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Synthesis of Fused Acetal Derivatives by Manganic Acetate Promoted Additions to Endocyclic Enol Ethers

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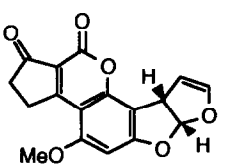
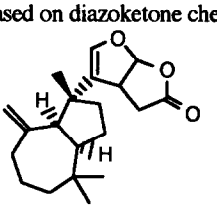
Abstract: Reaction of manganic acetate in acetic acid with β–diketones and β-ketoesters leads to generation of intermediates, which add efficiently to endocyclic unsaturated enol ethers to afford fused acetals.

The importance of pheromonal bicyclic spiroacetals, and of antibiotic polycyclic spiroacetals has stimulated the development of efficient methods of synthesis of spiroacetals. By contrast the interest in the synthesis of fused acetals has been more modest. The aflatoxins such as aflatoxin B1 (1), having a furobenzofuran subunit, attracted early interest[1] and their potential as serious food toxins has led to a continued synthetic activity.[2] The importance of developing efficient methods of synthesis of fused acetals has recently been increased by the discovery of novel fused acetal antibiotics. Thus the furofuran moiety is found in the dendrillolides[3] e.g. (2), asteltoxin[4], and rhyacophiline[5], in addition to the structurally more complex sterepolide[6]. The furopyran moiety is found in paraherquonin[7], the striatins[8], astepyrone[9] and rubrolone[10]. Fused acetal substructures are a feature of a number of structurally complex carbohydrates such as the affinosides[11], acmimycin[12], caerulomycin D[13], ranuncoside[14], and spectinomycin[15]. Important anti-feedant activity of fused acetals is established in azadirachtin and related compounds and certain clerodanes[16]. The observed biological activity of relatively simple fused acetals emphasizes the importance of the synthesis of both natural products and their fused acetal sub-fragments. Recently one general method based on diazoketone chemistry has been developed[17] for



(1)



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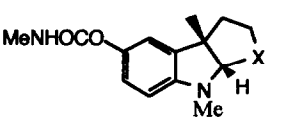


(3) X = NMe (4) X = O

the synthesis of such fused acetals, and the potential application to aflatoxin synthesis was noted. The reaction proceeding by addition of a β-dicarbonyl derivative to furan, can also be applied, by addition to pyrroles, to the construction of fused aminoethers. Such bicyclic systems having either geminal oxygen and nitrogen functionality, or two geminal nitrogens, are a feature of the important Calabar alkaloids. The alkaloid

Table 1

Synthesis of Fused Acetals

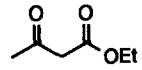
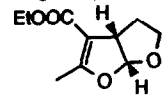
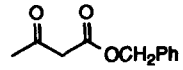
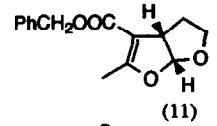
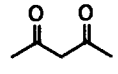
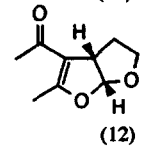
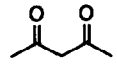
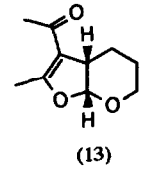
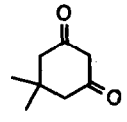
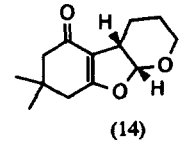
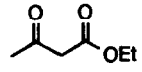
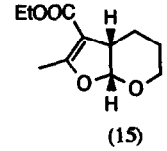
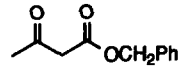
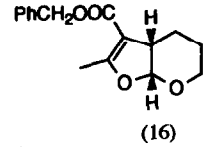
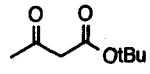
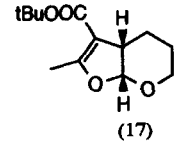
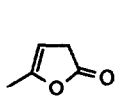
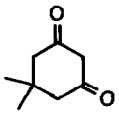
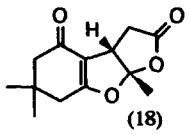
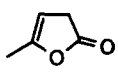
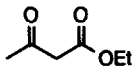
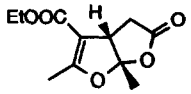
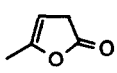
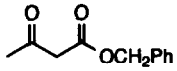
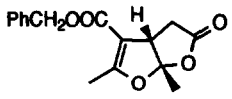
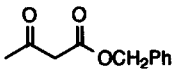
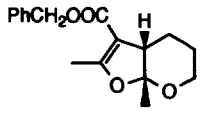
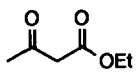
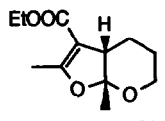
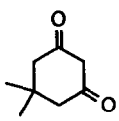
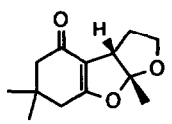
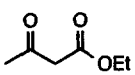
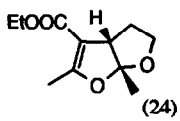
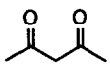
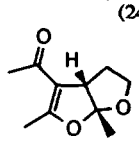
Reactants		Product	(Yield %)
 (5)		 (10)	53
 (5)		 (11)	56
 (5)		 (12)	26
 (6)		 (13)	38
 (6)		 (14)	43
 (6)		 (15)	47
 (6)		 (16)	50
 (6)		 (17)	31

