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STRATEGIES FOR BREVISAMIDE SYNTHESIS, BASED ON THE METHOD FOR CONSTRUCTING THE TETRAHYDROPYRANYL CORE

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Abstract – Brevisamide is a monocyclic ether alkaloid produced by the red tide dinoflagellate *Karenia brevis*. Brevisamide has attracted the attention of organic chemists because it is the smallest molecule that can be used to understand the biosynthetic 6-endo epoxide cyclization of polycyclic ethers. Within nine years of its discovery, several diverse approaches to synthesizing this monocyclic ether amide have been explored, culminating in the publication of eight total and seven formal total syntheses. In the first part of this review, we discuss strategies for the introduction of the key elements—the (2*E*,4*E*)-3,4-dimethyl-2,4-heptadienal side chain, acetamide side chain, C9 axial methyl group, and tetrahydropyran (THP) core. In the following sections, each of the total and formal syntheses is overviewed, based on the method for constructing the THP core.

CONTENTS

This paper is dedicated to Professor Masakatsu Shibasaki on the occasion of his 70th birthday.

1. INTRODUCTION

Red tide is an algal bloom that causes serious damage to the fishing industry through massive fish kill and food poisoning.[1] *Karenia brevis* is a notorious red tide dinoflagellate that produces potent neuro- and ichthyotoxic polycyclic ethers such as brevetoxin A and B (Figure 1).[2] Recently, *K. brevis* was found to produce the penta- to heptacyclic ethers brevenal,[3] brevisin,[4] and tamulamides,[5] all of which have an antagonistic effect against brevetoxins by blocking the brevetoxin binding site of voltage-gated Na channels of nerve cells.[6,7] Brevisamide (**1**) is a monocyclic ether alkaloid isolated from *K. brevis*, as reported by Wright and co-workers in 2008;[8] it has a hybrid structure comprising the A ring of brevenal and brevisin, with an axial methyl group and a 3,4-dimethylhepta-2,4-dienal side chain, and the A ring of tamulamides, possessing an acetamide side chain. It has been revealed using a synthetic sample that brevisamide possesses weak cytotoxic activity against P388 mouse leukemia cells (ED_{50} > 30 μg/mL).[9b] Wright proposed that brevisamide was biosynthesized by the epoxidation of olefinic alcohol **2** to epoxy alcohol **3**, followed by the 6-endo cyclization reaction—a well-known proposed mechanism for natural polycyclic ethers (Scheme 1).[10] Brevisamide has understandably attracted much attention, as it is the smallest known biological molecule produced by the 6-endo cyclization reaction. Recently, the proposed biosynthetic precursor, epoxide **3**, was synthesized by Satake et al., and the 6-endo cyclization was attempted under the non-enzymatic conditions referenced to in Jamison's reports,[11] where polycyclic ethers were synthesized via a 6-endo cyclization reaction under aqueous conditions without any catalysts

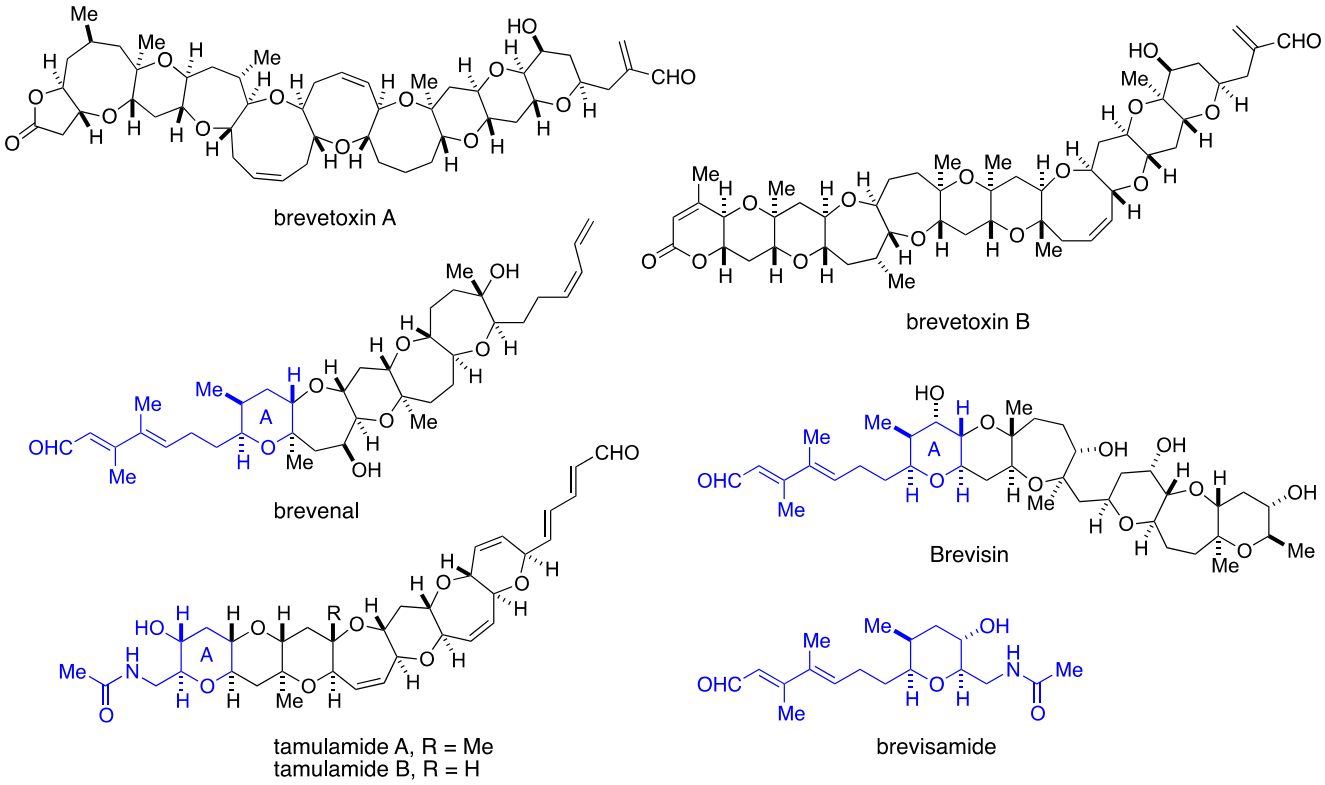
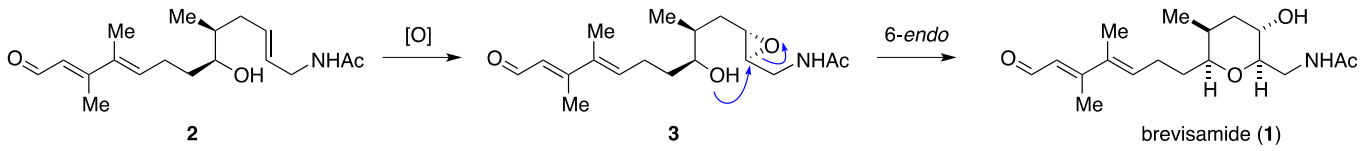
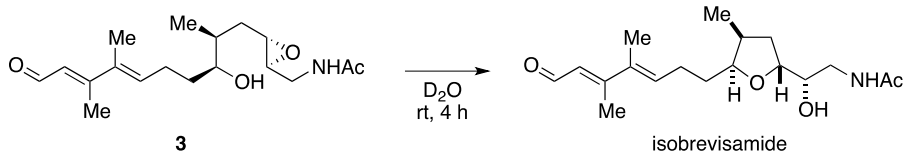


Figure 1. Natural cyclic ethers isolated from the dinoflagellate *Karenia brevis*

or enzymes. However, brevisamide was not successfully obtained under these conditions; instead, isobrevisamide, the 5-exo cyclization product of **3**, was formed exclusively (Scheme 2).[12] Therefore, it was speculated that brevisamide was biosynthesized through an enzyme-catalyzed 6-endo cyclization reaction.[13]



Scheme 1. Proposed biosynthetic pathway of brevisamide (**1**) (ref. 8)



Scheme 2. Attempted biomimetic cyclization reaction for brevisamide (ref. 12b)

Since its discovery, organic chemists all over the world are investigating its synthesis; so far, eight total and seven formal total syntheses have been reported by 13 different research groups: Tachibana,[9] Lindsley,[14] Ghosh,[15] Panek,[16] Smith III,[17] Sabitha,[18] Zakarian,[19] Yadav,[20] Kumaraswamy,[21] Sridhar,[22]

Kang,[23] Mohapatra,[24] and Mori.[25] Fadeyi and Lindsley summarized eight syntheses reported until 2012, and focused mainly on the six total syntheses.[26] In the first part of our review, we summarize the key points of these brevisamide syntheses. We then discuss in depth each of the total and formal syntheses.

2. SYNTHETIC OVERVIEW OF BREVISAMIDE

A generally applicable retrosynthetic analysis for brevisamide (**1**) is shown in Figure 2. Installation of the 3,4-dimethylhepta-2,4-dienal side chain and acetamide group is usually performed at the final stage of the synthesis, because these functional groups can be influenced by several different reactions. The stereoselective construction of four stereogenic centers at C8, C9, C11, and C12 on the tetrahydropyran (THP) core, including the axial methyl group at C9, is usually executed at an earlier synthetic stage. In this section, we discuss how these key steps have been achieved in each synthetic study.

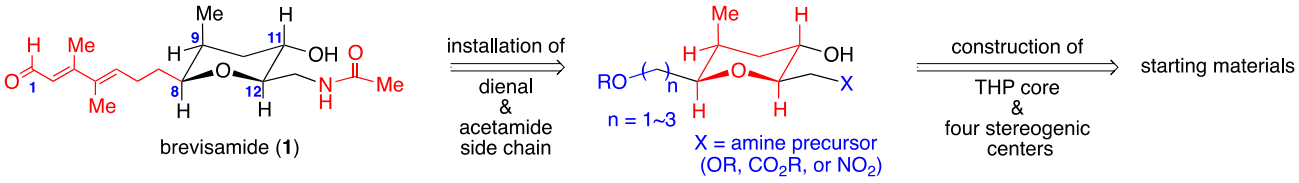
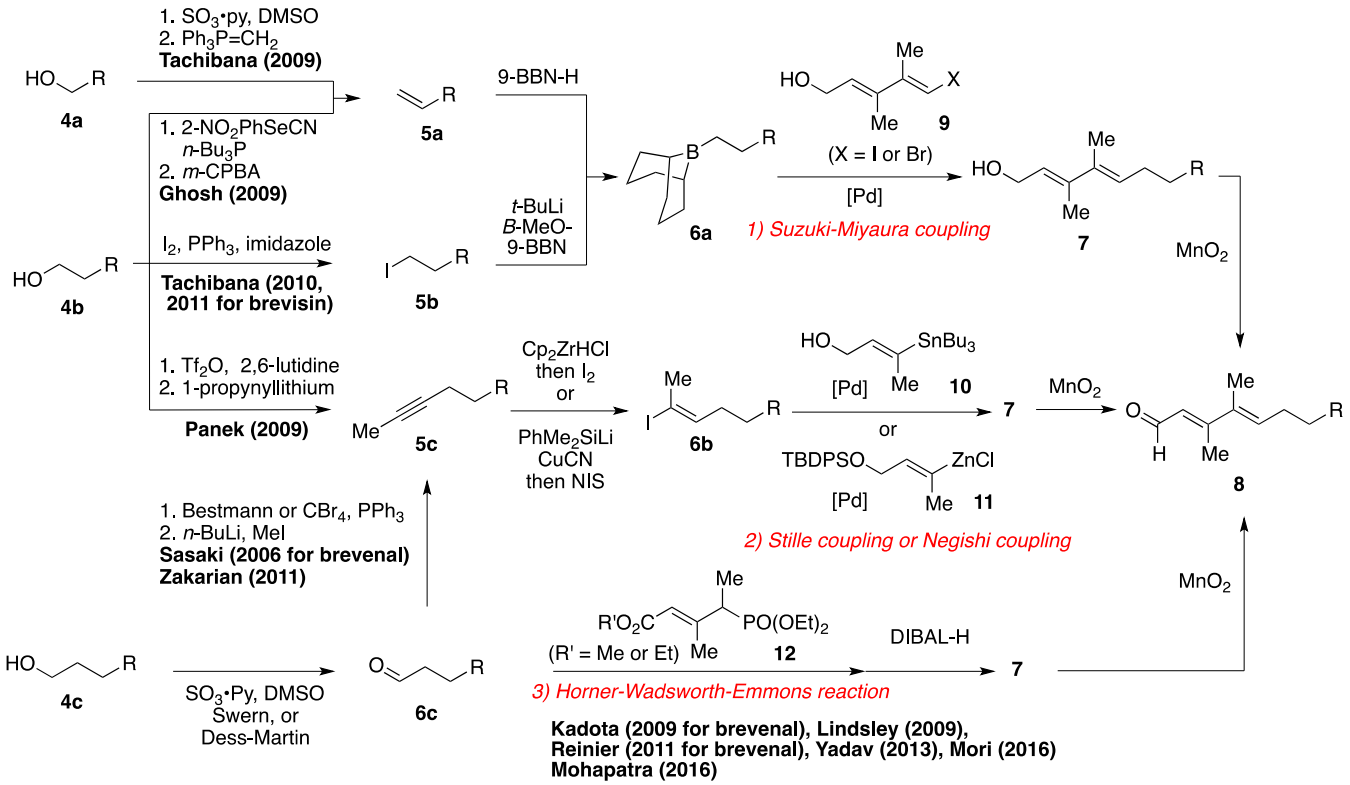


Figure 2. Retrosynthetic analysis for brevisamide applied in most total syntheses

2-1. Installation of the (2*E*,4*E*)-3,4-dimethyl-2,4-heptadienal side chain

The 3,4-dimethylhepta-2,4-dienal side chain is the common substituent in brevisamide, brevenal, and brevisin. The approach for the incorporation of 3,4-dimethylhepta-2,4-dienal group **8** can be classified into three types: 1) Suzuki-Miyaura coupling[27] between alkylborane **6a** and vinyl halide **9**; 2) Stille[28] or Negishi[29] coupling between vinyl iodide **6b** and vinylstannane **10** or vinylzinc **11**; and 3) Horner-Wadsworth-Emmons reaction between aldehyde **6c** and phosphonate **12** (Scheme 3). In most reports on total synthesis of brevisamide, brevenal, and brevisin, key precursors **6a-c** are prepared from the corresponding alcohols **4a-c**. Hydroxymethyl group **4a** is oxidized to the aldehyde followed by Wittig olefination to **5a**, which is converted to **6a** by the hydroboration reaction with 9-BBN-H. Alkylborane **6a** can also be prepared from hydroxyethyl group **4b** through dehydration to olefin **5a**, followed by hydroboration to **6a**, or by iodination to iodide **5b** followed by transformation to **6a** using the lithiation-boration protocol. Alternatively, hydroxyethyl group **4b** is subjected to the triflation-alkynylation reaction to give alkyne **5c**, which is converted into vinyl iodide **6b** by the hydrozirconation-iodination or silyl cuprate addition-iodination sequences. Hydroxypropyl group **4c** undergoes oxidation to aldehyde **6c** by Parikh-Doering oxidation, Swern oxidation, or Dess-Martin oxidation. In the first reported synthesis of brevenal by Sasaki et al., aldehyde **6c** is converted to alkyne **5c** using the Bestmann reagent in the Stille coupling strategy.[3b,30] After Kadota reported the

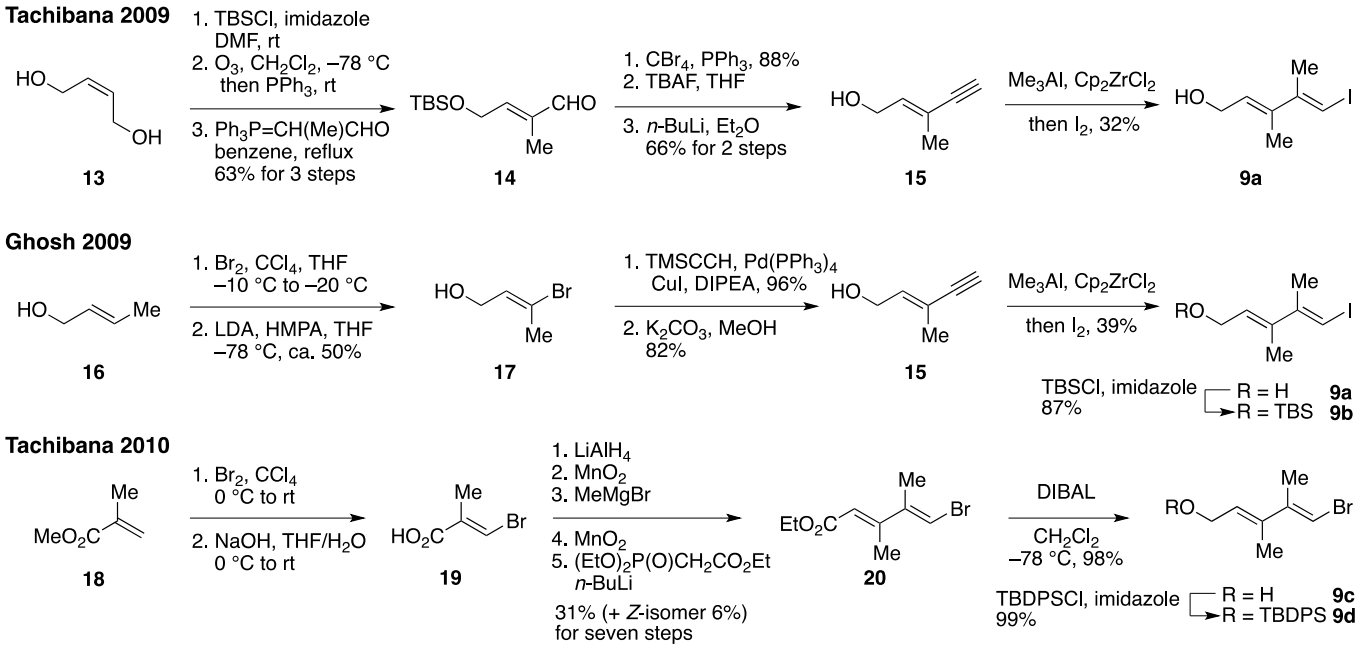
Horner-Wadsworth-Emmons (HWE) route using **6c** and phosphonate **12** (R' = Me) for the total synthesis of brevenal,[31] this HWE strategy became standard for the side-chain construction from the substituted propanol **4c**.



