Syntheses of Cerulenin and Its Analogs. I. Cerulenin and Its Analogs with Modified Side Chain

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Optically active cerulenin 1, a potent inhibitor of fatty acid synthetase, was prepared *via* the condensation of the epoxy aldehyde 8 and the alkenyl lithium 16. In order to evaluate the effects of (*E*,*E*)-1,4-double bonds of the cerulenin side chain on the interaction with the enzyme, a series of optically active cerulenin analogs 32a—i with modified side chains and tetrahydrocerulenin 3 were synthesized by similar procedures.

Keywords cerulenin; cerulenin analog; fatty acid synthetase inhibitor; synthesis

Cerulenin (**1**)[3] is an antibiotic isolated from *Cephalosporium caerulens*.[4] The structure of **1** (Fig. 1) was determined by chemical and spectral studies[5] and the absolute configuration was established by synthesis from D-glucose.[6] Other synthetic studies of (±)-cerulenin[7a-g] and (+)-cerulenin[7h] have also been reported. Cerulenin is known to have the structure **1a** in aprotic solvents such as chloroform and to form a pair of epimers of the hydroxylactam **1b** in protic solvents such as methanol.[7e,8c] Cerulenin is a potent inhibitor of β-ketoacyl synthetase (condensing enzyme)[9] which catalyzes one of six processes involved in the fatty acid synthetase system.[10] Cerulenin irreversibly binds to cysteine-SH at the active center of the condensing enzyme[8] and inhibits condensation of malonyl thioester and acyl thioester to elongate the acyl thioester in fatty acid biosynthesis.

In the structure of cerulenin, the epoxide moiety is essential to form a covalent bond with the cysteine-SH group at the active center of the enzyme; this was verified by the fact that the reaction of cerulenin and cysteine methyl ester gave an adduct **2a**,[8c] and proteolytic digestion of yeast fatty acid synthetase–cerulenin adduct gave **2b**,[8d] The importance of the number and the position of the double bonds in the cerulenin side chain for the activity was suggested by the fact that partial or complete saturation of C–C double bonds[9e,11] decreases the activity. Being interested in the contribution of the two double bonds of the side chain to the potent and specific cerulenin activity, we undertook syntheses of the optically active cerulenin and a series of analogs with a modified side chain. We report here stereoselective syntheses of cerulenin **1**[12] and its analogs **3** and **32a—i**, in which the molecules were built up by connecting the optically active epoxyaldehyde **8** with various alkyl- and alkenylmetals (**16**, **26a—j**). The double bonds in the side chain of the analogs were fixed at the same positions as in cerulenin to clarify the role of the (*E*,*E*)-1,4-diene system. This synthetic method should be generally applicable to the preparation of a variety of cerulenin analogs, including isotope-labeled derivatives.

Synthesis of Cerulenin The optically active epoxy aldehyde **8** was prepared from (2*S*,3*R*)-4-benzyloxy-2,3-epoxybutan-1-ol (**4**)[13] (Chart 1). The enantiomeric composition of **4** was determined from the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of its (−)-(*S*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester)[14] to be 84% ee.[13,15] Swern oxidation[16] of the epoxide **4** afforded the aldehyde **5**. Acetalization[17] of **5** gave the acetal **6** in the yield of 76% from **4**. The benzyl group of **6** was removed by Na/NH_3 reduction[18] to give the alcohol **7**. Swern oxidation of **7** gave the optically active epoxy aldehyde **8** in 65% yield from **6**.

(*E*,*E*)-3,6-Octadienyllithium **16** was prepared by Corey's method[7c] (Chart 2). The vinyllithium derivative **10**, obtained from the vinylstannane **9** (*E*:*Z*=78:22),[19] was allowed to react with crotyl bromide **11** to give the coupling product as the tetrahydropyranyl (THP) ether (**12**). Hydrolysis of **12** gave 3,6-octadienyl alcohol **13** and its stereoisomers. The dienol **13** was purified by column chromatography on silica gel impregnated with 5%

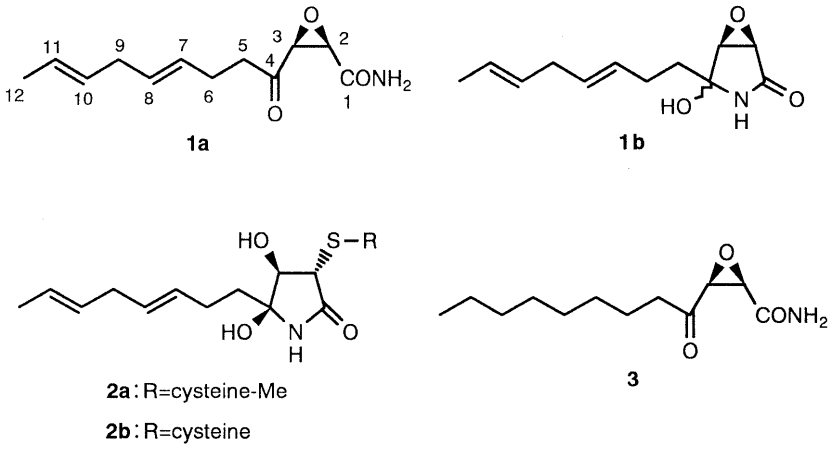

Fig. 1

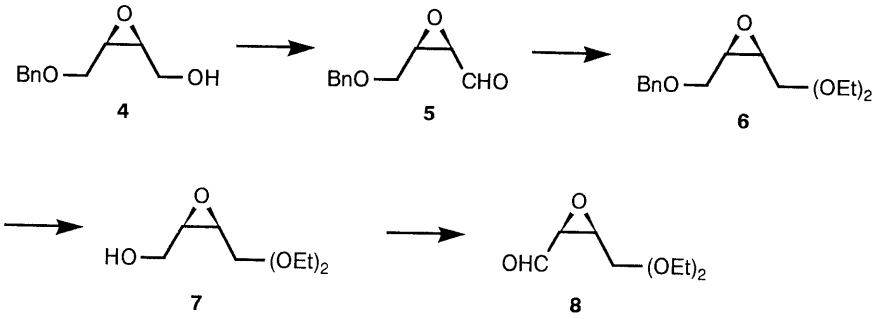

Chart 1

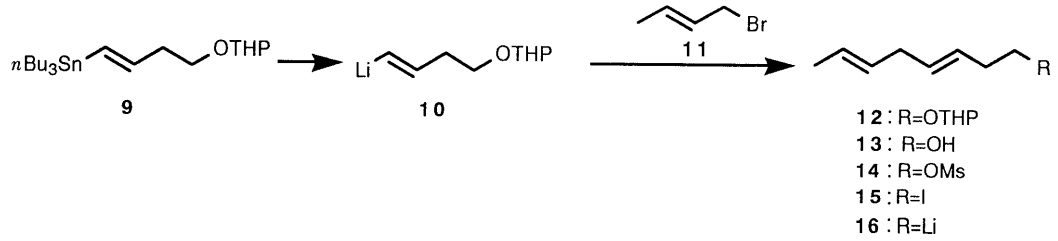

Chart 2

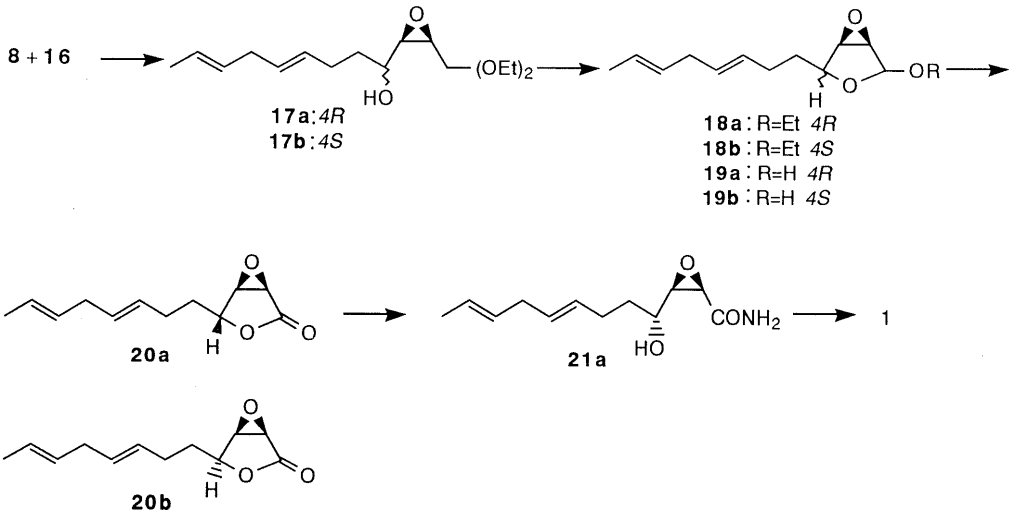

Chart 3

$AgNO_3$. The early fractions gave the desired (*E*,*E*)-dienol (**13**). The alcohol **13** was converted into the iodide **15**[7c,20] *via* the mesylate **14**[21] in 74% yield. The iodination was carried out with NaI and a phase-transfer catalyst, Aliquat 336 (tricaprylylmethylammonium chloride).[22] The dienyllithium **16** was obtained by lithiation of the iodide **15** with *tert*-butyllithium (*tert*-BuLi).[7c]

The epoxy aldehyde **8** was coupled with the lithio derivative **16** and the reaction was quenched with saturated aqueous Na_2SO_4 solution at $-78\,^{\circ}C$ to give a pair of epimers **17a** and **17b** in 63% and 16% yields, respectively (Chart 3), both of which gave a peak at *m/z* 238 (M − EtOH) in the mass spectra (MS). In the ^{1}H-NMR spectra, the signals of olefinic protons at δ 5.36—5.52 (4H, m), protons of two ethoxy groups, a proton on C-4 at δ 3.49 (**17a**) and 3.53 (**17b**), and epoxide protons at δ 2.91 and 3.14 (**17a**) and at δ 2.99 and 3.19 (**17b**) were observed. Stereochemistry at C-4 of these epimers was assigned at the stage of the known lactones **20a** and **20b** by comparisons of the spectral data with reported data.[6,7a,b,d,e] Hydrolysis of **17a** to **19a**[6] and **17b** to **19b** were critical steps.[23] Compounds **17** afforded the hemiacetals **18** upon acid hydrolysis at room temperature. Heating was necessary for further hydrolysis of **18** to **19**, though drastic reaction conditions destroyed **19**. After examination of the reaction conditions, the major acetal **17a** was hydrolyzed with 1% H_2SO_4 in aqueous acetone at 55—60 °C for 15 h to give a mixture of **18a** and **19a**.[6] The hemiacetal **18a** was separated by silica gel column chromatography and was subjected to repeated hydrolysis under the same conditions. By this procedure, **19a** was obtained in 62% yield from **17a**. Compared to the major acetal **17a**, the minor acetal **17b** was unstable to acid hydrolysis, and the yield of **19b** from **17b** was 20% after a single treatment with H_2SO_4 in aqueous acetone.

By the same procedure as already reported,[6,7a-e] **19a** was converted into cerulenin **1**. Collins' oxidation[24] of **19a** afforded **20a**[6,7d,e] (66% yield). Its ^{1}H-NMR data were identical with the values given by Tishler *et al.*,[7e] and the

stereochemistry at C-4 was assigned as *R*. Compound **19b** gave the lactone **20b**.[7a,b] Its ^{1}H-NMR spectrum was identical with that reported by Boeckman and Thomas,[7b] and the stereochemistry of **20b** at C-4 was assigned as *S*. Ammonolysis of **20a** afforded **21a**,[6,7d,e] which was oxidized to give cerulenin **1**[6,7b,d] (yield of **1** from **19a**, 45%). Purification of cerulenin at the final step was carried out on a short silica gel column with CH_2Cl_2–Et_2O (1 : 1), and the product was recrystallized from benzene (mp 93 °C, lit., 93—94 °C).[3a] Under the same conditions, compound **20b** was converted to **21b**.[7a,b] Because of a shortage of material, **21b** was not converted to **1**. The ^{1}H-NMR, MS, infared (IR) spectral data and melting point of the synthetic **1** were identical with those of natural cerulenin.[3a,7e]

Though the $[\alpha]_D$ values of **20a** and **21a** were similar to those reported (**20a**, +53.1°, lit., 56.5°[6a]; **21a**, +65°, lit., +70°[6b]), that of synthesized **1** was different from the reported value (−0.1°, lit., −12°[3a]). Because the equilibrium ratio of **1a** and **1b** readily changes even under chromatographic conditions, the difference might be due to contamination by the hydroxylactam **1b** in the synthesized cerulenin, whose $[\alpha]_D$ value was reported as +56.5° in methanol after standing for 100 min.[3a] The optical purity of the synthesized cerulenin is expected to be the same as that of the epoxide **4** (84% ee).

