Supporting Information

Enantioselective Direct Aldol-Tishchenko Reaction – Access to Chiral Stereopentads

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Determination of relative configuration

Relative configuration of stereopentads **3a** – **3d** was determined by analyzing coupling constants and chemical shifts of corresponding signals in the ^1H NMR spectra. The obtained data were compared with published data of other 1.3.5-triol monoesters whose configuration was determined undoubtedly by X-ray structure analysis.^{1,2,3} In addition the configuration was determined by the analysis of ^1H NMR spectra of the acetonide of **ent-3a**.

80 mg 1.3.5-triol monoester **ent-3a** (0.2 mmol) were dissolved in 10 ml 2.2-dimethoxypropane. 5 mg p-toluenesulfonic acid was added. The solution

was allowed to stand at r.t. for 3-4 h. At the end of the reaction (TLC-control) the resulting mixture was extracted by diethylether and successively by saturated aq. NH_4Cl - and NaHCO_3 -solution. The organic layers were separated, dried (MgSO_4) and the solvent was removed i. vac. The residue was purified by flash column chromatography.

^1H -NMR: 7.99 (m, 2H, CH_{Ph}), 7.39-7.18 (m, 13 H, CH_{Ph}), 5.88 (d, 1H, $J = 6.0$ Hz, CH), 4.19 (d, 1H, $J = 7.5$ Hz, CH), 3.78 (dd, 1H, $J = 4.9, 8.7$ Hz, CH), 2.33 (m, 2H, 2xCH), 1.19 (s, 6H, 2x CH_3), 1.07 (d, 3H, $J = 6.8$ Hz, CH_3), 0.92 (d, 3H, $J = 6.8$ Hz, CH_3); ^{13}C -NMR: 165.4, 141.8, 138.0, 133.0, 129.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.4, 127.0, 101.3, 77.9, 76.9, 69.6, 41.9, 38.2, 24.5, 23.8, 12.3, 11.6.

The coupling constants of 8.7 Hz and 7.5 Hz indicate a 3,4-diaxial and 3,5-diaxial configuration. These results give support for the relative 1,2-anti, 1,3-syn, 1,4-anti, 1,5-syn configured acyclic structure of 1,3,5-triol monoesters **3a-d** and *ent*-**3a-d**.

1,3,5-Triol monoester **3a** was debenzoylated by cat. amounts of NaOMe in excess of methanol. ^{13}C NMR data indicate a symmetrical configured triol. 4 signals of aliphatic carbon atoms were found only. An *all-syn-meso*-

configuration is the consequence of the discussion of the results of these NMR-experiments.

all-syn-2,4-Dimethyl-1,5-diphenyl-pentane-1,3,5-triol

m.p.: 131°C (CCl₄); ¹H-NMR: 7.22-7.11 (m, 10 H, CH_{Ph}), 4.58 (d, 2H, J= 5.6 Hz, 2x CH), 3.84 (d, 1H, J= 6.4 Hz, CH), 1.96 (ddq, 2H, J=6.0, 6.8, 7.2 Hz, 2x CH), 0.83 (d, 6H, J=7.2 Hz, 2xCH₃); ¹³C-NMR: 143.4, 128.2, 127.3, 126.1, 78.6, 72.2, 42.3, 12.8.

HRMS: calc. for C₁₉H₂₄O₃Na: 323.1617 found: 323.1618.

Determination of absolute configuration

We did not succeed in isolating suitable crystals for X-ray structure analysis so far. Even the p-brombenzoates of the stereopentads were isolated as oils. The characterization of the p-brombenzoate of **3c** is described as an representative example here.

