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Synthesis of thiapyranoside precursors using the building-block approach from a phosphonodifluorodithioacetate

Emmanuel Pfund, Thierry Lequeux,* Michel Vazeux and Serge Masson

Laboratoire de Chimie Moléculaire et Thio-organique, UMR-CNRS 6507, Université de Caen-ISMRA, 6 Bd du Maréchal Juin, F 14050 Caen, France

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Abstract—Phosphonodifluorodithioacetate **2** demonstrates high reactivity towards dienes due to the presence of the two fluorine atoms. A hetero Diels–Alder reaction afforded the corresponding dihydrothiapyrans in 60–90% yields. These adducts can be submitted to a selective dihydroxylation and desulfanylation to produce phosphonodifluorothiaglycoside precursors. © 2002 Elsevier Science Ltd. All rights reserved.

Carbohydrate analogues possessing a phosphoester linkage were reported as potent inhibitors of glycosyltransferases. Phosphono isosteres in which the phosphorus is linked to the sugar through a methylene bridge are known as physiologically stable analogues of glycosyl 1-phosphates.[1] However, such structural modification strongly influences the affinity of the phosphorylated moiety towards enzymes. The introduction of fluorine atoms on the bridging carbon atoms affords better isopolar analogues of the corresponding phosphates. Thus, fluorinated phosphonates have been shown to possess a better activity than the corresponding methylene phosphonates.[2] Moreover, in the field of carbohydrates, the synthesis of fluorophosphonates appears attractive in order to prepare new classes of inhibitors of glycosyltransferases.

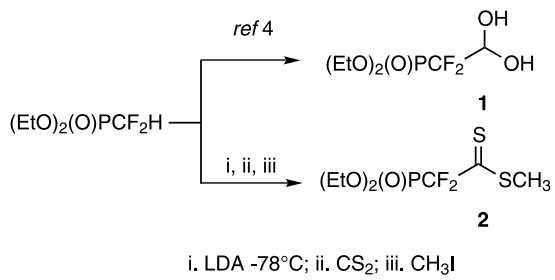
The introduction of a such fluorinated functionality into complex molecules can usually be done using metallated phosphonodifluoromethyl or free radicals species.[3] Recently, the development of functionalized building-blocks bearing the $CF_2P(O)(OR)_2$ group was reported as an alternative. For example, the large-scale synthesis of the aldehyde dihydrate **1** opened new routes to alicyclic and aromatic difluoromethylphosphonates[4] (Scheme 1).

In the field of analogues of carbohydrates, we have been interested in the synthesis of sulfur-containing phosphonoglycosides.[5] In our previous approach, phosphonodithioformates were involved in hetero Diels–Alder reaction to produce dihydrothiapyrans.[6] We have now investigated the synthesis of fluorinated phosphonodithioacetate **2** and explored its potential as new building-block to prepare thiapyranoside precursors.

We prepared the phosphonodifluorodithioacetate **2** by applying the Blackburn's procedure (Scheme 1).[7]

The yield was optimized up to 80% on a 10–15 g scale, when the reaction was performed in the presence of 5 equiv. of CS_2 and CH_3I, and by avoiding the distillation step. In our hands, **2** was found to be thermally unstable during distillation, and its purification by flash column chromatography was shown to be enough.

We examined the potential of dithioester **2** as dienophile and thioformaldehyde equivalent. Dithioesters are relatively poor dienophiles,[8] but they have been shown to possess good reactivity in the Diels–Alder reaction when the thiocarbonyl is substituted by an electron withdrawing group.[6,9,12]



Scheme 1.

