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Cobalt(0)-mediated addition of α-haloesters and α-haloketones to (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde

Fulvia Orsini * and Cristina Leccioli
Dipartimento di Chimica Organica e Industriale, via Venezian 21, 20133 Milano, Italy

Abstract: Low-valent cobalt complexes were used in Reformatsky-type additions of α-haloesters and in aldol-type reactions of α-haloketones to (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde. Addition products were obtained in good yield with reasonable to high diastereoselection. The addition of methyl 4-bromocrotonate, which took place exclusively at the γ-carbon, was regioselective. © 1997 Elsevier Science Ltd. All rights reserved.

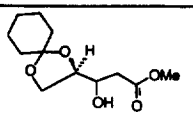
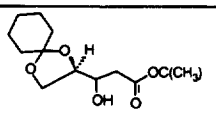
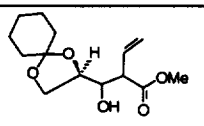
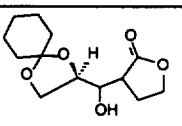
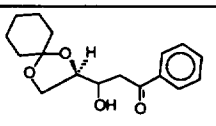
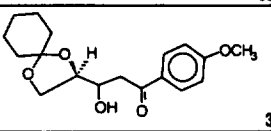
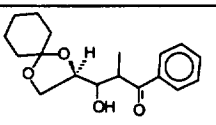
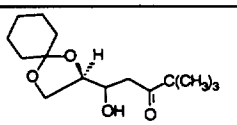
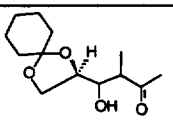
Carbohydrates and modified carbohydrates are frequently employed as chiral synthons and templates for stereoselective syntheses of compounds with multiple stereocentres. In this context the application of newly explored carbon–carbon bond forming reactions may offer new potential. It has previously been reported that some low-valent cobalt–phosphine complexes are efficient mediators for Reformatsky-type and aldol-type reactions between halogen derivatives and carbonyl compounds.[1–4] Based on these results the cobalt-mediated addition of various α-halo compounds (α-haloesters and α-haloketones) has been extended to substrates such as (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde **1** with two objectives. One was to verify the effectiveness of the cobalt-mediated Reformatsky-type and aldol-type reactions with polyfunctionalized carbonyl compounds; the second was to explore if these methods could provide a flexible route to monosaccharides, which are particularly rare or unnatural sugars of biological relevance.

In a first series of experiments the α-halo compound and (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde **1** were simultaneously added via a 'one pot' procedure to tetrakis(trimethylphosphine)cobalt(0), $[Co\{P(CH_3)_3\}_4]$ in equimolar amounts. All the reactions performed resulted in reasonable to good yields of the addition products **2** and **3** with reasonable to high diastereoselection (Table 1). The addition of methyl 4-bromocrotonate, which took place exclusively at the γ-carbon, was regioselective. In some cases the reactions have been performed substituting trimethylphosphine, as the ligand on cobalt, with the more convenient triphenylphosphine without significant differences in the course of the reaction. At the end of the reaction triphenylphosphine was separated from the reaction products by column chromatography.[5]

The reactions also proceeded cleanly when carried out with a 10:1 molar ratio of the organic reagents to cobalt, in the presence of magnesium metal. The course and the end point of the reaction were easily monitored by the alternation of the yellow–brown colour of the Co(0) complex and the deep purple–blue colour of the Co(II) complex during the addition of the α-halo compound/carbonyl compound reagents. A high yield of the addition product was obtained when the reaction was worked up as soon as the organic reagents were added and the yellow–brown colour of Co(0) complex persisted for few minutes.[6] The fact that the reaction can be carried out with a substoichiometric amount of the Co–phosphine complex offsets the disadvantage inherent in the use of trimethylphosphine. In this case, the crude material was pure enough to be examined directly by ^1H NMR spectroscopy and used for further transformations without being chromatographed.

* Corresponding author.

Table 1. Cobalt-mediated addition of α-halo compounds to (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde **1**

α -Halo compound	Product	Yield (%)	Ligand	Procedure[a]	3,4 anti/ 3,4-syn	2,3-anti/ 2,3-syn
Methyl Bromoacetate	 **2a**	90[b]	Ph_3P	B	94/6	
tert-Butyl Bromoacetate	 **2b**	70[b,c] 66 73	Me_3P Ph_3P Ph_3P	A A B	75/25 78/22 83/17	
Methyl 4-Bromocrotonate	 **2c**	57 75[b] 78	Ph_3P Me_3P Ph_3P	A B B	67/33 83/17 85/15	64/36 75/25 78/22
α-Bromo-γ-butyrolactone	 **2d**	54 80[b]	Ph_3P Ph_3P	A B	ref. 13	ref. 13
2-Bromoacetophenone	 **3a**	70[b]	Me_3P	B	89/11[d]	
2-Bromo-4'-methoxy-acetophenone	 **3b**	60	Me_3P	A	> 95/<5[e]	
2-Bromopropiophenone	 **3c**	66 81[b]	Ph_3P Me_3P	A B	98/<2[e] 98/<2[e]	ref. 14
1-Bromo-3,3-dimethyl-2-butanone	 **3d**	80[b,c]	Me_3P	A	> 95/<5[e]	
3-Iodo-2-butanone	 **3e**	50[f] 61[b,f]	Me_3P Me_3P	A B	98/<2[e] 98/<2[e]	57/43[g] 60/40[g]

a)Procedure A (stoichiometric in Co(0)-complex): the halocompound and 1 were added to the Co-complex in a 1/1/1 molar ratio at 0°C. Procedure B (substoichiometric in Co(0)-complex): the halocompound and 1 were added to the Co-complex in a 10/10/1 molar ratio at 0 °C. b) Yield determined by ^1H NMR. c) The crude material was dissolved in ethyl acetate and washed with a saturated EDTA solution (bisodium salt). d) In one run, after flash-chromatography the yield was 54 % and the diastereoisomeric ratio 80/20. e) The other diastereoisomers were detected in traces in the ^1H NMR spectrum. f) Yield calculated from 3-chloro-2-butanone. g) The ratio refers to the two diastereoisomers which were identified and characterised (98% of the total diastereoisomeric mixture).

