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# Total synthesis of the proposed structure of macrocaffrine

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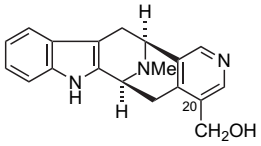
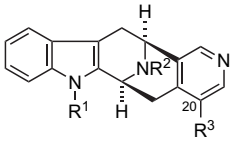
**Abstract**—A full account of the total synthesis of 18-demethyl-19-hydroxy-$N_a$-demethyl-$N_b$-methylsuaveoline (**1**), the structure assigned to macrocaffrine isolated from *Rauwolfia caffra*, is presented. The key steps involved are an intramolecular cycloaddition reaction of the oxazole–olefin **10** and a subsequent dehydration that generated the pentacyclic pyridine derivative **14**. The spectral data and specific rotation of synthetic **1** were dissimilar to those reported for a natural sample, leaving the structure of this *R. caffra* alkaloid undefined.


## 1. Introduction

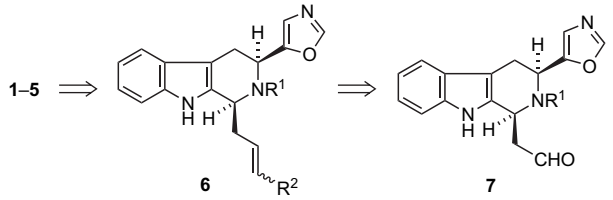
In 1983, Nasser and Court reported the isolation of the macroline/sarpagine related alkaloid 18-demethyl-19-hydroxy-$N_a$-demethyl-$N_b$-methylsuaveoline (**1**),[1] which was named macrocaffrine,[2] from the leaves of South African *Rauwolfia caffra*. To date, four additional alkaloids [i.e., suaveoline (**2**),[2,3] norsuaveoline (**3**),[2] macrophylline (**4**),[1,2,3h,4] and sellowiine (**5**)[5]] possessing the same skeleton as that of **1** have been found in various species of *Rauwolfia*. In connection with our continuing interest in the synthesis of pyridine-containing natural products exploiting an intramolecular oxazole–olefin Diels–Alder reaction,[6,7] we have recently achieved the synthesis of suaveoline (**2**),[8] norsuaveoline (**3**),[8] and $N_a$-demethyl-20-deethylsuaveoline (**5**),[9] the structure proposed for sellowiine. An important feature of our synthetic strategy is that all of the suaveoline-related alkaloids, which possess a variety of substituents at the 20-position, would be derived from the oxazole–olefins **6** that are readily available through carbonyl olefination of the aldehyde **7**, postulated as a common intermediate (Scheme 1). In the present paper, we wish to record the details of a study directed toward the synthesis of macrocaffrine.




**1**




**2**: $R^1$ = Me, $R^2$ = H, $R^3$ = Et
**3**: $R^1$ = $R^2$ = H, $R^3$ = Et
**4**: $R^1$ = H, $R^2$ = Me, $R^3$ = $CH_2CH_2OH$
**5**: $R^1$ = $R^2$ = $R^3$ = H




**Scheme 1**.

## 2. Results and discussion

For the synthesis of macrocaffrine, which has a hydroxymethyl group at the 20-position, we envisaged the α,β-unsaturated ester **10** as an oxazole–olefin substrate for an intramolecular Diels–Alder reaction. The ester **10** was prepared from the *cis*-1,3-disubstituted tetrahydro-β-carboline **8**, readily available from L-tryptophan methyl ester according to our previously reported procedure.[8] Protection of the amino group in **8** with benzyl bromide and $Na_2CO_3$ provided the *N*-benzyl derivative **9** in 75% yield (Scheme 2). The $^1$H NMR spectrum of **8** exhibited two methylene protons adjacent to the ester group at $\delta$ 2.80 and 2.88, whereas one of the corresponding protons of **9** appeared at $\delta$ 1.89, probably due to the shielding effect arising from the oxazole ring of the conformer **9A**, in analogy with the *N*-Boc derivative **11**.[8] Reduction of **9** with diisobutylaluminum hydride (DIBALH) at −78 °C, followed by the Wittig reaction

