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Highly Diastereoselective Electrophilic Additions to the Vinylcyclopropane Moiety of a Homotropylidene System#

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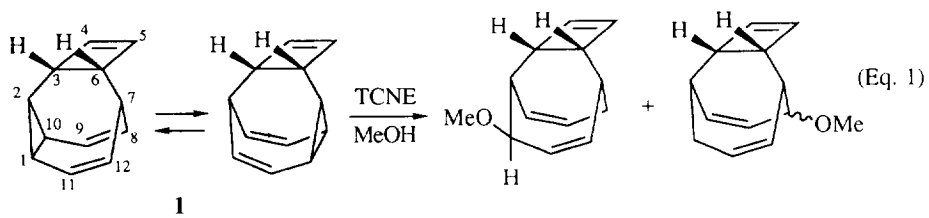
Abstract. *The acid catalyzed addition of AcOH and MeOH to the vinylcyclopropane moiety of tetracyclo[5.3.2.0^{2,10}.0^{3,6}]dodeca-4,8,11-triene (**1**) afforded kinetic mixtures of 9-acetoxy and, respectively, 9-methoxytricyclo[4.3.3.0^{2,5}]dodeca-3,7,10-trienes in which the β derivatives are always, even when sterically more congested, highly prevalent over their α counterparts. Studies with deuterated acetic acid showed that there was not any relationship between the stereochemistry of the deuteron (proton) attack and that of the nucleophilic trapping of the intermediate carbocation. These findings can be rationalized on the basis of a two step process i) proton attack to the homotropylidene moiety of **1** with formation of a cyclopropylcarbinyl carbocation ii) opening of its cyclopropane ring under tight assistance by the nucleophilic solvent to give the final products with high β diastereoselectivity. By contrast, the reaction of dichloroketene, a strong uniparticulate electrophile, involved only the cyclobutene system of **1**.*

INTRODUCTION

In the attempt to trap dipolar intermediates in the reaction of tetracyanoethene (TCNE) with tetracyclo[5.3.2.0^{2,10}.0^{3,6}]dodeca-4,8,11-triene (**1**) (whose homotropylidene moiety is involved in a very fast degenerate Cope rearrangement) we carried out this reaction in methanol.[1] Huisgen has demonstrated, in his very ingenious and elegant investigation of two step [2+2] dipolar cycloadditions of TCNE to vinylethers, how efficient methanol and ethanol can be in trapping dipolar intermediates.[2] However, neither adducts of the type **1**-TCNE nor adducts of the type **1**-TCNE-MeOH could be detected in our experiment but a mixture of methylethers were isolated in good yields (Eq. 1).[1]

It is quite evident that this finding was the result of catalyzed addition of methanol to **1** because in the absence of TCNE no reaction took place. Actually when pure TCNE was added to MeOH in the presence of methyl orange the solution turned red at once, indicating that the medium had become acidic, and the acidity of



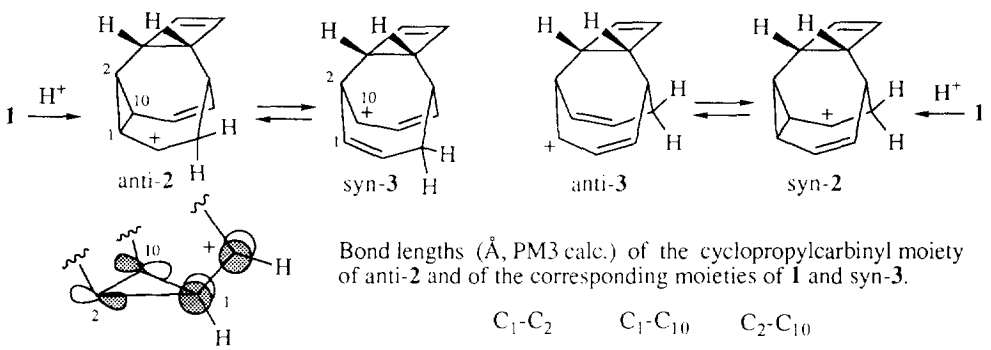
(Eq. 1)

1

#Dedicated to Prof. Paolo Grünanger on the occasion of his 70th birthday

the solution increased with time. Thus, the interaction of TCNE with methanol produces acidity at once, most probably, through a donor-acceptor complex MeOH-TCNE which, in turn, in a slower process, gives rise to more acidic compounds.[3] Our surprise was tempered when a literature search disclosed to us that Bartlett et al. had already reported a very similar observation for the reaction of TCNE with anti-sesquinorbornene in the presence of methanol.[4]

However, this serendipitious finding offered us the opportunity to study the electrophilic addition of solvent to **1**. An electrophilic attack to the homotropylidene system of **1** can lead to formation of cyclopropylcarbinyl carbocations, i.e. anti- **2** and syn-**2**,[5] whose cyclopropane ring is almost exactly "bisected" by the plane of the cationic center. It is well established that in this orientation the cyclopropane ring can exploit all its strong stabilizing conjugative ability[6] and the reaction, owing to the rigidity of the system, should take advantage of this stabilization yet from its very beginning. The cyclopropylcarbinyl cations are remarkable not only for their unusual stability but also for their ability to rearrange rapidly.[7] An easy way to rearrange for **2** is to open to the homoallyl-allyl cation **3** in a process favored by a significant angle strain relief. The classical cations **2** and **3**, most probably, correspond to two well differentiated minima on the potential energy surface of this system. That is, they are "real equilibrating structures" and not simply canonical Lewis structures whose weighted average (a "non classical" structure) is the most proper description of the actual molecule in resonance terms. This statement is supported by AM1 and PM3 calculations which indicate **3** as much more stable than **2** (by, respectively, 14.7 and 11.2 kcal mol^{-1} in the case of the anti-**2**/syn-**3** pair) while this difference in stability reduces to $\approx$ 1 kcal mol^{-1} (for the anti-**2**/syn-**3** pair) with STO-3G calculations.[8a,8b] Interestingly, the calculated geometry of **2** exhibited a lengthening of the C_1-C_2 and C_1-C_{10} bonds and a shortening of the C_2-C_{10} bond of the cyclopropane ring as compared to **1**.[8c] This observation can be nicely explained as the result of the strong interaction between the empty p_z orbital of the cationic center and the antisymmetric component of the degenerate highest occupied pairs of cyclopropane Walsh orbitals (see the following Scheme).[6]



Bond lengths (Å, PM3 calc.) of the cyclopropylcarbinyl moiety of anti-**2** and of the corresponding moieties of **1** and syn-**3**.

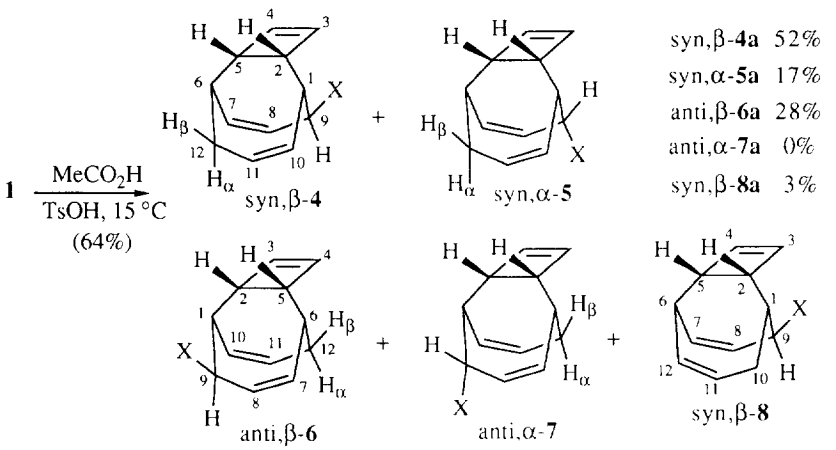
	C_1-C_2	C_1-C_{10}	C_2-C_{10}
1	1.51	1.52	1.51
anti-**2**	1.56	1.62	1.47
syn-**3**	1.50	2.40	1.48

The chemistry of the cyclopropylcarbinyl cations has received steady attention yet from the early studies of the i-cholesteryl system.[7] However, the nature of carbocation intermediates in solvolysis studies as well as in electrophilic additions which can involve cyclopropylcarbinyl cations has not been clearly defined.[7] Thus, we decided to study the addition of acetic acid and methanol to **1** in the presence of p-toluensulfonic acid. It is a common practice to use this acid to catalyze addition reaction of acetic acid,[9] methanol, water [4] etc. For our system p-toluensulfonic acid not only can assume the catalytic role of tetracyanoethene but also it gives rise to cleaner reactions. Our aim was to find out whether ions **2** and **3** are formed as discrete equilibrating intermediates or whether trapping by the solvent takes place well before they become free ions. The rigid carbon

skeleton of **1** and of cations **2** and **3** allows one to easily determine the diastereoselectivity of attack of both the electrophilic and nucleophilic part of the solvent.

