Organic LETTERS

Letter

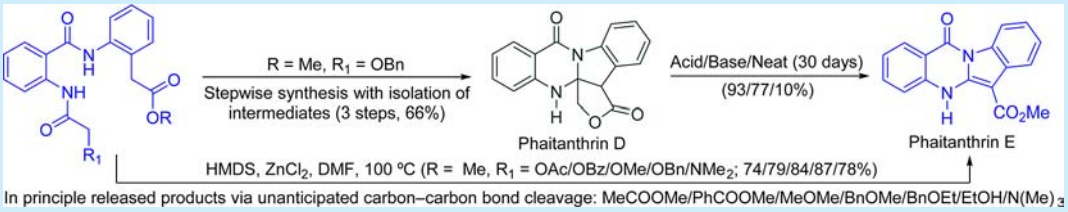
pubs.acs.org/OrgLett

A Biomimetic Synthesis of Phaitanthrin E Involving a Fragmentation of sp^3 Carbon–Carbon Bond: Synthesis and Rearrangement of Phaitanthrin D to Phaitanthrin E

Sagar D. Vaidya and Narshinha P. Argade*

Division of Organic Chemistry, National Chemical Laboratory (CSIR), Pune 411 008, India

Supporting Information



ABSTRACT: A biogenetic type total synthesis of alkaloids phaitanthrin D and phaitanthrin E has been described. The Csp^3–Csp^3 bond cleavage with the release of several heteroatoms bearing unexpected leaving groups in intramolecular substitution reactions on an iminium double bond in the quinazolinones has been demonstrated using HMDS/$ZnCl_2$ or NaHMDS. The mechanistic aspects have been supported by isolation and characterization of appropriate intermediates.

Quinazolinones are an important class of clinically useful compounds and building blocks for a large number of structurally diverse alkaloids with a wide range of promising biological activities.[1] Wu and co-workers isolated five different quinazolinone based cytotoxic natural products phaitanthrins A–E from *Phaius mishmensis* orchid (Figure 1).[2] The

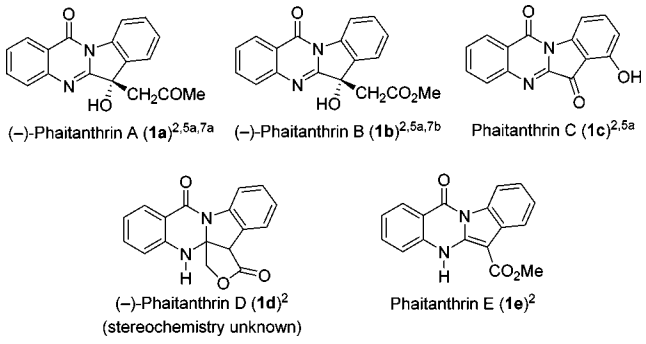
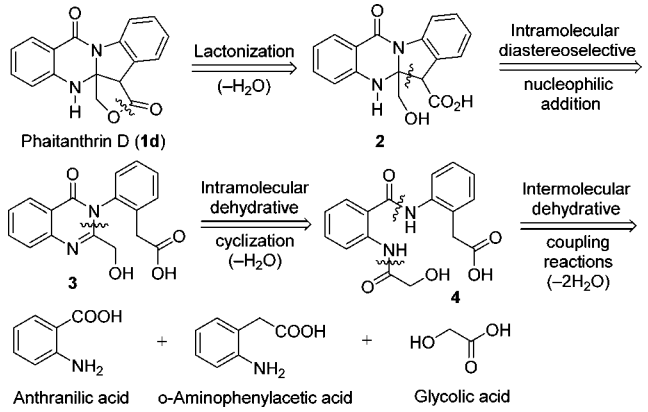


Figure 1. Recently isolated bioactive quinazolinone and dihydroquinazolinone alkaloids.

nucleophilic substitution reactions play a very important role in biogenesis and chemical synthesis.[3] The nucleophilic substitution reactions involving both carbon as a nucleophile and leaving groups are limited, wherein actually the stable nitrile/carbon anions are the departing units.[4] Conversely, the carbon–carbon bond forming substitution reactions with release of unstable carbanions/carbon free radicals/carbenes remain as the most crucial strategic challenge. In continuation of our studies on total synthesis of quinazolinone alkaloids,[5] we achieves substitution of unexpected leaving groups by a stable carbanion in intramolecular reactions on an iminium double bond in quinazolinones via an exceptional Csp^3–Csp^3 bond clevage[6] due to the relatively higher stability of the formed product. In this context, we herein report the investigation results accomplishing first total synthesis of phaitanthrins D and E (Schemes 1–3).

