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# Synthetic study of manzamine B: synthesis of the tricyclic central core by an asymmetric Diels–Alder and RCM strategy

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**Abstract**—Tricyclic core of manzamine B was successfully synthesized through asymmetric Diels–Alder reaction and RCM strategy. Cr–salen–F complex was found to be the most effective catalyst in DA reaction of aminodienes with heterocyclic dienophiles to give up to 97% ee. In the construction of 11-membered ring by RCM, first-Grubbs cat. gave better stereoselectivity.


Manzamine B (**1**) was isolated in 1987 by Higa and coworkers from the marine sponge *Haliclona* sp., collected at Okinawa (Fig. 1).[1] Its unique structure, which contains a β-carboline and tetracyclic ring system, such as a hydroisoquinoline core and 11- and 13-membered azacycles with (*Z*)-olefins, is a highly challenging target in synthetic organic chemistry. While its biological activity, such as cytotoxicity against P388 mouse leukaemia cells ($IC_{50}$ 6 μg/mL), has been reported,[1] a good supply of this material is required for a complete survey of its biological activity.

In contrast to manzamine A (**2**),[2] the total synthesis of which has been described by Winkler and Martin,[3] there has been no previous report on the synthesis of **1**. We describe here our model study focusing the asymmetric synthesis of the ABC ring system of manzamine B (**1**).

Our retrosynthetic analysis of **1** is outlined in Scheme 1. The introduction of a β-carboline core and epoxy ring will be set at a late stage of the total synthesis.[4,5] Therefore, ircinal B (**3**) is regarded to be a precursor of **1**. (*Z*)-Selective formation of both the C and D rings should be achieved by ring-closing metathesis (RCM) using the corresponding α,ω-dienes **5** and **7**, respectively. Therefore, we can consider hydroisoquinoline (**8**) as a key intermediate, which should be synthesized by the Diels–Alder (DA) method. Through a synthetic study of manzamine A (**2**) and (−)-nakadomarin A (**4**),[6] we have already studied the synthesis of chiral hydroisoquinoline derivatives using the DA reaction. This methodology was quite efficient for access to a cyclic core with a cis functional-group arrangement that is favorable for the total synthesis. In this synthetic study of manzamine B (**1**), an asymmetric DA reaction could be used to construct the chiral hydroisoquinoline core (AB ring) while controlling three consecutive stereocenters and introducing a key nitrogen functionality for C-ring formation. An asymmetric DA reaction using amino-siloxydienes catalyzed by chromium(III)–salen complex[7] developed by Rawal[8] would be suitable for this purpose. DA precursors of **9** and **10** are easily prepared from commercially available compounds such as **11**–**13**, respectively.

The substrates for the asymmetric DA reaction were prepared by the following procedure (Scheme 2). Demethylation of **11** by 1-chloroethyl chloroformate,[9] followed by N-protection with benzenesulfonyl (Bs) chloride, gave dehydropiperidine ester (**14**). Subsequent reduction by DIBAL followed by Swern oxidation of the resulting alcohol gave dienophile (**9**) in 73% overall yield in six steps from **11**. N-Protected aminodienes such as **10a**,**b** were prepared by Rawal's protocol,[8c] and the synthesis of **10c**,**d** was achieved by its modification.[10]

Only two cyclic dienophiles were tested in the asymmetric DA reaction under Rawal's conditions and they were reported to have lower reactivities compared to acyclic

