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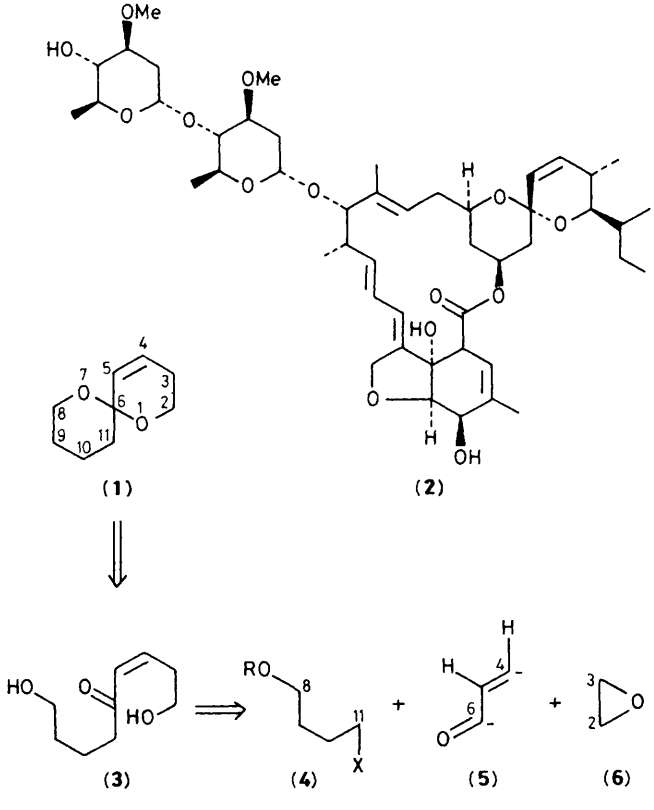
Sequential dialkylation of methoxypropadiene *via* the corresponding lithium derivatives gives 1,3-dialkylated methoxyallenes which undergo acid-catalysed ring closure to 1,7-dioxaspiro[5.5]undec-4-enes; by this route (6*S**,9*S**)-9-ethyl-1,7-dioxaspiro[5.5]undec-4-ene (**15b**) has been prepared which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

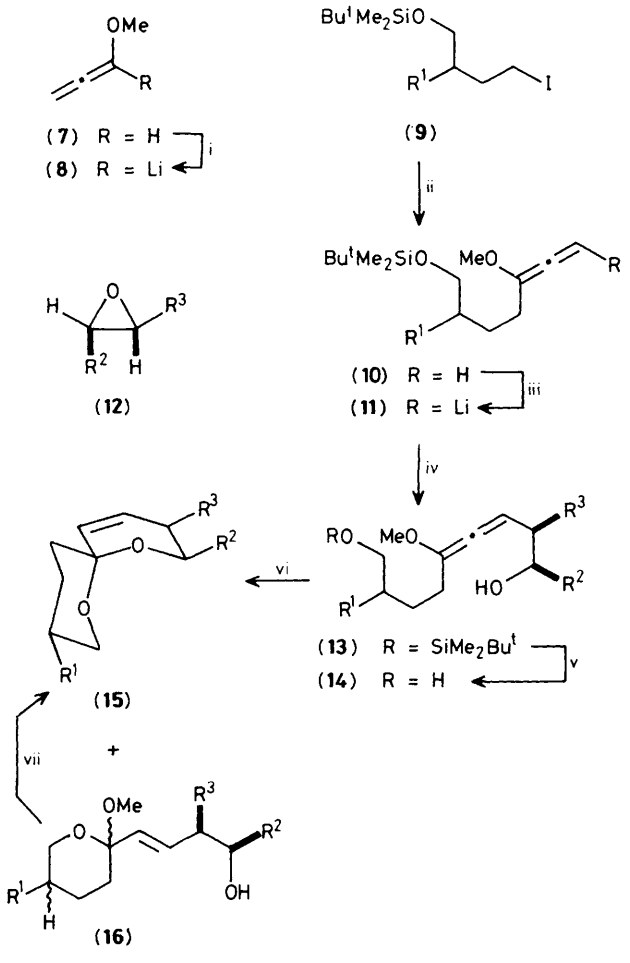
The 1,7-dioxaspiro[5.5]undec-4-ene ring system (**1**) is an important structural feature of the avermectins. In recent approaches[1] to avermectin B_{1a} (**2**) the unsaturated spiroacetal moiety was constructed by a modification of the procedure of Deslongchamps and co-workers[2] in which the requisite *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



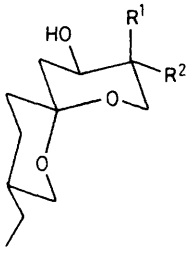
a; $R^1 = R^2 = R^3 = H$
b; R^1 = Et, $R^2 = R^3 = H$
c; $R^1 = R^3 = H$, R^2 = Me
d; $R^1 = H$, $R^2 = R^3$ = Me

Scheme 2. *Reagents and conditions:* i, Bu^{n}Li (0.95 equiv.), THF–hexane, −25 °C, 0.5 h; ii, (**8**) (1.8 equiv.), THF–hexane, −25 °C, 4 h; iii, Bu^{t}Li (1.1 equiv.), THF–pentane, −50 °C, 0.75 h; iv, add (**12**) (4 equiv.) and hexamethylphosphoramide (HMPA) (2 equiv.), −20 °C; v, Bu$^n_4$NF (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.

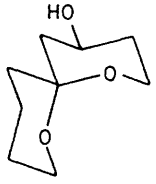
Table 1. Preparation of spiroacetals (**15a—d**).

	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).

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