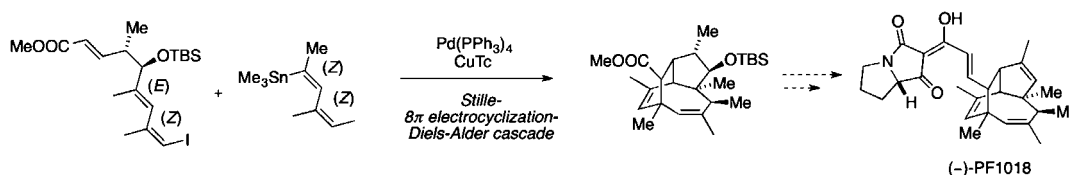


Studies toward the Biomimetic Total
Synthesis of (–)-PF-1018Robert Webster,[†] Boris Gaspar,[†] Peter Mayer, and Dirk Trauner**Fakultät für Chemie und Pharmazie, Ludwig-Maximilians-Universität München, and
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ABSTRACT



Pericyclic reaction cascades are unparalleled in their ability to quickly generate complex structures with excellent stereocontrol. Herein, the use of a biomimetic Stille/ 8π electrocyclization/Diels–Alder cascade to successfully assemble the core structure of (–)-PF-1018 is reported.

In addition to bioactivity, the molecular architecture of a natural product can provide a major impetus for its choice as a target in total synthesis. This is especially true when a beautiful structure can be coupled with efficient and innovative construction methods. Pericyclic reaction cascades have been shown to play an important role in the biosynthesis of numerous natural product scaffolds,¹ enabling chemists to borrow wisdom from nature by choosing bold retrosynthetic disconnections that rapidly build complexity.²

(–)-PF-1018 (**1**), an insecticidal polyketide isolated from a fungal strain *Humicola* sp.,³ would certainly appear attractive to many synthetic chemists (Scheme 1). The molecule features a complex tricyclic core that contains a total of two quaternary and four secondary stereocenters, all of which are contiguous. This compact nucleus is connected to a bicyclic tetramic acid moiety bearing one additional stereocenter. At the time of its isolation, the relative stereochemistry and overall structure of (–)-PF-1018 (**1**) were confirmed by X-ray crystallography, whereas its absolute stereochemistry was inferred by

degradation of the natural product and correlation with L-proline.

Biosynthetically, (–)-PF-1018 (**1**) could arise from linear polyene **4** (Scheme 1), itself assembled on a polyketide synthase (PKS)⁴ from L-proline, four acetyl CoA units, and four methylmalonyl CoA units. This hypothetical polyene **4**, contains five trisubstituted double bonds, four *Z*-configured and one *E*-configured, as well as two disubstituted double bonds, each with the *E*-configuration, in addition to the bicyclic tetramic acid headgroup. A thermal 8π conrotatory electrocyclization of the terminal alkenes would yield a 1,3,5-cyclooctatriene **2** that could subsequently engage in an intramolecular Diels–Alder reaction to afford (–)-PF-1018 (**1**). It is common, however, for cyclooctatrienes of type **2** to rapidly undergo thermal 6π disrotatory electrocyclizations to yield bicyclo[4.2.0]octadienes, such as compound **3**.⁵ At least

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(5) For examples of biomimetic syntheses featuring $8\pi/6\pi$ electrocyclization cascades, see (endriatric acids): (a) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560. SNF4435 C/D: (b) Parker, K. A.; Lim, Y.-H. *J. Am. Chem. Soc.* **2004**, *126*, 15968. (c) Beaudry, C.; Trauner, D. *Org. Lett.* **2005**, *7*, 4475. (d) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron* **2006**, *62*, 1675. Shimalactones: (e) Sofiyev, V.; Navarro, G.; Trauner, D. *Org. Lett.* **2008**, *10*, 149. Elisiapyrones A/B: (f) Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901. Ocellapyrones A/B: (g) Miller, A. K.; Trauner, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4602. Prekingianin A: (h) Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem Commun.* **2011**, *47*, 10605. Kingianin A: (i) Lim, H. N.; Parker, K. A. *Org. Lett.* **2013**, *15*, 398.

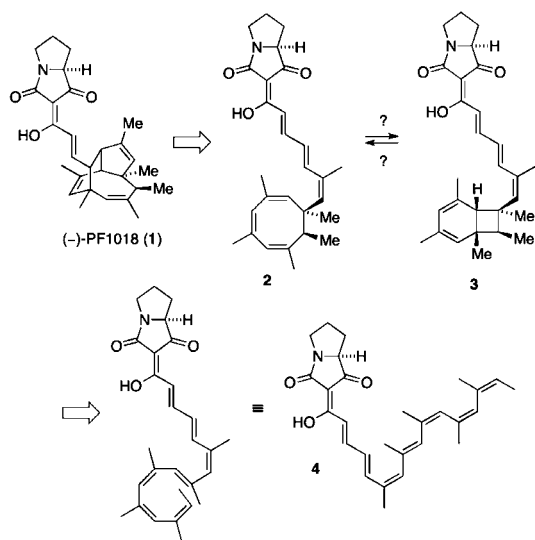
[†] These authors contributed equally to this work.

