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Biomimetic Total Synthesis of Hyperjapones A–E and Hyperjaponols A and C

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Abstract: *Hyperjapones A–E and hyperjaponols A–C are complex natural products of mixed aromatic polyketide and terpene biosynthetic origin that have recently been isolated from Hypericum japonicum. We have synthesized hyperjapones A–E using a biomimetic, oxidative hetero-Diels–Alder reaction to couple together dearomatized acylphloroglucinol and cyclic terpene natural products. Hyperjapone A is proposed to be the biosynthetic precursor of hyperjaponol C through a sequence of: 1) epoxidation; 2) acid-catalyzed epoxide ring-opening; and 3) a concerted, asynchronous alkene cyclization and 1,2-alkyl shift of a tertiary carbocation. Chemical mimicry of this proposed biosynthetic sequence allowed a concise total synthesis of hyperjaponol C to be completed in which six carbon–carbon bonds, six stereocenters, and three rings were constructed in just four steps.*

Hyperjapones A–E[1] (Figure 1, **1**–**5**) are a family of five structurally related meroterpenoids isolated from *Hypericum japonicum*, a plant used to treat hepatitis in traditional Chinese medicine. Hyperjapone A is a racemic natural product with an 11-6-6 tricyclic ring system. Hyperjapones B–E are enantiopure natural products which share a common 4-9-6-6 ring system. Further racemic natural products, hyperjaponols A–C[2] (**6**–**8**), have also been isolated from *Hypericum japonicum*. The most structurally intriguing of these natural products is hyperjaponol C (**8**) because its stereochemically complex, but racemic, *trans*-isodaucane framework implies a highly predisposed, non-enzymatic biosynthesis.

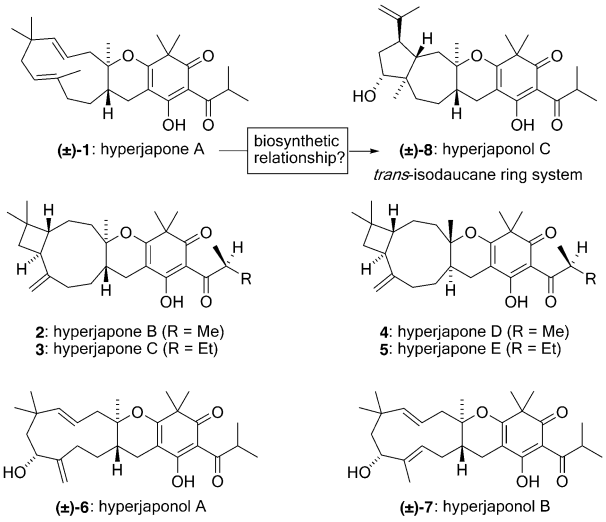

Figure 1. Hyperjapones A–E and hyperjaponols A–C.

Our detailed proposal for the biosynthesis of hyperjapone A (**1**) and its conversion into hyperjaponols A–C (**6**–**8**) is presented in Scheme 1. First, trimethylation of acylphloroglucinol **9** would give the dearomatized natural product norflavesone (**10**).[3] Oxidation of **10** would give the α,β-unsaturated ketone **12**, which could be expected to exhibit similar reactivity to an *o*-quinone methide.[4] It could therefore undergo a non-enzymatic, hetero-Diels–Alder reaction with humulene (**11**) to give racemic hyperjapone A (**1**). The $\Delta^{1,2}$ alkene of humulene was shown to be the most reactive dieneophile in hetero-Diels–Alder reactions between humulene and an *o*-quinone methide in both the biomimetic synthesis of lucidene by Baldwin et al.[5] and the biomimetic synthesis of guajadial B by Liu and co-workers.[6] The biosynthesis of hyperjapone A (**1**) should therefore be inherently regioselective with respect to humulene (**11**). The hetero-Diels–Alder reaction would also be expected to be regioselective with respect to the α,β-unsaturated ketone **12** as its most stable tautomer would be stabilized by an intramolecular hydrogen bond (as shown in Scheme 1). Hyperjapones B–E (**2**–**5**) could arise from a similar non-enzymatic, oxidative hetero-Diels–Alder reaction between a trimethylated acylphloroglucinol and the reactive *trans* $\Delta^{4,5}$ alkene of caryophyllene (**18**).[7]

