

# Fast Aldol-Tishchenko Reaction Utilizing 1,3-Diol Monoalcoholates as the Catalysts

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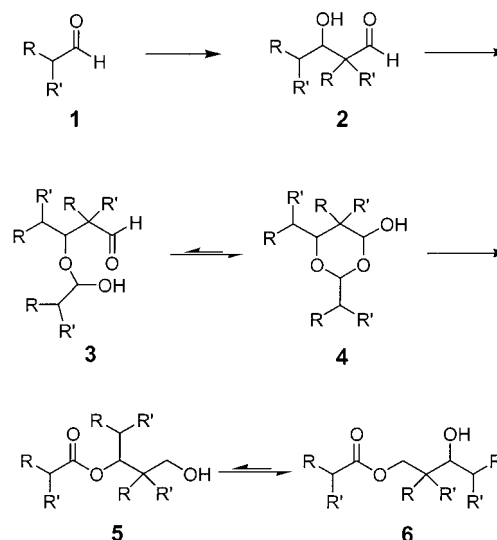
## Abstract:

The aldol-Tishchenko reaction of enolizable aldehydes is a simple and effective way to prepare 1,3-diol monoesters, which are widely used as coalescing agents in the paint industry. The use of monoalcoholates of 1,3-diols as catalysts gives fast and clean reactions compared with the previous use of several inorganic catalysts. The use of the proper 1,3-diol moiety in the catalyst also reduces the amount of side products which are due to ester interchange between product esters and the catalyst. The rapid water-free method developed herein allows fast preparation of monoesters with excellent yield and minimized formation of side products.

## Introduction

In many cases traditional Tishchenko<sup>1</sup> and aldol-Tishchenko<sup>2</sup> reactions are competitive with each other.<sup>3</sup> However, these reactions can sometimes proceed selectively with the proper choice of catalyst. The aldol-Tishchenko reaction usually requires a basic metal hydroxide catalyst which can activate both aldol reaction and Tishchenko esterification.<sup>4</sup> Some other catalysts have also been used such as metal alkoxides of monofunctional alcohols,<sup>5,6</sup> LiWO<sub>2</sub>,<sup>7</sup> Cp\*<sub>2</sub>Sm-(thf)<sub>2</sub>,<sup>8</sup> polynuclear carbonyl ferrates,<sup>9</sup> and simple metal hydroxides.<sup>10</sup> Traditional Tishchenko esterification is usually activated in the presence of Lewis acidic catalysts such as aluminum alcoholates.<sup>11</sup> In a typical aldol-Tishchenko reaction (Scheme 1), an aldol reaction of the easily enolizable

**Scheme 1.** Aldol-Tishchenko reaction of enolizable aldehydes



aldehyde first takes place, and the product forms a hemiacetal-like 1,3-dioxan-4-ol **4** (also called aldoxan at this case) with the free aldehyde.<sup>12</sup> Dioxanol **4** reacts to give the diol monoester **5** via a Tishchenko reaction in which an intramolecular hydride shift takes place.<sup>13</sup> In the presence of the catalyst, for example, Ca(OH)<sub>2</sub>, and with heating, the balance between monoesters **5** and **6** is slowly converted to the more stable monoester **6** having a secondary alcohol group instead of a primary one as in **5**.<sup>2</sup> This aldol-Tishchenko reaction is very closely related to the Evans-Tishchenko reaction in which  $\beta$ -hydroxyketones react with a free aldehyde to give a glycol monoester with excellent *anti*-selectivity.<sup>14</sup>

In our previous work we have studied the chemistry of 1,3-dioxan-4-ols and their behaviour in the Tishchenko reaction. It is well-known that several metal hydroxides destroy esters by hydrolysis and thereby reduce the yield. We started to search for substitute catalysts and found that diol monoalcoholates solve this problem.<sup>15</sup> Herein we wish to report the results of our studies on the homogeneous aldol-Tishchenko reaction, wherein we have achieved fast reactions from enolizable aldehyde **1** to monoesters **5** and **6** with

