OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

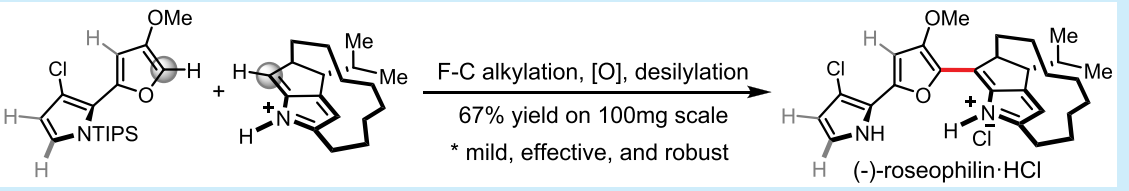
pubs.acs.org/OrgLett

Mild Friedel−Crafts Reactions Enable a Robust Synthesis of Roseophilin

Xiao Zhang, Cuifang Zhang, Xiaobin Wang, and Guangxin Liang*

State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China

Supporting Information



ABSTRACT: An 11-step total synthesis of either enantiomer of roseophilin has been developed. The chemistry features effective production of a challenging carbocation on a macrocyclic segment **25** and a highly efficient intermolecular Friedel−Crafts alkylation reaction to integrate a complex furan-pyrrole unit **5** regioselectively with this carbocation under very mild reaction conditions.

(−)-Roseophilin (**1**, Figure 1) is the enantiomer of the naturally occurring (+)-roseophilin (**2**, Figure 1), a structurally unique metabolite identified from the culture broth of a member of actinomycete *Streptomyces griseoviridis*.[1] Roseophilin is believed to be biosynthesized partially through the same pathway as the prodigiosin family of alkaloids.[2] Given that the related prodigiosin alkaloids have demonstrated a range of appealing bioactivities such as antitumor,[1] antibiotic,[3a] antibacterial,[3b] antimalarial,[3c] and immunosuppressive activities,[3d] roseophilin has been enthusiastically studied for biological functions since its isolation in 1992. Fascinatingly, a very rare bioactivity feature of roseophilin was observed in the previous assays: the non-natural enantiomer **1** exhibits higher biological activities than its naturally occurring antipode **2** in multiple independent assays in both cytotoxicity and phosphatase inhibition studies.[4,5]

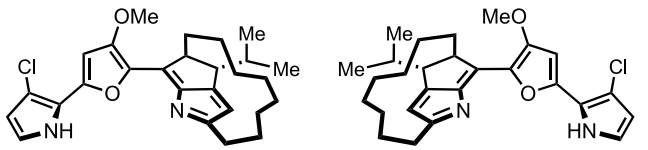


Figure 1. (−)-Roseophilin and its naturally occurring antipode.

In 2001, Boger and Hong first disclosed that the unnatural enantiomer **1** was approximately 2- to 10-fold more potent than its naturally occurring antipode in a range of cytotoxic assays.[4] Later that year, Fürstner and co-workers reinforced this finding in their study searching for new protein tyrosine phosphatase inhibitors based on roseophilin: while naturally occurring **2** proved to be an inhibitor of phosphatases, **1** was 5- to 6-fold more potent in inhibition of PTP1B as well as VHR and was identified as a new class of protein tyrosine phosphatase inhibitors.[5]

Considering aberrant protein phosphorylation is responsible for development of many human diseases such as cancer and diabetes and the scarcity of specific protein phosphatase inhibitors, **1** could serve as a promising scaffold for further development of potent and selective agents for chemical biology and medicinal research.[5] It is noteworthy that the mechanism of cytotoxicity observed on both enantiomers of roseophilin is largely different from prodigiosin and its derivatives.[5] Unlike prodigiosins, roseophilins do not cleave DNA in the presence of Cu^{II} and O_2.[5] In addition, inhibition of phosphatase by **1** is speculated to be linked to the unknown mechanism of cytotoxicity.[5] Taken together, the appealing biological activities, elusive mode of functions, and the intricate topology render **1** a very attractive and rewarding target for total synthesis.

