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The Piancatelli rearrangement of non-symmetrical furan-2,5-dicarbinals for the synthesis of highly functionalized cyclopentenones

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Substituted and non-symmetrical furan-2,5-dicarbinals were readily prepared from hydroxymethylfurfural (HMF), a renewable raw material from biomass. The Piancatelli rearrangement of these furan-2,5-dicarbinals, catalyzed by DyCl_3 and under microwave activation, affords 5-substituted-4-hydroxymethyl-4-hydroxycyclopentenones in a regio- and diastereoselective manner. This methodology can be extended to *aza*-Piancatelli type reactions by using nitrogen nucleophiles, to furnish the corresponding aminocyclopentenone derivatives. These synthesized bis-hydroxylated cyclopentenone derivatives exhibited significant cytotoxicity against eight human tumor cell lines.

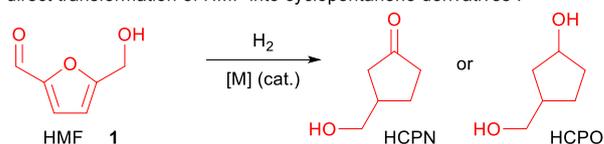
Introduction

In the field of biomass transformation, the production of 5-hydroxymethylfurfural (HMF) **1**, as a versatile sustainable substitute of petrochemical building blocks, is one of the most successful and promising routes.¹ HMF is considered as one of the "Top 10" bio-based building blocks listed by the U.S. Department of Energy.² The HMF can be obtained either by catalytic dehydration of C6 carbohydrates³ or by direct degradation of lignocellulosic biomass.⁴ Taking advantage of the primary hydroxyl, aldehyde and furan functionalities, numerous synthetic transformations have been described, supporting the versatility of HMF as a building block platform.⁵ Under reductive conditions, HMF can be converted specifically into cyclopentanone derivatives HCPN⁶ or HCPO⁷ (Scheme 1a). Otherwise, cyclopentenones which have the same degree of unsaturation as the starting furan derivatives, could be obtained directly via a Piancatelli rearrangement.⁸ Despite the number of studies on the Piancatelli rearrangement and the effectiveness of this process, direct transformations of HMF close derivatives and, more generally C-5 substituted 2-furylcarbinols have scarcely been explored.⁹ This rearrangement was only described with substrates containing a methyl,¹⁰ a phenyl¹¹ and an ethoxymethyl group¹² at the C-5 position (Scheme 1b). The intramolecular versions have been also explored with a tethered nucleophile at the C-5 position, as hydroalkyl¹³ or aminoalkyl¹⁴ side chain and also an electron rich aromatic¹⁵ moiety, triggered respectively intramolecular *O*-, *N*- and *C*-Piancatelli rearrangement for an access to spirocyclic cyclopentenones derivatives.

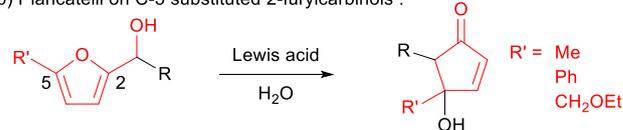
Thus, our purpose has been to expand the Piancatelli rearrangement to HMF derived furan-2,5-dicarbinals, as it

should offer an efficient access to 4-hydroxycyclopentenones and also substituted by an hydroxymethyl function in C-4 position (Scheme 1c).

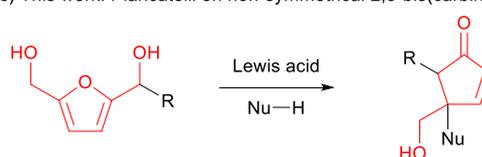
(a) direct transformation of HMF into cyclopentanone derivatives :



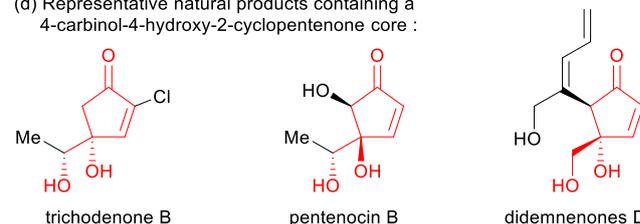
(b) Piancatelli on C-5 substituted 2-furylcarbinols :



(c) This work: Piancatelli on non-symmetrical 2,5-bis(carbinol)furan



(d) Representative natural products containing a 4-carbinol-4-hydroxy-2-cyclopentenone core :



