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Synthesis of the Pyrrolo[2,3-*i*]isoquinoline Substructure of the Manzamine Family of Alkaloids

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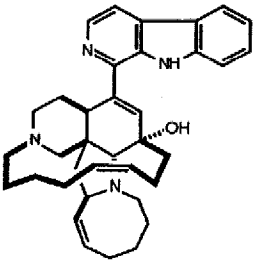
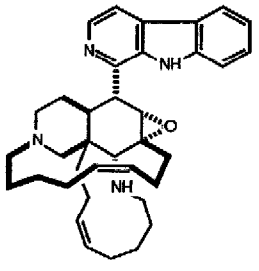
Abstract: The first synthesis of the tricyclic pyrrolo[2,3-*i*]isoquinoline substructure of manzamines A, B ,E and F is described. Reductive alkylation of benzoic acid followed by a 3-aza-6-heptenyl radical cyclization gave octahydroisoquinoline **9**. An electrophile initiated cyclization was used to complete construction of the title ring system.

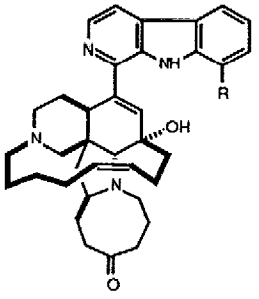
Manzamines A, B, E and F are complex alkaloids recently isolated from several species of marine sponges.[1,2] The impressive array of heterocyclic systems that appear in these cytotoxic natural products render them formidable targets for total synthesis. This letter describes one approach to a tricyclic pyrroloisoquinoline substructure common to several of these alkaloids.



Manzamine A



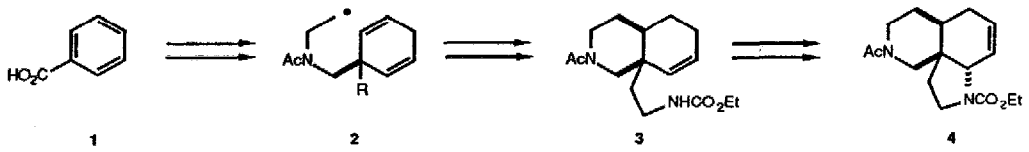
Manzamine B



Manzamine E R = H
Manzamine F R = OH

Based on our interest in using annellations of 1,4-dihydrobenzoic acids in organic synthesis,[3] we decided to pursue the strategy outlined in Scheme I.[4] Some precedent for this strategy can be found in related reaction sequences developed in the Beckwith and Danishefsky laboratories.[5,6] Preparation of a precursor to a free radical of type **2** is outlined in Scheme II. Reductive alkylation of benzoic acid (**1**) using 2-bromoethyl methyl ether gave 1,4-dihydrobenzoic acid **5** in 95% yield.[7] Treatment of **5** with diphenylphosphoryl azide[8] and 2-(phenylseleno)ethylamine[9] in the presence of Hunig's base afforded amide **6** (87%). Reduction of the amide using lithium aluminum hydride in tetrahydrofuran under reflux gave amine **7** (49%) and acetylation of **7** afforded free radical precursor **8** in 84% yield.

