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Tetrahedron
Tetrahedron 63 (2007) 10337–10344

Intramolecular Diels–Alder reactions of oxazole–olefins: synthesis of the *Rauwolfia* alkaloids suaveoline and norsuaveoline

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Received 26 June 2007; revised 13 July 2007; accepted 17 July 2007
Available online 27 July 2007

Abstract—A full account of the highly stereoselective total synthesis of two indole alkaloids, suaveoline (**4**) and norsuaveoline (**5**), is presented. Central features of the synthetic strategy include the conversion of L-tryptophan methyl ester (**12**) into the oxazole derivative **11** and the intramolecular Diels–Alder reaction of the oxazole–olefin **19** leading to the pentacyclic pyridine derivative **21**.

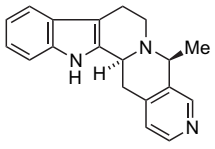
1. Introduction

The Diels–Alder reactions of oxazoles with olefins have become useful tools for the preparation of highly substituted pyridines, such as pyridoxine and its analogs, since the first example of this cycloaddition reaction was reported by Kondrat'eva in 1957.[1,2] Although numerous studies have described the utility of oxazoles for the construction of pyridines, there have been few reports exploiting the intramolecular Diels–Alder reactions of oxazole–olefins for the synthesis of pyridine-containing natural products.[3,4] Recently, we have achieved the synthesis of the indolopyridonaphthyridine alkaloid normalindine (**1**)[5] and two monoterpene alkaloids plectrodorine (**2**) and oxerine (**3**)[6] through a route featuring the construction of the annulated pyridines by intramolecular oxazole–olefin Diels–Alder reactions. The extension of this approach to the synthesis of the macroline/sarpagine related indole alkaloids suaveoline (**4**) and norsuaveoline (**5**) is described here.[7]

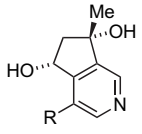
Suaveoline (**4**) was isolated for the first time from the trunk bark of *Rauwolfia suaveolens* by Potier and co-workers in 1972[8] and has since been found in other species of *Rauwolfia*.[9] The structure and absolute stereochemistry of suaveoline, proposed on the basis of spectroscopic data and chemical correlation with ajmaline,[8] were confirmed by racemic[10] and enantiospecific[11] syntheses of **4**. On the other hand, norsuaveoline (**5**) was reported as one of the 32 alkaloids isolated from the stem bark of *Rauwolfia caffra*[9e] and was synthesized by Cook and co-workers.[12]

2. Results and discussion

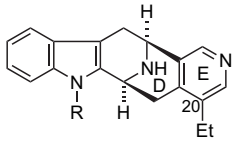
For the efficient construction of the DE rings of **4** and **5**, exploiting the intramolecular oxazole–olefin Diels–Alder reaction, we planned to employ **9** as a precursor (Scheme 1). The requisite oxazole–olefin **9** would be obtained from **11** through the cis-selective Pictet–Spengler reaction[11h,13] and the subsequent introduction of an appropriate olefin moiety to the oxazole aldehyde **10**. According to our previously reported procedure for the preparation of chiral 5-(aminomethyl)oxazoles from α-amino esters,[14] L-tryptophan methyl ester (**12**) would be readily converted into the oxazole **11**. An important feature of this strategy is that other suaveoline-related alkaloids, macrophylline (**6**),[9e,g,15] macrocaffrine (**7**),[9e,15b] and sellowiine (**8**),[16] which possess different substituents at the 20-position, should be derived from a variety of oxazole–olefins **9** that are readily available via the Wittig reaction of the aldehyde **10**.



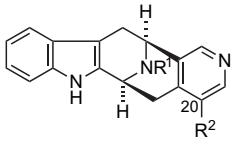
1



2: R = CO_2Me
3: R = H



4: R = Me
5: R = H



6: R^1 = Me, R^2 = CH_2CH_2OH
7: R^1 = Me, R^2 = CH_2OH
8: R^1 = R^2 = H

Keywords: Amino acids; Diels–Alder reaction; Indole alkaloids; Oxazoles.
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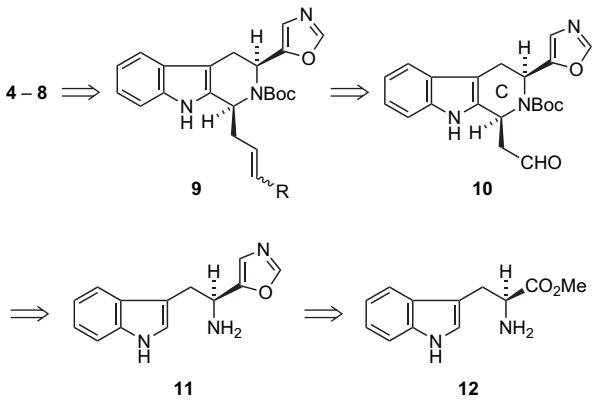
doi:10.1016/j.tet.2007.07.070



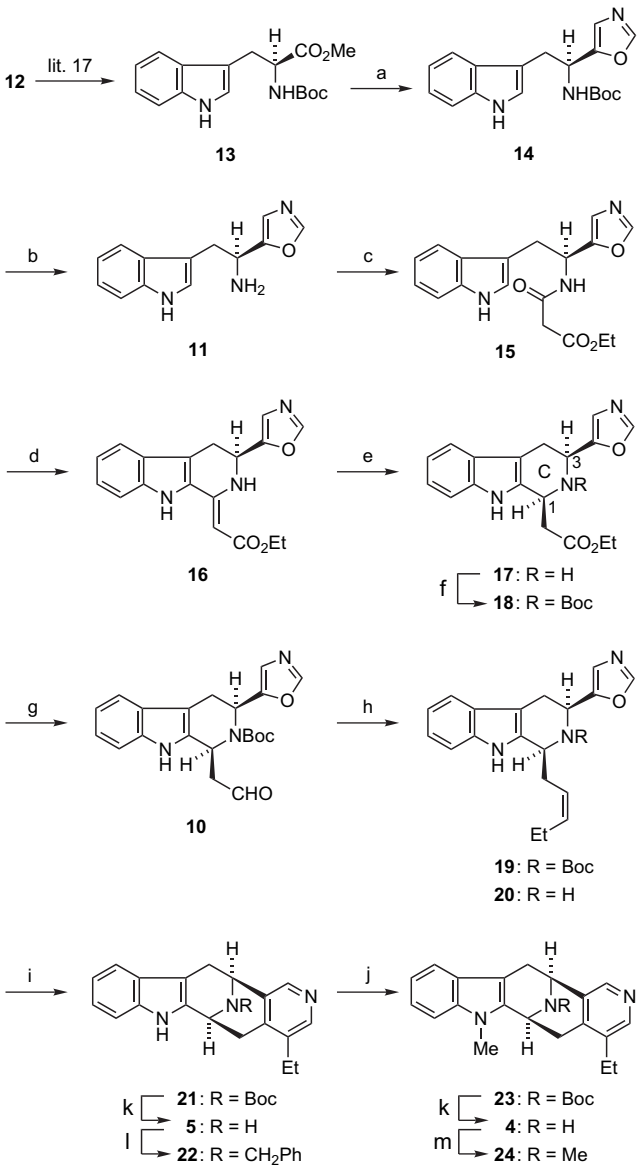
Scheme 1.

