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Total Synthesis of the *Kopsia lapidilecta* Alkaloid (±)-Lapidilectine B

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The total synthesis of *Kopsia lapidilecta* alkaloid (±)-lapidilectine B is described. Notable elements of this synthesis include the first natural products application of the Smalley azido−enolate cyclization to form the 1,2-dihydro-3*H*-indol-3-one (indoxyl) core and installation of the pyrrolidine ring by a 2-azaallyllithium [3+2] cycloaddition with the acetylene equivalent phenyl vinyl sulfide. Closure of the eight-membered perhydroazocine ring is accomplished via the intramolecular S_N2 substitution of a mesylate. This constitutes the first synthesis of a member of the 5,6,12,13-tetrahydro-11a,13a-ethano-3*H*-pyrrolo[1′,2′:1,8]azocino[5,4-*b*]indole class of alkaloids.

Introduction

The *Kopsia* (*Apocynaceae*, subfamily *Plumerioideae*) genus[1] of flowering plants grows in South and Southeast Asia and has been a rich source of alkaloidal natural products.[2−4] *Kopsia lapidilecta* is one of about 30 species in this genus and is distinguished by a number of structurally interesting alkaloids bearing the novel 5,6,-12,13-tetrahydro-11a,13a-ethano-3*H*-pyrrolo[1′,2′:1,8]azocino[5,4-*b*]indole ring system (Figure 1).[2−4] Among these is (+)-lapidilectine B (**1**), which was isolated by Awang and co-workers in 1992 from the leaves of *Kopsia lapidilecta* (Figure 1).[3] The structure of (+)-lapidilectine B was elucidated by two-dimensional NMR experiments and its absolute configuration was tentatively assigned as drawn in Figure 1 based on biogenesis and a positive Cotton effect.[2,3] Although no pharmacological effects have been reported for *Kopsia lapidilecta* alkaloids, extracts from other *Kopsia* species have been used medicinally for the treatment of rheumatoid arthritis, dropsy (edema), tonsillitis, and hypertension.[1b,4,5] A number of *Kopsia* alkaloids have attracted the attention of synthetic chemists,[6] but only one synthetic study on *Kopsia lapidilecta* alkaloids has recently been reported.[7]

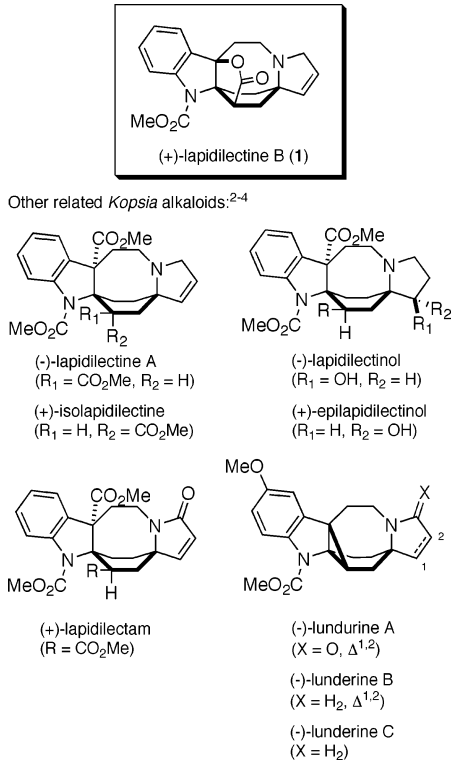

FIGURE 1. (+)-Lapidilectine B and related *Kopsia* alkaloids.

We have long been interested in the generation and cycloaddition of nonstabilized 2-azaallyllithiums (i.e.,

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(1) (a) Margraf, F. *Blumea* **1972**, *20*, 416−425. (b) Sévenet, T.; Allorge, L.; David, B.; Awang, K.; Hadi, A.; Hamid, A.; Kan-Fan, C.; Quirion, J.-C.; Remy, F.; Schaller, H.; Teo, L. E. *J. Ethnopharmacol.* **1994**, *41*, 147−183.

(2) Awang, K.; Sévenet, T.; Päis, M.; Hadi, A. H. A. *J. Nat. Prod.* **1993**, *56*, 1134−1139.

(3) Awang, K.; Sévenet, T.; Hadi, A. H. A.; David, B.; Päis, M. *Tetrahedron Lett.* **1992**, *33*, 2493−2496.

(4) (a) Kam, T.-S.; Yoganathan, K.; Chuah, C.-H. *Tetrahedron Lett.* **1995**, *36*, 759−762. (b) Kam, T.-S.; Yoganathan, K.; Koyano, T.; Komiyama, K. *Tetrahedron Lett.* **1996**, *37*, 5765−5768. (c) Kam, T.-S.; Yoganathan, K.; Li, H.-Y.; Harada, N. *Tetrahedron* **1997**, *53*, 12661−12670. (d) Rho, M.-C.; Toyoshima, M.; Hayashi. M.; Koyano, T.; Subramanian, G.; Kam, T.-S.; Komiyama, K. *Planta Med.* **1999**, 307−310. (e) Kam, T.-S.; Yoganathan, K.; Wei, C. *J. Nat. Prod.* **1996**, *59*, 1109−1112.

(5) (a) Burkhill, I. H. *A Dictionary of the Economic Products of the Malay Penisula*; Ministry of Agriculture and Cooperatives: Kuala Lumpur, Malaysia, 1966. (b) Xiao, Z. F.; Kan, C.; Potier, P.; Kan, S. K.; Lounasmaa, M. *Planta Med.* **1983**, *48*, 280−282. (c) Feng, X. Z.; Kan, C.; Husson, H.-P.; Potier, P.; Kan, S. K.; Lounasmaa, M. *J. Nat. Prod.* **1984**, *47*, 117−122. (d) Mok, S.-L.; Yoganathan, K.; Lim, T.-M.; Kam, T.-S. *J. Nat. Prod.* **1998**, *61*, 328−332.

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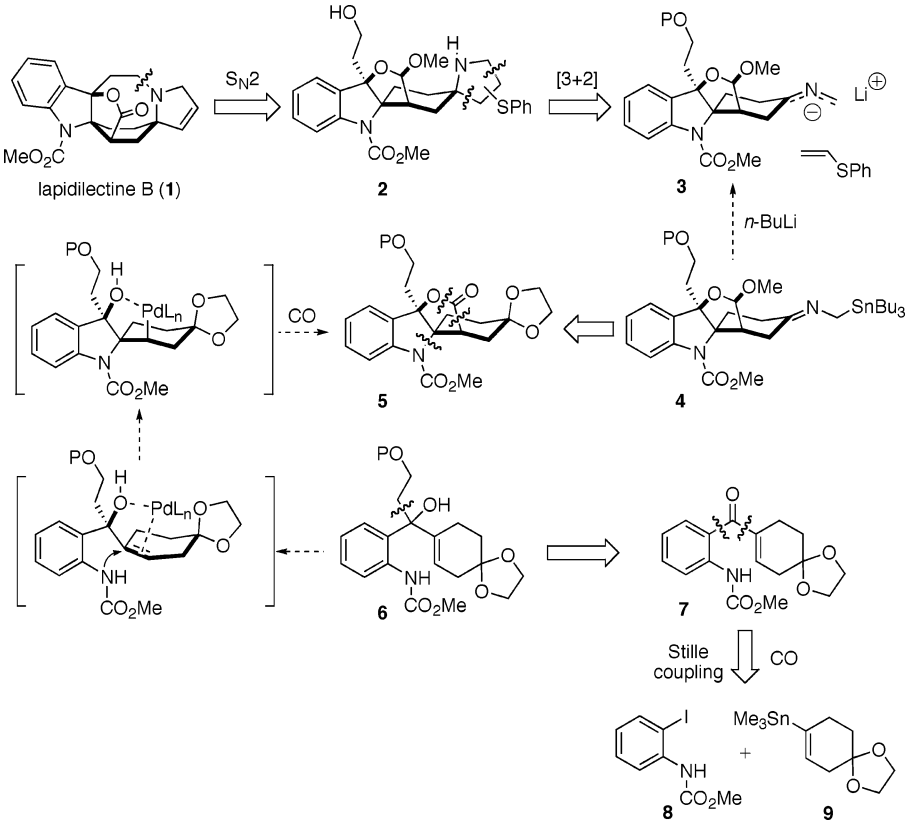
SCHEME 1. Initial Retrosynthesis



azaallyl anions) derived from (2-azaallyl)stannanes as a synthetic method for the formation of pyrrolidine rings.[8] The synthetic utility of both inter- and intramolecular cycloadditions of nonstabilized 2-azaallyllithiums has been highlighted with the synthesis of several pyrrolidine-containing alkaloids of moderate complexity.[9] We embarked on the total synthesis of (±)-lapidilectine B to broaden the use of intermolecular cycloadditions of nonstabilized 2-azaallyllithiums to a more complex natural product setting. Specifically, it provided an opportunity to employ the anionophile phenyl vinyl sulfide as an acetylene synthetic equivalent to form the 2,5-dihydropyrrole ring in the alkaloid.

We describe herein our synthetic studies which culminated in the total synthesis of (±)-lapidilectine B (**1**).[10] In addition to the successful installation of the 2,5-dihydropyrrole ring with use of a 2-azaallyllithium [3+2] cycloaddition, the synthesis demonstrates the first application of the Smalley azido−enolate cyclization[11] to form the indoxyl core of the alkaloid. The eight-membered perhydroazocine ring is formed by the intramolecular S_N2 displacement of a mesylate by a 2,5-dihydropyrrole. These synthetic studies also serve to confirm the structure and relative configuration of lapidilectine B.

Initial Retrosynthetic Plan

In our original retrosynthetic analysis for lapidilectine B (**1**) (Scheme 1), we envisioned disconnection of the eight-membered perhydroazocine ring via an intramolecular substitution of a leaving group by a 2,5-dihydropyrrole. The 2,5-dihydropyrrole in **2** would be installed by the [3+2] cycloaddition of 2-azaallyllithium **3** with the acetylene equivalent phenyl vinyl sulfide. The (2-azaallyl)stannane **4**, necessary for generating 2-azaallyllithium **3** by tin−lithium exchange, would be formed from a suitably protected cyclohexanone **5**. To efficiently form the fused 2,3-dihydroindole ring system in **5**, we initially opted for a palladium-catalyzed aminocarbonylation strategy[12] starting with aniline **6**. Aniline **6** would be elaborated from enone **7**, which was formed by a carbonylative Stille coupling from protected 2-iodoaniline **8** and alkenyl stannane **9**.

(6) For recent synthetic work on other *Kopsia* alkaloids, see: (a) Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Rainey, T. J.; Westlund, N.; Lynch, V. *Tetrahedron* **2002**, *58*, 3423−3443. (b) Magnus, P.; Hobson, L. A.; Westlund, N. *Tetrahedron Lett*. **2001**, *42*, 993−997. (c) Magnus, P.; Westlund, N. *Tetrahedon Lett.* **2000**, *41*, 9369−9372. (d) Kuehne, M. E.; Li, Y.-L.; Wei, C.-Q. *J. Org. Chem.* **2000**, *65*, 6434−6440. (e) Magnus, P.; Payne, A. H.; Hobson, L. *Tetrahedron Lett*. **2000**, *41*, 2077−2081. (f) Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Lynch, V. *Tetrahedron Lett*. **1999**, *40*, 5135−5138. (g) Kuehne, M. E.; Li, Y.-L. *Org. Lett.* **1999**, *1*, 1749−1750.

(7) Watanabe, T.; Arai, S.; Nishida, A. *Synlett* **2004**, 907−909.

(8) (a) Pearson, W. H.; Szura, D. P.; Harter, W. G. *Tetrahedron Lett.* **1988**, *29*, 761−764. (b) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329−1345. For a review, see: (c) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903−921. For recent work, see: Pearson, W. H.; Mans, D. M.; Kampf, J. W. *J. Org. Chem.* **2004**, *69*, 1235−1247.

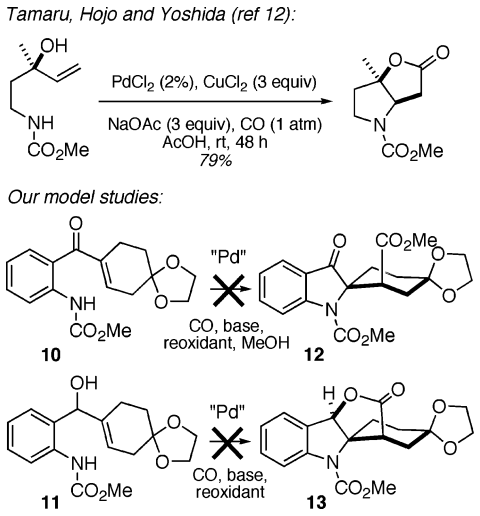
(9) For reviews of alkaloid synthesis with 2-azaallyllithiums see ref 8c and: Pearson, W. H. *Pure Appl. Chem.* **2002**, *74*, 1339−1347.

(10) For an initial communication of this work, see: Pearson, W. H.; Mi, Y.; Lee, I.-Y.; Stoy, P. *J. Am. Chem. Soc.* **2001**, *123*, 6724−6725.

(11) (a) Ardakani, M. A.; Smalley, R. K. *Tetrahedron Lett.* **1979**, *20*, 4769−4772. (b) Azadi-Ardakani, M.; Alkhader, M. A.; Lippiatt, J. H.; Patel, D. I.; Smalley, R. K.; Higson, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1107−1111.

(12) For the most relevant example of such an aminocarbonylation strategy, see: (a) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731−5741. (b) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994−4002.

SCHEME 2. Aminocarbonylation Model Studies



Beginning with model compounds **10**[13] and **11**,[13] we attempted aminocarbonylative cyclization of these substrates using the procedure of Tamaru,[12] as well as a number of alternative conditions from the literature (Scheme 2).[19] The desired cyclization products **12** and **13** were not isolated in any of these experiments. Replacement of the methyl carbamate protecting group in **10** and **11** with a *p*-toluenesulfonamide moiety[12] gave similar results. Since these model studies failed to yield any aminocarbonylative cyclization products, we abandoned this approach and reconsidered our retrosynthesis.

Revised Retrosynthetic Plan

We decided to make the same retrosynthetic disconnections as before, but this time using an umpolung approach in the construction of the 1,2-dihydro-3*H*-indol-3-one ("indoxyl") substructure by employing the aniline nitrogen in **17** as an electrophile instead of a nucleophile (Scheme 3). Such a process for indoxyl synthesis has been elegantly demonstrated by Smalley[11] featuring the intramolecular attack of an enolate on an aryl azide (Scheme 4). However, the Smalley cyclization has never before been applied in a natural products setting.

