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La^{III}-Induced Addition of Tetrahydrofurfuryl Alcohol, Tetrahydropyran-2-ylmethanol, D-Gluconate, Methanol and Ethanol to Maleate

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La^{III}-mediated Michael-type addition of tetrahydrofurfuryl alcohol (thfa) and tetrahydropyran-2-ylmethanol (thpm) to maleate **1**, to form the corresponding alkoxybutanedioic acids in high yields (>89%) is described. Small amounts (<5%) of the products from competitive addition of water were formed when hydrated salts were used. Larger amounts of water interfere with this reaction. The extension of this reaction to D-gluconate **3**, methanol and ethanol, to prepare 2-[(D-gluconate)-2-*O*-yl]butanedioate **4**, methoxybutanedioic acid **2e** and ethoxybutanedioic acid **2f**, has also been achieved.

The search for new phosphate substitutes as detergent builders and co-builders has been an active field of research for the past two decades and much attention has been focused on organic polycarboxylates.[1] Compounds having α-oxycarboxylate structural units have been introduced since they form relatively stable water-soluble complexes with Ca^{II}, e.g., oxydiacetate (ODA),[2] carboxymethoxysuccinate (CMOS),[3,4] oxydisuccinate (ODS)[5] and carboxymethyltartronate (CMT).[6] Polysaccharides like starch, maltodextrins and inulin, have been oxidised by various vicinal-diol cleaving agents leading to polycarboxylates containing oxydiacetate residues with excellent Ca^{II} sequestering properties.[7–10] An important issue is and will be the biodegradability of the compounds and materials applied as (co-)builder. The synthetic polycarboxylates of the polyacrylic-type, presently applied as co-builder (together with zeolite NaA), are not biodegradable.

An interesting synthetic route to ether-carboxylates is the Michael-type addition of compounds containing hydroxy groups to α,β-unsaturated dicarboxylates mediated by multivalent metal ions. An example is the addition of, e.g., glycolate, glyoxylate, malate, tartrate, glycerol, etc., to maleate **1** in aqueous alkaline slurry (pH>11) in the presence of a large amount of Ca^{II}. Studies of this reaction using lanthanide, aluminium and titanium ions have been reported.[11–14] Open-chain polyhydroxy compounds are weak ligands for metal ions in aqueous media[15–17] and the La^{III}-catalysed addition of ethylene glycol, diethylene glycol and glycerol to maleate, could be performed, with the polyol-reactant as the solvent. The *O*-alkylation adducts were found to have potential as phosphate substitutes. The reaction was successfully extended to (*meso*)-erythritol and D-mannitol using small amounts of water as co-solvent.[14] However, cyclic polyols (cyclitols and sugars) only form stable complexes, in detectable quantities, with multivalent cations (e.g., Ca^{II} and La^{III}) in aqueous media when they possess three *syn*-axial hydroxy groups or three neighbouring hydroxy groups in an ax–eq–ax sequence for six-membered rings or a *cis–cis* sequence for five-membered rings.[18] Thus D-ribose is the only sugar, among all the sugars common in Nature, that complexes readily with metal ions in aqueous media. On the other hand, carbohydrates are known to be very soluble in anhydrous methanol containing sufficient calcium chloride, undoubtedly due to complex formation.[19] The introduction of carboxylate groups to cyclic sugars to produce acceptable detergent builders is still a major challenge and the lanthanide-catalysed *O*-alkylation by maleate in aqueous media seems to be a possible synthetic route. This is particularly the case for the addition of maleate to the exocyclic hydroxymethyl groups of sugars. The *O*-alkylation of polyols by maleate in aqueous media occurs in competition with the addition of water, the extent of which depends on the ability of the hydroxy group(s) of the polyol to form a complex by displacement of water

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molecules from the inner coordination sphere of the metal ions.

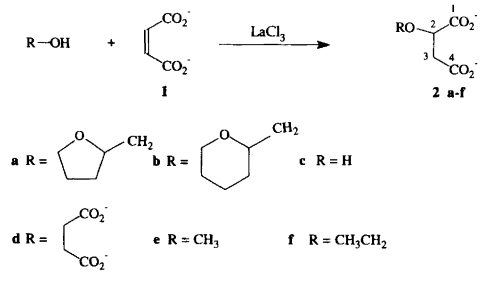
Addition of simple alcohols to the double bond in α,β-unsaturated dicarboxylates is rare in the literature. Alkoxy substituents, methoxy and ethoxy, have been introduced through several steps by alkylating hydroxy groups with prior protection of reactive functional groups, such carboxy groups, present in the starting compound and subsequent deprotection. Methoxybutanedioic acid **2e** was prepared from dimethyl fumarate and sodium methoxide in methanol while ethoxybutanedioic acid **2f** from diethyl fumarate, sodium ethoxide and ethanol by Purdie *et al.*[20] Attempts to prepare **2e** and **2f** from the potassium salts of maleic and fumaric acids with the corresponding sodium alkoxides were unsuccessful.[21] Compound **2e** has since been prepared from 2-hydroxybutanedioic acid,[22] 2-*O*-methyl-3-deoxy-D-mannose,[23] and 6-methoxytropan-3-one,[24] while **2f** has been prepared from 2-bromo-2-ethoxyacetyl chloride[25] and 2-ethoxy-2-butenediamide.[26]

