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Easy Access to Glycosyl Phosphorothioates with Microwaves Technique

Laura Cipolla, Cristina Redaelli, Iris Faria, and Francesco Nicotra

Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milano, Italy

A simple, efficient, and general method for the synthesis of glycosyl phosphorothioate through a one-pot reaction of glycosyl bromide with diethyl phosphite, ammonium acetate, and sulphur in the presence of alumina under solvent-free conditions using microwave irradiation has been developed.

Keywords Glycosyl phosphorothioates, Green chemistry, Stereoselectivity, Microwave, Solvent-free reaction

INTRODUCTION

Glycosyl phosphonate and thiophosphate analogs of naturally occurring phosphates have found a wide range of applications as regulators, activators, or inhibitors of carbohydrate-processing enzymes[1–3] since they are isosteric and nonhydrolyzable analogs of phosphate esters. For example, mannopyranosyl thiophosphate analogs of dolichylphosphomannose (Dol-P-Man) have been reported as potential inhibitors of mannosyl transferases operating in the endoplasmic reticulum.[4]

In addition, many studies have shown the pharmacological value of the thiophosphate group in oligonucleotide analogs with a phosphorothioate group as internucleotide linkage that would confer stability to nucleases while preserving the specificity and efficiency of complexation.[5–7] Furthermore, phosphorothioates and phosphorodithioates possess most favorable

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Address correspondence to Laura Cipolla, Department of Biotechnology and Biosciences, University of Milano-Bicocca, P.za della Scienza 2, 20126 Milano, Italy. E-mail: laura.cipolla@unimib.it

biological and pharmacological properties as potential antisense or antigen agents,[8–10] and also as nucleic acid-based clinical diagnostics.[11–13]

Thiophosphate esters can be also useful as synthetic intermediates in the preparation of many biologically active molecules such as nucleoside phosphorodithioates, phosphoramidothioates, or phosphoro fluorodithioates,[11,14] or used as building blocks for solid-phase synthesis.[15] Moreover, phosphorothioate leaving group at the anomeric position of monosaccharides have been recently used for the preparation of *C*-glycosides.[16]

Many synthetic methods for the introduction of a phosphorothioate moiety have been reported,[17–19] but drastic reaction conditions with some severe side reactions, prolonged reaction times, and an elaborate purification procedure are frequently required; other methods use toxic compounds, as thiocynates, as starting material, and harsh conditions due to the low nucleophilicity of the NCS^- incompatible with the termally instable thiocyanate moieties.[20,21]

In light of these considerations, an alternative and more efficient synthetic method toward phosphorothioates is desirable.

Starting from the mid-1980s microwave activation as a nonconventional energy source has become a very popular and useful technology in organic chemistry.[22] Acceleration of organic reactions by microwave dielectric heating has been widely exploited in organic syntheses under solvent-free conditions.[23–25] The use of microwave dielectric heating may dramatically reduce reaction times from days to minutes. In addition, there is an important increase of the yields of the desired products reducing the decomposition of reactants as well as the formation of side products due to local overheating observed under conventional conditions. The use of microwave-assisted methods should satisfy the rapidly increasing demand of speedy synthetic methods of new molecules for organic and medicinal chemistry. The combination of the advantages of the solvent-free reactions and microwave irradiations renders these reactions particularly attractive in the field of green chemistry.

Despite the well-known advantages of microwave techniques, only a limited number of microwave-assisted reactions have found application in carbohydrate chemistry.[26,27] Carbohydrates play an important role in a vast array of biological processes, and they are particularly interesting in the field of drug discovery, thanks to their low toxicity and immunogenicity.[28–33]

In this context we describe a new methodology for the synthesis of glycosyl phosphorothioates assisted by microwave dielectric heating.

