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

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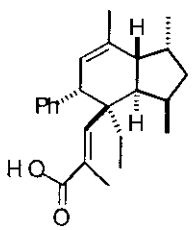
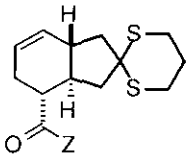
Abstract- Diastereoselective asymmetric intramolecular Diels-Alder reaction of 5,5-(trimethylenedithio)-2(*E*),7(*E*),9-decatrienoyl amides (**13a-e**) having various chiral auxiliaries was performed to give optically active *trans*-hydrindanes, which would be an important intermediate for a total synthesis of plakotenin (**1**), 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.

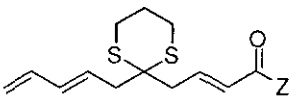
Plakotenin (**1**), a new cytotoxic carboxylic acid, was isolated from the Okinawan marine sponge *Plakoritis sp*. by Kobayashi in 1992.[1] Its stereostructure was deduced by spectroscopic data to possess *trans*-hydrindane skeleton bearing six contiguous asymmetric centers.[1] However, its absolute 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 diastereoselective[3-8] and enantioselective[9-10] intramolecular Diels-Alder reaction are employed. Since a plausible biogenesis[1] of plakotenin (**1**) similar to that of ircinianin[11] 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



Plakotenin (**1**)



