STUDIES ON A TOTAL SYNTHESIS OF PLAKOTENIN: SYNTHESIS OF OPTICALLY ACTIVE trans-HYDRINDANES BY DIASTEREOSELECTIVE ASYMMETRIC INTRAMOLECULAR DIELS-ALDER REACTION

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Abstract- Diastereoselective asymmetric intramolecular Diels-Alder reaction of 5,5-(trimethylenedithio)-2(E),7(E),9-decatrienoyl amides (13a-e) having various chiral auxiliaries was performed to give optically active trans-hydrindanes, which would be an important intermediate for a total synthesis of plakotenin (I), was described. In the several chiral auxiliaries, Saigo's oxazolidinone was found to give trans-hydrindane (15a) in the highest stereoselectivity (96% e.e.), after conversion to benzyl ester.

Plakotenin (1), a new cytotoxic carboxylic acid, was isolated from the Okinawan marine sponge Plakoritis sp. by Kobayashi in 1992.1 Its stereostructure was deduced by spectroscopic data to possess trans-hydrindane skeleton bearing six contiguous asymmetric centers.1 However, its absolute configuration was not determined. Since amount of 1 in the sponge was extremely low (0.0005% yield based on wet weight), the synthesis of 1 and the related compounds is an attractive target because of determination of the absolute configuration as well as exploitation of their new biological activities. Several reports on synthesis of optically active trans-hydrindanes without functional group on five-membered ring have appeared so far, in which enzymatic method,2 and diastereoselective3-8 and enantioselective9,10 intramolecular Diels-Alder reaction are employed. Since a plausible biogenesis of plakotenin (1) similar to that of ircinianin11 has been proposed to be intramolecular [4+2] cycloaddition, we planned to synthesize trans-hydrindane skeleton by diastereoselective asymmetric Diels-Alder reaction. Although Narasaka et al.12 have reported
functionalized trans-hydridane (2) by enantioselective Diels-Alder reaction of 5 using a catalytic amount of chiral Lewis acid, we examined synthesis of chiral trans-hydridanes (3) by diastereoselective Diels-Alder reaction\textsuperscript{13} of chiral trienes (6), because the chiral auxiliary seems to be repeatedly used more readily than the chiral Lewis acid. This paper deals with synthesis of chiral functionalized trans-hydridanes (3, 4) by diastereoselective intramolecular Diels-Alder reaction.\textsuperscript{13} Synthesis of chiral Diels-Alder reaction precursors (6) is as follows. Lithiation of 1,3-dithiane in THF-HMPA with $n$-BuLi, followed by the reaction with 2-bromodioxolane gave 7 in 81% yield. In this reaction, 7 was obtained in less than 10% yield, when HMPA was absent. Reaction of lithiated 7 with 2,4-pentadienyl bromide\textsuperscript{14} in THF afforded 8 in 40% yield,\textsuperscript{15} hydrolysis of which with 3 N HCl gave an aldehyde (9) in 85% yield.

In order to synthesize chiral trienes (13a-e) by modified Wittig-Horner reaction\textsuperscript{19} of the aldehyde (9) with several chiral auxiliaries (10a-e),\textsuperscript{5,16-18} Wittig-Horner type reagents (12a-e)\textsuperscript{20} were prepared. Namely, bromoacetylation of chiral auxiliaries (10a-e), followed by the treatment with triethyl phosphate in boiling benzene, produced 12a-e. Reaction of aldehyde (9) with Wittig-Horner reagents (12a-e) obtained thus according to Masamune-Roush method\textsuperscript{19} gave chiral trienes (13a-e) in 25-62% yield.

With chiral trienes (13a-e) in hand, asymmetric intramolecular Diels-Alder reaction of trienes (13a-e) in the presence of Lewis acid was examined. In all cases, unfortunately, the reaction was sluggish and not completed at -25 °C even after 4 days.\textsuperscript{22} Moreover, as chromatographic separation of starting trienes and
cyclized products was unsuccessful, diastereoselectivities in the products could not be determined. Therefore, the crude reaction mixture was treated with BnOLi to lead to 15 together with benzyl ester (16) of triene. E.e. of resulting benzyl esters (15) was estimated by HPLC analysis using chiral column. Results are shown in Table 1.

Contrary to our expectation,22 diastereoselectivities were low to moderate in the reaction of 13a-c (Entries 1-3). Especially, remarkable decrease of stereoselectivity was observed in the reaction of 13b,c, which had more sterically congested circumstances around C-4 on oxazolidinone than 13a (Entries 2, 3). Interestingly, the sense of face selectivity in 13b was opposite to others. Phenyl group at C-5 position on oxazolidinone in 13b might affect π-π interaction between each alkenyl group, although the reason was not clear. Among the reaction examined, 13d gave the best result to furnish cyclized product (15a) in 55% yield (96% e.e.: Entry 4) and chiral auxiliary (10d) was recovered in 51% yield. Camphorsultam (13e) gave also good diastereoselectivity, although total yield was low (Entry 6).

\[
\begin{align*}
13a : X &= X_N \\
13b : X &= X_P \\
13c : X &= X_C \\
13d : X &= X_S \\
13e : X &= X_O
\end{align*}
\]

![Scheme 3](image)

