

# Highly Diastereoselective Diels–Alder Reaction Using a Chiral Auxiliary Derived from Levoglucosenone

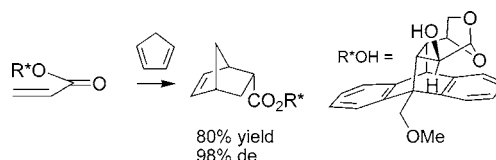
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## ABSTRACT



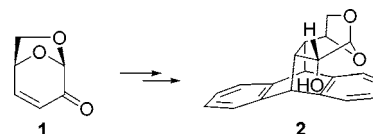
A new chiral auxiliary derived from levoglucosenone is reported. The compound is obtained by a cycloaddition reaction with 9-methoxy methylanthracene followed by a diastereoselective reduction of the C-2 keto function. The auxiliary has been used as a chiral template in an asymmetric Diels–Alder reaction of the corresponding acrylic ester derivative with cyclopentadiene. The results showed excellent diastereomeric excess even at room temperature when the reaction was promoted by  $\text{Et}_2\text{AlCl}$  as the Lewis acid.

The transfer of chirality through the use of chiral auxiliaries has been demonstrated as an effectual means for preparing enantiopure materials. Most chiral auxiliaries reported in the literature are derived from naturally occurring compounds. As part of our program on the pyrolytic conversion of biomass into high value chemicals, we have been concerned with the synthetic application of levoglucosenone (**1**) (1,6-anhydro-3,4-dideoxy- $\beta$ -D-glycero-hex-3-enopyranos-2-ulose) as a chiral building block in the development of new tools for asymmetric synthesis. This bicyclic enone is the major product of the pyrolysis of cellulose or cellulose-containing material such as waste paper.<sup>1,2</sup>

The Diels–Alder reaction has been among the most popular and successful synthetic applications of carbohydrate auxiliaries, particularly when they are attached to the

dienophile. Recently, we have reported the design and synthesis of an alcohol **2** derived from levoglucosenone (Scheme 1) and its use as a chiral inductor in Diels–Alder

Scheme 1



reactions of the corresponding acrylate yielding the product with 80% diastereomeric excess.<sup>3,4</sup> Attempts to improve the  $\pi$ -facial diastereoselectivity in these cycloaddition reactions led us to envisage a new acrylate derived from levoglucosenone. The introduction of a substituent at the benzylic position closer to the ester group would introduce a new element of steric control, therefore imposing an additional restriction to the transition state. Our approach for the design of the new molecular scaffold simply relies on the use of a suitable 9-substituted anthracene derivative as a possible

(1) Witczak, Z. J., Ed. *Levoglucosenone and Levoglucosans: Chemistry and Applications*; ATL Press: Mount Prospect, 1994.

(2) Witczak, Z. J., Tatsuka, K., Eds. *Carbohydrate Synthons in Natural Products Chemistry. Synthesis, Functionalization, and Applications*. ACS Symposium Series; American Chemical Society: Washington, DC, 2003.

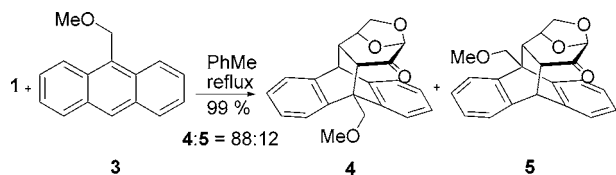
(3) Sarotti, A. M.; Spavevello, R. A.; Suárez, A. G. *Tetrahedron Lett.* **2004**, *45*, 8203.

(4) Sarotti, A. M.; Spavevello, R. A.; Suárez, A. G. *Tetrahedron Lett.* **2005**, *46*, 6987.

source of molecular diversity to tune the efficiency of the asymmetric inductor.

Our first choice was to use 9-methoxymethyl anthracene (**3**) derived from the commercially available 9-anthracene-methanol. Cycloaddition reaction of **1** with **3** afforded only two of the four possible isomeric products in 99% overall yield (Scheme 2).