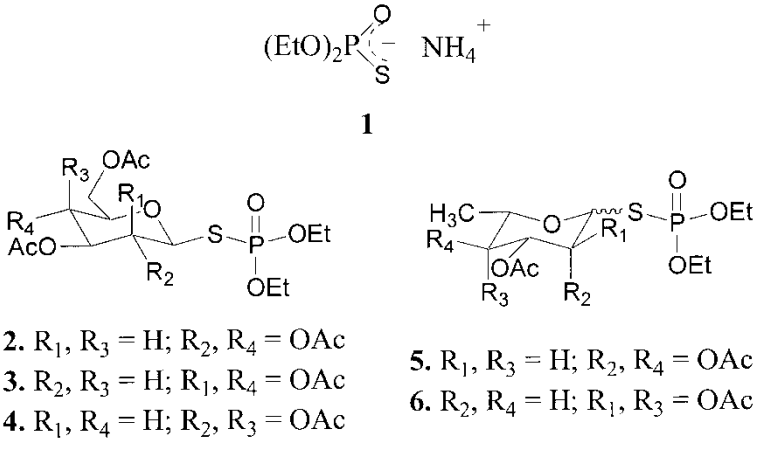
RESULTS AND DISCUSSION

A general method for alkyl phosphorothioate synthesis was recently reported using microwave irradiation under solvent-free conditions.[34] We envisaged the possibility to extend this methodology to the preparation of glycosyl

phosphorothioates. Hence, per-*O*-acetylated glycosyl bromides were reacted with a mixture of diethyl phosphite and an equimolar amount of ammonium acetate and sulphur, in the presence of a slight excess of alumina (Fig. 1). The reaction proceeded under solvent-free conditions using microwave irradiation at 2.45 GHz. Both acidic (Al_2O_3 W-4)[34] and neutral alumina were used as adsorbant; however, neutral alumina was preferred since yields in most cases were higher (Table 1, entries 3, 5, 7, and 9).

The reaction involves in situ formation of the *O,O*-diethyl phosphorothioate ammonium salt **1**,[19] followed by reaction of **1** with the peracetylated glycosyl bromides, affording the corresponding glycosyl phosphorothioates **2–6**. The products were isolated after filtration over a Celite pad and purification by flash chromatography. In general, the reactions are very clean; the only byproduct that can be observed in variable amounts depending on the substrate is the aldose deriving from the hydrolysis of the corresponding glycosyl halide to the free anomeric hydroxyl group. The phosphorothioate/hydrolyzed aldose ratios (Table 1) were determined by ^{1}H NMR spectroscopy of the crude mixture.

Phosphorothioates **2**, **4**, and **6** were obtained in good yields (82–94%), while compounds **3** and **5** were obtained in low yields. In particular, 2,3,4,6-tetra-*O*-acetyl-β-D-mannosyl phosphorothioate **3** was obtained in 35% yield; however, this result is in agreement with related phosphorothioate already reported;[18] 2,3,4-tri-*O*-acetyl-L-rhamnosyl phosphorothioate **5** was obtained in only 26% yield (as a mixture of anomers), but to the best of our knowledge this is the first example of a rhamnosyl phosphorothioate. The reactivity of the different peracetylated sugars was found to be in agreement with the corresponding glycosyl halide used as glycoside donors in oligosaccharide



2. R_1, R_3 = H; R_2, R_4 = OAc
3. R_2, R_3 = H; R_1, R_4 = OAc
4. R_1, R_4 = H; R_2, R_3 = OAc

5. R_1, R_3 = H; R_2, R_4 = OAc
6. R_2, R_4 = H; R_1, R_3 = OAc

Figure 1: Diethyl phosphorothioate ammonium salt and the glycosyl phosphorothioates synthesized.

Table 1: Yields and product compositions in the preparation of glycosyl phosphorothioate.

Entry	Compound	Phosphorothioate/ anomeric OH[a]	Yield %[b]
1	2 (Al_2O_3)	9/1	82
2	2 (Al_2O_3W-4)	9/1	82
3	3 (Al_2O_3)	4/6	35[c]
4	3 (Al_2O_3 W-4)	3/7	14[c]
5	4 (Al_2O_3)	>99% Phosphorothioate	94
6	4 (Al_2O_3 W-4)	9/1	84
7	5 (Al_2O_3)	3/7	26[c] (α/β)
8	5 (Al_2O_3 W-4)	>99% hydrolyzed	N.R.
9	6 (Al_2O_3)	9/1	87[c]
10	6 (Al_2O_3 W-4)	8/2	73[c]

[a]Phosphorothioate/anomeric OH composition was established by ^{1}H NMR of the crude.
[b]All yields refer to isolated products after purification.
[c]Yields are calculated over two steps: formation of the glycosyl halide and its subsequent thiophosphorylation.

synthesis,[35] with mannosyl derivatives being the less reactive; however, higher yields have been reported in the synthesis of mannosyl phosphorodithioates.[36]

The anomeric configuration of the products was determined by ^{1}H NMR and NOESY NMR experiments. All products were obtained with total stereoselection at the anomeric position, with the exception of compound **5**, which was obtained as an inseparable 2 : 1 α/β mixture, as evidenced by ^{1}H NMR spectroscopy. Confirmatory evidence was obtained also from ^{31}P NMR data, which exhibited signals at $\delta = 23.71$ ppm for stereoisomer α and at $\delta = 24.03$ ppm for the β one.

