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New stereoselective synthesis of phosphono analogues of glycosyl phosphates

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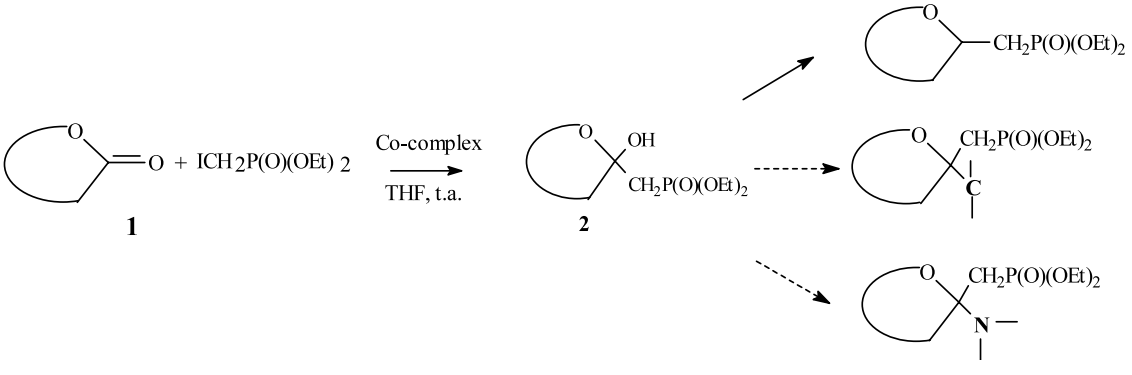
Abstract—A new and stereoselective synthesis of isosteric phosphono analogues of glycosyl phosphates is reported. Appropriately protected glyconolactones, easily available from the parent sugars are reacted with ethyl-α-iodomethylphosphonate in THF in the presence of a soluble low-valent cobalt–phosphine complex, either in stoichiometric or sub-stoichiometric amounts, in the latter case in the presence of magnesium metal. The use of magnesium metal alone works, but in a less efficient and predictable way. The intermediate addition product can be subsequently deoxygenated with triethylsilane in the presence of boron trifluoride.

1. Introduction

The replacement of the oxygen atom of the phosphoesteric linkage in a phosphate with a carbon atom produces a modified molecule, which *may still fit* the active sites or receptors of the parent phosphate, but importantly has enhanced physiological stability[1] (due to the stability of the carbon–phosphorus bond to enzymatic degradation by phosphatase enzymes) and better cell permeability[2] (due to its lower polarity). These features explain the considerable interest in phosphonates as biologically active surrogates of naturally occurring phosphates. Among them, glycosyl phosphates are of great interest as they behave as glycosyl donors in the biosynthesis of oligo- and polysaccharides, and glycoconjugates;[3] *C*-glycosides are also of interest for their potential biological activities.[4] Therefore, the *C*-glycosidic analogues of glycosyl phosphates have been the object of significant efforts in synthetic chemistry[5] and the development of new synthetic methodologies is still an appealing target.

2. Results and discussion

We have found that appropriately protected glyconolactones (of general formula **1**), react with α-halophosphonates in THF in the presence of a soluble low-valent cobalt complex with trimethyl- or triphenylphosphine to give addition products **2**, as shown in Scheme 1.



Scheme 1.

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The lactose **2** are useful intermediates for the presence of the 'anomeric' hydroxyl which can be further elaborated to give a variety of compounds, among them the *C*-glycosidic analogues of glycosyl phosphates, obtainable from lactols **2** by dehydroxylation with triethylsilane in acidic conditions.

The cobalt complexes mentioned above have already been reported as efficient mediators for Reformatsky- and aldol-type reactions to produce β-hydroxy esters,[6] β-hydroxy ketones[7] and β-hydroxy phosphonates.[8]

To find the best experimental conditions for the synthesis of the title compounds, different experiments were designed. The obtained results are summarised in Table 1.

In a first series of experiments (procedure A, stoichiometric method), a variety of glyconolactones, obtained from different or differently protected parent sugars, was reacted with diethyl-α-iodomethylphosphonate (selected as a model for an α-halophosphonate) in the presence of $(Me_3P)_4Co(0)$.[9] The stoichiometry of the reaction was investigated using different molar ratios of the halophosphonate, the electrophile and the Co(0) complex, and different orders of addition of the organic reagents to the Co(0) complex were also examined. The best results were obtained with a 'one pot' procedure in which the two organic reagents were added simultaneously to the Co(0) complex, using a 2.0:2.0:1.0 mol ratio of halophosphonate:cobalt(0) complex:lactone, and a 0.2–0.3 M solution with respect to the sugar lactone.[10] Diethyl-α-chloromethylphosphonate was also tested but afforded lower yields of the expected lactols. Conveniently, as ancillary ligand to cobalt, the volatile trimethylphosphine can be replaced by the non-volatile triphenylphospine without affecting the yields and the course of the reactions.

