Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5555–5561

TETRAHEDRON

To what extent does the substituent conformation influence the kinetics of addition reactions on 5X-bicyclo[4.4.0]decan-2-ones?

Giada Catanoso and Elisabetta Vecchi*

Dipartimento di Chimica, Università 'La Sapienza', P.le A. Moro 5, 00185 Rome, Italy

Received 28 March 2003; revised 30 April 2003; accepted 22 May 2003

Abstract—Stereochemistry and relative rates k_{ax} and k_{eq} of addition reactions on the title compounds have been measured under four different reaction conditions (CH_3MgI in Et_2O and C_6H_6, and CH_3Li in Et_2O at 20°C and −78°C). In strict accordance with previous findings we show that the axial substituents are far less electronegative than their equatorial counterparts in equatorial attack reactions. Axial attack, however, is independent of the substituent conformation. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The nature and role of the electronic interactions which govern the stereocontrol of a reaction has repeatedly attracted our interest. Central to our deliberations is the relative importance of electrostatic and orbital effects in determining the difference in energy between the respective diastereomeric transition states of the kinetically controlled addition processes.

We have been particularly intrigued by the generality of stereoelectronic control. In particular, we have found that additions to a trigonal stereogenic centre occur at quite different reactions rates, on each side of the molecule and each one with its own kinetic controls. Recently we published[1] the stereochemical and kinetic results for reductions performed on title compounds.

Pursuing our interest in issues concerning π-facial selectivity, we further investigated in which way the substituent conformation could affect the axial and equatorial reactivity. In this paper we describe the stereochemical and kinetic results of addition reactions performed on a series of (1*S*,5*R*,6*S*)*-5X-bicyclo[4.4.0]-decan-2-ones and (1*S*,5*S*,6*S*)*-5X-bicyclo[4.4.0]decan-2-ones. This series consisted of **1** (X=**H**); **2** and **5** (X=**OAc**); **4** (X=**CO_2Me**); **3** and **6** (X=**Cl**), namely conformationally rigid substrates carrying the same substituent in the axial (**2** and **3**) and in the equatorial (**4**, **5**, and **6**) position, respectively (Fig. 1). It was not possible to have a consistent amount of pure (1*S*,5*R*,6*S*)*-5-carbomethoxy-bicyclo[4.4.0]decan-2-one in order to fulfil a comparison between substrate **4** and its epimer.

2. Results and discussion

We carried out our experiments under the following reaction conditions: (a) CH_3MgI in Et_2O; (b) CH_3MgI in C_6H_6; (c) CH_3Li in Et_2O at 20°C and (d) CH_3Li in Et_2O at −78°C.

Under all reaction conditions the only reaction products obtained were the methylcarbinols **1′**-**6′** derived from an axial attack, and **1″**-**6″** derived from an equatorial attack (Fig. 1). A small amount of lactone **4‴** (derived from methylcarbinol **4″**) was detected when employing compound **4**, particularly under reaction conditions (a).

Products **1′** and **1″** are known compounds.[2–4] The separation of reaction products **2′**-**6′** and **2″**-**6″** from one another was achieved by HPLC (see experimental for full spectroscopic characterization). Assignment of stereochemistry was achieved using various methods. In the ^{13}C NMR spectra, the compounds assigned as axial hydroxyl diastereomers exhibited the quaternary carbinol carbon signal at higher fields compared to the equatorial hydroxyl diastereomer,[5] and showed increased propensities towards the loss of water from the parent ion in mass spectrometry.[6] Moreover, the ^1H NMR spectra of compounds (**2**-**6**)′ showed the signal of axial methyl protons at higher field with respect to their equatorial counterparts,[7] and were more slowly eluted on silica gel.[8]

For each set of reaction conditions, we first determined the stereochemistry of the addition reactions by GLC.

Tables 1 and 2, in which the X groups are listed according to

Keywords: addition reactions; kinetics; substituent conformation.

* Corresponding author. Tel.: +39-6-49913675; fax: +39-6-490631; e-mail: elisabetta.vecchi@uniroma1.it

0040–4020/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00810-X

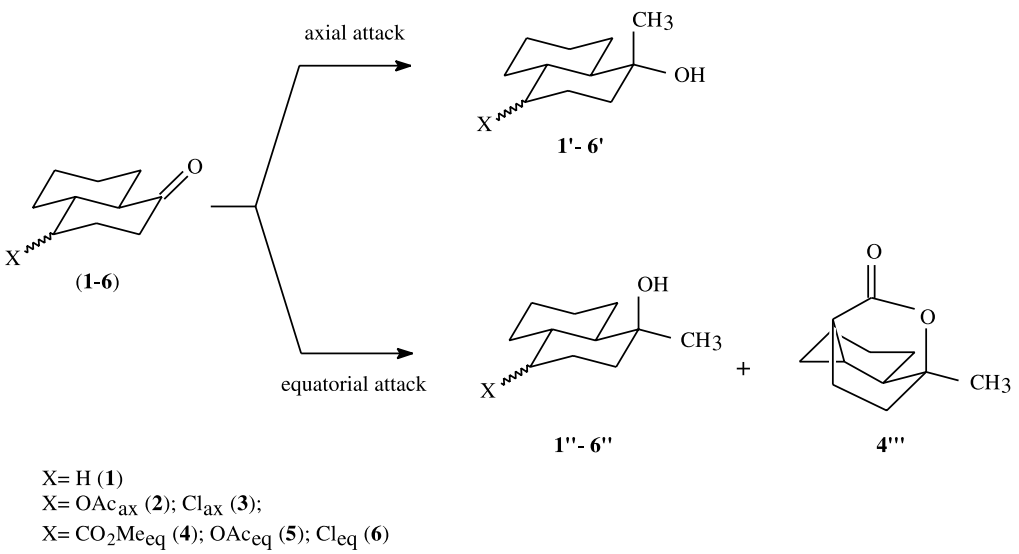

Figure 1.