Table 1 (continued)

Reactants		Product	Yield
 (7)		 (18)	24
 (7)		 (19)	28
 (7)		 (20)	15
 (8)		 (21)	39
 (8)		 (22)	39
 (9)		 (23)	40
 (9)		 (24)	51
 (9)		 (25)	44

physostigmine (3) is clinically useful in the treatment of glaucoma, and related compounds show promise as therapeutic agents in relation to Alzheimer's disease. The synthesis[18] of physostigmine (3) and the related physovenine (4) have been recently described. Hence there are many important synthetic targets featuring fused acetal, aminoether, and diamine fuctionality. The most widely adopted method of synthesis of these systems has proceeded via a final ring closure between a nucleophilic heteroatom and an electrophilic carbon centre. In this paper we describe a general procedure permitting the synthesis of fused acetals by additions to dihydrofurans, dihydropyran and endocyclic lactones. We are also studying related additions to permit the synthesis of alkaloids. In contrast to earlier methods based on ionic additions or carbene chemistry[17] our methodology relies on a manganic acetate promoted radical addition. In conjunction with the preliminary communication[19] these results constitute a general synthesis of fused acetals via radical chemistry. Hoffmann *et al* [20] have recently reported a tandem radical cyclisation affording both pyranofuran and furanofuran fused acetals. In the preceeding paper[21] we describe the related manganic acetate promoted addition to exocyclic enol lactones, which permits the synthesis of oxaspirolactones. In the following paper[22] we describe the related synthesis of unsaturated spiro-acetals.

Five readily available alkenes, dihydrofuran (5), dihydropyran (6), 5-methylfuran-2(3H)-one (7), 2-methyldihydropyran (8) and 2-methyldihydrofuran (9) were chosen as suitable substrates with which to investigate the generality of synthesis of fused acetals via manganic acetate promoted radical additions. Dihydrofuran (5) reacted with ethyl acetoacetate in acetic acid in the presence of one equivalent of manganic acetate to afford after work up and chromatography the fused acetal (10) in 53% yield. The assignment of structure is facilitated by observation of resonances associated with the acetal methine centre. In the ^{1}H n.m.r. spectrum the methine proton was observed at δ6.09 as a doublet (J 6Hz), and in the ^{13}C n.m.r. spectrum the carbon resonance was observed at 109.88ppm. These data are consistent with values found in related fused acetals. Thus in *cis*-fused aflatoxins the vicinal coupling constant associated with the proton at the acetal centre is typically 5.5-6Hz[2,23]. In a related sulfone the acetal carbon is observed[24] at 100.93ppm and in asteltoxin the acetal carbon is seen at 104.8ppm. In Table 1 the results are shown of 16 examples of reaction between one of the five alkenes, and one of the five β-dicarbonyl substrates. In each case a single fused acetal product was obtained. In reactions involving dihydrofuran (5) and dihydropyran (6), leading to the the acetals (10-12) and (13-17) respectively, the assignment of structure with a *cis* ring fusion is evident by direct observation of the vicinal coupling constant of the methine proton at the acetal centre. Similarly a *cis* fusion could be assigned to the three lactones (18-20) isolated from the lactone (7). Although the cis fusion cannot be observed from a vicinal coupling in the case of the products (21 and 22) and (23-25), obtained from 2-methyldihydropyran (8) and 2-methyldihydrofuran (9) respectively, the strong nuclear Overhauser enhancement between the methyl group and the ring junction methine proton in each of these products permits the unambiguous assignment of the *cis* stereochemistry.

Under the reaction conditions acid catalysed equilibration of *cis* and *trans* fused products might occur. Although it is likely that a kinetic closure would lead to a *cis* fused product, the isolation of *cis* products is probably more a reflection of their greater thermodynamic stability. In no case was a *trans* fused acetal observed. Observation of

the carbonyl group at 1810 cm.$^{-1}$ in the ir spectrum of the tricyclic acetal (18), and at 1795-1800 cm.$^{-1}$ in the bicyclic acetals is consistent with the *cis* assignments.

