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Total Synthesis and Structure Revision of (−)-Illisimonin A, a Neuroprotective Sesquiterpenoid from the Fruits of *Illicium simonsii*

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Supporting Information

ABSTRACT: Illisimonin A was isolated from *Illicium simonsii* and has a previously unreported tricyclic carbon framework. It displayed neuroprotective effects against oxygen-glucose deprivation-induced cell injury in SH-SY5Y cells. It incorporates a highly strained trans-pentalene ring system. We report the first synthesis of (±)-illisimonin A. Notable steps in the route include a 1,3-dioxa-2-silacyclohexene templated Diels−Alder cycloaddition and type-3 semipinacol rearrangement to generate the trans-pentalene. The final step is an iron-catalyzed C−H oxidation. The synthetic route is robust, with 94 mg of racemic material prepared in a single pass. Resolving an intermediate enabled the synthesis of natural (−)-illisimonin A. The absolute configuration of (−)-illisimonin A was revised to 1*S*,4*S*,5*S*,6*S*,7*R*,9*R*,10*R* based on the X-ray structure of a heavy-atom analogue.

The ornate structures of the *Illicium* sesquiterpenes have challenged chemists' creativity for decades. Isolated from roughly 40 species of plants, these molecules can be classified on the basis of their carbon skeleton.[1] Members of the *allo*-cedrane,[2] *seco*-prezizaane,[3] and anislactone[4] families have succumbed to total synthesis. Illisimonin A (**1**) was recently isolated from *Illicium simonsii* and is the first example of a sesquiterpenoid with a tricyclo[5.2.1.$0^{1,6}$]decane carbon framework (Figure 1).[5] The absolute configuration was assigned by matching a calculated electronic circular dichroism (ECD) spectrum with the experimental CD data.[6] It has already inspired methods development from other groups.[7] Herein, we report the first total synthesis of this strained molecule.[8]

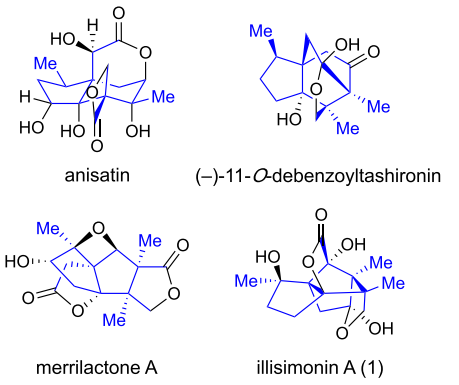

Figure 1. Illisimonin A and other *Illicium* natural products. The four unique carbon skeletons are outlined in blue.

A historically important member of the *Illicium* sesquiterpenoids is the *seco*-prezizaane, anisatin.[9] Anisatin and several other related molecules can cause convulsions, acting as noncompetitive antagonists for $GABA_A$ channels. However, seemingly similar molecules such as jiadefenolide,[10] merrilactone,[11] and *O*-debenzoyltashironin[12] are known to be neurotrophic. That is, they can promote the survival or growth of neural cells. This interesting phenotypic observation is of great interest, but interrogation of the biochemical basis for this activity has been hampered, in part, by the limited supply of these precious natural products. Recently, Shenvi and coworkers have reported elegant syntheses of jiadefenolide[13] and *O*-debenzoyltashironin.[2c] The material obtained from these syntheses has been leveraged to characterize several differences between the actions of "neurotrophic" and "convulsant" sesquiterpenoids.[14] Access to other, distinct *Illicium* sesquiterpenoids would be valuable to understanding more clearly how these molecules work.

Illisimonin A displayed neuroprotective effects against oxygen-glucose deprivation-induced cell injury in SH-SY5Y cells. Given that only 4 mg of **1** was isolated from 96 kg of the fruits of *Illicium simonsii*, further studies were constrained by material availability. Motivated by the promising bioactivity of **1** as well as the unprecedented structure, we developed a laboratory synthesis capable of delivering over 100 mg of this scarce molecule.