With the exception of Harran's total synthesis,[6] previous synthetic efforts all focused on the condensation of a furan-pyrrole unit with a keto pyrrole macrocyclic segment to construct the *ansa*-brideged 1-azafulvene core in the natural product (Figure 2).[4,7,8] This seemingly straightforward proposal turned out to be a formidable task. Although model studies worked nicely in simplified systems,[9] the only method that fulfilled the need in real total synthesis was through an organocerium species **3** with *N*-SEM (2-(trimethylsilyl)-ethoxymethyl) protected **4**. This successful solution was originally reported by Fürstner and Weintritt. They found that both the organocerium species **3** and a carefully chosen coupling partner **4** were vital to the success of the condensation. This breakthrough led to the very first total

Received: March 28, 2019

Org. Lett. Downloaded from pubs.acs.org by KEAN UNIV on 04/22/19. For personal use only.

© XXXX American Chemical Society

DOI: 10.1021/acs.orglett.9b01100
Org. Lett. XXXX, XXX, XXX−XXX

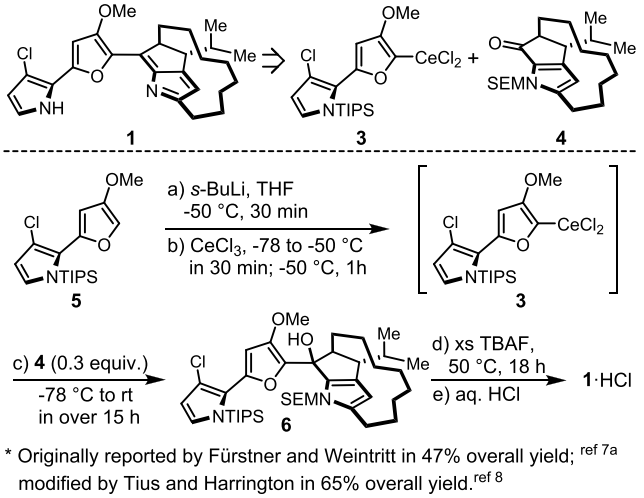


Figure 2. Previous solution to incorporate a furan-pyrrole unit to a pyrrole macrocyclic segment.

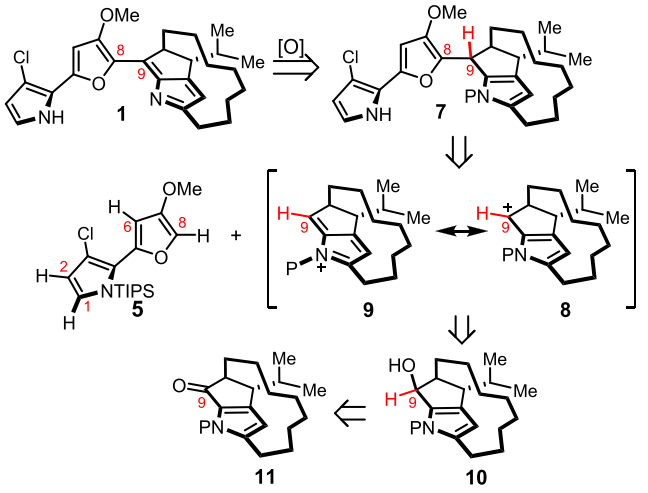


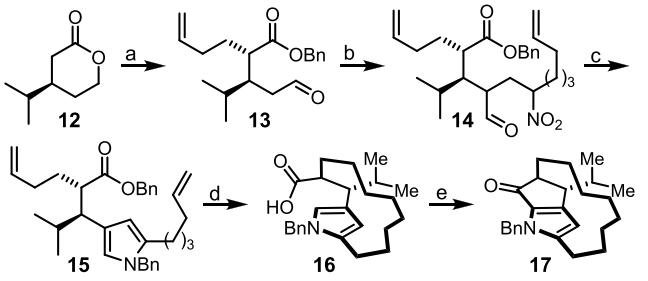
Figure 3. An intermolecular Friedel–Crafts alkylation strategy for coupling of **5** with **10**.

synthesis of (±)-roseophilin.[7a] Later on, in applying the same chemistry in their total synthesis, the Tius group discovered that precise control of reaction temperature and time at each stage was critical to the success of the reaction.[8] Eventually, they contributed a detailed protocol for this delicate key reaction, which helped Boger's synthesis of (−) -roseophilin as well.[4] Tius also commented that even the particle size of $CeCl_3$ could affect the transmetalation step which might be responsible for the capricious results they encountered.[8] The perplexing condensation step might explain why only three total syntheses have been accomplished this way, considering nearly ten other synthetic efforts stopped at advanced macrocyclic intermediates even though they are only two steps away from the ultimate synthetic target,[9] given that the preparation of **5** is well-documented in the literature.[10]

