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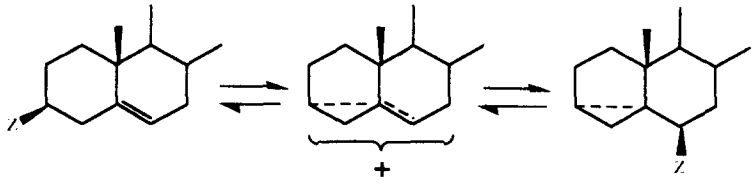
π Participation in Nucleophilic Displacement of α-Cyclogeranyl Tosylate.

Alfonso Fernández Mateos*, Gustavo Pascual Coca, Jose J. Pérez Alonso, Rosa Rubio González and Carolina Tapia Hernández

Departamento de Química Orgánica, Facultad de C. Químicas,
Plaza de los Caídos 1-5, 37008 Salamanca, Spain.

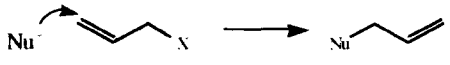
Abstract: A study of α-cyclogeranyl tosylate displacement by several nucleophiles is reported. Cyclopropane derivatives C were formed by homoallylic participation only with hydroxide and diethyl malonate anions.

There is much evidence that double bonds in the homoallylic position [1], as well as in positions further away, can afford anchimeric assistance in the departure of tosyl and other leaving groups. The norbornyl and cyclopropylmethyl systems are the most broadly studied and their reactions with polar protic solvents the best known [2]. An example of double bond participation is the methanolysis of cholesteryl tosylate which affords two isomeric derivatives, depending on the presence or absence of a buffer. Cholesteryl methyl ether is formed in the absence of potassium acetate, whereas the species arising under buffered conditions is the 3,5-cyclosteroid.



In both compounds, the entering nucleophile has the β orientation. Transitional species were formulated as a homoallylic bridged ion. Participation by π electrons of 5,6 double bond in the 3,5-cyclosteroid is stereoselectively α.

A reaction related to the one above is the nucleophilic displacement of allylic substrates denominated S_N2'.

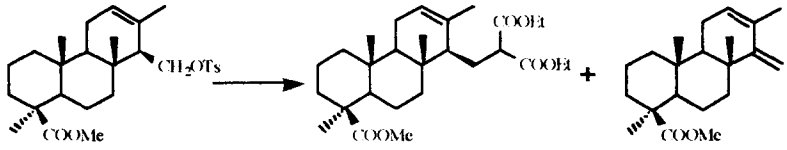


Many factors affecting the S_N2' reaction have been studied [3], such as the nature of the attacking nucleophile. This is not the case of homoallylic substrates on which, to our knowledge, carbon nucleophiles, such as malonate anions or alkyl cuprates, have not been tested.

Our incursion in this matter was motivated by the rare experimental results obtained in the nucleophilic displacement of the tosyl derivative **A** with malonate anion in toluene (Scheme 1, $X=CH(COOEt)_2$).

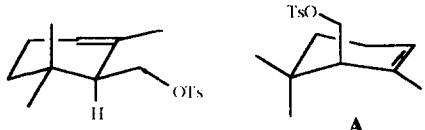
To our knowledge this is the first time that a carbon-carbon double bond has been found to participate in the departure of a leaving group induced by a carbon nucleophile in homoallylic substrates.

The same reaction conditions with the similar substrate **D** only produced the expected nucleophilic displacement and some elimination [4].



D

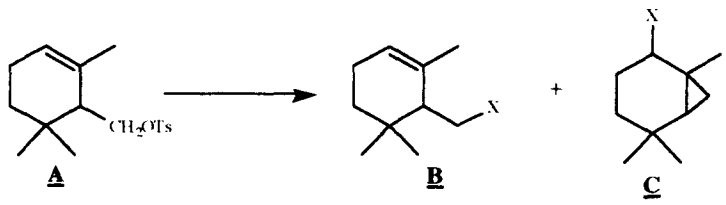
The differences in reactivity of compounds **A** and **D** could be attributed, among other factors, to conformational freedom. While the tricyclic tosylate **D** is in a very rigid conformation, the monocyclic tosylate **A** can adopt two main conformations A_{eq} and A_{ax}. As in the methanolysis reaction of cholesteryl tosylate, the double bond in conformation A_{ax} is in a geometrically favorable position for backwards attack on the carbon bearing the leaving group.



