39 (m, 2H), 8.25−8.22 (m, 2H), 7.75−7.73 (m, 4H), 7.53−7.44 (m, 6H), 6.09 (td, J = 5.6, 11.1 Hz, 1H), 5.94 (d, J = 11.1 Hz, 1H), 5.41 (td, J = 7.1, 15.5 Hz, 1H), 5.33 (td, J = 6.1, 15.5 Hz, 1H), 4.72 (dd, J = 5.6, 17.0 Hz, 1H), 4.61 (dd, J = 5.6, 17.0 Hz, 1H), 3.71 (t, J = 6.6 Hz, 2H), 3.67 (s, 3H), 3.20 (d, J = 13.8 Hz, 1H), 3.00 (d, J = 13.8 Hz, 1H), 2.30−2.24 (m, 2H), 2.07−1.97 (m, 1H), 1.86−1.70 (m, 2H), 1.44 (ddd, J = 5.2, 11.6, 13.8 Hz, 1H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 170.6, 150.4, 144.4, 135.6, 135.5, 133.9, 130.1, 130.0, 129.5, 128.0, 127.5, 123.8, 123.7, 63.6, 52.5, 49.1, 41.7, 40.8, 37.9, 35.8, 27.0, 26.8, 19.1. HRMS (ESI): exact mass calcd for $C_{36}H_{42}N_2NaO_8SSi$ $[M + Na]^+$ 713.2323. Found: 713.2303.

To a solution of the above *N*-Ns protected lactam (812 mg, 1.17 mmol) in THF/MeOH (2 mL/2 mL) at rt was added NaOMe (126 mg, 2.34 mmol) in one portion. The reaction mixture immediately turned purple. After 30 min, Et_2O (20 mL) and a saturated aqueous solution of NH_4Cl (10 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (gradient from 20% to 50%), gave compound **30** (753 mg, 89%) as a colorless oil: $[\alpha]^{23}_D$ +7.64 (*c* 0.68, $CHCl_3$); IR (neat) 3287, 1734, 1531, 1428, 1349 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 6.9 Hz, 2H), 8.08 (d, J = 6.9 Hz, 2H), 7.68−7.66 (m, 4H), 7.44−7.37 (m, 6H), 5.51 (d, J = 12.0 Hz, 1H), 5.47−5.31 (m, 3H), 5.20 (t, J = 6.0 Hz, 1H), 3.67 (t, J = 7.0 Hz, 2H), 3.65 (s, 3H), 3.64 (s, 3H), 3.61−3.55 (m, 2H), 2.84 (d, J = 15.5 Hz, 1H), 2.60 (d, J = 15.5 Hz, 1H), 2.24 (q, J = 6.5 Hz, 2H), 1.93−1.74 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 171.1, 149.9, 146.1, 135.5, 134.1, 133.9, 130.4, 129.5, 128.2, 127.8, 127.5, 127.0, 124.2, 63.6, 52.4, 51.8, 48.7, 41.2, 40.9, 38.9, 35.8, 27.5, 26.7, 19.1. HRMS (ESI): exact mass calcd for $C_{37}H_{46}N_2NaO_9SSi$ $[M + Na]^+$, 745.2610. Found: 745.2611.

{(3*R*)-3-[6-(*tert*-Butyldiphenylsilanyloxy)hex(3*E*)-3-enyl]-2-oxo-1,2,3,6-tetrahydropyridin-3-yl}acetic Acid Methyl Ester (31). Compound **30** (703 mg, 0.97 mmol) was dissolved in CH_3CN (10 mL) at rt, and to this solution was added dropwise DBU (0.15 mL, 1.45 mmol). The reaction mixture, which turned purple, was refluxed in an oil bath for 1 h and was allowed to cool to rt after that. A saturated aqueous solution of NH_4Cl (10 mL) followed by Et_2O (15 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (30%), gave six-membered *N*-Ns lactam (550 mg, 82%) as a colorless oil: $[\alpha]^{23}_D$ +10.8 (*c* 0.98, $CHCl_3$); IR (neat) 1736 1695, 1533, 1350, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 9.1 Hz, 2H), 8.24 (d, J = 9.1 Hz, 2H), 7.68−7.64 (m, 4H), 7.45−7.36 (m, 6H), 5.97 (td, J = 3.2, 10.1 Hz, 1H), 5.39−5.27 (m, 3H), 4.63 (ddd, J = 1.7, 3.2, 17.0 Hz, 1H), 4.50 (td, J = 3.2, 17.0 Hz, 1H), 3.64 (t, J = 6.9 Hz, 2H), 3.47 (s, 3H), 2.89 (d, J = 17.0 Hz, 1H), 2.29 (d, J = 17.0 Hz, 1H), 2.24−2.19 (m, 2H), 1.98−1.72 (m, 3H), 1.37−1.31 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 170.6, 150.3, 144.3, 143.0, 135.4, 133.8, 130.1, 129.8, 129.4, 127.7, 127.4, 123.4, 121.7, 63.6, 51.4, 48.1, 46.7, 43.5, 39.9, 35.7, 27.4, 26.7, 19.1. HRMS (ESI): exact mass calcd for $C_{36}H_{42}N_2NaO_8SSi$ $[M + Na]^+$, 713.2323. Found: 713.2323.

