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SYNTHETIC STUDIES TOWARD 11-*O*-DEBENZOYLTASHIRONIN

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This paper is dedicated to Professor Masayoshi ANDO, an emeritus professor of Niigata University.

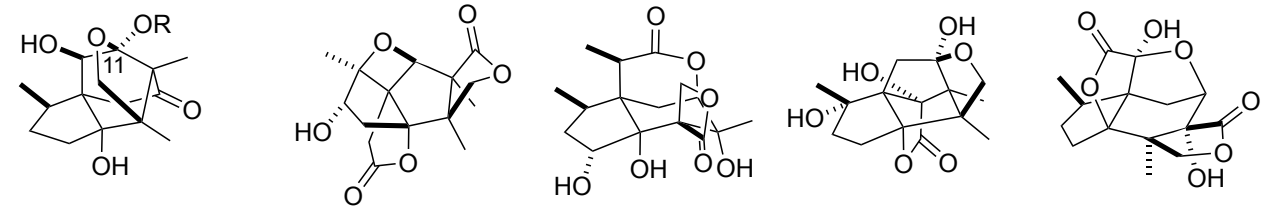
Abstract – 11-*O*-Debenzoyltashironin is a highly oxygenated *allo*-cedrane sesquiterpenoid with seven contiguous chiral centers in a compact fused ring, and shows remarkable neurite extension activity. Total syntheses of the title and related compounds are reviewed.

CONTENTS

1. Introduction

Illicium sesquiterpenoids are densely oxygenated and strained complex sesquiterpenoids that feature unique *allo*-cedrane and *seco*-prezizaane-type frameworks. These compounds originate in plants of the genus *Illicium* (Figure 1). The genus comprises approximately 40 known species, with 36 species native

to southern China. Only two species, *Illicium anisatum* and *Illicium tashiroi*., occur in Japan on the other hand. Among these, Japanese star anise, known as Shikimi, was recognized as a toxic plant due to the presence of anisatin (**4**), one of the most potent plant-derived neurotoxins.[1] Since then, more than 50 sesquiterpenoids, generated by the same biosynthetic pathway as anisatin (**4**) (Scheme 1), have been isolated from *Illicium* species.



R=H, 11-*O*-debenzoyl-tashironin (**1**)
R=Bz, tashironin (**2**)

merrilactone (**3**)

anisatin (**4**)

illisimonin A (**5**)

jiadifenolide (**6**)

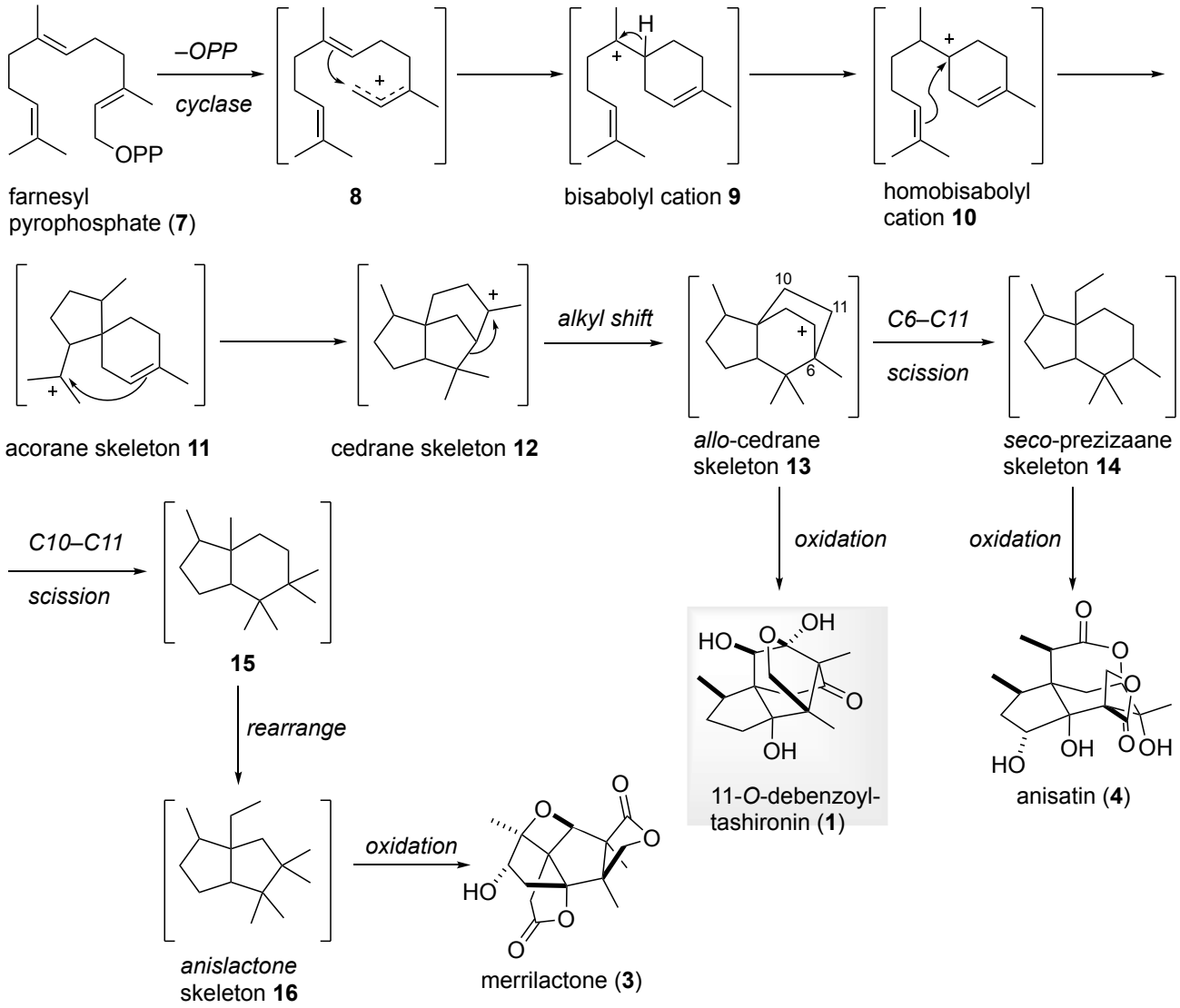
Figure 1. Representative neurotrophic *Illicium* sesquiterpenoids

Examples include 11-*O*-debenzoyltashironin (**1**), tashironin (**2**), merrilactone (**3**), illisimonin A (**5**), jiadifenolide (**6**), and others, which exhibited prominent activity in promoting neurite outgrowth in cultured rat cerebral cortex at micro-molar concentrations.[2] These results have implications in the study of neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's diseases, and so on. Among these compounds, 11-*O*-debenzoyltashironin (**1**) was isolated along with tashironin (**2**) from *Illicium merrillianum* in Yunnan Province, China by Fukuyama *et al*.[3] It has the *allo*-cedrane framework and showed the activity to promote neurite extension in cultured fetal rat cortical neurons at concentrations of 0.1 μM, whereas tashironin (**2**) was inactive in this assay. However, due to its very scarce natural supply (3 mg from pericarps of 3.7 kg of *Illicium* Merr.), there is strong demand to develop an efficient synthetic method for its pharmacological evaluation.

