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# Aza-Annulation as a Route To Hydroxylated Alkaloid Lipids. The Synthesis of (±)-Prosopinine.

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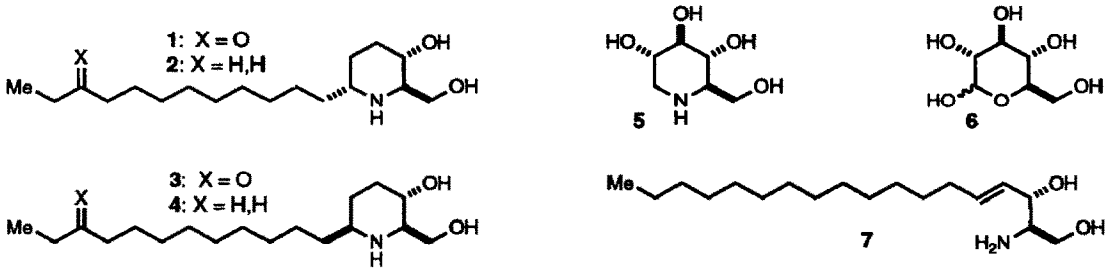
***Abstract:*** The total synthesis of (±)-prosopinine is described. Aza-annulation was used to generate the six-membered nitrogen heterocycle, stereochemical control was achieved through the use of the δ-lactam template, and homologation of the lactam introduced the alkyl chain substituent on the piperidine ring.

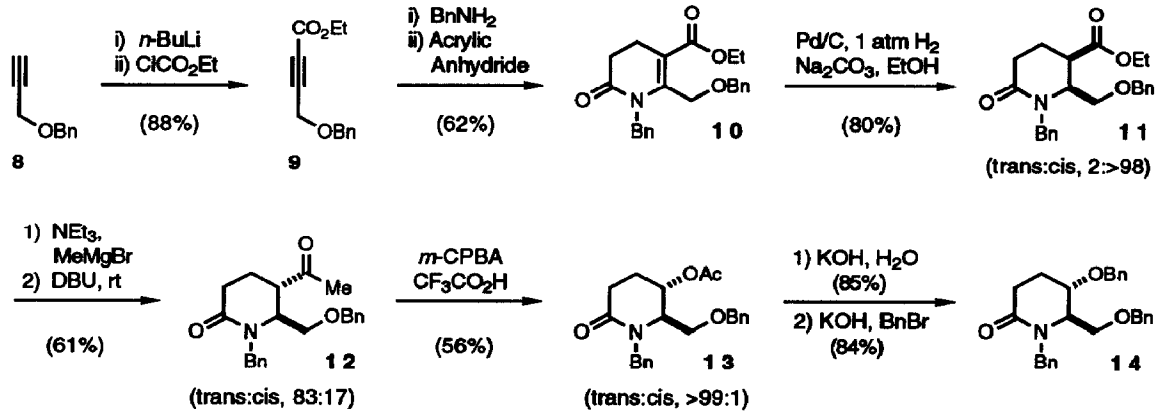
Prosopinine (**1**) and prosophylline (**3**) are naturally occurring alkaloids isolated from the leaves of the African mimosa *Prosopis africana* Taub. These intriguing molecules possess a variety of antibiotic and anesthetic properties due to the blend of physiologically important structural features.[1] The polar head group of this class of lipids consists of a piperidine ring with similarities to the alkaloid deoxynorjirimycin (**5**), a potent α-glucosidase inhibitor with demonstrated antitumor activity and inhibition of syncytia formation in HIV-1.[2] Each of these compounds, in turn, have hydroxyl functionality with the same stereochemistry found at C-4 and C-6 of glucose (**6**). The tail portion of naturally occurring **1** and **3** produces a striking resemblance to the membrane lipid sphingosine (**7**). Previous synthetic efforts directed toward the preparation of *Prosopis* alkaloids have resulted in the synthesis of desoxoprosopinine (**2**),[3] prosophylline (**3**),[4] and desoxoprosophylline (**4**).[3a,3b,3e]




