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Tetrahedron Letters 46 (2005) 6987–6990
Tetrahedron Letters

A chiral auxiliary derived from levoglucosenone in asymmetric Diels–Alder transformations

Ariel M. Sarotti, Rolando A. Spanevello and Alejandra G. Suárez*

Instituto de Química Orgánica de Síntesis, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario—CONICET Suipacha 531, S2002LRK Rosario, Argentina

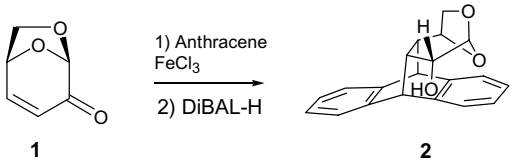
Received 31 July 2005; revised 13 August 2005; accepted 16 August 2005

Abstract—The Diels–Alder reaction of the acrylate derived from levoglucosenone with cyclopentadiene was studied under several conditions, in the presence and absence of a Lewis acid. The results showed satisfactory diastereomeric excess and the ratio of cycloadducts was found to depend on the reaction conditions. A reversal in stereoselectivity was observed when $EtAlCl_2$ or Et_2AlCl were employed as Lewis acids.

The generation of useful chemicals from cellulosic waste materials has been investigated through the pyrolysis of acid-pretreated waste paper. Levoglucosenone (**1**) (1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose), a bicyclic enone, is the major product of the pyrolysis of cellulose or cellulose-containing materials.[1,2] During the last decade, this versatile and readily available member of the carbohydrate derived chiral pool has been intensively used as chiral synthon in the synthesis of natural products, thiosugars, C-glycosyl compounds, and annelated pyranosides.[1,3] Our interest in this field is focused on the potential use of this chiral building block in the synthesis of asymmetric inductors.

In a previous letter, we reported the first preparation of chiral auxiliary **2** starting from levoglucosenone (Scheme 1) and a preliminary study of its application in a Diels–Alder transformation.[4]

In this letter, we report the cycloaddition reaction of chiral acrylic ester **3** derived from **2** as dienophile with cyclopentadiene. In particular, we are focused on the role of the Lewis acid employed in the Diels–Alder reaction. Acrylate **3** was simply prepared in 90% yield by the reaction of acryloyl chloride with alcohol **2** in the presence of triethylamine at room temperature.[5] Diels–Alder



1 **2**

Scheme 1.

reaction between chiral acrylate **3** and cyclopentadiene was carried out under thermal and Lewis acid conditions. The reaction afforded the expected four isomers depicted in Scheme 2.

The stereochemical assignments of each compound were based on ^1H and ^{13}C NMR data as well as 2D NMR experiments. Two *endo* adducts (**4a** and **4b**) showed larger chemical shift differences for the vinylic protons H-6′ (5.84 and 6.13 for **4a** and **4b**, respectively),[6] in contrast to the magnetically similarity for the corresponding protons in the *exo* isomers **4c** and **4d**.

The difference in the chemical shift between the two *endo* and the *exo* diastereoisomers allowed to determine the ratio *endo*/*exo* and *endo* **4a**/*endo* **4b** by the analysis of ^1H NMR spectra of the mixture of isomers.

Acrylate **3** was reacted with cyclopentadiene under several conditions. Table 1 shows the Diels–Alder reactions carried out in the presence and absence of a Lewis acid as catalyst.

Keywords: Levoglucosenone; Chiral auxiliary; Diels–Alder; Cycloadditions; Acrylate.
* Corresponding author. Tel./fax: +54 (341) 4370477; e-mail: asuarez@fbioyf.unr.edu.ar

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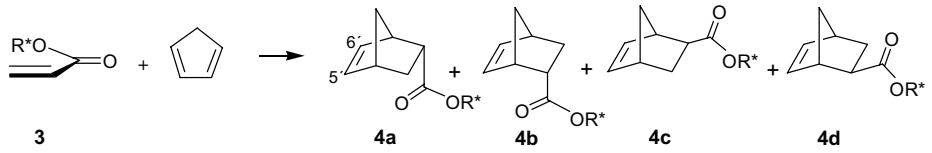
doi:10.1016/j.tetlet.2005.08.073



Scheme 2.

