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Total synthesis of suaveoline and norsuaveoline via intramolecular oxazole–olefin Diels–Alder reaction

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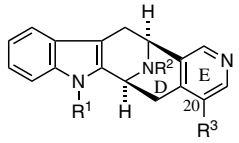
Abstract—Total synthesis of two *Rauwolfia* alkaloids, suaveoline (**1**) and norsuaveoline (**2**), has been achieved through a highly stereoselective route starting from L-tryptophan methyl ester (**9**) and exploiting the intramolecular Diels–Alder reaction of the oxazole–olefin **16**.

In 1972, Potier and co-workers reported the isolation of a novel indole alkaloid suaveoline from the trunk bark of *Rauwolfia suaveolens* and proposed the structure **1** for it on the basis of spectroscopic data and chemical correlation with ajmaline.[1,2] The structure and absolute stereochemistry have been confirmed via racemic[3] and enantiospecific[4] syntheses of **1** by two independent research groups, respectively. Thereafter, four additional alkaloids [i.e., norsuaveoline (**2**),[2e,5] macrophylline (**3**),[2e,g,6] macrocaffrine (**4**),[2e,6b] and sellowiine (**5**)[7]] containing a skeleton similar to that of suaveoline have been isolated from a number of *Rauwolfia* species. In connection with our ongoing interest in the synthesis of annulated pyridine systems[8] exploiting intramolecular oxazole–olefin Diels–Alder reactions,[9] we sought possible new routes to suaveoline (**1**) and norsuaveoline (**2**) in the present study.



1: R^1 = Me, R^2 = H, R^3 = Et
2: R^1 = R^2 = H, R^3 = Et
3: R^1 = H, R^2 = Me, R^3 = CH_2CH_2OH
4: R^1 = H, R^2 = Me, R^3 = CH_2OH
5: R^1 = R^2 = R^3 = H

From a retrosynthetic perspective, we envisaged the oxazole derivative **6** as a precursor for an efficient construction of the DE rings of the target molecules, **1** and **2**, by adopting intramolecular Diels–Alder reaction. The oxazole–olefin **6** would be obtained from **8** via the formation of the C ring and subsequent introduction of an appropriate olefinic dienophile to the derived aldehyde **7**. Furthermore, the requisite enantiomer **8**, in turn, would arise from L-tryptophan methyl ester (**9**) through the conversion of α-amino esters into chiral 5-(aminomethyl)oxazole derivatives developed earlier.[10] The strategy is applicable to the synthesis of other suaveoline-related alkaloids **3**–**5** comprising different substituents at the 20-position because a variety of oxazole–olefins **6** would be readily accessible from the aldehyde **7** postulated as a key intermediate (Scheme 1).

The initial step was treatment of the *N*-protected amino ester **10**,[11] derived from **9**, with α-lithiated methyl isocyanide, which was performed in THF at −78 °C for 2.5 h according to our previous procedure,[10] giving the oxazole **11** [mp 163–164 °C;[12] $[\alpha]_D^{25}$ −34.5 (*c* 0.50, MeOH)] in 82% yield. Deprotection of **11** with CF_3CO_2H (CH_2Cl_2, 0 °C, 4 h) provided the amino oxazole **8** in 98% yield. The enantiomeric purity of **8** thus obtained was estimated to be 97% ee by Mosher's method. For the formation of the C ring in the aldehyde **7**, the amino oxazole **8**