Syntheses of Cerulenin Analogs The analogs **32a**—**i** and tetrahydrocerulenin **3**[23,25] were synthesized by procedures similar to that used for cerulenin (Fig. 2). Alkyl- and alkenylmetals **26a**—**j** to be connected with **8** were derived from the corresponding halides **25a**—**j** (Chart 4).

For the synthesis of **32a**, **32b** and **3**, commercially available iodoethane (**25a**), 1-iodopropane (**25b**) and 1-iodooctane (**25j**) were utilized. In the case of **32c**, the Grignard reagent (**26c**) derived from commercial 4-bromobutene (**25c**) was reacted with **8** at −78 °C. The iodide for **32d**, (*E*)-1-iodo-3-pentene (**25d**),[26a] was synthesized from cyclopropyl methyl carbinol by treatment with MgI_2 in 61% yield.[26] The iodide **25d** thus obtained was a mixture of stereoisomers (*E* : *Z* = 9 : 1). This mixture was used for further reaction and the stereoisomers were separated at the stage of the final product **32d** by high-performance liquid chromatography (HPLC). The starting material for **32e** was (*E*)-3-hexenoic acid. This was reduced with $LiAlH_4$ (LAH) to (*E*)-3-hexen-1-ol (**24e**),[27] which was then transformed to the iodide **25e** in the same way as in the case of **13** to **15** (40% yield from the acid).

The diene system for **24f**—**i** was constructed by utilizing the vinylstannane **9**. (*E*)-1-Hydroxy-3,6-heptadiene (**24f**) was prepared by a coupling of allyl bromide (**23f**) and **9** in the presence of palladium(0)bis(dibenzylideneacetone) ($Pd(dba)_2$) and triphenylphosphine[28] as catalysts, because, unlike the other allyl bromides **11** and **23g**—**i**, **23f** was inactive toward the vinyllithium **10**. Removal of the THP group followed by silica gel column chromatography and distillation gave **24f**[29] in 24% yield. Since the double bond isomers in **24f** could not be separated by $AgNO_3$-impregnated silica gel column chromatography, the mixture was used for further reaction and the isomers were separated at the stage of the final product (**32f**) by HPLC. The alcohol **24g** was prepared from commercial (*E*)-2-hexenol (**22g**). The alcohol **22h**[30] was prepared from commercial (*E*)-octenal by LAH reduction in 67% yield. The alcohol

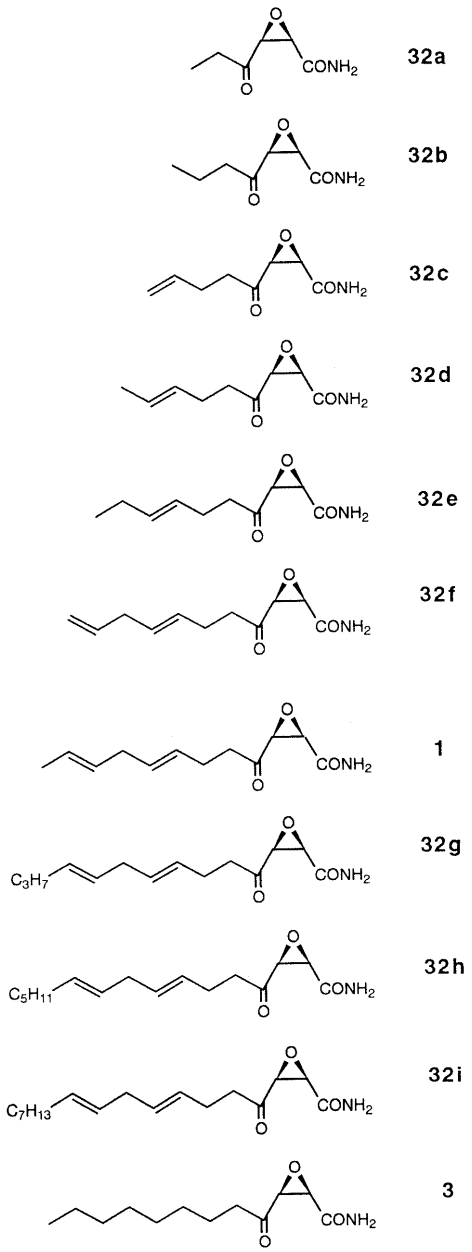

Fig. 2

22i[31] was prepared by coupling of *n*-octylaldehyde with $(C_6H_5)_3P{=}CHCOOEt$ to give ethyl (*E*)-2-decanoate[32] followed by reduction with diisobutylaluminum hydride (DIBAH). All these alcohols **22g**—**i** were transformed to the corresponding (*E*,*E*)-dienols **24g**—**i** by bromination with PBr_3 (70—90% yield), followed by coupling with **10**, hydrolysis of the THP ethers, and chromatographic purification of the resulting **24g**—**i** using 5% $AgNO_3$-impregnated silica gel (26—43% yield). (*E*,*E*)-Configuration of the double bonds in the alcohols **24g**—**i** was confirmed by a ^{1}H-NMR double decoupling experiment ($J_{3,4} = ca.$ 15 Hz, $J_{6,7} = ca.$ 15 Hz). The alcohols **24f**—**i** were iodinated to **25f**—**i** by the use of a similar procedure to that employed in cerulenin synthesis.

The iodides **25a**, **b** and **25d**—**j** were lithiated with *tert*-BuLi and the resulting alkyl- or alkenyllithiums were coupled with the epoxyaldehyde **8** to give the epoxyalcohols **27a**, **b** and **27d**—**j** (Chart 5). These alcohols as well as the Grignard

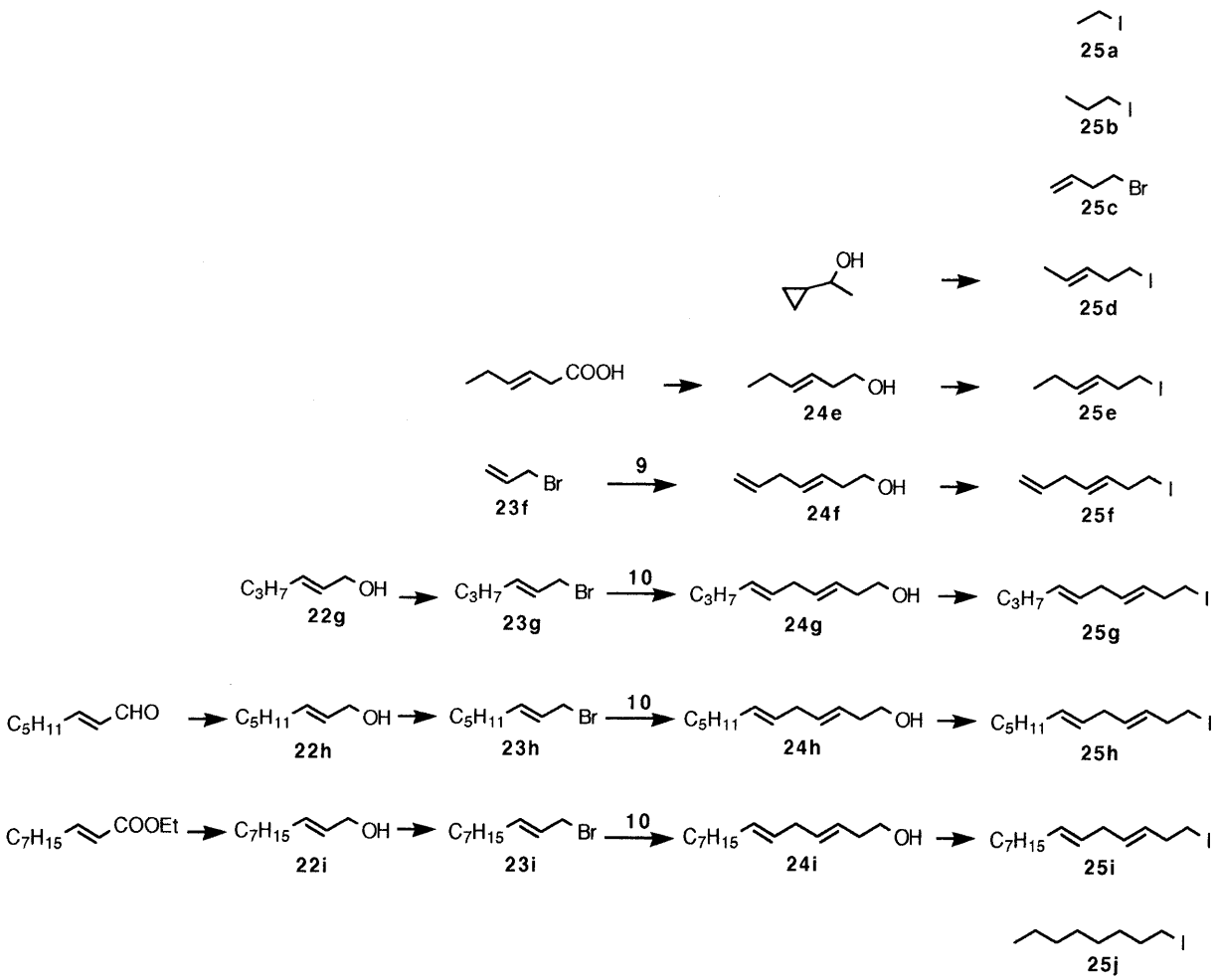

Chart 4

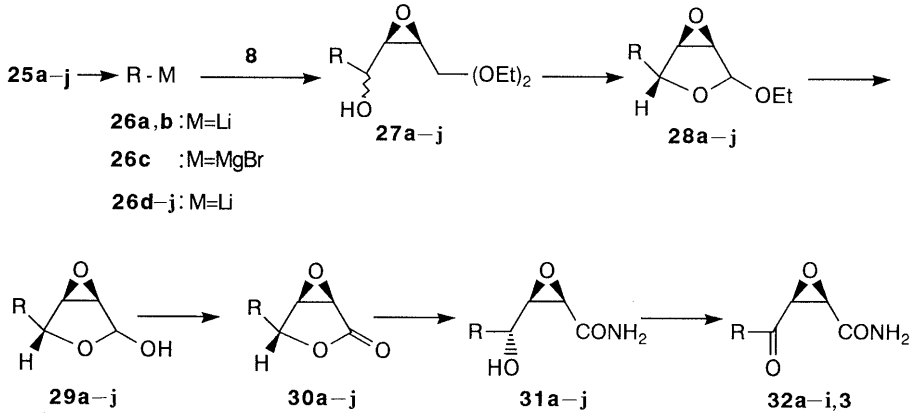

Chart 5

reaction product **27c** gave a pair of epimers at C-4, as in the case of cerulenin synthesis. The acid hydrolyses of **27a—j** were carried out with 1.5—2% H_2SO_4 in aqueous acetone at *ca.* 60 °C, and the reaction times were chosen by monitoring the reaction by thin layer chromatography (TLC). After work-up, recovered ethyl acetals (**28a—j**) were recycled. The resulting hemiacetals **29a—j** were oxidized to the lactones **30a—j**. Oxidation of **30g**, **30h** and **30j** was carried out by Swern oxidation. The other compounds were oxidized with CrO_3–pyridine. After ammonolysis of these lactones **30a—j**, the resulting amide alcohols **31a—j** were oxidized with CrO_3–pyridine to give **32a—i** and **3**. Compounds **32a—c**, **32g—i** and **3** were purified by chromatography on a short silica gel column eluted with CH_2Cl_2–Et_2O (1 : 1). Purified products were mostly composed of the open form, like **1a**, as the major component, but contained more or less hydroxylactam form, like **1b**. Compounds **32d** and **32f**, containing (*Z*)-isomers of the side chain, and **32e** were finally purified by HPLC on an ODS column. Because they were eluted with CH_3CN–H_2O, each final product was obtained as a mixture of a keto form and a pair of hydroxylactam forms.

