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Asymmetric construction of substituted pyrrolidines via 1,3-dipolar cycloaddition of azomethine ylides and chiral acrylates derived from biomass

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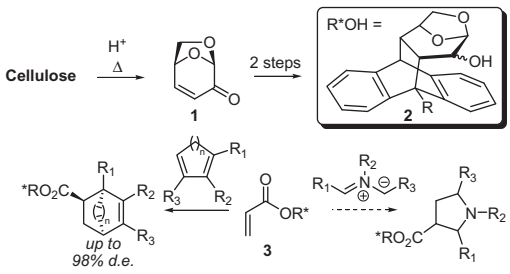
ABSTRACT

The first application of chiral auxiliaries synthesized from levoglucosenone (a biomass-derived anhydrosugar) in asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides is herein reported. The corresponding pyrrolidinic cores were obtained in excellent levels of regio and stereocontrol, good to excellent π-facial selectivities, and could be isolated enantiomerically pure by column chromatography. Unexpected NMR observations coupled with DFT calculations allowed the stereochemical assignment of the synthesized adducts. The stereochemical assignment performed in silico was further unambiguously validated by structural X-ray diffraction analysis.

Asymmetric synthesis has gained a privileged position in modern organic chemistry, mainly because of the growing demand for a wide variety of chiral compounds from both academic research and industrial activities.[1] Despite this discipline has reached unsuspected levels of sophistication, the development of new, simple, and efficient synthetic procedures for enantioselective chemical transformations is still a tremendous challenge. In particular, several features of asymmetric synthesis must be updated, especially those related to environmental security and sustainable development, being the use of abundant and renewable sources of chirality one of the main alternatives to achieve sustainability.[2] Within this field, biomass has received increasing attention as raw material for the manufacture of high-added-value compounds.[3] Carbohydrates, and in particular cellulose, are by far the most important fraction of renewable biomass from which to obtain useful chiral compounds. The pyrolysis of cellulosic materials under controlled experimental conditions affords levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose).[4,5] Our research interest is focused on the synthesis of new chiral template derivatives as new tools in asymmetric synthesis using levoglucosenone as starting material.[6] In this context, we have developed chiral alcohols **2** easily obtained in two steps from **1** and were found to be excellent chiral auxiliaries in Diels–Alder reactions between the corresponding acrylic esters **3** and a variety of dienes (Scheme 1).[6b–e]

The high levels of asymmetric induction achieved, along with the sustainable access of the chiral inductors, prompted us to expand the scope of these systems. Thus, we next turned our attention to the 1,3-dipolar cycloaddition reactions using chiral acrylates **3** and azomethine ylides as a source of enantiomerically pure chiral pyrrolidines (Scheme 1). These privileged structural



Scheme 1.

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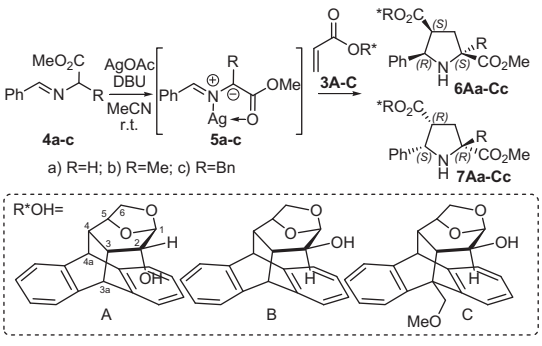
motifs are found in a wide variety of natural products, synthetic pharmaceutical and agrochemical agents. Several biologically active compounds share this five-membered heterocycle in their molecular architectures.[7] For instance, poly-substituted prolines were pointed as potent inhibitors of the hepatitis C virus (HCV) polymerase, hence affording a promising alternative treatment to a disease that affects more than 190 million people around the world.[8] In addition, recent studies revealed that such compounds display promising organocatalytic activity, opening a new door in the vast field of asymmetric organocatalysis.[6a,9]

Levoglucosenone was obtained from the microwave-assisted pyrolysis of acid pretreated microcrystalline cellulose.[4b] The enantiomerically pure chiral acrylates **3A–C** were synthesized from **1** in three steps following our previously reported methodology.[6d,6e] The introduction of a substituent at the benzylic position of the chiral auxiliary proved to be a key element of stereocontrol in asymmetric Diels–Alder reactions. However, as the azomethine ylides are more sterically demanding than the previously evaluated dienes, the reactivity and selectivity trends might be affected. For that reason, the acrylic esters **3A–B** were chosen to determine the effect of the absolute configuration at the carbinolic center of the chiral auxiliary, and compound **3C** would allow to establish the influence of a bulky group at the benzylic position closer to the alkene moiety. The methoxymethyl group present in acrylate **3C** was found to be the most effective substituent (in terms of facial selectivity) among several evaluated in our group (Scheme 2).[6b–e]

