Pergamon

Tetrahedron Letters, Vol. 38, No. 39, pp. 6819-6822, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01603-1

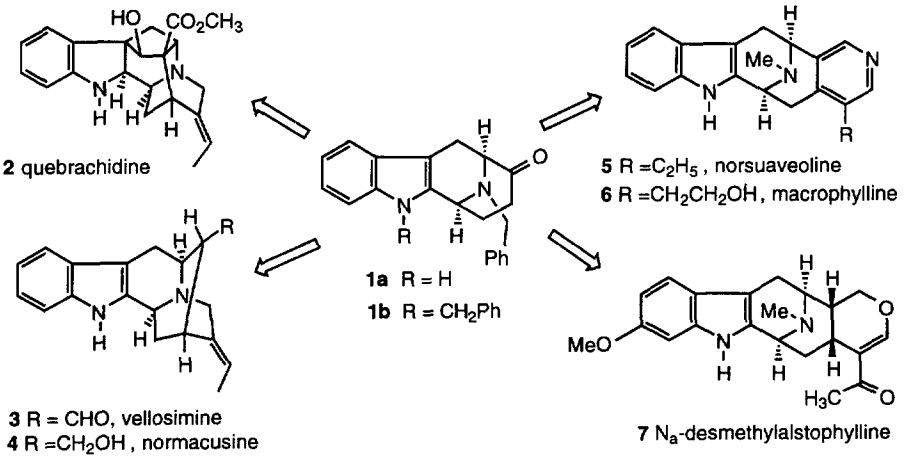
General Approach for The Synthesis of Macroline/Sarpagine Related Indole Alkaloids *Via* The Asymmetric Pictet-Spengler Reaction: The Enantiospecific Synthesis of The N_a-H, Azabicyclo[3.3.1]Nonone Template

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

Abstract: *N_a-H, N_b-benzyltetracyclic ketone **1a**, a potential intermediate for the synthesis of numerous sarpagine-related alkaloids, has been synthesized enantiospecifically from D-(+)-tryptophan via* the *asymmetric Pictet-Spengler reaction.* © 1997 Elsevier Science Ltd.

Over 80 indole alkaloids have been isolated from species of *Alstonia* over the last several years[1]; among them more than 20 are N_a-H substituted bases[2,3] a few of which are depicted in Scheme 1 (see 2-6). Several N_a-methyl macroline/sarpagine alkaloids have fallen to total synthesis, however, the inability to synthesize stereospecifically the key tetracyclic ketone **1a** in the N_a-H series has retarded efforts to prepare alkaloids such as quebrachidine **2**, vellosimine **3**, normacusine **4**, norsuaveoline **5** and macrophylline **6**.

