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Asymmetric Total Synthesis of (+)-Cannabisativine

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The asymmetric total synthesis of natural (+)-cannabisativine **1** was completed in 19 steps and 7% overall yield. The key synthetic intermediate **29** was prepared with a high degree of stereocontrol in 12 steps starting from chiral 1-acylpyridinium salt **10**. Addition of zinc enolate **11** to pyridinium salt **10** furnished dihydropyridone **12** containing two contiguous stereocenters of the correct absolute configuration. Luche reduction of ketone **16** afforded diol **17** in high yield (96%) and excellent diastereoselectivity. The Mukaiyama−Michael reaction of pyridones **27a/b** with *O*-silyl ketene acetal **32** gave phenyl selenyl ketones **33a/b** with complete stereoselectivity. Elimination of *cis*-*β*-hydroxyselenides **34** and **35** effected the regiocontrolled preparation of tetrahydropyridine derivative **29**. Several approaches to the macrocyclic ring closure of the 13-membered ring were investigated, ultimately leading to the completion of an asymmetric synthesis of the target compound with a high degree of stereocontrol.

Macrocyclic polyamine alkaloids containing the biogenetic base spermidine have been isolated from a variety of plant sources.[1] Many of these natural products contain a 13-membered lactam ring system that is annulated to a disubstituted tetrahydropyridine ring (i.e., cannabisativine (**1**), anhydrocannabisativine (**2**), and palustrine (**3**)). However, lactam alkaloids possessing a 17-, 18-, and 22-membered spermidine skeleton with a monosubstituted piperidine ring such as oncinotine (**5**) and isooncinotine (**6**) have also been isolated (Figure 1).[2,3] These piperidine-based alkaloids have received considerable attention in recent years due to their unique architecture which presents significant synthetic challenges.[4−7] Perhaps the most unusual and challenging alkaloid of this class is (+)-cannabisativine which was isolated from the roots and leaves of the common marijuana plant, *Cannibis sativa* L.[8] Cannabisativine was the first reported nonquaternary alkaloid possessing the pyrido[1,2-*d*]-[1,5,9]-triazacyclotridecine nucleus isolated from *Cannabis sativa* L. The relative structure of cannabisativine was determined by single-crystal X-ray analysis,[8] and the absolute stereochemistry was established through synthesis of the unnatural (−)-enantiomer.[4c] Recently, we reported the first asymmetric synthesis of natural (+)-cannabisativine based on the addition of a metallo enolate to a chiral 1-acylpyridinium salt.[9] Herein, we provide a complete account of our work in this area.

Results and Discussion

Our retrosynthetic approach to (+)-cannabisativine is outlined in Scheme 1, where the natural product was envisioned as arising from key intermediate **7**. The acetic acid moiety and the double bond of **7** would then come from a highly diastereoselective 1,4-addition to the enone functionality of **8** followed by a regioselective ketone to alkene conversion. Finally, dihydropyridone **8** would be prepared by elaboration of dioxolanone **9**, which in turn would come from the addition of zinc enolate **11** to chiral 1-acylpyridinium salt **10** (TCC = *trans*-2-(α-cumyl)-cyclohexyl).

The synthesis of (+)-cannabisativine began with the addition of the zinc enolate **11**, prepared by deprotonation of 2,2-diethyl-1,3-dioxolan-4-one[10] with LDA followed by transmetalation with $ZnCl_2$, to chiral 1-acylpyridinium

(1) For reviews of macrocyclic spermidine alkaloids, see: (a) Matsuyama, H. *Yuki Gosei Kagaku Kyokaishi* **1981**, *39*, 1152. (b) Wasserman, H. H.; Wu, J. S. *Heterocycles* **1982**, *17*, 581. (c) Guggisberg, A.; Hesse, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1983; Vol. 22, Chapter 3, p 85.

(2) For the isolation of (−)-oncinotine and (−)-isooncinotine and related alkaloids, see: (a) Badawi, M. M.; Guggisberg, A.; van den Broek, P.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1813. (b) Guggisberg, A.; Badawi, M. M.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 414.

(3) For the synthesis of (−)-oncinotine and (−)-isooncinotine and related alkaloids, see: (a) Ina, H.; Ito, M.; Kibayashi, C. *J. Org. Chem.* **1996**, *61*, 1023. (b) Ina, H.; Ito, M.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1995**, 1015. (c) Bienz, S.; Guggisberg, A.; Walchli, R.; Hesse, M. *Helv. Chim. Acta* **1988**, *71*, 1708. (d) Schneider, F.; Bernauer, K.; Guggisberg, A.; van den Broek, P.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 434. (e) Guggisberg, A.; van den Broek, A.; Hesse, M.; Schmid, H.; Schneider, F.; Bernauer, K. *Helv. Chim. Acta* **1976**, *59*, 3013.

(4) For racemic syntheses of cannabisativine, see: (a) Ogawa, M.; Kuriya, N.; Natsume, M. *Tetrahedron Lett.* **1984**, *25*, 969. (b) Wasserman, H. H.; Leadbetter, M. R. *Tetrahedron Lett.* **1985**, *26*, 2241. For an enantioselective synthesis of the unnatural (−)-enantiomer of cannabisativine, see: (c) Hamada, T.; Zenkoh, T.; Sato, H.; Yonemitsu, O. *Tetrahedron Lett.* **1991**, *32*, 1649.

(5) For the synthesis of anhydrocannabisativine, see: (a) Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240. (b) Wasserman, H. H.; Pearce, B. C. *Tetrahedron Lett.* **1985**, *26*, 2237.

(6) For the synthesis of palustrine, see: Natsume, M.; Ogawa, M. *Chem. Pharm. Bull.* **1984**, *32*, 3789.

(7) For the synthesis of dihydropalustrine, see: (a) Natsume, M.; Ogawa, M.; Yoda, I.; Shiro, M. *Chem. Pharm. Bull.* **1984**, *32*, 812. (b) Wasserman, H. H.; Leadbetter, M. R.; Kopka, I. E. *Tetrahedron Lett.* **1984**, *25*, 2391.

(8) (a) Lotter, H. L.; Abraham, D. J.; Turner, C. E.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. J. *Tetrahedron Lett.* **1975**, *7*, 2815. (b) Turner, C. E.; Hsu, M.-F. H.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. L. *J. Pharm. Sci.* **1976**, *65*, 1084.

(9) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855.

10.1021/jo049724+ CCC: $27.50
Published on Web 04/29/2004

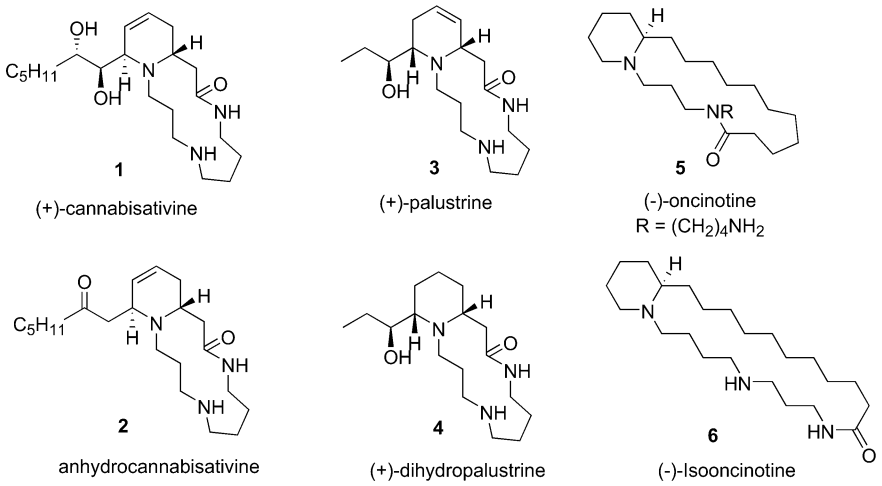
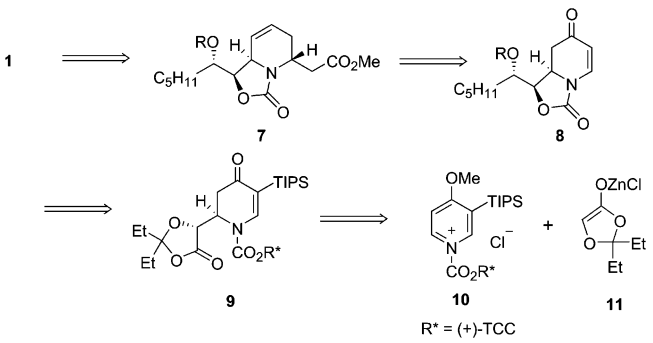
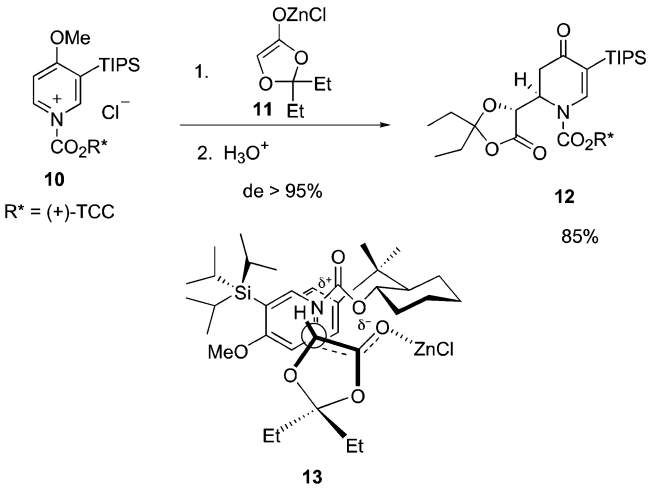


FIGURE 1.

SCHEME 1. Retrosynthetic Approach to (+)-Cannabisativine

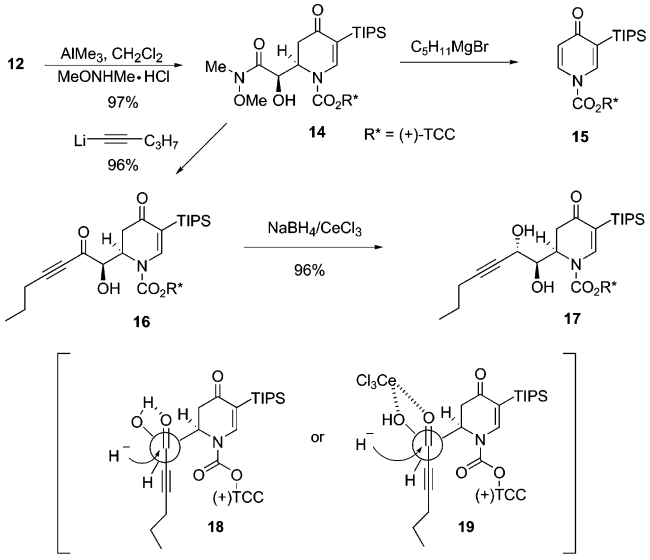


SCHEME 2



salt **10** (Scheme 2).[9,11−12] The stereochemistry of an enolate (*E*/*Z*) can often determine the relative configuration (syn/anti) of two new chiral centers in a product derived from the addition of a prochiral enolate to an electrophile having diastereotopic faces. Accordingly, we

SCHEME 3

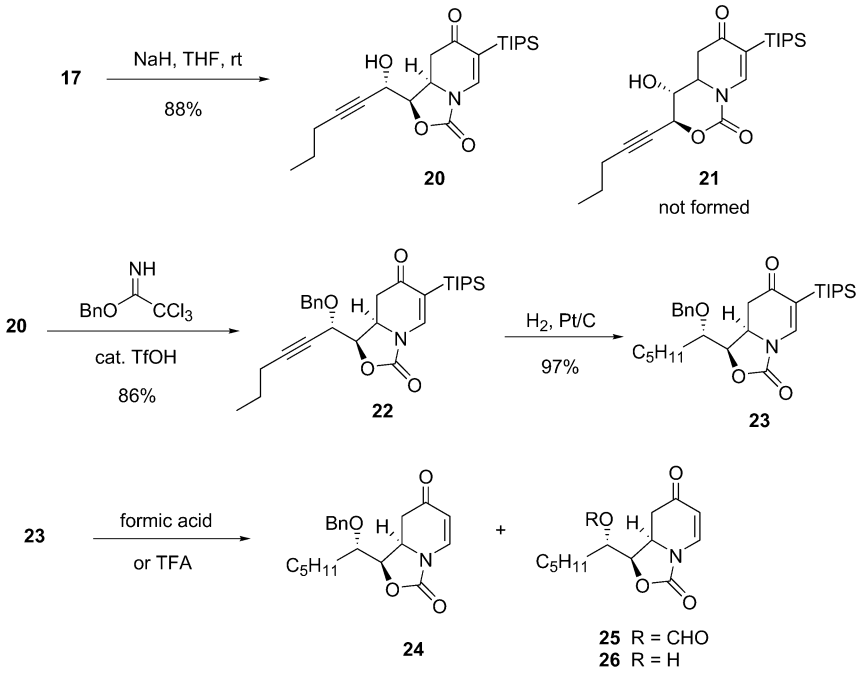


were pleased that the addition of **11** to **10** provided dihydropyridone **12** as the major diastereomer (>95 de) in 85% isolated yield. The stereochemistry was determined to be anti by ^{1}H NMR and single-crystal X-ray analysis. The facial selectivity can be explained by assuming an acyclic transition state (**13**) with a synclinal orientation. This transition-state conformation may be favored due to reduced nonbonded interactions with the pyridinium ring and electrostatic attraction of the positively charged nitrogen and the negative enolate oxygen.[13]

Reaction of **12** with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of $AlMe_3$[14] provided the Weinreb's amide **14** in near quantitative yield (Scheme 3).[12] Reaction of **14** with pentylmagnesium bromide at low temperature (−78 °C) or at rt did not give the expected ketone. Instead, the only identifiable reaction product was pyridone **15** resulting from a retro-Michael elimination of the chiral side chain. Attempts to install the alkyl side chain by the direct addition of pentylmagnesium bromide to dioxolanone **12** also afforded **15** as

(10) Fairbanks, A. J.; Sinay, P. *Tetrahedron Lett.* **1995**, *36*, 893.
(11) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.
(12) For an account on the diastereoselective addition of prochiral metallo enolates to chiral 1-acylpyridinium salts, see: Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J.; Concolino, T. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 2651.
(13) An acyclic TS is proposed on the basis of an apparent low-energy conformation that does not favor a chelate; however, some sort of chelation control cannot be ruled out.