Our approach to the synthesis of prosopinine involved five phases. Of initial importance was the construction of the six-membered nitrogen heterocycle, which involved the synthesis of the corresponding δ-lactam with the use of recently developed aza-annulation methodology.[5] Once prepared, this versatile δ-lactam intermediate served as a framework for the introduction of the correct relative stereochemistry of the -OH and $-CH_2OR$ substituents. The third phase of the synthesis addressed the homologation necessary for the stereochemically controlled transformation of the lactam carbonyl to the alkyl chain substituent. The preparation of the tail portion, and subsequent Wittig coupling of this fragment with the hydroxylated piperidine head group, completed the synthesis.

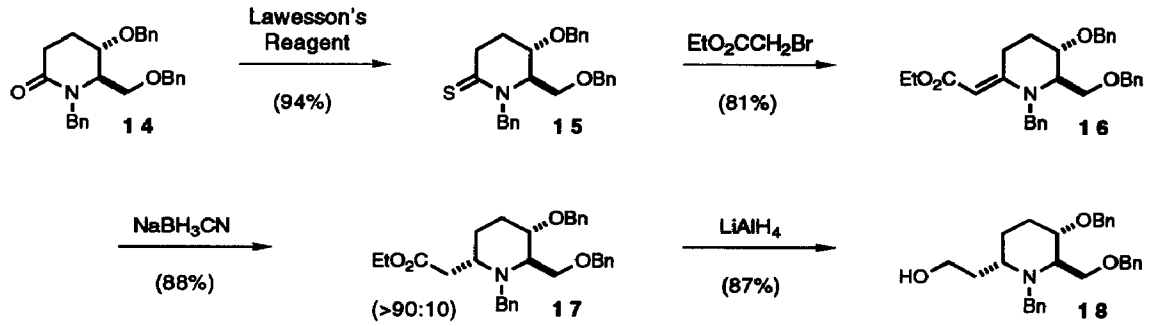
The first facet of this synthesis, the construction of the six-membered nitrogen heterocycle, was accomplished through aza-annulation methodology for the formation of **10** (Scheme I). Deprotonation and ethoxycarboxylation of **8** generated **9**, the substrate required for the two step annulation procedure. Conjugate addition of $BnNH_2$ to **9** produced the corresponding β-enamino ester intermediate, which led to the formation of **10** when treated with acrylic anhydride. Analogous use of acryloyl chloride was less effective for the transformation of **9** to **10** (35%).

**Scheme I.** Synthesis and Use of The δ-Lactam Template for The Formation of **14**.




The δ-lactam template provided a means through which the relative stereochemistry of the ring substituents could be controlled in the next stage of this synthesis. Catalytic hydrogenation of **10** was performed in the presence of $Na_2CO_3$, which prevented the deprotection of the hydroxyl group, to stereoselectively give the reduced δ-lactam **11**.[6] Transformation of **11** to **12** was accomplished through the use of $MeMgBr/NEt_3$,[7] and base catalyzed epimerization at the position α to the ketone produced an equilibrium 83:17 trans:cis ratio of **12**. The subsequent Baeyer-Villiger oxidation produced only the trans isomer **13** under these conditions, with efficiency of the reaction directly proportional to the original trans:cis ratio of **12**.[8] Hydrolysis of the acetyl group, followed by benzyl protection of the resultant hydroxyl group, gave **14**.

