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Bioinspired Synthesis of (–)-PF-1018

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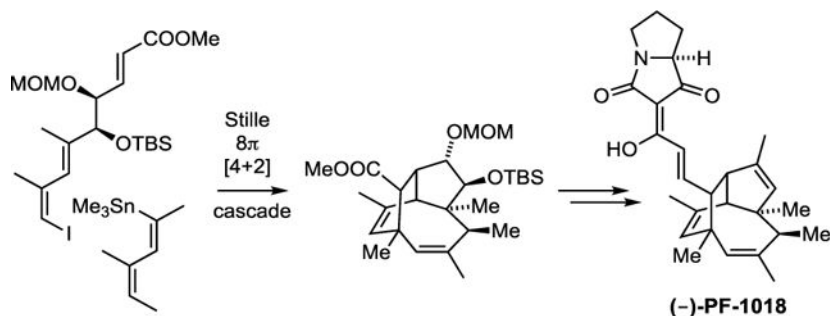
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Abstract

The combination of electrocyclizations and cycloadditions accounts for the formation of a range of fascinating natural products. Cascades consisting of 8π electrocyclizations, followed by 6π electrocyclization, and a cycloaddition are relatively common. We now report the synthesis of the tetramic acid PF-1018 through an 8π electrocyclization, the product of which is immediately intercepted by a Diels–Alder cycloaddition. The success of this pericyclic cascade was critically dependent on the substitution pattern of the starting polyene and could be rationalized through DFD calculations. The completion of the synthesis required the instalment of a trisubstituted double bond via radical deoxygenation. An unexpected byproduct formed through 4-exo-trig radical cyclization could be recycled through an unprecedented triflation/fragmentation.

Graphical Abstract



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Supporting information for this article is given *via* a link at the end of the document.

Keywords

Diels–Alder Cycloaddition; Electrocyclization; Total Synthesis; Biomimetic Synthesis; Tetramic Acids

The combination of an 8π – 6π -electrocyclization cascade with a cycloaddition has been implicated in the biosynthesis of a range of natural products (Fig. 1). In the well-known endriandric acid family, for instance, conrotatory 8π electrocyclization of **1** yields cyclooctatriene **2**, which then undergoes disrotatory 6π electrocyclization to afford the bicyclo[4.2.0]octadiene endriandric acid G. This is followed by an intramolecular Diels–Alder reaction that leads to endriandric acid C (Fig. 1A).^[1–3] In the case of kingianin A, the electrocyclization cascade yields cyclooctatriene **3** and then bicyclo[4.2.0]octadiene **5**, which engages in intermolecular Diels–Alder dimerization (Fig. 1B).^[4,5] Other examples that have been validated by biomimetic or bioinspired synthesis include ocellapyrone A,^[6] where the electrocyclizations are followed by an intramolecular hetero Diels–Alder reaction, and orinocin,^[7] where they are followed by a *retro* [2+2]-cycloaddition, resulting in “polyene splicing”.

The unusual natural product PF-1018 appears to stem from a fascinating variation of this pericyclic chemistry (Fig. 1C). The anionic lipid was isolated from a fungal strain identified as *Humicola sp. 1018* in a screen against *Plutella xylostella*, the diamond back moth, which accounts for massive agricultural losses worldwide.^[8,9] Its structure was established by NMR and X-ray analysis and was shown to feature a rare proline derived tetramic acid linked to a complex tricyclic hydrocarbon core. This core features six stereocenters, two of them quaternary, and three trisubstituted double bonds bearing methyl groups.

Biosynthetically, PF-1018 could originate, at least in principle, from the complex polyene **6** (Fig. 1C). A diastereoselective 8π electrocyclization would generate the cyclooctatriene **7**. Unlike the cascades above, instead of a subsequent conrotatory 6π electrocyclization to afford a bicyclo[4.2.0]octadiene, the cyclooctatriene engages in an intramolecular cycloaddition with one of the disubstituted alkenes to generate the tricyclic hydrocarbon core of the molecule.

