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A novel design of a levoglucosenone derived chiral auxiliary

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

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Abstract—A two-step general approach to a new chiral auxiliary starting from levoglucosenone is reported. The compound is obtained by a [4+2] cycloaddition reaction with anthracene followed by a diastereoselective reduction of the C-2 keto function in high overall yield. The auxiliary has been used as chiral template in an asymmetric Diels–Alder reaction of the corresponding acrylic ester derivative with cyclopentadiene and shown to be efficient for asymmetric induction.

Levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose) (**1**) is a versatile and readily available member of the carbohydrate derived chiral pool. The synthesis of **1** is most efficiently accomplished by the pyrolysis of cellulose or cellulose-containing material such as waste paper.[1,2] Levoglucosenone possesses several features that make it an attractive chiral raw material for the synthesis of a wide variety of compounds. Like an ordinary sugar it is a highly functionalized compound, furthermore the internal acetal ring renders the molecule structurally rigid with the pyranoside ring locked in the $^1C_4$ conformation. During the last decade this substrate has been employed as chiral synthon in the synthesis of a wide variety of natural and unnatural products with interesting biological activities.[1,3,4]

Our interest in this field is focused on the potential use of this chiral building block in the synthesis of an asymmetric inductor. To succeed in the design of a new chiral auxiliary, the development should take into account not only its capacity to produce an asymmetric induction but also the simplicity and efficiency of its synthesis. In this report we wish to present the preparation of a chiral auxiliary in two steps starting from levoglucosenone, and its further application in an asymmetric Diels–Alder transformation.

Levoglucosenone was obtained from the pyrolysis of acid pretreated waste paper or microcrystalline cellulose as it is described in the literature.[1,2] With a convenient access to large amounts of **1** as the chiral starting material, we considered the possibility of a [4+2] cycloaddition of levoglucosenone with a suitable diene. Among the different dienes analyzed, our first choice was anthracene. The symmetry of this aromatic compound would avoid any problem with the *endo*/*exo* selectivity in the Diels–Alder reaction. As it is well known, the aromatic systems are not the most reactive diene for this type of organic transformation and after testing thermal conditions and different Lewis acids, such as $BF_3{\cdot}Et_2O$, $LiClO_4$, and $FeCl_3$, we found that the latter one was the catalyst that afforded the best yields. These results are in agreement with a literature report that accounts for the use of $FeCl_3$ as catalyst in Diels–Alder reactions with anthracene as the diene.[5]

Treatment of **1** in dichloromethane solution with anthracene and a catalytic amount of anhydrous $FeCl_3$ during 4 h at room temperature resulted in the total consumption of **1**. The reaction might be expected to yield up to two isomeric products since the aromatic substrate can add from the bottom or the top face of the dienophile, however, after column chromatography to remove the excess of anthracene, only one compound was isolated. As it was desired, the cycloadduct resulted to be a highly crystalline compound, which was a great advantage for further purification. The stereochemical assignments were made possible by the use of ^1H NMR spin decoupling and NOE data. The adduct **2** was the only isomer isolated in 78% yield and identified as the product derived from the attack of the diene from the

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* Corresponding author. Tel./fax: +54 341 4370477; e-mail: asuarez@fbioyf.unr.edu.ar

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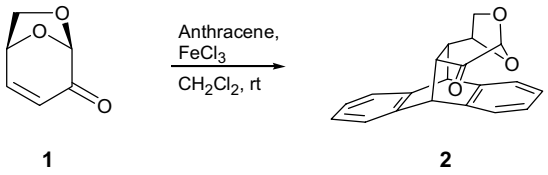


Scheme 1.

opposite face of the 1,6-anhydro bridge (Scheme 1).[6] There are precedents in the literature that suggest that the 1,6-bridge blocks the top face of the molecule favoring the approach of the reagent from the opposite face.[7]

The signal enhancement of H-4 and H-6 observed in the NOE experiment (Fig. 1) demonstrates that the annealed aromatic rings lie below the plane of the 1,6-anhydro sugar. The remaining ^{1}H and ^{13}C NMR signals can also be reconciled with the structural assignment of **2**. It is worth to mention the shielding effect observed by the anomeric proton in the ^{1}H NMR spectrum of this product that appears at 4.59 ppm compared with the values of the same anomeric protons in the levoglucosenone or in the dihydro-levoglucosenone structures that appear at 5.36 and 5.09 ppm, respectively.[8] This upfield shifting can be explained by the anisotropic effect produced by aromatic ring that lies just below this proton.

