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Does substituent's conformation influence the kinetics of reduction reactions on *trans*-4-X-decal-1-ones and to what extent?

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Abstract—Stereochemistry and relative rates k_{ax} and k_{eq} of reduction reactions on title compounds have been measured under five different reaction conditions ($NaBH_4$ in *i*-PrOH, $LiBH_4$ and $NaAlH_4$ in THF and $LiAlH_4$ in THF and in Et_2O). Experiments indicate that axial substituents behave as far less electronegative than their equatorial counterpart in reactions at the equatorial side of molecules.

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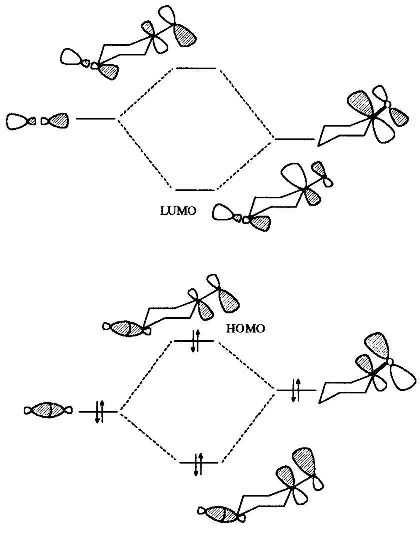
1. Introduction

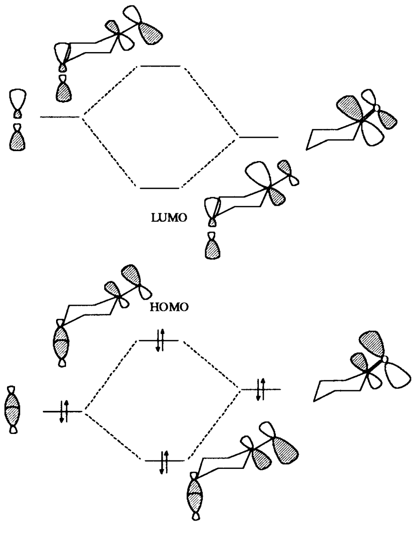
We have been interested in understanding π-face selectivity in addition and reduction reactions in cyclohexanone systems.[1,2]

Our previous experiments and MO considerations[1] suggest (see Schemes 1 and 2) that the LUMO carbonyl orbital is more extended on the axial face of the molecule both under the influence of β-CC bond's hyperconjugation and the C_4–X bond irrespective of their axial or equatorial conformation. The HOMO carbonyl orbital suffers instead opposite distortion effects from the β-CC and the axial C_4–X bond hyperconjugation the balance being determined by the identity of the X group. Actually, we have found, for instance, that the axial reactivities behave monotonically i.e. they always increase with increasing electronegativity of the X group, whereas the changes in equatorial reactivity strictly depend on the conformation of the X group and the reaction conditions.



Scheme 1. Distortions of the carbonyl group HOMO and LUMO orbitals with a C_4–X equatorial substituent.

The limit of our previous experiments was that we used two different rigid systems, one for the axial and the second for the equatorial substituent. Therefore, the rate values we obtained could hardly be removed from the intrinsic



Scheme 2. Distortions of the carbonyl group HOMO and LUMO orbitals with a C_4–X axial substituent.

Keywords: reduction reactions; substituents'conformation; kinetics; *trans*-4-X-decal-1-ones.

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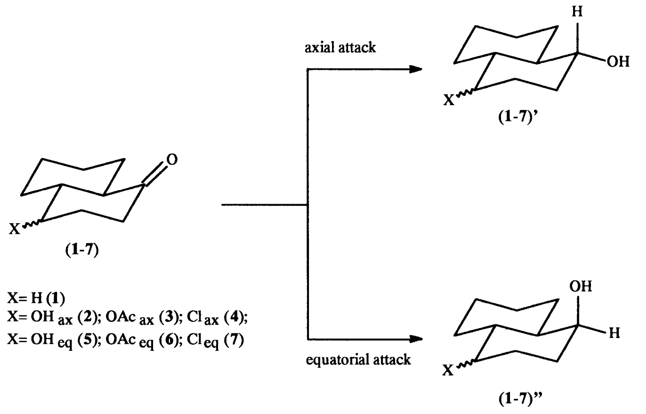

Figure 1.

