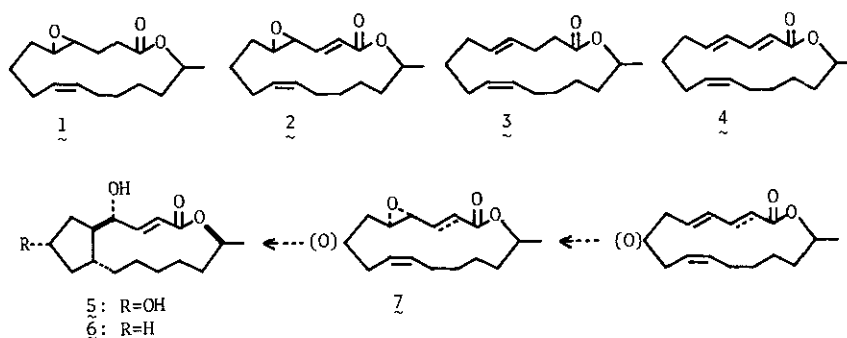


SYNTHESIS OF 9-HEXADECEN-15-OLIDES; HYPOTHETICAL INTERMEDIATES
IN THE BIOSYNTHESIS OF BREFELDIN A

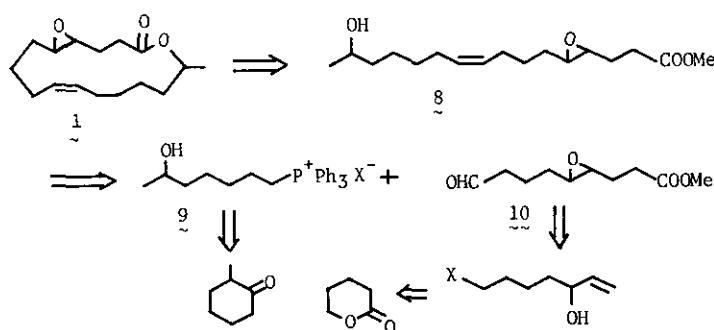
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Abstract--- Four types of lactones 1-4 which might be biosynthetic intermediates of brefeldin A have been synthesized. In the course of their synthesis, it was found that coupling of a hydroxy phosphonium salt and a carbomethoxy-aldehyde gave a macrocyclic lactone in onepot probably by a sequential reaction in which intramolecular Wittig condensation followed transesterification.

Recent progress in the biosynthetic investigations¹ on macrolide antibiotics has not only elucidated their carbon chain assembly from acetates, malonates and their homologues, but it has enabled to uncover their biogenetic pathways such as introductory steps of oxygen functions. The mode of biosynthesis of macrolide antibiotic brefeldin A (5) which has an alicyclic ring has been of interest^{1,2} because of its unique structure resembling that of the prostanoid fatty acids. In spite of their structural similarity, however, Hutchinson et al.³ have proved that two oxygens of brefeldin A, 4- and 7-hydroxyl, originate from two different oxygen molecules which is not the case with prostanoids. Although their result does not contradict the possibility of the contribution of those oxygens to the cyclopentanol ring formation in the biosynthetic course of brefeldin A, Hutchinson et al.³ have proposed a biogenetic hypothesis in which 4-oxygen plays an important part. (Scheme 1) Since we have demonstrated that brefeldin C⁴ (6) is incorporated into brefeldin A in *Eupenicillium brefeldianum* at a high incorporation ratio (99.5%), which indicates that 7-oxygen is introduced after the cyclopentane ring closure in the course of brefeldin A biosynthesis, we have been interested in the possibility of 4-oxygen's contribution to the cyclopentane ring formation. If Hutchinson's proposal were true, chemically synthesized epoxy lactone 7 could be converted to brefeldin A or its analogue by fungi or by enzymes. In this paper, we report on our synthesis of four types of lactones 1-4 related to the Hutchinson's lactone 7. We have omitted the 7-oxygen function for the lactones being studied, because we know