Scheme 3. General route to 3,4-dimethylhepta-2,4-dienal side chain (R is the THP core of brevisamide or the polycyclic ether skeletons of brevenal and brevisin)

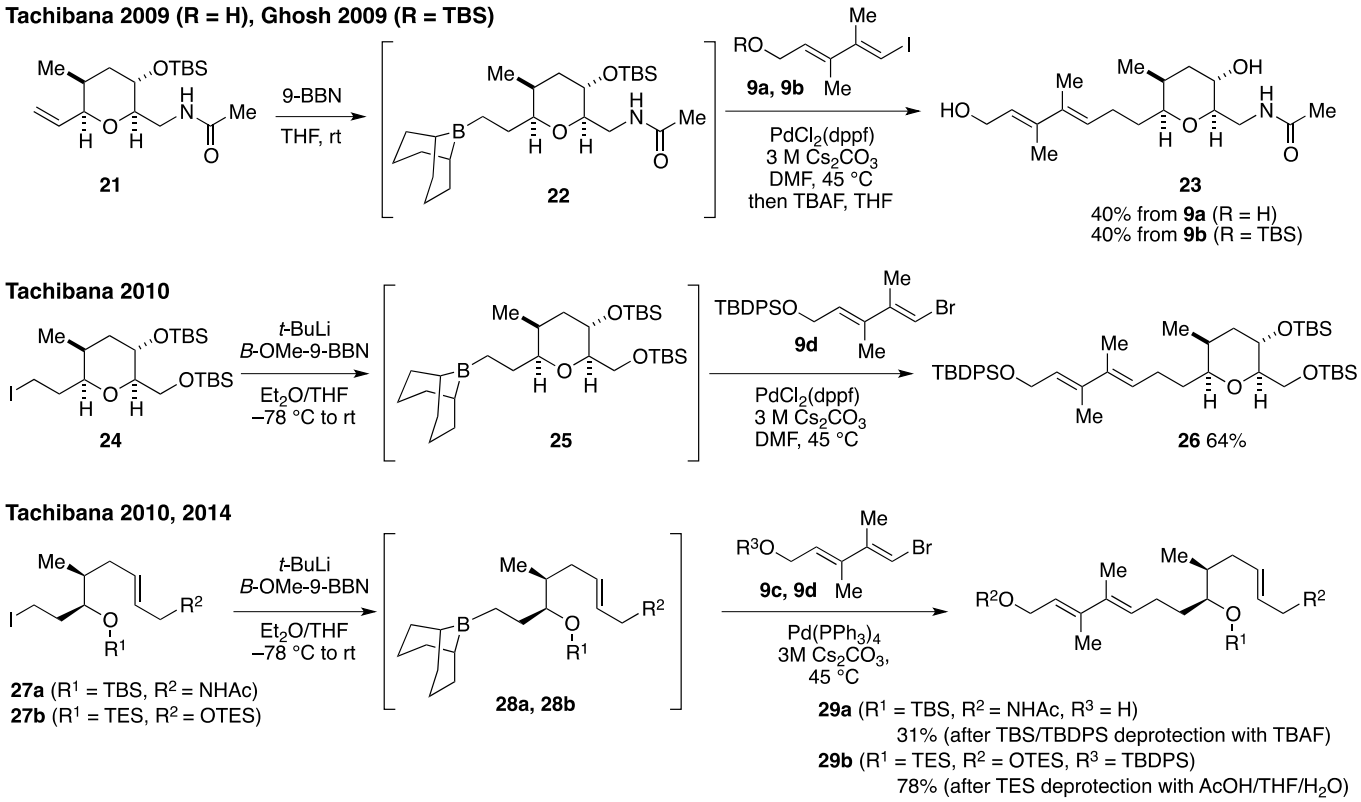
2-1-1. Suzuki-Miyaura coupling

Three separate syntheses have been reported for vinyl halides **9** (Scheme 4). Tachibana and Satake prepared conjugated aldehyde **14** from *cis*-2-butene-1,4-diol (**13**) through TBS protection, ozonolysis, and the Wittig reaction according to Leahy's report.[32] The modified Corey-Fuchs bromoalkyne synthesis,[33] followed by debromination with *n*-BuLi, afforded conjugated enyne **15**. Vinyl iodide **9a** was obtained by Negishi's methylalumination-iodination[34] of enyne **15**.[9a] Ghosh synthesized enyne **15** from *trans*-crotyl alcohol **16** via bromination,[35] elimination, and Sonogashira coupling according to Roush's report.[15,36] Tachibana and Satake synthesized vinyl bromides **9c** and **9d** from the two-step bromination of methyl methacrylate (**18**) to (*E*)-3-bromomethacrylic acid (**19**). After five steps,[37,38] ethyl ester **20** was reduced to alcohol **9c**, which was protected with a TBDPS group to provide **9d** quantitatively. It should be noted that the synthesis of **20** from **18** was carried out without purification until the separation of the desired *E*-isomer from the *Z*-isomer generated by the HWE reaction.[9b]



Scheme 4. Synthesis of vinyl halides **9**

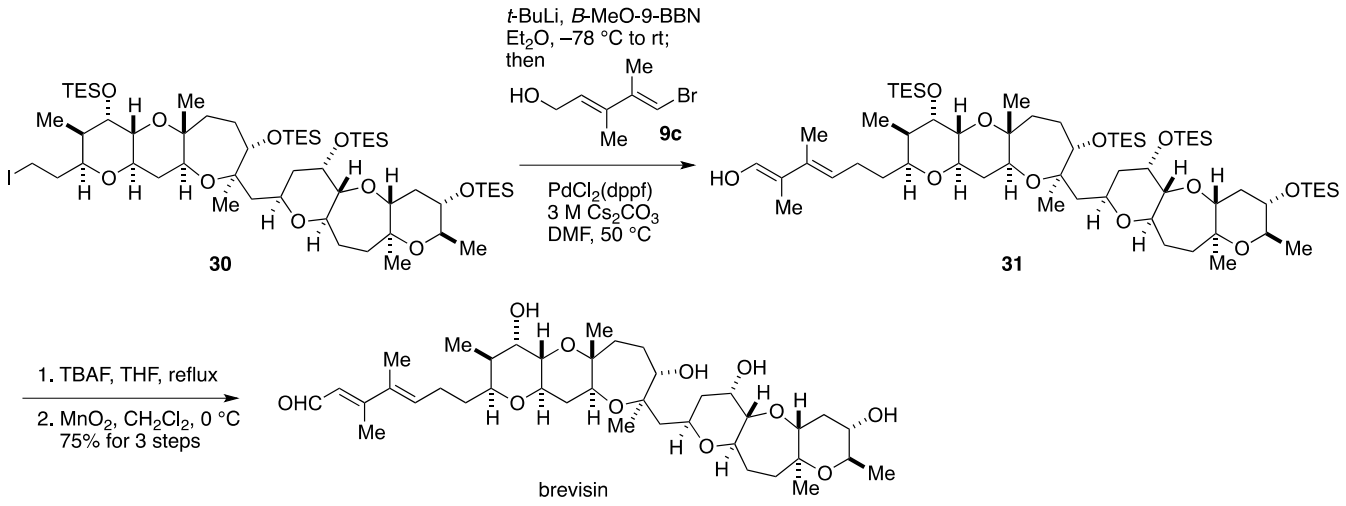
The Suzuki-Miyaura cross coupling reaction of vinyl halide **9** is summarized in Scheme 5. Tachibana reported the hydroboration of amide olefin **21** with 9-BBN, and the generated alkylborane **22** was subjected to the Suzuki-Miyaura cross coupling with vinyl iodide **9a**.[9a] Ghosh also reported a similar coupling reaction using the TBS-protected vinyl iodide **9b**.[15] However, these coupling reactions resulted



Scheme 5. Incorporation of the dienal side chain using Suzuki-Miyaura coupling

in low yields (40%) and poor reproducibility. In Tachibana's second total synthesis, the yield of the coupling reaction was improved to 64% by using vinyl bromide **9d** and alkylborane **25**, which was prepared *in situ* through the lithium-iodine exchange reaction of amide-free iodide **24**.[9b] The presence of the acetamide moiety adversely affects the yield of the coupling reaction; alkyl iodide **27a** involving an acetamide group gave coupling product **29a** in low yield, while the reaction with amide-free iodide **27b** provided a much better yield.[12]

The Suzuki-Miyaura coupling with vinyl bromide **9c** was employed in the final stage of Tachibana's total synthesis of brevisin (Scheme 6).[39] Alkyl iodide **30** was subjected to the borylation-coupling sequence to give product **31**. After global deprotection of the TES groups, selective oxidation of the allylic alcohol afforded brevisin in good overall yield.

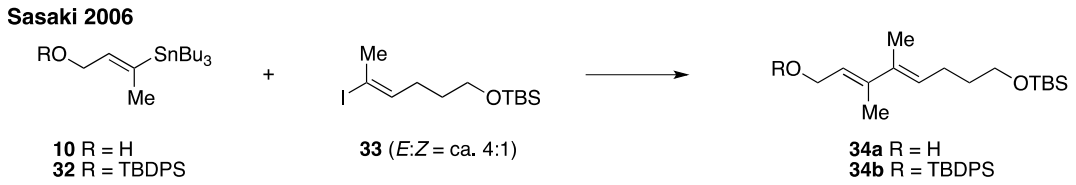


Scheme 6. Suzuki-Miyaura coupling using **9c** in the brevisin total synthesis

2-1-2. Stille coupling and Negishi coupling

Stille coupling with vinylstannane **10**[40] was employed in the first total synthesis of brevenal reported by Sasaki et al.[3b,30] They initially investigated the coupling conditions using vinylstannane **32** and vinyl iodide **33** as model compounds for the dienal side chain (Table 1). Under the conventional conditions using $PdCl_2(MeCN)_2$ in DMF, only a trace amount of coupling product was obtained due to the sterically hindered substrates (entry 1). The reaction improved when soft ligands such as tri(2-furyl)phosphine and triphenylarsine were employed for the acceleration of the transmetallation step,[41] and when a copper(I) salt was added for the generation of a more reactive organocopper specimen in the catalytic cycle[42] (entries 2 and 3). Elevating the reaction temperatures decreased the (*E*,*E*):(*E*,*Z*) ratio of the coupling product (entries 4 and 5). Use of copper(I) thiophene-2-carboxylate instead of copper(I) iodide provided coupling product **34** in a better yield with exclusive (*E*,*E*)-selectivity for both the non-protected and *O*-protected vinylstannanes **10** and **32** (entries 6 and 8).

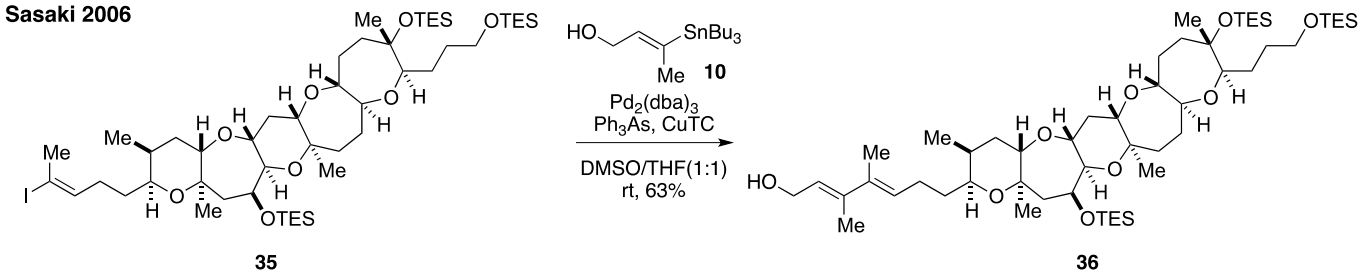
Table 1. Investigation of reaction conditions for the Stille coupling using vinylstannanes[3b]



entry	vinylstannane	reagents and conditions	% yield	(*E*,*E*):(*E*,*Z*)
1	**32**	$PdCl_2(MeCN)_2$, DMF, rt to 45 °C	trace	not determined
2	**10**	$Pd_2(dba)_3$, (2-furyl)$_3$P, CuI, DMSO/THF, rt	57	ca. 3.5:1
3	**10**	$Pd_2(dba)_3$, Ph_3As, CuI, DMSO/THF, rt	54	ca. 5:1
4	**10**	$Pd_2(dba)_3$, (2-furyl)$_3$P, CuI, DMSO/THF, 60 °C	48	1:1
5	**10**	$Pd_2(dba)_3$, Ph_3As, CuI, DMSO/THF, 60 °C	66	1:1
6	**10**	$Pd_2(dba)_3$, Ph_3As, CuTC, DMSO/THF, rt	84	ca. 10:1
7[a]	**32**	$Pd_2(dba)_3$, Ph_3As, CuI, DMSO/THF, rt	40	1:0
8[a]	**32**	$Pd_2(dba)_3$, Ph_3As, CuTC, DMSO/THF, rt	69	1:0

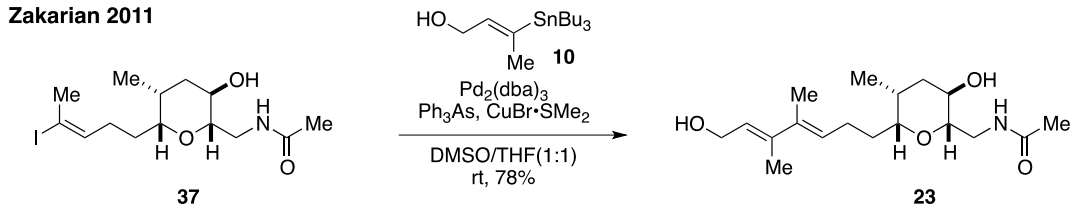
a) Isolated as an inseparable mixture of **34b** and 1,6-bis(*tert*-butyldiphenylsilyloxy)-3,4-dimethylhexa-2,4-diene (homocoupling product of **32)**. Yield was estimated based on ^{1}H NMR of the mixture.