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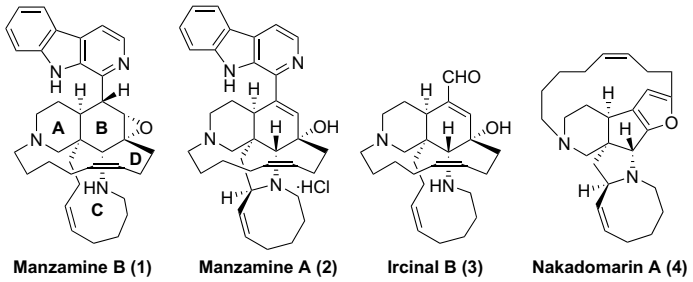
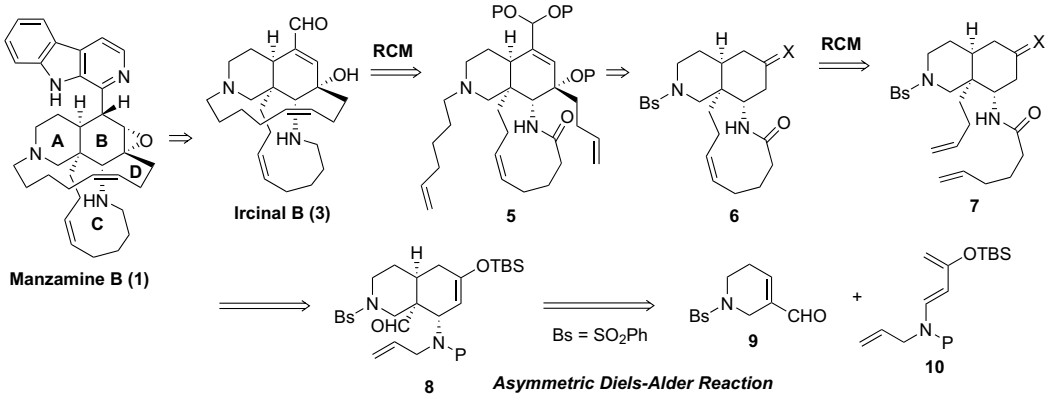
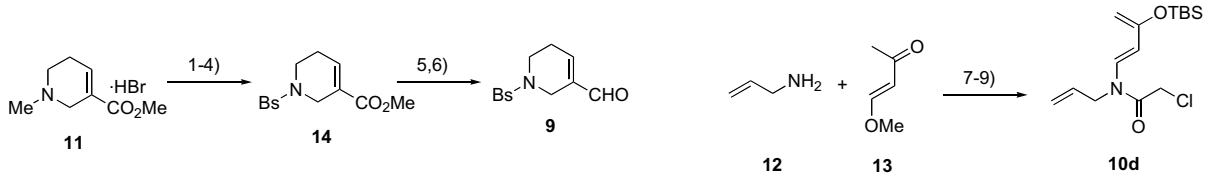



**Figure 1.** Structure of manzamine alkaloid.




**Scheme 1.** Retrosynthetic analysis of **1**.

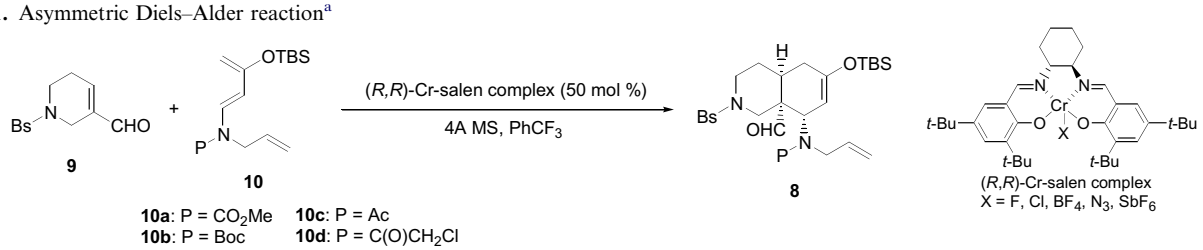



**Scheme 2.** Synthesis of dienophile (**9**) and aminodiene (**10**). Reagents and conditions: (1) satd $NaHCO_3$, (2) $ClCO_2CH(Cl)CH_3$, DCE, (3) MeOH, reflux, (4) BsCl, $Et_3N$, DCM. 90% (4 steps), (5) DIBAL, $PhCH_3$, (6) Swern oxidation, 81% (2 steps), (7) DCM, (8) $ClCH_2COCl$, pyridine, DCM, 0–30 °C, (9) TBSOTf, $Et_3N$, DCM, 79% (3 steps).