Table 1. Asymmetric intramolecular Diels-Alder reaction of trienes (13a-e).a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Lewis acid</th>
<th>Yield of 15 (%)</th>
<th>Yield of 16 (%)</th>
<th>Ratio of 15a : 15b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13a</td>
<td>Me2AlCl</td>
<td>54</td>
<td>10</td>
<td>4.41 : 1 (63)</td>
</tr>
<tr>
<td>2</td>
<td>13b</td>
<td>Me2AlCl</td>
<td>57</td>
<td>8</td>
<td>1 : 1.64 (22)</td>
</tr>
<tr>
<td>3</td>
<td>13c</td>
<td>Me2AlCl</td>
<td>65</td>
<td>19</td>
<td>1.64 : 1 (22)</td>
</tr>
<tr>
<td>4c</td>
<td>13d</td>
<td>Me2AlCl</td>
<td>55</td>
<td>9</td>
<td>46.7 : 1 (96)</td>
</tr>
<tr>
<td>5</td>
<td>13d</td>
<td>Me2AlCl</td>
<td>52</td>
<td>10</td>
<td>38.7 : 1 (95)</td>
</tr>
<tr>
<td>6</td>
<td>13e</td>
<td>EtAlCl2</td>
<td>26</td>
<td>7</td>
<td>14.4 : 1 (87)</td>
</tr>
</tbody>
</table>

a) All reactions were carried out at -25 °C in CH2Cl2 for 4 days, otherwise indicated. b) Determined by HPLC analysis. Values in parenthesis mean e.e.(%) of 15a (except for Entry 2). c) The reaction was performed at 0 °C.
To determine absolute stereochemistry of benzyl ester (15a), 15a was converted to known trans-hydrindane (19). Namely, alkaline hydrolysis of benzyl ester (15a) gave in 85% yield carboxylic acid (17), conversion of which to acid chloride (18), followed by the treatment with lithiated oxazolidinone, furnished 19 in 74% yield. Thus, the stereochemistry of synthetic 19 was determined by comparison of spectral data and sign of specific rotation for 19 with those reported in the literature.

In summary, we have synthesized trans-hydrindanes (15), which would be important intermediate for a total synthesis of plakotenin (1), by asymmetric intramolecular Diels-Alder reaction of trienes (13a-e) having various chiral auxiliaries. Among them, reaction of triene (13d) having Saigo’s chiral oxazolidinone gave 15a in high e.e. after treatment with BnOLi. Moreover, it is noteworthy that product from triene (13b) showed opposite stereoselectivity to that obtained from other trienes (13a,c-e).

EXPERIMENTAL SECTION

General. All melting points were measured on a Yanagimoto (hot plate) melting point apparatus and are uncorrected. IR spectra were performed with a Hitachi 260-10 spectrophotometer in CHCl₃ solution, and ¹H NMR spectra were taken with a JEOL EX-270 (270 MHz) spectrometer in CDCl₃ solution with tetramethylsilane as an internal standard. Following abbreviations were used in the NMR data; s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, br s: broad singlet, m: multiplet. MS spectra were measured on a Hitachi M-80 or a JEOL JMS D-300 spectrometer. Elementary analysis was performed with a Heraeus CHN-O-RAPID apparatus. HPLC analysis was performed with SSC flow system 3100 and SSC UV detector 3000A-II using Daicel Chiral Cel OJ (4.6 φ x 25 cm). Specific rotation was measured by JASCO DIP-360 polarimeter. Column chromatography was performed over silica gel (Wako gel C-200 or Merck Kieselgel 60). Preparative TLCs were run on Merck 5744 or Merck 7730 plate. All reactions were performed under argon atmosphere except the reaction in boiling benzene and the solvent was removed in vacuo.

2-[2-(1,3-Dioxolanyl)methyl]-1,3-dithiane (7). To a stirred solution of 1,3-dithiane (2.40 g, 20 mmol) in THF (50 mL) at -78 °C was added n-BuLi (13.5 mL, 21.2 mmol, 1.57 M in hexane) over a period of 15 min. After being stirred at -20 °C for 2.5 h, the mixture was cooled to -78 °C. Then, HMPA
(7.0 mL, 40 mmol) was added over a period of 10 min, and 2-bromomethyl-1,3-dioxolane (2.4 mL, 20 mmol) was added for 10 min. After the mixture was warmed up to rt, the reaction was quenched with water. The mixture was extracted with ether. The extract was dried (K<sub>2</sub>CO<sub>3</sub>), and removal of the solvent gave a residue, which was purified by column chromatography (200 g, hexane then hexane : AcOEt = 5 : 1) to give 7 (3.334 g, 81%) as an oil; <sup>1</sup>H NMR δ 5.15 [1H, t, J = 5.2 Hz, CH<sub>2</sub>CH(OCH<sub>2</sub>)], 4.23 [1H, t, J = 7.3 Hz, CH<sub>2</sub>CH(SCH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>], 3.84-4.02, 2.78-2.97 (each 4H, m), 2.05-2.17, 1.80-1.98 (each 2H, m); EI MS m/z 206 (M⁺); high-resolution MS m/z calcd for C<sub>12</sub>H<sub>14</sub>O<sub>2</sub>S, (M⁺) 206.0429, found: 206.0434.

2-[2-(1,3-Dioxolanyl)methyl]-2-(2,4-pentadienyl)-1,3-dithiane (8). To a stirred solution of 7 (0.42 g, 2.0 mmol) in THF (10 mL) at -78 °C was added n-BuLi (2.0 mL, 3.2 mmol, 1.60 M in hexane) over a period of 5 min. After being stirred at -20 °C for 2 h, 2,4-pentadienyl bromide<sub>14</sub> (0.50 g, 3.4 mmol) was added over a period of 5 min. The mixture was stirred at the same temperature for 6 h. Work-up similar to that noted above gave a residue, preparative TLC (hexane : AcOEt = 6 : 1) of which gave 8 (0.221 g, 40%) as an oil; <sup>1</sup>H NMR δ 6.00-6.42 (2H, m), 5.81 (1H, dt, J = 7.26, 14.9 Hz CH=CHCH<sub>2</sub>), 4.98-5.24 (2H, m), 5.14 [1H, t, J = 4.3 Hz, CH<sub>2</sub>CH(OCH<sub>2</sub>)], 3.78-4.02 (4H, m), 2.70-2.94 (6H, m), 2.31 [2H, d, J = 4.3 Hz, CH<sub>2</sub>CH(OCH<sub>2</sub>)<sub>2</sub>], 1.80-1.98 (2H, m); IR 1630, 1601, 1416 cm<sup>-1</sup>; EI MS m/z 272 (M⁺); high-resolution MS m/z calcd for C<sub>12</sub>H<sub>16</sub>O<sub>2</sub>S<sub>2</sub> (M⁺) 272.0642, found: 272.0642.

