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Total syntheses of sesquiterpenes from *Illicium* species

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Contents

1. Introduction

Illicium is a genus of flowering plants, evergreen shrubs and trees, and is distributed in eastern North America, Mexico, the West Indies, and eastern Asia. The fruits of the *Illicium* species are distinctive star-shaped follicles with characteristic flavors. In fact, the dried fruits of *Illicium verum* Hook, Chinese star anise, have been widely used as spices for Chinese and Asian cooking through the ages. On the other hand, the fruits of *Illicium anisatum*, Japanese star anise, are known to contain toxic compounds.

In 1952, the convulsant toxic principal component of *I. anisatum*, named anisatin (**1**, Fig. 1), was isolated by Lane,[1] and its complete structure was elucidated in 1968 by Yamada and Hirata as an unprecedented sesquiterpenoid.[2] Anisatin is regarded as one of the most potent neurotoxins of plant origin [LD_{50}=1 mg/kg (mice)]. Neuropharmacological studies have shown **1** to be a potent non-competitive GABA antagonist.[3]

Since the isolation of **1**, constituents of the *Illicium* species have been subjected to intense chemical investigation, resulting in structural determination of a number of biologically active compounds (e.g., **2**–**8**, Fig. 1).[4] Fukuyama and co-workers[4] revealed that a number of these natural products (**3**, **6**, and **7**) had potent neurite outgrowth activity in primary cultured rat cortical neurons. Accordingly, these sesquiterpenes have attracted much attention from the perspective of developing small-molecule neurotrophic factors, which could be useful for development of lead compounds for the treatment of neurodegenerative diseases, such as Alzheimer's, Huntington's or Parkinson's disease.[5,6]

Many sesquiterpenoids from the genus *Illicium* possess various fused-ring structures (Fig. 1).[4,7] While anisatin (**1**),[2] majucin (**2**),[8] jiadifenin (**3**),[9] and (1*R*)-minwanenone (**4**)[10] share the same bicyclo[4.3.0]nonane carboskeleton, merrilactone A (**7**)[11] and anislactone A (**8**)[12] both have bicyclo[3.3.0]octane skeletons. In addition, tashironin (**5**)[13] and 11-*O*-debenzoyltashironin (**6**)[13] have a unique 2-oxatricyclo[4.3.1.$0^{4,9}$]heptane framework. Despite this structural diversity,

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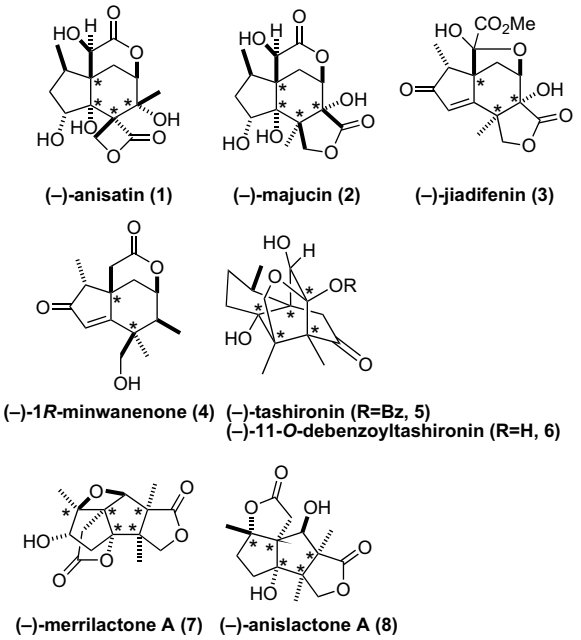


Figure 1. Representative sesquiterpenes from *Illicium* species. Tetrasubstituted carbons are marked with asterisks.

compounds **1**–**8** are considered to be biosynthetically related.[4,7,14] As shown in Scheme 1, Fukuyama proposed that compound **E**, which originates from **A** through **B**, **C**, and **D**, is a common intermediate. Compound **E**, which matches the structure of **5**, undergoes cleavage of bond *a* to provide **1**, **2**, **3** or **4** through **F**. On the other hand, the cleavage of bond *b* of **E** leads to a skeleton corresponding to **H** through **G**, resulting in biosynthetic generation of **7** and **8**.

These complex molecular architectures and significant biological activities have strongly motivated synthetic chemists to devote their efforts to the total syntheses of this class of natural products. From a synthetic viewpoint, stereoselective introduction of multiple tetrasubstituted carbons [marked with asterisks (*) in Fig 1] within highly functionalized matrices is the greatest challenge for efficient construction of the target molecules.[15] This review describes the reported total syntheses of sesquiterpenes from the *Illicium* species with particular focus on the methodologies for introduction of tetrasubstituted carbons. The reactions employed for the introduction of these carbons and the resulting stereocenters are indicated with bold-faced text below the arrow, and the carbon number within the structure, respectively, throughout the manuscript. The total number of steps in the synthesis is counted from commercially available materials.

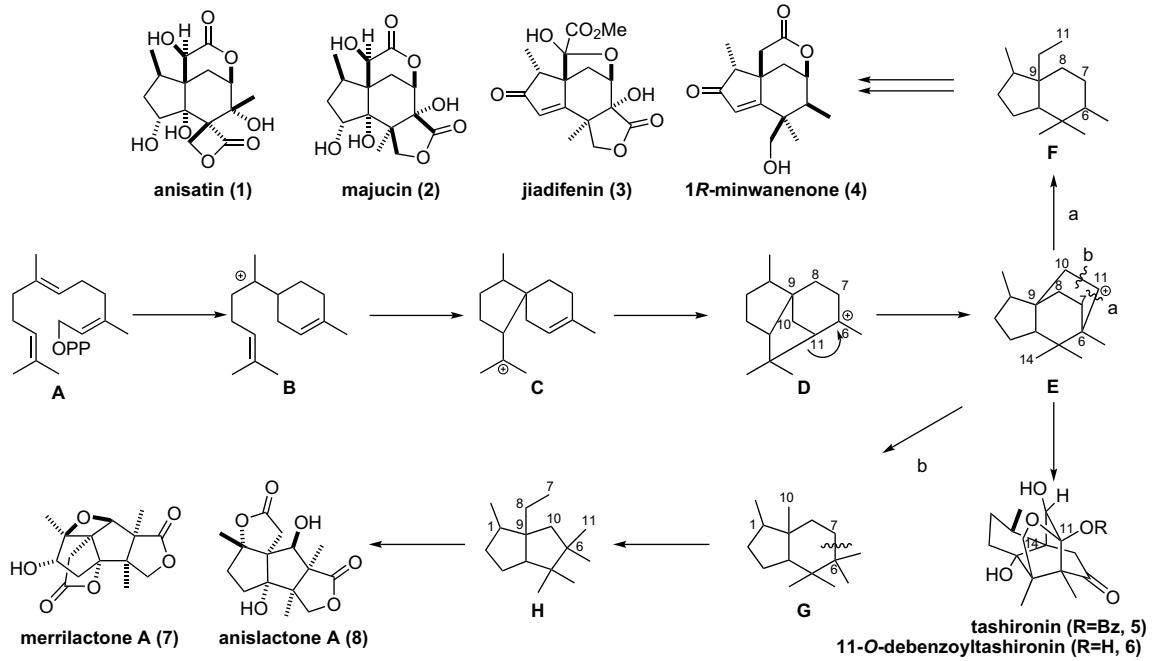
2. Synthetic studies of anisatin and its analogues

The highly oxygenated cage architecture of anisatin (**1**, Fig. 1) contains an α-hydroxy-δ-lactone, a spiro β-lactone and four contiguous tetrasubstituted carbons.[16] Synthetic studies of **1** were first reported by the Woodward group in 1982, featuring an ene reaction for construction of the α-hydroxy-δ-lactone.[17,18] We discuss here the synthesis of (±)-8-deoxyanisatin (**9**) by Kende,[19] the total syntheses of (−)-anisatin (**1**)[20] and (−)-neoanisatin (**58**; see Scheme 9)[21] by Yamada, and the formal total synthesis of (±)-8-deoxyanisatin (**9**) by Loh.[22]

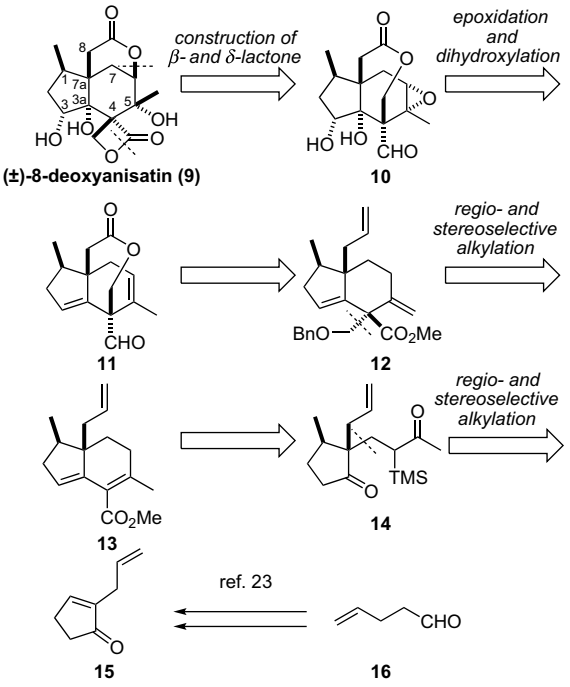
2.1. Kende's synthesis of (±)-8-deoxyanisatin (1985)

In 1985, the Kende group reported the synthesis of (±)-8-deoxyanisatin (**9**), an analogue of **1**. As shown in Scheme 2, their synthesis was divided into two stages, assembly of the carbon skeleton (**16**→**12**) and subsequent adjustments of oxidation states and functional-group patterns (**12**→**9**). Specifically, constructions of the spiro β-lactone and the δ-lactone were planned in the final stage of the synthesis (**10**→**9**). Oxidation from the less hindered side of ϵ-lactone **11** was envisioned to introduce the tetrasubstituted carbons at C3a and C5. Two intramolecular aldol reactions (**14**→**13** and **16**→**15**) were designed to build the fused-ring framework of 8-deoxyanisatin (**9**), and two alkylations (**13**→**12** and **15**→**14**) were planned to install the quaternary carbons at C4 and C7a.

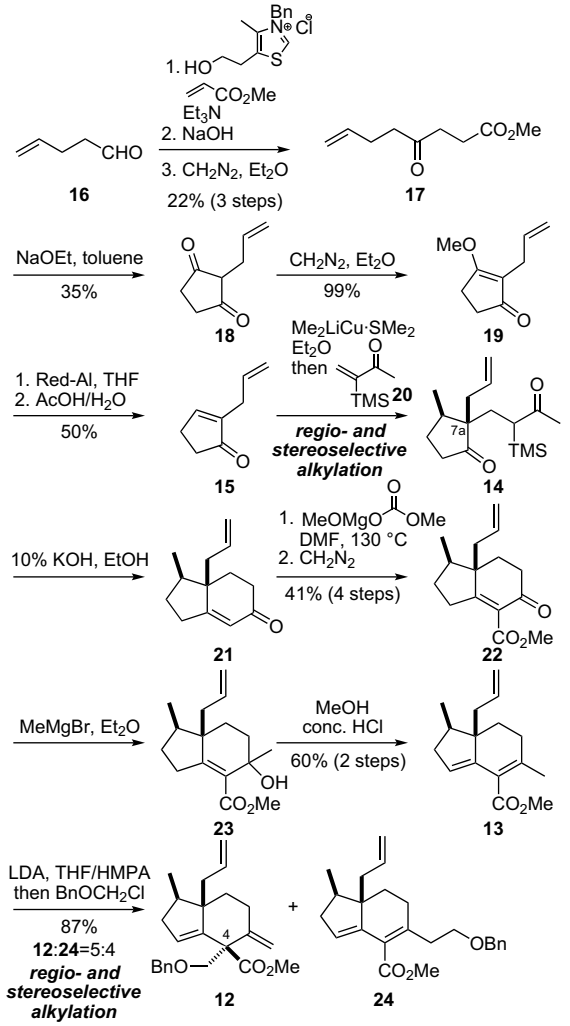
The construction of the carboskeleton is illustrated in Scheme 3. 2-Allyl-2-cyclopentenone **15** was prepared from **16** in the seven known steps.[23] The Stetter reaction of **16** with methyl acrylate provided **17**. Hydrolysis of the methyl ester and re-methylation was necessary for isolation of pure **17** from the self-condensation by-product in the first reaction. The base-induced intramolecular cyclization of **17**, and subsequent methylation (**18**→**19**), reduction,



Scheme 1. Proposed biosynthetic pathway of sesquiterpenes from *Illicium* species.[4,7,14]



Scheme 2. Synthetic plan of (±)-8-deoxyanisatin (**9**) (Kende, 1985).

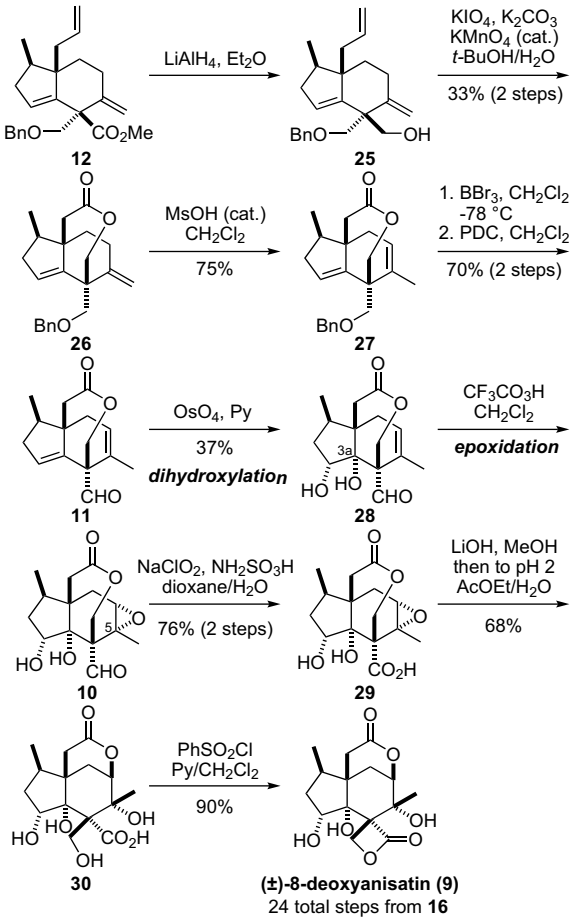


Scheme 3. Construction of carboskeleton containing two quaternary carbons at C4 and 7a (Kende, 1985).

and hydrolysis led to **15**. The conjugate addition of Me_2LiCu to α,β-unsaturated ketone **15**, followed by trapping of the resulting enolate with 2-(trimethylsilyl)-1-butene-3-one (**20**), was performed stereoselectively to introduce the C7a-tetrasubstituted carbon of **14**. Subsequent aldol cyclization of diketone **14** under basic conditions generated **21**,[24] which was subjected to carbonylation and methylation to provide methyl ester **22**. The substrate for the second regio- and stereoselective alkylation (**13**) was prepared by chemoselective addition of MeMgBr to the keto ester **22** and subsequent dehydration from **23**. Introduction of the C4-quaternary carbon was carried out by alkylation of **13** using BOMCl in the presence of LDA to afford a 5:4 ratio of the desired α-alkylated **12** and γ-alkylated **24**.

