



**GEM-DISUBSTITUENT EFFECTS IN SMALL RING FORMATION:
NOVEL KETAL RING SIZE EFFECT¹**

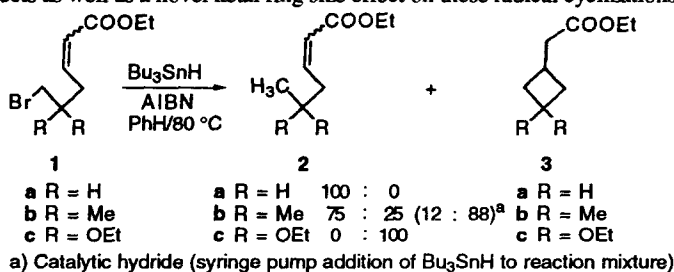
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Summary: While reaction of the bromoalkene with a 5-membered ketal **6a** with tributyltin hydride gave only the acyclic product **18a**, reaction of the corresponding bromoalkene with a 6-membered ketal **6b** gave good yields of the cyclobutane **17b**, in a novel ketal ring size effect. Also the *gem*-dicarboalkoxy effect was operative in these systems, e.g., cyclization of the bromo alkene triester **11a** afforded reasonable yields of the cyclobutane **19**.

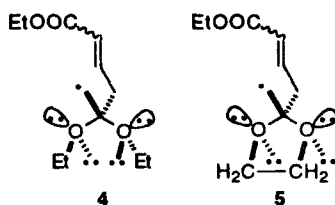
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Our research group has been studying for some time substituent and solvent effects on the rates and equilibria of various cyclization reactions, among them the Diels-Alder reaction, the ene reaction, dipolar cycloadditions, electrophilic and radical cyclizations.⁴ Our results have provided evidence for the greater importance of rotamer effects (higher population of reactive rotamer or selective destabilization of ground state) as compared with angle compression (Thorpe-Ingold Effect). The cycloadditions exhibited much larger than normal rate increases when an oxygen atom was attached to the substituent carbon (increase up to 10⁵ going from H to CH₃) compared to those seen in all carbon cases (normal rate increases of 5-10).^{4d,e} This heteroatom effect permitted an efficient synthesis of cyclobutane rings.^{4f} Thus the *gem*-dialkoxy effect caused the cyclization of **1c** to be much more efficient than that of **1b** which is aided by a *gem*-dialkyl effect (making it much more efficient than the cyclization of **1a**). We now report mechanistic studies on *gem*-disubstituent effects in cyclobutane formation which include both *gem*-dialkoxy and *gem*-dicarboalkoxy effects as well as a novel ketal ring size effect on these radical cyclizations.

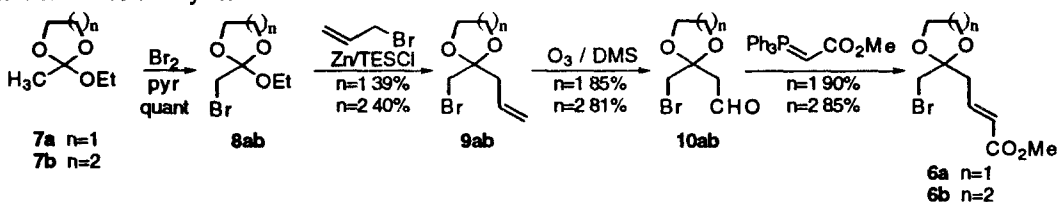


One possible explanation of the greater size of the *gem*-dialkoxy effect in this reaction compared to the *gem*-dialkyl effect is that a double exo-anomeric effect holds the 5-pentenyl radical **4** in the conformation shown (lone pairs antiperiplanar to O-C bonds) which places one ethyl group on the front and one on the back of the molecular plane (to avoid a cis-pentane interaction). Thus the ethyl substituent on each face limits the conformation of the syn

substituent on the central carbon and essentially helps position those substituents closer to the reaction transition geometry. The same should not be true for cyclic ketals, shown for the dioxolane **5**, since now the two 'alkyl' substituents are on the same face on the molecule. Thus we decided to test this hypothesis by carrying out the cyclization of cyclic ketals analogous to **1c**.