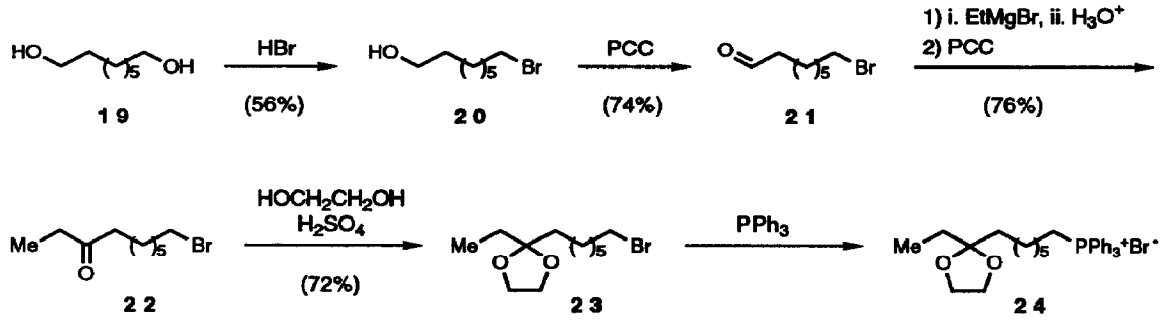
**Scheme II.** Homologation of The Lactam Carbonyl.



The next segment of this synthesis centered around the homologation of the lactam carbonyl in a stereoselective manner that would accommodate subsequent elaboration of the molecule (Scheme II). Conversion of **14** to the thiolactam **15**,[9] followed by alkylation and Eschenmoser contraction,[10] gave the vinylogous carbamate **16**. Hydride reduction selectively produced **17**, with the stereochemical configuration of **1** rather than **3**, and $LiAlH_4$ reduction of the ester functionality gave **18**.

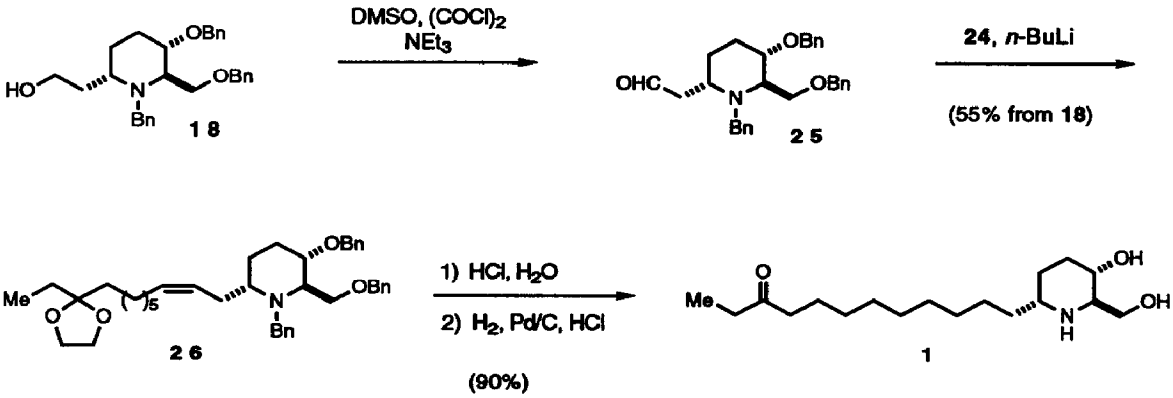
Preparation of the phosphonium salt **24**, required for Wittig coupling with the aldehyde derived from **18**, is illustrated in Scheme III. Monobromination of **19** produced **20**,[11] which was oxidized to the corresponding aldehyde, **21**. Addition of EtMgBr, followed by oxidation gave **22**, which was subsequently protected as dioxolane **23**. Treatment with $PPh_3$ resulted in generation of the corresponding phosphonium salt **24**.

