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ALKYLATION REACTIONS OF ANIONS DERIVED FROM 2-BENZENESULPHONYL TETRAHYDROPYRAN AND THEIR APPLICATION TO SPIROKETAL SYNTHESIS

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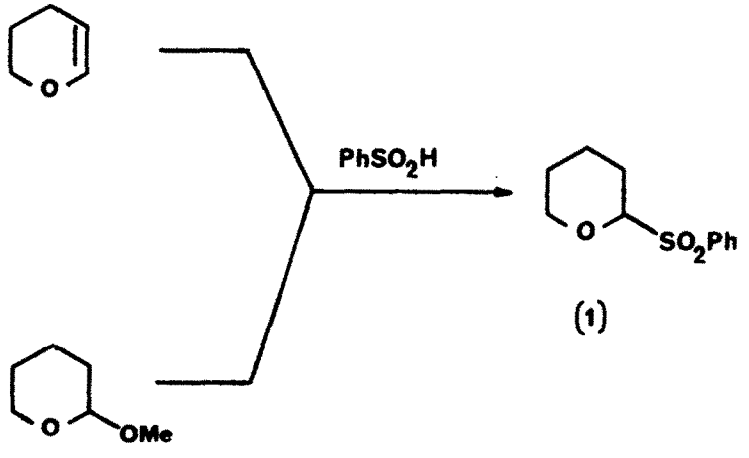
Abstract: Reaction of 3,4-dihydro-2H-pyran or 2-methoxytetrahydropyran with benzenesulphinic acid gave 2-benzenesulphonyl tetrahydropyran (1). Deprotonation of (1) followed by alkylation with carbonyl compounds or halides gave cyclic enol ether addition products by spontaneous elimination of benzenesulphinic acid. Interception of the initial addition products with aldehydes by reductive desulphonylation to give alkylated tetrahydropyran derivatives proceeded in moderate yield using sodium naphthalenide. Several of the cyclic enol ether addition products were further converted to spiroketals including syntheses of natural product pheromones from Dacus oleae and Paravespula vulgaris.

New methods of forming carbon-carbon bonds at the 2-position of cyclic ethers are of increasing importance in the total synthesis of many natural products. Here we report a detailed study on the preparation and alkylation reactions of anions derived from 2-benzenesulphonyl tetrahydropyran.[1] This approach provides an alternative method for the formation of carbon-carbon bonds at the 2-position of cyclic ethers and is complementary to recently reported routes using Wittig or Horner-Wittig strategies.[2-5] Other groups have also recently disclosed reactions of 2-deoxy-D-glucopyranosyl sulphones for C-glucoside synthesis.[6]

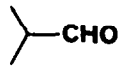
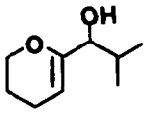
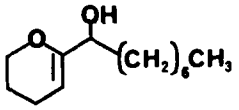
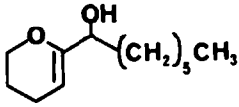
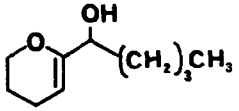
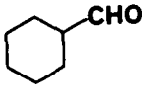
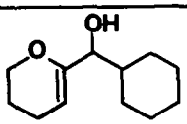
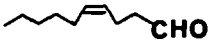
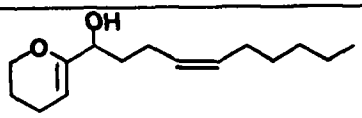
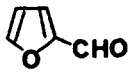
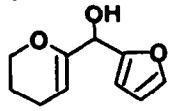
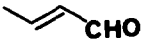
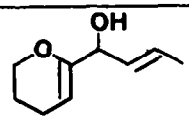
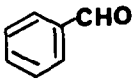
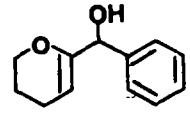
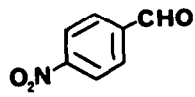
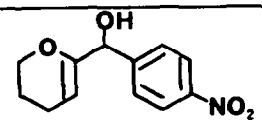
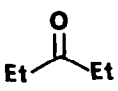
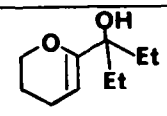
The crystalline sulphone 1 was prepared by reaction of either 3,4-dihydro-2H-pyran or 2-methoxy tetrahydropyran with benzenesulphinic acid in dicholoromethane at room temperature for 2 h (Scheme 1). Deprotonation of (1) was achieved with n-butyl lithium or lithium diisopropyl amide at -78°C in tetrahydrofuran. The pale yellow anion formed could be quenched with a variety of electrophiles (Table 1) and after aqueous work-up the endo-enol ethers were obtained in reasonable yields, although many of these products were rather volatile and hydroscopic. Benzenesulphinic acid was spontaneously eliminated from the intermediate alkylated products as the reaction warmed to room temperature presumably due to the slightly basic media and the inherent leaving ability of the benzenesulphonyl group. The only exception to this was the reaction with alkyl and aryl chloroformates, where the acylated sulphones were isolated. X-ray crystal structure determination showed the sulphone adopted the equatorial position in all examples.

