A New Synthetic Route to Optically Active \( \alpha,\beta' \)- and \( \beta',\gamma' \)-Unsaturated Alcohols, and Its Application to the Synthesis of a Fungitoxic C-18 Hydroxy Unsaturated Fatty Acid

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A new synthetic route to optically active \( \alpha,\beta' \)-, \( \beta',\gamma' \)-unsaturated alcohols was established. The chiral enones (6 and 8), prepared from dimethyl malate via chiral phosphonates (4 and 5), were diastereoselectively reduced with Zn(BH)_4 to afford the 1,3-syn derivatives (9 and 11). As an application of this 1,3-asymmetric induction, the fungitoxic C-18 hydroxy unsaturated fatty acid isolated from stromata of Epichloe typhina was synthesized.

Keywords 1,3-asymmetric induction; diastereoselective reduction; 1,3-syn diol; \( \alpha,\beta' \)-, \( \beta',\gamma' \)-unsaturated alcohol; hydroxy unsaturated fatty acid

Several groups of biologically active compounds, such as prostaglandins (PGs), leukotrienes (LTs) and self-defensive substances against rice blast disease, have been found as metabolites of arachidonic acid, eicosapentaenoic acid, linolenic acid and linoleic acid. In these compounds (PG 3 type, (12S) hydroxyeicosatetraenoic acid (HETE), etc.), an \( \alpha,\beta' \)-, \( \beta',\gamma' \)-unsaturated alcohol partial structure is commonly found (Chart 1).

Usual methods for the preparation of a chiral \( \alpha,\beta' \)-, \( \beta',\gamma' \)-unsaturated alcohol moiety are based on i) Wittig reaction of an \( \alpha \)-silyloxy aldehyde, ii) Wittig reaction of an oxide ylide, iii) asymmetric reduction of an ynone system, iv) reduction of an enone system, and v) alkylation of a 1-yne-3-ol.

In this paper, we report a new method for the preparation of the \( \alpha,\beta' \)- and \( \beta',\gamma' \)-unsaturated alcohol function (A) on the basis of 1,3-asymmetric induction. The retro synthetic analysis of A is shown in Chart 2. The \( \beta',\gamma' \)-unsaturated alcohol function of A may be introduced from the triol (C) via the oxidative cleavage of the C\(_1\)-C\(_2\) bond followed by Wittig reaction. The triol C may be obtained diastereoselectively by \( \beta \)-hydroxy-directed reduction of the enone (D). The enone D may be prepared by Horner-Wadsworth-Emmons (HWE) reaction of an aldehyde and the phosphonate (E), which may be obtainable from chiral malic acid. Thus, the key step for the synthesis of A from (S)-malic acid seems to be diastereoselective reduction of D.

In the literature on hydroxy-directed reduction of \( \beta \)-hydroxy ketones, 1,3-syn selectivity was achieved by Narasaki and Pai, Kiyooka et al., and Suzuki et al., and 1,3-anti selectivity was reported by Anwar and Davis and Evans and Chapman. But, there has been no example of diastereoselective reduction of \( \beta' \)-hydroxy-\( \alpha \)-unsaturated ketones except for Suzuki et al.’s method (LiAlH\(_4\), LiI), which prompted us to investigate the diastereoselectivity.

The designed sequence starts with the synthesis of chiral phosphonates (4 and 5) from (–)-malic acid. The diol (I), prepared from (–)-malic acid according to Moriwaki’s procedure, was converted into the acetone (2) and the tert-butyldiphenylsilyl ether (3) in a usual manner in 85% and 92% yields, respectively. Compounds 2 and 3 were converted into the corresponding phosphonates (4 (95%) and 5 (78%)) by reaction with the lithium salt of dimethyl methylphosphonate at –78°C in tetrahydrofuran (THF). In the proton nuclear magnetic resonance (\( ^1 \)H-NMR) spectra of 4 and 5, the signals attributable to C\(_1\)-H were observed at \( \delta \) 3.16 (2H, d, \( J_{HH} = 22 \) Hz) and \( \delta \) 3.15 (2H, d, \( J_{HH} = 23 \) Hz), respectively. HWE reaction of 4 with cyclohexanecarboxaldehyde in CH\(_2\)Cl\(_2\) in the presence of LiCl and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded 6a (42%) and an undesired acetal-exchanged product (7, 38%). In the case of using diisopropylethylamine instead of DBU, the reaction proceeded more slowly to afford 6a in 72% yield as a single product. The enones (6b, 8a, b) were also

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prepared in 74—80% yields in a similar manner (Chart 3).