Thus, the *Illicium* sesquiterpenoids with neurotrophic activity have attracted significant attention as synthetic targets for many organic chemists, because of their highly oxygenated and diverse caged architectures along with pharmacological potential for age-related diseases. A variety of creative synthetic works have been disclosed for these compounds so far. Theodrakis *et al*.[4] compiled and reviewed these works in 2014, and later in 2018 Maimone *et al*.[5] provided a comprehensive review. The emergence of new total syntheses and synthetic approaches for 11-*O*-debenzoyltashironin (**1**) since then has prompted the author to review the synthetic efforts on this structurally intriguing and physiologically fascinating compound, along with related compounds.

The biogenetic pathway of some representative *Illicium* sesquiterpenoids is proposed as follows[2,6] (Scheme 1). Cyclization of farnesyl pyrophosphate (**7**) delivers bisabolyl cation **9**, which undergoes hydride transfer to form homobisabolyl cation **10** and then *spiro*-cyclization to create the acorane skeleton

11. Alkyl shift of the cedrane skeleton **12** results the *allo*-cedrane skeleton **13**, which after multiple oxidations leads to 11-*O*-debenzoyltashironin (**1**). Anisatin (**4**) is formed from the *seco*-prezizaane framework **14** obtained by C6–C11 bond cleavage of **13**. Subsequent C10–C11 bond cleavage of **14** provides perhydroindan **15**, which furnishes merrilactone (**3**) *via* anislactone skeleton **16**.



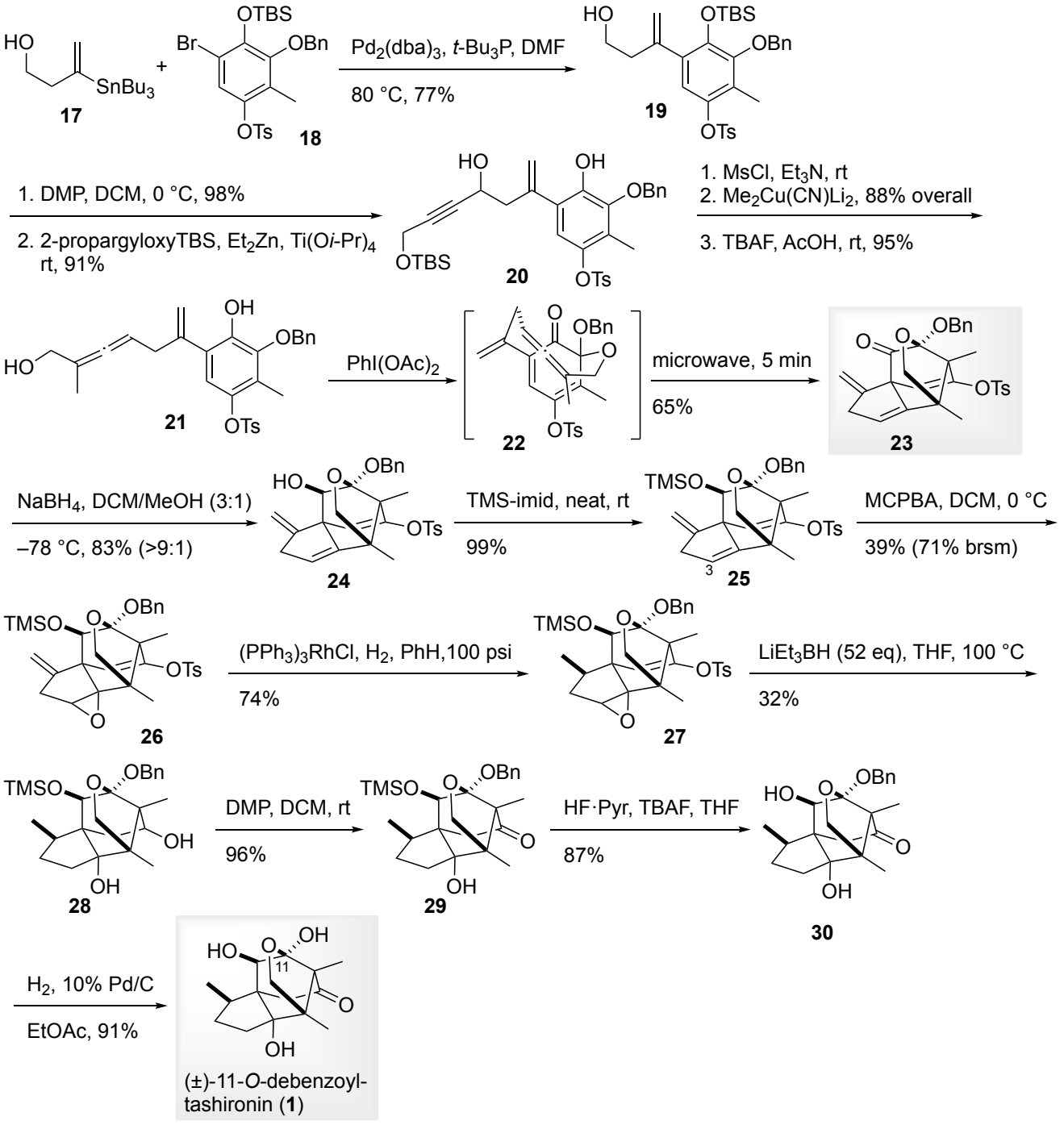
Scheme 1. Proposed biosynthetic pathway to representative *Illicium* sesquiterpenoids

The total synthesis of 11-*O*-debenzoyltashironin (**1**) poses several challenges. The construction of the *oxa*-tetracyclic architecture, including the *allo*-cedrane framework **13**, and the installation of seven contiguous stereogenic centers are highly demanding. Additionally, achieving selective introduction of tertiary α-hydroxyl group at C-4, secondary hydroxyl group at C-10, and primary hydroxyl group at C-14 chemo-, regio- and stereoselectively is very challenging in the presence of other functional groups. This review sheds light on how these issues have been addressed and solved.

