

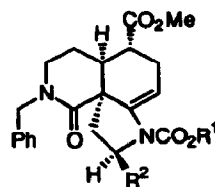
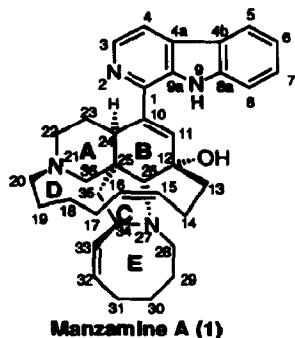
## The First Synthesis of the ABCD Ring System of Manzamine A. Construction of the Macrocyclic Ring D.

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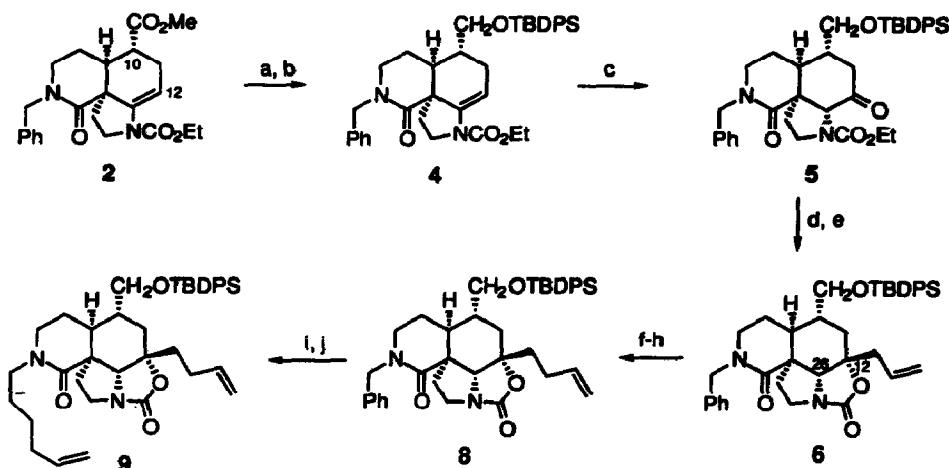
**Abstract** - The synthesis of the ABCD ring system of manzamine A has been achieved using the olefin metathesis cyclization reaction for the crucial macrocyclic ring D formation step.

Since its discovery and structure elucidation in 1986,<sup>1</sup> the alkaloid manzamine A (1) has prompted a number of research groups to undertake its synthesis.<sup>2</sup> The unique structure of manzamine A consists of 8- and 13-membered rings annulated to a pyrrolo[2,3-*i*]isoquinoline bearing a pendant  $\beta$ -carboline moiety. The tricyclic pyrrolo[2,3-*i*]isoquinoline template, which constitutes the central core of the molecule, was chosen as the key building block for the further elaboration to manzamine A.



- (2)  $R^1 = Et, R^2 = H$   
 (3)  $R^1 = Bn, R^2 = CH_2OTBDPS$

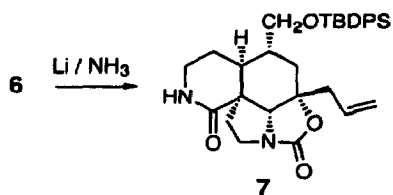
We have previously published a route to the racemic pyrroloisoquinoline 2 and the corresponding homochiral system 3, utilizing a highly diastereoselective intramolecular Diels-Alder reaction.<sup>2b</sup> Additionally, strategies have been developed for both the annulation of the 8-membered ring onto the tricycle, to form the ABCE ring system<sup>3</sup> and for the introduction of the  $\beta$ -carboline moiety.<sup>4</sup> In this communication we wish to present the first synthesis of an advanced manzamine A intermediate incorporating the 13-membered ring D. The readily accessible racemic tricycle 2 was chosen for this study. Three general approaches for the annulation of the macrocyclic ring onto the tricycle 2 were considered: a) attachment of an appropriate 8-carbon chain to C-12, followed by cyclization onto N-21; an approach attempted by Simpkins and de Oliveira Imbroisi;<sup>2h</sup> b) addition of the same fragment in the opposite sequence, and c) attachment of suitable groups to N-21 and C-12, followed by cyclization to form the 15-16 double bond. The last approach was chosen in view of its flexibility and expediency. For the crucial cyclization step we favored the metathesis cyclization of two terminal olefins, employing an air-stable ruthenium carbene catalyst recently described by Grubbs.<sup>5</sup>



