Asymmetric Vinylogous Mukaiyama Aldol Reactions Using Vinylketene *N,O*-Acetals in Total Syntheses of Natural Products

Seijiro Hosokawa* and Kuniaki Tatsuta*

Department of Applied Chemistry, Faculty of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

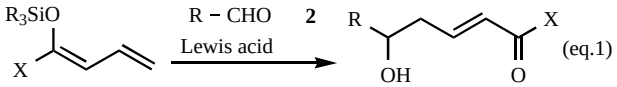
Abstract: Asymmetric vinylogous aldol reaction is a powerful methodology to introduce a multi functional group in the stereoselective manner. Recently, we have developed highly stereoselective vinylogous Mukaiyama aldol reactions using vinylketene *N,O*-acetals possessing the chiral oxazolidone. Our methodology has been applied to the asymmetric syntheses of natural products to establish the short and efficient routes. This review focuses on the asymmetric vinylogous Mukaiyama aldol reactions using vinylketene *N,O*-acetals in total syntheses of natural products.

Keywords: Vinylogous Mukaiyama aldol reaction, vinylketene *N,O*-acetal, remote stereoinduction, total synthesis, natural product, polyketide.

1. INTRODUCTION

Polyketides have attracted chemists with their elegant figures and remarkable bioactivities, and have contributed to the growth of synthetic organic chemistry including the methodologies of stereoselective construction of a carbon chain, organometallic chemistry, macrocyclization, and stereoselective glycosylation as well as protection of functional groups. Polyketides have been a big group and their polypropionate and/or polyacetate chains possess a variety of chiral center arrangement and oxidation state. The acyclic asymmetric syntheses are applicable to these systems and the success to the short step synthesis depends on the choice and delivery of the chiral sources. Convergency is also indispensable to establish an efficient route. We already achieved the total syntheses of the natural products belonging to this group [1].

Vinylogous Mukaiyama aldol reaction is one of the popular methodology of natural product synthesis [2,3]. Silyl dienol ether **1** couples with aldehyde **2** in the presence of Lewis acid to give homoallylic alcohol **3** (eq. 1). In the stereoselective synthesis of natural products, the reaction has been used by combination of an achiral dienol ether and a chiral aldehyde. Recently, asymmetric vinylogous Mukaiyama aldol reactions have been developed, by which the functionalized C4 unit is introduced with stereoselective construction of a hydroxyl group. These methodologies have made it possible to synthesize polyketides in short steps.



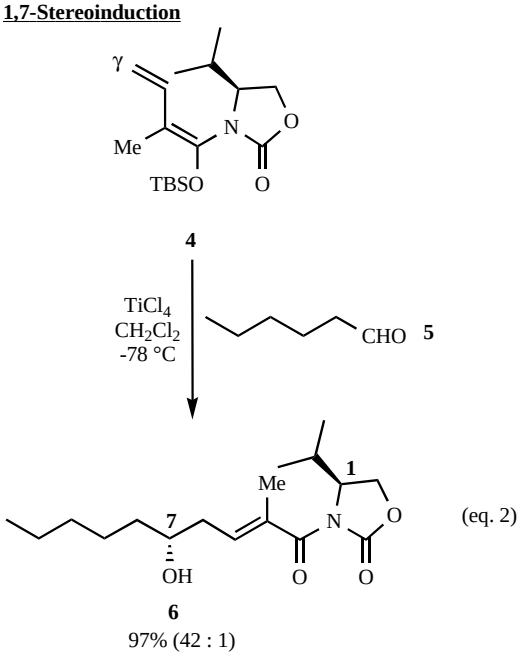
1 **3**

Recently, catalytic asymmetric vinylogous Mukaiyama aldol reactions have been developed, which have been described in excellent reviews [4]. In this review we focus on the application of vinylogous Mukaiyama aldol reactions using vinylketene *N,O*-acetals to the total synthesis of natural products [5].

2. REMOTE STEREOINDUCTION WITH VINYLKETENE *N,O*-ACETALS

Recently, we developed highly stereoselective vinylogous Mukaiyama aldol reactions using vinylketene *N,O*-acetals possessing the chiral oxazolidone (eq. 2 and 3) [5]. The reaction proceeded at the γ position to give homoallylic alcohol in the stereoselective manner. Vinylketene *N,O*-acetal **4** promoted 1,7-stereoinduction to furnish **6** in high yield with excellent stereoselectivity, and vinylketene *N,O*-acetal **7** advanced 1,6,7-stereoinduction to give *anti* adduct **9** as a single isomer in quantitative yield. The vinylogous Mukaiyama aldol reactions using vinylketene *N,O*-acetals proceeded with typical aldehydes in high stereoselectivity (Table **1** and **2**).

1,7-Stereoinduction



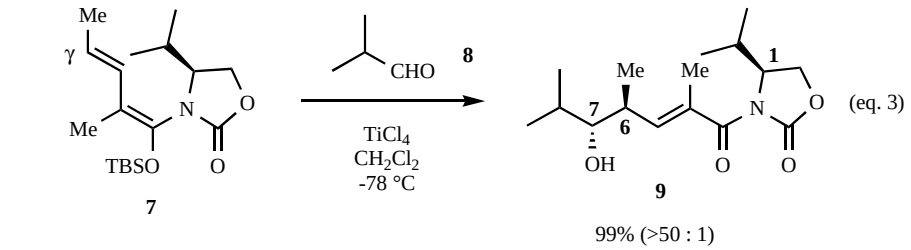
6

97% (42 : 1)

*Address correspondence to these authors at the Department of Applied Chemistry, Faculty of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan; E-mail: seijiro@waseda.jp; tatsuta@waseda.jp

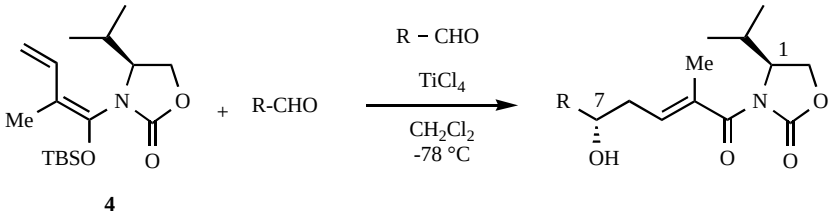
1570-193X/08 $55.00+.00 **© 2008 Bentham Science Publishers Ltd.**

1,6,7-Stereoinduction



99% (>50 : 1)

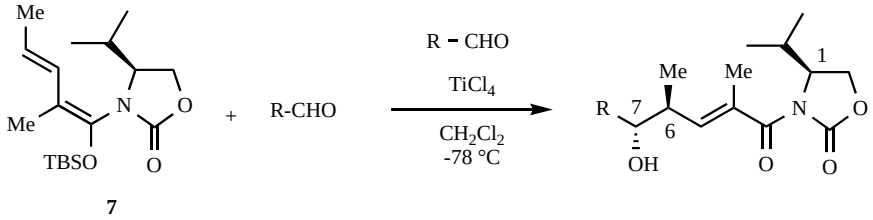
Table 1. Vinylogous Mukaiyama Aldol Reaction Using Vinylketene *N,O*-acetal 4



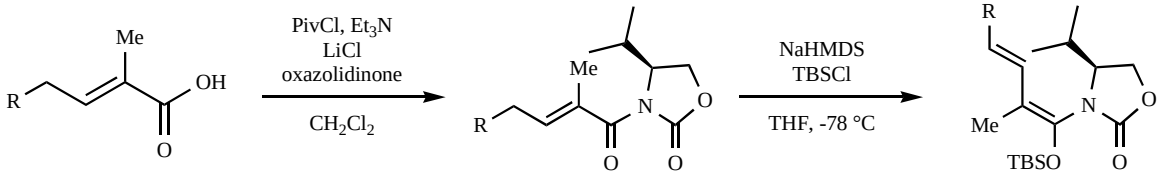
Entry	R	Yield (%)	ds
1	$CH_3(CH_2)_4$	97	42:1
2	$CH_3(CH_2)_{10}$	92	94:1
3	$(CH_3)_2CH$	95	40:1
4	(*E*)-CH_3CH=CH	54 (87)[a]	20:1
5	(*E*)-CH_3CH_2CH=C(CH_3)	55 (65)[a]	86:1
6	Ph	94	30:1

[a]The yield in parentheses is based on the recovery of vinylketene **4**.

Table 2. Vinylogous Mukaiyama Aldol Reaction Using Vinylketene *N,O*-acetal 7



Entry	R	Temp. (°C)	Yield (%)	ds
1	$CH_3(CH_2)_4$	-78	87	>50:1
2	$(CH_3)_2CH$	-78	99	>50:1
3	(*E*)-CH_3CH_2CH=C(CH_3)	-78~-40	67 (81)	>50:1
4	Ph	-78~-55	90	20:1



R = H : Tiglic acid (**10**)
R = Me : 2-Methyl-2-pentenoic acid (**11**)

R = H : **12**
R = Me : **13**

R = H : **4**
R = Me : **7**

Scheme 1. Preparation of vinylketene *N,O*-acetals **4** and **7**.

The vinylketene *N*,*O*-acetals **4** and **7** are prepared in two steps from commercially available carboxylic acids (Scheme **1**). They are crystals easy to handle and are so stable that they are purified by silica gel column chromatography.

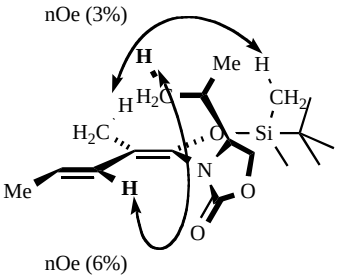


Fig. (1). nOe correlation of vinylketene *N*,*O*-acetal **7** in $CDCl_3$.

NMR studies revealed the geometry of the diene (Fig. **1**). The nOe relations were observed between methyl group at the α-position of the vinylketene *N*,*O*-acetal and a methyl group of TBS, and between the olefinic proton at the β-position of the vinylketene *N*,*O*-acetal and methyl group of the isopropyl group. Namely, the larger methyl group (sp^3 carbon) located *trans* to the bulky oxazolidone and the smaller olefinic carbon (sp^2) located *cis*. X-ray crystallography confirmed the stereochemistry of the vinylketene *N*,*O*-acetals including the location of the oxazolidone (Fig. **2**) [6]. These feature the impressible structure including axial chirality between the diene planer and the oxazolidone. The isopropyl group covers over the one face, which interferes the attack of an electrophile. The rotation of oxazolidone was restricted by TBS group and the dienolate chain. It is quite reasonable that in the solution the vinylketene *N*,*O*-acetal would take a similar conformation as crystalline state at low temperature. Therefore, the electrophile approached from another face to proceed the reaction stereoselectively. The proposed transition state of vinylogous Mukaiyama aldol reactions is shown in Fig. (**3**). The stereochemistry of the methyl group at the α-position is important in achieving a high level of stereoselectivity in the present vinylogous Mukaiyama aldol reaction. The stereochemistry of vinylketene *N*,*O*-acetal **15**, the α-Me-missing analogue of **4** derived from crotonic acid, was established to be *trans* configuration of the terminal olefin and the chiral auxiliary by nOe experiment (Scheme **2**). Vinylogous Mukaiyama aldol reaction using **15** and hexanal (**5**) was carried out to obtain the aldol adduct **16** in moderate yield (38%) with moderate stereoselectivity (*syn*:*anti* = 4:1). Interestingly, the stereochemistry at C7 position of the adduct **16** was opposite to that of **6** [5]. The lower selectivity is due to the longer distance between the stereogenic center of **15** and the terminal carbon, the reaction site of the diene. On the other hand, methyl group at the α-position of the vinylketene *N*,*O*-acetal **4** (eq. 2) enforces the direction of the diene moiety to make close to the chiral auxiliary.

Since these reactions afford the multifunctional products with high stereoselectivity, the vinylogous Mukaiyama aldol reactions using vinylketene *N*,*O*-acetals **4** and **7** are applicable to the total synthesis of natural products and make it possible to construct a polyketide skeleton in short steps.

3. TOTAL SYNTHESES OF NATURAL PRODUCTS HAVING POLYPROPIONATE STRUCTURE

3.1. Total Synthesis of (+)-trichostatin D

Trichostatin D (**17**) was isolated as an inducer of phenotypic reversion in oncogene-transformed cells from the broth of an actinomycete *Streptomyces violaceusniger* (Fig. **4**) [7]. Because various oncogenes correlate with tumor phenotypes, the inducers of phenotypic reversion in oncogene-transformed cells are expected to be selective antitumor agents. Trichostatin D (**17**) has a chiral center at the middle of the chain structure. This structure was suitable for application of our remote stereoinduction reaction [5]. The total

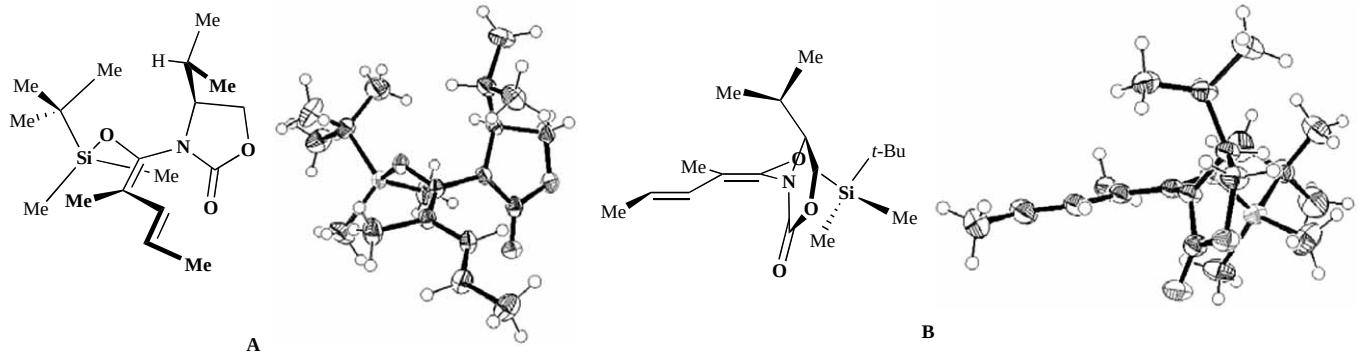


Fig. (2). ORTEP drawing of crystalline **7**. **A**). front view, **B**). side view.