Formation of the Smalley cyclization precursor **16** began with known 4-benzyloxycyclohexanone **20**,[15] which was converted to alkenyl triflate **21** through *O*-sulfonylation of the corresponding enolate with *N*-phenyltriflamide[16] in 72% yield (Scheme 5). Alkenyl triflate **21** was transformed into alkenyl stannane **19** with use of Wulff's palladium-catalyzed stannylation protocol.[17] Carbonylative Stille coupling[18,19] of **19** with known triazinone-protected iodoaniline **22**[19] provided enone **23**[10] in excellent yield. Conjugate addition of vinylmagnesium bromide to **23** in the presence of lithium 2-thienyl cyanocuprate under the conditions of Lipshutz[20] furnished ketone **24** as an inseparable 4.7:1 mixture of diastereomers. The relative configuration of the vinyl group and benzyloxy group in **24** could only be determined after the Smalley cyclization (vide infra). The yield of this reaction was found to vary depending on the batch used of commercially available vinylmagnesium bromide and lithium 2-thienylcyanocuprate. The triazinone protecting group in **24** was removed with hydrochloric acid in aqueous methanol to give aniline **25** in good yield. It was necessary to closely monitor the progress of this reaction since prolonged reaction times led to erratic isolated yields, apparently through decomposition of the desired product. Finally, diazotization of aniline **25** with sodium nitrite and hydrochloric acid furnished an aryl diazonium salt (not shown),[10] which was converted to the Smalley cyclization precursor **16**[10] by treatment with sodium azide.[21]

Initial cyclization experiments with **16**, using Smalley's optimized potassium hydroxide−ethanol conditions,[11b] gave a 1.9:1 ratio of desired indoxyl **15**[10] to undesired diastereomer **26**[10] in 60% combined yield. After some experimentation it was found that potassium hydroxide in 2-propanol constituted the best Smalley cyclization conditions for our system, giving a 2.2:1 ratio of **15** to **26** in 68% combined yield (Scheme 6).

Structure Elucidation of Intermediates

Analysis of ^{1}H NMR coupling constants in diastereomers **15** and **26** suggested that in both compounds the vinyl and benzyloxy groups had a trans relationship. However, we were not able to distinguish which diastereomer corresponded with the desired structure **15**. Therefore, we undertook a series of chemical transformations which would leave no doubt as to the identity of the diastereomers **15** and **26**.

Initially, we converted the minor Smalley cyclization product **26** into **33** by the transformations shown in Scheme 7. This sequence began with the installation of a methyl carbamate group onto the indoxyl nitrogen using *tert*-butyllithium and methyl chloroformate to give **27** in 37% yield. Dihydroxylation of the vinyl group in **27** with OsO_4−NMO to give **28** was accompanied by spontaneous cyclization to **29** when reaction times where prolonged or upon treatment with base or silica gel. The formation of **29** is strong evidence that the vinyl group and indoxyl nitrogen are cis in the cyclohexane ring of **26**. Attempts to add allylmagnesium bromide to the indoxyl carbonyl of **28** led only to cyclic carbamate **30** in moderate yield. This cyclization pathway could be circumvented by protection of the 1,2-diol in **28** as trimethylsilyl (TMS) ethers to form **31**, followed by allylmagne-

(13) See the Supporting Information.
(14) (a) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584−3585. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800−5807. (c) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407−7408.
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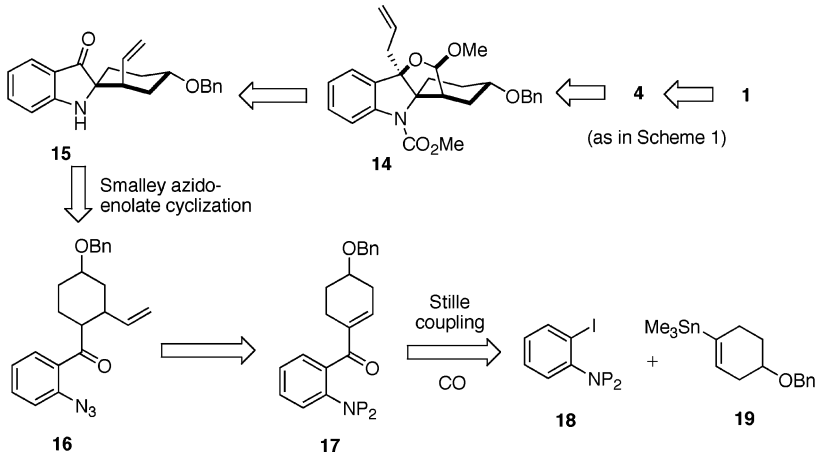
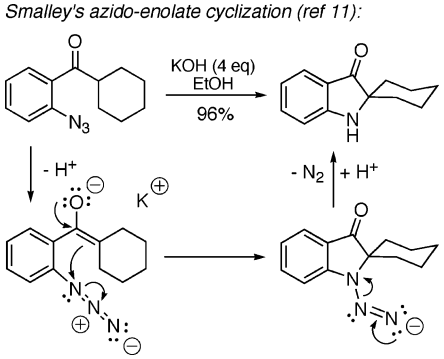
(18) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776−5788.
(19) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833−5847.
(20) (a) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945−948. (b) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959−5962.
(21) (a) Fukuyama, T.; Xu, L.; Goto, S. *J. Am. Chem. Soc.* **1992**, *114*, 383−385. (b) Duclos, R. I., Jr.; Tung, J. S.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 5243−5246.

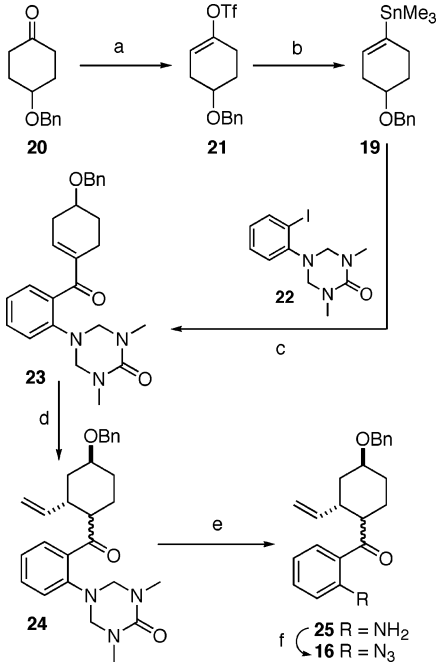
SCHEME 3. Revised Retrosynthesis



SCHEME 4. The Smalley Indoxyl Synthesis

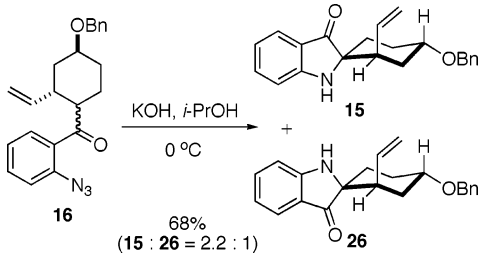


SCHEME 5. Synthesis of the Smalley Precursors[a]



[a] Reagents and conditions: (a) (1) LDA, −78 °C, (2) $PhNTf_2$ (72%); (b) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$, LiCl, THF (91%); (c) **22**, Pd_2dba_3·$CHCl_3$, Ph_3As, LiCl, NMP, CO (70 psi), 75 °C (98%); (d) CH_2=$CHMgBr$, Li-2-thienylcyanocuprate, BF_3·Et_2O, THF, −78 °C (82%); (e) HCl (conc), MeOH, rt (83%); (f) (1) HCl (conc), $NaNO_2$, H_2O, 0 °C, (2) NaN_3 (aq), 0 °C (not isolated).

SCHEME 6. Smalley Cyclization

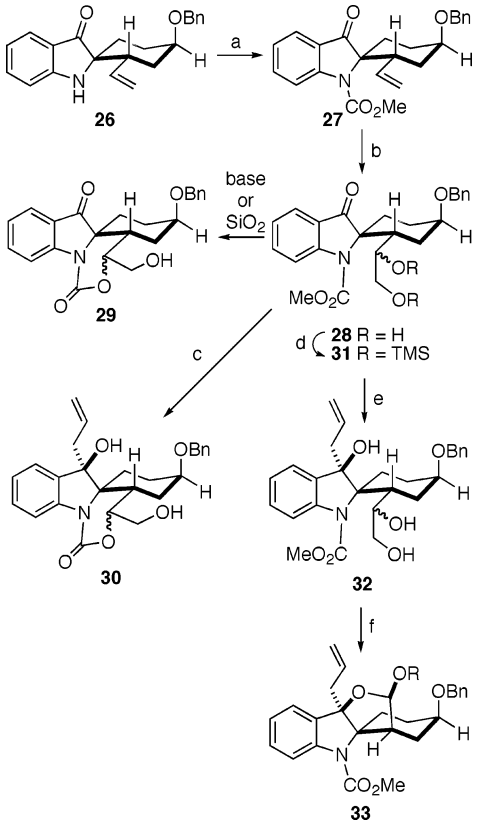


sium bromide addition, which gave **32** in good yield after in situ TMS deprotection with HF·pyridine. Oxidative cleavage of the 1,2-diol in **32** with sodium periodate formed a hemiacetal, which was immediately treated with camphorsulfonic acid in methanol to furnish methyl acetal **33** in 45% yield. Apparently an epimerization of the aldehyde initially formed from **32** occurs under the oxidation conditions.

The major Smalley cyclization diastereomer **15** was converted to **14** via a similar sequence (Scheme 8). Incorporation of the methyl carbamate with use of *tert*-butyllithium and methyl chloroformate gave **34** in 89% yield. Dihydroxylation of **34** with OsO_4−NMO formed **35** in 82% yield as an inseparable 6:1 ratio of diastereomers, but was never accompanied by any cyclized carbamate products such as **29**. Addition of allylmagnesium bromide to indoxyl **35** proceeded in an excellent 90% yield to give **36**, although the diastereoselectivity of this addition could not immedately be determined. Oxidative cleavage of the 1,2-diol **36** with sodium periodate followed by treatment with methanolic camphorsulfonic acid led to the desired methyl acetal **14** in 59% yield. As in **33**, formation of the cyclic acetal confirmed the facial selectivity of the allyl Grignard addition, which presumably results from steric shielding of one face of the carbonyl group by the diol moiety. All doubts about the stereostructure of **14** and **33** were dispelled by an X-ray crystallographic structure determination of **14**.[10]

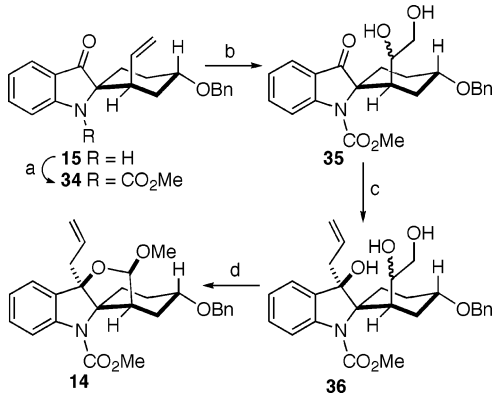
Although the structure of **14** was now confirmed, and **33** was thought to be a diastereomer of **14**, it was not entirely clear what were the relative configurations of the acetal and benzyloxy carbons in **33**. From the ^1H NMR spectra, it appeared that **14** and **33** had the same relative configuration at the acetal carbon, but were epimeric at the benzyloxy carbon. To confirm this hypothesis, both **14** and **33** were converted to the γ-lactones

SCHEME 7. Elaboration of Indoxyl 26 to 33[a]



[a] Reagents and conditions: (a) (1) *t*-BuLi, THF, −20 °C, (2) $ClCO_2Me$ (37%); (b) OsO_4, NMO, acetone (72%); (c) allylMgBr, THF, −40 °C (57%); (d) TMS−imidazole, 100 °C (81%); (e) (1) allylMgBr (3 equiv), THF, −50 °C, (2) HF·pyr, THF (75%); (f) (1) $NaIO_4$, 4:1 THF/H_2O, (2) CSA, MeOH, rt (45%).

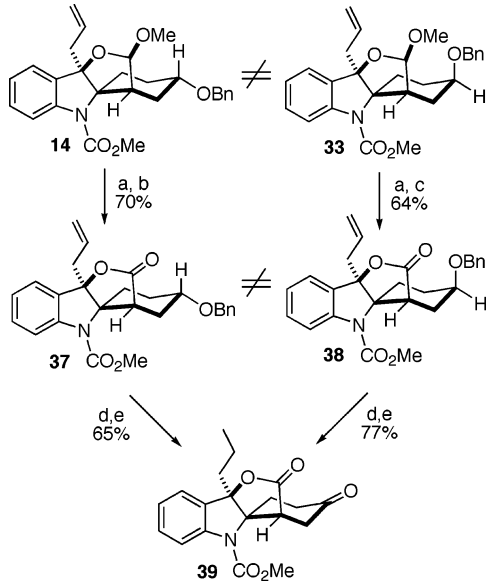
SCHEME 8. Elaboration of Indoxyl 15 to 14[a]



[a] Reagents and conditions: (a) *t*-BuLi, $ClCO_2Me$, −10 °C (89%); (b) OsO4 (cat.), NMO, acetone, rt (82%); (c) allylMgBr, THF, −40 °C (90%); (d) (1) $NaIO_4$, THF, rt, (2) CSA, MeOH, rt (59%).

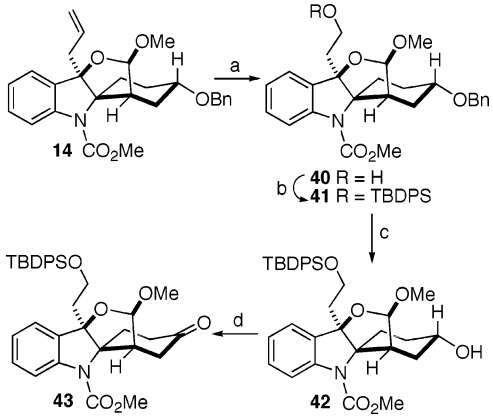
37 and **38** through dimethylboron bromide demethylation[22] followed by oxidation with Fétizon's reagent[23] or PCC[24] (Scheme 9). Since lactones **37** and **38** were not equivalent, they must be epimeric at the benzyloxy carbon. This supposition was confirmed by conversion of **37** and **38** to a common ketone **39** by debenzylation with Pearlman's catalyst[25] and oxidation with PCC. The possibility that **14** and **33** were *also* epimeric at the acetal carbon was discounted due to a severe steric interaction between the acetal methoxy group and axial benzyloxy group in such a hypothetical compound.

SCHEME 9. Elucidating the Stereostructure of 14 and 33[a]



[a] Reagents and conditions: (a) Me_2BBr, CH_2Cl_2; (b) Ag_2CO_3−Celite, C_6H_6, 80 °C; (c) PCC, silica gel, CH_2Cl_2; (d) $Pd(OH)_2$−C, H_2, EtOH−THF; (e) PCC, silica gel, CH_2Cl_2.

SCHEME 10. Preparation of the [3+2] Cycloaddition Precursor[a]



[a] Reagents and conditions: (a) (1) O_3, Sudan III, CH_2Cl_2−MeOH, −78 °C, (2) $NaBH_4$, MeOH (87%); (b) TBDPSCI, DIEA, CH_2Cl_2 (91%); (c) $Pd(OH)_2$−C, H_2 (1 atm), AcOH (cat.), EtOH−THF (92%); (d) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2 (95%).