*Keywords*: Cycloaddition reaction; Indole alkaloids; Macrocaffrine; Oxazoles.
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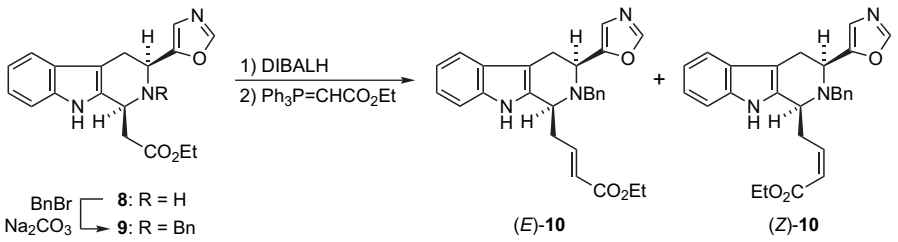
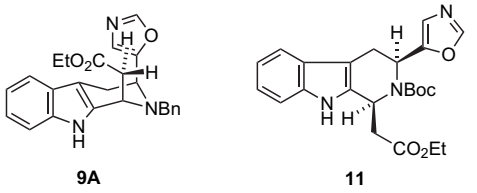
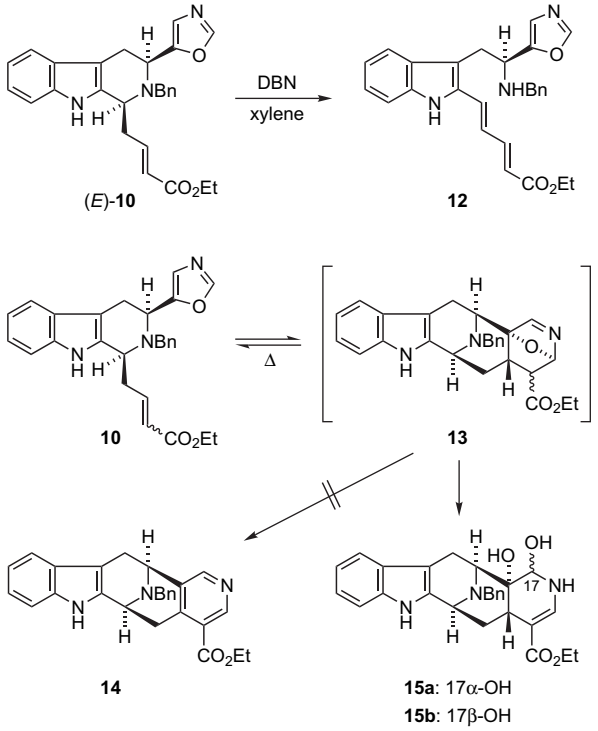



**Scheme 2**.

with ethyl (triphenylphosphoranylidene)acetate, was performed as a one-pot procedure, affording the desired esters (*E*)-**10** and (*Z*)-**10** in 54% and 24% yields, respectively.




With the oxazole–olefins (*E*)-**10** and (*Z*)-**10** in hand, we set out to explore their intramolecular Diels–Alder reaction. Although treatment of (*E*)-**10** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in boiling xylene was first tried according to our precedent in the synthesis of suaveoline (**2**) and norsuaveoline (**3**),[8] the diene **12** was obtained through a retro-Michael reaction (Scheme 3). Therefore, the Diels–Alder reaction of **10** was conducted in the absence of DBN, and the results are given in Table 1. When (*E*)-**10** was treated in boiling toluene for 2 h, the diol **15a** was obtained in 19% yield together with unaltered (*E*)-**10** (entry 1). Similar




**Scheme 3**.

treatment of (*Z*)-**10** also afforded **15a** in 17% yield, accompanied by the recovered starting material (entry 2). No significant improvement was observed by elongation of the reaction time to 24 h (entry 3). It is likely that the oxazole–olefin **10** comes to equilibrium with the initially formed Diels–Alder cycloadduct **13**, which provided the diol **15a** in the work-up process, instead of the desired pyridine **14**, since the elimination of water leading to **14** from **13** is slow. With a view to isolating the cycloaddition product as the diol **15a**, solvent containing water was next employed. Thus, treatment of (*E*)-**10** in boiling THF–$H_2O$ (10:1, v/v) for 48 h afforded the diol **15a** in 61% yield along with another diol **15b** in 33% yield (entry 4). Similar results were also obtained from (*Z*)-**10** (entry 5).

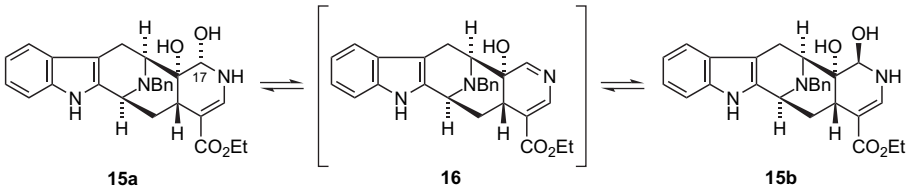
Having successfully developed an effective intramolecular cycloaddition reaction of **10**, we next examined this step in further detail. On treatment in boiling THF–$H_2O$ (10:1) for 48 h, the diol **15a** gave a 75:25 equilibrium mixture of **15a** and **15b**, probably through the imine **16** (Scheme 4). Similarly, the minor diol **15b** came to the same equilibrium after 48 h. The time-course of the intramolecular cycloaddition reaction of (*E*)-**10** at 60 °C was followed by means of $^1$H NMR spectroscopic analysis. It may be seen from Table 2 that the diol **15a** is first produced and then the isomeric diol **15b** is slowly formed by epimerization of **15a** at the 17-position. This view is consistent with the result described in Table 1 where treatment of (*E*)-**10** in boiling toluene yielded **15a** as a sole product.

