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Enantioselective Aldol Reactions of Aliphatic Aldehydes with Singh's Catalyst

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ABSTRACT

Aldols from aliphatic aldehydes had been synthesized enantioselectively using Singh's catalyst. Self and crossed aldol reactions with several linear aldehydes were performed.

Keywords: Aldol Reaction; Aldehydes; Enantioselectivity; Diastereoselectivity; Stereoselective Synthesis

1. Introduction

The aldol reaction is one of the most important carbon-carbon bond forming reactions [1]. There are only few studies where aldol reactions between two aliphatic aldehydes have been described [2-14]. In these reactions different amino acids [9], especially L-proline and its derivatives [15-18], diarylprolinols [11,14] and imidazolidinones [5], have been used as catalysts. Singh et al. designed an L-proline based chiral catalyst with a gem-diphenyl group at the *β*-carbon, which is essential for high enantioselectivities [17]. So far, this catalyst has been used in aldol reactions only between an aldehyde and a ketone [19-25]. To the best of our knowledge, this is the first time when enantioselective aldol reactions between two aliphatic aldehydes with Singh's catalyst 1 are reported.

With Singh's catalyst, the stereochemistry of aldol products can be explained by their transition state (**Figure 1**), which is based on a model supported by DFT calculations [26]. Since aldehyde oxygen forms hydrogen bonds with the NH and OH groups of catalyst 1, the new C-C bond is formed from its Re face [17]. The thermodynamically favorable *E*-enamine is mainly formed by giving syn-aldol products [27].

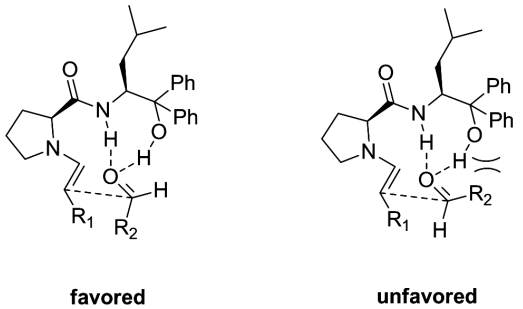
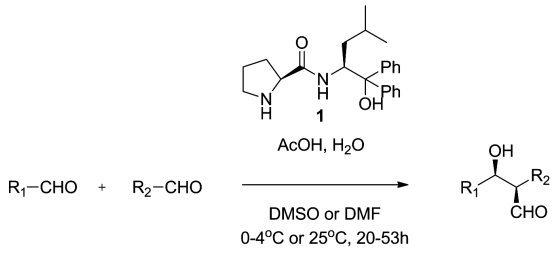


Figure 1. Transition states with Singh's catalyst.

2. Results and Discussion

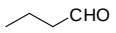
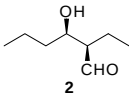
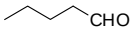
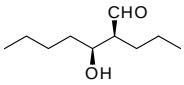
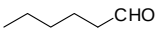
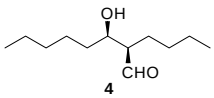
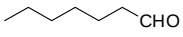
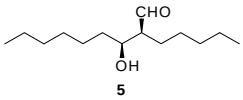
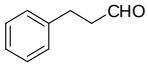
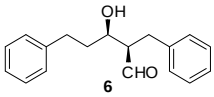
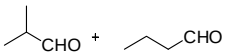
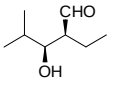
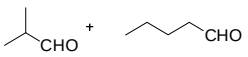
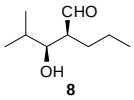
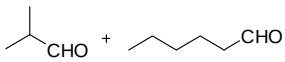
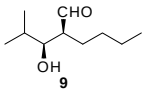
Reaction conditions for self-aldol reactions (**Table 1**, Entries 1 - 8) were optimized with monoacetal protected glutaraldehyde [28] in a reaction that has been published earlier by us [29]. The aldol reactions presented in this article (**Scheme 1**) were reproducible and no water elimination was observed. The self-aldol reactions were done at 25˚C in DMSO for 20 - 21 h. Correspondingly, the conditions for cross-aldol reactions were 0˚C - 4˚C, DMF, 50 - 53 h.

