Synthetic Approach to 1,3-Polymethyl Function Based on Diastereoselective Conjugate Addition

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A new method for diastereo- and enantioselective preparation of 1,3-polymethyl functions was studied. The reaction of (1'R,2'R,5'R)-(2E)-2'-hydroxycyclohexyl5,9-dimethyl-2,8-decadienoate (6) with Me₂CuLi afforded a diastereomeric mixture of conjugate addition products ((3'R,5'R)-9 and (3'S,5'R)-9) in a ratio of 77 to 23.

Keywords diastereoselective conjugate addition; 1,3-polymethyl function; dimethylcopper lithium; enantioselective synthesis; (R,R)-cyclohexane-1,2-diol; double asymmetric induction

In the course of our studies on diastereoselective conjugate addition of dialkylcopper lithium to α,β-unsaturated ester of (R,R or S,S)-cyclohexane-1,2-diol, we have developed a new method for enantio- and diastereoselective preparation of 1,3-polymethyl functions. 1,3-Polymethyl functions are commonly observed in the structures of antibiotic macrolides and insect pheromones, so the method should be synthetically valuable. So far, Oppolzer et al., Heathcock et al., and Marshall and Blough have independently reported their own methods. As shown in Chart 1, our method starts from diastereoselective conjugate addition of Me₂CuLi to a chiral α,β-unsaturated ester (A). The addition product (B) is converted to the second substrate (D) for conjugate addition via an aldehyde (C). By repeating this method, 1,3-polymethyl functions (E, F) may be constructed in optically active form.

The primary conjugate addition (A→B) has already been developed by us to afford addition products in a diastereomeric ratio of 10 to 1, in which the (R,R)-cyclohexane-1,2-diol moiety as a chiral auxiliary effected C₂-attack of the reagent from the re-face. For study of the second conjugate addition, enantioselectively pure substrates were needed. Substrates 5 and 6 were synthesized from commercially available (R)- and (S)-citronellals by means of the Horner–Emmons reaction with an optically active phosphonate (3). Compound 3 could be easily prepared by monobromoacetylation (69%) of (R,R)-cyclohexane-1,2-diol followed by Albusov reaction (86%) with triethyl phosphite (Chart 2). The second conjugate addition represents “double asymmetric induction”. The effect of chirality at C₅ on the conjugate addition was estimated by the reaction of the methyl ester ((dl)-4) with Me₂CuLi, which afforded a mixture (72%) of syn-7 and anti-7 in a ratio of 65 to 35. This finding suggests that the C₅-methyl group results in predominant syn-addition. Reaction of the substrate 5 with Me₂CuLi afforded a mixture of (3S,5S)-8 and (3R,5S)-8 in a ratio of 55 to 45. Reaction of the other diastereomer 6 gave a mixture of (3R,5R)-9 and (3S,5R)-9 in a ratio of 77 to 23. These results (Table I) suggest that the (1R,2R)-2-hydroxycyclohexyl ester function predominantly effects C₅-attack of the reagent from the re-face, similarly to primary conjugate addition.

Relative stereochemistry of the 3,5-dimethyl function of 7, 8 and 9 was determined as follows based on the 13C-NMR spectra. An authentic sample of a 3 to 1 mixture of racemic syn and anti methyl 3,5-dimethyldecanoates ((dl)-13) was synthesized from a 3 to 1 mixture of cis- and trans-3,5-dimethylcyclohexanone (10) via four steps (i. Baeyer-Villiger oxidation, ii. solvolysis, iii. tosylation, iv. substitution) as shown in Chart 3. A diastereomeric mixture of conjugate addition products 7 was also converted to (dl)-13 via three steps (i. ozonolysis, ii. Wittig

![Chart 1](image1.png)

*Chart 1. Synthetic Strategy for 1,3-Polymethyl Functionalized Compounds

![Chart 2](image2.png)

*Chart 2

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TABLE I. Diastereoselective Conjugate Addition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd. No.</th>
<th>RO</th>
<th>Absolute config. at C5</th>
<th>Yields (%)</th>
<th>Compd. No.</th>
<th>3,5-syn : 3,5-anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>MeO</td>
<td>RS</td>
<td>72</td>
<td>7</td>
<td>(3RS,5RS) : (3SR,5RS) = 65 : 35</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>R</td>
<td>S</td>
<td>40</td>
<td>8</td>
<td>(3S,5S) : (3R,5S) = 55 : 45</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>R</td>
<td>R</td>
<td>42</td>
<td>9</td>
<td>(3R,5R) : (3S,5R) = 77 : 23</td>
</tr>
</tbody>
</table>

