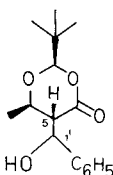


3) 6-Methyl-2-phenyl-1,3-dioxan-4-one (m.p. 75°, one diastereomer from trimethylsilyl (*R*)-3-(trimethylsilyloxy)butanoate and benzaldehyde, CH₂Cl₂, -75°, cat. Me₃SiOTf) is also suitable (*René Imwinkelried and J. Z.*, hitherto unpublished results, ETH Zürich, 1986).

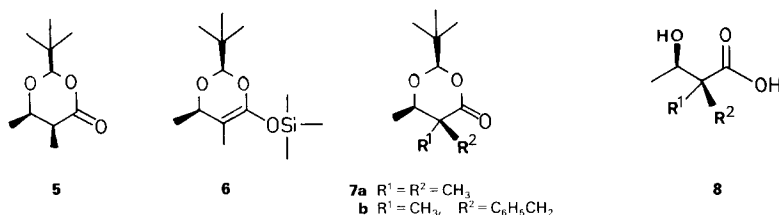
The lithium enolate **2**, generated from **1a** with LDA at -75° in THF, is surprisingly stable; it does not undergo β -elimination⁴⁾ at the low temperature employed.

Alkylation of **2** diastereoselectively produces 5,6-*trans*-disubstituted 1,3-dioxanones **3**. The reaction of **2** with benzaldehyde gives a mixture of two products **4** (probably epimeric at the C(1') center)⁵⁾, the ratio of which depends to some extent upon the metal used in the enolate.

	Metal on enolate	Li	MgBr	Ti[O(<i>i</i> -Pr)] ₃
	4a/4b	2:1	2:3	1.8:1

Diastereoisomer **4a** ($J(\text{H}-\text{C}(5), \text{H}-\text{C}(1')) = 3.3 \text{ Hz}$)
 Diastereoisomer **4b** ($J(\text{H}-\text{C}(5), \text{H}-\text{C}(1')) = 6.2 \text{ Hz}$)

The 1,3-dioxanone method of alkylating 3-hydroxy-carboxylic acids is superior to the procedure involving dithio-alkoxide-enolates [11]. Only 1 equiv. of strong base is necessary, the products are all crystalline, and it is possible to prepare products of either *l*- or *u*-configuration: enolate derivatives of 5,6-disubstituted 1,3-dioxanones **3** can be diastereoselectively protonated (which was not possible with the corresponding alkoxide-enolates⁶⁾). Thus, the *trans*-5,6-dimethyl-1,3-dioxanone **3a** was converted (85% ds) to the *cis*-5,6-dimethyl isomer **5** by protonation of the silyl-enol ether **6**. It is also possible to prepare 5,5-disubstituted 1,3-dioxanones **7**.



Mild acid-catalysed hydrolysis of the 1,3-dioxanones leads to the enantiomerically pure α -branched or α,α -disubstituted β -hydroxybutyric acids such as the 2-benzyl-3-hydroxybutyric acid⁷⁾ (**8**, $\text{R}^1 = \text{C}_6\text{H}_5\text{CH}_2$, $\text{R}^2 = \text{H}$, from **3c**).

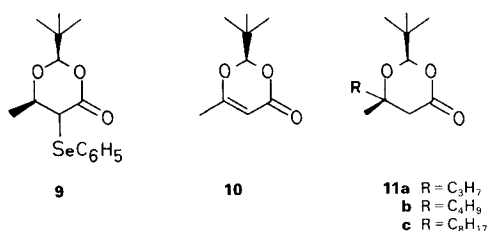
The enolate **2** also reacts with hetero-electrophiles. It can, for instance, be selenated with phenylselenenyl chloride to give **9** which is oxidised to the selenoxide derivative,

⁴⁾ See the discussions in [8] [9].

⁵⁾ The $^3J(\text{H}-\text{C}(5), \text{H}-\text{C}(6))$ values of both stereoisomers of **4** is 9.1 Hz, similar to compound **3** (10 Hz) and unlike compound **5** (4.5 Hz). Assuming that the intramolecularly H-bonded conformer prevails, we can tentatively assign the (*S*)-configuration at C(1') to the diastereoisomer **4a** [10].

⁶⁾ Hitherto unpublished results by J. Z.¹⁾. The diastereoselectivity was about 66% in the best case. Products of *threo*-configuration (*Fischer* nomenclature) are obtained by α -alkylation of β -hydroxy-carbonyl compounds only in cyclic cases, see for instance the γ - and δ -lactones of 3,4- and 3,5-dihydroxy-carboxylic acids [12].

