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Π-Face Diastereoselection: Stereochemistry and Reactivity of Addition Reactions on Conformationally Rigid Substrates: 5-X-Adamantan-2-ones and *trans*-10-X-Decal-2-ones

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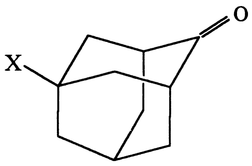
Abstract—Stereochemistry and relative rates k_{ax} and k_{eq} of addition reactions on title compounds have been measured under eight different reaction conditions (MeMgI in Et_2O and C_6H_6, MeMgCl in THF, MeLi at 20 and −78°C, Me_2Zn in Et_2O, Me_3Al in the ratio 1:1 reactant:substrate in toluene and Me_2CuLi/MeLi in Et_2O at −78°C). Our kinetic data do not fit with current theories of π-face diastereoselection. © 2000 Elsevier Science Ltd. All rights reserved.

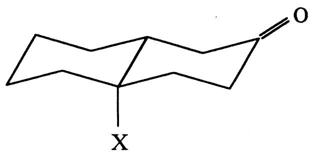
Introduction

Π facial stereoselectivity by various reagents in additions to unsaturated organic substrates through remote electronic perturbation is a question which continues to attract considerable theoretical and experimental[1–6] attention. Mechanistic investigations can be usefully carried out by changing the electronic properties of a stereogenic centre without concomitant steric perturbation and determining the stereochemistry of addition reactions (k_{ax}/k_{eq}) and especially the rates of attack (k_{ax} and k_{eq}). Good LFER between stereochemical ratios and substituents Taft's σ_I's are usually-at first glance-considered a probe of the prominent role played by electronic effects in the control of π-face diastereoselection. However, as previously described and pointed out by some of us,[7–13] the stereochemical bias represents an average outcome of the two addition routes of a reactant to a trigonal centre, routes which are not always linear, or monotonic. In fact changes in k_{ax}/k_{eq} sometimes originate from an uneven increase (or decrease), or, from divergent changes of k_{ax} and k_{eq}. Therefore, only the kinetic data, usually lacking in the literature, allow what happens on the two sides of the molecule to be clearly distinguished.

In the present paper we describe the stereochemical and kinetic results obtained under the following reaction conditions: (1) MeMgI in Et_2O (20°C); (2) MeMgCl in THF (20°C); (3) MeMgI in C_6H_6 (20°C);(4) MeLi in Et_2O (20°C);[14] (5) MeLi in Et_2O (−78°C); (6) Me_2Zn in Et_2O (20°C); (7) Me_3Al (in ratio 1:1 reactant:substrate) in toluene (20°C);[16] (8) Me_2CuLi/MeLi in Et_2O (−78°C) on a series of 10-X-adamantan-2-ones, namely with X=H (**1**), Ph (**2**), OMe (**3**), CO_2Me (**4**), Cl (**5**) and Br (**6**).



X=H (**1**); Ph (**2**); OMe (**3**); CO_2Me (**4**); Cl (**5**); Br (**6**)



X=H (**7**); CO_2Me (**8**); Cl (**9**)

The choice of a rigid molecular skeleton eliminates all questions arising from conformational uncertainty.[8,12]

Their reactivity has—whenever possible (reaction conditions 1 to 5)[17]—been compared to that of *trans*-10-X-2-decalones: X=H (**7**), CO_2Et (**8**),[10] and Cl (**9**)[13] investigated previously.

Keywords: addition reactions; π-face diastereoselection; kinetics; 5-X-adamantan-2-ones.

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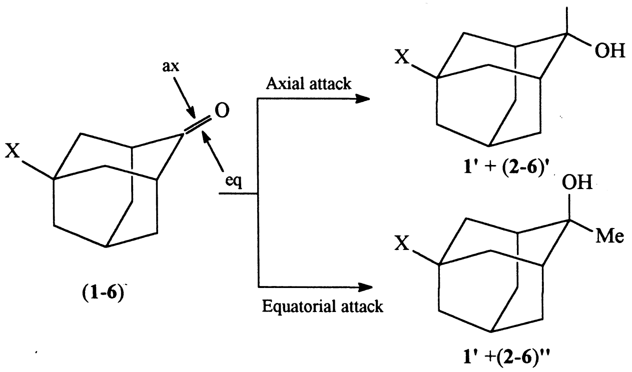
Table 1. Stereochemical product ratios (k_{ax}/k_{eq}) for 10-X-adamantan-2-ones (**1**–**6**)