It should be noted that the endriandric acids and kingianin A were isolated as racemates and spontaneously form from their achiral polyene precursors **1** and **3**.^[1,4] By contrast, PF-1018 was isolated as a single enantiomer and diastereomer. It seems unlikely that the existing stereocenter in the hypothetical precursor **6** would govern the diastereoselectivity of the initial 8π electrocyclization. This indicates that the pericyclic cascades could already occur on a shorter intermediate, such as **8**, within the chiral environment of a molecular assembly line (Fig. 1D).^[10,11] The cyclization of an intermediate bound to a polyketide synthase–nonribosomal peptide synthetase (PKS–NRPS) via a thioester, could also explain why interception of the cyclooctadiene **9** *via* Diels–Alder reaction to afford **10** is favoured over a relatively fast 6π electrocyclization, which is essentially irreversible at ambient temperatures.^[12–15]

Given these considerations, a biomimetic laboratory synthesis of PF-1018 poses considerable challenges. We have previously developed an 8π electrocyclozation/Diels–Alder cascade that gave rise to the partially saturated tricyclic core of PF-1018.^[16] However, our synthesis faltered because we were unable to install the remaining double bond in this highly hindered, caged intermediate. We now report the successful, asymmetric synthesis of PF-1018 that could overcome these issues through careful engineering of the cyclization substrate. It demonstrates that our strategy for the Diels–Alder interception of a cyclooctatriene is generalizable. It also features unusual and unexpected reactivity associated with the caged and congested tricyclic hydrocarbon core of our target.

Our synthesis started with the asymmetric addition of Brown's chiral allyl borane **12**^[17] to the known aldehyde **11**. This gave the mono methoxymethyl (MOM)-protected diol **13** in decent yield and with excellent enantiomeric purity. Subsequent olefin cross-metathesis with methyl acrylate was achieved through sequential addition of the second-generation Hoveyda–Grubbs catalyst over several hours to overcome low conversion. This was followed by protection of the secondary alcohol as a silyl ether and afforded the unsaturated ester **14**. The stage was now set for the key step of the synthesis, which commenced with cross-coupling of **14** with the known vinyl stannane **15** under Stille–Liebeskind conditions. The initial cross-coupling product **16** was not isolated but was heated gradually in solution from 65 °C to 125 °C and then maintained for 20 hours at this temperature to promote the 8π electrocyclozation (**16** → **17**) and Diels–Alder interception (**17** → **18**). Under these conditions we could isolate the tricycle **18** in 42% yield. The X-ray structure of **18** is shown in Fig. 1 confirming the configuration and highly congested nature of this caged compound. With **18** in hand, our next task was to convert the doubly protected diol into the trisubstituted C2,C3 double bond of PF-1018 (original nomenclature). To this end, we first cleaved the silyl ether at C2 to afford the secondary alcohol **19** and then activated its hydroxy group as the benzyl xanthate **20**. Barton–McCombie deoxygenation under highly optimized conditions (see below) then gave MOM ether **21**. Cleavage of this ether using a modification of Fujioka's-conditions,^[18] followed by oxidation with Dess–Martin periodinane, yielded ketone **22**. Conversion to the enol triflate, followed by Negishi coupling, installed the required olefinic double bond. Subsequent reduction of the ester with DIBAL then gave the primary alcohol **23**.

In the final stage of our synthesis, **23** was oxidized to an unstable aldehyde, which was condensed with tetramic acid phosphonate **25**.^[19] This gave (–)-PF-1018 as an inseparable 3.5:1 mixture of (*E*) and (*Z*) isomers with respect to the C19-C2' double bond. The analytical data of our synthetic samples were identical with those reported for the natural product, with the exception of the optical rotation, which is significantly lower in our case. However, we have confirmed the high optical purity of alcohol **19** by Mosher ester analysis (see Supporting Information) and it seems unlikely that the final steps of the synthesis result in partial racemization. The difference in optical rotation probably stems from variations of the (*E*)/(*Z*) ratio of the C19-C2' double bond (3.2:1 reported for the natural sample).^[9]

The preparation of tetramic acid phosphonate **25** from proline through a modified route is shown in the lower portion of Fig. 2. Acetylation and conversion to the Weinreb amide gave **24**. A subsequent Dieckmann condensation then afforded an unstable pyrrolizidinedione,