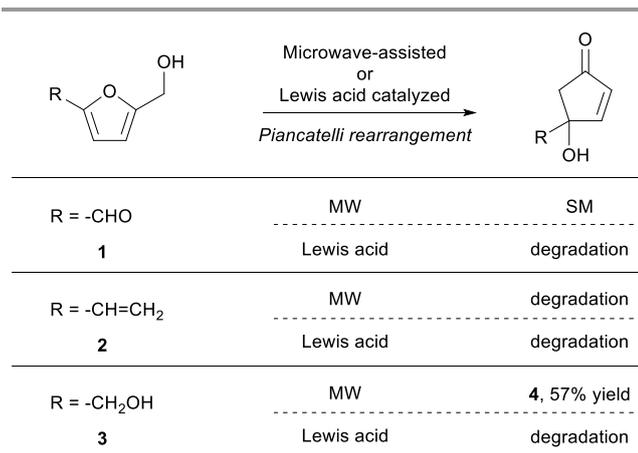
Scheme 1. Direct conversion of HMF and its close derivatives into C5-carbocycles.

These motifs are fully relevant targets as far as many natural products possess a 4-hydroxycyclopentenone core and substituted by a hydroxymethyl side chain. Examples include trichodenone B,¹⁶ pentenocin B¹⁷ or didemnenones D¹⁸ (Scheme 1d). Moreover, the 1,2-diol function of the expected final products can allow further chemical transformations for the synthesis of more complex compounds.

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Initial studies were conducted by examining the Piancatelli reaction directly on HMF **1** or simple derivatives such as 2-(hydroxymethyl)-5-vinylfuran **2** and 2,5-bis(hydroxymethyl)furan BHMf **3**, using two representative reaction conditions, that means using a lanthanide salt as catalyst^{10f,19} or using thermal conditions under microwave irradiation (Scheme 2).²⁰ All attempts to transform directly HMF **1** into cyclopentenone failed. Under thermal conditions no reaction was observed and the starting material was cleanly recovered unchanged. On the other hand, when dysprosium(III) triflate was used as catalyst to promote the rearrangement, HMF **1** was consumed but no product could be isolated or identified from the crude reaction mixture, likely due to the deactivating aldehyde functionality. These same attempts performed on **2**, have led to complete decomposition of the starting material, probably due in this case to the instability of the highly conjugated 2-vinylfuranoxonium ion intermediates **A** and **B** (Scheme S1, Part I in the Supporting Information) and the ring-opened intermediate **C** (Scheme S1, Part I in the Supporting Information).²¹ Nonetheless, we were pleased to find that 2,5-bis(hydroxymethyl)furan BHMf **3** led to the desired 4-hydroxymethyl-4-hydroxycyclopentenone **4** in 57% yield, while only degradation was observed using a Lewis acid catalyst.



MicroWave conditions : H₂O, 200 °C

Lewis acid conditions : Dy(OTf)₃ (10 mol%), *t*-BuOH/H₂O, 80 °C

Scheme 2. Attempted of Piancatelli rearrangement on HMF and its derivatives **2** and **3**.

Encouraged by this first result and in order to apply this methodology to the preparation of C5-substituted cyclopentenones, we next turned our attention reactions involving non-symmetrical furan-2,5-dicarbinols **5**. These substrates are expected to provide cyclopentenones with two contiguous stereogenic centres. Thus, the efficient control of the relative configuration of these carbon centers will be a key issue of these reactions. First, we examined the reactivity of the biscarbinol **5a**, substituted by a phenyl group, readily obtained by addition of phenylmagnesium bromide on HMF **1**.²² The microwave conditions have been applied on substrate **5a** to produce the rearranged product in 44% yield, i.e. in the same range as the unsubstituted biscarbinol **3** (Table 1, Entry 1). Since substrate **5a** possess two different carbinol moieties, the Piancatelli rearrangement can occur by two pathways (Scheme

S1, Part I in the Supporting Information). As expected, the rearrangement takes place selectively, through removal of the hydroxyl function from the secondary carbinol group. However, the Piancatelli rearrangement led to a mixture of two diastereoisomers **6a** and **7a** in a poor 60:40 ratio.

