Natural Product Synthesis

Deutsche Ausgabe: DOI: 10.1002/ange.201608040
Internationale Ausgabe: DOI: 10.1002/anie.201608040

Convergent Assembly of the Tetracyclic Meroterpenoid (−)-Cyclosmenospongine by a Non-Biomimetic Polyene Cyclization

*Klaus Speck, Raphael Wildermuth, and Thomas Magauer**

Abstract: *The cationic cyclization of polyenes constitutes a powerful and elegant transformation, which has been utilized by nature's biosynthetic machinery for the construction of complex polycyclic terpenoids. Previous studies by chemists to mimic this cyclization in the laboratory were limited to different modes of activation using biosynthetic-like precursors, which accommodate only simple methyl-derived substituents. Here we describe the development of an unprecedented and highly efficient polyene cyclization of an aryl enol ether containing substrate. The cyclization was shown to proceed in a stepwise manner to generate three rings and three consecutive stereocenters, two of which are tetrasubstituted, in a single flask. The developed transformation is of great synthetic value and has enabled the convergent assembly of the tetracyclic meroterpenoid (−)-cyclosmenospongine.*

Nature utilizes cationic polyene cyclizations as a powerful tool to construct terpenoids of remarkable structural complexity.[1] The carbon decoration of these natural products originates from the individual alkyl substituents along the acyclic polyene precursors and varies depending on the degree of post-modifications. The underlying enzymatic processes have been extensively studied during the last decades[2,3] and the development of methods to mimic these steps in the chemical laboratory have also received great attention.[3] Owing to the substitution pattern of most terpenoids, cyclization precursors with methyl-substituted olefins represent the majority of investigated substrates thus far (Figure 1 a). To the best of our knowledge, precursors that contain more complex substituents or heteroatoms at the central olefin unit have been unexplored (Figure 1 b). We envisaged the investigation of such substrates as part of our program to develop highly convergent and efficient synthetic approaches to polycyclic terpenoids.[4] Herein we describe the first realization of a non-biomimetic cationic polyene cyclization and its application to the convergent assembly of the marine natural product (−)-cyclosmenospongine (**1**),[5] whose tetracyclic carbon framework is conserved among a whole family of meroterpenoids with remarkable biological activities.[6,7] Our studies revealed that subtle modifications within the acyclic precursor proved to be crucial for the successful cyclization, which generates three rings and sets three stereocenters in a single transformation.

