Approaches to the 1,6,8-Trioxadispiro[4.1.5.3]pentadec-13-en-15-ol Ring System of Salinomycin and Related Polyether Antibiotics

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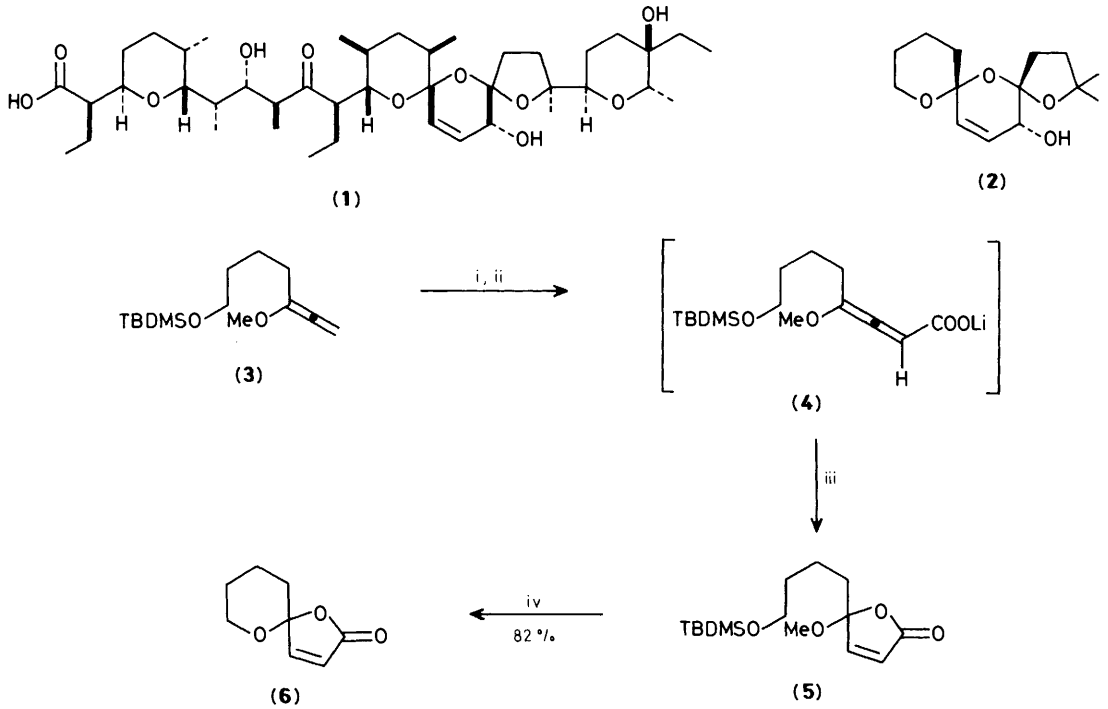
The acid-catalysed rearrangement of 2,5-dialkyl-2,5-dioxy-2,5-dihydrofurans (**9**) and (**15**) are key steps common to two alternative approaches to the dispiroacetal ring system of salinomycin and related polyether antibiotics.

The 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system is a structural feature common to the polyether antibiotics salinomycin, narasin, noboritomycin, and CP 44,661.[1] Recent synthetic approaches to salinomycin (**1**) have exploited the addition of carbanions to δ-valerolactones followed by cyclisation to generate the unsaturated central ring.[2] We now report two alternative approaches to the 1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-en-15-ol ring system (**2**) in which a key step is the acid-catalysed rearrangement of a 2,5-dialkyl-2,5-dioxy-2,5-dihydrofuran intermediate.

The first approach required the spirocyclic butenolide (**6**) which was prepared as shown in Scheme 1. Metallation of the methoxyallene (**3**)[3] followed by carboxylation gave the intermediate (**4**) which underwent stereoselective protonation[4] and cyclisation to give the butenolide (**5**). Subsequent hydrolysis and cyclisation to the spirocyclic butenolide (**6**) was best achieved using 40% aqueous HF in acetonitrile.[5]

Addition (Scheme 2) of the butenolide (**6**) to 2 equiv. of the lithiated dihydrofuran (**8**)[6] at −60 °C followed by aqueous work-up and treatment of the crude reaction mixture with acid gave a complex mixture from which the dispiroacetals (**10**) and (**11**) (1:1) were isolated in 15% combined yield after column chromatography on silica gel eluting with Et_2O–hexanes (1:4).