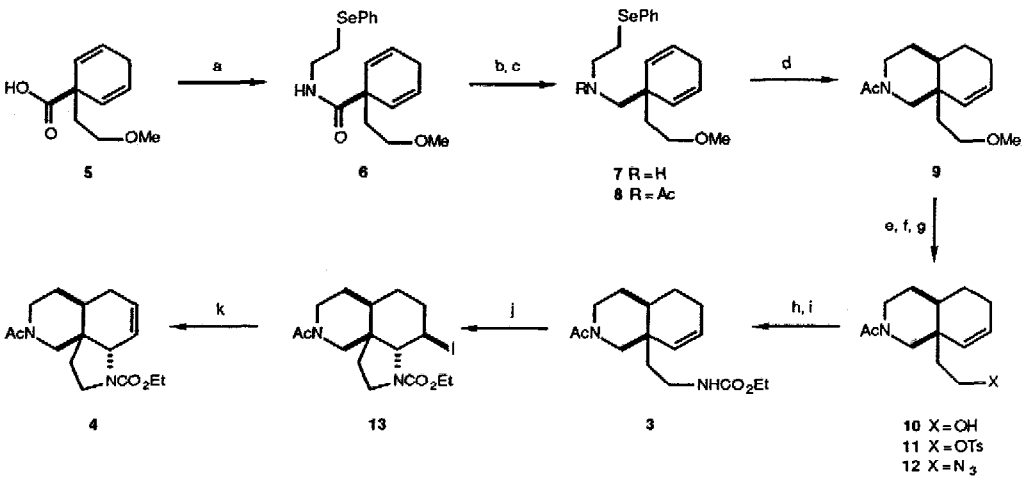
Scheme I



1 2 3 4

Slow addition of a benzene solution of tri-*n*-butyltin hydride (2.0 equiv) and azo(bis)isobutyronitrile (0.05 equiv) to a 0.05 M solution of **8** in benzene under reflux afforded a 4:1 mixture of two isomeric cyclization products in 67% combined yield.[10] The major isomer was assigned structure **9** on the basis of spectral data recorded on the mixture and by analogy with model studies performed in these laboratories (*vide infra*).[11] The minor isomer was presumed to be either the corresponding trans-fused octahydroisoquinoline or the product derived from a 7-endo cyclization.[12] The isomeric cyclization products were inseparable by liquid chromatography and thus, separation was postponed to a later stage of the synthesis.

Scheme II

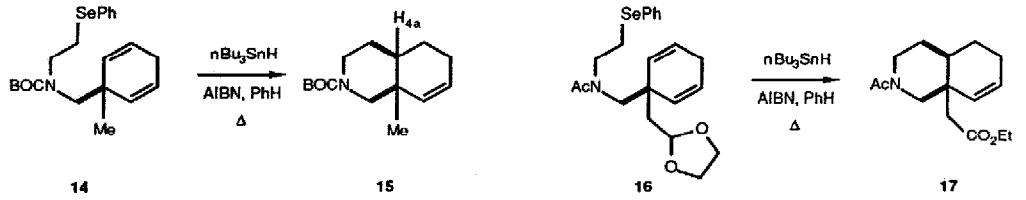


5 6 7 R=H, 8 R=Ac 9 10 X=OH, 11 X=OTs, 12 X=N3 3 13 4

(a) $(PhO)_2PON_3$, $PhSeCH_2CH_2NH_2$, iPr_2NEt (b) $LiAlH_4$, THF, Δ (c) CH_3COCl, Et_3N (d) nBu_3SnH, AIBN, PhH, Δ (e) BBr_3, CH_2Cl_2, -78°C → r. t. (f) TsCl, pyridine, 0 °C (g) NaN_3, DMF, r.t. → 40°C (h) Ph_3P, H_2O, THF (i) $ClCO_2Et$, Et_3N (j) I_2, K_2CO_3 (k) DBU, $PhCH_3$, Δ

Treatment of **9** with boron tribromide gave alcohol **10** (74%) which was converted to tosylate **11** in 64% yield.[13,14] Treatment of **11** with sodium azide in N,N-dimethylformamide gave pure azide **12** in 60% yield after separation from diastereomeric material by flash chromatography.[15] Azide **12** was converted to carbamate **3** in 70% yield upon treatment with triphenylphosphine followed by acylation of the resulting primary amine using ethyl chloroformate.[16] Electrophile initiated ring closure of carbamate **3** to iodide **13** (76%) was accomplished using iodine in the presence of potassium

carbonate.[17] Dehydrohalogenation of **13** using DBU in toluene under reflux completed the synthesis of pyrroloisoquinoline **4** (62%).[18]



14 **15** **16** **17**

In addition to providing access to the tricyclic substructure of the manzamine family of alkaloids, the annellation protocol described here is potentially applicable to the synthesis of a variety of perhydroisoquinolines. Although we have not pursued this strategy to its limit, two relevant examples are presented above. Tri-*n*-butyltin hydride mediated cyclization of selenide **14** gave octahydroisoquinoline **15** in 55% yield.[19] The cis ring fusion was assigned based on difference NOE experiments that established the proximal relationship between the angular methyl group and H(4a).[20] In another experiment, treatment of selenide **16** with tri-*n*-butyltin hydride and AIBN under high dilution conditions gave **17** (25%) as the major cyclization product. This ester presumably arises from sequential radical cyclization, intramolecular hydrogen atom transfer, fragmentation and reduction processes. Efforts to streamline the sequence outlined in Scheme II as well as alternative routes to the manzamines are in progress.[21]