Table 1. Lewis acid promoted cycloadditions (Scheme 2)

Entry	Lewis acid (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]	*endo*/*exo*	*endo* **4a**/*endo* **4b**
1	None	Toluene	110	1.5	100	70/30	76/24
2	None	CH_2Cl_2	25	52	87	79/21	71/29
3	Et_2AlCl (0.2)	CH_2Cl_2	25	24	98	80/20	78/22
4	Et_2AlCl (0.5)	CH_2Cl_2	25	24	96	83/17	60/40
5	Et_2AlCl (1)	CH_2Cl_2	25	4	71	90/10	28/72
6	Et_2AlCl (2)	CH_2Cl_2	25	1	80	92/8	22/78
7	Et_2AlCl (1)	CH_2Cl_2	5	6	86	96/4	15/85
8	Et_2AlCl (2)	CH_2Cl_2	5	<1	85	96/4	16/84
9	Et_2AlCl (2)	CH_2Cl_2	−10	<1	87	98/2	11/89
10	Et_2AlCl (2)	CH_2Cl_2	−30	<1	86	98/2	10/90
11	$EtAlCl_2$ (2)	CH_2Cl_2	0	0.7	79	96/4	26/74
12	$EtAlCl_2$ (2)	CH_2Cl_2	−20	0.7	82	98/2	22/78
13	$EtAlCl_2$ (2)	CH_2Cl_2	−40	0.7	91	98/2	15/85
14	$AlCl_3$ (1)	CH_2Cl_2	25	4	24	82/18	74/26
15	$Al(O^iPr)_3$ (1)	CH_2Cl_2	25	51	100	76/24	72/28
16	$BF_3{\cdot}OEt_2$ (1)	CH_2Cl_2	25	2	64	83/17	66/34
17	$LiClO_4$ 5 M	Ether	25	30	67	85/15	66/34
18	Yb-FOB (0.25)	CH_2Cl_2	25	21	99	82/18	66/34
19	$SnCl_4$ (1)	CH_2Cl_2	25	21	33	87/13	68/32
20	$Ti(O^iPr)_4$ (1)	CH_2Cl_2	25	50	98	78/22	70/30

[a] Yield corresponds to isolated products.

The cycloaddition of cyclopentadiene with acrylic ester **3** were *endo* diastereoselective, as predicted by the Alder *endo* rule.[7] As expected, the reactions performed under thermal conditions furnished a mixture of adducts in low π-facial diastereoselectivity and moderate *endo*/*exo* ratio.

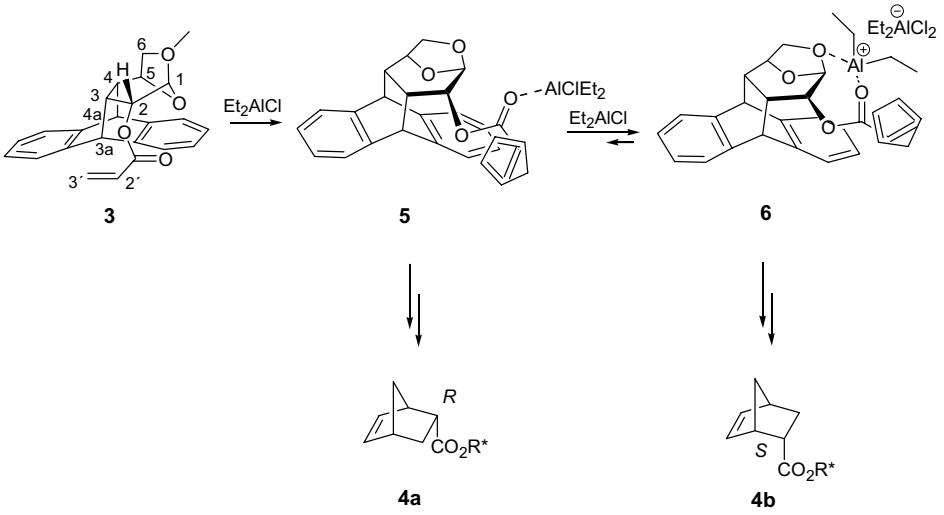
These experimental results were rationalized in terms of the fact that the conformation of dienophile **3** is not fixed in the absence of Lewis acid.

