Tetrahedron Vol. 49, No. 38, pp. 8529-8540, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

l-Menthyl (*R*)-2-Phenyl-4-oxo-1,3-dioxine-2-carboxylate: Diastereofacial Selectivity for Conjugate Addition and its Explanation[1]

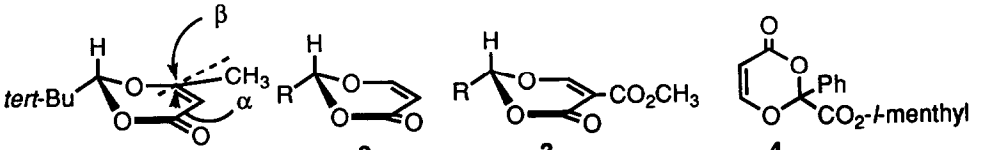
Masayuki Sato,* Masayuki Murakami, and Chikara Kaneko,*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Toshio Furuya
Tsukuba Research Laboratories, Yamanouchi Pharmaceutical Co. Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305, Japan

(*Received in Japan* 7 *June* 1993; *accepted* 16 *July* 1993)

Summary: *l*-Menthyl (*R*)- and (*S*)-2-phenyl-4-oxo-1,3-dioxine-2-carboxylates are synthesized from *l*-menthyl phenylglyoxylate by reacting with formylketene followed by fractional crystallization. Conjugate addition to the (*R*)-2-phenyl-4-oxo-1,3-dioxine-2-carboxylate by RMgBr/CuI has revealed that the reagent attacks from the phenyl side which takes the quasi-equatorial orientation in the sofa comformation of the dioxinone ring with complete diastereoselection. This finding is contrast to the reverse diastereoselectivity in the same reaction of 2-*tert*-butyl-6-methyl-1,3-dioxin-4-one and its 2-methyl derivative. A possible reason to account for this difference is proposed.

Previously, Seebach *et al.* have synthesized (*R*)-2-*tert*-butyl-6-methyl-1,3-dioxin-4-one **1** and examined its reaction with dialkylcuprates. They found remarkable β-side preference and reasoned that the selectivity was due to pyramidalization of the trigonal centers in the 4- and 6-positions of the dioxinone as depicted in formula **1**.[2] We have found, to the contrary, that either photoadditions to alkenes or Diels-Alder reactions with alkadienes of 2-monosubstituted dioxinones (e.g., **2** for the photoaddition and **3** for the Diels-Alder reaction) proceed with α-side preference.[3] Knowing that these dioxinones exist in a sofa conformation with the acetal carbon out of plane having the 2-substituent in a quasi-equatorial orientation, we explained the selectiv-



R=*tert*-Bu, cyclohexyl

ity by assuming that the reagents approach from the more exposed α-side of the sofa conformation. Though both assumptions concerning the origin of the diastereofacial selectivities of **1**[2] and and related compounds[4-6] were verified by X-ray crystallographic analysis, there is an urgent need to clarify to what extent the pyramidalization (origin for the β-side preference) of the trigonal carbon atoms in the sofa conformations (origin for the α-side attack) can be used as a guide to predict the diastereofacial selectivity. After thorough understanding of the respective roles of the pyramidalization and the sofa conformation, it would become possible to utilize dioxinones[7] having a stereogenic center at the 2-position as versatile intermediates for the synthesis of enantiomerically pure compounds (EPC).

In this paper, we will describe our results concerning the use of chiral title compounds **4** as the substrate for the conjugate addition and propose that β-side preference in the conjugate addition reaction holds only for a limited number of derivatives of the dioxinones (e.g. the 2-monosubstituted[2] and some spirocyclic dioxinones[8]) and is not a general phenomenon for the corresponding 2,2-disubstituted dioxinones (e.g. **4**).

By the reaction of *l*-menthyl phenylglyoxylate **7**[9] with formylketene generated in situ either from formylated Meldrum's acid **8**[10] (reflux in toluene)[11] or from 2,2-dimethyl-1,3-dioxin-4-one **9** (reflux in benzene),[12] a 1:1 mixture of two diastereomers (*R*)- and (*S*)-**4** were obtained. Due to a large solubility difference, two isomers could be separated readily to the less soluble isomer (*R*)-**4** and the more soluble isomer (*S*)-**4** by mere fractional recrystallization. X-ray crystallographic analysis of (*R*)-**4** was then undertaken in order to determine its relative and absolute configuration and the result was presented in Figure 1.

Formally, the quasi-axial conformation of the *l*-menthyloxycarbonyl group of (*R*)-**4** seemed to be explained in terms of the steric requirements of the two substituents at the 2-position (A-values of COOR are 1.15[13] for R=Et and 1.3[13] for R=Me and that of Ph is 2.87[13,14]). In the related heterocyclic compounds, 5-benzylidene-1,3-oxazine-4,6-diones **5**[15] and **6**,[16] it has been verified that, while the

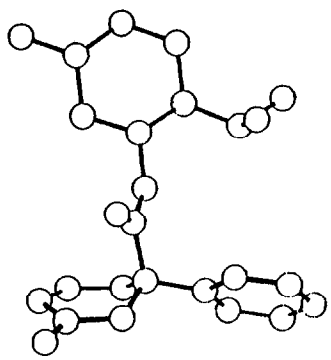
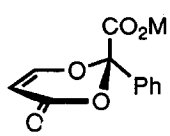
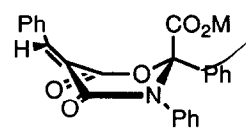


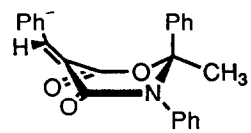
Figure 1. X-ray crystal structure of (*R*)-**4**.



