New Results on the Stereoselective Alkylations of Malic Acid Derivatives Supported by Molecular Modeling

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Dedicated to my teacher, Professor Dr. *Dieter Seebach*, on the occasion of his 65th birthday

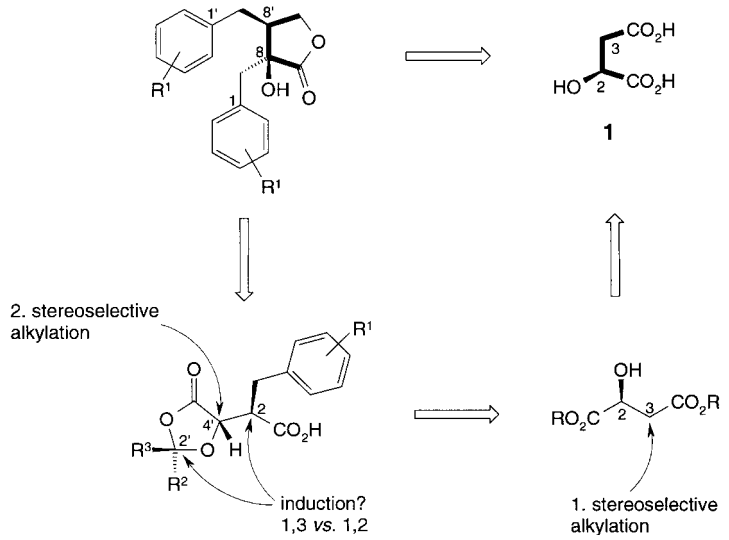
The stereoselectivity of the alkylation of dialkyl malates is dependent on steric hindrance of both ester alkyl groups. It was found that the two alkyl groups have opposite effects on diastereoselectivity. Increased steric hindrance at the C(1) carboxy group increases the *anti*-selectivity, whereas increased steric hindrance at the C(4) carboxy group decreases it. The results are explained by comparing the structures of the enolates, which were obtained by molecular modeling. Alkylation at C(4′) of dioxolanones, derived from benzyl-substituted malic acids, with an additional stereogenic center on the side chain is dependent on the stereogenic centers of the ring acetal *and* of the side chain. Alkylation at low temperatures occurs only with *cis*-dioxolanones having an (*R*)-configured side-chain stereogenic center. The corresponding *trans*-dioxolanone and the *cis*-dioxolanone with a (*S*)-configured side-chain stereogenic center were recovered unchanged. A rationale is presented with models of monolithiated dioxolanones obtained by *ab initio* calculations.

1. Introduction. – α-Hydroxylated lactone lignans [1], *e.g.*, wikstromol [2], are interesting targets for diastereo- and enantioselective synthesis, since these natural products possess a variety of biological activities [3]. We have recently developed a new strategy for the enantioselective synthesis of α-hydroxylated lactone lignans [4]. The compounds were obtained in six to seven steps from malic acid (**1**) and in overall yields of up to 30%. The key reactions were the two diastereoselective alkylations of malic acid derivatives (*Scheme 1*), both previously described by *Seebach* and co-workers [5][6].

The first stereoselective alkylation, the diastereoselective reaction of dialkyl malates, has been frequently used in the past [7]. However, according to the original procedure [5b] (dialkyl malate, base, $-78 \rightarrow -20°$, then $-78°$, electrophile, $-78 \rightarrow 0°$, 16 h), the alkylation proceeded with average yields of *ca.* 50–60% and with diastereoselectivities in the range of 9:1 *anti*/*syn*. We have reported that the alkylation could be carried out with improved yields when the ester, electrophile, and base were mixed together at $-78°$, and the mixture was warmed to 10° [4]. In the first part of this paper, we describe the effect of differently encumbered ester groups on yield and stereoselectivity of the benzylation of dialkyl malates.

The second stereoselective alkylation at C(2) of malic acid was achieved at the dioxolanone stage (*Scheme 1*). This reaction with unsubstituted dioxolanones has been reported [6]. We have recently shown that complete stereoselective alkylation was achieved with dioxolanones having an (*R*)-configured stereogenic center on the side chain [4].

Scheme 1



We will demonstrate in the second part of this paper that alkylation of dioxolanones with a stereogenic center at C(2) (derived from substituted malic acids) is dependent on the configuration at the side chain (C(2)) *and* at the ring acetal (C(2′)) (*Scheme 1*).

Both the steric effect of the ester groups on the alkylation of dialkyl malates and the different reactivity of the dioxolanone stereoisomers are explained by the structures of the corresponding intermediates (enolates or carboxylates), which were calculated by *ab initio* methods.

2. Results. – 2.1. *Alkylation of Dialkyl Malates.* We have recently examined the dependence of both yield and diastereoselectivity on the alkylation of the symmetric dialkyl malates **2**–**5** (*Scheme 2*; R, R′ = Me, Et, ^{i}Pr, ^{t}Bu) [4c][8]. The reactions were carried out with benzyl bromide **6** as the electrophile and lithium hexamethyldisilazide (LHMDS) [9] as base (*Table*, *Entries 1–4*). The major conclusions were: *1*) diethyl ester **8** and di(*tert*-butyl) ester **10** were obtained in high yields (91 and 94%); *2*) dimethyl ester **7** and diisopropyl ester **9** were formed in significantly lower yields (75 and 80%), although diisopropyl ester **4** was not completely converted; *3*) the highest ratio of *anti*/*syn* product was achieved with diisopropyl ester **4** (**9a**/**9s** 95:5) and the lowest with di(*tert*-butyl) ester **5** [10] (**10a**/**10s** 86:14).

We reasoned that only one of the *tert*-butyl groups of malate **5** was responsible for the low stereoselectivity, and we prepared the mixed esters, isopropyl-(*tert*-butyl) ester **11** and (*tert*-butyl)-isopropyl ester **12**. The hitherto unknown esters **11** and **12** were obtained in 85 and 20% overall yields, respectively, from malic acid (**1**; *Scheme 3*). Hydrolysis of dioxolanone **13** [4a] (90% from **1**) in hot ^{i}PrOH in the presence of a catalytic amount of $NaHCO_3$ [11] afforded the ester **11** in 96% yield. The ester **12** was prepared by esterification of the carboxy group of dioxolanone **14** (→ **15**, 76%), followed by selective hydrolysis of the acetal moiety with 2N HCl (→ **16**, 68%), and

Scheme 2

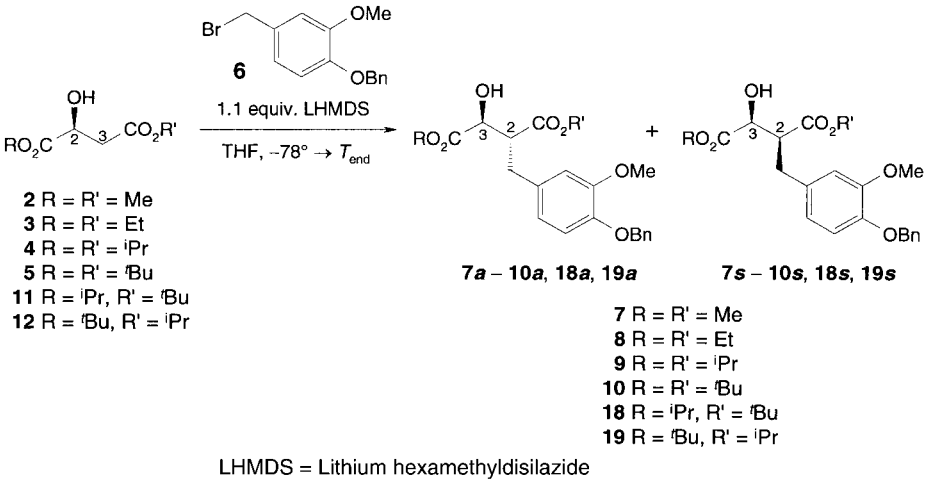


Table. *Yields and Stereoselectivities of the Alkylation of Malates* **2**–**5**, **11**, *and* **12**

Entry	Educt	R	R′	T_{end} [°]	Products	d.r.	Yield [%]	Remarks
1	**2**	Me	Me	14	***7a*/*7s***	8:1	75	
2	**3**	Et	Et	14	***8a*/*8s***	9:1	91	
3	**4**	iPr	iPr	9	***9a*/*9s***	19:1	80	(17:1; 78%)[a])
4	**5**	tBu	tBu	9	***10a*/*10s***	7:1	94	(9:1; 90%)[a])
5	**11**	iPr	tBu	16	***18a*/*18s***	9:2	90	
6	**12**	tBu	iPr	16	***19a*/*19s***	40:1	78	