RESULTS AND DISCUSSION

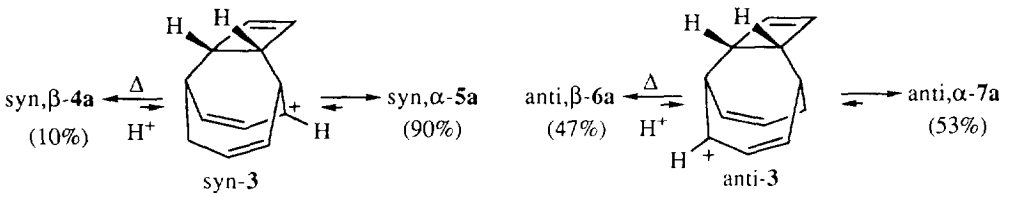
The reaction of **1** with glacial acetic acid , used as solvent, was carried out at 15 °C under stirring in the presence of p-toluensulfonic acid for 2-3 hours. No significant conversion was detected in the absence of p-toluensulfonic acid under otherwise identical conditions. The crude product from the catalyzed reaction exhibited only two spots on TLC but GC analysis disclosed the presence of at least three products. The higher R_f product comprised only one compound , i.e., anti,β-**6a**, while the lower R_f product was mainly constituted of syn,β-**4a** with minor amounts of syn,α-**5a** and very small amounts of syn,β-**8a**.[5] Only trace amounts of alcohols syn,β-**4b** and anti,β-**6b** were present in the reaction mixture. While compound **4a** could be obtained in a pure state by repeated crystallizations, identification of compounds **5a** and **8a** was made possible by reduction of the mixture of acetoxy derivatives by $LiAlH_4$ and separation of the resulting alcohols by column chromatography. Compound anti,α-**7a** could not be detected in the reaction mixture.



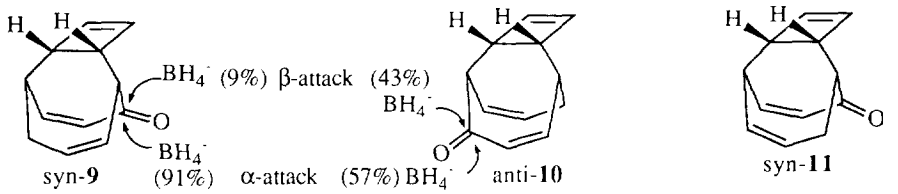
a: X = AcO; **b**: X = OH

In order to assess whether the product ratio was under kinetic or thermodynamic control we performed equilibration reactions by heating pure syn,β-**4a** and, respectively, anti,β-**6a** at 25 °C in acetic acid in the presence of TsOH until TLC and GC analysis showed no further change in the product ratio. Only syn,α-**5a** was formed as a new product from syn,β-**4a** and the former was highly prevalent at the equilibrium in keeping with the observation that it is sterically less congested than the latter. Consistently, only anti,α-**7a** was formed (in a slower process) from anti,β-**6a** and now, at the equilibrium, the two isomers are present in a ratio very close to 1 as a consequence of their very similar steric crowding. On the basis of these results one can safely conclude that the exclusive (in the anti attack) or dominant (in the syn attack) formation of the β isomers is the result of kinetic control. These results suggest that syn,α-**5a** derives , at least in part, from isomerization of syn,β-**4a** (or of syn,β **8a**, see below). Moreover, the observation that in the isomerization of **4a** (**6a**) there was not any formation of **6a** and **7a** (**4a** and **5a**) demonstrates that the equilibrium did not involve formation of **1** (i.e., the attack by proton is not reversible).

Equilibration between α and β isomers, reasonably, should involve the free ions syn-**3** and anti-**3**. A hint about what would be the kinetic face selectivity of the reaction of carbocations of the type **3** with nucleophiles



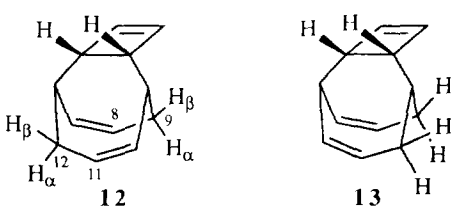
could be obtained from the $NaBH_4$ reduction of ketones **9** and **10** (easily prepared, as well as **11**, by pyridinium chlorochromate oxidation of alcohols **4b**, **6b** and **8b**, respectively). The diastereoisomer ratio in these reductions should mainly reflect the steric hindrance to the approach of the nucleophile. In fact, the attack from the bottom, i.e. from the α side, is slightly dominant in the case of anti-**10** while in the case of syn-**9** the shielding of the β side, by the cyclobutene moiety against the negatively charged nucleophile, is more efficient leading to clear-cut prevalence of approach from the α side.



Notice how, maybe by chance, the effect of steric crowding in unbalancing the relative stability of acetoxy derivative pairs syn,β-**4a** vs syn,α-**5a** (β/α = 10:90) and anti,β-**6a** vs anti,α-**7a** (β/α = 47:53) is very similar to the steric bias to nucleophile β vs α approach in the reduction of ketones syn-**9** (β/α = 9:91) and anti-**10** (β/α = 43:57) , respectively. It should be emphasized that the facial selectivity observed in the reduction reactions of **9** and **10** seems to eliminate the possibility that in the addition of acetic acid to **1** the acetoxy derivatives originate from a nucleophilic attack on free ions of the type **3**.

Structures **4a**-**8a** and **4b**-**8b** (the two series were correlated by reduction and acylation reactions) could be definitely established on the basis of NMR data (Tables 1-3). Compounds **4**-**7** exhibit a 1,5-diene system in their "bottom" octadiene moiety while only compound **8** shows a 1,4-diene (homodiene) system. The choice between these two systems was easy because in **4**-**7** H-1 and H-6, both, are coupled to one vinyl proton with a large coupling constant (J = 8.0 Hz, which safely indicates vicinal coupling) while in **8b** H-6 is coupled to two vicinal vinyl protons ($J_{6,7}$ = 8.0 Hz and $J_{6,12}$ = 9.0 Hz) and H-1 only to protons attached to saturated carbons.

No adducts with 1,4-diene structure, i.e. of the type **8a**, were detected in the equilibration reactions involving the **4a**/**5a** pair as well as the **6a**/**7a** pair described above. Moreover, when the catalyzed addition of acetic acid to **1** was carried out under "thermodynamic" control (at 25 °C and for long reaction time) compound **8a** was not present in the reaction mixture (more precisely **8b** could not be detected in the alcohol mixture obtained by $LiAlH_4$ reduction of the acetoxy derivative mixture). These findings clearly indicate that structures of the type **12** are at least 3 kcal mol^{-1} more stable than their isomers of the type **13**. Structure **12** is indicated as more stable than **13** also by AM1 and PM3 (however, by only ≤ 1 kcal mol^{-1}), MM2 (2.2 kcal mol^{-1}) and STO-3G (1.4 kcal mol^{-1}) calculations.