Self-aldol reactions with linear aldehydes, *i.e*. butyraldehyde (Entry 1, **Table 1**), valeraldehyde (Entry 2, **Table 1**), hexanaldehyde (Entry 3, **Table 1**), heptanaldehyde (Entry 4, **Table 1**) and 3-phenylpropionaldehyde (Entry 5, **Table 1**) gave relatively good yields (45% - 71% yield, 2.9 - 12.5:1 dr, 80% - 89% ee). Since self-aldol reactions were successful, we also wanted to



Scheme 1. Aldol reaction of aliphatic aldehydes with Singh's catalyst 1.

Table 1. Aldol reactions tested with Singh's catalyst 1.

Entry	Aldehyde	Main product	T/˚C	Solvent	Time/h	Yield%	Syn:anti[a]	ee%[b]
1		 **2**	25	DMSO	21	56	5.9:1	83
2		 **3**	25	DMSO	21	47	2.9:1	80
3		 **4**	25	DMSO	21	67	6.0:1	85
4		 **5**	25	DMSO	20	45	5.8:1	86
5		 **6**	25	DMSO	20	71	12.5:1	89
6		 **7**	0-4	DMF	53	81	9.1:1	94
7		 **8**	0-4	DMF	52	73	12.5:1	86
8		 **9**	0-4	DMF	50	60	11.1:1	88

[a]Diastereoselectivities were determined by ^{1}H NMR analysis; [b]Enantioselectivities were determined by HPLC with a chiral column.

test some crossed aldol reactions. When isobutyraldehyde was treated with linear aldehydes (Entries 6 - 8, **Table 1**) the reactions gave as supposed even better yields and enantioselectivities (60% - 81% yield, 9.1:1 - 12.5:1dr, 86% - 94% ee).

3. Conclusions

In conclusion, enantioselective aldol reactions of aliphatic aldehydes have been obtained in good enantiomeric excess (80% - 94%).

4. Experimental Section

4.1. General

All solvents and reagents were used as obtained from supplier. Analytical TLC was performed using Merck siliga gel F_{254} (230 - 400 mesh) plates and analyzed by heating upon staining with $KMnO_4$ solution. For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230 - 400 mesh) and p.a. grade solvents were used. ^{1}H (399.98 MHz) and ^{13}C NMR (100.59 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$. The chemical shifts are reported in ppm relative to TMS (δ 0.00) for ^{1}H NMR and in ppm relative to $CDCl_3$ (δ 77.0) for ^{13}C NMR. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer. High resolution mass spectrometric data were obtained using MicroMass LCT Premier Spectrometer. The enantiomeric excess (ee) values of the products were determined by HPLC analysis.

4.2. General Procedures for Aldol Preparation

In self-aldol reactions (Entries 1 - 5, **Table 1**) aldehyde (2 mmol) was dissolved in DMSO (2 mL). H_2O (0.04 mL), catalyst 1 (0.15 mmol) and AcOH (0.15 mmol) were added. The mixture was stirred at room temperature for 20 - 21 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O. Combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude products were purified with flash chromatography (20% Et_2O/hexane).

In crossed aldol reactions (Entries 6 - 8, **Table 1**) iso-

butyraldehyde (6 mmol) was dissolved in DMF (2 mL). H_2O (0.04 mL), catalyst 1 (0.15 mmol) and AcOH (0.15 mmol) were added. The linear aldehyde (1 mmol) in DMF (5 mL) was added during 48 h at 0˚C - 4˚C and the mixture was stirred further 2 - 5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O. Combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude products were purified with flash chromatography (20% Et_2O/hexane).