The best conditions in Table 1, entry 6, were employed for incorporating the 3,4-dimethylhepta-2,4-dienal side chain into brevenal (Scheme 7).[3b,30]



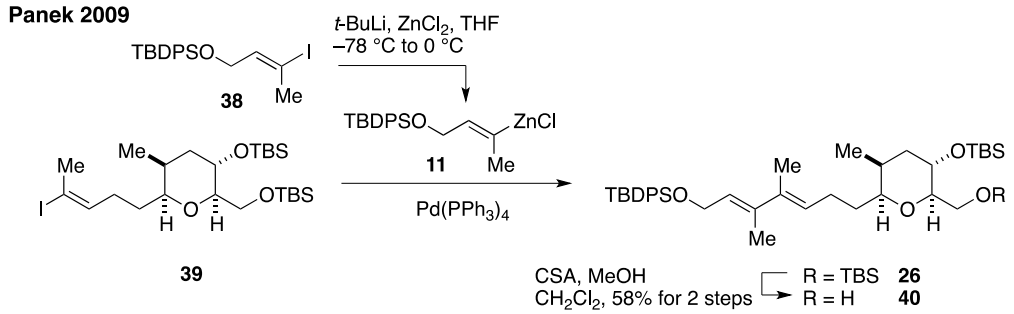
Scheme 7. Stille coupling in the total synthesis of brevenal

Zakarian succeeded in the Stille coupling reaction of **37** and **10** without the protection of the hydroxy and acetamide groups by using CuBr·SMe_2 instead of CuTC and obtained product **23** in good yield (Scheme 8).[19]



Scheme 8. Stille coupling for construction of the dienal side chain of brevisamide

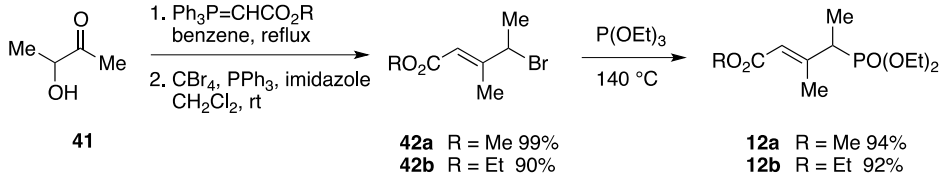
A similar cross-coupling reaction was achieved by the Negishi coupling reaction (Scheme 9).[43] Panek prepared vinyl zinc species **11** from vinyl iodide **38** through a lithiation-zincation protocol. Negishi coupling reaction with vinyl iodide **39** afforded product **40** in good overall yield after the removal of the TBS group of **26**.[16]



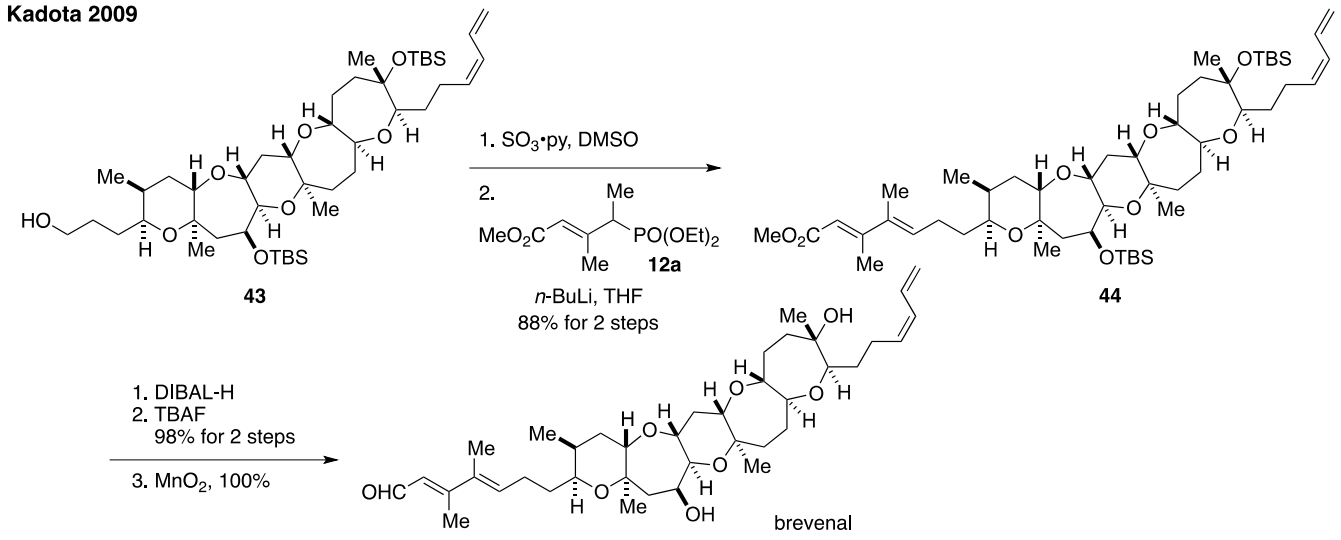
Scheme 9. Negishi coupling for construction of the dienal side chain of brevisamide

2-1-3. Horner-Wadsworth-Emmons reaction

The third method for the synthesis of the 3,4-dimethylhepta-2,4-dienal side chain is the HWE reaction using phosphonate **12**, which was synthesized from 3-hydroxy-2-butanone (**41**) in three steps: the Wittig reaction, bromination, and Arbuzov reaction (Scheme 10).

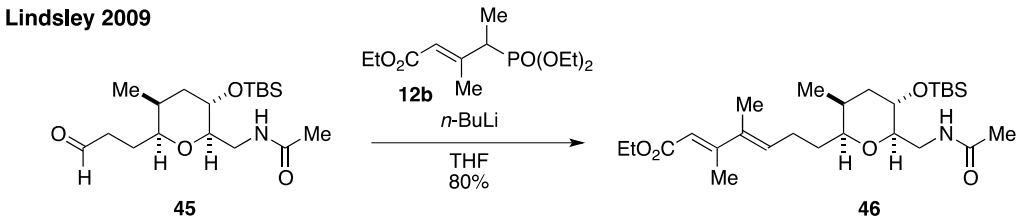


Scheme 10. Syntheses of phosphonates **12**



Scheme 11. HWE reaction for construction of the dienal side chain of brevenal (ref. 31)

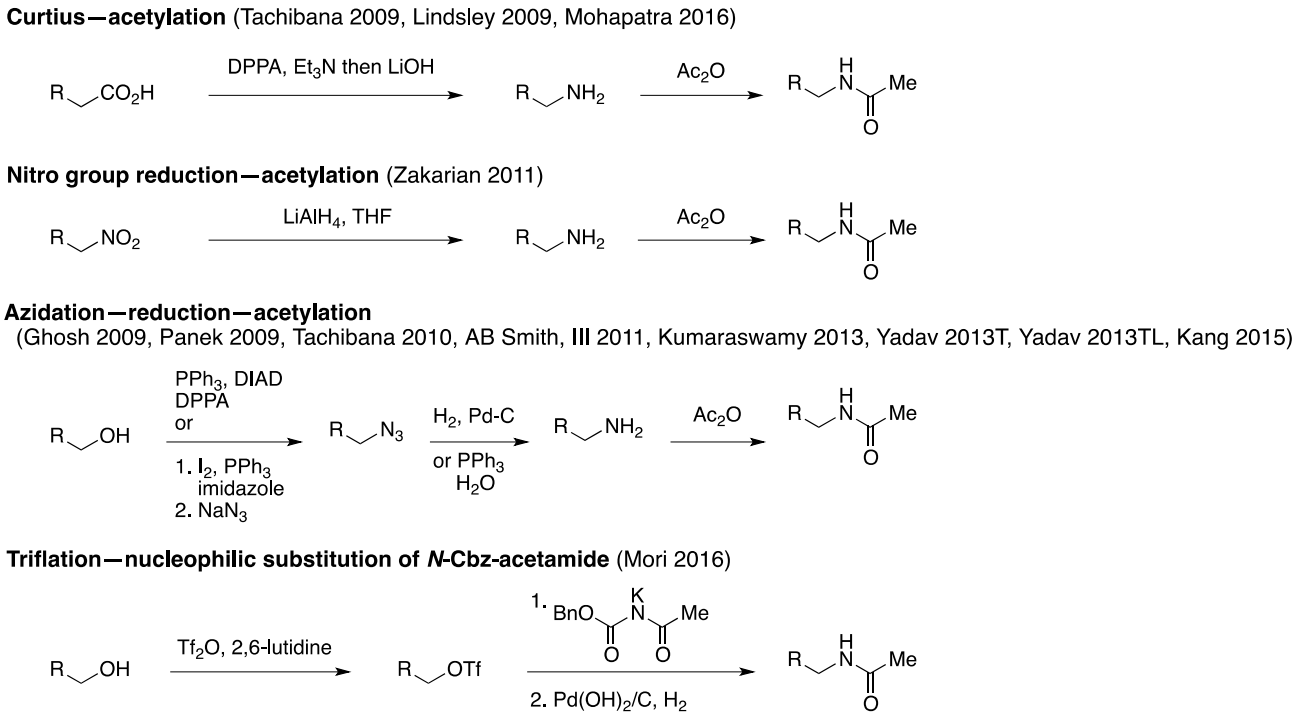
Kadota used this HWE reaction for the pentacyclic aldehyde obtained by Parikh-Doering oxidation of alcohol **43** at the final stage of the total synthesis of brevenal. A further three-step reaction sequence completed the total synthesis (Scheme 11).[31] Lindsley reported the total synthesis of brevisamide using the HWE reaction with ethyl ester **12b** and aldehyde **45** (Scheme 12),[14] in which the presence of the acetamide group did not affect the reaction, and dienoate **46** was obtained in good yield. Thus, the HWE strategy is often adopted in the later total syntheses of brevisamide[20,24,25] and brevenal[44] for the construction of the dienal side chain because of easy access to phosphonate **12** (83–93%, 3-step overall) and tolerability for an acetamide group.



Scheme 12. HWE reaction for construction of the dienal side chain of brevisamide (ref. 14)

2-2. Installation of the acetamide side chain

In most reports, the acetamide side chain was installed at a later stage of the synthesis by acetylation of the corresponding primary amine, which was typically introduced either by the Curtius rearrangement of a carboxylic acid using DPPA[45] or the reduction of a nitro or azido group (Scheme 13).

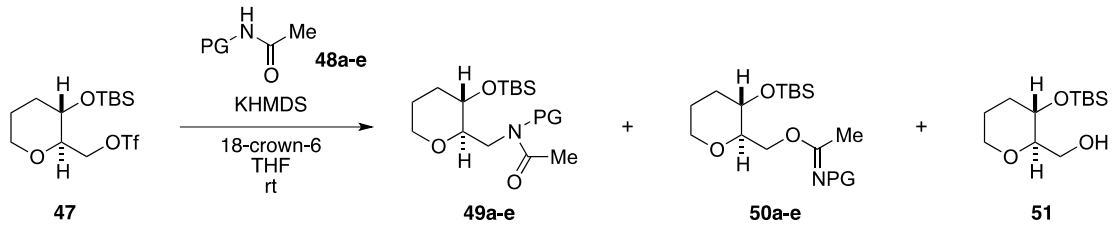


Scheme 13. Acetamide side chain installation

Recently, Mori and coworkers investigated the N-alkylation reaction of acetamide nucleophiles for the direct installation of the acetamide moiety using the model alkyl triflate **47** with KHMDS/18-crown-6 in THF (Table 2).[25] Direct nucleophilic substitution by acetamide (**48a)** did not provide the N-alkylation product because of low solubility of the anion of **48a** in THF (entry 1). *N*-Methoxyacetamide (**48b**) and diacetamide (**48c**) afforded both the desired N-alkylated products **49b** and **49c**, respectively, along with O-alkylated products **50b**, **50c**, and **51** (entries 2 and 3). When *N*-Boc- and *N*-Cbz-acetamides **48d** and **48e** were employed, desired N-alkylated products **49d** and **49e** were obtained in good yield (entries 4 and 5). A stoichiometric amount of 18-crown-6 was necessary to attain good conversion (entry 6).

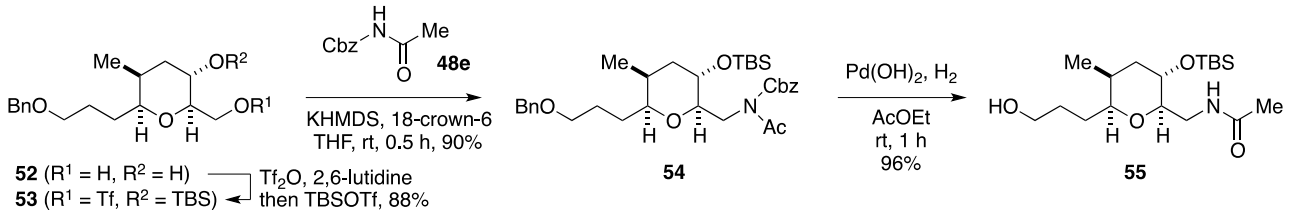
In the actual synthetic route, N-alkylation using *N*-Cbz-acetamide **48e** with alkyl triflate **53**, prepared by the one-pot reaction for triflation-TBS protection of diol **52**, provided the desired product **55** in good overall yield after removal of the benzyl and Cbz groups of **54** by hydrogenation (Scheme 14). This direct introduction of the acetamide group is apparently convenient and useful in organic synthesis.

Table 2. N-Alkylation of acetamide nucleophiles



entry	PG	18-crown-6 (equiv)	time (h)	N-alkylated product (%)	O-alkylated product (%)
1	H **48a**	2.0	1	0	0
2	OMe **48b**	2.0	1	49 (**49b**)	29 (**50b**)
3	Ac **48c**	2.0	1	70 (**49c**)	24 (**50c**: 6 + **51**: 18)
4	Boc **48d**	2.0	0.5	90 (**49d**)	–[a]
5	Cbz **48e**	2.0	1.5	89 (**49e**)	7 (**50e**)
6	Cbz **48e**	0.2	22	23 (**49e**)	–
7	Cbz **48e**	–	16	8 (**49e**)	–

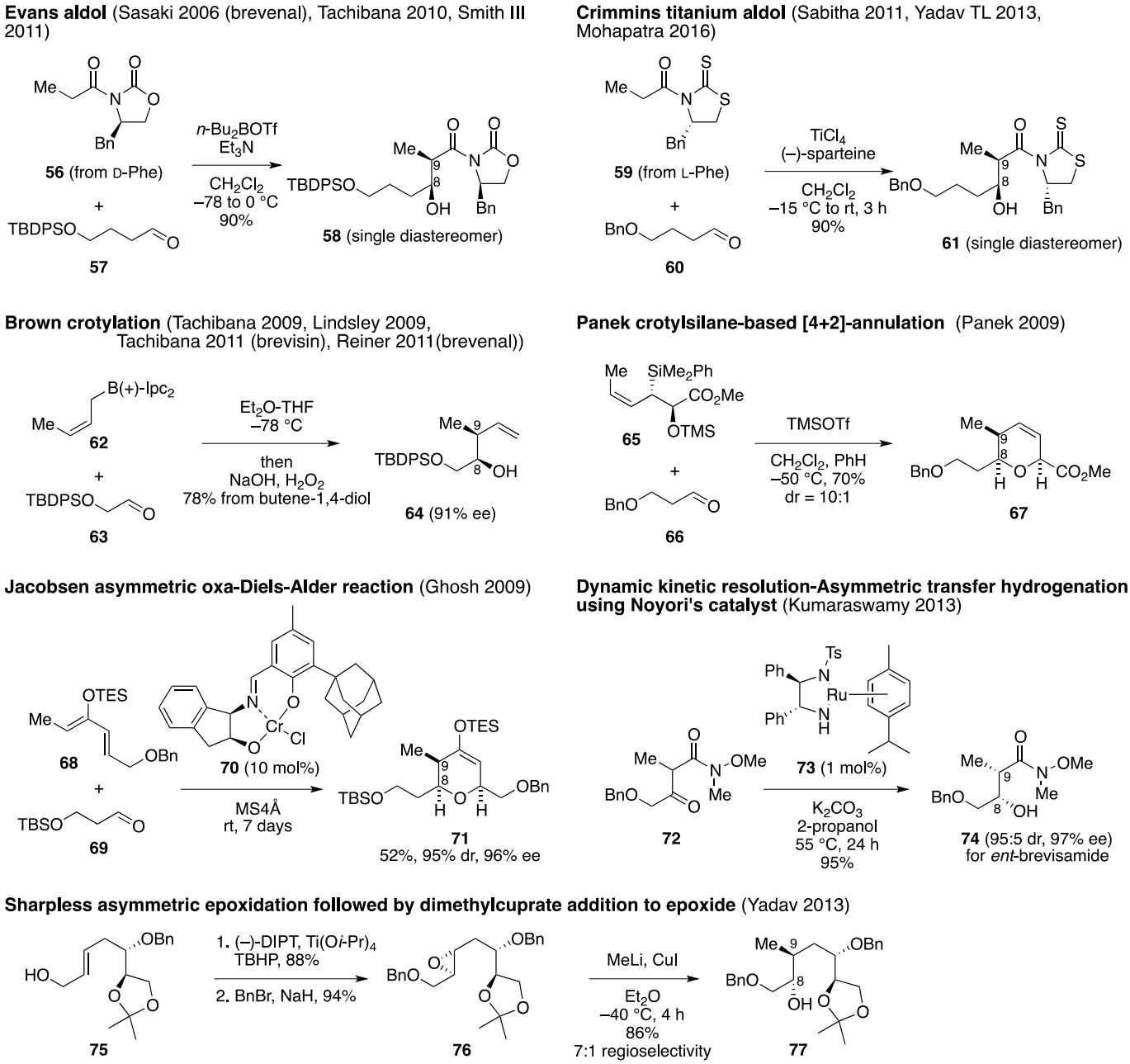
a) A small amount of product was detected by TLC but not isolated.



