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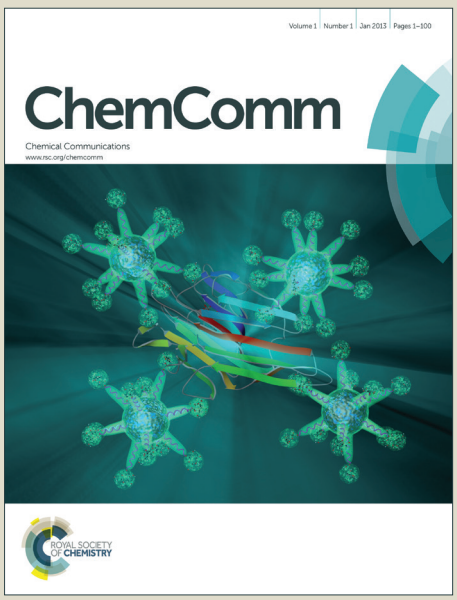

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Novel regio- and stereoselective phosphonyl radical addition to glycals promoted by Mn(II)/air: syntheses of 1, 2-dideoxy 2-*C*-diphenylphosphinylglycopyranosides†

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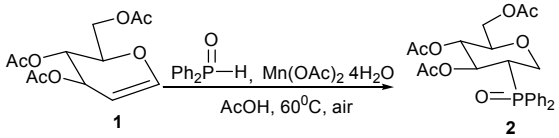
1,2-Dideoxy-2-*C*-diphenylphosphinylglycopyranosides were first synthesized by the novel Mn(II)/air promoted reaction of diphenylphosphine oxide with various glycals in high yields with excellent regio- and stereoselectivities, which was clarified as a radical addition reaction controlled by the oxygen of vinyl ether.

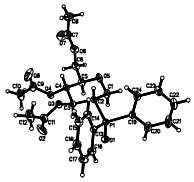
Because carbohydrate-derived organophosphorus compound plays an important role in the biosynthesis of oligosaccharides, the synthesis of nonhydrolyzable analogues has been an interesting subject.[1] These analogues are considered to be metabolically inert and used as enzyme inhibitors in the study of enzyme mechanisms as well as the carbohydrate metabolic pathways.[2] Among them, the carbohydrates that lack the hydroxyl group at the C-1 position are promising candidates. Besides, analogues such as carbohydrate-derived phosphine oxides and phosphines have also been successfully prepared and applied to homogeneous catalysis as enantiomerically pure ligands in the enantioselective syntheses.[3]

There are a number of naturally occurring carbohydrate 2-phosphates.[4] Therefore, The development of a general and efficient method for the formation of C-P bond at C-2 position of carbohydrates to synthesize 2-phosphono sugar analogues has become very important. The introduction of phosphonate at the C-2 position of carbohydrate was achieved by several groups,[5] and lithium diphenylphosphide was also introduced at C-2 position of pyranoses to generate 2-deoxy-2-*C*-diphenylphosphinyl-α-**D**-altropyranoside as an enantiomerically pure ligand.[6] However, most previous syntheses require many steps and suffer bad regio- and stereoselectivities. The carbohydrate containing C-P bond at C-2 position that lacks the hydroxyl group at C-1 position remains sparse, although it is nonhydrolyzable analogue and enantiomerically pure ligand. In continuation of our interest in the syntheses of 2-*C*-substituted sugar analogues[7] and biologically active carbohydrate analogues,[8] we wish to describe a general and efficient synthesis of 1,2-dideoxy-2-*C*-diphenylphosphinylglycopyranosides by novel regio- and stereoselective phosphonyl radical addition to glycals, which was promoted via Mn(II)/air .

In recent years, manganese(III)-based oxidative free radical reaction has become a valuable synthetic method, in which $Mn(OAc)_3$ is most commonly used as a single-electron-transfer reagent to generate radicals from various carbonyl compounds.[9] Mn(II)/Co(II)/O_2 catalyzed phosphonation of arenes[10] and Mn(III) acetate promoted phosphonation of heteroaryl compounds[11] were also achieved. We envisaged that the Mn(II)/O_2 Redox Couple or Mn(III) promoted phosphonyl radicals could add to unsaturated sugars to form phosphorus-containing carbohydrates.