2 : Z = Ox
3 : Z = X
4 : Z = Bn



5 : Z = Ox
6 : Z = X

X = chiral auxiliary Ox = 

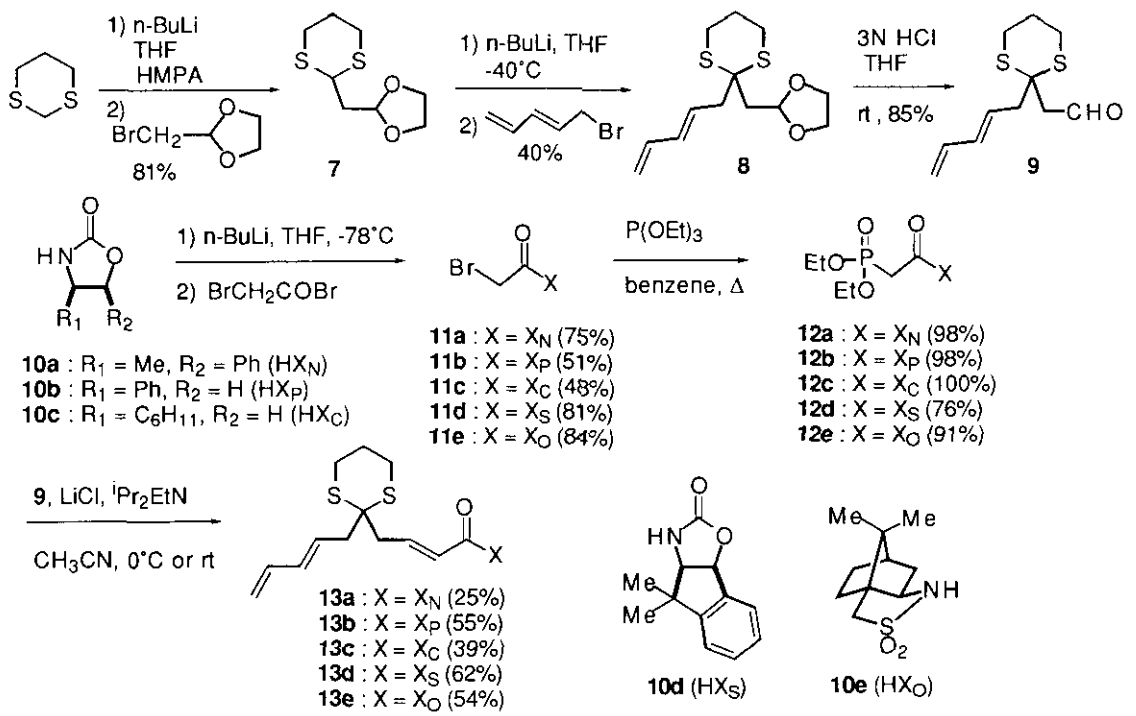
Scheme 1

functionalized *trans*-hydrindane (**2**) by enantioselective Diels-Alder reaction of **5** using a catalytic amount of chiral Lewis acid, we examined synthesis of chiral *trans*-hydrindanes (**3**) by diastereoselective Diels-Alder reaction[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*-hydrindanes (**3**, **4**) by diastereoselective intramolecular Diels-Alder reaction.[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[14] in THF afforded **8** in 40% yield,[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[19] of the aldehyde (**9**) with several chiral auxiliaries (**10a-e**),[5,16-18] Wittig-Horner type reagents (**12a-e**)[20] were prepared. Namely, bromoacetylation of chiral auxiliaries (**10a-e**), followed by the treatment with triethyl phosphite in boiling benzene, produced **12a-e**. Reaction of aldehyde (**9**) with Wittig-Horner reagents (**12a-e**) obtained thus according to Masamune-Roush method[19] gave chiral trienes (**13a-e**) in 25-62% yield.

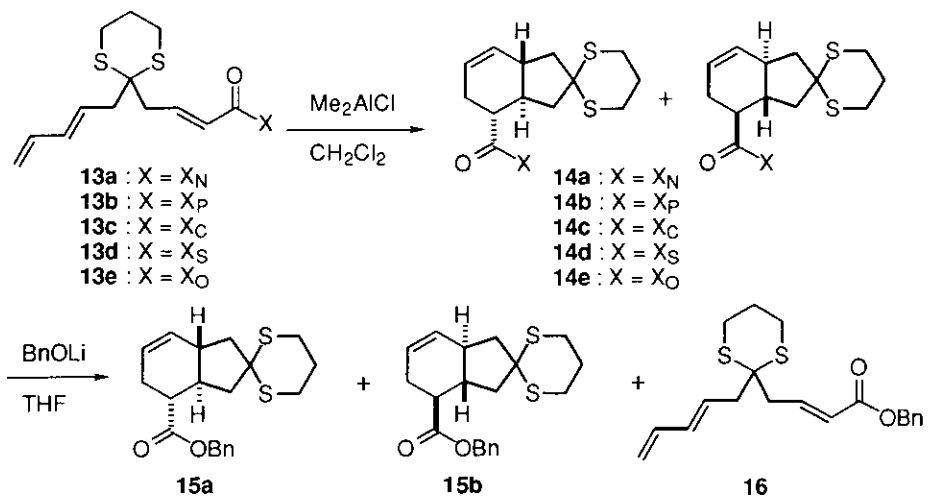
With chiral trienes (**13a-e**) in hand, asymmetric intramolecular Diels-Alder reaction of trienes (**13a-e**) in the presence of Lewis acid was examined. In all cases, unfortunately, the reaction was sluggish and not completed at -25 °C even after 4 days.[22] Moreover, as chromatographic separation of starting trienes and



Scheme 2

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**)[21] 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).



