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Esters of 2,5-multisubstituted-1,3-dioxane-2-carboxylic acid: their conformational analysis and selective hydrolysis

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ABSTRACT

The carbomethoxy group at the C2 position of the 2,5-multisubstituted 1,3-dioxanes prefers the axial conformation rather than the equatorial one due to an anomeric effect. The trans isomers of the 5-monosubstituted compounds are more selectively hydrolyzed than the cis isomers. Based on the calculated results, hydrolysis to the trans isomers is attributed to the larger carbonyl charges of the trans than those of the cis isomers. The anomeric and homoanomeric effects will explain the axial preference of the carbomethoxy group and selective hydrolysis to the trans isomers. Furthermore, the calculated stability between the cis and trans isomers is in good agreement with the experimental results in the equilibrium state.

1. Introduction

Some 2,5-multisubstituted-1,3-dioxane derivatives have been identified to have significant biological activities or can be converted into active compounds; e.g., a bioactive natural product **I**[1] isolated from marine sources, a multivalent heterofunctional inhibitor-adaptor (**II**, BAIT),[2] a purine derivative **III**[3] having antitumorigenic activity, and **NS-220 (IV)**[4] having a novel peroxisome proliferator-activated receptor α agonist activity, as shown in Figure 1. Especially, the cis isomers often have a more efficient activity than the trans isomers. Nevertheless, there are few efficient synthetic methods to supply the desired cis compounds.

In our previous study,[5] we reported that the 2-carbomethoxy-1,3-dioxanes prefer the cis isomers rather than the trans isomers in an equilibrium state and indicated a rapid hydrolysis rate of the *trans* esters, as shown in Figure 2. For the 5-monosubstituted 5-methyl-2-carbomethoxy-1,3-dioxanes, the calculated results have shown that the cis isomers are more stable than the trans isomers and the axial conformation of the 2-carbomethoxy groups dominates all the other conformers, and the trans-axial conformers have the largest charge on the carbon of the carbonyl group in all conformers (Fig. 3). Furthermore, the combination of the cis preference in the equilibrium state after the 1,3-dioxane ring formations and selective hydrolysis of the trans isomers can give rise to the highly pure cis isomers. In this paper, we elucidate these characteristics of the 1,3-dioxane.

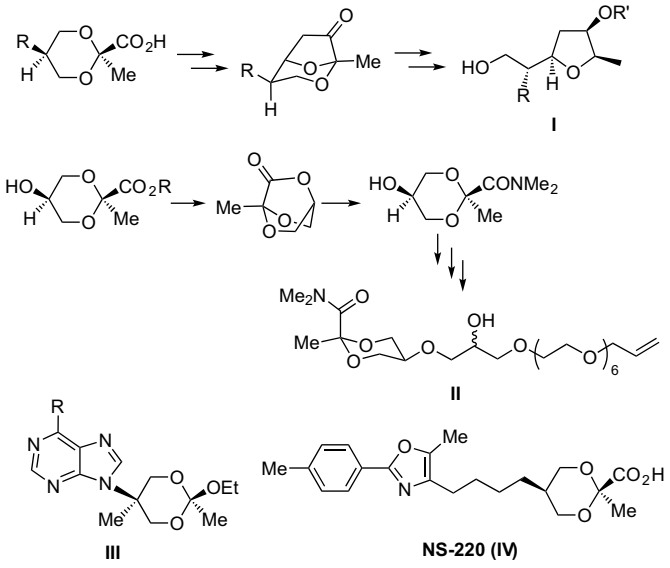

Figure 1.

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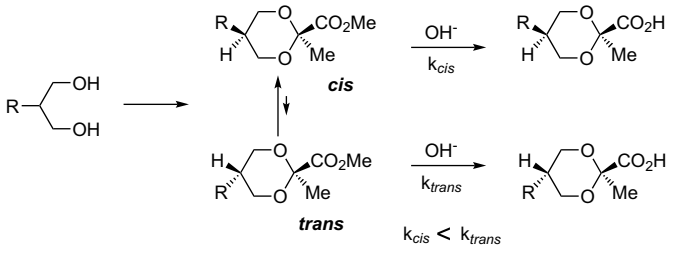


Figure 2.

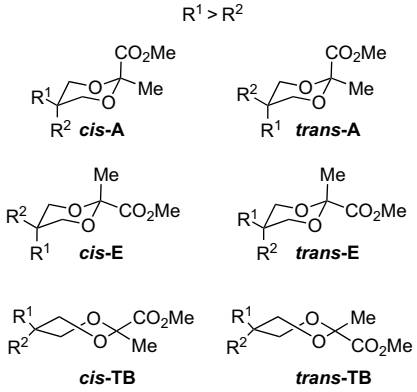


Figure 3.

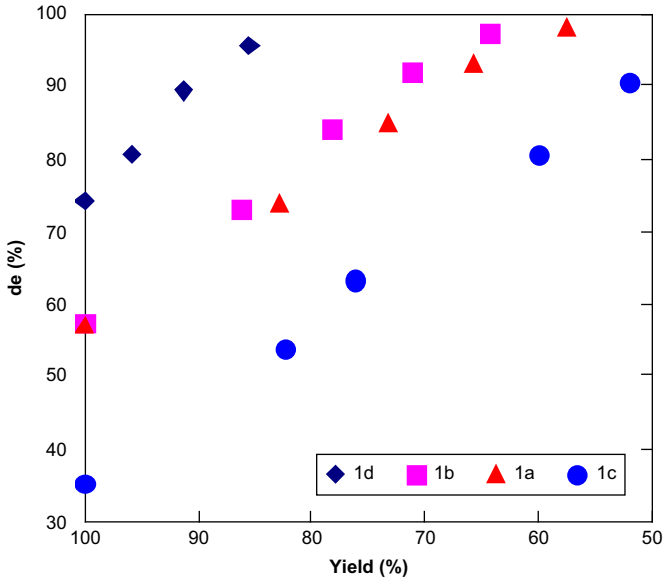


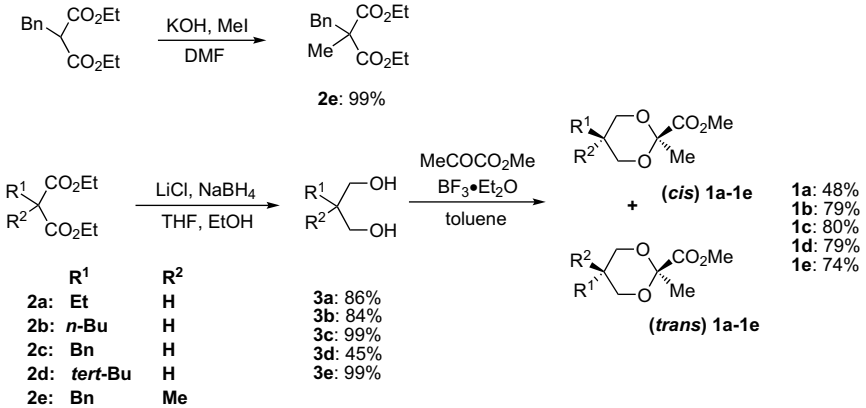
Figure 4. Diastereomeric excess (de) of the *cis* esters versus yield of the remaining esters after the hydrolysis of **1** by the treatment with aq NaOH in MeOH at 298 K [**1** (100 mg) in MeOH (1 mL)].