Potassium carbonate (811 mg, 5.88 mmol) was added to a solution of the above *N*-nosyl lactam (1.36 g, 1.96 mmol) in DMF (5 mL). Thiophenol (0.24 mL, 2.35 mmol) was added dropwise, and the reaction mixture was stirred at rt for 1 h. Next, a saturated aqueous solution of $NaHCO_3$ (5 mL) and Et_2O (15 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (gradient from 50% to 100%), gave lactam **31** (912 mg, 92%) as a colorless viscous oil: $[\alpha]^{23}_D$ +29.1 (*c* 2.85, $CHCl_3$); IR (neat) 3213, 1740, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76−7.74 (m, 4H), 7.52−7.43 (m, 6H), 6.90 (s, br, 1H), 5.83 (d, J = 10.1 Hz, 1H), 5.46 (td, J = 2.0, 10.1 Hz, 1H), 5.49−5.46 (m, 2H), 4.00 (d, J = 17.7 Hz, 1H), 3.89 (d, J = 17.7 Hz, 1H), 3.65 (t, J = 6.6 Hz, 1H), 3.61 (s, 3H), 3.11 (d, J = 15.8 Hz, 1H), 2.36 (d, J = 15.8 Hz, 1H), 2.23−2.221 (m, 2H), 2.00−1.95 (m, 3H), 1.39−1.36 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 171.1, 135.4, 133.8, 131.2, 129.4, 128.6, 127.4, 126.9, 122.1, 63.7, 51.3, 44.0, 43.6, 43.3, 39.6, 35.8, 27.6, 26.7, 19.1. HRMS (ESI): exact mass calcd for $C_{30}H_{39}NNaO_4Si$ $[M + Na]^+$, 528.2541. Found: 528.2547.

2-{(3*R*)-3-[6-(*tert*-Butyldiphenylsilanyloxy)hex(3*E*)-3-enyl]-2-oxo-1,2,3,6-tetrahydropyridin-3-yl}-*N*-(3,4-dimethoxyphenyl)acetamide (27). To a solution of compound **31** (279 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) at rt were added 3,4-dimethoxyaniline **6** (169 mg, 1.10 mmol) in one portion followed by dropwise addition of $AlMe_3$ (0.55 mL, 2 M in hexanes, 1.10 mmol). Stirring was continued for 48 h, and the resulting reaction mixture was quenched with a saturated aqueous solution of Rochelle's salt (5 mL) and then diluted with CH_2Cl_2 (5 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc, gave diamide **27** (332 mg, 96%) as a white foam: $[\alpha]^{23}_D$ −2.1 (*c* 0.90, $CHCl_3$); IR (neat) 3306, 1681, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, br, 1H), 7.66−7.64 (m, 4H), 7.43−7.34 (m, 6H), 7.29 (d, J = 2.1 Hz, 1H), 6.85 (J = 8.6 Hz, 1H), 6.72 (dd, J = 2.1, 8.6 Hz, 1H), 6.52 (s, br, 1H), 5.84 (d, J = 10.5 Hz, 1H), 5.67 (d, J = 10.5 Hz, 1H), 5.44−5.32 (m, 2H), 3.98−3.86 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.64 (t, J = 6.5 Hz, 2H), 3.00 (d, J = 13.5 Hz, 1H), 2.35 (d, J = 13.5 Hz, 1H), 2.23−2.19 (m, 2H), 2.04−1.88 (m, 3H), 1.50−1.41 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 168.1, 148.9, 145.5, 135.5, 133.9, 131.9, 130.9, 129.5, 129.4, 127.5, 127.3, 121.3, 111.4, 111.3, 104.6, 63.7, 56.0, 55.8, 47.2, 45.5, 43.6, 39.9, 35.9, 27.7, 26.8, 19.2. HRMS (ESI): exact mass calcd for $C_{37}H_{46}N_2NaO_5Si$ $[M + Na]^+$, 649.3068. Found: 649.3061.

