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Aluminum enolates via retroaldol reaction: catalytic tandem aldol-transfer—Tischtschenko reaction of aldehydes with aldol adducts of ketones to ketones

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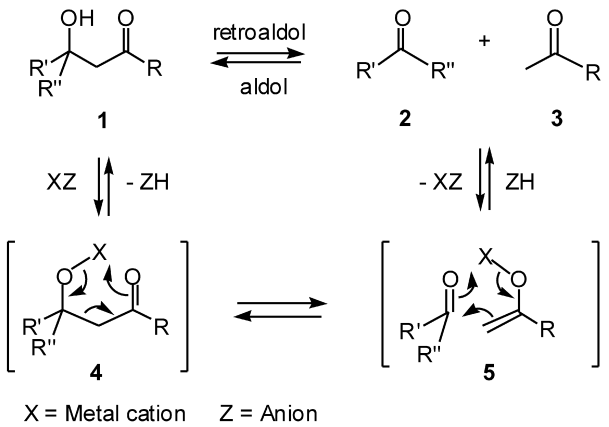
Abstract—Bidentate aluminum chelates derived from biphenol, binaphthol and catechol were found to be efficient catalysts for aldol-transfer reactions of ketone to ketone aldol adducts with aliphatic or aromatic aldehydes giving rise to the formation of aldol adducts of ketones to the aldehydes. In the presence of an excess of an aliphatic aldehyde, a catalytic tandem aldol-transfer—Tischtschenko reaction is observed. The tandem reaction produces monoesters of 1,3-diols with high *anti* selectivity and with modest to good chemical yield. 1,2-Unsaturated aldehydes are less reactive in the aldol-transfer reaction and require 2–4 times higher load of the catalyst to be used than aliphatic and aromatic aldehydes. Poor diastereoselectivity was observed in the formation of α-substituted aldols and 2-substituted monoesters of *anti*-1,3-diols indicating that the aldol-transfer reaction is not diastereoselective with the catalysts studied. The utility of the highly 1,3-*anti* selective formation of diolmonoesters was found to be limited by acyl migration.

1. Introduction

Aldol and retro aldol reactions (Scheme 1) are catalyzed by either acid or base. The reversibility of the aldol reaction, i.e. an equilibrium between aldol **1** and carbonyl compounds **2**+**3**, is one of the most important characteristics of the aldol reaction.[1] The equilibrium lies far on the side of aldol **1** in reactions between two molecules of aldehyde (R, R′=H) whereas in reactions between two molecules of ketone the equilibrium lies on the side[2] of retroaldol products **2**+**3** (R,R′,R″=alkyl, aryl). Conversion of aldol **1** (R,R′,R″≠H) to **2** and **3** is catalyzed, for example by metal alkoxides (generic XZ, Scheme 1) which deprotonate **1** giving rise to the formation of metal chelate **4**. Rearrangement of chelate **4** leads to the formation of a ketone–metal enolate complex **5**. When **5** is protonated (generic ZH), carbonyl compounds **2** and **3** are formed and the catalyst XZ is regenerated.

The retroaldol reaction has recently found several new applications. For instance, antibodies and enzymes have been found to catalyze retroaldol reactions allowing efficient kinetic resolution of racemic aldols.[3] Lewis- and Brønsted-acids as well as heating can promote epimerization of aldols proposed to occur[4] via retroaldol. The retroaldol reaction has been utilized for the synthesis of bicyclo[2.2.1]heptane and cyclopentane derivatives which in turn have been employed in the synthesis of variety of diterpenoids,[5] sesquiterpenes,[6] biarylcompounds,[7] and bicyclo[4,3,0]nonane derivatives.[8]

Recently, we presented[9] a novel aldol reaction of aldehydes, a so called aldol-transfer reaction, which in the presence of an aldehyde converts one aldol (source aldol, inexpensive)



Scheme 1. Retroaldol and aldol reactions illustrated with the equilibrium between aldol **1** and carbonyl compounds **2**+**3**. The equilibrium can be facilitated by a catalyst such as a metal alkoxide (generic XZ) which forms chelate **4** with aldol **1**. Cleavage of chelate **4** leads to complex **5** in which **2** is coordinated to the metal center of the enolate of **3**.

Keywords: aldol adducts; aluminum enolates; aldol-transfer.

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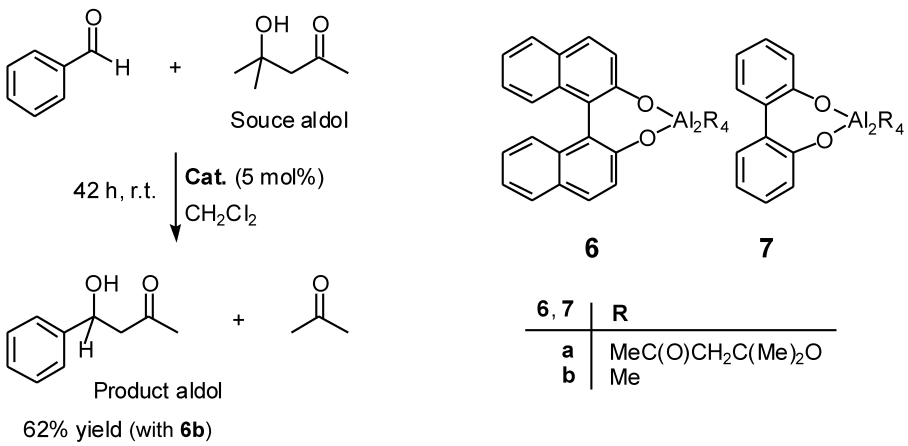
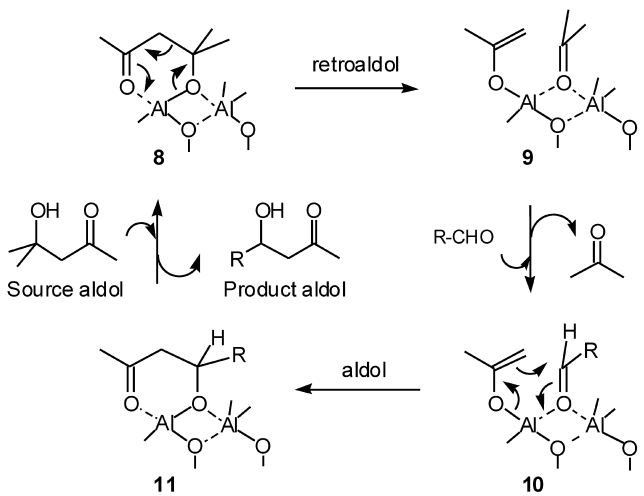


Scheme 2. An aldol-transfer reaction of diacetonealcohol (source aldol) with benzaldehyde can be catalyzed either by aluminum chelate **6** or **7**.

to another (product aldol, valuable) as described in Scheme 2.

With benzaldehyde and diacetone alcohol (as a source aldol), we found this reaction to be catalyzed by two metal units per ligand containing aluminum chelates of binaphthol and biphenol (Cat.=**6a** or **7a**, Scheme 2) and to give the product aldol with 62% yield. The catalyst **6a** (or **7a**) was prepared by allowing the ligand (1 equiv.) to react with trimethylaluminum (2 equiv.) to give **6b** (or **7b**) which was then reacted further with the source aldol to give **6a** (or **7a**). The corresponding reaction with a catalyst containing only one aluminum center gave a poor yield. Due to the involvement of two metal centers we proposed[9] the formation of the product aldol to occur via intermediates **8**–**11**, as described in Scheme 3.

When a terminal alkoxy group of the source aldol (diacetone alcohol in Scheme 3) is bound to the Lewis acidic aluminum atoms (in **6a** or **7a**) and the carbonyl group of the residue is activated by coordination to one of the aluminum atoms (as in **8**), a retroaldol reaction can occur giving rise to the formation of aluminum enolate complex **9** of acetone. This catalytic in situ formation of the aluminum enolate complex



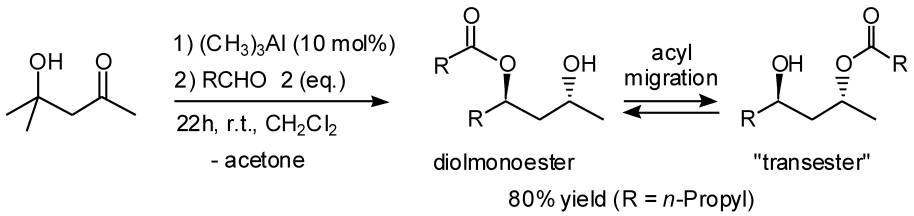
Scheme 3. A plausible mechanism for the aldol-transfer reaction of diacetonealcohol (source aldol) with an aldehyde R–CHO catalyzed by chelate **6** or **7**.

allows a subsequent ketone–aldehyde exchange reaction to occur and **9** is converted to more stable **10**. The subsequent aldol reaction of **10** leads to the formation of **11**, which, when reacting with diacetonealcohol, releases the product aldol and regenerates chelate **8** therefore, closing the catalytic cycle. This process renders the product aldol in modest to good yield[9] with electron poor aromatic or bulky aliphatic aldehydes.

The generality of our aldol-transfer technology was thereafter, confirmed by Schneider et al.[10] who after having studied a number of metal alkoxides discovered that, at lower temperatures and in a Lewis basic solvent (e.g. at −20°C in THF), $Zr(O^tBu)_4$ acts as a good catalyst for aldol-transfer reactions of aromatic aldehydes. From the mechanistic point of view the most interesting discovery of Schneider et al.[10] was the observation that $Zr(O^iPr)_4$ is a significantly poorer catalyst than $Zr(O^tBu)_4$. This reveals that enhanced steric crowding in the close neighborhood of the active center of the catalyst can be important for the performance of the aldol-transfer process.

