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Enantioselective, Lewis Base-Catalyzed Sulfenocyclization of Polyenes

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Supporting Information

ABSTRACT: A sulfenium-ion-initiated, catalytic, enantioselective polyene cyclization is described. Homogeranylarenes and *ortho*-geranylphenols undergo polycyclization in good yield, diastereoselectivity, and enantioselectivity. The stereodetermining step is the generation of an enantiomerically enriched thiiranium ion from a terminal alkene and a sulfenylating agent in the presence of a chiral Lewis basic catalyst. The use of hexafluoroisopropyl alcohol as the solvent is crucial to obtain good yields. The thioether moiety resulting from the reaction can be subsequently transformed into diverse oxygen and carbon functionality postcyclization. The utility of this method is demonstrated by the enantioselective syntheses of (+)-ferruginol and (+)-hinokiol.

Polyene cyclization is one of the most fundamental transformations in biosynthetic chemistry. Since the identification of the direct conversion of squalene to lanosterol as the key step of cholesterol biosynthesis,[1] chemists have been fascinated by these complexity-generating processes. The ability to construct multiple rings and stereogenic centers in one step from a simple, linear, achiral starting material has obvious synthetic utility. Stork[2] and Eschenmoser[3] first proposed that polyene cyclizations in nature are electrophilically initiated and proceed through a cationic cascade pathway. Although the Stork-Eschenmoser hypothesis was widely accepted, polyene cyclizations were thought to be limited to the domain of enzymatic transformations until the pioneering works of W. S. Johnson[4] and E. E. van Tamelen,[5] who demonstrated that these reactions still proceed with high diastereoselectivity and synthetically useful yield using solely chemical methods. In the following decades, cationic, anionic, and radical cyclizations of polyenes have been employed as the key step in the laboratory syntheses of hundreds of natural products.[6]

In the vast majority of these syntheses that generate enantiomerically enriched products, a defined stereogenic center is preinstalled on the linear polyene prior to the diastereoselective cascade cyclization step. Indeed, the squalene to lanosterol biosynthetic pathway begins with an enantioselective epoxidation to form (3*S*)-2,3-oxidosqualene, which in turn serves as the substrate for acid-mediated, cationic cyclization by oxidosqualene cyclase.[7] By contrast, enantioselective variants of polyene cyclization are less well-developed.[8,9] Since the seminal report by Yamamoto,[9a] several methods for enantioselective, proton-initiated polyene cyclizations have been disclosed, but most of these require stoichiometric amounts of chiral Lewis or Brønsted acids.[9a−f] and the early catalytic, enantioselective variants require high catalyst loadings.[9g−i] In recent years, a few examples of truly catalytic, enantioselective, polyene cyclizations have been reported. In 2017, Yamamoto disclosed an enantioselective bromocyclization of polyenes using a BINOL-derived thiophosphoramide as a chiral Lewis basic catalyst.[10] The method suffers from incomplete cyclization cascades (−90 °C), requiring a stoichiometric amount of strong acid to force the subsequent ring closure, which leads to variable yields. Organometallic catalysis has also been developed by Gagné (Pt),[11a] Toste (Au)[11b] and Carreira (Ir),[11c] as well as by Snyder (Hg) albeit with a stoichiometric amount of $Hg(OTf)_2$.[11d] The products contain halides, olefins or vinyl groups for further manipulation. Organocatalytic initiation methods developed by Jacobsen,[12a] MacMillan,[12b] and Zhao,[12c] although highly selective, require specially engineered substrates that are not easily diversifiable postcyclization. A high-yielding, selective, and operationally simple method for the cyclization of unmodified polyene substrates which also installs useful A-ring functionality is still lacking.

The ability of Lewis bases to enhance the electrophilicity of Lewis acids by the generation of cationic donor−acceptor complexes is now well-established for elements in groups 13, 14, 16, and 17.[13] In group 16, activation of *S*-arylthiophthalimides with chiral Lewis basic catalysts allows for the formation of enantiomerically enriched thiiranium ions from unactivated alkenes.[14a,b] These thiiranium ions may be intercepted by pendant nucleophiles to form a wide variety of 1,2-sulfeno-functionalized products in a highly stereoselective fashion. Previous reports from these laboratories have demonstrated the enantioselective intramolecular oxy-,[14c,d] amino-,[14e,f] and carbosulfenylation[14g,h] of double bonds. For the oxy- and carbosulfenylation processes, we envisioned that by insertion of an alkene between the initiating alkene and terminating group that an enantioselective polyene sulfenocyclization could be developed (Scheme 1).[15]