4.2.1. 2-*Ethyl*-3-*hydroxyhexanal* (2)

Colorless oil. Yield: 56%. IR: 3425, 2875, 2731, 1719 cm^{-1}; for main diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 9.74 (1 H, d, J = 3.0 Hz, CHO), 3.90 - 3.86 (1 H, m, CHOH), 2.52 (1 H, brs, OH), 2.29 - 2.23 (1 H, m, CHCHO), 1.77 (1 H, dddd, J = 7.5, 7.5, 7.5, 14.0 Hz, CH_3CH_2CHCHO), 1.66 (1 H, dddd, J = 7.5, 7.5, 7.5, 14.0 Hz, CH_3CH_2CHCHO), 1.58 - 1.45 (4 H, m, $CH_3CH_2CH_2$-CHOH), 0.95 (3 H, t, J = 7.5 Hz, CH_3), 0.94 (3 H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.0, 70.9, 58.7, 37.1, 19.3, 18.6, 13.8, 11.4; HRMS *m/z* [M + Na]$^+$ calcd for $C_8H_{16}O_2$: 167.1048, found: 167.1046. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [^1H NMR ($CDCl_3$): δ 9.79 (1 H, d, J = 3.5 Hz, CHO), 8.03 - 8.00 (2 H, m, Ph), 7.60 - 7.55 (1 H, m, Ph), 7.47 - 7.42 (2 H, m, Ph), 5.26 (1 H, dt J = 4.5, 8.5 Hz, CHOAr), 2.54 - 2.48 (1 H, m, CHCHO), 1.85 - 1.75 (1 H, m, CH_2CHCHO), 1.74 - 1.52 (3 H, m, CH_2CHCHO, CH_2CHOAr), 1.47 - 1.35 (2 H, m, $CH_3CH_2CH_2CHOAr$), 0.97 (3 H, t, J = 7.5, CH_3), 0.94 (3 H, t, J = 7.5, CH_3); ^{13}C NMR ($CDCl_3$): δ 203.0, 166.0, 133.2, 129.7, 128.9, 128.5, 73.4, 57.1, 34.6, 19.2, 18.7, 13.8, 11.7] using Daicel Chiralpak IA column (25 cm) along with precolumn (5 cm). Eluent: 0.5% ethanol in hexane; Flow rate: 1.0 mL/min; λ = 220 nm; Major isomer: t_r = 6.2 min, minor isomer: t_r = 6.7 min.

4.2.2. 3-*Hydroxy*-2-*propylheptanal* (3)

Colorless oil. Yield: 47%. IR: 3425, 2873, 2730, 1721 cm^{-1}; for main diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 9.75 (1 H, d, J = 3.0 Hz, CHO), 3.87 - 3.81 (1 H, m, CHOH), 2.35 (1 H, dddd, J = 3.0, 5.5, 5.5, 8.0 Hz, CHCHO), 2.10 (1 H, brs, OH), 1.77 - 1.67 (1 H, m, CH_3-CH_2CH_2CHCHO), 1.61 - 1.42 (3 H, m, $CH_3CH_2CH_2$-CHCHO, $CH_3CH_2CH_2CH_2CHOH$), 1.40 - 1.29 (6 H, m, $CH_3CH_2CH_2CHCHO$, $CH_3CH_2CH_2CH_2CHOH$), 0.94 (3 H, t, J = 7.0, CH_3), 0.92 (3 H, t, J = 7.0, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.8, 71.6, 57.0, 34.8, 28.5, 27.7, 22.6, 20.4, 14.1, 14.0; HRMS *m/z* [M + Na]$^+$ calcd for $C_{10}H_{20}O_2$: 195.1361, found: 195.1356. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [^1H NMR ($CDCl_3$): δ 9.78 (1 H, d, J = 3.5 Hz, CHO), 8.03 - 8.00 (2 H, m, Ph), 7.60 - 7.55 (1 H, m, Ph), 7.47 - 7.43 (2 H, m, Ph), 5.44 (1 H, dt J = 5.0, 8.0 Hz, CHOAr), 2.66 - 2.57 (1 H, m, CHCHO), 1.81 - 1.60 (4 H, m, $CH_3CH_2CH_2CHCHO$, $CH_3CH_2CH_2$-CH_2CHOH), 1.56 - 1.26 (6 H, m, $CH_3CH_2CH_2CHCHO$, $CH_3CH_2CH_2CH_2CHOH$), 0.97 (3 H, t, J = 7.0, CH_3), 0.91 (3 H, t, J = 7.0, CH_3); ^{13}C NMR ($CDCl_3$): δ 203.0, 169.5, 133.2, 129.9, 129.7, 128.5, 73.9, 55.3, 35.0, 28.1, 27.5, 22.5, 20.4, 13.9, 13.7] using Daicel Chiralpak IA column (25 cm) along with precolumn (5 cm). Eluent: 0.5% ethanol in hexane; Flow rate: 1.0 mL/min; λ = 220 nm; Major isomer: t_r = 6.3 min, minor isomer: t_r = 6.8 min.

