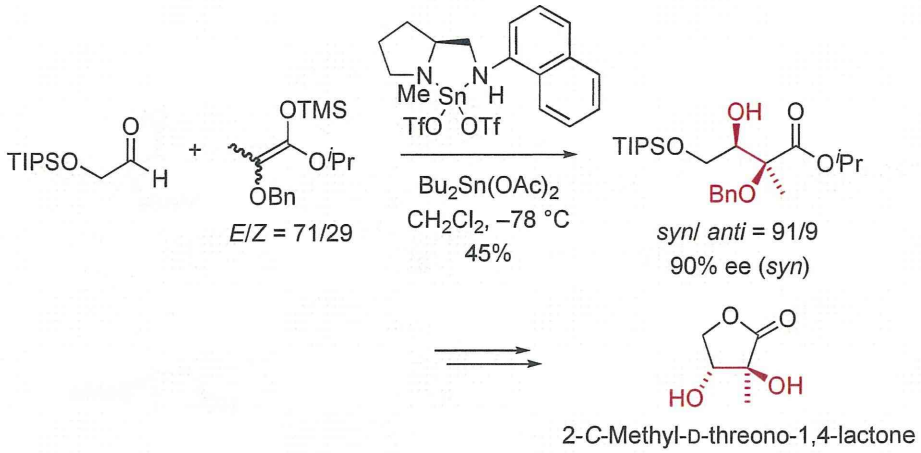
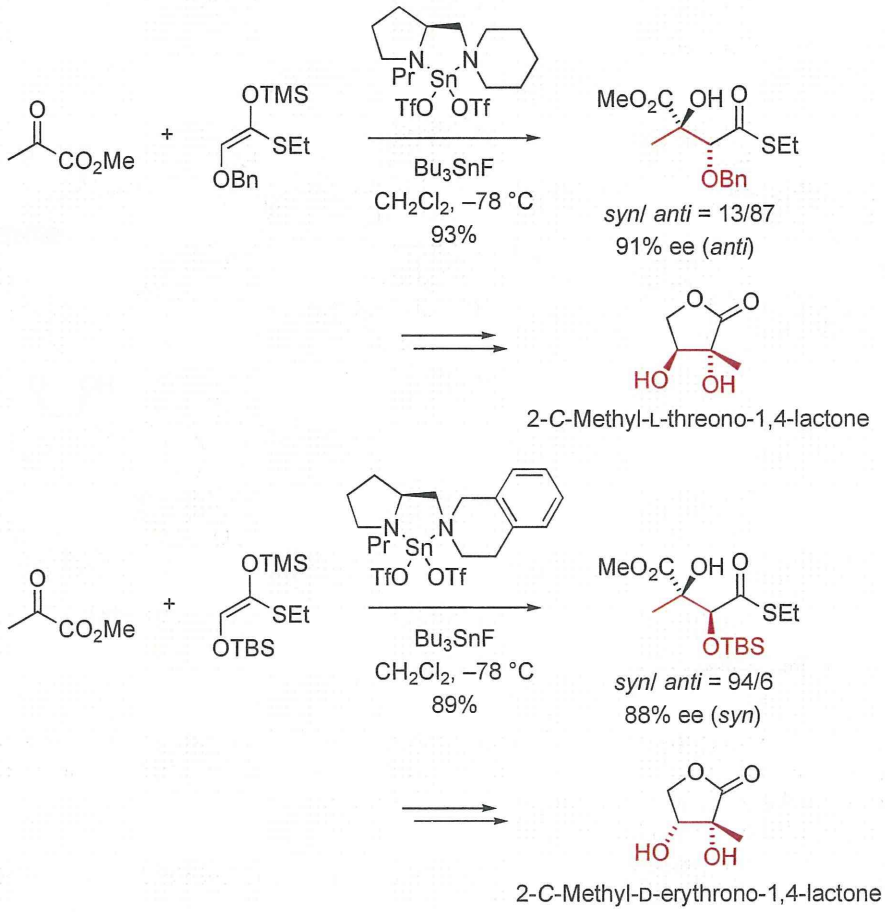
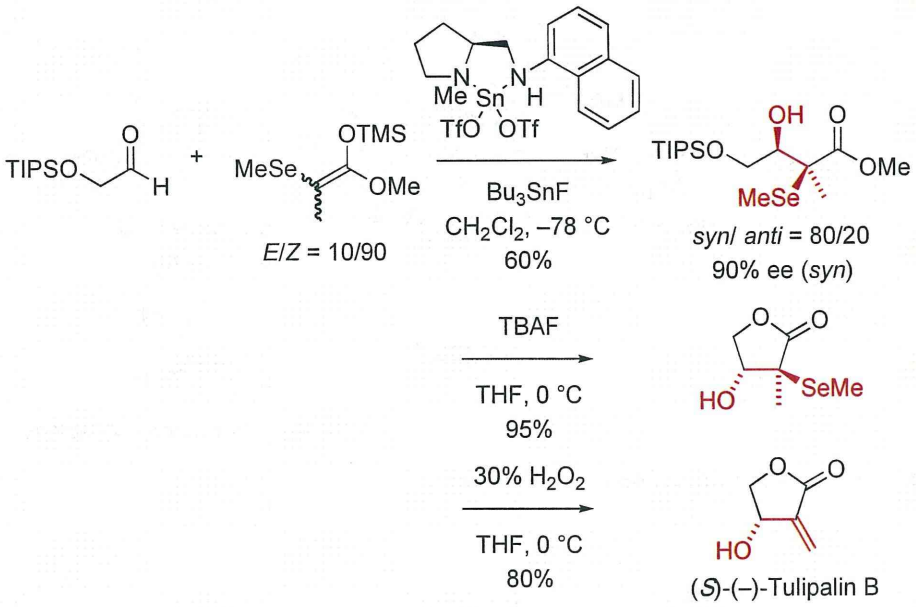