On the other hand, when (*E*)-**10** was heated in anhydrous THF at 60 °C for 12 h, we observed the cycloadduct **13a** as a 1:1 mixture with (*E*)-**10** by $^1$H NMR spectroscopy. Matsuo and Miki reported that the stereochemistries of the cycloadducts **17** and **18** can be determined based on the value of the coupling constant between the protons $H_A$ and $H_B$.[10] The proton $H_A$ in **17**, where $H_B$ occupies the *exo*-position, appears as a doublet ($J_{AB}$=4 Hz), whereas the singlet $H_A$ ($J_{AB}$=0 Hz) indicates that $H_B$ occupies the *endo*-position

**Table 1**. Intramolecular cycloaddition reactions of the oxazole–olefins (*E*)-**10** and (*Z*)-**10**[a]

| Entry | Substrate | Solvent | Time (h) | Yield (%) | | Recovery (%) |
|---|---|---|---|---|---|---|
| | | | | **15a** | **15b** | **10** |
| 1 | (*E*)-**10** | Toluene | 2 | 19 | 0 | 42 |
| 2 | (*Z*)-**10** | Toluene | 2 | 17 | 0 | 23 |
| 3 | (*E*)-**10** | Toluene | 24 | 26 | 0 | 27 |
| 4 | (*E*)-**10** | THF–$H_2O$[b] | 48 | 61 | 33 | 0 |
| 5 | (*Z*)-**10** | THF–$H_2O$[b] | 48 | 62 | 34 | 0 |

[a] All reactions were carried out in boiling solvent.
[b] 10:1, v/v.



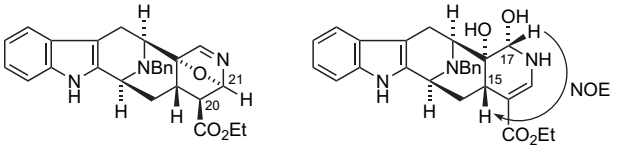

**Scheme 4**.

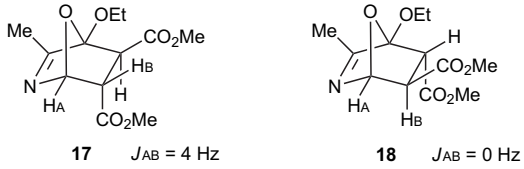
**Table 2**. Time-course of the intramolecular cycloaddition reaction of the oxazole–olefin (*E*)-**10** in THF–$H_2O$ (10:1, v/v) at 60 °C

| Time (h) | Ratio[a] | | |
|---|---|---|---|
| | (*E*)-**10** | **15a** | **15b** |
| 3 | 91 | 9 | 0 |
| 6 | 66 | 34 | 0 |
| 12 | 38 | 56 | 6 |
| 24 | 21 | 70 | 9 |
| 48 | 5 | 74 | 21 |
| 60 | 0 | 75 | 25 |

[a] Estimated by $^1$H NMR spectroscopy.

as shown in **18**. Since the C(21)-proton of the cycloadduct **13a** was observed as a doublet ($J$=4 Hz) at $\delta$ 6.18 in $CDCl_3$, the C(20)-proton was assigned the *exo*-position. In addition, the structure of the major diol **15a** was confirmed by a 10% NOE enhancement observed for the C(15)-proton signal on irradiation of the C(17)-proton signal. Accordingly, the minor diol, the C(17)-epimer of **15a**, was determined to have the structure **15b**.




Conversion of the diols **15a**,**b** into the pyridine derivative **14** was next investigated. After considerable experimentation, we observed the formation of **14** in 21% yield through dehydration of **15a** employing the Burgess reagent.[11] Similarly, the diol **15b** was dehydrated to provide **14** in 44% yield. The best result was obtained on treatment with DBN in boiling *o*-dichlorobenzene (*o*-DCB) for 3 h: under these conditions, the pyridine **14** was produced in 78% and 67% yields, respectively, from **15a** and **15b** (Scheme 5).

The final transformations from **14** to **1** proceeded without incident. Debenzylation of **14** by means of catalytic hydrogenolysis afforded **19** (91% yield), which was then subjected to reductive methylation[3a] with aqueous HCHO, Pearlman's catalyst, and hydrogen in the presence of a trace of acetic acid in MeOH for 1.5 h, affording the $N_b$-methyl derivative **20** in 96% yield. On application of the reductive methylation conditions to the $N_b$-benzyl derivative **14**, except for elongation of the reaction time to 5 h, debenzylation and methylation proceeded at the same time to give the $N_b$-methyl analog **20** in quantitative yield. Finally, reduction of **20** with $LiAlH_4$ furnished the desired compound **1** in 94% yield. Unfortunately, the $^1$H NMR and mass spectral data and specific rotation for synthetic **1** were in disagreement with those reported for macrocaffrine,[1] and thus its chemistry is not yet fully understood.

## 3. Conclusion

The total synthesis of 18-demethyl-19-hydroxy-$N_a$-demethyl-$N_b$-methylsuaveoline (**1**), the structure proposed for macrocaffrine isolated from *R. caffra*, has been accomplished through a route featuring the construction of the annulated pyridine by the intramolecular cycloaddition reaction of the oxazole–olefin **10** and subsequent dehydration of the diol **15**. Owing to the dissimilarity of the spectral properties and specific rotations of the two samples, the structure of macrocaffrine needs to be corrected, although we are unable to propose a new structure for this alkaloid. It is hoped that the knowledge obtained on synthetic **1** will be of great help toward further isolation of this alkaloid, if it is present, from natural sources.