2. Danishefsky's total synthesis

The first total synthesis of 11-*O*-debenzoyltashironin (**1**) was accomplished in racemic form by

Danishefsky *et al*.[7] They employed a series of steps, including successive oxidative dearomatization and an intramolecular transannular Diels-Alder reaction (IMDA), as a key step to construct the tetracyclic core (Scheme 2).[8]



Scheme 2. Synthesis of racemic 11-*O*-debenzoyltashironin (**1**) by Danishefsky *et al*.[7]

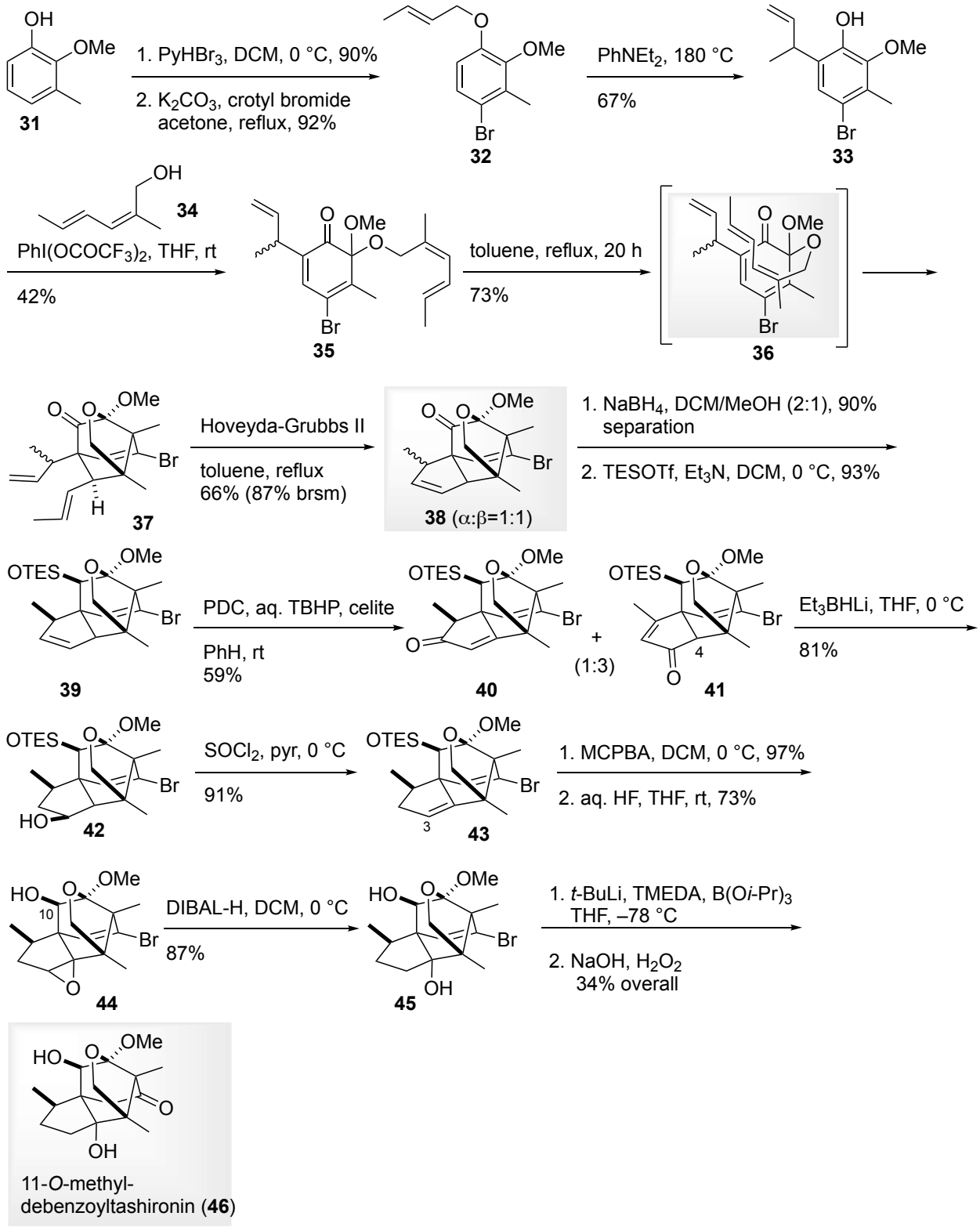
Stille coupling of vinylstannane **17** with aryl bromide **18** resulted in the formation of alcohol **19**, using a $Pd_2(dba)_3$ and *t*-Bu_3P catalytic system effectively. Oxidation of **19** to an aldehyde with Dess-Martin periodinane (DMP) was followed by the addition of 2-propargyloxyTBS in the presence of Et_2Zn and Ti(O*i*-Pr)$_4$, yielding propargyl alcohol **20**. Mesylation of **20**, followed by S_N2' substitution and

deprotection, provided allene **21**, a crucial precursor for the key reaction. Difficulty encountered in the deprotection of TBS ether was overcome by employing tetrabutylammonium fluoride (TBAF) in acetic acid. The key oxidative dearomatization and subsequent IMDA reaction was successful by the treatment with phenyliodine diacetate [$PhI(OAc)_2$] according to Pelter[9] and Tamura[10] protocol followed by brief microwave irradiation to efficiently afford the *oxa*-tetracyclic compound **23**. This reaction allowed the construction of all four rings in a single step. The remaining task involved selective transformations of olefinic groups to introduce oxygen functionalities. Sodium borohydride ($NaBH_4$) reduction of **23**, followed by protection, gave silylether **25**. Regio- and stereoselective epoxidation at C-3 was achieved effectively by brief treatment with MCPBA at 0 °C, yielding epoxide **26**. Catalytic reduction of the *exo*-methylene group of the epoxide **26** proceeded stereoselectively with Wilkinson's catalyst [$(PPh_3)_3RhCl$] at high pressure to provide epoxide **27**. The opening of the epoxide **27** required harsh conditions employing super hydride at elevated temperature in a sealed tube, but it allowed the enol tosyl ether moiety to be reductively cleaved to generate alcohol **28**. Oxidation followed by deprotections finally completed the first total synthesis of racemic 11-*O*-debenzoyltashironin (**1**).

An effort to synthesize chiral 11-*O*-debenzoyltashironin (**1**) was carried out from racemic propargyl alcohol **20**, which was transformed into chiral propargyl alcohol **20** by oxidation followed by reduction with alpine borane. Chiral *oxa*-tetracyclic compound **23** was obtained in 93% ee by intramolecular oxidative dearomatization with phenyliodine bis(trifluoroacetate) (PFIA), followed by IMDA reaction at room temperature.[11]

3. Mehta and Maity's synthesis of racemic 11-*O*-methyldebenzoyltashironin (46)

Mehta and Maity elaborated the synthesis of 11-*O*-methyldebenzoyltashironin (**46**) using successive oxidative dearomatization-IMDA and subsequent ring closing olefin metathesis (RCM) reactions to assemble the *oxa*-tetracyclic key rings (Scheme 3).[12,13] The synthesis involved several key steps starting from phenol **31**. Regioselective bromination of phenol **31** was followed by *O*-crotylation to provide crotyl ether **32**. Claisen rearrangement of **32** resulted in the formation of phenol **33**. Oxidative dearomatization with PFIA in the presence of allyl alcohol **34** delivered cyclohexadienone **35**. Subsequent IMDA reaction of **35** afforded the tricyclic adduct **37**.[14] RCM reaction of the diene **37** was carried out with the Hoveyda-Grubbs' second-generation catalyst, leading to the requisite *oxa*-tetracyclic compound **38** as an inseparable 1:1 diastereomeric mixture. The carbonyl group of **38** was then reduced stereoselectively from the side of bromovinyl using $NaBH_4$. Separation of the diastereomers followed by protection provided TES ether **39**. Allylic oxidation of the ether **39** with pyridinium dichromate (PDC) resulted in formation of regioisomeric enones **40** and **41**.



