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TOTAL SYNTHESIS OF ASPERGILLIDES A, B, AND C

Tomohiro Nagasawa and Shigefumi Kuwahara*

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan. E-mail: skuwahar@biochem.tohoku.ac.jp

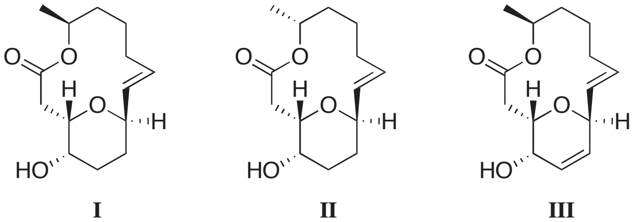
Abstract – Aspergillides A, B, and C are cytotoxic macrolides produced by the marine-derived fungus *Aspergillus ostianus* strain TUF 01F313. The unique molecular architectures of the aspergillides featuring 14-membered marocyclic structures embedded with a tetrahydro- or dihydropyran unit have attracted significant attention from the synthetic chemistry community, and thereby various synthetic approaches to these structurally as well as pharmacologically intriguing molecules have been reported by as many as 12 research groups in the past 3 years. This review describes all of the syntheses disclosed to date, focusing mainly on the methodologies employed for the diastereoselective installation of the pyran ring systems.

CONTENTS

13. Synthesis of Both Enantiomers of Aspergillide C and Their Respective C4-Epimers by Srihari and Sridhar

1. INTRODUCTION

In 2003, Namikoshi and co-workers reported the identification of three new chlorine-containing γ- and δ-lactones with antibacterial activity from a seawater-containing 1/2 PD (potato-dextrose) culture medium of the marine-derived fungus *Aspergillus ostianus* strain TUF 01F313 isolated from an unidentified marine sponge collected at Pohnpei, Micronesia.[1] This finding led Kusumi and co-workers to the expectation that some bromine-containing congeners might be obtained if the fungus is cultivated in a 1/2 PD medium containing bromine-modified artificial seawater instead of natural seawater. Contrary to their expectation, however, the modified cultivation conditions gave no such compounds, but instead, they succeeded in isolating three novel substances named aspergillides A–C,[2,3] which exhibited significant cytotoxicity against mouse lymphocytic leukemia cells (L1210) with LD_{50} values of 2.1, 71.0, and 2.0 μg/mL, respectively. Based on extensive spectroscopic analyses including the modified Mosher method,[4] the structures of the macrolides were initially proposed to be **I**, **II**, and **III** shown in Figure 1.



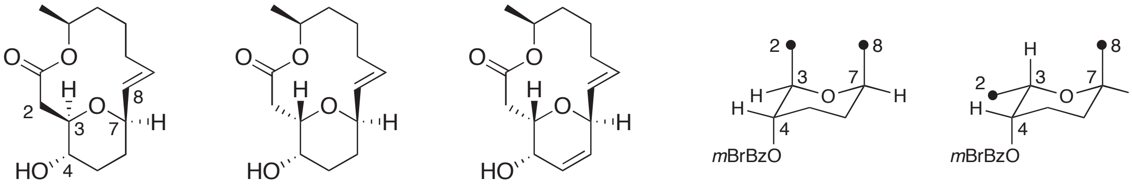
I
aspergillide A

II
aspergillide B

III
aspergillide C

Figure 1. Initially proposed structures of aspergillides A (**I**), B (**II**), and C (**III**)

The molecular architectures of the aspergillides immediately captured the interest of synthetic organic chemists, since these compounds were the first examples of 14-membered macrolides incorporating a 2,6-trans-substituted tetrahydro- or dihydropyran ring as a nonhemiacetal form.[5,6] The stereochemistries of aspergillides A and B (Figure 1) initially assigned by the Kusumi group were soon revised to those depicted in Figure 2 (compounds **1** and **2**, respectively) through a synthetic study by Hande and Uenishi[7] as well as X-ray crystallographic analysis of the corresponding *m*-bromonenzoates by Ooi and co-workers,[8] while the originally proposed structure of aspergillide C (**3**) was confirmed by its total synthesis in our laboratory.[9] Interestingly, the crystal structure of the *m*-bromobenzoate of **1** revealed that its tetrahydropyran moiety adopts the conformation shown in Figure 2 (*m*BrBz-**1**), in which the substituents at the C3, C4, and C7 positions are all axially oriented. As described later, this all-axial nature of the substituents in **1** made its synthesis by macrolactonization and ring-closing metathesis protocols quite difficult. The conformation of *m*-bromobenzoate of **2** (*m*BrBz-**2**) was, on the other hand, shown to accord with that predicted by Kusumi *et al.* from NOESY analysis of **2**.[2]



1 aspergillide A (revised) **2** aspergillide B (revised) **3** aspergillide C (confirmed) *m*BrBz-**1** *m*BrBz-**2**

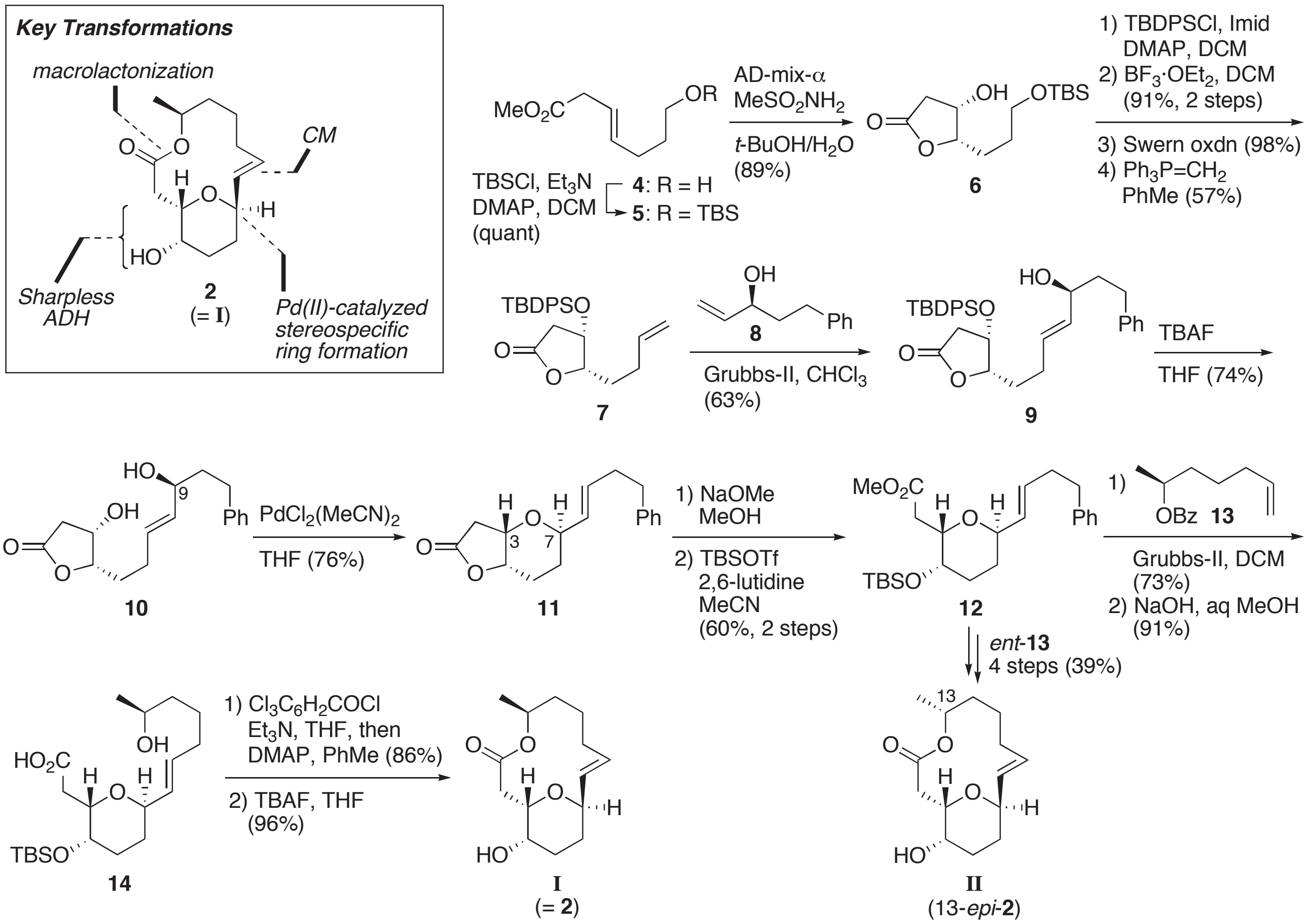
Figure 2. Structures of aspergillides A (**1**), B (**2**), and C (**3**), and conformations of the tetrahydropyran moieties of the *m*-bromobenzoates of **1** and **2** (*m*BrBz-**1** and *m*BrBz-**2**, respectively)

The present review summarizes a variety of approaches to these structurally as well as pharmacologically intriguing molecules, which have culminated to date in seven, seven, and five total/formal syntheses of aspergilides A, B, and C, respectively.

2. FIRST SYNTHESIS AND STEREOCHEMICAL REVISION OF ASPERGILLIDE B BY HANDE AND UENISHI

Intrigued by the significant biological activity as well as the unique 2,6-trans-substituted tetrahydropyran structural motif embedded in the 14-membered macrocyclic ring, Hande and Uenishi embarked on the total synthesis of the originally proposed structures of aspergillides A and B (**I** and **II** in Figure 1). The most crucial step in their synthesis was the installation of the 2,6-trans tetrahydropyran ring system by a Pd(II)-catalyzed stereospecific ring-forming reaction developed by themselves.[7]

Their synthesis of **I** commenced with the protection of known olefinic ester **4**[10] to **5** and subsequent Sharpless asymmetric dihydroxylation (ADH)[11] to give **6** (Scheme 1). The lactone **6** was converted through 4 standard steps into **7**, the cross-metathesis (CM)[12] of which with allylic alcohol **8**[13] using the second-generation Grubbs' catalyst (Grubbs-II)[14] followed by deprotection afforded **10** *via* **9**. Treatment of **10** bearing a 2-heptene-1,7-diol structural unit with a catalytic amount of $PdCl_2(MeCN)_2$ in THF induced an efficient stereospecific cyclization accompanied by 1,3-chirality transfer from the C9 to C7 position,[15] giving 3,7-trans-substituted tetrahydropyran derivative **11** in 76% yield along with a 3% yield of the corresponding 3,7-cis isomer (7-*epi*-**11**); the same reaction conditions, when applied to 9-*epi*-**10**, provided 7-*epi*-**11** in an excellent yield of 80% together with a trace amount (2%) of **11**. Methanolysis of **11** followed by TBS-protection in MeCN gave **12**, the chain-elongation of which with **13**[16] by olefin cross-metathesis afforded an intermediate *E*-olefin exclusively. Hydrolysis of the two ester groups in the olefin then gave seco acid **14**. Finally, the Yamaguchi lactonization[17] of **14** and deprotection of the resulting macrolactone completed the total synthesis of **I**. Compound **12** was also converted into **II** by using *ent*-**13**[16] as a coupling partner in the metathesis reaction *via* the same 4-step sequence employed for the conversion of **12** into **I**.