2. Results and discussion

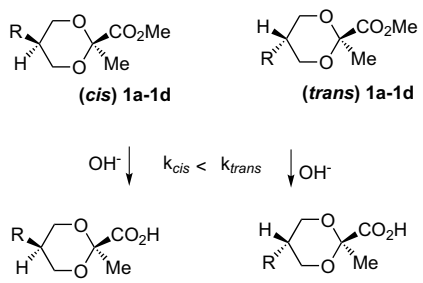
2.1. Synthesis and selective hydrolysis

Five kinds of 1,3-dioxane compounds **1a–e** were straightforwardly synthesized from diols **3a–e**, which were prepared by the reduction of the corresponding diethyl malonates **2a–e** with LiCl–$NaBH_4$. The malonate **2e** was obtained by methylation of 2-benzyl-malonate under basic conditions with KOH, while the other malonates **2a–d** were commercially obtained. The coupling reaction of diols **3a–e** with methyl pyruvate into the dioxanes **1a–e** proceeded in the presence of 1 equiv of $BF_3{\cdot}Et_2O$, as shown in Scheme 1. The dioxane formation reaction produced a 1/1 ratio of the cis/trans mixture at 15 °C and then the ratio reached equilibrium at 25 °C. The 5-monosubstituted dioxanes **1a–d** were found to be cis-preferential within the ratio of 2.1–6.8. On the other hand, the formation of the dioxane **1e** was reversely provided in trans-preference with a cis/trans ratio of 0.6. The cis and trans configurations together with conformations of the monosubstituted dioxanes **1a–d** were determined by the ^1H NMR spectral and NOE studies, as described in our previous paper.[5] The configuration of the 5-disubstituted dioxane **1e** was empirically determined by comparison of the δ value (ppm) with **1c** because of **1e** having no C5-proton. The *trans* **1e** was observed to have a higher δ value (ppm) of the methylene protons in the benzyl group similar to *trans* **1c**. An NOE study of the *trans* **1e** was also carried out to ensure the assignments of the trans configuration of **1e**. The axial position of the CO_2Me group was supported by the strong NOE between the C4,6-axial protons and methyl protons of the 2-CO_2Me group.

Moreover, the hydrolysis rates of the trans isomers **1a–d** were greater than those of cis isomers. In order to obtain highly pure cis isomers, 1,3-dioxanes **1a–d** prepared as a mixture of the cis/trans isomers were subjected to hydrolysis of the trans isomers to give the *cis* esters in over 90% diastereomeric excess (Fig. 4). The hydrolysis rate constants measured by pseudo-first-order kinetics revealed that the 5-monosubstituted trans series **1a–d** were more than six times more rapidly hydrolyzed than the cis series at 25 °C. (Scheme 2, Table 1). On the other hand, the disubstituted dioxane at the 5-position **1e** showed a poor selectivity.



Scheme 1.



Scheme 2.

Table 1
Pseudo-first-order rate constants, k_{trans} and k_{cis} for the hydrolysis reaction of **1a**–**1e**[a]

Dioxane	$k_{trans}\times10^{-2}$ (dm^3 mol^{-1} s^{-1})	$k_{cis}\times10^{-3}$ (dm^3 mol^{-1} s^{-1})	k_{trans}/k_{cis}
1a	6.26	5.26	11.9
1b	6.90	5.27	12.4
1c	3.84	5.90	6.5
1d	14.9	7.41	20.1

[a] Obtained by treatment with aq NaOH in MeOH at 298 K.

2.2. Relationship among stability, charges, and dipole moment

Based on the generation and optimization of the conformers for **1a**–**e**, the detailed results of the conformers are categorized as axial (A), equatorial (E), and twist-boat (TB) (see Fig. 3). As for the stability of both the *cis* and *trans* **1d**, Figure 5 shows that the COOMe group prefers the axial position rather than the equatorial and twist-boat ones. The population order of each conformer is *cis*-A>*trans*-A>*cis*-TB≈*trans*-E>*trans*-TB>*cis*-E (see Supplementary data). Figure 6 represents the most stable conformation of each isomer. The energy difference between the cis and trans isomers was 1.06 kcal mol^{-1}. Consequently the calculated ratio (cis/trans) of 6.0 was in good agreement with the experimental ratio (cis/trans) of 6.8. Similarly the calculated energy differences of **1a**, **1b**, **1c**, and **1e** led to the cis/trans ratios, which were also in good agreement with the experimental results (Table 2).

Next, the different hydrolysis rates were attributable to the charge difference of the carbonyl carbons between the cis and trans isomers. The relations between the calculated charges of the carbonyl carbon and distribution of each conformer are summarized in

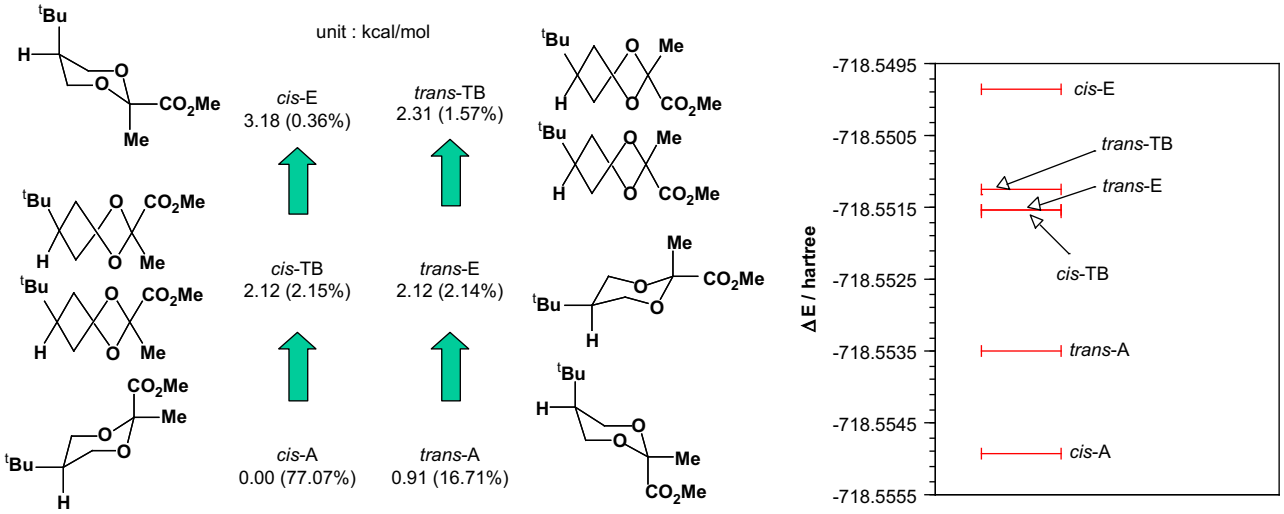


Figure 5. Results of stability for cis/trans isomers for the ^{t}Bu/H group (**1d**).