Scheme 14. Acetamide side chain installation by nucleophilic substitution of **48e**

2-3. Installation of the axial methyl group

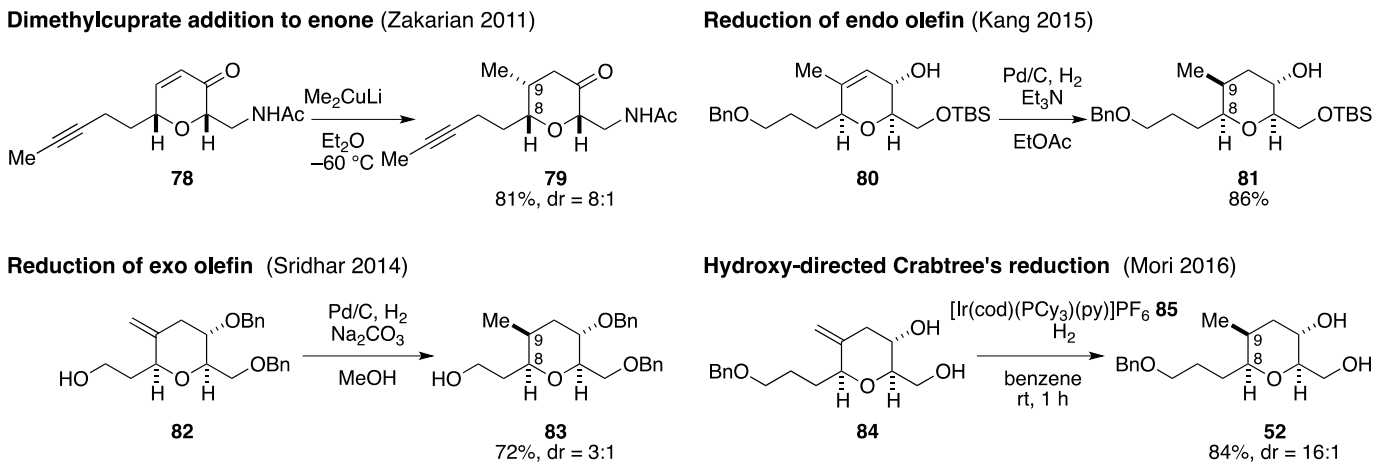
Stereoselective introduction of the C9 axial methyl group is a key feature of the synthesis of brevisamide. The most popular strategy is the asymmetric addition or asymmetric cycloaddition reaction to C8 aldehydes. Sasaki, Tachibana, and Smith employed the Evans aldol reaction,[46] which afforded *syn*-adducts with high diastereoselectivity. In the case of the Evans aldol, D-phenylalanine-derived chiral oxazolidinone **56** was required to obtain the natural (8*S*,9*R*)-configuration (Scheme 15). Thus, Sabitha, Yadav, and Mohapatra chose the Crimmins titanium aldol reaction using L-phenylalanine-derived thiazolidithione **59**, which gave a non-Evans *syn* aldol product through a trident-chelate model.[47]



Scheme 15. C9 axial methyl introduction using asymmetric reaction

Brown asymmetric crotylation[48] with commercially available *cis*-crotyl-diisopinocampheylborane **62** was used by Tachibana, Lindsley, and Reiner. Panek simultaneously constructed the C9 axial methyl and the THP ring by the [4+2]-annulation reaction using (*Z*)-*anti*-crotylsilane **65**.[49] The Jacobsen oxa-Diels-Alder reaction catalyzed by asymmetric chromium catalyst **70**[50] was applied in Ghosh's total synthesis. Alternatively, *syn*-3-hydroxy-2-methylalkanamide **74** was prepared by the dynamic kinetic resolution-asymmetric transfer hydrogenation (DKR–ATH) reaction[51] using Noyori's catalyst **73**[52] by Kumaraswamy. In the second synthesis of Yadav, the C9 methyl group of **77** was introduced by regioselective methyl cuprate addition[53] to epoxide **76** prepared by the Sharpless epoxidation of **75**.[54]

There are four reports in which the axial methyl group was introduced on six-membered oxa-cycles (Scheme 16). Axial attack of dimethylcuprate to enone **78** was demonstrated by Zakarian to afford the axial adduct **79** with 8:1 diastereoselectivity.[19,55] Kang reported that hydrogenation of an endo-cyclic tri-substituted olefin **80** gave the axial methyl product **81** preferentially.[23,56] Although exo-cyclic olefin **82** was predominantly reduced from the equatorial face to give the axial methyl product **83** with moderate selectivity (3:1),[22] the hydroxy-directed reduction of the exo-cyclic olefin **84** using Crabtree's catalyst **85** was found to afford the axial-methyl product **52** with good selectivity of 16:1.[25,57]



Scheme 16. C9 axial methyl introduction using diastereoselective reaction

2-4. Tetrahydropyran (THP) core synthesis

A variety of methods for constructing the THP core[58] of brevisamide have been explored (Figure 3). Some are classified by C12-O bond formation, which involves lactonization,[9] epoxide ring-opening,[17,20a] oxa-Michael cyclization,[18] iodoetherification,[21] and oxonium ion allylation.[24] Alternatively, the Williamson ether synthesis is used for C8-O bond formation.[20b] SmI_2-mediated cyclization is applied to form the C11-C12 bond.[14] All of these cyclization and annulation strategies, including the oxa-Diels-Alder approach[15] and crotylsilane-based [4+2] annulation strategy,[16] involve the installation of

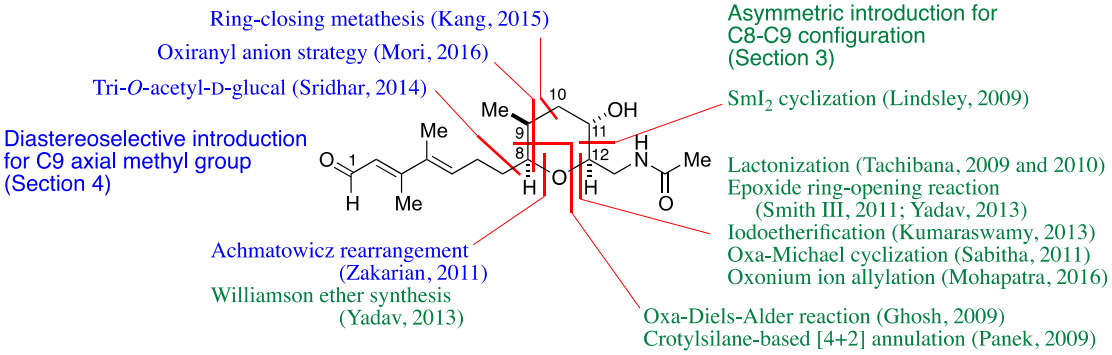


Figure 3. THP core construction

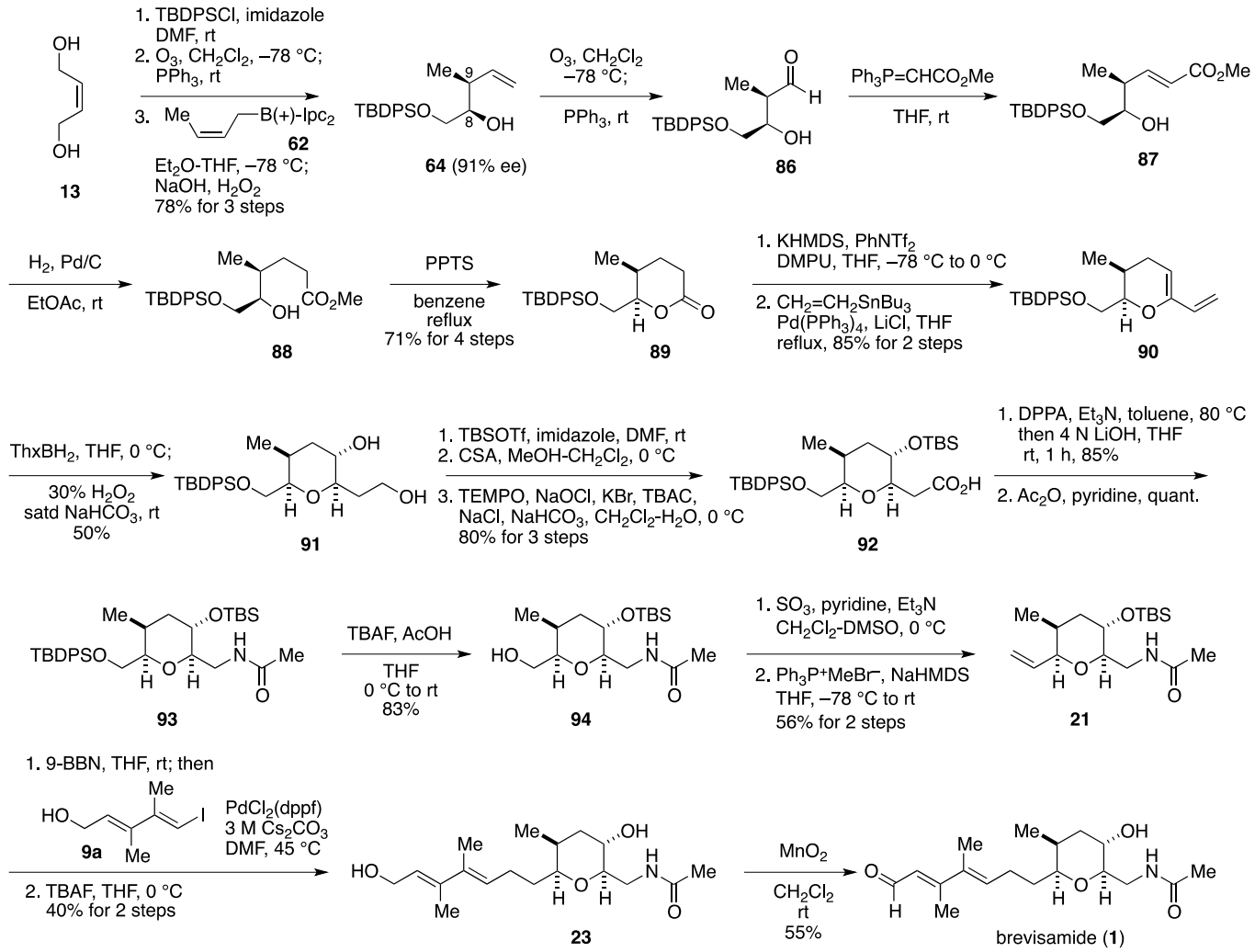
the C9 methyl group using asymmetric reactions, as shown in Scheme 15. The THP core can be further constructed by an Achmatowicz rearrangement,[19] an oxiranyl anion strategy,[25] ring-closing metathesis,[23] and from 3-deoxy-D-glucal,[22] followed by the installation of the axial methyl group, as shown in Scheme 16. In the following section, we discuss individual studies in more detail according to the type of THP synthesis.

3. BREVISAMIDE SYNTHESIS USING AN ASYMMETRIC REACTION FOR C9 AXIAL METHYL INSTALLATION

3-1. Lactonization (Tachibana's total syntheses)

Tachibana's first total synthesis[9a] involved conversion of *cis*-2-butene-1,4-diol (**13**) to chiral alcohol **64** through TBS protection, ozonolysis, and Brown asymmetric crotylation (Scheme 17). The terminal olefin was cleaved by ozonolysis to aldehyde **86**, which was subjected to a Wittig reaction to give hydroxy conjugate ester **87**. Hydrogenation, followed by the PPTS-catalyzed lactonization, led to valerolactone **89**.[59] Transformation to the vinyl triflate and subsequent Stille coupling with tributylvinylstannane gave diene **90**. Diol **91** was stereoselectively obtained by double hydroboration with thexylborane from the less-hindered α-face of the diene.[60] After protection of the secondary alcohol with a TBS group, the primary alcohol was oxidized to carboxylic acid **92** by treatment with TEMPO, NaClO, and TBAC. A Curtius rearrangement, followed by acetylation of the resulting primary amine, furnished acetamide **93**, in which all of the stereogenic centers of the THP core were confirmed by comparing with natural brevisamide. Deprotection of the TBDPS group, oxidation, and Wittig reaction afforded olefin **21**. Finally, the 3,4-dimethyl-2,4-dienal side chain was furnished through a sequence of hydroboration of **21**, Suzuki-Miyaura coupling with **9a**, desilylation, and allylic oxidation. In this first synthesis of brevisamide, Tachibana intended to install the amide side chain before Suzuki-Miyaura coupling in order to compare the stereochemistry of **93** with that of brevisamide. However, as mentioned in Section 2-1-1, the presence

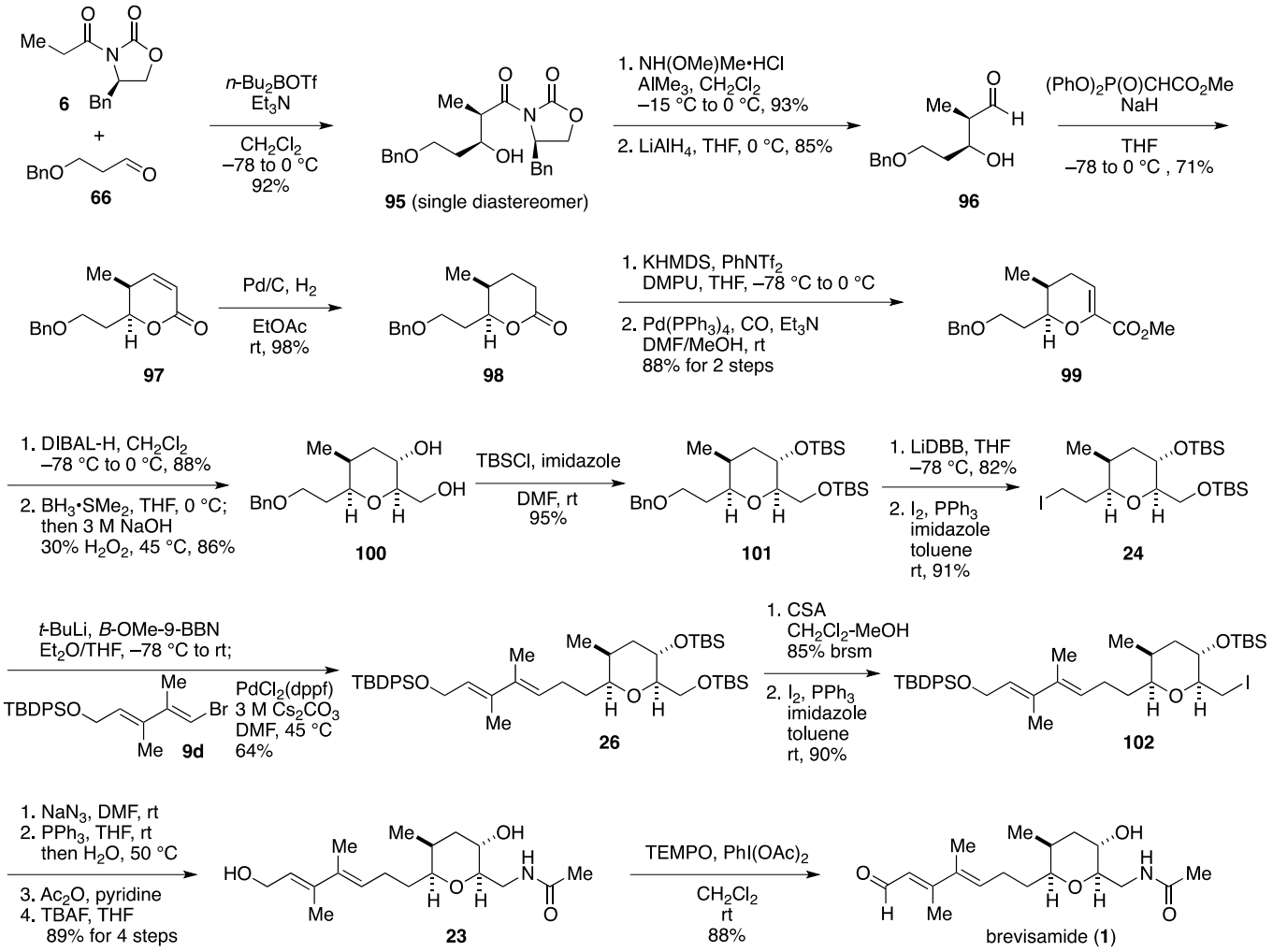
of the acetamide group caused an unexpected low yield of the Suzuki-Miyaura coupling. Thus, a more effective second route was investigated.



