Strategies of Synthesis based on Cyclohexadienes: Part 3.[1] A Novel Route to Macrolide Aromatic Polyketides

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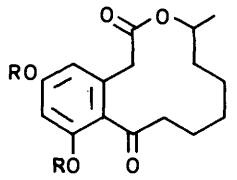
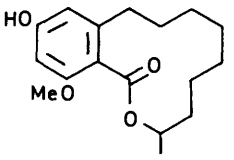
A novel route to macrolide aromatic polyketides, having an alkyl-β-resorcylate skeleton has been developed. A formal synthesis of (±)-curvularin (**1**), and (±)-lasiodiplodin (**3**) involving the preparation of the seco acid (**31**) and the acyclic precursor (**34**) using a one pot Alder–Rickert reaction from 1,3-dimethoxycyclohexa-1,3-diene (**7**) and the long-chain acetylenic dienophiles (**10**) and (**11**) is reported.

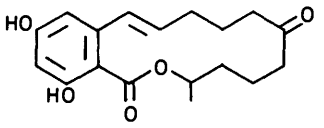
Curvularin[2] (**1**) and lasiodiplodin[3] (**3**) are members of a rare class of biologically active natural products, commonly known as macrolide polyketides—a term derived from the polyketide hypothesis[4] to explain the origin of these molecules. Curvularin was isolated from the culture filtrate of the species *Curvularia*. Lasiodiplodin was isolated from a strain of *Lasiodiplodia theobromae* and is shown to be a plant growth inhibitor. A structural feature common to both these molecules is the presence of an alkyl-β-resorcylate skeleton with a 12-membered macrocyclic lactone ring. Zearalenone (**4**), another structurally related macrocyclic lactone having a 14-membered ring, is known for its potent steroid-like anabolic and uterotrophic activity.[5] Although there have been a number of procedures[6] for the preparation of simple resorcylates there is a need to develop improved methodology which may be adopted to complex systems. We have shown earlier[1] that the thermal, Alder–Rickert reaction involving methoxycyclohexadienes (**7**) and activated acetylenic dienophiles (**8**) offers an excellent general method for the synthesis of a variety of polyketide natural products (**9**). It was, therefore, of interest to extend this methodology as a convenient route to the more complex, biologically active macrolides. The synthesis of the acyclic precursors (**32**) and (**36**) which can be readily converted by macrolactonisation to (±)-lasiodiplodin[7] and (±)-curvularin[8] is described in this paper.



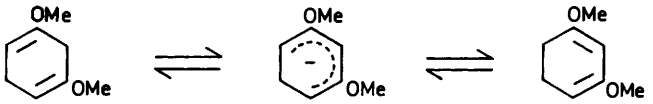
(**1**) R = H
(**2**) R = Me



(**3**)



(**4**)



(**5**) (**6**) (**7**)

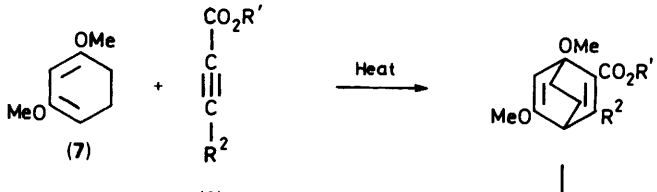
Results and Discussion

The key reaction in our approach towards the synthesis of lasiodoplodin is a regiospecific, Alder–Rickert reaction between the conjugated diene (**7**) and the long-chain acetylenic ester (**10**) to furnish the required seco acid (**31**). Similarly, the acetylenic ketone (**11**) would provide the acyclic intermediate (**34**) leading to (±)-di-*O*-methylcurvularin.

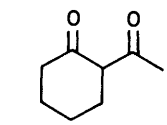
The diene (**7**) is readily available by the base catalysed isomerisation[9] of the unconjugated diene (**5**) through the mesomeric anion (**6**). The acetylenic ester (**10**) was prepared from cyclohexanone by established methods. Thus by using Fieser's procedure[10] cyclohexanone was converted into 2-acetylcyclohexanone (**12**) in good yield. Alkaline cleavage of the diketone using aqueous NaOH gave[11] the ketoacid (**13**) which on reduction with $NaBH_4$ in aqueous methanol furnished the hydroxy acid (**18**) in good yield. Homologation of the hydroxy acid (**18**) was achieved through its acetyl derivative (**19**), acid chloride (**20**) and the diazoketone (**21**) followed by Wolff rearrangement of (**21**) to give the methyl ester (**22**) in 46% overall yield. Hydrolysis of (**22**) with NaOMe–MeOH furnished the hydroxy ester (**23**), the tetrahydropyranyl derivative (**24**) which was reduced with $LiAlH_4$ to the alcohol (**25**). This alcohol (**25**) was converted into the bromide (**27**) through the tosylate (**26**) followed by displacement using lithium bromide in acetone.[12] When the bromide (**27**) was treated with monosodium acetylide in liquid ammonia, coupling occurred without difficulty to give the undecyne (**28**) in 78% yield. Conversion into the acetylenic ester (**10**) was achieved by treatment of the undecyne (**28**) with butyl-lithium followed by reaction with ethyl chloroformate.[13]

