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Symmetric esters by Tischtschenko reaction of aldehydes catalyzed by bi- and tridentate catalysts derived from catechol or gallol, trimethylaluminum and isopropanol

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Abstract—New inexpensive aluminum-based bidentate and tridentate chelates were found to be efficient catalysts for the Tischtschenko reaction of aldehydes. The conversion of *n*-butanal to *n*-butyl *n*-butyrate using catechol-derived catalysts at room temperature was complete (the yield of the butyrate was 99%) in two hours. High yields of symmetric esters were obtained in the case of *n*-alkyl and α-branched aliphatic aldehydes whereas reactivity of unsaturated aldehydes was found to be poor. Selected reactive intermediates were studied computationally at the (pBP)/DNPP level using the Spartan program. The results of computational studies indicate that in the case of the catechol-derived catalyst bidentate chelation of two aluminum atoms to an oxygen atom of aldehyde to form a structure '$(O{-}Al)_2O{=}C_{Ald.}$' is less favorable than monodentate chelation to one aluminum atom activated by the other aluminum to form a structure '$O{-}Al{-}O{-}Al{-}O{=}C_{Ald.}$'. The structure of this activated monodentate system clearly resembles more closely the transition state of the hydride-transfer step of the Tischtschenko reaction than the corresponding non-activated monodentate system '$O{-}Al$'+'$O{-}Al{-}O{=}C_{Ald.}$'. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

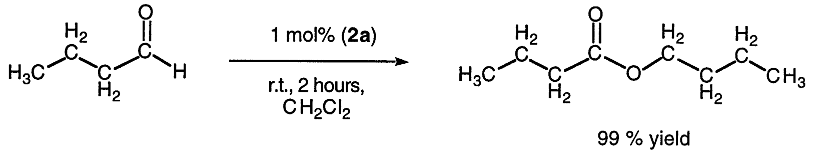
The Tischtschenko reaction (e.g. Scheme 1) opens an efficient pathway for the synthesis of symmetric esters (i.e. RCO_2CH_2R) via a direct conversion of aldehydes through a reduction–oxidation procedure. Although the Tischtschenko reaction has been known for almost a century it is still studied by several groups.[1]

Earlier studies indicate that this reaction can be carried out using aluminum alkoxides as catalysts[2] whereas Maruoka et al.[3] have recently emphasized the importance of highly reactive bidentate chelating biaryldioxy-bis-dialkoxyaluminum derivatives (both the free electron pairs of $O_{C=O}$ of the reacting aldehyde are bound to Lewis acidic aluminum atoms), such as **1**, as environmentally efficient catalysts for Tischtschenko reactions. In order to explore the utility of inexpensive aluminum complexes for the purposes of catalytic Tischtschenko reactions we turned our attention to aryldioxy-bis-dialkoxyaluminum **2a** (derived from catechol) and aryltrioxy-tris-dialkoxyaluminum **3** (derived from gallol), potentially capable of bidentate chelation. Tischtschenko conversion (Scheme 1) of nine aldehydes catalyzed by **2a** and **3** (prepared in situ) is described (Chart 1).

In the present study the interest was in combining experimental work with theoretical calculations.[4] The computational study was aimed at comparing structures potentially formed when aldehydes coordinate to **2a**. Structure **2b** was used as a model of **2a**.

2. Experimental results and discussion

Synthetic results of the conversion of aldehydes to symmetric esters are summarized in Tables 1 and 2. In



Scheme 1.

Keywords: symmetric esters; Tischtschenko reaction; bidentate catalysts; tridentate catalysts.