SCHEME 4



the only identifiable reaction product in low isolated yield. With these results in hand, our attention turned to the addition of the less basic pentynyl anion to amide **14**. Addition of pentynylmagnesium bromide to **14** provided the desired ketone **16** in 80% yield. Better results were obtained with the corresponding pentynyllithium. Addition of pentynyllithium (5 equiv) to **14** at −78 °C followed by warming to −25 °C gave **16** in 96% isolated yield. Reduction of **16** under standard Luche conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) provided diol **17** as a single diastereomer in 96% yield, where the diastereoselectivity was determined to be greater than 95% by HPLC analysis. Our rationalization of this observed diastereoselectivity can best be explained by Cram's rule,[15] where hydride is delivered from the least sterically demanding side of intermediate **18**, although a chelation-controlled intermediate **19** cannot be ruled out and would also be attacked by hydride from the same side.

To elaborate the dihydropyridone functionality, protection of diol **17** was required. Initial attempts (base/BnBr, Ag_2O/BnBr, $BnOCNHCCl_3$/cat. acid) to protect **17** as its bis-benzyl ether proved difficult and led to multiple reaction products. Interestingly, reaction of **17** first with NaH followed by the addition of BnBr did not give the expected bis-benzyl ether, but gave carbamate **20** in 58% yield (Scheme 4). Optimization of the reaction conditions led to the isolation of **20** in 88% yield when **17** was treated with sodium hydride in THF. In addition, the released chiral auxiliary, (+)-TCC,[16] was recovered in 94% yield. There was no evidence that the six-membered carbamate **21** was formed under these reaction conditions.[17] The remaining secondary hydroxyl group of **20** was protected as its benzyl ether using benzyl trichloroacetimidate/cat. TfOH[18] and gave **22** in 86% yield. The previous steps were accomplished in high overall yield due to the C-5 TIPS group which protected the dihydropyridone against nucleophilic attack. With the TIPS group still protecting the enone system, clean reduction of the alkyne bond was achieved via catalytic hydrogenation over Pt/C which gave **23** in 97% yield.

Removal of the TIPS protecting group of dihydropyridone **23** was first accomplished by protodesilylation using refluxing formic acid[19] for 30 min and gave bicyclic carbamate **24** in 60% yield. The major byproduct of this reaction was identified as formate ester **25** (36%). Evidently the harsh reaction conditions resulted in cleavage of the benzyl ether with concomitant reaction with formic acid to give **25**. Attempts to conduct the deprotection at a lower temperature (50 °C) did not improve the ratio of **24**:**25**, and, when conducted at rt, no reaction was observed. After considerable experimentation, it was discovered that the yield of **24** was improved to 77% by reaction with refluxing 1:1 TFA/$CHCl_3$. Under these conditions, cleavage of the benzyl ether was minimized but not totally eliminated, as alcohol **26** was also formed in 10% yield. The separation of **24** from formate ester **25** or alcohol **26** could easily be effected by chromatography.

It was envisioned that the double bond of the target molecule could be installed regioselectively through the use of selenium chemistry (Scheme 5). It was anticipated that reaction of dihydropyridone **24** with phenylselenyl chloride would give phenylselenide **27**. Subsequent 1,4-

(14) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685 and references therein.

(15) For a discussion of such rules, see: Eliel, E. L. *The Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 68−74. For reviews of the stereochemistry of addition to carbonyl compounds, see: (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

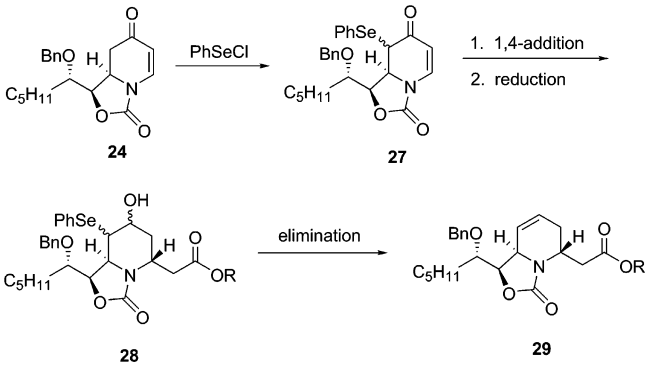
(16) (a) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656. (b) (+)- and (−)-TCC alcohols are available from Aldrich Chemical Co.

(17) For a complete analysis of structures of type **21**, see: Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035.

(18) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.

(19) Comins, D. L.; Huang, S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett.* **2001**, *3*, 469.

SCHEME 5



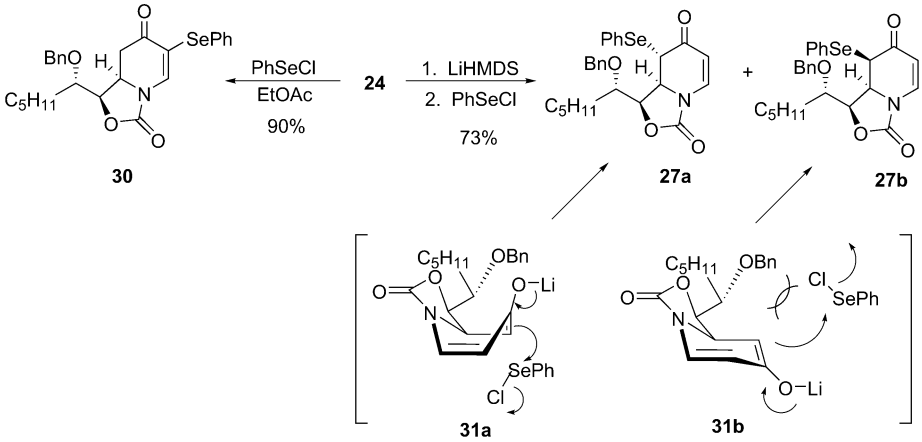
conjugate addition of an acetic acid unit to the enone moiety followed by reduction of the resulting ketone would provide *β*-hydroxyselenide **28**. Olefin formation by elimination of the *β*-hydroxyselenide moiety would give key intermediate **29** possessing the double bond and all of the required stereochemical features of cannabisativine.

To this end, phenylselenyl chloride was added to **24** in EtOAc at rt, but the expected selenide **27a/b** was not obtained (Scheme 6).[20] Instead, phenylselenide **30** was isolated in 90% yield. To avoid this undesired reaction pathway, deprotonation of **24** with LiHMDS followed by quenching with phenylselenyl chloride afforded an inseparable mixture (3.5:1) of diastereomeric selenides **27a** and **27b** in 73% combined yield. We assume that the major diastereomer **27a** arises from selenation occurring through a boat-type transition state **31a**. Because the *β*-face is blocked by the benzyl ether and a pentyl group, attack of the phenylselenyl group occurs from the α-face, giving predominantly the equatorial phenylselenyl group in the isolated product. However, some selenation occurs through chair transition state **31b** leading to the minor isomer **27a** with the phenylselenyl group occupying an axial orientation. The structures of isomers **27a/b** were rigorously determined by NMR analysis.

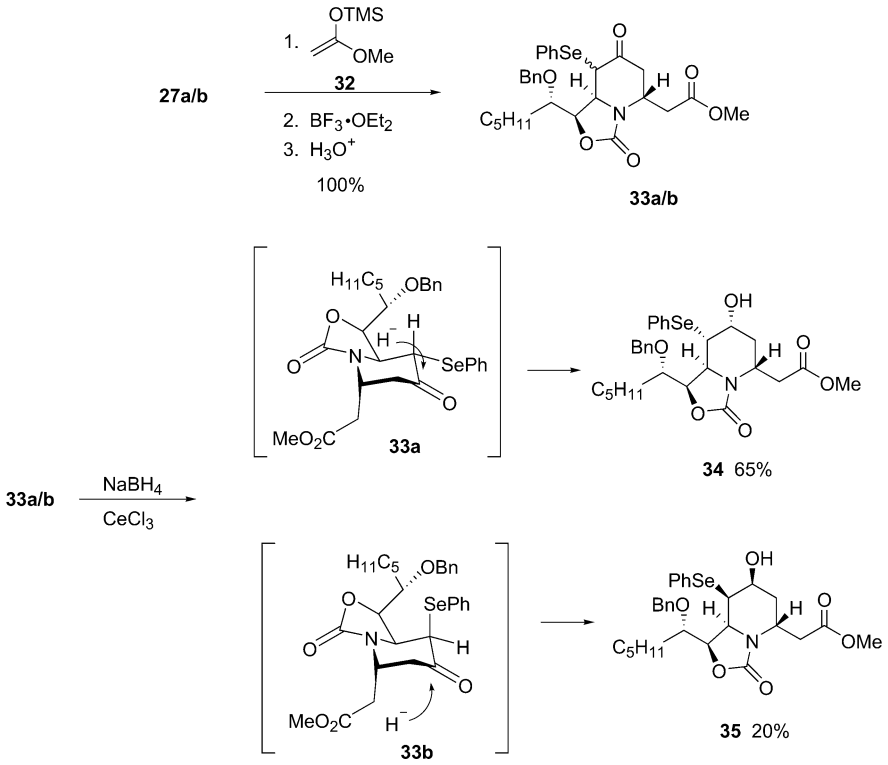
At this stage, a latent acetic acid unit needed to be introduced stereoselectively at the C-6 position of **27** (Scheme 7). Treatment of the diastereomeric mixture of **27a** and **27b** with BF_3 etherate in the presence of *O*-silyl ketene acetal **32**[21] under standard Mukaiyama−Michael reaction conditions,[20,22] followed by acidic workup, afforded ketones **33a/b** as an inseparable mixture of diastereomers in quantitative yield. The stereochemical outcome of this reaction is in full agreement with similar studies from these laboratories where 1,4-addition to a 1-acyl-2,3-dihydropyridone enone moiety occurs via stereoelectronically controlled axial attack of the nucleophile.[23] Because the C-2 side chain of the piperidine ring occupies an equatorial position, axial attack leads to **33** where the C-2 substituent and the C-6 acetic acid unit are in a trans-relationship. Luche reduction of ketones **33a/b** gave an 85% combined yield of two alcohols **34** and **35** which could easily be separated from one another by chromatography. Interestingly, the reduction of the diastereomeric ketones **33a/b** gave exclusively *cis*-*β*-hydroxyselenides **34** and **35** as the sole reaction products. Evidently, the α-phenylselenyl functionality is sufficiently large to cause hydride delivery from the least sterically demanding side of the ketone carbonyl. In the case of **33a**, the equatorial phenylselenyl group caused the hydride to be delivered from the *β*-face to give **34**. In the case of **33b**, the axial phenylselenyl group directed hydride to be delivered from α-face leading to **35**. The stereochemistry of each individual isomer was assigned by NMR experiments which clearly showed a cis-orientation of the hydroxyl and phenylselenyl groups.

While *trans*-*β*-hydroxyselenides are known to eliminate to olefins under a variety of reaction conditions (TsOH, $HClO_4$, MsCl/TEA, TFAA/TEA), *cis*-*β*-hydroxyselenides fail to undergo this type of elimination.[24] Attempted elimination of **34** or **35** under conditions known to affect this type of reaction led to recovered starting materials in all cases, thus providing further support for our stereochemical assignment. Earlier model studies[20] indicated that the desired elimination could be obtained by taking advantage of the fact that both phenylselenyl groups and thiocarbamates are effective radical precursors. Reaction of **34** with 1,1′-thiocarbonyldiimidazole in refluxing toluene containing a catalytic amount of DMAP provided thiocarbamate **36** in 91% yield (Scheme 8). On treatment with Bu_3SnH/AIBN in refluxing toluene (10 min), **36** was converted to **29** in 91% yield. It was more convenient to directly add Bu_3SnH/AIBN to the crude reaction mixture containing **36** to afford tetrahydropyridine **29** in high overall yield. In similar fashion, reaction of *β*-hydroxyselenide **35** under identical reaction conditions afforded thiocarbamate **37** in 95% yield. Reduction of **37** with Bu_3SnH/AIBN also gave **29** in high yield. A

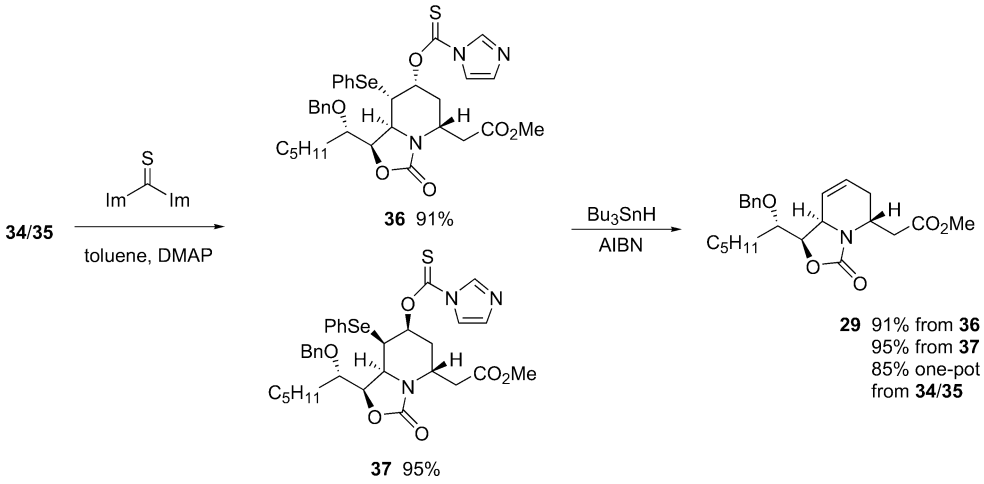
SCHEME 6



SCHEME 7



SCHEME 8



one-pot procedure was developed whereby the crude mixture containing **34**/**35** was subjected to thiocarbamate formation and in situ reduction to give **29** in an 85% overall yield.