2-(Formylmethyl)-2-(2,4-pentadienyl)-1,3-dithiane (9). A solution of 8 (0.830 g, 3.05 mmol) and 3 N HCl (20 mL) in THF (10 mL) was stirred at rt for 24 h. The mixture was extracted with ether. Usual work-up of the extract gave 9 (0.589 g, 85%) as an oil; <sup>1</sup>H NMR δ 9.80 (1H, t, J = 2.6 Hz, CH=CHCHO), 5.93-6.34 (2H, m), 5.65 (1H, dt, J = 7.6, 15.2 Hz, CH=CHCH<sub>3</sub>), 4.98-5.23 (2H, m), 2.74-2.93 (8H, m), 1.85-2.03 (2H, m); IR 2910, 1716 cm<sup>-1</sup>; EI MS m/z 228 (M⁺); high-resolution MS m/z calcd for C<sub>11</sub>H<sub>16</sub>O<sub>2</sub>S<sub>2</sub> (M⁺) 228.0642, found: 228.0642.

**General Procedure for Preparation of N-Bromoacetoxazolidin-2-ones (11a-d) and D-N-Bromoacetlycamphorsultam (11e).** To a stirred solution of oxazolidin-2-ones (10a-d) and camphorsultam (10e) in THF at -78 °C was added n-BuLi over a period of 5 to 10 min. After being stirred for 50 min to 2 h, BrCH<sub>2</sub>COBr was added to the mixture. Stirring was continued at the same temperature for 1 h. The reaction was quenched with 3 N HCl and the product was taken up in AcOEt. Usual work-up of the extract gave a residue, which was purified by column chromatography (hexane : AcOEt = 1 : 3 for 11a-d, CHCl<sub>3</sub> for 11e).

(4R, 5S)-N-Bromoacetyl-4-methyl-5-phenyloxazolidin-2-one (11a): Compound (10a)<sup>5</sup> (3.54 g, 20 mmol), n-BuLi (12 mL, 21.1 mmol, 1.69 M in hexane), THF (60 mL), BrCH<sub>2</sub>COBr (1.9 mL, 21.8 mmol), and THF (8 mL) were used: 11a (4.44 g, 75%) as an oil; [α]<sub>D</sub><sup>29</sup> +17.2° (c 1.02, CHCl<sub>3</sub>); <sup>1</sup>H NMR δ 7.26-7.47 (5H, m), 5.74 (1H, d, J = 6.8 Hz, CHPh), 4.80 (1H, qu, J = 6.8 Hz, CHCH<sub>2</sub>CH<sub>3</sub>),
5.75, 5.51 (each 1H, d, J = 12.9 Hz, BrCH₂CO), 0.94 (3H, d, J = 6.8 Hz, CHCH₃); EI MS m/z 297 (M⁺), 299 (M⁺+2); high-resolution MS m/z calcd for C₁₂H₁₁NO₃Br (M⁺) 296.9999, found: 296.9987.

(4R)-N-Bromoacetyl-4-phenyloxazolidin-2-one (11b): Compound (10b)⁵ (2.00 g, 12.3 mmol), n-BuLi (8 mL, 12.8 mmol, 1.6 M in hexane), THF (45 mL), and BrCH₂COBr (1.1 mL, 12.6 mmol) were used: 11b (1.77 g, 51%) as colorless crystals; mp 119-120 °C (AcOEt-hexane); [α]D³⁻ = -67.0° (c 1.02, CHCl₃); ¹H NMR 8 7.26-7.44 (5H, m), 5.44 (1H, dd, J = 3.9, 8.7 Hz, PhCHCH₂), 4.76 (1H, t, J = 8.7 Hz, PhCHCH(H)), 4.56, 4.46 (each 1H, d, J = 12.6 Hz, BrCH₂CO), 4.35 (1H, dd, J = 3.9, 8.7 Hz, PhCHCH(H)); IR 3031, 1786, 1709 cm⁻¹; EI MS m/z 283 (M⁺), 285 (M⁺+2); Anal. Calcd for C₁₂H₁₀NO₃Br: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.60; H, 3.81; N, 5.22.

(4R)-N-Bromoacetyl-4-cyclohexyloxazolidin-one (11c): Compound (10c)⁴ (5.91 g, 35 mmol), n-BuLi (23 mL, 36.8 mmol, 1.6 M in hexane), THF (130 mL), and BrCH₂COBr (3.2 mL, 36.7 mmol) were used: 11c (4.91 g, 48%) as colorless crystals; mp 113-114 °C (Et₂O-hexane); [α]D³⁻ = -92.6° (c 1.02, CHCl₃); ¹H NMR 8 4.58, 4.46 (each 1H, d, J = 12.2 Hz, BrCH₂CO), 4.30-4.36 (3H, m), 1.97-2.10 (1H, m), 1.54-1.97, 0.90-1.37 (each 5H, m); IR 2933, 1782, 1701 cm⁻¹; EI MS m/z 289 (M⁺), 291 (M⁺+2); high-resolution MS m/z calcd for C₁₁H₁₆NO₃Br (M⁺) 289.0313, found: 289.0339.