The X-ray crystal structure of hyperjapone A (**1**) shows that it adopts a conformation with one face of the $\Delta^{8,9}$ alkene exposed, while the other face is sterically hindered inside the 11-membered ring (Scheme 1).[1] Diastereoselective epoxidation of the exposed face of the $\Delta^{8,9}$ alkene would therefore give epoxide **13**, which has a 1*R**2*R**8*S**9*S** relative configuration. A similarly regio- and diastereoselective result was obtained in a recent diepoxidation of humulene (**11**) by Fujita and co-workers, in which the structure of the diepoxide product was elucidated using the crystalline sponge method.[8] Acid-catalyzed ring opening of epoxide **13** would generate tertiary carbocation **14**, with the carbocation centered at the C9 position. Deprotonation of **14** could then give either hyperjaponol A (**6**) or hyperjaponol B (**7**). Alternatively, a stereoselective cation–alkene cyclization of **14** could give secondary carbocation **15**, with the relative configuration of the newly formed *trans* ring junction dictated by the orientation of the $\Delta^{4,5}$ alkene in the favored hyperjapone A conformation. A stereospecific 1,2-alkyl shift of secondary

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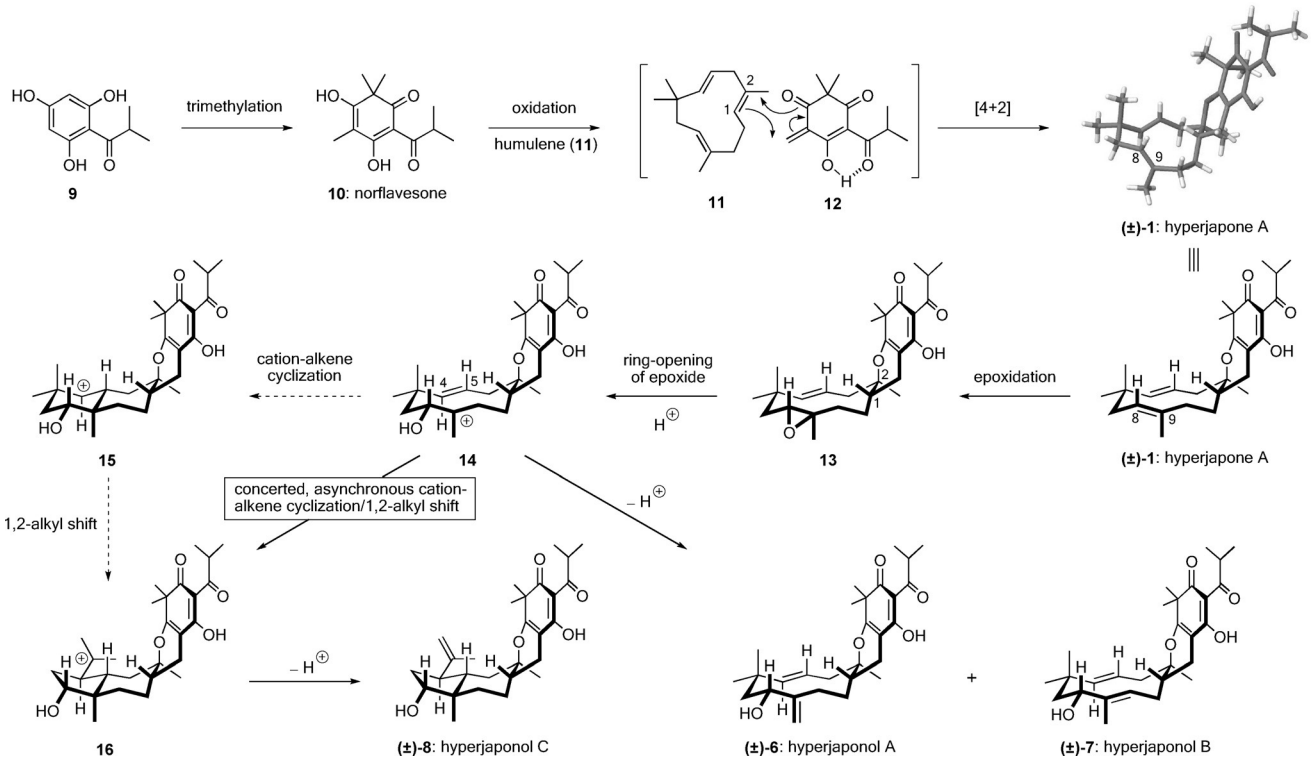
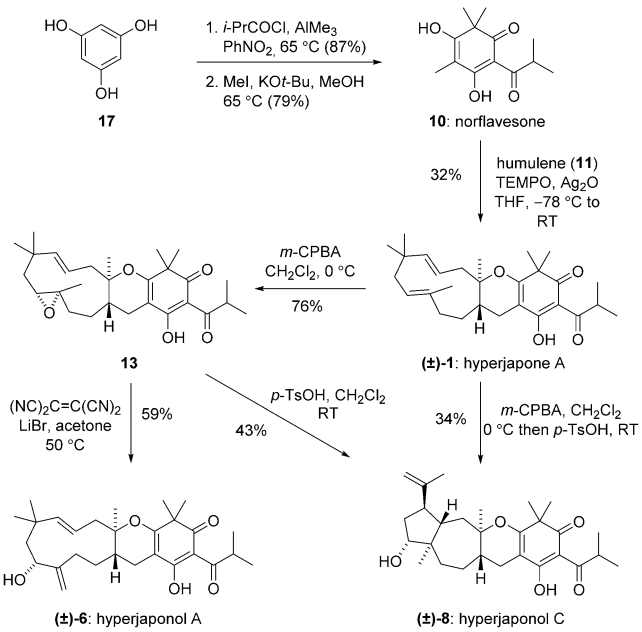


Scheme 1. Proposed biosynthesis of hyperjaponol C from hyperjapone A through a concerted, asynchronous alkene cyclization/1,2-alkyl shift.

