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Highly Selective Diels–Alder Reactions of Dienophiles with 1,3-Cyclohexadiene Mediated by $Yb(OTf)_3 \cdot 2H_2O$ and Ultrahigh Pressures

Aaron C. Kinsman and Michael A. Kerr*

Department of Chemistry, University of Western Ontario,
London, Ontario N6A 5B7, Canada

makerr@julian.uwo.ca

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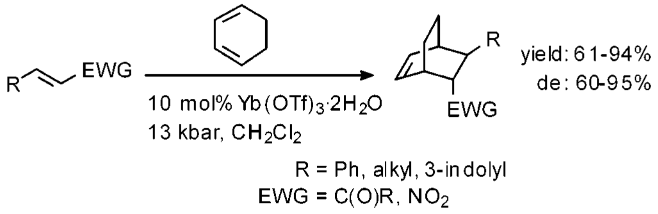
ABSTRACT



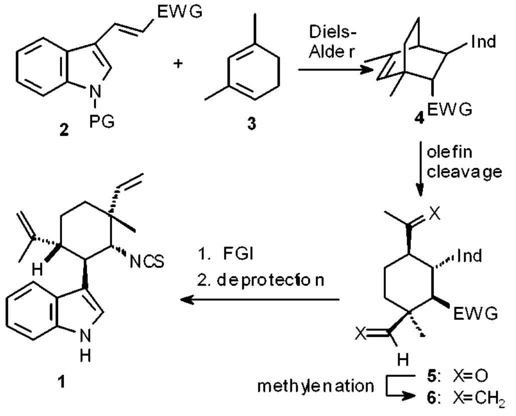
Ultrahigh pressures and catalytic $Yb(OTf)_3 \cdot 2H_2O$ were found to mediate Diels–Alder reactions of various electron-deficient dienophiles with 1,3-cyclohexadiene to produce *endo*-bicyclo[2.2.2]oct-2-enes in moderate to excellent yield and selectivity. The proposed total synthesis of hapalindole Q based on bicyclo[2.2.2]oct-2-ene construction by Diels–Alder reaction and subsequent olefin cleavage is outlined. Preliminary results demonstrating the viability of this strategy are presented.

The total synthesis of the hapalindoles is currently underway in our laboratory. This group of 20 structurally related alkaloid natural products was isolated from the terrestrial blue-green algae *Hapalosiphon fontinalis*, an organism found to exhibit antibacterial, antimycotic, and antifungal activity.[1]

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

The importance of the key cycloaddition step prompted us to undertake a study of the reaction of 1,3-cyclohexadiene

Scheme 1. Proposed Hapalindole Q Synthesis



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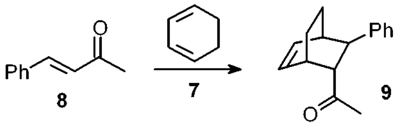
[1] (a) Moore, R. E.; Cheuk, C.; Yang, X.-Q.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036. (b) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*,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

[2] Hapalindole Q has been synthesized previously, see: Vaillancourt, V. Albizati, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 3499.

10.1021/ol0065773 CCC: $19.00

Table 1. Diels−Alder Reactions of Benzylidene Acetone with 1,3-Cyclohexadiene



entry	time /d	eq diene	catalyst[a]	mol% of cat.	pressure /bar	solvent[b]	temp. /°C	yield **9**[c] /%	de[d] /%	recovered **8** /%
1	4	4.0	-	-	sealed tube	-	180-220	75	25	-
2	2	4.0	-	-	sealed tube	-	155-160	59[e]	26	41[e]
3	**2**	**3.1**	**$Yb(OTf)_3$**	**10**	**13 000**	**CH_2Cl_2**	**Ambient**	**96**	**>95**	**<1**
4	4	3.0	-	-	13 000	CH_2Cl_2	Ambient	<5[e]	-	>95
5	3	3.0	$Yb(OTf)_3$	10	1	CH_2Cl_2	Ambient	NR[e]	-	>95
6	2	6.0	$Yb(OTf)_3$	10	1	PhMe	135-145	<30[f]	>95	<8[f]
7	3	3.0	$Yb(OTf)_3$	5	13 000	CH_2Cl_2	Ambient	92	>95	-
8	5	3.1	$Yb(OTf)_3$	**1**	13 000	CH_2Cl_2	Ambient	35[e]	76	65[e]
9	3	**1.1**	$Yb(OTf)_3$	10	13 000	CH_2Cl_2	Ambient	87[e]	>95	13[e]
10	4	3.1	$Sc(OTf)_3$	10	1	CH_2Cl_2	Ambient	**54**	>95	**12**
11	4	3.0	$Cu(OTf)_2$	10	1	CH_2Cl_2	Ambient	<49[f]	>95	-
12	3	3.0	$Sc(OTf)_3$	10	13 000	CH_2Cl_2	Ambient	<56[f]	>95	-
13	3	3.0	$Cu(OTf)_2$	10	13 000	CH_2Cl_2	Ambient	<36[f]	>95	-
14[g]	0.5	3.1	$BF_3{\cdot}Et_2O$	110	1	CH_2Cl_2	-78 → RT	11	>95	30
15[g]	0.5	3.1	$SnCl_4$	110	1	CH_2Cl_2	-78 → RT	15	90	32