For compounds **2** and **4** coupling constants between $J_{1,2} = 9.2$ and $J_{1,2} = 10.0$ Hz, respectively, typical for a trans-diaxial arrangement of the substituents, indicated a β-orientation of the phosphorothioate group in a $^4C_1$ chair conformation. Similar considerations can be drawn for compound **6** ($J_{1,2} = 10.0$ Hz, in a $^1C_4$ chair conformation). For compound **3**, a small value of the coupling constant $J_{1,2} = 1.3$ Hz, together with a NOE effect between H-1 and H-5, indicated a β-configuration of the anomeric group in a $^4C_1$ chair conformation.

Finally, ^{31}P NMR of derivatives **2**–**6** confirmed the presence of the S–P=O group in which the phosphorous atom resonates at approximately 20 ppm, while no resonance was observed at around 60 ppm, as expected for the isomers possessing an O–P=S group.[18]

In conclusion, a new and mild procedure for the synthesis of glycosyl phosphorothioates has been developed through the application of microwave

dielectric heating under solvent-free conditions and without any acidic, basic, or even aqueous work-up.

The proposed methodology gave variable yields ranging from 94% for galactose to 26% for rhamnose, shortened reaction times, and limited byproduct formation compared to other procedures reported for the synthesis of glycosyl phosphorothioates.

EXPERIMENTAL

Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (Merck) charring with a solution containing conc. H_2SO_4/EtOH/H_2O in a ratio of 5/45/45. Flash column chromatography was performed on silica gel 230–400 mesh (Merck). ^{1}H, ^{13}C, ^{31}P NMR spectra were recorded at 400 MHz on a Varian Mercury instrument using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Coupling constants (J) are given in Hz. For all compounds the assignments of the ^{1}H NMR spectra were based on 2D proton–proton shift-correlation spectra. The assignments of ^{13}C NMR spectra were based on carbon–proton shift-correlation spectra. Optical rotations were measured at rt with a Krüss-Optronic P3002 polarimeter.

General Procedure

A mixture of ammonium acetate (2.0 equiv.) and sulphur (2.0 equiv.) was finely grounged with alumina (2.7 equiv.) in a crucible until a homogeneous powder was obtained. Diethyl phosphite (2.0 equiv.) was added, and the mixture was irradiated by microwaves for 3 to 15 min at 720 W. The glycosyl bromide (1.0 equiv.) was then added and the mixture irradiated by microwaves for a further 6 to 15 min at 720 W. The alumina was filtered over a Celite pad and washed with dichloromethane, and the crude purified by flash chromatography with petroleum ether/EtOAc (1:1).

All reactions were performed with a domestic microwave oven. The multimode domestic ovens is well suited for many classical organic reactions, provided that adequate safety precaution was undertaken.

The required protected glycosyl bromides were prepared from the per-*O*-acetylated monosaccharide by reaction with HBr/AcOH (33% w/w), according to literature procedures.[37]

2,3,4,6-Tetra-*O*-acetyl-β-D-glucosyl phosphorothioate 2. $[\alpha]_D^{20} + 11.5^\circ$ (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.16$ (t, 1 H, $J = 9.2$ Hz, H3), 5.02 (2t, 2 H, $J = 9.2$ Hz, H2, H4), 4.96 (dd, 1 H, $J_{H\text{-}P} = 10.0$, $J = 9.2$ Hz, H1), 4.18–4.07 (m, 6 H, H6a, H6b, CH_3CH_2P), 3.75–3.70 (ddd, 1 H, $J = 10.1$, 4.5, 2.6 Hz, H5), 2.01, 2.00, 1.97, 1.94 (4s, 12 H, CH_3CO), 1.32–1.28 (m, 6 H, CH_3CH_2P).