Table 1. Optimization of the reaction conditions^a

Entry	Catalyst	Temp. ^b (°C)	Time (h)	Yield ^c (%) ^c	d.r. ^d 6a:7a
1 ^e	-	MW-180	0.05	44	60:40
2	Dy(OTf) ₃	80	18	28	95:5
3	Dy(OTf) ₃ + TFA ^f	80	18	24	90:10
4 ^f	TFA	80	18	18	80:20
5	DyCl ₃	80	18	31	95:5
6	-	80	18	NR	-
7	Sc(OTf) ₃	80	18	28	90:10
8	ZnCl ₂	80	18	12	95:5
9	Fe(OTf) ₃	80	18	23	95:5
10	FeCl ₃ ·6H ₂ O	80	18	9	95:5
11	CuCl ₂	80	18	18	95:5
12	DyCl ₃	MW-80	1.5	36	95:5
13	DyCl ₃	MW-100	1.5	51	>95:5
14 ^g	DyCl ₃	MW-100	1.5	43	95:5
15 ^h	HCl	MW-100	1.5	16	55:45
16 ⁱ	DyCl ₃ + DTBMP	MW-100	1.5	23	95:5

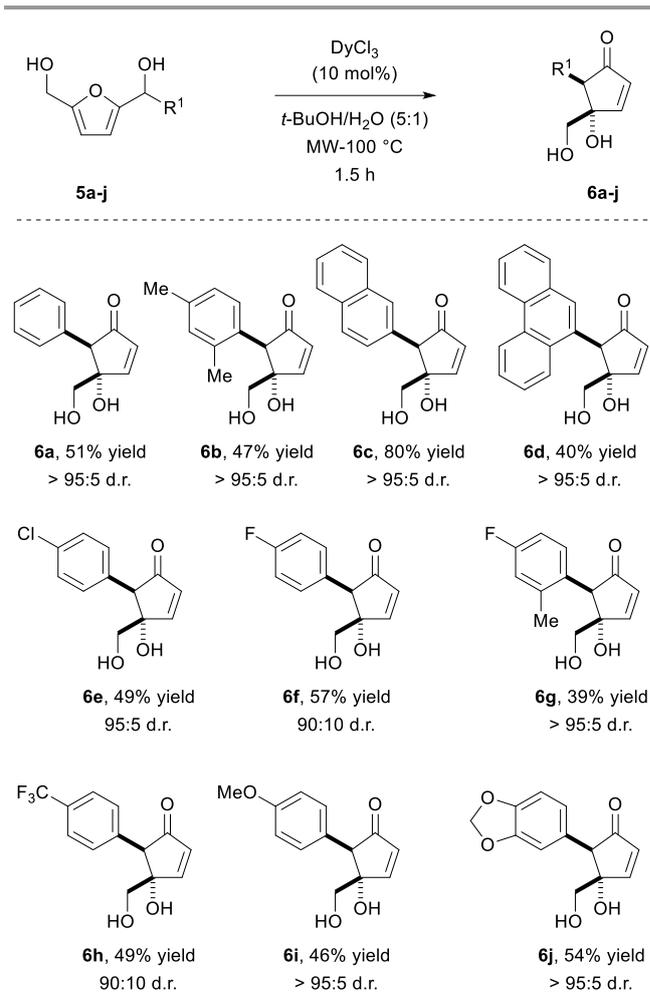
^a Reactions performed on 0.25 mmol scale in a *t*-BuOH/H₂O, 5:1 mixture, at 0.1 M.
^b MW: microwave heating. ^c Isolated yield. ^d The diastereoisomeric ratio (d.r.) was determined by ¹H NMR on the crude mixture. ^e Reaction performed in water. ^f TFA (5 mol%). ^g Reaction performed on a 1 mmol scale. ^h Reaction performed in a *t*-BuOH/HCl 1N, 5:1 mixture. ⁱ DTBMP = 2,6-Di-*tert*-butyl-4-methylpyridine (100 mol%).