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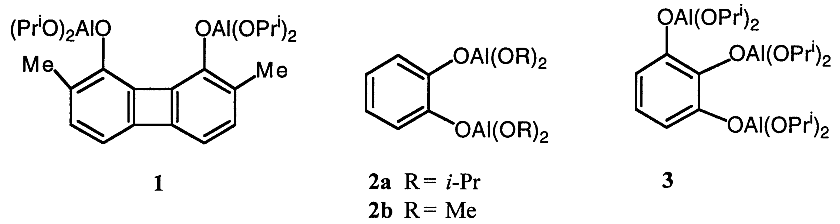
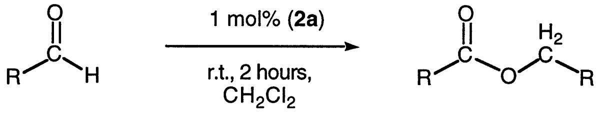


Chart 1.

Table 1. Tischtschenko reactions (yields after flash chromatography) of aldehydes R–CHO catalyzed by **2a**



Entry	R	Reaction time (h)	Yield (%)
1	*n*-Propyl	2	99
2	*n*-Heptyl	2	83
3	*n*-Hept-3-yl	2	86
4	*n*-Pent-2-yl	2	89
5	1-Phenylethyl	2	87
6	*c*-Hexyl	2	96
7	*t*-Butyl	2	63
8	*n*-Hept-3-en-3-yl	2	3
9	Phenyl	23	58

The amount of catalyst **2a** prepared in situ was 1 mol% (relative to the amount of aldehyde).

order to rationalize the results, a plausible reaction mechanism was considered, as depicted in Scheme 2.

In the case of **2a** the catalytic cycle is potentially initiated via a Meerwein–Ponndorf–Verley (MPV) reaction of aldehyde complex **A** of **2a** (Scheme 2) and subsequent coordination of another aldehyde molecule to the active center of the catalyst leading to the formation of **B**. Intermediate **C** may form via a rearrangement reaction of the aldehyde and alkoxide units of **B**. Coordination of aldehyde to **C** could give rise to the rupture of the 4-membered ring of **C** and the formation of hemiacetal **A**′ (a hemiacetal analog of **A**, Scheme 2). A subsequent intramolecular MPV reaction occurring in **A**′ could lead to the formation of **B**′ (an ester analog of **B**) of which a further reaction with aldehyde renders the product ester and regenerates **B**.

In order to choose reaction conditions for the conversions summarized in Table 1, the catalytic performance of **2a** and **3** was compared on the basis of reactions of *n*-butanal shown in Table 2. Addition of aldehyde into the reaction vessel immediately gave rise to an exothermic reaction. This observation indicates that the reaction runs much faster at the start. Indeed, about 50% of the total yield of butyl butyrate is produced during the first 30 min of the reaction catalyzed by **2a** whereas the second half takes three times longer to form (entries 1 and 3, Table 2). In the case of **3** already 62% of butanal is converted to the ester product (entry 4; Table 2) during the first 30 min (the yield is enhanced only by about 8% during the next 30 min (entry 5; Table 2)).

The conversion of *n*-butanal (entry 3; Table 2) catalyzed by **2a** is complete in 2 h. Although the initial rate of the conversion catalyzed by **3** (entries 1 and 4, Table 2) is higher, **2a** looks more productive than **3** (entries 3 and 5, Table 2). Furthermore, solutions of **3** were not fully homogenous. In order to ensure reliable comparison of different aldehydes, **2a** was chosen for further studies (Table 1).