(1S,5R)-N-Bromoacetyl-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (11d): Compound (10d)¹⁸ (2.40 g, 11.8 mmol), n-BuLi (8 mL, 13.3 mmol, 1.66 M in hexane), THF (40 mL), and BrCH₂COBr (1.2 mL, 13.8 mmol) were used: 11d (3.10 g, 81%) as colorless crystals; mp 138-139 °C (AcOEt-hexane); [α]D³⁻ = -297.1° (c 1.0, CHCl₃); ¹H NMR 8 7.26-7.52 (4H, m), 5.87 (1H, d, J = 7.9 Hz, NCHCHO), 4.87 (1H, d, J = 7.9 Hz, NCHCHO), 4.63, 4.57 (each 1H, d, J = 12.7 Hz, BrCH₂), 1.58, 1.18 (each 3H, s, CH₃x2); IR 3027, 2970, 1780, 1703 cm⁻¹; EI MS m/z 323 (M⁺), 325 (M⁺+2); Anal. Calcd for C₁₄H₁₄NO₃Br: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.89; H, 4.30; N, 4.22.

D-N-Bromoacetylcamphorsultam (11e): Compound (10e)¹⁷ (4.30 g, 20 mmol), n-BuLi (13 mL, 20.8 mmol, 1.58 M in hexane), THF (80 mL), and BrCH₂COBr (1.82 mL, 20.9 mmol) were used: 11e (5.63 g, 84%) as colorless crystals; mp 121-122 °C (AcOEt-hexane); [α]D³⁻ = -99.5° (c 1.03, CHCl₃); ¹H NMR 8 4.34, 4.20 (each 1H, d, J = 13.1 Hz, BrCH₂CO), 3.91 (1H, dd, J = 5.1, 7.6 Hz, NCHCH₂), 3.54, 3.46 (each 1H, d, J = 13.5 Hz, CH₂SO₂), 2.04-2.20 (2H, m), 1.84-2.00 (3H, m), 1.32-1.53 (2H, m), 1.16, 0.98 (each 3H, s, CH₃x2); IR 2964, 1701 cm⁻¹; EI MS m/z 335 (M⁺), 335 (M⁺+2); Anal. Calcd for C₁₂H₁₆BrNO₃S: C, 42.87; H, 5.40; N, 4.17. Found: C, 42.64; H, 5.55; N, 4.19.

Synthesis of Wittig-Horner reagents (12a-e)

(4R, 5S)-N-Diethoxyphosphonoacetyl-4-methyl-5-phenyloxazolidin-2-one (12a). A solution of 11a (4.304 g, 14.4 mmol) and (EtO)₃P (2.762 g, 16.6 mmol) in benzene (30 mL) was refluxed
for 5 h. Removal of the solvent gave a residue, column chromatography (150 g, AcOEt : hexane = 1 : 3 then 1 : 1 then AcOEt) of which afforded 12a (5.048 g, 98%) as an oil; \([\alpha]_D^{30} +17.8^\circ\) (c 1.04, CHCl_3); \(^1\)H NMR \(\delta\) 7.27-7.46 (5H, m), 5.69 (1H, d, \(J = 6.8\) Hz, PhCHCHCH_3), 4.81 (1H, q, \(J = 6.8\) Hz, PhCHCHCH_3), 4.14-4.30 (4H, m), 3.63-3.98 (2H, m), 1.36 (6H, t, \(J = 5.9\) Hz, CH_2CH_3x2), 0.93 (3H, d, \(J = 6.8\) Hz, CH(CH_3)); IR 2960, 1770, 1680 cm\(^{-1}\); El MS mlz 355 (M\(^+\)); high-resolution MS mlz calcd for C_{16}H_{22}NO_6P (M\(^+\)) 355.1178, found: 355.1178.

(4R)-N-Diethoxyphosphonoacetyl-4-phenyloxazolidin-2-one (12b). A solution of 11b (1.578 g, 5.6 mmol) and (EtO)_3P (1.027 g, 6.2 mmol) in benzene (20 mL) was refluxed for 10 h. Removal of the solvent gave a residue, which was purified by column chromatography (40 g, AcOEt) to afford 12b (1.860 g, 98%) as an oil; \([\alpha]_D^{30} -55.3^\circ\) (c 1.01, CHCl_3); \(^1\)H NMR \(\delta\) 7.27-7.42 (5H, m), 5.47 (1H, dd, \(J = 3.8, 8.8\) Hz, PhCHCH(CH_3)), 4.71 (1H, t, \(J = 8.8\) Hz, PhCHCH(CH_3)), 4.29 (1H, dd, \(J = 3.8, 8.8\) Hz, each 2H, q, \(J = 7.4\) Hz, CH_2CH_3x2), 3.86, 3.72 (each 1H, d, \(J = 15.2\) Hz, OPCH_2CO), 1.94-2.70 (1H, m), 1.55-1.85 (5H, m), 1.53, 1.34 (each 3H, t, \(J = 7.3\) Hz, CH_2CH_3x2), 0.90-1.45 (1H, m); IR 3001, 2933, 1784, 1695 cm\(^{-1}\); El MS mlz 341 (M\(^+\)); high-resolution MS mlz calcd for C_{16}H_{22}NO_6P (M\(^+\)) 341.1029, found: 341.1024.