Reaction conditions	Stereochemical product ratios (k_{ax}/k_{eq})					
	1′ (σ_I=0.00)	**2**′/**2**″ (σ_I=0.12)	**3**′/**3**″ (σ_I=0.30)	**4**′/**4**″ (σ_I=0.32)	**5**′/**5**″ (σ_I=0.47)	**6**′/**6**″ (σ_I=0.47)
MeMgI, Et_2O, 20°C	1	1.31	1.71	1.83	1.66	1.39
MeMgCl, THF, 20°C	1	1.40	1.87	1.61	2.09	1.64
MeMgI, C_6H_6, 20°C	1	1.19	1.71	1.52	1.67	1.15
MeLi, Et_2O, 20° C	1	1.68	1.70	1.24	1.69	1.49
MeLi, Et_2O, −78°C	1	2.00	1.91	1.54	2.64	1.88
Me_2Zn, Et_2O, 20°C	1	1.32	1.99	2.36	1.81	1.65
Me_3Al, toluene, 20°C	1	1.87	2.87	2.49	3.10	4.21
Me_2CuLi, Et_2O, −78°C	1	1.70	1.90	n.c.	2.65	1.95

Reaction products



X = H (**1**); Ph (**2**); OMe (**3**); CO_2 Me (**4**); Cl (**5**); Br (**6**)

In all the above mentioned reaction conditions we obtained, besides methylcarbinol **1**′, methylcarbinols (**2**–**6**)′ that derived from axial attack of the alkylation agents, and (**2**–**6**)″ derived from equatorial attack.

Alcohols derived from 5-X-adamantan-2-ones (**2**–**6**) were separated from each other by HPLC, individually characterized (MS, IR, NMR) and compared to those already known.[15,18]

The assignment of the stereochemistry of the methylcarbinols is founded on the fact that the axial hydroxyl diastereoisomers exhibit the ^{13}C quaternary carbinol carbon signal at higher fields compared to the equatorial diastereomer.[19] In the experimental section we report all spectroscopic data lacking in the literature (MS, IR, ^1H NMR).

Stereochemistry. Relative axial and equatorial reactivities

For each set of reaction conditions we determined the stereochemistry of alkylation reactions by GLC. Table 1 collects the stereochemical outcome of several reactions (five experiments at least for each substrate in all reaction conditions).

We performed competitive reaction sets on equimolecular mixtures of compounds **1**, **4**, **5**; **1**, **2**, **6** and **1**, **3**.

As a consequence of peaks overlapping in the GLC analysis it was not possible to perform competition experiments in which all the six compounds **1**, **2**, **3**, **4**, **5** and **6** were present at the same time. The relative reaction rates were obtained by GLC determination of the reaction yields. They were calculated by assuming that all reactions are first order in ketone and the same order in alkylation agent for all ketones. We measured the areas of starting materials and products; each area was divided[20] by the corresponding molecular weight and the obtained values were used for calculating the yields of each competing reaction. Although yields varied from run to run, the material balance (i.e. the sum of starting and final products) was always greater than 90% of the starting material. We used only data from reactions with yields ranging from 10 to 90% to compute the relative rates. Competitive kinetic experiments provided highly reproducible results largely independent of the concentration of the reactants.