Among the different strategies developed for the formation of azomethine ylides (AMYs), one of the most simple, mild, and reliable procedures consists of the in situ generation of stabilized N-metalated AMYs **5** from iminoesters **4**,[10] which in turn can be easily obtained from the condensation of aminoesters and aldehydes. To evaluate the effect of the steric hindrance of the AMY in the outcome of the reactions, we synthesized three iminoesters derived from glycine (**4a**), alanine (**4b**), and phenylalanine (**4c**) methyl esters and benzaldehyde as the carbonylic moiety. As shown in Table 1, the use of AgOAc/DBU in MeCN proved to be effective experimental conditions to carry out the reactions.[6a]

The corresponding *endo* adducts **6–7** were exclusively obtained in good to excellent yields in all cases, hence proving that the three chiral auxiliaries under study afforded excellent levels of stereo and regiocontrol. Interestingly, the acrylate **3A** displayed higher reactivity and lower π-facial selectivity than the parent **3B**, in contrast to what was observed in DA reactions, though the inversion of the selectivity with the absolute configuration at C-2 remained.[6d] As expected, the introduction of a substituent at the benzylic position has a profound consequence in terms of selectivity, as the acrylate **3C** afforded the highest levels of asymmetric induction (up to >99% de).

The increment of silver salt and base allowed to increase both the reactivity and yield of the reactions, though at the expense of



Scheme 2.

Table 1
Asymmetric 1,3-dipolar cycloadditions between acrylates **3A–C** and azomethine ylides **5a–c**

Entry	3	5	Method[a]	Time (h)	Yield[b] (%)	**7**/**6** ratio[c]
1	**A**	**a**	A	0.5	96	61:39
2	**A**	**b**	A	24	77	61:39
3	**A**	**c**	A	22	81	66:34
4	**B**	**a**	A	1.5	95	22:78
5	**B**	**b**	A	48	43	18:82
6	**B**	**b**	B	24	69	20:80
7	**B**	**c**	A	144	62	2:98
8	**B**	**c**	B	2	84	26:74
9	**C**	**a**	A	1	61	83:17
10	**C**	**b**	A	48	61	99:1
11	**C**	**b**	C	1	99	91:9
12	**C**	**c**	C	48	91	>99:1

[a] Method A: 1.5 equiv imine, 0.2 equiv AgOAc, 0.2 equiv DBU, MeCN, rt. Method B: 1.5 equiv imine, 0.4 equiv AgOAc, 0.4 equiv DBU, MeCN, rt. Method C: 1.5 equiv imine, 1.0 equiv AgOAc, 1.0 equiv DBU, MeCN, rt.
[b] Isolated yield after column chromatography.
[c] Determined on the ^{1}H NMR spectra of the mixtures obtained after column chromatography.

the lower diastereoselectivity (entries 7-8 and 10-11). A similar observation can be drawn regarding the nature of the R substituent of the azomethine ylide, being the derivative of glycine (**5a**) the most reactive and lowest selective among the studied amino esters.

One of the most noteworthy properties of this system is the possibility of separation of all pairs **6-7** by standard column chromatographic techniques. Therefore, regarding the π-facial selectivity achieved in each case, all chiral pyrrolidines **6Aa–Cc** and **7Aa–Cc** could be obtained enantiomerically pure in a simple and straightforward manner.

The structural assignment of each compound was done by careful analysis of the ^{1}H, ^{13}C as well as 2D NMR spectra (COSY, HSQC, and HMBC). The relative stereochemical assignments were unequivocally established through NOE experiments. Figure 1 shows the key NOE interactions that allowed us to determine the *endo* nature of all isolated compounds.

Noticeable, we found that the acetal protons (H-1) of the chiral auxiliary moieties of all major isolated diastereoisomers were significantly shifted up-field (up to 1.35 ppm) compared with the H-1 signals of the corresponding minor isomers, regardless the nature of the chiral auxiliary and the azomethine ylide employed in the cycloaddition process. Interestingly, the opposite situation was observed for the benzylic H-3a signals, which were found considerably shielded (up to 0.94 ppm) in all minor adducts derived from the chiral auxiliaries **A** and **B**. Based on the magnitude of the above mentioned shifts, it was not until HSQC analysis that we could unequivocally locate this signal, as the C-1 and C-3a carbons, much less affected by anisotropic effects, are always in the ~97–100 ppm and ~44–48 regions, respectively.[11] As a representative example, Figure 2 shows the partial ^{1}H NMR spectra of both adducts derived from acrylate **3A** and **5a**. A complete data set for all isomers is presented in Table 2.