[20] which was coupled with diethyl phosphonoacetic acid to afford the tetramic acid phosphonate **25**.^[19,21] This building block was also condensed with octanal to afford the recently isolated anionic lipid pyreudione C.^[20,22]

The key step of our synthesis warrants further analysis. Given the many possible isomers that can be formed, we consider this a remarkable result both in terms of selectivity and yield (see SI Fig. S1). In preliminary studies, we had established that the relative stereochemistry at C2 and C3, as well as the size of the silyl group at C2 are crucial to achieve high yields in the cascade.^[16] Bicyclo[4.2.0]octadienes resulting from competing 6π electrocyclization cascades were never observed but are likely destroyed *via* formal retro [2+2] cycloaddition under our optimized conditions.^[7] Other isomers could not be isolated either.

To explain such reactivities and selectivities of the pericyclic cascade, density functional theory calculations were employed at the SMD(DMF)- ω B97X-D/def2-QZVPP//SMD(DMF)- ω B97X-D/6-311+G(d,p) level of theory (see SI for computational details).^[23–33]

These calculations indicate that the polyene **16** can engage in two conrotatory 8π electrocyclizations to form **17** and its diastereomer **17'** *via* **TS-1** and **TS-2**, respectively (Fig. 2, S2). The cyclooctatrienes **17** and **17'** are nearly isoenergetic with their precursor **16** (Figure S3), resulting in an initial equilibrium between the species **16**, **17**, and **17'**. The subsequent intramolecular cycloaddition of **17**, forming **18** *via* **TS-3**, is 4.7 kcal·mol⁻¹ lower in Gibbs-free energy than the diastereomeric cycloaddition *via* **TS-4**. Consequently, the equilibrium mixture of **16**, **17**, and **17'** will funneled through **TS-3** to selectively form the isolated product **18**. The Diels–Alder transition states **TS-3** and **TS-4** are both stabilized by favourable secondary orbital interactions between the diene and ester oxygen of the dienophile. The difference in Gibbs-free energy between **TS-3** and **TS-4** ($\Delta G^\ddagger = 4.7$ kcal·mol⁻¹) is due to the MOM-ether being forced into a *pseudo*-axial position in **TS-4**. In **TS-3**, both the MOM-ether and silyl-ether groups on the emerging cyclopentane are in *pseudo*-equatorial positions. The silyl ether greatly affects the energy difference between the Diels–Alder cycloaddition *via* **TS-3** and a competing 6π electrocyclization *via* **TS-5**. Decreasing the size of this substituent would favour the 6π electrocyclization according to our calculations (Fig. 2, S4, S5a). A substrate with the double bond in place at C2,3 will also predominately form the 6π -product, suggesting that an enzyme is necessary for the Diels–Alder reaction to occur in Nature (Fig. S5b).

A step in our synthesis that delivered unexpected but interesting results was the Barton–McCombie deoxygenation. (Scheme 3 and Table 1). Standard conditions involving the methyl xanthate **26** only gave a low yield of the desired product **21**. It was accompanied by substantial amounts of methyl ether **28** (byproduct previously reported in these reactions)^[34–36] and, to our surprise, cyclobutane **29**. The latter results from a rare 4-*exo-trig* radical cyclization, which generates a secondary radical.^[37] This unusual selectivity presumably results from the constrained nature of the caged precursor. Increasing the concentration of tributyl tin hydride suppressed this cyclization but also led to higher yields of the unwanted methyl ether **28**. This problem could be finally overcome by variation of the xanthate: use

of the larger benzyl xanthate **20** to promote fragmentation gave a good yield of the desired intermediate **21**.^[38]