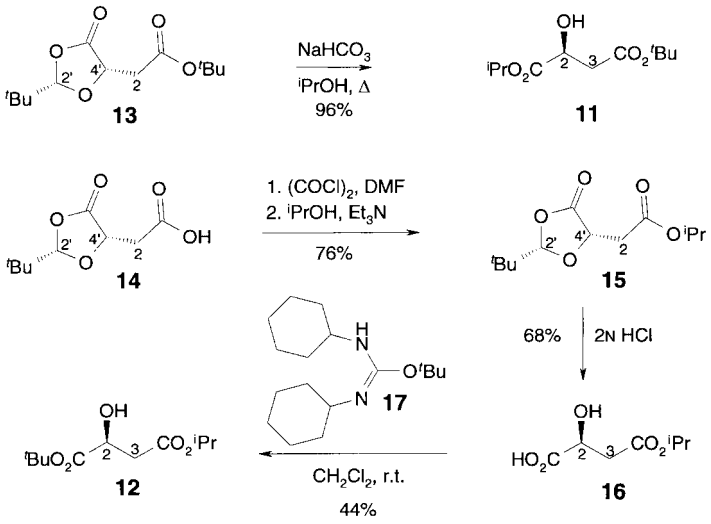
[a]) Results of a repetition experiment ($T_{end} = 16°$).

esterification of the C(1) carboxy group with isourea **17** [12] (→ **12**, 42%). Alternative routes to the diester **12** such as the base-catalyzed hydrolysis of dioxolanone **15** in tBuOH or regioselective hydrolysis of diisopropyl ester **4** to monoester **16** followed by re-esterification, were not successful.

The alkylations of dialkyl malates **4**, **5**, **11**, and **12** with bromide **6** and LHMDS were carried out simultaneously in one dewar to assure comparative results. A thin-layer chromatogram (TLC) obtained after 14 h from the reaction mixtures ($T_{end} = 16°$) (*Fig. 1*) already provided the most-important information, which is summarized as follows: *1*) The malates **4**, **5**, **11**, and **12** were alkylated in good yields, and only minor amounts of the starting esters or other by-products were detected. *2*) With respect to the stereoselectivity, the dialkyl malates can be divided into two groups: malates **4** and **12** afforded the *anti*-isomers ***9a*** and ***19a*** almost exclusively, whereas malates **5** and **11** produced compounds ***10a*** and ***18a*** with significantly lower diastereoselectivity.

The diastereoisomers ***9a*/*s*** and ***10a*/*s*** were isolated with ratios similar to those reported previously (***9a*/*9s*** 17:1; ***10a*/*10s*** 9:1). On the other hand, malates **11** and **12** were alkylated with a very different diastereoselectivity (***18a*/*18s*** 4.5:1 and ***19a*/*19s*** 40:1). It is remarkable that double benzylated dialkyl malates were obtained as minor

Scheme 3



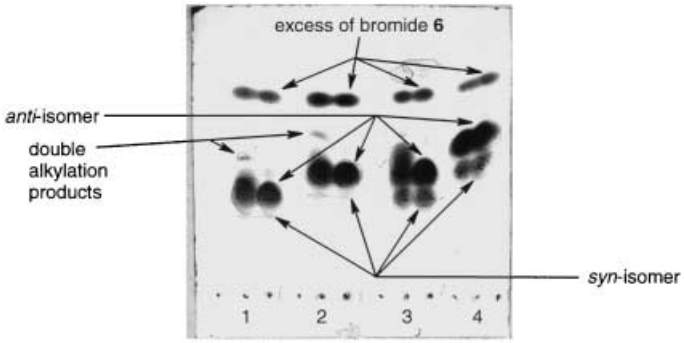


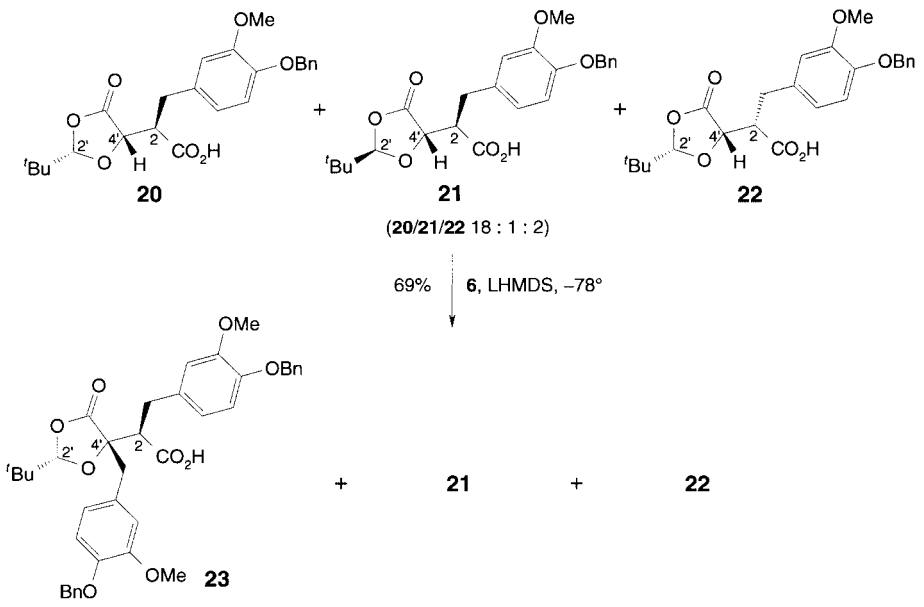
Fig. 1. *TLC from the reaction mixtures of diester* **4** (*Lane 1*), **12** (*Lane 2*), **11** (*Lane 3*), *and* **5** (*Lane 4*) *after alkylation with 1.3 equiv. of bromide* **6** *and 1.1 equiv. of LHMDS.* Double alkylation products were observed with **4** and **12** as starting materials.

products (*ca.* 5%) only when malates **4** or **12** were used as starting material. Additionally, malates with an isopropyl ester at C(1) (**4** and **12**) reacted slower, and the conversion was incomplete even after a 14 h reaction period. In these cases, *ca.* 10% of the starting material were recovered, and 78% of the products were isolated. In contrast, the malates with the bulkier *tert*-butyl ester at C(1) (**5** and **11**) were completely converted after 14 h, and the alkylation products were obtained in good yields (*ca.* 90%) (*Table 1*, *Entries 3–6*).

2.2. *Alkylation of Dioxolanones Derived from Benzyl-Substituted Malic Acids.* The (2*R*,2′*S*,4′*S*)-dioxolanone **20** was prepared in two steps from diisopropyl malate **9** as described previously [4a]. The reaction also yielded the (2*R*,2′*R*,4′*S*)-isomer **21** and the (2*S*,2′*S*,4′*S*)-isomer **22** (82%, **20**/**21**/**22** 18:1:2). Diastereoisomerically pure *cis*-dioxolanone **20** was obtained by recrystallization from EtOH/H_2O. However, this process

was not reliably reproducible, and the yield for stereoisomerically pure **20** was low (50–70%). Therefore, a mixture of the unseparated isomers was reacted with bromide **6** in presence of LHMDS at −78° (*Scheme 4*). Surprisingly, only one alkylation product, dioxolanone **23**, derived from dioxolanone **20**, was formed according to the ^{1}H-NMR spectrum of the crude reaction mixture. Dioxolanones **21** and **22** were recovered unchanged. Product **23** was isolated in 69% yield from the mixture of dioxolanones (80% yield with respect to the amount of dioxolanone **20**).