The synthesis of (±)-8-deoxyanisatin (**9**) from **12** was achieved through a series of functional-group transformations (Scheme 4). Compound **12** was reduced to carbinol **25**, the allyl group of which was oxidatively cleaved to give ϵ-lactone **26**.[25] Brønsted-acid-promoted isomerization of the *exo*-olefin of **26** into the *endo*-olefin produced **27**. Then, BBr_3-promoted debenzylation of **27** and PDC oxidation of the resulting alcohol afforded aldehyde **11**. The stereoselective dihydroxylation of **11** and the epoxidation of the resulting **28** both proceeded from the opposite side of the bridged lactone of **11** to give epoxy diol **10**, establishing all the tetrasubstituted carbons of the target molecule **9**.

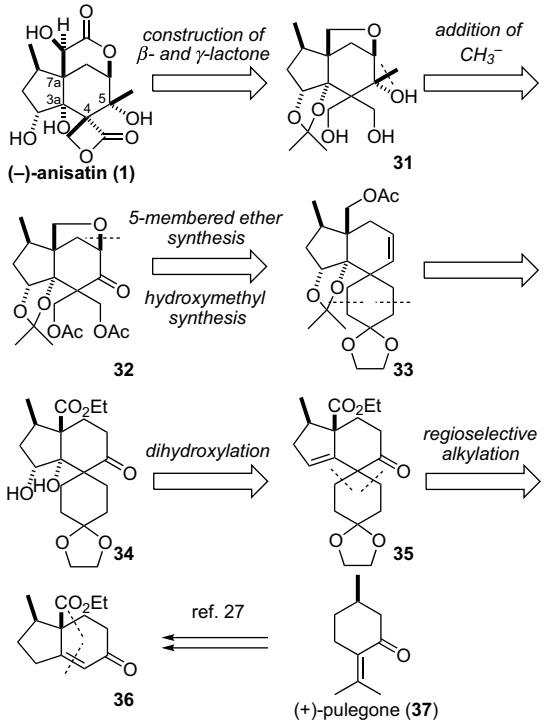
It remained to construct the β- and γ-lactones. Oxidization of aldehyde **10** using $NaClO_2$ generated carboxylic acid **29**.[26] Treatment of **29** with LiOH in MeOH followed by acidification gave the desired γ-lactone **30** directly via the epoxide-opening reaction. Finally, formation of the spiro β-lactone from **30** was realized in the presence of $PhSO_2Cl$, completing the synthesis of (±)-8-deoxyanisatin (**9**, 24 total steps from **16**).



Scheme 4. Synthesis of (±)-8-deoxyanisatin (**9**) (Kende, 1985).

2.2. Yamada's syntheses of (−)-anisatin and (−)-neoanisatin (1990, 1991)

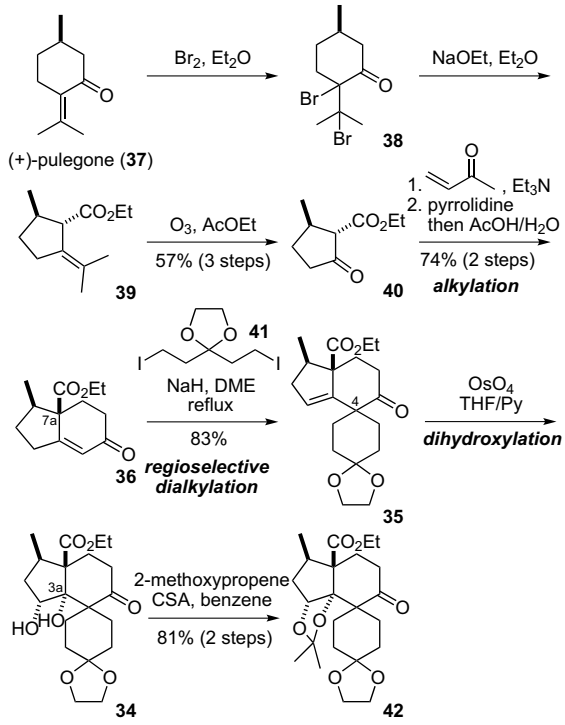
The Yamada group reported the first total syntheses of (−)-anisatin (**1**) and (−)-neoanisatin (**58**; see Scheme 9) in 1991. Their synthetic plan is illustrated in Scheme 5. Their strategy prepared the spiro β-lactone and the α-hydroxy-γ-lactone of **1** from **31** in the last stage of the synthesis. The five-membered ether and the two hydroxymethyl groups were to be constructed from **33**, prior to introduction of the methyl group at C5 of **32**. Dihydroxylation of the trisubstituted olefin of **35** would deliver *cis*-diol **34** while introducing the C3a-tetrasubstituted carbon. The protected cyclohexanone moiety of **35** was used as the synthetic equivalent of two hydroxylmethyl groups of **32**. Regioselective alkylation of the known enone **36**[27] was envisioned to establish the C4-quaternary carbon of **35**.



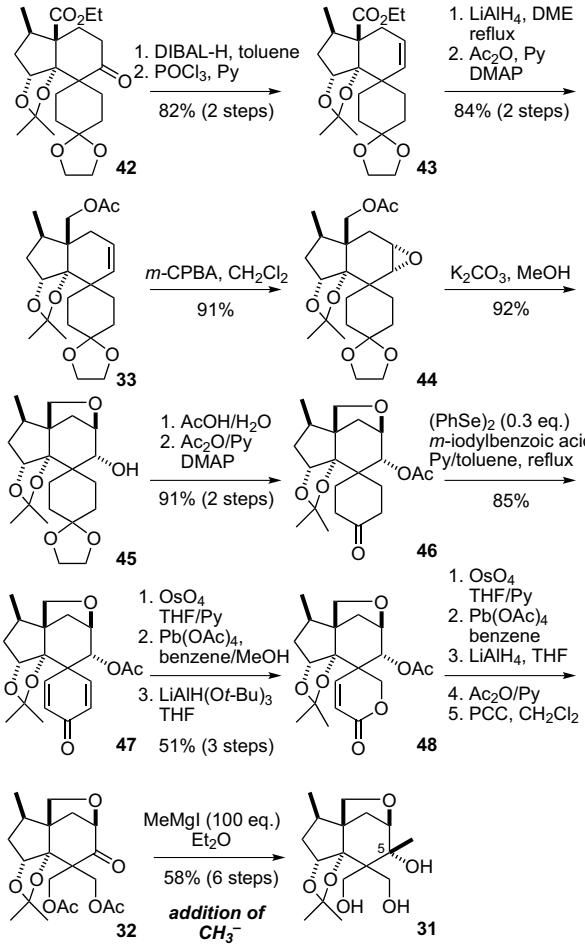
Scheme 5. Synthetic plan of (−)-anisatin (**1**) (Yamada, 1991).

The initial phase of Yamada's synthesis focused on construction of the hydrindane skeleton **34**, having three of the four contiguous tetrasubstituted carbons at C3a, C4, and C7a (Scheme 6). The synthesis started with bromination of (+)-pulegone (**37**), followed by Favorskii rearrangement (**38**→**39**) and ozonolysis to afford ketone **40**. Stereoselective Robinson annulation of **40** using methyl vinyl ketone resulted in enone **36** with the C7a-quaternary carbon.[27] The spiral cyclohexane was then attached to **36** by regioselective reaction with diiodide **41**, establishing the C4-quaternary carbon of **35**. Subsequent stereoselective dihydroxylation of the trisubstituted olefin of **35** afforded diol **34** with the C3a-tetrasubstituted carbon. The resulting diol **34** was protected as the acetal to give **42**.

Next, the five-membered ether and the bis-hydroxymethyl moiety from **42** were constructed (Scheme 7). Reduction of ketone **42** and subsequent dehydration provided olefin **43**. Ester **43** was sequentially subjected to $LiAlH_4$ reduction and acetylation to afford **33**. Stereoselective epoxidation of **33** with *m*-CPBA provided α-epoxide **44**, which was treated under basic conditions to induce epoxide opening, resulting in five-membered ether **45**. Two manipulations from **45** led to ketone **46**, which was



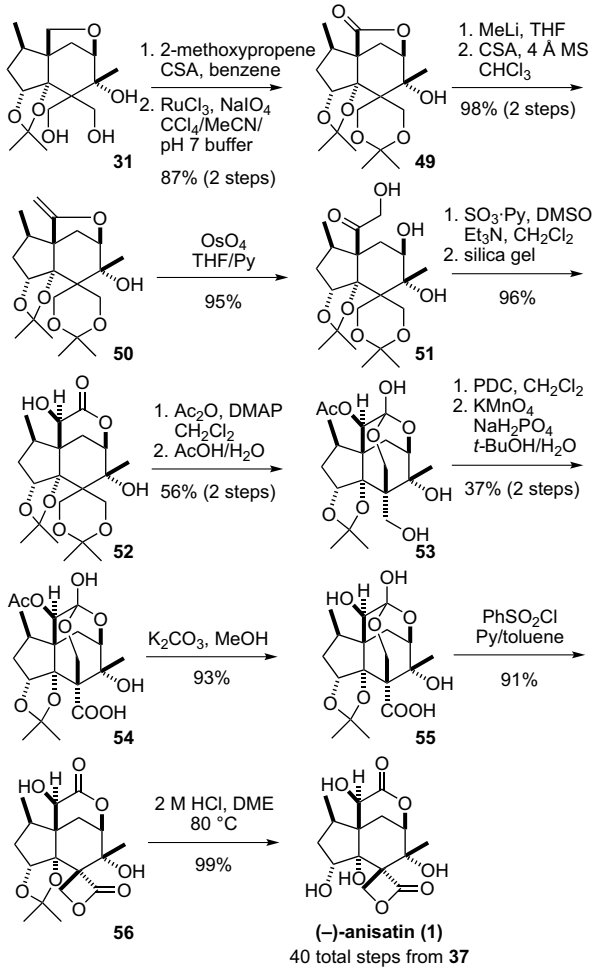
Scheme 6. Construction of carboskeleton containing three tetrasubstituted carbons at C3a, C4, and C7a (Yamada, 1991).



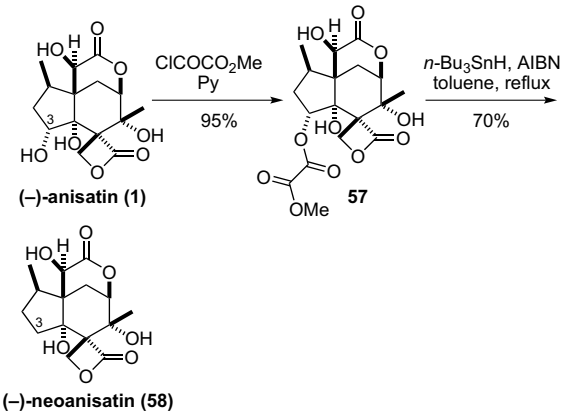
Scheme 7. Construction of 5-membered ether and bis-hydroxymethyl moieties (Yamada, 1991).

oxidized to dienone **47** using the Barton method.[28] Compound **47** was further transformed into α,β-unsaturated lactone **48** through a three-step sequence: OsO_4-mediated dihydroxylation, oxidative cleavage of the resulting diol with $Pb(OAc)_4$, and reduction of the resulting aldehyde with $LiAlH(Ot\text{-}Bu)_3$. After **48** was subjected to a similar three-step sequence, selective acetylation of the resultant primary hydroxy groups and oxidation of the secondary alcohol provided **32**. Treatment of **32** with MeMgI furnished triol **31**, establishing all the tetrasubstituted carbons of anisatin (**1**).

The total synthesis was achieved through construction of the spiro β-lactone and the α-hydroxy-δ-lactone (Scheme 8). After the two primary hydroxy groups of **31** were protected as the acetonide, the five-membered ether was oxidized using RuO_4 to afford γ-lactone **49**.[29] Methylenation of the carbonyl group of **49** by addition of MeLi and dehydration provided enol ether **50**, oxidation of which with OsO_4 generated α-hydroxy ketone **51**. Further oxidation of **51** using $SO_3\cdot Py$ resulted in α-hydroxy lactone **52** after smooth isomerization on silica gel. Acetylation of **52** and selective hydrolysis of the six-membered acetonide afforded orthoester **53**. Two-step oxidation of the primary alcohol[30] of **53** to the carboxylic acid (**53**→**54**) was followed by methanolysis to furnish carboxylic acid **55**. Treatment of **55** with $PhSO_2Cl$ led to the formation of a spiro β-lactone to yield **56**.[31] Finally, deprotection of the acetonide with aqueous HCl gave rise to (−)-anisatin (**1**). Overall, the Yamada group accomplished the first total synthesis of **1** in 40 steps from (+)-pulegone (**37**).



Scheme 8. Total synthesis of (−)-anisatin (**1**) (Yamada, 1991).

