The Stereochemistry of the Cyclic β-Halogeno-ether Synthesis of Olefinic Alcohols

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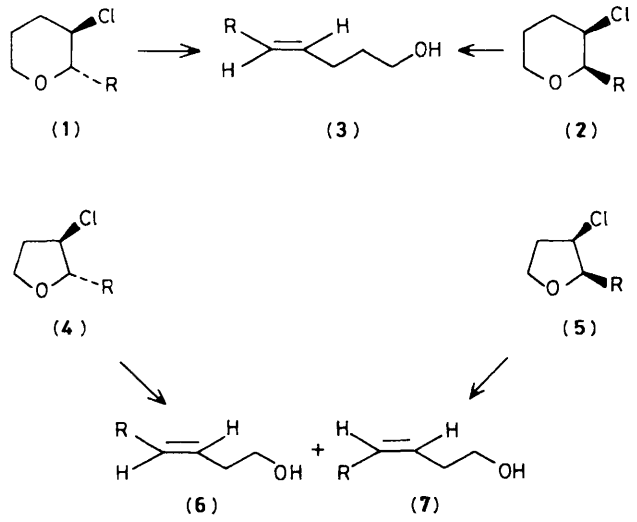
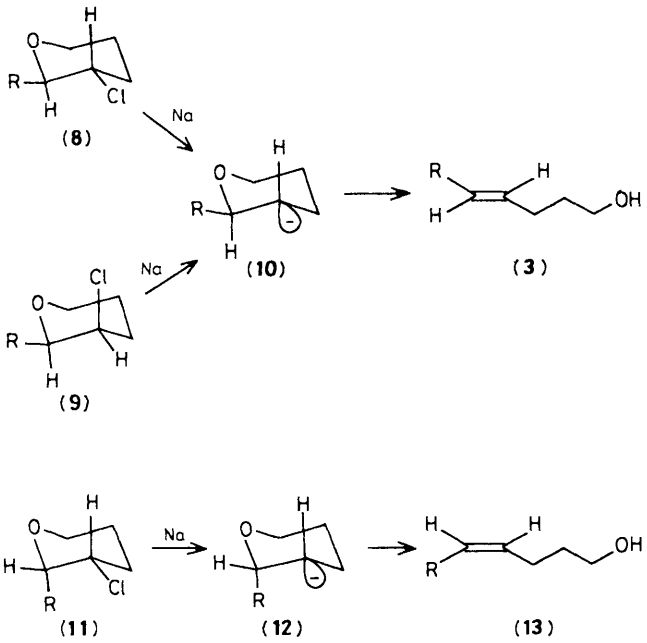
The (*Z*)/(*E*) composition of olefinic alcohols produced by sodium ring-scission of cyclic β-halogeno-ethers can be accounted for by a mechanism involving fast electron transfer and carbanion inversion, with ring-cleavage speedier than conformational inversion.

Treatment of 2-alkyl(or aryl)-3-chlorotetrahydro-pyrans or -furans with sodium (β-halogeno-ether synthesis) is a good synthetic procedure for introducing a 5- or a 4-carbon olefinic chain terminated by a versatile functional group (Scheme 1).[1,2] The reaction proceeds in excellent yield and has been employed in a variety of natural product or model compound syntheses:[3,4] branching can be introduced by using substituted tetrahydro-pyrans or -furans. Mixtures of *cis*- and *trans*-tetrahydro-pyrans or -furans (separable by distillation) are readily made by treating 2,3-dichloro-precursors with a Grignard reagent,[1,5] but whilst the ring-scission reaction is regiospecific, its stereoselectivity has remained puzzling.[1,2] Thus both *cis*- and *trans*-2-alkyl-3-chlorotetrahydropyrans (**1**) and (**2**) give (*E*)-5-substituted alk-4-en-1-ols (**3**) with high stereoselectivity (>95%), whilst the corresponding tetrahydrofurans give (*E*)-(**6**)/(*Z*)-(**7**) mixtures of 4-substituted alk-3-en-1-ols (*ca.* 53 : 47 for *cis* where R = Me, Pr^n, Pr^i, *etc.*, and *ca.* 82 : 18 for the corresponding *trans*). We have now studied further the origins of stereochemical control in this synthesis of olefinic alcohols.