All the enol ether reactants and the products, including the lactones (18-20) are acid sensitive. The major manifestations of this sensitivity are the moderate yields obtained in certain examples shown in Table 1, and the tendency of these compounds to decompose on chromatography over silica gel. The results in Table 1 establish a general route to fused acetals based on addition to alkenes of radical intermediates generated by manganic acetate oxidation of diverse β-dicarbonyl compounds. Following the first report[20] of a radical route to fused acetals, these results establish a second strategy based on radical chemistry for the synthesis of fused acetals.In view of the significant anti-feedant activity[16] found in relatively simple fused acetals, the discovery of new routes to such structures is important. With the diversity of substrates shown in Table 1, although product stability is a limiting factor, this extension of manganese acetate methodology provides a rapid access to fused acetals of many skeletal types. It should be noted that all the examples are based on readily available starting materials.

Experimental

General procedures have been described elsewhere[21]. Commercial samples of dihydrofuran (5) and dihydropyran (6) were used. 5-Methylfuran-2(3H)-one (7) was prepared by distillation of levulinic acid in the presence of acid[26]. 2-Methyldihydropyran (8) and 2-methyldihydrofuran (9) were obtained by base promoted elimination from the appropriate chlorides[27].

General Procedure for Synthesis of Fused Acetals

Manganese (3) acetate dihydrate (2.0mmol) was heated in acetic acid (20ml) under nitrogen at 60-70^{o}C until a black homogeneous solution was obtained. The β–dicarbonyl compound (1.5mmol) and the alkene (1.0mmol) were added and the reaction mixture was kept at 60^{o}C until the colour had disappeared (10-120min). To the cold mixture water (50ml) was added and the solution was extracted with dichloromethane (3x25ml). The combined organic extracts were washed with saturated sodium bicarbonate solution and evaporated under reduced pressure to give an oil. Products were purified by flash chromatography, either on silica gel or alumina. The following compounds were obtained in the above manner.

***cis* (3a,6a)-3-Ethoxycarbonyl-2-methyl-3a,4,5,6a-tetrahydro-furo[2,3-b]furan (10)**

Ethyl acetoacetate (2.41g), dihydrofuran (5) (1.0g) and manganese acetate (7.65g) in acetic acid (40ml) afforded after chromatography on alumina as a colourless oil the title compound (10) (1.49g, 53% yield) ν_{max} ($CHCl_3$) 3000, 1695, and 1650 cm.$^{-1}$; δ_H 1.32 (3H, t, J 7,CH_3), 2.09 (2H, m, CH_2), 2.23 (3H, d, J 1.5, CH_3), 3.64 (1H, m), and 4.09 (1H, m) (CH_2O), 3.75 (1H, m, CH), 4.19 (2H, m, CH_2O) and 6.09 (1H, d, J 6, OCHO); δ_C 14.14 (CH_3), 14.44 (CH_3), 31.63 (CH_2), 47.05 (CH), 59.58 (OCH_2), 67.01 (OCH_2), 103.52 (*C*=CO), 109.61 (OCHO), 164.45 (C=*C*O), and 168.57 (CO); m/z 198 (27%) (Found: M^+ 198.0893 $C_{10}H_{14}O_4$ requires M^+ 198.0892).

***cis* (3a,6a)-3-Benzyloxycarbonyl-2-methyl-3a,4,5,6a-tetrahydro-furo[2,3-b]furan (11)**
Benzyl acetoacetate (3.56g), dihydrofuran (5) (1.0g) and manganese acetate (7.65g) in acetic acid (40ml) afforded after chromatography on alumina as a colourless oil the title compound (11) (2.08g, 56% yield) ν_{max} ($CHCl_3$) 3000, 1700, and 1650 cm.$^{-1}$; δ_H 2.09 (2H, m, CH_2), 2.23 (3H, d, J 1.5, CH_3), 3.68 (1H, m) and 4.08 (1H, m) (CH_2O), 3.78 (1H, m, CH), 5.09 (1H, d J 12.5) and 5.13 (1H, d, J 12.5) ($PhCH_2$), 6.10 (1H, d, J 6, OCHO) and 7.35-7.40 (5H, complex, Ar); δ_C 14.41 (CH_3), 31.80 (CH_2), 47.11 (CH), 65.61 (OCH_2), 67.18 (OCH_2), 103.42 (*C*=CO), 109.88 (OCHO), 128.08, 128.17 and 128.67 (CHAr), 136.59 (CHAr), 165.34 (C=*C*O), and 169.42 (CO); m/z 260 (22%) (Found: M$^+$ 260.1047 $C_{15}H_{16}O_4$ requires M$^+$ 260.1048).