Table 1. Stereochemical product ratios (k_{ax}/k_{eq}) for *trans*-4-X-decal-1-ones (**1**–**7**)

Reaction conditions		Stereochemical product ratios (k_{ax}/k_{eq})					
		Axial substituent			Equatorial substituent		
	$\mathbf{1}'/\mathbf{1}''$ σ_I=0.00	$\mathbf{2}'/\mathbf{2}''$ σ_I=0.24	$\mathbf{3}'/\mathbf{3}''$ σ_I=0.38	$\mathbf{4}'/\mathbf{4}''$ σ_I=0.47	$\mathbf{5}'/\mathbf{5}''$ σ_I=0.24	$\mathbf{6}'/\mathbf{6}''$ σ_I=0.38	$\mathbf{7}'/\mathbf{7}''$ σ_I=0.47
(a) $NaBH_4$, *i*-PrOH, 20°C	2.43	6.97	7.35	10.44	2.72	6.17	3.27
(b) $LiBH_4$, THF, 20°C	3.08	7.48	8.23	13.01	3.25	7.36	3.52
(c) $NaAlH_4$, THF, 20°C	2.78	5.78	4.70	7.10	2.66	3.62	2.25
(d) $LiAlH_4$, THF, 20°C	3.05	8.49	7.63	12.64	2.62	7.77	2.40
(e) $LiAlH_4$, Et_2O, 20°C	3.54	8.11	6.12	10.64	2.93	6.51	3.01

reactivities of the two unsubstitued systems to neatly show the effect of changing the conformation of the C_4–X group.

Two principal questions needed an answer. Are the axial reactivities independent of the C_4–X group conformation as MO considerations suggest? How much does the equatorial reactivity depend on the C_4–X group conformation?

The title compounds having the same substituent once in the axial and once in the equatorial conformation represent a suitable model for exploring in more detail changes in k_{ax} and k_{eq}.

In this paper, we describe the stereochemical and kinetic results of reduction reactions on a series of *trans*-4-X-decal-1-ones namely **1** (X=H); **2** and **5** (X=OH); **3** and **6** (X=OAc); **4** and **7** (X=Cl) carrying the same substituent respectively in the axial (**2**–**4**) and in the equatorial (**5**–**7**) conformation (Fig. 1).

Their reactivity has been compared in the following reaction conditions: (a) $NaBH_4$/*i*-PrOH; (b) $LiBH_4$/THF; (c) $NaAlH_4$/THF; (d) $LiAlH_4$/THF; (e) $LiAlH_4/Et_2O$.

Houk[3] already studied the stereochemical product ratios (k_{ax}/k_{eq}) for reaction condition (a) on the same compounds.

We succeeded in separating the reaction products from one another by HPLC (see Section 4 for full spectroscopic characterization).

Under all the above-mentioned reaction conditions, the only reaction products were alcohols (**1**–**7**)′ that derived from axial attack of the reduction agents, and (**1**–**7**)″[†] derived from equatorial attack (Fig. 1).

2. Results and discussion

For each set of reaction conditions we determined the stereochemistry of reduction reactions by GLC. Table 1 collects the stereochemical outcome of several reactions (five experiments at least for each substrate under all reaction conditions). Stereochemical ratios k_{ax}/k_{eq} (Table 1) show

1. a monotonic trend, that is an increase with increasing the axial substituent electronegativity, just for the axial substituents and for reactions with boron reactants;
2. the increasing k_{ax}/k_{eq} trend is interrupted for X=OAc (**3**′/**3**″) for aluminium reactants in reactions on substrates with X_{ax};
3. under all reaction conditions the reactions on X_{eq} bearing substrates show a maximum in the k_{ax}/k_{eq} values when X=OAc (**6**′/**6**″).

We also performed a series of competitive kinetic experiments[‡] on equimolecular mixtures of compounds **1** and compounds **2**–**7**, respectively. The overall and relative reaction rates are reported in Table 2 as the mean of at least five separate experiments.