The configuration of the new stereocentres created during the addition has been assigned by NMR analysis of the compounds **2** and **3**. The 2,3-*syn* and *anti* relationships were based on the ^1H NMR vicinal coupling constant $J_{2,3}$ [$J_{2,3}$ (*anti*)>$J_{2,3}$ (*syn*)][7] and on the ^{13}C NMR resonances of C_2 and C_3[8] and assuming hydrogen-bonded structures in a chair conformation with the maximum number of R substituents equatorial. In addition, H-3 resonates at higher field in the 2,3-*anti* isomer. The 3,4-*syn* and *anti* relationship was suggested by comparison of the ^1H NMR chemical shifts of the CHO and CH_2O

with the reported pattern in a variety of compounds.[9,10] In almost all cases the *anti* isomer showed two separable multiplets or a complex multiplet at 3.8–4.0 δ, whereas separated multiplets were observed in the *syn* isomers. In addition, in compounds **2a**, **2b**, **3a** and **3b**, the signals of the methylene protons at C-2 (α to the ester or keto group) were less separated in the *syn* isomer giving an AA′ (or even an A_2) rather than an AB system as observed in the *anti* isomer. Based on NMR analysis, predominant formation of the 3,4- and 2,3-*anti* configuration was generally observed: the former being higher than the latter. In some cases, when the reaction was performed under substoichiometric conditions with respect to cobalt, an enhancement of the 3,4-*anti* preference was observed.[11]

The cobalt-mediated addition of activated halogen compounds, and in particular of haloesters, to carbonyl compounds offers several advantages compared to the similar zinc-mediated Reformatsky reactions, the most notable being milder conditions and higher yields of the addition product.[12] Compounds **2** and **3** can be useful starting material for functionalized 2-deoxy sugars via removal of the protecting acetal function and reduction of the ester moiety, followed by cyclization. Alternatively, the sequence: reduction of the ester moiety to an aldehyde and cobalt-mediated additions of the haloester, could be repeated on compounds **2a–2d** to give polyhydroxylated compounds of variable size.

In conclusion, the cobalt-mediated Reformatsky-type and aldol-type additions of halo compounds to protected glyceraldehyde proceed cleanly and smoothly both under stoichiometric and substoichiometric conditions with respect to cobalt and represent a valid supplement to the existing procedures.

Experimental

General

Trimethylphosphine (1 M solution in tetrahydrofuran), triphenylphosphine, anhydrous tetrahydrofuran (THF) and ACS reagent tetrahydrofuran, were purchased from Aldrich and used as received. Anhydrous cobalt(II) chloride was heated at 120–150°C for 2 h prior to use. Magnesium metal (as turnings) was activated by treatment with a solution of 1,2-dichloroethane in THF followed by washing with THF. α-Chloroketones, α-bromoketones and α-bromoesters were purchased from Aldrich and used as received. (*R*)-2,3-*O*-Cyclohexylideneglyceraldehyde was prepared as described in the literature.[9] 3-Iodo-2-butanone was prepared from 3-chloro-2-butanone (Aldrich) by reaction with KI in tetrahydrofuran/dimethylformamide and directly used. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained with Varian XL-200 and Bruker AC-300 instruments. Protons at C_2–C_5 were assigned by double resonance experiments. Thin layer chromatography (TLC) was carried out on silica gel plates (60 F254, Merck); zones were detected visually by ultraviolet irradiation (254 nm) or by spraying with methanol:H_2SO_4 (9:1) followed by heating at 100°C. The diastereoisomeric products, depending on their structure, were partially or completely separated by flash-chromatography (silica gel, eluting with ethyl acetate:n-hexane). When partial separation occurred, enriched mixtures of diastereoisomers were obtained, in which the main component percentage ranged from 85 to 96%. The diastereoisomeric ratios were determined by analysis of the NMR (^{1}H and ^{13}C) spectra run at 300 MHz.

The tetrakis(trimethylphosphine)cobalt(0), [Co{$P(CH_3)_3$}$_4$] was prepared as previously reported.[1]

Preparation of the low-valent cobalt–triphenylphosphine complex

Activated magnesium turnings (300 mg), anhydrous cobalt(II) chloride (130 mg, 1 mmol), and triphenylphosphine (1.05 g, 4 mmol) were added to THF (4 mL). The mixture was stirred until the original blue colour turned to brown. The clear supernatant solution was transferred by syringe to another flask immediately before use.

Typical procedure for the cobalt-mediated stoichiometric reactions using triphenylphosphine as a ligand to cobalt

The solution of the Co–triphenylphosphine complex prepared as described above was treated dropwise with a solution containing 2-bromopropiophenone (1 mmol) and (*R*)-2,3-*O*-

cyclohexylideneglyceraldehyde **1** (1 mmol) in THF (4 mL) at 0°C. The progress of the reaction was monitored by TLC (ethyl acetate:n-hexane=20:80). When the organic reagents were no longer present, the solution was diluted with ethyl acetate (4 mL), poured into crushed ice:0.1 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic solutions were washed with water, dried (Na_2SO_4), and evaporated to dryness. The crude material was flash-chromatographed over silica gel (ethyl acetate:n-hexane=15:85) and gave two main diastereoisomers of **3c**.