Ring opening of a common intermediate could involve a radical or carbanion.[6] Treatment of a mixture of (**1**, R = Me) and (**2**, R = Me) with tri-n-butyltin hydride and benzoyl peroxide gave only 2-methyltetrahydropyran and no hex-4-enol, and similar results were obtained with (**4**) and (**5**). On the other hand, treatment of (**4**, R = Me) or (**5**, R = Me) with n-butyl-lithium gave n-butyl chloride and mixtures of (*Z*)- and (*E*)-pent-3-enols of the same composition as produced by the



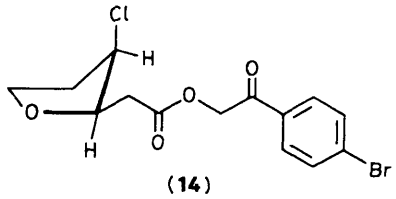
Scheme 1. Cyclic β-halogeno-ether ring scission.



Scheme 2. Ring scission of 2-alkyl-3-chlorotetrahydropyrans.

sodium ring scission. Thus a carbanion not a radical is apparently involved, though all attempts to trap it using CH_3OD failed: ring opening must be very rapid. However, electron transfer[6,7] and carbanion inversion[8] are expected to be still more rapid, all three processes being faster than ring inversion (*i.e.* the Curtin–Hammett principle is not directly operative).

The preferred conformation of *trans*-2-alkyl(or aryl)-3-chlorotetrahydropyrans is (**8**) with $J_{2a,3a}$ *ca.* 9.7 Hz and that of the *cis*-isomer is (**9**) with $J_{2a,3e}$ *ca.* 1.5 Hz (Scheme 2).[9] Ring scission involves the common carbanion (**10**) leading to an (*E*)-alk-4-enol. In this way the ring scission of both *cis*- and *trans*-tetrahydropyrans (**8**) and (**9**) will be highly stereoselective. A few percent of the (*Z*) (*ca.* 4% for R = Pr^i by ^{13}C n.m.r. analysis) may accompany the dominant (*E*)-product,



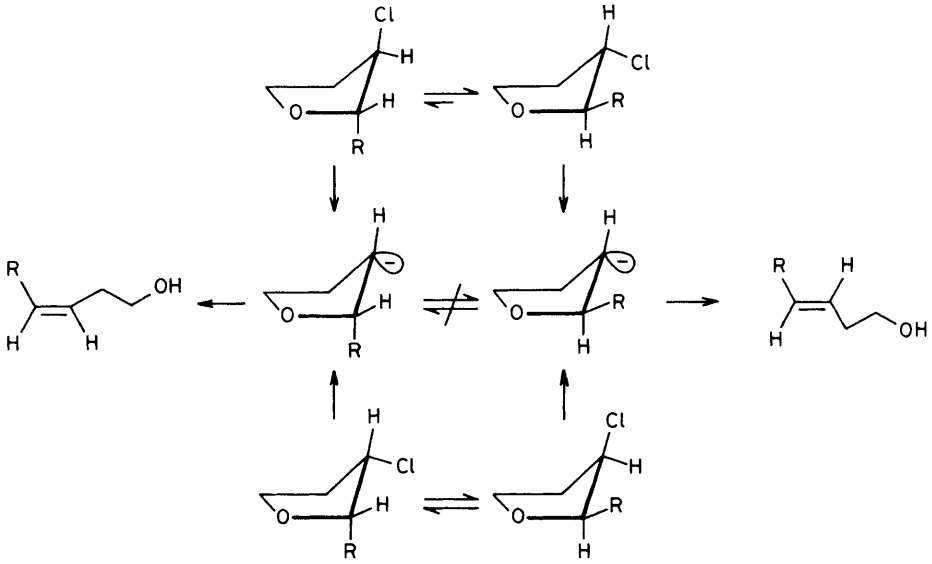
probably originating from minor amounts of the alternative conformer (**11**) in equilibrium with (**9**), ring scission proceeding *via* (**12**) to give (**13**). Ring scission of *cis*- and *trans*-2,3-dimethyl-3-chlorotetrahydropyrans, reported to give only (*E*)-4-methylhex-4-enol,[10] can be treated along similar lines.