The cycloaddition was carried out by heating a mixture of the acetylenic ester (**10**) and the conjugated diene (**7**) under nitrogen at 180 °C for 100 h. The crude reaction product was found to be a complex mixture by TLC and IR and was subjected to alkaline hydrolysis followed by purification by thin layer chromatography to give the seco acid (**31**) in 30% overall yield. The properties of the acid (**31**) were identical with the published data.[3]

The acid (**31**) was demethylated with 10% HBr in acetic acid to give the dihydroxy acid (**32**), which was benzylated and treated with ethereal diazomethane in ethanol to yield methyl 4-(benzyloxy)-6-(8-hydroxynonyl)-2-methoxy benzoate (**32**) in an



(7) (8)



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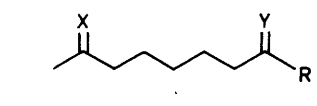
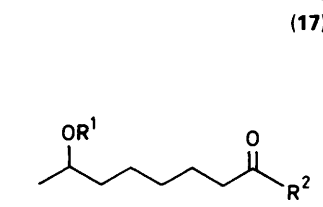
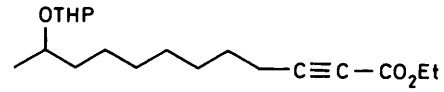


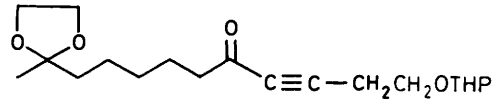
(13) R = OH, X = O, Y = O
(14) R = OEt, X = O, Y = O
(15) R = OEt, X = $O(CH_2)_2O$, Y = O
(16) R = OH, X = $O(CH_2)_2O$, Y = H_2
(17) R = H, X = $O(CH_2)_2O$, Y = O



(9)

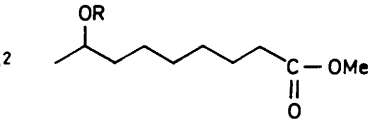


(10)

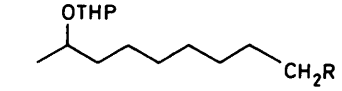


(11)

(18) R^1 = H, R^2 = OH
(19) R^1 = Ac, R^2 = OH
(20) R^1 = Ac, R^2 = Cl
(21) R^1 = Ac, R^2 = CHN_2



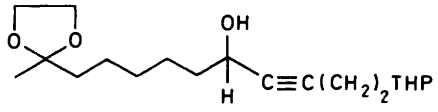
(22) R = Ac
(23) R = H
(24) R = THP



(25) R = OH
(26) R = OTs
(27) R = Br
(28) R = C≡CH

$HC\equiv C(CH_2)_2OTHP$

(29)



(30)

overall yield of 38% from (**31**). Compound (**32**) had spectral properties identical with those reported by Gerlach.[7] Since the ester (**32**) has been converted into the macrocyclic lactone, (±)-lasiodiplodin (**3**), this constituted a formal synthesis of (±)-lasiodiplodin.

The acetylenic ketone (**11**) required for the synthesis of curvularin (**1**) was prepared starting from the keto acid (**13**). The ketal (**15**), obtained from the ester (**14**) was reduced with $LiAlH_4$ to the corresponding alcohol (**16**) which was oxidised with PDC to the aldehyde (**17**). Treatment of the aldehyde (**17**) with the lithium salt of (**29**) in THF at −78 °C followed by mild oxidation of the resulting alcohol (**30**) using activated manganese dioxide furnished the required acetylenic ketone (**11**) in good yield.

The cycloaddition was carried out by heating an equimolar mixture of the conjugated diene (**7**) and the acetylenic ketone (**11**) under nitrogen at 180 °C. The crude reaction product was hydrolysed with dilute acid to afford the ketone (**34**) which was further purified by preparative TLC to yield the required aromatic precursor (**34**) in 38% yield. Mild oxidation using PDC in DMF[14] furnished the diketo acid (**35**) in 70% yield.

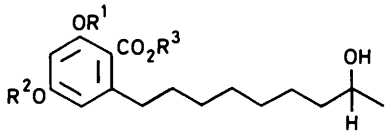
The diketo acid (**35**) could be readily converted with sodium borohydride into the hydroxy acid (**37**).[8] Since the intramolecular acylation reaction of the acid (**37**) to the macrocyclic lactone resulting in di-*O*-methylcurvularin (**2**) is known to be unsuccessful, preparation of the diphenyloxazole (**36**) was attempted. Thus reaction of the diketo acid (**34**) with benzoin in the presence of DCC and DMAP afforded the benzoin ester as an oil which was refluxed with ammonium acetate in acetic acid to give the diphenyloxazole (**36**). The structure of (**36**) was deduced from its spectral data which was in conformity with the published data.