We decided to investigate the scope of application of the La^{III}-mediated *O*-alkylation reaction. This paper deals with the *O*-alkylation of tetrahydrofurfuryl alcohol (thfa) and tetrahydropyran-2-ylmethanol (thpm), as simple models for furanose and pyranose forms, respectively, and with D-gluconate **3**, methanol and ethanol by maleate **1**.

Results and Discussion

La^{III}-Promoted O-alkylation of thfa and thpm by maleate. There was no observed reaction when a mixture of thfa (10 ml) and sodium maleate (**1**, 0.73 M) was heated at 90 °C. Furthermore, no reaction had occurred 23 h after addition of catalytic amounts of La^{III} (3 mol% with respect to **1**), added as $LaCl_3 \cdot 7H_2O$. Increasing the amount of $LaCl_3 \cdot 7H_2O$ to 90 mol% resulted in 84% conversion after 138 h forming **2a** (81%) and malate **2c** (3%), the side-product from addition of water (Scheme 1).

Plots of the formation of **2a** as a function of $LaCl_3 \cdot 7H_2O$ content are shown in Fig. 1. The initial reaction rate increased with increasing amounts of La^{III} present up to stoichiometric amounts. This suggests that a ternary complex [La^{III}(thfa)(**1**)] of La^{III} with the two reactants plays a key role in the reaction. Furthermore,



Scheme 1

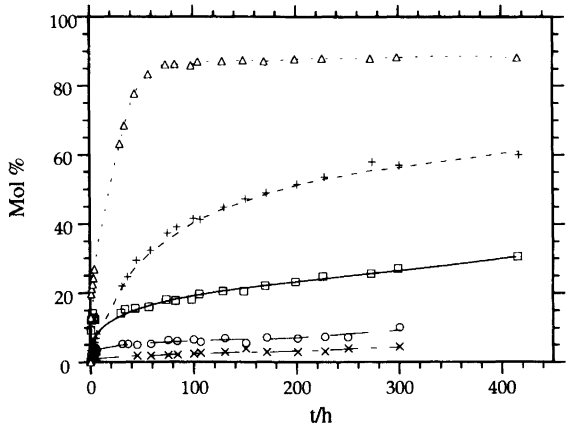


Fig. 1. The effect of La^{III} content (mol% w.r.t. **1**), added as $LaCl_3 \cdot 7H_2O$, on the *O*-alkylation of thfa by Na_2maleate$\cdot 2H_2O$ (**1**, 0.74 M) at 90 °C. Formation of **2a** as a function of La^{III}: (×) 10%, (○) 30%, (□) 60%, (+) 80% and (△) 100%.

these plots show that product inhibition occurs, probably due to chelation of La^{III} by **2a**. The solubility of this chelate appeared to be low, and therefore, La^{III} is withdrawn from the reaction mixture. The mechanism of this reaction is probably similar to that of the previously studied addition of glycolate to maleate.[11,13] Thus, La^{III} acts as a template and contributes to the reaction by lowering the pK_a of the hydroxy groups of the alcohol upon coordination. Previously, we have shown, by multinuclear NMR techniques, that thpm binds to Ln^{III} ions in a bidentate fashion forming a complex with a 1:2 metal:ligand stoichiometry. In this reaction the hydroxy donor is also the solvent. An attack by the activated OH group of thfa will lead to formation of the product **2a**. In addition, **2a** has a higher affinity for La^{III} than both thfa and **1** and so will preferentially be bound to La^{III} when formed.

