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Biomimetic Synthesis Enables the Structure Revision of Littordials E and F and Drychampone B

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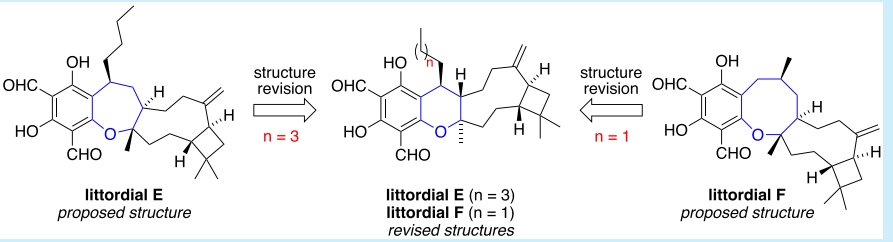

ABSTRACT: Structural reassignments for littordial E, littordial F, and drychampone B are proposed on the basis of consideration of their biosynthetic origin. The key step in the proposed biosynthesis of each of these meroterpenoids is an intermolecular hetero-Diels–Alder reaction between an *o*-quinone methide and caryophyllene or humulene. Biomimetic total synthesis of the natural products gave sufficient material to allow their structure revision by NMR studies.

Despite the availability of increasingly powerful spectroscopic tools, the accurate characterization of complex natural products remains challenging. In particular, structural assignments based primarily on the analysis of 2D NMR spectra are vulnerable to human error. We believe that consideration of the probable biosynthesis of a natural product can greatly assist in its initial structural assignment or its subsequent reassignment.[1] In addition, total synthesis continues to play an important role in natural product structure revisions,[2] alongside modern DFT predictions of NMR spectra.[3] Herein we apply biosynthetic analysis and biomimetic total synthesis to revise the structures of three dubiously assigned meroterpenoid natural products: littordials E and F and drychampone B.

The isolation of littordials A–E (**1**–**5**) (Figure 1) from the leaves of *Psidium littorale* (commonly known as strawberry guava) was reported in 2019,[4] followed by the discovery of littordial F (**6**) from the same plant later that year.[5] These meroterpenoids are presumably biosynthesized via the union of (−)-caryophyllene (**9**) and a diformylphloroglucinol derivative. Littordials A–D all feature a 6–6–9–4 ring system that could arise from a hetero-Diels–Alder reaction between an *o*-quinone methide[6] (*o*-QM) and the reactive *trans* $\Delta^{4,5}$ alkene of caryophyllene. Indeed, similar cycloadditions have been achieved in the biomimetic synthesis of several caryophyllene-derived meroterpenoids.[7] However, the proposed seven- and eight-membered rings of littordials E and F (highlighted in blue in Figure 1) are biosynthetically implausible. On the basis of our biosynthetic analysis, we speculated that the true structure of littordial E (**7**) is probably

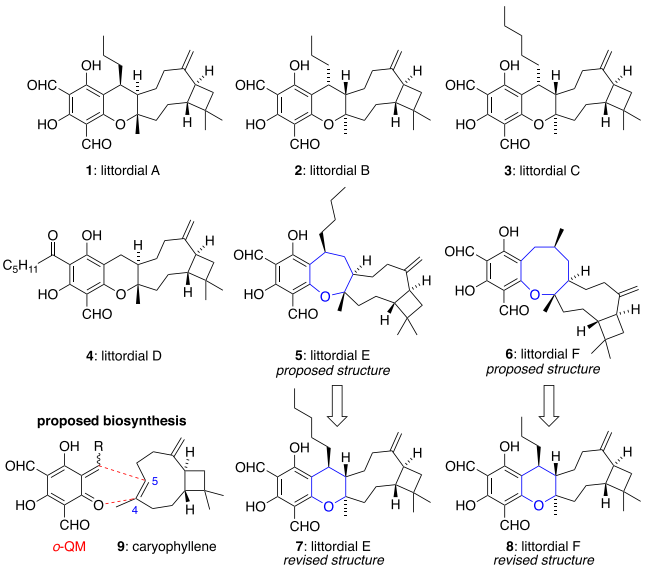

Figure 1. Littordials A–F, with biosynthetically inspired structure revisions suggested for littordials E and F.

