Effect of Substituents on Radical Induced Cyclization of Bromoacetals of 3-hydroxyhexa-1,5-dienes

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The radical cyclization of bromoacetals of 3-hydroxyhexa-1,5-dienes produces monocyclic or bicyclic products depending upon the substituent present at C-2; the synthesis of (+)-eldanolide is described.

In the last decade there has been a rapid development of free radical reactions as a new method for C–C bond formation and several reviews[1] have appeared. The radical cyclization of mixed bromoacetals, introduced independently by Stork[2] and Ueno,[3] which allows essentially the stereo- and regio-selective addition of a 'detachable' two-carbon chain to the double bond of allylic alcohol, has now been developed as a general route[4] for the synthesis of γ-lactones. In these reactions, the formation of a *trans*-2-alkyl-3-methyltetrahydrofuryl radical (**4**) has been taken for granted.[2a,3a] The initial radical formed by reduction of bromide (**1**) by tributylstannane may undergo 5-*exo*-cyclization[5] to produce intermediates (**3**) and/or (**4**) (Scheme 1). Radical (**3**) may further undergo a tandem cyclization to give a bicyclic system (**5**), whereas the radical (**4**) could be quenched without any further cyclization to produce a monocyclic acetal, a precursor of butyrolactone (**7**). In order to answer the above queries, we studied the radical cyclization of bromoacetals from 3-hydroxyhexa-1,5-dienes.

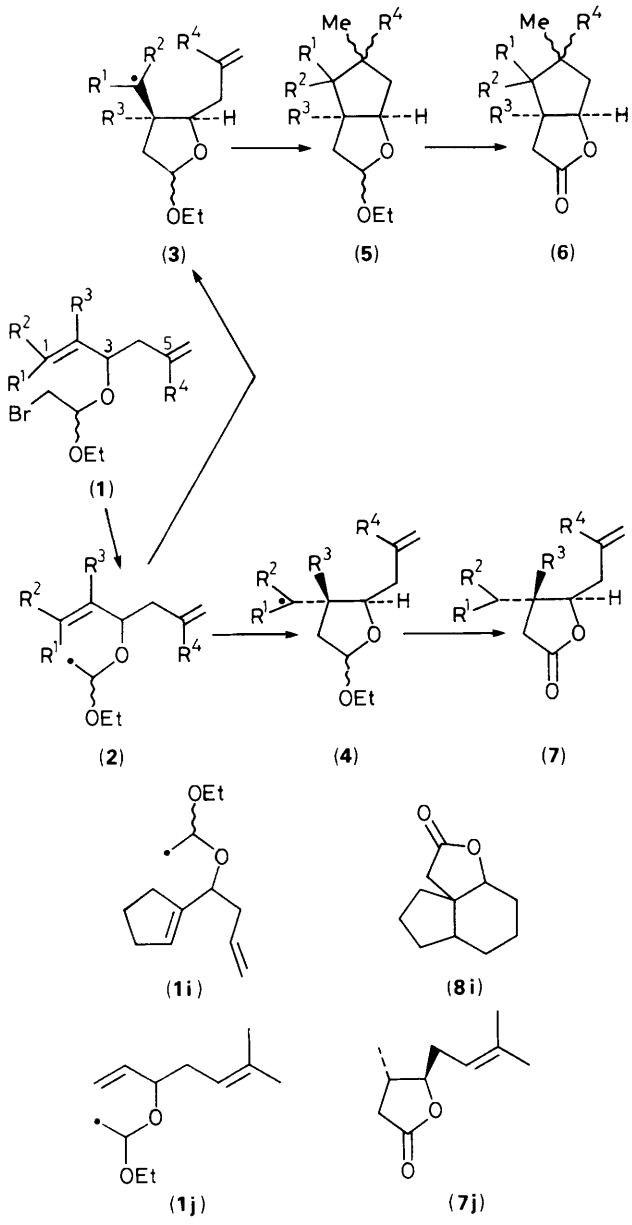
Various substituted 3-hydroxyhexa-1,5-dienes were prepared by allylic Grignard reaction on the corresponding substituted acroleins. They were utilized to synthesize the corresponding bromoacetals by the usual procedure.[3a] The bromoacetals were reduced either by a stoicheiometric amount of tri-n-butyltin hydride in refluxing toluene or by slow generation of radicals using a catalytic amount of tri-n-butyltin chloride with sodium cyanoborohydride in refluxing t-butyl alcohol in the presence of azoisobutyronitrile (AIBN). The products were oxidized with Jones' reagent to their corresponding lactones which were isolable. The results are summarized in Table 1.