Scheme 1



Scheme 2

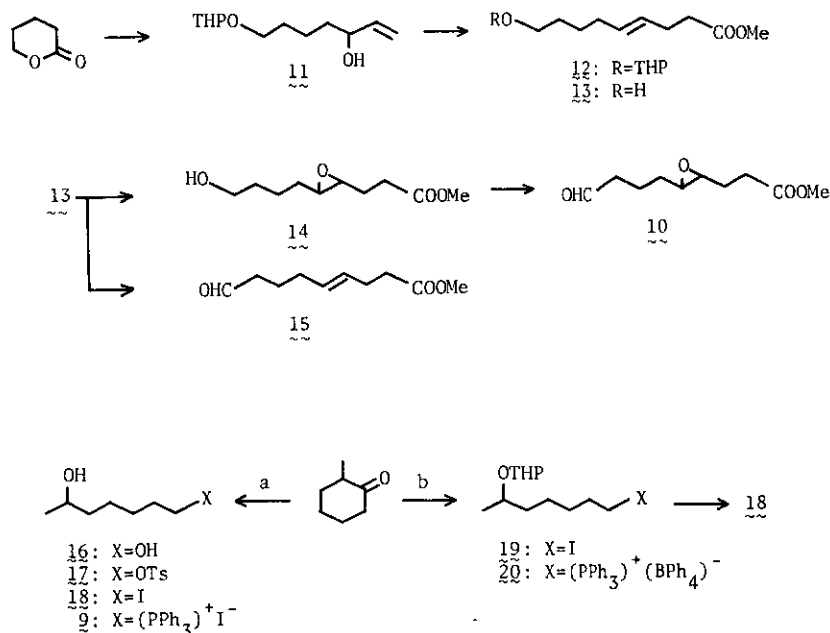
that 7-hydroxyl is introduced after the cyclopentane ring formation, as mentioned above.

Synthetic approach.

Our essential plan for the synthesis of lactones $\underline{1-4}$ is to use facile reaction. Thus we planned first to synthesize a hydroxy ester $\underline{8}$ by Wittig reaction using a C_7 -phosponium salt which has an oxygen function at C-6 ($\underline{9}$) and an 8-carbomethoxyoctanal synthon ($\underline{10}$). Both synthons $\underline{9}$ and $\underline{10}$ could be derived from less expensive 2-methylcyclohexanone and δ -valerolactone respectively. 8-Carbomethoxyoctanal which is easily derived from methyl oleate was also an attractive synthon because it already has an essential functions as a C_9 -fragment. However, methyl 4,5-epoxy-8-formyl-2-octenoate obtainable by a double unsaturation followed by an epoxidation at the 4,5-double bond was considered to be too labile for successive reactions. Hence, we took a longer but facile route for the synthesis of C_9 -fragment starting from δ -valerolactone.

Preparation of C_9 -fragments.

The key intermediate for the target lactones $\underline{1-4}$ is methyl 9-hydroxy-4-nonenolate $\underline{13}$. Trans-4,5-double bond was introduced by Claisen rearrangement⁶ in which 7-tetrahydropyranyloxy-1-hepten-3-ol $\underline{11}$ prepared from δ -valerolactone in 5 steps was heated at 90-100° C with trimethyl orthoacetate and a catalytic amount of propionic acid. After 1 day of heating, ester $\underline{12}$ was



Scheme 3

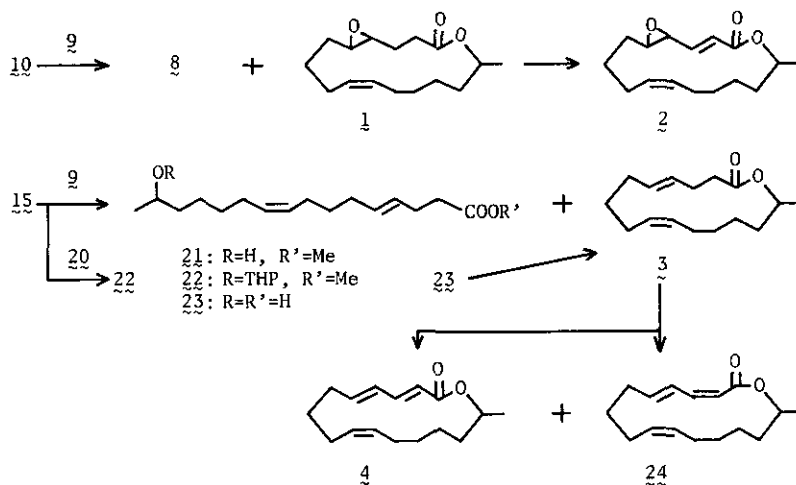
obtained in 88% yield. Successive removal of the tetrahydropyranyl function gave hydroxy ester 13 in 54% yield from starting δ -valerolactone. Ester 13 was then transformed to 8-carbomethoxyaldehyde 10 and 15 in 75.5% and 83% yield, respectively.

Preparation of phosphonium salts 9 and 20.

(6-Hydroxyheptyl)triphenyl phosphonium iodide 9 was produced from 2-methylcyclohexanone in 5 steps with 42% yield (route a) or in 8 steps with 36% yield (route b) as shown in Scheme 3. Route a was advantageous and shorter way than route b inspite of having less selective monotosylation (monotosylate 17:ditosylate=3.8:1). Tosylation of the diol (16) was achieved with 1.3 molar equivalent of tosyl chloride and N-methylimidazole in CH_2Cl_2 at -15 – -5°C . Phosphonium salt 20 was made by route b in 21% yield from 2-methylcyclohexanone.

