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Synthesis of a simple chiral auxiliary derived from levoglucosenone and its application in a Diels–Alder reaction

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ABSTRACT

The synthesis of a chiral alcohol derived from levoglucosenone has been studied. The alcohol was employed as chiral template in an asymmetric Diels–Alder reaction of the corresponding acrylic ester derivative with cyclopentadiene, and was shown to be an efficient asymmetric inductor. The oxidation reaction detected during the hydrogenation of a secondary allylic alcohol intermediate with Pd/C was also investigated.

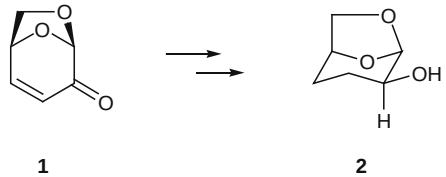
The generation of highly valuable chemicals from biomass has been investigated through the pyrolysis of cellulose or cellulose-containing materials. Levoglucosenone (**1**) (1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose) is the major product of the pyrolysis of acid-pretreated waste paper.[1,2] This bicyclic enone has been intensively used as chiral synthon in the synthesis of a wide variety of compounds.[1,3] Our interest in this field is focused on the potential use of this easily available member of the carbohydrate pool for the development of new tools for asymmetric induction. The use of stoichiometric chiral auxiliaries is, for many chemists, the most flexible and predictable method by which stereocontrol can be imposed on a chemical transformation, particularly in the formation of new carbon–carbon bonds. For this reason, there is currently a considerable interest in auxiliary-based synthetic methods.

The Diels–Alder reaction is among the most popular and successful synthetic application of carbohydrate chiral auxiliaries, particularly when they are attached to the dienophile. Recently, we reported the synthesis of the first chiral auxiliaries derived from levoglucosenone. The asymmetric inductors were obtained by a [4+2] cycloaddition reaction of **1** with anthracene, 9-substituted anthracenes or cyclopentadiene, followed by a diastereoselective reduction of the C(2) keto functionality in high overall yield. The auxiliaries were used as chiral templates in asymmetric Diels–Alder reactions of the corresponding acrylic ester derivatives with cyclopentadiene, and were shown to be efficient for asymmetric induction.[4,5] To investigate the relationship between the structure of the synthetic chiral auxiliary and its effectiveness in asymmetric synthesis, we were interested to test the inductive capacity of the chiral auxiliary without any added carbon skeleton.

In this Letter, we report the preparation of a chiral auxiliary in two steps starting from levoglucosenone, and its further application in an asymmetric Diels–Alder transformation, Scheme 1.

Levoglucosenone was obtained through a conventional or microwave-assisted pyrolysis of microcrystalline cellulose.[1,2,6] With a convenient access to large amounts of **1** as the chiral starting material, we studied the reduction of the enone system to obtain the corresponding saturated alcohol **2**.

The reduction of levoglucosenone with lithium aluminum hydride or sodium borohydride had been already reported.[7] For this reason, we performed the reduction of **1** with sodium borohydride using water instead of methanol as solvent, to make the process greener. This reaction afforded stereoselectively the allylic alcohol **3** in 82% of isolated material. The newly formed stereocenter arised from the addition of the hydride ion from the less hindered side of the carbonyl group. Catalytic hydrogenation of the double bond of



1 **2**

Scheme 1.

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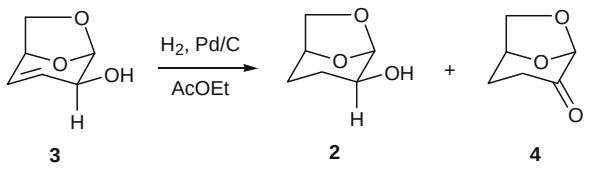


Scheme 2.

3 was performed with hydrogen and 10% Pd/C to obtain the chiral inductor **2**. Surprisingly, this reduction afforded a mixture of two compounds that were identified as the saturated alcohol **2** and the saturated ketone **4**, Scheme 2.

The formation of an oxidation product like **4** has never been observed in previously reported hydrogenation of the allylic alcohol **3** catalyzed by $Pd/BaSO_4$.[7] This competitive oxidation pathway can be attributed to a hydrogen-transfer reaction under the reductive conditions employed. The transformation of the hydroxyl group into the corresponding carbonyl is one of the most frequently used reactions in organic synthesis. Therefore, in order to have a better understanding of the experimental conditions that produce the oxidation product **4**, we decided to study the reaction of **3** under different hydrogenation conditions, Table 1.