- (a)  $\text{LiBH}_4$  (b) TBDPS-Cl, imidazole, DMF (c)  $\text{OsO}_4/\text{pyridine}$  then  $\text{H}^+$  (d) allyl-MgCl, THF (e) NaH  
 (f) 9-BBN/ $\text{H}_2\text{O}_2$  (g) Dess-Martin periodinane (h)  $\text{Ph}_3\text{P}=\text{CH}_2$  (i) Li /  $\text{NH}_3$  then  $\text{Br}_2\text{O}$   
 (j)  $1-(\text{CH}_2)_4\text{CH}=\text{CH}_2$ , KOH, DMSO.

Scheme 1. Synthesis of the cyclization precursor

Having previously described the synthesis of the tricycle **2**,<sup>1a</sup> we turned our attention to its functionalization at C-12 (Scheme 1). It was presumed that a variety of organometallic reagents would add to a ketone function at C-12 from the least hindered top face of the molecule, to generate an alcohol with the desired stereochemistry. To this end, the C-10 ester group was reduced ( $\text{LiBH}_4$ ) and the primary alcohol was protected as the *tert*-butyldiphenylsilyl ether **4** (70%). Dihydroxylation of the ene-carbamate **4** using osmium tetroxide followed by an acid catalyzed dehydration afforded ketone **5** in a 66% yield.<sup>6</sup> In order to achieve the olefin metathesis cyclization, addition of a homoallyl organometallic reagent to **5** was required. However, neither the homoallyl Grignard reagent nor a variety of other magnesium, lithium or cerium reagents added to the ketone, due to steric hindrance. Fortunately, it was found that allyl magnesium chloride gave exclusive top face addition to the ketone in a 60% yield. This is not surprising since it is known that allyl Grignard reagents react readily even with very hindered ketones.<sup>7</sup> The resulting tertiary alcohol was conveniently protected by its transformation into the cyclic carbamate **6** (NaH in THF, 93%). The stereochemistry at C-12 and C-26 (in **6**) is based upon the X-ray diffraction analysis of crystalline lactam **7** (Figure 1),<sup>8</sup> which was obtained by debenzoylation of **6** ( $\text{Li}/\text{NH}_3$ ) (Scheme 2).



Scheme 2

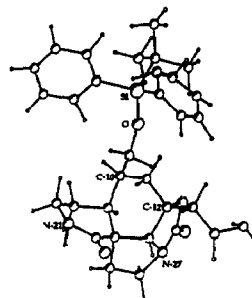
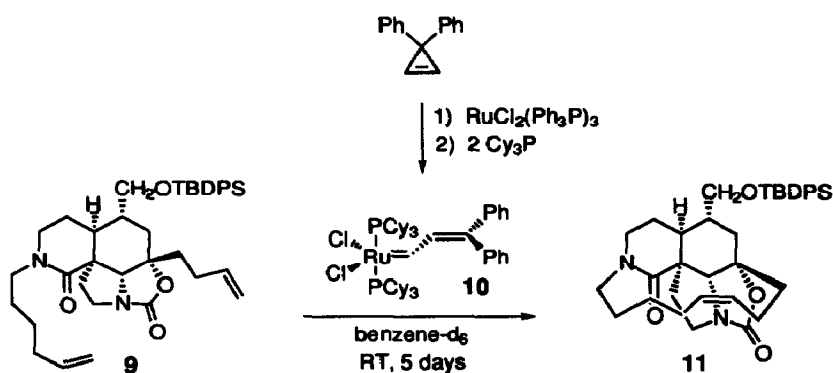


Figure 1. X-ray structure of compound **7**

The allyl substituent was extended by one carbon to the homoallyl group by a straightforward three step transformation involving (i) hydroboration/H<sub>2</sub>O<sub>2</sub> oxidation, (ii) oxidation of the resulting alcohol to the corresponding aldehyde and (iii) Wittig olefination, to give **8** (48% overall). Next, in order to attach the second olefinic side chain, the *N*-benzyl protecting group was cleaved using lithium in ammonia and employing dibenzyl ether as a quench to avoid Birch reduction of the benzene rings in the *t*-butyldiphenylsilyl group.<sup>9</sup> Finally, the amide nitrogen was alkylated (KOH in DMSO<sup>10</sup> 77%) with the appropriate 6-iodohex-1-ene to give the cyclization precursor **9**.