As the aldol-transfer reaction (Schemes 2 and 3) produces an aluminum alkoxide of an aldol as a reactive intermediate (i.e. **11**, Scheme 3) it could be useful to combine an aldol-transfer reaction with another reaction needing such an aluminum alkoxide intermediate as its precursor. Such reactions, as the Tischtschenko reaction leading to the formation of diolmonoesters (Scheme 4), occur in a tandem fashion with aldol-transfer. We have recently, briefly reported[11] high yields and high *anti*-diastereoselectivities for a few diolmonoesters obtained using trimethylaluminum as a catalyst in the presence of two fold excess of aldehyde (relative to the source aldol). In the case of straight chain aldehydes diolmonoesters were accompanied with small amounts of transester (Scheme 4) formed via acyl migration.[11]

The formation of diolmonoester described in Scheme 4 can be rationalized as depicted in Scheme 5. An aldol-transfer reaction converts aluminum chelate **12** to chelate **13** of the product aldol. Insertion of aldehyde R–CHO into the Al–O bond of chelatete **13** (analogous to **11**, Scheme 3) can take place leading to the formation of hemiacetal derivative **14** (particularly in the presence of excess of R–CHO). A



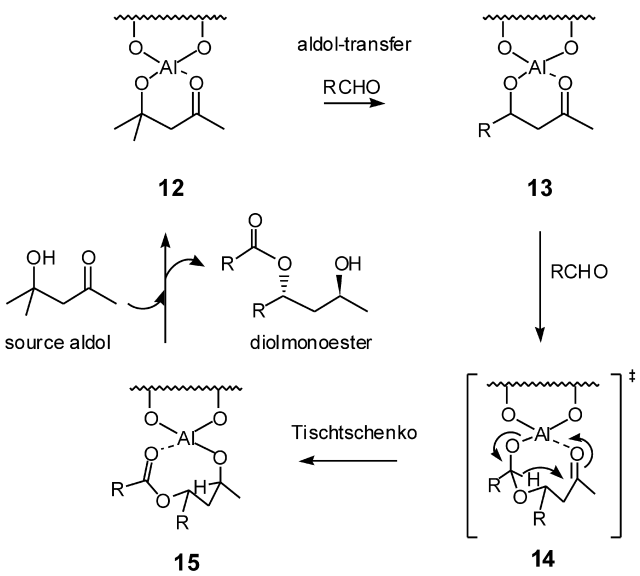
Scheme 4. A tandem aldol-transfer—Tischtschenko reaction of diacetonealcohol and aldehyde R–CHO catalyzed by aluminun chelate **20a** formed in situ when diacetonealcohol reacts with trimethylaluminum.

hydride-transfer reaction in **14** leads first to the formation of aluminum chelate **15** which reacts with the source aldol rendering diolmonoester **14**, regenerating chelate **12** and thereby, closing the catalytic cycle.

Later, Schneider et al. described[10] a similar formation of diolmonoesters–transester mixtures but using different catalysts. The intramolecular Tischtschenko reaction[12] has been studied by several groups as it has been recognized as a simple, mild and highly *anti*-diastereoselective method for the reduction of β-hydroxycarbonyl compounds to mono-acylated diols which can (including the transester side-product) be easily converted to an *anti*-1,3-diol. In the absence of source aldol, aluminum alkoxides convert aldehyde R–CHO highly efficiently[13] to symmetric esters via a Tischtschenko pathway.

Herein we report the synthesis of nine aldols **16a–i** and 11 diolmonoesters **17a–k** of which three aldols (**16b**, **16c** and **16g**) and seven diolmomoesters (**17b–g**, **17i**, **17k**) were not mentioned in the scientific literature before our studies (Chart 1).[9,11]

For the formation of these products, we describe four aluminum aryloxides **6a**, **7a**, **18a** and **19a** as catalysts which were prepared in situ from **6b**, **7b**, **18b**, **19b** reacted with diacetonealcohol. Results obtained with **6a** and **7a** (biphenol derivatives) were compared with those obtained using **19a** (catechol derivatives) and **20a–d** (Chart 2).



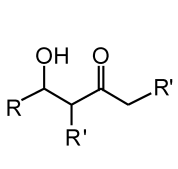
Scheme 5. A plausible mechanism of the tandem aldol-transfer—Tischtschenko reaction.

Catalysts **20a–d** form in situ from aldols **21a–d** when the aldols are reacted with trimethylaluminum. Reactions involving **20a–d** as catalysts can be considered autocatalytic because the catalyst is formed from a starting material and the catalyst is catalyzing both its own degradation and the formation of the final product. Neither aldol-transfer nor the related tandem aldol-transfer—Tischtschenko reactions of aldols **21b–d** appear to be published earlier in the scientific literature. Reactions of aldehydes with **21a** have been earlier briefly described by us (Al-based catalysts)[9,11] and then later by Schneider et al.[10] (Zr-based catalysts). With catalyst **19a** a simple model was computationally studied in order to probe bidentate chelating interactions of a C=O group of one alkoxy residue with the two Lewis acidic aluminum center of **19a**. The structure of the model was optimized using the Spartan[14] program (Chart 3).

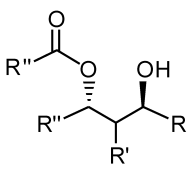
2. Results and discussion

The synthetic results on the preparation of diolmonoesters are summarized in Table 1 whereas, those related to the formation of aldols are shown in Table 2.

We have reported earlier[9] that both binaphtholic **6** and biphenolic **7** are good catalysts for aldol-transfer reactions of electron deficient aromatic and sterically hindered aliphatic aldehydes with **21a** (e.g. 73% yield of the product aldol with 2-ethylhexanal and 72% with pivaldehyde) whereas, poor catalytic performance with straight chain aliphatic aldehydes (e.g. 26% yield of the product aldol with butanal) was observed. On the other hand, we have observed earlier[11] that straight chain aliphatic aldehydes are good substrates for the tandem aldol-transfer—Tischtschenko reaction catalyzed by **20a** (e.g. 79% yield of diolmonoester with octanal). Therefore, the poor yield of aldol-transfer products with straight chain aldehydes in the reactions catalyzed by **6** or **7** are potentially attributable to the favor of Tischtschenko reaction, which converts the newly formed Al-chelate (**11**, Scheme 3) to a diolmonoester via a pathway similar to that described in Scheme 5 (**11** in place of **13**). Indeed, when **7** was allowed to catalyze the reaction of **21a** and butanal (2 equiv.) for 24 h diolmonoester **17a** was produced in 49% yield (entry 1, Table 1). With a prolonged reaction time the yield of **17a** improved considerably (e.g. 69% in 72 h, entry 2). Under the same reaction conditions and stoichiometry catalyst **19** (entry 4) showed clearly lower performance than **7** (entry 1). When yet a larger excess of butanal (4 equiv.) was used the yield improved further by 10% and we obtained **17a** in 47% yield (entry 5). However, when 5 mol% excess trimethylaluminum was added when **19** was prepared (i.e. the ligand/trimethylaluminum ratio



16



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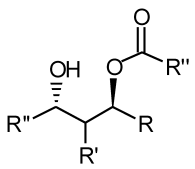


17'

16	R	R'
a	Ph	H
b	3-Heptyl	H
c	2-Pentyl	H
d	1-Phenylethyl	H
e	1-Heptyl	H
f	2,2-Dimethyl-2-propyl	H
g	3-Hept-3-enyl	H
h	Phenylethen-2-yl	H
i	Phenylethen-2-yl	Me

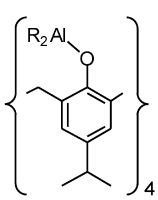
17, 17'	R	R'	R''
a	Me	H	*n*-Pr
b	Me	H	Et
c	Me	H	*n*-Hept
d	Me	H	*i*-Pr
e	Me	H	2-Pentyl
f	Me	H	*c*-Hex
g	*i*-Pr	H	*n*-Pr
h	Et	Me	*n*-Pr
i	*i*-Pr	H	*i*-Pr
j	Et	Me	Et
k	Et	Br	Et

Chart 1.

was 1:3) the yield of **17a** still improved significantly (to the level of 67%, entry 6 Table 1). Further, enhancing the amount (to 10 mol% excess, the ligand/trimethylaluminum ratio 1:4) had an adverse effect (58%, yield of **17a**, entry 7). Both reactions with extra trimethylaluminum gave rise to the formation of a small amount of isomeric transester **17a** of diolmonoester **17a** (**17a**/**17′a**=4:1, entries 6 and 7, Table 1). These attempts to improve the catalytic performance of **19** for the optimal formation of **17a** from butanal and **21a** did not reach the level of performance of **20a**. Catalyst **20a** produced **17a** in 80% yield and gave a more favorable ester/transester ratio (**17a**–**17′a**=5:1, entry 8, Table 1). In order to find out whether **19** could be a better catalyst (than **20a**) for any aldehyde we undertook a study in which we compare the best conditions found for **19** (i.e. **19a** with 5 mol% excess of trimethylaluminum, entry 6, Table 1) with those of **20a** (10 mol% catalyst **20a** formed in situ when trimethylaluminum is reacted with **21a**, entry 8) with aldehydes other than butanal. Both of these catalysts systems have the same relative aluminum/ligand ratio so that results are not blurred by effects related to different amounts of metal in the reaction mixtures.

