Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 12689–12694

Total synthesis of the proposed structure of macrocaffrine

Masashi Ohba[a,*] and Itaru Natsutani[b]

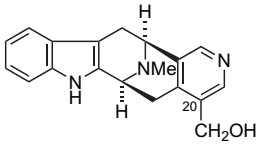
[a]*Advanced Science Research Center, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan*
[b]*Faculty of Pharmaceutical Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan*

Received 14 September 2007; revised 29 September 2007; accepted 1 October 2007
Available online 5 October 2007

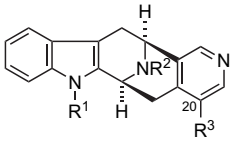
Abstract—A full account of the total synthesis of 18-demethyl-19-hydroxy-N_a-demethyl-N_b-methylsuaveoline (**1**), the structure assigned to macrocaffrine isolated from *Rauwolfia caffra*, is presented. The key steps involved are an intramolecular cycloaddition reaction of the oxazole–olefin **10** 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

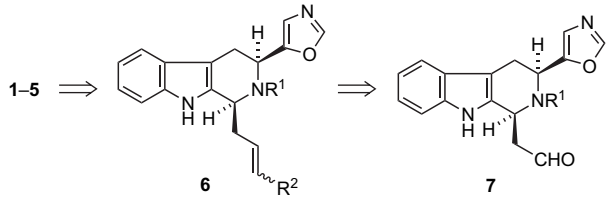
In 1983, Nasser and Court reported the isolation of the macroline/sarpagine related alkaloid 18-demethyl-19-hydroxy-N_a-demethyl-N_b-methylsuaveoline (**1**),[1] which was named macrocaffrine,[2] from the leaves of South African *Rauwolfia caffra*. To date, four additional alkaloids [i.e., suaveoline (**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



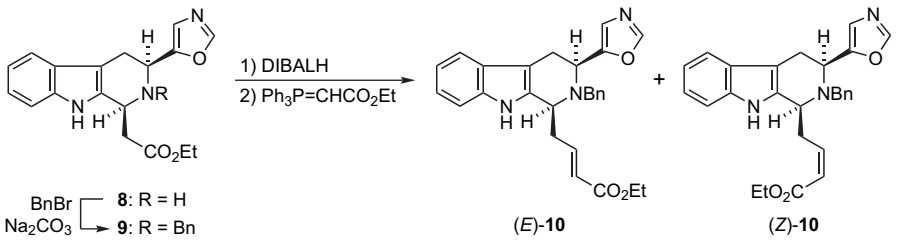
Scheme 1.

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 δ 2.80 and 2.88, whereas one of the corresponding protons of **9** appeared at δ 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

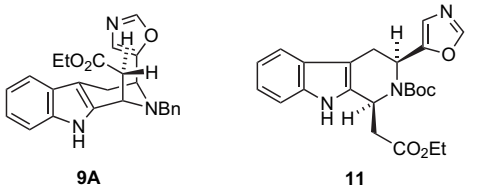
Keywords: Cycloaddition reaction; Indole alkaloids; Macrocaffrine; Oxazoles.
* Corresponding author at present address: Yokohama College of Pharmacy, 601 Matano-cho, Totsuka-ku, Yokohama 245-0066, Japan. Tel./fax: +81 45 859 1369; e-mail: m.ohba@hamayaku.ac.jp

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.10.005

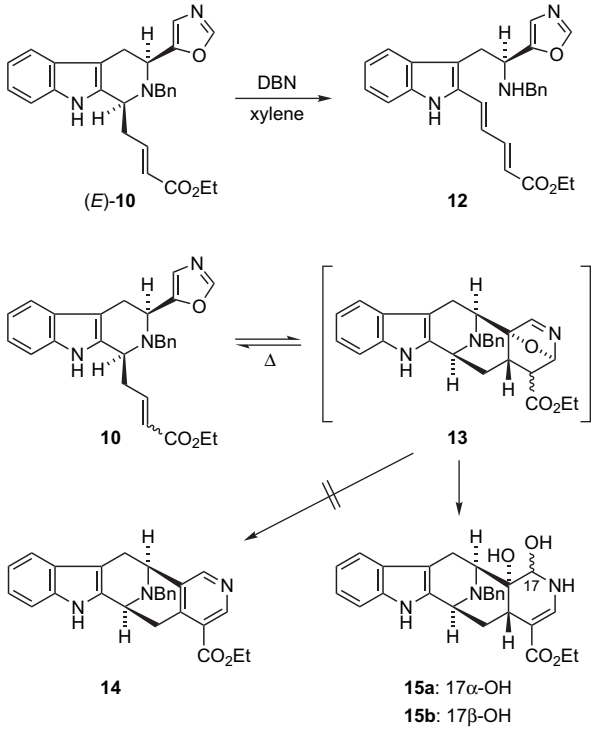


Scheme 2.

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.