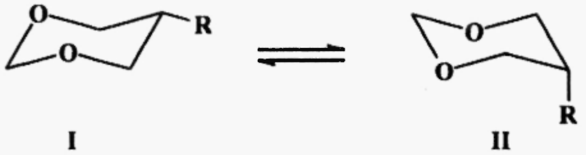
NEW 2,4,6-SUBSTITUTED 1,3-DIOXANES: SYNTHESIS, STEREOCHEMISTRY AND THERMODYNAMIC DATA DETERMINATIONS BY *CIS-TRANS* ISOMERS EQUILIBRIUM

Mircla Balog[a,b], Yvan Ramondenc[b], Ioan Oprean[a], Ion Grosu*[a] and Gerard Plé[b]
[a]"Babes-Bolyai" University, Organic Chemistry Department and CSOFSTM, 11 Arany Janos str., 400028, Cluj-Napoca, Romania
[b]Université de Rouen, IRCOF, UMR 6014, Faculte des Sciences, 76821 Mont Saint-Aignan, Cedex, France.

Abstract: The thermodynamic data (A-values) for some substituents located at position 2 of the 1,3-dioxane ring are calculated from the ratio (measured by GC-MS and NMR) of *cis* and *trans* isomers of some 2,4,6-substituted-1,3-dioxanes obtained by the condensation reaction of *meso* 2,4-pentanediol with several aldehydes and ketones. The stereochemistry of these compounds is deduced from high-field NMR experiments.

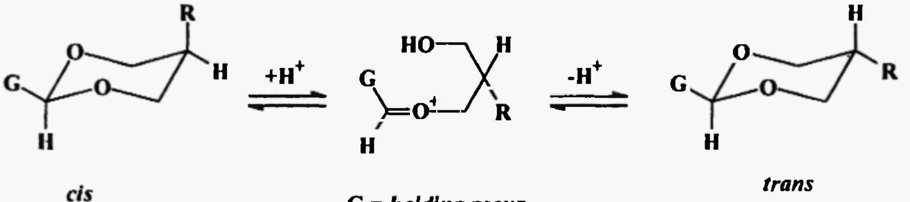
Introduction

The free conformational enthalpy of a substituent located at a six-membered ring (*e.g.* 1,3-dioxane, Scheme-1) is defined as the difference between the free enthalpy of the conformer exhibiting the substituent in axial orientation and the free enthalpy of the conformer showing the same substituent in equatorial position ($A_R = \Delta G^o = G^o_{II} - G^o_I$, Scheme-1).[1] The free conformational enthalpy of a substituent (R) is denoted with A_R and it exhibits a positive value if the substituent prefers the equatorial orientation. Negative A-values are characteristic for the substituents displaying a preference for the axial position. The A-values are calculated using the relations $A = \Delta G^o = -RT\ln K$; $K = n_{II} / n_I$ (n_{II} and n_I are the populations of conformers I and II, Scheme-1).



Scheme-1

The A values for many substituents of the 1,3-dioxane ring were determined using the equilibrium between *cis* and *trans* isomers.[2-6] The investigated compounds exhibit a substituent with high A-value ("holding group") which strongly prefers the equatorial orientation (G, Scheme-2) and another substituent (R; the investigated one) which can occupy alternatively the equatorial and axial orientations generating *cis* and *trans* isomers (*e.g.* the 2,5-substituted-1,3-dioxane derivative of Scheme-2).



G = *holding group*
R = investigated substituent

Scheme-2

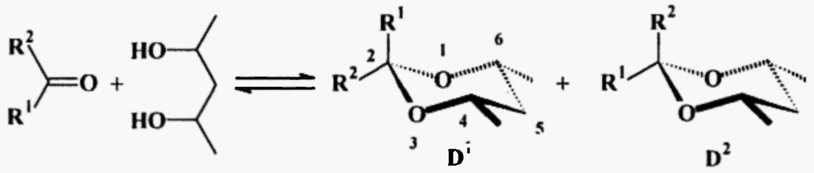
Cis and *trans* isomers are separated and after that, starting from a single isomer, they are equilibrated (usually by the opening and the closure of the ring under acidic conditions) and the ratio of *cis* and *trans* isomers at equilibrium is measured by different methods. It is assumed that the ratio of *cis* and *trans* isomers of the disubstituted 1,3-dioxane (Scheme-2) is equal with the ratio of conformers II and I of the monosubstituted 1,3-dioxane of scheme-1. In these conditions the determination of the ratio of *cis* and *trans* isomers of the disubstituted 1,3-dioxane makes possible the calculation of A-value for R group at position 5 of the 1,3-dioxane ring (in the given example).

