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Total Synthesis of (±)-Hapalindole Q

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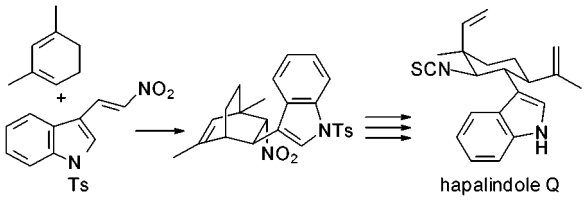
ABSTRACT

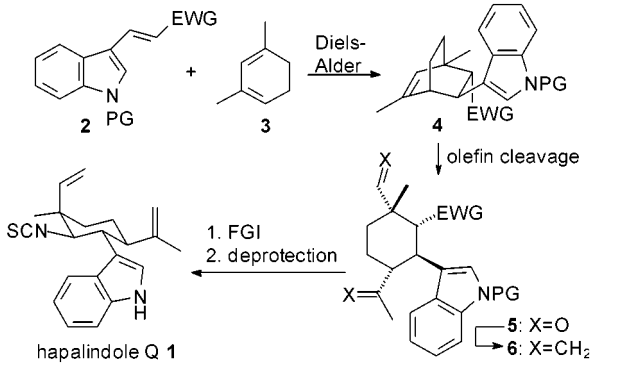


The total synthesis of the antibacterial and antimycotic alkaloid hapalindole Q has been achieved in eight steps and 12.4% overall yield. The key step involves a regio- and diastereoselective Diels−Alder reaction to afford a bicyclo[2.2.2]oct-2-ene. This cycloadduct was subsequently dihydroxylated, cleaved, and converted to the natural product.

The hapalindoles are a group of 20 structurally related alkaloid natural products isolated from the terrestrial blue-green algae *Hapalosiphon fontinalis*, an organism found to exhibit antibacterial and antimycotic activity.[1] The complex structures and biological activity have encouraged several syntheses of these compounds.[2] Indeed, Vaillancourt and Albizati achieved an elegant enantioselective synthesis of hapalindole Q (**1**) based on a camphor derivative.[2e] Our successful approach to hapalindole Q is presented herein.

The strategy for the synthesis of hapalindole Q (**1**) is presented in Scheme 1. The Diels−Alder reaction (**2** + **3** → **4**) is the cornerstone of our strategy since it allows expedient generation of the carbon skeleton and secures the proper relative stereochemistry. Bicyclo[2.2.2]oct-2-ene **4** is then cleaved to cyclohexane **5**, which would be subjected to double methylenation, yielding **6**. Finally, functional group interconversion (FGI) and deprotection would complete the synthesis of **1**.

Scheme 1. Synthetic Strategy for Hapalindole Q



We initially undertook a model study to determine the feasibility of this sequence. It was found that ultrahigh pressures and catalytic $Yb(OTf)_3 \cdot 2H_2O$ mediate Diels−Alder reactions of various electron-deficient dienophiles with 1,3-cyclohexadiene to produce *endo*-bicyclo[2.2.2]oct-2-enes in moderate to excellent yield and selectivity (Scheme 2).[3] Unfortunately, 1,3-dimethyl-1,3-cyclohexadiene (**3**)[4] tends to polymerize in the presence of $Yb(OTf)_3 \cdot 2H_2O$, especially at high pressure. However, it was discovered that nitro dienophiles are sufficiently activated that the Lewis acid is

(1) (a) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456. (b) Moore, R. E.; Cheuk, C.; Yang, X.-Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036.

(2) (a) Hapalindole G: Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125. (b) Hapalindoles H and U: Muratake, H.; Kumagami, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6351. (c) Hapalindoles J and M: Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 1815. Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331. (d) Hapalindole O: Sakagami, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393. (e) Hapalindole Q: Vaillancourt, V. Albizati, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 3499.

(3) Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2000**, *2*, 3517.

(4) Mirrington, R. N.; Schmalzl, K. L. *J. Org. Chem.* **1969**, *34*, 2358.

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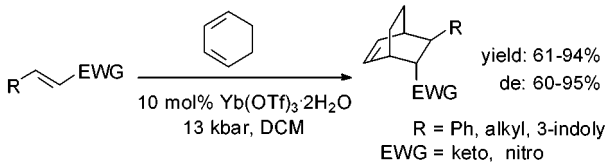
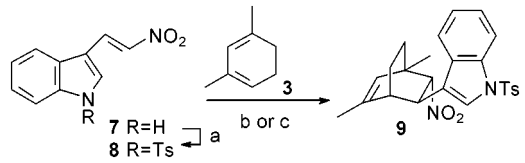
Scheme 2. Diels−Alder Reactions of 1,3-Cyclohexadiene



not required for the Diels−Alder reaction.[3] Furthermore, use of the nitro group would avoid subsequent conversion of a C−C attachment to the required C−N attachment.

