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Concise Total Synthesis of (±)-Aloperine and 6-*epi*-Aloperine

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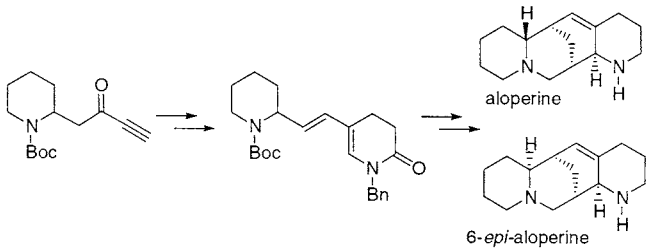
ABSTRACT



Total synthesis of aloperine and 6-*epi*-aloperine is reported. The crucial steps of the synthetic strategy are an aza-annulation reaction and an intermolecular Diels–Alder reaction. The synthetic plan proceeds from commercially available piperidine-2-ethanol.

Aloperine **1**, a member of a small family of C_{15} lupinine alkaloids,[1] was first isolated in 1935 from the seeds and leaves of *Sophora alopecuroides*,[2] a shrub that grows in China and Russia, and later from *Leptorhabdos parviflor* Benth.[2f] The use of the plant in traditional chinese medicine[3] and the results of the recent investigation concerning the pharmacological activity (cardiovascular, antiinflammatory, antiallergic) of the isolated alkaloid[4] moved the Overman group toward an intense synthetic interest, recently culminating in the first enantioselective total synthesis.[5] The central element of the Overman synthetic strategy is an intramolecular Diels−Alder reaction in which the cycloaddendes are temporarily tethered by a removable *N*-silylamine linkage. We report here a synthesis of (±)-aloperine and 6-*epi*-aloperine using an efficient intermolecular Diels−Alder reaction as crucial step where the required diene is prepared following an aza-annulation reaction sequence.[6]

Our retrosynthetic plan (Scheme 1) is based on the key cleavage of the N−C10 bond that reveals the octahydroquinoline system of type **A**. This moiety is accessible by an intermolecular Diels−Alder reaction of a 5-alkenyl-3,4-dihydropyridin-2-one **B** with methyl acrylate. We planned to build this *N*-acylaminodiene[7] by aza-annulation reaction

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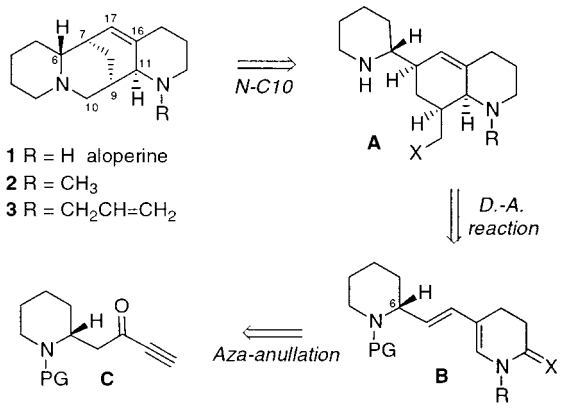
Scheme 1. Retrosynthetic Analysis



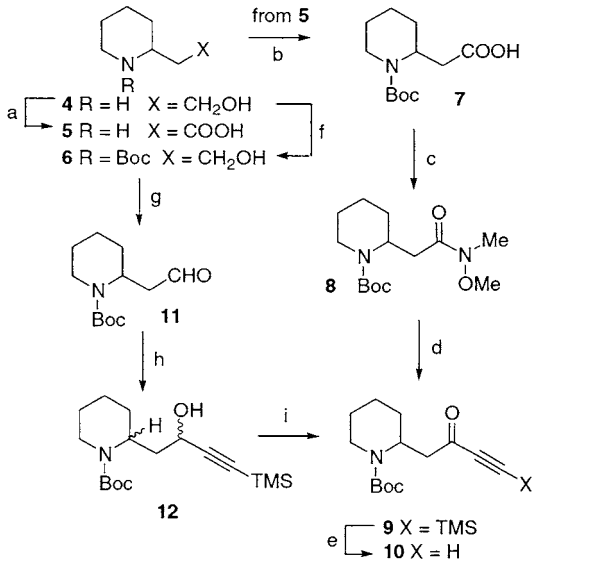
using an acetylenic ketone of type **C** as a substrate. The presence of the ketone functionality was necessary to induce the aza-annulation reaction that proceeds by an initial addition of the primary amine to the electrophilic triple bond.

We were confident of the success of the crucial Diels−Alder step considering our previous results in the diastereoselective synthesis of 3-oxo-14,15-dihydro-andranginine[8] where we have demonstrated the successful use of 5-ethenyl-*N*-alkyl-3,4-dihydropyridin-2-one in the regio- and stereoselective endo Diels−Alder reaction.

