The Chemistry of Pseudomonic Acid. Part 4.[1] αβ-Unsaturated Ketones derived from Monic Acid A and its Derivatives

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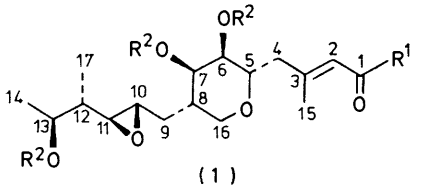
Routes to the preparation of αβ-unsaturated ketones (1k—m) have been investigated. n-Butylmanganese(II) chloride was particularly useful for preparing the ketones (1m) from the readily available monic acid A (1b), the nucleus of pseudomonic acid A (1a).

PSEUDOMONIC ACID A (1a) is the major member of a family of naturally occurring antibiotics produced by fermentation of a strain of *Pseudomonas fluorescens*.[2-6] The compound possesses a clinically useful spectrum of antimicrobial activity.[7,8] When given systematically to mammalian species including man, pseudomonic acid A is rapidly metabolised with loss of antibacterial activity.[8] Pseudomonic acid A is also highly bound to serum protein.[7] As part of a general programme designed to study the effect of chemical modification of pseudomonic acids[8,9] on biological properties, the preparation of αβ-unsaturated ketones (1k—m) have been investigated.

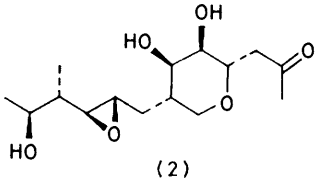


(1)

	R^1	R^2
a;	$O[CH_2]_8CO_2H$	H
b;	OH	H
c;	SMe	H
d;	SEt	H
e;	SEt	$SiMe_3$
f;	2-pyridylthio	H
g;	$OC(O)OBu^t$	H
h;	$OC(O)OBu^t$	$SiMe_3$
i;	$O[CH_2]_8CO_2Me$	H
j;	$OP(O)(OEt)_2$	H
k;	Me	H
l;	Et	H
m;	Bu^n	H

A number of standard procedures for the preparation of ketones from carboxylic acids and their derivatives have been examined. It is well established that organolithium reagents react with the lithium salts of carboxylic acids to give ketones.[10,11] Neither methyl- nor n-butyl-lithium reacted with the lithium salt of monic acid A (1b),[9] which was found to be very insoluble in ethereal solvents. Reactions of the thiol esters (1c, d, and f) and the mixed anhydride (1g) after protection of the hydroxy-groups as trimethylsilyl ethers with alkyl-lithium or alkylmagnesium bromides failed to yield the desired αβ-unsaturated ketones (1k—m).

As an alternative approach the ozonolysis product of methyl pseudomonate (1i), the methyl ketone (2),[9] was treated with the stabilised Wittig reagent (3). No reaction took place even after refluxing in toluene for 16 h in the presence of a catalytic amount of benzoic acid.[12]



(2)

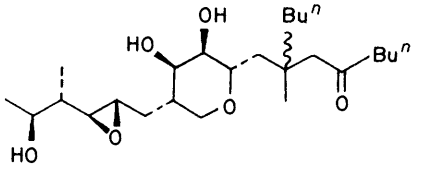
$CH_3COCH{=}PPh_3$

(3)

Organocopper reagents preferentially undergo conjugate addition to αβ-unsaturated carbonyl substrates.[13] However, Anderson *et al.*[14] have shown that under certain conditions of temperature, solvent, and carbonyl substrate 1,2-addition becomes the dominant reaction. The ethanethiol ester of monic acid, (1d), prepared from the mixed anhydride (1j) formed from monic acid A and diethyl phosphorochloridate with thallium(I) ethanethiolate, was converted into its tris(trimethylsilyl) ether (1e) with *N*,*O*-bis(trimethylsilyl)acetamide. The ether (1e) was treated with lithium dimethylcuprate in ether–tetrahydrofuran (THF) to give, after work-up and purification by chromatography on silica, the crystalline methyl ketone (1k) in 45% yield, m.p. 104—106 °C. Its u.v. absorption at $\lambda_{max.}$ 239 nm (ε 10 500) and the C=O and C=C stretching frequencies at $\nu_{max.}$ 1 682 and 1 618 cm^{-1} respectively were indicative of an αβ-unsaturated ketone. In the ^1H n.m.r. spectrum the olefinic C(2)-*H* signal appeared as a one-proton singlet at δ 6.15 and the C(15)-H_3 and methyl ketone signals as a six-proton singlet at δ 2.16. The structure was confirmed by the ^{13}C n.m.r. spectrum in which the CH_2CO-group appeared as a quartet at δ 31.7 and a singlet at δ 199.3 p.p.m., respectively. Following the success of this reaction, several attempts were made to prepare the n-butyl ketone (1m) using lithium dibutylcuprate and (1c) or (1d), but only the dibutyl product of conjugate addition (4) could be isolated. Conditions could not be found for producing the desired compound in sufficient quantities for isolation.

In contrast with the organocuprate reagents, many αβ-unsaturated aldehydes predominantly undergo 1,2-additions with Grignard reagents.[15] Therefore, a less direct but more successful approach to the αβ-unsatu-

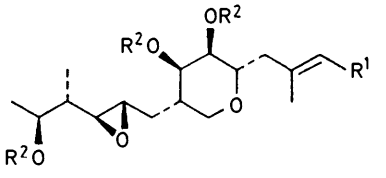
rated ketones (1k—m), involving Grignard addition to the aldehyde (5a) followed by oxidation of the resulting secondary allylic alcohol to the desired ketone, has been studied. The key intermediate in this proposed reaction



(4)

sequence, the aldehyde (5a), was prepared from methyl pseudomonate (1i) *via* the allylic alcohol (5c).