Typical procedure for cobalt-mediated stoichiometric reactions using trimethylphosphine as a ligand to cobalt

A 1 M solution of trimethylphosphine in THF (6 mL) was added to a mixture of activated magnesium turnings (350 mg) and anhydrous $CoCl_2$ (195 mg, 1.5 mmol) in THF (3 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere until a dark brown colour developed. The excess of magnesium was filtered off, and to the resulting solution were added dropwise 1-bromo-3,3-dimethyl-2-butanone (268 mg, 1.5 mmol) and (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde **1** (318 mg, 1.5 mmol) in THF (3 mL). The progress of the reaction was monitored by TLC (ethyl acetate:n-hexane=20:80). When the organic reagents were no longer present, the solution was diluted with ethyl acetate (5 mL), poured into crushed ice:0.1 N HCl, and extracted with ethyl acetate (3×10 mL). The combined organic solutions were washed with water, dried (Na_2SO_4), and evaporated to dryness.

The crude material was chromatographed over silica gel (ethyl acetate:n-hexane=15:85; silica gel:substrate=10:1) and afforded 80% of **3d**.

In another run, the crude material was dissolved in ethyl acetate (10 mL) and stirred with a saturated solution of EDTA disodium salt dihydrate (5 mL) until the organic phase turned colorless. The organic phase was washed with water, dried and the solvent removed under reduced pressure to afford a residue which was directly analysed by NMR spectroscopy.

Typical procedure for the cobalt-mediated substoichiometric reactions using trimethylphosphine as a ligand to cobalt

A 1 M solution of trimethylphoshine (1.6 mL) in THF was added to a mixture of activated magnesium turnings (300 mg) and anhydrous $CoCl_2$ (52 mg, 0.4 mmol) in THF (2 mL). The reaction was stirred at room temperature until the yellow–brown colour of the low-oxidation-state cobalt complex developed. The mixture was then cooled at 0°C, and a THF solution (5 mL) of 2-bromopropiophenone (580 µl, 3.5 mmol) and (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde **1** (0.69 g, 3.5 mmol) was added dropwise at 0°C: the speed of addition was modulated so as to preserve the original brown colour and reduce to a minimum the time of development of the blue colour [Co(II)-complex]. At the end of the reaction, indicated by the persistence for a few minutes of the brown colour of the low-oxidation-state Co complex, the reaction mixture was diluted with ethyl acetate, poured into crushed ice:0.1 N HCl, and extracted three times with ethyl acetate as described above for the stoichiometric reactions. The organic layers were collected, dried (Na_2SO_4), and evaporated to dryness. The crude product was flash-chromatographed over silica gel (ethyl acetate:n-hexane=15:85) and gave two fractions with two main diastereoisomers of **3c** in 6:4 molar ratio and 81% total yield. One fraction contained only one diastereoisomer; the second fraction contained the other diastereoisomer impure by 7% of the first one.

4-(R) Methyl (4,5-O-cyclohexylidene)-3,4,5-tri-hydroxy-pentanoate 2a

Major diastereoisomer; 3,4-*anti*; ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 2.45 (1H, dd, J=15.8, 7.8 Hz), 2.70 (1H, dd, J=15.8, 3.9 Hz), 3.65 (3H, s), 3.85–4.0 (2H), 4.0–4.1 (2H); ^{13}C NMR ($CDCl_3$): 22.0 (t), 23.7 (t), 24.0 (t), 25.1 (t), 34.6 (t), 36.4 (t), 51.8 (q), 66.3 (t), 69.3 (d), 77.2 (d), 110.1 (s), 173.1 (s); MS, m/z: 244 (M^+). Calcd for $C_{12}H_{20}O_5$ C, 59.02; H, 8.20. Found: C, 59.20; H, 8.12.

4-(R) Methyl (4,5-O-cyclohexylidene)-3,4,5-tri-hydroxy-pentanoate 2a

Minor diastereoisomer; 3,4-*syn* (detected in the ^{1}H NMR spectrum of the mixture); ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 2.45 (2H, s), 3.63 (3H, s), 3.80 (1H, m), 3.90 (1H, m), 4.0 (2H); ^{13}C NMR ($CDCl_3$) (detected in the ^{13}C NMR spectrum): 22.0 (t), 24.0 (t), 25.6 (t), 36.0 (t), 37.4 (t), 38.1 (t), 51.3 (q), 65.2 (t), 68.3 (d), 77.2 (d), 110.1 (s), 173.1 (s); MS, m/z: 244 (M^+).

4-(R) tert-Butyl (4,5-O-cyclohexylidene)-3,4,5-tri-hydroxy-pentanoate 2b

Major diastereoisomer; 3,4-*anti*; ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.45 (9H, s), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.4 (1H, dd, J=15.9, 8.0 Hz), 2.64 (1H, dd, J=15.9, 2.7 Hz), 3.85–4.0 (3H), 4.05–4.15 (1H, m); ^{1}H NMR (C_5H_5N+D_2O): δ, 1.45 (9H, s), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.73 (1H, dd, J=15.0, 9.4 Hz), 2.98 (1H, dd, J=15.0, 3.8 Hz), 4.18–4.50 (3H), 4.48 (ddd, 1H, J=9.4, 6.5, 3.8 Hz); ^{13}C NMR ($CDCl_3$): 24.4 (t), 24.6 (t), 25.7 (t), 3×28.7 (q), 35.3 (t), 36.3 (t), 39.7 (t), 66.9 (t), 66.9 (d), 77.8 (d), 82.1 (s), 110.5 (s), 172.7 (s); MS, m/z: 286 (M^+). Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.81; H, 9.12.

Acetylated derivative; ^{1}H NMR ($CDCl_3$): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 1.45 (9H, s), 2.05 (3H, s), 2.50 (1H, dd, J=15.3, 7.5 Hz), 2.62 (1H, dd, J=15.3, 4.5 Hz), 3.75 (1H, dd J=7.5, 6.0 Hz), 4.01 (1H, dd, J=7.5, 6.0 Hz), 4.15 (1H, ddd, J=6.0, 6.0, 6.0 Hz), 5.25 (1H, ddd, J=7.5, 6.0, 4.5 Hz); ^{13}C NMR: 21.0 (q), 23.7 (t), 23.9 (t), 25.1 (t), 3×28.0 (q), 34.6 (t), 35.9 (t), 37.1 (t), 65.9 (t), 70.8 (d), 75.8 (d), 81.1 (s), 110.5 (s), 169.4 (s); MS, m/z: 328 (M^+).