Scheme 3. Total synthesis of racemic 11-*O*-methyldebenzoyltashironin (**46**) by Mehta and Maity[12,13]

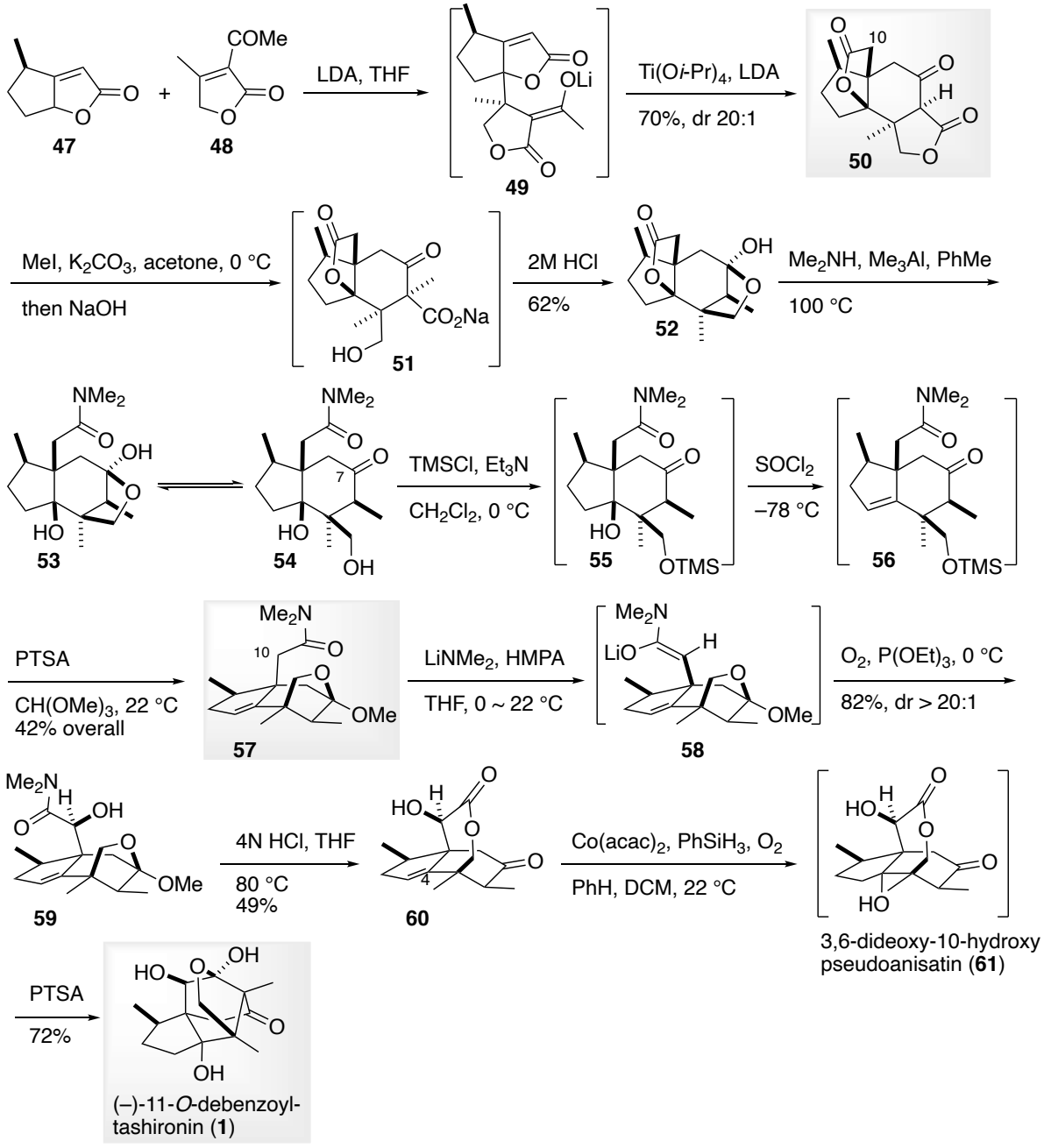
Treatment of the major enone **41** with super hydride led to alcohol **42** stereoselectively by conjugate reduction and subsequent 1,2-reduction from the bottom face of the enone **41** probably due to steric shielding of the TES ether. Dehydration of **42** gave desired Δ^3-olefin **43** regioselectively. Treatment of **43** with MCPBA followed by aq. HF resulted in the formation of to give α-epoxide **44**. Chelation controlled

opening of the epoxide **44** with DIBAL-H delivered diol **45** regio- and stereoselective manner. The bromovinyl moiety of the diol **45** was transformed into borate by lithiation and boration, which was unmasked by oxidation with H_2O_2 to complete the total synthesis of 11-*O*-methyldebenzoyltashironin (**46**).

The hydrolysis of **46** to 11-*O*-debenzoyltashironin (**1**) was described in the patent report of Danishefsky and Cook.[15]

4. Shenvi's total synthesis

Shenvi *et al*. achieved a unique and compact total synthesis of (−)-11-*O*-debenzoyltashironin (**1**) in only 6 pots in gram scale, with a double Michael reaction as a key step (Scheme 4).[16]



Scheme 4. Total synthesis of (−)-11-*O*-debenzoyltashironin (**1**) by Shenvi *et al*.[16]