A_{eq} A_{ax}

Although the ionization of tosylate must be very low in toluene, a " concerted" process as described by McLennan [5] for S_N2' reaction would explain our case (Table I entry 7a). The change of apolar toluene to DMF , which increases the nucleophilicity of the malonate anion, only promotes the abnormal substitution (Table I entry 7b); this result is consistent with the finding of Stork [6] on hindered allylic substrates.

To see the scope of the π participation on α-cyclogeranyl tosylate **A**, we assayed several nucleophiles. The results are shown in Table I.



A B C

Scheme I

Table I

Entry	Nucleophile	Reaction Conditions	Products	Yield
1	OH^-	$NaHCO_3$, H_2O,acetone [2]	**1C** (100)[7]	92%
2	N_3^-	NaN_3,DMF [8]	**2B** (100)	71%
3	NO_2^-	$NaNO_2$,DMF [9]	**3B** (100)	60%
4	I^-	KI,DMF [8]	**4B** (100)	80%
5	Br^-	KBr,DMF [8]	**5B** (100)	75%
6	CH_3^-	Me_2CuLi,ether [10]	**6B** (100)	55%
7a	$^-CH(COOMe)_2$	diethyl malonate,Na,toluene [12]	**7B** (60) **7C** (40)[11]	72%
7b	"	diethyl malonate,NaH,DMF [13]	**7C** (100)	80%
8	PhS^-	PhSH,benzene,NaOH,H_2O [14] NH_4Br	**8B** (100)	100%
9	CN^-	NaCN,DMSO [15]	**9B** (100)	100%

Only two nuclophiles gave the abnormal substitution products.The behaviour of our homoallylic system **A** against nucleophiles such as the thiolate anion and dimethyl copper lithium is different from that found with allylic systems: while the allylic system gave normal (S_N2) and abnormal (S_N2') substitution products [3], our homoallylic system gave only S_N2 products.

A rationalization of the results found in the table is difficult to establish in the light of the nucleophilic character or by invoking the principle of HSAB.

Among soft nucleophiles we found two modes of action:

Normal S_N2: RS^-, I^-, CN^-," CH_3^-". Abnormal: $^-CH(COOEt)_2$

The hard nucleophile ^-OH only gave abnormal substitution.

Borderline nucleophiles: Br^-, N_3^-, NO_2^- only gave the S_N2 reaction.

The structures of the compounds described were assigned from their ^1H and ^{13}C NMR spectra.

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(7).-Compound **1C**, ^{1}H n.m.r. ($CDCl_3$) δ: 0.15 (1H, dd, J 4.8 Hz, J' 9.1 Hz), 0.44 (1H, dd, J 4.8 Hz, J' 5.6 Hz), 0.65 (1H, dd, J 5.6 Hz, J' 9.1 Hz), 0.89 (3H, s), 1.04 (3H, s), 1.16 (3H, s), 3.89 (1H, m) ppm; ^{13}C n.m.r. ($CDCl_3$) δ: 11.73, 23.75, 25.21, 27.75, 28.03, 28.77, 31.93, 34.01, 34.58, 72.09 ppm.

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(11).- Compound **7B**, ^{1}H n.m.r. ($CDCl_3$) δ: 0.81 (3H, s), 0.88 (3H, s), 1.18 (6H, t, J 7 Hz), 1.62 (3H, s), 3.42 (1H, t, J 6 Hz), 4.12 (4H, q, J 7 Hz), 5.24 (1H, s) ppm; ^{13}C n.m.r. ($CDCl_3$) δ: 13.61, 13.61, 22.54, 22.80, 26.87, 26.88, 29.77, 30.47, 32.28, 46.37, 52.07, 60.59, 60.59, 120.54, 135.36, 168.73, 168.73 ppm.

Compound **7C**, ^{1}H n.m.r. ($CDCl_3$) δ: 0.12 (1H, dd, J 5 Hz, J' 9.3 Hz), 0.25 (1H, dd, J 5 Hz, J' 5.7 Hz), 0.42 (1H, dd, J 5.7 Hz, J' 9.3 Hz), 0.86 (3H, s), 1.06 (6H, s), 1.26 (3H, t, J 7 Hz), 1.27 (3H, t, J 7 Hz), 3.47 (1H, d, J 8 Hz), 4.17 (2H, q, J 7 Hz), 4.18 (2H, q, J 7 Hz) ppm; ^{13}C n.m.r. ($CDCl_3$) δ: 13.19, 13.98, 13.98, 19.34, 21.43, 27.24, 28.20, 29.06, 31.97, 32.94, 34.57, 38.92, 55.27, 60.88, 60.88, 169.23, 169.23 ppm.

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