4-(R) tert-Butyl (4,5-O-cyclohexylidene)-3,4,5-tri-hydroxy-pentanoate 2b

Minor diastereoisomer; 3,4-*syn* (detected in the ^{1}H NMR spectrum of the mixture): ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.45 (9H, s), 1.30–1.45 (2H), 1.45–1.65 (10H), 2.80 (2H, J=5.0 Hz), 3.80 (1H, m), 4.0 (1H, m), 4.10 (1H, m); ^{1}H NMR (C_5D_5N+D_2O): δ, 1.4 (9H, s), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.78 (2H, J=5.0 Hz), 4.20 (3H), 4.55 (1H, ddd J=5.0, 5.0, 5.0 Hz); ^{13}C NMR ($CDCl_3$): 24.4 (t), 24.6 (t), 25.7 (t), 3×28.7 (q), 31.6 (t), 35.3 (t), 39.8 (t), 65.8 (t), 69.0 (d), 77.82 (d), 82.1 (s), 110.5 (s), 172.7 (s).

Acetylated derivative (detected in the spectrum of the mixture): ^{1}H NMR ($CDCl_3$): δ, 1.40 (9H, s), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.07 (3H, s), 2.51 (1H, J=16.5, 6.0 Hz), 2.58 (1H, dd, J=16.5, 3.0 Hz), 3.73 (1H, dd, J=7.5, 6.0 Hz), 3.98 (1H, dd, J=7.5, 6.05 Hz), 4.20 (1H, ddd, J=6.0, 6.0, 4.5 Hz), 5.32 (1H, ddd, J=6.0, 4.5, 3.0 Hz); ^{13}C NMR ($CDCl_3$): 21.0 (q), 23.7 (t), 23.9 (t), 25.1(t), 3×27.9 (q), 29.7 (t), 34.6 (t), 37.1 (t), 65.0 (t), 69.8 (d), 75.3 (d), 81.1 (s), 110.4 (s), 169.9 (s).

4-(R) Methyl (4,5-O-cyclohexylidene)-3,4,5-tri-hydroxy-2-vinyl-pentanoate 2c

3,4-*anti*/2,3-*anti* (40% of the total diastereoisomeric mixture in the stoichiometric reaction; 60% of the total diastereoisomeric mixture in the substoichiometric reaction using trimethylphosphine as a ligand to cobalt; 63% of the total diastereoisomeric mixture in the substoichiometric reaction using triphenylphosphine as a ligand to cobalt); ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 3.26 (1H, dd, J=8.6, 6.8 Hz), 3.68 (1H, ddd, J=7.0, 7.0, 7.0 Hz), 3.70 (3H, s), 3.87 (1H, dd, J=7.0, 6.8 Hz), 3.90–4.0 (2H), 5.22 (1H, d, J=9.0 Hz), 5.23 (1H, d, J=16 5 Hz), 5.90 (1H, ddd, J=16.5, 9.0, 8.6 Hz); ^{13}C NMR ($CDCl_3$): 24.4 (t), 24.5 (t), 25.7 (t), 35.3 (t), 36.9 (t), 52.7 (d), 52.6 (q), 65.8 (t), 73.4 (d), 76.8 (d), 110.1 (s), 120.0 (t), 132.9 (d), 170.0 (s); MS, m/z: 270 (M^+). Calcd for $C_{14}H_{22}O_5$: C, 62.21; H, 8.20. Found: C, 62.51; H, 8.23.

Acetylated derivative; ^{1}H NMR ($CDCl_3$): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 2.04 (3H, s), 3.35 (1H, dd, J=9.0, 6.5 Hz), 3.68 (3H, s), 3.80 (1H, dd, J=7.5, 6.3 Hz), 3.97 (1H, dd, J=7.5, 6.2 Hz), 4.20 (1H, ddd, J=6.5, 6.3, 6.2 Hz), 5.19 (1H, d, J=17.4 Hz), 5.22 (1H, d, J=10.0 Hz), 5.38 (1H, dd, J=6.5, 6.5 Hz), 5.90 (1H, ddd, J=17.4, 10.0, 9.0 Hz); MS, m/z: 312 (M^+).

4-(R) Methyl (4,5-O-cyclohexylidene)-3,4,5-tri-hydroxy-2-vinyl-pentanoate 2c

3,4-*anti*/2,3-*syn* (27% of the total diastereoisomeric mixture in the stoichiometric reaction; 23% of the total diastereoisomeric mixture in the substoichiometric reaction using trimethylphosphine as a

ligand to cobalt; 22% of the total diastereoisomeric mixture in the substoichiometric reaction using triphenylphosphine as a ligand to cobalt); ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 3.38 (1H, dd, J=9.0, 2.0 Hz), 3.72 (3H, s), 3.70–4.10 (4H), 5.23 (1H, d, J=12.0 Hz), 5.25 (1H, d, J=8.0 Hz), 5.92 (1H, ddd, J=12.0, 9.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$): 24.4 (t), 24.5 (t), 25.7 (t), 35.3 (t), 36.9 (t), 52.7 (d) 52.6 (q), 65.7 (t), 73.3 (d), 76.5 (d), 110.1 (s), 121.67 (t), 132.7 (d), 170.0 (s); MS, m/z: 270 (M^+).

Acetylated derivative; ^{1}H NMR ($CDCl_3$): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 2.04 (3H, s), 3.40 (1H, dd, J=9.5, 6.5 Hz), 3.72 (3H, s), 3.70–3.72 (2H), 4.05 (1H, ddd, J=6.5, 6.5, 6.5 Hz), 5.19 (1H, d, J=17.4 Hz), 5.22 (1H, d, J=10.0 Hz), 5.29 (1H, dd, J=6.5, 6.5 Hz), 5.82 (1H, ddd, J=17.4, 10.0, 9.5 Hz); MS, m/z: 312 (M^+).