The influence of the length of the alkyl chain of the aldehyde to the performance of the catalyst was studied by comparing the behaviour of *n*-propanal and *n*-octanal with that of *n*-butanal discussed above. With propanal both catalysts gave diolmonoester **17b** in practically the same yield (72% and 73%, entries 9 and 10, Table 1). This indicates that with the shorter alkyl chain the performance of **20a** declined whereas that of **19** improved. Both of these yields (72 and 73%) are similar to the 75% value reported[10] by Schneider et al. for the formation of **17b** using $Zr(O^tBu)_4$ as a catalyst. With octanal, results similar to these of butanal were produced. Diolmonoester **17c** was obtained in 61% yield with **19** and in 79% yield with **20a** (entries 11 and 12). The most similar reaction among those report[10] by Schneider et al. was the $Zr(O^tBu)_4$ catalyzed reaction of **21a** and *n*-heptanal which produced the corresponding diolmonoester **17** (R=Me; R′=H; R″=*n*-hexyl) even in 89% yield (in THF at −20°C).

With α-branched aldehydes effects different from those described above with the straight chain aldehydes were observed. When *i*-butyraldehyde (α-branched) was used instead of *n*-butyraldehyde the yield of diolmonoester produced by **21a** declined by 21% (59% yield of **17d**) from the 80% level of straight chain analog **17a** (entries 8 and 14, Table 1). With catalyst **19** an opposite change took place. The yield of **17d** was 72% whereas, the straight chain analog **17a** was obtained only in 67% yield (entries 6 and 13). Indeed, for the aldol-transfer reaction of *i*-butanal with **21a** we conclude that **19** can be a better catalyst than **20a**. However, when one of the symmetric branches of isobutanal was extended by two methylene units both catalysts **19** and **20a** gave diolmonoester **17e** in the same yield (81%, entries 15 and 16). With a rigid and symmetric α-branched substituent the catalytic activity of **19** was retained at the



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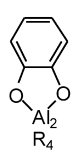
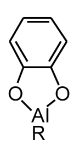
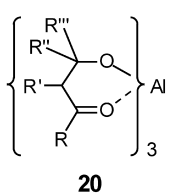


19



19'

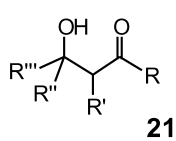
18, 19, 19'	R
a	$MeC(O)CH_2C(Me)_2O$
b	Me



20

20	R	R'	R''	R'''
a	Me	H	Me	Me
b	*i*-Pr	H	Me	*i*-Pr
c	Et	Me	Et	Et
d	Et	Br	Me	Me

Chart 2.

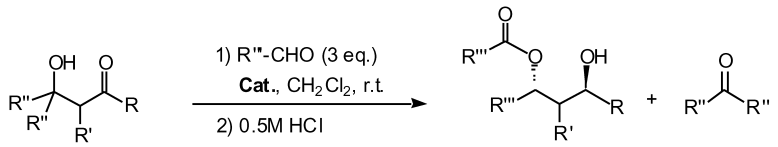


21

21	R	R'	R''	R'''
a	Me	H	Me	Me
b	*i*-Pr	H	Me	*i*-Pr
c	Et	Me	Et	Et
d	Et	Br	Me	Me

Chart 3.

Table 1. Tanden aldol-transfer—Tischtschenko reactions of six aliphatic aldehydes with self-aldols of acetone (**21a**), 3-methyl-2-butanone (**21b**), pentan-3-one (**21c**) and 4-bromo-5-hydroxy-5-methyl-hexan-3-one (**21d**) catalyzed by aluminum chelates in which the Lewis acidic aluminum can form a 7-memberred (**7**), 6-membered (**20**), or 5-membered (**19**) chelate ring



21 **17**

#	Aldehyde R″–CHO	Catal.[a] (mol%)	Additive used (mol%)[a]	Source aldol **21**	Rxn time (h)	Yield of **17** (%)[a,b]	Ester **17**/*trans*-ester **17**′[c]
1	Butanal[d]	**7** (5)	–	**21a**	24	**17a** (49)	–
2	Butanal[d]	**7** (5)	–	**21a**	48	**17a** (67)	–
3	Butanal[d]	**7** (5)	–	**21a**	72	**17a** (69)	–
4	Butanal[d]	**19** (5)	–	**21a**	20	**17a** (39)	–
5	Butanal[e]	**19** (5)	–	**21a**	20	**17a** (47)	–
6	Butanal	**19** (5)	Me_3Al (5)	**21a**	20	**17a** (67)	4:1
7	Butanal	**19** (5)	Me_3Al (10)	**21a**	20	**17a** (58)	4:1
8	Butanal	**20a** (10)	–	**21a**	21	**17a** (80)	5:1
9	Propanal	**19** (5)	Me_3Al (5)	**21a**	18	**17b** (72)	3:2
10	Propanal	**20a** (10)	–	**21a**	22	**17b** (73)	3:1
11	Octanal	**19** (5)	Me_3Al (5)	**21a**	21	**17c** (61)	4:1
12	Octanal	**20a** (10)	–	**21a**	22	**17c** (79)	4:1
13	2-Methylpropanal	**19** (5)	Me_3Al (5)	**21a**	20	**17d** (72)	–
14	2-Methylpropanal	**20a** (10)	–	**21a**	22	**17d** (59)	–
15	2-Methylpentanal	**19** (5)	Me_3Al (5)	**21a**	20	**17e** (81)	–
16	2-Methylpentanal	**10a** (10)	–	**21a**	22	**17e** (81)	–
17	*c*-Hexylaldehyde	**19** (5)	Me_3Al (5)	**21a**	21	**17f** (80)	4:1
18	*c*-Hexylaldehyde	**20a** (10)	–	**21a**	22	**17f** (74)	4:1
19	Butanal	**20b** (10)	–	**21b**	23	**17g** (62)	5:2[f]
20	Butanal	**20c** (10)	–	**21c**	22	**17h** (72)	4:3[f,g]
21	2-Methylpropanal	**20b** (10)	–	**21b**	21	**17i** (64)	–[f]
22	Propanal	**20c** (10)	–	**21c**	20	**17j** (53)	–[f]
23	Propanal	**20d** (10)	–	**21d**	20	**17k** (71)	–[h]

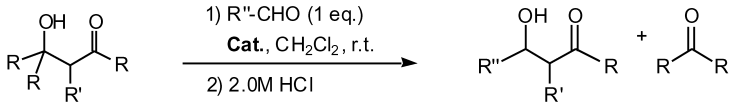
[a] The amount relative to source aldol **21**.
[b] Yield after a single run of flash chromatography (hexane/EtOAc 4:1); the values reported are calculated relative to the molar amount of source aldol **21** used.
[c] Migration of the R″C=O group to the adjacent OH gave rise to the formation of *trans*-ester **17**′.
[d] Only 2 equiv. of butanal used (instead of standard 3 equiv.).
[e] Four equivalent of butanal used (instead of standard 3 equiv.).
[f] Flash chromatography with hexane/EtOAc 10:1.
[g] Isolated as a 1:1 mixture of diastereomers.
[h] Isolated as a 65:35 mixture of diastereomers.

same level (**17f** produced in 80% yield, entry 17) whereas, that of **20a** slightly declined (**17f** produced in 74% yield, entry 18). Schneider et al. reported[10] a slightly higher yield (85%) for **17d** and a somewhat lower yield (70%) for **17f** using $Zr(O^tBu)_4$.

In addition to the comparison of the relative performance of reactions of **21a** catalyzed by **19** and **20a**, the general utility of the tandem aldol-transfer—Tischtschenko reaction was studied using precursor aldols **21b–d** of which the functional groups are more crowded than those of diacetonealcohol **21a**. The catalysts **20b–d** were prepared in situ from trimethylaluminum and **21b–d**. Therefore, when **20b** was used to catalyze the reaction **21b** with butanal, diolmonoester **17g** was obtained in 62% yield (entry 19, Table 1). This yield is 18% lower than that of the corresponding reaction catalyzed by **20a** (entry 8, Table 1) and the relative amount of transester formed with **21b** (5:2, entry 19) was higher than that obtained with **21a** (5:1, entry 8). When the *n*-propyl group of the aldehyde was replaced with an isopropyl group the yield did not change significantly (transester identical with the parent diolmonoester **17i** obtained in 64% yield, entry 21). The yield decreased less when all three methyl groups of source aldol **20a** were replaced with ethyl groups and the α-position was branched—with catalyst **20c** diolmonoester **17h** was obtained in 72% yield and as a 1:1 mixture of diastereomers (entry 20). Interestingly, this yield is only slightly lower than that obtained by Mahrwald et al.[15] using 20 mol% butyllithium–$Ti(O\text{-}i\text{-}Pr)_4$ adduct as a catalyst. As in the case of butanal (entries 8 and 20), the reaction of propanal and **21c** catalyzed by (more crowded) **20c** gave about 20% lower yield of **17j** than did the corresponding reaction of **21a** catalyzed by (less crowded) **20a** (entries 10 and 22). Diolmonoester **17j** was also provided as a 1:1 mixture of diastereomers. Finally, the formation of halogenated diolmonoester **17k** in 71% yield and as a 3:2 mixture of diastereomers, indicates that also enolates of α-halogenated ketones can be generated in situ and reacted with aldehydes using our tandem aldol-transfer—Tischtschenko methodology.