After an extensive survey of Lewis acid addends, some of which appear in Table 1, we were surprised to find that none of the catalysts we felt likely to maintain bidentade chelation led to acceptable levels of reaction stereoselectivity. As it is shown in Table 1, the *endo* **4a**/*endo* **4b** ratio varied considerably with temperature, Lewis acid, and molar ratio of **3** and Lewis acid employed in the reaction.

A striking reversal in stereoselectivity was obtained from the cycloaddition reactions promoted with more than 1 equiv of ethylaluminum dichloride ($EtAlCl_2$) or diethylaluminum chloride (Et_2AlCl). These experimental results suggest that the metal coordination plays a key role in determining the π facial selectivity of this chiral dienophile. Surprisingly, Et_2AlCl promoted by far the most diastereoselective Diels–Alder reaction observed in this study. The use of Et_2AlCl (2 equiv) in dichloromethane at −30 °C (entry 10) afforded both high levels of *endo* diastereoselection (9:1) and the highest *endo*–*exo* ratio (49:1) for all the Lewis acid screened.

It is generally accepted that the outcome of the reaction stereoselectivity depends upon the *s-trans*/*s-cis* conformation of the acrylic ester.[8] Examination of the results shown in Table 1 allows to postulate that at least two types of acrylate/Lewis acid complexes can be formed (Scheme 3). The Diels–Alder reactions with less than 1 equiv of Et_2AlCl (entries 3 and 4) proceed through complex **5** in the *s-trans* conformation to afford predominantly the *endo* isomer **4a**. The sense of asymmetric induction in these Diels–Alder reactions was already established by hydrolysis of adduct **4a**. The absolute configuration of 5-norbornene-2-carboxylic acid isolated corresponded to 2-(*R*)-enantiomer.[4] On the other hand, the stereochemical outcome of Et_2AlCl and $EtAlCl_2$ promoted cycloaddition reactions (entries 5–13) is consistent with the addition of diene from the more accessible face of the *s-cis* Lewis acid–dienophile complex **6**, leading to cycloadduct **4b**. This complex is expected to be both more reactive and highly organized as a result of the bidentade chelated geometry (Scheme 3). This type of Lewis acid behavior has precedent for other systems.[8]

Stereoelectronic factors operating in the intermediate species generated by interaction of **3** with Lewis acid,



3 5 6

4a 4b

Scheme 3.

may account for the observed stereoselectivities. Experiments were conducted to detect the formation of complexes between **3** and $BF_3{\cdot}Et_2O$ or Et_2AlCl using ^1H NMR, since they give opposite *endo* diastereoselectivity. Spectra of **3** in $CDCl_3$ solution were recorded prior to and after addition of Lewis acid. The spectra of **3** with or without $BF_3{\cdot}Et_2O$ were practically identical. In contrast, progressive variations in chemical shifts were observed when ^1H NMR spectra of **3** were recorded in the presence of increasing amounts of Et_2AlCl,[9] as is shown in Table 2. When 0.5 equiv of Lewis acid was added, the deshielding effect on the vinylic protons suggests that coordination of Lewis acid takes place with the carbonyl oxygen rather than with the other oxygen-coordination sites present in ligand **3**. The shifting of 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_2AlCl was added to the solution of compound **3**, the deshielding effect in the vinylic protons increased. The downfield shifts for H-5, H-6 *endo*, and H-6 *exo* were noteworthy, suggesting the formation of a chelate species involving the acryloyl oxygen and oxygen of the 1,6-anhydro bridge. These experimental data are consistent with the presence of an intermediate complex like **6** to be responsible for the outcome of the cycloaddition reaction and the observed inversion of selectivity.

