A Biomimetic Synthesis of the Pauciflorine A, B Skeleton

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The pauciflorines A and B (**1** and **2**, Figure 1) were isolated from *Kopsia pauciflora* Hook. f. (Apocyanaceae) in1996.[1] Their intriguing biological activity of inhibition of melanin biosynthesis in melanoma cells, without cytotoxicity, and their biogenetically unusual structures, make these compounds interesting synthetic targets. The relatively novel briged bis-spiroindoline lactam structure of the pauciflorines **1** and **2**, found previously only in kopsijasminilam ,[2] includes the additional synthetic challenge of a bridgehead double bond in a ten-membered ring, which also contains two trigonal atoms of a lactam function.

Our approach to the synthesis of this strained pentacyclic ring system was based on its presumed biogenetic derivation from an aspidosperma alkaloid precursor. Thus, racemic minovincine (**3**, 19-oxovincadifformine, Scheme 1), an alkaloid that we had obtained previously by three alternative synthetic routes,[3,4] and its cyclization in acid,[5] provided a hexacyclic ketone **4**. This compound was envisioned as the key precursor for a fragmentation reaction that would give the pentacyclic skeleton of the pauciflorines, including the bridgehead double bond.

Reduction of the hexacyclic ketone **4** withDIBALH at -78 ^{o}C provided a 1 : 4 ratio of two epimeric alcohols **5** and **6**. The alcohols could be chromatographically separated, and their stereochemistry defined by an NOE spectrum of epimer **6**, which showed correlations of the hydrogens adjacent to the *tert*- amine (C-3) and the hydroxyl (C-19) groups, as well as a C-3 to C-9 hydrogen correlation. A Swern oxidation of the C-19 *R** hydroxy epimer **5** allowed regeneration of the ketone **4.**

Assignment of the relative stereochemistry of the hydroxyl groups in the alcohols **5** and **6** was also based on the results of subsequent ring fragmentation of the latter.

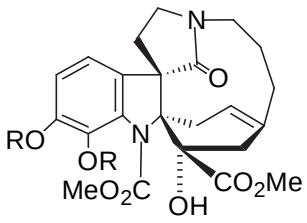
A reaction of the aminoalcohol **6** with tosyl anhydride in pyridine gave the sulfonamide tosylate **7**. Since elimination of its tosylate function was expected to lead to the stereoelectronically favored desired ring fragmentation, with formation of a hydrolytically sensitive imonium salt, the reaction was carried out in the presence of cyanide. The resulting nitrile **8** was obtained in 89% yield. Oxidation of this α-aminonitrile with potassium *tert*-butoxide and oxygen then furnished the pentacyclic lactam **9** in 90% yield.

The *N*-tosyl substituent of the fragmentation product **9** could be removed with sodium amalgam and NaH_2PO_4, or with sodium naphthalenide. It was also lost in variable yields on formation of the ester enolate with LDA, and subsequent aqueous work-up; perhaps assisted by bridging to the ester enolate oxygen (see below).

Formation of a carbamate from the amine **10** did not occur as easily as the derivatization of the amine **4** (methyl chlorocarbonate and K_2CO_3) but required a reaction with triphosgene, followed by treatment with methanol. At 0 ^{o}C the cyclic ketene acetal-acylal **11** was obtained. Its reaction with sodium methoxide in refluxing methanol provided the carbamate ester **12** (demethoxy-deoxypauciflorine B).

