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Acidic Isomerization of Vicinally Substituted (*cis*)-Acceptor-Donor Cyclopropanes *via* an Open Ring Mechanism.

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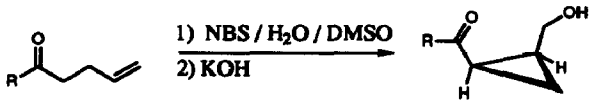
Abstract: Many (*cis*)-cyclopropanes bearing 1-electronwithdrawing and 2-hydroxymethylene groups were synthetised and isomerized under mild acidic conditions to afford the corresponding trans isomers. The mechanism is reported.

The analogy between the reactivity of olefins and cyclopropanes can be explained by the π type orbitals of the strained three membered carbocycles and their interaction with activating substituents [1]. Cyclopropanes bearing acceptor substituents are prone to ring cleavage by nucleophiles to provide 1,5 addition products [2] (homo Michael addition). The carbonyl, cyano, or sulfonyl groups are usually used as strong π-acceptors [3]. The combination with a donor substituent, for example an oxy, amino or thio group, will enhance the reactivity of the cyclopropane towards nucleophilic attack [4].

This communication gives a detailed account of our investigations concerning the isomerization process of (*cis*)-cyclopropanes bearing an acceptor function such as a carbonyl and a hydroxymethylene donor function. In a previous report, we published the diastereoselective synthesis of (*cis*)-cyclopropanes involving the intramolecular opening of a γ,δ-epoxy ketone intermediate with KOH in DMSO (scheme 1) [5].

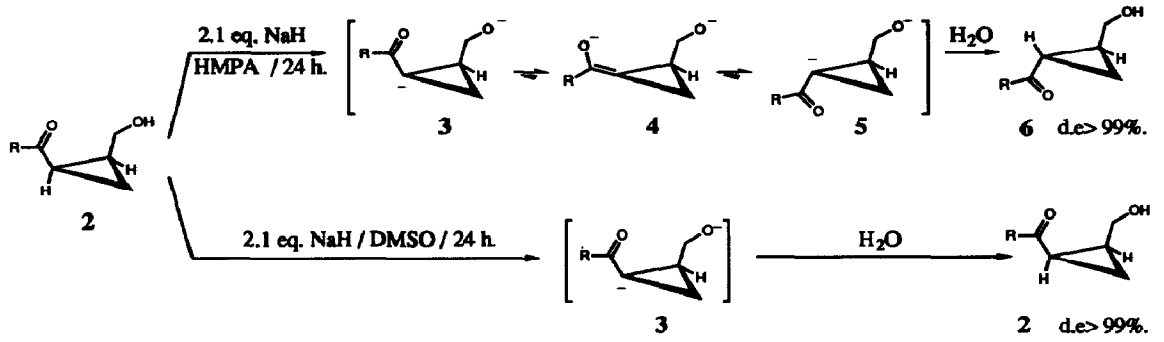


1 **2** d.e> 99%.

Scheme 1

The rearrangements of γ,δ-epoxy ketones were also performed using NaH as base. DMSO as solvent led to a kinetically controlled reaction affording the cis isomer in high d.e, whereas the use of HMPA gave the trans

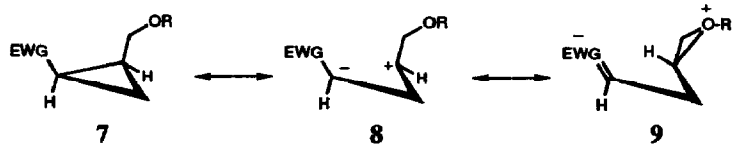
isomer by a thermodynamically controlled process involving the isomerization of the (*cis*)-cyclopropane intermediate. As expected isomerization attempts under basic conditions of **2** in DMSO were unsuccessful while HMPA led effectively to the isomerized product **6** (scheme 2).



Scheme 2

The cyclopropyl ring must therefore provide an energy barrier to the inversion or delocalization of the carbanion **3** while the presence of HMPA offers the driving force for the planarity of the "carbanion" to ensure the total isomerization towards the more stable trans isomer [6]. If 1 molar equivalent of base is used, the initially formed cyclopropyl methylene alcoholate is configurationally stable and no isomerization is observed.

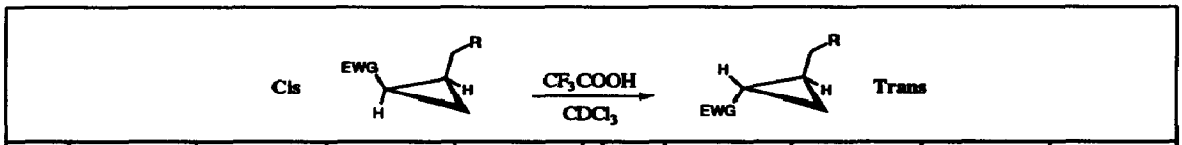
Cyclopropanes vicinally bearing an electronwithdrawing group and a hydroxymethylene as electron donor substituent should combine the features of an homo Michael system and those of an homoenolate equivalent (scheme 3) [7].