[a] $Yb(OTf)_3$ is a dihydrate. [b] Toluene solution is 0.4 M. DCM solutions are 1.0 M. [c] Combined isolated yields of diastereomers. [d] Determined by ^1H NMR of mixture of diastereomers or from isolated yields. [e] Conversion: determined by ^1H NMR of crude reaction mixture following silica gel filtration and concentration. [f] Isolated compound contains intractable polymeric material. [g] Concentration of **8** is 0.1 M.

7 with electron-deficient dienephiles. The antidepressant and CNS stimulation activity[3] displayed by bicyclo[2.2.2]oct-2-ene derivatives provided further impetus for the investigation presented herein.

In the course of surveying the literature, it became clear that optimizing the Diels−Alder reaction of **7** with dienophiles of type **2** would not be a trivial task; what appears to be a textbook cycloaddition is, in practice, very difficult. For example, thermal reaction of **7** with β-nitrostyrene,[4] *trans*-cinnimaldehyde,[3,5] or *cis*-ethyl cinnamate[6] reportedly gives only low to moderate yields of the corresponding cycloadducts (20−25%, 22−54%, and 38%, respectively). Reaction of benzylidene acetone **8** with cyclopentadiene occurs in marginally better yield (35−64%),[7] and so the reaction of **7** with **8** was chosen as an initial model for our system.

The results of the optimization study are summarized in Table 1. Thermal conditions were found to give acceptable yields of cycloadducts **9** (75%) but poor selectivity (entries 1 and 2, ∼25% de). It is known that in the Diels−Alder reaction, enhanced diastereoselectivity and higher yields are achieved by using Lewis acid catalysis,[8] high pressure (HP), or these conditions in concert.[9] Indeed, employing hyperbaric conditions and the mild Lewis acid $Yb(OTf)_3{\cdot}2H_2O$ we observed remarkably superior selectivity (>95% de) and yield (96%, entry 3).[10] In addition, reaction times were reduced compared with the thermal conditions (2 vs 4 d). It was found that the ytterbium catalyst is essential for the reaction at high pressure; in its absence <5% conversion was observed (entry 4). Conversely, reaction at ambient pressure and temperature with 10 mol % catalyst produced no reaction, illustrating the necessity of the hyperbaric condition (entry 5). Heating **8** and **7** in toluene with 10 mol % $Yb(OTf)_3{\cdot}2H_2O$ led to significant reduction in yield and extensive polymerization (entry 6).

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(3) Cashin, C. H.; Fairhurst, J.; Horwell, D, C.; Pullar, I. A.; Sutton, S.; Timms, G. H.; Wildsmith, E.; Wright, F. *Eur. J. Med. Chem.* **1978**, *13*, 495.

(4) Allen, C. F. H.; Bell, A.; Gates, J. W., Jr. *J. Org. Chem.* **1943**, *8*, 373. Allen, C. F. H.; Bell, A. *J. Am. Chem. Soc.* **1939**, *61*, 521.

(5) Sopov, N. P.; Kovner, M. L. *J. Gen. Chem. USSR* **1958**, *28*, 2184.

(6) Akbulut, N.; Hartsough, D.; Kim, J.-I.; Schuster, G. B. *J. Org. Chem.* **1989**, *54*, 2549.

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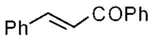
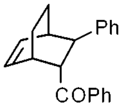
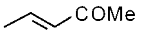
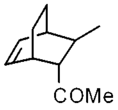
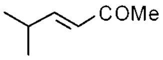
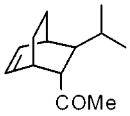
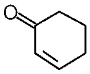
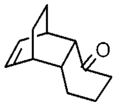
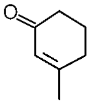
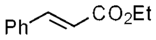
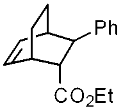
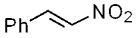
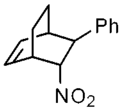
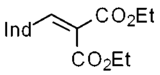
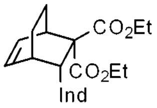
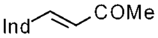
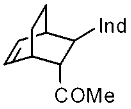
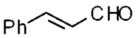
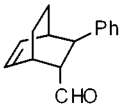
(8) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: New York, 1990. Oppolzer, W. In *Comprehesive Organic Synthesis*; Trost, M. B., Fleming, I., Paquette, L. A., Eds.; Pergamon: 1991, New York; Vol 5, p 315.

