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A CONCISE SYNTHESIS OF A POTENTIAL KEY INTERMEDIATE FOR 12-*EPI*-MYCALAMIDE A[#]

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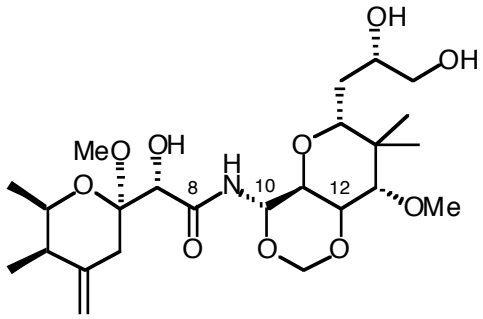
Abstract- Intramolecular nitrile oxide cycloaddition (INOC) reaction of the oximes (**7**) provides the isoxazoline (**9**), a possible key intermediate for 12-*epi*-mycalamide A (**2**).

Mycalamide A (**1**) is an immunosuppressant that was isolated from a New Zealand sponge of the genus *Mycale* in 1988 by Munro and his co-workers.[1] The unique structure of **1** was shown to consist of a pederic acid sub-unit (left segment) and an *N*-acyl aminal unit (right segment) (Figure 1). Mycalamide A (**1**) possesses exceptionally potent *in vitro* immunosuppressive activity. As compared to other immunosuppressants, mycalamide A (**1**) is about 10 times more potent than FK 506 and about 1000 times more potent than cyclosporin A.[2] More interestingly, the molecular mechanism of action of mycalamide A (**1**) is different from that of cyclosporin A and FK 506.[2]