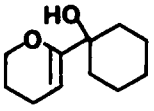
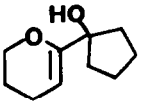
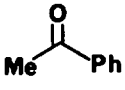
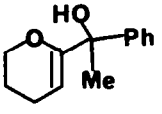
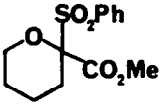
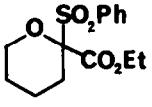
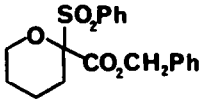
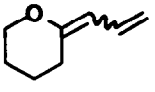
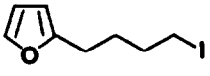
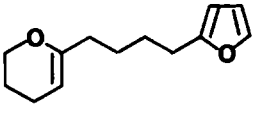
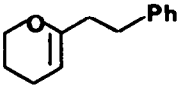
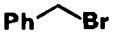
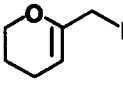
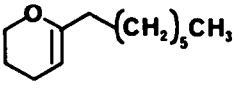
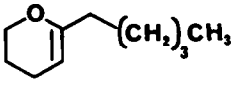
Scheme 1



By quenching the anion from (1) with deuterium oxide, assignment of the anomeric proton could be made by nmr spectrocopy, from which it was determined that the sulphone moiety was also equatorial.

Table 1

Electrophile	Product		Yield%*
		(2)	65
$CH_3(CH_2)_6CHO$		(3)	58
$CH_3(CH_2)_5CHO$		(4)	62
$CH_3(CH_2)_3CHO$		(5)	59
		(6)	88
		(7)	64
		(8)	50
		(9)	50
		(10)	46
		(11)	25
		(12)	58

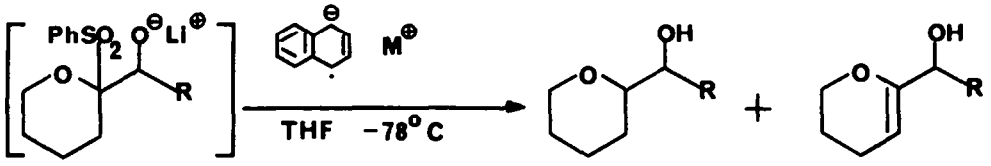
		(13)	70
		(14)	66
		(15)	42
$ClCO_2Me$		(16)	81
$ClCO_2Et$		(17)	74
$ClCO_2CH_2Ph$		(18)	48
		(19)	51
		(20)	57
		(21)	53
		(22)	29
$CH_3(CH_2)_5CH_2I$		(23)	37
$CH_3(CH_2)_3CH_2I$		(24)	49.

* All yields of pure products prepared under optimized conditions and purified by Kugelrohr distillation or column chromatography on florisil.

In an effort to extend this sulphone-based methodology, ways of reductively removing the sulphone group at low temperature prior to sulphinic acid elimination were investigated. In this way it was hoped that simple alkylation at the 2-position of tetrahydropyrans could be achieved.

In situ reductive desulphonylation of the intermediate alkylated species at -78°C with 5 equivalents of lithium or sodium naphthalenide (generated by ultrasonic methods) was moderately successful, affording good yields of mixtures of the required ether and enol ether which could be separated by chromatography. (Scheme 2) (Table 2).

Scheme 2

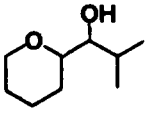
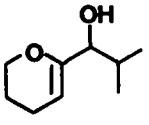
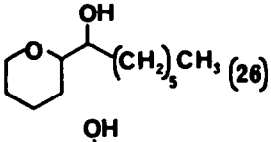
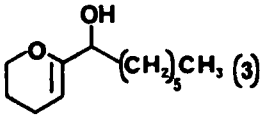
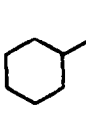
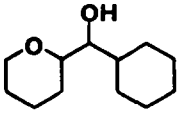
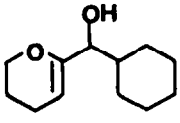


A degree of diastereoselectivity was observed in the formation of the cyclic ether products. Although this was low for condensation with isobutyraldehyde (7 : 3) and cyclohexanecarboxaldehyde (3:1), the adduct with octanal was formed with apparent complete stereoselectivity.

Unfortunately, treatment of the acyl sulphones (16), (17) and (18) with lithium and sodium naphthalenide or sodium amalgam did not afford the desired reductively desulphonylated tetrahydropyran products.

Ethers (25) and (27) could also be prepared by catalytic hydrogenation (H_2, Pd/C) of (2) and (6) respectively, with different diastereoselection from that observed for reductive desulphonylation.

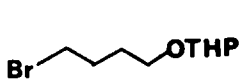
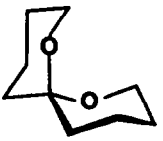
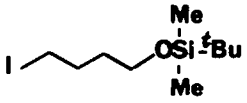
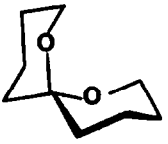
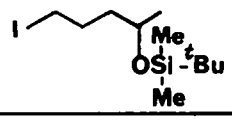
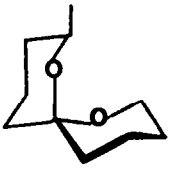
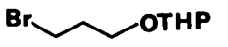
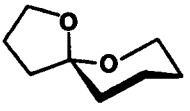
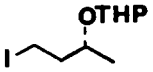
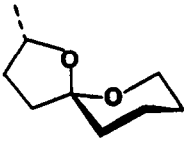
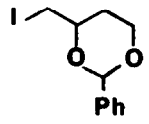
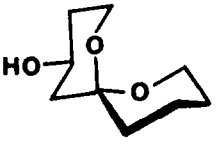
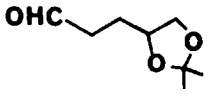
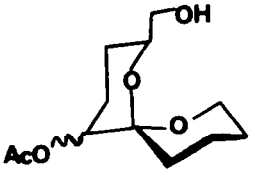
Table 2

Electrophile	Products	Yields $Li^+[C_{10}H_8]^-$	Yields $Na^+[C_{10}H_8]^-$
	 (25)	47	53
	 (2)	36	26
$CH_3(CH_2)_5CHO$	 (26)	-	57
	 (3)	-	16
	 (27)	27	50
	 (6)	25	24

* All yields of pure products purified by column chromatography on silica.

