An Asymmetric Synthesis of Lactones from Cyclic Acid Anhydrides with Chiral Binaphthyldiamines

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Asymmetric ring opening of the cyclic acid anhydrides cis-2, 3 ~ 6 with the axially dissymmetric binaphthyldiamines (S)-1a ~ d and subsequent esterification gave diastereoisomeric mixtures of the amide-esters 7a ~ h. Successive reduction of the ester group and ring closure by hydrolysis afforded (−)-cis-2,4-dimethyl-β-valerolactone (8, 92% e.e.), (−)-mevalonolactone (9, 58% e.e.), (+)-3-isopropyl-β-valerolactone (10, 42% e.e.), and (+)-2,3-methylene-γ-butyrolactone (11, 46% e.e.). Through kinetic resolution of the racemic anhydride trans-2, (−)-trans-2,4-dimethyl-β-valerolactone (12) was yielded in a 74% e.e., whose absolute configuration was established to be 2R,4R.

Among various types of asymmetric reactions, it is an effective method to prepare optically active products from symmetrical molecules. From this viewpoint, dehydrogenases and esterases have been used for the discrimination between enantiotopic groups, and optically active lactones were prepared by subsequent chemical conversion. As a non-enzymatic counterpart, selective acyl-substitution has been successfully performed in which active amides with a chiral leaving group were employed. Asymmetric syntheses of lactones based on the discrimination have also been effected by chemical oxidation and reduction.

It has been reported that diastereoisomeric mixtures of a half-amide and a half-ester were formed with low selectivity by treating cyclic acid anhydrides with a chiral amine and a chiral alcohol, respectively. However, if the selectivity could be improved by choosing appropriate nucleophiles, the reaction might be a promising candidate for enantiotopic group differentiation. Because an axially dissymmetric structure was considered to be suitable for the selection, we chose (S)-1,1′-binaphthyl-2,2′-diamine (1a) as an axially dissymmetric parent compound. We also attempted to elaborate the chiral nucleophile for exhibiting high selectivity through acylation or alkylation of one of the two amino groups in 1a.

Selective monoacylation of 1a with trifluoroacetic anhydride provided the trifluoroacetyl derivative 1b in a 67% yield. The piperidino derivative 1c was afforded in a 38% yield by reductive N-alkylation with glutaraldehyde and sodium cyanoborohydride. A one-pot synthesis through ozonolysis of 2,5-dihydrofuran and subsequent reductive N-alkylation gave the morpholino derivative 1d in a 42% yield. Taking account of naturally occurring lactones or the analogs, the prochiral acid anhydrides 2 ~ 6 were subjected to the present asymmetric synthesis.

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The stereoselectivity of the asymmetric ring opening was assessed on the diastereoisomeric ratios of the amide-esters (IV) by HPLC (Scheme 1). A preliminary examination of the selectivity on (IV) revealed that it was not always satisfactory in every combination of the acid anhydrides (I) and the amines (II). However, the selectivity was particularly high in several cases (Table I).

Based on these observations, optically active cis-2,4-dimethyl-\(\delta\)-valerolactone (8) was synthesized. An equimolar amount of cis-2,4-dimethylglutaric anhydride (cis-2)\(^13\)) reacted with 1c to give the half-amide. After treatment with diazomethane, the diastereoisomeric ratio in the resulting amide-ester 7b was determined by HPLC (Table I, run 2). The amide-ester 7b was subjected to selective reduction of the ester group by lithium borohydride. Hydrolysis then gave \((-\)-(2R,4S)-cis-2,4-dimethyl-\(\delta\)-valerolactone (8)\(^14\)) in an overall yield of 77% from cis-2. The optical purity was 92% based on the maximum rotation which coincided with the diastereoisomeric ratio in 7b. The diastereoisomers of 7a from cis-2 and 1a were separated from each other by silica gel chromatography (Table I, run 1). The major isomer of 7a was \(N\)-acetylated and then subjected to successive reduction and hydrolysis as earlier mentioned to afford optically pure \((-\)-8).