Methyl pseudomonate (1i) was treated with *N,O*-bis(trimethylsilyl)acetamide and the protected derivative was reduced with excess of di-isobutylaluminium hydride (DIBAL) in dry THF at room temperature for 2 d. After deprotection and chromatography on silica gel, the allylic alcohol (5c) was isolated as an oil in 41% yield. Selective oxidation of (5c) with activated manganese dioxide [16] afforded the αβ-unsaturated aldehyde (5a) in 63% yield. The hydroxy-groups of the aldehyde (5a) were protected as trimethylsilyl ethers



(5)

	R^1	R^2
a;	CHO	H
b;	CHO	$SiMe_3$
c;	CH_2OH	H
d;	CH(Et)OH	H
e;	CH(Et)OH	$SiMe_3$
f;	$CH(Bu^n)OH$	H
g;	$CH(Bu^n)OH$	$SiMe_3$

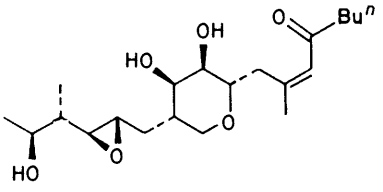
following treatment with *N,O*-bis(trimethylsilyl)acetamide, and the resulting compound (5b) was allowed to react with excess of ethylmagnesium bromide and a catalytic amount of copper(I) iodide in dry THF at room temperature for 16 h. After deprotection, the resulting secondary allylic alcohol (5d) was purified by chromatography on silica and isolated as an oil in 87% yield. The alcohol was obtained as an epimeric mixture at C-1. The absence of a C=O stretching frequency and a greatly reduced C=C stretching frequency in the i.r. spectrum, together with the absence of u.v. absorption, were indicative of the structural change. Confirmation of the structure was afforded by the ^1H and ^{13}C n.m.r. spectra. The C(2)-*H* signal appeared as a broad doublet at δ 5.25, being coupled to the double triplet of C(1)-*H* at δ 4.27, and the ethyl-CH_2 signal appeared as a complex multiplet at δ 1.4. These assignments were confirmed by spin–spin decoupling. The ^{13}C n.m.r. spectrum confirmed the structure of (5d) and its epimeric nature by revealing twin resonances for C(1), C(2), C(3), and C(4) only. The remaining resonances were consistent with the structure. Selective oxidation of the allylic hydroxy-group in (5d) to the desired ethyl ketone (1l) was performed with pyridinium chlorochromate (PCC) in 11.5% yield. The u.v. absorption of the product at $\lambda_{max.}$ 238 nm and i.r. absorptions at 1 620 and 1 682 cm^{-1} were characteristic of an αβ-unsaturated ketone, the structure being confirmed by the ^1H and ^{13}C n.m.r. spectra. The overall yield of the ethyl ketone (1l) from methyl pseudomonate (1i) was 2.6%. Thin-layer chromatography indicated that in the reaction of (5d) with PCC, oxidation occurred to some extent at the secondary non-allylic hydroxy-groups. In the subsequent preparation of the butyl ketone (1m), this problem was avoided by retaining the trimethylsilyl protecting-groups throughout the reaction sequence. In other words, the tris(trimethylsilyl) secondary allylic alcohol (5g), produced from reaction of the protected aldehyde (5b) with butylmagnesium bromide with or without a catalytic quantity of copper(I) iodide, was not isolated, but reacted directly with PCC to give, after deprotection, the butyl ketone (1m) in 14% yield. The allylic alcohol (5f), however, has been isolated as an oil and fully characterised. It is worth noting that selective re-protection of (5f) to give (5g) is not practicable. The overall yield of the butyl ketone (1m) from methyl pseudomonate was 3.8%.

The yields described in the above four-step reaction sequence have been optimised as a result of attempts to produce larger quantities of the butyl ketone, in particular, for biological evaluation. Alternative reducing agents such as RED-AL [17] [$NaAlH_2(OCH_2CH_2OMe)_2$] and Super Hydride [18] ($LiEt_3BH$) have been investigated and offer no advantages over DIBAL. Triphenylbismuth carbonate was recently reported [19] as an efficient oxidant for allylic alcohols. However, when the allylic alcohol (5c) was treated with this reagent, oxidation was slow, resulting in a multicomponent mixture after 18 h and none of the products corresponded to the αβ-unsaturated aldehyde (5a). Finally, oxidation of the protected secondary allylic alcohol (5g) with activated manganese dioxide offered no advantages over PCC.

Clearly, the preparation of gram quantities of these ketones (1k—m), and particularly functionalized ketones, by the above route was not a practical proposition and it was, therefore, necessary to investigate more direct routes from readily available intermediates. Organomanganese(II) chlorides (RMnCl) were reported by Normant *et al.*[20] to react with αβ-unsaturated carboxylic–carbonic mixed anhydrides to give αβ-unsaturated ketones in good yields. More practical details were given in a second publication [21] and the use of these reagents in the preparation of the butyl ketone (1m) was investigated.

