Enantioselective Aldol Reactions of Aliphatic Aldehydes with Singh’s Catalyst

Heli Kylmälä, Antti Neuvonen, Reija Jokela
Department of Chemistry, Aalto University, Espoo, Finland
Email: heli.kylmala@aalto.fi

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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].

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

Figure 1. Transition states with Singh’s catalyst.

Scheme 1. Aldol reaction of aliphatic aldehydes with Singh’s catalyst 1.
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 silica gel F254 (230 - 400 mesh) plates and analyzed by heating upon staining with KMnO4 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. 1H (399.98 MHz) and 13C NMR (100.59 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in CDCl3. The chemical shifts are reported in ppm relative to TMS (δ 0.00) for 1H NMR and in ppm relative to CDCl3 (δ 77.0) for 13C 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). H2O (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 NH4Cl solution. The layers were separated and the aqueous layer was extracted with Et2O. Combined organic layers were dried over Na2SO4, filtered and concentrated under reduced pressure. Crude products were purified with flash chromatography (20% Et2O/hexane).

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Main product</th>
<th>T/˚C</th>
<th>Solvent</th>
<th>Time/h</th>
<th>Yield%</th>
<th>Syn:anti</th>
<th>ee%a</th>
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<td>CHO</td>
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<td>DMSO</td>
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<td>47</td>
<td>2.9:1</td>
<td>80</td>
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<td>CHO</td>
<td>25</td>
<td>DMSO</td>
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<td>71</td>
<td>12.5:1</td>
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<td>81</td>
<td>9.1:1</td>
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<td>60</td>
<td>11.1:1</td>
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</table>

*aDiastereoselectivities were determined by 1H NMR analysis; Enantioselectivities were determined by HPLC with a chiral column.
butyraldehyde (6 mmol) was dissolved in DMF (2 mL). H₂O (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 NH₄Cl solution. The layers were separated and the aqueous layer was extracted with Et₂O. Combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude products were purified with flash chromatography (20% Et₂O/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, CDCl₃) δ: 9.74 (1 H, d, δ = 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, δ = 7.5, 7.5, 7.5, 14.0 Hz, CH₂CH₂CH₂CHO), 1.68 (1 H, dddd, δ = 7.5, 7.5, 7.5, 14.0 Hz, CH₂CH₂CH₂CH₂CHO), 1.58 - 1.45 (4 H, m, CH₃CH₂CH₂-CHOH), 0.95 (3 H, t, δ = 7.5 Hz, CH₃), 0.94 (3 H, t, δ = 7.5 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ: 206.0, 70.9, 58.7, 37.1, 19.3, 18.6, 13.8, 11.4; HRMS m/z [M + Na⁺] calec for C₉H₁₃O₅: 167.1048, found: 167.1046. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [¹H NMR (CDCl₃)] δ: 9.79 (1 H, d, δ = 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, δ = 4.5, 8.5 Hz, CHOAr), 2.54 - 2.48 (1 H, m, CHCHO), 1.85 - 1.75 (1 H, m, CH₂CHCHO), 1.74 - 1.52 (3 H, m, CH₂CHCHO, CH₂CHOAr), 1.47 - 1.35 (2 H, m, CH₂CH₂CHOAr), 0.97 (3 H, t, δ = 7.5 Hz, CH₃), 0.94 (3 H, t, δ = 7.5 Hz, CH₃); ¹³C NMR (CDCl₃) δ: 203.0, 166.0, 133.2, 129.3, 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: tᵣ = 6.2 min, minor isomer: tᵣ = 6.7 min.

