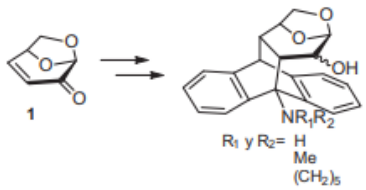
Graphical abstract

Synthesis of new chiral 1,3-aminoalcohols derived from levoglucosenone and their application in asymmetric pp xxx–xxx alkylations María M. Zanardi, Alejandra G. Suárez *



Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of new chiral 1,3-aminoalcohols derived from levoglucosenone and their application in asymmetric alkylations

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http://dx.doi.org/10.1016/j.tetlet.2015.04.051 0040-4039/

Please cite this article in press as: Zanardi, M. M.; Suárez, A. G. Tetrahedron Lett. (2015), http://dx.doi.org/10.1016/j.tetlet.2015.04.051

Article info

Abstract

We have developed a simple procedure for the preparation of chiral 1,3-aminoalcohols using the biomass derivative levoglucosenone, as the chiral starting material. 1,3-aminoalcohols, bearing primary and tertiary amino groups, were tested as chiral catalysts in the asymmetric addition of diethyl zinc to benzaldehyde.

Article history:

Received 3 March 2015

Revised 10 April 2015

Accepted 12 April 2015

Available online xxxx

Keywords:

Levoglucosenone

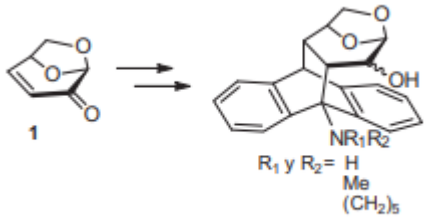
1,3-Aminoalcohols

Chiral ligands

Asymmetric induction

Introduction

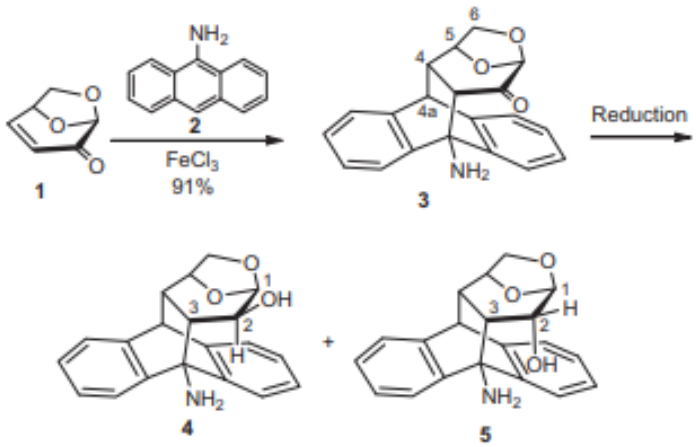
Aminoalcohols are important building blocks represented in natural products and pharmaceuticals and are useful synthons for organic syntheses. In particular, they have been extensively used in asymmetric synthesis, both as chiral ligands and auxiliaries.[1,2] While less frequently employed than 1,2-aminoalcohols, 1,3-aminoalcohols have also contributed significantly to the development of asymmetric synthesis. There are some examples of their uses in diverse chemical transformations such as Diels–Alder and other cycloaddition reaction, sigmatropic rearrangement, aldolic reactions, ring opening reactions, transition-metal-catalyzed reactions, etc.[3] However, the catalytic asymmetric carbon–carbon bond formation is one of the most active research areas in which aminoalcohols have been tested as catalysts.[4] Despite the variety of chiral ligands that have been synthesized and tested, the development of cost-effective catalysts that could exhibit high reactivity and enantioselectivity still remains an active research topic. In this context, we focused our attention on the development of new tools for asymmetric synthesis using biomass derivatives as chiral starting material. We have already synthesized new and efficient chiral auxiliares and organocatalysts starting from levoglucosenone (**1**) (1,6-anhydro-3,4-dideoxy-b-Dglycero-hex-3-enopyranos-2-ulose) which is the major product of the pyrolysis of acid-pretreated waste paper.[5,6] This bicyclic enone has also been used as a chiral synthon in the synthesis of a wide variety of compounds.[7] In order to explore new applications for levoglucosenone, we wish to report our recent progress on the use of this easily available member of the carbohydrate pool for the development of new chiral 1,3-aminoalcohols (Scheme 1) and their applications in the enantioselective diethylzinc addition to benzaldehyde.



Scheme 1.

Results and discussion

The design of the new chiral 1,3-aminoalcohols derived from levoglucosenone was envisaged by functionalizing the double bond of **1**, using a general procedure which involves a Diels– Alder reaction between **1** and a suitable 9-anthracene derivative **2** to afford the cycloadduct **3**, followed by the reduction of the carbonyl group to afford the diastereomeric alcohols **4** and **5** Scheme 2. The choice of 9-aminoanthracene as diene relies on the possibility to prepare the corresponding aminoalcohols with different substitution at the amino group. In this way, the design of the new



Scheme 2.

