Biogenetic Syntheses of Kopsijasminilam and Deoxykopsijasminilam

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The hexacyclic ketoester **7**, derived from cyclization of racemic minovincine (**6**), was reduced to two C-19 epimeric alcohols **8** and **9**. Stereoelectronically controlled fragmentations of corresponding *O*-sulfonyl derivatives provided, respectively, the hexacyclic enamine **14** and, after oxidation of the olefin **16**, the pentacyclic lactam **17** with a brigehead double bond. Formation of a carbamate, introduction of a second double bond at C-16, and conjugate reductive hydroxylation at C-20, or hydrogenation, gave the title products.

Kopsijasminilam (**1**) and deoxykopsijasminilam (**2**) are two nonbasic indoline alkaloids (Figure 1) isolated in Thailand from Kopsia jasminiflora.[1] Their unprecedented structural skeleton is shared by 14,15-dehydrokopsijasminilam (**3**),[1] and by the pauciflorines A and B (**4**, and **5**),[2] which contain the additional unusual feature of a bridgehead double bond. In continuation of our long-standing efforts in biomimetic syntheses of indole and indoline alkaloids,[3] our approach to syntheses of these pentacyclic lactams was based on a cyclization of the biogenetically presumed precursor minovincine (**6**) and a subsequent ring fragmentation.

While the generation of pentacyclic alkaloids of the minovincine (**6**) type from a Δ-20,21-secodine precursor has been biosynthetically established,[4] and synthetically mimicked,[3] extension of such endeavors to the eventual formation of kopsijasminilam (**1**) or pauciflorine (**4**, **5**) type structures was still in the realm of biogenetic speculation. In this context, the presence of a C-19 oxygen function in minovincine (**6**) suggested not only the option of cyclization to a pleiocarpine type hexacyclic intermediate,[5] but also the use of this functionality for a following ring fragmentation, to yield the Δ-19,20 bridgehead double bond of the pauciflorines.

Thus, the acid-mediated cyclization of racemic minovincine (**6**, 19-oxovincadifformine, Scheme 1),[6] an alkaloid that we had obtained previously by three alternative synthetic routes,[7,8] provided a hexacyclic ketone **7**. This compound was envisioned as the key precursor for a fragmentation reaction that would give the pentacyclic skeleton of the target lactams, and include the remarkable bridgehead double bond of the pauciflorines.[9]

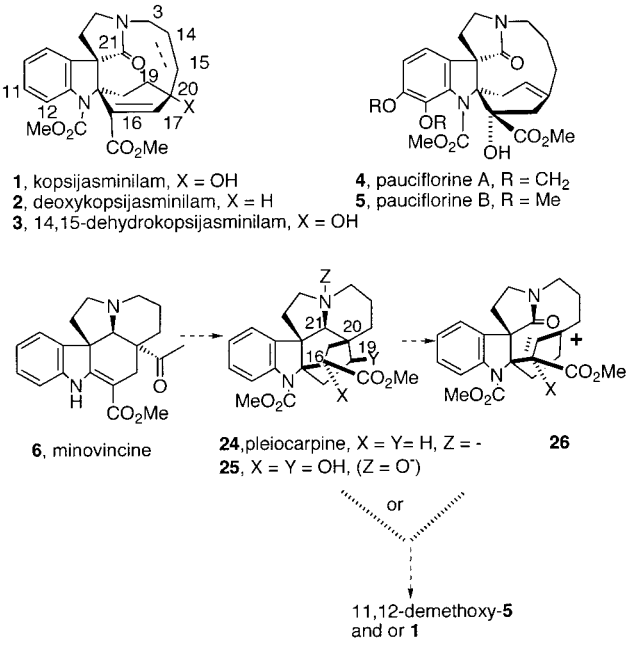

Figure 1. Structures and biogenetic pathways to the C-21 oxolactams kopsijasminilam and the pauciflorines.

Reduction of the hexacyclic ketone **7** with sodium borohydride led to a 1.3:1 mixture of two epimeric alcohols, **8** and **9**. A reduction with $NaBH_4/CeCl_3$ gave a 2:1 mixture of alcohols **8**, **9**, and Super Hydride at −78 °C gave a 15:1 ratio, while DIBALH at −78 °C provided the opposite 1:4 ratio of these products. The alcohols could be separated and their stereochemistry defined by an NOE spectrum of epimer **9**, which showed correlations of the hydrogens adjacent to the *tert*-amine (C-21) and

(1) Ruangrungsi, N.; Likhitwitayawuid, K.; Jongbunprasert, V.; Ponglux, D.; Aimi, N.; Ogata, K.; Yasuoka, M.; Haginiwa, J.; Sakai, S. *Tetrahedron Lett.* **1987**, *28*, 3679.

(2) Kam, T.-S.; Yoganathan, K.; Koyano, T.; Komiyama, K. *Tetrahedron Lett.* **1996**, *37*, 5765.

(3) For pertinent reviews of our syntheses see (a) Overmann, L. E.; Sworin, M. *Alkaloids: Chemical and Biological Perspectives*; John Wiley & Sons: New York, 1985; Vol. 3, p 275. (b) Kuehne, M. E.; Marko, I. *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: New York, 1990; Vol. 37, p 77. (c) Bornmann, W. G.; Kuehne, M. E. *J. Org. Chem.* **1992**, *57*, 1752.

(4) (a) Qureshi, A. A.; Scott, A. I. *J. Chem. Soc.* **1968**, 948. (b) Scott, A. I.; Reichardt, P. B.; Slaytor, M. B.; Sweeney, J. G. *Bio-Org. Chem.* **1971**, *1*, 157. (c) Kutney, J. P.; Beck, J. F.; Eggers, N. J.; Hanssen, H. W.; Sood, R. S.; Westcott, N. D. *J. Am. Chem. Soc.* **1971**, *93*, 7322.

(5) (a) Guggisberg, A.; Gorman, A. A.; Bycroft, B. W.; Schmid, H. *Helv. Chim. Acta* **1969**, *52*, 76. (b) Schnoes, H. K.; Biemann, K. *J. Am. Chem. Soc.* **1964**, *86*, 5693.

(6) Langlois, N.; Andriamialisoa, R. Z. *J. Org. Chem.* **1979**, *44*, 2468.

(7) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707.

(8) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3715.

(9) For an initial report of this fragmentation, see Kuehne, M. E.; Li, Y.-L. *Org. Lett.* **1999**, *1*, 1749. Such a fragmentation was also independently postulated by Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A. H.; Lynch, V. *Tetrahedron Lett.* **1999**, *40*, 5135.

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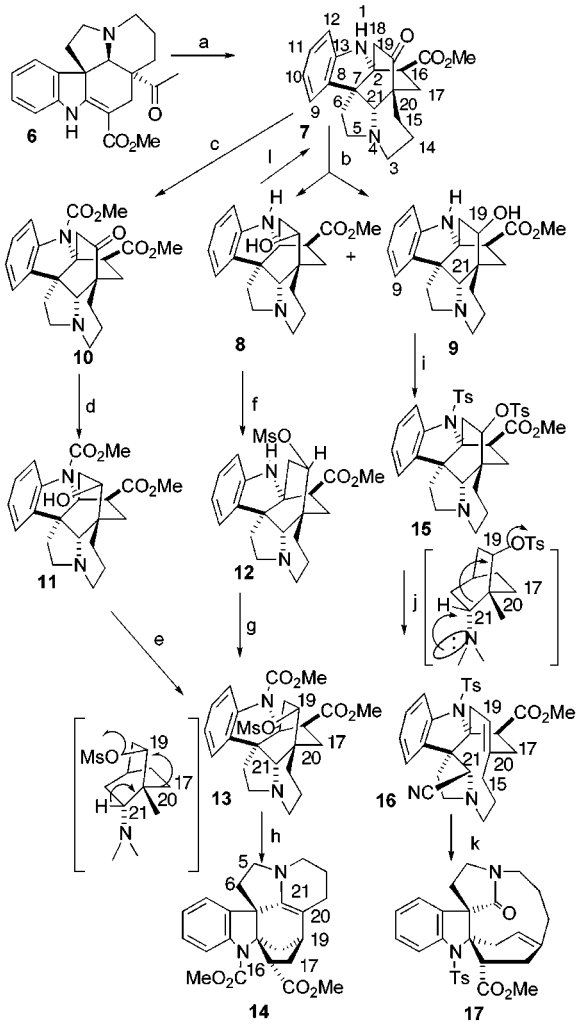
Scheme 1[a]