The finicky nature of the reaction urged us to seek a more user-friendly approach to incorporate a furan-pyrrole unit to the pyrrole macrocyclic segment in our synthesis toward roseophilins. We envisioned that a Friedel–Crafts alkylation reaction between a stabilized carbocationic species such as **8**/**9** and a neutral mild nucleophile such as **5** could serve as a good solution (Figure 3). This strategy will capitalize on the inherent nucleophilicity at C8 in the furan[11] so as to avoid the requirement for regioselective prefunctionalization of the nucleophile. Furthermore, such a solution could facilitate easy preparation of roseophilin analogues bearing diverse electron-rich species in the place of the original furan-pyrrole unit. The desired carbocation **8** was expected to be formed readily through activation of the hydroxyl group in **10** due to the stabilization effect provided by the pyrrole in the resonance form **9**. It was encouraging that a compound similar to the Friedel–Crafts product **7** had been successfully oxidized to afford **1** in Harran's synthesis.[6]

Our exploration commenced from a concise preparation of **17** depicted in Scheme 1. An optically pure lactone **12**, readily derived in 2 steps from *R*-carvone,[12] was used as a starting material. Enolate alkylation using homoallylic iodide installed the desired carbon chain with complete stereochemical control in 65% yield. Subsequent saponification of the intermediate lactone followed by formation of the benzyl ester and Swern oxidation afforded **13** in 80% overall yield. Michael addition of **13** to 2-nitroocta-1,7-diene catalyzed by D-proline cleanly

Scheme 1. Convenient Preparation of 17[a]



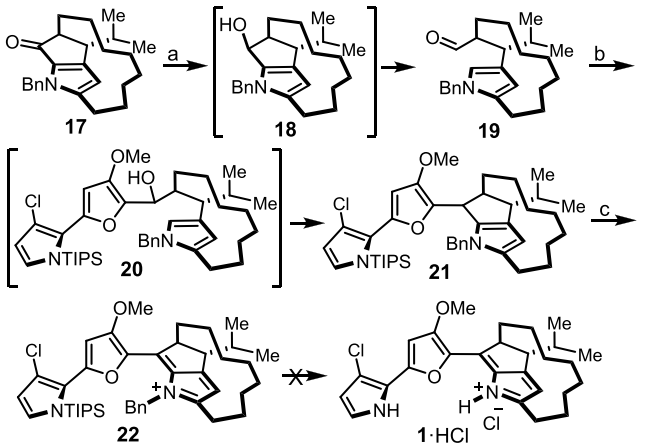
[a]Reagents and conditions: (a) (1) LiHMDS, THF, −78 °C, then 4-iodobut-1-ene (65%); (2) NaOH, $MeOH/H_2O$; K_2CO_3, acetone, BnBr; DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2 (80% in 3 steps); (b) D-proline, MeOH, NaOAc, 2-nitroocta-1,7-diene (97%); (c) $BnNH_2$, $MgSO_4$, DMSO, rt−110 °C (70%); (d) (1) Grubbs I cat. (20 mol %), $Ti(Oi\text{-}Pr)_4$ (50%); (2) H_2, Pd/C (94%); (e) PPh_3, Cl_3CCN, rt−40 °C (80%); LiHMDS = lithium bis(trimethylsilyl) amide, Bn = benzyl.

produced **14** as a precursor for the formation of pyrrole **15**.[13] Condensation between **14** and benzyl amine at room temperature followed by Grob–Camenisch pyrrole synthesis produced **15** in 70% yield.[14] The one-pot transformation of **14** to **15** takes advantage of the versatile role of the nitro group which serves as both an electrophile upon tautomerization and a leaving group. Catalyzed by Grubbs' first-generation catalyst, ring-closing metathesis (RCM) of **15** produced a macrocyclic alkene,[15] which was subjected to hydrogen and Pd/C to undergo hydrogenation of the alkene as well as removal of a benzyl group to afford carboxylic acid **16**. Upon activation with a combination of PPh_3 and trichloroacetonitrile, **16** underwent an intramolecular Friedel–Crafts acylation reaction to afford **17** in 80% yield.[16] This 9-step sequence from **12** provided optically pure **17** in 13% overall yield, which allowed us to accumulate multiple grams of **17** conveniently.