Scheme 4



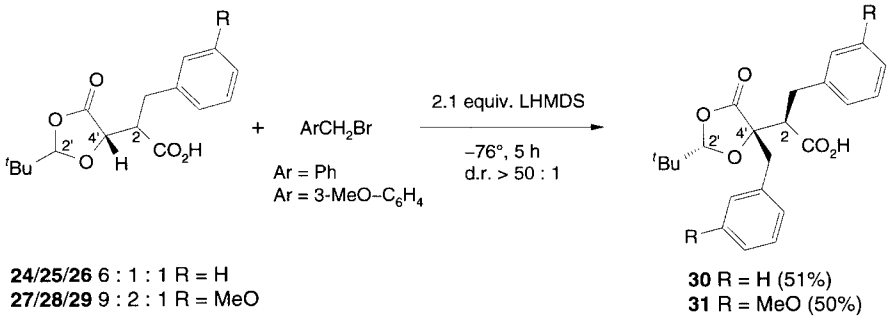
LHMDS = Lithium hexamethyldisilazide

Other benzyl-substituted dioxolanones ((2*R*,2′*S*,4′*S*)-**24**/(2*R*,2′*R*,4′*S*)-**25**/(2*S*,2′*S*,4′*S*)-**26** 6:1:1 and (2*R*,2′*S*,4′*S*)-**27**/(2*R*,2′*R*,4′*S*)-**28**/(2*S*,2′*S*,4′*S*)-**29** 9:2:1) (*Scheme 5*) reacted similarily [4b]. The dioxolanones **30** and **31** were obtained in 51% (68%) and 50% (67%) yield as single isomers.

The result that, from a mixture of dioxolanones, only one diastereoisomer was alkylated was independently confirmed by alkylation experiments of stereoisomerically pure dioxolanones **20** and **21** with bromide **6** and LHMDS. Dioxolanone **20** was alkylated within 5 h at −78° to afford product **23** whereas dioxolanone **21** was recovered unchanged in over 90% yield under the same conditions.

3. Discussion. – 3.1. *Alkylation of Dialkyl Malates.* The results described in *Sect. 2.1* show that the diastereoselectivity of the alkylation of dialkyl malates is dependent on steric hindrance of either of the alkyl groups. For a rationalization of this effect, we have calculated the structures of the lithium enolates, derived from the dialkyl esters **4**,

Scheme 5



24/25/26 6 : 1 : 1 R = H
27/28/29 9 : 2 : 1 R = MeO

30 R = H (51%)
31 R = MeO (50%)

LHMDS = Lithium hexamethyldisilazide

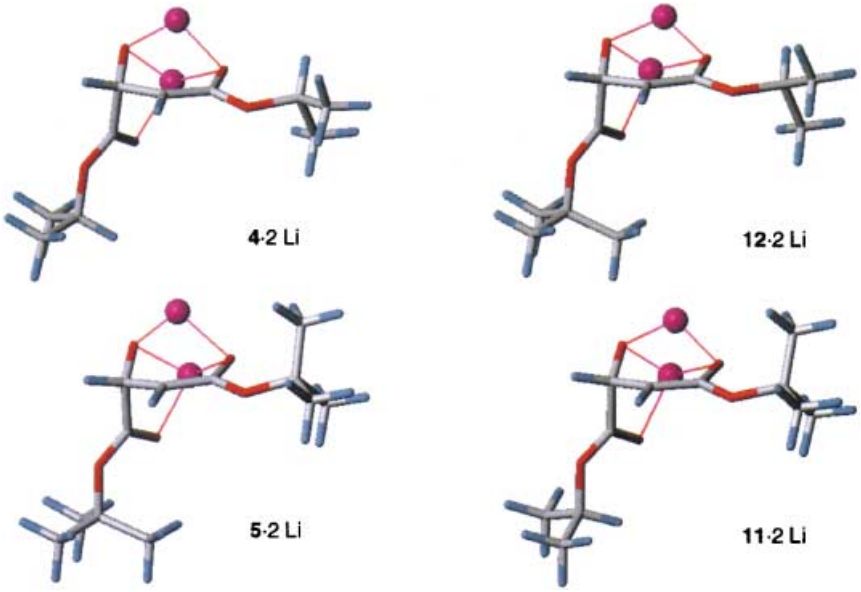


Fig. 2. *Molecular-modeling calculations of* **4**·2 *Li*, **12**·2 *Li*, **5**·2 *Li, and* **11**·2 *Li by means of the 6-31G* split-valence basis set*

5, **11**, and **12** (*Fig. 2*). The calculations were carried out by means of the HF/6-31G* level of theory and were optimized without restrictions [13]. Different initial conformations of the enolates were calculated to afford the enolate structures at their global energy minima. These conformations were the result of a conformational search at PM3 semiempirical level.

The minimum-energy conformations of all four enolates are of similar structure. In these, both Li-atoms are intramolecularly coordinated providing a tricyclic enolate structure. Interestingly, the alkoxylate Li-atom was coordinated threefold between the

carbonyl O-atom at C(1), the alkoxylate O-atom, and the enolate O-atom. As a consequence, the alkoxylate O-atom and the enolate Li-atom were positioned above the C(2)–C(3)–C(4)–O plane.

Since the electrophile approaches the enolate perpendicular to the C=C double bond [14], steric hindrance of the alkyl groups is pivotal for either the *Re*- or the *Si*-face attack (*Fig. 3*). The *anti*-selectivity was enhanced by a factor of two when the isopropyl ester at C(1) (malate **4**) was substituted by a *tert*-butyl ester (malate **12**). In this case, the *Re*-face was more effectively blocked because one of the Me substituents of the ^{t}Bu group is positioned exactly in the trajectory of the electrophile. On the other hand, steric repulsion on the opposite *Si*-face should lower the *anti*-selectivity. In fact, this is the case with malate **5** having a ^{t}Bu group at C(4). The difference with an ^{i}Pr group in which both Me groups are positioned away from the enolate moiety is the third Me group of the ^{t}Bu moiety, which unavoidably shields the *Si*-face. As a result, malate **5** was alkylated with lower stereoselectivity compared to malate **4**. Consequently, the lowest *anti*-selectivity was achieved with malate **11** in which the bulky ^{t}Bu group is at C(4) and the comparably smaller ^{i}Pr group at C(1). Thus, increased steric hindrance at C(1) increases the *anti*-selectivity, whereas increased steric hindrance at C(4) decreases it. Therefore, dialkyl malate **12** may be described as a matched and dialkyl malate **11** as a mismatched pair of differently encumbered alkyl esters.

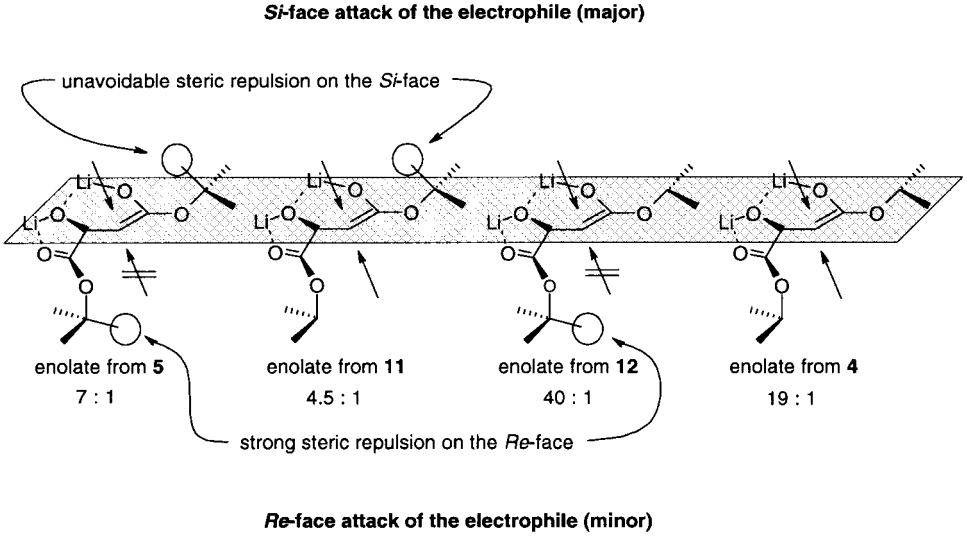
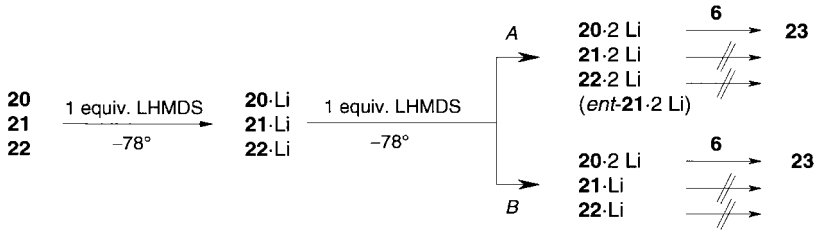