Since the diphenyloxazole (**36**) has been converted into di-*O*-methylcurvularin (**2**) through the hydroxy compound (**38**) followed by macrolactonisation using photo-oxygenation,[8a] the preparation of (**36**) constituted a formal synthesis of curvularin.

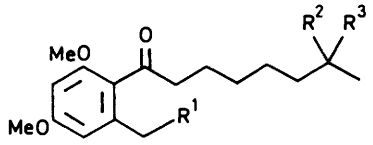
Experimental

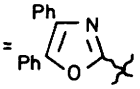
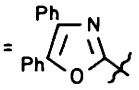
M.p.s and b.p.s are uncorrected. IR spectra were recorded as liquid films or Nujol mulls on a Perkin-Elmer, model 781 instrument. The ^1H MR spectra were recorded on Varian T-60, JEOL-FX 90Q or Bruker WH 270 MHz spectrometers. Chemical shifts are given in ppm (δ) using tetramethylsilane as an internal standard. In all the sealed tube reactions, the reactions were taken in thick walled Pyrex glass tube and sealed *in vacuo* prior to heating. Hexane refers to light petroleum boiling in the range 40–60 °C.

7-Oxo-octanoic Acid (**13**).—2-Acetylcyclohexanone (**12**) (28 g, 0.2 mol) was added to 5% aqueous NaOH (200 ml) and the resulting solution was refluxed for 1.5 h. The solution was then cooled and neutralised with dilute HCl. The mixture was extracted with chloroform and the extract washed with water



(31) $R^1 = R^2 = Me$, $R^3 = H$
(32) $R^1 = R^2 = R^3 = H$
(33) $R^1 = R^3 = Me$, $R^2 = CH_2Ph$



(34) $R^1 = CH_2OH$, R^2, $R^3 = O$
(35) $R^1 = CO_2H$, R^2, $R^3 = O$
(36) R^1 =  , R^2, $R^3 = O$
(37) $R^1 = CO_2H$, $R^2 = OH$, $R^3 = H$
(38) R^1 =  , $R^2 = OH$, $R^3 = H$

and dried. After concentration, the residue was distilled under reduced pressure to afford the keto acid (**13**) as a colourless liquid (21 g, 60%); b.p. 160 °C at 4 mmHg (lit.,[11] 160–162 °C at 4 mmHg) (Found: C, 60.6; H, 8.9. Calc. for $C_8H_{14}O_3$: C, 60.7; H, 8.8%); ν_{max}(film) 3 450, 1 720, and 1 700 cm^{-1}; δ 1.4–1.8 (6 H, m, $CH_2 \times 3$), 2.14 (3 H, s, $COCH_3$), 2.4 (4 H, m, $COCH_2 \times 2$), and 8.5 (1 H, 3, COOH).

7-Hydroxyoctanoic Acid (**18**).—To a solution of the keto acid (**13**) (15.8 g, 0.1 mol) in 10% aqueous NaOH (200 ml) was added $NaBH_4$ (3.8 g, 0.1 mol) in small amounts. The reaction mixture was stirred for 4 h, after which it was neutralised with dilute HCl and extracted into chloroform. The combined organic extracts were washed with brine and water, dried, and evaporated under reduced pressure. The residue was distilled *in vacuo* to give the hydroxy acid (**18**) as a colourless liquid (14.6 g, 85%), b.p. 150–155 °C at 5 mmHg (lit.,[11] 133 °C at 2 mmHg) (Found: C, 60.3; H, 10.1. Calc. for $C_8H_{16}O_3$: C, 60.2; H, 10.0%); ν_{max}(film) 3 450 and 1 700 cm^{-1}.

7-Acetoxyoctanoic Acid (**19**).—The hydroxy acid (**18**) (12.4 g, 0.78 mol) was acetylated by treatment with acetic anhydride in pyridine at 0 °C. After work-up, the crude acetate obtained was distilled *in vacuo* to give the acetoxy acid (**19**) as a pale yellow liquid (14 g, 89%); b.p. 128 °C at 1 mmHg (lit.,[11] 126–128 °C at 1 mmHg) (Found: C, 59.3; H, 8.8. Calc. for $C_{10}H_{18}O_4$: C, 59.4; H, 8.9%); ν_{max}(film) 1 738, 1 710, and 1 250 cm^{-1}; δ 1.2 (3 H, d, *J* 7 Hz, CH_3), 1.4–1.8 (8 H, br, $CH_2 \times 4$), 2 (3 H, s, CH_3), 2.25 (2 H, t, *J* 8 Hz, CH_2), and 4.9 (1 H, m, CHOAc).

7-Acetoxyoctanoyl Chloride (**20**).—The acetoxy acid (**19**) (10 g, 0.05 mol) and redistilled thionyl chloride (10 ml) were heated on a water-bath for 1 h. Distillation of the mixture yielded the acid chloride (**20**) as a colourless liquid (6.1 g, 60%), b.p. 158 °C at 5 mmHg; ν_{max}(film) 1 800 (COCl) and 1 738 cm^{-1} (OAc).