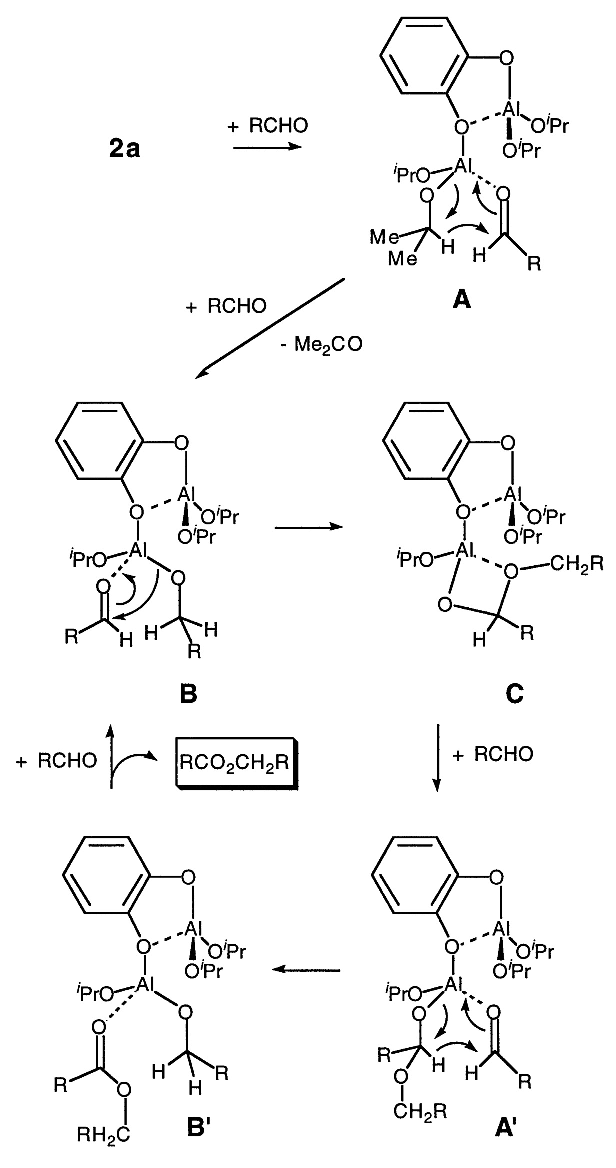
The Tischtschenko reaction of aliphatic aldehydes gave symmetric esters in good yields (83–99%, entries 1–6, Table 1), except in the case of 2,2-dimethylpropanal (63% only, entry 7, Table 1). The lower yield in the case of 2,2-dimethylpropanal could be attributable to steric hindrance in **C** (contains a *t*-butyl substituted 4-membered ring) that hampers the formation of **A**′ (would contain three *t*-butyl groups) (Scheme 2). A comparison of the yields and the size of the R group (Table 1) reveals that the size of the group correlates with the yield. For instance, the yield of the reaction of *n*-butanal (entry 1, Table 1) is substantially better than that of *n*-octanal (entry 2, Table 1). The lower yield observed in the case of *n*-octanal could originate from the higher flexibility of the (longer) alkyl chain of *n*-octanal. In the case of *n*-octanal the long *n*-heptyl chain may block the active site of **C** more efficiently than the shorter alkyl chain of *n*-butanal. Furthermore, in intermediate **A**′ the two *n*-heptyl chains of the hemiacetal counterpart may wrap the hydride to be transferred so that the rate of the MPV reaction of **A**′ decreases (Scheme 2). The high yield observed in the case of cyclohexanecarboxaldehyde (entry 6, Table 1) could be rationalized on the basis of the limited

Table 2. The optimal reaction time of the catalytic Tischtschenko conversion of *n*-butanal

Entry	Catalyst	Ligand[a] (mol%)	Me_3Al[a] (mol%)	Reaction time (min)	Yield (%)
1	**2a**	1	2	30	49
2	**2a**	1	2	60	77
3	**2a**	1	2	120	99
4	**3**	0.66	2	30	62
5	**3**	0.66	2	60	70

Catalyst prepared in situ; reactions conducted at rt in CH_2Cl_2. Yields after flash chromatography.

[a] Relative to the molar amount of *n*-butanal.



Scheme 2.

ability of the *c*-hexyl group to move and disturb the active center of the catalyst (Scheme 2). The better performance observed in the case of α-substituted aldehydes (entries 3–5, Table 1) could be explained on the same basis. The α-substituents of 2-ethylhexanal, 2-methylpentanal and 2-phenylpropanal may limit the conformational freedom of the alkyl chain and allow faster uptake of the reactant aldehyde than in the case of *n*-octanal (entry 2, Table 1).

