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Note

Montmorillonite K-10 promoted synthesis of chiral dioxa-caged compounds derived from levoglucosenone

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ABSTRACT

A short and efficient methodology for the synthesis of chiral dioxa-caged compounds from levoglucosenone, a biomass-derived enone, is herein presented. The key transformation, that involves a cascade 3-step cationic cyclization, was efficiently carried out in high yields and selectivities by Montmorillonite K-10 catalysis. The usefulness of K-10 in related semi-pinacol rearrangements to obtain pyran-3-ones is also shown. Interesting differences in the reactivity pattern was found for epimeric alcohols, and the origins of these findings were determined by DFT calculations.

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The synthesis of highly strained organic molecules constitutes a challenging task. In the past decades, many efforts were dedicated to the development of synthetic strategies toward carbacycles.[1] More recently there has been an interest growth in the preparation of heteroatom substituted cages and bowls compounds.[2] As these molecular architectures possess both hydrophobic and hydrophilic surfaces, they are expected to have application as chelating agents for metal ions, properties that in turn could be useful in ion transportation.[3] In addition, perhaps the most promising application of these compounds constitutes their use in medicinal chemistry, mainly in the treatment of neurodegenerative diseases (Parkinson and Alzheimer) as well as other important ills such as influenza, HIV and tuberculosis.[4]

Among different strategies that were efficiently employed for the synthesis of oxa-cages, most were developed in a racemic form.[2] However, considering the dramatic impact that chirality has on several branches of science (particularly in drug discovery), the access to enantiomerically pure materials remains an attractive goal. For this reason, we devoted our efforts to the synthesis of novel chiral dioxa-caged compounds derived from biomass, which are reported herein.

During the course of our studies toward the development of new tools for asymmetric synthesis using levoglucosenone (**1**),[5] a biomass derived chiral enone,[6] we found that certain alcohols **2** rearranged to the corresponding ketone **3** in low yields upon heating under acidic conditions (Scheme 1).

As this transformation provides an interesting strategy for the synthesis of chiral pyran-3-ones, it prompted us to optimize and explore the scope of this reaction. Thus, alcohols **5** and **6** were first chosen as templates as they can be easily obtained from **1** in high yields (Scheme 2).[7] Following an experimental procedure previously developed in our group, levoglucosenone (**1**) was treated with freshly distilled cyclopentadiene at room temperature to afford the corresponding Diels–Alder adduct **4** in high yield and *endo* selectivity. Further reduction of **4** with $NaBH_4$ in aqueous ethanol yielded a ~50:50 mixture of the target alcohols **5** and **6** in excellent yield. As will be discussed later, a selective reduction toward **5** was an important need. In order to obtain good facial selectivity in this reductive stage, we considered that the use of a bulky reducing agent under mild reaction conditions would allow to discriminate between the 1,6-anhydro bridge and the cyclopentadienyl moiety, blocking the β and α face of the carbonyl group, respectively. As expected, treatment of **4** with DIBAL-H in CH_2Cl_2 at −80 °C afforded the desired alcohol **5** in good yield and selectivity.

In a pilot experiment, compounds **5** and **6** were separately treated with TFA (0.5 equiv) and heated for 10 min at 120 °C under microwave irradiation. Interestingly, while **6** remained chemically unaltered, the total consumption of **5** was observed. Apart from the desired ketone **7** (63%), a new compound **8** was isolated in 24% yield with the same molecular formula (determined by HRMS) as **5** and **7** (Scheme 3). The ^{13}C NMR spectra revealed the presence

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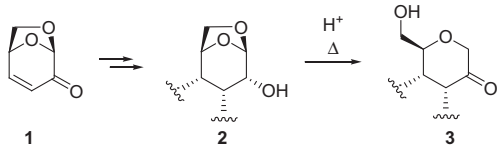
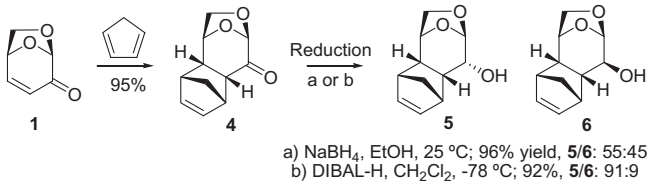


Scheme 1.



Scheme 2.