(4R)-N-Diethoxyphosphonoacetyl-4-cyclohexyloxazolidin-2-one (12c). A solution of 11c (4.546 g, 15.7 mmol) and (EtO)_3P (3.121 g, 18.8 mmol) in benzene (30 mL) was refluxed for 10 h. Removal of the solvent gave a residue, whose column chromatography (150 g, AcOEt) gave 12c (5.438 g, 100%) as an oil; \([\alpha]_D^{31} -65.6^\circ\) (c 1.17, CHCl_3); \(^1\)H NMR \(\delta\) 4.44 (1H, d, \(J = 5.1\) Hz, NCHCH(CH_3)), 4.27 (1H, d, \(J = 5.1\) Hz, NCHCH(CH_3)), 4.20, 4.17 (each 2H, q, \(J = 7.3\) Hz, CH_2CH_3x2), 3.86, 3.72 (each 1H, d, \(J = 13.8\) Hz, CH(H)PO), 1.94-2.70 (1H, m), 1.55-1.85 (5H, m), 1.53, 1.34 (each 3H, t, \(J = 7.3\) Hz, CH_2CH_3x2), 0.90-1.45 (5H, m); IR 3003, 1778, 1691 cm\(^{-1}\); El MS mlz 347 (M\(^+\)); high-resolution MS mlz calcd for C_{16}H_{22}NO_6P (M\(^+\)) 347.1497, found: 347.1497.

(1S,5R)-N-Diethoxyphosphonoacetyl-7,5-benzo-6,6-dimethyl-3-oxo-4-aza-Z-oxabicyclo-[3.3.0]octane (12d). A solution of 11d (2.906 g, 8.97 mmol) and (EtO)_3P (1.686 g, 10.1 mmol) in benzene (30 mL) was refluxed for 14 h. Removal of the solvent gave a residue, whose column chromatography (60 g, AcOEt) gave 12d (2.602 g, 76%) as colorless crystals; mp 130-131 °C (AcOEt-hexane); \([\alpha]_D^{30} -245.7^\circ\) (c 1.01, CHCl_3); \(^1\)H NMR \(\delta\) 7.25-7.52 (4H, m), 5.80, 4.87 (each 1H, d, \(J = 7.8\) Hz, NCHCHO, NCHCHO), 4.15-4.27 (4H, m), 4.01, 3.92, 3.78, 3.70 (2H, each d, \(J = 14.2\) Hz, OPCH_2CO), 1.36, 1.34 (each 3H, t, \(J = 7.3\) Hz, CH_2CH_3x2), 1.56, 1.17 (each 3H, s, CH_3x2); IR 3003, 1778, 1701 cm\(^{-1}\); El MS mlz 381 (M\(^+\)); high-resolution MS mlz calcd for C_{16}H_{26}NO_6P (M\(^+\)) 381.1349, found: 381.1340.

D-N-Diethoxyphosphonoacetylcamphorsultam (12e). A solution of 11e (3.020 g, 8.99 mmol) and (EtO)_3P (1.703 g, 10.2 mmol) in benzene (30 mL) was refluxed for 20 h. Removal of the solvent gave
a residue, whose column chromatography (100 g, hexane : AcOEt = 1 : 1) gave 12e (3.228 g, 91%) as an oil; \([\alpha]_D^{30} = -63.6^\circ\) (c 1.06, CHCl₃); \(^1H\) NMR \(\delta 4.23, 4.13\) (each 2H, q, \(J = 7.3\) Hz, CH₂CH₃x2), 3.89 (1H, dd, \(J = 5.4, 7.3\) Hz, NCH₂CH₂), 3.61, 3.53, 3.25, 3.16 (2H, each d, \(J = 15.4\) Hz, OPCH₂CO), 3.52, 3.44 (each 1H, d, \(J = 8.6\) Hz, CH₂SO₂), 2.03-2.23 (2H, m), 1.18, 0.97 (each 3H, s, CH₂x2); IR 2999, 2966, 1697 cm⁻¹; EI MS \(m/z\) 393 (M⁺); high-resolution MS \(m/z\) calcd for C₁₆H₂₅NO₆PS (M⁺) 393.1375, found: 393.1375.

**Synthesis of Trienes (13a-c)**

(4R,5S)-\(\text{N-}[5,5,-(\text{Trimethylenedithio})-2(E),7(E),9-decatrienoyl]-4-methyl-5-phenyloxazolidin-2-one\) (13a). A suspension of 9 (0.589 g, 2.58 mmol), 12a (1.000 g, 2.82 mmol), LiCl (0.140 g, 3.30 mmol), and \(i\)-Pr₂EtN (0.7 mL, 5.84 mmol) in MeCN (30 mL) was stirred at 0 °C for 24 h. After addition of water, the mixture was extracted with ether. The extract was washed with brine, and dried (K₂CO₃). Removal of the solvent gave a residue, whose column chromatography (60 g, hexane : AcOEt = 10 : 1) afforded 13a (0.279 g, 25%) as an amorphous solid; \(^1H\) NMR \(\delta 7.15-7.46\) (7H, m), 6.29-6.43 (2H, m), 5.78 (1H, dt, \(J = 7.4, 14.9\) Hz, CH=CHCH₂), 5.68 (1H, d, \(J = 6.6\) Hz, CHCHPh), 5.20-5.31 (2H, m), 4.83 (1H, qui, \(J = 6.6\) Hz, CHCHCH₃), 2.74-2.96 (6H, m), 2.69 (2H, d, \(J = 7.6\) Hz, CH₂CH=), 1.80-2.20 (2H, m), 1.94 (3H, d, \(J = 6.6\) Hz, CHCl₃); EI MS \(m/z\) 429 (M⁺); high-resolution MS \(m/z\) calcd for C₂₂H₂₇NO₆S₂ (M⁺) 429.1444, found: 429.1455.

