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Asymmetric Synthesis of *ent*-Fissistigmatin C

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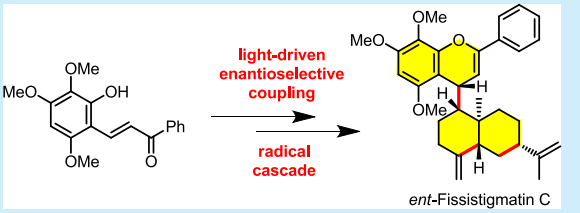
ABSTRACT: The asymmetric synthesis of *ent*-fissistigmatin C is successively accomplished in 12 steps (longest linear sequence (LLS)). Relying on the enantioselective coupling of aliphatic aldehyde with 2-hydroxychalcone promoted by cooperative organocatalysts, the pivotal linkage of *ent*-fissistigmatin C between the flavonoid and the sesquiterpenoid fragment was stereoselectively established. An unprecedented final-stage radical cascade was also featured in this synthesis, which enabled the simultaneous establishment of the *trans*-decalin framework via forging two consecutive C−C bonds in one step.



Fissistigmatins are a novel type of sesquiterpenoid hybrid flavonoid isolated from *Fissistigma bracteolatum Chatt.* (Annonaceae) by Adam and coworkers (Figure 1).[1] Structurally, fissistigmatins contain a flavonoid and a sesquiterpenoid fragment connected by the C4−C1′′ bond. Light has played an import role in the biosynthesis of flavonoids, and it is well established that 2-hydroxychalcone **4** and flavylium salt **5** are in equilibrium under the irradiation of ultraviolet light with the aid of Brønsted acid, which is responsible for the biosynthesis of related hybrid flavonoids.[2] In this context, Adam speculated that the initial double-bond isomerization of 2-hydroxychalcone **4** promoted by ultraviolet light leads to *Z*-enone, which undergoes a dehydrated cyclization to afford flavylium cation **5** in the presence of Brønsted acid.[1,2] Subsequently, a cationic cascade is initiated via the nucleophilic attack of germacrene A **6** to flavylium cation **5**, enabling the construction of the *trans*-decalin moiety via the consecutive formation of C4−C1′′ and C5′′−C10′′ bonds. Because the stereogenic center of C4 fissistigmatins A and C is opposite to that of fissistigmatin B, it is evident that the initial nucleophilic addition step might spontaneously proceed without the aid of an enzyme, thus leading to mixtures of diastereoisomers.

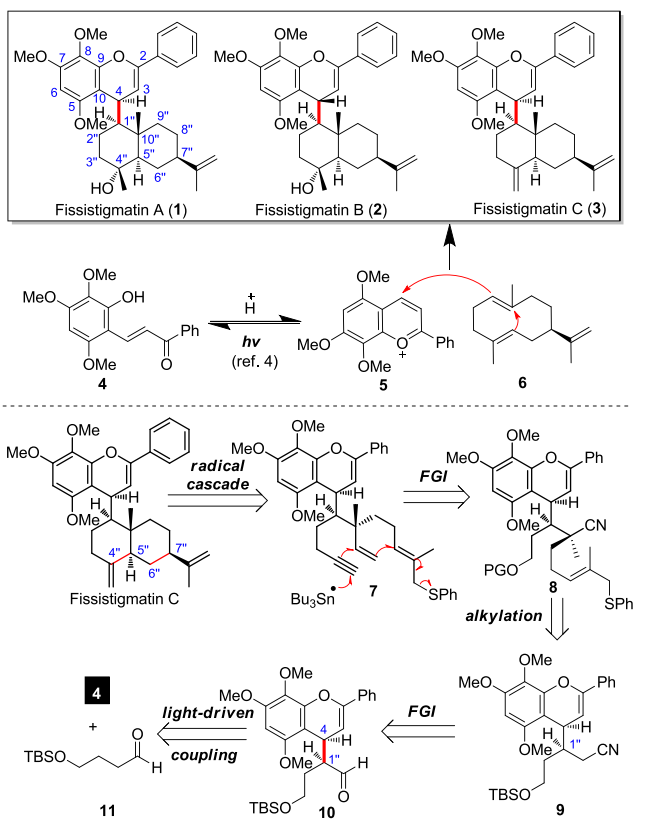


Figure 1. Structure of fissistigmatins and retrosynthetic analysis of fissistigmatin C.