<Diagram>

Experimental

Infrared (IR) spectra were measured on a JASCO A-202 spectrometer. 1H- and 13C-nuclear magnetic resonance (NMR) spectra were measured with a JEOL JNM-PX-100 or a JNM-GX 270 spectrophotometer. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. Diethyl ether (Et2O) and THF were dried and distilled from sodium-benzophenone ketyl under an Ar atmosphere prior to use. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used.

(1R,2R)-2-Bromooctoxycyclohexanol (2) A mixed solution of (R,R)-cyclohexane-1,2-diol-d10 (1) (4.9 g, 4.2 mmol) and bromoacetyl chloride (7.5 g, 47 mmol) in CH2Cl2 (100 mL) was refluxed for 4 h. The reaction mixture was washed with brine and dried. Removal of the solvent in vacuo gave an oil residue, which was chromatographed on silica gel. The fraction eluted with 25% AcOEt in hexane (v/v) yielded 2 (6.4 g, 64%) as a colorless solid. [α]D 25 = -42.1° (c = 1.85, CHCl3). IR (Nujol): 3400, 1700, 1400, 1180, 1060 cm⁻¹. 1H-NMR (CDCl3): δ 3.73 (1H, m, 1-H), 4.09 (2H, s, CH2Br), 4.62 (1H, m, 2-H). MS m/z: 236 (M⁺), 219, 146, 128.

(1R,2R)-2-Hydroxycyclohexyl Diethylphosphonate (3) A solution of 2 (2.37 g, 10 mmol) in triethyl phosphate (15 mL) was heated at 100 °C for 10 h. After removal of excess triethyl phosphate in vacuo, the oil residue was purified by silica gel column chromatography. The fraction eluted with 10% hexane in AcOEt afforded 3 (2.15 g, 80%) as a colorless oil. [α]D 25 = -49.9° (c = 1.74, CHCl3). IR (neat): 3450, 1740, 1450, 1270, 1020 cm⁻¹. 1H-NMR (CDCl3): δ 1.34 (6H, m, CH2×2), 2.87 (1H, dd, J = 13.6, 18.1 Hz, 2-H), 3.09 (1H, dd, J = 13.6, 20.3 Hz, 2-H), 3.55 (1H, m, 2-H), 4.17 (4H, m, OCH2×2), 4.63 (1H, m, 1'-H). MS m/z: 304 (M⁺), 286.