Cyclobutane **29** was not a waste product but could be converted into a late-stage intermediate of our synthesis through an unusual fragmentation (Scheme 4). We reasoned that ketone **30** could fragment after electrophilic activation of the carbonyl compound with triflic anhydride to yield unsaturated vinyl triflate **31**.^[39,40] Deprotection and oxidation of **29** with Dess–Martin periodinane gave cyclobutyl ketone **30**, the X-ray structure of which is shown in Fig 1 (right). It confirmed that the carbonyl group, the C,C-bond, and the requisite C-H bond are indeed stereoelectronically well aligned to allow for smooth formation of the two π bonds. Attempts to convert **30** into vinyl triflate **31** however, were unsuccessful and led to decomposition. We assigned this result to the interference of the methyl ester, which was accordingly reduced to afford primary alcohol **32**. Cleavage of the MOM-ether, DIBAL-reduction, selective protection of the primary alcohol with a bulky silyl group, and oxidation of the secondary alcohol then yielded cyclobutyl ketone **32**. Treatment of this ketone with triflic anhydride in the presence of a sterically hindered pyridine base elicited the desired fragmentation and gave vinyl triflate **33**. Although the methyl group could also be deprotonated and is less hindered, only a small amount of the corresponding *exo*-methylene isomer was observed. To the best of our knowledge, a fragmentation of this type with concomitant enol triflate formation has only been reported once in the literature.^[40] Negishi cross-coupling of **33** with dimethyl zinc and deprotection then afforded primary alcohol **23**, which could be used in the final steps of our total synthesis.

In summary, we have achieved the first total synthesis of the unusual polyketide tetramic acid PF-1018. Our 15-step asymmetric synthesis is marked by a bioinspired cascade that combines an 8π electrocyclicization with a Diels–Alder cycloaddition. Computational studies indicate that the size of substituent at C2 determines whether a 6π electrocyclicization or Diels–Alder will be preferred, while the stereochemistry at C3 determines facial selectivity of the cycloaddition. This synthesis also rests on an unusual strategy to install a trisubstituted double bond. In the course of this sequence, we observed a 4-*exo-trig* radical cyclization that generated an unexpected tetracycle. The product of this radical cyclization could be recycled by way of a stereoelectronically favourable fragmentation that simultaneously generated a trisubstituted double bond and a vinyl triflate. Future work will be directed towards exploring the biosynthesis, biological activity and structure activity-relationships of PF-1018 and other anionic lipids that feature proline-derived tetramic acids, such as talarotoxin^[41] and the pyreudiones.^[10,20,42]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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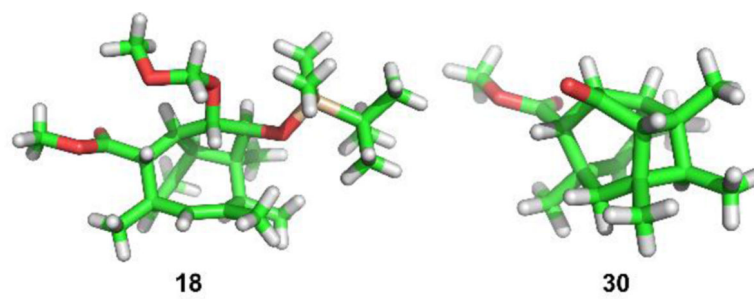


Figure 1.
X-ray crystal structure of compounds **18** and **30**.