The required ruthenium carbene catalyst **10** was prepared according to the procedure published by Grubbs and coworkers,<sup>11a</sup> in which RuCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>3</sub> was condensed with 3,3-diphenylcyclopropene<sup>12</sup> to give an intermediate metal-carbene complex; subsequent ligand exchange with tricyclohexylphosphine gave the desired catalyst (**10**).<sup>11b</sup> With this catalyst in hand, we turned our attention to the olefin metathesis cyclization reaction of precursor **9** (Scheme 3).



Scheme 3. Olefin metathesis cyclization

A preliminary investigation of the reaction was performed in an NMR tube [400 MHz, **9** and **10**, 1:1, 3x10<sup>-3</sup> M in benzene-d<sub>6</sub>, RT]. The spectra of the reaction with time showed the gradual disappearance of the terminal olefin protons at  $\delta$  4.94-5.07 ppm and the emergence of an internal double bond at  $\delta$  5.05-5.25 ppm, corresponding to a new product. In order to isolate this product, the reaction was scaled up using benzene-d<sub>6</sub> (under argon), in order to follow the course of the reaction (NMR). After stirring at room temperature for 5 days, the reaction showed no further progress. The resulting product was isolated and purified by preparative TLC (30%). This compound has been assigned structure **11**<sup>13</sup> based on detailed analysis of its NMR spectra. In particular, the location of the double bond has been established by a combination of <sup>1</sup>H-<sup>1</sup>H COSY and NOE experiments, and the *cis* nature of the olefin was determined by double resonance experiments (*J* = 10.8 Hz). Additional support for the structure came from the FAB mass spectral data of **11** [FAB-MS *m/z* 569 (*M*<sup>+</sup> -CO<sub>2</sub>)], which showed the clear loss of C<sub>2</sub>H<sub>4</sub> from diene **9** [FAB-MS *m/z* 597 (*M*<sup>+</sup> -CO<sub>2</sub>)]. Although the molecular ions are observed for **9** and **11**, the peaks involving loss of CO<sub>2</sub> from the carbamates constitute the base ions in the mass spectra of these compounds. The molecular formula was established by HR-FAB mass spectroscopy [Found 613.3494; C<sub>37</sub>H<sub>49</sub>N<sub>2</sub>O<sub>4</sub>Si (*M*<sup>+</sup> +H) requires 613.3462].

This result represents the first report of the introduction of the macrocyclic 13-membered ring onto an advanced tricyclic core structure of manzamine A. Additionally, it extends the methodology of the Grubbs catalytic ring closing olefin metathesis reaction to complex macrocycles. We are currently incorporating this methodology into our efforts on the total synthesis of manzamine A.