3c

$^1\text{H-NMR}$: 7.76 (m, 2H, CH_{Ph}), 7.69 (m, 2H, CH_{Ph}), 7.40-7.00 (m, 12H, CH_{Ph}), 5.84 (d, 2H, $J=7.9$ Hz, 2xCH), 3.69 (dd, 1H, $J=4.9, 9.8\text{Hz}$, CH), 2.36 (m, 2H, 2xCH), 2.34 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 0.85 (d, 3H, $J=6.8$ Hz, CH_3), 0.84 (d, 3H, $J=6.8$ Hz, CH_3); $^{13}\text{C-NMR}$: 166.2, 165.3, 143.8, 137.8, 137.7, 135.9, 135.6, 131.6, 131.1, 129.7, 129.2, 129.1, 129.0, 128.9, 128.2, 128.1, 127.2, 127.1, 78.6, 78.2, 69.4, 42.0, 41.9, 21.7, 21.1 (2x CH_3), 10.9, 10.8.

For that reason we used calculations of results of ^1H NMR-studies of Mosher esters of stereopentads **3a–d** and **ent-3a–d** for the determination of the absolute configuration.⁴ The accordance of results of **both** enantiomers gives much more support and significance of assignment of absolute configuration. The results support the assignments of configurations shown here.

$\Delta\delta$: $\delta S - \delta R$ (ppm) for method B (use of cinchonidine)

$\Delta\delta$: $\delta S - \delta R$ (ppm) for method A (use of cinchonine)

The calculated differences of chemical shifts in the ^1H NMR spectra of the Mosher ester indicate the above assigned configuration of the 1,3,5-triol monoesters.

Experimental Procedures and Characterization of the Products

All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Toluene was distilled, dried and stored over molecular sieves (3A). $\text{Ti}(\text{OtBu})_4$ purchased from Merck chemical company was used without prior purification. Aldehydes were freshly distilled before use. ^1H -NMR und ^{13}C -NMR spectra were recorded at 300 and 75 MHz in CDCl_3 (if not stated otherwise), respectively using an AC-300 spectrometer. Chemical shifts are given in ppm. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) was determined by analyzing the ^1H NMR spectra of the corresponding Mosher-ester. Suitable signals were used for these measurements. The ratios found were compared with results obtained by HPLC analysis. HPLC was performed on Merck-HITACHI LaChrom-System at 254 nm; Eurocel OD (KNAUER); mobile phase, hexane-isopropanol 98/2, H_2O -saturated; flow rate 1ml / min. Purification of products was accomplished by flash chromatography. Thin layer chromatography was performed with Merck Silica Gel 60 F₂₅₄ TLC plates.

Aldol compounds **2a** – **f** were prepared by TiCl_4 -mediated direct aldol addition.⁵

1-Hydroxy-2-methyl-1-phenyl-3-pentanone (2a)

^1H -NMR: 7.32-7.19 (m, 5H, CH_{ph}), 4.97 (d, 1H, $J=4.1\text{Hz}$, CH_{syn}), 4.69 (d, 1H, $J=8.7\text{Hz}$, CH_{anti}), 2.94-2.76 (m, 1H, $\text{CH}_{\text{syn/anti}}$), 2.57-2.19 (m, 2H, $\text{CH}_{2,\text{syn/anti}}$), 1.04 (d, 3H, $J=6.8\text{Hz}$, $\text{CH}_{3,\text{syn}}$), 0.94 (t, 3H, $J=7.2\text{Hz}$, $\text{CH}_{3,\text{syn}}$), 0.99 (t, 3H, $J=7.2\text{Hz}$, $\text{CH}_{3,\text{anti}}$), 0.87 (d, 3H, $J=7.2\text{Hz}$, $\text{CH}_{3,\text{anti}}$);

^{13}C -NMR: syn: 216.0, 141.8, 128.1, 127.2, 125.8, 73.3, 52.3, 35.3, 10.7, 7.3.; anti: 215.9, 142.1, 128.3, 127.8, 126.4, 76.5, 52.5, 36.3, 14.3, 7.3.

