# Bioinspired Total Synthesis of Hyperirreflexolides A and B

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**ABSTRACT:** Hyperirreflexolides A and B have been synthesized in six steps using a strategy based on the dearomatization and fragmentation of a simple acylphloroglucinol starting material. The dearomatized acylphloroglucinol undergoes a sequence of oxidative radical cyclization, retro-Dieckmann fragmentation, stereodivergent intramolecular carbonyl-ene reactions and final α-hydroxy-β-diketone rearrangements to give the target natural products. This sequence is based on a biosynthetic proposal that claims the hyperirreflexolides as highly rearranged polycyclic polyprenylated acylphloroglucinols (PPAPs), which is supported by a biosynthetically anticipated structure revision of hyperirreflexolide B. In addition, hyperirreflexolides A and B were synthesized using a convergent, non-biomimetic strategy that diastereoselectively constructs five C–C bonds onto a 2-cyclopentenone core.

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a diverse family of natural products isolated from over 500 species of *Hypericum* plants that have an almost worldwide distribution.[1] As classical examples of meroterpenoids,[2] they are biosynthesized via the prenylation and dearomatization of polyketide-derived acylphloroglucinols.[3] Although the bicyclo[3.3.1]nonane ring system is the archetypal PPAP ring system (e.g. hyperforin),[4] many other cyclizations, rearrangements and fragmentations in biosynthetic pathways are possible, resulting in natural product structures whose biogenetic origins are often unclear.[5] For example, when hyperirreflexolides A and B (**1** and **2**, **Figure 1**) were first isolated from *Hypericum reflexum*, a plant species endemic to the Canary Islands, they were classified as rearranged abietane terpenoid natural products.[6] However, we recently proposed that the hyperirreflexolides are in fact highly rearranged PPAP natural products, while also suggesting that the initial structural assignment **3** of hyperirreflexolide B was incorrect.[7] Herein, we validate both these proposals with the first total synthesis of hyperirreflexolides A and B. We also rationalize the unusual fact that **1** and **2** were both isolated as racemates, despite their stereochemically complex polycyclic structures.[8]

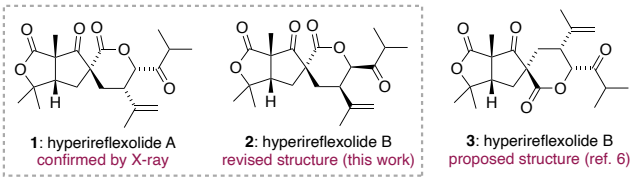



**Figure 1.** Hyperirreflexolides A and B.

While the structure of hyperirreflexolide A (**1**) was unambiguously determined by X-ray crystallography, the incorrect structure of hyperirreflexolide B (**3**) was derived by comparison of its $^1$H NMR spectrum to **1** and analysis of *J*-couplings, but it was not supported by observation of any NOE interactions.[6] The X-ray structure of **1** shows the δ-lactone ring adopts an expected half-chair conformation,[9] with the C13 alkene substituent in a pseudoequatorial position while the C12 ketone substituent is pseudoaxial (**Figure 2**). NMR *J*-couplings of H13 to H14-α (12.2 Hz), H14-β (4.8 Hz) and H12 (also 4.8 Hz) confirm the pseudoaxial nature of H13. The $^1$H and $^{13}$C NMR spectra of hyperirreflexolide B are very similar to that of hyperirreflexolide A, with almost identical *J*-couplings in the $^1$H spectrum. The originally proposed hyperirreflexolide B structure **3**, in which the relative configurations at C8, C12 and C13 have been inverted compared to **1**, is therefore plausible based purely on 1D NMR data. However, our biosynthetic proposal predicts that both hyperirreflexolides A and B must share the same relative configuration at the spirocyclic quaternary stereocentre C8. We therefore realized that structure **2**, in which just the C12 and C13 stereocentres are inverted with respect to **1**, is also a plausible candidate for hyperirreflexolide B, and we endeavored to prove this subtle stereochemical reassignment through total synthesis.