Table 1. Stereochemical product ratios (k_{ax}/k_{eq}) for 5X-bicyclo[4.4.0]-decan-2-ones **1**, **2** and **3** (axial substituents)

Reaction conditions	Stereochemical product ratios (k_{ax}/k_{eq})		
	1′/1″ (σ_I=0.00)	**2′/2″** (σ_I=0.38)	**3′/3″** (σ_I=0.47)
(a) MeMgI, Et_2O, 20°C	0.08	0.18	0.27
(b) MeMgI, C_6H_6, 20°C	0.15	0.24	0.45
(c) MeLi, Et_2O, 20°C	0.15	0.45	1.23
(d) MeLi, Et_2O, −78°C	0.12	0.53	0.71

Table 2. Stereochemical product ratios (k_{ax}/k_{eq}) for 5X-bicyclo[4.4.0]-decan-2-ones **1**, **4**, **5** and **6** (equatorial substituent)

Reaction conditions	Stereochemical product ratios (k_{ax}/k_{eq})			
	1′/1″ (σ_I=0.00)	**4′/(4″+4‴)** (σ_I=0.32)	**5′/5″** (σ_I=0.38)	**6′/6″** (σ_I=0.47)
(a) MeMgI, Et_2O, 20°C	0.08	0.32	0.22	0.16
(b) MeMgI, C_6H_6, 20°C	0.15	0.35	0.38	0.17
(c) MeLi, Et_2O, 20°C	0.15	0.33	0.35	0.20
(d) MeLi, Et_2O, −78°C	0.12	0.07	0.16	0.09

Taft's σ_I values,[9] summarize the results of these preliminary experiments (a minimum of five separate experiments for each substrate under all reaction conditions).

Stereochemical ratios show with respect to Taft sigmas a linear trend with axial substituents (Table 1), that is a regular, rather sharp increase on increasing the substituent elecronegativity. With equatorial substituents (Table 2) there was but little difference between X=H and X=Cl, whereas the substrates bearing an ester group (X=CO_2Me or X=OAc) showed, under almost all the reaction conditions, a maximum value of k_{ax}/k_{eq}.

A good correlation between stereochemical ratios and substituent Taft σ_I values is considered a probe of the prominent role played by electronic effects in π-face diastereoselection.

But, as repeatedly stated in our previous works,[1,10–16] the stereochemical bias could hide complex situations and therefore does not give exact insight into what happens on each side of the molecule.

The stereochemical bias represents the average outcome of the axial and equatorial attack routes to a trigonal centre. The axial and equatorial rates variations are not always parallel: sometimes k_{ax}/k_{eq} originates from uneven increases (or decreases), or, from divergent changes of k_{ax} and k_{eq}. Relative rates can be desumed from kinetic experiments. Therefore, we performed a series of competitive kinetic experiments on equimolar mixtures of compounds **1** and compounds **2**-**6**, respectively.

We chose to do competition experiments just in order to avoid all complications associated with kinetic analysis of fast reactions and to provide at the same time highly reproducible sound results. The methods used for GLC standardization of both substrates and reaction products and for computing the yields of reactions and the relative reaction rates are described in Section 4.

The overall and the relative rates are reported in Tables 3 and 4 (axial substituents and equatorial substituents, respectively). Once again each of the listed entries represents the mean value of at least five different experiments.

With regard to kinetic data we tried to construct a linear free energy relationship (LFER) with substituent electronegativity. This was unattainable due to the behaviour of compounds **3**, **4** and **5** (in which X is an ester group) the points of which deviate from linearity, notwithstanding that the reliability and reproducibility of the experimental values for them were equal to all other substrates. Such anomalous behaviour for the ester group is well precedented in the literature[17,18] with numerous explanations.[10,12,14] Among

Table 3. Overall ratio of rates and relative rates for 5X-bicyclo[4.4.0]decan-2-ones **1**, **2** and **3** (axial substituents)

Reaction conditions	Overall ratio of rates, $k_1/k_2/k_3$[a]	Relative rates					
		k_{ax}			k_{eq}		
		1	**2**	**3**	**1**	**2**	**3**
(a) MeMgI, Et_2O, 20°C	1/1.69/1.48	1	1.23	2.00	12.70	6.88	7.35
(b) MeMgI, C_6H_6, 20°C	1/1.88/1.55	1	0.78	1.57	6.75	3.36	3.50
(c) MeLi, Et_2O, 20°C	1/1.13/1.0	1	2.11	4.25	6.70	4.70	3.45
(d) MeLi, Et_2O, −78°C	1/0.87/0.64	1	3.72	6.00	8.28	7.04	8.48

[a] Mean standard deviation: 0.02.