Fig. 3. *Schematic summary of the structures of* **5**·2 *Li*, **11**·2 *Li*, **12**·2 *Li*, *and* **4**·2 *Li* (from *Fig. 2*) *and possible steric interactions of the alkyl ester groups with the electrophile*

3.2. *Alkylation of Dioxolanones.* The different reactivity of dioxolanone **20** *vs.* dioxolanones **21** and **22** toward alkylation may be explained by either of the following mechanisms (*Scheme 6*). The initial step in both routes is deprotonation of the carboxy group by the first equivalent of LHMDS to form the lithium carboxylates of dioxolanones **20**–**22** (**20**·Li, **21**·Li, **22**·Li). This reaction is very exothermic and could be easily monitored with an internal thermometer. The structures of **20**·Li–**22**·Li

(*Fig. 4*) were calculated by means of the same methods as described in *Sect. 3.1.* All substituents on the aromatic ring were omitted for shorter calculation times, because calculation of dioxolanone **20** showed that the substituents were of negligible influence. The Li^+-ion is coordinated in these dioxolanones to the O-atoms of the carboxy group and to the carbonyl group of the dioxolanone moiety. The Li···O distances were between 1.92 and 2.0 Å, which is in accord with similarly coordinated Li-atoms as can be found in several X-ray structures in the *Cambridge Crystallographic Data Base* (*e.g.*, ref.-codes FADHEX, PAJFAH, VEYVUQ). Remarkably, the most stable conformer of the *cis*-dioxolanones **20** and **22** was envelope like, whereas the *trans*-dioxolanone **21** shows a twist-chair conformation at the minimum energy.

Scheme 6



LHMDS = Lithium hexamethyldisilazide

The mono-anions may be deprotonated by a second equivalent of LHMDS to afford the enolates **20**·2 Li, **21**·Li, **22**·2 Li (*Scheme 6, Path A*). The latter two are enantiomers and have the same relative configuration. Therefore, a comparison of the enolate structures is only necessary between **20**·2 Li and **21**· 2 Li (data not shown). If the enolates were formed in all cases, then steric interactions of the enolates with the incoming electrophile should be responsible for the different reactivity (*Scheme 6*, *Path A*). However, LHMDS is a bulky base and, more likely, kinetic deprotonation at C(4′) may not occur with **21**·Li and **22**·Li (*Scheme 6*, *Path B*).

The calculated structures of the lithium carboxylates **20**·Li, **21**·Li, and **22**·Li revealed that the H-atom at C(4′) is shielded by either the *t*Bu group of the dioxolanone moiety (**21**·Li, $d_{H-C(4')\cdots H-C(tert)} = 3.15$ Å) or the CH_2 group of the side chain (synaxial interaction between H–C(4′) and H–C(3) in **22**·Li, $d_{H-C(4')\cdots H-C(3)} = 2.43$ Å). In the case of dioxolanone **20**·Li, the stereogenic centers do not interfere with the base and deprotonation to the enolate is possible even at −78° (*Figs. 4* and *5*).

The assumption that enolization of the lithium carboxylates is selective for **20**·Li at −78° is supported by experimental evidence: upon treatment with 2.4 equiv. of LHMDS at −78° in presence of bromide **6**, dioxolanone **21** was recovered unchanged after workup in >90% yield. No alkylation or isomerization products were obtained. If the enolate **21**·2 Li had been formed then reprotonation should occur from both stereofaces. This was observed when the reaction of diastereoisomerically pure dioxolanone **20**·2 Li with bromide **6** was quenched before complete consumption of the nucleophile. In this case, product **23** was accompanied by *cis*-dioxolanone **20** and the corresponding *trans*-dioxolanone in a 2:1 ratio.

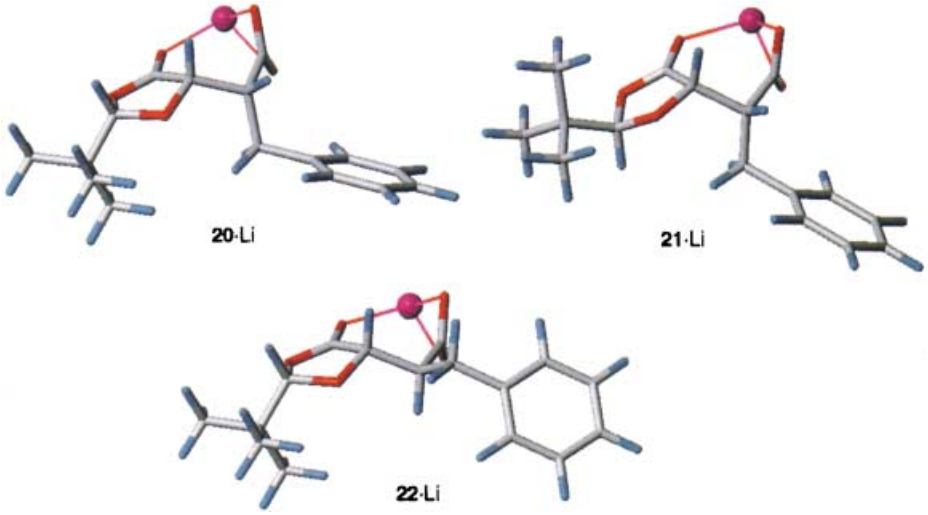


Fig. 4. *Molecular-modeling calculations of* **20** · *Li*, **21** · *Li*, *and* **22** · *Li by means of the 6-31G* split-valence basis set*. The Li-atom is positioned in the middle of the two O-atoms at the carboxy group and the dioxolanone C=O group. The O···Li distances are between 1.93 and 2.0 Å, which is in accord with comparable X-ray structures.

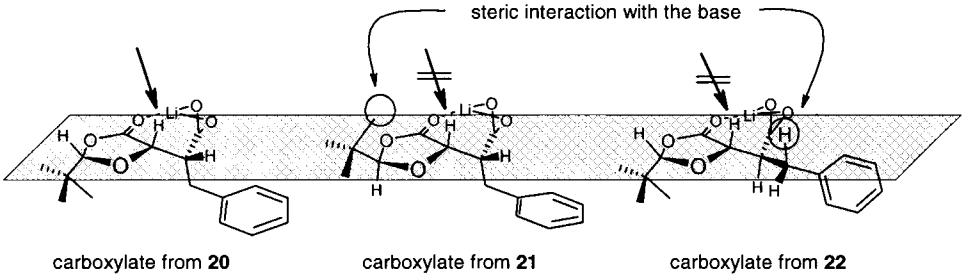


Fig. 5. *Schematic summary of the structures of* **20** · *Li*, **21** · *Li*, *and* **22** · *Li* (from *Fig. 4*) *and possible steric interactions with the base*

Conclusions. – The diastereoselectivity of the alkylation of dialkyl malates is dependent on the steric hindrance of the employed alkyl groups. It was found that the two alkyl groups have an opposite effect on the *anti*-selectivity. Increased steric hindrance at the C(1) carboxy group increases the *anti*-selectivity and increased steric hindrance at the C(4) carboxy group decreases it. Thus, the best *anti*-selectivity was achieved with dialkyl malate **12** ('matched pair of alkyl esters'), and the highest amount of *syn*-product was obtained with dialkyl malate **11** ('mismatched pair of alkyl esters'). An explanation for the experimental results is given by calculated structures of the enolates of ester **4**, **5**, **11**, and **12**. These structures revealed that a ^{t}Bu group at the C(1) carboxy group shields the *Re*-face most effectively whereas the *Si*-face is blocked when a ^{t}Bu group is at C(4).

Alkylation at C(4′) of dioxolanones derived from benzyl-substituted malates was dependent on the stereogenic centers of ring acetal *and* side chain. Thus, alkylation at

$-78°$ was achieved only with *cis*-dioxolanones having an (*R*)-configured stereogenic center in the side chain (**20**). The corresponding *trans*-dioxolanone **21** and the *cis*-dioxolanone **22** with (*S*)-configured stereogenic center were recovered unchanged. Most probably, they were not enolized by LHMDS at $-78°$. The structures of the initially formed lithium carboxylates **20**·Li–**22**·Li were calculated by *ab initio* methods. They reveal steric repulsion of the base with either the ^{t}Bu group in *trans*-dioxolanone **21**·Li or the vicinal CH_2 group in the (*S*)-configured *cis*-dioxolanone **22**·Li. This supports the assumption that **21**·Li and **22**·Li are not enolized at $-78°$.

