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Diels-Alder Reactions of 5,6-Dihydro-2(1*H*)-pyridones. Preparation of Partially Reduced *cis*-Isoquinolones and *cis*-3,4-Disubstituted Piperidines

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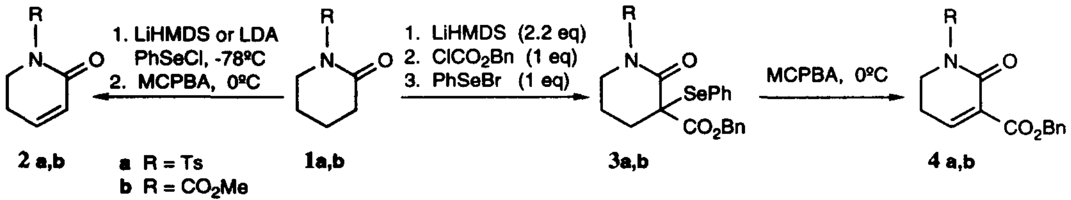
***Abstract*:** The Diels-Alder reactions of 5,6-dihydro-2(1*H*)-pyridones with a variety of diversely substituted butadienes to give partially reduced isoquinolones is reported. Reductive ozonolysis of the resulting octahydroisoquinolones gave *cis*-3,4-disubstituted piperidines.

Both the reduced isoquinoline ring system and the 3,4-disubstituted piperidine moiety are present in a large number of alkaloids. We present here a common, straightforward synthetic entry to these structural units that involves the Diels-Alder reaction of 5,6-dihydro-2(1*H*)-pyridones as dienophiles[1] with subsequent oxidative cleavage of the resulting partially reduced isoquinolones.

The required dihydropyridones **2a,b** and **4a,b** were prepared from either 1-tosyl-[2] or 1-methoxycarbonyl-2-piperidone,[1a] as outlined in Scheme 1. All of them incorporate an electron-withdrawing group on the piperidine nitrogen because it is known[1a,c] that this kind of substituent increases the reactivity of the carbon-carbon double bond as a dienophile. In dihydropyridones **4** an additional activating benzyloxycarbonyl group has been introduced at the 3 position.[3]

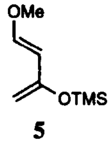
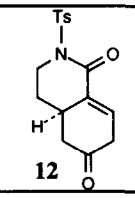
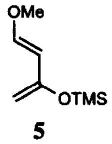
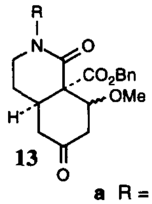
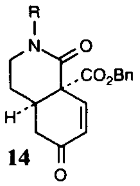
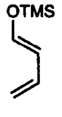
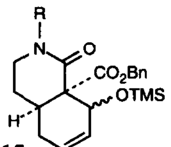
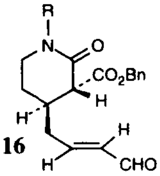
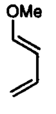
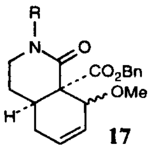
The results of the Diels-Alder reactions between dihydropyridones **2** and **4** and dienes **5-11**, under a variety of experimental conditions, are summarized in Table 1. Thermal induced Diels-Alder reactions of **2** only worked, although in moderate yield, with the *N*-tosyldihydropyridone **2a** and the highly reactive Danishefsky's diene **5** in refluxing *p*-cymene. Treatment of the initially formed adduct with camphorsulfonic acid brought about both the hydrolysis of the silyl enol ether functionality and elimination of methanol to give **12** (entry 1). When using either **2b** or other dienes or solvents with a lower boiling point, the reactants were recovered unchanged.[4] In contrast, 3-(benzyloxycarbonyl)dihydropyridones **4** satisfactorily reacted with dienes **5-11**, both under thermal conditions and when using Lewis-acid catalysis[5] ($ZnBr_2$, $ZnCl_2$, or $EtAlCl_2$). In general, the yields of the Lewis-acid catalyzed reactions were higher. However, with dienes **6**, **7**, and **8** a Michael-type addition of the diene upon the conjugate double bond of the dienophile occurred to some extent (entries 7, 9, 14, and 18) to give the unsaturated aldehydes **16**. As Table 1 indicates, the reaction allows the preparation of a variety of *cis*-octahydroisoquinolones bearing different substituents and functionalization at the carbocyclic ring. On the other hand, the presence of easily removable substituents at the N and C-8a positions makes these azabicyclic derivatives attractive synthons for alkaloid synthesis.