Scheme 17. Tachibana's total synthesis (first generation)

In the second-generation synthesis,[9b] Tachibana used the Evans aldol reaction of oxazolidinone **6** and 3-(benzyloxy)propanal (**66**) for the construction of the C8-C9 chiral centers (Scheme 18). The imide group was transformed to Winreb's amide moiety, and subsequent reduction with $LiAlH_4$ afforded aldehyde **96**.[61] The HWE reaction using Ando's phosphonate[62] advanced the olefination and spontaneous lactonization to enoate **97**, which was hydrogenated to valerolactone **98**. This transformation saved one step compared to the previous route (Scheme 17, **86**→**89**). After vinyl triflate formation, palladium-catalyzed carbonylation in the presence of methanol provided unsaturated methyl ester **99**. Reduction of methyl ester **99** followed by hydroboration from the less-hindered face furnished diol **100**, which was protected with TBS groups to **101**. The benzyl group was then removed using LiDBB. The resulting hydroxy group was transformed to iodide **24**, which was subjected to lithiation, borylation, and

Suzuki-Miyaura coupling with the dienyl bromide **9d** to give coupling product **26** in better yield (64%) than the previous synthesis. After selective removal of the TBS group of the primary alcohol with CSA, the resulting alcohol was iodinated to **102**. The acetamide side chain was furnished through azidation, reduction, and acetylation, and subsequent treatment with TBAF provided diol **23**. Finally, selective oxidation of the allylic alcohol with TEMPO afforded brevisamide (**1**).

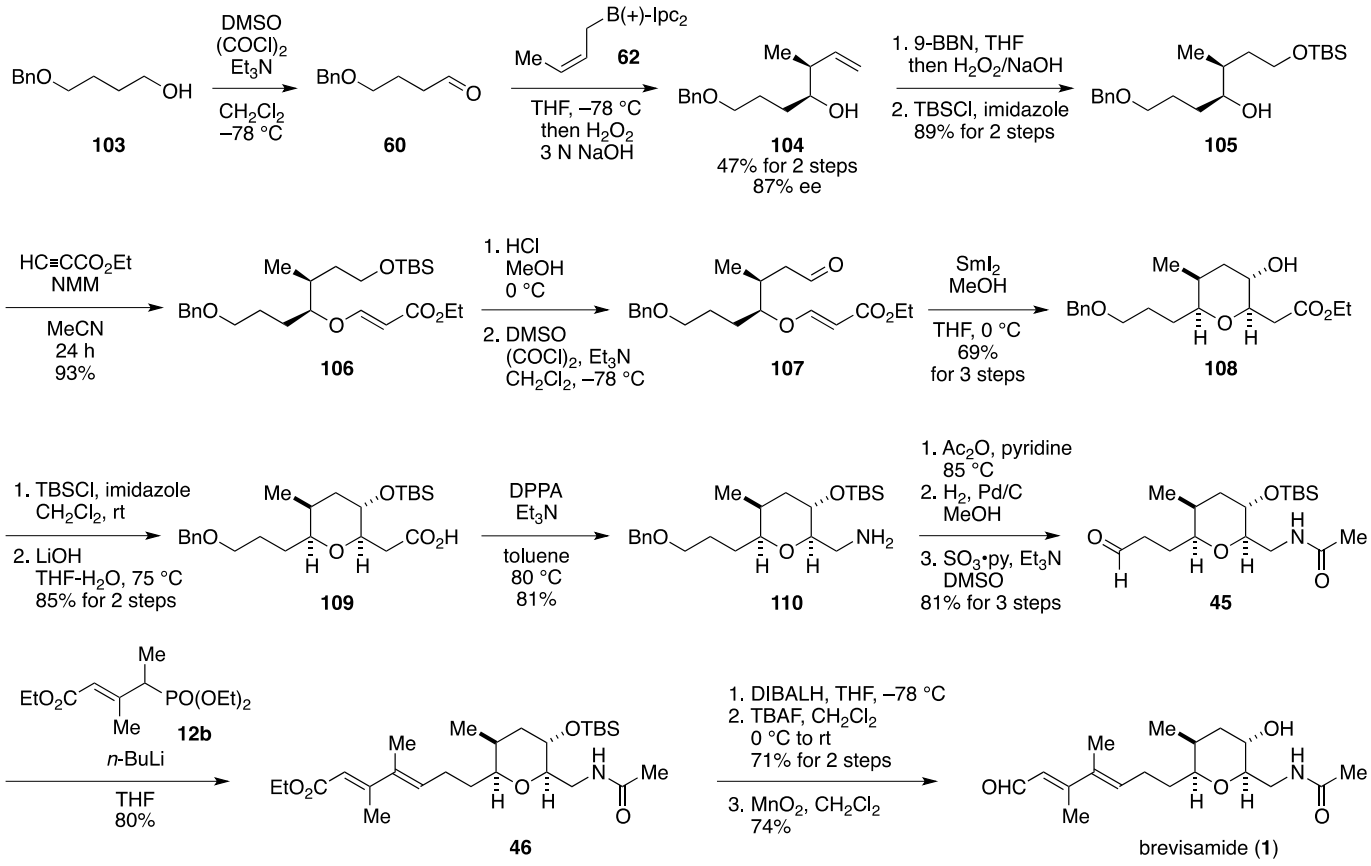


Scheme 18. Tachibana's total synthesis (second generation)

3-2. SmI_2-induced ketyl radical cyclization (Lindsley's total synthesis)

Lindsley reported the second total synthesis of brevisamide[14] using the SmI_2-induced ketyl radical cyclization[63] for the construction of the THP ring (Scheme 19). 4-Benzyloxy-1-butanol (**103**) was oxidized to aldehyde **60**, which was subjected to the Brown asymmetric crotylation reaction to homoallylic alcohol **104**. The hydroboration reaction of the terminal olefin provided the primary alcohol, which was then protected with a TBS group. The secondary alcohol **105** was subjected to conjugate addition with ethyl propiolate to give alkoxy acrylate **106**. Removal of the TBS group followed by Swern oxidation afforded aldehyde **107**. The SmI_2-mediated ketyl radical cyclization reaction furnished the

C11-C12 bond with the desired stereochemistry. The obtained hydroxy ester **108** was protected with a TBS group, and the ethyl ester was hydrolyzed to the corresponding carboxylic acid **109**, which then underwent a Curtius rearrangement to primary amine **110**. After acetylation, debenzylation, and Swern oxidation, the resulting aldehyde **45** underwent the HWE reaction with phosphonate **12b** to provide dienoate **46**. Completion of the synthesis was achieved through three additional steps: DIBAL reduction, TBS deprotection, and allylic oxidation with MnO_2.

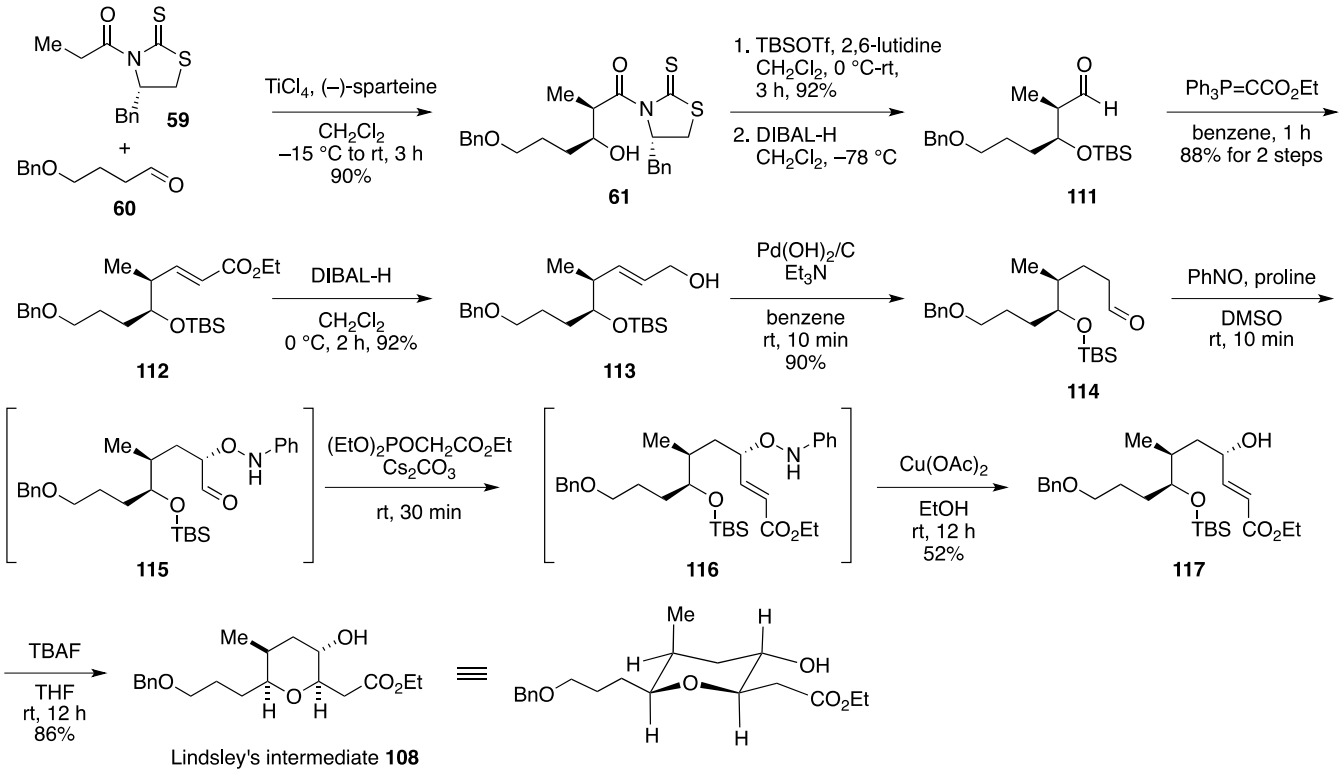


Scheme 19. Lindsley's total synthesis

3-3. Addition of alcohol to olefin (Sabitha's and Kumaraswamy's formal syntheses)

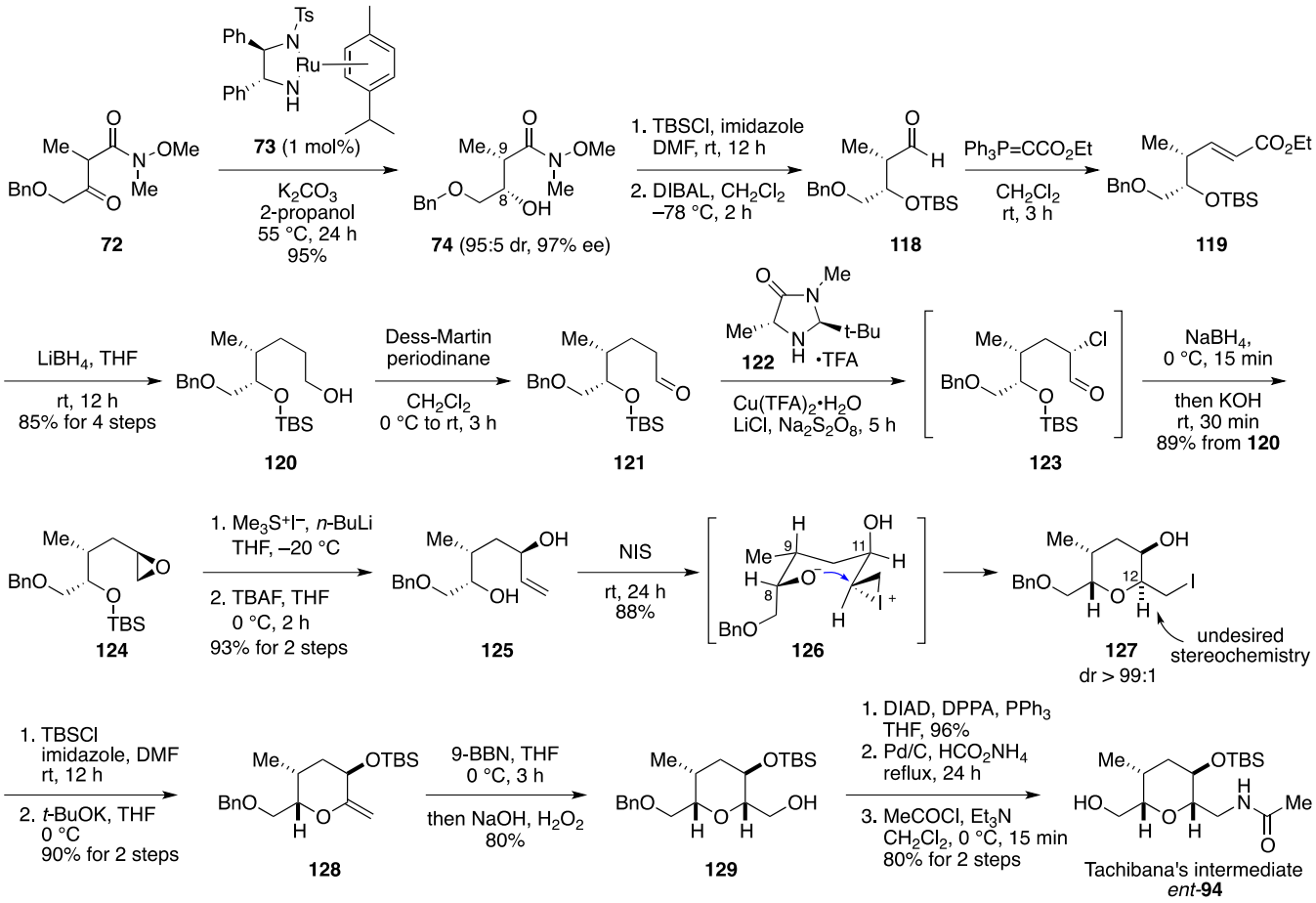
There are two reports wherein the THP core is accessed by intramolecular addition of an alcohol to an olefin: Sabitha used the oxa-Michael reaction and Kumaraswamy used the iodoetherification reaction. Sabitha's synthesis[18] commenced with the Crimmins aldol reaction, and aldol product **61** was reduced with DIBAL-H after TBS protection to aldehyde **111** (Scheme 20). Wittig reaction followed by DIBAL-H reduction provided allylic alcohol **113**, which was isomerized by $Pd(OH)_2/C$ to aldehyde **114**. A one-pot synthesis involving a proline-catalyzed enantioselective α-alkoxyamination,[64] a HWE addition, and cleavage of the N-O bond afforded γ-hydroxy enoate **117**.[65] Treatment with TBAF advanced the

spontaneous desilylation and cyclization reaction[66] to the desired, thermodynamically stable THP core **108**—the intermediate of Lindsley's synthesis.



Scheme 20. Sabitha's formal synthesis

Kumaraswamy employed the DKR–ATH reaction for the preparation of hydroxy amide **74**, which was subjected to TBS protection followed by reduction to aldehyde **118** (Scheme 21).[21] Wittig olefination and conjugate reduction with $LiBH_4$ provided alcohol **120**, and Dess-Martin oxidation gave aldehyde **121**. MacMillan's asymmetric α-chlorination generated α-chloroaldehyde **123**, and the subsequent *in situ* reduction-epoxidation sequence afforded chiral epoxide **124**.[67] Treatment with a sulfonium ylide followed by desilylation with TBAF provided diol **125**.[68] The key iodoetherification reaction of allylic alcohol **125** unfortunately led to the exclusive formation of iodide **127**,[69] which had the undesired C12 stereochemistry because of the cyclization conformation of **126**, in which the C9 methyl group was oriented in the equatorial position, and the C8 benzyloxymethyl and C11 hydroxy groups were axial. This result contrasted with Sabitha's oxa-Michael reaction, which provided the thermodynamically stable isomer **108**. Fortunately, inversion of the C12 stereocenter was accomplished by TBS protection, elimination, and hydroboration to give alcohol **129**, which was converted to the enantiomer of Tachibana's intermediate *ent*-**94** by a three-step process.