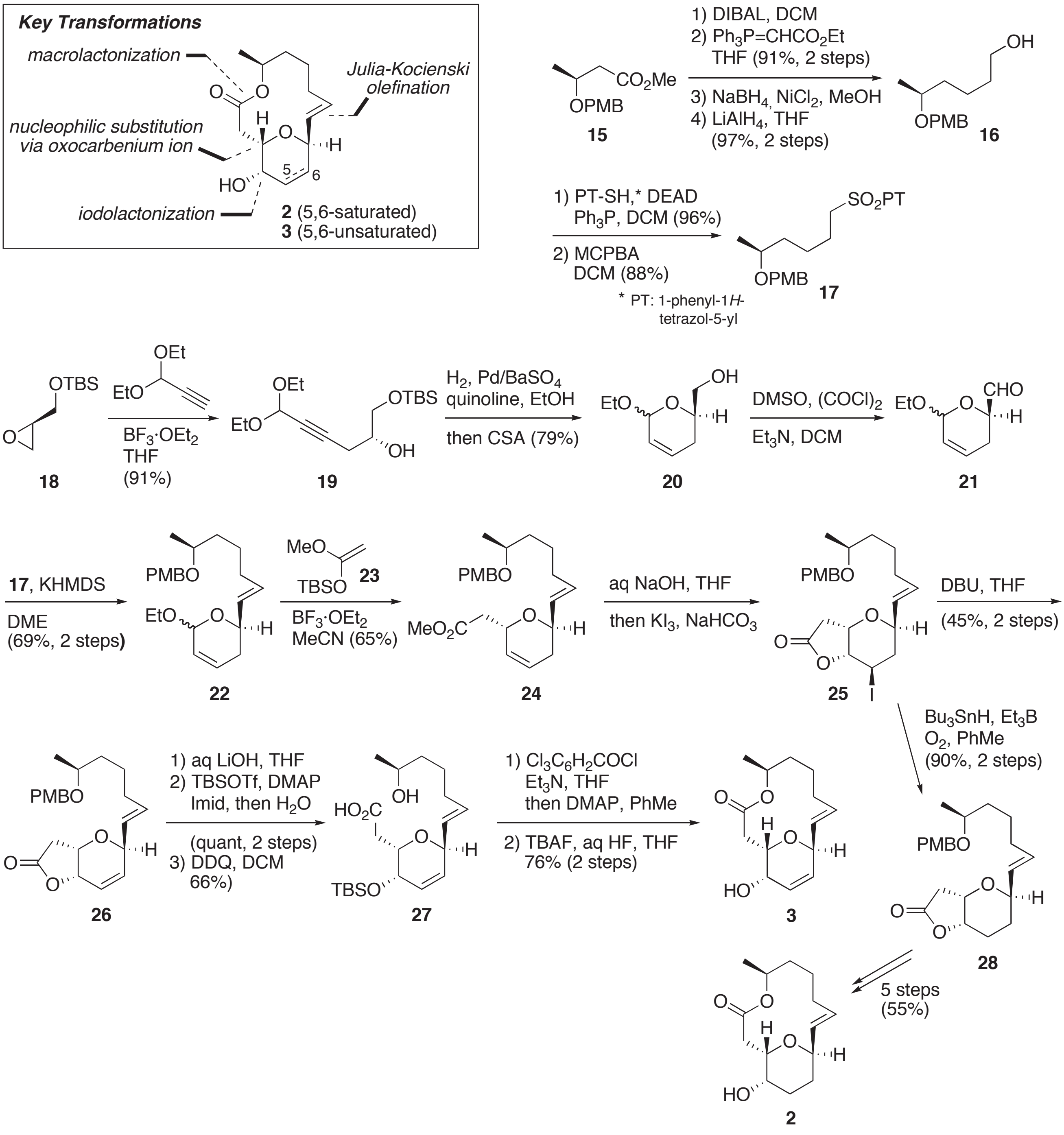


Scheme 1. First synthesis of aspergillide B (**2**) and its C13-epimer (13-*epi*-**2**) by Hande and Uenishi

Unexpectedly, comparison of the spectral and specific rotation data of **I** and **II** with those reported for aspergillides A and B revealed that the data of **I** are identical with those reported for aspergillide B, and structure **II** represents neither aspergillide A nor aspergillide B. Based on these facts, the stereochemistry of aspergillide B was revised as shown in Figure 2 (compound **2**), while the structure of aspergillide A was thrown into confusion. As mentioned above, this deadlock concerning the real structure of aspergillide A was solved through X-ray crystallographic studies by Ooi *et al.*, and structure **1** was assigned to aspergillide A as its genuine structure.

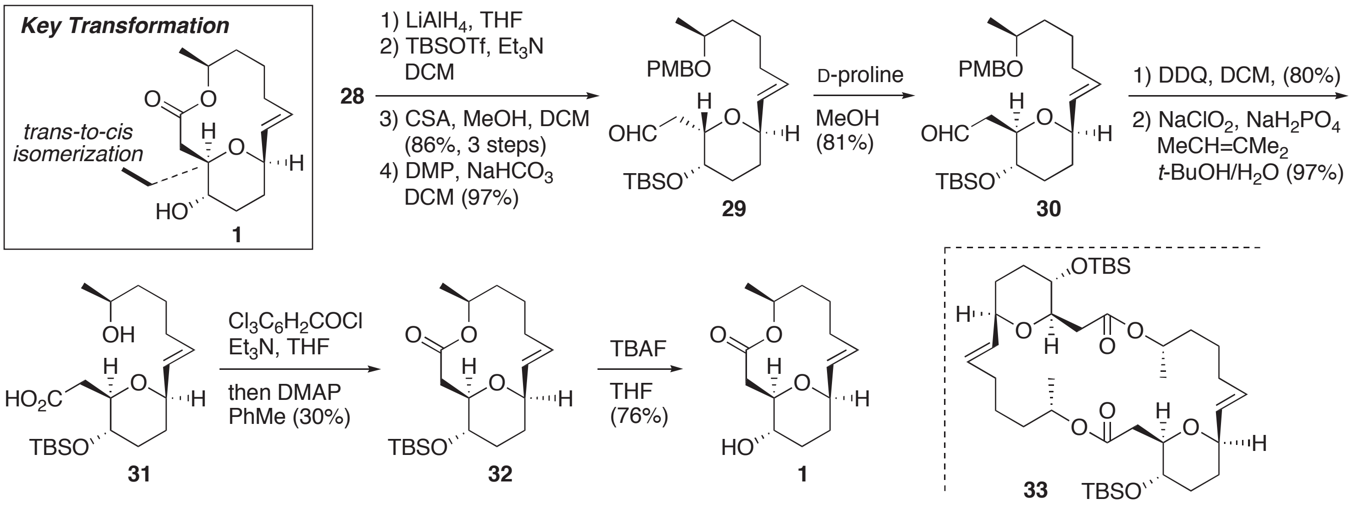
3. SYNTHESIS OF ASPERGILLIDES A, B, AND C BY NAGASAWA AND KUWAHARA

The first synthesis of aspergillide C (**3**) was achieved in our laboratory by utilizing a Lewis acid-promoted nucleophilic substitution of a dihydropyranyl acetal intermediate with a silyl ketene acetal to construct its 2,6-trans-substituted dihydropyran core structure (Scheme 2).[9]



Scheme 2. First synthesis of aspergillide C (**3**) and conversion of its synthetic intermediate **25** into aspergillide B (**2**) by Nagasawa and Kuwahara

Sulfone segment **17** was prepared from known ester **15** *via* alcohol **16** in 75% overall yield by a straightforward 6-step sequence. The preparation of cyclic acetal fragment **21**, which was required for chain-elongation with the sulfone unit **17**, was carried out from commercially available glycidol derivative **18** *via* 3 steps including a one-pot sequence consisting of semi-hydrogenation, deprotection, and cyclic acetal formation (**19** → **20**). The Julia-Kocienski olefination[18] of **21** with **17** gave **22** as a 10:1 *E*/*Z* mixture favoring the desired *E* isomer. $BF_3 \cdot OEt_2$-promoted substitution of the acetal **22** with silyl ketene acetal **23** *via* an oxocarbenium ion intermediate[19] proceeded with moderate diastereoselectivity, providing the 2,6-trans-substituted dihydropyran **24** in 65% isolated yield along with the corresponding cis isomer (25%). Saponification of **24** followed by in situ iodolactonization gave **25**, which was subjected to elimination to afford **26** in 45% yield for the 2 steps. The modest chemical yield was ascribed to the fact that the β-elimination of **25** requires an energetically unfavorable conformation in which the iodine atom and the olefinic side chain are in a 1,3-diaxial relationship. After a 3-step functional group manipulation of **26**, the resulting seco acid **27** was exposed to the Yamaguchi lactonization and subsequent deprotection conditions to furnish aspergillide C (**3**), identical spectroscopically to natural aspergillide C. Subjection of the iodolactone intermediate **25** to radical reduction conditions, on the other hand, gave **28**, which was converted into aspergillide B (**2**) in 55% overall yield by the same 5-step sequence as employed for the conversion of **26** into **3**.[20]



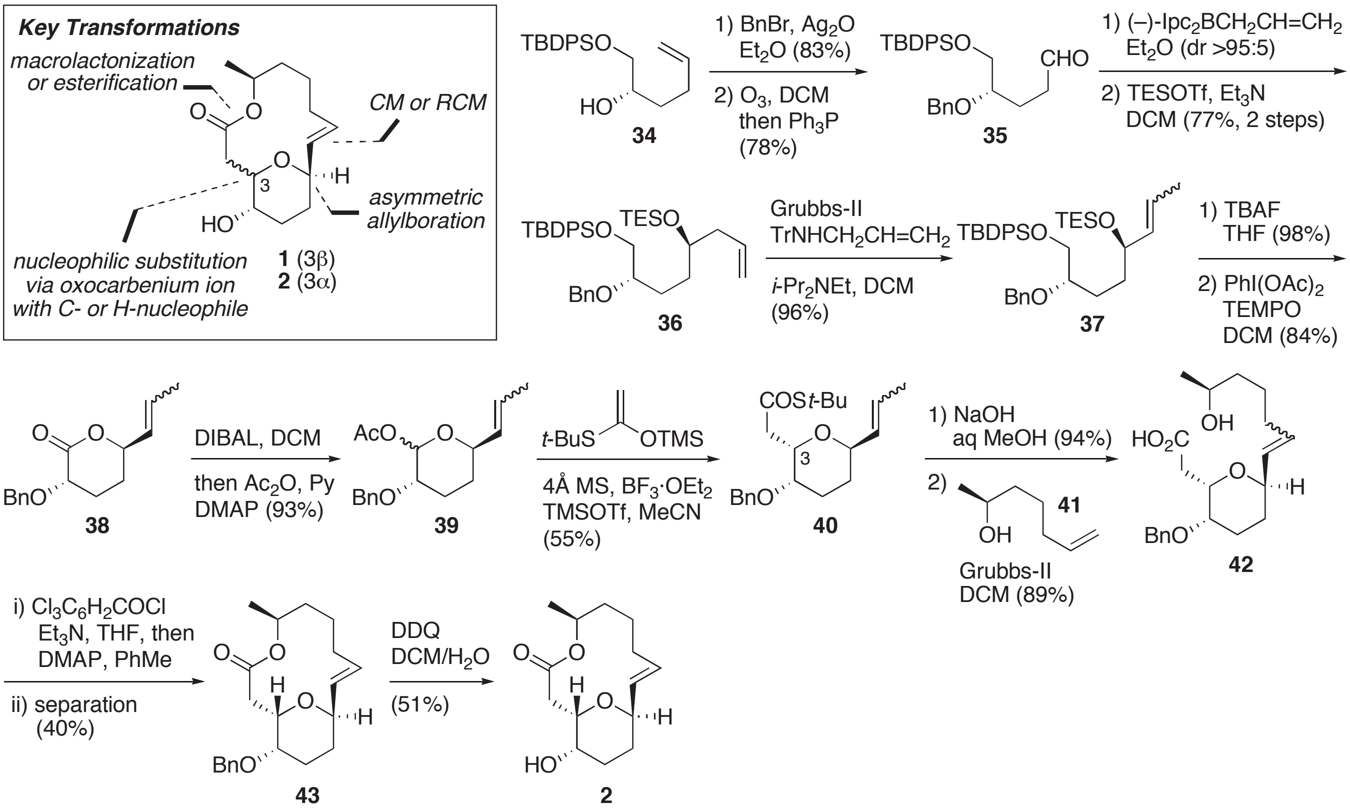
Scheme 3. First synthesis of aspergillide A (**1**) from intermediate **28** by Nagasawa and Kuwahara

For the synthesis of aspergillide A (**1**) incorporating the 2,6-cis-substituted tetrahydropyran core, an efficient proline-catalyzed trans-to-cis isomerization[21] of intermediate **29** derived from **28** in 4 steps was employed, providing, *via* a retro-oxa-Michael/oxa-Michael sequence, the desired thermodynamically more stable product **30** with excellent selectivity (cis/trans = 95:5) in an isolated yield of 81% (Scheme 3).