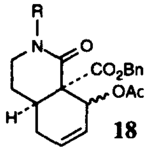
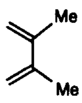
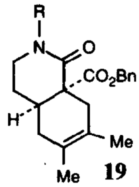
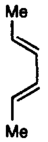
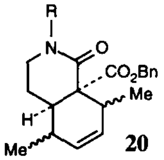
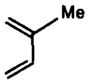
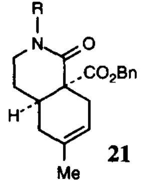
The expected *cis* fusion in the resulting partially reduced isoquinolones was confirmed by ^{1}H-NMR from the *J* values of H-4a, which indicate the existence of only one trans-diaxial coupling. Usually, epimeric



Scheme 1

Table 1. Diels-Alder Reactions of 5,6-Dihydro-2(1*H*)-pyridones[a]

Entry	Dienophile	Diene	Conditions	Products (yield)[b]	
1	**2a**	 **5**	1. *p*-cymene, Δ, 6 h 2. CSA	**12** (34%)	 **12**
2	**2b**		1. *p*-cymene, Δ, 6 h 2. CSA	no reaction	
3	**4a**	 **5**	1. *p*-cymene, Δ, 1 h 2. CSA	**13a** (58%) (*endo*:*exo* = 2:1)	 **13**  **14** **a** R = Ts **b** R = CO_2Me
4	**4a**		1. benzene, Δ, 30 min 2. CSA	**13a** *endo* (41%) **14a** (30%)	
5	**4b**		1. benzene, Δ, 1 h 2. CSA	**13b** *endo* (17%) **14b** (62%)	
6	**4a**	 **6**	1. *p*-cymene, Δ, 2 h 2. CSA	**15a** (28%) (*endo*:*exo* = 3:2)	 **15**  **16** **a** R = Ts **b** R = CO_2Me
7	**4a**		$ZnBr_2$, CH_2Cl_2, r.t., 30 min	**16a** (50%)	
8	**4b**		*p*-cymene, Δ, 2.5 h	**15b** (31%) (*endo*:*exo* = 1:1)	
9	**4b**		$EtAlCl_2$, CH_2Cl_2, 0ºC, 1 h, r.t., 30 min	**16b** (45%)	
11	**4a**	 **7**	*p*-cymene, Δ, 2 h	**17a** (48%) (*endo*:*exo* = 3:2)	 **17** **a** R = Ts **b** R = CO_2Me **c** R = H
12	**4a**		$ZnBr_2$, CH_2Cl_2, r.t., 1 h	**17a** (89%) (*endo*:*exo* = 1:1)	
13	**4b**		*p*-cymene, Δ, 4 h	**17b** (12%) (*endo*:*exo* = 1:1) **17c** *endo*(24%)[c]	
14	**4b**		$ZnBr_2$, CH_2Cl_2, r.t., 7 h	**16b** (34%) **17b** (32%) (*endo*:*exo* = 1:1)	