We then considered the Lewis acid conditions and we were pleased to find that the use of dysprosium(III) triflate as catalyst can ensure good stereocontrol of the reaction where **6a** and **7a** were formed in 95:5 ratio. However, a significant decrease of the yield was observed (Entry 2). We therefore achieved the reaction using Dy(OTf)₃, and TFA as co-catalyst, since a combination of Lewis and Brønsted acids can improve the yield of these rearrangements.^{10f,23} However, with substrate **5a** a decrease of the diastereoselectivity has been noted, without any improvement of the yield (Entry 3). This result is consistent with that obtained by using only TFA as catalyst, where low yield and poor diastereoselectivity were obtained (Entry 4). The use of dysprosium(III) chloride gave a slight improvement, in terms of yield and diastereoselectivity (Entry 5). No reaction was observed in the absence of Lewis or Brønsted acid catalysts (Entry 6). Switching from lanthanoid-based catalyst to other metal catalysts failed to improve the effectiveness of the rearrangement. Thus, the use of Sc(OTf)₃, that displays strong Lewis acidity properties, gave similar yield than dysprosium salts with a lower diastereoselectivity (Entry 7).^{10f,19} In contrast,

the use of a weak Lewis acid such as ZnCl₂ led to higher stereoselectivity but a much lower yield (Entry 8).²⁴ Neither iron nor copper salts did significantly improve the reaction (Entries 9-11).

In order to develop effective conditions for this rearrangement, we have decided to combine the beneficial effects of microwave heating and Lewis acid catalyst, for efficient chemical yields and good relative stereocontrol of the two contiguous newly generated stereocenters, respectively. The first attempt, combining both activation modes, was performed at 80 °C for 1.5 h with DyCl₃ as catalyst, and we were pleased to find that, in a much shorter reaction time, slightly better yields were obtained, compared to conventional heating (Entry 12 vs entry 5). A significant increase of the yield was observed when the reaction was carried out at 100 °C and the Piancatelli rearrangement occurred in 51% yield with a high diastereoselectivity (Entry 13). These optimized conditions have been applied to a 1 mmol scale (Entry 14). The diastereoselectivity was maintained but the yield decreased slightly. Control experiments confirmed that the catalytic effect does not result from HCl, possibly generated from dysprosium chloride. When the reaction was carried out in the presence of HCl, a near 1:1 mixture of cyclopentenones **6a** and **7a** was obtained in poor yield (Entry 15). The use of DyCl₃ as catalyst in the presence of a stoichiometric amount of DTBMP as acid scavenger led to the product with a high level of stereocontrol, although a lower yield (Entry 16).

Under the optimized reaction conditions (DyCl₃ 10 mol%, *t*-BuOH/H₂O (5:1), microwave heating, 100 °C, 1.5 h) a variety of substituted furan-2,5-dicarbinols **5a-j** delivered the expected 5-substituted-4-hydroxymethyl-4-hydroxycyclopentenones **6a-j** in moderate to good isolated yields (Scheme 3). Increasing the steric hindrance of the aryl substituent R¹ resulted in a slight decrease of the yields, without affecting the diastereoselectivity of the process (products **6a**, **6b**, **6c** and **6d**). The reaction was proven to be quite general, since both electron-withdrawing and electron-donating groups were tolerated on the aromatic substituent of **5**, affording products in a regio- and diastereoselective manner. Products were obtained in moderate yields, however in the high range of Piancatelli rearrangement for C-5 substituted 2-furylcarbinols.¹⁰⁻¹² This reduced efficiency of C-5 substituted 2-furylcarbinols for Piancatelli rearrangement can be assigned to a decrease of reactivity of substituted oxonium A1 towards nucleophilic addition or by destabilizing *syn*-hexane²⁵ interactions developed in intermediate C1 (Scheme S1, Part I in the Supporting Information). The best yield was obtained with substrate **5c** containing a 2-naphtyl substituent, that provides cyclopentenone **6c** in 80% yield. On the other hand, when the aryl group was changed to an alkyl substituent, no reaction was observed.²⁶



Scheme 3. Substrate scope in the DyCl₃-catalyzed Piancatelli rearrangement of non-symmetrical furan-2,5-dicarbinols.

The structural features and the *trans* relative stereochemistry of the C4-hydroxyl and the C5-aryl substituent, have been unambiguously assigned by X-ray diffraction studies on a representative compound **6d**.²⁷ The ORTEP drawing of **6d** is shown in Figure 1.