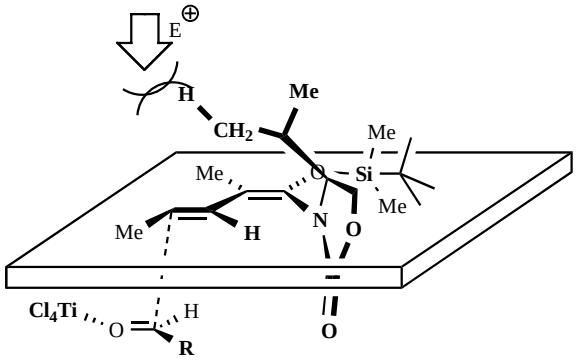
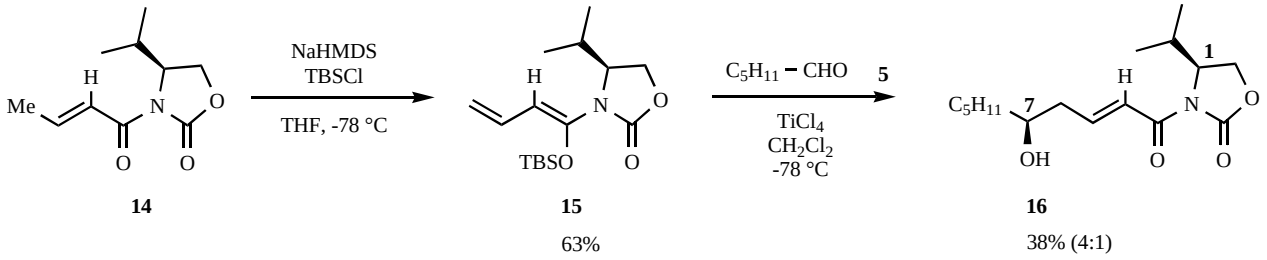
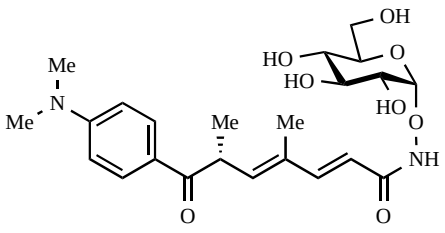


Fig. (3). The proposed transition state of the vinylogous Mukaiyama aldol reaction.



Scheme 2. Vinylogous Mukaiyama aldol reaction with crotonic acid derivative.

synthesis of trichostatin D was accomplished as shown in Scheme **3** [6].



Trichostatin D (17)

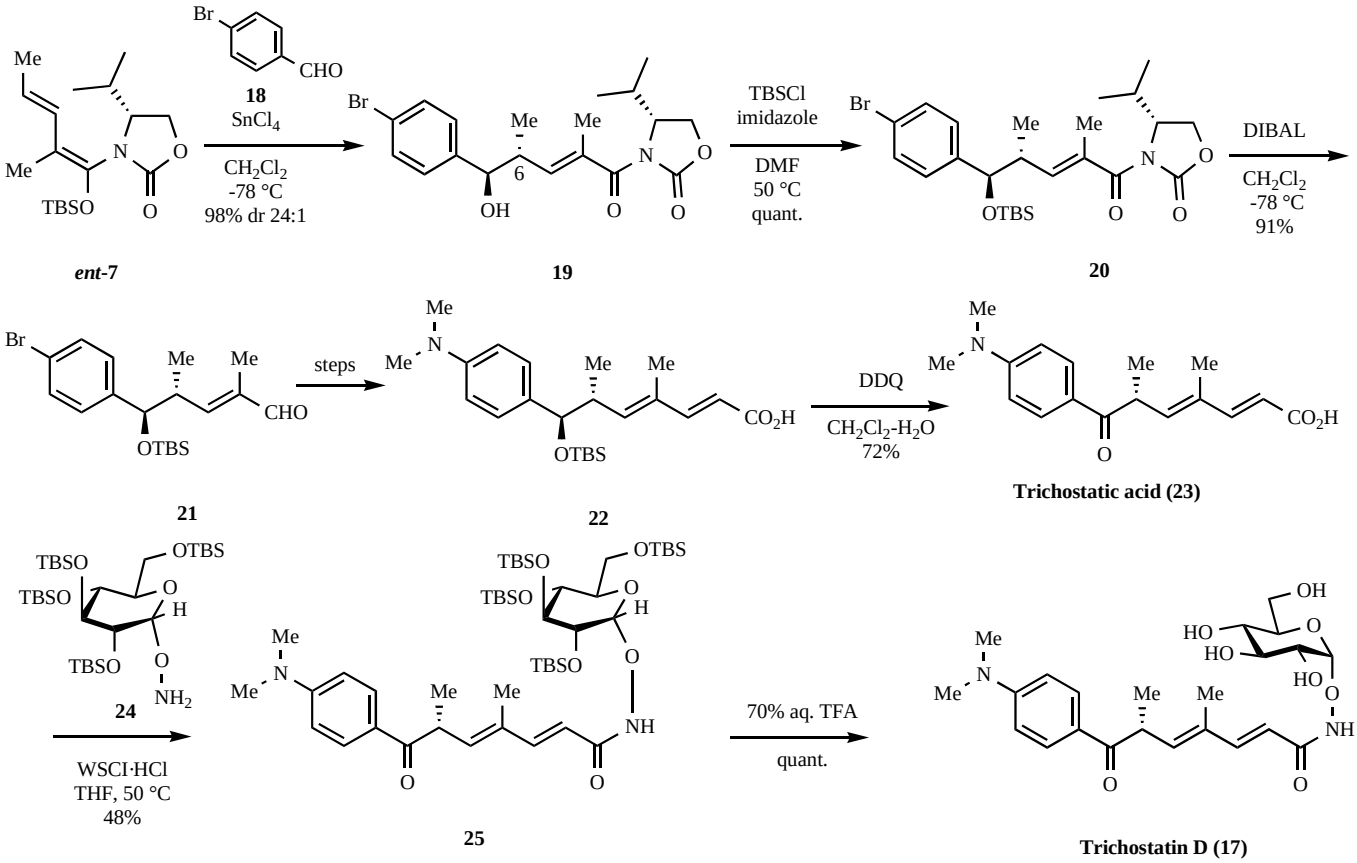
Fig. (4). Structure of trichostatin D.

The remote stereoinduction method with the enantiomer of the vinylketene *N,O*-acetal **7** (***ent*-7**) and *p*-bromobenzaldehyde (**18**) proceeded to give the *anti* adduct **19** in excellent yield (98%) with high diastereosmeric ratio (dr 96:4, both isolated isomers possessed the desired 6*R* configuration). After protection as the TBS ether **20**, the imide **20** was directly converted to the α,β-unsaturated aldehyde **21** in high yield (91%) by treatment with DIBAL at -78°C. After transformation to the dienoic acid **22**, oxidation at the benzylic position gave (+)-trichostatic acid (**23**), the common polyketide chain of the trichostatin family.

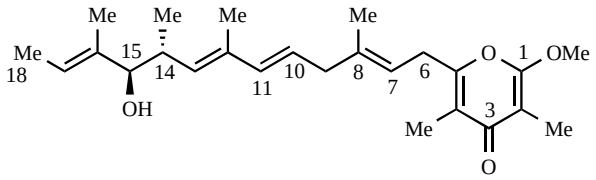
Finally, condensation of **23** and **24**, the glycoside prepared by our glycosylation method [8], and successive de-O-protection afforded (+)-trichostatin D (**17**).

3.2. Total Synthesis of (+)-actinopyrone A

Actinopyrone A (**26**) was isolated from *Streptomyces pactum* S12538 as a relatively unstable compound possessing coronary vasodilating activity and antimicrobial activity (Fig. **5**) [9]. Later, it was also found to exhibit potent anti-*Helicobacter pylori* activity [10].



Scheme 3. Total synthesis of trichostatin D.



Actinopyrone A (26)

Fig. (5). Structure of actinopyrone A.

In addition to multi-bioactivity, little toxicity makes actinopyrone A (**26**) an attractive candidate for chemotherapy. However, the instability of **26** makes further research difficult; even the absolute structure had not been disclosed until our total synthesis. The total synthesis of actinopyrone A (**26**) was achieved as below [11].

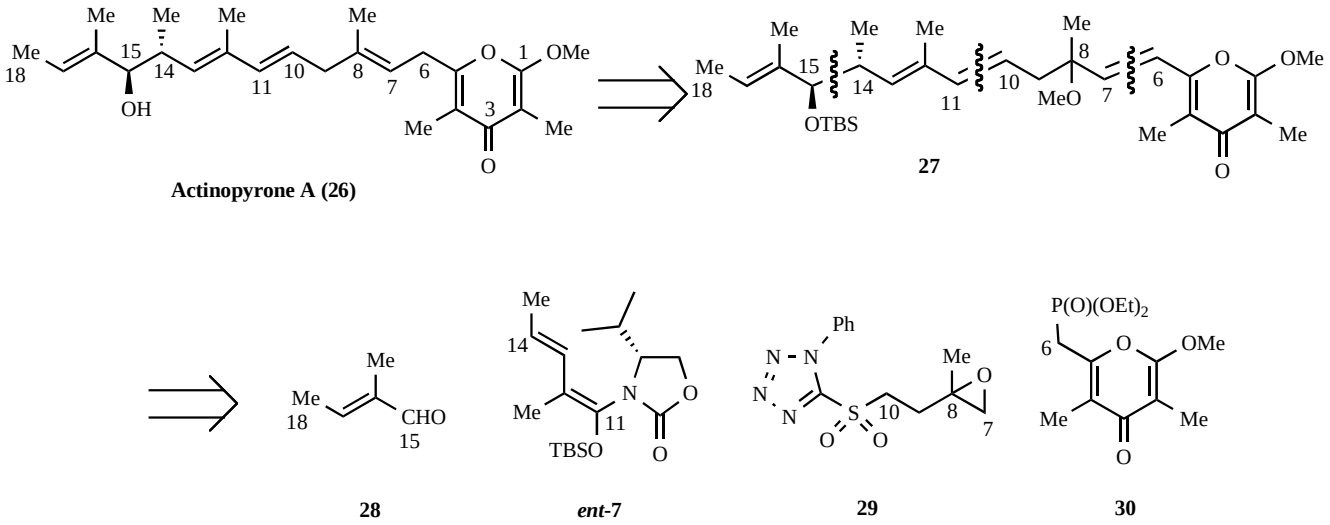
Our synthetic plan is shown in Scheme **4**. To avoid instability of actinopyrone A (**26**), the conjugated pyrone **27** was set up as the precursor. The precursor **27** would be subjected to the reductive de-conjugation of the conjugated pyrone moiety in the final stage of the synthesis. The conjugated pyrone **27** might be synthesized by connection of the four components **28**, ***ent*-7**, **29**, and **30**. The stereogenic centers C14 and C15 of **27** should be constructed by our developed methodology using the chiral vinylketene *N*,*O*-acetal ***ent*-7** [6].

Stereoselective construction of the C11-C18 unit **31** was achieved by our remote stereocontrol method (Scheme **5**) [5]. The coupling of silyl dienolate ***ent*-7** and tiglic aldehyde (**28**) in the presence of $TiCl_4$ gave the C14-C15 *anti* adduct **31** as a single isomer. Protection of **31** as TBS ether followed by reduction with DIBAL at -78°C to remove the chiral auxiliary gave the aldehyde **32** [6]. The aldehyde **32** was converted to the triene **33** by Kocienski's method [12] using the sulfone **29**. The epoxide **33** was transformed under acidic conditions to the primary alcohol **34**, which was oxidized to afford the aldehyde **35**. The pyrone moiety was introduced by the Horner-Wadsworth-Emmons reaction of **35** with the phosphonate **30** to give the stable intermediate **27**. De-O-silylation of **27** under acidic conditions proceeded to provide **36**. Treatment of the vinylpyrone **36** with SmI_2 in the presence of *i*-PrOH promoted reductive de-conjugation to give actinopyrone A (**26**) in 70% yield *via* the intermediate **37**. The absolute structure of actinopyrone A (**26**) was determined to be the (14*R*, 15*R*)-configuration by the total synthesis.