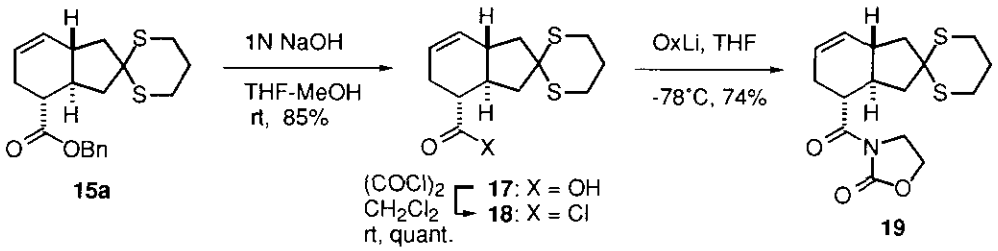
Scheme 3

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

Entry	Substrate	Lewis acid	Yield of **15** (%)	Yield of **16** (%)	Ratio of **15a** : **15b**[b]
1	**13a**	Me_2AlCl	54	10	4.41 : 1 (63)
2	**13b**	Me_2AlCl	57	8	1 : 1.64 (22)
3	**13c**	Me_2AlCl	65	19	1.64 : 1 (22)
4[c]	**13d**	Me_2AlCl	55	9	46.7 : 1 (96)
5	**13d**	Me_2AlCl	52	10	38.7 : 1 (95)
6	**13e**	$EtAlCl_2$	26	7	14.4 : 1 (87)

a) All reactions were carried out at -25 °C in CH_2Cl_2 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**).[12] 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.[12]



Scheme 4

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 $CHCl_3$ solution, and ^1H NMR spectra were taken with a JEOL EX-270 (270 MHz) spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Following abbreviations were used in the NMR data; s: singlet, d: doublet, t: triplet, q: quartet, qui : 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 Kiegelsel 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_2CO_3), 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; ^{1}H NMR δ 5.15 [1H, t, J = 5.2 Hz, $CH_2C\underline{H}(OC\underline{H}_2)_2$], 4.23 [1H, t, J = 7.3 Hz, $CH_2C\underline{H}(SCH_2)_2CH_2$], 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 $C_8H_{14}O_2S_2$ (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[14] (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; ^{1}H NMR δ 6.00-6.42 (2H, m), 5.81 (1H, dt, J = 7.26, 14.9 Hz CH_2=C$\underline{H}$), 4.98-5.24 (2H, m), 5.14 [1H, t, J = 4.3 Hz, $CH_2C\underline{H}(OCH_2)_2$], 3.78-4.02 (4H, m), 2.70-2.94 (6H, m), 2.31 [2H, d, J = 4.3 Hz, $C\underline{H}_2CH(OCH_2)_2$], 1.80-1.98 (2H, m); IR 1630, 1601, 1416 cm^{-1}; EI MS *m/z* 272 (M^+); high-resolution MS *m/z* calcd for $C_{13}H_{20}O_2S_2$ (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; ^{1}H NMR δ 9.80 (1H, t, J = 2.6 Hz, $CH_2C\underline{H}O$), 5.93-6.34 (2H, m), 5.65 (1H, dt, J = 7.6, 15.2 Hz, CH=C$\underline{H}CH_2$), 4.98-5.23 (2H, m), 2.74-2.93 (8H, m), 1.85-2.03 (2H, m); IR 2910, 1716 cm^{-1}; EI MS *m/z* 228 (M^+); high-resolution MS *m/z* calcd for $C_{11}H_{16}O_2S_2$ (M^+) 228.0642, found: 228.0642.

General Procedure for Preparation of *N*-Bromoacetyloxazolidin-2-ones (11a-d) and D-*N*-Bromoacetylcamphorsultam (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, $BrCH_2COBr$ 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**, $CHCl_3$ for **11e**).

(4*R*, 5*S*)-*N*-Bromoacetyl-4-methyl-5-phenyloxazolidin-2-one (11a): Compound (**10a**)[5] (3.54 g, 20 mmol), *n*-BuLi (12 mL, 21.1 mmol, 1.69 M in hexane), THF (60 mL), $BrCH_2COBr$ (1.9 mL, 21.8 mmol), and THF (8 mL) were used: **11a** (4.44 g, 75%) as an oil; $[\alpha]_D^{29}$ +17.2° (c 1.02, $CHCl_3$); ^{1}H NMR δ 7.26-7.47 (5H, m), 5.74 (1H, d, J = 6.8 Hz, C$\underline{H}$Ph), 4.80 (1H, qui, J = 6.8 Hz, CHC$\underline{H}CH_3$),

5.75, 5.51 (each 1H, d, J = 12.9 Hz, $BrCH_2CO$), 0.94 (3H, d, J = 6.8 Hz, $CHCH_3$); EI MS m/z 297 (M^+), 299 (M^++2); high-resolution MS m/z calcd for $C_{12}H_{12}NO_3Br$ (M^+) 296.9999, found: 296.9987.