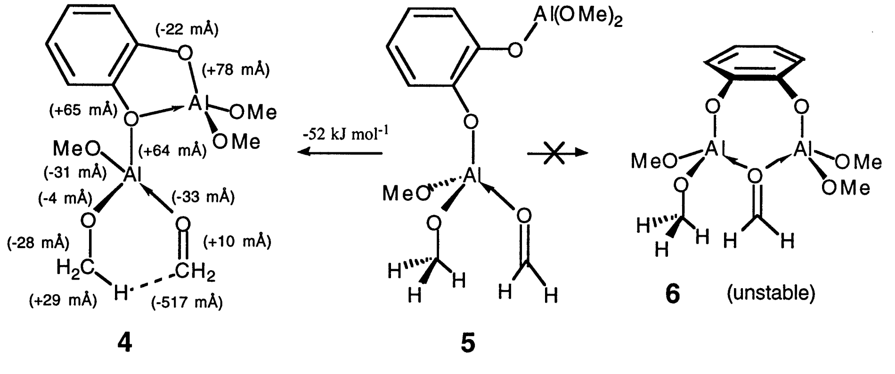
The results shown in Table 1 (entries 8 and 9) indicate that the conversion rates of conjugated unsaturated aldehydes are lower than those of the corresponding saturated ones (entries 3/8 and 6/9, Table 1). The lower reactivity could be attributable to the higher stability of conjugated aldehydes that decreases the rate of MPV reactions (for both formation of **B** and **B′**, Scheme 2). Also the rate of formation of **C** and **A′** should be lower in the case of conjugated aldehydes because the formation of the hemiacetal structure leads to the rupture of conjugation.

2.1. Computational studies—methods and models

Two simple isomeric analogs **4** (activated via chelation, Scheme 3) and **5** (not activated via chelation) of aldehyde adduct of **2b** were used as models of aldehyde adducts of **2a**. Plausible involvement of an isomeric 7-membered chelate ring system, in which both aluminum atoms of the catalyst would coordinate to the oxygen of the aldehyde moiety, was also considered using **6** as a model (Scheme 3). In **6** the aldehyde could be more activated (via bidentate chelation) than in **4** or **5**. All computational studies were carried out employing density functional methods using the non-local perturbative Becke–Perdew pBP model as implemented in the Spartan program[4] (version 5.0.3). All structures were fully optimized employing the standard options of the program (except, in the case of **5** a constraint of one torsion angle was used to prevent chelation).

2.2. Computational studies—results and discussion

Results of the computational studies indicate that **4** is significantly (i.e. 52 kJ mol^{-1}, Scheme 3) more stable than the open chain analog **5**. The 7-membered chelate system was found to be unstable (Scheme 3) indicating that this type of bidentate chelation is not favoring for aldehyde adducts of **2b**. A comparison of structural parameters of **4** and **5** reveals that, when the aluminum atom that binds the aldehyde moiety ($\mathrm{Al}_{\mathrm{H2CO}}$) is not activated (i.e. in the case of **5**, Scheme 3), the aldehyde moiety is less tightly bound to the catalyst than in complex **4** in which the Lewis acidity of the $\mathrm{Al}_{\mathrm{H2CO}}$ center is enhanced by the other aluminum atom (of the 5-ring), that coordinates on the adjacent phenoxyl oxygen. When the chelate structure is formed (**5**→**4**, Scheme 3) the Al–$\mathrm{O}_{\mathrm{H2CO}}$ bond shortens significantly and



Scheme 3.