(*R*)-**4**



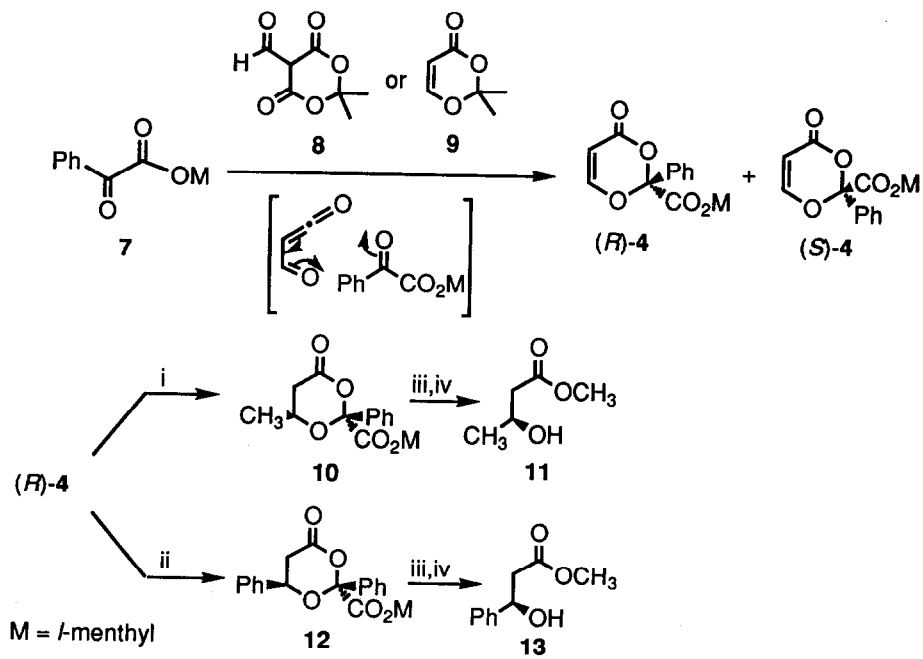
5



6

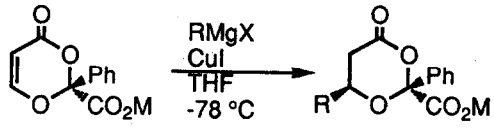
ester group takes again the quasi-axial conformation in **5**, the less bulky methyl group (A value of Me = 1.70) in **6** takes the equatorial conformation.[17] This fact suggested that an additional stereoelectronic interaction,[18,19] n_N (and/or n_O) → $\sigma^*_{C\text{-}COOR}$ or $\sigma^*_{C\text{-}Ph}$, may also participate in determination of the conformation of the 2-substituents. Since the $\sigma^*_{C\text{-}COOR}$ is obviously lower in energy (and hence a better electron acceptor) than $\sigma^*_{C\text{-}Me}$ or $\sigma^*_{C\text{-}Ph}$, such stereoelectronic effect plays the major role in determining the respective stable conformation of **4**-**6**.[19,20]

When (*R*)-**4** was subjected to reaction with methylmagnesium bromide/cuprous iodide, a single product **10** was obtained. In the same manner, the reactions using phenylmagnesium bromide in the above reaction also lead to the single product **11**. Stereostructures of **10** and **12** were determined by their conversion to the methyl esters (**11**[21]: $[\alpha]_D$ = +45.8° and **13**[22]: $[\alpha]_D$ = +17.0°). Use of other alkylmagnesium halides also gave the respective single products **14**-**16**. None of the stereoisomer was found in all cases. These results are summarized in Table I. Thus, it is reasonable to assume that dioxinone (*R*)-**4** exists in solution with a sofa conformation[23] as determined by X-ray analysis, whose α-side (phenyl side) is much more exposed than the β-side. It is clear, therefore, that the pyramidalization is not an important factor in the conjugate addition reactions of (*R*)-**4**.



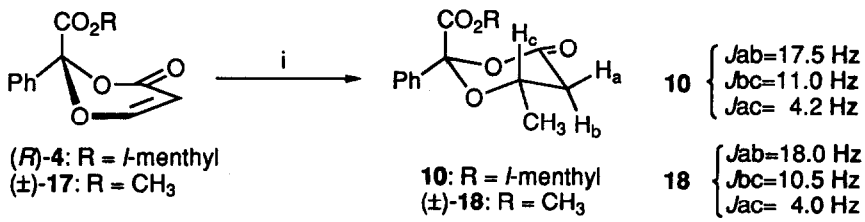
Scheme 1. Reagents and Conditions : i , CH_3MgBr , CuI , THF , -78 °C ; ii , PhMgBr , CuI , THF , -78 °C ; iii , KOH , H_2O , r.t. ; iv , CH_2N_2 , ether .

Table I. Conjugate Addition of Alkylmagnesium Halides to the Dioxinone (*R*)-4 in the Presence of CuI



entry	RMgX	additive	product	% yield
1	MeMgBr	---------	**10**	71
2	PhMgBr	---------	**12**	89
3	n-BuMgCl	---------	**14**[a]	40
4	AllylMgBr	---------	**15**[a]	10
5	AllylMgBr	TMSCl	**15**[a]	60
6	VinylMgBr	---------	**16**[a]	70

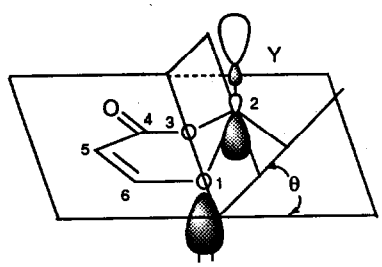
[a] The stereochemistries of the products were assigned tentatively by analogy.



