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Ferrier Rearrangement and 2-Deoxy Sugar Synthesis from D-Glycals Mediated by Layered α-Zirconium Sulfophenylphosphonate-Methanphosphonate as Heterogeneous Catalyst

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Abstract Layered α-zirconium sulfophenylphosphonate-methanphosphonate is a solid acid catalyst that catalyzes Ferrier rearrangement from D-glycals and alcoholic nucleophiles under mild reaction conditions in short time and good yields. Notably, the combination of α-zirconium sulfophenylphosphonate-methanphosphonate and lithium bromide change the regioselectivity of this process affording 2-deoxy sugars in good yields.

Keywords Heterogeneous catalysis · Ferrier rearrangement · 2-Deoxy sugars · *O*-glycosides

1 Introduction

There is a growing interest in surface-mediated solid-phase reactions due to their ease to set-up, mild reaction conditions, short reaction times, selectivity, increased yield, higher purity of compounds and lower cost when compared with their homogeneous counterparts [1]. We have recently reported that layered zirconium sulfophenylphosphonate-methanphosphonate [α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$ = α-ZrP–SO_3H: FW = 392.24] [2, 3] is an excellent heterogeneous catalyst in liquid phase organic synthesis [4–6].

In continuation of our ongoing effort to develop new synthetic applications in the field of heterogeneous catalysis, we decided to investigate the use of layered zirconium sulfophenylphosphonate as acidic heterogeneous catalyst in sugar chemistry.

Starting from a common precursor such as a glycal derivative, acidic catalysts represent the most frequent choice as promoters in Ferrier rearrangement processes [7–12] and less frequently in the synthesis of 2-deoxy sugars [13–16].

The synthesis of 2-deoxy sugars under acidic conditions is usually affected by the presence of Ferrier rearranged byproducts. To solve the problem related to the regioselectivity, however, several methodologies have been reported in the literature [17–21].

The continuous interest in new selective methodologies to afford Ferrier's rearranged derivatives and 2-deoxy sugars is due to the great importance of these compounds as strategic synthetic intermediates [22–27] in the preparation of complex carbohydrates and different natural compounds, or well-known structural components of several biologically active compounds [16, 21, 28–40].

Sabesan and Coll. in 1991 [16] reported an interesting procedure for the synthesis of 2-deoxy sugars performed by the use of AG 50W-X8 cation exchange resin as solid acidic catalyst in the presence of lithium bromide as co-catalyst with high yields. In this process the most plausible mechanism elucidation about the regioselectivity toward Ferrier rearranged derivatives or 2-deoxy sugars could be based upon the necessity of generating a "nonhydrated" proton source that would preferentially protonate the C-2 carbon of the starting glycal to give the deoxy glycoside. Such a nonhydrated proton would have lesser tendency to protonate the C-3 acetoxy oxygen that normally leads to the rearranged products.

In this procedure LiBr can be considered, indeed, a co-catalyst being able to generate, in situ, traces of HBr as a source of "nonhydrated" protons.

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The limitation of this procedure is due to the high water content in commercial AG 50W-X8 cation exchange resin (~80 % w/w); thus a previous dehydration by dry acetonitrile treatment is required for the resin to be used as solid acid catalyst.

It is important to note that AG 50W-X8 cation exchange resin is not able to catalyze the addition of alcohols to the double bond in the absence of LiBr as co-catalyst, and even rearranged products did not form to significant extent.

α-ZrP–SO_3H is a solid acid catalyst that shares the same –SO_3H moiety as AG 50W-X8 cation exchange resin and, moreover, has the advantage that it does not need to be dehydrated, because its water content is very low (about 5 %) and it is normally combined as crystallization water.

For these reasons we thought to use α-ZrP–SO_3H as a possible source of "nonhydrated" proton to catalyze the formation of 2-deoxy sugars.

Preliminary experiments to test regioselective capability of α-ZrP–SO_3H were performed by adding methanol to a solution of 3,4,6-tri-*O*-acetylglucal and α-ZrP–SO_3H (6 mol%) in dichloromethane, using different methanol/glucal molar ratios. Under these reaction conditions only the Ferrier rearranged compound was obtained without formation of 2-deoxy sugars. This means that α-ZrP–SO_3H is not capable to furnish the "nonhydrated" protons necessary for the formation of 2-deoxy sugar, but it can still catalyze the Ferrier rearrangement process.

2 Results and Discussion

In order to evaluate the general applicability of this process a range of different alcohols as nucleophiles and 3,4,6 tri-*O*-acetylglucal and 3,4,6-tri-*O*-acetyl-galactal as starting glycals were used under optimized reaction conditions (Scheme 1).

As expected, 3,4,6 tri-*O*-acetylglucal afforded Ferrier adducts with good yields and short reaction time (Table 1). Surprisingly the reactions carried out with 3,4,6-tri-*O*-acetyl-galactal afforded also 2-deoxy sugars.

These results show a substantial inability of α-ZrP–SO_3H to generate "nonhydrated" proton and, at the same time, that regioselectivity is also dependent on the structure of the starting material.