Glucal **1** (Scheme 1) prepared according to the known procedure[12] was first used as a radical acceptor to react with diphenylphosphine oxide in the presence of very cheap $Mn(OAc)_2{\cdot}H_2O$ in atmosphere. The formation of **2** was investigated under various conditions. The ratio of $Mn(OAc)_2{\cdot}4H_2O$ to glucal and the solvent have major influence on the reaction. The optimum is 3:1. Below 3:1, the yield decreases (Table 1, Entry 1-5). Acetic acid as a solvent is efficient at 60 °C, and a isolated yield of 92% was attained by use of acetic acid and 3 equiv of $Mn(OAc)_2{\cdot}4H_2O$ (Table 1, Entry 4). Above 60 °C, the yield decreases. The structure of **2** was definitely characterized by spectroscopic data. **2** also gave crystal suitable for X-ray analysis after recrystallization from methanol. Its X-ray crystal structure (Scheme 1) indicates the newly formed C-P bond at C-2 locates in equatorial position and the sugar ring keeps in chair conformation.





Scheme 1 regio- and stereoselective synthesis of 2-*C*-diphenylphosphinylglucopyranoside **2** *via* Mn(II)/air promoted radial addition to glucal and its X-ray crystal structure.

To investigate the generality of this method and to synthesize various 1,2-dideoxy-2-*C*-diphenylphosphinylglycoside, the reaction was performed with the various glycals in acetic acid and

at 60 °C in the presence of 3 equiv of $Mn(OAc)_2·4H_2O$. Fortunately, all the reaction gave regio- and stereoselectivities, and the corresponding products were obtained in good to excellent yields, which were shown in Table 2. The reaction of acetyl protected glycal with diphenylphosphine oxide was much cleaner than the benzyl protected one and gave higher yield. In all cases, yields were higher than 65%. Besides, the by-product 1,2-dideoxy 1-*C*-diphenylphosphinylglycoside from phosphonyl addition to C-1 position was not obtained. All the new compounds were characterized by ^1H NMR, ^{13}C NMR, 2D NMR, MS and IR spectra.

Table 1 synthesis of 2-*C*-diphenylphosphinylglucopyranoside **2** under various conditions[a]

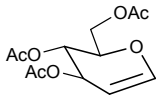
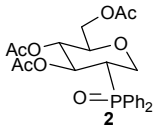
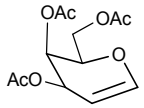
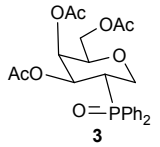
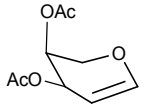
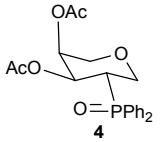
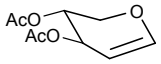
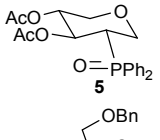
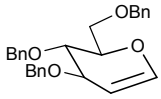
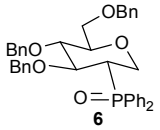
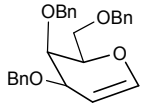
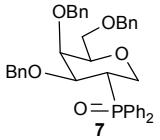
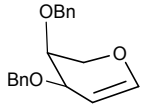
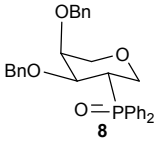
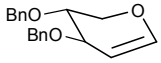
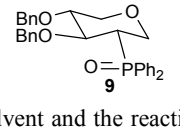
Entry	$Mn(OAc)_2$·$4H_2O$/**1**	Solvent	T(°C)	Time (h)	Yield (%)[c]
1	0:1	AcOH	60	24	0
2	1:1	AcOH	60	36	trace
3	2:1	AcOH	60	16	58
4	**3:1**	**AcOH**	**60**	**2**[b]	**92**
5	3:1	AcOH	80	1.5	72
6	3:1	CH_3CN	60	24	67
7	3:1	EtOH	60	16	32
8	3:1	DMF	60	24	trace
9	3:1	HCOOH	60	24	trace

[a]190 mg (0.4 mmol) of **1** was used. [b]TLC indicated the reaction went completely and it was stopped immediately. [c]Isolated yield.

In order to uncover this novel reaction further, the solvent AcOH was degassed, it was then performed in the presence of 3 equiv of $Mn(OAc)_2·4H_2O$ under Ar atmosphere. No desired product was obtained. When this reaction was performed in the presence of the other Lewis acid such as $FeCl_3$, $AlCl_3$, $Cu(OTf)_2$ and $InCl_3·4H_2O$ rather than $Mn(OAc)_2·4H_2O$/air, the desired product was also not obtained, which indicate Lewis acid can't promote this kind of addition reaction. The reaction was then carried out using $Mn(OAc)_3$ instead of $Mn(OAc)_2·4H_2O$/air or other Lewis acid. As expected, the various same products 1,2-dideoxy-2-*C*-diphenylphosphinylglycopyranosides were obtained. Obviously, in the course of the reaction, $Mn(OAc)_3$ took effect as a single-electron-transfer reagent rather than a Lewis acid. $Mn(OAc)_2·4H_2O$ itself can't promote this addition reaction. Under air atmosphere, it was oxidized into $Mn(OAc)_3$, which reacted with diphenylphosphine oxide by one-electron oxidation to generate diphenylphosphinyl radical **10** (Scheme 2). This radical could attack C-2 and C-1 position of glycal to give the corresponding adducts **11** and **12**, respectively. In the C-2 adduct **11**, the newly formed C-1 radical next to an oxygen is stabilized by *p-p* orbital conjugation. However, in the C-1 adduct **12**, the *p-p* conjugation is interrupted by C-1. The energy of **11** should be considerably lower than that of **12**, thus the reaction to **12** would be suppressed. In this way, the stable radical **11** could be more favourably formed, which was reduced by manganese(II) species followed by protonation to give the desired product **13**.

