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Acid-catalyzed aldol-Meerwein–Ponndorf–Verley-etherification reactions—access to defined configured quaternary stereogenic centers

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ABSTRACT

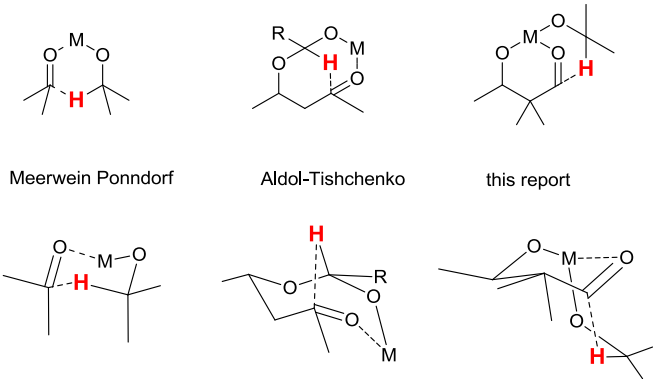
A novel asymmetric aldol-reduction–etherification process of aliphatic enolizable aldehydes is described. The intermediately formed aldol adducts—β-hydroxyaldehydes—were reduced and transformed into the corresponding 1,3-diol ethers by external secondary alcohols at the same time. Thus, with the help of chiral secondary alcohols an access to optically active 1,3-diol ether is given. Furthermore, asymmetric cross-aldol-Meerwein–Ponndorf reactions of enolizable aldehydes can also be realized under these reaction conditions.

1. Introduction

The Meerwein–Ponndorf–Verley reduction (MPVR) of ketones has a prominent significance and a striking usefulness in organic synthesis. It is reversible, and the reverse reaction is known as the Oppenauer oxidation (OO). Several highly diastereoselective MPV-processes[1] and their extension to the synthesis of chiral 1,3-mercapto alcohols[2] were reported. On the other hand, examples of asymmetric MPV-processes are rare and lacking in general application.[3] Several chiral metal complexes were tested in enantioselective execution of the MPV-reaction but they are mostly devoted to aromatic ketones.[4] Satisfying examples of asymmetric execution in the aliphatic series are still unknown, with the exception of biocatalytical hydrogen transfer reactions.[5] In contrast, several synthetic enlargements of this important redox process have been reported, where the MPV-reaction is incorporated into C–C bond formation processes. These are MPV-aldol condensation processes,[6] and MPV/Brook rearrangement/aldol addition.[7] Also, the formal MPV-alkynylation,[8] MPV-cyanation,[9] MPV-allylation,[10] and MPV-transfer aldol reaction[11] should be mentioned here.

During the Meerwein–Ponndorf–Verley-reaction a 1,5-hydride shift occurs. A metal ion increases the electrophilic nature of the carbonyl group and a 1,5-hydride shift occurs from an external secondary alcohol (mostly isopropanol) to reduce the carbonyl compound.[12] A cyclic six-membered transition state is generally accepted as the mechanism of this hydride transfer.[13]

Also, a similar hydride shift is observed in the aldol-Tishchenko reaction. During this reaction a second molecule of the starting aldehyde generates an acetal intermediate to reduce the ketone by a 1,5-hydride shift. As a consequence corresponding 1,3-diol esters were obtained with extremely high degrees of diastereoselectivity. But again, high enantioselectivities were obtained in these reactions only when used with aromatic ketones as substrates.[14] When starting with corresponding racemic aldol adducts 1,3-diol esters were detected with good enantioselectivities.[15]



Scheme 1. Comparison of 1,5-hydride transfer-reactions.

These findings contrast results we have observed in enantioselective aldol-Meerwein–Ponndorf–Verley-etherification processes of enolizable aldehydes.[16] In these transformations enolizable

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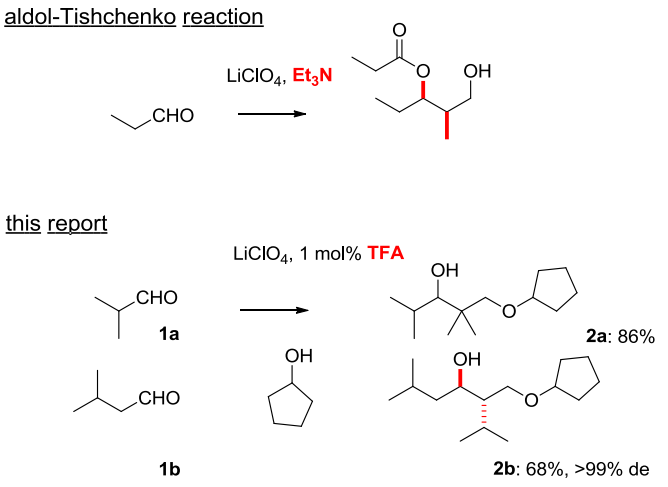
aldehydes react in the presence of catalytic amounts of acids and an external secondary alcohol to give the corresponding 1,3-diol ether—a product derived from an aldol addition, Meerwein–Ponndorf–Verley reduction and etherification sequence. Again, a 1,5-hydride shift, as is shown in Scheme 1, is observed under these reaction conditions. As a consequence, the formation of a primary alcohol followed by etherification is observed. The real reaction mechanism is still unknown so far. A Meerwein–Ponndorf–Verley reduction of intermediately formed hemiacetals to give 1,3-diol ethers cannot be excluded.

Herein we expand this novel transformation to a highly stereoselective intramolecular version with dialdehydes. Furthermore, we describe this transformation for both series—the synthesis of *R*- and *S*-configured 1,3-diol methyl ether. In addition, we provide a mild and useful procedure for the cleavage of resulting methyl ether.

2. Results and discussion

During our ongoing studies of the application of $LiClO_4$ in organic reactions we observed aldol reactions attended by a simultaneous hydride transfer. The type of hydride transfer strongly depends on reaction conditions. When used with bases an aldol-Tishchenko process is observed. The corresponding *syn*-configured 1,3-diol monoesters were detected in this case.[17] In contrast to that an aldol addition/MPV-reduction/etherification reaction sequence is observed by deployment of acids[18] and an external alcohol (cyclopentanol for **2a** and **2b**). The corresponding 1,3-diol cyclopentyl ethers **2a** and **2b** were isolated in high yields. By application of α-unbranched aldehydes extremely high degrees of anti-diastereoselectivity were noticed (**2b**, Scheme 2).



Scheme 2. Comparison of aldol-Tishchenko reaction and aldol-Meerwein–Ponndorf–Verley-etherification reaction.