An anticipated retrobiogenetic pathway and the proposed retrosynthetic analysis of unprecedented indolofuroquinazolinone phaitanthrin D (**1d**) has been depicted in Scheme 1. Nature creates the phaitanthrin D (**1d**) starting from anthranilic acid, *o*-aminophenylacetic acid, and glycolic acid via

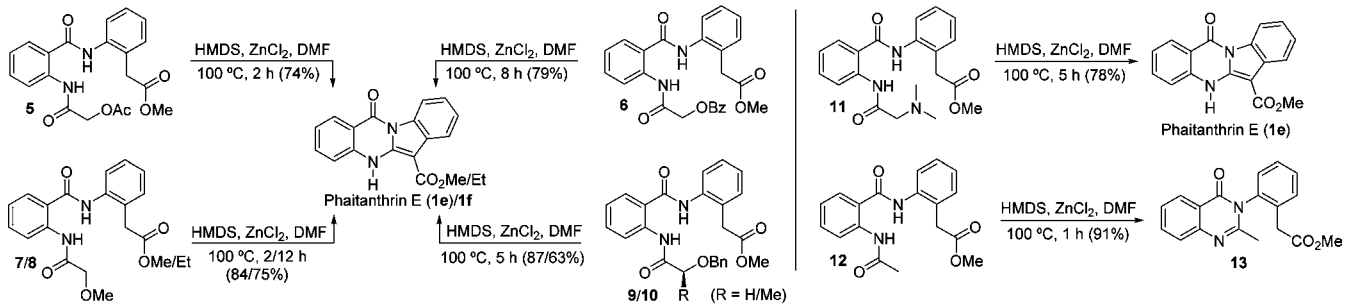
Scheme 1. Proposed Retrobiogenetic Pathway and Retrosynthetic Analysis of Phaitanthrin D



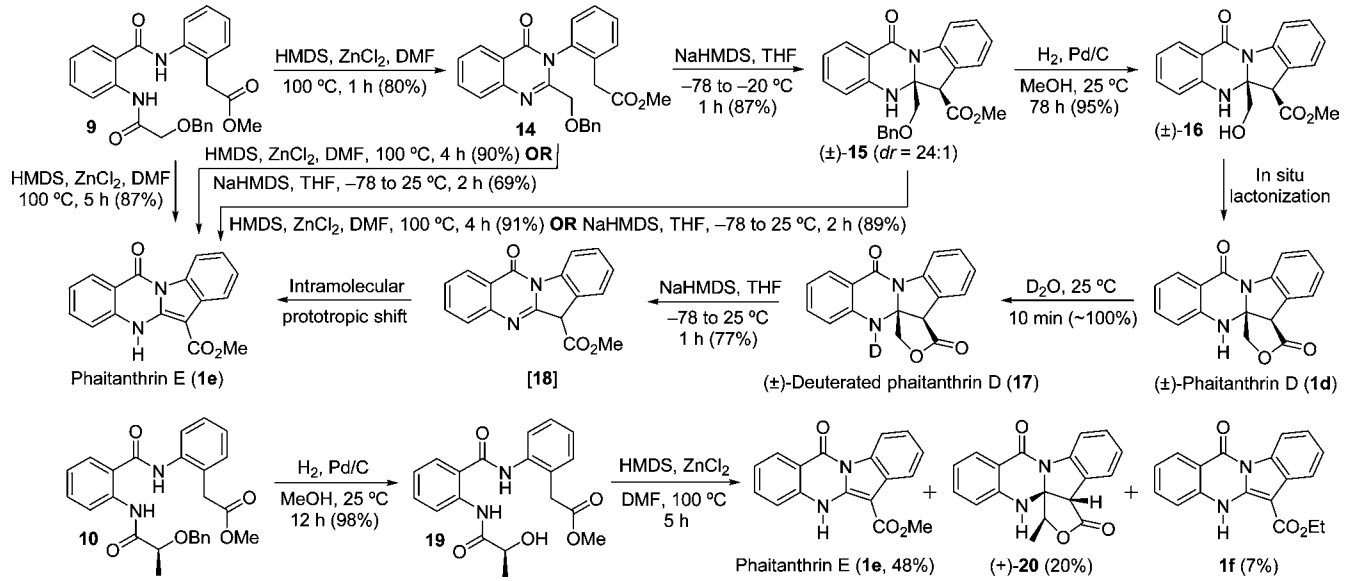
Received: November 6, 2015
Published: December 9, 2015

