New Approaches to Total Synthesis of Manzamine A, Ircinal A and Related Compounds

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Abstract: *New approaches to total asymmetric synthesis of ircinal A and manzamine A are described. The synthesis utilizes a highly efficient Diels-Alder reaction of the suitably functionalized dihydropyridinones and siloxydienes as a key step, followed by expedient conversion to manzamine A.*

1. Introduction

Manzamines are naturally occurring cytotoxic and antibiotic indole alkaloids of the fascinating heterocyclic compounds. Since the first isolation and structural elucidation of manzamine A **1** from a marine sponge collected off Manzano, Okinawa, isolated by Higa (ref. 1) and subsequent characterization of the congeners (manzamine B - F) coupled with the independent isolation of the same alkaloids as keramamines (ref. 2), there has been widespread interest in the unprecedented structures, the biogenesis, and synthesis of these β -carboline alkaloids, in addition to their biological activities. Further progress was made thereafter by the isolation of new and biogenetically closely related members, which support an ingenious proposal for their biosynthetic pathway, by Baldwin, Whitehead, and Marazano (ref. 3).

Figure 1. Manzamine A, B and C

While the simplest congener manzamine C and related compounds have been synthesized in this (ref. 4) and Languor's laboratories (ref. 5), the more complex manzamine A has been a challenging target for total synthesis (ref. 6). Quite recently, Winkler (ref. 7) and Martin (ref. 8) have succeeded in the total synthesis of manzamine A and its related compounds.

We have been interested in developing an efficient route to the tetraazacyclic intermediate **4** for **1** which was based on initial construction of tricyclic intermediate **5**: 1) by intermolecular Diels-Alder reaction of functionalized dihydropyridinone as a dienophile with siloxydiene leading to the construction of the *cis* relationship of the central AB ring system of this unique structure, followed by intramolecular Michael addition to the tricyclic core **5** (*path a*) or 2) by an intramolecular fashion (*path b*). We also

focused attention on *path c* which is suitable for the construction of the AB ring system, especially for the β -carboline connection (ref. 9)

Scheme 1

2. Synthesis of the Tetracyclic Core Structure ($\pm$)-20

Our initial studies along *path a* revealed that *N*-alkyl protected (i.e., R_1 =alkyl) dihydropyridinones were quite sluggish towards dienes even in an intramolecular case, and the electron-withdrawing character of an *N*-protecting group was essential for the successful intermolecular cycloadditions (ref. 10). Further investigation into these thermal transformations led us to select the *N*-benzenesulfonyl dihydropyridinones or *p*-chlorobenzenesulfonyl derivatives as a dienophile in view of the thermal stability of the *N*-arylsulfonyl group. As expected, in the model study using a simple dienophile having an aminoacid residue, it was found that *N*-tosyl-3-alkyldihydropyridinone **6** undergoes Diels-Alder reaction with Danishefsky's diene under conventional thermal conditions affording **7**, which after treatment with an acid followed by a base, was converted to the expected central pyrroloisoquinoline ring system **9** in ca. 40% yield. We achieved a more facile construction of **9** by utilization of a high-pressure Diels-Alder reaction of **6** with the Danishefsky diene in 60% overall yield for 4 steps (ref. 10).

Scheme 2

The new dienophiles **10** and **11**, each having a COCF_3 protecting group instead of a thermally unstable BOC group, were found to be suitable due to the ease of preparation (ref. 11) and appropriate reactivity in Diels-Alder reaction under thermal conditions (ref. 12). Thus, treatment of **10** and **11**, respectively, with Danishefsky's diene in refluxing *p*-cymene afforded the corresponding enones **12** and **13**. The SEM enone **12** was deprotected by trifluoroacetic acid (TFA) to furnish the NH-enone, which was readily converted to the tricyclic system **14** by brief treatment with 1,4-diazabicyclo-[2,2,2]octane (DABCO) at room temperature. Subsequent ketalization of **15** afforded the stable ketal **16**

as a *ca* 1 : 1 diastereoisomeric mixture, which could easily be separated by recrystallization from CH₂Cl₂/Et₂O, although the diastereomers corresponding to **15** and **16** could be separated by column chromatography. For a large scale preparation, these deprotection-cyclization-ketalization steps were conveniently conducted without purification, to furnish the desired isomer **16** in 30% yield from the *N*-SEM dienophile **10**. Another efficient preparation of **15** was realized by the reaction of *N*-MOM adduct **13** with triethyl triflate (TESOTf) in the presence of SiO₂ powder and Na₂SO₄.