(9) Klärner, F.-G.; Diedrich, M. K.; Wigger, A. E. In *Chemistry Under Extreme or Non-Classical Conditions*; van Eldik, R., Hubbard, C. D., Eds.; Wiley: New York, 1997; Chapter 3. Jurczak, J.; Gryko, D. T. In *Chemistry Under Extreme or Non-Classical Conditions*; van Eldik, R., Hubbard, C. D., Eds.; Wiley: New York, 1997; Chapter 4. Isaacs, N. S. In *High-Pressure Techniques in Chemistry and Physics*; Harwood, L. M., Moody, C. J., Eds.; Oxford: New York, 1997; Chapter 7. Ibata, T. In *Organic Synthesis at High Pressures*; Matsumoto, K., Acheson, R. M., Eds.; Wiley: Toronto, 1991; Chapter 9.

(10) The stereochemistry of the major product was assigned as *endo* on the basis of ^1H NMR, ^{13}C NMR, gCOSY, gHSQC, gHMBC, and NOESY experiments.

Table 2. Diels–Alder Reactions of Various Dienophiles with 1,3-Cyclohexadiene

entry	dienophile	**10**	time /d	eq diene	conditions[a]	temp. /°C	major cycloadduct **11**	yield[b] /%	de[c] /%
1		a	9	3.0	HP	ambient		94	90
2		b	7	2.5	HP	ambient		68[d]	87
3			3	2.5	Δ (neat)	180-195		58	18
4		c	7	2.5	HP	ambient		67	88
5		d	7	3.0	HP	ambient		66	>95
6			1	1.0	Δ (neat)	170-175		6[e]	>95
7		e	4	3.0	HP	ambient	-	NR[f,g]	-
8		f	4	3	HP	ambient		<5[g]	-
9		g	3	3.1	HP	ambient		60	92
10			3	3.0	HP(no cat.)	ambient		83	92
11			3	5.2	Δ (neat)	180-185		68[h]	74
12		h[i]	7	1.2	HP	ambient		79	60
13			3	3.0	HP(no cat.)	ambient		NR[f,g]	-
14			3	40.5	Δ (neat)	145-165		trace[f,g]	-
15		i[j]	5	3.0	HP	ambient		78	>95
16		j	4	3.0	HP	ambient		-[k]	-
17			10	3.0	HP(no cat.)[l]	ambient		13	60
18			6	5.2	Δ (PhMe)	180-220		22-54[m]	-

[a] HP: 1.0 M **10** in CH_2Cl_2, 13 kbar, 10 mol% $Yb(OTf)_3 \cdot 2H_2O$; Δ: Sealed tube or autoclave, (solvent).
[b] Combined yield of diastereomers. [c] Determined by ^1H NMR of mixtures of diastereomers or from isolated yields. [d] Yield following chromatography and distillation. [e] Ref. 14. [f] Unreacted **10** was recovered.
[g] Conversion: determined by ^1H NMR of crude reaction mixture following silica gel filtration and concentration.
[h] Yield reported in ref. 3 is 20-25%. No de is given. [i] Ind = 3-(*N*-tosylindoyl)-, concentration of 10h = 0.2 M.
[j] Concentration of 10i = 0.5 M. [k] Intractable mixture. [l] Concentration = 2 M. [m] Ref. 4.

Under the hyperbaric conditions, the catalyst loading could be reduced to 5 mol % without significant effect on the yield or selectivity (entry 7). However, when it was reduced further to 1 mol %, the conversion was low (35% after 5 days) and the selectivity was reduced (76% de, entry 8). If a stoichiometric proportion of cyclohexadiene was used instead of a 3-fold excess, the reaction rate was somewhat retarded (86% conversion after 3 days, entry 9).

Use of $Sc(OTf)_3$ or $Cu(OTf)_2$, either at high or ambient pressure, led to polymerization and lower yields (<60%), but selectivity remained high (>90% de, entries 10–13). The greater reactivity of $Sc(OTf)_3$ compared to $Yb(OTf)_3 \cdot 2H_2O$ in the Diels–Alder reaction has been observed previously.[11]

Conventional Lewis acid conditions were then employed for comparison. At −78 °C, both $BF_3 \cdot Et_2O$ (entry 14) and $SnCl_4$ (entry 15) resulted in poor yields (<20%) and extensive polymerization. Several groups have achieved high yields (>90%) in the Lewis acid catalyzed reaction of cyclohexadiene with α,β-unsaturated esters, ketones, and aldehydes.[12] This suggests that the origin of the polymerization in the current case may be the benzylidene acetone **8**. Furthermore, in the presence of Lewis acids, reaction of

8 with other dienes affords only low to moderate yields (30–57%) of cycloadducts.[13]

The optimized conditions[14] were applied to a number of other substrates to determine the scope of the reaction (Table 2). Results of thermal reaction conditions are provided for comparison in some cases.