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excellent yields. This work was focused on converting isobutyraldehyde **7** to diol monoesters **9** and **10** which are the most common coalescing agents, for example, for latex paints. Consumption of **7** to condensation and esterification products was 260 million pounds in 1997 exclusively in the U.S.<sup>16</sup>

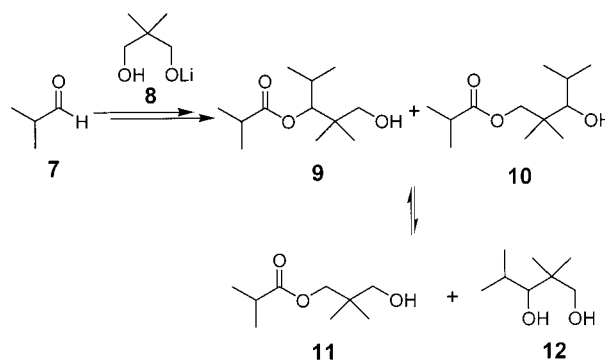
## Results and Discussion

To our knowledge, this is the first time that monoalcoholates of 1,3-diols have been studied as catalysts for aldol-Tishchenko reactions. The use of sodium alcoholates of monofunctional alcohols has been reported, but in this case the yield of monoesters of the diol was reduced due to ester interchange between the catalyst and the product ester.<sup>17</sup> The effect of the catalyst on the reaction rate was found to be crucial in our experiments, giving a reaction several times faster than that obtained with the metal hydroxides traditionally used. This is partly due to the completely homogeneous reaction system. In some industrial processes the use of metal hydroxides can require the presence of some water which can create quantities of wastewater and thus extra costs.<sup>18</sup> Another considerable disadvantage with metal hydroxide catalysts is the fast and irreversible hydrolysis of the product esters. In our procedure, water-free reaction conditions are used, and after the reaction and short workup, the solvent and products can be easily separated by means of fractional distillation. However, rather fast ester interchange between the catalyst and the product ester can still cause slight loss in the yield. This can be avoided by choosing a suitable 1,3-diol as the catalyst. We have here studied the role of different alkali metals in the catalyst and optimized the reaction conditions for this process. In our previous experiments we used the monolithium alcoholate of 2,2-dimethylpropan-1,3-diol (neopentyl glycol; later NPG) **8** as the catalyst in the Tishchenko esterification of 1,3-dioxan-4-ol derivatives.<sup>15</sup>

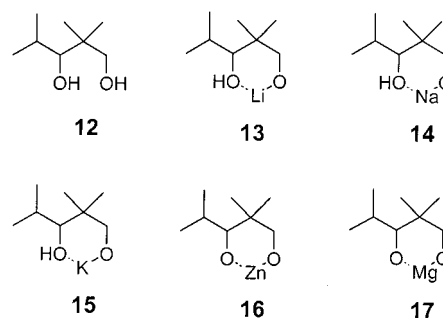
In the first experiment of this paper, it was figured out how unavoidable the ester interchange between the catalyst and the product is. The same Li-NPG catalyst **8** (30 mol %) was used here in the case of the aldol-Tishchenko reaction. Isobutyraldehyde **7** ( $R=R'=\text{CH}_3$  in Scheme 1) was used as the starting material and added directly into the catalyst solution (0.5 M in THF, 30 mol %). At room temperature, the reaction was found to be surprisingly fast.

The desired products were the glycol monoesters (2,2-dimethyl-3-hydroxy-1-isopropyl-propyl)-2-methylpropionate **9** and (3-hydroxy-2,2,4-trimethylpentyl)-2-methylpropionate **10**. Formation of NPG-monoisobutyrate **11** and 2,2,4-trimethylpentan-1,3-diol **12** were observed after only 15 min, proving that there was fast ester interchange between products (**9** and **10**) and the catalyst **8** (Scheme 2). In later experiments, we decided to use monoalcoholates prepared from diol **12** as the catalysts to avoid the formation of side