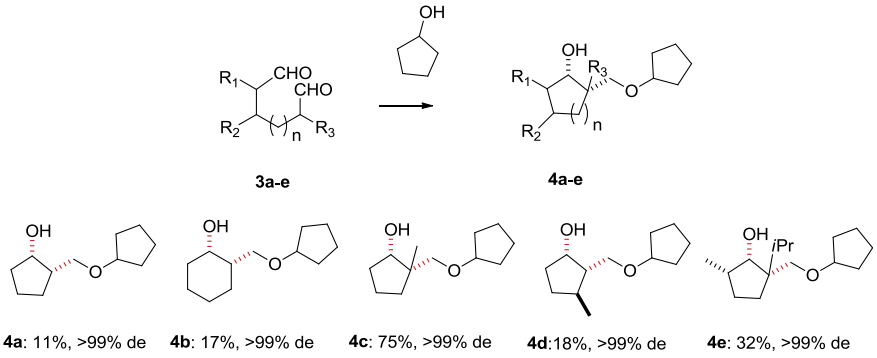
In a following first series we explored the intramolecular version of this reaction. To this end we reacted several enolizable dialdehydes with cyclopentanol in the presence of $LiClO_4$ and catalytic amounts of trifluoroacetic acid (TFA). Extremely high degrees of diastereoselectivities were detected. The 1,3-diol cyclopentyl ethers **4a**–**e** were isolated as a single diastereoisomer (Scheme 3). A typical tendency for preferring the formation of a quaternary carbon atom is observed under these reaction conditions, if one compares the results of intramolecular aldol addition-MPV-etherification of adipaldehyde **3a** (**4a**: 11% yield) and heptanedial **3b** (**4b**: 17% yield) with those of α-methyl adipaldehyde **3c** (**4c**: 75% yield).

To analyze the source and fate of hydride deuterated cyclohexanol was deployed in these reactions. Isobutyraldehyde was reacted with C1-deuterated cyclohexanol in the presence of catalytic amounts of trifluoroacetic acid and lithium perchlorate. The expected 1,3-diol cyclohexyl ether was isolated in addition to equimolar amounts of cyclohexanone (Scheme 4).

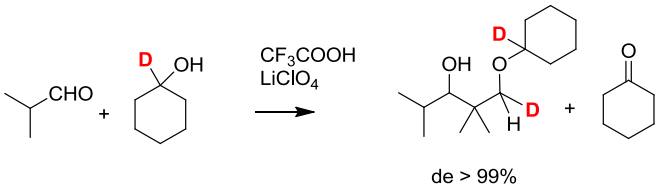
One equivalent of C1-deuterated cyclohexanol was oxidized to reduce the assumed intermediate β-hydroxyaldehyde. A second equivalent of C1-deuterated cyclohexanol was used for the etherification. Subsequent analysis revealed the full incorporation of deuterium.[19,20] Again, one single diastereoisomer was detected by ^1H NMR experiments. These interesting findings should offer the possibility of an enantioselective access to optically active 1,3-diol ether. To this end several chiral secondary alcohols were tested in these reactions, but only with moderate success. Racemization of the starting chiral secondary alcohols was observed under the conditions of this aldol-MPV process. At that point we decided to deploy two alcohols in these reactions—one for the etherification process and an additional chiral alcohol for the hydride transfer. To this end we have tested a series or different alcohols in homo-aldol-MPV-etherification reaction of isobutyraldehyde (Scheme 5).

The results clearly indicate the fundamental role played by the alcohols deployed in these reactions. The observed yields correspond to the oxidation enthalpies of the according alcohols.[21] Cyclopentanol, the alcohol with the lowest oxidation enthalpy, is oxidized very easily to give cyclopentanone and thus the highest yields of 1,3-diol ether (**2a**: 86%). On the other hand—methanol is the alcohol with the highest oxidation enthalpy in this series—is nearly resistant against oxidation under these reaction conditions. As a consequence, the 1,3-diol methyl ether was observed in very low yield (**5a**: 12%). Based on these remarkable differences a following comfortable situation appeared: methanol can be used as the etherification-alcohol and optical pure menthol, a secondary and competitive sterically demanding alcohol, should serve as the chiral hydride source.[22] By a careful optimization of the reaction conditions the following protocol was elaborated.

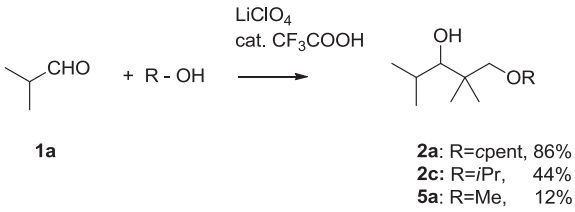
The reactions were carried out in the presence of dry $LiClO_4$[23] and catalytic amounts of trifluoroacetic acid (0.1 mol %) at rt. Best results with regard to yields were obtained in the absence of any



Scheme 3. Intramolecular aldol-Meerwein–Ponndorf–Verley-etherification process. Reaction conditions: rt, neat, 6 equiv $LiClO_4$, 1 mol % TFA, 2 equiv cyclopentanol.



Scheme 4. Stereoselective incorporation of deuterium. Reaction conditions: 2 equiv C1-deuterated cyclohexanol, 10 equiv $LiClO_4$, 1 mol % TFA, rt, 2 h.



Scheme 5. Aldol-Meerwein–Ponndorf–Verley-etherification with different external alcohols.

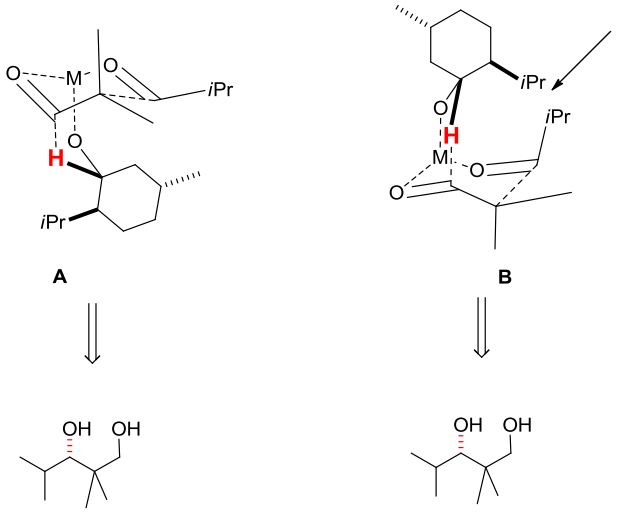
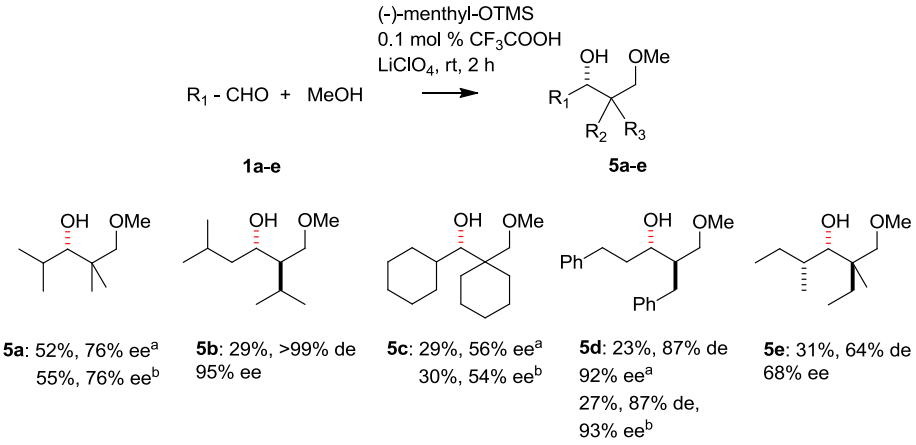


Fig. 1. Transition state models.

solvents. By application of oxygen-containing solvents no reactions were observed.[24] Furthermore, higher yields and shorter reactions times were obtained by deployment of trimethylsilyl ether of optically pure menthol. An optional and selective access to both enantiomers is given by the use of (−)- or (+)-menthyl trimethylsilyl ethers. By application of (−)-menthyl trimethylsilyl ether *S*-configured 1,3-diol ethers were obtained. When used with (+)-menthyl trimethylsilyl ether *R*-configured 1,3-diol ethers were obtained with same results concerning to yields and stereoselectivities.[20] Also, a slight increasing of yields is noticed when using with the corresponding trioxane instead of the aldehyde.[25] The results of these investigations are shown in Scheme 6.

conditions. α-Branched enolizable aldehydes act exclusively as ene components in every reaction we tried (**6a** and **6b**, Scheme 7). Even in reactions of two different α-branched enolizable aldehydes an extremely strong differentiation is observed. In these cases, the less sterically demanding aldehyde acts exclusively as the ene component (**6c** and **6d**, Scheme 7). Other cross-aldol adducts or self-aldol adducts were not detected under these reaction conditions. In addition, high enantioselectivities were detected.