(4*R*)-*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 $BrCH_2COBr$ (1.1 mL, 12.6 mmol) were used: **11b** (1.77 g, 51%) as colorless crystals; mp 119-120 °C (AcOEt-hexane); $[\alpha]_D^{31}$ -67.0° (c 1.02, $CHCl_3$); ^1H NMR δ 7.26-7.44 (5H, m), 5.44 (1H, dd, J = 3.9, 8.7 Hz, $PhCHCH_2$), 4.76 [1H, t, J = 8.7 Hz, $PhCHCH(H)$], 4.56, 4.46 (each 1H, d, J = 12.6 Hz, $BrCH_2CO$), 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 $C_{11}H_{10}NO_3Br$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.60; H, 3.81; N, 5.22.

(4*R*)-*N*-Bromoacetyl-4-cyclohexyloxazolidin-2-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 $BrCH_2COBr$ (3.2 mL, 36.7 mmol) were use: **11c** (4.91 g, 48%) as colorless crystals; mp 113-114 °C (Et_2O-hexane); $[\alpha]_D^{31}$ -92.6° (c 1.02, $CHCl_3$); ^1H NMR δ 4.58, 4.46 (each 1H, d, J = 12.2 Hz, $BrCH_2CO$), 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 $C_{11}H_{16}NO_3Br$ (M^+) 289.0313, found: 289.0339.

(1*S*,5*R*)-*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 $BrCH_2COBr$ (1.2 mL, 13.8 mmol) were used: **11d** (3.10 g, 81%) as colorless crystals; mp 138-139 °C (AcOEt-hexane); $[\alpha]_D^{30}$ -297.1° (c 1.0, $CHCl_3$); ^1H NMR δ 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, $BrCH_2$), 1.58, 1.18 (each 3H, s, CH_3x2); IR 3027, 2970, 1780, 1703 cm^{-1}; EI MS m/z 323 (M^+), 325 (M^++2); Anal. Calcd for $C_{14}H_{14}NO_3Br$: 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 $BrCH_2COBr$ (1.82 mL, 20.9 mmol) were used: **11e** (5.63 g, 84%) as colorless crystals; mp 121-122 °C (AcOEt-hexane); $[\alpha]_D^{31}$ -99.5° (c 1.03, $CHCl_3$); ^1H NMR δ 4.34, 4.20 (each 1H, d, J = 13.1 Hz, $BrCH_2CO$), 3.91 (1H, dd, J = 5.1, 7.6 Hz, $NCHCH_2$), 3.54, 3.46 (each 1H, d, J = 13.5 Hz, CH_2SO_2), 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, CH_3x2); IR 2964, 1701 cm^{-1}; EI MS m/z 335 (M^+), 335 (M^++2); Anal. Calcd for $C_{12}H_{18}BrNO_3S$: 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)

(4*R*, 5*S*)-*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° (c 1.04, $CHCl_3$); ^1H NMR δ 7.27-7.46 (5H, m), 5.69 (1H, d, *J* = 6.8 Hz, PhC<u>H</u>CHCH$_3$), 4.81 (1H, qui, *J* = 6.8 Hz, PhCHC<u>H</u>CH$_3$), 4.14-4.30 (4H, m), 3.63-3.98 (2H, m), 1.36 (6H, t, *J* = 5.9 Hz, CH$_2$C<u>H</u>$_3$x2), 0.93 (3H, d, *J* = 6.8 Hz, CHC<u>H</u>$_3$); IR 2960, 1770, 1680 cm^{-1}; EI MS *m/z* 355 (M^+); high-resolution MS *m/z* calcd for $C_{16}H_{22}NO_6P$ (M^+) 355.1182, found: 355.1178.