4.2.2. 3-Hydroxy-2-propyloctanal (3)
Colorless oil. Yield: 47%. IR: 3425, 2873, 2730, 1721 cm⁻¹; for main diastereomer: ¹H NMR (400 MHz, CDCl₃) δ: 9.75 (1 H, d, δ = 3.0 Hz, CHO), 3.87 - 3.81 (1 H, m, CHOH), 2.35 (1 H, dddd, δ = 3.0, 5.5, 5.5, 8.0 Hz, CHCHO), 2.10 (1 H, brs, OH), 1.77 - 1.67 (1 H, m, CH₂-CH₂CH₂CH₂CHO), 1.61 - 1.42 (3 H, m, CH₂CH₂CH₂-CHOH, CH₂CH₂CH₂CH₂CHOH), 1.40 - 1.29 (6 H, m, CH₂CH₂CH₂CH₂CHOH, CH₂CH₂CH₂CH₂CHOH), 0.94 (3 H, t, δ = 7.0, CH₃), 0.92 (3 H, t, δ = 7.0, CH₃); ¹³C NMR (100 MHz, CDCl₃) 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⁺] calec for C₁₃H₂₅O₅: 195.1361, found: 195.1356. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [¹H NMR (CDCl₃)] δ: 9.78 (1 H, d, δ = 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, δ = 5.0, 8.0 Hz, CHOAr), 2.66 - 2.57 (1 H, m, CHCHO), 1.81 - 1.60 (4 H, m, CH₂CH₂CH₂CH₂CHOH, CH₂CH₂CH₂CH₂CH₂CHOH), 1.56 - 1.26 (6 H, m, CH₂CH₂CH₂CH₂CH₂CHOH, CH₂CH₂CH₂CH₂CH₂CH₂OH), 0.97 (3 H, t, δ = 7.0, CH₃), 0.91 (3 H, t, δ = 7.0, CH₃); ¹³C NMR (CDCl₃): 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: tᵣ = 5.7 min, minor isomer: tᵣ = 6.0 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, CDCl₃) δ: 9.74 (1 H, d, δ = 3.0 Hz, CHO), 3.86 - 3.82 (1 H, m, CHOH), 2.33 (1 H, dddd, δ = 3.0, 5.5, 5.5, 8.5 Hz, CHCHO), 2.06 (1 H, brs, OH), 1.78 - 1.68 (1 H, m, CH₂CH-CHOH, 1.63 - 1.45 (3 H, m, CH₂CHCHO, CH₂CH₂CHOH), 1.38 - 1.26 (10 H, m, CH₂), 0.91 (3 H, t, δ = 7.0, CH₃), 0.90 (3 H, t, δ = 7.0, CH₃); ¹³C NMR (100 MHz, CDCl₃) 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⁺] calec for C₁₂H₂₅O₅: 223.1674, found: 223.1664. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [¹H NMR (CDCl₃)] δ: 9.77 (1 H, d, δ = 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, d, δ = 5.0, 8.0 Hz, CHOAr), 2.58 (1 H, dddd, δ = 3.5, 5.0, 5.0, 9.0 Hz, CHOCH), 1.84 - 1.64 (1 H, m, CH₂CHCHO), 1.63 - 1.46 (1 H, m, CH₂CH₂CHO), 1.41 - 1.21 (10 H, m, CH₂), 0.93 - 0.82 (6 H, m, CH₃); ¹³C NMR (CDCl₃): 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, 22.5, 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: tᵣ = 5.7 min, minor isomer: tᵣ = 6.0 min.
4.2.5. 2-Benzyl-3-hydroxy-5-phenylnentalenal (6)
Colorless oil. Yield: 71%. IR: 3441, 2871, 2733, 1720 cm⁻¹; for main diastereomer: ¹H NMR (400 MHz, CDCl₃) δ: 9.80 (1 H, d, J = 7.0 Hz, CHO), 7.31 - 7.11 (4 H, m, Ph), 4.14 - 3.75 (6 H, m, Ph), 3.49 - 2.55 (1 H, m, CHCHO), 2.77 - 2.71 (1 H, m, CHCHO), 2.66 (1 H, d, J = 7.0, 9.0, 14.0 Hz, CH₂CH₂CHOH), 2.17 (1 H, d, J = 6.0 Hz, OH), 1.94 - 1.87 (2 H, m, CH₃CH₂CHOH); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₆H₁₈O₃: 291.1361, found: 291.1368. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [¹H NMR (CDCl₃): 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, Ph), 7.32 - 7.08 (10 H, m, Ph), 5.50 (1 H, ddd, J = 4.0, 4.5, 8.5 Hz, OCH₂OAr), 3.12 (1 H, dd, J = 8.0, 14.0 Hz, CHOCH₂CH₂), 3.05 - 2.99 (1 H, m, CHOCH₂CH₂), 2.86 (1 H, dd, J = 6.0, 14.0 Hz, CHOCH₂CH₂), 2.79 - 2.66 (2 H, m, CH₂CH₂OCHO), 2.27 - 2.16 (1 H, m, CH₂CH₂OCHO), 2.10 - 2.00 (1 H, m, CH₂CH₂OCHO); ¹³C NMR (CDCl₃) 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: δt = 9.4 min, minor isomer: δt = 11.0 min.