***cis* (3a,6a)-3-Acetyl-2-methyl-3a,4,5,6a-tetrahydro-furo[2,3-b]furan (12)**
Acetylacetone (1.85g), dihydrofuran (5) (1.0g) and manganese acetate (7.65g) in acetic acid (40ml) afforded after chromatography on silica gel as a colourless oil the title compound (12) (0.51g, 26% yield) ν_{max} ($CHCl_3$) 3000, 1680, and 1630 cm.$^{-1}$; δ_H 1.97-2.21 (2H, m, CH_2), 2.26 (6H, 2xCH_3), 3.68 (1H, m) and 4.10 (1H, m) (CH_2O), 3.80 (1H, m, CH) and 6.11 (1H, d, J 6.7, OCHO); δ_C 15.23 (CH_3), 29.41 (CH_3), 31.95 (CH_2), 47.41 (CH), 67.04 (OCH_2), 109.74 (OCHO), 114.66 (*C*=CO), 168.05 (C=*C*O), and 193.77 (CO); m/z 168 (30%) (Found: M$^+$ 168.0782. $C_9H_{12}O_3$ requires M$^+$ 168.0786).

***cis* (3a,7a)-3-Acetyl-2-methyl-3a,5,6,7a-tetrahydro-4H-furo[2,3-b]pyran (13)**
Acetylacetone (0.89g), dihydropyran (6) (0.5g) and manganese acetate (3.19g) in acetic acid (20ml) afforded after chromatography on silica gel as an oil the title compound (13) (0.41g, 38% yield) ν_{max} ($CHCl_3$) 2990, 1710, and 1620 cm.$^{-1}$; δ_H 1.55 (2H, m, CH_2) , 2.08 (2H, m, CH_2), 2.25 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.00 (1H, m, CH), 3.81 (2H, m, OCH_2) and 5.78 (1H, d, J 7, OCHO); δ_C 15.26 (CH_3), 20.14 (CH_2), 23.36 (CH_2), 29.07 (CH_3), 37.82 (CH), 61.19 (OCH_2), 104.23 (OCHO), 118.34 (*C*=CO), 166.80 (C=*C*O), and 194.23 (CO); m/z 182 (68%) (Found: M$^+$ 182.0942 $C_{10}H_{14}O_3$ requires M$^+$ 182.0942).

***cis* (4a,9a)-7,7-Dimethyl-3,4,4a,5,6,7,8,9a-octahydro-2H-pyrano[2,3-b]benzofuran-5-one (14)** Dimedone (1.25g), dihydropyran (6) (0.5g) and manganese acetate (3.19g) in acetic acid (20ml) afforded after chromatography on silica gel an orange oil, which slowly crystallised. Recrystallisation (dichloromethane-pentane) afforded as white crystals the title compound (14) (0.56g, 42% yield) m.p. 94-96^{0}C ν_{max} ($CHCl_3$) 2990 and 1685 cm.$^{-1}$; δ_H 1.16 (6H, s, 2xCH_3), 1.55-1.98 (4H, complex, 2xCH_2), 2.23 (2H, m, CH_2), 2.39 (2H, m, CH_2), 3.18 (1H, m, CH), 3.81 (2H, m, OCH_2), and 5.98 (1H, d, J 8, OCHO); δ_C 19.33 (CH_2), 20.15 (CH_2), 28.23 (CH_3), 29.27 (CH_3), 34.01 (*C* (CH_3)$_2$), 35.29 (CH), 37.68 (CH_2), 51.08 (CH_2), 60.41 (OCH_2), 106.99 (OCHO), 114.64 (*C*=CO), 175.58
(C=*C*O), and 195.03 (CO); m/z 222 (100%) (Found: M$^+$ 222.1256 $C_{13}H_{18}O_3$ requires M$^+$ 222.1256).

***cis* (3a,7a)-3-Ethoxycarbonyl-2-methyl-3a,5,6,7a-tetrahydro-4H-furo[2,3-b]pyran (15)**
Ethyl acetoacetate (1.16g), dihydropyran (6) (0.5g) and manganese acetate (3.19g) in acetic acid (20ml) afforded after chromatography on silica gel as a colourless oil the title compound (15) (0.59g, 47% yield) ν_{max} ($CHCl_3$)

2995, 1695, and 1648 cm.$^{-1}$; δ_H 1.28 (3H, t, J 7,CH_3), 1.66 (3H, complex, CH_2 + CH), 1.98 (1H, m, CH), 2.23 (3H, s, CH_3), 3.00 (1H, m, CH), 3.78 (2H, m, OCH_2), 4.18 (2H, m, OCH_2) and 5.78 (1H, d J 7, OCHO); δ_C 14.39 (CH_3), 14.51 (CH_3), 19.97 (CH_2), 22.26 (CH_2), 37.99 (CH), 59.58 (OCH_2), 60.89 (OCH_2), 104.18 (OCHO), 106.96 (*C*=CO), 165.92 (C=*C*O), and 167.51 (CO); m/z 212 (22%) (Found: M$^+$ 212.1046 $C_{11}H_{16}O_4$ requires M$^+$ 212.1048).

