A New Synthesis of 1,7-Dioxaspiro[5.5]undec-4-enes *via* Metallated Allenol Ethers. A Formal Synthesis of Talaromycins A and B†

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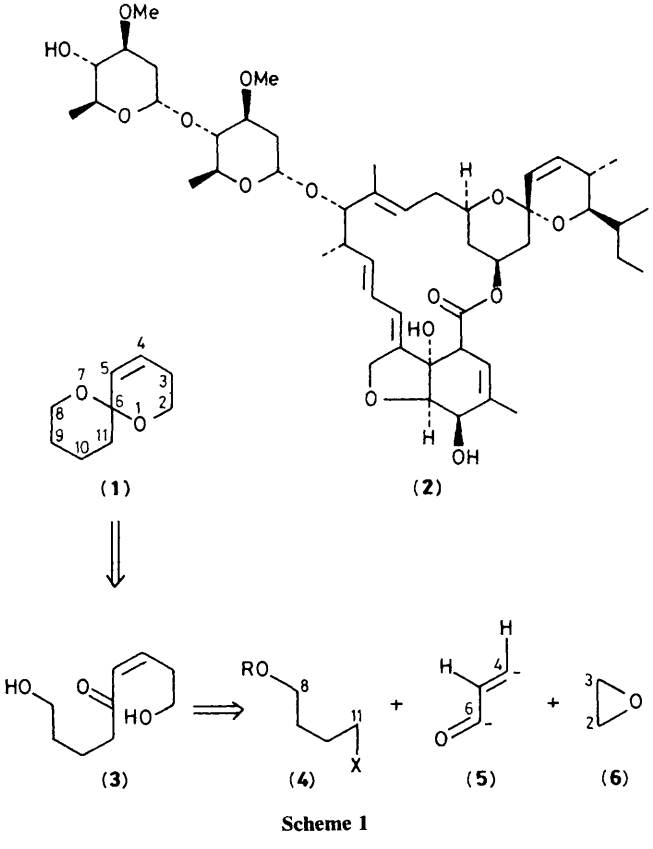
Sequential dialkylation of methoxypropadiene *via* the corresponding lithium derivatives gives 1,3-dialkylated methoxyallenes which undergo acid-catalysed ring closure to 1,7-dioxaspiro[5.5]undec-4-enes; by this route (6*S**,9*S**)-9-ethyl-1,7-dioxaspiro[5.5]undec-4-ene (**15b**) has been prepared which has previously been converted into talaromycins A and B.

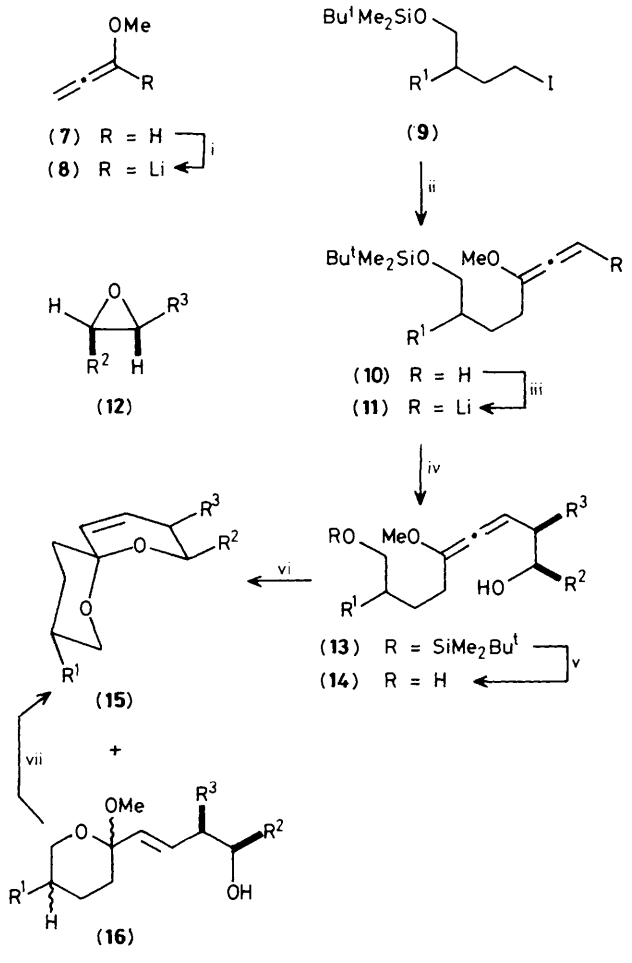
The 1,7-dioxaspiro[5.5]undec-4-ene ring system (**1**) is an important structural feature of the avermectins. In recent approaches[1] to avermectin B_{1a} (**2**) the unsaturated spiroacetal moiety was constructed by a modification of the procedure of Deslongchamps and co-workers[2] in which the requisite *cis* double bond was introduced by reduction of an alkyne. Other promising routes to related systems involve pyrolytic elimination of sulphoxides[3] and selenoxides.[4] We now report a new route to 1,7-dioxaspiro[5.5]undec-4-enes based on the retrosynthetic analysis shown in Scheme 1 in which the principal feature is the use of metallated derivatives of readily available methoxypropadiene[5] as a synthon for the dianion (**5**).[6]

The preparation of the four spiroacetals (**15a—d**) (Scheme 2) illustrates the scope and some of the limitations of the method. The sequence of metallation and alkylation reactions used to prepare the key allenol ether intermediates (**14a—d**) were generally clean and efficient and easy to perform on a substantial scale. The poor yield (27%) in the alkylation of (**11d**) with *trans*-1,2-dimethyloxirane was exceptional (Table 1). Although the cause of the inefficiency could not be ascertained, it is noteworthy that the analogous alkylation of 1-lithio-3-methoxyocta-1,2-diene went in 60% yield.