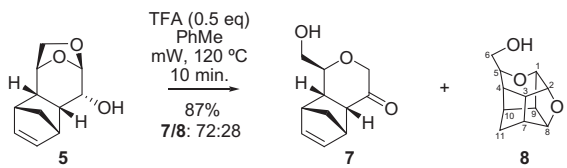
of 11 carbons, 5 of them (4 CH and 1 CH_2) at the C–O region (65–90 ppm), and the rest (5 CH and 1 CH_2) at higher fields (30–50 ppm). The lack of carbonyl, alkene and acetal carbons in the new compound represented a challenge regarding its structural elucidation. The IR data showed an intense band at 3439 cm^{-1} typical of alcohols. Moreover, treatment of **8** with Ac_2O and pyridine resulted in the formation of a single-acetylated compound as observed in the ^1H and ^{13}C NMR spectra. After extensive 1D and 2D NMR experiments (COSY, HMBC, HSQC, NOE) we arrived at the pentacyclic caged structure of **8** (Fig. 1).[8]

Additional evidence in support of our proposal was obtained from GIAO NMR calculations, a useful technique in the structural assignment of organic compounds.[9] Table 1 shows the Boltzmann averaged ^{13}C and ^1H chemical shifts computed at the mPW1PW1/6-31G*//B3LYP/6-31G* level of theory, using the multi-standard approach (MSTD).[10] A very good match between experimental and calculated NMR shifts was observed (R^2 = 0.999 and 0.997 for ^{13}C and ^1H NMR, respectively). The maximum absolute difference between predicted and observed shifts was 2.3 ppm (C-3) and 0.23 ppm (H-2), for ^{13}C and ^1H NMR, respectively, and the mean absolute differences were only 1.3 ppm (^{13}C NMR) and 0.09 ppm (^1H NMR).

Mechanistically, this reaction was assumed to proceed via the formation of oxocarbenium ion [**5+H**] from acid-promoted opening of the 1,6-anhydro bridge, Scheme 4. Next, it may undergo the expected semi-pinacol rearrangement to afford **7** (path A) or it can undergo a cyclization with the internal olefin to generate the carbocation **B**, which is subsequently trapped by the hydroxyl group at C-2 leading to **8** (path B).

The serendipitous formation of **8** provided a paramount opportunity for the development of a new method for the synthesis of enantiomerically pure dioxa-caged compounds from renewable sources. For that reason, we next explored the effect of the experimental conditions in the yield and selectivity of the transformation shown in Scheme 3. The results are summarized in Table 2.

We started our study using TFA as the acid promoter (entries 1–4), whose molar ratio reduction resulted in longer reaction times and lower yields. Interestingly, an inverse relationship between



Scheme 3.

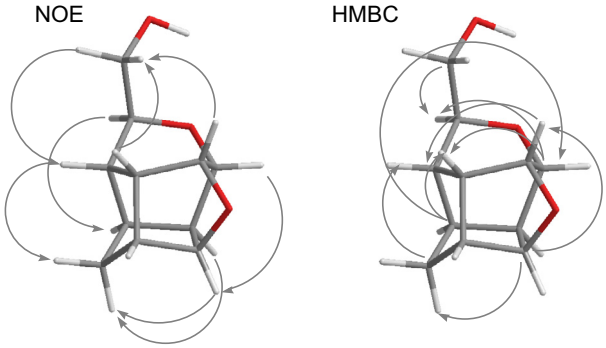
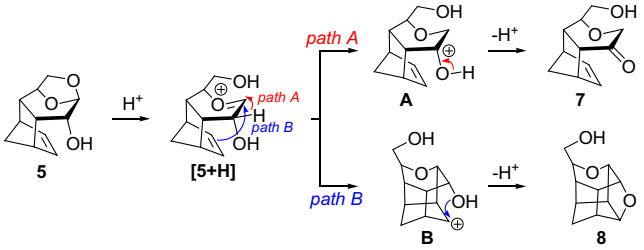


Figure 1. B3LYP/6-31G* optimized geometry (global minima) found for compound **8**, with key NOE (left) and HMBC (right) correlations for the structural assignment.