Geometry data for **12** and **13**, as well as for compounds **4-8**, from all kind of calculations show that the torsion angle (≈ 50°) between H-α (both at position 9 and 12) and its vicinal vinyl proton (H-8 and, respectively, H-11) is lower by ≈ 15-20° than that (≈ 65-70°) between H-β and the same vinyl vicinal proton. This finding explains, on the basis of the Karplus' relationship, why $J_{8,9}$ in compounds **4**, **6** and **8** (≥ 3.5 Hz) is larger than $J_{8,9}$ in compounds **5** and **7** (≤ 2.6 Hz). Calculated structures also clearly display a W relationship between H-2 and H-9 in **4** and **8** and between H-5 and H-12α in **6** and **7**. Accordingly, a long range coupling constant (^4J) between H-2 and H-9 (1.0, 1.5 Hz) was present in the NMR spectra of **4** and **8** (but not in those of **5-7**) and between H-5 and H-12α (1.2 Hz) in the NMR spectra of **6** and **7** (missing in those of **4**, **5** and **8**).

Table 1. 1H NMR data [δ($CDCl_3$) in ppm, J in Hz)] of alcohols **4b-8b**.[a]

	4b	**5b**	**6b**	**7b**	**8b**		**4b**	**5b**	**6b**	**7b**	**8b**
H-1	2.84	3.02	2.81	2.98	2.52	$J_{2,9}$	1.0	-	-	-	1.5
H-2	3.38	3.38	3.53	3.09	3.25	$J_{3,4}$	2.8	3.0	2.9	2.9	2.9
H-3	6.36	6.10	6.21	6.19	6.41	$J_{4,5}$	1.0	1.0	0.9	1.0	1.0
H-4	6.02	6.06	6.12	6.13	5.93	$J_{5,6}$	4.0	4.5	5.8	5.8	4.9
H-5	3.29	3.10	3.31	3.22	3.51	$J_{5,12\alpha}$	-	-	1.2	1.2	-
H-6	2.78	2.77	2.73	2.78	3.03	$J_{6,7}$	8.8	8.3	8.8	8.5	8.0
H-7	5.60	5.7[b]	5.90	5.83	5.72	$J_{6,11}$	1.0	1.0	1.0	0.9	-
H-8	5.79	5.7[b]	5.71	5.63	5.76	$J_{6,12\alpha}$	4.0	4.3	4.0	3.9	-
H-9	4.26	4.31	4.26	4.36	4.37	$J_{6,12\beta}$	4.0	4.0	4.0	3.9	-
H-10	5.73	5.7[b]	5.61	5.65	c	$J_{7,8}$	11.9	-	11.8	12.0	11.5
H-11	5.50	5.7[b]	5.52	5.75	5.48	$J_{7,9}$	1.3	-	1.0	2.0	1.0
H-12α	2.31	2.28	2.12	2.16	c	$J_{8,9}$	4.7	≤1.0	4.8	2.6	3.5
H-12β	2.40	2.40	2.34	2.42	c	$J_{9,12\beta}$	-	1.0	-	1.0	
$J_{1,2}$	5.4	5.8	4.8	4.4	4.6	$J_{10,11}$	11.9	b	11.8	11.9	-
$J_{1,8}$	1.5	0.8	1.5	1.5	1.4	$J_{10,12\alpha}$	1.6	1.0	1.0	1.0	-
$J_{1,9}$	3.8	4.1	4.0	4.6	2.0	$J_{10,12\beta}$	3.0	2.5	2.5	2.5	-
$J_{1,10}$	8.6	8.5	8.2	8.0	-	$J_{11,12\alpha}$	5.0	4.3	5.0	5.1	-
$J_{2,3}$	1.0	0.8	1.1	1.1	1.0	$J_{11,12\beta}$	3.0	2.5	2.5	2.5	-
$J_{2,4}$	-	-	0.6	0.6	-	$J_{12\alpha,12\beta}$	19.0	18.5	18.5	18.5	-
$J_{2,5}$	4.5	4.5	4.5	4.7	4.6						

[a]OH proton at ≈ δ 1.5- 1.9. [b]Complex multiplet. In deuteroacetone the signals of H-10 (δ 5.73, $J_{10,11}$ = 12.0 Hz) and H-11 (δ 5.54) are separated from those of H-7 and H-8 (δ 5.59). [c]**8b**: δ 2.33 (H-10α, $J_{1,10\alpha}$ = 2.1 Hz, $J_{10\alpha,11}$ = 4.5 Hz, $J_{10\alpha,12}$ = 2.4 Hz, $J_{10\alpha,10\beta}$ = 19.0 Hz), 2.48 (H-10β, $J_{1,10\beta}$ = 6.0 Hz, $J_{10\beta,11}$ = 3.8 Hz, $J_{10\beta,12}$ = 2.8 Hz), 5.97 (H-12, $J_{6,12}$ = 9.0 Hz, $J_{11,12}$ = 11.5 Hz); $J_{1,11}$ = 1.4 Hz; $J_{6,8}$ = 1.5 Hz.

Further diagnostic features about configuration of the stereogenic center at position 9 in **4-8** were provided by $Eu(fod)_3$ induced shifts and by NOE experiments.

In the presence of the europium complex the proton H-9 of alcohols **4b-8b** experiences, as expected, the highest shift to lower fields (extrapolated molar shift, ΔM ≈ 26 ppm) while large shifts were also displayed by H-8 (≈ 19 ppm) and H-1 (≈ 17 ppm). Moreover, diagnostic strong molar shifts were observed for H-3 in **4b** (13.5 ppm) and **8b** (11.3 ppm), for H-2 in **6b** (18.3 ppm) and for H-10 in **5b** (14.2 ppm) and **7b** (12.9 ppm) (Table 2). In fact, these shifts are only consistent with the β-position of the OH group in **4b**, **6b** and **8b** and the α position of the same group in **5b** and **7b**.

Table 2. $Eu(fod)_3$ induced shifts (molar shifts, ppm, $CDCl_3$)[a] of protons in **4b**-**8b**[b] and **9**-**10**.

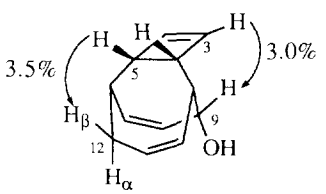
	4b	**5b**	**6b**	**7b**	**8b**	**9**	**10**
H-1	17.2	18.4	16.7	16.6	17.5	13.9	13.4
H-2	8.1	4.6	18.3	5.7	7.4	4.6	5.7
H-3	13.5	2.5	3.6	2.8	11.3	4.3	1.9
H-4	6.6	1.6	3.4	2.6	5.9	2.4	1.9
H-5	5.4	4.4	8.6	4.2	4.9	3.2	4.2
H-6	5.8	4.9	5.6	4.9	5.2	3.3	3.0
H-7	7.5	7.0	7.6	7.1	7.0	3.2	3.0
H-8	19.3	20.6	18.2	18.7	16.9	12.8	12.7
H-9	26.0	26.0	26.0	26.0	26.0		
H-10	2.8	14.2	4.3	12.9	3.8[c]	5.1	4.9
H-11	4.1	7.0	2.9	7.1	2.8	2.3	3.5
H-12α,	3.7	5.4	4.0	5.8	3.4[d]	2.7	2.6
H-12β	3.7	5.4	3.4	4.8		2.7	2.6

[a]Extrapolated molar shifts [b]In the case of alcohols **4b**-**8b** the reported shifts are relative shifts with respect to that of H-9 (assumed as 26.0 ppm in all of the alcohols; see introduction of Experimental) [c]H-10α and H-10β [d]H-12

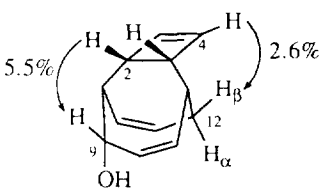
Table 3. Differential NOE enhancements (%) observed upon irradiation of H-3 and H-5 in **4b** and **5b**, of H-2 and H-4 in **6b** and **7b** and of H-2 and H-3 in **8b**.