DOI: 10.1021/acs.orglett.5b03203
Org. Lett. 2015, 17, 6218–6221

Scheme 2. Unexpected Leaving Groups in One Pot Synthesis of Phaitanthrin E and Its Ethyl Analogue



Scheme 3. Diastereoselective Total Synthesis of (±)-Phaitanthrin D and Its Methyl Analogue and Their Structural Rearrangement to Phaitanthrin E and Its Ethyl Analogue



an appropriate sequence of dehydrative coupling reactions and intramolecular cyclization pathways with complete carbon economy involving overall loss of four water molecules. Accordingly the building block **5** was synthesized via appropriate stepwise intermolecular dehydrative coupling reactions. As per the recently developed protocol, compound **5** was subjected for intramolecular dehydrative cyclization using hexamethyldisilazane/zinc chloride (HMDS/$ZnCl_2$) in DMF at 100 °C to obtain the corresponding quinazolinone.[8] A careful examination of the analytical and spectral data of the formed purified product revealed that the above specified reaction has directly delivered a phaitanthrin E (**1e**, 74% yield) (Scheme 2). The present one-pot transformation of compound **5** to phaitanthrin E (**1e**) was unusual from a basic chemistry point of view, and it was suggestive of some interesting chemical transformation taking place. In principle there was an overall loss of water and methyl acetate from the parent system **5** in the formation of phaitanthrin E (**1e**). The reactions of similarly designed compounds **6**–**10** with HMDS/$ZnCl_2$ in DMF at 100 °C again directly furnished the phaitanthrin E (**1e**) and its ethyl ester analogue **1f** in very good yields. Another type of an additional nitrogen atom containing building block, **11**, on reaction with HMDS/$ZnCl_2$ also followed the similar pathway and delivered phaitanthirn E (**1e**) in 78% yield. However, the formally designed building block **12**, without a heteroatom in the departing unit, on reaction with HMDS/$ZnCl_2$ only formed the corresponding quinazolinone **13** in 91% yield.

The search for a suitable precursor which allowed isolation of the intermediate products led to success with benzyl ether **9**. As depicted in Scheme 3, the reaction of compound **9** with HMDS/$ZnCl_2$ in DMF at 100 °C was arrested after 1 h to obtain the anticipated intermediate quinazolinone **14** in 80% yield along with ~2% of phaitanthrin E (**1e**). Compound **14** on treatment with NaHMDS in THF at −78 to −20 °C underwent an intramolecular diastereoselective nucleophilic addition of the formed α-stabilized benzylic carbanion to the proximal iminium double bond in a quinazolinone moiety to deliver yet another intermediate product dihydroquinazolinone **15** in 87% yield (92% *de* by ^{1}H NMR). The quinazolinone **14** and dihydroquinazolinone **15** on reaction with either HMDS/$ZnCl_2$ in DMF at 100 °C or NaHMDS in THF at −78 to 25 °C again furnished the target product phaitanthrin E (**1e**) in very good yields. The deprotection of the benzyl group in dihydroquinazolinone **15** produced alcohol **16**, which on concomitant lactonization provided the expected (±)-phaitanthrin D (**1d**) in 95% yield in 78 h. The alcohol **16** was unstable; however its immediate characterization by ^{1}H NMR was feasible. The phaitanthrin D (**1d**) on treatment with 2 N HCl in chloroform at 25 °C underwent structural rearrangement to phaitanthrin E (**1e**) in 93% yield via an unusual carbon−carbon bond cleavage. Phaitanthrin D (**1d**) on treatment with D_2O