The readily available monic acid A (1b) [9] was treated with isobutyl chloroformate and triethylamine in THF at −10 °C and, without isolation, the resulting mixed anhydride (1g) was converted into its tris(trimethylsilyl) ether (1h) by reaction with trimethylsilyl chloride and triethylamine. n-Butylmanganese(II) chloride was

prepared under argon either by addition of n-butyl-lithium to a THF solution of a pre-formed complex, $MnCl_2 \cdot 2LiCl$, or by addition of n-butyl-lithium to a suspension of manganese(II) chloride in THF. Both preparations resulted in very dark solutions of n-butyl-manganese(II) chloride, to which at −10 °C a pre-prepared THF solution of the fully protected mixed anhydride (1h) was added dropwise with stirring, the temperature being maintained at −10 °C during the addition and finally at room temperature for 1—2 h. After work-up, deprotection, and purification by chromatography on silica, the butyl ketone (1m) was isolated as an oil in yields varying from 17 to 36%. The *Z*-butyl ketone (6) was also formed during the reaction (7—20%) and presumably arises from proton abstraction by the manganese reagent from either the C(15)-H_3 or the C(4)-H_2 groups with enolisation of the mixed anhydride and subsequent isomerization of the double bond in the reverse reaction.



(6)

This process is undoubtedly superior to the previously described four-step procedure and has been amenable to preparations of the butyl ketone (1m) in excess of gram quantities.

The three ketones (1k—m) displayed interesting antimicrobial activity, whilst the intermediates (5a), (5c), (5d), (5f), and (6) were inactive.

EXPERIMENTAL

M.p.s were determined on a Büchi apparatus and are uncorrected. Mass spectra were obtained at 70 eV using a VG 70-70F instrument operating at 8 kV. ^1H N.m.r. data were recorded at 90 MHz on a Perkin-Elmer R32 instrument, and ^{13}C measurements using a Varian CFT 20 spectrometer, both at ambient temperature with Me_4Si as internal standard. The numbering system used for assigning the chemical shifts is that shown in formula (1). Column chromatography was carried out on Merck Kieselgel H (type 60). Analytical t.l.c. was performed on pre-coated Merck Kieselgel 60 F_{254} plates with chloroform–methanol (9 : 1 v/v) as eluant and the components visualized by either u.v. light or charring with sulphuric acid. H.p.l.c. was performed on a Waters Associates instrument using a C_{18} μ-Bondapak reverse-phase column with ammonium acetate–water–methanol buffer solutions as eluant. Both t.l.c. and h.p.l.c. were performed routinely on all compounds. Acetonitrile was distilled from phosphorus pentaoxide. Tetrahydrofuran (THF) was dried over calcium hydride and freshly distilled immediately before use.

S-*Ethyl* (E)-4-{(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*]-3,4-*dihydroxytetrahydropyran*-2-*yl*}-3-*methylbut*-2-*enethioate* (1d).—To a solution of monic acid A (1b) (2.064 g) and triethylamine (0.84 ml) in dry THF (60 ml) was added a solution of diethyl phosphorochloridate (1.035 g) in dry THF (20 ml) at room temperature under argon. The mixture was stirred at room temperature for 3 h and the precipitated triethylamine hydrochloride was filtered off. To the filtrate was added thallium(I) ethanethiolate (1.59 g) and the resulting suspension was stirred at room temperature for 16 h and then filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and aqueous sodium hydrogen carbonate. The organic layer was washed with saturated brine, dried ($MgSO_4$), and the solvent removed under reduced pressure to give an oil which was chromatographed on silica (25 g) with 5% methanol–chloroform as eluant. Fractions containing pure *product* (h.p.l.c. and t.l.c.) were combined and evaporated to give the *ethanethiol ester* (1d) (0.99 g, 43%), m.p. 80—81 °C (ether); $[\alpha]_D^{20}$ −8.3° (*c*, 1.0 in $CHCl_3$); $\nu_{max.}$ ($CHBr_3$) 3 425, 1 680, and 1 620 cm^{-1}; $\lambda_{max.}$ (EtOH) 237 (ε 9 682) and 268 nm (ε 8 150); δ_H ($CDCl_3$) 6.0 (1 H, s, 2-H), 2.13 (3 H, s, 15-H_3), 1.25 (6 H, d + t, 14-H_3 and SCH_2CH_3), and 0.92 (3 H, d, 17-H_3); δ_C ($CDCl_3$) 189.6 (C-1), 153.6 (C-3), 124.7 (C-2), 75.0 (C-5), 71.3 (C-13), 70.3 (C-7), 68.9 (C-6), 65.4 (C-16), 61.3 (C-11), 55.6 (C-10), 42.8 (C-12), 42.6 (C-4), 39.5 (C-8), 31.6 (C-9), 23.2 (SCH_2), 20.8 (C-14), 20.0 (C-15), 14.8 (SCH_2CH_3), and 12.7 p.p.m. (C-17); *m/e* 227 (5), 111 (50), and 62 (100) (Found: C, 59.0; H, 8.2; S, 8.4. $C_{19}H_{32}O_6S$ requires C, 58.7; H, 8.3; S, 8.3%).

