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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 5311–5315

# Toward the synthesis of xestocyclamine A: investigation of double Michael reaction and direct aza Diels–Alder reaction

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Received 21 April 2006; revised 18 May 2006; accepted 19 May 2006
Available online 12 June 2006

**Abstract**—An efficient synthesis of the isoquinuclidone core of xestocyclamine A is described. The key step is a direct aza Diels–Alder reaction of enone **14** and *p*-anisidine to assemble the isoquinuclidone core of xestocyclamine A.


Xestocyclamine A (**1**), isolated from the *Xestospongia* sp., from the Milne Bay province of Papua, New Guinea (Fig. 1),[1] has been shown to inhibit protein kinase C (PKC), an enzyme that plays a central role in cellular signal transduction.[2] The development of a selective kinase inhibitor could potentially be of great value to the field of cancer chemotherapeutics.[3]

The suggested connectivity of xestocyclamine A is consistent with an elegant biosynthetic pathway proposed by Baldwin and Whitehead for the formation of manzamines (Fig. 1).[4] In that sequence, a substrate possessing dihydropyridine and dihydropyridinium functionalities (cf. **2a** or **2b**) undergoes intramolecular Diels–Alder (IMDA) reaction to produce the central tricyclic core structure, as shown. Oxidation of the piperidine of IMDA adduct **3a** allows entry to the ingenamine family, which includes xestocyclamine A (**1**), while the IMDA adduct of **2b** undergoes intramolecular redox between the two piperidines, followed by hydrolysis of the pyridinium unit and condensation with a tryptophan unit to provide access to the manzamine series.[5]

We formulated a strategy toward the synthesis of xestocyclamine A (**1**) that would commence with Diels–Alder cycloaddition of a dihydropyridone moiety (cf. **5**) to afford, following appropriate functionalization, an intermediate of type **6** (Fig. 2). In order to install one of the two ansa bridges of **1**, a bridging annulation strategy was envisioned, consisting of sequential Michael addition reactions of an amine nucleophile to the di-Michael acceptor (cf. **6** → **7**). The latter would then be advanced to **8** through *B*-alkyl Suzuki coupling.

We recently disclosed the results of preliminary efforts toward a total synthesis of xestocyclamine A according to the strategy delineated above.[6] We report herein the details of further investigations of the novel double Michael annulation and describe how we ultimately achieved complete diastereoselectivity in the isoquinuclidone forming reaction.

As previously described,[6] we first investigated the double Michael addition between **9** and vinyl iodo amine **10** (Scheme 1). In the event, the reaction produced a mixture of diastereomeric products (**11** and **12**), in favor of the desired adduct, **11** (2.6:1.0). The diastereoselectivity was found to be largely unaffected by permutations of solvent, temperature, and additives.

We next conducted a simple control experiment in which the Michael acceptor (**9**) was treated with dimethylamine, which, of course, cannot undergo the second addition (Scheme 2). We monitored the reaction progress by $^1$H NMR, and observed exclusive formation of **13**. The Michael addition, which is presumably under thermodynamic control, gives rise exclusively to the α-stereoisomer, as shown. This addition was found

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doi:10.1016/j.tetlet.2006.05.126

