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Stereoselective Acyclic Synthesis *via* Allylmetals: Vicinal Diols from γ-Alkoxyallylaluminium Compounds and Aldehydes or Ketones

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The reaction of *in situ* generated γ-alkoxyallylaluminium compounds with aldehydes or ketones at −78 °C leads to the highly diastereoselective formation of mono-protected vicinal diols; the precursor to *exo*-brevicomin was efficiently synthesised using this method.

The vicinal diol moiety is one of the most common functional units in biologically significant natural products, particularly in macrocyclic antibiotics and in carbohydrates. Considerable attention has been focused on the problem of stereocontrolled syntheses of various structural types containing this unit.[1] One solution may be *via* formation of the carbon–carbon bond of the vicinal diol with concomitant generation of two contiguous chiral centres.[2] We describe here a novel, highly diastereoselective approach along this line, which involves the use of *in situ* generated γ-alkoxyallylaluminium compounds.[3]

Although allylaluminium compounds have two potential sites (α and γ) for reaction with electrophiles, γ-alkylation is expected to predominate in reactions with aldehydes[4] leading to the formation of the vicinal diols in which one of the hydroxy-groups is protected. The requisite (*Z*)-γ-alkoxyallyldiethylaluminium compounds (**1**)† were generated *in situ* from the corresponding allyl ethers (**3**) through deprotonation with

† Owing to the rather unstable nature of γ-alkoxyallylaluminium compounds, attempts to isolate them have not been successful. However, the structure (**1**) including its *Z*-stereochemistry was based on analogies with similar allylmetals[2b,2e] prepared under identical conditions, which were isolated and their structures ascertained by n.m.r. measurements.

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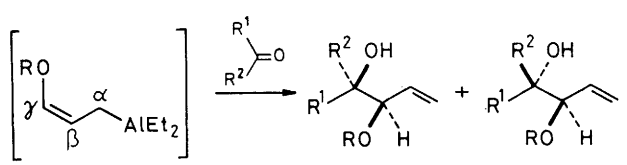
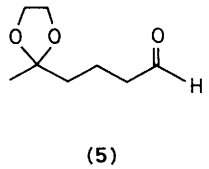
Table 1. Reactions of γ-alkoxyallyldiethylaluminium compounds, generated *in situ*, with carbonyl compounds.[a,b]

Entry	(3)	Carbonyl compounds R^1R^2CO		(2a):(2b)[c]	Total yields/%[d]
	R	R^1	R^2		
1	Me	Ph	H	11:1	91
2	Me	Ph	H	5:1[e]	85
3	Et	Ph	H	9:1	95
4	$Me_2C(OMe)$	Ph	H	9:1[f]	46 (90)[g]
5	Me	Pr^i	H	9:1	50 (85)[g]
6	Me	Ph	Me	4:1	34 (72)[g]

[a] In a typical procedure, to a solution of the allyl ether (**3**) (15 mmol) and TMEDA (15 mmol) in 20 ml of tetrahydrofuran (THF), was added s-butyl-lithium (15 mmol) in 13 ml of cyclohexane at −78 °C. After 15 min at −78 °C, the resulting carbanion was treated with diethylaluminium chloride (15 mmol) in 8.1 ml of toluene at −78 °C and the temperature was maintained for another 15 min before the addition of an aldehyde or ketone (13.2 mmol) in 5 ml of THF. After 2 h (aldehyde) or 3—5 h (ketone), the reaction was quenched with excess methanol–H_2O (5:1) at −78 °C. Usual work-up and purification gave the desired vicinal diol derivatives. [b] The stereochemistry of the products for entries 1, 2, and 6 was substantiated by the synthesis of their dihydromethyl ether derivatives (**9**) from the corresponding olefins (**10**) *via* OsO_4-*cis*-dihydroxylation followed by methylation with NaH–MeI. The coupling constants between the carbinyl protons in the vicinal diol unit [*J* 6—7 and 3—4 Hz for (**2a**) and (**2b**), respectively] were used as a criterion for the products from entries 3 and 4. It is noteworthy that in the products from entry 5, the coupling constants of the carbinyl protons are reversed in magnitude, *i.e.*, 4.64 and 7.32 Hz for (**2a**) and **2b**), respectively. [c] The diastereoisomeric ratio was determined by 360 MHz ^1H and 90 MHz ^{13}C n.m.r. analyses of the crude products. [d] Yields are of the chromatographically pure products and based on the carbonyl compounds used. [e] The reaction mixture was kept at 0 °C for 1 h before the aqueous methanol quenching. [f] The unprotected vicinal diols (**2a**/**2b**: R = H) were obtained (see the text). [g] Yields based on the consumed carbonyl compounds.