Subsequent reactions were therefore carried out using equimolar amounts of La^{III} and at temperatures of 90 °C and above. The results from optimisation using equimolar amounts of La^{III} and **1** (0.74 M) are shown in Table 1. There was 91% conversion at 90 °C after 105 h (entry 1). The reaction went to completion at higher temperatures, the reaction time was considerably reduced and the amount of **2c** formed was less than 5% (entries 2–4). The concentration could also be increased to 1.25 M

Table 1. Effect of temperature on the *O*-alkylation of thfa.[a]

Entry	*t*/h	*T*/°C	Conversion (%)	**2a** (%)	**2c** (%)
1	105	90	91	87	4
2	19	116	98	95	3
3	15	127	98	94	4
4	7.7[b]	140	97	>96	<1

[a] $LaCl_3 \cdot 7H_2O$ (7.4 mmol, 0.74 M), **1** added as Na_2maleate$\cdot 2H_2O$ (7.4 mmol) and thfa (0.103 mol, 10ml) were used. [b] $LaCl_3 \cdot 1.8H_2O$ (25 mmol, 1.25 M), Li_2maleate$\cdot 1H_2O$ (25 mmol) and thfa (0.206 mol, 20 ml) were used.

when the lithium salt of **1** was used, and, by adding La^{III} as $LaCl_3 \cdot 1.8H_2O$, the reaction was complete after only 7.7 h at 140 °C (entry 4). In addition, only a trace amount (<1%) of **2c** was formed. The ratio of the diastereoisomers of **2a** was 2:3, which is attributed to the differences in steric strain in the reaction's intermediate complexes.[14,27]

The *O*-alkylation of thpm by **1** is analogous to thfa yielding the adduct **2b** (Scheme 1). This reaction proceeded throughout in the form of a slurry and the rate was lower (Table 2, entries 1–3). This is attributed to $LaCl_3$ not being completely soluble in thpm, even at 140 °C, because it is less polar. However, the reaction was virtually complete after 22 h at 140 °C, when the lithium salt of **1** (1.25 M) and $LaCl_3 \cdot 1.8H_2O$ (1.25 M) were used and afforded **2b** in good yield (93%) (entry 3). The advantage of using the lithium salt of **1** over the sodium salt is that it has a higher solubility. A smaller diastereomeric preference (4.5:5.5) was observed in this reaction.

If this reaction is to be extended to the furanose and pyranose sugars, which are solids, the best solvent will probably be water. It is therefore important to investigate the effect of using water as co-solvent. The two reactions discussed above were repeated using 40% (v/v) of water at 90 and 100 °C. No reaction occurred, the pH of the solutions being 5.[11] However, when the pH was adjusted to 7.0 with solid NaOH, the two reactions commenced forming **2a** (56%) from thfa, and **2b** (31%) from thpm, after 139 h at 90 °C. This steep increase in the reaction rate upon increasing the pH is in agreement with the reported dissociation constant of a Ln^{III}-bound $-CH_2OH$ group.[11] Substantial amounts of the water addition products, **2c** (33% in thfa and 37% in thpm) and oxydi(butanedioate) **2d** (6% in thfa and 7% in thpm), formed by addition of **2c** to **1**, were also present. After 43 h at 100 °C, **2a** (64%), **2c** (25%) and **2d** (8%) were formed from the reaction in thfa, while **2b** (23%), **2c** (35%) and **2d** (9%) were formed from the reaction in thpm. Small amounts of fumarate (up to 2%), from isomerisation of **1**, were also formed. The strong competition of water during the addition of thfa and thpm is in agreement with the previously observed relatively high preference of Ln^{III} for coordination of water compared to thpm.[28]

Table 2. Effect of temperature on the *O*-alkylation of thpm[a].

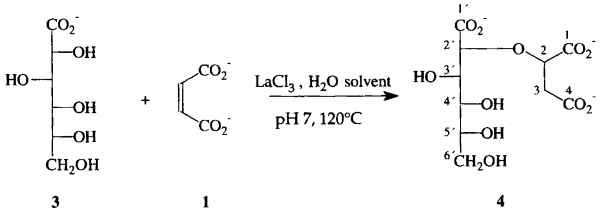
Entry	*t*/h	*T*/°C	Conversion (%)	**2b** (%)	**2c** (%)
1	166	123	88	83	5
2	144	128	94	92	2
3	22[b]	140	98	93	5

[a] $LaCl_3 \cdot 7H_2O$ (7.4 mmol, 0.74 M), **1** added as Na_2maleate$\cdot 2H_2O$ (7.4 mmol) and thpm (88 mmol, 10ml) were used. [b] $LaCl_3 \cdot 1.8H_2O$ (25 mmol, 1.25 M), Li_2maleate$\cdot 1H_2O$ (25 mmol) and thpm (0.177 mol, 20 ml) were used.

La^{III}-promoted O-*alkylation of sugars by maleate.* The *O*-alkylation reaction was performed with D-ribose using water as the solvent at 90 °C and initial pH 7. Equimolar quantities of D-ribose, **1** and $LaCl_3 \cdot 7H_2O$ (13.7 mmol, 0.457 M) were used and the predominant products formed were **2c** and **2d**, from addition of water to **1**. Similar results were obtained for D-lyxose, D-glucose, D-fructose, sucrose, methyl α- (and β)-D-galactopyranoside, methyl α- (and β) -D-glucopyranosides, D-(+)-galacturonate and D-glucuronate at 90, 100 and 110 °C. Increasing the concentration of the hydroxy compounds by up to six-fold did not result in any addition of the cyclic sugar substrates to **1**. This shows that in aqueous solution water replaces the sugars as nucleophile, thus leading to addition of water to form the adducts **2c** and **2d**.