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Experimental Part

General. All reactions were performed in dried glassware under N_2 atmosphere. Standard reagents and solvents were purified according to known procedures [15]. Thin-layer chromatography (TLC): silica-gel plates *Merck 60* F_{254}. Column chromatography ('flash chromatography', FC): performed as described [16]. M.p.: *Büchi SMP-20* apparatus, uncorrected. Optical rotations: *JASCO DIP-1000* polarimeter. ^{1}H-NMR and ^{13}C-NMR Spectra: *Bruker ARX-300*; at 300.1 and 75.4 MHz, resp. in $CDCl_3$ unless otherwise stated; δ in ppm; *J* in Hz. EI-MS: *Finnigan MAT-SSQ-710*; 70 eV; *m/z* (rel.).

*(2*S*)-2-Hydroxybutanedioic Acid Di(*tert*-butyl) Ester* (**5**). To an ice-cold suspension of finely powdered *malic acid* (**1**) (2.73 g, 20.3 mmol) in CH_2Cl_2 (30 ml) was added N,N′*-dicyclohexylcarbamimidic acid* tert*-butyl ester* (**17**; 10 ml). The suspension was warmed to r.t. when it became clear. The precipitation of urea commenced. The reaction mixture was stirred for 7 d at r.t. Every 24 h, an additional amount of **17** (2–3 ml) was added. After 7 d, the suspension was filtered through a short plug of SiO_2 and washed with CH_2Cl_2, then with Et_2O. The solvent was removed under reduced pressure, and the residue was purified by FC (SiO_2, 4×30 cm; Et_2O/pentane $1:2 \rightarrow 1:0$). The fraction containing the product was concentrated and further purified by bulb-to-bulb distillation (5×10^{-3} mbar, 110° (air bath)) to afford 2.30 g (46%) of **5**. Colorless crystals. M.p. 34.6–36.0°. $[\alpha]_D^{29} = -11.7$ ($c = 0.72$, CH_2Cl_2). ^{1}H-NMR: 3.94 (*td*, *J* = 5.7, 4.4, H–C(2)); 3.20 (*d*, *J* = 5.7, OH); 2.73 (*dd*, *J* = 16.4, 4.4, H–C(3)); 2.64 (*dd*, *J* = 16.4, 5.7, H–C(3)); 1.49 (*s*, ^{t}Bu); 1.46 (*s*, ^{t}Bu). ^{13}C-NMR: 172.77 (*s*); 169.76 (*s*); 82.62 (*s*); 81.32 (*s*); 67.55 (*d*); 39.89 (*t*); 28.05 (*q*); 27.95 (*q*). MS: 247 (100), 191 (97), 163 (57), 135 (100), 57 (74).

*(2*S*)-2-Hydroxybutanedioic Acid 4-(*tert*-Butyl) 1-Isopropyl Ester* (**11**). A suspension of *(2*S*,4*S*)-2-(*tert*-butyl)-5-oxo-1,3-dioxolane-4-acetic acid* tert*-butyl ester* (**13**; 3.00 g, 11.6 mmol) and powdered $NaHCO_3$ (0.30 g, 3.2 mmol) in ^{i}PrOH (150 ml) was heated to reflux for 48 h. The solid was filtered off, and the soln. was concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (7.8×10^{-1} mbar, 110° (airbath)) to afford 2.60 g (96%) of **11**. Colorless oil. $[\alpha]_D^{29} = -8.5$ ($c = 1.25$, CH_2Cl_2). ^{1}H-NMR: 5.12 (*sept.*, *J* = 6.3, Me_2CH); 4.38 (br. *q*, *J* = 5, H–C(2)); 3.30 (br. *d*, *J* = 5.1, OH); 2.75 (*dd*, *J* = 16.4, 4.6, H–C(3)); 2.69 (*dd*, *J* = 16.4, 5.6, H–C(3)); 1.46 (*s*, ^{t}Bu); 1.28 (*d*, *J* = 6.3, 3 H, Me_2CH); 1.27 (*d*, *J* = 6.3, 3 H, Me_2CH). ^{13}C-NMR: 173.05 (*s*); 169.64 (*s*); 81.38 (*s*); 69.60 (*d*); 67.37 (*d*); 39.70 (*t*); 27.97 (*q*); 21.66 (*q*); 21.63 (*q*). MS: 233 (100), 177 (20).

*(2*S*,4*S*)-2-(*tert*-Butyl)-5-oxo-1,3-dioxolane-4-acetic Acid Isopropyl Ester* (**15**). A suspension of *(2*S*,4*S*)-2-(*tert*-butyl)-5-oxo-1,3-dioxolane-4-acetic acid* (**14**; 4.65 g, 23.0 mmol) in toluene (50 ml), containing three drops of DMF, was treated with oxalyl chloride (2.15 ml, 3.18 g, 25 mmol) at 0°. The solid disappeared slowly at r.t., and a clear soln. was obtained after *ca*. 4 h. The soln. was decanted from some precipitate. The solvent and excess oxalyl chloride were removed *in vacuo*. The remaining oily acid chloride was dissolved in CH_2Cl_2 (40 ml) at 0°, and ^{i}PrOH (2.0 ml, 26.1 mmol) followed by Et_3N (4.0 ml, 28.7 mmol) were added dropwise. The soln. turned red, and a dark precipitate emerged. The mixture was stirred at r.t. for 16 h and filtered through a short plug of *Celite* and SiO_2. The soln. was concentrated *in vacuo*, and the residue was purified by FC (SiO_2, 3×25 cm; AcOEt/hexane 1:3) to provide 4.25 g (76%) of **15**. Pale yellow oil that solidified upon standing at r.t. ^{1}H-NMR: 5.18 (*d*, *J* = 0.8, H–C(2)); 5.07 (*sept.*, *J* = 6.2, Me_2CH); 4.68 (*ddd*, *J* = 7.6, 3.8, 0.8, H–C(4)); 2.89 (*dd*, *J* = 16.7, 3.8, 1 H, CH_2CO); 2.71 (*dd*, *J* = 16.7, 7.6, 1 H, CH_2CO); 1.26 (*d*, *J* = 6.2, Me_2CH); 0.98 (*s*, ^{t}Bu). ^{13}C-NMR: 172.34 (*s*); 168.50 (*s*); 109.66 (*d*); 71.74 (*d*); 68.84 (*d*); 36.01 (*t*); 34.16 (*s*); 23.38 (*q*); 21.69 (*q*). MS: 245 (38), 202 (17), 187 (37), 185 (30), 145 (100).

*(2S)-2-Hydroxybutanedioic Acid 1-(*tert*-Butyl) 4-Isopropyl Ester* (**12**). A soln. of **15** (4.20 g, 17.1 mmol) in THF/2N HCl (50 ml/30 ml) was heated to reflux for several hours until the starting material was consumed (monitored by TLC). *(2S)-2-Hydroxybutanedioic acid 4-isopropyl ester* (**16**) and **1** were formed. THF was removed under reduced pressure. The aq. residue was saturated with solid NaCl and extracted with Et_2O (3 × 30 ml). (In contrast to **1**, **16** is soluble in Et_2O.) The org. phase was dried ($MgSO_4$), and filtered, and the solvent was removed *in vacuo* to afford 2.0 g (66%) of **16**. Pale yellow oil.

The crude acid was dissolved in CH_2Cl_2 and **17** (2 ml) was added at r.t. The resulting suspension was stirred for 5 d at r.t. while additional amounts of **17** (2 × 2 ml) were added. After 5 d, the mixture was filtered through a short plug of *Celite* and SiO_2. The clear soln. was concentrated under reduced pressure. The residue was purified by FC (SiO_2, 3 × 25 cm; AcOEt/hexane 1:5 → 1:2) and bulb-to-bulb distillation (1 × 10^{-1} mbar, 130° (air bath)) providing 1.10 g (42%) of **12**. Pale yellow oil. $[\alpha]_D^{20} = -14.3$ ($c = 1.18$, CH_2Cl_2). ^{1}H-NMR: 5.04 (*sept.*, $J = 6.2$, Me_2CH); 4.35 (br. *q*, $J = 5$, H–C(2)); 3.27 (br. *d*, $J = 5.2$, OH); 2.77 (*dd*, $J = 16.1$, 4.8, H–C(3)); 2.70 (*dd*, $J = 16.1$, 5.9, H–C(3)); 1.49 (*s*, ^{t}Bu); 1.25 (*d*, $J = 6.2$, 3 H, Me_2CH). ^{13}C-NMR: 172.59 (*s*); 169.90 (*s*); 82.68 (*s*); 68.30 (*d*); 67.43 (*d*); 39.15 (*t*); 27.86 (*q*); 21.70 (*q*). MS: 233 (100), 177 (74), 135 (6), 57 (12).