Thus, 3-(2-nitroethenyl)indole **7**[5] was protected to give the tosylindole **8** in 88% yield (Scheme 3). Indolyl dienophile **8**

Scheme 3. Preparation of Key Nitro Cycloadduct[a]

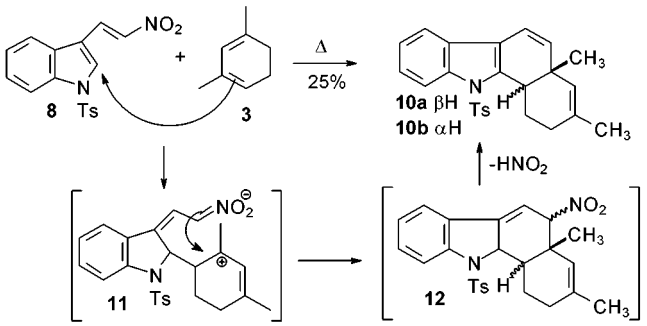


[a] (a) K_2CO_3, TsCl, THF reflux, 3 h (88%); b) 3 equiv of **3**, 13 kbar, DCM, 50 °C, 5 d (77%, 80% de); (c) 3 equiv of **3**, sealed tube, PhMe, 155−165 °C, 2 d (60%, 72% de).

was reacted with cyclic diene **3** to selectively afford the key cycloadduct **9**[6] in good yield. High-pressure conditions gave greater selectivity (80% de) and higher yields (77%), but extensive polymerization of the diene made purification of these reactions problematic, even by flash chromatography. The cleaner reaction produced under thermal conditions (60%, 72% de) allowed more facile purification. Preparative scale reactions (∼3 g of **7**) could be conveniently purified simply by trituration (49% yield, 73% de).

Although the thermal conditions produced less polymerization of the diene, tetracyclic byproducts **10a**,**b** (Scheme 4) were formed in ∼25% yield as a mixture of isomers (**10a**:**b**, 60:40). It is possible that tetracycles **10a** and **10b** result from an inverse electron demand Diels−Alder reaction (with the **8** acting as diene and **3** as the dienophile) followed by nitrous acid elimination. An ensuing epimerization of the *cis* product **10a** (*β*H) could produce the mixture of *cis* and *trans* observed.[7] An alternative mechanism is that formation of **10** occurs via 1,6-addition of the diene at the 2-position of the indole to give stable carbocation **11**. Ring closure at this stage accounts for the mixture of isomers and gives a

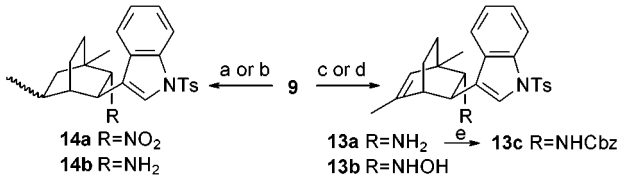
Scheme 4. Proposed Mechanism for Formation of Tetracycle **10**



second intermediate, **12**, which loses nitrous acid to afford the tetracycles **10a**[6] and **10b**.

With the key nitro cycloadduct **9** in hand, our attention turned to reduction of the nitro group to the amine **13a**. As shown in Scheme 5, none of the conditions screened reliably

Scheme 5. Reductions of Nitro Cycloadduct **9**[a]



[a] (a) NH_4OCHO, Pd/C, MeOH, THF, 0 °C to rt, 16 h (55% **14a**); (b) H_2/Raney Ni, EtOH, H_2O, THF, rt, 1 h (77% **14b**); (c) SmI_2, MeOH, THF, rt, 16 h (95% **13b**); (d) Zn (20−80% **13a**); (e) CbzCl, TEA, DCM, 0 °C to rt, 16 h (10−25%).

produced the desired amine **13a**.[8] Furthermore, poor yields (10−25%) were obtained in the attempts to prepare carboxybenzyl (Cbz) derivative **13c**. The troublesome reductions and problematic derivatization led us to abandon this approach and focus on the cleavage of bicyclic olefin **9**.

Ozonolysis of the bicyclic alkene was ineffective,[9] and we chose a dihydroxylation/cleavage protocol instead. It was found that dihydroxylation of the olefin in **9** could be best achieved with a modification of a racemic Sharpless procedure to afford diol **15** as a single diastereomer (Scheme 6).[10] Interestingly, under these conditions *endo*-**9** reacted faster than *exo*-**9**, allowing a kinetic resolution of these isomers in this step.

(5) Markgraf, J. H.; Finkelstein, M.; Cort, J. R. *Tetrahedron* **1996**, *52*, 461.

(6) Structure assigned by ^1H, ^{13}C, COSY, HSQC, HMBC, and NOESY experiments.