Scheme 1. Potential Target Alkaloids

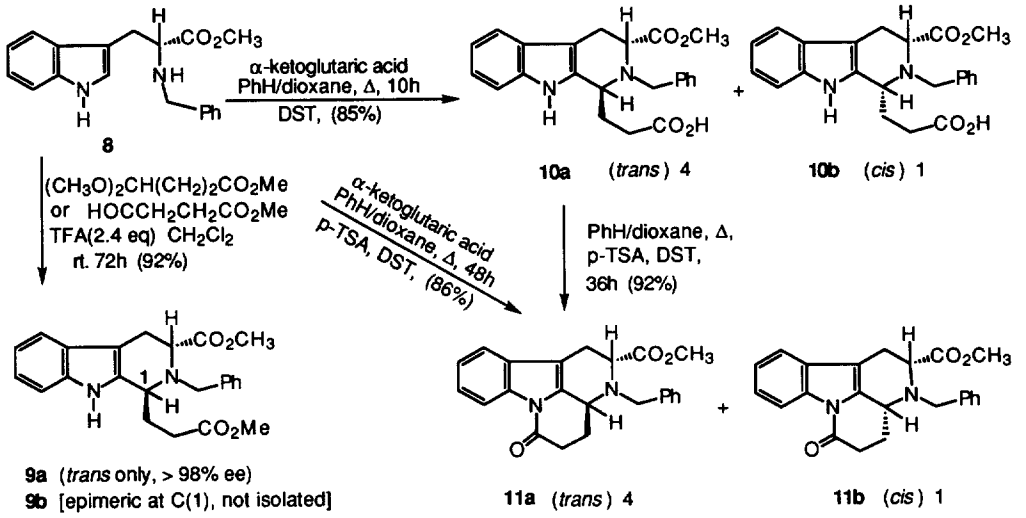


Magnus[4] prepared N_a-Bn, N_b-benzyltetracyclic ketone **1b** and employed it in an elegent synthesis of koumine[4]; however, the route to **1b** required 9 steps and was not diasterospecific (2:1 selectivity) while Bailey[5] later synthesized **1b** with higher diastereoselectivity (4:1) but in lower overall yield. Both routes required the later removal of the N_b-benzyl protecting group from **1b** with Na/NH_3, reaction conditions that are not compatible with some indoles in the sarpagine series.

In keeping with our interest in a general route to macroline/sarpagine alkaloids we wish to report the 5 step synthesis of template **1a** in 60% overall yield in a stereospecific, enantiospecific fashion. The route

presented here has been scaled up to above the 100 gram level and does not require protection of the N_a-H function.

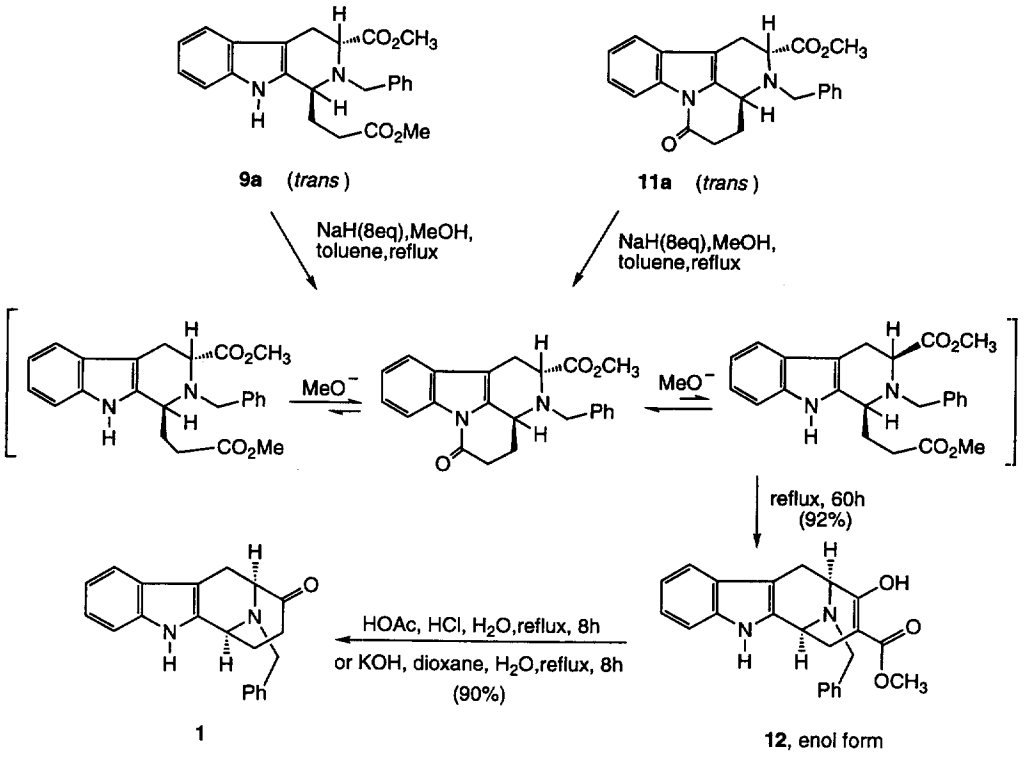
Scheme 2. The Asymmetric Pictet-Spengler Reaction