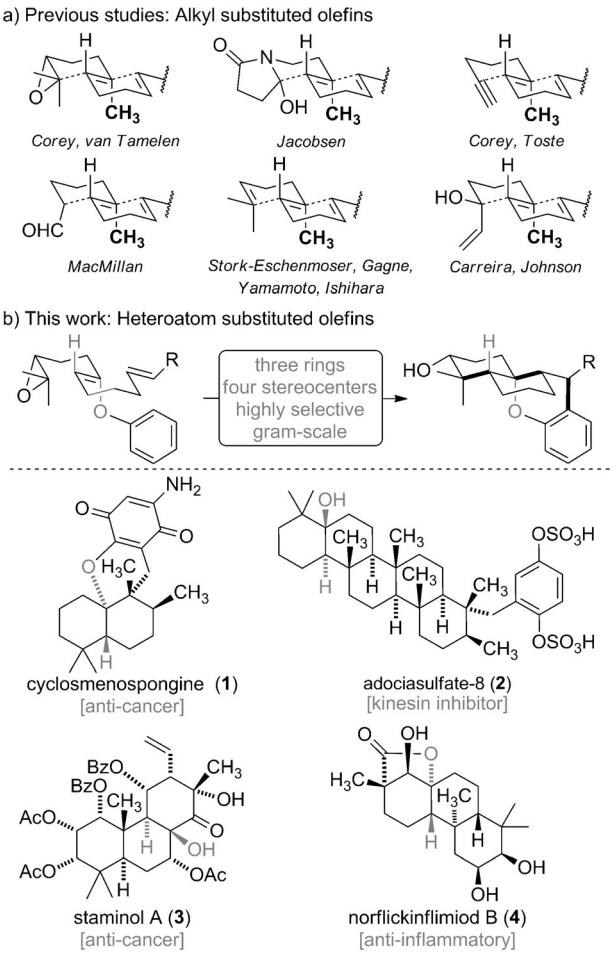
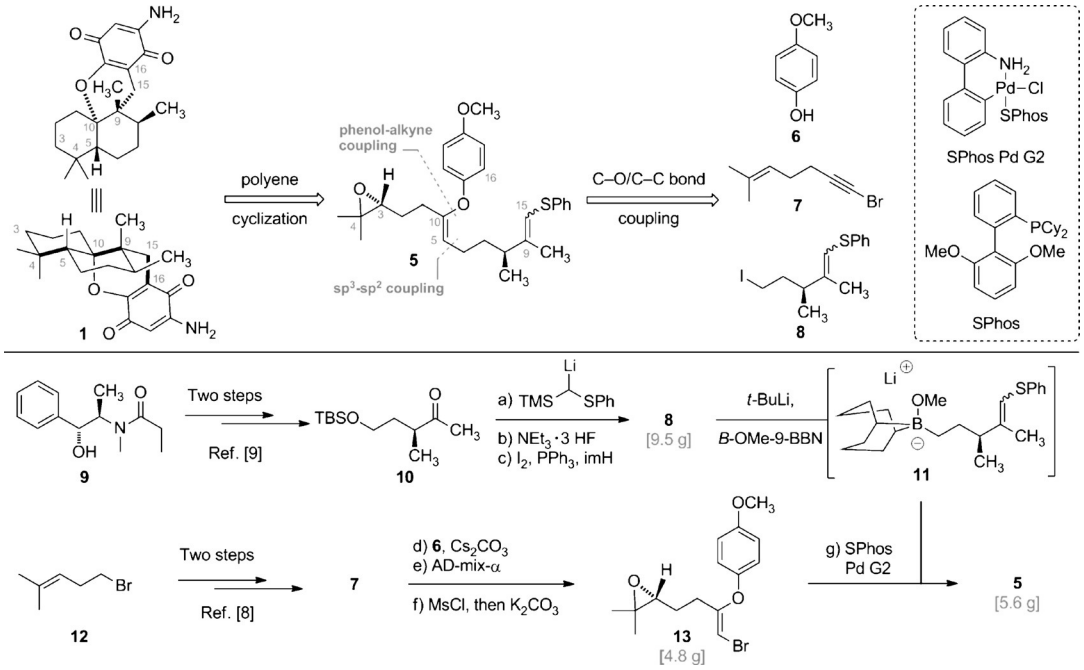


Figure 1. a) Chemists have developed various methods to mimic nature's stereospecific cationic polyene cyclization to assemble complex polycyclic terpenoids. b) The cyclization of aryl enol ether containing substrates has been unexplored and would enable rapid access to hydroxylated decalin subunits of polycyclic terpenoids.

For the realization of this concept, we first analyzed the structure of **1** from several three-dimensional perspectives and thereby identified the retrosynthetic bond disconnections as depicted in Scheme 1. This operation revealed the highly simplified cyclization precursor **5**, itself derived from the convergent component coupling of commercially available phenol **6**, known 1-bromoalkyne **7**,[8] and alkyl iodide **8**. The aryl substituent in **5** not only served as the masked *p*-quinone subunit of **1** but also led to increased chemical stability when compared to alkyl enol ethers.

[*] M. Sc. K. Speck, M. Sc. R. Wildermuth, Dr. T. Magauer
Department of Chemistry and Pharmacy
Ludwig Maximilians University Munich
Butenandtstrasse 5–13, 81377 Munich (Germany)
E-mail: thomas.magauer@lmu.de

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201608040.