Stereoselection was moderate in 3-hydroxy-3-methylglutaric anhydride (3),\(^15\) 3-isopropylglutaric anhydride (4),\(^16\) and 1,2-cyclopropanedicarboxylic anhydride (5)\(^17\) (Table I, run 4~7). Successive reduction and hydrolysis of 7e, 7f and 7g as described for 7b afforded \((-\)-(R)-mevalonolactone (9, 58% e.e. run 5), \(+(+)-(R)-3\)-isopropyl-\(\delta\)-valerolactone (10, 42% e.e. run 6) and \(+(+)-(2R,3S)-2,3\)-methylene-\(\gamma\)-butyrolactone (11, 46% e.e. run 7), respectively. Because the rotatory method for determining the enantiomeric excess (e.e.) of 9 has been reported to be unreliable,\(^18\) it was determined by using a chiral shift reagent, and was somewhat lower than the value expected from the diastereoisomeric ratio in 7e (run 5). This may have been due to partial racemization during the isolation process. As expected from the separation factor of 7f \((x=1.22)\), the chromatographic separation of each diastereoisomer was successfully performed. The stereochemical outcome showed that the pro-\(R\) carbonyl group was preferentially attacked in the reactions. The selectivity of the reaction with cis-1,2-cyclohexane-

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**Scheme 2.** Chiral Amines, Acid Anhydrides, Amide-esters and Lactones.
Differentiation of Enantiotopic Groups of Acid Anhydrides

Table I. Asymmetric Synthesis of Lactones through Differentiation between Enantiotopic Groups or Enantiomers

<table>
<thead>
<tr>
<th>Run</th>
<th>Acid anhydride</th>
<th>Amine</th>
<th>Amide-ester Lactone</th>
<th>Ratio</th>
<th>$\alpha$</th>
<th>Lactone</th>
<th>Yield (%)</th>
<th>Config.</th>
<th>$[\alpha]_{D}$</th>
<th>e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cis-2</td>
<td>1a</td>
<td>7a</td>
<td>20:80</td>
<td>1.40</td>
<td>8</td>
<td>77</td>
<td>2R,4S</td>
<td>-37.8</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>cis-2</td>
<td>1c</td>
<td>7b</td>
<td>4:96</td>
<td>1.05</td>
<td>9</td>
<td>44</td>
<td>R</td>
<td>-12.2</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>cis-2</td>
<td>1d</td>
<td>7c</td>
<td>10:90</td>
<td>1.39</td>
<td>10</td>
<td>38</td>
<td>R</td>
<td>+7.1</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1e</td>
<td>7d</td>
<td>20:80</td>
<td>1.17</td>
<td>11</td>
<td>65</td>
<td>2R,3S</td>
<td>+28.0</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1f</td>
<td>7e</td>
<td>17:83</td>
<td>1.16</td>
<td>12</td>
<td>47</td>
<td>2R,4R</td>
<td>-60.1</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>1g</td>
<td>7f</td>
<td>79:21</td>
<td>1.22</td>
<td>14</td>
<td>41</td>
<td>2R,4R</td>
<td>-53.4</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>1h</td>
<td>7g</td>
<td>29:71</td>
<td>1.06</td>
<td>15</td>
<td>42</td>
<td>2R,4R</td>
<td>-60.1</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>1i</td>
<td>7h</td>
<td>38:62</td>
<td>1.40</td>
<td>16</td>
<td>43</td>
<td>2R,4R</td>
<td>-53.4</td>
<td>66</td>
</tr>
<tr>
<td>9</td>
<td>trans-2</td>
<td>1c</td>
<td>7b</td>
<td>87:13</td>
<td>1.20</td>
<td>17</td>
<td>44</td>
<td>2R,4R</td>
<td>-60.1</td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td>trans-2</td>
<td>1d</td>
<td>7c</td>
<td></td>
<td></td>
<td>18</td>
<td>45</td>
<td>2R,4R</td>
<td>-53.4</td>
<td>66</td>
</tr>
</tbody>
</table>

This was the best ratio in several experiments and does not coincide with the e.e. of 10 that was actually synthesized.

Separation factor.

Ethyl acetate–hexane–triethylamine = 1:2:0.03, 3 ml/min.

Ethyl acetate–hexane–triethylamine = 1:7.5:0.05, 3 ml/min.

Ethyl acetate–hexane–triethylamine = 1:4:0.05, 3 ml/min.

Hexane–2-propanol–triethylamine = 20:1:0.2, 0.4 ml/min.

Ethyl acetate–hexane–triethylamine = 2:3:0.05, 3 ml/min.

HPLC separation was incomplete for assessing the ratio.


$[\alpha]_{D,\text{max}} = 23.0^\circ$ (c = 6, EtOH); R. H. Cornforth, J. W. Cornforth and G. Popjak, Tetrahedron, 18, 1351 (1962).

$[\alpha]_{D,\text{max}} = 16.9^\circ$ (c = 1.037, EtOH); G. Yabuya and K. Mori, Nippon Nogeikagaku Kaishi, 56, 1121 (1982).