In light of the discussion above we conclude that our tandem aldol-transfer—Tischtschenko reaction appears to be an efficient and general method for the preparation of diolmonoesters **17** in 60–80% yields (Table 1) from aliphatic aldehydes and inexpensive self-aldols of ketones, particularly diacetonealcohol. Catechol-based catalyst **19**

Table 2. Aldol-transfer reactions of eight aromatic and aliphatic aldehydes with self-aldols of acetone (**21a**) and pentan-3-one (**21c**) catalyzed by aluminum chelates in which the Lewis acidic aluminum can form a 5-membered (**19**), 7-membered (**6** and **7**) or 8-membered (**18**) chelate ring



21a or **21c** **16**

#	Aldehyde R″CHO	Reaction time (h)	Catalyst (mol%)[a]	Source aldol	Additive (mol%)[a]	Yield of **1** (%)[a,b]
1	Benzaldehyde	22	**6** (5)	**21a**	–	**16a** (43)
2	Benzaldehyde	42	**6** (5)	**21a**	–	**16a** (62)
3	Benzaldehyde	22	**7** (5)	**21a**	–	**16a** (39)
4	Benzaldehyde	22	**7** (10)	**21a**	–	**16a** (53)
5	Benzaldehyde	3	**19** (5)	**21a**	–	**16a** (46)
6	Benzaldehyde	3	**19** (5)	**21a**	Me_3Al (5)	**16a** (47)
7	Benzaldehyde	18	**19** (5)	**21a**	–	**16a** (43)
8	Benzaldehyde	3	**19** (20)	**21a**	–	**16a** (42)
9	Benzaldehyde	4	**19** (5)	**21a**	**21a** (100)	**16a** (41)
10	Benzaldehyde	20	**18** (2.5)	**21a**	–	**16a** (45)
11	2,2-Dimethylpropanal	22	**6** (5)	**21a**	–	**16f** (72)
12	2,2-Dimethylpropanal	20	**19** (5)	**21a**	–	**16f** (55)
13	2-Methylpentanal	20	**19** (5)	**21a**	–	**16c** (25)[c,d]
14	2-Phenylpropanal	22	**7** (10)	**21a**	–	**16d** (63)[d]
15	2-Phenylpropanal	21	**19** (5)	**21a**	–	**16d** (40)[d,e]
16	2-Ethylhexanal	26	**6** (5)	**21a**	–	**16b** (73)[d]
17	2-Ethylhexanal	5	**19** (5)	**21a**	–	**16b** (33)[d]
18	2-Ethylhexanal	9	**19** (5)	**21a**	**21a** (100)	**16b** (52)[d]
19	Octanal	21	**19** (5)	**21a**	**21a** (100)	**16e** (25)[f]
20	2-Ethylhexenal	20	**19** (5)	**21a**	–	**16g** (27)
21	Cinnamaldehyde	22	**6** (5)	**21a**	–	**16h** (11)
22	Cinnamaldehyde	4	**19** (20)	**21a**	–	**16h** (58)
23	Cinnamaldehyde	4	**7** (20)	**21a**	–	**16h** (51)
24	Cinnamaldehyde	4	**19′** (100)	**21a**	–	**16h** (41)
25	Cinnamaldehyde	4	**19** (20)	**21c**	–	**16i** (54)[g]

[a] The amount relative to source aldol **21**.
[b] Yield after a single run of flash chromatography (hexane/EtOAc 4:1); the values reported are calculated relative to the molar amount of source aldol **21** used.
[c] Diolmonoester **17e** as an additional product (27%).
[d] The product aldol obtained as a 1:1 mixture of diastereomers.
[e] The corresponding diolmonoester as an additional product (19%).
[f] Diolmonoester **17c** as an additional product (19%).
[g] The *syn*/*anti* ratio was determined 46:54.

provided slightly better performance than **20a** with some α-branched aldehydes, particularly when the branches are symmetric (e.g. with *i*-butanal and cyclohexylcarbaldehyde). With straight chain aliphatic aldehydes **20a** is a better catalyst than **19**. Interestingly, the best yields of diolmonoester (81%, entries 15 and 16, Table 1) were obtained in the reactions of 2-methylpentanal with **21a**. In this reaction both catalysts **19** and **20a** gave **17e** in the same 81% yield. As expected on the basis of the mechanism (Scheme 5) of the formation of diolmonoesters, practically a complete control of the 1,3-*anti* diastereoselectivity was observed also with the formation of **17**. As we have described earlier,[11] we confirmed the relative stereochemistry of **17a** and **17d** produced in reactions of *n*-butanal and *i*-butanal with **21a** (entries 1–8, 13, 14 and 21, Table 1) by hydrolyzing **17a** and **17d** to the corresponding known[16] *anti*-1,3-diol. The diastereoselectivity of the process must be high because using NMR we detected only the signals of the *anti*-1,3-diol (i.e. signals of the corresponding *cis*-diol were not visible in the spectra).

As catalyst **19** appeared to be useful and an even better catalyst than **20a** for syntheses of some diolmonoesters **17**, we decided to test its performance in aldol-transfer reactions of aromatic and α,β-unsaturated aldehydes (Table 2) which are known to be less reactive substrates (than aliphatic aldehydes) for the Tischtschenko reaction. With aromatic and α,β-unsaturated aldehydes the second step of the tandem reaction (i.e. reaction of **13** with the aldehyde R–CHO leading to the formation of adducts **14** and **15**, Scheme 5) should be suppressed and the product of the reaction should remain at the aldol level (i.e. intermediate **13** would, instead of entering the pathway towards **14**, react with precursor aldol **21**, generate product aldol **16**, and regenerate intermediate **12**, Scheme 5). For purposes of a comparison we also studied the catalytic performance of **19** in aldol-transfer reactions with a few α-branched aldehydes which were found to be good substrates for the tandem aldol-transfer—Tischtschenko reactions discussed above.

When we compare aldol-transfer reactions of aromatic aldehydes catalyzed by **19** with those catalyzed by **6** and **7** we observe that **19** appears to work somewhat faster (Table 2). It catalyzes the formation of **16a** in 46% yield (entry 5, Table 2) in 3 h whereas, both **6** and **7** need 22 h to produce **16a** in 43 and 39% yields (entries 1 and 3). With **6** and **7** prolonged reaction times, as well as higher catalyst loading clearly improve the yield of **16a** (entries 2 and 4). We also have shown earlier[9] that using precursor aldol **21a** in excess can significantly improve the yield of **16**.

Furthermore, we also observed that adding a small excess of trimethylaluminum to **19** improves the yield of diolmonoester **17a** derived from **16a** (entries 5 and 6, Table 1). However, when we applied these techniques in order to enhance the catalytic performance of **19** for the formation of **16a**, we observed only adverse effects. With 5 mol% excess of trimethylaluminum (ligand/trimethylaluminum ratio 1:3) the yield of **16a** hardly changed (entries 5 and 6, Table 2). To our great surprise, prolonged reaction time (entry 7), higher catalyst loading (entry 8) and an excess of **21a** (entry 9) only decreased the yield of **16a**. In the light of these results we conclude that with catalyst **19** only 50% or less of benzaldehyde can be easily utilized for the formation of **16a**. Thus, the behaviour of **19** in aldol-transfer reactions of aromatic aldehydes appears to be very different from that of **6** or **7** (of which the catalytic performance was found to be significantly affected by changes of reaction conditions).

Catalyst **18** studied briefly for curiosity gave **16a** in 45% yield in 20 h (entry 10, Table 2). Thus, the behaviour of **18** resembles that of **6** and **7** indicating that not only conformationally restricted biphenol- or binaphthol-based systems (in **6** and **7** the active center of the catalyst in a 7-memberred ring) can be turned to an active catalyst for aldol-transfer reactions but also their analogs in which the aryl groups are separated with a methylene bridge (in **18** the active center of the catalyst in a 8-memberred ring) are capable of catalyzing the reaction.

The reactions of α-branched aldehydes catalyzed by **19** gave aldols **16** in considerably poor yields. The yields were also clearly lower that those obtained with **6** or **7** (entries 11–18, Table 2), including pivaldehyde, which as a very bulky aldehyde gave a clearly better yield of **16f** with **3** (72%, entry 11) than with **19** (55%, entry 12). The largest difference was seen in the case of 2-ethylhexanal which gave aldol **16b** in 73% yield with **6** (entry 16) but only in 33% yield with **19** (entry 17). The prolonged reaction time and the use of **21a** in 100 mol% excess improved the yield by about 20% but only to the level of 52% (entry 18). The proposed role of Tischtschenko reaction as a side-pathway leading to the decreased yields of aldols **16** was confirmed in the case of **16c** (25% yield from 2-methylpentanal, entry 13) and **16d** (40% from 2-phenylpropanal, entry 15). Aldol **16d** was obtained as a 35:65 mixture of diastereomers. In the former case diolmonoester **17e** was actually observed as the main product (27%) whereas, aldol **16d** was accompanied with 19% of the corresponding diolmonoester. Taking into account that the formation of diolmonoester requires 2 equiv. of the reactant aldehyde we calculate that both reactions consumed the aldehyde in almost equal 79% (25%+2×27%=79%) and 78% (40%+2×19%=78%) amounts. Therefore, it looks as if the formation of aldol **16** would stop when about 80% of the aldehyde precursor is consumed. Interestingly, the formation of diolmonoester **17** also stops when 81% of the precursor aldol **21a** is consumed (or earlier) in the presence of 2–3 equiv. of aldehyde (Table 1).