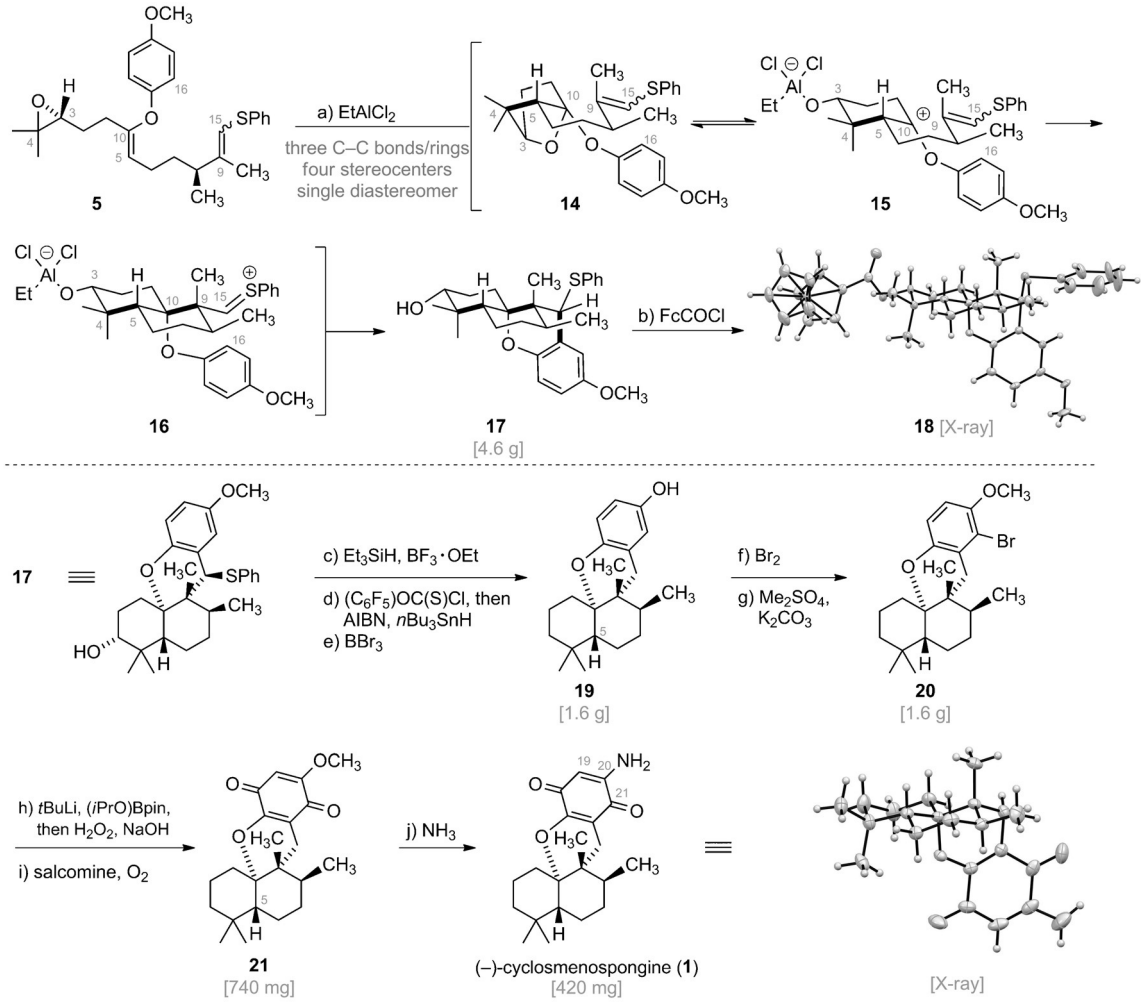


Scheme 1. The non-biomimetic guided retrosynthetic bond disconnection of **1** at C4–C5, C9–C10, and C15–C16 produces enol ether **5**, which can be rapidly assembled by a highly convergent three-component coupling strategy. Reagents and conditions: a) $TMSCH_2SPh$, *n*BuLi, THF, 0 °C to 23 °C, 86 %; b) $NEt_3{\cdot}3\,HF$, CH_3CN, 23 °C, 95 %; c) I_2, PPh_3, imH, CH_2Cl_2, 0 °C, 81 %; d) **6** (10 equiv), Cs_2CO_3, DMF, 70 °C, 56 %; e) AD-mix-α, *t*BuOH, H_2O, 0 °C to 23 °C, 94 %; f) MsCl, NEt_3, CH_2Cl_2, 0 °C to 23 °C, then K_2CO_3, MeOH, 23 °C, 76 %; g) **8**, *t*BuLi, *B*-OMe-9-BBN, THF, −78 °C to 23 °C; SPhos Pd G2 (5 mol %), SPhos (5 mol %), Cs_2CO_3, DMF/H_2O (9:1), 40 °C, 85 %; *B*-OMe-9-BBN = 9-methoxy-9-borabicyclo[3.3.1]nonane, imH = imidazole, MsCl = methanesulfonyl chloride, THF = tetrahydrofuran, TMS = trimethylsilyl.

To overcome the lack of cation stabilization at C15 upon C9–C10 bond formation, we equipped iodide **8** with a thiophenyl ether unit. While the devised synthetic strategy accounts for maximum modularity and allows rapid structural adjustments, we were uncertain at this stage about the impact of the enol ether geometry on the *cis*/*trans*-decalin selectivity.

We commenced our investigations with the synthesis of iodide **8** from the known ketone **10** (Scheme 1).[9] Subjecting a solution of **10** in tetrahydrofuran to trimethyl((phenylthio)methyl)silane and *n*-butyllithium cleanly afforded the thiophenyl ether as a mixture of double-bond isomers (E/Z = 2:3). Since the double-bond geometry was inconsequential for the subsequent steps, cleavage of the silyl ether and iodination was carried out without further separation of the isomers to give iodide **8** in good yield on multigram scale. Initial attempts to establish a gold(I)-catalyzed addition of *p*-methoxyphenol (**6**) to **7** were unsuccessful due to a competing enyne cyclization.[8] We then adopted a recently reported procedure for the base-mediated addition of phenols to 1-bromoalkynes.