Methyl 8-Acetoxynonanoate (**22**).—A solution of the acid chloride (**20**) (6 g, 27 mmol) in anhydrous ether (25 ml) was added to an ethereal solution of diazomethane in small amounts and the mixture set aside overnight. The ether was removed under reduced pressure to give the diazo ketone (**21**) (6 g, 100%) as a pale yellow liquid; ν_{max}(film) 2 100 ($COCHN_2$), 1 730 (OAc), and 1 640 cm^{-1} ($COCHN_2$); δ 1.2 (3 H, d, *J* 7 Hz, CH_3), 1.3–1.8 (8 H, m, $CH_2 \times 2$), 2.0 (3 H, s, CH_3), 2.25 (2 H, t, *J* 8 Hz, CH_2), 4.9 (1 H, m, C*H*Me), and 5.2 (1 H, s, CHN_2). The diazo ketone (**21**) was found to be pure by analytical TLC and was submitted to the next reaction without further purification.

A solution of the diazo ketone (**21**) (6 g, 27 mmol) in warm dioxane (100 ml) was added in drops to a suspension of freshly precipitated silver oxide (2 g) in methanol (200 ml). The mixture was heated under reflux for 1 h after which the precipitate was filtered off and washed with methanol. The combined filtrates were concentrated and distilled under reduced pressure to yield the *methyl ester* (**22**) as a colourless oil (5.6 g, 90%), b.p. 142 °C at 5 mmHg (Found: C, 62.6; H, 9.5. $C_{12}H_{22}O_4$ requires C, 62.6 and 9.6%); ν_{max}(film) 1 736 and 1 740 cm^{-1} (C=O); δ 1.2 (3 H, d, *J* Hz, CH_3), 1.3–1.8 (10 H, br, $CH_2 \times 5$), 1.96 (3 H, s, CH_3) 2.25 (2 H, t, *J* 8 Hz, CH_2), 3.6 (3 H, s, OAc), and 4.8 (1 H, m, CH).

Methyl 8-Hydroxynonanoate (**23**).—A solution of the acetate ester (**22**) (3 g, 13 mmol) in dry methanol (30 ml) containing a catalytic amount of sodium methoxide was stirred for 15 h. The reaction mixture was neutralised with acid and filtered. The filtrate was concentrated and the residue purified by chromatography (benzene–chloroform, 4:1) to yield the *hydroxy ester* (**23**) as a colourless oil (2.2 g, 91%) (Found: C, 63.7; H, 10.6. $C_{10}H_{20}O_3$ requires C, 63.8; H, 10.7%); ν_{max}(film) 3 450 (OH) and 1 740 cm^{-1} (OAc); δ 1.12 (3 H, d, *J* 8 Hz, CH_3), 1.3–1.8 (10 H, br, $CH_2 \times 5$), 2.4 (2 H, t, *J* 7.8 Hz, CH_2), 3.5 (1 H, m, D_2O exchange, OH), 3.72 (3 H, s, OCH_3), and 5.4 (1 H, m, CH).

Methyl 8-(2-Tetrahydropyranyloxy)nonanoate (**24**).—The hydroxy ester (**23**) (2.8 g, 15 mmol) and dihydropyran (1.68 g, 20 mmol) in dry ether (20 ml) at 10 °C were treated with a trace amount of toluene-*p*-sulphonic acid. After 5 h, the reaction mixture was diluted with ether (50 ml) and washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated to afford the product. This was chromatographed on silica gel and eluted with benzene to afford the pyranyl ester (**24**) as a colourless oil (3.7 g, 90%); ν_{max}(film) 1 740, 1 445, and 1 220 cm^{-1}; δ 1.12 (3 H, dd, J_1 5 Hz, J_2 8 Hz, CH_3), 1.3–1.8 (16 H, br, $CH_2 \times 8$), 2.22 (2 H, t, *J* 8 Hz, CH_2CO), 3.6–4 (5 H, m, CH_2, CHO), 4.8 (1 H, m, OCHO).

8-Tetrahydropyran-2-yloxynonan-1-ol (**25**).—To a suspension of LAH (210 mg) in dry ether (80 ml) was added, a solution of the ester (**24**) (2.7 g, 10 mmol) at 0 °C. The mixture was stirred for 8 h and then decomposed with methanol. After aqueous work-up, the solvents were evaporated under reduced pressure and the crude product was purified by chromatography (chloroform–hexane, 1:2); to give the desired *alcohol* (**25**) as a colourless oil (2.3 g, 96%) (Found: C, 68.8; H, 11.4. $C_{14}H_{28}O_3$ requires C, 68.85; H, 11.5%); ν_{max}(film) 3 450, 1 440, and 1 280 cm^{-1}; δ, 1.2 (3 H, dd, J_1 8 Hz, J_2 5 Hz, CH_3), 1.3–1.8 (16 H, br, CH_2), 3.4–3.8 (6 H, m, $CH_2O \times 2$, CHO, OH), and 4.8 (1 H, br t, OCHO).