The synthesis of many 1,3-dioxane derivatives is performed by the acetalisation reaction of different 1,3-diols and the corresponding aldehydes or ketones, using PTSA (*para*-toluene sulfonic acid) or other acids as catalyst. This procedure involves the chemical equilibrium which is generally shifted toward the acetals by removing the water formed during the reaction. If the target compounds exhibit *cis* and *trans* isomers, during the synthesis the equilibrium is established between the possible configurational diastereoiosmers, too. The ratio between these isomers, as they resulted from the synthesis, can be used for the calculation of the A-values for different substituents. As a conclusion, if the ratio between the *cis* and *trans* isomers in crude products is measured with satisfactory precision by NMR spectra or/and by GC-MS the A-values can be determined without the separation of diastereoisomers and their separate equilibration.

We considered of interest to determine the axial or equatorial preference of some unsaturated groups and of some substituted methyl groups in new 1,3-dioxane derivatives and to determine thermodynamic values using the ratios of possible *cis* and *trans* isomers (measured in the crude products).

Results and Discussions

A series of 2,4,6-substituted-1,3-dioxane derivatives was obtained by the acetalization reaction of *meso*-2,4-pentanediol (2R4S) with several aldehydes and ketones (Scheme-3).

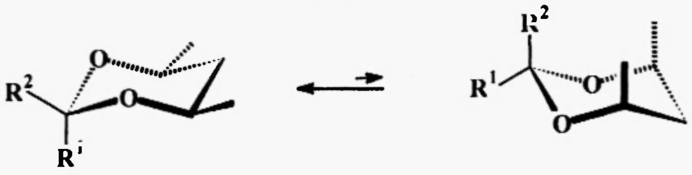


$R^1 = H; R^2 = -CH=CH-CH_3$ **1**
$R^1 = H; R^2 = -CH=CH-C_6H_5$ **2**
$R^1 = CH_3; R^2 = CH_2CH_3$ **3**
$R^1 = CH_3; R^2 = CH_2C_6H_5$ **4**
$R^1 = CH_3; R^2 = CH_2OCH_3$ **5**
$R^1 = CH_3; R^2 = CH_2Cl$ **6**
$R^1 = CH_3; R^2 = CH_2COOC_2H_5$ **7**
$R^1 = C_2H_5; R^2 = C_6H_5$ **8**

Scheme-3

In D^1 the methyl groups (positions 4 and 6) exhibit *cis* orientation [referred to the group of highest precedence located at position 2 (R^2)], while in D^2 these methyl groups show *trans* orientation.

Compounds **1**-**8** exhibit anancomeric structures. The methyl groups at positions 4 and 6 are efficient "holding groups" (A_{Me} = 12.3 kJ/mol)[7,8] and the conformation displaying both of these methyl groups in equatorial orientation is highly preferred. The other possible conformations (*e.g.* for D^1, Scheme-4) resulted by the flipping of the 1,3-dioxane ring exhibit the methyl groups at positions 4 and 6 in axial orientation and are not stable due to the important 1,3-*syn*-axial interactions between the methyl groups at positions 4 and 6 themselves and because of their 1,3-*syn*-axial interactions with the axial substituent at position 2.



Scheme-4

In order to establish the stereochemistry and the chromatographic identity of the derivatives **1**-**8** the mixtures of diastereoisomers were purified by distillation or by crystallization and then investigated by NMR and by GC-MS. The NMR spectra discriminate the two diastereoisomers (Table-1). The protons of the axial substituent at position 2 are more deshielded than the homomorphic protons of the similar substituent in equatorial orientation. The assignments of the signals were supported by the results of NOEDiff spectra. As for other 1,3-dioxane derivatives[9-12] the irradiation of the signal belonging to the protons of the axial group at C^2

produces a strong influence on the signal pertaining to the axial protons at positions 4 and 6, while the irradiation of the signal of the protons of the same group in equatorial orientation determines a weak influence, both on the signal of the axial protons at C^4, C^6 and on the signal of the equatorial methyl groups at the same positions.

Table-1: NMR data (selected) for compounds **1-8**.

Compound	2-H_a	2-H_e	2-CH_{3a}	2-CH_{3e}	2-CH_{2a}-	2-CH_{2e}-
1	4.92	5.28	-	-	-	-
2	5.16	-	-	-	-	-
3	-	-	1.33	1.28	1.81	1.58
4	-	-	1.17	1.08	3.05	2.79
5	-	-	1.44	1.33	3.60	3.31
6	-	-	1.49	1.44	3.74	3.44
7	-	-	1.54	1.48	2.84	2.59
8	-	-	-	-	-	1.63

The ratios between the two diastereoisomers (Table-2) were estimated using the specific signals in ^{1}H NMR spectra (Table-1) and were precisely determined by GC-MS on separated and crude products (these results were very close).