1-Hydroxy-2-methyl-1-(p-methoxyphenyl)-3-pentanone (2b)

¹H-NMR: 7.09-6.70 (m, 4H, CH_{Ph}), 4.69 (d, 1H, J =5.7 Hz, CH_{syn}), 4.50 (d, 1H, J=9.0Hz, CH_{anti}), 3.63 (s, 3H, CH₃), 2.75 (dq, 1H, J=1.9, 9.0Hz, CH_{anti}), 2.41 (dq, 2H, J=1.9,7.5Hz, CH_{2,anti}), 2.22 (dq, 1H, J=1.9,5.7Hz, CH_{syn}), 2.07 (dq, 1H, J=1.0,7.5Hz, CH_{2,syn}), 0.90 (t, 3H, J=7.2, CH_{3,anti}), 0.68 (d, 3H, J=7.2Hz, CH_{3,anti}), 0.96 (d, 3H, J=7.2Hz, CH_{3,syn}), 0.77 (t, 3H, J= 7.2 Hz, CH_{3,syn}); ¹³C-NMR: syn: 215.2, 158.4, 134.2, 126.9, 113.1, 73.3, 54.7, 52.6, 35.3, 11.3, 7.0.; anti: 215.5, 158.7, 134.3, 127.4, 113.3, 75.8, 54.7, 52.4, 36.0, 13.8, 7.0.

1-Hydroxy-2-methyl-1-(p-methylphenyl)-3-pentanone (2c)

¹H-NMR: 7.18-7.08 (m, 4H, CH_{Ph}), 4.92 (d, 1H, J=3.8Hz, CH_{syn}), 4.65 (d, 1H, J=8.3Hz, CH_{anti}), 3.20 (br, 1H,OH), 2.88 (dq, 1H, J=7.5,8.6Hz, CH_{anti}), 2.79 (dq, 1H, J=3.0,7.2Hz, CH_{syn}), 2.47 (m, 2H, CH₂), 2.31 (s, 3H, CH_{3,anti}), 2.30 (s, 3H, CH_{3,syn}), 1.05 (d, 3H, J=7.2Hz, CH_{3,syn}), 1.00 (t, 3H, J=7.2Hz, CH_{3,anti}), 0.94 (t, 3H, J=7.2Hz, CH_{3,syn}), 0.85 (d, 3H, J=7.2Hz, CH_{3,anti}); ¹³C-NMR: syn: 216.0, 138.9, 136.8, 126.4, 125.8, 73.3, 52.4, 35.4, 21.0, 7.3(2x).; anti: 216.0, 139.2, 137.4, 129.0, 128.8, 76.4, 52.5, 36.3, 21.0, 14.3, 10.8.

1-Hydroxy-2-methyl-1-(p-nitrophenyl)-3-pentanone (2d)

¹H-NMR: 8.14-7.44 (m, 4H, CH_{Ph}), 5.17 (m, 1H, CH_{syn}), 4.81 (dd, 1H, J=2.3,7.2Hz, CH_{anti}), 3.66 (d, 1H, J=2.3, OH), 2.92-2.76 (m, 1H, CH_{syn/anti}), 2.62-2.30 (m, 2H, CH_{2,syn/anti}), 0.98 (d, 3H, J=7.2Hz, CH_{3,syn/anti}), 0.96 (t, 3H, J=7.5Hz, CH_{3,syn/anti});

¹³C-NMR: syn: 215.5, 147.0, 127.3, 126.7, 123.3, 72.0, 51.4, 35.0, 9.9, 7.4.; anti: 216.0, 149.2, 127.3, 126.7, 123.3, 75.5, 52.2, 36.3, 14.3, 7.3.