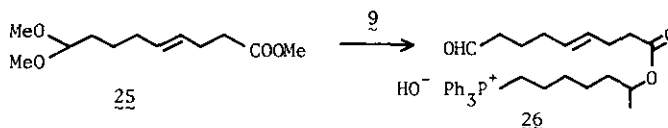
Synthesis of lactones 1–4.

Since phosphonium salt 9 had not been crystallized in the initial attempts at Wittig condensation aimed at obtaining the hydroxy ester (8), we had to use a polar solvent to dissolve salt 9. We chose hexamethylphosphoramide (HMPA) which is known as an effective additive for Wittig reaction⁷. To a solution of phosphonium salt 9 in THF-HMPA (8:1 or 11:1), n-butyllithium (1 equiv.) was added at -78°C , the mixture was stirred at -78°C for 1 h and at -20°C for 1 h, then aldehyde 10 (0.5 equiv.) was added. The reaction mixture was taken out of the cooling bath and was stirred at rt for 3 h. The product isolated from the reaction mixture was chromatographed on silica gel eluted with 10% Et_2O in n-hexane to obtain the major product (35%). Contrary to expectation, the major



Scheme 4

product was not the hydroxy ester (8) which was obtained in 4% yield by the elution with n-hexane-ether (6:4-1:1). The less polar product has a molecular formula $C_{16}H_{26}O_3$, an olefin (ν 885, 719 cm^{-1} , δ 5.2-5.6 (2H, m)), an epoxide (δ 2.30-2.72 (2H, m)), a secondary methyl (δ 1.20 (3H, d, $J=7$ Hz)) and an ester group (ν 1727, 1175 cm^{-1} , δ 5.00 (1H, m)). On reviewing through the above data, the major product was felt to be macrocyclic lactone 1. 8-Carbomethoxy-5-octenal 15 also gave a lactone 3 in a similar reaction to the above. The structure of 3 was confirmed by an alternative synthesis aided with a known lactonization of a hydroxy acid.⁸ Namely, (4E,9Z)-15-hydroxy-4,9-hexadecadienoic acid (23) which was prepared by Wittig condensation of aldehyde 15 and phosphonium salt 20 followed by deprotection of carbonyl and carbonyl function was transformed to a 2-pyridinethiol ester and lactonized by heating with $AgBF_4$. (4E,9Z)-4,9-Hexadecadien-15-olide thus obtained in 19.7% yield from aldehyde 15 showed spectral properties (ms, ir, pmr) identical with those of lactone 3 given by the onepot synthesis from aldehyde 15 and phosphonium salt 9. Lactones 1 and 3 were unsaturated by an elimination of a selenoxide following α -selenenylation of an ester.⁹ α,β -Unsaturated lactone 2 was obtained in 35% yield and 4 in 11% yield. In the latter case, 2Z-isomer 24 was given in 31% yield. The onepot synthesis of a lactone (1 or 3) from a carbomethoxy-aldehyde (10 or 15) and hydroxy phosphonium salt 9 consists of two parts. One is Wittig condensation and the other is transesterification. We found the yield of lactone 1 was higher when the molar ratio of n-butyllithium to phosphonium salt 9 was 1:1 than when it was 2:1. This implies that transesterification proceeds faster than Wittig condensation. HMPA may facilitate the former. To demonstrate this, we have prepared methyl 9,9-dimethoxy-4-nonenoate 25 and reacted this with phosphonium salt 9 under similar condition to that used for the synthesis of lactone 3. After the



Scheme 5

addition of 30% HBr in HOAc, the reaction mixture was stirred further with water to deprotect the acetal group. Transesterification proceeded in moderate yield and ester 26 was obtained in 56% yield after silica gel chromatography. Hence, the above unusual lactone formation may be considered to be a sequential reaction in which intramolecular Wittig condensation follows transesterification. Application of this onepot lactone synthesis to the other type of macrolides is under investigation.

EXPERIMENTAL

Melting points were obtained on a Yanagimoto micro melting point apparatus and are uncorrected. Mass spectra were recorded on a Hitachi M-52G mass spectrometer or a JEOL JMS-01CG-2 instrument interfaced with a JMA-2000 data system; ir spectra on a Hitachi IR-27G spectrophotometer; ^1H nmr spectra on a Hitachi R-20 or a JEOL FX-100 spectrometer in CDCl_3 with tetramethylsilane as an internal standard, except where noted otherwise.