$[\alpha]_{D,\text{max}} = 61.8^\circ$ (c = 6.6, CHCl₃); I. J. Jakovac, G. Ng, K. P. Lok and J. B. Jones, J. Chem. Soc, Chem. Commun., 515 (1980).

Dicarboxylic anhydride (6) was low, but chromatographic separation of 7h was also successful ($\alpha = 1.40$).

The piperidino derivative 1e reacted with a five-fold excess of racemic 2,4-dimethylglutaric anhydride (trans-2). The stereoselectivity of this kinetic resolution was evaluated on the ratio of 7b (Table I, run 9). In the same manner as that for the cis-isomer 8, (−)-trans-2,4-dimethyl-δ-valerolactone 12 with $[\alpha]_{D} = -60.1^\circ$ was obtained in an overall yield of 47% from 1c. The e.e. of 12 was calculated to be 74% from the diastereoisomeric ratio in 7b. Using 1d, 12 with $[\alpha]_{D} = 53.4^\circ$ was also synthesized, whose e.e. was determined to be 66% by a comparison of the specific rotations of 12 (run 9, 10). The absolute configuration of (−)-12 was established by the chiroptical method, a simple comparison of its CD spectrum with those of (−)-8 and (R)-(−)-2-methyl-δ-valerolactone (13) suggesting the $2R,4R$ configuration of (−)-12 (Table II). This conclusion was confirmed by the lactone chirality rule which correlated the Cotton effect with the dihedral angle around the ester group. The conformation (A) pre-
dicted by 1H NMR spectroscopy (400 MHz, Fig. 1) and the negative maximum at 221 nm in its CD spectrum also indicated the 2R,4R configuration of (−)-12. Accordingly, it was the 2R,4R-enantiomer of trans-2 that reacted preferentially with 1c and 1d.

**EXPERIMENTAL**

IR spectra were recorded with a Hitachi 215 spectrometer, and 1H NMR spectra were measured in deuteriochloroform with Varian EM-360 (60 MHz), JEOL FX-100 (100 MHz) and GX-400 (400 MHz) spectrometers. Mass spectra were recorded with a JEOL JMS-DX-300, and optical rotations were measured with a Perkin-Elmer R-241 polarimeter. A Jasco Model J-20 spectropolarimeter was employed for CD spectra. HPLC analyses were carried out on a Jasco BIP-1 chromatograph system equipped with a silica gel column (NUCLEOSIL 50-5, 4 mm × 25 cm). GLC analysis was performed on a Shimadzu GC-4CM gas chromatograph (4 mm × 1 m column, 5%, XE-60). A Varian Aerograph Model 920 gas chromatograph (1/4" × 1 m column, 10%, SE-30) was used for preparative GLC. (S)-(-)[1,1′-Bianaphthyl]-2,2′-diamine [1a; [α]D25 = −151.5° (c = 1.47, pyridine); lit., [α]D = −149.5°] was prepared according to the literature.10

**Preparation of the trifluoroacetyl derivative 1b.** Trifluoroacetic anhydride (1.62 g, 7.7 mmol) was added to a mixture of 1a (2.0 g, 7.0 mmol), trifluoroacetic acid (5.4 ml) and CH2Cl2 (10 ml) with ice-cooling. The mixture was stirred at room temperature overnight and poured into sat. NaHCO3 (50 ml). The organic layer was separated and the aqueous layer was extracted with CH2Cl2 (50 ml x 3). The combined extracts were washed with sat. NaCl and dried over anhyd. Na2SO4. After evaporation, the residue was subjected to MPLC (silica gel, 14% 2-propanol in hexane) to afford 1b as an amorphous powder (1.8 g, 67%); [α]D25 = 12.3° (c = 1.97, CHCl3). Mass m/z: 352 (M+). IR υmax cm⁻¹: 3380, 1620, 1505, 810, 750. 1H NMR δ: 7.4–7.6 (m, 12H, aromatic protons), 3.5 (broad s, 2H, –NH2), 0.9–1.5 (m, 6H, –CH2CH2CH2–), 2.8–3.1 (m, 4H, –N(CH2)2), 3.7 (broad s, 2H, –NHCO–).

