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Enantioselective Total Syntheses of Manzamine A and Related Alkaloids

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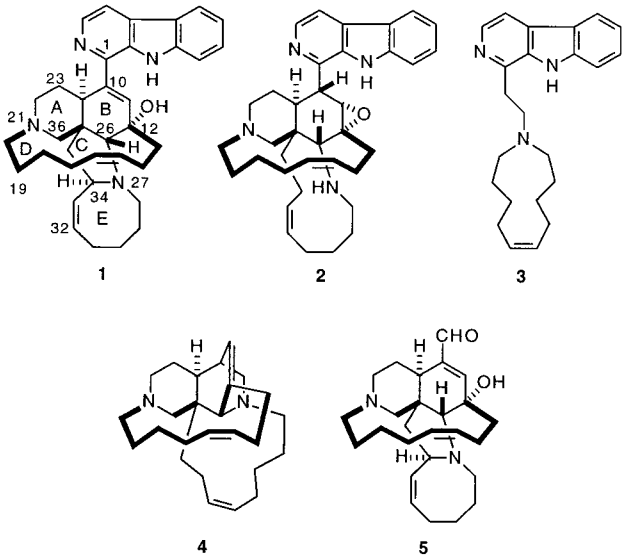
Abstract: As a prelude to undertaking the total syntheses of the complex manzamine alkaloids, a series of model studies were conducted to establish the scope and limitations of intramolecular [4 + 2] cycloadditions of *N*-acylated vinylogous ureas with the trienic substrates **17a**,**b**, **28a**,**b**, and **34**. These experiments clearly demonstrated that the geometry of the internal double bond and the presence of an electron-withdrawing group on the diene moiety were essential for the facile and stereoselective formation of the desired cycloadducts. The enantioselective syntheses of the manzamine alkaloids ircinol A (**75**), ircinal A (**5**), and manzamine A (**1**) were then completed by employing a convergent strategy that featured a novel domino Stille/Diels−Alder reaction to construct the tricyclic ABC ring core embodied in these alkaloids. Thus, the readily accessible chiral dihydropyrrole **58** was first converted in a single chemical operation into the key tricyclic intermediate **60**. Two ring-closing metathesis reactions were then used to form the 13- and 8-membered rings leading to ***Z*-72** and **74**, the latter of which was quickly elaborated into ircinal A (**5**) via ircinol A (**75**). The synthetic **5** thus obtained was converted into manzamine A (**1**) following literature precedent. This concise synthesis of ircinal A required a total of 24 operations from commercially available starting materials with the longest linear sequence being 21 steps.

Introduction

The manzamines constitute a growing and important family of structurally complex indole alkaloids that have been isolated from marine sponges of the genera *Haliclona* and *Pellina* found off the coast of Okinawa.[1] Manzamine A (**1**) attracted considerable attention because of its potent antitumor activity and was the first member of this group of alkaloids to be isolated.[2] After this exciting discovery, a number of related alkaloids including manzamine B (**2**), manzamine C (**3**), keramaphidin B (**4**), and ircinal A (**5**)[3] were isolated. Baldwin has proposed a novel biosynthetic pathway to the manzamine alkaloids and has supported this hypothesis by demonstrating that key reactions are indeed viable in the laboratory.[4] Interest in the manzamine alkaloids has been further stimulated by the recent discoveries that manzamine A exhibits potent antimalarial and antituberculosis activity.[5]



The combination of the complex and unusual structure of manzamine A (**1**) and its promising biological activity has inspired numerous synthetic investigations.[6] Despite these extensive efforts, the only two reports of its synthesis via ircinal

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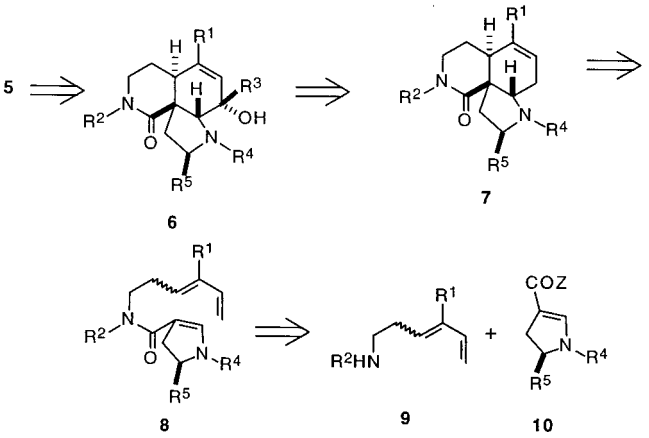
(1) For reviews, see: (a) Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765. (b) Matzanke, N.; Gregg, R.; Weinreb, S. *Org. Prep. Proc. Intl.* **1998**, *30*, 1. (c) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201.
(2) (a) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404. (b) Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake, Y.; Matsuzaki, T.; Hirata, Y. *Tetrahedron Lett.* **1987**, *28*, 621.
(3) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.
(4) (a) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059. (b) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2661. (c) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem Eur. J.* **1999**, *5*, 3154.

10.1021/ja0202964 CCC: $22.00

Scheme 1



A (**5**), which had been previously converted into **1** by Kobayashi,[3] have been recorded by Winkler and ourselves.[7,8] Herein we report the details of our work leading to the enantioselective syntheses of manzamine A and ircinal A.[8,9]

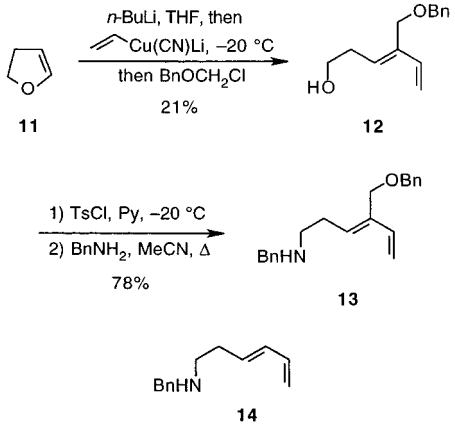
In our retrosynthetic analysis of **5** (Scheme 1), we envisioned that the tricyclic intermediate **6** would be a key intermediary objective. Indeed, most of the approaches to ircinal A and related alkaloids have targeted the ABC tricyclic core as the initial goal. R^1 would be any group that could be transformed into an aldehyde, and the paired substituents R^2/R^3 and R^4/R^5 would be suitably functionalized for elaboration into the 13- and 8-membered rings, respectively. This advanced intermediate would in turn evolve from **7**, which we reasoned would be accessible via the intramolecular Diels−Alder reaction of triene **8**. Assembly of **8** simply required coupling substituted diene **9** with chiral dienophile **10**.