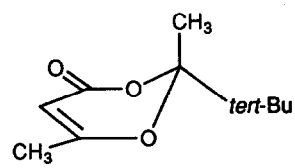
Scheme 2. Reagents and Conditions: i, CH_3MgBr, CuI, THF, -78 °C

Finally, the corresponding methoxycarbonyl derivative **17** was synthesized and subjected to reaction with methylmagnesium bromide/cuprous iodide. Here again, a single adduct **18** was obtained. Since 500 MHz ^1H NMR spectra of **10** and **18** are very similar, its structure was deduced as **18**. It is obvious that the stereoselectivity observed in the present conjugate addition (the α-side preference) was solely due to the sofa conformation of the dioxinone ring and not to the bulkiness of the alkoxyl group in the ester group. Similar to the well-known reverse of facial selectivities between the reactions of norbornene (*exo* attack preference)[24] and those of its 7,7-dimethyl derivative (*endo* attack preference),[25] the difference between the facial selectivities of **1** and **4** is due to steric factors caused by the quasi-axial hydrogen and alkoxycarbonyl group at the 2-position. If one assumes that the kind of 2-substituents does not distort the sofa conformation of the dioxinone ring (in more strict sense, the

angle (θ) between plane of O^1-C^6-C^5-C^4-O^3 and that of O^1-C^2-O^3 remains constant irrespective of the substituents, cf. A), then one can conclude that the pyramidalization[26] is important only in the former case (**1**), while the steric interactions from the axial substituent in the sofa conformation takes the primary role in the latter case (**4**).



A



20

Very recently, Lange and Organ reported that the cuprate addition of 2-*tert*-butyl-2,6-dimethyl-1,3-dioxin-4-one under the same condition as in our case resulted in selective attack from β-side.[27] Their result suggests that the pyramidarization of the enone system dominates over the additional hindrance of the 2-methyl group in **20**. The A value of methyl group is 1.7 and larger than those (CO_2Me = 1.3 and CO_2Et = 1.15) of alkoxycarbonyl groups.[13] Hence, there is an obvious discrepancy between diastereofacial selectivities for the same cuprate addition reactions of **17** and **20**. One reasonable explanation for this discrepancy is the change of angle (θ). If this angle becomes larger, the steric demand of the 2-axial substituent at the reaction site (C^6) also becomes larger due to their close proximity. We believe that the interaction (n_O-$\sigma^*_{C(2)\text{-}COOR}$)[28] which is surely one of the major factors to take the sofa conformation is only dominant for **17** and (*R*)-**4**. The same interaction would not be expected to **1**, **2**, and **20**, since the corresponding LUMO [$\sigma^*_{C(2)\text{-}H}$ and $\sigma^*_{C(2)\text{-}Me}$] should have much higher energy than the n_O-$\sigma^*_{C(2)\text{-}COOR}$ of in **17** and (*R*)-**4**.

In summary, the following could be said: 1) The title dioxinone could serve as new intermediates for the synthesis of EPCs and 2) the prediction of diastereofacial selectivity can be made simply from the sofa conformation they have and the reagents are expected to attack from the more exposed α-side (the same side of the quasi-axial substituent at the acetal carbon) of the sofa conformation.

We are currently synthesizing derivatives of **4** including a hydrogen atom or an alkyl group instead of the 2-phenyl group and their 5- and/or 6-substituted derivatives in order to examine not only their respective conformations but also stereoselectivities in a variety of reactions. At present, we assume that irrespective of the bulkiness of the 2-substituents, the alkoxyacrbonyl group would take quasi-axial conformation, since the latter group has, due to its electronegativity, low lying σ*–bond, which should accept the lone-pairs of oxygen. Such electronic interaction would afford the presumed conformer as the most stable. The determination of the angle θ

for a variety of dioxinone derivatives is an another important project which is also under current investigation.

Experimental Section

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Optical rotations were measured on a JASCO DIP-340 polarimeter. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer. ^{1}H NMR spectra were recorded with a JEOL JNM-GX 500 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were taken with a JEOL JMS-OISG-2 spectrometer.

X-Ray Analysis of (*R*)-4. A crystal of (*R*)-**4** found suitable for X-ray analysis was obtained by recrystallization from methanol. Crystal data for (*R*)-**4**, $C_{21}H_{26}O_4$, are as follows: Orthorhombic, $P2_12_12_1$, a = 17.168(8) Å, b = 19.239(7) Å, c = 6.014(3) Å, Z = 4, Mr = 358.43, V = 1986(2) Å^3, and D(calc) = 1.199 g/cm^3. X-ray diffraction data were collected at room temperature on a 0.3 x 0.05 x 0.05 mm crystal for 2715 independent reflections having $3° < 2\theta < 110°$ by a Rigaku AFC-5R automated four-circle diffractometer using graphite-monochromated Cu K_α radiation (λ = 1.54184 Å). Lorentz and polarization corrections were applied to the data. The structure was solved by direct methods using SHELXS86, and all non-hydrogen atoms were located from E maps and refined anisotropically by block-diagonal least-squares calculations. All hydrogen atoms were included at fixed positions with idealized geometry. The final values for R and R_w were 0.076 and 0.060, respectively.

***l*-Menthyl (*R*)- and (*S*)-2-Phenyl-4-oxo-1,3-dioxine-2-carboxylates [(*R*)- and (*S*)-4]. (a) Use of Formylated Meldrum's Acid as the Source of Formylketene.**

Formylated Meldrum's acid (**8**, 1.72 g, 10 mmol)[10] was added over 1 h to a refluxing solution of **7** (4.32 g, 15 mmol)[9] in toluene (100 ml). The solution was refluxed for an additional 2 h and then evaporated *in vacuo*. The residue was chromatographed on silica gel. Elution with hexane-ethyl acetate (20:1) gave **7** (3.15 g, 73%) and then a mixture of (*R*)-**4** and (*S*)-**4** (1:1, 1.37 g, 37%). Fractional recrystallization of this mixture from hexane-ether gave less soluble (*R*)-**4** and more soluble (*S*)-**4**.