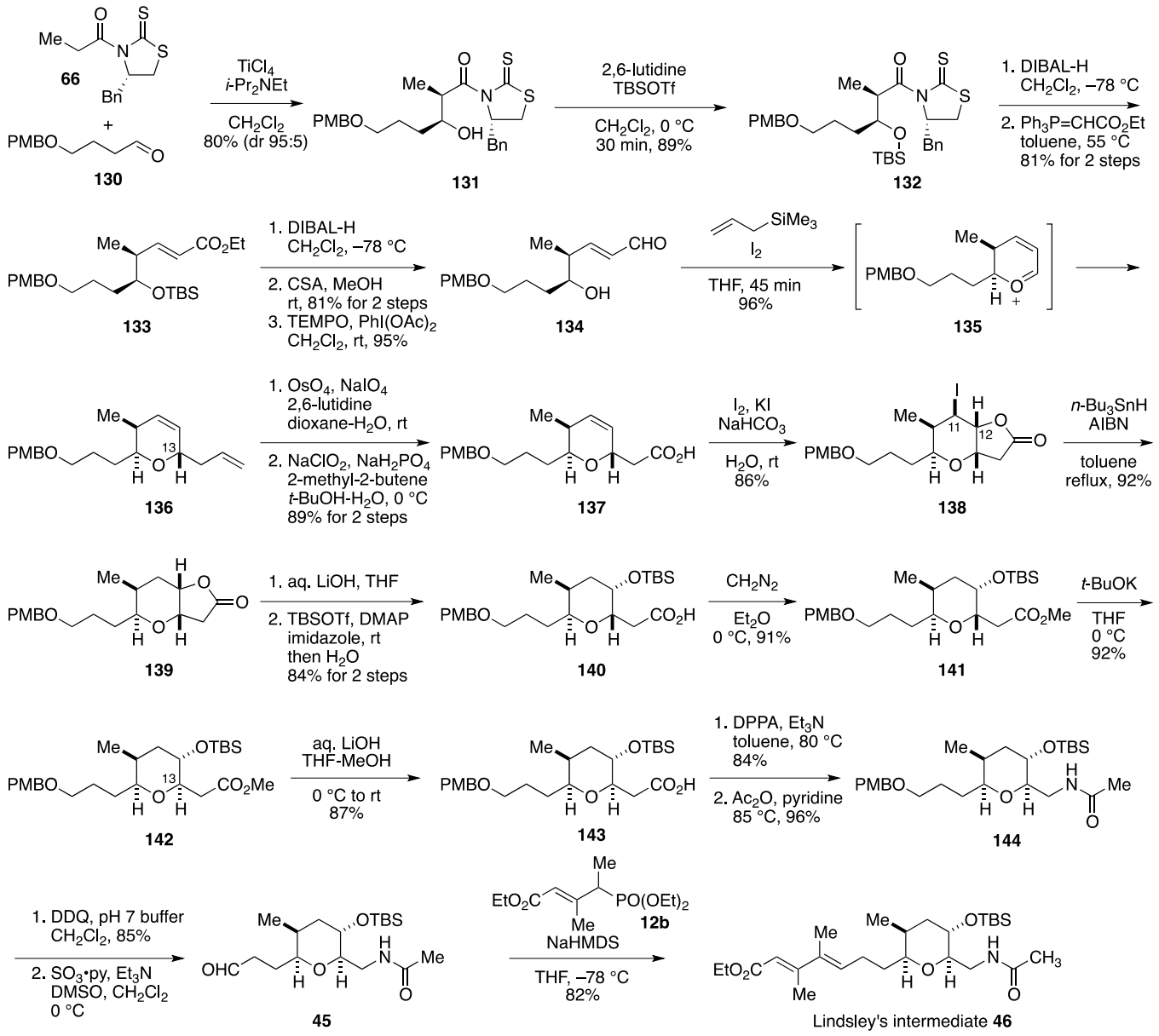


Scheme 21. Kumaraswamy's formal synthesis

3-4. Allylation of oxonium ion (Mohapatra's formal syntheses)

Recently, Mohapatra reported another formal total synthesis of brevisamide using the iodine-catalyzed allylation reaction of an oxonium ion (Scheme 22).[24] A Crimmins aldol adduct **131** was transformed to enoate **133** according to Sabitha's report. After three steps, the unsaturated aldehyde **134** was subjected to cyclization with excess allyltrimethylsilane in the presence of a catalytic amount of iodine. The trimethylsilyl iodide (TMSI) generated *in situ* promoted the isomerization of the enoate and formation of oxonium **135**; subsequent attack by allyltrimethylsilane gave *trans*-2,6-disubstituted-3,4-dihydropyran **136** exclusively, which had a C13 stereocenter epimeric to that of brevisamide.[70] After oxidative cleavage of the terminal vinyl group to the carboxylic acid by Lemieux-Johnson oxidation, followed by Pinnick oxidation, the oxygen functional group at C12 was furnished by the iodolactonization reaction. The resulting iodide **138** was reduced to lactone **139** under radical conditions, and the subsequent hydrolysis of the lactone gave a hydroxy carboxylic acid, which was converted to the TBS-protected methyl ester **141**. The C13 stereogenic center was epimerized under basic conditions, and methyl ester **142** was then hydrolyzed to carboxylic acid **143**. Curtius rearrangement of the acid, followed by acetylation, afforded amide **144**. The PMB group was deprotected by DDQ, and the resulting alcohol was oxidized to aldehyde

45. Finally, the HWE reaction using **12b** provided intermediate **46**. Although the C12 stereogenic center was efficiently introduced by iodolactonization in this synthesis, the necessity of the removal of iodine at C11 and epimerization at the C13 stereogenic center made this synthesis a longer route.

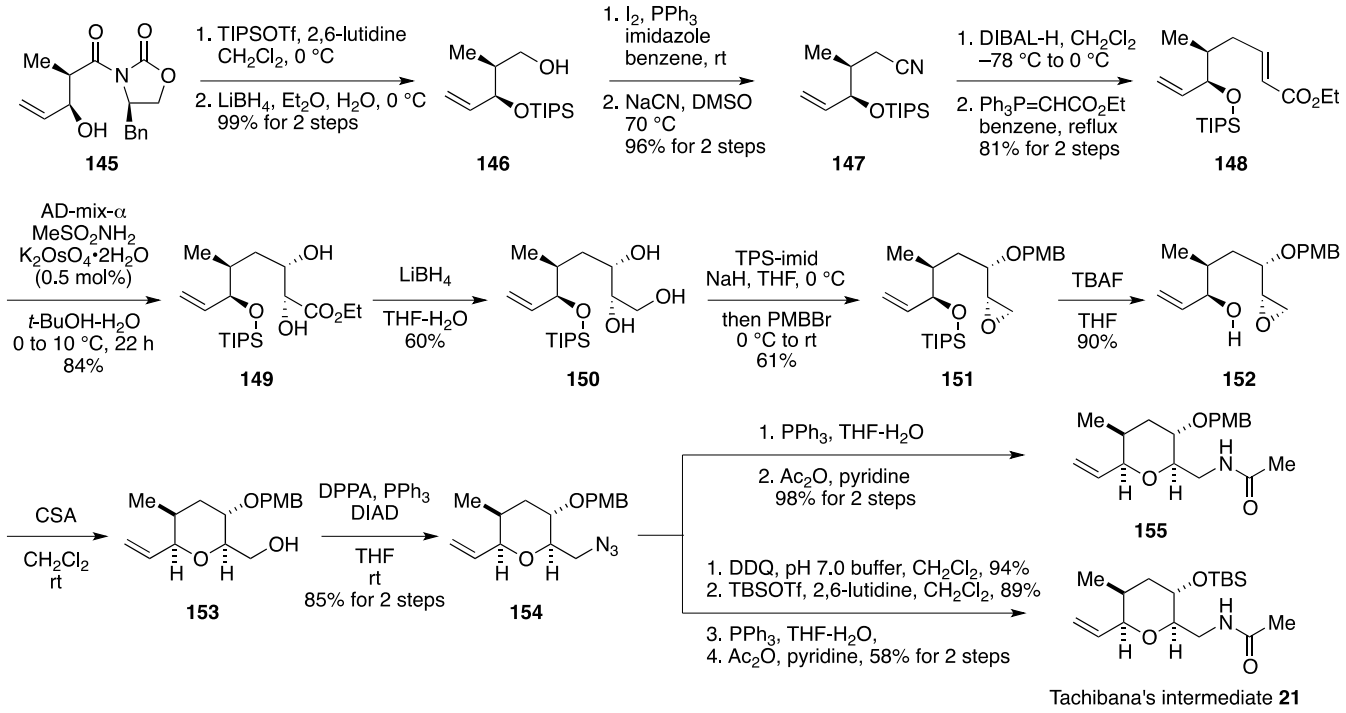


Scheme 22. Mohapatra's formal synthesis

3-5. Epoxide ring-opening reactions (Smith's and Yadav's formal syntheses)

Smith employed the 6-exo-epoxide ring-opening reaction of a hydroxy epoxide in his formal synthesis (Scheme 23).[17] The acrolein-derived aldol adduct **145**[71] was subjected to TIPS protection, and $LiBH_4$ reduction gave alcohol **146**. Alcohol **146** was transformed to cyanide **147** through the Appel iodination and subsequent S_N2 substitution with NaCN. Reduction of the cyanide group to the aldehyde followed by a Wittig reaction afforded enoate **148** in good yield. The Sharpless asymmetric dihydroxylation of **148**

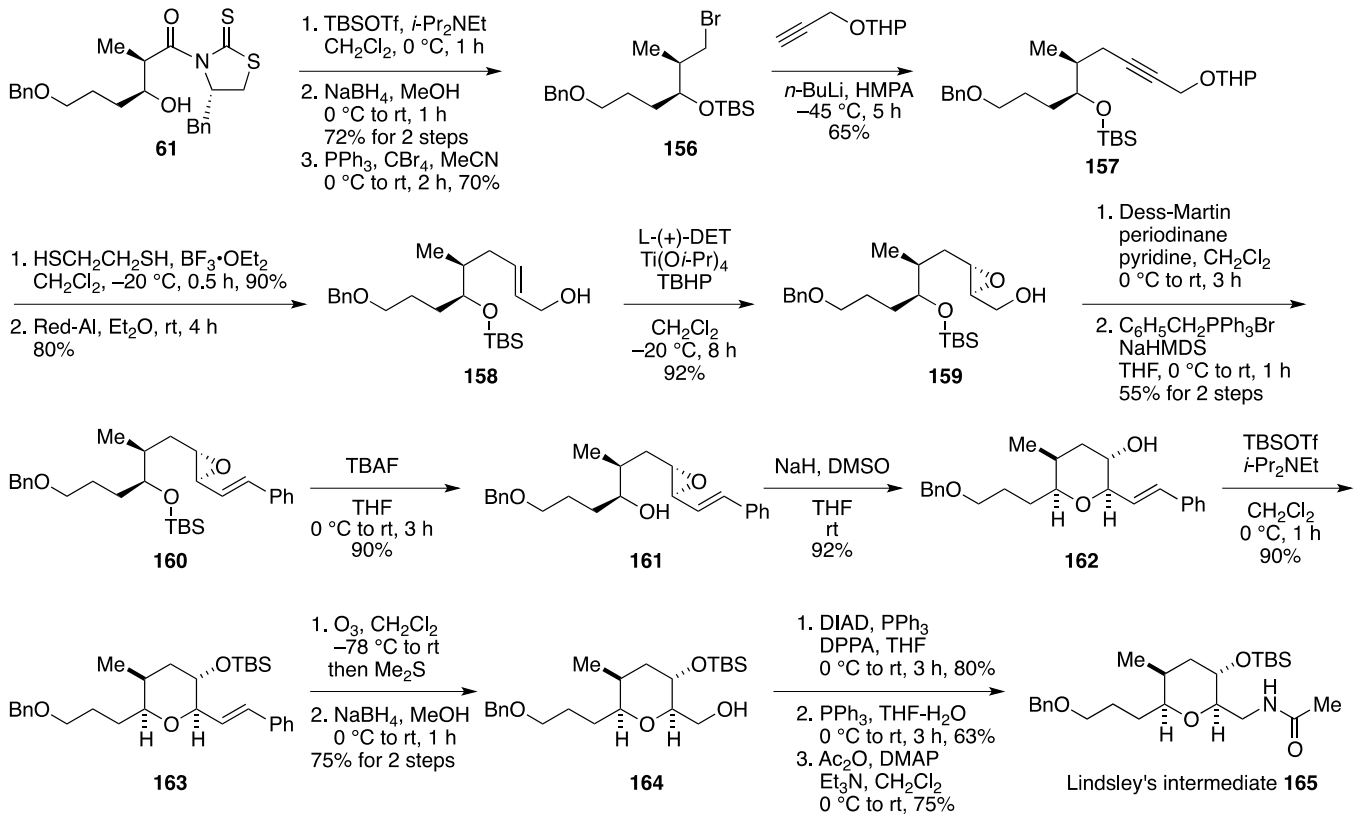
using AD-mix-α[72] provided dihydroxy ester **149** with the terminal olefin remaining intact. The ester was reduced with $LiBH_4$ to triol **150**, wherein the primary alcohol was selectively sulfonated with 2,4,6-triisopropylbenzenesulfonyl imidazole (TPS-imid). The resulting sulfonate underwent cyclization mediated by NaH to yield an epoxide,[73] and the remaining hydroxy group was protected with a PMB group to **151**. After removal of the TIPS group, epoxy alcohol **152** was exposed to the acid-catalyzed 6-exo-cyclization reaction to yield **153**. The potential brevisamide intermediate **155** was obtained after introducing an acetamide through azidation-reduction-acetylation. Synthesis of Tachibana's intermediate **21** through a four-step sequence from **154** completed this formal synthesis of brevisamide.



Scheme 23. Smith's formal synthesis

The THP core was constructed by a 6-endo epoxide-opening reaction in Yadav's first synthesis (Scheme 24).[20a] Aldol adduct **61** was subjected to TBS protection, reduction, and bromination to give bromide **156**. Nucleophilic substitution of the bromide with THP-protected propargyl alcohol to alkyne **157** was followed by the removal of the THP group with dithiol and Red-Al reduction to afford allyl alcohol **158**.[74] The Sharpless asymmetric epoxidation reaction furnished epoxide **159**, where the alcohol group was transformed to the *trans*-styryl group in **160** in preparation for the regioselective 6-endo cyclization reaction.[75] After TBS removal, 6-endo cyclization of vinyl epoxide **161** was mediated by sodium hydride in DMSO. After protection of the secondary alcohol with TBS, the styryl group was cleaved by ozonolysis, followed by reduction with $NaBH_4$, to afford alcohol **164**. The alcohol was then transformed to acetamide **165**, which was the intermediate of Lindsley's total synthesis. The bio-mimetic 6-endo

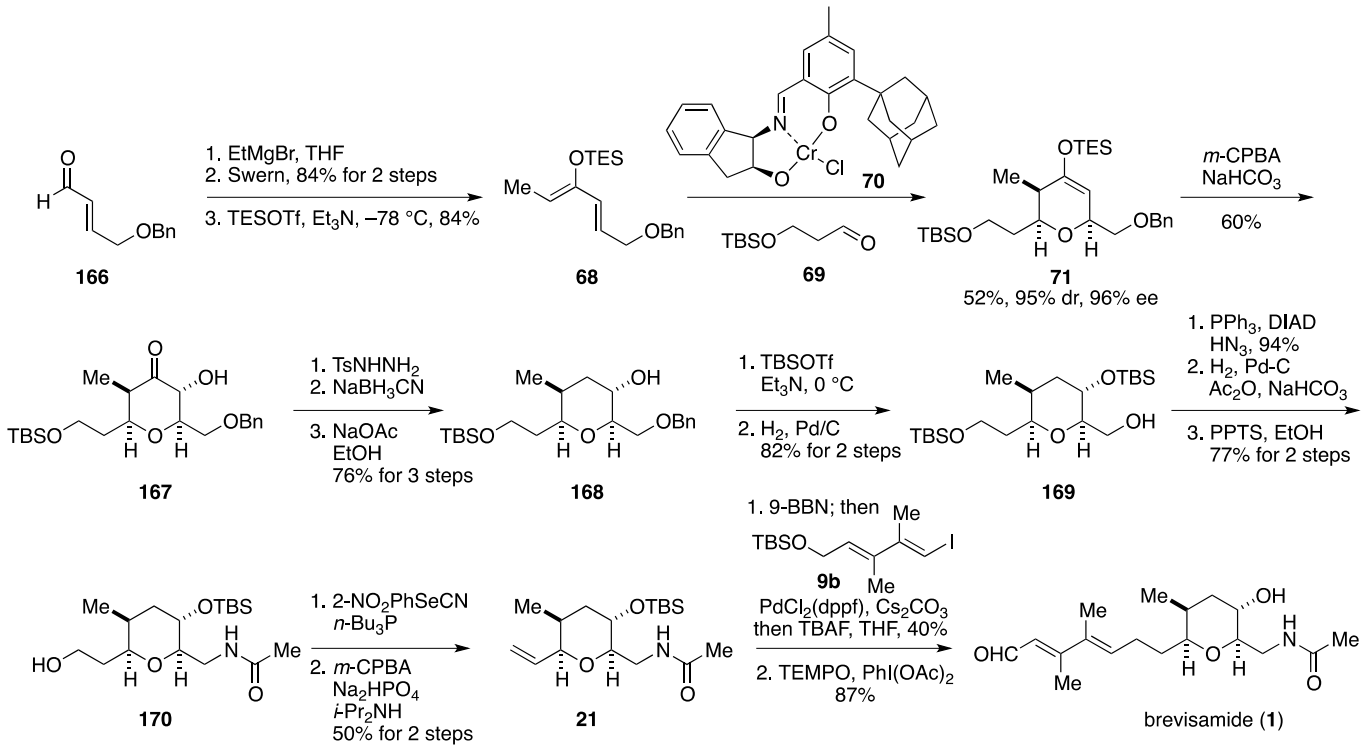
cyclization approach is interesting; however, this synthesis required four additional steps for the introduction and removal of the styryl group that was necessary for 6-endo cyclization.



