Pergamon

Tetrahedron Letters 39 (1998) 8009–8012

TETRAHEDRON LETTERS

The Enantiospecific Total Synthesis of Norsuaveoline

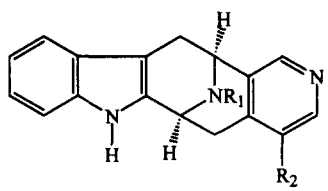
Tao Wang, Peng Yu, Jin Li and James M. Cook*
Department of Chemistry, University of Wisconsin-Milwaukee
Milwaukee, WI 53201

Received 23 June 1998; revised 12 August 1998; accepted 18 August 1998

Abstract: *Norsuaveoline* ***1a*** *has been synthesized enantiospecifically in 28% overall yield from commercially available D-(+)-tryptophan methyl ester via the asymmetric Pictet-Spengler reaction and a stereocontrolled oxy-anion Cope rearrangement as key steps.* © 1998 Elsevier Science Ltd. All rights reserved.

During the last several years over 80 indole alkaloids have been isolated from various species of *Alstonia*.[1] An extract of *Alstonia scholaris R.Br.* "dita bark" has been reported to exhibit antimalarial properties,[2] moreover, villastonine and macrocarpamine have been shown by Wright *et al.*[3] to exhibit antimalarial and antiamoebic activities, respectively. In addition, Manalo *et al.* described the hypotensive effect of the bisindole macralstonine[4,5] which had been isolated from *Alstonia macrophylla* Wall *and Alstonia muelleriana* Domin. However, the paucity of material isolated in regard to some of the other alkaloids has prohibited screening for biological activity. This situation has prompted the investigation of the synthesis of the suaveoline bases, as well as a route to their enantiomers.

Figure 1. Potential targets



1a R_1=H, R_2=C_2H_5, norsuaveoline
1b R_1=CH_3, R_2=CH_2CH_2OH, macrophylline
1c R_1=CH_3, R_2=CH_2OH, 18-desmethyl-19-hydroxy-N_a-desmethyl-N_b-methylsuaveoline(18-normacrophylline)

Recently, the development of the stereocontrolled Pictet-Spengler reaction[6] has permitted the synthesis of several N_a-methylsubstituted indole alkaloids. The inability, however, to stereospecifically and enantiospecifically synthesize the N_a-H, N_b-benzyltetracyclicketone **4a** had retarded efforts to prepare the N_a-H series of alkaloids represented here by norsuaveoline **1a**,[7] macrophylline **1b**[8] and 18-normacrophylline **1c**.[8]

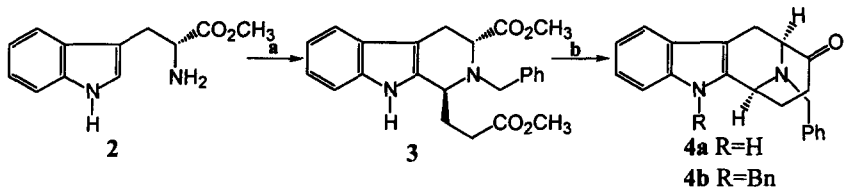
Magnus *et al.*[9] reported the preparation of the N_a-Bn, N_b-Bn tetracyclicketone **4b** and employed it in an elegant synthesis of koumine; however, the route required 9 steps and was not diastereospecific(only 2:1 selectivity), while Bailey[10] later synthesized this ketone with higher diastereoselectivity (4:1) but in lower

PII: S0040-4039(98)01788-2

overall yield. Both routes required the later removal of the N_a-benzyl protecting group with Na/NH_3; reaction conditions that are not compatible with suaveoline indole alkaloids.

To solve this problem, a five-step synthesis of the N_a-H, N_b-benzyltetracyclicketone **4a** has been developed in 60% overall yield in greater than 98% ee without the need to protect the indole N_a-H functional group.[11] Moreover, recently the steps have been successfully reduced to two reaction vessels on large scale, as shown in Scheme 1. Benzylation of the N_b-amino moiety of D-tryptophan methyl ester **2** provided N_a-H N_b-benzyl D-tryptophan methyl ester **3**, which (without isolation and purification) was easily converted into the *trans* diastereomer stereospecifically under the improved conditions of the Pictet-Spengler reaction (83% yield for the complete process). The purified *trans* diester **3** was subjected to a Dieckmann cyclization in scales above the 100 gram level to provide the β-ketoester which (without workup) was hydrolyzed to (-)-N_a-H, N_b-benzyltetracyclicketone **4a** in >98% ee (80% yield for this process). Hundreds of grams of the key intermediate N_a-H, N_b-benzyltetracyclicketone **4a** can now be obtained in this two pot process.