In undertaking the synthesis of a complex natural product such as manzamine A, there are typically many uncertainties and steps for which there may be little or no precedent. Consequently, preliminary studies must be conducted to establish the viability of key steps. Because discovering new chemistry should be a paramount objective of exercises in total synthesis, the approach should be planned to optimize opportunities for developing new methods and techniques. Indeed, analysis of the basic plan set forth in Scheme 1 reveals several opportunities to explore new chemistry. The first of these involved developing a general method for the stereoselective synthesis of trisubstituted homoallylic amines and dienes that might be applied to the preparation of **9**, and one such technique was invented during the course of our studies.[10] The underlying viability of the key intramolecular Diels−Alder reaction to form the tricyclic ABC core with its attendant stereochemistry was not well precedented. There were only a few examples of intramolecular Diels−Alder reactions of vinylogous amides as dienophiles, and none of these had the connectivity of **8**.[11] Whether such dienophiles were electron rich or poor had not been probed experimentally. Equally challenging were the problems posed by the construction of the 13- and 8-membered, unsaturated nitrogen heterocyclic rings with *Z*-olefins. Hence, toward the goal of exploring new chemistry associated with the synthesis of the manzamines, a series of model studies were first undertaken.

Discussion and Results

Initial Model Studies. The first phase of our investigations was specifically designed to probe the feasibility and stereochemical outcome of intramolecular Diels−Alder reactions to produce the tricyclic ABC core of the manzamines. Toward this end, a series of trienes having different geometries and substitution on the internal double bond were prepared by coupling geometrically defined dienes with requisite dienophilic components related to **10**. The dienol **12** was first prepared in an unoptimized variation of a reaction developed by Kocienski for the stereoselective synthesis of alkenes (Scheme 2).[12] The tosylate derived from **12** was treated with benzylamine to give **13**. The corresponding 3-unsubstituted diene **14** was prepared by reaction of benzylamine with a known dienic tosylate.[13]

Scheme 2



The dienophile component **16** was then fabricated from **15** by a straightforward sequence of reactions and coupled via its acid chloride with **13** and **14** to give the trienic substrates **17a**,**b** (Scheme 3). When **17a** was heated (toluene, sealed tube, 180 °C bath temperature), a mixture (ca. 2:1) of the two cycloadducts **18a**, which possesses the tricyclic ABC subunit of manzamine A, and **19a** was obtained (81%). The structures of **18a** and **19a**

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(6) For selected studies, see: (a) Kamenecka, T.; Overman, L. *Tetrahedron*, **1994**, *35*, 4279. (b) Pandit, U.; Borer, B.; Bieraugel, H. S. *Pure Appl. Chem.* **1996**, *68*, 659. (c) Magnier, E.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 837. (d) Brands, K.; DiMichele, L. *Tetrahedron Lett.* **1998**, *39*, 1677. (e) Li, S.; Kosemura, S.; Yamamura, S. *Tetrahedron* **1998**, *54*, 6661. (f) Li, S.; Yamamura, S. *Tetrahedron* **1998**, *54*, 8691. (g) Nakagawa, M.; Torisawa, Y.; Uchida, H.; Nishida, A. *J. Synth. Org. Chem., Jpn.* **1999**, *57*, 112. (h) Uchida, H.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 113. (i) Coldham, I.; Crapnell, K. M.; Fernandez, J.-C.; Haxell, T. F. N.; Treacy, A. B.; Coles, S. J.; Hursthouse, M. B.; Moseley, J. D. *Chem. Commun.* **1999**, 1757. (j) Bland, D.; Chambournier, G.; Dragan, V.; Hart, D. J. *Tetrahedron* **1999**, *55*, 8953. (k) Clark, J. S.; Townsend, R. J.; Blake, A. J.; Teat, S. J.; Johns, A. *Tetrahedron Lett.* **2001**, *42*, 3235. (l) Herdemann, M.; Al-Mourabit, A.; Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 1890. (m) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947.

(7) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425.

(8) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866.

(9) For preliminary accounts of other parts of this work, see: (a) Martin, S. F.; Rein, T.; Liao, Y. *Tetrahedron Lett.* **1991**, *32*, 6481. (b) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691.

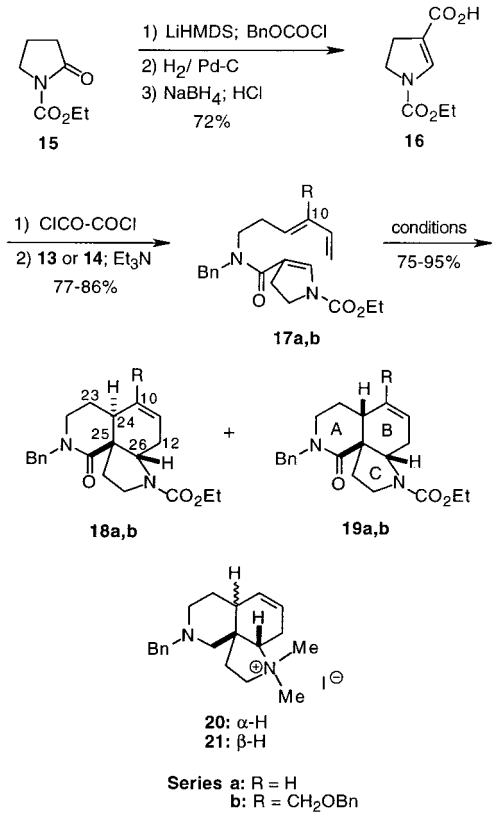
(10) Neipp, C. E.; Humphry, J. M.; Martin, S. F. *J. Org. Chem.* **2001**, *66*, 531.

(11) (a) Morgans, D. J., Jr.; Stork, G. *Tetrahedron Lett.* **1979**, 1959. (b) Kraus, G. A.; Raggon, J.; Thomas, P. J.; Bougie, D. *Tetrahedron Lett.* **1988**, *29*, 5605. (c) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913.

(12) (a) Kocienski, P.; Wadman, S.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363. (b) Kocienski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933.

(13) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170.