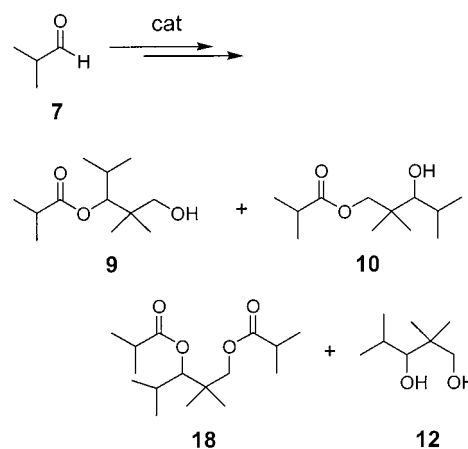
Scheme 2



Scheme 3. The catalysts related to diol **12** used in experiments



Scheme 4



products related to monoester **11**. The catalysts used in the experiments are shown in Scheme 3. Catalysts **13**, **14**, and **15** were prepared in a straightforward fashion by adding a solution of **12** in THF (or hexanes) into the hydride slurry at 0 °C under argon. When BuLi (**13**) or Et<sub>2</sub>Zn (**16**) were used, these were added directly into the precooled THF or hexane solution of diol **12**. The catalyst solution was stirred for 60 min at 0 °C before use.

In the experiment series, freshly distilled isobutyraldehyde **7** (4.50 g, 50 mmol) was fed over 2 min into the reaction containing the catalyst solution, giving an exothermic reaction (Scheme 4). The amount of catalyst used was always 1 mol % except entry 5 (30 mol %) in which case ester interchange with a bulky catalyst was studied. In all entries of Table 1 the temperature was kept stable at +55 °C (±3 °C) with external cooling and heating at the very end of the reaction. After a reaction time of 30 min the reaction was

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**Table 1.** Effect of solvent, catalyst and reaction times on yields in the aldol-Tishchenko reaction of 2-methylpropanal at (+55 °C)

entry	catalyst <sup>a</sup>	catalyst concentration (M)	solvent	time (add) (min)	time (react) (min)	<b>12<sup>b</sup></b>	<b>9<sup>b</sup></b>	<b>10<sup>b</sup></b>	<b>18<sup>b</sup></b>	<b>7<sup>b,c</sup></b>	yield <sup>d</sup> ( <b>9</b> and <b>10</b> ) (%)
1	<b>13</b>	0.5	THF	6.5	20	9.1	27.5	39.6	7.7	16.0	77
2	<b>13</b>	0.067	Hex	2.5	40	14.9	22.2	36.5	8.7	17.7	73
3	<b>13</b>	0.1	Hex	2	60	15.0	23.8	36.1	14.8	10.3	65
4	<b>14</b>	0.25	THF	3.5	20	5.1	22.8	34.0	1.3	36.7	76
5	<i>t</i> -BuOLi	0.5	THF	3	30	11.3	25.7	39.3	13.2	13.2	69
6	<b>13</b>	0.1	Hex	2	30	6.6	32.4	40.8	1.3	19.0	87
7	<b>13</b>	0.1	THF	2	30	10.6	23.7	45.9	9.4	10.5	77
8	<b>14</b>	0.1	THF	2	30	8.3	27.2	50.8	3.1	10.6	92
9 <sup>e</sup>	<b>15</b>	0.1	THF	2	30	4.3	17.1	29.1	0.0	49.5	41

<sup>a</sup> 1.0 mol % of catalyst was used in every experiment. <sup>b</sup> mol % of the product mixture. <sup>c</sup> Contains both unreacted free aldehyde and aldolan. <sup>d</sup> (wt)% of **9** & **10** (compared to theoretical yield if all **7** would have reacted to **9** and **10**). <sup>e</sup> Prepared from diol **12** and KHMDS (method b).

quenched with 2 M HCl, the water phase was saturated with NaCl, and the layers were separated. The product mixture from all reactions usually contained mainly the desired product esters **9** and **10**.

Some diester **18** and diol **12** were observed as side products, and their amount increased considerably if the reaction time was extended. This was due to the similar acidity of the primary hydroxyl groups in both product ester **9** and catalyst **13** and thus their ability to exchange lithium.

