

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

Fuyi Zhang,^{*a} Liming Wang,^a Cui Zhang^a and Yufen Zhao^{ab}Cite this: *Chem. Commun.*, 2014, 50, 2046Received 19th November 2013,
Accepted 19th December 2013

DOI: 10.1039/c3cc48806c

www.rsc.org/chemcomm

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.

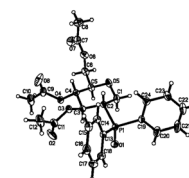
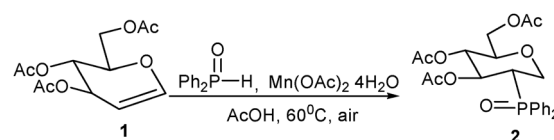
Because carbohydrate-derived organophosphorus compounds play an important role in the biosynthesis of oligosaccharides, the synthesis of nonhydrolyzable analogues has been an interesting subject.¹ These analogues are considered to be metabolically inert and used as enzyme inhibitors in the study of enzyme 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 bonds at the 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 the 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 required many steps and suffered from low regio- and stereoselectivities. The carbohydrate containing C–P bond at the C-2 position, which lacks the hydroxyl group at the C-1 position, remains sparse, although it is a nonhydrolyzable analogue

and an enantiomerically pure ligand. In continuation of our interest in the syntheses of 2-C-substituted sugar analogues⁷ 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)/O₂ catalyzed phosphonation of arenes¹⁰ and Mn(III) acetate promoted phosphonation of heteroaryl compounds¹¹ were also achieved. We envisaged that the Mn(II)/O₂ 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 procedure¹² was first used as a radical acceptor to react with diphenylphosphine oxide in the presence of very cheap Mn(OAc)₂·4H₂O in the atmosphere. The formation of **2** was investigated under various conditions. The ratio of Mn(OAc)₂·4H₂O to glucal and the solvent have major influence on the reaction. The optimum is 3 : 1. Below 3 : 1, the yield decreases (Table 1, entries 1–5). Acetic acid as a solvent is efficient at 60 °C, and an isolated yield of 92%



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

^a The College of Chemistry and Molecular Engineering, The Key Lab of Chemical Biology and Organic Chemistry, Zhengzhou University, Zhengzhou 450052, China. E-mail: zhangfy@zzu.edu.cn; Fax: +86-371-67763845; Tel: +86-371-67763845

^b College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, China

† 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/c3cc48806c

Table 1 Synthesis of 2-*C*-diphenylphosphinylglycopyranoside **2** under various conditions^a

Entry	Mn(OAc) ₂ ·4H ₂ O/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 ₃ CN	60	24	67
7	3:1	EtOH	60	16	32
8	3:1	DMF	60	24	Trace
9	3:1	HCOOH	60	24	Trace

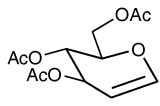
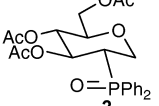
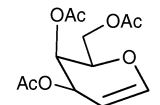
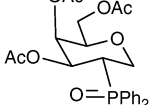
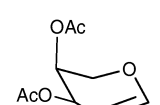
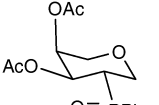
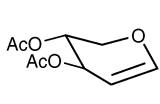
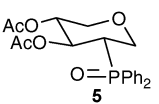
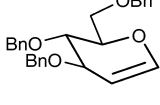
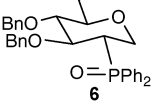
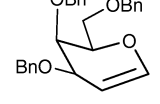
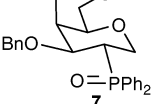
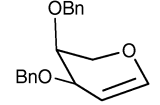
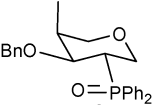
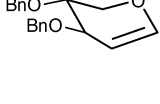
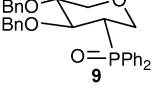
^a 190 mg (0.4 mmol) of **1** was used. ^b TLC indicated that the reaction ran completely and it was stopped immediately. ^c Isolated yield.

was attained by use of acetic acid and 3 equiv. of Mn(OAc)₂·4H₂O (Table 1, entry 4). Above 60 °C, the yield decreases. The structure of **2** was definitely characterized by spectroscopic data. **2** also gave crystals suitable for X-ray analysis after recrystallization from methanol. Its X-ray crystal structure (Scheme 1) indicates that the newly formed C–P bond at C-2 locates in the equatorial position and the sugar ring remains in a chair conformation.‡