(1) Beaudry, C.; Melarich, J.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

(2) (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, Germany, 1996. (b) Bulger, P. G.; Bagal, S. K.; Marquez, R. *Nat. Prod. Rep.* **2008**, *25*, 254.

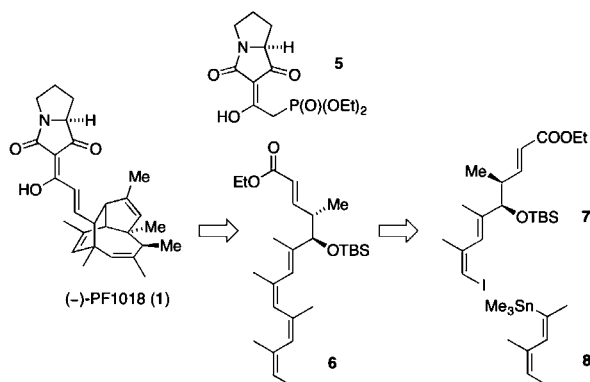
(3) Gomi, S.; Imamura, K.; Yaguchi, T.; Kodama, Y.; Minowa, N.; Koyama, M. *J. Antibiot.* **1994**, *47*, 571.

Scheme 1. Biosynthetic Analysis of PF-1018



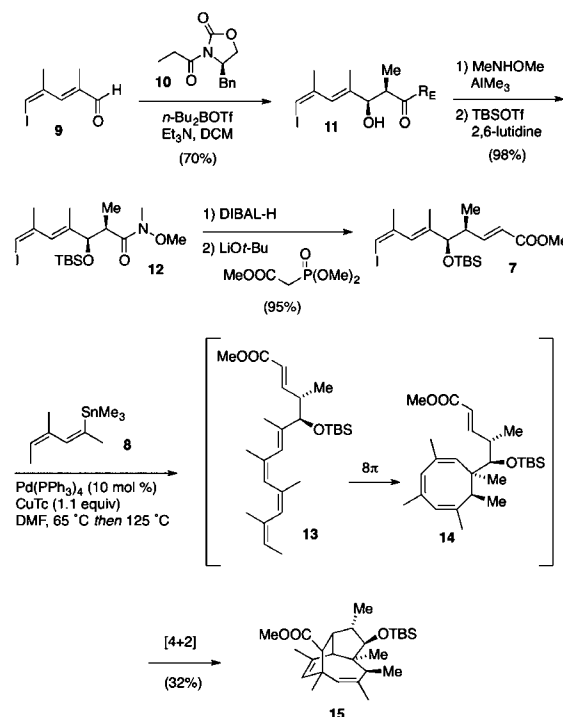
conceivably, the chemical environment of the PKS may be required for the Diels–Alder reaction to outpace the 6π electrocyclization, representing a potential design challenge in our synthesis. Additionally, the potential reversibility of the 6π electrocyclization also has to be taken into account, although the relevance of this process under biosynthetic conditions is questionable given the relatively high temperatures typically required for 6π cycloreversions.⁶

Scheme 2. Retrosynthetic Analysis of PF-1018



From a synthetic point of view, polyene **4** was deemed an unsuitable intermediate for various reasons. We anticipated that this polyene would be highly unstable due to its inbuilt acidic functionality. Second, polyene **4** could potentially engage in multiple pericyclic reaction modes that would be difficult to control. Finally, even if the 8π electrocyclization involving the terminal double bonds

Scheme 3. Asymmetric Synthesis of the Tricyclic Core



was to occur preferentially, we felt that the sole stereo-center in the tetramic acid portion would be unlikely to control its stereochemical outcome. Therefore, we opted to dissect (–)-PF-1018 (**1**) into the known proline-derived phosphonate **5**⁷ and the “hydrated” polyene component of type **6** (Scheme 2). The latter fragment would fulfill three purposes: (a) to reduce the number of available electrocyclic modes, (b) to potentially suppress the 6π electrocyclization in favor of the desired intramolecular Diels–Alder reaction, and (c) to enable an asymmetric approach to the tricyclic core, independent from the bicyclic tetramic acid moiety. Further retrosynthetic disconnection led us to vinyl iodide **7** and vinyl stannane **8**,⁸ using a strategy that we had successfully employed in the synthesis of other highly unsaturated polyketides.^{5e–g}