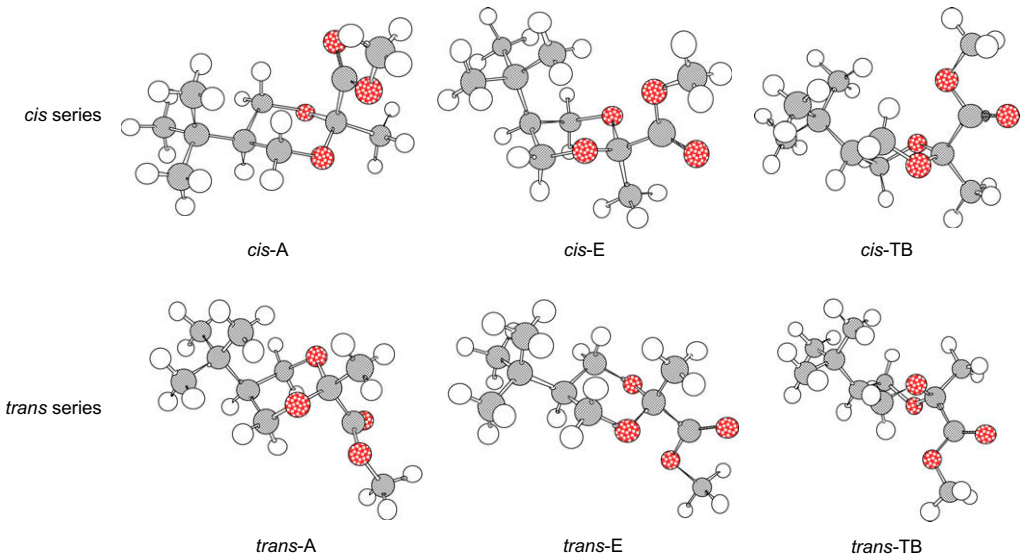


Figure 6. Most stable conformation of each isomer (**1d**).

Table 2
Observed and calculated results of cis/trans ratio of 1,3-dioxane derivatives **1**

Dioxane	R^1/R^2	Experimental ratio (cis/trans)	Calculated ratio (cis/trans)	$\Delta E_{Experiment}$ (kcal mol^{-1})	$\Delta E_{Calculation}$[a] (kcal mol^{-1})
1a	Et/H	3.7[b]	4.1	0.775	0.840
1b	Bu/H	3.7[b]	4.3	0.775	0.870
1c	Bn/H	2.1[b]	2.0	0.440	0.420
1d	^{t}Bu/H	6.8[c]	6.0	1.062	1.060
1e	Bn/Me	0.6[b]	0.6	0.340	0.280

[a] $\Delta E_{Calculation}=\Delta E_{trans}-\Delta E_{cis}$.
[b] Determined by GC.
[c] Determined by ^{1}H NMR.

Figure 7, where *trans*-E, *trans*-TB, *cis*-E, and *cis*-TB are neglected due to their low distribution. The 5-monosubstituted dioxanes **1a**–**d** are classified into two groups; the *trans*-A group and the *cis*-A group. The positive charges of the *trans*-A group are significantly larger than those of the *cis*-A group. These results strongly indicate that the *trans*-A group is more selectively hydrolyzed than the *cis*-A group because of the stronger electrostatic interaction to the hydroxyl ion. On the other hand, **1e**, having a poor hydrolysis selectivity, shows a smaller charge difference between the *trans*-A and *cis*-A. Generally, the hydroxyl ion cannot efficiently discriminate between *trans*-A and *cis*-A. That is the reason why the selective hydrolysis of 5-monosubstituted 1,3-dioxanes affects the differences in charges on the carbonyl carbons with the higher population of the dominant conformers.

The selective hydrolysis of the trans isomers in the 5-monosubstituted dioxanes **1a**–**1d** can be ascribed to the charge difference of the carbonyl carbon in spite of the fact that both isomers possess axial 2-COOMe groups as the dominant conformer. This difference in the charges causes environmental differences between the cis and trans isomers. Therefore, the distribution in the charges on other atoms was focused in detail. Table 3 shows the charges of some atoms and the differences of these charges between the cis and trans isomers. Apparently, the charge differences in some atoms such as O1, O3, C2 are comparatively larger between the cis and trans isomers like the carbonyl carbon (C=O) in the case of dioxanes **1a**–**d**. When compared to the trans forms, the O1, O3 atoms have larger negative charges and the differences of the C2 atoms are also larger in the cis forms. On the other hand, their charge differences in **1e** are relatively small. The charge differences of the carbonyl carbon between the cis and trans are linearly

Table 3
Weighted charges on some atoms

Dioxane		O1	O3	C2	C(C=O)	O(C=O)	O(OMe)	C5
1a	*cis*-A	−0.276	−0.280	0.205	0.843	−0.453	−0.352	0.305
	trans-A	−0.171	−0.174	−0.054	0.958	−0.469	−0.347	0.271
	Diff (*cis*–*trans*)	−0.105	−0.106	0.259	−0.116	0.016	−0.005	0.033
1b	*cis*-A	−0.292	−0.291	0.211	0.835	−0.453	−0.344	0.418
	trans-A	−0.165	−0.165	−0.078	0.960	−0.467	−0.342	0.302
	Diff (*cis*–*trans*)	−0.128	−0.125	0.289	−0.125	0.014	−0.002	0.117
1c	*cis*-A	−0.302	−0.296	0.221	0.836	−0.454	−0.347	0.459
	trans-A	−0.151	−0.147	−0.099	0.976	−0.469	−0.346	0.432
	Diff (*cis*–*trans*)	−0.151	−0.149	0.320	−0.140	0.015	−0.001	0.027
1d	*cis*-A	−0.271	−0.274	0.172	0.842	−0.452	−0.351	0.409
	trans-A	−0.156	−0.155	−0.116	0.977	−0.470	−0.340	0.134
	Diff (*cis*–*trans*)	−0.115	−0.119	0.288	−0.135	0.018	−0.011	0.275
1e	*cis*-A	−0.225	−0.219	0.006	0.918	−0.461	−0.334	0.677
	trans-A	−0.176	−0.179	−0.053	0.941	−0.464	−0.335	0.627
	Diff (*cis*–*trans*)	−0.048	−0.041	0.047	−0.023	0.003	0.001	0.050

correlated to both those of C2 and the average of the O1 and O3 between them, respectively (Fig. 8).

The calculated dipole moment shows that the *cis*-A group has a larger dipole moment than the *trans*-A group in **1a**–**d**, however, the difference between the dipole moment of the two isomers in **1e** was small (see Supplementary data). This trend is also observed in the carbonyl charge and stability. In Figure 9, there is a clear positive correlation between the differences in the dipole moment and the stability of the cis and trans isomers. The differences in the carbonyl charge are also related to that of the dipole moment in all dioxanes except for **1c** as shown in Figure 10.