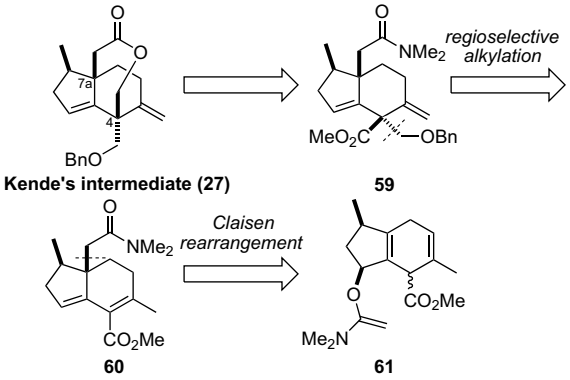


Scheme 9. Total synthesis of (−)-neoanisatin (**58**) (Yamada, 1991).

(−)-Neoanisatin (**58**), 3-deoxyanisatin, was also synthesized from (−)-anisatin (**1**) by removal of the C3-hydroxy group by a two-step procedure: formation of methyl oxalate **57** from **1** and treatment of the resulting oxalate using *n*-Bu_3SnH in the presence of AIBN (Scheme 9).

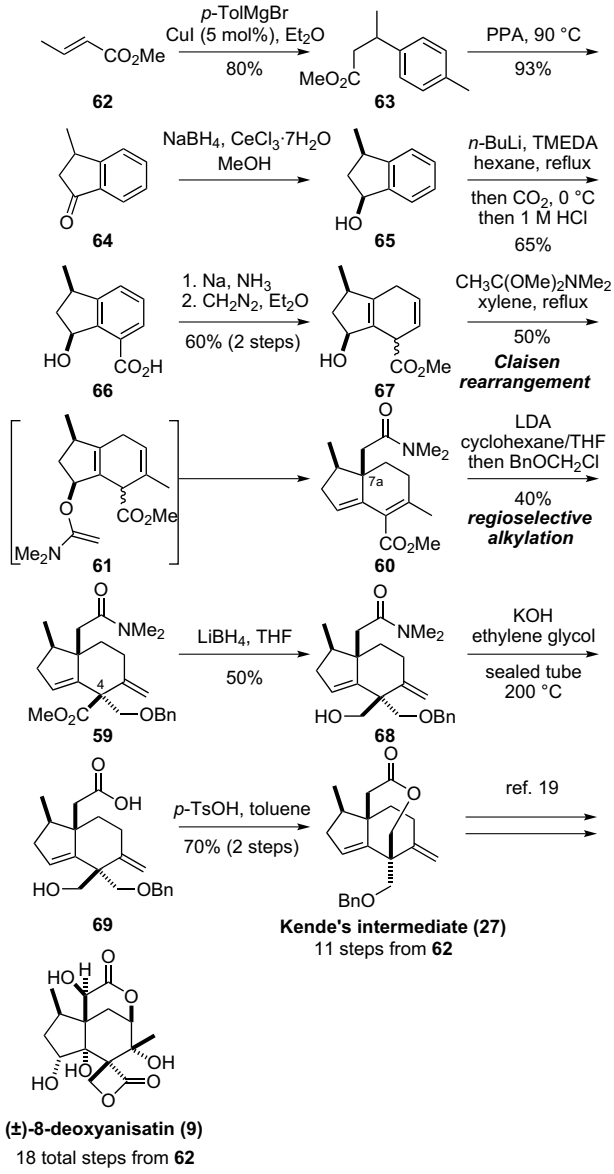
2.3. Loh's formal synthesis of (±)-8-deoxyanisatin (2001)

The Loh group reported a formal total synthesis of (±)-8-deoxyanisatin (**9**) by synthesizing Kende's intermediate **27** (Scheme 10). The C4-quaternary carbon was envisioned to be constructed using Kende's alkylation method (**60**→**59**). The key step of their synthesis was the [3,3]-Claisen rearrangement from **61** to establish the C7a-quaternary center.



Scheme 10. Synthetic plan for formal total synthesis of (±)-8-deoxyanisatin (**9**) (Loh 2001).

The formal total synthesis of (±)-8-deoxyanisatin (**9**) is illustrated in Scheme 11. Michael addition of *o*-TolMgBr to methyl crotonate **62** in the presence of CuI afforded **63**, which was transformed into **64** through intramolecular Friedel–Crafts acylation.[32] Reduction of ketone **64** under Luche conditions[33] selectively provided *syn*-indanol **65**. Directed metallation[34] of the aromatic ring of **65** and subsequent CO_2 quench gave carboxylic acid **66**, Birch reduction of which afforded 1,4-diene **67** as a diastereomeric mixture. Eschenmoser–Claisen rearrangement[35] of **67** established the C7a-quaternary stereocenter, leading to amide **60**. Regioselective alkylation of α,β-unsaturated ester **60** provided α-alkylated compound **59**. A formal total synthesis of **9** was then achieved by reduction of the methyl ester (**59**→**68**), hydrolysis of the dimethyl amide (**68**→**69**), and lactone formation (**69**→**27**). Overall, the synthesis of **27** from **62** was achieved in 11 steps, while Kende employed 16 total steps for the synthesis of **27** from **16**.



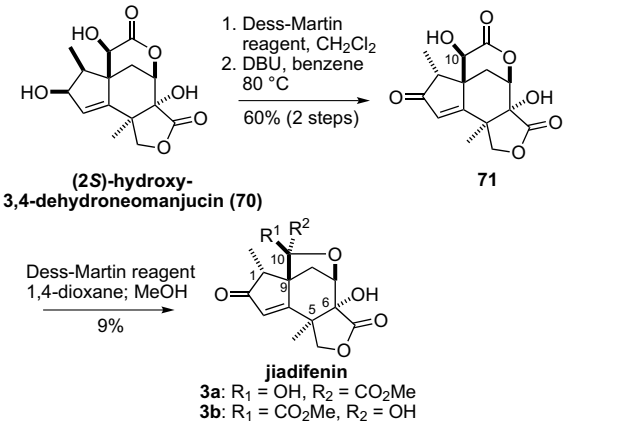
Scheme 11. Loh's formal total synthesis of (±)-8-deoxyanisatin (**9**) (2001).

3. Total synthesis of jiadifenin (2004)

Jiadifenin (**3ab**), an equilibrated mixture of compounds **3a** and **3b**, was isolated from *Illicium jiadifengpi* by Fukuyama in 2002.[9] Jiadifenin (**3ab**) contains a γ-lactone and three tetrasubstituted carbons at C5, C6, and C9. Fukuyama and co-workers demonstrated that jiadifenin (**3ab**) promoted neurite outgrowth in the primary cultures of rat cortical neurons at concentrations as low as 0.1 μM. Therefore, **3ab** is classified as a small-molecule neurotrophic factor.[9]

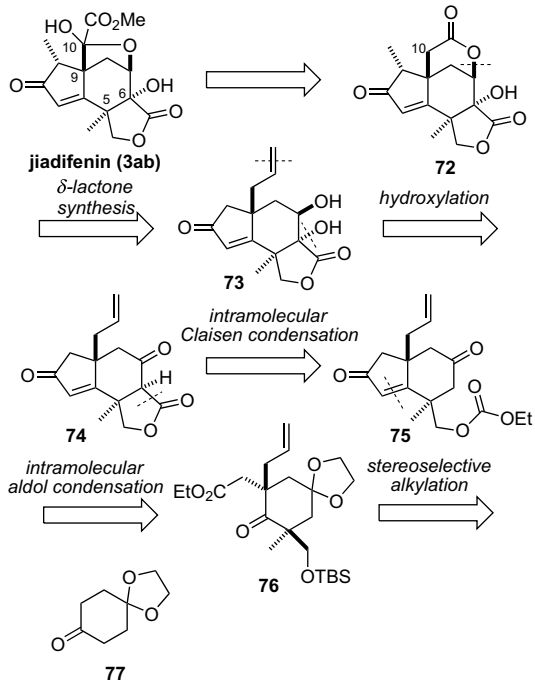
(2*S*)-Hydroxy-3,4-dehydroneomanjucin (**70**), isolated along with **3ab**, is regarded as a potential biosynthetic precursor of jiadifenin (Scheme 12). Indeed, Fukuyama and co-workers demonstrated chemical conversion of **70** into **3ab** through **71** by three-step functional-group manipulations.[9]

In 2004, the Danishefsky group reported the total synthesis of (±)-jiadifenin (**3ab**) (Scheme 13).[36] In their synthesis, **72** was transformed into **3ab** by applying a reaction sequence similar to that shown in Scheme 12. The δ-lactone of **72** was, in turn, to be synthesized from **73** through the oxidative cleavage of the vinyl group. The tertiary hydroxy group at C6 of **73** was expected to be introduced through hydroxylation of **74**. Intramolecular aldol condensation and intramolecular Claisen condensation would deliver

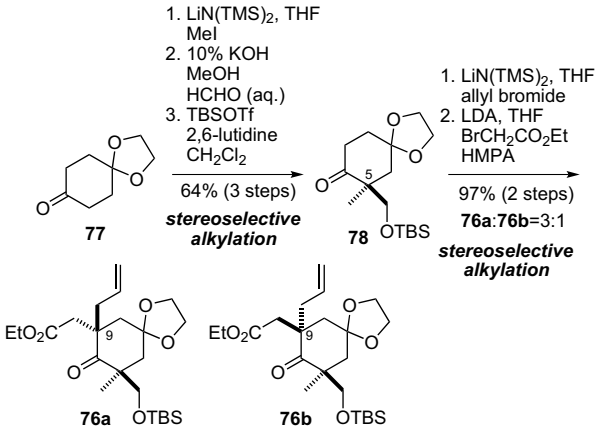


Scheme 12. Transformation of (2*S*)-hydroxy-3,4-dehydroneomanjucin (**70**) into jiadifenin (**3ab**) by Fukuyama.

the tricyclic skeleton **74** from **76** through **75**. Introduction of the two quaternary carbons at C5 and C9 of cyclohexanone **77** was envisioned to be constructed by stepwise stereoselective alkylations.



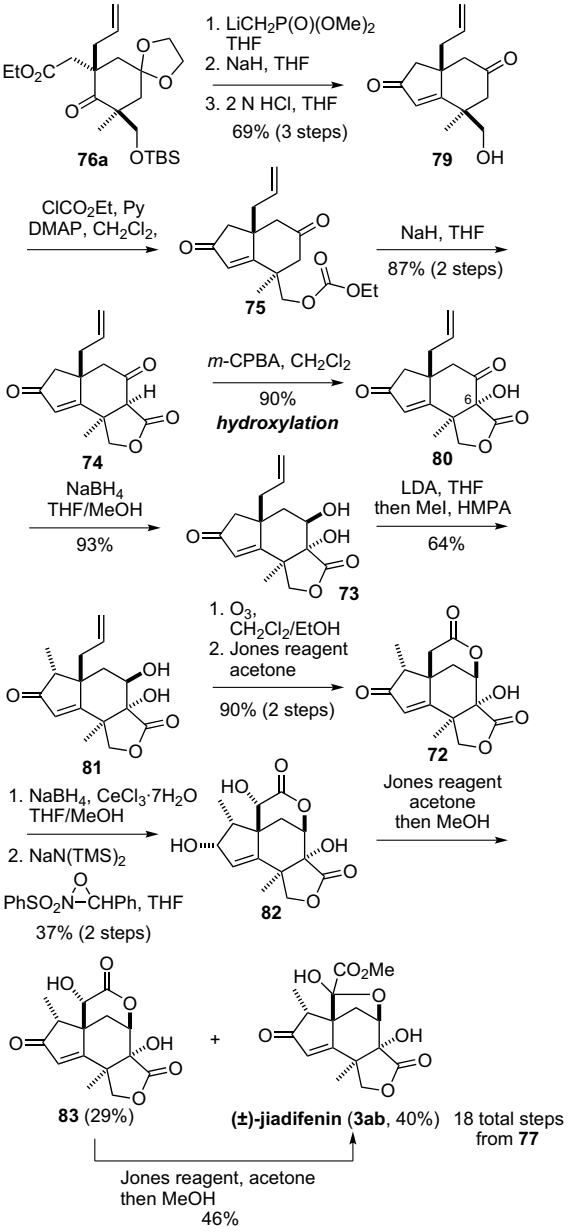
Scheme 13. Synthetic plan of (±)-jiadifenin (**3ab**) (Danishefsky, 2004).



Scheme 14. Stereoselective alkylation at C5 and C9 (Danishefsky, 2001).

Stereoselective introduction of C5- and C9-quaternary centers was realized by four alkylations (Scheme 14). Methylation of ketone **77**, followed by hydroxymethylation at C5 and protection of the resulting alcohol as the TBS ether, produced **78** in a racemic form. The C9-quaternary center was then introduced by stepwise alkylation of the lithium enolate, giving rise to a 3:1 mixture of **76a** and **76b** from **78**.

The total synthesis of **3ab** from **76a** is shown in Scheme 15. Conversion of the ester moiety of **76a** into a β-ketophosphonate, followed by intramolecular Horner–Wadsworth–Emmons reaction[37] and deprotection, led to cyclopentenone **79**. After attachment of the ethyl carbonate to the primary alcohol of **79**, intramolecular Claisen condensation of **75** was realized using NaH, leading to diketolactone **74**. The tertiary alcohol at C6 was then introduced by stereoselective *m*-CPBA oxidation of 1,3-dicarbonyl compound **74** to furnish **80** as a single isomer, setting all the tetrasubstituted carbons of **3ab**. The subsequent reduction of **80** proceeded stereoselectively to afford *trans*-diol **73**, which was methylated to generate **81**. Two manipulations of **81** produced lactone **72**. Reduction of the enone of **72** under Luche conditions[33] and introduction of the C10-hydroxyl group using a Davis oxaziridine gave rise to α-hydroxyl lactone **82**.[38] Finally, Jones oxidation of **82** delivered (±)-jiadifenin (**3ab**) and dehydroneomajucin **83**, and the latter was transformed into **3ab** under similar conditions (18 total steps from **77**).



Scheme 15. Total synthesis of (±)-jiadifenin (**3ab**) (Danishefsky, 2001).

To establish an SAR profile, the in vitro neurotrophic activity and stimulation of NGF-mediated neurite outgrowth activity of several synthetic analogues were evaluated. Importantly, non-natural products, **83** and normethyljiadifenin **84**, were found to exhibit strong neuritogenic activities (Fig. 2).