Scheme 3



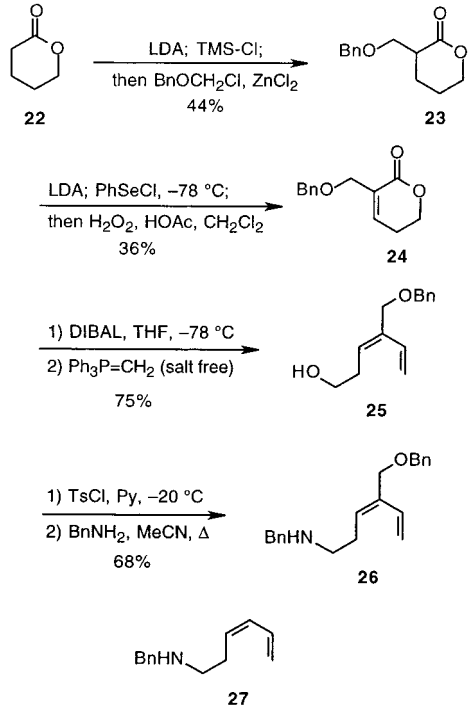
were initially based upon nOe studies, but these relative stereochemical assignments were later verified by single-crystal X-ray analyses of the derived quaternary salts **20** and **21**.[14] Similarly we found that heating **17b** produced a mixture (2:3) of **18b** and **19b**, the structures of which were tentatively assigned based upon their NMR spectra. For example, nOe difference experiments showed a nOe between the hydrogen atoms at C(24) and C(26) of **19b** that was absent in **18b**.[15] A large coupling constant of 13.4 Hz also indicated a trans diaxial arrangement between the C(24)−H and the axial proton at C(23) of **19b**. The fortuitous overlap of the signals for the hydrogen atoms at C(24) and C(12) in **18b** unfortunately rendered it impossible to obtain a coupling constant between the C(24)−H and either of the protons at C(23). The ^{13}C NMR spectra of **18a**,**b** and **19a**,**b** were also diagnostic of the relative stereochemistry in that the signals for the C(24) and C(26) carbon atoms in **18a**,**b** were slightly downfield from the corresponding carbon atoms in **19a**,**b**, and signals for the C(25) carbon atoms in **19a**,**b** were downfield from those in **18a**,**b**.

We briefly probed the effects of using Lewis acids and found that cyclizations of both **17a** and **17b** proceeded more readily in the presence of $EtAlCl_2$. Moreover, there was a slight increase in the stereoselectivity of the acid-catalyzed reaction favoring formation of the *cis*-hydroisoquinolines **18a**,**b** over the corresponding trans-isomers **19a**,**b** in ratios of 6:1 and 3:2, respectively.

The foregoing experiments not only demonstrated that vinylogous imides could participate as dienophiles in intramolecular Diels−Alder reactions, but they also established the feasibility of a key step in our projected synthesis of **1**. However, prior to implementing such a cycloaddition in this venture, it was necessary to discover a more stereoselective variant. In this context, it was known that the intramolecular [4 + 2] cycloadditions of trienes having *Z* internal double bonds gave cis-cycloadducts with high selectivity because of geometric constraints.[16] We therefore set to the task of preparing the *Z*-trienes **28a**,**b** to ascertain whether they would undergo efficient cyclization to produce the desired cis-fused products **18a**,**b**.

The dienol **25** was first prepared from δ-valerolactone by an unoptimized sequence proceeding via the unsaturated lactone **24** (Scheme 4). It was perhaps noteworthy that **23** was converted via its enolate into **24** without excessive β-elimination. The conversion of **24** into **25** was effected in analogy with prior art from our laboratory,[13] and the syntheses of **26** and **27** by reactions of benzylamine with the corresponding precursor hexadienyl tosylates occurred without difficulty.

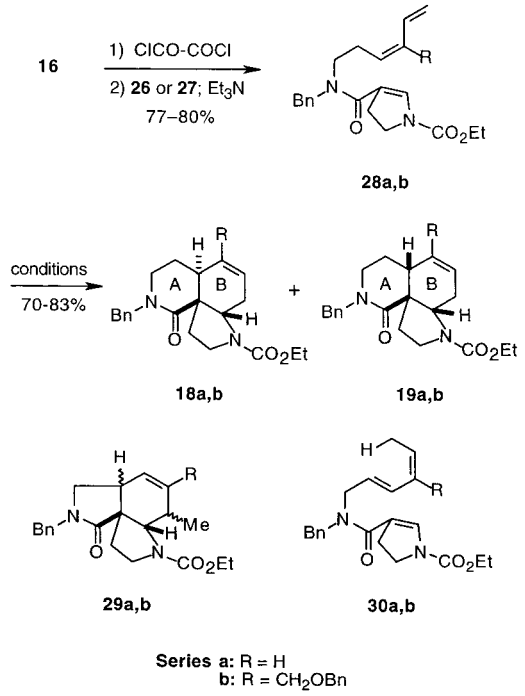
Scheme 4



The unsaturated amines **27** and **26** were then coupled with the acid chloride derived from **16** to give the corresponding trienes **28a** and **28b** (Scheme 5). Heating **28a** in refluxing mesitylene surprisingly gave a mixture (4:1:7) of the three cycloadducts **18a**, **19a**, and **29a**; **29a** was a mixture (3:1) of two diastereomers. When **28a** was heated in toluene at reflux in the presence of $EtAlCl_2$ (1.5 equiv), a mixture (ca. 8:1) of **18a** and **19a** was obtained in 70% combined yield. The substituted triene **28b** was much less prone to undergo intramolecular Diels−Alder reactions. For example, **28b** was relatively stable at temperatures up to about 150 °C, although it did cyclize upon heating to 200 °C to give primarily **29b**. It also cyclized

(14) Lynch, V. M.; Liao, Y.-S.; Martin, S. F.; Davis, B. E. *Acta Crystallogr.* **1992**, *C48*, 1703.
(15) Numbering of all compounds corresponds to that for manzamine A.
(16) For example, see: (a) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48. (b) Boeckman, R. K., Jr.; Alessi, T. R. *J. Am. Chem. Soc.* **1982**, *104*, 3216. (c) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719. (d) Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133. (e) Wattanasin, S.; Kathawala, F. G.; Boeckman, R. K., Jr. *J. Org. Chem.* **1985**, *50*, 3810.

Scheme 5

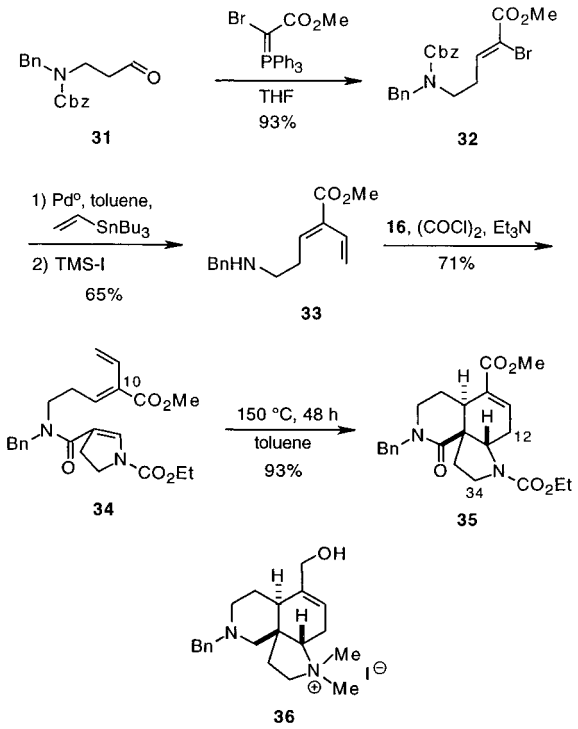


upon heating at 150 °C in the presence of $EtAlCl_2$ (1.1 equiv) to give poor yields (<20%) of **18b** together with recovered starting material (>60%).

