Tetrahedron Letters 50 (2009) 101–103

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diphenylphosphinoylethylidene (DPE) acetals: an alternative protective strategy in glycochemistry

Leonardo Pellizzaro [a], Arnaud Tatibouët [b], Fabrizio Fabris [a], Patrick Rollin [b,*], Ottorino De Lucchi [a]

[a] Dipartimento di Chimica, Università Ca' Foscari di Venezia, Dorsoduro 2137, I-30123 Venezia, Italy
[b] Institut de Chimie Organique et Analytique—UMR 6005, Université d'Orléans, B.P. 6759, F-45067 Orléans, France

ARTICLE INFO

Article history:
Received 19 September 2008
Revised 16 October 2008
Accepted 21 October 2008
Available online 25 October 2008

Keywords:
Carbohydrates
Cyclic acetals
Protective groups
Ethynylphosphine oxide

ABSTRACT

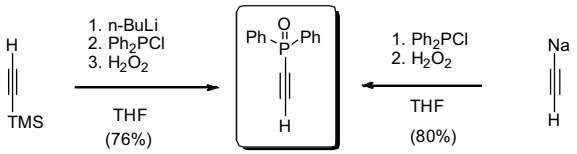
Diphenylphoshinoylethyne reacts with diols under basic conditions to produce cycloacetalic phosphine oxides. The reaction appears to be general and particularly effective with carbohydrate derivatives. The 2-(diphenylphoshinoyl)ethylidene (DPE) acetals produced are stable in acidic media while they can be cleaved under reductive and/or basic conditions: base-catalyzed transacetalization is a method of choice for their mild and effective deprotection.

Selective introduction-expulsion of protective groups still remains a major concern in polyol and carbohydrate chemistry strategies, in which cyclic acetals—mainly 1,3-dioxolanes and 1,3-dioxanes—play an impressive role.[1,2] In addition to being useful for selective protection of mono-and oligosaccharides, cyclic acetals can undergo a number of interesting transformations such as regiospecific oxidative and reductive openings.[3] Hence, there is a persistent demand for new cyclic acetals showing atypical properties. On those grounds, we have recently developed novel types of substituted ethylidene acetals: phenylsulfonylethylidene (PSE)[4] and phenylsulfinyl-ethylidene[5] acetals, which are easily prepared from miscellaneous diols through base-promoted reaction with either 1,2-bis-(phenylsulfonyl)ethylene (BPSE) or 1-(phenylsulfinyl)-2-(phenylsulfanyl)ethylene (SOSE): those unusual acetals strongly resist cleavage in acidic media[4,6] and display original properties.[7] In the present work, we wish to introduce diphenylphosphinoylethyne as a new reagent for the protection of carbohydrates, building up in the lineage of PSE acetals,[4] a novel class of cyclic acetals resistant to cleavage under acidic conditions and potentially offering additional reactivity features.

Diphenylphosphinoylethyne is readily obtainable in good yield from ethynyltrimethylsilane though a base-promoted nucleophilic attack to P-chlorodiphenylphosphine, followed by in situ hydrogen peroxide oxidation, which at the same time removes the trimethylsilyl moiety.[8] Alternatively, inexpensive sodium acetylide can be used as precursor to produce diphenylphosphinoylethyne with equally good yields[9] (Scheme 1).

The ability of diphenylphosphinoylethyne to react as Michael acceptor has been scarcely reported, notably towards amines[10a] and halide ions,[10b] and only a mono-additive process was observed, producing the corresponding vinyl phosphine oxides. However, when considering the case of related electron-poor alkynes such as alkyl propynoates[11a] or arylsulfonylethynes,[11b,c] it appears that double nucleophilic additions can take place under forced conditions[12] allowing, for example, formation of cyclic acetals and thioacetals.