3.3. Stereoselective Construction of the Vinylogous *Anti* Aldol Compounds

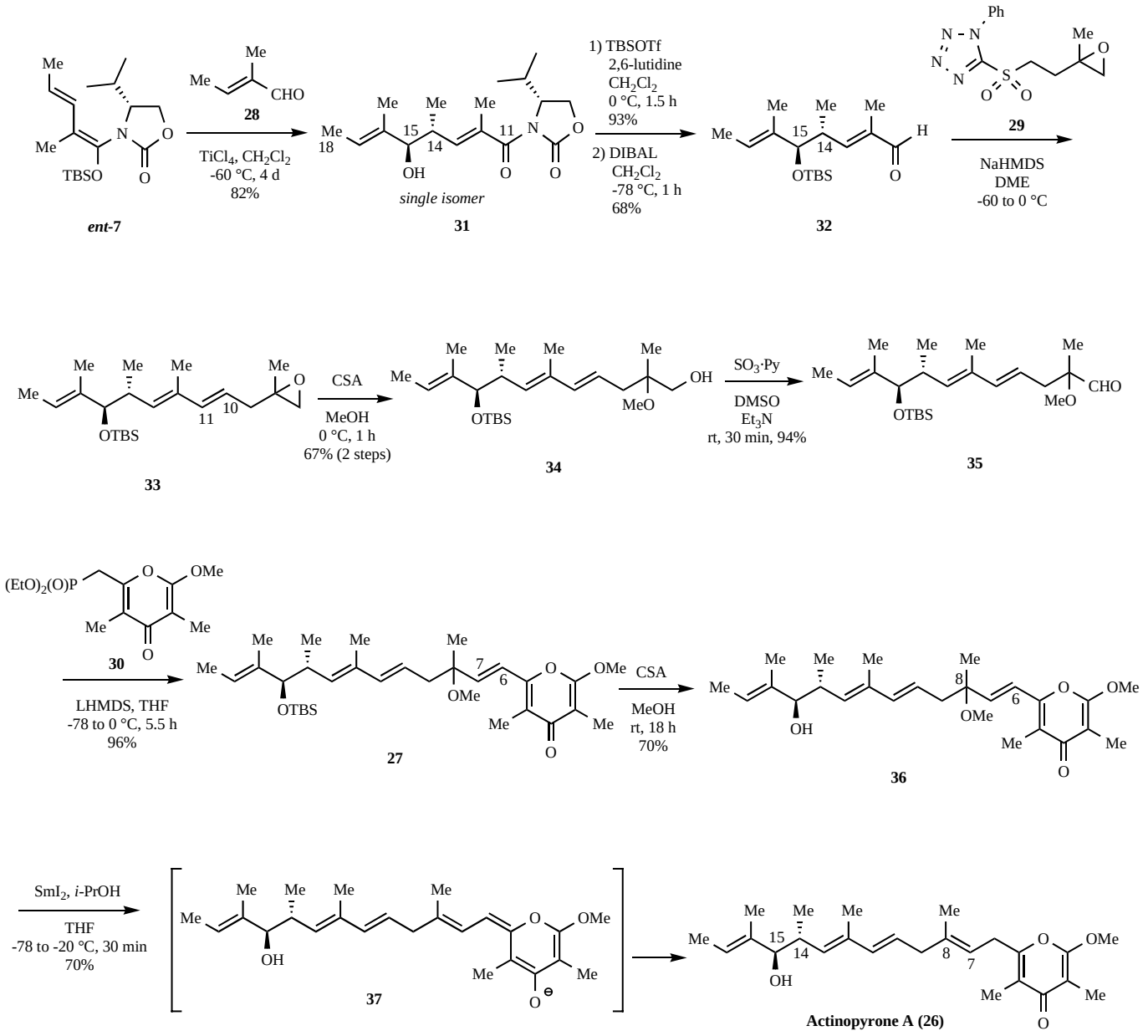
Although the vinylogous *anti* aldol is the structure available by hitherto asymmetric synthesis, stereoselective synthesis of the arrangement takes a long sequence to give the desired product in low yield over all.

Boger and co-workers accomplished the total synthesis of piericidin A1 (**38**) [13] possessing the same side chain as actinopyrone A (**26**) (Fig. **6**) [14]. In the synthesis, they examined some methods to construct aldehyde **32**, the C6-C13 unit of piericidin A1 (**38**) (C11-C18 unit of actinopyrone A) (Scheme **6**). At First, Primary alcohol **41** was synthesized by Whiting procedure [15]. Although Mukaiyama aldol reaction with **39** gave *anti* aldol adduct **40** in good yield, successive protection and reduction proceeded in moderate yield and thus alcohol **41** was obtained in low yield over 3 steps. Additional 4 steps were required to obtain aldehyde **32**. Secondly, Nakao's synthesis of aldehyde **42** [16a], utilizing the procedure developed by Heathcock using 2 equivalent of *n*-Bu_2BOTf to promote *anti* aldol reaction, was applied to **32** [16b]. Boger group adopted this procedure and obtained *anti* aldol adduct **46** in 67% yield. Finally, Evans method using $MgCl_2$ [17] was carried out to obtain *anti* aldol adduct **48** in 49% yield. Both Heathcock and Evans methods gave *anti* aldol adducts in high stereoselectivity, however, yields were not so high and additional several steps were necessary to obtain aldehyde **32**. On the other hand, our procedure in the total synthesis of actinopyrone A afforded **31** in high yield as a single isomer (Scheme **5**) [11]. Additional 2 steps including protection and reduction gave the desired aldehyde **32** in good yield. Thus, the remote asymmetric induction methodology is an effective and straightforward method to obtain the vinylogous *anti* aldol compounds.



Actinopyrone A (26) **27** **28** ***ent*-7** **29** **30**

Scheme 4. Synthetic plan of actinopyrone A.



Scheme 5. Total synthesis of actinopyrone A.

3.4. Total Synthesis of (-)-lagunamycin

Lagunamycin (**49**), a metabolite isolated from the culture filtrate of *Streptomyces* sp. AA0310, showed inhibitory activity against 5-lipoxygenases and antibacterial activity against Gram-positive bacteria (Fig. **7**) [18a]. The structure of lagunamycin (**49**) has been elucidated to possess the diazotetraoxoquinoline skeleton with the branched alkyl chain by a combination of NMR studies and chemical degradations [18b]. Existence of the rotational isomers caused by the bulky side chain against the 9-methyl group attached to the quinoline plane has been believed because of the complexity of the NMR spectra of lagunamycin (**49**) [18b]. Interested in the structure and bioactivities, we embarked on synthetic studies of lagunamycin (**49**) [19].

Our retrosynthetic analysis is shown in Scheme **7**. The diazo group would be introduced in the final step and oxygenated quinoline moiety could be synthesized from **50** by Knorr condensation to avoid the difficulty from steric interaction between the side chain and the quinolone moiety. The β-ketoamide **50** would be obtained by coupling of the β-hydroxycarboxylic acid **51** and the aniline **52** followed by oxidation.

The actual synthesis of lagunamycin (**49**) started from stereoselective and efficient construction of the side chain moiety **51** (Scheme **8**). The remote stereoinduction using the ketene *N,O*-acetal **7** and isobutyraldehyde (**8**), gave the adduct **9** in almost quantitative yield (99%) with excellent stereoselectivity in multigram scale [5]. De-oxygenation at C5' position was realized by hydride reduction with the sulfonate **53**. Treatment of phenylsulfonate **53** with super hydride ($LiBEt_3H$) made rapid progress of the reductive removal of oxazolidone ring at -78 °C and promoted desulfonation at room temperature to give the primary alcohol

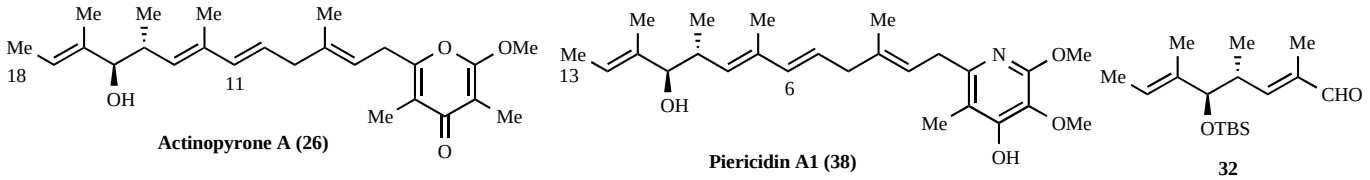
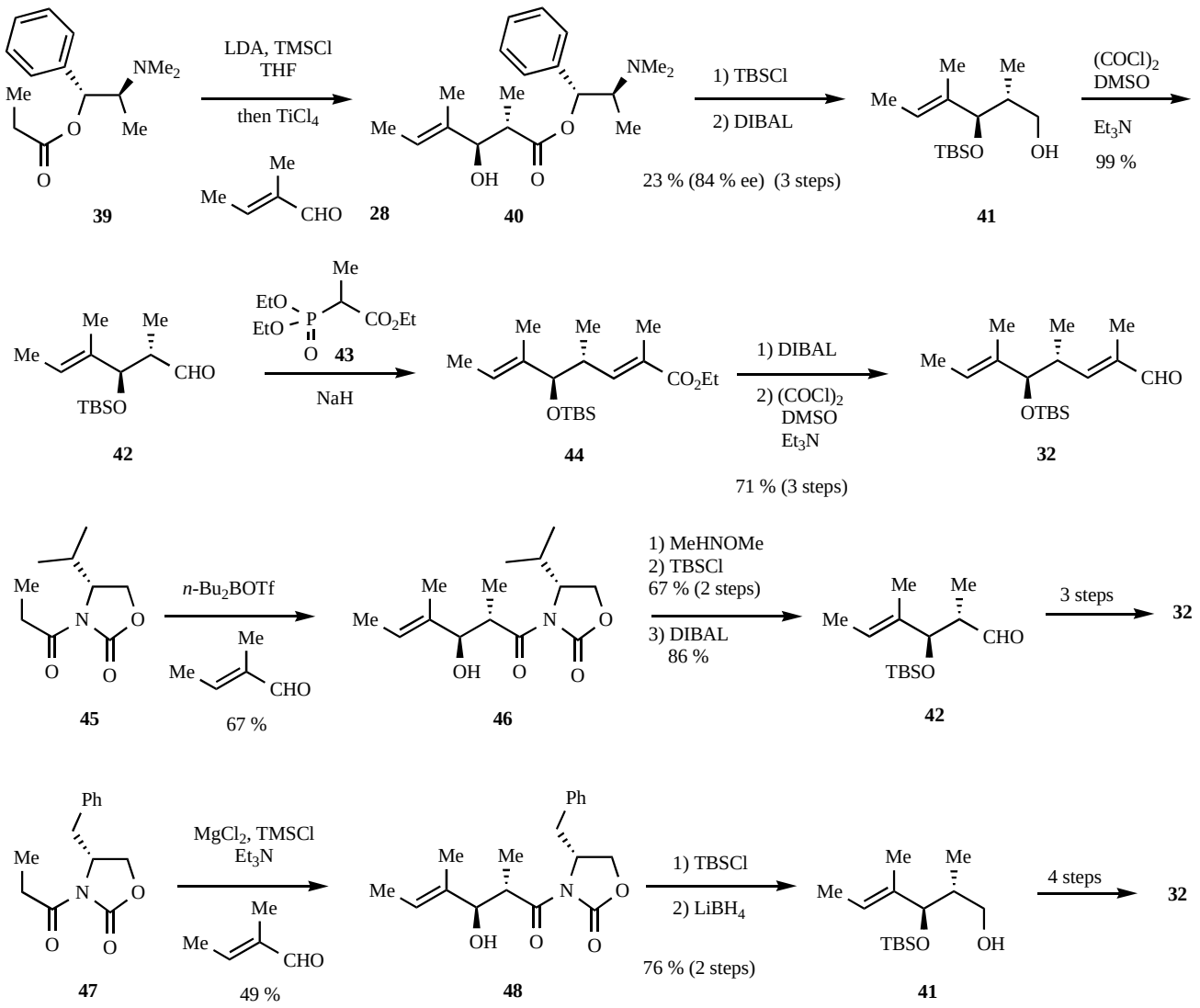


Fig. (6). Structure of actinopyrone A, piericidin A1, and aldehyde **32**.



Scheme 6. Synthetic studies on aldehyde **32** using aldol reactions.

54. The resulting allylic alcohol **54** was oxidized to aldehyde **55**, which was submitted to aldol reaction with the dianion derived from propionic acid to give β-hydroxycarboxylic acid **51**.