Forming the *trans*-hydroisoquinolines **19a** and **19b** by intramolecular Diels−Alder cyclizations of **28a** and **28b** was implausible based upon transition state analysis and prior art.[16] Rather it seemed more likely that these cycloadducts were produced by cyclizations of *E*-trienes **17a**,**b** that were formed in situ by acid-catalyzed isomerizations of **28a**,**b**. Supporting this hypothesis, we found that **28a** underwent partial equilibration to **17a** in the presence of catalytic amounts of $EtAlCl_2$ (toluene, 72 h, 40 °C; ca. 30% conversion). The formation of **29a**,**b** presumably arose from the cyclizations of **30a**,**b** that would be formed by a 1,5-hydrogen shift of **28a**,**b**, but we were unable to confirm this conjecture by isolating or detecting **30a**,**b** in the reaction mixtures.

Second Generation Model Studies. In these initial investigations, we established the underlying viability of intramolecular [4 + 2] cycloadditions of trienes containing a vinylogous imide dienophile for constructing the ABC tricyclic core of the manzamine alkaloids. However, the reactions examined were neither facile nor sufficiently stereoselective to meet the demands of the total synthesis of **1**. It then occurred to us that the vinylogous imide might behave as an electron-rich dienophile, and therefore the presence of an electron-withdrawing group on the diene at C(10) might both facilitate the key cycloaddition and render it more stereoselective. To evaluate this hypothesis, we synthesized the trienic substrate **34** (Scheme 6). The α-bromo unsaturated ester **32** was first prepared in 93% yield by stereoselective Wittig olefination of the known aldehyde **31**[17] with carbomethoxybromomethylidene triphenylphosphorane;[18] the corresponding *E*-isomer was also isolated in about 4% yield. Stille coupling of **32** with vinyl tributylstannane and

Scheme 6



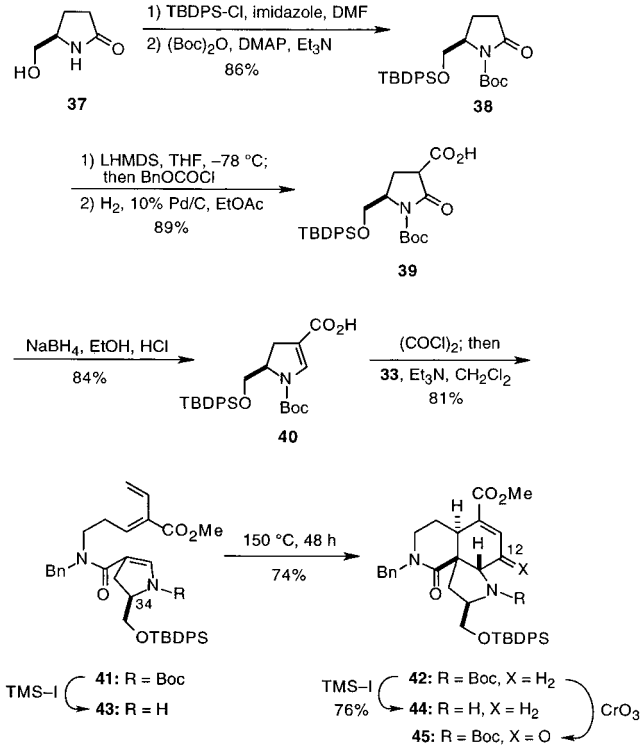
subsequent *N*-deprotection gave **33**. The amino diene **33** was then coupled with the acid chloride derived from **16** to give **34**, which underwent facile and efficient cyclization upon heating to give **35** as the only isolable product. Hence, activation of the diene with an ester group enabled the [4 + 2] cycloaddition to proceed to the virtual exclusion of deleterious diene isomerization pathways. The structure of the tricycle **35** was initially based upon nOe studies; however, this assignment was unequivocally confirmed by X-ray analysis of the crystalline salt **36**, which was prepared from **35** by sequential hydride reduction (DIBAL-H) and methylation (MeI).

The successful intramolecular [4 + 2] cycloaddition of **34** clearly established the efficacy of our basic strategy for the synthesis of the manzamine ABC ring core. Moreover, the fact that an electron-withdrawing group on the dienic component facilitated the reaction was consistent with our preliminary hypothesis that the vinylogous imide would behave as an electron-rich dienophile in the Diels−Alder reaction. There remained, however, several major issues that needed to be addressed prior to embarking upon the syntheses of **5** and **1**. For example, we had not yet established a workable provision for an enantioselective synthesis of the target alkaloids. We had also not formulated specific tactics that would optimally enable us to construct the 8- and 13-membered rings. It was now time to focus upon solving these problems.

The commercially available pyroglutaminol **37** emerged as an attractive starting material because the absolute stereochemistry in **37** corresponds to that at C(34) in the manzamine alkaloids. We anticipated that this stereocenter would serve as the pivotal stereochemical control element for introducing all the remaining stereocenters. In the event, **37** was converted in two steps into **38**.[19] Subsequent elaboration of **38** by sequential acylation, hydrogenolysis, and a hydride reduction under

(17) Pandit, U. K.; Brands, K. M. J. *Heterocycles* **1990**, *30*, 257.
(18) Denney, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998.
(19) The enantiomer of **38** is known: Pickering, L.; Malhi, B. S.; Coe, P. L.; Walker, R. T. *Nucleosides & Nucleotides* **1994**, *13*, 1493.

Scheme 7



conditions that enabled concomitant dehydration provided the unsaturated carboxylic acid **40** (Scheme 7). The acid chloride derived from **40** was then coupled with the diene **33** to give **41**. Cyclization of **41** proceeded smoothly to deliver the tricyclic ABC ring intermediate **42** as the only isolable product. The structure of **42** was assigned by NMR spectroscopy, including COSY and nOe experiments, and comparison of its NMR spectra and those of its deprotected derivative **44** (see Figure 1) with those of **35**, the structure of which had been previously established by X-ray analysis of **36**. Removal of the *N*-Boc group from **41** afforded **43**, which underwent cyclization to furnish **44** upon heating overnight at 80 °C. The facility of this intramolecular Diels−Alder reaction lends further support to our original hypothesis that the vinylogous imide serves as an electron-rich dienophile in these cyclizations.