The diastereoselective conversion of **2** to the corresponding alcohol derivative 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. A simple reduction of the ketone **2** with sodium borohydride led to the formation of two diastereomeric alcohols **3** and **4** (Scheme 2). Separation of these products was easily performed by column chromatography. The major isomer (the less polar one) was isolated in 74% yield and identified as the alcohol derivative **3** (Scheme 2).[9]

The most significant data in the ^{1}H NMR spectrum of **3** is the signal assigned to the anomeric proton that appears at 4.95 ppm as a singlet, this observation suggests that the dihedral angle between H-1 and H-2 is closed to 90°. The second isomer was isolated in 24% yield and proved to be the epimeric alcohol **4** according to the spectroscopic evidences. The ^{1}H NMR spectrum of **4** showed a signal for the anomeric proton at 4.92 ppm as a doublet ($J_{1,2} = 3.2$ Hz) and a signal for the

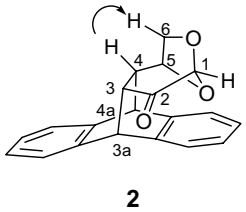
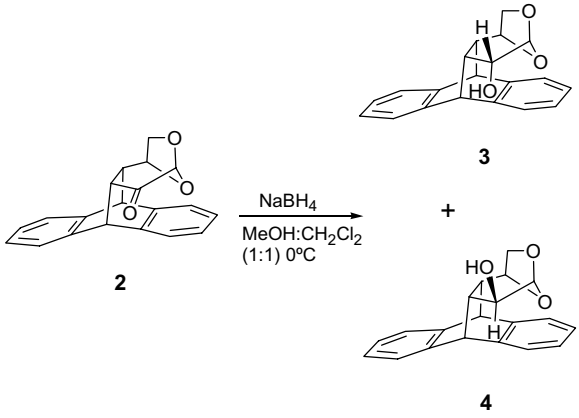


Figure 1. NOE data of compound **2**.



Scheme 2.

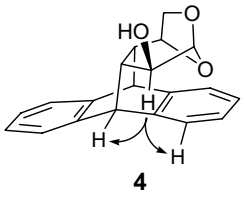


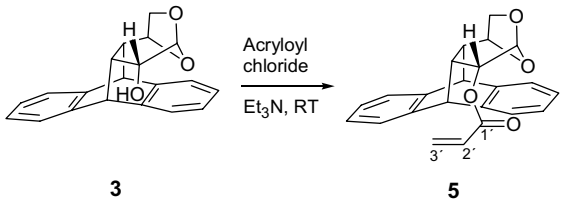
Figure 2. NOE data of compound **4**.

carbinolic proton H-2 as a singlet at 3.09 ppm. This signal was significantly shifted upfield compared with the value of 3.87 ppm observed for the equivalent proton in the major isomer (**3**). This protecting effect suggests that in the minor isomer the H-2 is probably affected by the anisotropy of the aromatic system. The NOE observed between H-2 and H-3a and between H-2 and H-aromatic (Fig. 2) suggested the proximity of these nuclei through the space verifying without ambiguity the configuration of C-2 in compound **4**.

The formation of compounds **3** and **4** in a 3:1 ratio is indicative of the relative steric contribution between the annealed aromatic system below the plane of the carbonyl group and the 1,6-anhydro bridge above it.

Alcohols **3** and **4** are colorless and crystalline solids. In order to improve the diastereoselectivity of this process we investigated the use of other reducing agents and found that the reaction of **2** with DIBAL-H in dichloromethane at −80 °C gives only compound **3** in quantitative yield.

Once the synthesis of the model inductor **3** was achieved in a straightforward and efficient manner, we tested its synthetic usefulness as chiral auxiliary. There are several possibilities to prove the inductive capacity and our initial choice was a Diels–Alder reactions. For this reason we examined the use of the acrylic ester derived from **3** as dienophile. The cycloaddition reaction of the corresponding acrylate with cyclopentadiene would produce a bicyclic system that has significant synthetic utility for the construction of complex natural products.[10]



Scheme 3.

The acrylate **5** was simply prepared by the reaction of acryloyl chloride with alcohol **3** in the presence of triethylamine at room temperature (Scheme 3). The ester **5** was obtained as pale yellow crystalline solid in 90% yield.