(E)-5-{(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*]-3,4-*dihydroxytetrahydropyran*-2-*yl*}-4-*methylpent*-3-*en*-2-*one* (1k).—The ethanethiol ester (1d) (0.78 g) was dissolved in dry acetonitrile (25 ml) and stirred at room temperature for 1 h with *N,O*-bis(trimethylsilyl)-acetamide (4 ml). The solvent was removed under reduced pressure at 40 °C. Copper(I) iodide (1.14 g) was suspended in dry ether (50 ml) under argon and the solution was cooled to 0 °C. Methyl-lithium (2M solution in ether; 6 ml) was added and the suspension stirred at 0 °C for 0.5 h; it was then treated with a solution of the tris(trimethylsilyl)ether (1e) in dry THF (50 ml). The mixture was then stirred at 0 °C for 2 h and at room temperature for 16 h, under argon. The reaction was quenched by the dropwise addition of saturated aqueous ammonium chloride (10 ml) and the product was extracted with ethyl acetate. The organic layer was washed with water, and saturated aqueous sodium chloride and then dried ($MgSO_4$). After filtration the solvent was removed under reduced pressure and the residue was dissolved in 1,4-dioxan–water (4 : 1; 10 ml). Two drops of 1M hydrochloric acid were added and the solution was stirred for 3 min. Excess of aqueous sodium hydrogen-carbonate was added and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried ($MgSO_4$). Filtration and removal of the solvent under reduced pressure gave the crude *ketone* as an oil which was purified by column chromatography on silica gel (20 g). Elution with 5% methanol–chloroform afforded the pure αβ-*unsaturated methyl ketone* (1k) (0.31 g, 45%), m.p. 104—106 °C (ether–hexane); $\nu_{max.}$ ($CHBr_3$) 3 410, 1 682, and 1 618 cm^{-1}; $\lambda_{max.}$ (EtOH) 239 nm (ε 10 500); δ_H ($CDCl_3$) 6.15 (1 H, s, 2-H), 2.16 (6 H, s, 15-H_3 and $COCH_3$), 1.21 (3 H, d, 14-H_3), and 0.93 (3 H, d, 17-H_3); δ_C ($CDCl_3$) 199.3 (s, C-1), 156.1 (s, C-3), 125.5 (d, C-2), 75.0 (d, C-5), 70.9 (d, C-13), 70.3 (d, C-7), 68.9 (d, C-6), 65.5 (t, C-16), 61.1 (d, C-11), 55.6 (d, C-10), 43.2 (t, C-4), 42.7 (d, C-12), 39.7 (d, C-8), 31.7 (q + t, C-9 and $COCH_3$), 20.7 (q, C-14), 19.6 (q, C-15), and 12.5 p.p.m. (q, C-17); *m/e*

342 (M^+, 0.5), 227 (20), and 43 (100) (Found: C, 62.9; H, 8.7%; M^+ 342.2061. $C_{18}H_{30}O_6$ requires C, 63.1; H, 8.8%; *M*, 342.2079).

(7RS)-7-{(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*]-3,4-*dihydroxytetrahydropyran*-2-*yl*}*methyl*}-7-*methylundecan*-5-*one* (4).—The methanethiol ester (1c) (0.374 g), prepared in a similar manner to (1d), was dissolved in dry acetonitrile (25 ml) and the solution was stirred at room temperature for 1 h with *N*,*O*-bis-(trimethylsilyl)acetamide (2 ml), followed by removal of the solvent under reduced pressure at 40 °C. Copper(I) iodide (0.570 g) was suspended in dry ether (25 ml) under argon and the solution was cooled to 0 °C. n-Butyl-lithium (2M solution in hexane; 3 ml) was added and the suspension was stirred at 0 °C for 0.5 h. The protected thiol ester was dissolved in dry THF (25 ml) and the solution was added to the mixture which was stirred at 0 °C for 2 h and at room temperature for 16 h, under argon. The reaction was quenched by the dropwise addition of saturated aqueous ammonium chloride (5 ml) and the product was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was dissolved in 1,4-dioxan–water (4 : 1; 5 ml), one drop of 1M HCl was added, and the solution was stirred for 2.5 min. Excess of aqueous sodium hydrogencarbonate was added and the product was extracted with ethyl acetate, washed with water and saturated brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a yellow oil which was chromatographed on silica gel (30 g) with 5% methanol–chloroform as eluant. Fractions containing the pure product were combined and evaporated to yield the *conjugate addition product* (4) as an oil (0.045 g, 11%); $\nu_{max.}$ ($CHBr_3$) 3 430 and 1 710 cm^{-1}; δ_H ($CDCl_3$) 2.35 (4 H, m, CH_2COCH_2), 1.1—1.5 (13 H, m + d, $[CH_2]_3CH_3$, $COCH_2[CH_2]_2CH_3$, and 14-H_3), 0.95 (12 H, m, 15-H_3, 17-H_3, and $[CH_2]_3CH_3 \times 2$); *m/e* 442 (M^+, 0.5), 424 (5), 406 (1), 294 (40), 227 (40), 85 (100), and 57 (100) (Found: M^+ 442.3266. $C_{25}H_{46}O_6$ requires *M*, 442.3240); *m/e* (NH_3 c.i.) 460 ($M + NH_4^+$, 35) and 443 ($M + H^+$, 100).