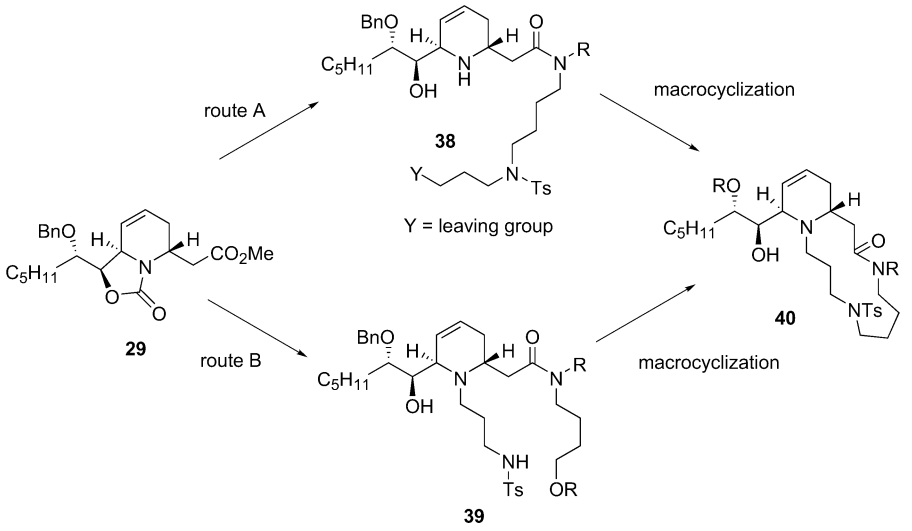
At this point, there were two possible synthetic approaches considered for macrocyclization and completion of the synthesis (Scheme 9). The first approach (route A) would rely on the preparation of an intermediate of type **38** where macrocyclization might occur between the secondary amine and a suitable leaving group to provide macrocycle **40**. The second approach (route B) would be to follow a more classical macrocyclization procedure between tosylated amine of **39** and the tethered mesylate. Because route A appeared to be more novel and direct, this approach was pursued first.

Exploration of route A began with the synthesis of the requisite side chain (Scheme 10). Treatment of **41**[25] with methyl acrylate in MeCN in the presence of anhydrous K_2CO_3 gave Michael addition product **42** in quantitative yield. Reduction of **42** with LAH afforded amino alcohol **43** in 70% yield. Reductive amination of **43** with benzal-

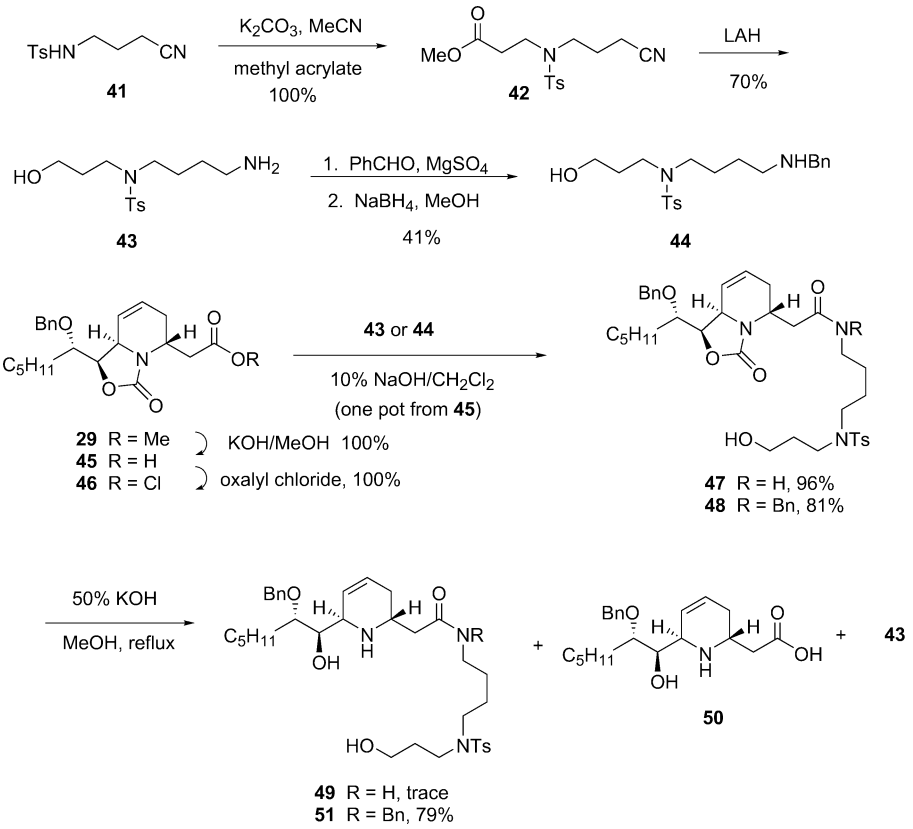
(20) Comins, D. L.; Kuethe, J. T. *Org. Lett.* **1999**, *1*, 1031.
(21) The 1-methoxy-1-trimethylsiloxyethene (**32**) was prepared by a literature procedure: Collins, D. J.; Cullen, J. D. *Aust. J. Chem.* **1988**, *41*, 735.
(22) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163.
(23) For leading references, see: Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press, Inc.: Greenwich, CT, 1996; Vol. 2, pp 251−294 and references therein.
(24) (a) Reich, H. J.; Chow, F. *J. Chem. Soc., Chem. Commun.* **1975**, 790. (b) Rémion, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1976**, *17*, 1385.

(25) Hoffmann-LaRoche; Neth. Appl. 6,603,655, 1966; *Chem. Abstr.* **1966**, *66*, 37642.

SCHEME 9



SCHEME 10



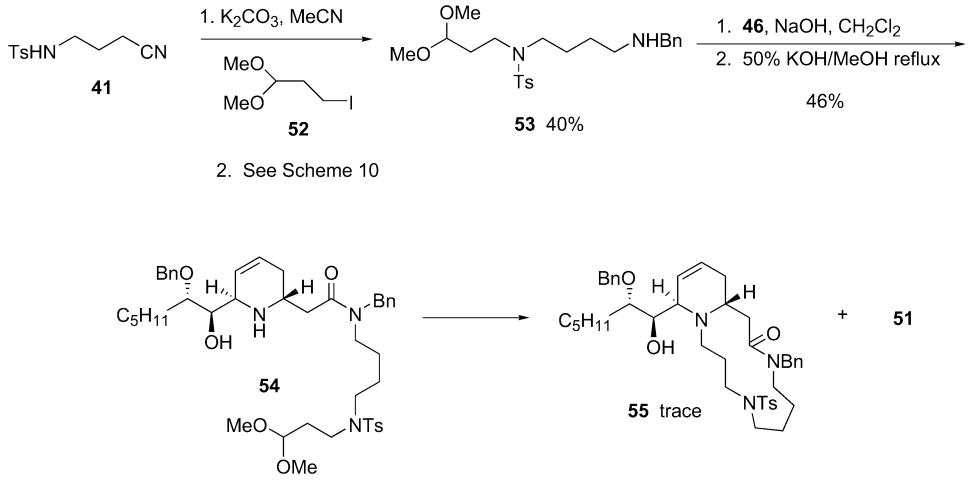
dehyde yielded *N*-benzylamino alcohol **44** in 41% yield. Hydrolysis of ester **29** gave acid **45** which was converted to its acid chloride **46** with oxalyl chloride. Reaction of **46** with either **43** or **44** using Schotten−Baumann conditions (NaOH, CH_2Cl_2, rt) gave amides **47** (96%) and **48** (81%). Attempted opening of the oxazolidinone ring of **47** with 50% KOH/MeOH at reflux only afforded trace amounts of the desired aminodiol **49**. The major byproducts of the reaction were identified as amino acid **50**[26] and recovered amine **43** where hydrolysis of the amide was competitive with hydrolysis of the carbamate. On the other hand, reaction of tertiary amide **48** with 50% KOH/MeOH at reflux gave the desired aminodiol **51** in 79% yield. Unfortunately, despite a considerable amount of effort to form either the primary triflate, mesylate, or tosylate and have it undergo macrocyclization under dilute reaction conditions in the presence of various bases, only complex mixtures of products resulted.[27]

The reductive cyclization of **54** was also investigated (Scheme 11). Reaction of **41** with iodide **52**[28] in the presence of K_2CO_3 in MeCN followed by reduction with LAH and then reductive amination with benzaldehyde

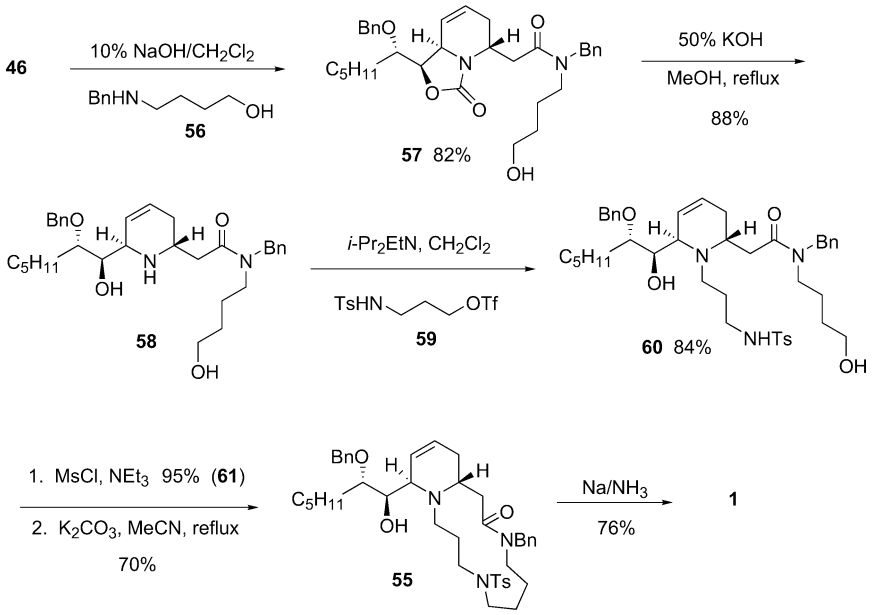
(26) Amino acid **50** could not be isolated cleanly due to its high solubility in water and low solubility in most organic solvents.

(27) For a similar approach to macrocyclization, see: Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425.

SCHEME 11



SCHEME 12



gave amino dimethyl acetal **53** in 40% overall yield. Reaction of **53** with acid chloride **46** and subsequent hydrolysis afforded amino alcohol **54** in 46% unoptimized yield. Hydrolysis of dimethyl acetal **54** with aqueous acid, buffering the reaction mixture to pH 5.5 with citrate: phosphate buffer, and subsequent treatment with $NaBH_3$-CN[3a] gave only trace amounts of macrocyclization product **55**. The major product was identified as aminodiol **51** in all attempts. Although considerable experimentation with regard to both reaction times and temperature was investigated, the yield of **55** never rose above 3% and this approach was abandoned.

Having been unsuccessful in obtaining an acceptable macrocyclic ring closure through route A, we elected to pursue route B in an effort to complete the synthesis (Scheme 12). Reaction of acid chloride **46** with *N*-benzyl protected amino alcohol **56**[29] gave the expected amide **57** in 82% overall yield from ester **29**. Hydrolysis of the oxazolidinone ring of **57** afforded aminodiol **58** in 88% yield. Treatment of **58** with triflate **59** in the presence of Hunig's base yielded the tertiary amine **60** in 84% yield.[30] After conversion of the primary alcohol of **60** to the corresponding mesylate with methanesulfonyl chloride in the presence of triethylamine (95%), cyclization was carried out in acetonitrile/K_2CO_3 to provide lactam **55** in 70% yield. Global deprotection using sodium in liquid ammonia gave a 76% yield of (+)-cannabisativine (**1**), which exhibited spectral data in agreement with reported data for authentic material.[8] The melting point (165−166 °C) and optical rotation, $[\alpha]^{23}_D$ +51.8 (*c* 0.425, $CHCl_3$), were also in agreement with the literature values [mp 167−168 °C; $[\alpha]_D$ +55.1 (*c* 0.53, $CHCl_3$)].[8]

In conclusion, the first asymmetric synthesis of (+)-cannabisativine (**1**) was accomplished in 19 synthetic steps with a high degree of stereocontrol. Key to the success of this synthesis was the metallo enolate addition to chiral 1-acylpyridinium salt **10**, which allowed for the

(28) Clive, D. L.; Chua Paul, C.; Wang, Z. *J. Org. Chem.* **1997**, *62*, 7028.
(29) Lesher, G. Y.; Surrey, A. R. *J. Am. Chem. Soc.* **1955**, *77*, 636.
(30) Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

preparation of dihydropyridone building block **12** containing the two required contiguous stereocenters of the correct absolute stereochemistry. Conversion of dihydropyridone **17** to bicyclic carbamate **24** set the stage for a highly diastereoselective addition of an acetic acid unit with complete control of stereochemistry. Elimination of *cis*-*β*-hydroxyselenides **34** and **35** allowed for the regiocontrolled preparation of tetrahydropyridine **29**, a key intermediate which was efficiently converted to the natural product in seven steps. The strategy described herein should be useful for the enantioselective preparation of other complex piperidine-containing alkaloids. Efforts in this direction are ongoing in our laboratories.