Table-2: Thermodynamic data for compounds **1-8**

Compound	R^1	R^2	D^2 %	D^1 %	$K = D^2/D^1$	ΔG° Kj/mol*
1	H	-HC=CH-CH_3	7.0	93.0	0.075	7.5
2	H	$\text{-HC=CH-C}_6\text{H}_5$	3.8	96.2	0.039	9.4
3	CH_3	C_2H_5	39.2	60.8	0.64	1.3
4	CH_3	$CH_2\text{-}C_6H_5$	46.0	54.0	0.85	0.5
5	CH_3	$CH_2\text{-}OCH_3$	53.1	46.9	1.13	-0.4
6	CH_3	$CH_2\text{-}Cl$	54.8	45.2	1.21	-0.6
7	CH_3	$CH_2\text{-}COOC_2H_5$	62.0	38.0	1.63	-1.4
8	C_2H_5	C_6H_5	96.3	3.7	26.02	-9.5

A precision of 0.1 % in the determination of the ratio of diastereoisomers is considered. ΔG° values are calculated with a precision of ± 0.2 kJ/mol

The conformational energy calculations (*i.e.* A-values) showed high equatorial preference for crotonyl and cynamyl groups. The equatorial preference of these groups is lower than for alkyl and aryl groups (*e.g.* A_{Me} = 16.6 kj/mol[13] and A_{Ph} = 13.0 kj/mol[13]). The substituted methyl groups (CH_2-X) exhibit a conformational energy close to that of the methyl group.

The non-polar groups, as compared with methyl group, somewhat prefer the equatorial orientation (ΔG° = 0.5-1.3 kJ/mol) while the polar CH_2X groups exhibit a slight preference for the axial orientation (in the competition with methyl group; ΔG° = -0.4 - -1.4 kJ/mol). Ethyl group exhibits a considerably higher equatorial preference than phenyl group.

The value of the equatorial preference of ethyl group *vs.* phenyl group for compound **8** is similar with the equatorial preference of the methyl over the phenyl group (ΔG° = -10.11 Kj/mol).[14]. The equatorial preference of the ethyl group over the methyl group at position 2 of the 1,3-dioxane ring was already determined (by other methods) and our result (ΔG°= 1.3 kj/mol) agrees with the reported data (ΔG° = 1.21-1.71 kJ/mol).[14-16]

For compound **4**, D^1 isomer was separated by flash chromatography and was submitted to the chemical equilibration under acidic conditions. The equilibrium between the diastereoisomers was reached after 12 h (GC-MS control) and the ratio of isomers (D^2/D^1 = 0.88) was similar to that obtained during the synthesis of 4 by the acetalization reaction.

Conclusions

The stereochemistry of new 1,3-dioxane derivatives obtained by the acetalization of *meso*-2,4-pentanediol was investigated by NMR. The ratio of *cis* and *trans* isomers obtained in the crude product were measured by GC-MS. The equatorial preference of unsaturated groups (crotonyl and cinamyl) located at position 2 of the 1,3-dioxane ring was demonstrated. Non-polar CH_2X groups ($X = CH_3$, C_6H_5) exhibit a higher equatorial preference than methyl or phenyl groups, while polar CH_2X groups (X = Cl, OCH_3, $COOC_2H_5$) at position 2 of 1,3-dioxane, compared with methyl group, show a slight conformational preference for the axial orientation.

Experimental

^{1}H and ^{13}C NMR spectra were recorded using $CDCl_3$ as solvent, in 5 mm tubes, on a Bruker 300 or Bruker AM 400 NMR spectrometer. The GC-MS study was performed on a Hewlett-Packard 6890 GC coupled with an Autospec mass spectrometer (Micromass, Manchester) of EBE geometry and OPUS 3.1. acquisition system. The resolution of diastereoisomers was performed on Optima-5MS (30 m, 0.25 mm ID, 0.25 µm, Macherey Nagel) column. The samples (0.5 µl) were injected at 60°C under a He flow of 0.8 ml/minute. This temperature was kept for one minute and was followed by a heating program of 10 °C / minute till 180 °C. The EI mass spectra of resolved diastereoisomers were recorded at 70 eV at the sourse temperature of 250 °C. Melting points were measured with a Kleinfeld APOTEC apparatus and are uncorrected. Elemental analyses were obtained at the University of Rouen. Their results agreed favorably with the calculated values. Thin-layer chromatography was performed on Merck 60F 254 silicagel. Merck silicagel (40-63 µm) was used for flash chromatography.