In a second series of experiments (procedure B, sub-stoichiometric method) we observed that the addition product was also formed very cleanly when the reaction was carried out with a 10:10:1 mol ratio of the organic reagents to the cobalt(0) complex, provided that magnesium metal was present to carry out the reduction of Co(II) to Co(0). The yields and the stereochemical outcome of the reactions are comparable with those obtained in the first series of experiments.

In all cases, the only isolated product was the addition compound to the carbonyl. Yields ranged from 50 to 82% and depended on the experimental conditions and, chiefly, on the starting lactone which was recovered unchanged in 10–40%, easily separated by chromatography and recycled.

Only one stereoisomer was generally obtained, with the exception of the lactone from 2,3,5-tri-*O*-benzyl-arabinofuranose, which afforded the two diastereomers in a 3:1 ratio. The anomeric configuration of compounds **2a**–**g** 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.

Compared to procedure A, procedure B has the advantage of using a lower quantity of cobalt and phosphine, offsetting the disadvantage of their use, and making purification of the product easier. A further advantage is the colour of the solution, which continuously changes from yellow-brown (Co(0) complex) to dark blue-violet (Co(II) complex) during the addition of the organic reagent to the Co complex. This colour change allows easy monitoring of the course of the reaction.

To investigate whether an organomagnesium compound might be involved in the sub-stoichiometric procedure, we designed a third series of experiments (procedure C) and we performed parallel experiments, adding the halophosphonate and the glyconolactone to magnesium alone in THF.

We observed that the reaction proceeded equally well (comparable yields and stereochemical outcome) with magnesium alone[11] as far as the reaction was frequently monitored by thin-layer chromatography and worked-up as soon as the starting lactone disappeared. However, in the absence of cobalt, the reactions, depending on magnesium activation, were slower, less reproducible and required variable time of induction, therefore, affording side products and lowering the yields. These observations point to a key role of cobalt under sub-stoichiometric conditions. One more piece of evidence that might prove the actual involvement of cobalt is the colour of the solution that continuously changes from yellow-brown (Co(0) complex) to deep blue-violet (Co(II) complex) during the addition of the organic reagents and allows a facile visualisation of the end point of the reaction and thus minimises the formation of by-products.

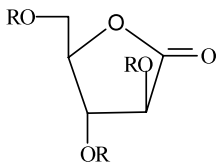
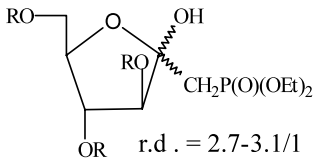
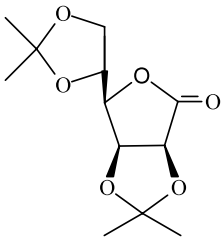
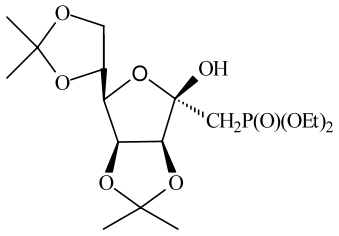
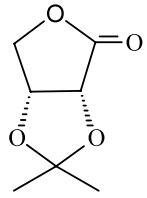
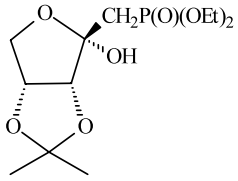
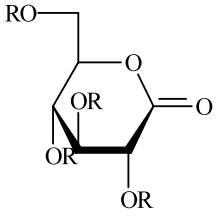
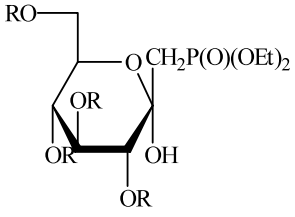
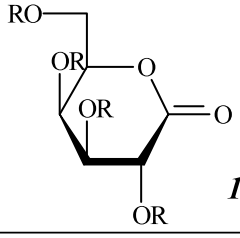
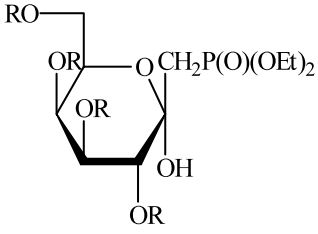
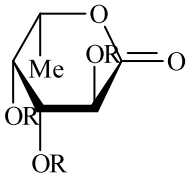
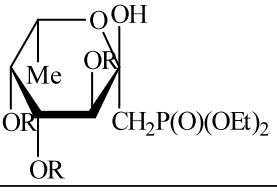
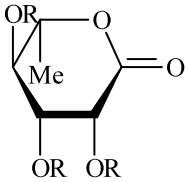
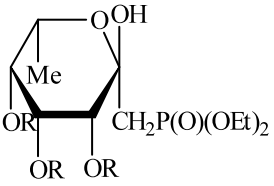
Once the experimental conditions to obtain lactols **2** were optimised, compound **2f**, chosen as a model for the dehydroxylation reaction, was treated with triethylsilane in the presence of a Lewis acid. The reaction afforded the glycosyl phosphonate **3f** in good yields (Scheme 2).

