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An Efficient Access to the Optically Active Manzamine Tetracyclic Ring System

Hideharu Uchida, Atsushi Nishida, and Masako Nakagawa*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

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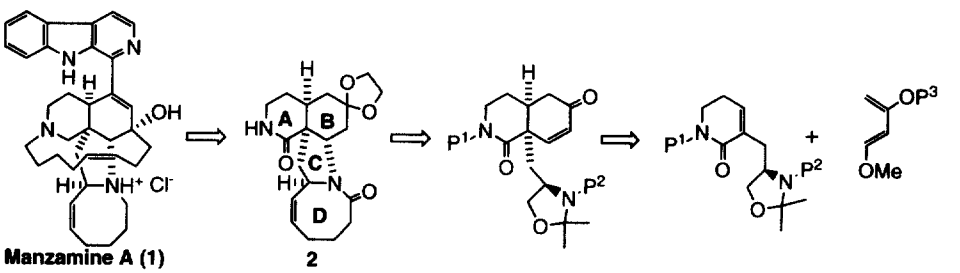
Abstract

The highly stereoselective synthesis of the optically active tetracyclic core **2** of Manzamine A **1** was achieved *via* the Diels-Alder reaction of dihydropyridinone **12b**, derived from L-serine, with siloxydienes, followed by sequential new and conventional pathways.

Keywords: *Alkaloids; Asymmetric Synthesis; Cycloadditions; Azocines;*

Since their isolation in 1986 [1], the antitumor and antibiotic marine alkaloids manzamine A **1** and biologically related congeners, such as ircinal A and keramaphidin B, have been attractive molecules for total synthesis due to their biological activities and the structural complexity of the novel poly-aza-ring system [2,3]. Recently, two total syntheses of manzamine A **1** have been accomplished by Winkler's [4] and Martin's groups [5], respectively. In our previous paper in this series, we reported the synthesis of the tetracyclic core structure **2** of manzamine A in a racemic form [6-9]. In this paper, we report the synthesis of optically active **2** *via* a more efficient method based on the Diels-Alder reaction of a new dienophile with siloxydienes.



The four-step synthesis of the protected serinal **5** begins with ester formation followed by *N*-protection of L-serine by a Boc or benzenesulfonyl group to give the methyl ester **3**, which is converted to the corresponding acetonide **4**. Ester **4** is then reduced to aldehyde **5** in excellent yield by treatment with DIBAL-H. A key reaction of *N*-benzenesulfonylpiperidone

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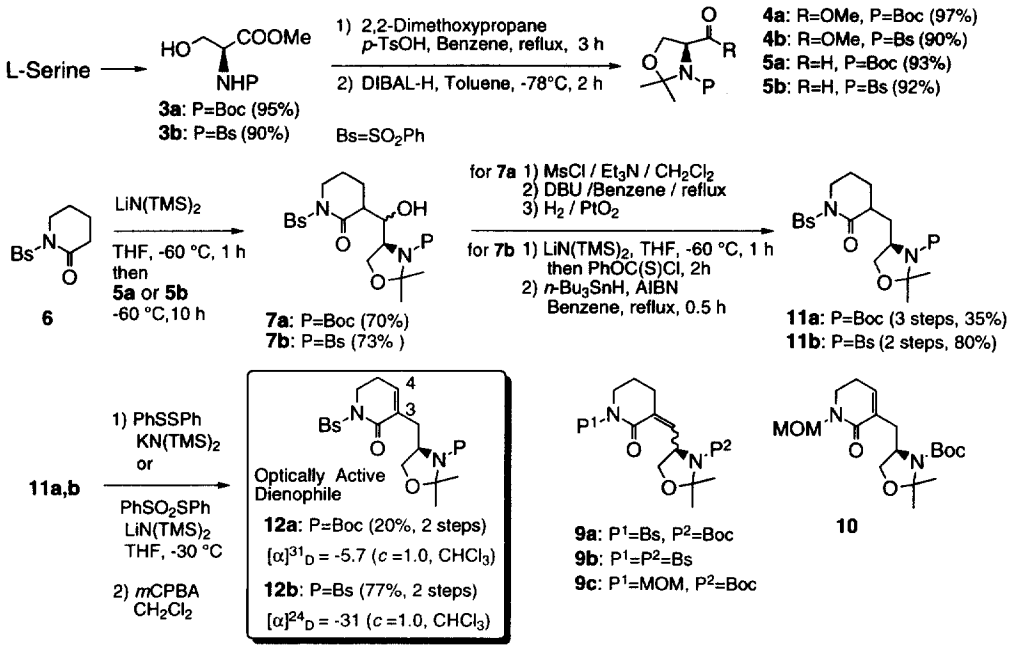
6 with the Garner aldehyde **5a** using $LiN(TMS)_2$ proceeded at -60 °C to give the alcohol **7a** as a mixture of diastereomers in 70% yield. A similar reaction of **5b** with **6** gave **7b** (73%).