Despite the intriguing structural features of fissistigmatins, no synthetic approach has been reported to date. From a synthetic viewpoint, the stereoselective construction of the pivotal C4−C1′′ linkage constituted the major challenge for the asymmetric synthesis of this type of natural product. Recently, we developed a bioinspired strategy for the synthesis of a hybrid flavonoid driven by visible light[3] and also disclosed a cooperative organocatalyst-promoted enantioselective coupling of aliphatic aldehyde with 2-hydroxychalcone under the

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irradiation of visible light,[3c] which provided a facile solution for the stereoselectivity of our previous work. Herein we accomplished the asymmetric synthesis of fissistigmatins.

As depicted in Figure 1, we chose to set the construction of the sesquiterpenoid moiety in the final stage and envisioned a tributylstannyl-initiated radical cascade via the double *6-exo-trig* cyclization of dienyne **7** followed by the elimination of the thioether moiety.[4] Despite the concern of regioselectivity and stereoselectivity, this strategy was appealing because it would enable forging of the *trans*-decalin scaffold and two terminal olefins of fissistigmatin C via consecutive formation of the C4′′−C5′′ and C6′′−C7′′ bonds. The alkyne and terminal alkene moieties of **7** could, in turn, be derived from the TBS-protected alcohol and nitrile moieties of **8** through functional group manipulations. Next, we surmised that a sequential alkylation of nitrile **9** would diastereoselectively set up the quaternary carbon center induced by the stereogenic C1′′ with a bulky flavonoid fragment. To this end, we came to a hybrid flavonoid **10**, which could be transferred to nitrile **9** by the derivatization of the aldehyde moiety. In this context, an enantioselective coupling of aldehyde **11** with 2-hydroxychalcone **4** promoted by cooperative organocatalysts driven by visible light was utilized.[3c]

As shown in Scheme 1, the synthesis commenced with the gram-scale synthesis of flavonoid ***ent*-10** by using the cooperative organocatalyst-promoted (*R*-TRIP and chiral imidazolidinone **A4**) coupling of 2-hydroxylchalcone **4** with a TBS-protected aliphatic aldehyde **11** driven by visible light.[3c] The stereoselectivity of this reaction originated from the synergistic action of both organocatalysts. As shown in **TS1** (Figure 1), the enamine derived from imidazolidinone **A4** rendered the electrophile coming from the *si* face, and the ion pairing of flavylium with the (*R*)-TRIP anion made the *si* face less steric for the attack of enamine. Importantly, the reaction provided satisfactory results (90% yield with 98% ee and >20:1 dr) on the gram scale, and two organocatalysts could be recycled 10 times in the gram -scale synthesis without a noticeable loss of reactivity. (See the Supporting Information.) With the reliable supply of flavonoid ***ent*-10**, we set out to execute the construction of the cyclization precursor **7**. Conversion of the aldehyde moiety of ***ent*-10** to nitrile by successive reduction with DIBAL-H, mesylation of the resulting alcohol, and substitution of the mesylate with potassium cyanide produced nitrile ***ent*-9** (82% yield in three steps). To stereoselectively install the quaternary carbon center C10′′, a sequential methylation followed by alkylation with **12** was intentionally executed, which gave access to ***ent*-8** in 50% yield (83% brsm) 4.5:1 dr.[6] This outcome could be rationalized by the transition state **TS2**, in which the smaller ketenimine anion rested between the bulkiest flavonoid fragment and the linear carbon chain.[5] The electrophile came from the opposite direction to the flavonoid moiety to give the desired diastereoisomer ***ent*-8**, which was confirmed by the subsequent elaboration to *ent*-fissistigmatin C. (*vide infra*). The subsequent removal of the TBS of ***ent*-8** with HCl, oxidation with Dess−Martin periodinane, followed by Seyferth−Gilbert homologation[7] smoothly delivered the alkyne **14**. Fortunately, the minor stereoisomer could be separated after the deprotection of TBS. Eventually, the reduction of the nitrile to aldehyde mediated with DIABL-H followed by the Wittig reaction furnished the cyclization precursor **7**.