Competitive reactions were also performed on equimolecular mixtures of compounds **1**, **7**; **4**, **8** and **5**, **9**.[21]

Table 2. Overall ratio of rates and relative rates for 5-X-adamantan-2-ones

Reaction conditions	Overall ratio of rates	Relative rates											
	$k_1/k_2/k_3/k_4/k_5/k_6$	k_{ax}						k_{eq}					
		1	2	3	4	5	6	1	2	3	4	5	6
MeMgI Et_2O	1/1.44/2.10/1.39/3.97/2.71	1	1.64	2.65	1.79	4.96	3.15	1	1.25	1.55	0.98	2.98	2.27
MeMgCl THF	1/1.46/1.58/1.59/2.42/2.67	1	1.71	2.06	1.97	3.28	3.32	1	1.22	1.10	1.22	1.57	2.02
MeMgI C_{6H6}	1/1.64/2.16/1.83/2.80/4.12	1	1.78	2.72	2.20	3.50	4.41	1	1.50	1.59	1.45	2.10	3.84
MeLi Et_2O 0°C	1/1.28/1.31/1.39/2.10/1.73	1	1.61	1.65	1.54	2.64	2.07	1	0.96	0.97	1.24	1.56	1.39
MeLi Et_2O −78°C	1/1.49/1.45/1.43/2.10/2.37	1	1.99	1.91	1.74	3.10	3.10	1	0.99	1.00	1.13	1.17	1.65
Me_2Zn Et_2O	1/0.50/0.33/0.17/0.14/0.16	1	0.57	0.44	0.24	0.21	0.17	1	0.43	0.22	0.10	0.11	0.11
Me_3Al toluene	1/0.88/0.79/0.87/0.93/0.83	1	1.15	1.17	1.24	1.50	1.26	1	0.61	0.41	0.50	0.36	0.40
Me_2CuLi Et_2O −78°C	1/1.00/1.01/n.c./1.00/1.00	1	1.26	1.32	n.c.	1.45	1.32	1	0.74	0.70	n.c.	0.55	0.68

Table 3. Relative rates (k_{ax} and k_{eq}) of 5-X-adamantan-2-ones and *trans*-10-X-decal-2-ones

Reaction conditions	Relative rates											
	$k_{ax(adam.)}$			$k_{ax(dec.)}$			$k_{eq(adam.)}$			$k_{eq(dec.)}$		
	1	4	5	7	8	9	1	4	5	7	8	9
MeMgI Et_2O	1	1.79	4.96	4.28	9.70	56.50	1	0.98	2.98	9.72	9.70	78.48
MeMgCl THF	1	1.97	3.28	2.87	18.88	37.68	1	1.22	1.57	5.13	38.54	73.87
MeMgI C_6H_6	1	2.20	3.50	21.14	7.19	32.38	1	1.45	2.10	52.90	7.41	34.82
MeLi Et_2O 0°C	1	1.54	2.64	0.61	6.00	3.35	1	1.24	1.56	1.39	2.34	0.86
MeLi Et_2O −78°C	1	1.74	3.10	1.39	6.10	3.02	1	1.13	1.17	4.62	2.51	1.25

The experimental data are collected in Tables 2 and 3 as a mean of at least five separate experiments. Relative rates k_{ax} and k_{eq} were computed taking the overall rate of compound **1** ($k_{ax}=k_{eq}=1$) as two.

Discussion

For the results obtained in the adamantanone series, the values in Table 1 show a similar trend[22] for all the examined reaction conditions, that is an increase of the k_{ax}/k_{eq} ratio with the increasing electronegativity of substituents. However, as stated in the introduction, our present experiments also provide evidence of the fact that the stereochemical results are far from being the entire story: an exact insight to what happens on the two sides of the ketonic group can be inferred only from kinetic data. As a matter of fact (Table 2, reaction conditions (1) to (5)) we find increasing rates (with a slight prevalence for k_{ax}) on increasing the substituent's electronegativity, both for k_{ax} and k_{eq}: in this case the reagent behaves as a nucleophile on both sides of the molecule. From a plot (see Fig. 1[23]) of k_{rel} vs. the substituent electronegativity, as expressed by their σ_I,[24] the fastest reaction (k_{ax}) is also the most sensitive one towards the effect of substituent.

The origin of the positive slope of the stereochemical bias (Table 1) found for reaction condition (6) is due, instead (see k_{rel} in Table 2), to an uneven decrease of both k_{ax} and k_{eq} which is in agreement with an electrophilic behaviour of the reagent on both sides of the molecule. This means that in the reaction's transition state the bond O…Metal is more developed than the C–C bond. Again the axial attack is the fastest but less sensitive towards substituents.