2.3. Rationale for larger charge in trans isomers than in cis isomers

The charge differences in the carbonyl carbon between the cis and trans isomers could be interpreted in terms of the stereoelectronic effect in the 1,3-dioxanes. The C-2 position in the 1,3-dioxane derivatives is the α-position of the endocyclic oxygen of the 1,3-dioxane. This is well known to accept the anomeric effect,[6] which is stabilized by two interactions as depicted in Figure 11. (1)

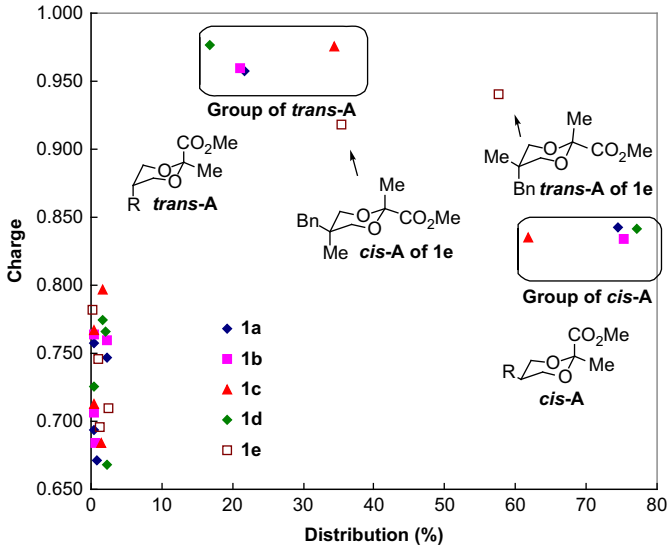


Figure 7.

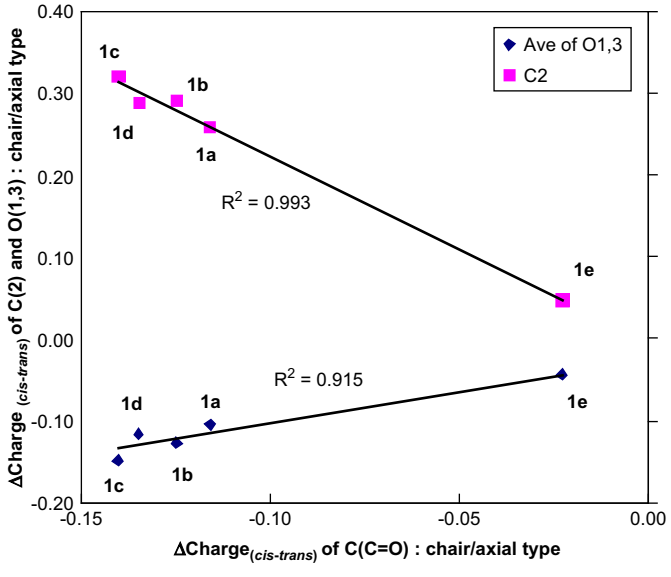


Figure 8.

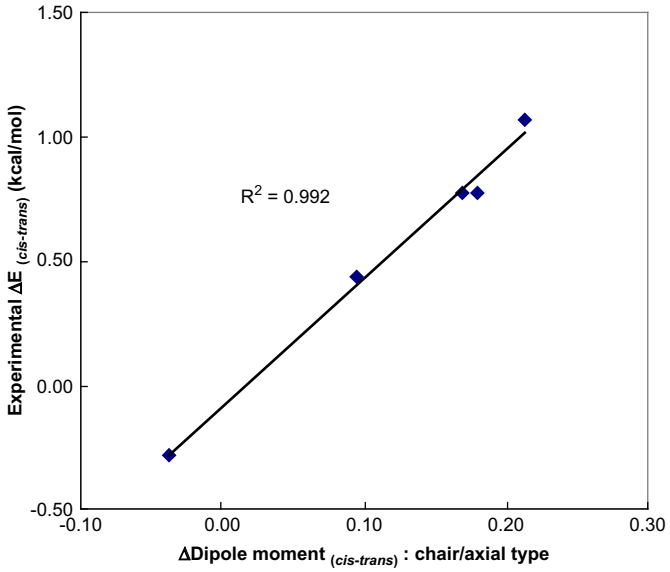


Figure 9. Relation of stability and dipole moment difference.

The dipole–dipole interaction; the dipole moment raised from the oxygen toward exocyclic direction is weakened by the opposite directed dipole moment from an electron-withdrawing substituent at the axial position. (2) The hyperconjugative interaction; delocalization of the lone pair on the 1,3-oxygens into the anti-periplanar (axial) adjacent polar bond (anti-bonding orbital); $n(O_{1,3})\rightarrow\alpha$–$\sigma^*(C_2\text{-Y})$ax. In the case of Y=COOMe, the anomeric effect is comparatively not so large. At the same time, the β-position of the endocyclic oxygen is reported to have another hyperconjugative interaction from the 1,3-oxygens, which is the homoanomeric effect; $n(O_{1,3})\rightarrow\beta$–$\sigma^*(C_5\text{-H})$eq.[7] This equatorial substituent of C-5 is known to be more affected from the pseudoaxial orbital of the 1,3-oxygen (Plough effect)[8] and the influence of the C-5 substituents is known to be slightly stronger in hydrogen than in the alkyl groups.[9]

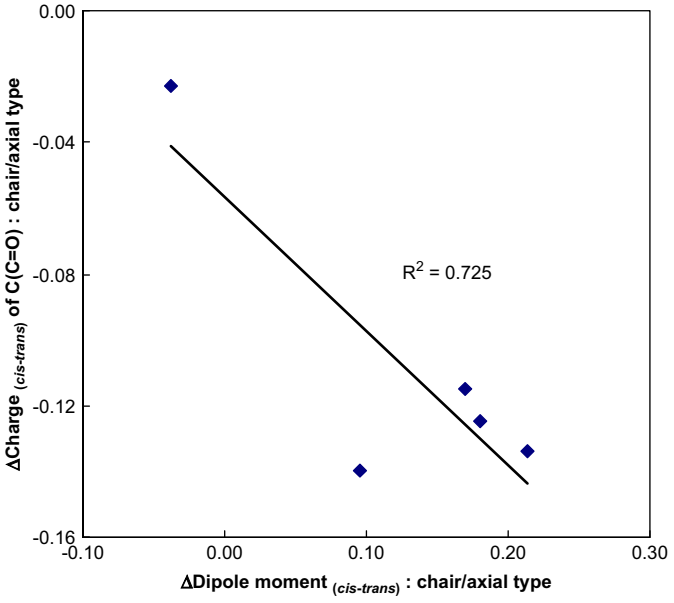


Figure 10. Relation of carbonyl charge and dipole moment difference.