The kinetic data show that the overall reaction rates always increase on increasing the substituent's (both axial and equatorial) electronegativity. Relative rates show instead a far less homogeneous pattern: k_{ax} almost always increase under the influence of both axial and equatorial substituents. The changes in k_{ax} between X=H and X=Cl strictly parallel those previously found in the β-decalone systems. The k_{eq} show instead a less homogeneous pattern: they almost always increase under the influence of the equatorial substituents (columns 1, 5–7 in Table 2). Instead, the axial substituents produce a less definite trend which sharply contrasts with the behaviour previously described for the β-decalone systems in which the k_{eq} decrease and finally vanish for X=Cl thus mimicking an elecrophilic attack of

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[†] Compounds **2**′ and **5**″ are the same: the choice of indicating them with different numbers is due to simplicity in reading the entries in Tables 1 and 2.

[‡] See Ref. 2 concerning competitive kinetic experiments, their reliability, the methods of GLC standardization of both substrates and reaction products and the methods used for computing the yields of reactions.

Table 2. Overall ratio of rates and relative rates for *trans*-4-X-decal-1-ones (**1**–**7**)

Reaction conditions	Overall ratio of rates		Relative rates													
	X_{ax}	X_{eq}	k_{ax}							k_{eq}						
	$k_1/k_2/k_3/k_4$[a]	$k_1/k_5/k_6/k_7$[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
(a) $NaBH_4$ *i*-PrOH	1/1.23/5.35/5.83	1/2.16/6.05/6.10	1	1.53	6.61	7.52	2.23	7.34	6.57	0.41	0.22	0.90	0.72	0.82	1.19	2.01
(b) $LiBH_4$ THF	1/1.50/3.81/6.43	1/2.87/5.06/5.90	1	1.72	4.44	7.94	2.89	5.89	6.05	0.32	0.23	0.54	0.61	0.89	0.80	1.72
(c) $NaAlH_4$ THF	1/0.79/1.66/2.53	1/1.04/2.30/2.85	1	0.92	1.88	2.98	1.04	2.46	2.68	0.36	0.16	0.40	0.42	0.39	0.68	1.19
(d) $LiAlH_4$ THF	1/0.83/1.65/1.94	1/0.96/1.83/1.66	1	1.02	1.91	2.40	0.92	2.18	1.56	0.33	0.12	0.25	0.19	0.35	0.28	0.65
(e) $LiAlH_4$ Et_2O	1/0.97/1.28/1.63	1/1.14/1.42/1.51	1	1.13	1.41	1.91	1.08	1.56	1.44	0.28	0.14	0.23	0.18	0.37	0.24	0.48

[a] Mean standard deviation: 0.02.

Table 3. LFER data (ρ in decreasing order and corresponding r^2) in different reaction conditions

Reaction conditions	Axial attack		Equatorial attack	
	ρ	r^2	ρ	r^2
Axial substituents				
(a) $NaBH_4$ *i*-PrOH	2.03	0.87	0.75	0.32
(b) $LiBH_4$ THF	1.91	0.93	0.67	0.45
(c) $NaAlH_4$ THF	0.98	0.69	0.2	0.05
(d) $LiAlH_4$ THF	0.83	0.79	−0.36	0.16
(e) $LiAlH_4$ Et_2O	0.55	0.84	−0.31	0.24
Equatorial substituents				
(a) $NaBH_4$ *i*-PrOH	1.94	0.93	1.40	0.97
(b) $LiBH_4$ THF	1.76	0.97	1.37	0.87
(c) $NaAlH_4$ THF	1.00	0.78	1.02	0.77
(d) $LiAlH_4$ THF	0.60	0.48	0.39	0.25
(e) $LiAlH_4$ Et_2O	0.40	0.78	0.27	0.17