DOI: 10.1021/acs.orglett.5b03203
Org. Lett. 2015, 17, 6218−6221

formed the *N*-deuterated phaitanthrin D (**17**) in quantitative yield (by ^{1}H NMR). The compound **17** on reaction with NaHMDS transformed to phaitanthrin E (**1e**) in 77% yield with complete loss of the label proving that the deuterium atom on nitrogen is relatively more acidic than the active methine proton. Accordingly in the transformation of phaitanthrin D to phaitanthrin E, the methyl group originates from the methylene unit in a lactone moiety. The specifically designed compound **10** on debenzylation provided requisite alcohol **19** in quantitative yield. As expected the compound **19** on treatment with HMDS/$ZnCl_2$ delivered the mixture of phaitanthrin E (**1e**, 48%), in situ formed lactone **20** (20%, 98% *de* by ^{1}H NMR), and the rearranged product **1f** (7%). The in situ formed carbanion approached the iminium double bond from the expected less hindered α-side to form product **20**. The purified lactone **20** on treatment with HMDS/$ZnCl_2$ was slowly transformed into the rearranged product **1f** in good yield. The transformations of **1d** to **1e** and **20** to **1f** provide compelling evidence for the proposed carbon−carbon bond cleavage and affirm that phaitanthrin D (**1d**) is the biogenetic precursor of phaitanthrin E (**1e**).

In principle the one-pot formation of phaitanthrin E can take place via a host of alternative reaction pathways, namely: (i) redox, (ii) carbenoid, (iii) radical, (iv) unstabilized carbanions serving as a leaving group, and (v) alternative internal structural rearrangement accounting for carbon−carbon bond cleavage. The consistent formation of phaitanthrin E (**1e**) and analogues at both 100 and −78 °C in the absence of metal and/or molecular oxygen in very good yields ruled out the possibility of a redox mechanism. All attempts to isolate primary and/or secondary products derived from the released carbon species in the above specified reactions met with failure. The slow transformation of phaitanthrin D (**1d**) in its solid form to phaitanthrin E (**1e**) was noticed and confirmed by ^{1}H NMR (∼10% in four week time). This important observation substantiated that it would be possible to isolate the formed product from the corresponding released species under neutral conditions. Accordingly scanned ^{1}H and ^{13}C NMR spectra of preserved compound **15** for 10 days indicated its complete transformation into phaitanthrin E (**1e**) along with the appropriate presence of all requisite signals for the expected released benzyl methyl ether. The presence of released benzyl methyl ether was further confirmed by HPLC and HRMS data. Finally a small amount of benzyl methyl ether released in the transformation of compound **15** to phaitanthrin E (**1e**) was isolated by using preparative thin layer chromatography and confirmed by comparison with authentic sample using analytical and spectral data. The isolation of benzyl methyl ether rules out the carbenoid mechanistic pathways. The reactions reported in Schemes 2 and 3 clearly indicate that in the last step they follow a radical pathway releasing the corresponding reactive radical species such as $^{\bullet}CH_2OCOCH_3$, $^{\bullet}CH_2OCOPh$, $^{\bullet}CH_2OCH_3$, $^{\bullet}CH_2OCH_2Ph$, $^{\bullet}CH(Me)OCH_2Ph$, $^{\bullet}CH(Me)OH$, and $^{\bullet}CH_2N(CH_3)_2$. Such type of radical formation on quinazolinone nucleus is known utilizing copper catalysis in the presence of oxygen.[4a] In the specifically formed/designed quinazolinones the Csp^3−Csp^3 bond appears to be quite delicate and undergoes aromaticity-driven facile homolytic fission leading to the corresponding radicals. However, an alternative ionic pathway releasing the corresponding high energy carbanionic species such as $^{-}CH_2OCOCH_3$, $^{-}CH_2OCOPh$, $^{-}CH_2OCH_3$, $^{-}CH_2OCH_2Ph$, $^{-}CH(Me)OCH_2Ph$, $^{-}CH(Me)OH$, and $^{-}CH_2N(CH_3)_2$ appears almost impossible. Accordingly compound **13** on further treatment with NaHMDS in THF remained completely unreacted and did not deliver phaitanthrin E (**1e**). This proved that the presence of an adjacent heteroatom on all methanide leaving groups was essential for natural Csp^3−Csp^3 bond cleavage. The observation that CH_2O leaves well, CH_2N leaves slowly, and CH_3 does not leave at all suggests that the oxygen better stabilizes an adjacent radical thermodynamically and, more important, kinetically. Finally to conclude, all the above-mentioned novel reactions became feasible due to the formation of very stable quasi-aromatic products with an overall negative Gibbs free energy.