(4*R*)-*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; $[\alpha]_D^{31}$ -55.3° (c 1.01, $CHCl_3$); ^1H NMR δ 7.27-7.42 (5H, m), 5.47 (1H, dd, *J* = 3.8, 8.8 Hz, PhC<u>H</u>CH$_2$), 4.71 [1H, t, *J* = 8.8 Hz, PhCHC<u>H</u>(H)], 4.29 [1H, dd, *J* = 3.8, 8.8 Hz, PhCHCH(<u>H</u>)], 4.13, 4.10 (each 2H, q, *J* = 7.4 Hz, C<u>H</u>$_2$CH$_3$x2), 3.86, 3.72 (each 1H, d, *J* = 15.2 Hz, OPCH$_2$CO), 1.30, 1.27 (each 3H, t, *J* = 7.4 Hz, CH$_2$C<u>H</u>$_3$x2); IR 3001, 1784, 1705 cm^{-1}; EI MS *m/z* 341 (M^+); high-resolution MS *m/z* calcd for $C_{15}H_{20}NO_6P$ (M^+) 341.1029, found: 341.1024.

(4*R*)-*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° (c 1.17, $CHCl_3$); ^1H NMR δ 4.44 [1H, dd, *J* = 5.1, 9.9 Hz, NCHCH(<u>H</u>)], 4.27 [1H, d, *J* = 5.1 Hz, NCHC<u>H</u>(H)], 4.20, 4.17 (each 2H, q, *J* = 7.3 Hz, C<u>H</u>$_2$CH$_3$x2), 3.86 3.72 [each 1H, d, *J* = 13.8 Hz, CH(<u>H</u>)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$_2$C<u>H</u>$_3$x2), 0.90-1.45 (5H, m); IR 3000, 2933, 1782, 1697 cm^{-1}; EI MS *m/z* 347 (M^+); high-resolution MS *m/z* calcd for $C_{15}H_{26}NO_6P$ (M^+) 347.1497, found: 347.1497.

(1*S*,5*R*)-*N*-Diethoxyphosphonoacetyl-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-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 : hexane = 1 : 1 then AcOEt) afforded **12d** (2.602 g, 76%) as colorless crystals; mp 130-131 °C (AcOEt-hexane); $[\alpha]_D^{30}$ -245.7° (c 1.01, $CHCl_3$); ^1H NMR δ 7.25-7.52 (4H, m), 5.80, 4.87 (each 1H, d, *J* = 7.8 Hz, NCHC<u>H</u>O, NC<u>H</u>CHO), 4.15-4.27 (4H, m), 4.01, 3.92, 3.78, 3.70 (2H, each d, *J* = 14.2 Hz, OPCH$_2$CO), 1.36, 1.34 (each 3H, t, *J* = 7.3 Hz, CH$_2$C<u>H</u>$_3$x2), 1.56, 1.17 (each 3H, s, CH$_3$x2); IR 3003, 1778, 1701 cm^{-1}; EI MS *m/z* 381 (M^+); high-resolution MS *m/z* calcd for $C_{18}H_{24}NO_6P$ (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° (c 1.06, $CHCl_3$); ^1H NMR δ 4.23, 4.13 (each 2H, q, *J* = 7.3 Hz, $C\underline{H}_2CH_3$x2), 3.89 (1H, dd, *J* = 5.4, 7.3 Hz, $NC\underline{H}CH_2$), 3.61, 3.53, 3.25, 3.16 (2H, each d, *J* = 15.4 Hz, $OPCH_2CO$), 3.52, 3.44 (each 1H, d, *J* = 8.6 Hz, CH_2SO_2), 2.03-2.23 (2H, m), 1.81-2.00 (3H, m), 1.33, 1.32 (each 3H, t, *J* = 7.3 Hz, $CH_2C\underline{H}_3$x2), 1.27-1.48 (2H, m), 1.18, 0.97 (each 3H, s, CH_3x2); IR 2999, 2966, 1697 cm^{-1}; EI MS *m/z* 393 (M^+); high-resolution MS *m/z* calcd for $C_{16}H_{28}NO_6PS$ (M^+) 393.1375, found: 393.1375.

