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The Addition of Organometallic Reagents to 3-Oxabicyclo[3.2.0]hept-6-en-2-ol: A Stereoselective Route to 6-Oxygenated (2*Z*,4*E*)-Alkadienals

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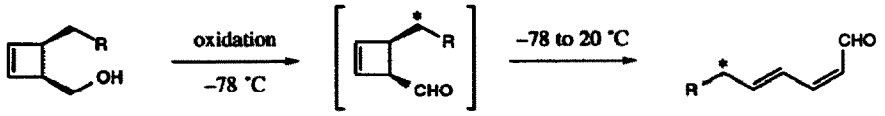
Abstract: The additions of various organometallic species to 3-oxabicyclo[3.2.0]hept-6-en-2-ol are diastereoselective; the results are consistent with addition to the less hindered face of a metal-chelated form of the corresponding γ-hydroxyaldehyde.

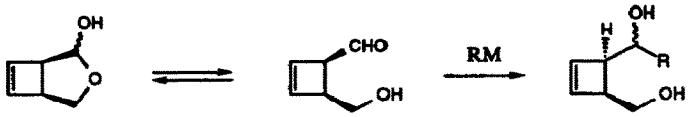
We recently demonstrated that the thermal electrocyclic ring-opening reactions of 4-alkyl-2-cyclobutene-1-carbaldehydes **1** proceed stereospecifically and at sub-ambient temperature, leading to the formation of only one of the two symmetry-allowed dienal products, *viz.* the (2*Z*,4*E*)-isomer **2** (Scheme 1), and we exploited this selectivity in the preparation of various achiral naturally-occurring polyenes with strictly defined geometries.[1]



1 **2**
isomeric purity >97%

SCHEME 1

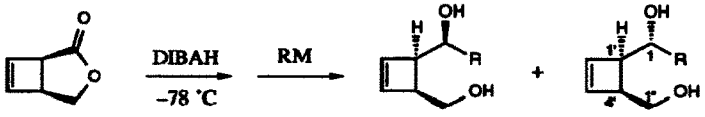
It has been our intention to develop this sequence for use in the synthesis of some of the many biologically-active polyenes which bear oxygen substituents in allylic positions, and the mildness of the electrocyclic process suggested that it would be expedient to functionalise the pro-allylic position (*) of the aldehyde **1** prior to ring-opening. We now report that this can be achieved stereoselectively, using a strategy based on the addition of organometallic reagents to the lactol **3**,[2] which exists in equilibrium with the aldehyde **4** (Scheme 2).



3 **4** **5 + 6**

SCHEME 2

We anticipated that the addition of nucleophiles to **4** would be diastereoselective, the hydroxymethyl group being well placed to mediate chelation control, and so it proved. Treatment of the lactol **3**, generated *in situ* from the lactone **7**,[3] with various organometallic reagents gave good yields of the mixed diols **5** and **6**, with the former predominant (Table 1). In the methyl series the stereoselectivity improved considerably on changing from the lithium to the Grignard reagent, and was essentially complete using a methyltitanium reagent[5] (entry 4).

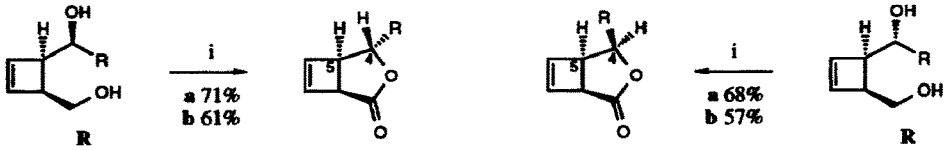


7 5 6

ENTRY	R	M	ADDITIVE	MAJOR PRODUCT	ISOLATED YIELD (%)	RATIO 5 : 6
1	CH_3	Li	–	**5a**	65	4 : 1
2	CH_3	MgBr	–	**5a**	74	14 : 1
3	CH_3	MgBr	$ZnBr_2$	**5a**	72	16 : 1
4	CH_3	$Ti(O^iPr)_3$	–	**5a**	86	> 99 : 1
5	CH_2CH_3	MgBr	–	**5b**	70	9 : 1
6	$(CH_2)_2CH_3$	MgCl	–	**5c**	69	6 : 1
7	$(CH_2)_3CH_3$	MgCl	–	**5d**	69	7 : 1
8	$(CH_2)_5CH_3$	MgBr	–	**5e**	66	6 : 1
9	$-C(CH_3)=CH_2$	MgBr	–	**5f**	70	7 : 1
10	$-C(CH_3)=CH_2$	MgBr	$ZnBr_2$	**5f**	76	13 : 1