[a] (a) HCl−MeOH, reflux, 44% (85% based on recovered **6**); (b) DIBALH, THF, −78 °C, **8**:**9** = 1:4, 72%; Super Hydride, THF, −78 °C, **8**:**9** = 15:1, 85%; (c) $ClCO_2Me$, Na_2CO_3, CH_2Cl_2, rt, 84%; (d) $NaBH_4$, $CeCl_3$, MeOH, 88%; (e) MsCl, TEA, DMAP, CH_2Cl_2, 91%; (f) MsCl, TEA, CH_2Cl_2, 91%; (g) $ClCO_2Me$, Na_2CO_3, CH_2Cl_2, rt, 86%; (h) TEA, EtOH, H_2O, 60 °C, 83%; (i) Ts_2O, pyridine, rt, 89%; (j) NaCN, EtOH−H_2O, reflux, 89%; (k) ^{t}BuOK, THF, O_2, rt, 90%; (l) Swern oxidation, 70%.

the hydroxyl (C-19) groups, as well as a C-21 to C-9 hydrogen correlation. Furthermore, IR absorption at 1718 cm^{-1} distinguished the hydrogen bonded ester **9** from its epimer **8**, which gave a normal ester absorption at 1730 cm^{-1}.

Alternatively, prior derivatization of the secondary amine **7** as its methyl carbamate **10** (a functionality found in all of the lactam alkaloids **1**−**5**) and subsequent reduction with sodium borohydride and ceric chloride, led only to the alcohol **11**, corresponding to the amino alcohol **8**. On the other hand, reduction of the ketone **10** with L-Selectride yielded only the hydroxy epimer of **11**, but here the reduction was very slow and the product yield poor (∼25%).

Assignment of the relative stereochemistry of the hydroxyl groups in the alcohols **8** and **11** vs **9** was also based on the results of subsequent ring fragmentations. Formation of an *O*-mesylate **12** from the alcohol **8**, followed by carbamate formation, provided a derivative **13**, which matched the product of mesylation of the alcohol **11**. It might be noted here that because of steric constraints, the usual preferential derivatization of an amine over an alcohol was not seen and amino *O*-mesylate or *O*-acetate derivatives were formed from alcohols **8** or **9**, even with a 3-fold excess of mesylation or acylation agent.

When the mesylate **13** was warmed with triethylamine in aqueous alcohol or heated with sodium acetate in DMF, methanesulfonic acid was eliminated. The product **14** displayed, in addition to the expected downfield ^{13}C NMR signals for the two carbonyl substituents and two substituted aromatic carbons, two additional signals for a tetrasubstituted double bond (and no vinyl H signals in the ^1H NMR spectrum). Formation of the hexacyclic enamine **14** is in accord with an anti-periplanar bond migration (C-17 to C-19), with loss of the C-19 mesylate and C-21H substituents. NOE correlations of the C-16 β-H with C-5 and C-6 β-H's established the relative stereochemistry of the product **14**.

A reaction of the amino alcohol **9** with tosyl anhydride in pyridine gave the sulfonamide tosylate **15**. Since elimination of its tosylate function was expected to lead to the stereoelectronically favored desired ring fragmentation and formation of a hydrolytically sensitive imonium salt, the reaction was carried out in the presence of cyanide. The resulting nitrile **16** was obtained in 89% yield. Oxidation of this α-aminonitrile with potassium *tert*-butoxide and oxygen then furnished (through a cyanohydrin) the pentacyclic lactam **17** in 90% yield. Under these conditions, the C-16 carbon bearing the ester substituent was not hydroxylated. Our hope of simultaneous introduction of hydroxyl groups adjacent to the nitrile and ester functions, by enolate formation with LDA and reaction with oxygen, led only to destruction of the nitrile **16**.

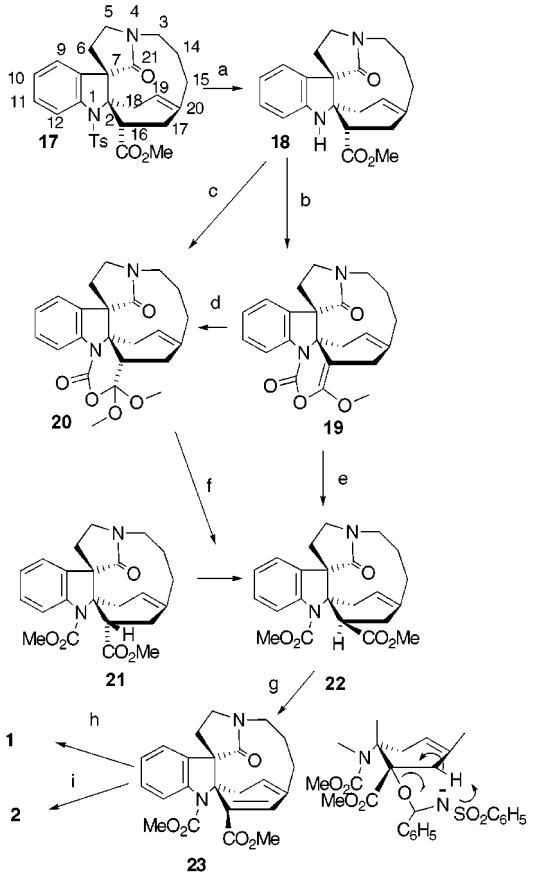
The *N*-tosyl substituent of the fragmentation product **17** could be removed with sodium amalgam and NaH_2PO_4, or with sodium naphthalenide (Scheme 2). It was also lost in variable yields on formation of the ester enolate with LDA and subsequent aqueous workup; perhaps assisted by bridging to the ester enolate oxygen (see below). Synthesis of a pauciflorine without aryl oxygen substituents now seemed only two simple steps away from the product pentacyclic amine **18**.

Formation of a carbamate from the amine **18** did not occurr as easily as the derivatization of the amine **7** (methyl chlorocarbonate and K_2CO_3) but required a reaction with triphosgene, followed by treatment with methanol. At 0 °C the cyclic ketene acetal−acylal **19** was obtained, while addition of methanol at room temperature led to the ortho ester **20**. Its reaction with sodium methoxide in refluxing methanol provided the carbamate ester **21** and its epimer **22**, which was most directly obtained from the ketene acetal−acylal **19** with sodium methoxide.

To introduce a hydroxyl group at C-16, adjacent to the ester function, generation of an enolate with potassium hexamethyldisilazide at −78 °C, or with LDA, or with potassium hydride, and its reaction with molecular oxygen was attempted. Invariably, this led to recovery of the carbamate ester **22**. However, a reaction of the lithiium enolate with 2-(phenylsulfonyl)-3-phenyloxaziridine[10] provided the diene ester **23** in 86% yield. Genera-

(10) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

Scheme 2[a]



[a] (a) Na naphthalenide, DME, −78 °C, 95%; (b) triphosgen, pyridine, CH_2Cl_2, 0 °C; MeOH, pyridine, 0 °C, 91%; (c) triphosgen, pyridine, CH_2Cl_2, 0 °C; MeOH, pyridine, rt, 94%; (d) PPTS, MeOH, rt, 3 d, <50%; (e) NaOMe, MeOH, reflux, 92%; (f) NaOMe, MeOH, reflux, **21** 60%, **22** 30%; (g) KHMDS, 2-(phenylsulfonyl)-3-phenyloxaziridine, −78 °C, 86%; (h) O_2, $Mn(dpm)_2$, $PhSiH_3$, −10 °C, 85%; (i) H_2/Pd, 92%.

tion of the diene arises, perhaps, from an intramolecular proton abstraction by the oxidizing reagent (as shown in Scheme 2).