(b) Use of 2,2-Dimethyl-1,3-dioxin-4-one as the Source of Formylketene

A solution of 2,2-dimethyl-1,3-dioxin-4-one (**9**, 1.20 g, 10 mmol)[11] and **7** (14.4 g, 50 mmol) in toluene (10 ml) was refluxed for 50 min. Work-up as in a) gave (*R*)-**4** (0.74 g, 21%) and (*S*)-**4** (0.72 g, 20%).

Less soluble diastereomer (*R*)-**4**: Colorless needles. mp 154-155 °C (from hexane). $[\alpha]_D^{26}$ -67.0° (*c* =1.05, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{26}O_5$: C, 70.39; H, 7.26. Found: C, 70.09; H, 7.27. IR ($CHCl_3$): 1770, 1745, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.55 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.78 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.83 (1H, dq, *J*=

3.0, 13.0 Hz, $C_{4'}$-*axial* H), 0.86 (3H, d, *J*=6.0 Hz, $C_{5'}$-CH_3), 0.93 (1H, q, *J*=11.5 Hz, $C_{6'}$-*axial* H), 0.98 (1H, dq, *J*=3.0, 13.0 Hz, $C_{3'}$-*axial* H), 1.41 (1H, tt, *J*=3.0, 12.0 Hz, $C_{2'}$-H), 1.40-1.47 (1H, m, $C_{5'}$-*axial* H), 1.52 (1H, dh, *J*=3.0, 7.0 Hz, -C<u>H</u>$(CH_3)_2$), 1.62-1.68 (2H, m, $C_{3'}$-*equatorial* H and $C_{4'}$-*equatorial* H), 1.80 (1H, ddt, *J*=11.5, 4.0, 2.0 Hz, $C_{6'}$-*equatorial* H), 4.71 (1H, dt, *J*=4.5, 11.5 Hz, $C_{1'}$-H), 5.59 (1H, d, *J*=6.0 Hz, C_5-H), 7.44 (1H, d, *J*=6.0 Hz, C_6-H), 7.42-7.48 and 7.70-7.74 (5H, m, Ph).

More soluble diastereomer (*S*)-**4**: Colorless prisms. mp 111-112 °C (from pentane). $[\alpha]_D^{26}$ -76.4° (*c* =1.01, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{26}O_5$: C, 70.39; H, 7.26. Found: C, 70.30; H, 7.27. IR ($CHCl_3$): 1775 (sh), 1745, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.50 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.74 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.84 (1H, dq, *J*=3.0, 13.0 Hz, $C_{4'}$-*axial* H), 0.87 (3H, d, *J*=6.5 Hz, $C_{5'}$-CH_3), 0.97 (1H, dq, *J*=3.0, 13.5 Hz, $C_{3'}$-*axial* H), 0.99 (1H, q, *J*=12.0 Hz, $C_{6'}$-*axial* H), 1.42 (1H, dq, *J*=3.0, 13.0 Hz, $C_{2'}$-H), 1.45 (1H, m, $C_{5'}$-*axial* H), 1.38-1.49 (1H, m, -C<u>H</u>$(CH_3)_2$), 1.63 (1H, dq, *J*=13.5, 3.5 Hz, $C_{3'}$-*equatorial* H), 1.65 (1H, m, $C_{4'}$-*equatorial* H), 1.85 (1H, ddt, *J*=12.0, 4.0, 2.0 Hz, $C_{6'}$-*equatorial* H), 4.69 (1H, dt, *J*=4.0, 13.0 Hz, $C_{1'}$-H), 5.58 (1H, d, *J*=6.0 Hz, C_5-H), 7.43 (1H, d, *J*=6.0 Hz, C_6-H), 7.42-7.48 and 7.71-7.74 (5H, m, Ph).

l-Menthyl (2*R*, 6*S*)-6-Methyl-4-oxo-2-phenyl-1,3-dioxane-2-carboxylate (10).

A solution of methylmagnesium bromide (2 M THF solution, 3.0 ml, 6.0 mmol) was added to a mixture of CuI (570 mg, 3.0 mmol) and THF (7 ml) under argon at -78 °C. The whole was stirred for 30 min at -78 °C. A solution of (*R*)-**4** (358 mg, 1.0 mmol) in THF (6 ml) was added to the solution and the mixture was stirred at -78 °C for 20 min. Saturated NH_4Cl solution was added to the mixture. The mixture was extracted with ether. The organic layer was dried over $MgSO_4$, evaporated *in vacuo*, and chromatographed on silica gel using hexane-ethyl acetate (20:1) to give **8** (267 mg, 71%) as prisms of mp 117-118 °C (recrystallized from pentane).
$[\alpha]_D^{22}$ -79.3° (*c* =2.2, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.49; H, 8.13. IR ($CHCl_3$): 1760, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.49 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.66 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.78-0.90 (1H, m, $C_{4'}$-*axial* H), 0.89 (3H, d, *J*=6.5 Hz, $C_{5'}$-CH_3), 0.95 (1H, m, $C_{3'}$-*axial* H), 0.99 (1H, q, *J*=11.5 Hz, $C_{6'}$-*axial* H), 1.17 (1H, dh, *J*=3.0, 7.0 Hz, -C<u>H</u>$(CH_3)_2$), 1.17 (1H, tt, *J*=11.5, 3.0 Hz, $C_{2'}$-H), 1.30 (1H, tt, *J*=11.5, 3.0 Hz, $C_{2'}$H), 1.47 (3H, d, *J*=6.0 Hz, C_6-CH_3), 1.55-1.70 (3H, m, $C_{3'}$-*equatorial* H, $C_{4'}$-*equatorial* H and $C_{5'}$-*axial* H), 1.92 (1H, m, $C_{6'}$-*equatorial* H), 2.48 (1H, dd, *J*=17.5, 11.0 Hz, C_5-*axial* H), 2.75 (1H, dd, *J*=17.5, 4.2 Hz, C_5-*equatorial* H), 4.19 (1H, ddq, *J*=11.0, 6.0, 4.2 Hz, C_6-H), 4.65 (1H, dt, *J*=4.2, 11.0 Hz, $C_{1'}$-H), 7.35-7.75 (5H, m, Ph). MS *m/z*: 191 (M^+-183), 139 (M^+-235).