On the other hand, in the case of too short a reaction time or too low a temperature (<+40 °C), substantial amounts of starting material **7** and aldolan diastereomers **4** (R=R'=CH<sub>3</sub>) were observed and the reaction did not proceed to completion. The reaction temperature was also kept below the boiling point of **7**, but the temperature can be raised in scale-up to the reactor scale if the system allows higher pressure. If the results with catalysts **13–15** are compared with studies performed with metal hydroxides, the reaction times are remarkably shorter, the yields are always much higher, and the conversions of starting material **7** to products **9** and **10** are excellent. Thus, direct comparison between the reaction rates of alcoholates and alkali earth metal hydroxide catalysts cannot be drawn because in the latter case the reaction is partly heterogeneous and the rate can be partly mass-transfer limited. Results from optimizing the reaction conditions are presented in Table 1. The reaction time has been optimized, and 30 min was found to be optimal for obtaining good conversion of **7** without substantial formation of **18** (entries 2, 3, and 6). The composition of the product mixture was checked with <sup>1</sup>H NMR and GC before and after the purification with column chromatography and the reaction was not boosted over the silica gel. In other words the ratio of the products was not changed during the purification.

Meth-Cohn has reported that lithium alcoholates gave efficient ester interchange when THF was used as the solvent.<sup>19</sup> Lithium also gives a fast aldol reaction in THF because of its ability to coordinate with the slightly polar THF and thus make the solvated enolate more reactive.<sup>20</sup>

To avoid diester formation, coordination has to be prevented. The effect of the solvent was studied by changing THF to hexanes, and significant differences were observed (entries 6–7). Reduced formation of the diester was observed in hexanes but also worse conversion of **7**, due to a slower aldol reaction.

Steric effects might also have an effect on the course of the reaction. Bulky *t*-BuOLi was expected to give weaker coordination of the catalyst to the carbonyl group of the product ester. We expected that this might slow the ester interchange. However, noticeable effects were not observed (entry 5). The use of TMEDA to chelate lithium had no effect either. To study further the effect of the counteraction a series of experiments was performed (entries 7–9). The effect of the counteraction was studied by using sodium instead of lithium. Ester interchange was slower, but longer reaction times were needed to reach the same conversion. Obviously, bulkier metals (weaker coordination to carbonyl oxygen) give slower ester interchange but also a slightly slower aldol reaction. Again, the reduced rate of the aldol reaction can be observed as a worse conversion of **7** to the products (entry 4). Results from the potassium alcoholate were expected to be the best of the alkali metal alcoholates. Measurement of an exact amount of 30% KH–oil dispersion was difficult, and this was the reason for the distortion of results. The amount of KH was too large which was observed as a loss in the yield of esters **9** and **10** via efficient ester interchange to **12** and **18**. An alternative way to prepare the catalyst **15** was to treat diol **12** with KHMDS and remove the silylamide residues before use. The effect of the potassium alcoholate can be observed in entry 9, and the results are in line with the theory. It should be noticed that the formation of diester **18** was not observed at all (NMR, TLC). On the other hand, the conversion of **7** was poor due to sluggish aldol reaction with potassium counteraction. The catalyst **14** was also studied on a larger scale (3 mol of **7**) but the cooling capacity was found to be the limiting factor of the system and, the experiment failed. This can be avoided with slower addition of **7**, but then conversion of product monoesters to diester **18** is increased as a function of time. On the basis of the results of Table 1, the use of hexane as the solvent and an alcoholate catalyst bearing a bulky cation such as potassium

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could partly solve this problem of limited cooling capacity to give a sluggish aldol reaction but also slow formation of diester **18**.

The effect of the water and acid content in aldehyde **7** towards the reaction rate was also studied. If the amount of isobutyric acid in aldehyde was close to the amount of the catalyst, the reaction terminated halfway. In experiments with 10 mol % of the catalyst and aldehyde containing 1–2 mol % of water, a copious LiOH precipitate formed during the reaction which made stirring impossible and the system totally heterogeneous. In larger scales such precipitation can obstruct stirring and cause serious safety risks due to exothermicity. Further, in such a heterogeneous system the heat transfer is limited, and local overheating can occur. Additionally, the water content of aldehyde forms lithium hydroxide which hydrolyses some of the product esters.