Experimental Section

(2*S*)-2-((5*S*)-2,2-Diethyl-1,3-dioxolan-4-one)-1-[((1*S*,2*R*)-2-(1-methyl-1-phenylethyl) cyclohexyloxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (12). To a solution of LDA, prepared at −23 °C from diisopropylamine (1.85 mL, 13.18 mmol) and *n*-butyllithium (6.13 mL, 13.18 mmol, 2.15 M in hexane) in 25 mL of THF, was added dropwise 1.90 g (13.18 mmol) of 2,2-diethyl-1,3-dioxolan-4-one[10] in 2 mL of THF at −78 °C. After 10 min, 13.18 mL of a 1 M solution of anhydrous zinc chloride in ether was added, and stirring was continued for 20 min. The resulting zinc enolate was cannulated into a solution of pyridinium salt **10** at −78 °C, which was formed from 1.0 g (3.77 mmol) of 4-methoxy-3-(triisopropylsilyl)pyridine and 3.77 mL of a 1 M solution of (1*S*,2*R*)-2-(α-cumyl)cyclohexyl chloroformate in toluene at −23 °C for 40 min. After the mixture was stirred for 3 h, 25 mL of aqueous 10% HCl was added. The mixture was allowed to warm to rt and was extracted with ethyl acetate (3 × 20 mL). The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to give 2.05 g (85%) of **12** as a white solid: mp 141−142 °C (hexane); $[\alpha]^{23}_D$ +17.2 (*c* 0.5, $CHCl_3$); IR (thin film) 2948, 1796, 1718, 1662, 1588, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 0.80−1.39 (m, 38H), 1.59−2.08 (m, 8H), 2.24 (m, 1H), 2.47 (dd, 1H, *J* = 16.4 and 7.2 Hz), 3.35 (m, 1H), 4.15 (m, 1H), 4.95 (m, 1H), 7.12 (m, 1H), 7.30 (m, 4H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 7.7, 11.4, 19.0, 21.6, 24.9, 25.9, 26.9, 29.6, 30.0, 31.3, 33.6, 37.2, 39.6, 51.3, 52.7, 75.1, 78.5, 110.8, 115.6, 125.3, 128.1, 128.3, 147.8, 151.7, 152.4, 169.9, 194.9. Anal. Calcd for $C_{37}H_{57}NO_6Si$: C, 69.44; H, 8.98; N, 2.19. Found: C, 69.37; H, 8.92; N, 2.20.

2-(2*S*-Hydroxy-*N*-methoxy-*N*-methylacetamide)-1-[((1*S*,2*R*)-2-(1-methyl-1-phenylethyl) cyclohexyloxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (14). To a suspension of 2.29 g (23.44 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 75 mL of CH_2Cl_2 at 0 °C was added 7.81 mL (2.0 M in toluene, 15.6 mmol) of trimethylaluminum. The mixture was warmed to rt and stirred for 45 min. A solution of 1.00 g (1.56 mmol) of **12** in 3 mL of CH_2Cl_2 was added dropwise, and the mixture was stirred at rt for 1.5 h. The reaction was carefully quenched with 3 mL of 10% HCl and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 35% EtOAc/hexanes) to afford 931 mg (97%) of **14** as a colorless solid: mp 174−175 °C (EtOAc/hexanes); $[\alpha]^{23}_D$ +18.4 (*c* 0.44, $CHCl_3$); IR (thin film) 3439, 2936, 2859, 1714, 1661, 1578, 1385, 1327, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 1.02−1.38 (m, 33H), 1.67−2.20 (m, 6H), 3.05 (br s, 1H), 3.24 (s, 3H), 3.68 (s, 3H), 4.33−4.62 (br m, 1H), 4.88 (m, 1H), 7.13 (m, 1H), 7.28 (m, 4H), 7.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 11.5, 19.2, 22.5, 24.9, 26.0, 27.3, 30.8, 33.9, 36.7, 40.0, 51.3, 54.0, 55.1, 61.7, 69.7, 78.4, 110.6, 125.1, 125.2, 125.6, 128.1, 148.1, 148.6, 152.1, 195.9. Anal. Calcd for $C_{34}H_{54}N_2O_6Si$: C, 66.41; H, 8.85; N, 4.56. Found: C, 66.30; H, 8.85; N, 4.58.

(2*R*)-2-((1*R*)-Hydroxy-1-hept-3-yn-2-one)-1-[((1*S*,2*R*)-2-(1-methyl-1-phenylethyl) cyclohexyoxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (16). To a solution of 440 mg (0.716 mmol) of **14** in 30 mL of THF at −78 °C was added dropwise 7.20 mL (3.58 mmol) of a 0.5 M solution of 1-pentynyllithium. The reaction was allowed to slowly warm to −25 °C and quenched with saturated aqueous NH_4Cl. The mixture was extracted with ethyl acetate (3 × 15 mL). The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 20% EtOAc/hexanes) to give 427 mg (96%) of **16** as a colorless oil: $[\alpha]^{23}_D$ −36.6 (*c* 0.99, $CHCl_3$); IR (neat) 3469, 2935, 2849, 2208, 1719, 1666, 1580, 1463, 1383, 1324, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 1.02−1.38 (m, 33H), 1.68 (m, 5H), 2.09 (m, 4H), 2.41 (m, 3H), 3.03 (m, 1H), 3.13 (m, 1H), 4.12 (m, 1H), 4.91 (m, 1H), 7.13 (m, 1H), 7.28 (m, 4H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 11.4, 13.8, 19.0, 21.3, 21.6, 24.9, 26.0, 27.0, 31.3, 33.4, 37.4, 39.7, 51.3, 54.5, 78.7, 81.6, 101.2, 111.3, 125.3, 125.6, 128.3, 147.9, 151.8, 152.3, 186.3, 195.6; HRMS calcd for $C_{37}H_{55}NO_5Si$, 622.3928 $[M + H]^+$; found, 622.3927 $[M + H]^+$.

(2*R*)-2-((1*R*,2*S*)-Dihydroxy-hept-3-yne)-1-[((1*S*,2*R*)-2-(1-methyl-1-phenylethyl) cyclohexyloxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (17). To a solution of 100 mg (0.161 mmol) of **16** in 7 mL of methanol was added 66 mg (0.177 mmol) of cerium(III) chloride heptahydrate in one portion. After being stirred for 10 min, the mixture was cooled to −50 °C, and 9 mg (0.241 mmol) of sodium borohydride was added. The reaction mixture was stirred for an additional 10 min, quenched with 10 mL of water, and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 30% EtOAc/hexanes) to give 96 mg (96%) of **17** as a colorless oil: $[\alpha]^{23}_D$ +49.5 (*c* 0.28, $CHCl_3$); IR (neat) 3422, 2931, 2868, 2241, 1718, 1650, 1577, 1462, 1389, 1326, 1248, 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 0.97−1.40 (m, 33H), 1.49−1.89 (m, 7H), 1.92−2.52 (m, 7H), 2.87 (m, 1H), 3.49 (m, 1H), 4.14 (m, 1H), 4.89 (m, 1H), 7.15 (m, 1H), 7.30 (m, 4H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 11.4, 13.8, 19.1, 21.1, 22.2, 24.9, 26.0, 27.2, 29.9, 31.0, 33.7, 37.1, 39.7, 51.2, 52.8, 64.8, 75.1, 89.5, 111.3, 125.5, 128.4, 148.2, 152.2, 153.3, 196.8; HRMS calcd for $C_{37}H_{57}NO_5Si$, 624.4084 $[M + H]^+$; found, 624.4077 $[M + H]^+$.

(1*R*,1′*S*,9*R*)-1-(1′-Hydroxyhex-2-ynyl)-1,2,8,8a-tetrahydro-6-triisopropylsilyl-2-oxaindolizine-3,7-dione (20). To a solution of 91 mg (0.146 mmol) of **17** in 15 mL of THF was added 12 mg (0.306 mmol) of 60% NaH in mineral oil. After 3 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 20% EtOAc/hexanes) to give 52 mg (88%) of **20** as a clear oil: $[\alpha]^{23}_D$ −284.6 (*c* 0.45, $CHCl_3$); IR (neat) 3414, 2938, 2865, 1778, 1659, 1568, 1399, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *δ* 0.98 (t, 3H, *J* = 7.3 Hz), 1.06 (m, 18H), 1.33 (m, 3H), 1.52 (m, 2H), 2.19 (t, 2H, *J* = 7.1 Hz), 2.53 (d, 1H, *J* = 6.8 Hz), 2.71 (dd, 1H, *J* = 15.4 and 4.0 Hz), 3.29 (t, 1H, *J* = 15.4 Hz), 4.63 (m, 2H), 4.77 (d, 1H, *J* = 8.3 Hz), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 11.2, 13.8, 18.9, 20.9, 22.0, 37.2, 53.6, 62.7, 75.4, 78.2, 91.1, 112.9, 143.7, 152.1, 195.7; HRMS calcd for $C_{22}H_{35}NO_4Si$, 406.2414 $[M + H]^+$; found, 406.2421 $[M + H]^+$.

(1*R*,1′*S*,9*R*)-1-((1′-Phenylmethoxy)hex-2-ynly)-1,2,8,8a-tetrahydro-6-triisopropylsilyl-2-oxaindolizine-3,7-dione (22). To a solution of 955 mg (2.35 mmol) of **20** in 50 mL of anhydrous ether was added 773 mg (3.10 mmol) of benzyl 2,2,2-trichloroacetimidate followed by 3 drops of triflic acid. The mixture was stirred at rt for 5 h and then quenched with 10 mL of 5% HCl. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 15% EtOAc/hexanes) to give 1.00 g (86%) of **22** as a colorless oil: $[\alpha]^{23}_D$ −118.1 (*c* 0.21, $CHCl_3$); IR (neat) 2941, 2864, 2241, 1782, 1659, 1397, 1265, 1210, 1064 cm^{-1}; ^1H NMR ($CDCl_3$, 300

MHz) δ 1.01 (m, 21H), 1.29 (m, 3H), 1.56 (m, 2H), 2.22 (t, 2H, J = 7.0 Hz), 2.72 (dd, 1H, J = 15.4 and 4.2 Hz), 3.32 (t, 1H, J = 15.4 Hz), 4.55 (m, 3H), 4.74 (dd, 1H, J = 8.0 and 2.4 Hz), 4.83 (d, 1H, J = 11.6 Hz), 7.28 (m, 5H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.2, 13.8, 18.9, 20.9, 27.0, 38.0, 53.8, 69.0, 71.3, 73.4, 77.4, 91.9, 112.1, 127.8, 128.0, 128.7, 137.0, 143.7, 152.1, 196.1; HRMS calcd for $C_{29}H_{41}NO_4Si$, 496.2883 $[M + H]^+$; found, 496.2860 $[M + H]^+$.

(1*R*,1′*S*,9*R*)-1-((1′-Phenylmethoxy)hexane)-1,2,8,8a-tetrahydro-6-triisopropylsilyl-2-oxaindolizine-3,7-dione (23). To a solution of 360 mg (0.726 mmol) of **22** in 10 mL of ethyl acetate was added 160 mg (2.17 mmol) of lithium carbonate followed by 10 mg of 5% Pt/C. The mixture was stirred under a balloon pressure of hydrogen for 12 h. The reaction mixture was filtered over Celite and concentrated under reduced pressure. The crude residue was purified by radial PLC (silica gel, 20% EtOAc/hexanes) to give 352 mg (97%) of **23** as a colorless oil: $[\alpha]^{23}_D$ −160.0 (*c* 0.15, $CHCl_3$); IR (neat) 2942, 2860, 1772, 1659, 1570, 1464, 1397, 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 6.6 Hz), 1.04 (m, 18H), 1.34 (m, 9H), 1.74 (m, 2H), 2.65 (dd, 1H, J = 15.0 and 4.2 Hz), 2.97 (t, 1H, J = 15.0 Hz), 4.49 (d, 1H, J = 10.5 Hz), 4.60 (m, 4H), 7.31 (m, 5H), 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.3, 14.4, 19.1, 22.9, 24.5, 29.9, 32.2, 38.4, 54.5, 72.6, 78.0, 112.8, 128.4, 128.9, 137.6, 144.2, 152.3, 196.3; HRMS calcd for $C_{29}H_{45}NO_4Si$, 500.3196 $[M + H]^+$; found, 500.3173 $[M + H]^+$.