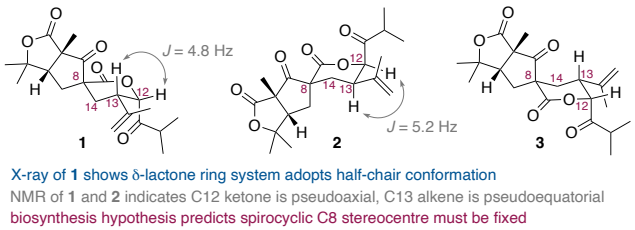
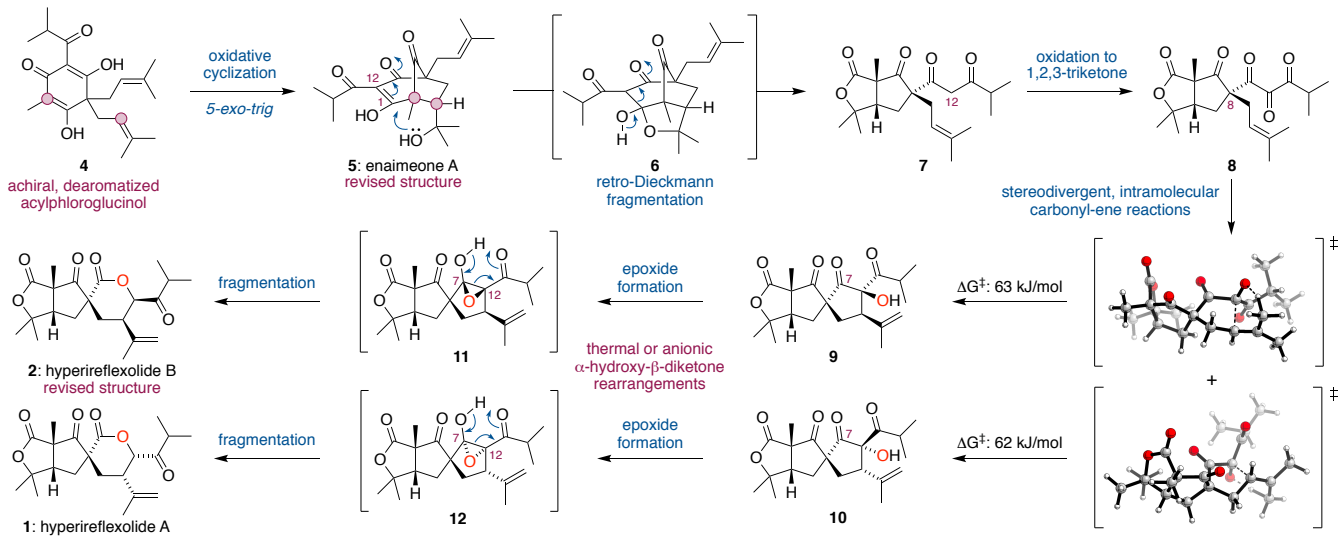



**Figure 2.** Conformational analysis of hyperirreflexolides A and B.

As outlined in **Scheme 1**, we propose that both hyperirreflexolides A and B originate from fragmentation and rearrangement of a more obvious PPAP meroterpenoid, enaimeone A (**5**),[10] which could be formed by the oxidative cyclization of the achiral, dearomatized acylphloroglucinol **4**. The oxidative cyclization of **4** could involve *5-exo-trig* cyclization of an α-keto radical,[11] or else occur via epoxidation of one of the prenyl groups. Next, cleavage of the C1–C12 bond of **5** is required to generate the [5,5]-bicyclic lactone of the hyperirreflexolides. This could be triggered by initial oxidation at C12, or else by a retro-Dieckmann fragmentation of the keto tautomer of **5** to give the 1,3-diketone **7** via the tetrahedral intermediate **6** (as shown).