(E)-4-{(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*]-3,4-*dihydroxytetrahydropyran*-2-*yl*}-3-*methylbut*-2-*en*-1-*ol* (5c).—Methyl pseudomonate A (1i) (10.28 g) was dissolved in THF (50 ml) and the solution was treated with *N*,*O*-bis(trimethylsilyl)acetamide (13.4 g). After the mixture had been stirred for 2 h at room temperature the solvent was removed under reduced pressure to afford the tris(trimethylsilyl) ether which was dried at 50 °C/1 mmHg for 0.75 h. The tris(trimethylsilyl) ether was dissolved in THF (100 ml), and the solution was cooled to −10 to −20 °C, and treated with di-isobutylaluminium hydride (25% solution in toluene; 80 ml) under nitrogen. Stirring was continued for 48 h under nitrogen and the reaction was quenched with methanol–water. The mixture was filtered, the filtrate was evaporated under reduced pressure, and the residue was dissolved in 1,4-dioxan–water (4 : 1, 40 ml). 10M-Hydrochloric acid (10 drops) was added and the solution was stirred for 10 min after which excess of aqueous sodium hydrogencarbonate solution was added and the product was extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was chromatographed on silica (40 g) with gradient elution with 0—12% methanol–chloroform; fractions containing pure *allylic alcohol* (5c) were combined and evaporated to yield an oil (2.7 g, 41%), $\nu_{max.}$ ($CHBr_3$) 3 400 and 1 665 cm^{-1}; δ_H ($CDCl_3$) 5.48 (1 H, br. t, 2-H), 4.13 (2 H, d, CH_2OH), 1.72 (3 H, s, 15-H_3), 1.21 (3 H, d, 14-H_3), and 0.92 (3 H, d, 17-H_3); δ_C (CD_3OD) 136.7 (s; C-3), 126.9 (d, C-2), 76.5 (d, C-5), 71.5 (d, C-13), 70.6 (d, C-7), 70.1 (d, C-6), 66.1 (t, C-16), 61.3 (d, C-11), 59.3 (t, C-1), 56.8 (d, C-10), 43.5 (d, C-12), 42.3 (t, C-4), 41.1 (d, C-8), 32.8 (t, C-9), 20.3 (q, C-14), 16.6 (q, C-15), and 12.2 p.p.m. (q, C-17); *m/e* 330 (M^+), 312, 267, 244, 227, 141 (100), 129, 111, and 99.

(E)-4-{(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*]-3,4-*dihydroxytetrahydropyran*-2-yl}-3-*methylbut*-2-*enal* (5a).—The allylic alcohol (5c) (2.7 g) was dissolved in acetone (100 ml) and the solution was treated with activated manganese dioxide (25 g). After 2 h the reaction was complete (t.l.c.) and the suspension was filtered and the filtrate evaporated to afford an oil which was chromatographed on silica (25 g) with gradient elution with 0—8% methanol–chloroform. Fractions containing pure αβ-*unsaturated aldehyde* (5a) were combined and evaporated to yield an oil (1.7 g, 63%); $\nu_{max.}$ ($CHBr_3$) 3 425 and 1 665 cm^{-1}; δ_H ($CDCl_3$) 9.9 (1 H, d, *J* 8 Hz, CHO), 5.92 (1 H, d, *J* 8 Hz, 2-H), 2.20 (3 H, s, 15-H_3), 1.17 (3 H, d, 14-H_3), 0.92 (3 H, d, 17-H_3); δ_C ($CDCl_3$) 191.7 (d, C-1), 162.5 (s, C-3), 128.8 (dd, C-2), 74.9 (d, C-5), 71.0 (d, C-13), 70.3 (d, C-7), 68.8 (d, C-6), 65.5 (t, C-16), 61.1 (d, C-11), 55.6 (d, C-10), 42.7 (d + t, C-4 and -12), 39.7 (d, C-8), 31.7 (t, C-9), 20.7 (q, C-14), 18.2 (q, C-15), and 12.6 p.p.m. (q, C-17); *m/e* 310 ($M^+ - H_2O$, 1), 293 (1), 227 (15), 141 (15), and 43 (100) (Found: 310.1781. $C_{17}H_{28}O_6 - H_2O$ requires 310.1783).

(3RS)-(E)-6-{(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*]-3,4-*dihydroxytetrahydropyran*-2-*yl*}-5-*methylhex*-4-*en*-3-*ol* (5d).—The αβ-unsaturated aldehyde (5a) (0.19 g) was dissolved in dry acetonitrile (20 ml) and the solution was stirred at room temperature for 1 h with *N*,*O*-bis(trimethylsilyl)acetamide (1 ml). The solvent was removed under reduced pressure at 40 °C to afford the protected aldehyde (5b). Ethylmagnesium bromide (2M solution in diethyl ether; 0.9 ml) was added to a suspension of copper(I) iodide (0.30 g) in dry THF (50 ml) at −78 °C under argon. The suspension was stirred at this temperature for a further 0.25 h. The protected αβ-unsaturated aldehyde (5b) was added as a solution in dry THF (10 ml) to the reaction mixture which was then stirred at −78 °C for 0.25 h, 0 °C for 1 h, and room temperature for 16 h under argon. The reaction was quenched by the addition of excess of saturated aqueous ammonium chloride and the product was extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogen carbonate and saturated brine, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was dissolved in 1,4-dioxan–water (4 : 1; 10 ml). Two drops of 1M hydrochloric acid were added and the solution was stirred at room temperature for 3 min. Excess of aqueous sodium hydrogen carbonate was added and the solution layered with ethyl acetate. The aqueous layer was saturated with sodium chloride and the organic layer separated, washed with water and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded the crude product as an oil which was purified by column chromatography on silica gel (4 g) with 5% methanol–chloroform as eluant. The pure *secondary allylic alcohol* (5d) was obtained as an oil (0.18 g, 87%); $\nu_{max.}$ ($CHBr_3$) 3 400 and 1 622 cm^{-1}; δ_H ($CDCl_3$) 5.25 (1 H, d, 2-H), 4.27 (1 H, m, 1-H), 1.72 (3 H, s, 15-H_3), 1.45 (2 H, m, CH_2CH_3), 1.21 (3 H, d, 14-H_3), and 0.9