Synthesis of Trienes (13a-e)

(4*R*,5*S*)-*N*-[5,5-(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*-Pr_2EtN (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 (K_2CO_3). Removal of the solvent gave a residue, whose column chromatography (60 g, hexane : AcOEt = 10 : 1) afforded **13a** (0.279 g, 25%) as amorphous solid; ^1H NMR δ 7.15-7.46 (7H, m), 6.29-6.43 (2H, m), 5.78 (1H, dt, *J* = 7.4, 14.9 Hz, $CH{=}C\underline{H}CH_2$), 5.68 (1H, d, *J* = 6.6 Hz, $CHC\underline{H}Ph$), 5.20-5.31 (2H, m), 4.83 (1H, qui, *J* = 6.6 Hz, $CHC\underline{H}CH_3$), 2.74-2.96 (6H, m), 2.69 (2H, d, *J* = 7.6 Hz, $C\underline{H}_2CH{=}$), 1.80-2.20 (2H, m), 1.94 (3H, d, *J* = 6.6 Hz, $CHC\underline{H}_3$); EI MS *m/z* 429 (M^+); high-resolution MS *m/z* calcd for $C_{23}H_{27}NO_3S_2$ (M^+) 429.1444, found: 429.1455.

(4*R*)-*N*-[5,5-(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*-Pr_2EtN (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° (c 1.03, $CHCl_3$); ^1H NMR δ 7.10-7.42 (7H, m), 6.34 (1H, dt, *J* = 10.2, 16.6 Hz, $CH_2{=}C\underline{H}$), 6.15 (1H, dd, *J* = 10.2, 15 Hz, $=CHC\underline{H}{=}CH$), 5.75 (1H, dt, *J* = 7.3, 15 Hz, $CH{=}C\underline{H}CH_2$), 5.49 (1H, dd, *J* = 3.6, 8.7 Hz, $PhC\underline{H}CH_2$), 5.17 [1H, d, *J* = 16.6 Hz, $C\underline{H}(H){=}CH$], 5.05 [1H, d, *J* = 10.2 Hz, $C(\underline{H})H{=}CH$], 4.71 [1H, t, *J* = 8.7 Hz, $PhCHC\underline{H}(H)$], 4.30 [1H, t, *J* = 8.7 Hz, $PhCHCH(\underline{H})$], 2.69-2.91 (6H, m), 2.64 (2H, d, *J* = 7.3 Hz, $=CHC\underline{H}_2$), 1.87-2.04 (2H, m); IR 2989, 2910, 1780, 1689, 1633 cm^{-1}; EI MS *m/z* 415 (M^+); high-resolution MS *m/z* calcd for $C_{22}H_{25}NO_3S_2$ (M^+) 415.1275, found: 415.1270.

(4*R*)-*N*-[5,5-(Trimethylenedithio)-2(*E*),7(*E*),9-decatrienoyl]-4-cyclohexyloxazolidin-2-one (13c). A suspension of **9** (1.00 g, 4.40 mmol), **12c** (1.68 g, 4.84 mmol), LiCl (0.21 g, 4.95 mmol), and *i*-Pr_2EtN (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° (c 1.07, $CHCl_3$); ^1H NMR δ 7.13-7.38 (2H, m),

6.36 (1H, dt, J = 10.2, 16.5 Hz, CH_2=C<u>H</u>), 6.18 (1H, dd, J = 10.2, 14.8 Hz, =CHC<u>H</u>=CH), 5.78 (1H, dt, J = 7.3, 14.8 Hz, CH=C<u>H</u>CH_2), 5.18 [1H, d, J = 16.5 Hz, C<u>H</u>(H)=CH], 5.09 [1H, d, J = 10.2 Hz, CH(<u>H</u>)=CH], 4.40-4.50 (1H, m), 4.27 (2H, d, J = 5.3 Hz, NCHC<u>H</u>$_2$O), 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}; EI MS m/z 421 (M^+); high-resolution MS m/z calcd for $C_{22}H_{31}NO_3S_2$ (M^+) 421.1746, found: 421.1761.