Methyl (*S*)-3-Hydroxybutanoate (11).

A mixture of **10** (374 mg, 1.0 mmol), KOH (162 mg, 3.0 mmol), and methanol (10 ml) was stirred for 15 min. After evaporation of methanol, the residue was extracted with pentane to recover *l*-menthol. The residue was then acidified with 10% HCl and extracted with a mixture of THF-ether (1:1). The organic layer was dried over

$MgSO_4$, evaporated, and treated with ethereal diazomethane under ice-cooling. The oily product was subjected to silica gel column chromatography. Elution with hexane-ethyl acetate (10:1) gave methyl phenylglyoxylate (147 mg). Further elution with hexane-ethyl acetate (2:1) gave **11** (84 mg, 71%) as an oil. $[\alpha]_D^{23}$ +45.8° (*c*=1.00, $CHCl_3$) [lit.[21] $[\alpha]_D$ +47.3° ($CHCl_3$)].

***l*-Menthyl (2*R*, 6*R*)-4-Oxo-2,6-diphenyl-1,3-dioxane-2-carboxylate (12).**

A solution of phenylmagnesium bromide (2 M THF solution, 1.5 ml, 3.0 mmol) was added to a stirred mixture of CuI (570 mg, 3.0 mmol), (*R*)-**4** (358 mg, 1.0 mmol), and THF (10 ml) at -78 °C over 30 min. The whole was stirred at -78 °C for an additional 1 h. Saturated NH_4Cl solution was added to the mixture. The mixture was extracted with ether. The organic layer was dried over $MgSO_4$, evaporated, and chromatographed on silica gel using hexane-ethyl acetate (20:1) to give **12** (388 mg, 89%) as an oil. $[\alpha]_D^{22}$ -33.3° (*c* =2.0, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{32}O_5$: C, 74.28; H, 7.39. Found: C, 74.27; H, 7.37. IR ($CHCl_3$): 1770, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.50 (3H, d, *J*=6.5 Hz, isopropyl CH_3), 0.65 (3H, d, *J*=8.0 Hz, isopropyl CH_3), 0.77-1.02 (2H, m, $C_{3'}$-*axial* H and $C_{4'}$-*axial* H), 0.89 (3H, d, *J*=6.5 Hz, $C_{5'}$-CH_3), 1.19 (1H, dh, *J*=3.0, 7.0 Hz, -C<u>H</u>$(CH_3)_2$), 1.29 (1H, tt, *J*=11.5, 3.0 Hz, $C_{2'}$-H), 1.48 (1H, m, $C_{5'}$-*axial* H), 1.57-1.68 (2H, m, $C_{3'}$-*equatorial* H and $C_{4'}$-*equatorial* H), 1.98 (1H, ddt, *J*=11.5, 4.0, 2.0 Hz, $C_{6'}$-*equatorial* H), 2.87 (1H, dd, *J*=18.0, 11.0 Hz, C_5-*axial* H), 3.02 (1H, dd, *J*=18.0, 4.5 Hz, C_5-*equatorial* H), 4.70 (1H, dt, *J*=4.3, 11.0 Hz, $C_{1'}$-H), 5.10 (1H, dd, *J*=11.0, 4.3 Hz, C_6-H), 7.35-7.48 and 7.71-7.75 (10H, m, Ph x 2). MS *m/z*: 253 (M^+-183), 139 (M^+-297).

Methyl (*R*)-3-Hydroxy-3-phenylpropanoate (13).

Following the procedure given for preparation of **11**, compound **13** (193 mg, 0.44 mmol) was hydrolyzed with methanolic KOH. The reaction mixture was evaporated. The residue was extracted with ether to recover *l*-menthol (62 mg, 90%). The aqueous layer was extracted with ether. The organic layer was dried over $MgSO_4$ and then treated with etheral diazomethane. The product was chromatographed on silica gel with hexane-$CHCl_3$ (1:1) to give methyl phenylglyoxylate (67 mg, 93%). Further elution with hexane-ethyl acetate (5:1) gave **13** (53 mg, 73%) as an oil. $[\alpha]_D^{26}$ +17.0° (*c*=4.60, EtOH) [lit.[22] $[\alpha]_D$ +17.9° (EtOH)].