[10] Extensive experimentation revealed that the reaction proceeded best in *N*,*N*-dimethylformamide (DMF; 1.0 M) at 70 °C, employing excess phenol (10 equiv) and cesium carbonate as base (3 equiv). The intermediate bromo enol ether, which is surprisingly stable to flash-column chromatography on silica gel, was then converted into **13** by dihydroxylation of the sterically less hindered olefin using freshly prepared AD-mix-α [$K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2Phal$, K_2CO_3, $K_3Fe(CN)_6$] and subsequent intramolecular displacement of the secondary alcohol via the corresponding mesylate. Since low yields were encountered in a Negishi cross-coupling reaction between iodide **8** and enol ether **13**, we considered the *B*-alkyl Suzuki–Miyaura coupling reaction[11] as a viable alternative. Under the optimized reaction conditions (5 mol % SPhos Pd G2, 5 mol % SPhos, Cs_2CO_3, THF, DMF, H_2O, 40 °C), coupling of **11** with **13** proceeded efficiently to afford the cyclization precursor **5** in excellent yield (85 %, 5.6 g). Extensive screening revealed that the choice of Buchwald's SPhos ligand[12] in synergism with cesium carbonate was crucial for high conversion and also essential for avoiding β-hydride elimination from the intermediate palladium(II) species. It is noteworthy that an intramolecular coupling process to give the corresponding benzofuran product was not observed in any of these experiments.[10]

With large quantities of **5** in hand, we focused our attention on the crucial polyene cyclization as illustrated in Scheme 2. To our delight, addition of ethylaluminum dichloride ($EtAlCl_2$) to a solution of **5** in dichloromethane at −78 °C resulted in rapid consumption of the starting material and immediate formation of two new products as judged by thin-layer chromatography. After 30 minutes at −78 °C, we observed complete disappearance of the less polar intermediate and accumulation of the lower component as a single product. Isolation of this compound and extensive two-dimensional NMR spectroscopy supported the structure and stereochemistry as depicted for **17**. Further evidence was