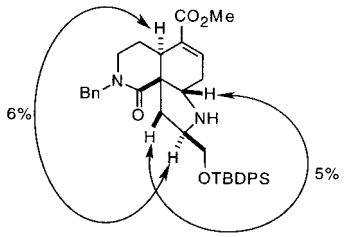
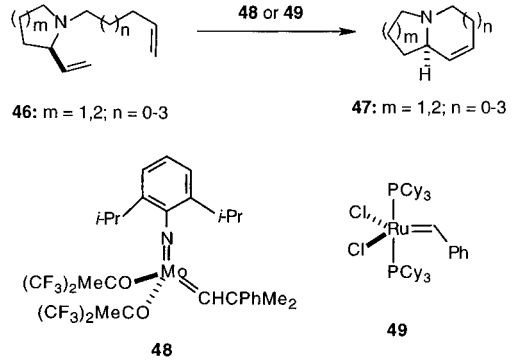


Figure 1. Selected nOes for **44**.

Ultimately, it would be necessary to functionalize C(12) to enable fabrication of the 13-membered ring, so we thought it would be prudent to ascertain whether selective allylic oxidation at C(12) might be achieved. This oxidation proved somewhat troublesome, however, and a number of reagents and conditions were screened with minimal success.[20] We did discover in one preliminary experiment that reaction of **42** with excess CrO_3 in the presence of 3,5-dimethylpyrazole provided the desired unsaturated ketone **45**, albeit in modest yield.[21]

E Ring Synthesis by Ring-Closing Metathesis. Having thus completed the concise, enantioselective assembly of the tricyclic ABC ring core **42** and the derived ketone **45**, it remained to address the equally important issue of developing a tactic for annelating the eight-membered azocine E ring. The methodology then available for effecting such constructions was largely limited to the two obvious possibilities of Wittig and reductive coupling reactions. However, the opportunity for developing new chemistry with such tactics seemed minimal, and hence we were attracted contemporaneously to the timely report by Grubbs, who had just revealed a novel route to monocyclic nitrogen and oxygen heterocycles (5- to 7-membered rings) via the ring-closing metathesis (RCM) of α,ω-dienes.[22] Following this exciting lead, we quickly conducted a series of experiments and established for the first time that fused azabicyclic systems, including those containing 8-membered rings, could be formed by the RCM of dienes having a nitrogen atom in the chain linking the two olefinic subunits (Scheme 8);[23] both the Schrock molybdenum catalyst **48**[24] and the Grubbs ruthenium catalyst **49**[25] were used effectively with different substrates.

Scheme 8



It was apparent at this juncture that monocyclic and bicyclic nitrogen heterocycles could be readily accessed via RCM reactions. However, such cyclizations had never been used in the context of natural product synthesis, and the viability of performing metathesis reactions with highly functionalized substrates was completely unknown. We thus converted **44** in four simple operations into the complex RCM substrate **51** (Scheme 9). When **51** was heated in the presence of the Schrock catalyst **48**, it did indeed undergo facile and efficient cyclization to deliver the tetracyclic product **52** in good yield. It was then obvious that RCM reactions held forth considerable promise in synthetic organic chemistry.

(20) For example, see: (a) Pearson, A. J.; Han, G. R. *J. Org. Chem.* **1985**, *50*, 2791. (b) Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 4665. (c) Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048. (d) Åkermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729. (e) Grennberg, H.; Simon, V.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1994**, 265−266. (f) Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1992**, *57*, 922. (g) Campbell, E.; Martin, J. J.; Bordner, J.; Kleinman, E. F. *J. Org. Chem.* **1996**, *61*, 4806.
(21) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
(22) Grubbs, R. H.; Fu, G. C. *J. Am. Chem. Soc.* **1992**, *114*, 7324.
(23) (a) Martin, S. F.; Liao, Y.; Chen, H.-J.; Pätzel, M.; Ramser, M. *Tetrahedron Lett.* **1994**, *35*, 6005. (b) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (c) Fellows, I.; Kaelin, D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781.
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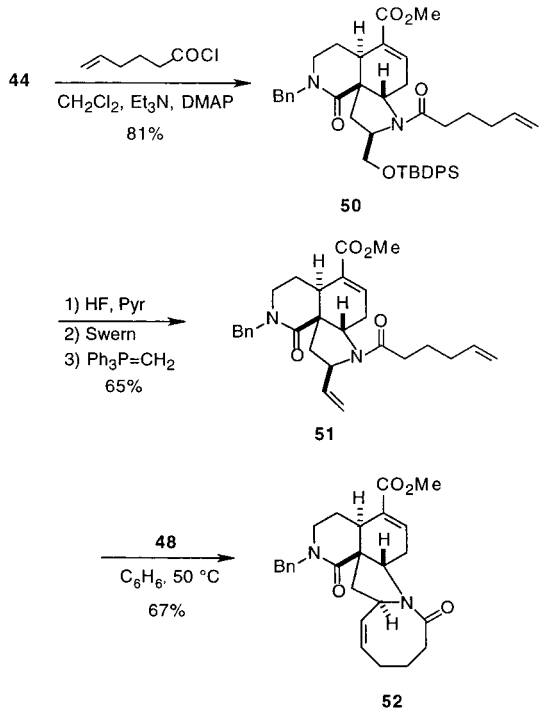
(25) Schwab, P. E.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

Scheme 9

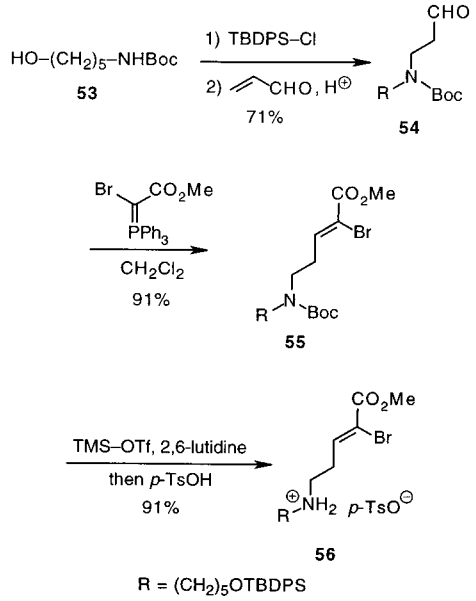


The successes of these early experiments convincingly validated several key aspects of our strategy for the synthesis of the manzamine alkaloids. In particular, we had shown that an intramolecular [4 + 2] cycloaddition of a dienic vinylogous imide related to **8** provided an expeditious entry to the ABC tricyclic core. We had also discovered that a RCM reaction of an α,ω-diene could be implemented to form the eight-membered E ring in a highly functionalized setting. These accomplishments notwithstanding, we recognized that the tetracyclic ABCE subunit **52** was not ideally endowed for facile transformation into ircinal A (**5**), and further refinements of our approach were needed.