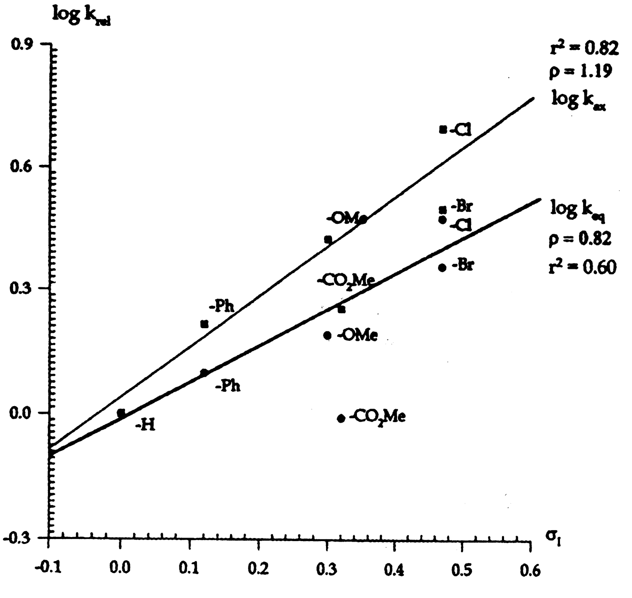


Figure 1. Plot of log k_{rel} vs. Taft's σ_I's (MeMgI in Et_2O).

Finally, reaction conditions (7) and (8) show a divergent change of the attack to the carbonyl function: increasing rate for the axial attack and decreasing rate for the equatorial.

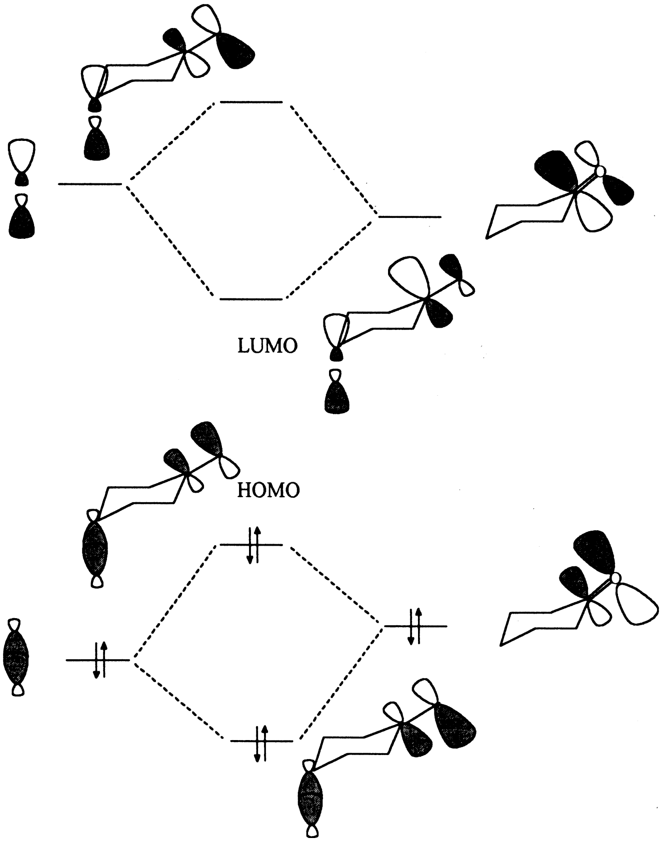
To use Cieplak's words the results in lines 7 and 8 of Table 2 represent a new 'paradoxical kinetic divergence' to be added to those he already listed.[1] As a matter of fact the first paradox is not the private communication of Ref. 59 in Cieplak's review: two of them (see Ref. 139 and 142 in that review) came earlier from our group.

For the competition experiments performed between the compounds of the adamantanone series, and those of the decalone series (see Table 3) we can see that, for the substituents being the same but with different conformation:

(a) k_{ax} and k_{eq} are always much more greater in the decalone series in reactions with Grignard reagents. Reactions with MeLi show a much less definite pattern.
(b) Electronegative equatorial substituents (adamantanone series) always produces an increase of both k_{ax}, and k_{eq}. The electronegative axial substituent (decalone series), however, always produces increases of k_{ax} and changes in k_{eq} which depend on reactant and solvent: Table 3 shows an increase of k_{eq} (decalone series) in lines 1 and 2, and a decrease in lines 3, 4 and 5.
(c) In all reaction conditions $k_{ax}>k_{eq}$ either when they increase, decrease or diverge.