***cis* (3a,7a)-3-Benzyloxycarbonyl-2-methyl-3a,5,6,7a-tetrahydro-4H-furo[2,3-b]pyran (16)**

Benzyl acetoacetate (3.41g), dihydropyran (6) (1.0g) and manganese acetate (6.38g) in acetic acid (40ml) afforded after chromatography on silica gel as a colourless oil the title compound (16) (1,63g, 50% yield) ν_{max} ($CHCl_3$) 2995, 1700, and 1645 cm.$^{-1}$; δ_H 1.66 (3H, complex, CH_2 + CH), 1.99 (1H, m, CH), 2.25 (3H, d, J 1, CH_3), 3.00 (1H, m, CH), 3.78 (2H, m, OCH_2), 5.14 (1H, d, J 12.5) and 5.20 (1H, d, J 12.5) (CH_2), 5.78 (1H, d J 7.5, OCHO) and 7.35-7.40 (5H, complex, Ar); δ_C 14.51 (CH_3), 19.95 (CH_2), 22.40 (CH_2), 37.86 (CH), 60.92 (OCH_2), 65.45 ($PhCH_2$), 104.31 (OCHO), 106.73 (*C*=CO), 128.00, 128.07 and 128.62 (CHAr), 136.64 (CAr), 165.61 (C=*C*O), and 168.20 (CO); m/z 274 (15%) (Found: M$^+$ 274.1212 $C_{16}H_{18}O_4$ requires M$^+$ 274.1205).

***cis* (3a,7a)-3-t-Butoxycarbonyl-2-methyl-3a,5,6,7a-tetrahydro-4H-furo[2,3-b]pyran (17)**

t-Butyl acetoacetate (2.26g), dihydropyran (6) (1.0g) and manganese acetate (6.38g) in acetic acid (40ml) afforded after chromatography on alumina as a colourless oil the title compound (17) (0.88g, 31% yield) ν_{max} ($CHCl_3$) 2995, 1690, and 1648 cm.$^{-1}$; δ_H 1.48 (9H, s, 3xCH_3), 1.64 (3H, complex, CH_2 + CH), 1.96 (1H, m, CH), 2.19 (3H, d, J 1.5, CH_3), 2.95 (1H, m, CH), 3.78 (2H, m, OCH_2), and 5.76 (1H, d J 7.5, OCHO); δ_C 14.32 (CH_3), 20.08 (CH_2), 22.31 (CH_2), 28.55 (C (*C*H_3)$_3$), 38.24 (CH), 60.84 (OCH_2), 79.76 (*C* (CH_3)$_3$), 103.88 (OCHO), 108.27 (*C*=CO), 165.38 (C=*C*O), and 166.44 (CO); m/z 240 (11%) (Found: M$^+$ 240.1374 $C_{13}H_{20}O_4$ requires M$^+$ 240.1361).

***cis* (3a,8a)-6,6,8a-Trimethyl-2,3,3a,4,5,6,7,8a-octahydro-furo[2,3-b]benzofuran-2,4-dione (18)**

Dimedone (0.85g), the lactone (7) (0.5g) and manganese acetate (2.73g) in acetic acid (15ml) afforded after chromatography on silica gel an oil, which slowly crystallised. Recrystallisation (dichloromethane-pentane) afforded as white flakes the title compound (18) (0.25g, 24% yield) m. p.161-163^{o}C ν_{max} ($CHCl_3$) 3000, 1810, and 1655 cm.$^{-1}$; δ_H 1.15 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.82 (3H, s, CH_3) 2.25 (2H, m, CH_2), 2.37 (2H, m, CH_2), 2.80 (1H, dd, J 18.5 and 2) and 2.96 (1H, dd, J 18.5 and 9) (CH_2) and 3.62 (1H, ddd, J 9,5 and 2, CH); δ_C 23.68 (CH_3), 28.39 (CH_3), 28.88 (CH_3), 33.17 (CH_2), 34.16 (*C* (CH_3)$_2$), 37.22 (CH_2), 43.87 (CH), 50.95 (CH_2), 114.02 (OCO), 118.08 (*C*=CO), 173.43 (C=*C*O), 174.16 (CO) and 194.14 (CO); m/z 236 (41%) (Found: M$^+$ 236.1053. $C_{13}H_{16}O_4$ requires M$^+$ 236.1048). (Found: C, 66.0; H, 6.85. $C_{13}H_{16}O_4$ requires C, 66.1, H, 6.8%)