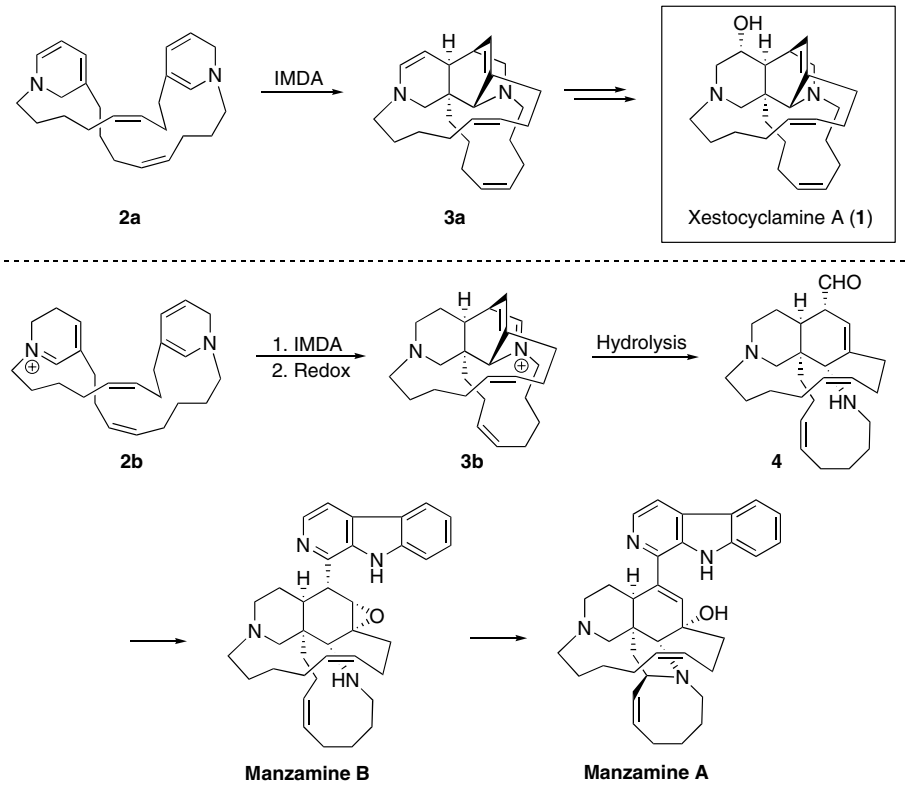



**Figure 1.** Biosynthetic pathway proposed by Baldwin and Whitehead.[4]

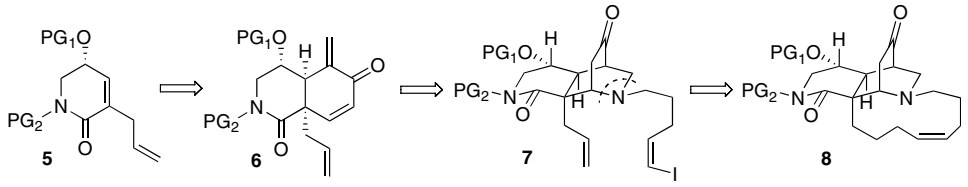
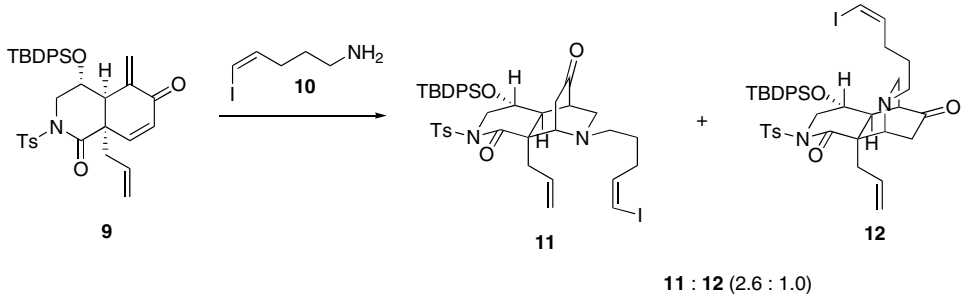
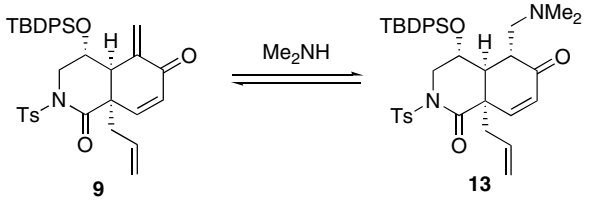



**Figure 2.** Summary of our original approach.[6]




**Scheme 1.** Double Michael reaction with **9**.




**Scheme 2.** Mechanistic study of double Michael reaction.

to be reversible, and under prolonged reaction times, we observed the reversion of **13** to starting material **9**.

Returning to our system, we postulated that the observed isomeric mixture may arise from the reversibility of the first conjugate addition, as the second addition is presumably irreversible. Under this hypothesis, we reasoned that if the size of the alkoxy protecting group in the ketone (**9**) were decreased, it might be possible

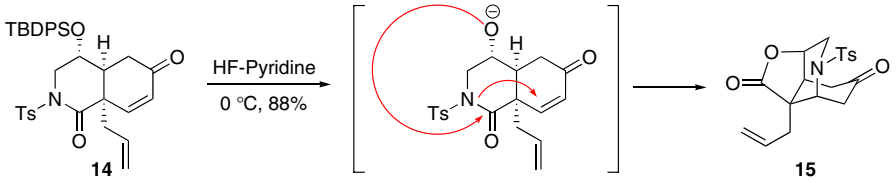
to bias the reaction in favor of formation of the desired isomer (**11**). The thought was that this might come about due to decreased steric interactions between the aminomethylene unit and the siloxy function.

At this juncture, the expedient route to a modified substrate would be through exchange of the –TBDPS group for a smaller –TBS protecting group at the stage of **14**, en route to **9**. In the event, treatment of **14** with hydrogen fluoride in pyridine produced **15**. Presumably this compound arises from a skeletal rearrangement, wherein the liberated hydroxyl group participates in a transacylation (i.e., lactonization) from the α-face of the molecule, allowing for the resulting sulfonamide to add to the enone in a conjugate fashion (Scheme 3).