The aldehyde **30** was converted into seco acid **31** and subjected to the Yamaguchi macrolactonization conditions to furnish **32**, albeit in a modest yield of 30%, together with dimeric macrodiolide **33** and some unidentified products. Several attempts to improve the yield of **32** by varying the reaction conditions did not give any better outcome, and the application of the Mukaiyama, Gerlach, or Shiina macrolactonization protocols[22] afforded none of the desired product, resulting in the formation of complex mixtures or the production of **33** in low yield under Shiina's conditions. Finally, removal of the silyl protecting group completed the first synthesis of aspergillide A (**1**).[23]

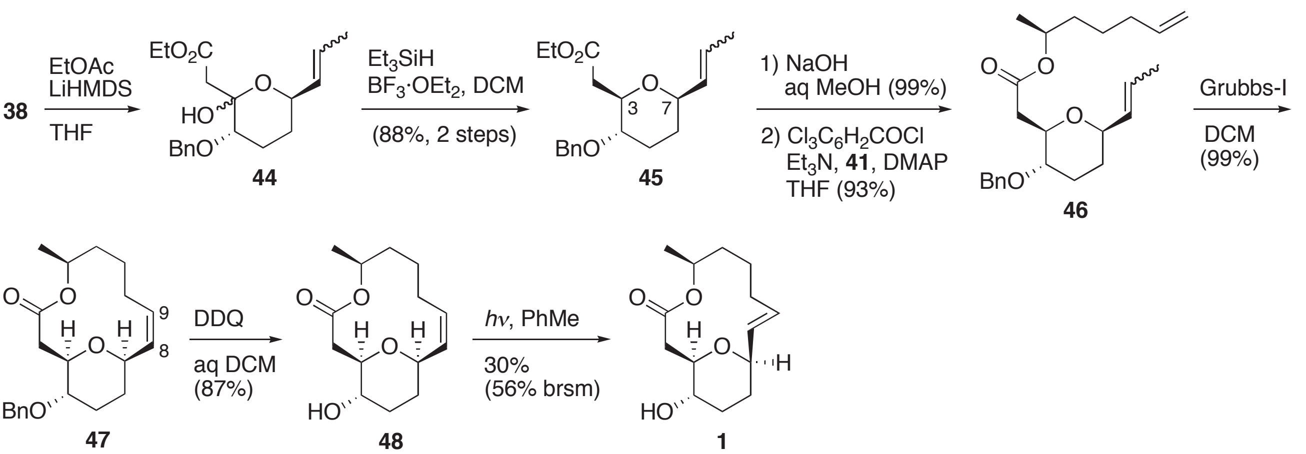
4. SYNTHESIS OF ASPERGILLIDES A AND B BY THE MARCO GROUP

Marco and co-workers accomplished the synthesis of apergillides A (**1**) and B (**2**) using two types of Lewis acid-induced nucleophilic substitution reactions for the installation of the 2,6-cis- and 2,6-trans-substituted tetrahydropyran moieties embedded in **1** and **2**, respectively.[24]



Scheme 4. Synthesis of aspergillide B (**2**) by Marco's group

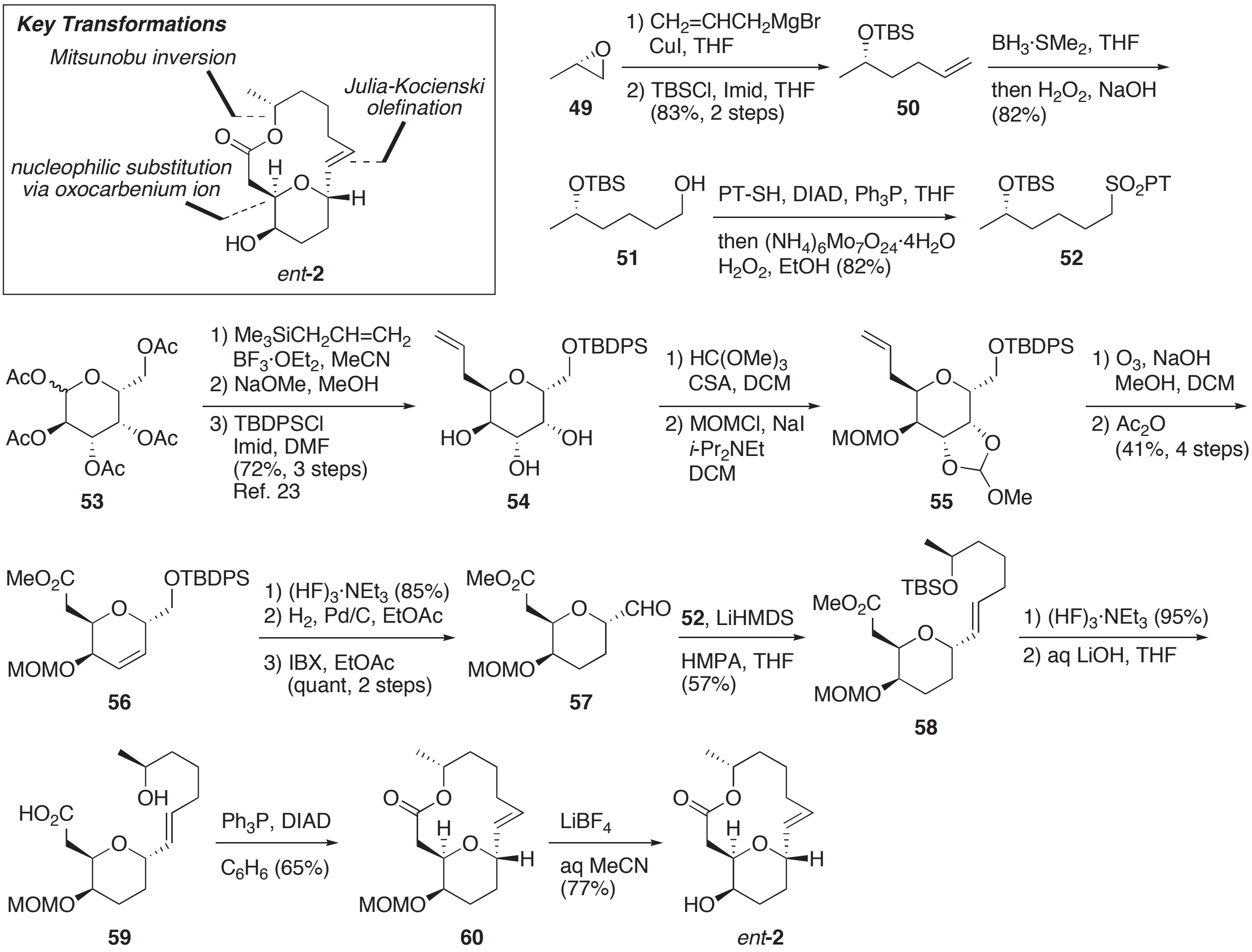
Their synthesis of **2** began with the ozonolysis of the benzyl ether of known olefinic alcohol **34**[25] to deliver **35** (Scheme 4). The aldehyde **35** was subjected to Brown's asymmetric allylboration[26] to give **36** (dr >95:5) after TES-protection of the resulting alcohol. Migration of its terminal double bond to the adjacent internal position was implemented efficiently by Wipf's procedure[27] to give **37** as a ca. 9:1 *E*/*Z* mixture, which was then deprotected and oxidized[28] to lactone **38**. Reduction of **38** followed by in situ acetylation of the resulting lactol[29] furnished **39**, which was treated with the TMS enol ether derived from *t*-butyl thioacetate in the presence of $BF_3 \cdot OEt_2$ and TMSOTf to induce the addition of the nucleophile to an oxocarbenium ion intermediate generated from **39**. The reaction proceeded with moderate diastereoselectivity, giving **40** and its C3-epimer in yields of 55% and 21%, respectively. Saponification of **40** followed by cross-metathesis with **41**[30] afforded seco acid **42** as a 7:3 *E*/*Z* mixture, which was then subjected to the Yamaguchi lactonizaion. The desired macrolide **43**, obtained in 40% isolated yield after purification, was converted into aspergillide B (**2**) by debenzylation with DDQ in wet dichloromethane.[24a] To obtain aspergillide A (**1**) bearing the 2,6-cis-substituted tetrahydropyran core, the lactone **38** was first exposed to an aldol reaction with ethyl acetate (Scheme 5), and the resulting lactol **44** was reduced with $Et_3SiH/BF_3 \cdot OEt_2$[19] to furnish **45** with exclusive 3,7-cis selectivity. Hydrolysis of **45** and subsequent esterification with **41** gave **46**, the ring-closing metathesis (RCM)[31] of which using the first-generation Grubbs' catalyst afforded 8,9-*Z* macrolactone **47** as a sole product in 99% yield. The exclusive formation of **47** was explained based on molecular mechanics calculations which indicated **47** to be much more stable than the corresponding *E* isomer and therefore the thermodynamically controlled product; the authors also deduced that the formation of **47** might be kinetically favored due to certain conformational restraints imposed by the presence of the bridged tetrahydropyran ring.[32] Finally, deprotection of **47** and subsequent photochemical isomerization of the resulting alcohol **48** provided aspergillide A (**1**), albeit in a modest isolated yield of 30% [56% based on recovered starting material (brsm)]. It is worth mentioning that compound **48** exhibited much higher cytotoxicity (18–45 times) than **1** and **2** against the human cancer cell lines HL-60 and MDA-MB-231.[24c]



Scheme 5. Conversion of intermediate **38** into aspergillide A (**1**) by the Marco group

5. SYNTHESIS OF THE UNNATURAL ENANTIOMER OF ASPERGILLIDE B BY SHE AND CO-WORKERS

The synthesis of the unnatural enantiomer of aspergillide B (*ent*-**2**) by She and co-workers exploited a Lewis acid-promoted nucleophilic substitution of D-galactose pentaacetate **53** with allylsilane to construct the 2,6-trans-substituted tetrahydropyran structural motif (Scheme 6).[33]

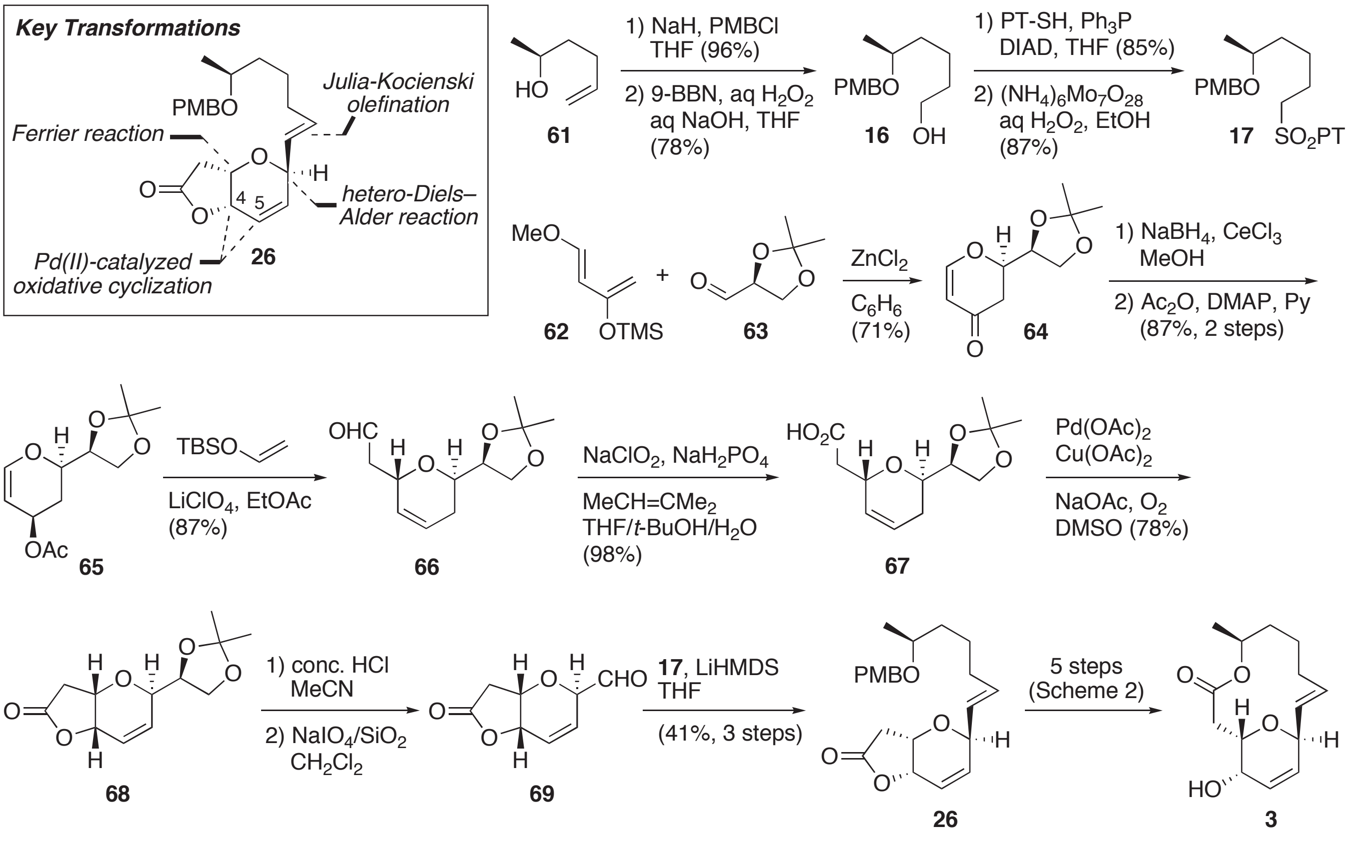


Scheme 6. Synthesis of the unnatural enantiomer of aspergillide B (*ent*-**2**) by She and co-workers

Sulfone segment **52** was prepared in 4 steps consisting of ring-opening of the starting epoxide **49**, protection to form **50**, hydroboration–oxidation to alcohol **51**, and sulfoxide formation *via* the Mitsunobu reaction.[18,34] The construction of the 2,6-trans-substituted tetrahydropyran ring system in *ent*-**2** was performed by nucleophilic addition of allylsilane to a cyclic oxocarbenium ion intermediate generated from **53** followed by solvolytic deprotection and TBS-protection to give **54**.[35] The cis-diol moiety of **54** was selectively converted into its cyclic orthoester, and the remaining β-oriented hydroxy group was protected as its MOM ether **55**. Ozonolysis of **55** in methanolic NaOH directly afforded the corresponding methyl ester,[36] the orthoester functionality of which was then pyrolytically converted to a double bond to furnish **56**.[37] After a 3-step functional group manipulation of **56**, the product **57** was coupled with the sulfone **52** to give **58** in 57% yield along with the corresponding *Z* isomer (5%). Removal of the TBS protecting group of **58** was followed by ester hydrolysis to deliver seco acid **59**. Exposure of **59** to the Mitsunobu inversion conditions afforded macrolactone **60**, which was smoothly deprotected by treatment with $LiBF_4$ in aqueous MeCN to furnish the target molecule *ent*-**2**.