(1) (2a) (2b)



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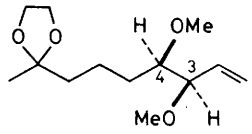
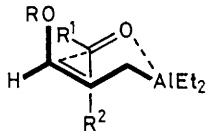


(6)

(3)



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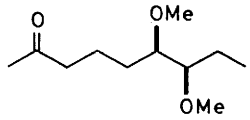

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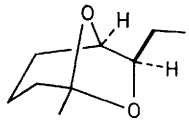

(8)

s-butyl-lithium[4] in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) followed by treatment with diethylaluminium chloride. The results in Table 1 show that γ-alkoxyallylaluminium compounds react with aldehydes or ketones exclusively at the γ-position,‡ with high diastereoselectivity. Interestingly, increase in the size of the R group in (**1**) or the aldehydes does not appreciably affect the stereochemical outcome of the reaction. This is particularly significant since α-methoxyisopropyl allyl ethers can be employed in the reaction, and the protecting group can be removed from the vicinal diol products under very mildly acidic conditions (0.05 M HCl) (entry 4). It should also be noted that the diastereoselectivity is highly dependent upon temperature. Thus, warming the reaction mixture from −78 to 0 °C before aqueous methanol quenching decreases the diastereoselectivity considerably (see entry 2), presumably owing to an increased tendency for equilibration of the two stereoisomeric adducts at temperatures near 0 °C or above. Furthermore, ketones (*e.g.*, entry 6) undergo similar γ-addition to the γ-alkoxyallyldiethylaluminium compounds with somewhat decreased diastereoselectivity, even though the reactions are generally slightly slower (3—5 h at −78 °C). These results may be explained by assuming a chair-like transition state (**4**) in which a bulkier R^1 adopts a quasi-equatorial orientation.

The utility of the reaction is well demonstrated in the following efficient synthesis of (**6**), the precursor to *exo*-brevicomin (**8**).[2b,5] Treatment of the readily available aldehyde acetal (**5**)§ with (*Z*)-γ-methoxyallyldiethylaluminium followed by methylation (NaH, MeI) afforded the vicinal diol dimethyl ether (**6**) in 89% yield ($J_{3,4}$ 5.37 Hz) along with a trace amount of the stereoisomer (< 5%). Catalytic hydrogenation over 10% Pd–C in ethanol, after purification by distillation, provided the diastereoisomerically pure ketone (**7**) (94% yield), whose spectroscopic data are identical with the reported values.[6] The ketone (**7**) has been converted into *exo*-brevicomin (**8**) in three steps by Mori.[6]

‡ Detailed 360 MHz ^1H n.m.r. analysis of the crude products revealed, in all cases described here, the absence of products resulting from alkylation at the α-position.

§ B.p. 82—85 °C (5 mmHg, kugelrohr). Synthesised from hex-5-en-2-one in four steps [i, $(CH_2OH)_2$, *p*-$MeC_6H_4SO_3H$, benzene; ii, 9-borabicyclo[3.3.1]nonane; iii, H_2O_2, NaOH, tetrahydrofuran; iv, pyridinium dichromate, CH_2Cl_2] with an overall yield of 73%.

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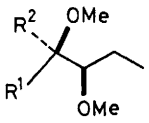

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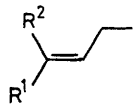

(10)

The methodology described herein represents a convergent, highly diastereoselective route to selectively protected sec.–sec.– and sec.–tert.–vicinal diol derivatives.¶ It should be noted that the reaction is carried out conveniently in one vessel and any inorganic products can be readily removed by several washings with dilute acid.

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¶ The mono methyl ethers of the vicinal diols (**2a**/**2b**) and their dihydro derivatives can be deprotected using BCl_3 in CH_2Cl_2 containing triethylamine, providing the corresponding vicinal diols in about 50 and 90% yields, respectively.

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