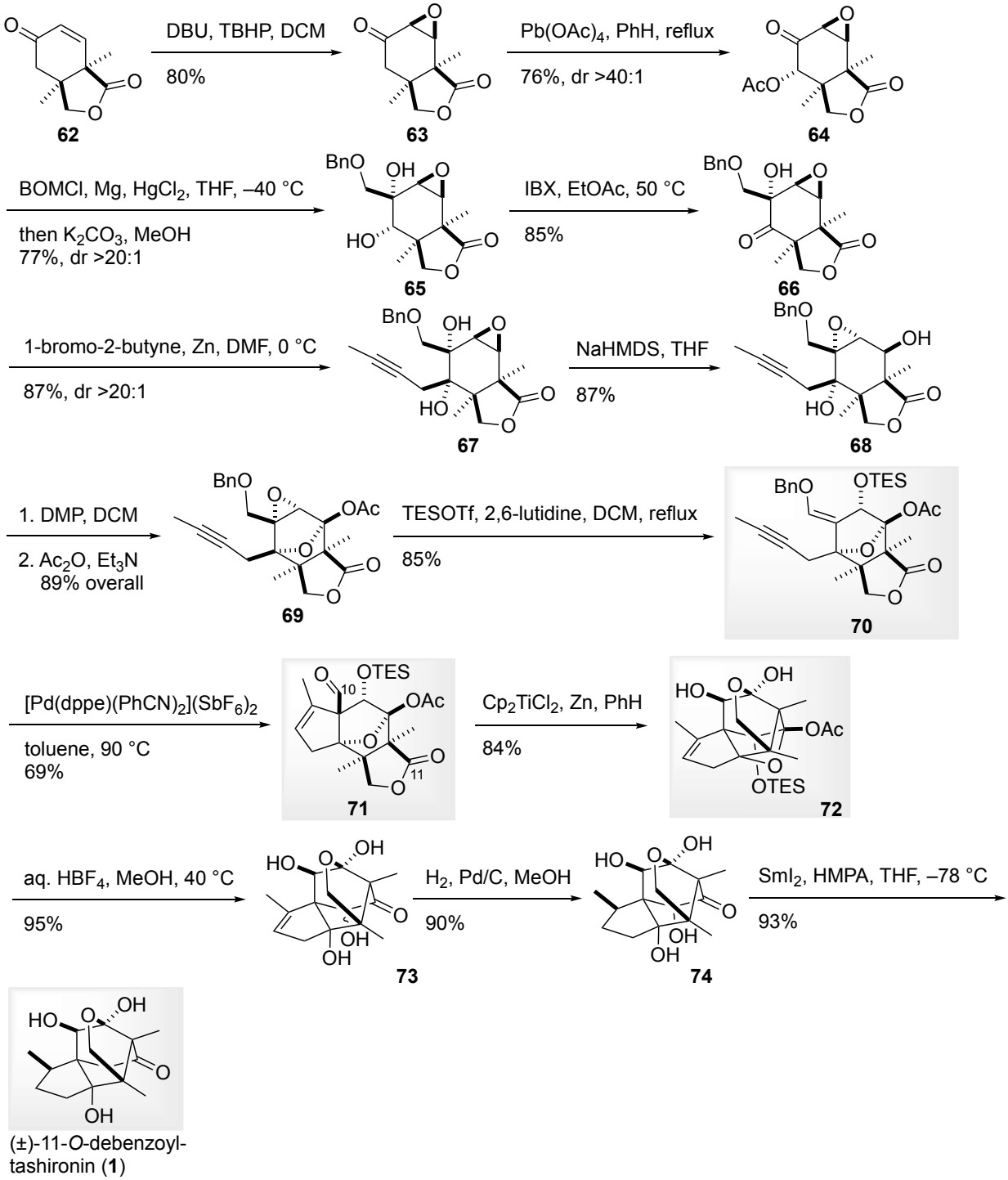
Chiral butenolide **47** was prepared from (*R*)-(+)-citronellal in 3 steps. Intermolecular Michael reaction of the enolate of the butenolide **47** with acetylbutenolide **48** to result in the formation of enolate **49**, which then underwent a chelation-controlled intramolecular Michael reaction (formal [4+2] cycloaddition) to yield the heterodimerization product **50** with a bicyclo[3.2.0]nonane core and a *bis*-lactone moiety with 20:1 diastereoselectivity. C-Methylation of the *bis*-lactone **50** proceeded from the α-face of the molecule stereoselectively, followed by regioselective hydrolysis to afford carboxylate **51** by the addition of NaOH. Upon acidification, decarboxylation and concomitant hemiacetal formation occurred, generating hemiacetal **52**. The opening of the lactone ring was carried out with Me_2N-$AlMe_2$ at an elevated temperature to afford an equilibrium mixture of tautomers **53** and **54**, which were protected as mono-silyl ether **55** to prevent cyclic sulfite formation in the next step. Without isolation, dehydration was carried out with thionyl chloride ($SOCl_2$) to afford olefin **56**. Subsequently, the more acidic carbonyl group at C-7 was protected as a ketal by the treatment with trimethyl orthoformate, and acetal **57** was obtained in one pot. To this end, four reactions were carried out successively in one pot, reducing the number of work-up and purification process. Deprotonation at C-10 was successful only with lithium dimethylamide in the presence of HMPA, and hydroxyamide **59** was obtained with triplet oxygen and triethyl phosphite stereoselectively, due to the steric shielding at C-10 by the bridging acetal moiety. The proximity of the acetal and the amide moieties in the hydroxyamide **59** prompted the transformation to ε-lactone **60** easily. The hydroxyl group at C-4 was introduced regio- and stereoselectively with Mukaiyama conditions[17] to result in the formation of 3,6-dideoxy-10-hydroxypseudoanisatin (**61**).[18] Addition of *p*-toluenesulfonic acid (PTSA) to the crude reaction mixture induced facile transannular Claisen cyclization to complete the pot-economical gram-scale total synthesis of 11-*O*-debenzoyltashironin (**1**). Purification of 3,6-dideoxy-10-hydroxypseudoanisatin (**61**) was difficult owing to partial intramolecular cyclization to 11-*O*-debenzoyltashironin (**1**) on silica-gel.

Moreover, the authors completed the total synthesis of (–)-jiadifenolide (**6**) starting from the *bis*-lactone **50**.[19]

5. Wang's total synthesis

Wang *et al*. accomplished the total synthesis of racemic 11-*O*-debenzoyltashironin (**1**) through key steps involving Pd(II)-catalyzed 5-*endo* ene-yne cyclization and late-stage Ti(III)-mediated reductive coupling of aldehyde and lactone moieties (Scheme 5).[20] The lactone **62**, previously used in the synthesis of Danishefsky's merrilactone (**3**) synthesis,[21] was predominantly converted to β-epoxide **63**. Equatorial acetoxylation using $Pb(OAc)_4$ resulted in α-acetate **64**. The addition of benzyloxymethyl Grignard reagent, generated *in situ*, followed by basic workup, afforded benzyloxy-diol **65** with high diastereoselectivity. Oxidation of the diol with 2-iodoxybenzoic acid (IBX) successfully produced α-hydroxyketone **66**

without cleaving the diol moiety of the starting material. Stereoselective propargylation was carried out using 1-bromo-2-butyne and zinc to obtain diol **67**, which was treated with NaHMDS to provide isomeric hydroxy-epoxide **68** *via* the Payne rearrangement. Subsequent Dess-Martin oxidation, followed by acetylation of the resulting hemi-acetal, led to acetate **69** bearing an oxabicyclo[2.2.1] core. The hydroxyl group at C-4 was protected to prevent epimerization of the hydrindane core during the later stage by retro-aldol process. Treatment of the acetate **69** with TESOTf and 2,6-lutidine resulted in isomerization to effect benzyl enol ether **70**.