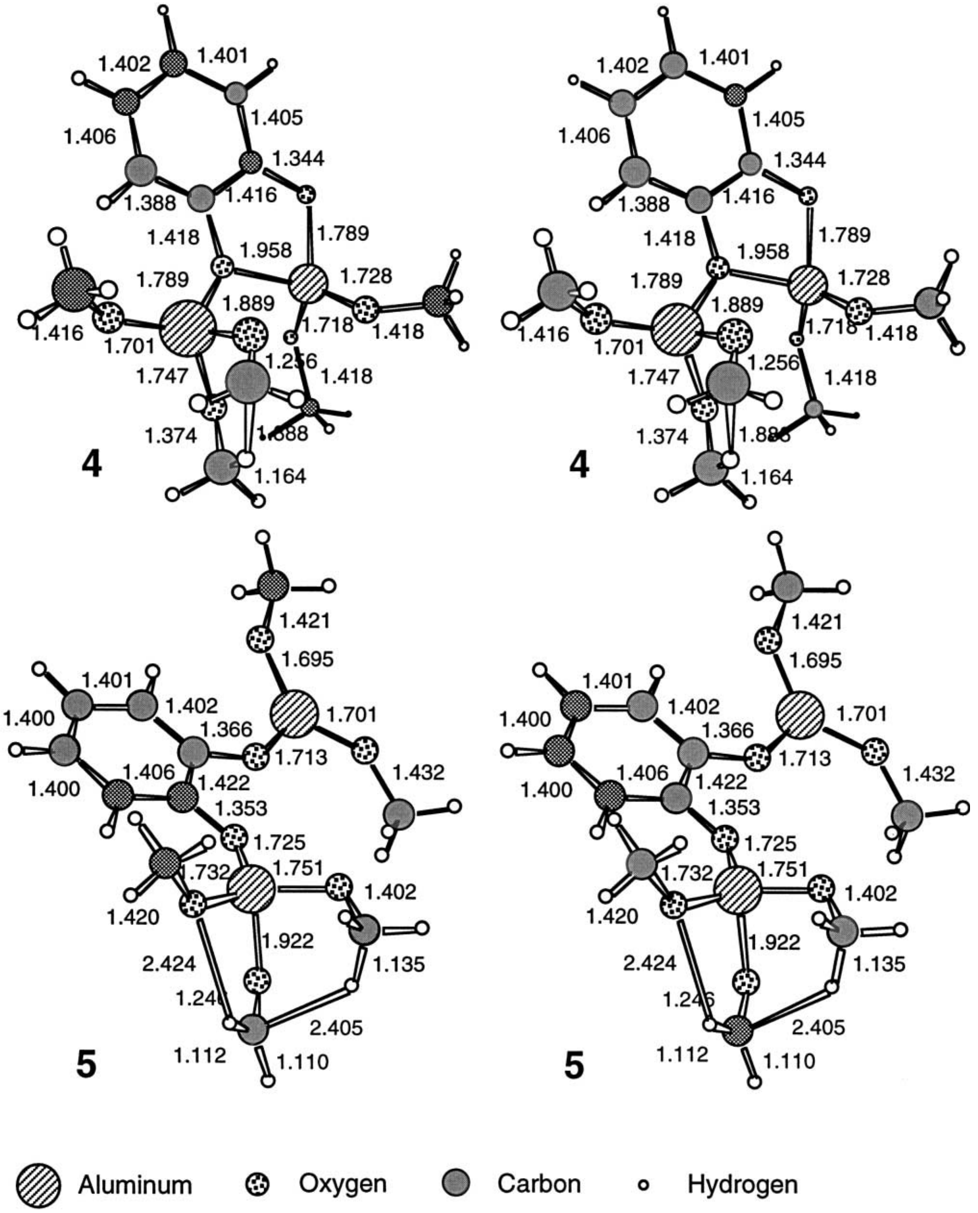


Figure 1. Optimized geometries (pBP/DNPP level) of isomers **4** and **5**. For the optimization of isomer **5** the trigonal aluminum was forced to the plane of the aromatic ring by fixing the torsion angle C–C–O–Al to zero degrees.