	syn,β-**4b**	syn,α-**5b**		anti,β-**6b**	anti,α-**7b**		syn,β-**8b**
	{H-3}	{H-3}		{H-4}	{H-4}		{H-3}
H-1	1.4	1.3	H-6	1.7	1.6	H-1	1.1
H-2	1.5	2.2	H-5	2.4	2.3	H-2	1.9
H-9	-	3.0	H-12β	2.5	2.6	H-9	-
	{H-5}	{H-5}		{H-2}	{H-2}		{H-2}
H-6	2.8	4.4	H-1	4.2	4.1	H-1	3.5
H-12β	2.5	3.5	H-9	-	5.5	H-10β	2.2

As the distance between H-9 and H-3 in compounds **5** is ≈ 2.7 Å while that between H-9 and H-2 in compounds **7** is ≈ 2.6 Å (from semiempirical and MM2 geometries) one should expect substantial NOE effects for these pairs of protons in these compounds. In fact, irradiation of H-3 in syn,α-**5b** led to a 3% intensity increase of the H-9 signal while saturation of H-2 in anti,α-**7b** brought about intensity enhancement of H-9 by 5.5% (Table 3 and Scheme). No NOE effects were observed for the signal of H-9 in the β derivatives **4b**,**8b** and **6b**, respectively, upon irradiation of H-3 (in **4b** and **8b**) and H-2 (in **6b**).



syn,α-**5b**

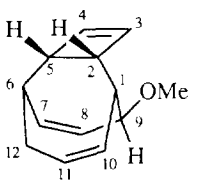


anti,α-**7b**

It was also possible to reliably demonstrate, by NOE experiments, that of the two signals attributable to the two protons at position 12, that is H-12-α and H-12-β, that one at lower fields has to be attributed to H-12-β. Irradiation of H-5 in **4b** and **5b** and of H-4 in **6b** and **7b** gave rise to a 2.5-3 5% NOE effect (Table 3) for the lower field H-12 signal in all these compounds and no effect for the higher field H-12 signal.

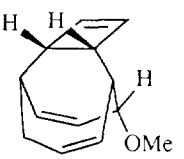
Thus, NMR data secured beyond any doubt the structure of compounds **4-8** and, in particular, definitely substantiated the complete (in the case of anti attack, formation of the sole **6a**) or high (in the case of syn attack, i.e., dominant formation of **4a** over **5a**) β diastereoselectivity of the nucleophilic attack to protonated **1**.

To confirm this noteworthy face selectivity we also studied the catalyzed (TsOH) addition of methanol to **1**.[10] The addition was significantly slower than that with acetic acid and it took 24 hours at 35 °C to reach ≈ 90% completion. Structures of the methoxy derivatives **4c-7c** (total yield: 77%) rest firmly on their correlation with alcohols **4b-7b** through methylation reactions of these latters to give the formers. The kinetic ratios reported in the Scheme refer to a reaction carried out at 20 °C (40 hours). These data show that the reaction mixture comprised almost only, and in similar amounts, the β isomers, i.e., anti,β-**6c** and the sterically most congested syn,β-**4c**. The most remarkable difference with respect to the reaction with acetic acid is the enhancement in facial selectivity of the syn nucleophilic attack, namely, in the syn,β-**4c**/syn,α-**5c** ratio (**4c**/**5c** ≥ 91:9 versus **4a**/**5a** ≥ 75:25).



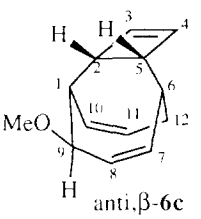
syn,β-**4c**

53% (7%)



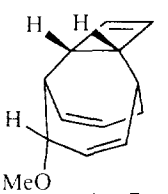
syn,α-**5c**

5% (53%)



anti,β-**6c**

42% (19%)



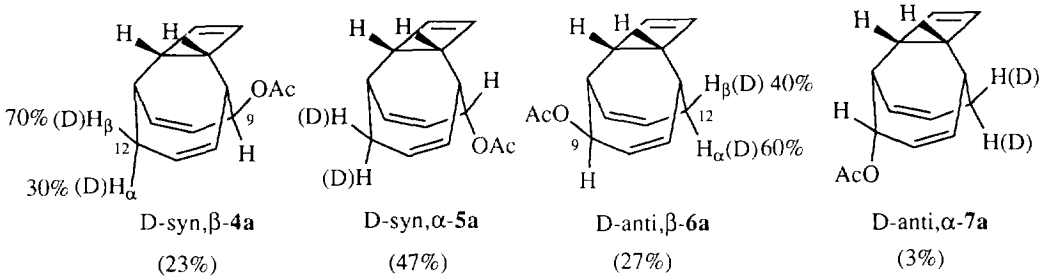
anti,α-**7c**

0% (21%)

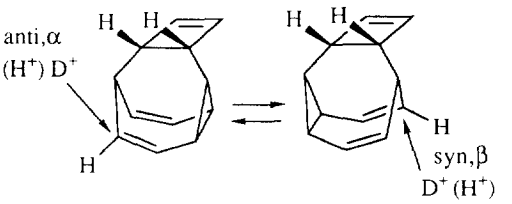
The thermodynamic mixture [obtained at reflux for 80 hours (values in parentheses in the Scheme)] exhibited a clear-cut dominance of syn,α-**5c** over syn,β-**4c** while anti,β-**6c** and anti,α-**7c**[11] were present in similar amounts.

At this point we can conclude that the diastereoselectivity of nucleophilic attack to protonated **1** is not far from 100% even when it has to overcome sizable steric shielding as in formation of syn,β-**4c** (≥ 91%).

It remained then to determine whether there was any relationship between the face selectivity of nucleophilic attack and that of proton addition. An answer to this question was provided by the addition of deuterated acetic acid to **1**. The reaction was slower than that in acetic acid (16% of unreacted **1** was recovered after 20 hours at 15 °C) as a result of a primary kinetic isotope effect on the rate determining first step of the reaction pathway. Recovered **1** did not display any deuterium content (^{1}H NMR) (suggesting, once again, an irreversible deuteration as the first step) while the four acetoxy derivatives contained only one deuterium atom at position 12. As for face selectivity of deuterium approach, there was a prevalence of α attack (α:β = 60:40, see Scheme) in formation of D-anti,β-**6a** while β attack was dominant (α:β = 30:70) in formation of D-syn,β-**4a**. The % of deuterium content at positions 12α and 12β in the α isomers, i.e., D-syn,α-**5a** and D-anti,α-**7a**, was the very same as that of their β counterparts. This supports the hypothesis that α isomers (now present in the reaction mixture in significantly larger amounts than in the addition of non deuterated acetic acid) are secondary products owing to the fact that in the deuterated solvent equilibration processes involving the acetoxy derivatives are slowed down less than the deuterium addition to **1**.[12] By the way, equilibration of D-anti,β-**6a** in acetic acid afforded a mixture of D-anti,β-**6a** and of D-anti,α-**7a**, in which deuterium remained localized at position 12 and the intensity ratio of H-12-α vs H-12-β (≈ 40:60) did not appreciably change.



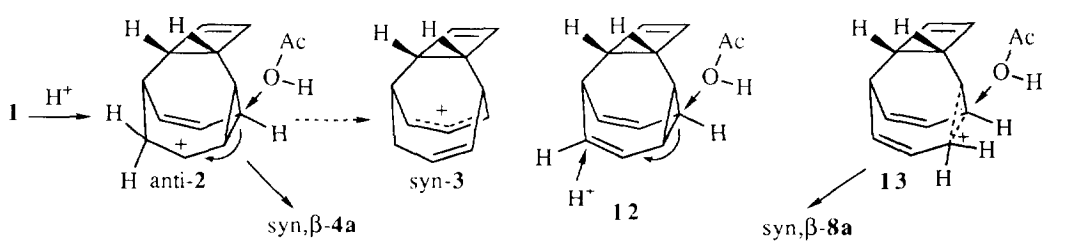
Facially favored electrophilic attack on the anti and, respectively, syn side of **1**.