2-(Hydroxybenzyl)-cyclopentanone

¹H-NMR: 7.26 (m, 5H, CH_{Ph}), 5.20 (m, 1H, CH_{syn}), 4.62 (d, 1H, J=9.1Hz, CH_{anti}), 2.41-1.36 (m, 7H, CH, 3xCH₂); ¹³C-NMR: syn: 220.4, 142.8, 128.2, 127.9, 127.2, 71.3, 56.0, 39.1, 22.6, 20.4.; anti: 223.0, 141.3, 128.3, 126.4, 125.5, 75.1, 55.2, 38.7, 26.8, 20.3.

2-(Hydroxybenzyl)-cyclohexanone

¹H-NMR: syn: 7.26-7.18 (m, 5H, CH_{Ph}), 5.32 (dd, 1H, J=2.6,3.0Hz, CH), 2.94 (d, 1H, J=3.3Hz, OH), 2.53 (ddd, 1H, J=1.1,2.6,3.4Hz, CH), 2.39-2.25 (m, 2H, CH₂), 2.02 (m, 1H, CH), 1.77 (m, 1H, CH), 1.41-1.61 (m, 4H, 2xCH₂); anti: 7.27-7.19 (m, 5H, CH_{Ph}), 4.72 (dd, 1H, J=2.6,9.0Hz, CH), 3.89 (d, 1H, J=2.1Hz, OH), 2.55 (ddd, 1H, J=1.1,5.3,6.4Hz, CH), 2.46-2.24 (m, 2H, CH₂), 2.02 (m, 1H, CH), 1.71 (m, 1H, CH), 1.42-1.63 (m, 4H, 2xCH₂); ¹³C-NMR: syn: 214.9, 141.4, 128.1, 127.0, 125.7, 70.6, 57.2, 42.7, 28.0, 26.0, 24.9.; anti: 215.6, 140.9, 128.4, 127.9, 127.0, 74.7, 57.4, 42.7, 30.8, 27.8, 24.7.

1-Hydroxy-2-methyl-1-(2,4-dimethoxy-phenyl)-3-pentanone (2e)

¹H-NMR: 6.84-6.78 (m, 3H, CH_{Ph}), 4.92 (d, 1H, J=4.5Hz, CH_{syn}), 4.66 (d, 1H, J=7.5, CH_{anti}), 3.85 (s, 3H, CH_{3,syn}), 3.82 (s, 3H, CH_{3,anti}), 3.07 (br, 1H, OH), 2.79 (m, 1H, CH), 2.53-2.19 (m, 2H, CH₂), 1.07 (d, 3H, J=7.2Hz, CH_{3,syn}), 1.01 (t, 3H, J=7.2Hz, CH_{3,anti}), 0.94 (t, 3H, J=7.2Hz, CH_{3,syn}), 0.88 (d, 3H, J=7.2Hz, CH_{3,anti}); ¹³C-NMR: syn: 216.1, 148.8, 148.1, 134.5, 118.0, 110.8, 109.1, 73.3, 55.8 (2xCH₃), 52.5, 35.5, 11.0, 7.4.; anti: 216.0, 149.0, 148.6, 134.7, 119.0, 110.7, 109.1, 76.5, 55.8 (2xCH₃), 52.7, 36.3, 14.4, 14.1.

1-(2,4-Dimethyl-phenyl)-1-hydroxy-2-methyl-3-pentanone (2f)

¹H-NMR: 7.46-7.01 (m, 3H, CH_{Ph}), 5.27 (d, 1H, J=4.4Hz, CH_{syn}), 5.11 (dd, 1H, J= 4.1,8.7Hz, CH_{anti}), 3.07 (dq, 1H, J=7.2,8.7Hz, CH_{anti}), 3.04 (br, 1H, OH), 2.87 (dq, 1H, J=4.1,7.2Hz, CH_{syn}), 2.58 (m, 2H, CH_{2syn/anti}), 2.41 (s, 3H, CH_{3anti}), 2.38 (s, 3H, CH_{3anti}), 2.38 (s, 3H, CH_{3syn}), 2.32 (s, 3H, CH_{3syn}), 1.18 (d, 3H, J=7.2Hz, CH_{3syn}), 1.12 (t, 3H, J=7.2Hz, CH_{3anti}), 1.08 (t, 3H, J=7.2Hz, CH_{3syn}), 0.99 (d, 3H, J=7.2Hz, CH_{3anti}); ¹³C-NMR: syn: 216.0, 136.7, 136.6, 133.6, 131.1, 126.6, 126.3, 69.6, 50.1, 35.2, 20.9, 18.9, 10.5,7.5.; anti: 216.1, 137.2, 137.1, 135.1, 131.1, 127.0, 126.1, 72.3, 52.2, 36.5, 20.9, 19.3, 14.0, 7.4.

