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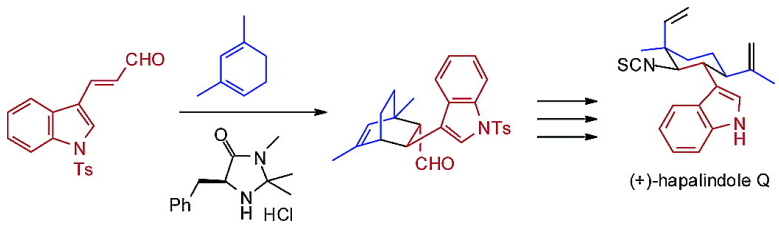

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The Total Synthesis of (+)-Hapalindole Q by an Organomediated Diels−Alder Reaction

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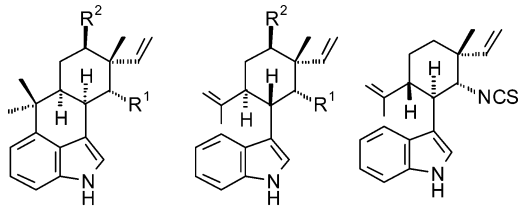
Abstract: The total synthesis of (+)-hapalindole Q has been achieved. The key step is a Diels−Alder reaction mediated by MacMillan's organocatalyst to provide the critical intermediate with high enantioselectivity (93% ee). This step establishes the proper arrangement of the required four contiguous stereocenters, including the quaternary center, and represents the first successful application of an enantioselective organomediated Diels−Alder reaction in total synthesis.

Introduction

The hapalindoles are a group of structurally related tri- and tetracyclic alkaloid natural products first isolated by Moore and co-workers from the terrestrial blue-green alga *Hapalosiphon fontinalis* in the mid-1980s (Chart 1).[1] This soil cyanobacterium is indigenous to the Marshall Islands (located in the central Pacific Ocean north of New Zealand); however, the hapalindoles are not exclusive to *H. fontinalis* and have been isolated from a number of other organisms.[2] The impetus for the original isolation was the finding that extracts from *H. fontinalis* exhibited anti-algal and antimycotic activity. Recent investigations suggest the biological activity is derived from the compound's ability to directly inhibit RNA polymerase.[2g,h]

The hapalindoles have multiple rings and stereocenters coupled with a deficiency of heteroatoms to aid in carbon−carbon bond formation. Despite these challenges, several elegant approaches have been successfully implemented for hapalindole syntheses.[3] Hapalindole Q, with its cyclohexane ring containing four contiguous stereocenters, invites a Diels−Alder disconnection. Indeed, we have recently achieved a concise synthesis of racemic hapalindole Q by employing a Diels−Alder reaction to construct the carbon skeleton with the required relative stereochemistry at all four stereogenic carbons.[4]

Chart 1. Selected Tri- and Tetracyclic Hapalindoles.



	R^1	R^2		R^1	R^2
A	NC	Cl	C	NC	H
B	NCS	Cl	D	NCS	H
J	NC	H	E	NC	Cl
M	NCS	H	F	NCS	Cl
O	NCS	OH			

Intrigued by the prospect of an enantioselective synthesis of hapalindole Q, we were drawn to the most obvious approach, which would entail enantiofacial differentiation in the Diels−Alder reaction. This type of strategy could involve the use of a chiral catalyst, a chiral dienophile or a chiral diene. However, there was concern in using a Lewis acid because of the polymerization of required diene **3**[5] (vide infra, Scheme 1) under these conditions.[6] This would obviously exclude the use of conventional chiral catalysts. In addition, the chiral dienophile strategy would be precluded since an ester- or amide-based auxiliary would require Lewis acid activation. Furthermore, no elegant manner for introduction of an auxiliary to all-carbon diene **3** was apparent.

We were then inspired by the recent work of MacMillan describing the use of organocatalysts in the Diels−Alder reaction.[7] Diene **3** might be compatible with the mild amino acid-based catalyst and partial aqueous conditions employed.

(1) (a) Moore, R. E.; Cheuk, C.; Yang, X.-Q.; 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. (b) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456.

(2) (a) Schwartz, R. E.; Hirsh, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113. (b) Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B.; Yoshida, W. Y.; Prinsep, M. R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1992**, *57*, 857. (c) Park, A.; Moore, R. E.; Patterson, G. M. L *Tetrahedron Lett.* **1992**, *33*, 3257. (d) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935. (e) Klein, D.; Daloze, D.; Braekman, J. C. *J. Nat. Prod.* **1995**, *58*, 1781. (f) Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1998**, *61*, 1304. (g) Doan, N. T.; Rickards, R. W.; Rothschild, J. M.; Smith, G. D. *J. Appl. Phycol.* **2000**, *12*, 409. (h) Doan, N. T.; Stewart, P. R.; Smith, G. D. *Microbiol. Lett.* **2001**, *196*, 135.

(3) (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 1815. (b) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, *6331*. (c) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6343. (d) Muratake, H.; Kumagami, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6351. (e) Vaillancourt, V.; Albizati, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 3499. (f) Sakagami, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393. (g) Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125.

(4) Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3189.

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

(6) Diene **3** was found to undergo polymerization even with mild Lewis acids such as SiO_2, $Yb(OTf)_3$, and $Sc(OTf)_3$.

(7) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

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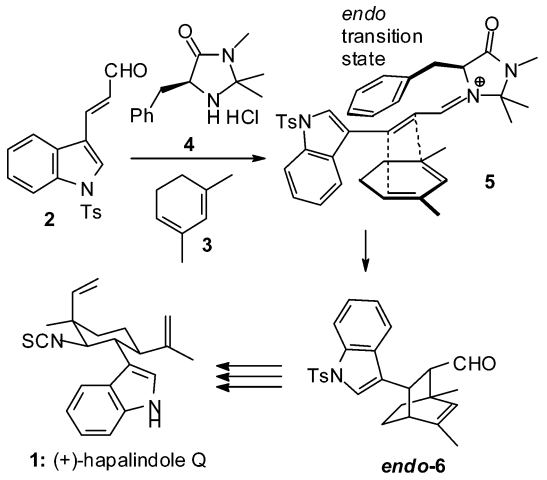
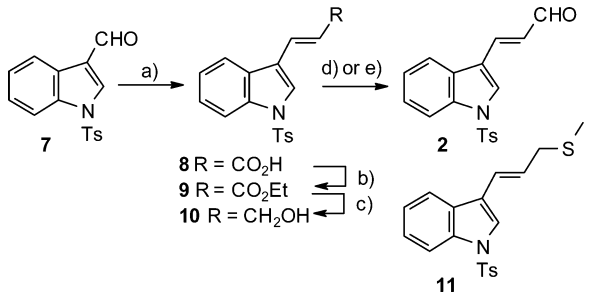
Scheme 1. Proposed Transition-State Model for the Synthesis of (+)-Hapalindole Q