The synthesis of suaveoline (**4**) and norsuaveoline (**5**) began with the conversion of the *N*-protected amino ester **13**,[17] derived from **12**, into the oxazole **14** (Scheme 2). Reaction of **13** with α-lithiated methyl isocyanide at −78 °C was effected according to our previous method,[14] affording **14** in 82% yield. Deprotection of **14** with trifluoroacetic acid gave the amino oxazole **11** (98% yield), which was shown to have 97% enantiomeric purity by Mosher's method.

With the amino oxazole **11** in hand, we set out to explore the cis-selective Pictet–Spengler reaction.[11h,13] Bailey et al. reported that the kinetically controlled Pictet–Spengler reaction of **25** with the aldehyde **26**, where the hydroxy-protecting group is bulky and contains two remote aromatic rings that are able to π-stack to the indole moiety, yielded only the *cis*-tetrahydro-β-carboline **27**,[11h] although the related reaction of **12** possessing the methyl ester group instead of the cyanomethyl group in **25** furnished a 3:1 mixture of the *cis*-isomer **28** and the *trans*-isomer **31** (Scheme 3).[18] Unfortunately, application of this procedure to the amino oxazole **11** gave a mixture of **29** and **32** in 36% yield with poor stereoselectivity (cis–trans=3:1).

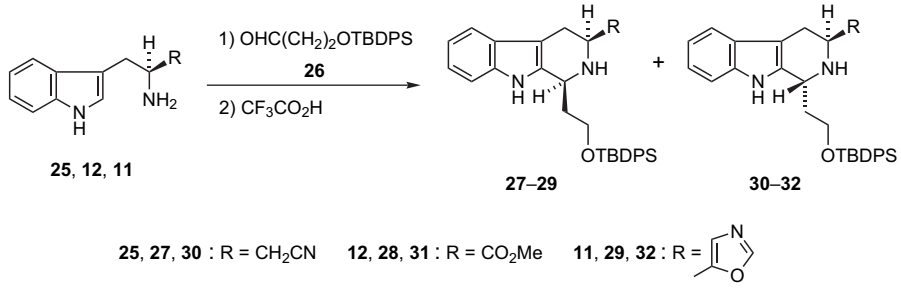
In 1984, Massiot's group published a modification of the Pictet–Spengler cyclization of tryptamines using activated alkynes as partners.[19] Treatment of **11** with ethyl propiolate followed by trifluoroacetic acid, however, afforded an inseparable 2:1 mixture of **17** and **35** in 57% yield (Scheme 4). The modified Pictet–Spengler cyclization of the N_b-benzyl derivative **33**, prepared by reductive alkylation of **11**, was also tried, but provided **34** and **36** as an inseparable mixture in 74% yield with high trans-selectivity (cis–trans=1:19).[20]

Since the Pictet–Spengler reaction of the amino oxazole **11** failed to give the desired *cis*-1,3-disubstituted tetrahydro-β-carboline in satisfactory yield and with the desired selectivity, we next investigated the construction of the C ring by taking advantage of the Bischler–Napieralski cyclization/reduction technology. Condensation of **11** with monoethyl malonate using diethyl phosphorocyanidate[21] as a coupling reagent provided the amide **15** (88% yield), which was then subjected to the Bischler–Napieralski cyclization with $POCl_3$ according to the method of Hino and co-workers.[22] Basification of the resulting iminium salt with Na_2CO_3 afforded the (*Z*)-ester **16** in 50% yield from **15**. The



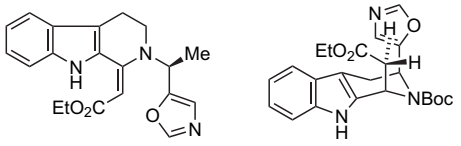
Scheme 2. Reagents and conditions: (a) $LiCH_2NC$, THF, −78 °C, 2.5 h; (b) CF_3CO_2H, CH_2Cl_2, 0 °C, 4 h; (c) $HO_2CCH_2CO_2Et$, $(EtO)_2P(O)CN$, Et_3N, DMF, 0 °C, 30 min then rt, 30 min; (d) (1) $POCl_3$, rt, 6 days; (2) 10% aqueous Na_2CO_3; (e) 20% $Pd(OH)_2$–C, H_2, EtOH, 1 atm, rt, 22 h; (f) $(Boc)_2O$, $CHCl_3$, reflux, 24 h; (g) DIBALH, CH_2Cl_2, −78 °C, 80 min; (h) $Ph_3P{=}CHCH_2CH_3$, benzene, rt, 30 min; (i) DBN, xylene, reflux, 9 h; (j) NaH, MeI, DMF, rt, 20 min; (k) CF_3CO_2H, CH_2Cl_2, 0 °C, 3 h; (l) $PhCH_2Br$, Et_3N, CH_3CN, rt, 40 min; (m) 35% aqueous HCHO, $NaBH_4$, AcOH, rt, 1 h.

enamino ester structure and geometry of the exocyclic double bond in **16** were assigned on the basis of the facts that one olefinic proton appeared at δ 5.03 and the indole N_a-proton (δ 8.21 or 8.59) resonated at higher field than the corresponding proton (δ 13.05) of the previously reported enamino ester **37**[5b] that possesses the *E* configuration due to intramolecular hydrogen bonding between the N_a-proton and the ester carbonyl group. Hydrogenation of **16** employing Pearlman's catalyst proceeded stereoselectively, furnishing the *cis*-tetrahydro-β-carboline **17** in 84% yield with no accompanying trans-isomer. The cis relationship for the C(1)- and C(3)-protons in **17** was confirmed by NOE experiments.



Scheme 3.