The *O*-alkylation reaction was successfully extended to D-gluconate **3** using water as the solvent. The reaction was complete after 10.5 h at 120 °C by using La^{III} (25 mmol), **3** (50 mmol, 1.25 M) and **1** (46 mmol) at pH 6.7. The reaction was highly regioselective forming only the 2′-*O*-alkylated adduct **4** in 69% yield (Scheme 2). This result can be rationalised by assuming that, after complexing with the carboxylate group of **3**, La^{III} assists, preferentially, in the activation of the α-hydroxy group at C-2′ which is closest in space. The introduction of a carboxylate group confers on D-gluconate a higher affinity for La^{III} and thus prevents water from reacting. However, by increasing the water content (from 40 ml to 50 ml) in the reaction mixture, with respect to La^{III} (0.41 M), **3** (0.83 M) and **1** (0.74 M) at pH 7.6, up to 20% of malate **2c** was formed after 95% conversion of **1**. In addition, there was a high degree of diastereoselection. The ratio of the diastereoisomers was 1:8.6.

La^{III}-promoted O-*alkylation of methanol and ethanol by Maleate.* When equimolar quantities of **1** and $LaCl_3 \cdot 7H_2O$ (0.73 M) were refluxed in methanol (10 ml) no reaction occurred after several days. The reaction was therefore performed in an autoclave at higher temperatures (Table 3). Heating the reactants at 120 °C for 19 h resulted in a 27% conversion of **1** into the adducts **2e** (24%) and **2c** (3%) (entry 1 and Scheme 1). Methanol displays a lower nucleophilicity than water towards metal ions.[29] It is a monodentate ligand and therefore, has a lower affinity for La^{III} than the bidentate ligands thfa and thpm. Consequently, the concentration of the intermediate complex [La^{III}(MeOH)(**1**)] is relatively low,



3 **1** **4**

Scheme 2

Table 3. Effect of concentration of **1** and temperature on the *O*-alkylation of MeOH with **1**.

Entry	**1**:MeOH/mol l^{-1}	*t*/h	*T*/°C	Conversion (%)	**2e** (%)	**2c** (%)
1	0.73[a]	19	120	27	24	3
2	0.37[b]	6	150	99	89.5	9.5
3	1.00[c]	6	150	98	93	5
4	1.00[d]	6	150	100	97	3
5	1.00[e]	6	150	100	98.5	1.5

[a] $LaCl_3 \cdot 7H_2O$ (7.4 mmol), **1** added as Na_2maleate$\cdot 2H_2O$ (7.4 mmol) and (70 ml) were used. [b] $LaCl_3 \cdot 7H_2O$ (36.7 mmol), **1** added as Na_2maleate$\cdot 2H_2O$ (36.7 mmol) and MeOH (100 ml) were used. [c] Anhydrous $LaCl_3$ (50 mmol), **1** added as Na_2maleate$\cdot 2H_2O$ (50 mmol) and MeOH (50 ml) were used. [d] Anhydrous $LaCl_3$ (50 mmol), **1** added as Li_2maleate$\cdot H_2O$ (50 mmol) and MeOH (50 ml) were used. [e] $LaCl_3 \cdot 7H_2O$ (50 mmol) and **1** added as Li_2maleate$\cdot H_2O$ (50 mmol), pre-dehydrated with trimethyl orthoformate (0.425 mol, 45.12 g), and MeOH (50 ml) were used.

which leads to a relatively low reaction rate. Thus, by performing the reaction at 150 °C, the adducts **2e** (89%) and **2c** (10%) were formed after 6 h (entry 2). The water of hydration present in $LaCl_3 \cdot 7H_2O$ and sodium maleate **1** competes with the added methanol. When anhydrous $LaCl_3$ and Na_2maleate$\cdot 2H_2O$ or anhydrous $LaCl_3$ and Li_2maleate$\cdot 1H_2O$ were used 5% and 3% of **2c** were formed, respectively (entries 3 and 4). It was therefore necessary to perform the reactions under strictly anhydrous conditions to minimise or prevent the formation of **2c**. Co-dehydration of $LaCl_3 \cdot 7H_2O$ and **1** using trimethyl orthoformate (trimethoxymethane) [30,31] prior to performing the reaction gave the best results (entry 5), besides being the cheapest and easiest way to obtain the anhydrous salts so far.