Scheme 2. Realization of a stepwise cationic polyene cyclization that creates three rings and sets four stereocenters in a highly efficient manner on gram scale, and advancement of the tetracycle **17** to the natural meroterpenoid (−)-cyclosmenospongine (**1**). Reagents and conditions: a) $EtAlCl_2$, CH_2Cl_2, −78 °C, 83 %; b) FcCOCl, DMAP, CH_2Cl_2, 23 °C, 70 %; c) Et_3SiH, CH_2Cl_2, BF_3·OEt, 0 °C, 97 %; d) $(C_6F_5)OC(S)Cl$, DMAP, CH_2Cl_2, then AIBN, nBu_3SnH, benzene, 64 %; e) BBr_3, CH_2Cl_2, −78 °C to 23 °C, 85 %; f) Br_2, CH_2Cl_2, −55 °C, 93 %; g) Me_2SO_4, K_2CO_3, acetone, 23 °C, 87 %; h) *t*BuLi, (*i*PrO)Bpin, THF, −78 °C to 0 °C, then H_2O_2, NaOH, 0 °C to 23 °C, 75 %; i) salcomine, O_2, DMF, 23 °C, 77 %; j) NH_3, MeOH, H_2O, pyridine, 23 °C, 60 %. Thermal ellipsoids shown at 50 % probability.[19] AIBN = azobisisobutyronitrile, DMAP = 4-dimethylaminopyridine, Fc = ferrocene, pin = pinacol.

provided after esterification with ferrocenecarboxylic acid chloride (FcCOCl)[13] and subsequent single-crystal X-ray diffraction of **18**.

The cyclization of **5**, which is remarkable in many ways, produces **17** as a single diastereomer. This highly efficient sequence of carbon–carbon bond forming events leads to the formation of three rings and installation of four stereocenters, three of which are part of the final meroterpenoid skeleton. The excellent stereoselectivity in this transformation can be attributed to a highly organized transition state, which is fully controlled by the double-bond geometry of the enol ether and the stereocenters at C3 and C8. In view of our results and seminal work by Corey,[14] we believe that only epoxide activation and carbon–carbon bond formation between C4–C5 to give **14** might proceed via a concerted process (Scheme 2). Acetal **14**, which is short-lived using ethylaluminum dichloride ($EtAlCl_2$), and was initially only observed by thin-layer chromatography, could be isolated in pure form after exposure of **5** to the less reactive diethylaluminum chloride (Et_2AlCl) and hydrolysis of excess Lewis acid at −78 °C. Further cyclization presumably proceeds via a non-concerted, stepwise mechanism and involves the transient species **15** and **16**. Support for this hypothesis also comes from the observation that both thioenol ether double-bond isomers fully equilibrate to give **17** as a single diastereomer. Notably, the presence of the thioenol ether[15] turned out to be critical for successful promotion of the polyene cyclization. Substrates that were lacking this substitution pattern proved to be unreactive, as nucleophilic attack of the remote C9–C15 olefin at C10 would generate an energetically unfavorable primary carbocation at C15, thus suppressing any further productive pathway.

For the final stage of the synthesis, we had to develop a sequence that allowed us to remove the traceless conforma-

tional anchor at C3 and liberate the benzylic position at C15. Desulfurization of **17** using Raney nickel proved to be sluggish in many cases and gave moderate yields (63%) in large-scale experiments. Gratifyingly, we found that removal of the thiophenyl substituent could be accomplished in excellent yield upon exposure of **17** to triethylsilane in the presence of boron trifluoride diethyerate (97%, 3.3 g; Scheme 2). Subsequent Barton deoxygenation[1b] of the secondary alcohol and methyl ether cleavage (BBr_3, −78 °C) afforded 5-*epi*-aureol (**19**; 1.6 g), which has yet to be isolated from natural sources.[7e,16] Although efforts to isomerize the *trans*-decalin to the *cis*-form were unsuccessful at this stage, we were able to convert **19** into (−)-cyclosmenospongine (**1**) via sequential functionalization and oxidation of the arene portion.