Diastereoselective reductions of 6a with hydride reagents such as NaBH₄, L-Selectride and Zn(BH₄)₂ were investigated. The results are summarized in Table I. Among the conditions employed, the best result was obtained under the conditions of entry 5 (Zn(BH₄)₂ in Et₂O at −30 °C), which afforded a mixture of 9a and 10a in the ratio of 9 to 1. The 1,3-syn stereoselectivity with Zn(BH₄)₂ was rationalized similarly to a chelation-controlled mechanism proposed by Ohishi and Nakata. Reduction of 6b under the same conditions afforded a mixture of 9b and 10b in the ratio of ca. 9 to 1 (entry 6).

The β'-hydroxy-α,β-unsaturated ketones (8a, b) were also subjected to dihydride reduction. The results are summarized in Table II. When diisobutylaluminum hydride (DIBAL-H) (entries 1 and 2) and Zn(BH₄)₂ (entries 7 and 8) were used, the diastereomer ratios of the reduction products were approximately 4 to 1 with the predominance of 1,3-syn selectivity.

On the other hand, in the case of using Me₂NBH(OAc)₃ in CH₂CN, which was reported to afford 1,3-anti reduction

![Chemical Structures]

products of β-hydroxy ketones by Evans and Chapman, the 1,3-anti products (12a, b) were predominantly obtained (entries 5 and 6).

The stereochemistry of the reduction products was determined by spectroscopic analysis and chemical conversion, independently. In the carbon-13 nuclear magnetic resonance (¹³C-NMR) spectrum of a mixture of 9a and 10a, C₂ was observed at δ 71.40 and 69.84, respectively. The upper field shift of C₂ in 10a was considered to be caused by γ-gauche effect.¹¹¹

The absolute stereochemistry of 9a was finally clarified by chemical conversion to dimethyl O-benzyloxymalate (15) (Chart 4). Benzoylation of the hydroxy group in 9a (80% diastereomeric excess (d.e.), entry 5 in Table 1) and subsequent decatalization in the usual manner afforded the diol (13, 76%). Oxidative C₁-C₂ bond cleavage with NaIO₄ of 13 followed by Jones oxidation and esterification with CH₂N₂ afforded 14 (82%). Ozonolysis of 14, subsequent Jones oxidation, and esterification with CH₂N₂ afforded (+)-15 (86%) ([α]⁺D = 2.56° (c = 5.89, CHCl₃)). By comparison with authentic (S)-15 ([α]⁺D = 3.46° (c = 5.09, CHCl₃)), the absolute configuration of (+)-15 was clarified to be R. Therefore, the absolute structure of 9a should be (2S, 4R).

Next, as a part of our synthetic study on biologically active compounds, we describe the application of this method to the synthesis of a fungitoxic C-18 hydroxy unsaturated fatty acid (23), which was isolated from stromata of Epiclote typhina by Sakamura et al., in 1987.¹²•

HWE reaction of the phosphonate 5 and methyl 8-oxooctanoate¹³ afforded the enone (16) in 61% yield as a single product. Reduction of 16 with Zn(BH₄)₂ afforded the

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Table II. Diastereoselective Reduction of 8a, b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reagent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
<th>Ratio (9:10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>NaBH₄</td>
<td>0</td>
<td>99</td>
<td>46:54</td>
</tr>
<tr>
<td>2</td>
<td>8a</td>
<td>L-Selectride</td>
<td>0</td>
<td>84</td>
<td>69:31</td>
</tr>
<tr>
<td>3</td>
<td>8a</td>
<td>L-Selectride</td>
<td>−78</td>
<td>99</td>
<td>62:38</td>
</tr>
<tr>
<td>4</td>
<td>8a</td>
<td>Zn(BH₄)₂</td>
<td>23</td>
<td>89</td>
<td>84:16</td>
</tr>
<tr>
<td>5</td>
<td>8a</td>
<td>Zn(BH₄)₂</td>
<td>−30</td>
<td>91</td>
<td>90:10</td>
</tr>
<tr>
<td>6</td>
<td>8a</td>
<td>Zn(BH₄)₂</td>
<td>−30</td>
<td>73</td>
<td>88:12</td>
</tr>
</tbody>
</table>

a) The combined yield of 9 and 10.