The reaction was more difficult when extended to ethanol (Scheme 1 and Table 4). When $LaCl_3 \cdot 1.8H_2O$ (64.4 mmol), the lithium salt of **1** (68.5 mmol) and anhydrous EtOH (100 ml) were heated at 140 °C the adducts **2f** (14%) and **2c** (28%) were formed after 15 days (entry 1). There was an improvement at 150 °C when anhydrous $LaCl_3$ was used, with the formation of **2f** (56%) and **2c** (6%) (entry 2). Although EtOH has been shown to exhibit a similar coordinating ability to MeOH towards Co^{II} in concentrated solutions,[29,32] it is a weaker nucleophile because of the inductive effect of its ethyl group. The lower solubility of the reactants may play a role in the observed lower rate and incomplete reaction. The yield was improved by using anhydrous reagents and increasing the reaction temperature. There was a 98% conversion after 24 h at 175 °C to form **2f** (79.5%), **2c** (15.5%) and fumarate (3%, formed by isomerisation of **1**), when $LaCl_3 \cdot 7H_2O$ and the lithium salt of **1**, co-dehydrated with triethyl orthoformate, were used (entry 3). Although there is complete conversion above 175 °C this rather high temperature increases the side-reactions (entry 4–6, addition of water and isomerisation of **1**). The formation of substantial amounts of **2c** is attributed to residual water still present in EtOH and the other reagents used.

The metal-sequestering ability of the adducts was determined as the calcium-sequestering capacity (mmol of Ca^{II} that can be added per gram of ligand). The calcium-sequestering capacity of **4** was 5.4, which is good compared with trisodium nitrilotriacetate NTA (7.4) and is therefore a potential phosphate substitute in detergents. Compounds **2a** and **2b** showed moderate capacities. The biodegradability of these adducts is currently being investigated.

In conclusion, La^{III}-promoted addition of maleate (Li and Na salts) to the exocyclic hydroxymethyl groups of thfa and thpm to form ether-carboxylates has been achieved in high yields. The products formed from competitive addition of water were small ($\leqslant 5\%$) even when hydrated salts were used. Larger amounts of water interfere with this reaction. This was also observed when the reaction was extended to naturally occurring cyclic sugars, such as D-ribose, D-lyxose, D-glucose, D-fructose and sucrose, using water as the solvent. However, the extent of formation of the solvent addition products

Table 4. Effect of concentration of **1** and temperature on the *O*-alkylation of EtOH with **1**.

Entry	**1**:EtOH /mol l^{-1}	*t*/h	*T*/°C	Conversion (%)	**2f** (%)	**2c** (%)	Fumarate (%)
1	0.65[a]	360	140	42	14	28	0
2	0.5[b]	168	150	62	56	6	0
3	1.25[c]	24	175	98	79.5	15.5	3
4	1.25[d]	24	182	>99	>78	13	8
5	1.25[c]	24	182	100	77	17	6
6	1.25[c]	24	185	>99	>73	16	10

[a] $LaCl_3 \cdot 1.8H_2O$ (64.4 mmol), Li_2maleate$\cdot H_2O$ (68.5 mmol) and EtOH (100 ml) were used. [b] Anhydrous $LaCl_3$ (50 mmol), Li_2maleate$\cdot H_2O$ (50 mmol) and EtOH (100 ml) were used. [c] $LaCl_3 \cdot 7H_2O$ (25 mmol) and Li_2maleate$\cdot H_2O$ (25 mmol), dehydrated with triethyl orthoformate (250 mmol), and EtOH (20 ml, molecular sieve 3 Å) were used. [d] Same conditions as in [c] except that, in addition, EtOH was stirred with triethyl orthoformate (0.5 ml) for 8 h at ambient temperature before addition of the other reactants.

depends on the affinity of the sugar substrates for La^{III}. Therefore, this reaction is expected to be feasible if an alternative less nucleophilic solvent is found. The reaction was successfully extended to D-gluconate **3** using water as the solvent and it resulted in high diastereo- and regio-selection. *O*-Alkylation of the simple, primary, aliphatic alcohols, MeOH and EtOH, by maleate (Li and Na salts) has also been accomplished in a one-step-one-pot procedure in high yields through La^{III}-promotion at higher temperatures. These reactions are, however, more sensitive to the presence of water and anhydrous conditions are necessary for improved yields. Finally, $LaCl_3$ is relatively cheap and La^{III} can be recovered and re-used after precipitation as the oxalate or carbonate or after being bound on a cation exchange resin.