The yields of **32a—i** and **3** from **27a—j** were 4—26%.

Biological activities of synthetic cerulenin and its analogs will be reported elsewhere.[33]

Experimental

^{1}H-NMR spectra were measured on JEOL GX-400 and GX-500 FT-NMR spectrometers (400 and 500 MHz for ^{1}H, respectively) and chemical shifts were recorded in δ units relative to internal tetramethylsilane (TMS) ($\delta=0$) in $CDCl_3$. IR spectra were measured on a JASCO A-102 instrument. GC-MS were measured on a Shimadzu LKB-9000 instrument with a 1% OV-1 column (4 mm i.d. × 1 m). GC column temperature is indicated in parenthesis. Electron-impact mass spectra (EI-MS) at 70 eV, fast-atom bombardment mass spectra (FAB-MS) at accelerating voltage 10 kV with *m*-nitrobenzyl alcohol matrix, and high-resolution mass sepctra (HR-MS) were measured on a JEOL JMS-HX110 instrument. Elementary analyses were performed by the Microanalytical Laboratory, Institute of Applied Microbiology, the University of Tokyo. Optical rotations were measured on a JASCO DIP-181 polarimeter. HPLC was performed on a Shimadzu LC-3A apparatus equipped with a Nucleosil $5C_{18}$ column (2.1 mm i.d. × 70 + 4.6 mm i.d. × 250): mobile phase, acetonitrile (20—95%)–water.

(2*S*,3*R*)-4-Benzyloxy-2,3-epoxybutan-1-ol (4)[13,15] The epoxyalcohol **4** was obtained from 4-benzyloxy-(*Z*)-2-buten-1-ol by the literature method.[13] **4**: ^{1}H-NMR ($CDCl_3$) δ: 2.1 (1H, br t, $J=7.0$ Hz), 3.22 (1H, dt, $J=5.0$, 5.0 Hz), 3.29 (1H, dt, $J=5.0$, 6.1 Hz), 3.65 (1H, dd, $J=10.9$, 5.0 Hz), 3.74 (3H, m), 4.54 (1H, d, $J=12.0$ Hz), 4.62 (1H, d, $J=12.0$ Hz), 7.34 (5H, m). MS *m/z*: 194 (M^+), 91 ($C_6H_5CH_2$). IR ($CHCl_3$) *v*: 3610, 3010, 1100 cm^{-1}. $[\alpha]_D^{26}$ −23.9° (*c*=2.04, $CHCl_3$), lit., $[\alpha]_D^{25}$ −27° (*c*=1.5, $CHCl_3$),[15] Sharpless' enantiomer, $[\alpha]_D^{25}$ +25.9° (*c*=1.45, $CHCl_3$).[13]

MTPA Ester of 4 The alcohol **4** (32 mg, 0.17 mmol) and (−)-MTPACl (43 mg, 0.17 mmol) were mixed with pyridine (0.1 ml) and CCl_4 (0.1 ml), and the mixture was allowed to stand overnight at room temperature.[14] After work-up and purification by silica gel column chromatography, the enantiomeric composition of the ester (37 mg, 53% yield) was analyzed by ^{1}H-NMR spectroscopy. The signals for methyl protons in C_6D_6 (δ 3.40) and benzyl protons in $CDCl_3$ (δ 4.58) were observed as a singlet and a doublet, respectively. From the ratio of their intensity (92:8), the composition was calculated to be 84% ee. ^{1}H-NMR ($CDCl_3$) δ: 3.29 (2H, m), 3.56 (3H, s), 3.61 (1H, dd, $J=11.0$, 5.5 Hz), 3.67 (1H, dd, $J=11.0$, 4.0 Hz), 4.35 (1H, dd, $J=12.0$, 6.5 Hz), 4.52 (1H, d, $J=12.0$ Hz), 4.53 (1H, dd, $J=12$, 4.0 Hz), 4.58 (1H, d, $J=12.0$ Hz), 7.28—7.56 (10H, m). ^{1}H-NMR (C_6D_6) δ: 2.79 (1H, dt, $J=7.0$, 4.0 Hz), 2.83 (1H, dt, $J=5.8$, 4.0 Hz), 3.19 (1H, dd, $J=11.0$, 5.8 Hz), 3.23 (1H, dd, $J=11.0$, 4.0 Hz), 3.40 (3H, s), 3.93 (1H, dd, $J=12.0$, 4.0 Hz), 4.13 (1H, dd, $J=12.0$, 7.0 Hz), 4.18 (1H, d, $J=12.0$ Hz), 4.24 (1H, d, $J=12.0$ Hz), 7.0—7.8 (m). FAB-MS *m/z*: 411 (M + H), 409.

(2*R*,3*R*)-4-Benzyloxy-2,3-epoxybutylaldehyde (5) Dimethyl sulfoxide (DMSO) (4.45 ml, 57.6 mmol) in CH_2Cl_2 (13 ml) was added dropwise to a solution of $(COCl)_2$ (3.9 g, 28.6 mmol) in CH_2Cl_2 (72 ml) at −78 °C.[16] The mixture was stirred for 10 min, then compound **4** (5 g, 25.8 mmol) in CH_2Cl_2 (26 ml) was added over 10 min. Fifteen minutes later, triethylamine (TEA, 13.4 g, 132 mmol) was added and stirring was continued for another 5 min. The cooling bath was removed and, when the reaction mixture had reached room temperature, 50 ml of water was added. The whole was extracted with CH_2Cl_2. The CH_2Cl_2 solution was successively washed with 1 N HCl, saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent gave 5 g of **5**. The product was used as such in subsequent experiments. For purification, crude **5** was chromatographed on a silica gel column (benzene:AcOEt = 9:1) and then distilled (137 °C (4 mmHg)). **5**: ^{1}H-NMR ($CDCl_3$) δ: 3.43 (1H, dd, $J=5.0$, 5.0 Hz), 3.50 (1H, ddd, $J=3.0$, 4.4, 5.0 Hz), 3.77 (1H, dd, $J=4.4$, 11.8 Hz), 3.84 (1H, dd, $J=3.0$, 11.8 Hz), 4.56 (1H, d, $J=11.0$ Hz), 4.57 (1H, d, $J=11.0$ Hz), 7.28—7.39 (5H, m), 9.44 (1H, d, $J=5$ Hz). GC-MS (150 °C) *m/z*: 192 (M^+), 91 ($C_6H_5CH_2$). IR ($CHCl_3$) *v*: 1726 cm^{-1} (C=O). $[\alpha]_D^{26}$ +102.9° (*c*=2.05, $CHCl_3$).

(2*R*,3*R*)-4-Benzyloxy-1,1-diethoxy-2,3-epoxybutane (6) Crude **5**, obtained from 10 g of **4** was dissolved in 42 ml of $CH(OEt)_3$, and 2.5 g of Amberlyst-15, strong cation-exchange resin, was added to the mixture with stirring.[17] Stirring was continued at room temperature and the acetalization was completed within 6 h. The Amberlyst was filtered off and the filtrate was concentrated with a rotary evaporator at around 80 °C. The residual oil was purified on a silica gel column (*n*-hexane:AcOEt = 4:1), and 10 g of **6** was obtained (73% yield for the 2 steps from **4**). **6**: ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, $J=6.6$ Hz), 1.24 (3H, t, $J=6.6$ Hz), 3.15 (1H, dd, $J=4.4$, 6.2 Hz), 3.27 (1H, ddd, $J=2.9$, 4.4, 6.8 Hz), 3.53—3.71 (4H, m), 3.58 (1H, dd, $J=6.8$, 11.5 Hz), 3.85 (1H, dd, $J=2.9$, 11.5 Hz), 4.34 (1H, d, $J=6.2$ Hz), 4.56 (1H, d, $J=11.8$ Hz), 4.65 (1H, d, $J=11.8$ Hz), 7.25—7.40 (5H, m). GC-MS (170 °C) *m/z*: 221 (M − OEt), 103 ($CH(OEt)_2$), 91 ($C_6H_5CH_2$). IR ($CHCl_3$) *v*: 2980 cm^{-1}. $[\alpha]_D^{26}$ +1.88 (*c*=1.92, $CHCl_3$).

(2*R*,3*R*)-4,4-Diethoxy-2,3-epoxybutanol (7) A solution of **6** (5 g) in Et_2O (40 ml) was added dropwise to a solution of Na (2.2 g, 50 eq) in NH_3 (80 ml) at −78 °C over about 10 min. After 5 min of stirring, NH_4Cl was added until the blue color of Na–NH_3 disappeared.[18] The dry ice–acetone bath was removed and 150 ml of Et_2O was slowly added. Ammonia was evaporated off and the NH_4Cl cake was removed by filtration. Removal of the solvent gave the alcohol **7**, which was purified by silica gel column chromatography (*n*-hexane:AcOEt = 1:1) (2.8 g, 85% yield). **7**: ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, $J=7.1$ Hz), 1.27 (3H, t, $J=7.1$ Hz), 2.10 (1H, br dd, $J=6.0$, 8.0 Hz), 3.18 (1H, dd, $J=4.5$, 5.7 Hz), 3.23 (1H, dt, $J=4.5$, 5.6 Hz), 3.63 (2H, m), 3.75 (3H, m), 3.87 (1H, ddd, $J=5.6$, 8.0, 12.5 Hz). GC-MS (100 °C) *m/z*: 175 (M − H), 145 (M − CH_2OH), 131 (M − OEt), 103 ($CH(OEt)_2$). IR ($CHCl_3$) *v*: 2990, 3600 cm^{-1}. $[\alpha]_D^{26}$ +4.26° (*c*=1.69, $CHCl_3$).

(2*S*,3*R*)-4,4-Diethoxy-2,3-epoxybutylaldehyde (8) The alcohol **7** (2.9 g) was oxidized with DMSO and $(COCl)_2$ using the same procedure employed for the preparation of **5**.[16] Crude **8** thus obtained was chromatographed on a silica gel column with *n*-hexane–AcOEt (2:1), and then distilled (80 °C (4 mmHg)) to give pure **8** (2.2 g, 77% yield). **8**: ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, $J=7.0$ Hz), 1.24 (3H, t, $J=7.0$ Hz), 3.38 (1H, dd, $J=4.4$, 4.5 Hz), 3.42 (1H, dd, $J=3.2$, 4.5 Hz), 3.57 (2H, m), 3.70 (2H, m), 4.77 (1H, d, $J=3.2$ Hz), 9.50 (1H, d, $J=4.4$ Hz). GC-MS (70 °C) *m/z*: 129 (M − OEt), 103 ($CH(OEt)_2$). IR ($CHCl_3$) *v*: 1722, 2980 cm^{-1}. $[\alpha]_D^{26}$ −105.6° (*c*=1.90, $CHCl_3$). *Anal.* Calcd for $C_8H_{14}O_4$: C, 55.17; H, 8.05. Found: C, 55.05; H, 8.19.

4-Tributylstannyl-3-butenyl THP Ether (9)[19] A mixture of 3-butyn-1-ol THP ether (69.4 g, 0.45 mol), tributyltin hydride (139 g, 0.478 mol) and 2,2′-azobisisobutyronitrile (AIBN, 0.3 g) was heated at 100 °C for 1 h. It was cooled, then additional AIBN (0.3 g) was added and heating was continued for another 1 h. Distillation under vacuum at around 200 °C gave 188 g (0.43 mol, 89% yield) of **9**[10c] and its *Z*-isomer.[19] Composition of the products was determined from the intensity of the ^{1}H-NMR signal at δ 2.44 and 2.34 (allylic-H) of each isomer (*Z*:*E* = 78:22). **9**: ^{1}H-NMR ($CDCl_3$) δ: 0.90 (9H, t), 1.22—1.9 (24H, m), 2.44 (2H, dt, $J=2.8$, 4.2 Hz), 3.40—3.55 (2H, m), 3.75—3.90 (2H, m), 4.61 (1H, dd, $J=1.9$, 2.5 Hz), 6.0 (2H, m). GC-MS (220 °C) *m/z*: 385, 387, 389 (M − C_4H_9), 301, 303, 305 (M − C_4H_9 − tetrahydropyran).