TABLE 1[4] REACTIONS OF ORGANOMETALLIC REAGENTS WITH THE LACTOL 3

It was possible to distinguish and assay the diols **5** and **6** *via* 300 MHz ^{1}H-n.m.r. spectroscopy.[4] The relative stereochemistry of the diols in two series (**a** and **e**) was established by oxidation of the isolated diols **5** and **6** to the corresponding lactones **8** and **9** with tetrapropylammonium perruthenate (TPAP)/4-methylmorpholine *N*-oxide (NMO)[6] (Scheme 3). The value of the vicinal coupling constant $J_{4,5}$ in these rigid bicyclic structures is consistent with the *exo* and *endo* orientations of the R-substituents, as depicted for **8** and **9** respectively. The structures of the diols of series **b**–**d** and **f** are assigned by analogy (*cf.* characteristic ^{1}H-n.m.r. signals[4]).

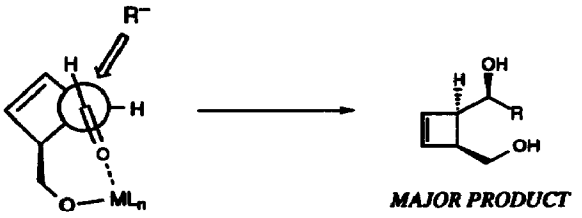


	R
5a	CH_3
5e	nC_6H_{13}

	R
6a	CH_3
6e	nC_6H_{13}

SCHEME 3[4] *Reagents:* i, TPAP, NMO, 4Å sieves, CH_2Cl_2, 25 °C.

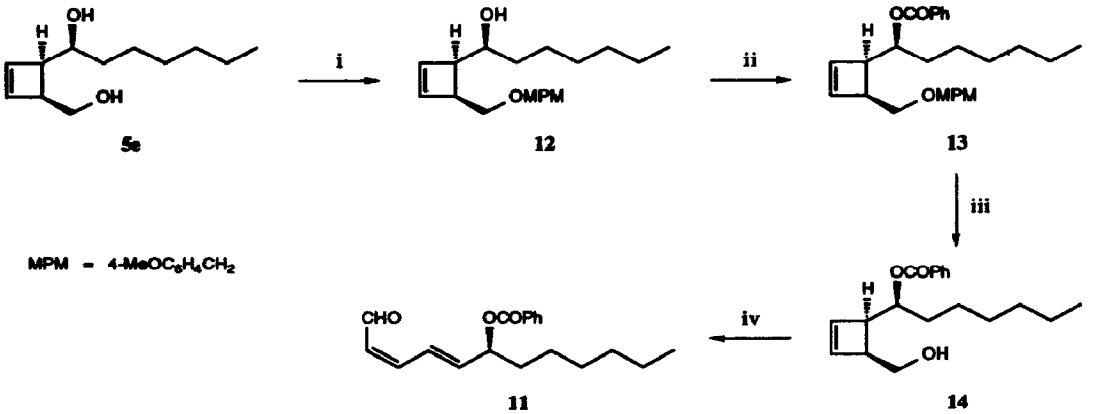
The preferential formation of a diol **5** *via* nucleophilic addition to **4** is consistent with the approach of the nucleophile to the less hindered face of a chelated intermediate **10** (Scheme 4). The proximity of the aldehyde and hydroxymethyl groups, inevitable by virtue of their *cis* disposition and the rigidity of the four-membered ring, engenders the coordination. The observed variation in the degree of diastereoselection on changing the metal (Ti > MgX > Li) or by the inclusion of a Lewis acid (zinc bromide) are in accord with such a model.[7]



10

SCHEME 4

The potential of the above sequence is illustrated by the conversion of the diol **5e** into the known (2*Z*,4*E*)-dienal **11**[8] as outlined in Scheme 5. The primary hydroxyl of **5e** was protected by methoxybenzylation as **12**, which was benzoylated under conventional conditions to obtain **13**. Treatment of **13** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[9] gave the alcohol **14**, which was transformed into the (*Z*,*E*)-dienal **11** *via* Swern oxidation. Florisil chromatography was used to isolate **11** with high (>97%)[10] isomeric purity.



SCHEME 5[4] *Reagents:* i, NaH, THF, MPM–Br (86%); ii, PhCOCl, pyridine (82%); iii, DDQ, CH_2Cl_2–H_2O, 20 °C (89%); iv, oxalyl chloride, Me_2SO, CH_2Cl_2, –78 °C, 1 h, then Et_3N, –78 to 20 °C, Florisil column (72%).

In order to exploit fully the above chemistry in the synthesis of biologically-active polyenes, it is necessary to develop routes to intermediates such as **3**, **5**, and **7** in homochiral form. Experiments with these objectives are currently in progress and will be described in due course.