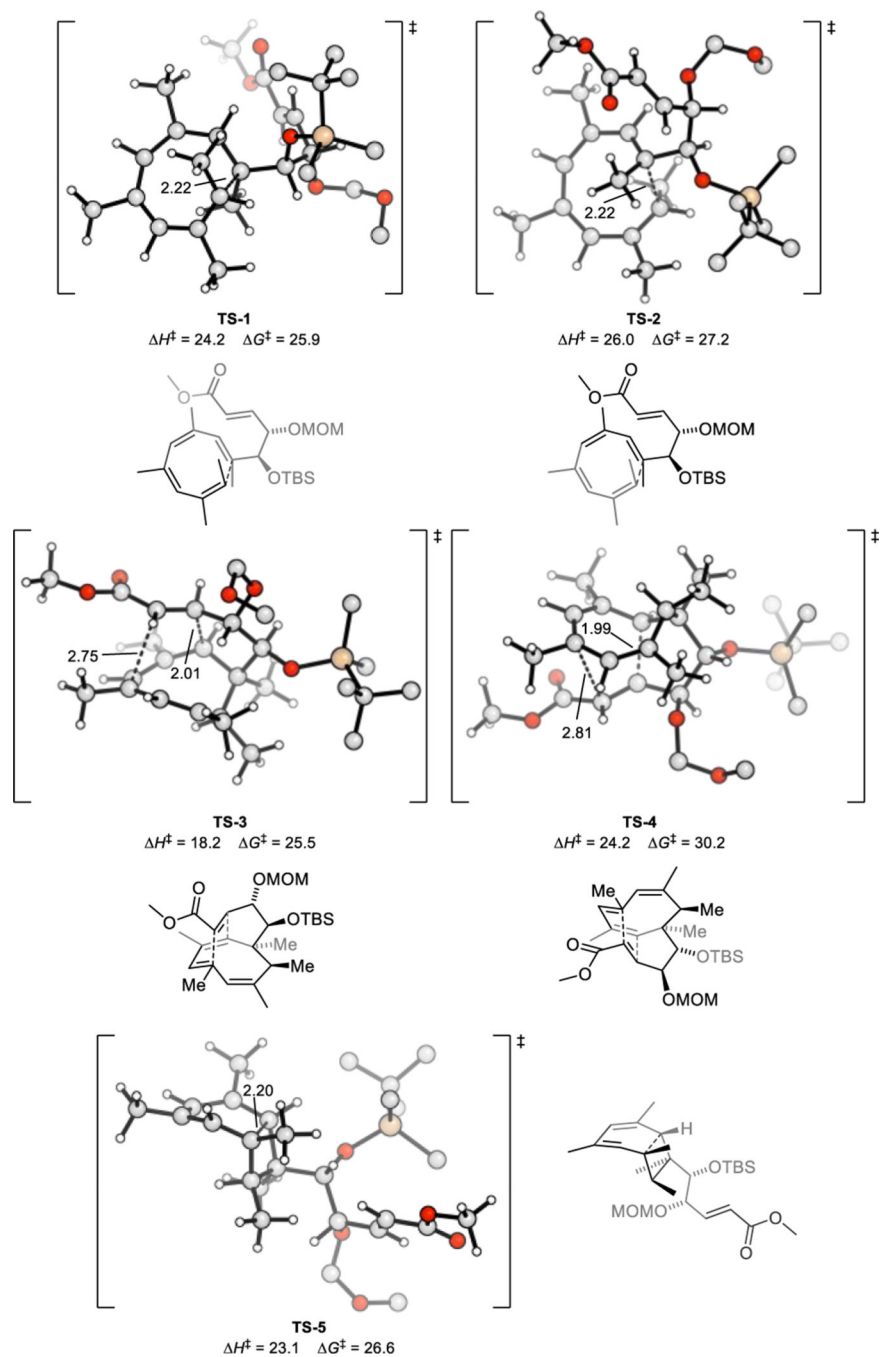
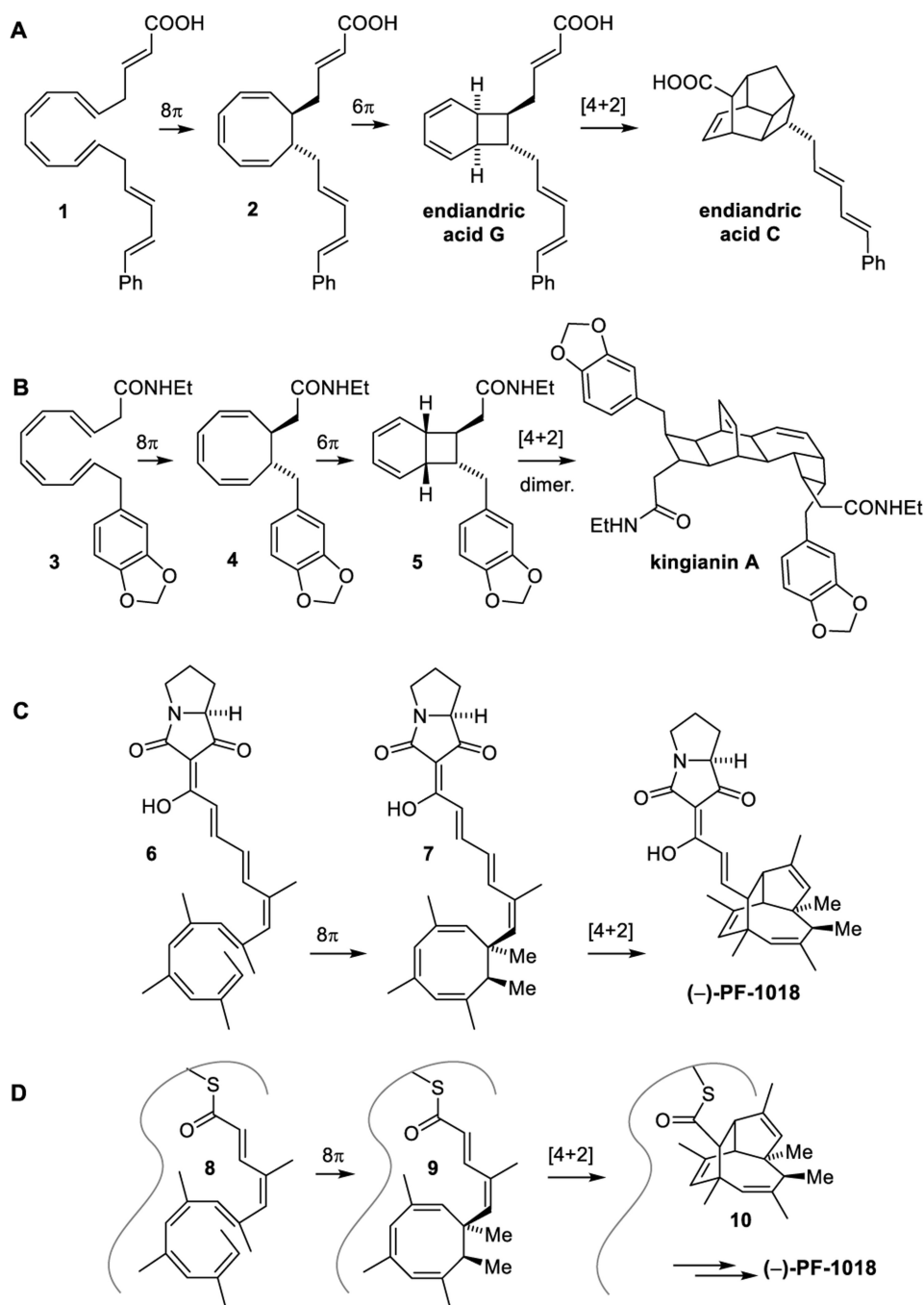