7-Tetrahydropyranyloxy-1-hepten-3-ol (11). 5-Tetrahydropyranyloxypentanal (1 g, 5.4 mmol) prepared from δ -valerolactone in 77% yield by 4 steps (methanolysis of δ -valerolactone was followed by tetrahydropyranylation, by LiAlH_4 reduction and by Collins oxidation) in THF (10 ml) was added to the solution of vinyl magnesium bromide in THF (5 ml, prepared from 10.8 mmol of vinyl bromide and 10.8 mg atom of magnesium) dropwise over a period of 10 min at 0°C . The reaction mixture was stirred at 0°C for 30 min, quenched with sat NH_4Cl aq and extracted with Et_2O . The organic layer was washed with 10% NaHCO_3 aq and sat NaCl aq, dried on anhyd Na_2SO_4 and evaporated. Silica gel chromatography afforded 11 as an oil (0.975 g, 84%): ms m/z 157 (M^+ - $\text{C}_2\text{H}_5\text{O}$); ir (neat) ν 3470, 1118, 1020 cm^{-1} ; ^1H nmr δ 3.3-3.9 (4H, m), 4.1 (1H, m), 4.6 (1H, m), 5.1 (1H, dd, $J = 3, 10$ Hz), 5.22 (1H, dd, $J = 3, 16$ Hz), 5.92 (1H, ddd, $J = 6, 10, 16$ Hz).

Methyl (E)-9-tetrahydropyranyloxy-4-nonenoate (12). A mixture of 11 (1.5 g, 7 mmol) and propionic acid (0.03 ml, 0.42 mmol) in trimethyl orthoacetate (6.16 ml, 49 mmol) was stirred at 88°C for 18h, diluted with Et_2O , washed with 10% NaHCO_3 aq and sat NaCl aq, dried and evaporated. The oily residue was chromatographed on silica gel to give 1.67 g (88%) of 12: ms m/z 270 (M^+); ir (neat) ν 1738, 1159, 1025, 969 cm^{-1} ; ^1H nmr δ 3.2-4.1 (4H, m), 3.67 (3H, s), 4.58 (1H, m), 5.3-5.7 (2H, m).

Methyl (E)-9-hydroxy-4-nonenoate (13). A mixture of 12 (3.41 g, 12.6 mmol) and pyridinium *p*-toluenesulfonate (315 mg, 1.26 mmol) in EtOH (60 ml) was stirred at 55° C for 3 h. The residue was dissolved in Et₂O and the Et₂O layer was washed with 10% NaHCO₃ and sat NaCl aq, dried and evaporated. Chromatography of the residue on a silica gel column afforded 13 (2.23 g, 95%): ms *m/z* 168 (M⁺-H₂O); ir (neat) ν 3380, 1718, 1162, 1038, 970 cm⁻¹; ¹H nmr δ 3.45 (2H, m), 3.67 (3H, s), 5.3-5.6 (2H, m).

Methyl 4,5-epoxy-9-hydroxynonanoate (14). 13 (2.12 g, 11.4 mmol) in CH₂Cl₂ (60 ml) was treated with *m*-chloroperbenzoic acid (4.22 g, 17.1 mmol) at rt for 3 h. Insoluble parts were filtered off and the filtrate was washed with 10% NaHSO₃, 10% NaHCO₃ and sat NaCl aq. The extract was chromatographed on silica gel to give 14 (1.92 g, 83%): ms *m/z* 184 (M⁺-H₂O); ir (neat) ν 3377, 1723, 1169, 876 cm⁻¹; ¹H nmr δ 2.60-2.95 (2H, m), 3.60 (2H, m), 3.70 (3H, s).

9-Carbomethoxy-4,5-epoxyoctanal (10). 14 (85.8 mg, 0.42 mmol) in dry CH₂Cl₂ (2 ml) was added to a stirred suspension of Collins reagent (1.6 g, 6.3 mmol) in dry CH₂Cl₂ (20 ml); the mixture was stirred at rt for 1 h and passed through a silica gel column. Elution with 20% CH₂Cl₂ in Et₂O gave 10 (76.9 mg, 91%): ms *m/z* 200 (M⁺); ir (neat) ν 1722, 1166, 882 cm⁻¹; ¹H nmr δ 2.6-2.9 (2H, m), 3.70 (3H, s), 9.84 (1H, bs).

(E)-9-Carbomethoxy-5-octenal (15). A mixture of 13 (261 mg, 1.4 mmol) and PCC (907 mg, 4.2 mmol) in dry CH₂Cl₂ (15 ml) was stirred at rt for 2 h and passed through a silica gel column. Elution with 20% CH₂Cl₂ in Et₂O gave 15 (214 mg, 83%): ms *m/z* 152 (M⁺-MeOH); ir (neat) ν 1723, 1162, 970 cm⁻¹; ¹H nmr δ 3.66 (3H, s), 5.2-5.7 (2H, m).