Having succeeded in the stereoselective construction of the C ring, our attention turned next to the introduction of an olefinic dienophile into the amino ester **17**. For this purpose, the amino group of **17** was first protected with di-*tert*-butyl dicarbonate to give **18** in 87% yield. The ^{1}H NMR spectrum of **17** indicated two methylene protons adjacent to the ester group at δ 2.80 and 2.88, whereas one of the corresponding protons of the *N*-Boc derivative **18** appeared at δ 1.85 and 1.99.[23] The large upfield shift in **18** is probably due to the shielding effect arising from the oxazole ring of the conformer **18A**, where both C(1)- and C(3)-substituents occupy pseudo-axial positions.[13b] Such a conformation, after the introduction of an olefinic dienophile at the 1-position, is favorable for the intramolecular Diels–Alder reaction. The *N*-protected ester **18** was then reduced with diisobutylaluminum hydride (DIBALH) at −78 °C to afford the aldehyde **10**, a key intermediate of our strategy, in 95% yield. To achieve the synthesis of suaveoline (**4**) and norsuaveoline (**5**), which have an ethyl group at the 20-position, the Wittig reaction of **10** was carried out using the phosphorane prepared from *n*-propyltriphenylphosphonium bromide and *t*-BuOK, furnishing the (*Z*)-olefin **19** in 73% yield. The assignment of geometry in **19** was based on the coupling constant (J=10.5 Hz) between the two olefinic protons of the amine **20** derived from **19**.



37 **18A**

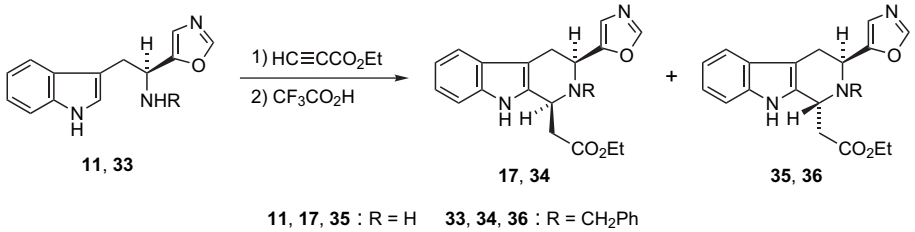
The results of the intramolecular Diels–Alder reaction of the oxazole–olefin **19** are summarized in Table 1 and several comments are in order. When a solution of **19** in *o*-dichlorobenzene (*o*-DCB) was heated at 160 °C for 8 h, the desired pyridine **21** was obtained, but only in 12% yield (entry 1).

Table 1. Intramolecular Diels–Alder reactions of the oxazole–olefin **19**

Entry	Solvent	Additive (equiv)	Temp (°C)	Time (h)	**21**, yield (%)
1	*o*-DCB	—	160	8	12
2	*o*-DCB	$Cu(OTf)_2$ (0.05)	160	3	0
3	*o*-DCB	DBN (1.5)	160	12	21
4	Xylene	DBN (1.6)	Reflux	24	50
5	Xylene	DBN (5.0)	Reflux	24	65
6	Xylene	DBN (20)	Reflux	9	69

Addition of $Cu(OTf)_2$ failed to give **21** due to rapid decomposition of **19** (entry 2), although we reported that this Lewis acid prompted the cycloaddition leading to cyclopenta[*c*]-pyridines.[24] However, treatment of **19** in *o*-DCB at 160 °C in the presence of 1.5 equiv of 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN), an application of Weinreb's procedure,[3,4c] improved slightly the yield of **21** (entry 3). Furthermore, alteration of the solvent from *o*-DCB to xylene raised the yield of **21** to 50% (entry 4). By use of 5.0 equiv of DBN, the pyridine **21** was obtained in 65% yield (entry 5). Ultimately, treatment of **19** with 20 equiv of DBN in boiling xylene for 9 h gave **21** in 69% yield as the best result (entry 6). It is likely that DBN might serve as a scavenger of H_2O and promote the conversion of the initially formed Diels–Alder cycloadduct into the pyridine **21**.[3b]

Methylation of **21** with MeI was performed in the presence of NaH in DMF, affording the indole N_a-Me derivative **23** in 98% yield. Finally, removal of the Boc group in **23** with trifluoroacetic acid provided the first target compound **4** [$[\alpha]_D^{28}$ −1.4 (*c* 0.50, $CHCl_3$)] in 82% yield. The ^{1}H and ^{13}C NMR ($CDCl_3$), UV (EtOH), CD (cyclohexane), and mass spectral data for this sample were in agreement with those reported for natural suaveoline [$[\alpha]_D$ 0±2 (*c* 1, $CHCl_3$)][8,9f] and/or Cook's synthetic sample [$[\alpha]_D^{25}$ −9.33 (*c* 0.30, $CHCl_3$)].[11a,b] In addition, the spectral properties and specific rotation of **24** [$[\alpha]_D^{29}$ −91.1 (*c* 0.92, $CHCl_3$)], prepared from **4** according to Potier's procedure,[8] were



Scheme 4.

found to match those reported for N_b-methylsuaveoline [$[\alpha]_D$ −93 (*c* 0.89, $CHCl_3$),[8] $[\alpha]_D^{25}$ −89.25 (*c* 0.37, $CHCl_3$)[11a,b]]. On the other hand, deprotection of **21** with trifluoroacetic acid furnished the second target compound **5** [$[\alpha]_D^{30}$ +19.6 (*c* 0.50, $CHCl_3$)] in 88% yield. Although the ^1H and ^{13}C NMR ($CDCl_3$), CD (EtOH) spectra, and TLC mobility (three solvent systems) of this sample were shown to be virtually identical with those of Cook's synthetic norsuaveoline [$[\alpha]_D^{27}$ −3.2 (*c* 1.00, $CHCl_3$)],[12] the specific rotations of the two synthetic samples were in disagreement.[25] However, we found again that the specific rotation of **22** [$[\alpha]_D^{27}$ −132.2 (*c* 0.50, $CHCl_3$)], derived from **5**, matched that recorded for N_b-benzylnorsuaveoline [$[\alpha]_D^{27}$ −143.2 (*c* 1.00, $CHCl_3$)].[12]

3. Conclusion

The total synthesis of the *Rauwolfia* alkaloids, suaveoline (**4**) and norsuaveoline (**5**), was achieved with 10% and 11% overall yields, respectively, from L-tryptophan methyl ester (**12**) through a route featuring the efficient construction of the annulated pyridine by the intramolecular Diels–Alder reaction of the oxazole–olefin **19**. The utility of the aldehyde **10**, a key intermediate of our synthetic strategy, has been exemplified by our recent synthesis of N_a-demethyl-20-deethylsuaveoline, the structure proposed for sellowiine (**8**).[26]

4. Experimental

4.1. General methods

All melting points were determined on a Yamato MP-1 capillary melting point apparatus. Flash chromatography[27] was carried out using Merck silica gel 60 (No. 9385). Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous K_2CO_3 and concentrated under reduced pressure. The ratios of solvents in mixtures are shown in v/v. Spectra reported herein were recorded on a JEOL JMS-SX102A mass spectrometer, a Hitachi U-3010 UV spectrophotometer, a Shimadzu FTIR-8400 IR spectrophotometer, a JASCO J-820 spectropolarimeter, or a JEOL JNM-GSX-500 (^1H 500 MHz, ^{13}C 125 MHz) NMR spectrometer. Chemical shifts are reported in δ values relative to internal Me_4Si. Optical rotations were measured with a Horiba SEPA-300 polarimeter using a 1-dm sample tube.