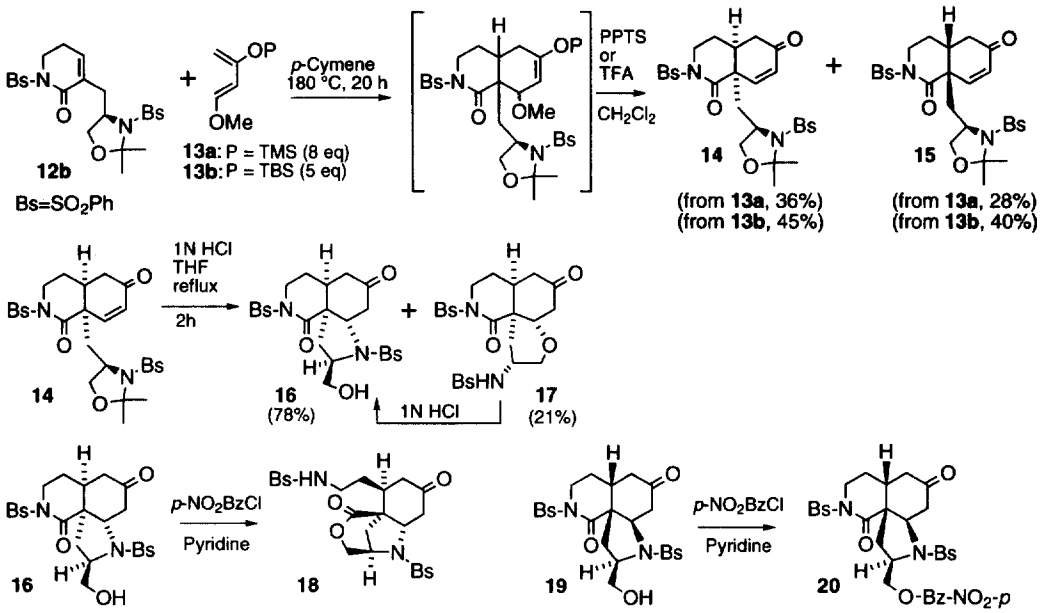


Scheme 1

Dehydration of **7a** *via* mesylation followed by treatment with DBU gave **9a** in 75% yield (2 steps). Originally, we had envisioned installing the C3-C4 double bond through *exo-endo* isomerization. In previous studies, we achieved isomerization of the *exo*-enone **9c** to the *endo*-enone **10** by use of silane-Rh-mediated conditions [9]. However, in contrast to **9c**, similar *exo-endo* isomerization of either **9a** or **9b** to the corresponding *endo* isomer failed. Therefore, we turned to the reduction-oxidation sequence. Catalytic hydrogenation of **9a** gave **11a**, but hydrogenation of **9b** under similar conditions was unsuccessful. Therefore, we applied Barton's deoxygenation method *via* the phenoxythiocarbonyl ester for **7b** [10]. Conversion of **11a,b** to the desired enantiomerically pure dienophile **12a,b** was achieved by base-induced thiophenylation at the 3 position of **11** followed by oxidative elimination using standard methods.

With an efficient route to the dienophile **12b** established, we turned our attention to the Diels-Alder reaction of **12b** with Danishefsky diene **13a**.[1] Thus, the reaction of **12b** with an excess amount (8 equiv) of **13a** in *p*-cymene at 180 °C proceeded smoothly to give regioselective cycloaddition. Without isolation, the cycloadduct was readily transformed into the corresponding enones (**14**:**15**=36:28) in 64% yield after deprotection with PPTS. A similar reaction of **12b** with **13b** (5 equiv) gave the corresponding enone in 85% yield.