Coupling of the carboxylic acid **51** and aniline **52** [20] with WSCI afforded anilide **56** in high yield. The anilide **56** was treated with *o*-iodoxybenzoic acid (IBX) to promote Nicolaou oxidation [21] quickly to give the quinone moiety and oxidation of allylic alcohol slowly (overnight) at room temperature to give β-ketoamide **57**. The *o*-quinone **57** was transformed to quinolone **60** in a one-pot procedure. Sub-

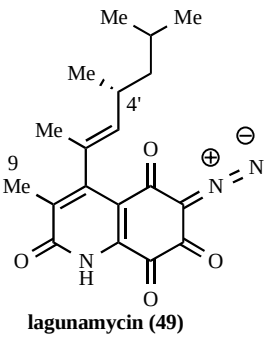
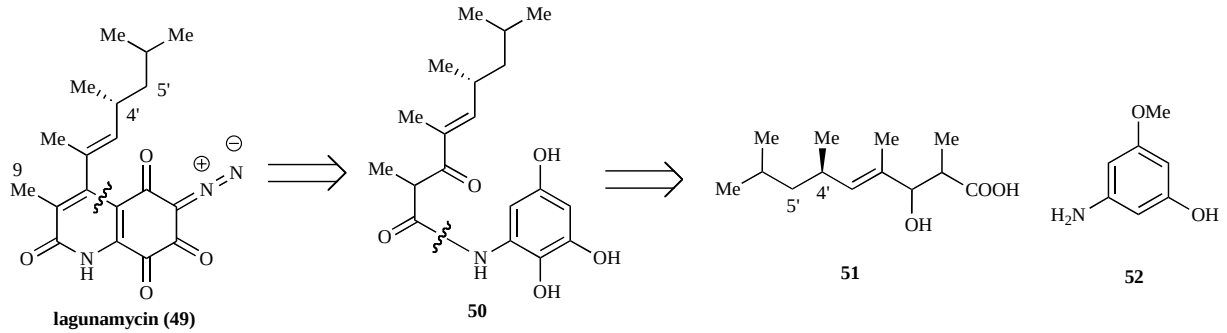
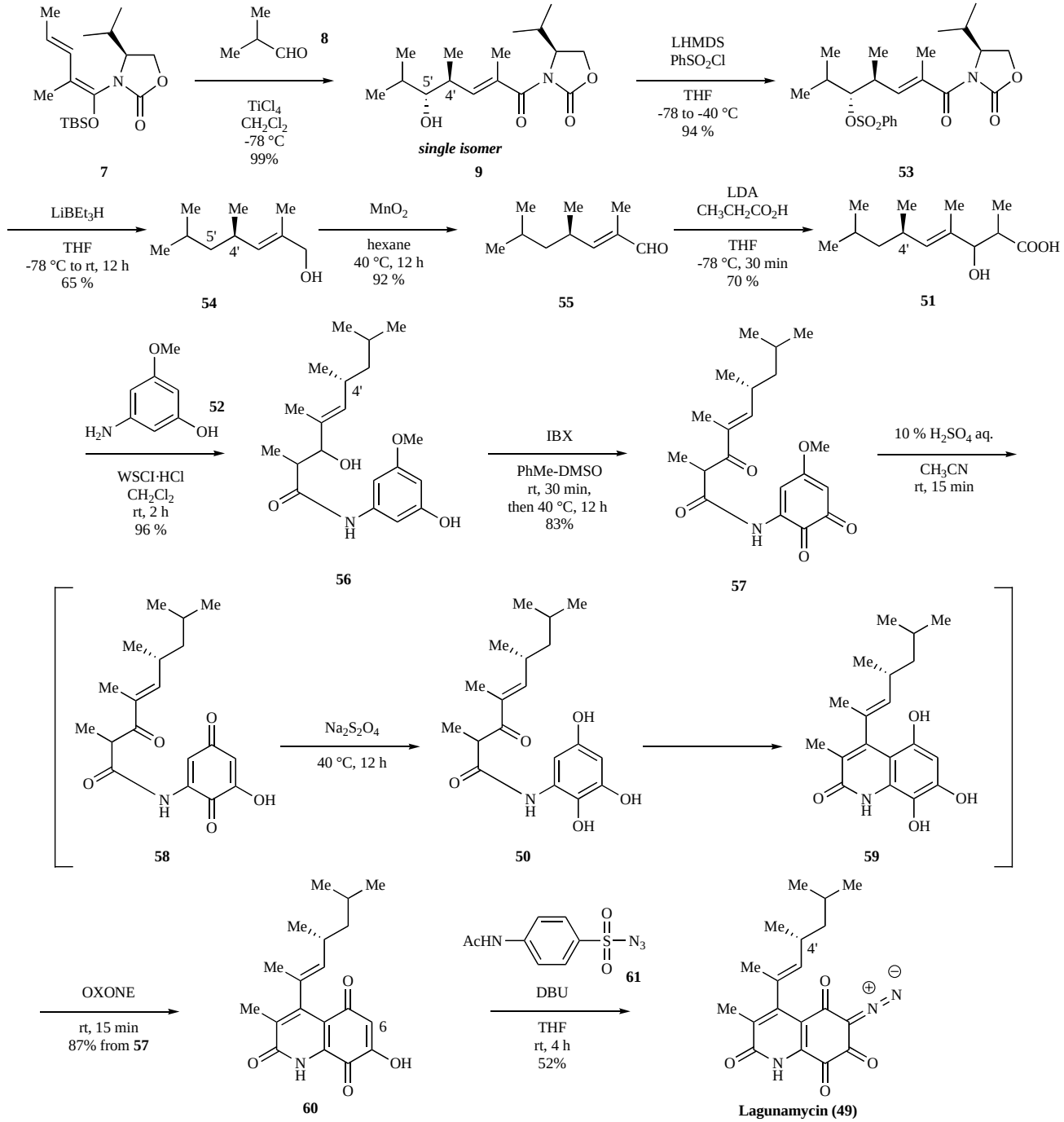


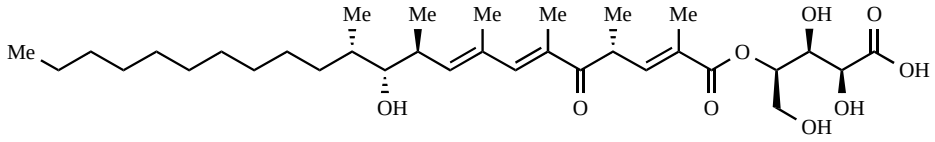
Fig. (7). Structure of lagunamycin.



Scheme 7. Synthetic plan of lagunamycin.



Scheme 8. Total synthesis of lagunamycin.



Khafrefungin (62)

Fig. (8). Structure of khafrefungin.

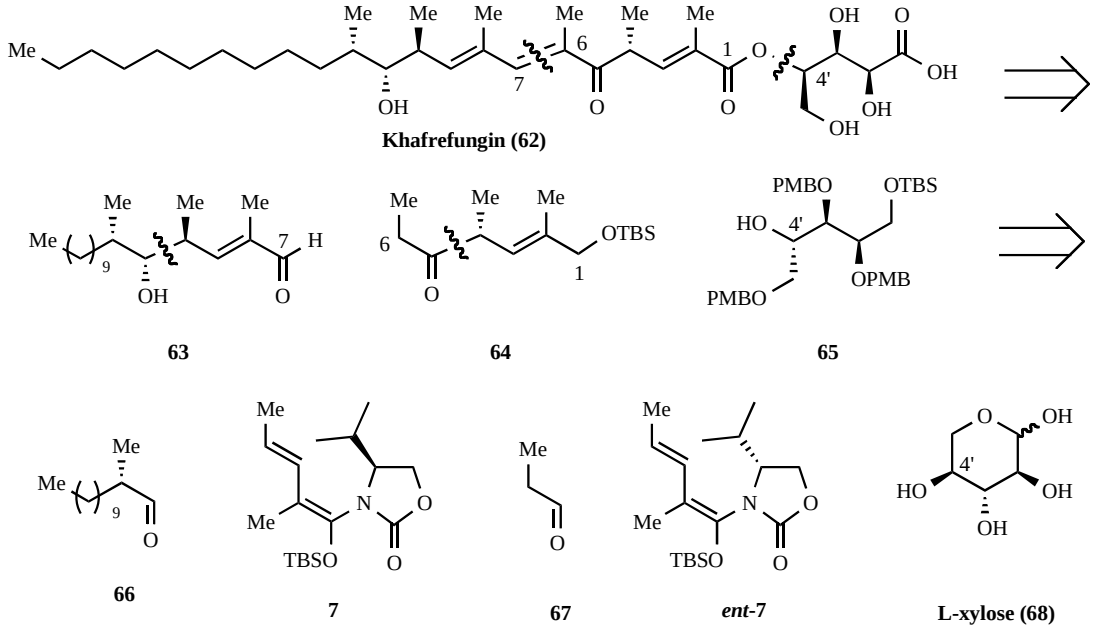
sequent manipulation of quinone **57** including i) hydrolysis of methyl ether to convert to quinone **58**, ii) selective reduction of the quinone moiety with $Na_2S_2O_4$ to provide the labile trihydroxyanilide **50**, iii) Knorr condensation under acidic conditions [22] to give quinolone **59**, and iv) oxidation of hydroquinone with Oxone delivered *p*-quinone **60** in 87% over all yield. Finally, treatment of **60** with *p*-acetoaminophenylsulfonyl azide (**61**) in the presence of DBU gave lagunamycin (**49**), of which the analytical data were consistent with those reported previously [18]. Thus, total synthesis of lagunamycin was accomplished, and the absolute structure of **49** was determined as 4'*R* configuration.

3.5. Total Synthesis of Khafrefungin

Khafrefungin (**62**) is an antifungal agent isolated from the fermentation culture MF6020 by Merck group in 1997 as an inhibitor of inositol phosphorylceramide (IPC) synthase (Fig. **8**) [23]. IPC synthase catalyzes the fungal specific step in *Saccharomyces cerevisiae* and pathogenic fungi such as *Cryptococcus neoformans* and *Candida albicans* in picomolar and nanomolar concentrations and causes ceramide accumulation [24]. Distinct from other sphingolipid inhibitors, khafrefungin does not impair sphingolipid synthesis in mammals. Therefore, khafrefungin is a candidate of drugs working as specific antibiotics. The first total synthesis and structural determination of khafrefungin have been achieved by Kobayashi and co-workers on the basis of their catalytic and enantioselective aldol reaction [25]. Recently, we have achieved the stereoselective and convergent synthesis of khafrefungin using vinylketene *N,O*-acetals [26].

Our synthetic plan of khafrefungin (**62**) is shown in Scheme **9**. The target molecule **62** was divided into three chiral building blocks **63**, **64**, and **65**. Propionates **63** and **64** would be constructed by vinylogous Mukaiyama aldol reactions with *N,O*-acetals **7** and ***ent*-7**, respectively. Polyhydroxy unit **65** might be derived from L-xylose (**68**), in which the stereochemistry of C4' position should be inverted by Mitsunobu conditions at the stage of coupling with the aliphatic chain.

The fragment **63** was constructed in stereoselective manner as shown in Scheme **10**. *Anti* aldol adduct **70** was obtained in almost quantitative yield with excellent stereoselectivity by our methodology using vinylketene *N,O*-acetal **7** and aldehyde **66** derived from commercially available methyl (*R*)-β-hydroxyisobutyrate (**69**). Protection of alcohol followed by reduction gave aldehyde **63**, the left end fragment, in good yield. The center unit **64** was synthesized in 4 steps starting from propionaldehyde (**67**). The addition reaction of ***ent*-7** to propionaldehyde (**67**) also afforded *anti*-adduct **71** in high yield with excellent stereoselectivity. Reductive removal of the chiral auxiliary and successive selective protection and oxidation gave the C1-C6 unit **64**. Titanium-mediated aldol reaction with **63** and **64** proceeded stereoselectively to afford C6-C7 *syn* aldol **72** [27]. The al-



Khafrefungin (62)