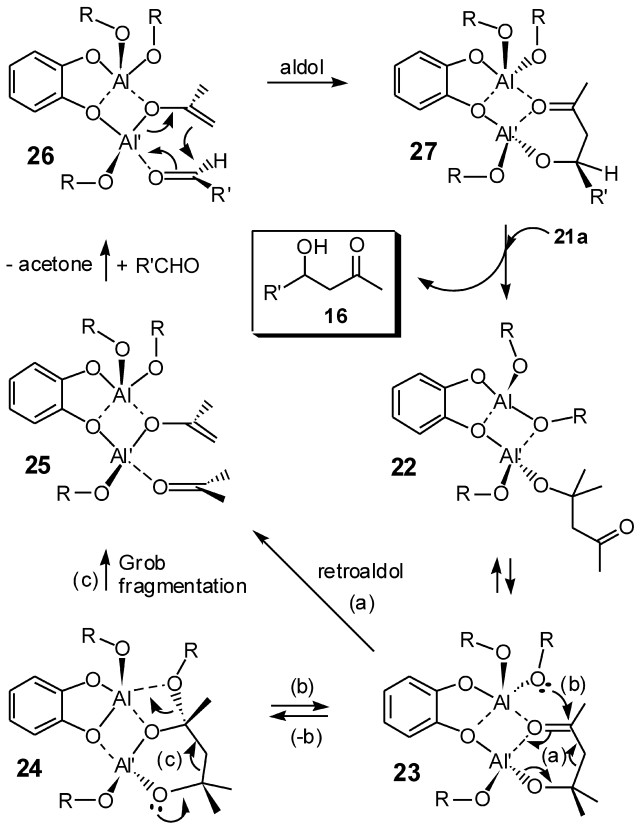
With reactions of straight chain aldehydes (such as of *n*-octanal) with **21a** catalyzed by **19** the yield remained low (e.g. aldol **16e** was obtained in 25% yield, entry 19, Table 2) despite of 100 mol% excess of **21a** used to promote the reaction. When the side-products of the reaction were analyzed diolmonoester **17c** was found to accompany **16e** in 19% yield (entry 19). Therefore, the aldol-transfer reaction of *n*-octanal stopped when 63% (25%+2×19%=63%) of *n*-octanal was consumed via the aldol-transfer pathway. Interestingly, the corresponding tandem aldol-transfer Tischtschenko reaction stopped practically at the same level but relative to the amount of **21a** (i.e. when 61% of **21a** was consumed, entry 11, Table 1).

Our earlier studies[9] suggested that catalysts **6** and **7** would be inefficient for the aldol-transfer reactions of α,β-unsaturated aldehydes (e.g. 11% yield of **16h** with the reaction of **21a** and cinnamaldehyde catalyzed by 5 mol% of **6**, entry 21, Table 2). However, we observed that with α,β-unsaturated 2-ethylhexenal catalyst **19** gave aldol **16g** in a yield which was only a few percent lower than that in which it gave **16b** with the corresponding saturated aldehyde (entries 17 and 20). Therefore, we decided to re-examine the aldol-transfer reaction of cinnamaldehyde and **21a**. However, when higher catalyst loading was used the rate of the reaction and the yield of **16h** (51% with **7** in 4 h, entry 23) improved substantially. Even better yield of **16h** was obtained by **19** (58%, entry 22). The related monometallated analog **19′** gave **16h** only in 41% yield although **19′** was used as a reagent (i.e. 100 mol% of **19′** relative to **21a**, entry 24). Finally, precursor aldol **21c**, which is more sterically hindered than **21a**, gave product aldol **16i** in 54% yield (entry 25) and with a 46:54 *syn*/*anti* ratio. These results on the formation of **16i** are practically equal to those (57% and 2.3:1 *syn*/*anti* ratio) reported earlier by Kobayashi et al.[17] Our results suggest that the poorer yields of diolmonoesters obtained with sterically hindered precursor aldols **21b–d** (Table 1) were not attributable to a decreased performance of the aldol-transfer reaction but to that of the subsequent Tischtschenko one.

2.1. Mechanism of the aldol-transfer reaction catalyzed by phenolic Al-chelates

The mechanism of aldol-transfer we proposed earlier is shown in Scheme 3. However, that mechanism based on the involvement of two Lewis acidic aluminum centers may be represented in a form, in which the carbonyl oxygen of the chelated diacetone alcohol residue is bound to both aluminum cations (i.e. involving bidentate chelation) as illustrated with the reactions catalyzed by **19a** (of which one plausible isomer is **22**) shown in Scheme 6.

Chelate **19a** may exist in a number of forms of intramolecular Lewis acid-base self-adducts, such as **22**. Inserting a carbonyl group to the alkoxy bridge in **22** could lead, potentially involving **23**, to the formation of **24** (via pathway (b), Scheme 6). Therefore, the required cleavage of diacetonealcohol bound to a catalyst such as **19a** could occur via the normal retroaldol pathway (a) from **23** to **25**, or via a Grob fragmentation type pathway (c) from **24** to **25**. A ketone–aldehyde exchange taking place in **25** could give intermediate **26** of which an aldol reaction leads to the formation of aluminum chelate **27** of the product aldol. An aldol exchange reaction of **27** would render the product (aldol **16**), regenerate the aluminum chelate **22** of the source aldol, and close the catalytic cycle.



Scheme 6. A plausible mechanism of the catalytic aldol-transfer reaction involving intermediates **23** and **24** with bidentate chelation of a carbonyl group with two aluminum centers of catalyst **19b**.

The major distictive feature of the mechanism depicted in Scheme 6 is the bidentate chelation of the carbonyl group (intermediates **23** and **24**). Maruoka et al. have demonstrated the utility of bidentate chelation[18] for activating carbonyl compounds and our discovery of the aldol-transfer technology was inspired[18b] by their studies. Our brief preliminary study using the non-local perturbative Becke–Perdew pBP model (pBP/DNPP) as implemented in the Spartan program (version 5.0.3 installed on a Silicon Graphics Origin 200 computer)[14] on a model compound **24′** (an analog of **24** of which the R groups are replaced with methyl groups, Scheme 6) indicates that intermediates such as **24** may exist. The optimized structure (provided employing the standard options of the program till the satisfactory stationary points were found, i.e. when the rms gradient converged to the tolerance 0.0003 a.u.) of **24′** along with selected information on bond lengths is shown in Figure 1. The optimized structure clearly reveals a 5-coordinate aluminum center and the oxygen of the carbonyl group in a bidentate chelate interaction with two aluminum atoms. The carbonyl seems to be stabilized and by a hemiacetal interaction with one of the methoxyl groups of the adjacent aluminum.

3. Conclusions

Herein we report an efficient, catalytic, convenient and highly diastereoselective method for the synthesis of *anti*-1,3-diolmonoesters from inexpensive aldols and aldehydes via a tandem aldol-transfer—Tischtschenko reaction. Modest to good yields of diolmonoesters were obtained. The utility of the method was illustrated with reactions of six different aliphatic aldehydes with two different precursor aldols (majority with diacetonealcohol) catalyzed by five aluminum chelates of aromatic phenolic compounds (majority with catechol, biphenol and binaphthol) and four aluminum chelates derived from aldols adducts of ketones to ketones (majority with diacetonealcohol). The utility of these catalysts for purposes of aldol-transfer reactions was also evaluated via the syntheses of nine different aldol adducts of ketones to aldehydes. Yields of the aldol-transfer reactions were lower than those of the related tandem aldol-transfer—Tischtschenko reactions. Analysis of side-products of a few aldol-transfer reactions revealed that the yields of the wanted product aldols are lower because the product of the aldol-transfer reaction undergoes a subsequent Tischtschenko reaction even when the precursor aldol/aldehyde ratio is 1:1.

4. Experimental

4.1. General

Aldehydes, diacetonealcohol and all solvents were dried, distilled and preserved under inert atmosphere until use. Calix[4]arene bi-2-naphthol, and biphenol and catechol were provided from Fluka and were used as such. Dry CH_2Cl_2 was freshly distilled over CaH_2. Trimethylaluminum (2 M in toluene or heptane) was obtained from Fluka.

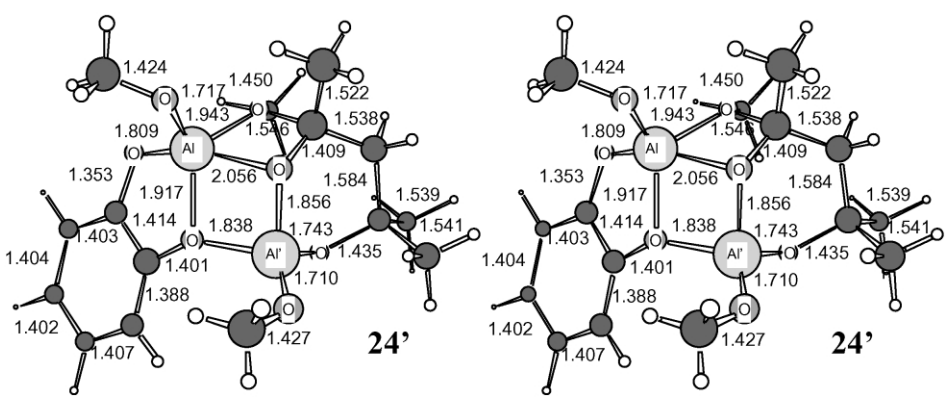


Figure 1. Optimized geometries (pBP/DNPP level) of model **24′**. Values of selected bond lengths are shown (Å).

^{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). No IR data is reported because most reactions gave mixtures of diastereomers. Diolmonoesters **17** contained always some amount of **17′**, because the isomerization reaction of **17** to **17′** is spontaneous under the Lewis acidic conditions of their synthesis and because the diastereomers were not separable with flash chromatography. Mixtures of non-separable diastereomers were produced also with α-branched aldehydes when converted to their aldol derivatives. Flash chromatography was carried out using Merck silica gel (40–63 μm) and thin layer chromatography (TLC) using Merck silica gel plates ($60/_{F254}$).