**Scheme 37.** Synthesis of 2-*C*-methyl-D-threono-1,4-lactone.

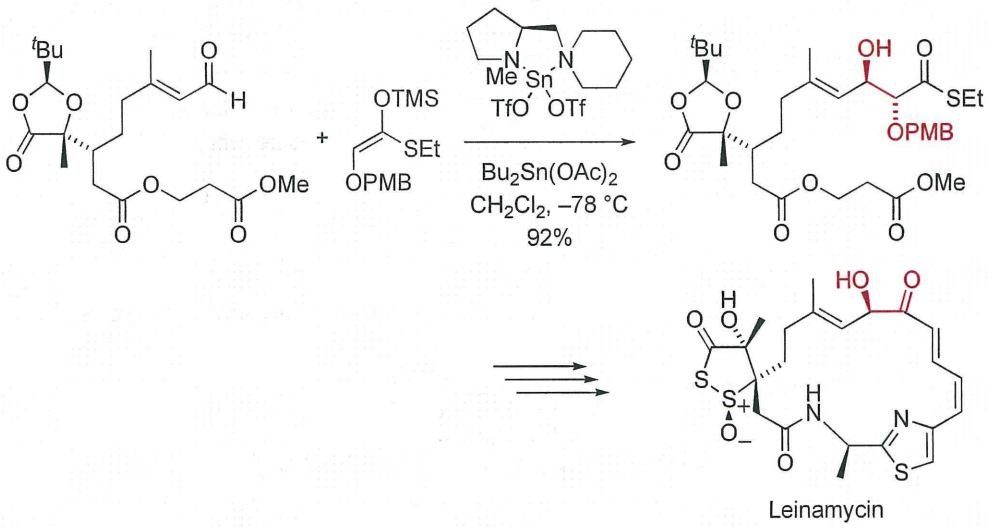



**Scheme 38.** Synthesis of 2-*C*-methyl-L-threono- and D-erythrono-1,4-lactones.


*Chem. Rec.* **2014**, *14*, 144–183 




**Scheme 39.** Synthesis of (*S*)-(–)-tulipalin B.




**Scheme 40.** Total synthesis of leinamycin.

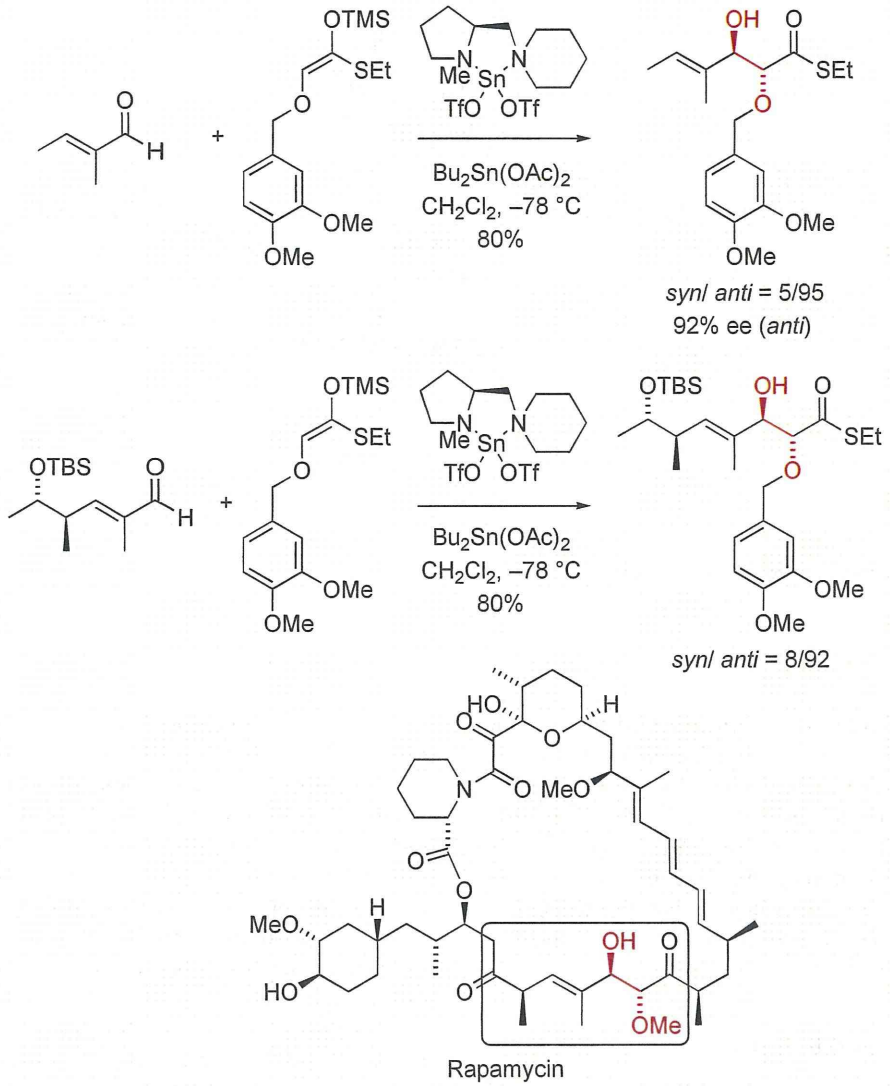
As shown in Section 2.6, Shiina succeeded in developing an alternative method for the preparation of various chiral α-methylene-β-hydroxy esters that correspond to asymmetric MBH adducts via the facile oxidative deselenization of chiral aldol compounds (Scheme 30).[32] The author extended this strategy to the synthesis of (*S*)-(–)-tulipalin B, a natural product with antibiotic effects, as shown in Scheme 39.[40]

Because the key asymmetric aldol reaction has a wide flexibility in controlling newly created chiral centers, the present methods are expected to provide useful routes to the synthesis of various monosaccharides from achiral KSAs and aldehydes.

### 3.2. Leinamycin and the Fragment of Rapamycin

Fukuyama utilized the asymmetric formation of a 1,2-diol unit for the total synthesis of leinamycin, in which it was shown that the KSA having a *p*-methoxybenzyloxy group at the C2




**Scheme 41.** Synthesis of the fragment of rapamycin.

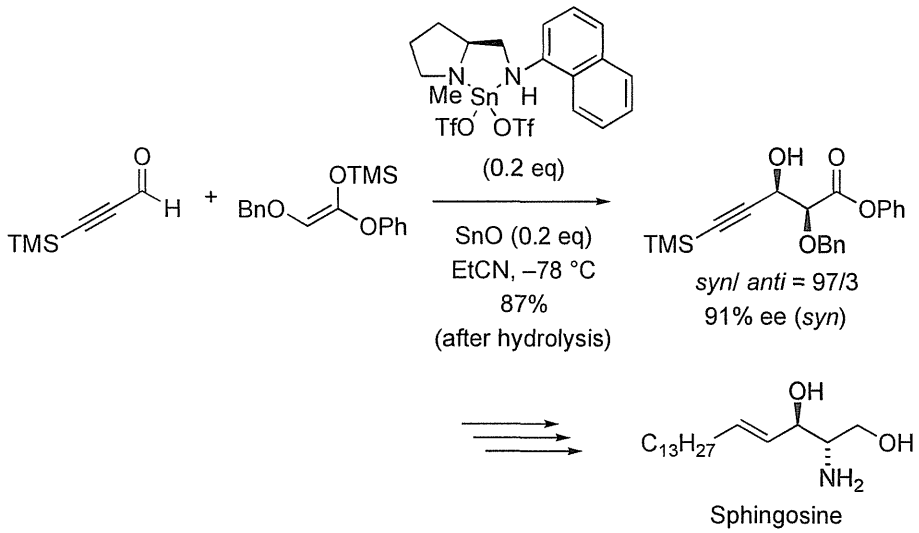
position functions as a suitable nucleophile for the multi-functionalized aldehyde (Scheme 40).[41] Furthermore, White also reported that the reaction of the KSA generated from *S*-Et (3,4-dimethoxybenzyloxy)ethanethioate with α,β-unsaturated aldehydes proceeded smoothly to afford the corresponding diol units in high yields with excellent stereoselectivities, as shown in Scheme 41.[42]

### 3.3. Sphingosine, Sphingofungins and Khafrefungin

Kobayashi continuously employed the asymmetric reactions for the stereoselective synthesis of various polyoxygenated natural compounds. Initially, a new method for the preparation of sphingosine was developed using the catalytic asymmetric aldol reaction of a KSA with α,β-ynal as a key step (Scheme 42).[43]

Sphingofungins B and F were also totally synthesized from small molecules according to the asymmetric aldol strategy as shown in Scheme 43.[43b,44] Here the optically active polyol part was obtained by the reaction of a trisubstituted KSA using a chiral diamine *ent*-**2a**, and the sole stereogenic center in the side chain was constructed by the reaction of a KSA derived from an acetic acid derivative using the chiral diamine **2a**. These segments were coupled to form the basic skeleton of sphingofungins in the total synthesis.


*Chem. Rec.* **2014**, *14*, 144–183 




**Scheme 42.** Synthesis of sphingosine.

The total synthesis of khafrefungin and the determination of its stereochemistry were further achieved by Kobayashi through the chiral induction technology for giving the optically active aldol compounds (Scheme 44).[45] The asymmetric aldol reaction of the KSA derived from *S*-Et propanethioate with aldehydes was applied not only to the first step to afford the corresponding thioester with high ee but also to the following stage to give the multifunctionalized linear thioester with excellent diastereoselectivity.

### 3.4. Febrifugine and Isofebrifugine

Kobayashi also reported the enantioselective total synthesis of febrifugine and isofebrifugine using the chiral diamine–$Sn(OTf)_2$ complex–mediated catalytic asymmetric aldol reaction giving the optically active diol units (Scheme 45).[46] The correct absolute stereochemistries of natural febrifugine and isofebrifugine were shown by comparison with the spectral data and the sense of the optical rotations of four synthetic samples including enantiomorphs.

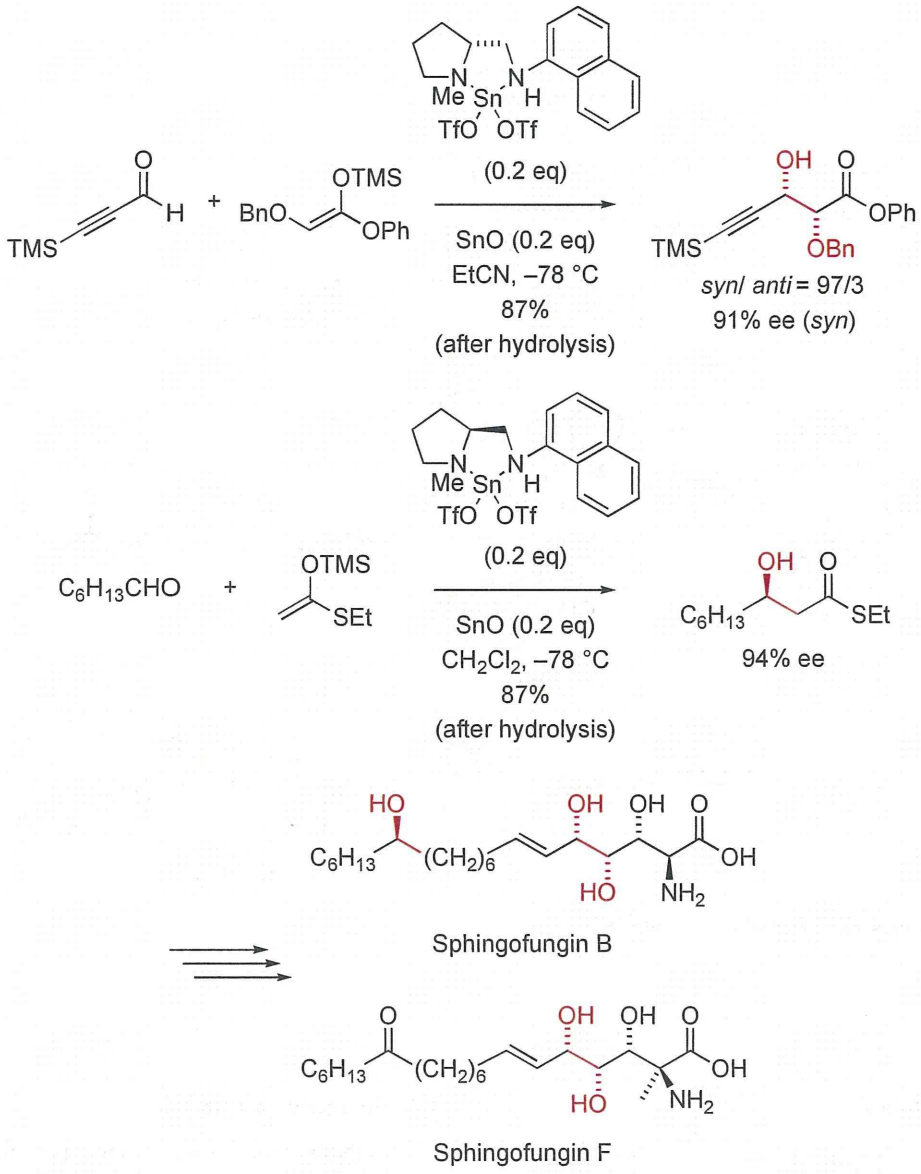
### 3.5. Paclitaxel (Taxol)

Mukaiyama and Shiina accomplished the total synthesis of paclitaxel (Taxol) according to the following strategy (Scheme 46); that is, synthesis of the eight-membered B ring first starting from an optically active polyoxy precursor generated by the highly controlled enantioselective aldol reaction and successive construction of the fused A and C ring systems onto the B ring.[47]

The optically active diol unit **9** was prepared by the asymmetric aldol reaction of a KSA possessing a benzyloxy group at the C2 position with an achiral aldehyde **8** using the chiral diamine–$Sn(OTf)_2$ complex (Scheme 47). Synthesis of the eight-membered ring aldols from an optically active polyoxy unit **10** containing all the functionalities necessary for the construction of Taxol was performed by the intramolecular aldol cyclization using $SmI_2$. Successive acetylation of this mixture of isomeric alcohols and treatment with DBU gave the desired eight-membered enone **11** in good yield.