General procedure for preparing 1.3.5-diol monoesters **3a-d** and *ent-3a-d*

2.0 ml Ti(OtBu)₄ (5 mmol), 1.47 g cinchona alkaloids (cinchonine or cinchonidine) (5 mmol) and 5.0 mmol of aldol adducts **2a – d** were stirred at room temperature under inert conditions for 30 min. 25.0 mmol of the corresponding aldehyde **1a - d** were carefully added to the reaction mixture. The reaction was continuously monitored by thin layer chromatography. At the end of the reaction, the resulting mixture was extracted by diethylether and successively by saturated aq. NH₄Cl- and NaHCO₃-solution. The organic layers were separated, dried (MgSO₄) and the solvent was removed i. vac. The residue was purified by flash-column chromatography.

[(1S, 2S, 3S, 4R, 5R)-3.5-Dihydroxy-2.4-dimethyl-1.5-diphenyl]-benzoate (**3a**)

¹H-NMR: 7.95-7.88 (m, 2H, CH_{Ph}), 7.50-7.03 (m,13H, CH_{Ph}), 5.78 (d, 1H, J=7.2Hz, CH), 4.69 (d, 1H, J=5.3Hz, CH), 3.79 (dd, 1H, J=3.0,5.3 Hz, CH), 2.29-2.18 (m, 1H, CH), 2.18-2.08 (m, 1H, CH), 0.98 (d, 3H, J=7.2Hz, CH₃), 0.83 (d, 3H, J=7.2Hz, CH₃); ¹³C-NMR: 165.8, 143.4, 138.3, 132.9, 130.0, 129.6, 128.4, 128.3, 128.1, 127.7, 127.2, 127.0, 126.0, 78.2, 77.9, 70.4, 42.7, 41.3, 12.1, 11.1; HPLC: *t*_R 29.2 min.

HRMS: calc. for C₂₆H₂₈O₄Na: 427.1880. found: 427.1874.

$[\alpha]_D^{25} + 21.5^\circ$ (c 1.0, CH₂Cl₂).

[(1R, 2R, 3R, 4S, 5S)-3.5-Dihydroxy-2.4-dimethyl-1.5-diphenyl]-benzoate
(*ent*-3a)

HPLC: *t*_R 27.2 min.

$[\alpha]_D^{25} - 21.4^\circ$ (c 1.0, CH₂Cl₂).

[(1S, 2S, 3S, 4R, 5R)-3.5-Dihydroxy-2.4-dimethyl-1.5-di(p-methoxyphenyl)]-p-methoxybenzoate (3b)

¹H-NMR: 7.81-7.78 (m, 2H, CH_{Ph}), 7.10-6.64 (m, 10H, CH_{Ph}), 5.68 (d, 1H, J=7.2Hz, CH), 4.58 (d, 1H, J=4.9Hz, CH), 3.66 (m, 1H, CH), 3.64 (s, 3H, CH₃), 2.18 (m, 1H, CH), 2.02 (m, 1H, CH), 0.91 (d, 3H, J=7.2Hz, CH₃), 0.79 (d, 3H, J=6.8Hz, CH₃); ¹³C-NMR: 165.5, 163.2, 158.9, 158.5, 135.6, 131.5, 130.7, 128.2, 127.2, 122.4, 113.6, 113.5, 113.4, 77.7, 77.3, 70.5, 55.3, 55.1, 55.0, 42.7, 41.2, 12.0, 11.0;

HRMS: calc. for C₂₉H₃₄O₇Na: 517.2202 found: 517.2197 .