(6 H, d + t, 17-H_3 and CH_2CH_3); δ_C ($CDCl_3$) 135.5 and 135.1 (C-3), 130.4 and 130.0 (C-2), 75.5 (C-5), 71.0 (C-13), 70.5 (C-7), 69.8 (C-6), 69.3 and 68.9 (C-1), 65.4 (C-16), 61.2 (C-11), 55.7 (C-10), 42.7 (C-12), 41.7 and 41.2 (C-4), 39.3 (C-8), 31.9 (C-9), 30.5 (CH_2CH_3), 20.8 (C-14), 17.2 (C-15), 12.6 (C-17), and 9.8 p.p.m. (CH_2CH_3); *m/e* 358 (M^+, 1), 340 (8) and 96 (100) (Found: M^+, 358.2358. $C_{19}H_{34}O_6$ requires *M*, 358.2361).

(E)-6-{(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*]-3,4-*dihydroxytetrahydropyran*-2-*yl*}-5-*methylhex*-4-*en*-3-*one* (1l).—The secondary allylic alcohol (5d) (0.089 g) was dissolved in dry dichloromethane (10 ml) and the solution was stirred at room temperature for 1 h with pyridinium chlorochromate (0.080 g) and powdered sodium acetate (0.050 g). Ether was added to the mixture which was then filtered. The filtrate was evaporated to dryness and partitioned between ethyl acetate and aqueous sodium hydrogen carbonate. The organic layer was washed with saturated brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude ketone as a black oil (0.70 g) which was purified by column chromatography on silica gel (1.5 g) with 5% methanol–chloroform as eluant to afford the pure αβ-*unsaturated ketone* (1l) as an oil (0.01 g, 11%); $\nu_{max.}$ ($CHCl_3$) 3 430, 1 682, and 1 620 cm^{-1}; δ_H ($CDCl_3$) 6.11 (1 H, s, 2-H), 2.43 (2 H, q, CH_2CH_3), 2.16 (3 H, s, 15-H_3), 1.20 (3 H, d, 14-H_3), and 0.95 (6 H, d + t, 17-H_3 and CH_2CH_3); *m/e* 356 (M^+, 1), 338 (2), 320 (2), 244 (20), 227 (40), and 57 (100) (Found: M^+, 356.2233. $C_{19}H_{32}O_6$ requires *M*, 356.2268).

(4RS)-(E)-1-{(2S,3R,4R,5S)-[(2S,3S,4S,5S)-2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*]-3,4-*dihydroxytetrahydropyran*-2-*yl*}-2-*methyloct*-2-*en*-4-*ol* (5f).—The αβ-unsaturated aldehyde (5a) (0.15 g) was dissolved in dry acetonitrile (20 ml) and the solution was stirred at room temperature for 1 h with *N*,*O*-bis (trimethylsilyl)acetamide (1 ml). The solvent was removed under reduced pressure at 40 °C. n-Butylmagnesium bromide (2M solution in diethyl ether; 0.8 ml) was added to a suspension of copper(I) iodide (0.030 g; 0.16 mM) in dry THF (50 ml) at −78 °C under argon. The suspension was stirred at this temperature for a further 0.25 h. The protected αβ-unsaturated aldehyde (5b) was then added as a solution in dry THF (10 ml) to the reaction mixture, which was then stirred at −78 °C for 0.25 h, 0 °C for 1 h, and room temperature for 16 h, under argon. The reaction was quenched by the addition of excess of saturated aqueous ammonium chloride and the product was extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate and saturated brine, dried ($MgSO_4$), and the solvent then removed under reduced pressure. The residue was dissolved in 1,4-dioxan–water (4 : 1; 10 ml) and two drops of 1M hydrochloric acid were added; the solution was then stirred at room temperature for 3 min. Excess of sodium hydrogen carbonate solution was added, the solution layered with ethyl acetate, and the aqueous layer saturated with sodium chloride. The organic layer was separated, washed with water and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded the crude product as a pale yellow oil (0.140 g) which was purified by column chromatography on silica gel (10 g) with 5% methanol–chloroform as eluant. The pure *alcohol* (5f) was obtained as an oil (0.076 g, 43%); $\nu_{max.}$ ($CHBr_3$) 3 400 and 1 640 cm^{-1}; δ_H ($CDCl_3$) 5.26 (1 H, d, 2-H), 4.32 (1 H, br t, 1-H), 1.72 (3 H, s, 15-H_3), 1.30 (6 H, m, $[CH_2]_3$), 1.22 (3 H, d, 14-H_3), and 0.93 (6 H, d + t, 17-H_3 and $[CH_2]_3CH_3$); δ_C ($CDCl_3$) 135.5 and 135.0 (2 × s, C-3), 131.0 and 130.6 (2 × d, C-2), 75.6 (d, C-5), 71.3 (d, C-13), 70.7 (d, C-7), 69.6 and 69.1 (2 × d, C-1), 68.7 (d, C-6), 65.6 (t, C-16), 61.4 (d, C-11), 55.9 (d, C-10), 42.9 (d, C-12), 41.9 and 41.3 (2 × t, C-4), 39.5 and 39.3 (2 × d, C-8), 37.6 [t, $C(OH)CH_2$], 32.1 (t, C-9), 27.8 [t, $C(OH)CH_2CH_2$], 22.9 [t, $C(OH)CH_2CH_2CH_2$], 21.1 (q, C-14), 17.4 (q, C-15), 14.3 (q, $[CH_2]_3CH_3$), and 12.8 p.p.m. (q, C-17); *m/e* (NH_3 c.i.) 404 ($M^+ + NH_4$, 8) 386 ($M^+ - H_2O + NH_4$, 10), 369 ($M^+ - H_2O + H$, 65), and 351 ($M^+ - 2H_2O + H$, 85).