3. Conclusions

The most direct way to prepare isosteric phosphono analogues of glycosyl phosphates is the reaction of an appropriately protected aldose with the ylide, (diphenylphosphoranylidine)methanephosphonate, or with the anion of a tetraalkyl methylenediphosphonate, a reaction which affords the desired *C*-glycosyl methylene phosphonate in two steps (via an α,β-unsaturated phosphonate intermediate), but unfortunately, is not stereoselective and is not generally applicable. A more general procedure requires the preparation of a *C*-glycosyl halide, followed by its reaction with a trialkyl phosphite.

More recently a three step synthesis of *C*-glycosyl analogues of β-fucopyranosyl phosphate and β-L-rhamnopyranosyl phosphate was reported, based on the reaction of the corresponding glycono lactones with

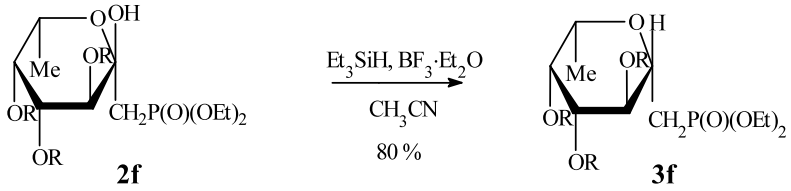
Table 1. Co(0)- and/or Mg-mediated reactions of glyconolactones **1a–g** with diethyl-α-iodomethylphosphonate

LACTONE	PRODUCT	YIELD(%)	PROCEDURE[a]
 **1a**	 r.d . = 2.7-3.1/1 **2a**	54 [43][b] 60 [30][b] 37 [57][b]	A B C
 **1b**	 **2b**	72 [4][b] 82 [7][b,c] 80 [10][b]	A B C
 **1c**	 **2c**	63 [25][b]	B C
 **1d**	 **2d**	60 [28][b] 65 [30][b,c] 35 [45][b]	A B C
 **1e**	 **2e**	50 [20][b,c] 47 [23][b]	B C
 **1f**	 **2f**	65 [17][b] 62 [19][b]	B C
 **1g**	 **2g**	70 [10][b] 65 [10][b]	B C

[a] Procedure A: glyconolactone, ethyl-α-iodomethylphosphonate and $[Co(PMe_3)]_4$ has been used in a 1:2.5:2.5 ratio. Procedure B: the reaction has been performed using a sub-stoichiometric quantity of $Co(PMe_3)_4$ (10%). Procedure C: the reaction has been performed using metallic magnesium only.

[b] The brackets refer to recovered starting ester.

[c] Yields determined by H NMR.



Scheme 2.

lithium dimethyl methyl phosphonate at low temperature.[12]

With respect to known procedures, the reported cobalt- or magnesium-mediated syntheses of the phosphonate analogues of glycosyl phosphates, via addition of α-halophosponates to glyconolactones, represent valid alternatives, with some advantages: mild experimental conditions; user-friendly and easily stored reagents; high stereoselection; no requirement of strictly anhydrous conditions; and, with respect to procedures using glycosyl halides, more readily available substrates.

When magnesium alone is used, the purification of the product is easier, but the reaction has the disadvantage of heterogeneous conditions and it is less reproducible. A good compromise can be the use of the Co(0) complex under sub-stoichiometric conditions: a protocol that overcomes the problems with separation of cobalt salts; offsets the disadvantage of using phosphines; appears to be less sensitive to the activation of magnesium; allows very easy monitoring of the course and the end point of the reaction by the alternation of the Co(0) and Co(II) colours in the solution.