**Preparation of the piperidino derivative 1c.** To a mixture of 1a (2.0 g, 7.0 mmol), DMF (8 ml) and CH2CN (25 ml), an aqueous solution of glutaraldehyde (25%, 7.0 ml) and NaBH3CN (0.44 g, 7.0 mmol) were added with ice-cooling. The mixture was then stirred at room temperature for 2 hr, during which a solution of acetic acid (1.3 g, 21 mmol) in CH2CN (5 ml) was added portionwise to maintain the pH around 7. After stirring overnight, 3 N HCl (50 ml) was added and the acidic solution was washed with ether (30 ml). The aqueous layer was made alkaline with 15% NaOH and extracted with CH2Cl2 (50 ml × 3). The combined extracts were washed with sat. NaCl and dried over anhyd. Na2SO4. After evaporation, the residue was subjected to MPLC (silica gel, 14% EtOAc in hexane) to afford 1c as an amorphous powder (0.95 g, 38%); [α]D=12.3° (c = 1.97, CHCl3). Mass m/z: 352 (M+). IR υmax cm⁻¹: 3380, 1620, 1505, 810, 750. 1H NMR δ: 7.4–7.6 (m, 12H, aromatic protons), 3.7 (broad s, 2H, –NH2), 0.9–1.5 (m, 6H, –CH2CH2CH2–), 2.8–3.1 (m, 4H, –N(CH2)2), 3.7 (broad s, 2H, –NH2), 6.9–8.1 (m, 12H, aromatic protons).

**Preparation of the morpholino derivative 1d.** Ozone gas was passed into a solution of 2,5-dihydrofuran (1.12 g, 16 mmol) in MeOH (25 ml) at −60°C until a blue color developed. The excess ozone was expelled by passing argon gas at −60°C. NaBH3CN (3.0 g, 48 mmol) and a solution of 1a (4.3 g, 15 mmol) in DMF (30 ml) were added at −50°C. The mixture was stirred with ice-cooling for 2.5 hr, during which acetic acid (8.6 g, 0.14 mol) was added portionwise to maintain the pH around 7. After evaporation, 5% NaOH (50 ml) was added and the mixture was extracted with CH2Cl2 (50 ml × 3). The combined extracts were washed with sat. NaCl and dried over anhyd. Na2SO4. After evaporation, the residue was subjected to MPLC (silica gel, 3% 2-propanol in hexane) to afford 1d as an amorphous powder (2.3 g, 42%); [α]D25 = 53.3° (c = 1.1, CHCl3). Mass m/z: 354 (M+). IR
Synthesis of (2R,4S)-2,4-dimethyl-3-valerolactone 8. With 1c (Table I, run 2): cis-2,4-Dimethylglutaric anhydride (cis-2, 0.19g, 1.3 mmol) was added to a solution of 1c (0.47g, 1.3 mmol) in toluene (15ml) at −20°C. The mixture was allowed to stand at −20°C for 3 days and then treated with an ethereal solution of diazomethane. To a solution of 7b in dry EtOH (10ml), LiCl (0.17g, 3.9 mmol) and NaNH (0.15g, 3.9 mmol) were added with ice-cooling. The mixture was heated at 50°C for 24 hr. After cooling, 3 n HCl (20ml) was added and the mixture was extracted with CHCl₃ (30 ml × 3). The combined extracts were washed with sat. NaCl, dried over anhyd. Na₂SO₄ and evaporated. 2n Sulfuric acid (20ml) and MeOH was distilled off under reduced pressure. The aqueous solution was continuously extracted with ether at pH 3.0 for 3 days. The extract was dried over anhyd. Na₂SO₄ and evaporated. The residue was subjected to preparative TLC (silica gel, 33% EtOAc in benzene) to afford 9 (0.05g, 38%), [α]D⁵+7.1° (c=0.83, EtOH). The amide-ester 7f was separated and hydrolyzed according to the previous procedure to afford 8 (0.08g, 46%), [α]D⁵−42.4°.

Synthesis of (R)-3-isopropyl-3-valerolactone 10. To a solution of 1b (0.5g, 1.3 mmol) in toluene (10ml), 3-isopropylglutaric anhydride (4, 0.23g, 1.5 mmol) was added at room temperature. After stirring overnight, diazomethane was added. By the same treatment for the synthesis of 8 from 7b, the amide-ester 7f was converted to 10 (0.05g, 38%), [α]D⁵−7.3° (c=1.01, CHCl₃); mass m/z: 550 (M⁺); 1H NMR (400 MHz) δ: 0.82 and 0.96 (2 × d, J=7.2 Hz, 6H, 2 × CH₃), 1.0~1.4, 1.7~2.1 and 2.2~2.5 (m, 4H, -CH(CH₃)CH₂CH(CH₃)₃), 3.48 (s, 3H, OCH₃), 3.8 (broad s, 2H, -NH₂), 6.8~8.0 (m, 12H, aromatic protons). 8.50 and 8.59 (2 × s, 1H, -NHCO-).