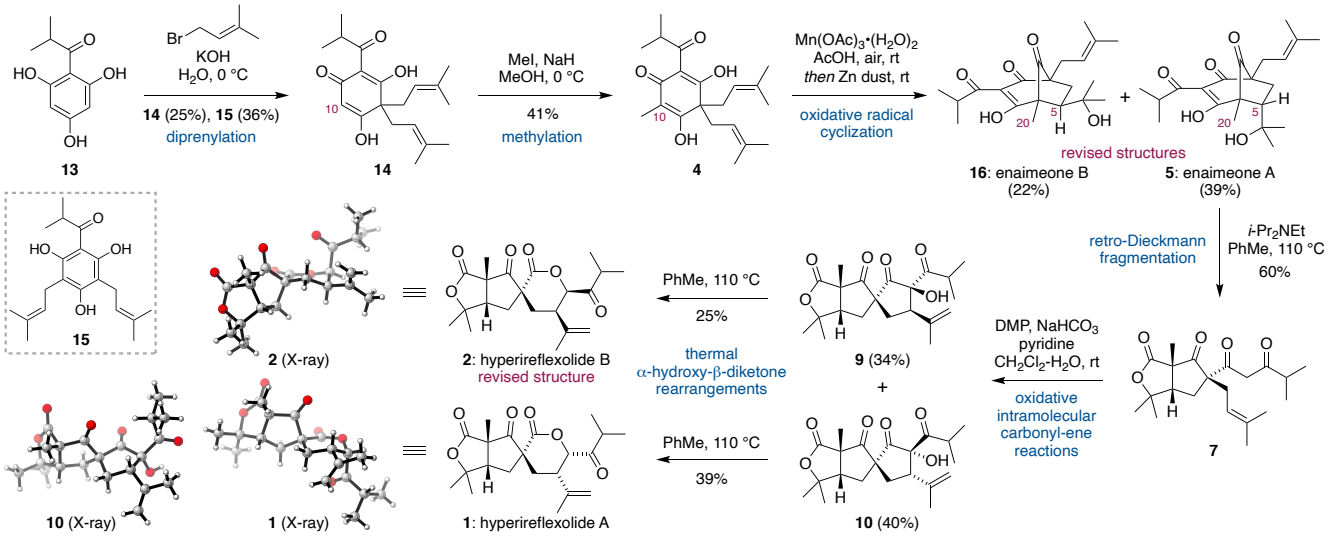
**Scheme 1. Proposed Biosynthesis of Hyperireflexolides A and B via the Rearrangement of Enaimeone A**




Aerobic oxidation of **7** at C12 could then generate a highly electrophilic 1,2,3-triketone **8**,[12] which could undergo stereodivergent intramolecular carbonyl-ene reactions[13] with the C8 prenyl group to give spirocyclic cyclopentanones **9** and **10**. Previous calculations predict that the intramolecular carbonyl-ene reactions of **8** have a low activation energy and should be spontaneous at room temperature, with the diastereomers **9** and **10** formed at roughly equal rates.[7] We also previously demonstrated that simpler intramolecular carbonyl-ene reactions of model systems readily proceed at room temperature, while some less reactive 1,2,3-triketone intermediates were isolated and observed to undergo thermal intramolecular carbonyl-ene reactions upon heating.[7] Finally, we propose that the δ-lactone of the hyperireflexolides arises via thermal or base-catalyzed α-hydroxy-β-diketone rearrangements of **9** and **10**.[14] This unusual rearrangement involves attack of the tertiary alcohol of **9** and **10** to the adjacent C7 ketone to give epoxides **11** and **12**, followed by fragmentation of the C7–C12 bond to give hyperireflexolides A and B.