Scheme 2. Synthesis of Enal **8**[a]



[a] Reaction conditions: (a) malonic acid, pyridine, ~20 mol % pyrrolidine, reflux, 2 h, 86%. (b) EtOH, cat H_2SO_4, reflux, Dean−Stark, 24 h, 96%. (c) DIBAL, CH_2Cl_2, −10 to 0 °C, 2 h, >95%. (d) DMP, CH_2Cl_2, 0 °C, 1 h, 72%. (e) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, TEA, 1 h, 81% (plus 8% of **11**).

Examination of the proposed transition state with iminium complex **5** formed from enal **2** and organocatalyst **4** (derived from natural phenylalanine) suggested diene attack would be restricted to the appropriate face of the alkene to afford cycloadduct **6** and, eventually, (+)-hapalindole Q **1** (Scheme 1). In this article, we report the details of our efforts, and ultimate success, in the total synthesis of (+)-hapalindole Q using as the key step an enantioselective organomediated Diels−Alder reaction.

Results and Discussion

The required enal dienophile **2** was prepared in four steps from known indole **7**.[8] A Knoevenagel reaction[9] followed by esterification of acid **8** gave ester **9**. A reduction−oxidation procedure afforded the desired enal in acceptable yield. Comparable yields were obtained for the oxidation of allylic alcohol **10** with Dess−Martin periodinane (DMP)[10] or Swern conditions[11] (Scheme 2). The latter technique provided a cleaner overall reaction but thioether **11** was formed in about 8% yield. Formation of this type of byproduct has been observed previously in the Swern reaction.[12] The DMP procedure was scaled up to give about 15 g of **2**.

With dienophile **2** in hand, asymmetric Diels−Alder reactions mediated by organocatalyst **4** could now be attempted. A variety of solvents were screened for this reaction but had little effect on the yield (Table 1). Generally, the yields were low (~20%), and high catalyst loadings were required (up to 100 mol %) to achieve acceptable conversions to the product. As observed by MacMillan and co-workers, reactions carried out in MeOH resulted in some of the aldehyde products **6** being converted to the dimethyl acetal.[7] It was found that treatment of the reaction mixture with either catalytic TsOH in acetone or 5% HCl (aq) in THF provided an effective means for deprotecting aldehyde **6**.

Generally, it was found that more polar solvents such as MeOH and DMF produced the highest yields and best enantioselectivity (Table 1, entries 1−6). Acetonitrile (entry 8) and CH_2Cl_2 (entry 9) gave slightly lower yields and selectivity while biphasic systems (CH_2Cl_2/water) produced no reaction with or without the presence of a phase transfer catalyst (entries 10 and 11, respectively). A reaction carried out in THF met a similar fate (entry 12).

The water in the reaction mixture has been found to increase enantioselectivities and reaction rates and may aid in hydrolysis of the product iminium species.[7a] Replacement of the water with a phosphate buffer (pH = 7) offered no improvement (compare entries 2 and 13 in Table 1). Switching the counterion from a chloride to a triflate or perchlorate also had little effect (entries 14 and 15).

Ultimately, an acceptable set of reaction conditions was developed which employed a solvent system of a 1:1 mixture of DMF and MeOH containing 5% water (Table 1, entry 7). The DMF provides superior solubility of dienophile **2**, while MeOH seems to afford greater reactivity. This reaction gave a 35% yield of cycloadducts **6** with excellent selectivity (70% de;[13] 93% ee for desired *endo*-**6**). Although the yield is moderate, *the rapid and enantioselective assembly of the complex intermediate from readily accessible achiral starting materials makes this route attractive*. To the best of our knowledge, these are the most structurally complex substrates used to date in a Diels−Alder reaction mediated by MacMillan's organocatalyst.

It is interesting to note that 1,3-cyclohexadiene was completely unreactive under these conditions in either DMF or MeOH solvent. This clearly indicates the higher reactivity of the dimethyl analogue **3**, as well as the significant substrate dependence for the success of the organocatalytic Diels−Alder reaction.

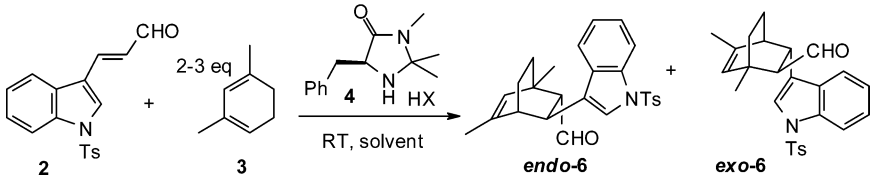
It is of note that the racemic product (prepared by heating enal **2** with diene **3** at 140 °C in a sealed tube in DMF) crystallized readily and allowed X-ray analysis to secure the relative stereochemistry of *endo*-**6**. This also permitted facile removal of the minor exo isomer. Interestingly, this was in stark contrast to the enantioenriched samples, which defied all efforts at crystallization and had to be carried through the synthesis as mixtures of diastereomers.

In an attempt to better understand this reaction, a series of experiments were carried out with 100 mol % of catalyst **4** in deuterated solvents (DMSO-d_6, $CDCl_3$, and MeOH-d_4) to facilitate convenient analysis by ^{1}H NMR. The reaction conducted in chloroform proceeded to <2% conversion after 2

(8) Evans, D. D. *Aust. J. Chem.* **1973**, *26*, 2555.
(9) Moffatt, J. S. *J. Chem. Soc.* **1957**, 1442.
(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
(11) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(12) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(13) For the purposes of this discussion "de" refers to the endo:exo excess.