As shown in Scheme 48, fully functionalized BC ring system **12** was then synthesized from the optically active eight-membered ring compound **11** via successive reactions of Michael addition and intramolecular aldol cyclization of the ketoaldehyde. Furthermore, the intramolecular pinacol coupling reaction of the diketone derived from the above BC ring system using a low-valent titanium reagent resulted in the formation of ABC ring system **13**, a new taxoid, in good yield. 7-Triethylsilylbaccatin III was prepared from the above new taxoid **13** by oxygenation at the C13 position and construction of the oxetane ring.

It was also shown that the asymmetric aldol reaction is useful for preparation of the chiral side chains of Taxol (Scheme 49). Because the reaction of the KSA derived from *S*-Et benzyloxyethanethioate with benzaldehyde afforded the corresponding aldol adduct **14** in high yield with excellent selectivity as shown in the former section, this adduct was successfully converted into the targeted β-amino acid **15** in good yield with the inversion of chirality at the β-position using the Mitsunobu

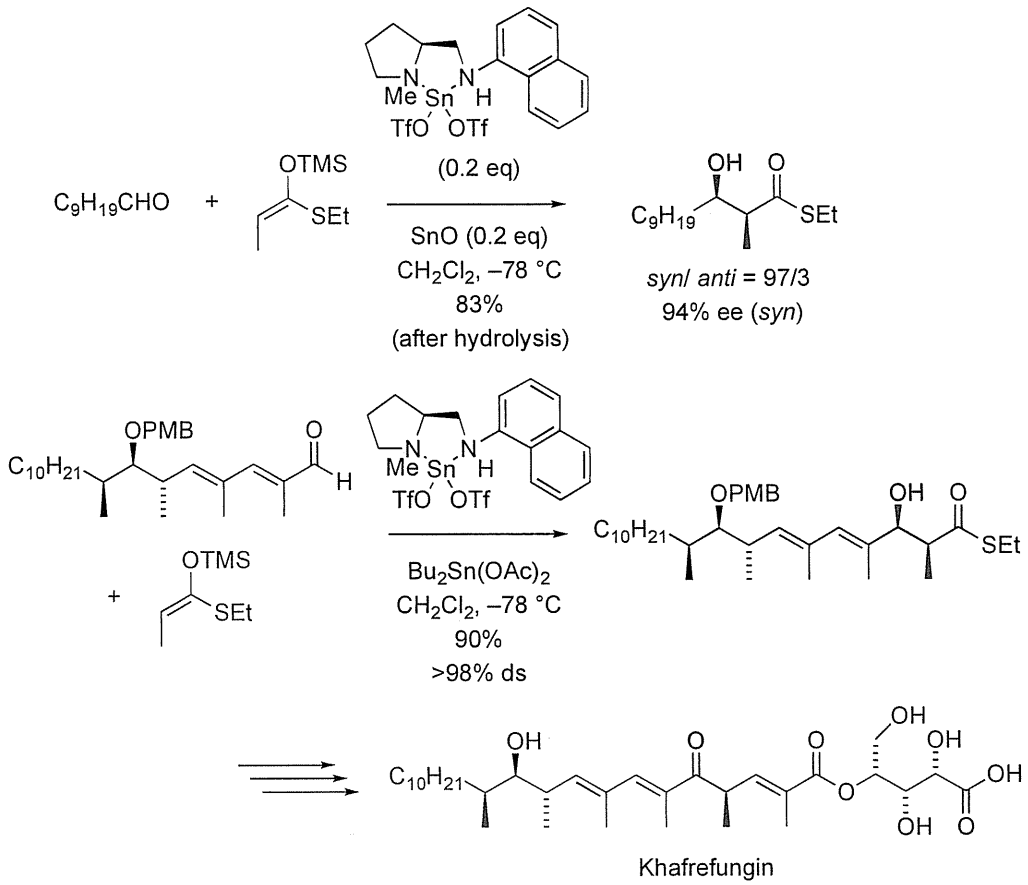



**Scheme 43.** Total synthesis of sphingofungins B and F.

reaction. Introduction of *N*-benzoylphenylisoserine derivative **15** to 7-triethylsilylbaccatin III was further studied, and dehydration condensation was found to proceed smoothly using *O*,*O*-di(2-pyridyl)thiocarbonate (DPTC)[48] as a novel coupling reagent in the presence of (4-dimethylamino)pyridine (DMAP) to afford the desired ester in 95% yield at 93% conversion (Scheme 50). Finally, deprotection of the intermediate gave the final target molecule Taxol in excellent yield.

Thus, the establishment of a new method for the asymmetric synthesis of baccatin III by way of B to BC to ABC to ABCD ring construction was demonstrated, as well as completion of the total synthesis of Taxol through preparation of the side chain by the asymmetric Mukaiyama aldol reaction and subsequent dehydration condensation with 7-triethylsilylbaccatin III using DPTC. This synthetic route would be widely applicable to the preparation of various derivatives of Taxol and related taxoids.


*Chem. Rec.* **2014**, *14*, 144–183 




**Scheme 44.** Total synthesis of khafrefungin.

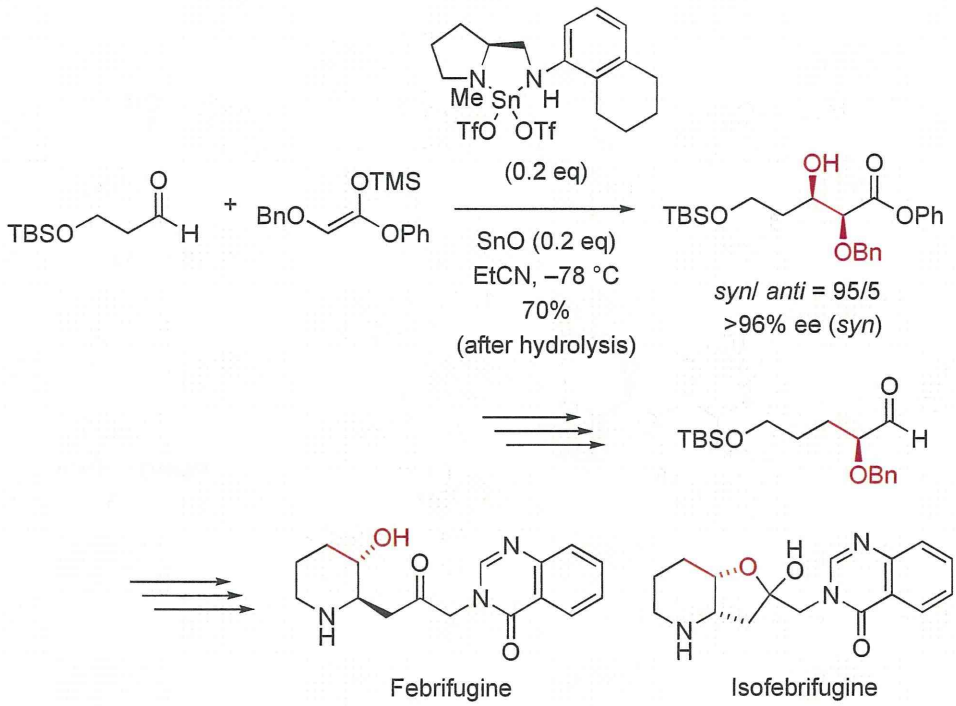
### 3.6. Cephalosporolide D

Shiina developed a method for the preparation of cephalosporolide D, a natural eight-membered lactone, and the exact stereochemistry of this compound was determined through the first total synthesis (Scheme 51).[49] In this synthetic strategy, two stereogenic centers were both constructed by the asymmetric aldol reactions using the KSA derived from *S*-Et ethanethioate. It is also mentioned that the second diastereoselective aldol reaction afforded the desired compound in 3/97 ratio when using the chiral diamine *ent*-**2a**–$Sn(OTf)_2$ complex, whereas the ratio ranges from 97/3 to 59/41 when employing the chiral diamine **2a**–$Sn(OTf)_2$ complex or $SnCl_4$ as catalyst. The desired eight-membered lactone moiety was constructed by the cyclization of the seco acid via a novel mixed anhydride method using (4-trifluoromethyl)benzoic anhydride (TFBA)[50] with $Hf(OTf)_4$.