Table 1
Experimental and mPW1PW91/6-31G*//B3LYP/6-31G* calculated ^1H and ^{13}C NMR chemical shifts of **8**

Atom	δ_{exp}	δ_{calc}	Atom	δ_{exp}	δ_{calc}
C-1	74.4	73.7	H-1	3.75	3.70
C-2	76.6	75.9	H-2	4.34	4.11
C-3	36.1	38.4	H-3	2.32	2.34
C-4	39.7	40.4	H-4	1.73	1.61
C-5	72.0	71.2	H-5	4.00	3.91
C-6	65.9	64.1	H-6a	3.59	3.51
C-7	49.1	49.9	H-6b	3.51	3.45
C-8	87.1	85.0	H-7	2.57	2.49
C-9	36.7	38.7	H-8	4.63	4.43
C-10	39.4	41.0	H-9	2.17	2.04
C-11	31.9	32.7	H-10	2.22	2.11
			H-11a	1.56	1.56
			H-11b	1.36	1.38



Scheme 4.

the amount of acid employed and the selectivity obtained toward the generation of **7** was found. This trend was also observed for other Brønsted acids, such as TsOH (entries 5–7) and HCl (entries 8–10). However, in these cases the desired compound **8** could be obtained in good selectivity using equimolecular quantities of acid promoter (**8**/**7** ratio = 99:1 and 96:4, respectively), though the yields were only good for TsOH (89% and 34%, respectively). A substantial decomposition product was observed by TLC analysis with the use of HCl, as was also observed for H_3PO_4 (entry 11). On the other hand, weaker acids proved to be inefficient promoters. For instance, heating a solution of **5** with up to 5 equiv of acetic acid at 120 °C for 30 min resulted in the quantitative recovery of the starting material (entry 12). Due to the fact that we could obtain the desired pentacycle **8** in good yield and selectivity only using equivalent amounts of TsOH, we decided to develop a more sustainable and greener procedure. Thus, we next evaluated the performance of acidic solid heterogeneous catalysts, such as Amberlyst 15 (a strongly acidic synthetic resin) and Montmorillonite K-10 (a commercially available acidic aluminosilicate clay). The use of these materials in heterogeneous catalysis has several

Table 2

Entry	Conditions[a]	Yield[b] (%)	**7:8**[c]
1	**5**, TFA (1 equiv), 10 min	96%	47:53
2	**5**, TFA (0.5 equiv), 10 min	87%	72:28
3	**5**, TFA (0.1 equiv), 20 min	86%	90:10
4	**5**, TFA (0.05 equiv), 30 min	54%	95:5
5	**5**, TsOH (1.0 equiv), 10 min	89%	1:99
6	**5**, TsOH (0.5 equiv), 10 min	93%	17:83
7	**5**, TsOH (0.1 equiv), 10 min	85%	49:51
8	**5**, HCl (0.2 equiv)[d], 30 min	84%	15:85
9	**5**, HCl (0.1 equiv)[d], 30 min	79%	41:59
10	**5**, HCl (1.0 equiv)[d], 10 min	34%	4:96
11	**5**, H_3PO_4 (1.0 equiv), 10 min	14%	1:99
12	**5**, AcOH (5.0 equiv), 30 min	0%	–
13	**5**, Amberlyst 15 (10%)[e], 30 min	76%	15:85
14	**5**, K-10 (10%)[e], 30 min	88%	3:97

[a] All reactions were carried out at 120 °C in PhMe under microwave irradiation.
[b] Isolated yield after column chromatography.
[c] Determined on the ^{1}H NMR spectra of the mixtures obtained after column chromatography.
[d] 6 N aqueous solution of HCl was used.
[e] Refers to the percentage (in weight) of the solid catalyst added (10% is equivalent to 20 mg of solid/mmol of **5**).

advantages, such as reusability, selectivity, low cost, non-toxicity, and operational simplicity.[11] As is shown in Table 2, very good yields and selectivities were obtained in both cases (Amberlyst 15: 76% yield, **8**/**7** ratio = 85:15, entry 13; K-10: 88% yield, **8**/**7** ratio = 97:3, entry 14). The experimental finding employing K-10 was particularly interesting, considering that very good results were achieved with a small amount of a non-expensive and synthetic valuable clay. Several chemical transformations can be successfully catalyzed with K-10, besides the remarkable features of being non-toxic, air and water compatible and easy to handle.[12] For that reason, we next thoroughly studied the effect of the reaction conditions in the outcome of K-10 promoted synthesis of dioxa-cage compound **8**. The most representative results are shown in Table 3.

