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NOTE

Furan-iminium cation cyclization (FIC) in a total synthesis of manzamine alkaloids

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Furans are highly electron-rich aromatic compounds and this structure is often found in natural products and medicines. Furans are also useful as a four-carbon unit with oxygen functionalities, and are used in organic syntheses as a building block.[1,2] In 2003, we reported the first total synthesis of nakadomarin A (**1**),[3] a manzamine alkaloid containing a furan ring. In this synthesis, we first reported that a new type of furan-iminium cation cyclization (FIC)[4,5] through intermediate [**A**] was highly effective for constructing the central core of nakadomarin A (Figure 1). In the structure of intermediate [**A**], the 3-position of the furan ring was directly bound to a spiro-ring system, and cyclization occurred at the 2-position of the furan ring to give the tetracyclic core of nakadomarin A.

Since then, we have been studying a new version of FIC in which a furan ring is connected to the spiro-ring system at the 2-position with a two-carbon tether, shown as [**B**]. This intermediate also cyclized to give spiro-tetracyclic products **4** efficiently with complete regio- and stereoselectivity.[6] The ABC tricyclic core of ircinal A (**3**), including a tetra-substituted stereogenic center, could be constructed by this procedure. Based on model studies, we started a total synthesis of manzamine A (**2**),[7–14] which shows potent biological activities, such as anticancer, antibacterial and antimalarial activities, and related alkaloids such as ircinal A, a key synthetic and biogenetic precursor for manzamine A.

Based on this strategy, a new synthetic route is shown in Scheme 1. Among the five rings in the structure of ircinal A, both 13- and 8-membered unsaturated rings should be constructed by ring closing metathesis (RCM) at a later stage in the synthesis. The disconnection of ring B gives the iminium cation intermediate **7**, which should be simplified to the known spirolactam intermediate **8**.

The Horner–Wadsworth–Emmons reaction of spirolactam **8**, which was prepared according to a procedure described in supporting information, gave unsaturated ester in 80% yield (Scheme 2), which was stereoselectively reduced to saturated ester **9a** by hydrogenation catalyzed by PtO_2 in aqueous MeOH, along with **9b**, which was obtained by partial ester exchange to methyl ester. A mixture of **9a** and **9b** was converted to their Weinreb amide without purification. The diastereomer ratio was determined to be 14:1 by ^{1}H NMR. The Weinreb amide was then converted to furylketone **10** by reaction with 2-furyl lithium, and compound **10** was purified by crystallization to remove the minor diastereomeric isomer. The aldol reaction of **10** with formaldehyde in the presence of DBU gave hydroxymethylated **11** in a diastereomer ratio of 10:1.

Conditions for Scheme 2: **a** $Ph_3P=CHCO_2Et$, toluene, reflux, 12 h (80%), **b** H_2, cat. PtO_2, MeOH–H_2O (5:1), rt, 24 h, **c** HNMe(OMe), *i*PrMgCl, tetrahydrofurane (THF), −20 °C, 2 h. **d** 2-furyl lithium, THF, −78 °C, 2 h (84%, 3 steps). **e** HCHO, DBU (74%). **f** $NaBH_4$, MeOH, 0 °C, 1 h. **g** *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h. **h** Li, NH_3, −40 °C, 4.5 h. **i** benezenesulfonyl chloride (BsCl), $NaHCO_3$, AcOEt–H_2O, rt, 3 h (61%, 4 steps). **j** tetrabutylammoniumu fluoride (TBAF), THF, rt, 12 h. **k** Ac_2O, pyridine, rt, 5.5 h. **l** *p*-TsOH, *i*PrOH–CH_2Cl_2, rt, 12 h, (88%, 3 steps). **m** MsCl, pyridine, rt, 2.5 h. **n** *o*-NO_2PhSeCN, $NaBH_4$, DMF, rt, 12 h. **o** 30% H_2O_2 aq, THF, rt, 2.5 h, (64%, 3 steps). **p** Boc_2O, Et_3N, cat. dimethylaminopyridine (DMAP), THF, rt, 4.5 h, (98%). **q** $LiBH_4$, THF, rt, 2.5 h. **r** Ac_2O, pyridine, rt, 4 h. **s** *p*-TsOH, acetone–H_2O, rt, 48 h. **t** IBX, dimethylsulfoxide (DMSO), 50 °C, 6 h (4 steps, 70%).