^{31}P NMR (162.01 MHz, $CDCl_3$):$\delta = 23.65$. ^{13}C NMR (100.57 MHz, $CDCl_3$): $\delta = 170.53$, 170.04, 169.44, 169.27 (4 CH_3CO), 83.41 (d, $J_{C\text{-}P} = 3.8$ Hz, C-1), 76.50 (C-5), 73.92 (C-3), 70.80 (C-2), 68.14 (C-4), 64.49, 64.24 (2d, $J_{C\text{-}P} = 5.3$ Hz, 2 PCH_2CH_3), 62.11 (C-6), 21.11, 21.11, 21.09, 20.97 (4 CH_3CO), 16.46, 16.28 (2 d, $J_{C\text{-}P} = 7.7$ Hz, CH_3CH_2P). Anal. Calcd for $C_{18}H_{29}O_{12}PS$: C, 43.20; H, 5.84. Found: C, 43.22; H, 5.81.

2,3,4,6-Tetra-*O*-acetyl-*β*-D-mannosyl phophorothioate 3. $[\alpha]_D^{20} + 58.8^\circ$ (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.75$ (dd, 1 H, $J = 1.6$ Hz, $J_{H\text{-}P} = 12.4$ Hz, H1), 5.40 (dd, 1 H, $J = 2.9$, 1.6 Hz, H2), 5.34 (t, 1 H, $J = 9.9$ Hz, H4), 5.24 (dd, 1 H, $J = 9.9$, 2.9 Hz, H3), 4.22–4.14 (m, 5 H, H-6a, H5, PCH_2CH_3), 4.10 (dd, 1 H, $J = 12.3$, 2.2 Hz, H6b), 2.17, 2.09, 2.07, 2.01 (4s, 12 H, CH_3CO), 1.38 (t, 6 H, $J = 7.1$ Hz, CH_3CH_2P). ^{31}P NMR (162.01 MHz, $CDCl_3$): $\delta = 23.34$. ^{13}C NMR (100.57 MHz, $CDCl_3$): $\delta = 170.62$, 169.95, 169.85, 169.66 (4 CH_3CO), 83.51 (d, $J_{C\text{-}P} = 3.1$ Hz, C-1), 71.90 (d, $J_{C\text{-}P} = 9.2$ Hz, C-2), 71.51 (C-5), 69.16 (C-3), 66.01 (C-4), 64.74, 64.47 (2d, $J_{C\text{-}P} = 5.3$ Hz, PCH_2CH_3), 62.54 (C-6), 21.31, 21.17, 21.14, 21.07 (4 CH_3CO), 16.52, 16.44 (CH_3CH_2P). Anal. Calcd for $C_{18}H_{29}O_{12}PS$: C, 43.20; H, 5.84. Found: C, 43.24; H, 5.85.

2,3,4,6-Tetra-*O*-acetyl-*β*-D-galactosyl phosphorothioate 4. $[\alpha]_D^{20} + 26.4^\circ$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.42$ (dd, 1 H, $J = 3.4$, 1.0 Hz, H4), 5.27 (t, 1 H, $J = 10.0$ Hz, H2), 5.03 (dd, 1 H, $J = 10.0$, 1.0 Hz, H3), 5.02 (t, 1 H, $J = 10.0$ Hz, $J_{H\text{-}P} = 16.3$ Hz, H1), 4.22–4.00 (m, 7 H, H5, H6a, H6b, PCH_2CH_3), 2.09, 2.01, 1.97, 1.91 (4s, 12 H, CH_3CO), 1.32–1.28 (m, 6 H, CH_3CH_2P). ^{31}P NMR (162.01 MHz, $CDCl_3$): $\delta = 24.03$. ^{13}C NMR (100.57 MHz, $CDCl_3$): $\delta = 170.40$, 170.22, 169.94, 169.51 (4 CH_3CO), 84.04 (d, $J_{C\text{-}P} = 3.8$ Hz, C-1), 75.30 (C-5), 71.96 (C-3), 68.10 (d, $J_{C\text{-}P} = 10.0$ Hz, C-2), 67.47 (C-4), 64.49, 64.22 (2d, $J_{C\text{-}P} = 5.4$ Hz, PCH_2CH_3), 61.77 (C-6), 21.16, 21.11, 21.09, 20.99 (4 CH_3CO), 16.51, 16.37 (CH_3CH_2P). Anal. Calcd for $C_{18}H_{29}O_{12}PS$: C, 43.20; H, 5.84. Found: C, 43.18; H, 5.82.

