

## Total Synthesis of (+)-Manzamine A

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**Abstract:** A novel synthetic route to (+)-manzamine A was developed. It highlights an amazingly efficient construction of a highly strained 15-membered ring across a cyclohexenone ring with the aim of installing the requisite functionalities in a completely stereocontrolled manner. Other key features include a stereoselective Diels–Alder reaction of an optically active butenolide, construction of the 15-membered ring by intramolecular Mitsunobu reaction of a nosyl amide, [3,3]-sigmatropic rearrangement of allyl cyanate for stereoselective introduction of nitrogen functionality at a sterically congested position, and a ring-closing metathesis in the presence of labile functional groups.

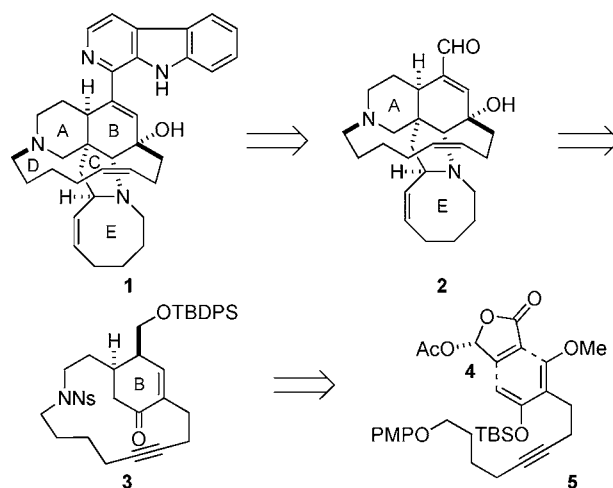
Manzamine A (**1**), which has been isolated from marine sponges of the genera *Haliclona*<sup>1</sup> and *Pellina*,<sup>2</sup> exhibits broad biological activity, including cytotoxic,<sup>1</sup> antibacterial,<sup>2</sup> antimalarial,<sup>3</sup> insecticidal,<sup>4</sup> anti-inflammatory,<sup>5</sup> and anti-HIV.<sup>6</sup> The combination of the outstanding biological activity and unique structure of manzamine A has driven a number of synthetic studies aimed at the construction of the pentacyclic core skeleton<sup>7</sup> of ircinal A (**2**), a known precursor of **1**.<sup>8</sup> Despite intensive investigations, including those conducted in our laboratories,<sup>9e</sup> only three total syntheses have been reported to date.<sup>9</sup> Herein, we report a total synthesis of (+)-**1** in which a unique 15-membered ring intermediate was employed.

As illustrated in our retrosynthetic analysis (Scheme 1), we envisioned that the bicyclic ketone **3** would be ideal for controlling the stereochemistry of all of the stereogenic centers on ring B and for stereoselective introduction of a C1 unit to build ring A. A powerful nosyl chemistry could be applied for the construction of the strained 15-membered ring.<sup>10</sup> Ring B in turn would be constructed by the Diels–Alder reaction between butenolide **4**, which is readily available in almost optically pure form,<sup>11</sup> and siloxydiene **5**.

Execution of the above strategy required the preparation of vinyllogous ester **9** (Scheme 2). Alcohol **7**, prepared from known bromide **6**,<sup>12</sup> was converted to diol **8** in a three-step sequence involving iodination, alkylation with methyl acetoacetate, and reduction of both carbonyl groups. Dess–Martin oxidation of the 1,3-diol in the presence of *t*-BuOH, which promoted the second oxidation, and subsequent one-pot esterification afforded **9**. Initial attempts to perform the Diels–Alder reaction between siloxydiene **5**, which was readily prepared from **9**, and **4** met with limited success because of the extreme lability of **5** to moisture. However, addition of a solid base such as sodium acetate and molecular sieves proved to block hydrolysis of **5**, affording **10** in 97% yield. Methanolysis of acetoxy lactone **10** gave a mixture of hydroxylactone and aldehyde, but they were converted to the same methyl ester **11** by a one-pot Wittig reaction and methylation.