The cascade radical cyclization of dienyne **7** proved to be quite challenging. After extensive optimization, the radical cascade of **7** was successively realized by employing AIBN/*n*-Bu_3SnH via heating in dilute toluene (Table 1, entry 1). To our delight, *ent*-fissistigmatin C could be isolated, albeit in 10% yield, from reaction mixtures after HPLC purification, and the other stereoisomers of *ent*-fissistigmatin C could not be identified. The analytic data (^1H and ^{13}C NMR spectra and optical rotation) of synthetic *ent*-fissistigmatin C were in good accordance with those of the natural product. (See the Supporting Information.) Unfortunately, the 5,7-fused ring products **15a**, **15b**, and **15c** were isolated in 20, 23, and 8% yield, respectively as the major products, which resembled fissistigmatin D,[3] a congener of fissistigmatins A−C. The structure of **15** was established by extensive NMR analysis. (See the Supporting Information.) The stereochemistry of C5′′ and C7′′ originated from the boat conformation of **I** and **II** via a double *6-exo-trig* cyclization/elimination process (path a). In this transition state, all substituents occupied the pseudoequatorial position that ensured the correct stereochemistry of C5′′ and C7′′. The 5/7 fused ring product **15** was envisioned to be generated via *3-exo-dig* cyclization of **II** (path b), then the ring opening followed by the *5-exo-dig* cyclization/elimination process (path b).[8] Although the cycloheptanyl radical **IV** might be directly formed through the *7-endo-trig* cyclization of the vinyl radical to alkene (path c), this process was kinetically unflavored based on previous observations and mechanistic studies.[8] The survey of reaction conditions for the radical cascade was thus extensively performed to improve the regioselectivity of the radical cascade. As shown in Table 1,