General Procedure 1 (*GP 1*): *Alkylation of Dialkyl Malates with Benzyl Bromide* **6**. To a cold (– 76°) soln. of 1 equiv. of the malate and 1.3 equiv. of *1-(benzyloxy)-4-(bromomethyl)-2-methoxybenzene* (**6**) in THF (10 ml) was added 2.1 equiv. of a 1.06N soln. of lithium hexamethyldisilazide (LHMDS) in THF while the temp. remained below – 70°. The mixture was warmed to *ca.* 10° over a period of 12–16 h. The reaction was quenched with sat. NH_4Cl (10 ml) and acidified with 2N HCl soln. to pH ~ 2. The aq. layer was extracted with Et_2O (3 × 5 ml). The combined org. phases were dried ($MgSO_4$) and filtered, and the solvents were removed *in vacuo*. The residue was purified by FC affording the alkylated malates as colorless oils.

(2R,3S)- and (2S,3S)-2-[4-(Benzyloxy)-3-methoxybenzyl]-3-hydroxybutanedioic Acid Dimethyl Ester (**7*a*** and **7*s***). According to *GP 1*, with *(2S)-2-hydroxybutanedioic acid dimethyl ester* (**2**; 165 mg, 1.02 mmol), **6** (435 mg, 1.42 mmol), and LHMDS (2.0 ml, 2.12 mmol, 1.06N in THF) in THF (15 ml). FC (SiO_2, 3 × 24 cm; Et_2O/pentane 1:1 → 1:0; then 2 × 25 cm; Et_2O/CH_2Cl_2 1:5) afforded 300 mg (76%) (**7*a***/**7*s*** 8:1) of **7*a*** and **7*s***.

Data of **7*a***: ^{1}H-NMR: 7.43–7.23 (*m*, 5 arom. H); 6.81 (*d*, $J = 8.1$, 1 arom. H); 6.80 (*d*, $J = 1.8$, 1 arom. H); 6.72 (*dd*, $J = 8.1$, 1.8, 1 arom. H); 5.09 (*s*, CH_2O); 4.12 (*dd*, $J = 7.1$, 2.5, H–C(3)); 3.85 (*s*, MeO); 3.72 (*s*, MeO); 3.64 (*s*, MeO); 3.36 (*d*, $J = 7.1$, OH); 3.19–3.09 (*m*, 2 H); 2.91 (*m*, 1 H). MS: 388 (24), 357 (7), 237 (20), 219 (16), 177 (20), 91 (100).

Data of **7*s***: ^{1}H-NMR: 6.76 (*d*, $J = 1.8$, 1 arom. H); 6.64 (*dd*, $J = 8.2$, 1.8, 1 arom. H); 4.45 (*d*, $J = 4.7$, H–C(3)); 3.82 (*s*, MeO); 3.61 (*s*, MeO).

(2R,3S)- and (2S,3S)-2-[4-(Benzyloxy)-3-methoxybenzyl]-3-hydroxybutanedioic Acid Diethyl Ester (**8*a*** and **8*s***). According to *GP 1*, with *(2S)-2-hydroxybutanedioic acid diethylester* (**3**; 191 mg, 1.00 mmol), **6** (435 mg, 1.42 mmol), and LHMDS (2.0 ml, 2.12 mmol, 1.06N in THF) in THF (15 ml). FC (SiO_2, 3 × 26 cm; Et_2O/pentane 1:2 → 1:0; then 2 × 25 cm, Et_2O/CH_2Cl_2 13:87) afforded 388 mg (92%) (**8*a***/**8*s*** 9:1) of **8*a*** and **8*s***.

Data of **8*a***: ^{1}H-NMR: 7.44–7.24 (*m*, 5 arom. H); 6.82 (*d*, $J = 1.8$, 1 arom. H); 6.81 (*d*, $J = 8.1$, 1 arom. H); 6.74 (*dd*, $J = 8.1$, 1.8, 1 arom. H); 5.10 (*s*, CH_2O); 4.29–4.01 (*m*, 2 MeCH_2); 4.11 (*dd*, $J = 7.1$, 2.3, H–C(3)); 3.86 (*s*, MeO); 3.31 (*d*, $J = 7.1$, OH); 3.16–3.09 (*m*, 2 H); 2.92 (*dd*, $J = 15.4$, 11.1, 1 H); 1.26 (*t*, $J = 7.1$, *Me*CH_2); 1.21 (*t*, $J = 7.1$, *Me*CH_2). MS: 416 (25), 371 (9), 251 (26), 233 (22), 177 (24), 91 (100).

Data of **8*s***: ^{1}H-NMR: 6.78 (*d*, $J = 1.8$, 1 arom. H); 6.66 (*dd*, $J = 8.2$, 1.8, 1 arom. H); 4.44 (*d*, $J = 4.6$, H–C(3)); 3.83 (*s*, MeO); 3.40 (*d*, $J = 4.6$, 1 H); 1.12 (*t*, $J = 7.1$, *Me*CH_2); 1.05 (*t*, $J = 7.1$, *Me*CH_2).

(2R,3S)- and (2S,3S)-2-[4-(Benzyloxy)-3-methoxybenzyl]-3-hydroxybutanedioic Acid Diisopropyl Ester (**9*a*** and **9*s***). According to *GP 1*, with *(2S)-2-hydroxybutanedioic acid diisopropyl ester* (**4**; 220 mg, 1.01 mmol), **6** (435 mg, 1.42 mmol), and LHMDS (2.0 ml, 2.12 mmol, 1.06N in THF) in THF (15 ml). FC (SiO_2, 3 × 28 cm; Et_2O/pentane 1:2 → 1:0; then 2 × 25 cm; Et_2O/CH_2Cl_2 13:87) afforded 360 mg (80%) of **9*a*** and **9*s*** (**9*a***/**9*s*** 19:1). Colorless oil.

Data of **9*a***: ^{1}H-NMR (400 MHz): 7.44–7.27 (*m*, 5 arom. H); 6.82 (*d*, $J = 1.8$, 1 arom. H); 6.82 (*d*, $J = 8.2$, 1 arom. H); 6.74 (*dd*, $J = 8.1$, 1.8, 1 arom. H); 5.13 (*s*, CH_2O); 5.08 (*sept.*, $J = 6.2$, Me_2CH); 4.99 (*sept.*, $J = 6.2$, Me_2CH); 4.06 (*d*, $J = 2.8$, H–C(3)); 3.88 (*s*, MeO); 3.25 (br. *s*, OH); 3.11 (*dd*, $J = 12.4$, 6.4, 1 H, CH_2–C(2)); 3.06 (*ddd*, $J = 8.1$, 6.4, 2.8, H–C(2)); 2.90 (*dd*, $J = 12.4$, 8.1, 1 H, CH_2–C(2)); 1.27 (*d*, $J = 6.2$, 3 H, Me_2CH); 1.25 (*d*, $J = 6.3$, 3 H, Me_2CH); 1.20 (*d*, $J = 6.2$, 3 H, Me_2CH); 1.15 (*d*, $J = 6.3$, 3 H, Me_2CH). MS: 444 (100), 402 (9), 385 (20), 269 (26), 207 (35), 91 (33).

Data of **9*s***: ^{1}H-NMR (400 MHz): 6.77 (*d*, $J = 8.2$, 1 arom. H); 6.77 (*d*, $J = 1.9$, 1 arom. H); 6.66 (*dd*, $J = 8.2$, 1.9, 1 arom. H); 4.38 (*d*, $J = 3.8$, H–C(3)); 1.11 (*d*, $J = 6.3$, 3 H, Me_2CH).