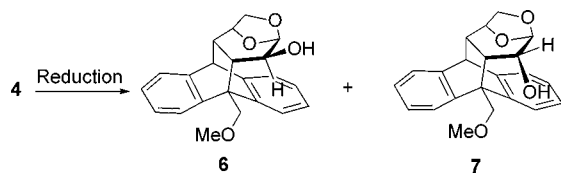
**Scheme 2.** Synthesis of Cycloadduct **4**



The stereochemical assignments of the new compounds were made possible by the use of  $^1\text{H}$  NMR spin decoupling and NOE data. Both adducts corresponded to the products derived from the attack of the diene from the opposite face of the 1,6-anhydro bridge of **1**. Adducts **4** (87%) and **5** (12%) were identified as the ortho and meta regioisomers, respectively. It was already observed that the ortho regioisomer is generally preferred in cycloaddition reactions of 9-substituted anthracenes with dienophiles.<sup>5</sup>

The diastereoselective conversion of **4** to the corresponding alcohol derivatives relies mainly on the competitive steric encumbrance exerted by the 1,6-anhydro bridge above the plane of the pyranoside ring and the aromatic rings below it. The reduction of ketone **4** led to the formation of two diastereomeric alcohols **6** and **7** (Scheme 3). Separation of these products was easily performed by column chromatography.

**Scheme 3.** Reduction of Cycloadduct **4**



As shown in Table 1, the conversion of **4** to the epimeric alcohols **6** and **7** depends on the reaction conditions. It is noteworthy to mention that the outcome of the reduction of **4** with  $\text{NaBH}_4$  is a function of the  $\text{MeOH}$  concentration, favoring the product obtained from the attack of the hydride from the more crowded face of the carbonyl group (entries 2–4). These results can be understood considering a coordination between the boron atom and the oxygen of the methoxy group.

(5) Fringuelli, F.; Tatichi, A. *Dienes in the Diels–Alder Reaction*; John Wiley & Sons: New York, 1990; Chapter 6.

**Table 1.** Reduction of **4** at 0 °C

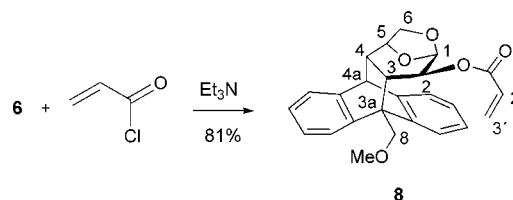
entry	reagent	solvent	yield (%) <sup>a</sup>	ratio <b>6/7</b>
1	$\text{LiAlH}_4$	THF	100	47:53
2	$\text{NaBH}_4$	MeOH	54	51:49
3	$\text{NaBH}_4$	MeOH/ $\text{CH}_2\text{Cl}_2$ 1:2	98	59:41
4	$\text{NaBH}_4$	MeOH/ $\text{CH}_2\text{Cl}_2$ 5:95	90	70:30
5	L-selectride	$\text{CH}_2\text{Cl}_2$	80	0:100

<sup>a</sup> Yield corresponds to isolated products.

Both alcohol **6** and **7** have the appropriate functionality to be tested as chiral auxiliaries in the asymmetric Diels–Alder reaction of the corresponding acrylic ester and cyclopentadiene.

The acrylate **8** was simply prepared by the reaction of acryloyl chloride with alcohol **6** in the presence of triethylamine at 0 °C (Scheme 4). The ester **8** was obtained as a

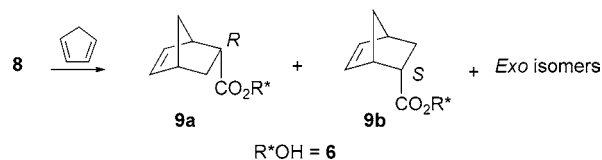
**Scheme 4.** Synthesis of Acrylate **8**



colorless oil in 81% yield. All attempts to synthesize the acrylic ester from **7** failed, probably because of the steric hindrance surrounding the alcohol position. However, alcohol **7** can be reused by oxidation with PCC to generate the ketone **4** in 94% yield.