(1*R*,1′*S*,9*R*)-1-((1′-Phenylmethoxy)hexane)-1,2,8,8a-tetrahydro-2-oxaindolizine-3,7-dione (24). To 284 mg (0.57 mmol) of **23** was added 15 mL of a 1:1 mixture of TFA/$CHCl_3$. The mixture was heated to reflux for 12 h, cooled to rt, and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 40% EtOAc/hexanes). The first product (150 mg, 77%) to elute was identified as **24** and isolated as a colorless solid: mp 68−69 °C (EtOAc); $[\alpha]^{22}_D$ −265.9 (*c* 0.085, $CHCl_3$); IR (thin film) 2933, 2858, 1773, 1666, 1596, 1438, 1359, 1262, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, 3H, J = 6.4 Hz), 1.35 (m, 6H), 1.73 (m, 2H), 2.69 (dd, 1H, J = 15.9 and 4.2 Hz), 2.97 (t, 1H, J = 15.9 Hz), 3.83 (q, 1H, J = 5.2 Hz), 4.47 (d, 1H, J = 11.0 Hz), 4.64 (m, 3H), 5.47 (d, 1H, J = 7.9 Hz), 7.34 (m, 5H), 7.60 (d, 1H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.7, 24.3, 29.7, 32.1, 37.7, 54.7, 72.3, 77.0, 108.7, 128.1, 128.3, 128.8, 137.4, 138.8, 152.1, 192.3. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.67; H, 7.44; N, 3.97.

The second product (18.7 mg, 13%) to elute, (1*R*,1′*S*,9*R*)-1-((1′-hydroxy)hexane)-1,2,8,8a-tetrahydro-2-oxaindolizine-3,7-dione (**26**), was isolated as a white solid: mp 112−113 °C (EtOAc/hexanes); $[\alpha]^{22}_D$ −392.5 (*c* 0.24, $CHCl_3$); IR (thin film) 3447, 2931, 2860, 1777, 1665, 1598, 1445, 1363, 1330, 1264, 1182, 1102, 989 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (m, 3H), 1.31 (m, 5H), 1.54 (m, 2H), 1.73 (m, 2H), 2.79 (dd, 1H, J = 16.0 and 4.1 Hz), 2.99 (t, 1H, J = 16.0 Hz), 3.93 (m, 1H), 4.51 (m, 1H), 4.62 (m, 1H), 5.49 (d, 1H, J = 7.8 Hz), 7.59 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 24.7, 31.8, 33.6, 37.6, 54.8, 69.8, 78.6, 108.8, 139.1, 152.1, 193.1. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.71; H, 7.59; N, 5.43.

(1*R*,1′*S*,8*S*,9*R*)-1-((1′-Phenylmethoxy)hexane)-1,2,8-tetrahydro-8-phenylselenyl-2-oxaindolizine-3,7-dione (27a/b). To a solution of 183 mg (0.533 mmol) of **24** in 20 mL of THF at −78 °C was added 0.64 mL of a 1.0 M solution of lithium hexamethyldisilazide in THF. The reaction mixture was stirred for 15 min at −78 °C and then allowed to warm to −40 °C for 30 min. The mixture was cooled to −78 °C, and 122 mg (0.637 mmol) of phenylselenyl chloride in 1 mL of THF was added dropwise. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and then extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 30% EtOAc/hexanes) to give 195 mg (73%) as an inseparable 3:1 mixture of diastereomers (**27a/b**) as a colorless oil: $[\alpha]^{24}_D$ −206.2 (*c* 0.095, $CHCl_3$); IR (neat) 2931, 1783, 1666, 1601, 1437, 1325, 1249, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (major isomer) 0.86 (t, 3H, J = 6.9 Hz), 1.17−1.61 (m, 7H), 1.77 (m, 1H), 3.89 (m, 1H), 4.08 (d, 1H, J = 15.0 Hz), 4.43 (dd, 1H, J = 15.0 and 7.3 Hz), 4.55 (d, 1H, J = 11.4 Hz), 4.60 (d, 1H, J = 11.4 Hz), 4.91 (dd, 1H, J = 7.3 and 2.1 Hz), 5.47 (d, 1H, J = 7.9 Hz), 7.33 (m, 8H), 7.48 (d, 1H, J = 7.9 Hz), 7.56 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 25.3, 30.6, 31.8, 44.3, 58.0, 72.7, 78.2, 79.0, 107.2, 125.6, 128.2, 128.7, 129.5, 129.6, 135.8, 136.4, 137.5, 138.3, 152.2, 188.5; HRMS calcd for $C_{26}H_{29}NO_4Se$, 500.1342 $[M + H]^+$; found, 500.1341 $[M + H]^+$.

(1*R,1′*S**,9*R**)-1-(1′-Phenylmethoxy)heptane)-1,2,8,8a-tetrahydro-6-phenylselanyl-2-oxaindolizine-3,7-dione (30).** To a solution of 25 mg (0.073 mmol) of **24** in 7 mL of EtOAc was added 17 mg (0.087 mmol) of phenylselenyl chloride. The resulting mixture was stirred for 3 h at rt and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 30% EtOAc/hexanes) to give 33 mg (90%) of **30** as a colorless oil: IR (neat) 2931, 2860, 1778, 1672, 1572, 1401, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (m, 3H), 1.37 (m, 6H), 1.69 (m, 2H), 2.87 (d, 1H, J = 16.0 Hz), 3.08 (t, 1H, J = 15.1 Hz), 3.82 (m, 1H), 4.44 (m, 1H), 4.61 (m, 3H), 7.29 (m, 8H), 7.44 (m, 2H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.7, 24.4, 29.8, 32.0, 37.7, 54.6, 72.5, 77.1, 111.4, 128.1, 128.3, 128.8, 129.7, 133.4, 137.2, 141.4, 151.4, 152.0, 169.3, 188.8.

(1*R*,1′*S*,5*R*,8*S*,9*S*)-1-((1′-Phenylmethoxy)hexane)-8-phenylselenyl-1,2,5,6,6a,8-hexahydro-2-oxaindolizine-3,5-dione Acetic Acid Methyl Ester (33a/b). To a solution of 70 mg (0.140 mmol) of **27a/b** and 103 mg (0.704 mmol) of 1-methoxy-1-trimethylsiloxyethene (**32**)[21] in 15 mL of CH_2Cl_2 at −78 °C was added dropwise 22 mg (0.154 mmol) of boron trifluoride etherate. The reaction mixture was allowed to stir at −78 °C for 30 min and then quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and concentrated under reduced pressure. The crude residue was redissolved in 7 mL of THF, and 1 mL of H_2O followed by 2 drops of 5% HCl was added. After 1 h, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 20% EtOAc/hexanes) to give 79 mg (100%) of **33a/b** as an inseparable mixture of diastereomers and a clear oil: $[\alpha]^{23}_D$ +66.7 (*c* 0.075, $CHCl_3$); IR (neat) 2935, 1761, 1732, 1402, 1213, 1074, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (major isomer) 0.89 (t, 3H, J = 6.5 Hz), 1.29 (m, 3H), 1.44 (m, 3H), 1.87 (m, 2H), 2.44 (m, 2H), 2.56 (m, 2H), 3.65 (s, 3H), 3.96 (m, 1H), 4.10 (d, 1H, J = 9.6 Hz), 4.35 (m, 1H), 4.60 (m, 4H), 7.29 (m, 8H), 7.53 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.8, 24.2, 30.1, 32.0, 37.9, 41.3, 45.3, 47.8, 52.1, 58.1, 71.8, 77.4, 128.0, 128.2, 128.6, 129.6, 129.8, 135.1, 136.7, 137.9, 156.0, 170.4, 202.4; HRMS calcd for $C_{29}H_{35}NO_6Se$: 574.1710 $[M + H]^+$; found, 574.1721 $[M + H]^+$.

Luche Reduction of 33a/b. To a solution of 20 mg (0.0349 mmol) of **33a/b** in 8 mL of MeOH was added 14 mg (0.0376 mmol) of cerium(III) trichloride heptahydrate. After 5 min, 2 mg (0.0529 mmol) of $NaBH_4$ was added in one portion, and stirring was continued for 15 min. The reaction mixture was diluted with 10 mL of water and then extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 30% EtOAc/hexanes). The first product to elute (13 mg, 65%) was identified as (1*R*,1′*S*,5*R*,7*R*,8*S*,9*S*)-7-hydroxy-1-((1′-phenylmethoxy)hexane)-8-phenylselenyl-1,2,5,6,6a,7,8-hexahydro-2-oxaindolizine-3,5-dione acetic acid methyl ester (**34**) as a colorless oil: $[\alpha]^{22}_D$ −56.5 (*c* 0.115, $CHCl_3$); IR (neat) 3434, 2936, 2858, 1751, 1736, 1405, 1331, 1253, 1051 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, 3H, J = 7.0 Hz), 1.21 (m 5H), 1.51 (m, 2H), 1.72 (m, 1H), 1.83 (m, 1H), 2.22 (dd, 1H, J = 14.6 and 2.4 Hz), 2.89 (m, 3H), 3.18 (d, 1H, J = 12.0 Hz), 3.67 (s, 3H), 3.90 (m, 1H), 4.09

(m, 1H), 4.17 (dd, 1H, J = 12.0 and 8.0 Hz), 4.35 (m, 1H), 4.55 (d, 1H, J = 11.5 Hz), 4.67 (d, 1H, J = 11.5 Hz), 4.79 (dd, 1H, J = 8.0 and 3.5 Hz), 7.33 (m, 8H), 7.45 (d, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.9, 24.6, 29.6, 32.0, 32.2, 37.3, 45.2, 47.5, 51.8, 52.0, 65.9, 70.8, 125.9, 128.0, 128.2, 128.6, 129.2, 130.0, 135.1, 138.3, 156.5, 171.8; HRMS calcd for $C_{29}H_{37}NO_6Se$, 576.1867 $[M + H]^+$; found, 576.1876 $[M + H]^+$.

The second product to elute (4 mg, 20%) was (1*R*,1′*S*,5*R*,7*S*,8*R*,9*S*)-7-hydroxy-1-((1′-phenylmethoxy)hexane)-8-phenylselenyl-1,2,5,6,6a,7,8-hexahydro-2-oxaindolizine-3,5-dione acetic acid methyl ester (**35**) as a colorless oil: $[\alpha]^{23}_D$ −31.5 (*c* 0.13, $CHCl_3$); IR (neat) 3430, 2938, 2860, 1755, 1732, 1400, 1338, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 6.9 Hz), 1.32 (m, 6H), 1.77 (m, 3H), 1.91 (dd, 1H, J = 14.0 and 4.3 Hz), 2.62 (d, 2H, J = 8.1 Hz), 2.67 (s, 1H), 3.05 (d, 1H, J = 10.8 Hz), 3.64 (m, 1H), 3.73 (s, 3H), 3.91 (m, 1H), 4.08 (d, 1H, J = 10.8 Hz), 4.12 (m, 1H), 4.29 (dt, 1H, J = 10.2 and 3.6 Hz), 4.50 (dd, 1H, J = 10.2 and 7.2 Hz), 4.61 (m, 1H), 7.01 (m, 2H), 7.33 (m, 6H), 7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.6, 22.7, 29.8, 32.3, 35.3, 38.1, 45.9, 52.2, 56.8, 57.5, 66.3, 69.7, 75.1, 76.4, 127.3, 127.8, 128.1, 128.5, 129.9, 138.1, 155.9, 170.4; HRMS calcd for $C_{29}H_{37}NO_6Se$, 567.1867 $[M + H]^+$; found, 567.1873 $[M + H]^+$.

(1*R*,1′*S*,5*R*,7*R*,8*S*,9*S*)-7-(Imidazole-1-carbothioyloxy)-1-((1′-phenylmethoxy)hexane)-8-phenylselenyl-1,2,5,6,6a,7,8-hexahydro-2-oxaindolizine-3,5-dione Acetic Acid Methyl Ester (36). To a solution of 10 mg (0.0174 mmol) of **34** and 9 mg (0.0505 mmol) of 1,1′-thiocarbonyldiimidazole in 10 mL of toluene was added 1 mg of DMAP, and the mixture was heated to reflux for 3 h. The reaction was cooled to rt and concentrated under reduced pressure. The crude reaction mixture was purified by radial PLC (silica gel, 40% EtOAc/hexanes) to give 10.8 mg (91%) of **36** as a colorless solid: mp 138−139 °C (EtOAc/hexanes); $[\alpha]^{23}_D$ −73.9 (*c* 0.13, $CHCl_3$); IR (thin film) 2946, 2858, 1758, 1385, 1322, 1282, 1224, 1104, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, 3H, J = 7.0 Hz), 1.25 (m, 5H), 1.55 (m, 2H), 1.89 (m, 2H), 2.45 (dd, 1H, J = 14.5 and 9.4 Hz), 2.54 (m, 1H), 2.69 (dd, 1H, J = 14.2 and 6.9 Hz), 3.46 (dd, 1H, J = 11.7 and 3.0 Hz), 3.53 (s, 3H), 4.08 (m, 1H), 4.27 (dd, 1H, J = 11.7 and 8.0 Hz), 4.45 (m, 1H), 4.57 (d, 1H, J = 11.5 Hz), 4.69 (d, 1H, J = 11.5 Hz), 4.88 (dd, 1H, J = 7.6 and 3.5 Hz), 5.72 (m, 1H), 7.10 (s, 1H), 7.33 (m, 10H), 7.59 (s, 1H), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.8, 24.7, 29.9, 30.1, 31.9, 36.6, 41.7, 44.9, 52.2, 53.8, 71.3, 77.1, 78.2, 118.0, 126.0, 128.1, 128.3, 128.7, 129.4, 129.9, 131.5, 135.6, 137.1, 138.1, 156.2, 170.4, 182.5. Anal. Calcd for $C_{33}H_{39}N_3O_6SSe$: C, 57.89; H, 5.74; N, 6.14. Found: C, 57.83; H, 5.88; N, 6.06.