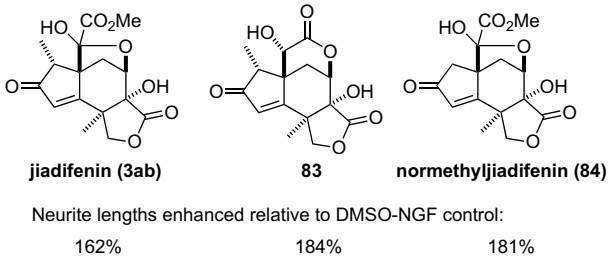
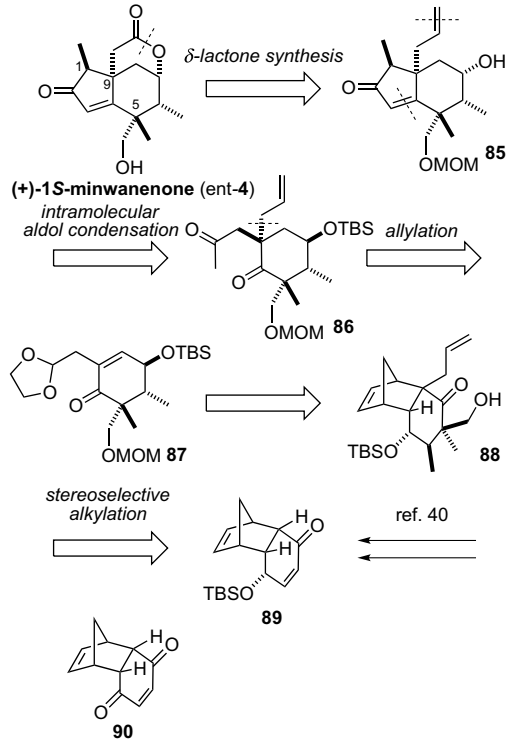


Figure 2. Biologically active compounds related to jiadifenin (**3ab**).

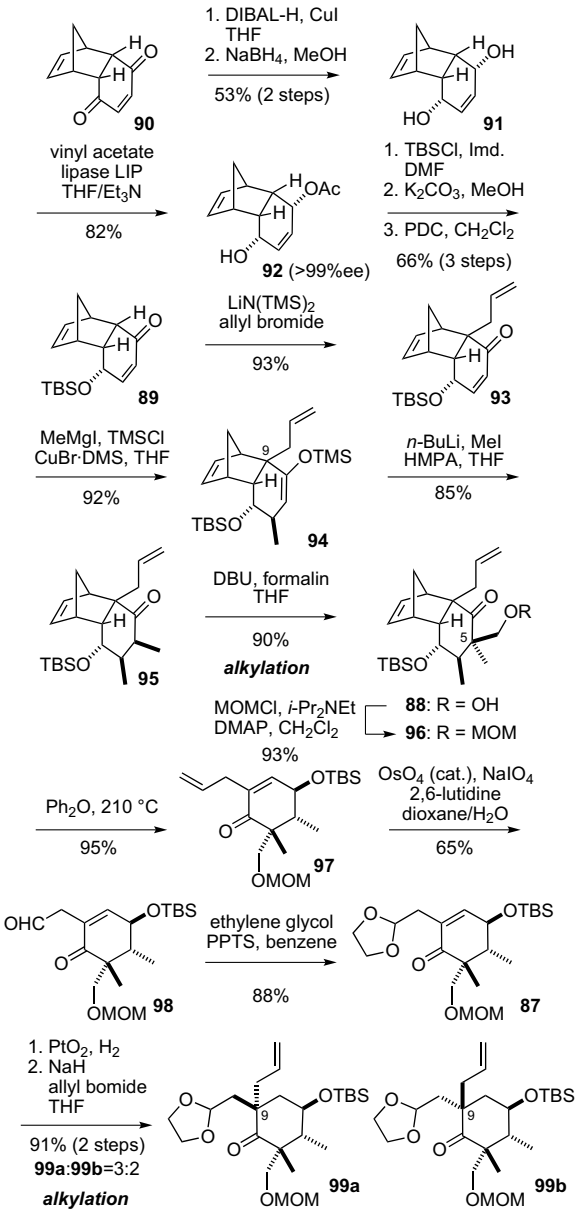
4. Total synthesis of (+)-1*S*-minwanenone (2007)

(−)-1*R*-Minwanenone (**4**) was isolated from *Illicium minwanense* by Fukuyama.[10] The notable structural features of **4** are the δ-lactone and the two quaternary carbons at C5 and C9. In 2007, the Mehta group reported the total synthesis of (+)-1*S*-minwanenone (*ent*-**4**), an enantiomer of the natural product.[39]

Their synthetic plan is shown in Scheme 16. The δ-lactone and the cyclopentenone moieties of the target *ent*-**4** were to be constructed via intramolecular aldol condensation (**86**→**85**) and lactonization (**85**→*ent*-**4**), respectively. While the C9-quaternary center of **86** would be introduced by allylation of **87**, construction of the C5-quaternary carbon was to be realized by stereoselective alkylation of (+)-**89**, which would be synthesized from achiral **90** by Ogasawara's method.[40]



Scheme 16. Synthetic plan of (+)-1*S*-minwanenone (*ent*-**4**) (Mehta, 2007).



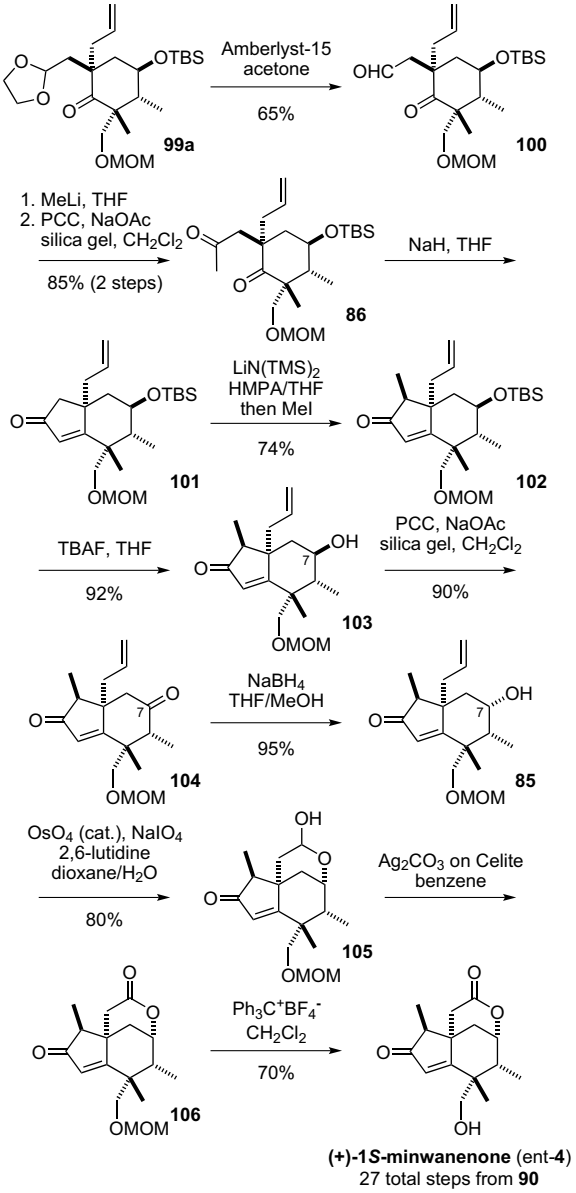
Scheme 17. Stereoselective alkylations for construction of the C5- and C9-quaternary centers (Mehta, 2007).

Ogasawara's chiral synthon **89** was prepared from **90** by applying six transformations (Scheme 17).[40] Diketone **90** was reduced to *meso*-diol **91**, which was subjected to kinetic resolution by the action of lipase LIP to generate **92** in optically pure form. Acetate **92** was then transformed into **89** in three steps: protection of the alcohol as its TBS ether, removal of the acetyl group, and oxidation. The intrinsic three-dimensional structure of **89** directed the series of stereoselective functionalizations from the convex face. Namely, allylation at C9 (**89**→**93**), copper-catalyzed 1,4-addition of MeMgI (**93**→**94**),[41] methylation of the resultant enolate (**94**→**95**), and α-hydroxymethylation of the ketone (**95**→**88**) proceeded in highly stereoselective manners to afford **88**, establishing the C5-quaternary carbon. Protection of the primary alcohol of **88** as the MOM ether delivered **96**, and then cyclopentadiene was removed via a retro-Diels–Alder reaction to provide the highly functionalized cyclohexenone **97**. Oxidative cleavage of the allyl group of **97** using OsO_4-$NaIO_4$ and subsequent protection of the resulting aldehyde **98** as the acetal produced **87**. After catalytic hydrogenation of olefin **87**, the C9-quaternary carbon was installed by allylation, giving rise to the diastereomers **99a** and **99b** in a 3:2 ratio. Despite the low stereoselectivity, both isomers were serviceable in the synthesis of the target molecule (**99** to **101**), because the allyl group could be used either as a carbocycle or as a side chain.

The total synthesis of (+)-1*S*-minwanenone (*ent*-**4**) from **99a** is illustrated in Scheme 18. Removal of the acetal of **99a** provided aldehyde **100**. Chemo- and regioselective addition of MeLi to **100**, followed by PCC oxidation, generated diketone **86**. Exposure of **86** to NaH in THF then effected the intramolecular aldol condensation to deliver bicyclic enone **101**. Stereoselective methylation of **101** and subsequent removal of the TBS group from **102** resulted in the formation of **103**. The stereochemistry of the C7-OH of **103** was inverted through an oxidation (**103**→**104**) and reduction (**104**→**85**). Oxidative cleavage of the allyl group of **85**, followed by Fetizon oxidation of lactol **105**,[42] gave rise to tricyclic lactone **106**. Finally, the MOM group of **106** was removed by the action of triphenylcarbenium tetrafluoroborate to provide (+)-1*S*-minwanenone (*ent*-**4**, 27 total steps from **90**).

5. Total synthesis of (±)-11-*O*-debenzoyltashironin (2006)

Tashironin (**5**) and 11-*O*-debenzoyltashironin (**6**) were both isolated from the pericaps of *Illicium merrillianum* by Fukuyama

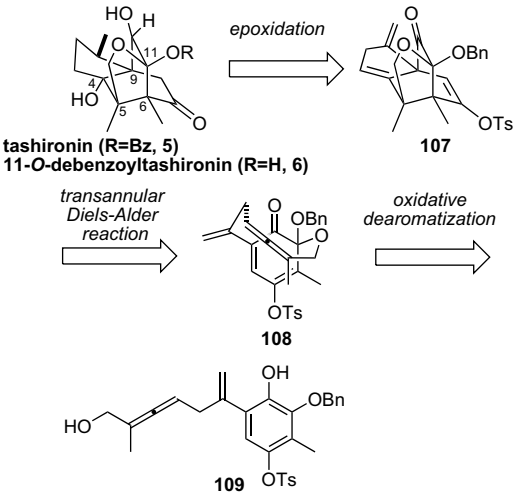


Scheme 18. Total synthesis of (+)-1*S*-minwanenone (*ent*-**4**) (Mehta, 2007).

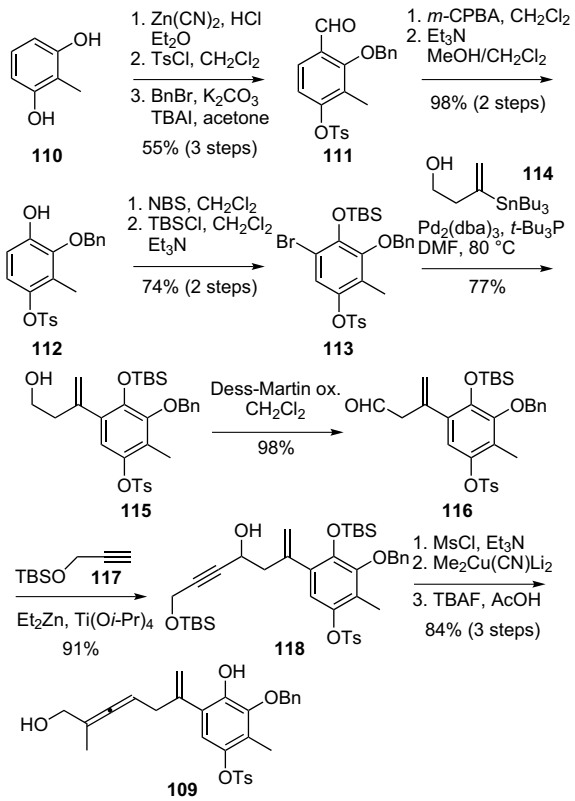
(Scheme 19).[13] Interestingly, 11-*O*-debenzoyltashironin (**6**) was found to induce neurite outgrowth in fetal rat cortical neurons at low concentrations (0.1 μM), although tashironin had no neurotrophic activity. [13] The structures of the tashironins are characterized by the highly substituted 2-oxatricyclo[4.3.1.0^{4,9}]heptane skeleton.

The Danishefsky group employed a biomimetic cascade strategy to establish the four tetrasubstituted carbons at C5, C6, C9 and C11 for the total synthesis of (±)-11-*O*-debenzoyltashironin (**6**) (Scheme 19).[43,44] Specifically, oxidative dearomatization of the allenic phenol **109**, followed by transannular Diels–Alder reaction, was planned to provide tetracyclic **107** through the intermediacy of bicyclic **108**.