As expected, hydrogenation of the diene ester **23** gave the conjugated ester deoxykopsijasminilam (**2**) by preferential reduction of the terminal, sterically less encumbered and more strained double bond.

Reductive α-hydroxylation of α,*β*-unsaturated esters has been achieved in good yields by their reaction with phenylsilyl hydride, a catalytic amount of bis(dipivaloylmethanato)manganese(II) and oxygen.[11] With the present diene ester **23** this presents the interesting possibility of an initial Michael (*β*) or a conjugated (*δ*) addition, followed by oxidation. In the event, only the latter process was observed in substantial degree, and kopsijasminilam (**1**) was obtained in 85% yield.

Conclusion. Utilization of the C-19 oxygen function of synthetic minovincine allowed cyclization and, after reduction of the ketone, a stereoelectronically controlled ring fragmentation, to generate the novel lactam structures represented by kopsijasminilam (**1**) and 11,12-didemethoxypauciflorine.

(11) Inki, S.; Kato, K.; Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1990**, 1869. We thank Prof. P. Magnus for pointing out the potential of this reaction for introduction of a 16-hydroxyl function in syntheses of *Kopsia* alkaloids.

Biogenetically, cyclization of minovincine may be linked to introduction of the C-16 hydroxyl function of the pauciflorines through generation of a 16-α-hydroxyimine, or its more reactive *N*-carbamate derivative, thus leading to a pleiocarpine (**24**) with C-16 and C-19 hydroxyl substituents (i.e., **25**, Figure 1). A mimic of such an oxidative cyclization is conceivable, with avoidance of rearrangement to vincamine-type products, by formation of an initial N^b-oxide. However, methodology would have to be developed to divert a favored C-16-*β*-hydroxylation to the required α-hydroxylation of minovincine (**6**).

While the C-20 to C-21 bond fragmentation was successful, one can also consider an alternative biogenetic derivation of such products from a pleiocarpine type precursor (Figure 1), which might entail successive oxidations at N^b, rather than use of a C-19 hydroxyl derivative, followed by cleavage of the C-20 to C-21 bond with generation of a C-20 carbocation **26**, that could then provide a C-20 alcohol, i.e., kopsijasminilam (**1**) or a Δ-19,20 double bond, i.e., the pauciflorines (**4**, **5**). Biosynthetic studies of these alternatives with labeled synthetic precursors should prove interesting.

Experimental Section

16-*epi*-19-Oxokopsinine (7). A solution of racemic minovincine (**6**,[7,8] 1.27 g, 3.64 mmol) in dry HCl−MeOH (30 mL, ~5 M) was heated at reflux for 24 h (oil bath temperature 105 °C).[6] The reaction mixture was concentrated, made alkaline with aqueous sodium carbonate, and extracted with dichloromethane. The dried (Na_2SO_4) extracts were concentrated and subjected to chromatography on silica gel, eluting with dry ether, to give 16-*epi*-19-oxokopsinine (**7**, 560 mg, 44%, 85% based on recovered material) and recovered minovincine (**6**, 612 mg). TLC R_f = 0.27 (100% Et_2O, CAS: orange); UV (EtOH) λ_{max} 210, 240, 294 nm; IR (KBr, CO) ν_{max} 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.13 (1 H, d, J = 7.3 Hz), 7.05 (1 H, dd, J = 7.5 and 7.8 Hz), 6.78 (1 H, dd, J = 7.3 and 7.5 Hz), 6.70 (1 H, d, J = 7.8 Hz), 4.33 (1 H, s), 3.77 (3 H, s), 3.42 (2 H, ddd, J = 3.0 and 3.7 and 11.2 Hz), 3.18−3.10 (2 H, m), 3.01 (1 H, s), 2.92 (1 H, m), 2.81 (1 H, m), 2.65 (1 H, m), 1.81−1.64 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.12, 173.94, 148.23, 137.51, 127.35, 121.61, 119.90, 110.86, 67.24, 64.23, 57.86, 52.06, 50.43, 47.43, 46.83, 42.97, 40.99, 35.39, 26.87, 26.40, 17.30; CI (methane, 40 eV) MS (relative abundance) 353 (M^+ + 1, 5), 352 (M^+, 15), 294 (17), 138 (59), 109 (100).

16-*epi*-19-Oxokopsinine Methyl Carbamate (10). 16-*epi*-19-Oxokopsinine (**7**, 1.00 g, 2.84 mmol) was stirred with methyl chloroformate (11.8 mL, 0.11 mol) and sodium carbonate (11.84 g, 0.11 mol) in dichloromethane (50 mL) at room temperature overnight. After filtratration of the solid, the filtrate was concentrated under reduced pressure. The residue was purified on a silica gel column (1:2 EtOAc/hexane) to generate the carbamate **10** (1.02 g, 88%). TLC R_f = 0.59 (1:1 EtOAc/hexane, CAS: reddish orange); mp 187−189 °C (from Et_2O); UV (EtOH) λ_{max} 246, 288 nm; IR (KBr, CO) ν_{max} 1732, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (1 H, br s), 7.10 (1 H, dd, J = 7.6 and 7.6 Hz), 6.83 (1 H, dd, J = 7.4 and 7.6 Hz), 6.66 (1 H, d, J = 7.6 Hz), 4.55 (1 H, br s), 4.29 (1 H, br s), 3.82 (3 H, s), 3.79 (3 H, s), 3.58 (1 H, dt, J = 4.9 and 11.5 Hz), 3.38 (1 H, td, J = 2.8 and 11.5 Hz), 3.28 (br s), 3.10 (1 H, dt, J = 4.0 and 11.7 Hz), 2.88 (1 H, dd, J = 2.5 and 18.9 Hz), 2.79 (1 H, dd, J = 11.9 and 15.1 Hz), 2.45 (1 H, J = 5.0 and 13.2 Hz), 2.24 (1 H, m), 2.20 (1 H, d, J = 18.9 Hz), 2.03 (1 H, dd, J = 3.2 and 15.4 Hz), 2.01 (1 H, m), 1.77 (1 H, dd, J = 8.5 and 14.5 Hz), 1.59 (1 H, m), 1.43 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.09, 173.21, 157.37, 148.39, 130.68, 128.58, 126.84, 120.42, 110.47, 69.06, 57.44, 56.67, 53.39, 52.56, 45.94, 42.28, 41.95, 41.04, 39.03, 35.70, 26.45, 20.84, 17.41; CI (methane, 40 eV) MS (relative abundance) 411 (M^+, 100), 352 (9), 154 (94).

(±)-16-*epi*-19-*R-Hydroxykopsinine Carbamate (11).** To a solution of ketone **10** (235 mg, 0.573 mmol) in dry methanol

(15 mL) was added $CeCl_3 \cdot 7H_2O$ (248 mg, 0.665 mmol), and the temperature of the mixture was lowed to − 20 °C. $NaBH_4$ (108 mg, 2.86 mmol) was added in small portions. The reaction was quenched with 5% HCl, poured over crushed ice, made basic with NH_4OH, and then extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography on silica gel (1:1 Et_2O/hexane) generated the alcohol **11** (215 mg, 91%) as a single isomer, mp 205−207 °C. TLC R_f = 0.32 (1:1 EtOAc/hexane, CAS: reddish orange); UV (EtOH) λ_{max} 246, 274 nm; IR (KBr, CO) ν_{max} 1740, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (1 H, br s), 7.06 (1 H, dd, J = 7.5 and 7.5 Hz), 6.81 (1 H, dd, J = 7.3 and 7.5 Hz), 6.61 (1 H, d, J = 7.5 Hz), 4.24 (1 H, m), 4.16 (1 H, s), 3.85 (3 H, s), 3.82 (3 H, br s), 3.57 (1 H, dt, J = 5.2 and 11.5 Hz), 3.42 (1 H, d, J = 8.5 Hz), 3.26 (1 H, m), 3.20 (1 H, m), 3.06 (1 H, m), 2.44−2.29 (5 H, m), 2.20 (1 H, m), 1.92 (1 H, m), 1.87 (1 H, dd, J = 8.5 and 13.9 Hz), 1.54 (1 H, m), 1.13 (1 H, m); CI (methane, 40 eV); MS (relative abundance) 413 (M^+ + 1, 100), 412 (M^+, 10), 355 (40), 354 (24), 337 (30), 154 (54).