(*E*,*E*)-3,6-Octadien-1-ol (13)[7c] The alcohol **13** was obtained by Corey's method.[7c] A tetrahydrofuran (THF, 800 ml) solution of **9** (200 g, 0.45 mol) was treated with 1 eq of *n*-BuLi in 280 ml of *n*-hexane at −78 °C. Crotyl bromide **11** (61.3 g, 0.45 mol; the commercial **11** was a mixture of *Z*-, *E*- and iso-isomers) in THF (190 ml) was added to the solution. After 1 h of stirring, the dry ice–acetone bath was removed and stirring was continued for 3 h. At the end of the reaction, saturated aqueous Na_2SO_4 was added dropwise, the formed precipitates were filtered off, and the precipitates were washed with Et_2O. The organic solution was dried over Na_2SO_4, and the solvent was removed under vacuum to give an oil containing the reaction product **13** and $(n\text{-Bu})_4Sn$. To this oil, MeOH was added and $(n\text{-Bu})_4Sn$ in the lower layer was removed. A catalytic amount of Amberlyst 15 was added and methyl THP ether was azeotropically removed with methanol (bp 66—69 °C). After the hydrolysis, the Amberlyst was filtered off, and the filtrate was concentrated. Distillation (160—180 °C) gave crude 3,6-octadien-1-ols (**13** and its isomers). After redistillation (43 g), **13** was separated by 5% $AgNO_3$-impregnated silica gel column chromatography with 2% MeOH in CH_2Cl_2. Twenty grams of pure alcohol **13** was obtained.[7c] **13**: ^{1}H-NMR ($CDCl_3$) δ: 1.40 (1H, br s), 1.66 (3H, d, $J=4.5$ Hz), 2.28 (2H, ddt, $J=6.5$, 1.0, 6.2 Hz), 2.71 (2H, m), 3.64 (2H, t, $J=6.2$ Hz), 5.50 (4H, m). GC-MS (110 °C) *m/z*: 126 (M^+), 108 (M − 18), 95 (M − CH_2OH).

(*E*,*E*)-3,6-Octadien-1-iodide (15)[7c] A solution of MsCl (2.2 g, 23.8 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a mixture of the alcohol **13** (4 g, 15.9 mmol) in Et_3N (2.4 g, 23.8 mmol) and CH_2Cl_2 (50 ml) at 0 °C.[21] The mixture was stirred for 1 h, then ice-water (30 ml) was added. The water layer was separated and extracted with CH_2Cl_2. The combined CH_2Cl_2 solution was washed successively with 1 N HCl, saturated $NaHCO_3$ and brine. After being dried over Na_2SO_4 the solution was evaporated to give the methanesulfonate **14**[7c] as an oil (3.03 g, 94% yield). A mixture of **14** (1.47 g, 7.2 mmol), Aliquat 336 (0.18 g, 2 mmol), NaI (9.4 g, 63 mmol) and H_2O was heated at 80 °C for 7 h. After cooling, the mixture was

extracted with *n*-pentane and the pentane solution was dried over Na_2SO_4. The dried solution was passed through a silica gel column, and removal of the pentane furnished the iodide **15**, 1.34 g (78% yield). **14**: ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, br d, J=5.0 Hz), 2.45, (2H, dt, J=8.0, 7.5 Hz), 2.70 (2H, m), 3.00 (3H, s), 4.22 (2H, t, J=7.5 Hz), 5.34—5.65 (4H, m). **15**: ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, d, J=5.0 Hz), 2.56 (2H, dt, J=7.5, 7.3 Hz), 2.68 (2H, br t, J=6.3 Hz), 3.15 (2H, t, J=7.5 Hz), 5.45 (4H, m). GC-MS (110 °C) *m/z*: 236 (M^+), 109 (M−I). IR ($CHCl_3$) ν: 975, 1430 cm^{-1}.

(2*R*,3*R*,4*R*)-1,1-Diethoxy-2,3-epoxy-7,10-(*E*,*E*)-dodecadien-4-ol (17a) and (2*R*,3*R*,4*S*)-1,1-Diethoxy-2,3-epoxy-7,10-(*E*,*E*)-dodecadien-4-ol (17b) The iodide **15** (440 mg, 1.9 mmol) was dissolved in *n*-pentane (11 ml) and cooled to −78 °C. To this solution, *tert*-BuLi (1.8 M in *n*-pentane, 4.1 ml, 7.2 mmol) was added under Ar and the whole was stirred for 20 min. A solution of **8** (650 mg, 3.7 mmol) in THF (12 ml) was added dropwise, and stirring was continued for 20 min. The reaction was quenched with 0.7 ml of saturated Na_2SO_4 solution, the dry ice–acetone bath was removed and the solution was warmed to room temperature. A small amount of Na_2SO_4 was added and, after filtration, the organic solvent was removed with a rotary evaporator. The residual oil was chromatographed on a silica gel column with *n*-hexane–AcOEt (4 : 1). **17a**, 332 mg (63% from **15**) and **17b**, 88 mg (16% from **15**). **17a**: ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.0 Hz), 1.27 (3H, t, J=7.0 Hz), 1.65 (3H, br d, J=4.5 Hz), 1.74 (2H, m), 2.10—2.28 (2H, m), 2.67 (2H, m), 2.71 (1H, br d, J=2.0 Hz), 2.91 (1H, dd, J=4.1, 8.1 Hz), 3.14 (1H, dd, J=4.1, 5.9 Hz), 3.49 (1H, br dt, J=8.0, 8.0 Hz), 3.55—3.83 (4H, m), 4.52 (1H, d, J=5.9 Hz), 5.36—5.52 (4H, m). GC-MS (180 °C) *m/z*: 238 (M−EtOH), 220 ($M-H_2O-EtOH$), 103 ($CH(OEt)_2$). IR ($CHCl_3$) ν: 970, 1060, 3500 cm^{-1}. $[\alpha]_D^{22}$ +14.0° (c=0.26, $CHCl_3$). **17b**: ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz), 1.26 (3H, t, J=7.0 Hz), 1.65 (5H, m), 2.04 (1H, br d, J=3.6 Hz), 2.08—2.28 (2H, m), 2.67 (2H, m), 2.99 (1H, dd, J=4.3, 7.4 Hz), 3.19 (1H, dd, J=4.3, 6.4 Hz), 3.53 (1H, dq, J=7.0, 9.3 Hz), 3.62—3.78 (4H, m), 4.41 (1H, d, J=6.4 Hz), 5.36—5.52 (4H, m). GC-MS (180 °C) *m/z*: 266 ($M-H_2O$), 238 (M−EtOH), 220 ($M-H_2O-EtOH$), 103 ($CH(OEt)_2$). IR ($CHCl_3$) ν: 970, 1055, 3590 cm^{-1}. $[\alpha]_D^{22}$ −1.6° (c=0.25, $CHCl_3$).

(3*R*,4*R*,5*R*)-3,4-Epoxy-2-hydroxy-5-(3,6-(*E*,*E*)-octadienyl)oxolane (19a)[6] Water (4 ml) and 15% H_2SO_4 (1 ml) were added to a solution of the alcohol **17a** (237 mg) in acetone (10 ml), and the mixture was heated at 55—60 °C for 15 h. After being cooled to room temperature, the solution was neutralized with saturated $NaHCO_3$ and was extracted with Et_2O. The combined ether solution was dried over Na_2SO_4 and the organic solvent was removed with a rotary evaporator to give an oil containing **18a** and **19a**.[6] The reaction products **18a** and **19a** were separated on a silica gel column (*n*-hexane : AcOEt = 3 : 1), and **19a** (72 mg) and **18a** (84 mg) were obtained. The hydrolysis of the hemiacetal **18a** was repeated twice using the same procedure, and in total 108 mg of **19a** was obtained (62% yield). **18a**: ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz), 1.5—1.7 (2H, m), 1.65 (3H, br d, J=4 Hz), 2.05—2.25 (2H, m), 2.68 (2H, br s), 3.52 (1H, dq, J=9.5, 7.2 Hz), 3.61 (1H, d, J=2.5 Hz), 3.68 (1H, d, J=2.5 Hz), 3.80 (1H, dq, J=9.5, 7.2 Hz), 4.09 (1H, dd, J=8.7, 5.0 Hz), 5.03 (1H, s), 5.43 (4H, m). GC-MS (150 °C) *m/z*: 238 (M^+), 192 (M−EtOH). **19a**: ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.75 (2H, m), 1.65 (3H, br d, J=4.0 Hz), 2.1—2.25 (2H, m), 2.68 (2H, br s), 2.78 (1H, d, J=4.0 Hz), 3.63 (1H, d, J=2.5 Hz), 3.66 (1H, d, J=2.5 Hz), 4.12 (1H, dd, J=5.5, 8.3 Hz), 5.35—5.52 (5H, m). GC-MS (150 °C) *m/z*: 210 (M^+), 192 ($M-H_2O$).

(3*R*,4*R*,5*S*)-3,4-Epoxy-2-hydroxy-5-(3,6-(*E*,*E*)-octadienyl)oxolane (19b) Using the same procedure as described above, **17b** (38 mg) was hydrolyzed and, after column chromatography, **18b** (8 mg, 28%) and **19b** (6 mg, 21%) were obtained. **18b**: ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.2 Hz), 1.66 (3H, br d, J=4.8 Hz), 1.74 (2H, m), 2.16 (2H, m), 2.67 (2H, br t), 3.53 (1H, dq, J=9.6, 7.2 Hz), 3.61 (1H, d, J=2.9 Hz), 3.63 (1H, d, J=2.9 Hz), 3.79 (1H, dq, J=9.6, 7.2 Hz), 4.00 (1H, dd, J=6.8, 6.8 Hz), 5.03 (1H, s), 5.37—5.51 (4H, m). GC-MS (150 °C) *m/z*: 238 (M^+), 192 (M−EtOH). **19b**: ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, br d, J=4.5 Hz), 1.74 (2H, m), 2.16 (2H, m), 2.67 (2H, m), 2.75 (1H, br d, J=4 Hz), 3.67 (2H, s), 4.12 (1H, t, J=6.7 Hz), 5.36—5.51 (5H, m). GC-MS (150 °C) *m/z*: 192 ($M-H_2O$).

(2*R*,3*R*,4*R*)-2,3-Epoxy-4-hydroxy-7,10-(*E*,*E*)-dodecadienoic Lactone (20a)[6,7d,e] **and (2*R*,3*R*,4*S*)-2,3-Epoxy-4-hydroxy-7,10-(*E*,*E*)-dodecadienoic Lactone (20b)**[7a,b] CrO_3 (320 mg, 3.2 mmol) was added to a solution of pyridine (510 mg, 6.5 mmol) in CH_2Cl_2 (8 ml) and the mixture was stirred for 15 min. A solution of **19a** (112 mg, 0.53 mmol) in a small amount of CH_2Cl_2 was added and, after 20 min, the solution was passed through a silica gel column. After removal of the solvent, the oily product **20a** was purified by a silica gel column chromatography (*n*-hexane : AcOEt = 3 : 1). (74 mg, 66% yield). Starting from **19b** (21 mg), **20b** was obtained under similar conditions. **20a**: ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, br d, J=4.7 Hz), 1.76 (2H, m), 2.20 (2H, m), 2.68 (2H, m), 3.77 (1H, d, J=2.2 Hz), 3.96 (1H, d, J=2.2 Hz), 4.59 (1H, dd, J=6.3, 6.8 Hz), 5.34—5.55 (4H, m). GC-MS (150 °C) *m/z*: 208 (M^+). IR ($CHCl_3$) ν: 972, 1180, 1789 cm^{-1}. $[\alpha]_D^{22}$ +53.1° (c=0.51, $CHCl_3$) (lit., $[\alpha]_D^{20}$ +56.5° (c=0.8, $CHCl_3$),[6a] $[\alpha]_D^{20}$ +45° (c=2.44, $CHCl_3$).[6b] **20b**: ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, br d, J=4.7 Hz), 1.84 (1H, m), 1.93 (1H, m), 2.21 (2H, m), 2.68 (2H, m), 3.77 (1H, d, J=2.5 Hz), 4.06 (1H, dd, J=2.5, 1.3 Hz), 4.47 (1H, ddd, J=1.3, 6.3, 7.4 Hz), 5.36—5.56 (4H, m). GC-MS (150 °C) *m/z*: 208 (M^+). IR ($CHCl_3$) ν: 970, 1182, 1785 cm^{-1}. $[\alpha]_D^{22}$ +29.7° (c=0.175, $CHCl_3$).