The data presented in Table 3 highlight the robustness of the system, as very good yields (76–100%) and excellent selectivities (94:6–99:1) were obtained in all cases. The solvent has the most significant influence among the evaluated parameters. Under the same experimental conditions (entries 4–7) the best results were obtained using PhMe and CH_2Cl_2, and were the solvents of choice for further evaluation. On the other hand, lowering the amount of K-10 required slightly prolonged irradiation time and/or higher temperature to achieve total consumption of the starting material (entries 7–11). The optimal temperatures were between 120 and 140 °C, since irradiation at lower temperatures resulted in a significant increase in the reaction time and did not improve the yield nor the selectivity toward **8** (entry 3) It is important to point out that the reaction proceeded very well even with very small amounts of solid catalyst (entry 11). Moreover, the K-10 clay could be easily recovered by simple filtration, dried, and reused without losing its catalytic activity.

Table 3
Montmorillonite K-10 promoted synthesis of **8**

Entry	K-10[a]	Solvent	*T* (°C)	Time (min)	Yield[b]	**8:7**[c]
1	10%	PhMe	120	30	88%	97:3
2	34%	PhMe	120	30	97%	98:2
3	36%	PhMe	80	150	76%	98:2
4	38%	PhMe	120	10	98%	98:2
5	36%	Hexane	120	10	81%	94:6
6	36%	THF	120	10	77%	94:6
7	36%	CH_2Cl_2	120	10	95%	99:1
8	20%	CH_2Cl_2	120	10	100%	99:1
9	10%	CH_2Cl_2	120	60	94%	99:1
10	10%	CH_2Cl_2	140	10	95%	99:1
11	5%	CH_2Cl_2	140	15	100%	98:2

[a] Refers to the percentage (in weight) of the solid catalyst added (10% is equivalent to 20 mg of solid/mmol of **5**).
[b] Isolated yield after column chromatography.
[c] Determined on the ^{1}H NMR spectra of the mixtures obtained after column chromatography.

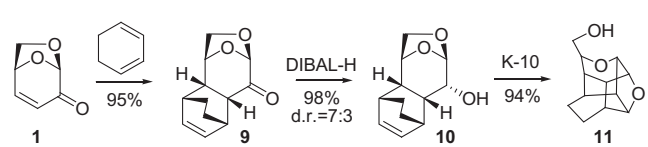
Once the synthesis of **8** was optimized, we aimed to explore the scope of the proposed synthetic procedure herein presented. We next envisaged the preparation of an additional caged compound bearing a pentacyclic dioxa-tridecane core. Accordingly, alcohol **10** was synthesized in good yield by a Diels–Alder reaction between **1** and cyclohexadiene followed by the reduction of the carbonyl group of the *endo* adduct **9**. To our delight, treatment of **10** with K-10 under the optimized reaction conditions found in Table 3 (entry 8) yielded the caged compound **11** in 94% yield and optimal selectivity (Scheme 5). The pentacyclic caged structure of **11** was confirmed by 1D and 2D NMR experiments (COSY, HMBC, HSQC, NOE), and was further validated with GIAO NMR calculations.[8,13]

Based on the proposed mechanisms shown in Scheme 4, it is clear that the use of K-10 favors the electrophilic cyclization over the 1,2-hydride shift. In order to evaluate if the methodology developed in this work could also promote semi-pinacol rearrangement in related systems, we next prepared the saturated alcohols **12** and **13** under standard hydrogenation conditions. Treatment of **12**–**13** with 20% of K-10 in toluene at 120 °C for 30 min yielded the expected pyran-3-one derivatives **14**–**15** in very good yields (Scheme 6), indicating that K-10 is also a good catalyst for the originally targeted rearrangement (Scheme 1).