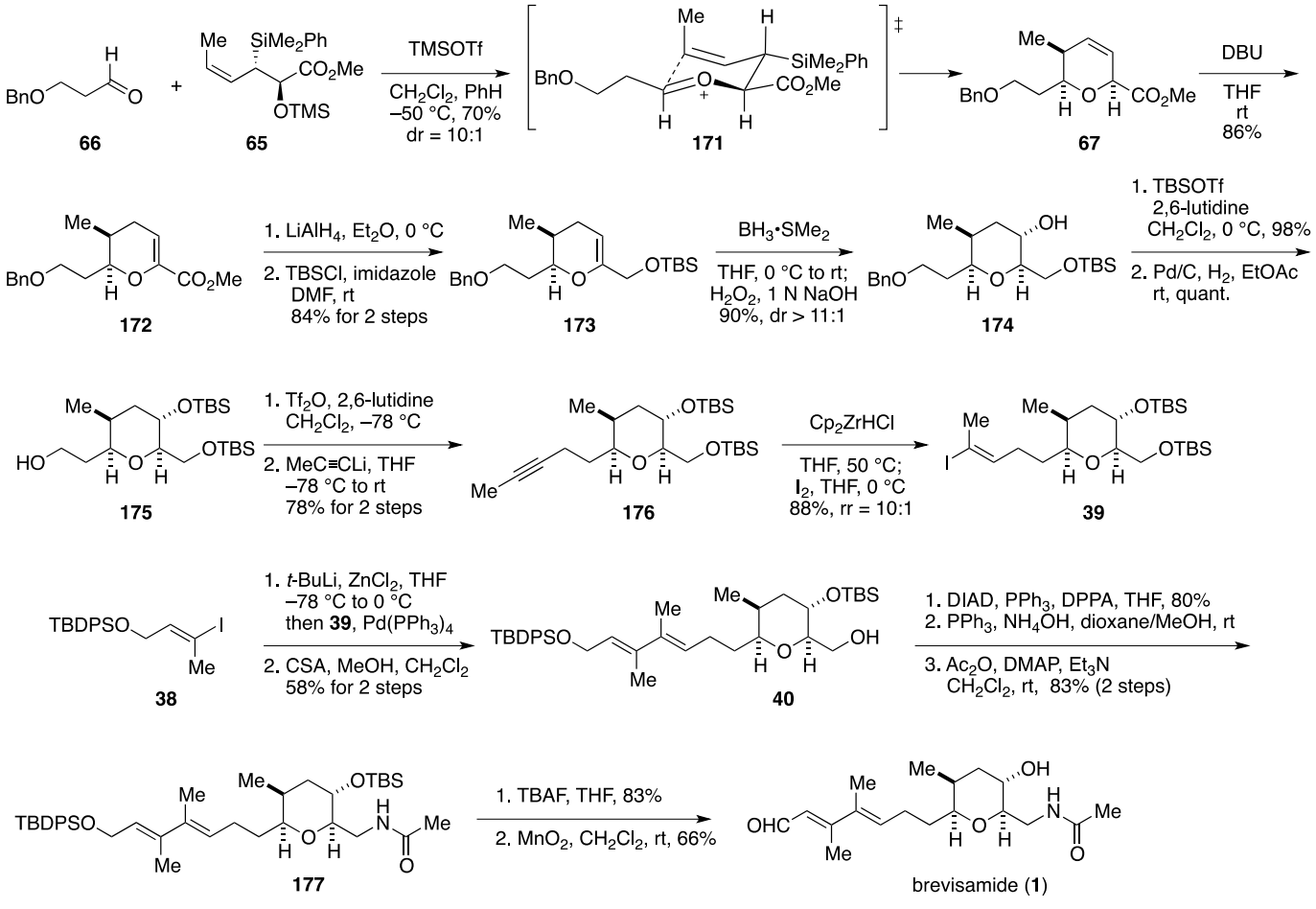
Scheme 24. Yadav's first synthesis

3-6. Annulation reaction for the THP core (Ghosh's and Panek's total syntheses)

Two total syntheses of brevisamide based on the annulation strategy have been reported so far. Ghosh's total synthesis[15] commenced with the addition of ethylmagnesium bromide to conjugate aldehyde **166**,[76] Swern oxidation, and enal silylation (Scheme 25). The resulting diene **68** was subjected to an asymmetric oxa-Diels-Alder reaction with aldehyde **69**, catalyzed by the Jacobsen chromium catalyst **70**,[50] to produce the cyclic TES enol ether **71**. Oxidation with *m*-CPBA to α-hydroxy ketone **167**[77] was followed by removal of the ketone moiety by the Wolff-Kishner reduction to afford **168**.[78] The secondary alcohol was protected with a TBS group, and the benzyl group was removed by hydrogenation. The resulting primary alcohol **169** was transformed to acetamide **170** via azidation, hydrogenation, and acetylation. Finally, vinyl derivative **21** obtained from **170** by elimination using Grieco's method[79] was subjected to hydroboration with 9-BBN, followed by Suzuki-Miyaura coupling with iodide **9b**. The TEMPO oxidation then completed the total synthesis of brevisamide (**1**).



Scheme 25. Ghosh's total synthesis

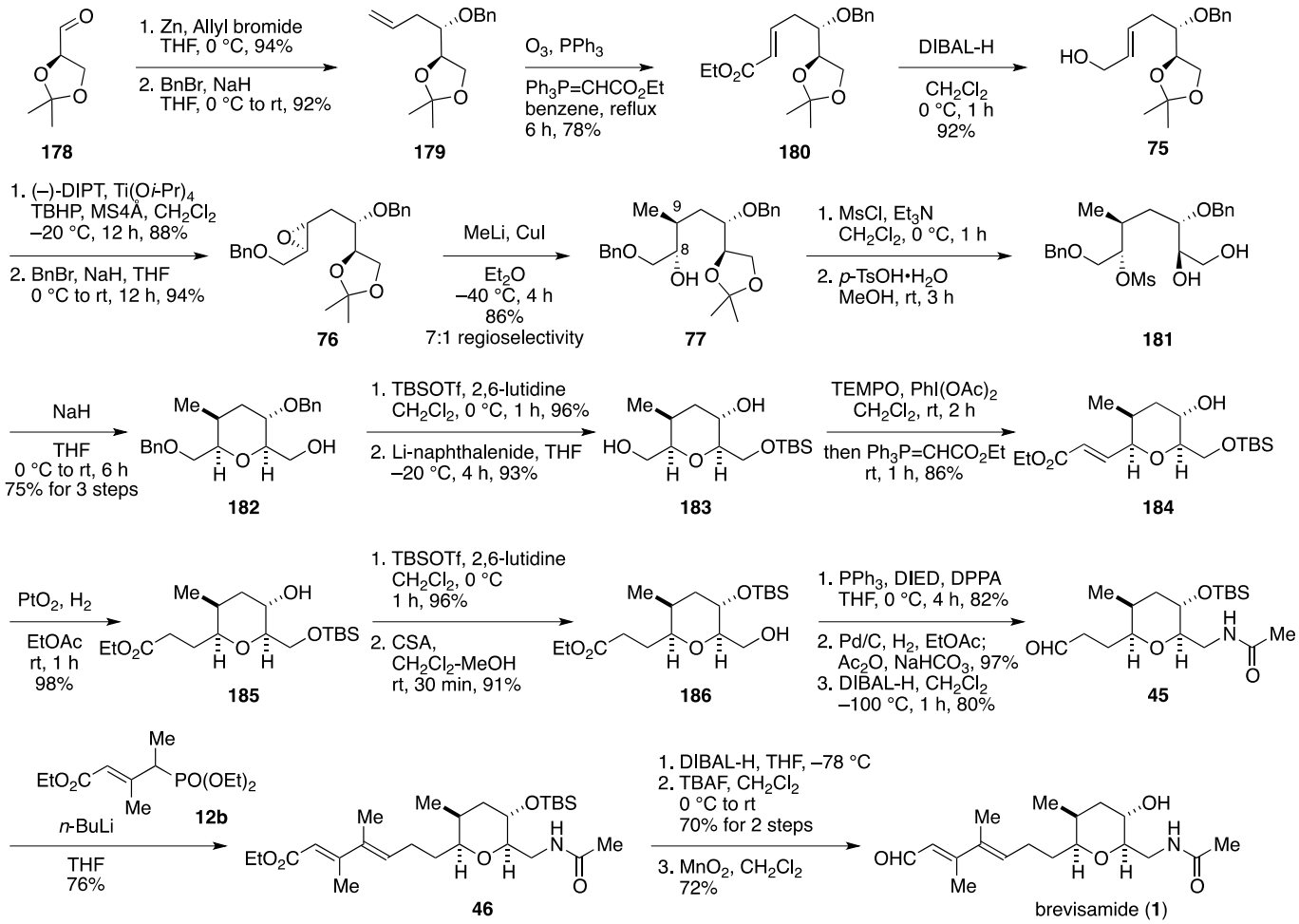


Scheme 26. Panek's total synthesis

Panek achieved the total synthesis of brevisamide through an oxonium-ene cyclization reaction (Scheme 26).[16] Crotylsilane **65** and 3-(benzyloxy)propanal **66** were treated with TMSOTf to afford **67** via *in situ*-generated oxonium salt **171**.[49] After isomerization of the double bond with DBU to the conjugate system, the methoxycarbonyl group of **172** was reduced to the hydroxymethyl group, and the resulting alcohol was protected with TBS to give **173**. Hydroboration from the axial face afford alcohol **174**, and subsequent TBS protection followed by debenzylation gave alcohol **175**. Triflation with trifluoromethanesulfonic anhydride and substitution with 1-propynyllithium provided acetylene **176**. Hydrozirconation using the Schwarz reagent followed by iodination gave vinyl iodide **39**,[77,80] which was subjected to Negishi coupling with vinylzinc derived from iodide **38** to give **40**.[43] After assembling the acetamide side chain to **177**, the TBDPS and TBS groups were removed with TBAF, and the resulting allylic alcohol was oxidized with MnO_2 to complete the total synthesis of brevisamide (**1**).

3-7. SN2 cyclization at the C8-O bond (Yadav's total syntheses)

Yadav's second synthesis[20b] commenced with the allylation reaction of D-glyceraldehyde acetonide (**178**) followed by protection to benzyl ether **179** (Scheme 27).



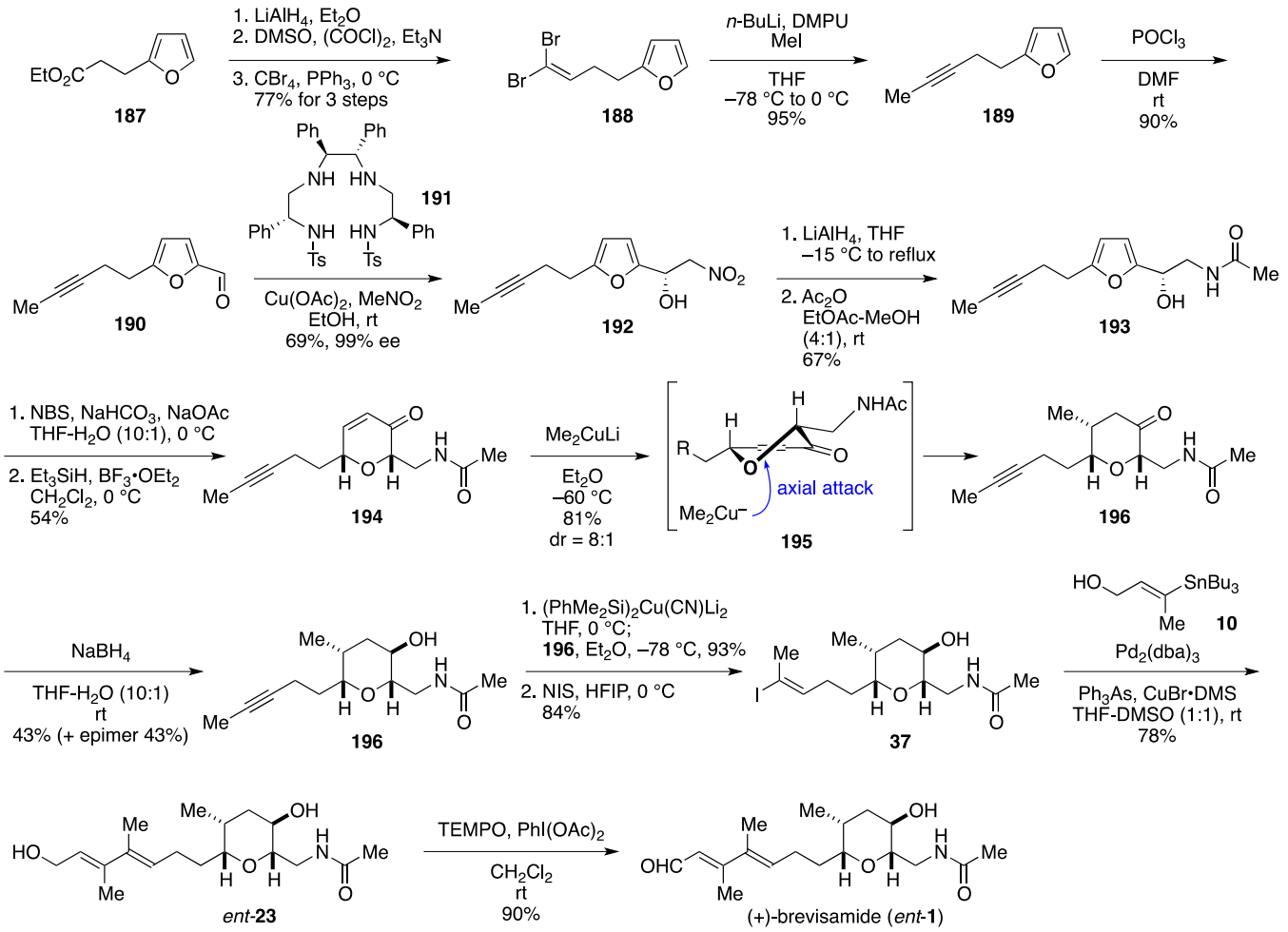
Scheme 27. Yadav's second synthesis

The terminal olefin was subjected to one-pot ozonolysis and Wittig olefination to afford enoate **180**. The ester group was reduced with DIBAL-H, and the resulting allylic alcohol **75** underwent Sharpless asymmetric epoxidation[54] to give epoxide **76** after benzylation. Regioselective methyl cuprate addition to the epoxide afforded alcohol **77** with the desired stereochemistry for the C9 methyl group, while the C8 hydroxy group had the unnatural *S* configuration.[53] Thus, alcohol **77** was converted to mesylated diol **181** and subjected to NaH-mediated S_N2 cyclization, which advanced the THP core formation and inverted the C8 oxygen functional group.[81] The remaining primary alcohol was protected with TBSOTf, and two benzyl groups were removed with Li-naphthalenide to diol **183**. The selective oxidation of the primary alcohol in **183** with TEMPO/$PhI(OAc)_2$ and one-pot Wittig reaction provided enoate **184**. The C=C double bond was reduced to **185** by hydrogenation and the secondary alcohol in **186** was protected with a TBS group. Installation of the acetamide side chain by the conventional method, followed by DIBAL-H reduction, afforded aldehyde **45**. Synthesis of brevisamide was completed after carrying out four more steps based on Lindsley's total synthesis.