Scheme 1. Preparation of N_a-H, N_b-benzyltetracyclicketone **4a**



a) $PhCHO/CH_3OH$,rt; $NaBH_4$,-5°C, on 400 gram scale;
$(CH_3O)_2CHCH_2CH_2CO_2CH_3$/TFA (2.4eq)/$CH_2Cl_2$,rt,48h.
(83% overall yield)

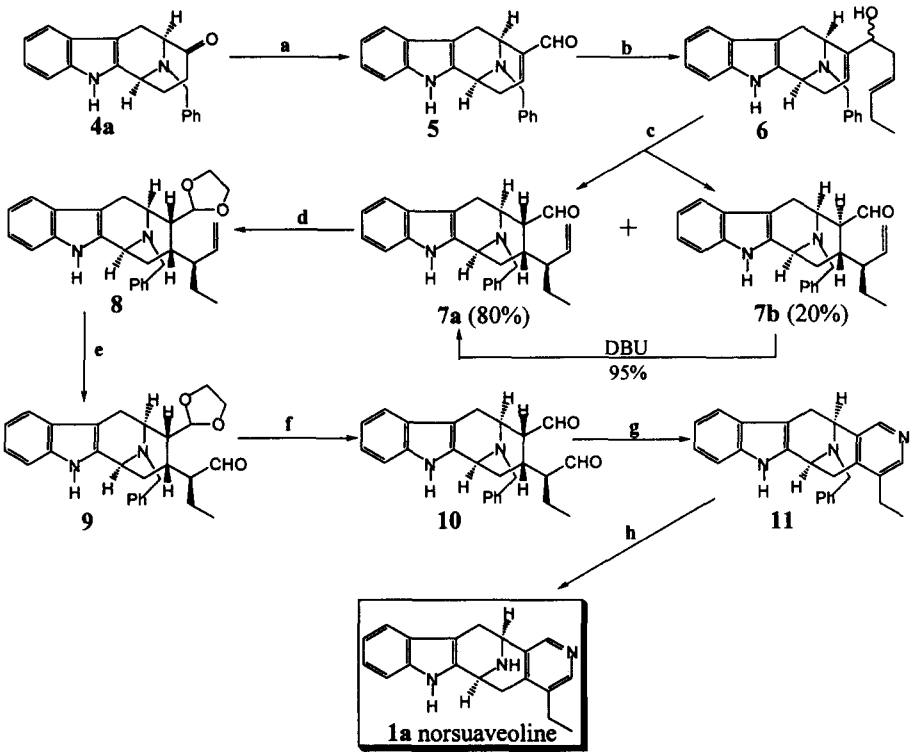
b) NaH (8eq)/CH_3OH/toluene,reflux,48h, on 100gram scale;
HOAc/HCl/H_2O,reflux,10h, 80% overall yield.

With large amounts of ketone **4a** in hand, the execution of the synthesis of several suaveoline alkaloids is underway. Here we wish to report the total synthesis of norsuaveoline **1a** in 10 reaction vessels (12 steps) in 28% overall yield from the commercially available D-tryptophan methyl ester **2**. This approach should also provide a general and efficient route to other N_a-H substituted suaveoline alkaloids such as **1b** and **1c**.

The N_a-H, N_b-benzyltetracyclicketone **4a** was added to the anion of α-chloromethylphenylsulfoxide, followed by the addition of potassium hydroxide to provide a 1:1 mixture of diastereomers of the phenylsulfinyloxirane. These two diastereomers (without separation and purification) were rearranged to the desired α,β-unsaturated aldehyde **5** on heating in the presence of lithium perchlorate. The overall yield for this one pot (two reactions) functional group transformation was 87%. A mixture of the α,β-unsaturated aldehyde **5** and the *trans*-1-bromo-2-pentene was added dropwise at -78°C to freshly prepared barium metal to provide the 1,2-addition product, allylic alcohol **6**, in 92% yield. Barium was employed here in the place of magnesium

or lithium metal based on the work of Yamamoto.[12] The use of magnesium or lithium results in allylic rearrangement of the 2-pentenyl-1-anion to the 1-pentenyl-3-anion immediately and provides only byproducts. When barium was employed no allylic rearrangement was detected.