For this purpose, **19** was first selectively brominated and methylated to give **20** (1.6 g). Exchange of the bromine substituent for a hydroxy group could be best achieved by formation of the boronic ester (*t*BuLi, (*i*PrO)Bpin) followed by oxidation (H_2O_2, NaOH). Treating a solution of the phenol in *N*,*N*-dimethylformamide with salcomine under an atmosphere of oxygen[17] led to selective *p*-quinone formation to give 5-*epi*-smenoqualone (**21**; 740 mg), whose spectroscopic data were in full agreement with those reported previously.[7e,18] From there, (−)-cyclosmenospongine **1** (420 mg) was obtained as a dark-red solid after aminolysis (NH_3, MeOH, 23 °C)[5] and column chromatography on silica gel. Crystallization from diethyl ether yielded crystals suitable for single-crystal X-ray diffraction and allowed us to unambiguously validate the proposed structure of **1**. However, we were surprised to observe that the ^1H and ^{13}C NMR data ($CDCl_3$) showed major inconsistencies ($\Delta = 1.0$–4.7 ppm) when compared to the values reported for the isolated natural product.[5] To rationalize the exact origin of this discrepancy, we conducted a series of NMR experiments. While concentration effects could be excluded, successive addition of hydrogen chloride led to immediate formation of a deep-purple solution and significant shifts of the key NMR signals, in particular the C17 to C21 region of the aminoquinone subunit of **1**. The so-obtained ^1H and ^{13}C NMR data were now in better agreement ($\Delta \leq 2.5$ ppm) with those reported in the literature.[5] Interestingly, formation of the hydrogen chloride adducts was reversible as concentration and re-measurement in acid-free chloroform gave the same spectra as before (see the Supporting Information for NMR studies and details).

In summary, we developed a powerful and operationally simple cationic polyene cyclization for the convergent assembly of tetracyclic terpenoids. This work, which enables rapid access to the cyclization precursor via a modular three-fragment coupling strategy, has enabled the total synthesis of the unique meroterpenoid (−)-cyclosmenospongine (**1**). The highlights of this synthesis are a base-mediated phenol–alkyne addition to give a bromoenol ether, a highly efficient $C(sp^2)$–$C(sp^3)$ Suzuki coupling to provide the trisubstituted aryl enol ether and an unprecedented polyene cascade cyclization to forge the crucial benzo[*d*]xanthene skeleton. In the key step, four adjacent stereocenters, two of which are tetrasubstituted, are generated in a highly diastereoselective manner. We hope to stimulate further research in the area of cationic polyene cyclizations and thereby further enhancing the power of organic synthesis. An application of this strategy to other polycylic terpenoids, investigations aimed at the influence of the enol ether geometry on the *cis*/*trans*-decalin selectivity, and detailed biological studies of **1** are currently underway.

Acknowledgments

We gratefully acknowledge financial support from the Funds of the Chemical Industry (Sachkostenzuschuss and Dozentenpreis to T.M., Doktorandenstipendium to K.S.) and the German Research Foundation (DFG Emmy Noether Fellowship to T.M. and SFB TRR 152). We thank Dr. Peter Mayer (LMU Munich) for X-ray crystal structure determination, Prof. Lothar Brecker (University of Vienna), Prof. Scott Denmark (University of Illinois at Urbana-Champaign), Dr. David Barber (Bayer AG), and Cedric L. Hugelshofer (LMU Munich) for helpful discussions.

