Enantioselective Total Synthesis of the Marine Alkaloid Lepadin B

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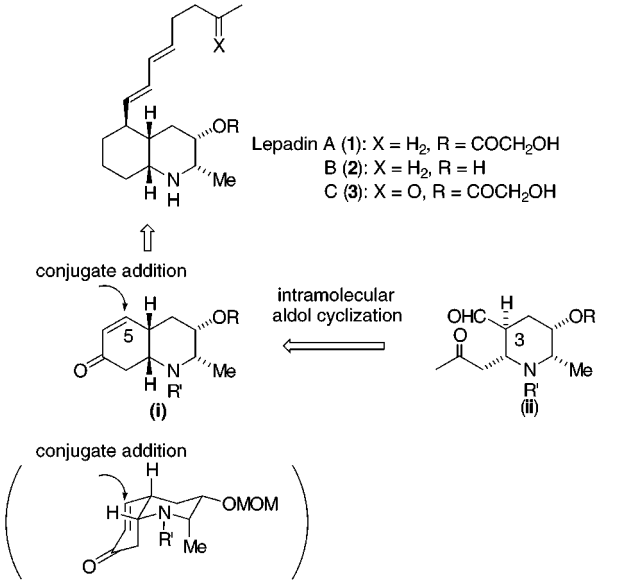
The decahydroquinoline alkaloids continue to be of interest as synthetic targets due to their intriguing biological properties,[1] and several methods for the enantioselective construction of this ring system have been reported.[2] The structurally interesting decahydroquinoline alkaloids lepadins A (**1**), B (**2**), and C (**3**), isolated from the tunicate *Clavelina* lepadiformis by Steffan[3] and Andersen and coworkers,[4] showed significant cytotoxic activity toward a variety of murine and human cancer cell lines.[4] Although their relative stereochemistry has been determined by the extensive NMR studies, the absolute stereochemistry is still unknown.

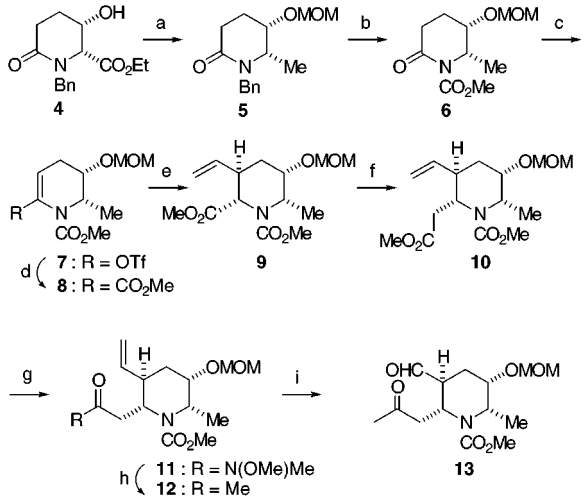


We planed a new strategy for the construction of the cis hexahydroquinolinone ring system (**i**) based on an intramolecular aldol type of cyclization of the functionalized piperidine (**ii**) accompanying the epimerization at the C-3 position. It also seemed likely that this hexahydroquinolinone would lead to desired trisubstituted decahydroquinoline core for the synthesis of lepadins with correct stereochemistry at the C-5 position using the conjugate addition.

We have previously shown that the efficient synthesis of the piperidone **4** as a chiral building block for alkaloid synthesis[5] and its application to the synthesis of the marine alkaloid clavepictines A and B.[6] Herein, we describe the first enantioselective total synthesis of lepadin B (**2**) starting from **4** using the novel strategy mentioned above as the key step and the determination of its absolute stereochemistry.