the attractive electrostatic interaction between one of the H_{H2CO} atoms and one of the oxygens of the adjacent methoxyl groups (the distance between these atoms is 2.424 Å in **5**, Fig. 1) is replaced with a favoring electrostatic H_{MeO}–C_{H2CO} interaction. When the reaction **5→4** occurs, the H_{MeO}–C_{H2CO} distance shortens by 517 mÅ (Scheme 3). In **4** the H_{MeO}–C_{H2CO} distance is surprisingly short, only 1.888 Å (Fig. 1). Consequently, also the $(H–C)_{MeO}$ bond lengthens by 29 mÅ and the adjacent $(C–O)_{MeO}$ shortens by 28 mÅ (Scheme 3), respectively. Interestingly, the geometry of the Al_{H2CO} center of **4** is highly favorable for the hydride-transfer to occur (much more favorable than in **5**, Fig. 1). In the case of a real working catalyst, the value of the corresponding H_{RO}–C_{RCHO} distance would depend significantly on the substituents of the alkoxy group (H_{RO} donator) and the aldehyde moiety (H_{RO} acceptor).

When the chelate **4** is formed (via **5→4**, Scheme 3) there is a newly formed 1.958 Å long dative Al–O bond between the aluminum atom of the 5-ring and the oxygen of the aryloxy group (O_{ArO}) adjacent to the Al_{H2CO} center (Fig. 1). Although this bond is clearly longer than any other of the Al–O bonds of **4** or **5** its formation has clear consequences. The bond between the O_{ArO} and Al_{H2CO} atoms lengthens 64 mÅ and consequently the Lewis acidity of the adjacent Al_{H2CO} center increases substantially. This enhanced Lewis acidity is reflected by all off-ring Al–O bonds of the Al_{H2CO} center. They all shorten (4, 31 and 33 Å, Scheme 3, Fig. 1). Both O_{MeO}–Al bonds of the trigonal aluminum center of **5** also shorten slightly. The Al–O_{ArO} bond of the trigonal aluminum lengthens 78 mÅ whereas the adjacent C_{Ar}–O bond shortens by 22 mÅ (Scheme 3).

In summary, inspection of all changes of bond lengths described above leads to the same rational conclusion: When the reaction **5→4** occurs (Scheme 3): (a) a dative

Al–O bond is formed, (b) other bonds of the aluminum forming the dative bond lengthen, (c) the (MeO)$_2$Al–O=CH$_2$ moiety at the oxygen end of the dative bond moves away from the newly formed 5-ring, (d) the Lewis acidity of the aluminum atom of the (MeO)$_2$Al–O=CH$_2$ moiety increases, and (e) the distance between one of hydrogens (of MeO) and the $\mathrm{C_{C=O}}$ shortens. Because the geometry of the (MeO)$_2$Al–O=CH$_2$ moiety of **4** resembles clearly more closely the transition state of the hydride-transfer step of the Tischtschenko reaction than the corresponding system of **5** does, we conclude that there could be clearly a co-operative effect of two aluminum atoms also in aldehyde complexes of the original catalyst **2a** favoring the Tischtschenko reaction that occurs via an intermediate analogous to **4** (Scheme 3).

3. Conclusions

Herein we have introduced a new and efficient method for synthesis of symmetric esters from aldehydes. Although the catalytic performance of **2a** is not better than that of **1**, this new method has an advantage in that catalyst **2a** is inexpensive. The new catalysts can efficiently utilize both straight-chain and branched-chain aldehydes, many of which are important starting materials for industrial processes (e.g. 2-ethylhexanal). Further studies on **2a–b** and **3** are in progress.