The ketone carbonyl group in **11** was removed by stepwise reduction to methylene to increase the electron density of the furan group. Thus, **11** was converted to the secondary alcohol **12**, which was protected as a silyl ether. Silyl ether **13** was further reduced by lithium–ammonia to give **14** after reprotection of the secondary amine by a benzenesulfonyl group. After conversion of the silyl ether to acetate **15**, a tetrahydropyranyl (THP) group was removed and the primary alcohol **16** was converted to phenylselenoether **18** via mesylate **17**.[15] Oxidative elimination followed by Boc protection gave **19**. Reduction of lactam carbonyl in **19** to *N*-Boc aminal followed by acetylation of the primary alcohol gave a cyclization precursor **20**. A crucial FIC of **20** proceeded slowly to give hemiacetal **21**, which was oxidized to lactone **22** by 2-iodoxybenzoic acid (IBX). No diastereomeric isomer was observed under this cyclization.

Conditions for Scheme 3: a $NaBH_4$, cat. $NiCl_2$, MeOH, rt, 1 min. **b** trifluoroacetic acid (TFA), CH_2Cl_2, 0 °C to rt. **c** 5-hexenoyl chloride,

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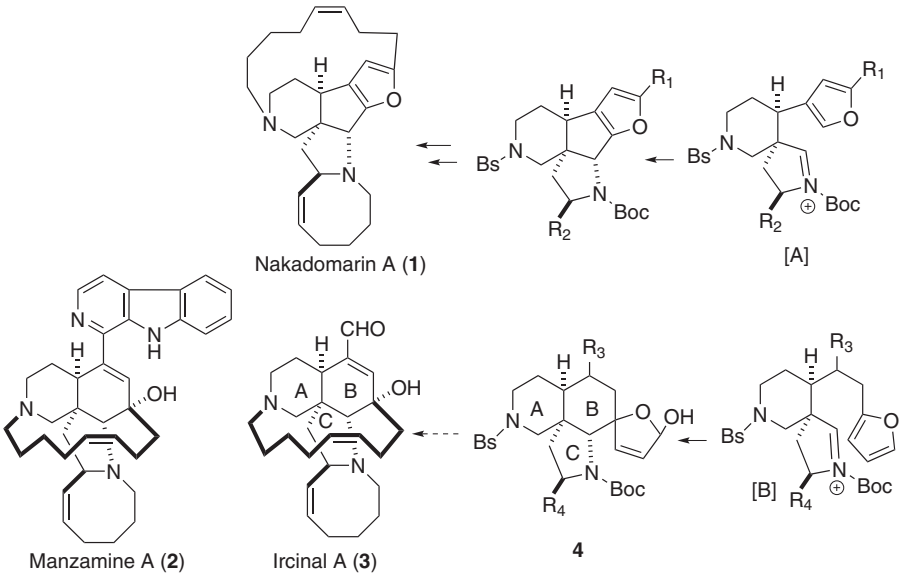
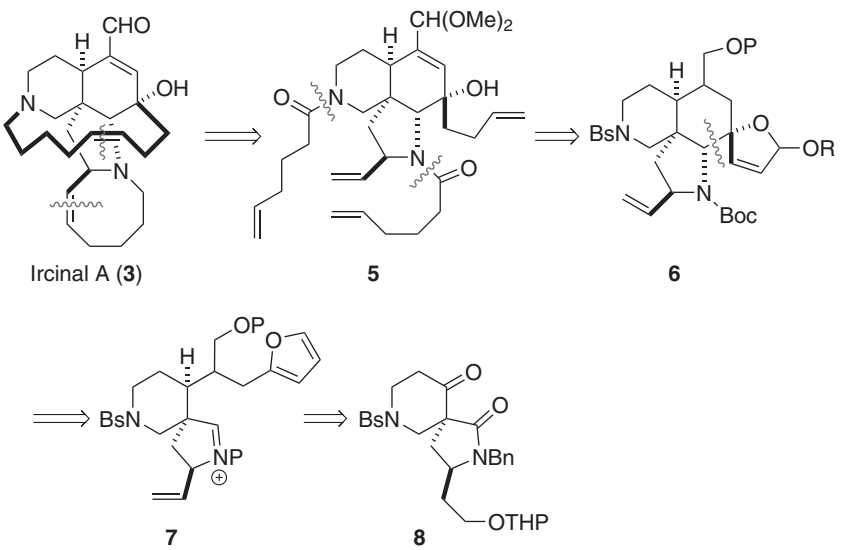