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References and Notes

\# 1988 Lubrizol Predoctoral Fellow

1. Manzamine A: Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404. Manzamine B and C: Sakai, R.; Kohmoto, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1987**, *28*, 5493. Manzamines E and F: Ichiba, T.; Sakai, R.; Kohmoto, S.; Saucy, G.; Higa, T. *Tetrahedron Lett.* **1988**, *29*, 3083.
2. Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T.; Hirata, Y. *Tetrahedron Lett.* **1987**, *28*, 621. The structure of keramine A reported in this paper is identical to manzamine A. The structure of keramine B has been revised to the structure reported for manzamine F.
3. Chuang, C.-P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1782. Chuang, C.-P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1988**, *53*, 3210. Chuang, C.-P.; Gallucci, J. C.; Hart, D. J.; Hoffman, C. *J. Org. Chem.* **1988**, *53*, 3218.
4. For other annellation strategies involving 1,4-dihydrobenzoic acids see: Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.*, **1977**, *42*, 1794. Mander, L. N.; Hamilton, R. J. *Tetrahedron Lett.* **1981**, *22*, 4115. Tamai, Y.; Hagiwara, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1982**, 502. Beckwith, A. L. J.; O'Shea, D. M.; Roberts, D. H. *J. Chem. Soc., Chem. Commun.*, **1983**, 1445. Schultz, A. G.; Staib, R. R.; Eng, K. K. *J. Org. Chem.* **1987**, *52*, 2968.
5. Beckwith, A. L. J.; Roberts, D. H. J. *Am. Chem. Soc.* **1986**, *108*, 5893.
6. Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.*, **1987**, *109*, 917.

7. Van Bekkum, H.; Van Den Bosch, C. B.; Van Minnenpathius, G.; De Mos, J. C.; Van Wijk, A. M.; *Rec. Trav. Chim. Pays-Bas* **1971**, *90*, 137.
8. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am.Chem. Soc.* **1972**, *94*, 6203.
9. Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739.
10. This ratio was determined by capilliary gas chromatography assuming identical response factors for each isomer. The elemental composition of each isomer was established by GC-MS.
11. Compounds **9-11**, all contaminated with a diastereomer, displayed ^{1}H-NMR and IR spectra in accord with the assigned structures. All other compounds displayed ^{1}H-NMR, ^{13}C-NMR, IR and high resolution mass spectra in accord with the assigned structures. NMR spectra of **3**, **4**, **6**, and **8-13** were recorded at 400 K as spectra were complicated due to amide and urethane geometrical isomerism at lower temperatures.
12. For comparison, tri-*n*-butyltin radical mediated cyclization of methyl 1-(4-bromobutyl)cyclohexa-2,5-diene-1-carboxylate has been reported to afford the expected cis-fused octahydronaphthalene (67%) and methyl bicyclo[4.3.1]decan-1-carboxylate (12%) along with 21% of reduced starting material.
13. Benton, F. L.; Dillon, T. E. *J. Am. Chem. Soc.* **1942**, *64*, 1128. Youssefyeh, R. D.; Mazur, Y. *Chem. Ind. (London)* **1963**, 609. Ayer, W. A.; Bowman, W. R.; Joseph, T. C.; Smith, P. *J. Am. Chem. Soc.* **1968**, *90*, 1648.
14. Yields represent 4:1 mixtures of **10** (**11**) and an isomer in which **10** (**11**) predominate.
15. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
16. Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635. Knouzi, N.; Vaultier, M.; Carrie, R. *Bull. Soc. Chim. Fr.* **1985**, 815. Nagarajan, S.; Ganem,. B. *J. Org. Chem.* **1987**, *52*, 5044.
17. Aida, T.; Legault, R.; Dugat, D.; Durst, T. *Tetrahedron Lett.*, **1979**, 4993.
18. Treatment of **3** with PhSeCl and silica gel (Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C.-K.; Kiel, W. A.; Menchen. S. M. *J. Org. Chem.* **1980**, *45*, 2120) gave the selenide corresponding to **13** in 49% yield. Oxidation of the selenide with hydrogen peroxide gave **4** in only 37% yield.
19. The cyclization afforded a 6:1 mixture of **15** and a diastereomer, respectively.
20. Two dimensional carbon-hydrogen correlation experiments aided in the identification of H(4a) as a multiplet at δ 1.50 (500 MHz). A difference NOE experiment afforded enhancement of this signal upon irradiation of the angular methyl group.
21. This paper is dedicated to the memory of Dr. Devon W. Meek (1936-1988).

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