Illisimonin A's 5−5−5−5−5 pentacyclic scaffold contains several challenges which we considered when designing our route, Figure 2. There are seven contiguous fully substituted stereocenters, five of which are on the central cyclopentane ring, and two of which are vicinal and quaternary. Additionally there is a trans-pentalene ring system. The instability of trans 5−5 systems relative to their cis counterparts is well documented.[15] Illisimonin A is only the fourth natural product with an embedded trans-pentalene subunit to be synthesized.[16] Thus, the strain embedded in the molecule, stereochemical complexity, and steric congestion led us to the following retrosynthesis.

A retrosynthetic plan is outlined in Figure 2. Excision of the bridging lactone via a White acid-directed C−H oxidation[17] had close precedent in Maimone's pseudoanisatin synthesis,[18] and gives **2** after some functional group manipulations. The semipinacol rearrangement has been used in numerous

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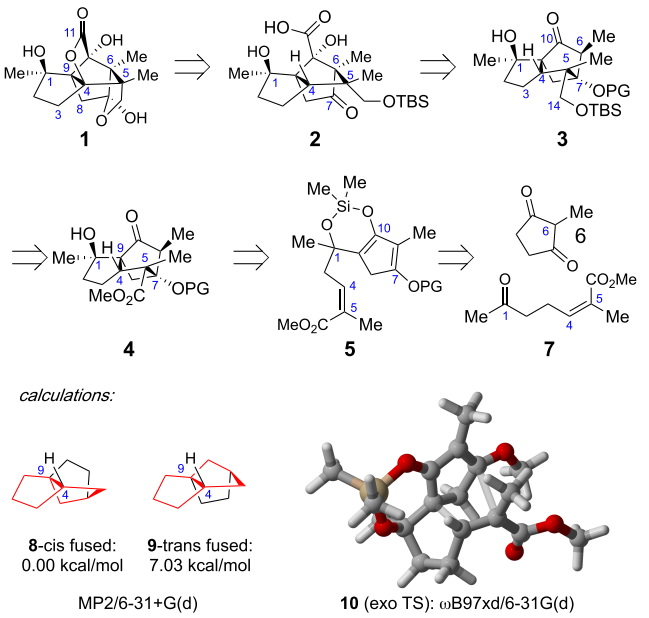


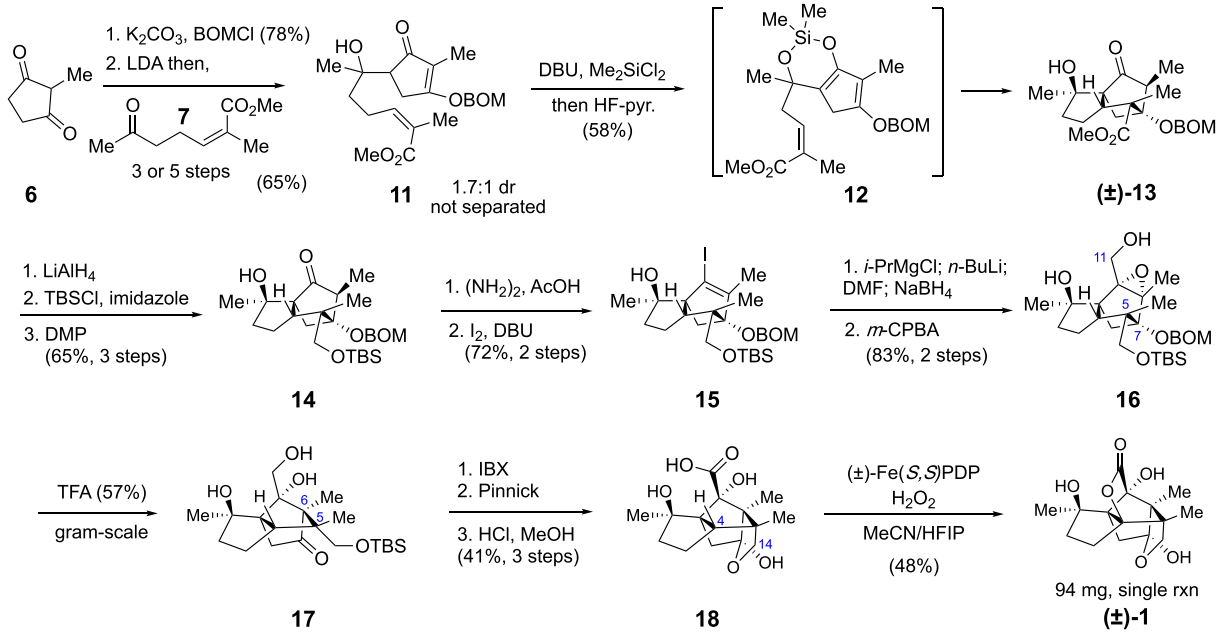
Figure 2. Retrosynthetic analysis and calculations of ring strain energies