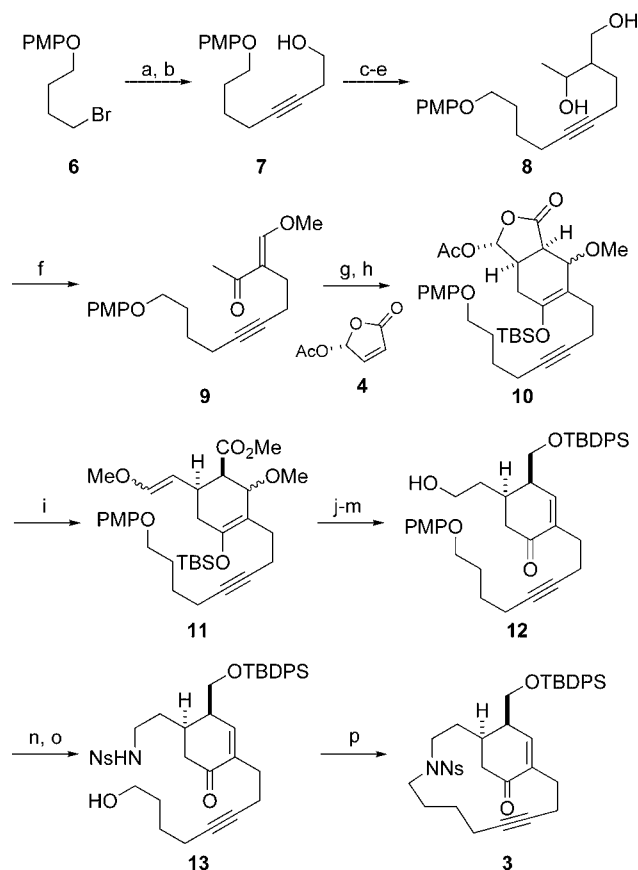
Reduction of the methyl ester, protection of the resulting alcohol, hydrolysis of the enol ethers, and then selective NaBH(OAc)<sub>3</sub> reduction of the aldehyde in the presence of the enone afforded

Scheme 1

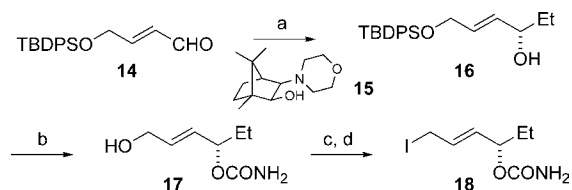


**12.** Introduction of an amine functional group by Mitsunobu reaction followed by a one-pot deprotection of the Boc group and the PMP group afforded **13**. With alcohol **13** in hand, we next focused on the formation of the 15-membered ring by performing an intramolecular Mitsunobu reaction. Although the target molecule was a highly strained 15-membered ring containing a cyclohexenone ring and an alkyne, the macrocyclization proceeded smoothly without the need for high dilution, affording **3** in good yield.

Our next challenge was to construct the quaternary stereogenic center. Initial attempts to construct ring A from the amine derived from **3** by means of Mannich reaction with formaldehyde<sup>13</sup> met with failure, primarily because of steric problems. In another approach, conversion of **3** to the corresponding  $\beta$ -ketoester followed by direct introduction of ring E was attempted. However, the reactivity of the  $\beta$ -ketoester was so poor that allyl iodides were the only electrophiles that could be used in practice. Thus, we decided to pursue a [3,3]-sigmatropic rearrangement of allyl cyanate for stereoselective introduction of the nitrogen functionality (Scheme 4).<sup>14</sup> Allyl iodide **18** was chosen as a key electrophile for accessing the substrate for the sigmatropic rearrangement (Scheme 3). Enantioselective addition of diethylzinc<sup>15</sup> to known aldehyde **14**<sup>16</sup> afforded the desired alcohol **16** in 93% ee. Introduction of a carbamate group and then deprotection and iodination of the primary alcohol followed by recrystallization afforded enantiomerically pure iodide **18**. According to Mander's protocol,<sup>17</sup> ketone **3** was converted to a  $\beta$ -ketoester, which was subjected to allylation with **18** (Scheme 4). As expected, stereoselective alkylation occurred from the sterically less crowded  $\alpha$ -face to give a single product.<sup>18</sup> Similarly, treatment with TBHP and Triton B afforded epoxyketone **19** as a single diastereomer.<sup>19</sup> Upon dehydration of **19** with TFAA and Et<sub>3</sub>N,<sup>20</sup> the critical [3,3]-sigmatropic rearrangement proceeded even at 0 °C to give the corresponding isocyanate with complete control of the stereochemistry. For construction of ring C, the

