SYNTHETIC STUDIES TOWARD 11-O-DEBENZOYLTAHIRONIN

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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.

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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. Since then, more than 50 sesquiterpenoids, generated by the same biosynthetic pathway as anisatin (4) (Scheme 1), have been isolated from *Illicium* species.

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. 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. 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.* compiled and reviewed these works in 2014, and later in 2018 Maimone *et al.* 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 (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.
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 chem-, 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.* 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).

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$_3$P 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$_2$Zn and Ti(Oi-Pr)$_4$, yielding propargyl alcohol 20. Mesylation of 20, followed by S$_N$2’ 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 Pelter⁹ and Tamura¹⁰ protocol followed by brief microwave irradiation to efficiently afford the oxatetra cyclic 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 (NaBH₄) reduction of 23, followed by protection, gave silyl ether 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 [(PPh₃)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 oxatetra cyclic 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 oxatetra cyclic 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 oxatetra cyclic compound 38 as an inseparable 1:1 diastereomeric mixture. The carbonyl group of 38 was then reduced stereoselectively from the side of bromovinyl using NaBH₄. 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.
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 \( \Delta^3 \)-olefin 43 regioselectively. Treatment of 43 with MCPBA followed by aq. HF resulted in the formation of to give \( \alpha \)-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\textsubscript{2}O\textsubscript{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.\textsuperscript{15}

4. Shenvi’s total synthesis

Shenvi \textit{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).\textsuperscript{16}

Scheme 4. Total synthesis of (−)-11-O-debenzoyltashironin (1) by Shenvi \textit{et al.}\textsuperscript{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 Me2N-AlMe2 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 (SOCl2) 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 to result in the formation of 3,6-dideoxy-10-hydroxypseudoanisatin (61). 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.

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-end ene-yne cyclization and late-stage Ti(III)-mediated reductive coupling of aldehyde and lactone moieties (Scheme 5). The lactone 62, previously used in the synthesis of Danishefsky’s merrilactone (3) synthesis, was predominantly converted to β-epoxide 63. Equatorial acetoxylation using Pb(OAc)4 resulted in α-acetate 64. The addition of benzylomethyl 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.\textsuperscript{20}
The *trans*-hydrindane skeleton was constructed via 5-*endo* ene-yne cyclization catalyzed by [Pd(dppe)(PhCN)₂](SbF₆)₂, providing aldehyde 71 as the single isomer. The key C10-11 bridge was formed through McMurry reductive coupling between the formyl group and the proximal lactonic carbonyl group, utilizing Cp₂TiCl₂ and Zn to yield *trans*-diol 72, while reductive coupling with SmI₂ 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, SmI₂-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(sp³)-H oxidations (Scheme 6).⁶

![Scheme 6. Formal synthesis of (−)-11-*O*-debenzoyltashironin (1) by Maimone et al.⁶](image)
The alkoxyradical-mediated C(sp³)-H oxidation at C-14 of (+)-cedrol (75) under photoirradiation, according to Suaretz's protocol, 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 RuCl₃ to afford keto-acid, which underwent transformation to lactone 78 through CuBr₂-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(sp³)-H oxidation at C-4 was carried out with iron(mep) catalyst and t-butyl hydroperoxide (TBHP) 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-debenzyoltashironin (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). Chiral cyclohexadiene 86 was obtained by enzymatic cis-dihydroxylation of aryl iodide, followed by protection. 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 OsO₄ led to diol 92 with high stereoselectivity. 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-acloyl 97 using a sterically demanding oxoammonium salt derived from the PTSA-promoted disproportionation of 4-acetamido-TEMPO. Benzoylation provided the triester, which was treated with SmI₂ 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.\textsuperscript{25,26}

8. Zhu’s approach

Zhu et al. reported the synthesis of the \textit{allo}-cedrane core 107, which is related to tashironins through cascade Diels-Alder and carbocyclization reactions (Scheme 8).\textsuperscript{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 tashiron 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-Benzooquinone 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 4a-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(sp3)-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.

REFERENCES
Prof. Hisahiro Hagiwara obtained his B.Sc. and M.Sc. degrees from Tohoku University, and joined as a research associate in the Chemical Research Institute of Non-aqueous Solutions, Tohoku University. After receiving his Ph.D degree in 1979 from Tohoku University, he joined as a postdoctoral fellow in the University of Wisconsin in 1980~1982. After coming back to his alma mater, he was promoted to a full professor in Niigata University in 1996 and is an emeritus Professor of Niigata University since 2011. He has a broad spectrum of research interests toward developments of organic solid-state reaction, reaction on heterogeneous catalysts, synthetic protocols employing ionic liquids, domino Michael reaction for construction of carbocyclic ring and its application to natural product synthesis, and total synthesis of physiologically interesting terpenoid.