The different behaviour of the two glycals is probably due to spatial disposition of the acetoxy groups, indeed the presence of substituent groups on both faces of the 3,4,6 tri-*O*-acetyl glucal could promote the C-3 acetoxy group elimination with consequent Ferrier adduct formation. On the other hand 3,4,6-tri-*O*-acetyl-galactal has less tendency to produce this kind of elimination. Thus, if 2-deoxy sugars are the final targets, 3,4,6-tri-*O*-acetyl-galactal should be the first choice starting material.

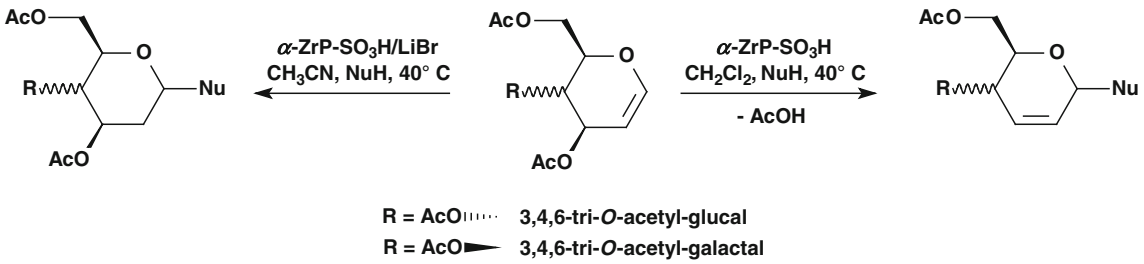
Since α-ZrP–SO_3H shows a poor regioselectivity towards 2-deoxysugars, LiBr was added as co-catalyst to generate nonhydrated protons, as proposed by Sabesan [16] (Scheme 1). Moreover, acetonitrile was chosen to carry out reaction of alcohols with 3,4,6-tri-*O*-acetylglucal and 3,4,6-tri-*O*-acetylgalactal, due to the good solubility of the LiBr in this solvent. It is important to highlight that the amount of LiBr used in our process was halved, from three equivalents used by Sabesan and Coll. [16] to 1.5 equivalent, without any loss of catalytic activity. Also the alcohol equivalents were reduced from 2.0 to 1.3.

The strategic combination of two catalysts to promote regioselectivity toward 2-deoxy sugar was also reported by Yadav ($CeCl_3 \cdot 7H_2O$–NaI) [18].

As reported in Table 2, the reactions carried out in the presence of LiBr afforded 2-deoxy sugars with good yields in short time. It is important to note that the reaction of 3,4,6-tri-*O*-acetyl-glucal is still affected by the presence of Ferrier rearrangement products, while 3,4,6-tri-*O*-acetyl-galactal showed a complete regioselectivity toward 2-deoxy sugars.

A lower reactivity of phenolic nucleophile (*entry 6*) compared with the alcoholic ones was observed in both glycals. The different reactivity can be exploited to obtain a specific regioselectivity when both alcoholic and phenolic moieties are present in the same compound such as 4-(2-hydroxyethyl)phenol.

The reaction of 4-(2-hydroxyethyl)phenol and 3,4,6-tri-*O*-acetyl glucal (Scheme 2) could possibly lead to the formation of four isomers. Actually, the purification of the crude reaction mixture by column chromatography on



Scheme 1 Preparation of Ferrier rearrangement and 2-deoxy sugar derivatives

Table 1 Reaction of 3,4,6-tri-*O*-acetyl-glycal with nucleophiles (2.0 eq.), at 40 °C, in CH_2Cl_2, catalyzed by α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$

No.	Nucleophile	3,4,6-Tri-*O*-acetylglucal		3,4,6-Tri-*O*-acetylgalactal		
		Time (h)	Ferrier's adduct yield (a) (%)	Time (h)	Ferrier's adduct yield (b) (%)	2-Deoxysugar yield (c) (%)
1	Cyclohexylmethanol	2	73 (9:1)[a]	2	44	25 (1:1)[a]
2	Cyclohexanol	5	90 (4:1)[a] [38]	5	23	32 (3:2)[a]
3	Allyl alcohol	3.5	83 (4:1)[a] [41]	5	36 [41]	45 (1:1)[a] [16]
4	Benzyl alcohol	2	87 (2:1)[a] [41]	2	48 [41]	10 (1:1)[a]

[a] α/β Molar ratio of Ferrier's adducts and 2-deoxysugars were measured by GC–MS analysis

Table 2 Reaction of 3,4,6-tri-*O*-acetyl-glycal with different nucleophiles

No.	Nucleophile	3,4,6-Tri-*O*-acetyl glucal			3,4,6-Tri-*O*-acetyl galactal	
		Time (h)	2-Deoxysugar yield (a) (%)	Ferrier's adduct yield (b) (%)	Time (h)	2-Deoxysugar yield (c) (%)
1	Methanol	2	65 (10:1)[a] [16]	6	2	87 (5:1)[a] [16]
2	Cyclohexyl methanol	2	84 (11:1)[a]	11	2	78 (7:1)[a]
3	Allyl alcohol	2	89 (7:1)[a] [16]	8 [41]	2	95 (6:1)[a] [16]
4	Pent-4-en-1-ol	2	77 (9:1)[a] [16]	10	2	96 (11:1)[a] [16]
5	Benzyl alcohol	2	87 (8:1)[a]	6 [41]	3	76 (5:1)[a]
6	4-*Tert*-butylphenol	4	46 (9:1)[a]	–	4	23 (4:1)[a]
7	4-(2-Hydroxyethyl)phenol	2	74 (9:1)[a]	8	2	71 (5:1)[a]