Compounds **1**, **2** and **4-8** are new, while the synthesis of **3** was already mentioned in the literature.[16]

Compounds 1-8 (*General Procedure*)

Stoechiometric amounts of 1,3-diol (0.1 mol), of aldehyde or ketone (0.1 mol) and catalytic amounts of (0.1 g) of *p*-toluenesulfonic acid (PTSA) were dissolved in 200 cm^3 benzene. The mixture was relluxed and reaction H_2O was removed by a Dean-Stark trap. When the H_2O was separated, after cooling at room temperature, PTSA was neutralised (under stirring 0.5 h) with (2 g) sodium acetate. The reaction mixture was washed twice with 100 cm^3 H_2O. After drying with Na_2SO_4, the solvent was removed and the compounds were purified by crystallisation from ethanol or by vacuum distillation. Before purification samples of crude product were collected for GC-MS analysis.

4,6-Dimethyl-2-(1-propenyl)-1,3-dioxane 1

Mixture of diastereoisomers. D_1: *cis*-4,*cis*-6-dimethyl-*r*-2-(1-propenyl)-1,3-dioxane; D_2: *trans*-4,*trans*-6-dimethyl-*r*-2-(1-propenyl)-1,3-dioxane. Yield: 69 %; colorless oil; b.p. = 40-41 ^{0}C /1 mmHg. Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32; Found: C, 69.35; H, 10.44. ^{1}H NMR (300 MHz, $CDCl_3$): δ (overlapped signals for D_1 and D_2) = 1.22 (d, *J* = 6.4 Hz, 6H, 4-CH_3, 6-CH_3), 1.25 [q (overlapped dt), *J* = 13.1 Hz, 1H, 5-H_{ax}], 1.50 (dt, *J* = 13.1 Hz, *J* = 2,3 Hz, 1H, 5-H_{eq}), 1.70 (d, *J* = 6.7 Hz, 3H, 2-CH=CH-C$\underline{H}_3$), 3.75 [doublet of sextets (overlapped ddq), *J* = 13.1, 6.4, 2.3 Hz, 2H, 4-H_{ax}, 6-H_{ax}], 4.92 [(D_1): d, *J* = 5.6 Hz, 1H, 2-H_{ax}], 5.28 [(D_2): d, *J* = 5.6 Hz, 1H, 2-H_{eq}], 5.56 (ddd, *J* = 15.5, 5.6, 1.5 Hz, 1H, 2-C$\underline{H}$=CH-CH_3), 5.90 ppm (dq, *J* = 15.5, 6.4 Hz, 1H, 2-CH=C$\underline{H}$-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ (overlapped signals for D_1 and D_2) = 17.96 (2-CH=CH-$\underline{C}H_3$), 21.94 (4-CH_3, 6-CH_3), 40.57 (5-C), 72.65 (4-C, 6-C), 100.81 (2-C), 128.87 (2-CH=$\underline{C}$H-CH_3), 130.68 ppm (2-$\underline{C}$H=CH-CH_3). GC-MS (EI, 70 eV) *m/z* (rel. int.): [D_1 (r. t. = 5.05 min., 93%); D_2, (r. t. = 4.77 min., 7%)]: 141 (M^+-15, 9), 87 (4), 71 (100), 55 (20).