Many of the intermediate enol ethers prepared in the initial study readily underwent acid catalysed cyclisation to spiroketals (See table 3). The spiroketal group is an important functional arrangement in many natural products and this new method therefore provides a short synthetic pathway to several insect pheromones derived from the olive fly Dacus oleae (29) (33)[7] and the common wasp Paravespula vulgaris (32)[8].

Table 3

Electrophile	Product	Yield %
	 (29)	71
	 (29)	52
	 (30)	47
	 (31)	57
	 (32)	79
	 (33)	48
	 (34)*	33

* After Ac_2O trapping of intermediate hydroxy enol ether.

EXPERIMENTAL

^{1}H NMR spectra were obtained on Bruker WH-400, Bruker WH-250, Jeol FX90Q and Varian EM-360A spectrometers in deuteriochloroform solutions with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 983 G spectrophotometer as liquid films or chloroform solutions. Mass spectra were obtained on a VG Micromass 7070B instrument. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on MN-silica gel 60 230-400 mesh or florisil 200-300 U.S. mesh., under pressure. Light petroleum refers to the fraction boiling in the range 40°-60°C and ether to diethyl ether. Solutions were dried over anhydrous sodium sulphate, and solvents by standard methods.

Preparation of 2-Benzenesulphonyltetrahydro-2H-pyran (1) (Method A).- 3,4-Dihydro-2H-pyran (1.11g, 13.2 mmol) was added dropwise to a stirred solution of benzenesulphinic acid (1.88 g, 13.2 mmol) in dry dichloromethane at room temperature under argon. Stirring was continued for 2 h, then the solvent removed under reduced pressure and the product recrystallised from ether-petrol to give 2-benzenesulphonyl tetrahydro-2H-pyran (2.45 g, 82%) as white needles, m.p. 78°C; IR ($CHCl_3$) 1315, 1150, 1084, 692 cm^{-1}; NMR δ (90 MHz): 7.91 (2H, m, ArH), 7.58 (3H, m, ArH), 4.39 (1H, dd J = 3.1, 10 Hz, H2), 4.11 (1H, m, H6) 3.45 (1H, m, H6), 2.18-1.46 (6H, m); m/z 142 and 85, (Found C 58.24; H 6.14. $C_{11}H_{14}O_3S$ requires C 58.39; H 6.24%).

(Method B)

2-Methoxytetrahydropyran (1.54 g, 13.3 mmol) was added dropwise to a stirred solution of benzenesulphinic acid (2.83 g, 19.9 mmol) in dry dichloromethane at room temperature under argon with a suspension of calcium chloride. After 4 h, the solution was washed with water, dried and evaporated and the product recrystallised from ether-petrol to give 2-benzenesulphonyl-tetrahydro-2H-pyran (2.38 g, 79%) identical to the material prepared above.

General Procedure for condensation of the anion of 2-Benzenesulphonyltetrahydro-2H-pyran with electrophiles.

The sulphone was dissolved in dry THF at -78°C under argon. n-Butyllithium was added dropwise and the mixture stirred at -78°C for 15 min, then the electrophile added and the solution warmed to room temperature over ½ - 2 h. It was poured into sodium bicarbonate solution and extracted with ether (2 x 20 cm^3). The ethereal extracts were dried and evaporated to give the crude adduct which was purified by column chromatography on florisil eluting with petrol-ether mixtures or by kugelrohr distillation.

Preparation of enol ether (2).- Isobutyraldehyde (0.09 cm^3, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work up gave (2), 2-(1'-hydroxy-2'-methyl-propyl)-5,6-dihydro-4H-pyran) (102 mg, 65%). IR 3446, 2955, 1675, and 1062 cm^{-1}; NMR δ (90 MHz): 4.70 (1H, t, J = 3.7 Hz, H3), 4.00 (2H, t, J = 5.2 Hz, H6), 3.50 (1H, br.m. H1'), 2.15-1.05 (6H, m), 0.9 (6H, d, J = 5.2 Hz, H3'); m/z 156 (M^+), 113, 85, 55. (Found M^+ 156.1154, $C_9H_{16}O_2$ requires 156.1150).

Preparation of enol ether (3).- Octanal (0.174 cm^3, 1.11 mmol) was added to a solution of the anion of (1) (1.112 mmol). Chromatography after work-up gave (3), 2-(1'-hydroxy-octyl)-5,6-4H-pyran (137 mg, 58%). IR 3422, 2926, 1675, 1465, and 1064 cm^{-1}; NMR δ (90 MHz): 4.70 (1H, t, J = 3.85 Hz, H3), 4.00 (2H, m, H6), 3.85 (1H, br t, J = 6.4 Hz, H1') 2.6 (1H, br, J = 7.7 Hz, OH), 2.4-1.1 (16H, m), 0.9 (3H, t, J = 3.9 Hz, CH_3), m/z 212 (M^+), 114, 85, 55. (Found M^+ 212.1771, $C_{13}H_{24}O_2$ requires 212.1776).

Preparation of enol ether (4).- Heptanal (0.134 cm^3, 1 mmol) was added to a solution of the anion of (1), (1 mmol). Chromatography after work-up gave (4) 2-(1'-hydroxy-heptyl)-5,6-dihydro-4H-pyran. (122 mg, 62%). IR 3407, 2926, 1675 and 1063 cm^{-1}; NMR δ (90 MHz): 4.70 (1H, t, J = 3.6 Hz, H3), 4.00 (2H, t, J = 5.1 Hz, H6), 3.85 (1H, br.d, J = 7.2 Hz, H1') 2.10-1.1 (15H, m) 0.9 (3H, t, J = 3.6 Hz, CH_3). m/z 198 (M^+), 114, 85, 83, 55 (Found: C 72.69; H, 11.45. $C_{12}H_{22}O_2$ requires C, 72.68, H 11.18%).