Table 1
Study of the reduction reaction of cycloadduct **3**

Entry	Reductor	Solvent	Temp (°C)	Yield[a] (%)	**4**/**5**[b]
1	$NaBH_4$	CH_2Cl_2/MeOH 50:50	0	86	60/40
2	$NaBH_4$	CH_2Cl_2/MeOH 80:20	0	89	61/39
3	$NaBH_4$	CH_2Cl_2/MeOH 85:15	0	99	67/33
4	$NaBH_4$	CH_2Cl_2/MeOH 90:10	0	92	74/26
5	$NaBH_4$	CH_2Cl_2/MeOH 95:5	0	97	72/28
6	$NaBH_4$	CH_2Cl_2/MeOH 98:2	0	92	85/15
7	DIBAL-H	THF	−78	48	0/100
8	$LiAlH_4$	THF	0	52	40/60

[a] Yield based on the isolated product.
[b] Ratio between the epimeric aminoalcohols determined by ^1H NMR analysis.

chiral 1,3-aminoalchools was conceived in order to determine the relationship between the absolute configuration of the carbinolic center and the substitution of the amino group with the inductive capacity.

Using the procedures described in our previous reports,[6,7] we have developed a convenient access to a large amount of levoglu-cosenone which was employed as the chiral starting material for the cycloaddition reaction with 9-aminoanthracene. The synthesis of **2** was made in two steps starting

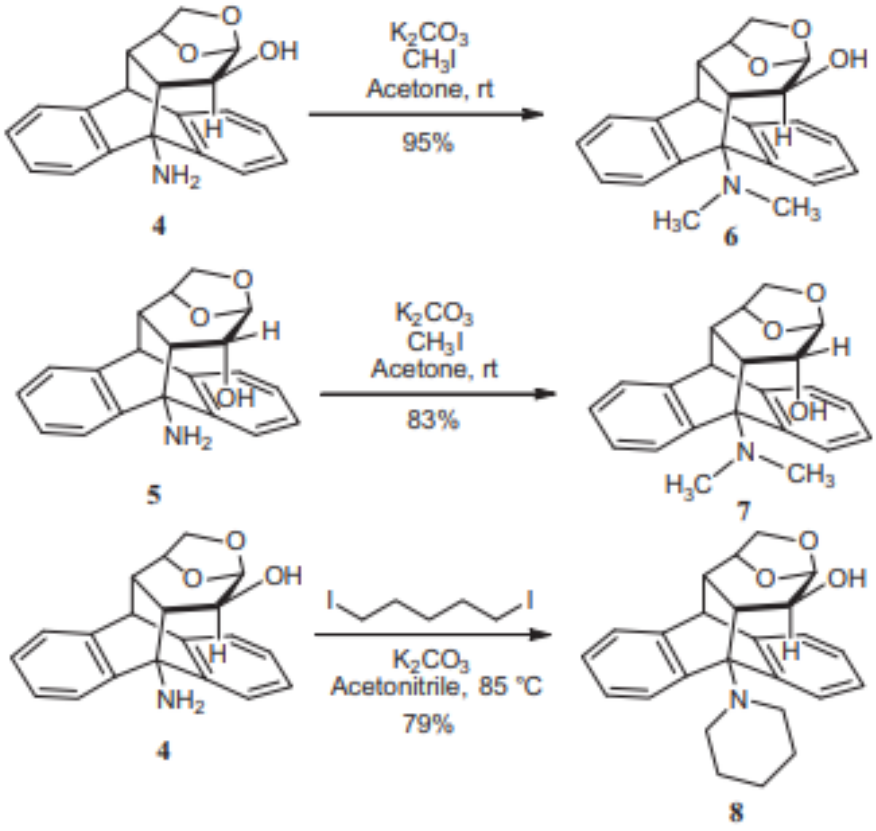
from anthracene by a nitration reaction[8] with HNO3 and HCl followed by the reduction of the nitro group by hydrogenation reaction catalyzed by Pd/C,[9] affording **2** with 94% overall yield. This compound was used as a diene in the Diels–Alder reaction with **1** employing a catalytic amount of anhydrous FeCl3. The reaction might be expected to yield up to four isomeric products since the aromatic substrate can add from the bottom or the top face of the dienophile, besides the possibility of the formation of the ortho and meta regioisomers. However, after column chromatography only the ortho cycloadduct **3** was isolated as a single diastereomer in 91% yield. This selectivity could be explained due to the exclusively attack of the diene through the α face of the pyranose ring because of the steric hindrance produced by the 1,6-anhydro bridge.[10] It was already observed that the ortho regioisomer is generally preferred in cycloaddition reactions of 9-substituted anthracenes with dienophiles.[11] The stereochemical assignments of the new compound were made possible by the use of ^{1}H NMR spin decoupling and NOE data. The NOE observed between H-4 and H-6 indicates that the diene approached from the α-face of the dienophile, whereas the NOE between H-4a and H-5 reveals the formation of the ortho adduct.