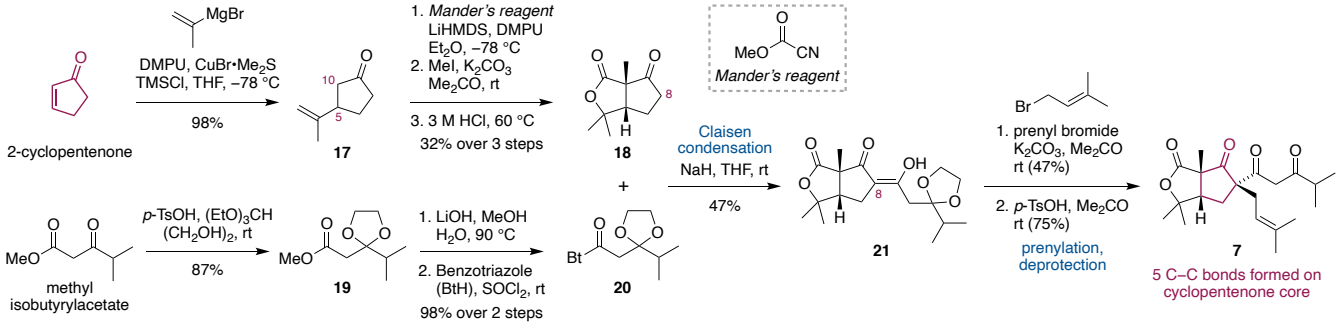
The chemical realization of this bold biosynthetic proposal is described in **Scheme 2**. The total synthesis began with *C*-prenylation of the readily available[15] acylphloroglucinol **13** using prenyl bromide in aqueous KOH, which gave a separable mixture of the desired dearomatized, geminally diprenylated product **14** (as a complex mixture of tautomers) alongside the aromatic major product **15**.[16] Next, *C*-methylation of **14** at C10 gave **4**, also formed as a complex tautomeric mixture. At this stage, all the carbon atoms of the hyperireflexolides have been introduced after just two steps. One-electron oxidation of **4** using catalytic $Mn(OAc)_3$ generated a stabilized α-keto radical at C10, which underwent *5-exo-trig* cyclization with one of the pendant prenyl substituents and trapping with triplet oxygen followed by *in situ* reduction with zinc dust to give a separable mixture of enaimeone A (**5**) and enaimeone B (**16**) in good overall yield.[17]

**Scheme 2. Bioinspired Total Synthesis of Enaimeones A and B, and Hyperireflexolides A and B**



At this point we revised the relative configuration of enaimeones A and B at C5, which had been previously misassigned. Contrary to the original isolation work,[6] we found that the NOE between H5 and H20 is non-diagnostic as it is observed in both enaimeones A and B. Further NMR analysis of the enaimeones is complicated by their existence as mixtures of β-hydroxyenone tautomers. However, conclusive chemical evidence in favor of the structure of enaimeone A (**5**) is that only this diastereomer undergoes thermal rearrangement to give the [5,5]-bicyclic lactone of **7** via a retro-Dieckmann fragmentation. Most conveniently, heating the revised enaimeone A (**5**) in PhMe at 110 °C with catalytic Hünig's base gave **7** in good yield (as a mixture of keto and enol tautomers), while the revised enaimeone B (**16**) was unreactive under these conditions. Next, oxidation of **7** with Dess–Martin periodinane (DMP)[18] gave a separable mixture of spirocycles **9** (34% yield) and **10** (40% yield) via intramolecular carbonyl-ene reactions of the unisolated intermediate 1,2,3-triketone **8**. The formation of a roughly equimolar mixture of diastereomers **9** and **10** is in line with our calculated energy barriers for these stereodivergent carbonyl-ene reactions. Thermal α-hydroxy-β-diketone rearrangement of the major carbonyl-ene product **10** in PhMe at reflux gave hyperireflexolide A (**1**), with the structures of **10** and **1** both confirmed by single crystal X-ray diffraction. Gratifyingly, thermal α-hydroxy-β-diketone rearrangement of the minor carbonyl-ene product **9** gave hyperireflexolide B (**2**), which exhibits identical NMR data to the natural product. The verification of this anticipated structure revision of hyperireflexolide B, which was confirmed by single crystal X-ray diffraction, is strong evidence in favor of our proposed biosynthetic pathway. Furthermore, the non-obvious fate of the dearomatized and fragmented acylphloroglucinol starting material **13** highlights the power of dearomatization strategies in complex molecule synthesis.[19]

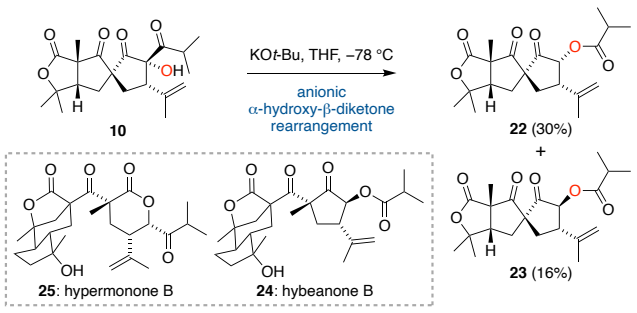
**Scheme 3. Total Synthesis of Hyperireflexolides A and B via Diastereoselective Functionalization of 2-Cyclopentenone**