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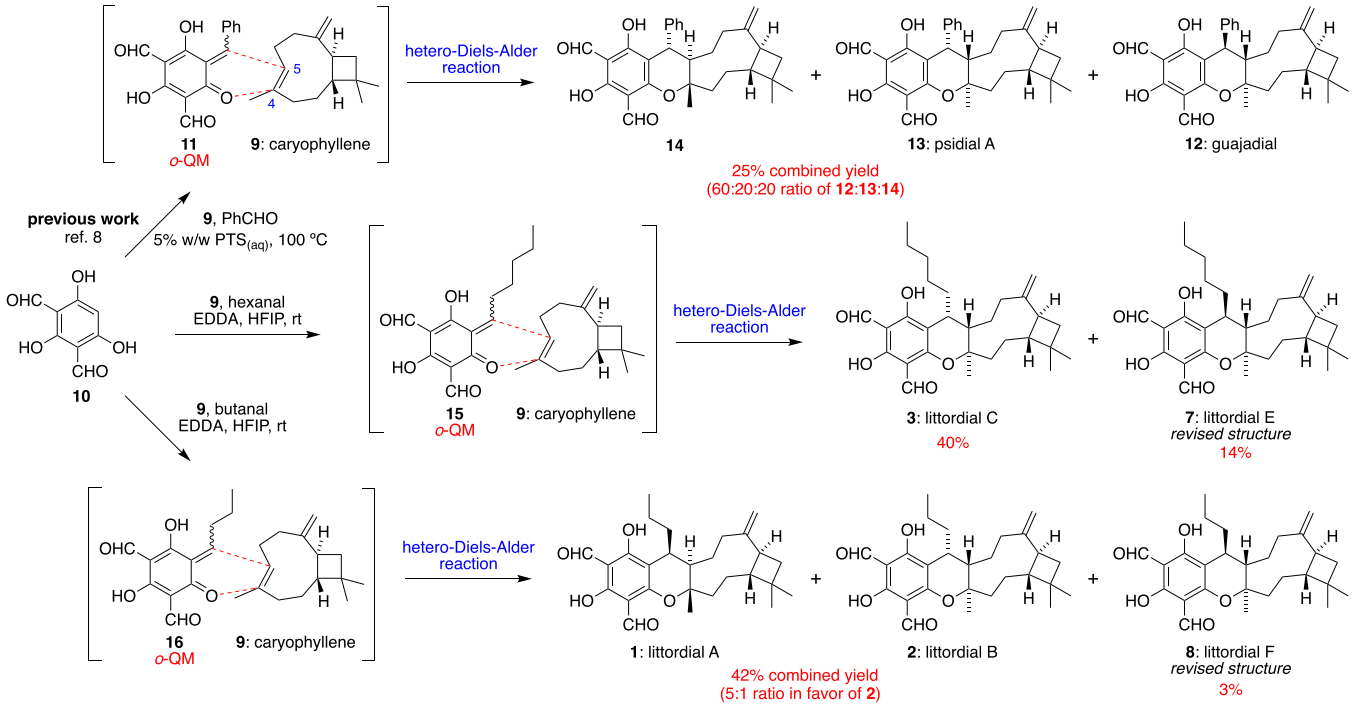
Scheme 1. Biomimetic Synthesis of Littordials A, B, C, E, and F



a diastereomer of littordial C (**3**) and that littordial F (**8**) is a diastereomer of littordials A and B (**1** and **2**). To verify this hypothesis, we planned to synthesize the hypothetical structures **7** and **8** from caryophyllene and the appropriate *o*-QM intermediates. In addition to providing samples of littordials E and F for further detailed spectroscopic analysis, their synthesis via a biomimetic Diels–Alder-based strategy would be strong evidence in favor of the proposed structural reassignments.