Scheme 3

The benzenesulfonyl group used for nitrogen protection and for activation of dihydropyridinone as an efficient dienophile for successive cycloaddition now had to be removed after the Diels-Alder reaction to prevent ring-opening due to the instability of benzenesulfonyl lactam toward nucleophiles.

Subsequent selective deprotection of the two *N*-protecting groups (i.e., PhSO₂ and CF₃CO) was best carried out by using Na/anthracene in 1,2-dimethoxyethane (DME) at -60 °C, giving **17**. Then, the reductive removal of the CF₃CO group by LiBH₄/B(OMe)₃ followed by protection of the newly generated NH group by the BOC group gave the aldehyde **18** (87%, 3 steps yield). Expedient conversion of **18** to the precursor **19** was followed by the azocine lactam ring closure to give the desired tetracyclic core structure **20** in a racemic form (ref. 12).

3. Synthesis of Optically Active Dienophiles

From the results obtained, some dihydropyridinones have emerged as potential precursors for the construction of a highly functionalized perhydroisoquinoline ring system in our synthetic approaches to the manzamine alkaloids. We envisioned that developing a general and efficient synthesis for dihydropyridinone derivatives bearing a chiral side chain, would significantly enhance the utility of our Diels-Alder methodology. Therefore, we next directed our attention to the synthesis of optically active tetracyclic core structure **4** via a more efficient method based on the Diels-Alder reaction of siloxydienes with new dienophiles such as **20** and **21** as shown in Scheme 4.

We initially investigated the feasibility of a coupling reaction of vinyl iodide **22** with a chiral organozinc reagent **23**, in the presence of a Pd catalyst under various conditions to introduce the chiral amino acid unit into the 3 position of the pyridinone ring system.

Among the catalyst systems examined, PdCl₂(PhCN)₂ (0.2 eq) combined *in situ* with tri-*o*-tolylphosphine (0.4 eq) in DMF provided a suitable catalytic species. Under these conditions, dihydropyridinone **25a** was produced in the best yield (37%). However, a similar reaction of

oxazolidine derivative **24** failed to give **25b**. Therefore, we investigated another efficient route to obtain **20** which involves the aldol reaction of **26** with Garner aldehyde **27**.

Scheme 4

Scheme 5

Scheme 6

a $\text{LiN}(\text{TMS})_2$, THF, $-60\text{ }^\circ\text{C}$, 1 h, then **27** (91%), b 1) Et_3N , MsCl , $-40\sim 0\text{ }^\circ\text{C}$, 2) DBU, benzene, rt then $80\text{ }^\circ\text{C}$, c $(\text{EtO})_3\text{SiH}$, $(\text{PPh}_3)_3\text{RhCl}$ (cat.), Cs_2CO_3 , toluene, reflux (80% from *(E)*-**29**), d Amberlyst-15, MeOH, rt (85%), e Dess-Martin ox., CH_2Cl_2 , $0\text{ }^\circ\text{C}$ (85%).

The coupling reaction of **27** with *N*-MOM-piperidone **26** under basic conditions [$\text{LiN}(\text{TMS})_2$, THF] gave alcohols (**28**, a mixture of two diastereomers) in a yield of 80-90%, which were then dehydrated to give **29** under usual conditions. After purification, only *exo*-enones (**29**, *E* and *Z* mixture) were obtained in a 1.5 : 1 ratio (91% combined yield) which were then subjected to the critical double-bond isomerization to an endo cyclic position as in **30**. Extensive experimentation under various conditions, a previously reported protocol [Et_3SiH , $\text{RhCl}(\text{Ph}_3\text{P})_3$, toluene, reflux] (ref. 13) gave more satisfactory

results, but further optimization was needed. A high-yield isomerization reaction was finally realized when the silane was changed to $(\text{EtO})_3\text{SiH}$, and the reaction was conducted in the presence of Cs_2CO_3 . In this way, the chiral dihydropyridinone derivative **30** was obtained in 80% yield from the major isomer (*E*)-**29**. Deacetonization of **30** gave aminoalcohol **31**, which was then oxidized to the labile aldehyde **32** by Dess-Martin periodinane in excellent yield.

Scheme 7

For elongation of the C5-carbon chain, Wittig reactions of a conventional Wittig ylide derived from 4-carboxybutyltriphenylphosphonium bromide or 5-hydroxypentyltriphenylphosphonium bromide **33** (ref. 14) with **32** were carried out, but none of the desired products were obtained with these anionic oxido-ylides. However, Wittig reaction of **32** with the protected ylide **35** gave the desired product **36** in 70% yield, which was further transformed into **37**.