Initial attempts to cyclize homogeranylarenes **3** using the standard carbosulfenylation conditions (1.0 equiv sulfenylating agent **1**, 0.1 equiv catalyst (*S*)-**2**, 0.4 equiv MsOH, 1 M in CH_2Cl_2) gave unsatisfactory results. Numerous products were observed, including one resulting from competitive thiiranium ion generation on the internal alkene. The desired tricycles **4** were isolated only in low yield, but encouragingly, the enantiomeric ratio of these products was consistently 90:10

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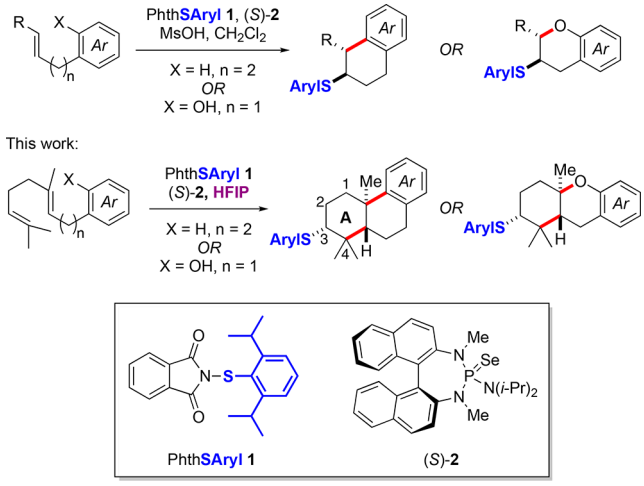
Scheme 1. Lewis Base-Catalyzed Oxy- and Carbosulfenylation, and Extension to Polyene Cyclization

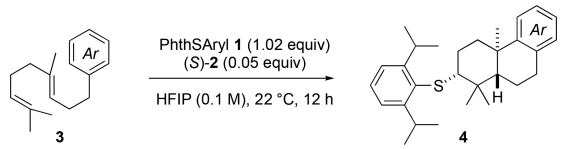


or greater. After a survey of reaction conditions, hexafluoroisopropyl alcohol (HFIP) was identified as a highly effective solvent for this transformation which suppressed the sulfenylation of the internal alkene and led to **4** as the major product of the reaction. The striking effect of HFIP on reaction selectivity is attributed to solvophobic interactions.[16] In such a highly polar medium, lipophilic polyene substrates prefer to adopt a conformation that minimizes surface area, leaving the distal alkene more exposed. An additional benefit of HFIP is its mild acidity, which obviates the need for MsOH to assist with the generation of the catalytically active, cationic complex.

Under the optimized conditions, a wide variety of electron-neutral to electron-rich homogeranylarenes[17] cyclized efficiently in synthetically useful yields and enantioselectivities (Table 1).[18] In addition to homogeranylbenzene **3a** (entry 1), substrates **3b**, **3c**, and **3d** bearing one or more electron-donating groups on the arene (entries 2–4) all cyclized in greater than 59% yield. The cyclization of **3e** (entry 5) was of interest because the arene substitution pattern of the resulting tricycle **4e** is shared by multiple natural products (*vide infra*). Although **3e** contains an unsymmetrically substituted arene, sulfenocyclization afforded **4e** as a single constitutional isomer (likely influenced by the steric bulk of the isopropyl group) in 68% yield and 92:8 e.r. Silyl-protected phenol **3f** (entry 6) also cyclized efficiently. Cyclization of protected aniline **3g** (entry 7) proceeded in 78% yield and 92:8 e.r. and is notable for two reasons. First, to our knowledge, this is the first example of a nitrogen-substituted arene being used as a terminating group for an enantioselective polyene cyclization. Second, a Boc-protecting group would have been incompatible with MsOH required previously. Finally, the extended aromatic system of **3h** (entry 8) was also an effective terminal nucleophile. Electron-poor substrates did not cyclize efficiently and resulted in complex product mixtures.