the reactants and suggesting that the carbonyl group HOMO has lesser and lesser amplitude on the equatorial side of the molecule as described in Scheme 2. A similar conclusion is hard to attain if one looks at the k_{eq} values in Table 2 (columns 1–4). However, that the binding of the molecule is smaller on the equatorial side and when C_4–X is axial is evidenced by the k_{eq} values which are systematically smaller ($2\div4$ times) in this case (compare columns 2, 3 and 4 to 5, 6 and 7, respectively). This behaviour is in keeping with the MO description of Schemes 1 and 2 (see HOMO). The difference in the trend of k_{eq} in the α and β-decalone systems we mentioned above means that not only equatorial and axial substituents behave differently but also that the same can be done by the C_4–X axial substituents in two strictly related molecules. We suggest that this difference could perhaps be related to the fact that the distances and geometries of an axial substituent vs. the carbonyl group are more rigidly fixed in the β-decalone system than in the α-decalone one, thus producing either different dipole–dipole interactions, or a different amount of the MO perturbation.[§]

Kinetic data in Table 2 show something more if we use them to construct LFER ($1+\log k_{ax}$ and $1+\log k_{eq}$ vs. substituents $\sigma_I s$[4]). From each LFER we calculated the values of ρ and r^2 respectively which are reported in Table 3. Each line in Table 3 contains figures originated from the same experiment and should be affected by the same systematic experimental errors. Nevertheless, we go from fairly good to very poor correlation coefficients. This is particularly true when the axial and equatorial attack are compared for reactions with an axial substituent. We have already discussed[2] this phenomenon in MO terms and defined equatorial reactivity as less predictable, when the C_4 substituent is axial.

Table 3 also contains the answers to the questions we posed at the beginning: the ρ_{ax} show small changes when the substituent conformation is changed (compare equally lettered lines in the axial attack column). Even the reaction rates do not change, see Table 2. One can infer that the LUMO suffers the same distortion towards the axial side of the molecule irrespective of substituent conformation.

The ρ_{eq}, however, depend on the substituent conformation (compare equally lettered lines in the equatorial attack column).

So, for axial attack on the molecule, we are left with the traditional situation that is one ρ set and one σ set independently of the substituent conformation. For the equatorial attack on the molecule, things are less comfortable since a choice must be made between duplicating ρ values (as in Table 3) or duplicating σ values: this last choice seems, in our opinion, more reasonable. The situation could be even more complicated in the way described by Van Bekkum et al.[5] of a multiplicity of σ_I values. The chlorine substituent is the only one for which some calculations can be done: we trust less the OH and OCOMe substituents owing, as mentioned, to complexation or anchimeric assistance phenomena they can give in different amounts on changing their conformation.[6–9] Therefore, using LFER obtained for reaction conditions (a), (b) and (c) and adopting as ρ values those obtained when the substituent is equatorial (1.4, 1.37, 1.02,[‖] Table 3) one obtains for $(\sigma_{ax})_{Cl}$ three very close values which are: 0.16, 0.12, and 0.13, respectively. Perhaps close enough to rule out, so far, the hypothesis involving a multiplicity of σ values. This means that the chlorine atom '*in the axial conformation and for reactions on the equatorial side behaves as far less electronegative*'. In other words, what is called the 'electronegativity' of a substituent can be modulated by its MO interactions with the reacting site (and, in this case, with the β-CC bonds).

Table 3 shows the same phenomenon we already recently[2]

[§] No surprise that the two hypotheses could result in the same thing in the future.

[‖] Smaller ρ values give higher errors in reading plots.

discussed, that is the reaction sensitivities are correlated to the III Group metal which has a prominent role in determining the structure of the transition state shape.

3. Conclusions

We determined the axial and equatorial rates of attack on a series of *trans*-4-X-decal-1-ones in reduction reactions.

As formerly evidenced,[2] the reaction sensitivity is mainly affected by the changes of Group III metal (B and Al) while changes of Group I metals (Li and Na) only have a minor influence.

The LUMO of a carbonyl group is more distorted on the axial face of a cyclohexanone system irrespective of the conformation of the remote substituent.

Axial reactivity is independent from the substituent's conformation, but axial substituents behave differently depending on which molecular skeleton they are bonded to.

Equatorial reactivity is instead related to the substituent conformation. We suggest that HOMO is less developed on the equatorial side of the molecule under the influence of an axial C_4–X substituent.