Table 4. Overall ratio of rates and relative rates for 5X-bicyclo[4.4.0]decan-2-ones **1**, **4**, **5** and **6** (equatorial substituents)

Reaction conditions	Overall ratio of rates, $k_1/k_4/k_5/k_6$[a]	Relative rates							
		k_{ax}				k_{eq}			
		1	**4**	**5**	**6**	**1**	**4**	**5**	**6**
(a) MeMgI, Et_2O, 20°C	1/1.36/1.77/0.81	1	2.47	1.41	2.35	12.70	7.64	6.35	14.82
(b) MeMgI, C_6H_6, 20°C	1/1.07/1.19/0.57	1	1.89	1.82	1.96	6.75	5.43	4.75	11.61
(c) MeLi, Et_2O, 20°C	1/0.94/0.99/1.11	1	2.04	2.02	1.16	6.70	6.18	5.77	5.84
(d) MeLi, Et_2O, −78°C	1/0.75/0.83/0.49	1	0.84	1.56	1.56	8.28	11.52	9.64	17.40

[a] Mean standard deviation: 0.02.

them, a higher reaction order is sometimes suggested.[10] A higher reaction order for substrate **4**, with respect to substrates **1**, **2**, **3**, **5** and **6**, under reaction conditions (b), (c) and (d) was, as a matter of fact, evidenced by kinetic competition experiments performed with decreasing concentration of the added reagent. Under these reaction conditions, the relative rates of compounds **2**, **3**, **5** and **6** are largely independent of the concentration of added reagent, whereas for compound **4**, the stereochemical outcome being the same, a systematic decrease in the relative rates was observed as the concentration of the added reagent was decreased (0.1–0.05 M)[†]. Therefore the k_{rel} points of compound **4** should be excluded from any tentative correlation. No suitable reason was instead found to account for the scattering behaviour of compound **5**. So, the limited number of useful available points prevented us from using all the figures of k_{rel} of Tables 3 and 4 to construct a LFER.

All experimental data are tabulated, but our discussion is necessarily restricted to the variations observed between X=H and X=Cl (that is to data relative to substrates **1** and **3** in Table 3 and **1** and **6** in Table 4, substrates having the greatest σ_I's difference). The discussion is based on the fact that our data are in strict accordance with those found for reduction experiments on the same substrates. On this ground we suggest the following generalization.

About the overall reaction rates (columns 2 of both Tables 3 and 4) we can observe that:

1. In the case of Grignard reagents, the overall reaction rate increases on increasing the substituents electronegativity for axial substituents (Table 3), decreases for equatorial substituents (Table 4);
2. With CH_3Li the overall reaction rate seems instead to be independent of the substituents conformation and electronegativity. It shows a flat trend at room temperature, and, at −78°C, a decrease of reactivity.

The relative rates (k_{ax} and k_{eq}) meaningfully allow a more detailed insight. They display a non-homogeneous pattern, which differs on varying the reactants.

1. With Grignard reagents, axial attack (k_{ax}) seems to be not influenced by the substituents conformation: going from H to Cl we found a similar increase: 1.00→2.00, 1.00→2.35 (lines 1, in Tables 3 and 4, respectively) and 1.00→1.57, 1.00→1.96 (lines 2, in Tables 3 and 4).
2. The equatorial attack (k_{eq}) shows instead divergent kinetic effects: once a decrease: 12.70→7.35; 6.75→3.50 (axial substituent, lines 1 and 2, Table 3); once an increase: 12.70→14.82, and 6.75→11.61 (equatorial substituent, lines 1 and 2, Table 4).
3. With CH_3Li, going from H to Cl, the axial attack shows a sharp increase for the axial substituents, that is, 1.00→4.25 and 1.00→6.00 (Table 3, lines 3 and 4, respectively); a milder increase for the equatorial substituents, that is, 1.00→1.16 and 1.00→1.56 (Table 4, lines 3 and 4, respectively).
4. For equatorial attack we had strong and non-homogeneous (that is once a decrease, once an increase) sensitivities with regard to the substituents conformation. Going from H to Cl: 6.70→3.45 and 8.28→8.48 (Table 3, lines 3 and 4, respectively), vs 6.70→5.84 vs 8.28→17.40 (Table 4, lines 3 and 4, respectively).

Theories which discuss reactivity in terms of ground state properties partially fit our experimental data.

[†] k_1/k_4 in Table 4 are referred to competition reactions in which the concentration of the added reagent was 0.1 M. At lower regent concentration (0.05 M) the k_1/k_4 ratio was 1/1.32, 1/0.88, 1/0.67 and 1/0.42 for reaction conditions (a), (b), (c) and (d), respectively.

Table 5. Relative rate ratios (k_{ax} and k_{eq}) of β-decalones and α-decalones

Reaction conditions	k_{ax} (β-dec)/k_{ax} (α-dec)[a]		k_{eq} (β-dec)/k_{eq} (α-dec)[a]	
	X=H	X=Cl	X=H	X=Cl
(a) MeMgI, Et_2O, 20°C	5.9	6.3	1.1	2.4
(b) MeMgI, C_6H_6, 20°C	3.6	4.7	1.3	2.3
(c) MeLi, Et_2O, 20°C	2.3	1.9	0.8	0.6
(d) MeLi, Et_2O, −78°C	4.0	1.6	1.6	0.5

[a] Mean standard deviation: 0.02.