2-{(3*R*)-3-[6-(*tert*-Butyldiphenylsilanyloxy)hex(3*E*)-3-enyl]-2-methoxy-3,6-dihydropyridin-3-yl}-*N*-(3,4-dimethoxyphenyl)acetamide (33). To a vigorously stirred solution of diamide **27** (327 mg, 0.522 mmol) in CH_2Cl_2 (5.2 mL) at rt were added Cs_2CO_3 (510 mg, 1.56 mmol) followed by trimethyloxonium tetrafluoroborate (116 mg, 0.782 mmol) in one portion. After 1 h, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (12 mL) and then taken up in CH_2Cl_2 (15 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (50%), gave imidate **33** (172 mg, 87%) as a colorless oil: $[\alpha]^{23}_D$ −1.6 (*c* 3.5, $CHCl_3$); IR (neat) 3315, 1689, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.67 (m, 4H), 7.46−7.37 (m, 6H), 7.27 (d, J = 2.5 Hz, 1H), 7.15 (s, br, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.70 (dd, J = 2.5, 8.5 Hz, 1H), 5.96 (td, J = 3.0, 10.0 Hz, 1H), 5.55 (d, J = 10.0 Hz, 1H), 5.40−5.37 (m, 2H), 4.10−4.08 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H), 3.66 (t, J = 6.5 Hz, 2H), 2.85 (d, J = 13.6 Hz, 1H), 2.30 (d, J = 13.6 Hz, 1H), 2.26−2.22 (m, 2H), 1.93−1.87 (m, 2H), 1.78−1.72 (m, 1H), 1.40−1.38 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 162.3, 149.0, 145.8, 135.5, 133.9, 131.4, 131.2, 129.4, 128.1, 127.5, 127.1, 126.8, 111.7, 111.3, 105.0, 63.8, 56.1, 55.8, 52.3, 48.7, 47.5, 41.2, 39.5, 35.9, 27.9, 26.8, 19.1. HRMS (ESI): exact mass calcd for $C_{38}H_{49}N_2O_5Si$ $[M + H]^+$, 641.3405. Found: 641.3424.

(3*aR*)-3*a*-[6-(*tert*-Butyldiphenylsilanyloxy)hex(3*E*)-3-enyl]-1-(3,4-dimethoxyphenyl)-1,3,3*a*,6-tetrahydropyrrolo[2,3-*b*]pyridin-2-one (26). To a solution of compound **33** (32 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) at rt was added dropwise Me_2AlCl solution (0.25 mL, 1 M in hexanes, 0.25 mmol). Stirring was continued for 48 h, and the resulting reaction mixture was quenched with a saturated aqueous solution of Rochelle's salt (2 mL), and then diluted with CH_2Cl_2 (2 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with EtOAc/hexanes (25%), gave amidine **26** (20.7 mg, 68%) as a colorless oil: $[\alpha]^{23}_D$ +0.6 (*c* 0.9, $CHCl_3$); IR (neat) 1744, 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.64 (m, 4H), 7.44−7.35 (m, 6H), 6.92 (d, J = 8.4 Hz, 1H), 6.86 (dd, J = 2.0, 8.4 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.09 (ddd, J = 1.4, 4.6, 9.6 Hz, 1H), 5.98 (dd, J = 2.8, 9.6 Hz, 1H), 5.45−5.40 (m, 2H), 4.24 (dd, J = 4.6, 21.0 Hz, 1H), 4.01 (ddd, J = 1.4, 2.8, 21.0 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.66 (t, J = 6.4 Hz, 1H), 2.77 (d, J = 16.8 Hz, 1H), 2.70 (d, J = 16.8 Hz, 1H), 2.23 (q, J = 6.4 Hz, 1H), 2.12−2.07 (m, 2H), 1.72−1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 166.1, 149.3, 148.8, 135.6, 134.0, 133.9, 130.4, 129.6, 129.0, 128.1, 127.6, 126.4, 119.4, 111.3, 110.4, 63.7, 56.0, 55.9, 49.3, 41.6, 41.0, 39.2, 35.9, 27.7, 26.8, 19.2. HRMS (ESI): exact mass calcd for $C_{37}H_{45}N_2O^4Si$ $[M + H]^+$, 609.3143. Found: 609.3149.

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Supporting Information Available: X-ray data for compound **20b**, and experimental details and copies of NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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