*4-(*R*) Methyl (4,5-*O*-cyclohexylidene)-3,4,5-tri-hydroxy-2-vinyl-pentanoate* **2c**

3,4-*syn*/2,3-*anti* (24% of the total diastereoisomeric mixture in the stoichiometric reaction; 15% in the substoichiometric reaction using trimethylphosphine as a ligand to cobalt; 15% of the total diastereoisomeric mixture in the substoichiometric reaction using triphenylphosphine as a ligand to cobalt) identified in the ^{1}H NMR spectrum by the H-2 signal at 3.28 δ (dd, J=8.0, 8.0 Hz).

Acetylated derivative (signals identified in the ^{1}H NMR spectrum); ^{1}H NMR ($CDCl_3$): δ, 1.30–1.45 (2H), 1.50–1.65 (8H), 2.03 (3H, s), 3.59 (1H, dd, J=9.5, 9.5 Hz), 3.72 (3H, s), 3.93 (1H, dd, J=6.0, 6.0 Hz), 3.70 (1H, dd, J=6.0, 6.0 Hz), 4.18 (1H, ddd, J=6.0; 6.0, 3.5 Hz), 5.21 (1H, dd, J=9 5, 3.5 Hz).

*4-(*R*) Methyl (4,5-*O*-cyclohexylidene)-3,4,5-tri-hydroxy-2-vinyl-pentanoate* **2c**

3,4-*syn*/2,3-*syn* (9% of the total diastereoisomeric mixture in the stoichiometric reaction; 2% in the substoichiometric reaction using trimethylphosphine as a ligand to cobalt; not isolated in the substoichiometric reaction using triphenylphosphine as a ligand to cobalt) identified in the ^{1}H NMR spectrum by the H-2 signal at 3.15 δ (dd, J=9.0, 6.0 Hz).

Acetylated derivative; identified in the ^{1}H NMR spectrum by the H-3 signal at 3.35 δ (1H, m).

*2′-(*R*) (α-[(2′,3′-O-Cyclohexylidene)-1′,2′,3′-tri-hydroxypropyl]-γ-butyrolactone* **2d**

The crude material was partially separated by flash chromatography and gave two fractions mainly composed of one diastereoisomer named L_1 and L_4 respectively.

The signals in the ^{1}H NMR spectrum were overlapping in $CDCl_3$ and were partially resolved using C_5D_5N.

^{1}H NMR ($CDCl_3$+D_2O) (mixture of diastereoisomers): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 2.17 (1H, m), 2.45 (1H, m), 2.8 (1H, m), 3.60–4.10 (3H), 4.10–4.45 (3H); MS, m/z: 256 (M^+). Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.02; H, 7.91.

L_1 **2d** (23% of the total diastereoisomeric mixture in the stoichiometric reaction; 47% in the substoichiometric reaction); ^{1}H NMR (C_5D_5N+D_2O): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 2.2–2.5 (2H), 3.3 (1H, ddd, J=8.0, 8.0, 3.2 Hz), 4.12 (1H, dd, J=8.2, 3.2 Hz), 4.30 (1H, dd, J=12.0, 6.0 Hz), 4.10–4.40 (3H), 4.72 (1H, ddd, J=8.2, 6.0, 6.0 Hz); ^{13}C NMR (C_5D_5N): 22.0 (t), 2×25.0 (t), 25.5 (t), 26.2 (t), 35.6 (t), 37.1 (t), 43.0 (d), 67.3 (t), 68.0 (t), 73.7 (d), 76.1 (d), 110.2 (s), 178.0 (s); ^{13}C NMR ($CDCl_3$): 2×23.8 (t), 25.1 (t). 26.4 (t), 34.7 (t), 36.3 (t), 43.2 (d), 67.1 (t), 67.2 (t), 2×73.3 (d), 110.0 (s), 178.0 (s); MS, m/z: 256 (M^+).

L_1 *Acetylated derivative*; ^{1}H NMR ($CDCl_3$): δ, 1.30–1.45 (2H), 2.05 (3H, s), 2.18 (1H, m), 2.38 (1H, m), 3.05 (1H, ddd, J=9.0, 9.0, 3.0 Hz), 3.73 (1H, dd, J=9.0, 6.0 Hz), 4.12–4.32 (2H), 4.20 (1H, dd, J=9.0, 6.0 Hz), 4.46 (1H, ddd, J=8.0, 6.0, 6.0 Hz), 5.10 (1H, dd, J=8.0, 3.0 Hz); MS, m/z: 298 (M^+).

L_2 **2d** (22% of the total diastereoisomeric mixture in the stoichiometric reaction; 16% in the substoichiometric reaction) (signals detected in the spectrum of the mixture): ^{1}H NMR (C_5D_5N): δ, 1.30 1.45 (2H), 1.45–1.65 (8H), 2.97 (1H, m), 4.10–4.35 (3H), 4.81 (1H, dd, J=8.0, 8.0 Hz).

L_2 *Acetylated derivative*; ^{1}H NMR ($CDCl_3$) (signals detected in the spectrum of the mixture): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 2.1 (3H, s), 2.35–2.40 (2H), 2.88 (1H, m), 3.73 (1H, dd, J=9.0, 6.0 Hz), 4.42 (1H, dd, J=6.0, 5.5 Hz), 5.15 (1H, dd, J=5.2, 5.2 Hz).

L_3 **2d** (10% of the total diastereoisomeric mixture in the stoichiometric reaction; 15% in the substoichiometric reaction) (signals detected in the spectrum of the acetylated mixture);

L_3 *Acetylated derivative*; ^{1}H NMR (detected in the mixture) ($CDCl_3$): δ, 2.05 (3H, s), 2.94 (1H, ddd, J=9.0, 9.0, 4.5 Hz), 5.34 (1H, dd, J=4.5, 4.5 Hz).