However, in our planned synthesis, presence of the stereogenic carbon (C6) in diene **B** determines the *like* (*lk*) and *unlike* (*ul*) facial selectivity problem[9] that could not be addressed a priori.

The synthesis began with the CrO_3 in H_2SO_4[10] oxidation of the commercially available piperidine-2-ethanol **4** to the corresponding carboxylic acid **5** in 65% yield (Scheme 2). The protection of the nitrogen as carbamate[11] (86% yield) and the subsequent condensation reaction with *N*,*O*-dimethylhydroxylamine hydrochloride gave the Weinreb amide **8**

Scheme 2[a]



[a] Reagents and conditions: (a) CrO_3, H_2SO_4 (65%); (b) $(Boc)_2O$, NaOH, *t*-BuOH (86%); (c) $CH_3NH(OCH_3)$·HCl, DCC, DMPA (71%); (d) $LiCCSi(CH_3)_3$, −78 °C, THF (42%); (e) TBAF (84%); (f) $(Boc)_2O$, AcOEt (95%); (g) Dess−Martin periodinane (89%); (h) $BrMgCCSiMe_3$, −78 °C (86%); (i) $(COCl)_2$, DMSO, Et_3N (87%).

(71% yield). The introduction of the ethynyl fragment was accomplished by reaction of **8** with the lithium derivative of trimethylsilylacetylene[12] in THF at −78 °C to give **9** that, by desilylation with TBAF, gave **10** in 84% yield. The unsatisfactory yield for the preparation of **8** and the use of the Cr(VI) moved us toward the elaboration of a more convenient preparation of **10**.

The aminol **4** was first transformed into the corresponding carbamate **6** (95% yield) by a conventional procedure[13] and subsequently oxidized to the aldehyde **11** by Dess−Martin periodinane[14] in 89% yield. Ethynylation of aldehyde **11** with the Grignard reagent, prepared from trimethylsilyl acetylene,[15] gave cleanly the diastereomeric alcohols **12** (1:1) in 86% yield. Swern oxidation to ketone and cleavage of the C−Si bond with TBAF gave compound **10** (53% overall yield from **4**).

Compound **10** was reacted with benzylamine (Scheme 3) in THF at 25 °C, and the intermediate enamine was directly cyclized with acryloyl chloride in THF at 65 °C to give dihydropyridinone **13** in 56% yield. Reduction of **13** with $NaBH_4$ gave a mixture of diastereoisomeric alcohols **14**, which by direct thermal treatment furnished exclusively the desired *E* diene **15**. Heating a solution of **15** in toluene with methyl acrylate led to compounds **16** (56%) and **17**[16] (28%), which were separated by column chromatography. In a more

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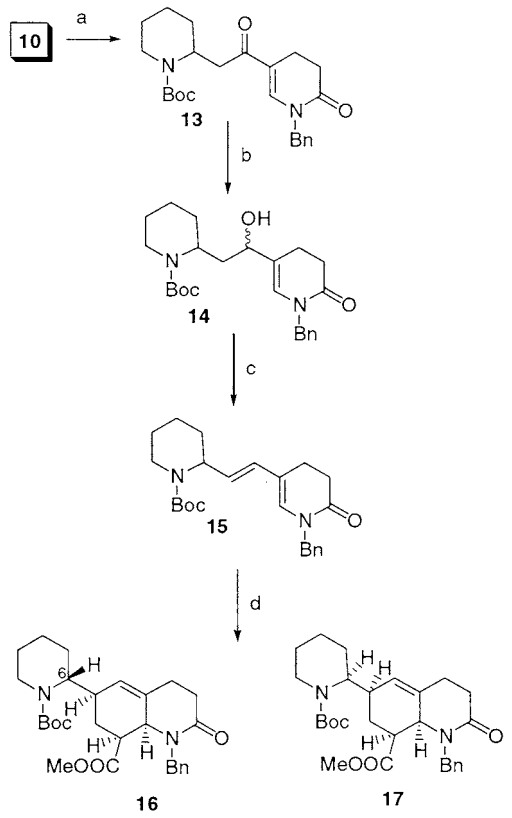
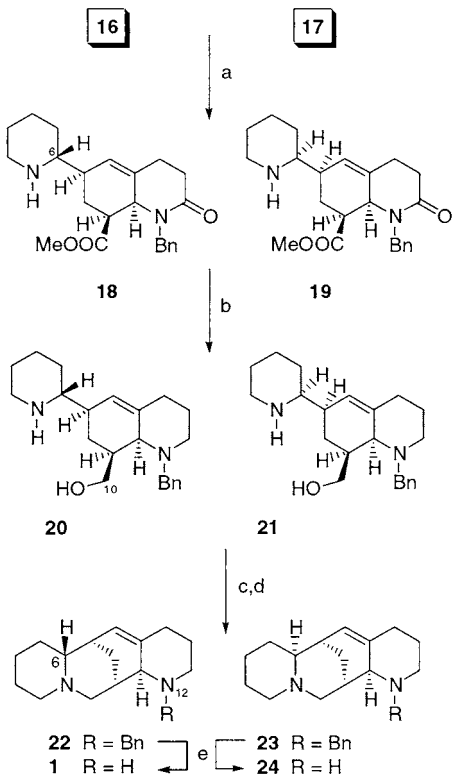
(16) Reported structures represent a mixture of enantiomers.