syntheses to construct strained ring systems and congested bonds.[19] Disconnection of the C5−C6 bond via a semipinacol rearrangement leads to tricycle **3** after the application of additional routine transforms. We imagined that two of the rings within **3** or a similar structure could be constructed by the Diels−Alder reaction. Finally, **5** could be traced back to **6** and **7** via an aldol reaction.

Intermediate **2** has the all-carbon framework of **1**, and is expected to carry significant ring strain. We estimated the relative ring strain of **2** and its proposed precursor **3** by MP2 calculations on the hydrocarbons **9** and **8**.[20] Hydrocarbon **8** is favored by ca. 7.0 kcal/mol, which suggests that **3** is much less strained than **2**. The difference can be attributed to the embedded strained trans 5−5 ring system in **2** (and **1**). We planned to take advantage of this stability difference by first synthesizing **4**, with a cis 5−5 ring system, in an intramolecular Diels−Alder (IMDA) reaction. The required exo preference should be enforced by the much higher energy expected in the trans 5−5 endo product. Transition state calculations supported this hypothesis, with calculated structure **10** being 7.3 kcal/mol more stable than corresponding endo transition state.[21] High selectivity in the exo IMDA reaction would introduce four stereogenic centers, and the more strained ring system would arise in a semipinacol reaction leading to compound **2**. Ring strain preferences enhance the stereoselectivity in the central IMDA reaction.

The synthesis is outlined in Scheme 1. To begin, 2-methylcyclopenta-1,3-dione (**6**) was captured in its enol form as the benzyloxymethyl ether in good yield. Next, an aldol reaction united vinylogous ester with known ketone **7** (available in 3 or 5 steps from commercial material),[22] to afford tertiary alcohol **11** as a mixture of diastereomers. At this stage, we drew inspiration from the Bélanger lab's work targeting the core ring structure of calyciphylline B type alkaloids.[23] They trap an aldehyde aldol as the 1,3-dioxa-2-silacyclohexene, and use this motif to template a Vilsmeier−Haack cyclization. A similar silacycle should template our proposed IMDA reaction. Silyl triflates were initially explored, but dimethyldichlorosilane was superior in practice. The silacycle **12** was formed in situ from the mixture of diastereomers; it was warmed to 40 °C for 15 h. Desilylation and purification gave the desired Diels−Alder adduct, racemic **13**, in good yield as a single diastereomer. Presumably, silylation of the tertiary alcohol leads to intramolecular activation of the cyclopentenone, which is trapped as the silyl-enol ether upon deprotonation. The resultant cyclopentadiene[24] then engages the dienophile in a Diels−Alder cyclization, whose diastereofacial selectivity is templated by the silacycle. The IMDA sequence introduces five additional stereocenters and two rings in a single step. To our

Scheme 1. Synthesis of (±)-Illisimonin A



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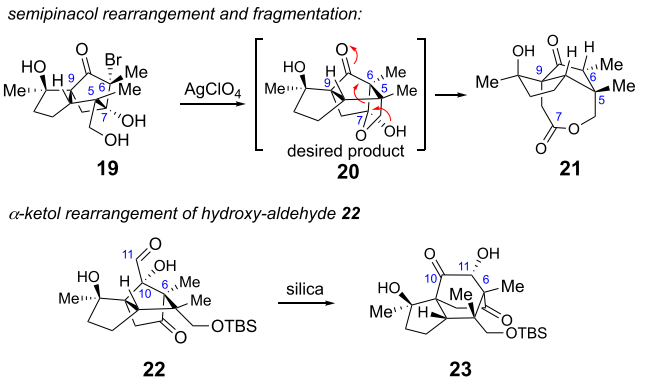
knowledge, there are only four other examples of generating a 1,3-dioxa-2-silacyclohexene from an aldol, and none in a completed total synthesis.[25] We are eager to explore this as a method to generate other ring systems in the future.