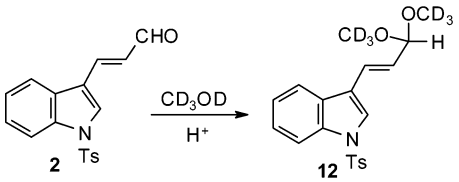
Table 1. Optimization of the Asymmetric Diels−Alder Reaction



entry[a]	solvents (v/v)	time/d	**4** (mol %)	yield[b]/%	de[c]/%	ee[d] (endo)/%	ee[d] (exo)/%
1	MeOH/H_2O (95/5)	0.7	15 (X = Cl)	18[e]	66	85	93
2	MeOH/H_2O (95/5)	0.7	100 (X = Cl)	29[e]	68	92	
3	MeOH/H_2O (95/5)	4	11 (X = Cl)	*f*			
4	DMF/H_2O (95/5)	2	11 (X = Cl)		74		
5	DMF/H_2O (95/5)	2	49 (X = Cl)	21	80	93	96
6	DMF/H_2O (95/5)	2	100 (X = Cl)	20	76	91	85
7	DMF/MeOH (1:1) (5% H_2O)	1.5	40 (X = Cl)	35	70	93	92
8	MeCN/H_2O (95/5)	2	9 (X = Cl)	20	73	85	80
9	CH_2Cl_2 (100)	3	100 (X = Cl)	18	60	89	87
10	CH_2Cl_2/H_2O (50/50)	4	11 (X = Cl)				
11	CH_2Cl_2/H_2O (50/50) + cat *n*-Bu_4NHSO_4	1	10 (X = Cl)				
12	THF/H_2O (95/5)	0.7	100 (X = Cl)				
13	MeOH/buffer[g] (95/5)	1.1	15 (X = Cl)	26[e]	65	96	95
14	MeOH/H_2O (95/5)	1.1	100 (X = OTf)	20[e]	67	94	92
15	MeOH/H_2O (95/5)	1.1	100 (X = ClO_4)	20[e]	59	92	95

[a] Experiments performed on 0.37−0.50 mmol of **2** in 2−4 mL of solvent. [b] After purification by chromatography. [c] Refers to endo:exo selectivity. Determined by ^{1}H NMR analysis of the crude extracts or by HPLC. [d] Determined by HPLC analysis (area %) of the isolated products. [e] The dimethyl acetal products from the reactions in MeOH were treated with 5% HCl (aq)/THF (1:1) or cat. TsOH/Acetone to convert the to the aldehydes **6**. In some cases, hydrolysis conditions led to the formation of an unknown impurity (9−30%). [f] Extensive polymerization observed. [g] Buffer was 0.05 M KH_2PO_4−NaOH (Fisher).

Scheme 3. Acetalization of Enal **8**



days at RT, while the reaction in DMSO reached 21% conversion after 3 days at RT. Unfortunately, no intermediates, major side products, or clear degradation pathways could be discerned from this analysis.

A most interesting result was obtained when MeOH-d_4 was used as solvent. In less than 10 min, there was clean formation of a new product with complete consumption of the starting aldehyde **2**. We had hoped to witness the formation of the iminium complex **5** (Scheme 1). However, dimethyl acetal **12** (Scheme 3) was more consistent with the spectroscopic data, with the remaining signals in the spectrum arising from the catalyst. This complete conversion to the acetal with no evidence of iminium ion formation implies that (at least in methanolic media) the dominant species present is an acetal and that it is possible that the rate-limiting step is iminium ion formation.

In this case, a clear picture of conversion could not be obtained directly because both the starting material and product were at least partially ketalized by the solvent. After appropriate treatment of reaction aliquots, it was determined that there was 60% conversion after 6 h and 86% conversion after an additional 12 h. This clearly shows that of the solvents examined, the reaction proceeds fastest in MeOH. It is possible that ketalization of the product tends to remove this from the reaction equilibrium and thus drives the reaction to completion. Furthermore, this finding might be useful for unstable enals, which could be protected as the dimethylacetals and used directly in the organocatalytic Diels−Alder reaction.

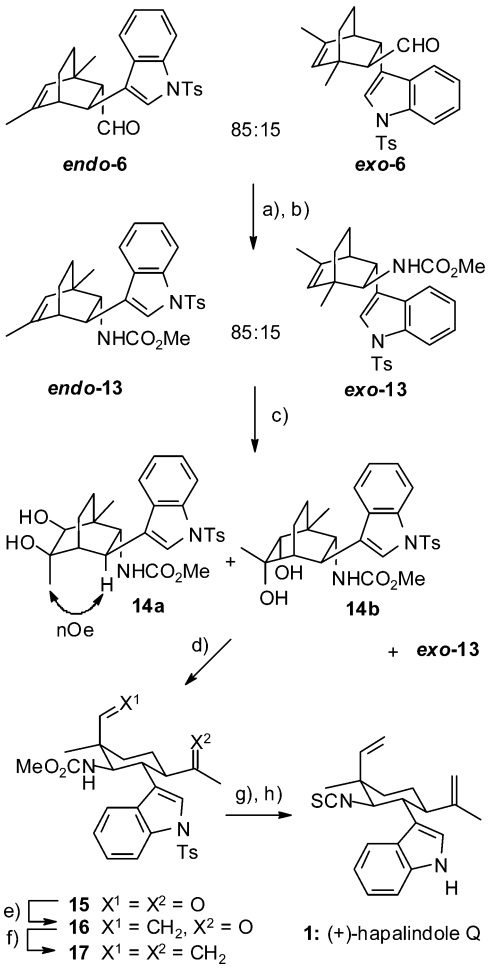
It should be noted that the catalyst could be easily recovered (85−90%) by extracting the basified aqueous phase with methylene chloride (following product extraction). Obviously, this means that the catalyst was not appreciably consumed in the formation of byproducts. Furthermore, in control experiments it was found that both the diene and dienophile could be individually treated with the catalyst and then recovered without any significant decomposition. This would seem to implicate the nucleophilicity of the diene **3** as the source of the many side products, as observed in our synthesis of the racemate.[4]

With the key Diels−Alder product in hand, the synthesis was reduced to a series of functional group interconversions. The essential elements include the oxidative olefin cleavage followed by double methylenation and conversion of the aldehyde to an amine by a Curtius or Hoffman rearrangement. A number of unsuccessful pathways were investigated before the following sequence was discovered.