4,6-Dimethyl-2-(2-phenylethylene-1-yl)-1,3-dioxane 2

Mixture of diastereoisomers D_1: *cis*-4,*cis*-6-dimethyl-*r*-2-(2-phenylethylene-1-yl)-1,3-dioxane; D_2: *trans*-4,*trans*-6-dimethyl-*r*-2-(2-phenylethylene-1-yl)-1,3-dioxane. Yield: 80 %; colorless oil; b.p. = 125-128 ^{0}C /1 mmHg. Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; Found: C, 76.88; H, 8.51. ^{1}H NMR (300 MHz, $CDCl_3$): δ (overlapped signals for D_1 and D_2) = 1.27 (d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3), 1.35 [q (overlapped dt), *J* = 13.2, 1H, 5-H_{ax}], 1.56 (dt, *J* = 13.2, 2.6 Hz, 1H, 5-H_{eq}), 3.84 [doublet of sextets (overlapped ddq), *J* = 13.2, 6.0, 2.6 Hz, 2H, 4-H_{ax}, 6-H_{ax}], 5.16 (d, *J* = 4.9 Hz, 1H, 2-H), 6.22 (dd, J = 16.2, 4.9 Hz, 1H, 2-C$\underline{H}$=CH-C_6H_5), 6.77 (d, *J* = 16.2 Hz, 1H, 2-CH=C$\underline{H}$-C_6H_5), 7.20-7.41 ppm (aromatic protons, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (overlapped signals for D_1 and D_2) = 22.02 (4-CH_3, 6-CH_3), 40.73 (5-C), 73.08 (4-C, 6-C), 100.76 (2-C), 126.24 (2-$\underline{C}$H=CH-C_6H_5), 127.29, 128.44, 128.84 (tertiary aromatic carbon atoms), 133.83 (2-CH=$\underline{C}$H-C_6H_5), 136.57 ppm (quaternary aromatic carbon atom). GC-MS (EI, 70 eV) *m/z* (rel. int.): [D_1 (r.t. = 14.25 min., 96.2%); D_2, (r. t. = 16.03 min., 3.8%)]: 218 (M^+, 17), 131 (31), 115 (17), 104 (100), 91 (6), 77 (62), 69 (44), 63 (14), 51 (41).

***2-Benzyl-2,4,6-trimethyl-1,3-dioxane* 4**
Mixture of diastereoisomers D_1: *r*-2-benzyl-2,*cis*-4,*cis*-6-trimethyl-1,3-dioxane; D_2: *r*-2-benzyl-2,*trans*-4,*trans*-6-trimethyl-1,3-dioxane. Yield: 71 %; colorless oil; b.p. = 130 – 133 ^{0}C /1 mmHg. Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; Found: C, 76.19; H, 9.02. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 [(D_1): d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3], 1.18 [(D_2) : s, 3H, 2-CH_3], 1.22 [(D_2) : d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3], 1.27 [(D_1) : s, 3H, 2-CH_3], 1.05-1.24 [(D_1, D_2) : overlapped signals, 1H, 5-H_{ax}], 1.47 [(D_1) : dt, *J* = 12.0, 2.2 Hz, 1H, 5-H_{eq}], 1.58 [(D_2) : (dt, *J* = 12.0, 2.2 Hz, 1H, 5-H_{eq}], 2.89 [(D_1) : s, 2H, 2-$C\underline{H}_2$-C_6H_5], 3.16 [(D_2) : s, 2H, 2-$C\underline{H}_2$-C_6H_5], 3.93 [(D_1) : doublet of sextets (overlapped ddq), *J* = 12.0, 6.0, 2.2 Hz, 2H, 4-H_{ax}, 6-H_{ax}], 4.23 [(D_2) : doublet of sextets (overlapped ddq), *J* = 12.0, 6.0, 2.2 Hz, 2H, 4-H_{ax}, 6-H_{ax}], 7.14-7.36 ppm [(D_1, D_2) : aromatic protons, 5H]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.10 [(D_1) : 2-CH_3], 22.50 [(D_2) : 4-CH_3, 6-CH_3], 22.57 [(D_1) : 4-CH_3, 6-CH_3], 27.85 [(D_2) : 2-CH_3], 38.34 [(D_2) : 2-CH_2-C_6H_5], 40.44 [(D_2) : 5-C], 41.02 [(D_1) : 5-C], 49.71 [(D_1) : 2-$\underline{C}H_2$-C_6H_5], 65.37 [(D_1) : 4-C, 6-C], 65.58 [(D_2) : 4-C, 6-C], 99.86 [(D_1) : 2-C], 100.62 [(D_2) : 2-C], 126.51, 127.99, 131.32 [(D_1) : tertiary aromatic carbon atoms], 126.63, 128.57, 130.25 [(D_2) : tertiary aromatic carbon atoms), 137.62 ppm [(D_1) : quaternary aromatic carbon atom], 138.18 [(D_2) : quaternary aromatic carbon atom]. GC-MS (EI, 70 eV) *m/z* (rel. int.): D_1 (r. t. = 12.18 min., 54.0 %); 205 (M$^+$-15, 8), 129 (100), 87 (30), 135 (9), 119 (5), 69 (98).D_2, (r. t. = 12.46 min., 46.0 %)]: 205 (M$^+$-15, 0.4), 129 (100), 87 (30), 135 (6), 119 (0.6), 69 (84).

D_1 (rf = 0.6 ; elution system: cyclohexane/ether = 6/1) : Colorless crystals ; m.p. 41-42 ^{0}C.