Preparation of enol ether (5).- Pentanal (0.106 cm^3, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work-up gave (5), 2-(1'hydroxy-pentyl)5,6-dihydro-4H-pyran (101 mg, 59%). IR, 3422, 2955, 1675 and 1062 cm^{-1}; NMR δ (90 MHz): 4.75 (1H, t, J = 3.6 Hz, H3), 4.00 (2H, t, J = 5.2 Hz, H6), 3.85 (1H, br.d, J = 6.9 Hz, H1'), 2.25 (1H, m, OH), 2.10-1.2 (10H, m) 0.9 (3H, t, J = 3.7 Hz, CH_3). m/z 170 (M^+), 114, 113, 85, 57. (Found: M^+ 170.1305, $C_{10}H_{18}O_2$ requires 170.1306)

Preparation of enol ether (6).- Cyclohexanecarboxaldehyde (0.134 cm^3, 1.108 mmol) was added to a solution of the anion of (1) (1.1 mmol). Chromatography after work-up gave (6), 2-(1'-hydroxy-cyclohexyl)5,6-dihydro-4H-pyran (191 mg, 88%). IR, 3431, 1675, 1448 and 1060 cm^{-1}. NMR δ (90 MHz), 4.65 (1H, t, J = 3.8 Hz, H3), 4.00 (2H, m, H6), 3.5 (1H, dd, J = 5.1 Hz, 5.1 H1'), 2.10-0.6 (16H, m). m/z 196 (M^+), 114, 113, 85. (Found: M^+ 196.1467 $C_{12}H_{20}O_2$ requires 196,1463).

Preparation of enol ether (7).- Dec-4,5-enal (0.154 g, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work-up gave (7), 2-(1'-hydroxy-non-4',5'-enol)5,6 dihydro-4H-pyran (152 mg, 64%). IR 3384, 2926, 1675 and 1066 cm^{-1}. NMR δ (90 MHz): 5.35 (2H, t, J = 3.6 Hz, H4' H5'), 4.75 (1H, t, J = 3.9 Hz, H3), 4.00 (2H, t, J = 5.4 Hz, H6), 3.85 (1H, m, H1') 2.25-1.35 (17H, m), 0.9 (3H, t, J = 3.6 Hz, CH_3). m/z 238 (M^+), 183, 114, 85, 57. (Found: M^+ 238.1931, $C_{15}H_{26}O_2$ requires 238.1932).

Preparation of enol ether (8).- 2-Furaldehyde (0.082 cm^3, 1mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work-up gave (8), 2-(1-hydroxy-2'furfuryl) 5,6-dihydro-4H-pyran (89 mg, 50%). IR 3426, 2929, 1675, 1499 and 1062 cm^{-1}. NMR δ (90 MHz): 7.35 (1H, s, H5'), 6.30 (2H, s, H4' H3'), 5.00 (1H, br.d J = 5.1 Hz, H1'), 4.85 (1H, t J = 3.8 Hz, H3), 4.05 (2H, t, J = 5.4 Hz, H6), 2.6 (1H, br.d J = 15 Hz, OH), 2.1-1.6 (4H, m). m/z 180 (M^+), 163, 97, 85, 55. (Found: 180.0794, $C_{10}H_{12}O_3$ requires 180.0786).

Preparation of enol ether (9).- Trans-2-Butenal (0.083 cm^3, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Chromatography after work-up gave (9), 2-(1'-hydroxy-but-2',3'-enyl)5,6-dihydro-4H-pyran (77 mg, 50%). IR 3446, 2930, 1675, 1628 and 1064 cm^{-1}. NMR δ (90 MHz): 5.75 (2H, m, H2' H3'), 4.75 (1H, t, J = 3.6 Hz, H3), 4.45 (1H, m, H1'), 4.00 (2H, t, J = 5.2 Hz, H6), 2.05-1.35 (8H, m). m/z 154 (M^+) 130, 85, 69. (Found: M^+ 154.0989. $C_9H_{14}O_2$ requires 154.0994)

Preparation of enol ether (10).- Benzaldehyde (0.102 cm^3, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Distillation after work-up gave (10), 2-(1'-hydroxy-phenyl)5,6-dihydro-4H-pyran) (87 mg, 46%) b.p. 90°C at 0.1 mmHg. IR 3422, 2927, 1674 and 1086 cm^{-1}. NMR δ (90 MHz): 7.6-7.2 (5H, m, Ar H), 5.05 (0.7H, br.s H1'), 4.75 (1H, t, J = 4.1 Hz, H3), 4.00 (2H, t, J = 4.9 Hz, H3), 3.75 (0.3H, s, H1') 2.5 (1H, br.s, OH), 2.00-1.60 (4H, m). m/z 190 (M^+), 106, 105, 85, 77. (Found: M^+ 190.0985 $C_{12}H_{14}O_2$ requires 190.0993).

Preparation of enol ether (11).- Paranitrobenzaldehyde (0.150g, 1 mmol) was added to a solution of the anion (1) (1 mmol). Chromatography after work-up gave (11) 2-(1'-hydroxy-1'-paranitro-benzaldehyde)5,6-dihydropyran, (59 mg, 25%). IR ($CHCl_3$) 3580, 3400, 1675, 1151, 1058 cm^{-1}. NMR δ (90 MHz): 8.3-8.2 (2H, m, ArH), 7.7-7.5 (2H, m, ArH), 5.1 (1H, d, J = 5 Hz, H1'), 4.85 (1H, t, J = 3.9 Hz, H3), 4.0 (2H, t, J = 5.4 Hz, H6), 2.55 (1H, d, J = 5 Hz, OH), 2.2-0.8 (4H, m). m/z 235 (M^+) 156, 150, 101, 85, 83, 77, 55. (Found M^+ 235.0547, $C_{12}H_{13}NO_4$ requires 235.0844).

