Mechanistic and Synthetic Aspects of Intramolecular Alkoxide–Allene Cyclizations

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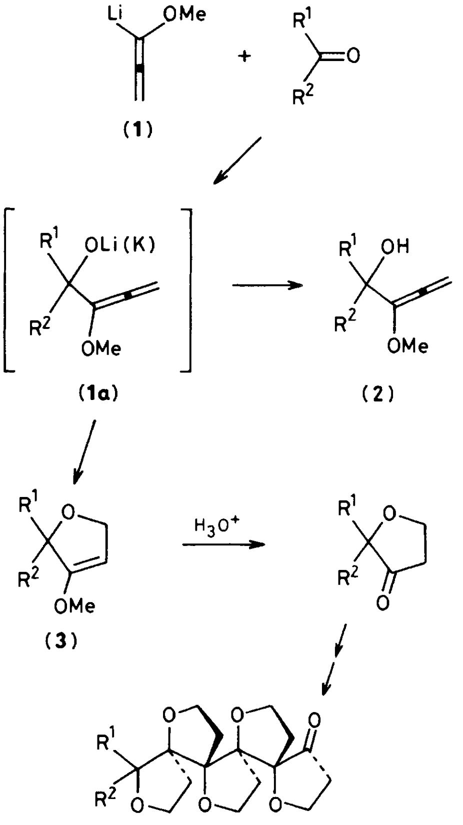
Intramolecular cyclization of the methoxyallene–alkoxide adducts (**1a**) proceeds along two different pathways *via* a methoxyallyl radical anion to give either a dihydrofuran, or vinyl epoxide, depending upon the steric environment of the radical anion.

Treatment of ketones or aldehydes with α-lithio-α-methoxyallene (**1**) gives the adducts (**2**). When these adducts are treated with $KOBu^t$ (catalytic amount, cat.)–dimethyl sulphoxide (DMSO), or $KOBu^t$ (cat.)–$HOBu^t$–18-crown-6 (cat.), the generated potassium alkoxide apparently adds to the terminus of the allene in an intramolecular cyclization process to give a dihydrofuran (**3**).[1] We have used this type of reaction in an iterative manner to construct a primary helical molecule composed of spiro-linked tetrahydrofuran rings (Scheme 1).[2]

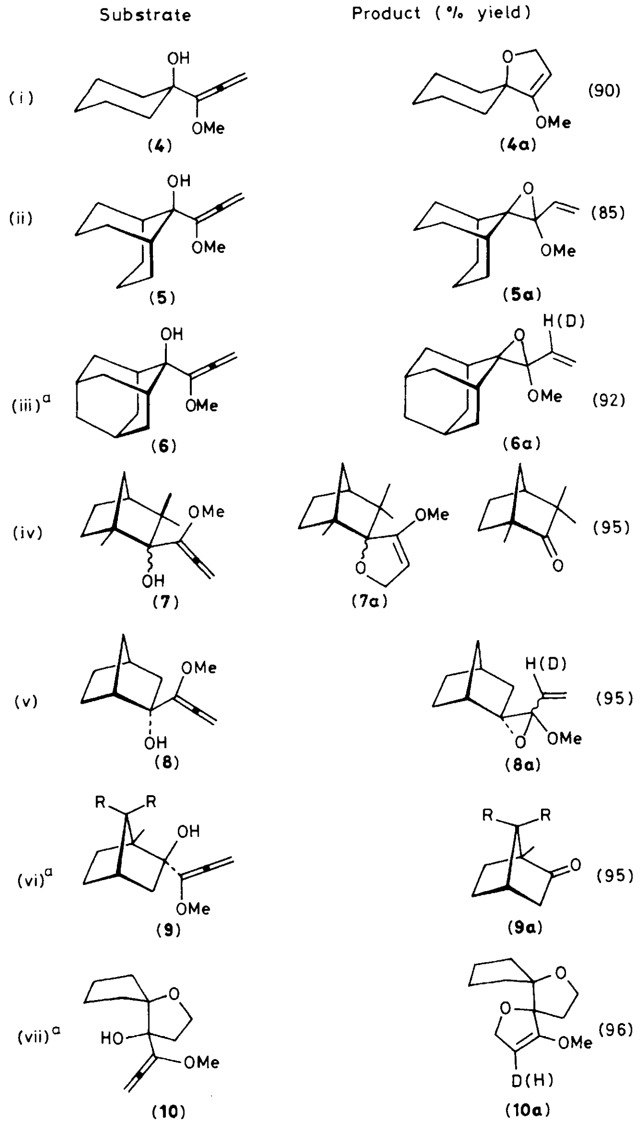
It is clearly impossible that the potassium alkoxide (**1a**) can reach the terminus of the allene in an intramolecular fashion without generating an exceedingly strained transition state.[3] Consequently we were intrigued as to how this facile cyclization takes place. Table 1 lists a number of key experimental results. The cyclization is catalytic in $KOBu^t$, although concentrations less than 0.1 equiv. are ineffective; DMSO is essential. The cyclization will take place in the absence of DMSO only if 18-crown-6 is present. For entries (iii), (v), and (vii), conducting the cyclization in $[^2H_6]$DMSO results only in the vinylic hydrogen being replaced by deuterium. Treatment of (**10a**) (^{1}H-compound) with $KOBu^t$–$[^2H_6]$DMSO did not result in deuterium incorporation. These data preclude any allenyl–prop-2-ynyl isomerism prior to cyclization, and any double bond isomerism in the dihydrofuran enol ether product.