(±)-16-*epi*-19-*R-Mesyloxykopsinine Carbamate (13).** To a solution of alcohol **11** (37 mg, 0.090 mmol), triethylamine (0.020 mL, 0.14 mmol), and DMAP (1 mg) in dichloromethane (5 mL) was added mesyl chloride (0.010 mL, 0.14 mmol), dropwise, at 0 °C under argon. After being stirred at room temperature overnight, the mixture was diluted with aqueous sodium carbonate, and extracted with dichloromethane. The extracts were dried (Na_2SO_4), concentrated, and applied to a silica gel column and eluted with 1:100 MeOH/CH_2Cl_2 to give the mesylate **13** (55.5 mg, 91%). TLC R_f = 0.32 (1:1 EtOAc/hexane, CAS: reddish orange); UV (EtOH) λ_{max} 210, 252 nm; IR (KBr, CO) ν_{max} 1739, 1697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (1 H, br s), 7.09 (1 H, dd, J = 7.5 and 7.5 Hz), 6.84 (1 H, dd, J = 7.4 and 7.5 Hz), 6.62 (1 H, d, J = 7.5 Hz), 4.69 (1 H, s), 4.59 (1 H, br s), 4.27 (1 H, br s), 3.94 (1 H, s), 3.84 (3 H, s), 3.83 (3 H, s), 3.54 (1 H, dt, J = 4.6 and 10.8 Hz), 3.25 (1 H, br s), 3.17 (1 H, m), 3.04 (1 H, br s), 2.92 (3 H, s), 2.68 (1 H, dd, J = 11.8 and 15.1 Hz), 2.32 (1 H, dt, J = 5.0 and 13.3 Hz), 2.15 (2 H, ddd, J = 2.5 and 6.1 and 14.4 Hz), 2.03−1.96 (3 H, m), 1.63 (1 H, m), 1.42 (1 H, m); CI (methane, 40 eV) MS (relative abundance) 491 (M^+ + 1, 5), 395 (20), 337 (2), 233 (3), 117 (77), 99 (100), 59 (52); FAB HRMS calcd for $C_{24}H_{31}N_2O_7S$ (M^+ + 1): 491.1853; found: 491.1866.

(±)-2-*S,4-*S**,5-*S**,13-*R**-Methyl 6,16-Diaza-6-(methoxycarbonyl)hexacyclo[11.6.1.1⟨2,5⟩.0⟨5,3⟩.0⟨7,12⟩.0⟨16,20⟩]henicosa-1(20),7(12),8,10-tetraene-4-carboxylate (14).** A mixture of mesylate **13** (6.0 mg, 0.012 mmol) and triethylamine (0.010 mL, 0.07 mmol) in ethanol−water (4.8 mL/1.2 mL) was heated at 60 °C for 6 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was diluted with water, and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (2:1 Et_2O/hexane) to yield enamine **14** (4.0 mg, 83%). TLC R_f = 0.23 (1:1 EtOAc/hexane, CAS: pale red); UV (EtOH) λ_{max} 216 nm; IR (KBr, CO) ν_{max} 1717, 1701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (1 H, d, J = 7.5 Hz), 7.14 (1 H, d, J = 7.1), 7.07−7.03 (2 H, m), 3.84 (1 H, m), 3.80 (3 H, s), 3.70 (3 H, s), 3.61 (1 H, m), 3.45 (1 H, m), 3.01 (1 H, dd, J = 5.4 and 8.6 Hz), 2.45 (1 H, m), 2.39 (1 H, m), 2.22 (2 H, m), 2.17 (1 H, m), 2.10−2.00 (3 H, m), 1.87 (2 H, m), 1.72 (1 H, m), 1.28 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.21 (C), 155.84 (C), 154.99 (C), 150.98 (C), 132.34 (C), 131.51 (C), 126.03 (CH), 125.20 (CH), 121.81 (CH), 118.20 (CH), 89.58 (C), 62.62 (C), 53.32 (CH_2), 52.47 (CH), 51.9 (CH), 46.13 (CH_2), 43.63 (CH_3), 40.63 (CH_3), 37.96 (CH_2), 33.70 (CH_2), 29.66 (CH_2), 28.00 (CH_2), 24.08 (CH_2); CI (methane, 40 eV) MS (relative abundance) 395 (M^+ + 1, 100), 394 (M^+, 51), 308 (22), 221 (13), 149 (18), 99 (26); FAB HRMS calcd for $C_{23}H_{27}N_2O_4$ (M^+ + 1): 395.1971; found: 395.1967.

Altenatively, when mesylate **13** was treated with 5 equiv of sodium acetate in anhydrous DMF at 100 °C, the compound **14** was generated in comparable yield.

(±)-16-*epi*-(19-*R and 19-*S**)-Hydroxykopsinine (8 and 9).** $NaBH_4$ (104 mg, 2.74 mmol) was added to a stirred solution of 16-*epi*-19-oxokopsinine (**7**, 483 mg, 1.37 mmol) in methanol (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and then quenched with 5% aqueous sodium hydroxide, and extracted with dichloromethane. The dried (Na_2SO_4) organic layers were evaporated to dryness under reduced pressure. The resulting residue was applied to a silica gel column and eluted (2:98 to 4:96 to 1:10 MeOH/CH_2Cl_2) to furnish the 19-*S** isomer **9** (137 mg), together with the 19-*R** isomer **8** (182 mg), total yield 86%. For the 19-*S** isomer **9**: TLC R_f = 0.36 (1:9 MeOH/CH_2Cl_2, CAS: orange); UV (EtOH) λ_{max} 210, 244, 294 nm; IR (KBr, CO) ν_{max} 1718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (1 H, d, J = 7.3 Hz), 7.02 (1 H, dd, J = 7.5 and 7.6 Hz), 6.77 (1 H, dd, J = 7.3 and 7.5 Hz), 6.66 (1 H, d, J = 7.6 Hz), 3.83 (3 H, s), 3.81 (1 H, br s), 3.31 (1 H, d, J = 9.4 Hz), 3.25 (1 H, dt, J = 2.6 and 11.5 Hz), 3.20 (1 H, m), 3.10 (1 H, m), 2.97 (1 H, m), 2.91 (1 H, td, J = 12.9 and 2.9 Hz), 2.82 (1 H, s), 2.78 (1 H, br s), 2.59 (1 H, m), 2.32 (1 H, t, J = 14.2 Hz), 2.16 1 H, m), 2.03 (1 H, d, J = 14.9 Hz), 1.94 (1 H, d, J = 13.5 Hz), 1.74 (1 H, m), 1.63 (1 H, m), 1.34 (1 H, d, J = 14.0 Hz), 1.27 (1 H, m), 1.25 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.16, 148.77, 139.00, 127.14, 121.89, 119.92, 110.83, 73.95, 66.63, 65.53, 57.91, 52.51, 50.85, 47.78, 41.72, 37.66, 36.57, 35.02, 32.32, 24.51, 17.36; CI (methane, 40 eV) MS (relative abundance) 354 (M^+, 2), 336 (15), 95 (80), 65 (100). For the 19-*R** isomer **8**: TLC R_f = 0.18 (1:9 MeOH/CH_2Cl_2, CAS: orange); UV (EtOH) λ_{max} 212, 244, 292 nm; IR (KBr, CO) ν_{max} 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (1 H, d, J = 7.0 Hz), 7.01 (1 H, ddd, J = 1.0, 7.6 and 7.6 Hz), 6.77 (1 H, dd, J = 7.0 and 7.6 Hz), 6.64 (1 H, d, J = 7.6 Hz), 3.94 (1 H, br s), 3.78 (3 H, s), 3.50−3.44 (3 H, m), 3.16 (1 H, dt, J = 11.2 and 3.1 Hz), 3.10 (1 H, m), 3.06 (1 H, d, J = 11.7 Hz), 2.93 (2 H, m), 2.57 (1 H, m), 2.42 (1 H, dd, J = 11.5 and 14.5 Hz), 1.92−1.83 (3 H, m), 1.65 (1 H, m), 1.56 (2 H, m), 1.35 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.28, 148.85, 138.65, 127.00, 122.18, 120.04, 110.47, 71.70, 65.50, 60.74, 58.36, 52.12, 50.69, 47.47, 41.51, 37.61, 36.86, 35.10, 29.77, 29.22, 16.59; CI (isobutane, 40 eV) MS (relative abundance) 355 (M^+ + 1, 100), 337 (48), 310 (12); FAB HRMS calcd for $C_{21}H_{27}N_2O_3$: 355.2022 (M^+ + 1); found: 355.2034.