Scheme 2<sup>a</sup>

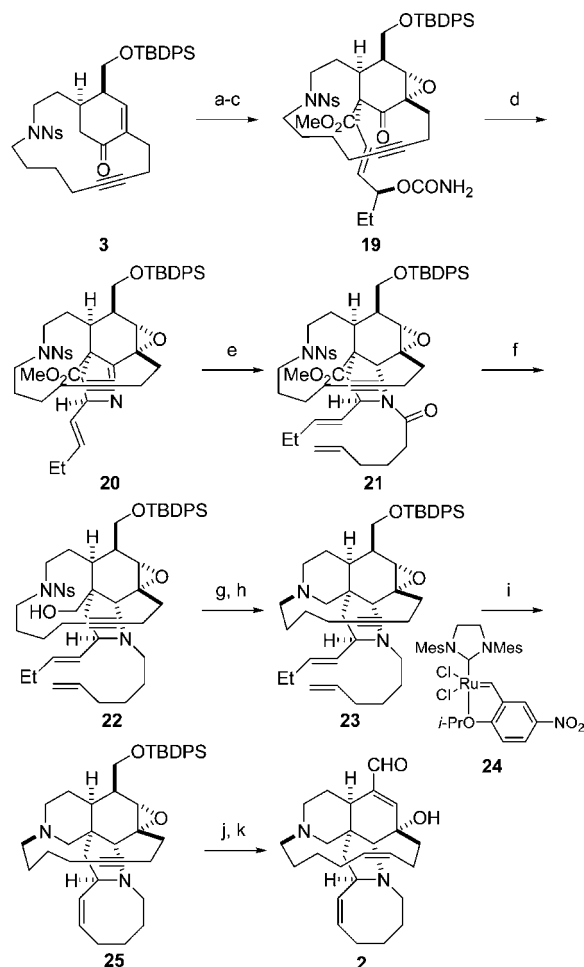
<sup>a</sup> Reaction conditions: (a) *n*-BuLi, THPO(CH<sub>2</sub>)<sub>2</sub>CCH, TMEDA, *n*-Bu<sub>4</sub>Ni, THF/HMPA, -78 °C to rt, 91%. (b) CSA, MeOH, rt, 93%. (c) I<sub>2</sub>, PPh<sub>3</sub>, imidazole, CH<sub>3</sub>CN/Et<sub>2</sub>O, 0 °C to rt, 97%. (d) Methyl acetoacetate, NaH, THF, reflux, 86%. (e) LiAlH<sub>4</sub>, THF, rt, 91%. (f) Dess–Martin periodinane, *t*-BuOH, CH<sub>2</sub>Cl<sub>2</sub>, rt; *p*-TsOH·H<sub>2</sub>O, Na<sub>2</sub>SO<sub>4</sub>, MeOH, rt, 66%. (g) TBSOTf, Et<sub>3</sub>N, Et<sub>2</sub>O, 0 °C. (h) **4**, NaOAc, toluene, MS3A, reflux, 97% (two steps, endo/exo = 2:1). (i) Et<sub>3</sub>N, MeOH, rt; evaporation; MeOCH<sub>2</sub>PPh<sub>3</sub>Cl, KHMDS, THF, -78 to 0 °C; MeI, *i*-Pr<sub>2</sub>NEt, DMF, 0 °C, 89% (*E/Z* = 1:1 for endo, 1:4 for exo). (j) LiAlH<sub>4</sub>, Et<sub>2</sub>O, 0 °C, 99%. (k) TBDPSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, rt, 99%. (l) *p*-TsOH·H<sub>2</sub>O, acetone, rt, 97%. (m) NaBH(OAc)<sub>3</sub>, AcOH, benzene, 40 °C, 88%. (n) NsNH(Boc), DEAD, PPh<sub>3</sub>, benzene, rt, 97%. (o) TFA, rt; evaporation; CAN, CH<sub>3</sub>CN/H<sub>2</sub>O, 0 °C, 81%. (p) DEAD, PPh<sub>3</sub>, toluene (0.01M), rt, 85%.

Scheme 3<sup>a</sup>

<sup>a</sup> Reaction conditions: (a) **15** (8 mol %), Et<sub>2</sub>Zn, hexane/toluene, -10 °C, 75%, 93% ee. (b) Cl<sub>3</sub>CCONCO, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; evaporation; Et<sub>3</sub>N, MeOH, rt; evaporation; TBAF, THF, 50 °C, 99%. (c) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C. (d) NaI, acetone, 50 °C, 51% (two steps), >99% ee.

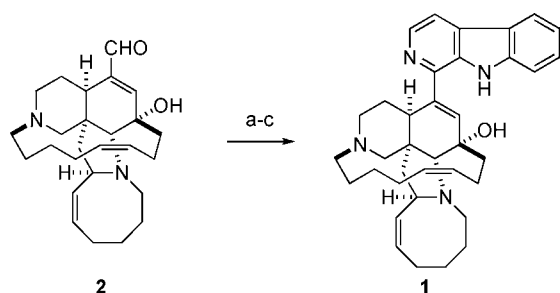
resultant isocyanate had to be converted to imine **20** under anhydrous conditions because **20** was susceptible to hydrolysis even under neutral conditions, triggering irreversible lactamization with the methyl ester. After extensive experimentation, we found that treatment of the isocyanate with AcOH and magnesium perchlorate in the presence of molecular sieves enabled the desired transformation.