63 **64** **65**

66 **7** **67** ***ent*-7** **L-xylose (68)**

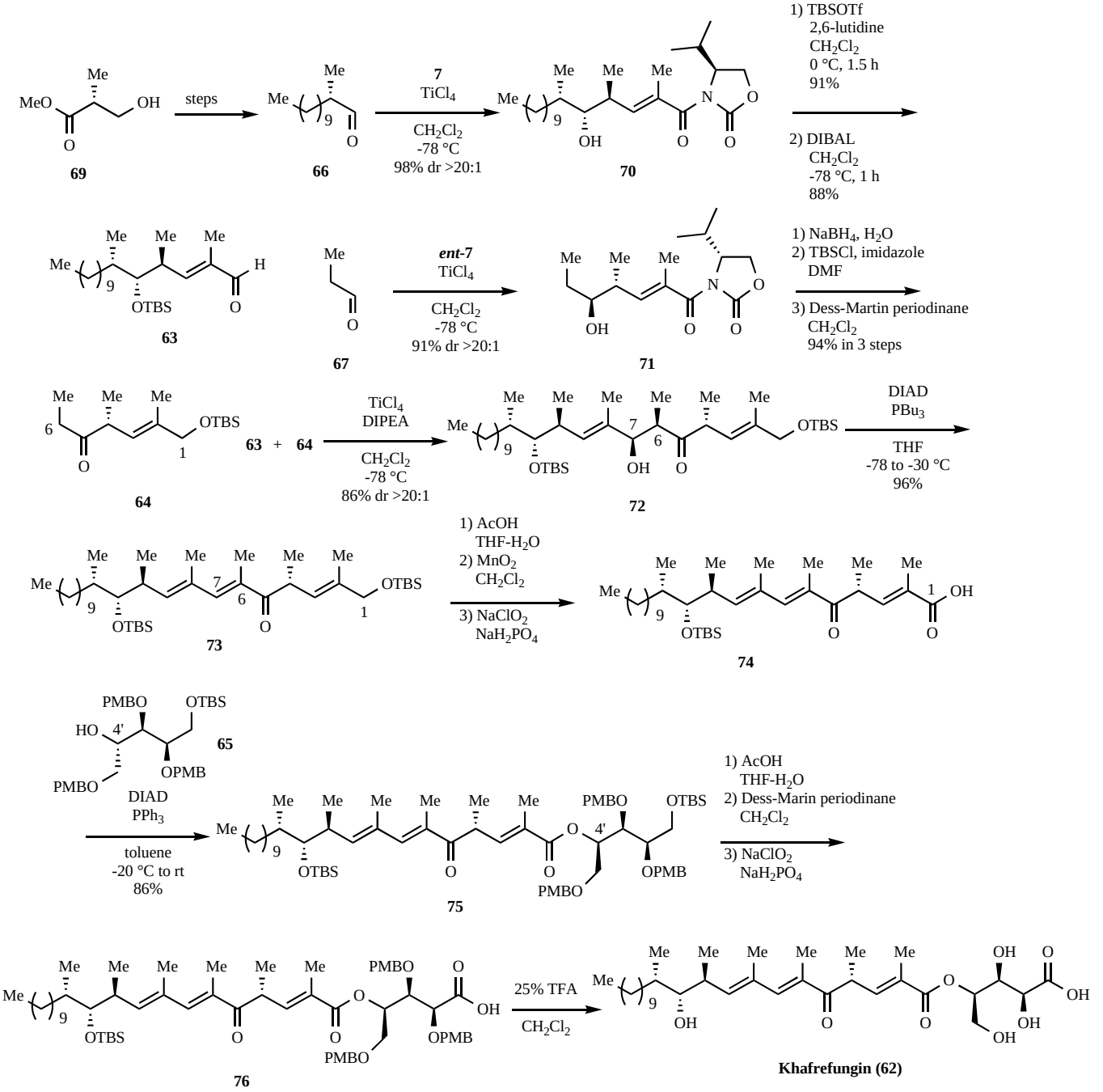
Scheme 9. Synthetic plan of khafrefungin.

dol adduct was submitted to dehydration in the presence of DIAD and PBu_3 to give C6-C7 double bond of conjugated enone **73** in excellent yield [28]. Sequential deprotection and oxidation of the terminal alcohol furnished carboxylic acid **74**. Mitsunobu reaction with **74** and **65** provided ester **75** possessing the desired stereogenic centers. Selective de-O-protection of the primary alcohol and successive oxidation gave the carboxylic acid **76**. Simultaneous removal of TBS and PMB groups under the acidic conditions furnished khafrefungin (**62**).

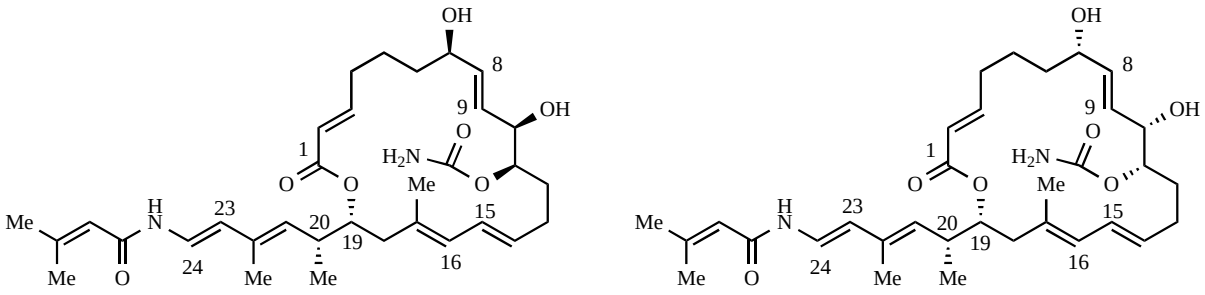
Therefore, the vinylogous Mukaiyama aldol reaction using vinylketene *N,O*-acetal was applied twice to stereoselective synthesis of khafrefungin. Both proceeded to give *anti* adduct in high yield with excellent stereoselectivity. The method realizes efficient and convergent synthesis of the multifunctional polyketides chain with flexibility on stereochemistry.

3.6. Total Synthesis and Structure Revision of Palmerolide A

Recently, an antitumor macrolide palmerolide A [29] was synthesized by two groups independently and the structure was revised by the total syntheses (Fig. **9**) [30, 31]. Interestingly, both groups used the vinylogous Mukaiyama aldol



Scheme 10. Total synthesis of khafrefungin.



Palmerolide A (proposed) (77) **Palmerloide A (revised) (78)**

Fig. (9). Structure of palmerolide A (the proposed structure and the revised structure).

reaction to construct the same moiety of the attractive macrolide.

Palmerolide A has drawn attention with an impressive molecular architecture and bioactivity including selective cytotoxicity against the melanoma cell line UACC-62 [29]. Palmerolide was isolated from an organism found in shallow waters around Anvers Island on the Antarctic Peninsula, one of the most inaccessible areas of the world in conjunction with commercial exploitation prohibit by Antarctic Treaty. Therefore, total synthesis remains as the only option to ensure investigation of bioactivities of palmerolide.

3.6.1. Total Synthesis of Palmerolide A by De Brabander Group

De Brabander group divided the proposed structure **77** into three segments **79**~**81** as shown in Scheme **11** [30].

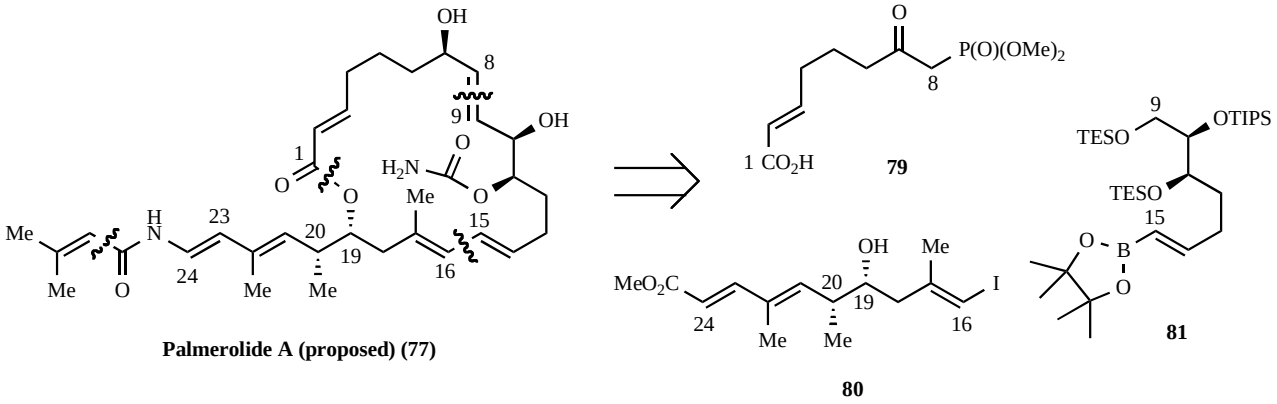
The C16-C24 unit **80**, possessing C19-C20 *syn* relationship, was constructed by the vinylogous Mukaiyama aldol reaction followed by Mitsunobu reaction (Scheme **12**). Aldehyde **82** [32] was submitted to the vinylogous Mukaiyama aldol reaction with ketene *N*,*O*-acetal ***ent*-7** to furnish *anti* adduct **83**. The configuration of C19 was inverted by Mitsunobu reaction to give C19-C20 *syn* product **84**. Subsequent DIBAL reduction and Wittig reaction afforded hydroxyester **80** in high yield. Thus, the C16-C24 unit **80** was synthesized in 4 steps from aldehyde **82**. Suzuki-Miyaura coupling [33] of hydroxyester **80** and vinyl borane **81** was followed by esterification with **79** under Yamaguchi conditions [34] to afford **85**. After transformation to macrolactone **86**, carboxylic acid was submitted to Crutius rearrangement sequences, in which the intermediary ketene was trapped with Grignard reagents **87** to provide vinylamide **88** [35]. Manipulation of protective groups gave the proposed palmerolide A (**77**), whose NMR data were incongruent with those of the natural product.

Next, diastereomer 19-*epi*-20-*epi*-**77** was synthesized by using the enantiomer of vinyliodide **80** derived from vinylketene *N*,*O*-acetal **7**. The NMR spectra, TLC, and analytical HPLC behavior of the synthetic 19-*epi*-20-*epi*-**77** were identical with those of the natural palmerolide A. However, the mirror image CD spectra were obtained with the synthetic 19-*epi*-20-*epi*-**77** and the natural palmerolide A. Therefore, the absolute structure of the natural palmerolide A has been revised as **78**, the enantiomer of 19-*epi*-20-*epi*-**77**.

3.6.2. Total Synthesis of Palmerolide A by Nicolaou Group

Nicolaou group divided the proposed structure (**77**) into three segments including C1-C8 unit **89**, C9-C15 unit **91**, and C16-C23 unit **90** (Scheme **13**) [31]. They also applied vinylketene *N*,*O*-acetal ***ent*-7** to C16-C23 unit **90**.

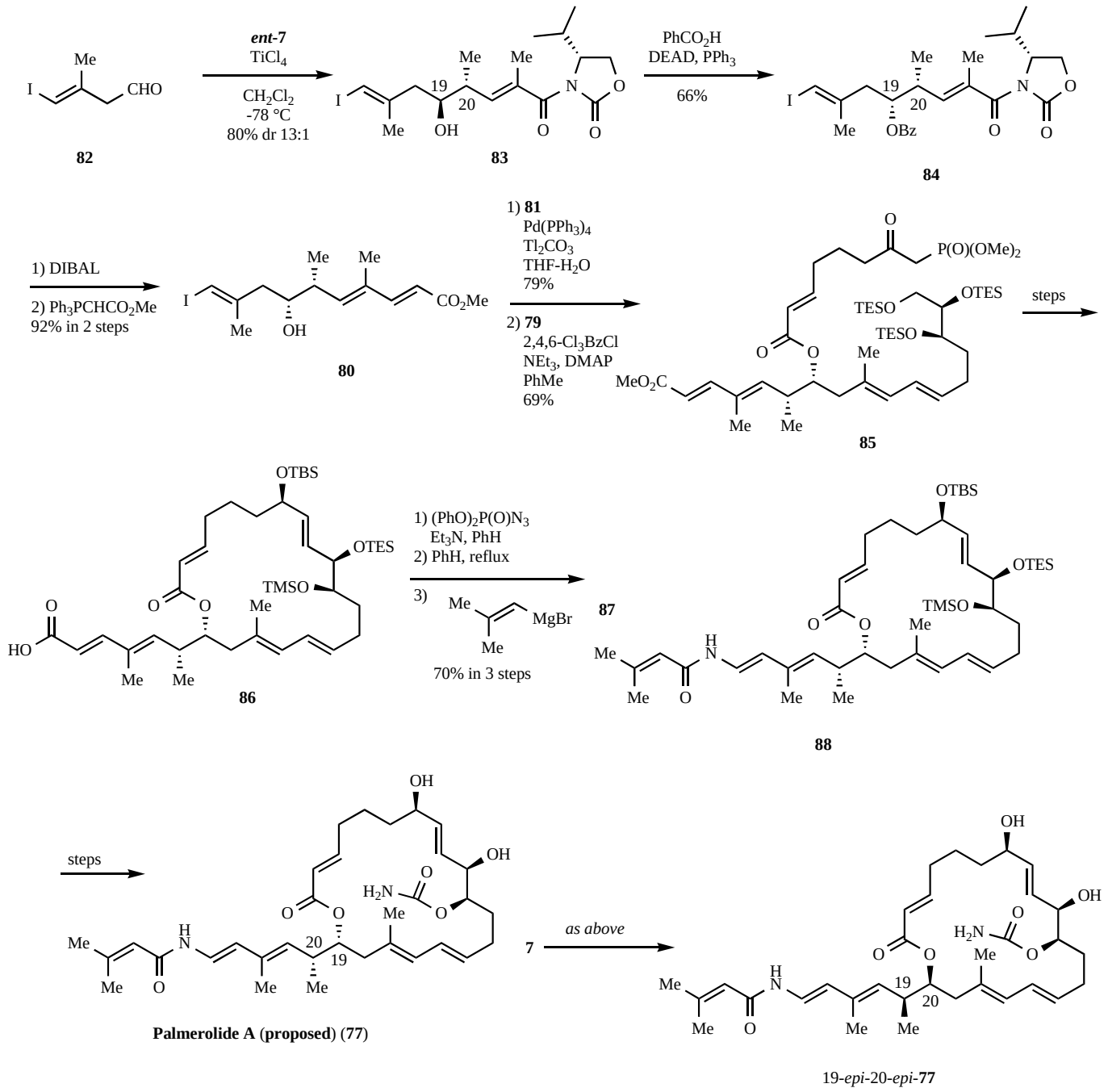
In the total synthesis, they examined two procedures to synthesize C16-C23 unit **90**. One utilized Evans aldol reaction to construct C19-C20 configuration, and the other applied the vinylogous Mukaiyama aldol reaction with a vinylketene *N*,*O*-acetal **95** (Scheme **14**). Evans aldol reaction [36] with β,γ-unsaturated aldehyde **82** proceeded to give *syn* adduct **92** in moderate yield with high stereoselectivity. Protection of the secondary alcohol of adduct **92** followed by