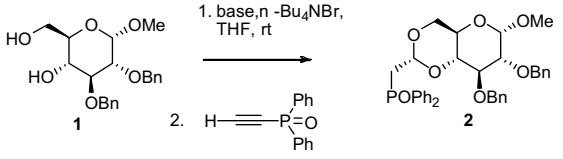
Initial exploration was performed on the carbohydrate pyranotemplate **1** which has been currently used as the standard substrate in many of our previous works,[4–6] and diverse basic reagents were tested to activate the hydroxyl groups. As shown in Scheme 2, the reaction produced the expected chiral 1,3-dioxane **2** in variable yields, depending on the base involved: DBU showed unreactive, whereas stronger bases such as *t*BuOK and LiHMDS only allowed partial condensation; in concordance with our previous observations,[4,5] optimal conversion into acetal **2** was attained by the use



Scheme 1. Preparation of diphenylphosphinoylethyne.

* Corresponding author.
E-mail address: arnaud.tatibouet@univ-orleans.fr (P. Rollin).

0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.10.111



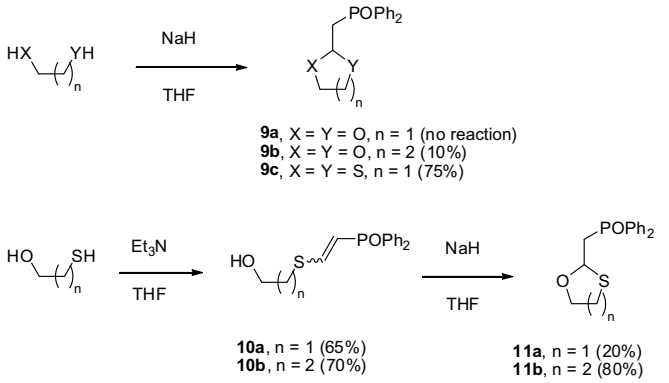
Scheme 2. Formation of a carbohydrate-based DPE acetal.

of sodium hydride in the presence of a catalytic amount of *n*-Bu_4NBr.[13]

The base-promoted protocol established above was applied to a range of structurally diverse saccharidic diols in order to put up an introductory evaluation of diphenylphosphinoylethyne's potential as protective agent in glycosynthesis. Cyclic DPE acetals of 1,3-dioxolane- or 1,3-dioxane-type were obtained in 50–75% yields in the D-fructopyrano (**3**), D-psicopyrano (**4**), D-glucofurano (**5**), D-xylofurano (**6**)[14] and L-sorbofurano (**7** and **8**) series (Fig. 1). As expected from previous reports, dioxolanic DPE **3**, **4** and **5** were formed with poor diastereoselectivity with regard to the newly introduced stereogenic centre, whereas dioxanic DPE **2**, **6**, **7** and **8** bore a strictly equatorially oriented phosphinoyl appendage.

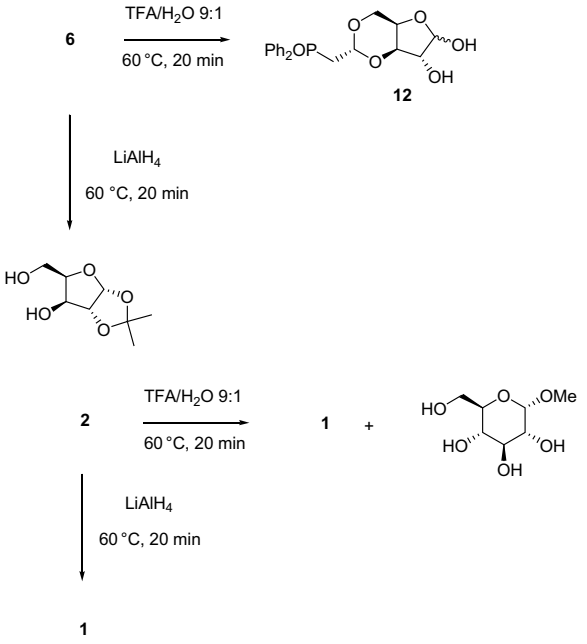
Close functional associations between a phosphine oxide and an acetal[15] or a thioacetal[16] moiety have seldom been mentioned in the literature. It appeared therefore interesting to try and expand the scope of the reactivity of diphenylphosphinoylethyne towards simple, flexible diol-type structures; surprisingly and in sharp contrast with previous results from our labs,[5,7a,11c] neither 1,2-ethanediol nor 1,3-propanediol could be converted satisfactorily into DPE acetals. We have observed however, that 1,2-ethanedithiol behaved more favourably, affording a 75% yield of the corresponding dithiolane **9c**.[17] Oxathiolane **11a**[18] and oxathiane **11b**[19] were obtained from 2-mercaptoethanol in low yield and from 3-mercaptopropanol in good yield, using a modified sequential chemoselective procedure.[20] Initially, primary triethylamine-catalyzed thiol addition on diphenylphosphinoylethyne produced a Z/E mixture of sulfanylvinyl phosphine oxides. This first step proceeded in both cases with good yields to give intermediates **10a** and **10b**, which further underwent NaH-promoted cyclization under standard conditions.[13] (see Scheme 3).