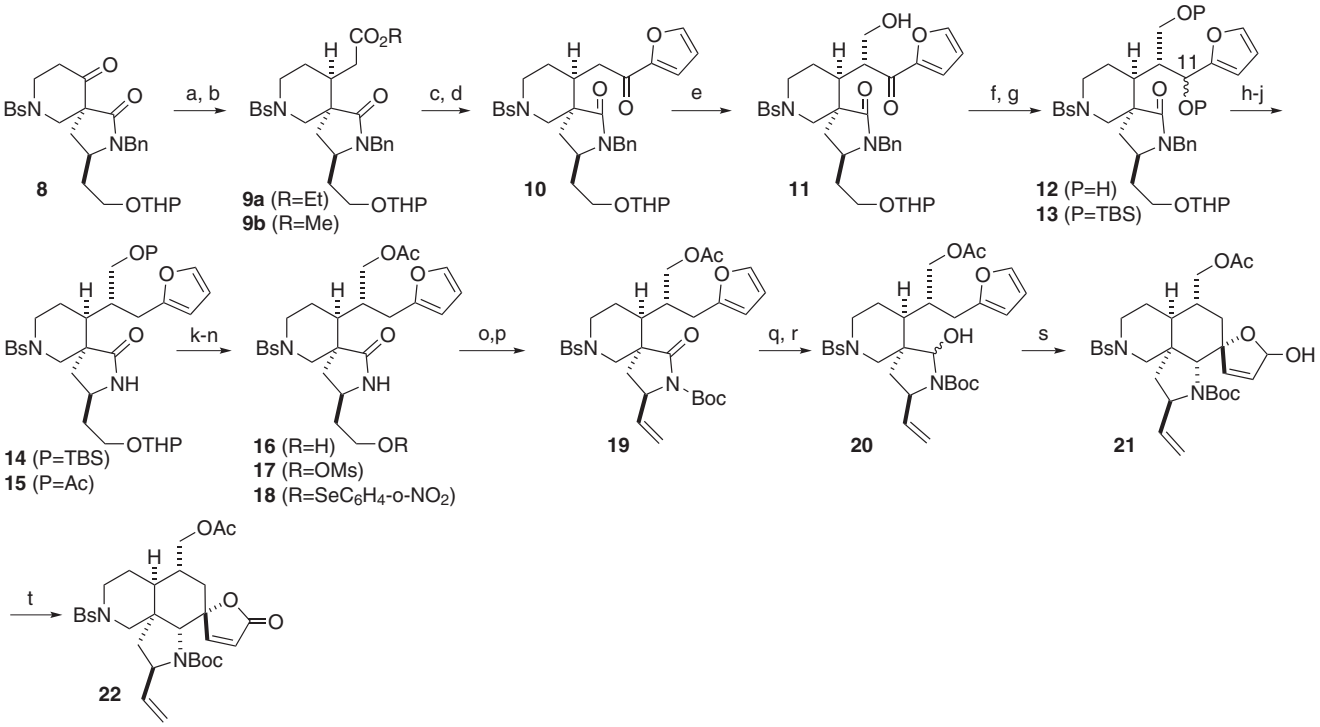
Figure 1 Furan-iminium cation cyclization (FIC) in the synthesis of manzamine alkaloids.



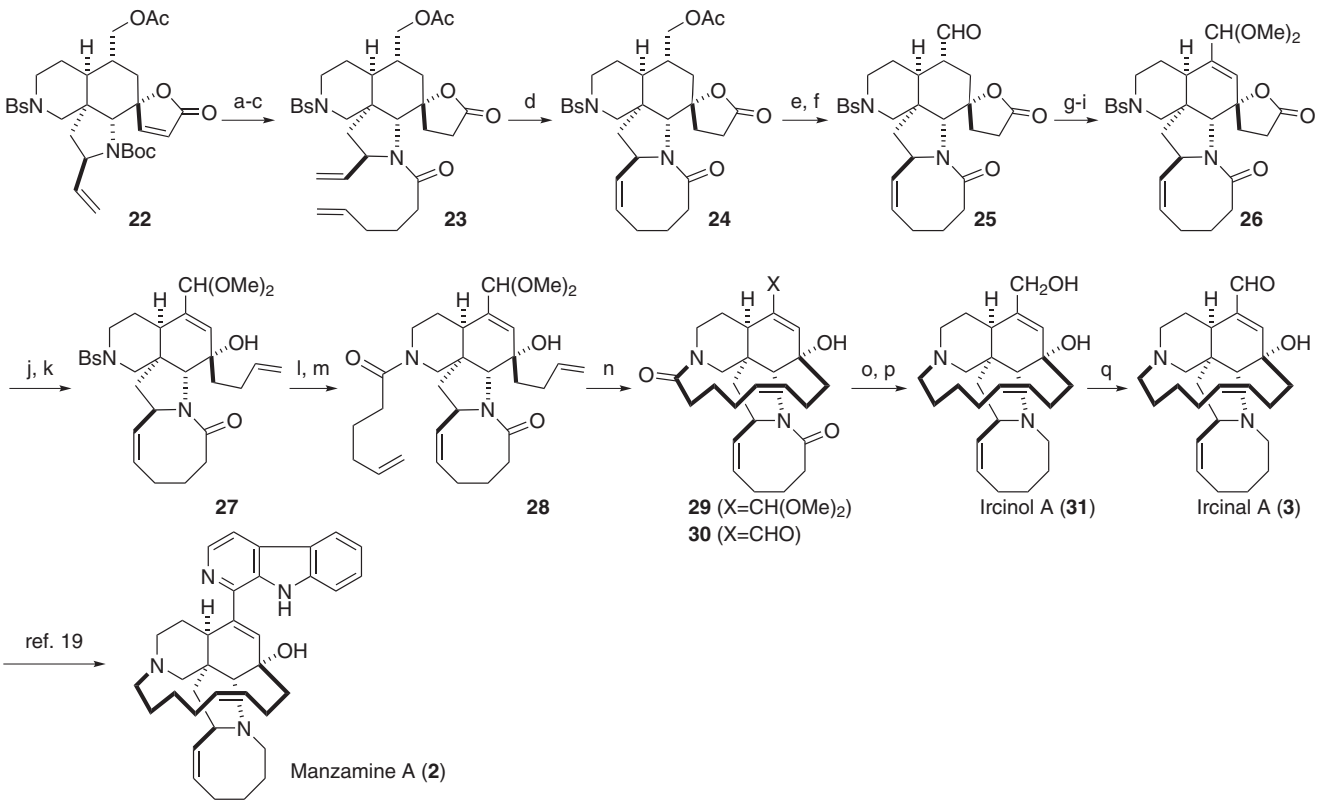
Scheme 1 Retrosynthetic analysis of ircinal A. A full color version of this figure is available at *The Journal of Antibiotics* journal online.

