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SmI_2-mediated reactions of diethyl iodomethylphosphonate with esters and lactones: a highly stereoselective synthesis of a precursor of the *C*-glycosyl analogue of thymidine 5′-(β-L-rhamnosyl)diphosphate

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Abstract—In the presence of samarium iodide diethyl iodomethylphosphonate reacts with esters to afford β-ketophosphonates. The protocol has been applied to sugar lactones to afford in fairly good yields intermediates that are useful precursors for a variety of potentially bioactive compounds, such as the *C*-glycosyl analogue of thymidine 5′-(β-L-rhamnosyl)diphosphate.

β-Ketophosphonates are quite important organic compounds for their metal-complexing ability[1] and for their many applications as organic intermediates in the synthesis, for example, of α,β-unsaturated compounds (via the Horner–Emmons reaction);[2] of chiral β-hydroxyacids and chiral β-aminophosphonic acids, both endowed with interesting biological properties,[3,4] for which several methods of preparation have been reported, albeit not fully satisfactory ones.[5]

Also, *C*-glycosylphosphonates are quite interesting compounds as they can act as stable biomimetics of the corresponding glycosyl phosphates (which play a crucial role in the biosynthesis of oligo- and polysaccharides, and glycoconjugates) and are important as enzymatic inhibitors.[6] Therefore they have been the subject of significant efforts in synthetic chemistry[7] and the development of new efficient methodologies for their synthesis is an appealing target.

Samarium iodide has been found to be a very versatile and mild reagent, useful in a wide variety of new types of electron transfer reactions (such as radical cyclization, pinacol coupling reactions, ketyl–olefin coupling reactions, Reformatsky-type and aldol type reactions) which are quite superior for efficiency and selectivity to the traditional ones.[8]

Keywords: β-ketophosphonates; *C*-glycosylphosphonates; samarium iodide.

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In the present work we have investigated the ability of samarium iodide to promote the reaction between α-halophosphonates and esters to produce β-ketophosphonates. Once this possibility had been verified, we were particularly interested to extend the reaction to sugar lactones, as easy available and convenient precursors of a variety of potentially bioactive compounds such as *C*-glycosyl phosphonates and aminophosphonates inserted on a sugar anomeric carbon.[9]

The reactions have been tested in tetrahydrofuran solution, using the convenient, commercially available diethyl iodomethylphosphonate. As observed in the synthesis of β-hydroxyphosphonates reported in the preceding paper, the best results have been obtained by simultaneous addition of the organic reagents to the solution of samarium iodide (0.1 M in tetrahydrofuran), the latter being used as at least 2.0 (usually 2.2) molar equivalents.

Addition to esters produced the expected β-ketophosphonates, and in reasonable to moderate yields (30–49%) depending on the ester structure (Table 1). In all cases unreacted starting ester was recovered in generally comparable amounts with respect to the β-ketophosphonate, but it was easily separated by chromatography and recycled (in most cases a simple filtration on a very short column of silica gel was enough: a procedure easily applicable also if the reaction has to be scaled up). Methanephosphonate was also formed, a side product that a priori could derive from different path-

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ways: acid–base exchange between an unreacted organosamarium and water during work-up; or by acid–base exchange between the organosamarium itself and the β-ketophosphonate,[10] this last assumption being strongly supported by the higher acidity of the latter.

The partly disappointing results (maximum 50% yields) obtained with esters prompted us to investigate the reaction of diethyl iodomethylphosphonate with glyconolactones. For this purpose 2,3,5-tri-*O*-benzyl-β-D-arabinono-1,4-lactone, 2,3,4,6-tetra-*O*-benzyl-D-mannono-1,5-lactone and 2,3,4-tri-*O*-benzyl-L-rhamnono-1,5-lactone (easily prepared from the parent sugars by oxidation with pyridinium chlorochromate, in 3.5 molar ratio, in methylene chloride in the presence of molecular sieves) were reacted with diethyl iodomethylphosphonate in tetrahydrofuran in the presence of 2.2 equiv. of samarium iodide, according to the protocol used with esters. The reaction worked better in these cases, affording the expected addition compounds with yields ranging from 45 to 82% depending on the starting lactone which was recovered in 10 to 40% yield, and was easily separated by chromatography and recycled (Scheme 1).

The reaction was stereoselective and afforded only one stereomer for the mannono- and rhamnono-lactone, whereas the lactone from 2,3,5-tri-*O*-benzyl-arabinofuranose afforded the two diastereomers in a 3/1 ratio. The anomeric configuration of the lactols **1**–**3** was determined by NOE experiments, which evidenced a correlation between one or both the methylenic hydrogens adjacent to the carbonyl carbon and the hydrogen at C-2.