*(2R,3S)- and (2S,3S)-2-[4-(Benzyloxy)-3-methoxybenzyl]-3-hydroxybutanedioic Acid Di(*tert*-butyl) Ester* (**10*a*** and **10*s***). According to *GP 1*, with **5** (249 mg, 1.01 mmol), **6** (435 mg, 1.42 mmol), and LHMDS (2.0 ml,

2.12 mmol, 1.06N in THF) in THF (15 ml). FC (SiO_2, 3 × 30 cm; Et_2O/pentane 1:2 → 1:0; then 2 × 25 cm, Et_2O/CH_2Cl_2 13:87) affording 450 mg (94%) of **10*a*** and **10*s*** (**10*a*/10*s*** 7:1). Colorless oil.

Data of **10*a***: ^{1}H-NMR: 7.44–7.24 (*m*, 5 arom. H); 6.81 (*d*, *J* = 1.8, 1 arom. H); 6.81 (*d*, *J* = 8.1, 1 arom. H); 6.73 (*dd*, *J* = 8.1, 1.8, 1 arom. H); 5.11 (*s*, CH_2O); 3.96 (*dd*, *J* = 7.8, 2.8, H–C(3)); 3.86 (*s*, MeO); 3.29 (*d*, *J* = 7.8, OH); 3.07 (*dd*, *J* = 12.3, 6.2, 1 H, CH_2–C(2)); 2.98 (*ddd*, *J* = 8.3, 6.2, 2.8, H–C(2)); 2.87 (*dd*, *J* = 12.3, 8.3, 1 H, CH_2–C(2)); 1.46 (*s*, ^{t}Bu); 1.39 (*s*, ^{t}Bu). ^{13}C-NMR: 172.52 (*s*); 171.38 (*s*), 149.39 (*s*); 146.58 (*s*); 137.08 (*s*); 131.72 (*s*); 128.23 (*d*); 127.51 (*d*); 127.04 (*d*); 121.09 (*d*); 114.05 (*d*); 112.81 (*d*); 82.17 (*s*); 81.28 (*s*); 70.86 (*t*); 69.88 (*d*); 55.72 (*q*); 50.75 (*d*); 33.55 (*t*); 27.78 (*q*). MS: 472 (100), 360 (6), 343 (4), 91 (16), 57 (22).

Data of **10*s***: ^{1}H-NMR: 6.78 (*d*, *J* = 1.9, 1 arom. H); 6.78 (*d*, *J* = 8.2, 1 arom. H); 6.68 (*dd*, *J* = 8.2, 1.9, 1 arom. H); 4.30 (*dd*, *J* = 5.4, 3.7, H–C(3)); 3.25 (*d*, *J* = 5.4, OH); 2.75 (*dd*, *J* = 11.3, 3.1, 1 H, CH_2–C(2)); 1.49 (*s*, ^{t}Bu); 1.36 (*s*, ^{t}Bu). ^{13}C-NMR: 172.11 (*s*); 171.34 (*s*); 149.31 (*s*); 146.48 (*s*); 137.12 (*s*); 132.24 (*s*); 127.00 (*d*); 120.89 (*d*); 82.72 (*s*); 80.96 (*s*); 70.90 (*t*); 55.68 (*q*); 51.63 (*d*); 32.43 (*t*).

*(2*R*,3*S*)- and (2*S*,3*S*)-2-[4-(Benzyloxy)-3-methoxybenzyl]-3-hydroxybutanedioic Acid 1-(*tert*-Butyl) 4-Isopropyl Ester* (**18*a*** and **18*s***). According to *GP 1*, with **11** (238 mg, 1.02 mmol), **6** (396 mg, 1.29 mmol), and LHMDS (2.0 ml, 2.12 mmol, 1.06N in THF) in THF (10 ml). FC (SiO_2, 2 × 25 cm; EtOAc/hexane 14:86; then 2 × 28 cm; Et_2O/CH_2Cl_2 11:89) afforded 423 mg (90%) of **18*a*** and **18*s*** (**18*a*/18*s*** 9:2). Colorless oil.

Data of **18*a***: ^{1}H-NMR (400 MHz): 7.44–7.27 (*m*, 5 arom. H); 6.81 (*d*, *J* = 1.8, 1 arom. H); 6.81 (*d*, *J* = 8.1, 1 arom. H); 6.74 (*dd*, *J* = 8.1, 1.8, 1 arom. H); 5.13 (*s*, CH_2O); 5.08 (*sept.*, *J* = 6.2, Me_2CH); 4.02 (*d*, *J* = 2.8, H–C(3)); 3.88 (*s*, MeO); 3.08 (*dd*, *J* = 13.1, 6.4, 1 H, CH_2–C(2)); 3.00 (*ddd*, *J* = 9.0, 6.4, 2.8, H–C(2)); 2.88 (*dd*, *J* = 13.1, 9.0, 1 H, CH_2–C(2)); 1.39 (*s*, ^{t}Bu); 1.26 (*d*, *J* = 6.3, 3 H, Me_2CH); 1.24 (*d*, *J* = 6.2, 3 H, Me_2CH). MS: 458 (44), 403 (8), 223 (12), 207 (19), 91 (100), 57 (27).

Data of **18*s***: ^{1}H-NMR (400 MHz): 6.77 (*d*, *J* = 8.2, 1 arom. H); 6.76 (*d*, *J* = 1.9, 1 arom. H); 6.66 (*dd*, *J* = 8.2, 1.9, 1 arom. H); 5.12 (*s*, CH_2O); 5.04 (*sept.*, *J* = 6.2, Me_2CH); 4.35 (*d*, *J* = 3.7, H–C(3)); 3.87 (*s*, MeO); 2.82–2.75 (*m*, 2 H); 1.37 (*s*, ^{t}Bu); 1.28 (*d*, *J* = 6.3, 3 H, Me_2CH); 1.25 (*d*, *J* = 6.3, 3 H, Me_2CH).

*(2*R*,3*S*)- and (2*S*,3*S*)-2-[4-(Benzyloxy)-3-methoxybenzyl]-3-hydroxybutanedioic Acid 4-(*tert*-Butyl) 1-Isopropyl Ester* (**19*a*** and **19*s***). According to *GP 1*, with **12** (237 mg, 1.02 mmol), **6** (398 mg, 1.30 mmol), and LHMDS (2.0 ml, 2.12 mmol), 1.06N in THF) in THF (10 ml). FC (SiO_2, 2 × 25 cm; EtOAc/hexane 1:4; then 2 × 28 cm; Et_2O/CH_2Cl_2 11:89) afforded 365 mg (78%) of **19*a*** and **19*s*** (**19*a*/19*s*** 40:1). Colorless oil.

Data of **19*a***: ^{1}H-NMR (400 MHz): 7.44–7.27 (*m*, 5 arom. H); 6.82 (*d*, *J* = 8.1, 1 arom. H); 6.81 (*d*, *J* = 1.5, 1 arom. H); 6.74 (*dd*, *J* = 8.1, 1.5, 1 arom. H); 5.13 (*s*, CH_2O); 5.00 (*sept.*, *J* = 6.2, Me_2CH); 3.99 (*d*, *J* = 2.6, H–C(3)); 3.88 (*s*, MeO); 3.10 (*dd*, *J* = 12.9, 6.6, 1 H, CH_2–C(2)); 3.03 (*ddd*, *J* = 8.4, 6.6, 2.6, H–C(2)); 2.89 (*dd*, *J* = 12.9, 8.4, 1 H, CH_2–C(2)); 1.47 (*s*, ^{t}Bu); 1.21 (*d*, *J* = 6.2, 3 H, Me_2CH); 1.16 (*d*, *J* = 6.3, 3 H, Me_2CH). MS: 458 (66), 403 (12), 343 (12), 223 (16), 207 (17), 91 (100), 57 (36).

Data of **19*s***: ^{1}H-NMR: 4.31 (*d*, *J* = 4.2, H–C(3)); 1.50 (*s*, ^{t}Bu); 1.10 (*d*, *J* = 6.2, 3 H, Me_2CH).

General Procedure 2 (*GP 2*): *Alkylation of Dioxolanones.* To a cold (–78°) soln. of 1 equiv. of the dioxolanone and 1.4 equiv. of the benzyl bromide in THF (10 ml) was added 2.1 equiv. of LHMDS (1.06N in THF) in THF (T_i < –72°). The resulting pale orange soln. was stirred for 5 h at –75° and quenched with sat. NH_4Cl soln. (10 ml). The aq. layer was acidified (pH ~ 2) with a 2N aq. HCl soln. and extracted with Et_2O (3 × 10 ml). The combined org. extracts were dried ($MgSO_4$) and filtered, and the solvents were removed *in vacuo*. FC of the residue provided the dioxolanones as diastereoisomerically pure compounds.