Diels–Alder reactions of acrylate **8** and cyclopentadiene were carried out under different thermal or Lewis acid promoted conditions. An extensive survey of Lewis acids afforded the expected four isomers depicted in Scheme 5.

**Scheme 5.** Cycloaddition Reaction of **8** with Cyclopentadiene



The stereochemical assignments of each cycloadduct were based on the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data as well as 2D NMR experiments. The difference in the chemical shift between the two endo and exo diastereoisomers allowed us to determine the ratio of endo/exo and *endo-9a/endo-9b* by the analysis of the  $^1\text{H}$  NMR spectra of the mixture of isomers.<sup>6</sup>

(6) These results were also confirmed by HPLC analysis.

**Table 2.** Lewis Acid Promoted Cycloaddition Reactions (Scheme 5)

entry	Lewis acid (equiv)	solvent	temp (°C)	time (h)	yield (%) <sup>a</sup>	endo/exo	endo- <b>9a</b> /endo- <b>9b</b>
1	none	toluene	110	1.5	72	71:29	29:71
2	none	toluene	25	48	90	71:29	17:83
3	none	CH <sub>2</sub> Cl <sub>2</sub>	25	48	95	76:24	23:77
4	Et <sub>2</sub> AlCl (0.2)	CH <sub>2</sub> Cl <sub>2</sub>	25	48	93	78:22	22:78
5	Et <sub>2</sub> AlCl (0.5)	CH <sub>2</sub> Cl <sub>2</sub>	25	48	90	80:20	23:77
6	Et <sub>2</sub> AlCl (1)	CH <sub>2</sub> Cl <sub>2</sub>	25	4	76	91:9	92:8
7	Et <sub>2</sub> AlCl (1.5)	CH <sub>2</sub> Cl <sub>2</sub>	25	1	80	92:8	94:6
8	Et <sub>2</sub> AlCl (2)	CH <sub>2</sub> Cl <sub>2</sub>	25	1	70	94:6	95:5
9	Et <sub>2</sub> AlCl (2)	CH <sub>2</sub> Cl <sub>2</sub>	0	1	70	94:6	97:3
10	Et <sub>2</sub> AlCl (2)	CH <sub>2</sub> Cl <sub>2</sub>	-20	1	73	95:5	99:1
11	Et <sub>2</sub> AlCl (2)	CH <sub>2</sub> Cl <sub>2</sub>	-40	1	75	97:3	98:2
12	Et <sub>2</sub> AlCl (2)	CH <sub>2</sub> Cl <sub>2</sub>	-80	1	80	98:2	99:1
13	EtAlCl <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	25	1	88	93:7	92:8
14	EtAlCl <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	0	1	89	93:7	93:7
15	EtAlCl <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	-20	1	87	95:5	95:5
16	EtAlCl <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	-40	1	97	96:4	95:5
17	EtAlCl <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	-80	1	94	97:3	93:7
18	TiCl <sub>4</sub> (0.5)	CH <sub>2</sub> Cl <sub>2</sub>	-20	1	92	95:5	86:14
19	TiCl <sub>4</sub> (0.5)	CH <sub>2</sub> Cl <sub>2</sub>	-40	1	83	96:4	89:11
20	TiCl <sub>4</sub> (0.5)	CH <sub>2</sub> Cl <sub>2</sub>	-80	1	79	97:3	93:7
21	LiClO <sub>4</sub> 5M	ether	25	5	84	85:15	53:47
22	AlCl <sub>3</sub> (1.3)	CH <sub>2</sub> Cl <sub>2</sub>	0	1	98	92:8	10:90
23	AlCl <sub>3</sub> (1.3)	CH <sub>2</sub> Cl <sub>2</sub>	-40	1	97	96:4	6:94

<sup>a</sup> Yield corresponds to isolated products.