4. Experimental

4.1. General

Aldehydes and all the solvents were dried, distilled and preserved under inert atmosphere until use. Trimethyl aluminum (2 M in toluene or heptane) was obtained from Fluka. ^{1}H NMR spectra were provided using Varian spectrometer at 200 MHz and ^{13}C NMR spectra using Varian spectrometer at 50.3 MHz. For all samples CDCl$_3$ was used as a solvent and the measurements were conducted at 20°C. Chloroform CHCl$_3$ was used as a reference for ^{1}H NMR spectra (7.27 ppm) and D-chloroform for ^{13}C NMR spectra (77.0 ppm). Flash chromatography was carried out using Merck silica gel (40–63 μm) and thin layer chromatography (TLC) using Merck silica gel plates (60/$_{\mathrm{F254}}$).

4.2. Preparation of catalysts 2a (and 3)

Under inert argon atmosphere catechol (13.2 mg, 0.12 mmol; in the case of **3**: 13.2 mg, 0.10 mmol of gallol instead of catechol) was added to an oven-dried Schlenk flask equipped with a stirring bar. To the flask was added 1 mL dry CH$_2$Cl$_2$ (freshly distilled over CaH$_2$). The reaction flask was then carefully degassed and 2 M toluene solution of Me$_3$Al (0.12 ml, 0.24 mmol) was added followed by stirring at rt for 30 min. Addition of isopropanol (0.037 mL, 0.48 mmol; freshly distilled over CaH$_2$) followed by further stirring for 15 min gave the catalyst.

4.3. The Tischtschenko reactions

The reaction was initiated by adding freshly distilled *n*-butanal (1.1 ml, 12 mmol) drop-wise into the reaction flask containing the catalyst (under argon). The resulting mixture was stirred at rt for 2 h, quenched by adding 5 mL of HCl (0.5 M in water) and extracted with diethyl ether (3×10 mL). The combined extracts were dried over MgSO$_4$. After flash chromatography (ethyl acetate/hexane 1:4) gave *n*-butyl *n*-butyrate (845 mg, 5.9 mol) as colorless oil (99% yield). The other esters were prepared in the same way. The esters gave the following ^{1}H and ^{13}C NMR spectrometric data.

4.4. Spectroscopic data

^{1}H NMR and ^{13}C NMR data consistent with the literature in the case of *n*-butyl *n*-butanoate,[1] *n*-octyl *n*-octanoate,[1,5] 2-methylpentyl 2-methylpentanoate,[1] *c*-hexylmethyl *c*-hexylcarboxylate,[1,6] 2,2-dimethylpropyl pivaloate,[1,7] and benzyl benzoate.[1,8]

4.4.1. 2-Phenylpropyl 2-phenylpropanoate ^{1}H NMR data consistent with the literature.[9] ^{13}C NMR: δ (two diastereomers) 174.3 (C=O), 174.3 (C=O), 143.1 (C), 143.0 (C), 140.4 (C), 140.4 (C), 128.5 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 127.0 (CH), 126.5 (CH), 69.5 (OCH$_2$), 69.5 (OCH$_2$), 45.5 (CH), 45.5 (CH), 38.9 (CH), 38.8 (CH), 18.2 (CH$_3$), 18.2 (CH$_3$), 17.7 (CH$_3$), 17.7 (CH$_3$).

4.4.2. 2-Ethylhexyl 2-ethylhexanoate ^{1}H NMR data consistent with the literature (not all shifts given).[10] ^{1}H NMR: δ 4.0 (2H, d, J=5.5 Hz, OCH$_2$), 2.37–2.18 (1H, m, CH), 1.75–1.13 (16H, m, CH and 2CH$_2$), 1.00–0.86 (12H, m, 4CH$_3$). ^{13}C NMR: δ 176.5 (C=O), 66.3 (OCH$_2$), 47.6 (CH), 38.8 (CH), 31.9 (CH$_2$), 30.5 (CH$_2$), 29.7 (CH$_2$), 28.9 (CH$_2$), 25.6 (CH$_2$), 23.9 (CH$_2$), 23.0 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$), 14.0 (CH$_3$), 11.9 (CH$_3$), 11.0 (CH$_3$).

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