4.2. Preparation of precatalysts 6b and 7b

A suspension of bi-2-naphthol (23.2 mg, 80 μmol) in dry CH_2Cl_2 (1 mL) was degassed, and a 2 M solution of Me_3Al in toluene/heptane (80 μL, 0.16 mmol) was added at room temperature under argon and stirred for 60 min. Immediately after evolution of gas the solution obtained (containing **6b**) was cooled to 0°C. The cooled solution was used immediately to catalyze reactions of aldehydes. The preparation of **7b** (or **18b**) was carried out exactly in the same way, except instead of using 80 μmol bi-2-naphthol, biphenol (or Calix[4]arene for the formation of **18b**) was used the same molar amount.

4.3. Preparation of precatalysts 19b and 19b′

Under inert argon atmosphere catechol (13.2 mg, 0.12 mmol) was added to an oven-dried Schlenk flask equipped with a stirring bar. To the flask was added 1 mL dry CH_2Cl_2. The reaction flask was then carefully degassed and 2 M toluene solution of Me_3Al (0.12 mL, 0.24 mmol) was added followed by stirring at room temperature for 30 min. Precatalyst **19b′** was prepared exactly in the same way as **19b**, except instead of 0.12 mL (0.24 mmol) Me_3Al and 13.2 mg (0.12 mmol) catechol were used 1.00 mL (2.00 mmol) Me_3Al and 220 mg (2.00 mmol) catechol. The resulting solution was used immediately to catalyze reactions of aldehydes. In the case of reactions of which the catalyst was activated by Me_3Al simply 5 mol% (catechol/Me_3Al ratio=1:3) or 10 mol% (catechol/Me_3Al ratio=1:4) excess of Me_3Al was used for the preparation of the catalyst.

4.4. Preparation of precatalysts 20a–d

Trimethylaluminum in toluene (0.2 mmol, 0.1 mL) and 1 mL dry CH_2Cl_2 were added at room temperature to an oven-dried Schlenk flask filled with argon and equipped with a stirring bar. The resulting solution was immediately reacted with a large excess of precursor aldol **21a–d** in order to generate catalyst **20a–d** in situ. For example, in the case of a typical experiment 2 mmol (0.25 mL, 1 equiv.) of 4-hydroxy-4-methyl-2-pentanone **21a** was added in order to prepare a reaction media containing 10 mol% of **20a**. The resulting solution was used immediately to catalyze reactions of aldehydes.

4.5. Tandem aldol-transfer—Tischtschenko reactions catalyzed by 19a (5 mol%) synthesis of 17a

To a CH_2Cl_2 solution of catalyst **19a** (0.1 mmol in dry 1 mL), prepared under argon at room temperature in a Schlenk flask as described above, was added 0.248 mL diacetonealcohol (2.0 mmol) and 0.36 mL butanal (4.0 mmol) under, both dissolved in 1 mL of dry dichloromethane, by syringe. The reaction mixture was stirred for 20 h at room temperature and then poured to aqueous HCl (2 M) solution (5 mL) and extracted with diethylether (3×15 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvent and purification of the crude product by flash chromatography (hexane/ethylacetate=4:1) gave 2-hydroxyhept-4-ylbutanoate in 39% yield (**17a**, 160 mg, 1.6 mmol) as a colourless oil.

4.6. Tandem aldol-transfer—Tischtschenko reactions catalyzed by 21a–d (10 mol%)

Me_3Al in toluene (0.2 mmol, 0.1 mL) was added at room temperature under argon to dry CH_2Cl_2 (1 mL). To this solution was injected first 4-hydroxy-4-methyl-2-pentanone (**21a**, 2 mmol, 0.25 mL, 1 equiv.; in situ formation of **20a**) and immediately after that butanal (6 mmol, 0.54 mL, 3 equiv.). After stirring for 22 h the reaction mixture was poured into aqueous HCl solution (0.5 M, 5 mL) and extracted with diethylether (3×10 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvent and purification of the residual oil by flash chromatography gave 2-hydroxyhept-4-ylbutanoate in 80% yield (**17a**, 324 mg, 1.6 mmol) as a colourless oil. The reactions catalyzed by **10b–d** were conducted in the same way, except instead of **21a** (2 mmol) was used **21b**, **21c** or **21d** (each 2 mmol) and instead of butanal (6 mmol) another appropriate aldehyde was used (6 mmol).

4.7. Aldol-transfer reactions catalyzed by 6a, 7a and 18a (5 mol%)—synthesis of 16a

A suspension of bi-2-naphthol (23.2 mg, 80 μmol) in dry CH_2Cl_2 (1 mL) was degassed, and a 2 M solution of Me_3Al in toluene/heptane (80 μL, 0.16 mmol) was added at room temperature under argon and stirred for 60 min. Immediately after evolution of gas the solution obtained (containing **6b**) was cooled to 0°C. To the cooled solution were simultaneously added equal amounts (1.6 mmol) of benzaldehyde (0.16 mL) and diacetonealcohol (0.20 mL). After production of gas (in situ formation of **6a**) the clear light yellow solution obtained was allowed to warm up to room temperature. After stirring for 43 h, the mixture was poured into aqueous HCl (0.5 M) solution (5 mL) and extracted with diethyl ether. The combined extracts were dried over $MgSO_4$. Evaporation of solvents and purification of the residual oil by flash chromatography (silica gel, hexane/ethyl acetate=1:5) gave 3-oxo-1-phenyl-butan-1-ol (**16a**, 164 mg, 1.0 mmol) as colorless oil (62% yield). ^{1}H NMR (200 MHz, $CDCl_3$, 20°C, $CHCl_3$ 7.27 ppm): δ=7.4–7.2 (5H, m, Ph), 5.1 (1H, m, CH), 3.3 (1H, s, OH), 2.8 (2H, m, CH_2), 2.1 (3H, s, CH_3). For the corresponding reactions

catalyzed by **7a** (or **18a**) was used 26.5 mg/mL (0.14 mmol) biphenol (or 25.8 mg, 0.044 mmol Calixarene-4) instead of bi-2-naphthol.

4.8. Aldol-transfer reaction promoted by 19a (5 mol%)—synthesis of 16a

To a CH_2Cl_2 solution of catalyst **19a** (0.1 mmol in dry 1 mL), prepared under argon at room temperature in a Schlenk flask as described above, was added 0.26 mL diacetonealcohol (2.1 mmol) and 0.2 mL benzaldehyde (2.0 mmol) both dissolved in 1 mL of dry dichloromethane by syringe. The reaction mixture was stirred for three hours at room temperature and then poured to aqueous HCl (2 M) solution (5 mL) and extracted with diethylether (3×15 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvent and purification of the crude product by flash chromatography (hexane/ethylacetate=4:1) gave gave 3-oxo-1-phenyl-butan-1-ol (**16a**, 152 mg, 1.0 mmol) as colorless oil (46% yield).

4.9. Aldol-transfer reaction promoted by 19′a (100 mol%)—synthesis of 16h

Catechol 103.4 mg (0.9 mmol) was added to a Schlenk flask filled with argon. Dry CH_2Cl_2 (5 mL) was added to the flask. Trimethylaluminum 0.45 mL, 2 M in toluene or heptane (0.9 mmol) was added to the flask by syringe. The resulting mixture was stirred half an hour at room temperature. Subsequently 0.12 mL diacetonealcohol (**21a**, 0.9 mmol) and 0.12 mL cinnamaldehyde (0.9 mmol), both dissolved in 1 mL of dichloromethane and placed in separate syringes, were added to the reaction vessel. The reaction mixture was stirred for four hours at room temperature and then poured to aqueous HCl (2 M) solution (5 mL) and extracted with diethylether (3×15 mL). The combined extracts were dried over $MgSO_4$. Evaporation of the solvent and purification of the crude product by flash chromatography (hexane/ethylacetate=4:1) gave (*E*)-5-oxo-1-phenyl-hex-1-en-3-ol in 41.4% yield (**16h**, 74 mg, 0.39 mmol).

4.10. Spectroscopic data and elemental analyses

NMR data consistent with the literature was obtained in the case of known compounds **16a**,[19] **16d**,[20] **16e**,[21] **16f**,[22] **16h**,[23] **16i**,[17] **17a**,[24] **17h**,[15] **17j**,[25] **21b**.[26] Compound **21d** was prepared according to Masuda *et al.*[27] Our spectroscopic data for some of these compounds is reported below, because we obtained mixtures of diastereomers (including ester–transester mixtures). For aldol **16f**, which is well known,[22] we did not find original NMR data and therefore, we report our values. Compounds **17b**, **17d**, and **17f** have been mentioned by Schneider[10] and us[11] but without spectroscopic data. Compound **16b** has been mentioned earlier in the scientific litarature by[9] us and also in the patent literature.[28] Although the samples were purified with a single run of flash chromatography some minor impurities (roughly 10–15%) remained in the products. Therefore, we conclude that the accuracy of the determination of ester–transester and of diastereomeric ratios might not be better than 15%±5%.

We did not record IR spectra for new compounds synthesized because many of them were obtained as inseparable mixtures of diastereomers or a mixtures of isomers, such as diolmonoesters–transesters mixtures formed via acyl migration.

Elemental analyses were provided for compounds **17b**, **17b′**, **17c**, **17c′**, **17d**, **17e**, **17e′**, **17f**, **17f′**, **17g**, **17g′**, **17i**, **17k** and **17k′** using EAGER EA 1110 CHNS–O instrument. HMRS analyses were provided for compounds **16b**, **16e** and **16g** using JEOL JMS-SX102 Instrument. All new compounds prepared were oils.