(1*R*,1′*S*,5*R*,7*S*,8*R*,9*S*)-7-(Imidazole-1-carbothioyloxy)-1-((1′-phenylmethoxy)hexane)-8-phenylselenyl-1,2,5,6,6a,7,8-hexahydro-2-oxaindolizine-3,5-dione Acetic Acid Methyl Ester (37). To a solution of 15 mg (0.0261 mmol) of **35** and 14 mg (0.0786 mmol) of 1,1′-thiocarbonyldiimidazole in 5 mL of toluene was added 1 mg of DMAP, and the mixture was heated to reflux for 3 h. The reaction was cooled to rt and concentrated under reduced pressure. The crude product was purified by radial PLC (silica gel, 40% EtOAc/hexanes) to give 17 mg (95%) of **37** as a colorless oil: $[\alpha]^{23}_D$ +112.4 (*c* 0.105, $CHCl_3$); IR (neat) 2934, 2861, 1763, 1736, 1388, 1325, 1283, 1229, 1096, 996 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, J = 7.5 Hz), 1.36 (m, 6H), 1.81 (m, 2H), 2.04 (dd, 1H, J = 13.2 and 3.6 Hz), 2.68 (m, 3H), 3.72 (s, 3H), 3.74 (d, 1H, J = 11.1 Hz), 4.22 (m, 2H), 4.40 (d, 1H, J = 11.1 Hz), 4.57 (m, 2H), 4.77 (m, 1H), 5.74 (m, 1H), 6.91 (s, 1H), 7.11 (m, 2H), 7.20 (m, 2H), 7.33 (m, 7H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.6, 22.8, 29.7, 29.8, 32.3, 38.3, 45.8, 47.0, 52.4, 56.3, 70.0, 74.7, 76.4, 78.6, 117.9, 127.6, 127.9, 128.1, 128.8, 129.0, 129.8, 131.1, 132.6, 137.0, 138.0, 155.7, 170.2, 182.6; HRMS calcd for $C_{33}H_{39}N_3O_6SSe$, 686.1805 $[M + H]^+$; found, 686.1793 $[M + H]^+$.

(1*R*,1′*S*,5*R*,9*R*)-3-Oxo-1-((1′-phenylmethoxy)hexane)-1,5,6,8a-tetrahydro-oxazolo[3,4-*a*]pyridin-5-yl Acetic Acid Methyl Ester (29). From 36: To a refluxing mixture of 158 mg (0.231 mmol) of **36** and 2 mg of AIBN in 10 mL of toluene was added dropwise 74 mg (0.254 mmol) of tributyltin hydride. After 5 min, the reaction mixture was cooled and concentrated under reduced pressure. The crude residue was purified by radial PLC (silica gel, 25% EtOAc/hexanes) to give 85 mg (91%) of **29** as a colorless oil: $[\alpha]^{23}_D$ +27.3 (*c* 1.40, $CHCl_3$); IR (neat) 2931, 2860, 1760, 1736, 1413, 1372, 1219, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 6.3 Hz), 1.32 (m, 3H), 1.45 (m, 2H), 1.78 (m, 2H), 1.93 (dd, 1H, J = 18.3 and 3.6 Hz), 2.59 (m, 4H), 3.64 (m, 1H), 3.70 (s, 3H), 4.38 (d, 1H, J = 11.0 Hz), 4.46 (m, 1H), 4.54 (m, 2H), 4.63 (d, 1H, J = 11.0 Hz), 5.74 (m, 1H), 5.84 (m, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.8, 23.0, 27.3, 29.1, 32.3, 37.1, 45.8, 52.2, 52.9, 70.6, 76.6, 123.2, 126.8, 127.9, 128.1, 128.7, 138.0, 157.2, 171.1; HRMS calcd for $C_{23}H_{31}NO_5$, 402.2280 $[M + H]^+$; found, 402.2286 $[M + H]^+$.

From 37: To a refluxing mixture of 16 mg (0.0234 mmol) of **37** and 1 mg of AIBN in 5 mL of toluene was added dropwise 7.5 mg (0.0257 mmol) of tributyltin hydride. After 5 min, the reaction mixture was cooled and concentrated under reduced pressure. The crude residue was purified by radial PLC (silica gel, 25% EtOAc/hexanes) to give 8.56 mg (95%) of **29**.

One-Pot Synthesis of 29 from a Diastereomeric Mixture of 34 and 35. To a solution of 89 mg (0.155 mmol) of **33a/b** in 8 mL of MeOH was added 64 mg (0.172 mmol) of cerium(III) trichloride heptahydrate. After 5 min, 7.1 mg (0.188 mmol) of $NaBH_4$ was added in one portion, and stirring was continued for 15 min. The reaction mixture was diluted with water, extracted with CH_2Cl_2, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was filtered over a small plug of silica gel to give 76 mg (85%) of a mixture of **34** and **35** which was used without further purification.

To a solution of 76 mg (0.132 mmol) of **34** and **35** and 60 mg (0.337 mmol) of 1,1′-thiocarbonyldiimidazole in 5 mL of toluene was added 3 mg of DMAP, and the mixture was heated to reflux for 3 h. To the reaction mixture was added 3 mg of AIBN followed by 46 mg (0.158 mmol) of tributyltin hydride. The mixture was refluxed for an additional 15 min, cooled to rt, and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, EtOAc/hexanes) to give 45 mg (85%) of **29**.

3-[(3-Cyanopropyl)-*p*-toluenesulfonylamino]propionic Acid Methyl Ester (42). To 715 mg (3.00 mmol) of **41**[25] in 20 mL of acetonitrile was added 2.74 g (19.80 mmol) of anhydrous K_2CO_3 followed by 1.35 mL (15.0 mmol) of methyl acrylate. After being stirred for 4 h at rt, the reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by radial PLC (silica gel, EtOAc/hexanes) to give 973 mg (100%) of **42** as a colorless oil: IR (neat) 2954, 2249, 1736, 1595, 1437, 1339, 1200, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 (m, 2H), 2.44 (m, 5H), 2.64 (t, 2H, J = 7.1 Hz), 3.20 (t, 2H, J = 6.8 Hz), 3.40 (t, 2H, J = 7.1 Hz), 3.68 (s, 3H), 7.33 (d, 2H, J = 8.0 Hz), 7.69 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.6, 21.5, 25.0, 34.3, 45.1, 48.2, 51.9, 119.1, 127.3, 130.0, 135.6, 144.0, 171.6; HRMS calcd for $C_{15}H_{20}N_2O_4S$, 325.1222 $[M + H]^+$; found, 325.1232 $[M + H]^+$.

***N*-(4-Aminobutyl)-*N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (43).** To a solution of 1.00 g (3.08 mmol) of **42** in 35 mL of THF at 0 °C was added dropwise 6.20 mL (6.16 mmol) of a 1.0 M solution of LAH in THF. The resulting mixture was allowed to warm to rt and stirred for 5 h. The solution was cooled to 0 °C, carefully quenched with water, and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by radial PLC (silica gel, EtOAc/hexanes) to give 645 mg (70%) of **43** as a colorless oil: IR (neat) 3367, 2939, 2870, 1597, 1460, 1331, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (m, 5H), 1.75 (t, 2H, J = 5.9 Hz), 2.40 (s, 3H), 2.71 (t, 2H, J = 6.2 Hz), 3.00 (br m, 2H), 3.10 (t, 2H, J = 7.0 Hz), 3.19 (t, 2H, J = 6.5 Hz), 3.67

(t, 2H, J = 5.3 Hz), 7.28 (d, 2H, J = 8.1 Hz), 7.66 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 26.3, 29.9, 31.9, 41.4, 45.6, 49.3, 58.9, 127.3, 128.9, 136.4, 143.4; HRMS calcd for $C_{14}H_{24}N_2O_3S$, 301.1586 $[M + H]^+$; found, 301.1591 $[M + H]^+$.

***N*-(4-Benzylaminobutyl)-*N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (44).** To a solution of 380 mg (1.26 mmol) of **43** in 20 mL of $CHCl_3$ was added 1.00 g of $MgSO_4$ followed by 134 mg (1.26 mmol) of benzaldehyde. The resulting mixture was heated at reflux for 18 h, cooled to rt, and concentrated under reduced pressure. The crude imine was dissolved in 15 mL of methanol, cooled to 0 °C, and 62 mg (1.64 mmol) of sodium borohydride was added. The mixture was stirred an additional 1 h at rt, quenched with water, and extracted with CH_2Cl_2. The solvent was removed under reduced pressure, and the product was purified by radial PLC (silica gel, EtOAc/hexanes) to give 200 mg (41%) of **44** as a colorless oil: IR (neat) 3366, 2940, 2869, 1595, 1460, 1330 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52 (m, 3H), 1.74 (m, 2H), 2.39 (s, 3H), 2.59 (t, 2H, J = 6.1 Hz), 2.75 (m, 2H), 3.09 (m, 2H), 3.20 (m, 2H), 3.67 (m, 3H), 3.75 (s, 2H), 7.28 (m, 7H), 7.65 (d, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 26.7, 27.2, 31.8, 45.4, 48.7, 49.1, 54.0, 58.9, 127.1, 127.2, 128.3, 128.6, 129.8, 136.6, 140.1, 143.1; HRMS calcd for $C_{21}H_{30}N_2O_3S$, 391.2065 $[M + H]^+$; found, 391.2055 $[M + H]^+$.

(1*R*,1′*S*,5*R*,9*R*)-3-Oxo-1-((1′-phenylmethoxy)hexane)-1,5,6,8a-tetrahydro-oxazolo[4,3-*a*]pyridin-5-yl Acetic Acid (45). To a stirred solution of 40 mg (0.10 mmol) of **29** in 3 mL of MeOH was added 39 mg (0.70 mmol) of KOH in 1 mL of H_2O. The resulting mixture was stirred for 2 h at rt and then concentrated to a small volume. The crude material was redissolved in 10 mL of H_2O and then washed with ether. The aqueous layer was acidified with 10% HCl and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford 39 mg (100%) of **45** as a colorless oil: $[\alpha]^{23}_D$ +23.5 (c 1.95, $CHCl_3$); IR (neat) 2930, 1749, 1414, 1224, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 6.4 Hz), 1.31 (m, 4H), 1.44 (m, 3H), 1.75 (m, 2H), 1.95 (dd, 1H, J = 18.2 and 3.6 Hz), 2.61 (m, 3H), 3.63 (m, 1H), 4.37 (d, 1H, J = 11.1 Hz), 4.46 (m, 1H), 4.56 (m, 1H), 4.62 (d, 1H, J = 11.1 Hz), 5.74 (m, 1H), 5.85 (m, 1H), 7.33 (m, 5H), 9.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.8, 23.0, 27.3, 29.1, 32.3, 36.9, 45.7, 52.8, 70.6, 76.6, 123.1, 126.7, 127.9, 128.0, 128.7, 137.9, 157.3, 175.6; HRMS calcd for $C_{22}H_{29}NO_5$, 388.2124 $[M + H]^+$; found, 388.2130 $[M + H]^+$.

2-[1-(1-Bezyloxyhexyl)-3-oxo-1,5,6,8a-tetrahydro-oxazolo[3,4-*a*]pyridine-5-yl]-*N*-{4-[(3-hydroxypropyl)-(toluene-4-sulfonyl)-amino]-butyl}acetamide (47). To a stirred solution of 19 mg (0.049 mmol) of carboxylic acid **45** in 5 mL of CH_2Cl_2 was added 7 mg (0.0568 mmol) of oxalyl chloride followed by 1 drop of DMF. The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The crude acid chloride (**46**) was redissolved in 1 mL of CH_2Cl_2 and added dropwise to a mixture of 44 mg (0.146 mmol) of **43** in a mixture of 3 mL of CH_2Cl_2 and 0.5 mL of 10% NaOH. The reaction mixture was allowed to stir for 1.5 h, diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by radial PLC (silica gel, EtOAc) to give 32 mg (96%) of **47** as a colorless oil: IR (thin film) 3332, 2934, 2863, 1743, 1646, 1549, 1417, 1330, 1228, 1157, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, J = 6.5 Hz), 1.30 (m, 5H), 1.44 (m, 2H), 1.56 (m, 4H), 1.78 (m, 3H), 2.00 (dd, 1H, J = 17.6 and 4.3 Hz), 2.43 (s, 3H), 2.54 (m, 3H), 3.10 (m, 2H), 3.21 (m, 4H), 3.59 (m, 1H), 3.72 (t, 2H, J = 5.3 Hz), 4.39 (m, 2H), 4.58 (m, 3H), 5.78 (m, 1H), 5.86 (m, 1H), 6.31 (m, 1H), 7.33 (m, 7H), 7.68 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 21.7, 22.8, 23.1, 26.4, 26.6, 27.6, 29.0, 32.0, 32.3, 39.1, 39.3, 45.8, 46.0, 49.3, 52.6, 59.2, 70.7, 76.6, 77.0, 122.7, 126.4, 127.4, 127.9, 128.1, 128.7, 130.0, 136.3, 137.9, 143.6, 157.4, 169.9.