Oxidation[14] of **6** as an 85:15 mixture of endo:exo isomers (70% de) gave the corresponding acid, which underwent Curtius rearrangement with DPPA[15] (Scheme 4). Interestingly, rearrangement of the acyl azide to the isocyanate progressed easily in refluxing toluene; however, the addition of the methanol to the isocyanate was very slow at this temperature. It is noteworthy that the methanol addition was faster on the exo substrate, presumably because of steric hindrance associated with addition to the endo compound. The methanol addition was successfully completed by extended heating in a sealed tube at 150 °C to give an inseparable mixture of *endo*- and *exo*-carbamates **13** also as an 85:15 mixture of endo:exo isomers (70% de). We were pleasantly surprised that our fears of skeletal rearrangements of the bicyclo[2.2.2]octane system during the Curtius rearrangement were unfounded.

(14) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(15) (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

Scheme 4. Synthesis of (+)-Hapalindole Q[a]



[a] Reaction conditions: (a) $NaClO_2$, NaH_2PO_4 (aq), 2-methyl-2-butene, *t*-BuOH, 1 h, 85%. (b) (i) DPPA, TEA, PhMe, reflux; (ii) MeOH, sealed tube 150 °C, 17 h, 79%. (c) 5 mol % $K_2OsO_2(OH)_4$, 15 mol % DABCO, $MeSO_2NH_2$, K_2CO_3, $K_3Fe(CN)_6$, THF, water, RT, 2 d, 75% (**14a**/**14b**, ~3:1). (d) $NaIO_4/SiO_2$, CH_2Cl_2, 2 h, >95%. (e) KOtBu, Ph_3PCH_3I, THF, RT, 1.5 h, 81%. (f) KOtBu, Ph_3PCH_3I, PhMe, 60 °C, 2 h, 67%. (g) TBAF, THF, reflux, 12 h. (h) TCDI, CH_2Cl_2, 0 °C, 20 h, 29% (two steps).

Carbamate *endo*-**13** underwent dihydroxylation to give a mixture of diols **14a** and **14b** (~3:1). Usually the dihydroxylation of these substrates would have been expected to proceed selectively to give diol **14a** almost exclusively, a result of sterics forcing the osmium attack from the face opposite to the endo substituent (carbamate).[16] In this case, however, it is believed that the carbamate provides a ligand for the osmium and, thus, is able to direct its attack from this more hindered face to give minor diol **14b**. The structural assignments of the diols are based on the observation of an NOE, as shown in Scheme 4. As found in our racemic hapalindole Q synthesis,[4] a kinetic separation of the diastereomers was achieved at this stage, and ***exo*-13** remained unreacted and could be separated by flash chromatography. The mixture of diols **14a** and **14b** could be cleanly cleaved with silica-supported $NaIO_4$[17] to give keto-aldehyde **15**.

Achieving the double methylenation proved to be an unexpectedly challenging transformation in the synthesis, possibly due to the acidic carbamate hydrogen. The use of Tebbe's reagent gave only a poor yield of the desired bis-olefin **17** and overall poor recovery of material. Increasing the equivalents of Tebbe's reagent resulted in an intractable mixture. The conditions of Fitjer and Quabeck[18] gave inconsistent results, with the best case providing less than 50% yield of **17**. If *n*-BuLi was used as the base, intramolecular aldol products were isolated. Ultimately, a sequential Wittig olefination was chosen which gave the most consistent results and best yields (81% and 67%, or 54% over two steps).

To complete the synthesis, deprotections of the indole and the amine were required. The amine was deprotected with a mixture of TMSCl and NaI in acetonitrile.[19] The crude product was then detosylated with TBAF[20] to give the desired fully deprotected substrate, which was converted to (+)-hapalindole Q **1** by the method of Vaillancourt and Albizati.[3e] It was subsequently found that TBAF permits the *double* deprotection in one pot in similar yield. HPLC analysis indicated an enantiomeric excess of 93% for the final product. Furthermore, the synthetic product was found to be dextrorotatory by polarimetric analysis, establishing that the absolute stereochemistry matches that of the natural product. Accordingly, this was as predicted by the transition-state model for the asymmetric Diels−Alder reaction (Scheme 1).

Conclusions

The enantioselective total synthesis of (+)-hapalindole Q has been accomplished. MacMillan's organocatalyst allowed high enantioselectivity in an asymmetric Diels−Alder reaction to produce the key intermediate in the synthesis. To the best of our knowledge, this is the first total synthesis achieved employing an organomediated Diels−Alder reaction. In this step, impressive enantioselective complexity was generated from simple achiral starting materials. The intermediate then underwent a series of functional group transformations to converge with the amine of Vaillancourt and Albizati. The isothiocyanate was introduced according to their method to afford (+)-hapalindole Q **1** (93% ee) in 12 steps from **7** and 1.7% overall yield.

Experimental Section

Melting points were uncorrected. Infrared spectra were recorded as thin films on NaCl plates. Unless otherwise indicated, NMR experiments were performed at 400 MHz (or 100 MHz for ^{13}C) in $CDCl_3$ (referenced to residual $CHCl_3$ at 7.24 ppm for ^1H or solvent at 77.00 ppm for ^{13}C). Spectra obtained in DMSO-d_6 were referenced to residual DMSO-d_5 at 2.49 ppm for ^1H or solvent at 39.5 ppm for ^{13}C. Coupling values (*J*) are in Hz.

Dichloromethane, toluene, and THF were distilled according to the standard procedures.[21] All other reagents were used as supplied from commercial sources. Reactions were checked for completion by TLC (EM Science, silica gel 60 F_{254}) or ^1H NMR or both. Flash chromatography (FC) was performed using silica gel (230−400 mesh).