In order to test the ability of DPE acetals to undergo cleavage under acidic conditions,[21] model acetals **2** and **6** were treated by a 9:1 (v/v) trifluoroacetic acid/water mixture at room temperature. The glucopyranoside **2** remained unaffected after 48 h, whereas the xylofurano compound **6** was selectively 1,2-*O*-deprotected in ca 45 min to yield an anomeric mixture of 3,5-*O*-diphenylphosphinoylethylidene-D-xylofuranoses **12** (Scheme 4). These results are



Scheme 3. Formation of simple DPE acetals.

analogous to those reported for β-phenylsulfonyl- and β-phenylsulfinylethylidene acetals, whose protonated forms are believed to gain stabilization from a S=O bond.[22] However, when submitted to 90% aqueous trifluoroacetic acid at 60 °C, compound **2** under-



Scheme 4. Behaviour of DPE acetals under deprotection conditions.

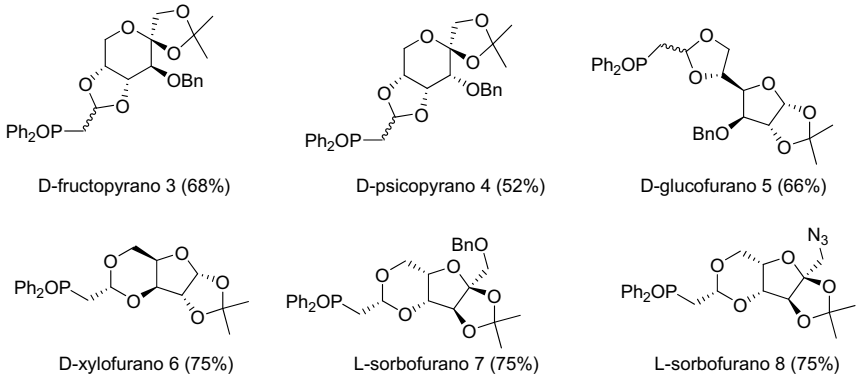
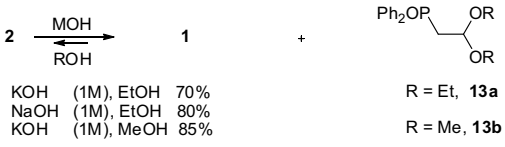


Figure 1. Carbohydrate-based DPE acetals.



Scheme 5. Retro-Michael transacetalation for deprotection.

went fast (20 min) removal of the 4,6-*O*-DPE acetal protection together with partial 2,3-de-*O*-benzylation: this observation denotes a marked contrast with the behaviour of PSE acetals and is indicative of a much less efficient stabilization of protonated forms by a P═O bond.