dienophiles.[8a,d] Since there have been no reports on the use of a heterocyclic dienophile, we started to investigate the reactivity of **9** in detail using four types of *N*-acyl-aminodienes (**10a–d**) (Table 1, entries 1–4). When **9** was stirred with 2 equiv of **10a** for 72 h with 50 mol % of (*R*,*R*)-Cr–salen–F complex[7d] in benzotrifluoride ($PhCF_3$), which was the best solvent of choice, cycloadduct (**8a**) was obtained in 70% yield with 92% ee (entry 1). Although the use of *N*-Boc aminodiene (**10b**) gave **8b** in 58% yield, the reaction had to proceed for 282 h, probably because of bulkiness of its protecting group (entry 2). The reaction of amide-type aminodienes (**10c**,**d**) gave cycloadducts (**8c**,**d**) within a shorter reaction time compared to **10a** and **10b**. In particular, the DA reaction using *N*-chloroacetyl aminodiene (**10d**) gave the best result (entry 4). Furthermore, we found that the reactivity and enantiomeric excess each depended on the counter anions in chiral Cr–salen complexes. For example, the reaction using Cr–salen–F complex[7d] (50 mol %) gave **8d**[11] in 77% yield with 93% ee within 20 h (entry 4). Other Cr–salen complexes with Cl, $BF_4$, $N_3$, and $SbF_6$ as counter anions gave a slow reaction or a low ee compared to entry 4 (entries 5–8). Under reflux conditions, the reaction proceeded faster and gave **8d** in 52% yield with 79% ee within 2.5 h (entry 9). The reaction at 0 °C gave **8d** in 58% yield with the highest ee within 64 h (entry 10). Competitive decomposition of aminodiene (**10d**) was always observed under the reaction conditions because of the Lewis acidity of Cr–salen complexes. Thus, the use of 1 equiv of **10d** decreased the chemical yield to 41% (entry 11). Under reduced catalyst loading of Cr-complex (25 mol %), **8d** was obtained in 58% yield without any loss of ee (entry 12). The absolute stereochemistry of **8d** (>99% ee, $[\alpha]_D^{23}$ +97 (*c*, 0.5, $CHCl_3$), mp 166–169 °C) was determined by X-ray crystallographic analysis, based on an anomalous dispersion effect (Fig. 2). All three of the stereocenters were assigned to be *S*, in accord with natural manzamine B (**1**).

With the key intermediate (**8d**) in hand, we next investigated the construction of an 11-membered azacycle (ring C) by RCM (Scheme 3).[12] Olefination of a formyl group in **8d** was unsuccessful, since the formyl carbon was

**Table 1.** Asymmetric Diels–Alder reaction[a]




**10a**: P = $CO_2Me$ **10c**: P = Ac
**10b**: P = Boc **10d**: P = $C(O)CH_2Cl$

| Entry | Substrate | Cr–salen–X | Temperature (°C) | Time (h) | Product | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | **10a** | X = F | rt | 72 | **8a** | 70 | 92 |
| 2 | **10b** | X = F | rt | 282 | **8b** | 58 | — |
| 3 | **10c** | X = F | rt | 42 | **8c** | 57 | — |
| 4 | **10d** | X = F | rt | 20 | **8d** | 77 | 93 |
| 5 | **10d** | X = Cl | rt | 87 | **8d** | 65 | 75 |
| 6 | **10d** | X = $BF_4$ | rt | 20 | **8d** | 65 | 88 |
| 7 | **10d** | X = $N_3$ | rt | 160 | **8d** | 12 | 89 |
| 8 | **10d** | X = $SbF_6$ | rt | 87 | **8d** | 0 | — |
| 9 | **10d** | X = F | 102 | 2.5 | **8d** | 52 | 79 |
| 10 | **10d** | X = F | 0 | 64 | **8d** | 58 | 97 |
| 11 | **10d** | X = F | rt | 20 | **8d** | 41 | 90 |
| 12[b] | **10d** | X = F | rt | 38 | **8d** | 58 | 93 |

[a] All reaction was carried out in the ratio of **9** and **10** (1:2) except entry 11 (1:1).
[b] 25 mol % of Cr–salen-complex was employed.