Debenzylation of the enantiopure lactam **5**,[5] obtained from **4** in four steps, under Birch condition followed by protection of the resulting amide with methyl chloroformate gave the carbamate **6**,[7] which was converted to vinyltriflate **7**[8] using Comins' reagent (Scheme 1).[9] Palladium-catalyzed carbonylation of **7** using Cacchi's procedure[10] afforded the enecarbamate **8**, which was subjected to conjugate addition of in situ generated divinylcuprate to give the 2,3,4,6-tetrasubstituted piperidine **9** as a single isomer.[11] Carbon-chain

Scheme 1[a]



[a] Key: (a) 85% overall yield from **4**; see ref 5; (b) Na, liquid, NH_3−THF (91%), then *n*-BuLi, $ClCO_2Me$, THF, −78 °C to rt (77%); (c) LiHMDS, *N*-(chloro-2-pyridyl)trifimide,[9] THF, −78 to −50 °C (80%); (d) $Pd(PPh_3)_4$, Et_3N, Ph_3P, MeOH, CO balloon, DMF, rt (74%); (e) vinyl lithium, CuI, Et_2O, −78 to −30 °C (89%) and **8** (7% recovered); (f) $LiOH·H_2O$, MeOH−H_2O (3:1), 60 °C; $ClCO_2Et$, Et_3N, THF, 0 °C; CH_2N_2, Et_2O; $PhCO_2Ag$, Et_3N, Et_2O (71% in four steps); (g) $LiOH·H_2O$, MeOH−H_2O (3:1), 60 °C; 1,1′-carbonyldiimidazole, Et_3N, *O*,*N*-dimethylhydroxylamine·hydrochloride, CH_2Cl_2, 0 °C to rt (83% in two steps); (h) MeMgBr, THF, 0 °C to rt (97%); (i) OsO_4, $NaIO_4$, dioxane−H_2O (1:1), rt (84%).

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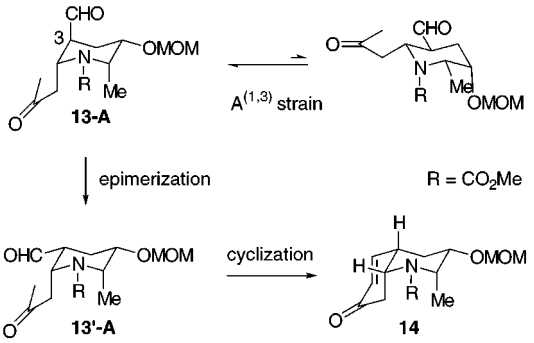
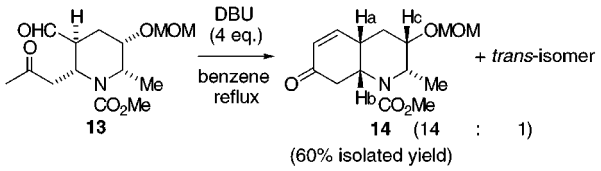
elongation at C-2 position on **9** was performed by an Arndt−Eistert sequence to provide the homologated ester **10**. This ester was transformed into ketone **12** via Weinreb's amide[12] **11**, and subsequent oxidative cleavage of the terminal alkene in **12** yielded the aldehyde **13**.

With the requisite aldehyde in hand, the stage was now set for the key intramolecular aldol cyclization. The stereochemistry of C-3 position in **13** was unfavorable for the synthesis of target alkaloid; however, we expected that the epimerization of the C-3 position would be possible during the aldol cyclization step. It is anticipated that the conformation of **13** is restricted to comformer **13-A** owing to $A^{(1,3)}$ strain and the appendages on C-2 and C-3 in **13-A** lie in no cyclizable trans diaxial relationship. Consequently, this epimerization will proceed first to give **13′-A**, which will cyclize easily to afford the desired 4a,8a-*cis*-hexahydroquinolinone **14**.



Thus, the treatment of **13** with 4 equiv of DBU in refluxing benzene gave the cyclized product in a ratio of 14:1 (in the ^{1}H NMR spectrum of the crude product), and fractionation by chromatography on silica gel furnished the major product in 60% isolated yield (Scheme 2). The stereochemistry of the