Ethyl 2-(3-(*N*-Tosyl)indolyl)acrylate (9). A mixture of *N*-tosylindole-3-carboxaldehyde[8] **7** (74.47 g, 248.8 mmol), pyridine (200 mL), malonic acid (39.06 g, 375.3 mmol), and pyrrolidine (5.0 mL, 60 mmol) was heated at reflux for 2 h. After cooling to ~60 °C, the reaction mixture was poured into water (300 mL), and then 100 mL of 5% HCl (aq) and 300 mL of EtOH were added. The thick yellow slurry was

(16) Königsberger, K.; Faber, K.; Marschner, C.; Penn, G.; Baumgartner, P.; Grieng, H. *Tetrahedron* **1989**, *45*, 673.
(17) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.
(18) Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855.
(19) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225.
(20) Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595.
(21) Perrin, D. D.; Armarego, W. L. F. In *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1988.

pulped at RT for 1 h and then filtered. The cake was washed with EtOH/water (1:1, 200 mL) and then with EtOH (2 × 100 mL) and dried on the filter overnight to afford the crude acid **8** (72.90 g, 86%). A slurry of the crude acid in EtOH (500 mL, anhydrous) and H_2SO_4 (4.5 mL) was refluxed with a Dean−Stark trap attached for 24 h. The mixture was allowed to cool to RT over 24 h, then cooled to 5−10 °C, and filtered, and the product was washed with EtOH (5−10 °C, 2 × 70 mL) to afford **9** (75.65 g, 96%) as an off-white solid: mp 144−146 °C (CH_2Cl_2/hexanes). ^{1}H NMR (300 MHz): δ 7.98 (d, J = 7.6, 1H), 7.82−7.74 (m, 7H), 7.38−7.21 (m, 4H), 6.50 (d, J = 16.1, 1H), 4.26 (q, J = 7.1, 2H), 2.33 (s, 3H), 1.33 (t, J = 7.1, 3H). ^{13}C NMR (75 MHz): δ 167.0, 145.4, 135.5, 134.7, 130.0, 128.3, 128.0, 126.9, 125.4, 124.0, 120.6, 118.3, 118.1, 113.7, 60.4, 21.5, 14.3. IR: 1707, 1636, 1447, 1370, 1176 cm^{-1}; MS *m*/*z* (relative intensity): 369 (M^+, 100), 324 (15), 214 (48), 186 (63), 158 (62), 91 (91). HRMS calcd for $C_{20}H_{19}NO_4S$: 325.0773; found: 325.0780.

3-(3-(*N*-Tosyl)indolyl)acrolein (2). To a cooled (ice−methanol bath) slurry of ethyl 2-(3-(*N*-tosylindolyl)acrylate **9** (20.00 g, 54.14 mmol) in CH_2Cl_2 (100 mL), DIBAL (74.23 g, 130.5 mmol, 25% w/w in toluene) was slowly added via an addition funnel. Once the reaction was complete, the mixture was slowly quenched with Rochelle's Salt, which gave a thick gel. This gel was broken down with slow addition of 5% HCl (aq) (**exothermic!**), and then the mixture was diluted with EtOAc and water and then separated. Following two additional extractions with EtOAc, the combined organics were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated to afford the crude allylic alcohol **10** as an off-white solid (18.49 g, >95%), which was used directly in the next step. To a solution of **10** in CH_2Cl_2 (200 mL, reagent grade) at 0 °C was added Dess−Martin periodinane[22] (25.05 g, 59.08 mmol) portionwise over 10 min. The reaction mixture was stirred at 0 °C for 30 min and another 30 min at RT, then re-cooled to 0 °C, and 100 mL of 15% $Na_2S_2O_3$ (aq) was slowly added. The mixture was diluted with water and CH_2Cl_2 and separated. The aqueous portion was treated with 1 M NaOH (aq) and extracted again with CH_2Cl_2. The combined organic portions were washed with water, $NaHCO_3$ (sat aq), and brine, dried with $MgSO_4$, filtered, and concentrated. Purification by FC followed by trituration in EtOAc/hexanes (1:1) gave enal **2** (12.76 g, 72% over two steps): mp 150−152 °C (hexane trit). ^{1}H NMR: δ 9.65 (d, J = 7.7, 1H), 7.99 (d, J = 8.0, 1H), 7.92 (s, 1H), 7.80 (d, J = 8.2, 2H), 7.77 (d, J = 8.3, 1H), 7.56 (d, J = 16.0, 1H), 7.39 (ddd, J = 8.3, 7.2, 1.0, 1H), 7.34 (ddd, J = 8.0, 7.2, 1.2, 1H), 7.25 (d, J = 8.2, 2H), 6.79 (dd, J = 16.0, 7.7, 1H), 2.35 (s, 3H). ^{13}C NMR: δ 193.4, 145.6, 143.5, 135.4, 134.3, 130.0, 129.3, 128.4, 127.4, 126.9, 125.6, 124.2, 120.5, 117.8, 113.7, 21.7. IR: 1675, 1628, 1447, 1378, 1176 cm^{-1}. MS *m*/*z* (relative intensity): 325 (M^+, 47), 170 (100), 115 (20), 91 (33). HRMS calcd for $C_{18}H_{15}NO_3S$: 325.0773; found: 325.0780.