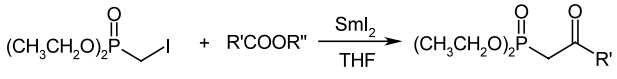
Lactol **3** is a particularly valuable compound, because it is a precursor of the *C*-glycosyl analogue of thymidine 5′-(β-L-rhamnopyranosyl diphosphate), a potential inhibitor of rhamnosyltransferase, a quite important enzyme for the biosynthesis of mycobacterial cell wall. Therefore inhibitors of this enzyme have a potential therapeutic interest.[11]

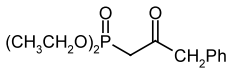
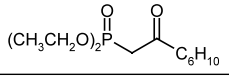
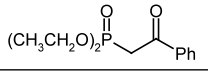
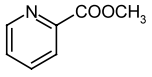
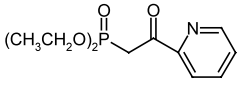
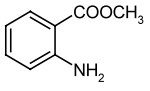
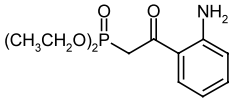
In summary, the protocol reported above allows the synthesis of β-ketophosphonates under mild and neutral conditions, and with some advantages with respect to known procedures: easily available substrates; no strong bases, acids or heat required; no side products deriving from the attack on the carbonyl carbon of the β-ketophosphonate.

When the protocol is applied to glyconolactones, in particular six-membered 1,5-lactones, the reaction proceeds in high yields and stereoselection and may represent a convenient entry to a variety of bioactive compounds of therapeutic potential.

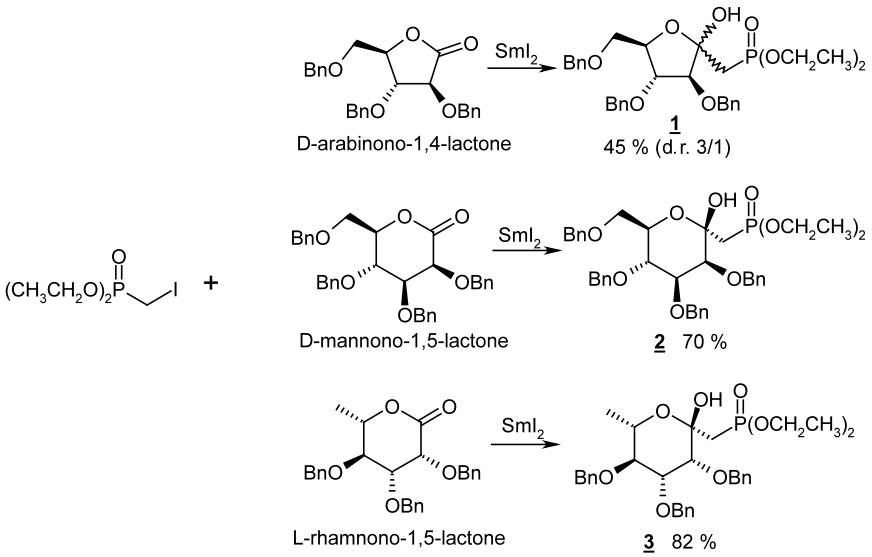
Typical procedure. In a typical procedure a THF solution (2 mL) of diethyl iodomethylphosphonate (0.5 mmol) and carbonyl compound (0.5 mmol) was added dropwise over a 20 min period to a room temperature stirred solution of SmI_2 in tetrahydrofuran (0.1 M, 12 mL). Soon after the addition the original blue solution

Table 1. Reactions between diethyl iodomethylphosphonate and esters[a]



Entry	Substrate	Product	Yield[b] %	Recovery[c] %
1	$PhCH_2COOCH_3$		49 (46)	48
2	$C_6H_{10}COOCH_3$		40 (56)	42
3	$PhCOOCH_3$		35 (65)	30
4			30 (60)	62
5			42 (52 %)	52

[a] All new compounds gave satisfactory ^1H, ^{13}C NMR and MS spectroscopic analyses.
[b] Yields refer to % of isolated products, unless otherwise stated; yields between parentheses refer to diethyl methanephosphonate formed under the reaction conditions.
[c] Yields refer to % of recovered unreacted carbonyl compound.



Scheme 1.

turned to a yellowish suspension. The reaction mixture was stirred at room temperature for 12 h, monitored by TLC (EtOAc/*n*-hexane), treated with aqueous HCl (0.1N solution, 3 mL) and extracted with ethyl acetate (3×4 mL); the organic layer was washed with a saturated Na_2SO_3 aqueous solution (2 mL), dried with sodium sulfate, filtered, the solvent was evaporated and the crude was purified by column flash-chromatography (Scheme 1).

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