carbocation **15** would then generate tertiary carbocation **16**, and a final deprotonation would give hyperjaponol C (**8**). Alternatively, it is perhaps more likely that carbocation **14** would directly rearrange to give carbocation **16** through a concerted, asynchronous alkene cyclization/1,2-alkyl shift. Similar concerted carbocation rearrangements in terpene biosynthesis have been proposed and studied computationally by Tantillo and co-workers.[9]

The primary aim of this project was to use the biosynthetic hypothesis outlined in Scheme 1 as the blueprint for a divergent, biomimetic synthesis of hyperjaponols A–C (**6**–**8**) from hyperjapone A (**1**). Our synthesis of hyperjapone A began with Friedel–Crafts acylation of phloroglucinol (**17**) with isobutyryl chloride to give an acylphloroglucinol,[10] which was dearomatized by means of trimethylation[11] to give norflavesone (**10**) in good yield over two steps (Scheme 2). Oxidation of **10** with TEMPO and Ag_2O in the presence of humulene (**11**) then generated hyperjapone A (**1**) in 32% yield, presumably through a hetero-Diels–Alder reaction between the α,β-unsaturated ketone **12** generated in situ and humulene (**11**). The use of TEMPO and Ag_2O in tandem was the result of extensive reaction optimization (see the Supporting Information for full details). Ag_2O has previously been used for the oxidative generation of *o*-quinone methides,[12] but not in the oxidative formation of α,β-unsaturated ketones. We have previously used a combination of TEMPO and PhI(OAc)$_2$ to induce a similar oxidation to generate an α,β-unsaturated ketone that underwent a 6π-electrocyclization in our biomimetic synthesis of hyperguinone B.[13]