3-[(2*S*,3*R*,4*R*)-4,6-Dimethyl-3-formylbicyclo[2.2.2]oct-5-en-2-yl]-1-tosyl-1*H*-indole (*endo*-6). To a solution of **2** (5.82 g, 17.9 mmol) in DMF, MeOH, and water (38, 38, and 4 mL, respectively) was added organocatalyst **4**[7] (1.808 g, 7.10 mmol). After the solution was stirred for 20 min at RT, 1,3-dimethyl-1,3-cyclohexadiene **3**[5] (5.6 mL, ∼45%, 25.0 mmol) was added dropwise. The reaction was stirred for 36 h, then diluted with water and MTBE and separated. The aqueous portion was extracted again with MTBE, and the organic portions were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was treated with 5% HCl (aq) THF (1:1) for 12 h. The reaction was then diluted with MTBE and water. The aqueous portion was extracted again with MTBE, and the organics were combined, washed with $NaHSO_3$ (saturated aq), water, and brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by FC (EtOAc/hexanes, 1:9) afforded **6** as an 85:15 mixture (70% de) of endo:exo isomers (2.39 g, 35%, 70% de, 93% ee for endo, 92% ee for exo by HPLC) as a yellow gum: mp (racemate) 192−194 °C (CH_2Cl_2/hexanes). ^{1}H NMR: δ 9.38 (d, J = 4.3, 1H), 7.94 (d, J = 8.2, 1H), 7.71 (d, J = 8.4, 2H), 7.47 (d, J = 7.8, 1H), 7.43 (s, 1H), 7.29 (t, J = 8.2, 7.2, 1H), 7.22 (obscured t, 1H), 7.19 (d, J = 8.4, 2H), 5.61 (s, 1H), 3.18 (br d, J = 6.1, 1H), 2.52 (br s, 1H), 2.49 (dd, J = 6.1, 4.3, 1H), 2.31 (s, 3H), 1.93 (d, J = 1.4, 3H), 1.53 (m, 2H), 1.27 (s, 3H), 1.21−1.07 (m, 2H). ^{13}C NMR: δ 203.4, 144.7, 144.2, 135.4, 134.8, 130.4, 129.7, 127.9, 126.6, 124.8, 123.2, 123.0, 122.8, 119.2, 113.8, 61.2, 40.2, 37.5, 35.8, 35.5, 23.4, 21.7, 20.3, 20.1. IR: 1718, 1448, 1369, 1175, 1135 cm^{-1}; MS *m*/*z* (relative intensity): 433 (M^+, 22), 326 (29), 170 (29), 108 (100). HRMS calcd for $C_{26}H_{27}NO_3S$: 433.1712; found: 433.1706.

Methyl (1*S*,2*R*,3*R*)-1,5-Dimethyl-3-(1-tosyl-1*H*-indol-3-yl)bicyclo-[2.2.2]oct-5-en-2-ylcarbamate (13). To a solution of **6** (2.39 g, 5.51 mmol) in *t*-BuOH (85 mL) and 2-methyl-2-butene (12 mL) was slowly added (over 30 min) a solution of $NaClO_2$ (5.50 g, 48.7 mmol) and NaH_2PO_4·H_2O (5.31 g, 38.5 mmol) in water (80 mL). After the addition was complete, the mixture was stirred at RT for 1 h and then concentrated. The aqueous residue was diluted with CH_2Cl_2 and water and separated. Following further extraction (CH_2Cl_2 × 2), the combined organic portions were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude residue by FC (EtOAc/hexanes, 3:7) gave the corresponding acid (2.11 g, 85%, 73% de by ^{1}H NMR) as a white solid: mp 122−124 °C dec (hex trit). ^{1}H NMR: δ 7.93 (d, J = 8.4, 1H), 7.70 (d, J = 8.2, 2H), 7.46 (s, 1H), 7.44 (d, J = 8.0, 1H), 7.27 (t, J = 7.4, 1H), 7.18 (t, J = 7.9, 1H), 7.14 (d, J = 8.2, 2H), 5.57 (s, 1H), 3.17 (d, J = 7.5, 1H), 2.61 (d, J = 7.5, 1H), 2.42 (br s, 1H), 2.32 (br s, 1H), 2.25 (s, 3H), 1.91 (d, J = 1.0, 3H), 1.52 (d, J = 10.0, 2H), 1.24 (s, 3H), 1.15 (m, 2H). ^{13}C NMR: δ 180.3, 144.6, 142.6, 135.5, 134.7, 130.5, 129.6, 128.8, 126.9, 124.7, 123.5, 123.0, 122.6, 119.3, 113.8, 53.4, 40.7, 40.4, 37.8, 36.5, 23.3, 21.6, 20.2, 19.6. IR: 1701, 1449, 1174 cm^{-1}; MS *m*/*z* (relative intensity): 449 (M^+, 13), 341 (41), 108 (100). HRMS calcd for $C_{26}H_{27}NO_4S$: 449.1661; found: 499.1659. To the above acid (2.19 g, 4.87 mmol) dissolved in toluene (20 mL) were added TEA (0.70 mL, 5.51 mmol) and diphenylphosphoryl azide (1.1 mL, 5.10 mmol). The mixture was heated at reflux for 30 min, and then MeOH (10 mL, dried over 4 Å molecular sieves) was added and heating continued for another 30 min. The reaction was then transferred to a sealed tube (rinsing the initial reaction flask with 5 mL of MeOH) and heated at 150 °C for 17 h. After cooling to RT, the mixture was diluted with EtOAc and $NaHCO_3$ (saturated aq). The layers were separated, and the aqueous portion was extracted again with EtOAc. The combined organic portions were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude residue by FC (EtOAc/hexanes, 3:7) gave **13** (1.84 g, 79%, 70% de by ^{1}H NMR) as a white solid: mp 140−142 °C dec (hex trit). ^{1}H NMR (600 MHz, major isomer): δ 7.96 (d, J = 8.2, 1H), 7.76 (d, J = 7.9, 2H), 7.63 (s, 1H), 7.40 (d, J = 7.6, 1H), 7.27 (t, J = 7.6, 1H), 7.19 (t, J = 7.6, 1H), 7.16 (d, J = 7.9, 2H), 5.50 (s, 1H), 4.40 (d, J = 10.1, 1H), 3.91 (dd, J = 10.1, 5.0, 1H), 3.57 (s, 3H), 2.56 (s, 1H), 2.41 (s, 1H), 2.29 (s, 3H), 1.89 (s, 3H), 1.54 (m, 1H), 1.43 (m, 1H), 1.23 (m, 1H), 1.17 (s, 3H), 1.02 (m, 1H). ^{13}C NMR (150 MHz): δ 156.7, 145.3, 144.5, 135.8, 134.9, 130.9, 129.7, 127.4, 126.9, 124.6, 123.4, 123.3, 123.0, 119.2, 114.0, 59.1, 51.8, 46.5, 40.7, 39.1, 33.2, 21.8, 21.5, 20.1, 20.1. IR: 3395, 1720, 1517, 1448, 1369, 1174 cm^{-1}. MS *m*/*z* (relative intensity): 478 (M^+, 8), 370 (100), 215 (68), 91 (12). HRMS calcd for $C_{27}H_{30}N_2O_4S$: 478.1926; found: 478.1921.