4.2.3. 2-*Butyl*-3-*hydroxyoctanal* (4)

Colorless oil. Yield: 67%. IR: 3426, 2860, 2728, 1720 cm^{-1}; for main diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 9.74 (1 H, d, J = 3.0 Hz, CHO), 3.86 - 3.82 (1 H, m, CHOH), 2.33 (1 H, dddd, J = 3.0, 5.5, 5.5, 8.5 Hz, CH-CHO), 2.06 (1 H, brs, OH), 1.78 - 1.68 (1 H, m, CH_2CH-CHO), 1.63 - 1.45 (3 H, m, CH_2CHCHO, CH_2CHOH), 1.38 - 1.26 (10 H, m, CH_2), 0.91 (3 H, t, J = 7.0, CH_3), 0.90 (3 H, t, J = 7.0, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.8, 71.6, 57.2, 35.1, 31.7, 29.3, 26.1, 25.2, 22.8, 22.6, 14.0, 13.8; HRMS *m/z* [M + Na]$^+$ calcd for $C_{12}H_{24}O_2$: 223.1674, found: 223.1664. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [^1H NMR ($CDCl_3$): δ 9.77 (1 H, d, J = 3.5 Hz, CHO), 8.04 - 7.99 (2 H, m, Ph), 7.61 - 7.55 (1 H, m, Ph), 7.48 - 7.43 (2 H, m, Ph), 5.44 (1 H, ddd, J = 5.0, 5.0, 8.0 Hz, CHOAr), 2.58 (1 H, dddd, J = 3.5, 5.0, 5.0, 9.0 Hz, C*H*CHO), 1.84 - 1.64 (3 H, m, CH_2CHCHO, CH_2CHOAr), 1.63 - 1.46 (1 H, m, CH_2CHCHO), 1.41 - 1.21 (10 H, m, CH_2), 0.93 - 0.82 (6 H, m, CH_3); ^{13}C NMR ($CDCl_3$): δ 203.0, 165.9, 133.2, 129.9, 129.7, 128.5, 73.9, 55.4, 32.4, 31.5, 29.3, 25.7, 25.0, 22.6, 22.4, 13.9, 13.8] using Daicel Chiralpak IA column (25 cm) along with precolumn (5 cm). Eluent: 0.5% ethanol in hexane; Flow rate: 1.0 mL/min; λ = 220 nm; Major isomer: t_r = 5.7 min, minor isomer: t_r = 6.0 min.

4.2.4. 3-*Hydroxy*- 2-*pentylnonanal* (5)

Colorless oil. Yield: 45%. IR: 3426, 2858, 2728, 1720 cm^{-1}; for main diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 9.74 (1 H, d, J = 3.0 Hz, CHO), 3.86 - 3.82 (1 H, m, CHOH), 2.33 (1 H, dddd, J = 3.0, 5.5, 5.5, 8.0 Hz, CHCHO), 2.04 (1 H, brs, O*H*), 1.77 - 1.67 (1 H, m, CH_2CHCHO), 1.63 - 1.45 (3 H, m, CH_2CHCHO, CH_2CHOH), 1.37 - 1.25 (14 H, m, CH_2), 0.89 (6 H, t, J = 7.0, CH_3)); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.9, 71.6, 57.3, 35.1, 31.9, 31.8, 29.2, 26.8, 26.3, 25.5, 22.6, 22.4, 14.0, 13.9; HRMS *m/z* [M + Na]$^+$ calcd for $C_{14}H_{28}O_2$: 251.1987, found: 251.1988. The enantiomeric purity was determined by HPLC analysis of the corresponding ben-