Our data suggest that axial substituents have a much lower electronegativity than their equatorial counterparts in reactions on the equatorial side of the molecule.

Additions to a trigonal stereogenic centre occur at quite different reaction rates, one on each side of the molecule and each one with its own controls. The idea which persists in questions focussed on 'π-face diastereoselection' that it is possible to infer what happens on both sides of a molecule by simple determinations of the k_{ax}/k_{eq} ratios should be definitively abandoned.

4. Experimental

4.1. Instruments

Melting points were determined on a Mettler FP82HP apparatus and are uncorrected. HRMS were 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 with a HP 5890 gas chromatograph using a capillary column coated with fluid methyl silicone (12.5 m, 0.2 mm i.d.). ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were recorded on a GEMINI 200 and on a VARIAN XL 300 spectrometers with $CHCl_3$ 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 CARBOWAX 20 M), 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′**), (**5**, **5″**, **5′**), (**6**, **6″**, **6′**) and (**7**, **7′**,**7″**). We report the most suitable GLC conditions (initial oven temperature, isotherm time, temperature increase rate, final oven temperature): 80°C, 4 min, 15°C/min, 180°C, 20 min; $T_{inj}=T_{det}=230$°C. **1**, **1″** and **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[4.4.0]decan-2-one is commercially available (Aldrich) and was used as such. Published procedures[3] were used for the preparation of (1*S*,5*R*,6*S*)*-5-hydroxybicyclo[4.4.0]decan-2-one **2** and (1*S*,5*S*,6*S*)*-5-hydroxybicyclo[4.4.0]decan-2-one **5**, for (1*S*,5*R*,6*S*)*-5-acetoxybicyclo[4.4.0]decan-2-one **3** and (1*S*,5*S*,6*S*)*-5-acetoxybicyclo[4.4.0]decan-2-one **6**, for (1*S*,5*R*,6*S*)*-5-chlorobicyclo[4.4.0]decan-2-one **4** and for (1*S*,5*S*,6*S*)*-5-chlorobicyclo[4.4.0]decan-2-one **7**.

4.3. Preparation of reagents, reactions and competition experiments

Standard procedures previously described[2] were adopted.

4.3.1. Reaction products. We performed separate reduction reactions on compounds (**1**–**7**) using standard procedure. After working up, the crude reaction mixtures were separated into their components by HPLC: the purity of each compound was tested by GLC. Besides physical chemical properties, we report the most suitable HPLC solvent composition and the elution order of compounds from each mixture.

Purification by HPLC (CH_2Cl_2/EtOAc=80:20), gave, in order, **1″** and **1′**

Compound **1′**. White needles, mp 60–61°C (lit.[10] 63°C); ν_{max} ($CHCl_3$) 3620, 3460, 3020, 2930, 2860, 1620, 1450, 1365, 1260, 1240, 1100, 1020, 950, 810 cm^{-1}; *m/z* (%): 154 (M$^+$, 11) 136 (100), 121 (43), 111 (39), 94 (60), 81 (43), 67 (66), 55 (36), 41 (38); ^{1}H NMR δ (200 MHz $CDCl_3$) 3.15–3.08 (bm, 1H, CH_{ax}OH) (lit.[10] 3.05), 2.07–1.87 (m, 4H), 1.68–0.81 (m, 12H); ^{13}C NMR δ 74.04 (*C*HOH), 49.44, 40.11, 34.80, 32.58, 32.42, 27.99, 25.33, 25.14, 23.03.

Compound **1″**. Pale yellow viscous oil (lit.[10] 49°C); ν_{max} ($CHCl_3$) 3620, 2930, 2860, 1460, 1260, 1230, 1100, 1015, 820 cm^{-1}; *m/z* (%): 154 (M$^+$, 3.1), 136 (100), 121 (36), 111 (26), 107 (34), 95 (43), 94 (57), 81 (39), 67 (64), 57 (22), 55 (36), 41 (42); ^{1}H NMR δ (300 MHz, $CDCl_3$) 3.73 (bs, 1H, CH_{eq}OH) (lit.[10] 3.7), 1.58–1.42 (m, 8H), 1.23–1.2 (m, 8H); ^{13}C NMR δ: 70.66 (*C*HOH), 47.13, 35.56, 34.31, 33.84, 33.67, 29.69, 26.71, 26.36, 19.96.