L_4 **2d** (45% of the total diastereoisomeric mixture in the stoichiometric reaction; 22% in the substoichiometric reaction); ^{1}H NMR (C_5D_5N+D_2O): δ, 1.25–1.45 (2H), 1.45–1.65 (8H), 2.45 (1H, m), 2.7 (1H, m), 3.29 (1H, ddd, J=10.0, 10.0, 2.0 Hz), 4.10–4.35 (5H), 4.57 (1H, dd, J=8.8, 2.0 Hz); ^{13}C NMR ($CDCl_3$): 21.8 (t), 24.0 (t), 24.0 (t), 25.1 (t), 34.7 (t), 36.6 (t), 43.1 (d), 66.8 (t), 67.2 (t), 2×70.2 (d), 110.0 (s), 178.0 (s); ^{13}C NMR (C_5H_5N): 24.2 (t), 24.4 (t), 25.4 (t), 35.3 (t), 37.1 (t), 43.5 (d), 67.3 (t), 67.9 (t), 70.7 (d), 77.3 (d), 110.0 (s), 178.0 (s); MS, m/z: 256 (M^+).

L_4 *Acetylated derivative*; ^{1}H NMR ($CDCl_3$): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 2.01 (3H, s), 2.35–2.45 (2H), 3.02 (1H, ddd, J=9.0, 9.0, 3.0 Hz), 4.0 (1H, dd, J=9.0, 6.0 Hz), 4.04 (1H, ddd, J=6.0, 6.0, 6.0 Hz), 4.15–4.35 (3H), 5.34 (1H, dd, J=6.0, 3.0 Hz); MS, m/z: 298 (M^+).

[3-(R) (3,4-O-Cyclohexylidene)-2,3,4-tri-hydroxybutyl] phenyl ketone ***3a***

Major diastereoisomer; 3,4-*anti*; ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 3.12 (1H, dd, J=15.8, 7.9 Hz), 3.40 (1H, dd, J=15.8, 3.2 Hz), 4.0–4.15 (4H), 7.45 (5H); ^{13}C NMR ($CDCl_3$): 2×23.8 (t), 24.0 (t), 34.7 (t), 36.5 (t), 41.8 (t), 66.8 (t), 69.6 (d), 77.3 (d), 110.4 (s), 120.0 (d), 120.4 (d), 128.2 (d), 128.6 (d), 135.5 (d), 136.7 (s), 200.7 (s); MS, m/z: 290 (M^+). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.55. H, 7.85.

[3-(R) (3,4-O-Cyclohexylidene)-2,3,4-tri-hydroxybutyl] phenyl ketone ***3a***

Minor diastereoisomer; 3,4-*syn*; (detected in the ^{1}H NMR spectrum of the mixture); ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.30–1.45 (2H), 1.46–1.65 (8H), 3.15 (1H, dd, J=15.0, 4.3 Hz), 3.22 (1H, dd, J=15.0, 6.9 Hz), 3.92 (2H), 4.05 (1H, m), 4.3 (1H, m), 7.5 (5H).

[3-(R) (3,4-O-Cyclohexylidene)-2,3,4-trihydroxybutyl] (4′-methoxy)-phenyl ketone ***3b***

3,4-*anti*; $[\alpha]_D$=−26.0 (c=0.004 g/mL; $CHCl_3$) ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.35–1.45 (2H), 1.45–1.65 (8H), 3.05 (1H, dd, J=18.0, 7.5 Hz), 3.65 (1H, dd, J=18.0, 2.7 Hz), 3.9 (3H, s), 4.08 (1H, m), 4.41 (3H), 6.92 (2H, d, J=7.9 Hz), 7.95 (2H, d, J=7.9 Hz); ^{1}H NMR (C_5H_5N+D_2O): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 3.05 (1H, dd, J=18.0, 7.5 Hz), 3.65 (1H, dd, J=18.0, 2.7 Hz), 3.70 (3H, s), 4.0–4.10 (3H), 4.70 (1H, ddd, J=7.0, 7.0, 4.5 Hz), 7.0 (2H, d, J=7.9 Hz), 8.18 (2H, d, J=7.9 Hz); ^{13}C NMR ($CDCl_3$): 24.5 (t), 24.5 (t), 24.8 (t), 35.6 (t), 32.3 (t), 42.2 (t), 56.1 (q), 67.5 (t), 70.3 (d), 70.7 (d), 110.8 (s), 2×114.6 (d), 131.0 (s), 2×131.3 (d), 164.2 (s), 199.5 (s); MS, m/z: 320 (M^+). Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.60; H, 7.45.

Acetylated derivative; ^{1}H NMR ($CDCl_3$): δ, 1.30–1.45 (2H), 1.45–1.65 (8H), 1.98 (3H, s), 3.19 (1H, dd, J=16.5, 4.5 Hz), 3.31 (1H, dd, J=16.5, 9.0 Hz), 3.81 (1H, dd, J=9.0, 6.0 Hz), 3.85 (3H, s), 4.06 (1H, dd, J=9.0, 6.4 Hz), 4.27 (1H, ddd, J=6.4, 6.0, 6.0 Hz), 5.44 (1H, ddd, J=9.0, 6.0, 4.5 Hz), 6.93 (2H, d, 8.4 Hz), 7.94 (2H, d, 8.4 Hz); MS, m/z: 362 (M^+).