(2*R*,3*R*,4*R*)-2,3-Epoxy-4-hydroxy-7,10-(*E*,*E*)-dodecadienamide (21a)[6,7d,e] **and (2*R*,3*R*,4*S*)-2,3-Epoxy-4-hydroxy-7,10-(*E*,*E*)-dodecadienamide (21b)**[7a,b] A solution of the lactone **20a** (28 mg) in MeOH (0.4 ml) was cooled to 0 °C and treated with 25% ammonia (0.1 ml). After 30 min of stirring, the product was extracted with CH_2Cl_2, and the CH_2Cl_2 solution was dried over Na_2SO_4. The CH_2Cl_2 was removed to give the amide **21a** as a white powder, which was purified by silica gel column chromatography (5% MeOH in CH_2Cl_2) (27.5 mg, 92% yield). Compound **20b** (4.5 mg) was treated with ammonia under similar conditions to give **21b** (2.7 mg, 58% yield). **21a**: ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, d, J=4.5 Hz), 1.76 (2H, m), 2.20 (2H, m), 2.50 (1H, br s), 2.67 (2H, m), 3.14 (1H, dd, J=4.6, 8.2 Hz), 3.49 (1H, ddd, J=5.2, 8.0, 8.2 Hz), 3.55 (1H, d, J=4.6 Hz), 5.42 (4H, m), 5.78 (1H, br s), 6.14 (1H, br s). EI-MS *m/z*: 225 (M^+), 208 (M−17), 207 ($M-H_2O$), 181 ($M-CONH_2$), 163 ($181-H_2O$). IR ($CHCl_3$) ν: 970, 1573, 1691, 3400, 3520 cm^{-1}. $[\alpha]_D^{20}$ +65.0° (c=1.03, $CHCl_3$) (lit. $[\alpha]_D^{20}$ +70° (c=1.66, $CHCl_3$).[6b] **21b**: ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, d, J=4.5 Hz), 1.62—1.67 (2H, m), 2.04—2.23 (2H, m), 2.66 (2H, m), 3.20 (1H, dd, J=4.9, 8.1 Hz), 3.56 (1H, ddd, J=4.5, 8.0, 8.1 Hz), 3.58 (1H, d, J=4.9 Hz), 5.34—5.50 (5H, m), 6.16 (1H, br s).

Cerulenin (1) The amide **21a** (18 mg, 0.08 mmol) was oxidized with CrO_3–pyridine using the procedure employed for the preparation of **20a**.[7e] The reaction mixture was stirred for 80 min at room temperature, then passed through a short silica gel column. The product was purified by short silica gel column chromatography. ($Et_2O : CH_2Cl_2$ = 1 : 1) (8.1 mg, 45% yield). The recrystallization of the product from benzene gave colorless prisms, mp 93 °C (lit., 93—94 °C).[3a] Spectral data of the synthetic **1** were identical with those of natural cerulenin.[3a] **1**: ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, br d, J=4.8 Hz), 2.32 (2H, br dt, J=7.0, 7.0 Hz), 2.58—2.74 (4H, m), 3.73 (1H, d, J=5.4 Hz), 3.87 (1H, d, J=5.4 Hz), 5.32—5.51 (5H, m), 6.28 (1H, m). EI-MS *m/z*: 223 (M^+), 179 ($M-CONH_2$). IR ($CHCl_3$) ν: 970, 1580, 1695, 1724, 3390, 3510 cm^{-1}. $[\alpha]_D^{20}$ −0.1° (c=0.99, $CHCl_3$) (lit., $[\alpha]_D^{20}$ −12° (c=1, $CHCl_3$),[3a] $[\alpha]_D$ +56.6° (MeOH, after 100 min)).[3a]

(*E*)-1-Iodo-3-pentene (25d)[26a] The iodide **25a** was obtained by the literature method.[26a] A mixture of Mg turnings (0.57 g, 23.5 mmol), I_2 (2.92 g, 11.5 mmol) and anhydrous Et_2O (15 ml) was stirred overnight at room temperature. The solution over Mg, which contained MgI_2,[26b] was transferred to another flask. To this solution, cyclopropyl methyl carbinol (1 g, 11.6 mmol) in Et_2O (4.5 ml) was added dropwise at room temperature and the mixture was heated at 34 °C for 70 h. The reaction was followed by GC (1.5% OV-17, 1.5 m, 70—90 °C (2 °C/min), retention time of the carbinol, 0.8 min, **25d**, 1.9 min). The reaction product was extracted with Et_2O, and the Et_2O solution was washed successively with 1% $Na_2S_2O_3$ and brine, then dried over Na_2SO_4. The solvent was removed, and the iodide was purified by silica gel column chromatography (*n*-pentane). Yield: 2.76 g (61%). The stereochemistry of **25d** was determined from the olefinic proton signal in the ^{1}H-NMR spectrum (E : Z = 9 : 1). The mixture was used for further reactions. **25d**: ^{1}H-NMR ($CDCl_3$) δ: 1.67 (3H, dq, J=6.4, 1.2 Hz), 2.55 (2H, br dt, J=*ca.* 7.0 7.0 Hz), 3.14 (2H, t, J=7.2 Hz), 5.38 (1H, dtq, J=15.0, 6.8, 1.2 Hz), 5.55 (1H, dqt, J=15.0, 6.4, 1.2 Hz). GC-MS (50 °C) *m/z*: 196 (M^+), 155 (CH_2CH_2I), 141 (CH_2I), 127 (I).

(*E*)-3-Hexen-1-ol (24e)[27] To a solution of LAH (377 mg, 9.9 mmol) in anhydrous Et_2O (7 ml), 3-hexenoic acid (1.08 g, 9.5 mmol) in Et_2O (2.5 ml) was added dropwise at 0 °C. After 1 h, the ice-water bath was removed and stirring was continued for 2 h. After the addition of a small amount of saturated aq. Na_2SO_4, the Et_2O solution was filtered and the Et_2O was removed. The alcohol **24e** was purified by silica gel column chromatography (CH_2Cl_2), (0.58 g, 61% yield). **24e**: ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.5 Hz), 2.04 (2H, br dq, J=7.0, 7.5 Hz), 2.26 (2H, br dt, J=6.3, 6.2 Hz), 3.63 (2H, t, J=6.2 Hz), 5.38 (1H, dtt, J=15.5, 7.0, 1.5 Hz), 5.61 (1H, dtt, J=15.5, 6.3, 1.2 Hz). GC-MS (70 °C) *m/z*: 100 (M^+), 82 ($M-H_2O$), 69 ($M-CH_2OH$), 67 ($M-H_2O-CH_3$).

(3*E*)-3,6-Heptadien-1-ol (24f)[29] A solution of allylbromide (**23f**) (3.0 g, 25 mmol), $Pd(dba)_2$ (430 mg, 0.75 mmol), PPh_3 (390 mg, 1.5 mmol) and **9** (11 g, 25 mmol) in THF was stirred for 25 h at 50 °C.[28] The solvent was evaporated off, and the residue was chromatographed on a silica gel column

to obtain **24f**-THP ether (*n*-hexane : Et_2O = 9 : 1). The crude THP-ether (4.4 g) was dissolved in MeOH (20 ml) and refluxed with Amberlyst 15 (0.2 g) for 3 h. After cooling of the mixture, Amberlyst was removed by filtration, and the filtrate was evaporated. The residue was applied to a 3—5% $AgNO_3$-impregnated silica gel column (2.5% MeOH–CH_2Cl_2), but the stereoisomers could not be separated under these conditions. Distillation (120 °C (110 mmHg)) gave **24f** 0.61 g (24% from **23f**) (*E* : *Z* = 3 : 1). **24f**. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (2H, dt, *J* = 6.5, 6.5 Hz), 2.79 (2H, dd, *J* = 6.5, 6.5 Hz), 3.65 (2H, t, *J* = 6.5 Hz), 5.00 (1H, dq, *J* = 10, 1.2 Hz), 5.03 (1H, dq, *J* = 17, 1.2 Hz), 5.44 (1H, dtt, *J* = 15.5, 7.0, 1.5 Hz), 5.58 (1H, dtt, *J* = 15.5, 6.5, 1.5 Hz), 5.82 (1H, dtt, *J* = 17, 10, 6.5 Hz). GC-MS (70 °C) *m/z*: 112 (M^+), 94 ($M-H_2O$). *Z*-Isomer of **24f**: ^{1}H-NMR ($CDCl_3$) δ: 2.35 (2H, dt, *J* = 7.0, 7.0 Hz), 2.85 (2H, dd, *J* = 6.6, 6.5 Hz), 4.99 (1H, dq, *J* = 10, 1.5 Hz), 5.05 (1H, dq, *J* = 17, 1.4 Hz), 5.48 (1H, dtt, *J* = 11, 7.0, 1.5 Hz), 5.60 (1H, dtt, *J* = 11, 7.5, 1.4 Hz), 5.82 (1H, dtt, *J* = 17, 10, 6.5 Hz).

(*E*)-2-Decen-1-ol (22i)[31] A mixture of octylaldehyde (7.7 g, 60 mmol) and Ph_3P=CHCOOEt (20.9 g, 60 mmol) in dry CH_2Cl_2 (150 ml) was stirred for 2 h at room temperature and then the solvent was removed with a rotary evaporator. The precipitated crystals were filtered off with a small amount of *n*-pentane and all the solvent was removed *in vacuo*. Residual oil (*ca.* 17 g) was chromatographed on silica gel (2% EtOAc in *n*-hexane) to give ethyl 2-decanoate[32] as a colorless oil (11 g, 95% yield). The ester (4.5 g) in anhydrous Et_2O (100 ml) was reduced with DIBAH (1.2 eq) in *n*-hexane. After work-up with 1 N HCl, the solution was washed successively with saturated $NaHCO_3$ and brine, then dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (*n*-hexane : AcOEt = 5 : 1) to give **22i** (3.1 g, 87% yield). **22i**: ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, *J* = 7.0 Hz), 1.2—1.4 (10H, m), 2.04 (2H, dt, *J* = 7.0, 7.0 Hz), 4.09 (2H, br s), 5.63 (1H, dt, *J* = 15.5, 6.0 Hz), 5.70 (1H, dt, *J* = 15.5, 6.0 Hz). GC-MS (180 °C): 156 (M^+), 138 ($M-H_2O$).

(*E*)-1-Bromo-2-hexane (23g) and Its Analogs 23h and 23i (*E*)-2-Hexenol (**22g**) (2.4 g, 23.6 mmol) in dry ether (25 ml) was added to a solution of PBr_3 (2.4 g, 8.8 mmol) in dry ether (25 ml), and the mixture was stirred overnight at room temperature. Water (2 ml) was added, and the mixture was neutralized with $NaHCO_3$. The ether solution was washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The oily product (3.6 g, 90% yield) was used as such in subsequent experiments. Similarly, the other bromides (**23h** and **23i**) were synthesized from the allylalcohols **22h**[30] and **22i** in 73% and 70% yields, respectively. The alcohol **22h** was obtained by LAH reduction of 2-octenal in 71% yield (96—105 °C (25 mmHg)). **23g**: ^{1}H-NMR ($CDCl_3$) δ: 0.905 (3H, t, *J* = 7.3 Hz), 1.41 (2H, tq, *J* = 7.3, 7.3 Hz), 2.05 (2H, dt, *J* = 7.0, 7.0 Hz), 3.96 (2H, d, *J* = 7.0 Hz), 5.69 (1H, dt, *J* = 15, 7.0 Hz), 5.77 (1H, dt, *J* = 15, 6.5 Hz). GC-MS (50 °C) *m/z*: 164 (M^+), 162. **23h**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, *J* = 6.7 Hz), 1.24—1.42 (6H, m), 2.05 (2H, dt, *J* = 7.0, 7.0 Hz), 3.95 (2H, d, *J* = 7.0 Hz), 5.68 (1H, dt, *J* = 15.5, 7.0 Hz), 5.78 (1H, dt, *J* = 15.5, 7.0 Hz). **23i**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, *J* = 7 Hz), 1.3—1.4 (10H, m), 2.06 (2H, dt, *J* = 7.0, 7.0 Hz), 3.95 (2H, d, *J* = 7.0 Hz), 5.69 (1H, m), 5.76 (1H, m). EI-MS *m/z*: 220, 218 (M^+), 83.