Once the synthesis of cycloadduct **3** was achieved in a straightforward and efficient manner, we proceeded to the generation of the desired 1,3-aminoalcohols **4** and **5** by reduction of the carbonyl functionality of **3**. In order to provide a methodology to synthesize selectively each epimeric 1,3-aminoalcohol, we studied the reaction employing different reducing agents and experimental conditions. The results are summarized in Table 1.

The diastereoselective conversion of **3** 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. A simple reduction of the ketone **3** with NaBH4 employing CH2Cl2/MeOH (50/ 50) as the solvent mixture, led to the formation of two diastereomeric alcohols **4** and **5**. Separation of these products was easily performed by flash column chromatography affording **4** and **5** in a 60/40 ratio (Table 1, entry 1). The most significant data in the ^{1}H NMR spectrum of the main product **4** are the signals assigned to the anomeric proton that appear at 5.05 ppm as a doublet, with a coupling constant of 3.2 Hz, and the carbinolic signal H-2 that appears at 3.16 ppm. The second isomer proved to be the epimeric alcohol **5** according to the spectroscopic evidences. The ^{1}H NMR spectrum of **5** showed a signal at 5.03 ppm as a singlet for the anomeric proton, suggesting that the dihedral angle between H-1 and H-2 is close to 90, and a doublet at 4.01 ppm that corresponds to the carbinolic proton H-2. It is important to note that the carbinolic signal of **4** was significantly shifted upfield (3.16 ppm) compared to the equivalent proton in **5** (4.01 ppm). This protecting effect suggests that in the epimer **4** the H-2 is probably affected by the anisotropy of the aromatic system. The NOE observed between H-2 and the aromatic proton suggested the proximity of these nuclei through the space verifying without ambiguity the S configuration of C-2 in compound **4**. The preferred formation of the major epimer **4** can be justified on the basis of coordination of the boron atom to the nonbonding electron pair of the nitrogen atom, which would facilitate the hydride attack by α face of the pyranoside ring. For this reason, the use of a less coordinating solvent mixture with higher percentage of CH2Cl2 (entries 2–6), promoted the increases ratio **4**–**5**. In contrast, when the reducing agent employed was bulkier and more selective as DIBAL-H or less coordinating as LiAlH4 the attack of the hydride occurs preferably from the β face giving the corresponding epimer **5** as sole or main product (entries 7–8). These results

are in good agreement with our previous reports which demonstrated that the hydride attack takes place through the less crowded face of the carbonyl group.[5e,10]

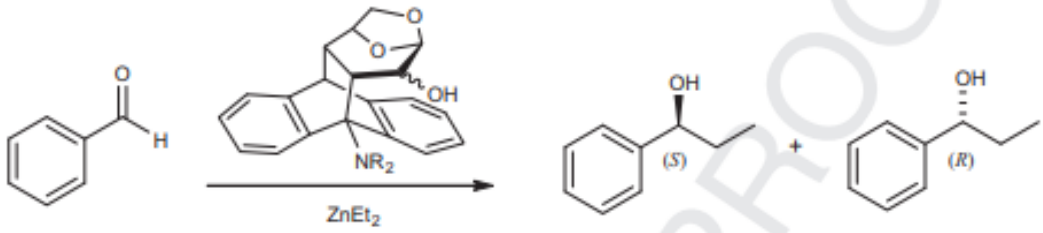
We next studied the synthesis of chiral 1,3-aminoalcohols with different substitution at the amino groups, Scheme 3. Our objective was to determine if the amino substitution could exert any influence on the enantioselective capacity of these chiral ligands, as it was reported for other catalysts.[12,13] To achieve this goal, we decided to carry out a controlled alkylation of the amino functionality. The preparation of the secondary amino derivative was performed by a methylation reaction of the amine **4** with methyl iodide and NEt3. All attempts produced the desired product in very low yield and could not be properly purified to be employed as a chiral inductor. However, treatment of either aminoalcohols **4** and **5** with K2CO3 and MeI in acetone enables us to synthesize the 1,3-aminoalcohols with tertiary amino group **6** and **7** in very good yields. There are precedents in the literature which demonstrates that aminoalcohols with piperidine as amino group produce better enantioselectivities in the asymmetric addition of dialkylzinc to aldehydes.[12,13] For this reason, **4** was treated with 1,5-diiodopenthane and K2CO3 in refluxing acetonitrile. The reaction afforded the cyclic amino derivative **8** with a piperidine like structure.