2,3,4-Tri-*O*-acetyl-*α,β*-L-rhamnosyl phosphorothioate 5. 5*α* ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.60$ (dd, 1 H, $J = 1.7$ Hz, $J_{H\text{-}P} = 12.2$ Hz, H1), 5.32 (dd, 1 H, $J = 3.2$, 1.7, Hz, H2), 5.15 (ddd, 1 H, $J = 9.8$, 3.2 Hz, $J_{H\text{-}P} = 1.3$ Hz, H3), 5.04 (t, 1 H, $J = 9.8$ Hz, H4), 4.20–4.04 (m, 4 H PCH_2CH_3), 4.02–3.98 (m, 1 H, H5), 2.13, 2.09, 2.00 (3s, 9 H, CH_3CO), 1.32–1.27 (m, 6 H, CH_3CH_2P), 1.20–1.17 (m, 6 H, H-6). ^{31}P NMR (162.01 MHz, $CDCl_3$): $\delta = 23.71$. **5β** ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.44$ (d, 1 H, $J = 1.7$ Hz, H2), 5.18 (dd, 1 H, $J = 1.7$ Hz $J_{H\text{-}P} = 12.4$ Hz H1), 5.01–5.00 (m, 2 H, H3, H4) 4.20–4.04 (m, 4 H, PCH_2CH_3), 3.59–3.55 (m, 1H, H5), 1.98, 1.93, 1.91 (3s, 9 H, CH_3CO), 1.32–1.27 (m, 6 H, CH_3CH_2P), 1.20–1.17 (m, 3 H, H6). ^{31}P NMR (162.01 MHz, $CDCl_3$ $\delta = 24.03$. ^{13}C NMR **5α + 5β** (100.57 MHz,

$CDCl_3$): $\delta = 170.18$, 170.03, 170.00, 169.98, 169.95, 169.77 (6s, CH_3CO), 83.24 (d, $J_{C\text{-}P} = 3.5$ Hz, C-1α), 81.82 (d, $J_{C\text{-}P} = 2.6$ Hz, C-1β), 75.61 (C-5β), 72.14 (d, $J_{C\text{-}P} = 9.2$ Hz, C-2α), 71.94 (C-4β), 71.57 (d, $J_{C\text{-}P} = 8.2$ Hz, C-2β), 70.89 (C-4α), 70.14 (C-3β), 69.73 (C-5α), 69.19 (C-3α), 64.62, 64.30 (2d, $J_{C\text{-}P} = 6.0$ Hz, PCH_2CH_3), 21.27, 21.20, 21.20, 21.07, 21.07, 21.03, (6 CH_3CO), 17.82, 17.81 (2 C-6) 16.50, 16.48, 16.47, 16.40 (4 CH_3CH_2P).

2,3,4-Tri-*O*-acetyl-β-D-fucosyl phosphorothioate 6. $[\alpha]_D^{20}$ $-23{,}4^\circ$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.20$ (dd, 1 H, $J = 0.8$, 3.3 Hz, H4), 5.19 (t, 1 H, $J = 10.0$ Hz, H2), 4.97 (dd, 1 H, $J = 3.3$, 10.0 Hz, H3), 4.92 (dd, 1 H, $J = 10.0$ Hz, $J_{H\text{-}P} = 12.0$ Hz, H1), 4.19–4.04 (m, 4 H, PCH_2CH_3), 3.86–3.81 (bd, 1 H, H 5), 2.11, 1.99, 1.91 (3s, 9 H, CH_3CO), 1.31–1.27 (m, 6 H, CH_3CH_2P), 1.14 (t, 3 H, $J = 2.2$ Hz, H6). ^{31}P NMR (162.01 MHz, $CDCl_3$): $\delta = 24.63$. ^{13}C NMR (100.57 MHz, $CDCl_3$): $\delta = 170.61$, 170.02, 169.59 (3 CH_3CO), 83.70 (d, $J_{C\text{-}P} = 3.2$ Hz, C-1), 73.99 (C-5), 72.42 (C-3), 70.49 (C-4), 68.29 (d, $J_{C\text{-}P} = 10.7$ Hz, C-2), 64.39, 64.20 (2d, $J_{C\text{-}P} = 5.4$ Hz, PCH_2CH_3), 21.17, 21.12, 21.01 (3 CH_3CO), 16.73 (C-6) 16.46, 16.36 (2 CH_3CH_2P). Anal. Calcd for $C_{16}H_{27}O_{10}PS$: C, 43.44; H, 6.15. Found: C, 43.40; H, 6.16.