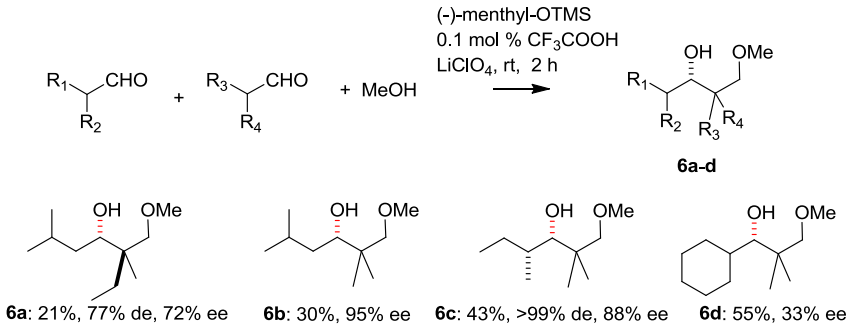
Next, the isolated 1,3-diol ethers were transformed into the corresponding 1,3-diols. The use of methyl ethers as a protecting group for aliphatic alcohols is often limited by low yields and difficulties during the isolation-process of the corresponding alcohols. Several well-established methods, such as the application of boron reagents (BF_3/AcOH,[26] BBr_3/NaI[27] or BBr_3/CH_2Cl_2[28]) or TMSI[29] yielded the expected 1,3-diols in very low yields only (<11%). An increasing of yields was noticed when used with in situ generated trimethylsilyl iodide.[30] But the expected 1,3-diols were isolated with yields not higher than 30%. Further optimization revealed equimolar amounts of Me_3SiI in the presence of catalytic amounts of NaI (1 mol %) as the reagent of choice. Under these conditions the reaction proceeds very easy and selectively at rt in carbon tetrachloride. After 10–16 h the corresponding 1,3-diols **8a**–**e** were isolated in good yields (Scheme 8). Enantioselectivity as well as diastereoselectivity of the starting methyl ether **5a**–**e** were not



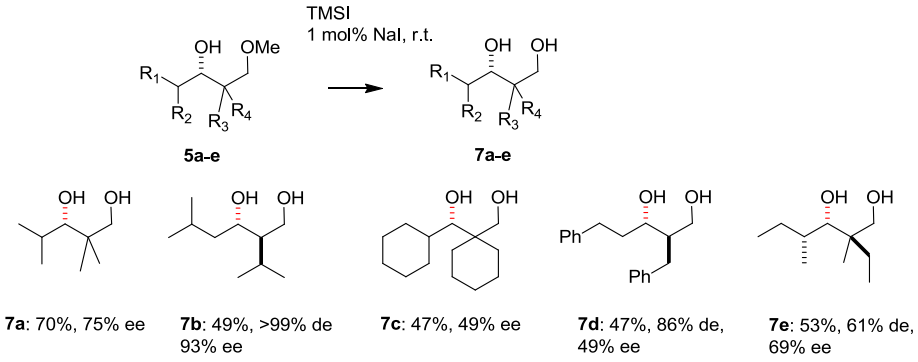
Scheme 6. Asymmetric homo-aldol-Meerwein–Ponndorf–Verley-etherification reactions. [a]Results obtained by use of freshly distilled aldehydes. [b]Results obtained when used with the corresponding trioxanes.

Two bicyclic transition state models are likely to be conceivable as is depicted in Fig. 1. For reasons of simplification these transitions states are given for the homo-aldol-MPV-etherification reaction of isobutyraldehyde and (−)-menthol. Both transition states explaining the configurative outcome—the formation of *S*-configured products. Due to steric interactions of the isopropyl groups there should be a preference of transition state **A** over transition state **B** (see also Supplementary data).

In a further series reactions of two different enolizable aldehydes were investigated. An extremely high differentiation between the employed aldehydes was observed. The key to the regioselectivity of this reaction is the preferred formation of enolates of α-branched enolizable aldehydes under these reaction



Scheme 7. Asymmetric cross-aldol-Meerwein–Ponndorf–Verley ether formation reactions.



Scheme 8. Methyl ether-cleavage.

influenced by the reaction conditions described. This fact was approved by NMR-spectroscopy of the corresponding Mosher-ester.[20]

3. Conclusions

In summary, we have developed an access to optically active 1,3-diol ethers. During a new aldol-Meerwein–Ponndorf–Verley reduction etherification process the 1,3-diol ethers were formed with extremely high degrees of diastereoselectivity. The process can be performed out intramolecularly as well as intermolecularly. By the deployment of two different alcohols—one for the hydride transfer and one for the etherification—an access to enantiomerically enriched 1,3-diol ethers can be realized. An extremely high differentiation of deployed aldehydes is observed in cross-aldol-MPV-etherification reactions. This differentiation is controlled by steric interactions. By a following optimization of established protocols of methyl ether-cleavage we were able to isolate the corresponding 1,3-diols in good yields.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz in $CDCl_3$, respectively, using an AC-300 spectrometer. Chemical shifts are given in parts per million. HRMS were measured at 70 eV using an ESI-TOF-spectrometer. Purification of products was accomplished by flash-chromatography. Thin layer chromatography was performed with Merck Silica Gel 60 F_{254} TLC plates. Aldehydes were freshly distilled before use. $LiClO_4$ was dried at 140 °C in vacuo for 10 h before use.

4.2. General procedure for the synthesis of products 2a–c

Trifluoroacetic acid (480 mg, 0.0042 mmol) was added to a mixture of corresponding aldehydes **1a** or **1b** (4.2 mmol), dry isopropanol (4.2 mmol for **2c**) or dry cyclopentanol (4.2 mmol for **2a** or **2b**) and dry $LiClO_4$ (2.65 g, 25 mmol). The reaction mixture was stirred 2 h at rt and monitored by TLC. After completion (DC-control) the reaction mixture was quenched with saturated aqueous solution of Na_2CO_3 (50 ml) and extracted with diethyl ether (2×100 ml). The organic layer was dried ($MgSO_4$), filtrated and the solvent was removed in vacuo to give crude product. Purification by column chromatography yielded the products **2a**–**c** (hexane/ethyl acetate–95/5; R_f~0.15–0.2).