Synthesis of the ABC Ring Subunit. We evaluated various options that might lead to an improved synthesis of the ABC ring precursor of manzamine A, and several promising tactics emerged from these deliberations. In our preliminary work, an *N*-benzyl group was ever present on N(21). If this protecting group were replaced at the outset with a functionalized alkyl side chain that could be directly utilized in forming the 13-membered D ring, several unnecessary steps would be eliminated. A five-carbon chain terminated by a protected alcohol group seemed well-suited to the task. Further streamlining of the sequence would eventuate if the Stille and Diels−Alder reactions were performed in a tandem process to fabricate the ABC ring core in a single step from a monocyclic precursor.

Toward realizing these collective objectives, we prepared the diene precursor **56** (Scheme 10). The known protected amino alcohol **53**,[26] which was prepared in one step from commercially available 5-aminopentan-1-ol, was first silylated, and the resulting carbamate was allowed to react with an excess of acrolein in the presence of camphorsulfonic acid to give the aldehyde **54**. Wittig olefination of **54** then proceeded with high

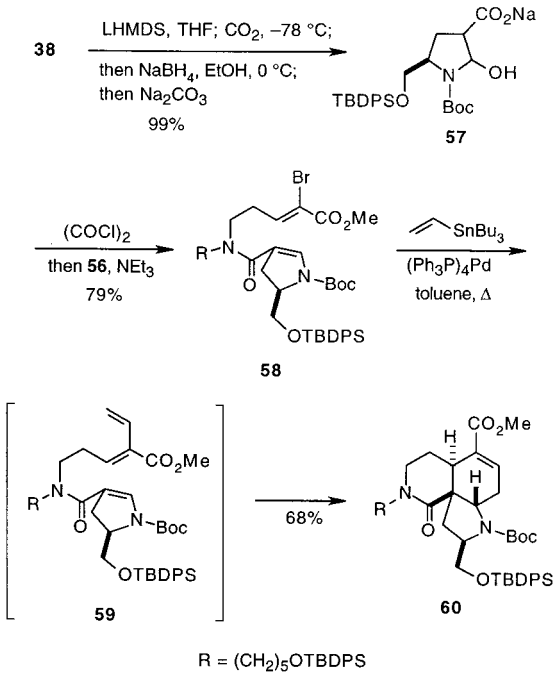
Scheme 10



selectivity to give **55** in 91% yield together with small quantities (7%) of the corresponding *E*-isomer. Subsequent selective removal of the nitrogen protecting group with trimethylsilyl triflate followed by precipitation of the amine with *p*-toluenesulfonic acid afforded the tosylate salt **56** as a stable crystalline solid.[27]

The pyrrolidine **57**, which served as the precursor of the requisite chiral dienophile, was prepared in virtually quantitative yield by a convenient one-pot procedure involving the carboxylation and reduction of the imide **38** (Scheme 11). Although the carboxylic acid derived from **57** could be isolated, it was unstable and suffered facile decarboxylation, whereas the sodium salt **57** could be stored without noticeable decomposition. Sequential reaction of **57** with oxalyl chloride (2.5 equiv) and

Scheme 11



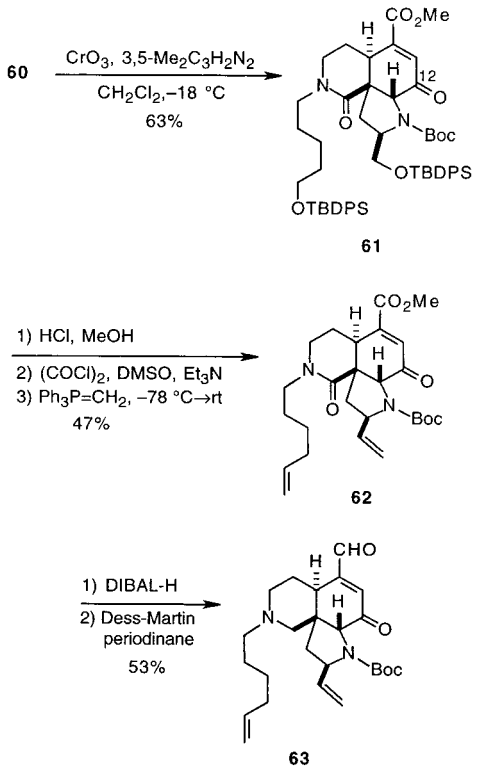
(26) Miyashita, M.; Sato, H.; Yoshikoshi, A.; Toki, T.; Matsushita, M.; Irie, H.; Yanami, T.; Kikuchi, Y.; Takasaki, C.; Nakajima, T. *Tetrahedron Lett.* **1992**, *33*, 2833.

(27) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.

then the free base of **56** afforded **58** (79% overall yield), thereby setting the stage for the critical domino Stille/Diels−Alder reaction. Reaction of **58** with vinyl tributylstannane in the presence of Pd(0) afforded the triene **59**, which underwent an intramolecular [4 + 2] cycloaddition upon continued heating to give solely **60** in 68% overall yield. In this novel sequence, three new carbon−carbon bonds are produced in a single operation, and the lone stereocenter in **58** defined the absolute and relative stereochemistry at the three newly formed stereocenters.