Methyl acetal **14** was further converted into the 2-azaallyllithium cycloaddition precursor **43** through the transformations in Scheme 10. Careful ozonolysis of **14**

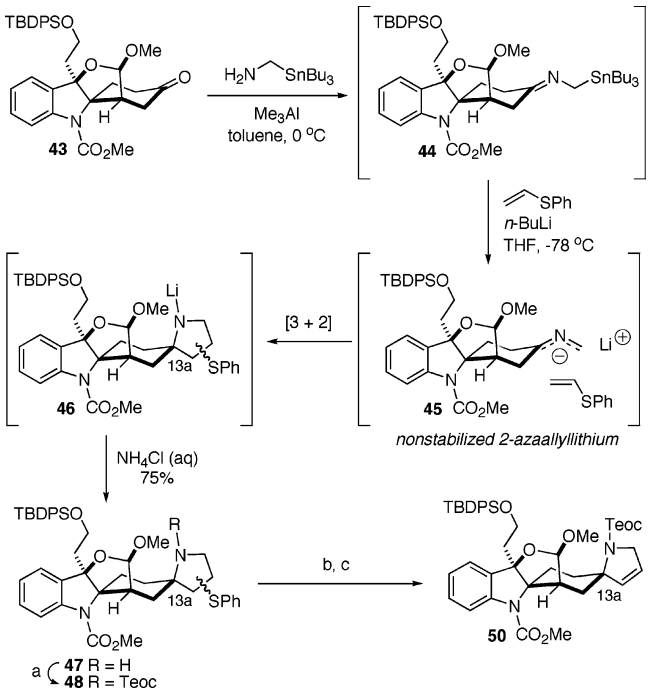
(22) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912−3920.

(23) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401−422. For recent examples of oxidation of cyclic hemiacetals to γ-lactones with Fétizon's reagent, see: (a) Tatsuta, K.; Takahashi, M.; Tanaka, N.; Chikauchi, K. *J. Antibiot.* **2000**, *53*, 1231−1234. (b) Enders, D.; Kroll, M.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1673−1675.

(24) For recent examples of oxidation of cyclic hemiacetals to γ-lactones with PCC, see: (a) Clayden, J.; Kenworthy, M. N.; Helliwell, M. *Org. Lett.* **2003**, *5*, 831−834. (b) Hölemann, A.; Reissig, H.-U. *Org. Lett.* **2003**, *5*, 1463−1466. (c) Breit, B.; Heckmann, G.; Zahn, S. K. *Chem. Eur. J.* **2003**, *2*, 425−434.

(25) Pearlman, W. M. *Tetrahedron Lett.* **1967**, *8*, 1663−1664.

SCHEME 11. 2-Azaallyllithium [3+2] Cycloaddition[a]



[a] Reagents and conditions: (a) Teoc−Cl, DIEA, CH_2Cl_2 (91%); (b) *m*-CPBA (1 equiv), $NaHCO_3$, CH_2Cl_2, −30 °C to rt (88%); (c) $Cl_2C{=}CCl_2$, pyr, 125 °C (85%).

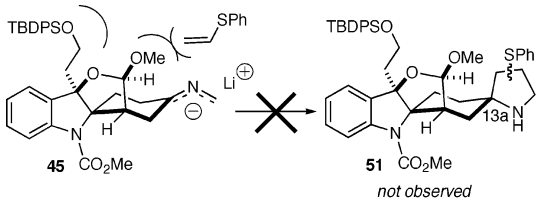
with Sudan III as an indicator[26] of complete reaction produced primary alcohol **40** in 87% yield after reductive workup with sodium borohydride. Protection of **40** as the *tert*-butyldiphenylsilyl (TBDPS) ether gave **41** in 91% yield, which was debenzylated with Pearlman's catalyst[25] under hydrogen to give secondary alcohol **42** in 92% yield. Finally, **42** was oxidized to ketone **43** by tetra-*n*-propylammoniumperruthenate/*N*-morpholine oxide (TPAP−NMO)[27] in 95% yield, setting the stage for the subsequent [3+2] cycloaddition.

2-Azaallyllithium Cycloaddition

The generation and [3+2] cycloaddition of nonstabilized 2-azaallyllithiums has previously been reported by our group in both the inter- and intramolecular mode of cycloaddition.[8,9,28−30] In the intermolecular mode, we found that phenyl vinyl sulfide is a very useful anionophile since it can serve as either an ethylene[8b,28,29] or acetylene[8b,29] synthetic equivalent. In the present case, we required it to serve as an acetylene equivalent.

The necessary (2-azaallyl)stannane precursor **44** was prepared in situ from ketone **43**, using (tri-*n*-butyl)-stannylmethylamine[30] and trimethylaluminum[28,29] in toluene (Scheme 11). Stannane **44** was then sequentially treated with phenyl vinyl sulfide, THF, and 1 equiv of *n*-butyllithium at −78 °C to effect formation of transient nonstabilized 2-azaallyllithium **45** via tin−lithium exchange. 2-Azaallyllithium **45** was trapped in situ with phenyl vinyl sulfide to initially give *N*-lithiopyrrolidine **46** and pyrrolidine **47**[10] after aqueous workup. After column chromatography an inseparable complex mixture of three major and at least six minor diastereomers or rotamers was obtained in 75% yield, and the stereoselectivity of the cycloaddition could not be immediately discerned. It was found that *n*-butyllithium could be used in excess (2.5 equiv) with no loss in yield, which facilitated conducting the cycloaddition reactions on small scale. Attempts at conducting the cycloaddition sequence in the presence of an unprotected lactone moiety instead of a methyl acetal were met only with decomposition. Similarly, attempts at installing a phenyl sulfoxide (vide infra) moiety directly by using phenyl vinyl sulfoxide as an anionophile also failed.

Since the newly formed quaternary carbon at C-13a (according to the IUPAC numbering of **1**; see ref 10) needed a specific relative configuration to allow closure of the eight-membered ring later in the synthesis, the facial selectivity of the cycloaddition was of particular interest to us. We felt that the methyl acetal and bulky TBDPS ether would sterically shield the "upper" face of the 2-azaallyllithium and prevent formation of the undesired pyrrolidine **51** (eq 1). To clarify this issue,

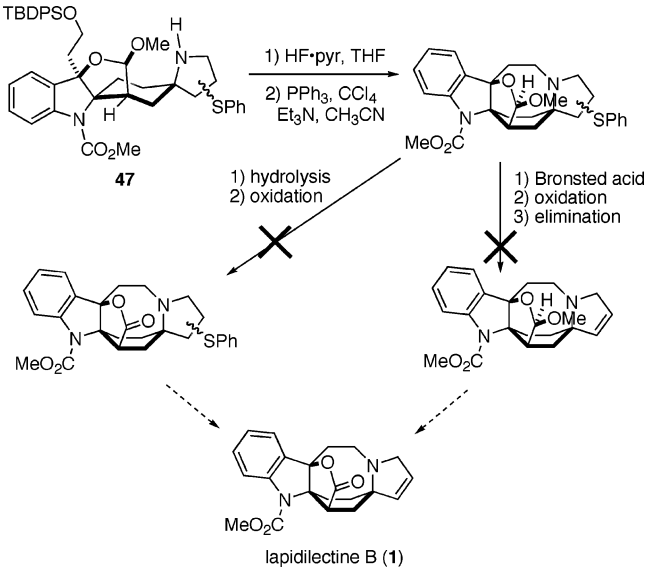


(Eq. 1)

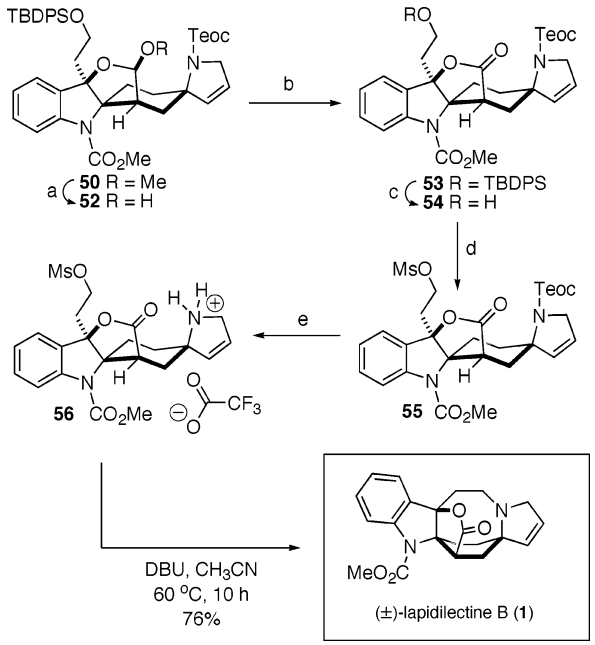
pyrrolidine **47** was transformed to the *N*-Teoc[31] derivative **48** with 2-(trimethylsilyl)ethylchloroformate[31] in 91% yield, also isolated as a complex mixture of diastereomers (Scheme 11). Direct quenching of the *N*-lithiopyrrolidine **46** with chloroformates gave inferior yields of the *N*-protected pyrrolidines, a phenomenon we have previously observed.[8b] Judicious oxidation of phenyl sulfide **48** furnished the sulfoxide **49** (not shown), which underwent thermal elimination away from the nitrogen[32] to give the 2,5-dihydropyrrole **50** in good yield. Although the ^{1}H NMR spectra of **50** was complicated by two sets of rotamer resonances with differing coalescence points, variable-temperature ^{1}H NMR established the presence of a single diastereomer.[33] The all-important relative configuration of **50** at C-13a could not immediately be confirmed by NOE experiments and would only be borne out by completion of the synthesis of lapidilectine B.

(26) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807−810.
(27) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.
(28) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369−3372.
(29) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688−689.
(30) (a) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354−6357. (b) Pearson, W. H.; Stoy, P.; Mi, Y. *J. Org. Chem.* **2004**, *69*, 1919−1939.
(31) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346−349.
(32) Sulfoxides and selenoxides are known to prefer thermal elimination away from heteroatoms, see ref 8b and: (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. (b) Haraguchi, K.; Tanaka, H.; Maeda, H.; Itoh, Y.; Saito, S.; Miyasaka, T. *J. Org. Chem.* **1991**, *56*, 5401−5408.
(33) In our initial communication (ref 10), we reported in error that **50** was isolated as an inseparable mixture of two diastereomers, which we have presently shown to be carbamate rotamers. See the Supporting Information.

SCHEME 12. The Initial Unsuccessful Endgame Strategy



SCHEME 13. Completion of the Synthesis[a]



[a] Reagents and conditions: (a) BCl_3, CH_2Cl_2, 0 °C (67%); (b) PCC, Celite, CH_2Cl_2 (91%); (c) HF·pyr, THF (88%); (d) MsCl, CH_2Cl_2, −10 °C to rt (92%); (e) TFA−CH_2Cl_2 (1:2), rt, 30 min (quant).

Completion of the Synthesis

Our initial strategy for completing the synthesis of **1** from **47** involved closing the eight-membered ring first, followed by installation of the lactone and alkene moieties (Scheme 12). Although we achieved some initial success closing the eight-membered ring via a triphenylphosphine/carbon tetrachloride-promoted dehydrative cyclization, we were unable to hydrolyze the methyl acetal to a lactol or oxidize the sulfide to a sulfoxide due to the presence of the basic tertiary nitrogen. We decided to circumvent this problem by proceeding from compound **50** in which the nitrogen is protected as an *N*-Teoc carbamate and the alkene is already installed.

With 2,5-dihydropyrrole **50** in hand, completion of the synthesis required only the transformation of a methyl acetal into a γ-lactone followed by closure of the eight-membered perhydroazocine ring. We accessed lactone **53** through a sequence of demethylation to form the hemiacetal **52**, followed by oxidation (Scheme 13). Conversion of methyl acetal **50** to the hemiacetal **52** with use of aqueous Brønsted acids failed, but after some experimentation, boron trichloride[34] emerged as the most reliable reagent for this transformation, giving **52** in 67% yield. Although a variety of oxidative conditions were examined including Swern, Dess−Martin, TPAP−NMO,[27] and PDC, only PCC[24] reliably provided lactone **53** in 91% yield.

We found that once the lactone moiety was present, the dehydrative cyclization shown in Scheme 12 no longer worked well. Instead, we resorted to the displacement of a mesylate leaving group to close the eight-membered ring. Transformation of the TBDPS silyl ether to a mesylate was uneventfully accomplished by treatment of **53** with HF·pyridine to give alcohol **54**, followed by *O*-sulfonylation with methanesulfonyl chloride to furnish **55**. Deprotection of the *N*-Teoc protecting group with reactive fluoride reagents such as TBAF, TASF,[35] or CsF proved to be sluggish or accompanied by partial elimination of the mesylate leaving group. However, brief treatment of **55** with trifluoroacetic acid (TFA) in dichloromethane followed by evaporation of solvent cleanly gave the 2,5-dihydropyrrole·TFA salt **56**, setting the stage for the intramolecular S_N2 displacement of the mesylate.[36] The penultimate compound **56** was not isolated, but treated with diisopropylethylamine (DIEA) for 2 h at room temperature, then heated to 60 °C in acetonitrile for 10 h to give (±)-lapidilectine B (**1**) in excellent yield (76%). Although no natural (+)-lapidilectine B remains from the original isolation work for direct comparison, the NMR, IR, UV, and mass spectra of synthetic (±)-**1** match those reported for natural (+)-**1**.[37]

Conclusion

We have completed the total synthesis of (±)-lapidilectine **1** in 23 linear steps and 0.10% overall yield from 4-benzyloxycyclohexanone. This represents the first synthesis of a 5,6,12,13-tetrahydro-11a,13a-ethano-3*H*-pyrrolo[1′,2′:1,8]azocino[5,4-*b*]indole alkaloid from *Kopsia lapidilecta*, and demonstrates the utility of a nonstabilized 2-azaallyllithium [3+2] cycloaddition in a complex

(34) For a related process involving demethylation of a methyl tetrahydrofuryl ether with BBr_3, see: Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8453−8463.

(35) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436−6437.

(36) For recent examples of formation of perhydroazocine rings by intramolecular S_N2 reactions, see: (a) Pauly, R.; Sasaki, N. A.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 237−240. (b) Monterde, M. I.; Nazabadioko, S.; Rebolledo, F.; Brieva, R.; Gotor, V. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3449−3455. (c) Winkler, J. D.; Stelmach, J. E.; Axten, J. *Tetrahedron Lett.* **1996**, *37*, 4317−4318.

(37) In the original isolation work, several impurities in the ^{1}H NMR spectrum were observed. We also noted these peaks but were able to show they were due to carbamate rotamers by variable-temperature ^{1}H NMR spectroscopy, see ref 10.

setting. Other notable features include the first application of the Smalley azido−enolate cyclization in total synthesis as well as an intramolecular S_N2 displacement to close the eight-membered perhydroazocine ring.

Experimental Section

For general experimental procedures, see the Supporting Information.