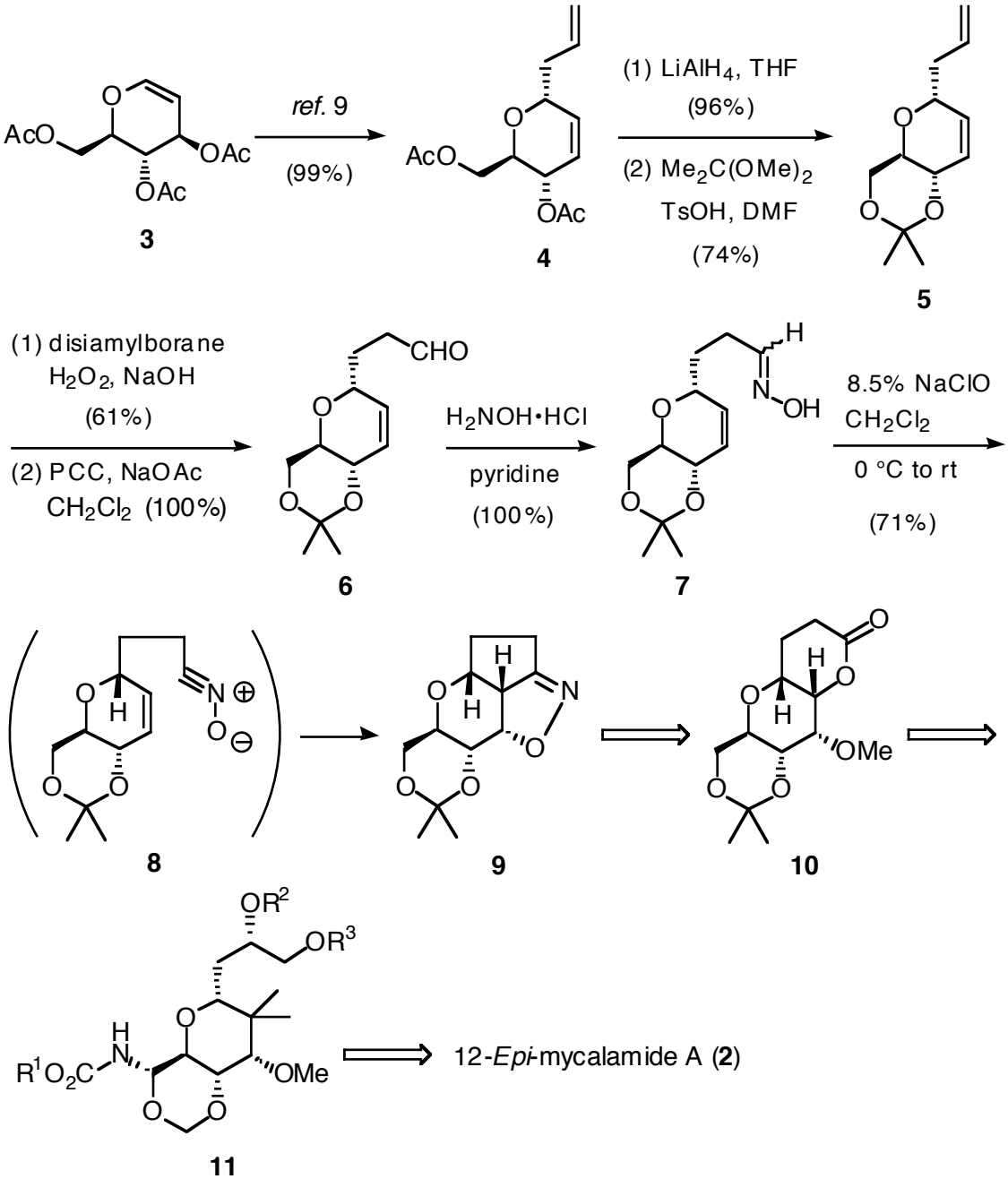


Mycalamide A (**1**): 12-α-H
12-*Epi*-mycalamide A (**2**): 12-β-H

Figure 1

Given its complex architecture coupled with its strong immunosuppressant activity, this family of natural products has attracted considerable attention. Total syntheses of mycalamide A (**1**) have been independently reported by Kishi,[3] Nakata,[4] and Roush.[5] Kociensky has achieved total synthesis of mycalamide B.[6] In addition, studies on mycalamide synthesis have been reported by Hoffmann.[7] As our

own contribution to this area, we have reported synthetic routes to the left and right segments.[8] The binding nature of **1** to the active site is not yet clearly understood. Now we speculate that the bioassay of 12-*epi*-mycalamide A (**2**), having a *trans*-trioxadecalin ring system, may throw some light on the binding nature of **1** with proteins. In this direction we herein report a concise synthesis of a potential key intermediate (***9***) for 12-*epi*-mycalamide A (**2**), starting from commercially available (–)-tri-*O*-acetyl-D-glucal (**3**).



Scheme 1

After diastereoselective allylation (99%),[9] the diacetate (**4**) was subjected to $LiAlH_4$ reduction to afford the corresponding diol (96%), which was treated with 2,2-dimethoxypropane in the presence of TsOH.

Hydroboration of the resulting olefin (**5**) with disiamylborane followed by oxidation provided the primary alcohol (61%), which was oxidized with PCC in the presence of NaOAc to give the aldehyde (**6**). The compound (**6**) was quantitatively transformed into the oximes (**7**) by treatment with hydroxylamine hydrochloride in pyridine.

With convenient access to **7** secure, the stage was now set for the ring closure sequence (INOC reaction).[10] On exposure of the oximes (**7**) to 1.15 equivalent of 8.5% sodium hypochlorite in CH_2Cl_2 (0 °C to room temperature), the desired isoxazoline (**9**) was produced in 71% yield as a single stereoisomer. All protons and carbons of the [2+3] cycloadduct (**9**) were assigned by ^{1}H-^{1}H COSY and ^{1}H-^{13}C COSY experiments. The relative configuration of **9** was established on the basis of NOESY correlations between angular protons as depicted in Figure 2.

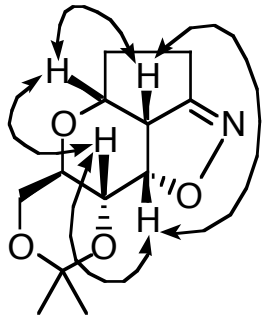


Figure 2. NOE experiments of isoxazoline (**9**)

We anticipate that the crucial [2+3] cycloadduct (**9**) might be conveniently converted to 12-*epi*-mycalamide (**2**) by appropriate functional group manipulations as depicted in Scheme 1. After reductive hydrolysis of the isoxazoline ring of **9** followed by methylation and Baeyer–Villiger oxidation, the resulting lactone (**10**) could be transformed into 12-*epi*-mycalamide A (**2**) through carbomate (**11**).

In conclusion, the potential key intermediate (**9**) for 12-*epi*-mycalamide A (**2**) has been easily prepared employing intramolecular nitrile oxide cycloaddition (INOC) reaction of the oximes (**7**). The significant features of our synthesis are as follows: (i) the present synthesis commences with commercially available (–)-tri-*O*-acetyl-D-glucal (**3**) and (ii) the route is 7 steps in the longest linear sequence with an average yield of 86% per step.

REFERENCES AND NOTES

Dedicated to Professor A. I. Meyers on the occasion of his 70th birthday.

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