4.10.1. Compound (16b). ^{1}H NMR: δ 4.06 (m, 1H, CH), 2.90 (s_{br}, 1H, OH), 2.54 (m, 2H, CH_2), 2.14 (s, 3H, CH_3), 1.54–1.09 (m, 9H, 3×CH_2+CH), 0.88 (t, J=7 Hz, 3H, CH_3) 0.87 (t, J=7 Hz, 3H, 2×CH_3). ^{13}C NMR: δ 210.30, 210.25, 68.75, 46.90, 44.51, 44.44, 30.79, 30.73, 29.57, 29.53, 28.92, 28.59, 23.03, 22.32, 21.86, 13.97, 11.65, 11.55. HRMS: $C_{11}H_{22}O_2-H_2O$ requires 168.1514 found168.1498.

4.10.2. Compound (16c). ^{1}H NMR: δ 4.01–3.83 (m, 1H, CH), 3.06 (s_{br}, 0.46H, OH), 2.93 (s_{br}, 0.54H, OH), 2.59–2.52 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.64–1.0 (m, 5H, 2×CH_2+CH), 0.95–0.82 (m, 6H, CH_3). ^{13}C NMR: δ 210.49, 210.33, 71.29, 70.71, 47.21, 46.20, 37.68, 37.63, 34.90, 34.51, 30.80, 30.76, 20.29, 20.19, 14.79, 14.26, 14.23.

4.10.3. Compound (16d). ^{1}H NMR: δ 7.30–7.11 (m, 5H, 5×CH), 4.17–4.04 (m, 1H, CH), 3.23–3.10 (s_{br}, 1H,OH), 2.81–2.66 (m, 1H, CH), 2.60–2.20 (m, 2H, CH_2), 2.10 (s, 1.05H, CH_3), 2.02 (s, 1.95H, CH_3), 1.32 (d, J=7 Hz 1.95H, CH_3), 1.26 (d, J=7.3 Hz, 1.05H, CH_3). ^{13}C NMR: 209.94, 143.78, 142.70, 128.48, 128.31, 128.05, 127.57, 126.55, 126.52, 72.16, 71.67, 47.92, 47.32, 45.46, 44.96, 30.82, 30.69, 17.65, 17.03.

4.10.4. Compound (16e). ^{1}H NMR: δ 4.02 (m, 1H, CH), 2.68–2.44 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 1.7–1.15 (m, 12H, 6×CH_2), 0.9–0.8 (m, 3H, CH_3). ^{13}C NMR: 209.94, 67.53, 49.93, 36.38, 31.78, 30.74, 29.49, 29.22, 25.44, 22.63, 14.08. HRMS: $C_{11}H_{22}O_2-H_2O$ requires 168.1514 found 168.1493.

4.10.5. Compound (16f). ^{1}H NMR: δ 3.70 (ddd, J=9.9, 2.9, 2.6 Hz, 1H, CH), 2.93 (d_{br}, J=2.9 Hz, 1H, OH), 2.61 (dd, J=17.2, 2.6 Hz, 1H, CH_2), 2.45 (dd, J=17.2, 9.9 Hz, 1H, CH_2), 2.18 (s, 3H, CH_3), 0.88 (s, 9H, 3×CH_3). ^{13}C NMR: 210.29, 74.76, 45.04, 34.13, 30.86, 25.61.

4.10.6. Compound (16g). ^{1}H NMR: δ 5.42 (t, J=7.2 Hz, 1H, CH), 4.49 (m, 1H, CH), 2.81 (d, J=3 Hz 1H, OH), 2.66 (d, J=7.7 Hz, 1H, CH_2), 2.65 (d, J=4.4 Hz, 1H, CH_2), 2.19 (s, 3H, CH_3), 2.06 (q, J=7.7 Hz, 2H, CH_2), 2.01 (dt, J=7.3, 7.3 Hz, 2H, CH_2), 1.44–1.22 (m, 2H, CH_2), 1.00 (t, J=7.7 Hz, 3H, CH_3), 0.90 (t, J=7.3 Hz, 3H, CH_3). ^{13}C NMR: δ 209.45, 141.57, 126.28, 71.33, 49.35, 30.77, 29.35, 22.79, 20.61, 14.16, 13.83. HRMS: $C_{11}H_{20}O_2$ requires 184.1463 found 184.1475.

4.10.7. Compound (16h). ^{1}H NMR: δ 7.23–7.4 (m, 4H, CH), 6.63 (dd, J=15.8, 1.1 Hz, 1H, CH), 6.2 (dd, J=15.8, 6.2 Hz, 1H, CH), 4.75 (tdd, J=6.2, 6.2, 1.1 Hz, 1H, CH),

2.75 (d, J=6.2 Hz, 2H, CH_2), 2.22 (s, 3H, CH_3). ^{13}C NMR: δ 208.80, 136.37, 130.32, 129.95, 128.48, 127.66, 126.39, 68.41, 49.92, 30.87.

4.10.8. Compound (16i). ^{1}H NMR: δ 7.35–7.10 (m, 5H, CH), 6.55 (dd, J=15.8, 1.4 Hz, 0.46H, CH), 6.53 (d, J=15.8 Hz, 0.54H, CH), 6.08 (dd, J=15.8, 7 Hz, 0.54H, CH), 6.07 (dd, J=15.7, 5.9 Hz, 0.46H, CH), 4.53 (m, 0.46H, CH), 4.30 (m, 0.54H, CH), 2.81 (d, 0.46H, J=3.6 Hz, OH), 2.77–2.62 (m, 1H, CH), 2.57 (d, J=4.6 Hz, 0.54H, OH), 2.53–2.33 (m, 2H, CH_2), 1.10 (d, J=7.4 Hz, 0.46×3H, CH_3), 1.03 (d, J=7.4 Hz, 0.54×3H, CH_3), 0.98 (t, J=7.4 Hz, 3H, CH_3). ^{13}C NMR: δ 215.90, 215.87, 136.43, 132.07, 131.17, 129.69, 129.03, 128.59, 128.56, 127.84, 127.67, 126.53, 126.46, 75.13, 72.41, 51.15, 50.46, 36.24, 35.42, 14.16, 10.96, 7.53, 7.46.

4.10.9. Compound (17a). ^{1}H NMR: δ=5.10–4.97 (1H, m), 3.65–3.56 (1H, m), 3.19 (1H, d_{br}, J=2.9 Hz), 2.28 (2H, t, J=7.5 Hz), 1.85–1.1 (8H, m), 1.16 (3H, d, J=6.2 Hz), 0.96 (3H, J=7.3 Hz), 0.87 (3H, J=7.1 Hz). ^{13}C NMR: δ=174.85, 71.23, 63.21, 44.58, 36.91, 36.32, 22.79, 18.66, 18.52, 13.8, 13.6.

4.10.10. Compound (17b/17b′). ^{1}H NMR: δ=5.27–5.08 (0.3H, m), 5.06–4.90 (0.7H, m), 3.74–3.55 (0.7H, m), 3.49–3.34 (0.3H, m), 3.1 (0.7H, s_{br}), 2.84 (0.3H, s_{br}), 2.36 (2.1H, q, J=7.7 Hz), 2.33 (0.9H, q, J=7.7 Hz), 1.70–1.40 (4H, m), 1.26 (0.9H, d, J=6.2 Hz), 1.17 (2.1H, d, J=6.2 Hz), 1.15 (2.1H, t, J=7.7 Hz), 1.14 (0.9H, t, J=7.7 Hz), 0.93 (0.9H, t, J=7.7 Hz), 0.90 (2.1H, t, J=7.6 Hz). ^{13}C NMR: δ=175.82, 175.19, 72.87, 68.73, 68.05, 63.30, 44.14, 43.94, 29.93, 27.81, 27.81, 27.73, 22.82, 20.75, 10.00, 9.80, 9.26, 9.16. MS m/z (Relative intensity), 156 (3, M^+-H_2O), 57 (100). Calc. C, 62.04; H, 10.41; O, 27.55 Meas. C, 62.10; H, 10.45; O, 26.82.

4.10.11. Compound (17c/17c′). ^{1}H NMR: δ=5.27–5.13 (0.15H, m), 5.12–4.96 (0.85H, m), 3.73–3.55 (0.85H, m), 3.54–3.41 (0.15H, m), 3.15 (1H, s_{br}), 2.33 (3H, t, J=7.3 Hz), 1.71–1.47 (4H, m), 1.36–1.21 (20H, m), 1.16 (3H, J=6.2 Hz), 0.87 (6H, m). ^{13}C NMR: δ=175.3, 175.23, 174.63, 71.58, 67.98, 67.40, 63.27, 44.68, 44.46, 37.14, 34.84, 34.59, 34.51, 31.79, 31.70, 31.62, 29.57, 29.26, 29.25, 29.13, 29.11, 29.09, 29.06, 28.87, 25.74, 25.47, 25.08, 25.05, 22.76, 22.62, 22.59, 22.54, 20.78, 14.01, 13.99. MS m/z (Relative intensity), 314 (1, $M^+-C_3H_8$), 127 (100). Calc. C, 72.56; H, 12.18; O, 15.26 Meas. C, 73.45; H, 13.27; O, 15.29.