According to Klein's MO considerations[19] the hyperconjugation of the carbonyl π system and the ring β-CC bonds produces non-equivalent distortion of π-electron density. An extension (see for complete schemes and their construction Refs. 1,15) to substituents in axial and equatorial conformation in the 4 position leads to the following statements: the LUMO carbonyl orbital is more extended on the axial face of the molecule under the influence of β-CC bond's hyperconjugation and the C_4–X bond. The amplitude of such a distortion is presumably the same‡ irrespective of the axial or equatorial conformation of the substituent: it follows that axial reactivity is independent of the substituent's conformation.

Vice-versa the HOMO carbonyl orbital suffers opposite distortion effects from the β-CC bond's hyperconjugation and the C_4–X bond. The balance between these two effects is determined by the identity and conformation of X: in particular, as formerly suggested,[6–8] the HOMO of a carbonyl orbital is less developed on the equatorial side of the molecule when the C_4–X bond is axial: it ensues that axial substituents behave as having a lower electronegativity than their equatorial counterparts in reactions on the equatorial side of the molecule.

Analogously substituted β-decalones (*trans*-10-X-decal-2-ones with X=H and X=Cl previously investigated in our lab) showed,[12,13] under the same reaction conditions, for X=Cl, a systematic sharp decrease in the equatorial reactivity, that finally vanished. This is in keeping with the above description of the carbonyl HOMO having decreasing amplitude on the equatorial side of the molecule. In the α-decalone system, the equatorial reactivity decrease is no greater than twofold. Therefore, with respect to the equatorial attack, the C_4–X axial substituents behave differently not only from their equatorial counterparts, but there is a difference in behaviour between the same axial substituents in two strictly related molecules. Such a difference, as we have already suggested,[1] could most likely be ascribed to the fact that the distances and geometries of an axial substituent vs the carbonyl group are more rigid in the β-decalone system.

The reactivity of α-decalones (**1**, and **3**) was also compared, (by means of competitive kinetic experiments), to that of the above mentioned analogously substituted β-decalones. In Table 5 we tabulate the ratios of axial and equatorial rates of attack in the two series of compounds.

‡ As far as we know, there is no way, as yet to compute such MO distortion.

1. The axial reactivity of β-decalones was always higher than that of the α-decalone series.
2. Equatorial reactivity changes are again (especially in CH_3Li) discontinuous.

3. Conclusions

Pursuing our interest in the influence of substituent conformation we have determined the axial and equatorial rates of attack on a series of 5X-bicyclo[4.4.0]decan-2-ones in addition reactions. The experimental data are in strict accordance with our recently published results.[1]

1. The LUMO of a carbonyl group is more distorted, towards the axial face of a cyclohexanone system: it ensues that axial reactivity, increases with increasing substituent electronegativity and is independent of the substituent conformation.
2. The carbonyl HOMO is less developed on the equatorial side of the molecule when the C_4–X substituent is axial. Equatorial reactivity is therefore connected to the substituent conformation. Axial and equatorial substituents behave differently from one another in reactions on the equatorial side of the molecule so that the same set of σ values cannot simply be used disregarding the substituents conformation.
3. The equatorial reactivity is overall much less predictable. It probably depends not only on the substituent conformation, but also on the molecular skeleton object of study as evidenced by a comparison between equally substituted α-and β- decalones.

4. Experimental

4.1. Instruments

Melting points were determined on a Mettler FP82HP apparatus and are uncorrected. HRMS was performed on a Bruker Spectrospin APEX TM 47e FT-IRC instrument. Microanalyses were carried out on a CE instrument EA 1110. IR spectra were recorded on a Perkin–Elmer 1600 Series FTIR. GC–MS analyses were performed with a GC-MS HP 5970 Chemstation Mass Selective Detector connected to a HP 5890 gas chromatograph using a capillary column coated with fluid methyl silicone (12.5 m, 0.2 mm i.d.). ^1H and ^{13}C NMR spectra ($CDCl_3$) were recorded on a GEMINI 200 spectrometer and, where specified in parentheses, on a VARIAN XL 300. Chemical shifts are reported in parts per million (ppm) down field from TMS using residual $CDCl_3$ (7.27 ppm) for ^1H NMR and the middle resonance of $CDCl_3$ (77.0 ppm) for ^{13}C NMR as internal standard. GLC analyses were carried out on a Carlo Erba HRGC Mega Series 5300 apparatus using a 25 m, 0.25 mm i.d. fused silica capillary column (stationary phase O.V.1, 30 m×25 mm i.d.), He flow=0.5 ml/min. Reaction mixtures were eluted in the order (**1**, **1**″, **1**′), (**2**, **2**″, **2**′), (**3**, **3**″, **3**′), (**4**, **4**″, **4**′ and **4**‴), (**5**, **5**″, **5**′) and (**6**, **6**″, **6**′). We report the most suitable GLC conditions (initial oven temperature, isotherm time, temperature increase rate, final oven temperature): 110°C, 3 min, 15°C/min, 150°C, 10 min; T_{inj}=T_{det}=230°C. **1**, **1**″, **1**′ were detected during the initial

isotherm. The separations by HPLC were performed on a Varian 9001 instrument equipped with a Varian RI-4 differential refractometer. Solvents were HPLC grade.