To investigate the generality of this method and to synthesize various 1,2-dideoxy-2-*C*-diphenylphosphinylglycosides, the reaction was performed with the various glycols in acetic acid and at 60 °C in the presence of 3 equiv. of Mn(OAc)₂·4H₂O. Fortunately, all the reactions gave regio- and stereoselectivities, and the corresponding products were obtained in good to excellent yields, which are shown in Table 2. The reaction of acetyl protected glycol 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 obtained from phosphonyl addition at the C-1 position was not obtained. All the new compounds were characterized by ¹H NMR, ¹³C NMR, 2D NMR, MS and IR spectra.

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)₂·4H₂O under an Ar atmosphere. No desired product was obtained. When this reaction was performed in the presence of other Lewis acids such as FeCl₃, AlCl₃, Cu(OTf)₂ and InCl₃·4H₂O rather than Mn(OAc)₂·4H₂O–air, the desired product was also not obtained, which indicates that Lewis acid cannot promote this kind of addition reaction. The reaction was then carried out using Mn(OAc)₃ instead of Mn(OAc)₂·4H₂O–air or other Lewis acids. 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)₂·4H₂O itself cannot promote this addition reaction. Under an air atmosphere, it was oxidized to 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 positions of glycol 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

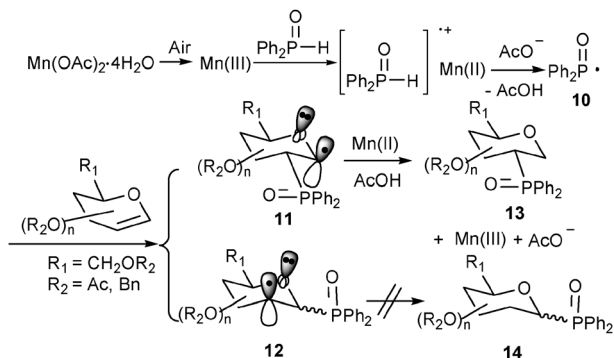
Table 2 Regio- and stereoselective syntheses of various 1,2-dideoxy-2-*C*-diphenylphosphinylglycopyranosides via Mn(II)–air promoted phosphonyl radical addition to glycols^a

Entry	Glycol ^b	Product	Time ^c (h)	Yield ^d (%)
1			2.5	92
2			2.5	85
3			2	80
4			2	82
5			3	65
6			4	73
7			0.5	62
8			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)₂·4H₂O in air. ^b 9.0 mmol of glycol was used. ^c TLC indicated that the reaction ran completely and it was stopped immediately. ^d Isolated yield.

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 radicals **11** and **12** (R₁ = CH₂OAc, R₂ = Ac) as examples was modelled using the Gaussian 09 program.¹³ The structures of **11** and **12** were optimized at the B3LYP¹⁴/6-31G(d) level in AcOH, using the integral equation formalism polarisable continuum model (IEF-PCM).¹⁵ The energy of **11** is 3.49 kcal mol⁻¹ lower than that of **12**, indicating that **11** is much more stable than **12**.



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

The calculated molecular orbitals of **11** definitely reveal that this p-p conjugation exists (figure is shown in page 12 in ESI.†). 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.

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 moieties are also novel enantiomerically pure ligands and the precursors of chiral phosphine ligands in the enantioselective syntheses.

The authors thank the National Natural Science Foundation of China (No. 21272219, 20972142) and the State Key Laboratory of Bio-organic and Natural Products Chemistry, CAS (08417) for financial support.

Notes and references

‡ Crystallographic data for **2**: C₂₄H₂₇O₈P, *M* = 474.43, hexagonal, space group *P6*(1), *a* = 11.6460(8) Å, *b* = 11.6460(8) Å, *c* = 31.3727(3) Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 120^\circ$, *V* = 3684.96(5) Å³, *Z* = 6, ρ_{calcd} = 1.283 g cm⁻³, *T* = 293(2) K, 19 381 reflections measured, 4240 unique (*R*_{int} = 0.0264) which were used in all calculations. The final *wR*(*F*₂) was 0.0995 (all data). *R* = 0.0365, *R*_w = 0.0978, GOF = 1.033. CCDC 968911.