Table 2. Selected ^1H NMR chemical shifts (in ppm) for **3**, recorded in the presence of Et_2AlCl

Atom	Lewis acid added		
	None	0.5 equiv	1 equiv
H-1	4.93	5.01	5.31
H-2	5.11	5.20	5.40
H-3	2.72	2.78	2.89
H-4	2.06	2.03	2.05
H-5	4.50	4.51	4.64
H-6 *endo*	3.68	3.68	3.80
H-6 *exo*	3.60	3.60	3.71
H-3a	4.23	4.18	4.14
H-4a	4.24	4.23	4.24
H-2′	6.31	6.53	6.76
H-3′ *cis*	6.58	6.74	ND
H-3′ *trans*	6.01	6.27	6.47

ND: not determined as they appeared with the aromatic protons.

As we have observed in our previous study, the high incidence of crystallinity associated with this chiral auxiliary is of great practical advantage. Chiral auxiliary removal from these cycloadducts may be accomplished in quantitative yields providing a straightforward access to both enantiomers of 5-norbornene-2-carbocyclic acid, depending on the reaction conditions. On the other hand, the *endo*/*exo* and the π facial selectivity obtained with chiral auxiliary **3** are between the highest found for Diels–Alder reaction of acrylic esters derived from carbohydrates and cyclopentadiene.

In summary, this is the first application of a levoglucosenone derivative as chiral auxiliary in a Diels–Alder reaction. The level of induction obtained, in addition to the fact that the starting material is inexpensive, makes this system an excellent model to be further exploited in other asymmetric reactions and a starting point for new chiral templates. The synthesis and application of other chiral auxiliaries derived from levoglucosenone are in progress and will be published in due course.

Acknowledgments

This research was supported by the Third World Academy of Sciences, Trieste, Italy, the International Foundation for Science, Stockholm, Sweden and the Organization for the Prohibition of Chemical Weapons, The Hague, The Netherlands, through the grants to A.G.S. and R.A.S., respectively. A.M.S. thanks CONICET and Fundación Josefina Prats for the award of a fellowship.