The reaction was carried out at 40 °C, in CH_3CN, in the presence of α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$/LiBr

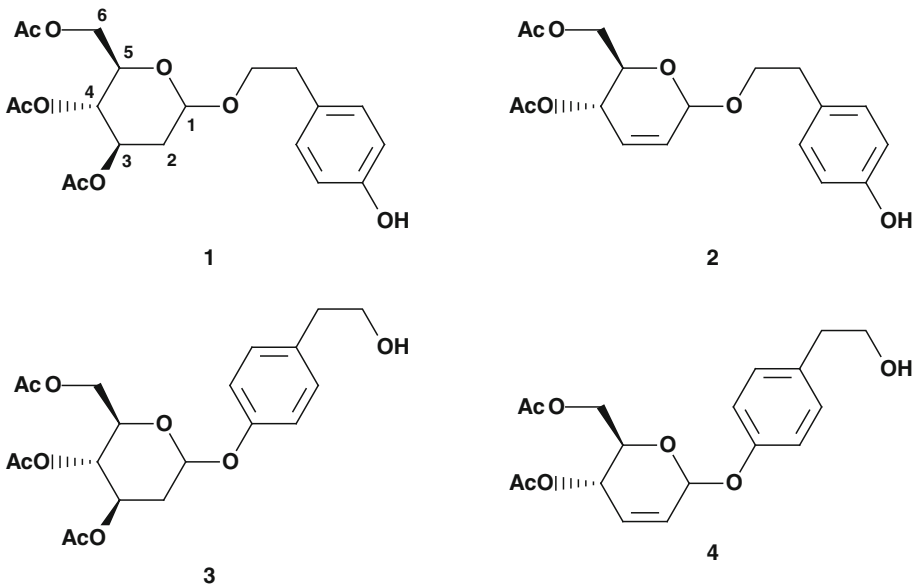
[a] α/β Molar ratio of 2-deoxy sugars were measured by GC–MS analysis

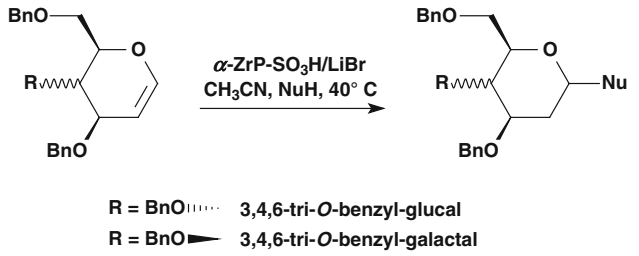
silica gel afforded only two final products: a 2-deoxyglucal with 74 % yield and a Ferrier adduct with 8 % yield, both as alcoholic glycosides.

As expected the reaction of 4-(2-hydroxyethyl)phenol and 3,4,6-tri-*O*-acetyl galactal gave only the alcoholic glycoside derivative of 2-deoxygalactal.

The ^{1}H-NMR spectrum of compound **1** shows the alcoholic methylene signal of 4-(2-hydroxyethyl)phenol side chain as a doublet of triplets that can be explained with the proximity of CH_2O protons to the anomeric chiral centre. Also NOESY experiment highlights a consistent coupling between the H-1 at 5.26 ppm and the CH_2O

Scheme 2 Possible isomers from reaction of 4-(2-hydroxyethyl)phenol and 3,4,6-tri-*O*-acetyl glucal





Scheme 3 Preparation of 2-deoxy sugars from 3,4,6-tri-*O*-benzyl glycals

Table 3 Reaction of 3,4,6-tri-*O*-benzyl-glycals with nucleophiles

No.	Nucleophile	Tri-*O*-benzyl-glucal (a)		Tri-*O*-benzy-galactal (b)	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1	Cyclohexylmethanol	5	97 [42]	2	88
2	Allyl alcohol	0.25	77 [43]	1.5	85 [43]
3	Benzyl alcohol	2	92 [44]	18	50 [43]

The reaction was carried out at 40 °C, in CH_3CN, in the presence of α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$/LiBr

protons at 3.62 and 3.76 ppm, respectively. Among the synthesized 2-deoxy glucals, compound **1** presents a particular shielding effect on H-5 proton with a chemical shift at 3.47 ppm (about 0.5 ppm less than normal). This shielding could be explained by an anisotropic effect of the aromatic ring on H-5, probably due to the stabilization of the conformation of **1** by intermolecular hydrogen bonds between the phenolic hydroxyl group and the oxygen of acetoxy group on C-6.