Preparation of enol ether (12).- Pentan-3-one (0.050 cm^3, 0.5 mmol) was added to a solution of the anion of (1), (1.25 mmol). Chromatography after work-up gave (12), 2-(1'-hydroxy-1'-ethyl-propyl)5,6-dihydro-4H-pyran (0.049 g, 58%). IR 3478, 2930, 1670, 1058 cm^{-1}. NMR δ (90 MHz): 4.78 (1H, t, J = 3.6 Hz, H3), 3.95 (2H, t, J = 4.3 Hz, H6), 2.15-1.25 (9H, m), 0.95-0.85 (6H, m), m/z 170 (M^+), 141, 113, 83, 57. (Found: 170.1310, $C_{10}H_{18}O_2$ requires 170.1306).

Preparation of enol ether (13).- Cyclohexanone (0.125 cm^3, 1.21 mmol) was added to a solution of the anion of (1) (3.02 mmol). Chromatography after work-up gave (13) 2-(1'-hydroxy-1'-cyclohexyl) 5,6-dihydro-4H-pyran (153 mg, 70%). IR 3398, 2926, 1667, 1448, 1235, 1150, 1067 cm^{-1}. NMR δ (90 MHz): 4.80 (1H, t, J = 3.9 Hz, H3), 4.00 (2H, t, J = 5.1 Hz, H6), 2.3-1.0 (14H, m). m/z 182 (M^+), 139, 55 (Found: M^+ 182.1303, $C_{11}H_{18}O_2$ requires 182.1307).

Preparation of enol ether (14).- Cyclopentanone (0.088 cm^3, 1 mmol) was added to a solution of (1) (2.5 mmol). Chromatography after work-up gave (14), 2-(1'-hydroxy-1'-cyclopentyl)5,6-dihydropyran (111 mg, 66%) IR 3422, 2947, 1670 and 1066 cm^{-1}. NMR δ (90 MHz) 4.8 (1H, t, J = 3.6 Hz, H3), 4.00 (2H, t, J = 5.4 Hz, H6), 2.2-1.55 (13H, m). m/z 168 (M^+), 151, 137, 111, 85, 83. (Found: M^+ 168.1151, $C_{10}H_{16}O_2$ requires 168.1150).

Preparation of enol ether (15).- Acetophenone (0.116 cm^3, 1 mmol) was added to a solution of the anion of (1) (2.5 mmol). Chromatography after work-up gave (15) 2-(1'-hydroxy-methyl, phenyl)-5,6-dihydro-4H-pyran (83 mg, 42%). IR 3446, 2930, 1670, 1599, 1087 and 766 cm^{-1}. NMR δ (90 MHz): 7.6-7.3 (5H, m, ArH), 5.00 (1H, t J_+ = 3.750 (1H, m, OCH_2) 3.75-3.50 (1H, m, OCH_2), 2.70-2.45 (1H, m), 1.40-1.15 (5H, m). m/z No M^+, 218, 142, 91, 77. (Found C 63.11; H, 5.57; C $_{19}H_{20}O_5S$ requires C 63.32; H 5.59%).

Preparation of the acylated sulphone (16).- Methyl chloroformate (0.077 cm^3, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Recrystallisation of the solid obtained after work-up from ether-petrol gave (16) as a white solid, 2-methyl(benzenesulphonyl) tetrahydropyran-2-yl)formate (230 mg, 81%), m.p. 52°C. IR ($CHCl_3$), 1744, 1073, 689 cm^{-1}. NMR δ (90 MHz): 7.88-7.28 (5H, m, ArH), 4.35-3.30 (5H, m, including 3.75 s, Me). 2.70-1.20 (6H, m). m/z no M^+, 143, 141, 125, 1.09, 77 and 59. (Found: C 54.81; H, 5.65. $C_{13}H_{16}O_5S$ requires C 54.91; H, 5.65%).

Preparation of the acylated sulphone (17).- Ethyl chloroformate (0.095 cm^3, 1 mmol), was added to a solution of the anion of (1) (1 mmol). Recrystallisation of the solid obtained after work-up from petrol-ether gave (17) as white solid, 2-ethyl(benzenesulphonyl)tetrahydropyran-2-yl)formate (223 mg, 74%) m.p. 59°C. IR ($CHCl_3$) 2948, 2871, 1733, 1325, 1155, 1085, 1039 and 605 cm^{-1}. NMR δ (90 MHz): 7.91 (2H, m, ArH), 7.65-7.52 (3H, m, ArH), 4.25-4.05 (3H, m, OCH_2), 3.75-3.55 (1H, m, OCH_2), 2.60-2.45 (1H, m), 2.15-1.45 (5H,m), 1.15 (3H, t, J = 20 Hz). m/z No (M^+), 156, 127, 142, 83. (Found: C, 56.35, H, 6.37. $C_{14}H_{18}O_5S$ requires C 56.36, H 6.09%).