Our first indications that an electron transfer process is involved came from the observation that dioxygen inhibited the cyclization of (**10**) to (**10a**). Furthermore, treatment of (**10**) with $KOBu^t$–$HOBu^t$ (conditions that do not cause cyclization), followed by $Cu(OAc)_2$, results in cyclization to (**10a**) (55%). It is well known that $Cu(OAc)_2$ will initiate

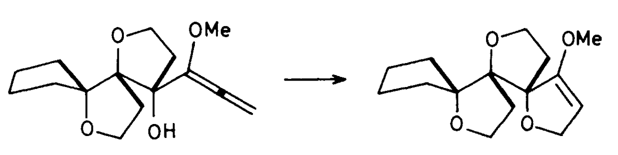


Scheme 1

Table 1. Reactions of the methoxyallenes (4)—(10).[a]



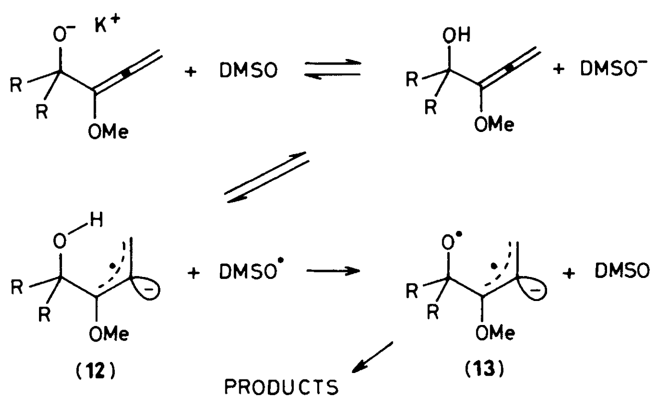
[a] Reaction conditions: KOBu^t (0.1 equiv.)–DMSO, 80 °C, 24 h. For entries (iii), (v), and (vii), the use of $[^2H_6]$DMSO gave the deuterium-substituted product.

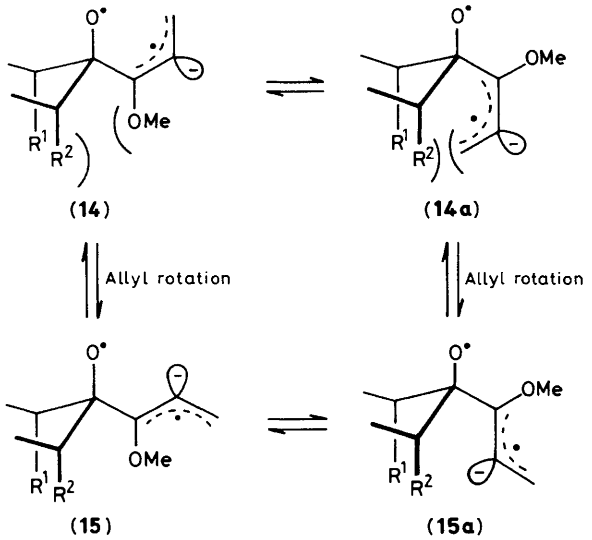


(11) **(11a)**

electron transfer from alkoxides.[4] Similarly, treatment of (**6**) with KOBu^t–HOBu^t in the presence of azoisobutyronitrile gave (**6a**) (20%). When (**10**) was treated with KOBu^t (0.33 equiv.)–DMSO (conditions that cause rapid cyclization), in the presence of galvinoxyl (0.33 equiv.), the formation of (**10a**) was completely inhibited.[5] Lower concentrations of galvinoxyl only partially inhibited the cyclization.

If the cyclization were a simple intramolecular process, then first-order kinetics should be followed. The kinetics of the cyclization of (**11**) to (**11a**) show complex kinetic behaviour, even at low substrate (**11**) concentrations, suggesting that both inter- and intra-molecular electron transfer is taking place.





A most surprising result was observed for entries (ii), (iii), and (v), only the vinyl epoxides (**5a**), (**6a**), and (**8a**), respectively, being formed. These vinyl epoxides did not rearrange under the cyclization conditions, or thermally into the dihydrofurans.[6] This unprecedented cyclization of an allenyl alkoxide to a vinyl epoxide can be formally considered to be a 3-*exo-trig* cyclization and is favoured, whereas the formal addition of an alkoxide to the allene terminus is a 5-*endo-trig* process, and disfavoured.[3] We have not found an allenyl alcohol that gives a mixture of dihydrofuran and vinyl epoxide. In entry (vi), compounds (**9**, R = Me or H) gave only the ketones (**9a**, R = Me or H).

These data are compatible with a single electron transfer, S.E.T., mechanism to give the radical anion (**12**),[7] which can lose a hydrogen atom to give (**13**).[8] There are two ways in which the alkoxy radical (**13**) can cyclize, depending upon the steric environment of the methoxyallyl radical anion group. If R^1, R^2 in (**14**) are conformationally rigid axial substituents, then cyclization to a dihydrofuran is sterically prohibited. Allyl radical rotation (*ca.* 65 kJ mol^{-1})[9] leads to (**15**), which can only cyclize to give an epoxide. This corresponds to entries (ii), (iii), and (v). In entry (iv), compound (**7a**) must be formed *via* (**14**)/(**14a**), since (**15**)/(**15a**) would force the –OMe group into the adjacent Me-groups. The relatively high energy of the allyl radical rotation accounts for the fact that either the dihydrofuran or the vinyl epoxide product is formed, and not a mixture of both. The radical anion mechanism is consistent with the deuterium labelling results.

In summary, the cyclization of (**1a**) to either (**3**) or the vinyl epoxides (**5a**), (**6a**), or (**8a**) is not a simple intramolecular anionic process, but can best be explained by a S.E.T. mechanism. The formation of vinyl epoxides from this type of process (formally a 3-*exo-trig* reaction) is without literature analogy.

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