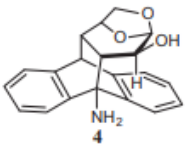
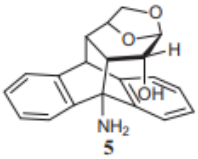
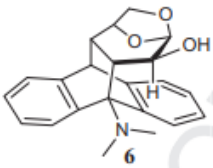
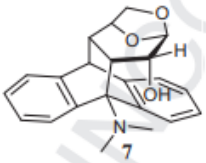
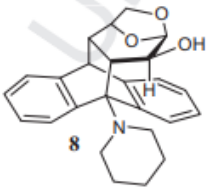


Scheme 3.

Table 2

Study of the ZnEt2 [a] addition to benzaldehyde catalyzed by 1,3-aminoalcohols



Entry	Ligand	mol %[a]	Time (h)	Yield (%)	ee (%)	Config[b]
1		5	68	40	32	R
2		10	46	76	42	R
3		20	24	94	54	R
4		30	24	90	50	R
5		20	48	78	36	R
6		30	48	80	74	R
7		5	72	75	40	R
8		10	72	62	44	R
9		20	22	70	10	R
10		10	96	64	20	R
11		20	72	76	14	R
12		10	24	64	20	S
13		20	24	96	24	S

[c] Main enantiomer of 1-phenyl-1-propanol assigned by the literature data[15] and confirmed by polarimetry through [a]D measurements.

[a] 1,1 M in hexane, 2 equiv regarding to benzaldehyde.

[b] Determined by HPLC with Chiralcel OD-H column.

Once the syntheses of inductors **4–8** were achieved in a straightforward manner, they were evaluated as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde. The reactions were performed using standard conditions with 2 equiv of ZnEt2 in the presence of the chiral ligand,[14] Table 2.

The enantioselective diethylzinc addition to benzaldehyde catalyzed by the 1,3-amonialcohols **4–8** produced 1-phenyl-1-propanol. It has been reported that the outcome of this enantioselective reaction depends upon the aldehyde, dialkylzinc, and the catalyst ratio, which strongly affects the reactivity and selectivity. For this reason, we started our study using the 1,3-aminoalcohol **4**. We could observe that the increment of the amount catalyst from 5 to 20 mol % (entries 1–3) increased the yield (from 40% to 94%) and enantioselectivity (from 32% to 54%). When the amount of **4** rose to 30 mol % the ee fallen to 50%. We then evaluated the epimeric 1,3-aminoalcohol **5**, employing the amount of catalyst that produced the best results with **4**. It was found that the best enantioselectivity was obtained with the use of 30 mol % of catalyst producing a 74% of ee. Next, we turned our attention to evaluate the effect of the substitution at the amino group. For this reason, we evaluated aminoalcohols **6–7** with tertiary amino group, however, the induction capacities observed were between good to low using 10–20 mol % of catalysts. The evaluation of catalyst **8** with a cyclic amino group related to the most selective 1,3-aminoalcohol **5**, produced high yield of product with poor enantioselectivity. Comparison of the inductive capacity between all chiral ligands evaluated demonstrates that the most efficient one was **5**, having a primary amino group and *R* configuration at the carbinolic center. Considering structurally related 1,2-aminoalcohols previously reported in our group,[12] it is possible to determine that the 1,3-aminoalcohols are more enantioselective in the ZnEt2 addition to benzaldehyde. One salient feature is that for 1,2-aminoalcohols the best selectivities are observed with tertiary amino groups, meanwhile the most efficient 1,3-aminoalcohols are the ones with the primary amino group.

In summary, this is the first report of the preparation of 1,3-aminoalcohols with primary and tertiary amino groups derived from levoglucosenone and their application in the enantioselective diethylzinc in addition to benzaldehyde. The syntheses of the aminoalcohols were simple and effective, allowing to obtain the desired compounds in two or three steps from levoglucosenone. The different substitution of amino groups present in this new family of aminoalcohols, show the adequate functionalization for further transformation into other chiral derivatives. The level of induction obtained, in addition to the fact that the starting material is easily obtained from biomass, makes this system an excellent model to be exploited in other asymmetric reactions and a starting point for the development of new chiral catalysts or organocatalysts.

Acknowledgments

This research was supported by UNR, ANPCyT, CONICET, Fundación J. Prats, Argentina, M.M.Z. thanks CONICET for the award of a fellowship.

Supplementary data

Supplementary data (experimental procedures for the synthesis of all compounds, characterization data, copies of ^{1}H and ^{13}C NMR spectra of new products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04. 051.

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