The diols (**14a—d**) and to a lesser extent the precursors (**10a—b**) and (**13a—d**) were labile compounds which were



Scheme 1



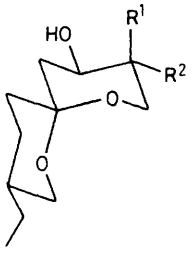
a; $R^1 = R^2 = R^3 = H$
b; $R^1 = Et$, $R^2 = R^3 = H$
c; $R^1 = R^3 = H$, $R^2 = Me$
d; $R^1 = H$, $R^2 = R^3 = Me$

Scheme 2. *Reagents and conditions:* i, Bu^nLi (0.95 equiv.), THF–hexane, −25 °C, 0.5 h; ii, (**8**) (1.8 equiv.), THF–hexane, −25 °C, 4 h; iii, Bu^tLi (1.1 equiv.), THF–pentane, −50 °C, 0.75 h; iv, add (**12**) (4 equiv.) and hexamethylphosphoramide (HMPA) (2 equiv.), −20 °C; v, Bu^n_4NF (2 equiv.), THF, 20 °C, 12 h; vi, pyridinium toluene-*p*-sulphonate (0.2 equiv.), MeOH (1 equiv.), CH_2Cl_2, 20 °C, 12 h; vii, trace I_2, 20 °C, 12 h.

† All compounds reported are racemic.

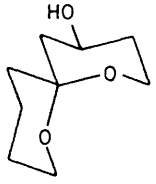
Table 1. Preparation of spiroacetals (**15a—d**).

	Yields/%				
	(9)→(10)	(10)→(13)	(13)→(14)	(14)→(15)	Overall
a	99	88	85	60	44
b	100	98	86	80	67
c	—	91	91	77	63
d	—	27	100	55	15



(**17**) $R^1 = CH_2OH$, $R^2 = H$

(**18**) $R^1 = H$, $R^2 = CH_2OH$



(**19**)

best purified by rapid column chromatography on basic alumina eluting with Et_2O–light petroleum (b.p. 40—60 °C) containing *ca.* 5% NEt_3. In the case of the diols (**14a—d**) Grade 1 basic alumina deactivated with 15—20% H_2O was essential. The neat purified products were stable at −30 °C for a week or more in the presence of a trace of NEt_3.

In the crucial cyclisation of diols (**14a—d**) to spiroacetals (**15a—d**) we exploited the known[6] stereoselective protonation of 1,3-disubstituted allenol ethers to give *cis*-double bonds. Thus, treatment of diols (**14a—d**) with pyridinium tosylate in CH_2Cl_2 containing 1 equiv. of MeOH gave a mixture of the desired spiroacetals (**15a—d**) as the major product along with variable amounts (10—25%) of the diastereoisomeric monocyclic acetals (**16a—d**) containing a *trans*-double bond. Quantitative conversion of (**16a—d**) into (**15a—d**) was achieved by adding a trace of I_2 to the reaction medium followed by stirring at room temperature.

This work constitutes a new and efficient synthesis of certain unsaturated spiroacetals. The synthetic utility of this approach is illustrated by the preparation of (**15b**) which is a late intermediate in a recent synthesis[7] of the avian toxins talaromycins A (**17**) and B (**18**)[8] and by the synthesis of (**15a**) and its hydration in 83% yield to the olive fly pheromone (**19**)[9] using dilute HCl in tetrahydrofuran (THF).

We thank Smith, Kline and French Ltd. for generous financial support.

Received, 13th February 1987; Com. 198

References

1 S. Hanessian, A. Ugolini, and M. Therien, *J. Org. Chem.*, 1983, **48**, 4430; R. Baker, C. J. Swain, and J. C. Head, *J. Chem. Soc., Chem. Commun.*, 1985, 309; M. Hirama, T. Nakamine, and S. Ito, *Tetrahedron Lett.*, 1986, **27**, 5281.
2 P. Deslongchamps, D. D. Rowan, N. Pothier, T. Sauve, and J. K. Saunders, *Can. J. Chem.*, 1981, **59**, 1105.
3 D. R. Williams, B. A. Barner, K. Nishitani, and J. G. Phillips, *J. Am. Chem. Soc.*, 1982, **104**, 4708.
4 A. G. Gonzalez, C. Betancor, C. G. Francisco, R. Hernandez, J. A. Salazar, and E. Suarez, *Tetrahedron Lett.*, 1977, 2959.
5 S. Hoff, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1968, **87**, 916.
6 J. C. Clinet and G. Linstrumelle, *Tetrahedron Lett.*, 1978, 1137; F. Derguini and G. Linstrumelle, *ibid.*, 1984, **25**, 5763.
7 A. B. Smith and A. S. Thompson, *J. Org. Chem.*, 1984, **49**, 1469.
8 Metallated enol ethers have previously been used to synthesise Talaromycin B: P. Kocieński and C. Yeates, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1879.
9 R. Baker, R. H. Herbert, and A. H. Parton, *J. Chem. Soc., Chem. Commun.*, 1982, 601. See also P. Kocieński and C. Yeates, *Tetrahedron Lett.*, 1983, **24**, 3905.