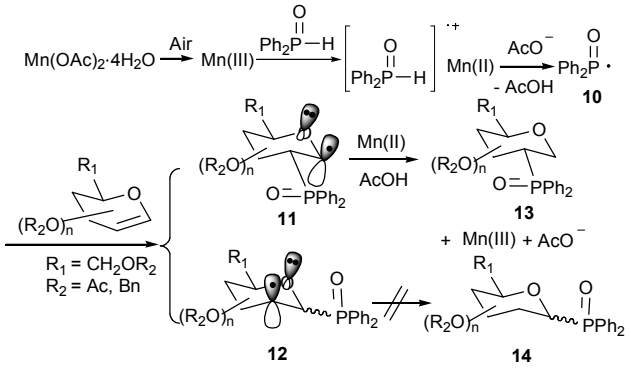
To authenticate the proposed mechanism, the structure of the radical **11** and **12** (R_1 = CH_2OAc, R_2 = Ac) as examples were modelled using Gaussian 09 program.[13] The structures of the **11** and **12** were optimized at the B3LYP[14]/6-31G(d) level in AcOH, using the integral equation formalism polarisable continuum model (IEF-PCM).[15] The energy of **11** is 3.49 kcal/mol lower than that of **12**, indicating that **11** is much more stable than **12**. The calculated molecular orbitals of **11** definitely reveal this p-p conjugation exists (Figure is shown in Page 12 in supporting information). The C-1 adduct **14** was not observed in TLC in this case. All of these have confirmed the proposed mechanism. The selective radical addition of phosphonyl to C-2 to form **13** is controlled by the oxygen atom of the vinyl ether.

Table 2 Regio- and stereoselective syntheses of various 1,2-dideoxy-2-*C*-diphenylphosphinylglycopyranosides *via* Mn(II)/air promoted phosphonyl radical addition to glycals[a]

Entry	Glycal[b]	Product	Time (h)[c]	Yield(%)[d]
1		 **2**	2.5	92
2		 **3**	2.5	85
3		 **4**	2	80
4		 **5**	2	82
5		 **6**	3	65
6		 **7**	4	73
7		 **8**	0.5	62
8		 **9**	3	75

[a]AcOH was used as the solvent and the reaction was performed at 60 °C in the presence of 3 equiv of $Mn(OAc)_2·4H_2O$ under air. [b]9.0 mmol of glycal was used. [c]TLC indicated the reaction went completely and it was stopped immediately. [d]Isolated yield.

In summary, this work demonstrated a novel Mn(II)/air promoted phosphonyl radical addition reaction of glycals with regio- and stereoselectivities. The selectivity of phosphonyl radical addition at C-2 was controlled by the oxygen atom of vinyl ether in the sugar ring due to the energy superiority and the formation of *p-p* orbital conjugation. The mechanism has been confirmed by theoretical calculation and experimental results. This novel reaction is mild, clean and efficient, suitable for various glycals. In this way, various metabolically inert 1,2-dideoxy 2-*C*-diphenylphosphinylglycopyranosides were first synthesized in good to excellent yields. These sugars containing diphenylphosphine oxide moiety are also novel enantiomerically pure ligands and the precursors of chiral phosphine ligands in the enantioselective syntheses.



Scheme 2 The mechanism for the formation of 1,2-dideoxy 2-*C*-diphenylphosphinylglycopyranosides.

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Notes and references

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†Electronic supplementary information (ESI) available: Experimental procedures and spectral data. CCDC 968911 (**2**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

‡ Crystallographic data for **2**: $C_{24}H_{27}O_8P$, M = 474.43, hexagonal, space group *P*6(1), a = 11.6460(8) Å, b = 11.6460(8) Å, c = 31.3727(3) Å, α = 90^0, β = 90^0, γ = 120^0, V = 3684.96(5) Å^3, Z = 6, ρ_{calcd} = 1.283 gcm^{-3}, T = 293(2) K, 19381 reflections measured, 4240 unique (R_{int} = 0.0264) which were used in all calculations. The final w$R(F_2)$ was 0.0995 (all data). R = 0.0365, R_w = 0.0978, GOF = 1.033. CCDC 968911 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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