The Diels–Alder reaction between the chiral acrylate and cyclopentadiene was carried out under thermal conditions. A toluene solution of **5** was treated with freshly distilled cyclopentadiene and stirred during 1.5 h under reflux.

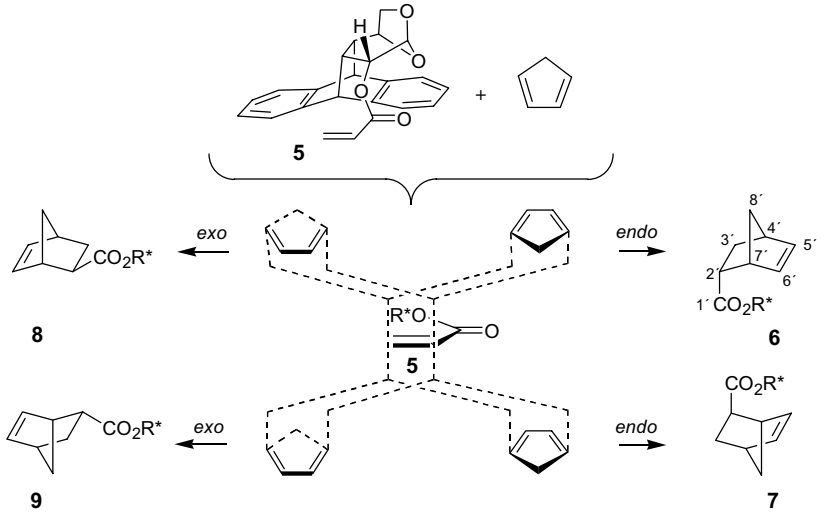
The reaction afforded the four expected isomers depicted in Scheme 4, in quantitative overall yield. It is noteworthy to mention as a key feature of this new structural system that it was possible to separate the mixture by flash column chromatography allowing the quantification of each isomer as follows: *endo* adducts **6** (49.7%) and **7** (21.7) and *exo* adducts **8** (21.0%) and **9** (7.6%).

The stereochemical assignments of each compound were based on the ^{1}H and ^{13}C NMR data as well as by 2D NMR experiments. Two of the isomers (the most polar ones **6** and **7**) showed larger chemical shift differences for the vinylic protons H-5′ and H-6′, compared with those of the other pair of isomers isolated (the least polar ones **8** and **9**). The magnetically similarity for the corresponding protons in **8** and **9** is consistent with the absence of any shielding effect exerted by the chiral auxiliary, as it was expected for the *exo* adducts. In contrast, the olefinic protons of products **6** and **7**, which were assigned as the *endo* adducts, are relative closer to the auxiliary, and its anisotropy induces larger chemical shift differences between H-5′ and H-6′. The carbon signal of the methylene bridge (C-8′) is more shielded (between 3 and 4 ppm) in the *exo* isomers **8** and **9** than in the *endo* ones **6** and **7** as it was found for similar carbocycles systems reported.[11] The analysis of the ^{1}H and ^{13}C NMR data corresponding to the *exo* and *endo* adducts were in complete agreement with other examples of the Diels–Alder reactions of chiral acrylates with cyclopentadiene described in the literature.[12]

The thermal cycloaddition of cyclopentadiene and the acrylic ester **5** was *endo* diastereoselective, as predicted by the Alder *endo* rule,[13] the ratio of the *endo*/*exo* adducts was 2.5:1. The stereoselectivity between the *endo* adducts **6** and **7** was found to be 2.3:1. On the other hand when the Diels–Alder reaction was performed under the catalysis of Et_2AlCl an important increment in the stereoselectivity was observed with a **6**/**7** ratio of 1:9 and an *endo*/*exo* ratio of 98:2. This result demonstrates that under Et_2AlCl catalysis conditions not only an important increment of the diastereoselectivity is achieved but also an inversion of the major *endo* regioisomer is obtained. The influence of Lewis acids on the facial selectivity in cycloaddition reactions was also observed with other dienophiles.[12,14]

The absolute configuration of the *endo* adduct **6** was determined by hydrolysis of the ester with LiOH and correlation of its optical rotation with the reported one for the (2*S*) enantiomer of the 5-norbornene-2-carboxylic acid.[15] The carboxylic acid derived from **6** displayed an $[\alpha]_D$ +148.4 (*c* 0.73, $CHCl_3$) [lit.[15] −151.5 (*c* 2.0, $CHCl_3$)] indicating that the (2*R*) enantiomer was the predominant one in the Diels–Alder reaction under thermal conditions. It is important to point out that the chiral auxiliary **3** was recovered quantitatively.