Having served its role as an electron accepting group in the Diels–Alder reaction, the methyl ester in **13** needed to be reduced to a primary alcohol. The transformation was most easily accomplished by global lithium aluminum hydride (LAH) reduction, *tert*-butyldimethylsilyl ether (TBS) protection of the newly formed primary alcohol, and reoxidation of the C10 ketone to deliver **14** in good overall yield. At this point the semipinacol rearrangement was attempted. Deprotection of **14** and bromination of the resulting ketone proceeded as expected to give bromide **19**, Scheme 2. Upon

Scheme 2. Rearrangements and Fragmentations



treatment with silver(I), the anticipated lactol product was not observed. Instead, ε-lactone **21** was isolated. Apparently, the semipinacol shift of C5 from C7 to C6 took place to generate the desired trans 5,5-ring system (**20**), but the resulting lactol spontaneously underwent a retro-Claisen fragmentation. The inferred formation of **20** was very promising, but the sequence was not viable for the synthesis of illisimonin A. In order to avoid this reactivity, we chose to install the C11 carbon first prior to the semipinacol shift.

After many failed attempts to add a carbon atom to the C10 ketone via methylenation,[26] Corey–Chaykovsky epoxidation,[27] triflation and palladium catalyzed carboxy-methylation,[28] and even intramolecular alkoxyacyl radical addition to the ketone,[29] a solution was found. Vinyl iodide **15** was formed using Barton's method.[30] Bouvealt aldehyde synthesis[31] and *in situ* reduction[32] delivered the crude allylic alcohol, which was oxidized with *m*-CPBA to give epoxide **16** in good overall yield.[33]

To our delight, a type-3 semipinacol proceeded in chloroform in the presence of a substoichiometric amount of trifluoroacetic acid (TFA), and the rearrangement was successful on a multigram scale. Competing hydride migration from the primary alcohol was a concern, but only small amounts of an aldehyde were seen in the crude nuclear magnetic resonance (NMR). Evidently, the rigid conformation of the molecule facilitates selective migration of the σ_{C5-C7} bond over the σ_{C11-H}. Having established the two vicinal quaternary centers and trans-pentalene contained within illisimonin A, three oxidations separated us from our target.

Sequential oxidation of the C11 carbon to the aldehyde then carboxylic acid was accomplished using standard chemistry.[34] When attempting to purify α-hydroxy aldehyde **22** by column chromatography, rearrangement to α-hydroxyl ketone **23** occurred, Scheme 2. The rearrangement could be avoided by taking the material forward directly without chromatographic purification. While the transformation can be rationalized as a retro-aldol/aldol sequence, it is likely due to an α-ketol rearrangement, as rearrangements of strained α-hydroxy aldehydes and ketones catalyzed by silica have been reported in the literature.[35] The facile isomerization to the more stable [2.2.2]-bicycle highlights the strain contained within illisimonin's ring system. It is interesting to note that the isolation team proposed that the illisimonane skeleton could arise from a carbocation shift of the *allo*-cedrane skeleton.[5] The conversion of **22** to **23**, which bears the *allo*-cedrane skeleton, is the synthetic reverse of the proposed biosynthetic step.