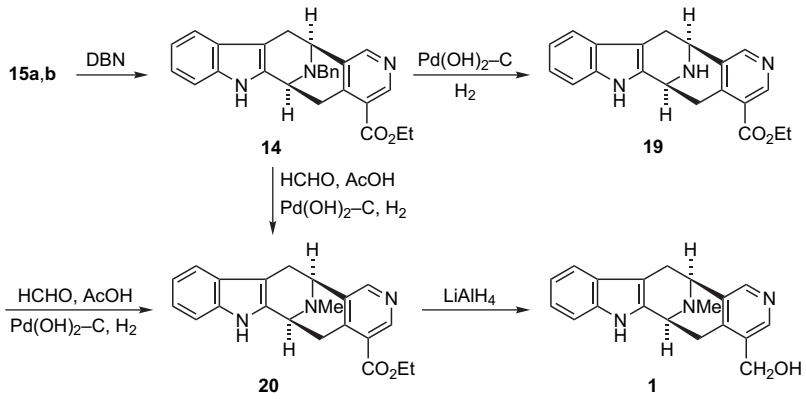
## 4. Experimental

### 4.1. General methods

Melting point was determined on a Yamato MP-1 capillary melting point apparatus. Flash chromatography[12] was carried out using Merck silica gel 60 (No. 9385). Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous $MgSO_4$ 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 ($^1$H 500 MHz, $^{13}$C 125 MHz) NMR spectrometer. Chemical shifts are reported in $\delta$ values relative to internal $Me_4Si$. Optical rotations were measured with a Horiba SEPA-300 polarimeter using a 1-dm sample tube.

### 4.2. (1*S*,3*S*)-2,3,4,9-Tetrahydro-3-(5-oxazolyl)-2-(phenylmethyl)-1*H*-pyrido[3,4-*b*]indole-1-acetic acid ethyl ester (9)

A mixture of **8**[8] (4.07 g, 12.5 mmol), $Na_2CO_3$ (13.3 g, 125 mmol), and benzyl bromide (7.4 mL, 62 mmol) in




**Scheme 5**.

DMF (50 mL) was stirred at room temperature for 25 h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between $H_2O$ and $CHCl_3$. The $CHCl_3$ extracts were washed with brine, dried, and concentrated to leave a brown oil. Purification by flash chromatography [AcOEt–hexane (1:2)] provided **9** (3.88 g, 75%) as a pale yellow glass. $[\alpha]_D^{28}$ +132 (*c* 0.25, $CHCl_3$); MS *m*/*z*: 415 ($M^+$); IR ($CHCl_3$) $\nu$, $cm^{-1}$: 3440 (NH), 1715 (CO); $^1H$ NMR ($CDCl_3$) $\delta$: 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, br d, *J*=10.5 Hz), 4.40 (1H, br d, *J*=6.5 Hz), 6.64 (1H, s), 7.13 (1H, dd, *J*=8, 7 Hz), 7.19 (1H, dd, *J*=8, 7.5 Hz), 7.25–7.5 (6H, m), 7.57 (1H, d, *J*=7.5 Hz), 7.84 (1H, s), 8.78 (1H, s); HRMS calcd for $C_{25}H_{25}N_3O_3$: 415.1896, found: 415.1887.

### 4.3. [1*S*(*E*),3*S*]-4-[2,3,4,9-Tetrahydro-3-(5-oxazolyl)-2-(phenylmethyl)-1*H*-pyrido[3,4-*b*]indol-1-yl]-2-butenoic acid ethyl ester [(*E*)-10] and [1*S*(*Z*),3*S*]-4-[2,3,4,9-tetrahydro-3-(5-oxazolyl)-2-(phenylmethyl)-1*H*-pyrido[3,4-*b*]indol-1-yl]-2-butenoic acid ethyl ester [(*Z*)-10]