***l*-Menthyl (2*R*, 6*S*)-6-Butyl- and (2*R*, 6*R*)-6-Vinyl-4-oxo-2-phenyl-1,3-dioxane-2-carboxylates (14 and 16)**

Using the procedure for the preparation of **10**, the title compounds were prepared with the yields shown in Table I. **14**: oil. IR ($CHCl_3$): 1755 (br) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.47 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.64 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.89 (3H, d, *J*=6.5 Hz, $C_{5'}$-CH_3), 1.13 (1H, dh, *J*= 2.5, 7.0 Hz, -C<u>H</u>$(CH_3)_2$), 1.26 (1H, tt, *J*=12.0, 3.0, Hz, $C_{2'}$-H), 1.94 (1H, m, $C_{6'}$-*equatorial* H), 2.50 (1H, dd, *J*=17.5, 11.0 Hz, C_5-*axial* H), 2.71 (1H, dd, *J*=17.5, 4.0 Hz, C_5-*equatorial* H), 4.02 (1H, ddt, *J*=11.0, 7.5, 4.0 Hz C_6-H), 4.65 (1H, dt, *J*=5.5, 11.0 Hz, $C_{1'}$-H), 7.31-7.76 (5H, m, Ph), CH_2 and CH_3 signals of the butyl group are overlapped with those of *l*-menthyl group. MS *m/z*: 417 (M^++1), 233 (M^+-183), 139 (M^+-277). High resolusion MS calcd for $C_{25}H_{37}O_5$ (M^++1) 417.2641.

Found: 417.2638. **16**: oil. *Anal.* Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.47; H, 7.82. IR ($CHCl_3$): 1765 (sh), 1735, 1690 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.49 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.65 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.89 (3H, d, *J*=6.5 Hz, $C_{5'}$-CH_3), 0.99 (1H, q, *J*=12.0 Hz, $C_{6'}$-*axial* H), 0.78-1.02 (2H, m, $C_{4'}$-*axial* H and $C_{3'}$-*axial* H), 1.16 (1H, dh, *J*=3.0, 7.0 Hz, -C<u>H</u>$(CH_3)_2$), 1.30 (1H, tt, *J*=12.0, 3.0, Hz, $C_{2'}$-H), 1.47 (1H, m, $C_{5'}$-*axial* H), 1.57-1.68 (2H, m, $C_{4'}$-*equatorial* H and $C_{3'}$-*equatorial* H), 1.93(1H, ddt, *J*=11.5, 4.5, 2.0 Hz, $C_{6'}$-*equatorial* H), 2.63 (1H, dd, *J*=17.5, 11.0 Hz, C_5-*axial* H), 2.80 (1H, dd, *J*=17.5, 4.2 Hz, C_5-*equatorial* H), 4.55 (1H, ddd, *J*=11.0, 5.5, 4.2 Hz, C_6-H), 4.67 (1H, dt, *J*=4.2,11.0 Hz, $C_{1'}$-H), 5.37 (1H, d, *J*=11.0 Hz, -CH=C<u>H</u>$_2$(*trans*)), 5.45 (1H, d, *J*=17.5 Hz, -CH=C<u>H</u>$_2$(*cis*)), 5.95 (1H, ddd *J*=17.5, 11.0, 5.5 Hz, -C<u>H</u>=CH_2), 7.37-7.41 and 7.66-7.71 (5H, m, Ph). MS *m/z*: 203 (M^+-183), 139 (M^+-247).

The preparation of **15** with the same reaction conditions gave the product only in *ca.* 10% yield. However, the yield increased appreciably by the reaction using chlorotrimethylsilane as an accelerator[29] as described below.

***l*-Menthyl (2*R*, 6*S*)-6-Allyl-4-oxo-2-phenyl-1,3-dioxane-2-carboxylate (15)**

1 M etheral solution of allylmagnesium bromide (0.9 ml, 0.9 mmol) was slowly added to the slurry of cuprous iodide (171 mg, 0.9 mmol) in THF (3 ml) under argon atomosphere at -78 °C. After 30 minutes, a mixture of (*R*)-**4** (107 mg, 0.3 mmol) and chlorotrimethylsilane (0.4 ml, 0.3 mmol) in THF (1 ml) was added to the slurry and the whole was stirred for 30 minutes at -78 °C. After addition of acetic acid, the reaction mixture was allowed to warm to room temperature. The products were extracted into ether and the organic layer was washed with brine, dried with $MgSO_4$, and evaporated. The product was purified by PTLC (hexane-ethyl acetate 5:1) to give **15** (72 mg, 60 %) as colorless oil. *Anal.* Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.68; H, 8.05. IR ($CHCl_3$) :1755 (sh), 1740, 1610 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 0.58 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.65 (3H, d, *J*=7.0 Hz, isopropyl CH_3), 0.89 (3H, d, *J*=6.5 Hz, $C_{5'}$-CH_3), 0.76-0.97 (2H, m, $C_{4'}$-*axial* H and $C_{3'}$-*axial* H), 1.14 (1H, dh, *J*=7.0, 3.0 Hz, -C<u>H</u>$(CH_3)_2$), 1.28 (1H, tt, *J*=12.0, 3.0, Hz, $C_{2'}$-H), 1.46 (1H, m, $C_{5'}$-*axial* H), 1.57-1.68 (2H, m, $C_{4'}$-*equatorial* H and $C_{3'}$-*equatorial* H), 1.92 (1H, ddt, *J*=11.5, 4.0, 2.0 Hz, $C_{6'}$-*equatorial* H), 2.41-2.48 (1H, m, -C<u>H</u>$_2$CH=CH_2), 2.50-2.55 (1H, m,.-C<u>H</u>$_2$CH=CH_2), 2.55 (1H, dd, *J*=17.5, 11.0 Hz, C_5-*axial* H), 2.71 (1H, dd, *J*=17.5, 4.5 Hz, C_5-*equatorial* H), 4.12 (1H, ddt, *J*=11.0, 6.5, 4.5 Hz, C_6-H), 4.65 (1H, dt, *J*=11.0, 4.5 Hz, $C_{1'}$-H), 5.22 (1H, dd, *J*=10.5, 1.5 Hz, -CH=C<u>H</u>$_2$(*trans*)), 5.24 (1H, dd, *J*=17.0, 1.5 Hz, -CH=C<u>H</u>$_2$(*cis*)), 5.89 (1H, ddt, *J*=17.0, 10.5, 6.5 Hz, -C<u>H</u>=CH_2), 7.37-7.41 and 7.65-7.69 (5H, m, Ph). MS *m/z*: 217 (M^+-183), 139 (M^+-261).