The synthesis of **109** commenced with functionalization of 2-methylresorcinol (Scheme 20). Formylation of **110**[45] and stepwise



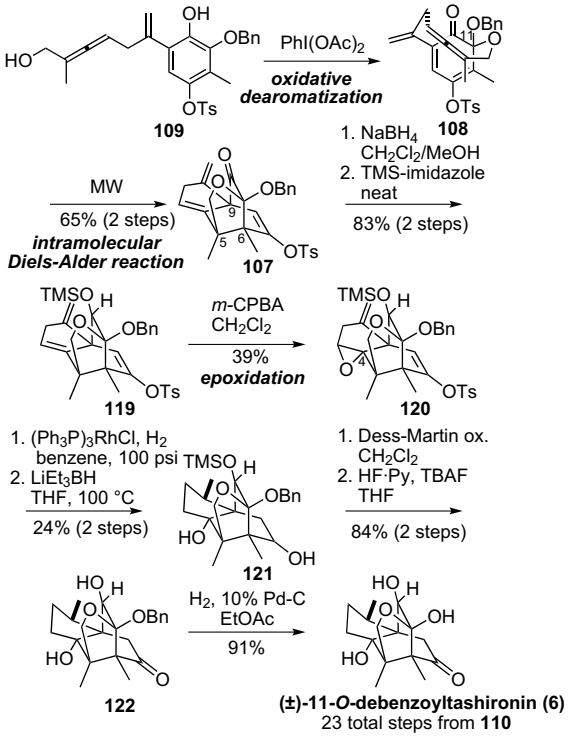
Scheme 19. Synthetic plan of (±)-11-*O*-debenzoyltashironin (**6**) (Danishefsky, 2006).



Scheme 20. Synthesis of substrate **109** for biomimetic cascade reaction (Danishefsky, 2006).

tosylation and benzylation of the phenolic alcohols provided **111**. Aldehyde **111** was subjected to Bayer-Villiger oxidation, and then hydrolysis of the resultant formate afforded phenol **112**. NBS-mediated *ortho*-bromination and subsequent attachment of the TBS group yielded bromide **113**. Stille reaction of **113** with vinylstannane **114**[46] under Fu's conditions (**113**→**115**)[47], was followed by Dess–Martin oxidation to provide aldehyde **116**. Addition of acetylene **117** to the sensitive β,γ-unsaturated aldehyde **116** was realized by employing Et_2Zn-$Ti(Oi\text{-}Pr)_4$, giving rise to the propargyl alcohol **118**.[48] Mesylation of alcohol **118** and subsequent S_N2' nucleophilic addition of $Me_2Cu(CN)_2Li_2$ produced the allene, desilylation of which delivered **109**, the substrate for the crucial biomimetic cascade reaction.

Exposure of **109** to diacetoxyiodobenzene generated the ten-membered ring **108** (Scheme 21), which underwent an intramolecular Diels–Alder reaction under microwave irradiation to give the adduct **107** as the only isolable compound.[49] Thus, the three fused rings and the four tetrasubstituted carbons at C5, C6, C9, and C11 were established in these two steps. The total synthesis was completed from **107** with eight more transformations. Stereoselective reduction of ketone **107** was followed by silylation using neat trimethylsilylimidazole[50] to afford **119**. The oxygen functionality at the C4 position was introduced by stereoselective epoxidation of the trisubstituted olefin of **119** to provide **120**. Hydrogenation of *exo*-olefin **120** in the presence of a Wilkinson catalyst[51] and subsequent $LiEt_3BH$-promoted reduction gave rise to **121**. The latter reductive conditions not only converted the epoxide into the tertiary alcohol, but also the tosyl enol ether into the secondary alcohol. Finally, Dess–Martin oxidation and desilylation from **121**, followed by removal of the Bn group of **122**, yielded (±)-11-*O*-debenzoyltashironin (**6**, 23 total steps from **110**).



Scheme 21. Total synthesis of (±)-11-*O*-debenzoyltashironin (**6**) (Danishefsky, 2006).

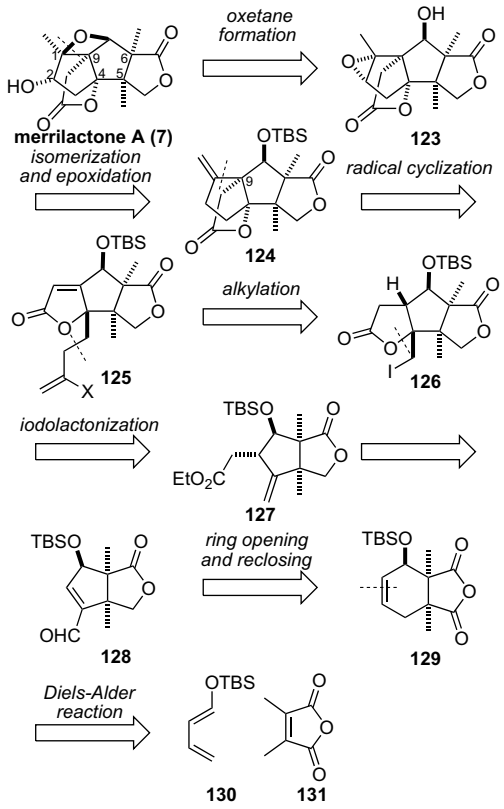
6. Total syntheses of merrilactone A

Merrilactone A (**7**), isolated from *I. merrillianum* by Fukuyama in 2000,[11] is a novel neurotrophic sesquiterpene bis-lactone. Preliminary studies have shown that **7** strongly promotes neurite outgrowth in fetal rat cortical neurons at concentrations of

0.1–10 μM. Accordingly, merrilactone A (**7**) has been regarded as a promising lead compound for small-molecule neurotrophic substances. Structurally, compound **7** has a highly fused compact architecture with seven chiral centers, five of which are contiguous tetrasubstituted carbons. Total syntheses of this intriguing molecule were accomplished by the Danishefsky,[52] Inoue,[53] Mehta,[54] and Frontier groups.[55]

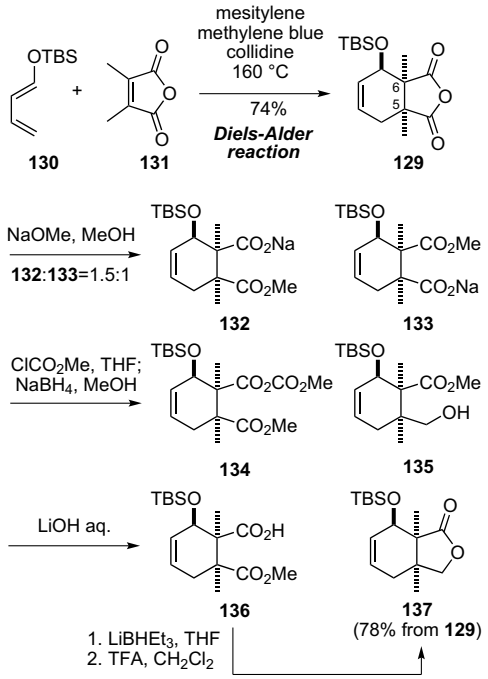
6.1. Danishefsky's synthesis (2002, 2005)

The Danishefsky group reported the first total synthesis of (±)-merrilactone A (**7**) in 2002.[52] Their synthetic plan is outlined in Scheme 22. Oxetane formation was to be performed as the last reaction from epoxy alcohol **123**. The C1-oxygen functionality of **123** would be introduced by epoxidation after isomerization of olefin **124**, and the C9-quaternary center would be installed through the radical cyclization of **125**. Compound **125** was in turn envisioned to be obtained via carbon-chain extension from **126**, which could arise by iodolactonization from **127**. The cyclopentene moiety of **128**, which would be derivatized into **127**, was to be constructed from six-membered ring **129**. Diels–Alder reaction of **130** and **131** was planned to establish the contiguous quaternary stereocenters at C5 and C6 of **129**.



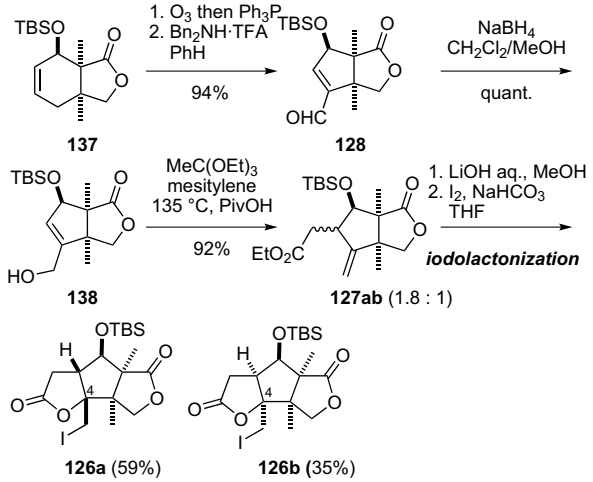
Scheme 22. Synthetic plan of (±)-merrilactone A (**7**) (Danishefsky, 2002).

The synthesis began with a Diels–Alder reaction between 2,3-dimethylmaleic anhydride **131** and **130** to afford adduct **129**, establishing the C5- and C6-quaternary carbons with a cis-relationship (Scheme 23). Compound **129** was subsequently converted into lactone **137** over several steps. Methoxide addition to **129** gave a 1.5:1 mixture of **132** and **133**. Treatment of the mixture with $ClCO_2Me$ was followed by reduction with $NaBH_4$ in MeOH to generate reduced **135** and unchanged **134**.[56] Subsequent addition of lithium hydroxide to the mixture afforded the desired lactone **137** and carboxylic acid **136**, and the latter was further treated with $LiBHEt_3$ to afford the same lactone **137**.



Scheme 23. Introduction of the contiguous quaternary carbons at C5 and C6 by Diels–Alder reaction (Danishefsky, 2002).

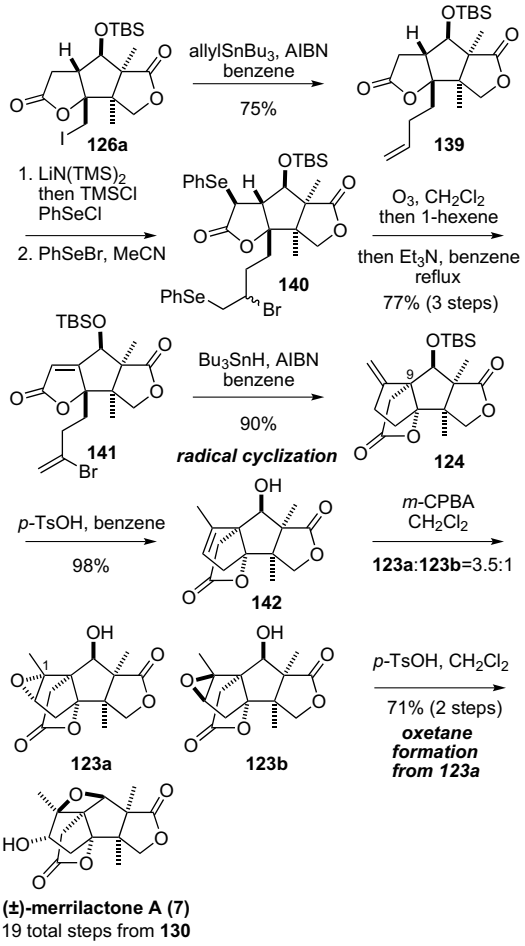
Ozonolysis of **137**, followed by treatment with triphenylphosphine, led to the bis-aldehyde, aldol condensation of which under Corey's conditions afforded the five-membered ring in **128** (Scheme 24).[57] Next, reduction of the α,β-unsaturated aldehyde **128** gave allylic alcohol **138**. Johnson-Claisen rearrangement of the orthoester, generated from **138**, resulted in formation of diastereomixture **127ab**.[58] After hydrolysis of ester **127ab**, the γ-lactone was formed by the action of iodine, giving rise to **126a** with the desired C4-tetrasubstituted stereocenter, along with **126b**.



Scheme 24. Synthesis of the cyclopentane and γ-lactone moieties (Danishefsky, 2002).

Chain extension of isomer **126a** was accomplished by the Keck C-allylation method to give **139** (Scheme 25).[59] Selenylation at C10 from lactone **139** was followed by bromoselenylation of the terminal vinyl group,[60] resulting in the bis-selenide **140**. Next, oxidation-induced *syn*-elimination of **140** afforded bis-olefin **141**. The crucial radical cyclization of vinyl bromide **141** delivered the desired compound **124**, establishing the C9-quaternary center. Isomerization of *exo*-olefin **124** into *endo*-olefin **142**, followed by

stereoselective epoxidation, gave a diastereomeric mixture of **123a** and **123b** in a 3.5:1 ratio. Finally, H^+-induced oxetane formation from the major isomer led to (±)-merrilactone A (**7**, 18 total steps from **131**).

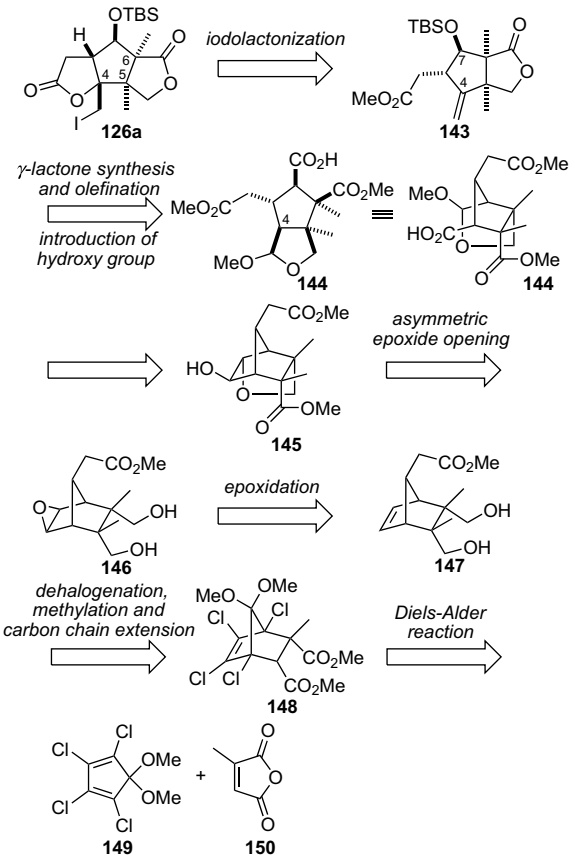


Scheme 25. Total synthesis of (±)-merrilactone A (**7**) (Danishefsky, 2002).