In summary, one-pot synthesis of phaitanthrin E has been demonstrated from different types of starting materials in very good yields with the release of unexpected carbon species. To the best of our knowledge, this is a unique example of spontaneous sp^3 carbon−carbon bond cleavage in the absence of a metal catalyst and molecular oxygen. A diastereoselective biogenetic type total synthesis of phaitanthrin D with very good overall yield and stereoselectivity has also been demonstrated. We could successfully mimic nature to perform the rearrangements of phaitanthrin D to phaitanthrin E and confirmed an unusual carbon−carbon bond cleavage. There is potential for (+)-methylfuroindoloquinazolinone to be isolated as a bioactive natural product in the near future. The present concept of designing an appropriate type of structural unit bearing precisely situated heteroatoms to release certain types of carbon leaving groups at the cost of relatively higher formed product stability has a broad scope. These results prove that under special circumstances the esters, ethers, alcohols, and amines can also function as good leaving groups via unexpected carbon−carbon bond cleavages, and conceptually it will be useful to organic chemists to achieve what appears implausible.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03203.

Experimental procedures and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: np.argade@ncl.res.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.D.V. thanks CSIR, New Delhi, for the award of a research fellowship. N.P.A. thanks the Department of Science and Technology, New Delhi for financial support.

■ REFERENCES

(1) (a) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787. (b) Kshirsagar, U. A. *Org. Biomol. Chem.* **2015**, *13*, 9336.

(2) Jao, C. W.; Lin, W. C.; Wu, Y. T.; Wu, P. L. *J. Nat. Prod.* **2008**, *71*, 1275.

(3) (a) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625. (b) Borthwick, A. D. *Chem. Rev.* **2012**, *112*, 3641. (c) Westheimer, F. H. *Science* **1987**, *235*, 1173. (d) Butler, A.; Sandy, M. *Nature* **2009**, *460*, 848. (e) Newhouse, T.; Lewis, C. A.; Eastman,

DOI: 10.1021/acs.orglett.5b03203
Org. Lett. 2015, 17, 6218−6221

K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119. (f) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940.

(4) (a) Hu, B.-Q.; Wang, L.-X.; Yang, L.; Xiang, J.-F.; Tang, Y.-L. *Eur. J. Org. Chem.* **2015**, *2015*, 4504. (b) Mohammed, S.; Vishwakarma, R. A.; Bharate, S. B. *J. Org. Chem.* **2015**, *80*, 6915. (c) Drahl, M. A.; Manpadi, M.; Williams, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 11222. (d) Mahoney, S. J.; Lou, T.; Bondarenko, G.; Fillion, E. *Org. Lett.* **2012**, *14*, 3474. (e) Cordaro, J. G.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 3432. (f) Anand, R. C.; Milhotra, A. *Chem. Commun.* **1999**, *15*, 1415. (g) Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *8*, 215.

(5) (a) Vaidya, S. D.; Argade, N. P. *Org. Lett.* **2013**, *15*, 4006. (b) Kshirsagar, U. A.; Argade, N. P. *Org. Lett.* **2010**, *12*, 3716. (c) Kshirsagar, U. A.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2010**, *75*, 2702.

(6) (a) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410. (b) Chen, Y.-C.; Zhu, M.-K.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 2712. (c) Yada, A.; Fujita, S.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 7217. (d) Chen, F.; Wang, T.; Jiao, N. *Chem. Rev.* **2014**, *114*, 8613. (e) Murphy, G. K.; Hama, N.; Bedermann, A.; Dong, P.; Schneider, C. M.; McMahon, T. C.; Tao, R. N.; Twenter, B. M.; Spiegel, D. A.; Wood, J. L. *Org. Lett.* **2012**, *14*, 4544. (f) Cai, S.; Zhao, X.; Wang, X.; Liu, Q.; Li, Z.; Wang, D. Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 8050. (g) Youn, S. W.; Kim, B. S.; Jagdale, A. R. *J. Am. Chem. Soc.* **2012**, *134*, 11308. (h) Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17502. (i) Dreis, A. M.; Douglas, C. J. *J. Am. Chem. Soc.* **2009**, *131*, 412. (j) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610.

(7) (a) Kang, G.; Luo, Z.; Liu, C.; Gao, H.; Wu, Q.; Wu, H.; Jiang, J. *Org. Lett.* **2013**, *15*, 4738. (b) Gao, H.; Luo, Z.; Ge, P.; He, J.; Zhou, F.; Zheng, P.; Jiang, J. *Org. Lett.* **2015**, *17*, ASAP, DOI: 10.1021/acs.orglett.5b02891.

(8) Kshirsagar, U. A.; Mhaske, S. B.; Argade, N. P. *Tetrahedron Lett.* **2007**, *48*, 3243.

DOI: 10.1021/acs.orglett.5b03203
Org. Lett. 2015, 17, 6218−6221