The structures and conformations of the spiroacetals (**10**) and (**11**) were established by n.m.r. studies† (Tables 1—3). 2D COSY and C–H correlation experiments in both C_6D_6 and $CDCl_3$, together with coupling constants, allowed the assignment of most of the ^{13}C and ^1H resonances. The stereochemistry of the protons around the tetrahydrofuran ring and the relative stereochemistry of the anomeric centres at C-5 and C-7 were assigned with the aid of n.O.e. difference experiments. Thus for spiroacetal (**10**) in C_6D_6, irradiation of the methyl resonance at δ 1.48 caused enhancement of 12e-H and 11a-H on the tetrahydropyran ring establishing it as Me′ with the stereochemistry shown. Enhancement of the protons at δ 1.998 and 2.286 was also observed establishing these as 3-H′ and 4-H′. By comparison irradiation of the δ 1.370 methyl resonance gave n.O.e. enhancements only of the signals at δ 1.878 (3-H) and δ 3.002 (4-H). The structure was further supported by a small n.O.e. enhancement of 4-H′ on irradiation of 9a-H,



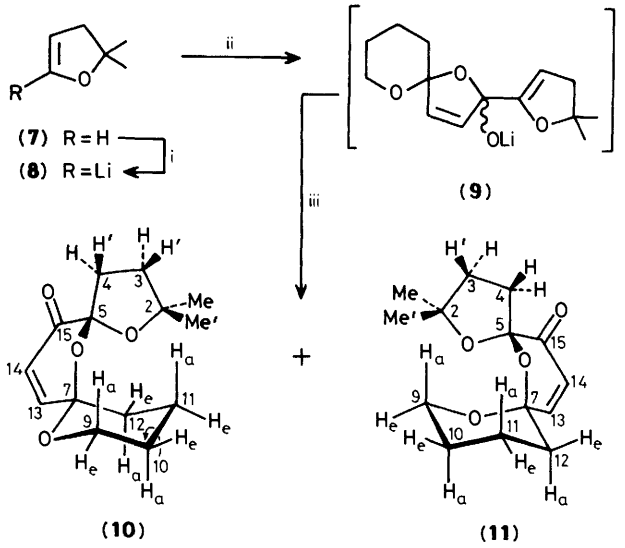
Scheme 1. *Reagents:* i, Bu^{t}Li/THF, −70 °C, 1 h; ii, CO_2; iii, 10% H_2SO_4–Et_2O, 0 °C, 1 h; iv, HF/MeCN, 20 °C, 2 h

† ^1H, COSY, and n.O.e. difference experiments were recorded at 360 MHz on a Bruker AM-360 spectrometer. ^{13}C and C-H correlation experiments were carried out on a JEOL GX-270 machine at 270 MHz (proton) and 65 MHz (carbon).

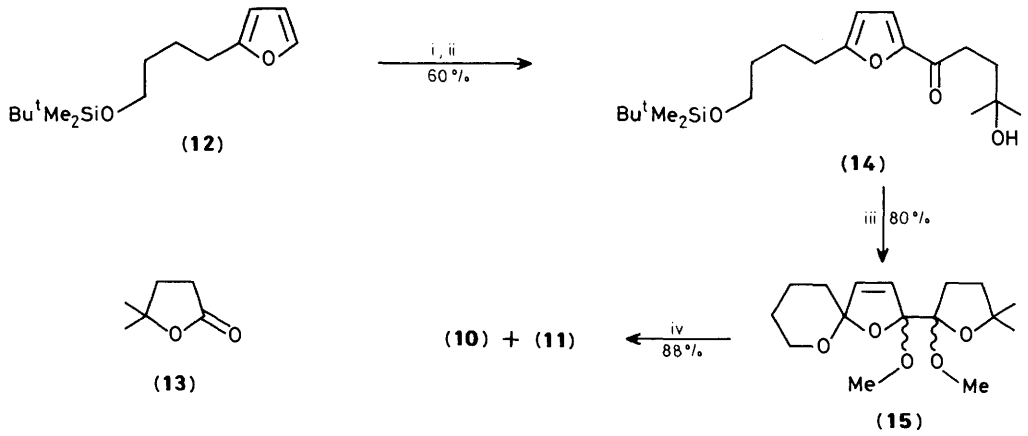
Table 1. ^{13}C N.m.r. data for dispiroacetal products[a]