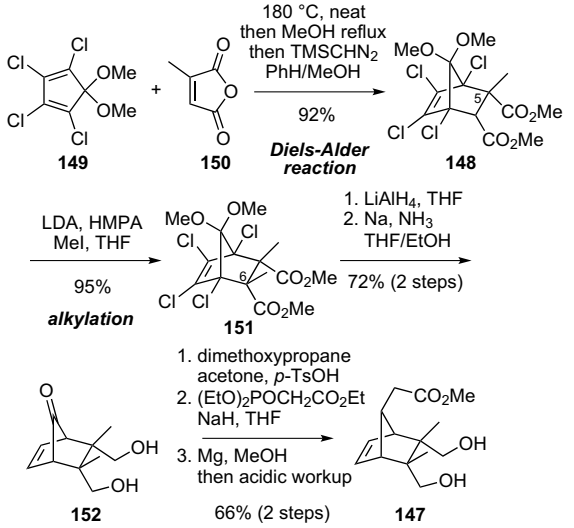
Danishefsky's second approach was designed to synthesize their advanced intermediate **126a** in enantiomerically pure form through asymmetric epoxide opening of *meso*-diol **146** (Scheme 26). Specifically, **126a** would arise via formation of the C7-alcohol, δ-lactone and C4-*exo*-olefin from **144** through **143**. Compound **144** was, in turn, to be synthesized from the tricyclic intermediate **145**. The key step was envisioned to produce enantiopure **145** from *meso*-diol **146** by employing Jacobsen's catalyst.[61] Retrosynthetic removal of the epoxide gave olefin **147**, which would be prepared from **148**, the Diels–Alder product of **149** with **150**.

The reaction between **149** and **150** provided the *endo*-adduct and installed the C5-quaternary center (Scheme 27).[62] Subsequently, methanolysis of the anhydride and methylation of the resulting acid led to **148**. Construction of the C6-quaternary carbon was realized by stereoselective methylation of **148**,[63] affording *meso*-**151**. Next, stepwise $LiAlH_4$ and Birch reduction of **151** yielded ketone **152**. After protection of diol **152** as the acetonide, Horner–Emmons olefination, Mg-promoted 1,4-reduction and removal of the acetonide delivered *meso*-diol **147**.

The asymmetric total synthesis of merrilactone A (**7**) was realized by employing an enantioselective epoxide-opening reaction (Scheme 28). DMDO epoxidation of olefin **147** resulted in the formation of *meso*-**146**. Exposure of epoxide **146** to Jacobsen's catalyst (*R*,*R*)-**153** caused enantioselective ether formation, affording **154** in 86% ee.[61] PDC oxidation of the two hydroxy groups of **154**, followed

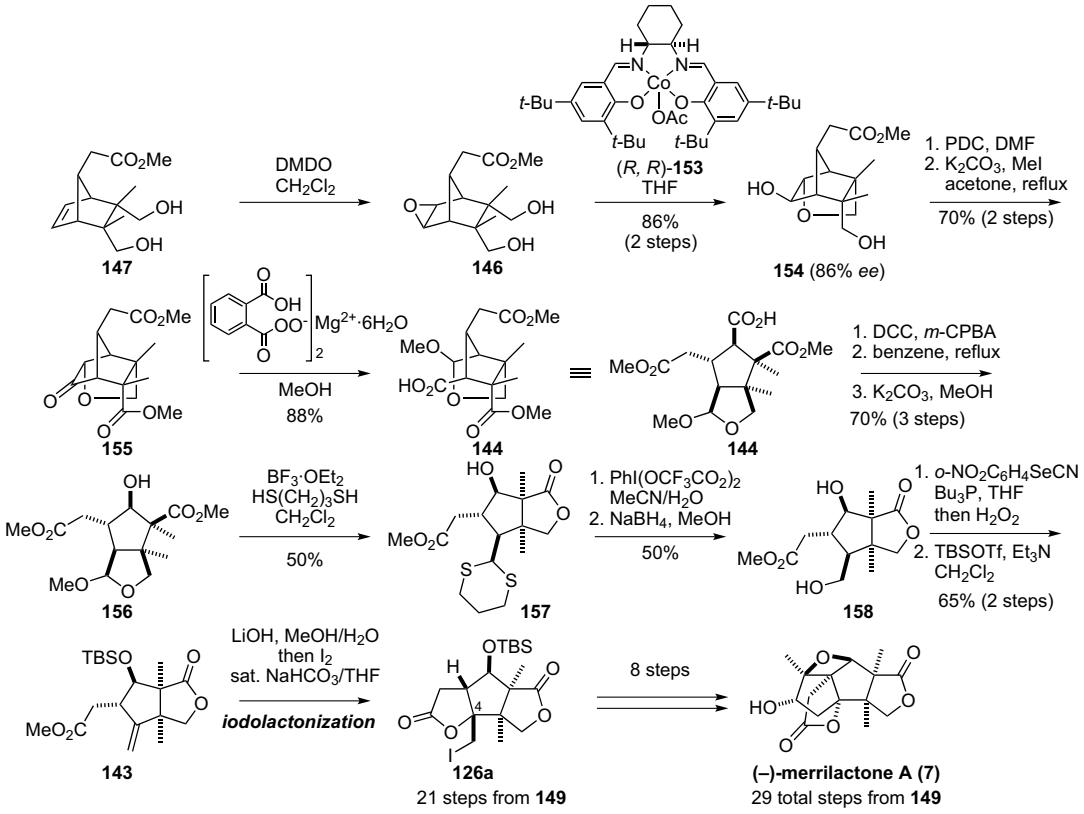


Scheme 26. Enantioselective synthetic approach to intermediate **126a** (Danishefsky, 2005).



Scheme 27. Synthesis of *meso*-diol **147** by Diels–Alder reaction (Danishefsky, 2005).

by esterification, led to ketoester **155**. Bayer–Villiger oxidation was applied to **155** to generate acid **144**, which was subjected to another Bayer–Villiger oxidation to stereoselectively construct the C7-secondary alcohol of **156** after methanolysis.[64] Transacetalization of cyclic acetal **156** into a dithioacetal promoted the concomitant formation of the γ-lactone, resulting in the formation of **157**. Oxidative removal of the dithiane and subsequent reduction of the resulting aldehyde afforded diol **158**. *exo*-Olefin formation from the primary alcohol of **158**,[65] followed by silylation of the secondary alcohol, delivered **143**, which was further transformed into the



Scheme 28. Enantioselective total synthesis of (−)-merrilactone A (**7**) (Danishefsky, 2005).

advanced intermediate **126a** by hydrolysis of the ester and iodolactonization. In this manner, a more efficient pathway to **126a** than the previous route was established. The eight transformations from **126a** (see Scheme 26) generated (−)-merrilactone A (29 total steps from **149**).

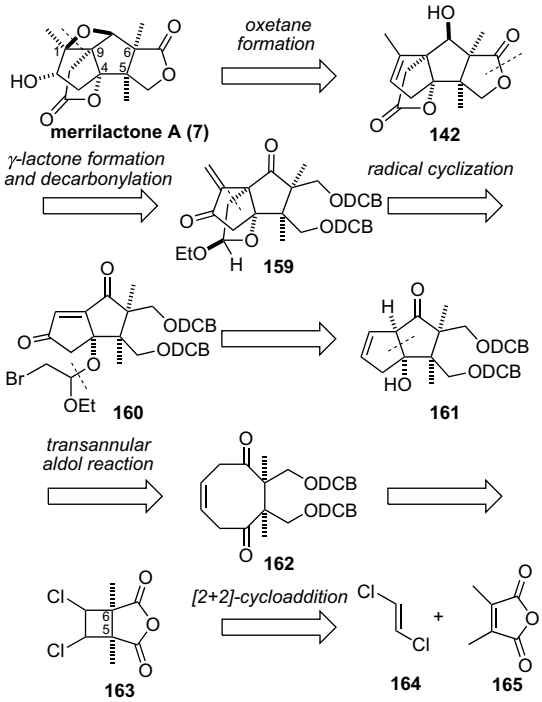
6.2. Inoue's synthesis (2003, 2006, 2007)

Inoue and co-workers reported the total synthesis of merrilactone A (**7**) in racemic form in 2003,[53a] and in optically pure form in 2006[53b] and in 2007.[53c] All three syntheses employed a transannular aldol reaction of an eight-membered diketone to construct the bicyclo[3.3.0]octane core of merrilactone A (**7**).

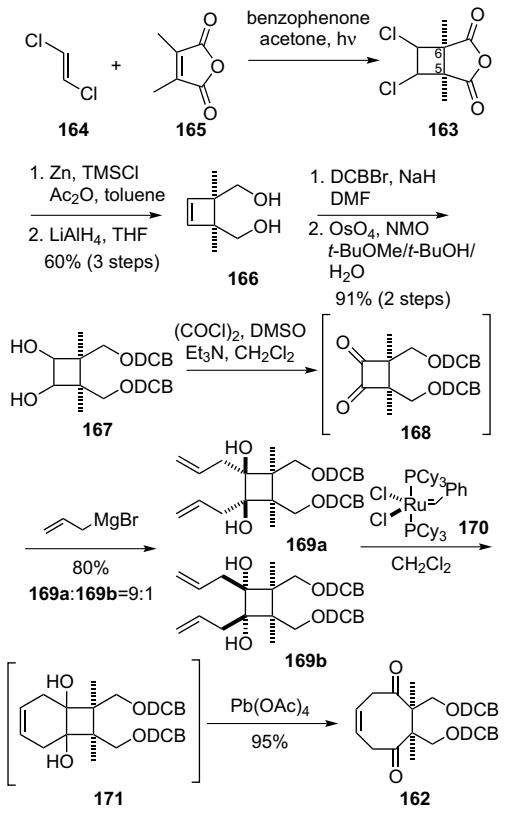
An overview of their synthetic strategy of **7** is shown in Scheme 29. Oxetane formation was planned in the last stage of the synthesis (**142**→**7**). Compound **142** would be obtained from **159** through standard synthetic manipulations. Radical cyclization from bromo acetal **160** was expected to establish the stereochemistry of the C9-quaternary carbon of **159**. Straightforward simplification of **160** gave the key bicyclo[3.3.0]octane system **161**, which would be synthesized from the single transannular aldol reaction of C_2-symmetric *meso*-diketone **162**. This single step would establish the absolute stereochemistries of four centers including the C4-tetrasubstituted carbon. Taking advantage of the C_2-symmetry, **162** was planned to be synthesized using pairwise functionalizations from **163**. The two contiguous quaternary carbons at C5 and C6 would be introduced using a [2+2]-cycloaddition reaction.

Preparation of *meso*-diketone **162** is illustrated in Scheme 30. [2+2]-Photocycloaddition between **164** and **165** installed the consecutive C5–C6-quaternary stereocenters.[66] Reductive dehalogenation of **163** and subsequent $LiAlH_4$ reduction of the anhydride yielded *meso*-diol **166**, which was masked with 2,6-dichlorobenzyl (DCB) ethers, and then subjected to dihydroxylation to afford **167**. Swern oxidation of diol **167** and allylation of the resultant diketone **168** was performed in one pot to generate a mixture of **169a** and **169b**.[67] Ring-closing olefin metathesis in the presence of Grubbs I **170** effectively provided bicyclo[4.2.0]octane system **171**,[68] which was treated with $Pb(OAc)_4$ in situ to yield the desired eight-membered *meso*-diketone **162**.[69]

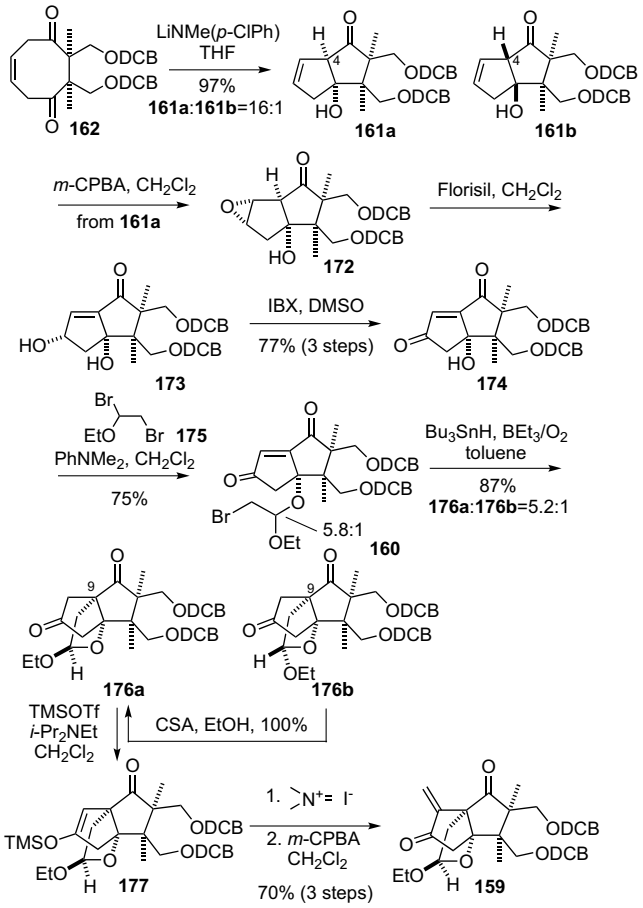
The total synthesis of merrilactone A (**7**) was first achieved in racemic form (Scheme 31). Stereoselective transannular aldol



Scheme 29. Synthetic plan of merrilactone A (**7**) (Inoue, 2003, 2006, 2007).



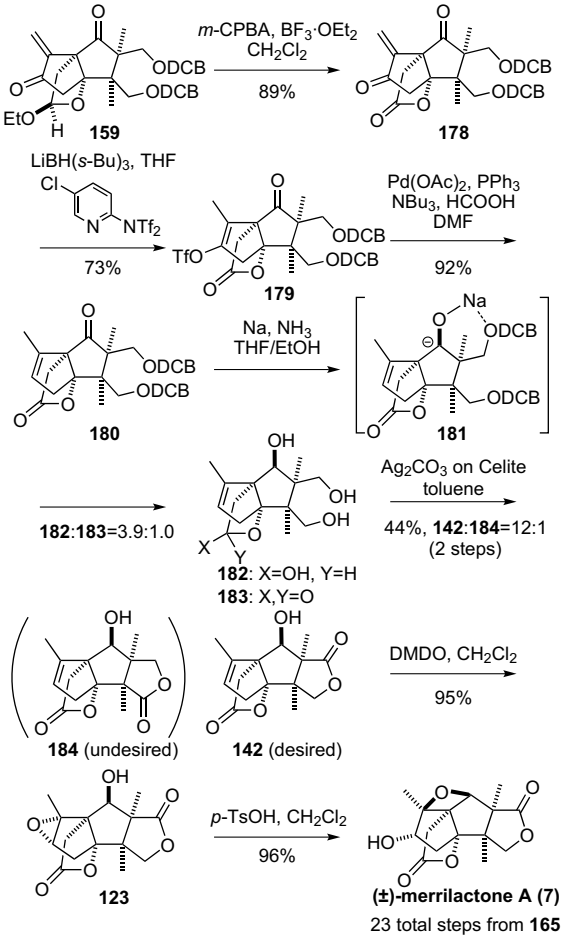
Scheme 30. Synthesis of *meso*-eight-membered diketone **162** (Inoue, 2003, 2007).