4. Experimental

Reagent grade THF was heated under reflux over $LiAlH_4$ and distilled. Reagent grade dichloromethane was heated under reflux over CaH_2 and distilled. Reagent grade acetonitrile was heated under reflux over CaH_2 and distilled. 2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose were purchased from Sigma and converted to the corresponding lactones **1a**[13] and **1d**[14] and **1b**[15] according to the procedure reported below. 2,3,4-Tri-*O*-benzyl-L-fucopyranose, 2,3,4,6-tetra-*O*-benzyl-galattopyranose and 2,3,4-tri-*O*-benzyl-L-rhamnopyranose were purchased from Toronto Research Chemicals (Canada) and converted to the corresponding lactones **1f**,[16] **1e**[17] and **1g**[12] according to the procedure reported below. 2,3-*O*-Isopropylidene-D-erythronolactone **1c** was purchased from Aldrich. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded at 200 and 300 MHz on Bruker spectrometers. MS spectra were recorded with a VG7070 E9 spectrometer. Melting points were obtained by using a Buchi 535 apparatus. Optical rotation measurements were obtained with a Perkin–Elmer 241 Polarimeter and elemental analyses for the new compounds were determined on a Perkin–Elmer 240 Analyser. Flash-column chromatography purification was performed on silica gel Merck Kieselgel 60 (230–400 mesh ASTM). Thin-layer chromatography was performed on silica gel plates (60 F254, Merck): zones were detected visually by ultraviolet irradiation (254 nm) and/or using Pancaldi reagent, followed by heating at 100°C. All reactions were performed under a dry nitrogen atmosphere, using glassware dried by flaming in a stream of dry nitrogen.

Dry THF (99.9% from Aldrich) was generally used for the cobalt-mediated reactions.

4.1. Typical procedure for the synthesis of glyconolactones

A solution of the protected sugar (1 mmol) in dry methylene chloride (5 mL) was added under nitrogen to a suspension of pyridinium chlorochromate (0.75 g, 3.5 mmol) and molecular sieves (0.3 mm from Merck, 0.5 g) in methylene chloride (2 mL). The reaction mixture was stirred under nitrogen in the dark and was monitored by thin layer chromatography (silica gel, eluting with ethyl acetate:petroleum ether 6:4). At the end of the reaction, the reaction mixture was filtered over silica gel eluting with ethyl acetate:petroleum ether 4:6. Removal of the solvent under reduced pressure afforded the glyconolactone (80–85% yields), which was used directly.

4.2. Typical procedure for the stoichiometric reaction mediated by $(Me_3P)_4Co$ (procedure A)

A 1 M solution of trimethylphosphine in THF (10 mL) was added to a mixture of activated magnesium turnings[18,19] (ca. 0.3 g) and anhydrous $CoCl_2$ (0.32 g, 2.5 mmol). The reaction mixture was stirred at room temperature until a dark brown colour developed.[20] The excess of magnesium was filtered off, and to the resulting solution were added diethyl-α-iodomethylphosphonate (0.41 mL, 2.5 mmol) and the lactone (0.54 g, 1 mmol) in THF, dropwise over a period of 1 h. The reaction was monitored by thin layer chromatography (silica gel, eluting with ethyl acetate–petroleum ether 7:3). At the end of the reaction, the mixture was stirred under air until a green blue colour developed. Two different work-up procedures were then used depending on the water-solubility of the lactone and of the product.

For water-insoluble compounds the reaction mixture was diluted with ethyl acetate and poured into aqueous HCl (5%, 2–3 mL). The aqueous phase was extracted with ethyl acetate (3×15 mL). The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. Occasionally a light blue or green colour still persistent

in the crude material was eliminated by dissolving in ethyl acetate and by washing with a saturated EDTA (bis-sodium salt) solution.

For partially water soluble-compounds, the reaction mixture was filtered through silica gel eluting with ethyl acetate:petroleum ether to remove cobalt salts.

The crude material was purified by chromatography over silica gel, eluting with ethyl acetate:petroleum ether 7:3 and ethyl acetate:methanol 9:1, to separate the product from unreacted starting lactone. Trimethylphosphine can be conveniently substituted with triphenylphosphine without affecting the course of the reaction.

Compound **2a** (mixture of diastereoisomers): colourless viscous oil; ^{1}H NMR ($CDCl_3$): δ (major), 1.26 (3H, t, $J=6.5$ Hz), 1.30 (3H, t, $J=6.5$ Hz), 2.28 (1H, dd, $J=17.5$, 15.0 Hz), 2.46 (1H, dd, $J=17.5$, 15.0 Hz), 3.53 (1H, dd, $J=10.0$, 4.8 Hz), 3.58 (1H, dd, $J=10.0$, 4.6 Hz), 3.91 (1H, dd, $J=4.9$, 4.8 Hz), 4.02 (1H, d, $J=4.9$ Hz), 4.05 (2H, dq, $J=6.3$ Hz), 4.18 (1H, dq, $J=6.9$ Hz), 4.36 (1H, ddd, $J=4.8$, 4.8, 4.6 Hz), 7.25–7.45 (15H, m); ^{13}C NMR ($CDCl_3$): δ (major), 2×16.34 (q), 32.20 (dt, $J_{CP}=134.4$), 2×62.05 (dt, $J_{CP}=106.1$), 70.20 (t), 72.01 (t), 73.30 (t), 73.42 (t), 80.93 (d), 82.89 (d), 88.08 (dd, $J_{CP}=35.4$), 104.4 (s), 6×127.67 (d), 6×127.82 (d), 3×128.41 (d), 137.66 (s), 137.79 (s), 138.48 (s); ^{31}P NMR ($CDCl_3$): δ 29.29. MS, m/z: 552 (M^+-H_2O), 507 ($M^+-H_2O-CH_3CH_2O$), 444 ($M^+-H_2O-PhCH_2OH$), 151 [$CH_2P(O)(OEt)_2$].

