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Dihydropyridinone Approach to Manzamines: An Expedient Construction of the Tetracyclic Core of Manzamine A

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Abstract: *A construction of the central tetracyclic core (19) of manzamine A (1) was successfully achieved by a highly efficient Diels-Alder reaction of the suitably protected dihydropyridinones (5) and Danishefsky 's diene as a key strategy. Expedient conversion of the D-A product (7) to the precursor (15) was followed by the azocine lactam ring closure to furnish the titled core.*

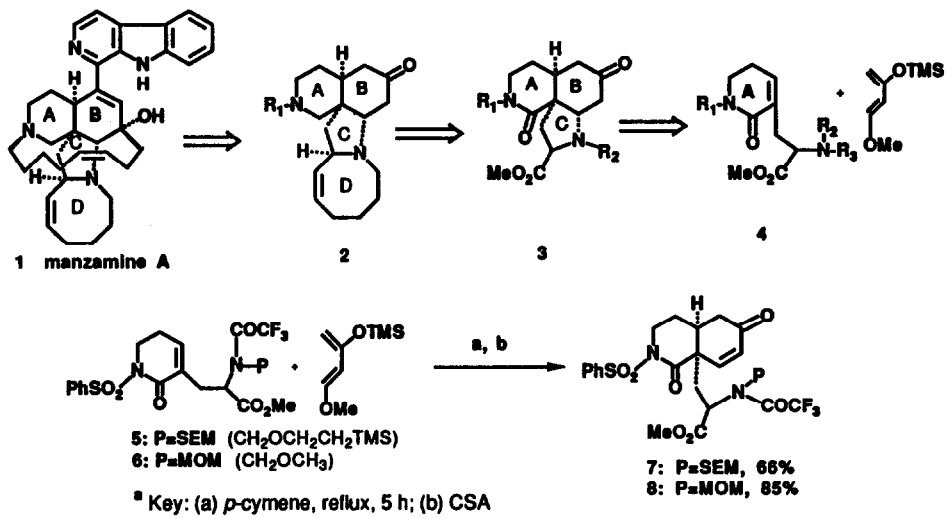
Marine alkaloids manzamines are a unique family of oncolytic β-carboline-linked azacycles isolated from several Okinawan marine sponges by Higa since 1986,[1] to which was added recently the new and closely related member ircinals.[2] The first isolated congener manzamine A (**1**)[1a] has been the subject of recent synthetic investigations[3] owing to its unique molecular structure and significant biological properties including antitumor[1a] and antibacterial activities.[1d] Several groups have already reported the successful construction of the central ABC tricyclic heart[3] (Scheme I) including our own approach.[4]

Quite recently, Hart announced the first synthetic entry into the tetracyclic core,[5] which in turn prompted us to report here our own venture to the ABCD tetracyclic core (**19**) based on the Diels-Alder (D-A) reaction of 3-substituted dihydropyridinones as a key strategy, as well as novel protocols for azocine lactam formation

Based on our retrosynthetic analysis shown in Scheme I, we have developed a route to the key tricyclic intermediate (**3**; R_1 = Ts, R_2 = Me) utilizing a super high-pressure D-A reaction of the dihydropyridinone (**4**).[4b, c] As has already been described,[4c] attempted transformation from **3** to **2** proved to be unsuccessful, therefore requiring further search for a suitable dienophile and more practical reaction conditions.

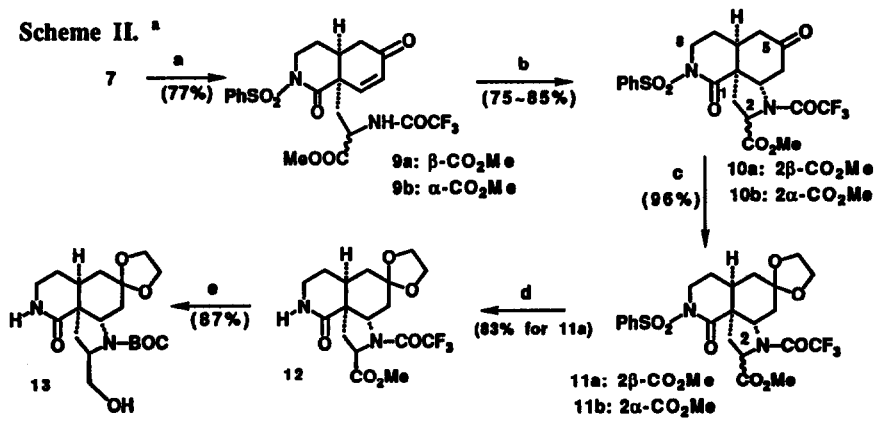
After several attempts, the new dienophiles (**5**, **6**),[6] each containing a $COCF_3$ protecting group, were found to be most suitable due to the ease of preparation and appropriate reactivity in D-A reaction. Thus, treatment of **5** and **6**, respectively, with Danishefsky's diene in refluxing *p*-cymene furnished the corresponding enones (**7** and **8** respectively)[7] in 66~85 % yield after acid treatment (Scheme I). Conveniently enough, the crude SEM-protected adduct (**7**) was easily deprotected by TFA to furnish the NH-enone (**9**),[7] which was converted to the new tricyclic system (**10**)[7] by the brief treatment of DABCO at rt in 85% yield (Scheme II). Subsequent ketalization of **10** afforded the stable ketal (**11**)[7, 8] as ca. 1:1 diastereomeric mixture, which could easily be separated by the recrystallization from AcOEt / *n*-hexane (**11a**: 49%; **11b**: 47%).