zoate ester [^{1}H NMR ($CDCl_3$): δ 9.77 (1 H, d, J = 3.5 Hz, CHO), 8.03 - 7.99 (2 H, m, Ph), 7.60 - 7.55 (1 H, m, Ph), 7.49 - 7.43 (2 H, m, Ph), 5.44 (1 H, ddd, J = 5.0, 5.0, 8.0 Hz, CHOAr), 2.58 (1 H, dddd, J = 3.5, 5.0, 5.0, 8.5 Hz, CHCHO), 1.82 - 1.65 (3 H, m, CH_2CHCHO, CH_2CHO-Ar), 1.64 - 1.48 (1 H, m, CH_2CHCHO), 1.41 - 1.16 (12 H, m, CH_2), 0.88 (3 H, t, J = 7.0 Hz, CH_3), 0.86 (3 H, t, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 203.0, 166.0, 133.1, 130.0, 129.7, 128.5, 73.9, 55.5, 32.5, 31.7, 31.6, 29.0, 26.8, 26.0, 25.3, 22.5, 22.4, 14.2, 14.0] using Daicel Chiralpak IA column (25 cm) along with precolumn (5 cm). Eluent: 0.5% ethanol in hexane; Flow rate: 1.0 mL/min; λ = 220 nm; Major isomer: t_r = 5.5 min, minor isomer: t_r = 5.7 min.

4.2.5. 2-*Benzyl*-3-*hydroxy*-5-*phenylpentanal* (6)

Colorless oil. Yield: 71%. IR: 3441, 2861, 2733, 1720 cm^{-1}; for main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.80 (1 H, d, J = 2.0 Hz, C*H*O), 7.31 - 7.26 (4 H, m, Ph), 7.25 - 7.14 (6 H, m, Ph), 3.81 (1 H, ddd, J = 4.0, 6.0, 8.0 Hz, CHOH), 3.04 (1 H, dd, J = 8.0, 14.0 Hz, CH_2-CHCHO), 2.95 (1 H, dd, J = 7.0, 14.0 Hz, CH_2CHCHO), 2.81 (1 H, ddd, J = 6.0, 9.0, 13.5 Hz, CH_2CH_2CHOH), 2.77 - 2.71 (1 H, m, CHCHO), 2.66 (1 H, ddd, J = 7.0, 9.0, 14.0 Hz, CH_2CH_2CHOH), 2.17 (1 H, d, J = 6.0 Hz, OH), 1.94 - 1.87 (2 H, m, CH_2CH_2CHOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.1, 141.4, 138.2, 129.0, 128.7, 128.5, 128.4, 126.6, 126.0, 70.7, 58.1, 37.0, 32.6, 32.1; HRMS m/z [M + Na]$^+$ calcd for $C_{18}H_{20}O_2$: 291.1361, found: 291.1368. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [^{1}H NMR ($CDCl_3$): δ 9.87 (1 H, d, J = 2.5 Hz, CHO), 8.02 - 7.99 (2 H, m, Ph), 7.63 - 7.57 (1 H, m, Ph), 7.49 - 7.44 (2 H, m, Ph), 7.32 - 7.08 (10 H, m, Ph), 5.50 (1 H, ddd, J = 4.0, 4.5, 8.5 Hz, CHOAr), 3.12 (1 H, dd, J = 8.0, 14.0 Hz, $CHOCHCH_2$), 3.05 - 2.99 (1 H, m, CHO-$CHCH_2$), 2.86 (1 H, dd, J = 6.0, 14.0 Hz, $CHOCHCH_2$), 2.79 - 2.66 (2 H, m, CH_2CH_2CHOAr), 2.27 - 2.16 (1 H, m, CH_2CH_2CHOAr), 2.10 - 2.00 (1 H, m, CH_2CH_2CHO-Ar); ^{13}C NMR ($CDCl_3$): δ 201.7, 165.9, 142.8, 138.1, 133.3, 130.6, 129.7, 129.0, 128.9, 128.7, 128.5, 128.3, 126.6, 126.2, 73.1, 56.8, 34.2, 31.9, 29.6] using Daicel Chiralpak IA column (25 cm) along with precolumn (5 cm). Eluent: 0.5% ethanol in hexane; Flow rate: 1.0 mL/min; λ = 220 nm; Major isomer: t_r = 9.4 min, minor isomer: t_r = 11.0 min.