Keywords: cations · cyclization · natural products · total synthesis · terpenoids

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 14131–14135
Angew. Chem. **2016**, *128*, 14337–14341

[1] a) K. U. Wendt, G. E. Schulz, E. J. Corey, D. R. Liu, *Angew. Chem. Int. Ed.* **2000**, *39*, 2812–2833; *Angew. Chem.* **2000**, *112*, 2930–2952; b) M. Baunach, J. Franke, C. Hertweck, *Angew. Chem. Int. Ed.* **2015**, *54*, 2604–2626; *Angew. Chem.* **2015**, *127*, 2640–2664; c) E. Oldfield, F.-Y. Lin, *Angew. Chem. Int. Ed.* **2012**, *51*, 1124–1137; *Angew. Chem.* **2012**, *124*, 1150–1163; d) S. Lodeiro, Q.-B. Xiong, W. K. Wilson, M. D. Kolesnikova, C. S. Onak, S. P. T. Matsuda, *J. Am. Chem. Soc.* **2007**, *129*, 11213–11222; e) D. W. Christianson, *Chem. Rev.* **2006**, *106*, 3412–3442; f) D. E. Cane, *Chem. Rev.* **1990**, *90*, 1089–1103.

[2] For an overview, see: a) K. Ishihara in *From Biosynthesis to Total Synthesis*, Wiley, Hoboken, **2016**, pp. 296–330; b) R. A. Yoder, J. N. Johnston, *Chem. Rev.* **2005**, *105*, 4730–4756; c) W. S. Johnson, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 9–17; *Angew. Chem.* **1976**, *88*, 33–41.

[3] For recent examples, see: a) O. F. Jeker, A. G. Kravina, E. M. Carreira, *Angew. Chem. Int. Ed.* **2013**, *52*, 12166–12169; *Angew. Chem.* **2013**, *125*, 12388–12391; b) Y. Tian, X. Xu, L. Zhang, J. Qu, *Org. Lett.* **2016**, *18*, 268–271; c) G. Rajendar, E. J. Corey, *J. Am. Chem. Soc.* **2015**, *137*, 5837–5844; d) S. V. Pronin, R. A. Shenvi, *Nat. Chem.* **2012**, *4*, 915–920; e) Q. Zhang, K. Tiefenbacher, *Nat. Chem.* **2015**, *7*, 197–202; f) M. J. Geier, M. R. Gagné, *J. Am. Chem. Soc.* **2014**, *136*, 3032–3035; g) Z. Yang, H. Li, L. Zhang, M.-T. Zhang, J.-O. Cheng, S. Luo, *Chem. Eur. J.* **2015**, *21*, 14723–14727; h) M. A. Schafroth, D. Sarlah, S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2012**, *134*, 20276–20278; i) S. Rendler, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 5027–5029; j) S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8276–8277; k) K. Surendra, E. J. Corey, *J. Am. Chem. Soc.* **2012**, *134*, 11992–11994; l) R. R. Knowles, S. Li, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 5030–5032.

[4] a) R. Wildermuth, K. Speck, T. Magauer, *Synthesis* **2016**, 1814–1824; b) C. L. Hugelshofer, T. Magauer, *J. Am. Chem. Soc.* **2016**, *138*, 6420–6423; c) C. L. Hugelshofer, T. Magauer, *J. Am. Chem. Soc.* **2015**, *137*, 3807–3810.