8-Tetrahydropyran-2-yloxynonan-1-yl Tosylate (**26**).—To a solution of the alcohol (**25**) (2 g, 8 mmol) in dry pyridine (20 ml) at −5 °C was added toluene-*p*-sulphonyl chloride (1.62 g, 8.5 mmol). The mixture was stirred for 2 h and then poured onto

crushed ice and extracted with ether. The organic extract was washed with brine, aqueous $CuSO_4$, and water, dried, and evaporated to furnish the tosylate (**26**) as a pale yellow syrup (2.6 g, 80%); ν_{max}(film) 1 600, 1 440, and 1 280 cm^{-1}; δ 1.2 (3 H, dd; J_1 5 Hz; J_2 8 Hz, CH_3), 1.3–1.8 (16 H, br, CH_2), 2.4 (3 H, s, CH_3Ar), 3.4–4 (5 H, CH_2O × 2, CHO), 4.75 (1 H, m, OCHO), 6.34 (2 H, d, *J* 3 Hz), and 6.7 (2 H, d, *J* 2 Hz). The tosylate was found to be pure by TLC and directly used in the next reaction without further purification.

1-*Bromo*-8-*tetrahydropyran*-2-*yloxyonane* (**27**).—Lithium bromide (3 g) was added to a solution of the tosylate (**26**) (2.6 g, 6.6 mmol) in dry acetone (25 ml). The mixture was refluxed for 5 h, poured into water, and worked up. The crude product obtained was purified by chromatography (benzene–hexane) to give the required *bromide* (**27**) as a pale yellow oil (1.75 g, 86%) (Found: C, 54.6; H, 8.7%; $C_{14}H_{27}BrO_2$ requires C, 54.7; H, 8.8%); ν_{max}(film) 1 450, 1 280, 865, and 800 cm^{-1}; δ 1.2 (3 H, dd; J_1 5 Hz, J_2 8 Hz, CH_3), 1.3–1.8 (16 H, br, CH_2 × 8), 3.2–3.8 (4 H, m, CH_2O, CH_2Br), and 4.8 (1 H, m, CHO).

10-*Tetrahydropyran*-2-*yloxyundec*-1-*yne* (**28**).—To a solution of sodium acetylide in liquid ammonia (100 ml) containing DMSO (50 ml) was added the bromide (**27**) (3 g, 9.8 mmol) in dry THF (10 ml). The mixture was stirred for 4 h after which the ammonia was allowed to evaporate and the mixture was treated with saturated aqueous ammonium chloride and extracted with ether (3 × 50 ml). The organic extract was concentrated and the resulting product was purified by chromatography (benzene–ether, 10:1), followed by short-path distillation to yield the *undecyne* (**28**) as a pale yellow oil (1.9 g, 78%), b.p. 148–152 °C at 3 mmHg (Found: C, 76.3; H, 11.0. $C_{16}H_{28}O_2$ requires C, 76.2; H, 11.1%); ν_{max}(film) 3 300 (C≡H) and 2 120 cm^{-1} (C≡C); δ 1.2 (3 H, dd, J_1 5 Hz, J_2 8 Hz, CH_3), 1.3–1.72 (16 H, br, CH_2 × 8), 1.8 (1 H, t, *J* 3 Hz, ≡CH), 2.18 (2 H, m, CH_2C≡), 3.4–3.8 (3 H, m, CH_2O, CHO), and 5.0 (1 H, m, OCHO).

Ethyl 11-*Tetrahydropyran*-2-*yloxydodec*-2-*ynoate* (**10**).—To a solution of butyl-lithium (6 mmol) in dry ether (30 ml) at −30 °C, was added the undecyne (**28**) (1.26 g, 5 mmol) in dry ether (10 ml). After 10 min, a solution of ethyl chloroformate (650 mg, 6 mmol) in dry ether (5 ml) was added in one portion. The reaction mixture was stirred at −30 °C for 5 h, after which it was allowed to warm to the room temperature (5 h) and then poured into cold water (50 ml) and quickly extracted with ether (3 × 50 ml). The combined extracts were washed with water, dried, and evaporated under reduced pressure and the residue was purified by chromatography (ether–hexane, 1:2 to give the *acetylenic ester* (**10**) as a pale yellow oil (1 g, 65%) (Found: C, 70.3; H, 9.8. $C_{19}H_{32}O_4$ requires C, 70.4; H, 9.9%); ν_{max}(film) 2 240 and 1 720 cm^{-1}; δ 1.35 (6 H, m, CH_3 × 2), 1.4–1.8 (18 H, br, CH_2 × 9), 2.5 (2 H, m, CH_2C≡C), 3.4–4 (4 H, m, 2 × CH_2O), 4.1 (1 H, m), and 5.1 (1 H, m, CHO).