The study described vide supra is the first report on the use of a levoglucosenone derivative **3** as chiral auxiliary in a Diels–Alder reaction. This enantiomerically pure



Scheme 4.

alcohol is a crystalline and easily purified substrate, readily available in two steps from levoglucosenone in high overall yields. 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.

Further optimization of the reaction conditions with other Lewis acids catalysts using this chiral template are in progress and will be published in due course.

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6. Compound **2**: mp=235–236 °C (hexane/ethyl acetate); $[\alpha]_D$ −109.7 (*c* 0.50, $CHCl_3$); IR (KBr) ν_{max} 1732 (C=O), 1478, 1458, 1223, 1117, 987 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.36–7.01 (m, 8H, aromatics), 4.83 (d, $J_{3,3a}$ = 3.2 Hz, 1H, H-3a), 4.67 (d, $J_{5,6}$ = 4.4 Hz, 1H, H-5), 4.59 (s, 1H, H-1), 4.30 (d, $J_{4,4a}$ = 1.8 Hz, 1H, H-4a), 3.72–3.61 (m, 2H, H-$6_{endo,exo}$), 2.84 (dd, $J_{3,4}$ = 9.8 Hz, $J_{3,3a}$ = 3.2 Hz, 1H, H-3), 2.19 (dd, $J_{3,4}$ = 9.8 Hz, $J_{4,4a}$ = 1.8 Hz, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 198.6 (C, C-2), 143.8 (C, aromatic), 140.9 (C, aromatic), 140.4 (C, 2C, aromatic), 126.2 (CH, aromatic), 126.1 (CH, 2C, aromatic), 125.9 (CH, aromatic), 124.5 (CH, 2C, aromatic), 123.9 (CH, aromatic), 122.8 (CH, aromatic), 99.0 (CH, C-1), 76.7 (CH, C-5), 69.4 (CH_2, C-6), 49.7 (CH, C-4a), 46.6 (CH, C-3a), 45.1 (CH, C-3), 43.2 (CH, C-4). Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.94; H, 5.28.
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9. Compound **3**: mp=225–226 °C (hexane/ethyl acetate); $[\alpha]_D$ +58.3 (*c* 0.73, $CHCl_3$); IR (KBr) ν_{max}: 3521, 2958, 2900, 1458, 1138, 1095, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.02 (m, 8H, aromatics), 4.95 (s, 1H, H-1), 4.70 (d, $J_{3,3a}$ = 2.1 Hz, 1H, H-3a), 4.47 (d, $J_{5,6exo}$ = 3.9 Hz, 1H, H-5), 4.19 (d, $J_{4,4a}$ = 2.1 Hz, 1H, H-4a), 3.87 (dd, $J_{2\text{-OH}}$ = 12.4 Hz, $J_{2,3}$ = 10.4 Hz, 1H, H-2), 3.66 (d, J_{gem} = 6.9 Hz, 1H, H-6 *endo*), 3.58 (dd, J_{gem} = 6.9 Hz, $J_{5,6exo}$ = 3.9 Hz, 1H, H-6 *exo*), 2.58 (td, $J_{3,4}$ = $J_{2,3}$ = 10.4 Hz, $J_{3,3a}$ = 2.1 Hz, 1H, H-3), 1.98 (dd, $J_{3,4}$ = 10.4 Hz, $J_{4,4a}$ = 2.1 Hz, 1H, H-4), 1.61 (d, $J_{2\text{-OH}}$ = 12.4, OH). ^{13}C NMR ($CDCl_3$) δ 144.2 (C, aromatic), 143.3 (C, aromatic), 143.1 (C, aromatic), 141.7 (C, aromatic), 126.3 (CH, aromatic), 126.1 (CH, aromatic), 125.9 (CH, aromatic), 125.6 (CH, aromatic), 124.8 (CH, aromatic), 124.5 (CH, aromatic), 123.3 (CH, aromatic), 122.7 (CH, aromatic), 102.4 (CH, C-1), 76.0 (CH, C-5), 71.0 (CH_2, C-6), 69.2 (CH, C-2), 51.0 (CH, C-4a), 46.0 (CH, C-3a), 42.1 (CH, C-4), 36.2 (CH, C-3). Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 77.70; H, 5.91.
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