(E)-1-(2S,3R,4R,5S)-5-[(2S,3S,4S,5S)-2,3-*Epoxy*-5-*hydroxy*-4-*methylhexyl*]-3,4-*dihydroxytetrahydropyran*-2-*yl*}-2-*methyloct*-2-*en*-4-*one* (1m).—(a) *From aldehyde* (5a). The αβ-unsaturated aldehyde (5a) (0.2 g) was dissolved in dry acetonitrile (20 ml) and the solution was stirred at room temperature for 1 h with *N*,*O*-bis(trimethylsilyl)acetamide (1 ml). The solvent was then removed under reduced pressure at 40 °C. n-Butylmagnesium bromide (2M solution in diethyl ether; 1 ml) was added to a suspension of copper(I) iodide (0.038 g) in dry THF (50 ml) at −78 °C under argon. The suspension was stirred at this temperature for a further 0.25 h and then the protected αβ-unsaturated aldehyde (5b) was added in dry THF (10 ml). The reaction mixture was stirred at −78 °C for 0.25 h, at 0 °C for 1 h, and at room temperature for 72 h under argon. The reaction was quenched by the addition of excess of saturated aqueous ammonium chloride. The resulting solution was extracted with ethyl acetate after which the organic layer was washed with water and saturated sodium chloride solution and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded a pale yellow oil which was dissolved in dry dichloromethane (20 ml); powdered sodium acetate (0.110 g) followed by pyridinium chlorochromate (0.263 g) was then added to the solution. The suspension was stirred at room temperature for 1 h and this was followed by trituration with dry ether (50 ml). The resulting black suspension was filtered through a pad of Florosil which was washed several times with ether. The combined washings and filtrate were evaporated to dryness under reduced pressure and the residual oil was partitioned between ethyl acetate and water. The organic layer was washed with aqueous sodium hydrogencarbonate and aqueous sodium chloride after which it was dried ($MgSO_4$). The solvent was then removed under reduced pressure to afford a pale yellow oil which was redissolved in 1,4-dioxan–water (4 : 1; 5 ml). 1M Hydrochloric acid (two drops) was added to the solution which was then shaken at room temperature for 3 min. Excess of aqueous sodium hydrogencarbonate was added and the solution was saturated with sodium chloride prior to extraction of the product with ethyl acetate. The organic layer was washed with aqueous sodium chloride, dried ($MgSO_4$), and the solvent evaporated under reduced pressure to yield the crude αβ-unsaturated n-butyl ketone as a pale yellow oil (0.110 g). The product was purified by column chromatography on silica gel (3 g) with 2% methanol–chloroform as eluant to afford the pure *ketone* (1m) as an oil (0.027 g, 12%); $\nu_{max.}$ ($CHBr_3$) 3 400, 1 680, and 1 615 cm^{-1}; $\lambda_{max.}$ (EtOH) 239 nm (ε 9 800); δ_H ($CDCl_3$) 6.12 (1 H, s, 2-H), 2.42 (2 H, t, $COCH_2$), 2.15 (3 H, s, 15-H_3), 1.5—1.1 (7 H, d + m, 14-H_3 and $COCH_2[CH_2]_2CH_3$), and 0.93 (6 H, br d, 17-H_3 and $[CH_2]_3CH_3$); δ_C ($CDCl_3$) 201.7 (C-1), 155.0 (C-3), 125.2 (C-2), 75.1 (C-5), 71.3 (C-13), 70.4 (C-7), 69.0 (C-6), 65.5 (C-16), 61.3 (C-11), 55.6 (C-10), 44.2 ($COCH_2$), 43.2 (C-4), 42.8 (C-12), 39.6 (C-8), 31.7 (C-9), 26.4 ($COCH_2CH_2$), 22.4 ($CO[CH_2]_2CH_2$), 20.8 (C-14), 19.6 (C-15), 13.9 $[CH_2]_3CH_3$), and 12.7 p.p.m. (C-17); *m/e* 384 (M^+, 2),

366 (2), 348 (3), 244 (30), 227 (55), 209 (20), 152 (65), and 85 (100) (Found: M^+, 384.2487. $C_{21}H_{36}O_6$ requires M, 384.2462).