6. FORMAL SYNTHESIS OF ASPERGILLIDE C BY PANARESE AND WATERS

In their formal synthesis of aspergillide C (**3**), Waters and co-workers combined a $ZnCl_2$-mediated hetero-Diels–Alder reaction with a Ferrier-type substitution to construct the 2,6-trans-substituted tetrahydropyran moiety in **3**, and exploited a Pd(II)-catalyzed oxidative cyclization to install the C4 oxygen functionality as well as the C5–C6 double bond (Scheme 7).[38]



Scheme 7. Formal synthesis of aspergillide C (**3**) by Panarese and Waters

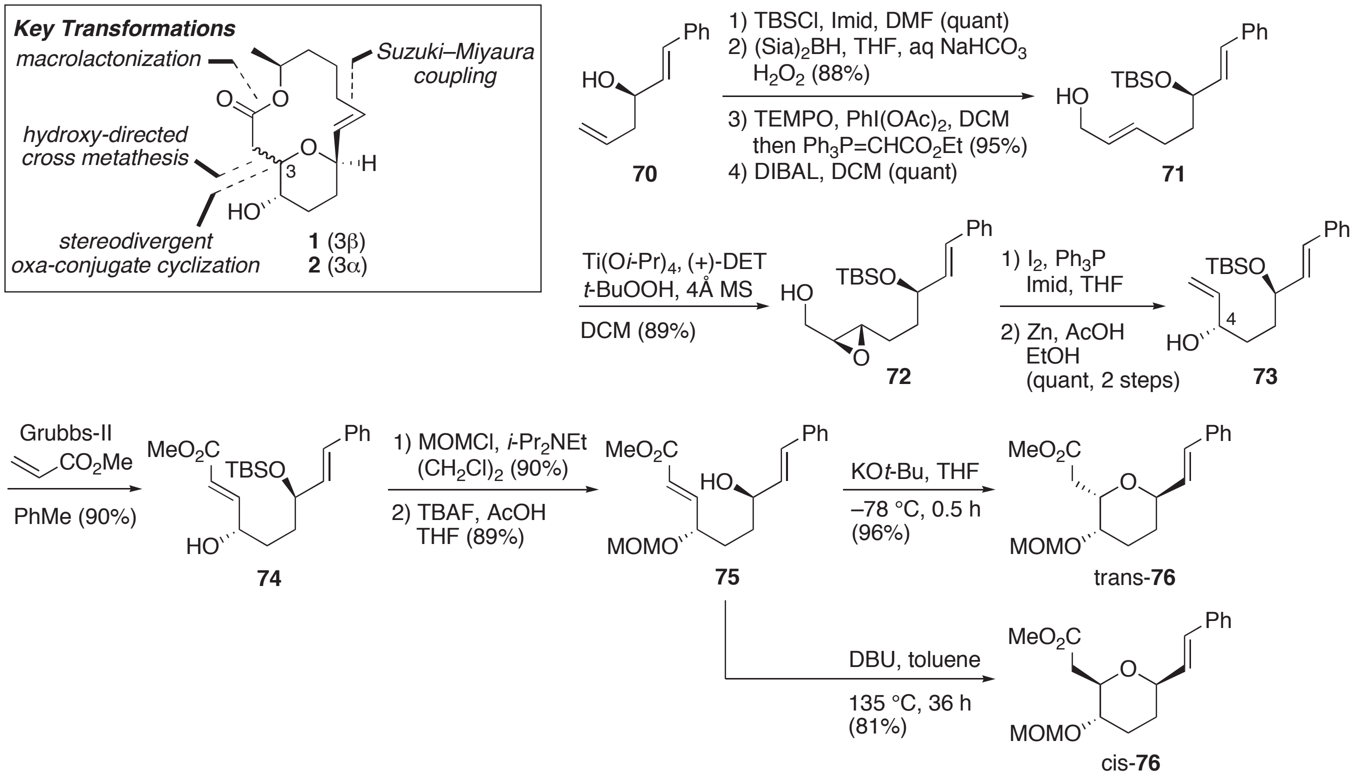
The sulfone segment **17** was prepared in a straightforward fashion from commercially available olefinic alcohol **61** *via* **16**. Preparation of its coupling partner **69** was, on the other hand, commenced with the hetero-Diels–Alder reaction of the Danishefsky–Kitahara diene **62** and aldehyde **63** prepared from

L-arabinose to give **64** as a single diastereomer.[39] The product **64** was reduced and then acetylated to afford **65**, which was exposed to the TBS enol ether of acetaldehyde in EtOAc in the presence of $LiClO_4$. The resulting Ferrier reaction product **66** obtained as an almost exclusive diastereomer was oxidized to γ,δ-unsaturated carboxylic acid **67**, the Pd(II)-catalyzed oxidative cyclization of which according to Larock' protocol[40] afforded lactone **68** with double bond migration. Hydrolysis of the acetonide in **68** and oxidative cleavage of the resulting diol intermediate with silica gel-supported $NaIO_4$ gave aldehyde **69**, which was then condensed with the sulfone **17** to furnish almost exclusively the *E*-olefin **26**, an intermediate in the total synthesis of aspergillide C by Nagasawa and Kuwahara (Scheme 2).

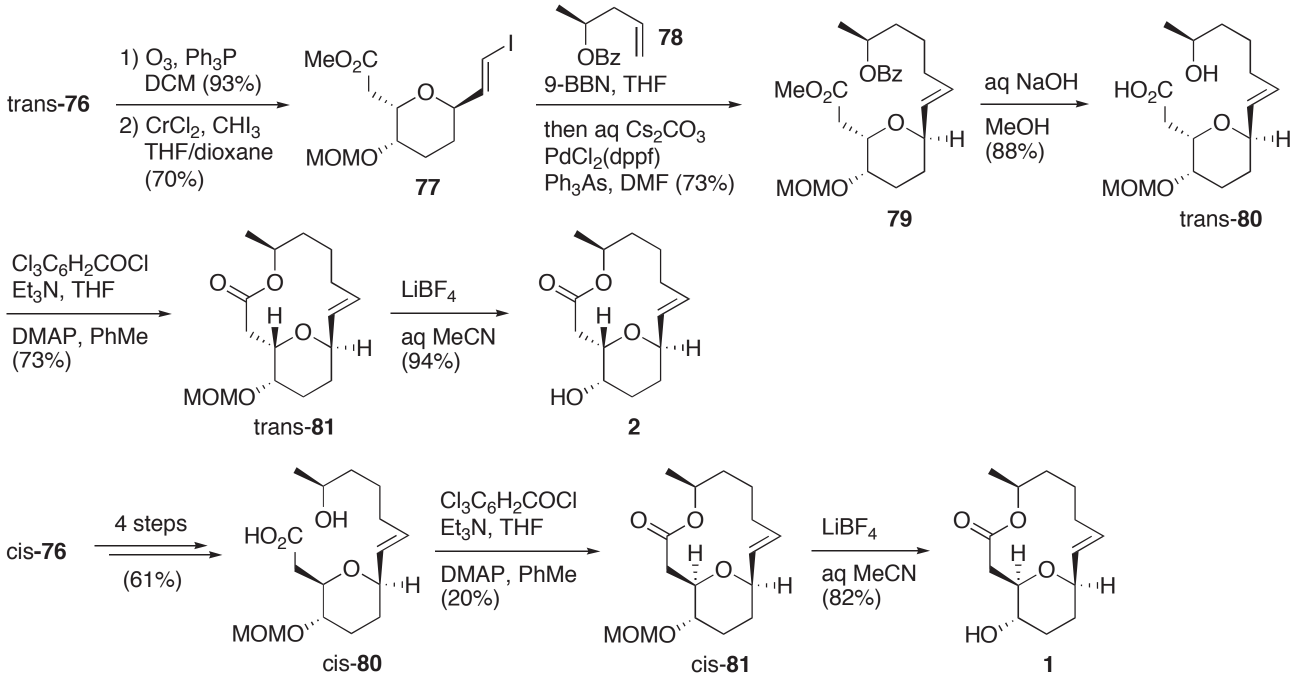
7. STEREODIVERGENT SYNTHESIS OF ASPERGILLIDES A AND B BY FUWA AND CO-WORKERS

Fuwa and co-workers achieved the total synthesis of aspergillides A and B based on a stereodivergent strategy which exploited thermodynamic and kinetic intramolecular oxa-conjugate addition reactions on a common acyclic intermediate for the installation of the 2,6-cis- and 2,6-trans-substituted tetrahydropyran cores, respectively.[41]

Known alcohol **70** was converted into allylic alcohol **71** by a 4-step sequence consisting of protection, chemoselective hydroboration/oxidation, TEMPO oxidation followed by in situ Wittig olefination (*E*/*Z* >20:1), and DIBAL reduction (Scheme 8). The Sharpless asymmetric epoxidation of **71** gave **72** as a single diastereomer, and the epoxy alcohol **72** was converted into **73** in 2 steps *via* iodination and zinc reduction. Treatment of **73** with methyl acrylate in the presence of the second-generation Grubbs' catalyst furnished **74** as a sole isolable product without giving even a trace amount of the possible six-membered RCM product. This remarkable chemoselectivity was ascribed to the formation of a hydrogen bonding between the OH at the C4 position and one of the two chlorine atoms on the ruthenium atom in an intermediary ruthenium alkylidene complex, which would render the RCM process unfavorable. Protection of **74** as its MOM ether and subsequent desilyation afforded hydroxy enoate **75**, the pivotal intermediate for this stereodivergent synthesis of **1** and **2**. Exposure of **75** to a catalytic amount of KO*t*-Bu in THF at –78 °C for 30 min provided trans-**76** as a kinetically controlled product with an excellent diastereoselectivity of 17:1. The preparation of the corresponding cis-isomer (cis-**76**) from the common intermediate **75**, on the other hand, proved to be difficult contrary to their expectation that the thermodynamically more favored isomer cis-**76** would be obtained predominantly by just elevating the reaction temperature. After several unsuccessful attempts, they found the best conditions (DBU, toluene, 135 °C, 36 h) to efficiently promote the equilibration between trans- and cis-**76**, providing cis-**76** in good yield (81%) and diastereoselectivity (11:1), and thus realizing their stereodivergent strategy to obtain both trans- and cis-**76** (precursors to **2** and **1**, respectively) from the common intermediate **75**.



Scheme 8. Stereodivergent preparation of key synthetic intermediates, trans- and cis-**76**, by Fuwa's group



Scheme 9. Transformation of trans- and cis-**76** to aspergillides B (**2**) and A (**1**), respectively, by Fuwa and co-workers

Ozonolytic cleavage of the double bond of trans-**76** and subsequent application of Takai' protocol afforded **77** (*E*/*Z* = ca. 5:1) (Scheme 9). The (*E*)-vinyl iodide **77** was, after separation, subjected to *B*-alkyl Suzuki–Miyaura coupling with olefin **78**,[42] prepared in 2 steps from (*S*)-propylene oxide, to give **79**. Hydrolysis of **79** and treatment of the resulting seco acid trans-**80** under the Yamaguchi lactonization conditions furnished mactolactone trans-**81**, the deprotection of the MOM group of which with $LiBF_4$ completed the total synthesis of aspergillide B (**2**). Exposure of cis-**76** to the same 6-steps sequence employed for the conversion of trans-**76** into **2** gave aspergillide A (**1**), although the macrolactonization of cis-**80** to cis-**81** was low-yielding as in the case of the synthesis by Nagasawa and Kuwahara (Scheme 3);[23] they reasoned the difficulty would be ascribable to the fact that cis-**80** with an all-equatorial conformation needs to flip to an energetically unfavorable all-axial conformer, which is adopted by aspergillide A itself (Figure 2), for the macrolactonization to take place.