(1*R,1′*S**,5*R**,9*R**)-*N*-Benzyl-*N*-{4-[((3-hydroxypropyl)-(toluene-4-sulfonyl)amino]-2-[3-oxo-1-(1′-phenylmethoxyhexyl)-1,5,6,8a-tetrahydro-oxazolo[3,4-*a*]pyridin-5-yl]-acetamide (48).** To a stirred solution of 19 mg (0.049 mmol) of carboxylic acid **45** in 5 mL of CH_2Cl_2 was added 7 mg (0.057 mmol) of oxalyl chloride followed by 1 drop of DMF. The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The crude acid chloride (**46**) was redissolved in 1 mL of CH_2Cl_2 and added dropwise to a mixture of 57 mg (0.146 mmol) of **44** in a mixture of 3 mL of CH_2Cl_2 and 0.5 mL of 10% NaOH. The reaction mixture was allowed to stir for 1.5 h, diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by radial PLC (silica gel, EtOAc) to give 30 mg (81%) of **48** as a colorless oil: IR (neat) 3455, 2931, 2867, 1750, 1637, 1450, 1413, 1333, 1221, 1157, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 6.3 Hz), 1.26−1.77 (m, 14H), 2.13 (m, 1H), 2.41 (s, 3H), 2.64 (m, 4H), 3.18 (m, 6H), 3.42 (m, 1H), 3.63 (m, 3H), 4.37 (t, 1H, J = 11.2 Hz), 4.56 (m, 5H), 5.68 (m, 1H), 5.80 (m, 1H), 7.26 (m, 12H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 21.7, 22.8, 23.0, 24.8, 25.6, 26.4, 27.5 and 27.7 (due to rotamers), 29.1, 32.0 and 32.3 (due to rotamers), 35.9 and 36.1 (due to rotamers), 45.6 and 46.0 (due to rotamers), 45.8, 47.0, 48.4, 49.0 and 49.3 (due to rotamers), 51.3, 52.9 and 53.0 (due to rotamers), 59.2, 70.6, 76.6, 122.9 and 123.1 (due to rotamers), 126.4, 126.6, 126.8, 127.3, 127.6, 127.9, 128.1, 128.7, 128.8, 129.2, 129.9, 136.5 and 136.7 (due to rotamers), 137.7 and 138.1 (due to rotamers), 143.4 and 143.7 (due to rotamers), 157.0, 169.9 and 170.4 (due to rotamers). HRMS calcd for $C_{43}H_{57}N_3O_7S$, 760.3995 $[M + H]^+$; found, 760.4002 $[M + H]^+$.

(1′*R,2*R**,2′*S**,6*R**)-*N*-Benzyl-2-[6-(2′-phenylmethoxy-1′-hydroxyheptyl)-1,2,3,6-tetrahydropyridin-2-yl]-*N*-[4-[(3-hydroxypropyl)-(toluene-4-sulfonyl)amino]butyl]acetamide (51).** To a solution of 20 mg (0.0263 mmol) of **48** in 1.5 mL of MeOH was added 1.5 mL of 50% KOH in water. The resulting solution was heated at reflux for 18 h and concentrated to dryness under reduced pressure. The crude residue was extracted with CH_2Cl_2, and the organic extracts were filtered over anhydrous K_2CO_3. The solvent was removed under reduced pressure, and the product was purified by radial PLC (silica gel, 7% MeOH/$CHCl_3$) to give 15 mg (79%) of **51** as a colorless oil: IR (neat) 3401, 2931, 2856, 1627, 1450, 1333, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (m, 3H), 1.26−1.73 (m, 16H), 2.26 (m, 2H), 2.42 (s, 3H), 2.53 (m, 1H), 2.81−3.40 (m, 8H), 3.67 (m, 6H), 4.56 (m, 4H), 5.82 (m, 2H), 7.28 (m, 12H), 7.66 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1 and 14.3 (due to rotamers), 21.7, 22.9, 24.6, 24.7 and 24.8 (due to rotamers), 25.6, 26.4 and 26.5 (due to rotamers), 29.2 and 29.4 (due to rotamers), 30.4 and 30.5 (due to rotamers), 32.2 and 32.3 (due to rotamers), 37.0, 45.4, 45.8 and 46.0 (due to rotamers), 46.7, 48.4, 49.3, 51.0, 52.3 and 52.5 (due to rotamers), 71.8, 74.6 and 74.7 (due to rotamers), 79.6 and 79.7 (due to rotamers), 125.6 and 125.8 (due to rotamers), 126.4, 126.7, 127.3, 127.6, 127.8, 127.9, 128.1, 128.6, 128.9, 129.2, 129.9, 130.0, 136.6, 138.8, 143.5 and 143.7 (due to rotamers), 172.5. HRMS calcd for $C_{42}H_{59}N_3O_6S$, 734.4203 $[M + H]^+$; found, 734.4243 $[M + H]^+$.

***N*-(4-Benzylaminobutyl)-*N*-(3,3-dimethoxypropyl)-4-methylbenzenesulfonamide (53).** To a solution of 100 mg (0.420 mmol) of **41**[25] in 6 mL of acetonitrile was added 290 mg (2.10 mmol) of K_2CO_3 followed by 193 mg (0.840 mmol) of iodide **52**.[28] The mixture was heated to reflux for 16 h, filtered, and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, EtOAc/hexanes) to give 135 mg (94%) of *N*-(3-cyanopropyl)-*N*-(3,3-dimethoxypropyl)-4-methyl-benzenesulfonamide as a colorless oil: IR (neat) 2942, 2249, 1596, 1459, 1338, 1156, 1121, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.85 (m, 2H), 1.94 (m, 2H), 2.44 (m, 5H), 3.18 (m, 4H), 3.31 (s, 6H), 4.38 (t, 1H, J = 5.4 Hz), 7.32 (d,

2H, $J = 8.1$ Hz), 7.68 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.7, 21.6, 25.3, 32.4, 45.3, 47.9, 53.5, 102.5, 119.2, 127.3, 129.9, 136.0, 143.8.

To a solution of 135 mg (0.397 mmol) of the above cyano compound in 10 mL of THF at 0 °C was added dropwise 0.40 mL (0.400 mmol) of a 1.0 M solution of LAH in THF. The resulting mixture was allowed to warm to rt and stirred for 5 h. The solution was cooled to 0 °C, carefully quenched with water, and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by radial PLC (silica gel, EtOAc/hexanes) to give 117 mg (85%) of *N*-(4-aminobutyl)-*N*-(3,3-dimethoxypropyl)-4-methyl-benzenesulfonamide as a colorless oil: IR (neat) 3374, 2936, 1597, 1458, 1335, 1157, 1123, 1061 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (m, 2H), 1.57 (m, 3H), 1.86 (m, 3H), 2.41 (s, 3H), 2.67 (t, 2H, $J =$ 7.0 Hz), 3.14 (m, 4H), 3.31 (s, 6H), 4.38 (m, 1H), 7.27 (d, 2H, $J = 7.9$ Hz), 7.67 (d, 2H, $J = 7.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 26.3, 30.9, 32.5, 41.9, 44.4, 48.8, 53.4, 102.7, 127.3, 129.8, 136.9, 143.3; HRMS calcd for $C_{16}H_{28}N_2O_4S$, 345.1848 [M + H]$^+$; found, 345.1848 [M + H]$^+$.

To a solution of 220 mg (0.64 mmol) of the above amine in 20 mL of $CHCl_3$ was added 1.00 g of $MgSO_4$ followed by 68 mg (0.64 mmol) of benzaldehyde. The resulting mixture was heated at reflux for 18 h, cooled to rt, and concentrated under reduced pressure. The crude imine was dissolved in 15 mL of methanol, cooled to 0 °C, and 29 mg (0.767 mmol) of sodium borohydride was added. The mixture was stirred an additional 1 h at rt, quenched with water, and extracted with CH_2Cl_2. The combined organic extracts were dried (K_2CO_3), and the solvent was removed under reduced pressure. The crude product was purified by radial PLC (silica gel EtOAc/hexanes) to give 139 mg (50%) of **53** as a colorless oil: IR (neat) 3204, 2940, 1595, 1460, 1332 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45−1.71 (m, 4H), 1.85 (m, 3H), 2.43 (s, 3H), 2.62 (t, 2H, $J =$ 7.0 Hz), 3.17 (m, 4H), 3.30 (s, 6H), 3.77 (s, 2H), 4.38 (t, 1H, J = 5.0 Hz), 7.31 (m, 7H), 7.67 (d, 2H, $J = 7.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 26.6, 27.3, 32.5, 44.3, 48.8, 48.9, 53.4, 54.1, 102.7, 127.1, 127.3, 128.2, 128.5, 129.8, 136.9, 140.5, 143.2.

(1′*R,2*R**,2′*S**,6*R**)-*N*-Benzyl-2-[6-(2′-phenylmethoxy-1′-hydroxyheptyl)-1,2,3,6-tetrahydropyridin-2-yl]-*N*-[4[((3,3-dimethoxypropyl)-(toluene-4-sulfonyl)-amino]-butyl]acetamide (54).** To a stirred solution of 20 mg (0.052 mmol) of carboxylic acid **45** in 5 mL of CH_2Cl_2 was added 7 mg (0.057 mmol) of oxalyl chloride followed by 1 drop of DMF. The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The crude acid chloride was redissolved in 1 mL of CH_2Cl_2 and added dropwise to a mixture of 67 mg (0.154 mmol) of **53** in 3 mL of CH_2Cl_2 and 0.5 mL of 10% NaOH. The reaction mixture was stirred for 1.5 h, diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by radial PLC (silica gel, EtOAc) to give 24 mg (57%) of (1*R**, 1′*S**,5*R**,9*R**)-*N*-benzyl-*N*-[4-[(3,3-dimethoxypropyl)-(toluene-4-sulfonyl)amino]butyl]-2-[3-oxo-1-(1′-phenylmethoxyhexyl)-1,5,6,8a-tetrahydro-oxazolo[3,4-*a*]pyridin-5-yl]acetamide as a colorless oil: IR (neat) 2930, 1637, 1455, 1336, 1152, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, $J = 6.4$ Hz), 1.26−1.84 (m, 16H), 1.97−2.19 (m, 1H), 2.41 (s, 3H), 2.61 (m, 1H), 3.10 (m, 6H), 3.25 (m, 1H), 3.30 (s, 6H), 3.40 (m, 1H), 3.60 (m, 1H), 4.32−4.58 (m, 6H), 5.68 (m, 1H), 5.82 (m, 1H), 7.51 (m, 12H), 7.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 21.7, 22.8 and 23.0 (due to rotamers), 24.7, 25.4, 26.4, 27.5, 29.1, 32.3 and 32.5 (due to rotamers), 35.8 and 35.9 (due to rotamers), 41.6, 44.6 and 44.7 (due to rotamers), 45.8 and 45.9 (due to rotamers), 46.9, 48.4 and 48.7 (due to rotamers), 51.3, 53.0, 53.4 and 53.6 (due to rotamers), 70.6, 76.5 and 76.6 (due to rotamers), 78.0, 102.7, 123.0 and 123.2 (due to rotamers), 123.8, 126.4 and 126.9 (due to rotamers), 127.3, 127.5, 127.8, 128.0, 128.1, 128.7, 128.8, 129.2, 129.6, 130.0, 136.8 and 137.0 (due to rotamers), 137.7 and 138.1 (due to rotamers), 170.2.

To a solution of 11 mg (0.0137 mmol) of the above carbamate in 1.5 mL of MeOH was added 1.5 mL of 50% KOH in water. The resulting solution was heated at reflux for 18 h and concentrated to dryness under reduced pressure. The crude residue was extracted with CH_2Cl_2, and the organic extracts were dried over anhydrous K_2CO_3. The solvent was removed under reduced pressure, and the product was purified by radial PLC (silica gel, 7% MeOH/$CHCl_3$) to give 8.5 mg (80%) of **54** as a colorless oil: IR (neat) 3412, 2931, 1631, 1454, 1337, 1155, 1119, 1089 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (m, 3H), 1.30−1.89 (m, 18H), 2.24−2.63 (m, 6H), 3.10 (m, 6H), 3.30 (s, 6H), 3.39−3.80 (m, 4H), 4.35 (m, 1H), 4.50 (m, 1H), 4.57 (m, 2H), 5.80 (m, 1H), 5.88 (m, 1H), 7.13 (m, 1H), 7.30 (m, 11H), 7.65 (d, 2H, $J = 7.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 21.7, 22.9, 24.7 and 24.8 (due to rotamers), 25.6, 26.3 and 26.5 (due to rotamers), 29.3 and 29.4 (due to rotamers), 29.8 and 30.2 (due to rotamers), 32.4 and 32.6 (due to rotamers), 36.5, 44.7, 45.8, 36.9 and 47.1 (due to rotamers), 48.6 and 48.8 (due to rotamers), 51.1, 52.3 and 52.5 (due to rotamers), 53.5 and 53.6 (due to rotamers), 71.8, 74.3 and 74.4 (due to rotamers), 79.1, 102.5, 125.5, 126.4, 126.7, 127.4, 127.6, 127.8, 128.6, 128.9, 129.2, 130.0, 136.7 and 136.8 (due to rotamers), 137.8 and 138.8 (due to rotamers), 143.4, 171.8 and 172.3 (due to rotamers). HRMS calcd for $C_{44}H_{63}N_3O_7S$, 778.4465 [M + H]$^+$; found, 778.4508 [M + H]$^+$.

