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

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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**.

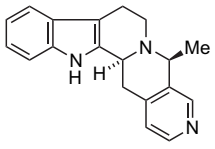
1. Introduction

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]

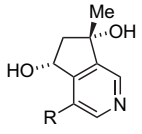
Suaveoline (**4**) was isolated for the first time from the trunk bark of *Rauwolfia suaveolens* by Potier and co-workers in 1972[8] and has since been found in other species of *Rauwolfia*.[9] The structure and absolute stereochemistry of suaveoline, proposed on the basis of spectroscopic data and chemical 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

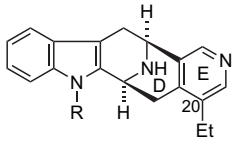
For the efficient construction of the DE rings of **4** and **5**, exploiting the intramolecular oxazole–olefin Diels–Alder reaction, we planned to employ **9** as a precursor (Scheme 1). The requisite oxazole–olefin **9** would be obtained from **11** through the cis-selective Pictet–Spengler reaction[11h,13] 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**.



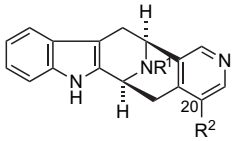
1



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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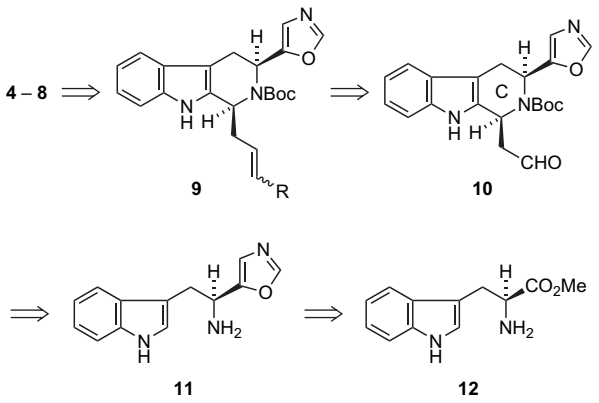


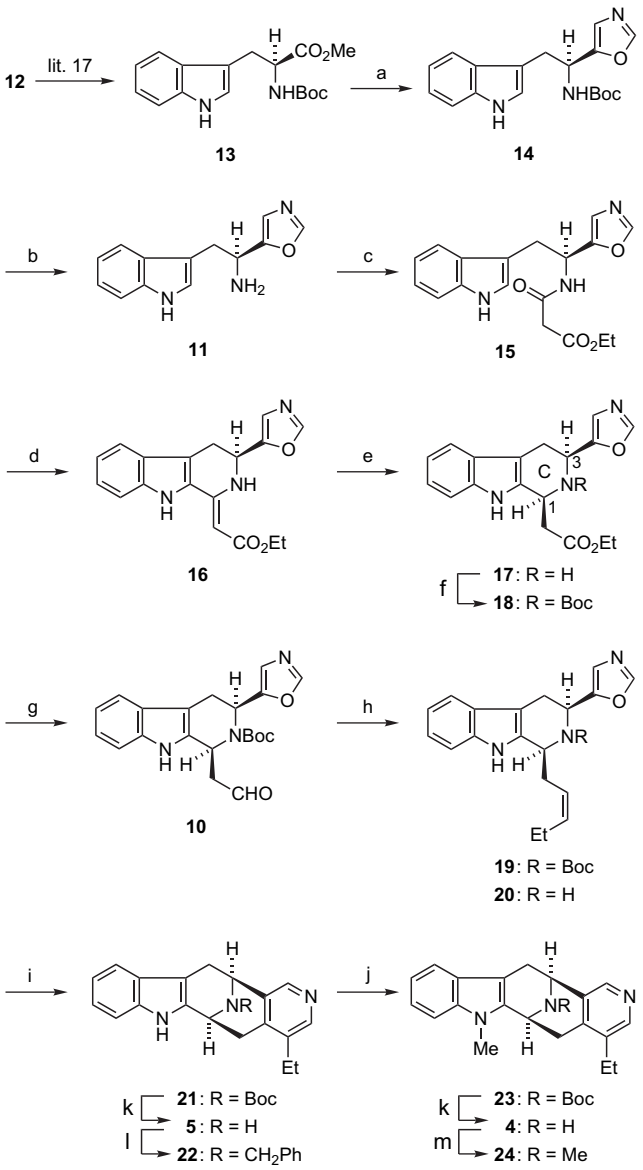
Scheme 1.

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.