7-Tosyloxy-2-heptanol (17). To a mixture of heptane-1,6-diol (16, 1.51 g, 11.4 mmol) derived from 2-methylcyclohexanone in 90% yield, and *N*-methylimidazole (1.4 ml, 17.6 mmol) in CH₂Cl₂ (60 ml) was added tosyl chloride (2.8 g, 14.8 mmol) in CH₂Cl₂ (15 ml) at -15° C dropwise over a period of 5 min. The reaction mixture was stirred at -5° C for 3 h and filtered; the filtrate was washed with water, 1N HCl, 5% NaHCO₃ aq and sat NaCl aq, dried over anhyd MgSO₄ and evaporated. Silica gel chromatography (benzene elution) gave a ditosylate (773 mg, 15%) and monotosylate 17 (1.93 g, 59%). 17: ms *m/z* 286 (M⁺); ir (neat) ν 3350, 1595, 1345, 1170, 1095 cm⁻¹; ¹H nmr δ 1.12 (3H, d, *J* = 6 Hz), 2.42 (3H, s), 3.75 (1H, m), 4.03 (2H, t, *J* = 6 Hz), 7.38 (2H, d, *J* = 8 Hz), 7.81 (2H, d, *J* = 8 Hz).

1-Iodo-6-heptanol (18). A mixture of 17 (1.30 g, 4.54 mmol) and NaI (1.37 g, 9.1 mmol) in acetone (30 ml) was refluxed for 4 h. The cooled mixture was filtered and the filtrate was evaporated. Trituration of the residue with *n*-hexane and evaporation of the solvent gave 18 (1.03 g, 94%): ms *m/z* 242 (M⁺), 224 (M⁺-H₂O); ¹H nmr δ 1.08 (3H, d, *J* = 6.4 Hz), 3.25 (2H, t, *J* = 6 Hz), 3.65 (1H, m).

(6-Hydroxyheptyl)triphenyl phosphonium iodide (9). A mixture of 18 (2.0 g, 8.3 mmol), triphenyl

phosphine (3.38 g, 14.9 mmol) and anhyd K_2CO_3 (1.47 g, 10.8 mmol) was refluxed for 1 day; filtered, evaporated and triturated with benzene. Salt **9** (3.7 g, 89%) was crystallized from Et_2O . **9**, mp 129–130° C: FD-ms m/z 377 ($M^+ - I$); ir (KBr) ν 3360, 3067, 1590, 1117, 750, 722, 690 cm^{-1} ; 1H nmr (CD_3COCD_3) δ 1.08 (3H, d, $J = 6.4$ Hz), 3.4–4.2 (3H, m), 7.6–8.4 (15H, m). Anal. Calcd for $C_{25}H_{30}OPI$: C, 59.53; H, 6.00. Found: C, 59.45; H, 5.93.

(6-Tetrahydropyranyloxyheptyl)triphenyl phosphonium tetraphenyl borate (**20**).

1-Iodo-6-tetrahydropyranyloxyheptane (**19**, 3.08 g, 9.45 mmol), triphenyl phosphine (5.16 g, 32.13 mmol) and potassium carbonate (2.23 g, 16.07 mmol) was stirred under reflux for 1 day. After filtration, the filtrate was evaporated and the residue was subjected to silica gel chromatography. Elution with 5% MeOH in EtOAc gave (6-tetrahydropyranyloxyheptyl)triphenyl phosphonium iodide (4.322 g, 78%). 3.42 g (5.8 mmol) of this salt was dissolved in MeOH (8 ml) to which was added sodium tetraphenyl borate (2.17 g, 6.38 mmol) in MeOH (16 ml). The resulting white precipitate was filtered and dried. **20** (3.79 g, 94%), mp 112–114° C: FD-ms m/z 461 ($M^+ - BPh_4$); ir (KBr) ν 3032, 1591, 1110, 1021, 734, 708, 696 cm^{-1} ; 1H nmr δ 1.06 (3H, d, $J = 6$ Hz), 3.2–4.2 (5H, m), 4.60 (1H, m), 6.6–7.1 (15H, m), 7.1–7.9 (20H, m). Anal. Calcd for $C_{54}H_{58}O_2PB$: C, 83.06; H, 7.49. Found: C, 82.68; H, 7.41.