Thus, we can conclude that the reaction is highly selective in favour of 2-deoxyglucal that derives from the nucleophilic attack of alcoholic OH.

To verify the role of the acidic catalyst in the catalytic system, the reaction of 3,4,6-tri-*O*-acetylglucal and cyclohexyl methanol was repeated with LiBr in the absence of α-ZrP–SO_3H. Under this reaction condition lower yield of 2-deoxy sugars (57 %) and longer reaction time (24 h) were obtained confirming the necessity of the simultaneous presence of LiBr and α-ZrP–SO_3H (LiBr providing regioselectivity and α-ZrP–SO_3H reaction rate). In order to verify the influence of the leaving group, tri-*O*-benzyl glucal and galactal were used as starting materials (Scheme 3). Benzyloxy group is less likely to act as a leaving group than acetoxy. As a result the formation of Ferrier rearrangement compounds was completely prevented and 2-deoxy sugars were the exclusive reaction products (Table 3).

3 Experimental

3.1 General

All chemicals were purchased from the major chemical suppliers as highest purity grade and used without any further purification. Column chromatography was performed with Merck silica gel 60 (70–230 mesh ASTM), using dichloromethane/ethyl acetate or dichloromethane/methanol mixture. ^1H NMR were recorded in $CDCl_3$ with a Brucker Avance DPX 400 spectrometer at a frequency of 400.13 MHz. GC–MS analysis were obtained with HP-6890 gas chromatograph (dimethyl silicone column, 12.5 m) equipped with an HP-5973 mass-selective detector at an ionizing voltage of 70 eV

3.2 General Experimental Procedure

3.2.1 Procedure 1 (Synthesis of Ferrier Rearrangement Compounds)

To a solution of glycal (1 mmol) and alcohol (2.0 mmol) in dichloromethane (1 ml/mmol of glycal) at room temperature, under magnetic stirring and nitrogen atmosphere, α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$ (6 mol %) was added and the temperature was raised to 40 °C.

The reaction mixture was monitored by TLC and GC–MS and after appropriate time was filtered on buchner funnel and washed with dichloromethane.

The organic solution was dried over Na_2SO_4 and concentrated under vacuum. Column chromatography of the crude product over silica gel was required to separate the reaction products.

3.2.2 Procedure 2 (Synthesis of 2-Deoxysugar)

To a solution of glycal (1 mmol) and alcohol (1.3 mmol) in acetonitrile (1 ml/mmol of glycal) at room temperature, under magnetic stirring and nitrogen atmosphere, anhydrous lithium bromide (1.5 mmol) and α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$ (6 mol%) were added and the temperature was raised to 40 °C.

The reaction mixture was monitored by TLC and GC–MS and after appropriate time was filtered on buchner funnel and washed with dichloromethane.

The organic solution was washed with water, dried over Na_2SO_4 and concentrated under vacuum. Column chromatography of the crude product over silica gel was required to separate the reaction products.

3.3 Characterization Data

All the compounds have been identified by NMR and GC–MS and comparison with literature data.

Cyclohexylmethyl 4,6-di-O-acetyl-2,3-dideoxy-α/β-D-erythro-es-2-enopyranoside (Table 1, entry **1a**—procedure 1), purification: SiO_2 column chromatoghraphy, eluent: Petroleum ether/Et_2O 9:1, yellow oil ^{1}H-NMR (400 MHz, $CDCl_3$) δ (*α anomer*) 5.90 (bd, $J = 11.3$ Hz, 1H, H-3), 5.85 (ddd, $J = 1.6$, 2.3, 10.2 Hz, 1H, H-2), 5.31 (m, 1H, H-4), 5.02 (bs, 1H, H-1), 4.26 (dd, $J = 5.3$, 12.1 Hz, 1H, H-6_a), 4.20 (dd, $J = 2.4$, 12.1 Hz, 1H, H-6_b), 4.12 (ddd, $J = 2.4$, 5.3, 9.6 Hz, 1H, H-5), 3.60 (dd, $J = 7.0$, 9.3 Hz, 1H, O–HCH), 3.34 (dd, $J = 6.1$, 9.3 Hz, 1H, *O*-HCH), 2.12 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 1.85–1.56 (m, 6H, cyclohexyl), 1.25 (m, 3H, cyclohexyl), 0.96 (m, 2H, cyclohexyl). GC–MS: *m/z* 325 [M^+], 253, 213, 182, 153.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (*β anomer*) 5.97 (m, 2H, H-2, H-3), 5.20 (m, 1H, H-4), 5.10 (m, 1H, H-1), 4.26 (m, 2H, H-$6_{a,b}$), 4.04 (dd, $J = 5.9$, 10.7 Hz, 1H, H-5), 3.68 (dd, $J = 6.6$, 9.0 Hz, 1H, O–HCH), 3.29 (dd, $J = 6.7$, 9.3 Hz, 1H, O–HCH), 2.12 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.82–1.55 (m, 6H, cyclohexyl), 1.23 (m, 3H, cyclohexyl), 0.94 (m, 2H, cyclohexyl).

Cyclohexylmethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-threo-es-2-enopyranoside (Table 1, entry **1b**—procedure 1), purification: SiO_2, column chromatoghraphy, eluent: CH_2Cl_2, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.14 (dd, $J = 4.7$, 10.0 Hz, 1H, H-3), 6.06 (dd, $J = 2.5$, 10.0 Hz, 1H, H-2), 5.05 (m, 2H, H-1, H-4), 4.42–4.22 (m, 3H, H-5, H-$6_{a,b}$), 3.62 (dd, $J = 6.9$, 9.3 Hz, 1H, O–HCH), 3.33 (dd, $J = 6.1$, 9.3 Hz, 1H, O–HCH), 2.11 (s, 6H, 2xCH_3), 1.91–1.55 (m, 6H, cyclohexyl), 1.41–1.13 (m, 3H, cyclohexyl), 1.09–0.85 (m, 2H, cyclohexyl). GC–MS: *m/z* 325 [M^+], 213, 182, 153, 111.

Cyclohexylmethyl-2-deoxy-3,4,6-tri-O-acetyl-α/β-D-galactopyranoside (Table 1, entry **1c**; Table 2, entry 2c—procedure 1/2) purification: SiO_2 column chromatoghraphy, eluent: CH_2Cl_2/EtOAc 8:2, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (*α anomer*) 5.35 (d, $J = 2.8$ Hz, 1H, H-4), 5.30 (ddd, $J = 3.6$, 5.1, 2.8 Hz, 1H, H-3), 4.99 (d, $J = 2.9$ Hz, 1H, H-1), 4.11 (m, 3H, H-5, H-$6_{a,b}$), 3.45 (dd, $J = 6.9$, 9.3 Hz, 1H, O–HCH), 3.21 (dd, $J = 6.1$, 9.3 Hz, 1H, O–HCH), 2.15 (s, 3H, CH_3), 2.10 (dd, $J = 3.6$, 12.6 Hz, 1H, H-2_{eq}), 2.07 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.88 (dd, $J = 5.1$, 12.6 Hz, 1H, H-2_{ax}), 1.73 (m, 5H, cyclohexyl), 1.58 (m, 1H, cyclohexyl), 1.24 (m, 3H, cyclohexyl), 0.96 (m, 2H, cyclohexyl). GC–MS: *m/z* 385 [M^+], 327, 289, 213, 185, 153, 111, 97.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (*β anomer*) 5.27 (d, $J = 2.7$ Hz, 1H, H-4), 5.00 (dd, $J = 2.7$, 5.9 Hz, 1H, H-3), 4.54 (dd, $J = 3.3$, 8.7 Hz, 1H, H-1), 4.24–4.08 (m, 3H, H-5, H-$6_{a,b}$), 3.75 (dd, $J = 6.3$, 9.6 Hz, 1H, O–HCH), 3.27 (dd, $J = 7.2$, 9.5 Hz, 1H, O–HCH), 2.15 (s, 3H, CH_3), 2.10 (m, 1H, H-2_{eq}), 2.07 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.99 (m, 1H, H-2_{ax}), 1.74 (m, 5H, cyclohexyl), 1.62 (m, 1H, –CH), 1.22 (m, 3H, cyclohexyl), 0.95 (m, 2H, cyclohexyl).

Cyclohexyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-threo-es-2-enopyranoside (Table 1, entry **2b**—procedure 1), purification: SiO_2 column chromatoghraphy, eluent: CH_2Cl_2/EtOAc 9:1, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.15 (dd, $J = 5.0$, 10.1 Hz, 1H, H-3), 6.05 (ddd, $J = 0.7$, 2.9, 10.1 Hz, 1H, H-2), 5.25 (d, $J = 2.7$ Hz, 1H, H-1), 5.06 (ddd, $J = 0.5$, 2.4, 5.0 Hz, 1H, H-4), 4.46 (m, 1H, H-5), 4.26 (d, $J = 6.3$ Hz, 2H, H-$6_{a,b}$), 3.68 (m, 1H, O–CH), 2.12 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.02–1.75 (m, 4H, cyclohexyl), 1.47–1.23 (m, 6H, cyclohexyl). GC–MS: *m/z* [M^+], 311, 239,213, 168, 153, 111.

Cyclohexyl-2-deoxy-3,4,6-tri-O-acetyl-α-D-galactopyranoside (Table 1, entry **2c**—procedure 1), purification: SiO_2 column chromatoghraphy, eluent: CH_2Cl_2/EtOAc 9:1, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.42 (d, $J = 2.7$ Hz, 1H, H-4), 5.34 (ddd, $J = 5.1$, 3.6, 2.7 Hz, 1H, H-3), 5.21 (d, $J = 3.0$ Hz, 1H, H-1), 4.25 (m, 1H, H-5), 4.13 (m, 2H, H-$6_{a,b}$), 3.77 (m, 1H, O–CH), 2.17 (s, 3H, CH_3), 2.10 (m, 1H, H-2_{eq}), 2.08 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.88 (m, H-2_{ax}), 1.84–1.69 (m, 4H, cyclohexyl), 1.45–1.23 (m, 6H, cyclohexyl). GC–MS: *m/z* 371 [M^+], 289, 273, 252, 214, 171, 111, 99.

