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A synthetic investigation into the biosynthesis of hypsampsone A†

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A simplified proposal for the biogenetic origin of hypsampsone A, a complex meroterpenoid, is supported by a bioinspired cascade reaction that rapidly assembles its polycyclic core. The key steps in both the proposed biosynthesis and the bioinspired cascade are a spontaneous intramolecular carbonyl–ene reaction, an α-hydroxy-β-diketone rearrangement and a terminating intramolecular aldol reaction. The feasibility of this model cascade reaction strongly suggests that hypsampsone A is a highly rearranged member of the polycyclic polyprenylated acylphloroglucinol (PPAP) family of natural products.

Hypsampsone A (**1**, Fig. 1) is a complex meroterpenoid natural product recently isolated from *Hypericum sampsonii* by Zhang *et al.*[1] Since this plant is a prolific source of polycyclic polyprenylated acylphloroglucinols (PPAPs), hypsampsone A (**1**) was classified as a highly rearranged member of the PPAP family.[2] The unique polycyclic ring system of **1** was determined by 2-D NMR studies, and its absolute configuration was deduced by comparison of predicted and experimental electronic circular dichroism spectra.[1] While re-drawing the congested depiction of hypsampsone A presented by the isolation team, we recognized a possible 5-*exo-trig* intramolecular aldol reaction of a bis-spirocyclic enol could link its biosynthetic pathway to 7-*epi*-clusianone (**2**),[3] which contains the bicyclo[3.3.1]nonane-2,4,9-trione core that is common to canonical PPAPs, including hyperforin.[4]

To rationalize the structure of **1**, Zhang *et al.* also proposed its biosynthesis *via* the extensive oxidation and rearrangement of 7-*epi*-clusianone, a classical PPAP formed by the tetra-prenylation and dearomatization of 2,4,6-trihydroxybenzophenone (Scheme 1a). However, their proposal invokes a rather unlikely intramolecular aldol reaction of **2** to give the highly strained 6–4–4 tricyclic ring system of **3**. Subsequently, two separate Baeyer–Villiger ring expansions are invoked to give the bis-lactone **4**, followed by hydrolysis to give 1,2-diketone **5**. Finally, oxidation of the C5 prenyl group of **5** followed by an intramolecular carbonyl–ene reaction of **6** at the C3 ketone and double lactonization of the bis-carboxylic acid **7** gives hypsampsone A.

Herein we propose an alternative biosynthesis of hypsampsone A (Scheme 1b), which is later supported by a biomimetic synthesis of the natural product core. While retaining 7-*epi*-clusianone (**2**) as the biosynthetic precursor, and a key intramolecular carbonyl–ene reaction, the remainder of the biosynthesis is simpler and more feasible than the previous proposal. The pathway also features several oxidation steps that might proceed without requiring catalysis by enzymes. First, oxidation of the C5 prenyl group of **2** (perhaps *via* a Schenck ene reaction with singlet oxygen and reduction of the resultant hydroperoxide[5]) gives allylic alcohol **8**. The C18 hydroxyl group

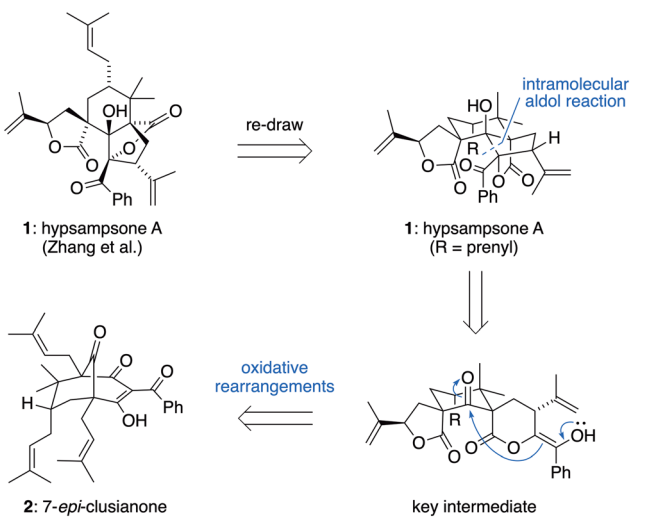

Fig. 1 Hypsampsone A and its biosynthetic relationship to 7-*epi*-clusianone.

