Tetrahedron Letters,Vol.30,No.40,pp 5473-5476,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

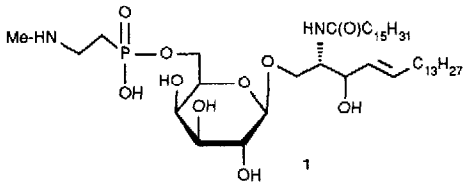
A NEW AND VERSATILE PHOSPHONYLATION APPROACH

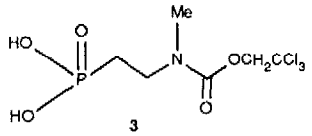
P.A.M. van der Klein, C.E. Dreef, G.A. van der Marel and J.H. van Boom

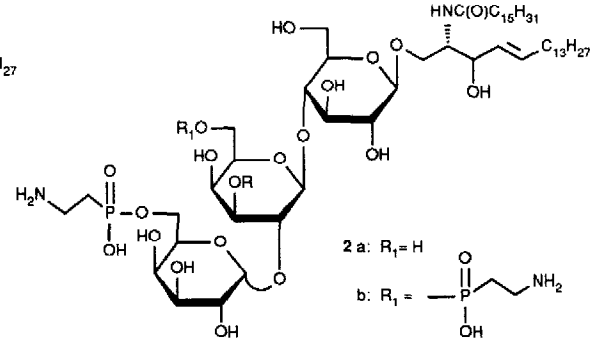
Gorlaeus Laboratories, P.O. Box 9502, 2300 RA Leiden, The Netherlands

SUMMARY: The bifunctional reagent *bis*(benzotriazolyl)-2-bromoethylphosphonate has been used successfully for the preparation of 2-amino-, 2-N-methylamino- and 2-N-dimethylaminoethylphosphonates of methyl 2,3,4-tri-O-benzoyl-β-D-galactopyranoside.

The structures of the phosphonosphingolipids **1** and **2a,b** [R=3-O-Me-D-Gal*p*-β(1-3)-D-GalNAc*p*-α(1-] isolated from muscle tissues of the marine snail *Turbo cornutus* and the skin of *Aplysia kuroday*, respectively, were recently elucidated by Hayashi *et al.*[1,2]. An essential feature of these molecules is the presence at C-6 of the D-galactopyranosyl unit of a 2-amino or a 2-N-methylaminoethylphosphonyl function (*e.g.*, **2a,b** or **1**) and a β-linked unsaturated ceramide.