***cis* (3a,6a)-2,6a-Dimethyl-3-ethoxycarbonyl-3a,6a-dihydro-furo[2,3-b]furan-5(4H)-one (19)**

Ethyl acetoacetate (0.79g), the lactone (7) (0.5g) and manganese acetate (2.73g) in acetic acid (15ml) afforded after chromatography on silica gel as an oil the title compound (19) (0.31g, 28% yield) ν_{max} ($CHCl_3$) 3000, 1800, 1705 and 1665 cm.$^{-1}$; δ_H 1.32 (3H, t J 7,CH_3), 1.78 (3H, s, CH_3), 2.25 (3H, d J 1.5, CH_3), 2.80 (1H, dd J 18 and 3) and 2.95 (1H, dd, J 18 and 8) (CH_2) 3.63 (1H, m, CH) and 4.21 (2H, m, OCH_2); δ_C 14.21 (CH_3), 14.49 (CH_3), 23.87 (CH_3), 34.58 (CH_2), 47.25 (CH), 60.28 (CH_2), 106.00 (*C*=CO), 115.33 (OCO), 164.45 (C=*C*O), 166.77 (CO) and 174.01 (CO); m/z 226 (45%) (Found: M$^+$ 226.0834. $C_{11}H_{14}O_5$ requires M$^+$ 226.0841).

***cis* (3a,6a)-3-Benzyloxycarbonyl-2,6a-dimethyl-3a,6a-dihydro-furo[2,3-b]furan-5(4H)-one (20)**

Benzyl acetoacetate (1.07g), the lactone (7) (0.5g) and manganese acetate (2,73g) in acetic acid (15ml) afforded after chromatography on silica gel as an oil the title compound (20) (0.23g, 15% yield) ν_{max} ($CHCl_3$) 3000, 1795, 1705 and 1665 cm.$^{-1}$; δ_H 1.76 (3H, s, CH_3), 2.22 (3H, d, J 1, CH_3), 2.84 (1H, dd, J 18.5 and 2.7) and 2.98 (1H, dd, J 18.5 and 8.5) (CH_2), 3.63 (1H, m CH), 5.18 (1H, d, J 12) and 5.23 (1H, d, J 12) ($PhCH_2$) and 7.35-7.40 (5H, complex, Ar); δ_C 14.27 (CH_3), 23.83 (CH_3), 34.57 (CH_2), 47.12 (CH), 66.11 (CH_2), 105.72 (*C*=CO), 115.37 (OCO), 128.41, 128.59 and 128.75 (CHAr), 135.96 (CAr), 164.18 (C=*C*O), 167.38 (CO) and 173.88 (CO); m/z 288 (17%) (Found: M$^+$ 288.0987. $C_{16}H_{16}O_5$ requires M$^+$ 288.0997).

***cis* (3a,7a)-3-Benzyloxycarbonyl-2,7a-dimethyl-3a,5,6,7a-tetrahydro-furo[2,3-b]-4H-pyran (21)**

Benzyl acetoacetate (0.73g), the alkene (8) (0.5g) and manganese acetate (2.5g) in acetic acid (15ml) afforded after chromatography on silica gel as an oil the title compound (21) (0.58g, 39% yield) ν_{max} ($CHCl_3$) 2975, 1700, and 1640 cm.$^{-1}$; δ_H 1.44 (3H, s, CH_3), 1.52 (2H, m, CH_2), 1.82 (2H, m, CH_2), 2.24 (3H, s, CH_3), 2.94 (1H, m, CH), 3.76 (2H, m, OCH_2), 5.12 (1H, d, J 13) and 5.28 (1H, d, J 13) ($PhCH_2$) and 7.22-7.38 (5H, complex, Ar); δ_C 14.62 (CH_3), 18.44 (CH_2), 21.26 (CH_2), 26.79 (CH_3), 43.08 (CH), 60.50 (CH_2), 65.48 ($PhCH_2$), 105.28 (OCO), 110.89 (*C*=CO), 128.07, 128.13 and 128.67 (CHAr), 136.72 (CAr), 165.82 (C=*C*O), and 168.08 (CO); m/z 288 (48%) (Found: M$^+$ 288.1358. $C_{17}H_{20}O_4$ requires M$^+$ 288.1361).