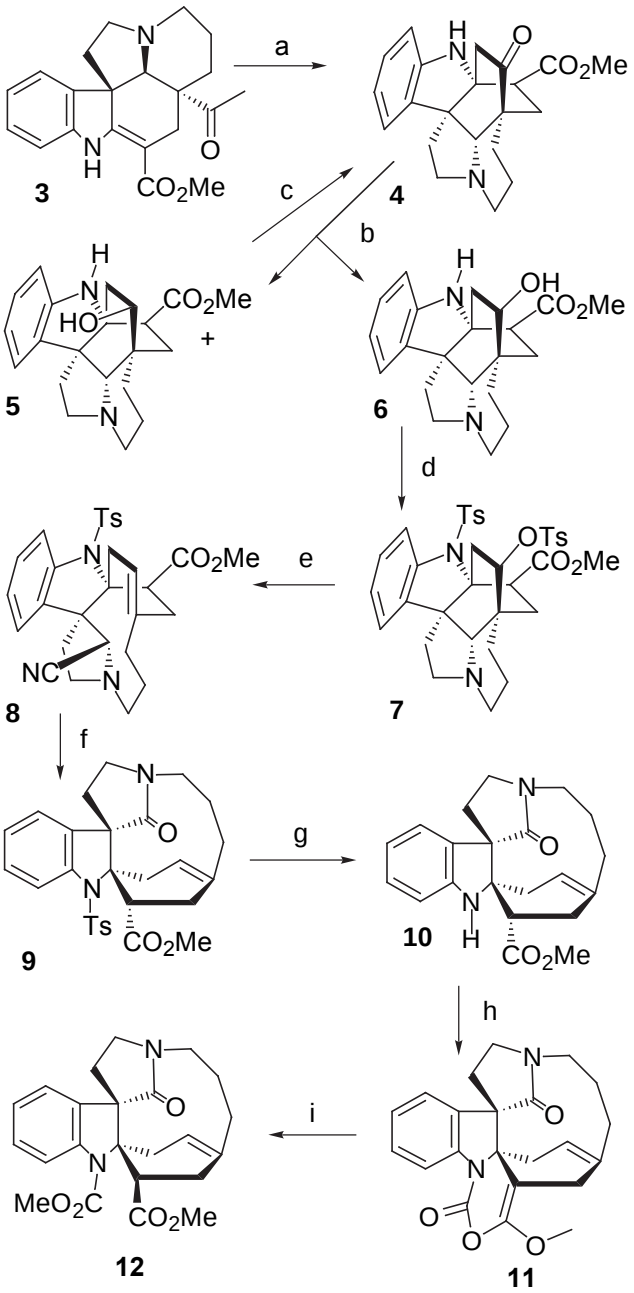
While oxidation of the enolate anion of the ester **12**, or oxidation of the enol derivative **11** were anticipated to provide the 16-α-hydroxy function of the pauciflorines, such an introduction of the hydroxyl group proved to be problematic.

Figure 1



1 pauciflorine A, R = CH_2
2 pauciflorine B, R = Me

Scheme 1



a: HCl-MeOH, reflux, 44% (85% based on recovery of **4**);
b: DIBALH, THF, -78 ^{o}C, 5 : 6 =1 : 4, 72%; Super Hydride,
THF, - 78 ^{o}C 5: 6 = 15 : 1, 85%; c:Swernoxid., 70%; d: Ts_2O,
pyd., rt, 89%; e: NaCN, EtOH-H_2O, refl., 89%; f: ^{t}BuOK,
THF, O_2, rt,90%; g: Na naphthalenide, DME, -78 ^{o}C, 95%;
h:triphosgene, pyr., CH_2Cl_2, 0 ^{o}C, MeOH, pyr., 91%;
i: NaOMe, MeOH, refl., 92%.

Acknowledgements: Low resolution mass spectra were obtained by Ms. Wenning Dai of our group and high resolution mass spectra by Dr. Michael Gross of the Washington University Mass Spec. Research Resource. The work was supported by the National Cancer Institute through grant RO1 CA 12010.

Footnotes:

1. Kam, T.-S.; Yoganathan, K.; Koyano, T.; Komiyama, K. *Tetrahedron Lett.* **1996**, *37*, 5765.
2. Ruangrungsi, N.; Likhitwitayawuid, K.; Jongbunprasert, V.; Ponglux, D.; Aimi, N.; Ogata, K.; Yasuoka, M.; Haginiwa, J.; Sakai, S. *Tetrahedron Lett*. **1987**, *28*, 3679.
3. Kuehne, M. E.; Earley, W. G. *Tetrahedron*, **1983**, *39*, 3707.
4. Kuehne, M. E.; Earley, W. G. *Tetrahedron*, **1983**, *39*, 3715.
5. Langlois, N.; Andriamialisoa, R. Z. *J. Org. Chem.* **1979**, *44*, 2468

SUPPLEMENTARY MATERIAL

Experimental Section

16-*epi*-19-Oxokopsinine (5): A solution of racemic minovincine (**3**,[3,4] 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).[5] The reaction mixture was concentrated, made alkaline with aqueous sodium carbonate and extracted with dichloromethane. The dried (Na_2SO_4) extracts were evaporated and subjected to chromatography on silica gel, eluting with dry ether, to give 16-*epi*-19-oxokopsinine(**4**, 560 mg, 44%, 85% based on recovered material),and recovered minovincine (**3**, 612 mg). TLC R_f = 0.27 (100% Et_2O, CAS: orange); UV (EtOH) λ_{max} 210, 240, 294 nm; IR (KBr) ν_{max} 3350, 2933, 2857, 2781, 1722, 1609, 1461, 1205, 750 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) ppm; ^{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; EI MS (methane): 353 (M^++1, 5.2), 352 (M^+, 15.4), 294 (17.0), 138 (59.3), 109 (100).