Reduction of 16-*epi*-19-Oxokopsinine (7) with DIBALH. To a solution of 16-*epi*-19-oxokopsinine **7** (1.56 g, 4.43 mmol) in anhydrous THF (30 mL) was added DIBALH (5.32 mL, 1 M in hexane, 5.32 mmol), dropwise, under argon at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and then quenched with methanol. Sodium tartarate was added to the mixture, which was stirred until two layers separated. The water layer was extracted with dichloromethane. The combined organic layers were worked up as above, to yield the 19-*S** isomer **9** (0.89 g) and 19-*R** isomer **8** (0.22 g) in a ratio of 4:1 in 72% total yield.

Swern Oxidation of the 19-*R Isomer 8.** DMSO (0.23 mL, 3.3 mmol) was added dropwise to a stirred solution of oxalyl chloride (2 M in CH_2Cl_2, 0.80 mL, 1.6 mmol) in dichloromethane (10 mL) at −78 °C, under a nitrogen atmosphere. The alcohol **8** (0.46 g, 1.3 mmol) in dichloromethane (5 mL) was then added dropwise. The resulting slightly cloudly solution was stirred for 1 h at −78 °C and dry triethylamine (0.92 mL, 6.4 mmol) was added dropwise. The mixture was then allowed warm to room temperature and stirred for 1 h at room temperature. The reaction mixture was quenched by pouring it into aq $NaHCO_3$ solution and extracted with dichloromethane. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. The resulting residue was applied to column chromatography, eluting with dry ether, to give 16-*epi*-19-oxokopsinine (**7**, 0.32 g, 70%).

(±)-16-*epi*-19-*R-Mesyloxykopsinine (12).** To a solution of amino alcohol **8** (50 mg, 0.14 mmol), triethylamine (0.079 mL, 0.57 mmol), and DMAP (5 mg) in dichloromethane (5 mL) was added mesyl chloride (0.033 mL, 0.42 mmol), dropwise, at 0 °C under argon. After being stirred at room temperature overnight, the mixture was diluted with aqueous sodium carbonate and extracted with dichloromethane. The extracts were dried (Na_2SO_4), concentrated, and applied to a silica gel column that was eluted with 1:100 MeOH/CH_2Cl_2, to give the amino mesylate **12** (56 mg, 91%). TLC R_f = 0.52 (1:9 MeOH/CH_2Cl_2, CAS: red); UV (EtOH) λ_{max} 210, 244, 290 nm; IR (KBr,

CO) ν_{max} 1728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (1 H, d, J = 7.1 Hz), 7.04 (1 H, ddd, J = 1.0, 7.6 and 7.6 Hz), 6.8 (1 H, dd, J = 7.1 and 7.0 7 Hz), 6.66 (1 H, d, J = 7.7 Hz), 4.46 (1 H, m), 4.00 (1 H, br s), 3.81 (3 H, s), 3.31 (1 H, d, J = 0.8 Hz), 3.20 (1 H, dt, J = 11.3 and 3.1 Hz), 3.08 (2 H, m), 2.92 (2 H, m), 2.87 (3 H, s), 2.58 (1 H, dd, J = 11.5 and 14.9 Hz), 2.55 (1 H, m), 2.08 (1 H, dd, J = 9.9 and 14.6 Hz), 1.93 (1 H, m), 1.82 (2 H, m), 1.63 (2 H, m), 1.49 (1 H, m), 1.40 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.71, 148.49, 137.86, 127.33, 122.09, 120.21, 110.66, 81.3, 65.38, 61.07, 58.03, 52.36, 50.54, 47.37, 40.94, 38.32, 36.46, 35.50, 35.35, 29.42, 28.91, 17.20; CI (methane 40 eV) MS (relative abundance) 433 (M^+ + 1, 0.1), 336 (3), 279 (4), 201 (3), 178 (100), 112 (22); FAB HRMS calcd for $C_{22}H_{29}N_2O_5S$ (M^+ + 1): 433.1798; found: 433.1798.

Conversion of Amine 12 to Carbamate 13. Amine **12** (43 mg, 0.10 mmol) was stirred with methyl chloroformate (0.42 mL, 5.4 mmol) and sodium carbonate (0.57 g, 5.4 mmol) in dichloromethane (5 mL) at room temperature overnight. After filtration of the mixture, the filtrate was concentrated under reduced pressure. The residue was purified on a silica gel column (1:1.5 EtOAc/hexane) to generate the carbamate **13** (42 mg, 86%). This product was identical with that produced from mesylation of alcohol **11**.

(±)-16-*epi*-19-*S-Tosyloxykopsinine *p*-Toluenesulfonamide (15).** To a solution of amino alcohol **9** (100 mg, 0.282 mmol) in anhydrous pyridine (1 mL) was added *p*-toluenesulfonic anhydride (277 mg, 0.847 mmol), at 0 °C, under argon. The mixture was then allowed to warm to room temperature and stirred overnight. After being quenched with saturated aqueous sodium carbonate at 0 °C, the mixture was extracted with dichloromethane. The organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was subjected to chromatography (1:1 EtOAc/hexane) to give the double tosylated product **15** (167 mg, 89%). TLC R_f = 0.18 (1:1 EtOAc/hexane, CAS: red); UV (EtOH) λ_{max} 212, 226 nm; IR (KBr, CO) ν_{max} 1747 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (2 H, d, J = 8.2 Hz), 7.65 (2 H, d, J = 8.2 Hz), 7.43 (1 H, d, J = 8.0 Hz), 7.29 (2 H, d, J = 8.1 Hz), 7.20 (2 H, d, J = 8.1 Hz), 7.17−6.99 (3 H, m), 4.19 (1 H, d, J = 9.8 Hz), 3.73 (3 H, s), 3.60 (1 H, dt, J = 12.3 and 3.1 Hz), 3.34 (1 H, dd, J = 1.4 and 15.6 Hz), 3.01(1 H, dd, J = 3.8 and 12.7 Hz), 2.93 (1 H, m), 2.69 (2 H, m), 2.58 (1 H, s), 2.56 (1 H, dd, J = 9.4 and 12.9 Hz), 2.43 (3 H, s), 2.37 (3 H, s), 1.84 (1 H, m), 1.74 (2 H, m), 1.69 (1 H, dd, J = 2.7 and 14.3 Hz), 1.63 (1 H, m), 1.33 (1 H, d, J = 13.3 Hz), 1.09 (1 H, m), 0.92 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.34 (C), 144.35 (C), 143.49 (C), 141.78 (C), 141.15 (C), 138.52 (C), 134.20 (C), 129.61 (CH), 129.47 (CH), 127.66 (CH), 127.49 (CH), 126.91 (CH), 125.28 (CH), 121.66 (CH), 118.52 (CH), 83.17, 72.45 (C), 66.13, 58.70 (C), 51.56, 50.42 (CH_2), 47.82 (CH_2), 38.04, 35.75 (CH_2), 35.41 (C), 33.48 (CH_2), 31.37 (CH_2), 27.06 (CH_2), 21.55, 21.43, 18.25 (CH_2); CI (isobutane 40 eV) MS (relative abundance) 492 (M^+ − TsO + 1, 15), 336 (5), 279 (4), 247 (30), 187 (79), 157 (100), 125 (95), 80 (74); FAB HRMS calcd for $C_{35}H_{39}N_2O_7S_2$ (M^+ + 1): 663.2199; found: 663.2201.