![Chemical Structures]

Table III. Reaction of 13

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reagent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
<th>Ratio (11:12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>PhCOCl, pyridine</td>
<td>a,b</td>
<td>80</td>
<td>74:26</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>p-TsOH, MeOH</td>
<td>c,d,e</td>
<td>80</td>
<td>58:42</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>NaIO₄, d</td>
<td>f,d,e</td>
<td>80</td>
<td>58:42</td>
</tr>
</tbody>
</table>

a) PhCOCl, pyridine. b) p-TsOH, MeOH. c) NaIO₄. d) Jones oxid. e) CH₂N₂. f) O₂; g) ZnO, AcOH.

Chart 4
1,3-syn diol (17, 70% d.e., 95% yield). Compound 17 was treated with Bu₄NF to give the triol (18, 89% yield). Oxidative cleavage of the diol of 18 with NaIO₄ gave the β-hydroxy aldehyde (19, 52%). The direct Wittig reaction of 19 with hexyldienetriphenylphosphorane under various conditions did not afford the desired product, because of easy enolization of 19 in basic media. After protection of the hydroxy group in 19 as the tert-butylidimethylsilyl ether (20), Wittig reaction afforded the 12Z-product (21, 24% from 19) predominantly (12Z: 12E = 95: 5). Desilylation of 21, and subsequent hydrolysis of 22 with porcine liver esterase (PLE) in 0.1 M phosphate buffer afforded the target molecule (23) (Chart 5).

The 270 MHz 1H-NMR spectrum of 22 was identical with that of an authentic sample. The specific rotation of 23 ([α]D°) = 5.6°) was also the same as the reported value ([α]D°) = 2.4°) in sign, which means that reduction of 16 had occurred with 1,3-syn selectivity. The enantimeric excess (e.e.) of 22 was reconfirmed to be 70% e.e. after conversion into the corresponding (+)-α-methoxy-α-trifluoromethylphenylacetic acid (MPA ester).

Thus, the new method described above was clarified to be effective for the preparation of the α,β,γ-unsaturated alcohols.

**Experimental**

Infrared (IR) spectra were measured with a JASCO A-202 spectrometer. 1H-NMR spectra were measured on a JEOL JNM-PS-100 and JNM-GX-270 spectrometers. Mass spectra (MS) were taken on a JEOL JMS-D-300 spectrometer. Specific rotations were measured on a JASCO DIP-4 polarimeter. For column chromatography, silica gel (Merck, Kieselgel 60, 70-230 mesh) was used. Thin layer chromatography (TLC) was performed on Silica gel 60 F₅₂₅₄ (Merck). All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

**Methyl (S)-4-tert-Butyldiphenylsilyloxy-3-hydroxybutanoate (3) tert-Butyldiphenylsilyl chloride (9.5 g) was added portionwise to a mixed solution of crude I (5.09 g), hexamethyldiphosphoric triamide (HMPPA) (2 ml) and pyridine (11.2 ml) in CH₂Cl₂ (50 ml) at 0°C. After being stirred for 3 h at room temperature, the reaction mixture was diluted with CH₂Cl₂ (100 ml), and washed with brine, then dried. Removal of the solvent in vacuo gave an oily residue, which was chromatographed on silica gel (70 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded 3 (11.8 g, 92%) as a colorless oil. [α]D° = 8.0° (c = 1.1, CHCl₃, IR) (neat): 3500, 1740, 1430, 1260, 1120 cm⁻¹. 1H-NMR (CDCl₃) δ = 1.07 (9H, s, COOMe), 2.55 (2H, d, J = 6 Hz, C₂H₃), 3.65 (2H, d, J = 5 Hz, C₂H₅), 3.67 (3H, s, COOMe), 4.16 (1H, d, J = 5, 6 Hz, C₂H₅). MS m/z = 373 (M⁺ + 1), 316, 315.