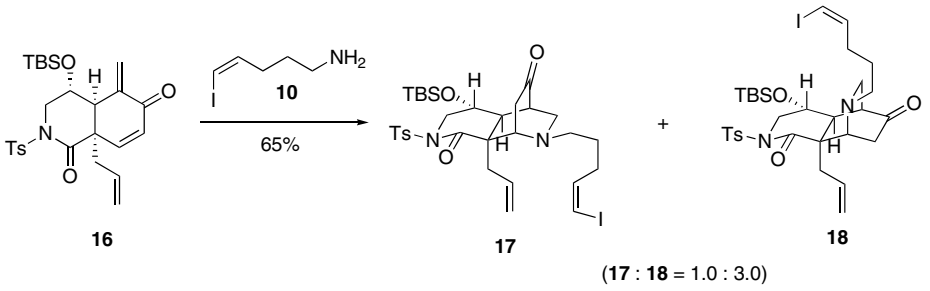
Having been unable to gain access to **16** from **14**, we revisited the beginning of the synthesis and **16** was secured from the hydroxy-oxopiperidine through the usual sequence.[6]

In the event, we found that the double Michael reaction of this less encumbered substrate (**16**) produced a mixture of isoquinuclidones **17** and **18**, this time in favor of the undesired isomer (**18**) (Scheme 4). We studied the likely intermediates of the reaction in an attempt to understand this trend. Thus, the first step of the sequence would involve the conjugate addition of the amine to the exocyclic olefin (Fig. 3). Protonation of the resultant enolate could occur from the β-face (cf. **A**) or the α-face (cf. **B**). Cyclization through intermediate **A** would ultimately lead to the desired isomeric adduct (cf. **20**), while cyclization through **B** would provide the undesired isomer (cf. **21**). When viewed in this way, the observed trend can, in retrospect, be readily explained. Thus, in the substrate with the smaller (–TBS) protecting group, hindrance to α-protonation is substantially diminished, allowing for the formation of a greater ratio of the undesired stereoisomer (cf. **18**).

In order to advance our synthesis of xestocyclamine A, a suitably functionalized isoquinuclidone core would be




**Scheme 3.** Rearrangement of **14** to **15**.




**Scheme 4.** Double Michael reaction with **16**.

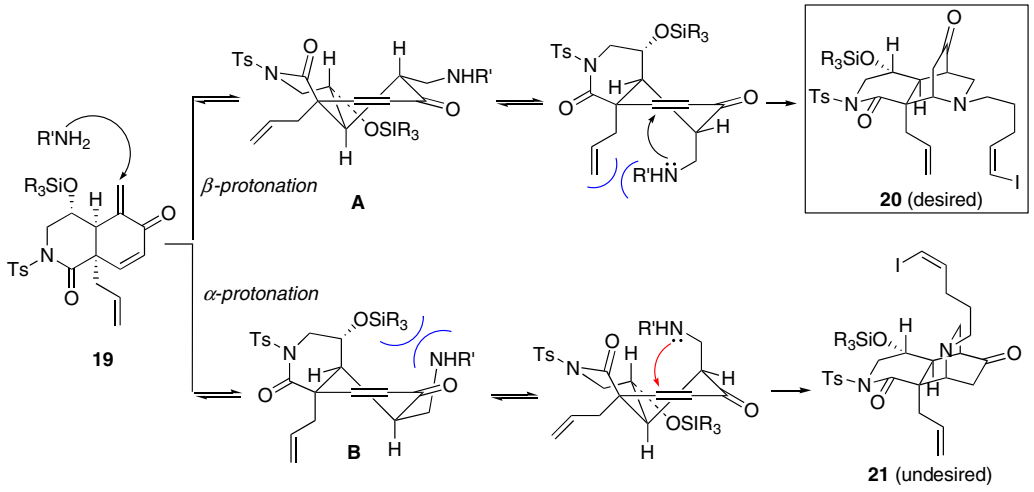
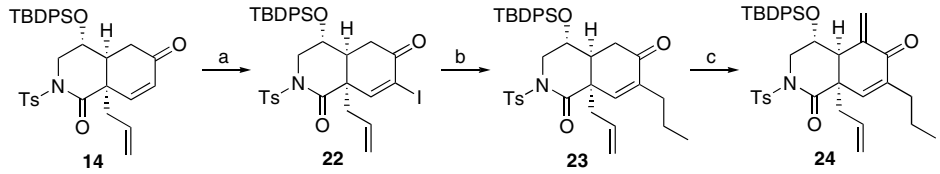
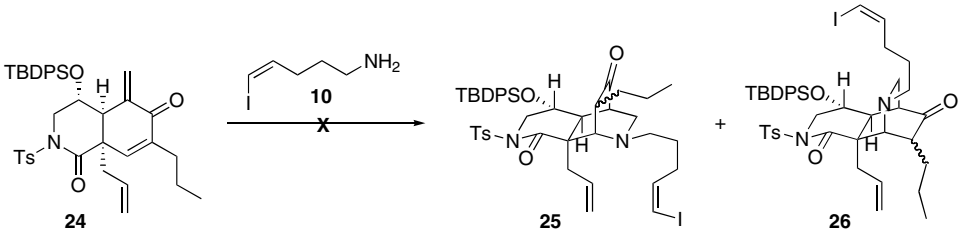