(4R)-\(\text{N-}[5,5,-(\text{Trimethylenedithio})-2(E),7(E),9-decatrienoyl]-4-phenyloxazolidin-2-one\) (13b). A suspension of 9 (0.825 g, 3.62 mmol), 12b (1.357 g, 3.98 mmol), LiCl (0.173 g, 4.08 mmol), and \(i\)-Pr₂EtN (0.91 mL, 6.49 mmol) in MeCN (30 mL) was stirred at 0 °C for 24 h. Similar work-up as described above gave a residue, whose column chromatography (50 g, hexane : AcOEt = 3 : 1) afforded 13b (0.830 g, 55%) as an oil; \([\alpha]_D^{30} = -86.8^\circ\) (c 1.03, CHCl₃); \(^1H\) NMR \(\delta 7.10-7.42\) (7H, m), 6.34 (1H, dt, \(J = 10.2, 16.6\) Hz, CH₂=CH), 6.15 (1H, dd, \(J = 10.2, 15\) Hz, =CHCH=CH), 5.68 (1H, d, \(J = 6.6\) Hz, CHCHPh), 5.20-5.31 (2H, m), 4.83 (1H, qui, \(J = 6.6\) Hz, CHCHCH₂), 2.74-2.96 (6H, m), 2.69 (2H, d, \(J = 7.6\) Hz, CH₂CH=), 1.80-2.20 (2H, m), 1.94 (3H, d, \(J = 6.6\) Hz, CHCl₃); EI MS \(m/z\) 415 (M⁺); high-resolution MS \(m/z\) calcd for C₂₂H₂₅NO₆S₂ (M⁺) 415.1275, found: 415.1270.

(4R)-\(\text{N-}[5,5,-(\text{Trimethylenedithio})-2(E),7(E),9-decatrienoyl]-4-cyclohexyloxazolidin-2-one\) (13c). A suspension of 9 (1.000 g, 4.40 mmol), 12c (1.68 g, 4.84 mmol), LiCl (0.21 g, 4.95 mmol), and \(i\)-Pr₂EtN (1.1 mL, 7.84 mmol) in MeCN (60 mL) was stirred at 0 °C for 24 h. Similar work-up as described above gave a residue, whose column chromatography (50 g, hexane : AcOEt = 3 : 1) afforded 13c (0.714 g, 39%) as an oil; \([\alpha]_D^{31} = -77.1^\circ\) (c 1.07, CHCl₃); \(^1H\) NMR \(\delta 7.13-7.38\) (2H, m),
6.36 (1H, dt, J = 10.2, 16.5 Hz, CH₂=CH), 6.18 (1H, dd, J = 10.2, 14.8 Hz, =CHCH=CH), 5.78 (1H, dt, J = 7.3, 14.8 Hz, CH=CH), 5.18 [1H, d, J = 16.5 Hz, CH(H)=CH], 5.09 [1H, d, J = 10.2 Hz, CH(H)=CH], 4.40–4.50 (1H, m), 4.27 (2H, d, J = 5.3 Hz, NCH₂CH₂O), 2.62–3.02 (6H, m), 1.50–2.17 (9H, m), 0.88–1.40 (6H, m); IR 2931, 1776, 1683, 1633, 1450 cm⁻¹; El MS m/z 421 (M⁺); high-resolution MS m/z calcd for C₂₂H₃₁NO₅S₂ (M⁺) 421.1746, found: 421.1761.

(1S,5R)-N-{5,5-(Trimethylenedithio)-2(E),7(E),9-decatrienoyl}-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (13d). A suspension of 9 (0.684 g, 3.0 mmol), 12d (1.257 g, 3.3 mmol), LiCl (0.141 g, 4.8 mmol), and i-Pr₂EtN (0.387 g, 3.0 mmol) in MeCN (30 mL) was stirred at 0 °C for 19 h. Similar work-up as described above gave a residue, whose column chromatography (50 g, hexane : Et₂O = 2 : 1) afforded 13d (0.846 g, 62%) as amorphous solid; [α]D³² -699.6° (c 1.05, CHCl₃); ¹H NMR δ 7.20–7.52 (6H, m), 6.36 (1H, dt, J = 10.2, 16.8 Hz, CH₂=CH), 6.18 (1H, dd, J = 10.2, 14.6 Hz, =CH-CH=CH), 5.80 (1H, d, J = 7.9 Hz, NCHCHO), 5.78 (1H, dt, J = 7.2, 14.6 Hz, CH=CHCH₂), 5.18 [1H, d, J = 16.8 Hz, CH(H)=CH], 5.06 [1H, d, J = 10.2 Hz, CH(H)=CH], 4.90 (1H, d, J = 7.9 Hz, NCHCHO), 2.76–2.94 (6H, m), 2.69 (2H, d, J = 7.2 Hz), 1.90–2.05 (2H, m), 1.59, 1.16 (each 3H, s, CH₃x₂); IR 2970, 1774, 1682, 1633 cm⁻¹; El MS m/z 455 (M⁺); high-resolution MS m/z calcd for C₂₅H₃₃NO₅S₂ (M⁺) 455.1589, found: 455.1581.