Palmerolide A (proposed) (77) **79** **81**

80

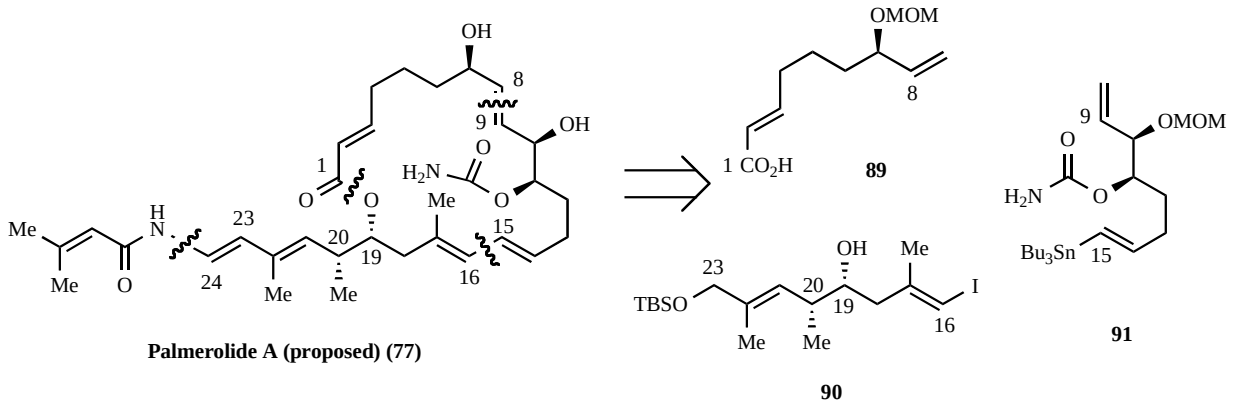
Scheme 11. De Brabander's synthetic plan of palmerolide A (proposed structure).



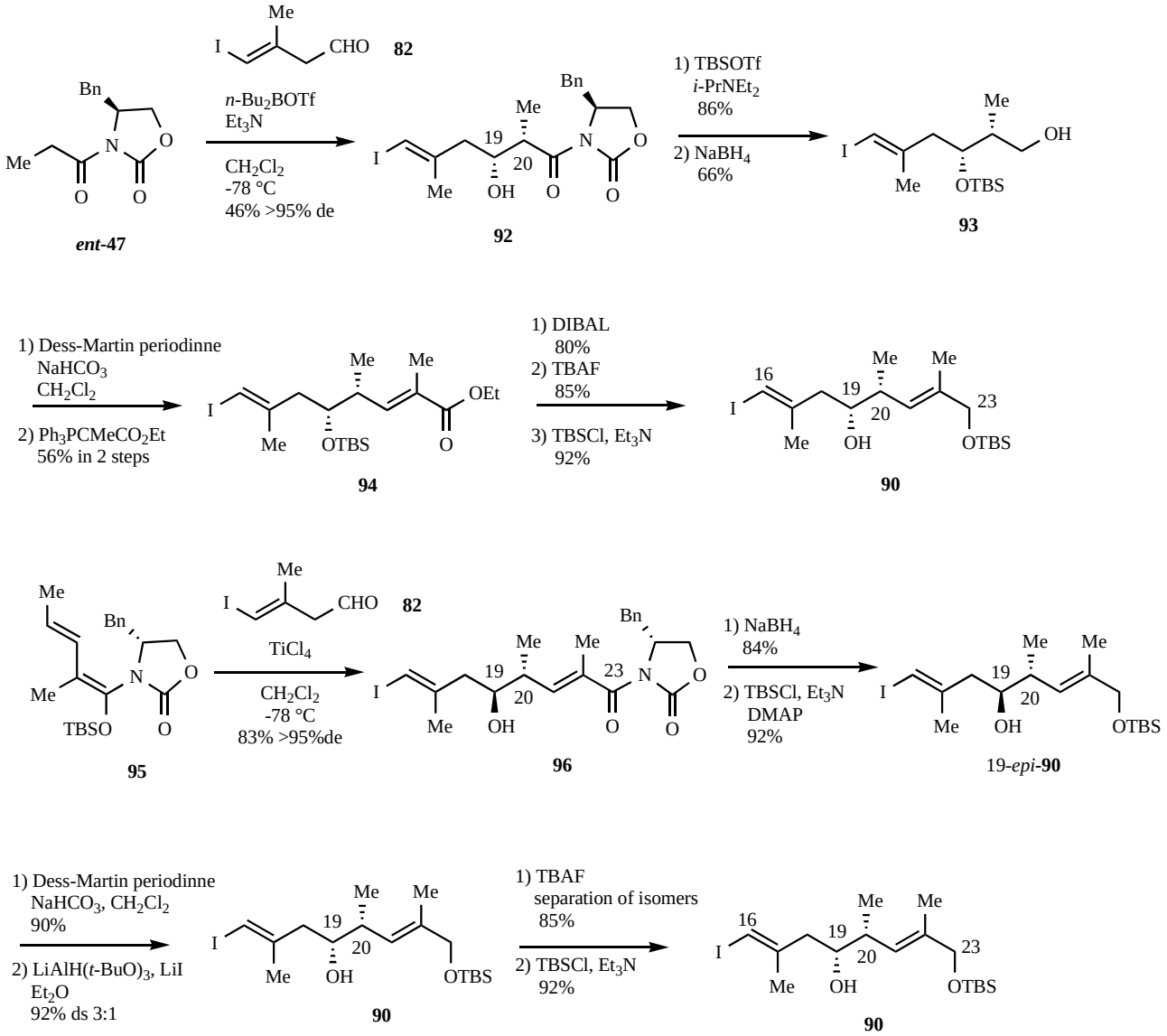
Scheme 12. De Brabander's synthesis of palmerolide A.

reduction of the imine moiety afforded primary alcohol **93**. Oxidation and elongation by Wittig reaction provided α-methyl-α,β-unsaturated ester **94**, which was converted to C16-C23 unit **90** in additional three steps including reduction of the ester group, deprotection of the secondary alcohol, and protection of the primary alcohol. Alternatively, vinylogous Mukaiyama aldol reaction using vinylketene *N*,*O*-acetal **95**, the D-phenylalanine derivative, furnished the C19-C20 *anti* adduct **96** possessing the requisite carbon length to construct **90**. Reductive removal of the chiral auxiliary and successive protection of the primary alcohol provided 19-*epi*-**90**. The configuration of C19 was inverted by Dess-Martin oxidation followed by reduction using $LiAlH(O\textit{t}\text{-}Bu)_3$ in the presence of LiI. A mixture containing **90** and 19-*epi*-**90** with 3:1 ratio was separated by silica gel column chromatography after de-O-silylation. The resulting primary alcohol was re-protected to obtain the pure **90**.

Stille coupling [37] of vinyl iodide **90** and vinyl stannane **91** afforded the C9-C23 unit **97**, which was esterified [34] with **89** to give **98** (Scheme **15**). Several steps were required to bis(allylalcohol) **99**, the precursor for the ring-closing olefin metathesis. The second generation Grubbs catalyst worked well to give 8,9-*E*-olefin **100** [38]. The enamide moiety was installed by Buchwald protocol [39] to achieve the synthesis of the proposed structure **77**, whose spectra

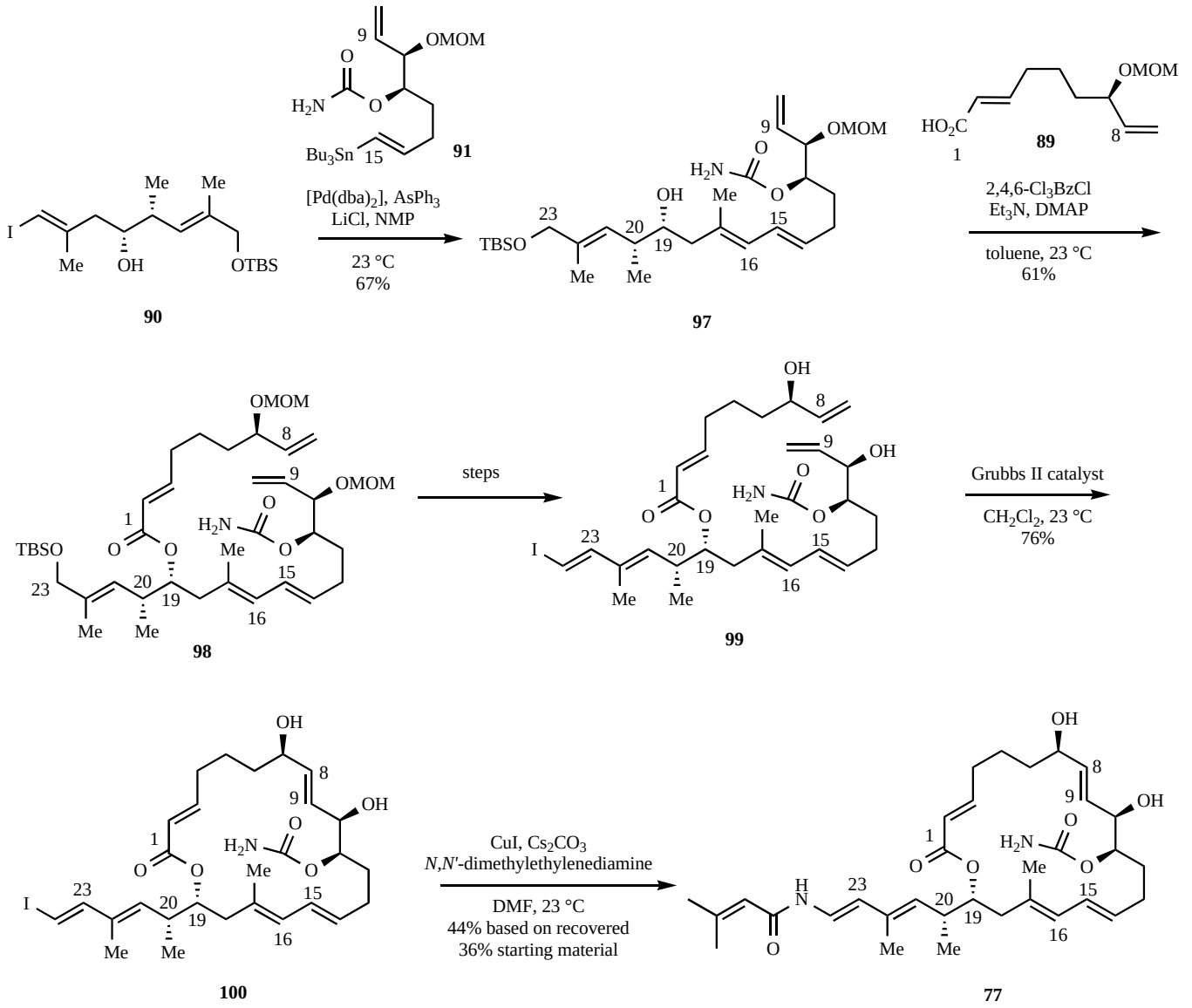


Scheme 13. Nicolaou's synthetic plan of palmerolide A (proposed structure).



Scheme 14. Nicolaou's synthesis of C16-C23 segment **90**.