Experimental

Materials and methods. Unless otherwise stated, m.p.s. were measured on a Reichert Microscope apparatus and are uncorrected. All pH measurements and adjustments were done at ambient temperatures. HPLC analyses were carried out using a Waters Associate M45 pump, a Rheodyne 7125 injection valve, a Biorad aminex HPX 87H column (300 × 7.8 mm) at 60 °C, a Waters Associate R401 detector or a Varian RI-3 detector, a Varian UV detector ($\lambda = 210$ nm) and a Spectra-Physics SP4100 computing integrator. The mobile phase was aqueous trifluoroacetic acid (TFA, 0.01 M) at a flow rate of 0.6 ml min^{-1}. The reactions were monitored by taking samples (50 µl), diluting with water (50 µl) and acidifying with TFA (1 M). The reaction products were purified on a Biorad AG 1-X8–100 or Dowex 1-X8–200 anion exchange column (formate form, diameter 3.9 cm, height 71 cm) with gradient elution (0 to 2.0 M formic acid). ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 S (400 MHz) and a Jeol EX-400 (400 MHz) spectrometer. *J*-Values are given in Hz. Sodium 3-(trimethylsilyl)propane-1-sulfonate (TSS), located at δ 0.0, was used as an internal standard for samples run in D_2O and at 30 °C. The multiplicities of the ^{13}C signals were established by DEPT experiments or attached proton tests (APT). ^1H and ^{13}C chemical shift assignments were obtained from 2D homonuclear- and heteronuclear-correlated spectroscopy, COSY and HETCOR, respectively. HPLC–MS spectra were recorded on a VG 70–250 SE hooked to the HPLC system described above with a plasma-spray interface. $LaCl_3 \cdot 7H_2O$ was purchased from Janssen Chimica while anhydrous $LaCl_3$ was purchased from Aldrich. $LaCl_3 \cdot 1.8H_2O$ was prepared by heating the heptahydrate *in vacuo* at 70 °C. The La content of the $LaCl_3 \cdot xH_2O$ was determined by EDTA titration with xylenol orange as the indicator, using utropine as the buffer. All the other reagents used were of analytical purity. The hydrated salts of disodium maleate (Na_2maleate$\cdot 2H_2O$) and dilithium maleate (Li_2maleate$\cdot 1H_2O$) were prepared from maleic acid anhydride by a method similar to that of van Westrenen *et al.*[2] The maleate content was determined by titration with aqueous HCl (0.100 M). The reactions with thfa and thpm were carried out under an atmosphere of nitrogen in order to reduce browning of the reaction mixtures attributed to oxidation of the reactant alcohols. This side-reaction did not affect the addition to **1** since a large excess of thfa and thpm was used.

Co-dehydration of $LaCl_3 \cdot 7H_2O$ and **1**: General procedure[30,31] $LaCl_3 \cdot 7H_2O$ (18.57 g, 50 mmol) and Li_2maleate$\cdot H_2O$ (7.30 g, 50 mmol) were added to trimethyl orthoformate (45.12 g, 425 mmol). The mixture was stirred at r.t. for 15 min and then at 40 °C for 1 h to form a white slurry. This was evaporated *in vacuo* (liquid N_2 trap), to remove MeOH and methyl formate, to form a white powder. Triethyl orthoformate was used instead for reactions in ethanol and the mixture stirred at r.t. overnight or heated at 55 °C for 6 h before *in vacuo* evaporation at 50 °C.

(Tetrahydrofuran-2-ylmethoxy)butanedioic acid **2a**. $LaCl_3 \cdot 1.8H_2O$ (6.92 g, 25 mmol) was added to thfa (20 ml, 0.206 mol) in a three-necked round-bottomed flask (100 ml) fitted with a reflux condenser and stirred at 90 °C to form a slightly opaque solution. Li_2-maleate (3.61 g, 25 mmol) was added and the temperature increased to 140 °C. A nearly clear solution was obtained. The reaction was complete after 7.7 h forming a white slurry. It was cooled and unreacted thfa was removed by stirring with diethyl ether (2 × 150 ml) and centrifugation. The precipitate was dissolved in water (800 ml; 65 °C) and the La^{III} ions were precipitated with a saturated aqueous solution of Na_2oxalate (65 °C), followed by filtration. The filtrate was decolourised with Darco G60, concentrated to a volume of 25–35 ml and purified on an anion exchange column. The appropriate fractions were combined after HPLC analysis, concentrated *in vacuo*, co-evaporated several times with water to remove traces of formic acid and lyophilised to give **2a** as a colourless syrup (5.3 g, 97%). MS: *m/z* (%) 219 ($[M+1]^+$, 100%), 201 ($M-OH$, 11), 173 ($M-CO_2H$, 5), 117 (7), 103 (30), 101 (4), 89 (2), 85 (18), 73 (32), 69 (82). ^1H NMR ($CDCl_3$, DMSO-d_6; Me_4Si): δ ABX-system for $-C(3)H_2-C(2)H-$, δ_A 2.71, δ_B 2.58, δ_X 3.96, $J_{AX} = 4.4$ Hz, $J_{BX} = 8.2$ Hz, $J_{AB} = -15.9$Hz, 3.98 (1 H, m, 2′-H) 3.79 and 3.67 (2 H, m, 5′-H), 3.63 and 3.42 (2 H, m, 6′-H), 1.91 and 1.62 (2 H, m, 3′-H) and 1.84 (2 H, m, 4′-H). ^{13}C NMR (DMSO-d_6; Me_4Si): ratio of diastereoisomers = 2:3: δ 172.38 (C-1), 171.13 (C-4), 67.31 (C-5′), 37.71 (C-3); diastereoisomer 1: 77.09 (C-2′), 75.63 (C-2), 72.66 (C-6′), 27.63 (C-3′), 25.06 (C-4′), diastereoisomer 2: 77.17 (C-2′), 75.48 (C-2), 72.60 (C-6′), 27.71 (C-3′) and 25.01 (C-4′).