These results demonstrate that the very high face selectivity of nucleophile attack is not the result of a similar very high face selectivity of proton approach. In other words, there is not any relationship between the diastereoselectivity of the proton attack and that of attack by the nucleophile.

CONCLUSION

The first step of the reaction, i.e. protonation of **1**, can involve both the π double bond (to give **2**) or the cyclopropane moiety (to give **13**). It is certainly reasonable to assume that the double bond is more reactive given that the attack at the double bond affords the very stable cyclopropylcarbinyl carbocations of the type **2**. These intermediates are then trapped by the solvent well before they relax to allylic ions **3**. In fact, acetoxy and methoxy derivatives can not derive from interception of the "free" ions syn-**3** and anti-**3** as this reaction channel should give rise to mixtures of products with clear cut dominance, in the case of syn **3**, of the α derivative over its β counterpart in striking contrast to the observed very high β selectivity. Thus, cations **3** are not present as intermediates in the addition reaction notwithstanding they are easily accessible structures as demonstrated by equilibration processes as well as by calculations (see Introduction). The cyclopropane ring opening of **2** must be assisted by solvent through a rearside nucleophilic attack which directly lead to the final products (e.g., formation of syn,β-**4a** in the Scheme). This SN_2 like ring opening reaction easily explain formation of β derivatives as dominant (or exclusive) reaction products. The α derivatives are most probably secondary products deriving from isomerization processes of the primary β products (**5** from **4** and **8**; **7** from **6**). Isomerization of the β,syn derivatives is easier (favored by steric congestion release) than that of the β,anti derivatives and that of the acetoxy derivatives more facile than that of the methoxy derivatives (the formers are better leaving groups than the latters).

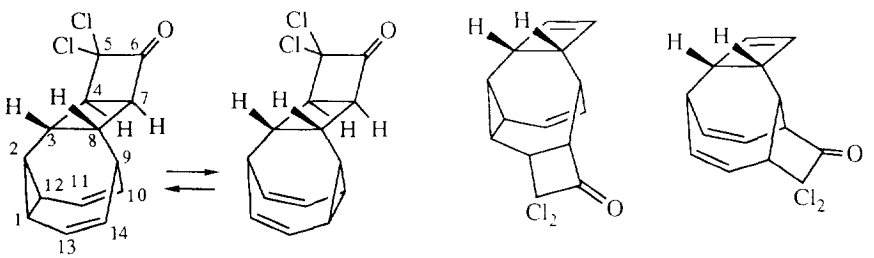


An AdE_3 one step mechanism[13] (e.g., **12**) (a vinylogous AdE_3), without formation even of free **2**, is a possible alternative to the two step pathway illustrated above. If we assume that the AdE_3 mechanism is operative our results demonstrate that it does not require a definite relationship (not found in the addition of $MeCO_2D$) between the stereochemistry of proton approach and that of the nucleophile.

Finally, the most straightforward explanation of formation of syn,β-**8a** features a corner protonation of the cyclopropane moiety (i.e., **13**) followed by a highly stereoselective capture by the nucleophile,[14] once again, well before it relaxes to a stable allylic carbocation.[15] Unfortunately we could not obtain further data to prove or disprove this hypothesis.

REACTION OF 1 WITH DICHLOROKETENE

The reactions reported above clearly show that, as expected, attack on **1** by biparticulate electrophiles takes place at the homotropylidene moiety and not at the cyclobutene double bond. This is true also for uniparticulate electrophiles such as TCNE.[1] On contrast cycloadditions (1,3-dipolar and Diels-Alder cycloadditions) were shown to preferably involve the cyclobutene system.[16] These different site selectivities made us curious about what would have been the behavior of a strongly electrophilic uniparticulate reagent such as ketene. The reactions of ketenes with double bonds[17a] feature highly asynchronous transition states (they are classified as a "quasi-pericyclic reactions") with appreciable electron transfer from alkene to ketene and consequent development of partial positive charge on the former[17b]. These considerations can lead to expectation that the attack of dichloroketene to **1** would involve its homotropylidene moiety which should be more able than the cycobutene ring to stabilize positive charges. Double bonds of homotropylidene moieties very similar to that of **1** have been shown to enter readily [2+2] cycloadditions with dichloroketene to give cyclobutanone derivatives.[18] Practically no data are known for the reaction of cyclobutenes with ketenes.[17a] However, Grimme and Schneider have reported that dichloroketene attacks bicyclo[4.2.2]deca-3,7,9-triene with complete site selectivity only at the cyclobutene double bond.[19]



14a **14b** **15** **16**

The reaction of **1** with dichloroketene took place readily at room temperature and we were able to detect (TLC and ^1H NMR) only one adduct. Ir absorption at 1800 cm^{-1} demonstrated the presence in the cycloadduct of a cyclobutanone moiety while the temperature dependence of its ^1H NMR spectrum clearly disclosed that it still contained a "fluxional" homotropylidene system. These data are obviously consistent with structure of the type **14** and definitely discard structures **15** and **16**. The small coupling constant between H-3 and H-4 ($J_{3,4}$ = 4.0 Hz) as well as that between H-7 and H-8 ($J_{7,8}$ = 3.0 Hz) are certainly more consistent with trans than with cis relationships in the cyclobutane system.[20] The two isomers **a** and **b** are not equally populated. If we assume that the proton next to the carbonyl group [H-7 (δ 3.70)] resonates at lower fields than that next to the chlorine atoms [H-4 (δ 3.24)] the equilibrium is shifted to the side of **14a** (**14a**/**14b** ≈ 1.5).

Our results demonstrate an unexpected prevalence of reactivity of the cyclobutene double bond over that of the double bonds of the homotropylidene system in accepting the electrophilic attack by ketene. This observation, together with that of Grimme and Schneider,[19] seems to suggest that cyclobutene double bonds are highly reactive with ketenes. We are now engaged in substantiating this conclusion and in finding out its origin.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were made on a Carlo Erba CHN analyser, model 1106. Infrared spectra were recorded as either Nujol suspensions or films on a Perkin-Elmer 881 spectrophotometer. ^{1}H NMR spectra were recorded either on a Bruker 80 (operating at 80 MHz) or on a Bruker AE 300 (operating at 300.3) spectrometers with tetramethylsilane as internal standard for $CDCl_3$ solutions unless otherwise stated. Protons were correlated by decoupling experiments. ^{1}H NMR spectra were evaluated as first order spectra.In Table 1 all the details of ^{1}H NMR spectra (300 MHz) of hydroxy derivatives **4b-8b** are reported. For the related acetoxy (**4a-8a**) and methoxy (**4c-7c**) derivatives only the signals of the proton at position 9 and of the methyl group are reported.

GC analyses were carried out with a DANI 6500, PTV injector, CP-Sil-19CB (25 m) capillary column and carrier H_2 (Retention time: **6a<5a<4a≈8a<7a** and **4c<6c<5c<7c**). Thin-layer chromatograms were done on plates precoated with silicagel 60 GF_{254} (Merck) [R_f (C_6H_{12}/AcOEt = 95:5 as eluant): **4b>8b>5b≥7b>6b**]. Spots were visualized either by spraying with 3% chromic oxide in sulfuric acid (50%) followed by heating at 120 °C or under UV light. Column chromatography was performed with Silicagel 60 (70-230 mesh) Merck.

Acetic acid (≥ 99.8%), p-toluensulfonic acid-monohydrate (99%) and acetic acid-d$_1$ (≥99.5%, ≤0.2% of D_2O) were used as such without further purification. Deuterated p-toluensulfonic acid was prepared by repeatedly dissolving in D_2O (99.95%) p-toluensulfonic acid-monohydrate and evaporating to dryness.