Scheme I. [a]



[a] Key: (a) *p*-cymene, reflux, 5 h; (b) CSA

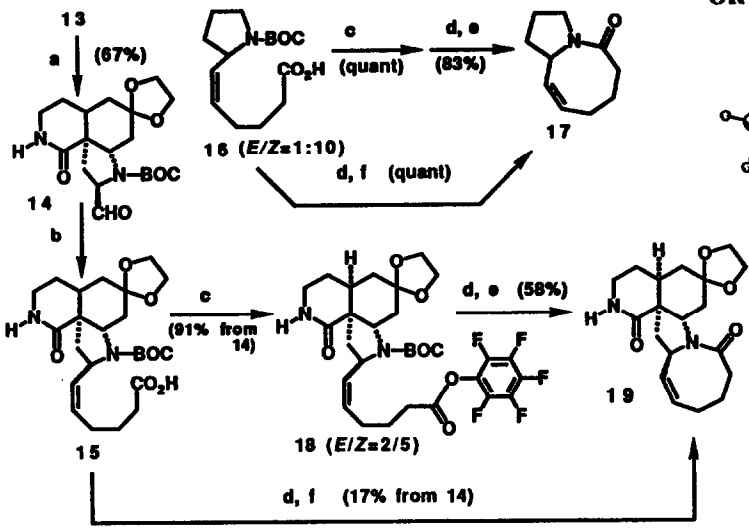
Scheme II. [a]



[a] Key: (a) CF_3COOH, CH_2Cl_2 rt; (b) DABCO, DME, rt; (C) ethylene glycol, PPTS, benzene, reflux; (d) Na, anthracene, DME, -60 °C; (e) i) $LiBH_4$, $B(OMe)_3$, THF, rt ii) NaOH, $(BOC)_2O$, rt

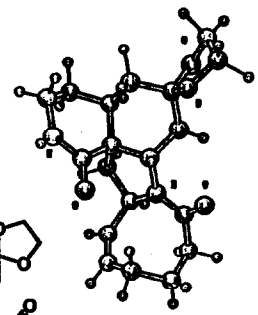
The hardest task in the next stage was a selective deprotection of the two N-protecting groups. After various abortive trials with typical reducing agents, we finally discovered that treatment of **11a** with Na / anthracene[9] in DME at - 60°C afforded **12** in 92 % yield.[10] The deprotected NH piperidone (**12**) was far more stable toward nucleophiles and quite suitable for the subsequent transformation under basic media, which were incompatible with the labile N-sulfonyl piperidones such as **9** or **10**. The reductive removal of $COCF_3$ group by $LiBH_4$ followed by protection of the newly generated NH group by BOC gave the alcohol (**13**)[7] in 87% yield from **12**. Careful oxidation of **13** by PCC afforded the aldehyde (**14**)[7] in 67% yield, which was then subjected to a Wittig reaction with the ylide generated from 4-carboxybutyltriphenylphosphonium bromide to afford the cyclization precursor (**15**).[11]

Scheme III.[a]



[a] Key: (a) PCC, CH_2Cl_2, Al_2O_3, rt (b) $Ph_3P{=}CH(CH_2)_3COOK$, toluene, rt (c) C_6F_5OH DCC, rt; (d) CF_3COOH, CH_2Cl_2, rt (e) DMAP, dioxane, 80~90 °C; (f) DPPA, DMF, 5°C~rt