4.2. Starting materials

trans-Bicyclo[4.4.2]decan-2-one **1** is commercially available (Aldrich) and was used as such. Published procedures[20] were used for the synthesis of (1*S*,5*R*,6*S*)*-5-acetoxybicyclo-[4.4.0]decan-2-one **2**, (1*S*,5*S*,6*S*)*-5-acetoxybicyclo[4.4.0]-decan-2-one **5**, (1*S*,5*R*,6*S*)*-5-chlorobicyclo[4.4.0]decan-2-one **3**, (1*S*,5*S*,6*S*)*-5-chlorobicyclo[4.4.0]decan-2-one **6** and (1*S*,5*S*,6*S*)*-5-carbomethoxybicyclo[4.4.0]decan-2-one **4**.[21]

4.3. Preparation of reagents

Et_2O and C_6H_6 were freshly distilled from Na wire using sodium benzophenone as indicator. CH_3MgI in Et_2O was prepared directly in this solvent in the usual way from Mg turnings and MeI (Aldrich). CH_3MgI in C_6H_6 was prepared by the solvent substitution method, i.e. an ethereal solution of CH_3MgI was evaporated nearly to dryness and then an equal volume of benzene was added. This same procedure was repeated at least three times to ensure complete elimination of Et_2O. The Grignard reagents were kept under inert gas and titrated[22] prior to use by sampling an aliquot of the supernatant clear soln. through a rubber septum. Commercial solns. of CH_3Li in Et_2O (Fluka) were titrated[23] and appropriately diluted just before use.

4.4. Reactions

All reactions were conducted under a dry inert atmosphere (nitrogen or argon) at 20°C (with CH_3MgI) and at 20 and −78°C (with CH_3Li). All glassware was dried in an oven (ca. 150°C), flame dried and cooled under dry inert atmosphere before use. Typically, 0.06 ml of standard Et_2O solution of the selected reagent (e.g. CH_3MeI, 2 M) were added, under magnetic stirring into a 10 ml two-necked flask containing either 15.2 mg (0.1 mmol) of compound **1** in 1 ml of anhydrous Et_2O, or the equimolar amount of compounds **2**, **3**, **4**, **5** or **6** (with a weighed amount of *n*-hexadecane as internal standard). Following completion of the reaction (2–3 min), the reaction mixtures were slowly hydrolyzed with sat. aq. NH_4Cl and extracted three times with Et_2O. The ethereal solutions were washed with water, combined, dried over Na_2SO_4, filtered and evaporated. GLC analyses of the reaction mixtures were carried out as described above (Section 4.1). Preliminary experiments showed that GLC responses (with respect to *n*-hexadecane) of compounds (**1**-**6**) and their reaction products (**1**-**6**)′, (**1**-**6**)″ and **4**‴ were very close to each other, therefore no correction was introduced. The sum of starting compounds and reaction products always accounted for 95–100% of the starting mass balance. The reaction of CH_3MgI in benzene and CH_3Li in Et_2O were carried out in analogous fashion.

4.5. Competition experiments

Four flasks (10 or 100 ml for competition experiments in more diluted conditions) were equipped with a magnetic stirrer and connected by means of a four-point star-rotating receiver to a graduated burette, gas inlet and $CaCl_2$ tube. Each flask contained an equimolar amount of **1** and **2** or, **3**, **4**, **5** and **6**, depending on the chosen partner for that particular experiment (0.2 mmol in all), which was dissolved in 2 ml of anhydrous solvent (Et_2O or C_6H_6). The graduated burette was filled via a syringe with the suitable, conveniently diluted (0.1–0.05 M), reactant, and the stoichiometric amount of it was rapidly added to the substrates mixture under vigorous stirring. It was not possible to perform competition experiments in which all substrates were present simultaneously due to overlapping peaks in the GLC trace. Reaction mixtures were hydrolyzed and worked up as formerly described. The relative reaction rates were obtained by GLC determination of the reaction yields, taking the k_{ax} of compound **1** as equal to 1 and assuming that all reactions are first order in ketone and are of the same order in reagent for all ketones. We measured the relative amounts of products and starting materials dividing the areas of each GLC peak by the corresponding molecular weight. The yields depend on quenching times and we used only the data of reactions whose yields ranged from 15 to 85% in order to minimize the errors in reading GLC areas and in computing the rates.

4.6. Reaction products

We performed separate reactions on compounds (**2**-**6**) on a larger scale using the above described standard procedure. Following work up, the crude reaction mixtures were separated into their components by HPLC and the purity of each compound tested by GLC. Besides physical chemical properties, we report the most suitable HPLC solvent composition and the elution order of compounds from each mixture.