- 1 For selected examples, see: (a) A. Vasella, G. Baudin and L. Panza, *Heteroat. Chem.*, 1991, **2**, 151; (b) A. Lopusiński, B. Bernet, A. Linden and A. Vasella, *Helv. Chim. Acta*, 1993, **76**, 94; (c) F. Stolz, M. Reiner, A. Blume, W. Reutter and R. R. Schmidt, *J. Org. Chem.*, 2004, **69**, 665; (d) X. P. Nie and G. J. Wang, *J. Org. Chem.*, 2005, **70**, 8687; (e) D. Lazarevic and J. Thiem, *Carbohydr. Res.*, 2006, **341**, 569; (f) Z. Dinev, C. T. Gannon, C. Egan, J. A. Watt, M. J. McConville and S. J. Williams, *Org. Biomol. Chem.*, 2007, **5**, 952; (g) C. Yuan and R. I. Hollingsworth, *Tetrahedron Lett.*, 2011, **52**, 5421.

- 2 (a) R. A. Ferrari, P. Mandelstam and R. K. Crane, *Arch. Biochem. Biophys.*, 1959, **80**, 372; (b) D. P. Losow and I. A. Rose, *J. Biol. Chem.*, 1968, **243**, 3623; (c) T. Y. Fang, O. Alcchina, A. E. Aldshin, H. J. Fromm and R. B. Honzatko, *J. Biol. Chem.*, 1998, **273**, 19548; (d) Y. Shiga, H. Mizuno and H. Akanuma, *J. Bacteriol.*, 1993, **175**, 7138; (e) T. Yamanouchi, N. Ogata, T. Yoshimura, T. Inoue, E. Ogata, T. Kawasaki, A. Kashiwabara and H. Muraoka, *Biochim. Biophys. Acta*, 2000, **1474**, 291; (f) T. Yamanouchi, T. Inoue, K. Ichiiyanagi, T. Sakai and N. Ogata, *Biochim. Biophys. Acta*, 2003, **1623**, 82.
- 3 (a) M. A. Brown, P. J. Cox, R. A. Howie, O. A. Melvin, O. J. Taylor and J. L. Wardell, *J. Organomet. Chem.*, 1995, **498**, 275; (b) J.-C. Shi, M.-C. Hong, D.-X. Wu, Q.-T. Liu and B.-S. Kang, *Chem. Lett.*, 1995, 685; (c) K. Yonehara, T. Hashizume, K. Ohe and S. Uemura, *Tetrahedron: Asymmetry*, 1999, **10**, 4029; (d) D. Steiborn and H. Junicke, *Chem. Rev.*, 2000, **100**, 4283; (e) O. Pamiez, M. Diéguez, G. Net, A. Ruiz and C. Claver, *J. Org. Chem.*, 2001, **66**, 8364; (f) M. Narsireddy and Y. Yamamoto, *J. Org. Chem.*, 2008, **73**, 9698.
- 4 For selected examples, see: (a) I. Sadovskaya, J. R. Brisson, P. Thibault, J. C. Richards, J. S. Lam and E. Altman, *Eur. J. Biochem.*, 2000, **267**, 1640; (b) E. Vinogradov, A. Korenevsky and T. J. Beveridge, *Carbohydr. Res.*, 2002, **337**, 1285; (c) M. Lahmann, P. J. Garegg, P. Konradsson and S. Oscarson, *Can. J. Chem.*, 2002, **80**, 1105; (d) K. Pekari and R. R. Schmidt, *J. Org. Chem.*, 2003, **68**, 1295; (e) S. Leone, V. Izzo, A. Silipo, L. Sturiale, D. Garozzo, R. Lanzetta, M. Parrilli, A. Molinaro and A. Didonato, *Eur. J. Biochem.*, 2004, **271**, 2691.
- 5 (a) J. Thiem, D. Rasch and H. Paulsen, *Chem. Ber.*, 1976, **109**, 3587; (b) C. M. Jessop, A. F. Parsons and A. Raoufledge, *Tetrahedron Lett.*, 2004, **45**, 5095; (c) F. Leonelli, M. Capuzzi, E. Bodo, P. Passacantilli and G. Piancatelli, *Carbohydr. Res.*, 2008, **343**, 1133; (d) E. Elamparuthi and T. Linker, *Angew. Chem., Int. Ed.*, 2009, **48**, 1853.