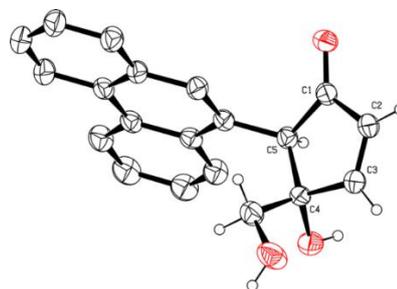
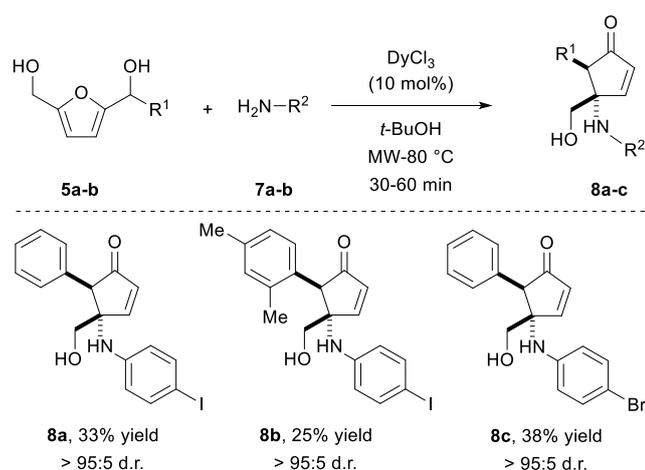


Figure 1. ORTEP view of 4-hydroxy-4-(hydroxymethyl)-5-(phenanthren-9-yl)cyclopent-2-en-1-one **6d** showing the *trans* relationship between the C4-hydroxyl and the C5-phenanthrenyl groups.

To expand the synthetic scope of the Piancatelli rearrangement on non-symmetrical furan-2,5-dicarbinol **5**, we have also performed *aza*-Piancatelli reactions by means of nitrogen nucleophiles **7**. These experiments provided the functionalized

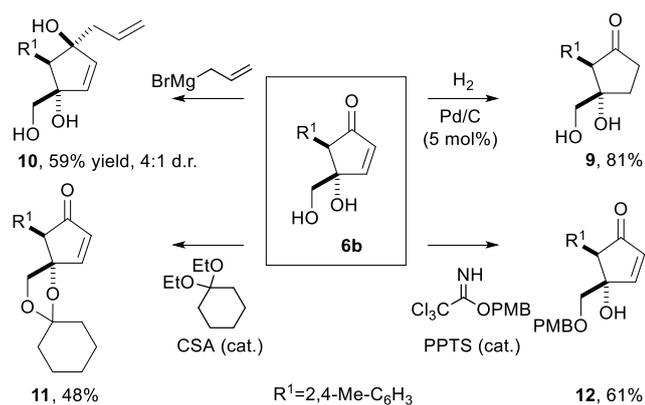
C4 fully substituted 4-hydroxymethyl-4-aminocyclopentenones **8** (Scheme 4).²⁸ These molecular units might serve as suitable scaffolds for the synthesis of biological active aminocyclopentitols,²⁹ non-proteinogenic amino acids³⁰ and more complex polycyclic structures.³¹

With anilines as nucleophiles, the reaction conditions were adjusted by reducing the temperature and the reaction time. The reactions were carried out successfully in pure *tert*-butanol, while other polar solvents gave disappointing results. In the end, the *aza*-Piancatelli rearrangement of **5a,b** with *p*-iodo- or *p*-bromoaniline as nucleophiles, led to the corresponding substituted aminocyclopentenones **8a-c** with high diastereoselectivity and moderate yields.³²



Scheme 4. Aza-Piancatelli rearrangement of non-symmetrical furan-2,5-dicarbinols with anilines **7**.

To illustrate the synthetic utility of the present method, cyclopentenone **6b** was submitted to further functionalization at different positions of the cyclopentenyl ring, as well as at the C4-hydroxymethyl side chain (Scheme 5).



Scheme 5. Derivatization of Piancatelli rearrangement product **6b**.

First, catalytic hydrogenation of the carbon-carbon double bond, with Pd/C under an H₂ atmosphere, cleanly provided cyclopentanone **9**. Then we carried out the selective 1,2-addition of an allyl Grignard reagent to afford cyclopentene **10**. This compound that displays three contiguous stereocenters, was obtained with good diastereoselectivity. The 1,2-diol moiety could be transformed into cyclohexylidene acetal derivative **11** by transacetalization reaction with cyclohexanone diethyl ketal. Finally, the steric discrimination between the primary and the secondary alcohol of compound **6b** enabled a monoprotection reaction to provide the *p*-methoxybenzyl ether **12** in 61% yield.

As some natural products with a hydroxylated cyclopentenone scaffold, such as trichodenone A, didemnenone D or Terrein exhibited significant cytotoxicity against P388 lymphocytic leukemia,^{16a,16c} L1210 murine leukemia^{18c} and MCF-7 breast cancer cell lines,³³ respectively, we have evaluated the cytotoxicity activities of the newly synthesized compounds **6**. Selected results are shown in Table 2.