The stage was then set for the crucial azocine ring-forming step. There are two options for the activation of the hydroxyl group towards azocine ring closure. Our previous protocol (ref. 15) suggested the use of a tosylate rather than iodide for such cyclization. However, conversion of **37** to the *O*-mono tosylate was simply accompanied with *N,O*-ditosylation, which did not lead to the desired cyclized product, but rather gave a simple elimination product. Alcohol **37** was then converted to iodide **38** via mesylation followed by treatment with NaI . The iodide **38** underwent cyclization in the presence of 18-crown-6 and $t\text{-BuOK}$ to give the desired chiral azocine **39** in moderate yield (60-70%) (ref. 15). However, unexpectedly, the replacement of the MOM group by a benzenesulfonyl group proved unsuccessful. Unfortunately, no satisfactory solution has been found to date. For these reasons, the decision was made to explore the introduction of the double-bond functionality at the 3 position of pyridinone at a later stage of the synthesis. Accordingly, we first reduced the *exo* double bond with $\text{NiCl}_2 / \text{NaBH}_4$ to *N*-MOM-piperidone **40**. Treatment of **40** with camphor sulfonic acid (CSA) gave **41**.

Oxidation of **41** with pyridine-sulfur trioxide-dimethyl sulfoxide- Et_3N , followed by Wittig reaction with $\text{Ph}_3\text{P}=\text{CH}(\text{CH}_2)_3\text{COOK}$, gave compound **43** in 60-70% yield. The acid was then converted to the alcohol **44** via reduction of the mixed anhydride formed *in situ*. Similar reaction conditions used for the formation of **39** were applied for the conversion of **44** to **47** as illustrated in Scheme 8. Deprotection of **47** was best carried out by treatment with concentrated HCl in refluxing methanol, which was followed by benzenesulfonylation of the secondary nitrogen to give **48**. Further treatment of **48** with arylsulfonylchloride under strong basic conditions afforded **49**, which was converted to the desired dienophile **50** via phenylselenation followed by oxidative elimination. However, the yields of the last two steps were low. This prompted us to develop an alternative synthesis of chiral dienophiles **51**, already carrying a benzenesulfonyl group at an earlier stage that was much easier to prepare on a multimolar scale.

Scheme 8

a NiCl₂•6H₂O (cat.), NaBH₄, MeOH, 0 °C (99%), **b** CSA, MeOH, 0 °C - rt (95%), **c** Py•SO₃, DMSO, Et₃N, CH₂Cl₂, rt, **d** Br•Ph₃P⁺(CH₂)₄COOH, KN(TMS)₂, toluene, 0 °C (60-70%, 2 steps), **e** ClCOOEt, Et₃N, THF, 0 °C, then NaBH₄, THF (77%), **f** MsCl, Et₃N, CH₂Cl₂, -60 °C (97%), **g** NaI, acetone, rt (93%), **h** *t*-BuOK, 18-Crown-6, THF, -60 °C (47%), **i** *o*-HCl, MeOH, reflux, **j** PhSO₂Cl, Et₃N, CH₂Cl₂, 0 °C (60%, 2 steps), **k** *p*-ClC₆H₄SO₂Cl, LiN(TMS)₂, THF, -20 °C-rt (54%), **l** PhSeCl, LiN(TMS)₂, THF, -20 °C (14%), **m** H₂O₂, THF, 0 °C (26%).

Scheme 9

Accordingly, we explored the synthesis of the optically active **20** via a more efficient method based on the Diels-Alder reaction of new dienophiles **51** with siloxydienes **52** (path e, Scheme 9).

We first prepared the protected serinal **55** in three steps from *N*-benzenesulfonyl-L-serine methyl ester **53** via **54**.

Scheme 10

a) 1) 2,2-dimethoxypropane, *p*-TsOH, benzene, reflux, 2) DIBALH, toluene, -78 °C (90% for **54**, 92% for **55**), b) LiN(TMS)₂, THF, -60 °C, then **27** or **55**, -60 °C, c) 1) MsCl, Et₃N, CH₂Cl₂, 2) DBU, benzene, reflux, 3) H₂, PtO₂, d) 1) LiN(TMS)₂, THF, -60 °C, then PhOC(S)Cl, 2) *n*-Bu₃SnH, AIBN, benzene, reflux, e) PhSO₂SPh, LiN(TMS)₂, THF, -30 °C, f) *m*CPBA, CH₂Cl₂, then heat.