4-Benzyloxy-1-[(trifluoromethanesulfonyl)oxy]cyclohexene (21). A solution of LDA was made from diisopropylamine (2.08 mg, 20.6 mmol) and *n*-butyllithium (7.63 mL of a 2.7 M solution in hexanes, 20.6 mmol) in THF (69 mL) at −10 °C and then cooled to −78 °C. A solution of the ketone **20** (3.83 g, 18.7 mmol) in THF (3 mL) was then slowly added. After 2 h at −78 °C, solid *N*-phenyltrifluoromethanesulfonimide[16] (6.68 g, 18.7 mmol) was added in one portion. The mixture was allowed to warm to 0 °C gradually, and stirred at 0 °C for an additional 1 h. The reaction was taken up in 20% ethyl acetate/hexanes, washed with water (2×) and brine (1×), dried ($MgSO_4$), and concentrated. Chromatography (5% to 7% ethyl acetate/hexanes gradient) afforded 4.55 g (72%) of **21** as a yellow oil. R_f 0.23 (7% ethyl acetate/hexanes); IR (neat) 1693 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5 H), 5.70−5.60 (m, 1 H), 4.56 (ABq, $\Delta\upsilon$ = 6.4 Hz, J_{AB} = 11.9 Hz, 2 H), 3.78−3.66 (m, 1 H), 2.60−2.20 (m, 4 H), 2.24−1.88 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.4, 127.6, 127.4, 115.4, 71.1, 70.4, 29.8, 27.4, 25.2; MS (CI, NH_3) *m/z* (rel intensity) 354 ($[M + NH_4]^+$, 100), 299 (15), 281 (8), 203 (4), 148 (5), 108 (18), 91 (18); HRMS (CI, NH_3) calcd for $C_{14}H_{19}NO_4F_3S$ ($[M + NH_4]^+$) 354.0987, found 354.0991.

4-Benzyloxy-1-trimethylstannylcyclohexene (19). Tetrakis(triphenylphosphine)palladium(0) (0.78 g, 0.68 mmol) was added to a solution of alkenyl triflate **21** (2.27 g, 0.68 mmol) and hexamethylditin (2.33 g, 7.10 mmol) in THF (14 mL), followed by addition of anhydrous lithium chloride (1.72 g, 40.6 mmol, flame-dried in air, cooled in vacuo). The mixture was heated at reflux for 4 h, then cooled to room temperature, and most of the solvent was removed in vacuo. The resulting residue was diluted with hexanes and washed with water (3×) and brine (1×). The combined aqueous phases were extracted with hexanes (1×) and the combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (3% to 7% ethyl acetate/hexanes gradient) provided 2.16 g (91%) of **19** as a colorless oil. R_f 0.19 (5% ethyl acetate/hexanes); IR (neat) 1623 (m), 1396 (s), 1188 (s), 1096 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.18 (m, 5 H), 5.72−5.66 (m, 1 H), 4.55 (ABq, $\Delta\upsilon$ = 11.7 Hz, J_{AB} = 12.1 Hz, 2 H), 3.64−3.54 (m, 1 H), 2.50−2.24 (m, 2 H), 2.24−2.04 (m, 2 H), 2.02−1.92 (m, 1 H), 1.66−1.54 (m, 1 H), 0.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 139.1, 135.6, 128.3, 127.5, 127.3, 73.8, 69.7, 34.1, 30.0, 28.8, −10.4. Anal. Calcd for $C_{16}H_{24}OSn$: C, 54.74; H, 6.89. Found: C, 55.06; H, 6.78.

(1*R,2*R**,4*R**)- and (1*S**,2*R**,4*R**)-4-Benzyloxy-1-[2-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazin-5-yl)benzoyl]-2-vinylcyclohexanes (24).** At −78 °C, vinylmagnesium bromide (6.80 mL of a 1.0 M solution in THF, 6.80 mmol) was added to a solution of lithium 2-thienylcyanocuprate (27.2 mL of a 0.25 M solution in THF, 6.80 mmol) in THF (23 mL). Boron trifluoride etherate (0.29 mL, 2.29 mmol) was added 10 min later at −78 °C, followed by the addition of a solution of the enone **23** (0.952 g, 2.27 mmol) in THF (4 mL). The mixture was allowed to warm to room temperature slowly and stirred at room temperature for an additional 2 h. The reaction was treated with saturated aqueous NH_4OH (20 mL) and NH_4Cl (20 mL). The mixture was stirred at room temperature for 15 min and then extracted with ether (3×). The combined etheral solution was washed with water (1×) and brine (1×), then dried ($MgSO_4$) and concentrated. Chromatography (60:40 hexanes/ethyl acetate to 60:30:10 hexanes/ethyl acetate/MeOH gradient) gave 0.83 g (82%) of **24** as a yellow oil that contains two inseparable diastereomers (1:4.7 by ^1H NMR integration). R_f 0.20 (60:30:10 hexanes/ethyl acetate/MeOH); IR ($CHCl_3$) 1685 (s), 1636 (s), 1596 (w), 1520 (s), 1305 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.80−7.10 (m, 9 H), 5.94−5.80 (m, 1 H × 0.17), 5.72−5.56 (m, 1 H × 0.83), 5.20−4.80 (m, 2 H), 4.62−4.38 (m, 6 H), 3.80−3.35 (m, 2 H), 3.10−2.65 (m, 7 H), 2.25−1.10 (m, 6 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 208.5, 208.2, 156.1, 146.7, 146.5, 141.4, 138.9, 138.8, 138.1, 137.2, 136.5, 131.5, 131.2, 128.6, 128.2, 127.5, 127.4, 127.3, 125.1, 125.0, 123.0, 122.9, 122.6, 115.8, 114.8, 114.6, 72.8, 71.8, 70.0, 69.7, 69.0, 68.8, 54.8, 51.2, 42.3, 39.7, 37.5, 36.3, 34.9, 32.0, 31.7, 29.8, 29.1, 28.4, 24.1, 27.8; MS (EI, 70 eV) *m/z* (rel intensity) 447 (M^+, 54), 356 (7), 302 (22), 272 (16), 259 (22), 231 (17), 146 (23), 132 (87), 113 (52), 91 (100); HRMS (EI, 70 eV) calcd for $C_{27}H_{33}N_3O_3$ (M^+) 447.2522, found 447.2515. The trans relationship between the vinyl and the benzyloxy group was determined based on the stereochemistry of the subsequent compounds, **15** and **26**. However, the relative configuration of the major diastereomer with respect to the third chiral center could not be determined.

(1*R,2*R**,4*R**)- and (1*S**,2*R**,4*R**)-1-[2-(Amino)benzoyl]-4-benzyloxy-2-vinylcyclohexanes (25).** Concentrated HCl (37%, 1.06 g, 10.8 mmol) was added to a solution of **24** (121 mg, 0.270 mmol) in MeOH (4 mL) at room temperature. The reaction was closely monitored by TLC and after 50 min the reaction was basified with 20% aqueous NaOH at 0 °C (pH >10). The mixture was extracted with ether (3×) and the etheral solution was washed with brine (1×), dried ($MgSO_4$), and concentrated. Chromatography (15% ethyl acetate/hexanes, 2 drops of concentrated NH_4OH per 100 mL of eluting solvent) provided 75 mg (83%) of **25** as a green-yellow oil that contained two inseparable diastereomers (1:5.4 by ^1H NMR integration). The relative configuration of the major diastereomer could not be determined. R_f 0.37 (20% ethyl acetate/hexanes); IR ($CHCl_3$) 3499 (m), 3352 (m), 1641 (s), 1613 (s), 1579 (s), 1548 (s), 1450 (s), 1161 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.75 (app d, J = 8.0 Hz, 1 H × 0.84), 7.70 (app d, J = 8.0 Hz, 1 H × 0.16), 7.50−7.10 (m, 6 H), 6.70−6.55 (m, 2 H), 6.40−6.10 (m, 2 H), 5.83 (ddd, J = 17.9, 10.4, 8.0 Hz, 1 H × 0.16), 5.68 (ddd, J = 17.5, 10.4, 7.1 Hz, 1 H × 0.84), 5.05−4.70 (m, 2 H), 4.60−4.50 (m, 2 H), 3.85−3.50 (m, 1 H), 3.26 (td, J = 11.1, 3.6 Hz, 1 H), 3.10−2.94 (m, 1 H), 2.30−2.00 (m, 2 H), 2.00−1.60 (m, 2 H), 1.58−1.35 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 205.8, 205.2, 150.8, 150.0, 141.5, 141.3, 139.1, 139.0, 134.7, 134.0, 133.9, 131.3, 130.7, 130.6, 128.32, 128.27, 128.26, 127.5, 127.4, 127.3, 127.2, 117.9, 117.4, 115.5, 114.0, 73.0, 72.0, 70.0, 69.7, 49.5, 37.1, 35.0, 31.5, 29.2, 25.0, 22.6, 22.2, 14.1, 14.0; MS (CI, NH_3) *m/z* (rel intensity) 336 ($[M + H]^+$, 100), 320 (4), 308 (1), 244 (39), 228 (25), 151 (12), 135 (12), 120 (94), 91 (49); HRMS (CI, NH_3) calcd for $C_{22}H_{26}NO_2$ ($[M + H]^+$) 336.1963, found 336.1961.

(1′*R,3′*R**,4′*R**)-1-Methoxycarbonyl-1,2-dihydroindol-3-one-2-spiro-4′-(1′-benzyloxy-3′-vinylcyclohexane) (27).** *tert*-Butyllithium (0.15 mL of a 1.7 M solution in pentane, 0.26 mmol) was added in a dropwise fashion to a solution of the indoxyl **26** (42 mg, 0.13 mmol) in THF (3.5 mL) at −20 °C. After 15 min, a solution of methyl chloroformate (54 mg, 0.58 mmol) in THF (0.5 mL) was added at −20 °C dropwise and the reaction was allowed to warm to room temperature. After 30 min, the reaction was quenched with aqueous saturated NH_4Cl. The aqueous layer was extracted with ether (3×) and the combined organic solution was dried ($MgSO_4$) and concentrated. Chromatography (15% to 20% ethyl acetate/hexanes gradient) gave 18 mg (37%; 70% based on the recovered starting material) of **27** as a yellow oil, along with 20 mg of recovered starting material. R_f 0.43 (30% ethyl acetate/hexanes); IR ($CHCl_3$) 1713 (s), 1609 (s), 1469 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.1 Hz, 1 H), 7.78−7.72 (m, 1 H), 7.65−7.58 (m, 1 H), 7.48−7.24 (m, 5 H), 7.14 (t, J = 7.3 Hz, 1 H), 5.43 (ddd, J = 17.3, 10.3, 7.7 Hz, 1 H), 4.90 (app d, J = 17.3 Hz, 1 H), 4.80 (app d, J = 10.3 Hz, 1 H), 4.60 (s, 2 H), 3.98−3.92 (m, 1 H), 3.90 (s, 3 H), 3.36−3.25 (m, 1 H), 2.44−2.34 (m, 1 H), 2.30−2.14 (m, 2 H), 2.06−1.92 (m, 2 H), 1.86−1.78 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 153.4, 152.4,

139.2, 136.9, 136.2, 128.3, 127.4, 127.3, 124.0, 123.2, 122.6, 117.5, 116.5, 77.8, 71.9, 69.6, 52.6, 41.4, 30.8, 28.4, 24.6; MS (EI, 70 eV) *m/z* (rel intensity) 392 ([M + H]$^+$, 5), 391 (M$^+$, 4), 285 (35), 246 (51), 203 (34), 178 (13), 146 (13), 129 (35), 111 (24), 91 (100); HRMS (EI, 70 eV) cacld for $C_{24}H_{26}NO_4$ ([M + H]$^+$) 392.1862, found 392.1854.

(1′*R,3′*S**,4′*R**)-1-Methoxycarbonyl-1,2-dihydroindol-3-one-2-spiro-4′-[1′-benzyloxy-3′-(1,2-dihydroxyethyl)cyclohexane] (28) and Cyclic Carbamate 29.** *N*-Methylmorpholine *N*-oxide (0.010 g, 0.086 mmol) was dissolved in a solution of the carbamate **27** (0.028 g, 0.072 mmol) in acetone (4 mL), followed by addition of osmium tetroxide (0.051 g of a 2.5 wt % solution in 2-propanol, 0.005 mmol). The reaction was stirred at room temperature overnight and quenched with aqueous 10% Na_2SO_3. The mixture was stirred for an additional 15 min and diluted with chloroform. The organic phase was dried ($MgSO_4$) and concentrated. Chromatography (60:40 hexanes/ethyl acetate to 60:30:10 hexanes/ethyl acetate/MeOH gradient) gave 22 mg (72%) of **28** as a yellow oil. Both ^{1}H and ^{13}C spectra showed a single isomer was formed. However, the relative configuration of −**C**H(OH)(CH$_2$OH) could not be determined. R_f 0.15 (60:30:10 hexane/ethyl acetate/MeOH); IR ($CHCl_3$) 3404 (w), 1706 (s), 1609 (m), 1352 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.5 Hz, 1 H), 7.72−7.50 (m, 2 H), 7.44−7.20 (m, 5 H), 7.14−7.04 (m, 1 H), 4.50 (ABq, $\Delta\upsilon$ = 30.3 Hz, J_{AB} = 12.1 Hz, 2 H), 3.96−3.80 (m, 1 H), 3.85 (s, 3 H), 3.60−3.10 (m, 3 H), 2.92−2.80 (m, 1 H), 2.40−1.50 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 152.4, 138.8, 136.8, 128.4, 127.5, 123.9, 123.2, 117.4, 76.3, 73.6, 70.2, 64.8, 52.9, 40.9, 30.1, 29.3, 25.5; MS (DCI, NH_3) *m/z* (rel intensity) 426 ([M + H]$^+$, 26), 425 (M$^+$, 3), 408 (34), 394 (100), 350 (60), 318 (30), 287 (41), 242 (13), 91 (45); HRMS (DCI, NH_3) calcd for $C_{24}H_{28}NO_6$ ([M + H]$^+$) 426.1917, found 426.1925.

When the reaction time was prolonged or when **28** was treated with silica gel or base, the cyclized carbamate **29** was also observed. **29**: R_f 0.21 (60:30:10 ethyl acetate/hexane/MeOH); IR ($CHCl_3$) 3408 (br s), 1708 (s), 1605 (s), 1469 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.4 Hz, 1 H), 7.75 (d, J = 7.7 Hz, 1 H), 7.67 (dt, J = 7.8, 1.1 Hz, 1 H), 4.65−4.58 (m, 1 H), 4.58 (ABq, $\Delta\upsilon$ = 23.0 Hz, J_{AB} = 12.1 Hz, 2 H), 3.94 (dd, J = 12.9, 2.6 Hz, 1 H), 3.91 (s, 1 H), 3.74−3.64 (m, 1 H), 3.67 (dd, J = 12.4, 4.0 Hz, 1 H), 2.67 (ddd, J = 14.0, 11.8, 4.8 Hz, 1 H), 2.48−2.38 (m, 1 H), 2.22−1.80 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 150.4, 148.6, 138.3, 137.3, 128.5, 127.7, 127.6, 124.6, 124.5, 122.2, 117.7, 80.1, 71.4, 70.4, 64.8, 62.6, 33.2, 28.2, 27.9, 25.3; MS (DCI, NH_3) *m/z* (rel intensity) 394 ([M + H]$^+$, 21), 350 (100), 242 (20), 215 (46), 170 (15), 91 (14); HRMS (DCI, NH_3) calcd for $C_{23}H_{24}NO_5$ ([M + H]$^+$) 394.1654, found 394.1670.