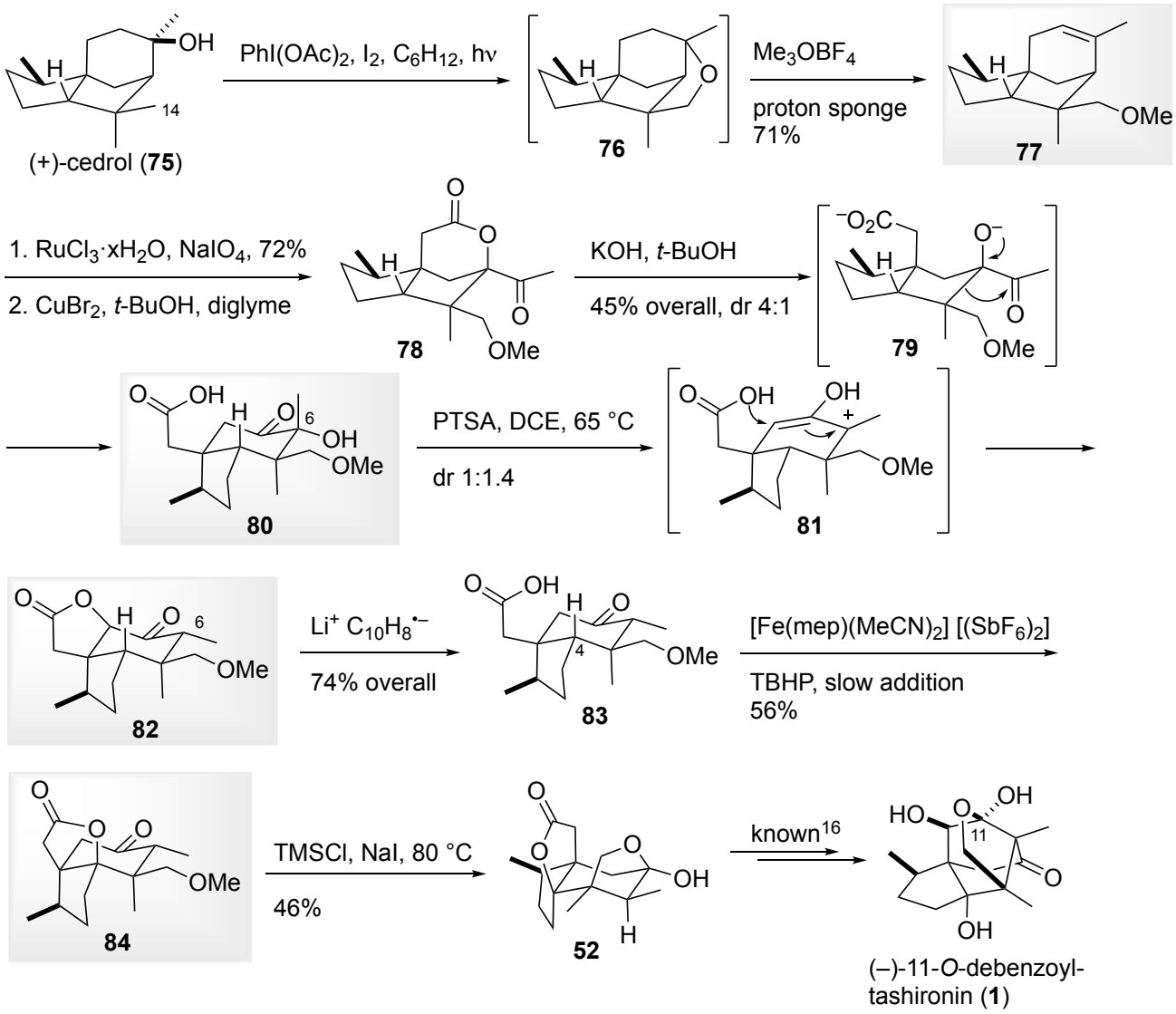


Scheme 5. Total synthesis of racemic 11-*O*-debenzoyltashironin (**1**) by Wang *et al.*[20]

The *trans*-hydrindane skeleton was constructed via 5-*endo* ene-yne cyclization catalyzed by $[Pd(dppe)(PhCN)_2](SbF_6)_2$, providing aldehyde **71** as the single isomer. The key C10-11 bridge was formed through McMurry reductive coupling[22] between the formyl group and the proximal lactonic carbonyl group, utilizing Cp_2TiCl_2 and Zn to yield *trans*-diol **72**, while reductive coupling with SmI_2 led to *cis*-diol. The reaction in nonpolar and non-chelating benzene was effective for the coupling reaction. Hydrolysis of the protecting groups resulted in keto-tetraol **73**, which underwent catalytic hydrogenation to afford hydroxyketone **74** as the single isomer. Finally, SmI_2-promoted deoxygenation completed the total synthesis of racemic 11-*O*-debenzoyltashironin (**1**).

6. Maimone's formal synthesis

Maimone *et al*. accomplished the formal synthesis of 11-*O*-debenzoyltashironin (**1**) starting from inexpensive (+)-cedrol (**75**) employing unique site-selective remote C(sp^3)-H oxidations (Scheme 6).[6]



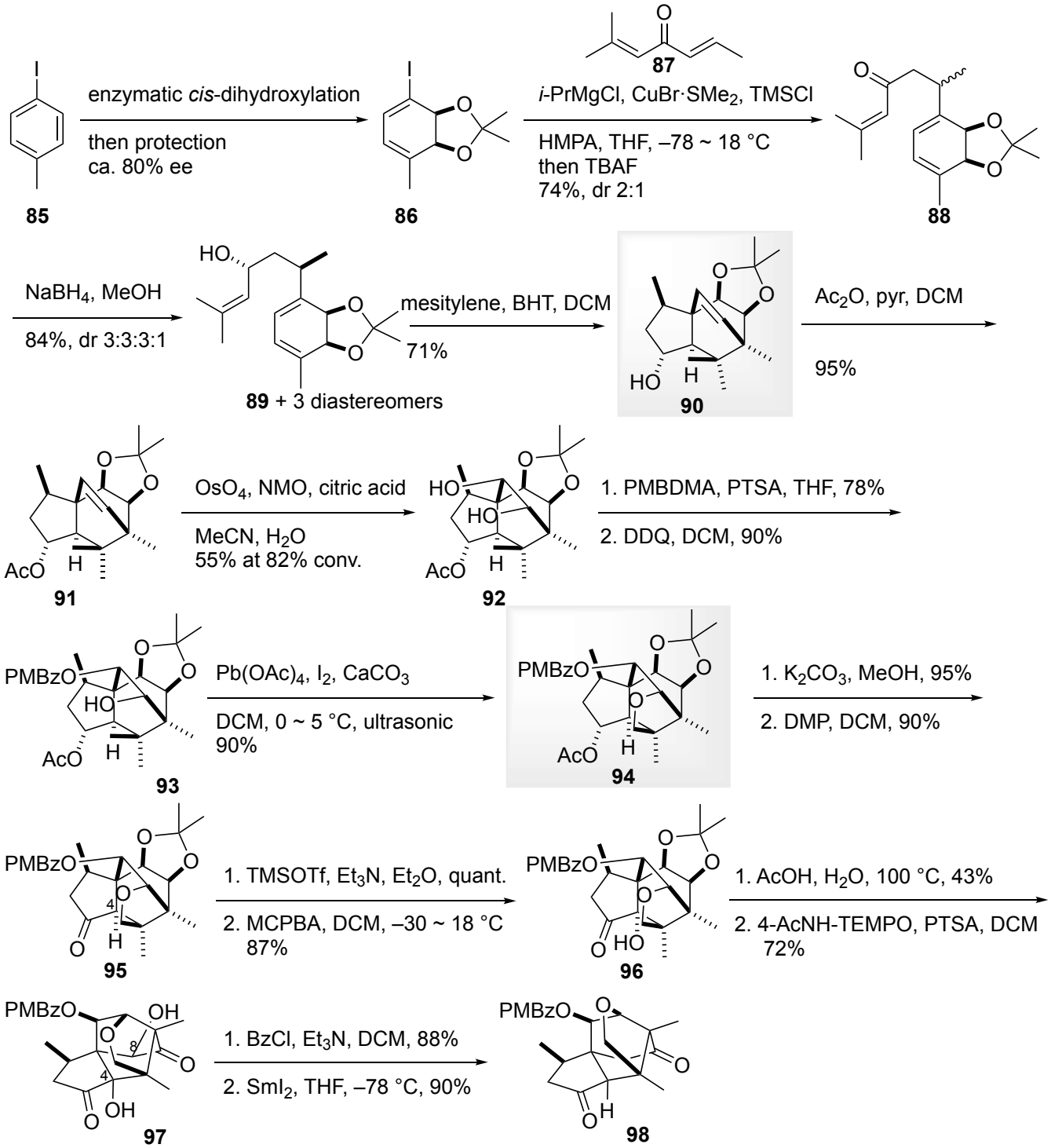
Scheme 6. Formal synthesis of (–)-11-*O*-debenzoyltashironin (**1**) by Maimone *et al*.[6]