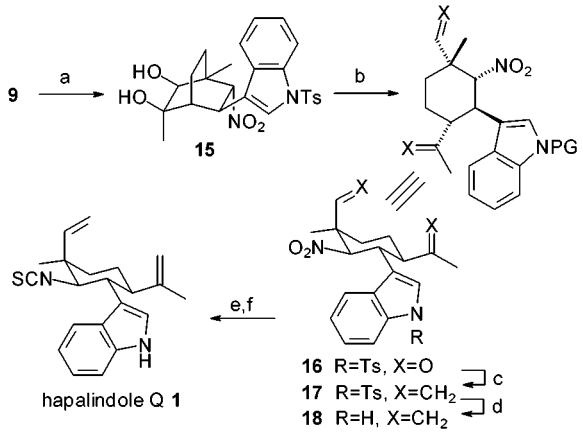
(7) It has been demonstrated that **10a** may be epimerized to **10b** under the reaction conditions. In point of fact, **10** (**a**:**b**, 85:15) was treated with HOAc and heated at 170−180 °C in a sealed tube. After 20 h, ^1H NMR analysis revealed the same ratio of isomers originally isolated from the reaction mixture (**10a**:**b**, 60:40). Although this implies that the successive Diels−Alder−epimerization pathway is possible, it does not preclude the ionic mechanism proposed.

(8) Attempted reduction with LAH in THF gave an intractable mixture. Ammonium formate with Pd/C selectively reduced the trisubstituted olefin to give **14a** while hydrogen over Raney Ni reduced both the olefin and the nitro group to afford **14b**. Use of 8 equiv of SmI_2 gave the hydroxylamine **13b** (95%). Inconsistent results were observed with a variety of conditions using zinc or increased equivalents of SmI_2.

(9) An intractable mixture was obtained. The ozonolytic cleavage of the pyrrole ring of indole is known (Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1952**, *74*, 3855) and provides a possible explanation of the results observed here.

(10) Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095.

Scheme 6. Synthesis of Hapalindole Q[a]



[a] (a) K_2CO_3, $K_2OsO_4 \cdot 2H_2O$ (3 mol %), $MeSO_2NH_2$, DABCO, THF, H_2O, rt, 16 h (60%); (b) $NaIO_4/SiO_2$, DCM, rt, 16 h (>95%); (c) KO*t*Bu, Ph_3PCH_3I, PhMe, 90−110 °C, 2 h (64%); (d) NaOH, EtOH reflux, 3 h (69%); (e) SmI_2, MeOH, THF, rt, 16 h; (f) $Imid_2CS$, DCM, 0 °C to rt, 16 h (73%, two steps).

Diol **15** was cleaved in high yield (>95%) using silica-supported sodium periodate.[11] The cyclohexane ring formed contains an equatorial indole flanked on either side by equatorial nitro and acetyl groups which induce atropisomerism of the indole moiety. Consequently, the NMR spectra of **16** exhibited broadening of several signals. As observed in the previous hapalindole Q synthesis,[2e] acquiring the spectra at elevated temperature (50 °C) alleviated this problem.[12][14]

The keto aldehyde **16** was converted to the diolefin **17**[12] in 64% yield using the method of Fitjer and Quabeck.[13] Interestingly, using methyltriphenylphosphonium bromide instead of the iodide resulted in a poor yield (24%). A more expedient synthesis of **17** was envisaged by ring opening metathesis of **9** with ethylene.[14] However, all attempts to promote this transformation failed (even using the highly reactive Nolan catalyst[15] gave starting material).

The detosylation of **17** to **18** could be effected using either TBAF[16] (65%) or NaOH[17] (69%). Both methods resulted in some epimerization of the nitro group from an equatorial to an axial position (7−12% isolated yield of *epi*-**18**). Note that the ambient temperature ^{1}H NMR spectrum of *epi*-**18** shows all sharp signals since the relocation of the nitro group now permits free rotation of the indole.[18] The nitro group of **18** was successfully reduced with a large excess of SmI_2 [19] (28.5 equiv) to give the same amine as reported by Vaillancourt and Albizati. The amine was subsequently converted to hapalindole Q according to their method (73%, two steps).[2e]

In conclusion, a new total synthesis of hapalindole Q (**1**) has been achieved. The key Diels−Alder reaction proceeds with good yield and selectivity to form the skeletal carbon−carbon bonds in a single step, including the quaternary center. Subsequent olefin cleavage and functional group interconversions provided the natural product in eight steps and 12.4% overall yield.

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Supporting Information Available: Full experimental procedures and spectroscopic data for compounds **1**, **9**, **10a**, **15**, **16**, **17**, **18**, and *epi*-**18**. This material is available free of charge via the Internet at http://pubs.acs.org

OL0165138

(11) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.
(12) The VT ^{1}H NMR experiments are provided in the Supporting Information.
(13) Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855.
(14) We thank Professor Maarten Postema (Wayne State University) for this suggestion.
(15) Nolan's catalyst: $(IMes)(PCy_3)(Cl)_2Ru{=}CHPh$; IMes = 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene. (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5375. (c) Scholl, M. Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.
(16) Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595.
(17) Gilbert, E. J.; Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1999**, *64*, 5670.
(18) A similar effect was observed in the previous hapalindole Q synthesis where *epi*-hapalindole Q (axial -NCS) was isolated. See ref 2e.
(19) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699.