Although we anticipated extreme sensitivity of *N*-benzenesulfonyllactam to a nucleophile under basic conditions, to our delight, a key reaction of **56** with **27** using LiN(TMS)₂ proceeded smoothly at -60 °C to provide us **57a** as a mixture of diastereomers.

A similar reaction of **55** with **56** gave **57b**. Dehydration of **57a** via mesylation followed by DBU treatment gave **59a**. Originally, we had envisioned installing the C3-C4 double bond through the *exo-endo* isomerization. In previous studies, we succeeded in the isomerization of the *exo*-enone **29** to the *endo*-enone **30** by use of silane-Rh-mediated conditions. In contrast to **29**, however, a similar *exo-endo* isomerization of either **59a** or **59b** to the corresponding *endo*-isomer failed. We, therefore, turned to the reduction-oxidation method. Catalytic hydrogenation of **59a** proceeded to give **61a**, but hydrogenation of **59b** under similar conditions was unsuccessful. Therefore, we applied the deoxygenation conditions using phenoxythiocarbonate for **57b** (ref. 16), and **61b** was obtained in 80% yield.

The conversion of **61** to the desired enantiomerically pure dienophiles **62** was achieved by base induced thiophenylation at the 3 position of **61** followed by oxidative elimination using previous methods.

4. Total Synthesis of Manzamine A and Ircinal A

With an efficient route to the dienophile **62** established, attention was turned toward the Diels-Alder reaction of **62** with Danishefsky diene **63**. Attempts to achieve Diels-Alder reaction of a new dienophile **62a** with Danishefsky diene **63a** were unsuccessful, leading only to extensive decomposition, probably due to the instability of the BOC group to high temperature. On the other hand, the reaction of **62b** and excess amount (8 equiv) of **63a** in refluxing *p*-cymene at 180 °C for 20 h smoothly underwent regioselective cycloaddition. Without isolation, the cycloadduct was readily transformed into the corresponding enones slightly in favor of the desired isomer **64** after deprotection with PPTS.

Scheme 11

Similar reaction of **62b** with TBS-diene **63b** afforded the corresponding enones (**64** and **65**) in 85% yield. Subsequently, the acetonide **64** was subjected to acid treatment with 1N HCl in THF to give a tricyclic alcohol **66**, together with **67** which could readily be converted to **66** by 1N HCl. The desired stereochemistry of **66** was secured through the chemical transformation and ¹H-NMR spectral data.

Scheme 12

a ethylene glycol, *p*-TsOH, benzene, reflux (99%), b Na, anthracene, DME, -65 °C (94%), c Na, naphthalene, DME, -65 °C, d Boc₂O, 1N NaOH, rt (92% from **73**), e TBAF, THF, rt, f Dess-Martin ox. CH_2Cl_2 , 0 °C (96% from **74**), g $\text{Br}^+ \text{Ph}_3\text{P}^+(\text{CH}_2)_4\text{COOH}$ (**76**), $\text{KN}(\text{TMS})_2$, toluene, rt (78%), h TFA, CH_2Cl_2 , rt, i BOP-Cl, Et₃N, CH_2Cl_2 , rt (32% from **77**), j $\text{C}_6\text{F}_5\text{OH}$, DCC.

When **66** was treated with *p*-nitrobenzoyl chloride in pyridine, the lactone **68** was newly formed, whereas the isomer **69**, obtained from **65** in analogous manner, gave the corresponding *p*-nitrobenzoate **70**, selectively. The unexpected formation of **68** supported the *cis* relationship of the hydroxymethyl group and the ring A in **66**. The alcohol **66** was then protected with TBDPS to give **71**, which was converted into the ketal **72**. Deprotection of two benzenesulfonyl groups of **72**, followed by reprotection with a BOC group, afforded **74**.

The remaining task was elongation of the side chain to construct the azocine ring system. Deprotection of the primary TBDPS ether was followed by Dess-Martin periodinane oxidation of the derived primary alcohol to give the labile aldehyde **75**. Homologation of the resulting aldehyde **75** using the Wittig reagent **76** furnished the olefin **77** (*E/Z* ratio 1:5) as the key cyclization substrate. A 1:5 ratio of the *E* and *Z* isomers was determined by ¹H-NMR spectroscopy of the resultant mixture of the pentafluorophenyl ester **78**. At this stage, we chose BOP-Cl for the final cyclization (ref. 17). Thus, the BOC group was first deprotected and the amino acid was treated with BOP-Cl to furnish the desired tetracyclic key compound **20** [$[\alpha]_D^{22} = -11$ ($c=0.3$, CHCl₃)]. Its spectroscopic properties were identical in all respects to those of (±)-**20** (ref. 12, 18).