Starting from aldehyde **9**, available in five steps from propargyl alcohol,^{5f} a *syn*-selective Evans aldol employing oxazolidinone **10** provided alcohol **11** as a single diastereomer (Scheme 3).⁹ A two-step trans-amidation/silylation protocol gave protected Weinreb amide **12**, which was in turn reduced to the corresponding aldehyde and subsequently olefinated to afford methyl ester **7**. The key domino Stille/ 8π electrocyclization/Diels–Alder cascade using Liebeskind-type Stille conditions,¹⁰ followed by heating, furnished the desired tricycle **15** in an optimized

(6) (a) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980. (b) Okamura, W. H.; de Lera, A. R. 1,3-Cyclohexadiene Formation Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, section 6, pp 699–750.

(7) Rosen, T.; Fernandes, P. B.; Marovich, M. A.; Shen, L.; Mao, J.; Pernet, A. *J. Med. Chem.* **1989**, 32, 1062.

(8) Vinyl stannane **8** was prepared in four steps from methyl angelate. Detailed procedures are provided in the Supporting Information.

(9) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, 68, 83.

(10) Zhang, S.; Zhang, D.; Liebeskind, L. *J. Org. Chem.* **1997**, 62, 2312.

yield of 32% as a single diastereomer. Compound **15** was the only isomer, among many conceivable ones, that could be isolated under these conditions.¹¹ Its structure was verified by X-ray crystallography which also confirmed its absolute configuration by virtue of the heavy silicon atom (Figure 1). It is noteworthy that employing the diastereomeric vinyl iodide *anti*-**7**, as well variants of the vinyl iodide **7** with the alcohol unprotected, yielded no isolable Diels–Alder products under the same conditions and only complex mixtures that contained isomeric bicyclo[4.2.0]octadienes were obtained.

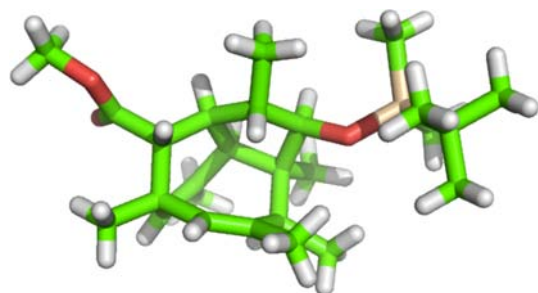


Figure 1. X-ray structure of tricyclic ester **15**.

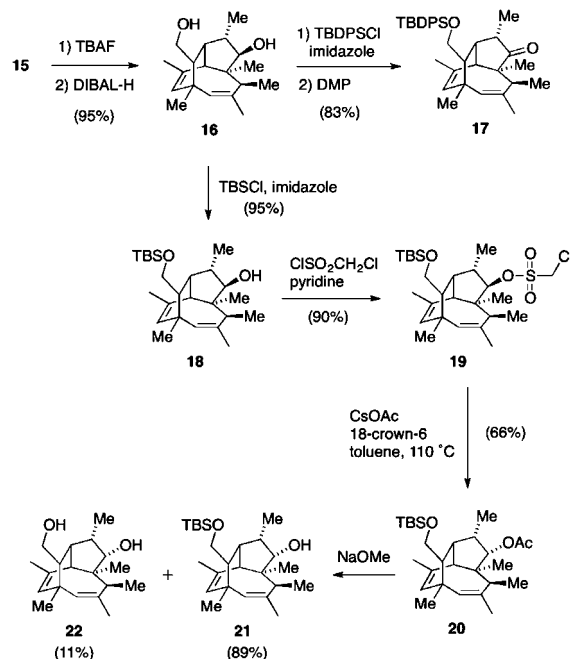
With the tricyclic diene **15** now in hand, we were faced with the challenge of converting it to the corresponding triene in order to complete the core structure of (–)-PF-1018 (**1**). We anticipated that removing the ester functionality would improve thermal stability toward homolytic or heterolytic bond cleavage of the carbon skeleton, and diene **15** was first desilylated and then reduced to give diol **16** (Scheme 4). After selective protection of the primary alcohol moiety, it was possible to obtain hindered ketone **17** via oxidation with DMP. However, further transformation into the corresponding enol triflate or hydrazone, as well as epimerization of the α -methyl group using base, proved unsuccessful, even under forcing conditions.

(11) The majority of the remaining mass balance from the key reaction cascade consisted of a nonpolar fraction containing a complex mixture of inseparable products. The various components of this intractable mixture likely originate from tetraene **6** via alkene isomerizations and/or alternate available pericyclic reaction modes. Despite attempted purification, no additional products could be successfully isolated or identified.