A stirred solution of **9** (3.88 g, 9.34 mmol) in $CH_2Cl_2$ (40 mL) was cooled to −78 °C in an atmosphere of $N_2$, and a 0.95 M solution (24.5 mL, 23.3 mmol) of DIBALH in hexane was added dropwise over 10 min. After the mixture had been stirred at −78 °C for 1 h, the reaction was quenched by adding MeOH (6 mL). Stirring was continued for a further 20 min, and a solution of ethyl (triphenylphosphoranylidene)acetate (3.77 g, 10.8 mmol) in $CH_2Cl_2$ (15 mL) was added. The reaction mixture was then stirred at −78 °C for 30 min and at room temperature for 1.5 h, washed successively with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated to leave a brown oil, which was subjected to flash chromatography [AcOEt–hexane (1:2)]. Earlier fractions afforded (*Z*)-**10** (1.00 g, 24%) as a pale yellow glass. $[\alpha]_D^{27}$ +79.7 (*c* 0.25, $CHCl_3$); MS *m*/*z*: 441 ($M^+$); IR ($CHCl_3$) $\nu$, $cm^{-1}$: 3465 (NH), 1705 (CO); $^1H$ NMR ($CDCl_3$) $\delta$: 1.25 (3H, t, *J*=7 Hz), 2.15 (1H, ddd, *J*=15, 8, 7.5 Hz), 3.00 (1H, dddd, *J*=15, 7.5, 4, 1.5 Hz), 3.15 (1H, dd, *J*=16, 4 Hz), 3.22 (1H, ddd, *J*=16, 5.5, 1.5 Hz), 3.92 and 3.97 (2H, d each, *J*=14 Hz), 4.13 (2H, q, *J*=7 Hz), 4.16 (1H, m), 4.40 (1H, dd, *J*=5.5, 4 Hz), 5.70 (1H, d, *J*=11.5 Hz), 6.38 (1H, ddd, *J*=11.5, 8, 7.5 Hz), 6.70 (1H, s), 7.13 (1H, dd, *J*=7.5, 7 Hz), 7.18 (1H, dd, *J*=8, 7.5 Hz), 7.2–7.4 (6H, m), 7.54 (1H, d, *J*=7.5 Hz), 7.73 (1H, s), 8.43 (1H, s); HRMS calcd for $C_{27}H_{27}N_3O_3$: 441.2052, found: 441.2047. Later fractions in the above chromatography gave (*E*)-**10** (2.21 g, 54%) as a pale yellow glass. $[\alpha]_D^{28}$ +94.5 (*c* 0.25, $CHCl_3$); MS *m*/*z*: 441 ($M^+$); IR ($CHCl_3$) $\nu$, $cm^{-1}$: 3470 (NH), 1709 (CO); $^1H$ NMR ($CDCl_3$) $\delta$: 1.31 (3H, t, *J*=7 Hz), 1.95–2.15 (2H, m), 3.15 (1H, dd, *J*=16, 3 Hz), 3.31 (1H, ddd, *J*=16, 6, 1.5 Hz), 3.95 and 4.02 (2H, d each, *J*=14 Hz), 4.04 (1H, dd, *J*=7, 6.5 Hz), 4.20 (2H, q, *J*=7 Hz), 4.45 (1H, dd, *J*=6, 3 Hz), 5.67 (1H, d, *J*=15.5 Hz), 6.69 (1H, s), 6.94 (1H, ddd, *J*=15.5, 8.5, 6.5 Hz), 7.16 (1H, dd, *J*=8, 7.5 Hz), 7.20 (1H, dd, *J*=8, 7.5 Hz), 7.25–7.45 (6H, m), 7.58 (1H, d, *J*=7.5 Hz), 7.79 (1H, br s), 7.81 (1H, s); HRMS calcd for $C_{27}H_{27}N_3O_3$: 441.2052, found: 441.2051.

### 4.4. Retro-Michael reaction of (*E*)-10: preparation of the diene 12

A solution of (*E*)-**10** (30 mg, 0.068 mmol) and DBN (42 mg, 0.34 mmol) in xylene (2 mL) was heated under reflux for 6 h in an atmosphere of $N_2$. The reaction mixture was concentrated in vacuo, and the residue was partitioned between $H_2O$ and $CHCl_3$. The $CHCl_3$ extracts were washed with brine, dried, and concentrated. Purification of the residual oil by flash chromatography [AcOEt–hexane (1:1)] afforded **12** (12 mg, 40%) as a yellow oil. MS *m*/*z*: 441 ($M^+$); $^1H$ NMR ($CDCl_3$) $\delta$: 1.34 (3H, t, *J*=7 Hz), 3.27 (1H, dd, *J*=14, 6.5 Hz), 3.30 (1H, dd, *J*=14, 7 Hz), 3.59 and 3.76 (2H, d each, *J*=13.5 Hz), 4.12 (1H, dd, *J*=7, 6.5 Hz), 4.25 (2H, q, *J*=7 Hz), 5.93 (1H, d, *J*=15 Hz), 6.54 (1H, dd, *J*=15, 11 Hz), 6.78 (1H, s), 6.84 (1H, d, *J*=15 Hz), 7.0–7.4 (9H, m), 7.41 (1H, dd, *J*=15, 11 Hz), 7.82 (1H, s), 8.35 (1H, s).

### 4.5. Diels–Alder reaction of (*E*)-10 and (*Z*)-10: preparation of the diols 15a and 15b

(i) *From (E)-**10*** (Table 1, entry 4): A solution of (*E*)-**10** (112 mg, 0.25 mmol) in THF–$H_2O$ (10:1, 13 mL) was heated under reflux for 48 h in an atmosphere of Ar. The reaction mixture was concentrated in vacuo, and the residue was subjected to flash chromatography [AcOEt–hexane (2:1)]. Earlier fractions furnished **15a** (71 mg, 61%) as a slightly yellow foam. $[\alpha]_D^{24}$ −264 (*c* 0.25, $CHCl_3$); MS *m*/*z*: 459 ($M^+$); IR ($CHCl_3$) $\nu$, $cm^{-1}$: 3470, 3445, 3335 (NH, OH), 1668 (CO), 1622 (α,β-unsaturated ester C=C); $^1H$ NMR ($CDCl_3$) $\delta$: 1.14 (3H, t, *J*=7 Hz), 1.94 (1H, ddd,