How do data in the present paper fit into the current theories of π-face diastereoselection? As a matter of fact the sole theory which explicitly refers to substituents in the 4 position in a cyclohexanone system is Houk's theory.[25] It predicts that because of dipole–dipole repulsion an axial substituent should retard the equatorial attack; but the values in lines 1 and 2 (k_{eq} in the decalone series) in Table 3 do not fit Houk's theory.

Klein[26] suggested that hyperconjugation of the carbonyl π system and the ring β-CC bonds produces non-equivalent distribution of π-electron density. This interaction causes the HOMO orbital to be more extended on the equatorial side of the CO bond whereas the LUMO orbital is more



Scheme 1.

extended on axial face. Klein MO considerations can be easily extended to substituents in the 4 position: that is, equatorial C_4–X bond and β-CC bonds beeing antiperiplanar, sum their hyperconjugative effects both in the HOMO and the LUMO of the CO bond. On the contrary an axial C_4–X should distort both the HOMO and the LUMO orbitals towards the axial face (see Scheme 1).

Thus the LUMO carbonyl orbital is more extended on the axial face both under the influence of β-CC bond hyperconjugation and C_4–X bonds 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 will be determined by the identity of the X group.[27] As far as we know, there is no way, as yet, to compute such MO distortion.

The above considerations have the same weak points as the Klein theory, which discusses reactivity in terms of ground state properties. Doing so it is impossible to explain, for instance, the kinetic divergences of Table 3, k_{eq} (decalones' series), between lines 1 and 2 on one side, and lines 3, 4 and 5 on the other.

Surely MO theories will be necessary to construct a transition state theory taking into account changes in reactant, solvent molecularity and so on, but—we agree with Cieplak's view—a TS theory is precisely what is needed. Such a lacuna is a legacy of having discussed π-face diastereoselection in terms of k_{eq}/k_{ax} changes instead of k_{eq} and k_{ax} changes.

The data for compound **4** (X=–CO_2Me) which deviate from linearity deserve some mention: k_{ax} and k_{eq} values are sometimes lower, sometimes higher than those expected on the basis of their tabulated σ_I values. The reliability and reproducibility of the experimental points obtained for compound **4** (in Table 2) are the same as for all other points in all reaction conditions. The ester group is often responsible for such anomalous behaviour: Kwart postulates anchimeric assistance by this functional group both in nucleophilic[28] and electrophilic[29] reactions. We could in some cases explain our anomalous data as due to differences in the order of reaction[8,10], whereas, in other cases,[12] we were not able to find a suitable explanation. As a matter of fact in the present case, the variations of k_1/k_4 ratios by varying the concentrations of the added reactant (0.1, 0.05 and 0.01 N, respectively) were not significant.

Conclusion

Alkylation reaction rates of axial and equatorial attack (k_{ax} and k_{eq}) were determined on 5-X-adamantan-2-ones and *trans*-10-X-decal-2-ones.

1. Kinetic data show that k_{ax}/k_{eq} measurements hardly indicate what is happening on the two sides of a stereogenic centre: the two faces of the molecule can behave independently from one another.

2. Axial reactivities behave monotonically, i.e. they always increase with increasing electronegativity of the X group. Instead k_{eq} changes depend on the conformation of the X group and on reaction conditions.

Simple theories such as those based on dipole–dipole interactions are unable to explain such a behaviour, nor can theories based on ground state MO calculations.