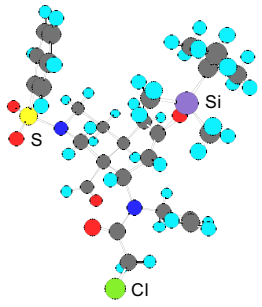
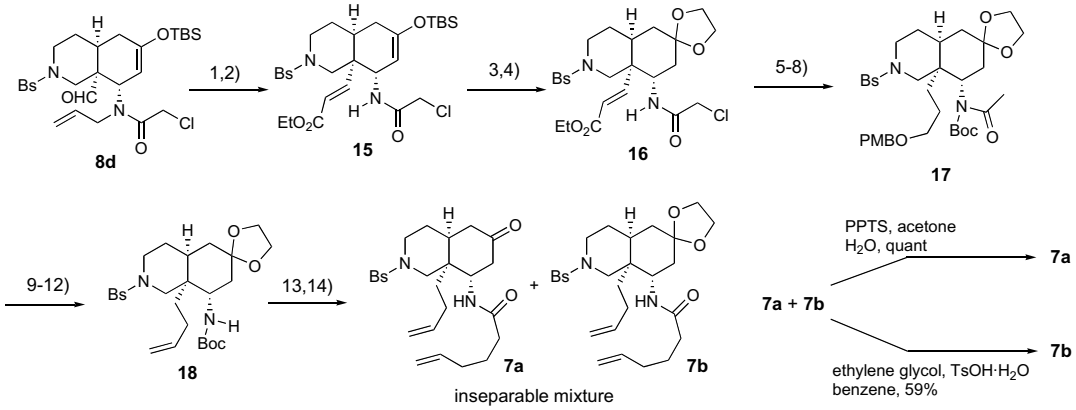


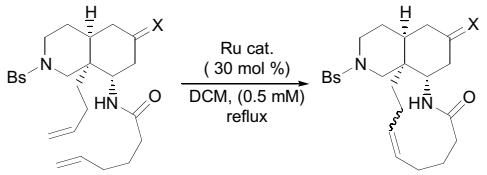

**Figure 2.** X-ray structure of **8d**.

located at a neopentyl position and suffered from steric hindrance by the adjacent nitrogen functionality. Therefore, the *N*-allyl group was first removed using the Pd-catalyzed deallylation reported by Nagakura.[13] A modified Horner–Wadsworth–Emmons reaction[14] was successfully applied to give **15** in 88% yield. Silyl enol ether was then converted to cyclic ketal (**16**) in 97% yield (2 steps). Subsequent hydrogenation followed by reduction of ester carbonyl and chloroacetyl moieties using $LiBH_4$ gave a *N*-acetyl primary alcohol, which was converted to **17** in excellent yield through protection of the hydroxyl group to PMB ether followed by *N*-Boc imide formation. After deprotection of the PMB group by DDQ, the resulting primary alcohol was converted to olefin by a standard method. The acetyl group was removed by treatment with CsOH to give **18** in 65% overall yield in five steps. Deprotection of the Boc group followed by acylation with hexenoyl chloride gave




**Scheme 3.** Conversion of DA adduct to α,ω-dienes (**7a**,**b**). Reagents and conditions: (1) $TolSO_2H$, $Pd(PPh_3)_4$, DCM, 91% (2 cycles), (2) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, MeCN, 88%, (3) HF–pyridine MeCN, 99%, (4) ethylene glycol, TsOH, benzene, 98%, (5) $H_2$, 5% Pd/C, MeOH, 99%, (6) $LiBH_4$, THF, quant, (7) NaH, PMBCl, THF, 90%, (8) $Boc_2O$, DMAP, $Et_3N$, THF, (9) DDQ, DCM–acetone (18:1), (10) Swern oxidation, (11) $Ph_3PCH_3Br$, *t*-BuOK, THF, (12) 50% CsOH, THF, 65% (5 steps), (13) TFA, DCM, (14) 5-hexenoyl chloride, $Et_3N$, DCM, 86% (2 steps, **7a**:**7b** = 4.7:1).