(1*S*,2*S*,3*R*,5*R*,6*R*)-1,3-Dimethyl-5-(1-tosyl-1*H*-indol-3-yl)-6-[(methoxycarbonyl)amino]bicyclo[2.2.2]octane-2,3-diol (14a) and (1*S*,2*R*,3*S*,5*R*,6*R*)-1,3-dimethyl-5-(1-tosyl-1*H*-indol-3-yl)-6-nitrobicyclo-[2.2.2]octane-2,3-diol (14b). To a RT solution of **13** (401 mg, 0.838 mmol) in THF (15 mL) and *t*-BuOH (15 mL) was added a solution of a homogenized (mortar and pestle) K_3FeCN_6 (0.829 g, 2.52 mmol), K_2CO_3 (0.360 g, 2.53 mmol), methane sulfonamide (80 mg, 0.845 mmol) in water (25 mL), DABCO (30 mg, 0.26 mmol), and K_2OsO_2-

(22) Dess−Martin periodinane was prepared according to literature procedure: Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J.; Minbiole, K. P.; Smith, A. B. *Org. Synth.* **1999**, *77*, 141.

$(OH)_4$ (25 mg, 0.068 mmol). After 24 h, more $K_2OsO_2(OH)_4$ (~10 mg) was added and stirring continued for another 16 h, at which time Na_2SO_3 (1.3 g) was added, and the mixture was diluted with water and MTBE (50 mL each). Following separation, the aqueous portion was extracted again, and the combined organic portions were washed with brine and concentrated. The residue was dissolved in EtOH (75 mL) and water (10 mL), treated with Na_2SO_3 (4 g), and heated at reflux for 1.5 h. After cooling to RT, the black precipitate was removed by filtering through Celite (washing with EtOH). The filtrate was concentrated, diluted with MTBE and water, and separated. Following separation, the aqueous portion was extracted again, and the combined organic portions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude residue by FC (EtOAc/hexanes, 1:1) gave **14a** (214 mg, 50%) and a mixture of **14a** and **14b** (109 mg, 25%, ~1:4). Subsequent FC (EtOAc/hexanes, 1:1) gave a pure sample of **14b** (19 mg) as a colorless film which was recrystallized from EtOAc/hexanes. For **14a**: $[\alpha]^{25}_D$ +46° (*c* 6.0, THF). ^{1}H NMR (600 MHz): δ 7.96 (d, J = 7.9, 1H), 7.78 (app d, J = 10.0, 3H), 7.50 (d, J = 7.6, 1H), 7.26 (d, J = 7.3, 1H), 7.15 (m, 3H), 5.51 (d, J = 10.0, 1H), 3.95 (app t, J = 10.0, 9.0, 1H), 3.59 (s, 3H), 3.47 (d, J = 9.0, 1H), 3.29 (s, 1H), 3.27 (s, 1H), 2.70 (s, 1H), 2.28 (s, 3H), 1.74 (s, 1H), 1.48 (m, 2H), 1.38 (s, 3H), 1.32 (m, 2H), 1.08 (s, 3H). ^{13}C NMR (150 MHz): δ 157.0, 144.4, 135.8, 135.1, 131.1, 129.6, 127.1, 124.5, 124.0, 122.9, 119.7, 113.8, 80.7, 71.1, 54.2, 51.8, 43.3, 38.5, 38.1, 30.1, 28.9, 21.5, 21.2, 17.0. IR: 3416, 1696, 1517, 1368, 1173 cm^{-1}. MS *m*/*z* (relative intensity): 512 (M^+, 5), 437 (42), 363 (100), 208 (27). HRMS calcd for $C_{27}H_{32}N_2O_6S$: 512.1981; found: 512.1976. For **14b**: mp 189−190 °C (EtOAc/hexanes). $[\alpha]^{25}_D$ +119° (*c* 1.5, $CHCl_3$). ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.73 (d, J = 8.2, 1H), 7.76 (d, J = 8.2, 2H), 7.63 (s, 1H), 7.36 (t, J = 8.2, 1H), 7.31 (d, J = 8.2, 2H), 7.28 (m, 1H), 7.20 (d, J = 9.7, 1H), 4.57 (d, J = 6.6, 1H), 4.34 (s, 1H), 3.86 (app t, J = 9.7, 9.4, 1H), 3.57 (s, 3H), 3.36 (d, J = 6.6, 1H), 2.96 (d, J = 9.4, 1H), 2.29 (s, 3H), 1.68 (m, 1H), 1.58 (m, 2H), 1.44 (s, 3H), 1.19 (m, 1H), 1.07 (t, 11.3, 2H), 0.77 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 157.2, 145.3, 135.2, 133.8, 130.6, 130.0, 126.6, 125.0, 123.9, 123.6, 123.2, 119.4, 113.7, 70.9, 70.4, 55.5, 51.3, 42.6, 38.4, 37.5, 26.4, 25.6, 21.0, 19.3, 16.4. IR: 3393, 1699, 1600, 1493, 1368, 1173 cm^{-1}. MS *m*/*z* (relative intensity): 512 (M^+, 15), 437 (34), 363 (100), 209 (43), 91 (32). HRMS calcd for $C_{27}H_{32}N_2O_6S$: 512.1981; found: 512.1986.