$J$=13.5, 12.5, 4.5 Hz), 2.62 (1H, ddd, $J$=12.5, 4.5, 2 Hz), 2.64 (1H, d, $J$=17.5 Hz), 2.85 (1H, ddd, $J$=13.5, 4.5, 3 Hz), 3.13 (1H, dd, $J$=17.5, 7.5 Hz), 3.38 (1H, d, $J$=7.5 Hz), 3.37 (1H, d, $J$=12 Hz), 3.67 and 3.69 (2H, d each, $J$=13.5 Hz), 3.9–4.05 (3H, m), 4.60 (1H, d, $J$=6.5 Hz), 4.85 (1H, br), 4.89 (1H, d, $J$=12 Hz), 7.12 (1H, dd, $J$=7.5, 7 Hz), 7.16 (1H, dd, $J$=8, 7.5 Hz), 7.25–7.35 (6H, m), 7.38 (1H, dd, $J$=6.5, 2 Hz), 7.49 (1H, d, $J$=8 Hz), 8.16 (1H, s); HRMS calcd for $C_{27}H_{29}N_3O_4$: 459.2158, found: 459.2161. Later fractions in the above chromatography provided **15b** (38 mg, 33%) as a slightly yellow foam. $[\alpha]_D^{24}$ −142 ($c$ 0.25, $CHCl_3$); MS $m/z$: 459 ($M^+$); IR ($CHCl_3$) $\nu$, $cm^{-1}$: 3465, 3340 (NH, OH), 1668 (CO), 1624 (α,β-unsaturated ester C=C); $^1H$ NMR ($CDCl_3$) $\delta$: 1.13 (3H, t, $J$=7.5 Hz), 1.96 (1H, ddd, $J$=13, 12.5, 4 Hz), 2.33 (1H, br), 2.50 (1H, dd, $J$=12.5, 4.5 Hz), 2.85 (1H, ddd, $J$=13, 4.5, 3 Hz), 3.0–3.1 (2H, m), 3.64 and 3.67 (2H, d each, $J$=13 Hz), 3.65 (1H, m), 3.9–4.0 (3H, m), 4.40 (1H, br), 5.05 (1H, br), 5.42 (1H, dd, $J$=5.5, 5 Hz), 7.09 (1H, dd, $J$=7.5, 7 Hz), 7.12 (1H, dd, $J$=7.5, 7 Hz), 7.25–7.35 (7H, m), 7.51 (1H, d, $J$=7.5 Hz), 8.17 (1H, s); HRMS calcd for $C_{27}H_{29}N_3O_4$: 459.2158, found: 459.2159.

(ii) *From (Z)-**10*** (Table 1, entry 5): A solution of (*Z*)-**10** (90 mg, 0.20 mmol) in THF–$H_2O$ (10:1, 10 mL) was heated under reflux for 48 h in an atmosphere of Ar. The reaction mixture was worked up as described above under method (i), giving **15a** (58 mg, 62%) and **15b** (32 mg, 34%). The products **15a** and **15b** thus obtained were identical (by comparison of the IR and $^1H$ NMR spectra and TLC behavior) with authentic samples prepared by method (i), respectively.

### 4.6. Equilibration of the diols 15a and 15b

A solution of **15a** (20 mg, 0.044 mmol) in THF–$H_2O$ (10:1, 2.2 mL) was heated under reflux for 48 h in an atmosphere of $N_2$. The reaction mixture was concentrated in vacuo to leave a yellow oil, which was estimated to be a 75:25 mixture of **15a** and **15b** by $^1H$ NMR analysis. Similar treatment of **15b** provided the same equilibrium mixture.

### 4.7. Time-course of the intramolecular cycloaddition reaction of (*E*)-10

A solution of (*E*)-**10** (70 mg, 0.16 mmol) in THF–$H_2O$ (10:1, 14 mL) was stirred at 60 °C under $N_2$. At intervals, aliquots (0.8 mL) were withdrawn and concentrated in vacuo. The ratio of the components in the residual oil was determined by $^1H$ NMR analysis. The results are summarized in Table 2.

### 4.8. Intramolecular cycloaddition reaction of (*E*)-10 in anhydrous THF

A solution of (*E*)-**10** (70 mg, 0.16 mmol) in anhydrous THF (14 mL) was stirred at 60 °C for 12 h under $N_2$. The reaction mixture was concentrated in vacuo to give a yellow oil, which was found to be a 1:1 mixture of (*E*)-**10** and the cycloadduct **13a** by $^1H$ NMR analysis. Compound **13a**: $^1H$ NMR ($CDCl_3$) $\delta$: 1.20 (3H, t, $J$=7.5 Hz), 1.71 (1H, m), 1.8–2.2 (2H, m), 2.87 (1H, dd, $J$=4, 3.5 Hz), 3.01 (1H, d, $J$=17 Hz), 3.45 (1H, dd, $J$=17, 6.5 Hz), 3.8–4.1 (6H, m), 6.18 (1H, d, $J$=4 Hz), 7.1–7.45 (8H, m), 7.56 (1H, d, $J$=7.5 Hz), 7.73 (1H, s), 8.04 (1H, s).