With **17** in hand, we carried out a reduction of the carbonyl group (Scheme 2). Reduction using $LiAlH_4$ went smoothly as indicated by ^1H NMR analysis on the crude reaction mixture. However, upon purification with silica gel chromatography, **18** was cleanly converted to **19** in 80% yield. Presumably, **18** underwent a retro-Friedel–Crafts reaction even when exposed to slightly acidic silica gel. Given that we planned to activate

DOI: 10.1021/acs.orglett.9b01100
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. A Detour Originated from Unexpected Production of 19[a]



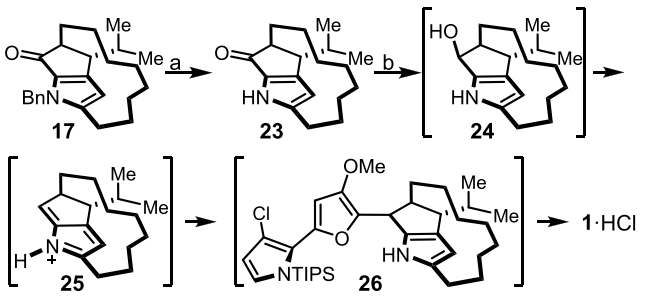
[a]Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, then silica gel (80%); (b) *sec*-BuLi, **5**, THF; then $SnCl_4$, CH_2Cl_2 (55% in 2 steps); (c) DDQ, CH_2Cl_2.

the hydroxyl group in **18** under acidic conditions so as to produce a stable carbocation **8** in our initial proposal, the unexpected acid lability of **18** temporarily prevented us from exploring the original idea at this stage. Instead, we decided to take a detour to investigate an intramolecular Friedel–Crafts reaction to synthesize the target. To this end, we first treated **19** with lithiated **5** to produce substrate **20**. To our delight, **20** is well suited for this strategy and it even partially cyclized to give **21** during purification on silica gel chromatography. Under optimal conditions, when subjected to $SnCl_4$, crude **20** generated **21** as a single diastereomer in 55% yield in 2 steps from **19**. Oxidation of **21** with DDQ seemed to be effective as indicated by the characteristic deep red color of an azafulvene chromophore. However, all efforts to isolate compound **22** failed due to its instability. Speculating that the benzyl group in **22** might be removed through either S_N2 reaction or oxidation, we then attempted to convert **22** directly to roseophilin. Unfortunately, these efforts were fruitless as well. The molecule either stayed intact under mild conditions or decomposed when more forcing conditions were applied.

Given that the benzyl group is hard to remove in **22**, we decided to remove it at an earlier stage (Scheme 3). We found that *t*-BuOK in a mixed solvent of THF and DMSO fulfilled the debenzylation nicely to convert **17** to **23** in 88% yield.[17] $LiAlH_4$ reduction of **23** proceeded uneventfully to give **24**. Compound **24** is still acid labile and also produced the corresponding aldehyde as **18** did when exposed to slightly acidic conditions. Unfortunately, addition of lithiated **5** to the aldehyde derived from **24** failed, which urged us to seek a new solution to accomplish the synthesis. Contemplating on the retro-Friedel–Crafts reaction responsible for the formation of aldehyde, we reasoned that if the pyrrole could be prevented from protonating during activation of the hydroxyl group in **24**, we should be able to suppress the retro-Friedel–Crafts reaction and generate the desired carbocation **25**. Guided by this assumption, we tested $[PPh_3PBr]^+$ for specific activation of the hydroxyl group in **24**.[18] Gratifyingly, this final solution succeeded, awarding us a highly effective union of **5** and **24** under mild conditions. After reduction of **23** with $LiAlH_4$, the crude product **24** and **5** were dissolved in CH_2Cl_2 and slowly added to a premixed solution of Ph_3P, CBr_4 in CH_2Cl_2 at 0 °C. The intermolecular Friedel–Crafts alkylation was completed immediately after the addition. Subsequent oxidation with DDQ, and desilylation with a mixture of hydrofluoric acid and hydrochloric acid, afforded (−)-roseophilin·HCl in 67% overall yield from **23**. The entire reaction sequence proved to be robust, and a reaction on a 100 mg scale showed no loss of efficiency. Both ^1H and ^{13}C NMR data for our synthetic **1**·HCl match those reported for the natural product. The optical rotation of the synthetic sample $[\alpha]_D^{19} = -7650$ (c = 0.01, $CHCl_3$) was of opposite sign to that of natural roseophilin,[4] indicating preparation of unnatural enantiomer **1**. Presumably, the route we have developed for synthesis of **1** is applicable to the synthesis of its natural enantiomer **2** as long as *S*-carvone is used.[19]

To further explore the Friedel–Crafts reaction, we also used unprotected indole and pyrrole as coupling partners. These alternatives effectively provided roseophilin analogues **27** and **28** in 73% and 53% overall yield, respectively (Figure 4).