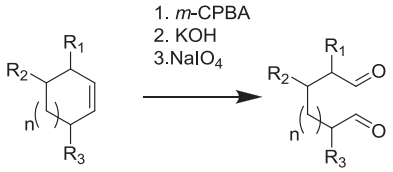
4.2.1. rac-1-Cyclopentoxy-2,2,4-trimethyl-pentan-3-ol ***2a***. Yield 86%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.78–3.72 (1H, m, CH), 3.22 (1H, d, J=8.7 Hz, CH_2), 3.20 (1H, d, J=2.4 Hz, CH), 3.10 (1H, d, J=8.7 Hz, CH_2), 1.80 (1H, dsept, J=2.2, 6.8 Hz, CH), 1.60–1.44 (8H, m, CH_2), 0.93 (3H, d, J=6.9 Hz, CH_3), 0.86 (3H, s, CH_3), 0.85 (3H, s, CH_3), 0.43 (3H, d, J=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=83.0, 82.0, 80.0, 38.5, 31.9, 31.9, 29.1, 23.6, 23.4, 23.3, 20.5, 16.4; HRMS-ESI (m/z): calcd for $C_{13}H_{26}O_2$+H^+: 215.2006, found: 215.2007.

4.2.2. (3S,4R*)-3-(Cyclopentyloxymethyl)-2,6-dimethylheptan-4-ol* ***2b***. Yield 68%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.88–3.82 (1H, m, CH), 3.67 (1H, dd, J=3.0, 9.4 Hz, CH_2), 3.62 (1H, br s, CH), 3.58 (1H, dd, J=5.0, 9.4 Hz, CH_2), 2.05–1.98 (1H, m, CH), 1.85–1.78 (1H, m, CH), 1.68–1.53 (8H, m, CH_2), 1.49–1.44 (1H, m, CH), 1.29–1.12 (2H, m, CH_2), 1.01 (3H, d, J=6.8 Hz, CH_3), 0.95–0.90 (9H, m, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=82.0, 70.8, 67.5, 48.9, 45.7, 32.2, 31.9, 26.1, 24.5, 23.5, 23.3, 22.4, 22.1, 21.3, 19.5. HRMS-ESI (m/z): calcd for $C_{15}H_{30}O_2$+H^+: 243.2319, found: 243.2319.

4.2.3. rac-1-Isopropoxy-2,2,4-trimethyl-pentan-3-ol ***2c***. Yield 44%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.47 (1H, sept, J=6.1 Hz, CH), 3.28 (1H, d, J=8.6 Hz, CH_2), 3.25 (1H, d, J=2.4 Hz, CH), 3.17 (1H, d, J=8.6 Hz, CH_2), 1.83 (1H, dsept, J=2.3, 6.8 Hz, CH), 1.11 (3H, d, J=6.8 Hz, CH_3), 1.09 (3H, d, J=6.8 Hz, CH_3), 0.97 (3H, d, J=6.9 Hz, CH_3), 0.90 (3H, s, CH_3), 0.89 (3H, s, CH_3), 0.87 (3H, d, J=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=83.0, 79.5, 72.5, 38.6, 29.1, 23.7, 23.4, 21.8, 21.7, 20.6, 16.5. HRMS-ESI (m/z): calcd for $C_{11}H_{24}O_2$+H^+: 189.1849, found: 189.1849.

4.3. General procedure for the synthesis of dialdehydes 3a–e

Dialdehydes **3a**–**e** were synthesized by the following sequence:



4.3.1. Adipaldehyde ***3a***[31]. (R_1=R_2=R_3=H, n=1): 51%, ^{1}H NMR ($CDCl_3$, 300 MHz): δ=9.65–9.64 (2H, m, CHO), 2.39–2.34 (4H, m, CH_2), 1.56–1.52 (4H, m, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=201.8, 43.2, 21.2.

4.3.2. Heptane-1,7-dial ***3b***[32]. (R_1=R_2=R_3=H, n=2): 89%, ^{1}H NMR ($CDCl_3$, 300 MHz): δ=9.63 (2H, t, J=1.7 Hz, CHO), 2.33 (4H, dt, J=1.6, 7.2 Hz, CH_2), 1.57–1.47 (4H, m, CH_2), 1.29–1.21 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=202.1, 43.3, 28.2, 21.4.

4.3.3. 2-Methyl-adipaldehyde ***3c***[33]. (R_1=Me, R_2=H, R_3=H, n=1): 63%, ^{1}H NMR ($CDCl_3$, 300 MHz): δ=11.72 (1H, t, J=1.4 Hz, CHO), 11.57 (1H, d, J=1.7 Hz, CHO), 4.46–4.41 (2H, m, CH_2), 4.35–4.26 (1H, m, CH), 3.74–3.56 (4H, m, CH_2), 3.07 (3H, d, J=7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=204.5, 201.8, 46.0, 43.6, 29.6, 19.3, 13.2.

4.3.4. 3-Methyl-adipaldehyde ***3d***[34]. (R_1=R_3=H, R_2=Me, n=1): 43%, ^{1}H NMR ($CDCl_3$, 300 MHz): δ=9.66–9.63 (2H, m, CHO), 2.40–1.92 (5H, m, CH, CH_2), 1.65–1.36 (2H, m, CH_2), 0.86 (3H, d, J=6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=202.0, 201.9, 50.4, 41.1, 28.3, 27.1, 19.3.

4.3.5. 2-Isopropyl-5-methyl-adipaldehyde ***3e***[35]. (R_1=Me, R_2=H, R_3=^{i}Pr, n=1): 43%, ^{1}H NMR ($CDCl_3$, 300 MHz): δ=9.61–9.60 (1H, d, J=3.0 Hz, CHO), 9.56 (1H, d, J=2.0 Hz, CHO), 2.30 (1H, dsept, J=2.1, 6.9 Hz, CH), 2.08–1.93 (2H, m, CH_2), 1.72–1.58 (2H, m, CH_2), 1.48–1.40 (1H, m, CH), 1.30–1.20 (1H, m, CH), 1.07 (3H, d, J=7.1 Hz, CH_3), 0.93 (3H, d, J=6.6 Hz, CH_3), 0.91 (3H, d, J=6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=205.2, 204.6, 58.2, 46.3, 28.4, 28.2, 23.0, 20.1, 19.6, 13.3.

4.4. General procedure for the synthesis of products *rac*-4a–e

Trifluoroacetic acid (480 mg, 0.0042 mmol) was added to a mixture of corresponding aldehyde **3a**–**e** (4.2 mmol), dry cyclopentanol (4.2 mmol), and dry $LiClO_4$ (2.65 g, 25 mmol). The reaction mixture was stirred 2 h at rt and monitored by TLC. After completion the reaction mixture was quenched with saturated aqueous solution of Na_2CO_3 (50 ml) and extracted with diethyl ether (2×100 ml). The organic layer was dried ($MgSO_4$), filtrated, and the solvent was removed in vacuo to give the crude products. Purification by column chromatography yielded products **4a**–**e** (hexane/ethyl acetate—95/5; R_f~0.15–0.2).