Scheme 2. Enantiospecific total synthesis of norsuveoline **1a**



a) $PhSOCH_2Cl$/LDA/THF, -78°C; $LiClO_4$/dioxane, reflux, 24h, 87%. b) Li/Ph_2/BaI_2/THF; **5** and *trans*-1-bromo-2-pentene were added as a mixture to freshly prepared barium metal at -78°C, 90%. c) KH/dioxane/18-crown-6, 100°C, 14h, 85%. d) glycol/p-TSA,reflux,20h, 95%. e) OsO_4/py/THF, 0°C, 16h; $NaHSO_3$(aq), rt, 4h; $NaIO_4$/CH_3OH, 0°C, 16h, 85%. f) p-TSA/acetone, reflux, 2d, 95%. g) NH_2OH-HCl/EtOH, reflux, 2d, 88%. h) Pd/C/H_2, 5%HCl-EtOH, rt, 12h, 92%.

The oxy-anion Cope rearrangement of allylic alcohol **6** in the presence of potassium hydride in dioxane at 100°C gave the desired alkenic aldehyde **7** in excellent yield(85%). Surprisingly, only two diastereomers **7a** and **7b** were obtained and attack occurred exclusively from the α-face of the 15-16 olefinic bond. The

structures of **7a** and **7b** were determined by methylation of diastereomers **7a** and **7b** followed by comparison of their proton and ^{13}C-NMR spectra to those of authentic samples obtained from the degradation of commercially available (+)-ajmaline.[13] The C(16) epimeric diastereomer **7b** can be completely transformed into **7a** in high yield(>95%) under mildly alkaline conditions such as DBU or by stirring with sodium methoxide. The significance of this work rests on the fact that almost all of the natural macroline-related alkaloids possess the same chirality at the C-3, C-5, C-15, C-16 and C-20 stereogenic centers as does diastereomer **7a**.

The protection/deprotection step (**9**→**10**) in regard to the aldehyde functional group was necessary since cleavage of the olefinic bond in **7a** by $OsO_4/NaIO_4$ was complicated by the presence of the C(16) aldehydic moiety in the molecule. The one-step cyclization process between dialdehyde **10** and hydroxylamine hydrochloride in ethanol followed by aromatization provided N_b-benzylnorsuaveoline **11**. The N_b-benzyl group of **11** was removed by catalytic hydrogenation (Pd/C, H_2) to provide norsuaveoline **1a** in 92% yield.

In summary, the enantiospecific synthesis of the N_a-H substituted indole alkaloid norsuaveoline **1a** has been accomplished from the commercially available D-(+)-tryptophan methyl ester **2** in only ten reaction vessels in 28% overall yield *via* the stereospecific Pictet-Spengler reaction and a stereocontrolled oxy-anion Cope rearrangement. The protection and deprotection of the N_a-H group was not necessary *via* this route. This approach provides easy access to **1a** or its enantiomer (from L-tryptophan) in optically pure form.

References:

1. Bi, Y.; Hamaker, L. K.; Cook, J. M. "The Synthesis of Macroline Related Alkaloids," in *Studies in Natural Products Chemistry, Bioactive Natural Products*, Part A, Basha, F. Z. and Atta-ur-Rahman, (eds.), Elsevier Science: Amsterdam, **1993**, *13*, 383.
2. Cook, J. M. Ph.D. Thesis, University of Michigan, **1971**.
3. Wright, C. W.; Allen, D.; Cai, Y.; Phillipson, J. D.; Said, I. M.; Kirby, G. C.; Warhurst, D. C. *Phytother. Res.* **1992**, *6*, 121.
4. Isidro, N.; Manalo, G. D. *J. Phillipine Pharm. Assoc.* **1967**, *53*, 8.
5. Talapatra, S. K.; Adityachaudhury, N. *Science and Culture* **1958**, *24*, 243.
6. Zhang, L. H.; Bi, Y.; Yu, F.; Menzia, G.; Cook, J. M. *Heterocycles* **1992**, *34*, 517.
7. Nasser, A.M.A.G.; Court, W.E. *Journal of Ethnopharmacology*, **1984**, *11*, 99-117.
8. Nasser, A.M.A.G.; Court, W.E. *Phytochemistry*, **1983**, *22*, 2297.
9. Magnus, P.; Mugrage, B.; Deluca M. R.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220.
10. Bailey, P. D.; McLay, N. R. *Tetrahedron Lett.* **1991**, *31*, 3895.
11. Yu, P.; Wang, T.; Yu, F.; Cook, J. M. *Tetrahedron Lett.* **1997**, *38*, 6819.
12. Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955. This is a modified procedure. The aldehyde and allylic bromide were added together to the freshly prepared barium metal.
13. Li, J.; Cook, J.M. This is from the degradation of N_b-benzylajmaline, manuscript in preparation.