Fragmentation of Tosylate 15. A mixture of tosylate **15** (95 mg, 0.14 mmol) and potassium cyanide (28 mg, 0.43 mmol) in ethanol−water (9.6 mL/2.8 mL) was gently heated at reflux for 2 h. A precipitate appeared during this course. The reaction mixture was evaporated to dryness under reduced pressure. The residue was diluted with water and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was triturated with a small amount of dichloromethane to yield the cyanide compound **16** (66 mg, 89%). UV (EtOH) λ_{max} 214 nm; IR (KBr, CO) ν_{max} 1720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (1 H, d, J = 7.3 Hz), 7.89 (2 H, d, J = 8.3 Hz), 7.27 (2 H, d, J = 8.3 Hz), 7.05 (1 H, dd, J = 7.5 and 7.8 Hz), 7.02 (1 H, dd, J = 7.3 and 7.5 Hz), 6.79 (1 H, d, J = 7.8 Hz), 5.57 (1 H, br s), 4.50 (1 H, s), 3.62 (3 H, s), 3.47 (1 H, dd, J = 6.7 and 9.2 Hz), 3.35 (1 H, d, J = 15.4 Hz), 3.09 (2 H, m), 2.93 (1 H, m), 2.83−2.72 (2 H, m), 2.66 (1 H, m), 2.54 (1 H, dd, J = 6.3 and 14.7 Hz), 2.45 (1 H, dd, J = 7.4 and 15.8 Hz), 2.40 (3 H, s), 2.19 (2 H, m), 1.87 (1 H, m), 1.71 (1 H, m), 1.28 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.69, 143.80, 142.52, 142.04, 138.56, 129.90, 129.66, 128.30, 127.76, 124.24, 123.70, 118.02, 117.49, 115.71, 82.91, 63.37, 59.87, 51.75, 47.96, 47.81, 45.54, 36.35, 36.31, 34.60, 31.86, 27.57, 21.51; CI (isobutane, 40 eV) MS (relative abundance) 518 (M^+ + 1, 6), 491 (30), 363 (3), 336 (38), 171 (45), 157 (79), 101 (100), 70 (87); FAB HRMS calcd for $C_{29}H_{31}N_3O_4$-SLi (MLi^+): 524.2195; found: 524.2206.

16-*epi*-11,12-Demethoxy-*N*-demethoxycarbonyl-16-deoxypauciflorine B *p*-Toluenesulfonamide (17). A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirring bar and an O_2 inlet. After being purged with O_2, the flask was charged with nitrile **16** (43.8 mg, 0.0847 mmol), 18-crown-6 ether (2.2 mg, 0.0085 mmol), and dry THF (5 mL). A solution of KO-*t*-Bu (0.254 mL, 1 M in *t*-BuOH, 0.254 mmol) was added in one portion at room temperature, and the suspension was allowed to stir under an O_2 atmosphere for 3 h, when the suspension became a clear solution. The mixture was then quenched with aqueous NH_4Cl at 0 °C and extracted with chloroform. The dried (Na_2SO_4) organic layers were concentrated under reduced pressure, and the residue was chromatographed on silica gel (1:1 EtOAc/hexane to 1:10 acetone/EtOAc) to provide lactam **17** (42.5 mg, 90%). TLC R_f = 0.54 (100% EtOAc, CAS: red); mp: 268−269 °C; UV (EtOH) λ_{max} 218 nm; IR (KBr, CO) ν_{max} 1748, 1685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (3 H, m), 7.21 (4 H, m), 6.98 (1 H, d, J = 6.9 Hz), 5.24 (1 H, d, J = 6.9 Hz), 4.00 (1 H, t, J = 12.9 Hz), 3.79 (3 H, s), 3.68 (1 H, br d, J = 16.1 Hz), 3.63 (1 H, br d, J = 9.4 Hz), 3.49 (1 H, m), 3.13 (1 H, t, J = 9.8 Hz), 2.83 (1 H, br d, J = 14.2 Hz), 2.71 (1 H, dd, J = 9.4 and 20.1 Hz), 2.50 (1 H, ddd, J = 2.4, 7.4 and 16.8 Hz), 2.38 (3 H, s), 2.25 (1 H, d, J = 18.6 Hz), 2.15 (2 H, m), 1.90 (1 H, m), 1.77 (1 H, dd, J = 7.6 and 15.3 Hz), 1.46 (1 H, m), 1.38 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.31, 173.26, 143.78, 142.62, 139.12, 137.97, 129.59, 128.42, 127.95, 127.51, 126.60, 125.35, 123.78, 120.76, 80.70, 61.53, 51.71, 44.98, 42.42, 40.50, 35.47, 32.13, 29.70, 29.60, 26.91, 21.58; CI (isobutane, 40 eV) MS (relative abundance) 507 (M^+ + 1, 13), 398 (62), 353 (39), 221 (12), 165 (19), 157 (100). Anal. Calcd for $C_{28}H_{30}N_2O_5S$: C, 66.38; H, 5.97; N, 5.53; S, 6.33. Found: C, 66.25; H, 6.21; N, 5.29; S, 6.28.

16-*epi*-11,12-Demethoxy-*N*-demethoxycarbonyl-16-deoxypauciflorine B (18). To a solution of sulfonamide **17** (9.0 mg, 0.018 mmol) in anhydrous THF (3 mL) was added lithium diisopropylamide (0.036 mL, 1.5 M in hexane, 0.053 mmol) at −78 °C, under argon. The reaction mixture was stirred at −78 °C for 30 min. The yellow mixture was then quenched with aqueous NH_4Cl solution and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and evaporated. Purification on a silica gel column (1:1 EtOAc/hexane) yielded the deprotected amine product **18** (2.6 mg, 42%), with starting material **17** recovered (5.0 mg). TLC R_f = 0.67 (100% EtOAc, CAS: red); mp: 217−218 °C; UV (EtOH) λ_{max} 212, 245, 296 nm; IR (KBr, CO) ν_{max} 1751, 1685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (1 H, dd, J = 7.5 and 7.7 Hz), 6.99 (1 H, d, J = 7.3 Hz), 6.77 (1 H, dd, J = 7.3 and 7.5 Hz), 6.59 (1 H, d, J = 7.7 Hz), 5.46 (1 H, m), 4.08 (1 H, dd, J = 13.0 and 13.6 Hz), 4.05 (1 H, br s), 3.76 (3 H, s), 3.67 (1 H, dd, J = 9.6 and 16.7 Hz), 3.37 (1 H, dd, J = 2.3 and 8.4 Hz), 3.19 (1 H, dd, J = 9.7 and 9.8 Hz), 2.91 (1 H, dd, J = 2.7 and 13.9 Hz), 2.74 (2 H, m), 2.57 (2 H, m), 2.34 (1 H, d, J = 18.3 Hz), 2.18 (2 H, m), 2.04 (1 H, m), 1.48 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.44, 175.04, 149.03, 131.38, 130.72, 128.21, 124.91, 122.81, 119.87, 109.67, 71.06, 60.76, 51.95, 43.87, 42.88, 42.45, 35.74, 30.61, 29.97, 29.69, 28.70, 21.33; CI (isobutane, 40 eV) MS (relative abundance) 353 (M^+ + 1, 54), 352 (M^+,15), 221 (26), 165 (25), 85 (50), 69 (100); FAB HRMS calcd for $C_{21}H_{25}N_2O_3$ (M^+ + 1): 353.1866; found: 353.1874.