(1*S*,2*R*,3*R*,4*S*)-4-Acetyl-1-methyl-3-[1-tosyl-1*H*-indol-3-yl]-2-(methoxycarbonyl)aminocyclohexanecarbaldehyde (15). A RT solution of **14** (154 mg, 0.299 mmol) in CH_2Cl_2 (3 mL) was treated with $NaIO_4$/SiO_2[17] (852 mg, 0.649 mmol). After 2 h, the reaction mixture was filtered. The solids were washed with CH_2Cl_2, and then the filtrate was concentrated to afford **15** (151 mg, >95%) as a colorless film. $[\alpha]^{25}_D$ +45° (*c* 9.3, $CHCl_3$). ^{1}H NMR (90 °C, DMSO-d_6): δ 9.79 (s, 1H), 7.77 (d, J = 8.0, 1H), 7.67 (app d, J = 7.0, 3H), 7.59 (s, 1H), 7.31 (d, J = 7.6, 2H), 7.23 (m, 2H), 6.38 (br s, 1H), 3.99 (t, J = 10.4, 1H), 3.28 (m, 2H), 3.11 (s, 3H), 2.30 (s, 3H), 2.12 (d, J = 13.9, 1H), 1.77 (d, J = 13.9, 1H), 1.69 (t, J = 13.9, 1H), 1.60 (s, 3H), 1.36 (m, 1H), 1.08 (s, 3H). ^{13}C NMR (90 °C, DMSO-d_6, two atropisomers): δ 208.4, 206.4, 206.3, 155.9, 144.5, 134.3, 134.0, 129.5, 129.4, 125.9, 125.8, 123.9, 123.8, 122.2, 120.2, 112.4, 58.6 (br), 54.9 (br), 50.6, 50.4, 32.3, 28.6, 28.6, 25.0, 24.9, 20.6, 20.6, 20.4, 20.3. IR: 3440, 1714, 1450, 1365, 1174 cm^{-1}. MS *m*/*z* (relative intensity): 510 (M^+, 95), 435 (10), 406 (100), 364 (16), 252 (29). HRMS calcd for $C_{27}H_{30}N_2O_6S$: 510.1825; found: 510.1822.

3-[(1*R*,2*R*,3*R*,6*S*)-6-Acetyl-3-methyl-2-(methoxycarbonyl)amino-3-vinylcyclohexyl]-1-tosyl-1*H*-indole (16). To a RT suspension of methyltriphenylphosphonium iodide (287 mg, 0.71 mmol) in THF (1 mL) was added potassium *tert*-butoxide (65 mg, 0.579 mmol). After being stirred for 5 min, the ylide slurry was added to a solution of **15** (37 mg, 73 μmol) in THF (1 mL) via syringe. The reaction was diluted with water and MTBE after 1 h and separated. After extracting again with MTBE, the combined organic portions were washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by FC (EtOAc/hexanes, 1:1) to give **16** (32 mg, 86%). $[\alpha]^{25}_D$ +30° (*c* 1.4, $CHCl_3$). ^{1}H NMR (major atropisomer): δ 7.83 (br s, 1H), 7.70 (br s, 2H), 7.60−7.41 (m, 3H), 7.23−1.17 (m, 3H), 6.22 (dd, J = 17.2, 10.9, 1H), 5.31 (d, J = 10.9, 1H), 5.17 (d, J = 17.2, 1H), 4.28 (d, J = 10.5, 1H), 2.28 (s, 3H), 2.96 (br s, 1H), 2.28 (s, 3H), 1.90−1.52 (m, 4H), 1.23 (s, 3H), 1.10 (s, 3H). IR: 3411, 1711, 1449, 1369, 1174 cm^{-1}. MS *m*/*z* (relative intensity): 508 (M^+, 68), 433 (100), 335 (62). HRMS calcd for $C_{28}H_{32}N_2O_5S$: 508.2035; found: 508.2032.

3-[(1*R*,2*R*,3*R*,6*S*)-6-Isopropenyl-3-methyl-2-(methoxycarbonyl)-amino-3-vinylcyclohexyl]-1-tosyl-1*H*-indole (17). A solution of **16** (32 mg, 0.063 mmol) in toluene (1 mL) was added dropwise to a suspension of methyltriphenylphosphonium iodide (199 mg, 0.492 mmol) and potassium *tert*-butoxide (65 mg, 0.579 mmol) in toluene (1 mL) at 55−60 °C. The flask was rinsed with toluene (0.5 mL) and this was also added. After 8 h, the reaction was cooled to RT, diluted with water and MTBE, and separated. After extraction again with MTBE, the combined organics were washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by FC (EtOAc/hexanes, 1:1) to afford **17** (20 mg, 54% over two steps). $[\alpha]^{25}_D$ +34° (*c* 4.0, $CHCl_3$). mp 80−82 °C ($CHCl_3$). ^{1}H NMR (51 °C): δ 7.83 (d, J = 7.8, 1H), 7.66 (br d, 2H), 7.38 (br d, 1H), 7.17 (m, 4H), 6.21 (br t, 1H), 5.32 (d, J = 10.9, 1H), 5.19 (d, J = 17.4, 1H), 4.58 (br s, 1H), 4.44 (br s, 1H), 4.23 (br d, 2H), 3.68 (br t, 1H), 3.01 (br s, 3H), 2.86 (br s, 1H), 2.54 (br s, 1H), 2.30 (s, 3H), 1.89−1.65 (m, 4H), 1.40 (s, 3H), 1.11 (s, 3H). IR: 3400, 1720, 1515, 1449, 1366, 1174 cm^{-1}. MS *m*/*z* (relative intensity): 506 (M^+, 100), 431 (16), 351 (23), 276 (47), 215 (52). HRMS calcd for $C_{29}H_{34}N_2O_4S$: 506.2239; found: 506.2238.

(+)-Hapalindole Q (1). A solution of bis-olefin **17** (64 mg, 0.13 mmol) in THF (5 mL) was treated with TBAF (2.0 mL, 1.0 M in THF, 2 mmol) and heated at reflux for 16 h. After cooling to RT, the mixture was diluted with water and EtOAc and separated. The aqueous portion was extracted again (2×), and the combined organic portions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C, and then 1,1′-thiocarbonyldiimidazole (TCDI) (24 mg, 0.13 mmol) was added. The ice bath was removed, and the reaction was stirred for 20 h, concentrated, and purified by FC (CH_2Cl_2/hexanes, 4:6) to give **1** (12 mg, 29% over two steps). Analysis by HPLC (Chiracel OD-H, 250 × 4.6 mm^2, Daicel Chemical Industries; 98:2, hexane/*i*-PrOH at 1.0 mL/min; 254 nm; (−)-**1** r_t = 14.7, (+)-**1** r_t = 17.1) indicated 93% ee. The pale yellow film had data consistent with that reported previously.[1,3e] $[\alpha]^{25}_D$ +34° (*c* 0.9, CH_2Cl_2).

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Supporting Information Available: ^{1}H or ^{13}C NMR spectra, or both, for compounds **2**, **6**, **13**, **14**, **15**, **16**, **17**, and hapalindole Q. HPLC traces for **6** and (+)-hapalindole Q **1** (PDF). X-ray data (CIF) for *endo*-**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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