Preparation of the acylated sulphone (18).- Benzyl chloroformate (0.143 cm^3, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Recrystallisation of the solid from petrol-ether gave (18) as a white solid, 2-benzyl-(benzenesulphonyl, tetrahydropyran-2-yl)formate (172 mg, 48%). m.p. 68-69°C. IR ($CHCl_3$), 2948, 2868, 1736, 1325, 1156, and 1085 cm^{-1}. NMR δ (90 MHz): 7.85-7.75 (2H, m, ArH), 7.60-7.30 (8H, m, including 7.35, s, Ph), 5.15 (2H, s, CH_2 Ph), 4.20-4.00 (1H, m, OCH_2), 3.75-3.50 (2H, m, OCH_2), 2.70-2.45 (1H, m), 1.40-1.15 (5H, m). m/z No M^+, 218, 142, 91, 77. (Found C 63.11; H, 5.57; $C_{19}H_{20}O_5S$ requires C 63.32; H 5.59%).

Preparation of enol ether (19).- Allyl bromide (0.0865 cm^3, 1 mmol) was added to a solution of the anion of (1) (1.5 mmol). Chromatography after work-up gave (19) (63 mg, 51%). IR 3077, 2938, 2870, 1713, 1638 and 1069 cm^{-1}. NMR δ (90 MHz): 6.0-5.6 (1H, m, H2') 5.2-4.9 (3H, m, H3, H1'), 3.7-3.3 (3H, m, H6, H3) 3.15 (1H, m, H3) 1.9-1.7 (4H, m). m/z 125 (M^+H), 124 (M^+), 101, 84, 57. (Found: 124.0884, $C_8H_{12}O$ requires 124.0888).

Preparation of enol ether (20).- 1-Iodo, 4-furyl butane (0.25 g, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Distillation after work-up yielded (20) 2-(4' furyl butyl)5,6-dihydro-4H-pyran (118 mg, 57%) b.p. 100°C/0.2 mm Hg. IR 2934, 1673, 1626 and 1064 cm^{-1}. NMR δ (90 MHz): 7.35 (1H, br.s, H2'), 6.32 (1H, m, H4'), 6.05 (1H, m, H3'), 4.55 (1H, m, H3), 4.05 (2H, m, H6), 2.61 (4H, m). 1.98-1.56 (8H, m). m/z 206 (M^+) 123, 83, 87, 67, 55. (Found: M^+ 206.1302, $C_{13}H_{18}O_2$ requires 206.1306).

Preparation of enol ether (21).- Bromo ethyl phenyl (0.136 cm^3, 1 mmol) was added to a solution of the anion of (1) (1 mmol). Distillation after work-up gave (21), 2-(2'phenylethyl)5,6-dihydro-4H- pyran (100 mg, 53%) b.p. 60°C/0.005 mmHg. IR 2933, 1675, 1088,1063 cm^{-1}. NMR δ (90 MHz): 7.30-7.15 (5H, m, Ar), 4.65 (1H, m, H3), 3.90 (2H, m, OCH_2), 2.85 (2H, m, CH_2-Ph), 1.85-1.5 (6H, m). m/z 188 (M^+), 104, 91, 85, 55. (Found: M^+ 188.1203, $C_{13}H_{16}O$ requires 188.1201).

Preparation of enol ether (22).- Benzylbromide (0.109 cm^3, 1 mmol) was added to a solution of the anion of (1) (1 mmol) (deprotonated using lithium diisopropylamide). Distillation after work-up yielded (22), 2(1'phenylmethyl)5,6-dihydro-4H-pyran (51 mg, 29%) b.p. 80°C/0.05 mmHg. IR 3029, 1673, 1068 and 692 cm^{-1}. NMR δ (90 MHz), 7.60-7.25 (5H, m, ArH), 5.21 (0.3H, s, Z isomer), 4.45 (0.7H, Z, J = 4.5 Hz, endo isomer), 3.75 (2H, m, OCH_2), 3.20 (1.4H, s, CH_2 endo), 2.1-1.85 (4.6H, m). m/z 174 (M^+), 91,90, 83 and 55. (Found: C 82.66; H 8.31. $C_{12}H_{14}O$ requires C 82.72, H 8.10%).

Preparation of enol ether (23).- 1-Iodoheptane (0.113 cm^3, 0.690 mmol) was added to a solution of the anion of (1) (2.07 mmol). Chromatography after work-up gave (23), 2-(heptyl) 5,6-dihydro-4H-pyran (46.5 mg, 37%). IR 2930, 2853, 1678, 1463, 1207, 1098, 1067, 898 cm^{-1}. NMR δ (60 MHz): 4.75 (1H, t, J = 3.9 Hz, H3), 4.0 (2H, t, J = 5. Hz, H6), 2.2-0.7 (19H, m). m/z 183 (M + 1$^+$), 182, 101, 86, 84. (Found: M^+ 182.1671, $C_{12}H_{22}O$ requires 182.1671).

Preparation of enol ether (24).- 1-Iodopentane (0.126 cm^3, 0.965 mmol) was added to a solution of the anion of (1) (2.983 mmol). Chromatography after work-up gave (24), 2-pentyl 5,6-dihydro-4H- pyran (72.5 mg, 49%). IR 3042, 1674, 1465, 1234, and 1066 cm^{-1}. NMR δ (90 MHz): 4.45 (1H, t, J = 3.9 Hz, H3), 3.95 (2H, t, J = 5.1 Hz, H6), 2.2-1.1 (12H, m), 0.9 (3H, t, J = 3.2 Hz, 3H). m/z 155, 154 (M^+), 111, 101, 981, 83, 55, 41, 29. (Found: M^+ 154.1356, $C_{10}H_{18}O$ requires 154.1358).

Preparation of sodium or lithium naphthalenide solution.

A mixture of the metal and naphthalene (1:1 molar equivs.) in dry THF at room temperature under argon was ultrasonified for 1h to afford a dark green solution.