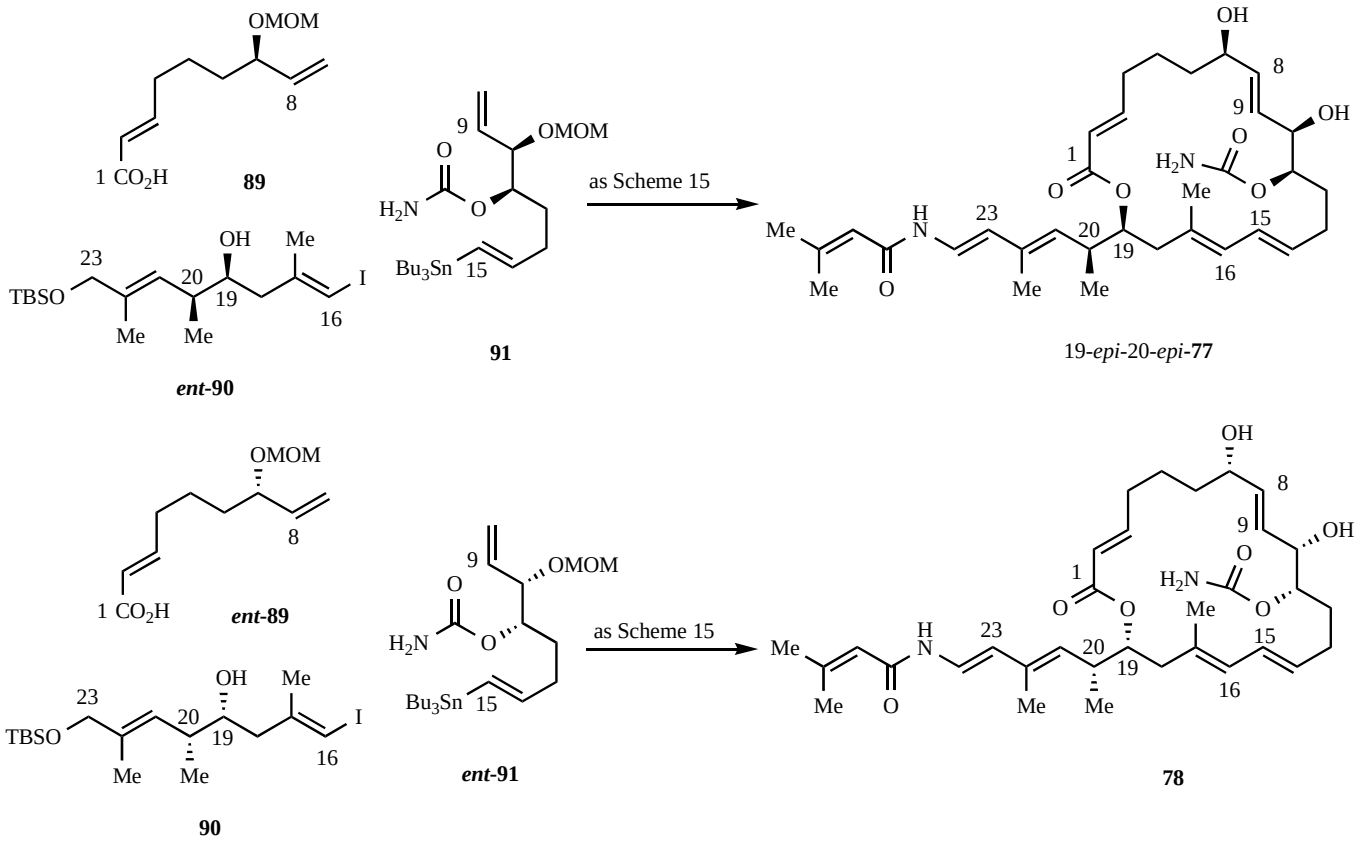
were not identical with those of the natural product. Next, the enantiomer of **90** was subsequently coupled with **89** and **91** to synthesize the 19-*epi*-20-*epi*-**77**, which was found to be the enantiomer of the natural product by comparison of CD spectra (Scheme **16**). Therefore, the structure of natural palmerolide A was revised as **78** (Fig. **9**). Finally, the natural form **78** was achieved using fragments **90**, ***ent*-89**, and ***ent*-91**.



Scheme 15. Nicolaou's synthesis of palmerolide A (proposed structure).

4. ASYMMETRIC SYNTHESES OF 3-HYDROXYOXINDOLES

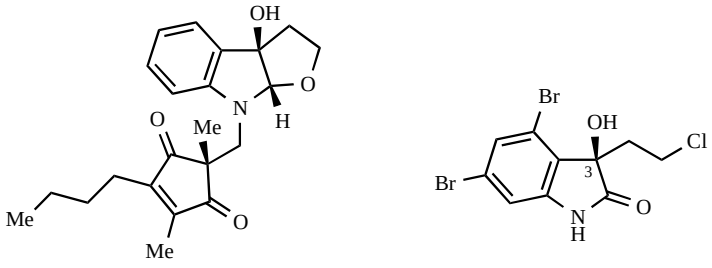
Some bioactive natural products possess the structure including 3-hydroxyoxindole (Fig. **10**) [40,41]. To establish the most straightforward approach to this class of compounds, we examined aldol reactions with some nucleophiles and isatin (**104**), a commercially available α-ketoamide (Scheme **17**, Table **3**) [42]. The vinylogous Mukaiyama aldol reaction using ketene *N,O*-acetal **4** and isatin (**104**) was examined under the various conditions. The problem of the reaction was the low solubility of **104** to the less-polar solvent, especially at low temperature. This was solved by precomplexation of **104** with Lewis acid prior to addition of enolates. The best result was obtained under the conditions including the mixture of **104** and $TiCl_4$ in CH_2Cl_2 stirred for 30 min at 0 ℃ prior to the addition of vinylketene *N,O*-acetal **4** at low temperature. This procedure afforded the adduct in good yield with excellent selectivity and reproducibility. Highly selective 1,7-stereoinduction was achieved with the α-ketoamide to obtain a stereogenic tertiary alcohol. The other nucleophiles **106**~**108** were also subjected to aldol reaction with isatin (**104**) under typical Mukaiyama and Evans aldol conditions (Table **3**). In all cases, the corresponding aldol adduct was obtained in low yield with low selectivity. Therefore, only the vinylogous Mukaiyama aldol reaction using **4** proceeded in the stereoselective manner. The straightforward and highly stereoselective method to construct 3-hydroxyoxindoles was established by the vinylogous Mukaiyama aldol reaction using vinylketene silyl *N,O*-acetal **4**, of which adduct was readily applicable to the natural product synthesis.



Scheme 16. Nicolaou's synthesis of palmerolide A.

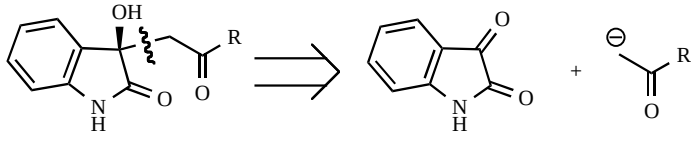
4.1. Total Synthesis of Madindoline A

Madindoline A was isolated from the culture of *Streptomyces nitrospoteus* K93-0711 by Ōmura group in 1996 as a selective inhibitor of IL-6 activity (Fig. **10**) [40]. Madindoline A is featured by 3-hydroxyfuroindoline connecting to the cyclopentenedione. The first total synthesis and structural determination were also reported by Ōmura group in 2000 [43]. In the total synthesis they performed one step enantioselective synthesis of 3-hydroxyfuroindoline under the Sharpless asymmetric epoxidation conditions with tryptophol. Recently, we established the original enantioselective synthesis of 3-hydroxyfuroindoline by the vinylogous Mu-



Madinoline A (101) **Convolutamydine B (102)**

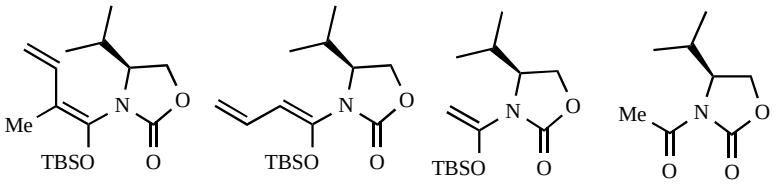
Fig. (10). Structure of natural products possessing 3-hydroxyoxindole skelton.



103 **104** **105**

Scheme 17. Aldol strategy to 3-hydroxyoxindole.

Table 3. Aldol Reactions Using Nucleophiles 4, 106, 107, and 108[a]



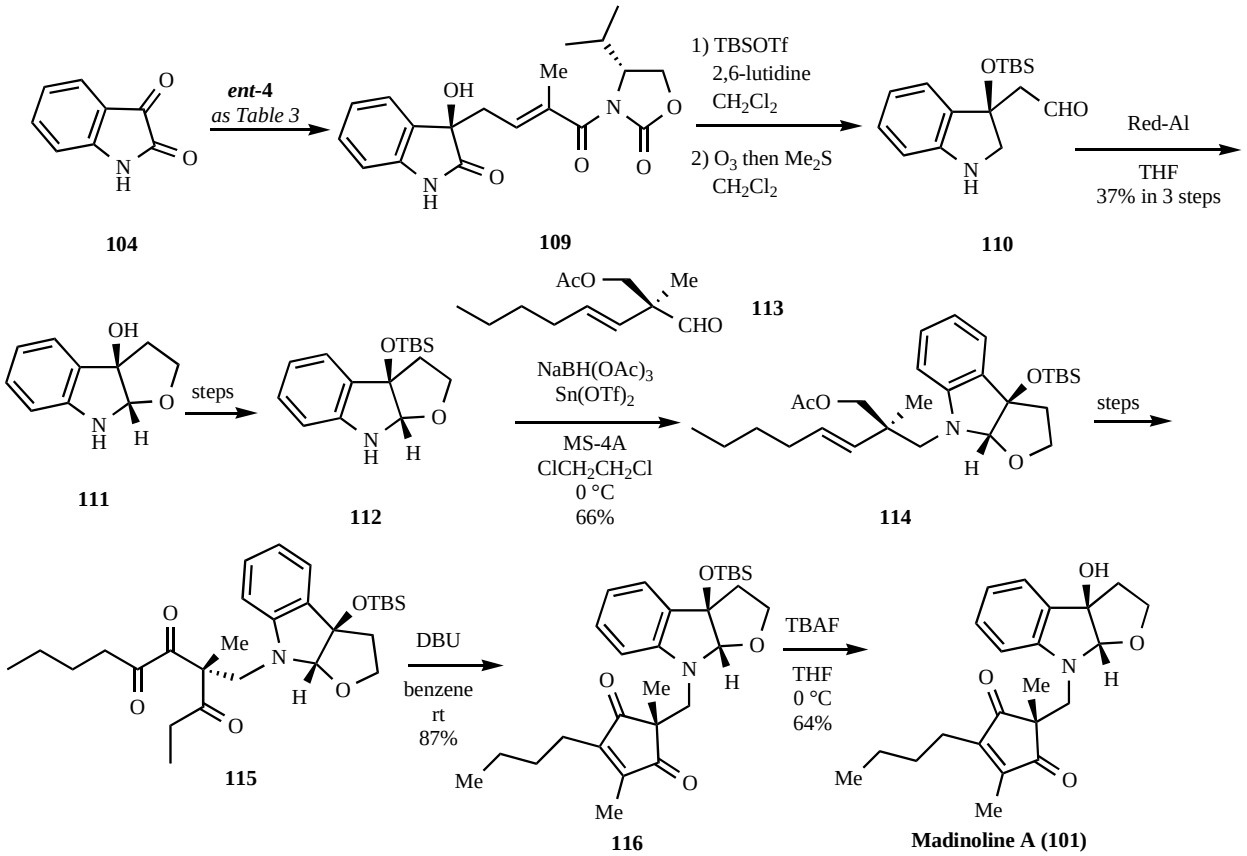
4 **106** **107** **108**

Nucleophile	Additive	Yield (%)	Selectivity
4	$TiCl_4$	69	60:1
106	$TiCl_4$	32	1.7:1
107	$TiCl_4$	38	2.8:1
108	$TiCl_4$, *i*-$PrNEt_2$	45	1.2:1

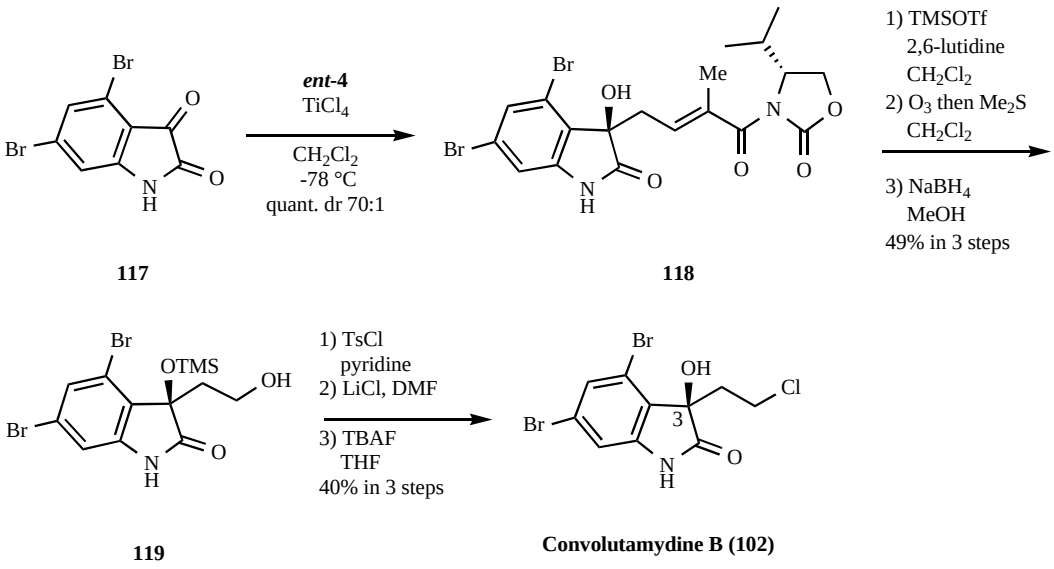
[a]Reactions were performed in CH_2Cl_2 at −78 °C.

kaiyama aldol reaction, which was applied to our total synthesis of madindoline A (Scheme **18**) [42].