4.1.1. (*S*)-[2-(1*H*-Indol-3-yl)-1-(5-oxazolyl)ethyl]carbamic acid 1,1-dimethylethyl ester (14). A solution of methyl isocyanide (9.21 g, 0.224 mol) in THF (250 mL) was cooled to −78 °C in an atmosphere of N_2, and a 1.6 M solution (140 mL, 0.224 mol) of BuLi in hexane was added dropwise over 30 min. After the mixture had been stirred for 40 min, a solution of **13**[17] (15.8 g, 49.6 mmol) in THF (120 mL) was introduced dropwise over 40 min. Stirring was continued at −78 °C for 2.5 h, and the reaction was quenched by adding AcOH (14 mL). The reaction mixture was warmed to room temperature and concentrated under reduced pressure. The residue was partitioned between H_2O and ether, and the ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to leave a pale brown solid. Purification by flash chromatography [AcOEt–hexane (1:1)] gave **14** (13.3 g, 82%) as a slightly yellow solid. Recrystallization from AcOEt–hexane (1:1) provided an analytical sample as colorless minute needles, mp 163–164 °C. $[\alpha]_D^{25}$ −34.5 (*c* 0.50, MeOH); IR (Nujol) ν, cm^{-1}: 3370 (NH), 1678 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.41 (9H, s), 3.31 (2H, br), 4.90 (1H, br), 5.25 (1H, br), 6.80 (1H, s), 6.88 (1H, s), 7.11 (1H, dd, *J*=8, 7.5 Hz), 7.19 (1H, dd, *J*=8, 7.5 Hz), 7.35 (1H, d, *J*=8 Hz), 7.50 (1H, d, *J*=8 Hz), 7.81 (1H, s), 8.06 (1H, s). Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.81; H, 6.51; N, 12.74.

4.1.2. (*S*)-α-(5-Oxazolyl)-1*H*-indole-3-ethanamine (11). A mixture of **14** (8.29 g, 25.3 mmol), trifluoroacetic acid (60 mL), and CH_2Cl_2 (60 mL) was stirred at 0 °C for 4 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in H_2O. The aqueous solution was made basic with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with brine, dried, and concentrated to leave a yellow oil. Purification by flash chromatography [AcOEt–EtOH (5:2)] furnished **11** (5.64 g, 98%) as a pale yellow oil. $[\alpha]_D^{26}$ +23.4 (*c* 0.50, MeOH); MS *m/z*: 227 (M^+); IR ($CHCl_3$) ν, cm^{-1}: 3480 (NH), 3370 (NH_2); ^1H NMR ($CDCl_3$) δ: 1.62 (2H, br), 3.08 (1H, dd, *J*=14, 9 Hz), 3.34 (1H, dd, *J*=14, 5 Hz), 4.41 (1H, dd, *J*=9, 5 Hz), 6.91 (1H, s), 7.01 (1H, d, *J*=2.5 Hz), 7.13 (1H, dd, *J*=8, 7 Hz), 7.21 (1H, dd, *J*=8.5, 7 Hz), 7.38 (1H, d, *J*=8.5 Hz), 7.58 (1H, d, *J*=8 Hz), 7.84 (1H, s), 8.11 (1H, s); HRMS calcd for $C_{13}H_{13}N_3O$: 227.1059, found: 227.1054. For determination of the enantiomeric purity of this sample, a mixture of the Mosher amides was prepared from (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. Based on ^1H NMR ($CDCl_3$) analysis employing the methoxy groups (major isomer: δ 3.19, minor isomer: δ 3.16) of the mixture, an enantiomeric purity of 97% was assigned to the oxazole amine **11**.

4.1.3. Pictet–Spengler reaction of the amino oxazole 11 and the aldehyde 26: preparation of the tetrahydro-β-carbolines 29 and 32. A mixture of **11** (50 mg, 0.22 mmol), **26** (90 mg, 0.29 mmol), and 3 Å molecular sieves in CH_2Cl_2 (5 mL) was stirred at room temperature for 24 h. After addition of trifluoroacetic acid (four drops) at −78 °C, the mixture was stirred at −78 °C for 1 h and at room temperature for 1 h, made basic with 10% aqueous Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with brine, dried, and concentrated. The residual oil was then subjected to flash chromatography [AcOEt–hexane (1:1)]. Earlier fractions afforded the 1,3-*trans*-isomer **32** (11 mg, 10%) as a pale yellow oil. MS *m/z*: 521 (M^+); ^1H NMR ($CDCl_3$) δ: 1.13 (9H, s), 2.05 (2H, m), 2.97 (1H, ddd, *J*=15.5, 7, 1.5 Hz), 3.18 (1H, dd, *J*=15.5, 5 Hz), 3.93 (1H, m), 3.98 (1H, m), 4.30 (1H, t, *J*=6.5 Hz), 4.44 (1H, dd, *J*=7, 5 Hz), 6.89 (1H, s), 7.1–7.7 (14H, m), 7.81 (1H, s), 8.43 (1H, s). Later fractions of the above chromatography furnished the 1,3-*cis*-isomer **29** (30 mg, 26%) as a pale yellow oil. MS *m/z*: 521 (M^+); ^1H NMR ($CDCl_3$) δ: 1.12 (9H, s), 1.94 (1H, ddd, *J*=14.5, 7.5, 4 Hz), 2.24 (1H, m), 2.97 (1H, ddd, *J*=15, 10.5, 2.5 Hz), 3.13 (1H, ddd, *J*=15, 4, 2.5 Hz), 3.96 (2H, m), 4.28 (1H, dd, *J*=10.5, 4 Hz), 4.46 (1H, m), 7.06 (1H, s), 7.1–7.7 (14H, m), 7.86 (1H, s), 8.91 (1H, s).