General Procedure for condensation of the anion of 2-Benzenesulphonyltetrahydro-2H-pyran with electrophiles and in situ reductive desulphonylation.

The sulphone was dissolved in anhydrous THF at -78°C under argon. n-Butyllithium was added dropwise, the mixture stirred at -78°C for 15 min and then the electrophile added. After stirring for 15 min at -78°C, a 1 M solution of freshly prepared lithium or sodium naphthalenide in THF was added then, after a further 1 h at -78°C, anhydrous methanol. The solution was warmed to room temperature over 2-3 h, poured into water (10 cm^3) and extracted with ether (3 x 30 cm^3). The ethereal extracts were dried and evaporated to give the crude adduct which was purified by column chromatography on silica, eluting with petrol-ether mixtures.

Preparation of ether (25).- A solution of the anion of (1) (1.001 mmol) was treated with isobutyraldehyde (0.091 cm^3, 1.001 mmol), sodium naphthalenide (5.01 cm^3 of 1 M solution, 5.01 mmol, 5 eq) and methanol (0.40 cm^3, 10 mmol, 10 eq) according to the general procedure. Chromatography after work-up (elution gradient 10:1 ⟶ 4:1 petrol-ether) gave (25), 2-(1'-hydroxy, 2'-methyl- propyl)-tetrahydropyran, (83.8 mg, 53%). IR 3470, 1465, 1207, 1087, 1000, 733 cm^{-1}. NMR δ (250 MHz): 4.03 (1H, ddd, J = 11.3, 1.9, 1.9 Hz, H6), 3.55-3.22 (2.3H, m, H6, H2, H1' (minor diastereomer), 3.22-3.11 (0.7H, ddd, J = 6.3, 4.8, 3.8 Hz, H1' (major diastereomer), 2.46 (0.7 H, d, J = 3.8 Hz, OH (major diastereomer), 2.00-1.05 (7H, m, H3', H4', H5', H2'), 1.05-0,81 (6H, m, H3'). m/z 159 (MH^+), 157, 141, 115, 113, 85, 84. (Found: 141.1277. $C_9H_{17}O$ requires 141.1279 (calculated for (MH^+ -OH)). Continued elution gave (2), (41.1 mg, 26%), identical to the material prepared above.

Preparation of ether (26).- A solution of the anion of (1) (1.016 mmol) was treated with octanal (0.159 cm^3, 1.016 mmol), sodium naphthalenide (5.08 cm^3 of 1 M solution, 5.08 mmol, 5 eq) and methanol (0.41 cm^3, 10.1 mmol, 10 eq) according to the general procedue. Chromatography after work-up (elution gradient 10:1 → 7:1 → 4:1 petrol-ether) gave (26) 2-(1'-hydroxy, octyl)-tetrahydropyran (124 mg, 57%). IR 3462, 1465, 1207, 1091, and 1045 cm^{-1}. NMR δ (400 MHz): 4.03 (1H, ddd, J = 11.5, 2.1, 1.8 Hz, H6), 3.41 (2H, m, H1', H6), 3.10 (1H, ddd, J = 11.5, 6.5, 2 Hz, H_2), 2.56 (1H, br.s, OH), 1.86 (1H, br.d, J = 12 Hz), 1.60-1.20 (17H, m), 0.85 (3H, t, J = 7 Hz, Me). m/z 215 (MH^+), 213, 197 (MH^+-H_2O), 1.69, 130, 115, 111, 85. (Found: 197.1900, $C_{13}H_{25}O$ requires 197.1905 (calculated for MH^+-H_2O)). Continued elution gave (3) (35 mg, 16.1%), identical to the previously prepared material.

Preparation of ether (27).- A solution of the anion of (1) (1.002 mmol) was treated with cyclohexanecarboxaldehyde (0.121 cm^3, 1.002 mmol), sodium naphthalenide (5.0 cm^3 of 1 M solution, 5.0 mmol, 5 eq) and methanol (0.40 cm^3, 9.9 mmol, 9.9 eq) according to the general procedure. Chromatography after work-up (elution gradient 10:1 → 7:1 → 4:1 petrol-ether) gave (27), 2-(1'-hydroxy, cyclohexyl)tetrahydropyran. (100 mg, 50%). IR 3462, 1448, 1085, 1048 cm^{-1}. NMR δ (250 MHz): 4.00 (1H, ddd, J = 11.6, 1.8, 1.8 Hz, H_6), 3.52-3.20 (2.4H, m, H_6, H_1, H_1, (minor diastereomer), 3.18-3.06 (0.6H, ddd, J = 4.6, 4.6, 4.6 Hz, H_1, (major diastereomer), 2.40 (0.67H, d, J = 4.6 Hz, OH (major diastereomer), 2.20 (0.22H, br.s, OH (minor diasteromer), 2.06-0.82 (17H, m). m/z 197 (M^+-H), 179, 115, 112, 85, 84. (Found: 197.1545, $C_{12}H_{21}O_2$ requires 197.1541 (calculated for M^+-1). Continued elution gave (6) (46 mg, 24%), identical to the material prepared previously.

General Procedue for catalytic hydrogenation of enol ethers.

The enol ether in dry methanol was stirred with palladium on activated carbon (25% catalyst system) under a H_2 atmosphere for 16-64 h. The catalyst was filtered off and the solvents evaporated to afford the pure ether.

Hydrogenation of (2).- (2) (100 mg, 0.64 mmol) was hydrogenated for 16 h according to the general procedure to provide (25) (90 mg, 89%) as a diastereomeric mixture (data as above).