[4-(R) (4,5-O-Cyclohexylidene)-3,4,5-trihydroxypentyl] phenyl ketone ***3c***

Major diastereoisomer; 3,4-*anti* (the 2,3-configuration is doubtful as $J_{2,3}$ are very similar) (52% of the total diastereoisomeric mixture in the stoichiometric reaction; 59% of the total diastereoisomeric mixture in the substoichiometric reaction); ^{1}H NMR ($CDCl_3$+D_2O): δ, 1.3 (3H, d, J=7.5 Hz), 1.30–1.45 (2H), 1.45–1.65 (8H), 3.83 (1H, dq, J=7.5, 7.5, 7.5, 3.0 Hz), 3.88 (1H, m), 3.94 (1H, dd, J=3.0, 8.0 Hz), 3.95 (1H, m), 4.10 (1H, m), 7.49 (2H, d, J=8.0 Hz), 7.55 (2H, dd, J=8.0, 8.0 Hz), 8.0 (1H, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$): 10.6 (q), 23.8 (t), 24.0 (t), 25.1 (t), 34.2 (t), 36.6 (t), 41.1 (d), 67.2 (t), 72.7 (d), 74.5 (d), 109.6 (s), 2×128.6 (d), 2×128.8 (d), 133.5 (d), 135.6 (s), 205.7 (s); MS, m/z: 304 (M^+). Calcd for $C_{18}H_{24}0_4$: C, 71.04; H, 7.95. Found: C, 70.95; H, 7.85.

Acetylated derivative; $[\alpha]_D$=−34.3 (c=0.029 g/mL; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ, 1.25 (3H, d, J=7.0 Hz), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.0 (3H, s), 3.72 (1H, dd, J=9.0, 6.0 Hz), 3.95 (1H, dq,

J=7.0, 7.0, 7.0, 4.0 Hz), 3.99 (1H, dd, J=9.0, 6.0 Hz), 4.17 (1H, ddd, J=8.0, 6.0, 6.0 Hz), 5.28 (1H, dd, J=8.0, 4.0 Hz), 7.48 (2H, d, J=8.0 Hz), 7.52 (2H, dd, J=8.0, 8.0 Hz), 7.95 (1H, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$): 11.1 (q), 20.7 (q), 2×23.7 (t), 23.8 (t), 2×36.1 (t), 41.5 (d), 66.6 (t), 74.2 (d), 74.6 (d), 110.4 (s), 2×128.4 (d), 2×128.6 (d), 133.0 (d), 136.4 (s), 169.8 (s), 201.0 (s); MS, m/z: 346 (M^+).

[4-(R) (4,5-O-Cyclohexylidene)-3,4,5-trihydroxypentyl] phenyl ketone ***3c***

Minor diastereoisomer; 3,4-*anti* (the 2,3-configuration is doubtful as $J_{2,3}$ are very similar) (46% of the total diastereoisomeric mixture in the stoichiometric reaction; 39% of the total diastereoisomeric mixture in the substoichiometric reaction); $[\alpha]_D=-29.0$ (c=0.049 g/mL; $CHCl_3$); ^1H NMR ($CDCl_3+D_2O$): δ, 1.35 (3H, d, J=7.0 Hz), 1.30–1.45 (2H), 1.45–1.65 (8H), 3.64 (1H, dd, J=4.0, 8.0 Hz), 3.88 (1H, dq, J=7.0, 7.0, 7.0, 4.0 Hz), 3.88 (1H, m), 3.95 (1H, m), 4.10 (1H, m) 7.49 (2H, dd, J=8.0 Hz), 7.55 (2H, dd, J=8.0, 8.0 Hz), 8.0 (1H, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$): 15.5 (q), 23.6 (t), 24.0 (t), 25.1 (t), 34.6 (t), 36.5 (t), 40.5 (d), 67.2 (t), 76.2 (d), 76.7 (d), 109.9 (s), 2×128.5 (d), 3×133.6 (d), 136.5 (s), 207.0 (s); MS, m/z: 304 (M^+). Calcd for $C_{18}H_{24}O_4$: C, 71.04; H, 7.95. Found: C, 71.05; H, 7.85.

Acetylated derivative; $[\alpha]_D=21.1$ (c=0.005 g/mL; $CHCl_3$) ^1H NMR ($CDCl_3$): δ, 1.25 (3H, d, J=7.5 Hz), 2.0 (3H, s), 1.30–1.45 (2H), 1.45–1.65 (8H), 3.75 (1H, dd, J=6.0, 9.0 Hz), 3.90 (1H, dq, J=7.5, 7.5, 7.5, 6.0 Hz), 3.98 (1H, dd, J=6.0, 9.0 Hz), 4.18 (1H, ddd, J=6.0, 6.0, 6.0 Hz), 5.32 (1H, dd, J=6.0, 6.0 Hz), 7.48 (2H, d, J=8.0 Hz), 7.51 (2H, dd, J=8.0, 8.0 Hz), 8.02 (1H, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$): 12.2 (q), 20.8 (q), 23.7 (t), 23.8 (t), 25.1 (t), 34.6 (t), 35.8 (t), 42.5 (d), 66.0 (t), 74.1 (d), 74.6 (d), 110.3 (s), 3×128.6 (d), 2×133.0 (d), 136.8 (s), 160.5 (s), 68.5 (s), 199.9 (s); MS, m/z: 346 (M^+).

[3-(R) (3,4-O-Cyclohexylidene)-2,3,4-trihydroxybutyl] tert-butyl ketone ***3d***

3,4-*anti*; ^1H NMR ($CDCl_3+D_2O$): δ, 1.45 (9H, s), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.37 (1H, dd, J=16.0, 8.0 Hz), 2.61 (1H, dd, J=16.0, 3.0 Hz), 3.85–4.05 (3H), 4.08 (1H, m); ^{13}C NMR ($CDCl_3$): 23.7 (t), 24.0 (t), 25.1 (t), 3×28.1 (q), 34.7 (t), 36.3 (t), 38.9 (t), 66.4 (t), 69.4 (d), 77.3 (d), 81.4 (s), 109.9 (s), 172.2 (s); MS, m/z: 270 (M^+). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64. H, 9.69. Found: C, 66.84. H, 9.69.