The alkoxyradical-mediated C(sp^3)-H oxidation at C-14 of (+)-cedrol (**75**) under photoirradiation, according to Suaretz's protocol,[23] led to a strained tetrahydrofuran **76**. This compound was methylated and eliminated in one pot by treatment with Meerwein reagent, yielding olefinic methyl ether **77**. The double bond of the methyl ether **77** was cleaved by $RuCl_3$ to afford keto-acid, which underwent transformation to lactone **78** through $CuBr_2$-mediated bromination and subsequent substitution. Hydrolysis of the δ-lactone **78** induced α-ketol rearrangement *via* carboxylate **79**, providing acid **80** as a diastereomeric mixture at C-6. Treatment of the hydroxy acid **80** with PTSA delivered γ-lactone **82** via an oxyallyl intermediate **81**. The γ-lactone **82** was reductively cleaved with lithium naphthalenide, furnishing acid **83** as a single diastereomer. The remote iron(oxo)-catalyzed C(sp^3)-H oxidation at C-4 was carried out with iron(mep) catalyst and *t*-butyl hydroperoxide (TBHP)[24] to achieve γ-lactone **84**. Cleavage of the methyl ether **84** led to hemiacetal **52** via epimerization at C-6, which was previously converted to 11-*O*-debenzoyltashironin (**1**) by Shenvi *et al*. in 5 steps (Scheme 4).

Cedrol (**75**) is a useful chiral starting block, and the authors additionally synthesized one dozen *Illicium* sesquiterpenoids from a variety of synthetic intermediates in Scheme 6.

7. Banwell's approach

Banwell *et al*. investigated the chemoenzymatic route towards the tashironin core **98** through the IMDA reaction (Scheme 7).[25,26] Chiral cyclohexadiene **86** was obtained by enzymatic *cis*-dihydroxylation of aryl iodide, followed by protection.[26] After metalation of the iodovinyl of diene **86** and subsequent transmetalation, the resulting cuprate was added conjugatively to dienone **87** to afford triene **88.** The IMDA reaction of a mixture of four isomeric allylic alcohols proceeded at 165 °C, resulting in the formation of *allo*-cedrane core **90**. Acetylation and subsequent dihydroxylation with OsO_4 led to diol **92** with high stereoselectivity.[27] Selective mono-protection of the hydroxy group at C-10 of the diol **92** was accomplished by protecting it as *p*-methoxyphenylbenzylidene acetal with *p*-methoxybenzaldehyde dimethyl acetal (PMBDMA), followed by oxidative cleavage with DDQ to generate hydroxy-benzoate **93**. The requisite tetrahydrofuran moiety was installed by the intramolecular alkoxy radical-mediated cyclization reaction of the alcohol **93** with $Pb(OAc)_4$ and iodine under ultrasound irradiation, yielding tetrahydrofuran **94**. Hydrolysis of the acetate **94**, followed by DMP oxidation, gave ketone **95**. The introduction of the α-hydroxyl group at C-4 was achieved by Rubottom oxidation to result in hydroxy-tetrahydrofuran **96** having the architecture of tashironins. Hydrolysis of the acetonide led to triol, which was then mono-oxidized to *bis*-acyloin **97** using a sterically demanding oxoammonium salt derived from the PTSA-promoted disproportionation of 4-acetamido-TEMPO.[28] Benzoylation provided the triester, which was treated with SmI_2 to afford the C4/8 deoxygenated compound **98** related to the tashironin class of sesquiterpenoids.