(Tetrahydropyran-2-ylmethoxy)butanedioic acid **2b**. The procedure used for the synthesis of **2a** was followed using $LaCl_3 \cdot 1.8H_2O$ (6.92 g, 25.0 mmol), thpm (20 ml, 0.177 mol) and Li_2maleate (3.65 g, 25.0 mmol) which formed

a slurry at 140 °C. HPLC analysis showed 98% conversion after 19 h. The reaction mixture was cooled and unreacted thpm removed by stirring with diethyl ether. The precipitate was worked-up and isolated as described above for **2a** to give **2b** as a colourless syrup (4.46 g, 89%). *MS*: *m/z* (%) 233 (*M*+1, 45%), 215 (*M*−OH, 4), 187 (2), 135 (*M*−99), 117 (11), 99 (3), 73 (37), 69 (100). ^{1}H NMR (D_2O, pD=2.7): δ ABX-system for $-C(3)H_2-C(2)H-$, δ_A 2.81, δ_B 2.89, δ_X 4.34, J_{AX}= 7.5 Hz, J_{BX} =4.4 Hz, J_{AB}= −16.1 Hz, 3.95 (1 H, m, 6′-H_{eq}), 3.66 (1 H, m, 7′-H_a), 3.50 (1 H, m, 7′-H_b), 3.48 (1 H, m, 6′-H_{ax}), 3.62 (1 H, m, 2′-H), 1.82 (1 H, m, 4′-H_{eq}), 1.53–1.46 (4 H, m, 3′-H_{eq}, 4′-H_{ax}, 2×5′-H) and 1.29 (1 H, m, 3′-H_{ax}). ^{13}C NMR (D_2O, pD=2.7): ratio of diastereoisomers=4.5:5.5:δ 178.53 (C-1), 177.32 (C-4), 29.97 (t, C-3′), 28.09 (t, C-5′), 25.04 (t, C-4′), diastereoisomer 1: 79.75 (d, C-2′), 78.86 (d, C-2), 76.77 (t, C-7′), 71.14 (t, C-6′), 40.38 (t, C-3), diastereoisomer 2: 79.83 (d, C-2′), 78.78 (d, C-2), 76.85 (t, C-7′), 70.99 (t, C-6′) and 40.52 (t, C-3).

Trisodium 2-[(D-gluconate)-2-O-yl]butanedioate **4**. $LaCl_3 \cdot 7H_2O$ (9.28 g, 25 mmol) was added to a stirred solution of sodium D-gluconate **3** (10.91 g, 50 mmol, 1.25 M) in water (40 ml). Na_2-maleate **1** (9.03 g, 46 mmol) was then added and the pH was adjusted from 6.2 to 6.7. The clear solution was heated at 120 °C under reflux. HPLC analysis showed 98% conversion of **1** after 10.25 h. The reaction mixture was cooled, transferred to a beaker (1 l) with water (500 ml) and heated to 65 °C. La^{III} ions were removed by precipitation with Na_2-oxalate. The filtrate was adjusted to pH 7.5, concentrated to 50 ml and purified by anion exchange column chromatography, as for **2a**, to give **4** as a colourless syrup. The syrup was neutralised with NaOH and heated at 100 °C for 30 min to remove lactones formed. The pH was adjusted to 8.3 and the product lyophilised to yield the trisodium salt as a white solid (12.1 g, 69.6%). MS: *m/z* 295 ($M+1-H_2O$, 1%), 277 (10, $M+1-2H_2O$), 259 (3, $M+1-3H_2O$), 251 (2, $M-CO_2-H_2O$), 223 (5), 191 (6), 179 (18), 161 (9), 135 (85, $179-CO_2$), 117 (53), 125 (36), 107 (38), 99 (100), 89 (53). ^{1}H (D_2O, pD= 10.8): δ 4.02 (1 H, t, $J_{2,3}$ =5.73 Hz, 2-H), 4.00 (1 H, m, 5′-H), 3.90 (1 H, d, $J_{2',3'}$=4.64 Hz, 2′-H), 3.72 (1 H, m, 6′$_b$-H), 3.72–3.63 (2 H, m, 3′-H and 4′-H), 3.59 (1 H, m, 6′$_a$-H), 2.62 (2 H, d, 3-H). ^{13}C NMR (D_2O, pD= 10.8): ratio of diastereoisomers=1:8.6:δ 182.46, 181.84, 180.67, (C-1, C-4 and C-1′), diastereoisomer 1: 85.72 (d, C-2′), 81.09 (d, C-2), 75.74 (d, C-4′), 75.16 (d, C-3′), 73.66 (d, C-5′), 65.81 (t, C-6′) and 43.20 (t, C-3), diastereoisomer 2: 86.06 (d, C-2′), 80.89 (d, C-2), 75.97 (d, C-4′), 74.99 (d, C-3′), 73.37 (d, C-5′), 65.62 (t, C-6′) and 44.24 (t, C-3).