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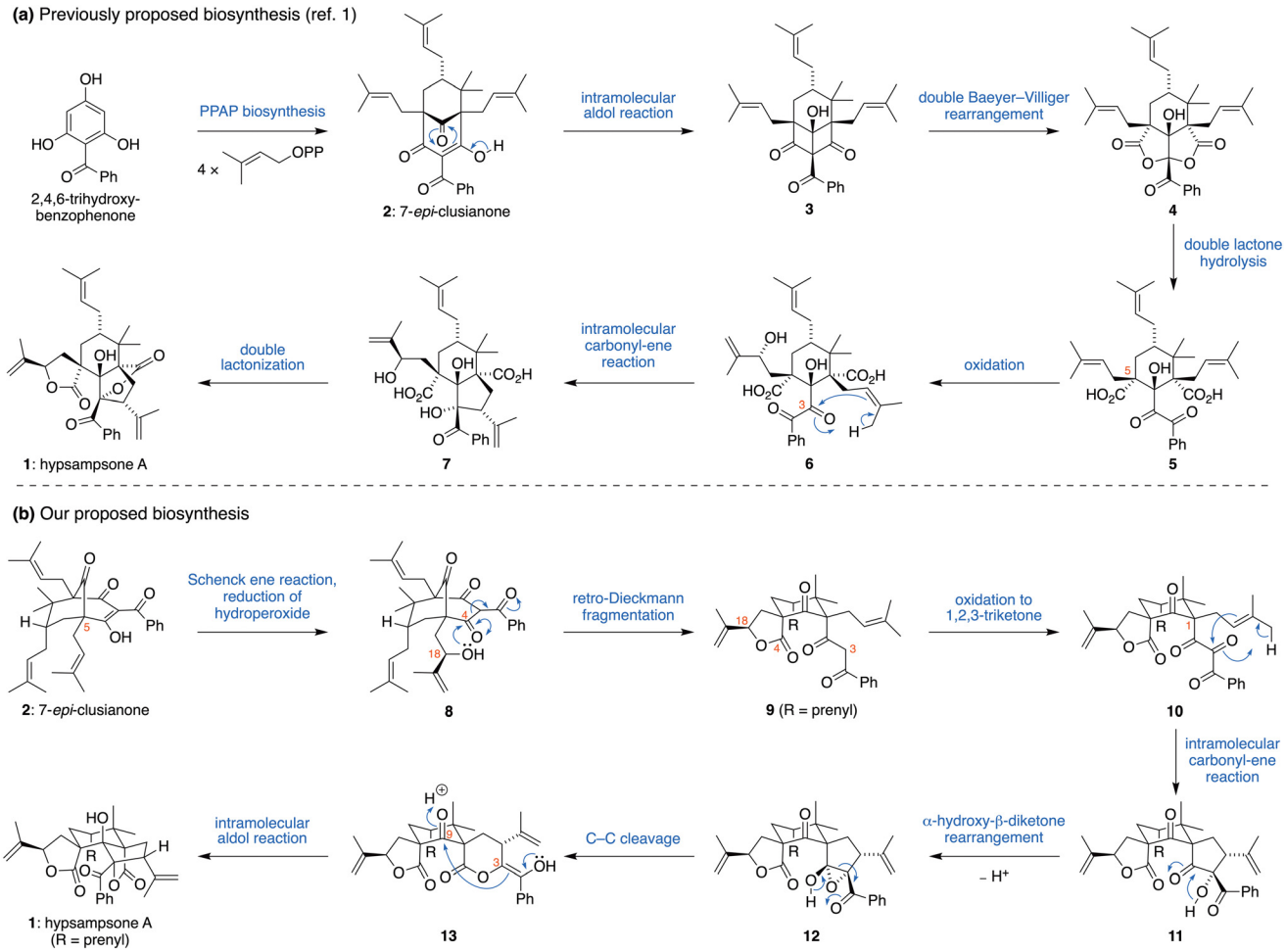
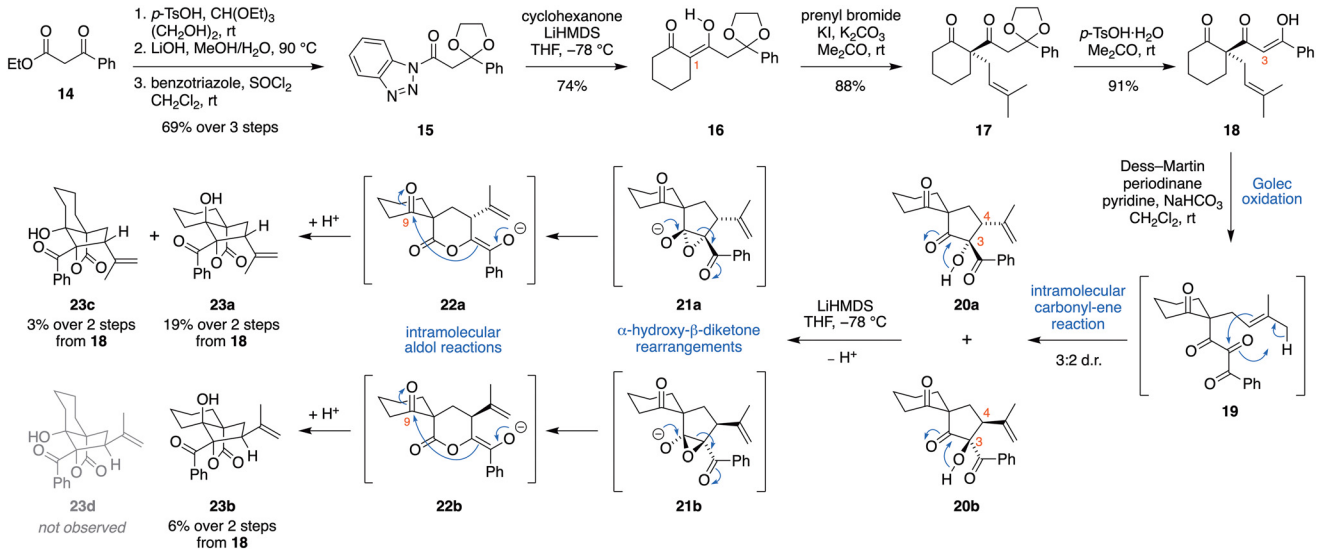