***2-Methoxymethyl-2,4,6-trimethyl-1,3-dioxane* 5**
Mixture of diastereoisomers D_1: *r*-2-methoxymethyl-2,*cis*-4,*cis*-6-trimethyl-1,3-dioxane; D_2: *r*-2-methoxymethyl-2,*trans*-4,*trans*-6-trimethyl-1,3-dioxane. Yield: 74 %; colorless oil; b.p. = 85 - 86 ^{0}C /2 mmHg. Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41; Found: C, 62.09; H, 10.52. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 [(D_2): d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3], 1.16 [(D_1): d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3], 1.10-1.20 [(D_1, D_2): overlapped signals, 1H, 5-H_{ax}], 1.37 [(D_1): s, 3H, 2-CH_3], 1.44 [(D_2): s, 3H, 2-CH_3], 1.49 [(D_1, D_2): dt, *J* = 13.1, 2.4 Hz, 1H, 5-H_{eq}], 3.31 [(D_2): s, 2H, 2-$C\underline{H}_2OCH_3$], 3.37 [(D_1): s, 3H, 2-CH_2OCH_3], 3.39 [(D_2): s, 3H, 2-$CH_2OC\underline{H}_3$], 3.61 [(D_1): s, 2H, 2-$C\underline{H}_2OCH_3$], 3.94-4.04 ppm [(D_1, D_2): overlapped signals, 2H, 4-H_{ax}, 6-H_{ax}]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.36 [(D_2): 2-CH_3], 22.31 [(D_2): 4-CH_3, 6-CH_3], 22.45 [(D_1): 4-CH_3, 6-CH_3], 26.52 [(D_1): 2-CH_3], 40.27 [(D_1): 5-C], 41.03 [(D_2): 5-C], 59.48 [(D_1): 2-$CH_2O\underline{C}H_3$], 59.83 [(D_2): 2-$CH_2O\underline{C}H_3$], 65.14 [(D_1): 4-C, 6-C], 65.77 [(D_2): 4-C, 6-C], 70.45 [(D_1): 2-$\underline{C}H_2OCH_3$], 80.12 [(D_2): 2-$\underline{C}H_2OCH_3$], 98.71 [(D_1): 2-C], 99.01 ppm [(D_2): 2-C]. GC-MS (EI, 70 eV) *m/z* (rel. int.): D_1 (r. t. = 5.31 min., 46.9 %); D_2, (r. t. = 5.26 min., 53.1 %): 159 (M$^+$-15, 4), 129 (M$^+$-45, 27), 87 (31), 69 (100), 58 (25).

2-Chloromethyl-2,4,6-trimethyl-1,3-dioxane 6
Mixture of diastereoisomers D_1: *r*-2-chloromethyl-2,*cis*-4,*cis*-6-trimethyl-1,3-dioxane; D_2: *r*-2-chloromethyl-2,*trans*-4,*trans*-6-trimethyl-1,3-dioxane. Yield: 79 %; colorless oil; b.p. = 93 - 94 ^{0}C / 2 mmHg; Anal. Calcd. for $C_8H_{15}ClO_2$: C, 53.78; H, 8.46; Cl, 19.84; Found: C, 53.97; H, 8.36; Cl, 20.02. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09-1.24 [(D_1, D_2): overlapped signals, 1H, 5-H_{ax}], 1.15, [(D_1): d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3], 1.17 [(D_2): d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3], 1.44 [(D_2): s, 3H, 2-CH_3], 1.49 [(D_1): s, 3H, 2-CH_3], 1.501 [(D_2): dt, *J* = 13.1, 2.6 Hz, 1H, 5-H_{eq}], 1.513 [(D_1): dt, *J* = 13.1, 2.6 Hz, 1H, 5-H_{eq}], 3.44 [(D_1): s, 2H, 2-CH_2Cl], 3.74 [(D_2): s, 2H, 2-CH_2Cl], 3.90 [(D_2): doublet of sextets (overlapped ddq), *J* = 13.1, 6.0, 2.6 Hz, 2H, 4-H_{ax}, 6-H_{ax}], 3.98 ppm [(D_1): doublet of sextets (overlapped ddq), *J* = 13.1, 6.0, 2.6 Hz, 2H, 4-H_{ax}, 6-H_{ax}]. ^{13}C NMR (75 MHz, $CDCl_3$): δ (overlapped signals for D_1 and D_2) = 17.31 [(D_2): 2-CH_3], 22.37 [(D_2): 4-CH_3, 6-CH_3], 22.43 [(D_1): 4-CH_3, 6-CH_3], 26.80 [(D_1): 2-CH_3], 39.99 [(D_1): 5-C], 40.81 [(D_1): 5-C], 42.94 [(D_2): 2-CH_2Cl], 52.02 [(D_1): 2-CH_2Cl], 66.08 [(D_2): 4-C, 6-C], 66.17 [(D_1): 4-C, 6-C], 98.63 [(D_2): 2-C), 98.79 ppm [(D_1): 2-C]. GC-MS (EI, 70 eV) *m/z* (rel. int.): D_1 (r. t. = 7.21 min., 45.2 %) 163 (M$^+$-15, 45), 129 (31), 121 (9), 87 (16), 93 (12), 77 (19), 69 (100);.D_2, (r. t. = 7.03 min., 54.8 %): 163 (M$^+$-15, 0.2), 129 (97), 121 (0.8), 87 (30), 93 (11), 77 (1), 69 (100).