(9Z)-4,5-Epoxy-9-hexadecen-15-olide (**1**). To a solution of **9** (268 mg, 0.5 mmol) in dry THF (12 ml) was added 15% n-butyllithium in n-hexane (0.323 ml, 0.5 mmol) at $-78^\circ C$. The mixture was stirred at $-78^\circ C$ for 1 h, then at $-20^\circ C$ for 1.5 h. After the addition of **10** (50 mg, 0.25 mmol) in THF (1 ml) at $-20^\circ C$, the reaction mixture was allowed to warm to rt and was stirred at the same temperature for 3 h. Following quenching with 10% NH_4Cl , the mixture was extracted with EtOAc, washed with sat NaCl aq, dried over anhyd Na_2SO_4 and evaporated. The residue was chromatographed on silica gel; elution with 10% Et_2O in n-hexane afforded lactone **1** (23.3 mg, 35%): ms m/z 266.1844 (M^+ , Calcd 266.1880 for $C_{16}H_{26}O_3$); ir (neat) ν 1727, 1175, 885, 719 cm^{-1} ; 1H nmr δ 1.20 (3H, d, $J = 7$ Hz), 2.3–2.7 (4H, m), 5.0 (1H, m), 5.2–5.6 (2H, m). Elution with 40–50% Et_2O in n-hexane gave hydroxy ester **8** (3 mg, 4%): ms m/z 299 ($M^+ + 1$), 280 ($M^+ - H_2O$); ir (neat) ν 3417, 1730, 1170, 876 cm^{-1} ; 1H nmr δ 1.17 (3H, d, $J = 6$ Hz), 2.3–2.8 (4H, m), 3.3–4.0 (1H, m), 3.67 (3H, s), 5.2–5.5 (2H, m).

(4E,9Z)-4,9-Hexadecadien-15-olide (**3**). Aldehyde **15** (50 mg, 0.27 mmol) was treated with a phosphorane prepared from **20** (289 mg, 0.54 mmol) according to the method for the synthesis of **4**. Silica gel chromatography (10% Et_2O in n-hexane) gave lactone **3**: ms m/z 250.1929 (M^+ , Calcd 250.1931 for $C_{16}H_{26}O_2$); ir ν 1728, 1130, 962, 695 cm^{-1} ; 1H nmr δ 1.20 (3H, d, $J = 7$ Hz), 4.86 (1H, m), 5.1–5.7 (4H, m). Elution with 40% Et_2O in n-hexane gave hydroxy ester **22** (3 mg, 4%): ms m/z 264 ($M^+ - H_2O$); ir (neat) ν 3367, 1723, 1168, 967 cm^{-1} ; 1H nmr δ 1.18 (3H, d, $J = 6.4$ Hz), 2.2–2.6 (4H, m), 3.4–4.1 (1H, m), 3.67 (3H, s), 5.2–5.6 (4H, m).

Methyl (4E,9Z)-15-tetrahydropyranyloxy-4,9-hexadecadienoate (22). 15% n-Butyllithium in n-hexane (0.967 ml, 1.63 mmol) was added to a solution of 20 (1.17 g, 1.63 mmol) and HMPA (4 ml) in dry THF (35 ml) at -78°C and the mixture was stirred at -78°C for 1 h. The reaction mixture, after aldehyde 15 (150 mg, 0.815 mmol) in THF (2 ml) was added to this, was stirred at -78°C for 1 h, allowed to warm to rt, stirred further for 3 h, then quenched with 10% NH_4Cl and extracted with EtOAc. The organic layer was washed with sat NaCl aq, dried over anhyd Na_2SO_4 and evaporated. Silica gel chromatography (10% Et_2O in n-hexane) of the residue afforded 22 (127.7 mg, 43%): ms m/z 282 ($\text{M}^+-\text{C}_5\text{H}_8\text{O}$), 264 ($\text{M}^+-\text{C}_5\text{H}_{10}\text{O}_2$); ir (neat) ν 1738, 1115 cm^{-1} ; ^1H nmr δ 1.22 (3H, d, $J = 6.4$ Hz), 3.3–4.2 (3H, m), 3.66 (3H, s), 4.69 (1H, m), 5.2–5.6 (4H, m).

(4E,9Z)-15-Hydroxy-4,9-hexadecadienoic acid (23). 127.7 mg (0.35 mmol) of 22 in EtOH was treated with PPTS at 55°C for 1 h to obtain hydroxy ester 21 (91.3 mg, 93%). 21 (83.7 mg, 0.3 mmol) was hydrolyzed with 1N LiOH (0.6 ml, 0.6 mmol) in MeOH (2 ml) at rt for 2 h. 23 (62.1 mg, 78%): ms m/z 250 ($\text{M}^+-\text{H}_2\text{O}$); ir (neat) ν 3317, 1700, 961 cm^{-1} ; ^1H nmr δ 1.18 (3H, d, $J = 6.4$ Hz), 3.6–4.1 (1H, m), 5.1–5.7 (4H, m).