Scheme 3

The "analogy" between the structure **9** and the enolate **4** leads us to attempt (*cis*)-cyclopropane isomerization under acidic conditions. The hydroxymethylene nucleophile provides the prerogative for isomerization when the ketone function is activated by acidic catalysis. The stabilization by an oxygen of a carbocationic center that might result from an acidic activation of the electronwithdrawing group should allow the isomerization process. Many substrates were treated, as outlined in ref. 8, by trifluoroacetic acid in $CDCl_3$ [11]. The reaction was monitored by ^1H NMR. No cyclopropane degradation products were observed. The *trans* / *cis* diastereo ratios were assessed after the time indicated in table 1 [9].

Some representative isomerisation attempts are summarized in table 1.

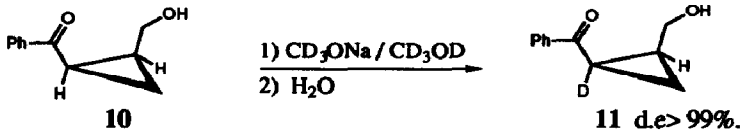


Entry	EWG	R	Trans / Cis	React.Time (days)	Entry	EWG	R	Trans / Cis	React.Time (days)
1	Ph-CO-	-OH	95 : 5	2	6	Ph-CO-	-Br	0 : 100	5
2	Ph-CO-	-OH	> 99 : 1	5	7	O_2N-	-OH	> 99 : 1	2
3	tBu-CO-	-OH	> 99 : 1	2	8	NC-	-OH	70: 30	2
4	Me-CO-	-OH	90 : 10	2	9	Ph-CO-	-OMe	5 : 95	2
5	Ph-CO-	-O-CO-Ph	0 : 100	5	10	Ph-CO-	-OMe	30 : 70	5

Table 1

When R is a bromine (entry 6) or a carboxylate (entry 5) no isomerization occured. As expected when R is an hydroxyl group isomerization proceeds well [10] (entries 1, 2, 3, 4). When R is a methoxyl group, slow isomerization occurs (entries 9, 10). The methodology can be extended to others electronwithdrawing groups, such as nitro (entry 7) or cyano (entry 8). No reverse isomerization towards (*cis*)-cylopropanes starting from the chromatographically pure trans products were detectable under the same reaction conditions.

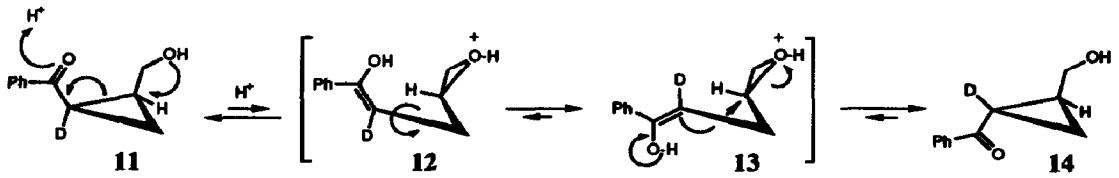
To prove the intramolecular 1,5 addition in acidic apolar medium, the synthesis of deuterium labelled cyclopropane was undertaken (Scheme 4). A solution of the cis isomer **10** in MeOD was treated with 5 molar equivalents of deuterated sodium methanolate. After one day, the reaction was quenched with H_2O, worked up as usual and chromatographied on silica gel [10].



10 **11** d.e> 99%.

Scheme 4

The cis deuterated compound **11** was isomerized with a five fold excess of TFA in an aprotic apolar solvent ($CDCl_3$). The isomerization of the deuterated cyclopropyl derivative **11** under our conditions gave complete inversion of configuration to the trans isomer **14** [10]. No D/H exchange was observed. This result suggests that the reaction involves a ring opening of the three membered carbocycle by intramolecular 1,5 addition (scheme 5). An enol intermediate structure without ring opening should lead with an excess of TFA to some D/H exchange.



11 **12** **13** **14**

Scheme 5

In summary, the isomerization of (*cis*)-1-keto-2-hydroxymethylene cyclopropanes in acidic conditions in an apolar aprotic solvent affords with high diastereoexcess the trans isomer. The mechanism of this isomerization process involves a 1,5 homo Michael addition of the alkoxy group *via* an oxiranium intermediate. This methodology provides some advantages over basic HMPA isomerization conditions as, for example, cost, toxicity and troublesome work up of the latter.

Acknowledgments: We thank Dr Jerry Harnett for reviewing this manuscript and Nathalie Petit for M.S measurements.

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8. The reactions were performed in 0.5 ml $CDCl_3$ using 0.1 mmole of the cyclopropane and 5 molar equivalents of trifluoroacetic acid at room temperature.
9. The *trans / cis* product ratios in each case were easily confirmed by examination of the relative intensities of the resonance for the two hydroxymethylene protons in the ^1H NMR spectrum of the crude mixture. The methylene protons are part of an AMX system. The δppm values of the two methylene quartet protons are upshielded in the (*trans*)-cyclopropane, relative to the cis isomer. The stereochemistry of the trans isomer was confirmed by a strong nuclear Overhauser effect (nOe) between the α-carbonyl hydrogen and the two hydrogens of the hydroxymethylene function indicating a spatial proximity .
10. Spectral data of compounds **10 / trans isomer (entry 1) - 11 / 14.** For analytical purpose TFA was previously neutralized with K_2CO_3 and subsequent filtration over SiO_2 led to the acid free trans product. GC-MS spectra were recorded on OH trimethyl silylated products by CI-NH_3.