8. FORMAL SYNTHESIS OF ASPERGILLIDE A BY SABITHA AND CO-WORKERS

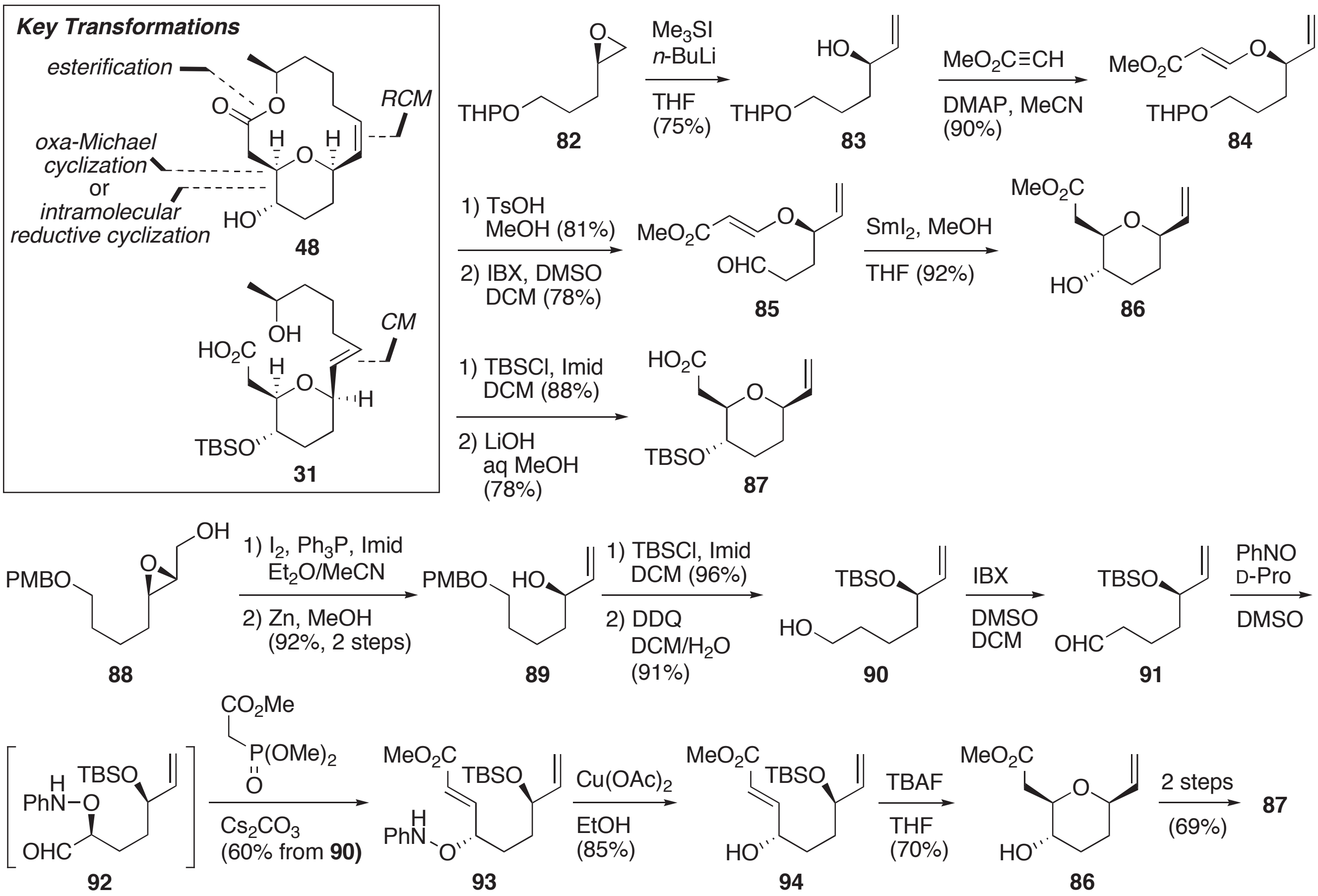
Sabitha and co-workers reported two approaches to 2,6-cis-substituted tetrahydropyran core **87** (Scheme 10) which was successfully transformed into two intermediates, **31** and **48** (Scheme 11), employed in previous syntheses of aspergillide A (**1**).[43]

Their first approach to **87** began with ring-opening homologation of terminal epoxide **82**[44] obtained from the corresponding racemate by Jacobsen's kinetic resolution.[45] Conjugate addition of the resulting allylic alcohol **83** to methyl propiolate afforded **84**, the treatment of which with acidic methanol followed by IBX oxidation provided **85**. Subjection of the β-alkoxy acrylate **85** containing an aldehyde group in the molecule to Nakata's SmI_2-induced reductive cyclization furnished **86** as a single diastereomer,[46] which was then protected and hydrolyzed to the key intermediate **87**.

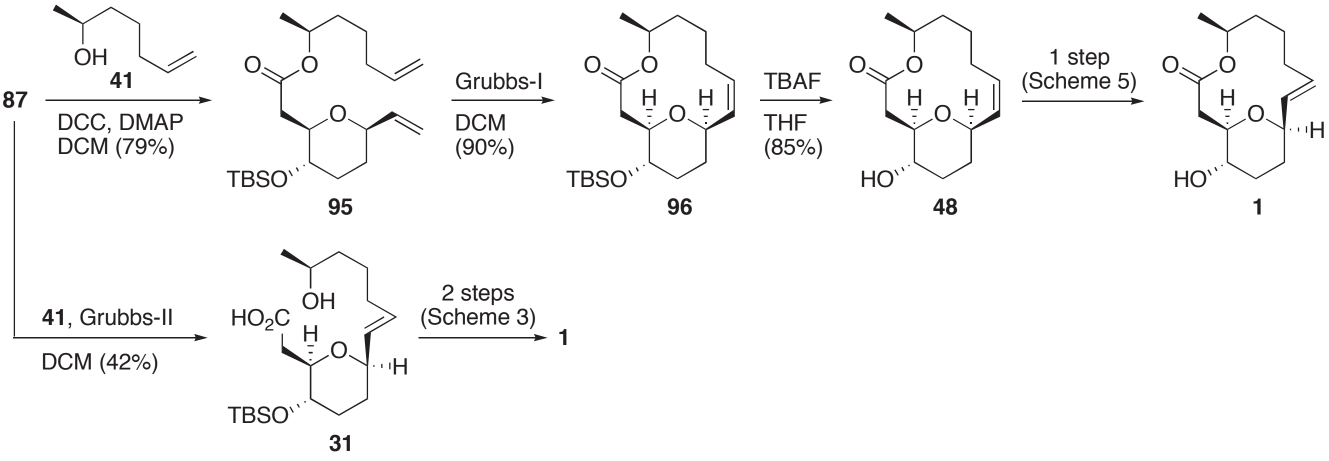
The other approach to **87** featuring an intramolecular oxa-Michael addition under thermodynamic conditions commenced with the preparation of **89** from epoxy alcohol **88**[47] in 2 steps consisting of iodination and reductive epoxide ring-opening. The allylic alcohol **89** was converted by a 3-step sequence *via* **90** into aldehyde **91**, which on exposure to proline-catalyzed asymmetric α-aminooxylation conditions[48] followed by in situ Horner–Wadsworth–Emmons olefination and subsequent Cu(II)-catalyzed N–O bond cleavage[49] gave **94** with excellent diastereoselectivity (>95:5) *via* **92** and **93**. Treatment of **94** with TBAF induced deprotection of the TBS group and concomitant intramolecular oxa-Michael addition to exclusively form **86**, which was converted into **87** as described above.

The olefinic carboxylic acid **87** was esterified with the known alcohol **41**[30] to give **95**, the treatment of which with the first-generation Grubbs' catalyst resulted in the exclusive formation of *Z*-macrolactone **96** in 90% yield in accord with the result observed in the corresponding Bn-protected congener (Scheme 5). Finally, deprotection of **96** gave **48**, the penultimate intermediate in the previous synthesis of **1** by

Marco's group (Scheme 5). In addition, the cross-metathesis of **87** with **41** provided a mixture of **31** and the corresponding *Z*-isomer in a ratio of 9:1, the former which had previously been converted into aspergillide A (**1**) by Nagasawa and Kuwahara (Scheme 3).



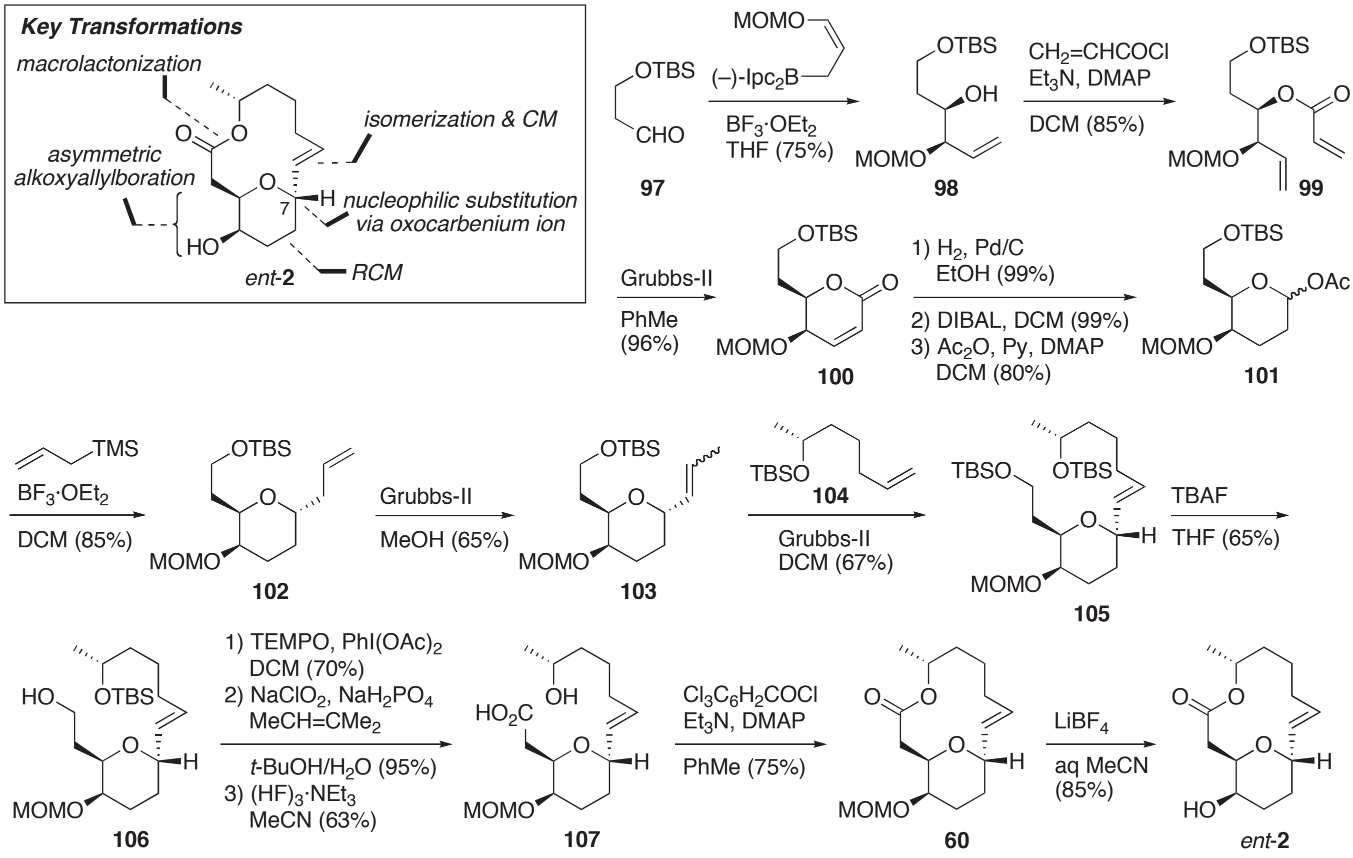
Scheme 10. Two approaches to key intermediate **87** by Sabitha and co-workers



Scheme 11. Two routes from **87** to aspergillide A (**1**) in the synthesis by Sabitha's group

9. SYNTHESIS OF THE UNNATURAL ENANTIOMER OF ASPERGILLIDE B BY HENDRIX AND JENNINGS

The synthesis of the unnatural enantiomer of aspergillide B (*ent*-**2**) by Hendrix and Jennings features the formation of the tetrahydropyran core by ring-closing metathesis coupled with nucleophilic substitution at the C7-position *via* an oxocarbenium ion intermediate (Scheme 12).[50]