### 4.9. (6*S*,13*S*)-6,7,12,13-Tetrahydro-14-(phenylmethyl)-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole-4-carboxylic acid ethyl ester (14)

(i) *From **15a***: A solution of **15a** (20.0 mg, 0.044 mmol) and DBN (56 mg, 0.45 mmol) in *o*-DCB (1 mL) was heated under reflux for 3 h in an atmosphere of $N_2$. The reaction mixture was concentrated in vacuo, and the residue was partitioned between $CHCl_3$ and $H_2O$. The $CHCl_3$ extracts were washed with brine, dried, and concentrated to leave a yellow oil, which was purified by flash chromatography [AcOEt–hexane (1:1)] to furnish **14** (14.4 mg, 78%) as a pale yellow solid. Recrystallization from AcOEt–hexane (1:2) afforded an analytical sample as colorless needles, mp 215–216 °C. $[\alpha]_D^{25}$ −30.7 ($c$ 0.30, $CHCl_3$); IR (Nujol) $\nu$, $cm^{-1}$: 3285 (NH), 1720 (CO); $^1H$ NMR ($CDCl_3$) $\delta$: 1.35 (3H, t, $J$=7 Hz), 2.72 (1H, d, $J$=16 Hz), 3.42 (1H, dd, $J$=18, 1.5 Hz), 3.50 (1H, dd, $J$=16, 5 Hz), 3.57 (1H, dd, $J$=18, 6 Hz), 3.81 and 3.93 (2H, d each, $J$=13.5 Hz), 4.22 (1H, d, $J$=6 Hz), 4.31 (2H, q, $J$=7 Hz), 4.45 (1H, d, $J$=5 Hz), 7.06 (1H, dd, $J$=7.5, 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), 7.84 (1H, s), 8.55 (1H, s), 8.89 (1H, s); $^{13}C$ NMR ($CDCl_3$) $\delta$: 14.2 (q), 25.8 (t), 34.1 (t), 49.4 (d), 53.5 (d), 56.4 (t), 61.0 (t), 104.7 (s), 110.9 (d), 118.2 (d), 119.6 (d), 121.9 (d), 125.2 (s), 127.1 (s), 127.4 (d), 128.5 (d), 128.7 (d), 133.6 (s), 136.1 (s), 136.4 (s), 138.3 (s), 145.0 (s), 149.9 (d), 151.5 (d), 166.0 (s). Anal. Calcd for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92. Found: C, 76.41; H, 6.11; N, 9.74.

(ii) *From **15b***: Dehydration of **15b** (20.0 mg, 0.044 mmol) with DBN and work-up of the reaction mixture were carried out in a manner similar to that described above under method (i), providing **14** (12.3 mg, 67%) as a pale yellow solid. This sample was identical (by comparison of the $^1H$ NMR spectrum and TLC mobility) with the one obtained by method (i).

### 4.10. (6*S*,13*S*)-6,7,12,13-Tetrahydro-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole-4-carboxylic acid ethyl ester (19)

A solution of **14** (56 mg, 0.13 mmol) in MeOH (3 mL) was hydrogenated over 20% $Pd(OH)_2$–C (56 mg) at room temperature and atmospheric pressure for 28 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to leave a yellow oil. Purification by flash chromatography [$CHCl_3$–MeOH (20:1)] gave **19** (40 mg, 91%) as a pale yellow oil. $[\alpha]_D^{24}$ +171 ($c$ 0.50, $CHCl_3$); MS $m/z$: 333 ($M^+$); IR ($CHCl_3$) $\nu$, $cm^{-1}$: 3465, 3375 (NH), 1713 (CO); $^1H$ NMR ($CDCl_3$) $\delta$: 1.36 (3H, t, $J$=7 Hz), 1.78 (1H, br), 2.88 (1H, dd, $J$=15.5, 1 Hz), 3.37 (1H, dd, $J$=15.5, 5 Hz), 3.49 (1H, dd, $J$=18.5, 1 Hz), 3.56 (1H, dd, $J$=18.5, 5.5 Hz), 4.32 (2H, q, $J$=7 Hz), 4.57 (1H, d, $J$=5.5 Hz), 4.74 (1H, d, $J$=5 Hz), 7.05 (1H, dd, $J$=8, 7.5 Hz), 7.12 (1H, dd, $J$=8, 7.5 Hz), 7.27 (1H, d, $J$=8 Hz), 7.38 (1H, d, $J$=8 Hz), 7.92 (1H, s), 8.60 (1H, s), 8.90 (1H, s); HRMS calcd for $C_{20}H_{19}N_3O_2$: 333.1477, found: 333.1478.

### 4.11. (6*S*,13*S*)-6,7,12,13-Tetrahydro-14-methyl-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole-4-carboxylic acid ethyl ester (20)

(i) *From* ***19***: A mixture of **19** (10 mg, 0.030 mmol), 35% aqueous HCHO (0.01 mL), acetic acid (0.01 mL), and MeOH (1 mL) was shaken under $H_2$ in the presence of 20% $Pd(OH)_2$–C (10 mg) at room temperature and atmospheric pressure for 1.5 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to leave an oil, to which were added 10% aqueous $Na_2CO_3$ (2 mL) and $H_2O$ (5 mL). The mixture was then extracted with $CHCl_3$, and the $CHCl_3$ extracts were washed with brine, dried over anhydrous $K_2CO_3$, and concentrated. Purification of the residue by flash chromatography [$CHCl_3$–MeOH (20:1)] furnished **20** (10 mg, 96%) as a colorless oil. $[\alpha]_D^{26}$ +85.6 (*c* 0.50, $CHCl_3$); MS *m*/*z*: 347 ($M^+$); IR ($CHCl_3$) $\nu$, $cm^{-1}$: 3465 (NH), 1715 (CO); $^1H$ NMR ($CDCl_3$) $\delta$: 1.35 (3H, t, *J*=7 Hz), 2.59 (3H, s), 2.71 (1H, d, *J*=16 Hz), 3.46 (1H, d, *J*=18.5 Hz), 3.47 (1H, dd, *J*=16, 5 Hz), 3.63 (1H, dd, *J*=18.5, 5.5 Hz), 4.18 (1H, d, *J*=5.5 Hz), 4.32 (2H, q, *J*=7 Hz), 4.35 (1H, d, *J*=5 Hz), 7.05 (1H, dd, *J*=7.5, 7 Hz), 7.12 (1H, dd, *J*=8, 7 Hz), 7.28 (1H, d, *J*=8 Hz), 7.39 (1H, d, *J*=7.5 Hz), 7.93 (1H, br), 8.58 (1H, s), 8.90 (1H, s); HRMS calcd for $C_{21}H_{21}N_3O_2$: 347.1634, found: 347.1631.