With a concise synthesis of hyperjapone A (**1**) established, we next focused on its biomimetic conversion into hyperjaponol C (**8**). As expected from molecular modelling studies and Fujita's humulene epoxidation work,[8] treatment of **1** with *m*-CPBA generated epoxide **13** as a single diastereomer in 76% yield through diastereoselective oxidation of the $\Delta^{8,9}$ alkene. We were then delighted to observe that acid-

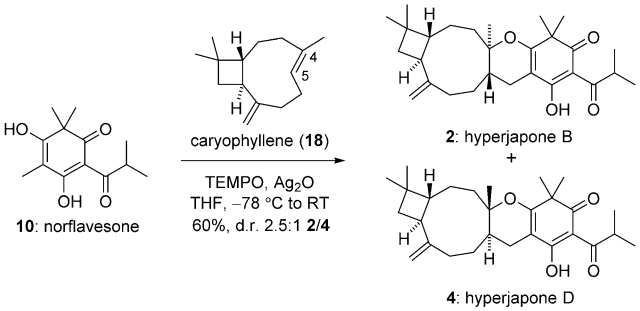


Scheme 2. Total synthesis of hyperjapone A and hyperjaponols A and C. TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; *m*-CPBA = 3-chloroperoxy-benzoic acid; *p*-TsOH = *p*-toluenesulfonic acid.

catalyzed rearrangement of **13** using *p*-TsOH in CH_2Cl_2 gave hyperjaponol C (**8**) in 43% yield, presumably by the concerted, asynchronous alkene cyclization/1,2-alkyl shift mechanism outlined in Scheme 1. The use of $AgNO_3/SiO_2$ chromatography was essential in the purification of **8** from trace reaction by-products.[14] The synthesis of **8** could be streamlined by combining the epoxidation and acid-catalyzed rearrangement steps into a one-pot procedure, which directly converts **1** into **8** in 34% yield.[15] This operationally simple reaction diastereoselectively generates four stereocenters of the unusual *trans*-isodaucane skeleton of **8**. Almost all isodaucane terpenoid natural products previously isolated possess a *cis*-fused ring junction that is likely to be biosynthesized through cyclization of a germacrene D derivative.[16] Several acid-catalyzed rearrangements of humulene[17] and humulene-8,9-epoxide[18] that are similar to the conversion of **1** into **8** have been previously reported. However, these rearrangements are generally unselective, giving rise to complex mixtures of products. Furthermore, our synthesis of **8** is the first time that this rearrangement mode of a humulene derivative has been used in a natural product synthesis, and it is the first time that it has been proposed to occur in a biosynthetic pathway.

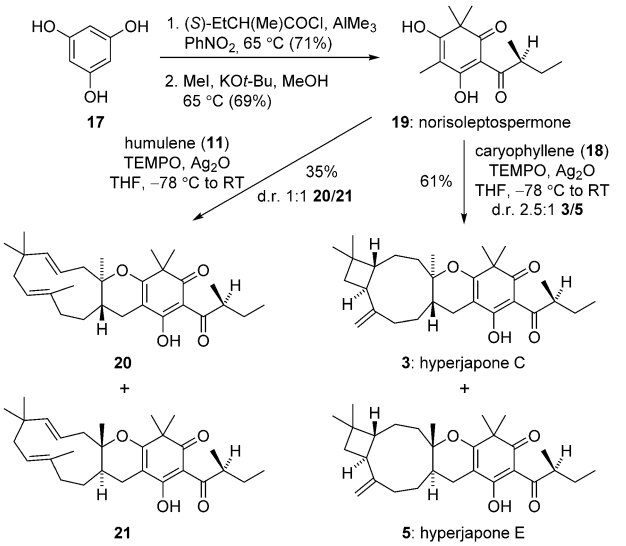
Conversion of epoxide **13** into hyperjaponol A (**6**) was achieved in 59% yield upon treatment with $(NC)_2C{=}C(CN)_2$ and LiBr in acetone.[19] Despite extensive screening of further Lewis and protic acids, the formation of hyperjaponol B (**7**) from **13** has not yet been observed.