Reduction of 16-epi-19-Oxokopsinine (4). $NaBH_4$ (104 mg, 2.74 mmol) was added to a stirred solution of 16-epi-19-Oxokopsinine (**5**, 483 mg, 1.37 mmol) in methanol (10 mL) at 0 °C. The reaction mixture was allowed to warm to rt, 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 (2 : 98 to 4 : 96 to 1 : 10 MeOH/CH_2Cl_2) to furnish the 19-S* isomer **7** (137 mg), together with the 19-R* isomer **6** (182 mg), total yield 86%. For the 19-S* isomer **7**: TLC R_f = 0.36 (1 : 9 MeOH/CH_2Cl_2, CAS: orange); UV (EtOH) λ_{max} 210, 244, 294 nm; IR (KBr) ν_{max} 3383, 2931, 2857, 1718, 1609, 1478, 1458, 1437, 1387, 1213, 1072, 1017, 910, 732 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 1H, 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; EI MS (methane) 354 (M^+, 2.0), 336 (14.9), 95 (80.0), 65 (100). For the 19-R* isomer **6**: TLC R_f = 0.18 (1 : 9 MeOH/CH_2Cl_2, CAS: orange); UV (EtOH) λ_{max} 212, 244, 292 nm; IR (KBr) ν_{max} 3379, 2935, 2859, 1730, 1608, 1461, 1386, 1267, 1200, 1153, 1074, 1008, 968, 88, 841, 737 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; EI MS (isobutane) 355 (M^++1, 100), 337 (47.9), 310 (12.2); FAB HRMS calcd for $C_{21}H_{27}N_2O_3$: 355.2022 (M^++1); found: 355.2034.

Reduction of 16-epi-19-Oxokopsinine (5) with DIBALH. To a solution of 16-epi-19-Oxokopsinine **5** (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, 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 concentrated and the residue was applied to a silica gel column (2 : 98 to 4 : 96 to 1 : 10 MeOH/CH_2Cl_2) to furnish the 19-S* isomer **6** (0.89 g), together with the 19-R* isomer **5** (0.22 g), total yield 72%. For the 19-S* isomer **6**: TLC R_f = 0.36 (1 : 9 MeOH/CH_2Cl_2, CAS: orange); UV (EtOH) λ_{max} 210, 244, 294 nm; IR (KBr) ν_{max} 3383, 2931, 2857, 1718, 1609, 1478, 1458, 1437, 1387, 1213, 1072, 1017, 910, 732 cm^{-1}; ^{1}H 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 1H, 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; EI MS (methane) 354 (M^+, 2.0), 336 (14.9), 95 (80.0), 65 (100). For the 19-R* isomer **5**: TLC R_f = 0.18 (1 : 9 MeOH/CH_2Cl_2, CAS: orange); UV (EtOH) λ_{max} 212, 244, 292 nm; IR (KBr) ν_{max} 3379, 2935, 2859, 1730, 1608, 1461, 1386, 1267, 1200, 1153, 1074, 1008, 968, 88, 841, 737 cm^{-1}; ^{1}H 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; EI MS (isobutane) 355 (M^++1, 100), 337 (47.9), 310 (12.2); FAB HRMS calcd for $C_{21}H_{27}N_2O_3$: 355.2022 (M^++1); found: 355.2034.

Swern oxidation of the19-R* isomer 5. 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 **6** (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 rt and stirred for 1 h at rt. 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 (**4**, 0.32 g, 70%).

Double Tosylation of Amino Alcohol 6. To a solution of amino alcohol **6** (100 mg, 0.282 mmol) in anhydrous pyridine (1 mL), was added*p*-toluenesufonic anhydride (277

mg, 0.847 mmol), at 0 °C, under argon. The mixture was then allowed to warm to rt and stirred overnight. After being quenched with saturated aqueous sodium carbonate at 0 °C, the mixture was extracted dichloromethane. The organic layers were dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was subjected to chromatography (1 : 1EtOAc/hexane) to give the double tosylated product **7**(167 mg, 89%). TLC R_f = 0.18 (1 :1 EtOAc/hexane, CAS: red); UV (EtOH) λ_{max} 212, 226 nm; IR (KBr) ν_{max} 2947, 1747, 1598, 1457, 1359, 1173, 1097, 1028, 902, 815, 731, 668 cm^{-1}; ^1H NMR (500 MHz, CDCl3): (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, $CDCl_3$) (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); EI MS (isobutane) 492 (M^+-TsO+1, 14.9), 336 (5.1), 279 (3.8), 247 (29.9), 187 (79.2), 157 (100), 125 (95.4), 80 (74.1); FAB HRMS calcd for $C_{35}H_{39}N_2O_7S_2$ (M^++1): 663.2199; found: 663.2201.