Cyclohexylmethyl-2-deoxy-3,4,6-tri-O-acetyl-α/β-D-glucopyranoside (Table 2, entry **2a**—procedure 2), purification: SiO_2 column chromatoghraphy, eluent: CH_2Cl_2/EtOAc 19:1, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (*α anomer)* 5.32 (ddd, $J = 5.4$, 9.5, 11.6 Hz, 1H, H-3), 4.98 (t, $J = 9.7$ Hz, 1H, H-4), 4.91 (bd, $J = 3.1$ Hz, 1H, H-1), 4.29 (dd, $J = 4.7$, 12.2 Hz, 1H, H-6_a), 4.06 (dd, $J = 2.2$, 12.2 Hz, 1H, H-6_b), 3.94 (ddd, $J = 2.2$, 4.6, 10.1 Hz, 1H, H-5), 3.42 (dd, $J = 6.9$, 9.4 Hz, 1H, O–HCH), 3.18 (dd, $J = 6.1$, 9.4 Hz, 1H, O–HCH), 2.22 (ddd, $J = 1.0$, 5.3, 12.8 Hz, 1H, H-2_{eq}), 2.09 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.81 (ddd, $J = 3.6$, 11.7, 12.7 Hz, 1H, H-2_{ax}), 1.81–1.62 (m, 4H, cyclohexyl), 1.58 (m, 1H, cyclohexyl), 1.33–1.10 (m, 4H, cyclohexyl) 1.0–0.83 (m, 2H, cyclohexyl). GC–MS: *m/z* 385 [M^+], 267, 253, 224, 213, 185, 153.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (*β anomer*) 5.05–4.97 (m, 2H, H-3, H-4), 4.53 (dd, $J = 1.9$, 9.6 Hz, 1H, H-1), 4.29 (dd, $J = 4.6$,12.1 Hz, 1H, H-6_a), 4.11 (dd, $J = 2.5$, 12.1 Hz, 1H, H-6_b), 3.69 (dd, $J = 6.2$, 9.4, 1H, O–HCH), 3.59 (ddd, $J = 2.4$, 4.7, 9.3 Hz, 1H, H-5), 3.24 (dd, $J = 7.0$, 9.4 Hz, 1H, O–HCH), 2.32 (m, 1H, H-2_{eq}), 2.08 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.81–1.62 (m, 4H, cyclohexyl, H-2_{ax}), 1.58 (m, 1H, cyclohexyl), 1.33–1.10 (m, 4H, cyclohexyl) 1.0–0.83 (m, 2H, cyclohexyl).

4′-Pentenyl-4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-es-2-enopyranoside (Table 2, entry **4b**—procedure 2) purification: SiO_2 column chromatography, eluent: CH_2Cl_2/EtOAc 19:1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 3H, H-2,H-3,H-4′), 5.35 (d, $J = 9.6$ Hz, 1H, H-4), 5.13–4.98 (m, 3H, H-1, H5′), 4.28 (dd, $J = 5.5$, 12.1 Hz, 1H, H-6),

4.21 (dd, $J = 2.4$, 12.1 Hz, 1H, H-6), 4.14 (ddd, $J = 2.4$, 5.5, 9.6 Hz, 1H, H-5), 3.84 (dt, $J = 6.7$, 9.8 Hz, 1H, H-1′), 3.55 (dt, $J = 6.7$, 9.8 Hz, 1H, H-1′), 2.17 (m, 2H, H-3′), 2.15 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.74 (m, 2H, H-2′). GC–MS: *m/z* 298 [M^+], 239, 225, 213,154, 111, 86.

Benzyl-2-deoxy-3,4,6-tri-O-acetyl-α/β-D-glucopyranoside (Table 2, entry **5a**—procedure 2) purification: SiO_2 column chromatoghraphy, eluent: Petroleum ether/Et_2O 1:1, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (*α anomer*) 7.4 (m, 5H, PhH), 5.38 (ddd, $J = 5.4$, 9.8, 11.4 Hz, 1H, H-3), 5.06 (m, 1H, H-1), 5.02 (t, $J = 9.7$ Hz, 1H, H-4), 4.68 (d, $J = 12.0$ Hz, 1H, HCH–Ph), 4.52 (d, $J = 12.0$ Hz, 1H, HCH–Ph), 4.32 (dd, $J = 5.3$, 10.0 Hz, 1H, H-6_a), 4.02 (m, 2H, H-5, H-6_b), 2.29 (dd, $J = 5.4$, 13.0 Hz, 1H, H-2 $_{eq}$), 2.10 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.86 (m, 1H, H-2_{ax}). GC–MS: *m/z* 379 [M^+], 289, 273, 183, 153, 111, 91.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (*β anomer*) 7.4 (m, 5H, PhH), 5.02–4.98 (m, 3H, H-1, H-3, H-4), 4.90 (d, $J = 12.0$ Hz, 1H, HCH–Ph), 4.63 (d, $J = 12.0$ Hz, 1H, HCH–Ph), 4.32 (m, 1H, H-6_a), 4.16 (dd, $J = 2.0$, 12.0 Hz, 1H, H-6_b), 3.61 (m, 1H, H-5), 2.35 (m, H-2_{eq}), 2.10 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.85–1.80 (m, H-2_{ax}).