Hydrogenation of (6).- (6) (46 mg, 0.23 mmol) was hydrogenated for 64 h according to the general procedure to afford (27) (41 mg, 90%) as a diastereomeric mixture (data as above).

Preparation of Spiroketals

1,7-Dioxaspiro[5,5]undecane (29).- A solution of the anion of (1) (2.2 mmol) was treated with 1-[tetrahydro-2H-pyran-2-yl]oxy, 4-bromobutane (0.52 g, 2.2 mmol). Work-up and distillation gave (29) (265 mg, 77%) as a colourless oil, b.p. 100°C/25 mmHg. IR 2940, 1171, 1045 and 948 cm^{-1}. NMR δ (250 MHz), 3.77-3.55 (4H, m, OCH_2), 1.95-1.73 (2H, m) and 1.68-1.36 (10H, m); m/z 156 (M^+), 101, 100, 98, 83, 55 and 41 and was identical to the natural product.

1,7-Dioxaspiro[5,5]undecane (29).- A solution of the anion of (1) (1 mmol) was treated with 1-[(t-butyldimethylsilyl)oxy] 4-iodobutane (0.314 g, 1 mmol). Work-up, immediate treatment of the intermediate with hydrogen fluoride and chromatography gave (29) (81 mg, 52%) identical to that prepared above.

2-Methyl-1,7-dioxaspiro[5.5]undecane (30).- A solution of the anion of (1) (1 mmol) was treated with 1-[(t-butyldimethylsilyl)oxy, methyl,] 4-iodobutane (0.329 mg, 1 mmol). Work-up, immediate treatment of the intermediate with hydrogen fluoride and chromatography gave (30) (79 mg, 47%). IR 2932 and 1058 cm^{-1}. NMR δ (90 MHz): 3.8-3.55 (3H, m, OCH_2), 1.92-1.35 (12H, m), 1.15 (3H, d, J = 6.3 Hz, CH_3). m/z 170 (M^+), 101, 85 (Found: M^+ 170.1303, $C_{10}H_{18}O_2$ requires 170.1307).

1,6-dioxaspiro[4.5]decane (31).- A solution of the anion of (1) (1 mmol) was treated with 1-[tetrahydro-2H-pyran-2-yl]oxy 3-bromopropane (0.22 g, 1 mmol). Work-up and distillation gave (31) (81 mg, 57%) as a colourless oil. IR 2940, 1079 and 1035 cm^{-1}. NMR δ (250 MHz): 3.95-3.35 (4H, m, OCH_2), 2.05-1.45 (10H, m). m/z 142 (M^+), 85, 71 and 55. (Found: M^+ 142.0996 $C_8H_{14}O_4$ requires 142.0994).

2-Methyl-1,6-dioxaspiro[4,5]decane (32).- A solution of the anion of (1) (11.1 mmol) was treated with 1-iodo[3-tetrahydro-2H-pyran-2-yl]oxybutane (3.1 g, 11 mmol). Work-up and distillation gave (32) (1.37 g, 79%) as a colourless oil (1:2 mixture cis:trans isomers), b.p. 75°C/10 mmHg. $[\alpha]_D^{22}$ -21.1°. IR 2929, 1435 and 1367 cm^{-1}. δ (250 MHz): 4.28-3.25 (3H, m), 2.20-1.40 (10H, m), 1.31 (1H, d, J = 5.4 Hz, Me cis isomer) and 1.24 (2H, d, J = 5.8Hz, Me trans isomer). m/z 156 (M^+), 85, 67, and 53 which was identical with the natural product.

4-Hydroxy 1,7-dioxaspiro[5,5]undecane (33).- A solution of the anion of (1) (0.13 g, 0.58 mmol) was treated with 2-phenyl-1,3-dioxolane-4-iodomethane (71 mg, 0.23 mmol) Work-up, immediate treatment with HCl (1M) in MeOH and chromatography gave (33) (19.3 mg, 49%) as waxy solid. IR (film) 3446, 2946, 2870, 1449, 1380, 1058, 1045 and 982 cm^{-1}. NMR (400 MHz) 4.08 (1H, tt, J = 11, 5 Hz, H4) 3.75-3.47 (4H, m, H2, H8), 2.01 (1H, ddd, J = 11.5, 5, 2 Hz, H5e), 1.89 (1H, ddd, J = 12, 5.2 Hz, H3e), 1.81 (1H, tt, J = 12, 5 Hz, H10a), 1.71 (1H, br.s OH), 1.68-1.44 (6H, m), 1.29 (1H, dd, J = 11.5, 11 Hz H5a). ^{13}C (22.51 MHz) 18.5, 25.1, 35.0, 35.6, 45.2, 58.8, 60.4, 64.1, 97.3. m/z 172 (M^+), 155, 117, 101, 83, 55 and was identical to the natural product.

E-2-hydroxymethyl-5-acetoxy-1,7-dioxaspiro[5,5]undecane (34).- A solution of the anion of (1) (1 mmol) was treated with 2,2-dimethyl-1,3-dioxolane-4-propanal (0.159 g, 1 mmol). The intermediate was trapped with acetic anhydride (0.142 cm^3, 2 mmol) then subsequently treated with CSA in MeOH. Chromatography gave (35) (62 mg 33%) as a pale yellow oil. IR 3456, 1734, 1373, 1180, 1078 and 1046 cm^{-1}. NMR δ (90 MHz): 4.8 (1H, m, H-OCOCH$_2$), 3.9-3.5 (5H, m, OCH), 2.25 (1H, m), 2.10 (3H, s, OCH3) 1.85-1.4 (10H, m). m/z 244 (M^+), 213, 153, 85, 59, (Found M^+ 244.1310 $C_{12}H_{20}O_5$ requires 244.1310).

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