D-N-[5,5-(Trimethylenedithio)-2(E),7(E),9-decatrienoyl]camphorsultam (13e). A suspension of 9 (0.990 g, 4.34 mmol), 12e (1.913 g, 4.87 mmol), LiCl (0.211 g, 4.97 mmol), and i-Pr₂EtN (0.573 g, 4.43 mmol) in MeCN (40 mL) was stirred at 0 °C for 24 h. Similar work-up as described above gave a residue (3.1 g), whose column chromatography (50 g, hexane : AcOEt = 3 : 1) afforded 13e (1.091 g, 54%) as amorphous solid; [α]D³² -521.8° (c 1.07, CHCl₃); ¹H NMR δ 7.13 (1H, dt, J = 7.3, 15 Hz, CH₂CH=CHCO), 6.64 (1H, d, J = 15 Hz, CH=CHCO), 6.35 (1H, dt, J = 10.2, 16.8 Hz, CH₂=CH), 6.18 (1H, dd, J = 10.2, 15 Hz, =CHCH=CH), 5.76 (1H, dt, J = 7.4, 15 Hz, CH=CHCH₂), 5.18 [1H, d, J = 16.8 Hz, CH(H)=CH], 5.05 [1H, d, J = 10.2 Hz, CH(H)=CH], 3.94 (1H, dd, J = 5.3, 7.3 Hz, NCH₂CH₂), 3.52, 3.44 [each 1H, d, J = 13.9 Hz, CH₂SO₂], 2.60–2.96 (7H, m), 1.80–2.22 (8H, m), 1.30–1.50 (2H, m), 1.18, 0.98 (each 3H, s, CH₃x₂); IR 2964, 1774, 1682, 1633 cm⁻¹; El MS m/z 467 (M⁺); high-resolution MS m/z calcd for C₂₅H₃₃NO₅S₃ (M⁺) 467.1636, found: 467.1623.

Diastereoselective Intramolecular Diels-Alder Reaction of Trienes (13a-e)

From 13a; To a stirred solution of 13a (0.086 g, 0.2 mmol) in CH₂Cl₂ (12 mL) at -78 °C was added Me₂AlCl (0.43 mL, 0.40 mmol, 0.94 M in hexane) and the mixture was stirred at -25 °C for 4 days. After addition of water, the mixture was extracted with CH₂Cl₂. Usual work-up of the extract gave 14a (0.088 g). To a stirred solution of PhCH₂OH (40 μL, 0.39 mmol) in THF (2 mL) at 0 °C was added n-BuLi (0.22 mL, 0.37 mmol, 1.66 M in hexane) and the mixture was stirred for 10 min. To this solution was added a
solution of 14a (0.088 g) in THF (2 mL) and the whole was stirred for 2 h. After addition of water, the mixture was extracted with ether. Usual work-up of the extract gave a residue, preparative TLC (Et$_2$O : hexane = 1 : 3) of which gave 15a (0.039 g, 54%, 63% e.e.) and 16 (0.007 g, 10%). HPLC analysis of 15a was performed using Daicel Chiral Cel OJ (4.6 \( \times \) 25 cm) with 1% 2-propanol in hexane (flow; 1.0 mL/min). Retention time: 39.1 min for a minor peak and 46.3 min for a major peak.

\((3aS,7R,7aR)\)-Benzyl 2,3,3a,4,5,7a-hexahydro-5,5-(trimethylenedithio)indene-7-carboxylate (15); \(^{1}H\) NMR \( \delta \) 7.37 (s), 5.75 (d, \( J = 9.9 \) Hz, CH=CH), 5.59-5.65 (m), 5.18, 5.13 (d, \( J = 12.4 \) Hz, PhCH$_2$), 2.80-2.92 (m), 2.64 (ddd, \( J = 7.3, 10.9, 11.1 \) Hz, CHCOO), 2.38-2.53 (m), 1.90-2.27 (m), 1.63-1.90 (m); IR 2908, 1727, 1439 cm$^{-1}$; EI MS m/z 360 (M$^+$); high-resolution MS m/z calcd for C$_{20}$H$_{24}$O$_4$S (M$^+$) 360.1216, found: 360.1217.

Benzyl 5,5-(trimethylenedithio)-2(E),7(E),9-decatrienoate (16); \(^{1}H\) NMR \( \delta \) 7.37 (s), 7.12 (dt, \( J = 7.5, 15.8 \) Hz, CH=CH), 6.00-6.13 (m), 5.96 (d, \( J = 15.8 \) Hz, CH=CH), 5.19 (s, CBPh), 5.11-5.23 (m), 3.15 (t, \( J = 7.9 \) Hz, =CHCH(H)), 2.70-2.99 (m), 1.80-2.08 (m); IR 1716 cm$^{-1}$; EI MS m/z 360 (M$^+$); high-resolution MS m/z calcd for C$_{20}$H$_{24}$O$_4$S (M$^+$) 360.1216, found: 360.1212.

From 13b; To a stirred solution of 13b (0.300 g, 0.72 mmol) in CH$_2$Cl$_2$ (43 mL) at -50 °C was added Me$_2$AlCl (1.38 mL, 1.45 mmol, 1.05 M in hexane) and the mixture was stirred for at -25 °C for 4 days. Work-up similar to that noted for 13a (except employment of MgSO$_4$) left 14b (0.300 g). The reaction similar to that noted for 13a by using PhCH$_2$OH (120 \( \mu \)L, 1.16 mmol), THF (3 mL), n-BuLi (0.65 mL, 1.08 mmol, 1.66 M in hexane), 14b (0.300 g), and THF (4 mL) gave a residue, preparative TLC (Et$_2$O : hexane = 1 : 3) of which produced 15b (0.143 g, 57%, 22% e.e.), \([\alpha]_D^{20} +5.0^\circ\) (c 1.09, CHCl$_3$) and 16 (0.020 g, 8%).