The analysis of the experimental results shown in Table 1 demonstrates that products **2** and **4** are produced in good to excellent yields. The amount of the oxidation product **4** varies between 11% and 29% depending on the reaction conditions (entries 1–7). The longer reaction time produces a slight increment on the amount of the ketone **4** (entries 1–4). However, increment in the Pd/C:substrate ratio (entries 4–6) diminishes the formation of **4**. When the reaction was performed under a H_2 pressure of 5 atm the yield of **4** diminished almost three times (entry 4 compared to 7). In order to know if the oxidation byproduct **4** is generated from the allylic alcohol **3** or from the saturated alcohol **2**, we performed the hydrogenation procedure using **2** as starting material (entry 8). The outcome of the reaction demonstrates that the ketone **4** is only formed from the allylic alcohol **3**.

The formation of the oxidation product can be explained by a hydrogen abstraction from the carbinolic carbon of **3** catalyzed by palladium. It was proposed that this mechanism can involve radical intermediates.[8] For this reason, we performed the hydrogenation of **3** in the presence of a radical inhibitor, such as benzoquinone. Under this condition, the hydrogenation of **3** afforded the ketone **4** in 27% yield similar to the one obtained in the absence of benzoquinone (entry 4 compared to 9).

With the purpose to have an insight of the active Pd species that is responsible for this metal-catalyzed oxidation or dehydrogenation transformation, we carried out the experiments with different ratios (in weight) of Pd/C: substrate in the absence of hydrogen. After one hour of reaction only the starting material **3** was recovered (entries 10 and 11). These results were interpreted in terms that a Pd^{II} species should be responsible for the transformation of the allylic alcohol **3** into the carbonyl compound **4**. We next examined the use of pre-treated Pd/C suspension in AcOEt stirred during 30 min under H_2 atmosphere. After evaporation of the solvent, a solution of **3** in AcOEt was incorporated and stirred for 1 h without H_2. The reaction afforded starting material **3** (25%) and the products **1** (49%), **2** (9%), and **4** (17%). The result indicated that an active palladium-hydride species is necessary for the formation of the carbonyl derivatives **1** and **4**. Another observation was that under this experimental condition the hydrogen transfer reaction to afford **1** and **4** was faster than the hydrogenation of the double bond of **3** to produce the saturated alcohol **2**.

Table 1
Hydrogenation reaction of **3** with Pd/C and H_2 (Scheme 2)

Entry	Reagent	Ratio[a] Pd/C: substrate	H_2 (atm)	Time (h)	Total yield (%)[b]	**4** (%)
1	**3**	0.1	1	0.5	95	20
2	**3**	0.1	1	1	94	23
3	**3**	0.1	1	1.5	94	25
4	**3**	0.1	1	2	93	29
5	**3**	0.5	1	2	93	25
6	**3**	1	1	2	84	24
7	**3**	0.1	5	2	93	11
8	**2**	0.1	1	2	86	—
9	**3** + BQ	0.1	1	1	86	27
10	**3**	0.1	—	1	—[c]	—
11	**3**	1	—	1	—[c]	—

[a] In weight.
[b] Yields correspond to isolated products **2** + **4**.
[c] Starting material is recovered in more than 90% yield.

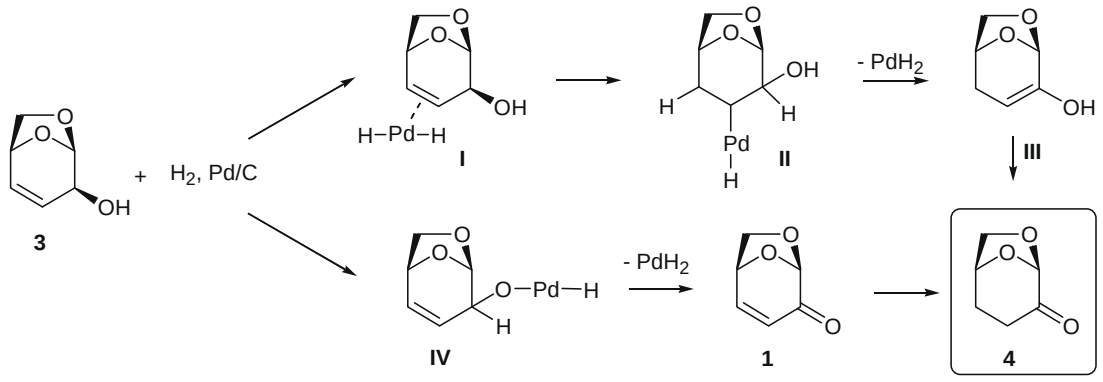
Based on all these experimental results, we postulate the mechanism depicted in Scheme 3 for the formation of ketone **4** from the allylic alcohol **3** in the presence of active palladium-hydride species. The reaction is initiated by coordination of the palladium center to the double bond of **3** to afford intermediate **I**, which generates the complex **II** by migratory-transfer reaction of the hydride ligand to the coordinated olefin. This complex decomposes by a β-hydride elimination to produce the enol **III** that isomerizes to the corresponding ketone **4**. Alternatively, **3** can produce the palladium hydride intermediate **IV** that can be transformed to **1** by a β-hydride elimination reaction. Under hydrogen atmosphere and the presence of Pd/C, **1** is hydrogenated to afford ketone **4**. Similar hydride-transfer mechanism was proposed for the oxidation of other allylic alcohols catalyzed by Pd, conversely, Pd(0) was invoked to be the origin for the formation of complex like **IV**.[8] This is a new example of a Pd-catalyzed oxidation of allylic alcohols to ketones in the absence of a re-oxidant, and is the first reported example for levoglucosenone derivatives.