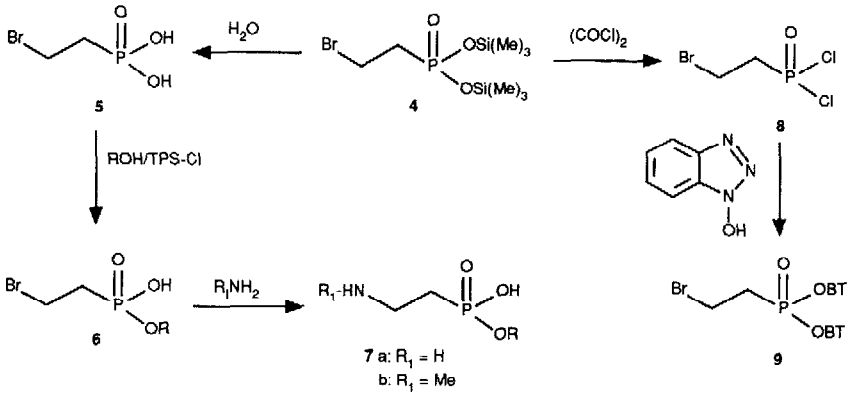




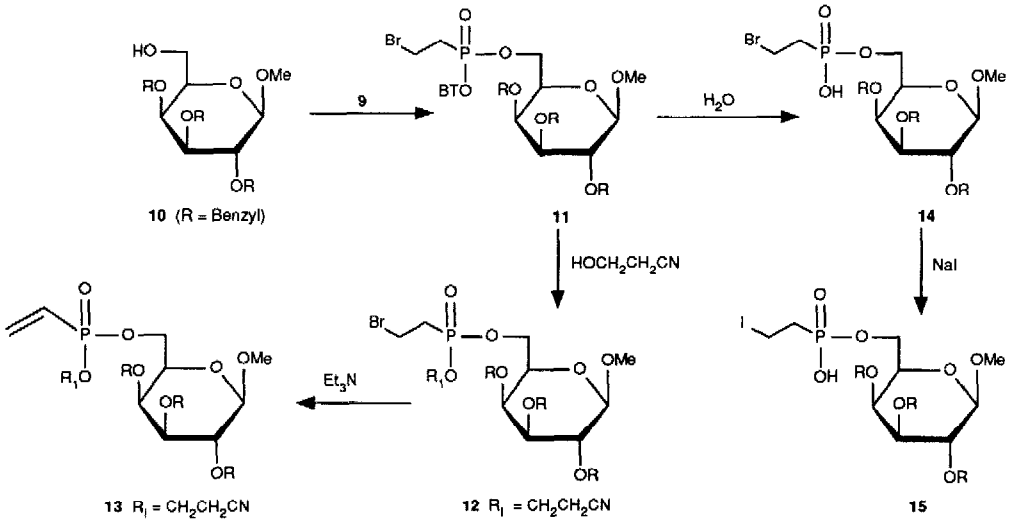


One of the crucial steps in a total synthesis of this class of compounds is the introduction of a 2-amino- or 2-N-methylaminoethylphosphonate function. To be successful, effective and reliable phosphonylation procedures are imperative. For instance, Ohashi *et al.*[3] used the not easily accessible and rather ineffective 2-N-methylaminoethylphosphonic acid **3** in the final stage of the synthesis of phosphonosphingolipid **1**. Earlier we published[4] an alternative two-step approach (see Scheme 1) which consisted of treating an alcohol (ROH) with 2-bromoethylphosphonic acid **5** in the presence of an activating reagent (*i.e.*, 2,4,6-triisopropylbenzenesulfonyl chloride) to give **6**. Subsequent nucleophilic displacement of the bromine atom in **6** with ammonia or methylamine gave the corresponding amino-derivatives **7a,b**. However, in this approach the phosphonylation and subsequent substitution are rather sluggish and the purification of intermediate and charged phosphonate **6** is also very time-consuming.

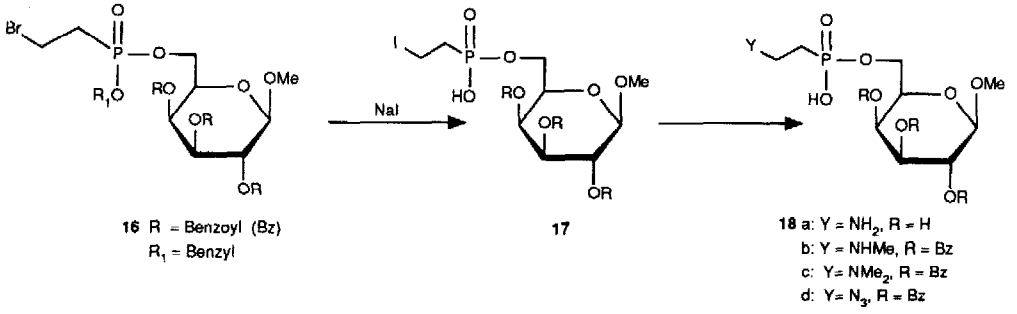
SCHEME 1



SCHEME 2



SCHEME 3



We now report that the rate of phosphonylation and substitution could be increased by applying the bifunctional reagent *bis*(benzotriazolyl)-2-bromoethylphosphonate **9**.

The new reagent **9** was easily accessible as follows. Treatment of 4[4] with oxalyl chloride in the presence of DMF according to Bhongle *et al.*[5] afforded, after distillation (b.p. 74°C, 0.05 mm Hg), pure **8** (δP: 42.31 ppm) in 80% yield. To a solution of **8** (10.8 mmol) in dioxane (54 ml) was now added 1-hydroxybenzotriazole (HOBT, 21.6 mmol) together with pyridine (1.75 ml), and the mixture was left for 2 h at 20°C, to yield after filtration a 0.2 M solution of **9** (δP: 40.37 ppm). The efficacy of *in situ* prepared **9** is illustrated in Scheme 2. Thus phosphonylation of methyl 2,3,4-tri-O-benzyl-β-D-galactopyranoside **10** (5 mmol), previously dried by coevaporation with pyridine, with **9** (0.2 M, 28.8 ml) to give intermediate **11** proceeded rapidly (10 min) as gauged by TLC-analysis. Addition of 2-cyanoethanol (0.68 ml) to **11** followed by work-up and purification (silica gel), after 4 h at 20°C, afforded **12** (δP: 27.53 and 27.38 ppm) in a yield of 75%. In an attempt to remove the cyanoethyl (R') group selectively from **12** with Et_3N in acetonitrile[6] (4 h at 20°C), we isolated the protected vinylphosphonate[7] **13** [δP: 18.60 ppm; IR (neat) ν 2250 cm^{-1}] in a yield of 85%. Further, hydrolysis of intermediate **11** gave, after purification (Sephadex LH-20), **14** [yield 92%; δP: 20.0 ppm; δC: 26.3 ($\underline{C}H_2Br$)]. Treatment of the latter with NaI in acetone (3 h, reflux) afforded the corresponding iodide derivative **15** [δP: 20.4; δC: -3.0 ($\underline{C}H_2I$)] in an isolated yield of 90%.