The origin of this interesting spectroscopic observation can be found considering the magnetic anisotropy exerted by the ring current of the phenyl group present in the pyrrolidine moiety. Indeed, the space-oriented anisotropic effects are the main principles of many chiral derivatizing agents (CDA), such as Mosher's reagent, commonly used to determine absolute configuration and enantiomeric purity of chiral alcohols, amines, etc.[12] For that reason, we envisaged the spectroscopic singularity above described as a paramount opportunity to assess the absolute configuration of each pair of *endo* adducts obtained.

As in the case of CDAs, the conformational dynamics of each system represents an important issue to understand the

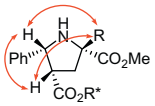


Figure 1. Key NOE correlations for stereochemical assignments of *endo* adducts **6Aa**–**Cc** and **7Aa**–**Cc**.

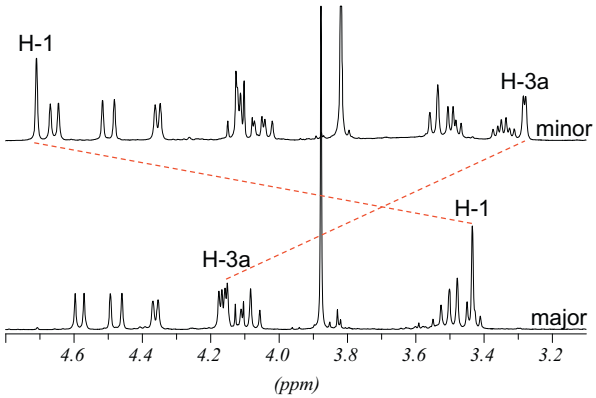


Figure 2. Partial ^{1}H NMR spectrum of both adducts derived from **3A** and **5a** recorded at 300 MHz in $CDCl_3$.

Table 2
^{1}H NMR chemical shifts of the H-1 and H-3a protons corresponding of all major and minor isolated isomers[a]

Entry	3	5	H-1 major	H-1 minor	H-3a major	H-3a minor
1	**A**	**a**	3.43	4.71	4.15	3.28
2	**A**	**b**	3.38	4.73	4.14	3.20
3	**A**	**c**	3.38	4.72	4.07	3.18
4	**B**	**a**	4.22	4.83	3.95	3.55
5	**B**	**b**	4.19	4.87	3.97	3.50
6	**B**	**c**	4.23	4.86	3.87	3.52
7	**C**	**a**	3.93	5.00	—	—
8	**C**	**b**	3.92	—	—	—
9	**C**	**c**	3.96	—	—	—

[a] Recorded at 300 MHz in $CDCl_3$.

experimental NMR observations.[12] This aspect is of critical importance considering that a 180° rotation around the C-1′/C-2′ bond produces two main types of conformers, namely *syn* and *anti* (Fig. 3). In the *syn* conformers the phenyl group is located in the same side of the acetal proton (H-1), while in the *anti* conformers the aromatic moiety is near H-3a. Consequently, the effective shielding exerted by the phenyl group at the pyrrolidine ring relies not only on the conformational preference of each compound, but also on the proximity and the relative orientation between the aromatic moiety with H-1 and H-3a. For that reason, the conformational equilibrium of these systems was next studied in detail using density functional theory (DFT) calculations, that have been successfully employed in related systems.[12,13]

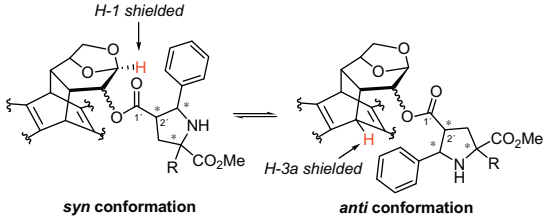


Figure 3. Schematic representation of the two main types of conformations for each compound.

The high spectroscopic resemblance found for all R groups (H, Me, Bn) prompted us to study theoretically only the glycine derivatives (R = H) for computational simplicity. Therefore, extensive conformational searches were run to locate all local minimum conformers of the systems **6Aa**, **6Ba**, **6Ca**, **7Aa**, **7Ba**, and **7Ca** at the B3LYP/6-31G* level of theory with the Polarisable Continuum Method (PCM) using chloroform as solvent.[11] In the case of compounds **6Aa** and **7Aa** a clear preference for the *anti* and *syn* conformations, respectively, was observed. A more complex situation was observed when dealing with the pair **6**–**7Ba**, in which both types of conformers were found to be representative for each isomer. Finally, the *syn* conformations were the only significantly populated for both **6Ca** and **7Ca**, mainly because the *anti* conformers suffer from unfavorable steric interactions with the methoxymethyl group.[11]