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### References and Notes

- Sakai, R.; Higa, T.; Jefford, C. W. and Bernardinelli, G. *J. Am. Chem. Soc.*, **1986**, *108*, 6404-6405; Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake, T.; Matsuzaki, T. and Hirata, Y. *Tetrahedron Lett.*, **1987**, *28*, 621-624; Ichiba, T.; Sakai, R.; Kohmoto, S.; Saucy, G. and Higa, T. *Tetrahedron Lett.*, **1988**, *29*, 3083-3086.
- (a) Brands, K. M. J. and Pandit, U. K. *Tetrahedron Lett.*, **1989**, *30*, 1423-1426; (b) Hart, D. J. and McKinney, J. A. *Tetrahedron Lett.*, **1989**, *30*, 2611-2614; (c) de Oliveira Imbroisi, D. and Simpkins, N. S. *Tetrahedron Lett.*, **1989**, *30*, 1423-1426; (d) Brands, K. M. J. and Pandit, U. K. *Heterocycles*, **1990**, *30*, 257-261; (e) Nakagawa, M.; Lai, Z.; Torisawa, Y. and Hino, T. *Heterocycles*, **1990**, *31*, 999-1002; (f) Torisawa, Y.; Nakagawa, M.; Arai, H.; Lai, Z.; Hino, T.; Nakata, T. and Oishi, T. *Tetrahedron Lett.*, **1990**, *31*, 3195-3198; (g) Brands, K. M. J.; Meekel, A. A. P. and Pandit, U. K. *Tetrahedron Lett.*, **1991**, *47*, 2005-2026; (h) de Oliveira Imbroisi, D. and Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1815-1823; (i) Martin, S. F.; Rein, T. and Liao, Y. *Tetrahedron Lett.*, **1991**, *32*, 6481-6484; (j) Leonard, J.; Feamley, S. P. and Hickey, D. M. B. *Synlett*, **1992**, 272-274; (k) Markó, I. E. and Chesney, A. *Synlett*, **1992**, 275-278; (l) Torisawa, Y.; Nakagawa, M.; Hosaka, T.; Tanabe, K.; Lai, Z.; Ogata, K.; Nakata, T.; Oishi, T. and Hino, T. *J. Org. Chem.*, **1992**, *57*, 5741-5747; (m) Markó, I. E.; Southern, J. M. and Adams, H. *Tetrahedron Lett.*, **1992**, *33*, 4657-4660; (n) Campbell, J. A. and Hart, D. J. *Tetrahedron Lett.*, **1992**, *33*, 6247-6250; (o) Nakagawa, M.; Torisawa, Y.; Hosaka, T.; Tanabe, K.; Da-te, T.; Okamura, K. and Hino, T. *Tetrahedron Lett.*, **1993**, *34*, 4543-4546; (p) Winkler, J. D.; Siegel, M. G. and Stelmach, J. E. *Tetrahedron Lett.*, **1993**, *34*, 6509-6512.
- H. Bieräugel, B. C. Borer and U. K. Pandit, Seminar on Chemistry of Rain Forest Plants and their Utilization for Development, Bukittinggi, Indonesia, Oct. 27-29, 1992, in press.
- Bieräugel, H.; Brands K. M. J. and Pandit, U. K. Studies on the Synthesis of Manzamine A; Attachment of the  $\beta$ -Carboline Moiety to the Tricyclic "Heart" of the Alkaloid. In *Essays in Science*, Vol. 6; Said, H. M., Ed.; Hamdard Foundation, Karachi, 1992; pp. 158-161.
- Fu, G. C.; Nguyen, S. T. and Grubbs, R. H. *J. Am. Chem. Soc.*, **1993**, *115*, 9856-9857.
- Satisfactory NMR ( $^1\text{H}$  and  $^{13}\text{C}$ ), IR, and mass spectral data were obtained for all new compounds using chromatographically homogeneous samples. Data for ketone 5:  $^1\text{H}$  NMR (400 MHz, toluene- $d_6$ , 363 K)  $\delta$  ppm 1.05 (s, 9H), 1.08 (dt, 3H,  $J=3.6, 7.1$ ), 1.40-1.53 (m, 4H), 1.89-2.06 (m, 2H), 2.32 (m, 2H), 2.64 (ddd, 1H,  $J=3.2, 5.9, 12.4$ ), 2.86 (ddd, 1H,  $J=5.2, 10.8, 12.4$ ), 3.37 (m, 2H), 3.49 (ddd, 1H,  $J=5.0, 8.2, 10.3$ ), 3.61 (ddd, 1H,  $J=7.7, 7.7, 10.3$ ), 4.06 (2xdq, 2H,  $J=7.1, 10.8$ ), 4.37 (2xd, 2H,  $J=14.4$ ), 4.90 (s, 1H), 6.96-7.24 (m, 6H), 7.56-7.66 (m, 4H).