Subsequent reduction of imine **20** and acylation with 5-hexenoyl chloride<sup>21</sup> afforded amide **21**. At this stage, a ring-closing metathesis

Scheme 4<sup>a</sup>

<sup>a</sup> Reaction conditions: (a) LHMDS, THF, -78 °C; NCCO<sub>2</sub>Me, -78 °C to rt. (b) **18**, K<sub>3</sub>PO<sub>4</sub>, DMF, rt, 69% (two steps). (c) TBHP, Triton B, CH<sub>3</sub>CN/benzene, rt, 62%. (d) TFAA, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; evaporation; AcOH, Mg(ClO<sub>4</sub>)<sub>2</sub>, benzene, 40 °C. (e) NaBH(OACF<sub>3</sub>)<sub>3</sub>, THF, rt; TFA; 5-hexenoyl chloride, Et<sub>3</sub>N, 0 °C, 80% (two steps). (f) LiAlH<sub>4</sub>, AlCl<sub>3</sub>, Et<sub>2</sub>O, -20 to -10 °C, 93%. (g) IBX, *t*-BuOH, 70 °C. (h) PhSH, Cs<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, 50 °C; NaBH(OACF<sub>3</sub>)<sub>3</sub>, THF, rt, 89% (two steps). (i) **24** (1.0 equiv), PMPOH, CH<sub>2</sub>Cl<sub>2</sub> (1 mM), rt, 41%. (j) TBAF, THF, 50 °C; evaporation; H<sub>2</sub>, Lindlar's catalyst, quinoline, MeOH, rt, 84%. (k) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, rt, 87%.

reaction for construction of ring E was attempted. Unfortunately, because of the rapid isomerization of the terminal alkene, the ring-closing metathesis reaction of substrate **21** afforded a significant amount of the undesired seven-membered ring. Thus, we decided to construct ring A prior to formation of ring E. While ring A was constructed by lactamization, all attempts to reduce the lactam were unsuccessful because of steric congestion. A reductive amination was therefore employed to form ring A. In the event, the methyl ester and amide groups were simultaneously reduced with a combination of lithium aluminum hydride and aluminum chloride to preserve the nitro group in the nosyl amide. IBX oxidation of **22** in *tert*-butyl alcohol,<sup>22</sup> removal of the nosyl group, and reduction of the resultant hemiaminal afforded diamine **23**. The last crucial step of the synthesis was the ring-closing metathesis reaction of diamine **23**. Although isomerization of the terminal alkene was not observed, participation of the tertiary amines<sup>23</sup> and the alkyne were the major problems. After extensive efforts, reproducible results were obtained when complex **24**<sup>24</sup> was utilized in the presence of *p*-methoxyphenol,<sup>25</sup> giving the eight-membered ring **25** in 41% yield. With the pentacyclic core constructed, simple functional group

Scheme 5<sup>a</sup>

<sup>a</sup> Reaction conditions: (a) tryptamine·TFA, CH<sub>2</sub>Cl<sub>2</sub>, MS3A, rt. (b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, rt. (c) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/benzene, rt, 75% (three steps).

manipulations were needed to complete the total synthesis of ircinal A (**2**). One-pot removal of the TBDPS group and partial reduction of the alkyne afforded a *cis*-alkene. Subsequent Dess–Martin oxidation caused opening of the epoxide to give **2**.<sup>26</sup>

Ircinal A was converted to manzamine A<sup>8</sup> by a modified procedure (Scheme 5). During our investigation of the Pictet–Spengler reaction, we found that the condensation of **2** with tryptamine and the subsequent cyclization required completely different acidic conditions. An efficient conversion of **2** to tetrahydromanzamine A was achieved when these reactions were conducted separately. Subsequent DDQ oxidation was hampered by incomplete conversion, which could eventually be solved by the use of DDQ recrystallized from dichloromethane. Manzamine A (**1**) was thus obtained in 75% overall yield from **2**.

In conclusion, an enantioselective total synthesis of manzamine A (**1**) from known, readily available compounds has been accomplished. Our synthesis highlights a unique strategy for controlling the stereochemistry of the six-membered ring that involves bridging it with a highly strained macrocycle. Other key features of the synthesis include a stereoselective Diels–Alder reaction of butenolide **4**, construction of a 15-membered ring by Mitsunobu reaction of a nosyl amide, [3,3]-sigmatropic rearrangement of allyl cyanate for stereoselective introduction of nitrogen functionality at a sterically congested position, and a ring-closing metathesis in the presence of labile functional groups.

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**Supporting Information Available:** Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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