1 With the reaction of **12a** and **13a**, only degradation products were observed.



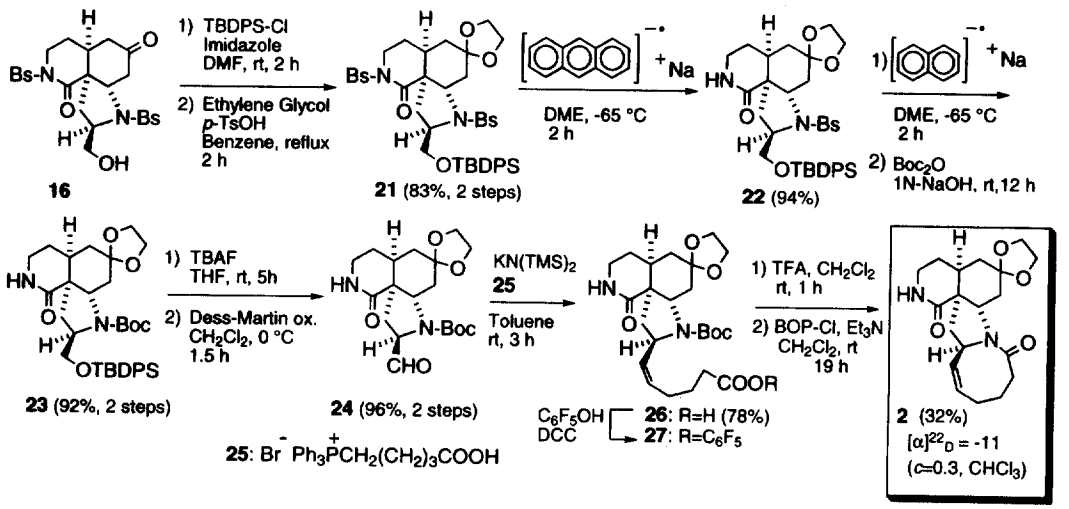
Scheme 2

The acetonide **14** was then treated with 1N HCl in THF to give a tricyclic alcohol **16** (78 %), together with **17** (21%), which could readily revert to **16** with HCl. The desired stereochemistry of **16** was confirmed by ^{1}H-NMR spectroscopy and chemical transformation. When **16** was treated with *p*-nitrobenzoyl chloride in pyridine, the lactone **18** was newly formed in 70% yield, whereas the isomer **19**, obtained from **15** in an analogous manner, selectively gave the corresponding *p*-nitrobenzoate **20**. These results supported the *cis* relationship of the hydroxymethyl group and ring A in **16**. The alcohol **16** was then protected with TBDPS and converted into the ketal **21**.

In a previous report [8], we noted that the *N*-benzenesulfonyllactam is susceptible toward the Wittig reagent and could be successfully deprotected using sodium anthracenide. We have now found that the highly functionalized *N*-benzenesulfonyllactam **21** is also a suitable substrate for this reaction. A sulfonyl group of the lactam **21** was selectively removed with sodium anthracenide to give **22** in 94% yield. Consequently, the sulfonyl group of the secondary amine was readily removed with sodium naphthalenide, and this was followed by reprotection with a Boc group to afford **23**.

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 **24**. Homologation of the resulting aldehyde **24** using the Wittig reagent, prepared from phosphonium bromide **25** *in situ*, furnished the olefin **26** (E/Z ratio 1:5) as the key cyclization substrate. A 1:5 ratio of the *E* and *Z* isomers was determined by ^{1}H-NMR spectroscopy of the resultant mixture of the pentafluorophenyl ester **27**. At this stage, we chose BOP-Cl [11] for the final cyclization.

Thus, a Boc group was first deprotected and the amino acid was treated with BOP-Cl to furnish the desired tetracyclic key compound **2** [$[\alpha]^{22}_D$ = -11 (c=0.3, $CHCl_3$)]. Its spectroscopic properties were identical in all respects to those of (±)-**2** [8].



Scheme 3

Acknowledgment

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