Cleavage of sulfonamide **17** with sodium naphthalenide: A solution of sodium naphthalenide in DME was prepared by adding dimethoxyethane (5 mL) to a mixture of sodium (0.150 g, 6.50 mmol) and naphthalene (1.05 g, 8.00 mmol), stirring at room temperature for 2 h. To a solution of the sulfonamide **17** (10.0 mg, 0.0198 mmol) in dry DME (5 mL) at −78 °C, under N_2, was added the above dark blue sodium naphthalenide solution, dropwise, until a light green color persisted. The reaction mixture was stirred for an additional 5 min at the same temperature and then quenched with saturated

aqueous $NaHCO_3$ and extracted with dichloromethane. The combined organic layers were dried and concentrated. Purification of the resulting residue on a silica gel column, eluting with 1:1 EtOAc/hexane, yielded compound **18** (6.6 mg, 95%). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.48; H, 6.98; N, 7.84.

Cleavage of sulfonamide **17** with sodium amalgam: To a solution of the sulfonamide **17** (15.0 mg, 0.0296 mmol) in dry methanol (5 mL) was added dibasic sodium phosphate (21 mg) and sodium amalgam (277 mg, 10% Na). The reaction mixture was then gently heated at reflux for 12 h. After cooling to room temperature, the reaction mixture was quenched with water (10 mL) and worked up to yield the amine **18** (9.0 mg, 86%). This compound was identical to the product generated by treating the sulfonamide with sodium naphthalenide.

Preparation of Cyclic Ketene Acetal−Acylal 19 and Its Methanol Adduct 20. Triphosgene (25.3 mg, 0.0852 mmol) was added to a solution of amine **18** (10.0 mg, 0.0284 mg, prepared by cleavage of sulfonamide **17** with sodium naphthalenide) and pyridine (0.037 mL, 0.45 mmol) in dichloromethane (3 mL) at 0 °C, under argon, and the mixture was stirred at room temperature for 40 min. After being cooled to 0 °C, the resulting violet solution was treated with more pyridine (0.037 mL, 0.45 mmol), followed by dry methanol (0.25 mL, excess). The reaction mixture was left 30 more min at 0 °C, brine was added, and the mixture was extracted with dichloromethane. Evaporation of the solvent and separation on a column (1:1, EtOAc/hexane) afforded compound **19** (10.6 mg, 91%). TLC $R_f = 0.28$ (2:1 EtOAc/hexane, CAS: pale red); mp: 168−170 °C; UV (EtOH) λ_{max} 222, 276 nm; IR (KBr, CO) ν_{max} 1738, 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (1 H, d, $J = 7.6$ Hz), 7.30 (1 H, dd, $J = 7.6$ and 7.7 Hz), 7.19 (1 H, dd, $J = 7.5$ and 7.7 Hz), 7.15 (1 H, d, $J = 7.5$), 5.32 (1 H, d, $J = 7.4$ Hz), 4.08 (1 H, t, $J = 13.5$ Hz), 3.83 (3 H, s), 3.67 (1 H, m), 3.23 (1 H, t, $J = 10.0$ Hz), 3.01 (2 H, m), 2.91 (1 H, d, $J = 14.1$ Hz), 2.78 (1 H, dd, $J = 7.8$ and 15.3 Hz), 2.60 (1 H, dd, $J = 7.9$ and 13.8 Hz), 2.27 (2 H, m), 2.19 (1 H, m), 2.06 (1 H, m), 1.52 (1 H, d, $J = 15.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.65 (C), 148.15 (C), 146.24 (C), 140.77 (C), 134.59 (C), 132.70 (C), 128.17 (CH), 126.25 (CH), 124.64 (CH), 120.65 (CH), 118.53 (CH), 85.32 (C), 73.82 (C), 61.35 (C), 56.77 (CH_3), 44.00 (CH_2), 42.19 (CH_2), 36.66 (CH_2), 35.71 (CH_2), 29.11 (CH_2), 25.63 (CH_2), 21.14 (CH_2); CI (isobutane, 40 eV) MS (relative abundance) 379 ($M^+ + 1$, 26), 334 (4), 291 (18), 226 (5), 212 (9), 170 (100), 101 (23). Anal. calcd for $C_{22}H_{22}N_2O_4 \cdot H_2O$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.70; H, 5.63; N, 6.89.

When the reaction mixture was allowed to warm to room temperature and stirred at room temperature for 2 d before quenching with brine, compound **20** was generated in a yield of 94%. When compound **18** was subjected to the same triphosgen/pyridine/methanol conditions as above and allowed to react at room temperature for 2 d, compound **19** was generated in 90% yield. However, when compound **19** was treated with PPTS in dry methanol at room temperature for 3 d, less than a half of compound **19** was converted into compound **20**.

For **20**: TLC $R_f = 0.17$ (2:1 EtOAc/hexane, CAS: pale red); UV (EtOH) λ_{max} 210, 238, 278 nm; IR (KBr, CO) ν_{max} 1710−1715, 1694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (1 H, d, $J = 8.0$ Hz), 7.28 (1 H, m), 7.14 (2 H, m), 5.35 (1 H, d, $J = 7.6$ Hz), 4.09 (1 H, dt, $J = 1.8$ and 13.8 Hz), 3.67 (1 H, dt, $J = 9.9$ and 6.8 Hz), 3.52 (3 H, s), 3.51 (3 H, s), 3.22 (1 H, t, $J = 9.7$ Hz), 2.94 (1 H, dt, $J = 2.6$ and 11.4 Hz), 2.85 (1 H, dt, $J = 2.7$ and 9.0 Hz), 2.66 (1 H, d, $J = 16.0$ Hz), 2.53 (1 H, dd, $J = 6.6$ and 14.5 Hz), 2.49−2.43 (3 H, m), 2.24 (1 H, m), 2.19 (1 H, dt, $J = 4.1$ and 12.6 Hz), 2.04 (1 H, m), 1.92 (1 H, dt, $J = 14.0$ and 9.6 Hz), 1.52 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.43 (C), 148.17 (C), 140.76 (C), 134.14 (C), 131.51 (C), 128.34 (CH), 125.21 (CH), 124.71 (CH), 121.21 (CH), 117.83 (CH), 116.34 (C), 70.75 (C), 61.45(C), 51.94, 49.58, 43.69 (CH_2), 42.49 (CH_2), 35.88 (CH_2), 34.26, 30.29 (CH_2), 30.25 (CH_2), 24.51 (CH_2), 21.09 (CH_2); CI (isobutane, 40 eV) MS (relative abundance) 411 ($M^+ + 1$, 24), 366 (7), 279 (4), 223 (100), 177 (41); FAB HRMS calcd for $C_{23}H_{27}N_2O_5$ ($M^+ + 1$): 411.1921; found: 411.1915.