The biomimetic synthesis of the meroterpenoids guajadial (**12**) and psidial A (**13**),[8] which are closely related to the littordials, via an intermolecular hetero-Diels–Alder reaction between (−)-caryophyllene (**9**) and an *o*-QM was previously investigated by Lee et al. (Scheme 1). They showed that condensation of commercially available diformylphloroglucinol (**10**)[9] with benzaldehyde in water gave *o*-QM **11**, which underwent a hetero-Diels–Alder reaction with caryophyllene to give a mixture of **12**, **13**, and a (yet to be isolated) diastereomer **14** in a combined yield of 25%. Under the optimized conditions, this multicomponent cascade reaction was conducted in an aqueous solution containing 5% w/w PEG-600/α-tocopherol-based diester of sebacic acid (PTS) as a surfactant. We reasoned that replacement of benzaldehyde with hexanal in this cascade reaction would allow the synthesis of littordial C (**3**) and the revised littordial E (**7**). Thus, condensation of **10** with hexanal in the presence of **9** and catalytic ethylenediammonium diacetate (EDDA) in hexafluoroisopropanol (HFIP) gave a 40% yield of **3** and a 14% yield of **7**. These conditions were previously used in Cramer's one-step synthesis of another related meroterpenoid, psiguadial B.[10]

The 1D and 2D NMR spectra of synthetic littordial E (**7**) in $CDCl_3$ matched the data for the isolated natural product. It is mechanistically implausible that the originally proposed littordial E structure **5** could form under the reaction conditions. Furthermore, close examination of the 2D NMR spectra strongly support the reassignment of littordial E from structure **5** to **7** (Figure 2). The key misassignment in the

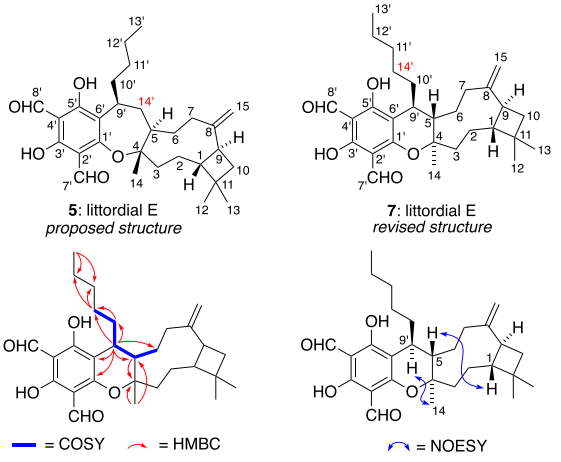


Figure 2. Key 2D NMR correlations in the structure revision of littordial E.

original isolation work is at H-14′. The claimed COSY correlation between one of the H-14′ signals (δ_H = 0.77) and H-5 (δ_H = 2.17) is difficult to assess because of overlapped peaks around H-5. Although we observe a weak correlation from this region to H-14′, the proximity of one of the H-10′ signals (δ_H = 2.18) makes this assignment questionable. Additionally, in our spectra we observe a COSY correlation in the region of δ_H = 1.41–1.45 to H-14′ (δ_H = 0.77). Signals from this region are assigned to the second proton of C-10′ (δ_H = 1.43) and H-2 (δ_H = 1.44). Considering that a COSY correlation from H-2 to H-14′ would be impossible, this correlation can only arise from the coupling of the H-10′ proton to H-14′. These two couplings, δ_H = 2.18 to δ_H = 0.77 and δ_H = 1.43 to δ_H = 0.77, therefore imply a correlation of H-

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10′ to H-14′ rather than H-14′ to H-5, which is only possible with the revised structure **7**. Further key HMBC and COSY correlations (Figure 2) confirm the 6−6−9−4 ring system of **7**. The NOESY spectrum of **7** in $CDCl_3$ was again difficult to interpret because of the overlapped region around the key H-5 resonance. However, the NOESY spectrum of **7** in C_6D_6 showed correlations between H-9′ (δ_H = 2.45) and Me-14 (δ_H = 0.76) and between H-5 (δ_H = 2.13) and H-1 (δ_H = 2.04). Littordial E (**7**) therefore has the same 6−6−9−4 ring system and relative configuration as guajadial (**12**).