Benzyl-2-deoxy-3,4,6-tri-O-acetyl-α-D-galactopiranoside (Table 1, entry **4c**; Table 2, entry **5c**—procedure 2) purification: SiO_2 column chromatography, eluent: CH_2Cl_2/EtOAc 9:1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H, PhH), 5.37 (d, $J = 2.6$ Hz, 1H, H-4), 5.33 (m, 1H, H-3), 5.12 (d, $J = 3.0$ Hz, 1H, H-1), 4.71 (d, $J = 11.8$ Hz, 1H, HCH–Ph), 4.52 (d, $J = 11.8$ Hz, 1H, HCH–Ph), 4.22 (m, 1H, H-5), 4.11 (m, 2H, H-6), 2.15 (s, 3H, CH_3), 2.10 (m, 1H, H-2_{eq}), 2.07 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.93 (m, 1H, H-2_{ax}). GC–MS: *m/z* 379 [M^+], 320, 289, 273, 213,153.

4′-(Tert-buthyl)phenyl-2-deoxy-3,4,6-tri-O-acetyl-α/β-D-glucopyranoside (Table 2, entry **6a**—procedure 2), purification: SiO_2 column chromatoghraphy, eluent: Hexane/EtOAc 3:1, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (*α anomer*) 7.65 (d, $J = 9.1$ Hz, 2H, PhH), 7.10 (d, $J = 9.1$ Hz, 2H, PhH), 5.67 (d, $J = 2.28$ Hz, 1H, H-1), 5.55 (ddd, $J = 5.4$, 9.5, 11.6 Hz, 1H, H-3), 5.11 (t, $J = 9.8$ Hz, 1H, H-4), 4.31 (dd, $J = 4.5$, 12.2 Hz, 1H, H-6_a), 4.09 (ddd, $J = 2.0$, 4.5, 10.2 Hz, 1H, H-5), 4.02 (dd, $J = 2.1$, 12.2 Hz, 1H, H-6_b), 2.47 (ddd, $J = 0.8$, 5.3, 13.0 Hz, 1H, H-2_{eq}), 2. 80 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.01 (ddd, $J = 3.6$, 11.8, 13.0 Hz, 1H, H-2_{ax}), 1.47 (s, 9H, *t*Bu). GC–MS: *m/z* 422 [M^+], 289, 213, 153.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (*β anomer*) 7.55 (d, $J = 9.0$ Hz, 2H, PhH), 6.95 (d, $J = 9.0$ Hz, 2H, PhH), 5.18 (dd, $J = 2.2$, 9.6 Hz, 1H, H-1), 5.41–5.50 (m, 2H, H-3, H-4), 4.30 (m, 1H, H-6_a), 4.16 (dd, $J = 2.5$, 12.1 Hz, H-6_b), 3.76 (ddd, $J = 2.5$, 9.2, 5.5 Hz, 1H, H-5), 2.52 (dd, $J = 2.0$, 4.8, 12.4 Hz, 1H, H-2_{eq}), 2.06 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.07–2.01 (m, 1H, H-2_{ax}), 1.47 (s, 9H, *t*Bu).

4′-(Tert-buthyl)phenil-2-deoxy-3,4,6-tri-O-acetyl-α/β-D-galactopiranoside (Table 2, entry **6c**—procedure 2), purification: SiO_2 column chromatoghraphy, eluent: CH_2Cl_2/Hexane 9:1, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (*α anomer*) 7.33 (d, $J = 9.0$ Hz, 2H, PhH), 7.01 (d, $J = 9.0$ Hz, 2H, PhH), 5.74 (d, $J = 2.8$ Hz, 1H, H-1), 5.53 (ddd, $J = 3.1$, 5.1, 12.4 Hz, 1H, H-3), 5.42 (d, $J = 2.9$ Hz, 1H, H-4), 4.29 (t, $J = 6.7$ Hz, 1H, H-5), 4.12 (dd, $J = 6.1$, 11.2 Hz, 1H, H-6_a,), 4.08 (dd, $J = 7.1$, 11.2 Hz, 1H, H-6_b), 2.27 (m, 1H, H-2_{eq}), 2.18 (s, 3H, CH_3), 2.12 (m, 1H, H-2_{ax}), 2.05 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.32 (s, 9H, *t*Bu). GC–MS: *m/z* 422 [M^+], 362, 273, 213, 150, 135, 111.