Support for this interpretation comes from the 2-deuterio-3-halogenotetrahydropyrans where there is minimal conformational bias by deuterium, and the 2-methoxy-compounds where there are anomeric influences; in both cases the stereoselectivity of the ring-scission is substantially degraded. Thus a *trans*/*cis*-mixture of (**8**, R = D)/(**11**, R = D) (65—72% of the former) gave 64% of the (*E*)-alcohol (**3**, R = D), and 36% of the (*Z*) (**13**, R = D). Had the carbanion equilibrated by ring-inversion, (**10**) ⇌ (**12**), a *ca.* 50 : 50 mixture of (*Z*)- and (*E*)-deuterio-alcohols would have been expected. However, with carbanions non-equilibrated in terms of ring-inversion, the (*E*)/(*Z*)-proportions should correlate with the *trans*/*cis*-proportions of the original tetrahydropyran mixture, and this is so within experimental error.

For *trans*-2-methoxy-3-chlorotetrahydropyran (in Et_2O), analysis using coupling constants for model compounds[11] indicates 62% of 2_{ax}-OMe and 38% of 2_{eq}-OMe; the corresponding *cis*-pyran was estimated as 44% of 2_{ax}-OMe and 56% of 2_{eq}-OMe. In the absence of equilibration in terms of ring inversion of the carbanion intermediate, an axially oriented methoxy group should produce the (*Z*)-alcohol. Sodium ring-scission of a 22% *trans*, 78% *cis*-mixture of 2-methoxy-3-chlorotetrahydropyrans gave a mixture of 40% (*Z*) (**13**, R = OMe) and 60% (*E*) (**3**, R = OMe) products.† However, a mixture of the corresponding bromopyrans gave a different (*Z*)/(*E*)- ratio for the alcohols (26 : 74) again indicating that an equilibrated ring-inverting carbanion (**10**) ⇌ (**12**) is not a common intermediate in the two series.

cis- and *trans*-Assignments[2] to 2-alkyl-3-chlorotetrahydrofurans which have $J_{2,3}$ 2.6—3.6 Hz and $J_{2,3}$ 4.5—5.9 Hz respectively, were confirmed by converting *cis*-2-allyl-3-chlorotetrahydrofuran on the one hand by hydrogenation into the *cis*-2-n-propyl compound (**5**, R = Pr^n), $J_{2,3}$ 3.3 Hz, and on the other by oxidation and derivatisation to the *p*-bromophenacyl ester (**14**), the structure of which was determined by *X*-ray analysis by the heavy atom method.[12] These tetrahydrofurans show pseudorotation in solution and are not expected to take a single preferred conformation but to participate in equilibria. Consequently some molecules have axial, some equatorial orientations of the group R, with the former giving (*Z*)- and the latter (*E*)-alk-3-enols on ring scission. As the anion is not equilibrated by ring inversion (pseudorotation) the *cis*- and *trans*-tetrahydrofurans give differing mixtures of (*Z*)- and (*E*)-olefinic alcohols. *trans*-2-Alkyl-3-chlorotetrahydrofurans probably gave *ca.* 82% (*E*)-alcohols because their conformational equilibria favour the R

† Yields of alcohol are poor (*ca.* 15%) and the situation is complicated since the main direction of β-halogeno-ether cleavage is exocyclic giving dihydropyran, rather than endocyclic giving 5-methoxypent-4-enols.



Scheme 3. Ring scission of 2-alkyl-3-chlorotetrahydrofurans.

group being predominantly equatorial in Scheme 3, whereas in *cis*-tetrahydrofurans R is only slightly favoured as an equatorial substituent, giving 53% (*E*)-alcohol.

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12 We thank Dr. M. Begley for this determination, which will be published separately.