The minor diastereoisomer was identified by the following signals in the NMR spectra. ^{1}H NMR ($CDCl_3$): δ 2.17 (1H, dd, $J=18.3$, 15.0 Hz), 2.34 (1H, dd, $J=18.3$, 15.0 Hz); ^{13}C NMR ($CDCl_3$): δ 2×16.34 (q), 34.76 (dt, $J_{CP}=134.4$), 72.79 (t), 80.52 (d), 84.34 (d), 86.43 (d), 101.35 (s); ^{31}P NMR: 27.19.

Compound **2b**: colourless crystals; mp = 88–89°C (petroleum ether–ethyl acetate); $[\alpha]_D=+9.5$ (*c* 11 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, s), 1.30 (3H, t, $J=7.0$ Hz), 1.31 (3H, t, $J=7.0$ Hz), 1.34 (3H, s), 1.41 (3H, s), 1.44 (3H, s), 2.14 (1H, dd, $J=18.4$, 15.6 Hz), 2.33 (1H, dd, $J=17.0$, 15.6 Hz), 3.9–4.1 (6H, m), 4.08 (1H, dd, $J=7.1$, 4.3 Hz), 4.31 (1H, dd, $J=12.7$, 5.7 Hz), 4.41 (1H, d, $J=5.6$ Hz), 4.78 (1H, dd, $J=5.6$, 4.3 Hz); ^{13}C NMR ($CDCl_3$): 2×16.13 (q), 24.33 (q), 24.93 (q), 25.76 (q), 26.59 (q), 30.88 (t, $J_{CP}=144.9$ Hz), 61.83 (t, $J_{CP}=58.0$ Hz), 61.98 (t, $J_{CP}=58.0$ Hz), 66.54 (t), 72.88 (d), 79.32 (d), 80.06 (d), 85.89 (d, $J_{CP}=8.7$ Hz), 103.48 (s, $J_{CP}=8.7$ Hz), 103.83 (s), 112.53 (s); ^{31}P NMR ($CDCl_3$): δ 29.18; MS, m/z: 410 (M^+), 392 (M^+-H_2O), 316 ($392-H_2O-CH_3COCH_3$), 259 ($M^+-CH_2P(O)(OEt)_2$). Anal. calcd for $C_{17}H_{31}O_9P$: C, 49.75; H, 7.56. Found: C, 49.35; H, 7.53%.

Compound **2c**: colourless viscous oil; $[\alpha]_D=-38.05$ (*c* 10.8 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.29 (3H, s), 1.30 (3H, d, $J=7.5$ Hz), 1.31 (3H, t, $J=7.5$ Hz), 1.43 (3H, s), 2.22 (1H, dd, $J=18.0$, 15.0 Hz), 2.43 (1H, dd, $J=18.0$, 15.0 Hz), 3.9 (1H, d, $J=10.5$ Hz), 4.35 (dd, 1H, $J=10.5$, 3.3 Hz), 4.10 (2H, dq, $J=7.5$, 7.5, 7.5, 7.5), 4.18 (2H, dq, $J=7.5$, 7.5, 7.5, 7.5 Hz), 4.40 (1H, d, $J=4.8$ Hz), 4.83 (1H, dd, $J=4.8$, 3.3 Hz); ^{13}C NMR ($CDCl_3$): δ 2×16.31 (q), 24.92 (q), 26.30 (q), 31.09 (t, $J_{CP}=140.6$ Hz), 2×62.27 (t, $J_{CP}=105.4$ Hz), 71.24 (t), 80.62 (d), 85.55 (d), 104.09 (s), 112.52 (s); ^{31}P NMR ($CDCl_3$): δ 29.42; MS, m/z: 292 (M^+-H_2O), 247 ($292-CH_3CH_2O$), 151 ($CH_2P(O)(OEt)_2$). Anal. calcd for $C_{12}H_{23}O_7P$: C, 46.45; H, 7.42. Found: C, 46.25; H, 7.40%.