We attempted to reduce the formation of diester **18** by changing the metal of the catalyst to an alkali earth metal (Mg) or a transition metal (Zn) both of which are known to catalyze at least aldol reactions and could coordinate weakly enough to the carbonyl oxygen of the monoesters. Attempts to prepare **17** from magnesium turnings and diol **12** in hexanes with iodine catalysis and reflux failed. After several hours refluxing, aldehyde **7** was added, but no reaction was obtained. Preparation of catalyst **16** was examined by treatment of diol **12** with 200 mol % of *n*-BuLi in hexane and then exchanging lithium with zinc using ZnCl<sub>2</sub>. The solution was separated from the LiCl precipitate into the reaction vessel, and aldehyde **7** was added. After 40 min monoesters **9** and **10** were obtained in a moderate 65% yield together with 11% of diester **18** in the product mixture. In the next reaction diol **12** was treated again with 200 mol % *n*-BuLi, but Et<sub>2</sub>Zn was used instead of ZnCl<sub>2</sub>. The yield of **9** and **10** was 87%. However, it is difficult to conclude if the metal interchange was complete before addition of **7** and whether lithium or zinc catalyzed the formation of **18**. In the final experiment diol **12** was directly treated with Et<sub>2</sub>Zn to obtain **16**. Isobutyraldehyde **7** was added to a 0.1 M catalyst solution of **16** (1.0 mol-%). After 35 min, the conversion of **7** was only 57%. However, monoesters **9** and **10** were the main products, and only traces of **18** were observed. Also, the presence of a small amount of 2-methyl-3-pentanol was observed in the <sup>1</sup>H NMR which was due to the reaction between unreacted Et<sub>2</sub>Zn and **7**.

On the basis of the fact that transesterification is a reversible reaction, we decided to use diester **18** as the solvent. NaOMe (30% in MeOH) was added into **18**, and MeOH was removed under reduced pressure at +40 °C to prepare the catalyst **14** via ester interchange. If the reaction mixture was quenched and analysed at this point, all of the products, **12**, **9**, **10**, and **18** were present. This was a clear indication of ester interchange and formation of **14** (and methyl isobutyrate) from **18**. The aldehyde was added over 2 min, and after 30 min the yield of monoesters was 93%. On a larger scale the advantages are that after the workup the products can be fractionally distilled and the least volatile component in the reactor, side product **18**, can be recycled as the solvent in the next batch.

## Conclusions

Monoalcoholates of 1,3-diols give very fast aldol-Tishchenko reactions with an excellent yield of monoesters of 1,3-diols. To our knowledge, only sodium monoesters of monofunctional alcohols have been used as catalysts for this particular reaction. On the basis of our results, 1,3-diol-based alcoholates give slightly better yields, the reaction temperature is lower, and the reaction itself is faster. The results are in accordance with literature, and different solvents and metals have clear effects on the reaction rates. Furthermore, these catalysts provide water-free reaction conditions, and no hydrolysis has been observed. Even if the formation of diester cannot be totally avoided here, it is a minor problem compared to the hydrolysis caused by metal hydroxide catalysts. The products can be easily separated by means of distillation, and the diester can be recycled as a solvent in the next batch if needed. Because of rather fast transesterification (**9** → **18**) it is important that the diol used in the catalyst is the same as the diol moiety in the product ester. Finally, the reaction can be run with 1.0 mol % of the catalyst (or even less), but use of an acid-free and dry aldehyde is required in this procedure. We avoided hydrolysis of the monoesters, but formation of diester **18** was found to be a new problem.