	δ_c[b]/p.p.m.								
Carbon	(10)	(11)	(16)[c]	(17)[c]	(19)[c]	(20)[c]	(22)[c]	(21)[c]	(23)[c]
2	85.14	85.24	84.39	83.77	84.53	83.74	83.53	84.34	84.13
3	37.77	37.90	37.14	36.87	36.93	37.29	37.22	37.36	37.30
4	35.25	34.89	36.41	36.16	36.44	36.19	36.11	35.39	35.85
5	106.12	104.95	105.69	104.04	104.99	109.52	107.19	108.37	106.46
7	95.22	93.51	93.48	93.94	93.48	96.49	96.58	95.37	96.06
9	61.64	61.66	62.18	61.84	61.49	62.31	62.28	61.88	61.76
10	25.04	25.20	25.18	25.05	25.19	25.22	25.15	25.11	25.15
11	18.89	18.50	18.47	18.28	18.88	18.48	18.32	18.96	18.76
12	34.79	36.07	35.62	35.43	35.76	30.36	31.23	35.31	35.70
13	149.78	148.84	131.06	132.10	135.90	131.35	132.36	131.17	134.02
14	125.87	125.57	129.62	122.45	122.60	129.35	126.37	129.83	124.83
15	190.44	190.94	66.07	68.47	68.33	67.67	69.28	65.87	67.52
Me	27.95	27.98	28.95	28.72	28.95	30.00	29.68	29.27	29.27
Me′	29.04	28.95	28.09	27.76	28.09	28.58	28.19	28.35	28.16
CH_3CO				21.19	21.29		21.19		21.32
CH_3CO				170.83	170.73		170.16		170.88

[a] Recorded on a JEOL GX-270 spectrometer. [b] Relative to $CDCl_3$. [c] The relative assignment of C-3, C-4, C-12, Me and Me′ may be interchanged.



Scheme 2. *Reagents:* i, Bu^{t}Li/THF, −20 °C, 30 min; ii, add (**6**) at −60 °C; iii, camphorsulphonic acid–CH_2Cl_2, 20 °C, 2 h



Scheme 3. *Reagents:* i, Bu^{t}Li/THF, −70 °C to 0 °C; ii, add lactone (**13**), −70 °C; iii, Br_2–MeOH–Et_2O, −35 °C, 1 h followed by addition of NH_3 (g); iv, HF–MeCN

Table 2. Selected ^{1}H n.m.r. data for dispiroacetal products[a]

	δ_H[b]/p.p.m.							
	(10)[c]	(10)[d]	(11)[c]	(11)[d]	(17)[c]	(19)[c]	(22)[c]	(23)[c]
3-H	1.878	1.902	1.941	1.95				
3-H′	1.998	2.036	2.009	2.05				
4-H	3.002	2.610	3.122	2.775				
4-H′	2.286	2.193	2.196	2.02				
9e-H	3.802	3.745	3.849	3.750	3.59	3.658	3.71	3.68
9a-H	4.228	4.037	4.297	4.102	3.94	4.046	4.003	4.02
10e-H	1.42	1.6	1.48	1.68				
10a-H	1.63	1.6	1.62	1.68				
11e-H	1.65	1.6	1.58	1.68				
11a-H	2.09	1.94	2.085	1.92				
12e-H	2.44	2.18	1.67	1.68				
12a-H	1.58	1.62	1.54	1.68				
13-H	6.54	6.68	6.47	6.75	5.584	5.983	5.663	5.809
14-H	6.14	6.10	6.15	6.14	5.700	6.057	5.715	5.870
15-H					5.245	4.869	5.332	5.218
Me	1.370	1.232	1.396	1.232	1.146	1.188	1.198	1.229
Me′	1.482	1.419	1.232	1.460	1.342	1.408	1.454	1.439
Ac					2.053	2.074	2.102	2.118

[a] Recorded on a Bruker AM 360 spectrometer. [b] Relative to Me_4Si. [c] $CDCl_3$. [d] C_6D_6.