Methyl (±)-4-Oxo-2-phenyl-1,3-dioxine-2-carboxylate [(±)-17]

Compound **6** (1.72 g, 10 mmol) was added over 20 min to a refluxing solution of methyl phenylglyoxylate (3.28 g, 20 mmol) in toluene (100 ml). The mixture was refluxed for an additional 2.5 h and then evaporated *in vacuo*. The residue was chromatographed on silica gel using hexane-ether (3:1) to give (±)-**17** (481 mg, 21%)

as prisms of mp 90-91 °C (recrystallized from pentane). *Anal.* Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.50; H, 4.38. IR ($CHCl_3$): 1775 (sh), 1760, 1615 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.78 (3H, s, CH_3), 5.58 (1H, d, *J*=6.0 Hz, C_5-H), 7.33 (1H, d, *J*=6.0 Hz, C_6-H), 7.25-7.89 (5H, m, Ph). MS *m/z*: 175 (M^+-59).

Methyl (2*R, 6*S**)-6-Methyl-4-Oxo-2-phenyl-1,3-dioxane-2-carboxylate [(±)-18]**

Following the procedure given for preparation of **10**, compound (±)-**17** (234 mg, 1.0 mmol) was treated with methylmagnesium bromide. Purification by silica gel column chromatography with hexane-ethyl acetate (1:1) gave (±)-**18** (114 mg, 46%) as an oil. *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.52; H, 5.81. IR ($CHCl_3$): 1775, 1755 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.46 (3H, d, *J*=6.0 Hz, C_6-CH_3), 2.47 (1H, dd, *J*=18.0, 10.5 Hz, C_5-*axial* H), 2.74 (1H, dd, *J*=18.0, 4.0 Hz, C_5-*equatorial* H), 3.77 (3H, s, OCH_3), 4.22 (1H, ddq, *J*=10.5, 6.0, 4.0 Hz, C_6-H), 7.43-7.50 and 7.65-7.75 (5H, m, Ph,). MS *m/z*: 191 (M^+-59).

References and Notes

1 Use of 1,3-dioxin-4-ones and related compounds in synthesis. 43. For the previous paper in this series: see, reference 20.

2 D. Seebach, J. Zimmerman, U. Gysel, R. Ziegler, and T.-K. Ha, *J. Am. Chem. Soc.*, **110**, 4763 (1987). See also, D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **29**, 1320 (1990).

3 M. Sato, Y. Abe, and C. Kaneko, *J. Chem. Soc. Perkin Trans. 1*, **1990**, 1779.

4 (a) M. Sato, K. Takayama, Y. Abe, T. Furuya, N. Inukai, and C. Kaneko, *Chem. Pharm. Bull.*, **38**, 336 (1990). (b) M. Sato, K. Takayama, T. Furuya, N. Inukai, and C. Kaneko, *Chem. Pharm. Bull.*, **35**, 3971 (1987).

5 M. Demuth, A. Palomer, H.-D. Sluma, A. K. Dey, C. Kruger, and Y.-H. Tsay, *Argew. Chem. Int. Ed. Engl.*, **25**, 1117 (1986).

6 M. Sato, H. Hisamichi, C. Kaneko, N. Suzaki, T. Furuya, and N. Inukai, *Tetrahedron Lett.*, **30**, 5281 (1989).

7 Reviews for the use of 1,3-dioxine-4-ones in organic synthesis: (a) C. Kaneko, M. Sato, J. Sakaki, and Y. Abe, *J. Heterocyclic Chem.*, **27**, 25 (1990); (b) M. Demuth and G. Mikhail, *Synthesis*, **1989**, 145.

8 M. Sato, K. Takayama, T. Furuya, N. Inukai, and C. Kaneko, *Chem. Pharm. Bull.*, **35**, 3971 (1987).

9 K. Matsumoto and K. Harada, *J. Org. Chem.*, **31**, 1956 (1966).

10 G. A. Bihlmayer, J. Derkosch, and O. E. Polansky, *Monatsh. Chem.*, **98**, 564 (1967).

11 (a) M. Sato, K. Sekiguchi, H. Ogasawara, and C. Kaneko, *Synthesis*, **1985**, 224; (b) M. Sato, N. Yoneda, N. Katagiri, H. Watanabe, M. Sato, and N. Yoneda, *Synthesis*, **1986**, 672.

12 M. Sato, N. Yoneda, and C. Kaneko, *Chem. Pharm. Bull.*, **34**, 4577 (1986).

13 The conformational free energies for substituted cyclohexanes and related heterocycles are defined by A values of the corresponding substituents. (a) F. A. Carey and R. J. Sundberg, "*Advanced Organic Chemistry*", Part A, *Structure and Mechanisms*, Plenum Press, New York, 1978, pp. 83-103; (b) J. A. Hirsch, "*Topics in Stereochemistry*", ed. by N. L. Allinger and E. L. Eliel, Vol. 1, Wiley, New York, 1967, pp. 199-222.