Experimental

Mps were taken on a Buchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 (FTIR) apparatus. ^{1}H NMR spectra were recorded on a VARIAN XL-300, GEMINI 200, BRUKER AC 300 P and on a BRUKER AMX 400 spectrometer. MS spectra were recorded on a GC-MS HP 5970 Chemstation Mass Selective Detector connected with a HP 5890 gas chromatograph and on a HP G1800A GCD System gas chromatograph. The relative intensities of the peaks (in parentheses) are referred to the most intense one taken as 100%. HRMS were performed on a Bruker Spectrospin APEX TM 47e FT-IRC instrument. HPLC separations were carried out on a VARIAN 9001 apparatus connected with a VARIAN RI-4 differential refractometer using a Microporasil 30 cm, 7.9 mm i.d. Waters column. GLC analyses were carried out on a Carlo Erba HRGC Mega Series 5300 apparatus using a 30 m, 0.25 mm i.d. fused silica capillary column (stationary phase O.V.1), He flow=0.5 ml/min. We report, in sequence, the elution order of compounds from each mixture and the most suitable temperature conditions (in parentheses T_{oven}, $T_{inj}=T_{det}$) of respectively: **1**, **1**′ (160, 230°); **2**, **2**′, **2**″ (220, 230°); **3**, **3**′, **3**″ (160, 230°); **4**, **4**′, **4**″ (170, 230°); **5**, **5**′, **5**″ (170, 230°); **6**, **6**′, **6**″ (160, 230°); **7**, **7**′, **7**″ (150, 230°); **8**, **8**′, **8**″ (170, 230°); **9**, **9**′, **9**″ (170, 230°).

Starting materials

2-Adamantanone is commercially available (Aldrich) and was used as such. Published procedures were used for the preparation of 5-phenyl-adamantan-2-one **2**,[30] 5-methoxy-adamantan-2-one **3**,[31] 5-carbomethoxy-adamantan-2-one **4**,[32] 5-chloro-adamantan-2-one **5** and 5-bromo-adamantan-2-one **6**,[33] *trans*-decal-2one **7**,[34] *trans*-10-carbethoxy-decal-2-one **8**[35] and *trans*-10-chloro-decal-2-one **9**.[11]

Preparation of reagents

Et_2O and C_6H_6 solutions of MeMgI were prepared by known methods,[7] diluted to the desired concentration and kept under dry N_2. Just before use, they were titrated by sampling the supernatant clear soln. through a rubber septum. Me_2Zn in Et_2O was prepared according to literature procedures.[36] For MeLi/Me_2CuLi in Et_2O we used the in situ technique of Donald and Still.[37] Commercial solns. of MeMgCl in THF (Aldrich), MeLi in Et_2O (Fluka) and Me_3Al in toluene (Aldrich) were titrated and diluted to the desired concentration just before use.

Reactions

All the reactions were carried out under a pure dry nitrogen atmosphere and the glassware was carefully flamed and flushed with dry nitrogen before use. Typically: a 0.2 ml of standard Et_2O solution of MeMgI (2 M, 0.4 mmol) was added via a syringe into a flask containing either 15 mg (0.1 mmol) of compound **1** in 3 ml of anhydrous Et_2O, or the equimolecular amounts of compounds **2**, **3**, **4**, **5** or **6** (with *n*-esadecane as internal standard). Reactions lasted 2–3 min. After this time, the reaction mixtures were cooled (ice bath), slowly hydrolyzed with NH_4Cl satd aq. and extracted three times with Et_2O. The ethereal solns washed with water were combined, dried over Na_2SO_4, filtered and evaporated. Analyses of reaction mixtures by GLC were carried out as described. Reactions of benzene soln of MeMgI, THF soln of MeMgCl, ethereal soln. of MeLi, Me_2CuLi Me_2Zn and toluene soln of Me_3Al were carried out in a similar fashion. Reactions with dimethylzinc lasted longer (≅30 min.)

Competition experiments

Three flasks (10 or 100 ml) were equipped with magnetic stirrer and connected by means of a three-point star-rotating receiver to a graduated burette, gas inlet and $CaCl_2$ tube. The apparatus was carefully dried by flaming it under a nitrogen flow. Each flask contained an equimolecular mixture of **1** and **3** (or **1**, **4**, **5**; **1**, **2**, **6**; **1**, **7**; **4**, **8**; **5**, **9** depending on the chosen partner for that particular experiment) (0.2 or, respectively, 0.3 mmol in all) dissolved in 2 or 3 ml of anhydrous solvent (C_6H_6, toluene, Et_2O or THF). The graduated burette was filled via a syringe with the suitable, conveniently diluted, reactant, and the stoichiometric amount of it was added to the substrates mixtures under vigorous stirring. Reaction mixtures were then hydrolysed and worked up as described and examined by GLC in order to measure the relative areas of products and starting materials. The same procedure was used for competitive experiments on compounds **1** and **4** with more diluted concentration of the added alkylation agent.