Cyclic Carbamate 30. Allylmagnesium bromide (0.10 mL of a 1.0 M solution in diethyl ether, 0.10 mmol) was added to a solution of diol **28** (10 mg, 0.024 mmol) in THF (1 mL) at −40 °C. The reaction was allowed to warm to room temperature slowly and stirred overnight. It was quenched with aqueous saturated NH_4Cl and diluted with ether. The etheral solution was washed with water (1×) and brine (1×), then dried ($MgSO_4$) and concentrated. Chromatography (60:30:10 hexanes/ethyl acetate/MeOH) produced 6.0 mg (57%) of **30** as a yellow oil. R_f 0.23 (60:30:10 ethyl acetate/hexanes/MeOH); IR ($CHCl_3$) 3405 (w), 1707 (s), 1604 (w), 1464 (m), 1417 (m), 1375 (m), 1265 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1 H), 7.40−7.08 (m, 9 H), 5.69−5.56 (m, 1 H), 5.25 (app d, J = 10.0 Hz, 1 H), 5.16 (d, J = 18.3 Hz, 1 H), 4.64−4.54 (m, 1 H), 4.55 (ABq, $\Delta\upsilon$ = 21.3 Hz, J_{AB} = 11.9 Hz, 2 H), 4.00 (dd, J = 13.2, 2.2 Hz, 1 H), 3.74 (dd, J = 12.8, 3.7 Hz, 1 H), 3.66−3.54 (m, 1 H), 2.80−2.72 (m, 1 H), 2.58 (br s, 1 H), 2.4 (dq, J = 13.6, 8.0 Hz, 1 H), 2.38−2.30 (m, 2 H), 2.24−1.90 (m, 5 H), 1.72 (td, J = 11.9, 5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 138.6, 138.2, 135.0, 131.6, 129.2, 128.5, 127.8, 127.6, 124.1, 123.6, 121.3, 117.9, 84.2, 71.3, 70.5, 68.8, 61.5, 41.7, 32.8, 29.9, 29.4, 28.8; MS (CI, NH_3) *m/z* (rel intensity) 436 ([M + H]$^+$, 10), 418 (6), 394 (6), 279 (12), 246 (6), 229 (15), 117 (64), 100 (100); HRMS (CI, NH_3) calcd for $C_{26}H_{30}NO_5$ ([M + H]$^+$) 436.2124, found 436.2132.

(1′*R,3′*S**,4′*R**)-1-Methoxycarbonyl-1,2-dihydroindol-3-one-2-spiro-4′-[1′-benzyloxy-3′-(1,2-bistrimethylsilanyloxy)ethylcyclohexane] (31).** The diol **28** (29 mg, 0.074 mmol) was dissolved in 1-(trimethylsilyl)imidazole (0.5 mL) and heated at 100 °C. After 1.5 h, the reaction was diluted in hexane, washed with water (2×) and brine (1×), dried ($MgSO_4$), and concentrated. Chromatography (10% ethyl acetate/hexanes) on a short column provided 34 mg (81%) of **31** as a light yellow oil. R_f 0.30 (10% ethyl acetate/hexanes); IR ($CHCl_3$) 1727 (s), 1706 (s), 1212 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.5 Hz, 1 H), 7.76 (dd, J = 7.1, 0.5 Hz, 1 H), 7.58 (td, J = 7.0, 1.5 Hz, 1 H), 7.50−7.20 (m, 5 H), 7.14 (t, J = 7.5 Hz, 1 H), 4.57 (ABq, $\Delta\upsilon$ = 13.3 Hz, J_{AB} = 12.1 Hz, 2 H), 4.02−3.88 (m, 4 H), 3.59 (dd, J = 10.4, 2.2 Hz, 1 H), 3.57−3.50 (m, 1 H), 3.43 (dd, J = 11.0, 5.1 Hz, 1 H), 3.16−3.08 (m, 1 H), 3.31 (td, J = 13.6, 4.8 Hz, 1 H), 2.10−1.80 (m, 4 H), 1.70−1.50 (m, 1 H), 0.06 (s, 9 H), −0.40 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 153.7, 151.1, 139.3, 135.8, 128.3, 127.3, 127.2, 124.9, 123.2, 123.1, 117.8, 75.6, 72.2, 72.0, 69.4, 65.1, 52.6, 39.3, 30.7, 28.5, 24.4, −0.04, −0.60; MS (DCI, NH_3) *m/z* (rel intensity) 570 ([M + H]$^+$, 100), 569 (M$^+$, 1), 512 (12), 480 (13), 466 (14), 372 (5), 282 (4), 163 (6), 91 (7); HRMS (DCI, NH_3) calcd for $C_{30}H_{44}NO_6Si_2$ ([M + H]$^+$) 570.2707, found 570.2700.

(1′*R,3′*S**,4′*R**,3*R**)-3-Hydroxy-1-methoxycarbonyl-3-(2-propenyl)-2,3-dihydro-1*H*-indole-2-spiro-4′-[1′-benzyloxy-3′-(1,2-dihydroxy)ethylcyclohexane] (32)** Allylmagnesium bromide (0.15 mL of a 1.0 M solution in diethyl ether, 0.15 mmol) was added to a solution of ketone **31** (42 mg, 0.074 mmol) in THF (3 mL) at −50 °C and was allowed to warm to room temperature. After 10 h, the reaction was quenched with aqueous saturated NH_4Cl and diluted with ether. The organic layer was washed with water (1×) and brine (1×), dried ($MgSO_4$), and concentrated. Without further purification, the crude mixture was dissolved in THF (1.5 mL) and treated with HF·pyridine (0.050 mL) and the mixture was stirred at room temperature. After 5 h the reaction was carefully quenched with aqueous saturated $NaHCO_3$, extracted with $CHCl_3$ (3×), dried (Na_2SO_4), and concentrated. Chromatography (60:30:10 hexanes/ethyl acetate/MeOH) gave 26 mg (75% over two steps) of **32** as a yellow oil. R_f 0.22 (60:30:10 hexane/ethyl acetate/MeOH); IR ($CHCl_3$) 3459 (w), 1708 (s), 1603 (m), 1214 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.10 (m, 8 H), 7.04−6.96 (m, 1 H), 5.82−5.60 (m, 1 H), 5.09 (app d, J = 9.8 Hz, 1 H), 5.04 (app d, J = 17.0 Hz, 1 H), 4.51 (s, 2 H), 4.30 (br s, 1 H), 3.80 (s, 3 H), 3.78−3.72 (m, 1 H), 3.64−3.56 (m, 1 H), 3.52−3.46 (m, 1 H), 3.36−3.28 (m, 1 H), 2.92−1.72 (m, 12 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.7, 140.7, 138.8, 135.8, 133.3, 128.5, 128.3, 127.6, 127.5, 127.4, 123.7, 123.1, 119.1, 117.1, 83.5, 76.2, 73.3, 69.9, 65.3, 52.5, 42.0, 38.9, 29.4, 27.0, 25.6; all attempts at obtaining MS/HRMS spectra by using various probes failed for this compound.

Methyl Acetal 33. Sodium periodate (27 mg, 0.13 mmol) was added to a solution of the triol **32** (30 mg, 0.064 mmol) in THF (4 mL) and pH 7 buffer (Na_2HPO_4/NaH_2PO_4, 0.8 mL) at 0 °C and allowed to warm to room temperature. After 12 h, the reaction was diluted with ether and water. The aqueous layer was separated and extracted with ether (3×). The combined organic layers were dried ($MgSO_4$) and concentrated. Without further purification, the crude lactol was dissolved in methanol (3 mL) and 10-camphorsulfonic acid (74 mg, 0.32 mmol) was added in one portion at room temperature. After 1 h, most of the solvent was removed in vacuo and the residue was chromatographed (20% ethyl acetate/hexanes) to provide 13 mg (45%) of **33** as a yellow oil. R_f 0.19 (20% ethyl acetate/hexanes); IR ($CHCl_3$) 1698 (s), 1602 (w), 1484 (s), 1387 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (br s, 1 H), 7.46−7.20 (m, 7 H), 7.02 (t, J = 7.3 Hz, 1 H), 5.85−5.70 (m, 1 H), 5.20 (app d, J = 17.6 Hz, 1 H), 5.02 (app d, J = 10.2 Hz, 1 H), 4.68 (s, 1 H), 4.60 (s, 2 H), 3.86 (s, 3 H), 3.82−3.70 (m, 1 H), 3.46−2.88 (m, 3 H), 2.72 (s, 3 H), 2.64−2.50 (m, 1 H), 2.40−2.28 (m, 1 H),

2.24−2.20 (m, 3 H), 1.64−1.50 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 138.7, 133.4, 132.3, 129.5, 128.4, 127.6, 124.3, 122.5, 116.9, 115.6, 108.5, 92.1, 74.9, 74.7, 70.6, 53.8, 52.4, 40.4, 33.7, 30.1, 29.7; MS (EI, 70 eV) *m/z* (rel intensity) 449 (M^+, 17), 286 (51), 254 (11), 240 (15), 167 (10), 105 (14), 91 (100); HRMS (EI, 70 eV) calcd for $C_{27}H_{31}NO_5$ (M^+) 449.2202, found 449.2218.

(1′*R,3′*R**,4′*S**)-1-Methoxycarbonyl-1,2-dihydroindol-3-one-2-spiro-4′-(1′-benzyloxy-3′-vinylcyclohexane) (34).** *tert*-Butyllithium (0.13 mL of a 1.7 M solution in pentane, 0.22 mmol) was added in a dropwise fashion to a solution of the indoxyl **15** (48 mg, 0.14 mmol) in THF (2 mL) at −10 °C. After 15 min, a solution of methyl chloroformate (54 mg, 0.58 mmol) in THF (0.5 mL) was added at −10 °C. The reaction was quenched with aqueous saturated NH_4Cl (1 mL) after 30 min. The aqueous layer was extracted with ether (3×) and the etheral solution was washed with brine (1×), dried ($MgSO_4$), and concentrated. Chromatography (15% to 20% ethyl acetate/hexanes gradient) gave 50 mg (89%) of **34** as a yellow oil. R_f 0.26 (20% ethyl acetate/hexanes); IR ($CHCl_3$) 1701 (s), 1640 (m), 1608 (w), 1495 (m) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.16 (br s, 1 H), 7.68 (dd, J = 7.7, 0.7 Hz, 1 H), 7.65−7.58 (m, 1 H), 7.46−7.28 (m, 5 H), 7.12 (td, J = 7.1, 0.6 Hz, 1 H), 5.37 (ddd, J = 17.0, 10.2, 8.6 Hz, 1 H), 4.96 (d, J = 16.8 Hz, 1 H), 4.82 (dd, J = 10.1, 1.0 Hz, 1 H), 4.58 (s, 2 H), 3.90−3.70 (m, 5 H), 2.95−2.85 (m, 1 H), 2.50−2.25 (m, 2 H), 2.05−1.90 (m, 2 H), 1.50−1.40 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 152.5, 139.3, 136.9, 136.3, 128.2, 127.3, 127.26, 123.4, 123.2, 123.1, 117.4, 117.1, 71.9, 71.8, 69.6, 52.6, 38.6, 30.1, 24.4, 23.9; MS (EI, 70 eV) *m/z* (rel intensity) 391 (M^+, 12), 300 (28), 283 (27), 246 (36), 204, (37), 203 (40), 170 (12), 146 (22), 130 (21), 91 (100); HRMS (EI, 70 eV) calcd for $C_{24}H_{25}NO_4$ (M^+) 391.1784, found 391.1774.

(1′*S,3′*R**,4′*R**)-1-Methoxycarbonyl-1,2-dihydroindol-3-one-2-spiro-4′-[1′-benzyloxy-3′-(1,2-dihydroxyethyl)cyclohexane] (35).** *N*-Methylmorpholine *N*-oxide (24 mg, 0.21 mmol) was dissolved in a solution of the carbamate **34** (67 mg, 0.17 mmol) in acetone (5 mL), followed by addition of osmium tetroxide (122 mg of a 2.5 wt % solution in 2-propanol, 0.012 mmol). The reaction was stirred at room temperature overnight and quenched with aqueous 10% Na_2SO_3. The mixture was stirred for an additional 15 min and diluted with chloroform. The organic phase was dried ($MgSO_4$) and concentrated. Chromatography (60:40 hexanes/ethyl acetate to 60:30:10 hexanes/ethyl acetate/MeOH, gradient) gave 60 mg (82%) of **35** as an orange oil. Both ^{1}H and ^{13}C spectra showed a single diastereomer was formed. However, the stereochemistry of −**C**H(OH)(CH_2OH) could not be determined. R_f 0.22 (60:30:10 hexanes/ethyl acetate/MeOH); IR ($CHCl_3$) 3601 (m), 1698 (s), 1609 (s), 1469 (s), 1064 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1 H), 7.72−7.68 (m, 1 H), 7.64−7.58 (m, 1 H), 7.44−7.24 (m, 5 H), 7.14 (t, J = 7.3 Hz, 1 H), 4.55 (ABq, $\Delta\upsilon$ = 19.7 Hz, J_{AB} = 12.1 Hz, 2 H), 3.88−3.80 (m, 1 H), 3.82 (s, 3 H), 3.50−3.30 (m, 4 H), 2.95 (dt, J = 13.5, 4.0 Hz, 1 H), 2.36 (dt, J = 13.2, 2.2 Hz, 1 H), 2.24−2.04 (m, 2 H), 2.00−1.80 (m, 3 H), 1.40−1.30 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 152.6, 139.2, 136.8, 128.4, 128.3, 127.5, 127.4, 123.6, 123.2, 123.1, 117.4, 74.2, 71.9, 70.6, 69.7, 65.0, 52.7, 37.0, 28.4, 25.9, 23.6; MS (EI, 70 eV) *m/z* (rel intensity) 425 (M^+, 15), 393 (7), 334 (17), 286 (10), 256 (10), 204 (36), 192 (11), 145 (17), 125 (14), 91 (100); HRMS (EI, 70 eV) calcd for $C_{24}H_{27}NO_6$ (M^+) 425.1838, found 425.1831.

(1′*S,3′*R**,4′*R**,3*R**)-3-Hydroxy-1-methoxycarbonyl-3-(2-propenyl)-2,3-dihydro-1*H*-indole-2-spiro-4′-[1′-benzyloxy-3′-(1,2-dihydroxyethyl)cyclohexane] (36).** Allylmagnesium bromide (0.66 mL of a 1.0 M solution in ether, 0.66 mmol) was added to a solution of ketone **35** (81 mg, 0.19 mmol) in THF (5 mL) at −40 °C. The resulting solution was allowed to warm to room temperature slowly and stirred overnight. The reaction was quenched with aqueous saturated NH_4Cl and diluted with ether. The etheral solution was washed with water (1×) and brine (1×), dried ($MgSO_4$), and concentrated. The residue was chromatographed (60:30:10 hexanes/ethyl acetate/MeOH) to afford 80 mg (90%) of **36** as an orange oil. The relative configuration at C(3) was based on the X-ray crystal structure of a subsequent compound (**14**, vide infra).[10] R_f 0.17 (60:30:10 hexanes/ethyl acetate/MeOH); IR ($CHCl_3$) 3572 (m), 3394 (s), 1729 (m), 1639 (m), 1609 (m), 1483 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 1 H), 7.42−7.12 (m, 7 H), 7.00−6.95 (m, 1 H), 5.74−5.62 (m, 1 H), 5.42 (s, 1 H), 5.03 (dd, J = 10.2, 0.7 Hz, 1 H), 4.90 (dd, J = 17.1, 1.4 Hz, 1 H), 4.55 (ABq, $\Delta\upsilon$ = 37.3 Hz, J_{AB} = 12.1 Hz, 2 H), 3.84−3.80 (m, 1 H), 3.80 (s, 3 H), 3.53 (dt, J = 9.5, 2.8 Hz, 1 H), 3.42−3.25 (m, 2 H), 2.82 (t, J = 10.0 Hz, 1 H), 2.71 (dd, J = 13.6, 6.6 Hz, 1 H), 2.61 (td, J = 13.9, 2.9 Hz, 1 H), 2.40 (dd, J = 13.5, 7.3 Hz, 1 H), 2.20−1.50 (m, 6 H), 2.19 (dt, J = 13.6, 3.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 140.5, 139.3, 135.2, 133.5, 128.7, 128.3, 127.4, 127.3, 123.6, 122.4, 118.7, 115.1, 83.1, 75.0, 72.5, 69.7, 65.8, 52.4, 44.3, 39.6, 34.9, 27.1, 24.6; MS (DCI, NH_3) *m/z* (rel intensity) 485 ($[M + NH_4]^+$, 4), 450 (100), 426 (38), 408 (25), 394 (14), 342 (13), 318 (60), 282 (13), 204 (11), 91 (29); HRMS (DCI, NH_3) calcd for $C_{27}H_{37}N_2O_6$ ($[M + NH_4]^+$) 485.2652, found 485.2632.