* Corresponding author. Tel.: +33-231452854; fax: +33-231452877; e-mail: lequeux@ismra.fr

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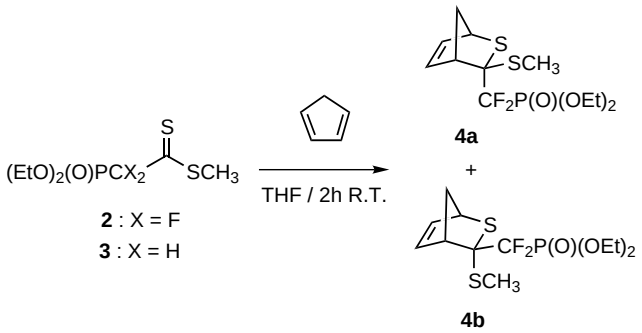
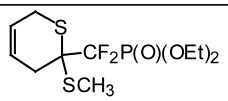
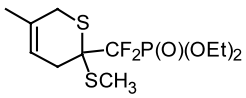
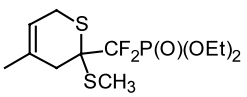
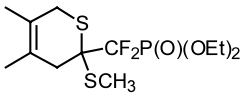
By using a highly reactive diene, such as cyclopentadiene, the reaction of **2** is complete after 2 h at room temperature in the presence of 2 equiv. of diene. After purification, the thia-norbornene derivatives **4a–b** were isolated in 70% yield. The cycloaddition occurred with a good stereoselectivity and the proton NMR analysis of the crude mixture showed two triplets for the SCH_3 signals (2.38 and 2.21 ppm, $^5J_{HF}=2.3$ Hz) in a 10/1 ratio.[16] By comparison with the results in the literature, the shielded signal at 2.21 ppm could be unambiguously attributed to the *endo*-SCH_3 adduct **4b** (Scheme 2).[11]

In contrast, using the phosphonodithioacetate **3**, the reaction was slower and no adduct was detected in the same conditions. This clearly shows the activating effect of the fluorine atoms on the electrophilic character of the thiocarbonyl function.[10]



Scheme 2.

Table 1. Cycloaddition of **2** with acyclic dienes

diene[a]	conditions	products	yield[b,c]
	50°C sealed tube, 15h	 **5**	92%
	THF reflux, 6h	 **6a**  **6b**	78%
	THF reflux, 4h	 **7**	80%

[a] Reactions were performed in presence of 2-5 eq of diene[c].

[b] Isolated yields.

[c] All new compounds present satisfactory analytical datas.

The dithioester **2** was also added to other acyclic dienes. The results are reported in Table 1.

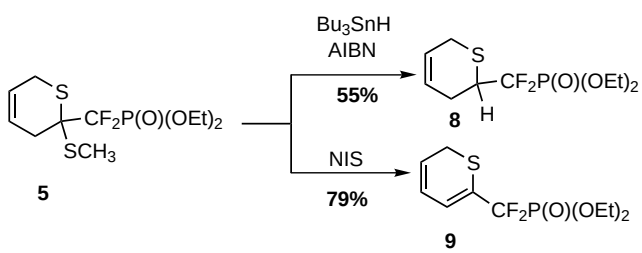
From butadiene, the cycloaddition reaction was slow at room temperature but adduct **5**[16] was obtained in a good yield when the reaction was performed at 50°C in a sealed tube. 2,3-Dimethylbutadiene, or isoprene are fairly reactive and, in refluxing THF, the reaction afforded adducts **6** and **7** in 78 and 80% yields, respectively. From isoprene, the cycloaddition was not regioselective and a 6/4 mixture of the two regioisomers **6a** and **6b** was obtained. According to previous work the major product was assigned as the '*para*' adduct.[12]

The reactivity of the dihydro-thiapyran **5** towards free radical desulfanylation and dihydroxylation conditions was then explored. In the first instance, thiapyran **5** was selectively desulfanylated according to the already described procedure (Bu_3SnH/AIBN),[6,13] to produce [(3,6-dihydro-2*H*-thiapyran-2-yl)-difluoromethyl]phosphonate **8** (Scheme 3). On the other hand by treating a solution of **5** in $CHCl_3$ by *N*-iodosuccinimide overnight at room temperature, the dienic derivative [(6*H*-thiapyran-2-yl)-difluoromethyl]-phosphonate **9** was selectively obtained in 79% yield. It is noticeable that this desulfanylation exclusively affects the exocyclic alkylsulfanyl group at the anomeric position. This sequence cycloaddition–desulfanylation shows that the dithioester **2** could be used as the corresponding unknown thioaldehyde equivalent.