***2-Ethyloxycarbonylmethyl-2,4,6-trimethyl-1,3-dioxane* 7**
Mixture of diastereoisomers D_1. *r*-2-ethyloxycarbonylmethyl-2,*cis*-4,*cis*-6-trimethyl-1,3-dioxane; D_2: *r*-2-ethyloxycarbonylmethyl-2,*trans*-4,*trans*-6-trimethyl-1,3-dioxane. Yield: 76 %; colorless oil; b.p. = 82 - 84 ^{0}C / 0.4 mmHg; Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32; Found: C, 61.21; H, 9.44. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08-1.15 [(D_1, D_2): overlapped signals, 1H, 5-H_{ax}], 1.10 [(D_1): d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3], 1.13 [(D_2): d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3], 1.22 [(D_1): t, *J* = 7.2 Hz, 3H, 2-CH_2-$COOCH_2CH_3$], 1.23 [(D_2): t, *J* = 7.2 Hz, 3H, 2-CH_2-$COOCH_2C\underline{H}_3$], 1.45 [(D_1): dt, *J* = 12.0, 2.6 Hz, 1H, 5-H_{eq}], 1.49 [(D_2): dt, *J* = 12.0, 2.6 Hz, 1H, 5-H_{eq}], 1.49 [(D_2): s, 3H, 2-CH_3], 1.54 [(D_1): s, 3H, 2-CH_3], 2.60 [(D_1): s, 2H, 2-$C\underline{H}_2$-$COOCH_2CH_3$], 2.85 [(D_2): s, 2H, 2-$C\underline{H}_2$-$COOCH_2CH_3$], 3.95 [(D_1): doublet of sextets, *J* = 12.0, 6.0, 2.6 Hz, 2H, 4-H_{ax}, 6-H_{ax}], 4.04 [(D_2): doublet of sextets, *J* = 12.0, 6.0, 2.6 Hz, 2H, 4-H_{ax}, 6-H_{ax}], 4.111 [(D_2): q, *J* = 7.2 Hz, 2H, 2-CH_2-$COOC\underline{H}_2CH_3$], 4.113 ppm [(D_1): q, *J* = 7.2 Hz, 2H, 2-CH_2-$COOC\underline{H}_2CH_3$].^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.36 [(D_2): 2-CH_2-$COOCH_2CH_3$], 14.42 [(D_1): 2-CH_2-$COOCH_2CH_3$], 18.62 [(D_1): 2-CH_3], 22.08 [(D_2): 4-CH_3,

6-CH_3], 22.18 [(D_1): 4-CH_3, 6-CH_3], 28.55 [(D_2): 2-CH_3], 38.67 [(D_2): 2-CH_2-$COOCH_2CH_3$], 39.99 [(D_2): 5-C], 40.51 [(D_1): 5-C], 48.35 [(D_1): 2-$\underline{C}H_2$-$COOCH_2CH_3$], 60.16 [(D_1): 2-CH_2-$COO\underline{C}H_2CH_3$], 60.49 [(D_2): 2-CH_2-$COO\underline{C}H_2CH_3$], 65.20 [(D_1): 4-C, 6-C], 65.69 [(D_2): 4-C, 6-C], 98.20 [(D_1): 2-C], 98.24 [(D_2): 2-C], 169.57 [(D_1): 2-CH_2-$\underline{C}OOCH_2CH_3$], 169.79 ppm [(D_2): 2-CH_2-$\underline{C}OOCH_2CH_3$]. GC-MS (EI, 70 eV) *m/z* (rel. int.): D_1 (r. t. = 10.21 min., 38 %) 201 (M^+-15, 55), 129 (37), 87 (17), 131 (23), 115 (48), 69 (100);.D_2, (r. t. = 10.01 min., 62 %): 201 (M^+-15, 0.8), 129 (100), 87 (24), 131 (17), 115 (3), 69 (68).