The method was further extended to the sulfenocyclization of *ortho*-geranylphenols (Table 2). Here, the phenolic oxygen serves as the terminating group for the cascade reaction. Electronically diverse *ortho*-geranylphenols **5** cyclize efficiently to afford products **6** in high yields and useful enantiomeric ratios. Parent *ortho*- geranylphenol **5a** as well as those bearing additional electron- donating groups (**5b** and **5c**) afford >70% yield of cyclized products. Naphthol **5d** (entry 4) was also competent in the reaction. Unlike the above carbosulfenylation reaction, this oxysulfenylation reaction still proceeds with good yields and enantioselectivities with substrates **5e**–**5h** which bear electron-withdrawing substituents on the aromatic ring. In general, enantioselectivities are consistently 90:10 or greater across the entire substrate scope. Yields are slightly higher for the oxy-sulfenocyclization process, presumably because of the more efficient cation trapping by a phenolic oxygen compared to an arene.

Table 1. Scope of Sulfenocyclization of Homogeranylarenes[a]



entry	substrate	product	yield (%)[b]	e.r.[c]
1	**3a**	**4a**	60%	90:10
2	**3b**	**4b**	60%	90:10
3	**3c**	**4c**	59%	92:8
4	**3d**	**4d**	78%	90:10 90:10[d]
5	**3e**	**4e**	68%	92:8
6	**3f**	**4f**	71%	93:7
7	**3g**	**4g**	78%	92:8
8	**3h**	**4h**	59%	92:8

[a]All reactions performed on a 1.00 mmol scale. [b]Yield of isolated, analytically pure product. [c]Determined by CSP-HPLC analysis. [d]Reaction run at 0 °C.

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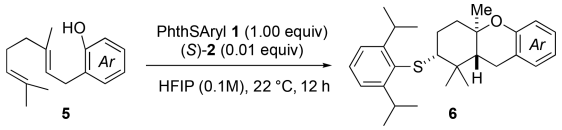
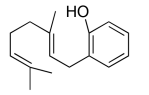
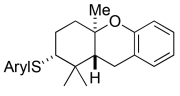
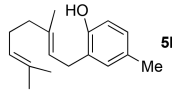
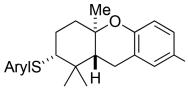
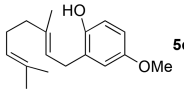
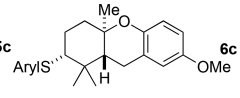
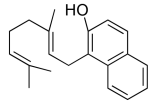
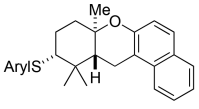
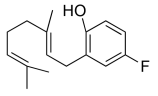
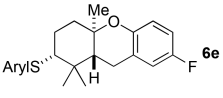
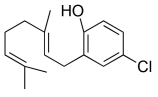
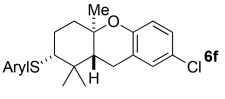
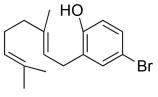
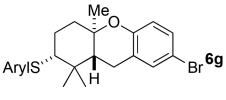
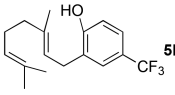
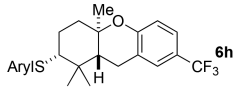
Table 2. Scope of Sulfenocyclization of *ortho*-Geranylphenols[a]

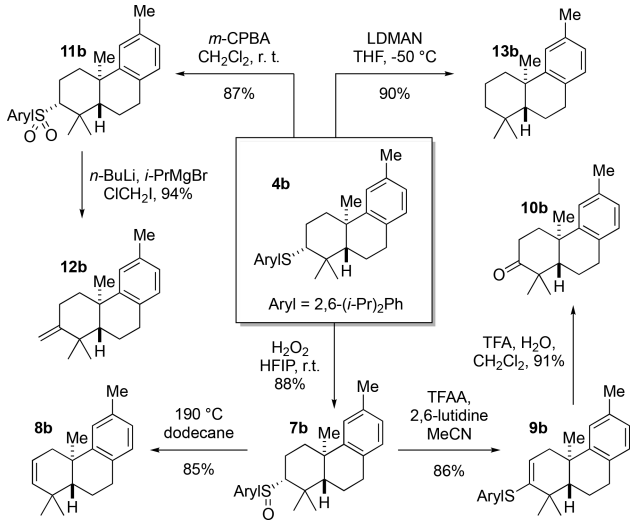


entry	substrate	product	yield (%)[b]	e.r.[c]
1	 5a	 6a	72	93:7
2	 5b	 6b	71	92:8
3	 5c	 6c	80	91:9
4	 5d	 6d	67	90:10
5	 5e	 6e	77	92:8
6	 5f	 6f	79	91:9
7	 5g	 6g	77	92:8
8	 5h	 6h	76	91:9

[a]All reactions performed on a 1.00 mmol scale. [b]Yield of isolated, analytically pure product. [c]Determined by CSP-HPLC analysis.