The yields range from good to excellent, and generally the selectivity is high. In the highest yielding case, chalcone **10a** underwent Diels–Alder reaction to give cycloadduct **11a** in 94% yield and 90% de (entry 1).[10]

The method was found to be effective for enones **10b–d** (entries 2, 4, and 5), but was unsuccessful on hindered enone **10e** (entry 7) and *trans*-ethyl cinnamate **10f** (entry 8). In the case of cyclohexenone **10d**, thermal conditions[15] are reported to afford only 6% yield of **11d**, while the current method provides a yield (66%, entry 5) comparable to that of conventional Lewis acid catalysis (65–80% with $AlCl_3$).[16] With pentenone **10b**, thermal conditions allow good yield of cycloadducts **11b** (58%, entry 3), but the selectivity is poor (18% de) relative to those achieved using HP and ytterbium catalysis.

The improved electron-withdrawing capacity of the nitro group permitted cycloaddition of β-nitrostyrene **10g** in the absence of catalyst (compare entries 9 and 10) and thus a cleaner reaction and improved yield of **11g**. The hindered indolylidene diethylmalonate **10h** gave a 79% yield of cycloadduct **11h**, but the selectivity was deemed unacceptably low for use in the synthesis of hapalindole Q (60% de, entry 12). It was demonstrated that the catalyst was essential for the success of this reaction (entry 13). An encouraging result for the synthesis project was achieved when reaction of indolylidene acetone **10i** afforded cycloadduct **11i** in 78% yield and >95% de (entry 15).[17]

Attempted cycloadditions between **7** and cinnamaldehyde **10j** at HP with and without Yb catalysis did not produce useful yields of desired cycloadducts (entries 16 and 17).

Unfortunately, 1,3-dimethyl-1,3-cyclohexadiene **3** was found to polymerize in the presence of the Yb catalyst at HP; however, it was stable in the absence of the Lewis acid. Since it has been demonstrated that nitrodienophiles undergo HP-mediated cycloaddition without activation, the reaction of **3** with such dienophiles should be feasible. In point of fact, **3** reacted (13 kbar, 7 d, CH_2Cl_2) with **2** (Scheme 1; PG = Ts, EWG = NO_2) to give adduct **4** in 25% unoptimized yield (86% de).[18]

In summary, a high yielding method for the selective construction of *endo*-bicyclo[2.2.2]oct-2-ene systems via Diels–Alder reaction has been developed. The reaction is facilitated by the combined effects of high pressure and $Yb(OTf)_3{\cdot}2H_2O$ catalysis and is particularly useful for electron-deficient ketodienophiles that may be prone to polymerization.

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Supporting Information Available: Full experimental procedures and spectroscopic data for compounds ***endo*-9**, ***exo*-9**, **10h**, **10i**, ***endo*-11a–c**, ***exo*-11a–b**, and **11g**, **11h**, ***endo*-11i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755.

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[13] Minami, T.; Chikugo, T.; Hanamoto, T. *J. Org. Chem.* **1986**, *51*, 2210. Shibata, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1999**, 313.

[14] **General Experimental Procedure.** In an argon-purged Teflon tube, 1,3-cyclohexadiene (~3 equiv) was added to a ~1 M solution of dieneophile (1~2 mmol) in CH_2Cl_2. Following addition of $Yb(OTf)_3{\cdot}2H_2O$ (~10 mol %), the tube was sealed and placed in a high-pressure reactor at ~13 kbar for the time indicated in Table 2. After depressurization, the reaction mixture was concentrated in vacuo and purified by flash chromatography.

[15] Nakazaki, M.; Naemura, K.; Kondo, Y.; Nakahara, S. Hashimoto, M. *J. Org. Chem.* **1980**, *45*, 4440. Hirao, K.; Unno, S.; Yonemitsu, O. *Chem. Commun.* **1977**, 577.

[16] Fringuelli, F.; Guo, M.; Minuti, L.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1989**, *54*, 710. Morlender-Vais, N.; Mandelbaum, A. *J. Mass Spectrom.* **1997**, *32*, 1124.

[17] See Supporting Information for X-ray structure and crystallographic data.

[18] Details of these results will be reported in due course.