4.4.1. (1S,2S*)-2-(Isopropoxymethyl)cyclopentanol* ***4a***. Yield 11%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.27 (1H, ddd, J=3.2, 5.1, 8.1 Hz, CH), 3.90–3.84 (1H, m, CH), 3.58 (1H, dd, J=4.7, 9.3 Hz, CH_2), 3.51 (1H, dd, J=7.3, 9.3 Hz, CH_2), 1.79–1.47 (15H, m, CH, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=81.8, 74.9, 68.9, 43.9, 34.8, 32.3, 32.0, 26.1, 23.4, 22.3. HRMS-ESI (m/z): calcd for $C_{11}H_{20}O_2$+H^+: 185.1536, found: 185.1536.

4.4.2. (1S,2S*)-2-(Cyclopentyloxymethyl)cyclohexanol* ***4b***. Yield 17%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.35 (1H, ddd, J=3.6, 5.6, 9.0 Hz, CH), 3.93–3.89 (1H, m, CH), 3.64 (1H, dd, J=4.1, 9.4 Hz, CH_2), 3.56 (1H, dd, J=6.9, 9.1 Hz, CH_2), 1.76–1.52 (17H, m, CH, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=81.9, 75.6, 67.7, 51.5, 33.9, 33.6, 32.4, 32.0, 32.0, 23.5, 21.0, 19.4. HRMS-ESI (m/z): calcd for $C_{12}H_{22}O_2$+H^+: 199.1693, found: 199.1694.

4.4.3. (1S,2S*)-2-(Cyclopentyloxymethyl)-2-methylcyclopentanol* ***4c***. Yield 75%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.87–3.83 (1H, m, CH), 3.81–3.78 (1H, m, CH), 3.44 (1H, d, J=9.0 Hz, CH_2), 3.32 (1H, d, J=9.0 Hz, CH_2), 1.70–1.48 (14H, m, CH_2), 0.93 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=82.0, 81.6, 74.5, 45.3, 34.1, 34.0, 32.1, 23.7, 23.4, 21.1. HRMS-ESI (m/z): calcd for $C_{12}H_{22}O_2$+H^+: 199.1693, found: 199.1689.

4.4.4. (1S,2S*,3R*)-2-(Cyclopentyloxymethyl)-3-methylcyclopentanol* ***4d***. Yield 18%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.99–3.92 (1H, m, CH), 3.90–3.86 (1H, m, CH), 3.63 (1H, dd, J=4.1, 8.8 Hz, CH_2), 3.25 (1H, pt, J=9.4 Hz, CH_2), 1.69–1.50 (14H, m, CH, CH_2), 1.00 (3H, d, J=6.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=81.8, 79.3, 72.1, 54.8, 34.6, 32.3, 32.2, 31.8, 31.0, 23.5, 20.0. HRMS-ESI (m/z):calcd for $C_{12}H_{22}O_2$+H^+: 199.1693, found: 199.1696.

4.4.5. (1S,2R*,5S*)-2-(Cyclopentyloxymethyl)-2-isopropyl-5-methylcyclopentanol* ***4e***. Yield 32%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.86 (1H, d, J=5.8 Hz, CH), 3.84–3.80 (1H, m, CH), 3.52 (1H, d, J=8.9 Hz, CH_2), 3.35 (1H, d, J=8.9 Hz, CH_2), 1.79–1.40 (14H, m, CH, CH_2), 1.00 (3H, d, J=6.9 Hz, CH_3), 0.90 (3H, d, J=6.8 Hz, CH_3), 0.85 (3H, d, J=6.9 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=81.9, 80.4, 71.6, 52.8, 39.9, 30.3, 32.1, 31.7, 23.4, 18.7, 17.8, 13.5. HRMS-ESI (m/z): calcd for $C_{15}H_{28}O_2$+H^+: 241.2162, found: 241.2162.

4.5. General procedure for the synthesis of methyl ethers 5a–e

Trifluoroacetic acid (480 mg, 0.0042 mmol) was added to a mixture of corresponding aldehydes **1a**–**e** (4.2 mmol), (+)- or (−)-menthyl TMS-ether (12.6 mmol), dry methanol (4.2 mmol), and dry $LiClO_4$ (2.65 g, 25 mmol). The reaction mixture was stirred 2 h at rt and monitored by TLC. After completion the reaction mixture was quenched with saturated aqueous solution of Na_2CO_3 (50 ml) and extracted with diethyl ether (2×100 ml). The organic layer was dried ($MgSO_4$), filtrated, and the solvent was removed in vacuo to give crude products. Purification by column chromatography yielded products **5a**–**e** (hexane/ethyl acetate—95/5; R_f~0.15–0.2).

*4.5.1. (S)-1-Methoxy-2,2,4-trimethyl-pentan-3-ol (S-***5a***).* Yield 52%, 76% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.27 (1H, d, J=8.7 Hz, CH_2), 3.27 (3H, s, OMe), 3.24 (1H, d, J=2.3 Hz, CH), 3.09 (1H, d, J=8.7 Hz, CH_2), 1.83 (1H, dsept, J=2.3, 6.8 Hz, CH), 0.95 (3H, d, J=6.9 Hz, CH_3), 0.90 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.86 (3H, d, J=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=83.4, 82.4, 59.1, 38.9, 29.0, 23.4, 23.4, 20.7,

16.4. HRMS-ESI (m/z): calcd for $C_9H_{20}O_2+H^+$: 161.1536, found: 161.1534. $[\alpha]_D^{25}$ (76% ee) −16.3 (c 1.0 g/100 ml, CH_2Cl_2).

*4.5.2. (R)-1-Methoxy-2,2,4-trimethyl-pentan-3-ol (R-**5a**).* Yield 48%, 81% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.29 (1H, d, J=8.8 Hz, CH_2), 3.28 (3H, s, OMe), 3.23 (1H, d, J=2.3 Hz, CH), 3.07 (1H, d, J=8.7 Hz, CH_2), 1.83 (1H, dsept, J=2.3, 6.8 Hz, CH), 0.95 (3H, d, J=6.9 Hz, CH_3), 0.90 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.85 (3H, d, J=6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=83.4, 82.3, 59.0, 38.8, 28.9, 23.4, 23.3, 20.6, 16.3. $[\alpha]_D^{25}$ (81% ee) +17.6 (c 1.0 g/100 ml, CH_2Cl_2).

*4.5.3. (3R,4S)-3-Methoxymethyl-2,6-dimethylheptan-4-ol (3R,4S-**5b**).* Yield 29%, de >99%, 95% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.81 (1H, ddd, J=4.3, 8.9, 13.6 Hz, CH), 3.61 (1H, dd, J=3.1, 9.5 Hz, CH_2), 3.55 (1H, dd, J=4.9, 9.5 Hz, CH_2), 3.30 (3H, s, OMe), 1.96 (1H, dsept, J=2.7, 7.1 Hz, CH), 1.85–1.72 (1H, m, CH), 1.50–1.40 (1H, m, CH), 1.24–1.11 (2H, m, CH_2), 0.97 (3H, d, J=6.8 Hz, CH_3), 0.91–0.87 (9H, m, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=71.9, 70.7, 59.0, 49.2, 45.7, 26.3, 24.6, 23.5, 22.0, 21.3, 19.6. HRMS-ESI (m/z): calcd for $C_{11}H_{24}O_2+H^+$: 189.1849, found: 189.1849 $[\alpha]_D^{25}$ (92% ee) −13.2 (c 1.0 g/100 ml, CH_2Cl_2).