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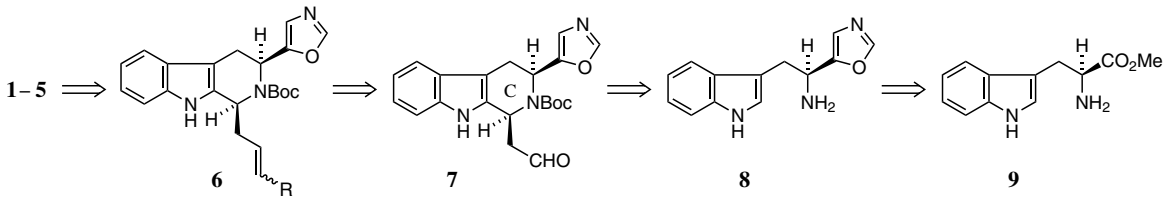
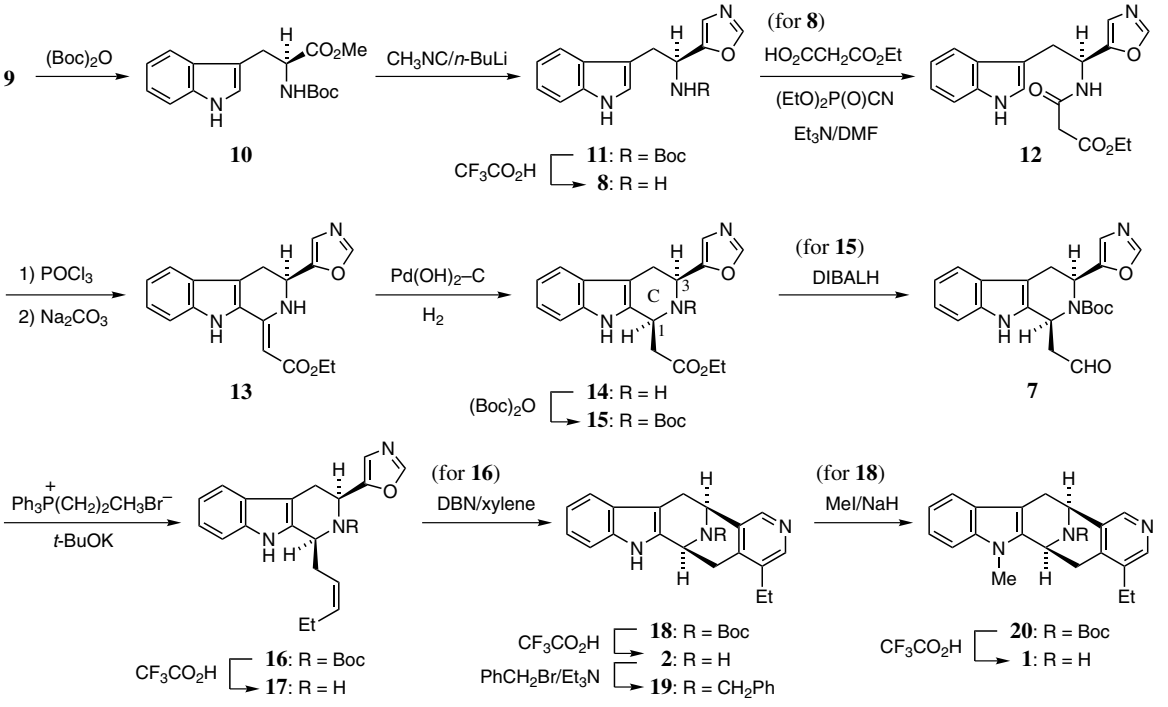


Scheme 1.

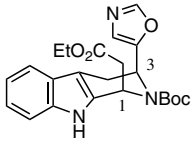
was first converted into the amide **12** in 88% yield by condensation with monoethyl malonate employing the coupling reagent diethyl phosphorocyanidate[13] (Et_3N, DMF, 0 °C, 30 min then room temperature, 30 min). The Bischler–Napieralski cyclization of **12** was effected in $POCl_3$ (room temperature, 6 days) without a co-solvent by following the method of Hino and co-workers,[14] affording the enamino ester **13** [mp 213–214 °C;[12] $[\alpha]_D^{29}$ −156 (*c* 0.20, $CHCl_3$)][15] in 50% yield after basification of the resulting iminium salt. On catalytic hydrogenation of **13** with Pearlman's catalyst and hydrogen (EtOH, 1 atm, room temperature, 22 h), the *cis*-1,3-disubstituted tetrahydro-β-carboline **14** was preferentially obtained in 84% yield without accompanying the *trans*-isomer. The stereochemical assignment of **14** was confirmed by a 10% NOE enhancement observed for the C(1)-proton signal on the irradiation of the C(3)-proton signal (Scheme 2).