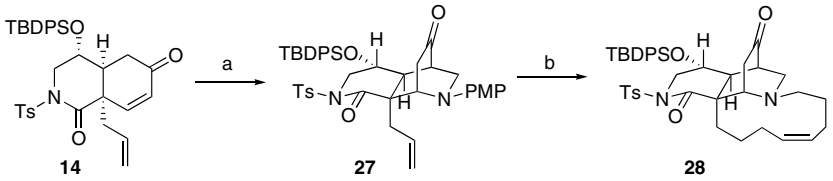

**Figure 3.** Proposed mechanism of double Michael reaction.




**Scheme 5.** Preparation of **24**. Reagents and Conditions : (a) $TMSN_3$, $I_2$, pyridine, $CH_2Cl_2$, 0 °C, 97%; (b) $ZnBr_2$, *n*-PrMgCl, THF, −78 °C to 0 °C then **22**, $(PPh_3)_2PdCl_2$, 52%; (c) (1) $Et_3N$, TMSOTf, $CH_2Cl_2$, 0 °C to rt, 100%; (2) $CH_2NMe_2I$, $CH_2Cl_2$, rt, then $SiO_2$, 36%.




**Scheme 6.** Attempted double Michael with **24**.




**Scheme 7.** Direct Aza Diels–Alder reaction approach. Reagents and Conditions: (a) HCHO, *p*-anisidine, D-proline, DMSO, rt, 72 h, 68%; (b) (1) CAN, acetonitrile, 70%; (2) NaH, 1*Z*-1,5-diiodo-1-pentene, THF, 70%; (3) $NaBH_4$, MeOH, 0 °C, 100%; (4) 9-BBN, THF, rt then $Pd(dppf)Cl_2$, DMF, $Ph_3As$, $Tl_2CO_3$, 60%; (5) Dess–Martin periodinane, $CH_2Cl_2$, 0 °C, 72%.

needed. Our plan had been to install such functional handles on the Michael acceptor platform. In the event, enone**14** was converted to iodoenone **22** (Scheme 5).[7] The latter was submitted to Negishi palladium coupling with propylzinc bromide, generated in situ. The usual sequence for the installment of the exo methylene gave Michael acceptor **24**, albeit in somewhat low yield. With the requisite substrate in hand, we were prepared to test the applicability of the double Michael reaction to this more demanding case.

Unfortunately, in this instance, the double Michael failed to give any product, either from mono addition or from annulation (Scheme 6). This lack of reactivity can most likely be attributed to a prohibitive 1,3-allylic interaction in the primary addition product prior to internal protonation. Moreover, severe destabilizing interactions between the propyl group and either the iodoalkenyl (**25**) or the allyl moiety (**26**) could be a complicating factor.

Recognizing the shortcomings of our 'double Michael' strategy, we came to consider an imino Diels–Alder route to the core.[8,9] It was our hope that if this cycloaddition were to proceed through a near-concerted transition state, we may be able to achieve enhanced levels of stereocontrol relative to the margins of our previous report.[6]

Indeed, we were pleased to find that direct aza Diels–Alder reaction of **14** proceeded smoothly to afford the desired adduct **27** as a single stereoisomer (Scheme 7). The reaction presumably proceeds through a concerted transition state, wherein the dienophile engages both centers of the diene simultaneously.[10] Following removal of the PMP group and elongation of the iodo side chain, a *B*-alkyl Suzuki macrocyclization strategy[11] was successfully implemented to afford compound **28**.

Throughout these studies, we have gained valuable insight into the double Michael addition strategy toward the core of xestocyclamine A. At the end, complete control of the stereoselectivity of the isoquinuclidone ring formation was achieved through a direct aza Diels–Alder reaction. Further advances toward the total synthesis of xestocyclamine A will be reported in due course.

## Acknowledgments

This work was supported by the NIH (HL25848 to S.J.D.). We would like to thank Eli Lilly and Company for the generous predoctoral fellowship awarded to H.Y.

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