Table 2 shows the selected experimental conditions of the Diels–Alder reactions performed in this study.

The cycloaddition reaction of cyclopentadiene with the acrylic ester **8** was endo diastereoselective, as predicted by the Alder endo rule.<sup>7</sup> As expected, the reactions performed under thermal conditions furnished a mixture of adducts in low  $\pi$ -facial diastereoselectivity and moderate endo/exo ratio. These experimental results were rationalized in terms of the fact that the conformation of the dienophile **8** is not fixed in the absence of Lewis acid.

As shown in Table 2, the *endo-9a/endo-9b* ratio varied considerably with temperature, Lewis acid, and substrate/Lewis acid molar ratio employed in the reaction. A striking reversal effect in stereoselectivity was obtained from the cycloaddition reactions promoted with TiCl<sub>4</sub> or with more than 1 equiv of aluminum Lewis acids. These experimental results suggest that the metal coordination plays a key role in determining the  $\pi$ -facial selectivity of this chiral dienophile. Surprisingly, diethylaluminum chloride (Et<sub>2</sub>AlCl) promoted the most diastereoselective Diels–Alder reaction observed in this study. The use of Et<sub>2</sub>AlCl (2 equiv) in dichloromethane afforded both high levels of endo diastereoselection and the highest endo/exo ratio for all the Lewis acids screened (entries 8–12). It is noteworthy to mention the high diastereoselectivity obtained even when the reaction was performed at room temperature (entries 6–8). The sense of asymmetric induction in these Diels–Alder reactions has been established by hydrolysis of the adduct **9a**. The absolute

configuration of the 5-norbornene-2-carboxylic acid isolated corresponded to the 2-*R*-enantiomer.<sup>8</sup> It is important to point out that the chiral auxiliary **6** was recovered quantitatively.

To have a better understanding of the diastereoselection process, we performed experiments to detect the formation of coordination compounds as intermediates of the reaction. Magnetic resonance spectroscopy has been a valuable tool for determining structures and charge distributions of Lewis acid complexes with carbonyl compounds.<sup>9</sup> Spectra of **8** in CDCl<sub>3</sub> solution were recorded prior to and after the addition of the Lewis acid. Progressive variations in chemical shifts were observed when the <sup>1</sup>H NMR spectra of **8** were recorded in the presence of increasing concentrations of Et<sub>2</sub>AlCl. As shown in Table 3, when 0.5 equiv of Lewis acid was added, the deshielding effect on the vinylic protons suggests that coordination of the Lewis acid takes place with the carbonyl oxygen rather than with the other oxygen-coordination sites present in **8**. The shifting of the other protons in the molecule diminished significantly because the shielding or deshielding effect is markedly attenuated with the distance from the interaction site. When 1 equiv of Et<sub>2</sub>AlCl was added to the solution of compound **8**, the deshielding effect in the vinylic protons increased. The downfield shifts for H-5, *endo*-H-6, and *exo*-H-6 were also significant, suggesting the formation of a chelate species involving the acryloyl oxygen and the oxygen of the 1,6-anhydro bridge. A progressive variation of the chemical shifts was observed with 1.5 equiv of Lewis

(8) Chang, H.; Zhou, L.; McCargar, R. D.; Mahmud, T.; Hirst, I. *Org. Process Res. Dev.* **1999**, *3*, 289.

(9) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 1.10.