Scheme 31. Construction of carboskeleton of merrilactone A (**7**) (Inoue, 2003).

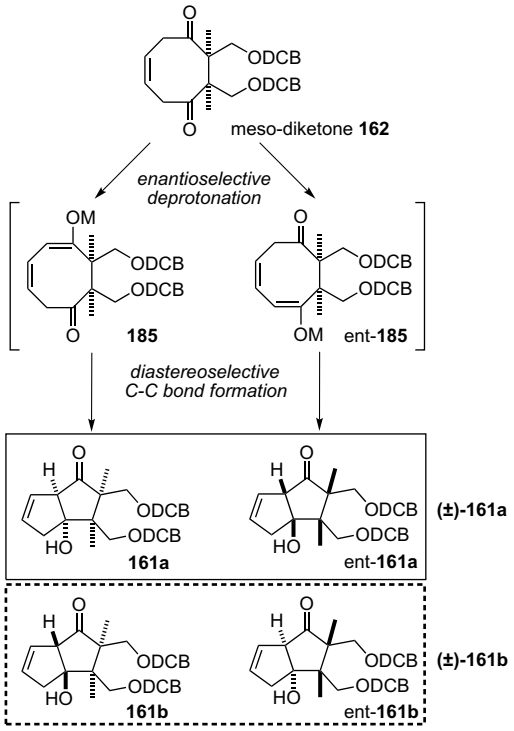
reaction of **162** was realized by the action of lithium methyl *p*-chlorophenyl amide to give (±)-**161a**, along with a minute amount of undesired **161b**. Consequently, the C4-tetrasubstituted carbon was introduced in a stereoselective fashion. Epoxidation of **161a**, followed by base-induced isomerization of the resulting epoxide **172** into allylic alcohol **173** and IBX oxidation, furnished the α,β-unsaturated ketone **174**. α-Bromoacetal **175** was then appended to **174** to generate **160** as a 5.8:1 mixture of diastereomers. Radical cyclization of the resultant diastereomixture constructed the C9-quaternary carbon of **176a** and epimeric **176b** through 5-*exo* cyclization.[70,71] Epimerization of **176b** to **176a** was realized using acidic ethanol. The combined **176a** was then subjected to a reagent combination of TMSOTf and *i*-Pr_2NEt, regioselectively generating **177**. Treatment of **177** with Eschenmoser's reagent followed by *m*-CPBA produced *exo*-olefin (±)-**159**.[72]

The total synthesis of (±)-**7** from (±)-**159** is shown in Scheme 32. γ-Lactone **178** was synthesized from ethyl acetal **159** by the action of *m*-CPBA and $BF_3\cdot OEt_2$.[73] Then, 1,4-reduction of enone **178** using LiBH(*s*-Bu)$_3$, followed by in situ triflation of the resulting enolate, generated **179**,[74] which was converted into tri-substituted olefin **180** through palladium-mediated hydrogenolysis.[75] Birch conditions effected a stereocontrolled reduction of ketone **180** through the intermediacy of **181**, as well as reductive removal of the two DCB groups, giving rise to a mixture of **182** and **183**. Fetizon oxidation of the C11- and C12-alcohols was applied to the mixture to produce the desired bis-lactone **142** along with regioisomer **184** in remarkable regio- and chemoselectivities. Lastly, highly stereoselective epoxidation of **142** with DMDO[76] generated **123**, which was subjected to acidic conditions to deliver (±)-merrilactone A (**7**, 23 total steps from **165**).



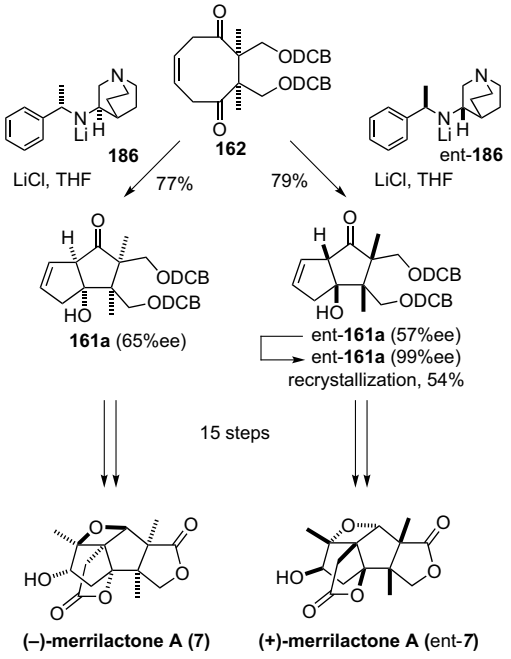
Scheme 32. Total synthesis of (±)-merrilactone A (**7**) (Inoue, 2003).

Inoue next explored the enantioselective synthesis of merrilactone A (Scheme 33). In order to do so, the key transannular aldol reaction needed to produce enantioselective material **161a** out of the four possible isomers. The aldol reaction consists of the first deprotonation step (**162**→**185** or *ent*-**185**) and the second diastereoselective C–C bond-formation step (**185**→**161a** or **161b**, and *ent*-**185**→*ent*-**161a** or *ent*-**161b**). As described in Scheme 31, the second highly diastereoselective C–C bond formation from **185** was realized by the action of an achiral lithium amide to give (±)-**161a** [**162**→(±)-**185**→(±)-**161a**]. It was envisioned that a chiral lithium amide would enable the first enantioselective formation of **185** over *ent*-**185** to realize the selective formation of **161a** over *ent*-**161a**.



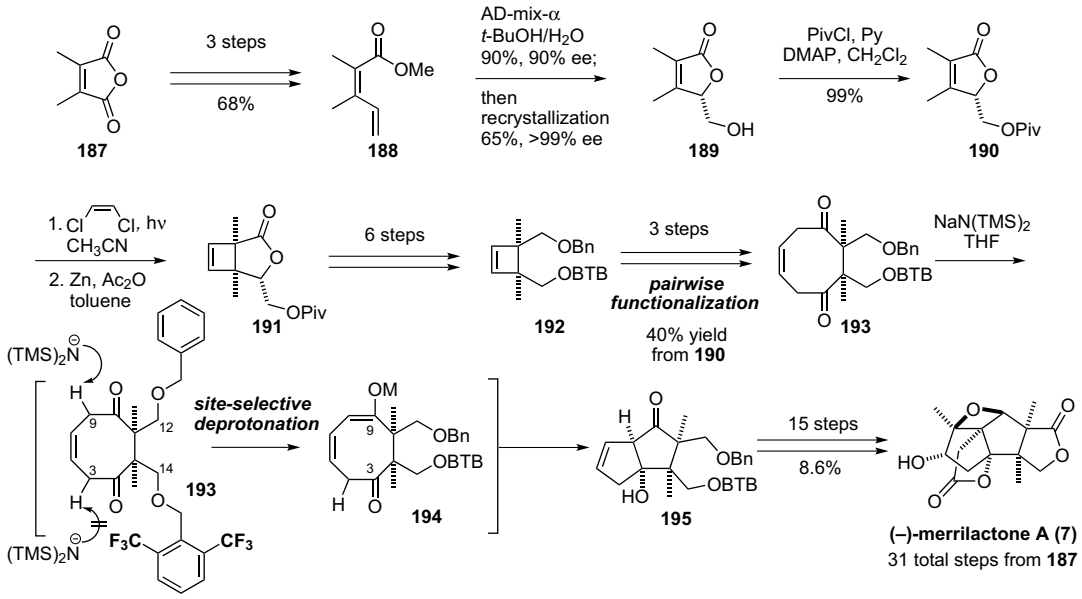
Scheme 33. Plan of transannular aldol reaction of *meso*-diketone **162** (Inoue, 2003, 2007).

Enantioselective deprotonation of *meso*-diketone **162** is shown in Scheme 34. After extensive screening of chiral bases, it was found that the lithium amide **186** exhibited the best performance in terms of enantioselectivity to afford **161a** in 65% ee.[77,78] On the other hand, *ent*-**186** enabled the formation of *ent*-**161a** in 57% ee. Enantiopure **161a** and *ent*-**161a** were obtained after one recrystallization. Total syntheses of both enantiomers of merrilactone A (**7**) were then accomplished from **161a** and *ent*-**161a** in 15 steps using the same reaction sequence shown in Schemes 31 and 32 (23 total steps from **165**).



Scheme 34. Enantioselective transannular aldol reaction and total syntheses of both enantiomers of merrilactone A (**7** and *ent*-**7**) (Inoue, 2007).

Interestingly, *ent*-merrilactone A (*ent*-**7**), the unnatural enantiomer, exhibited similar neurite outgrowth activity to merrilactone A (**7**) in a dose-dependent manner.[53c,d] These data are an important finding for the elucidation of the action mechanism of merrilactone A (**7**).



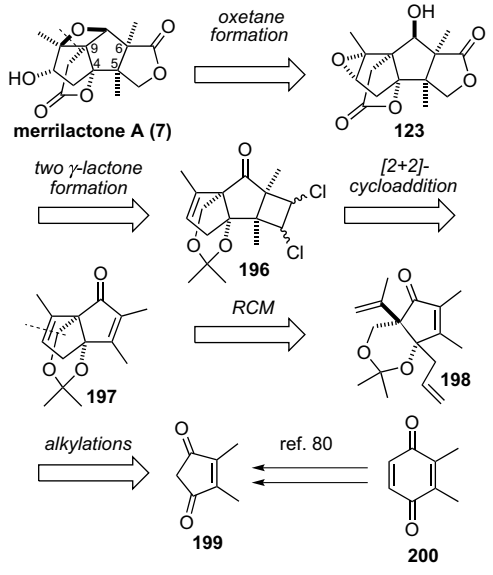
Scheme 35. Enantioselective total synthesis of (−)-merrilactone A (**7**) using bulky protecting group as long-range stereocontrolling element (Inoue, 2006).

Inoue and co-workers reported another distinct strategy for the total synthesis of (−)-merrilactone A (Scheme 35). In this strategy, they utilized the long-range steric effect of a new bulky protective group [2,6-bis(trifluoromethyl)benzyl (BTB) ether] to realize the site-selective deprotonation of chiral pseudo-*meso* diketone **193**.

The synthesis of chiral pseudo-*meso* diketone **193** is illustrated in Scheme 35. First, diene **188** was synthesized from **187** in three steps. Asymmetric dihydroxylation of **188** using AD-mix-α[79] and concomitant lactonization provided **189** in 90% ee, recrystallization of which gave enantiomerically pure **189**. After protection of the primary alcohol of **189** as the pivalate, [2+2]-cycloaddition of **190** with dichloroethylene, followed by Zn-mediated reduction, produced cyclobutene **191**. Six standard transformations were applied to **191** to give **192**, which was further converted into pseudo-*meso* diketone **193** by pairwise functionalizations. The crucial site-selective deprotonation of pseudo-*meso* diketone **193** and subsequent aldol reaction proceeded smoothly under the action of $NaN(TMS)_2$, selectively leading to **195** out of the four possible isomers. In this reaction, the selective access of the base to C9 was attained, because the bulky BTB ether of the C14-hydroxy group kinetically protected the deprotonation site at C3 through long-range steric interaction (**193**→**194**). Finally, 15 steps from **195** generated enantiomerically pure (−)-merrilactone A (**7**, 31 total steps from **187**).

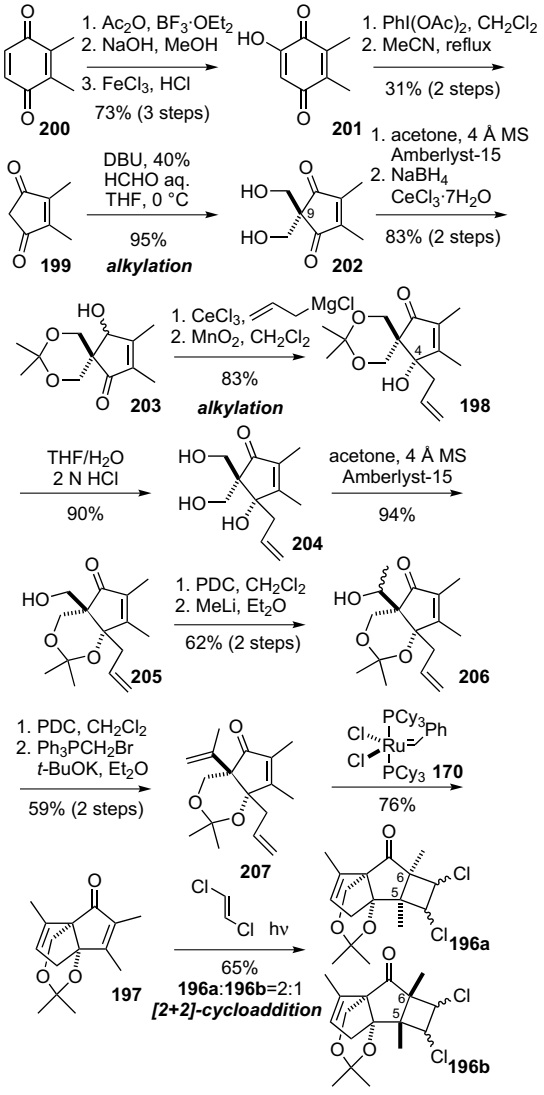
6.3. Mehta's synthesis (2006)

Mehta and co-workers reported the total synthesis of (±)-**7** in 2006.[54] In their synthetic plan, **123** was envisioned to be prepared from **196** through two γ-lactone syntheses (Scheme 36). [2+2]-Cycloaddition between **196** and dichloroethylene was designed to establish contiguous C5- and C6-quaternary carbons simultaneously. Ring-closing metathesis (RCM) of diene **198** was planned to construct the cyclopentene moiety of **197**. Diene **198**, possessing C4- and C9-tetrasubstituted carbons, was, in turn, to be synthesized from the known 2,3-dimethyl-2-cyclopentene-1,4-dione **199**, which would be prepared from **200** by a known procedure.[80]



Scheme 36. Synthetic plan of (±)-merrilactone A (**7**) (Mehta, 2006).