Table 3. *J*(HH) for the dispiroacetals (**10**), (**11**), and (**19**).

	J/Hz		
Coupling	(10)	(11)	(19)
3-3′	12.0	11.8	
3-4	8.2	8.1	
3-4′	4.5	5.6	
3′-4	9.5	8.6	
3′-4′	7.5	7.6	
4′-4′	13.2	13.0	
9a-9e	11.1	11.1	
9a-10a	11.8	12.6	
9e-10a	4.9	4.8	
9a-10e	3.4	2.6	
9e-10e	1.9	1.8	
9e-11e	1.9	0.5	
10a-10e			
10a-11a	12.9	13.0	
10a-11e			
10e-11a	3.9	3.9	
10e-11e			
10e-12e	1.6		
11a-11e	12.9	13.0	
11a-12a	12.9	13.0	
11a-12e	3.9	3.9	
11e-12a	3.6		
11e-12e	1.6		
12a-12e	12.5		
13-14	10.2	10.4	10.1
13-15			0.0
14-15			5.4

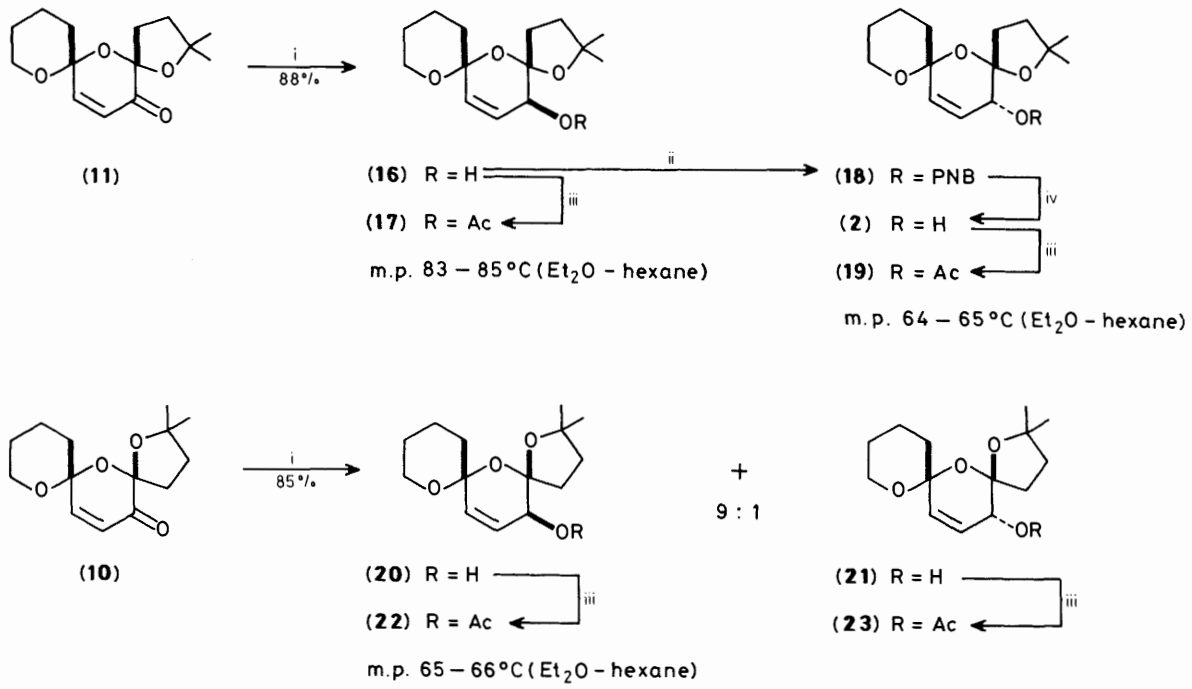
enhancements of 9e-H and 11a-H also being observed. The abnormally lowfield position of 12e-H [δ 2.18 in $CDCl_3$ compared with δ 1.68 for isomer (**11**)] is due to its close proximity to the tetrahydrofuran ring oxygen.