Methyl Acetal 14. A solution of the triol **36** (50 mg, 0.11 mmol) in THF (5 mL) and pH 7 buffer (Na_2HPO_4/NaH_2PO_4, 1 mL) was cooled to 0 °C and sodium periodate (46 mg, 0.22 mmol) was added in one portion. The reaction was allowed to warm to room temperature slowly and stirred overnight. The reaction was then extracted with ether (3×) and the combined ether layers were washed with brine (1×), dried ($MgSO_4$), and concentrated to provide 45 mg (100%) of the crude lactol. The crude lactol was dissolved in methanol (2 mL) and 10-camphorsulfonic acid (124 mg, 0.53 mmol) was added in one portion at room temperature. After the solution was stirred for 1 h, most of the solvent was removed in vacuo and the residue was directly chromatographed (15% ethyl acetate/hexanes) to provide 29 mg (59% from the triol) of **14** as colorless needle crystals (mp 168.5−170 °C). The relative configuration was established by single-crystal X-ray diffraction analysis.[10] R_f 0.20 (15% ethyl acetate/hexanes); IR ($CHCl_3$) 1698 (s), 1602 (m), 1481 (s), 1442 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.82 (m, 1 H), 7.42−7.30 (m, 5 H), 7.30−7.26 (m, 2 H), 6.88 (td, J = 7.5, 1.1 Hz, 1 H), 5.80−5.70 (m, 1 H), 5.12 (br dt, J = 1.5, 17.2 Hz, 1 H), 4.97 (br dt, J = 1.8, 10.3 Hz, 1 H), 4.63 (s, 1 H), 4.54 (ABq, $\Delta\upsilon$ = 5.5 Hz, J_{AB} = 11.5 Hz, 2 H), 3.79 (m, 1 H), 3.55 (s, 3 H), 3.42 (dd, J = 6.2, 12.4 Hz, 1 H), 3.20−3.12 (m, 1 H), 2.84 (dd, J = 9.4, 16.0 Hz, 1 H), 2.70 (s, 3 H), 2.67 (td, J = 14.2, 5.8 Hz, 1 H), 2.31−2.20 (m, 1 H), 2.02−1.92 (m, 1 H), 1.90−1.80 (m, 1 H), 1.64 (tdd, J = 14.1, 5.1, 2.9 Hz, 1 H), 1.45 (ddd, J = 13.0, 10.8, 2.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 142.6, 138.8, 133.4, 131.7, 129.5, 128.3, 127.6, 127.4, 123.8, 122.1, 116.6, 115.7, 108.8, 92.3, 75.1, 70.5, 69.9, 53.8, 51.9, 44.5, 40.7, 30.7, 27.1, 22.2; MS (EI, 70 eV) *m/z* (rel intensity) 449 (M^+, 22), 368 (30), 333 (40), 290 (100), 268 (15), 192 (90), 175 (30), 150 (61), 91 (71); HRMS (EI, 70 eV) calcd for $C_{27}H_{31}NO_5$ (M^+) 449.2202, found 449.2207.

Lactone 37. A solution of freshly prepared[22] dimethylboron bromide (excess) in CH_2Cl_2 (0.10 mL) was added to a solution of **14** (10 mg, 0.023 mmol) in CH_2Cl_2 (1 mL) at −78 °C. After 1 h at −78 °C the reaction was quenched with a mixture of THF and saturated aqueous $NaHCO_3$ (1:1 v/v) at −78 °C. The reaction was then extracted with ether (3×) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in benzene (2 mL), treated with Fétizon's reagent[23] (Ag_2CO_3/Celite, ∼1 mmol of Ag_2CO_3/0.57 g of reagent), and heated at reflux. After 12 h, the reaction was cooled to room temperature, filtered through a pad of Celite, and concentrated. Chromatography (30% ethyl acetate/hexanes) of the residue yielded 7.0 mg (70%) of **37** as a yellow oil. R_f 0.17 (20% ethyl acetate/hexanes); IR ($CHCl_3$) 1767 (s), 1710 (s), 1605 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 18.4 Hz, 1 H), 7.48 (dd, J = 7.7, 0.7 Hz, 1 H), 7.42−7.20 (m, 6 H), 7.08 (td, J = 7.3, 0.7 Hz, 1 H), 5.82 (dddd, J = 17.2, 10.2, 8.8, 4.8

Hz, 1 H), 5.21 (app d, J = 17.2 Hz, 1 H), 5.14 (app d, J = 10.2 Hz, 1 H), 4.60 (ABq, $\Delta\nu$ = 22.0 Hz, J_{AB} = 11.2 Hz, 2 H), 3.82−3.76 (m, 1 H), 3.68 (s, 3 H), 3.61 (dd, J = 9.4, 6.8 Hz, 1 H), 3.24−3.15 (m, 1 H), 2.90 (dd, J = 15.3, 8.8 Hz, 1 H), 2.62−2.45 (m, 2 H), 2.14−1.98 (m, 2 H), 1.90 (dt, J = 15.1, 4.8 Hz, 1 H), 1.82−1.70 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 158.0, 153.0, 142.2, 138.4, 131.5, 131.0, 128.4, 127.73, 127.67, 127.6, 125.2, 123.4, 119.0, 116.2, 92.9, 73.08, 70.3, 52.5, 42.6, 38.9, 29.7, 26.8, 21.9; MS (CI, NH_3) *m/z* (rel intensity) 451 ([M + NH_4]$^+$, 14), 434 ([M + H]$^+$, 100), 419 (11), 360 (6), 332 (10), 77 (13); HRMS (CI, NH_3) calcd for $C_{26}H_{28}NO_5$ (M + H$^+$) 434.1967, found 434.1982.

Lactone 38. A solution of freshly prepared[22] dimethylboron bromide (excess) in CH_2Cl_2 (0.10 mL) was added to a solution of **33** (13 mg, 0.029 mmol) in CH_2Cl_2 (1 mL) at −78 °C. After 1 h at −78 °C the reaction was quenched with a mixture of THF and saturated aqueous $NaHCO_3$ (1:1 v/v) at −78 °C. The reaction was extracted with ether (3×) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in CH_2Cl_2 and treated with pyridinium chlorochromate (30 mg, 0.12 mmol) and silica gel (30 mg) at room temperature. After 6 h the reaction was diluted with ether and filtered through a pad of silica and concentrated. Chromatography (15% ethyl acetate/hexanes) of the residue afforded 8.0 mg (64%) of **38** as a yellow oil. R_f 0.50 (30% ethyl acetate/hexanes); IR ($CHCl_3$) 1768 (m), 1696 (m), 1442 (m), 1412 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.60 (m, 1 H), 7.55−7.50 (m, 1 H), 7.40−7.27 (m, 5 H), 7.10−7.00 (m, 2 H), 5.95−5.90 (m, 1 H), 5.26 (app d, J = 17.2 Hz, 1 H), 5.15 (app d, J = 10.3 Hz, 1 H), 4.60 (ABq, $\Delta\nu$ = 51.3 Hz, J_{AB} = 11.7 Hz, 2 H), 3.88 (s, 3 H), 3.87−3.72 (m, 1 H), 3.59 (dd, J = 10.2, 7.3 Hz, 1 H), 3.30 (ddt, J = 15.4, 4.4, 2.2 Hz, 1 H), 3.04 (dd, J = 15.6, 9.0 Hz, 1 H), 2.66−2.52 (m, 1 H), 2.44−2.12 (m, 3 H), 2.10−1.95 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 152.8, 141.6, 138.4, 131.6, 131.0, 128.5, 128.4, 127.8, 128.7, 127.6, 125.5, 123.5, 118.9, 115.9, 92.7, 77.2, 72.8, 70.6, 52.8, 44.0, 38.7, 30.9, 28.7, 24.3; MS (CI, NH_3) *m/z* (rel intensity) 434 ([M + H]$^+$, 100), 328 (9), 219 (10); HRMS (CI, NH_3) calcd for $C_{26}H_{28}NO_5$ ([M + H]$^+$) 434.1967, found 434.1954.

Ketone 39. Palladium hydroxide on carbon (1.0 mg, containing ∼20% Pd, 0.014 mmol) and glacial acidic acid (1 drop) was added to a solution of lactone **37** (15 mg, 0.035 mmol) in THF (0.5 mL) and absolute EtOH (1 mL). The reaction flask was purged with N_2, equipped with a hydrogen balloon, and stirred at room temperature. After 15 h the reaction mixture was filtered through a pad of Celite and concentrated. Without further purification, the residue was dissolved in CH_2Cl_2 (2 mL) and treated with pyridinium chlorochromate (35 mg, 0.14 mmol) and silica gel (35 mg) at room temperature. After 5 h the reaction was diluted with ether, filtered through a pad of silica gel, and concentrated. Chromatography (30% ethyl acetate/hexanes) afforded 10 mg (65%) of **39** as a yellow oil. The same reaction sequence cound be performed from **38** to give **39** in 77% yield. R_f 0.19 (30% ethyl acetate/hexanes); IR ($CHCl_3$) 1775 (s), 1717 (s), 1483 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8 Hz, 1 H), 7.45−7.30 (m, 2 H), 7.20−7.10 (m,1 H), 3.95 (s, 3 H), 3.40−3.10 (m, 3 H), 2.95 (dd, J = 18.0, 2.5 Hz, 1 H), 2.70−1.80 (m, 5 H), 1.40−1.00 (m, 2 H), 0.90 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 175.2, 153.4, 130.9, 128.6, 125.2, 124.0, 115.6, 92.8, 53.2, 46.6, 38.5, 38.3, 36.1, 29.7, 22.6, 17.3, 16.2; MS (EI, 70 eV) *m/z* (rel intensity) 343 (M$^+$, 35), 270 (56), 229 (88), 199 (20), 159 (51), 132 (100), 105 (55); HRMS (EI, 70 eV) calcd for $C_{19}H_{21}NO_5$ (M$^+$) 343.1420, found 343.1429.

Alcohol 40. A solution of olefin **14** (150 mg, 0.334 mmol) in CH_2Cl_2/MeOH (4 mL, 1:1 v/v) was treated with a solution of Sudan Red III in CH_2Cl_2 (1 drop) as an indicator of complete reaction.[26] The solution was cooled to −78 °C and ozone was bubbled through it for 20-s periods, between which the reaction was closely monitored by TLC. The ozone flow was stopped upon complete conversion of starting olefin **14** (R_f 0.24, 20% ethyl acetate/hexanes, stains black in anisaldehyde) to the ozonide intermediate (R_f 0.10, 20% ethyl acetate/hexanes, stains maroon in anisaldehyde). The reaction time was typically 60 s of elapsed ozone bubbling, during which time the color of the reaction turned from pink to white. Sodium borohydride (25 mg, 0.67 mmol) was then added at −78 °C and the solution was allowed to warm to room temperature and stirred for an additional 2 h. After TLC indicated conversion of the intermediate ozonide to alcohol **40** (R_f 0.07, 20% ethyl acetate/hexanes, stains green in anisaldehyde), the reaction was quenched with 10% $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were washed with brine (1×), dried (Na_2SO_4), and concentrated. Chromatography (20% to 50% ethyl acetate/hexanes gradient) afforded 127 mg (84%) of **40** as a colorless oil. R_f 0.40 (60:30:10 hexanes/ethyl acetate/MeOH); IR ($CHCl_3$) 3396 (m), 1699 (s), 1602 (m), 1484 (s), 1360 (s), 1113 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.2 Hz, 1 H), 7.45−7.20 (m, 7 H), 7.02 (td, J = 7.6, 0.8 Hz, 1 H), 4.71 (s, 1 H), 4.58 (s, 2 H), 4.18−4.06 (m, 1 H), 3.98−3.86 (m, 1 H), 3.86−3.78 (m, 1 H), 3.59 (s, 3 H), 3.38 (dd, J = 12.1, 6.5 Hz, 1 H), 2.80 (s, 3 H), 2.90−2.70 (m, 1 H), 2.70−2.50 (m, 2 H), 2.40−2.20 (m, 2 H), 2.20−2.05 (m, 1 H), 1.80−1.64 (m, 2 H), 1.64−1.45 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 142.1, 138.8, 132.3, 130.0, 129.6, 128.3, 127.7, 127.5, 124.1, 122.4, 115.8, 109.3, 93.7, 75.5, 70.6, 70.1, 59.4, 54.1, 52.0, 44.7, 38.4, 30.5, 27.7, 23.3; MS (EI, 70 eV) *m/z* (rel intensity) 453 (M$^+$, 100), 422 (5), 394 (9), 348 (26), 286 (15), 242 (11), 192 (13), 161 (17), 91 (79); HRMS (EI, 70 eV) calcd for $C_{26}H_{31}NO_6$ (M$^+$) 453.2151, found 453.2144.

Silyl Ether 41. *tert*-Butylchlorodiphenylsilane (113 mg, 0.413 mmol) was added to a solution of the alcohol **40** (125 mg, 0.276 mmol) and imidazole (28 mg, 0.413 mmol) in CH_2Cl_2 (6 mL) at room temperature and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2, washed with water (2×) and brine (1×), dried (Na_2SO_4), and concentrated. Chromatography (10% to 30% ethyl acetate/hexanes) yielded 167 mg (87%) of **41** as a white solid (mp 174−175 °C). R_f 0.25 (20% ethyl acetate/hexanes); IR ($CHCl_3$) 1701 (s), 1484 (s), 1360 (s), 1060 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1 H), 7.65−7.60 (m, 4 H), 7.45−7.10 (m, 13 H), 6.89 (td, J = 7.4, 1.1 Hz, 1 H), 4.59 (s, 1 H), 4.54 (d, J = 1.7 Hz, 2 H), 3.95−3.80 (m, 1 H), 3.75−3.62 (m, 2 H), 3.58 (s, 3 H), 3.35 (dd, J = 12.3, 6.0 Hz, 1 H), 2.95−2.80 (m, 1 H), 2.75−2.50 (m, 2 H), 2.70 (s, 3 H), 2.50−2.38 (m, 1 H), 2.26−2.18 (m, 1 H), 1.60−1.30 (m, 3 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 142.2, 138.8, 135.59, 135.58, 135.57, 133.7, 133.6, 131.6, 129.6, 129.4, 128.3, 127.7, 127.67, 127.64, 127.63, 127.61, 127.4, 123.7, 122.3, 115.6, 108.9, 92.8, 75.0, 70.6, 69.9, 59.9, 53.8, 51.9, 44.7, 39.6, 30.5, 27.2, 26.8, 22.8, 19.0; MS (EI, 70 eV) *m/z* (rel intensity) 691 (M$^+$, 5), 634 (54), 574 (75), 383 (12), 290 (9), 213 (38), 199 (44), 91 (100); HRMS (EI, 70 eV) calcd for $C_{42}H_{49}NO_6Si$ (M$^+$) 691.3329, found 691.331.