## Experimental Section

**Materials and Instrumentation.** All chemicals were purchased from commercial sources (purity >98%) and used directly except isobutyraldehyde which was dried over Na<sub>2</sub>SO<sub>4</sub> and fractionally distilled under argon before use. All solvents used were dry and distilled immediately before use. Merck silica gel 60F (230–400 mesh) plates were used for TLC analyses. The TLC plates were stained with anisaldehyde in acidic ethanol. The <sup>1</sup>H- and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> with 0.25% of TMS or DMSO on a Bruker AM-200 instrument. Gas chromatography was performed on a Perkin-Elmer model PE8420 with OV-1701 column. Mass spectra were recorded on a Kratos MS80 RF Autoconsole instrument.

**Lithioxy-2,2-dimethyl-3-hydroxypropane (13).** Catalyst **13** was prepared by two alternative methods. **Method A.** To a cooled (–78 °C) solution of diol **12** (0.073 g, 0.5 mmol) in THF (4.78 mL) under argon *n*-BuLi (2.30 M in hexane, 0.22 mL, 0.5 mmol) was added dropwise to give 0.1 M catalyst solution. The solution was stirred for 60 min at 0 °C and used instantly. **Method B.** Diol **12** (0.74 g, 0.5 mmol) in 4 mL of THF was added dropwise to a cooled (0 °C) suspension of 95% LiH (0.004 g, 0.5 mmol) in 1 mL of THF under argon. The resulting solution was stirred for 60 min at 0 °C before use.

**Sodium Oxy-2,2-dimethyl-3-hydroxypropane (14).** Catalyst **14** was also prepared using two alternative methods. **Method A.** A 50% NaH suspension in mineral oil (0.024 g, 0.5 mmol) was first washed with 2 × 2 mL of dry hexanes under argon. THF (5 mL) (or hexanes) was added, and diol **12** (0.073 g, 0.5 mmol) was added into this suspension giving a 0.1 M solution of **14**. The catalyst solution was stirred for 60 min at 0 °C before use. **Method B.** Diol **12** (0.073 g, 0.5 mmol) and 30% NaOMe (in MeOH, 0.090 g, 0.05 mmol)

were mixed under argon, the solution was warmed to +40 °C, and MeOH was evaporated under reduced pressure (0.1–10 mmHg). After evaporation, THF or **18** (5 mL) was added, and the solution was ready for use.

**Potassium Oxy-2,2-dimethyl-3-hydroxypropane (15).** **Method A.** Preparation was as for method A of catalyst **14**. Exact measurement of the fluid 30% KH/mineral oil suspension (0.0681 g, 0.51 mmol) was difficult which caused some distortions of the results. **Method B.** Diol **12** (0.073 g, 0.5 mmol) was dissolved in 1 mL of dry THF under argon, and the solution was cooled to 0 °C. KHMDS (1.0 mL, 0.5 M in toluene, 0.5 mmol, Aldrich) was added dropwise, and the solution was stirred at 0 °C for 60 min. Solvents and formed bis(trimethylsilyl)amide residue were evaporated before use under reduced pressure (0.08 mmHg). Right before use 5 mL of dry THF was added to prepare 0.1 M solution of **15**.

**Zinc Oxy-2,2-dimethyl-3-hydroxypropane (16).** This catalyst was also prepared using two alternative methods, method A is more reliable. **Method A.** Diol **12** (0.074 g, 0.5 mmol) was dissolved in 4.5 mL of THF under argon, and the clear solution was cooled to 0 °C. Et<sub>2</sub>Zn (1 M, 0.5 mL, 0.5 mmol) was added dropwise. The solution was stirred for 60 min at 0 °C before use. **Method B.** Diol **12** (0.146 g, 1.0 mmol) was dissolved in 0.5 mL of THF under argon and cooled to 0 °C. *n*-BuLi (1.33 M, 1.3 mL, 2.0 mmol) was added dropwise and stirred for 60 min. The solution was cannulated into the flask charged with ZnCl<sub>2</sub> (0.143 g, 1.05 mmol, dissolved in 1.0 mL of THF); a slight LiCl precipitation was observed, but precipitation got faster during the ultrasonication. The clear solution was cannulated directly into the reaction flask. In this method, completion of metal interchange cannot be surely determined, and the presence of catalyst **13** is possible.