**Scheme III.** Synthetic Preparation of the Aliphatic Wittig Reagent.




Extension of the aliphatic chain was performed by Swern oxidation of **18** to **25**, followed by Wittig olefination to give **26** as an 85:15 mixture of cis and trans isomeric alkenes, respectively. The synthesis of prosopinine was completed by deprotection of the carbonyl followed by hydrogenation of the alkene with concomitant removal of the benzyl protecting groups to give **1** in 3% overall yield from **8**.[12]

**Scheme IV.** Wittig Homologation to Attach the Aliphatic Chain.



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## REFERENCES AND NOTES

1. (a) Ratle, G.; Monseur, X.; Das, B.; Yassi, J.; Khuong-Huu, Q.; Goutarel, R. *Bull. Soc. Chim. Fr.* **1966**, 2945, *[CA 66:18779h]*. (b) Bourrinet, P.; Quevauviller, A. *C. R. Soc. Biol.* **1968**, *162*, 1138, *[CA 70:95233k]*. (c) Fr. Patent; FR 1524395 *[CA 71:91733w]*. (d) Bourrinet, P.; Quevauviller, A. *Ann. Pharm. Fr.* **1968**, *26*, 787, *[CA 71:29012g]*. (e) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belges* **1972**, *81*, 425. (f) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belges* **1972**, *81*, 443.
2. For information on nojirimycin and related hydroxylated piperidines, see the following articles and the references cited within: (a) van den Brock, L. A. G. M.; Vermaas, D. J.; Heskamp, B. M.; van Boeckel, C. A. A.; Tan, M. C. A. A.; Bolscher, J. G. M.; Ploegh, H. L.; van Kemenade, F. J.; de Goede, R. E. Y.; Miedema, F. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 82. (b) Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; de Bello, I. C.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365. (c) Fleet, G. W. J.; Fellows, L. E.; Winchester, B. Plagiarizing Plants: Aminosugars as a Classs of Glycosidase Inhibitors, In: *Bioactive Compounds from Plants*, p 112-125, Wiley, Chichester (Ciba Foundation Symposium 154) **1990**. (d) Legler, G. *Adv. in Carbohydr. Chem. and Biochem.* **1990**, *48*, 319.
3. (a) Saitoh, Y.; Moriyama, Y.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 75. (b) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488. (c) Holmes, A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37. (d) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473. (e) Tadano, K.; Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Ogawa *Synlett* **1993**, 565.
4. Natsume, M.; Ogawa, M. *Heterocycles* **1981**, *16*, 973.
5. (a) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 5319. (b) Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215. (c) Paulvannan, K.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 6673.
6. (a) Barth, W.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 2438. (b) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988.
7. Kikkawa, I.; Yorifugi, T. *Synthesis* **1980**, 877.
8. Canan Koch, S. S.; Chamberlin, R. *Synth. Commun.* **1989**, *19*, 829.
9. Jain, S.; Sujatha, K.; Rama Krishna, K. V.; Roy, R.; Singh, J.; Anand, N. *Tetrahedron* **1992**, *48*, 4985.
10. (a) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255. (b) Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987**, *52*, 4665.
11. Kang, S.-K.; Kim, W.-S.; Moon, B.-H. *Synthesis*, **1985**, 1161.
12. The physical data for **1** were consistent with those reported for **1** and **2**,[1,3,4] and were as follows: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.05 (t, $J$ = 7.3 Hz, 3 H), 1.23-1.41 (m, 13 H), 1.44-1.61 (m, 5 H), 1.66 (m, 1 H), 1.74 (m, 1 H), 2.07 (bs, 3 H), 2.39 (t, $J$ = 7.5 Hz, 2 H), 2.41 (q, $J$ = 7.3 Hz, 2 H), 2.76 (m, 1 H), 2.87 (dt, $J$ = 5.5, 7.7 Hz, 1 H), 3.53 (ddd, $J$ = 4.0, 5.6, 6.9 Hz, 1 H), 3.61 (dd, $J$ = 5.4, 10.5 Hz, 1 H), 3.65 (dd, $J$ = 7.8, 10.5 Hz, 1 H); $^{13}$C NMR (75.5 MHz. $CDCl_3$) $\delta$ 7.8, 23.9, 26.3, 27.4, 28.6, 29.2, 29.3, 29.4, 29.6, 33.9, 35.8, 42.4, 49.7, 58.1, 62.3, 68.1, 212.0.

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