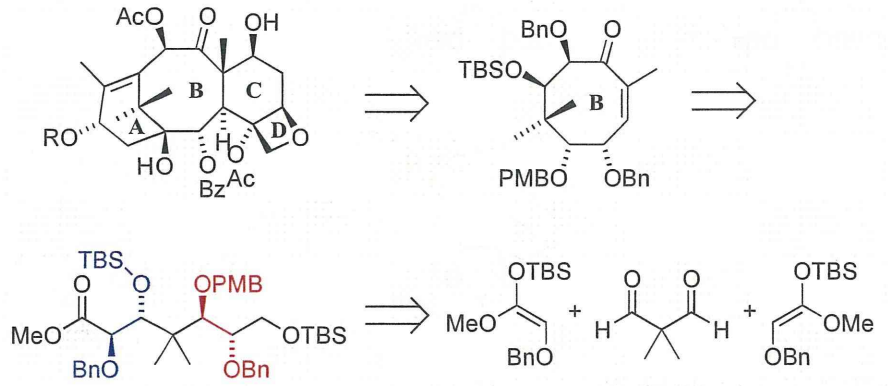
### 3.7. Buergerinins F and G

The synthesis of buergerinin F, a natural compound consisting of a unique tricyclic skeleton, was attained in the course of synthetic studies on utilizing the asymmetric aldol strategy by Shiina.[51] The first key step is producing the optically active α,β,γ-trioxy ester including a quaternary stereogenic center at the C2 position as shown in Scheme 52. It is also revealed that enantioselective aldol reaction of the tetrasubstituted KSA having four oxygenated functionalities is very effective for the preparation of this complex synthetic intermediate. Successive intramolecular Wacker-type ketalization, one-carbon elongation of the intermediate, and iodocyclization afforded the optically active buergerinin F. With the accomplishment of the total synthesis using the asymmetric aldol reaction promoted by the chiral diamine–$Sn(OTf)_2$ catalyst, the absolute stereochemistry of natural buergerinin F was determined.




**Scheme 45.** Total synthesis of febrifugine and isofebrifugine.

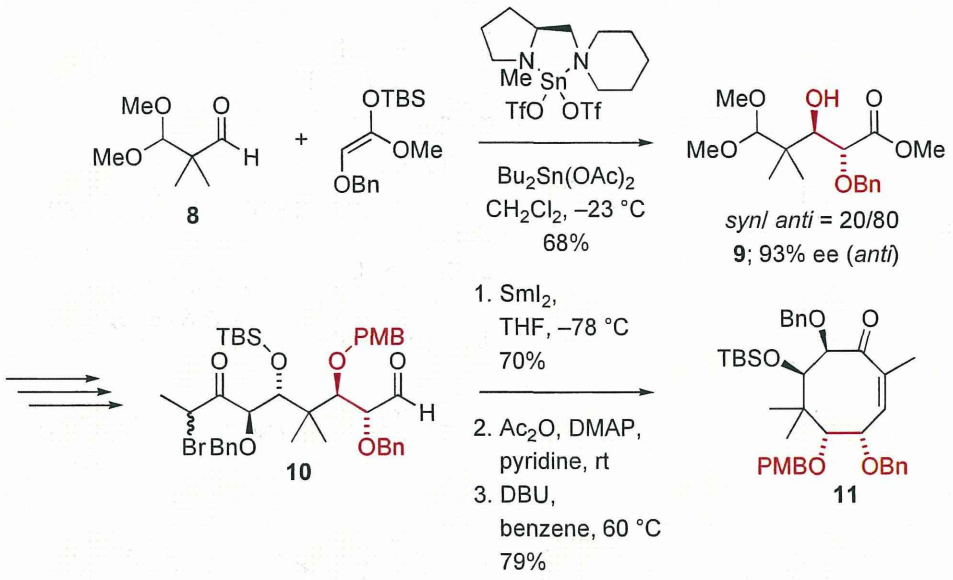



**Scheme 46.** Retrosynthetic analysis of Taxol.

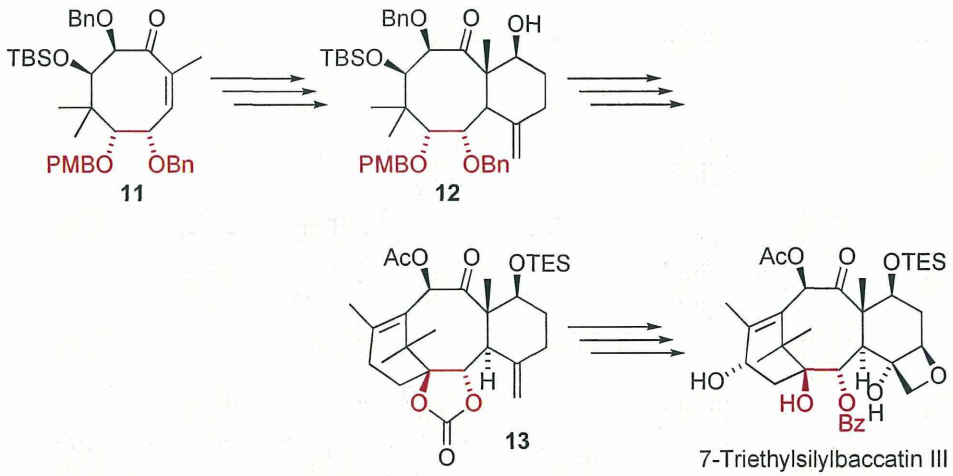
The high stereoselectivities attained in this aldol reaction can be explained by assuming the antiperiplanar transition state as depicted in Scheme 53. In the reaction of the tetrasubstituted KSA with crotonaldehyde, the chiral Sn(II) complex has a rigid structure in which the conformation is highly controlled by the coordination of nitrogens in the chiral diamine and oxygen in the benzyloxy group of KSA onto the central Sn(II) metal. The *re* face of the activated aldehyde is almost completely shielded during the nucleophilic addition process and the KSA attacks from the *si* face via forming a five-membered ring to give the *syn*-aldol adduct in high enantio- and diastereoselectivities.

Based on the strategy described in Scheme 54, we had successfully synthesized buergerinin F starting from the chiral aldol adduct using the Wacker-type cyclization to produce the hydroxyketal followed by iodine-mediated five-membered ether ring closure (Scheme 54, upper pathway; BC to A ring system formation). However, oxidative conversion of




**Scheme 47.** Synthesis of the B ring of Taxol.

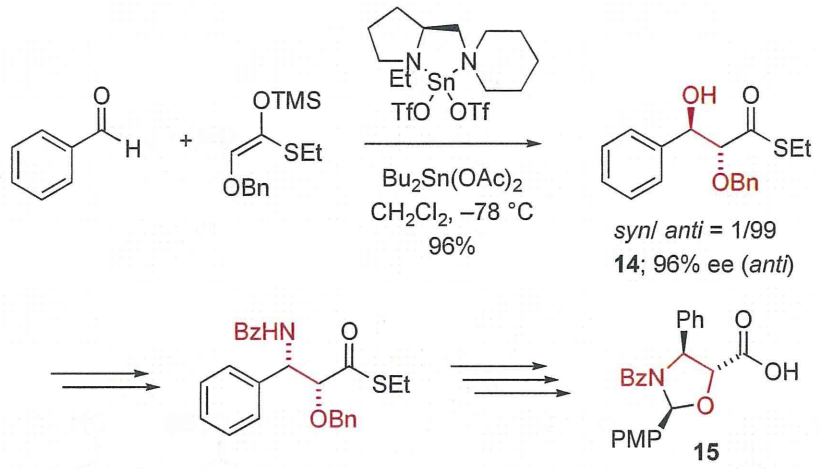



**Scheme 48.** Synthesis of the ABC ring system of Taxol.

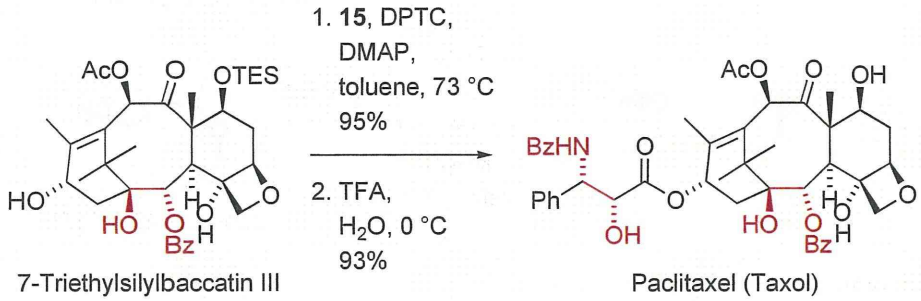
buergerinin F into buergerinin G was not successfully carried out by us due to the significant volatility of buergerinin F.[52] Therefore, we decided to develop an alternative method to prepare buergerinin G, not from buergerinin F via oxygenation, but directly from the precursor dihydroxy-γ-lactone using the intramolecular Wacker-type ketalization (Scheme 54, lower pathway; A to BC ring system formation).[33]

First, the ester function in the chiral aldol was reduced and the benzyl protective group was cleaved using lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) to afford the corresponding triol (Scheme 55). The attempted transformation of the primary hydroxy into a leaving group by treatment with tosyl chloride in pyridine produced the corresponding tosylate. The desired epoxide was formed in high yield by treatment of the tosylate with DBU. Coupling of lithiated 1,3-dithiane with the resulting epoxide afforded the epoxy-opened product, which was further converted into the dihydroxy-γ-lactone by the successive deprotection of the dithioacetal moiety, oxidation of the hemiacetal part, and removal of the TBS group. The intramolecular Wacker-type ketalization of the dihydroxy-γ-lactone




**Scheme 49.** Synthesis of the side chain of Taxol.




**Scheme 50.** Completion of the total synthesis of Taxol.

using a catalytic amount of palladium dichloride was finally carried out and the corresponding bicyclic ketal, the target molecule buergerinin G, was provided in good yield. The $^{1}H$ and $^{13}C$ NMR spectra and other properties of the obtained buergerinin G showed that the synthetic sample has the same relative and absolute stereochemistries as naturally occurring buergerinin G.