**(2,2-Dimethyl-3-hydroxy-1-isopropyl-propyl)-2-methylpropionate (9) and (3-Hydroxy-2,2,4-trimethylpentyl)-2-methylpropionate (10).** The catalyst solution (5.0 mL, 0.1 M **14** in THF) was placed into the reactor under argon, and addition of isobutyraldehyde was started. Aldehyde **7** (3.6048 g, 50 mmol) was added over 2 min. **Caution:** The reaction was very exothermic, and the internal temperature was allowed to rise to +55 °C and kept stable with external cooling. At the end of the reaction, external heating was used to keep the temperature at +55 °C (±3 °C). The reaction was stirred for 30 min and quenched with 3 mL of 2 M HCl. The reaction mixture was taken up with 15 mL of CH<sub>2</sub>Cl<sub>2</sub>, the water phase was saturated with NaCl, and the layers were separated. The water phase was washed with 3 × 10 mL of CH<sub>2</sub>Cl<sub>2</sub>. All organics were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The product mixtures from the reactions were analyzed by <sup>1</sup>H NMR. The products were separated with column chromatography (EtOAc:Hex/10:90). On a larger scale, purification by fractional distillation under reduced pressure can be considered. The combined yield of **9** and **10** was 3.323 g (92%). NMR data was used to obtain the yield from the product mixture.

**Monoester (9):** TLC (EtOAc:Hex/1:9) *R<sub>f</sub>* = 0.29. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 200 MHz) δ 4.76 (d, 1 H, OCH<sup>1</sup>Pr, <sup>3</sup>*J* = 2.8 Hz), 3.13 (dd, 2 H, CH<sub>2</sub>OH, <sup>2</sup>*J* = 11.6 Hz), 2.65 (sep, 1 H,

CHCOO, <sup>3</sup>*J* = 7.0 Hz), 2.07 (sep-*d*, 1 H, CHCHMe<sub>2</sub>, <sup>3</sup>*J* = 6.8 Hz, <sup>3</sup>*J* = 2.7 Hz), 1.22 (d, 6 H, Me<sub>2</sub>CHCOO, <sup>3</sup>*J* = 7.0 Hz), 1.02 (s, 3 H, CCH<sub>3</sub>), 0.97 (d, 3 H, CHCHCH<sub>3</sub>, <sup>3</sup>*J* = 6.8 Hz), 0.94 (d, 3 H, CHCHCH<sub>3</sub>, <sup>3</sup>*J* = 7.0 Hz), 0.86 (s, 3 H, CCH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>; 50 MHz) δ 178.3, 79.2, 69.9, 40.0, 34.5, 28.3, 22.9, 22.2, 19.6, 19.3, 17.7. MS (CI, NH<sub>4</sub>): (M + 1) = 217, ((M + 1 + NH<sub>3</sub>) = 234).

**Monoester (10):** TLC (EtOAc:Hex/1:9) *R<sub>f</sub>* = 0.21. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 200 MHz) δ 3.91 (dd, 2 H, OCH<sub>2</sub>C, <sup>2</sup>*J* = 10.9 Hz), 3.21 (d, 1 H, CCHOH, <sup>3</sup>*J* = 2.6 Hz), 2.54 (sep, 1 H, CHCOO, <sup>3</sup>*J* = 7.0 Hz), 1.88 (sep-*d*, 1 H, Me<sub>2</sub>CHCHOH, <sup>3</sup>*J* = 6.8 Hz, <sup>3</sup>*J* = 2.3 Hz), 1.15 (d, 6 H, Me<sub>2</sub>CHCOO, <sup>3</sup>*J* = 7.0 Hz), 0.97 (d, 3 H, CH<sub>3</sub>CHCHOH, <sup>3</sup>*J* = 6.9 Hz), 0.93 (s, 3 H, CH<sub>3</sub>C), 0.92 (s, 3 H, CH<sub>3</sub>C), 0.89 (d, 3 H, CH<sub>3</sub>-CHCHOH, <sup>3</sup>*J* = 6.8 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>; 50 MHz) δ 177.2, 79.4, 71.3, 39.3, 34.1, 28.6, 23.5, 22.0, 20.4, 19.0, 19.0, 16.7. MS (CI, NH<sub>4</sub>): (M + 1) = 217, ((M + 1 + NH<sub>3</sub>) = 234).