Scheme 3[a]



[a] Reagents and conditions: (a) $BnNH_2$, CH_2═$CHCOCl$, THF (56%); (b) $NaBH_4$; (c) Δ; (d) CH_2═$CHCOOCH_3$, $PhCH_3$, 110 °C (**16** 56%, **17** 28%).

Scheme 4[a]



[a] Reagents and conditions: (a) TFA (quantitative); (b) $LiAlH_4$ (94%); (c) CBr_4−PPh_3, CH_2Cl_2; (d) Et_3N, 40 °C (**22** 45%, **23** 42%); (e) Li, $NH_2(CH_2)_2NH_2$ (**1** 80%, **24**, 83%).

convenient protocol, alcohols **14** were directly dissolved in toluene and heated at 110 °C in the presence of methyl acrylate and a catalytic amount of PTSA to give compounds **16** and **17** in a two-step one-pot reaction.

Despite a detailed spectroscopic investigation, the similarity of the ^{1}H NMR spectra of compounds **16** and **17** prevented a definite relative stereochemical assignment. Our previous results suggested that the obtained products derive from the endo approach of the methyl acrylate to the two diastereotopic faces of the diene **15**.[8a,b]

That the two compounds **16** and **17** are epimers at C6 was demonstrated by removal of *t*-Boc group to give **18** and **19**, respectively. Treatment of **18** with NCS gave the corresponding *N*-chloride derivative that by direct elimination reaction in the presence of DBU[17] gave the N−C6 imine derivative, which was reduced with $NaBH_3CN$, to provide a mixture of compounds **18** and **19**. The same result was obtained using **19** as starting material. The definite stereochemical assignment could be ascertained only when the final compounds **1** and **24** were obtained.

The conversion of compounds **18** and **19** to the tetracyclic lupinine skeleton (Scheme 4) was separately obtained using as a first step the $LiAlH_4$ reduction to provide compounds **20** and **21**. The reduction of both the ester and the amide functions was possible by keeping the reaction at room temperature for 4 days. The formation of the final N−C10 bond was accomplished by reaction with CBr_4−PPh_3 followed by addition of triethylamine. Removal of the benzyl group from N12 was rather problematic: the application of the conventional procedure with sodium[18] or lithium[19] in ammonia gave poor results. Fortunately, the application of the protocol described by Angle et al.,[20] which employs the use of ethylenediamine (dry) and lithium, furnished aloperine **1** (80%, starting from **22**) and the analogue **24** (83% starting from **23**), identified as 6-*epi*-aloperine.[5b] Synthetic aloperine **1** appeared identical to a commercially obtained sample. The ^{1}H and ^{13}C NMR spectra of diamine **24** were significantly different from those of aloperine **1** different from quinolizidine signals are concerned. In particular, the chemical shift of C6 of compound **24** that appeared at δ 66.6 downfield shifted (6.5 ppm) relative to the corresponding line of aloperine **1** was structurally characteristic. This difference is in agreement with the *trans*-fused[21] quinolizidine ring

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system with respect to the *cis*-quinolizidine present in aloperine **1**[5] thus confirming the C6 stereochemistry depicted in **24**.

In conclusion, we have described a practical synthesis of aloperine and 6-*epi*-aloperine that proceeds toward the final products in 12 steps starting from the commercially available piperidine-2-ethanol. This strategy can be applied to the synthesis of differently N-substituted aloperine derivatives. The aza-annulation reaction appears to be a useful crucial step for the construction of skeletons containing the 1,2,3,4,6,7,8,8a-octahydroquinoline system.

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Supporting Information Available: Experimental procedures and characterization for all new compounds and ^{1}H and ^{13}C NMR spectra for compounds **8**−**10**, **12**, **13**, **15**−**24**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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