In contrast, the behaviour of DPE acetals in strongly basic media compares well with that of PSE acetals. For example, when treated by $LiAlH_4$ in THF,[4a] DPE acetals **2** and **6** smoothly release the corresponding diols in nearly quantitative yield (Scheme 4).

Furthermore, cleavage of DPE acetals could also be performed via base-catalyzed transacetalation using refluxing 1 M ethanol or methanol solutions of NaOH or KOH. The saccharidic diols were recovered in high yields, together with 2-(diphenylphosphinoyl)acetaldehyde dialkyl acetals **13**, the expected side-product of the deprotection process (Scheme 5).[23]

In summary, a new class of cyclic acetals bearing a phosphine oxide in β-position has been introduced in glycochemistry.[24] Those DPE acetals were readily obtained in reasonable yields from diols and inexpensive diphenylphosphinoylethyne under basic conditions. Although they do not match the high degree of stability of PSE acetals in acidic media, DPE acetals satisfactorily resist moderate acidic conditions, thanks to a P═O bond stabilization of activated species. Finally, DPE acetals can undergo efficient cleavage under basic or reductive conditions. Further chemical reactivity features of carbohydrate-based DPE acetals are under current investigation.

Acknowledgements

We thank Sandrina Silva and Dr. Charlotte Moine (ICOA) for helpful contribution and comments. This work was co-funded by MIUR (Rome) within the national PRIN framework. We are also grateful to EGIDE for support.