**Dimethyloxycarbonyl (S)-4-tert-Butyldiphenylsilyloxy-2-oxopropenylphosphonate (4) and Dimethyl (S)-5-tert-Butyldiphenylsilyloxy-4-hydroxy-2-oxopropenylphosphonate (5)** Butyl lithium (1.5 m in hexane, 30 ml) was added to a solution of dimethyl methylenephosphonate (7.0 g) in THF (40 ml) at -78°C under an Ar atmosphere. This was stirred for 0.5 h, and 2 (4.0 g) in THF (10 ml) was added dropwise. The whole was stirred for 1 h at the same temperature, and quenched by addition of NH₄Cl (6 g). The whole was diluted with ether (150 ml) and washed with brine (50 ml). The aqueous layer was re-extracted with CH₂Cl₂ (50 ml x 3). The combined extracts were dried, and removal of the solvent in vacuo afforded an oily residue, which was purified by column chromatography on silica gel (100 g). The fraction eluted with 30-40% hexane in AcOEt (v/v) afforded 4 (5.8 g, 95%) as a colorless oil. [α]D° = 1.08° (c = 1.30, MeOH, IR) (neat): 1715, 1460, 1375, 1260, 1190 cm⁻¹. 1H-NMR (CDCl₃) δ = 1.34, 1.40 (3H each, s, CMe₂), 2.78, 3.08 (1H each, dd, J = 6, 17 Hz, C₂H₅), 3.16 (2H, d, J = 22 Hz, C₂H₅), 3.74 (6H, d, J = 10 Hz, P(O)Me₂). MS m/z: 251 (M⁺ + 180).

Compound 5 was prepared from 3 in a similar manner to that described above. A reaction time of 4 h afforded 5 in 78% yield. Colorless oil. [α]D° = -16.9° (c = 1.02, CHCl₃, IR) (neat): 3400, 1720, 1430, 1250, 1110 cm⁻¹. 1H-NMR (CDCl₃) δ = 1.07 (9H, s, CMe₂), 2.79 (2H, d, J = 6 Hz, C₂H₅), 3.15 (2H, d, J = 23 Hz, C₂H₅), 3.62 (2H, d, J = 6 Hz, C₂H₅), 4.22 (1H, m, C₂H₅). MS m/z: 456 (M⁺ + 1800).

**General Procedure for HWE Reactions of Phosphonates (4, 5) and Aldehydes** The aldehyde (5.47 mmol) in CH₂Cl₂ (5 ml) was added to a mixed solution of LiCl (232 mg, 5.47 mmol), the phosphonate (5.47 mmol) and disopropylethylamine (707 mg 5.47 mol) in CH₂Cl₂ (45 ml) at room temperature. After being stirred for 43 h, the reaction mixture was diluted with ether (100 ml), washed with brine, and then dried. Removal of the solvent in vacuo afforded an oily residue, which was purified by column chromatography on silica gel (30 g).

**General Procedure for Reduction of Enones (6a, b and 8a, b) with Zn(BH₄)₂** Zn(BH₄)₂ (0.18 m ether solution, 13 ml) was added dropwise to a stirred solution of the enone (0.8 mmol) in ether (4 ml) at -20°C. The mixture was stirred for 4 h, H₂O (1 ml) was added, and the whole was stirred for 10 min at room temperature. The reaction mixture was diluted with ether (100 ml), washed with brine, and then dried. After removal of the solvent, the residue was purified by column chromatography on silica gel (5 g) to give a mixture of 9a and 10a (in the ratio of 9 to 1). Colorless oil. IR (neat): 3500, 1620, 1450, 1250, 1160 cm⁻¹. 1H-NMR (CDCl₃) δ = 0.91 (3H, t, J = 7 Hz, CH₃), 1.07 (9H, s, CMe₂), 2.75 (2H, d, J = 6 Hz, C₂H₅), 3.66 (2H, d, J = 6 Hz, C₂H₅), 6.11 (1H, d, J = 16 Hz, C₂H₅), 6.87 (1H, dt, J = 16, 7 Hz, C₂H₅). MS m/z: 425 (M⁺ + 1), 386, 367.