Compound **2d**: colourless viscous oil; $[\alpha]_D=-8.67$ (*c* 13.3 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.20 (3H, t, $J=7.7$ Hz), 1.26 (3H, t, $J=7.7$ Hz), 1.70 (1H, dd, $J=19.3$, 15.4 Hz), 2.28 (1H, d, $J=17.4$, 15.4 Hz), 3.25 (1H, d, $J=9.7$ Hz), 3.59 (dd, 1H, $J=11.6$, 3.1 Hz), 3.66 (1H, dd, $J=8.5$, 8.5 Hz), 3.74 (1H, dd, $J=11.6$, 3.9 Hz), 3.99 (2H, dq, $J=7.7$ Hz), 4.08 (2H, m), 4.10 (1H, m), 4.11 (1H, m), 4.45 and 4.5 (AB system, 2H, $J=11.6$ Hz), 4.57 (1H, d, $J=11.6$ Hz), 4.63 (1H, d, $J=11.6$ Hz), 4.84 (1H, d, $J=11.6$ Hz), 4.9 (2H, s), 4.96 (1H, d, $J=11.6$ Hz), 7.25–7.4 (20H); ^{13}C NMR ($CDCl_3$): δ 2×16.2 (q), 33.14 (t, $J_{CP}=140.6$ Hz), 2×62.0 (t, $J_{CP}=58.6$ Hz), 69.79 (t), 71.00 (d), 73.37 (t), 74.70 (t), 75.10 (t), 75.55 (t), 79.44 (d), 92.96 (d), 93.15 (d), 96.83 (s, $J_{CP}=11.72$ Hz), 4×127.65 (d), 4×127.84 (d), 4×129.30 (d), 8×129.57 (d), 2×137.98 (s), 139.33 (s), 139.82 (s); ^{31}P NMR ($CDCl_3$): δ 29.20; MS, m/z: 672 (M^+-H_2O), 539 ($M^+-CH_2P(O)(OEt)_2$), 152 [$CH_3P(O)(OEt)_2$], 91 ($PhCH_2$). Anal. calcd for $C_{39}H_{47}O_9P$: C, 67.83; H, 6.81. Found: C, 67.53; H, 6.78%.

Compound **2e**: colourless viscous oil; $[\alpha]_D=+9.7$ (*c* 10.5 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.19 (3H, t, $J=7.3$ Hz), 1.26 (3H, t, $J=7.3$ Hz), 1.77 (1H, dd, $J=17.2$, 15.1 Hz), 2.37 (1H, dd, $J=17.2$, 15.1 Hz), 3.51 (1H, dd, $J=9.9$, 6.5 Hz), 3.59 (1H, dd, $J=9.9$, 8.6 Hz), 3.74 (1H, d, $J=8.6$ Hz), 4.24 (1H, dd, $J=6.5$, 6.5 Hz), 4.44 (2H, s), 4.61 (1H, d, $J=11.6$ Hz), 4.68 (1H, d, $J=11.6$ Hz), 4.75 (2H, s), 4.95 (1H, d, $J=11.6$ Hz), 5.0 (1H, d, $J=11.6$ Hz), 7.25–7.40 (20H); ^{13}C NMR ($CDCl_3$): δ 2×16.27 (q), 34.19 (t, $J_{CP}=131.95$ Hz), 61.93 (t, $J_{CP}=88.0$ Hz), 61.99 (t, $J_{CP}=88.0$ Hz), 68.91 (t), 72.78 (t), 73.30 (t), 74.75 (t), 76.00 (t), 75.38 (d), 79.27 (d), 79.48 (d), 80.36 (d), 97.41 (s), 4×127.51 (d), 2×127.72 (d), 2×128.11 (d), 4×128.31 (d), 8×128.65 (d), 138.06 (s), 138.35 (s), 138.58 (s), 138.99 (s); ^{31}P NMR ($CDCl_3$): δ 29.68; MS, m/z: 672 (M^+-18), 581 ($M^+-18-19$), 91 ($PhCH_2$). Anal. calcd for $C_{39}H_{47}O_9P$: C, 67.83; H, 6.81. Found: C, 67.50; H, 6.70%.