Figure I.
ORTEP Drawing of 19



The key precursor (**15**) in hand, we next turned our attention to the crucial azocine lactam ring formation[12]. Careful model study was required for the effective azocine lactam ring formation from the corresponding amino-acid precursor.[12] The two convenient methods were soon found for the conversion of the model system (**16**, *E* / *Z* =ca. 1 / 10)[13] as shown in Scheme III. The direct DPPA method[14] afforded the bicyclic azocine lactam (**17**)[7] from **16** in nearly quantitative yield, while the indirect pentafluorophenyl (PFP) ester method[15] furnished **17** in 83% overall yield, in which the intermediate PFP ester was isolated and treated with DMAP at 90 °C for 3.5 h. This PFP method was then applied to the real substrate (**15**), treating the crude acid (**15**)[11] with pentafluorophenol and DCC to afford the easily separable PFP ester (**18**),[7] which was a *E*/ *Z* (2:5) mixture upon NMR analysis. Crucial cyclization was then carried out by heating **18** in the presence of DMAP in dioxane at 80 °C for 1.5 h to give the desired tetracycle (**19**) in 58% from **18** . The DPPA method was also effective for this crucial conversion albeit in lower yield (~20%). The structure of **19** was well confirmed by spectroscopic means including IR, NMR (^1H and ^{13}C including nOe experiments), MS, and furthermore, unequivocally determined by X-ray diffraction analysis.(Figure I)[16]

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7. Satisfactory spectral and analytical data (IR, ^{1}H NMR, MS, HRMS) were obtained for the new compounds.

8. Separation of each isomer was possible at this stage and the stereochemistry of 2-CO_2Me substituent was tentatively assigned based on the NOE study on the isomer (9a).

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10. The deprotection reaction for the 2α-CO_2Me isomer (**11b**) aforded NH compound in ~55 %.

11. Purification of **15** from the excess Wittig reagent was fairly difficult, so that the crude product was subjected to the next cyclization step without further purification.

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13. Prepared in a straightforward fashion from *N*-BOC-*L*-proline methyl ester as follows: (1) DIBAL, toluene -78 °C; (2) Ph_3P=$CH(CH_2)_3COOK$, toluene, rt.

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15. See for example: Wasserman, H. H.; Robinson, R. P.; Carter, C. G. *J. Am. Chem. Soc.* **1983**, *105*, 1697-1698.

16. Selected data for **19**: colorless needle , mp > 300°C; IR (KBr): 3300, 2950, 1670, 1620 cm^{-1}; HRFABMS Calcd for $C_{19}H_{27}O_4N_2$: 347.1971, Found: 347.1966; ^{1}H-NMR (500 MHz $CDCl_3$) δ: 1.58 (1H, m), 1.62 (1H, m), 1.68 (1H, br), 1.73 (1H, dd, *J*=14.84, 4.58 Hz), 1.81 (1H, t, *J*=13.19 Hz), 1.89 (1H, m), 2.02 (1H, m), 2.06 (1H, dd, *J*=12.82, 9.34 Hz), 2.18 (1H, m), 2.25 (2H, m), 2.34 (1H, dd, *J*=12.82, 7.32 Hz), 2.38 (1H, m), 2.64 (1H, td, *J*=12.28, 5.31 Hz), 3.19 (1H, ddd, *J*=14.84, 4.58, 2.2 Hz), 3.29 (1H, m, *J*=12.27, 4.95 Hz), 3.44 (1H, dd), 3.84-4.01 (4H, m), 4.62(1H, br), 4.78 (1H, t, *J*=4.58 Hz), 5.46 (1H, ddd, *J*=11.90, 3.84, 1.28 Hz), 5.61 (1H, m), 5.90 (1H, brs, NH). ^{13}C-NMR 125.65MHz ($CDCl_3$) δ: 23.7, 24.2, 24.3, 31.0, 32.8, 33.8, 36.9, 38.4, 43.3, 48.9 , 58.6, 61.4, 64.0, 64.9, 107.9, 126.4, 132.6, 173.0, 173.7. Crystal data for **19** ($C_{19}H_{26}N_2O_4$; FW=346.43): a = 10.274 (2), b = 5.658 (1), c = 20.801 (3) Å, β = 135.54 (1)°, U = 846.9 (3) Å^3, monoclinic, P c, Z = 2, Dx = 1.36g/cm^3, F(000) = 372, μ (Cu Ka) = 7.87 cm^{-1}. The final R value is 0.031(Rw=0.035).

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