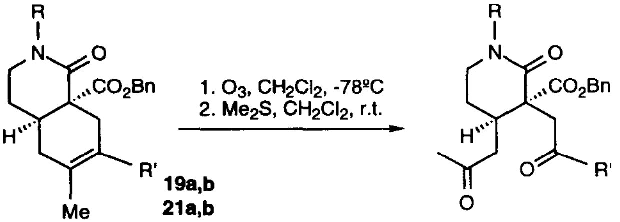
Entry	Dienophile	Diene	Conditions	Products (yield)	
15	**4a**	 **8**	*p*-cymene, Δ, 5 h	**18a** (38%) (*endo*:*exo* = 1:3)	 **18** a R = Ts b R = CO_2Me
16	**4a**		$ZnCl_2$, CH_2Cl_2, r.t., 5 h	**18a** (51%) (*endo*:*exo* = 1:2)	
17	**4b**		$EtAlCl_2$, CH_2Cl_2, 0°C, 1h, r.t., 30 min	**18b** (67%) (*endo*:*exo* = 6:1)	
18	**4b**		$ZnBr_2$, CH_2Cl_2, r.t., 7 h	**18b** (31%) (*endo*:*exo* = 3:2) **16b** (14%)	
19	**4a**	 **9**	*p*-cymene, Δ, 5 h	**19a** (25%)	 **19** a R = Ts b R = CO_2Me
20	**4a**		$ZnBr_2$, CH_2Cl_2, r.t., 2.5 h	**19a** (69%)[d]	
21	**4b**		*p*-cymene, Δ, 4 h	**19b** (11%)	
22	**4b**		$ZnBr_2$, CH_2Cl_2, r.t., 3 h	**19b** (73%)	
23	**4a**	 **10**	$ZnBr_2$, CH_2Cl_2, r.t., 2.5 h	**20a** (70%)[e]	 **20** a R = Ts b R = CO_2Me
24	**4b**		$ZnBr_2$, CH_2Cl_2, r.t., 2 h	**20b**(63%) (1:1)[e]	
25	**4a**	 **11**	$ZnBr_2$, CH_2Cl_2, r.t., 2 h	**21a** (65%)	 **21** a R = Ts b R = CO_2Me
26	**4b**		$ZnBr_2$, CH_2Cl_2, r.t., 2 h	**21b** (67%)	

[a] All compounds gave satisfactory analytical and spectroscopic data. [b] All yields are from material purified by column chromatography. [c] Formed during purification by column chromatography. [d] Similar results were obtained using $ZnCl_2$. [e] Undetermined relative configuration at C-5 and C-8.

mixtures of *endo*/*exo* adducts were obtained. Except in some cases (entries 23 and 24), the relative configuration at C-8 in these isomers was assigned from their NMR data, with the aid of ^1H-^1H decoupling and NOE difference experiments.[6] Diagnostic ^{13}C-NMR signals were those corresponding to C-3, C-4a and C-5 (see Table 2). The assigned relative configurations of ***endo*-17c** were confirmed by X-ray crystallography.

Finally, oxidative cleavage of octahydroisoquinolones **19a,b** and **21a,b** by reductive ozonolysis afforded the respective *cis*-3,4-disubstituted 2-piperidones **22a,b** and **23a,b** (Scheme 2) in excellent yield in most cases. The same reaction from a pure diastereomer of **20a** led to an unstable dialdehyde (nearly quantitative yield) that, on standing, underwent condensation reactions to give a complex mixture.

The Diels–Alder-ozonolysis approach constitutes an efficient and flexible route for the stereocontrolled preparation of highly functionalized 3,4-*cis* disubstituted piperidines.



R = Ts, R' = Me **22a** (91%)
R = CO_2Me, R' = Me **22b** (82%)
R = Ts, R' = H **23a** (92%)
R = CO_2Me, R' = H **23b** (44%)