Compound **2f**: colourless viscous oil; $[\alpha]_D=+5.5$ (*c* 4.8 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.1 (3H, d, $J=6.8$ Hz), 1.27 (3H, dt, $J=6.8$, 6.8, 3.8 Hz), 1.76 (1H, dd, $J=18.8$, 15.0 Hz), 2.34 (1H, dd, $J=18.0$, 15.0 Hz), 3.68 (1H, dd, $J=3.0$, 1.5 Hz), 3.72 (1H, d, $J=9.75$ Hz), 3.97 (2H, dq, $J=6.8$, 6.8, 6.8, 6.8 Hz), 4.13 (2H, dq, $J=6.8$ Hz), 4.08–4.18 (2H), 4.68 (1H, d, $J=10$ Hz), 4.70 (1H, d, $J=10$ Hz), 4.75 and 4.79 (2H, AB system, $J=10.5$ Hz), 4.96 (1H, d, $J=6.7$), 5.1 (1H, d, $J=6.7$), 7.25–7.45 (15H); ^{13}C NMR ($CDCl_3$): δ 2×16.46 (q, $J_{CP}=27.8$ Hz), 33.40 (t, $J_{CP}=138.76$ Hz), 63.4 (t, $J_{CP}=61.1$ Hz), 72.85 (t), 74.69 (t), 75.84 (t), 77.92 (d), 79.02 (d), 79.29 (d), 80.60 (d), 97.05 (s, $J_{CP}=13.88$ Hz),

2×127.49 (d), 127.64 (d), 4×129.12 (d), 4×129.28 (d), 4×128.61 (d), 138.29 (s), 138.59 (s), 138.76 (s); ^{31}P NMR ($CDCl_3$): δ 29.95; MS, m/z: 566 (M^+-H_2O), 475 ($M^+-H_2O-CH_2Ph$), 152 [$CH_2P(O)(OEt)_2$]. Anal. calcd for $C_{32}H_{41}O_8P$: C, 65.75; H, 7.02. Found: C, 65.45; H, 6.98%.

Compound **2g**: colourless viscous oil; $[\alpha]_D=-15.2$ (c 6.8 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.26 (3H, d, $J=7.2$ Hz), 1.28 (3H, t, $J=7.2$ Hz), 1.30 (3H, t, $J=7.2$ Hz), 1.65 (1H, dd, $J=17.2$, 14.3 Hz), 2.55 (1H, dd, $J=17.2$, 14.3 Hz), 3.60 (1H, t, $J=8.6$ Hz), 3.71 (1H, d, $J=2.9$ Hz), 4.04 (1H, dq, $J=7.2$ Hz), 4.04 (2H, m), 4.13 (1H, dd, $J=8.6$, 2.9 Hz), 4.16 (2H, m), 4.63 (1H, d, $J=11.4$ Hz), 4.65 (1H, d, $J=11.4$ Hz), 4.92 (1H, d, $J=11.4$ Hz), 4.98 (1H, d, $J=11.4$ Hz), 7.25–7.45 (15H); ^{13}C NMR ($CDCl_3$): δ 16.14 (q), 16.26 (q), 17.81 (q), 33.72 (dt, $J_{CP}=132.3$ Hz), 62.0 (dt, $J_{CP}=79.4$ Hz), 62.0 (dt, $J_{CP}=79.4$ Hz), 68.67 (d), 72.91 (t), 74.84 (t), 75.83 (t), 78.78 (d), 80.23 (d), 81.32 (d), 96.98 (s, $J_{CP}=5.29$ Hz), 2×127.50 (d), 127.68 (d), 2×127.93 (d), 2×128.23 (d), 4×128.33 (d), 4×128.45 (d), 138.33 (s), 2×138.88 (s); ^{31}P NMR ($CDCl_3$): δ 30.14; MS, m/z: 566 (M^+-H_2O), 475 ($M^+-H_2O-CH_2Ph$), 152 [$CH_2P(O)(OEt)_2$]. Anal. calcd for $C_{32}H_{41}O_8P$: C, 65.75; H, 7.02. Found: C, 65.40; H, 6.96%.

4.3. Typical procedure for the sub-stoichiometric reaction mediated by $(Me_3P)_4Co$ (procedure B)

A 1 M solution of trimethylphosphine in dry THF (1 mL) was added to a mixture of activated magnesium turnings (0.3 g) and anhydrous $CoCl_2$ (0.032 g, 0.25 mmol).[13b] The mixture was stirred at room temperature until the yellow-brown colour of the cobalt(0) complex developed. To the mixture a THF solution (10 mL) of lactone (1 mmol) and diethyl-α-iodomethylphosphonate (1.2 mmol, 0.2 mL) were added dropwise under stirring. The speed of addition was adjusted so as to minimise the time of persistence of the blue colour (Co(II) complex) developed during the addition. At the end of the reaction, indicated by the persistence of the yellow-brown colour of the original Co(0) complex, the magnesium was filtered off and the resulting solution was stirred under air until a blue colour developed. For water-insoluble compounds (procedure A) the reaction mixture was diluted with ethyl acetate and poured into aqueous HCl (5%, 2–3 mL). The aqueous phase was extracted with ethyl acetate (3×15 mL). The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. Occasionally, a light blue or green colour still persistent in the crude material was eliminated by dissolving in ethyl acetate and by washing with a sutured EDTA (bis-sodium salt) solution.