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5. Compound **3**: mp = 208–209 °C (hexane/ethyl acetate); $[\alpha]_D$ −71.4 (*c* 0.66, $CHCl_3$); IR (KBr) ν_{max}: 2948, 2886, 1714 (C=O), 1630, 1468, 1458, 1408, 1296, 1195, 1142 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.35–7.05 (m, 8H, aromatics), 6.58 (dd, J_{vic} = 17.3 Hz, J_{gem} = 1.6 Hz, 1H, H-3′ *cis*), 6.31 (dd, J_{vic} = 17.3 Hz, J_{vic} = 10.2 Hz, 1H, H-2′), 6.01 (dd, J_{vic} = 10.2 Hz, J_{gem} = 1.6 Hz, 1H, H-3′ *trans*), 5.11 (d, $J_{2,3}$ = 10.3 Hz, 1H, H-2), 4.93 (s, 1H, H-1), 4.50 (d, $J_{5,6exo}$ = 4.3 Hz, 1H, H-5), 4.24 (d, $J_{4,4a}$ = 2.8 Hz, 1H, H-4a), 4.23 (d, $J_{3,3a}$ = 2.1 Hz, 1H, H-3a), 3.68 (d, J_{gem} = 6.7 Hz, 1H, H-6 *endo*), 3.60 (dd, J_{gem} = 6.7 Hz, $J_{5,6exo}$ = 4.3 Hz, 1H, H-6 *exo*), 2.72 (td, $J_{3,4}$ = $J_{2,3}$ = 10.3 Hz, $J_{3,3a}$ = 2.1 Hz, 1H, H-3), 2.06 (dd, $J_{3,4}$ = 10.3 Hz, $J_{4,4a}$ = 2.8 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$): δ 165.5 (C, C-1′), 143.5 (C, aromatic), 143.3 (C, aromatic), 141.9 (C, aromatic), 140.8 (C, aromatic), 132.0 (CH_2, C-3′), 127.9 (CH, C-2′), 125.8 (CH, aromatic), 125.7 (CH, aromatic), 125.5 (CH, aromatic), 125.4 (CH, 2 C, aromatics), 123.9 (CH, aromatic), 123.1 (CH, aromatic), 122.9 (CH, aromatic), 100.3 (CH, C-1), 75.5 (CH, C-5), 70.2 (CH, C-2), 69.8 (CH_2, C-6), 51.0 (CH, C-4a), 45.8 (CH, C-3a), 40.5 (CH, C-4), 35.0 (CH, C-3). HREIMS Calcd for $C_{23}H_{20}O_4$ (M^+ + Na) 383.125929. Found 383.126684.
6. Compound **4a**: white solid, mp = 188–189 °C (hexane/ethyl acetate); $[\alpha]_D$ −4.6 (*c* 0.48, $CHCl_3$); IR (KBr) ν_{max}: 2985, 1728 (C=O), 1469, 1469, 1459, 1325, 1196, 1031 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.36–7.05 (m, 8H, arom), 6.24 (dd, $J_{5',6'}$ = 5.5 Hz, $J_{4',5'}$ = 3.1 Hz, 1H, H-5′), 5.84 (dd, $J_{5',6'}$ = 5.5 Hz, $J_{6',7'}$ = 2.3 Hz, 1H, H-6′), 4.95 (d, $J_{2,3}$ = 10.3 Hz, 1H, H-2), 4.81 (s, 1H, H-1), 4.45 (d, $J_{5,6exo}$ = 4.5 Hz, 1H, H-5), 4.27 (d, $J_{3,3a}$ = 2.2 Hz, 1H, H-3a), 4.24 (d, $J_{4,4a}$ = 3.0 Hz, 1H, H-4a), 3.63 (d, J_{gem} = 6.9 Hz, 1H, H-6 *endo*), 3.57 (dd, J_{gem} = 6.9 Hz, $J_{5,6}$ = 4.5 Hz, 1H, H-6 *exo*), 3.29–3.17 (m, 2H, H-7′ and H-2′), 3.00 (br s, 1H, H-4′), 2.62 (td, $J_{3,4}$ = $J_{2,3}$ = 10.3 Hz, $J_{3,3a}$ = 2.2 Hz, 1H, H-3), 2.14–2.00 (m, 2H, H-3′ *exo*, H-4), 1.62 (td, J_{gem} = 12.0 Hz, $J_{3'endo,2'}$ = $J_{3'endo,4'}$ = 2.7 Hz, 1H, H-3′ *endo*), 1.50 (d, J_{gem} = 8.2 Hz, 1H, H-8′ *syn*), 1.39 (d, J_{gem} = 8.2 Hz, 1H, H-8′ *anti*); ^{13}C NMR ($CDCl_3$): δ 174.1 (C, C9), 143.8 (C, aromatic), 