*(2*R*,2′*S*,4′*S*)-2-[4-[4-(Benzyloxy)-3-methoxybenzyl]-2-(*tert*-butyl)-5-oxo-1,3-dioxolan-4-yl]-3-[4′-(benzyloxy)-3′-methoxyphenyl]propanoic Acid* (**23**). According to *GP 2*, with a mixture of *(2*R*,2′*S*,4′*S*)-, (2*R*,2′*R*,4′*S*)-*, and *(2*S*,2′*S*,4′*S*)-3-[4-(benzyloxy)-3-methoxyphenyl]-2-[2-(*tert*-butyl)-5-oxo-1,3-dioxolan-4-yl]propanoic acid* (**20**/**21**/**22** 18:1:2; 0.77 g, 1.79 mmol), **6** (0.80 g, 2.60 mmol) in THF (30 ml), and LHMDS (3.7 ml, 3.9 mmol, 1.06N in THF). FC (SiO_2, 3 × 22 cm; EtOAc/hexane 1:2) afforded 0.81 g (69%) of **23**. Pale yellow foam. ^{1}H-NMR: 9.08 (br. *s*, COOH); 7.45–7.25 (*m*, 10 arom. H); 6.81 (*d*, *J* = 8.1, 1 arom. H); 6.80 (br. *s*, 1 arom. H); 6.78 (*d*, *J* = 8.1, 1 arom. H); 6.73 (br. *d*, *J* = 8.1, 1 arom. H); 6.72 (br. *s*, 1 arom. H); 6.67 (br. *d*, *J* = 8.1, 1 arom. H); 5.13 (*s*, CH_2O); 5.08 (*s*, CH_2O); 4.04 (*s*, H–C(2′)); 3.85 (*s*, MeO); 3.81 (*s*, MeO); 3.44 (*d*, *J* = 13.7, H–C(3)); 3.41 (br. *d*, *J* = 11, H–C(2)); 3.12 (*d*, *J* = 13.7, H–C(3)); 3.08 (br. *d*, *J* = 13, 1 H, CH_2–C(4′)); 2.97 (*dd*, *J* = 13, 11, 1 H, CH_2–C(4′)); 0.80 (*s*, ^{t}Bu). ^{13}C-NMR: 175.89 (*s*); 173.84 (*s*); 149.62 (*s*); 149.58 (*s*); 147.51 (*s*); 147.04 (*s*); 137.11 (*s*); 136.83 (*s*); 130.98 (*s*); 128.50 (*d*); 128.46 (*d*); 127.85 (*d*); 127.76 (*d*); 127.24 (*d*); 126.85 (*s*); 122.60 (*d*); 120.66 (*d*); 114.09 (*d*); 113.99 (*d*); 112.54 (*d*); 110.04 (*d*); 82.53 (*s*); 70.98 (*t*); 70.91 (*t*); 55.95 (*q*); 55.89 (*q*); 54.66 (*d*); 37.64 (*t*); 34.44 (*s*); 32.67 (*t*); 23.19 (*q*). MS: 655 (25), 654 (24), 568 (15), 317 (79), 227 (100).

*(2*R*,2′*S*,4′*S*)-2-[4-Benzyl-2-(*tert*-butyl)-5-oxo-1,3-dioxolan-4-yl]-3-phenylpropanoic Acid* (**30**). According to *GP 2*, with a mixture of *(2*R*,2′*S*,4′*S*)-*, *(2*R*,2′*R*,4′*S*)-*, and *(2*S*,2′*S*,4′*S*)-2-[2-(*tert*-butyl)-5-oxo-1,3-dioxolan-4-*

yl]-3-phenylpropanoic acid (**24**/**25**/**26** 6:1:1; 1.49 g, 5.10 mmol), benzyl bromide (1.03 g, 6.00 mmol) in THF (100 ml), and LHMDS (10 ml, 10.6 mmol, 1.06N in THF). FC (SiO_2, 4 × 20 cm, EtOAc/hexane 3:7 → 7:3) afforded 1.01 g (51%) of **30**: Pale yellow foam. ^{1}H-NMR: 8.52 (br. *s*, COOH); 7.34–7.19 (*m*, 10 arom. H); 3.93 (*s*, H–C(2′)); 3.60 (*d*, *J* = 13.6, H–C(3)); 3.54 (br. *d*, *J* = 11.3, H–C(2)); 3.22 (*d*, *J* = 13.6, H–C(3)); 3.12 (br. *d*, *J* = 12.5, 1 H, CH_2–C(4′)); 3.05 (*dd*, *J* = 12.5, 11.3, 1 H, CH_2–C(4′)); 0.80 (*s*, ^{t}Bu). ^{13}C-NMR: 176.38 (*s*); 173.67 (*s*); 137.87 (*s*); 134.01 (*s*); 130.56 (*d*); 128.72 (*d*); 128.66 (*d*); 128.62 (*d*); 127.59 (*d*); 126.78 (*s*); 110.07 (*d*); 82.35 (*s*); 54.87 (*d*); 37.83 (*t*); 34.47 (*s*); 32.97 (*t*); 23.14 (*q*). MS: 383 (25), 325 (2), 291 (11), 234 (15), 159 (32), 91 (100), 57 (24).

*(2*R*,2′*S*,4′*S*)-2-[2-(*tert*-Butyl)-4-(3-methoxybenzyl)-5-oxo-1,3-dioxolan-4-yl]-3-(3-methoxyphenyl)propanoic Acid* (**31**). According to *GP 2*, with a mixture of *(2*R*,2′*S*,4′*S*)-, (2*R*,2′*R*,4′*S*)-*, and *(2*S*,2′*S*,4′*S*)-2-[2-(*tert*-butyl)-5-oxo-1,3-dioxolan-4-yl]-3-(3-methoxyphenyl)propanoic acid* (**27**/**28**/**29** 9:2:1; 1.10 g, 3.42 mmol), 3-methoxybenzyl bromide (1.00 g, 4.9 mmol) in THF (30 ml), and LHMDS (8.0 ml, 8.5 mmol, 1.06N in THF). FC (SiO_2, 3 × 20 cm; EtOAc/light petroleum 3:7 → 2:1) afforded 0.77 g (50%) of **31**. Pale yellow foam. ^{1}H-NMR: 10.92 (br. *s*, COOH); 7.24–7.16 (*m*, 2 arom. H); 6.89–6.75 (*m*, 6 arom. H); 4.06 (*s*, H–C(2′)); 3.78 (*s*, MeO); 3.75 (*s*, MeO); 3.54 (*d*, *J* = 13.7, H–C(3)); 3.48 (br. *d*, *J* = 12, H–C(2)); 3.17 (*d*, *J* = 13.7, H–C(3)); 3.12 (br. *d*, *J* = 12, 1 H, CH_2–C(4′)); 3.03 (*t*, *J* = 12, 1 H, CH_2–C(4′)); 0.82 (*s*, ^{t}Bu). ^{13}C-NMR: 176.62 (*s*); 173.55 (*s*); 159.65 (*s*); 159.62 (*s*); 139.40 (*s*); 135.42 (*s*); 129.58 (*d*); 122.81 (*d*); 120.93 (*d*); 115.73 (*d*); 114.17 (*d*); 113.39 (*s*), 112.25 (*d*); 110.03 (*d*); 82.28 (*s*); 55.11 (*q*); 54.99 (*q*); 54.71 (*d*); 37.87 (*t*); 34.42 (*s*); 32.99 (*t*); 23.12 (*q*). MS: 442 (33), 311 (29), 265 (44), 235 (29), 191 (51), 189 (84), 161 (43), 121 (100), 57 (64).

Ab Initio *Calculations of* **4** · *2 Li*, **5** · *2 Li*, **11** · *2 Li, and* **12** · *2 Li and of* **20** · *Li*, **21** · *Li*, **22** · *Li*. Total energies of the compounds were calculated with the *ab initio* program GAUSSIAN 98 [13]. The calculations were carried out at the *Hartree–Fock* level by means of the 6-31G* split-valence basis set. The geometry optimizations of all conformations were performed without restrictions. The minimum-energy conformation of every compound is shown in *Figs. 2* and *4* by means of the modeling software SYBYL 6.8 [17]. The quantum-chemical calculations were processed on *SGI Octane* and *SGI Origin* computers at Potsdam University.

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