The molar induced shift (ΔM) values (Table 2) [i.e. the induced shift values for the 1/1 molar ratio (ρ = 1) between Eu(fod)$_3$) and substrate] for the single protons were obtained (at 80 MHz) by extrapolation from five spectra (with ρ ranging from 0.05 to 0.2). Then these values were normalized (in order to compare the relative induced shifts of protons in the five alcohols in a balanced way) with respect to an internal reference, that is, with respect to the induced shift of H-9 This was done by multiplying the extrapolated shifts of protons of each alcohol by ΔM(H-9)/26 (i.e., by the induced molar shift of H-9 in the same alcohol divided by 26). This procedure is equivalent to assume that the "natural" induced shift of H-9 in all the five alcohols is 26 (actually the extrapolated values range from 24 in syn,β-**4b** to 28 in syn,β-**8b**).

Compound **1** was synthesized according to literature procedure.[21]

*Reaction of acetic acid with **1**, reduction of **4a-8a** with $LiAlH_4$ and acetylation of **4b-8b**.*

To a solution of **1** (220 mg, 1.41 mmol) in acetic acid (3.0 ml) p-toluensulfonic acid-monohydrate (50 mg, 0.26 mmol) was added at 15 °C. After 2 hours at this temperature (15 ± 1 °C) under stirring TLC analysis showed that the reaction had gone to completion. The reaction mixture was poured carefully under stirring into a 5% solution of sodium bicarbonate in cold water and then extracted with ether (two times). The ether solution was dried over sodium sulfate, and the solvent evaporated to give a colourless oil. Column chromatography (cyclohexane/ethylacetate = 98:2 as eluant) allowed separation, in elution order, of compound anti,β-**6a** (18%) and of a mixture of syn,β-**4a**, syn,α-**5a**, and syn,β-**8a** (46%). In two further experiments under the same conditions the relative yields of the two fractions as well as the total yield did not change significantly (± 2%). GC analysis of the second fraction showed only two peaks (that of **5a** and that of **4a+8a**). Thus, in order to evaluate the ratio of **4a**, **5a** and **8a** the second fraction was reduced with $LiAlH_4$ in anhydrous ether at r.t. to quantitatively give a mixture of the three alcohols **4b**, **5b**, and **8b** [separated by column chromatography (cyclohexane/ethyl acetate = 95:5 as eluant; elution order: **4b**,**8b** and **5b**)]. Once again, the relative yields of these three compounds did not change appreciably in the three experiments and the average ratio was found to be: **4b**:**5b**:**8b** = 72:24:4. Reduction of the first fraction of the acetoxy derivatives afforded only one product, i.e. **6b**, which was homogeneous on TLC and by ^{1}H NMR analysis. We could not detect either the acetoxy derivative **7a** or the alcohol **7b**. This latter was prepared by reduction of **7a** obtained in the equilibration reaction (see below). The acetoxy derivatives **4a**, **5a**, **6a** and **8a** were easily obtained by acetylation of the corresponding alcohols (with acetic anhydride in pyridine at r.t.for 48 h; yield ≥ 90%).

Syn,β-**4a**: colorless prisms from petrol ether, mp 81-82 °C; IR ν_{max} = 1720 cm^{-1}; ^{1}H NMR (300 MHz), δ ($CDCl_3$) 2.07 (s, OCOMe), 5.41 (dddd, H-9, $J_{1,9}$ = 3.5 Hz, $J_{2,9}$ = 1.5 Hz, $J_{7,9}$ = 1.0 Hz, $J_{8,9}$ = 4.5 Hz);

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.8; H, 7.5. Found: C, 77.6; H, 7.5. Syn,α-**5a**: colorless oil; IR ν_{max} = 1728 cm^{-1}; ^1H NMR (300 MHz), δ (C_6D_6) 1.70 (s, OCOMe), 5.80 (m, H-9, $J_{1,9}$ = 4.6 Hz, $J_{7,9}$ = 2.3 Hz, $J_{8,9}$ = 2.3 Hz); Anal.Found: C, 77.5; H, 7.3. Anti,β-**6a**: colorless prisms from petrol ether (at -30 °C), mp 71-73 °C; IR ν_{max} = 1728 cm^{-1}; ^1H NMR (300 MHz), δ ($CDCl_3$) 2.08 (s, OCOMe), 5.33 (ddd, H-9, $J_{1,9}$ = 4.0 Hz, $J_{7,9}$ = 1.0 Hz, $J_{8,9}$ = 4.8 Hz); Anal. Found: C, 77.9; H, 7.7. Anti,α-**7a**: colorless solid, mp 70-72 °C; IR ν_{max} = 1735 cm^{-1}; ^1H NMR (300 MHz), δ ($CDCl_3$) 2.08 (s, OCOMe), 5.57 (m, H-9, $J_{1,9}$ = 4.2 Hz, $J_{7,9}$ = 2.0 Hz, $J_{8,9}$ = 2.3 Hz); Anal. Found: C, 78.0; H, 7.3. Syn,β-**8a**: colorless oil; IR ν_{max} = 1730 cm^{-1}; ^1H NMR (300 MHz), δ ($CDCl_3$) 2.09 (s, OCOMe), 5.50 (m, H-9, buried under the signals of vinyl protons); Anal. Found: C, 77.8; H, 7.5.

Syn,β-**4b**: colorless prisms from petrol ether (at -30 °C), mp 73-75 °C; IR ν_{max} = 3250 cm^{-1} (in CCl_4, 3589 cm^{-1}); Anal. Calcd for $C_{12}H_{14}O$: C, 82.7; H, 8.1. Found: C, 82.7; H, 8.4. Syn,α-**5b**: colorless prisms from petrol ether (at -30 °C), mp 45-46 °C; IR ν_{max} = 3175 cm^{-1} (in CCl_4, 3613 and 3589 cm^{-1}); Anal. Found: C, 82.4; H, 8.3. Anti,β-**6b**: colorless prisms from petrol ether, mp 71-73 °C; IR ν_{max} = 3250 cm^{-1} (in CCl_4, 3611 cm^{-1}); Anal. Found: C, 82.5; H, 8.4. Anti,α-**7b**: colorless needles from petrol ether, mp 80-81 °C; IR ν_{max} = 3220 cm^{-1}; Anal. Found: C, 82.5; H, 8.2. Syn,β-**8b**: colorless solid, mp 68-70 °C; IR ν_{max} = 3260 cm^{-1}; Anal. Found: C, 82.4; H, 8.3.

*Equilibration reactions of syn,β-**4a** and anti,β-**6a**.*

Compounds syn,β-**4a** (50 mg) and, respectively, anti,β-**6a** (50 mg) were dissolved in acetic acid (2 ml) in the presence of p-toluensulfonic acid-monohydrate (50 mg) and left equilibrating at 25 °C for 50 h. The mixture from syn,β-**4a** was reduced with $LiAlH_4$ and the resulting alcohols (total yield 64%; syn,β-**4b**:syn,α-**5b** = 10:90) separated by column chromatography (cyclohexane/ethylacetate = 95:5; elution order: **4b**, **5b**). In the case of anti,β-**6a** the equilibrated mixture was directly separated by column chromatography to give anti,β-**6a** (32%) as the first eluted product and anti,α-**7a** (36%) as the second eluted fraction. Very similar ratios (**6a/7a** = 47:53) were obtained by reducing the acetoxy mixture with $LiAlH_4$ and evaluating the alcohol ratio by column chromatography (cyclohexane/ethyl acetate = 95:5; elution order: **7b**, **6b**). The product ratios of both reactions were substantially confirmed by GC analysis of the crude acetoxy derivative mixtures.