In isomer (**11**) the most dramatic n.O.e. enhancement was observed between the methyl group (δ 1.460 in $CDCl_3$) and 9a-H on the tetrahydropyran ring. Irradiation of this methyl group also gave weak enhancements of the protons at δ 2.02 and 2.05 allowing their assignment as 3-H′ and 4-H′. Small n.O.e. enhancements of the same protons were also observed on irradiation of 9a-H. By comparison, irradiation of the methyl resonance at δ 1.232 gave n.O.e. enhancements of the signals at δ 1.95 (3-H) and δ 2.775 (4-H) only. Thus (**10**) has the same relative stereochemistry at the spiroacetal centres as (8-O)-deoxy-17-*epi*-salinomycin,[7] whereas (**11**) has the same relative stereochemistry as salinomycin.[8]

A second approach to the spiroacetals (**10**) and (**11**) based on the Achmatowicz pyranone synthesis[9,10] (Scheme 3) was much more efficient. Lithiation of the furan (**12**) followed by reaction with the lactone (**13**) gave the 2-acylfuran (**14**) in 60% yield. The key step in the sequence was the oxidation of the furan (**14**) with bromine in methanol to give the 2,5-dialkyl-2,5-dioxy-2,5-dihydrofuran intermediate (**15**) which rearranged to a 1:1 mixture of the dispiroacetals (**10**) and (**11**) in 88% yield on treatment with 40% aqueous HF in MeCN.[11]

Reduction of the enone (**11**) (Scheme 4) with a variety of reducing agents gave exclusively the allylic alcohol (**16**) with the wrong stereochemistry at C-15. Unfortunately, the inversion of this centre *via* the Mitsunobu procedure gave poor yields (*ca.* 8%) of the *p*-nitrobenzoate ester (**18**) with recovered starting material accounting for the bulk of the reaction products. Hydrolysis of (**18**) gave the desired allylic alcohol (**2**) as an acid-sensitive oil which was characterised as its acetate ester (**19**).

The reduction product (**20**) of the enone (**10**) provided a more efficient albeit roundabout route to (**2**). Reduction of the enone (**10**) was stereoselective giving an inseparable mixture of the allylic alcohols (**20**) and (**21**) (9:1 respectively) in 85% yield. These were converted into the corresponding acetates (**22**) and (**23**) in the usual way and then easily separated by column chromatography on silica gel eluting with hexane–ether (3:1). The crystalline acetate (**22**) isomerised on treatment with a catalytic amount of camphorsulphonic acid in CH_2Cl_2 at room temperature for 2 h to give a separable mixture of the acetate (**19**) and recovered (**22**) (2:3 respectively) in 97% yield. The composition of the reaction mixture at equilibrium was (**17**):(**19**):(**22**):(**23**) = 12:30:38:20. Similar isomerisation studies on the alcohol (**16**) resulted in initial partial conversion



Scheme 4. *Reagents:* i, $NaBH_4$, $CeCl_3$–MeOH, −70 °C; ii, diethyl azodicarboxylate, *p*-nitrobenzoic acid–benzene; iii, Ac_2O–pyridine; iv, KOH–MeOH

into (**21**) before decomposition set in. These results show that epimerisation of the allylic anomeric centre at C-7 is faster than isomerisation of the C-5 centre.

In conclusion we have developed an efficient synthesis of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-15-ol ring system which should be readily applicable to the synthesis of salinomycin and related polyether antibiotics.

Acknowledgements

We thank the S.E.R.C. for financial support. This is a contribution from the Southampton University Institute of Biomolecular Science.

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Received 26*th September* 1988; *Paper* 8/03746I