**General Procedure for Reduction of Enones (6a, b and 8a, b) with Zn(BH₄)₂** Zn(BH₄)₂ (0.18 m ether solution, 13 ml) was added dropwise to a stirred solution of the enone (0.8 mmol) in ether (4 ml) at -20°C. The mixture was stirred for 4 h, H₂O (1 ml) was added, and the whole was stirred for 10 min at room temperature. The reaction mixture was diluted with ether (100 ml), washed with brine, and then dried. After removal of the solvent, the residue was purified by column chromatography on silica gel (5 g) to give a mixture of 9a and 10a (in the ratio of 9 to 1). Colorless oil. IR (neat): 3500, 1620, 1450, 1250, 1160 cm⁻¹. 1H-NMR (CDCl₃) δ = 0.91 (3H, t, J = 7 Hz, CH₃), 1.07 (9H, s, CMe₂), 2.75 (2H, d, J = 6 Hz, C₂H₅), 3.66 (2H, d, J = 6 Hz, C₂H₅), 6.11 (1H, d, J = 16 Hz, C₂H₅), 6.87 (1H, dt, J = 16, 7 Hz, C₂H₅). MS m/z: 425 (M⁺ + 1), 386, 367.
t. J=6 Hz, CH$_3$), 1.36, 1.42 (3H each, s, CMe$_3$), 3.50 (1H, m, C$_6$H$_7$), 4.00–4.36 (2H, m, C$_7$H$_4$), 5.34–5.80 (2H, m, C$_8$H$_8$). MS m/z: 228 (M$^+$), 210. The ratio of 9b and 10b was determined from the $^{13}$C-NMR spectrum. $^{13}$C-NMR (CDC$_6$): δ 76.11 (C$_2$), 74.57 (C$_1$), 10.69 (C$_9$), 73.32 (C$_8$), 73.23 (C$_7$).

A mixture of 11a and 12a (in the ratio of 79 to 21). Colorless oil. IR (neat): 3500, 1620, 1450, 1260 cm$^{-1}$. $^{1}$H-NMR (CDCl$_3$): δ 1.07 (9H, s, CMe$_3$), 3.60 (2H, d, J=6 Hz, C$_6$H), 4.00 (1H, m, C$_7$H), 4.34 (1H, m, C$_7$H), 5.45, 5.66 (1H each, m, C$_8$H$_2$). MS m/z: 453 (M$^+$ +1), 396, 377. The ratio of 11a and 12a was determined from the 270 MHz $^{13}$C-NMR spectrum (CDCl$_3$): 11a: δ 10.16 (d, J=15.6, 6.6, 1.4 Hz, C$_8$H$_7$), 12a: δ 14.40 (d, J=15.6, 5.8, 1.4 Hz, C$_8$H$_7$).

A mixture of 11b and 12b (in the ratio of 80 to 20). Colorless oil. IR (neat): 3500, 1620, 1450, 1260 cm$^{-1}$. $^{1}$H-NMR (CDCl$_3$): δ 0.88 (3H, t, J=7 Hz, C$_3$H$_2$), 1.07 (9H, s, CMe$_3$), 2.60 (2H, d, J=6 Hz, C$_6$H), 3.96 (1H, m, C$_7$H), 4.34 (1H, m, C$_7$H), 5.45, 5.66 (1H each, m, C$_8$H$_2$). MS m/z: 457 (M$^+$ +1), 375, 351. The ratio of 11b and 12b was determined from the 270 MHz $^{13}$C-NMR spectrum. $^{13}$C-NMR (CDCl$_3$): δ 11b: 5.484 (dd, J=15.3, 6.6, 1.3 Hz, C$_8$H$_7$), 12b: 5.496 (dd, J=15.3, 6.6, 1.3 Hz, C$_8$H$_7$).