References and notes

1. (a) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley & Sons: New York, 1999; (b) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: New York, 2004.
2. For reviews in glycochemistry, see: (a) Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 13–70; (b) Gelas, J. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 71–156.
3. (a) Hanessian, S. *Methods Carbohydr. Chem.* **1972**, *6*, 183–189; (b) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10–C12; (c) Umemura, K.; Matsuyama, H.; Kobayashi, M.; Kamigata, N. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3026–3029; (d) Pohl, N. L.; Kiessling, L. L. *Tetrahedron Lett.* **1997**, *38*, 6985–6988.
4. (a) Chéry, F.; Rollin, P.; De Lucchi, O.; Cossu, S. *Synthesis* **2001**, 286–292; (b) Chéry, F.; Pillard, C.; Tatibouët, A.; De Lucchi, O.; Rollin, P. *Tetrahedron* **2006**, *62*, 5141–5151.
5. Cabianca, E.; Tatibouët, A.; Fabris, F.; De Lucchi, O.; Rollin, P. *Tetrahedron Lett.* **2005**, *46*, 1035–1037.
6. (a) Chevalier-du Roizel, B.; Cabianca, E.; Tatibouët, A.; Rollin, P.; Sinaÿ, P. *Tetrahedron* **2002**, *58*, 9579–9583; (b) Uttaro, J. P.; Uttaro, L.; Tatibouët, A.; Rollin, P.; Mathé, C.; Périgaud, C. *Tetrahedron Lett.* **2007**, *48*, 3851–3854.
7. (a) Cabianca, E.; Chéry, F.; Rollin, P.; Tatibouët, A.; De Lucchi, O. *Tetrahedron Lett.* **2002**, *43*, 585–587; (b) Cabianca, E.; Tatibouët, A.; Rollin, P. *Pol. J. Chem.* **2005**, *79*, 317–322; (c) Fernandes, A.; Dell'Olmo, M.; Tatibouët, A.; Imberty, A.; Philouze, C.; Rollin, P. *Tetrahedron Lett.* **2008**, *49*, 3484–3488.
8. Corriu, R. J. P.; Guérin, C.; Henner, B. J. L.; Jolivet, A. *J. Organomet. Chem.* **1997**, *530*, 39–48.
9. Charrier, C.; Chodkiewicz, W.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1966**, 1002–1011.
10. (a) Märkl, G.; Merkl, B. *Tetrahedron Lett.* **1983**, *24*, 5865–5868; (b) Huang, X.; Zhang, C.; Lu, X. *Synthesis* **1995**, 769–771.
11. (a) Ariza, X.; Costa, A. M.; Faja, M.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2000**, *2*, 2809–2811; (b) De Lucchi, O.; Cossu, S. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: USA, 2001; (c) Cossu, S.; De Lucchi, O.; Fabris, F.; Ballini, R.; Bosica, G. *Synthesis* **1996**, 1481–1484.
12. Back, T. G. *Tetrahedron* **2001**, *57*, 5263–5301.
13. *Typical experimental procedure for the preparation of DPE acetals*: To a solution of diol **1** (749 mg, 2 mmol)[4] in dry THF (20 mL) maintained at 0 °C under argon, NaH (60% dispersion in oil, 200 mg, 2.5 equiv) was introduced. After 15 min vigorous stirring of the obtained slurry, Bu_4NBr (65 mg, 0.05 equiv) was added, followed by a THF solution of diphenylphosphinoylethyne[9] (566 mg, 2.5 mmol in 10 mL). After stirring for 12 h at rt, the mixture was carefully treated with brine (15 mL), then extracted with AcOEt (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, concentrated in vacuo and the residue was purified by silica-gel column chromatography (petroleum ether/AcOEt 3:7). Selected data for acetal **2** (syrup, 1.06 g, 88% yield): $[\alpha]_D$ +189 (*c* 1.2, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 2.68-2.89 (m, 2H, H-8a, H-8b), 3.30 (t, 1H, $J_{3-4} = J_{4-5}$ = 9.2, H-4), 3.34 (s, 3H, OCH_3), 3.39 (t, 1H, $J_{5-6b} = J_{gem}$ = 10.1, H-6b), 3.43 (dd, 1H, J_{1-2} = 3.8, J_{2-3} = 9.2, H-2), 3.60 (m, 1H, H-5), 3.82 (t, 1H, J_{vic} = 9.2, H-3), 3.97 (dd, 1H, J_{5-6a} = 4.6, J_{gem} = 10.1, H-6a), 4.50 (d, 1H, J_{1-2} = 3.8, H-1), 4.58 (s, 2H, OCH_2Ph), 4.59 and 4.76 (2d, AB system, 2H, J_{gem} = 12.0, OCH_2Ph), 4.96 (bq, 1H, J_{7-8} = 5.5, $^2J_{H-P}$ = 10.7, H-7), 7.3 and 7.4 (2m, 16H, H–Ar), 7.6–7.8 (m, 4H, *ortho*-H–Ar *Ph*PO). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 35.9 (d, $^1J_{C-P}$ = 70.4, C-8), 55.4 (OMe), 61.9 (C-5), 68.6 (C-6), 73.8 and 75.0 (PhCH_2O), 78.5 (C-3), 79.2 (C-2), 81.8 (C-4), 98.0 (C-7), 99.1 (C-1), 127.5–128.7 (CH-Ar), 130.9, 131.0 (2d, $^3J_{C-P}$ = 9.6, CH-*meta*-*Ph*PO), 131.7, 131.9 (2d, $^4J_{C-P}$ = 2.7, CH-*para*-*Ph*PO), 133.0 (d, $^1J_{C-P}$ = 101.9, C_{IV}–*Ph*PO), 133.3 (d, $^1J_{C-P}$ = 102.7, C_{IV}–*Ph*PO), 138.1, 138.8 (2∗C_{IV}–Ar). HRMS calcd for $C_{35}H_{37}O_7P$: 600.2277; found 600.2271.
14. *Selected data for DPE acetal* **6**: $[\alpha]_D$ +12 (*c* 2.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 1.27, 1.44 (2s, 6H, Me), 2.61–2.82 (m, 2H, H-7a, H-7b), 3.87 (dd, 1H, J_{4-5b} = 2.0, J_{gem} = 13.1, H-5b), 3.95 (m, 1H, H-4), 4.13 (br s, 1H, H-3), 4.15 (bd, 1H, H-5a), 4.19 (bd, H-2), 5.01 (bq, 1H, J_{6-7} = 5.2, $^2J_{H-P}$ = 10.7, H-6), 5.90 (d, 1H, J_{1-2} = 3.7, H-1), 7.38–7.55 (m, 6H, H–Ar), 7.65–7.77 (m, 4H, *ortho*-H-Ar *Ph*PO). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 26.1, 26.6 (*i*Prd), 36.2 (d, $^1J_{C-P}$ = 71.6, C-7), 66.2 (C-5), 71.8 (C-4), 78.4 (C-3), 83.4 (C-2), 95.6 (C-1), 105.4 (C-6), 111.8 (C_{IV}–*i*Prd), 128.4, 128.5 (2d, $^2J_{C-P}$ = 12.0, CH-*ortho*-*Ph*PO), 130.8 (d, $^3J_{C-P}$ = 9.6, CH-*meta*-*Ph*PO), 131.7, 131.8 (2d, $^4J_{C-P}$ = 2.6, CH-*para*-*Ph*PO), 132.8 (d, $^1J_{C-P}$ = 102.3, C_{IV}–*Ph*PO), 133.1 (d, $^1J_{C-P}$ = 102.6, C_{IV}–*Ph*PO). HRMS calcd for $C_{22}H_{25}O_6P$: 416.1389; found 416.1395.
15. (a) Hansen, K. C.; Wright, C. H.; Aguiar, A. M.; Morrow, C. J.; Turkel, R. M.; Bhacca, N. S. *J. Org. Chem.* **1970**, *35*, 2820–2822; (b) Cates, L. A.; Jones, G. S., Jr.; Good, D. J.; Tsai, H. Y. L.; Li, V. S.; Caron, N.; Tu, S. C.; Kimball, A. P. *J. Med. Chem.* **1980**, *23*, 300–304; (c) Okauchi, T.; Nagamori, H.; Kouno, R.; Ichikawa, J.; Minami, T. *Heterocycles* **2000**, *52*, 1393–1398.
16. Schaumann, E.; Fittkau, S. *Bull. Soc. Chim. Belg.* **1985**, *94*, 463–474.
17. *Selected data for the syrupy dithiolane* **9c**: ^1H NMR (250 MHz, $CDCl_3$): δ 2.96 (dd, 2H, J_{vic} = 7.1, $^2J_{H-P}$ = 10.2, CH_2–PO), 3.05–3.30 (m, 4H, CH_2S), 4.83 (dd, 1H, J_{vic} = 7.1, J_{vic} = 13.9, H-2), 7.4–7.6 (m, 6H, H–Ar), 7.70–7.83 (m, 4H, *ortho*-H–Ar *Ph*PO). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 31.1 (CH_2S), 39.8 (d, $^1J_{C-P}$ = 67.2, CH_2–PO), 46.5 (d, $^2J_{C-P}$ = 3.2, C-2), 128.8 (d, $^2J_{C-P}$ = 11.8, CH-*ortho*-*Ph*PO), 131.1 (d, $^3J_{C-P}$ = 9.3, CH–*meta*-*Ph*PO), 132.1 (d, $^4J_{C-P}$ = 2.8, CH–*para*-*Ph*PO), 132.5 (d, $^1J_{C-P}$ = 99.2, C_{IV}–*Ph*PO). HRMS calcd for $C_{16}H_{17}OPS_2$: 320.0458; found 320.0452.