10: RMN ^1H ($CDCl_3$, 200 MHz) δ: 1.12-1.03 (m, 1H, -HC-HCH-CH-), 1.53-1.45 (m, 1H, HC-HCH-CH-), 2.01-1.89 (m, 1H, -CH-CH_2OH), 2.71-2.63 (m, 1H, OC-CH-), 3.57 (dd, J=6.8Hz-11.4Hz, 1H, -HCH-OH), 3.80 (dd, J=5.7Hz-11.4Hz, 1H, -HCH-OH), 7.61-7.43 (m, 3H, H arom.), 8.02 (m, 2H, H arom.). RMN ^{13}C ($CDCl_3$, 50 MHz) δ: 15.3 (-HC-HCH-CH), 22.7 (OC-CH-), 27.3 (-CH-CH_2OH), 64.6 (CH_2-OH), 128.0 (C arom.), 128.5 (C arom.), 132.7 (C arom.), 137.8 (C arom.), 199.2 (CO). GC-MS m/z (%): 266 M^++18 (13), 250 M^{+2} (36), 249 M^{+1} (100), 159 (36).

trans isomer (entry 1): RMN ^1H ($CDCl_3$, 200 MHz) δ: 1.12-1.05 (m, 1H, -HC-HCH-CH-), 1.57-1.48 (m, 1H, HC-HCH-CH-), 2.04-1.93 (m, 1H, -CH-CH_2OH), 2.05 (s, 1H, OH), 2.73-2.66 (m, 1H, OC-CH-), 3.99 (dd, J=7.9Hz-11.6Hz, 1H, -HCH-OH), 4.23 (dd, J=5.9Hz-11.6Hz, 1H, -HCH-OH), 7.59-7.44 (m, 3H, H arom.), 8.02 (m, 2H, H arom.). RMN ^{13}C ($CDCl_3$, 50 MHz) δ: 15.2 (-HC-HCH-CH-), 23.0 (-CH-CH_2OH), 23.5 (OC-CH-), 66.0 (CH_2-OH), 127.8 (C arom.), 128.3 (C arom.), 132.7 (C arom.), 137.4 (C arom.), 198.3 (CO). GC-MS m/z (%) : 266 M^++18 (13), 250 M^{+2} (44), 249 M^{+1} (100), 159 (33).

11: RMN ^1H ($CDCl_3$, 200 MHz) δ: 1.07 (dd, J=3.8Hz-6.0Hz, 1H, -DC-HCH-CH-), 1.48 (dd, J=3.8Hz-8.6Hz, 1H, -DC-HCH-CH-), 1.94 (m, 1H, -CH-CH_2OH), 3.57 (dd, J=6.8Hz-11.4Hz, 1H, -HCH-OH), 3.80 (dd, J=5.7Hz-11.4Hz, 1H, -HCH-OH), 7.52 (m, 3H, H arom.), 8.02 (m, 2H, H arom.). RMN ^{13}C ($CDCl_3$, 50 MHz) δ: 15.4 (-DC-HCH-CH-), 22.3 (t, J=24Hz, C-D), 27.4 (-CH-CH_2OH), 64.4 (CH_2-OH), 128.0 (C arom.), 128.5 (C arom.), 132.8 (C arom.), 137.8 (C arom.), 199.5 (CO). GC-MS m/z (%) : 267 M^++18 (11), 251 M^{+2} (51), 250 M^{+1} (100), 160 (32).

14: RMN ^1H ($CDCl_3$, 200 MHz) δ: 1.06 (dd, J=4.6Hz-6.0Hz, 1H, -DC-HCH-CH-), 1.49 (dd, J=4.6Hz-8.8Hz, 1H, -DC-HCH-CH-), 1.99 (m, 1H, -CH-CH_2OH), 3.99 (dd, J=8Hz-11.6Hz, 1H,-HCH-OH), 4.23 (dd, J=6Hz-11.6Hz, 1H, HCH-OH), 7.49-7.43 (m, 3H, H arom), 8.02 (m, 2H, H arom). RMN ^{13}C ($CDCl_3$, 50 MHz) δ: 15.2 (-DC-HCH-CH-), 22.8 (-CH-CH_2OH), 23.5 (t, J=24Hz, C-D), 66.2 (CH_2OH), 127.8 (C arom.), 128.3 (C arom.), 132.7 (C arom.), 137.5 (C arom.), 198.3 (CO). GC-MS m/z (%): 267 M^++18 (31), 251 M^{+2} (15), 250 M^{+1} (100), 162 (22).
11. If a catalytic amount of TFA is used, the reaction proceeds, but much more slowly.

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