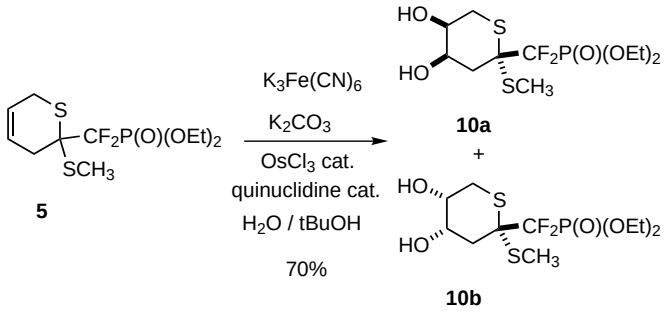
In order to approach carbohydrate structures, it was necessary to explore the dihydroxylation of simple adduct **5** and the use of functionalized dienes. Concerning the first aspect, the selective dihydroxylation of the thiapyran ring without affecting the sulfur centres was investigated.[14]

From **5**, using the modified Sharpless conditions, a mixture of the two dihydroxy-tetrahydrothiapyran diastereoisomers **10a** and **10b** was obtained in 8/2 ratio and isolated in 70% yield (Scheme 4). After determining the H_3 position by 2D-C/H correlation of the isolated major isomer, one of them showed a *trans* diaxial coupling constant ($^3J_{H3-H4}=11.5$ Hz) in the ^1H NMR spectrum. Assuming that the less bulky SCH_3 substituent on the anomeric carbon was placed in an axial position, we can deduce for **10a**[16] a *cis* relationship between the hydroxyl and the $CF_2P(O)(OEt)_2$ groups.

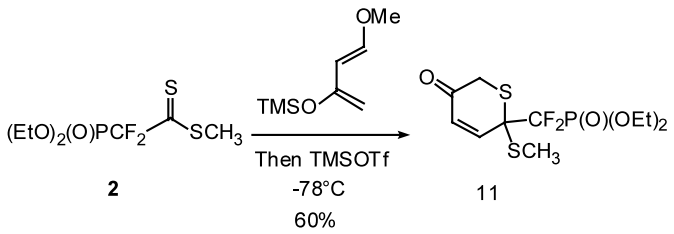
The other approach using functionalized dienes was investigated from Danishefsky's diene (Scheme 5). After refluxing **2** in presence of 2.5 equiv. of diene in THF for



Scheme 3.



Scheme 4.



Scheme 5.

2 h, the crude adducts were treated by TMSOTf at −78°C.[15] After purification the enone **11**[16] was isolated in 60% yield. The regioselectivity was easily assigned by ^{13}C NMR analyses. In this spectrum the C_3 ethylenic carbon exhibits a triplet at 143.4 ppm ($^3J_{CF}$ 2.5 Hz) indicating the proximity of the difluoromethylene group.

In conclusion, we have shown that the phosphono difluorodithioacetate **2** acts as a powerful heterodienophile and can be used to prepare a new class of phosphonodifluoromethyl thiapyran derivatives. From these adducts, chemical transformations could be performed under free radical or oxidative conditions and this opens new routes to obtain *C*-difluorophosphono substituted thiaglycosides. The design of polyhydroxylated thiapyrans from highly functionalized dienes are under investigation in view of the synthesis of new potential inhibitors of glycosyltransferases.

Acknowledgements

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16. *Selected NMR data*. **Major product 4a**: ^1H NMR ($CDCl_3$) δ 1.39 (t, $^3J_{HH}=7.0$ Hz, 6H), 1.81 (m, 1H, H_{7a}), 2.38 (t, 3H, $^5J_{HF}=2.0$ Hz, SCH_3), 2.50 (d, $^3J_{HH}=9.4$ Hz, 1H, H_{7b}), 3.78 (s, 1H, H_6), 4.13 (s, 1H, H_3), 4.30 (m, 4H), 5.98 (m, 1H, H_4), 6.52 (m, 1H, H_5); ^{19}F NMR ($CDCl_3$): δ −90.25 (dd, $^2J_{FF}=296.4$ Hz, $^2J_{FP}=102.0$ Hz, 1F, CF_2), −93.00 (dd, $^2J_{FF}=295.3$ Hz, $^2J_{FP}=112.1$ Hz, 1F, CF_2); ^{31}P NMR ($CDCl_3$) δ +5.20 (dd, $^2J_{PF}=103.0$ Hz, $^2J_{PF}=109.5$ Hz, $P(O)(OEt)_2$); ^{13}C NMR ($CDCl_3$) δ 16.67 (d, $^3J_{CP}=5.7$ Hz, 2 OCH_2CH_3), 52.42 (s, C_3), 54.43 and 54.45 (2s, SCH_3 and C_6), 54.67 (s, C_7), 65.05 (d, $^2J_{CP}=7.0$ Hz, 2 OCH_2CH_3), 73.46 (dt, $^2J_{CF}=17.6$ Hz, $^2J_{CP}=20.1$ Hz, C_2), 121.82 (dt, $^1J_{CP}=214.9$ Hz, $^1J_{CF}=275.0$ Hz, CF_2), 133.18 (s, C_5), 138.84 (t, $^4J_{CF}=2.7$ Hz, C_4); MS *m/z* (relative intensity) 344 (M^+ 11), 279 (24), 115 (14), 111 (28), 110 (24), 109 (100), 92 (36), 78 (25), 76 (30), 67 (90), 66 (88), 56 (28). **Adduct 5**: ^1H NMR ($CDCl_3$): δ 1.39 (t, $^3J_{HH}=7.1$ Hz, 6H), 2.25 (t, $^5J_{HF}=1.7$ Hz, 3H, SCH_3), 2.40–3.40 (m, 4H, H_3, H_6), 4.23 (m, 4H), 5.77 (m, 2H, H_4, H_5); ^{19}F NMR ($CDCl_3$) δ −102.93 (dd, $^2J_{FP}=107.1$ Hz,

$^2J_{FF}$ = 299.9 Hz, 1F, CF_2), −108.99 (dd, $^2J_{FP}$ = 103.1 Hz, $^2J_{FF}$ = 299.8 Hz, 1F, CF_2); ^{31}P NMR ($CDCl_3$) δ +6.33 (t, $^2J_{PF}$ = 105.2 Hz, P(O)$(OEt)_2$); ^{13}C NMR ($CDCl_3$) δ 12.73 (t, $^4J_{CF}$ = 3.3 Hz, SCH_3), 14.45 (d, $^3J_{CP}$ = 5.8 Hz, 2 OCH_2CH_3), 22.07 (s, C_6), 29.52 (t, $^3J_{CF}$ = 2.8 Hz, C_3), 57.48 (dt, $^2J_{CP}$ = 20.2 Hz, $^2J_{CF}$ = 41.5 Hz, C_2), 62.83 (d, $^2J_{CP}$ = 6.93 Hz, 2 OCH_2CH_3), 119.77 (dt, $^1J_{CP}$ = 211.8 Hz, $^1J_{CF}$ = 271.6 Hz, CF_2), 120.17–125.80 (s, C_4, C_5); MS *m*/*z* (relative intensity) 332 (M^+ 11), 264 (46), 209 (60), 115 (67), 109 (100), 98 (76), 92 (30), 82 (48), 66 (88), 54 (44). **Major diastereoisomer 10a**: ^{1}H NMR ($CDCl_3$): δ 1.39 (t, $^3J_{HH}$ = 7.5 Hz, 6H), 2.21 (s, 3H, SCH_3), 2.32 (dd, J_{gem} = 14.1 Hz, $^3J_{Heq-Hax}$ = 4.7 Hz, 1H, H_{3eq}), 2.51 (dd, J_{gem} = 14.1 Hz, $^3J_{Hax-Hax}$ = 11.5 Hz, 1H, H_{3ax}), 2.83 (dd, J_{gem} = 14.1 Hz, $^3J_{Hax-Heq}$ = 4.3 Hz, 1H, H_{6ax}), 2.97 (m, 1H, OH), 3.19 (m, 1H, OH), 3.24 (d, J_{gem} = 14.1 Hz, 1H, H_{6eq}), 3.89 (m, 1H, H_4), 4.03 (m, 1H, H_5), 4.23 (m, 4H); ^{19}F NMR ($CDCl_3$): δ −103.40 (dd, $^2J_{FF}$ = 301.1 Hz, $^2J_{FP}$ = 106.5 Hz, 1F, CF_2), −107.10 (dd, $^2J_{FF}$ = 301.1 Hz, $^2J_{FP}$ = 104.3 Hz, 1F, CF_2); ^{31}P NMR ($CDCl_3$) δ 4.16 (t, $^2J_{PF}$ = 106.1 Hz, P(O)$(OEt)_2$); ^{13}C NMR ($CDCl_3$) δ 15.49 (t, $^4J_{CF}$ = 2.7 Hz, SCH_3), 16.76 (d, $^3J_{CP}$ = 5.8 Hz, OCH_2CH_3), 31.16 (s, C_6), 32.00 (sbr, C_3), 63.62 (dt, $^2J_{CP}$ = 20.4 Hz, $^2J_{CF}$ = 41.3 Hz, C_2), 65.40, 65.61 (d, $^2J_{CP}$ = 6.8 Hz, OCH_2CH_3), 65.81 (s, C_5), 67.46 (s, C_4), 120.09 (dt, $^1J_{CP}$ = 211.6 Hz, $^1J_{CF}$ = 274.7 Hz, CF_2); MS *m*/*z* (relative intensity) 366 (M^+ 8), 320 (22), 302 (100), 256 (40), 148 (15), 45 (15). **Enone 11**: ^{1}H NMR ($CDCl_3$): δ 1.39 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 2.30 (s, 3H, SCH_3), 3.47 (m, 2H, H_6), 4.36 (m, 4H), 6.10 (d, $^3J_{HH}$ = 10.9 Hz, 1H, H_4), 7.14 (d, $^3J_{HH}$ = 11.0 Hz, 1H, H_3); ^{19}F NMR ($CDCl_3$): δ −102.91 (d, $^2J_{FP}$ = 104.8 Hz, $^2J_{FF}$ = 302.1 Hz, 1F, CF_2), −106.54 (dd, $^2J_{FP}$ = 99.6 Hz, $^2J_{FF}$ = 302.1 Hz, 1F, CF_2); ^{31}P NMR ($CDCl_3$) δ 5.25 (dd, $^2J_{PF}$ = 104.4 Hz, $^2J_{PF}$ = 104.2 Hz, P(O)$(OEt)_2$); ^{13}C NMR ($CDCl_3$) δ 15.63 (t, $^4J_{CF}$ = 1.8 Hz, SCH_3), 16.71 (d, $^3J_{CP}$ = 5.6 Hz, OCH_2CH_3), 34.00 (s, C_6), 59.54 (dt, $^2J_{CF}$ = 22.9 Hz, $^2J_{CP}$ = 19.6 Hz, C_2), 65.57 (d, $^2J_{CP}$ = 7.1 Hz, OCH_2CH_3), 65.80 (d, $^2J_{CP}$ = 7.1 Hz, OCH_2CH_3), 122.52 (dt, $^1J_{CF}$ = 274.7, $^1J_{CP}$ = 210.9 Hz, CF_2), 130.19 (s, C_4), 143.39 (t, $^3J_{CF}$ = 2.5 Hz, C_3), 190.57 (s, *C*O); MS *m*/*z* (relative intensity) 346 (M^+ 1), 299 (100), 243 (30), 186 (30), 109 (20), 81 (25), 65 (20).