After deprotection of the primary alcohol with methanolic HCl, only the C–H oxidation remained to complete the synthesis. As the C4 methine was doubly neopentylic, extreme steric hindrance could block oxidation. However, Snyder recently described an acid-directed White oxidation of a comparably congested C–H bond in his scaparvin B-D syntheses.[36] Our gamble was rewarded when acid **18** was oxidized to lactone **1** using White's FePDP catalyst with hydrogen peroxide as the stoichiometric oxidant. Some points about this reaction warrant further discussion. Hexafluoroisopropanol (HFIP) was included to improve the solubility of **18**, and may also play a role in suppressing the undesired oxidation of the C14 methylene by electronically deactivating the position through hydrogen bond donation.[37] The rigid conformation of **18** likely aids in the high reactivity for the C4 methine. We speculate that strain release in the transition state may also enhance the reactivity at this position.[38] The reaction proved to be effective after minimal optimization. We were pleased to obtain 94 mg of natural product **1** from 196 mg of acid **18** in our largest reaction.

The assigned absolute configuration of illisimonin A was unexpected because related *illicium* natural products had the opposite configuration at C1.[39] The racemic synthesis described above did not inform the discussion, but it was a starting point to revisit it. After several other methods were explored, intermediate allylic alcohol (±)-**24** was resolved by derivatizing with (*S*)-1-(1-naphthyl)ethyl isocyanate and separating the diasteriomers by silica gel chromatography (Scheme 3).[40] The lower R_f diastereomer **26** was deprotected, converted to the epoxide (−)-**16** and further derivatized. Esterification of the C11 alcohol with ferrocenecarboxylic acid (**28**) added a heavy atom. X-ray analysis of crystalline ester **29** allowed the absolute configuration of **26** to be assigned to the 1*R* series.[41] The higher R_f diastereomer **27**, inferred to have the 1*S* configuration, was deprotected and taken on to (−)-illisimonin A using the previously developed sequence. The CD of this synthetic material matched that reported for the natural product.[5] Thus, the absolute configuration of the natural product, (−)-illisimonin A, is revised to 1*S*,4*S*,5*S*,6*S*,7*R*,9*R*,10*R*.

We report the first synthesis of (±)-illisimonin A. The NMR data for synthetic illisimonin A matched that reported for the natural product, confirming its relative configuration. An enantioselective synthesis of (−)-illisimonin A, combined with an X-ray structure, led to a revision of the absolute configuration of the natural product. Notable steps in the synthetic route include a 1,3-dioxa-2-silacyclohexene templated Diels–Alder cycloaddition and type-3 semipinacol rearrangement. The final step is a White acid-directed C–H oxidation.

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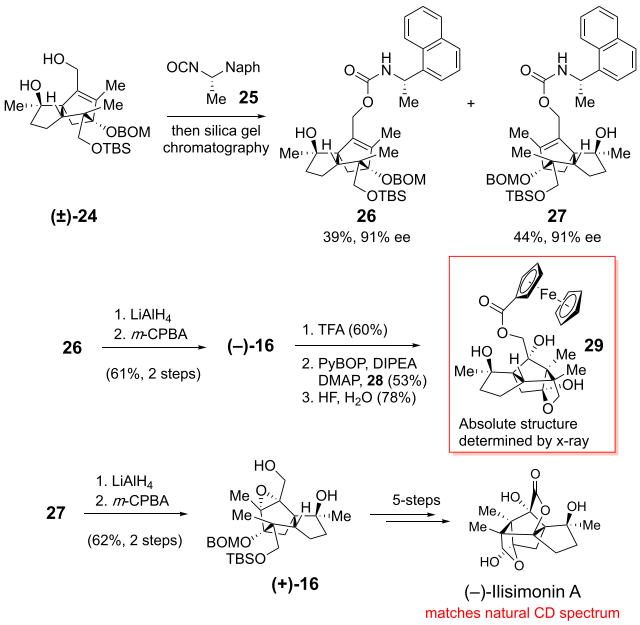
Scheme 3. Enantioselective Synthesis and Structure Revision



The route is effective, and has enabled the preparation of 165 mg of (±)-Illisimonin A. This material will be valuable in exploring its neurotrophic bioactivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b05065.

FID files for the NMR spectra of synthetic illisimonin A (ZIP)

Data for ester (+)-**29** (CIF)

Experimental procedures and characterization data for all compounds; coordinate files for computational modeling (PDF)

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Notes

The authors declare no competing financial interest.

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