18. *Selected data for the syrupy oxathiolane* **11a**: ^1H NMR (250 MHz, $CDCl_3$): δ 2.80 (dd, 1H, J_{vic} = 7.1, $^2J_{H-P}$ = 10.1, C*Hb*–PO), 2.98–3.05 (m, 3H, H-4a, H-4b, C*Ha*–PO), 3.57–3.72 (m, 1H, H-5b), 4.25 (ddd, 1H, H-5a), 5.41 (dd, 1H, J_{vic} = 5.8, J_{vic} = 12.5, H-2), 7.4–7.6 (m, 6H, H–Ar), 7.68–7.83 (m, 4H, *ortho*-H–Ar *Ph*PO). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 33.4 C-4, 37.9 (d, $^1J_{C-P}$ = 67.0, CH_2–PO), 71.2 (C-5), 80.5 (C-2), 128.5 (2d, $^2J_{C-P}$ = 10.1, CH–*ortho*-*Ph*PO), 130.9 (2d, $^3J_{C-P}$ = 9.0, CH–*meta*-*Ph*PO), 132.0 (2d, $^4J_{C-P}$ = 2.5, CH–*para*-*Ph*PO). HRMS calcd for $C_{16}H_{17}O_2PS$: 304.0687; found 304.0691.
19. *Selected data for the syrupy oxathiane* **11b**: ^1H NMR (250 MHz, $CDCl_3$): δ 1.53 bd, 1H, J_{gem} = 14.0, H-5b), 1.7–1.9 (m, 1H, H-5a), 2.44–2.67 (m, 2H, H-4b, C*Hb*–PO), 2.76–3.04 (m, 2H, H-4a, C*Ha*–PO), 3.41 (dt, 1H, H-6b), 3.82–3.93 (bd, 1H, H-6a), 5.16 dt, J_{vic} = 8.7, $^2J_{H-P}$ = 4.0, H-2), 7.32–7.50 (m, 6H, H–Ar), 7.63–7.76 (m, 4H, *ortho*-H–Ar *Ph*PO). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 25.2 (C-5), 28.4 (C-4), 37.4 (d, $^1J_{C-P}$ = 68.9, CH_2–PO), 69.9 (C-6), 77.3 (d, $^2J_{C-P}$ = 11.8, C-2), 128.4 (2d, $^2J_{C-P}$ = 11.9, CH–*ortho*-*Ph*PO), 130.7 (2d, $^3J_{C-P}$ = 9.7, CH–*meta*-*Ph*PO), 131.8 (d, $^4J_{C-P}$ = 2.8, CH–*para*-*Ph*PO), 133.0 (d, $^1J_{C-P}$ = 101.6, C_{IV}–*Ph*PO), 133.2 (d, $^1J_{C-P}$ = 100.7, C_{IV}–*Ph*PO). HRMS calcd for $C_{17}H_{19}O_2PS$: 318.0843; found 318.0839.
20. Cabianca, E.; Tatibouët, A.; Chéry, F.; Pillard, C.; De Lucchi, O.; Rollin, P. *Tetrahedron Lett.* **2003**, *44*, 5723–5725.
21. Christensen, J. E.; Goodman, L. *Carbohydr. Res.* **1968**, *7*, 510–512.
22. An initial mechanistic suggestion given to us by Professor E. Juaristi (Instituto Politecnico Nacional, Mexico) was later supported by our preliminary ab initio calculations.
23. *Typical experimental procedure for the base-catalyzed cleavage of DPE acetals*: A sample (0.102 g, 0.17 mmol) of the DPE acetal **2** was added to a 1 M KOH solution in ethanol (20 mL) and the mixture was refluxed for 12 h, then concentrated under reduced pressure and partitioned between AcOEt (50 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$, concentrated and the residue purified by silica-gel column chromatography (petroleum ether/AcOEt 1:1, then 3:7). After elution of the diethyl acetal side-product **13a**, the glycoside **1** was recovered (55 mg, 86% yield).
24. The diphenylphosphinoyl moiety was introduced via oxidation of a pyranose-derived phosphine: (a) Li, C.; Bernet, B.; Vasella, A.; Broger, E. A.; Meili, A. *Carbohydr. Res.* **1991**, *216*, 149–170; (b) Brown, M. A.; Cox, P. *J. Organomet. Chem.* **1995**, *498*, 275–282.