4.1.4. Modified Pictet–Spengler reaction of the amino oxazole 11 and ethyl propiolate: preparation of the tetrahydro-β-carbolines 17 and 35. A solution of **11** (43 mg, 0.19 mmol) and ethyl propiolate (91 mg, 0.93 mmol) in CH_2Cl_2 (2 mL) was heated under reflux for 4 days. After cooling to −78 °C, trifluoroacetic acid (0.15 mL) was added. The mixture was then stirred at −78 °C for 30 min and at room temperature for 1 h and worked up as described above for **29** and **32**. Purification of the crude oil by flash chromatography [AcOEt–hexane (4:1)] provided a 2:1 mixture (35 mg, 57%) of **17** and **35** as a yellow oil. ^{1}H NMR ($CDCl_3$) *trans*-isomer **35** δ: 1.29 (3H, t, J=7 Hz), 2.92 (2H, m), 2.95 (1H, m), 3.18 (1H, dd, J=16.5, 5 Hz), 4.25 (2H, q, J=7 Hz), 4.39 (1H, dd, J=8, 5 Hz), 4.50 (1H, t, J=7.5 Hz), 6.93 (1H, s), 7.12 (1H, dd, J=8, 7 Hz), 7.18 (1H, dd, J=8.5, 7 Hz), 7.35 (1H, d, J=8.5 Hz), 7.51 (1H, d, J=8 Hz), 7.84 (1H, s), 8.64 (1H, s). The ^{1}H NMR spectral data arising from the *cis*-isomer were in agreement with those of **17** obtained by reduction of **16**.

4.1.5. (*S*)-*N*-Benzyl-α-(5-oxazolyl)-1*H*-indole-3-ethanamine (33). A solution of **11** (225 mg, 0.99 mmol) and benzaldehyde (138 mg, 1.30 mmol) in MeOH (4 mL) was heated under reflux for 2 h. After cooling to 0 °C, $NaBH_4$ (61 mg, 1.6 mmol) was added, and the mixture was stirred at room temperature for 3 h and concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to leave a yellow oil. Purification by flash chromatography [AcOEt–hexane (2:1)] gave **33** (259 mg, 82%) as a slightly yellow oil. $[\alpha]_D^{26}$ −36.7 (c 0.51, MeOH); MS m/z: 317 (M^+); IR ($CHCl_3$) ν, cm^{-1}: 3480, 3300 (NH); ^{1}H NMR ($CDCl_3$) δ: 1.62 (1H, br), 3.23 (1H, dd, J=14.5, 8 Hz), 3.25 (1H, dd, J=14.5, 6.5 Hz), 3.59 and 3.77 (2H, d each, J=13.5 Hz), 4.18 (1H, dd, J=8, 6.5 Hz), 6.90 (1H, s), 6.92 (1H, br s), 7.05–7.25 (7H, m), 7.35 (1H, d, J=8 Hz), 7.50 (1H, d, J=8 Hz), 7.85 (1H, s), 8.01 (1H, s); HRMS calcd for $C_{20}H_{19}N_3O$: 317.1528, found: 317.1528.

4.1.6. Modified Pictet–Spengler reaction of the *N*-benzylamino oxazole 33 and ethyl propiolate: preparation of the tetrahydro-β-carbolines 34 and 36. The reaction of **33** (59 mg, 0.19 mmol) and work-up of the reaction mixture were effected in a manner similar to those described above for **17** and **35**. Purification of the crude oil by flash chromatography [AcOEt–hexane (1:2)] furnished a 1:19 mixture (57 mg, 74%) of **34** and **36** as a pale brown oil. ^{1}H NMR ($CDCl_3$) *cis*-isomer **34** δ: 1.22 (3H, t, J=7.5 Hz), 1.89 (1H, dd, J=17, 10.5 Hz), 2.60 (1H, dd, J=17, 2.5 Hz), 3.11 (1H, dd, J=16, 1.5 Hz), 3.31 (1H, ddd, J=16, 6.5, 1.5 Hz), 4.03 and 4.06 (2H, d each, J=13.5 Hz), 4.11 (2H, m), 4.36 (1H, d, J=10.5 Hz), 4.40 (1H, d, J=6.5 Hz), 6.64 (1H, s), 7.13 (1H, dd, J=8, 7 Hz), 7.19 (1H, dd, J=8, 7 Hz), 7.25–7.5 (6H, m), 7.57 (1H, d, J=8 Hz), 7.84 (1H, s), 8.78 (1H, s); *trans*-isomer **36** δ: 1.21 (3H, t, J=7 Hz), 2.95 (1H, dd, J=17, 9.5 Hz), 3.00 (1H, dd, J=17, 5 Hz), 3.07 (1H, dd, J=15.5, 4 Hz), 3.18 (1H, dd, J=15.5, 10.5 Hz), 3.44 and 3.72 (2H, d each, J=14 Hz), 4.10 (2H, m), 4.23 (1H, dd, J=9.5, 5 Hz), 4.54 (1H, dd, J=10.5, 4 Hz), 7.13 (1H, s), 7.1–7.35 (7H, m), 7.33 (1H, d, J=8 Hz), 7.57 (1H, d, J=8 Hz), 7.90 (1H, s), 8.66 (1H, s).

4.1.7. (*S*)-3-[[2-(1*H*-Indol-3-yl)-1-(5-oxazolyl)ethyl]-amino]-3-oxopropanoic acid ethyl ester (15). To a cooled solution of **11** (2.80 g, 12.3 mmol) in DMF (70 mL) were successively added monoethyl malonate (2.12 g, 16 mmol), diethyl phosphorocyanidate (4.08 g, 25 mmol), and Et_3N (2.51 g, 25 mmol). After stirring at 0 °C for 30 min and at room temperature for 30 min, the reaction mixture was concentrated in vacuo, and the residue was partitioned between H_2O and AcOEt. The AcOEt extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to leave a brown oil, which was purified by flash chromatography [AcOEt–hexane (10:1)] to give **15** (3.71 g, 88%) as a yellow solid. Recrystallization from AcOEt–hexane (1:2) afforded an analytical sample as colorless needles, mp 109–110 °C. $[\alpha]_D^{28}$ −51.6 (c 0.50, $CHCl_3$); IR (Nujol) ν, cm^{-1}: 3320 (NH), 1740 (ester CO), 1647 (amide CO); ^{1}H NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.5 Hz), 3.26 and 3.28 (2H, d each, J=18 Hz), 3.34 (2H, d, J=7 Hz), 4.14 (2H, q, J=7.5 Hz), 5.60 (1H, dt, J=8, 7 Hz), 6.83 (1H, s), 6.92 (1H, d, J=2 Hz), 7.10 (1H, dd, J=8.5, 8 Hz), 7.19 (1H, dd, J=8.5, 8 Hz), 7.34 (1H, d, J=8.5 Hz), 7.52 (1H, d, J=8.5 Hz), 7.60 (1H, d, J=8 Hz), 7.81 (1H, s), 8.10 (1H, s). Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.29; H, 5.56; N, 12.22.