**Table 2.** C-ring formation using RCM

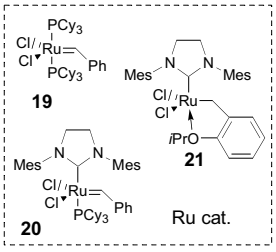



**7a**: X = O
**7b**: X = -O(CH$_2$)$_2$O-

**6a**: X = O
**6b**: X = -O(CH$_2$)$_2$O-

| Entry | Substrate | Ru cat. | Time (h) | Yield of **6**[a] (%) | |
|---|---|---|---|---|---|
| | | | | (*Z*)-**6** | (*E*)-**6** |
| 1 | **7a** | **19** | 5 | 39 | 11 |
| 2 | **7a** | **20** | 7 | 23 | 43 |
| 3 | **7a** | **21** | 7 | 32 | 28 |
| 4 | **7b** | **19** | 4 | 64 | 23 |
| 5 | **7b** | **20** | 6 | 9 | 22 |
| 6 | **7b** | **21** | 6 | 23 | 14 |

[a] Yields were determined by $^1$H NMR (entries 1–3) or isolated yield of **6b** (entries 4–6).




the desired α,ω-diene **7a** with **7b** as an inseparable mixture. Therefore, the mixture was treated with PPTS or ethylene glycol in the presence of TsOH·H$_2$O to give pure **7a** and **7b**, respectively.

The obtained dienes **7a**,**b** were exposed to RCM conditions (Table 2). The RCM reaction using **7a** with 30 mol % of first-generation Grubbs catalyst (**19**) gave **6a** as a separable mixture of (*E*)- and (*Z*)-isomers, and the desired (*Z*)-**6a** was obtained in 39% yield (entry 1). The cyclizations using second-generation Grubbs catalyst (**20**) and Hoveyda–Grubbs catalyst (**21**) showed no obvious improvement (entries 2 and 3). The reaction of **7b** in the presence of **19** gave **6b** in 87% yield and the desired (*Z*)-isomer was observed as a major product by $^1$H NMR[15] (entry 4), while (*E*)- and (*Z*)-**6b** were inseparable. The reactions using **20** or **21** were less effective compared to entry 4 (entries 5 and 6). Interestingly, remote functional groups (the carbonyl or ketal group in B-ring) can influence the selectivity of the RCM reaction.

In conclusion, we have constructed the tricyclic core of manzamine B (**1**) through DA and RCM strategies. The key asymmetric DA reaction proceeded efficiently in a highly enantioselective fashion (up to 97% ee) with complete stereocontrol using a Cr–salen–F complex. In the RCM reaction, the desired (*Z*)-11-membered ring was selectively formed in high yield. Further studies toward the total synthesis of manzamine B are currently underway.

## Acknowledgement

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10. Because the reaction of *N*-acylallylamine with **13** was unsuccessful, the modified preparation of **10c**,**d** was established via condensation, acylation, and silyl etherification.
11. Optically pure **8d** [>99.9% ee, determined by HPLC using DAICEL CHIRALCEL OD (hexane/*i*PrOH = 95:5, flow rate: 1.0 mL/min, retention time: 23.8 and 28.6 min)] could be obtained by recrystallization from MeOH.
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15. Both (*Z*)- and (*E*)-**6b** were identified by deprotection and separation to pure (*Z*)- and (*E*)-**6a**, respectively.