Our analysis of the 2D NMR spectra for synthetic **3** agreed with the original structure elucidation for littordial C,[4] and this was confirmed by single-crystal X-ray crystallography (Figure 3; see the Supporting Information).

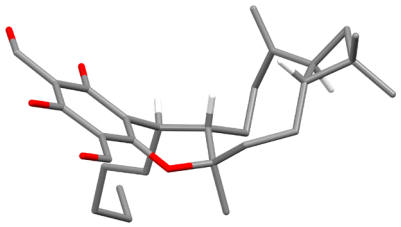

Figure 3. X-ray crystal structure of littordial C (for clarity, only H atoms at stereocenters are shown).

The use of butanal as the aldehyde component in the cascade reaction with **9** and **10** allowed the synthesis of the revised structure of littordial F (**8**) in 3% yield alongside littordials A (**1**) and B (**2**) as an inseparable mixture (5:1 ratio in favor of **2**) in a combined yield of 42% (Scheme 1). Since the structure of **1** was previously established by single-crystal X-ray crystallography[4] and the structure of **2** is also not in doubt because of its close similarity to **3**, we focused our attention solely on the characterization of **8**. The ^1H and ^{13}C NMR spectra of **8** are almost identical to the corresponding spectra of **7**, except for two additional methylene groups in the *n*-pentyl side chain appended to C-9′ of **7** compared with the *n*-propyl substituent of **8**. Thus, we propose that the revised littordial F structure **8** has the same 6−6−9−4 ring system and the same relative configuration as **7** and **12**. This assignment is also supported by 2D NMR studies (see the Supporting Information for full details). The formation of the originally assigned littordial F structure **6** under our reaction conditions is mechanistically implausible. Although the proposed littordial F structure **6** was supported by predicted ^{13}C NMR data calculated using DFT methods, the conformational flexibility of this compound makes such a calculation potentially misleading.[5]

The absolute configuration of isolated littordial A (**1**) was initially assigned by single-crystal X-ray diffraction analysis with Ga Kα radiation, which was supported by a comparison between experimental and calculated CD spectra for all of the littordials.[4,5] This configuration arises from the more common (−) enantiomer of caryophyllene. As expected, the CD spectra of synthetic littordials C, E, and F (also derived from (−)-caryophyllene) matched those of the isolated natural products. However, our measured optical rotations differed significantly from those of the reported natural products, which could be due to the presence of minor diastereomeric impurities in either the synthetic or natural samples.[11]

Caryophyllene can adopt four conformations in solution, termed $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$ according to the relative disposition of the exocyclic alkene and the vinyl methyl substituent. NMR studies have shown that caryophyllene exists as a 48:28:24 $\alpha\alpha/\beta\alpha/\beta\beta$ mixture.[12] While conformers $\alpha\alpha$ and $\beta\alpha$ are known to be in rapid exchange, their exchange with the $\beta\beta$ conformer is relatively slow, with an experimentally determined barrier of 68 kJ mol^{-1}. In line with previous studies on the biomimetic synthesis of guajadial and psidial A,[8] we propose that littordials B and C (**2** and **3**) and littordials E and F (**7** and **8**) arise from cycloaddition between *o*-QMs **15**/**16** and the $\beta\alpha$ conformation of **9** while littordial A (**1**) is formed from the $\beta\beta$ conformation (Figure 4).