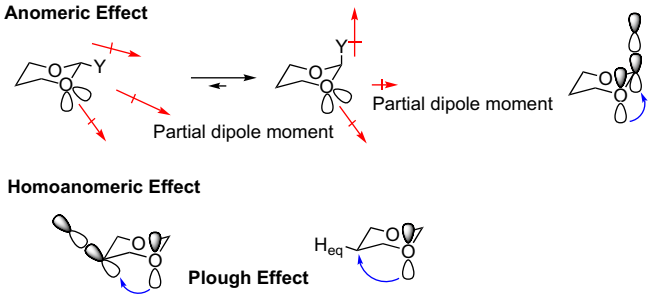


Figure 11. Anomeric effect and homoanomeric effect (the effect of O3 oxygen is not shown).

The trans isomers of the C-5 monosubstituted derivatives **1a–d** have larger positive carbonyl charges and smaller dipole moments and then are less stable than the corresponding cis isomers. These facts can be explained by the dipole–dipole interaction and two types of hyperconjugative interactions. The trans isomers of **1a–d** have equatorial C-5 protons, which tend to more efficiently delocalize the charges on the ring-oxygen by both the homoanomeric and anomeric effects than the cis isomers. In comparison to the calculated charges of the cis isomers, the trans isomers have smaller negative charges of O1, O3, and slightly negative charges of C2 in the 5-monosubstituted 1,3-dioxanes. The direction of the dipole moment from 1,3-oxygen atoms has a slight angle against the entirely opposite direction of the dipole moment generated by C-2 electron-withdrawing group due to 1,3-oxygen atoms having a pseudoequatorial orbital along with pseudoaxial orbital. Therefore, the generated dipole moments in the cis isomers are relatively larger than the trans isomer. On the other hand, in the case of the C-5 disubstituted **1e**, which is unlike **1a–d** in regard to the hydrolysis tendency, the differences of the charges on the carbonyl carbon, 1,3-oxygen, and C-2 carbon and also the dipole moment are apparently small (Fig. 12).

3. Conclusion

The 2,5-multisubstituted 1,3-dioxanes are formed with axial preference of the carbomethoxy group due to the anomeric effect, and the trans isomers of the 5-monosubstituted compounds are more easily hydrolyzed than the cis isomers. We tried to explain these phenomena and determined the following results. (1) The calculated stability of the cis/trans mixture in the equilibrium state is in good agreement with the experimental results. (2) From the calculated results, the larger positive carbonyl charges of the trans than those of the cis isomers cause hydrolysis to the trans isomers. (3) In addition, the differences in the charges of C2 and O1, O3 and the dipole moment as well as the carbonyl carbon charges are also well correlated in all the dioxanes. These can be explained by the combination of the anomeric and homoanomeric effects. The trans 5-monosubstituted derivatives with equatorial 5-protons are more affected by the homoanomeric effect than cis isomers. Work is now underway to expand the proposed theory to other 1,3-dioxane derivatives.

4. Experimental section

4.1. Calculation methods

To obtain the initial 3D molecular coordinates of **1**, CS Chem3D version 7.0 was used. All calculations were performed on a Linux PC-Cluster and Compaq Alpha XP1000 computers. All the conformational isomers of the dioxanes **1a–e** generated by CONFLEX 3.6/MM3 (92)[10] as conformational searching program were optimized by Gaussian 98 Rev.A.11.1[11] RHF/STO-3G.[12] The charges on the

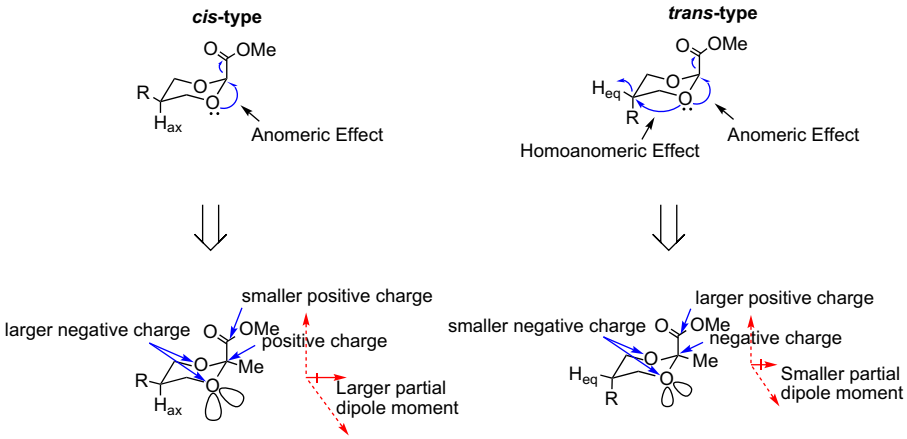


Figure 12. Relation between hyperconjugative and dipole–dipole interaction (the effect of O3 oxygen is not shown).

carbon in the carbonyl group were calculated using the electrostatic potential Mertz–Singh–Kollman method[13] in Gaussian 98 Rev.A.11.1[11] RHF/STO-3G.[12]

4.2. General

All reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined on a BUCHI 535 melting-point apparatus, and are uncorrected. Column chromatography was carried out on a silica gel column (Wako Wakogel® C-200). TLC was performed on Merck TLC aluminum sheets silica gel 60 F_{254}, and detection was carried out by UV quenching at 254 nm or spraying with phosphomolybdic acid. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) or a Varian Unity Plus 300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Varian Unity Plus 300 (75 MHz) spectrometer. Chemical shifts (δ) are given in parts per million from the internal standard, tetramethylsilane, chloroform or pyridine and coupling constants are given in hertz (Hz). Mass or high-resolution MS spectra were recorded on a JEOL JMS-700 mass spectrometer. IR spectra were measured with a Shimadzu FT IR-8200PC spectrometer. GC analysis was performed on an Agilent Technologies 6890 GC system.

4.3. Diethyl benzylmethylmalonate (2e)

To a solution of diethyl benzylmalonate (50.0 g, 0.20 mol) and iodomethane (34.0 g, 0.24 mol) in DMF (150 mL) was added KOH (powder, 85%, 15.8 g, 0.24 mol) at 10 °C during 20 min and the reaction mixture was stirred at 0–14 °C for 3 h. After addition of toluene (200 mL) and water (300 mL), the organic layer was separated and washed with water (100 mL) three times and 20% aq NaCl (100 mL), successively, and dried over $MgSO_4$. After removal of the solvent, 52.5 g (99%) of **2e** was obtained as a colorless oil. IR (neat) ν_{max} 3027, 2984, 1733, 1497, 1456, 1378, 1273, 1188, 1109, 1023, 863, 744, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, J=7.2 Hz, 6H), 1.34 (s, 3H), 3.23 (s, 2H), 4.19 (q, J=7.2 Hz, 4H), 7.09–7.14 (m, 2H), 7.22–7.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 19.7, 41.1, 54.8, 61.3, 126.9, 128.2, 130.2, 136.3, 172.0; HRMS (EI) calcd for $C_{15}H_{20}O_4$ (M^+) 264.1362, found 264.1355.