A major goal of this project was to develop facile and selective transformations of the resulting thioether moiety into useful carbon and oxygen functionality. Despite the sterically hindered environment created by the diisopropylphenyl group, the sulfide readily underwent a number of diverse reactions (Scheme 2). For example, sulfide **4b** was selectively oxidized to sulfoxide **7b** (64:36 d.r.) using hydrogen peroxide in 88% yield.[19] Thermal elimination (190 °C) of **7b** afforded endocyclic alkene **8b** in 85% yield.[20] Alternatively, treatment of **7b** with 2,6-lutidine and trifluoroacetic acid resulted in the formation of vinyl sulfide **9b** via a Pummerer rearrangement in 86% yield.[21] Acidic hydrolysis of **9b** afforded ketone **10b** in 91% yield.[22] Additionally, sulfide **4b** was oxidized to sulfone **11b** using mCPBA in 87% yield,[14d] which underwent Julia-type olefination to form exocyclic alkene **12b** in 94% yield.[23] Finally, reductive cleavage of sulfide **4b** with lithium *N*,*N*-dimethyl-1-

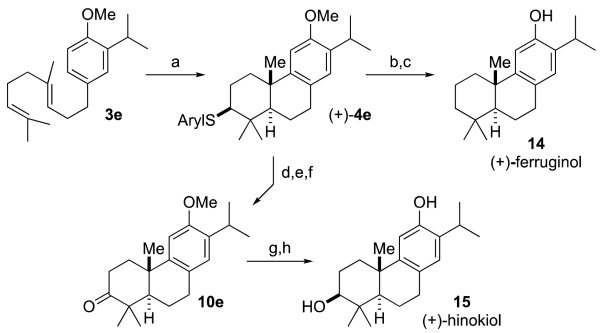
Scheme 2. Transformations of the Products



aminonaphthalenide (LDMAN) afforded alkane **13b** in 90% yield.[24]

To highlight the utility of the sulfenocyclization reaction and subsequent sulfide derivatizations, enantioselective syntheses of (+)-ferruginol **14** and (+)-hinokiol **15** were undertaken (Scheme 3). Both compounds are tricyclic diterpenoids that have been isolated from numerous plant species.[25a,b] Several syntheses of (+)-ferruginol have been reported, but nearly all of these begin with chiral pool staring materials. Tada has described a route employing a diastereoselective polyene cyclization,[26] but to our knowledge, a total synthesis of (+)-**14** has not been achieved by enantioselective polyene cyclization.[27] Only one total synthesis of (+)-hinokiol has been reported, and this too begins from a chiral pool starting material.[28]

Scheme 3. Application to Total Synthesis[a]



[a]Conditions: (a) **1** (1.02 equiv), (*R*)-**2** (0.05 equiv), HFIP (63%); (b) LDMAN, −50 °C (92%); (c) BBr_3 (91%); (d) H_2O_2 (95%); (e) TFAA, 2,6-lutidine (94%); (f) TFA, H_2O (93%); (g) $NaBH_4$ (88%); (h) MeMgI (85%).

Compounds (+)-**14** and (+)-**15** share the same pattern of arene substitution and differ only in the C(3) substituent. Thus, common intermediate (+)-**4e** was identified which could be easily accessed by enantioselective sulfenocyclization of linear polyene **3e**. In the event, cyclization of **3e** could be performed on a 3.0 mmol scale or greater, with no decrease in yield or enantioselectivity. Tricyclic sulfide (+)-**4e** was reductively cleaved to alkane **13e** and subsequently demethylated with

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boron tribromide to afford (+)-ferruginol **14** in 84% yield over 2 steps. To access (+)-hinokiol, (+)-**4e** was oxidized to the sulfoxide **7e**, converted to vinyl sulfide **9e**, and hydrolyzed to ketone **10e** in 83% yield over 3 steps. Substrate-controlled reduction using sodium borohydride afforded secondary alcohol **16** in 88% yield with a 12:1 epimer ratio in favor of the desired configuration. Finally, demethylation of the phenol by the method of Hoye[29] afforded (+)-hinokiol **15**.