(4E,9Z)-4,9-Hexadecadien-15-olide (3) from hydroxy acid 23. A mixture of 23 (20.2 mg, 0.0745 mmol), dipyridyl disulfide (24.2 mg, 0.112 mmol) and triphenyl phosphine (28.8 mg, 0.112 mmol) in dry benzene (0.3 ml) was stirred at rt for 4 h and diluted with dry acetonitrile (5 ml). This was added to a warmed solution (60°C) of silver tetrafluoroborate (47.9 mg, 0.224 mmol) in dry acetonitrile (20 ml) dropwise over a period of 2 h. The reaction mixture was stirred at 60°C for a further 18 h; diluted with Et_2O , washed with 1M NaCN aq, water and sat NaCl aq, dried over anhyd Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (10% Et_2O in n-hexane elution) to obtain lactone 3 (11.7 mg, 63%): ms m/z 250.1939 (M^+ , Calcd 250.1931 for $\text{C}_{16}\text{H}_{26}\text{O}_2$); ir (neat) ν 1728, 962, 695 cm^{-1} ; ^1H nmr δ 1.19 (3H, d, $J = 7$ Hz), 4.86 (1H, m), 5.08–5.64 (4H, m).

(2E,9Z)-4,5-Epoxy-2,9-hexadecadien-15-olide (2). 1 (50 mg, 0.188 mmol) in THF (0.5 ml) was added to a solution of lithium diisopropylamide–HMPA complex (0.25 mmol) in THF (5 ml) at -78°C and the mixture was stirred at -78°C for 30 min. Diphenyl diselenide (79 mg, 0.25 mmol) in THF (0.5 ml) was added to the mixture and stirring was continued for 1 h. The reaction mixture was extracted with EtOAc and evaporated. The residue in EtOAc (5 ml) was treated with 30% H_2O_2 (0.63 ml, 5.6 mmol) at 0°C for 1 h; the resulting mixture was washed with NaHSO_3 aq, NaHCO_3 aq and sat NaCl aq, dried and evaporated. Chromatography on silica gel (8% Et_2O in n-hexane elution) gave 2 (17.6 mg, 35%). ms m/z 264 (M^+); ir (neat) ν 1716, 1651, 1185, 1135, 979, 888, 710 cm^{-1} ; ^1H nmr δ 1.25 (3H, d, $J = 7$ Hz), 2.78 (1H, m), 3.20 (1H, dd, $J = 2, 8$ Hz), 5.15 (1H, m), 5.31 (2H, m), 6.16 (1H, d, $J = 16$ Hz), 6.66 (1H, dd, $J = 8, 16$ Hz).

(2E,4E,9Z)-Hexadecatrien-15-olide (4) and (2Z,4E,9Z)-isomer (24). 50 mg (0.2 mmol) of 3 was treated with lithium diisopropylamide-HMPA complex (0.3 mmol) in THF (5 ml) at -78°C (30 min); diphenyl diselenide (98 mg, 0.3 mmol) in THF (0.5 ml) was added to the mixture which was stirred further for 1 h. The product was taken up with EtOAc and treated with 30% H_2O_2 (0.158 ml, 1.39 mmol) at 0°C for 1 h. The mixture was washed with NaHSO_3 aq, NaHCO_3 aq and sat NaCl aq, dried and evaporated. Silica gel chromatography (5% Et_2O in n-hexane elution) of the residue afforded 24 (17.3 mg, 35%) and 4 (5.5 mg, 11%). 24: ms m/z 248 (M^+); ir (neat) ν 1693, 1633, 1593, 1273, 1193, 997, 957, 700 cm^{-1} ; ^1H nmr δ 1.29 (3H, d, $J = 6\text{ Hz}$), 4.95 (1H, m), 5.30 (2H, m), 5.54 (1H, d, $J = 11.5\text{ Hz}$), 5.95 (1H, m), 6.49 (1H, t, $J = 11.5\text{ Hz}$), 7.01 (1H, dd, $J = 11.5, 15\text{ Hz}$). 4: ms m/z 248 (M^+); ir (CHCl_3) ν 1706, 1636, 1590, 1261, 1174, 995, 730 cm^{-1} ; ^1H nmr δ 1.29 (3H, d, $J = 6\text{ Hz}$), 4.94 (1H, m), 5.32 (2H, m), 5.74 (1H, d, $J = 15\text{ Hz}$), 5.8-6.3 (2H, m), 7.55 (1H, dd, $J = 11, 15\text{ Hz}$).