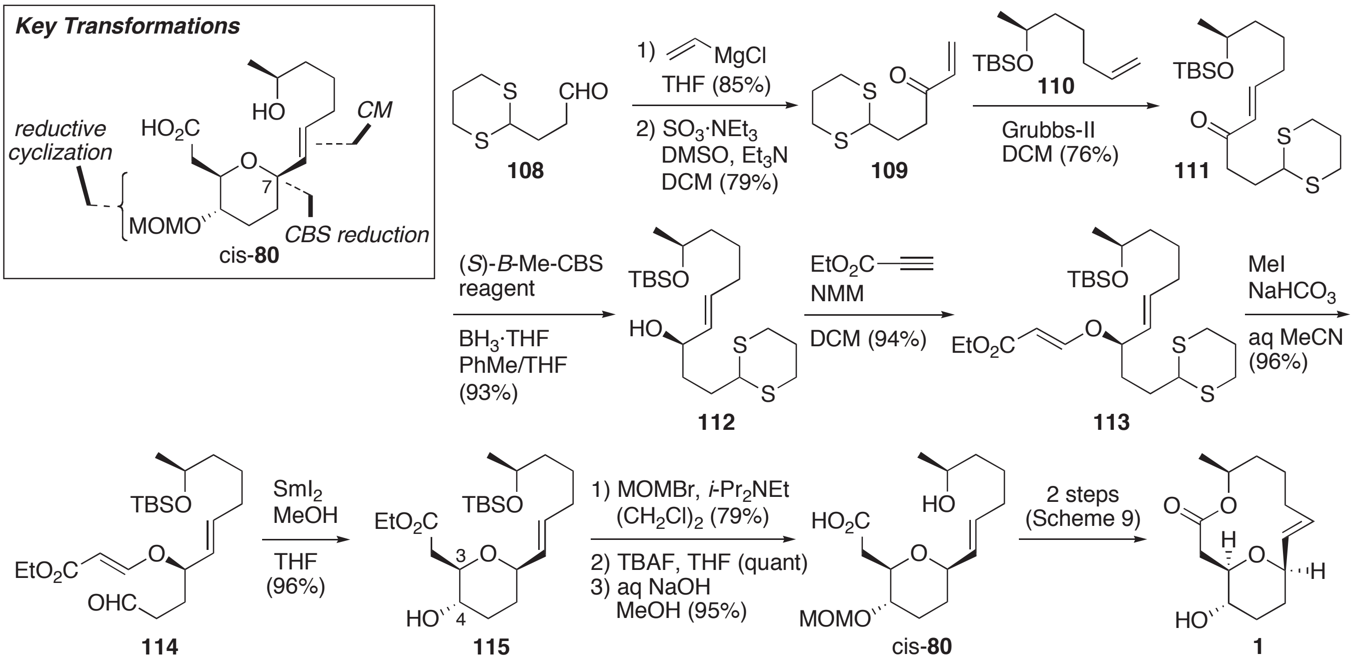


Scheme 12. Synthesis of the unnatural enantiomer of aspergillide B (*ent*-**2**) by Hendrix and Jennings

They employed Brown's asymmetric alkoxyallylboration on aldehyde **97** as the chirality-inducing step,[51] providing **98** with excellent diastereomeric and enantiomeric purity (dr >95:5, 94% ee). Esterification of **98** with acryloyl chloride gave **99**, which was then subjected to ring-closing metathesis using the second-generation Grubbs' catalyst to furnish **100**. The unsaturated lactone **100** was converted straightforwardly into **101**, the oxocarbenium ion precursor. Treatment of **101** with allylsilane in the presence of $BF_3{\cdot}OEt_2$ afforded 2,6-trans tetrahydropyran derivative **102** as a single diastereomer. Isomerization of the terminal double of **102** was effected by its treatment with the second-generation Grubbs' catalyst according to Hanessian's procedure[52] to give **103** as an 8:1 *E*/*Z* mixture, the cross-metathesis of which with olefin **104** derived from (*R*)-propylene oxide then afforded **105** with high geometrical selectivity (*E*/*Z* >20:1). Selective deprotection of its primary TBS group gave **106**, which was converted into **107** *via* 3 conventional steps. Finally, the seco acid **107** was exposed to the Yamaguchi lactonization conditions to provide *ent*-**2** after removal of the MOM protecting group of the macrolactonization product **60** (She's intermediate, Scheme 6).

10. FORMAL SYNTHESIS OF ASPERGILLIDE A BY TAKAHASHI AND CO-WORKERS

The formal synthesis of aspergillide A (**1**) by Takahashi and co-workers exploited, as key steps, the CBS reduction of an enone intermediate to install a stereogenic center and SmI_2-induced reductive cyclization of a formyl-containing β-alkoxy acrylate derivative, originally developed by their group and employed in Sabitha's approach to **1** (Scheme 10), for the construction of the 2,6-cis-substituted tetrahydropyran ring system (Scheme 13).[53]



Scheme 13. Formal synthesis of aspergillide A (**1**) by Takahashi's group

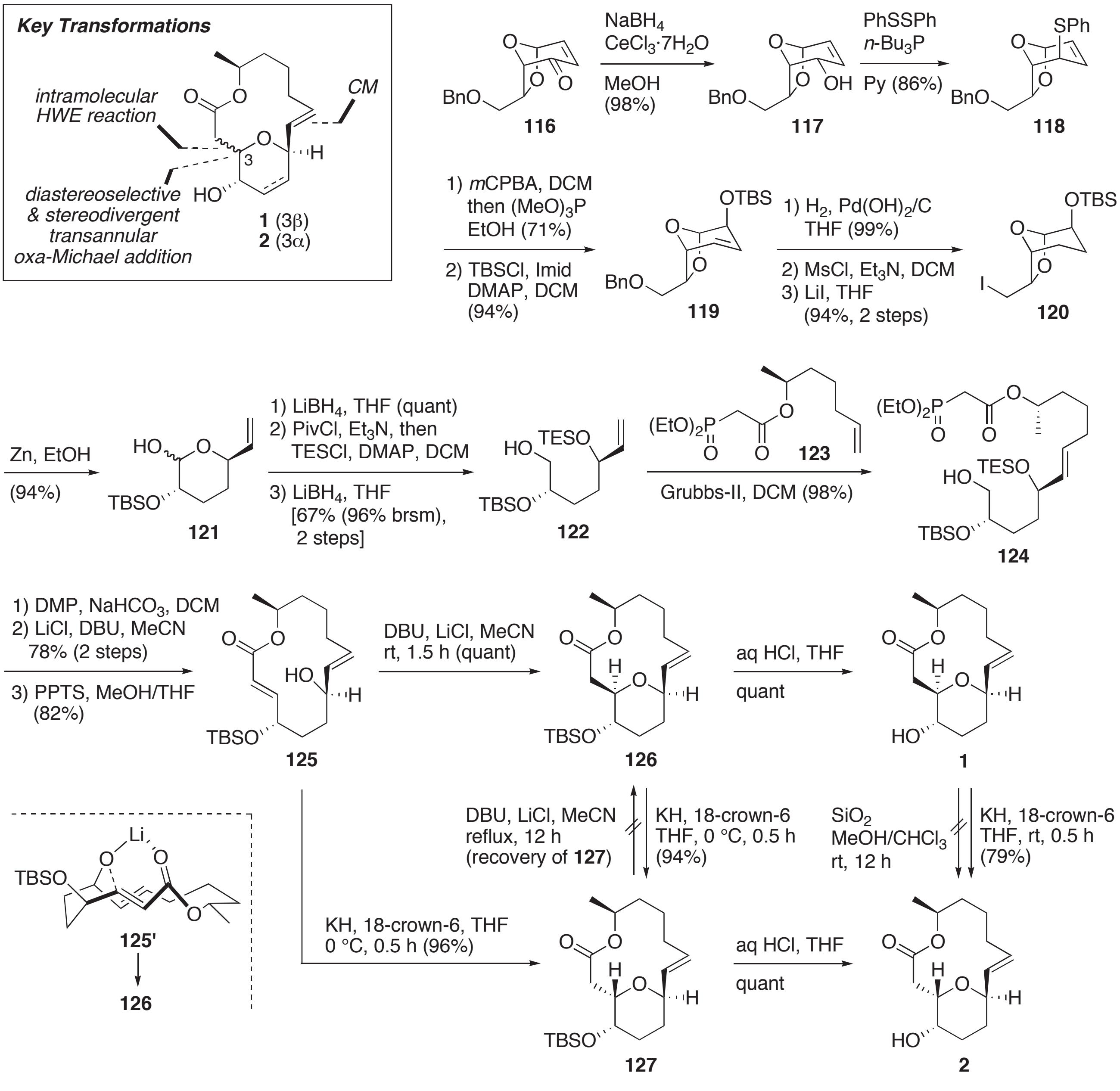
Enone **109**, obtained from known aldehyde **108**[54] by a 2-step sequence, was treated with terminal olefin **110**[55] in the presence of the second-generation Grubbs' catalyst to give **111**, which upon subjection the CBS reduction[56] afforded allylic alcohol **112** with good diastereoselectivity (dr 94:6). Oxa-conjugate addition of **112** to ethyl propiolate in the presence of *N*-methylmorpholine (NMM) gave β-alkoxy enoate **113**, and its dithiane group was hydrolyzed to provide **114**. Upon exposure to SmI_2 in THF in the presence of MeOH,[46] **114** was transformed in 96% yield into a 10:1 mixture of **115** and its (3*S*,4*R*)-isomer. Treatment of the mixture with MOMBr in dichloromethane in the presence of the Hünig base and subsequent purification of the product gave a diastereomerically pure MOM-protected intermediate, which was subjected to a 2-step deprotection sequence to furnish seco-acid cis-**80**, an intermediate in Fuwa's synthesis of aspergillide A (Scheme 9).

11. STEREODIVERGENT TRANSANNULAR OXA-MICHAEL APPROACH TO ASPERGILLIDES A, B, AND C BY SHISHIDO AND CO-WORKERS

Shishido and co-workers reported a remarkable approach to aspergillides A (**1**) and B (**2**) which exploited highly efficient stereodivergent transannular oxa-Michael reactions of a common macrocyclic intermediate (**125**) involving the formation of either the 2,6-cis- or 2,6-trans-tetrahydropyran ring system depending on the reaction conditions (Scheme 14).[57]

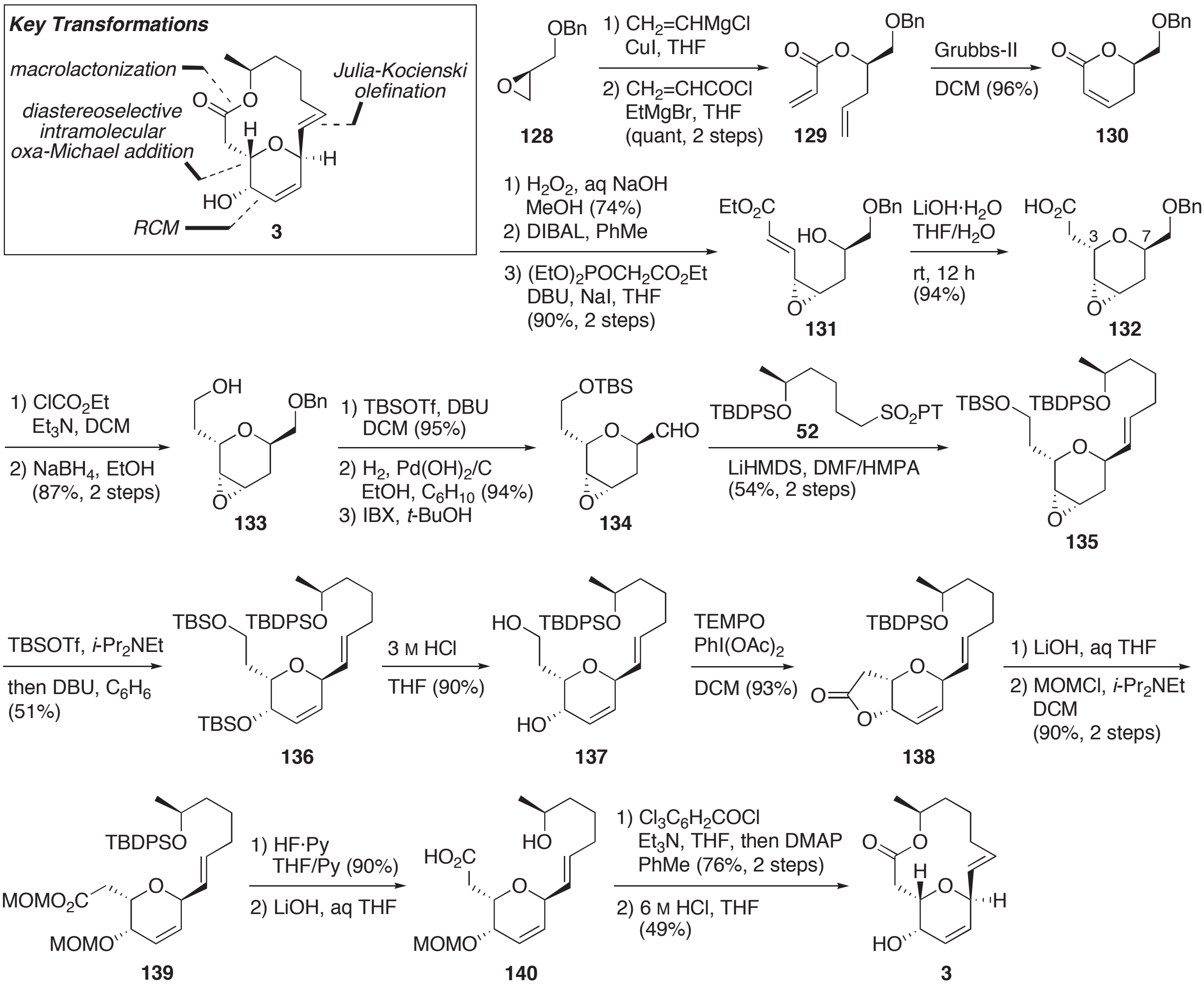
Their synthesis of **1** and **2** began with the stereoselective reduction of known enone **116**[58] to form allylic alcohol **117**, which was converted into sulfide **118** according to Hata's protocol.[59] Application of allyl sulfoxide–sulfenate rearrangement to **118** afforded **119** after TBS-protection. Hydrogenation of **119** accompanied by concomitant debenzylation and a subsequent mesylation/iodination sequence provided iodide **120**. Treatment of **120** with Zn in ethanol induced reductive ring-opening, furnishing cyclic hemiacetal **121**. Reduction of **121** with $LiBH_4$ gave a diol intermediate, the primary hydroxy group of which was protected as its pivaloyl ester and the remaining secondary one as its TES ether. The ester was then reduced to alcohol **122**, which was subjected to cross-metathesis with olefin **123**, prepared from (*S*)-2-methyloxirane in 2 steps, affording **124** with high geometrical selectivity (*E*/*Z* >20:1). Oxidation of the alcohol **124** to an aldehyde followed by intramolecular olefination under the Masamune–Roush conditions[60] and deprotection in acidic medium delivered macrocyclic hydroxy enoate **125**, the pivotal common substrate for the stereodivergent transannular oxa-Michael reactions leading either to **1** or to **2**.