From 13c; To a stirred solution of 13c (0.296 g, 0.70 mmol) in CH$_2$Cl$_2$ (43 mL) at -60 °C was added Me$_2$AlCl (1.34 mL, 1.41 mmol, 1.05 M in hexane) and the mixture was stirred for at -25 °C for 4 days. Work-up similar to that noted for 13a (except employment of MgSO$_4$) left 14c (0.289 g). The reaction similar to that noted for 13a by using PhCH$_2$OH (115 \( \mu \)L, 1.08 mmol), THF (3 mL), n-BuLi (0.63 mL, 1.05 mmol, 1.66 M in hexane), 14c (0.289 g), and THF (4 mL) gave a residue, preparative TLC (Et$_2$O : hexane = 1 : 3) of which produced 15a (0.158 g, 65%, 22% e.e.), \([\alpha]_D^{27} -6.7^\circ\) (c 1.05, CHCl$_3$) and 16 (0.048 g, 19%).

From 13d; To a stirred solution of 13d (0.250 g, 0.55 mmol) in CH$_2$Cl$_2$ (33 mL) at -50 °C was added Me$_2$AlCl (0.9 mL, 0.86 mmol, 0.95 M in hexane) and the mixture was stirred for at 0 °C for 4 days. Work-up similar to that noted for 13a (except employment of MgSO$_4$) left 14d (0.290 g). The reaction similar to that noted for 13a by using PhCH$_2$OH (90 \( \mu \)L, 0.87 mmol), THF (3 mL), n-BuLi (0.5 mL, 0.83 mmol, 1.66 M in hexane), 14d (0.290 g), and THF (2 mL) gave a residue, preparative TLC (Et$_2$O :
hexane = 1:3) of which produced **15a** (0.109 g, 55%, 96% e.e.), [\( \alpha \)]\( _D^{30} \) -31.0° (c 1.08, CHCl₃) and **16** (0.017 g, 9%).

**From 13e**: To a stirred solution of 13e (0.357 g, 0.72 mmol) in CH₂Cl₂ (45 mL) at -50 °C was added EtAlCl₂ (1.5 mL, 1.40 mmol, 0.93 M in hexane) and the mixture was stirred for at -25 °C for 4 days. Work-up similar to that noted for 13a (except employment of MgSO₄) left 14e (0.401 g). The reaction similar to that noted for 13a by using PhCH₂OH (160 μL, 1.55 mmol), THF (5 mL), n-BuLi (0.91 mL, 1.51 mmol, 1.66 M in hexane), 14e (0.401 g), and THF (4 mL) gave a residue, preparative TLC (Et₂O : hexane = 1:3) of which produced **15a** (0.072 g, 26%, 87% e.e.), [\( \alpha \)]\( _D^{29} \) -28.2° (c 1.07, CHCl₃) and **16** (0.019 g, 7%).

**Conversion of (-)-15a to (-)-19.** A solution of 15a (87% e.e.) (0.050 g, 0.14 mmol) and 1 N NaOH (2 mL, 2 mmol) in THF (2 mL) and MeOH (1 mL) was stirred at rt for 2 h. After the mixture was acidified with 3 N HCl, the mixture was extracted with CHCl₃. Usual work-up of the extract gave 17 (0.041 g, 85%); ¹H NMR δ 8.58 (1H, br s, CO₂H), 5.97 (1H, d, J = 10.4 Hz, CHCH=CH), 5.65 (1H, ddd, J = 2.8, 5.6, 10.4 Hz, CH=CHCH₂), 2.82-3.02 (4H, m), 2.30-2.69 (6H, m), 1.85-2.10 (4H, m), 1.71 (1H, t, J = 12.4 Hz). A solution of 17 (0.041 g) and (COCl)₂ (18 μL, 0.206 mmol) in CH₂Cl₂ (1 mL) was stirred at rt for 14 h. Acid chloride (18) obtained by removal of the solvent was used immediately. To a solution of oxazolidin-2-one (0.0465 g, 0.53 mmol) in THF (2 mL) at -78 °C was added n-BuLi (0.30 mL, 0.50 mmol, 1.66 M in hexane) in one portion and stirring was continued for 2 h. A solution of 18 in THF (2 mL) was added to the mixture. The mixture was stirred for 1 h and quenched with water. Usual work-up of the mixture gave a residue, whose preparative TLC (AcOEt : hexane = 3:4) afforded 19 (0.035 g, 74%) as crystals: [\( \alpha \)]\( _D^{29} \) -48.8° (c 1.03, CH₂Cl₂); [lit.¹² [\( \alpha \)]\( _D^{23} \) -50° (c 1.38, CH₂Cl₂)); ¹H NMR δ 5.79 (1H, d, J = 9.9 Hz, CHCH=CH), 5.64 (1H, ddd, J = 3.2, 6, 9.9 Hz, CH=CHCH₂), 4.43, 4.04 (each 2H, t, J = 8.1 Hz, OCH₂CH₂N, OCH₂CH₂N), 3.93 (1H, dt, J = 6.2, 10.7 Hz, COCH), 2.79-3.00, 2.45-2.61 (each 4H, m), 2.10-2.35, 1.97-2.06 (each 2H, m), 1.73 (2H, q, J = 13 Hz); IR 1782, 1697 cm⁻¹; EI MS m/z 339 (M⁺); high-resolution MS m/z calcd for C₁₆H₂₁NO₃S₂ (M⁺) 339.0962, found: 339.0964. ¹H-NMR spectral data and sign of specific rotation of synthetic 19 were identical with those reported in the literature.¹²

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**REFERENCES AND NOTES**

2579.


15. Reversed introduction of two substituents was unsuccessful, because the second reaction was complete recovery of starting material.


21. Racemic benzyl esters (15) were synthesized in 26% yield by intramolecular Diels-Alder reaction of 16 using EtAlCl2.

22. Evans et al.5 have been reported that the reaction of simple trienes without trimethylenedithio group completed within 5 h at -25 °C in high diastereomeric excess (70-97% d.e.).

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