By analogy to previous mechanistic work,[14a,b] the catalytic cycle in Figure 1 is proposed. With assistance of a proton provided by HFIP, sulfenylating agent **1** transfers the arylthio group to catalyst **2** to generate cationic complex ***i***.[30] This highly electrophilic complex reacts with the distal alkene of the polyene substrate **3** to generate an enantiomerically enriched thiiranium ion ***ii*** and regenerate the catalyst **2**. Species ***ii*** is opened diastereospecifically in the cationic cascade process[3] that is terminated by either arene or phenol capture to afford the observed product **4**.

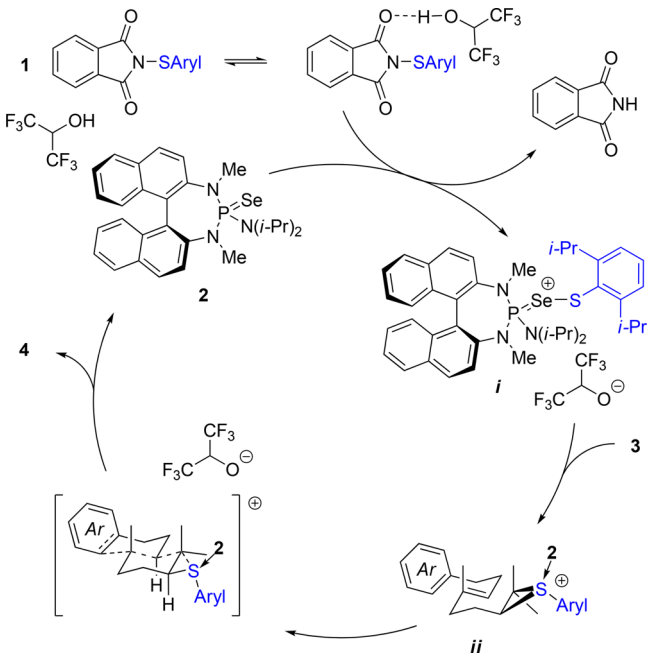

Figure 1. Proposed catalytic cycle.

In summary, an enantioselective Lewis base-catalyzed sulfenocyclization of polyenes has been described. This method is exceptionally mild and affords complex polycyclic products in useful yields and enantiomeric ratios from simple, unmodified substrates. The products may be diversified by a number of productive pathways to replace the thioether moiety with carbon and oxygen functionality. Future directions include the extension of this method to trienes and tetraenes, as well as employing diverse terminating groups beyond arenes and phenols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01660.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Langdon, R. G.; Bloch, K. *J. Am. Chem. Soc.* **1952**, *74*, 1869–1870. (b) Woodward, R. B.; Bloch, K. *J. Am. Chem. Soc.* **1953**, *75*, 2023–2024. (c) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812–2833.

(2) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068–5077.

(3) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011–3050.

(4) (a) Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, *90*, 2994–2996. (b) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1–8.

(5) van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111–120.

(6) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730–4756.

(7) (a) Corey, E. J.; Russey, W. E.; de Montellano, P. R. O. *J. Am. Chem. Soc.* **1966**, *88*, 4750–4751. (b) van Tamelen, E. E.; Willett, J. D.; Clayton, R. B.; Lord, K. E. *J. Am. Chem. Soc.* **1966**, *88*, 4752–4754.

(8) Ungarean, C. N.; Southgate, E. H.; Sarlah, D. *Org. Biomol. Chem.* **2016**, *14*, 5454–5467.

(9) (a) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906–4907. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505–1506. (c) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551–2554. (d) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900–903. (e) Zhao, Y.-J.; Chng, S.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 492–493. (f) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122–11123. (g) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2012**, *134*, 11992–11994. (h) Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 3130–3133. (i) Zhao, Y.-J.; Li, B.; Tan, L.-J. S.; Shen, Z.-L.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 10242–10244.

(10) Samanta, R. C.; Yamamoto, H. *J. Am. Chem. Soc.* **2017**, *139*, 1460–1463.