Scheme 1 (a) Zhang's proposed biosynthesis of hypsampsone A; (b) our proposed biosynthesis.

of **8** is well placed to attack the C4 carbonyl in a retro-Dieckmann fragmentation to give the spirocyclic lactone of **9**. Next, aerobic oxidation[6,9,10] of **9** at C3 would give a highly reactive 1,2,3-triketone **10**, which could participate in a spontaneous, intramolecular carbonyl–ene reaction[7] with the C1 prenyl side chain to give the cyclic α-hydroxy-β-diketone of bis-spirocyclic intermediate **11**. Under basic or thermal conditions, **11** could undergo an endocyclic α-hydroxy-β-diketone rearrangement[8] to give enol **13** *via* C–C cleavage of the intermediate epoxide **12**. Finally, an intramolecular aldol reaction between the C3 enol and the C9 ketone of **13** completes the biosynthesis of hypsampsone A. While we have previously put forward similar biosynthetic pathways involving intramolecular carbonyl–ene reactions and α-hydroxy-β-diketone rearrangements to rearranged PPAP natural products, including the hyperireflexolides[9] and biyoulactones,[10] the feasibility of the intramolecular aldol reaction of **13** to give the unusually congested ring system of hypsampsone A warranted further investigation.

To gain insight into the proposed biosynthesis of hypsampsone A (**1**), we conducted the biomimetic synthesis of a simplified analogue of the natural product (Scheme 2). The ketone of ethyl benzoylacetate (**14**) was first protected as a 1,3-dioxolane, and the ethyl ester was converted into the *N*-acylbenzotriazole **15** *via* amidation of an intermediate acid chloride with benzotriazole.[11] Claisen condensation between the lithium enolate of cyclohexanone and *N*-acylbenzotriazole **15** gave 1,3-diketone **16** as a single enol tautomer, which was prenylated at C1 with K_2CO_3 and prenyl bromide to give **17**. Removal of the 1,3-dioxolane protecting group under acidic conditions then furnished the 1,3,5-triketone **18**, again as a single enol tautomer. Oxidation of **18** at C3 using Dess–Martin periodinane[10,12] then formed the highly reactive 1,2,3-triketone **19** using Schreiber's modified conditions[13] of Golec's original protocol.[14] The unisolated intermediate **19** underwent a spontaneous, intramolecular carbonyl–ene reaction to generate the spirocyclic α-hydroxy-β-diketones **20a** and **20b** in 3 : 2 dr as shown by analysis of the crude ^{1}H NMR spectrum. The stereochemical outcome of this transformation agrees with our previous model synthetic studies and DFT calculations of the unusually facile intramolecular carbonyl–ene reaction of 1,2,3-triketones,[10] with a *cis* relationship between the hydroxyl and isopropenyl substituents at C3 and C4 in both **20a** and **20b** fixed by the bicyclic transition state. The formation of two diastereo-



Scheme 2 Bioinspired synthesis of a structural analogue of hypsampsone A.

mers of the cyclic α-hydroxy-β-diketones **20a** and **20b** in roughly equal amounts aligns with our previous synthetic work on the hyperireflexolides[9] in which a similarly low dr was observed. Given that **20a** and **20b** were difficult to separate by column chromatography due to their co-elution and propensity to undergo further rearrangements on silica gel, the next step was conducted on a crude mixture of the diastereomers. Thus, treatment of **20a**/**20b** with LiHMDS in THF at −78 °C triggered a pair of anionic cascade reactions to generate a mixture of the bridged 6–5–5 tricyclic products **23a**, **23b** and **23c** in a combined yield of 28% over 2 steps from compound **18**. In terms of the reaction mechanism, we propose that deprotonation of **20a**/**20b** first induces endocyclic α-hydroxy-β-diketone rearrangements to give enolates **22a**/**22b** *via* the epoxides **21a**/**21b**. Each enolate **22a** and **22b** can then undergo two possible intramolecular aldol reactions *via* addition to either face of the C9 ketone, which are both accessible due to rapid ring inversion of the cyclohexanone ring system. Three of the four possible diastereomeric aldol products are observed, with **23a** the major product alongside small amounts of **23b** and **23c**. Both **23a** and **23b** could arise from an aldol transition state in which the C9 ketone and C1 lactone are pointing away from each other in an anti-parallel orientation to minimise unfavourable dipole–dipole interactions. The resultant stereochemical outcome correlates with the observed structures of hypsampsone A and the related PPAP meroterpenoids, biyoulactones A–C,[15] and with our previous model studies on the biyoulactones.[10] The relative configurations of **23a**, **23b** and **23c** were established using 2-D NMR spectroscopy. The ^{1}H and ^{13}C NMR spectra of the major product **23a** show strong similarity to that of natural hypsampsone A (**1**), thus supporting the structural assignment of this complex natural product.[16]

In summary, we have proposed a simple biosynthetic pathway to the unusual meroterpenoid hypsampsone A, and provided evidence in the form of a biomimetic synthetic study that helps to verify its complex stereochemical structure and supports its possible status as a highly rearranged PPAP natural product.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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