***cis* (3a,7a)-2,7a-Dimethyl-3-ethoxycarbonyl-3a,5,6,7a-tetrahydro-furo[2,3-b]-4H-pyran (22)**

Ethyl acetoacetate (0.49g), the alkene (8) (0.5g) and manganese acetate (2.5g) in acetic acid (15ml) afforded after chromatography on silica gel as an oil the title compound (22) (0.58g, 39% yield) ν_{max} ($CHCl_3$) 2995, 1700, and 1660 cm.$^{-1}$; δ_H 1.28 (3H, t, J 7,CH_3), 1.51 (3H, s, CH_3), 1.58 (2H, m, CH_2), 2.22 (3H, d J 1.5, CH_3), 2.95 (1H, m, CH), 3.78 (2H, m, OCH_2) and 4.18 (2H, m, OCH_2); δ_C 14.47 (CH_3), 14.55 (CH_3), 18.44 (CH_2), 21.15 (CH_2), 26.78 (CH_3), 43.15 (CH), 59.52 (OCH_2), 60.47 (OCH_2), 105.51 (OCO), 110.68 (*C*=CO), 166.07 (C=*C*O), and 167.35 (CO); m/z 226 (29%) (Found: M$^+$ 226.1190. $C_{12}H_{18}O_4$ requires M$^+$ 226.1205).

***cis* (3a,8a)-6,6,8a-Trimethyl-2,3,3a,4,5,6,7,8a-octahydro-furo[2,3-b]benzofuran-4-one (23)**

Dimedone (1.0g), the alkene (9) (0.5g) and manganese acetate (2.7g) in acetic acid (10ml) afforded after chromatography on silica gel as an oil the title compound (23) (0.52g, 40% yield) ν_{max} ($CHCl_3$) 2990 and 1645 cm.$^{-1}$; δ_H 1.10 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.65 (3H, s, CH_3), 2.03-2.18 (2H, m, CH_2), 2.24 (2H, m, CH_2), 2.33 (2H, m, CH_2), 3.36 (1H, m, CH), 3.65 (1H, m, CH) and 4.10 (1H, m, CH); δ_C 23.91 (CH_3), 28.25 (CH_3), 29.23 (CH_3), 31.54 (CH_2), 34.01 (*C*(CH_3)$_2$), 37.82 (CH_2), 47.54 (CH), 51.13 (CH_2), 68.63 (OCH_2), 112.76 (*C*=CO), 122.87(OCO), 175.61 (C=*C*O) and 194.64 (CO); m/z 222 (42%) (Found: M$^+$ 222.1254. $C_{13}H_{18}O_3$ requires M$^+$ 222.1255).

***cis* (3a,6a)-2,6a-Dimethyl-3-ethoxycarbonyl-3a,4,5,6a-tetrahydro-furo[2,3-b]furan (24)**

Ethyl acetoacetate (0.85g), the alkene (9) (0.5g) and manganese acetate (2.7g) in acetic acid (10ml) afforded after chromatography on silica gel as an oil the title compound (24) (0.65g, 51% yield) ν_{max} ($CHCl_3$) 3000, 1705, and 1655 cm.$^{-1}$; δ_H 1.23 (3H, t, J 7,CH_3), 1.55 (3H, s, CH_3), 1.98-2.16 (2H, m, CH_2), 2.19 (3H, s, CH_3), 3.32 (1H, m, CH), 3.68 (1H, m) and 4.05 (1H, m) (OCH_2), and 4.15 (2H, m, OCH_2); δ_C 14.28 (CH_3), 14.48 (CH_3), 23.88 (CH_3), 32.61 (CH_2), 50.75 (CH), 59.50 (OCH_2), 67.65 (OCH_2), 103.71 (*C*=CO), 118.48(OCO), 165.63 (C=*C*O) and 167.94 (CO); m/z 212 (20%) (Found: M$^+$ 212.1044. $C_{11}H_{16}O_4$ requires M$^+$ 212.1048).

***cis* (3a,6a)-3-Acetyl-2,6a-dimethyl-3a,4,5,6a-tetrahydro-furo[2,3-b]furan (25)**

Acetylacetone (0.71g), the alkene (9) (0.50g) and manganese acetate (2.7g) in acetic acid (10ml) afforded after chromatography on silica gel as a colourless oil the title compound (25) (0.48g, 44% yield) ν_{max} ($CHCl_3$) 2995, 1685, and 1630 cm.$^{-1}$; δ_H 1.60 (3H, s, CH_3), 1.96-2.24 (2H, m, GH_2), 2.28 (6H, s, 2xCH_3), 3.42 (1H, m, CH), 3.68 (1H, m, CH), and 4.05 (1H, m, CH); δ_C 15.49 (CH_3), 23.88 (CH_3), 29.61 (CH_3), 33.07 (CH_2), 51.20 (CH), 67.77 (OCH_2), 114.96 (*C*=CO), 118.84 (OCO), 167.71 (C=*C*O) and 194.13 (CO); m/z 182 (40%) (Found: M$^+$ 182.0938. $C_{10}H_{14}O_3$ requires M$^+$ 182.0942).