(1*S*,5*R*)-*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*-Pr_2EtN (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 : Et_2O = 2 : 1) afforded **13d** (0.846 g, 62%) as amorphous solid; $[\alpha]_D^{32}$ -699.6° (c 1.05, $CHCl_3$); ^{1}H NMR δ 7.20-7.52 (6H, m), 6.36 (1H, dt, J = 10.2, 16.8 Hz, CH_2=C<u>H</u>), 6.18 (1H, dd, J = 10.2, 14.6 Hz, =CH-C<u>H</u>=CH), 5.80 (1H, d, J = 7.9 Hz, NCHC<u>H</u>O), 5.78 (1H, dt, J = 7.2, 14.6 Hz, CH=C<u>H</u>CH_2), 5.18 [1H, d, J = 16.8 Hz, C<u>H</u>(H)=CH], 5.06 [1H, d, J = 10.2 Hz, CH(<u>H</u>)=CH], 4.90 (1H, d, J = 7.9 Hz, NC<u>H</u>CHO), 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, CH_3x2); IR 2970, 1774, 1682, 1633 cm^{-1}; EI MS m/z 455 (M^+); high-resolution MS m/z calcd for $C_{25}H_{29}NO_3S_2$ (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*-Pr_2EtN (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; $[\alpha]_D^{32}$ -521.8° (c 1.07, $CHCl_3$); ^{1}H NMR δ 7.13 (1H, dt, J = 7.3, 15 Hz, CH_2C<u>H</u>=CHCO), 6.64 (1H, d, J = 15 Hz, CH=C<u>H</u>CO), 6.35 (1H, dt, J = 10.2, 16.8 Hz, CH_2=C<u>H</u>), 6.18 (1H, dd, J = 10.2, 15 Hz, =CHC<u>H</u>=CH), 5.76 (1H, dt, J = 7.4, 15 Hz, CH=C<u>H</u>CH_2), 5.18 [1H, d, J = 16.8 Hz, C<u>H</u>(H)=CH], 5.05 [1H, d, J = 10.2 Hz, CH(<u>H</u>)=CH], 3.94 (1H, dd, J = 5.3, 7.3 Hz, NC<u>H</u>CH_2), 3.52, 3.44 [each 1H, d, J = 13.9 Hz, CH_2SO_2], 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, CH_3x2); IR 2964, 1681, 1637 cm^{-1}; EI MS m/z 467 (M^+); high-resolution MS m/z calcd for $C_{23}H_{33}NO_3S_3$ (M^+) 467.1636, found: 467.1623.

<u>Diastereoselective Intramolecular Diels-Alder Reaction of Trienes (13a-e)</u>

From 13a; To a stirred solution of **13a** (0.086 g, 0.2 mmol) in CH_2Cl_2 (12 mL) at -78 °C was added Me_2AlCl (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 CH_2Cl_2. Usual work-up of the extract gave **14a** (0.088 g). To a stirred solution of $PhCH_2OH$ (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_2O : 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 ϕ x 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.

(3a*S*,7*R*,7a*R*)-Benzyl 2,3,3a,4,5,7a-hexahydro-5,5-(trimethylenedithio)indene-7-carboxylate (15); ^{1}H NMR δ 7.37 (5H, s), 5.75 (1H, d, *J* = 9.9 Hz, C<u>H</u>=CH), 5.59-5.65 (1H, m), 5.18, 5.13 (each 1H, d, *J* = 12.4 Hz, $PhCH_2$), 2.80-2.92 (4H, m), 2.64 (1H, ddd, *J* = 7.3, 10.9, 11.1 Hz, CHCOO), 2.38-2.53 (5H, m), 1.90-2.27 (2H, m), 1.63-1.90 (3H, m); IR 2908, 1727, 1439 cm^{-1}; EI MS *m/z* 360 (M^+); high-resolution MS *m/z* calcd for $C_{20}H_{24}O_2S_2$ (M^+) 360.1216, found: 360.1217.