Alcohol 42. The benzyl ether **41** (20 mg, 0.029 mmol) was dissolved in THF (0.25 mL), EtOH (1 mL), and cyclohexene (0.25 mL). Palladium hydroxide on carbon (20% Pd, 4.0 mg, 0.006 mmol) was added and the mixture was heated at reflux. The reaction was followed by TLC until all of the starting material disappeared (4−20 h). The reaction mixture was cooled to room temperature, filtered though a short pad of Celite, and concentrated. Chromatography (1:4 ethyl acetate/hexanes to 5:5:1 ethyl acetate/hexanes/MeOH, gradient) gave 16 mg (92%) of **42** as a colorless oil. R_f 0.25 (40% ethyl acetate/hexanes); IR ($CHCl_3$) 3312 (br, m), 1703 (s), 1379 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 4 H), 7.60−7.45 (m, 1 H), 7.45−7.30 (m, 6 H), 7.30−7.18 (m, 2 H), 6.92 (td, J = 7.7, 0.7 Hz, 1 H), 4.58 (s, 1 H), 4.08−3.99 (m, 2 H), 3.89 (s, 3 H), 3.90−3.82 (m, 1 H), 3.20 (dd, J = 13.5, 6.6 Hz, 1 H), 2.64 (s, 3 H), 2.60−2.30 (m, 4 H), 2.20−2.00 (m, 1 H), 1.90−1.80 (m, 2 H), 1.47−1.36 (m, 1 H), 1.30−1.15 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.6, 129.7, 129.4, 127.7, 127.6, 124.0, 122.7, 115.2, 109.1, 92.9, 73.6, 64.4, 60.2, 53.7, 52.9, 44.1, 39.2, 33.3, 30.3, 26.8, 21.9, 19.0; MS (DCI, CH_4) *m/z* (rel

intensity) 630 ([M + C_2H_5]$^+$, 3), 601 (M^+, 8), 570 (36), 544 (75), 484 (100), 464 (17), 314 (27), 288 (12), 213 (36), 135 (18), 91 (17); HRMS (DCI, CH_4) calcd for $C_{37}H_{48}NO_6Si$ ([M + C_2H_5]$^+$) 630.3251, found 630.3254.

Ketone 43. *N*-Methylmorpholine *N*-oxide (32 mg, 0.28 mmol) was added to a solution of the alcohol **42** (138 mg, 0.229 mmol) in CH_2Cl_2 (5 mL) at room temperature. Tetrapropylammonium perruthenate (16 mg, 0.046 mmol) was then added, followed by powdered 4 Å molecular sieves (140 mg). After 1 h the reaction mixture was filtered though a short pad of silica gel, washed well with 1% MeOH/CH_2Cl_2, and concentrated. The residue was chromatographed (10% to 30% ethyl acetate/hexanes, gradient) to afford 130 mg (95%) of **43** as a colorless foam. R_f 0.25 (30% ethyl acetate/hexanes); IR ($CHCl_3$) 1711 (s), 1362 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (br d, J = 8.0 Hz, 1 H), 7.58−7.53 (m, 2 H), 7.53−7.48 (m, 2 H), 7.45−7.30 (m, 6 H), 7.30−7.20 (m, 1 H), 7.15 (dd, J = 7.3, 0.7 Hz, 1 H), 6.97 (td, J = 7.3, 0.7 Hz, 1 H), 4.56 (d, J = 1.8 Hz, 1 H), 3.85 (s, 3 H), 3.57−3.47 (m, 1 H), 3.47−3.37 (m, 1 H), 3.10−2.95 (m, 1 H), 2.98 (s, 3 H), 2.91 (td, J = 6.0, 1.8 Hz, 1 H), 2.90−2.70 (m, 1 H), 2.65 (td, J = 18.3, 5.5 Hz, 1 H), 2.42−2.10 (m, 5 H), 0.98 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 154.5, 140.2, 135.53, 135.51, 133.3, 131.6, 129.7, 129.5, 127.68. 127.64, 123.6, 123.1, 115.5, 108.8, 93.2, 74.1, 59.4, 54.3, 52.7, 52.2, 41.2, 39.6, 36.4, 29.6, 26.7, 24.2, 18.9; MS (DCI, NH_3) *m/z* (rel intensity) 617 ([M + NH_4]$^+$, 30), 568 (100), 542 (14), 510 (6), 482 (17), 312 (9), 284 (4), 214 (4); HRMS (DCI, NH_3) calcd for $C_{35}H_{45}N_2O_6Si$ ([M + NH_4]$^+$) 617.3047, found 617.3052.

2-(Trimethylsilyl)ethylcarbamate 48. 2-(Trimethylsilyl)-ethylchloroformate[31] (14 mg, 0.078 mmol) and diisopropylethylamine (10 mg, 0.078 mmol) were added to **47**[10] (19 mg, 0.026 mmol) in CH_2Cl_2 (1 mL) at room temperature. After 1 h, the reaction was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic phases were washed with brine (1×), dried (Na_2SO_4), and concentrated. Chromatography (10% to 20% ethyl acetate/hexanes, gradient) afforded 21 mg (91%) of **48** as three fractions of inseparable diastereomers and/or rotamers. R_f 0.55, 0.45, 0.32 (20% ethyl acetate/hexanes). The major fraction (R_f 0.32) contained 4 inseparable diastereomers and/or rotamers based on the number of acetal methine ^{1}H NMR resonances observed at 4.61−4.54 ppm. Data for the major fraction (R_f 0.32, 20% ethyl acetate/hexanes): IR (CH_2Cl_2) 1698 (s), 1694 (s), 1598 (m), 1482 (s), 1356 (s), 1103 (s), 1045 (s), 857 (m), 836 (m), 702 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62−7.54 (m, 5 H), 7.45−7.29 (m, 11 H), 7.28−7.15 (m, 2 H), 6.93−6.87 (m, 1 H), 4.61−4.54 (m, 1 H), 4.38−4.30 (m, 1 H × 0.33), 4.23−4.10 (m, 2 H), 4.04−3.96 (m, 1 H × 0.33), 3.96−3.89 (m, 1 H), 3.89−3.60 (m, 5 H), 3.51−3.60 (m, 2 H), 3.04−2.86 (m, 2 H), 2.81−2.62 (m, 2 H), 2.66 (s, 3 H), 2.56−2.28 (m, 2 H), 2.19−1.92 (m, 1 H), 1.89−1.80 (m, 1 H), 1.74−1.60 (m, 1 H), 1.49−1.42 (m, 1 H), 1.31−1.23 (m, 2 H), 1.19−1.10 (m, 1 H), 1.00 (s, 9 H), 0.03−0.01 (m, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.6, 135.6, 133.6, 132.3, 131.7, 131.6, 129.7, 129.4, 129.1, 127.7, 127.6, 127.3, 122.5, 115.6, 108.5, 74.5, 63.1, 62.7, 59.8, 53.8, 52.2, 42.2, 38.6, 33.1, 31.2, 29.7, 27.8, 26.84, 26.76, 19.0, 17.7, 17.5, −1.4; MS (FAB + Na, 70 eV) *m/z* (rel intensity) 915 ([M + Na]$^+$, 7), 861 ([M − OMe]$^+$, 2), 807 (12), 197 (43), 135 (100); HRMS (FAB + Na, 70 eV) calcd for $C_{50}H_{64}N_2O_7NaSi_2S$ ([M + Na]$^+$) 915.3871, found 915.3878.

Sulfoxide 49. *m*-Chloroperbenzoic acid (1.55 mL of a 0.077 M solution in CH_2Cl_2, 0.119 mmol) was added at −78 °C to a solution of phenyl sulfide **48** (106 mg, 0.119 mmol) in CH_2Cl_2 (2.0 mL) in a dropwise fashion. The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction was diluted with aqueous sodium bicarbonate and extracted with CH_2Cl_2 (4×). The combined organic phases were washed with brine (1×), dried (Na_2SO_4), and concentrated. Chromatography (20% to 50% ethyl acetate/hexanes, gradient) afforded 99 mg (92%) of a complex mixture of diastereomers and/or rotamers of **49** as a colorless foam. R_f 0.20 and 0.61 (50% ethyl acetate/hexanes); IR (CH_2Cl_2) 1690 (s), 1599 (m), 1484 (s), 1363 (s), 1327 (s), 1110 (s), 1103 (s), 1042 (m), 835 (m), 748 (m), 700 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (br, 2 H × 0.15), 8.10 (app d, J = 7.5 Hz, 2 H × 0.85), 7.46−7.65 (m, 8 H), 7.42−7.28 (m, 7 H), 7.26−7.19 (m, 1 H), 6.98−6.90 (m, 1 H), 4.86 (s, 1 H × 0.04), 4.84 (s, 1 H × 0.15), 4.78 (s, 1 H × 0.15), 4.75 (s, 1 H × 0.50), 4.70 (s, 1 H × 0.08), 4.39−4.10 (m, 2 H), 3.95 (s, 3 H × 0.15), 3.93 (s, 3 H × 0.85), 3.66−3.56 (m, 4 H), 3.64−3.56 (m, 2 H × 0.20), 3.54−3.44 (m, 2 H × 0.80), 3.18−3.10 (m, 1 H × 0.20), 3.05−2.95 (m, 1 H), 2.88−2.81 (m, 1 H), 2.73 (s, 3 H × 0.15), 2.71 (s, 3 H × 0.50), 2.65 (s, 3 H × 0.30), 2.70−2.59 (m, 2 H), 2.12 (dd, J = 14.0, 7.5 Hz, 1 H), 1.99−1.81 (m, 2 H), 1.36−1.15 (m, 3 H), 1.01−0.99 (m, 9 H), 0.05 (s, 9 H × 0.15), 0.04 (s, 9 H × 0.85); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.2, 142.8, 141.0, 135.7, 133.6, 130.3, 129.4, 129.3, 128.8, 127.6, 125.3, 124.9, 122.7, 115.5, 109.0, 74.5, 67.4, 64.9, 62.6, 59.8, 53.8, 52.4, 47.9, 46.4, 38.4, 30.6, 30.4, 29.7, 26.8, 24.8, 21.0, 19.0, 17.7, 14.3, −1.4; MS (FAB + Na, 70 eV) *m/z* (rel intensity) 931 ([M + Na]$^+$, 2), 849 (4), 805 ([M + Na − SOPh]$^+$, 3), 739 (3), 607 (5), 197 (42), 135 (100); HRMS (FAB + Na, 70 eV) calcd for $C_{50}H_{64}N_2O_8NaSi_2S$ ([M + Na]$^+$) 931.3820, found 931.3844.

Alkene 50. Sulfoxide **49** (51 mg, 0.056 mmol) was dissolved in tetrachloroethylene (3 mL) and pyridine (0.1 mL) and heated at reflux for 4 h. The reaction was cooled and diluted with CH_2Cl_2, washed with 10% aqueous Na_2CO_3 (2×) and brine (1×), dried (Na_2SO_4), and concentrated. Chromatography (10% to 20% ethyl acetate/hexanes, gradient) yielded 37 mg (87%) of alkene **50** as a clear colorless oil. Judging by variable-temperature ^{1}H NMR alkene **50** was a single diastereomer that at room temperature in $CDCl_3$ appeared as a 3:2 ratio of rotamers due to the *N*-Teoc carbamate (coalescence point: 60 °C) (see the Supporting Information). An additional set of rotamers from the methyl carbamate was observed in $CDCl_3$ with a coalescence point of about 20 °C.[33] R_f 0.31 (20% ethyl acetate/hexanes); IR (CH_2Cl_2) 1697 (s), 1600 (m), 1484 (s), 1359 (s), 1322 (m), 1110 (s), 1099 (s), 1043 (m), 836 (m), 702 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.59 (m, 3 H), 7.59−7.55 (m, 2 H), 7.43−7.28 (m, 8 H), 7.25−7.17 (m, 1 H), 6.95−6.89 (m, 1 H), 6.94−6.86 (br, 1 H), 5.84 (d, J = 6.4 Hz, 1 H × 0.40), 5.76 (d, J = 6.8 Hz, 1 H × 0.60), 4.60 (s, 1 H × 0.40), 4.57 (s, 1 H × 0.60), 4.40−4.31 (m, 1 H × 0.40), 4.28 (br s, 1 H × 0.60), 4.26−4.14 (m, 2 H), 3.88 (s, 3 H × 0.60), 3.87 (s, 3 H × 0.40), 3.84−3.77 (m, 1 H × 0.40), 3.72−3.64 (m, 1 H × 0.60), 3.56−3.42 (m, 1 H), 3.06−2.56 (m, 4 H), 2.69 (s, 3 H × 0.40), 2.68 (s, 3 H × 0.60), 1.93−1.82 (m, 1 H), 1.81−1.74 (m, 1 H × 0.60), 1.74−1.66 (m, 1 H), 1.51−1.45 (m, 1 H × 0.40), 1.43−1.35 (m, 1 H × 0.60), 1.29−1.24 (m, 1 H × 0.40), 1.21−1.13 (m, 1 H), 1.01 (s, 9 H × 0.60), 1.00 (s, 9 H × 0.40), 0.05 (s, 9 H × 0.60), 0.03 (s, 9 H × 0.40); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 153.8, 135.6, 135.5, 135.4, 133.7, 133.6, 133.3, 133.2, 129.7, 129.4, 129.2, 127.7, 127.57, 127.56, 124.6, 123.2, 122.5, 115.8, 115.6, 108.8, 74.9, 74.6, 69.1, 68.4, 63.7, 62.5, 59.9, 59.7, 54.9, 54.0, 53.9, 53.8, 52.5, 52.4, 46.4 (br), 38.7, 38.6, 35.2, 34.1, 31.7, 30.5, 26.8, 25.4 (br), 19.1, 18.2, 17.8, −1.4, −1.6; MS (FAB + Na, 70 eV) *m/z* (rel intensity) 805 ([M + Na]$^+$, 10), 751 ([M − OMe]$^+$, 5), 697 (19), 679 (10), 665 (14), 637 (6), 213 (14), 199 (21), 197 (41), 135 (100); HRMS (FAB + Na, 70 eV) calcd for $C_{44}H_{58}N_2O_7NaSi_2$ ([M + Na]$^+$) 805.3680, found 805.3709.