Fragmentation of Tosylate 7. A mixture of tosylate **7** (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 **8** (66 mg, 89%). UV (EtOH) λ_{max} 214 nm; IR (KBr) ν_{max} 2924, 2845, 1720, 1596, 1483, 1458, 1434, 1326, 1247, 1158, 1087, 1021, 996, 816, 730, 665 cm^{-1}; ^1H 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; EI MS (isobutane) 518 (M^++1, 5.5), 491 (29.5), 363 (2.8), 336 (37.8), 171 (45.2), 157 (79.2), 101 (100), 70 (86.9); FAB HRMS calcd for $C_{29}H_{31}N_3O_4SLi$ (MLi^+): 524.2195; found: 524.2206.

Oxidation of Nitrile 8. 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 **8** (43.8 mg, 0.0847 mmol), 18-crown-6 (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 rt and the suspension was allowed to stir under an O_2 purge 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 **9** (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) ν_{max} 2923, 1748, 1685, 1457, 1433, 1358, 1272, 1171, 1146, 1093, 1035, 997, 920, 815, 671 cm^{-1}; ^1H 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; EI MS (isobutane) 507 (M^++1, 13.1), 398 (61.7), 353 (39.4), 221 (12.1), 165 (18.7), 157 (100); Analysis 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.

Preparation of Pentacyclic Amine 10. To a solution of sulfonamide **9** (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 **10** (2.6 mg, 42%), with starting material **9** recovered (5.0 mg). TLC R_f = 0.67 (100% EtOAc, CAS: red); mp: 217.0-218.0 °C; UV (EtOH) λ_{max} 212, 24, 296 nm; IR (KBr) ν_{max} 3359, 2922, 1751, 1685, 1457, 1358, 1272, 1166, 1146, 1092, 996, 672 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; EI MS (isobutane): 353 (M^++1, 53.9), 352 (M+, 14.5), 221 (25.6), 165 (25.2), 85 (50.3), 69 (100); FAB HRMS calcd for $C_{21}H_{25}N_2O_3$ (M^++1): 353.1866; found: 353.1874.

Cleavage of sulfonamide **9** with sodium naphthalenide: A solution of sodium naphthalenide in DME was prepared by adding dimethoxylethane (5 mL) to a mixture of sodium (0.150 g, 6.50 mmol) and naphthalene (1.05 g, 8.00 mmol), stirring at rt for 2 h. To a solution of the sulfonamide **9** (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, then quenched with sat. aq. $NaHCO_3$, 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 **10** (6.6 mg, 95%). ^{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), 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), 1.86 (1 H, m), 1.57 (1 H, br s), 1.48 (1 H, m); Analysis cald 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 **9** with sodium amalgam: To a solution of the sulfonamide **9** (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 rt, the reaction mixture was quenched with water (10 mL), and worked up to yield the amine **10** (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 11. Triphosgene (25.3 mg, 0.0852 mmol) was added to a solution of amine **10** (10.0 mg, 0.0284 mg, prepared by cleavage of sulfonamide **9** 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 rt during 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 was left 30 more min at 0 °C, then 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 **11** (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) ν_{max} 2929, 1738, 1690, 1483, 1427, 1380, 1272, 1243, 1168, 1116, 758, 732 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); EI MS (isobutane) 379 (M^++1, 26.4), 334 (3.5), 291 (17.6), 226 (5.0), 212 (9.0), 170 (100), 101 (22.5). Analysis calcd for $C_{22}H_{22}N_2O_4.H_2O$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.70; H, 5.63; N, 6.89.

11,12-Demethoxy-16-Deoxypauciflorine (12). Reaction of the cyclic ketene acetal **11** 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 **11** (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 **12** (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) ν_{max} 2951, 1724, 1694, 1600, 1487, 1439, 1357, 1267, 1217, 1087, 1014, 918, 754, 729 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), 2.11 (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; EI MS (isobutane): 412 (M^++2, 27.9), 411 (M^++1, 100), 411 (M^+, 48.8), 379 (1.7), 353 (1.4), 255 (15.9), 227 (8.4), 156 (10.1).