(11) (a) Cochrane, N. A.; Nguyen, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2013**, *135*, 628–631. (b) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276–8277. (c) Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2012**, *134*, 20276–20278. (d) Snyder, S. A.; Treitler, D. S.; Schall, A. *Tetrahedron* **2010**, *66*, 4796–4804.

(12) (a) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030–5032. (b) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027–5029. (c) Fan, L.; Han, C.; Li, X.; Yao, J.; Wang, Z.; Yao, C.; Chen, W.; Wang, T.; Zhao, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 2115–2119.

(13) *Lewis Base Catalysis in Organic Synthesis*; Vedejs, E., Denmark, S. E., Eds.; Wiley-VCH: Weinheim, 2016.

(14) (a) Denmark, S. E.; Hartmann, E.; Kornfilt, D. J. P.; Wang, H. *Nat. Chem.* **2014**, *6*, 1056–1064. (b) Hartmann, E.; Denmark, S. E. *Helv. Chim. Acta* **2017**, *100*, e1700158. (c) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308–15311. (d) Denmark, S. E.; Kornfilt, D. J. P. *J. Org. Chem.* **2017**, *82*, 3192–3222. (e) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*,

DOI: 10.1021/jacs.8b01660
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

8915−8918. (f) Denmark, S. E.; Chi, H. M. *J. Org. Chem.* **2017**, *82*, 3826−3843. (g) Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc.* **2013**, *135*, 6419−6422. (h) Denmark, S. E.; Jaunet, A. *J. Org. Chem.* **2014**, *79*, 140−171.

(15) For racemic sulfenocyclizations of polyenes, see: (a) Edstrom, E. D.; Livinghouse, T. *J. Org. Chem.* **1987**, *52*, 949−951. (b) Moore, J. T.; Soldi, C.; Fettinger, J. C.; Shaw, J. T. *Chem. Sci.* **2013**, *4*, 292−296. (c) Schevenels, F. T.; Shen, M.; Snyder, S. A. *Org. Lett.* **2017**, *19*, 2−5.

(16) (a) Zhao, Y.; Moore, J. S. *Foldamers*; Wiley-VCH: Weinheim, 2007; Chapter 3. (b) While this manuscript was under review, Gulder et al. reported the use of HFIP for haliranium induced polyene cyclizations. Arnold, A. M.; Pöthig, A.; Drees, M.; Gulder, T. *J. Am. Chem. Soc.* **2018**, DOI: 10.1021/jacs.8b00113.

(17) See Supporting Information for the synthesis of the precursors.

(18) The absolute configuration of the cyclization products was assigned on the basis of the previously established enantiofacial selectivity for catalyst **2** (ref 14). This assignment was confirmed by the conversion of (+)-**4e** to (+)-ferruginol of known absolute configuration (see Supporting Information).

(19) Ravikumar, K. S.; Bégué, J.-P.; Bonnet-Delpon, D. *Tetrahedron Lett.* **1998**, *39*, 3141−3144.

(20) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887−4902.

(21) Saint-Dizier, F.; Simpkins, N. S. *Chem. Sci.* **2017**, *8*, 3384−3389.

(22) Sato, T.; Okazaki, H.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1988**, *110*, 5209−5211.

(23) De Lima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, *1992*, 133−134.

(24) Cohen, T.; Matz, J. R. *Synth. Commun.* **1980**, *10*, 311−317.

(25) Isolation of **14**: (a) Brandt, C. W.; Neubauer, L. G. *J. Chem. Soc.* **1939**, 1031−1037. Isolation of **15**: (b) Yoshiki, Y.; Ishiguro, T. *Yakugaku Zasshi* **1933**, *53*, 73.

(26) Tada, M.; Nishiiri, S.; Zhixiang, Y.; Imai, Y.; Tajima, S.; Okazaki, N.; Kitano, Y.; Chiba, K. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 2657−2664.

(27) Yamamoto reports an enantioselective formal synthesis of this compound (ref 9b) and Zhao reports a catalytic, enantioselective synthesis of (−)-ferruginol (ref 12c).

(28) Matsumoto, T.; Usui, S.; Kawashima, H.; Mitsuki, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 581−584.

(29) Hoye, T. R.; Humpal, P. E.; Moon, B. *J. Am. Chem. Soc.* **2000**, *122*, 4982−4983.

(30) The exact composition of the counterion in ***i*** and ***ii*** is uncertain. For simplicity, it is represented as $(CF_3)_2CHO^-$.

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