4.2.6. 2-Ethyl-3-hydroxy-4-methylpentanenal (7)
Colorless oil. Yield: 81%. IR: 3449, 2876, 2724, 1719 cm⁻¹; for main diastereomer: ¹H NMR (400 MHz, CDCl₃) δ: 9.77 (1 H, d, J = 3.0 Hz, CHO), 3.59 (1 H, t, J = 6.0 Hz, CCHOH), 2.40 (1 H, dddd, J = 3.0, 5.5, 6.0, 8.5 Hz, CHCHO), 1.87 - 1.79 (1 H, m, (CH₃)₂CH), 1.78 - 1.59 (2 H, m, CH₂CH₃CHO), 0.98 (3 H, d, J = 6.5 Hz, (CH₃)₂CH), 0.95 (3 H, t, J = 6.5 Hz, CH₂CH₃CHO), 0.94 (3 H, d, J = 6.5 Hz, (CH₃)₂CH); ¹³C NMR (100 MHz, CDCl₃) δ: 206.1, 76.1, 56.0, 30.9, 19.7, 19.6, 16.7, 11.5; HRMS m/z [M + Na]⁺ calcd for C₁₃H₁₈O₃: 217.1052, found: 217.1052. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [¹H NMR (CDCl₃): δ: 9.80 (1 H, d, J = 4.0 Hz, CHO), 5.07 - 5.01 (2 H, m, Ph), 4.10 - 3.90 (1 H, m, Ph), 3.17 - 3.00 (1 H, m, Ph), 2.57 (1 H, dd, J = 5.0, 7.0 Hz, CHOAr), 2.60 - 2.54 (1 H, m, CHCHO), 2.13 (1 H, oct, J = 7.0 Hz, (CH₃)₂CH), 1.37 - 1.32 (1 H, m, CH₂CH₂CHO), 1.55 - 1.49 (1 H, m, CH₂CH₂CHO), 1.20 (3 H, d, J = 7.0 Hz, (CH₃)₂CH); ¹³C NMR (CDCl₃) 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: δt = 6.0 min, minor isomer: δt = 5.4 min.

4.2.7. 3-Hydroxy-4-methyl-2-propylnentalenal (8)
Colorless oil. Yield: 73%. IR: 3452, 2874, 2729, 1717 cm⁻¹; for main diastereomer: ¹H NMR (400 MHz, CDCl₃) δ: 9.76 (1 H, d, J = 3.0 Hz, CHO), 3.56 (1 H, q, J = 6.0 Hz, CCHOH), 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, (CH₃)₂CH), 1.78 - 1.66 (1 H, m, CH₂CH₃CH₂), 1.62 - 1.49 (1 H, m, CH₂CH₂CH₂), 1.35 (2 H, sext, J = 7.5 Hz, CH₂CH₂), 0.97 (3 H, d, J = 6.0 Hz, (CH₃)₂CH), 0.95 (3 H, d, J = 6.0 Hz, (CH₃)₂CH), 0.94 (3 H, t, J = 7.5 Hz, CH₂CH₃CH₂); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₃H₂₁O₂: 181.1204, found: 181.1202. The enantiomeric purity was determined by HPLC analysis of the corresponding benzoate ester [¹H NMR (CDCl₃): δ: 9.76 (1 H, d, J = 4.0 Hz, CHO), 5.07 - 5.01 (2 H, m, Ph), 4.10 - 3.90 (1 H, m, Ph), 3.17 - 3.00 (1 H, m, Ph), 2.57 (1 H, dd, J = 5.0, 7.0 Hz, CHOAr), 2.60 - 2.54 (1 H, m, CHCHO), 2.13 (1 H, oct, J = 7.0 Hz, (CH₃)₂CH), 1.37 - 1.32 (1 H, m, CH₂CH₂CHO), 1.55 - 1.49 (1 H, m, CH₂CH₂CHO), 1.20 (3 H, d, J = 7.0 Hz, (CH₃)₂CH); ¹³C NMR (CDCl₃) 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: δt = 6.0 min, minor isomer: δt = 5.4 min.
Hz, CHO), 2.46 (1 H, dddd, J = 3.0, 5.5, 5.5, 8.5 Hz, CHCHO), 1.88 - 1.78 (1 H, m, (CH3)2CH), 1.77 - 1.67 (1 H, m, CH2CHOCHO), 1.63 - 1.54 (1 H, m, CH2CHCHO), 1.38 - 1.25 (4 H, m, CH2CH2CH3), 0.97 (3 H, d, J = 7.0 Hz, (CH3)2CH), 0.94 (3 H, d, J = 7.0 Hz, (CH3)2CH), 0.91 (3 H, d, J = 7.0 Hz, CH2CH3); 13C NMR (100 MHz, CDCl3): 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 C10H20O2: 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 [1H NMR (CDCl3): 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, (CH3)2CH), 1.78 - 1.64 (1 H, m, CHOCHCH3), 1.58 - 1.48 (1 H, m, CHOCHCH3), 1.38 - 1.22 (4 H, m, CH2CH2CH3), 1.02 (3 H, d, J = 7.0 Hz, (CH3)2CH), 0.98 (3 H, d, J = 7.0 Hz, (CH3)2CH), 0.92 - 0.86 (3 H, m, CH2CH2CH3); 13C NMR (CDCl3): 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: tR = 5.8 min, minor isomer: tR = 5.4 min.

REFERENCES