(ii) *From* ***14***: A mixture of **14** (11 mg, 0.026 mmol), 35% aqueous HCHO (0.01 mL), acetic acid (0.01 mL), and MeOH (1 mL) was shaken under $H_2$ in the presence of 20% $Pd(OH)_2$–C (11 mg) at room temperature and atmospheric pressure for 5 h. Work-up of the reaction mixture in a manner similar to that described above under method (i) provided **20** (9.0 mg, 100%). This sample was identical (by comparison of the $^1H$ NMR spectrum and TLC behavior) with the one obtained by method (i).

### 4.12. (6*S*,13*S*)-6,7,12,13-Tetrahydro-14-methyl-6,13-imino-5*H*-pyrido[3′,4′:5,6]cyclooct[1,2-*b*]indole-4-methanol (1)

A stirred suspension of $LiAlH_4$ (25 mg, 0.66 mmol) in THF (3 mL) was cooled to 0 °C, and a solution of **20** (57 mg, 0.16 mmol) in THF (2 mL) was added. After the mixture had been stirred for 30 min, the reaction was quenched by adding 4% aqueous NaOH. The insoluble material was filtered off and washed with ether. The filtrate and washings were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography [$CHCl_3$–MeOH (10:1)] afforded **1** (47 mg, 94%) as a colorless foam. $[\alpha]_D^{23}$ −46.0 (*c* 0.30, MeOH); MS *m*/*z*: 305 ($M^+$); IR ($CHCl_3$) $\nu$, $cm^{-1}$: 3465, 3395 (NH, OH); UV (MeOH) $\lambda_{max}$ (log $\varepsilon$): 222 (4.46), 270 (3.88), 282 (sh) (3.83), 290 (3.71); CD (MeOH) $\lambda_{ext}$, nm ($\Delta\varepsilon$): 295 (2.98), 291 (1.79), 287 (2.93), 273 (−2.80), 259 (2.37), 251 (2.01), 240 (2.74), 224 (−24.5); $^1H$ NMR ($CDCl_3$) $\delta$: 2.41 (3H, s), 2.62 (1H, d, *J*=16 Hz), 2.80 (1H, d, *J*=17.5 Hz), 3.22 (1H, dd, *J*=17.5, 5.5 Hz), 3.36 (1H, dd, *J*=16, 5.5 Hz), 3.86 (1H, d, *J*=5.5 Hz), 4.15 (1H, d, *J*=5.5 Hz), 4.32 and 4.34 (2H, d each, *J*=13 Hz), 4.52 (1H, br), 7.05 (1H, dd, *J*=8, 7.5 Hz), 7.10 (1H, dd, *J*=8, 7.5 Hz), 7.25 (1H, d, *J*=7.5 Hz), 7.38 (1H, d, *J*=7.5 Hz), 8.07 (1H, s), 8.29 (1H, s), 8.59 (1H, br); $^1H$ NMR (acetone-$d_6$) $\delta$: 2.53 (3H, s), 2.66 (1H, dd, *J*=15.5, 1 Hz), 2.83 (1H, br), 3.03 (1H, dd, *J*=17, 2.5 Hz), 3.31 (1H, dd, *J*=17, 6 Hz), 3.41 (1H, dd, *J*=15.5, 5.5 Hz), 4.24 (1H, d, 6 Hz), 4.30 (1H, d, *J*=5.5 Hz), 4.53 (2H, s), 6.91 (1H, dd, *J*=8.5, 8 Hz), 6.99 (1H, dd, *J*=8, 8 Hz), 7.26 (1H, d, *J*=8.5 Hz), 7.33 (1H, d, *J*=8 Hz), 8.22 (1H, s), 8.39 (1H, s), 9.95 (1H, s); $^{13}C$ NMR ($CDCl_3$) $\delta$: 25.3 (t), 31.0 (t), 40.2 (q), 51.8 (d), 54.3 (d), 60.5 (t), 104.0 (s), 111.1 (d), 118.2 (d), 119.4 (d), 121.8 (d), 127.0 (s), 132.9 (s), 133.9 (s), 135.2 (s), 136.2 (s), 141.2 (s), 146.6 (d), 148.0 (d); HRMS calcd for $C_{19}H_{19}N_3O$: 305.1528, found: 305.1523.

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