D-(+)-tryptophan was converted into its N_b-benzyl D-(+)-tryptophan methyl ester **8** in two steps in high yield as reported.[6] Under the normal conditions of the aprotic Pictet-Spengler reaction (benzene/dioxane,Dean-Stark trap, reflux, 8h) with tryptophan methyl ester **8** and α-ketoglutaric acid, the ester acids were provided as a mixture of *trans* **10a** and *cis* **10b** (ratio = 4:1) diastereomers in 85% yield. This mixture could be gradually converted into δ-lactams (**11a**, **b**) when the solution was heated at reflux for longer periods in the presence of a catalytic amount of p-TSA (60h). The formation of the δ-lactam (see **11**) has been reported previously,[7,8,9] but it was earlier obtained as a trace byproduct or as a component of a complex mixture. The δ-lactams **11a** (*trans*) and **11b**(*cis*) were obtained in 86% yield in the ratio of *trans:cis* =4:1. The acid-catalyzed conversion of the lactam **11b** (*cis*) into **11a** (*trans*) failed. In order to improve the diasteroselectivity of this sequence either methyl γ-aldobutyrate or methyl 4,4-dimethoxybutyrate could be employed in the Pictet-Spengler process to avoid the formation of the δ-lactams in the presence of trifluoroacetic acid (TFA). The *trans* diester **9a** was obtained diastereospecifically in high yield on stirring **8** with either γ–ester and TFA at room temperature for 72 hours in CH_2Cl_2 (Scheme 2). During the process of this Pictet-Spengler reaction the *cis* diester **9b** was detected by TLC but it was converted entirely into *trans* diester **9a** as planned. Examination of the results suggests here that 1) kinetically, the *trans* isomer is prefered in this Pictet-Spengler reaction; 2) thermodynamically, the *trans* isomer is also favored, consequently, any *cis* diester **9b** formed from the γ–ester can be completely converted into the more stable *trans* diester **9a** in the presence of TFA; 3) formation of the δ-lactam is faster than epimerization of the *cis*

ester acid into the *trans* ester acid in the process catalyzed by p-TSA; 4) the substitution of an electron withdrawing group (amide) on the N_a-H function to provide the δ-lactam **11b** destabilizes the proposed cationic intermediate necessary for epimerization, consequently epimerization of lactam **11b** (*cis*) into lactam **11a** (*trans*) was not observed. These experiments are consistent with the proposed mechanism of C-N bond cleavage for epimerization of *cis* N_b-benzyltetrahydro β-carbolines into their *trans* courterparts recently reported from our laboratory.[6]

Scheme 3. The Dieckmann Cyclization



Hobson et.al. had earlier converted the racemic δ-lactam **11** into the (±)β-ketoester **12** by hydrolysis of the δ-lactam to a diacid followed by methylation and then Dieckmann cyclization.[7] This procedure required three steps and also risked epimerization of the stereogenic center at C-3. When *trans* diester **9a** was heated with base for 1/2 hr it was converted almost entirely into *trans* δ-lactam **11a**. However, when *trans* diester **9a** was treated under the same reaction conditions (NaOMe, toluene, reflux) for 60 hours, the desired Dieckmann product **12** was produced in 92% yield. Presumably, the δ-lactam **11a** formed and then opened up to **9a** under these conditions and eventually was converted entirely into β-ketoester **12** *via* the Dieckmann process. Acid-mediated decarboxylation of the β-ketoester function in **12** then gave the template (-)-N_a-H, N_b-benzyltetracyclic ketone [-(-)-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-

cyclooct[b]indole] **1a** in 90% yield ($[\alpha]_D^{28}$ = -240.20° (c=1.0, $CHCl_3$)). The enantiomeric purity of the key β-ketoester was shown to be greater than 98% ee by ^1H NMR spectroscopy in the presence of the chiral shift reagent (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

In summary, an enantiospecific, stereospecific synthesis of the key intermediate (-)-N_a-H, N_b-benzyltetracyclic ketone **1a** was accomplished in 5 steps from D-(+)-tryptophan *via* the *trans* transfer of chirality in the asymmetric Pictet-Spengler reaction. This procedure has been executed on multihundred gram scale and the intermediates can be purified by crystallization through the structure of the ketone **1a**. The total synthesis of indole alkaloids from this key intermediate will be reported in due course.

Acknowledgment: The authors wish to thank the NIMH for generous financial support and the graduate school (UWM) for a fellowship to Peng Yu.

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(*Received in USA* 27 *June* 1997; *revised* 15 *July* 1997; *accepted* 1 *August* 1997)