The following observations were made. Firstly in all cases (entries 1 to 8) excellent chemoselectivity for the expected 5-*exo*-cyclization was observed[2] and no product derived from the 6-*exo* mode was detected. Secondly, the substituent R^3 has a profound effect on the mode of cyclization of radical (**2**). (a) When R^3 = H (entries 1 to 4); products derived only from intermediate (**4**) were observed. The regio- and stereo-selec-

Table 1. Cyclizations of bromoacetals (**1**).

		Products/%				
		Method A[a]		Method B[a]		Overall yield of lactones /%[b]
Entry	Substrate	(**6**)	(**7**)	(**6**)	(**7**)	
1	(**1a**)	0	100	0	100	60
2	(**1b**)	0	100	0	100	55
3	(**1c**)	0	100	0	100	54
4	(**1d**)	0	100	0	100	50
5	(**1e**)	30	70	50	50	50
6	(**1f**)	25	75	50	50	50
7	(**1g**)	100	0	100	0	52
8	(**1h**)	100	0	100	0	55
9[c]	(**1i**)	(**7i**) 50 + (**6i**) 40 + (**8i**) 10				
10[c]	(**1j**)	(**7j**)				53

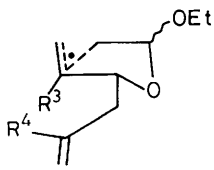
[a] Method A: Bu_3SnH, cat. AIBN, toluene, 110 °C, 20 min. B: Cat. Bu_3SnCl, AIBN, $NaCNBH_3$, Bu^tOH, reflux, 5 h. [b] Both methods A and B gave comparable yields. All compounds showed satisfactory spectral and analytical data. [c] Only method A was employed.



a; $R^1 = R^2 = R^3 = R^4 = H$
b; $R^1 = R^2 = R^3 = H, R^4 = Me$
c; $R^1 = R^3 = R^4 = H, R^2 = Me$
d; $R^1 = R^2 = Me, R^3 = R^4 = H$
e; $R^1 = R^2 = R^4 = H, R^3 = Me$
f; $R^1 = R^2 = H, R^3 = R^4 = Me$
g; $R^1 = R^2 = R^4 = H, R^3 = Ph$
h; $R^1 = R^2 = R^4 = H, R^3 = Bu^t$
i; $R^1 = H, R^2R^3 = -(CH_2)_3-, R^4 = H$

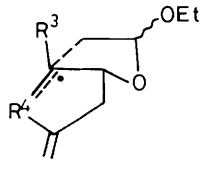
Scheme 1

tivity of the products formed may be explained by considering the chair-like transition state **X** for the cyclization step as proposed by Beckwith and coworkers.[5,6] Owing to steric repulsion, the carbon bearing the radical has a tendency to remain *trans* to the allyl group in the cyclized product (**4**). Therefore, further tandem cyclization of the product is prevented as it would lead to a strained *trans*-diquinane. (b) When R^3 = Me and $R^1 = R^2 = H$; $\cdot CH_2$ and –Me compete to remain away from the allyl group and, since they are approximately the same size, the formation of both (**3**) and (**4**)



R^3 = H or Me

X



R^3 = Bu^t, Ph, or Me

Y

is observed in equal quantities. The formation of (**3**) may arise from the transition state **Y** in which the bulky group R^3 and allyl group are in equatorial positions. This was further supported by the fact that when R^3 was more bulky than methyl, (entries 7 and 8) intermediate (**3**) was formed predominantly. Intermediate (**3**) undergoes further 5-*exo*-cyclization to produce bicyclic products.

It is pertinent to note that (**1g**) (entry 7) is conveniently predisposed to generate a carboxy group by oxidation of the phenyl group thus providing a handle for further chemical transformations.[7] Entry 10 represents a short and elegant synthesis of (3*R*,4*S*)-eldanolide,[8] $[\alpha]_D$ +49° ($CHCl_3$), a pheromone of African sugar cane borer, which was prepared from optically active allyl alcohol obtainable by the Sharpless asymmetric epoxidation method.[9]

Thus, the 5,6-double bond in the substrate (**1**) serves as a probe to determine the stereochemistry of the ring closure. The bicyclic product formed is a measure of the extent of *cis* ring closure. Conversely, the monocyclic product attributes the extent to which *trans* ring closure takes place. It is found that the substituent at C-2 greatly influences the formation of *cis* and/or *trans* products during the radical cyclization.

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