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REFERENCES

[1] Engel, R. Phosphonate as analogues of natural phosphates. Chem. Rev. **1977**, *77*, 349–367.

[2] Swierczek, K.; Pandey, A.S.; Peters, J.W.; Hengge, A.C. A comparison of phosphonothioic acids as phosphatase inhibitors. J. Med. Chem. **2003**, *46*, 3703–3708.

[3] Knight, W.B.; Sem, D.S.; Smith, K.; Miziorko, H.M.; Rendina, A.R.; Cleland, W.W. Phosphorylated thiosugars: synthesis, properties, and reactivity in enzymatic reactions. Biochemistry **1991**, *30*, 4970–4977.

[4] Kulesza, A.; Frank, C.G.; Aebi, M.; Vasella, A. Synthesis of stable dolichylphosphomannose analogues. Helv. Chim. Acta **2004**, *87*, 3106–3118.

[5] Zon, G. Oligonucleotide analogues as potential chemotherapeutic agents. Pharm. Res. **1988**, *5*, 539–349.

[6] Cieślak, J.; Jankowska, J.; Stawiński, J.; Kraszewski, A. Aryl H-phosphonates 12. Synthetic and 31P NMR studies on the preparation of nucleoside H-phosphonothioate and nucleoside H-phosphonodithioate monoesters. J. Org. Chem. **2000**, *65*, 7049–7054.

[7] Deshpande, M.C.; Garnett, M.C.; Vamvakaki, M.; Bailey, L.; Armes, S.P.; Stolnik, S. Influence of polymer architecture on the structure of complexes formed by PEG–tertiary amine methacrylate copolymers and phosphorothioate oligonucleotide. J. Controlled Release **2002**, *81*, 185–199.

[8] Cummins, L.; Graff, D.; Beaton, G.; Marshall, W.S.; Caruthers, M.H. Biochemical and physicochemical properties of phosphorodithioate DNA. Biochemistry **1996**, *35*, 8734–8741.

[9] Furrer, P.; Billeci, T.M.; Donati, A.; Kojima, C.; Karwowski, B.; Sierzchala, A.; Stec, W.; James, T.L. Structural effect of complete [Rp]-phosphorothioate and phosphorodithioate substitutions in the DNA strand of a model antisense inhibitor-target RNA complex. J. Mol. Biol. **1999**, *285*, 1609–1622.

[10] Mukherjee, S.; Bhattacharyya, D. Effect of phosphorothioate chirality on the grooves of DNA double helices: a molecular dynamics study. Biopolymers **2004**, *73*, 269–282.

[11] Seeberger, P.H.; Yau, E.; Caruthers, M.H. 2′-Deoxynucleoside dithiophosphates: synthesis and biological studies. J. Am. Chem. Soc. **1995**, *117*, 1472–1478.

[12] Brummer, O.; Wentworth, P.; Weiner, D.P.; Janda, K.D. Phosphorodithioates: synthesis and evaluation of new haptens for the generation of antibody acyl transferases. Tetrahedron Lett. **1999**, *40*, 7307–7310.

[13] Uhlmann, E.; Peyman, A. Antisense oligonucleotides: a new therapeutic principle. Chem. Rev. **1990**, *90*, 544–579.

[14] Kudelska, W. The cyanation reaction of O-acetylated S-glycosyl phosphorothioates. Carbohydr. Res. **2000**, *329*, 687–691.

[15] Seeberger, P.H.; Caruthers, M.H.; Bankaitis-Davis, D.; Beaton, G. Synthesis of phosphorodithioate DNA by the H-phosphonothioate method. Tetrahedron **1999**, *55*, 5759–5772.

[16] Kudelska, W. Synthesis of C-glycosides from S-glycosyl phosphorothioates. Zeitschrift fuer Naturfoschung, B: Chem. Sci. **2002**, *57*, 243–247.

[17] Michalska, M. Glycosylation of organic thio-and selenoacids of phosphorus. Tetrahedron **1978**, *34*, 617–622.