*4.5.4. (3S,4R)-3-Methoxymethyl-2,6-dimethylheptan-4-ol (3S,4R-**5b**).* Yield 31%, de >99%, 95% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.82 (1H, ddd, J=4.3, 8.9 Hz, CH), 3.62 (1H, dd, J=3.1, 9.5 Hz, CH_2), 3.56 (1H, dd, J=4.9, 9.5 Hz, CH_2), 3.32 (3H, s, OMe), 1.99 (1H, dsept, J=2.8, 7.0 Hz, CH), 1.88–1.75 (1H, m, CH), 1.53–1.41 (1H, m, CH), 1.27–1.15 (2H, m, CH_2), 0.99 (3H, d, J=6.7 Hz, CH_3), 0.93 (3H, d, J=6.8 Hz, CH_3), 0.92 (3H, d, J=6.7 Hz, CH_3), 0.89 (3H, d, J=6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=71.9, 70.8, 59.0, 49.2, 45.7, 26.3, 24.6, 23.5, 22.0, 21.3, 19.6. $[\alpha]_D^{25}$ (95% ee) +15.0 (c 1.0 g/100 ml, CH_2Cl_2).

*4.5.5. (S)-Cyclohexyl-(1-methoxymethyl-cyclohexyl)-methanol (S-**5c**).* Yield 29%, 56% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.48 (1H, d, J=9.2 Hz, CH_2), 3.34 (1H, d, J=9.2 Hz, CH_2), 3.27 (3H, s, OMe), 3.20 (1H, br s, CH), 1.71–1.19 (21H, m, CH, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=82.9, 78.0, 59.1, 40.8, 38.5, 34.2, 31.6, 30.6, 27.4, 27.1, 26.6, 26.3, 26.2, 21.7, 21.2. HRMS-ESI (m/z): calcd for $C_{15}H_{28}O_2+H^+$: 241.2162, found: 241.2161. $[\alpha]_D^{25}$ (56% ee) −10.1 (c 1.0 g/100 ml, CH_2Cl_2).

*4.5.6. (R)-Cyclohexyl-(1-methoxymethyl-cyclohexyl)-methanol (R-**5c**).* Yield 31%, 52% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.49 (1H, d, J=9.2 Hz, CH_2), 3.35 (1H, d, J=9.2 Hz, CH_2), 3.28 (3H, s, OMe), 3.19 (1H, m, CH), 1.69–1.17 (21H, m, CH, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=82.9, 78.0, 59.1, 40.7, 38.5, 34.2, 31.6, 30.6, 27.4, 27.2, 26.6, 26.3, 26.2, 21.7, 21.2. $[\alpha]_D^{25}$ (52% ee) +8.9 (c 1.0 g/100 ml, CH_2Cl_2).

*4.5.7. (2R,3S)-2-Benzyl-1-methoxy-5-phenyl-pentan-3-ol (2R,3S-**5d**).* Yield 23%, 87% de, 92% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=7.31–7.18 (10H, m, ph), 3.66 (1H, ddd, J=4.2, 8.6 Hz, CH), 3.60 (1H, dd, J=3.3, 9.4 Hz, CH_2), 3.34 (1H, dd, J=4.3, 9.4 Hz, CH_2), 3.30 (3H, s, OMe), 2.92–2.85 (2H, m, CH_2), 2.78–2.69 (2H, m, CH_2), 1.92–1.81 (3H, m, CH, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=142.4, 140.4, 129.1, 128.4, 128.3, 128.2, 125.9, 125.7, 73.6, 72.9, 59.1, 45.1, 37.9, 35.4, 32.4. HRMS-ESI (m/z): calcd for $C_{19}H_{24}O_2+H^+$: 285.1849, found: 285.1850 $[\alpha]_D^{25}$ (92% ee) −35.9 (c 1.0 g/100 ml, CH_2Cl_2).

*4.5.8. (2S,3R)-2-Benzyl-1-methoxy-5-phenyl-pentan-3-ol (2S,3R-**5d**).* Yield 25%, 87% de, 93% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=7.35–7.20 (10H, m, Ph), 3.67 (1H, ddd, J=4.1, 8.6 Hz, CH), 3.63 (1H, dd, J=3.3, 9.4 Hz, CH_2), 3.36 (1H, dd, J=4.3, 9.4 Hz, CH_2), 3.32 (3H, s, OMe), 2.99–2.66 (2H, m, CH_2), 2.79–2.71 (2H, m, CH_2), 1.96–1.80 (3H, m, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=142.3, 140.3, 129.1, 128.4, 128.3, 128.2, 125.9, 125.6, 73.5, 72.8, 59.0, 45.0, 37.9, 35.4, 32.4. $[\alpha]_D^{25}$ (93% ee) +36.2 (c 1.0 g/100 ml, CH_2Cl_2).

*4.5.9. (3R,4S,5S)-3-Methoxymethyl-3,5-dimethylheptan-4-ol (3R,4S,5S-**5e**).* Yield 31%, 64% de, 68% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.39 (1H, d, J=1.5 Hz, CH), 3.34 (1H, d, J=8.9 Hz, CH_2), 3.28 (3H, s, OMe), 3.16 (1H, d, J=9.0 Hz, CH_2), 1.59–1.31 (5H, m, CH, CH_2), 0.92–0.84 (9H, m, CH_3), 0.76 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=79.9, 79.3, 59.0, 41.1, 35.0, 30.2, 28.6, 18.3, 13.9, 12.0, 7.8. HRMS-ESI (m/z): calcd for $C_{11}H_{24}O_2+H^+$: 189.1849, found: 189.1849. $[\alpha]_D^{25}$ (68% ee) −17.5 (c 1.0 g/100 ml, CH_2Cl_2).

*4.5.10. (3S,4R,5R)-3-Methoxymethyl-3,5-dimethylheptan-4-ol (3S,4R,5R-**5e**).* Yield 25%, 61% de, 68% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.40 (1H, d, J=1.4 Hz, CH), 3.35 (1H, d, J=9.0 Hz, CH_2), 3.29 (3H, s, OMe), 3.17 (1H, d, J=9.0 Hz, CH_2), 1.60–1.16 (5H, m, CH, CH_2), 0.93–0.84 (9H, m, CH_3), 0.77 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=79.9, 79.3, 59.0, 40.9, 35.0, 30.2, 28.5, 18.3, 13.9, 12.0, 7.8. $[\alpha]_D^{25}$ (68% ee) +17.9 (c 1.0 g/100 ml, CH_2Cl_2).

4.6. General procedure for the synthesis of methyl ethers 6a–d

Trifluoroacetic acid (480 mg, 0.0042 mmol) was added to a mixture of corresponding aldehydes **1a**–**e** (4.2 mmol→2.1 mmol of each aldehyde), (+)- or (−)-menthyl TMS-ether (12.6 mmol), dry methanol (4.2 mmol), and dry $LiClO_4$ (2.65 g, 25 mmol). The reaction mixture was stirred 2 h at rt and monitored by TLC. After completion the reaction mixture was quenched with saturated aqueous solution of Na_2CO_3 (50 ml) and extracted with diethyl ether (2×100 ml). The organic layer was dried ($MgSO_4$), filtrated, and the solvent was removed in vacuo to give crude products. Purification by column chromatography yielded products **6a**–**d** (hexane/ethyl acetate—95/5; R_f∼0.15–0.2).