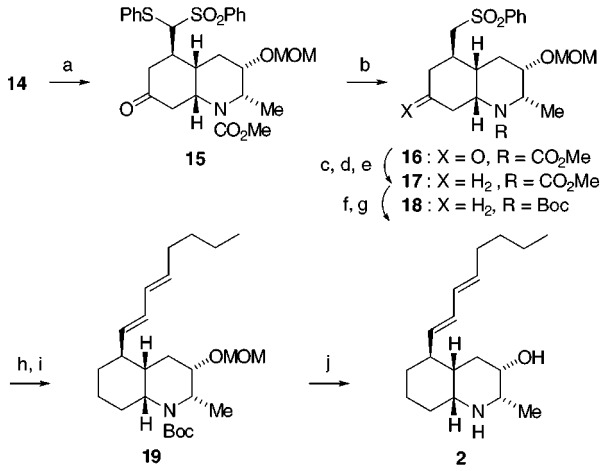
Scheme 2



major product was determined to be that of the desired *cis*-hexahydroquinolinone **14** on the basis of the observation of NOEs between Ha and Hb, Ha and Hc on the NOESY experiment.

This enone **14** was subjected to conjugate addition of the anion generated from phenylthiomethyl phenyl sulfone[13] with *n*-BuLi at −78 to 0 °C to afford the ketone **15** as a 2:1 mixture of the diastereomers (Scheme 3). Radical reduction of the phenylthio group in **15** gave the sulfone **16** as a sole

Scheme 3[a]



[a] Key: (a) $PhSCH_2SO_2Ph$, *n*-BuLi, THF, −78 to −10 °C (78%, 14% recovered of **14**); (b) *n*-Bu_3SnH, AIBN, benzene, reflux (85%); (c) $NaBH_4$, CH_2Cl_2−MeOH (10:1), 0 °C; (d) 1,1′-thiocarbonylimidazole, $ClCH_2CH_2Cl$, reflux (75% in two steps); (e) *n*-Bu_3SnH, toluene, reflux (84%); (f) *n*-PrSLi, HMPA−THF, rt; (g) $(Boc)_2O$, benzene, reflux (59% in two steps); (h) *n*-BuLi, THF, −78 to −70 °C then 2-heptenal, −78 to −50 °C; (i) Na−Hg, Na_2HPO_4, MeOH, rt (49% in two steps); (j) concd HCl, MeOH, reflux (85%).

product. Thus, the 1,4-addition at the C-5 position of **14** proceeded in a highly stereoselective manner.[14] Deoxygenation of **16** was performed in a three-step sequence. Reduction of **16** with $NaBH_4$ afforded the alcohol, which was deoxygenated with *n*-Bu_3SnH via Barton's ester[15] to give the product **17**. Deprotection at the methoxycarbonyl group in **17** with *n*-PrSLi in HMPA,[16] followed by treatment of the resulting amine with $(Boc)_2O$, furnished the Boc derivative **18**. Construction of the octadienyl moiety was accomplished by means of Julia coupling to give diene **19**. The synthesis of **2** was completed by cleaving both the methoxymethyl and Boc protecting groups with acid. The spectral data for trifluoroacetate salt of synthetic **2** $[[\alpha]^{26}_D$ −92.6 (MeOH)] were identical with those for trifluoroacetate salt of natural lepadin B $[[\alpha]_D$ −96 (MeOH)].

In summary, the first total synthesis of lepadin B (**2**) was accomplished by using the intramolecular aldol cyclization of the tetrasubstituted piperidine **3** as the key step, and the absolute stereochemistry of (−)-**2** was verified to be 2*S*,3*S*,-4a*S*,5*S*,8a*R* by the present chiral synthesis.

Acknowledgment. We are grateful to Professor Raymond J. Andersen, University of British Columbia, for kindly providing us with ^{1}H and ^{13}C NMR spectra of trifluoroacetate salt of natural lepadin B.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds.

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(11) The stereochemistry of the newly formed C-2 and C-3 positions in **9** was anticipated to be 2*S*,3*R* according to our previous investigation on the Michael addition reaction of the similar system; see: Momose, T.; Toyooka, N. *J. Org. Chem*. **1994**, *59*, 943−945. Toyooka, N. Tanaka, K. Momose, T.; Daly, J. W.; Garraffo, H. M. *Tetrahedron* **1997**, *53*, 9553−9574.

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