4.6.1. Purification by HPLC (CH_2Cl_2/EtOAc=80/20, Φ=2.6 ml/min), gave, sequentially, 2″and 2′. *Compound* **2′**. Pale yellow viscous oil. Anal. calcd for $C_{13}H_{22}O_3$: C, 68.98; H, 9.80; found: C, 68.94; H, 9.83; ν_{max} (CCl_4): 3600, 2935, 3860, 2560, 1715, 1450, 1380, 1265, 1150, 1048; *m/z* (%): 211 (M^+-15, 0.9), 166 (80), 151 (37), 148 (38), 133 (16), 123 (31), 108 (100), 95 (19), 93 (32), 81 (32), 79 (35), 71 (28), 67 (27), 55 (18), 43 (98); ^{1}H NMR δ: 4.85 (bs, 1H, C*H*OAc), 2.01 (s, 3H, OCOCH_3), 1.76–1.74 (bd, 1H, *J*=4.6 Hz), 1.70–1.68 (bd, *J*=3.6 Hz), 1.60–1.50 (m, 4H), 1.35–1.10 (m, 7H) 1.14 (s, 3H, CH_{3ax}OH); ^{13}C NMR δ: 170.79, 72.30 (*C*HOAc), 72.07 (HO*C*CH_{3ax}), 46.29, 41.99, 36.57, 29.08, 28.04, 26.11, 25.55, 21.23, 20.77.

Compound **2″**. Colourless needles, m.p. 92–92.5°C. Anal. calcd for $C_{13}H_{22}O_3$: C, 68.98; H, 9.80; found: C, 68.96; H, 9.81; ν_{max} (CCl_4): 3610, 3505, 2930, 2860, 2260, 1720, 1450, 1380, 1250, 1195, 1090; *m/z* (%): 211 (M^+-15, 4.8), 166 (45), 151 (64), 148 (58), 133 (20), 123 (23), 108 (89), 95 (19), 93 (31), 81 (32), 79 (35), 71 (33), 67 (29), 55 (19), 43 (100); ^{1}H NMR δ: 4.86 (bs, 1H, C*H*OAc), 2.01 (s, 3H, OCOCH_3) 1.88–1.36 (m, 10H), 1.25–1.18 (m, 5H), 1.18 (s, 3H, CH_{3eq}); ^{13}C NMR δ: 170.87, 73.31 (*C*HOAc), 70.49 (HO*C*CH_{3eq}), 43.92, 39.32, 34.76, 29.38, 28.31, 26.23, 25.97, 25.72, 25.09, 21.23.

4.6.2. Purification by HPLC (hexane/EtOAc=85/15, Φ=3.2 ml/min.), gave, sequentially, 3″ and 3′. Compound

3′. White prisms, mp 100–101.5°C; HRMS: found 202.1127. $C_{11}H_{19}ClO$ requires 202.1124; ν_{max} (CCl_4) 3590, 3465, 2940, 2860, 1450, 1380, 1300, 1260, 1150, 960; *m/z* (%): 202 (M^+0.11), 187 (M^+-15, 9.1), 148 (50), 133 (12), 108 (70), 93 (14), 79 (22), 71 (100), 67 (19), 58 (17), 55 (11), 43 (47); ^{1}H NMR δ: 4.20–4.18 (bq, 1H, C*H*Cl, *J*=2.1 Hz), 2.20–1.90 (m, 4H), 1.8 5–1.70 (m, 3H), 1.60–1.40 (m, 4H), 1.30–1.12 (m, 4H) 1.16 (s, 3H CH_{3ax}); ^{13}C NMR δ: 72.30 (HO*C*CH$_{3ax}$), 65.09 (*C*HCl), 45.17, 43.65, 36.18, 32.18, 31.09, 29.90, 25.94, 25.20, 24.15.

Compound **3″**. Pale yellow viscous oil. Anal. calcd for $C_{11}H_{19}ClO$: C, 65.31; H, 9.47; found: C, 65.33; H, 9.48; ν_{max} (CCl_4) 3610, 2940, 2860, 1450, 1386, 1300, 1260, 1125, 810; *m/z* (%): 187 (M^+-15, 27), 148 (50), 133 (16), 125 (16), 108 (71), 93 (15), 79 (24), 71 (100), 58 (17), 55 (12), 43 (47); ^{1}H NMR δ: 4.22–4.20 (bq, 1H, C*H*Cl, *J*=2.6 Hz), 2.10–1.96 (m, 2H), 1.85–1.70 (m, 4H), 1.55–1.45 (m, 4H), 1.25–1.12 (m, 5H) 1.20 (s, 3H CH_{3eq}); ^{13}C NMR (δ): 70.55 (HO*C*CH$_{3eq}$), 66.65 (*C*HCl), 42.77, 40.96, 34.30, 31.13, 29.95, 28.30, 26.03, 25.76, 24.66.