[18] Chmielewski, M.; BeMiller, J.N. Derivatives of S-alfa- and -beta-D-hexopyranosyl thiophosphates. Carbohydr. Res. **1981**, *96*, 73–78.

[19] Lipka, P.; Michalska, M. Efficient synthesis of S- and Se-(2,3,4,6-tetra-O-acetyl-β-D-glucosyl) thiophosphates and selenophosphates. Carbohydr. Res. **1983**, *113*, 317–320.

[20] Renard, P.-Y.; Schwebel, H.; Vayron, P.; Josien, L.; Valleix, A.; Mioskowski, C. Easy access to phosphonothioates. Chem. Eur. J. **2002**, *8*, 2910–2916.

[21] Bulman Page, P.C.; Wilkes, R.D.; Reynolds, D. *Comprehensive Organic Functional Group Transformation*; Katrizky, A.R., Meth-Cohn, O., Rees, C.W., Eds.; Elsevier: Oxford, 1995; Vol. 2, 252–259.

[22] Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. The use of microwave ovens for rapid synthesis. Tetrahedron Lett. **1986**, *27*, 279–282.

[23] Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. Microwave assisted organic synthesis a review. Tetrahedron **2001**, *57*, 9225–9283.

[24] Perreux, L.; Loupy, A. A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations. Tetrahedron **2001**, *57*, 9199–9223.

[25] Larhed, M.; Hallberg, A. Microwave-assisted high-speed chemistry: a new technique in drug discovery. Drug Discov. Today **2001**, *6*, 406–416.

[26] Das, S.K. Application of microwave irradiation in the synthesis of carbohydrates. Synlett. **2004**, *6*, 915–932.

[27] Corsaro, A.; Chiacchio, U.; Pistarà, V.; Romeo, G. Microwave-assisted chemistry of carbohydrates. Curr. Org. Chem. **2004**, *8*, 511–538.

[28] Wong, C.-H. Ed.; *Carbohydrate-Based Drug Discovery*; Wiley-VCH Verlag GmbH: Weinheim, 2003; Vol. 1.

[29] Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Baldwin, J.E., Ed.; Pergamon: Oxford, 1983.

[30] Peri, F.; Cipolla, L.; Forni, E.; Nicotra, F. Carbohydrate-based scaffolds for the generation of bioactive compounds. Monatshefte für Chemie **2002**, *133*, 369–382.

[31] Hirschmann, R.; Nicolau, K.C.; Pietranico, S.; Leahy, E.M.; Salvino, J.; Arison, B.; Cichy, M.A.; Spoors, P.G.; Shakespeare, W.C.; Sprengler, P.A.; Hamley, P.; Smith, A.B.; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R.M.; Cascieri, M.R.; Strader, C.D. De novo design and synthesis of somatostatin non-peptide peptidomimetics utilizing beta-D-glucose as a novel scaffolding. J. Am. Chem. Soc. **1993**, *115*, 12550–12568.

[32] Lohof, E.; Planker, E.; Mang, C.; Burkhart, F.; Dechantstreiter, M.A.; Haubner, R.; Wester, H.J.; Schwaiger, M.; Hölzemann, G.; Goodman, S.L.; Kessler, H.; Kessler, H. Carbohydrate derivatives for use in drug design: cyclic alpha(v)-selective RGD peptides. Angew. Chem. Int. Ed. Engl. **2000**, *39*, 2761–2764.

[33] Cipolla, L.; Peri, F.; La Ferla, B.; Redaelli, C.; Nicotra, F. Carbohydrate scaffolds for the production of bioactive compounds. Curr. Org. Synth. **2005**, *2*, 153–173.

[34] Kaboudin, B. A simple and new method for the synthesis of thiophosphates. Tetrahedron Lett. **2002**, *43*, 8713–8714.

[35] Zhang, Z.; Ollmann, I.R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. Programmable one-pot oligosaccharide synthesis. J. Am. Chem. Soc. **1999**, *121*, 734–753.

[36] Kudelska, W.; Michalska, M. A novel stereoselective synthesis of S-glycosyl phosphorodithioates from peracetylated sugars. Synthesis **1995**, 1539–1544.

[37] Tropper, F.D.; Andersson, F.O.; Braun, S.; Roy, R. Phase transfer catalysis as a general and stereoselective entry into glycosyl azides from glycosyl halides. Synthesis **1992**, 618–620.