4.1.8. [*S*-(*Z*)]-[2,3,4,9-Tetrahydro-3-(5-oxazolyl)-1*H*-pyrido[3,4-*b*]indol-1-ylidene]acetic acid ethyl ester (16). A mixture of **15** (219 mg, 0.64 mmol) and $POCl_3$ (3 mL) was stirred at room temperature for 6 days. After excess $POCl_3$ was removed by vacuum distillation, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was poured into 10% aqueous Na_2CO_3 (18 mL), and the aqueous layer was separated and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification of the residual oil by flash chromatography [AcOEt–hexane (1:2)] provided **16** (104 mg, 50%) as a slightly yellow solid, which was recrystallized from AcOEt–hexane (1:3) to give an analytical sample as colorless fine needles, mp 213–214 °C. $[\alpha]_D^{29}$ −156 (c 0.20, $CHCl_3$); IR ($CHCl_3$) ν, cm^{-1}: 3470, 3310 (NH), 1651 (CO); ^{1}H NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz), 3.31 (1H, dd, J=15.5, 8 Hz), 3.37 (1H, dd, J=15.5, 5.5 Hz), 4.19 (2H, q, J=7 Hz), 4.96 (1H, dd, J=8, 5.5 Hz), 5.03 (1H, s), 6.98 (1H, s), 7.16 (1H, dd, J=8, 7 Hz), 7.29 (1H, dd, J=7.5, 7 Hz), 7.38 (1H, d, J=8 Hz), 7.57 (1H, d, J=7.5 Hz), 7.82 (1H, s), 8.21 (1H, s), 8.59 (1H, s). Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.63; H, 5.27; N, 12.79.

4.1.9. (1*S*,3*S*)-2,3,4,9-Tetrahydro-3-(5-oxazolyl)-1*H*-pyrido[3,4-*b*]indole-1-acetic acid ethyl ester (17). A solution of **16** (3.18 g, 9.8 mmol) in EtOH (100 mL) was hydrogenated over 20% $Pd(OH)_2$–C (3.2 g) at room temperature and atmospheric pressure for 22 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to leave a yellow oil, which was purified by flash chromatography [AcOEt–hexane (5:1)] to afford **17** (2.70 g, 84%) as a pale yellow glass. $[\alpha]_D^{25}$ +27.9 (c 0.25, $CHCl_3$); MS m/z: 325 (M^+); IR ($CHCl_3$) ν, cm^{-1}: 3465, 3425 (NH), 1720 (CO); ^{1}H NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz), 1.75 (1H, br), 2.80 (1H, dd, J=16.5, 8.5 Hz), 2.88 (1H, dd, J=16.5, 4.5 Hz), 2.99 (1H, ddd, J=15, 10.5, 2.5 Hz), 3.13 (1H, ddd, J=15, 4, 2 Hz), 4.24 and 4.27 (2H,

dq each, J=14.5, 7 Hz), 4.30 (1H, dd, J=10.5, 4 Hz), 4.67 (1H, dddd, J=8.5, 4.5, 2.5, 2 Hz), 7.08 (1H, s), 7.12 (1H, dd, J=8, 7 Hz), 7.18 (1H, dd, J=8.5, 7 Hz), 7.35 (1H, d, J=8.5 Hz), 7.51 (1H, d, J=8 Hz), 7.89 (1H, s), 8.79 (1H, s); HRMS calcd for $C_{18}H_{19}N_3O_3$: 325.1427, found: 325.1429.

4.1.10. (1*S*,3*S*)-2-[(1,1-Dimethylethoxy)carbonyl]-2,3,4,9-tetrahydro-3-(5-oxazolyl)-1*H*-pyrido[3,4-*b*]indole-1-acetic acid ethyl ester (18). A mixture of **17** (2.34 g, 7.2 mmol) and di-*tert*-butyl dicarbonate (2.41 g, 11 mmol) in $CHCl_3$ (30 mL) was heated under reflux for 24 h. The reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography [AcOEt–hexane (1:2)] to give **18** (2.67 g, 87%) as a yellow solid. Recrystallization from AcOEt–hexane (1:1) provided an analytical sample as colorless needles, mp 188.5–190 °C. $[\alpha]_D^{26}$ +227 (c 0.25, $CHCl_3$); IR (Nujol) ν, cm^{-1}: 3420 (NH), 1709 (ester CO), 1690 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.27 (3H, br), 1.56 (9H, s), 1.85 and 1.99 (1H, br each), 2.60 and 2.71 (1H, br each), 3.28 (2H, d, J=3.5 Hz), 4.18 (2H, br), 5.44 and 5.55 (1H, br each), 5.91 and 6.09 (1H, br each), 6.61 (1H, s), 7.13 (1H, dd, J=8, 7.5 Hz), 7.19 (1H, dd, J=8.5, 7.5 Hz), 7.34 (1H, d, J=8.5 Hz), 7.55 (1H, d, J=8 Hz), 7.79 (1H, s), 8.96 and 9.08 (1H, br each). Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40; N, 9.88. Found: C, 64.83; H, 6.43; N, 9.76.

4.1.11. (1*S*,3*S*)-1,3,4,9-Tetrahydro-3-(5-oxazolyl)-1-(2-oxoethyl)-2*H*-pyrido[3,4-*b*]indole-2-carboxylic acid 1,1-dimethylethyl ester (10). A stirred solution of **18** (518 mg, 1.22 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C in an atmosphere of N_2, and a 1.0 M solution (2.4 mL, 2.4 mmol) of DIBALH in hexane was added dropwise over 5 min. The reaction mixture was stirred at −78 °C for 80 min and quenched by adding MeOH (0.2 mL). After stirring for a further 30 min at room temperature, the mixture was concentrated in vacuo. The residue was purified by flash chromatography (AcOEt) to furnish **10** (440 mg, 95%) as a colorless glass. $[\alpha]_D^{26}$ +181 (c 0.25, $CHCl_3$); MS m/z: 381 (M^+); IR ($CHCl_3$) ν, cm^{-1}: 3440 (NH), 1717 (aldehyde CO), 1690 (carbamate CO); ^1H NMR ($CDCl_3$) δ: 1.56 (9H, s), 2.10 (1H, br), 2.92 (1H, br), 3.28 (2H, d, J=3.5 Hz), 5.59 and 5.63 (1H, br each), 5.93 and 6.10 (1H, br each), 6.63 (1H, s), 7.14 (1H, dd, J=7.5, 7 Hz), 7.20 (1H, dd, J=7.5, 7 Hz), 7.33 (1H, d, J=7.5 Hz), 7.55 (1H, d, J=7.5 Hz), 7.83 (1H, s), 8.44 and 8.62 (1H, br each), 9.76 (1H, s); HRMS calcd for $C_{21}H_{23}N_3O_4$: 381.1689, found: 381.1673.