2-(8-*Hydroxynonyl*)-4,6-*dimethoxybenzoic Acid* (**31**).—A mixture of the acetylenic ester (**10**) (1 g, 3 mmol) and the diene (**7**) (560 mg, 4 mmol) were heated in a glass tube sealed under nitrogen to 180 °C for 100 h. After the mixture had cooled to room temperature, it was taken up in ethanol (10 ml) and mixed with 5% aqueous ethanolic KOH (15 ml) and refluxed for 2 h. It was neutralised with dilute HCl and extracted with ether. The combined organic layers were washed with distilled water, dried, and evaporated under reduced pressure. The crude product was purified by preparative TLC (chloroform–methanol, 4:1) to give the seco acid (**31**) as a pale yellow gummy material (230 mg, 30%) (Found: C, 66.6; H, 8.6. Calc. for $C_{18}H_{28}O_5$: C, 66.7; H, 8.6%); ν_{max}(film) 3 400–2 900, 1 710, 1 605, 1 590, and 1 500 cm^{-1}; δ 1.4 (3 H, d, *J* 8.6 Hz, CH_3), 1.5–2.0 (12 H, br, CH_2 × 6), 2.73 (2 H, t, *J* 6 Hz, CH_2CO), 3.6 (1 H, br, D_2O exchange, OH), 3.79 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 4.6 (1 H, m, CHO), 6.28 (1 H, d, *J* 2 Hz, ArH), and 6.34 (1 H, d, *J* 2 Hz, ArH).

Methyl 4-*Benzyloxy*-6-(8-*hydroxynonyl*)-2-*methoxybenzoate* (**32**).—The acid (**31**) (180 mg) in acetic acid (10 ml) was heated under reflux with hydrobromic acid (48%; 2 ml) for 5 h after which the reaction mixture was then poured into water (150 ml) and, extracted with ether (3 × 25 ml). The combined extracts were washed with water, dried, and evaporated to yield a residue (110 mg). This was dissolved in anhydrous THF (5 ml) and added to sodium hydride (140 mg freed from oil by washing with pentane) in dry THF (5 ml) and the mixture stirred with benzyl chloride (150 mg) followed by sodium iodide (5 mg). The reaction mixture was heated under reflux for 10 h, cooled to room temperature, poured into water, acidified with dilute HCl, and extracted with ether (3 × 25 ml). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to yield an oil which resisted crystallisation even after chromatography.

The above oil (100 mg) in methanol (10 ml) was treated with an excess of ethereal diazomethane. After 12 h the solvent was evaporated and the residue in ether was washed with 2% aqueous sodium hydroxide and water, dried, and evaporated to yield a residue. This was sublimed to yield the product (**32**) as an oil[7] (90 mg, 38%) (Found: C, 72.6; H, 8.2. Calc. for $C_{25}H_{34}O_5$: C, 72.5; H, 8.2%); ν_{max} 3 500, 1 730, 1 605, and 1 585 cm^{-1}; δ(CCl_4) 1.1 (d, *J* 7 Hz, 3 H), 1.1–1.7 (br, 12 H), 2.5 (m, 2 H), 3.5–3.8 (m, 1 H), 3.75 (s, 3 H), 3.78 (s, 3 H), 5.03 (s, 2 H), 6.33 (s, 2 H), and 7.38 (br, 5 H); M^+, 414.

Ethyl 7,7-*Ethylenedioxyoctanoate* (**15**).—A solution of the keto ester (**14**) (10 g, 54 mmol) was refluxed with ethylene glycol (6 ml) in dry benzene (75 ml) containing a trace of toluene-*p*-sulphonic acid. The water formed was continuously removed by a Dean–Stark trap. After 15 h, the reaction mixture was cooled, diluted with ether (40 ml), and the organic layer separated, washed with aqueous sodium hydrogen carbonate, and water, dried, and evaporated. Distillation of the residue *in vacuo* afforded the *ketal* (**15**) as a colourless liquid (10.1 g, 81%), b.p. 138 °C at 5 mmHg (Found: C, 62.5; H, 9.55. $C_{12}H_{22}O_4$ requires C, 62.5; H, 9.6%); ν_{max}(film) 1 739, 1 440, and 1 260 cm^{-1}; δ 1.15 (3 H, s, CH_3), 1.1–1.8 (10 H, br, CH_2 × 5), 2.19 (2 H, t, *J* 7 Hz, CH_2), 3.81 (4 H, s, OCH_2CH_2O), and 4.08 (2 H, q, *J* 6 Hz, CH_2O).

7,7-*Ethylenedioxyoctanal* (**17**).—To a suspension of LAH (200 mg, 5.25 mmol) in ether (30 ml) was added a solution of the ketal (**15**) (2.3 g, 10 mmol) in dry ether (30 ml). After being stirred for 5 h, the reaction mixture was quenched with methanol, diluted with water, and worked up to furnish the corresponding *alcohol* (**16**) as a colourless oil (2.1 g, 93%) (Found: C, 63.8; H, 10.6. $C_{10}H_{10}O_3$ requires C, 63.8; H, 10.6%); ν_{max}(film) 3 450 (OH), 1 440, and 1 280 cm^{-1}; δ 1.2 (3 H, s, CH_3), 1.3–1.8 (8 H, m, CH_2 × 4), 3.1–3.7 (3 H, m), and 3.84 (4 H, s, OCH_2CH_2O).