^{1}H-NMR (400 MHz, $CDCl_3$) δ (*β anomer*) 7.31 (d, $J = 9.0$ Hz, 2H, PhH), 6.97 (d, $J = 9.0$ Hz, 2H, PhH), 5.34 (d, $J = 2.9$ Hz, 1H, H-4), 5.17 (dd, $J = 2.6$, 9.6 Hz, 1H, H-1), 5.11 (ddd, $J = 3.12$, 5.0, 12.2 Hz, 1H, H-3), 4.25 (dd, $J = 7.0$, 11.2 Hz, 1H, H-6_a), 4.18 (dd, $J = 6.2$, 11.2 Hz, 1H, H-6_b), 3.96 (bt, $J = 6.3$ Hz, 1H, H-5), 2.29–2.16 (m, 2H, H-$2_{eq,ax}$), 2.12 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 1.32 (s, 9H, *t*Bu).

4′-Hydroxyphenetyl-2-deoxy-3,4,6-tri-O-acetyl-α-D-glucopyranoside (Table 2, entry **7a**—procedure 2) purification: SiO_2 column chromatoghraphy, eluent: CH_2Cl_2/EtOAc 2:1, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (*α anomer*) 7.6 (d, $J = 9.2$ Hz, 2H, PhH), 7.2 (d, $J = 9.2$ Hz, 2H, PhH), 5.27 (ddd, $J = 5.3$, 9.4, 11.6 Hz, 1H, H-3), 4.94 (d, $J = 9.8$ Hz, 1H, H-4), 4.91 (bd, $J = 2.8$ Hz, 1H, H-1), 4.15 (dd, $J = 4.3$, 12.3 Hz, 1H, H-6_a), 3.92 (dd, $J = 2.3$, 12.3 Hz, H-6_b), 3.74 (m, 1H, O–HCH), 3.62 (m, 1H, O–HCH), 3.47 (ddd, $J = 2.3$, 4.2, 10.1 Hz, 1H, H-5), 2.81 (t, $J = 6.7$ Hz, 2H, CH_2Ph), 2.23 (ddd, $J = 1.1$, 5.3, 12.9 Hz, 1H, H-2_{eq}), 2.08, (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.78 (ddd, $J = 3.6$, 11.7, 12.8 Hz, 1H, H-2_{ax}). GC–MS: *m/z* 410 [M^+], 273, 213, 120.

4′-Hydroxyphenetyl-2-deoxy-3,4,6-tri-O-acetyl-α-D-galactopyranoside (Table 2, entry **7c**—procedure 2), purification: SiO_2 column chromatoghraphy, eluent CH_2Cl_2/EtOAc 9:1, oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.10 (d, $J = 9.0$ Hz, 2H, PhH), 6.79 (d, $J = 9.0$ Hz, 2H, Ph–H α,β), 5.26 (m, 2H, H-3, H-4), 4.99 (d, $J = 2.6$ Hz, 1H, H-1), 4.00 (d, $J = 6.8$ Hz, 2H, H-$6_{a,b}$), 3.77 (m, 1H, O–HCH), 3.70 (bt, $J = 6.6$ Hz, 1H, H-5), 3.63 (m, 1H, O–HCH), 2.82 (t, $J = 7.6$ Hz, 2H, PhCH_2 β), 2.09 (m, H-2_{eq}), 2.13 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.86 (m, H-2_{ax}).

Cyclohexylmethyl-2-deoxy-3,4,6-tri-O-benzyl-α-D-galactopyranoside (Table 3, entry **1b**—procedure 2) purification: SiO_2, column chromatoghrapy, eluent: Petroleum ether/EtOAc 8:2, yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 15H, PhH), 4.95 (m, 2H, H-1, HCH–Ph), 4.64 (m, 3H, Benzylic), 4.54 (d, $J = 11.7$ Hz, 1H, O–HCH–Ph), 4.45 (d, $J = 11.7$ Hz, 1H, O–HCH–Ph), 3.94 (m, 3H, H-3, H-4, H-5), 3.61 (m, 2H, H-$6_{a,b}$), 3.43 (dd, $J = 7.2$, 9.5 Hz, 1H,

O–HCH–CH), 3.18 (dd, $J = 6.2$, 9.5 Hz, 1H, O–HCH–CH), 2.23 (td, $J = 3.6$, 12.6 Hz, 1H, H-2_{eq}), 2.01 (dd, $J = 4.5$, 12.6 Hz, 1H, H-2_{ax}), 1.83–1.52 (m, 6H, cyclohexyl), 1.24 (m, 3H, cyclohexyl), 0.93 (m, 2H, cyclohexyl).

4 Conclusions

In this paper we reported the use of α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$ as acidic catalyst for the synthesis of Ferrier rearrangement compounds and its combination with LiBr for the regioselective synthesis of 2-deoxysugars starting from glycals. The regioselectivity of this process is also affected by the different structure of the starting glycals (3,4,6-tri-*O*-acetyl-glucal and 3,4,6-tri-*O*-acetyl-galactal). Optimizations of 2-deoxy sugars synthesis mediated by α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$/LiBr catalytic system, such as LiBr and nucleophile equivalents reduction, were achieved. The use of benzylated glycals as starting material for a complete regioselective synthesis of 2-deoxysugars has been proposed. Thus the optimized mild reaction conditions, the recoverable and the recyclable nature of the catalyst that can be reused without loss of activity, make these processes simple and of general applicability with negligible chemical waste.

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