(12) Including, but not limited to, Burgess reagent: (a) Atkins, G. M., Jr.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744. (b) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26. (c) Ishikawa, H.; Elliott, G.; Velcicky, J.; Choi, Y.; Boger, D. *J. Am. Chem. Soc.* **2006**, *128*, 10596. Martin's sulfuran: (d) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003. (e) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604. Chugaev elimination: (f) Tschugaeff, L. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3118. (g) Nace, H. R. *Org. React.* **2011**, 57–100. Re_2O_7 -mediated elimination: (h) Korstjanje, T. J.; de Waard, E. F.; Jastrzebski, J. T.; Klein Gebbink, R. J. M. *ACS Catal.* **2012**, *2*, 2173. TiF_2O , 2,6-lutidine: (i) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498. POCl_3 , pyridine: (j) Birch, A. M.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1980**, 24, 1195. SOCl_2 , pyridine: (k) Watanabe, H.; Takano, M.; Umino, A.; Ito, T.; Ishikawa, H.; Nakada, M. *Org. Lett.* **2007**, *9*, 359. MsCl , Et_3N : (l) Bonikowski, R.; Kula, J.; Bujacz, A.; Wajs-Bonikowska, A.; Zakłós-Szyda, M.; Wysocki, S. *Tetrahedron: Asymmetry* **2012**, *23*, 1038. Mitsunobu-type elimination: (m) Izuhara, T.; Katoh, T. *Tetrahedron Lett.* **2000**, *41*, 7651.

Unfortunately, despite extensive efforts,¹² dehydration of alcohol **18** by *syn*-elimination or E1-elimination was also problematic and could never be effected in synthetically useful yields.

Scheme 4. Derivatization of the Tricyclic Core and Successful Inversion of the Alcohol Functionality



We reasoned that the hindered, neopentyl alcohol **18** may possess an unfavorable geometry for the requisite stereoelectronics of a *syn*-elimination, prompting us to investigate methods for its stereochemical inversion. Reduction of ketone **17** proceeded smoothly under Birch-type conditions (Li , NH_3/THF , -78°C) but was completely unselective, yielding a 1:1 dr. By contrast, conversion of alcohol **18** into its chloromethyl sulfonate derivative **19**, followed by treatment with CsOAc at elevated temperatures and prolonged reaction times,¹³ cleanly yielded the inverted acetate **20**. Solvolysis of acetate **20** delivered the inverted alcohol **21**, which was accompanied by a small amount desilylation to give diol **22**, the structure of which was confirmed by X-ray crystallography (Figure 2). We were encouraged by the axial orientation of the alcohol evident from the crystal structure, the geometry of which appears well-suited for *anti*-elimination. However, exposure of alcohol **21** to an array of standard elimination conditions has not yet successfully introduced the requisite alkene for the core structure of (–)-PF-1018 (**1**). All attempts to convert the secondary alcohol function in **21** into a leaving group led to its decomposition, presumably via interference of the proximate, highly nucleophilic alkene functionality.

(13) (a) Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6145. (b) Shirahata, T.; Sunazuka, T.; Yoshida, K.; Yamamoto, D.; Harigaya, Y.; Kuwajima, I.; Nagai, T.; Kiyohara, H.; Yamada, H.; Omura, S. *Tetrahedron Lett.* **2006**, *62*, 9483.

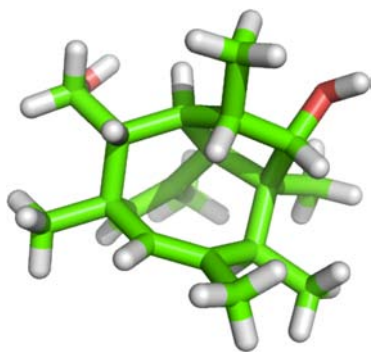


Figure 2. X-ray structure of diol **22**.

In summary, we have completed a concise asymmetric synthesis of the tricyclic core of (–)-PF-1018 (**1**), utilizing a three-fold domino Stille/ 8π electrocyclization/Diels–Alder sequence. Considering the number of pericyclic reaction modes available to the intermediate polyene **6** from the key cascade, as well as the potential formation of diastereomers,

the fact that tricycle **15** could be reproducibly isolated as a single diastereomer in synthetically useful yields is remarkable. Extensive effort was channeled into dehydration of this adduct, and studies directed at incorporation of the final alkene and completion of the total synthesis are currently underway.

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Supporting Information Available. Experimental procedures and characterization of all new compounds, including X-ray data for compounds **15** and **21**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.