7(E,25S,4R)-4-Benzoyl-6-cyclohexyl-5-hexene-1,2-diol (13) Benzoyl chloride (1.82 g) was added to a stirred solution of 9a (80% d.e., 1.63 g) in CH$_2$Cl$_2$ (30 ml) and pyridine (2.6 ml) under ice-water cooling. After 3 h, usual work-up afforded the benzene (2.36 g), which was stirred with TsOH (100 mg) in MeOH (30 ml) at room temperature. After 5 h, MeOH was removed in vacuo, and an oily residue was obtained in AcOEt. The AcOEt solution was washed and dried. Removal of the solvent in vacuo afforded an oily residue, which was submitted to silica gel (30 g) column chromatography. The fraction eluted with AcOEt (4:1, v/v) gave 13 as a colorless oil (1.55 g, 76%). IR (neat): 3400, 1710, 1600, 1500 cm$^{-1}$. After addition of HCl (1.0 ml) and mediated with silica gel (5 g), the crude 20, which was used in the next Wittig reaction without further purification. BuLi (1.5 mol solution in hexane, 0.15 ml) was added to a stirred solution of hexyltriphenylphosphonium bromide (70 mg in ether (7 ml) at ~78 °C under an Ar atmosphere. After being stirred for 10 min, 20 (110 mg) in ether (1 ml) was added, and the whole was stirred for 40 min at the same temperature. After addition of 20% AcOEt in hexane (5 ml), the reaction mixture was diluted with ether (50 ml), washed with brine, and then dried. The solvent was removed in vacuo to afford an oily residue, which was purified by preparative TLC (20% AcOEt in hexane). The crude 21 (53 mg, 41%) was obtained as a colorless oil. $^{1}$H-NMR (CDCl$_3$): δ 0.22–2.25 (2H, m, C$_7$H), 2.30 (2H, t, J=7 Hz, C$_6$H), 3.66 (2H, m, C$_8$H$_2$), 4.03 (1H, m, C$_7$H), 5.30–5.60 (4H, m, C$_9$H$_{12}$, 11H).

Methyl (8E,10R,12Z)-10-Hydroxy-8,10,12-tridecanedioate (22) Bu$_2$NF (1 mol solution in THF, 0.14 ml) was added to a stirred suspension of 22 (30 mg) in THF (15 ml) at 0 °C. The mixture was stirred for 7 h, then removal of the solvent in vacuo afforded an oily residue, which was purified by preparative TLC. Compound 22 (20 mg, 92%) was obtained as a colorless oil, [α]$_{D}^{20}$=−6.20 (c=1.0, EtOH). IR (CHCl$_3$): 3600, 1730, 1435, 1205, 970 cm$^{-1}$. $^{1}$H-NMR (CDCl$_3$): δ 0.89 (3H, t, J=7 Hz, C$_3$H$_2$), 2.01–2.06 (4H, m, CH$_{11}$-11), 2.30 (2H, t, J=7 Hz, C$_6$H), 3.67 (3H, s, COOMe), 4.07 (1H, m, C$_7$H$_2$), 5.30–5.75 (4H, m, C$_8$H$_{12}$, 11H). 270 MHz $^{13}$C-NMR (CDCl$_3$): δ 5.84 (1H, d, J=10.9, 6.9 Hz, C$_{12}$), 5.482 (1H, d, J=15.4, 6.6 Hz, C$_7$H), 5.566 (1H, dd, J=10.9, 6.9 Hz, C$_6$H), 5.662 (1H, d, J=15.4, 6.8 Hz, C$_5$H). FDMS m/z: 511 (M$^+$ +1), 293. The e.e. or 22 was confirmed to be 70% e.e. after conversion into the (+)-MTPA ester. (+)-MTPA ester of 22. 270 MHz $^{13}$C-NMR (CDCl$_3$): δ 3.539 (OMe); (10S)-epimer. 3.552 (OMe).

Acknowledgement The authors are grateful to Prof. S. Sakamura, Hokkaido University for providing a chart of the $^{1}$H-NMR spectrum of 22.

References and Notes
13) Methyl 8-oxooctanoate was prepared from 1,8-octanediol in a conventional manner.