Benzyl 5,5-(trimethylenedithio)-2(*E*),7(*E*),9-decatrienoate (16); ^{1}H NMR δ 7.37 (5H, s), 7.12 (1H, dt, *J* = 7.5, 15.8 Hz, C<u>H</u>=CHCO), 6.00-6.13 (2H, m), 5.96 (1H, d, *J* = 15.8 Hz, CH=C<u>H</u>CO), 5.19 (2H, s, C<u>H$_2$</u>Ph), 5.11-5.23 (3H, m), 3.15 [1H, t, *J* = 7.9 Hz, =CHC<u>H</u>(H)], 2.70-2.99 (7H, m), 1.80-2.08 (2H, m); IR 1716 cm^{-1}; EI MS *m/z* 360 (M^+); high-resolution MS *m/z* calcd for $C_{20}H_{24}O_2S_2$ (M^+) 360.1216, found: 360.1212.

From 13b; To a stirred solution of **13b** (0.300 g, 0.72 mmol) in CH_2Cl_2 (43 mL) at -50 °C was added Me_2AlCl (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 $PhCH_2OH$ (120 μL, 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_2O : hexane = 1 : 3) of which produced **15b** (0.143 g, 57%, 22% e.e.), $[\alpha]_D^{30}$ +5.0° (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_2Cl_2 (43 mL) at -60 °C was added Me_2AlCl (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 $PhCH_2OH$ (115 μL, 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_2O : hexane = 1 : 3) of which produced **15a** (0.158 g, 65%, 22% e.e.), $[\alpha]_D^{27}$ -6.7° (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_2Cl_2 (33 mL) at -50 °C was added Me_2AlCl (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 $PhCH_2OH$ (90 μL, 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_2O :

hexane = 1 : 3) of which produced **15a** (0.109 g, 55%, 96% e.e.), $[\alpha]_D^{30}$ -31.0° (c 1.08, $CHCl_3$) and **16** (0.017 g, 9%).

From 13e; To a stirred solution of **13e** (0.357 g, 0.72 mmol) in CH_2Cl_2 (45 mL) at -50 °C was added $EtAlCl_2$ (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 $MgSO_4$) left **14e** (0.401 g). The reaction similar to that noted for **13a** by using $PhCH_2OH$ (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 (Et_2O : hexane = 1 : 3) of which produced **15a** (0.072 g, 26%, 87% e.e.), $[\alpha]_D^{29}$ -28.2° (c 1.07, $CHCl_3$) 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 $CHCl_3$. Usual work-up of the extract gave **17** (0.041 g, 85%); ^{1}H NMR δ 8.58 (1H, br s, CO_2H), 5.97 (1H, d, *J* = 10.4 Hz, CHC<u>H</u>=CH), 5.65 (1H, ddd, *J* = 2.8, 5.6, 10.4 Hz, CH=C<u>H</u>CH_2), 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 CH_2Cl_2 (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, CH_2Cl_2); {lit.[12] $[\alpha]_D^{23}$ -50° (c 1.38, CH_2Cl_2)}; ^{1}H NMR δ 5.79 (1H, d, *J* = 9.9 Hz, CHC<u>H</u>=CH), 5.64 (1H, ddd, *J* = 3.2, 6, 9.9 Hz, CH=C<u>H</u>CH_2), 4.43, 4.04 (each 2H, t, *J* = 8.1 Hz, O<u>C</u>H_2CH_2N, OCH_2<u>C</u>H_2N), 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 $C_{16}H_{21}NO_3S_2$ (M^+) 339.0962, found: 339.0964. ^{1}H-NMR spectral data and sign of specific rotation of synthetic **19** were identical with those reported in the literature.[12]

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