$[\alpha]_D^{25} + 27.4^\circ$ (c 1.0, CH₂Cl₂).

[(1R, 2R, 3R, 4S, 5S)-3.5-Dihydroxy-2.4-dimethyl-1.5-di(p-methoxyphenyl)]-p-methoxybenzoate (*ent*-3b)

$[\alpha]_D^{25} - 27.0^\circ$ (c 1.0, CH₂Cl₂).

[(1S, 2S, 3S, 4R, 5R)-3.5-Dihydroxy-2.4-dimethyl-1.5-di(p-methylphenyl)]-p-methylbenzoate (3c)

¹H-NMR: 7.76 (m, 2H, CH_{Ph}), 7.11-6.93 (m, 10H, CH_{Ph}), 5.69 (d, 1H, J=7.2Hz, CH), 4.58 (d, 1H, J=4.9Hz, CH), 3.71 (m, 1H, CH), 3.40 (br, 1H, OH), 2.29 (s, 3H, CH₃), 2.20 (s, 3H, CH₃), 2.19 (m, 1H, CH), 2.18 (s, 3H, CH₃), 2.04 (m, 1H, CH), 0.92 (d, 3H, J=7.2Hz, CH₃), 0.78(d, 3H, J=6.8Hz, CH₃); ¹³C-NMR: 165.9, 143.5, 140.4, 139.0, 137.2, 136.5, 135.5, 129.6, 128.9, 128.8, 128.7, 126.9, 125.9, 78.0, 77.7, 70.5, 42.7, 41.2, 21.6, 21.1, 21.0, 12.0, 11.1;

HRMS: calcd. for C₂₉H₃₄O₄Na: 469.2349 found: 469.2349.

[α]_D²⁵ + 22.5° (c 1.0, CH₂Cl₂).

[(1R, 2R, 3R, 4S, 5S)-3.5-Dihydroxy-2.4-dimethyl-1.5-di(p-methylphenyl)]-p-methylbenzoate (*ent*-3c)

[α]_D²⁵ - 22.5° (c 1.0, CH₂Cl₂).

[(1S, 2S, 3S, 4R, 5R)-3.5-Dihydroxy-2.4-dimethyl-1.5-di(p-nitrophenyl)]-p-nitro-benzoate (3d)

¹H-NMR: 8.15-7.35 (m, 12H, CH_{Ph}), 5.83(d, 1H, J=8.3Hz, CH), 4.77 (d, 1H, J=5.3Hz, CH), 3.85 (m, 1H, CH), 2.22 (m, 1H, CH), 2.02 (m, 1H, CH), 1.00 (d, 3H, J=7.2Hz, CH₃), 0.80 (d, 3H, J=6.8Hz, CH₃); ¹³C-NMR: 163.6, 147.4, 146.7, 145.4, 134.5, 130.5, 128.3, 128.0, 126.9, 126.8, 123.7, 123.6, 123.5, 78.2, 77.6, 69.5, 43.6, 41.8, 12.2, 10.9; HRMS: calcd. for C₂₆H₂₅N₃O₁₀Na: 562.1434 found: 562.1432.

$[\alpha]_{\text{D}}^{25} + 26.7^{\circ}$ (c 1.0, CH₂Cl₂).

[(1R, 2R, 3R, 4S, 5S)-3,5-Dihydroxy-2,4-dimethyl-1,5-di(p-nitrophenyl)-p-nitro-benzoate (*ent*-3d)

$[\alpha]_{\text{D}}^{25} - 27.4^{\circ}$ (c 1.0, CH₂Cl₂).

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