*4.6.1. (4S,5R)-5-(Methoxymethyl)-2,5-dimethylheptan-4-ol (4S,5R-**6a**).* Yield 21%, 77% de, 72% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.50 (1H, dd, J=1.8, 10.6 Hz, CH), 3.36 (1H, d, J=9.0 Hz, CH), 3.31 (3H, s, OMe), 3.23 (1H, d, J=9.0 Hz, CH), 1.93–1.83 (1H, m, CH), 1.52–1.14 (5H, m, CH, CH_2), 0.94 (3H, d, J=6.7 Hz, CH_3), 0.88 (3H, d, J=6.5 Hz, CH_3), 0.84 (3H, t, J=7.5 Hz, CH_3), 0.74 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=79.6, 74.9, 59.2, 40.9, 40.4, 28.1, 24.6, 24.3, 21.4, 17.5, 7.7. HRMS-ESI (m/z): calcd for $C_{11}H_{24}O_2+H^+$: 189.1849, found: 189.1856. $[\alpha]_D^{25}$ (72% ee) −16.5 (c 1.0 g/100 ml, CH_2Cl_2).

*4.6.2. (4R,5S)-5-(Methoxymethyl)-2,5-dimethylheptan-4-ol (4R,5S-**6a**).* Yield 19%, 78% de, 75% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.50 (1H, dd, J=1.7, 10.6 Hz, CH), 3.36 (1H, d, J=9.0 Hz, CH), 3.30 (3H, s, CH_3), 3.23 (1H, d, J=9.0 Hz, CH), 1.92–1.83 (1H, m, CH), 1.53–1.23 (5H, m, CH, CH_2), 0.95 (3H, d, J=6.7 Hz, CH_3), 0.88 (3H, d, J=6.5 Hz, CH_3), 0.84 (3H, t, J=7.5 Hz, CH_3), 0.73 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=79.6, 74.8, 59.2, 40.8, 40.3, 28.1, 24.6, 24.3, 21.3, 17.4, 7.7. $[\alpha]_D^{25}$ (75% ee) +16.9 (c 1.0 g/100 ml, CH_2Cl_2).

*4.6.3. (3S)-1-Methoxy-2,2,5-trimethylhexan-3-ol (S-**6b**).* Yield 30%, 95% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.47 (1H, dd, J=1.9, 10.6 Hz, CH), 3.33 (3H, s, CH_3), 3.30 (1H, d, J=8.7 Hz, CH_2), 3.18 (1H, d, J=8.8 Hz, CH_2), 1.90–1.80 (1H, m, CH), 1.36–1.27 (1H, m, CH_2), 1.16–1.07 (1H, m, CH_2), 0.93 (3H, d, J=6.7 Hz, CH_3), 0.88 (3H, d, J=6.5 Hz, CH_3), 0.87 (3H, s, CH_3), 0.86 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=82.9, 76.4, 59.3, 40.9, 38.1, 24.5, 24.3, 22.8, 21.3, 19.4. HRMS-ESI (m/z): calcd for $C_{10}H_{22}O_2+H^+$: 175.1693, found: 175.1696. $[\alpha]_D^{25}$ (95% ee) −9.0 (c 1.0 g/100 ml, CH_2Cl_2).

*4.6.4. (3R)-1-Methoxy-2,2,5-trimethylhexan-3-ol (R-**6b**).* Yield 31%, 94% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.48 (1H, dd, J=1.8, 10.5 Hz, CH), 3.34 (1H, d, J=8.7 Hz, CH_2), 3.34 (3H, s, CH_3), 3.18 (1H, d, J=8.8 Hz, CH_2), 1.90–1.79 (1H, m, CH), 1.33–1.20 (1H, m, CH_2), 1.19–1.13 (1H, m, CH_2), 0.91 (3H, d, J=6.7 Hz, CH_3), 0.86 (3H, d,

J=6.5 Hz, CH_3), 0.85 (3H, s, CH_3), 0.84 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=82.4, 75.9, 59.0, 40.6, 37.9, 24.2, 24.0, 22.5, 21.1, 19.3. $[\alpha]_D^{25}$ (94% ee) +8.8 (*c* 1.0 g/100 ml, CH_2Cl_2).

*4.6.5. (3S,4R)-1-(Methoxymethyl)-2,4-dimethylhexan-3-ol (3S,4R-**6c**).* Yield 43%, de >99%, 88% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.37 (1H, d, J=1.4 Hz, CH), 3.30 (1H, d, J=8.7 Hz, CH), 3.30 (3H, s, OMe), 3.13 (1H, d, J=8.7 Hz, CH), 1.59–1.51 (1H, m, CH), 1.45–1.13 (2H, m, CH_2), 0.94 (3H, s, CH_3), 0.89 (3H, s, CH_3), 0.90–0.85 (6H, m, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=83.4, 80.7, 59.1, 38.9, 35.5, 29.9, 23.5, 21.0, 13.8, 12.0. HRMS-ESI (*m*/*z*): calcd for $C_{10}H_{22}O_2+H^+$: 175.1693, found: 175.1697. $[\alpha]_D^{25}$ (88% ee) −1.2 (*c* 1.0 g/100 ml, CH_2Cl_2).

*4.6.6. (3R,4S)-1-(Methoxymethyl)-2,4-dimethylhexan-3-ol (3R,4S-**6c**).* Yield 38%, de >99%, 88% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.35 (1H, d, J=1.5 Hz, CH), 3.30 (1H, d, J=8.7 Hz, CH_2), 3.28 (3H, s, OMe), 3.12 (1H, d, J=8.7 Hz, CH_2), 1.59–1.49 (1H, m, CH_2), 1.43–1.11 (2H, m, CH_2), 0.92 (3H, s, CH_3), 0.90–0.86 (6H, m, CH_3), 0.87 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=83.3, 80.6, 59.1, 38.8, 35.4, 29.8, 23.4, 20.9, 13.7, 11.9. $[\alpha]_D^{25}$ (88% ee) +1.0 (*c* 1.0 g/100 ml, CH_2Cl_2).

*4.6.7. (1S)-1-Cyclohexyl-3-methoxy-2,2-dimethylpropan-1-ol (S-**6d**).* Yield 55%, 33% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.29 (1H, d, J=8.6 Hz, CH_2), 3.29 (3H, s, CH_3), 3.19 (1H, d, J=1.8 Hz, CH), 3.11 (1H, d, J=8.7 Hz, CH_2), 1.90–1.09 (11H, m, CH, CH_2), 0.93 (3H, s, CH_3), 0.90 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=83.4, 82.7, 59.1, 39.5, 33.4, 27.0, 26.9, 26.4, 26.3, 23.4, 20.7, 16.4. HRMS-ESI (*m*/*z*): calcd for $C_{12}H_{24}O_2+H^+$: 201.1849, found: 201.1850. $[\alpha]_D^{25}$ (33% ee) −3.6 (*c* 1.0 g/100 ml, CH_2Cl_2).