4. BREVISAMIDE SYNTHESIS USING DIASTEREOSELECTIVE C9 METHYL INTRODUCTION

4-1. Achmatowicz rearrangement for the THP core (Zakarian's total synthesis)

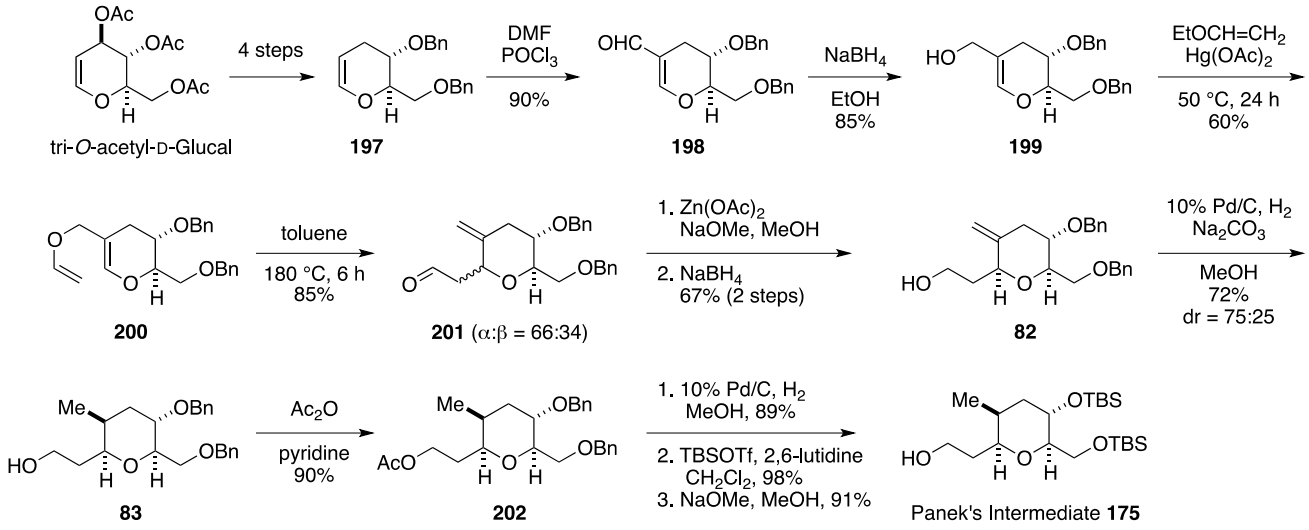
Zakarian used the Achmatowicz rearrangement for the construction of the THP core of brevisamide (Scheme 28).[19] Furanyl ester **187** was converted to the corresponding alkyne **189** through $LiAH_4$ reduction, Swern oxidation, and subsequent Corey-Fuchs alkyne synthesis. Formylation of the furan ring by the Vilsmeier-Haack reaction to aldehyde **190** and the asymmetric Henry reaction using Wang's catalyst gave **192**.[82] The nitro group of the resulting adduct was reduced to the primary amine, and subsequent acetylation afforded acetamide **193**. The Achmatowicz rearrangement using *N*-bromosuccinimide followed by reduction with Et_3SiH provided cyclic enone **194**, corresponding to the THP core of brevisamide.[83] Axial attack of dimethylcuprate to the conjugate enone gave the methyl adduct **196** with 8:1 diastereoselectivity.[55] The best axial reduction was obtained using $NaBH_4$ in an aqueous THF solvent system to give **196** in 43% yield along with its epimer (43%).[84] The reduction of the ketone under normal $NaBH_4$ reduction conditions (e.g., $NaBH_4$ in MeOH) exclusively provided the undesired epimer, having been reduced from the less-hindered equatorial face. The silyl cuprate addition to alkyne followed by iodination using NIS provided vinyl iodide **37**. Stille cross-coupling with vinylstannane **10** under modified Sasaki's conditions provided the coupling product *ent*-**23**. Finally, oxidation of the allylic alcohol with TEMPO provided (+)-brevisamide.



Scheme 28. Zakarian's total synthesis

4-2. THP core from tri-*O*-acetyl-D-glucal (Sridhar's formal synthesis)

Sridhar's synthesis[22] started from 3-deoxy-D-glucal dibenzyl ether **197** prepared from tri-*O*-acetyl-D-glucal[85] (Scheme 29). Formylation by the Vilsmeier-Haack reaction to aldehyde **198** and reduction to

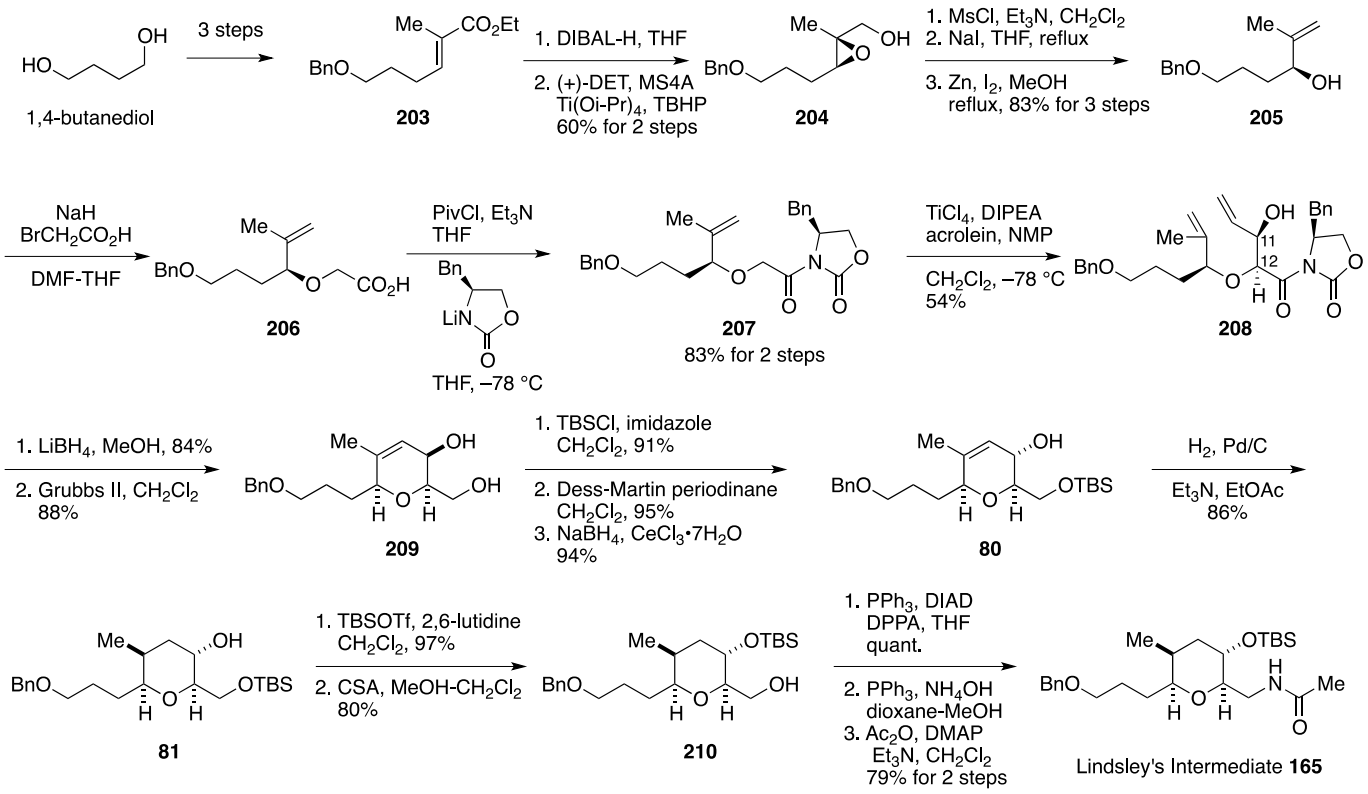


Scheme 29. Sridhar's formal synthesis

alcohol **199** were followed by treatment with ethyl vinyl ester in the presence of $Hg(OAc)_2$ to afford vinyl ether **200**. Claisen rearrangement of **200** provided aldehyde **201** in 66:36 diastereomeric ratio. The diastereomixture was isomerized to the more stable isomer using $Zn(OAc)_2$ and then reduced to alcohol **82**.[86] The exo-methylene in **82** was hydrogenated using 10% Pd/C to afford product **83** with 75:25 diastereoselectivity. A further three-step protecting group manipulation was necessary to obtain Panek's brevisamide intermediate **175**.

4-3. Ring-closing metathesis at C9-C10 bond (Kang's formal synthesis)

Kang achieved the formal total synthesis of brevisamide based on a unique retrosynthetic analysis that includes C9-C10 formation by ring-closing metathesis (Scheme 30).[23] Enoate **203** prepared in three steps from 1,4-butanediol[20a] was subjected to DIBAL-H reduction, followed by Sharpless epoxidation to epoxy alcohol **204**. The alcohol was converted to iodide, and subsequent Zn-mediated cleavage of the oxiranylmethyl iodide afforded allylic alcohol **205**. The alcohol was alkylated with bromoacetic acid, and the resulting carboxylic acid **206** was transformed to oxazolidinyl imide **207** by the mix anhydride protocol. The chlorotitanium-mediated aldol reaction with acrolein provided the Evans *syn*-aldol adduct **208**[87] with the desired configuration at C12, but epimeric at C11. The imide functional group was removed reductively using $LiBH_4$, and the diene moiety was subjected to ring-closing metathesis to afford

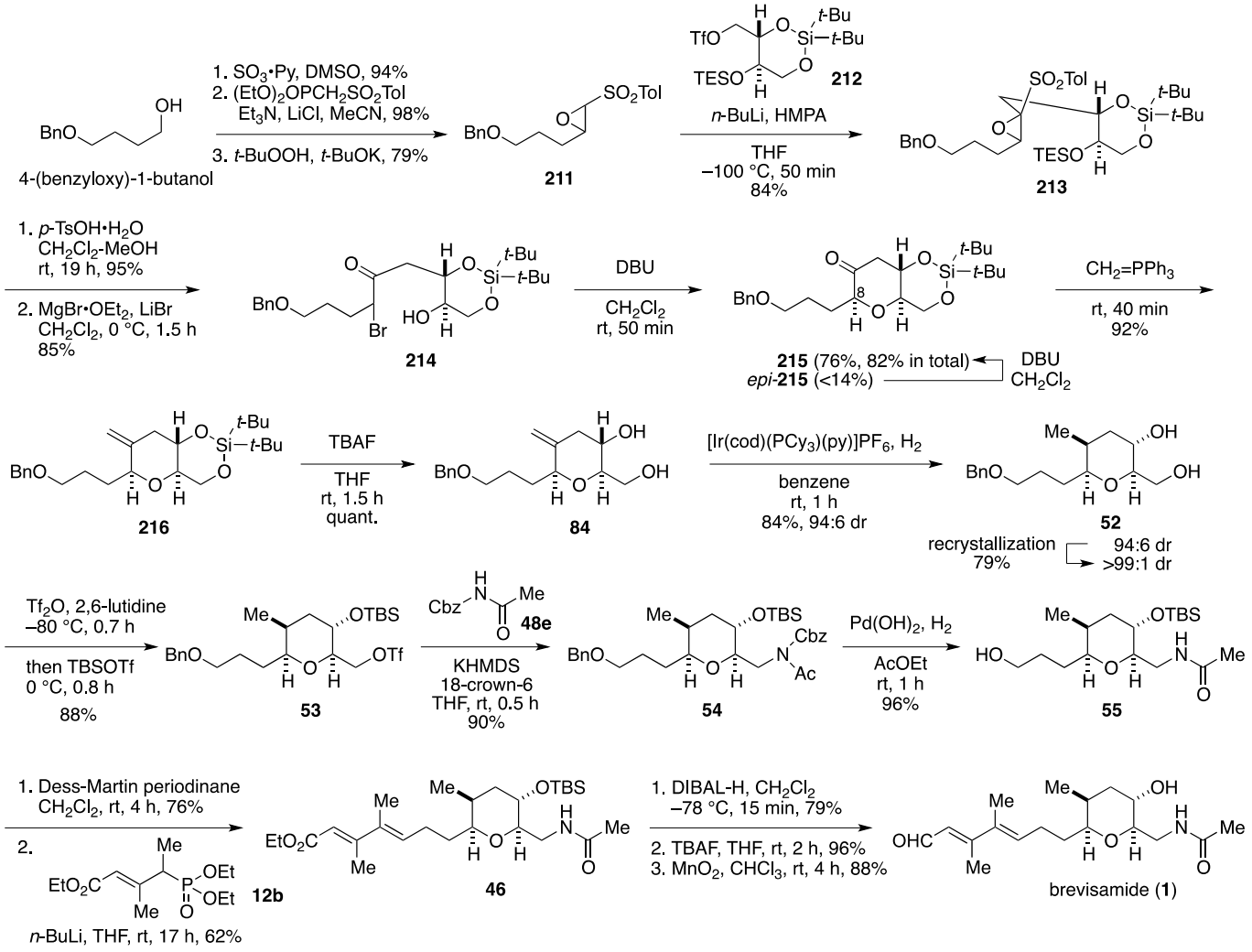


Scheme 30. Kang's formal synthesis

dihydropyran **209**.[88] After protection of the primary alcohol, the stereochemistry of the alcohol at C11 was inverted from β to α by oxidation and reduction to give **80**. The endo-olefin was hydrogenated to alkyne **81** diastereoselectively,[56] followed by TBS-protection of the secondary alcohol and deprotection of the primary alcohol. The resulting primary alcohol **210** was converted to Lindsley's acetamide **165** via the azidation route.

4-4. Oxiranyl anion strategy (Mori's total synthesis)

Mori's total synthesis[25] is characterized by the oxiranyl anion strategy for the THP core construction (Scheme 31). 4-(Benzyloxy)-1-butanol was subjected to a three-step transformation to epoxysulfone **211**, which was treated with *n*-BuLi at –100 °C in the presence of alkyl triflate **212** to afford the coupling product **213**.[89] The TES group was removed by *p*-TsOH·H_2O, and the epoxysulfone was treated with $MgBr_2$·OEt_2 to afford bromoketone **214**. The cyclization with DBU provided the six-membered ketone **215** along with its C8 diastereomer *epi*-**215**, which was epimerized to **215** using DBU. Ketone **215** was



Scheme 31. Mori's total synthesis

transformed to exo-methylene **216** by the Wittig reaction, and the di-*tert*-butylsilylene group was removed with TBAF. The resulting diol **84** was reduced using Crabtree's catalyst to afford the axial methyl product **52** in a 94:6 diastereomeric ratio,[57] from which the pure isomer was obtained by recrystallization. The triflation of the primary alcohol and TBS protection of the secondary alcohol were carried out in a one-pot operation to afford **53**. Nucleophilic substitution of *N*-Cbz-acetamide **48e** to N-alkylated product **54** and the subsequent removal of the benzyl and Cbz groups afforded alcohol **55**. The five additional steps carried out according to Lindsley's synthesis provided brevisamide (**1**).

5. TABULAR SUMMARY OF TOTAL SYNTHESIS OF BREVISAMIDE

A comprehensive tabular summary of eight total and seven formal total syntheses of brevisamide is provided in Table 3 for comparative purposes.

Table 3. Summary of the syntheses of brevisamide

	online publication	research group	THP core construction	dienal[a]	longest sequence[b]	overall yield[c]	ref
1	Dec. 2008	Tachibana	lactonization	Suzuki	21 steps	1.6%	9a
2	Jul. 2009	Lindsley	SmI_2 radical cyclization	HWE	18 steps	6.3%	14
3	Aug. 2009	Ghosh	oxa-Diels-Alder	Suzuki	18 steps	1.7%	15
4	Sep. 2009	Panek	crotylsilane-based [4+2]	Negishi	17 steps	6.4%	16
5	Jul. 2010	Tachibana	lactonization	Suzuki	21 steps	8.6%	9b
6	Nov. 2010	Smith III	6-exo-epoxide RO	—	14 (+3) steps	3.1%	17
7	Dec. 2010	Sabitha	Oxa-Michael	—	9 (+10) steps	6.5%	18
8	Jun. 2011	Zakarian	Achmatowicz rear.	Stille	16 steps	2.5%	19
9	Mar. 2013	Yadav	6-endo-epoxide RO	—	19 (+4) steps	1.35%	20a
10	Jul. 2013	Yadav	S_N2 cyclization	HWE	22 steps	5.3%	20b
11	Aug. 2013	Kumaraswamy	iodo etherification	—	16 (+5) steps	4.1%	21
12	Nov. 2014	Sridhar	tri-*O*-acetyl-D-Glucal	—	11 (+9) steps	1.9%	22
13	Jan. 2015	Kang	ring-closing metathesis	—	22 (+5) steps	1.9%	23
14	Apr. 2016	Mohapatra	oxonium ion allylation	HWE	22 (+3) steps	5.4%	24
15	Apr. 2016	Mori	oxiranyl anion strategy	HWE	18 steps	5.9%	25

a) Assembling method for the 3,4-dimethyl-2,4-dienal side chain. b) Longest linear sequence starting from the commercially available substrates (*cis*-2-butene-1,4-diol **13**, 3-(benzyloxy)-1-propanal **66**, 4-(benzyloxy)-1-butanol **103**, ethyl 3-(2-furyl)propionate **187**, and 1,4-butanediol) or the known starting materials ((Z)-crotylsilane **65**, conjugated aldehyde **166**, Winreb's amide **72**, acrolein aldol adduct **145**, glucal derivative **197**, and aldehyde **130)**, whose synthetic steps were not counted. For formal syntheses, the remaining steps toward brevisamide are shown in parentheses. c) Overall yield of the longest liner sequence. For formal syntheses, the yields were calculated using the yields of the cited total synthesis for the remaining steps.

6. CONCLUSION

Recent advances in synthetic methodology have allowed access to a variety of routes toward brevisamide, culminating in 15 total and formal total syntheses in the nine years since it was discovered. These syntheses involved highly diverse methods for constructing the THP core, installing the four stereogenic centers, and assembling the side chains. However, even the shortest total synthesis requires 16 steps, which is significant for such a small monocyclic molecule (i.e., Zakarian's total synthesis). The overall yields of all 15 synthetic processes remain in single digits. Therefore, the development of more efficient synthetic methods for highly functionalized oxa-cyclic compounds is still an important task.

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