Scheme 3. Total Synthesis of (−)-Roseophilin·HCl[a]



[a]Reagents and conditions: (a) *t*-BuOK, DMSO/THF, O_2, 0 °C (88%); (b) $LiAlH_4$, THF, rt; **5**, Ph_3P, CBr_4, CH_2Cl_2; DDQ, CH_2Cl_2; HF, HCl, MeOH (67% from **23**).

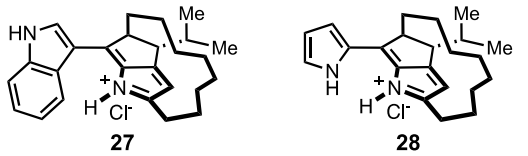


Figure 4. Roseophilin analogues produced through the protocol.

In summary, we have developed a robust total synthesis of either enantiomer of roseophilins from economically friendly carvones. The convenient sequence afforded roseophilin in 100 mg scale in 7.7% overall yield starting from **12**.[20] The chemistry features a 9-step[21] gram-scale preparation of optically pure pyrrole macrocyclic segment **17** and an intermolecular Friedel–Crafts reaction to solve the challenging integration of a furan-pyrrole unit into this segment. Furthermore, the chemistry enabled preparation of two new roseophilin analogues in either enantiomeric form as well.[22] We believe that the chemistry we have developed will help the preparation of more roseophilin analogues as well and expand the chemical biology and medicinal studies on this new family of cytotoxic agents and protein tyrosine phosphatase inhibitors. In addition, the neutral reaction conditions we developed for the Friedel–Crafts reaction might be useful and broadly applicable for acid sensitive substrates in related reactions.

DOI: 10.1021/acs.orglett.9b01100
Org. Lett. XXXX, XXX, XXX–XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01100.

Experimental procedures, spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lianggx@nankai.edu.cn.

ORCID

Guangxin Liang: 0000-0003-3122-0332

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Key Research and Development Program of China (2017YFD0201404) and the National Natural Science Foundation of China (21572104, 21772097) for financial support. We also thank Prof. Hans Renata at Scripps Florida and Prof. Christopher Beaudry at Oregon State University for helping us with the manuscript preparation.

■ REFERENCES

(1) Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.* **1992**, *33*, 2701−2704.

(2) (a) Wasserman, H. H.; Sykes, R. J.; Peverada, P.; Shaw, C. K.; Cushley, R. J.; Lipsky, S. R. *J. Am. Chem. Soc.* **1973**, *95*, 6874−6875. (b) Williamson, N. R.; Fineran, P. C.; Leeper, F. J.; Salmond, G. P. C. *Nat. Rev. Microbiol.* **2006**, *4*, 887−899. (c) Withall, D. M.; Haynes, S. W.; Challis, G. L. *J. Am. Chem. Soc.* **2015**, *137*, 7889−7897. For a review on pyodigininenatual products, see: (d) Hu, D. X.; Withall, D. M.; Challis, G. L.; Thomson, R. J. *Chem. Rev.* **2016**, *116*, 7818−7853.

(3) (a) Boger, D. L.; Patel, M. *Tetrahedron Lett.* **1987**, *28*, 2499−2502. (b) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405−1415. (c) Gerber, N. N. *J. Antibiot.* **1975**, *28*, 194−199. (d) Yamasaki, M.; Tsuji, R. F.; Yamamoto, M.; Nakamura, A.; Kataoka, T.; Magae, J.; Nagai, K. *J. Antibiot.* **1990**, *43*, 1293−1301.

(4) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515−8519.