The above alcohol (2 g, 11 mmol) was stirred with a suspension of pyridinium dichromate (4.75 g, 17 mmol) in methylene dichloride (25 ml). After all the alcohol has been consumed (by TLC) (10 h) the reaction mixture was quenched with ether (50 ml) and filtered through a short column of neutral alumina. The clear filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (ether–hexane, 1:2) to furnish the *aldehyde* (**17**) as a colourless oil (1.4 g, 70%) (Found: C, 64.3; H, 9.5. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.5%); ν_{max}(film) 2 730, 1 725, and 1 440 cm^{-1}; δ 1.18 (3 H, s, CH_3), 1.4–1.8 (8 H, m,

CH_2 × 4), 2.25 (2 H, br t, CH_2), 3.84 (4 H, s), and 9.58 (1 H, t, *J* 2 Hz).

1-*Tetrahydropyran*-2-*yloxybut*-3-*yne* (**29**).—A mixture of but-3-yn-1-ol (1.4 g, 20 mmol) and dihydropyran (1.7 g, 20.2 mmol) was cooled to 0 °C and treated with a trace amount of PTSA. After 10 h, the reaction mixture was diluted with ether and washed with aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was distilled *in vacuo* to yield the desired *tetrahydropyranyl ether* (**29**) as a colourless liquid (2.3 g, 75%), b.p. 114–116 °C at 5 mmHg (Found: C, 69.9; H, 9.1. $C_9H_{14}O_2$ requires C, 70.1; H, 9.2%); ν_{max}(film) 3 330 and 2 100 cm^{-1}; δ 1.4–1.8 (6 H, br, CH_2 × 2), 1.84 (1 H, t, *J* 2 Hz, C≡CH), 2.4 (2 H, m, CH_2) 3.4–4 (4 H, m, CH_2O × 2), and 4.8 (1 H, br, OCHO).

11-*Ethylenedioxy*-1-*tetrahydropyran*-2-*yloxydodec*-3-*yn*-5-*one* (**11**).—To a solution of butyl-lithium in dry ether (12 mmol) at −78 °C was added the alkyne (**29**) (1.69 g, 11 mmol) followed by the aldehyde (**17**) (1.86 g, 10 mmol). After being stirred for 5 h, the reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ether. The extract was washed, dried, and evaporated under reduced pressure to give the alcohol (**30**) as a pale yellow oil (2.24 g, 66%); ν_{max}(film) 3 450 (OH) and 2 240 cm^{-1} (C≡C). The crude alcohol dissolved in methylene dichloride (50 ml) was stirred with active manganese dioxide (10 g) for 15 h. The reaction was quenched by adding ether and the precipitate was filtered off and the filtrate evaporated under reduced pressure. The residue was purified by silica gel column chromatography followed by short-path distillation *in vacuo* (200 °C bath temp., at 1 mmHg) to give the *acetylenic ketone* (**11**) as a colourless oil (1.05 g, 60%) (Found: C, 67.5; H, 8.8. $C_{19}H_{30}O_5$ requires C, 67.5; H, 8.9%); ν_{max}(film) 2 240 (C≡C) and 1 680 cm^{-1} (C=O); δ 1.18 (3 H, s, CH_3), 1.4–1.8 (14 H, m, CH_2 × 7), 2.2–2.6 (4 H, m, CH_2 × 2) 3.2–3.8 (4 H, m, CH_2O × 2), 3.84 (4 H, s, OCH_2CH_2O), and 4.8 (1 H, m, CHO).

3,5-*Dimethoxy*-2-(1′,7′-*dioxo-octanyl*)*phenylethanol* (**34**).—A mixture of the acetylenic ketone (**11**) (50 mg, 1.48 mmol) and the diene (**7**) (200 mg, 1.4 mmol) was heated under nitrogen at 180 °C for 100 h. After the mixture had cooled, the dark gummy product was taken up in ethanol (15 ml), treated with a few drops of dilute HCl, and stirred for 30 min. It was concentrated under reduced pressure to 5 ml and neutralised with aqueous $NaHCO_3$ (25 ml). This was extracted with chloroform, washed with water and brine, dried, and concentrated. The residue, was purified by preparative TLC (silica gel, chloroform–methanol, 10:1), to furnish the *aromatic compound* (**34**) as a pale yellow amorphous solid (180 mg, 38%) (Found: C, 67.3; H, 8.1. $C_{18}H_{26}O_5$ requires C, 67.1, H, 8.1%); ν_{max} 1 710, 1 680, 1 605, and 1 600 cm^{-1}; δ 1.2–1.8 (6 H, br, CH_2 × 2), 2.08 (3 H, s, CH_3CO), 2.35 (4 H, br t, CH_2 × 2), 2.7 (2 H, t, *J* 6 Hz, $ArCOCH_2$), 3–3.5 (3 H, m, CH_2OH), 3.8 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 6.25 (1 H, d, *J* 2 Hz, ArH), and 6.39 (1 H, d, *J* 2 Hz, ArH).