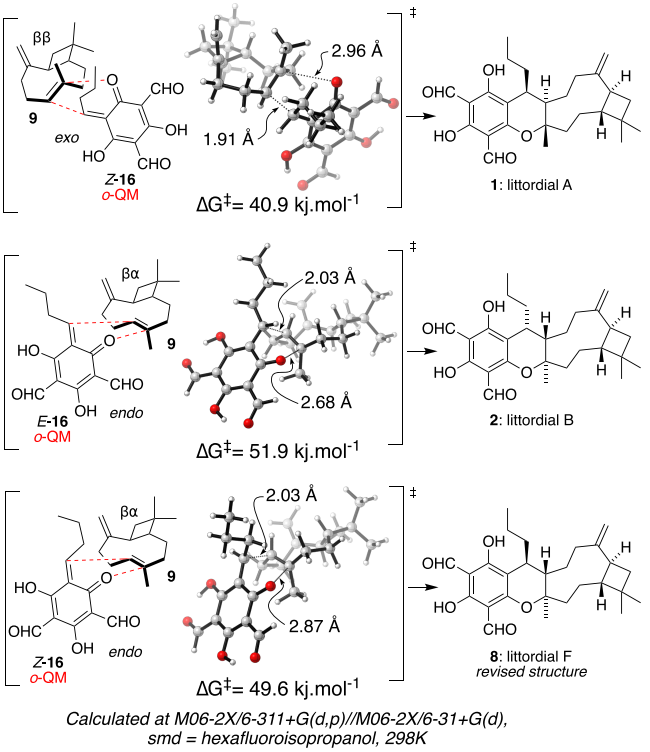

Figure 4. Plausible transition states leading to littordials A, B, and F.

Computational modeling was used to assess the possible cycloaddition pathways leading to littordials A, B, an F and an additional diastereomer analogous to **14**. Calculations were performed using DFT with the M06-2X functional and the 6-31+G(d) basis set for geometry optimizations and frequency analysis, with single-point energies calculated at the 6-311+(d,p) level.

Given that caryophyllene has four possible conformers and that *o*-QM **16** may be formed as either the *E* or *Z* isomer and taking into account the *endo*/*exo* stereoselectivity, there are 16 possible reaction pathways, of which those involving the nonpopulated $\alpha\beta$ conformer of caryophyllene are discounted. *o*-QMs *E*-**16** and *Z*-**16** are calculated to have essentially the same stability (ΔG = −1.2 kJ mol^{-1}), and any *E*/*Z* selectivity in the formation **16** is unknown, so both isomers must be considered as viable reactants. The lowest-energy TSs leading to littordials A, B, and F are illustrated in Figure 4. This analysis reveals that in general a concerted Diels−Alder cycloaddition between **9** and **16** is energetically feasible under the reaction conditions. The Diels−Alder transition

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structures are characteristically highly asynchronous, with C–O forming bond lengths ranging from 2.64 to 2.96 Å.[13]

Because of the isomeric complexity of both reactants, the high reactivity of *o*-QM intermediates, and the challenges of experimental analysis and purification, caution must be taken in rationalizing the product distributions. The lowest-energy pathway (caryophyllene-*ββ*–*Z*-*o*-QM–*exo*-TS) has a calculated barrier of $\Delta G^{\ddagger}$ = 40.9 kJ mol^{-1}. This leads to littordial A (isolated as a minor isomer), which is consistent with its arising from the minor *ββ* conformer of caryophyllene. The formation of littordial B from the *E*-configured *o*-QM has the predicted lowest-energy pathway shown, with a barrier of 51.9 kJ mol^{-1}, whereas littordial F forms from the *Z*-configured *o*-QM with a predicted barrier of 49.6 kJ mol^{-1}. Notably, the lowest-energy pathway leading to the diastereomer analogous to **14** (caryophyllene-*ββ*–*Z*-*o*-QM–*endo*-TS, not shown) has a barrier of $\Delta G^{\ddagger}$ = 55.6 kJ mol^{-1}, perhaps explaining its absence synthetically and in isolation studies.