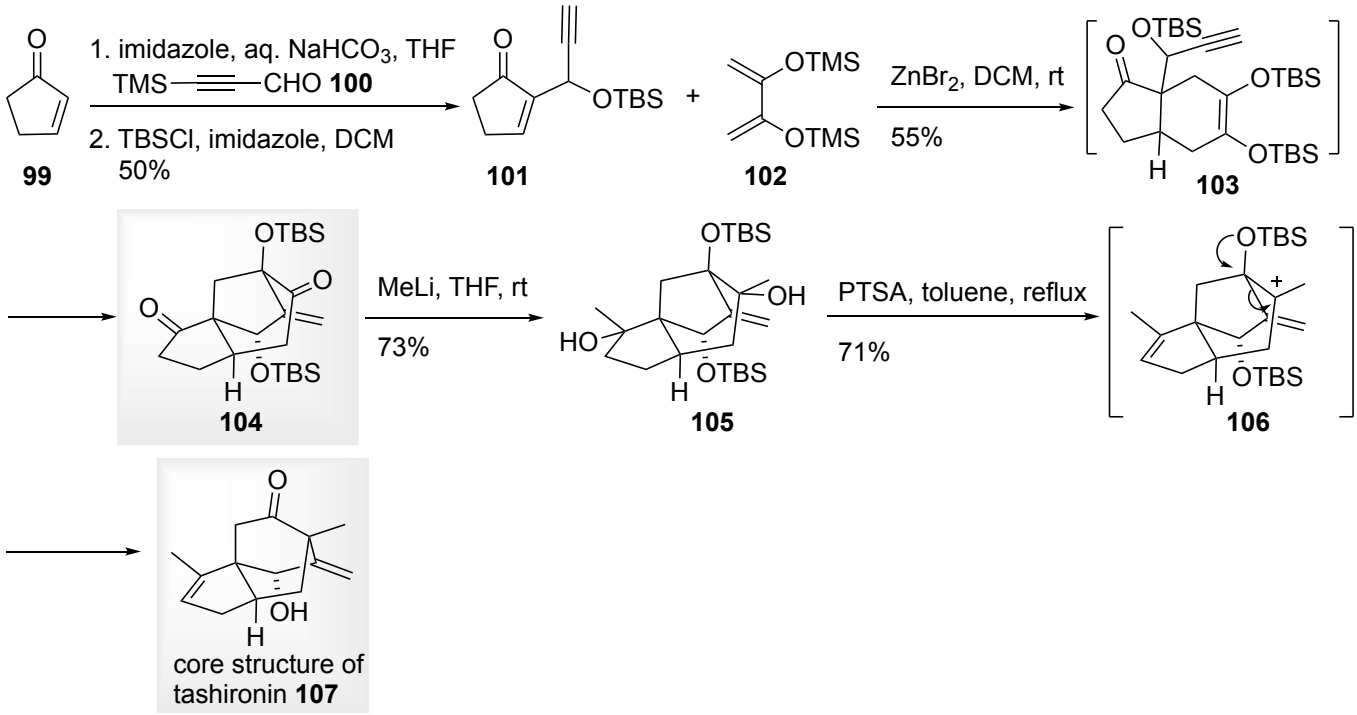


Scheme 7. Synthesis of tashironin core **98** by Banwell *et al*.[25,26]

8. Zhu's approach

Zhu *et al*. reported the synthesis of the *allo*-cedrane core **107**, which is related to tashironins through cascade Diels-Alder and carbocyclization reactions (Scheme 8).[29] Dienophile **101** was prepared by subjecting cyclopentenone **99** to a Morita-Baylis-Hillman reaction with 3-trimethylsilyl-2-propinal **100**, followed by protection. Subsequently, the Lewis acid mediated intermolecular Diels-Alder reaction of the

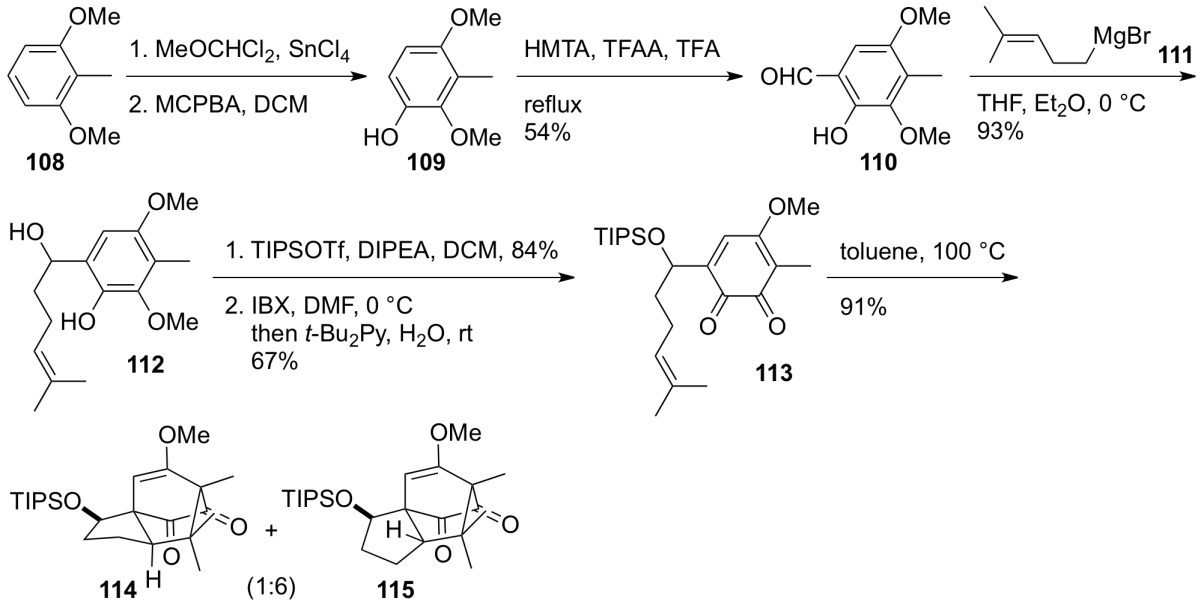
dienophile **101** with *bis*-trimethylsilyldiene **102** proceeded at room temperature, leading to the formation of tricyclic compound **104** diastereoselectively through a 5-*exo*-*dig* mode carbocyclization of resulting yne-enolate **103**. The addition of methyllithium to the diketone **104** provided diol **105**, which, upon heating at reflux with PTSA, underwent a pinacol rearrangement to furnish *allo*-cedrane core **107**.



Scheme 8. Synthesis of tashironin core **107** by Zhu *et al*.[29]

9. Tanino's approach

Tanino *et al*. reported the synthesis of *allo*-cedrane core **114** via the IMDA of *ortho*-benzoquinone **112** (Scheme 9).[30]



Scheme 9. Synthesis of tashironin core **114** by Tanino *et al*.[30]

Formylation of 1,3-dimethoxybenzene **108**, followed by Dakin oxidation according to the literature procedure,[31] yielded phenol **109**. Subsequent formylation using hexamethylenetetramine (HMTA) in trifluoroacetic anhydride (TFAA) afforded benzaldehyde **110**, which reacted with Grignard reagent **111** to produce alcohol **112**. *ortho*-Benzoquinone **113** was obtained by protecting the secondary alcohol in compound **112**, followed by IBX oxidation and hydrolysis of the resulting quinonium cation. The IMDA reaction of *ortho*-benzoquinone **113** proceeded smoothly, though the desired 4α-cycloadduct **114** was obtained as a minor product.

10. Conclusion

The highly oxidized and strained architecture, along with the intriguing physiological activity of (–)-11-*O*-debenzoyltashironin (**1**), has motivated synthetic organic chemists to pursue total syntheses. Significant efforts have been devoted to this pursuit, showcasing diverse creativity and revealing several innovative synthetic strategies. One effective approach involved the use of IMDA (intramolecular Diels-Alder) reactions to introduce the bicyclo[2.2.2]octane moiety into the *allo*-cedrane framework. Additionally, the *oxa*-tetracyclic core of tashironin was successfully constructed by combining dearomatization and IMDA or subsequent RCM (ring-closing metathesis). Furthermore, the bicyclo[4.3.0]nonane structure integrated into the *allo*-cedrane framework was installed using either the double Michael reaction or transition metal catalyzed cyclization. Remarkable skeletal transformations of chiral pools were achieved, including C(sp^3)-H oxidations. Diverse regio- and stereoselective functionalizations were elaborated to enable the manipulation of oxidation states in the presence of various functional groups. The outcomes presented in this review provide strong encouragement for further studies, not only in the area of total syntheses of neurotrophic sesquiterpenoids but also for highly oxidized natural products. The development of new lead compounds for neurodegenerative diseases is highly desirable, given the challenges faced by aging societies. These efforts hold promise for advancing the field of medicinal chemistry and its potential contributions to society.

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