Upon exposure to DBU in MeCN in the presence of LiCl at room temperature for 1.5 h, **125** was quantitatively converted into **126** with the 3,7-cis stereochemistry as a single product. On the other hand, treatment of **125** with KH in THF in the presence of 18-crown-6 at 0 °C for 0.5 h gave the corresponding 3,7-trans isomer **127** as a single diastereomer in a very high yield of 96%. The addition of LiCl in the formation **126** enabled the transannular reaction to proceed much faster than the reaction without it; the authors reasoned this effect by suggesting lithium-chelated transition state **125'**, the conformation of which is quite similar to that of the crystal structure of aspergillide A. Furthermore, it was revealed that the transformation of the 3,7-cis isomer **126** to the 3,7-trans isomer **127** could be achieved in very high yield (94%), while the reverse reaction from **127** to **126** was not realized, resulting the recovery of **127** in 90% yield. These results as well as some additional experiments indicated that the trans-isomer **127** was thermodynamically favored. Finally, hydrolytic removal of the TBS protecting group in **126** and **127** completed the total synthesis of aspergillides A (**1**) and B (**2**), respectively. Very interestingly, the conversion of **1** into **2** was also found to be possible by treating **1** with the same conditions as employed for the transformation of **126** to **127**, while the exposure of **1** to SiO_2 in $MeOH/CHCl_3$ (isolation conditions for the aspergillides) did not produce **2** at all, suggesting aspergillide B (**2**) is not an artifact.



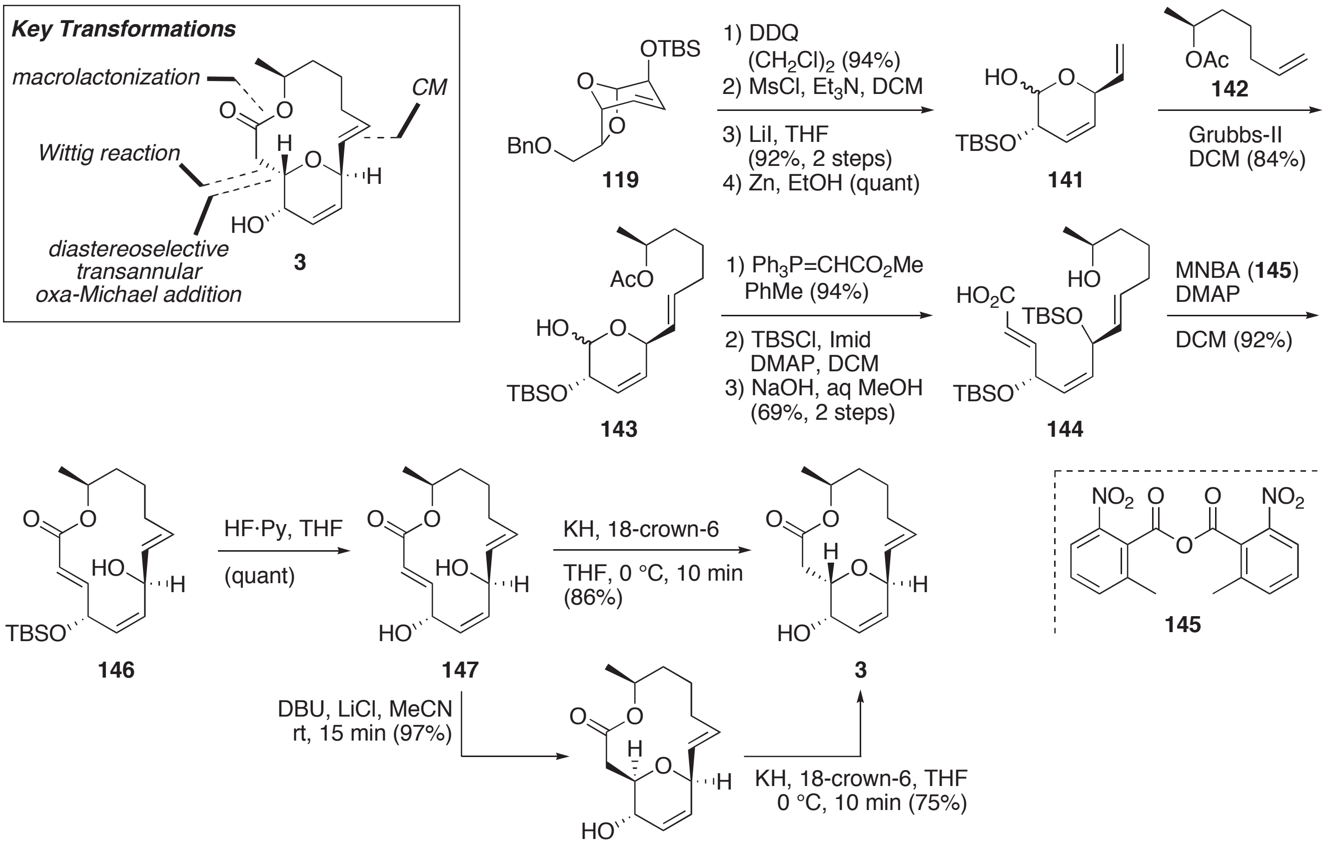
Scheme 14. Stereodivergent synthesis of aspergillides A (**1**) and B (**2**) by Shishido and co-workers *via* transannular oxa-Michael reactions of common macrocyclic intermediate **125**

Shishido and co-workers also disclosed two syntheses of aspergillide C (**3**) (Scheme 15), the first one of which utilized, as the key step, an intramolecular oxa-Michael reaction before macrolactonization, leading exclusively to a 2,6-trans-substituted pyran intermediate,[61] and the second one adopted the highly efficient transannular oxa-Michael strategy as employed for their synthesis of aspergillides A and B described above.[62]



Scheme 15. Shishido's first-generation synthesis of aspergillide C (**3**) *via* intramolecular oxa-Michael reaction prior to macrolactonization

Their first approach to **3** commenced with ring-opening of epoxide **128** with vinylmagnesium chloride followed by acrylation of the resulting alcohol to deliver **129**.[61] Ring-closing metathesis of **129** gave lactone **130**, which was converted by a conventional 3-steps sequence into hydroxy enoate **131**. Intramolecular oxa-Michael reaction of **131** by exposure to LiOH in aqueous THF (THF/H_2O = 3:1) proceeded very efficiently, furnishing cyclic carboxylic acid **132** with 3,7-trans stereochemistry as a single diastereomer in 94% yield. They revealed that the presence of water in this transformation was essential for acceleration of the reaction and for realizing the high yield and excellent diastereoselectivity, and also that the hydrolysis of the ester group took place after the ring formation. The use of NaOH and KOH resulted in lower yields (79% and 85%, respectively) and diastereoselectivity (6.1:1 and 6.3:1, respectively). From these results, the authors proposed a lithium-chelated transition state responsible for the exclusive formation of the 3,7-trans isomer **132**. Reduction of **132** in 2 steps and a subsequent 3-step functional group manipulation on the resulting alcohol **133** gave aldehyde **134**, the Julia–Kocienski olefination of which with sulfone **52**[33] afforded *E*-olefin **135** predominantly (*E*/*Z* >10:1). Installation of the double bond on the tetrahydropyran ring to form **136** was conducted by the Fuchs modification of Noyori's protocol.[63] After selective removal of the two TBS groups in **136**, the resulting diol **137** was converted by a straightforward 5-step sequence, *via* γ-lactone **138** and MOM ester **139**, into seco acid **140**, the macrolactonization of which followed by deprotection furnished aspergillide C (**3**).



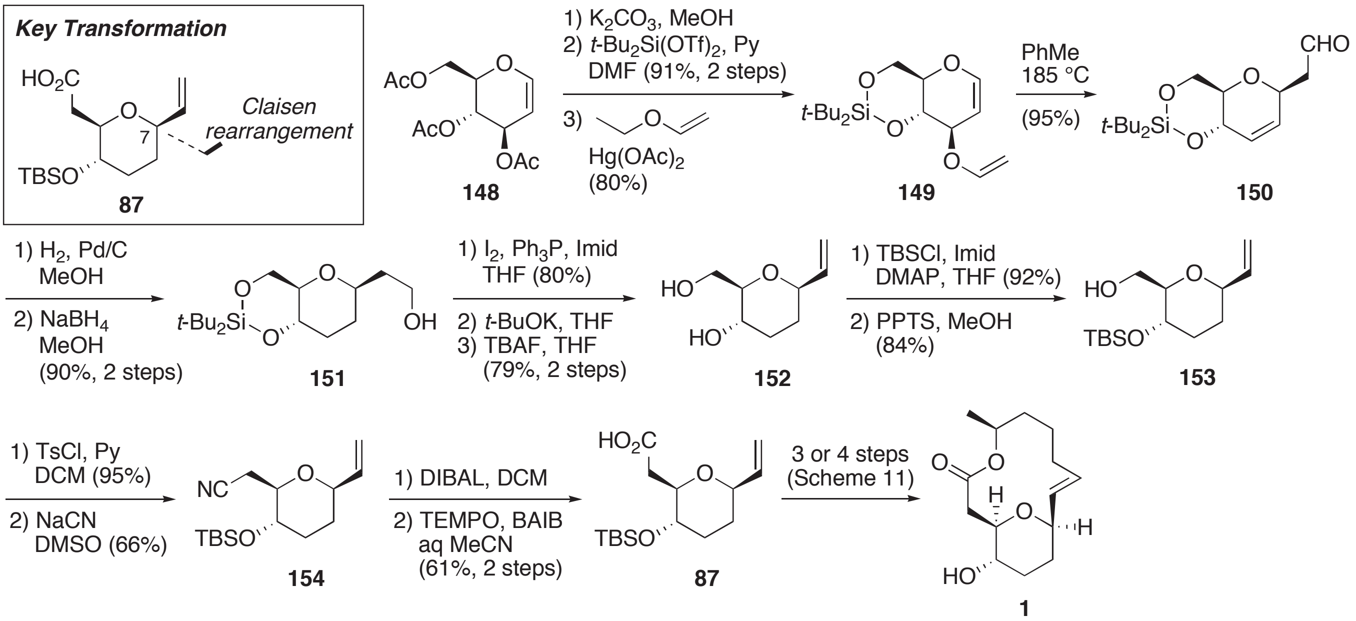
Scheme 16. Shishido's second-generation synthesis of aspergillide C (**3**) by diastereoselective transannular oxa-Michael strategy

The second-generation synthesis of **3** by Shishido and co-workers adopted **119**, an intermediate in their synthesis of aspergillides A and B (Scheme 14), as the starting point (Scheme 16).[62] Debenzylation of **119** followed by a 3-step transformation gave lactol **141**, the cross-metathesis of which with terminal olefin

142[64] to provide **143** and a subsequent olefination/protection/deprotetion sequence furnished seco acid **144**. The Shiina macrolactonization of **144** proceeded in a better yield of 92% than the Yamaguchi protocol (56%),[22] affording **146**, the desilylation of which provided dihydroxy macrolactone **147**. Treatment of **147** with KH in THF in the presence of 18-crown-6 for 10 min at 0 °C gave aspergillide C (**3**) as a single diastereomer in 86% yield, thus realizing the unified total synthesis of all of the aspergillides based on their transannular oxa-Michael strategy. Exposure of **147** to DBU in MeCN in the presence of LiCl for 15 min at room temperature, on the other hand, led to the exclusive formation of the corresponding 3,7-ci*s* isomer (3-*epi*-**3**) in 97% yield. Upon subjection to the same conditions as employed for the conversion of **147** into **3**, 3-*epi*-**3** was transformed into **3**, which, coupled with some additional experiments, clearly indicated that aspergillide C (**3**) and its C3-epimer (3-*epi*-**3**) were thermodynamic and kinetic products, respectively.