Stereoselective construction of the tertiary alcohol was accomplished using ***ent*-4** as Table **3**. After protection of the tertiary alcohol of the adduct **109**, ozonolysis gave the aldehyde **110**. The aldehyde **110** was submitted to the one-pot sequence to afford 3-hydroxyfuroindoline **111** including reduction of both amide and aldehyde moieties followed by cyclization to give the *N*,*O*-acetal and the subsequent de-O-protection of the tertiary alcohol. 3-Hydroxyfuroindoline **111**, the key compound applied to the total synthesis of madindoline A, was provided in 98%ee determined by HPLC. Coupling of *O*-protected furoindoline **112** and neopentyl aldehyde **113** [44] was problematic. Acid-sensitivity of **112** and bulkiness of **113** made it difficult to submit the typical hydroamination reactions to afford **114** [45]. After a numerous experiments, the combination of $NaBH(OAc)_3$ and $Sn(OTf)_2$ in the presence of molecular sieves 4A was found



Scheme 18. Total synthesis of madindoline A.



Scheme 19. Enantioselective synthesis of convolutamydine B.

to be effective to connect them. The cyclopentenedione moiety was constructed by intramolecular condensation of triketone **115**. The reaction proceeded smoothly and regioselectively under the mild conditions to afford cyclopentenedione **116** in high yield, which was submitted to de-O-protection to obtain madindoline A (**101**).

4.2. Total Synthesis of (+)-convolutamydine B

Convolutamydine B (**102**) was isolated from the Floridian marine bryozoans *Amathia convolute* by Kamano group as a member of a family of oxindole alkaloids (Fig. **10**) [41]. It induces the appearance of characteristic features, associated with normally differentiated cells, in the tumor cell line HL-60. The structure of convolutamydine B was elucidated as shown in Fig. (**10**), although the stereochemistry at C3 position had been not established and was assumed as *R* configuration on the basis of the empirical rule for the correlation of CD spectra [46]. To establish the absolute structure as well as the enantioselective synthesis of convolutamydines, the 1,7-stereoinduction methodology using vinylketene *N,O*-acetals **4** was applied to the synthesis [42].

The (*R*)-convolutamydine B (**102**) was synthesized as Scheme **19**. The vinylogous Mukaiyama reaction of 4,6-dibromoisatin (**117**) and vinylketene *N,O*-acetal ***ent*-4** proceeded smoothly to afford aldol adduct **118** quantitatively almost as a single isomer. After protection of the tertiary alcohol as TMS ether, ozonolysis followed by hydride reduction gave primary alcohol **119**. Transformation of **119** including tosylation, chlorination, and de-O-silylation afforded (*R*)-convolutamydine B (**102**). The stereochemistry of natural convolutamydine B was determined unambiguously as *R*-configuration, because the CD spectrum of the synthetic (*R*)-convolutamydine B (**102**) was perfectly matched with that of the natural product.

5. CONCLUSION

The vinylogous Mukaiyama aldol reaction using vinylketene *N,O*-acetal proved to be a powerful method to construct the polyketide structure. This methodology is applicable to not only a variety of polypropionates but also the 3-hydroxyloxindoles. The reaction proceeded with typical aldehydes in high stereoselectivity resulted from remote stereoinduction. Yield and stereoselectivity are not affected in scale so that the method is adequate to the multi gram scale synthesis. Both enantiomers of vinylketene *N,O*-acetals **4** and **7** are easily prepared from commercially available materials in multi gram scales and are stable solids easy to handle. The product of the reaction composes multi functional groups, which make this method flexible to the further transformation including stereogenic exchange. Therefore, the method is applicable to the total synthesis of natural products including stereochemically unknown compounds.

The vinylogous Mukaiyama aldol reaction using vinylketene *N,O*-acetal has been developed and widespread to apply to the enantioselective synthesis of natural products. Further studies to establish the methodology shortening the sequences to synthesize the complex compounds are in progress.

ACKNOWLEDGEMENT

This work was financially supported by the 21COE program “Center for Practical Nano-Chemistry”, the Consolidated Research Institute for Advanced Science and Medical Care, the Global COE program “Center for Practical Chemical Wisdom”, and Scientific Research on Priority Area “Creation of Biologically Functional Molecules” from the Ministry of Education, Culture, Sports, Science and Technology.

REFERENCES

[1] (a) Tatsuta, K.; Hosokawa, S. *Chem. Rec.*, **2006**, *6*, 217. (b) Tatsuta, K.; Hosokawa, *Sci. Tech. Adv. Mater.*, **2006**, *7*, 397. (c) Tatsuta, K.; Hosokawa, S. *Chem. Rev.*, **2005**, *105*, 4707.

[2] (a) Kalesse, M. *Top. Curr. Chem.*, **2005**, *244*, 43. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.*, **2000**, *100*, 1929.

[3] (a) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.*, **2000**, *29*, 109. (b) Bluet, G.; Campagne, J. M. *J. Org. Chem.*, **2001**, *66*, 4293.

[4] Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem. Int. Ed.*, **2005**, *44*, 4682.

[5] Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.*, **2004**, *126*, 13604.

[6] Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.*, **2005**, *46*, 333.

[7] Hayakawa, Y.; Nakai, M.; Furihata, K.; Shin-ya, K.; Seto, H. *J. Antibiot.*, **2000**, *53*, 179.

[8] (a) Toshima, K.; Tatsuta, K. *Chem. Rev.*, **1993**, *93*, 1503. (b) Tatsuta, K.; Takahashi, M.; Tanaka, N. *Tetrahedron Lett.*, **1999**, *40*, 1929. (c) Asami, Y.; Ogura, T.; Otake, N.; Nishimura, T.; Xinsheng, Y.; Sakurai, T.; Nagasawa, H.; Sakuda, S.; Tatsuta, K. *J. Nat. Prod.*, **2003**, *66*, 729.

[9] (a) Yano, K.; Yokoi, K.; Sato, J.; Oono, J.; Kouda, T.; Ogawa, Y.; Nakashima, T. *J. Antibiot.*, **1986**, *39*, 32. (b) Yano, K.; Yokoi, K.; Sato, J.; Oono, J.; Kouda, T.; Ogawa, Y.; Nakashima, T. *J. Antibiot.*, **1986**, *39*, 38.

[10] Taniguchi, M.; Watanabe, M.; Nagai, K.; Suzumura, K.; Suzuki, K.; Tanaka, A. *J. Antibiot.*, **2000**, *53*, 844.

[11] Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Tetrahedron Lett.*, **2006**, *47*, 5415.

[12] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett*, **1998**, 26.

[13] Takahashi, N.; Suzuki, A.; Tamura, S. *J. Am. Chem. Soc.*, **1965**, *87*, 2066.

[14] Schnermann, M.J.; Romero, F.A.; Hwang, I.; Nakamaru-Ogiso, E.; Yagi, T.; Boger, D.L. *J. Am. Chem. Soc.*, **2006**, *128*, 11799.

[15] Cox, C.M.; Whiting, D.A. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 1901.

[16] (a) Nakao, Y.; Yoshida, W.Y.; Takada, Y.; Kimura, J.; Yang, L.; Mooberry, S.L.; Scheuer, P.J. *J. Nat. Prod.*, **2004**, *67*, 1332. (b) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.*, **1990**, *55*, 173.

[17] Evans, D.A.; Tedrow, J.S.; Shaw, J.T.; Downey, C.W. *J. Am. Chem. Soc.*, **2002**, *124*, 392.

[18] (a) Nihei, Y.; Hasegawa, M.; Suzuki, K.; Yamamoto, S.; Hanada, M.; Furumai, T.; Fukagawa, Y.; Oki, T. *J. Antibiot.*, **1993**, *46*, 900. (b) Imae, K.; Nihei, Y.; Oka, M.; Yamasaki, T.; Konishi, M.; Oki, T. *J. Antibiot.*, **1993**, *46*, 1031.

[19] Hosokawa, S.; Kuroda, S.; Imamura, K.; Tatsuta, K. *Tetrahedron Lett.*, **2006**, *47*, 6183.

[20] Wendt, M. D.; Rockway, T. W.; Geyer, A.; McClellan, W.; Weitzberg, M.; Zhao, X.; Mantei, R.; Nienaber, V. L.; Stewart, K.; Klinghofer, V.; Giranda, V. L. *J. Med. Chem*., **2004**, *47*, 303.

[21] (a) Nicolaou, K. C.; Zhong, Y.-Li.; Baran, P. S. *Angew. Chem. Int. Ed*., **2000**, *39*, 622. (b) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y.-Li.; Sugita, K.; Zou, N. *Angew. Chem. Int. Ed.*, **2001**, *40*, 202.

[22] Kelly, T. R.; Field, J. A.; Li, Q. *Tetrahedron Lett*., **1988**, *29*, 3545.

[23] Mandala, S.M.; Thornton, R.A.; Rosenbach, M.; Milligan, J.; Garcia-Calvo, M.; Bull, H.G.; Kurtz, M. B. *J. Biol. Chem.*, **1997**, *272*, 32709.

[24] (a) Kolter, T.; Sandhoff, K. *Angew. Chem. Int. Ed.*, **1999**, *38*, 1532. See also: (b) Mandala, S. M.; Harris, G. H. *Methods Enzymol.*, **2000**, *311*, 335. (c) Dickson, R. C. *Annu. Rev. Biochem.*, **1998**, *67*, 27. (d) Other IPC inhibitors: Nagiec, M. M.; Nagiec, E. E.; Baltisberger, J. A.; Wells, G. B.; Lester, R. L.; Dickson, R. C. *J. Biol. Chem*., **1997**, *272*, 9809. (e) Mandala, R. A.; Thornton, R. A.; Milligan, J.; Rosenbach, M.; Garcia-Calvo, M.; Bull, H. G.; Harris, G.; Abruzzo, G. K.; Flattery, A. M.; Gill, C. J.; Bartizal, K.; Dreikorn, S.; Kurtz, M. B. *J. Biol. Chem.*, **1998**, *273*, 14942.

[25] (a) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc*., **2001**, *123*, 1372. (b) Kobayashi, S.; Mori, K.; Wakabayashi, T.; Yasuda, S.; Hanada, K. *J. Org. Chem*., **2001**, *66*, 5580. (c) Nakamura, M.; Mori, Y.; Okuyama, K.; Tanikawa, K.; Yasuda, S.; Hanada, K.; Kobayashi, S. *Org. Biomol. Chem*., **2003**, *1*, 3362.

[26] Shirokawa, S.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi S. *Org. Lett*., **2007**, *9*, 849.

[27] Evans, D. A.; Rieger, J. C.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc*., **1991**, *113*, 1047.

[28] Mitsunobu, O. *Synthesis*, **1981**, 1.

[29] Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc*., **2006**, *128*, 5630.

[30] Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. *J. Am. Chem. Soc*., **2007**, *129*, 6386.

[31] Nicolaou, K. C.; Guduru, R.; Sun, Y.-P.; Banerji, B.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.*, **2007**, *46*, 5896.

[32] Marshall, J. A.; Eidam, P. *Org. Lett.*, **2004**, *6*, 445.

[33] (a) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc*., **2003**, *125*, 13531. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.*, **1995**, *95*, 2457.

[34] Inanaga, J.; Hirata, K.; Saeki, H.; Kastuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*., **1979**, *52*, 1989.

[35] Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc*., **2002**, *124*, 3245.

[36] a) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.*, **1981**, *53*, 1109. b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*., **1981**, *103*, 2121.

[37] Yin, L.; Liebscher, J. *Chem. Rev.*, **2007**, *107*, 133.

[38] a) Grubbs, R. H. *Tetrahedron*, **2004**, *60*, 7117. b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.*, **2005**, *44*, 4490. c) Gradillas, A.; Perez-Castells, J. *Angew. Chem. Int. Ed*., **2006**, *45*, 6086.

[39] Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett*., **2003**, *5*, 3667.

[40] (a) Hayashi, M.; Kim, Y. P.; Takamatsu, S.; Enomoto, A.; Shinose, M.; Takahashi, Y.; Tanaka, H.; Komiyama, K.; Õmura, S. *J. Antibiot.*, **1996**, *49*, 1091. (b) Takamatsu, S.; Kim, Y. P.; Enomoto, A.; Hayashi, M.; Tanaka, H.; Komiyama, K.; Õmura, S. *J. Antibiot.*, **1997**, *50*, 1069.

[41] (a) Kamano, Y.; Zhang, H.-P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.*, **1995**, *36*, 2783. (b) Zhang, H.-P.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron*, **1995**, *51*, 5523. (c) Kamano, Y.; Kotake, A.; Hashima, H.; Hayakawa, I.; Hiraide, H.; Zhang, H.-P.; Kizu, H.; Komiyama, K.; Hayashi, M.; Pettit, G. R. *Collect. Czech. Chem. Commun.*, **1999**, *64*, 1147.

[42] Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett*., **2006**, *8*, 677.

[43] Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Õmura, S. *J. Am. Chem. Soc*., **2000**, *122*, 2122.

[44] Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett*., **2000**, *41*, 6429.

[45] Hosokawa, S.; Sekiguchi, K.; Hayase, K.; Hirukawa, Y.; Kobayashi, S. *Tetrahedron Lett.*, **2000**, *41*, 6435. (c) Hosokawa, S.; Kobayashi, S. *J. Synth. Org. Chem. Jpn*., **2001**, *59*, 1103.

[46] Takayama, H.; Shimizu, T.; Sada, H.; Harada, Y.; Kitajima, M.; Aimi, N. *Tetrahedron*, **1999**, *55*, 6841.

Received: September 02, 2007 **Revised: October 17, 2007** **Accepted: October 17, 2007**