The next step in the synthesis involved the introduction of the C₁ unit to the B ring and functionalization of the B ring to construct the E ring system. Although this transformation appeared fairly straightforward, it proved to be rather difficult. Treatment of **71** with MOMCl provided a 1:1 mixture of O-MOM derivative **79** and C-MOM derivative **80**. Reaction of **71** with ClCO₂Me gave O-methoxycarbonylated product **81** selectively. In contrast, exclusive formation of the desired ketoester **82** could be effected in 90% yield by treatment of **71** with Mander's reagent, CNCO₂Me (ref. 19).

Scheme 13

Deprotection of the benzenesulfonyl group of **82** provided lactam **83**, which was then converted to the ester **84** by reduction-dehydration. Oxidation of **84** to enone **85** was examined under a variety of reaction conditions and **85** was formed in the best yield of 62% by use of Salmond protocol (ref. 20). Sequential reduction of **85** with NaBH₄•CeCl₃ and DIBALH followed by acylation and oxidation, provided **86** which was subjected to reaction with 8-lithio-5-octyne-1-ol MOM ether **87** and cleanly produced **88**.

Scheme 14

a Na, anthracene, DME (84%), **b** 1) NaBH₄, 2) MsCl, 3) DBU (65%, 3 steps), **c** CrO₃-3,5-dimethylpyrazole (62%), **d** 1) NaBH₄•CeCl₃, 2) DIBALH, 3) PivCl, 4) Dess-Martin ox. (45%, 4 steps).

Scheme 15

a Na, naphthalene, DME (90%), **b** Boc-ON, Et₃N, rt (73%), **c** 1) NaBH₄, 2) MsCl, 3) DBU (77%, 3 steps) **d** CrO₃-3,5-dimethylpyrazole (65%), **e** HF, aq. CH₃CN, -30 °C (92%), **f** Swern ox. (83%), **g** 1) Br Ph₃P⁺(CH₂)₄COOH, KN(TMS)₂

On the other hand, replacement of the benzenesulfonyl group of **83** with a BOC group gave **90**. The submission of **90** to sequential reduction, dehydration, and oxidation gave rise efficiently to **92**. Deprotection of enone **92** by HF gave **93**. Oxidation of **93** to the aldehyde **94** was followed by Wittig reaction; however, none of the desired acid **95** was obtained.

Because high reactivity of the enone carbonyl was expected, we next converted **92** to **97**. Deprotection of enone **92** by HF gave the corresponding alcohol (Scheme 16). The acylation of the resulting alcohol, followed by reduction, and protection provided **96**. Deprotection of **96**, followed by oxidation gave **97**, which was subjected to Wittig reaction to afford the desired acid **98**. Cyclization of **98** to advanced tetracyclic intermediate **99** under a variety of conditions is now under investigation. On the other hand, **97** was converted diene **100**, a precursor for ring closing metathesis. Ring closing metathesis of **100** using 50 mol% of **101** in diluted solution of CH₂Cl₂, gave desired tetracyclic intermediate **102** in 75% yield (Scheme 17).

The intermediate **102** will be transformed to ircinal A (Scheme 17), which has been converted to manzamine A by Professor J. Kobayashi, of Hokkaido University (ref. 2d).

Scheme 16

a 1) HF, 2) Ac₂O, 3) NaBH₄, CeCl₃, 4) TBS-OTf, **b** 1) NaOMe, 2) Swern ox. or Dess-Martin ox., **c** BrPh₃P⁺(CH₂)₄COOH, KN(TMS)₂, **d** 1) TFA, 2) FDPP, (*i*Pr)₂NEt, **e** 1) BrPh₃P⁺CH₃, KN(TMS)₂, 2) TFA, 3) H₂C=CH(CH₂)₃COCl, Et₃N

Scheme 17

Acknowledgment

This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Science, Education, Sports and Culture. It is with great pleasure that we acknowledge the assistance of Associate Dr. M. Arisawa, Mr. Y. Kimura, Ms M. Yamabe, Ms N. Watanabe, Mr. Y. Sekine, Mr. T. Watanabe, and Ms K. Hyodo for their assistance in this synthesis.

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(Received August 3, 1999)