*4.6.8. (1R)-1-Cyclohexyl-3-methoxy-2,2-dimethylpropan-1-ol (R-**6d**).* Yield 53%, 31% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.29 (3H, s, CH_3), 3.28 (1H, d, J=8.7 Hz, CH_2), 3.20 (1H, d, J=1.9 Hz, CH), 3.11 (1H, d, J=8.8 Hz, CH_2), 1.90–1.10 (11H, m, CH, CH_2), 0.91 (3H, s, CH_3), 0.88 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=83.4, 82.7, 82.4, 59.1, 39.4, 33.4, 27.0, 26.4, 26.2, 23.4, 20.7, 16.3. $[\alpha]_D^{25}$ (31% ee) +3.1 (*c* 1.0 g/100 ml, CH_2Cl_2).

4.7. General procedure for the synthesis of diols 7a–e

Me_3SiI (0.6 mmol) and dry NaI (0.005 mmol) were added to a solution of 1,3-diol methyl ether **5a**–**e** (0.5 mmol) in CCl_4. The reaction mixture was stirred overnight at rt and monitored by TLC. After completion the reaction mixture was quenched with saturated aqueous solution of Na_2CO_3 (50 ml) and extracted with diethyl ether (2×100 ml). The organic layer was dried ($MgSO_4$), filtrated, and the solvent was removed in vacuo to give crude products. Purification by column chromatography yielded the 1,3-diols **7a**–**e**.

*4.7.1. (3S)-2,2,4-Trimethyl-pentan-1,3-diol (S-**7a**)[36].* Yield 70%, 75% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.53 (1H, d, J=10.6 Hz, CH_2), 3.39 (1H, d, J=10.6 Hz, CH_2), 3.36 (1H, d, J=2.4 Hz, CH), 3.29 (2H, s, OH), 1.90 (1H, dsept, J=2.4, 6.8 Hz, CH), 0.97 (3H, d, J=6.9 Hz, CH_3), 0.92 (3H, d, J=6.7 Hz, CH_3), 0.91 (3H, s, CH_3), 0.90 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=83.1, 73.3, 39.0, 29.1, 23.2, 19.6, 16.6. HRMS-ESI (*m*/*z*): calcd for $C_8H_{18}O_2+H^+$: 147.1380, found: 147.1380. $[\alpha]_D^{25}$ (75% ee) −9.5 (*c* 1.0 g/100 ml, CH_2Cl_2).

*4.7.2. (2R,3S)-2-Isopropyl-5-methylhexan-1,3-diol (2R,3S-**7b**)[37].* Yield 49%, 93% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.96–3.89 (2H, br s, CH and 1× CH_2), 3.79 (1H, dd, J=5.2, 10.9 Hz, CH_2), 3.26 (2H, s, OH), 1.95 (1H, sept, J=6.8 Hz, CH), 1.81–1.68 (1H, m, CH), 1.52 (1H, dd, J=5.1, 9.1, 13.9 Hz, CH_2), 1.30 (1H, ddd, J=3.9, 8.9, 12.9 Hz, CH_2), 1.10 (1H, m, CH), 0.99 (1H, d, J=6.7 Hz, CH_3), 0.92 (3H, d, J=6.0 Hz, CH_3), 0.90 (6H, d, J=6.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=71.9, 61.5, 50.3, 45.5, 25.9, 24.5, 23.5, 21.9, 21.3, 19.3. HRMS-ESI (*m*/*z*): calcd for $C_{10}H_{22}O_2+H^+$: 175.1693, found: 175.1689. $[\alpha]_D^{25}$ (93% ee) −5.7 (*c* 1.0 g/100 ml, CH_2Cl_2).

*4.7.3. (S)-Cyclohexyl-1-(hydroxymethyl-cyclohexyl)-methanol (S-**7c**)[38].* Yield 47%, 49% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.84 (1H, d, J=11.0 Hz, CH_2), 3.62 (1H, d, J=10.3 Hz, CH_2), 3.32 (1H, br s, CH), 2.82 (2H, s, OH), 1.78–1.16 (21H, m, CH, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=84.3, 67.3, 40.9, 38.4, 34.2, 31.0, 29.7, 27.5, 27.0, 26.4, 26.3, 26.2, 21.6, 21.2. HRMS-ESI (*m*/*z*): calcd for $C_{14}H_{26}O_2+H^+$: 227.2006, found: 227.2003. $[\alpha]_D^{25}$ (49% ee) −13.2 (*c* 1.0 g/100 ml, CH_2Cl_2).

*4.7.4. (2R,3S)-2-Benzyl-5-phenyl-pentan-1,3-diol (2R,3S-**7d**)[39].* Yield 52%, 92% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=7.34–7.20 (10H, m, ph), 3.96 (1H, dd, J=2.8, 10.9 Hz, CH_2), 3.78 (1H, ddd, J=4.3, 8.9 Hz, CH), 3.63 (1H, dd, J=4.4, 10.9 Hz, CH_2), 2.90–2.67 (4H, m, CH_2), 2.60 (2H, s, OH), 2.05–1.90 (2H, m, CH_2), 1.86–1.78 (1H, m, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=141.9, 140.2, 129.1, 128.4, 128.4, 128.4, 126.1, 125.9, 74.4, 62.9, 46.1, 37.6, 35.1, 32.3. HRMS-ESI (*m*/*z*): calcd for $C_{18}H_{22}O_2+H^+$: 271.1693, found: 271.1693. $[\alpha]_D^{25}$ (92% ee) −4.7 (*c* 1.0 g/100 ml, CH_2Cl_2).

*4.7.5. (2R,3S,4R)-2-Ethyl-2,4-dimethylhexan-1,3-diol (2R,3S,4R-**7e**)[40].* Yield 53%, 79% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ=3.68 (1H, d, J=10.8 Hz, CH_2), 3.53 (1H, br s, CH), 3.48 (1H, d, J=10.9 Hz, CH_2), 2.68 (2H, s, OH), 1.70–1.62 (1H, m, CH), 1.53–1.45 (2H, m, CH_2), 1.40–1.28 (2H, m, CH_2), 0.96 (3H, d, J=6.7 Hz, CH_3), 0.91–0.87 (6H, m, CH_3), 0.79 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=80.2, 69.8, 41.3, 35.0, 30.1, 28.1, 17.5, 13.9, 12.0, 7.7. HRMS: ESI (*m*/*z*): calcd for $C_{10}H_{22}O_2+H^+$: 175.1693, found: 175.1690. $[\alpha]_D^{25}$ (79% ee) −12.3 (*c* 1.0 g/100 ml, CH_2Cl_2).

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Supplementary data

Results of optimization work is provided. Spectral data of cyclohexyl and deuterated cyclohexyl ethers are provided. Proofs of relative configuration and determination of absolute configuration are given. ^1H NMR data for Mosher-esters of both series, *R*- as well as *S*-configured **5a**–**e** and **6a**–**d** and for diols **7a**–**e** are described. ^1H and ^{13}C NMR spectra are given for compounds **2a**–**c**, dialdehydes **3a**–**e**, cyclopentyl ethers **4a**–**e**, methyl ethers **5a**–**e**, **6a**–**d** and diols **7a**–**e**. These supplementary data can be found in the online version at doi:10.1016/j.tet.2011.11.069.

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