4.10.12. Compound (17d). ^{1}H NMR: δ=4.84 (1H, ddd, J=9.1, 5.1, 4 Hz), 3.66–3.44 (1H, m), 3.22 (1H, s_{br}), 2.57 (1H, dhept, J=0.7, 7 Hz), 1.78 (1H, octet, J=6.6 Hz), 1.59–1.47 (2H, m), 1.16 (3H, d, J=7 Hz), 1.156 (3H, d, J=6.2 Hz), 1.15 (3H, d, J=7 Hz), 0.89 (6H, d, J=6.6 Hz). ^{13}C NMR: δ=178.50, 75.40, 63.19, 41.49, 34.27, 32.04, 22.82, 19.10, 19.00, 18.72, 17.48. MS m/z (Relative intensity), 187 (16, M^+-CH_3), 97 (100). Calc. C, 65.31; H, 10.96; O, 23.73 Meas. C, 65.10; H, 11.84; O, 23.56.

4.10.13. Compound (17e/17e′). ^{1}H NMR: δ=5.06–4.88 (1H, m), 3.66–3.47 (1H, m), 3.41 (1H, s_{br}), 2.57–2.36 (3H, m), 1.75–1.23 (11H, m), 1.17 (3H, d, J=6.2 Hz), 1.15 (3H, d, J=7 Hz), 0.94–0.81 (9H,m). ^{13}C NMR: δ=178.42, 178.32, 178.19, 74.71, 74.68, 73.89, 73.83, 63.29, 63.27, 63.24, 41.82, 41.80, 40.60, 40.60, 39.80, 39.75, 39.63, 39.60, 36.77, 36.74, 36.65, 36.64, 35.87, 35.86, 35.83, 35.80, 35.49, 34.40, 34.37, 22.88, 22.81, 20.46, 20.44, 20.34, 20.31, 20.1, 20.02, 17.34, 17.29, 17.25, 15.32, 14.53, 14.50, 14.18, 14.12, 13.87, 13.85. MS m/z (Relative intensity), 243 (3, M^+-CH_3), 117 (100). Calc. C, 69.72; H, 11.70; O, 18.58 Meas. C, 69.97; H, 12.49; O, 18.21.

4.10.14. Compound (17f/17f′). ^{1}H NMR: δ=5.24–5.04 (0.17H, m), 4.92–4.80 (0.83H, m), 3.65–3.45 (1H, m), 3.21 (1H, s_{br}), 2.41–2.22 (1H, m), 1.98–0.94 (23H, m), 1.16 (3H, d, J=6.2 Hz). ^{13}C NMR: δ=177.56, 74.79, 63.16, 43.51, 41.89, 41.57, 29.24, 29.22, 29.15, 28.06, 26.31, 26.04, 25.97, 25.67, 25.43, 25.38, 22.79. MS m/z (Relative intensity), 282 (2, M^+), 111 (100).

4.10.15. Compound (17g/17g′). ^{1}H NMR: δ=5.18–5.01 (0.7H, m), 4.95–4.86 (0.3H, m), 3.43–3.32 (0.3H, m), 3.25–3.13 (0.7H, m), 3.07 (0.3H, d, J=3.7 Hz), 2.93 (0.7H, d, J=4.4 Hz), 2.33 (0.6H, t, J=7.3 Hz), 2.31 (1.4H, t, J=7.3 Hz), 1.85–1.2 (9H, m), 1.00–0.83 (12H, m). ^{13}C NMR: δ=174.92, 175.12, 75.65, 71.78, 71.47, 66.80, 39.81, 39.52, 39.19, 37.13, 36.41, 36.37, 33.41, 32.11, 19.00, 18.77, 18.72, 18.67, 18.56, 18.56, 17.87, 17.66, 13.99, 13.79, 13.66, 13.63. MS m/z (Relative intensity), 187 (28, $M^+-C_3H_8$), 71 (100). Calc. C, 67.79; H, 11.38; O, 20.84 Meas. C, 68.51; H, 11.47; O, 21.33.

4.10.16. Compound (17h/17h′). ^{1}H NMR: δ=5.35–5.10 (0.5H, m), 4.95–4.75 (0.5H, m), 3.65–3.35 (1H, m), 3.18–2.95 (0.5H, m), 2.52–2.43 (0.5H, m), 2.4–2.25 (2H, m), 1.85–1.15 (9H, m), 1.02–0.79 (12H, m). ^{13}C NMR: δ=175.08, 174.58, 174.50, 77.56, 76.23, 75.49, 73.75, 73.25, 71.86, 71.49, 69.54, 42.90, 42.80, 40.97, 40.91, 36.41, 36.31, 34.54, 34.21, 27.06, 26.76, 25.45, 24.93, 19.59, 19.27, 18.76, 18.62, 18.59, 18.55, 14.10, 14.00, 13.87, 13.78, 13.66, 10.80, 10.48, 9.88, 9.85, 9.78, 9.54, 9.05.

4.10.17. Compound (17i). ^{1}H NMR: δ=4.96–4.83 (1H, m), 3.16–3.01 (1H, m), 2.98 (1H, s_{br}), 2.57 (1H, hept, J=7 Hz), 1.92–1.37 (4H, m), 1.16 (6H, d, J=7 Hz), 0.90 (9H, d, J=6.6 Hz), 0.87 (3H, d, J=6.6 Hz). ^{13}C NMR: δ=178.35, 75.51, 71.81, 36.40, 34.31, 33.48, 32.22, 19.10, 19.08, 18.81, 18.69, 17.92, 17.52. MS m/z (Relative intensity), 187 (37, $M^+-C_3H_8$), 99 (100). Calc. C, 67.79; H, 11.38; O, 20.84 Meas. C, 68.31; H, 12.31; O, 20.67.

4.10.18. Compound (17j/17j′). ^{1}H NMR: δ=5.15 (0.55H, ddd, J=8.8, 4.8, 1.8 Hz), 4.82 (0.45H, dt, J=8.4, 3.7 Hz), 3.53–3.40 (0.55H, m), 3.38 (0.55H, s_{br}), 3.11–2.96 (0.45H, m), 2.46 (0.45H, s_{br}), 2.38 (1.35H, q, J=7.7 Hz), 2.36 (1.65H, q, J=7.7 Hz), 1.87–1.20 (5H, m), 1.16 (1.35H, t, J=7.7 Hz), 1.15 (1.65H, t, J=7.7 Hz), 1.00–0.79 (9H, m). ^{13}C NMR: δ=175.88, 175.34, 77.55, 75.52, 73.21, 71.46, 42.41, 40.41, 27.76, 27.05, 26.76, 25.41, 24.91, 10.80, 10.56, 9.77, 9.77, 9.52, 9.33, 9.29, 8.95.

4.10.19. Compound (17k/17k′). ^{1}H NMR: δ=5.16–5.03 (1H, m), 4.0 (0.4H, dd, J=8.06, 2.2 Hz), 3.91 (0.6H, dd, J=1.1, 4.6 Hz), 3.80 (0.6H, dd, J=9.5, 1.8 Hz), 3.48–3.31

(1H, m), 2.45 (1.2H, q, J=7.7 Hz), 2.41 (0.8H, q, J=7.7 Hz), 2.14–1.39 (4H, m), 1.20 (1.8H, t, J=7.7 Hz), 1.18 (1.2H, t, J=7.7 Hz), 0.99 (1.8H, t, J=7.3 Hz), 0.97 (1.2H, t, J=7.3 Hz), 0.93 (3H, t, J=7.3 Hz). ^{13}C NMR: δ=176.08, 174.45, 74.72, 72.76, 72.26, 70.70, 61.40, 60.34, 28.62, 27.58, 27.56, 27.05, 26.80, 25.26, 9.92, 9.76, 9.50, 9.18, 9.09, 9.09. MS *m/z* (Relative intensity), 249 and 251 (15, M^+-OH), 57 (100). Calc. C, 44.96; H, 7.17; O, 17.97 Meas. C, 46.91; H, 7.66; O, 17.59.

4.10.20. Compound (21b). ^{1}H NMR: δ 4.12 (s, 1H, OH), 2.58 (s, 2H, CH_2), 2.57 (sept., J=6.6 Hz, 1H, CH), 1.73 (sept., J=7.0 Hz, 1H, CH), 1.08 (s, 3H, CH_3), 1.07 (d, J=6.6 Hz, 6H, 2×CH_3), 0.90 (d, J=7.0 Hz, 3H, CH_3), 0.85 (d, J=7.0 Hz, 3H, CH_3). ^{13}C NMR: δ 217.70, 73.93, 46.60, 42.23, 37.26, 22.87, 17.81, 17.70, 17.60, 16.77.

4.10.21. Compound (21c). ^{1}H NMR: δ 3.65 (s, 1H, OH), 2.71 (1H, q, J=7.3 Hz, CH), 2.63 (dq, J=7.3, 18.3 Hz, 1H, CH_2), 2.45 (dq, J=7.3, 18.3 Hz, 1H, CH_2), 1.65–1.30 (m, 4H, 4×CH), 1.11 (d, J=7.3 Hz, 3H, CH_3), 1.05 (t, J=7.3 Hz, 3H, CH_3), 0.86 (t, J=7.3 Hz, 3H, CH_3), 0.80 (t, J=7.7 Hz, 3H, CH_3). ^{13}C NMR: δ 211.07, 75.51, 49.21, 37.37, 29.67, 26.42, 11.55, 7.81, 7.56, 7.37.

4.10.22. Compound (21d). ^{1}H NMR: δ 4.27 (s, 1H, CH), 3.50 (s, 1H, OH), 2.89 (dq, J=18.32, 7.3 Hz, 1H, CH_2), 2.62 (dq, J=18.32, 7.3 Hz, 1H, CH), 1.387 (s, 3H, CH_3), 1.383 (s, 3H, CH_3), 1.11 (t, J=7.3 Hz, 3H, CH_3). ^{13}C NMR: δ 206.94, 71.12, 60.16, 34.80, 27.44, 26.82, 7.91.

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