- Benkeser, R. A. *Synthesis*, **1971**, 347-358.
- The crystal data are as follows; Triclinic, space group P1,  $a = 10.34(1)$ ,  $b = 11.88(1)$ ,  $c = 14.400(6)$  Å,  $\beta = 96.51(6)^\circ$ ,  $V = 1521(3)$  Å $^3$ ,  $Z = 2$ ,  $D_x = 1.19$  g/cm $^3$ . The final R value was converged to 0.073 (2499 reflections were used). The final atomic coordinates were deposited in Cambridge Crystallographic Data Center.
- Kim, M. Y.; Starrett, Jr., J. E. and Weinreb, S. M. *J. Org. Chem.*, **1981**, *46*, 5383-5389.
- Johnstone, R. A. W. and Rose, M. E. *Tetrahedron*, **1979**, *35*, 2169-2173.
- (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. and Ziller, J. W. *J. Am. Chem. Soc.*, **1992**, *114*, 3974-3975; (b) Nguyen, S. T. and Grubbs, R. H. *J. Am. Chem. Soc.*, **1993**, *115*, 9858-9859.
- We wish to thank Prof. P. Binger, Max-Planck-Institute für Kohlenforschung, for providing us with the experimental procedure for the preparation of 3,3-diphenylcyclopropene.
- 11: m.p. 196-199 °C; Rf = 0.41 (EA); IR (CHCl $_3$ )  $\nu_{\text{max}}$  1730, 1612, 1485, 1450, 1420, 1395, 1350, 1275, 1255, 1105, 1080, 1005 and 695 cm $^{-1}$ ;  $^1\text{H}$ -NMR (benzene- $d_6$ , 400 MHz)  $\delta$  ppm 0.68 (m, 1H), 0.98-1.08 (m, 3H), 1.21 (s, 9H), 1.33-1.45 (m, 4H), 1.48-1.59 (m, 5H), 1.65-1.79 (m, 2H), 1.97 (dd, 1H,  $J=5.4, 13.8$ ), 2.09-2.21 (m, 2H), 2.45 (ddd, 1H,  $J=10.8, 10.8, 14.9$ ), 2.58 (ddd, 1H,  $J=3.5, 13.4, 13.4$ ), 2.76 (ddd, 1H,  $J=5.5, 12.7, 12.7$ ), 2.97 (dd, 1H,  $J=10.0, 10.0$ ), 3.31 (ddd, 1H,  $J=8.0, 10.0, 10.0$ ), 3.87 (m, ABX, 2H), 4.67 (s, 1H), 4.79 (ddd, 1H,  $J=5.0, 13.8, 13.8$ ), 5.11 (ddd, 1H,  $J=2.5, 10.8, 10.8$ ), 5.21 (br. appt. t, 1H,  $J=10.8$ ), 7.22-7.29 (m, 6H) and 7.97-7.80 (m, 4H);  $^{13}\text{C}$ -NMR (benzene- $d_6$ )  $\delta$  ppm 20.18, 22.62, 23.97, 25.15, 25.33, 25.51, 27.98, 30.86, 31.73, 35.23, 39.53, 40.02, 42.29, 42.74, 44.45, 49.76, 69.38, 70.08, 82.93, 129.36, 129.43, 129.59, 129.80, 130.48, 130.70, 130.73, 131.90, 134.84, 134.98, 136.83, 136.87, 159.91 and 170.60; MS  $m/z$  (FAB): 635 ( $M^+ + \text{Na}$ , 10.9%), 613 ( $M^+ + \text{H}$ , 8.8), 612 ( $M^+$ , 5.5), 569 ( $M^+ - \text{CO}_2\text{H}$ , 68.1), 555 ( $M^+ - t\text{-Bu}$ , 26.6), 535 ( $M^+ - \text{C}_6\text{H}_5$ , 52.0), 199 ( $\text{C}_{10}\text{H}_{15}\text{OSi}^+$ , 58.3), 197 ( $\text{C}_{10}\text{H}_{15}\text{OSi}^+$ , 85.0), 149 (58.9) and 135 ( $\text{C}_7\text{H}_7\text{OSi}^+$ , 100); HRMS (FAB) [Found 613.3494;  $\text{C}_{37}\text{H}_{49}\text{N}_2\text{O}_4\text{Si}$  ( $M^+ + \text{H}$ ) requires 613.3462].

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