(3*E*,6*E*)-3,6-Dodecadien-1-ol (24h)[29] **and Analogs 24g and 24i** *n*-BuLi (1.3 M in *n*-hexane, 28.5 ml, 37 mmol) was added to a solution of **9** (16.4 g, 37 mmol) in THF (70 ml) at −78 °C and stirred for 1 h. To this mixture, the allyl bromide **23h** (5.9 g, 31 mmol) in THF (15 ml) was added and stirring was continued at −78 °C.[10c] After 80 min, the dry ice–acetone bath was removed and the solution was warmed to room temperature. The reaction was quenched with saturated Na_2SO_4 solution and the Na_2SO_4 cake formed was removed by filtration. The THF solution was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residual oil was chromatographed on silica gel (*n*-hexane : CH_2Cl_2 = 1 : 1), to give the crude THP-ether (5.3 g). The THP-ether (4.8 g) was treated with Amberlyst 15 (1.5 g) in MeOH (70 ml) overnight at room temperature. The Amberlyst was removed by filtration, the MeOH was removed *in vacuo*, and the residual oil was chromatographed on 5% $AgNO_3$-impregnated silica gel (3% MeOH in CH_2Cl_2). The dienol **24h**, 1.3 g (26% yield from **23h**), was obtained as an oil. In a similar manner, analogs **24g** and **24i** were obtained from **23g** and **23i** in 43% and 26% yields, respectively. **24h**: ^{1}H-NMR ($CDCl_3$) δ: 0.885 (3H, t, *J* = 7.0 Hz), 1.23—1.38 (6H, m), 1.99 (2H, br dt, *J* = *ca.* 6.8, 6.8 Hz), 2.28 (2H, br dt, *J* = *ca.* 6.3, 6.3 Hz), 2.72 (2H, br dd, *J* = *ca.* 6.0, 6.0 Hz), 3.64 (2H, t, *J* = 6.2 Hz), 5.37—5.47 (3H, m), 5.54 (1H, m). Irradiation at δ 1.99 and 2.72 resulted in signals at δ 5.40 (1H, d, *J* = 15.5 Hz), 5.41 (1H, dt, *J* = 15, 6.0 Hz), 5.44 (1H, d, *J* = 15.5 Hz), 5.58 (1H, d, *J* = 15 Hz). EI-MS *m/z*: 182 (M^+), 164 ($M-H_2O$). **24g**: ^{1}H-NMR ($CDCl_3$) δ: 0.890 (3H, t, *J* = 7.3 Hz), 1.38 (2H, tq, *J* = 7.3, 7.3 Hz), 1.98 (2H, br dt, *J* = *ca.* 6.5, 6.5 Hz), 2.28 (2H, br dt, *J* = *ca.* 6.5, 6.5 Hz), 2.72 (2H, br dd, *J* = *ca.* 5.5, 5.5 Hz), 3.64 (2H, br t, *J* = 6.0 Hz), 5.41 (3H, m), 5.56 (1H, m). Irradiation at δ 1.98 and 2.72 resulted in signals at δ 5.39 (1H, d, *J* = 15 Hz), 5.41 (1H, dt, *J* = 15, 6.0 Hz), 5.44 (1H, d, *J* = 15 Hz) and 5.57 (1H, d, *J* = 15 Hz). GC-MS *m/z*: 154 (M^+), 136 ($M-H_2O$). **24i**: ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz), 1.2—1.4 (10H, m), 1.98 (2H, br dt, *J* = 6.5, 6.5 Hz), 2.28 (2H, br dt, *J* = 6.5, 6.5 Hz), 2.71 (2H, br dd, *J* = 6.0, 6.0 Hz), 3.65 (2H, br t, *J* = 6.0 Hz), 5.35—5.47 (3H, m), 5.54 (1H, m); irradiation at δ 1.98 and 2.71 resulted in signals at δ 5.40 (1H, d, *J* = 15 Hz), 5.41 (1H, dt, *J* = 15, 6.0 Hz), 5.44 (1H, d, *J* = 15 Hz), 5.57 (1H, d, *J* = 15 Hz). EI-MS *m/z*: 210 (M^+), 192 ($M-H_2O$).

1-Iodo-3-hexene (25e) and Its Analogs 25f—i The iodides **25e—g** and **25i** were synthesized from the corresponding alcohols **24e—g** and **24i** by similar procedures to those used in cerulenin synthesis (**13** to **15**). The yields were **25e** (65%), **25f** (59%), **25g** (56%), **25i** (65%). The iodide **25h** was obtained by heating the mesylate of **24h** (1.25 g, 4.8 mmol) and NaI (2.16 g, 14.4 mmol) in dry acetone (20 ml) at 50 °C for 3 h. The product was extracted with *n*-pentane, and chromatographed on silica gel (*n*-pentane); the iodide was obtained in earlier fractions. **25h**, 1.07 g (76% yield). **25e**: GC-MS (75 °C) *m/z*: 210 (M^+), 155 (C_2H_4I), 141 (CH_2I), 127 (I), 83 (M−I). **25f**: GC-MS (80 °C) *m/z*: 222 (M^+), 155 (C_2H_4I), 141 (CH_2I), 127 (I). **25g**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, *J* = 7 Hz), 1.39 (2H, tq, *J* = 7.0, 7.0 Hz), 1.98 (2H, dt, *J* = 7.0, 7.0 Hz), 2.57 (2H, dt, *J* = 7.0, 7.0 Hz), 2.69 (2H, br dd, *J* = 6.5, 6.5 Hz), 3.16 (2H, t, *J* = 7.0 Hz), 5.3—5.6 (4H, m). **25h**: ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 7.1 Hz), 1.23—1.39 (6H, m), 1.99 (2H, br dt, *J* = *ca.* 6.8, 6.8 Hz), 2.56 (2H, ddt, *J* = 1.2, 6.8, 6.8 Hz), 2.69 (2H, dd, *J* = 6.3, 6.3 Hz), 3.15 (2H, t, *J* = 7.2 Hz), 5.34—5.48 (3H, m), 5.50—5.57 (1H, m). **25i**: EI-MS *m/z*: 320 (M^+), 222 ($M-C_7H_{14}$), 193 (M−I).

Synthesis of Cerulenin Analogs 32a—i and 3 Starting from the corresponding iodides **25a—j**, cerulenin analogs **32a—i** and **3** were synthesized by a similar procedure to that used for cerulenin. Reaction conditions, yields and spectral data are described below.

(2*R*,3*S*)-2,3-Epoxy-4-oxo-hexanamide (32a) Starting from iodoethane (**25a**), **27a** was obtained in 75% yield. In the case of acid hydrolysis, the amount of solvent was reduced to 1/3 and the product **29a** was extracted with ether several times (44% yield). After **29a** was oxidized with CrO_3–pyridine, the reaction mixture was passed through a silica gel column and, without washing with water, the pyridine-containing product was treated with ammonia to give **31a**. CrO_3–pyridine oxidation of **31a** gave **32a** as a white solid (yield from **29a**, 26%). **27a**: ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, *J* = 7.0 Hz), 1.25 (2H, t, *J* = 7.0 Hz), 1.28 (2H, t, *J* = 7.0 Hz), 1.65—1.8 (2H, m), 2.77 (1H, s), 2.92 (1H, dd, *J* = 8.0, 4.5 Hz), 3.14 (1H, dd, *J* = 6.0, 4.5 Hz), 3.41 (1H, m), 3.6—3.85 (4H, m), 4.55 (1H, d, *J* = 6.0 Hz). **29a**: ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, *J* = 7 Hz), 1.55—1.7 (2H, m), 3.05 (1H, d, *J* = 4.0 Hz), 3.67 (1H, d, *J* = 2.5 Hz), 3.73 (1H, d, *J* = 2.5 Hz), 4.03 (1H, dd, *J* = 7.5, 6.8 Hz), 5.43 (1H, d, *J* = 4 Hz). **32a**: ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, *J* = 7.5 Hz), 2.59 (1H, dq, *J* = 18, 7.0 Hz), 2.66 (1H, dq, *J* = 18, 7.0 Hz), 3.73 (1H, d, *J* = 5.3 Hz), 3.89 (1H, d, *J* = 5.3 Hz), 5.39 (1H, br s), 6.30 (1H, br s). HR-MS *m/z*: 144.0654, Calcd for $C_6H_{10}NO_3$ (M+H), 144.0661.

(2*R*,3*S*)-2,3-Epoxy-4-oxo-heptanamide (32b) 1-Iodopropane (**25b**) was treated with *tert*-BuLi, and the product **26b** was allowed to react with **8** to give the epoxyalcohol **27b** (90% yield). Epimers were formed in a ratio of 4 : 1. The major 4*R*-alcohol was transformed to **32b**. The yields of intermediates were **29b** (61%), **30b** (60%), **31b** (76%) and **32b** (63%). **27b**: ^{1}H-NMR ($CDCl_3$) δ: 0.965 (3H, t, *J* = 7.4 Hz), 1.24 (3H, t, *J* = 7.0 Hz), 1.27 (3H, t, *J* = 7.0 Hz), 1.4—1.6 (2H, m), 1.66 (2H, br ddd, *J* = 8.0, 8.0, 6.5 Hz), 2.76 (1H, s), 2.90 (1H, dd, *J* = 8.0, 4.2 Hz), 3.14 (1H, dd, *J* = 6.0, 4.2 Hz), 3.50 (1H, ddd, *J* = 7.0, 7.0, 2.0 Hz), 3.58—3.87 (4H, m), 4.55 (1H, d, *J* = 6.0 Hz). **29b**: ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, *J* = 7.2 Hz), 1.4—1.6 (4H, m), 2.87 (1H, br s), 3.66 (1H, d, *J* = 2.6 Hz), 3.72 (1H, d, *J* = 2.6 Hz), 4.12 (1H, dd, *J* = 8, 5.5 Hz), 5.43 (1H, d, *J* = 4.0 Hz). **30b**: ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, *J* = 7.4 Hz), 1.43—1.6 (2H, m), 1.64—1.72 (2H, m), 3.77 (1H, d, *J* = 2.5 Hz), 3.97 (1H, d, *J* = 2.5 Hz), 4.58 (1H, dd, *J* = 6.5, 6.0 Hz). **31b**: ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, *J* = 7.5 Hz), 1.46 (1H, m), 1.55 (1H, m), 1.68 (2H, m), 2.30 (1H, br s), 3.13 (1H, dd, *J* = 8.0, 4.5 Hz), 3.48 (1H, br dd, *J* = *ca.* 7.5, 8.0 Hz), 3.56 (1H, d, *J* = 4.5 Hz), 5.67 (1H, br s), 6.15 (1H, br s). FAB-MS *m/z*: 182 (M+Na), 160 (M+H). **32b**: ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, *J* = 7.5 Hz), 1.65 (2H, m), 2.57 (2H, m), 3.73 (1H, d, *J* = 5.0 Hz), 3.88 (1H, d, *J* = 5.0 Hz), 5.45 (1H, br s), 6.32 (1H, br s). FAB-MS *m/z*: 180 (M+Na), 158 (M+H); HR-MS *m/z*: 158.0813. Calcd for $C_7H_{12}NO_3$ (M+H), 158.0817.