Acetic anhydride (0.29g, 2.8 mmol) and triethylamine (0.28g, 2.8 mmol) were added to a solution of (2R,4S)-7a (0.60g, 1.4 mmol) in CH₂Cl₂ (5 ml) at 0°C. The mixture was stirred at room temperature overnight. After adding sat. NaHCO₃ (10ml), the mixture was extracted with CH₂Cl₂ (20 ml × 3). The combined extracts were washed with sat. NaCl and dried over anhyd. Na₂SO₄. Evaporation gave the acetylated 7a (0.63g). This product was redissolved and hydrolyzed accordingly to the previous procedure to afford 8 (0.08g, 46%), [α]D⁵−42.4°.

Synthesis of (R)-3-isovalerolactone 11. To a solution of 1b (1.14g, 3.0 mmol) in toluene (15ml), 1,2-cyclopropanedicarboxylic anhydride (5, 0.4g, 3.6 mmol) was added at room temperature. After stirring...
overnight, diazomethane was added. By the same treatment as described in the synthesis of 8 from 7b, the amide-ester 7g was converted to 11 (0.19 g, 65%). [a]D 25 +28.0° (c=6.41, CHCl3).

The ring opening reaction of cis-1,2-cyclohexanedicarboxylic anhydride 6 with 1a. To a solution of 1a (0.5 g, 1.75 mmol) in benzene (15 ml), 6 (0.27 g, 1.75 mmol) was added at room temperature. Stirring was continued at room temperature for 72 hr and diazomethane was added. Evaporation gave a diastereomeric mixture of 7h, and this was subjected to MPLC (silica gel, 10% EtOAc in hexane). The isomer eluting faster (0.08 g, 10%), glass; [α]D -30.3° (c=1.03, CHCl3); mass m/z: 452 (M+); 1H NMR (100MHz) δ: 0.8~2.1 (m, 8H, -(CH2)4-), 2.3~2.6 and 2.6~2.9 (m, 2H, -COCHiHCO-), 3.5 (broad s, 2H, -NH2), 3.52 (s, 3H, OCH3), 6.8~8.0 (m, 12H, aromatic protons), 8.52 and 8.61 (2×s, 1H, -NHCO-). The isomer eluting slower (0.18 g, 22%), mp 165-166°C; [α]D -28.7° (c=1.35, CHCl3); mass m/z: 452 (M+); 1H NMR (100MHz) δ: 0.8~2.1 (m, 8H, -(CH2)4-), 2.4~2.7 (m, 2H, -COCHiHCO-), 3.5 (broad s, 2H, -NH2), 3.48 (s, 3H, OCH3), 6.8~8.0 (m, 12H, aromatic protons), 8.52 and 8.62 (2×s, 1H, -NHCO-).

The trans lactone 12 was also yielded using 1d according to this same procedure in a yield of 41%. [α]D 25 53.4° (c=1.9, CHCl3).

Synthesis of (2R,4R)-dimethyl-S-valerolactone 12 through kinetic resolution. To a solution of 1c (0.53 g, 1.5 mmol) in toluene (25 ml), trans-2 (1.1 g, 7.5 mmol) was added at -20°C. After stirring at -20°C for 2 days, diazomethane was added. After expelling the excess diazomethane, the solution was treated with propylamine (0.47 g, 7.9 mmol) at room temperature for 1 hr. The mixture was washed with sat. NaHCO3 three times and dried over anhyd. Na2SO4. Evaporation gave the amide-ester 7b, which was reduced and hydrolyzed as described for the cis counterpart of 7b. Distillation gave 12 (0.09 g, 47%), bp 135°C/15 mmHg. [α]D 25 -60.1° (c=2.13, CHCl3). The 1H NMR spectrum (400 MHz) is depicted in Fig. 1. The trans lactone 12 was also yielded using 1d according to this same procedure in a yield of 41%. [α]D 25 -53.4° (c=1.9, CHCl3).

REFERENCES

11) Recently, the diamine 1a was employed for chiral lithium aluminum hydride complexes; see K. Kabuto, T. Yoshida, S. Yamaguchi, S. Miyano and H. Hashimoto, J. Org. Chem., 50, 3013 (1985).
14) IR and 1H NMR spectra substantiated the proposed structures of all the lactones described here.