We next turned our attention to the introduction of an olefinic dienophile, required for the subsequent intramolecular oxazole–olefin Diels–Alder reaction, into the amino ester **14**. The secondary amino group of **14** was first protected with di-*tert*-butyl dicarbonate (boiling $CHCl_3$, 24 h) to afford **15** [mp 188.5–190 °C;[12] $[\alpha]_D^{26}$ +227 (*c* 0.25, $CHCl_3$)] in 87% yield. The ^1H NMR spectrum of **14** exhibited two methylene protons adjacent to the 1-position at δ 2.80 and 2.88 in $CDCl_3$, whereas the corresponding protons of the *N*-Boc derivative **15** appeared at δ 1.85 (4/9H), 1.99 (5/9H) and δ 2.60 (5/9H), 2.71 (4/9H) in $CDCl_3$.[16] The large upfield shift, which one of the two methylene protons of **15** in question showed, may be interpreted in terms of the shielding effect arising from the oxazole ring on the basis of the contribution of the conformer **15A**. Such conformation that both C(1)- and C(3)-substituents occupy pseudo-axial positions[17] is favorable for the intramolecular Diels–Alder reaction tried after the introduction of an olefinic moiety. The *N*-protected ester **15** was then treated with diisobutylaluminum hydride (DIBALH) in CH_2Cl_2 at −78 °C for 80 min to provide the aldehyde **7**, a key intermediate for our strategy, in 95% yield. The Wittig reaction of **7** with the phosphorane, derived from *n*-propyltriphenylphosphonium bromide and *t*-BuOK,



Scheme 2.

was performed in benzene (room temperature, 30 min) to give the oxazole–olefin **16** in 73% yield with high *Z* selectivity. The geometry in **16** was determined on the basis of the coupling constant ($J = 10.5$ Hz) between two olefinic protons of the amine **17** obtained by deprotection of **16**.



15A

Having succeeded in the synthesis of the oxazole–olefin **16**, we set out to explore its intramolecular Diels–Alder reaction. After considerable experimentation, we found that the best result was obtained by treatment of **16** in boiling xylene in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) for 9 h; under these conditions, the desired pyridine **18** [mp 230–232 °C;[12] $[\alpha]_D^{25}$ − 6.0 (*c* 0.25, $CHCl_3$)] was produced in 69% yield. It seems likely that DBN might serve as a scavenger of H_2O at the high temperature employed and promote the conversion of the initially formed Diels–Alder cycloadduct into the pyridine **18**.[18] Finally, methylation of **18** with MeI in DMF (NaH, room temperature, 20 min) and subsequent deprotection of the resulting N_a-methyl derivative **20** with CF_3CO_2H (CH_2Cl_2, 0 °C, 3 h) provided the first target compound **1** [$[\alpha]_D^{28}$ − 1.4 (*c* 0.50, $CHCl_3$)] in 80% yield from **18**. The ^1H and ^{13}C NMR ($CDCl_3$), UV (EtOH), CD (cyclohexane), and mass spectral data for the synthetic **1** proved to be virtually identical with those reported for natural suaveoline [$[\alpha]_D 0 \pm 2$ (*c* 1, $CHCl_3$)][1,2f] and/or Cook's synthetic sample [$[\alpha]_D^{25}$ − 9.33 (*c* 0.30, $CHCl_3$)].[4a,b] On the other hand, removal of the Boc group in **18** with CF_3CO_2H (CH_2Cl_2, 0 °C, 3 h) furnished the second target compound **2** [mp 258–262 °C; $[\alpha]_D^{30}$ + 19.6 (*c* 0.50, $CHCl_3$)] in 88% yield. Although the specific rotation of **2** thus obtained was in disagreement with that of norsuaveoline [$[\alpha]_D^{27}$ − 3.2 (*c* 1.00, $CHCl_3$)] synthesized previously by Cook and co-workers,[5,19] they were virtually identical with each other by comparison of the ^1H and ^{13}C NMR ($CDCl_3$) and CD (EtOH) spectra and TLC mobility (three solvent systems). In addition, we found that the spectral data and specific rotation for **19** [$[\alpha]_D^{27}$ − 132.2 (*c* 0.50, $CHCl_3$)], derived from benzylation of **2**, matched those of N_b-benzylnorsuaveoline [$[\alpha]_D^{27}$ − 143.2 (*c* 1.00, $CHCl_3$)] reported in the literature.[5]

In conclusion, a highly stereoselective total synthesis of two *Rauwolfia* alkaloids, suaveoline (**1**), and norsuaveoline (**2**), has been accomplished via a route featuring an efficient construction of the DE rings by the intramolecular Diels–Alder reaction of the oxazole–olefin **16**. Further studies directed toward the synthesis of suaveoline-related alkaloids **3**–**5** using the aldehyde **7**, a key intermediate of our synthetic strategy, are in progress in our laboratory.

Acknowledgements

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