Given the challenges met in the biomimetic synthesis outlined in Scheme 2, particularly the confusing misassignment of enaimeones A and B, we simultaneously conducted a more pragmatic and stepwise synthesis of hyperireflexolides A and B (**Scheme 3**). While we retained the bioinspired endgame of oxidative carbonyl-ene reactions and subsequent α-hydroxy-β-diketone rearrangements of the key 1,3-diketone **7**, we planned its convergent synthesis by diastereoselective acylation and prenylation of the [5,5]-bicyclic lactone **18**. This route began with a Michael rection between an organocuprate derived from isopropenylmagnesium bromide and 2-cyclopentenone to give **17**.[20] The C5-stereocentre introduced in **17** dictates the relative configuration of the remaining four stereocentres of the racemic hyperireflexolide natural products, so the route could be rendered enantioselective using a known asymmetric Michael reaction of 2-cyclopentenone.[21] Deprotonation of **17** with LiHMDS preferably formed an enolate at C10, which was trapped with Mander's reagent[22] to give a β-keto-ester. Diastereoselective methylation of this intermediate β-keto-ester at C10 followed by acid-catalyzed lactonization then furnished **18** in 32% yield over three steps.[23] Synthesis of the *N*-acylbenzotriazole fragment **20** was achieved by ketone protection of methyl isobutyrylacetate as 1,3-dioxolane **19**,[24] followed by ester hydrolysis and amidation of the *in situ* generated acid chloride with benzotriazole. The sodium enolate of **18** was then coupled to *N*-acylbenzotriazole **20** at C8 via a Claisen condensation to give **21** as a single enol tautomer.[25] Diastereoselective prenylation of **21** at C8 using prenyl bromide/$K_2CO_3$ in acetone followed by treatment with *p*-TsOH to remove the 1,3-dioxolane protecting group furnished the 1,3-diketone **7**, thus completing an alternative route to the hyperireflexolides.

Under thermal conditions, the α-hydroxy-β-diketone rearrangements of **9** and **10** occur in an *endocyclic* manner, with the tertiary alcohol oxygen atom incorporated within the δ-lactone ring of the hyperireflexolides. Conversely, treatment of **10** with KO*t*-Bu at low temperature triggered an *exocyclic* α-hydroxy-β-diketone rearrangement to give diastereomeric ester products **22** and **23** (**Scheme 4**), which share a similar cyclopentanone scaffold to another highly rearranged PPAP natural product, hybeanone B (**24**).[26] Based on our biosynthetic hypothesis for the hyperireflexolides, and the isolation of both **24** and the closely related hypermonone B (**25**) from *Hypericum* plants,[27] it is plausible that **22** and **23** are "undiscovered natural products", and we hope our synthesis will aid their future discovery.[28]

**Scheme 4. Anionic α-Hydroxy-β-Diketone Rearrangement of 10**

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In summary, we have achieved two total syntheses of hyperireflexolides A and B. The first, bioinspired approach relies on the comprehensive dearomatization and fragmentation of a simple acylphloroglucinol building block. Every step of this total synthesis constructs a skeletal C–C or C–O bond, with no protecting groups required due to the consistent use of the predisposed reactivity of all intermediates. Validation of a predicted structure revision of hyperireflexolide B adds weight to the overall biosynthetic proposal, which also explains the racemic status of the natural products. The second, highly convergent total synthesis involves the sequential attachment of five C–C bonds to a central cyclopentenone lynchpin. Every step of both total syntheses involves fundamental reactivity of the carbonyl group, underlining the enduring utility of this functional group in the synthesis of complex, highly oxygenated natural products.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectroscopic data and copies of NMR spectra for all compounds (PDF)

### Accession Codes

CSD 2267391-2267393 (compounds **1**, **2** and **10** respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## ACKNOWLEDGMENT

This work was supported by the Australian Research Council (DP200102964).

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TOC graphic: