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# Efficient Synthesis of Hydrophilic Phosphodiester Derivatives of Lipophilic Alcohols via the Glycosyl Hydrogenphosphonate Method

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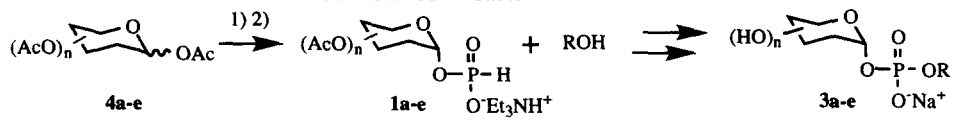
**Abstract :** The preparation of five peracetylated a-glycosyl-H-phosphonates and their use in the straightforward preparation of phosphodiesters derivatives of 25-hydroxycholesterol is described. Examples of the extension of this process to other lipophilic alcohols are presented. 

In the course of our studies on biologically active oxysterols, we were involved in the preparation of phosphodiesters between different oxysterols and monosaccharides in order to increase their water solubility and to permit a targeting of the drug to a specific organ. Therefore we have developped a method based on the use of 3b H-phosphonate monoester derivatives of cholesterol[1]. This approach allowed the direct phosphorylation of the primary alcohol of unprotected carbohydrates but it is limited by the narrow range of monosaccharides that can be efficiently phosphorylated. The need for a greater diversity in the type of carbohydrate moieties prompted us to elaborate a different approach based on the use of peracetylated-α-glycosyl H-phosphonates **1**[2]. We wish here to present the first application of this approach to the straightforward synthesis of derivatives **3** of 25-hydroxycholesterol **2**[3] (Scheme 1). Extension of this method to other types of alcohols has also been investigated.

Thus, we chose D-glucose, D-galactose, D-mannose and L-fucose as starting material for their biological interest and D-cellobiose as a model for the extension to more complex polysaccharides.

Compounds **1a-e** are accessible starting from the corresponding peracetylated carbohydrates **4a-e** via the sequence described in Scheme 1. Yields are indicated in Table 1.




2, R = 25-hydroxycholesteryl

**Scheme 1 :** 1) $NH_3$, THF/MeOH (7/3), 0°C, 24h ; 2)i) 1.5 eq. salicylchlorophosphite, dioxane/pyridine (1/1), r.t., 15 min. ; ii) $H_2O$, r.t., 5 min.

**Table 1 :** Isolated yields for 1-*O*-deacetylation (step 1) and phosphitylation (step 2)

| Starting Peracetylated Carbohydrate | Step 1 (ratio α/β)[a] | Step 2 |
|---|---|---|
| **4a** D-mannose | 73 % (9/1) | 62 % |
| **4b** D-galactose | 73 % (4/1) | 70 % |
| **4c** D-glucose | 77 % (4/1) | 77 % |
| **4d** L-fucose | 52 % (2/1) | 83 % |
| **4e** D-cellobiose | 67 % (9/1) | 81 % |

[a] estimated by 200 MHz $^1H$ NMR

Phosphitylation using the procedure developed by van Boom and coworkers[5] afforded, after silica gel

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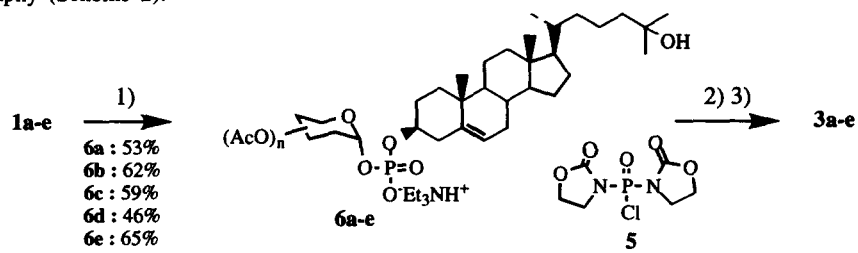
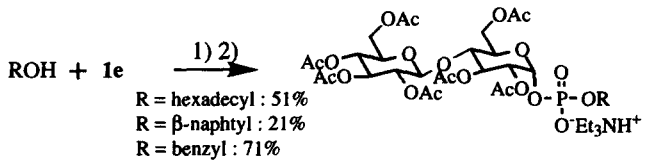
chromatography ($CH_2Cl_2$/MeOH/$Et_3N$ (98/1/1) → (91/8/1)), the compounds **1a-e** as their pure α anomers. In the next step H-phosphonates monoesters **1a-e** were regioselectively condensed with 25-hydroxycholesterol using bis(2-oxooxazolidin-3-yl) phosphinic chloride **5** as activating agent.[6] The corresponding H-phosphonates diesters were oxidized *in situ* (1.2 eq. $I_2$ ; pyridine/water : 98/2 (v/v)).[6] Silica gel chromatography ($CH_2Cl_2$/MeOH/$Et_3N$ (98/1/1) → (93/6/1)) followed by gel filtration (Sephadex LH20 ; $CHCl_3$/MeOH : 1/1) afforded the fully protected phosphodiesters **6a-e** (α anomers) in good yields (Scheme 3). The complete regioselectivity observed is in agreement with our previous data[1] and can be explained by the highly hindered nature of the intermediates resulting from the activation of the H-phosphonate monoester by the chlorophosphate **5**.[6] The use of **5** also permits the complete recovery of unchanged, unreacted 25-hydroxycholesterol. Derivatives **6a-e** can then be quantitatively converted to the target compounds **3a-e** after mild deacetylation ($NH_3$/MeOH) and cation exchange chromatography (Scheme 2).




**Scheme 2:** 1)i) 5eq. **2**, 5eq. **5**, pyridine, r.t., 45 min. ; ii) 1,2eq. $I_2$ pyridine-water , r.t., 15 min. ; 2) excess $NH_3$, MeOH, r.t., 24-48 h. ; 3) Dowex AG 50W-X8 ($Na^+$ form)

We have investigated the extension of the phosphorylation process to other types of lipophilic monoalcohols using **1e** and pivaloyl chloride (PivCl)[6] as condensating agent (Scheme 3). Purifications were achieved as described for derivatives **6**.




**Scheme 3 :** 1)3 eq. PivCl, pyridine, r.t., 30 min ; 2) 1,2 eq. $I_2$, pyridine/water, r.t., 15 min.

Physico-chemical and biological investigations with 25-hydroxycholesterol derivatives **3a-e** and extension of this method to more complex biologically active lipophilic alcohols are currently in progress.

In conclusion, we have described an easily and widely applicable technique for the preparation of phosphodiesters of biological interest using peracetylated glycosyl H-phosphonate of type **1** as versatile building blocks. This technique could be particularly useful for the synthesis of prodrugs.

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