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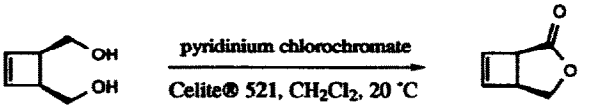
3 Kosugi, H.; Sekiguchi, S.; Sekita, R.; Uda, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 520. The lactone **7** can also be prepared by oxidation of *cis*-3-cyclobutene-1,2-dimethanol (reference 2), as shown below.



67%

4 All compounds are racemic. Yields refer to isolated, chromatographically homogeneous materials whose analytical data (including 300 MHz ^{1}H n.m.r. and high resolution mass spectra) are consistent with the proposed structures. 'Ether' refers to diethyl ether.

Typical Procedure (Table 1): A solution of the lactone **7** in tetrahydrofuran (THF) at –78 °C under N_2 was treated with a solution of DIBAH in hexanes (1.0 equiv.). After 1 h the mixture was treated with the additive (if any), and then the organometallic reagent (3–4 equiv.) in ether or THF (entries 2 and 3, toluene - ether, 3:1), stirred for 1 h at –78 °C, allowed to reach room temperature, and then stirred for a further 1 h. The mixture was then cooled to 0 °C, quenched with 1 M hydrochloric acid, saturated with NaCl, and the mixed diols **5** and **6** extracted into ether. The extract was washed with saturated aq. NaCl, dried, and evaporated, and the residue analysed by 300 MHz ^{1}H-n.m.r. spectroscopy to determine the composition of the **5** + **6** mixture. The major product **5** was then isolated by flash chromatography over silica gel (the isolated yields of **5** are indicated in Table 1). ^{1}H-N.m.r. data: **5a**, δ (300 MHz) 1.20 (3 H, d, *J* 6 Hz, Me), 2.85 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 10 Hz, 1'-H), 3.17 (1 H, ddd, $J_{1',4'}$ 4, $J_{4',1''}$ 4 and 11.5 Hz, 4'-H), 3.66 (1 H, apparent t, *J* 11.5 Hz, 1''-H), 3.80 (1 H, dd, *J* 4, 11.5 Hz, 1''-H), 3.8–4.0 (3 H, m, 1-H and 2 x OH), and 5.99 (2 H, s, 2'-H and 3'-H); R_f (EtOAc–CH_2Cl_2 1:1) 0.32; **6a**, δ (300 MHz) 1.26 (3 H, d, *J* 6.5 Hz, Me), 1.9–2.5 (2 H, br s, 2 x OH), 3.01 (1 H, dd, $J_{1,1'}$ 3, $J_{1',4'}$ 4 Hz, 1'-H), 3.13 (1 H, dt, $J_{1',4'}$ 4, $J_{4',1''}$ 4 and 4 Hz, 4'-H), 3.87 (2 H, d, *J* 4 Hz, 1''-H_2), 4.07 (1 H, dq, $J_{1,1'}$ 3, $J_{1,2}$ 6.5 Hz, 1-H), and 6.19 (2 H, s, 2'-H and 3'-H); R_f (EtOAc–CH_2Cl_2 1:1) 0.20.

In each series except **5f** + **6f**, the ^{1}H-n.m.r signals due to 1'-H and 4'-H in the minor diols **6** appeared between those due to 1'-H and 4'-H in the major diols **5**. The ratio **5**:**6** was determined by comparing the integrals of the respective signals due to 2'-H and 3'-H, which were clearly resolved in each series.

Data for lactones: **8a**, ν_{max} 1756 cm^{-1}; δ (300 MHz) 1.28 (3 H, d, *J* 6.5 Hz, Me), 3.15 (1 H, dd, $J_{4,5}$ *ca.* 1, $J_{1,5}$ 3.4 Hz, 5-H), 3.65 (1 H, d, $J_{1,5}$ 3.4 Hz, 1-H), 4.51 (1 H, br q, *J ca.* 1, 6.5 Hz, 4-H), 6.27 (1 H, d, *J* 2.8 Hz, 6-H), and 6.31 (1 H, d, *J* 2.8 Hz, 7-H); **9a**, ν_{max} 1757 cm^{-1}; δ (300 MHz) 1.37 (3 H, d, *J* 6.4 Hz, Me), 3.56 (1 H, dd, $J_{4,5}$ 6.8, $J_{1,5}$ 3.5 Hz, 5-H), 3.64 (1 H, d, $J_{1,5}$ 3.5 Hz, 1-H), 4.57 (1 H, dq, *J* 6.4, 6.8 Hz, 4-H), 6.28 (1 H, d, *J* 2.6 Hz, 6-H), and 6.32 (1 H, d, *J* 2.6 Hz, 7-H).

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