Reaction products

Compound **1**′ is well known. Also compounds (**2**–**6**)′ and (**2**–**6**)″ are already known but as epimeric mixture. Literature data concern ^{1}H NMR[15] for **2**′+**2**″ and ^{13}C NMR[18] for (**2**–**6**)′ and (**2**–**6**)″ as epimeric mixture. We performed Grignard reactions on compounds (**2**–**6**) using the standard procedure. After working up, the obtained mixtures were separated into their components by HPLC: the purity of each compound was tested by GLC. Our ^{13}C NMR spectra on single epimers coincide with those described.[18] Besides spectroscopic data lacking in the literature, the most suitable HPLC solvent composition and the elution order of compounds from each mixture, we report ^{1}H NMR for compounds **2**′ and **2**″ since they differ[15] in the CH_3 signal.

Purification by HPLC (CH_2Cl_2/EtOAc 80/20), gave, in the order, **2**″ and **2**′.

2′: White solid, plates, mp 89–91°C; HRMS: found 242.1673. $C_{17}H_{22}O$ requires 242.1671; ν_{max} ($CHCl_3$) 2910, 2860, 1445, 1140, 1095, 1052, 930, 910 cm^{-1}; δ (200 MHz $CDCl_3$) 7.35–7.15 (5H, m), 2.3–1.5 (14H, m), 1.4 (3H, s, CH_3); *m*/*z* 243 (M^{+1}, 5), 242 (M^+, 28), 228 (15), 227 (100), 224 (20), 155 (41), 115 (22), 91 (55), 43 (41%).

2″: White solid, needles, mp 104–105°C; HRMS: found 242.1670. $C_{17}H_{22}O$ requires 242.1671; ν_{max} ($CHCl_3$) 2920, 2865, 1470, 1445, 1140, 1090, 1055, 1030, 930 cm^{-1}; δ (200 MHz $CDCl_3$) 7.4–7.1 (5H, m), 2.5–1.6 (14H, m), 1.38 (3H, s, CH_3); *m*/*z* 243 (M^{+1}, 9), 242 (M^+, 45), 228 (17), 227 (100), 224 (31), 167 (20), 155 (54), 129 (18), 115 (20), 106 (18), 91 (62), 77 (24), 43 (51%).

Purification by HPLC (Hexane/EtOAc 40/70) gave, in the order, starting material **3**+**3′** and **3″**. A subsequent separation (CH_2Cl_2/EtOAc 60/40) gave pure **3′**.

3′: Viscous colourless liquid; HRMS: found 196.1465. $C_{12}H_{20}O_2$ requires 196.1463; ν_{max} ($CHCl_3$) 2940, 2910, 2865, 1456, 1375, 1350, 1180, 1135, 1110, 1050, 1035, 935, 890 cm^{-1}; δ (200 MHz $CDCl_3$) 3.16 (3H, s, OCH_3), 2.10–1.32 (14H m), 1.32 (3H, s, CH_3); *m*/*z* 197 (M^{+1}, 2) 196 (M^+, 14), 124 (18), 111 (100), 110 (21), 109 (78), 43 (47%).

3″: Viscous colourless liquid; HRMS: found 196.1463. $C_{12}H_{20}O_2$ requires 196.1463; ν_{max} ($CHCl_3$) 2930, 2865, 2825, 1455, 1360, 1140, 1110, 1090, 1050, 930 cm^{-1}; δ (400 MHz, $CDCl_3$) 3.20 (3H, s, OCH_3), 2.26–1.40 (14H m,) 1.30 (3H, s, CH_3); *m*/*z* 197 (M^{+1}, 3) 196 (M^+, 21), 123 (24), 111 (88), 110 (22), 109 (100), 91 (16), 79 (17), 43 (51%).

Purification by HPLC (CH_2Cl_2/EtOAc 80/20), gave, in the order, **4′** and **4″**.