(5) (a) Fürstner, A.; Grabowski, E. J. *ChemBioChem* **2001**, *2*, 706−709. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582−3603. (c) Fürstner, A.; Reinecke, K.; Prinz, H.; Waldmann, H. *ChemBioChem* **2004**, *5*, 1575−1579. (d) Manger, M.; Scheck, M.; Prinz, H.; Von Kries, J. P.; Langer, T.; Saxena, K.; Schwalbe, H.; Fürstner, A. *ChemBioChem* **2005**, *6*, 1749−1753.

(6) Frederich, J. H.; Harran, P. G. *J. Am. Chem. Soc.* **2013**, *135*, 3788−3791.

(7) (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817−2825. (b) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361−2366.

(8) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509−8514.

(9) (a) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601−2604. (b) Mochizuki, T.; Itoh, E.; Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1998**, *39*, 6911−6914. (c) Robertson, J.; Hatley, R. J. D. *Chem. Commun.* **1999**, *16*, 1455−1456. (d) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801−3810. (e) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157−1160. (f) Robertson, J.; Hatley, R. J. D.; Watkin, D. J. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 3389−3396. (g) Bitar, A. Y.; Frontier, A. J. *Org. Lett.* **2009**, *11*, 49−52. (h) Song, C.; Liu, H.; Hong, M.; Liu, Y.; Jia, F.; Sun, L.; Pan, Z.; Chang, J. *J. Org. Chem.* **2012**, *77*, 704−706. (i) Kerr, D. J.; Flynn, B. L. *Org. Lett.* **2012**, *14*, 1740−1743.

(10) For preparation of furan-pyrrole unit **5**, see: (a) Reference 7a. (b) Frederich, J. H.; Matsui, J. K.; Chang, R. O.; Harran, P. G. *Tetrahedron Lett.* **2013**, *54*, 2645−2647. (c) Kerr, D. J.; Flynn, B. L. *Aust. J. Chem.* **2015**, *68*, 1821−1828. (d) It was prepared on gram scale using a modified approach in 7 steps from commercially available 2-formyl-3-chloropyrrole in our synthesis; see the Supporting information (SI) for details.

(11) Nakatani, S.; Kirihara, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett.* **1995**, *36*, 8461−8464.

(12) Paquette, L. A.; Dahnke, K.; Doyon, J.; He, W.; Wyant, K.; Friedrich, D. *J. Org. Chem.* **1991**, *56*, 6199−6205.

(13) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423−2425.

(14) For seminal studies of the Grob−Camenisch reaction, see: (a) Grob, C. A.; Camenish, K. *Helv. Chim. Acta* **1953**, *36*, 49−58. (b) Grob, C. A.; Schad, H. P. *Helv. Chim. Acta* **1955**, *38*, 1121−1127. (c) Gomez-Sanchez, A.; Mancera, M.; Rosado, F.; Bellanato, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, *1*, 1199−1205. (d) Meyer, H. *Liebigs Ann. Chem.* **1981**, *1981*, 1534−1544. (e) Lim, S.; Jabin, I.; Revial, G. *Tetrahedron Lett.* **1999**, *40*, 4177−4180. (f) Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 866−868. (g) Liermann, J. C.; Opatz, T. *J. Org. Chem.* **2008**, *73*, 4526−4531.

(15) For use of different RCM reactions to synthesize the macrocycles in roseophilins, see refs 8, 9a, 9e, and 9i.

(16) Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323−5326.

(17) Fürstner has reported the debenzylation of **17** in 50% combined yield using calcium in liquid ammonium followed by reoxidation of carbonyl group with PDC; see: (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944−2945. (b) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. *Tetrahedron Lett.* **2002**, *43*, 399−402.

(18) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801−811.

(19) For a recent review on total syntheses using carvone, see: Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. *Chem. Rev.* **2017**, *117*, 11753−11795.

(20) For the importance and examples of scalable synthesis, see: Kuttruff, C. A.; Eastgate, M. D.; Baran, P. S. *Nat. Prod. Rep.* **2014**, *31*, 419−432.

(21) 2-Nitroocta-1,7-diene used in the sequence was prepared from hex-5-enal in 5 steps; please see SI for details.

(22) For a recent example of the benefit in exploring both enantiomers of the natural product for biological functions, see: Logan, M. M.; Toma, T.; Thomas-Tran, R.; Du Bois, J. *Science* **2016**, *354*, 865−869.

DOI: 10.1021/acs.orglett.9b01100
Org. Lett. XXXX, XXX, XXX−XXX