Due to the inconvenience detected in the hydrogenation pathway of the allylic alcohol **3**, we decided to carry out the synthesis of the chiral auxiliary **2** by inverting the synthetic sequence, thus performing the hydrogenation step previous to the reduction of the carbonyl group. Therefore, levoglucosenone was hydrogenated with Pd/C, and the saturated ketone **4** was reduced with $NaBH_4$ in aqueous media. Under these conditions, the chiral alcohol **2** was obtained in 82% overall yield.

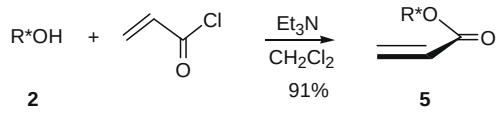
Once the synthesis of the model inductor **2** was achieved in a straightforward and efficient manner, we tested its synthetic usefulness as chiral auxiliary in asymmetric Diels–Alder reaction by examining the use of the corresponding acrylic ester as dienophile. The acrylate **5** was simply prepared by the reaction of acryloyl chloride with alcohol **2** in the presence of triethylamine at room temperature (Scheme 4). The ester **5** was obtained as pale yellow oil in 91% yield.[9]

Diels–Alder reactions of acrylate **5** and cyclopentadiene afforded the expected four isomers that are depicted in Scheme 5. The reaction was carried out under different thermal and Lewis acid conditions as shown in Table 2.

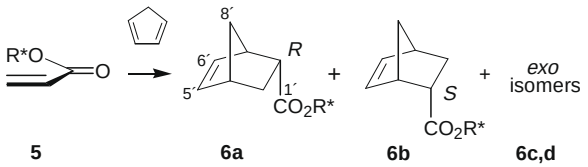
The stereochemical assignments of each product were based on the ^1H and ^{13}C NMR data, as well as 2D NMR techniques. The difference in chemical shifts between the vinylic protons of the two *endo* and *exo* diastereoisomers allowed to determine the *endo*/*exo* ratio by the analysis of the NMR ^1H spectra. However, the *endo* **6a**/*endo* **6b** ratio was obtained by HPLC analysis. The absolute configuration of the *endo* adducts was determined by hydrolysis with LiOH under standard conditions and correlation of their optical rotation with the reported ones for the pair of enantiomers of 5-norbornene-2-carboxylic acid.[10] The carboxylic acid derived from a 70:30 mixture of **6a**:**6b** displayed an $[\alpha]_D^{25}$ +45.2 (*c* 0.43; $CHCl_3$) [lit.[10] −151.5 (*c* 2.00; $CHCl_3$)], indicating that the major adduct **6a** has a 2*R* configuration.



Scheme 3.



Scheme 4.



Scheme 5.

The cycloaddition of cyclopentadiene with acrylic ester **5** was *endo* diastereoselective, as predicted by the Alder *endo* rule.[11] 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 the dienophile **5** is not fixed in the absence of Lewis acid.

After an extensive survey of Lewis acid addends, some of which appear in Table 2, 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 2, the *endo* **6a**/*endo* **6b** ratio varied considerably with temperature, Lewis acid and molar ratio of **5**, and the Lewis acid employed in the reaction.

Table 2
Diels–Alder reactions (Scheme 5)

Entry	Lewis acid (equiv)	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	*endo*/*exo*	*endo* R/S
1	—	Toluene	120	3.5	99	88/12	47/53
2	—	CH_2Cl_2	25	96	91	80/20	47/53
3	$AlCl_3$ (2)	CH_2Cl_2	−20	0.25	84	96/4	50/50
4	Et_2AlCl (2)	CH_2Cl_2	25	0.5	94	94/6	56/44
5	Et_2AlCl (2)	CH_2Cl_2	−20	1	81	94/6	20/80
6	$EtAlCl_2$ (2)	CH_2Cl_2	0	0.5	79	92/8	24/76
7	$EtAlCl_2$ (2)	CH_2Cl_2	−20	1	83	94/6	19/81
8	$EtAlCl_2$ (2)	CH_2Cl_2	−40	0.25	92	96/4	15/85
9	$TiCl_4$ (1)	CH_2Cl_2	25	1	81	93/7	42/58
10	$TiCl_4$ (1)	CH_2Cl_2	−20	1.5	94	99/1	30/70

[a] Yields correspond to isolated product.