2-[4-(R) (4,5-O-Cyclohexylidene)-3,4,5-trihydroxypentyl] methyl ketone ***3e***

3,4-*anti*/2,3-*anti* (56% of the total diastereoisomeric mixture in the stoichiometric reaction; 59% of the total diastereoisomeric mixture in the substoichiometric reaction); ^1H NMR ($CDCl_3+D_2O$): δ, 1.2 (3H, d, J=6.6 Hz), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.2 (3H, s), 2.88 (1H, dq, J=7.0, 7.0, 7.0, 5.5 Hz), 3.55 (1H, dd, J=6.5, 5.5, Hz), 3.87 (1H, ddd, J=6.5, 6.5, 6.5 Hz), 3.94 (1H, dd, J=6.5, 6.2 Hz), 4.03 (1H, dd, J=6.5, 6.2 Hz); ^{13}C NMR ($CDCl_3$): 13.9 (q), 23.8 (t), 24.0 (t), 25.1 (t), 30.2 (q), 34.7 (t), 36.4 (t), 47.1 (d), 66.5 (t), 75.1 (d), 76.6 (d), 109.9 (s), 214.5 (s); MS, m/z: 242 (M^+). Calcd for $C_{13}H_{22}O_2$: C, 64.44; H, 9.15. Found: C, 64.34; H, 9.10.

Acetylated derivative; ^1H NMR ($CDCl_3$): δ, 1.12 (3H, s, J=7.0 Hz), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.20 (3H, s), 2.84 (1H, dq, J=7.0, 7.0, 7.0, 6.0 Hz), 3.72 (1H, dd, J=7.5, 6.0 Hz), 3.97 (1H, dd, J=7.5, 6.0 Hz), 4.13 (1H, ddd, J=6.0, 6.0, 6.0 Hz), 5.22 (1H, dd, J=6.0, 6.0 Hz); ^{13}H NMR ($CDCl_3$): 11.4 (q), 20.9 (q), 23.8 (t), 23.8 (t), 25.0 (t), 28.8 (q), 34.6 (t), 35.6 (t), 48.8 (d), 66.3 (t), 73.9 (d), 74.1 (d), 110.4 (s), 169.9 (s), 207.7 (s); MS, m/z: 284 (M^+).

2-[4-(R) (4,5-O-Cyclohexylidene)-3,4,5-trihydroxypentyl] methyl ketone ***3e***

3,4-*anti*/2,3-*syn*; minor diastereoisomer (42% in the stoichiometric reaction; 39% in the substoichiometric reaction): ^1H NMR ($CDCl_3+D_2O$): δ, 1.15 (3H, d, J=7.5 Hz), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.18 (3H, s), 2.84 (1H, dq, J=7.5, 7.5, 7.5, 3.0 Hz), 3.85 (1H, dd, J=9.0, 3.0 Hz), 3.85–3.95 (2H), 4.0 (1H, m); ^{13}C NMR ($CDCl_3$): 10.0 (q), 23.7 (t), 23.9 (t), 25.1 (t), 28.8 (q), 34.7 (t), 36.5 (t), 48.1 (d), 67.1 (t), 72.0 (d), 74.9 (d), 109.8 (s), 213.5 (s); MS, m/z: 242 (M^+).

Acetylated derivative; ^1H NMR ($CDCl_3$): δ, 1.08 (3H, d, J=7.5 Hz), 1.30–1.45 (2H), 1.45–1.65 (8H), 2.2 (3H, s), 2.93 (1H, dq, J=7.5, 7.5, 7.5, 3.8 Hz), 3.75 (1H, dd, J=7.5, 5.0 Hz), 3.98 (1H, m),

4.07 (1H, m), 5.24 (1H, dd, J=7.5, 3.8 Hz); ^{13}C NMR ($CDCl_3$): 10.1 (q), 20.7 (q), 2×23.9 (t), 25.1 (t), 28.7 (q), 34.80 (t), 36.3 (t), 48.1 (d), 66.7 (t), 73.4 (d), 74.6 (d), 111.0 (s), 170.0 (s), 208.8 (s); MS, m/z: 284 (M^+). Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.29; H, 8.55.

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5. Trimethyl phosphine should be, however, preferred with reaction products unstable with respect to chromatography. Cobalt derivatives present in the organic phase can be separated by washing with a saturated EDTA sodium salt solution.
6. To investigate whether an organomagnesium compound might be involved, parallel experiments were performed adding the α-halo compound and (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde to magnesium alone in tetrahydrofuran. The amount of halo compound, aldehyde and magnesium were the same in both series of experiments and so were the other experimental conditions (temperature, time of reaction, speed of stirring). The reactions in the absence of cobalt were generally slower, less reproducible and required a variable period of induction. Once started the reaction afforded a mixture of products.
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10. Definitive and unequivocal stereochemical assignment, with particular reference to the 3,4-positions will, however, come from correlation to known compounds.
11. A tentative explanation could be the presence in solution of magnesium salts which may favour the β-chelation model with respect to α-chelation model and therefore reinforce the *anti*-selectivity according to the Felkin–Anh model. Magnesium bromide, however, was not effective in this respect in the addition of furyllithium to protected glyceraldehyde (Mukaiyama, T.; Suzuki, K; Yamada, T; Tabusa, F. *Tetrahedron* **1990,** *46,* 265–276).
12. In this particular case the classical Reformatsky reaction between tert-butyl α-bromoacetate and benzaldehyde did not proceed satisfactorily at room temperature.
13. In this case the stereochemical assignment was doubtful since $J_{2,3}$ were similar. Furthermore the CHO and CH_2O pattern was difficult to visualise due to the superimposition of the CH_2O of the lactone ring.
14. In this case the stereochemical assignment is doubtful since the $J_{2,3}$ are very similar (3.5 Hz and 3.0 Hz respectively). Other diastereoisomers were detected in traces in the NMR spectrum.

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