***2-Ethyl-4,6-dimethyl-r-2-phenyl-1,3-dioxane* 8**

Mixture of diastereoisomers D_1: 2-ethyl-*cis*-4,*cis*-6-dimethyl-*r*-2-phenyl-1,3-dioxane; D_2: 2-ethyl-*trans*-4,*trans*-6-dimethyl-r-2-phenyl-1,3-dioxane. Yield: 65 %; colorless oil; b.p. = 128-130 ^{0}C / 1 mmHg; Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; Found: C, 76.50; H, 9.09. ^{1}H NMR (300 MHz, $CDCl_3$,): δ (overlapped signals for D_1 and D_2) = 0.70 (t, *J* = 7.5 Hz, 3H, 2-$CH_2C\underline{H}_3$), 1.10 (d, *J* = 6.0 Hz, 6H, 4-CH_3, 6-CH_3), 1.13 [q (overlapped dt), *J* = 12.8 Hz, 1H, 5-H_{ax}], 1.21 [(D_1) : (t, *J* = 7.5 Hz, 3H, 2-CH_2CH_3], 1.23 (dt, *J* = 12.8, 2.6 Hz, 1H, 5-H_{eq}), 1.63 [(D_2) : q, *J* = 7.5 Hz, 2H, 2-$C\underline{H}_2CH_3$], 2.89 [(D_1) : q, *J* = 7.5 Hz, 2H, 2-$C\underline{H}_2CH_3$], 3.64 [doublet of sextets (overlapped ddq), *J* = 12.8, 6.0, 2,6 Hz, 2H, 4-H_{ax}, 6-H_{ax}], 7.10-7.40 ppm (aromatic protons, 5H).^{13}C NMR (75 MHz, $CDCl_3$): δ (overlapped signals for D_1 and D_2) = 7.85 (2-$CH_2\underline{C}H_3$), 22.18 (4-CH_3, 6-CH_3), 38.28 (2-CH_2CH_3) 40.71 (5-C), 66.66 (4-C, 6-C), 103.00 (2-C), 127.70, 127.80, 128.72 (tertiary aromatic carbon atoms), 141.94 ppm (quaternary aromatic carbon atom). GC-MS (EI, 70 eV) *m/z* (rel. int.): D_1 (r.t. = 9.37 min., 3.7 %); D_2, (r.t. = 10.18 min., 96.3 %): 191 (M^+-29, 34), 143 (M^+-77, 13), 123 (7), 105 (100), 77 (49), 69 (54), 57 (39).

References

1. E. L. Eliel, S. H. Wilen, M. P Doyle, *Basic Organic Stereochemistry*, Wiley & Sons, New York, p 442 (2001).
2. M. J. O. Anteunis, D. Tavernier, F. Borremans, *Heterocycles* **4**, 293 (1976).
3. F. G. Riddell, *The Conformational Analysis of Heterocyclic Compounds*, Academic Press, London, p 72 (1980).
4. E. Kleinpeter, *Advances in Heterocyclic Chemistry* 69, 217 (1998).
5. E. L. Eliel, S. H. Wilen, N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, p 696 (1994).
6. M. J. O. Anteunis, M. Coryn, *Bull. Soc. Chim. Belges* **82**, 413 (1973).
7. E. L. Eliel, M. C. Knoeber *J. Am. Chem. Soc.* **90**, 3444 (1968).
8. I. Grosu, S. Mager, G. Plé, R. Martinez, L. Muntean and E. Mesaros, *Heterocycles* **41**, 2233 (1995).
9. I. Grosu, G. Ple and S. Mager, *Tetrahedron* **51**, 2659 (1995).
10. I. Grosu, G. Plé, S. Mager, E. Mesaros, A. Dulau and C. Gego, *Tetrahedron* **54**, 2905 (1998).
11. I. Grosu, L. Muntean, L. Toupet, G. Plé, M. Pop, M. Balog, S. Mager and E. Bogdan, *Monatsh Chem* **133**: 631 (2002).
12. F.W. Nader and E. L Eliel *J. Am. Chem. Soc.* **92**, 3050 (1970).
13. W. F Bailey and E. L. Eliel *J. Am. Chem. Soc.* 96, 1798 (1974).
14. K. Pihlaja and P. Äyräs, *Suomen Kemistilehti* **43**, 41 (1970).
15. W. F. Bailey, H. Connon, E. L. Eliel and K. B. Wiberg *J. Am. Chem. Soc.* **100**, 2202 (1978).

Received on January 18, 2005