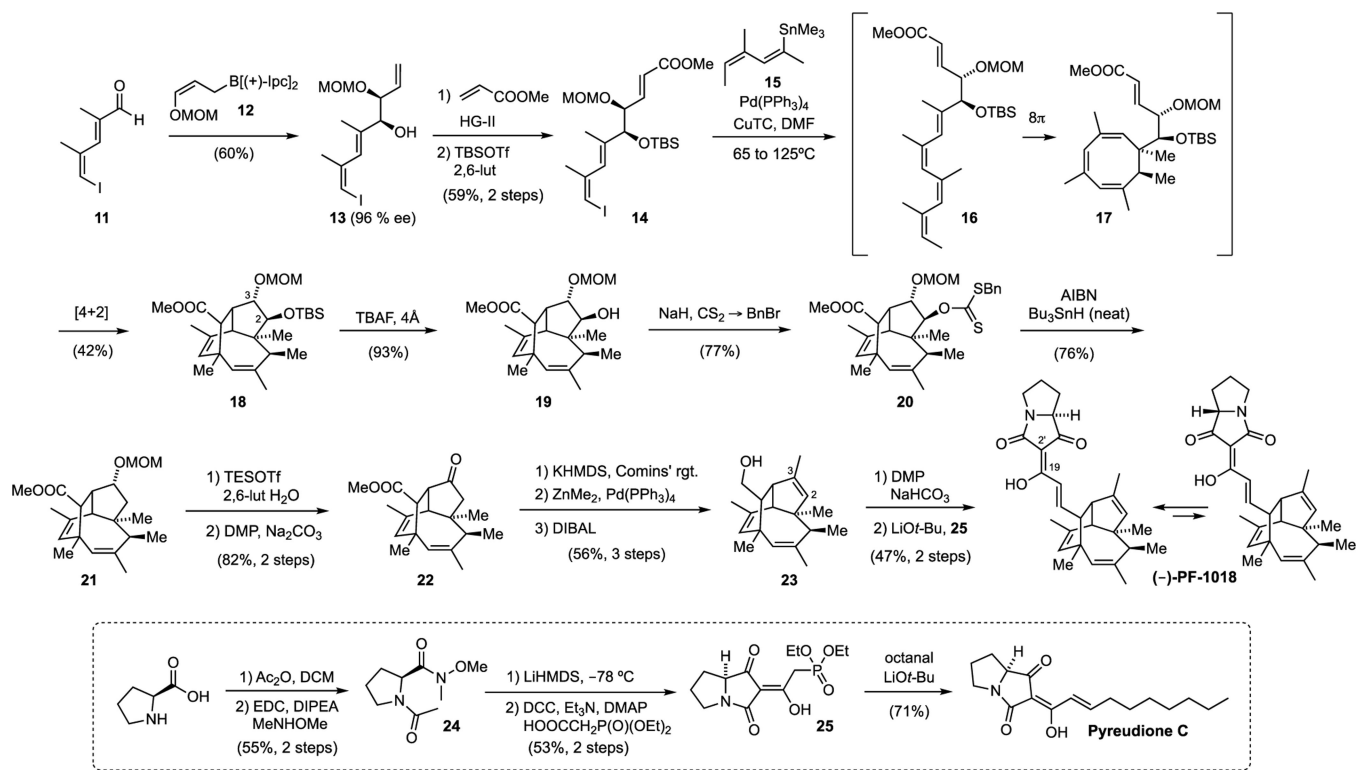