*Preparation of ketones **9-11** and reduction of **9-10** with sodium borohydride.*

To a mixture of pyridinium chlorochromate (100 mg) and dichloromethane (5 ml) a solution of syn,β-**4b** (50 mg) in dichloromethane (5 ml) was added dropwise under stirring at r.t.. After 2 h anhydrous ether was added to the reaction mixture, the precipitated brownish product filtered off and the solvent evaporated. The ketone syn-**9** (74%) was purified by column chromatography. The same ketone was obtained from syn,α-**5b** in 76% yield.

This very same protocol was used for the preparation of anti-**10** (85%) from anti,β-**6b** and of syn-**11** (70%) from syn,β-**8b**

Syn-**9**: colorless solid, mp 36-37 °C; IR ν_{max} = 1660 cm^{-1}; ^1H NMR (300 MHz), δ ($CDCl_3$) 2.42 (dddd, H-12α, $J_{6,12\alpha}$ = 4.0 Hz, $J_{10,12\alpha}$ = 1.4 Hz, $J_{11,12\alpha}$ = 5.0 Hz, $J_{12\alpha,12\beta}$ = 4.0 Hz), 2.51 (dddd, H-12β, $J_{6,12\beta}$ = 4.1 Hz, $J_{10,12\beta}$ = 2.6 Hz, $J_{11,12\beta}$ = 2.8 Hz), 3.01 (ddddd,H-6, $J_{5,6}$ = 4.3 Hz, $J_{6,7}$ = 9.2 Hz, $J_{6,11}$ = 1.0 Hz,), 3.42 (m, H-1, H-2 and H-5), 5.59 (dddd,H-11, $J_{1,10}$ = 8.0 Hz, $J_{10,11}$ = 11.8 Hz), 5.71 (dddd, H-10), 6.03 (m, 2 H, H-3 and H-4), 6.18 (dd, H-8, $J_{7,8}$ = 12.0 Hz and $J_{1,8}$ = 1.5 Hz), 6.49 (ddd, H-7, $J_{5,7}$ = 0.5 Hz); Anal. Calcd for $C_{12}H_{12}O$: C, 83.7; H, 7.0. Found: C, 83.4; H, 7.3. Anti-**10**: colorless solid, mp 54-56 °C; IR ν_{max} = 1665 cm^{-1}; ^1H NMR (80 MHz), δ ($CDCl_3$) 2.20 (m, H-12α), 2.54 (m, H-12β), 3.06 (m, H-6), 3.22 (m, H-2), 3.30 (m, H-5), 3.40 (m, H-1), 5.60 (m, H-10 and H-11), 6.05 (dd, H-8, $J_{7,8}$ = 12.0 Hz and J = 1.5 Hz), 6.20 (s, 2 H, H-3 and H-4), 6.75 (dd, H-7, $J_{6,7}$ = 9.0 Hz); Anal. Found: C, 83.5; H, 7.2. Syn-**11**: colorless oil; IR ν_{max} = 1650 cm^{-1}; ^1H NMR (80 MHz), δ ($CDCl_3$) 2.48 (m, H-10α and H-10β), 3.20 (m, 3

H, H-1, H-6, H-5 or H-2), 3.58 (bdd, H-5 or H-2, J = 4.0 and 5.0 Hz), 5.58 (ddd, H-11, $J_{11,12}$ = 11.0 Hz, $J_{10\alpha,11} = J_{10\beta,11}$ = 3.8 Hz), 5.93 (ddd, H-12, $J_{10\alpha,12} = J_{10\beta,12}$ = 2.0 Hz), 5.95 and 6.10 (two d, H-3 and H-4, $J_{3,4}$ = 3.0 Hz), 6.20 (dd, H-8, $J_{7,8}$ = 11.0 Hz and J = 1.5 Hz), 6.73 (dd, H-7, $J_{6,7}$ = 9.0 Hz).

The reduction of syn-**9** (50 mg) and anti-**10** (60 mg), respectively, with excess sodium borohydride (added portionwise under stirring to a solution of the carbonyl compound) was carried out in methanol at room temperature to afford (quantitative yields) alcohol mixtures whose ratio was evaluated by column chromatography (eluting with cyclohexane/ethyl acetate = 95:5; syn,β-**4b**:syn,α-**5b** = 9:91 from syn-**9** and anti,β-**6b**:anti,α-**7b** = 43:57 from anti-**10**).

*Addition of monodeuterated acetic acid to **1** and equilibration reaction of deuterated anti,β-**6a** in acetic acid.*

Compound **1** (510 mg, 3.27 mmol) was dissolved in monodeuterated acetic acid and to the solution deuterated p-toluensulfonic acid-monohydrate (0.135 mg, 0.7 mmol) was added under stirring. The solution was kept at 15 °C under stirring for 20 hours, then it was cautiously poured into a dilute solution of sodium bicarbonate in cold water. The resulting mixture was extracted with ethyl ether and the organic layers were washed with water and dried. The solvent was evaporated and the residue column chromatographed (cyclohexane/ethyl acetate = 98:2 as eluant) to give in addition to small amounts of the starting product **1** (8 mg) and and of the alcohols D-**4b**-**7b** (18 mg), D-**4a** (100 mg, 16%, first fraction) and D-**5a**+D-**6a**+D-**7a** (320 mg, 52%, second fraction). Evaluation of the deuterated acetoxy derivative ratios was carried out in the very same way as in the case of the non deuterated derivatives, i.e., by GC and by reduction to the hydroxy derivatives with $LiAlH_4$. The retention times in GC as well as the R_f values on TLC of deuterated acetoxy derivatives were the same as those of non deuterated compounds. The crude deuterated alcohols from column chromatography (same elution order of non deuterated compounds) were analyzed by ^1H NMR to determine the deuterium content. The signals of protons H-12 (two multiplets of differing intensity in which the large coupling constant $J_{12\alpha,12\beta}$ was missing) integrated for one proton and from the intensity ratio between the signals of H-12α and H-12β the α:β ratio between the attacks of D^+ to **1** could be determined (see Scheme in Results and Discussion). The presence of deuterium in both the acetoxy and hydroxy derivatives was also revealed by a very weak absorption at ≈ 2125 cm^{-1} in their IR spectra. The ^1H NMR spectrum of the recovered **1** looked exactly the same as that of the starting product : no significant protium deuterium exchange had taken place during the addition of deuterated acetic acid to **1**.

Equilibration of deuterated anti,β-**6a** was carried out in acetic acid at 30-35 °C for 40 hours in the presence of equimolar quantities of p-toluensulfonic acid. D-Anti,β-**6a** and D-anti,α-**7a** were isolated from the equilibrated mixture in 30% and 52% yields, respectively. Once again in both products protons H-12 integrated for one proton and the ratio H-12α/H-12β was not appreciably changed.

*Addition of methanol to **1** and synthesis of **4c**-**7c** by methylation of **4b**-**7b** with NaH/MeI.*

A solution of **1** (330 mg, 2.1 mmol) and p-toluensulfonic acid-monohydrate (330mg, 1.7 mmol) in anhydrous methanol was kept at 35 °C for 24 hours. After that time only small amounts of **1** were detected by TLC analysis. The solution was cautiously poured into a dilute solution of sodium bicarbonate in cold water and the resulting mixture extracted several times with petrol ether. The organic layers were dried, the solvent evaporated to give a colorless oil which was column chromatographed (cyclohexane/ethyl acetate = 98:2 as eluant). After elution of the starting product (≈ 8%), the first fraction (70%) consisted (GC, ^1H NMR and ^{13}C NMR) of two methoxy derivatives (i.e., syn,β-**4c** and anti,β-**6c**, ratio ≈ 52:48) while the second fraction (7%) consisted of only one compound, syn,α-**5c**. GC analysis of the crude reaction mixture led to the following ratio: syn,β-**4c**/syn,α-**5c**/anti,β-**6c** = 49.5:5.5:45. In addition to the peaks of these three products and of that of the starting product, other minor peaks were present in the gaschromatogram but no one attributable to compound anti,α-**7c**. The quantity of this isomer was under the detection limits (1-2 %) of our analytic techniques.