(1*R*,1′*S*,5*R*,9*R*)-*N*-Benzyl-2-[3-oxo-1-((1-phenylmethoxy)-hexane)-1,5,6,8a-tetrahydro-oxazolo[3,4-*a*]pyridin-5-yl]-*N*-(4-hydroxybutyl)acetamide (57). To a stirred solution of 20 mg (0.0516 mmol) of carboxylic acid **45** in 5 mL of CH_2Cl_2 was added 7 mg (0.0568 mmol) of oxalyl chloride followed by 1 drop of DMF. The resulting mixture was stirred for 1 h and then concentrated under reduced pressure. The crude acid chloride was redissolved in 1 mL of CH_2Cl_2 and added dropwise to a mixture of 54 mg (0.300 mmol) of 4-benzylamino-butan-1-ol (**56**) in 3 mL of CH_2Cl_2 and 0.5 mL of 10% NaOH. The reaction mixture was allowed to stir for 1.5 h and then diluted with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, EtOAc) to give 25.5 mg (82%) of **57** as a colorless oil: $[\alpha]^{23}_D$ +26.8 (*c* 1.70, $CHCl_3$); IR (neat) 3448, 2930, 2867, 1749, 1637, 1452, 1417, 1376, 1223, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (m, 3H), 1.29−1.75 (m, 15H), 2.05 (m, 1H), 2.61 (m, 3H), 3.25 (m, 1H), 3.62 (m, 3H), 4.38 (m, 2H), 4.57 (m, 4H), 5.78 (m, 2H), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.8 and 23.0 (due to rotamers), 24.1, 25.3, 27.4 and 27.6 (due to rotamers), 29.0, 29.7 and 29.8 (due to rotamers), 32.3, 36.0 and 36.2 (due to rotamers), 45.8 and 46.0 (due to rotamers), 47.3, 48.4, 51.4, 53.0 and 53.1 (due to rotamers), 62.2 and 62.6 (due to rotamers), 70.6, 76.6, 123.0, 126.4, 126.6, 127.0, 127.6, 127.9, 128.0, 128.1, 128.8, 129.2, 136.7, 137.7 and 138.0 (due to rotamers), 157.0, 169.9 and 170.4 (due to rotamers); HRMS calcd for $C_{33}H_{44}N_2O_5$, 549.3328 [M + H]$^+$; found, 549.3345 [M + H]$^+$.

(1′*R*,2*R*,2′*S*,6*R*)-*N*-Benzyl-2-[6-(2′-phenylmethoxy-1′-hydroxyheptyl)-1,2,3,6-tetrahydro-pyridin-2-yl]-*N*-(4-hydroxybutyl)acetamide (58). To a solution of 25 mg (0.0456 mmol) of **57** in 1.5 mL of MeOH was added 1.5 mL of 50% aqueous KOH. The resulting solution was heated at reflux for 18 h and then concentrated to dryness under reduced pressure. The crude residue was extracted with CH_2Cl_2 and filtered over anhydrous K_2CO_3. The solvent was removed under reduced pressure, and the product was purified by radial PLC (silica gel, 7% MeOH/$CHCl_3$) to give 21 mg (88%) of **58** as a colorless oil: $[\alpha]^{23}_D$ +36.8 (*c* 1.15, $CHCl_3$); IR (neat) 3401, 2920, 2856, 1627, 1450, 1359, 733, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (m, 3H), 1.26−1.72 (m, 13H), 1.92−2.80 (m, 4H), 3.21 (t, 1H, $J = 7.7$ Hz), 3.42 (m, 1H), 3.61 (m, 3H), 3.84 (m, 5H), 4.56 (m, 4H), 5.78 (m, 2H), 7.25 (m, 10H); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 14.3, 22.9, 24.3 and 24.7 (due to rotamers), 25.2, 29.4, 29.9 and 30.5 (due to rotamers), 32.4, 36.6 and 36.8 (due to rotamers), 46.0, 46.9 and 47.1 (due to rotamers), 48.5, 51.2, 52.1 and 52.3 (due to rotamers), 62.2 and 62.5 (due to rotamers), 71.7 and 71.9 (due to rotamers), 74.5, 79.7, 125.9, 126.4, 126.7, 127.9, 128.1, 128.6, 128.8, 129.2, 136.8 and 137.9 (due to rotamers), 138.3, 171.8 and 172.4 (due to rotamers); HRMS calcd for $C_{32}H_{46}N_2O_4$, 523.3536 $[M + H]^+$; found, 523.3560 $[M + H]^+$.

(1′*R*,2*R*,2′*S*,6*R*)-*N*-Benzyl-2-[6-(2′-phenylmethoxy-1′-hydroxyheptyl)-1-[3-(toluene-4-sulfonylamino)propyl]-1,2,3,6-tetrahydro-pyridin-2-yl]-*N*-(4-hydroxybutyl)acetamide (60). To a stirred solution of 45 mg (0.0861 mmol) of **58** in 7 mL of CH_2Cl_2 was added 45 mg (0.344 mmol) of *N*,*N*-diisopropylethylamine followed by 53 mg (0.146 mmol) of trifluoromethanesulfonic acid 3-(toluene-4-sulfonylamino)propyl ester (**59**).[30] After 3 h, the reaction was quenched with 1 mL of saturated $NaHCO_3$ and then extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by radial PLC (silica gel, 7% MeOH/$CHCl_3$) to give 53 mg (84%) of **60** as a clear oil: $[\alpha]^{23}_D$ +41.5 (*c* 0.40, $CHCl_3$); IR (neat) 3436, 3271, 2931, 2860, 1619, 1454, 1325, 1155, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (m, 3H), 1.30−2.08 (m, 17H), 2.43 (m, 8H), 2.95 (m, 2H), 3.00−3.65 (m, 6H), 3.79 (m, 2H), 4.54 (m, 4H), 5.61 (m, 1H), 5.91 (m, 1H), 6.05 (m, 1H), 7.29 (m, 12H), 7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 21.7, 22.9, 24.2 and 24.5 (due to rotamers), 25.3, 27.2 and 27.4 (due to rotamers), 29.6 and 30.2 (due to rotamers), 29.8, 32.4, 32.2 and 33.3 (due to rotamers), 41.3 and 41.5 (due to rotamers), 45.0 and 45.1 (due to rotamers), 46.4, 47.4, 48.7, 51.4, 58.8 and 58.9 (due to rotamers), 62.2 and 62.4 (due to rotamers), 71.5, 73.0 and 73.6 (due to rotamers), 79.8 and 80.1 (due to rotamers), 124.8 and 124.9 (due to rotamers), 126.4, 127.3, 127.5, 127.8, 127.9, 128.1, 128.6, 129.2, 129.8, 136.9 and 137.2 (due to rotamers), 137.4 and 137.9 (due to rotamers), 138.7, 143.2 and 143.3 (due to rotamers), 171.9 and 172.8 (due to rotamers); HRMS calcd for $C_{42}H_{59}N_3O_6S$, 734.4203 $[M + H]^+$; found, 734.4237 $[M + H]^+$.

(1′*R*,2*R*,2′*S*,6*R*)-Methanesulfonic Acid 4-[Benzyl-({6-(2′-phenylmethoxy-1′-hydroxy-heptyl)-1-[3-(toluene-4-sulfonylamino)propyl]-1,2,3,6-tetrahydro-pyridin-2-yl}amino]-butyl Ester (61). To a solution of 41 mg (0.56 mmol) of **60** in 7 mL of CH_2Cl_2 at −20 °C was added 12.4 mg (0.123 mmol) of triethylamine followed by 9 μL (0.112 mmol) of methanesulfonyl chloride. The reaction was stirred for 30 min at −20 °C, quenched with 1 mL of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by radial PLC (silica gel, 7% MeOH/$CHCl_3$) to afford 43 mg (95%) of the mesylate **61** as a colorless oil: $[\alpha]^{23}_D$ +59.0 (*c* 0.20, $CHCl_3$); IR (neat) 3283, 2928, 2869, 1625, 1453, 1352, 1329, 1160, 1093, 937, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (m, 3H), 1.30 (m, 4H), 1.48 (m, 2H), 1.70 (m, 8H), 2.01 (m, 3H), 2.43 (m, 7H), 3.05 (m, 5H), 3.27 (m, 2H), 3.48 (m, 3H), 3.81 (m, 2H), 4.23 (m, 2H), 4.57 (m, 4H), 5.76 (m, 2H), 7.28 (m, 12H), 7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 21.5, 22.7, 23.6 and 24.3 (due to rotamers), 24.6 and 24.8 (due to rotamers), 26.5 and 26.6 (due to rotamers), 27.2 and 27.5 (due to rotamers), 28.3, 29.8 and 30.1 (due to rotamers), 32.0 and 32.3 (due to rotamers), 37.3, 41.4 and 41.6 (due to rotamers), 44.5 and 45.2 (due to rotamers), 45.8 and 46.6 (due to rotamers), 48.6, 50.5, 50.9 and 51.2 (due to rotamers), 56.6 and 58.7 (due to rotamers), 69.4 and 69.8 (due to rotamers), 71.3 and 71.4 (due to rotamers), 72.7 and 73.5 (due to rotamers), 79.5 and 79.9 (due to rotamers), 125.0, 126.4, 127.3, 127.6, 127.8, 127.9, 128.2, 128.5, 128.8, 129.2, 129.8, 136.8 and 137.1 (due to rotamers), 137.4 and 137.9 (due to rotamers), 138.7 and 138.8 (due to rotamers), 143.2, 171.9 and 172.8 (due to rotamers); HRMS calcd for $C_{43}H_{61}N_3O_8S_2$, 812.3978 $[M + H]^+$; found, 812.3981 $[M + H]^+$.

(1′*R*,4*R*,2′*S*,15a*R*)-13-Benzyl-4-(2′-phenylmethoxy-1′-hydroxyheptyl)-8-(toluene-4-sulfonyl)-1,4,6,7,8,9,10,11,12,-13,15,15a-dodecahydro-5*H*-4a,8,13-triazabenzocyclotridecen-14-one (55). To a solution of 39 mg (0.048 mmol) of the above mesylate in 150 mL of anhydrous acetonitrile was added 2.0 g (14.5 mmol) of anhydrous potassium carbonate. The mixture was refluxed for 24 h, cooled to rt, and filtered through a pad of Celite. The solvent was removed under reduced pressure, and the crude residue was purified by radial PLC (silica gel, 7% MeOH/$CHCl_3$) to give 24 mg (70%) of **55** as a colorless oil: $[\alpha]^{23}_D$ +24.9 (*c* 0.225, $CHCl_3$); IR (neat) 3394, 2922, 2860, 1635, 1451, 1338, 1158, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (m, 3H), 1.27 (m, 6H), 1.60 (m, 7H), 1.70−2.17 (m, 5H), 2.43 (s, 3H), 2.55 (m, 1H), 2.74 (m, 1H), 2.85−3.18 (m, 4H), 3.53 (m, 3H), 3.76 (m, 1H), 4.00 (m, 3H), 4.60 (m, 3H), 5.25 (d, 1H, *J* = 14.7 Hz), 5.77 (m, 1H), 5.96 (m, 1H), 7.29 (m, 12H), 7.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3 and 14.4 (due to rotamers), 21.7, 22.9, 23.9 and 24.4 (due to rotamers), 24.9 and 25.2 (due to rotamers), 25.8, 26.6, 28.3 and 28.9 (due to rotamers), 29.6 and 29.9 (due to rotamers), 31.7 and 32.3 (due to rotamers), 34.6 and 35.4 (due to rotamers), 43.0 and 43.4 (due to rotamers), 46.9 and 47.0 (due to rotamers), 49.4, 50.8 and 51.0 (due to rotamers), 51.6 and 52.2 (due to rotamers), 60.1, 71.3 and 71.5 (due to rotamers), 74.4, 79.9, 126.3 and 126.5 (due to rotamers), 127.3 and 127.5 (due to rotamers), 127.7 and 127.8 (due to rotamers), 127.9 and 128.0 (due to rotamers), 128.2, 128.4, 128.7, 129.1, 129.9, 135.3, 138.0, 139.3, 143.6, 172.5; HRMS calcd for $C_{42}H_{57}N_3O_5S$, 716.4097 $[M + H]^+$; found, 716.4111 $[M + H]^+$.

Preparation of (+)-Cannabisativine (1). To a solution of 12 mL of liquid NH_3 at −78 °C was added 77 mg (0.108 mmol) of **55** in 3 mL of THF. Small pieces of sodium were added until a blue color persisted. The reaction mixture was refluxed for 20 min, and then the ammonia was allowed to evaporate. To the residue was carefully added 5 mL of water. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over K_2CO_3 and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography ($CHCl_3$/MeOH/NH_4-OH, 90:9:1) to give 31 mg (76%) of **1** as a colorless solid: mp 165−166 °C (lit.[5] 167−168 °C); $[\alpha]^{23}_D$ +51.76 (*c* 0.425, $CHCl_3$) [lit.[5] +55.1 (c 0.53, $CHCl_3$)]; IR (neat) 3300, 2995, 1635, 1540, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (m, 3H), 1.30 (m, 9H), 1.60 (m, 5H), 1.94 (m, 5H), 2.11 (d, 1H, *J* = 13.8 Hz), 2.47 (m, 3H), 2.65−2.95 (m, 5H), 3.05 (m, 1H), 3.25 (m, br s, 1H), 3.55 (m, 3H), 5.90 (m, 1H), 9.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4, 23.0, 25.4, 26.4, 27.6, 28.1, 29.9, 32.4, 32.9, 40.0, 40.1, 42.1, 47.7, 50.8, 52.5, 61.5, 75.0, 75.8, 125.7, 127.4, 171.3.

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Supporting Information Available: Comparison tables of NMR data for synthetic **1**, and ^1H and ^{13}C NMR spectra of **16**, **17**, **20**, **22**, **23**, **27**, **29**, **33**−**35**, **37**, **42**−**45**, **47**, **48**, **51**, **54**, **55**, **57**, **58**, **60**, **61**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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