[5] a) N. K. Utkina, V. A. Denisenko, O. V. Scholokova, M. V. Virovaya, N. G. Prokof'eva, *Tetrahedron Lett.* **2003**, *44*, 101 – 102; b) N. K. Utkina, V. A. Denisenko, O. V. Scholokova, A. E. Makarchenko, *J. Nat. Prod.* **2003**, *66*, 1263 – 1265.
[6] a) N. G. Prokof'eva, N. K. Utkina, E. L. Chaikina, A. E. Makarchenko, *Comp. Biochem. Physiol. Part B* **2004**, *139*, 169 – 173; b) K. Minagawa, S. Kouzuki, J. Yoshimoto, Y. Kawamura, H. Tani, T. Iwata, Y. Terui, H. Nakai, S. Yagi, N. Hattori, T. Fujiwara, T. Kamigauchi, *J. Antibiot.* **2002**, *55*, 155 – 164; c) A. E. Wright, S. A. Rueth, S. S. Cross, *J. Nat. Prod.* **1991**, *54*, 1108 – 1111; d) H. Prawat, C. Mahidol, W. Kaweetripob, S. Wittayalai, S. Ruchirawat, *Tetrahedron* **2012**, *68*, 6881 – 6886.
[7] For recent syntheses of related members, see: a) K. K. W. Kuan, H. P. Pepper, W. M. Bloch, J. H. George, *Org. Lett.* **2012**, *14*, 4710 – 4713; b) A. Rosales, J. Muñoz-Bascón, E. Roldan-Molina, N. Rivas-Bascón, N. M. Padial, R. Rodríguez-Maecker, I. Rodríguez-García, J. E. Oltra, *J. Org. Chem.* **2015**, *80*, 1866 – 1870; c) K. Watanabe, J. Sakurai, H. Abe, T. Katoh, *Chem. Commun.* **2010**, *46*, 4055 – 4057; d) J. Sakurai, T. Kikuchi, O. Takahashi, K. Watanabe, T. Katoh, *Eur. J. Org. Chem.* **2011**, 2948 – 2957; e) T. Taishi, S. Takechi, S. Mori, *Tetrahedron Lett.* **1998**, *39*, 4347 – 4350; f) I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Díez, J. G. Urones, *Tetrahedron* **2010**, *66*, 8280 – 8290; g) M. Gordaliza, *Mar. Drugs* **2012**, *10*, 358 – 402.
[8] K. Speck, K. Karaghiosoff, T. Magauer, *Org. Lett.* **2015**, *17*, 1982 – 1985.
[9] A. G. Myers, L. McKinstry, *J. Org. Chem.* **1996**, *61*, 2428 – 2440.
[10] S. Wang, P. Li, L. Yu, L. Wang, *Org. Lett.* **2011**, *13*, 5968 – 5971.
[11] a) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544 – 4568; *Angew. Chem.* **2001**, *113*, 4676 – 4701; b) A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412 – 443.
[12] a) N. C. Bruno, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916 – 920; b) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685 – 4696.
[13] C. Bucher, R. M. Deans, N. Z. Burns, *J. Am. Chem. Soc.* **2015**, *137*, 12784 – 12787.
[14] E. J. Corey, D. D. Staas, *J. Am. Chem. Soc.* **1998**, *120*, 3526 – 3527.
[15] For related thioenol ether cyclizations, see: a) T. A. Blumenkopf, M. Bratz, A. Castañeda, G. C. Look, L. E. Overman, D. Rodriguez, A. S. Thompson, *J. Am. Chem. Soc.* **1990**, *112*, 4386 – 4399; b) H. Kusama, R. Hara, S. Kawahara, T. Nishimori, H. Kashima, N. Nakamura, K. Morihira, I. Kuwaijima, *J. Am. Chem. Soc.* **2000**, *122*, 3811 – 3820; c) P. K. Sasmal, M. E. Maier, *J. Org. Chem.* **2003**, *68*, 824 – 831; d) P. K. Sasmal, M. E. Maier, *Org. Lett.* **2002**, *4*, 1271 – 1274.
[16] V. Lakshmi, S. P. Gunasekera, F. J. Schmitz, X. Ji, D. van der Helm, *J. Org. Chem.* **1990**, *55*, 4709 – 4711.
[17] M. Nakamura, A. Suzuki, M. Nakatani, T. Fuchikami, M. Inoue, T. Katoh, *Tetrahedron Lett.* **2002**, *43*, 6929 – 6932.
[18] R. J. Capon, *J. Nat. Prod.* **1990**, *53*, 753 – 756.
[19] CCDC 1499443 (**18**) and 1499442 (**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: August 17, 2016
Published online: October 12, 2016