Purification by HPLC (H_2O/CH_3CN=90:10), gave, in order, **2′** and **2″**.

Compound **2′**=**5″**. White needles, mp 161–162°C; Anal. calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.66; found: C, 70.56; H, 10.68; ν_{max} ($CHCl_3$) 3690, 3605, 2930, 2855, 1600, 1230, 790 cm^{-1}; *m/z* (%): 170 (M$^+$, 3), 152 (8), 134 (56), 123 (39), 112 (100), 108 (77), 95 (85), 81 (67), 79 (65), 67 (86), 58

(78), 41 (60); ^{1}H NMR δ (300 MHz, CDCl$_3$) 3.62 (bd, 1H, C*H*$_{eq}$OH, *J*=2.4 Hz), 3.18–3.14 (dt, 1H, C*H*$_{ax}$OH, J_t=9.9 Hz, J_d=4.8 Hz), 2.15–2.11 (m, 1H), 1.80–1.16 (m, 14÷15H); ^{13}C NMR (δ): 74.00 (*C*HOH$_{eq}$), 68.54 (*C*HOH$_{ax}$), 43.85, 41.84, 30.32, 28.27, 28.18, 28.12, 25.29, 24.79.

Compound **2″**. White needles, mp 137–138°C; Anal. calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.66; found: C, 70.49; H, 10.68; ν_{max} (CHCl$_3$) 3690, 3605, 3020, 2930, 2860, 1600, 1230, 1210 cm^{-1}; *m/z* (%): 152 (100), 134 (91), 123 (57), 108 (79), 95 (83), 79 (75), 67 (97), 55 (65), 41 (81); ^{1}H NMR δ (300 MHz, CDCl$_3$) 3.71–3.69 (bm, 2H, C*H*$_{eq}$OH), 1.86–1.84 (bd, 2H, *J*=9.3 Hz) 1.60–1.18 (m, 12H); ^{13}C NMR (δ): 70.08 (*C*HOH), 39.13, 29.39, 27.25, 26.31.

Purification by HPLC (CH$_2$Cl$_2$/EtOAc=80:20), gave, in order, **3′**and **3″**.

Compound **3′**. White viscous oil; HRMS: found 212.1416. $C_{12}H_{20}O_3$ requires 212.1412; ν_{max} (CHCl$_3$) 3620, 3010, 2930, 2860, 1720, 1450, 1380, 1260, 1025, 760 cm^{-1}; *m/z* (%):152 (18), 135 (14), 134 (100), 108 (30), 92 (25), 79 (20), 67 (18), 43 (32); ^{1}H NMR δ (300 MHz, CDCl$_3$) 4.84 (bt, 1H, C*H*OAc), 3.29–3.21 (m, 1H, C*H*$_{ax}$OH), 2.18 (d, 2H, *J*=9 Hz), 2.01 (s, 3H, OCOC*H*$_3$), 1.94 (d, 2H, *J*=9 Hz), 1.80–1.52 (m, 4H), 1.26–1.18 (m, 8H); ^{13}C NMR (δ): 170.61, 74.51 (*C*HOAc), 72.04 (*C*HOH), 43.67, 43.50, 29.74, 29.35, 28.87, 28.54, 26.13, 25.75, 21.27.

Compound **3″**. Pale yellow viscous oil; HRMS: found 212.1418. $C_{12}H_{20}O_3$ requires 212.1412: ν_{max} (CHCl$_3$) 3695, 3620, 2930, 2860, 1725, 1260, 1210 cm^{-1}; *m/z* (%):152 (33), 135 (15), 134 (100), 119 (17), 108 (24), 92 (28), 79 (23), 67 (22), 43 (42); ^{1}H NMR δ (300 MHz, CDCl$_3$) 4.85 (bs, 1H, C*H*OAc), 3.73 (s, 1H, C*H*$_{eq}$OH), 2.00 (s, 3H, OCOC*H*$_3$), 1.80–1.48 (m, 6H), 1.24–1.18 (m, 8H); ^{13}C NMR (δ): 170.86, 72.99 (*C*HOAc), 69.79 (*C*HOH), 40.21, 37.84, 29.68, 29.42, 27.99, 26.22, 26.09, 24.37, 21.24.