4′: Viscous colourless liquid; HRMS: found 224.1414. $C_{13}H_{20}O_3$ requires 224.1412; ν_{max} ($CHCl_3$) 2930, 2895, 2850, 1735, 1725, 1455, 1380, 1315, 1245, 1175, 1130, 1096s, 1070, 920 cm^{-1}; δ (300 MHz $CDCl_3$) 3.63 (3H, s, OCH_3), 2.19–1.45 (14H, m), 1.34 (3H, s, CH_3); *m*/*z* 224 (M^+, 0.3) 210 (14), 209 (100), 91 (17), 79 (19), 43 (31%).

4″: White solid, needles mp 68–70°C; HRMS: found 224.1415. $C_{13}H_{20}O_3$ requires 224.1412; ν_{max} ($CHCl_3$) 2990, 2930, 2865, 1735, 1720, 1460, 1335, 1140, 1100, 1030, 930 cm^{-1}; δ (200 MHz $CDCl_3$) 3.62 (3H, s, OCH_3), 2.42–1.58 (14H, m), 1.34 (3H, s, CH_3); *m*/*z* 224 (M^+, 0.3) 210 (14), 209 (100), 91 (16), 79 (19), 43 (34%).

Purification by HPLC (CH_2Cl_2/EtOAc 80/20) gave, in the order, **5″** and **5′**.

5′: White solid, needles mp 78–80°C; HRMS: found 200.0968. $C_{11}H_{17}ClO$ requires 200.0968; ν_{max} ($CHCl_3$) 2954, 2920, 2860, 1455, 1345, 1130, 1095, 1055, 1015, 930 cm^{-1}; δ (200 MHz $CDCl_3$) 2.31–1.44 (14H, m), 1.39 (3H, s, CH_3); *m*/*z* 187 (M^{+2}, 33), 186 (M^{+1}, 12), 185 (M^+, 100), 91 (17), 79 (22), 43 (37%).

5″: White solid, plates mp 95–97°C; HRMS: found 200.0970. $C_{11}H_{17}ClO$ requires 200.0968; ν_{max} ($CHCl_3$) 2930, 1460, 1345, 1140, 1090, 1050, 920 cm^{-1}; δ (300 MHz $CDCl_3$): 2.02–1.50 (14H, m), 1.27 (3H, s, CH_3); *m*/*z* 187 (M^{+2}, 31) 186 (M^{+1}, 12), 185 (M^+, 100), 91 (17), 79 (21), 43 (45%).

Purification by HPLC (CH_2Cl_2/EtOAc 80/20) gave, in the order, **6″** and **6′**.

6′: Viscous colourless liquid; HRMS: found 244.0461. $C_{11}H_{17}BrO$ requires 244.0463; ν_{max} ($CHCl_3$) 2950, 2913, 1454, 1343, 1140, 1095, 1030, 930 cm^{-1}; δ (400 MHz $CDCl_3$) 2.47–1.45 (14H, m), 1.35 (3H, s, CH_3); *m*/*z* 244 (M^+, 0.01) 231 (5), 166 (12), 165 (100), 147 (51), 105 (24), 91 (23), 79 (23), 43 (39%).

6″: White solid, needles mp 93–94°C; HRMS: found 244.0465. $C_{11}H_{17}BrO$ requires 244.0463; ν_{max} ($CHCl_3$) 2930, 2870, 1455, 1140, 1095, 1050, 1030, 920 cm^{-1}; δ (200 MHz $CDCl_3$) 2.89–1.71 (14H, m), 1.29 (3H, s, CH_3); *m*/*z* 244 (M^+, 0.01) 231 (2), 166 (12), 165 (100), 147 (16), 109 (20), 105 (14), 91 (13), 79 (15), 43 (34%).

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20. Preliminary experiments showed that GLC responses of compounds (**1**–**6**) on the one hand and the methylcarbinol, (**1**–**6**)′ and (**2**–**6**)″ on the other were very close to each other. Thus no correction was introduced.

21. See Refs. 10 and 13 for stereochemical ratios k_{ax}/k_{eq} of compounds **7**, **8** and **9**.

22. The observed scattering of some points will be discussed later.

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