Once the conformational dynamics for each compound was unraveled, we next performed GIAO ^{1}H and ^{13}C NMR calculations, which represent a valuable and indisputable tool in modern structure elucidation.[14] Thus, the magnetic shielding tensors of all significantly populated conformers were computed at the mPW1PW91/6-31G* level of theory in solution (PCM, $CHCl_3$), using the multi-standard approach to extract the chemical shifts.[15] Table 3 shows the Boltzmann-averaged chemical shifts computed for H-1 and H-3a, along with the experimental values found. Based on the computed results, we could propose that the mayor isolated adducts of the reactions of **2A** and **2C** are **7** (with a 2*R*,4*S*,5*S* absolute configuration at the pyrrolidine moiety), whereas **6** is the major isomer of the reaction using **2B** as dipolarophile. The calculation of the CP3 parameters to address the question of assigning two sets of experimental data to two possible structures supported our assignment.[11,16]

This stereochemical assignment performed in silico was further unambiguously established by structural X-ray diffraction analysis on single crystals of the major adducts of the reactions between **3A** and **3B** with **5a** (Fig. 4). Interestingly, compound **7Aa** is crystallized in a *syn* conformation which is remarkably similar to the global minimum computed at the B3LYP/6-31G* level of theory. On the other hand, compound **6Ba** shows an *anti* conformation in the solid state while the *syn* is the preferred one according to our computational results.

Finally, it is important to point out that the chiral auxiliary moiety can be easily removed to obtain the desired chiral polysubstituted-pyrrolidine. As a representative example (depicted in

Table 3
Experimental and calculated ^{1}H NMR δ and $\Delta\delta$ values (in ppm) for selected nuclei

	H-1		H-3a	
	Exp.	Calcd	Exp.	Calcd
δ_{5Aa}	4.72	4.58	3.30	3.11
δ_{6Aa}	3.45	3.58	4.17	4.23
$\Delta\delta$	−1.27	−1.00	0.87	1.12
δ_{5Ba}	4.23	3.62	4.03	4.22
δ_{6Ba}	4.86	4.35	3.57	3.82
$\Delta\delta$	0.63	0.73	−0.46	−0.40
δ_{5Ca}	5.00	4.62	—	—
δ_{6Ca}	3.93	3.68	—	—
$\Delta\delta$	−1.07	−0.94	—	—

$\Delta\delta = \delta_6 - \delta_5$.

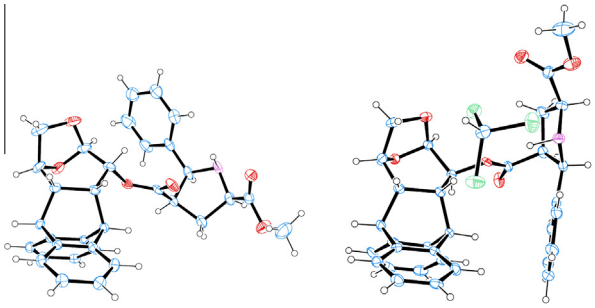
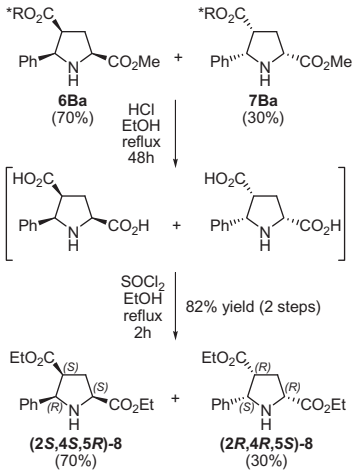


Figure 4. X-ray crystallographic structures of the major isolated adducts of the reactions between **2A** and **2B** with **3a** (**7Aa** and **6Ba**, respectively).



Scheme 3.

Scheme 3), treatment of a 70:30 mixture of adducts **6Ba** and **7Ba** (determined by ^{1}H NMR) with concentrated HCl in refluxing EtOH afforded the corresponding dicarboxylic acid, that was further re-esterified without isolation.[17] Thus, the crude material was treated with thionyl chloride in refluxing anhydrous ethanol, yielding diethyl-5-phenyl-pyrrolidine-2,4-dicarboxylate **8** in very good overall yield, and in a 70:30 ratio according to chiral HPLC analysis. The ^{1}H and ^{13}C NMR data were identical to the previously reported for **8**,[17] indicating that the chemical and stereochemical integrity of the pyrrolidine core remains unaffected upon the experimental conditions used for cleavage. Another salient feature of this protocol is that the chiral auxiliary was recovered in good yield.

In summary, this is the first application of levoglucosenone-derived chiral auxiliaries in asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides. The regio and *endo* selectivities were excellent and the yields and π-facial selectivities ranged from good to excellent (up to >99:1). As a key feature of this system, the synthesized pyrrolidines could be obtained enantiomerically pure after standard column chromatography. Unusual spectroscopic observations allowed the stereochemical assignment of the isolated adducts combining DFT calculations and structural X-ray analysis. A full study aimed at broadening the scope of these cycloadditions is currently in progress and the results will be published in due course.

Acknowledgments

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Supplementary data

Supplementary data (computational and spectroscopic data and experimental procedures) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.113.

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