4.1.12. (1*S*,3*S*)-1,3,4,9-Tetrahydro-3-(5-oxazolyl)-1-(2*Z*)-2-pentenyl-2*H*-pyrido[3,4-*b*]indole-2-carboxylic acid 1,1-dimethylethyl ester (19). A mixture of *n*-propyltriphenylphosphonium bromide (978 mg, 2.5 mmol) and *t*-BuOK (259 mg, 2.3 mmol) in benzene (10 mL) was heated under reflux for 2 h in an atmosphere of N_2. After cooling, a solution of **10** (440 mg, 1.15 mmol) in benzene (5 mL) was added, and the resulting mixture was stirred at room temperature for 30 min. The mixture was then poured into H_2O (20 mL), and the aqueous layer was separated from the organic layer and extracted with ether. The ethereal extracts and the above organic layer were combined, dried over anhydrous $MgSO_4$, and concentrated. Purification of the residue by flash chromatography [AcOEt–hexane (1:3)] afforded **19** (342 mg, 73%) as a slightly yellow glass. $[\alpha]_D^{25}$ +119 (c 0.56, $CHCl_3$); MS m/z: 407 (M^+); IR ($CHCl_3$) ν, cm^{-1}: 3460 (NH), 1686 (CO); ^1H NMR ($CDCl_3$) δ: 0.84 (3H, t, J=7.5 Hz), 1.57 (9H, s), 1.64 (1H, br), 1.79 (2H, br), 2.25 (1H, br), 3.27 (2H, m), 5.10 (1H, br), 5.45–5.65 (2H, m), 5.93 and 6.10 (1H, br each), 6.59 and 6.61 (1H, s each), 7.14 (1H, dd, J=7.5, 7 Hz), 7.18 (1H, dd, J=7.5, 7 Hz), 7.28 (1H, d, J=7.5 Hz), 7.55 (1H, d, J=7.5 Hz), 7.75 and 7.76 (1H, s each), 7.94 and 8.03 (1H, br each); HRMS calcd for $C_{24}H_{29}N_3O_3$: 407.2209, found: 407.2209. A portion of this sample was deprotected with trifluoroacetic acid in CH_2Cl_2 to furnish **20** as a pale yellow solid. ^1H NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.5 Hz), 1.71 (1H, br), 2.11 (2H, dt, J=7.5, 7.5 Hz), 2.53 (1H, m), 2.73 (1H, ddd, J=15, 9, 8 Hz), 2.96 (1H, dd, J=15, 11 Hz), 3.13 (1H, dd, J=15, 4 Hz), 4.29 (1H, dd, J=11, 4 Hz), 4.37 (1H, m), 5.52 (1H, ddd, J=10.5, 9, 5.5 Hz), 5.69 (1H, dt, J=10.5, 7.5 Hz), 7.08 (1H, s), 7.12 (1H, dd, J=8, 7.5 Hz), 7.18 (1H, dd, J=8, 7.5 Hz), 7.32 (1H, d, J=8 Hz), 7.50 (1H, d, J=8 Hz), 7.88 (1H, s), 8.09 (1H, s).

4.1.13. (6*S*,13*S*)-4-Ethyl-6,7,12,13-tetrahydro-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole-14-carboxylic acid 1,1-dimethylethyl ester (21). A mixture of **19** (297 mg, 0.73 mmol), DBN (1.80 g, 14.5 mmol), and xylene (10 mL) was heated under reflux for 9 h in an atmosphere of Ar. The reaction mixture was concentrated in vacuo to leave a dark brown oil, which was purified by flash chromatography [AcOEt–hexane (1:1) and then AcOEt] to give **21** (196 mg, 69%) as a yellow solid. Recrystallization from AcOEt–hexane (2:1) yielded an analytical sample as colorless needles, mp 230–232 °C. $[\alpha]_D^{25}$ −6.0 (c 0.25, $CHCl_3$); IR (Nujol) ν, cm^{-1}: 3300 (NH), 1661 (CO); ^1H NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.5 Hz), 1.48 and 1.50 (9H, s each), 2.50 (2H, q, J=7.5 Hz), 2.86 (1H, d, J=15.5 Hz), 2.91 and 2.94 (1H, d each, J=17 Hz), 3.22 and 3.27 (1H, dd each, J=17, 5.5 Hz), 3.43 and 3.47 (1H, dd each, J=15.5, 5.5 Hz), 5.58 and 5.60 (1H, d each, J=5.5 Hz), 5.76 and 5.78 (1H, d each, J=5.5 Hz), 7.04 and 7.06 (1H, dd each, J=8, 7.5 Hz), 7.11 and 7.13 (1H, dd each, J=8, 7.5 Hz), 7.27 (1H, d, J=8 Hz), 7.36 and 7.39 (1H, d each, J=8 Hz), 7.91 and 8.05 (1H, br each), 8.16 (1H, s), 8.37 (1H, s). Anal. Calcd for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.79. Found: C, 73.89; H, 7.02; N, 10.72.

4.1.14. (6*S*,13*S*)-4-Ethyl-6,7,12,13-tetrahydro-7-methyl-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole-14-carboxylic acid 1,1-dimethylethyl ester (23). A mixture of **21** (100 mg, 0.26 mmol) and 60% NaH (23 mg, 0.58 mmol) in DMF (3 mL) was stirred at 0 °C, and a solution of MeI (40 mg, 0.28 mmol) in DMF (2 mL) was added. After stirring for 20 min at room temperature, the reaction mixture was concentrated in vacuo. The residue was partitioned between H_2O and AcOEt. The AcOEt extracts were washed with brine, dried, and concentrated to furnish **23** (102 mg, 98%) as a slightly yellow glass. $[\alpha]_D^{30}$ −14.9 (c 0.50, $CHCl_3$); MS m/z: 403 (M^+); IR ($CHCl_3$) ν, cm^{-1}: 1686 (CO); ^1H NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.5 Hz), 1.49 (9H, s), 2.50 (2H, q, J=7.5 Hz), 2.86 (1H, d, J=17 Hz), 2.88 (1H, d, J=15 Hz), 3.25 and 3.29 (1H, dd each, J=17, 5.5 Hz), 3.43 and 3.48 (1H, dd each, J=15, 5.5 Hz), 3.74 (3H, s), 5.59 and 5.64 (1H, d each, J=5.5 Hz), 5.76 and

5.85 (1H, d each, J=5.5 Hz), 7.04 (1H, dd, J=8, 7.5 Hz), 7.16 (1H, dd, J=8, 7.5 Hz), 7.25 (1H, d, J=8 Hz), 7.38 and 7.40 (1H, d each, J=8 Hz), 8.16 (1H, s), 8.37 (1H, s); HRMS calcd for $C_{25}H_{29}N_3O_2$: 403.2260, found: 403.2257.