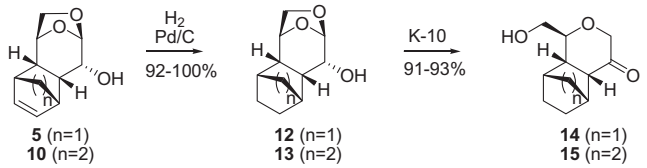
Notably, while all alcohols having a 2-*R* configuration at the carbinolic center (compounds **5**, **10**, **12,** and **13**) reacted smoothly to afford the rearranged products (**7**, **8**, **11**, **14,** and **15**), the corresponding epimers at C-2 were recovered unchanged after exposure of K-10 (up to 40%) at high temperatures (up to 150 °C). This suggests that the 1,6-anhydro bridge opening is strongly influenced by stereoelectronic effects exerted by the vicinal alcohol stereochemistry. To provide a better understanding of the origins of these findings, we envisaged a DFT study using Gaussian 09.[14] Thus, alcohols **5** and **6**, and their corresponding oxocarbenium ions [**5+H**] and [**6+H**] were optimized using the popular meta hybrid exchange-correlation functional M06-2X developed by Truhlar,[15] coupled with the 6-311+G(d,p) basis set.[8]

Our calculations supported the higher reactivity of 2-*R* alcohols experimentally found. The isodesmic equation shown in Scheme 7 is exergonic ($\Delta G = -6.6$ kcal/mol). Interestingly, even though **6** is 2.5 kcal/mol more stable than **5**, an inverse order is found for the oxonium ion [**5+H**], which is 4.1 kcal/mol more stable than [**6+H**]. This computational result suggests that the absolute configuration at C-2 influences the stability of the resulting cation, and might dictate its ease of formation.

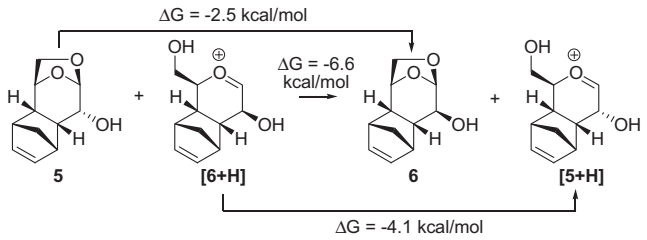
NBO analysis (M06-2X/6-311+G(d,p)) performed on both [**5+H**] and [**6+H**] revealed the origins of these findings. The lower energy computed for the former is due to a more efficient charge donation from occupied orbitals σ(C2–H2) and π(C8–C9) to the empty π*(C1–O1) orbital. The associated second order perturbation



Scheme 5.



Scheme 6.



Scheme 7.

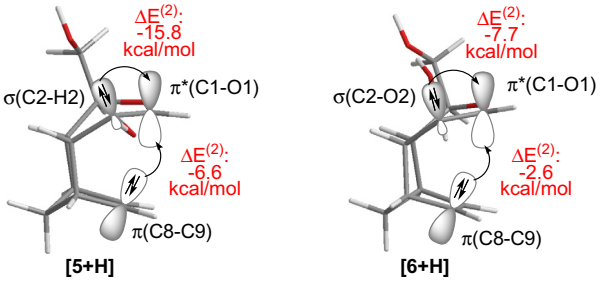


Figure 2.

energies ($\Delta E^{(2)}$) are −15.8 kcal/mol and −6.6 kcal/mol, respectively, much lower than those computed for the analogous interactions in [**6+H**]: −7.7 kcal/mol and −2.6 kcal/mol, respectively. Regarding the $\sigma//\pi^*$ interaction, the hyperconjugation is higher for [**5+H**] because it is well known that C–O bondings are worse electron donors than the C–H bondings due to the higher electronegativity of the oxygen atom. On the other hand, in the global minimum geometry found for [**6+H**] a hydrogen bonding was found between the hydroxyl groups at C-2 and C-6. This causes a slight distortion of the system, leading to a greater separation between the positively charged carbon (C-1) and the C-8/C-9 double bond. The C-1/C-8 and C-1/C-9 distances computed for [**5+H**] are 2.85 Å and 2.98 Å, respectively, and for [**6+H**] are 3.03 Å and 3.21 Å, respectively. The higher proximity between both centers in the former explains the higher $\pi \rightarrow \pi^*$ interaction computationally found (Fig. 2).

In summary, we have developed a short and efficient method for the synthesis of chiral dioxa-caged compounds using a biomass-derived starting material. The key transformation was successfully carried out using Montmorillonite K-10 clay, which afforded excellent yields and selectivities. The usefulness of this methodology in semi-pinacol rearrangements was also studied. Stereoelectronic effects were pointed to be responsible of a marked reactivity difference of epimeric alcohols, and DFT calculations were used to explain the origins of these findings.

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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.carres.2014.07.019.

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