3,5-*Dimethoxy*-2-(1′,7′-*dioxo-octanyl*)*phenylacetic acid* (**35**).—The alcohol (**34**) (65 mg, 0.2 mmol) was stirred with pyridinium dichromate (250 mg) in dry DMF (1 ml) for 24 h. The reaction mixture was diluted with ether (10 ml), and the organic layer was separated and washed with brine and water, dried, and evaporated to yield a residue which was purified by preparative TLC (chloroform–methanol, 9:1), to furnish the keto acid (**35**) as a white solid (48 mg, 70%), m.p. 84 °C (MeOH) [lit.,[8b] 81–83 °C (aq. MeOH)]; (Found: C, 64.5; H, 7.1. Calc. for $C_{18}H_{24}O_6$: C, 64.3; H, 7.1%); ν_{max} 1 705, 1 700, and 1 680 cm^{-1}.

2-[3′,5′-*Dimethoxy*-2′-(1′,7′-*dioxo-octyl*)*benzyl*]-4,5-*diphenyloxazole* (**36**).—A mixture of the acid (**35**) (100 mg), benzoin (120 mg), *N*,*N*′-dicyclohexylcarbodi-imide (150 mg), and 4-dimethylaminopyridine (5 mg) was stirred in dry THF (20 ml) for 12 h. The mixture was diluted with ether, filtered, and washed with 5% HCl and saturated brine. The ether layer was then separated, dried, and evaporated to give an oil (150 mg). This (100 mg) was refluxed with NH_4OAc (200 mg) in glacial AcOH (10 ml) for 1 h after which the reaction mixture was diluted with water and extracted with methylene dichloride (3 × 10 ml). The combined organic extracts were washed with saturated $NaHCO_3$ and water, dried, and evaporated to give an oil (60 mg) which was chromatographed on neutral alumina. Elution with ether–hexane (1:1) gave the oxazole (**36**) as an oil (Found: N, 2.8. Calc. for $C_{32}H_{33}NO_5$: N, 2.7%); ν_{max} 1 715, 1 690, and 1 610 cm^{-1}; δ 1.2–1.7 (m, 6 H), 2.0 (s, 3 H), 2.33 (t, *J* 7 Hz, 2 H), 2.85 (t, *J* 7 Hz, 2 H), 3.8 (s, 6 H), 4.2 (s, 2 H), 6.38 (d, *J* 2 Hz, 1 H), 6.5 (d, *J* 2 Hz, 1 H), 7.2, 7.4 (m, 6 H), and 7.5 (m, 4 H).

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References

1 Part 2, C. C. Kanakam and Neelakandha S. Mani, Halasya Ramanathan, and G. S. R. Subba Rao, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1907.
2 A. J. Birch, O. C. Musgrave, R. W. Rickards, and H. Smith, *J. Chem. Soc.*, 1959, 3246.
3 D. C. Aldridge, S. Galt, D. Giles, and W. B. Turner, *J. Chem. Soc. C*, 1971, 1623.
4 A. J. Birch, *Science*, 1967, **156**, 202.
5 M. Stob, R. S. Baldwin, J. Jute, F. N. Andrews, and K. G. Gillete, *Nature*, 1962, **196**, 1318.
6 T. M. Harris and C. M. Harris, *Tetrahedron*, 1977, **33**, 2159; R. N. Mirrington, E. Ritchie, C. W. Shoppe, S. Sternhell, and W. C. Tayler, *Aust. J. Chem.*, 1966, **19**, 1265; A. G. M. Barrett, T. M. Morris, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2272.
7 H. Gerlach and A. Talmann, *Helv. Chim. Acta*, 1977, **60**, 2866.
8 (*a*) H. H. Wasserman, J. Gamble, and M. J. Pullwer, *Tetrahedron*, 1981, **37**, 4059, (*b*) P. M. Baker, B. W. Bycroft, and J. C. Roberts, *J. Chem. Soc.*, 1967, 1913.
9 A. J. Birch, E. M. A. Shoukry, and F. Stansfield, *J. Chem. Soc.*, 1961, 5376.
10 L. F. Fieser, J. P. Schirmer, S. Archer, R. R. Lorenz, and P. I. Pfattenbach, *J. Med. Chem.*, 1967, **10**, 513.
11 O. C. Musgrave, R. Templeton, and (in part) H. D. Munro, *J. Chem. Soc.*, 1968, 250.
12 M. Uchida, K. Nakagawa, and K. Mori, *Agric. Biol. Chem.*, 1979, **43**, 1919.
13 L. Brandsma, 'Preparative Acetylenic Chemistry,' Elsevier, Amsterdam, 1971, 76.
14 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.

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