(2*R*,3*S*)-2,3-Epoxy-4-oxo-7-octenamide (32c) A solution of 4-bromobutene (**25c**) (730 mg, 5.4 mmol) in anhydrous ether (8 ml) was added to Mg (260 mg, 10.8 mmol) in ether (1 ml), and the mixture was refluxed for

40 min. The Grignard reagent thus obtained was added to a solution of **8** (500 mg, 3 mmol) in ether (15 ml) at −78 °C. The reaction mixture was stirred for 1 h, and warmed to room temperature. To the solution, saturated NH_4Cl was added, and after filtration and drying over $MgSO_4$, the ether was removed *in vacuo*. The residual oil was chromatographed on a silica gel column (*n*-hexane : AcOEt = 2 : 1) to give 340 mg of **27c** (50% yield). The adduct **27c** was converted to **32c**. The yield was **29c** (35%), **31c** (12% from **29c**) and **32c** (40%). **27c**: ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 7.0 Hz), 1.27 (3H, t, J = 7.0 Hz), 1.75—1.83 (2H, m), 2.15—2.33 (2H, m), 2.74 (1H, br d, J = 1.5 Hz), 2.92 (1H, dd, J = 8.0, 4.5 Hz), 3.14 (1H, dd, J = 5.5, 4.5 Hz), 3.50 (1H, m), 3.60—3.80 (4H, m), 4.53 (1H, d, J = 5.5 Hz), 4.99 (1H, d, J = 10 Hz), 5.06 (1H, d, J = 17 Hz), 5.83 (1H, ddt, J = 17, 10, 6.5 Hz). **29c**: ^{1}H-NMR ($CDCl_3$) δ: 1.6—1.8 (2H, m), 2.25 (2H, m), 2.75 (1H, d, J = 4.0 Hz), 3.66 (1H, d, J = 2.5 Hz), 3.73 (1H, d, J = 2.5 Hz), 4.13 (1H, dd, J = 9.0, 6.0 Hz), 5.01 (1H, ddt, J = 10, 1.8, 1.8 Hz), 5.07 (1H, ddt, J = 17.5, 1.8, 1.8 Hz), 5.43 (1H, d, J = 4.0 Hz), 5.83 (1H, ddt, J = 17.5, 10, 6.8 Hz). GC-MS (100 °C) m/z: 156 (M^+), 154 (M−2), 138 (M−H_2O). **30c**: ^{1}H-NMR ($CDCl_3$) δ: 1.80 (2H, m), 2.26 (2H, m), 3.78 (1H, dd, J = 2.5, 1.0 Hz), 3.98 (1H, d, J = 2.5 Hz), 4.61 (1H, dd, J = 7.5, 6.5 Hz), 5.08 (1H, ddt, J = 10, 1.8, 1.8 Hz), 5.11 (1H, ddt, J = 18, 1.8, 1.8 Hz), 5.80 (1H, ddt, J = 18, 10, 7.0 Hz). **32c**: ^{1}H-NMR ($CDCl_3$) δ: 2.37 (2H, br dd, J = *ca.* 7.0, 7.0 Hz), 2.66 (1H, ddd, J = 17.5, 7.5, 7.5 Hz), 2.73 (1H, ddd, J = 17.5, 7.5, 7.5 Hz), 3.73 (1H, d, J = 5.0 Hz), 3.88 (1H, d, J = 5.0 Hz), 5.02 (1H, d, J = 10 Hz), 5.05 (1H, d, J = 16.5 Hz), 5.48 (1H, br s), 5.78 (1H, ddt, J = 16.5, 10, 6.5 Hz), 6.30 (1H, br s). FAB-MS m/z: 170 (M+H); HR-MS m/z: 170.0806. Calcd for $C_8H_{12}NO_3$ (M+H), 170.0817.

(*E*)(2*R*,3*S*)-2,3-Epoxy-4-oxo-7-nonenamide (32d) Starting from the iodide **25d**, the epoxyalcohol **27d** was synthesized (48% yield). Compound **27d** was converted to **29d** (36% yield), **30d** (73% yield), **31d** (74% yield), and **32d** (47% yield). Epoxide proton signals in the ^{1}H-NMR spectrum of the lactone **30d** at δ 3.77, 3.97, 3.78 and 3.99 showed that **30d** contained about 13% *Z*-isomer. At the final stage, **32d** was purified by HPLC. Purified **32d** was mostly in hydroxylactam form. **27d**: GC-MS (130 °C) m/z: 199 (M−OEt), 198 (M−EtOH), 180 (M−EtOH−H_2O). **29d**: GC-MS (120 °C) m/z: 170 (M^+), 168 (M−2), 152 (M−H_2O). **30d**: ^{1}H-NMR ($CDCl_3$) δ: 1.67 (3H, dq, J = 6.0, 1.2 Hz), 1.74 (2H, m), 2.18 (2H, m), 3.77 (1H, dd, J = 2.5, 0.8 Hz), 3.97 (1H, d, J = 2.5 Hz), 4.59 (1H, br t, J = *ca.* 6.5 Hz), 5.39 (1H, dtq, J = 15, 6.5, 1.3 Hz), 5.52 (1H, dqt, J = 15, 6.0, 1.3 Hz). GC-MS (120 °C) m/z: 168 (M^+), 152 (M−16), 150 (M−H_2O). **31d**: EI-MS m/z: 185 (M^+), 168 (M−17), 167 (M−H_2O), 123 (M−$CONH_2$−H_2O); FAB-MS m/z: 186 (M+H). HR-MS m/z: 186.1119, Calcd for $C_9H_{16}NO_3$ (M+H), 186.1130. **32d**: ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, dd, J = 6.1, 1.3 Hz), 1.82 (1H, ddd, J = 13.6, 8.9, 7.1 Hz), 1.91 (1H, ddd, J = 13.6, 7.8, 7.1 Hz), 2.24 (2H, br ddd, J = 8.9, 7.8, 6.4 Hz), 3.59 (1H, dd, J = 2.5, 2.5 Hz), 3.82 (1H, dd, J = 2.5, 2.5 Hz), 4.28 (1H, s), 5.45 (1H, dtq, J = 15, 6.4, 1.1 Hz), 5.54 (1H, dqt, J = 15, 6.4, 1.0 Hz), 6.77 (1H, br s). Irradiation at 6.77 (NH) resulted 3.59 (1H, d, J = 2.5 Hz), 3.82 (1H, d, J = 2.5 Hz). EI-MS m/z: 183 (M^+), 165 (M−H_2O), 139 (M−$CONH_2$).

(*E*)(2*R*,3*S*)-2,3-Epoxy-4-oxo-7-decenamide (32e) Lithiation of the iodide **25e** followed by reaction with **8** gave **27e** in 74% yield. The alcohol **27e** was converted to **32e** through a similar procedure to that used in cerulenin synthesis. The yields of reaction products were **29e** (30%), **30e** (67%), **31e** (82%) and **32e** (57%). The cerulenin analog **32e** was purified by HPLC. The fractionated **32e** was a mixture of two hydrolactams. **27e**: GC-MS (140 °C) m/z: 212 (M−EtOH), 194 (M−EtOH−H_2O), 183 (M−EtOH−Et). **29e**: GC-MS (125 °C) m/z: 184 (M^+), 182 (M−2), 166 (M−H_2O). **30e** ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J = 7.5 Hz), 1.75 (2H, dt, J = 7.0, 7.0 Hz), 2.02 (2H, m), 2.19 (2H, m), 3.77 (1H, d, J = 2.5 Hz), 3.97 (1H, d, J = 2.5 Hz), 4.60 (1H, t, J = 6.5 Hz), 5.37 (1H, dt, J = 15, 6.5 Hz), 5.55 (1H, dt, J = 15, 6.5 Hz). GC-MS (125 °C) m/z: 182 (M^+), 166 (M−16), 164 (M−H_2O). **31e**: EI-MS m/z: 199 (M^+), 182 (M−OH), 181 (M−H_2O), 137 (M−H_2O−$CONH_2$). **32e**: ^{1}H-NMR ($CDCl_3$) δ: (major) 0.98 (3H, t, J = 7.5 Hz), 1.84 (1H, ddd, J = 14, 9.0, 7.0 Hz), 1.93 (1H, ddd, J = 14, 9.0, 7.0 Hz), 2.02 (2H, br dq, J = *ca.* 6.5, 7.5 Hz), 2.27 (2H, br ddd, J = 9.0, 7.0, 6.5 Hz), 3.38 (1H, s), 3.60 (1H, dd, J = 2.5, 2.5 Hz), 3.83 (1H, dd, J = 2.5, 2.5 Hz), 5.45 (1H, dtt, J = 15, 6.5, 1.0 Hz), 5.59 (1H, dtt, J = 15, 6.5, 1.0 Hz), 6.23 (1H, br s); (minor) 0.97 (3H, t, J = 7.5 Hz), 3.08 (1H, s), 3.64 (1H, dd, J = 2.5, 2.5 Hz), 3.82 (1H, dd, J = 2.5, 2.5 Hz), 5.40 (1H, dtt, J = 15, 6.5, 1.0 Hz), 5.54 (1H, dtt, J = 15, 6.5, 1.0 Hz), 5.71 (1H, br s). EI-MS m/z: 197 (M^+), 180 (M−17), 179 (M−H_2O), 153 (M−$CONH_2$). FAB-MS m/z: 198 (M+H). HR-MS m/z: 198.1122, Calcd for $C_{10}H_{16}NO_3$ (M+H), 198.1130.

(7*E*)(2*R*,3*S*)-2,3-Epoxy-4-oxo-7,10-undecadienamide (32f) The epoxyalcohol **27f** was prepared from the iodide **25f** (E : Z = 3 : 1) in 27% yield. Compound **27f** was converted to **32f** through a similar procedure to that used in cerulenin synthesis. The yields of the reaction products were **29f** (57%), **30f** (77%), **31f** (85%) and **32f** (70%). The stereoisomers of **32f** were separated by HPLC. The purified product was a mixture of a keto form and two hydroxylactams. **27f**: GC-MS (150 °C) m/z: 224 (M−EtOH), 206 (M−EtOH−H_2O). **29f**: GC-MS (130 °C) m/z: 194 (M−2), 178 (M−H_2O). **30f**: ^{1}H-NMR ($CDCl_3$) δ: 1.76 (2H, m), 2.23 (2H, m), 2.76 (2H, m), 3.77 (1H, dd, J = 2.5, 0.8 Hz), 3.97 (1H, d, J = 2.5 Hz), 4.59 (1H, br dd, J = 7.0, 6.0 Hz), 5.03 (2H, m), 5.44 (1H, m), 5.50 (1H, m), 5.81 (1H, m). GC-MS (130 °C) m/z: 194 (M^+), 178 (M−16), 176 (M−H_2O). **31f**: EI-MS m/z: 211 (M^+), 194 (M−OH), 193 (M−H_2O), 149 (M−$CONH_2$−H_2O). **32f**: ^{1}H-NMR ($CDCl_3$) δ: (ketoamide) 2.33 (2H, br dt, J = 7.0, 7.0 Hz), 2.63 (1H, dt, J = 17, 7.0 Hz), 2.70 (1H, dt, J = 17, 7.0 Hz), 2.75 (2H, br dd, J = 6.0, 6.0 Hz), 3.73 (1H, d, J = 5.0 Hz), 3.87 (1H, d, J = 5.0 Hz), 5.02 (2H, m), 5.40 (1H, dtt, J = 15, 6.0, 1.5 Hz), 5.49 (1H, dt, J = 15, 6.0 Hz), 5.79 (1H, ddt, J = 17, 10, 6.0 Hz), 6.09 (1H, br s), 6.30 (1H, br s); (major hydroxylactam) 1.88 (1H, dt, J = 14, 7.5 Hz), 1.97 (1H, dt, J = 14, 7.5 Hz), 3.61 (1H, dd, J = 2.5, 2.5 Hz), 3.82 (1H, dd, J = 2.5, 2.5 Hz), 5.49 (1H, dt, J = 15, 6.0 Hz), 5.57 (1H, dt, J = 16, 6.0 Hz), 5.81 (1H, ddt, J = 17, 10, 6.0 Hz); (minor hydroxylactam) 3.64 (1H, dd, J = 2.5, 2.5 Hz), 3.81 (1H, dd, J = 2.5, 2.5 Hz). EI-MS m/z: 209 (M^+), 192 (M−17), 191 (M−H_2O), 165 (M−$CONH_2$). HR-MS m/z: 210.1111, Calcd for $C_{11}H_{16}NO_3$ (M+H), 210.1130.