(R,S)-*Methoxybutanedioic acid* **2e**. $LaCl_3 \cdot 7H_2O$ (18.57 g, 50 mmol) and Li_2-maleate·H_2O (7.30 g, 50 mmol) were dehydrated with trimethyl orthoformate, added to dry methanol (molecular sieves 3 Å, 50 ml) in an autoclave vessel lined with Teflon and heated at 150 °C with stirring. HPLC analysis showed complete conversion after 6 h into **2e** (98.5%) and **2c** (1.5%). The product, a thick white slurry, was air dried and the white solid obtained was insoluble in water (800 ml, 60 °C). La^{III} ions were removed by stirring with Dowex 50W-X8–20 (H^+, 65 ml), and the filtrate was adjusted to pH 7.5 using NaOH, concentrated to 20 ml and purified by anion exchange column chromatography, as for **2a**, to give **2e** as a syrup which crystallised to a white solid (6.7 g, 91%), m.p. 104–106 °C (lit.,[24] 104–106 °C). MS: *m/z* (%) 149 (*M*+1, 82%), 131 (*M*−OH, 19), 117 (7), 107 (45), 103 (45), 89 (100), 73 (5), 71 (3), 69 (4). ^{1}H NMR (D_2O, pD=1.6): δ ABX-system for $-CH_2-CH-$, δ_A=2.88, δ_B=2.78, δ_X=4.22, J_{AX}=8.0 Hz, J_{BX}=3.8 Hz, J_{AB}= −16.5 Hz and 3.40 (3 H, s, OCH_3). ^{13}C NMR (D_2O; pD=1.6): δ 176.97 (C-1), 175.81 (C-4), 78.04 (d, C-2), 59.60 (q, OCH_3) and 38.55 (t, C-3).

(R,S)-*Ethoxybutanedioic acid* **2f**. The same procedure for the synthesis of **2e** was followed except that $LaCl_3 \cdot 7H_2O$ (9.29 g, 25 mmol) and Li_2maleate·H_2O (3.65 g, 25 mmol) were dehydrated with triethyl orthoformate (37.07 g, 250 mmol), added to dry absolute ethanol (molecular sieves 3 Å, 20 ml) in an autoclave vessel lined with Teflon and heated to 175 °C with stirring. HPLC analysis showed 98% conversion after 24 h into **2f** (79.5%), **2c** (15.5%) and fumarate (3%). The reaction mixture was worked-up and purified in a manner similar to **2e** to yield **2f** as a syrup which crystallised on standing, (2.8 g, 70%), m.p. 85–87 °C (lit.,[25] 85–87 °C). MS: *m/z* (%) 163 (*M*+1, 68%), 145 (*M*−OH, 4), 135 (6), 107 (14), 99 (2), 89 (67), 73 (100). ^{1}H NMR (D_2O, pD= 2.1): δ ABX-system for $-CH_2-CH-$, δ_A=2.9, δ_B=2.8, δ_X =4.37, J_{AX}=7.5 Hz, J_{BX}=4.4 Hz, J_{AB} = −16.2 Hz, ABX_3 system for $-OCH_2CH_3$), δ_A 3.70, δ_B 3.61, δ_X 1.19, J_{AX}= J_{BX}=6.8 Hz and J_{AB}= −16 Hz. ^{13}C NMR (D_2O, pD=2.1): δ 178.26 (C-1), 176.88 (C-4), 77.29 (d, C-2), 69.62 (OCH_2), 39.98 (t, C-3) and 16.83 (q, CH_3).

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