Lactol 52. Boron trichloride (0.014 mL of a 1.0 M solution in heptane, 0.014 mmol) was slowly added to a solution of methyl acetal **50** (8.7 mg, 0.011 mmol) in CH_2Cl_2 (1.0 mL) at −30 °C. After 45 min at −30 °C, the reaction was quenched with aqueous saturated NH_4Cl and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (1×), dried (Na_2SO_4), and concentrated. The residue was chromatographed (10% to 30% ethyl acetate/hexanes gradient) to afford 5.7 mg (67%) of **52** as a clear, colorless oil. Lactol **52** appeared in the ^{1}H NMR spectrum ($CDCl_3$) as a 2.3:1 mixture of carbamate rotamers. R_f 0.20 (30% ethyl acetate/hexanes); IR (CH_2Cl_2) 3407 (br), 1698 (s), 1695 (s), 1599 (m), 1483 (s), 1360 (s), 1318 (s), 1104 (s), 738 (m), 738 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.61 (m, 3 H), 7.60−7.50 (m, 2 H),

7.42−7.29 (m, 7 H), 7.24−7.20 (d, J = 7.7 Hz, 2 H × 0.70), 7.14 (d, J = 7.7 Hz, 1 H × 0.30), 6.93 (t, J = 7.3 Hz, 1 H), 6.82 (br, 1 H), 5.85 (d, J = 6.2 Hz, 1 H × 0.30), 5.78 (d, J = 6.2 Hz, 1 H × 0.70), 5.10 (d, J = 3.7 Hz, 1 H × 0.30), 5.09 (d, J = 3.3 Hz, 1 H × 0.70), 4.43−4.34 (m, 1 H × 0.30), 4.30−4.26 (m, 1 H × 0.70), 4.25−4.14 (m, 2 H), 3.89 (s, 3 H), 3.84−3.65 (m, 1 H), 3.62−3.47 (m, 1 H), 3.05−2.53 (m, 6 H), 2.00 (d, J = 3.3, 1 H × 0.30), 1.98 (d, J = 3.3 Hz, 1 H × 0.70), 1.86−1.68 (m, 2 H), 1.03 (s, 9 H × 0.70), 1.01 (s, 9 H × 0.30), 0.05 (s, 9 H × 0.70), 0.03 (s, 9 H × 0.30); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 135.7, 135.5, 135.4, 133.7, 133.6, 129.7, 129.6, 129.4, 127.7, 127.6, 123.4, 123.0, 115.9, 103.2, 69.1, 62.6, 59.8, 54.0, 52.6, 38.6, 33.9, 31.6, 30.3, 29.7, 26.8, 22.6, 19.1, 18.7, 18.2, 17.8, −1.4, −1.6; MS (FAB + Na, 70 eV) *m/z* (rel intensity) 791 ([M + Na]$^+$, 11), 751 ([M − OH]$^+$, 6), 683 (14), 679 (11), 197 (41), 135 (100); HRMS (FAB + Na, 70 eV) calcd for $C_{43}H_{56}N_2O_7NaSi_2$ ([M + Na]$^+$) 791.3524, found 791.3530.

Lactone 53. Pyridinium chlorochromate (10 mg, 0.046 mmol) was added to a solution of lactol **52** (15.3 mg, 0.020 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. After the solution was stirred for 1 h Celite (60 mg) was added, then the mixture was diluted with ether (2 mL) and stirred for 10 min. The mixture was filtered through a plug of silica gel and washed well with 2:1 ether/CH_2Cl_2. After concentration, the residue was chromatographed (10% to 20% ethyl acetate/hexanes, gradient) to yield 14.0 mg (92%) of **53**. Lactone **53** appeared in the ^{1}H NMR spectrum ($CDCl_3$) as a 4:1 mixture of carbamate rotamers. R_f 0.35 (30% ethyl acetate/hexanes); IR (CH_2Cl_2) 1775 (s), 1699 (s), 1603 (m), 1483 (s), 1360 (s), 1105 (s), 740 (m), 702 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (app d, J = 7.5 Hz, 3 H), 7.67−7.61 (m, 1 H), 7.56 (br, 1 H), 7.48−7.27 (m, 8 H), 7.12 (d, J = 7.6 Hz, 1 H × 0.20), 6.96 (t, J = 7.6 Hz, 1 H × 0.80), 6.89 (t, J = 7.6 Hz, 1 H × 0.20), 5.90 (d, J = 6.3 Hz, 1 H × 0.20), 5.83 (d, J = 6.3 Hz, 1 H × 0.80), 4.44−4.37 (m, 1 H × 0.20), 4.35−4.12 (m, 4 H), 4.08−4.05 (m, 1 H), 4.01−3.95 (m, 2 H), 3.90 (s, 3 H), 3.80−3.73 (m, 1 H × 0.20), 3.22 (t, J = 13.5 Hz, 1 H × 0.80), 3.15−3.08 (m, 1 H × 0.80), 3.07−2.89 (m, 2 H), 2.66 (td, J = 13.7, 4.6 Hz, 1 H × 0.20), 2.44 (br, 1 H × 0.80), 2.16 (ddd, J = 12.3, 7.6, 1.7 Hz, 1 H × 0.20), 2.07 (ddd, J = 13.4, 7.6, 2.2 Hz, 1 H × 0.80), 1.81 (br d, J = 14.5 Hz, 1 H × 0.80), 1.75 (br d, J = 15 Hz, 1 H × 0.20), 1.55−1.50 (m, 1 H × 0.20), 1.47−1.43 (m, 1 H × 0.80), 1.07 (s, 9 H × 0.80), 1.05 (s, 9 H × 0.20), 0.04 (s, 9 H × 0.80), 0.00 (s, 9 H × 0.20); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 153.8, 135.73, 135.66, 135.57, 135.45, 133.38, 133.34, 130.8, 129.65, 129.61, 127.89, 127.86, 127.72, 127.67, 123.4, 115.9, 73.6, 73.2, 68.5, 62.8, 59.7, 54.0, 53.0, 52.9, 36.2, 32.7, 29.3, 26.8, 26.8, 19.1, 17.8, −1.4, −1.6; MS (FAB + Na, 70 eV) *m/z* (rel intensity) 789 ([M + Na]$^+$, 11), 751 ([M − OH]$^+$, 6); HRMS (FAB + Na, 70 eV) calcd for $C_{43}H_{54}N_2O_7NaSi_2$ ([M + Na]$^+$) 789.3367, found 789.3393.

Alcohol 54. Lactone **53** (8.0 mg, 0.010 mmol) was dissolved in THF (1.0 mL) in a polyethylene vial and HF·pyridine (2 drops) was added by polyethylene pipet at room temperature. The reaction was monitored by TLC at 30-min intervals and additional HF·pyridine (2 drops) was added at the same time. After 4 h, the reaction was diluted with CH_2Cl_2 and carefully quenched with aqueous sodium bicarbonate. The aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with brine (1×), dried (Na_2SO_4), and concentrated. Chromatography (20% to 50% ethyl acetate/hexanes gradient) afforded 4.6 mg (84%) of **54** as a colorless film. Alcohol **54** appeared in the ^{1}H NMR spectrum ($CDCl_3$) as a 4:1 mixture of carbamate rotamers. R_f 0.16 (30% ethyl acetate/hexanes); IR (neat) 3440 (br), 1773 (s), 1698 (s), 1630 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.7 Hz, 1 H), 7.59 (d, J = 7.7 Hz, 1 H × 0.44), 7.36 (t, J = 7.6, 1 H), 7.11 (t, J = 7.5 Hz, 1 H), 6.80 (br s, 1 H), 5.91 (d, J = 6.6 Hz, 1 H × 0.16), 5.85 (d, J = 6.6 Hz, 1 H × 0.71), 4.30−4.21 (m, 2 H), 4.20−4.03 (m, 4 H), 3.93 (s, 3 H × 0.21), 3.92 (s, 3 H × 0.79), 3.19−2.97 (m, H × 2.4), 2.90−2.80 (m, 1 H), 2.79−2.70 (m, 1 H × 0.29), 2.52 (br, 1 H), 2.15 (ddd, J = 13.3, 7.6, 2.8 Hz, 1 H × 0.20), 2.09 (ddd, J = 13.1, 7.8, 2.2 Hz, 1 H × 0.80), 1.95−1.89 (br, 1 H), 1.65−1.54 (m, 1 H), 1.17−1.10 (m, 2 H × 0.20), 1.00 (dd, J = 9.2, 7.6 Hz, 2 H × 0.80), −0.06 (s, 9 H × 0.20), −0.05 (s, 9 H × 0.80); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 154.1, 132.7, 131.1, 125.5, 124.3, 123.7, 116.0, 73.7, 68.5, 63.9, 63.0, 58.73, 58.63, 54.9, 54.1, 53.1, 53.0, 42.1, 36.22, 36.05, 33.9, 32.6, 31.6, 30.6, 29.2, 24.0, 22.6, 18.3, 17.7, −1.4, −1.6; MS (FAB − Na$^+$, 70 eV) *m/z* (rel intensity) 551 ([M + Na]$^+$, 29), 529 ([M + H]$^+$, 15), 483 ([M + H − CO_2]$^+$, 32), 307 (15), 226 (12), 176 (19), 155 (24), 154 (100), 152 (13), 139 (14), 138 (32), 137 (59), 136 (95), 120 (15), 107 (26), 91 (20), 90 (19), 89 (27), 80 (19), 79 (10), 78 (15), 77 (30); HRMS (FAB − Na$^+$, 70 eV) calcd for $C_{27}H_{37}N_2O_7Si$ ([M + H]$^+$) 529.2370, found 529.2382.

Mesylate 55. Diisopropylethylamine (0.032 mL of a 1.0 M solution in CH_2Cl_2, 0.032 mmol) and methanesulfonyl chloride (0.032 mL of a 1.0 M solution in CH_2Cl_2, 0.032 mmol) were added at 0 °C to a solution of alcohol **54** (8.4 mg, 0.016 mmol) in CH_2Cl_2 (0.15 mL). After 1 h, the reaction was diluted with water and extracted with CH_2Cl_2 (4×). The combined organic phases were washed with brine (1×), dried (Na_2SO_4), and concentrated. Chromatography (10% to 50% ethyl acetate/hexanes, gradient) afforded 8.5 mg (89%) of **55** as a colorless film. Mesylate **55** appeared in the ^{1}H NMR spectrum ($CDCl_3$) as a 7:1 mixture of carbamate rotamers. R_f 0.36 (50% ethyl acetate/hexanes); IR (CH_2Cl_2) 1776 (s), 1695 (s), 1484 (s), 1360 (s), 1326 (s), 1175 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (br, 1 H), 7.53 (d, J = 7.2 Hz, 1 H), 7.54−7.52 (m, 1 H × 0.15), 7.41 (t, J = 8 Hz, 1 H × 0.15), 7.39 (td, J = 8.9, 1.2 Hz, 1 H), 7.17 (t, J = 7.3 Hz, 1 H × 0.15), 7.15 (td, J = 7.3, 1.0 Hz, 1 H × 0.80), 6.79 (br, 1 H), 5.93 (d, J = 6.8 Hz, 1 H × 0.15), 5.85 (d, J = 6.6 Hz, 1 H × 0.80), 4.72−4.50 (m, 2 H), 4.32−4.25 (m, 1 H × 0.80), 4.25−4.20 (m, 1.65 H), 4.78−4.14 (m, 1.80 H), 3.94 (s, 3 H × 0.15), 3.93 (s, 3 H × 0.85), 3.30−3.16 (m, 1.25 H), 3.13 (s, 3 H × 0.85), 3.10 (s, 3 H × 0.15), 2.95−2.94 (m, 2 H), 2.87−2.80 (m, 1 H × 0.18), 2.56 (br, 1 H), 2.18 (ddd, J = 13.6, 8.0, 2.4 Hz, 1 H × 0.15), 2.10 (ddd, J = 13.4, 7.4, 2.2 Hz, 1 H × 0.85), 1.91 (br app d, J = 16 Hz), 1.36−1.21 (m, 1 H), 1.14−1.08 (m, 2 H × 0.15), 1.00 (dd, J = 9.5, 7.1 Hz, 2 H × 0.85), 0.08 (s, 9 H × 0.15), 0.05 (s, 9 H × 0.85); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 154.0, 131.5, 125.0, 124.5, 123.9, 116.3, 107.6, 91.4, 73.5, 68.3, 65.3, 62.9, 54.0, 53.1, 42.0, 37.8, 32.6, 29.2, 17.7, −1.4, −1.6; MS (FAB + Na$^+$, 70 eV) *m/z* (rel intensity) 629 ([M + Na]$^+$, 46), 607 ([M + H]$^+$, 3), 579 ([M + H − HC≡CH]$^+$, 12), 483 ([M − CH_2CH_2OMs]$^+$, 69), 411 (17), 365 (10), 228 (10), 226 (24), 214 (26), 176 (11), 168 (12), 166 (10), 154 (64), 136 (100), 107 (27), 77 (33); HRMS (FAB + Na, 70 eV) calcd for $C_{28}H_{38}N_2O_9NaSi$ ([M + Na]$^+$) 629.1965, found 629.1995.

2,5-Dihydropyrrole·Trifluoroacetate Salt (56) and (±)-Lapidilectine B (1). Trifluoroacetic acid (0.75 mL) was added to a solution of mesylate **55** (9.4 mg, 0.016 mmol) in CH_2Cl_2 (2.0 mL) at room temperature. After 30 min the reaction was diluted with benzene and concentrated. The residue was codistilled twice with benzene and evaporated under high vacuum for 30 min. Examination of the residue with ^{1}H NMR showed the clean conversion of mesylate **55** to the 2,5-dihydropyrrole·trifluoroacetate salt **56**. The residue was taken up in CH_3CN (2.0 mL) and diisopropylethylamine (19 mg, 0.15 mmol) and allowed to stir at room temperature. After 2 h, the solution was heated to 60 °C for 10 h in the dark. The reaction mixture was allowed to cool to room temperature, diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3×). The combined organic phases were washed with brine (1×), dried ($MgSO_4$), and concentrated. The residue was chromatographed (20% ethyl acetate/hexanes to ethyl acetate, gradient) on silica gel to afford 4.2 mg (76%) of (±)-lapidilectine B (**1**) as a clear, colorless oil that matched the analytical data of natural (+)-lapidilectine B.[37] The analytical data and spectra for synthetic and natural lapidilectine B were previously reported by us in our initial communication.[10] Partial data for **56**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (br s, 1 H), 8.91 (br s, 1 H), 7.53 (d, J = 8.4 Hz, 1 H), 7.35 (d, J = 7.7 Hz, 1 H), 7.31 (t, J

= 8.4 Hz, 1 H), 7.07 (t, J = 7.7 Hz, 1 H), 6.46 (d, J = 6.2 Hz, 1 H), 5.87 (d, J = 5.9 Hz, 1 H), 4.32−4.18 (m, 2 H), 4.11 (br s, 2 H), 3.84 (s, 3 H), 3.59 (t, J = 7.3 Hz, 1 H), 2.83 (s, 3 H), 2.78−2.65 (m, 1 H), 2.64−2.45 (m, 4 H), 2.27−2.02 (m, 3 H), 1.15 (s, 9 H).

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Supporting Information Available: General experimental procedures, copies of ^{1}H spectra for all new compounds without elemental analysis, experimental procedures for the synthesis of **10** and **11**, procedures for the conversion of **29** to **31**, and variable-temperature ^{1}H NMR spectra of **50**. This material is available free of charge via the Internet at http://pubs.acs.org.

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