Compounds **6** were assayed on a panel of eight human tumor cell lines from different tissues, namely acute myeloid leukaemia HL60, Chronic myeloid leukaemia K562 and its multi-resistant equivalent K562R, colorectal carcinoma HCT116, breast adenocarcinoma MCF7, prostate cancer PC3, lung carcinoma A549 and primary glioblastoma U87-MG. As shown in Table 2, compound **6a**, together with three analogs **6f**, **6i** and **6j** exhibit a cytotoxic activity against the different cell lines at a micromolar concentration. These compounds are especially active on the human acute myeloid leukaemia cell line HL60. They are also cytotoxic against K562R cells, which overexpress the MDR1 protein, suggesting that they are not substrates of this drug efflux pump.

The impact of these products on HL-60 cells viability was further investigated with respect to cell cycle effects and apoptosis induction. After 24 h treatment at concentrations ranging from 1 to 10 μM, all the compounds tested displayed a significant increase in the number of cells arrested at the G2/M growth phase was observed (Figure S4, Part VI in the Supporting Information). Concomitantly, induction of apoptosis (appearance of PI-negative/annexin V-positive cells) was highlighted (17%) as compared to the control cells (0.1 %). This apoptotic effect was amplified after 48 h of treatment with the appearance of a PI-positive/annexin V-positive cell population (late apoptosis).

Table 2. Biological evaluation of synthesized compounds **6**

compound ^a	IC ₅₀ [μ M] HL60	IC ₅₀ [μ M] K562	IC ₅₀ [μ M] K562R	IC ₅₀ [μ M] HCT116	IC ₅₀ [μ M] MCF7	IC ₅₀ [μ M] PC3	IC ₅₀ [μ M] A549	IC ₅₀ [μ M] U87-MG
6a	0.65 \pm 0.08	12.4 \pm 4.72	10.4 \pm 2.96	5.34 \pm 0.70	10.1 \pm 0.15	6.55 \pm 0.78	11.5 \pm 2.42	13.5 \pm 2.35
6f	0.45 \pm 0.04	10.2 \pm 0.24	7.87 \pm 2.11	6.26 \pm 0.19	6.82 \pm 2.39	6.22 \pm 0.78	5.24 \pm 0.05	9.78 \pm 0.07
6i	0.77 \pm 0.06	7.56 \pm 0.65	2.62 \pm 2.12	2.92 \pm 0.49	8.18 \pm 0.38	5.69 \pm 0.57	6.18 \pm 0.82	17.7 \pm 8.7
6j	0.62 \pm 0.05	10.1 \pm 0.43	7.88 \pm 1.72	7.08 \pm 0.47	5.48 \pm 0.30	9.91 \pm 0.22	ND ^b	6.33 \pm 0.43

^a Cytotoxicity (IC₅₀) of hit compounds at micromolar concentration. Data are the mean \pm standard error (SEM) of three independent experiments. ^b ND: Not determined.

Conclusions

In summary we have demonstrated for the first time that substituted non-symmetrical furan-2,5-dicarbonyls, readily obtained by addition of Grignard reagent on HMF, can be suitably used as starting materials for the Piancatelli rearrangement. This rearrangement proceeds in a regioselective manner, on the more substituted carbinol moiety, to provide 5-substituted-4-hydroxymethyl-4-hydroxycyclopentenones, **6**. Microwave activation allows to achieve high conversion rates in short reaction times. Concomitantly, the use of DyCl₃ as a Lewis acid catalyst ensures control of the relative configuration of the two stereogenic centers that are created in the rearrangement. The method can also be extended to *az*-Piancatelli type reactions. Moreover, the bis-hydroxylated cyclopentenones **6** exhibited significant cytotoxic activities against several human tumor cell lines. Future studies will focus on the development of Piancatelli rearrangements on more complex biscarbonyl substrates, as well as on targeted synthetic applications, by taking advantage of the highly functionalized cyclopentenones obtained by this methodology as key building blocks. More extended bioactivity studies will be carried out also.

Author Contributions

All authors have given approval to the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interests.

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27. Crystallographic data for this compound have been deposited at the CCDC, Cambridge, UK, with the deposit number 1589305. The supplementary crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre via URL www.ccdc.cam.ac.uk/data_request/cif.
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