DMAP, Et_3N, CH_2Cl_2, (83%, 3 steps). **d** Grubbs' second (10 mol%), CH_2Cl_2, reflux, 3.5 h, (90%). **e** KCN, MeOH–CH_2Cl_2, rt, 24 h. **f** Dess–Martin periodinane, CH_2Cl_2, 0 °C, 3.5 h, (91%, 2 steps). **g** TMSBr, Et_3N, CH_2Cl_2, rt, **h** $Pd(OAc)_2$, CH_3CN, rt. **i** $HC(OMe)_3$, *p*-TsOH–H_2O, MeOH, rt, (78%, 3 steps). **j** diisobutylaluminum hydride (DIBAL), CH_2Cl_2, −78 °C, 1.5 h. **k** Ph_3PCH_3Br, potassium hexamethyldisilazane (KHMDS), THF, 0 °C to rt, 12 h, (65%, 2 steps). **l** Na, naphthalene, 1,2-dimethoxyethane (DME), −65 °C, 30 min. **m** 5-hexenoyl chloride, DMAP, Et_3N, CH_2Cl_2, (88%, 2 steps). **n** Grubbs' first (20 mol%), CH_2Cl_2 (degassed), reflux, 24 h. **o** 1 *N* HCl, AcOEt, rt, 5 min, (63%, 2 steps). **p** DIBAL, CH_2Cl_2, −78 °C to rt. **q** Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt (21%, 2 steps).

Chemoselective reduction of conjugated olefin in **22** (Scheme 3),[16] followed by removal of a Boc group and acylation with 5-hexenoyl chloride, gave diene **23**, a precursor for 8-membered ring formation. RCM using Grubbs' second generation catalyst gave cyclized product **24** in 90% yield. Acetate was removed under mild conditions[17] and the resultant primary alcohol was oxidized to aldehyde **25**. Saegusa–Ito oxidation[18] of **25** introduced unsaturation into ring B. After the aldehyde was protected by acetal as **26**, reduction of lactone to hemiacetal with DIBAL at −78 °C followed by methylenation furnished a butenyl moiety in **27**. Benzenesulfonyl protection was removed reductively and a secondary amine in the piperidine ring was acylated to give diene **28**, which is a precursor for the formation of a 13-membered ring by a second RCM. The second RCM was catalyzed by Grubbs' first generation catalyst to give the desired *Z*-olefin selectively (**29**). RCM using Grubbs' second generation catalyst gave a mixture of dimers as a major product. Hydrolysis of acetal in **29** gave



Scheme 2 Furan-iminium cation cyclization (FIC) for synthesis of core skeleton.



Scheme 3 Total synthesis of ircinal A.

aldehyde **30**. All three carbonyl groups in **30** were reduced to give ircinol A (**31**), which was oxidized to ircinal A (**3**). As the conversion of ircinal A to manzamine A (**2**) has been reported previously, the present findings represent a formal total synthesis of manzamine A.[19]

A highlight of this synthesis is the use of a highly efficient FIC for the formation of a 6-membered ring with stereoselective construction of a tetra-substituted carbon center. The furan ring in **20** was completely incorporated into the structure of ircinal A.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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