11,12-Demethoxy-16-deoxypauciflorine B (22). Reaction of the cyclic ketene acetal **19** with sodium methoxide: A ca. 1 M sodium methoxide in methanol solution was made by dissolving sodium (230 mg) in dry methanol (10 mL). A solution of compound **19** (10 mg, 0.026 mmol) in the above sodium methoxide solution (ca. 1 M, 5 mL) was gently heated at reflux for 2 h. After evaporation of most of the methanol, the residue was quenched with sat. NH_4Cl, and extracted with dichloromethane. Purification on a silica gel column (EtOAc/hexane 1:1) yielded compound **22** (10 mg, 92%). TLC $R_f = 0.31$ (2:1 EtOAc/hexane, CAS: pale purple-red); UV (EtOH) λ_{max} 214, 246, 286 nm; IR (KBr, CO) ν_{max} 1724, 1694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (1 H, br s), 7.19 (1 H, m), 7.00 (2 H, m), 5.30 (1 H, d, $J = 6.2$ Hz), 4.97 (1 H, br s), 4.05 (1 H, dd, $J = 13.0$ and 13.5 Hz), 3.88 (3 H, s), 3.80 (1 H, m), 3.70 (3 H, s), 3.20 (1 H, t, $J = 10.1$ Hz), 2.90 (2 H, m), 2.78 (1 H, m), 2.58 (1 H, dd, $J = 7.1$ and 15.7 Hz), 2.47 (2 H, m), 2.26−2.12 (3 H, m), 1.84 (1 H, m), 1.51 (1 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.54, 174.21, 154.03, 133.07, 132.55, 128.27, 124.63, 123.38, 121.34, 115.06, 74.82, 60.23, 52.39, 52.28, 44.22, 42.58, 40.78, 35.82, 33.32, 31.63, 27.60, 21.27; CI (isobutane, 40 eV) MS (relative abundance) 412 ($M^+ + 2$, 28), 411 ($M^+ + 1$, 100), 410 (M^+, 49), 379 (2), 353 (1), 255 (16), 227 (8), 156 (10); EI MS (relative abundance) 410 (M^+, 51), 379 ($M^+ -$ MeO, 6), 351 (7), 273 (27), 241 (42), 227 (98), 207 (68), 168 (59), 59 (100); FAB HRMS calcd for $C_{23}H_{26}N_2O_5$ (MLi^+): 417.2002; found: 417.1982.

Reaction of the Methanol Adduct 20 with Sodium Methoxide. A mixture of compound **20** (10 mg, 0.024 mmol) and a sodium methoxide in methanol solution (ca. 1 M, 6 mL), was heated to reflux. The reaction was monitored by TLC. After 30 min refluxing, a pale orange-red spot ($R_f = 0.19$, EtOAc/hexane 2:1) appeared with the starting material, which was almost consumed. As refluxing continued, one more pale purple-red spot appeared ($R_f = 0.31$, EtOAc/hexane) and its amount increased. After refluxing for a total of 5 h, the mixture was cooled, concentrated, and poured into sat. NH_4Cl, extracted with dichloromethane, and the extract was dried and concentrated. The residue was subjected to chromatography, eluting with 1:1 ether/hexane, to give ester **22** (3 mg, 30%) and a compound with $R_f = 0.19$ (6 mg, 60%). The latter was proposed to be the corresponding C-16 epimer **21**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (1 H, d, $J = 8.2$ Hz), 7.21 (1 H, m), 7.07 (2 H, m), 5.61 (1 H, m), 4.06 (1 H, t, $J = 12.8$ Hz), 3.76 (3 H, s), 3.71 (3 H, s), 3.61 (1 H, dd, $J = 8.2$ and 18.3 Hz), 3.22 (2 H, dd, $J = 7.9$ and 17.1 Hz), 2.99−2.87 (3 H, m), 2.72 (1 H, m), 2.40 (2 H, m), 2.27 (1 H, m), 2.21 (1 H, dt, $J = 3.9$ and 12.8 Hz), 1.95 (1 H, m), 1.85 (1 H, m), 1.51 (1 H, dd, $J = 3.0$ and 15.0 Hz); CI (isobutane, 40 eV) MS (relative abundance) 411 ($M^+ + 1$, 14.9), 409 (6.9), 221 (100), 165 (26.2).

16,17-Anhydro-11,12-demethoxypauciflorine B (23). To a solution of ester **22** (10 mg, 0.024 mmol) in THF (0.5 mL) at −78 °C was added KHMDS (0.5 M in toluene, 0.097 mL, 0.048 mmol). The resulting mixture was allowed to stir at −78 °C for 1 h; then a solution of 2-(phenylsulfonyl)-3-phenyloxaziridine (12.7 mg, 0.048 mmol) in THF (0.5 mL) was added. After further stirring at −78 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. Removal of solvent and purification by flash chromatography (hexane: EtOAc, 1:3) yielded diene ester **23** (8.4 mg, 86%). TLC $R_f = 0.28$ (1:3 hexane/EtOAc, CAS, pale red); UV (EtOH) λ_{max} 214, 244, 285, 290 nm; IR (KBr, CO) γ_{max} 1710, 1686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (two carbamate rotamers) 1.59 (1 H, d, $J = 12.3$ Hz), 1.75 (1 H, m), 1.91 (1 H, m), 2.19 (1 H, dt, $J = 4.1$, 13.2 Hz), 2.46 (1 H, d, $J = 13.3$ Hz), 2.69 (1 H, dd-like), 2.96 (4 H, m), 3.57 (1 H, br.s), 3.70, 3.78, 3.84 (each s, 6 H), 4.06 (1 H, t, $J = 13.1$ Hz), 5.81 (1 H, s), 7.00 (3 H, m), 7.25 (1 H, t-like), 7.49 (d-like) & 7.94 (d-like) (together 1 H); EI (40 eV) MS (rel abundance) 408 (M^+, 98), 376 ($M^+ -$ OMe + 1, 44), 349 (41), 317 (46), 289 (32), 274 (34), 261 (73), 232 (71), 218 (71), 204 (93), 188 (59), 59 (100); FAB HRMS calcd for $C_{23}H_{24}N_2O_5$ (MLi^+): 415.1845; found: 415.1830.

Kopsijasminilam (1). To a solution of diene **23** (10.2 mg, 0.025 mmol) in 2-propanol/DCE (2:1, v/v, 1.5 mL) at −10 °C,

under O_2, were added successively $Mn(dpm)_2$ (2.1 mg, 20 mol %) and $PhSiH_3$ (7.7 uL, 2.5 equiv). The resulting mixture was stirred at −10 °C for 1 h, quenched with saturated aqueous $Na_2S_2O_3$, and extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. Removal of solvent and purification by flash chromatography on silica gel (ethyl acetate) yielded kopsijasminilam (**1**, 9.1 mg, 85%). TLC $R_f = 0.18$ (ethyl acetate, CAS, pink); EI (40eV) MS (rel abundance) 426 (M^+, 60), 408 ($M^+ - H_2O$, 98.2), 376 (M^+ -MeO +1, $-H_2O$, 40), 349 (39), 317 (46), 289 (29), 274 (47), 261 (71) 232 (70), 218 (71), 204 (98), 59 (100). All spectroscopic data including UV, IR, ^{1}H NMR, and ^{13}C NMR matched the reported data.[1] FAB HRMS calcd for $C_{23}H_{26}N_2O_6$ (MLi^+): 433.1957; found: 433.1968.

Deoxykopsijasminilam (2). A mixture of compound **22** (10 mg, 0.024 mmol) and 10% Pd/C (5 mg) in EtOH (1 mL) was stirred at room temperature under a H_2 atmosphere for 1 h. After filtration and concentration, the residue was applied to flash chromatography (hexane:EtOAc, 1:3), to yield deoxykopsijasminilam (**2**, 9.2 mg, 92%). TLC $R_f = 0.3$ (1:3 hexane/EtOAc, CAS, deep blue); EI (40 eV) MS 410 (M^+, 31), 378 (25), 351 (18), 323 (100), 291 (15), 276 (32), 248 (29), 234 (29), 220 (33), 206 (34), 59 (50). All spectroscopic data including UV, IR, ^{1}H NMR, and ^{13}C NMR matched the reported data.[1] FAB HRMS calcd for $C_{23}H_{26}N_2O_5$ (MLi^+): 417.2002; found: 417.1999.

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Supporting Information Available: IR spectra for compounds **1**, **2**, **7**−**20**, **22**, **23**. ^{1}H NMR and ^{13}C NMR, except where marked by (), spectra for compounds **1**, **2**, **7**, **8**, **9**, **10**, (**11**), **12**, (**13**), **14**, **15**, **16**, **17**, **18**, **19**, **20**, (**21**), **22**, (**23**). This material is available free of charge via the Internet at http://pubs.acs.org.

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