4.4. 2-Ethyl-1,3-propanediol (3a)

To a suspension of LiCl (4.5 g, 0.106 mol) and $NaBH_4$ (80.0 g, 2.13 mol) in THF (500 mL) and EtOH (500 mL) was added diethyl ethylmalonate (100.0 g, 0.531 mol) at 20–30 °C during 1.5 h. Concd HCl (222 g, 2.13 mol) was added below 34 °C and the mixture was stirred at rt for 1 h. After filtration, the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (500 mL) and the solution was washed with 7.5% aq $NaHCO_3$ (50 mL) five times. After removal of the solvent, 47.4 g (86%) of **3a** was obtained as a colorless oil. IR (neat) ν_{max} 3351, 2965, 2919, 2879, 1650, 1464, 1419, 1379, 1261, 1208, 1131, 1096, 1042, 969, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J=7.3 Hz, 3H), 1.30 (dq, J=7.3, 7.3 Hz, 2H), 1.62–1.78 (m, 1H), 2.50 (br s, 2H), 3.62–3.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.7, 20.6, 43.6, 66.2; HRMS (FAB) calcd for $C_5H_{12}O_2$ (M^+) 105.0871, found 105.0912.

4.5. 2-Butyl-1,3-propanediol (3b)

To a suspension of LiCl (3.9 g, 0.092 mol) and $NaBH_4$ (70.0 g, 1.85 mol) in THF (500 mL) and EtOH (500 mL) was added diethyl butylmalonate (100.0 g, 0.462 mol) at 20–30 °C during 1 h. Concd HCl (193 g, 1.85 mol) was added below 20 °C and the mixture was stirred at rt for 1 h. After filtration, the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (500 mL) and the solution was washed with 7.5% aq $NaHCO_3$ (50 mL) five times. After removal of the solvent, 33.0 g (99%) of **3b** was obtained as a colorless oil. IR (neat) ν_{max} 3343, 2955, 2927, 2860, 1474, 1373, 1200, 1096, 1036, 965, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J=7.0 Hz, 3H), 1.12–1.40 (m, 6H), 1.68–1.88 (m, 1H), 2.41 (br s, 2H), 3.61–3.85 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.9, 27.4, 29.4, 41.9, 66.4; HRMS (FAB) calcd for $C_7H_{16}O_2$ (M^+) 133.1184, found 133.1233.

4.6. 2-Benzyl-1,3-propanediol (3c)

To a suspension of LiCl (1.7 g, 0.040 mol) and $NaBH_4$ (30.2 g, 0.80 mol) in THF (250 mL) and EtOH (250 mL) was added diethyl benzylmalonate (50.0 g, 0.20 mol) at 20–30 °C during 1 h. Concd HCl (83.2 g, 0.80 mol) was added below 30 °C and the mixture was stirred at rt for 2 h. After filtration, the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (200 mL) and the solution was washed with 7.5% aq $NaHCO_3$ (50 mL) five times. After removal of the solvent, 51.2 g (84%) of **3c** was obtained as white crystals. Mp 68–70 °C; IR (KBr) ν_{max} 3235, 3178, 2933, 2888, 1454, 1423, 1196, 1044, 1026, 900, 834, 746, 703, 550 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.00–2.17 (m, 1H), 2.25 (br s, 2H), 2.63 (d, J=7.6 Hz, 2H), 3.64–3.84 (m, 4H), 7.34–7.17 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.3, 43.8, 65.6, 126.2, 128.5, 129.0, 139.9; HRMS (FAB) calcd for $C_{10}H_{14}O_2$ (M^+) 167.1027, found 167.1087.

4.7. 2-*tert*-Butyl-1,3-propanediol (3d)

To a suspension of LiCl (3.5 g, 0.083 mol) and $NaBH_4$ (7.9 g, 0.209 mol) an THF (180 mL) was added diethyl *tert*-butylmalonate (9.0 g, 0.042 mol) at 25 °C. EtOH (180 mL) was added at 25 °C and the reaction mixture was stirred at rt for 3 days. Concd HCl (7.6 g, 0.209 mol) was added below 10 °C and the mixture was stirred at rt for 1 h. After filtration, the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (200 mL) and the solution was washed with 7.5% aq $NaHCO_3$ (50 mL) three times and was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc: 10/1). After removal of the solvent, 2.5 g (45%) of **3d** was obtained as white crystals. Mp 55–57 °C; IR (KBr) ν_{max} 3301, 2953, 2872, 1465, 1431, 1393, 1362, 1231, 1180, 1095, 1046, 1024, 1015, 979, 949, 723, 630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.92 (s, 9H), 1.58–1.71 (m, 1H), 2.47 (s, 2H), 3.79 (dd, J=10.2, 10.2 Hz, 2H), 4.00 (t, J=10.2, 3.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.6, 51.0, 31.3, 28.1; HRMS (FAB) calcd for $C_7H_{16}O_2$ (M^+) 133.1184, found 133.1233.

4.8. 2-Benzyl-2-methyl-1,3-propanediol (3e)

To a suspension of LiCl (1.6 g, 0.038 mol) and $NaBH_4$ (28.6 g, 0.757 mol) in THF (250 mL) and EtOH (250 mL) was added diethyl 2-benzyl-2-methylmalonate (50.0 g, 0.189 mol) at 16–27 °C during 1 h and the mixture was stirred at rt for 24 h. Concd HCl (78.8 g, 0.757 mol) was added below 20 °C and the mixture was stirred at rt for 0.5 h. After filtration, the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (300 mL) and the solution was washed with 7.5% aq $NaHCO_3$ (50 mL) five times. After removal of the solvent, 34.2 g (99%) of **3e** was obtained as white crystals. Mp 73 °C; IR (KBr) ν_{max} 3356, 2918, 1454, 1358, 1188, 1050, 1024, 785, 739, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.76 (s, 3H), 2.41 (t, J=5.2 Hz, 2H), 2.71 (s, 2H), 3.56 (d, J=5.2 Hz, 4H), 7.20–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.6, 39.8, 40.1, 70.1, 126.2, 128.0, 130.6, 137.8. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.15; H, 9.12; MS (FAB^+): 181.

4.9. Methyl 5-ethyl-2-methyl-1,3-dioxane-2-carboxylate (1a)

A mixture of **3a** (10 g, 0.096 mol), $MeCOCO_2Me$ (9.8 g, 0.096 mol), toluene (50 mL), and $BF_3\cdot Et_2O$ (13.6 g, 12.2 mL, 0.096 mol) was stirred at 25 °C for 24 h. After the reaction, 20% aq NaOH (76.8 g, 0.384 mol) was added below 20 °C and the mixture was stirred at rt for 10 min. The organic layer was washed with 10% aq NaOH, 10% aq NaCl, and dried over $MgSO_4$. After removal of the solvent in vacuo, **1a** (8.6 g, 48%) was obtained as a colorless oil. GC analysis for determination of the ratio of cis/trans of **1a**: Shimadzu CBP1-S25-050, FID, inj: 210 °C, det: 250 °C, column oven: 100 °C (0 min)–10 °C/min–130 °C (4 min), retention time *trans*-**1a**: 4.9 min, *cis*-**1a**: 5.1 min.