- 6 M. A. Brown, P. J. Cox, R. A. Howie, O. A. Melvin, O. J. Taylor and J. L. Wardell, *J. Organomet. Chem.*, 1995, **498**, 275.
- 7 (a) H.-M. Liu, F. Zhang and J. Zhang, *Carbohydr. Res.*, 2001, **334**, 323; (b) H.-M. Liu, F. Zhang, J. Zhang and S. Li, *Carbohydr. Res.*, 2003, **338**, 1737; (c) H.-M. Liu, F. Zhang and S. Wang, *Org. Biomol. Chem.*, 2003, **1**, 1641; (d) H.-M. Liu, F. Zhang and D.-P. Zou, *Chem. Commun.*, 2003, 2044; (e) F. Zhang, H. Liu, Y.-F. Li and H.-M. Liu, *Carbohydr. Res.*, 2010, **345**, 839; (f) Q. Zhang, J. Sun, F. Zhang and B. Yu, *Eur. J. Org. Chem.*, 2010, 3579; (g) H. Liu, F. Zhang, J.-P. Li, X. Yan, H.-M. Liu and Y.-F. Zhao, *J. Chem. Crystallogr.*, 2011, **41**, 1228; (h) F. Zhang, H. Liu, Y. Sheng and H.-M. Liu, *Chin. J. Chem.*, 2012, **30**, 195.
- 8 (a) D.-L. Ma, T. Y.-T. Shum, F. Zhang, C.-M. Che and M. Yang, *Chem. Commun.*, 2005, 4675; (b) Q. Zhang, J. Sun, Y. Zhu, F. Zhang and B. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 4933; (c) J. Yu, J. Sun, Y. Niu, R. Li, J. Liao, F. Zhang and B. Yu, *Chem. Sci.*, 2013, **4**, 389.
- 9 (a) B. B. Snider, *Chem. Rev.*, 1996, **96**, 339; (b) N. A. Swain, R. C. D. Brown and G. Bruton, *J. Org. Chem.*, 2004, **69**, 122; (c) B. B. Snider and J. R. Duvall, *Org. Lett.*, 2004, **6**, 1265; (d) Z. Zhang, G.-W. Wang, C.-B. Miao, Y.-W. Dong and Y.-B. Shen, *Chem. Commun.*, 2004, 1832; (e) J. W. Huang and M. Shi, *J. Org. Chem.*, 2005, **70**, 3859; (f) X.-J. Mu, J.-P. Zou, Q.-F. Qian and W. Zhang, *Tetrahedron Lett.*, 2006, **47**, 2323; (g) G.-W. Wang, Y.-W. Dong, P. Wu, T.-T. Yuan and Y.-B. Shen, *J. Org. Chem.*, 2008, **73**, 7088.
- 10 T. Kagayama, A. Nakano, S. Sakaguchi and Y. Ishii, *Org. Lett.*, 2006, **8**, 407.
- 11 (a) Y. Unoh, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2013, **52**, 12975; (b) Y.-R. Chen and W.-L. Duan, *J. Am. Chem. Soc.*, 2013, **135**, 16754; (c) X.-J. Mu, J.-P. Zou, Q.-F. Qian and W. Zhang, *Org. Lett.*, 2006, **8**, 5291.
- 12 J. Zhao, S. Wei, X. Ma and H. Shao, *Green Chem.*, 2009, **11**, 1124.
- 13 G. J. Frisch and H. B. Schlegel, *et al.*, Revision C. 01, 2010.
- 14 (a) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648; (b) C. T. Lee, W. T. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785; (c) B. Miehlich, A. Savin, H. Stoll and H. Preuss, *Chem. Phys. Lett.*, 1989, **157**, 200.
- 15 (a) V. Barone and M. Cossi, *J. Phys. Chem. A*, 1998, **102**, 1995; (b) B. Mennucci and J. Tomasi, *J. Chem. Phys.*, 1997, **106**, 5151.