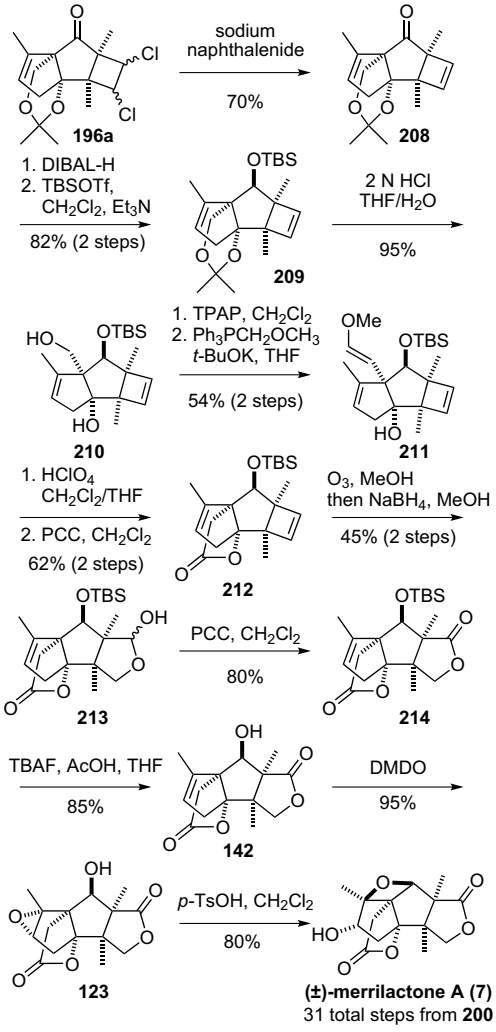
2,3-Dimethyl-2-cyclopentene-1,4-dione **199** was synthesized from 2,3-dimethyl-1,4-benzoquinone **200** in five steps (Scheme 37).[80] Treatment of **200** with Ac_2O and $BF_3\cdot Et_2O$, followed by hydrolysis and oxidation, resulted in the formation of **201**. PIDA oxidation of **201** and a subsequent Wolff-type rearrangement resulted in 2,3-dimethyl-2-cyclopentene-1,4-dione **199**. Subsequent bis-hydroxymethylation of **199** generated the C9-quaternary carbon of **202**. Treatment of **202** with acetone under acidic conditions furnished the protected compound, the ketone of which was reduced under Luche conditions[33] to afford the alcohol **203**. Addition of the allylcerium reagent to the remaining ketone of **203** afforded the allylic alcohol with stereoselective installation of the C4-tetrasubstituted carbon, and then the secondary alcohol was oxidized to the enone **198** using MnO_2. Removal of the acetonide of the tertiary alcohol **198** and reprotection of the resulting triol **204** with the acetonide furnished the primary alcohol **205**. The substrate for ring-closing metathesis was obtained from **205** by a four-step sequence: oxidation of the primary alcohol, addition of methyllithium (**205**→**206**), oxidation of the secondary alcohol, and Wittig methylenation (**206**→**207**). The cis-oriented allyl and propenyl chains of **207** were effectively cyclized by the action of Grubbs I **170**, delivering cyclopentene **197**. Construction of the contiguous C5/C6-quaternary carbons was achieved by [2+2]-cycloaddition of **197** with *trans*-1,2-dichloroethylene, giving rise to a 2:1 mixture of **196a** and **196b**.



Scheme 37. Alkylations and [2+2]-cycloaddition to construct four tetrasubstituted carbons at C4, C5, C6, and C9 (Mehta, 2006).

The total synthesis of **7** from the major isomer **196a** is illustrated in Scheme 38. Reductive dehalogenation of **196a** using sodium naphthalenide gave cyclobutene **208**. Ketone **208** was stereoselectively reduced to the alcohol, which was then protected as the TBS ether to

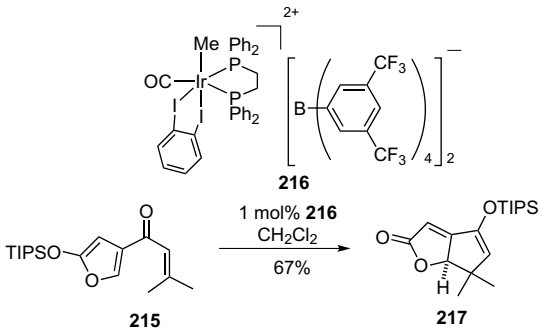
produce **209**. Deprotection of the acetonide of **209**, followed by oxidation of the resulting primary alcohol of **210** and homologation with Wittig olefination, furnished the enol ether **211**. Acid-mediated hydrolysis and subsequent oxidation of **211** led to the γ-lactone **212**. The second γ-lactone was constructed from the cyclobutene moiety of **212**. Namely, ozonolysis of **212** and in situ chemoselective reduction using $NaBH_4$ generated lactol **213**, which was then oxidized to deliver the second γ-lactone **214**. Desilylation of **214** was followed by epoxidation of **142** using DMDO to furnish the α-epoxide **123** stereoselectively. Final exposure of **123** to *p*-TsOH resulted in the formation of (±)-merrilactone A (**7**, 31 total steps from **200**).



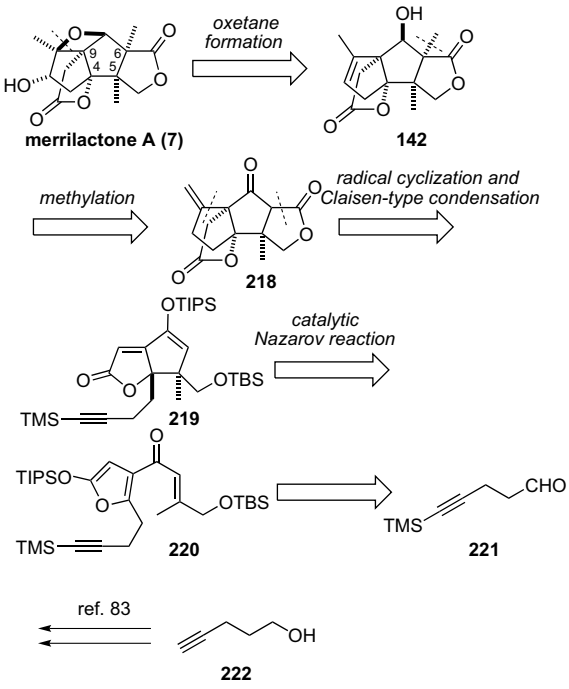
Scheme 38. Total synthesis of (±)-merrilactone A (**7**) (Mehta, 2006).

6.4. Frontier's synthesis (2007)

Frontier and co-workers developed the Ir-catalyzed Nazarov reaction of a silyloxyfuryl enone **215** in the presence of 1 mol% of **216** to assemble the oxabicyclo[3.3.0]octane skeleton **217** (Scheme 39).[55,81,82] This reaction was effectively incorporated into the total synthesis of (±)-merrilactone A (**7**) by Frontier in 2007 (Scheme 40). In their strategy, the C4- and C5-tetrasubstituted carbons of **219** were planned to be simultaneously introduced by the catalytic Nazarov reaction of **220**. Two intramolecular cyclizations from **219** would construct the cyclopentane and γ-lactone moieties to provide **218**. Stereoselective methylation of **218** would then set the C6-quaternary carbon to generate Danishefsky's intermediate **142**. The synthesis of siloxyfuran **220**, the substrate for the key Nazarov reaction, would be achieved from the known aldehyde **221**.



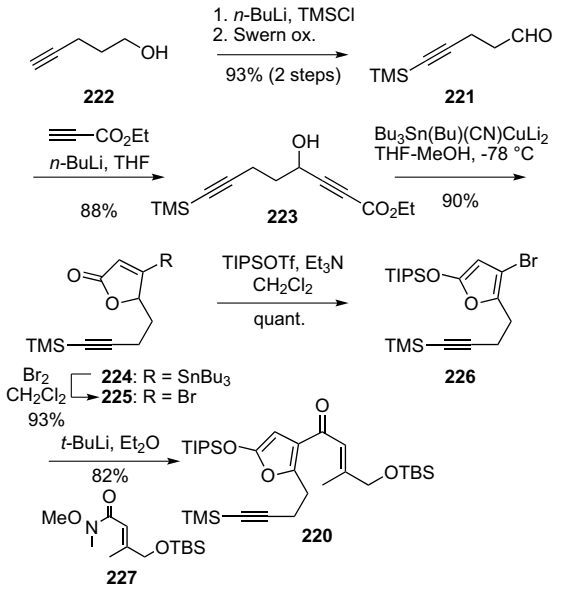
Scheme 39. Catalytic Nazarov reaction (Frontier, 2006).



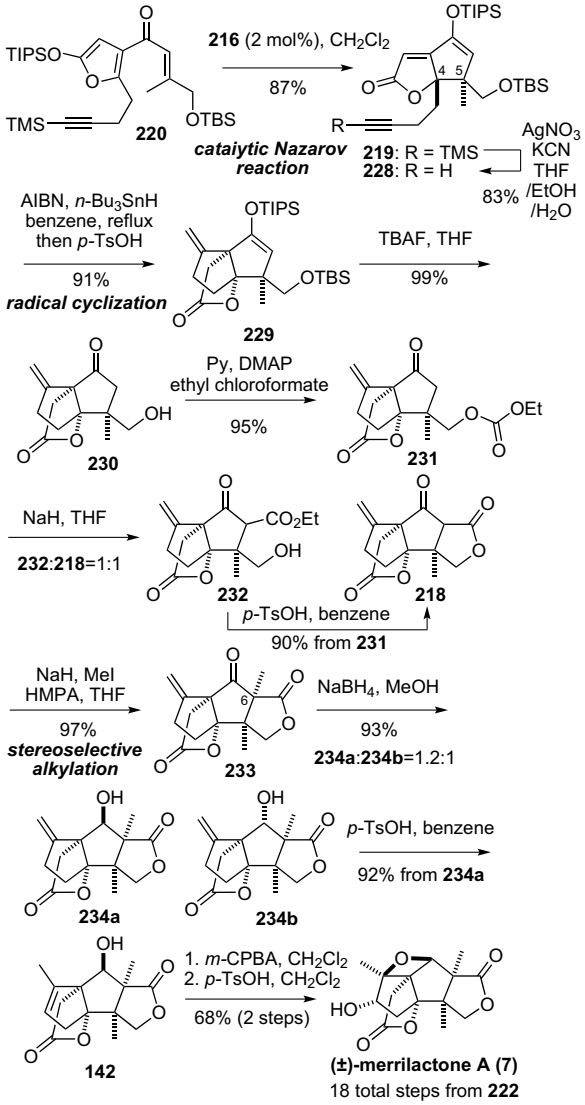
Scheme 40. Synthetic plan of (±)-merrilactone A (**7**) (Frontier, 2007).

The synthesis of the Nazarov substrate **220** is illustrated in Scheme 41. Aldehyde **221**[83] was prepared from **222** by silylation and subsequent oxidation. Addition of the lithium anion of ethyl propiolate to aldehyde **221** generated **223**. Introduction of the alkylstannane to **223** was accompanied by in situ lactonization, leading to vinyltin **224**.[84] Exchange of $SnBu_3$ of **224** with Br, followed by silyl enol ether formation from **225**, afforded furan **226**. Then, lithiation of **226**, and subsequent treatment with Weinreb amide **227**, prepared from acetol in three steps, gave rise to siloxyfuran enone **220**.

Nazarov cyclization of **220** was promoted by 2 mol% of dicationic iridium catalyst **216**, resulting in the formation of a single diastereomer **219** with the desired stereochemistries at C4 and C5 (Scheme 42). Terminal acetylene **228**, which was produced by desilylation from **219**, underwent radical cyclization upon treatment with *n*-Bu_3SnH, generating the exocyclic olefin **229** after acid removal of the resultant vinyltin.[85] Thus, three contiguous tetrasubstituted carbons were constructed at this stage. Deprotection of bis-silyl ether **229** furnished the hydroxyl ketone **230**, which was converted into the carbonate **231**. Treatment of **231** with excess NaH in THF triggered an intramolecular Claisen condensation to afford the desired γ-bislactone **218** and ester **232**, the mixture of which was exposed to *p*-TsOH, selectively delivering **218**. Then, α-methylation of the 1,3-dicarbonyl compound **218**, followed by



Scheme 41. Synthesis of substrate (**220**) for catalytic Nazarov reaction (Frontier, 2006).



Scheme 42. Total synthesis of (±)-merrilactone A (**7**) (Frontier, 2006).

chemoselective reduction of the ketone in **233**, gave a 1.2:1 ratio of the desired alcohol **234a** and its epimeric alcohol **234b**. Finally, isolated **234a** was converted into (±)-merrilactone A (**7**) in three steps (18 total steps from **222**).

7. Conclusions

The work described in this review demonstrates the significant progress that has been made in the field of total syntheses of complex natural products in terms of key transformations and overall strategies. Notably, most of the total syntheses of the neurotrophic sesquiterpenoids (**3**, **6**, and **7**) concentrated over the last 5 years only required about 20 total steps from commercially available materials. Creative integration of classical and contemporary technologies has contributed to the highly efficient total syntheses of *Illicium* sesquiterpenoids. However, the introduction of the sterically hindered tetrasubstituted carbon centers remains the most challenging problem, and thus the development of even more general strategies is necessary. The efficient synthetic routes developed here will accelerate structure–activity relationship studies and biological studies including identification of unknown biological targets of neurotrophic sesquiterpenes.

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