Scheme 2

Table 2. Significant ^{13}C-NMR Data of Diels-Alder Adducts

	1-C	3-C	4-C	4a-C	5-C	6-C	7-C	8-C	8a-C
***endo*-13a**	169.2	44.5	26.2	36.5	42.3	207.0	41.3	82.5	58.8
***exo*-13a**	166.6	44.1	26.4	31.6	40.4	206.2	42.1	80.6	60.8
***endo*-13b**	169.8	44.6	25.6	36.6	42.5	-	41.3	82.6	59.6
***endo*-15a**	169.4	46.1	23.8	31.7	27.6	124.8	127.0	66.0	60.5
***exo*-15a**	167.3	41.5	26.1	26.2	30.6	124.8	127.0	66.0	61.2
***endo*-15b**	170.1	46.2	23.5	32.1	27.8	124.8	127.2	66.5	60.7
***exo*-15b**	168.1	41.7	25.4	26.3	30.5	127.4	127.6	66.4	61.5
***endo*-17a**	169.3	46.3	24.0	31.7	27.7	123.5	125.8	74.9	59.7
***exo*-17a**	167.5	41.5	26.1	26.7	30.6	123.4	125.7	73.3	60.3
***endo*-17b**	169.1	46.2	23.5	31.9	27.8	123.7	125.9	74.9	60.4
***exo*-17b**	168.0	41.6	25.4	26.7	30.7	123.8	125.9	73.9	60.6
***endo*-17c**	170.6	41.3	23.3	32.0	28.1	124.0	125.9	74.3	57.7
***endo*-18a**	169.0	46.0	24.1	31.8	27.5	122.9	127.8	66.9	59.5
***exo*-18a**	169.3	41.6	25.8	27.2	30.2	123.2	130.5	67.0	59.0
***endo*-18b**	169.1	46.0	23.7	32.2	27.7	123.2	128.3	67.6	59.3
***exo*-18b**	169.4	41.8	25.1	27.2	30.2	123.5	133.6	67.6	59.1

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REFERENCES AND NOTES

1. For related Diels-Alder reactions, see: a) Imbroisi, D. O.; Simpkins, N. S. *J. Chem . Soc., Perkin Trans. I* **1991**, 1851. b) Gómez-Pardo, D.; d'Angelo, J. *Tetrahedron Lett.* **1992**, *33*, 6637. c) Torisawa, Y.; Nakagawa, M.; Takami, H.; Nagata, T.; Ayman Ali, M.; Hino, T. *Heterocycles* **1994**, *39*, 277. d) Torisawa, Y.; Hosaka, T.; Tanabe, K.; Suzuki, N.; Motohashi, Y.; Hino, T.; Nakagawa, M. *Tetrahedron* **1996**, *52*, 10597.
2. a) Grob, C. A.; Fischer, H. P.; Raundenbusch, W.; Zergeny, J. *Helv. Chim. Acta* **1964**, *47*, 1003. b) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 613.
3. Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36.
4. Dihydropyridone **2b** also failed to react with diene **9** in the presence of $ZnBr_2$.
5. Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis,* CRC Press: Boca Raton, 1996; pp. 257-328.
6. Significant ^{1}H-NMR (300 MHz) data of *endo-exo* epimers of **18b**. ***Endo*-18b**: 1.68 (dddd, J = 14, 5.5, 2.5, 2 Hz, 1H, 4-H), 1.96 (s, 3H, $COCH_3$), 2.02 (broad s, 2H, 5-H), 2.37 (m, 1H, 4-H), 2.75 (dq, J = 13, 4.4 Hz, 1H, 4a-H), 3.66 (td, J = 13, 6 Hz, 1H, 3-H), 3.87 (s, 3H, OCH_3), 3.97 (ddd, J = 13, 6, 2 Hz, 1H, 3-H), 5.13 and 5.29 (2d, J = 12.3 Hz, 1H each, CH_2Ph), 5.82 (dt, J = 10, 4 Hz, 1H, 6-H), 5.91 (ddt, J = 10, 4.2, 2 Hz, 1H, 7-H), 5.97 (d, J = 4.2 Hz, 1H, 8-H), 7.33 (s, 5H, PhH). ***Exo*-18b**: 1.55 (m, 1H, 4-H), 1.56 (s, 3H, $COCH_3$), 1.88 (dd, J = 18, 12 Hz, 1H, 5-H), 2.31 (dt, J = 18, 3 Hz, 1H, 5-H), 2.39 (m, 1H, 4-H), 2.90 (m, 1H, 4a-H), 3.21 (ddd, J = 15, 9, 5.5 Hz, 1H, 3-H), 3.85 (s, 3H, OCH_3), 4.15 (ddd, J = 16, 8, 4.5 Hz, 1H, 3-H), 5.12 and 5.20 (2d, J = 12 Hz, 1H each, CH_2Ph), 5.83-5.89 (m, 1H, 6-H), 5.90-5.97 (m, 1H, 7-H), 5.98 (d, J = 4.5 Hz, 1H, 8-H), 7.26 (s, 5H, PhH).

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