Surprisingly, Et_2AlCl and $EtAlCl_2$ promoted by far the most diastereoselective Diels–Alder reaction observed in this study. The use of $EtAlCl_2$ (2 equiv) in dichloromethane at −40 °C (entry 15) afforded the best level of *endo* diastereoselection and one of the highest *endo*–*exo* ratios for all the Lewis acids screened.

Compared to the chiral auxiliaries derived from levoglucosenone that was previously developed, the chiral alcohol **2** demonstrates to be more efficient than the ones with the same absolute configuration at C-2, which have cyclopentadienyl or anthracenyl fragment in the α face of the molecule.[4]

In summary, we prepared a chiral alcohol in two steps from levoglucosenone in high overall yield. A detailed study of the hydrogenation of the allylic alcohol allowed us to detect the formation of an oxidation product under the reductive conditions. We postulated a mechanism for this chemical transformation that involved a Pd-catalyzed hydrogen transfer. The chiral alcohol has been used as chiral auxiliary in a Diels–Alder transformation of the corresponding acrylic ester derivative and cyclopentadiene. 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.

Acknowledgments

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References and notes

1. *Levoglucosenone and Levoglucosans: Chemistry and Applications*; Witczak, Z. J., Ed.; ATL Press: Mount Prospect, 1994.
2. Swenton, J. S.; Freskos, J. N.; Dalidowicz, P.; Kerns, M. L. *J. Org. Chem.* **1996**, *61*, 459.
3. *Carbohydrate Synthons in Natural Products Chemistry. Synthesis, Functionalization, and Applications*; Witczak, Z. J., Tatsuta, K., Eds.; ACS Symposium Series, 2003.
4. (a) Sarotti, A. M.; Spanevello, R. A.; Duhayon, C.; Tuchagues, J.-P.; Suárez, A. G. *Tetrahedron* **2007**, *63*, 241; (b) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Tetrahedron Lett.* **2005**, *46*, 6987; (c) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Tetrahedron Lett.* **2004**, *45*, 8203.
5. Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Org. Lett.* **2006**, *8*, 1487.
6. Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Green Chem.* **2007**, *9*, 1137.
7. Shafizadeh, F.; Chin, P. P. S. *Carbohydr. Res.* **1977**, *58*, 79.
8. Muzart, J. *Tetrahedron* **2003**, *59*, 5789.
9. *Compound* **5**: Pale yellow oil, $[\alpha]_D = -114.6$ (*c* 1.47, $CHCl_3$); IR (NaCl, ν_{max} cm^{-1}): 1031, 1060, 1271, 1294, 1408, 1616, 1633, 1722 (CO), 2895, 2956; ^1H NMR ($CDCl_3$) δ: 6.44 (d, 1H, $J_{3'a\text{-}2'} = 17.2$ Hz, H-3′a), 6.14 (dd, 1H, $J_{2'\text{-}3'a} = 17.2$ Hz, $J_{2'\text{-}3'b} = 10.3$ Hz, H-2′), 5.84 (d, 1H, $J_{3'b\text{-}2'} = 10.3$ Hz, H-3′b), 5.42 (s, 1H, H-1), 4.82 (dd, 1H, $J = 5.7$ Hz, $J = 9.3$ Hz, H-2), 4.53 (sa, 1H, H-5), 3.94 (d, 1H, $J_{6\text{-}6} = 6.5$ Hz, H-6*endo*), 3.84 (dd, 1H, $J_{6\text{-}6} = 6.5$ Hz, $J_{6\text{-}5} = 6.5$ Hz, H-6*exo*), 2.11–1.61 (m, 4H, H-3 y H-4); ^{13}C NMR ($CDCl_3$) δ: 165.3 (C-1′), 131.1 (C-3′),

128.0 (C-2′), 100.2 (C-1), 72.9 (C-5), 71.3 (C-2), 68.3 (C-6), 27.6 y 21.7 (C-3 y C-4).
10. Chang, H.; Zhou, L.; Mahmud, R. D.; McCargar, T.; Hirst, I.. *Org. Process Res. Dev.* **1999**, *3*, 289.
11. (a) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510; (b) Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction. Selected Practical Methods*; J. Wiley & Sons: New York, 2002. Chapter 1.