Methyl (E)-9,9-dimethoxy-4-nonenolate (25). A mixture of aldehyde 15 (152 mg, 0.83 mmol), trimethyl orthoformate (0.27 ml, 2.49 mmol) and TsOH (7.9 mg, 0.0415 mmol) in MeOH (2 ml) was stirred at rt for 5 h and diluted with Et_2O . The organic layer was washed with 10% NaHCO_3 aq and sat NaCl aq, dried over anhyd Na_2SO_4 and evaporated. The residue was chromatographed on silica gel (10% Et_2O in n-hexane elution) to give 25 (154 mg, 81%). ms m/z 230 (M^+), 199 ($\text{M}^+ - \text{CH}_3\text{O}$); ir (neat) ν 1737, 1127, 1053, 971 cm^{-1} ; ^1H nmr δ 3.30 (6H, s), 3.67 (3H, s), 4.36 (1H, t, $J = 7.2\text{ Hz}$), 5.3-5.6 (2H, m).

6-[(E)-9-Oxo-4-nonenoyloxyheptyl]triphenylphosphonium hydroxide (26). 15% n-Butyllithium in n-hexane (0.278 ml, 0.43 mmol) was added to 9 (230 mg, 0.43 mmol) and HMPA (0.85 ml) in dry THF (10 ml) at -78°C and the mixture was stirred at -78°C for 1 h and at -20°C for 1 h, to a mixture of which was added acetal 25 (50 mg, 0.215 mmol) in THF (1 ml) at -20°C . The reaction mixture was allowed to warm to 0°C , stirred at 0°C for 2 h, then cooled to -20°C and 30% HBr in HOAc was added to it. The mixture, after 2.4 ml of water was added, was stirred at 0°C for 3 h, diluted with EtOAc, washed with water, dried and evaporated. Silica gel chromatography (10% EtOAc in CHCl_3 elution) of the residue gave 26 (73.5 mg, 56%). ms m/z 468 ($\text{M}^+ - \text{C}_6\text{H}_6$) (Found 468.2392, Calcd 468.2428 for $\text{C}_{28}\text{H}_{37}\text{O}_4$); ir (neat) ν 3412, 3062, 1716, 1108, 970, 749, 723, 699 cm^{-1} ; ^1H nmr δ 1.15 (3H, d, $J = 6\text{ Hz}$), 3.2-3.8 (2H, m), 4.85 (1H, m), 5.3-5.5 (2H, m), 7.4-8.0 (15H, m), 9.81 (1H, m).

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REFERENCES

1. C.R. Hutchinson, I. Kurobane, C.T. Mabuni, R.W. Kumola, A.G. McInnes and J.A. Walter,

- J. Amer. Chem. Soc., 1981, 103, 2474; C.R. Hutchinson, I. Kurobane, D.E. Cane, H. Hasler and A.G. McInnes, ibid., 1981, 103, 2477; C.R. Hutchinson, M.M. Sherman, J. C. Vederas and T.T. Nakashima, ibid., 1981, 103, 5953; C.R. Hutchinson, M.M. Sherman, A.G. McInnes, J.A. Walter and J.C. Vederas, ibid., 1981, 103, 5956; D.E. Cane, H. Hasler and T.-C. Liang, ibid., 1981, 103, 5960; D.E. Cane, T.-C. Liang and H. Hasler, ibid., 1981, 103, 5963.
2. J.D. Bu'Lock and P.T. Clay, Chem. Commun., 1969, 237; B.E. Cross and P. Hendley, J. Chem. Soc. Chem. Commun., 1975, 124.
3. C.T. Mabuni, L. Garlaschelli, R.A. Ellison and C.R. Hutchinson, J. Amer. Chem. Soc., 1979, 101, 707.
4. M. Sunagawa, T. Ohta and S. Nozoe, Heterocycles, 1979, 13, 267.
5. M. Sunagawa, T. Ohta and S. Nozoe, J. Antibiot., 1983, 36, 25.
6. W.S. Johnson, L. Werthemann, W.R. Bartlett, T.J. Brocksom, T. Li, D.J. Faulkner and M.R. Petersen, J. Amer. Chem. Soc., 1970, 92, 741.
7. H.J. Bestmann, O. Vostrowsky and A. Plenchette, Tetrahedron Lett., 1974, 779.
8. H. Gerlach and A. Thalmann, Helv. Chim. Acta, 1974, 57, 2661.
9. K.B. Sharpless, R.F. Lauer and A.Y. Teranishi, J. Amer. Chem. Soc., 1973, 95, 6137.

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