4.1.15. (6*S*,13*S*)-4-Ethyl-6,7,12,13-tetrahydro-7-methyl-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole (suaveoline) (4). A mixture of **23** (117 mg, 0.29 mmol) and trifluoroacetic acid (0.5 mL) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 3 h. The reaction mixture was then poured into cold 10% aqueous Na_2CO_3 (5 mL) and extracted with $CHCl_3$. The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by flash chromatography [$CHCl_3$–MeOH (10:1)] provided **4** (72 mg, 82%) as a colorless foam. $[\alpha]_D^{28}$ −1.4 (*c* 0.50, $CHCl_3$); MS *m*/*z*: 303 (M^+); UV (EtOH) λ_{max}, nm (log ε): 226 (4.47), 272 (3.89), 284 (3.85); CD (cyclohexane) λ_{ext}, nm ($\Delta\varepsilon$): 301 (+2.22), 295 (+0.85), 291 (+2.49), 275 (−0.70), 264 (+1.22), 254 (+0.07), 238 (+8.19), 217 (−14.4); HRMS calcd for $C_{20}H_{21}N_3$: 303.1736, found: 303.1739. The ^1H and ^{13}C NMR ($CDCl_3$) spectral data for this sample were in agreement with those reported for natural suaveoline.[9f]

4.1.16. (6*S*,13*S*)-4-Ethyl-6,7,12,13-tetrahydro-7,14-dimethyl-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole (N_b-methylsuaveoline) (24). Methylation of **4** (25 mg, 0.082 mmol) was effected by the same procedure as described in the literature,[8] affording **24** (23 mg, 84%) as a colorless oil. $[\alpha]_D^{29}$ −91.1 (*c* 0.92, $CHCl_3$); MS *m*/*z*: 317 (M^+); UV (EtOH) λ_{max}, nm (log ε): 225 (4.44), 272 (3.86), 283 (3.81); HRMS calcd for $C_{21}H_{23}N_3$: 317.1892, found: 317.1898. The ^1H and ^{13}C NMR ($CDCl_3$) spectral data for this sample were in agreement with those reported for (−)-N_b-methylsuaveoline by Fu and Cook.[11b]

4.1.17. (6*S*,13*S*)-4-Ethyl-6,7,12,13-tetrahydro-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole (norsuaveoline) (5). Deprotection of **21** (92 mg, 0.24 mmol) and work-up of the reaction mixture were performed as described above for **4**, giving **5** (60 mg, 88%) as a colorless solid. Recrystallization from AcOEt–hexane (2:1) furnished colorless needles, mp 258–262 °C. $[\alpha]_D^{30}$ +19.6 (*c* 0.50, $CHCl_3$); MS *m*/*z*: 289 (M^+); UV (EtOH) λ_{max}, nm (log ε): 225 (4.47), 272 (3.94), 283 (3.88), 291 (3.78); CD (EtOH) λ_{ext}, nm ($\Delta\varepsilon$): 295 (4.65), 291 (3.91), 288 (5.34), 274 (−0.20), 263 (3.56), 250 (1.92), 241 (2.74), 227 (−28.1); HRMS calcd for $C_{19}H_{19}N_3$: 289.1579, found: 289.1581. The ^1H and ^{13}C NMR ($CDCl_3$) and CD spectra and TLC mobility (three solvent systems) of this sample were virtually identical with those of synthetic norsuaveoline.[12]

4.1.18. (6*S*,13*S*)-4-Ethyl-6,7,12,13-tetrahydro-14-(phenylmethyl)-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole (N_b-benzylsuaveoline) (22). Benzyl bromide (37 mg, 0.22 mmol) and Et_3N (42 mg, 0.42 mmol) were successively added to a solution of **5** (24 mg, 0.083 mmol) in CH_3CN (1 mL). After stirring at room temperature for 40 min, the reaction mixture was concentrated in vacuo. The residue was dissolved in H_2O and $CHCl_3$, made basic with 10% aqueous Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with brine, dried, and concentrated. Purification of the residual solid by flash chromatography [AcOEt–hexane (2:1)] provided **22** (15 mg, 48%) as a colorless solid, mp 216–220 °C. $[\alpha]_D^{27}$ −132.2 (*c* 0.50, $CHCl_3$); MS *m*/*z*: 379 (M^+); ^1H NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.5 Hz), 2.48 (2H, q, J=7.5 Hz), 2.72 (1H, d, J=15.5 Hz), 2.80 (1H, d, J=17 Hz), 3.21 (1H, dd, J=17, 6 Hz), 3.47 (1H, dd, J=15.5, 5 Hz), 3.79 and 3.93 (2H, d each, J=13.5 Hz), 4.22 (1H, d, J=6 Hz), 4.40 (1H, d, J=5 Hz), 7.06 (1H, dd, J=8, 7.5 Hz), 7.12 (1H, dd, J=8, 7.5 Hz), 7.25–7.4 (6H, m), 7.42 (1H, d, J=8 Hz), 7.94 (1H, s), 8.13 (1H, s), 8.29 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 13.9 (q), 22.9 (t), 25.9 (t), 31.9 (t), 49.5 (d), 53.5 (d), 56.5 (t), 105.4 (s), 110.9 (d), 118.2 (d), 119.6 (d), 121.8 (d), 127.3 (s), 127.3 (d), 128.5 (d), 128.8 (d), 133.5 (s), 135.2 (s), 136.1 (s), 137.0 (s), 138.6 (s), 140.3 (s), 146.2 (d), 146.7 (d); HRMS calcd for $C_{26}H_{25}N_3$: 379.2049, found: 379.2054.

Acknowledgements

We are grateful to Prof. J. M. Cook (University of Wisconsin–Milwaukee) for providing us with a sample and spectral copies of synthetic norsuaveoline.

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