For partially soluble-compounds, the reaction mixture was filtered through silica gel, eluting with ethyl acetate:petroleum ether to remove cobalt salts.
The crude material was chromatographed on silica gel, eluting with ethyl acetate:petroleum ether 7:3 and ethyl acetate:methanol 9:1, to separate the product from unreacted starting lactone.

4.4. Typical procedure for the reaction mediated by magnesium (procedure C)

To a suspension of activated magnesium turnings (0.3 g), in freshly distilled dry THF (2 mL), was added dropwise a THF solution (10 mL) of lactone (1 mmol) and diethyl-α-iodomethylphosphonate (1.2 mmol, 0.2 mL). The reaction was monitored by thin layer chromatography (silica gel, eluting with ethyl acetate:petroleum ether 7:3). The magnesium was removed by filtration and the filtrate was treated according to one of the two procedures described in Section 4.3, depending on the water-solubility of the product.

4.5. Reduction of 2f with triethylsilane

Triethylsilane (0.08 mL, 0.5 mmol) was added at 0°C to a solution of **2e** (0.06 g, 0.1 mmol) in dry acetonitrile, followed by freshly distilled $BF_3{\cdot}Et_2O$ (0.05 mL, 0.5 mmol). The reaction was kept at 0°C and monitored by thin-layer chromatography (silica gel, eluting with ethyl acetate:petroleum ether 3:7). A saturated solution of $NaHCO_3$ was added until pH 8 and the aqueous phase was extracted with methylene chloride (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude material was chromatographed on silica gel (ethyl acetate:*n*-hexane 3:7) and afforded phosphonate **3f** (0.044 g, 80%).

Compound **3f**: colourless thick oil; $[\alpha]_D=-25.45$ (c 12.2 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.15 (d, 3H, $J=6.5$ Hz), 1.25 (t, 6H, $J=7.5$ Hz), 1.9 (ddd, 1H, $J=16.0$, 16.0, 8.5 Hz), 2.3 (ddd, 1H, $J=18.0$, 16.0, 2.5 Hz), 3.53 (bq, 1H, $J=6.5$), 3.60 (ddd, 1H, $J=9.0$, 8.5, 2.5 Hz), 3.6–3.7 (m, 3H), 3.98–4.1 (m, 4H), 4.65–4.75 (4H), 4.95–5 (2H), 7.25–7.40 (15H); ^{13}C NMR ($CDCl_3$): δ 16.24 (q), 16.35 (q), 17.17 (q), 28.70 (dt, $J=140.74$), 61.44 (dt, $J_{CP}=21.9$), 61.54 (dt, $J_{CP}=21.9$), 72.49 (t), 74.38 (d), 74.69 (d), 74.88 (t), 75.09 (t), 76.75 (d), 78.44 (d), 85.02 (d), 127.62 (d), 4×127.89 (d), 4×128.186 (d), 4×128.104 (d), 128.30 (s), 2×138.58 (s). ^{31}P NMR ($CDCl_3$): δ 30.30; MS, m/z: 477 (M^+-PhCH_2), 416 ($M^+-CH_3P(O)(OEt)_2$, 310 (417–$PhCH_2O$), 152 [$CH_2P(O)(OEt)_2$], 91 ($PhCH_2$). Anal. calcd for $C_{32}H_{41}O_7P$: C, 67.61; H, 7.22. Found: C, 67.71; H, 7.22%.

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9. $Co(PMe_3)_4$ is a well-identified complex, that can be conveniently obtained by reducing a mixture of Co(II) chloride and trimethylphosphine (1:4 mole ratio) with magnesium metal in THF. Trimethylphosphine can be conveniently replaced by triphenylphosphine without affecting the course of the reaction.
10. More diluted solutions (0.05–0.08 M) with respect to the starting lactone were tested for the substrates **1a** and **1c**, and gave worse results (33 and 25% yields, respectively, of **2a** and **2c**).
11. Grignard reagents of halophosphonates have been previously synthesised by reaction of diisopropylmagnesium chloride with diethyl α,α-difluoro-α-iodomethanphosphonate and were reported to react with ketones and aldehydes. See: Waschbusch, R.; Samadi, M.; Savignac, P. *J. Organomet. Chem.* **1997**, *529*, 267–278.
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18. Magnesium metal is used in excess and can be recycled after use.
19. Magnesium was activated by adding a few drops of 1,2-dichloroethane to metal turnings (0.5 g) in THF (3 mL) so that a vigorous reaction ensued. After a few minutes the mixture was ice-cooled, the solvent was removed and the magnesium was washed three times with THF (2 mL each time).
20. The solution can also be warmed with an external bath at ca. 50°C to speed the reduction of Co(II) to Co(0). Warming may be useful when triphenylphosphine is used instead of trimethylphosphine.