(b) *From monic acid A* (1b). Isobutyl chloroformate (1.95 ml) was added to a solution of monic acid A (1b) (5.16 g) and triethylamine (2.3 ml) at −10 °C in THF (100 ml). The mixture was stirred for 1 h at room temperature and filtered. The filtrate was cooled to −10 °C and treated with triethylamine (6.8 ml) and trimethylsilyl chloride (6.3 ml). The mixture was stirred overnight at room temperature, filtered, and the filtrate evaporated under reduced pressure. Under argon, n-butyl-lithium (1.6M in hexane; 21 ml) was added to a suspension of manganese(II) chloride (3.78 g) in dry THF (60 ml) at −10 °C and the dark solution was stirred for a further 0.75 h at room temperature. The solution of butylmanganese(II) chloride was cooled to −10 °C and treated with the protected mixed anhydride (1h) in THF (100 ml). The mixture was stirred at room temperature for 2 h after which it was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with aqueous sodium hydrogencarbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was dissolved in 1,4-dioxan–water (4 : 1, 50 ml) and shaken with 10M hydrochloric acid (20 drops) for 5 min when excess of aqueous sodium hydrogen carbonate was added. The solution was extracted with ethyl acetate and the combined extracts were washed with brine and dried ($MgSO_4$). Removal of the solvents under reduced pressure afforded an oil which was chromatographed on silica (40 g) with 0—9% methanol–chloroform as eluant. Fractions containing pure αβ-unsaturated butyl ketone (1m) were combined and evaporated to yield the ketone (2.1 g, 36%). A second component, an oil, was also isolated and identified as (6), the *Z*-isomer of (1m) (1.15 g, 20%); $\nu_{max.}$ ($CHCl_3$) 3 400, 1 675, and 1 610 cm^{-1}; $\lambda_{max.}$ (EtOH) 240 nm (ε 7 900); δ_H ($CDCl_3$) 6.20 (1 H, s, 2-H), 2.44 (2 H, t, $COCH_2$), 1.99 (3 H, s, 15-H_3), 1.19 (3 H, d, 14-H_3), and 0.90 (6 H, d + t, 17-H_3 and $[CH_2]_3$-CH_3); δ_C ($CDCl_3$) 203.9 (C-1), 157.5 (C-3), 125.8 (C-2), 76.6 (C-5), 71.3 (C-13), 70.2 (C-7), 67.6 (C-6), 65.7 (C-16), 61.4 (C-11), 56.0 (C-10), 44.0 ($COCH_2$), 43.0 (C-12), 39.0 (C-8), 36.2 (C-4), 31.9 (C-9), 27.4 (C-15), 26.4 ($COCH_2CH_2$), 22.4 ($[CH_2]_2CH_2CH_3$), 20.7 (C-14), 13.8 ($[CH_2]_3CH_3$), and 12.7 p.p.m. (C-17); *m/e* 384 (M^+, 1), 366 (5), 348 (2), 309 (2), 291 (2), 227 (40), 85 (100), and 57 (75) (Found: M^+, 384.2489. $C_{21}H_{36}O_6$ requires M, 384.2466).

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REFERENCES

[1] Part 3, J. P. Clayton, R. S. Oliver, N. H. Rogers, and T. J. King, *J. Chem. Soc., Perkin Trans. 1*, 1979, 838.
[2] A. T. Fuller, G. Mellows, M. Woolford, G. T. Banks, K. D. Barrow, and E. B. Chain, *Nature (London)*, 1971, **234**, 416; Beecham Group Ltd., B.P. 1,395,907.
[3] E. B. Chain and G. Mellows, *J. Chem. Soc., Chem. Commun.*, 1974, 847; *J. Chem. Soc., Perkin Trans. 1*, 1977, 294.
[4] R. G. Alexander, J. P. Clayton, K. Luk, N. H. Rogers, and T. J. King, *J. Chem. Soc., Perkin Trans. 1*, 1978, 561.
[5] E. B. Chain and G. Mellows, *J. Chem. Soc., Perkin Trans. 1*, 1977, 318.
[6] J. P. Clayton, P. J. O'Hanlon, and N. H. Rogers, *Tetrahedron Lett.*, 1980, **21**, 881.
[7] R. Sutherland, K. R. Comber, L. W. Mizen, B. Slocombe, and J. P. Clayton, ' Pseudomonic Acid, an Antibiotic Produced by *Pseudomonas fluorescens*,' presented at the 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, U.S.A., 1976.
[8] M. J. Basker, K. R. Comber, J. P. Clayton, P. C. T. Hannan, L. W. Mizen, N. H. Rogers, B. Slocombe, and R. Sutherland, *Current Chemotherapy and Infectious Disease*, ' Proceedings of the 11th I.C.C. and the 19th I.C.A.A.C.,' Am. Soc. Microbiol., 1980, 471.
[9] J. P. Clayton, K. Luk, and N. H. Rogers, *J. Chem. Soc., Perkin Trans. 1*, 1979, 308.
[10] M. J. Jorgenson, *Org. React.*, 1970, **18**, 1.
[11] T. M. Bare and H. O. House, *Org. Synth.*, 1969, **49**, 81.
[12] C. Ruechardt, S. Eichler, and P. Panse, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 619.
[13] G. H. Posner, *Org. React.*, 1972, **19**, 1.
[14] R. J. Anderson, C. A. Henrick, and L. D. Rosenblum, *J. Am. Chem. Soc.*, 1974, **96**, 3654.
[15] M. S. Kharasch and O. Reinmuth, ' Grignard Reactions of Non Metallic Substances,' Constable, London, 1954, p. 196.
[16] A. J. Fatiadi, *Synthesis*, 1976, 65.
[17] M. Schlosser and Z. Brich, *Helv. Chim. Acta*, 1978, **61**, 1903.
[18] H. C. Brown, S. C. Kim, and S. Krishnamurthy, *J. Org. Chem.*, 1980, **45**, 1.
[19] D. H. R. Barton, D. J. Lester, W. B. Motherwell, and M. T. Barros Papoula, *J. Chem. Soc., Chem. Commun.*, 1979, 705.
[20] G. Cahiez, A. Alexakis, and J. F. Normant, *Synth. Commun.*, 1979, **9**, 639.
[21] G. Friour, G. Cahiez, A. Alexakis, and J. F. Normant, *Bull. Soc. Chim. Fr.*, 1979, 515.