Purification by HPLC (CH$_2$Cl$_2$/EtOAc=80:20), gave, in order, **4′**and **4″**.

Compound **4′**. Pale yellow oil; HRMS: found 188.0969. $C_{10}H_{17}ClO$ requires 188.0968; ν_{max} (CHCl$_3$) 3620, 2930, 2860, 1450, 1370, 1260, 1100, 1060, 1020, 808 cm^{-1}; *m/z* (%):188 (M$^+$, 2.8), 135 (57), 134 (100), 108 (46), 93 (23), 67 (31), 57 (24), 41.00 (17); ^{1}H NMR δ (300 MHz, CDCl$_3$) 4.06 (bd, 1H, C*H*Cl, *J*=2.2 Hz), 3.20–3.10 (m, 1H, C*H*$_{ax}$OH), 2.20–2.12 (m, 1H), 2.03–1.96 (m, 1H), 1.80–1.68 (m, 4H), 1.45–1.15 (m, 8H); ^{13}C NMR (δ) 74.74 (*C*HOH), 64.29 (*C*HCl), 45.26, 42.48, 32.64, 30.51, 29.18, 29.08, 25.86, 25.50.

Compound **4″**. Pale yellow oil; HRMS: found 188.0963. $C_{10}H_{17}ClO$ requires 188.0968; ν_{max} (CHCl$_3$) 3020, 2930, 2860, 1455, 1260, 1210, 1100, 1020, 810 cm^{-1}; *m/z* (%):188 (M$^+$, 4), 135 (100), 134 (28), 108 (26), 67 (29), 41 (17); ^{1}H NMR δ (300 MHz CDCl$_3$) 4.26 (bd, 1H C*H*Cl, *J*=2.9 Hz), 3.57–3.55 (m, 1H, C*H*$_{eq}$OH), 2.10–1.8 (m, 2H), 1.6–1.3 (m, 4H), 1.22–1.18 (m, 8H); ^{13}C NMR (δ) 69.54 (*C*HOH), 66.17 (*C*HCl), 39.44, 39.04, 30.80, 28.97, 28.67, 27.58, 26.03, 25.91.

Purification by HPLC (H$_2$O/CH$_3$CN=87:13), gave, in order, **5′** and **5″**.

Compound **5′**. White needles, mp 156–157°C; Anal. calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.66; found: C, 70.50; H, 10.68; ν_{max} (CHCl$_3$) 3640, 2930, 2860, 1450, 1380, 1260, 1230, 1100, 1030 cm^{-1}; *m/z* (%): 170 (M$^+$, 1), 152 (76), 134 (77), 123 (43), 112 (53), 108 (71), 95 (80), 81 (64), 79 (62), 67 (100), 55 (58), 41 (66); ^{1}H NMR δ (300 MHz, CDCl$_3$) 3.32–3.12 (bm, 2H, C*H*$_{ax}$OH), 2.06–0.84 (m, 14H); ^{13}C NMR (δ) 74.09 (*C*HOH), 47.46, 32.96, 28.93, 25.55.

Purification by HPLC (*n*-hexane/EtOAc=80:20), gave, in order, **6″** and 6′.