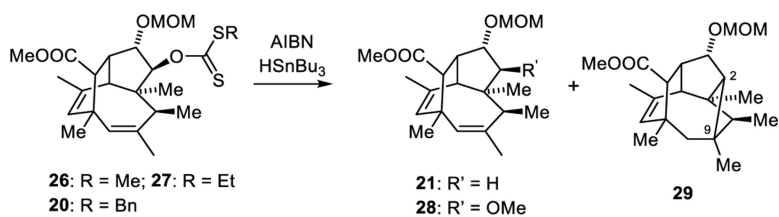
Figure 2. Density functional theory calculated transition state structures of pericyclic cascade. Hydrogens on protecting groups are omitted for clarity, silicon shown in wheat colour.



Scheme 1.
Electrocyclization-Cycloaddition cascades in natural product chemistry.

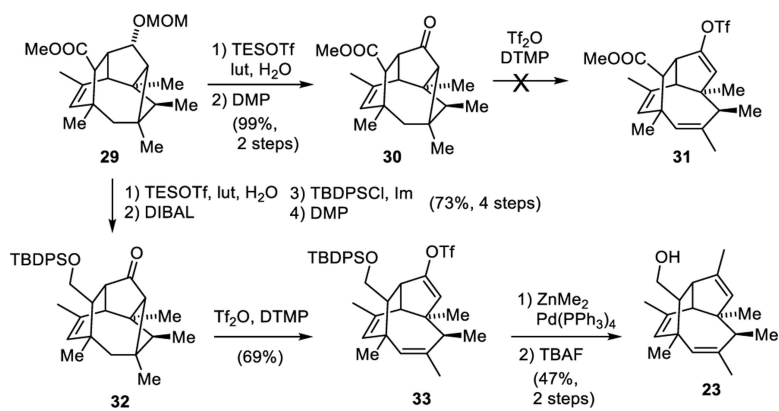


Scheme 2.
Total synthesis of (-)-PF-1018 and Pyreudione C.



Entry	Xanthate	HSnBu ₃ (equiv.)	Yield [%]:	21	28	29
1	26 R = Me	4.8		21	6	46
2	26 R = Me	50		41	29	10
3	27 R = Et	50		49	19	2
4	20 R = Bn	40		76	12	6

Scheme 3 and Table 1:
Products of the Barton–McCombie deoxygenation.



Scheme 4:
 Fragmentation of a cyclobutyl ketone and recycling of cyclobutane side product **29**.