**Table 3.** Selected  $^1\text{H}$  NMR Chemical Shifts (in ppm) for **8** Recorded in the Presence of  $\text{Et}_2\text{AlCl}$

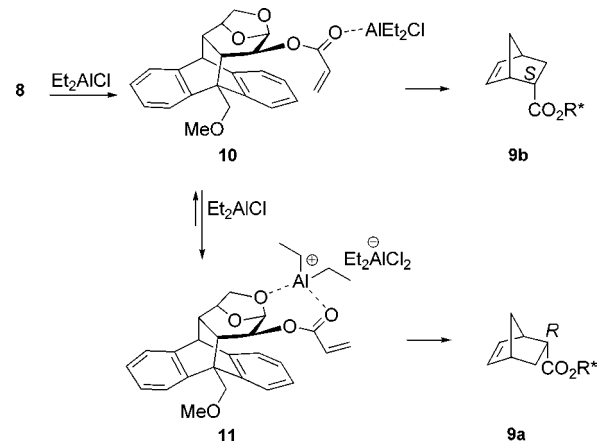
atom	Lewis acid added (equiv)				
	none	0.5	1	1.5	2
H-1	5.12	5.13	5.41	5.79	5.82
H-2	4.36	4.50	4.65	4.75	4.76
H-3	2.66	2.73	2.80	2.84	2.83
H-4	2.18	2.20	2.23	2.25	2.24
H-4a	4.17	4.16	4.18	4.19	4.18
H-5	4.65	4.66	4.76	4.89	4.88
endo-H-6	3.69	3.69	3.78	3.90	3.89
exo-H-6	3.75	3.75	3.87	4.03	4.02
H-7a	4.12	4.13	4.15	4.19	4.20
H-7b	4.37	4.39	4.40	4.41	4.41
H-8	3.49	3.48	3.48	3.49	3.49
H-2'	6.20	6.47	6.65	6.68	6.68
cis-H-3	6.51	6.74	6.91	6.95	6.96
trans-H-3	5.89	6.16	6.36	6.42	6.41

acid. An additional salient feature was that the chemical shift of the hydrogen at position 8 did not vary, demonstrating that the oxygen of the methoxy group was not involved in the formation of the chelated complex.

According to these experimental results, it is possible to postulate that at least two types of acrylate/Lewis acid complexes can be formed depending on the amount of Lewis acid employed as the promoter (Scheme 6). The Diels–Alder reactions with less than 1 equiv of  $\text{Et}_2\text{AlCl}$  (entries 4 and 5, Table 2) proceed through complex **10** in an s-trans conformation to afford predominantly the endo isomer **9b**. On the other hand, the stereochemical outcome of the  $\text{Et}_2\text{AlCl}$  promoted cycloaddition reactions (entries 6–12, Table 2) and the spectroscopic results are consistent with the presence of an intermediate complex such as **11** for the outcome of the cycloaddition reaction and the observed inversion of

(10) (a) Shida, N.; Kabuto, C.; Niwa, T.; Ebata, T.; Yamamoto, Y. *J. Org. Chem.* **1994**, *59*, 4068. (b) Cipiciani, A.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **2002**, *67*, 2665. (c) Gras, J. L.; Poncet, A.; Nougier, R. *Tetrahedron Lett.* **1992**, *33*, 3323. (d) Ferreira, M. L. G.; Pinheiro, S.; Perrone, C. C.; Costa, P. R. R.; Ferreira, V. F. *Tetrahedron: Asymmetry* **1998**, *9*, 2671.

**Scheme 6.** Diels–Alder Reaction of **8** Promoted by  $\text{Et}_2\text{AlCl}$



selectivity. This type of Lewis acid behavior has precedent for its occurrence in other systems.<sup>10</sup>

In conclusion, we have synthesized the excellent chiral auxiliary **6** for use in the Diels–Alder reaction. The adduct obtained from the reaction of the corresponding acrylate and cyclopentadiene is generally formed with high diastereo- and stereocontrol even at room temperature. Saponification of the acrylic ester provided the free carboxylic acid and the chiral auxiliary in good yields. Auxiliary **6** was easily separated from the acid and could be reused.

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**Supporting Information Available:** Experimental procedures for the synthesis of all compounds, characterization data, and copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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