**2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (18):** TLC (EtOAc:Hex/1:9) *R<sub>f</sub>* = 0.50. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 200 MHz) δ 4.78 (d, 1 H, -OCH<sup>1</sup>Pr, <sup>3</sup>*J* = 3.2 Hz), 3.84 (dd, 2 H, -OCH<sub>2</sub>C-, <sup>2</sup>*J* = 11.0 Hz), 2.60 (sept, 1 H, Me<sub>2</sub>CHCOO-, <sup>3</sup>*J* = 7.0 Hz), 2.57 (sept, 1 H, Me<sub>2</sub>CHCOO-, <sup>3</sup>*J* = 7.0 Hz), 2.04 (sept-*d*, 1 H, Me<sub>2</sub>CHCHO-, <sup>3</sup>*J* = 6.9 Hz, <sup>3</sup>*J* = 3.1 Hz), 1.204 (d, 3 H, CH<sub>3</sub>CHCOO-, <sup>3</sup>*J* = 7.0 Hz), 1.196 (d, 3 H, CH<sub>3</sub>CHCOO-, <sup>3</sup>*J* = 7.0 Hz), 1.18 (d, 6 H, CH<sub>3</sub>-CHCOO-, <sup>3</sup>*J* = 7.0 Hz), 0.99 (s, 3 H, CH<sub>3</sub>C-), 0.97 (d, 3 H, CH<sub>3</sub>CHCHO-, <sup>3</sup>*J* = 6.9 Hz), 0.97 (s, 3 H, CH<sub>3</sub>C-), 0.90 (d, 3 H, CH<sub>3</sub>CHCHO-, <sup>3</sup>*J* = 6.8 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>; 50 MHz) δ 176.9, 176.5, 79.5, 69.8, 38.9, 34.4, 34.1, 28.3, 23.1, 21.7, 21.3, 19.2, 19.2, 19.0, 18.9, 17.8.

**2,2,4-Trimethyl-1,3-pentanediol (12):** TLC (EtOAc:Hex/1:9) *R<sub>f</sub>* = 0.08. <sup>1</sup>H NMR (CDCl<sub>3</sub>; 200 MHz) δ 3.49 (dd, 2 H, CCH<sub>2</sub>OH, <sup>2</sup>*J* = 10.6 Hz), 3.39 (d, 1 H, CCHOH, <sup>3</sup>*J* = 2.5 Hz), 2.79 (s, 2 H, OH), 1.94 (sept-*d*, 1 H, Me<sub>2</sub>CH, <sup>3</sup>*J* = 6.9 Hz, <sup>3</sup>*J* = 2.4 Hz), 1.01 (d, 3 H, CH<sub>3</sub>CH, <sup>3</sup>*J* = 7.0 Hz), 0.96 (d, 3 H, CH<sub>3</sub>CH, <sup>3</sup>*J* = 7.0 Hz) 0.94 (s, 6 H, Me<sub>2</sub>C).

**Monoesters 9 and 10 Using Diester 18 as the Solvent.** Diol **12** (0.293 g, 2.0 mmol), 30% NaOMe (0.360 g, 2.0 mmol, in MeOH), and diester **18** (9.280 g, 32.4 mmol) were placed in the reaction flask under argon, heated to +55 °C and put under reduced pressure (1.5 mmHg) for 15 min. A yellowish and thick oily product was obtained. Isobutyraldehyde **7** (7.178 g, 100 mmol) was added over 2 min, and the reaction temperature (internal) was kept stable at +55 °C (± 3 °C) first with external cooling and then with slight heating. After 36 min the reaction was quenched with 5 mL of 1 M HCl, and the workup was done as for the previous example (the amounts here were 4 times), giving monoesters **9** and **10** in 6.637 g (92.5%) yield.

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