4.6.3. Purification by HPLC (H_2O/CH_3CN=60/40), gave, sequentially, 4′, 4″ and 4‴. *Compound* **4′**. White needles, mp 75.5–76°C; HRMS found: 226.1566. $C_{13}H_{22}O_3$ requires 226.1570; ν_{max} (CCl_4): 3660, 2930, 2860, 1730, 1450, 1380, 1260, 1150, 1090, 810; (*m/z*): 226 (M^+, 2.03), 211 (M^+-15, 2.4), 208 (13), 194 (11), 156 (14), 149 (20), 148 (17), 144 (100), 133 (20), 125 (65), 112 (70), 87 (36), 84 (43), 67 (21), 55 (22), 43 (56); ^{1}H NMR δ: 3.67 (s, 3H), 2.12–2.00 (m, 2H), 1.80–1.40 (m, 10H), 1.26–1.10 (m, 4H), 1.16 (s, 3H, CH_{3ax}); ^{13}C NMR (δ):176.36, 72.04 (*C*CH$_{3ax}$); 51.51, 50.42, 41.29, 40.89, 32.20 29.69, 27.05, 26.25, 25.89, 25.48, 21.31.

Compound **4″**. Colourless viscous oil; HRMS found: 226.1572. $C_{13}H_{22}O_3$ requires 226.1570; ν_{max} (CCl_4): 3640, 2980, 2940, 2250, 1730, 1380, 1275, 1195, 1110; *m/z*: 226 (M^+, 2.7), 211 (M^+-15, 2.6), 208 (13), 194 (8), 156 (16), 149 (52), 148 (55), 144 (100), 133 (39), 125 (54), 87 (32), 84 (40), 67 (21), 55 (20), 43 (47); ^{1}H NMR δ: 3.67 (s, 3H), 2.10–2.00 (m, 2H), 1.80–1.40 (m, 10H), 1.22–1.14 (m, 4H), 1.18 (s, 3H, CH_{3eq}); ^{13}C NMR δ: 176.36, 70.21 (*C*CH$_{3eq}$), 51.41, 50.46, 49.29, 39.33, 38.62, 31.85, 28.15, 26.37, 25.79, 25.16, 24.96.

Compound **4‴**. Colourless viscous oil; HRMS found: 196.1458; $C_{12}H_{20}O_2$ requires 196.1463; ν_{max} (CCl_4): 2930, 2860, 1765, 1260, 1045; (*m/z*): 166 (10), 150 (17), 135 (16), 112 (28), 108 (17), 93 (16), 84 (100), 79 (21), 67 (20), 43 (38%); ^{1}H NMR (300 MHz) δ: 2.40–2.32 (m, 1H), 2.20–2.10 (m, 1H), 1.90–1.80 (m, 4H), 1.70–1.60 (m, 4H), 1.50–1.30 (m, 4H), 1.27 (s 3H); ^{13}C NMR (δ) 177.06, 83.70, 47.56, 44.99, 41.77, 37.90, 30.20, 29.87, 28.15, 27.88, 27.04, 21.56.

4.6.4. Purification by HPLC (CH_2Cl_2/EtOAc=80/20, Φ=2.6 ml/min), gave, sequentially, 5″ and 5′. *Compound* **5′**. Pale yellow viscous oil; HRMS found: 226.1568. $C_{13}H_{22}O_3$ requires 226.1570; ν_{max} (CCl_4): 2930, 2855, 1730, 1720, 1545, 1450, 1380, 1240, 1120, 1026, 778; *m/z* (%): 211 (M^+-15, 0.008), 166 (60), 151 (20), 148 (38), 133 (14), 123 (26), 108 (100), 93 (30), 96 (19), 81 (27), 79 (30), 71 (26), 67 (24), 55 (14), 43 (82); ^{1}H NMR (300 Mz) δ: 4.52–4.38 (dt, 1H, C*H*OAc, J_t=10.4 Hz, J_d=4.8 Hz), 2.02 (s, 3H, OCOCH_3), 1.98–1.88 (m, 3H), 1.80–1.42 (m, 8H), 1.26–1.12 (m, 4H), 1.14 (s, 3H, CH_{3ax}OH); ^{13}C NMR δ: 170.86, 76.89 (*C*HOAc), 71.78 (HO*C*CH$_{3ax}$), 50.28, 49.01, 39.65, 29.87, 28.56, 25.92, 25.56, 25.45, 21.19, 21.13.

Compound **5″**. White needles, mp 109–109.5°C. Anal. calcd for $C_{13}H_{22}O_3$: C, 69.98; H, 9.80; found: C, 69.95; H, 9.79; ν_{max} (CCl_4) 3620, 2940, 2855, 1745, 1725, 1545, 1380, 1240, 1025, 765; *m/z* (%): 211 (M^+-15, 0.02), 166 (65), 151 (11), 148 (50), 133 (21), 123 (21), 108 (100), 95 (17), 91 (14), 81 (27), 79 (31), 71 (27), 67 (26), 55 (16), 43 (86); ^{1}H NMR δ (300 MHz): 4.52–4.38 (dt, 1H, C*H*OAc, J_t=10.4 Hz, J_d=4.8 Hz), 2.02 (s, 3H, OCOCH_3), 1.78–1.64 (m, 7H),1.60–1.40 (m, 6H), 1.20–1.10 (m, 2H), 1.16 (s, 3H CH_{3eq}OH), ^{13}C NMR (δ): 170.99, 76.87(*C*HOAc), 69.90 (HO*C*CH$_{3eq}$) 48.36, 41.04, 38.02, 29.27, 27.87, 26.67, 26.05, 25.32, 25.17, 21.21.