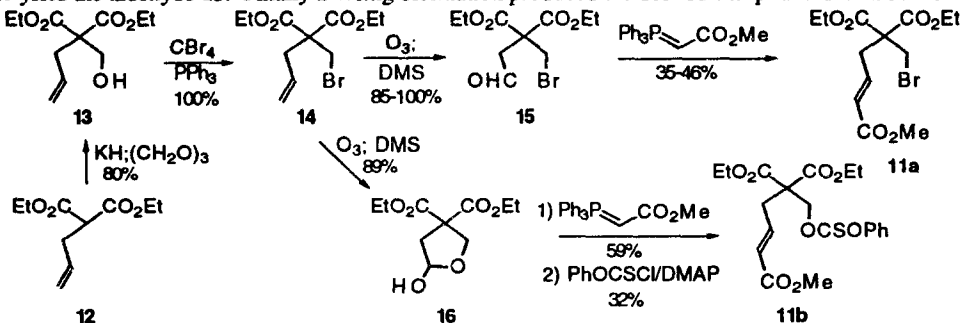


The dioxolane and dioxane ketals **6ab** were synthesized as shown in Scheme 1. The known orthoesters **7ab**⁵ were brominated in quantitative yield, with some decomposition occurring during purification.⁶ Zinc mediated allylation⁷ of the resultant α -bromo orthoesters **8ab** gave the olefins **9ab** in 39-40% yield. Ozonolysis followed by reductive workup produced in 81-85% yield the aldehydes **10ab** which on Wittig olefination gave the desired ketal esters **6ab** in 85-90% yield.



Scheme 1: Synthesis of Cyclic Ketals **6ab**.

To see if the *gem*-dicarboalkoxy effect was large enough to permit the easy synthesis of cyclobutane by a radical cyclization, we prepared the two diester cyclization precursors **11ab** (Scheme 2). Diethyl allylmalonate **12** (made by monoallylation⁸ of malonate in 40% yield) was hydroxymethylated with KH and 1,3,5-trioxane to give the alcohol **13** in 80% yield. We used the method of Hooz⁹ to prepare the bromo alkene **14** which was ozonolyzed to give in 85-100% yield the aldehyde **15**. Finally a Wittig olefination produced the desired compound **11a** in 35-46% yield.



Scheme 2: Synthesis of Dicarboethoxy Analogues **11a** and **11b**

The thionocarbonate **11b** was also made via ozonolysis of **13** to give the lactol **16** in 89% yield followed by Wittig olefination and conversion of the hydroxyl group into the thiocarbonate.¹⁰

The results of the radical cyclizations of these esters are shown in Figure 1. First of all, with the thionocarbonate precursor **11b**, no radical was formed and only starting material was recovered. It is possible that the hindered environment of the thionocarbonate together with the fact that a primary radical is being formed, may be energetically unfavorable.

The cyclizations of the cyclic ketals **6ab** also produced surprises, since unexpectedly, the ketal ring size was crucial to the success of the cyclization. The dioxolane **6a** gave only the acyclic product **18a** with none of the cyclobutane **17a** being formed. This finding is in agreement with the hypothesis described above namely that cyclic ketals would exist in a different conformation and therefore have an attenuated effect on cyclization. However the dioxane **6b** gave the expected cyclobutane **17b** in excellent yield with only a trace of the acyclic material **18b** being formed. Therefore the earlier hypothesis cannot be valid. We speculate that the smaller ring angle in the dioxolane ring would increase the angle between the radical bearing carbon and the electrophilic double bond, thus decreasing the likelihood of cyclization. On the other hand, the larger angles of the dioxane ring (and the free dialkoxy groups) would facilitate cyclization. Theoretical calculations are presently underway in order to try to explain this unusual ring-size effect.¹¹

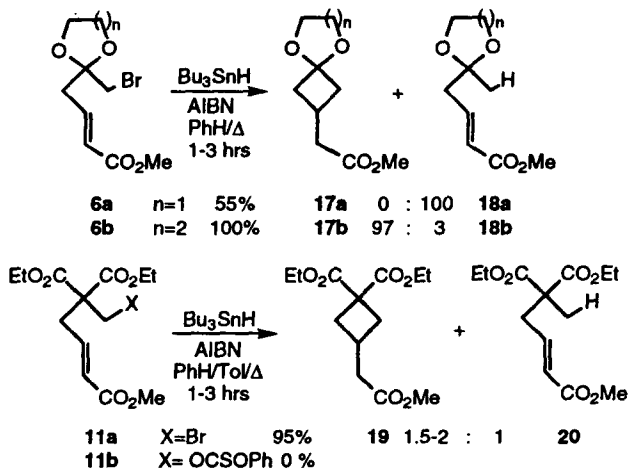


Figure 1. Radical Cyclizations.

The dicarboethoxy bromide **11a** showed similar product ratios to those of the dimethyl case described earlier (**1b**) and lower than the acyclic dialkoxy or dioxane cases. Treatment of **11a** with tributylstannane and catalytic AIBN in refluxing benzene for 1-3 h afforded a 95% yield of ca. 1.5-2:1 ratio of the cyclobutane **19** and the acyclic triester **20**. Thus our recently described gem-dicarboalkoxy effect^{4g} also is operative in this radical cyclization

process and permits the facile formation of strained rings such as cyclobutanes in good yield.

In conclusion, we have shown that the *gem*-dialkoxy effect also occurs with cyclic ketals but is ring size dependent and that the *gem*-dicarboalkoxy effect is not only operative in this small ring formation but is also somewhat larger than the *gem*-dialkyl effect. The use of these effects allows for the easy preparation of substituted cyclobutane ring systems.

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