Formation of D and E Rings by RCM. With the key tricyclic intermediate **60** in hand, the stage was set for elaborating the 8- and 13-membered rings. Although there was little precedent for forming 13-membered rings via ring-closing metathesis,[29] we were intrigued by the possibility that both rings might be formed by sequential RCM reactions, perhaps even in a single synthetic transformation. As the first step in this direction, it was necessary to introduce a carbonyl group at C(12) in **60** via allylic oxidation. Optimizing this oxidation using the Salmond protocol we had employed to convert **42** to **45** proved somewhat troublesome, but we eventually discovered that using a large excess of CrO_3 (20 equiv) and 3,5-dimethylpyrazole (30 equiv) provided **61** in 63% yield (80% based upon recovered **60**) (Scheme 12).[21] Use of equimolar ratios of chromium trioxide and dimethylpyrazole led to the formation of imide side products.[30]

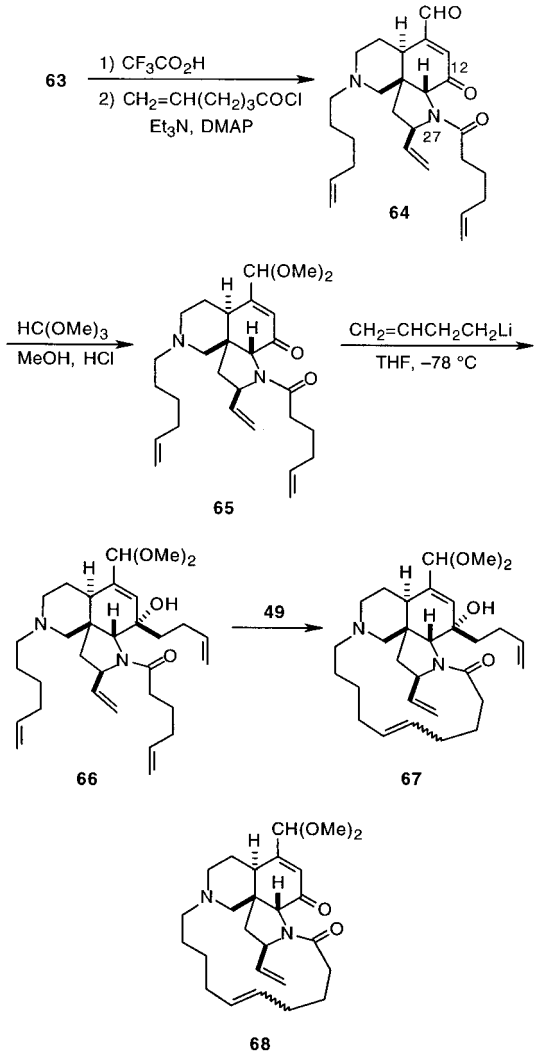
Scheme 12



The two protected primary alcohols in **61** were then refunctionalized in parallel fashion to optimize the overall efficiency. Thus, simultaneous desilylation of the two hydroxyl groups in **61** (84%) and Swern oxidation[31] of the intermediate bis-alcohol furnished a dialdehyde (89%) that underwent a double "salt-free" Wittig reaction under carefully controlled conditions to give **62** (63%).[32] When the Wittig reaction was conducted with other bases and solvents (e.g., *n*-BuLi/THF, NaH/DMSO, etc.), there was incomplete methylenation of the aldehyde function at C(33), and some methylenation of the ketone at C(12) was observed. Even under optimized conditions, small quantities (1−5%) of the trimethylene derivative of **62** were typically isolated. Global reduction of the carbonyl groups in **62** followed by oxidation of the allylic alcohol functions in the resulting diol with Dess−Martin periodinane[33] gave **63** in 53% overall yield.

To probe the feasibility of effecting a double RCM reaction to construct the pentacyclic skeleton of ircinal A in a single operation, it remained to introduce the alkenyl side chains onto C(12) and N(27). Toward this end, **63** was first transformed into **65** by an unoptimized sequence of reactions involving *N*-deprotection, *N*-acylation, and acetal formation (Scheme 13). Stereoselective addition of 3-butenyllithium[34] to **65** then furnished **66**. Despite our naive optimism, several exploratory

Scheme 13



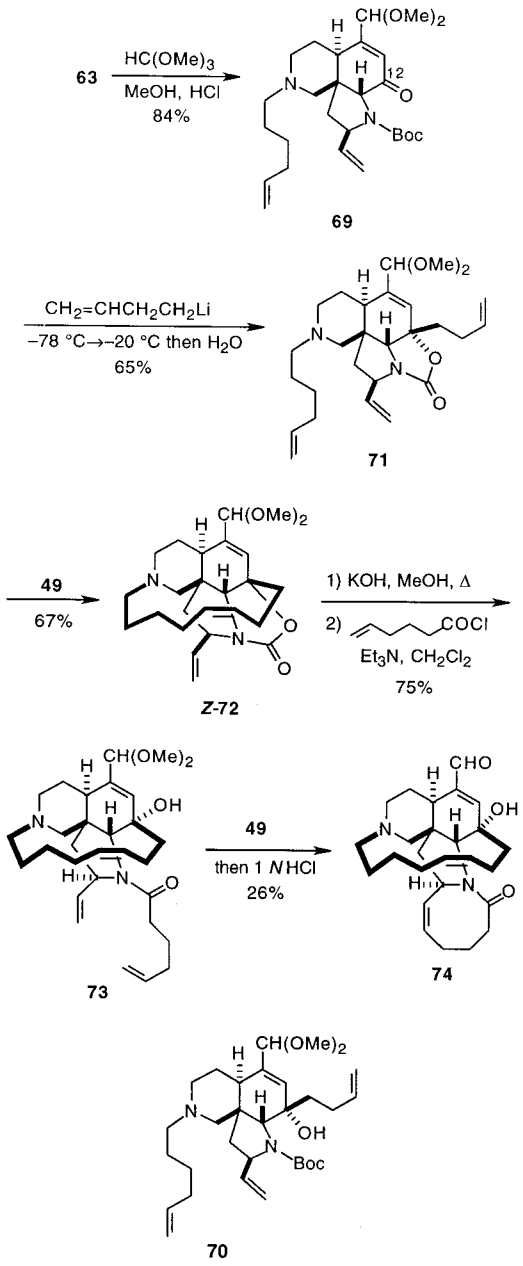
(28) For example, see: Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.
(29) For example, see: (a) Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191. (b) Kamenecka, T. M. Studies Towards the Enantioselective Total Synthesis of Manzamine A, Dissertation, University of California at Irvine, 1996.
(30) For example, see also: Blay, G.; Cardona, L.; Garcia, B.; Garcia, C. L.; Pedro, J. R. *Tetrahedron Lett.* **1997**, *38*, 8257.
(31) Tidwell, T. T. *Synthesis* **1990**, 857.
(32) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.
(33) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

attempts to induce the double RCM of **66** using the Grubbs' ruthenium catalyst **49** afforded no detectable amounts of the desired pentacyclic skeleton of ircinal A. Rather, an inseparable mixture was isolated that contained two compounds tentatively identified as the isomeric tetracyclic olefins **67**. In a subsequent experiment, we discovered that **65** underwent rapid RCM in the presence of Grubbs' catalyst **49** to give **68** as a mixture (ca 1:1) of geometric isomers; the structure of **68** was assigned upon extensive ^{1}H NMR and COSY spectral experiments and mass spectrometry. Addition of 3-butenyllithium to **68** provided a compound that was identical (TLC and MS) to **67**, thereby providing further support for the proposed structure of **67**. The preferential formation of a 15-membered ring by the ring-closing metatheses of **65** and **66** was somewhat surprising for entropic reasons and because we had found that an eight-membered ring was readily produced by the RCM of the closely related substrate **51** (see Scheme 9). Thus, these results serve as a reminder of the problems that may be encountered when preparing eight-membered rings via RCM.