Each isomer was obtained as a colorless oil from the mixture by silica gel column chromatography with hexane/EtOAc, 10/1.

4.10. Methyl 2-methyl-*c*-5-ethyl-1,3-dioxane-*r*-2-carboxylate (*cis*-1a)

IR (neat) ν_{max} 2965, 2873, 1747, 1681, 1458, 1373, 1266, 1212, 1158, 1123, 1060, 1019, 1000, 888, 807, 668 cm^{-1} (obtained as a mixture of cis/trans=1); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J=7.6 Hz, 3H), 1.25–1.31 (m, 2H), 1.51 (s, 3H), 1.88–2.00 (m, 1H), 3.39 (dd, J=11.8, 11.8 Hz, 2H), 3.83 (s, 3H), 3.98 (dd, J=11.8, 4.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.8, 21.1, 26.0, 34.8, 52.5, 68.3, 98.3, 171.2; HRMS (FAB) calcd for $C_9H_{16}O_4$ (M^+) 188.1082, Found 188.1133.

4.11. Methyl 2-methyl-*t*-5-ethyl-1,3-dioxane-*r*-2-carboxylate (*trans*-1a)

IR (neat) ν_{max} 2965, 2873, 1747, 1681, 1458, 1373, 1266, 1212, 1158, 1123, 1060, 1019, 1000, 888, 807, 668 cm^{-1} (obtained as a mixture of cis/trans=1); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, J=7.5 Hz, 3H), 1.72 (dq, J=7.5, 7.5 Hz, 2H), 1.25–1.31 (m, 1H), 1.51 (s, 3H), 3.81 (dd, J=12.0, 2.4 Hz, 2H), 3.84 (s, 3H), 3.98 (dd, J=12.0, 3.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.9, 22.0, 25.4, 35.1, 52.6, 66.2, 98.4, 171.3; HRMS (FAB) calcd for $C_9H_{16}O_4$ (M^+) 188.1082, found 188.1139.

4.12. Methyl 5-butyl-2-methyl-1,3-dioxane-2-carboxylate (1b)

A mixture of **3b** (10 g, 0.076 mol), $MeCOCO_2Me$ (7.7 g, 0.076 mol), toluene (50 mL), and $BF_3\cdot Et_2O$ (10.7 g, 9.6 mL, 0.076 mol) was stirred at 25 °C for 20 h. After the reaction, 20% aq NaOH (30.3 g, 0.152 mol) was added below 20 °C and the mixture was stirred at rt for 1 h. The organic layer was washed with 10% aq NaOH, 10% aq NaCl, and dried over $MgSO_4$. After removal of the solvent in vacuo, **1b** (12.9 g, 79%) was obtained as a colorless oil. GC analysis for determination of the ratio of cis/trans of **1b**: Shimadzu CBP1-S25-050, FID, inj: 210 °C, det: 250 °C, column oven: 100 °C (0 min)–10 °C/min–150 °C (5 min), retention time *trans*-**1b**: 7.3 min, *cis*-**1b**: 7.5 min.

Each isomer was obtained as a colorless oil from the mixture by silica gel column chromatography with hexane/EtOAc, 10/1.

4.13. Methyl 2-methyl-*c*-5-butyl-1,3-dioxane-*r*-2-carboxylate (*cis*-1b)

IR (neat) ν_{max} 2957, 2929, 2859, 2355, 1748, 1653, 1540, 1457, 1369, 1269, 1219, 1160, 1150, 1123, 1050, 1033, 976, 877, 808, 758, 682 cm^{-1} (obtained as a mixture of cis/trans=1); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J=6.6 Hz, 3H), 0.95–1.06 (m, 2H), 1.20–1.33 (m, 4H), 1.51 (s, 3H), 1.95–2.07 (m, 1H), 3.39 (dd, J=10.9, 10.9 Hz, 2H), 3.95 (s, 3H), 3.98 (dd, J=11.8, 4.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 22.8, 26.1, 27.8, 28.3, 33.2, 52.5, 68.5, 98.3, 171.2; HRMS (FAB) calcd for $C_{11}H_{20}O_4$ (M^+) 217.1395, found 217.1453.

4.14. Methyl 2-methyl-*t*-5-butyl-1,3-dioxane-*r*-2-carboxylate (*trans*-1b)

IR (neat) ν_{max} 2957, 2929, 2859, 2355, 1748, 1653, 1540, 1457, 1369, 1269, 1219, 1160, 1150, 1123, 1050, 1033, 976, 877, 808, 758, 682 cm^{-1} (obtained as a mixture of cis/trans=1); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, J=6.8 Hz, 3H), 1.40–1.29 (m, 5H), 1.51 (s, 3H), 1.64–1.71 (m, 2H), 3.79 (dd, J=10.8, 2.4 Hz, 2H), 3.83 (s, 3H), 3.96 (dd, J=10.8, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.8, 25.3, 28.8, 29.6, 33.3, 52.5, 66.5, 98.4, 171.3; HRMS (FAB) calcd for $C_{11}H_{20}O_4$ (M^+) 217.1395, found 217.1429.

4.15. Methyl 5-benzyl-2-methyl-1,3-dioxane-2-carboxylate (1c)

A mixture of **3c** (10 g, 0.060 mol), $MeCOCO_2Me$ (6.1 g, 0.060 mol), toluene (50 mL), and $BF_3\cdot Et_2O$ (8.5 g, 7.6 mL, 0.060 mol) was stirred at 25 °C for 12 h. After the reaction, 20% aq NaOH (24 g, 0.120 mol) was added below 20 °C and the mixture was stirred at rt for 1 h. The organic layer was washed with 10% aq NaOH, 10% aq NaCl, and dried over $MgSO_4$. After removal of the solvent in vacuo, **1c** (12.1 g, 80%) was obtained as a colorless oil. GC analysis for determination of the ratio of cis/trans of **1c**: Shimadzu CBP1-S25-050, FID, inj: 210 °C, det: 250 °C, column oven: 200 °C (6 min), retention time *trans*-**1c**: 4.1 min, *cis*-**1c**: 4.2 min.

Each isomer was obtained as a colorless oil from the mixture by silica gel column chromatography with hexane/EtOAc, 10/1.

4.16. Methyl 2-methyl-*c*-5-benzyl-1,3-dioxane-*r*-2-carboxylate (*cis*-1c)

IR (neat) ν_{max} 2949, 2859, 1750, 1496, 1460, 1373, 1270, 1215, 1188, 1150, 1197, 1049, 975, 883, 804, 745, 702, 676, 617 cm^{-1} (obtained as a mixture of cis/trans=1); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 3H), 2.33 (s, 2H), 2.29–2.40 (m, 1H), 3.49 (dd, J=12.2, 12.2 Hz, 2H), 3.84 (s, 3H), 3.90 (dd, J=12.2, 4.4 Hz, 2H), 7.10 (d, J=6.9 Hz, 2H), 7.20–7.33 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.9, 34.7, 35.0, 52.6, 68.1, 98.3, 126.5, 128.6, 128.6, 137.9, 171.1. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.86; H, 7.14; MS (FAB^+): 251.