4.2.6. 2-*Ethyl*-3-*hydroxy*-4-*methylpentanal* (7)

Colorless oil. Yield: 81%. IR: 3449, 2876, 2724, 1719 cm^{-1}; for main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.77 (1 H, d, J = 3.0 Hz, CHO), 3.59 (1 H, t, J = 6.0 Hz, CHOH), 2.40 (1 H, dddd, J = 3.0, 5.5, 6.0, 8.5 Hz, CHCHO), 1.87 - 1.79 (1 H, m, $(CH_3)_2CH$), 1.78 - 1.59 (2 H, m, CH_2CHCHO), 0.98 (3 H, d, J = 6.5 Hz, $(CH_3)_2CH$), 0.95 (3 H, t, J = 6.5 Hz, CH_3CH_2CHCHO), 0.94 (3 H, d, J = 6.5 Hz, $(CH_3)_2CH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.1, 76.1, 56.0, 30.9, 19.7, 19.6, 16.7, 11.5; HRMS m/z [M + Na]$^+$ calcd for $C_8H_{16}O_2$: 167.1048, found: 167.1052. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [^{1}H NMR ($CDCl_3$): δ 9.77 (1 H, d, J = 4.0 Hz, CHO), 8.07 - 8.01 (2 H, m, Ph), 7.65 - 7.59 (1 H, m, Ph), 7.50 - 7.43 (2 H, m, Ph), 5.28 (1 H, dd, J = 5.0, 7.0 Hz, CHOAr), 2.60 - 2.54 (1 H, m, CHCHO), 2.10 (1 H, oct, J = 7.0 Hz, $(CH_3)_2CH$), 1.81 - 1.71 (1 H, m, $CHOCHCH_2$), 1.65 - 1.55 (1 H, m, $CHOCHCH_2$), 1.02 (3 H, d, J = 7.0 Hz, $(CH_3)_2CH$), 0.99 (3 H, d, J = 7.0 Hz, $(CH_3)_2CH$), 0.96 (3 H, t, J = 7.5 Hz, CH_3CH_2); ^{13}C NMR ($CDCl_3$): δ 203.2, 162.3, 133.2, 129.8, 129.7, 128.5, 78.1, 55.4, 30.6, 19.8, 19.2, 17.9, 11.6] using Daicel Chiralpak IA column (25 cm) along with precolumn (5 cm). Eluent: 0.5% ethanol in hexane; Flow rate: 1.0 mL/min; λ = 220 nm; Major isomer: t_r = 6.0 min, minor isomer: t_r = 5.5 min.

4.2.7. 3-*Hydroxy*-4-*methyl*-2-*propylpentanal* (8)

Colorless oil. Yield: 73%. IR: 3452, 2874, 2729, 1717 cm^{-1}; for main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76 (1 H, d, J = 3.0 Hz, CHO), 3.56 (1 H, q, J = 6.0 Hz, CHOH), 2.48 (1 H, dddd, J = 3.0, 5.5, 6.0, 8.5 Hz, CHCHO), 1.99 (1 H, d, J = 6.0 Hz, OH), 1.88 - 1.78 (1 H, m, $(CH_3)_2CH$), 1.78 - 1.66 (1 H, m, $CH_3CH_2CH_2$), 1.62 - 1.49 (1 H, m, $CH_3CH_2CH_2$), 1.35 (2 H, sext, J = 7.5 Hz, CH_3CH_2), 0.97 (3 H, d, J = 6.0 Hz, $(CH_3)_2CH$), 0.95 (3H, d, J = 6.0 Hz, $(CH_3)_2CH$), 0.94 (3 H, t, J = 7.5 Hz, CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.9, 76.5, 54.4, 31.0, 28.8, 20.3, 19.6, 16.7, 14.1; HRMS m/z [M+Na]$^+$ calcd for $C_9H_{18}O_2$: 181.1204, found: 181.1202. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [^{1}H NMR ($CDCl_3$): δ 9.76 (1 H, d, J = 4.0 Hz, CHO), 8.05 - 8.01 (2 H, m, Ph), 7.60 - 7.55 (1 H, m, Ph), 7.49 - 7.43 (2 H, m, Ph), 5.26 (1 H, dd, J = 5.0, 7.0 Hz, CHOAr), 2.70 - 2.61 (1 H, m, CHCHO), 2.10 (1 H, oct, J = 7.0 Hz, $(CH_3)_2CH$), 1.77 - 1.66 (1 H, m, $CHOCHCH_2$), 1.55 - 1.45 (1 H, m, $CHOCHCH_2$), 1.41 - 1.30 (2 H, m, $CH_3CH_2CH_2$), 1.02 (3 H, d, J = 7.0 Hz, $(CH_3)_2CH$), 0.98 (3 H, d, J = 7.0 Hz, $(CH_3)_2CH$), 0.91 (3 H, t, J = 7.0 Hz, $CH_3CH_2CH_2$); ^{13}C NMR ($CDCl_3$): δ 203.3, 166.1, 133.2, 129.8, 129.7, 128.5, 78.3, 53.6, 30.6, 28.6, 20.3, 19.2, 17.9, 13.9] using Daicel Chiralpak IA column (25 cm) along with precolumn (5 cm). Eluent: 0.5% ethanol in hexane; Flow rate: 1.0 mL/min; λ = 220 nm; Major isomer: t_r = 6.0 min, minor isomer: t_r = 5.4 min.