The secondary aim of this project was to synthesize hyperjapones B–E using an oxidative hetero-Diels–Alder reaction to couple caryophyllene (**18**) with trimethylated acylphloroglucinol natural products. Thus, treatment of norflavesone (**10**) with TEMPO/Ag_2O in the presence of caryophyllene (**18**) gave a 2.5:1 mixture of hyperjapone B (**2**) and hyperjapone D (**4**) in 60% combined yield (Scheme 3). **18** exists as a 3:1 mixture of βα and ββ



Scheme 3. Total synthesis of hyperjapones B and D.

conformations in solution.[20] **2** is formed by the cycloaddition of the α,β-unsaturated ketone **12** generated in situ to the reactive *trans* $\Delta^{4,5}$ alkene of the more abundant βα conformation, while **4** is generated from addition to the less abundant ββ conformation.[7] In their isolation paper, Xu et al. reported the separation of **2** and **4** using preparative HPLC.[1] However, we also found that **2** could be purified from **4** by means of selective crystallization from MeOH.



Scheme 4. Total synthesis of hyperjapones C and E.

The total syntheses of hyperjapones C (**3**) and E (**5**) was achieved in a similar fashion (Scheme 4). Friedel–Crafts acylation of phloroglucinol (**17**) with (*S*)-2-methylbutyryl chloride[21] followed by trimethylation gave the dearomatized natural product norisoleptospermone (**19**). Exposure of **19** to TEMPO/Ag_2O in the presence of caryophyllene (**18**) gave a 2.5:1 mixture of hyperjapone C (**3**) and hyperjapone E (**5**) in 61% combined yield. Again, the product ratio of the oxidative hetero-Diels–Alder reaction approximately correlates to the ratio of the βα and ββ conformations of **18**.

Additionally, we synthesized **20** and **21** as an inseparable 1:1 mixture of diastereomers by treatment of **19** with TEMPO/Ag_2O in the presence of humulene (**11**). Given the probable biosynthesis of hyperjapones A–E in *Hypericum japoniucm* through non-enzymatic hetero-Diels–Alder reactions, it is highly likely that **20** and **21** are "undiscovered natural products". Samples of **20** and **21**, and also hyperjapone A epoxide (**13**), have therefore been distributed to isolation chemists in order to accelerate their discovery in nature.

In conclusion, we have used a biomimetic oxidative hetero-Diels–Alder reaction to synthesize hyperjapones A–E (**1**–**5**). This strategy allows for efficient coupling of dearomatized, trimethylated acylphloroglucinol natural products to the reactive *trans* alkenes of cyclic terpenes. Hyperjapone A (**1**) was converted into hyperjaponol A (**6**) and hyperjaponol C (**8**) through acid-catalyzed rearrangement of an intermediate epoxide. The four-step synthesis of hyperjaponol C (**8**) from simple starting materials involves the construction of six carbon–carbon bonds, six stereocenters, and three rings, and is thus a good example of the use of a biomimetic synthetic approach to rapidly generate molecular complexity. More generally, this work shows that a biomimetic approach to synthesis can lead to both naturally divergent strategies (nine natural products and three proposed "undiscovered natural products" have been synthesized, all for the first time) and naturally efficient syntheses

(all routes are protecting-group-free, with excellent step, redox, and pot economy).

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Keywords: biomimetic synthesis · carbocation rearrangements · cascade reactions · natural products · terpenoids

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