4.17. Methyl 2-methyl-*t*-5-benzyl-1,3-dioxane-*r*-2-carboxylate (*trans*-1c)

IR (neat) ν_{max} 2949, 2859, 1750, 1496, 1460, 1373, 1270, 1215, 1188, 1150, 1197, 1049, 975, 883, 804, 745, 702, 676, 617 cm^{-1} (obtained as a mixture of cis/trans=1); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.58 (s, 3H), 1.58–1.63 (m, 1H), 3.01 (d, J=8.1 Hz, 2H), 3.77 (dd, J=10.5, 1.5 Hz, 2H), 3.83 (s, 3H), 3.94 (dd, J=10.5, 2.7 Hz, 2H), 7.227–7.231 (m, 2H), 7.27–7.32 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.8, 35.3, 35.4, 52.5, 65.9, 98.6, 126.2, 128.5, 128.6, 140.1, 171.2. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.67; H, 7.18; MS (FAB^+): 251.

4.18. Methyl 5-(*tert*-butyl)-2-methyl-1,3-dioxane-2-carboxylate (1d)

A mixture of **3d** (92 mg, 0.698 mol), $MeCOCO_2Me$ (71.2 mg, 63.11 μL, 0.698 mol), toluene (0.5 mL), and $BF_3\cdot Et_2O$ (99.1 g, 88.4 μL, 0.060 mol) was stirred at 25 °C for 15 h. After the reaction, 20% aq NaOH was added below 20 °C and the mixture was stirred at rt for 1 h. The organic layer was washed with 10% aq NaOH, 10% aq NaCl, and dried over $MgSO_4$. After removal of the solvent in vacuo, **1d** (119 mg, 79%) was obtained as a colorless oil. The ratio of cis/trans of **1d** was determined by ^1H NMR analysis of *tert*-butyl protons, *trans*-**1d**: δ 0.99, *cis*-**1d**: δ 0.86.

Each isomer was obtained as a colorless oil from the mixture by silica gel column chromatography with hexane/EtOAc, 10/1.

4.19. Methyl 2-methyl-*c*-5-(*tert*-butyl)-1,3-dioxane-*r*-2-carboxylate (*cis*-1d)

IR (neat) ν_{max} 2958, 2874, 1747, 1430, 1369, 1266, 1210, 1188, 1155, 1119, 1060, 1011, 976, 883, 807, 755, 653 cm^{-1} (obtained as a mixture of cis/trans=1); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.86 (s, 9H), 1.50 (s, 3H), 1.77–1.88 (m, 1H), 3.64 (dd, J=11.0, 10.6 Hz, 2H), 3.84 (s, 3H), 4.02 (dd, J=10.6, 4.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.0, 27.3, 30.4, 42.5, 52.5, 65.2, 98.00, 171.3; HRMS (FAB) calcd for $C_{11}H_{20}O_4$ (M^+) 217.1395, found 217.1446.

4.20. Methyl 2-methyl-*t*-5-(*tert*-butyl)-1,3-dioxane-*r*-2-carboxylate (*trans*-1d)

IR (neat) ν_{max} 2958, 2874, 1747, 1430, 1369, 1266, 1210, 1188, 1155, 1119, 1060, 1011, 976, 883, 807, 755, 653 cm^{-1} (obtained as a mixture of cis/trans=1); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.99 (s, 9H), 1.38 (m, 1H), 1.51 (s, 3H), 3.81 (s, 3H), 3.92 (dd, J=12.2, 4.8 Hz, 2H), 4.03 (dd, J=12.2, 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.0, 28.2, 31.7, 42.6, 52.5, 62.6, 97.7, 170.9; HRMS (FAB) calcd for $C_{11}H_{20}O_4$ (M^+) 217.1395, found 217.1442.

4.21. Methyl 5-benzyl-2,5-dimethyl-1,3-dioxane-2-carboxylate (1e)

A mixture of **3e** (10 g, 0.055 mol), $MeCOCO_2Me$ (5.7 g, 0.055 mol), toluene (50 mL), and $BF_3\cdot Et_2O$ (7.9 g, 7.0 mL, 0.055 mol) was stirred at 25 °C for 65 h. After the reaction, 20% aq NaOH (24 g, 0.110 mol) was added below 20 °C and the mixture was stirred at rt for 1 h. The organic layer was washed with 10% aq NaOH, 10% aq NaCl, and dried over $MgSO_4$. After removal of the solvent in vacuo, **1e** (10.8 g, 74%) was obtained as a colorless oil. GC analysis for determination of the ratio of cis/trans of **1e**: Shimadzu CBP1-S25-050, FID, inj: 210 °C, det: 250 °C, column oven: 200 °C (6 min), retention time *trans*-**1e**: 4.1 min, *cis*-**1e**: 4.3 min.

Each isomer was obtained as white crystals from the mixture by silica gel column chromatography with hexane/EtOAc, 10/1.

4.22. Methyl 2,5-dimethyl-*t*-5-benzyl-1,3-dioxane-*r*-2-carboxylate (*trans*-1e)

Mp 83–85 °C; IR (KBr) ν_{max} 2967, 2869, 1746, 1456, 1373, 1277, 1261, 1196, 1144, 1118, 1078, 1059, 1032, 998, 976, 886, 814, 763, 705, 673 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.13 (s, 3H), 1.53 (s, 3H), 2.37 (s, 2H), 3.51 (d, J=11.4 Hz, 2H), 3.68 (d, J=11.4 Hz, 2H), 3.83 (s, 3H), 7.03–7.06 (m, 2H), 7.22–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.8, 25.5, 32.9, 42.6, 52.5, 72.6, 98.3, 126.5, 128.2, 130.1, 135.9, 171.1. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.98; H, 7.70; MS (FAB^+): 265.

4.23. Methyl 2,5-dimethyl-*c*-5-benzyl-1,3-dioxane-*r*-2-carboxylate (*cis*-1e)

Mp 74–75 °C; IR (KBr) ν_{max} 2998, 2970, 2858, 1740, 1457, 1390, 1368, 1274, 1258, 1219, 1186, 1138, 1122, 1079, 1057, 1032, 1014, 963, 920, 879, 800, 737, 711, 674 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.60 (s, 3H), 1.64 (s, 3H), 2.94 (s, 2H), 3.45 (d, J=11.4 Hz, 2H), 3.62 (d, J=11.4 Hz, 2H), 3.83 (s, 3H), 7.20–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.5, 26.0, 33.5, 40.0, 52.6, 71.3, 98.2, 126.2, 128.0, 130.8, 138.0, 171.3. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.62; H, 7.59. HRMS (FAB) calcd for $C_{15}H_{20}O_4$ (M^+) 265.1395, found 265.1448.

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Supplementary data

Supplementary data associated with stabilities and charges/dipole moments can be found in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.076.

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