14 E. L. Eliel and M. Manoharan, *J. Org. Chem.*, **46**, 1959 (1986).

15 M. Sato, S. Nagashima, T. Furuya, and C. Kaneko, *Chem. Pharm. Bull.*, **40**, 1972 (1992).

16 M. Sato, N. Kitazawa, S. Nagashima, K. Kano, and C. Kaneko, *Chemistry. Lett.*, **1992**, 485.

17 In the equilibrium of 1-methyl-1-phenylcyclohexane, the conformer with axial phenyl predominates despite the larger A-value. N. L. Allinger and M. T. Tribble, *Tetrahedron Lett.*, **1971**, 3259.

18 The greater manifestation of an anomeric effect with increasing electron demand by the substituent suppports the existence of a stabilizing hyper-conjugative interaction between the lone pairs on sulfur and the antiperiplanar σ* orbital on the axial *para*-substituted aryl bond in 2-aryl-1,3-dithianes. E. Kohler, C. Tschierske, H. Zaschke, and H. Kleinpeter, *Tetrahedron*, **46**, 4241 (1990).

19 The stabilizing interactions of σ-bonds or lone pairs of heteroatoms with an antibonding orbital of the adjacent C-Y bond have been employed to explain a wide spectrum of organic reactions. (a) E. Juaristi, "*Introduction to Stereo-chemistry and Conformational Analysis*", John Wiley & Sons Inc., New York, 1991. (b) P. Deslongchamps, "*Stereoelectronic Effects in Organic Chemistry*", Pergamon Press, Oxford, 1983.

20 M. Sato, S. Nagashima, M. Murakami, C. Kaneko, and T. Furuya, *Tetrahedron*, in press.

21 D. Seebach and M. F. Zuger, *Tatrahedron Lett.*, **25**, 2747 (1984).

22 C. Schoepf and W. Wuest, *Liebigs Ann. Chem.*, **626**, 150 (1959).

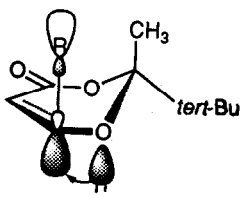
23 Detailed comparison of 500 MHz ^{1}H NMR spectra of (*R*)- and (*S*)-**4** has revealed that both compounds have the same conformation as that in crystalline state. Thus, the isopropyl methyl groups of (*S*)-**4** appeared at a higher field (δ 0.50 and 0.74) than those (0.55 and 0.78) of (*R*)-**4**. On the contrary, 6'-$H_{equatorial}$ (*cis* to isopropyl group) of (*R*)-**4** appears in a higher field (δ 1.80) than that (1.85) of (*S*)-**4**. Both upfield shifts are explained by shielding effect of the enone moiety of the dioxinone ring, as expected from the conformation verified by X-ray crystallographic analysis.

24 Norbornene *exo* side has been found in a variety of reactions (hydroboration, epoxidation, Diels-Alder reaction, *etc.*) to be more reactive than ethylene, which in turn is more reactive than norbornene *exo* side. Many proposals have been

made concerning the origin of the *endo* selectivity of norbornene and related compounds (e.g. norcamphor), such as torsional effect,[a] non-equivalent orbital extension,[b] staggering effect,[c] *endo* deformability effect:[d] (a) P. V. R. Schleyer, *J. Am. Chem. Soc.*, **89**, 701 (1967); (b) S. Inagaki, H. Fujimoto, and K. Fukui, *J. Am. Chem. Soc.*, **98**, 4054 (1976); (c) N. G. Rondon, M. N. Paddon-Row, P. Caramella, J. Mareda, H. Muller, and K. N. Houk, *J. Am. Chem. Soc.*, **104**, 4974 (1982); (d) G. Wipff and K. Morokuma, *Tetrahedron Lett.*, **21**, 4445 (1980). J. Spanget-Larsen and R. Gleiter, *Tetrahedron*, **39**, 3345 (1983). N. Koga, T. Ozawa, and K. Morokuma, *J. Phys. Org. Chem.*, **3**, 519 (1990).

25 7,7-Dimethylnorbornene showed an *endo* selectivity: C. H. Brown and J. H. Kawakami, *J. Am. Chem. Soc.*, **92**, 1990 (1970).

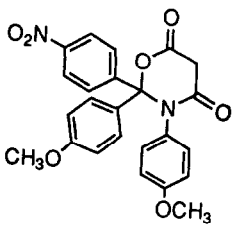
26 Throughout this paper, we adopted the pyramidarization concept proposed by Seebach *et al.*[2] in order to account for the preferential β-side attack. It should be noted, however, that the same preference can also be explained in terms of so-called Cieplack theory. Thus, taking the dioxin-4-one (**B**) as an example, the β-side attack is facilitated by the interaction [n_O-$\sigma^*_{\ddagger C(6)\text{-}R}$: R = reagent]. The C(6)-R bond is termed as an incipient bond ($\sigma_\ddagger$) by Cieplak], while the reverse side (α-side) has no such interaction. A. S. Cieplak, *J. Am. Chem. Soc.*, **103**, 4540 (1981); A. S. Cieplak, B. D. Tait, and C. R. Johnson, *ibid.*, **111**, 8447 (1989); A. S. Cieplak and K. B. Wiberg, *ibid.*, **114**, 9226 (1992).



B

27 G. L. Lange and M. G. Organ, *Tetrahedron Lett.*, **34**, 1425 (1993).

28 In the previous paper in this series,[20] we have synthesized the 2,2-diaryl-1,3-oxazin-4,6-dione **21** and, after X-ray crystallographic analysis, demonstrated that *p*-nitrophenyl group takes an axial conformation. Noteworthy fact is the angle between the plane of O^1-C^2-N^3 and that of O^1-N^3-C^4-C^6 is quite large (*ca.* 42°).



21

29 S. Matsuzawa, Y. Horiguchi, E. Nakamura, and I. Kuwajima, *Tetrahedron*, **45**, 349 (1989).