Scheme 1. Synthesis of the Cyclization Precursor

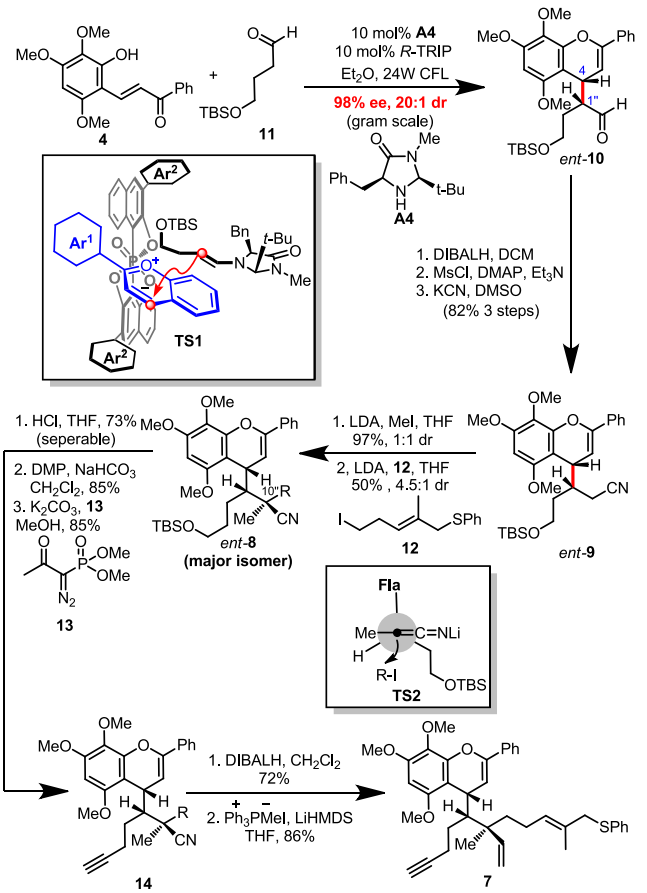

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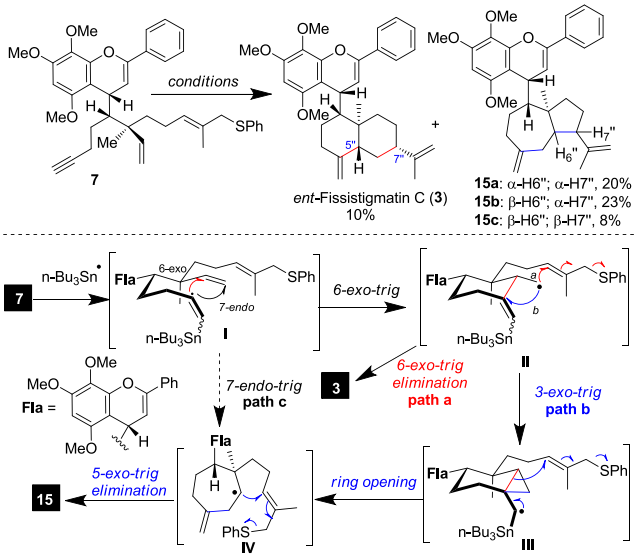
Table 1. Survey of the Reaction Conditions for the Radical Cascade



entry	reaction conditions	yield (%)[a]	3:15[b]
1	AIBN (3.0 equiv), n-Bu_3SnH (3.0 equiv), toluene (10 mL), 100 °C	68	1:7
2	ACHN (3.0 equiv), n-Bu_3SnH (3.0 equiv), toluene (10 mL), 100 °C	63	1:7
3	AIBN (3.0 equiv), Cy_3SnH (3.0 equiv), toluene (10 mL), 100 °C	71	1:9
4	AIBN (3.0 equiv), Et_3SnH (3.0 equiv), toluene (10 mL), 100 °C	32	1:7
5	AIBN (3.0 equiv), $(TMS)_3SIH$ (3.0 equiv), toluene (10 mL), 100 °C	ND	NA
6	AIBN (3.0 equiv), p-toluenethiol (3.0 equiv), t-BuOH, 100 °C	ND	NA
7	$(n\text{-}Bu)_3SnSn(n\text{-}Bu)_3$ (3.0 equiv), $h\nu$ (240 nm), THF, RT	ND	NA

[a]Isolated yield. [b]Determined by ^1H NMR. ACHN, 1,1′-azobis-(cyclohexylnitrile).

when ACHN was used as an initiator to obtain a moderate yield, no change in regioselectivity was observed (Table 1, entry 2). Using bulky (Cy_3SnH) or smaller (Et_3SnH) stannane led to detrimental results (Table 1, entries 3 and 4). Employing $(TMS)_3SiH$ and p-toluenethiol as a hydride source resulted in the decomposition of dienyne 7 (Table 1, entries 5 and 6). The generation of the stannane radical by the UV irradiation of distannane also gave no desired product (Table 1, entry 7). Eventually, different leaving groups instead of phenylsulfide were also evaluated, and no improvement of the regioselectivity was observed. (See the Supporting Information.)

In conclusion, the asymmetric synthesis of an enantioselective synthesis of *ent*-fissistigmatin C was accomplished in 12 steps (longest linear sequence (LLS)). By taking advantage of chiral phosphoric acid and chiral imidazolidinone as cooperative catalysts, the direct coupling of 2-hydroxychalcone to aliphatic aldehyde enabled the enantioselective forging of the C4−C1″ linkage of *ent*-fissistigmatin C. A radical cascade for establishing the *trans*-decalin from the linear precursor framework was also featured.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03766.

Procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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