Our inability to marshal a double RCM to form the 8- and 13-membered rings simultaneously simply meant that it would be necessary to elaborate these rings in a serial fashion. Toward this end, the aldehyde function in **63** was selectively protected as a dimethyl acetal to give **69** in 84% yield (Scheme 14). Reaction of **69** with 3-butenyllithium followed by quenching at −78 °C provided **70**. In a preliminary experiment, we discovered that **70** cyclized in the presence of the ruthenium catalyst **49** to give a 13-membered ring, but the reaction was both sluggish and low-yielding. On the other hand, the cyclic carbamate **71**, which was formed by treating **69** with 3-butenyllithium at −78 °C and allowing the reaction to warm to −20 °C prior to quenching, underwent facile RCM with **49** to furnish a mixture of geometric isomers (*Z*/*E* = ca. 8:1) from which ***Z*-72** was isolated in 67% yield. The structure of ***E*-72** was unequivocally established by X-ray crystallography. The preferential formation of the *Z*-isomer stands in contrast to the vast majority of RCM macrocyclizations that afford *E*-isomers as the major products.[35] Because there was evidence that free amines were incompatible with **49**,[36] it is perhaps noteworthy that catalyzing the RCM of **71** with **49** proceeded equally well irrespective of whether the tertiary amino function was protonated.

Hydrolysis of the cyclic carbamate in ***Z*-72** followed by *N*-acylation gave **73** (75% overall yield), thereby setting the stage for forming the eight-membered E ring of the ircinal A skeleton. Although we had previously found that **51** and other 1,9-dienes readily cyclized via RCM to give fused azocines,[9b,23] our experience inducing a double RCM with **66** (vide supra) suggested that the cyclization of **73** to provide **74** might be problematic. This was indeed the case, and forming the E ring proved to be the most difficult step in the synthesis. Under the best conditions identified, cyclization of **73** with an excess of the ruthenium catalyst **49** followed by an aqueous acid workup gave **74** in 26% overall yield.[37] Promoting the RCM with the Schrock molybdenum catalyst **48**, which has sometimes been used with substrates having tertiary alcohol groups,[38] gave lower

Scheme 14

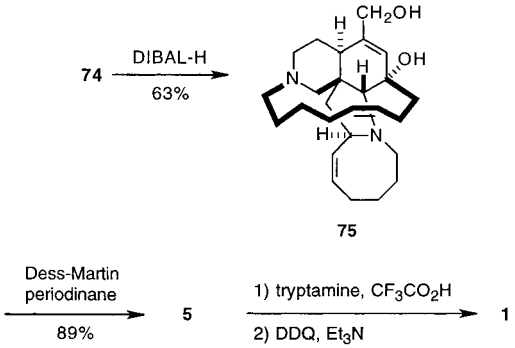


yields of cyclized product. To assess whether the presence of the tertiary hydroxyl or amino groups in **73** might be interfering with the RCM, these functions were protected by trimethylsilylation and protonation, respectively; however, cyclizations of these derivatives of **73** in the presence of either **48** or **49** were no more efficient. Because of rapidly dwindling supplies of **73**, we were unable to explore further the underlying reasons for the difficulties associated with forming the 8-membered ring in **74** via RCM. Perhaps the proximal double bond in the 13-membered ring is involved in competitive metathesis pathways, but this hypothesis remains to be evaluated.

Completion of the Total Synthesis of Manzamine Alkaloids. Reduction of **74** with DIBAL-H gave ircinol A (**75**) (63%),[39,40] which was oxidized with Dess−Martin periodinane to deliver synthetic ircinal A (**5**) (89%) (Scheme 15). The

(34) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (b) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.
(35) See Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blandra, G. *Chem. Eur. J.* **2001**, *7*, 5286 and references therein.
(36) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.
(37) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.
(38) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800. (b) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746.
(39) Tsuda, M.; Kawasaki, N.; Kobayashi, J. *Tetrahedron* **1994**, *50*, 7957.

Scheme 15



synthetic ircinal A thus obtained gave a ^{1}H NMR spectrum that was consistent with that of natural material, a ^{13}C NMR spectrum that matched the published data,[3] and a specific rotation that corresponded to previous reports {$[\alpha]_D$ +48° (*c* 0.07, $CHCl_3$); lit.[3] $[\alpha]_D$ +48° (*c* 2.9, $CHCl_3$); lit.[7] $[\alpha]_D$ +46° (*c* =0.23, $CHCl_3$)}. Inasmuch as we did not have an authentic sample of ircinal A, the identity of synthetic **5** was established by converting a small quantity into **1** following the published protocol of Kobayashi;[3] the material thus obtained exhibited the same properties (TLC, HPLC, ^{1}H NMR, HRMS) as an authentic sample of natural manzamine A.

Conclusions

We have thus completed the enantioselective syntheses of manzamine A (**1**) and the related manzamine alkaloids ircinol A (**75**) and ircinal A (**5**). The synthesis of **5** required a total of 24 operations from commercially available starting materials, and the longest linear sequence was only 21 steps. The concise approach detailed herein highlights a novel strategy for assembling the tricyclic ABC ring core by a domino Stille/Diels−Alder reaction. An unusual aspect of the key intramolecular Diels−Alder cycloaddition was the use of a vinylogous *N*-acyl urea as the dienophile. The synthesis of these complex indole alkaloids also demonstrates the power and versatility of RCM reactions for constructing 13- and 8-membered heterocyclic rings in highly functionalized settings, although the potential limitations of using RCM for forming 8-membered rings are also evident. Whether these deficiencies may be overcome with more recent generations of RCM catalysts or other experimental tactics must be established by further experimentation. Other applications of RCM to the syntheses of alkaloid natural products are being broadly pursued in our laboratories, and the results of these investigations will be reported in due course.

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Supporting Information Available: Experimental and full characterization of all new compounds (PDF) and X-ray data (CIF) for compounds **20**, **36**, and ***E*-72**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0202964

(40) The positive optical rotation originally observed for the reduction product (DIBAL-H) of natural ircinal A that led to the assignment of the antipodal structure for natural ircinol A has recently been reexamined by Professor Kobayashi and found to be incorrect (personal communication). Natural ircinol A and ircinal A thus have the same absolute configuration.