(7*E*,10*E*)(2*R*,3*S*)-2,3-Epoxy-4-oxo-7,10-tetradecadienamide (32g) The iodide **25g** was lithiated and reacted with **8** to give **27g** in 55% yield (4*R* : 4*S* = 3 : 1). Compound **27g** was converted to **32g** by hydrolysis (**29g** 53% yield), Swern oxidation (**30**, 57%), ammonolysis (**31**, 64%) and oxidation with CrO_3–pyridine (**32**, 59%). The analog **32g** was purified on a short silica gel column. **27g**: ^{1}H-NMR ($CDCl_3$) δ: (major) 0.87 (3H, t, J = 7.0 Hz), 1.20—1.28 (6H, m), 1.37 (2H, dq, J = 7.0, 7.0 Hz), 1.75 (2H, m), 1.97 (2H, m), 2.16 (1H, m), 2.23 (1H, m), 2.68 (2H, m), 2.71 (1H, br d, J = 2.0 Hz), 2.91 (1H, dd, J = 8.0, 4.3 Hz), 3.14 (1H, dd, J = 5.6, 4.3 Hz), 3.50 (1H, m), 3.58—3.83 (4H, m), 4.53 (1H, d, J = 5.6 Hz), 5.4 (2H, m), 5.46 (2H, m). EI-MS m/z: 312 (M^+), 279 (M−CH_3−H_2O), 266 (M−EtOH), 220 (M−2×EtOH). **29g**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.3 Hz), 1.3—1.4 (2H, m), 1.57—1.8 (2H, m), 1.97 (2H, m), 2.05—2.25 (2H, m), 2.68 (2H, m), 3.66 (1H, d, J = 2.5 Hz), 3.72 (1H, d, J = 2.5 Hz), 4.12 (1H, dd, J = 8.0, 5.5 Hz), 5.4—5.55 (5H, m). EI-MS m/z: 238 (M^+), 220 (M−H_2O). **30g**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.3 Hz), 1.38 (2H, m), 1.72—1.79 (2H, m), 1.98 (2H, m), 2.13—2.27 (2H, m), 2.69 (2H, m), 3.77 (1H, dd, J = 2.5, 0.5 Hz), 3.97 (1H, d, J = 2.5 Hz), 4.59 (1H, br dd, J = 7.0, 6.0 Hz), 5.35—5.54 (4H, m). EI-MS m/z: 236 (M^+). **31g**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.8 Hz), 1.37 (2H, m), 1.73—1.80 (2H, m), 1.97 (2H, m), 2.16 (1H, m), 2.24 (1H, m), 2.68 (2H, m), 3.14 (1H, dd, J = 6.4, 3.5 Hz), 3.49 (1H, m), 3.55 (1H, d, J = 3.5 Hz), 5.35—5.55 (4H, m), 5.68 (1H, br s), 6.13 (1H, br s). EI-MS m/z: 253 (M^+), 209 (M−$CONH_2$), 191 (M−$CONH_2$−H_2O). **32g**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.3 Hz), 1.37 (2H, m), 1.97 (2H, m), 2.32 (2H, m), 2.6—2.7 (4H, m), 3.73 (1H, d, J = 5.2 Hz), 3.87 (1H, d, J = 5.2 Hz), 5.35—5.50 (5H, m), 6.30 (1H, br s). HR-MS m/z: 252.1617, Calcd for $C_{14}H_{22}NO_3$ (M+H), 252.1600.

(7*E*,10*E*)(2*R*,3*S*)-2,3-Epoxy-4-oxo-7,10-hexadecadienamide (32h) The analog **32h** was synthesized from the idodide **25h** by the same procedure as used for the synthesis of **32g**. The yields of reaction products were as follows: **27h** (68%, 4*R* : 4*S* = 2 : 1), **29h** (45%), **30h** (48%), **31h** (68%), and **32h** (46%). Purified **32h** was a mixture of a ketoamide and a hydroxylactam. **27h**: ^{1}H-NMR ($CDCl_3$) δ: (major) 0.89 (3H, t, J = 7.1 Hz), 1.24 (3H, t, J = 7.0 Hz), 1.27 (3H, t, J = 7.0 Hz), 1.20—1.39 (6H, m), 1.74 (2H, m), 1.98 (2H, m), 2.19 (2H, m), 2.70 (2H, br dd, J = 5.0, 5.0 Hz), 2.91 (1H, dd, J = 8.0, 4.3 Hz), 3.13 (1H, dd, J = 6.0, 4.3 Hz), 3.50 (1H, m), 3.58—3.82 (4H, m), 4.53 (1H, d, J = 6.0 Hz), 5.35—5.51 (4H, m); (minor) 0.89 (3H, t, J = 7.0 Hz), 1.22 (3H, t, J = 7.0 Hz), 1.26 (3H, t, J = 7.0 Hz), 1.2—1.38 (6H, m), 1.66 (2H, m), 1.98 (2H, br dt, J = 6.8, 6.8 Hz), 2.1—2.27 (2H, m), 2.68 (2H, br t, J = 5.0 Hz), 2.99 (1H, dd, J = 7.5, 4.5 Hz), 3.19 (1H, dd, J = 6.5, 4.5 Hz), 3.53 (1H, m), 3.6—3.8 (4H, m), 4.41 (1H, d, J = 6.2 Hz), 5.35—5.5 (4H, m). **29h**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.1 Hz), 1.22—1.38 (6H, m), 1.62 (1H, m), 1.71 (1H, m), 1.99 (2H, br dt, J = 7.0, 7.0 Hz), 2.07—2.24 (2H, m), 2.68 (2H, br dd, J = *ca.* 5.5, 5.5 Hz), 3.67 (1H, d, J = 2.8 Hz), 3.72 (1H, d, J = 2.8 Hz), 4.12 (1H, m), 5.30—5.51 (5H, m). **30h**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.0 Hz), 1.22—1.38 (6H, m), 1.76 (2H, m), 1.99 (2H, dt, J = 6.5 Hz), 2.20 (2H, m), 2.69 (2H, br dd, J = 6.0, 6.0 Hz), 3.77 (1H, dd, J = 2.5, 0.5 Hz), 3.97 (1H, d, J = 2.5 Hz), 4.59 (1H, t, J = 6.5 Hz), 5.34—5.46 (3H, m), 5.48—5.54 (1H, m). **31h**: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.0 Hz), 1.22—1.38 (6H, m), 1.77 (2H, m), 1.98 (2H, dt, J = 7.0, 7.0 Hz), 2.1—2.3 (2H, m), 2.67 (2H, br dd, J = 5.5, 5.5 Hz), 2.73 (1H, br s), 3.13 (1H, dd, J = 8.2, 4.5 Hz), 3.49 (1H, m), 3.55 (1H, d, J = 4.5 Hz), 5.33—5.51 (4H, m), 5.88 (1H, br s), 6.16 (1H, br s). **32h**:

^{1}H-NMR ($CDCl_3$) δ: 0.885 (3H, t, J=7.0 Hz), 1.23—1.38 (6H, m), 1.98 (2H, m), 2.30 (2H, m), 2.60—2.72 (4H, m), 3.73 (1H, d, J=5.5 Hz), 3.87 (1H, d, J=5.5 Hz), 5.33—5.58 (4H, m), 5.97 (1H, br s), 6.29 (1H, br s). EI-MS m/z: 279 (M^+), 235 ($M-CONH_2$), 217 ($M-CONH_2-H_2O$). FAB-MS m/z: 302 (M+Na), 280 (M+H), 262 (M−OH). HR-MS m/z: 280.1884, Calcd for $C_{16}H_{26}NO_3$ (M+H), 280.1913.

(7*E*,10*E*)(2*R*,3*S*)-2,3-Epoxy-4-oxo-7,10-octadecadienamide (32i) The cerulenin analog **32i** was synthesized from the iodide **25i** by the same procedure as used for cerulenin synthesis. The yields of reaction products were as follows: **27i** (74%, 4*R*:4*S*=3.5:1), **29i** (51%), **30i** (21%), **31i** (65%) and **32i** (54%). **27i** (major): ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.4 Hz), 1.2—1.36 (10H, m), 1.24 (3H, t, J=7.0 Hz), 1.28 (3H, t, J=7.0 Hz), 1.75 (2H, m), 1.98 (2H, dt, J=6.2, 6.2 Hz), 2.12—2.27 (2H, m), 2.68 (2H, br s), 2.71 (1H, br d, J=2.0 Hz), 2.91 (1H, dd, J=7.3, 4.2 Hz), 3.14 (1H, dd, J=5.5, 4.2 Hz), 3.50 (1H, ddt, J=5.5, 2.0, 7.5 Hz), 3.6—3.8 (4H, m), 4.53 (1H, d, J=6.0 Hz), 5.36—5.50 (4H, m). EI-MS m/z: 322 (M−EtOH), 276 (M−2×EtOH); (minor): ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz), 1.22 (3H, t, J=7.0 Hz), 1.26 (3H, t, J=7.0 Hz), 1.2—1.35 (10H, m), 1.6—1.7 (2H, m), 1.98 (2H, dt, J=5.5, 5.5 Hz), 2.1—2.26 (2H, m), 2.68 (2H, br t, J=5.5 Hz), 2.99 (1H, dd, J=7.4, 4.5 Hz), 3.19 (1H, dd, J=6.2, 4.5 Hz), 3.53 (1H, m), 3.6—3.8 (4H, m), 4.41 (1H, d, J=6.5 Hz), 5.35—5.51 (4H, m). EI-MS m/z: 322 (M−EtOH), 276 (M−2×EtOH). **29i**: EI-MS m/z: 294 (M^+), 276 ($M-H_2O$). **30i**: ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz), 1.2—1.35 (8H, m), 1.46—1.56 (2H, m), 1.76 (2H, m), 1.99 (2H, m), 2.19 (2H, m), 2.69 (2H, m), 3.77 (1H, dd, J=2.5, 0.5 Hz), 3.97 (1H, d, J=2.5 Hz), 4.59 (1H, dd, J=6.5, 6.5 Hz), 5.35—5.50 (4H, m). EI-MS m/z: 292 (M^+). **32i**: ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz), 1.2—1.38 (10H, m), 1.98 (2H, m), 2.32 (2H, m), 2.63—2.70 (4H, m), 3.73 (1H, d, J=5.5 Hz), 3.87 (1H, d, J=5.5 Hz), 5.33—5.50 (5H, m), 6.27 (1H, br s). FAB-MS m/z: 330 (M+Na), 308 (M+H), 290 (M−OH). HR-MS m/z: 308.2218, Calcd for $C_{18}H_{30}NO_3$ (M+H), 308.2226.

(2*R*,3*S*)-2,3-Epoxy-4-oxo-dodecanamide (Tetrahydrocerulenin, 3)[23,25] Octyllithium, derived from the iodide **25j**, was added to **8** to afford the epoxy alcohol **27j** (41% yield, 4*R*:4*S*=5:1). Compound **27j** was transformed to **32j** by the same procedure as used in the synthesis of **32g**. The yields of the reaction products were as follows: **29j** (58%), **30j** (60%), **31j** (89%) and **3** (46%). **27j**: ^{1}H-NMR ($CDCl_3$) δ: (major) 0.88 (3H, t, J=7.0 Hz), 1.24 (3H, t, J=7.0 Hz), 1.27 (3H, t, J=7.0 Hz), 1.22—1.35 (10H, m), 1.35—1.55 (2H, m), 1.65—1.7 (2H, m), 2.72 (1H, d, J=2.0 Hz), 2.90 (1H, dd, J=8.0, 4.5 Hz), 3.13 (1H, dd, J=6.0, 4.5 Hz), 3.48 (1H, m), 3.58—3.83 (4H, m), 4.53 (1H, d, J=6.0 Hz). EI-MS m/z: 242 (M−EtOH), 197 (M−EtOH−OEt). FAB-MS m/z: 289 (M+H), 287 (M−H), 271 (M−OH). **29j**: FAB-MS m/z: 215 (M+H), 213 (M−H), 197 (M−OH). **30j**: FAB-MS m/z: 313 (M+H). **31j**: FAB-MS m/z: 230 (M+H). **3**: ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.0 Hz), 1.20—1.32 (10H, m), 1.61 (2H, m), 2.55 (1H, dt, J=17, 7.5 Hz), 2.61 (1H, dt, J=17, 7.5 Hz), 3.73 (1H, d, J=5.5 Hz), 3.87 (1H, d, J=5.5 Hz), 5.38 (1H, br s), 6.30 (1H, br s). FAB-MS m/z: 250 (M+Na), 228 (M+H). HR-MS m/z: 228.1618, Calcd for $C_{12}H_{22}NO_3$ (M+H), 228.1600.

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