143.1 (C, aromatic), 142.0 (C, aromatic), 141.0 (C, aromatic), 138.0 (CH, C-5′), 131.9 (CH, C-6′), 125.9 (CH, aromatic), 125.7 (CH, aromatic), 125.6 (CH, aromatic), 125.5 (CH, aromatic), 125.3 (CH, aromatic), 124.0 (CH, aromatic), 123.1 (CH, 2 C, aromatics), 100.5 (CH, C-1), 75.5 (CH, C-5), 70.1 (CH, C-2), 69.7 (CH_2, C-6), 51.1 (CH, C-7), 49.8 (CH_2, C-8′), 45.9 (CH, C-2′), 45.8 (CH, C-3a), 43.3 (CH, C-7′), 42.6 (CH, C-4′), 40.4 (CH, C-4), 35.2 (CH, C-3), 29.3 (CH_2, C-3′). Compound **4b**: white solid, mp = 178–179 °C (hexane/ethyl acetate); $[\alpha]_D$ −92.7 (*c* 1.25, $CHCl_3$); IR (KBr) ν_{max}: 2963, 2946, 1733 (C=O), 1469, 1458, 1337, 1181, 1173, 1137 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37–7.06 (m, 8H, aromatics), 6.24 (dd, $J_{5',6'}$ = 5.6 Hz,$J_{5',4'}$ = 3.0 Hz, 1H, H-5′), 6.13 (dd, $J_{5',6'}$ = 5.6 Hz, $J_{6',7'}$ = 2.6 Hz, 1H, H-6′), 4.93 (d, $J_{2,3}$ = 10.3 Hz, 1H, H-2), 4.79 (s, 1H, H-1), 4.42 (d, $J_{5,6exo}$ = 4.5 Hz, 1H, H-5), 4.31 (d, $J_{3,3a}$ = 2.1 Hz, 1H, H-3a), 4.25 (d, $J_{4,4a}$ = 2.8 Hz, 1H, H-4a), 3.63 (d, J_{gem} = 6.7 Hz, 1H, H-6 *endo*), 3.56 (dd, J_{gem} = 6.7 Hz, $J_{5,6exo}$ = 4.5 Hz, 1H, H-6 *exo*), 3.49 (br s, 1H, H-7′), 3.20 (td, $J_{2',3'exo}$ = 9.4 Hz, $J_{2'7'}$ = $J_{2'3'endo}$ = 4.0 Hz, 1H, H-2′), 2.97 (br s, 1H, H-4′), 2.62 (td, $J_{3,4}$ = $J_{2,3}$ = 10.3 Hz, $J_{3,3a}$ = 2.1 Hz, 1H, H-3), 2.12–1.97 (m, 2H, H-4 and H-3′ *exo*), 1.57 (td, J_{gem} = 8.3, $J_{3'endo,2'}$ = 4.0 Hz, $J_{3'endo,4'}$ = 1.9 Hz, 1H, H-3′ *endo*), 1.46–1.32 (m, 2H, H-8′ *syn*, H-8′ *anti*); ^{13}C NMR ($CDCl_3$): δ 174.2 (C, C-1′), 144.0 (C, aromatic), 142.9 (C, aromatic), 141.8 (C, aromatic), 141.1 (C, aromatic), 137.9 (CH, C-5′), 132.3 (CH, C-6′), 125.9 (CH, aromatic), 125.8 (CH, aromatic), 125.6 (CH, 2 C, aromatic), 125.4 (CH, aromatic), 124.0 (CH, aromatic), 123.2 (CH, aromatic), 123.0 (CH, aromatic), 100.6 (CH, C-1), 75.5 (CH, C-5), 70.4 (CH, C-2), 69.5 (CH_2, C-6), 51.1 (CH, C-4a), 49.6 (CH_2, C-8′), 45.9 (CH, C-2′), 45.7 (CH, C-3a), 43.5 (CH, C-7′), 42.5 (CH, C-4′), 40.3 (CH, C-4), 35.4 (CH, C-3), 30.0 (CH_2, C-3′).
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9. Complexation of **3** with Lewis acids: for ^1H NMR experiments acrylic ester (30 mg) was dissolved in dry $CDCl_3$ (0.5 mL) in a reaction tube under nitrogen. The appropriate amount of Lewis acid was added to the solution, which was stirred for 20 min at room temperature. This solution was transferred to an NMR tube under nitrogen. Compound **3** was stable during the time required for the acquisition of the spectra.