In two further experiments the reaction was carried out at 20 °C for 40 hours. After usual work-up GC analysis disclosed the following average product ratio:syn,β-**4c**/syn,α-**5c**/anti,β-**6c** = 53:5:42.

Equilibration was carried out by heating at reflux a solution of the kinetic mixture of the methoxy derivatives in methanol for 90 hours in the presence of equimolar amounts of p-toluensulfonic acid-monohydrate. The observed ratio (evaluated by GC analysis, syn,β-**4c**/syn,α-**5c**/anti,β-**6c**/anti,α-**7c** = 7:53:19:21) did not appreciably change after heating for further 40 hours.

The reaction of alcohols **4b-7b**, respectively, (≈ 30 mg) with an excess of sodium hydride (50 mg) and of iodomethane (1.0 ml) was performed in anhydrous ethyl ether (3.0 ml) under stirring in argon atmosphere at room temperature (five days). In addition to methoxy derivatives **4c-7c**, respectively, (≈ 80% yield) small amounts of ketones **9** (from **4b** and **5b**) and **10** (from **6b** and **7b**) were isolated.

Syn,β-**4c**: colorless oil; ^{1}H NMR (80 MHz), δ ($CDCl_3$) 3.45 (s, OMe), 3.81 (bt, H-9, $J_{1,9}$ = 3.8 Hz, $J_{8,9}$ 3.8 Hz); ^{13}C NMR (80 MHz), δ ($CDCl_3$) 57.0 (q, OMe), 80.8 (d, C-9); Anal. Calcd for $C_{13}H_{16}O$: C, 82.9; H, 8.6. Found: C, 82.7; H, 8.5. Syn,α-**5c**: colorless oil; ^{1}H NMR (80 MHz), δ ($CDCl_3$) 3.42 (s, OMe), 3.90 (bd, H-9, $J_{1,9}$ = 4.0 Hz, $J_{8,9}$ < 1.0 Hz); ^{13}C NMR (80 MHz), δ ($CDCl_3$) 56.8 (q, OMe), 83.5 (d, C-9); Anal. Found: C, 82.8; H, 8.8. Anti,β-**6c**: colorless oil; ^{1}H NMR (80 MHz), δ (C_6D_6) 3.17 (s, OMe), 3.67 (bt, H-9, $J_{1,9}$ ≈ 4.0 Hz, $J_{8,9}$ ≈ 4.0 Hz); ^{13}C NMR (80 MHz), δ ($CDCl_3$) 53.6 (q, OMe), 82.6 (d, C-9); Anal. Found: C, 82.7; H, 8.7. Anti,α-**4c**: colorless oil; ^{1}H NMR, δ (C_6D_6) 3.20 (s, OMe), 3.75 (bs, H-9, width at half height = 6.0 Hz); Anal. Found: C, 83.1; H, 8.7.

Reaction of dichloroketene with I

To a mixture of compound **1** (0.300 g, 1.9 mmol), activated zinc dust (0.250 g, 3.8 mmol) and freshly distilled phosphorus oxychloride (0.500 g, 3.3 mmol) in anhydrous ethyl ether (30 ml) freshly distilled trichloroacetylchloride (0.600 g, 3.3 mmol) was added dropwise under stirring. A slow stream of nitrogen was bubbled into the mixture from the beginning of the reaction. After 13 hours at room temperature zinc dust and inorganic salts were filtered off, the ethereal solution was washed with a dilute solution of sodium bicarbonate and then with water, dried and evaporated. The colorless residue was purified by column chromatography to afford pure **14** in 58% yield (0.296 g). This compound was homogeneous on TLC and by NMR. TLC analysis of the crude reaction mixture did not reveal any significant spot in addition to that of **14**.

Adduct **14**: colorless prisms from methanol (at -30 °C), mp 84 °C; IR ν_{max} = 1800 and 1640 cm^{-1}; ^{1}H NMR, δ ($CDCl_3$, +45 °C) 2.00 (ddd, H-2, $J_{1,2} = J_{2,12}$ = 8.5 Hz, $J_{2,3}$ = 5.6 Hz), 2.12 (ddd, H-9, $J_{8,9}$ = 5.0 Hz, $J_{9,10} = J_{9,14}$ = 8.6 Hz), 2.90 (ddd, H-8, $J_{3,8}$ = 9.3 Hz, $J_{7,8}$ = 3.0 Hz), 3.24 (dd, H-4, $J_{3,4}$ = 4.0 Hz, $J_{4,7}$ = 5.5 Hz), 3.30 (dddd, H-3, $J_{3,7}$ = 1.0 Hz), 3.38 (broad m, H-1 and H-12), 3.70 (ddd, H-7), 4.34 (broad m, H-10 and H-14), 5.78 and 6.00 (two dd, H-11 and H-13, J = 9.0 and 9.5 Hz). At -40 °C the signal of H-10, H-14, H-1 and H-12 was so broad and flat that it apparently disappeared from the spectrum. Anal. Calcd for $C_{14}H_{12}OCl_2$: C, 62.9; H, 4.6 . Found: C, 63.0; H, 4.5.

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5. (a) The syn and anti descriptors indicate the moieties of the homotropylidene system on the same side and, respectively, on the opposite side with respect to the cyclobutene ring. (b) The α and β descriptors are used to indicate the attack to the homotropylidene system from the bottom and, respectively, the top side.
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8. (a) Calculations were carried out by using the MM2, AM1, PM3 and STO-3G methods as implemented in the Hyperchem package of programs. (b) Also syn-**2** is predicted less stable than anti-**3** by 11.8 (AM1) and 8.2 (PM3) kcal mol^{-1}. This is the opposite of what is predicted (anti-**2** more stable than syn-**3** by 4.2 kcal mol^{-1} and syn-**2** more stable than anti-**3** by 3.4 kcal mol^{-1}). However, the MINDO/3 method is well known to underestimate the strain energy of three membered rings.[7] Anyway, it might well be that the large favor of **3** over **2** in AM1 and PM3 calculations is the result of some over-estimation by these two methods of three membered ring strain energy. We are now addressing this problem with higher level ab-initio calculations. (c) AM1 and STO-3G geometry data of **1**, anti-**2** and syn-**3** are similar to those of PM3 calculations.
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11. The relative energies (kcal mol^{-1}) of the methoxy derivatives predicted by PM3 calculations (for the most stable conformation with the methyl group pointing outside: torsion angle $C_8C_9OC \approx 162°$) are the following: syn,α-**5c** (0), anti,α-**7c** (0.15), anti,β-**6c** (0.19), syn,β-**4c** (1.42) and syn,β-**8c** (1.58).
12. (a) The rate controlling first step of the reaction should suffer (and it does suffer) a substantial rate retardation as as a result of a primary kinetic isotope effect. Deuteration in deuterated acetic acid has been reported to be ≈ 3-5 times slower than protonation in acetic acid.[9,22] (b) The equilibration process (involving a pair of facial isomers) comprises a fast protonation (deuteration) equilibrium followed by a slow SN1 exchange of the nucleophile in which the rate determining step is formation of carbocations **3**. Thus the whole isotope effect (k_{MeCOOH}/k_{MeCOOD}) is the result of an equilibrium isotope effect and of a secondary kinetic isotope effect (K_H/K_D k_H/k_D). By using a fractionating factor of 1 for TsOH[23] (this acid is largely undissociated in acetic acid)[9] and of 0.69 for protonated acetoxy derivatives[23] one can predict an equilibrium isotope effect of 1.4 (1/0.69) which is counteracted by a small inverse secondary kinetic isotope effect [i.e., $(0.69/1)^x$ in which 1 is the fractionating factor of acetic acid and x is the numerical value of the reaction coordinate at the transition structure (close to 1 as the TS should be closer in energy to the intermediate carbocation + acetic acid than to the starting protonated acetoxy derivative)].[23]
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