4.6.5. Purification by HPLC (H_2O/CH_3CN=60/40, Φ=3.2 ml/min.), gave, sequentially, 6″ and 6′. *Compound* **6′**. Pale yellow oil; HRMS: found 202.1122. $C_{11}H_{19}ClO$ requires 202.1124; ν_{max} (CCl_4) 2960, 1410, 1260, 1095, 1020, 820, 780; *m/z* (%): 187 (M^+-15, 12), 148 (40), 125 (38), 108 (62), 96 (10), 81 (14), 79 (19), 71 (100), 67 (20), 58 (16), 43 (64), 41 (19); ^{1}H NMR δ (300 MHz): 3.54–3.42 (ddd, 1H (C*H*Cl, J_{d1}=11.6 Hz, J_{d2}=10.2 Hz, J_{d3}=4.4 Hz), 2.28–2.10 (m, 2H), 1.8–1.6 (m, 5H), 1.40–1.10 (m, 8H), 1.18 (s, 3H, CH_{3ax}); ^{13}C NMR δ 72.21 (HO*C*CH3$_{ax}$), 65.86, 43.40, 40.18, 29.68, 29.90, 28.90, 26.50, 26.09, 24.91, 24.32.

Compound **6″**. Pale yellow oil; HRMS: found 202.1126. $C_{11}H_{19}ClO$ requires 202.1124; ν_{max} (CCl_4) 2930, 2855, 1450, 1260, 1100, 1010, 820; *m/z* (%): 187 (M^+-15, 18); 148 (56), 133 (16), 125 (46), 108 (68), 91 (13), 79 (21), 71 (100), 67 (22), 58 (16), 55 (12), 43 (57); ^{1}H NMR (300 Mz) δ: 3.56–3.46 (td, 1H C*H*Cl, J_t=11.0 Hz, J_d=4.6 Hz), 2.10–1.98 (m, 2H), 1.88–1.40 (m, 11H), 1.24–1.10 (m, 2H), 1.20 (s, 3H, CH_{3eq}).; ^{13}C NMR (δ) 70.05 (HO*C*CH$_{3eq}$), 66.34, 44.77, 39.93, 32.51, 31.09, 29.68, 27.99, 26.27, 25.66, 25.42.

Acknowledgements

We are indebted to the Italian MIUR and to the University of Rome 'La Sapienza' (National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni') for financial support and we wish to express our gratitude to Professor Giorgio Di Maio for his invaluable comments and suggestions.

References

1. Di Maio, G.; Mascia, M. G.; Vecchi, E. *Tetrahedron* **2002**, *58*, 3313–3318.
2. Suzuki, T.; Kobayashi, T.; Takegami, Y.; Kawasaki, Y. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1971–1976.
3. Ayer, A. W.; Browne, L. M.; Fung, S.; Stothers, J. B. *Org. Magn. Reson.* **1978**, *11*(2), 73–80.

4. Casadevall, E.; Povet, Y. *Tetrahedron Lett.* **1976**, *33*, 2841–2844.
5. Senda, Y.; Ishiyana, J.; Imaizumi, S. *Tetrahedron* **1975**, *31*, 1601–1605.
6. Green, M. M. *Top. Stereochem.* **1976**, *9*, 35–110.
7. Silverstein, R. M.; Bassler, G.; Morril, T. *Spectrometric Identification of Organic Compounds*; 4th ed. Wiley: New York, 1981; pp 189–190.
8. Barton, D. H. R.; Cookson, R. C. *Quart. Rev. (London)* **1956**, *10*, 44–82.
9. Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119–251.
10. Cianetti, C.; Di Maio, G.; Pignatelli, V.; Tagliatesta, P.; Vecchi, E.; Zeuli, E. *Tetrahedron* **1983**, *39*, 657–666.
11. Di Maio, G.; Li, W.; Vecchi, E. *Tetrahedron* **1985**, *41*, 4891–4896.
12. Di Maio, G.; Li, W.; Migneco, L. M.; Vecchi, E. *Tetrahedron* **1986**, *42*, 4837–4842.
13. Di Maio, G.; Migneco, L. M.; Vecchi, E. *Tetrahedron* **1990**, *46*, 6053–6060.
14. Migneco, L. M.; Vecchi, E. *Gazz. Chim. Ital.* **1997**, *127*, 19–24.
15. Di Maio, G.; Solito, G.; Varì, M. R.; Vecchi, E. *Tetrahedron* **2000**, *56*, 7237–7243.
16. Di Maio, G.; Innella, C.; Vecchi, E. *Tetrahedron* **2001**, *57*, 7403–7407.
17. Kwart, H.; Miller, L. J. *J. Am. Chem. Soc.* **1961**, *83*, 4552–4559.
18. Kwart, H.; Takeshita, T. *J. Am. Chem. Soc.* **1962**, *84*, 2833–2835.
19. Klein, J. *Tetrahedron Lett.* **1973**, *44*, 4307–4310.
20. Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5818–5827.
21. Nazarov, I. N.; Kucherov, V. F.; Andreev, V. M.; Segal, G. M. *Doklady Akad. Nauk S.S.S.R.* **1955**, *104*, 729–732.
22. Zerewitinoff, Th. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 2023–2031.
23. Bergbreiter, D. E.; Pendergrass, E. *J. Org. Chem.* **1981**, *46*, 219–220.