4.2.8. 2-(1-*Hydroxy*-2-*methylpropyl*)*hexanal* (9)

Colorless oil. Yield: 60%. IR: 3453, 2873, 2729, 1720 cm^{-1}; for main diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.75 (1 H, d, J = 3.0 Hz, CHO), 3.57 (1 H, t, J = 5.5

Hz, CHOH), 2.46 (1 H, dddd, J = 3.0, 5.5, 5.5, 8.5 Hz, CHCHO), 1.88 - 1.78 (1 H, m, $(CH_3)_2CH$), 1.77 - 1.67 (1 H, m, CH_2CHCHO), 1.63 - 1.54 (1 H, m, CH_2CHCHO), 1.38 - 1.25 (4 H, m, $CH_3CH_2CH_2$), 0.97 (3 H, d, J = 7.0 Hz, $(CH_3)_2CH$), 0.94 (3 H, d, J = 7.0 Hz, $(CH_3)_2CH$), 0.91 (3 H, t, J = 7.0 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.0, 76.5, 54.6, 31.0, 29.1, 26.4, 22.8, 19.6, 16.7, 13.8; HRMS m/z $[M + Na]^+$ calcd for $C_{10}H_{20}O_2$: 195.1361, found: 195.1361. Data of 9 in accordance with literature values [2a]. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [^{1}H NMR ($CDCl_3$): δ 9.76 (1 H, d, J = 4.0 Hz, CHO), 8.04 - 8.01 (2 H, m, Ph), 7.60 - 7.55 (1 H, m, Ph), 7.48 - 7.43 (2 H, m, Ph), 5.27 (1 H, dd, J = 5.0, 7.0 Hz, CHOAr), 2.68 - 2.61 (1 H, m, CHCHO), 2.10 (1 H, oct, J = 7.0 Hz, $(CH_3)_2CH$), 1.78 - 1.64 (1 H, m, $CHOCHCH_2$), 1.58 - 1.48 (1 H, m, $CHOCHCH_2$), 1.38 - 1.22 (4 H, m, $CH_3CH_2CH_2$), 1.02 (3 H, d, J = 7.0 Hz, $(CH_3)_2CH$), 0.98 (3 H, d, J = 7.0 Hz, $(CH_3)_2CH$), 0.92 - 0.86 (3 H, m, $CH_3CH_2CH_2$); ^{13}C NMR ($CDCl_3$): δ 203.3, 161.4, 133.2, 129.8, 129.7, 128.5, 78.3, 53.8, 30.6, 29.2, 22.6, 22.2, 19.2, 17.8, 13.9] using Daicel Chiralpak IA column (25 cm) along with precolumn (5 cm). Eluent: 0.5% ethanol in hexane; Flow rate: 1.0 mL/min; λ = 220 nm; Major isomer: t_r = 5.8 min, minor isomer: t_r = 5.4 min.

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