Methyl (RS)-(E)-5,5-Dimethyl-2,8-decadienoate (4), (1R,2R,5S)- and (1R,2R,5R)-2-Hydroxycyclohexyl (E)-5,5-Dimethyl-2,8-decadienoate (5 and 6) A solution of (S)-citronellal (500 mg, 3.25 mmol) in CH2CN (2 mL) was added to a stirred mixture of LiCl (180 mg, 4.22 mmol), 3 (1.28 g, 4.22 mmol) and N,N-dissopropylethylamine (554 mg, 4.22 mmol) in CH2CN (9 ml) at 0 °C under an Ar atmosphere. The whole was stirred for 6 h at room temperature. The reaction mixture was diluted with Et2O (100 mL), then washed with brine and dried. After removal of the solvent in vacuo, the oil residue was submitted to column chromatography on silica gel. The fraction eluted with 10% AcOEt in hexane gave 5 (678 mg, 71%) as a colorless oil. [α]D 25 = -26.6° (c = 1.32, CHCl3). IR (neat): 3420, 1710, 1650, 1440, 1270, 1030 cm⁻¹. 1H-NMR (CDCl3): δ 0.91 (3H, d, J = 6.6 Hz, 5-Me), 1.60, 1.68 (3H, each, s, =CMe2), 3.59 (1H, m, 2-H), 4.63 (1H, m, 1'-H), 5.09 (1H, m, 8-H), 5.84 (1H, dt, J = 15.5, 1.5 Hz, 2-H), 6.97 (1H, dt, J = 15.5, 7.6 Hz, 3-H). MS m/z: 294 (M⁺). 276, 238, 197, 192. Compound 6 (506 mg, 75%) was obtained by the similar reaction of (R)-citronellal (350 mg, 2.27 mmol) with 3 (690 mg, 2.27 mmol) as a colorless oil. [α]D 25 = -27.5° (c = 1.08, CHCl3). IR (neat): 3420, 1710, 1650, 1440, 1270, 1030 cm⁻¹. 1H-NMR (CDCl3): δ 0.91 (3H, d, J = 6.6 Hz, 5-Me), 1.60, 1.68 (3H, each, s, =CMe2), 3.59 (1H, m, 2-H), 4.63 (1H, m, 1'-H), 5.09 (1H, m, 8-H), 5.84 (1H, dt, J = 15.5, 1.5 Hz, 2-H), 6.97 (1H, m, 2-H).
of commercially available 3,5-dimethylcyclohexanone (3 to 1 mixture of cis- and trans-compounds) (5.0 g, 37.7 mmol) in CH₂Cl₂ (30 ml) at 0°C, and the whole was stirred for 15 min. The reaction mixture was diluted with CH₂Cl₂ (50 ml) and washed with 5% aqueous NaHCO₃ and brine, then dried. Removal of the solvent in vacuo afforded an oily residue, which was dissolved in MeOH (20 ml). K₂CO₃ (6 g, 43.7 mmol) was added to the solution and the whole was stirred at room temperature for 1 h. After removal of the solvent in vacuo, the oily residue was purified by silica gel column chromatography to give 11 (3.78 g, 55% from 3,5-dimethylcyclohexanone) as a colorless oil. A 3 to 1 mixture of syn and anti-diasteromers. IR (neat): 3410, 1730, 1240, 1100, 1030 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.97 (3H, 2 m, 3,5-Me), 3.47 (2H, m, 6-H), 3.67 (3H, s, OMe). MS m/z: 175 (M⁺ + 1), 156, 143, 112.

Methyl 3,5-Dimethyl-6-p-toluenesulfonyloxaziridane (12) p-Toluene-sulfonyl chloride (817 mg, 4.31 mmol) was added to a stirred mixture of compound 11 (500 mg, 2.87 mmol), 4-(dimethylamino)pyridine (5 mg) and pyridine (5 ml) in CH₂Cl₂ (7 ml) at 0°C. The whole was stirred at room temperature for 12 h. The reaction mixture was poured into brine (50 ml) and extracted with Et₂O (30 ml x 2). The combined extracts were washed successively with 10% aqueous HCl, 5% aqueous NaHCO₃ and brine, then dried. Removal of the solvent in vacuo afforded an oily residue, which was chromatographed on silica gel. The fraction eluted with 10% AcOEt in hexane (v/v) afforded 12 (760 mg, 81%) as a colorless oil. IR (neat): 1740, 1600, 1360, 1100, 1035 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.94 (3H, 2 m, 3,5-Me), 2.45 (3H, s, Ar-Me), 3.65 (3H, 1H, OMe). The 85% (2H, m, 6-H), 7.28 (2H, d, J = 8.2 Hz, Ar-H), 7.79 (2H, d, J = 8.2 Hz, Ar-H). FDMS m/z: 328 (M⁺).

Methyl 3,5-Dimethyloxaziridane (13) Reaction of 12 (100 mg, 0.3 mmol) with Bu₃Li (1.5 mmol) was performed according to the general procedure for 1h, but using BuLi instead of MeLi. Compound 13 (57 mg, 88%) was obtained as a colorless oil. A 3 to 1 mixture of syn and anti-diasteromers. IR (neat): 1740, 1240, 1130, 1025 cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.89 (3H, 3 m, 3,5-Me and 10-H), 2.20 (2H, 2 m, 2-H), 3.66 (3H, s, OMe). ¹³C-NMR (CDCl₃) δ: 14.1 (q), 20.1 (19.4) (q), 20.4 (19.5) (q), 22.7 (t), 26.5 (26.7) (t), 27.9 (d), 30.1 (d), 32.2 (t), 36.7 (37.7) (t), 41.6 (41.5) (t), 44.7 (44.5) (t), 51.3 (q), 173.8 (173.7) (s). Chemical shifts in parentheses are of the minor product. MS m/z: 214 (M⁺), 199, 183.

References and Notes