Compounf **6′**. White needles, mp 95.0–95.5°C; Anal. calcd for $C_{12}H_{20}O_3$: C, 67.88; H, 9.50; found: C, 67.91; H, 9.48; ν_{max} (CHCl$_3$) 3620, 3470, 2950, 2860, 1725, 1450, 1380, 1270, 1130, 1030 cm^{-1}; *m/z* (%):152 (11), 134 (100), 119 (16), 108 (45), 95 (14), 92 (31), 79 (27), 67 (23), 43 (47); ^{1}H NMR δ (300 MHz, CDCl$_3$): 4.49–4.41 (dt, 1H, C*H*OAc, J_t=10.2 Hz, J_d=3.6 Hz), 3.24–3.17 (m, 1H, C*H*$_{ax}$OH), 2.00 (s, 3H), 1.81–1.6 (m, 6H), 1.42–1.12 (m, 8H); ^{13}C NMR (δ):170.83, 75.96 (*C*HOAc), 73.73 (*C*HOH), 47.62, 44.62, 32.73, 29.30, 28.93, 28.78, 25.46, 25.39, 21.15.

Compound **6″**. Pale yellow oil; HRMS: found 212.1416. $C_{12}H_{20}O_3$ requires 212.1412: ν_{max} (CHCl$_3$) 3620, 3480, 2930, 2860, 1720, 1600, 1450, 1375, 1260, 1130, 1030, 950 cm^{-1}; *m/z* (%): 152 (15), 134 (100), 119 (21), 108 (37), 92 (26), 81 (17), 79 (23), 67 (20), 43 (38); ^{1}H NMR δ (300 MHz, CDCl$_3$) 4.53–4.44 (dt, 1H, C*H*OAc, J_t=10.5 Hz, J_d=5.1 Hz), 3.70 (bd, 1H, C*H*$_{eq}$OH, *J*=2.1 Hz), 2.05 (s, 3H), 1.95–1.76 (m, 6H), 1.63–1.59 (m, 8H); ^{13}C NMR (δ): 171.03, 76.92 (*C*HOAc), 69.19 (*C*HOH), 45.02, 39.71, 31.14, 29.19, 29.14, 26.18, 25.62, 25.46, 21.49.

Purification by HPLC (H$_2$O/CH$_3$CN=60:40), gave, in order, **7′**and **7″**.

Compound **7′**. Pale yellow needles; mp 97–98°C; HRMS: found 188.0970. $C_{10}H_{17}ClO$ requires 188.0968; ν_{max} (CHCl$_3$) 3620, 3465, 3028, 2920, 2860, 1450, 1260, 1120, 1040, 920 cm^{-1}; *m/z* (%): 188 (M$^+$, 5), 152 (15), 135 (100), 111 (89), 108 (40), 93 (29), 79 (26), 67 (43), 57 (21), 41 (20); ^{1}H NMR δ (200 MHz, CDCl$_3$) 3.55–3.42 (ddd, 1H, C*H*$_{ax}$Cl, J_{d1}=11.6 Hz, J_{d2}=10.4 Hz, J_{d3}=4.2 Hz), 3.28–3.15 (ddd, 1H, C*H*OH, J_{d1}=11.0 Hz, J_{d2}=9.2 Hz, J_{d3}=4.4 Hz), 2.26–2.05 (m, 2H), 1.8–1.6 (m, 4H), 1.43–1.1 (m, 8H); ^{13}C NMR (δ): 73.53 (*C*HOH), 65.08 (*C*HCl), 49.58, 48.35, 35.20, 34.71, 30.65, 29.11, 25.79, 25.73.

Compound **7″**. Pale yellow oil; HRMS: found 188.0965. $C_{10}H_{17}ClO$ requires 188.0968; ν_{max} (CHCl$_3$) 3620, 3014, 2930, 2856, 1450, 1260, 1210, 1118, 1025, 940 cm^{-1}; *m/z* (%):188 (M$^+$, 6), 152 (12), 135 (65), 111 (100), 93 (28), 67 (42), 41 (23); ^{1}H NMR δ (300 MHz, CDCl$_3$) 3.66 (bd, 1H, C*H*$_{eq}$OH, *J*=2.4 Hz), 3.55–3.46 (td, 1H, C*H*Cl, J_t=11.1 Hz, J_d=4.5 Hz), 2.10–1.93 (m, 2H), 1.70–1.50 (m, 4H), 1.25–1.10 (m, 8H). ^{13}C NMR (δ): 68.27 (*C*HOH), 65.11 (*C*HCl), 45.74, 42.34, 32.04, 30.17, 29.85, 28.46, 25.31, 24.80.

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