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References

1. Schuda, P.F. *Top. Curr. Chem.* **1980**, 91, 75.
2. Bujons, J; Sanchez-Baeza, F; Messeguer, A. *Tetrahedron Lett.*, **1992**, 33, 6387; Kraus, G. A.; Johnston, B. E.; Applegate, J. M.*J. Org. Chem.* **1991**, 56, 5688; Horne, S.; Weeratunga, G.; Rodrigo, R. *J. Chem. Soc. Chem. Commun.* **1990**, 39; Wolff, S.; Hoffmann, H. M. R. *Synthesis* **1988**, 760; Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1986**, 51, 1006.
3. Bobzin, S. C.; Faulkner, D. J. *J. Nat. Prod.* **1991**, 54, 225; Bobzin, S. C.; Faulkner, D. J. *J. Org. Chem.* **1989**, 54, 3902 and 5727.

4. Nishiyama, S.; Kanai, H.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1990**, 63, 1322; Tadano, K.; Yamada, H.; Idogaki, Y.; Ogawa, S.; Suami, T. *Tetrahedron Lett.* **1988**, 29, 655; Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, 106, 4186; Kruger, G. J.; Steyn, P. S.; Vleggaar, R. Rabie, C. J. *J. Chem. Soc. Chem. Commun.* **1979**, 441.
5. Fernandez, M. C.; Esquivel, B.; Cardenas, J.; Sanchez, A.A.; Toscano R. A.; Rodriguez-Hahn, L. *Tetrahedron* **1991**, 47, 7199.
6. Trost, B. M.; Chung, J. Y. L.; *J. Am. Chem. Soc.* **1985**, 107, 4586; Ayer, W. A.; Saeedi-Ghomi, M. H. *Tetrahedron Lett.* **1981**, 22, 2071.
7. Okuyama, E.; Yamazaki, M.; Kobayashi K.; Sakurai, T. *Tetrahedron Lett.* **1983**, 24, 3113.
8. Hecht, H-J.; Hofle, G.; Steglich, W.; Anke, T.; Oberwinkler, F. *J. Chem. Soc. Chem. Commun.* **1978**, 665.
9. Anke, H.; Casser, I.; Schrage, M.; Steglich, W. *J. Antibiot.* **1988**, 41, 1681.
10. Schuep, W.; Blount, J. F.; Williams, T. H. Stempel, A. *J. Antibiot.* **1978**, 31, 1226.
11. Al-Said, M. S.; Hifnawy, M. S.; McPhail, A. T.; McPhail, D. R. *Phytochemistry* **1988**, 27, 3245.
12. Sakakibara, H.; Awata, M.; Satoi, S.; Mutoh, N.; Takada, M.; Hayashi, M. *French Patent* **1984** No. Fr. 2532950 (*Chem. Abs.* **1984**, 101, 37205)
13. McInnes, A. G.; Smith, D. G.; Walter, J. A.; Wright, J. L. C.; Vining, L. C.; Arsenault, G. P. *Canad. J. Chem.* **1978**, 56, 1836.
14. Tschesche, R.; Welmar, K.; Wulff, G.; Snatzke, G. *Chem. Ber.* **1972**, 105, 290.
15. Cochran, T. G.; Abraham, D. J.; Martin, L. L. *J. Chem. Soc. Chem. Commun.* **1972**, 494.
16. Ley, S. V.; Toogood, P. L. *Chem. Brit.* **1990**, 31; Merritt, A.; Ley, S. V. *Nat. Prod. Rep.* **1992**, 9, 243.
17. Pirrung, M. C.; Zhang, J.; McPhail, A. T. *J. Org. Chem.* **1991**, 56, 6269.
18. Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, 56, 5982.
19. Mellor, J. M.; Mohammed, S. *Tetrahedron Lett.* **1991**, 32, 7107.
20. Albrecht, V; Wartchow, R; Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 910.
21. Mellor, J. M.; Mohammed, S. *Tetrahedron* Submitted for publication.
22. Mellor, J. M.; Mohammed, S. *Tetrahedron* Submitted for publication.
23. Buchi, G; Foulkes, D. M.; Kurono, M.; Mitchell, G. F. *J. Am. Chem. Soc.* **1966**, 88, 4534.
24. Welchert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, 56, 4098.
25. Corey, E. J.; Ghosh, A. K. *Chem. Lett.* **1987**, 223.
26. Wolff, L. *Annalen* 1885, **229**, 249; Helberger, J. H., Ulubay, S.; Civelekoglu, H. *Annalen* 1949, **561**, 215.
27. Brooks, L. A.; Snyder, H. R. *Org. Synth.* Coll. Vol. 3, **1955**, 698; Ansell, M. F.; Thomas, D. A. *J. Chem. Soc.* **1958**, 1163; Ansell, M. F.; Brown, S. S. *J. Chem. Soc.* **1957**, 1788.