The isolation of three racemic meroterpenoids, drychampones A–C, from the Chinese fern *Dryopteris championii* was reported in 2016.[14] Although the drychampones are most likely derived from a hetero-Diels–Alder reaction between an *o*-QM and the reactive $\Delta^{1,2}$ alkene of humulene (**19**),[15] drychampone B (**17**) was surprisingly assigned a *Z* configuration for its $\Delta^{4,5}$ alkene on the basis of a claimed $^{3}J_{4-5}$ coupling constant of <10 Hz (Figure 5). However, since

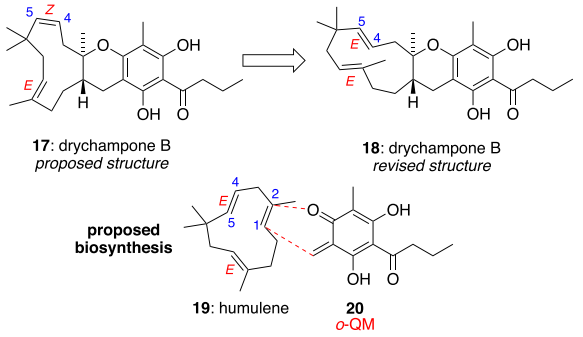


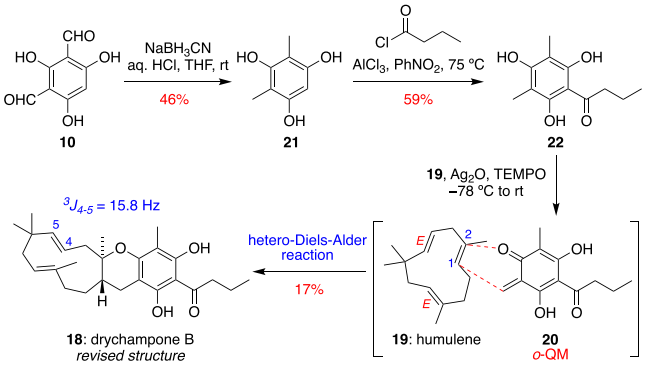
Figure 5. Proposed structure revision for drychampone B.

the ^{1}H NMR signals for H-4 and H-5 of drychampone B in $CDCl_3$ are overlapped and *cis*-humulenes are scarce in nature, we proposed that **18** (with an *E* configuration of its $\Delta^{4,5}$ alkene) is the true structure of drychampone B.

The synthesis of the revised structure of drychampone B (Scheme 2) started from readily available **10**, which was also used in our littordial syntheses. Reduction of the aldehyde functional groups of **10** with $NaBH_3CN$ under acidic conditions gave dimethylphloroglucinol (**21**),[16] which underwent Friedel–Crafts acylation with butyryl chloride to give acylphloroglucinol **22**.[17] Oxidation of **22** using Ag_2O and TEMPO[7d] then generated *o*-QM **20**, which was trapped in situ with **19** to give drychampone B (**18**) in 17% yield. The 1D and 2D NMR spectra of synthetic **18** in $CDCl_3$ fully matched the natural product isolation data for drychampone B. Furthermore, the ^{1}H NMR spectrum of **18** in C_6D_6 clearly showed a $^{3}J_{4-5}$ coupling constant of 15.8 Hz, consistent with an *E* configuration for the $\Delta^{4,5}$ alkene.

In conclusion, we have applied biosynthetic speculation to guide the structure revision of littordials E and F and drychampone B. The reassignments were confirmed through biomimetic total synthesis and NMR studies. Even with all of

Scheme 2. Biomimetic Synthesis and Structure Revision of Drychampone B



the advanced spectroscopic techniques at the disposal of organic chemists, often the interpretation of sophisticated spectroscopic data is subject to human error. We believe that the structure elucidation of a new natural product should not be based only on spectroscopic analysis; it is equally important that the putative structure should also be supported by a plausible biosynthetic hypothesis. The combination of these two approaches will minimize the number of incorrect structural assignments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03156.

Experimental procedures, NMR spectra, CD spectra, single-crystal XRD data, and computational methods for all new compounds (PDF)

Accession Codes

CCDC 2017518 contains 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, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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