### 3.8. Octalactins A and B

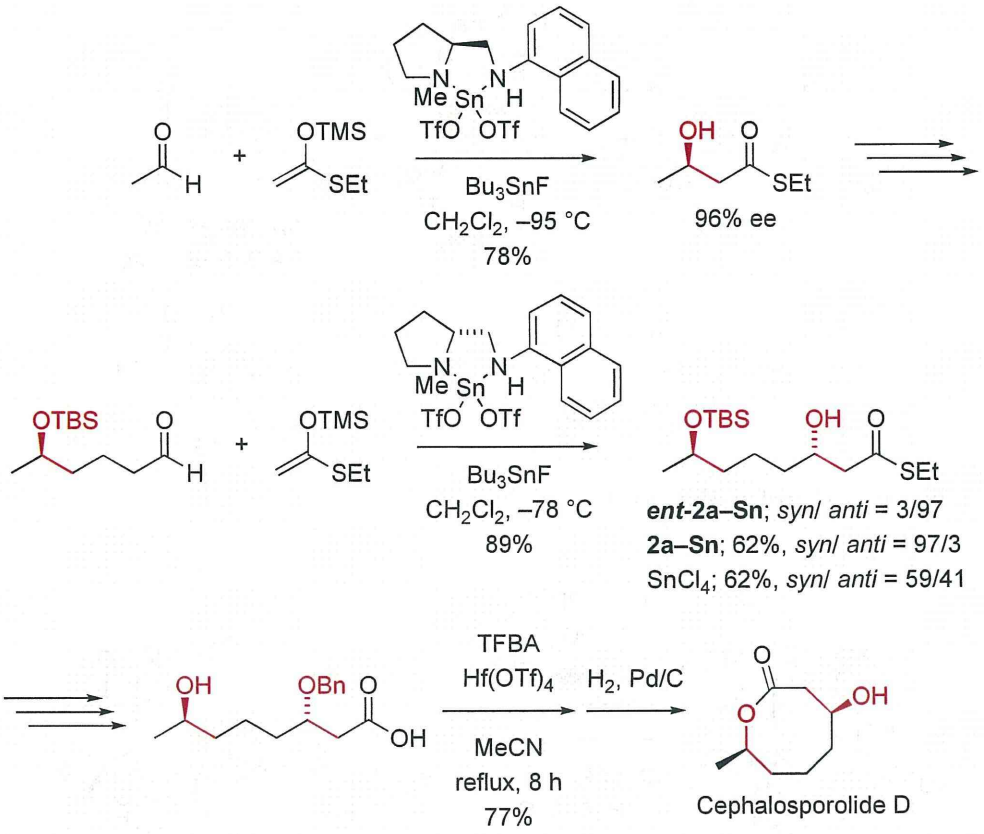
In 2005, Shiina developed a method for the synthesis of octalactin A, an antitumor agent consisting of an eight-membered lactone.[53] The lactone moiety includes two pairs of *anti*-β-hydroxy-α-methyl units; therefore, an enantioselective addition of the KSA derived from methyl 2-methylselenopropanoate was efficiently utilized for the construction of the desired components, namely, the asymmetric aldol reaction of the tetrasubstituted KSA with aldehydes[32] and the subsequent treatment of the formed optically active adducts by Guindon's reduction[54] afforded the desired two chiral segments **16** and **17** (Scheme 56).

On the other hand, the optically active side chain **18** was also produced by utilizing the asymmetric aldol reaction of the KSA derived from *S*-Et ethanethioate with 2-methylpropanal (Scheme 57). A chiral linear precursor having repeated *anti*-β-hydroxy-α-methyl units was obtained by the coupling of the segments **16** and **17**, and the resulting seco acid was then eventually cyclized to form the eight-membered lactone by a new quite effective mixed anhydride method using 2-methyl-6-nitrobenzoic anhydride (MNBA)[55,56] with DMAP as shown in Scheme 58. Finally, the side chain **18** was introduced to the eight-membered lactone moiety to afford the targeted multi-oxygenated compounds, octalactins A and B.

### 3.9. Oudemansin Antibiotic Analogue

Uchiro and Kobayashi reported the synthesis of β-methoxyacrylate antibiotics (MOAs) and their analogues.[57] In




**Scheme 51.** Total synthesis of cephalosporolide D.

accordance with their strategy for the preparation of related compounds, the asymmetric aldol reaction of the KSA generated from *S*-Et propanethioate with cinnamyl aldehyde was employed for the stereoselective synthesis of the intermediate of an MOA analogue as shown in Scheme 59.

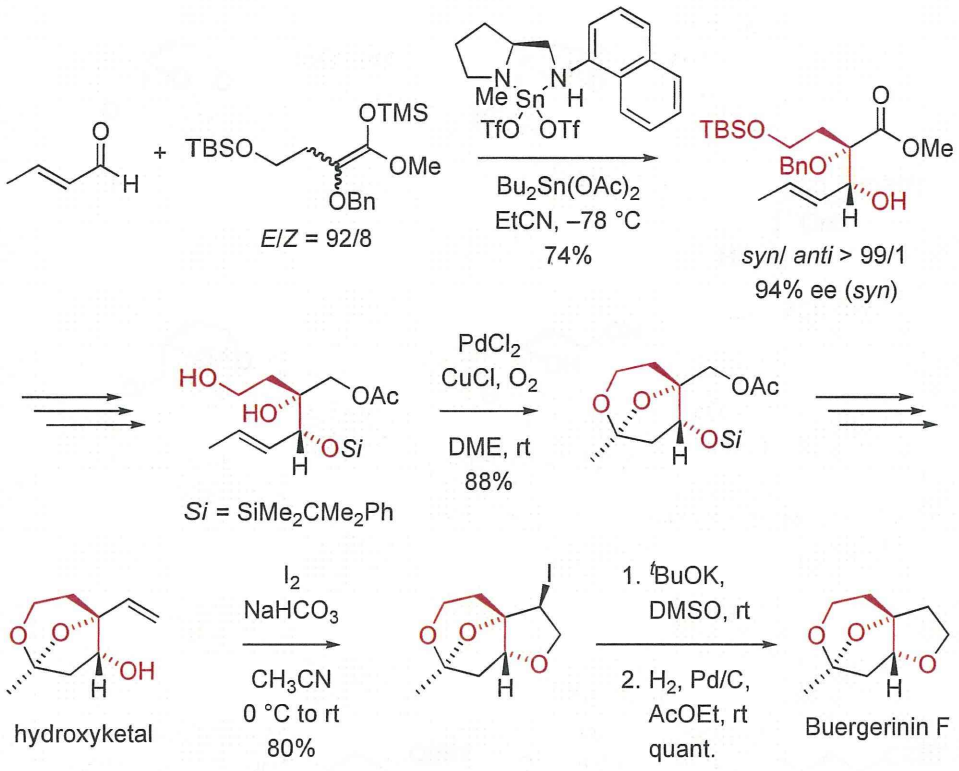
### 3.10. 2-Epibotcinolide

Shiina attained the stereoselective total synthesis of 2-epibotcinolide through several featured synthetic approaches.[58] The chiral side chain **19** was first prepared as shown in Scheme 60 using the asymmetric aldol reaction of the KSA derived from *S*-Et ethanethioate with pentanal. The desired aldol adduct was obtained in a good yield with high enantioselectivity (91% ee). After conversion of the aldol adduct into the corresponding siloxy aldehyde, sequential treatments including formation of the cyanohydrin, mesylation of the hydroxyl group, substitution with phenylselenol, oxidative elimination of the phenylseleno group, reduction of the nitrile group, and oxidation of the resulting aldehyde afforded the optically active α,β-unsaturated carboxylic acid.

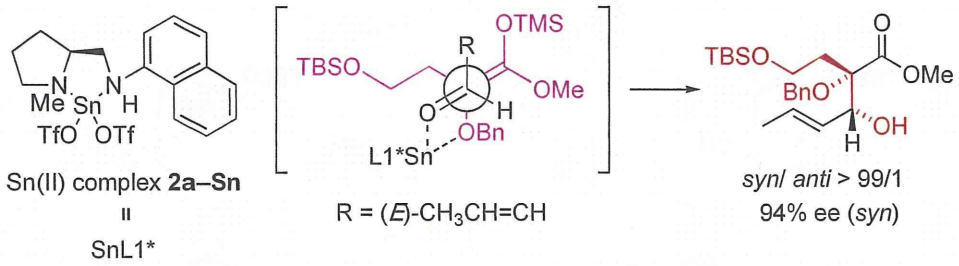
Next, an α-siloxy aldehyde was used as the starting material for the preparation of the chiral linear seco acid as shown in Scheme 61. The successive protection of methyl (*R*)-lactate and reduction with diisobutylaluminum hydride (DIBAL) afforded the chiral α-siloxy aldehyde, which in turn was treated with the KSA derived from *S*-Et propanethioate using the chiral diamine **2a**–Sn(OTf)$_2$ complex combined with $Bu_2Sn(OAc)_2$. The asymmetric aldol reaction proceeded smoothly, and the corresponding γ-siloxy-β-hydroxy-α-methyl thioester, which has the required stereochemistry, was exclusively obtained. The chiral linear precursor of the nine-membered ring compound is stereoselectively constructed, and the key cyclization reaction to form the nine-membered lactone is efficiently achieved by the facile and powerful mixed anhydride method promoted by MNBA with DMAP.[55]

Finally, the coupling reaction between the main nine-membered ring moiety and the chiral side chain **19** was also investigated using MNBA esterification[55] to form the desired lactone that contains all functionalities for producing the ideal structure of 2-epibotcinolide. This study disclosed that the synthesized 2-epibotcinolide was a very unstable product,




**Scheme 52.** Total synthesis of buergerinin F.



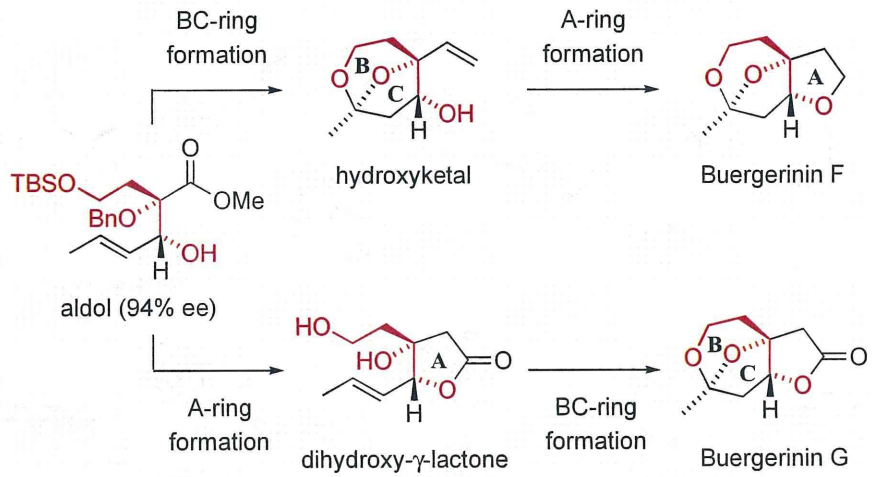

**Scheme 53.** Assumed transition state to give the aldol starting from a tetrasubstituted KSA with crotonaldehyde.

affording the corresponding intramolecular transacylated compound, which is facilely formed from the nine-membered lactone structure.[59]

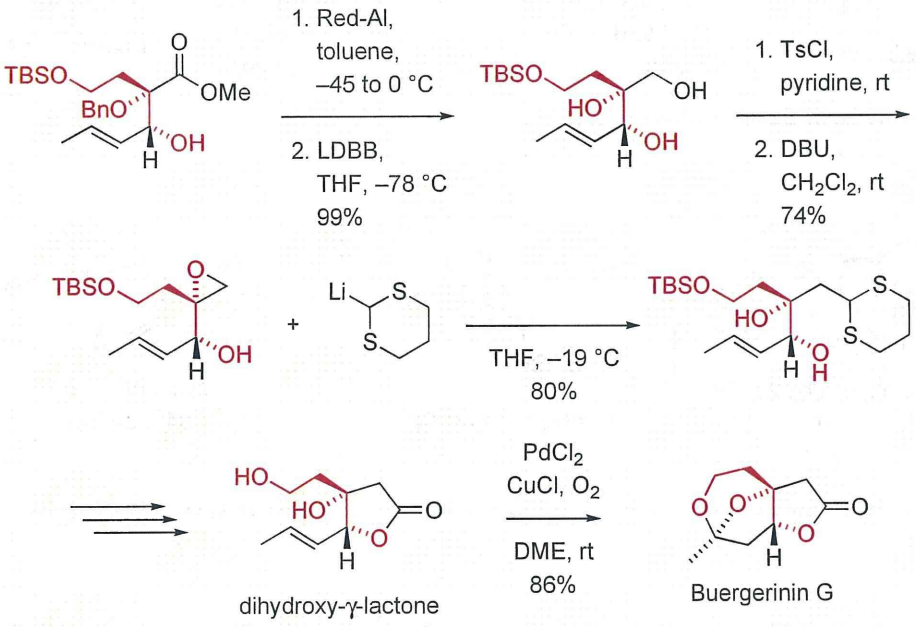
### 3.11. Botcinins A–F, Botcinic Acid, and Botcineric Acid

The chiral α,β-unsaturated carboxylic acids **20** and **21** in Scheme 62 were successfully prepared according to a similar strategy as in Section 3.10. For the synthesis of **20**, asymmetric aldol reaction of the KSA derived from *S*-Et ethanethioate with pentanal was carried out in the presence of a catalytic amount of the chiral diamine *ent*-**2a**–Sn(OTf)$_2$ complex, and the aldol adduct was obtained in a good yield with high enantioselectivity (93% ee). The longer side chain **21** was also generated from heptanal as a starting compound. These side chains **20** and **21** are the common moieties for the synthesis of antifungal botcinins A–F, botcinic acids, and botcineric acid as shown in Figure 2, and total syntheses of all botcinin derivatives and botcinic acid derivatives were achieved by Shiina using the effective coupling reactions of the main skeletons with **20** or **21**.[60]

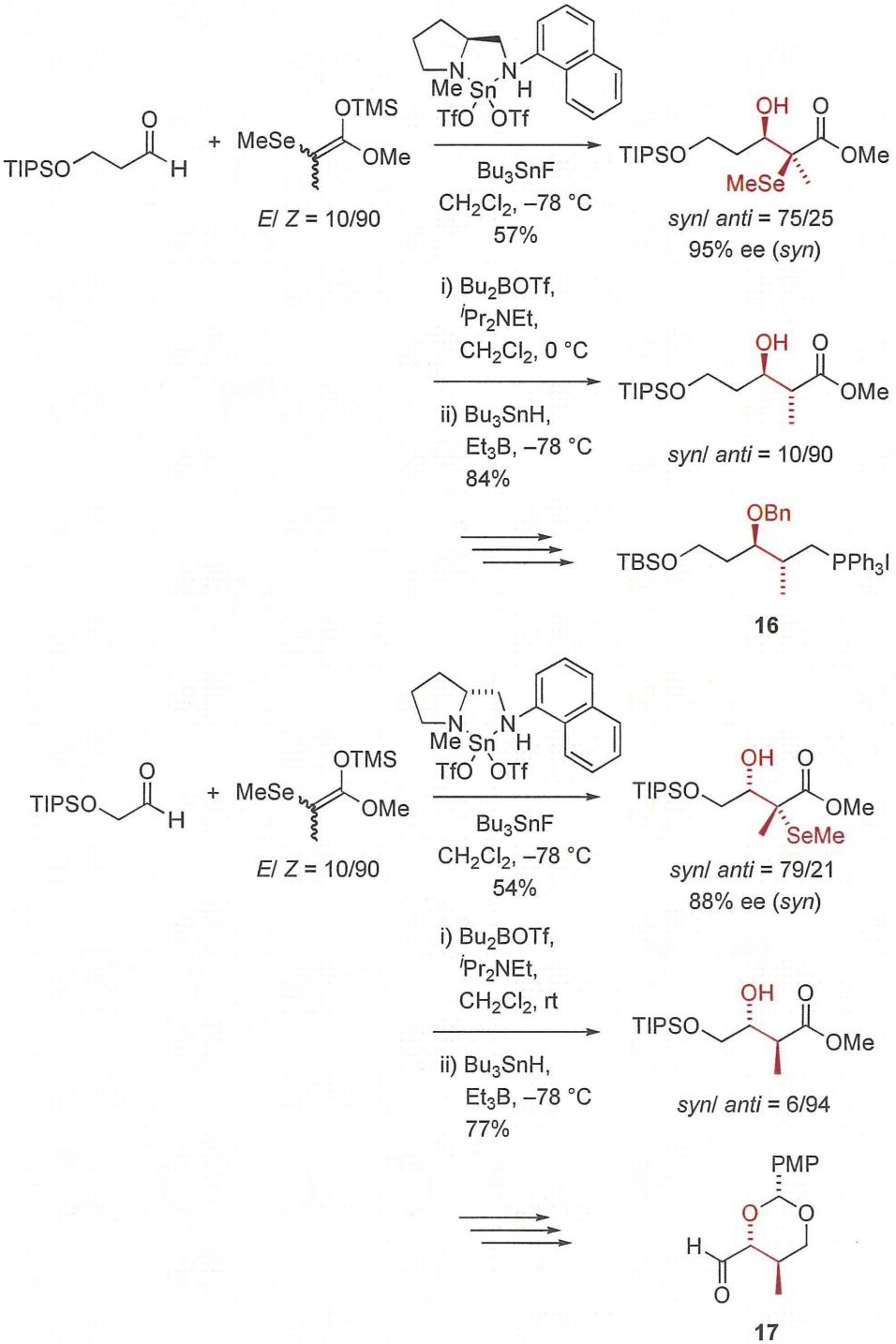



**Scheme 54.** Divergent synthetic pathways for buergerinins F and G.



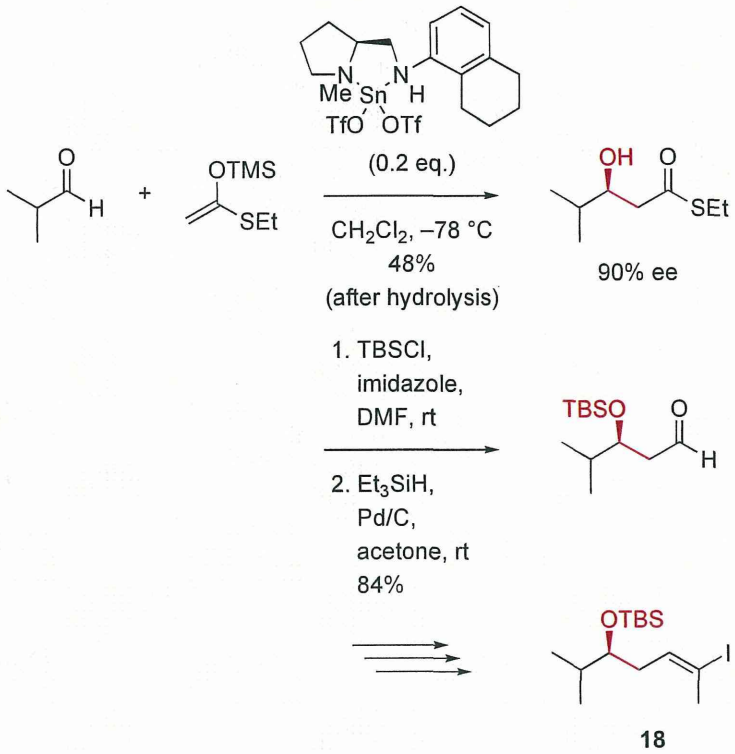

**Scheme 55.** Total synthesis of buergerinin G.

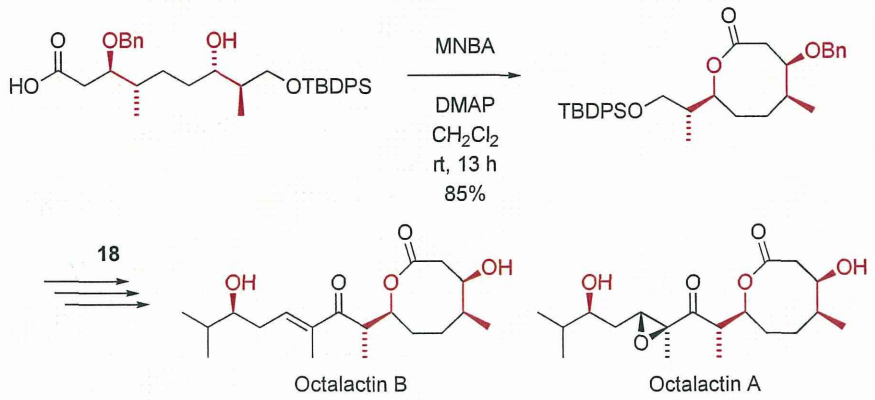



**Scheme 56.** Synthesis of two chiral segments of octalactins A and B.


*Chem. Rec.* **2014**, *14*, 144–183 

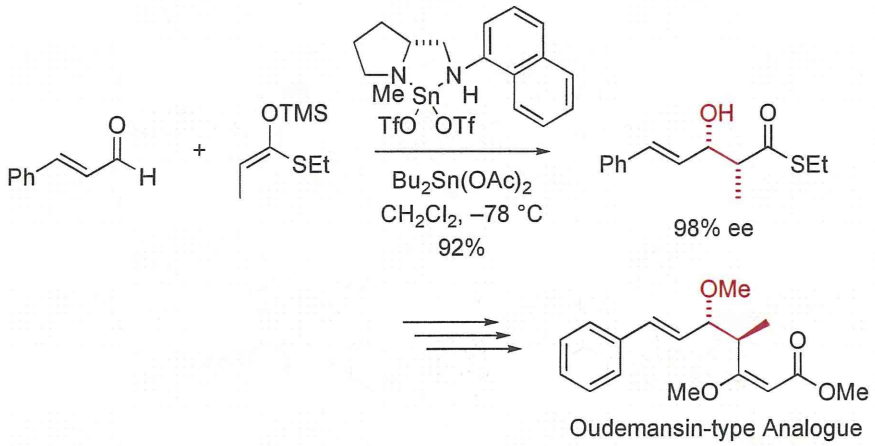



**Scheme 57.** Synthesis of the side chain of octalactins A and B.

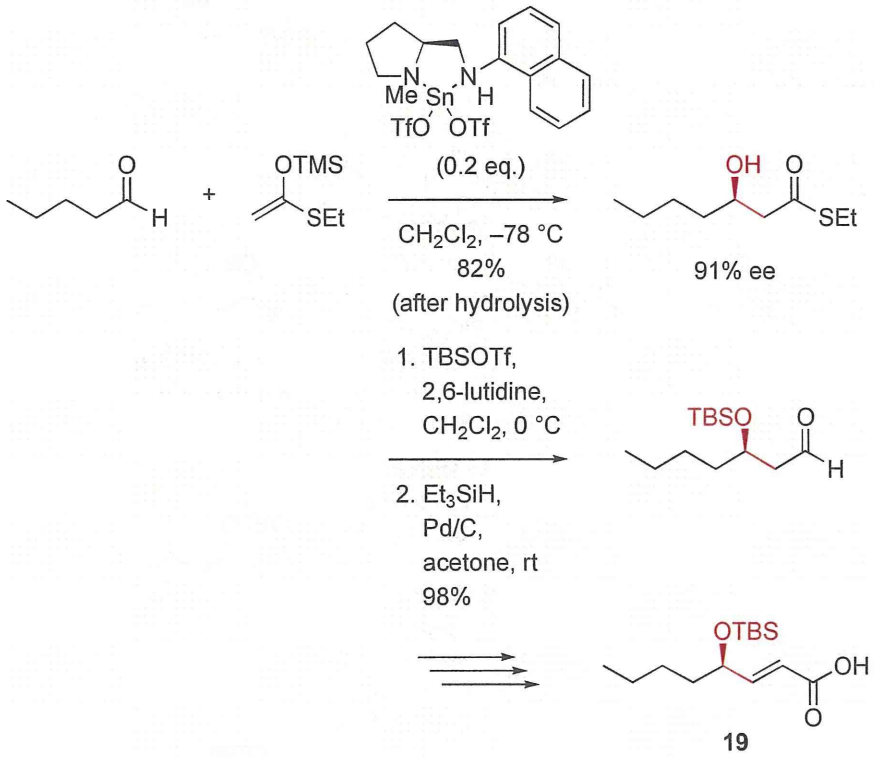



**Scheme 58.** Total synthesis of octalactins A and B.

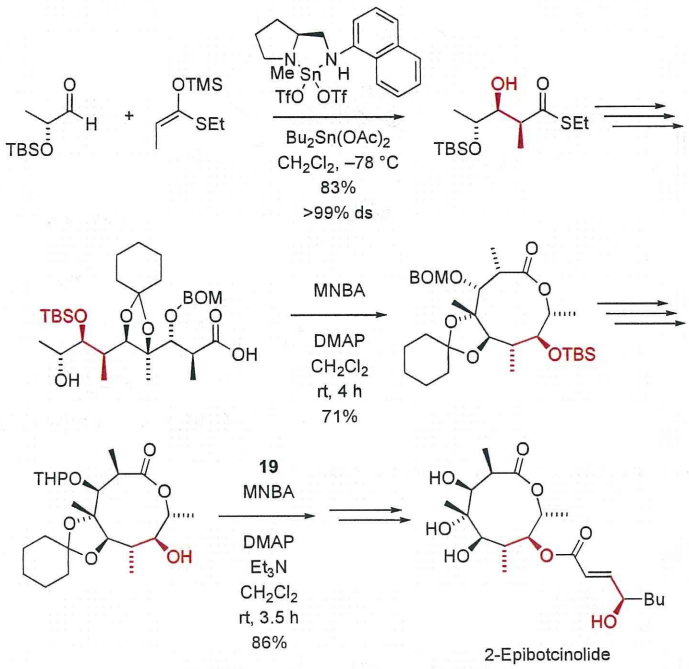



**Scheme 59.** Total synthesis of oudemansin-type antibiotic analogue.

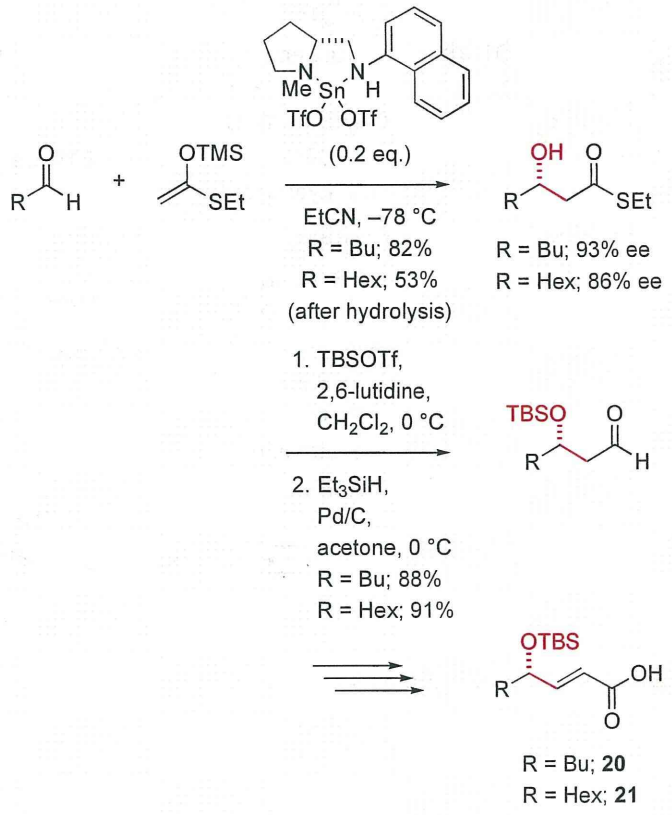



**Scheme 60.** Synthesis of the side chain of 2-epibotcinolide.


*Chem. Rec.* **2014**, *14*, 144–183 




**Scheme 61.** Total synthesis of 2-epibotcinolide.




**Scheme 62.** Synthesis of the side chains of botcinins A–F, botcinic acid, and botcineric acid.

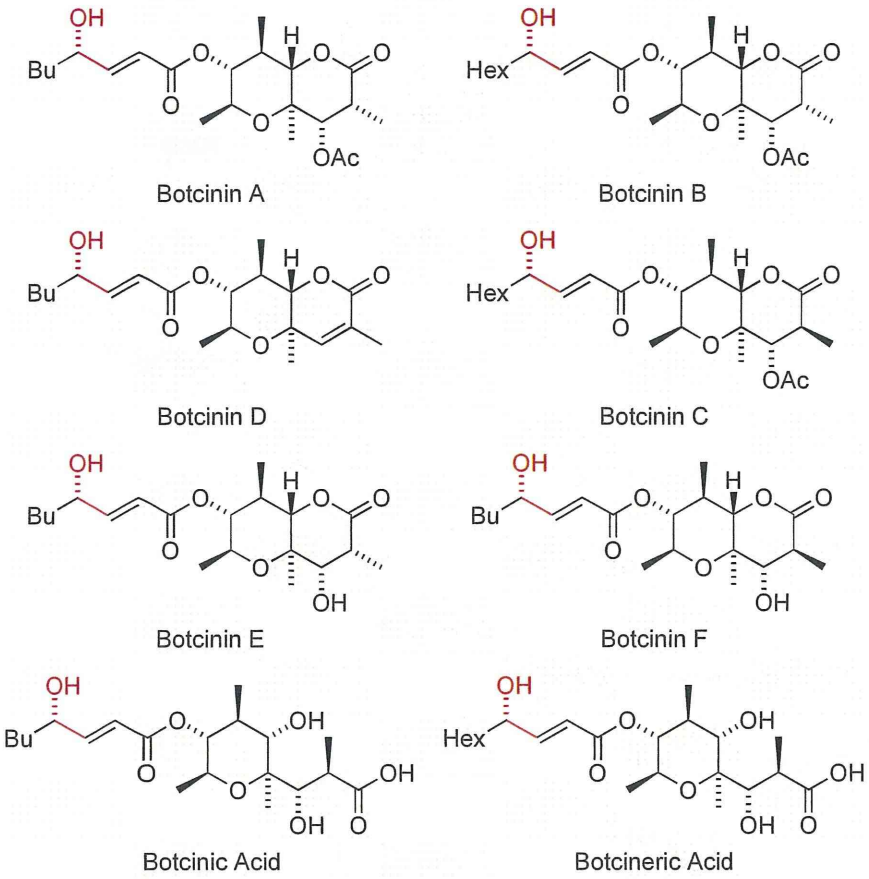



**Fig. 2.** Structures of botcinins A–F, botcinic acid, and botcineric acid.

### 3.12. Lactimidomycin

Kuwahara recently reported the formal synthesis of lactimidomycin (Scheme 63).[61] In this synthesis, the asymmetric aldol reaction of the KSA generated from *S*-Et propanethioate with an δ-siloxy-α,γ-dimethyl-α,β-unsaturated aldehyde was utilized for the stereoselective synthesis of the intermediate **22**. The asymmetric aldol reaction of the KSA derived from *S*-Et propanethioate with the aldehyde in the presence of catalytic amounts of $Sn(OTf)_2$ and the chiral diamine *ent*-**2a** in propionitrile furnished the desired aldol in 86% yield along with a small amount (ca. 10%) of an alcoholic product generated by deprotection of the TMS group.

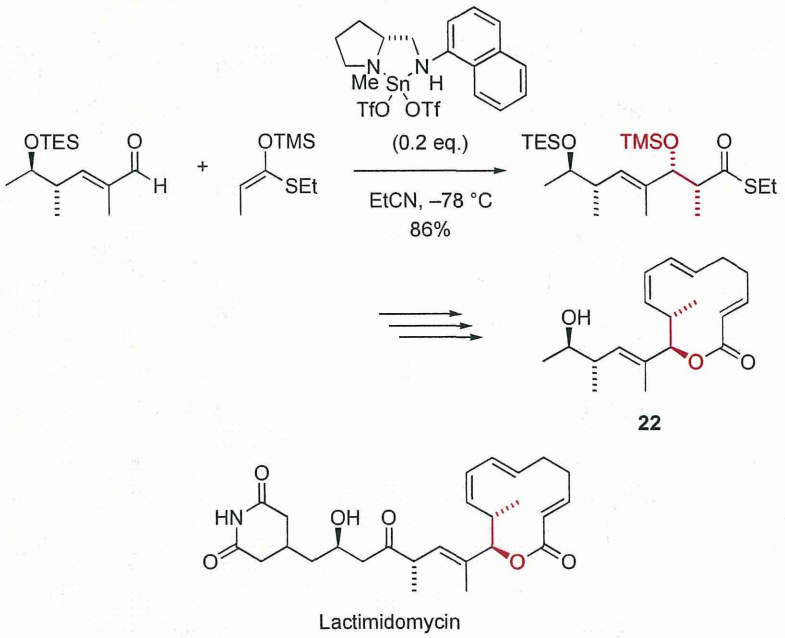
### 3.13. AMF-26

Very recently, an effective method for the total synthesis of AMF-26, a promising new anticancer drug that disrupts the Golgi system by inhibiting the ADP-ribosylation factor 1 (Arf1) activation, has been reported by Shiina as shown in Scheme 64.[62] Oxidation of the starting primary alcohol with tetrapropylammonium perruthenate (TPAP) afforded the (*E*,*E*)-dienealdehyde, and the construction of the chiral linear precursor was achieved by the asymmetric aldol reaction between the KSA derived from *S*-Et propanethioate and the aldehyde in the presence of the chiral diamine–$Sn(OTf)_2$ complex to exclusively provide the desired α,β,γ-trisubstituted thioester. The resulting chiral thioester was converted to the precursor of the bicyclic product, and the computer-assisted predictive intramolecular Diels–Alder (IMDA) reaction of **23** was stereoselectively carried out using $Et_2AlCl$ as a Lewis acid activator to form the desired octahydronaphthalene, which was further transformed into the final target AMF-26.

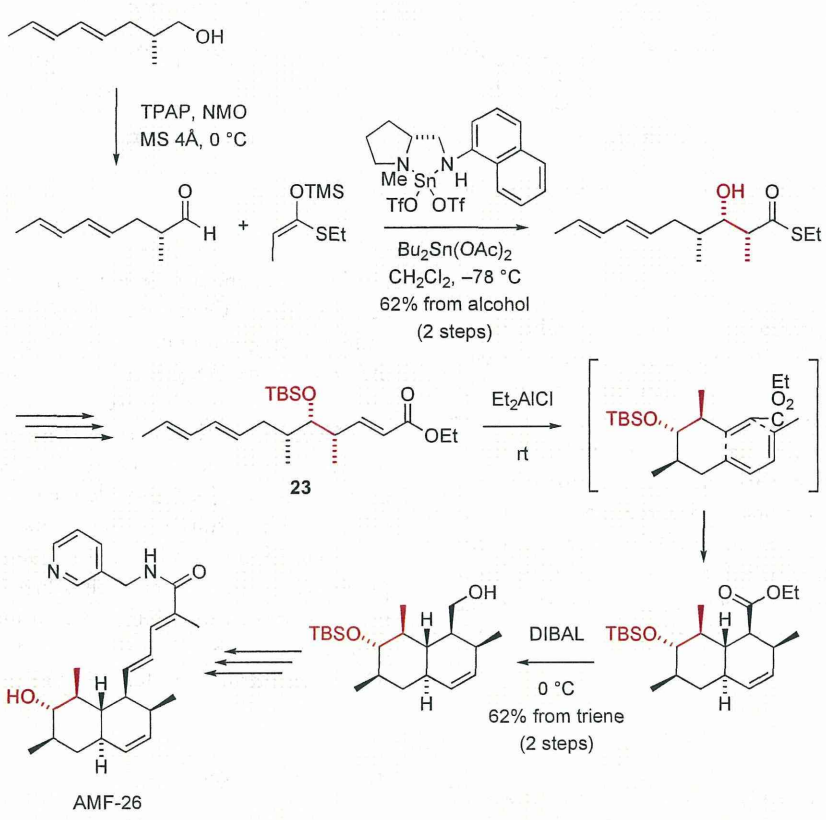
## 4. Conclusions

In this review, various aldol reactions mediated by stannous metallic species were presented along with their application

 *Chem. Rec.* **2014**, *14*, 144–183 




**Scheme 63.** Formal synthesis of lactimidomycin.




**Scheme 64.** Total synthesis of AMF-26.

to the synthesis of complicated molecules with multiple stereogenic centers. The enantioselective Mukaiyama aldol reaction promoted by the chiral diamine–$Sn(OTf)_2$ complex is now utilized as a general and powerful method for the construction of not only optically active small molecules but also highly functionalized compounds. Thus, the progress achieved with respect to the scope and selectivity of these aldol reactions using tin reagents has immensely contributed to the synthesis of many useful substrates over the last decade. This fruitful history may also render great service to the further development of organic and organometallic chemistry in the future.

## Acknowledgements

The author expresses his hearty thanks for the valuable efforts of former and current colleagues who contributed to the research on asymmetric Mukaiyama aldol reactions. Our investigations in this area were partly supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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