The above results indicate that the cyanoethyl group is not compatible with conditions to convert non-charged phosphonate **12** into the iodide **15** which, in turn, will be more prone to nucleophilic attack by amines or an azide than bromide **14**. We therefore selected the benzyl group as a phosphonate protecting group. We expected that NaI-mediated anionic debenzylation of **16** would be accompanied by replacement of the bromide by iodide to give **17** which readily undergoes nucleophilic substitution. Indeed, the pivatol role of benzoyl-protected[8] **16** [δP: 27.4; δC 22.9 ($\underline{C}H_2Br$)], obtained in 85% yield by condensation of **11** (R=Benzoyl) with benzyl alcohol, was illustrated (see Scheme 3) by its smooth and quantitative reaction with NaI in acetone (3 h, reflux) to give **17** [δP: 17.5; δC: -1.6 ($\underline{C}H_2I$)]. Crude **17** thus obtained could then readily be converted into the following phosphonates **18**: (i)[9a] the 2-amino **18a** [R=H,; yield 80%; δP: 21.15; δC 36.9 ($\underline{C}H_2NH_2$)]; (ii)[9b] the 2-N-methylamino **18b** [R=Bz, yield 85%; δP 20.2, δC 52.7 ($\underline{C}H_2NHMe$)]; (iii)[9c] the 2-N-dimethylamino **18c** [R=Bz, yield 90%; δP 18.0, δC 53.8 ($\underline{C}H_2NMe_2$)] and (iv)[9d] the 2-azido **18d** [R=Bz, yield 90%; δP 22.0, δC 46.5 ($\underline{C}H_2N_3$); IR (neat) .. 2100 cm^{-1}]. Reduction of the azido function in **18d** with hydrogen sulfide in pyridine[10] afforded the corresponding amino-derivative which, after removal of the benzoyl groups by ammonolysis, was in every aspect identical with **18a** (R=H) obtained earlier. Further, the homogeneity of compounds **18**a-d was unambiguously ascertained by elementary analysis.

In conclusion, the mild and effective phosphonylation method presented herein promises to be very convenient for the introduction of 2-amino or 2-N-alkylaminoethylphosphonate functions in sugars. Further, preliminary experiments indicated that this approach was also amenable to the preparation of nucleic acids containing functionalized (3'-5')-internucleotide phosphonate linkages. Finally, it is not excluded that the easy accessibility of sugar vinylphosphonates (*e.g.*, **16**) may open the way to synthesize interesting sugar phosphonates *via* Michael addition of for instance glycine Schiff base to

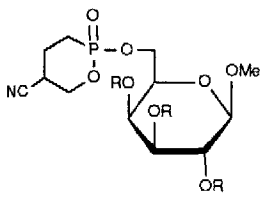
the vinyl function[11].

ACKNOWLEDGEMENT

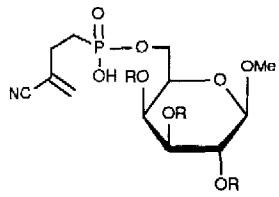
We thank the Netherlands Organization for the Advancement of Pure Research (NWO) for financial support, and the staff of the Analytical Laboratory, University College, Dublin, for performing the elemental analyses.

REFERENCES AND NOTES

1. A. Hayashi and F. Matsuura, Chem. Phys. Lipids, **22**, 9 (1978).
2. S. Araki, M. Satake, S. Ando, A. Hayashi and N. Fujii, J. Biol. Chem., **261**, 5138 (1986).
3. K. Ohashi, S. Kosai, M. Arizuka, T. Watanabe, Y, Yamagiwa and T. Kamikawa, Tetrahedron, **45**, 2557 (1989).
4. C.E. Dreef, A.R.P.M. Valentijn, E. de Vroom, G.A. van der Marel and J.H. van Boom , Tetrahedron Lett., **29**, 1199 (1988).
5. N.N. Bhongle, R.H. Notter and J.G. Turcott, Synthetic Commun., **17**, 1071 (1987).
6. M.J. Gait, Nucl. Acids Res., **s7**, 251 (1980).
7. Diethyl vinylphosphonate was obtained earlier by A.H. Ford-Moore and J.H. Williams (J. Chem. Soc., 1465, 1947) by heating (1 h) diethyl 2-bromoethylphosphonate with Et_3N in benzene. The ^{31}P-, ^{13}C- and ^{1}H-n.m.r. data of **13** were in full accord with the proposed structure. The latter excludes the possible formation of the isomeric compound B, the formation of which may be visualized by intramolecular Michael addition and subsequent Et_3N-mediated ring-opening of the intermediate Michael-adduct A.



A



B

8. The use of a benzoyl instead of benzyl protecting groups in model compound **16** is compatible with a synthetic strategy directed towards the preparation of **2a,b** containing a β-linked **unsaturated** ceramide.
9. Reagents and conditions for the conversion of **17** into **18a-d**. a) 25% aq. NH_3/DMF/CH_3CN, 8 h 20°C. b) $MeNH_2$/CH_3CN, 4 h 20°C. c) Me_2NH/CH_3CN, 4 h 20°C. d) LiN_3/dimethylacetamide, 3 h 100°C.
10. T. Adachi, Y. Yamada, I. Inoue and M. Saneyoshi, Synthesis, 45 (1977).
11. N. Minowa, M. Hirayama and S. Fukatsu, Bull. Chem. Soc. Jpn., **60**, 1761 (1987).

(Received in UK 18 August 1989)