12. FORMAL SYNTHESIS OF ASPERGILLIDE A BY FALL AND CO-WORKERS

Fall and co-workers reported the synthesis of the 2,6-cis-substituted tetrahydropyran derivative **87**, an intermediate in Sabitha's formal synthesis of aspergillide A (**1**) (Scheme 10), using commercially available tri-*O*-acetyl-D-glucal **148** as the starting material and the Claisen rearrangement as the key step to install the stereochemistry at the C7 position (Scheme 17).[65]



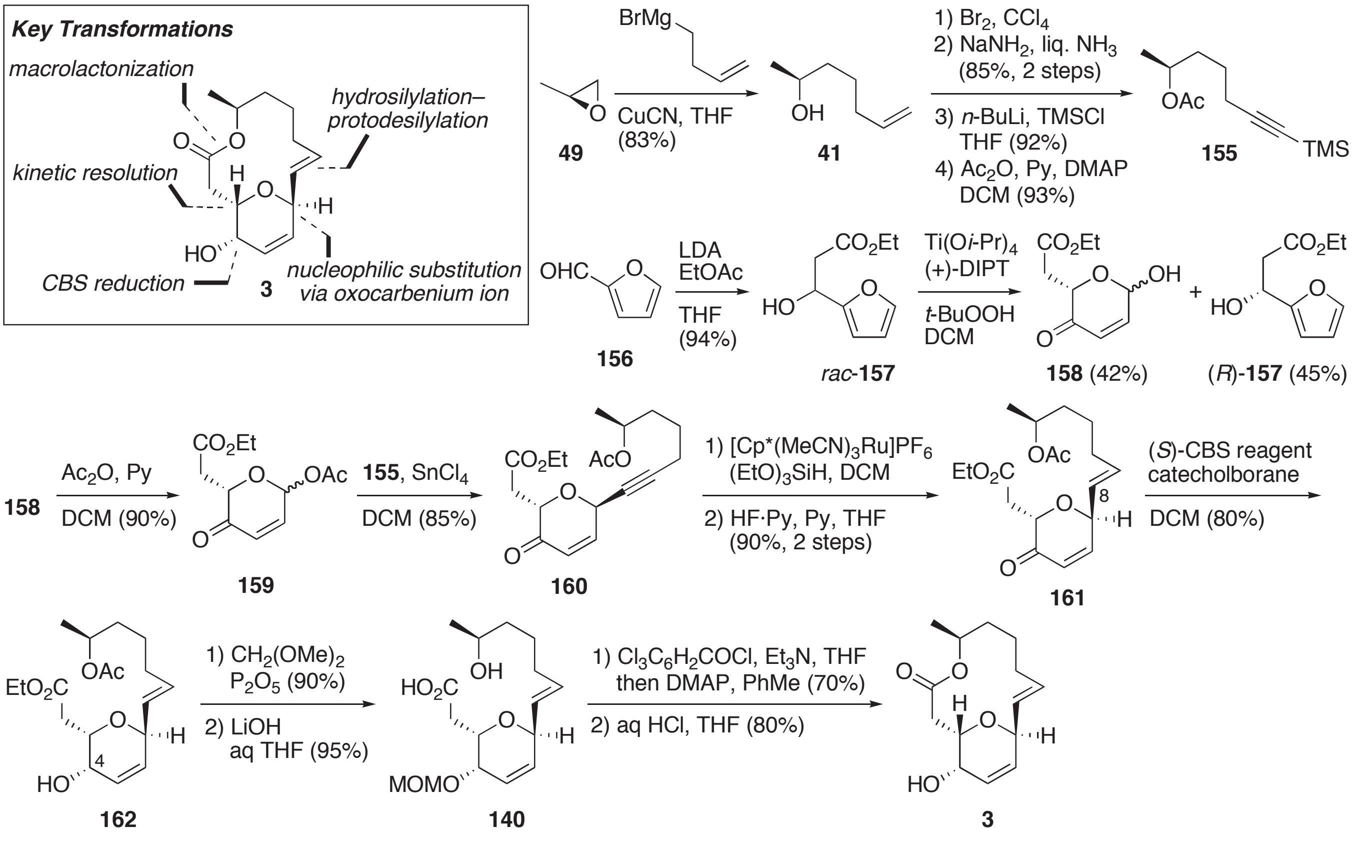
Scheme 17. Formal synthesis of aspergillide A (**1**) by Fall's group *via* the Claisen rearrangement

The glucal **148** was converted into allyl vinyl ether **149** *via* solvolytic removal of the acetate groups, protection of the resulting 1,3-diol moiety, and finally enol ether formation. The Claisen rearrangement of

149 afforded **150** with the desired stereochemical relationship, the double bond and the aldehyde groups of which were reduced in 2 steps to give **151**. Iodination of the alcohol **151** followed by elimination and desilylation furnished diol **152**. Its secondary hydroxy group was protected by a 2-step sequence, delivering **153**, which was then transformed, by a conventional 4-step sequence of reactions *via* nitrile **154**, into the target molecule **87**.

13. SYNTHESIS OF BOTH ENANTIOMERS OF ASPERGILLIDE C AND THEIR RESPECTIVE C4-EPIMERS BY SRIHARI AND SRIDHAR

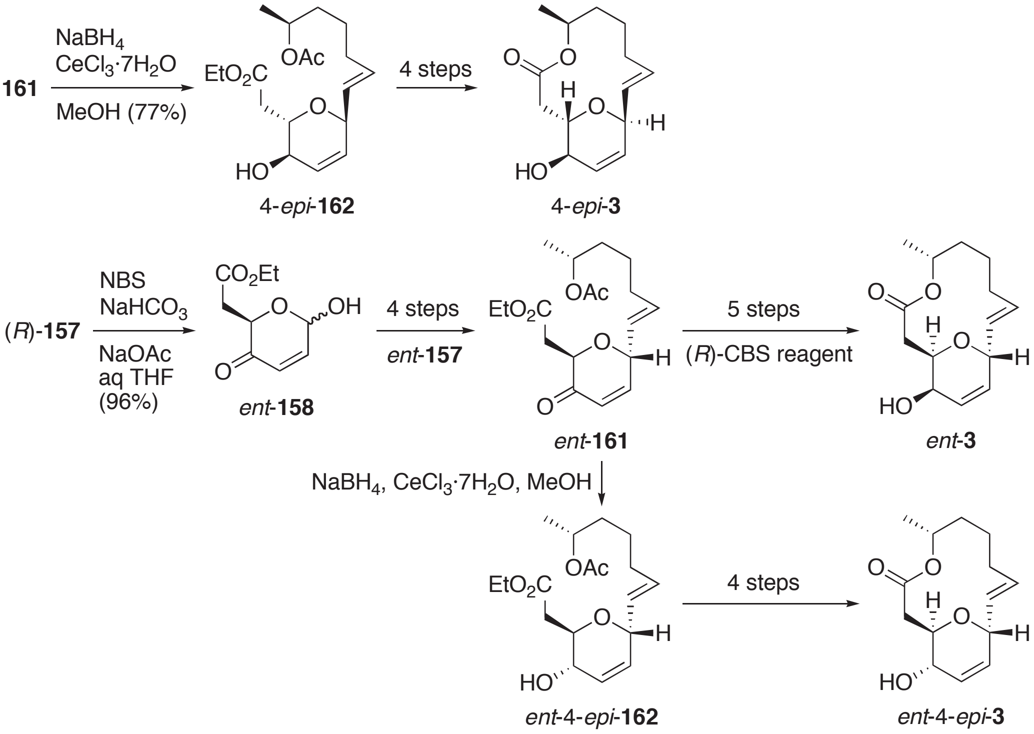
The most recent approach to aspergillides was disclosed by Srihari and Sridhar in their total synthesis of aspergillide C (**3**) and its stereoisomers, which included the Sharpless kinetic resolution of a furfuryl alcohol derivative as the chirality-inducing step and a Lewis acid-promoted nucleophilic substitution of a dihydropyranyl acetate intermediate with a silyl acetylene to construct the 2,6-trans-substituted dihydropyran ring system (Schemes 18 and 19).[66]



Scheme 18. Synthesis of aspergillide C (**3**) by Srihari and Sridhar

The silyl acetylene **155** was prepared in a 5-step straightforward manner from (*S*)-propylene oxide **49**, *via* olefinic alcohol **41**. To obtain its coupling partner **159**, they utilized the Sharpless kinetic resolution of the furfuryl alcohol derivative *rac*-**157** derived from furfural **156**,[67] providing oxidation product **158** along with enantiopure (*R*)-**157**. The lactol **158** was acetylated to **159** and then treated with the silyl acetylene **155** in dichloromethane in the presence of $SnCl_4$,[68] furnishing 2,6-trans-substituted dihydropyran derivative **160** as a single diastereomer in 4 steps from the simple starting material **156**. The installation of the *E* double bond at the C8 position was conducted by Trost's hydrosilylation/protodesilylation protocol,[69] resulting in the exclusive formation of *E*-olefin **161**. Subjection of the enone **161** to the CBS reduction conditions gave allylic alcohol **162** in 80% yield together with the corresponding C4-epimer (9%). After MOM-protection of **162** followed by hydrolysis, the resulting seco acid **140** (Shishido's intermediate, Scheme 15) was converted *via* 2 steps into aspergillide C (**3**).

They also synthesized the 4-*epi*-aspergillide C (4-*epi*-**3**) as well as the enantiomers of aspergillide C and 4-*epi*-**3** (*ent*-**3** and *ent*-4-*epi*-**3**, respectively) for future evaluation of their biological activity (Scheme 19). The syntheses are based on their findings that compound **161**, when exposed to $NaBH_4/CeCl_3/MeOH$, gave a separable mixture of the 4-*epi*-**162** and **162** in a ratio of 4:1 favoring the former, and that (*R*)-**157** was readily convertible into the enantiomer of **158** (*ent*-**158**) by NBS-oxidation in aqueous medium.



Scheme 19. Synthesis of stereoisomers of aspergillide C by Srihari and Sridhar

14. CONCLUSION

This review described all of the synthetic approaches to aspergillides A (**1**), B (**2**), and C (**3**) reported in the past 3 years by 12 research groups, focusing mainly on the methodologies for the construction of the

2,6-cis- and 2,6-trans-substituted tetrahydropyran ring systems contained in **1** and **2**, respectively, and of 2,6-trans-substituted dihydropyran core incorporated in **3**. The methodologies may be categolized into 6 groups: (1) Pd(II)-catalyzed stereospecific ring formation (Scheme 1); (2) nucleophilic substitution *via* an oxocarbenium ion intermediate (Schemes 2, 4, 5, 6, 7, 12, 18); (3) intramolecular oxa-Michael addition (Schemes 3, 8, 10, 15); (4) SmI_2-induced intramolecular reductive cyclization (Schemes 10, 13); (5) stereodivergent transannular oxa-Michael addition (Schemes 14, 16); and (6) the Claisen rearrangement (Scheme 17). The Pd(II)-catalyzed cyclization employed in the first synthesis of **2** by Hande and Uenishi (Scheme 1) deserves special mention in that the reaction is stereospecific and therefore can be applied to the construction of both 2,6-cis- and 2,6-trans-substituted tetrahydropyran units contained in various natural products. Among the intramlecular oxa-Michael approaches (Category 3), the one reported by Fuwa and co-workers (Scheme 8) is also worthy to note in that the methodology is stereodivergent, giving rise to either the trans- or the cis-substituted ring system at will by choosing reaction conditions. In addition, the synthesis of **3** and its stereoisomers by Srihari and Sridhar that nicely incorporated the readily available cyclic hemiacetal **158** in their concise synthetic design (Scheme 18) could be of importance from a viewpoint of stereochemistry–activity relationship. Finally, the strategy presented by Shishido and co-workers (Schemes 14, 16) that enabled the highly efficient stereodivergent synthesis of aspergillides A–C and overcame the difficulty in the macrocyclization of aspergillide A precursors (Schemes 3, 5, 9, 11) is quite useful and will be applied, as a general methodology, to the synthesis of various macrocyclic natural products incorporating a small ring in their structures.

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Tomohiro Nagasawa was born in Shizuoka, Japan in 1985. He received his B.Sc and M.Sc. degrees from Tohoku University under the supervision of Prof. Shigefumi Kuwahara. He is now a Ph.D. student at Graduate School of Agricultural Science, Tohoku University. He received Sendai Seminar Award for Young Synthetic Chemists (Tohoku Branch of the Society of Synthetic Organic Chemistry, Japan) in 2009 and Banyu Sendai Symposium Best Poster Award in 2011. His current research interests include the total synthesis of macrocyclic natural products of biological importance.

Shigefumi Kuwahara was born in Nagasaki, Japan in 1957. He received his B.Sc, M.Sc, and Ph.D. degrees from the University of Tokyo under the supervision of Prof. Kenji Mori. After serving as Assistant at the same university, he moved to Ibaraki University in 1990, and was promoted to Associate Professor in 1994. Then, he was appointed as Associate Professor at Tohoku University in 2000. Since 2001, he has been Professor at Graduate School of Agricultural Science, Tohoku university. He received the Japan Bioscience, Biotechnology and Agrochemistry Society Award for the Encouragement of Young Scientists in 1996. His research interests include the total synthesis of bioactive natural products and their structure–activity relationship.