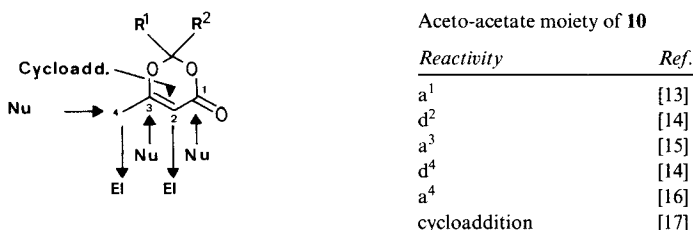
⁷⁾ The acid **8** was converted to the (2*R*, 3*R*)-configured ethyl ester which has about the same value but opposite sign of optical rotation as the known (2*S*, 3*S*)-configured ester [11c].



followed by spontaneous elimination to the crystalline, chiral aceto-acetic-acid derivative **10** (*ca.* 60% overall yield from **1a**).

As indicated in *Scheme 1*, the unsaturated heterocyclic system of **10** is known to exhibit reactivity towards nucleophiles and electrophiles, and its C=C bond is susceptible to cycloadditions.

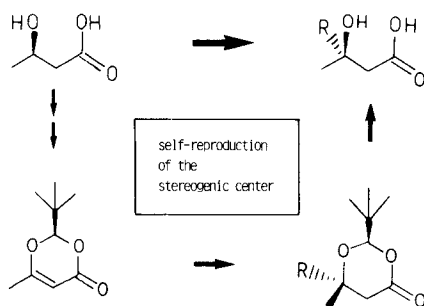
Scheme 1



Aceto-acetate moiety of 10	
<i>Reactivity</i>	<i>Ref.</i>
a ¹	[13]
d ²	[14]
a ³	[15]
d ⁴	[14]
a ⁴	[16]
cycloaddition	[17]

Of these different reactions, we have performed several with our chiral aceto-acetic acid derivative **10**. Thus, the *Michael* addition of dialkyl cuprates leads to single products **11** containing a new persubstituted stereogenic center⁸). The overall process is an example of the self-reproduction of stereogenic centers [18] (see *Scheme 2*), *i.e.* the overall enantioselective alkylation at the one stereogenic center of hydroxybutyrate without using a chiral auxiliary.

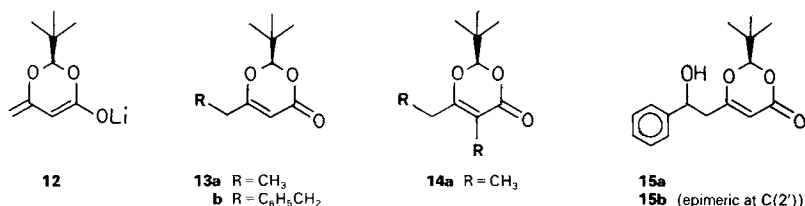
Scheme 2



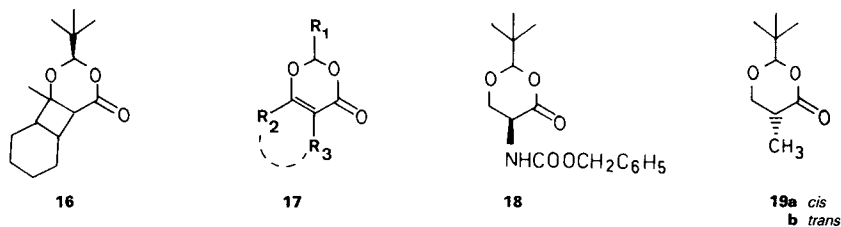
⁸) The configuration at C(4) was assigned by NMR spectroscopy, employing NOE techniques.

The alkylation⁹⁾ of the dienolate **12** of the 1,3-dioxinone **10** takes place preferentially in the γ -position to give the products of type **13** accompanied by the formation of only a minor amount of the dialkylated compound such as **14a**¹⁰⁾. The reaction with benzaldehyde led to a mixture of two diastereoisomers **15a/15b** 2.8:1 (yield 61%).

The double bond in the heterocyclic system can be diastereoselectively hydrogenated with H_2 (30 at, PtO_2): the unsaturated heterocycle **10** gives the (6*R*)-dioxanone **1a** from which it had originally been prepared. Thus, the hydrogenation takes place from the diastereotopic face opposite to the *t*-Bu group, as it is the case in the *Michael* addition.



The photochemical [2 + 2] cycloaddition¹¹⁾ of the 1,3-dioxinone **10** to cyclohexene was performed using a Hg lamp to give the tricyclic derivative **16** as a mixture of diastereoisomers. There is no doubt that **10** may be a source of a myriad of enantiomerically pure products.



There are numerous other β -hydroxy-carboxylic acids [1] [3] [5] which are available in enantiomerically pure form, and which should all be subject to application of the principle described here (see the general *Formula 17*). For example, the *N*-benzyloxycarbonyl-protected serine¹²⁾ forms two diastereoisomeric 1,3-dioxanones **18** in a ratio of 3:1, and the (*R*)-'Roche' acid gives a readily separable 1:1 mixture of the two *cis/trans*-isomeric 1,3-dioxanones **19**.

There are some remarkable mechanistic aspects of the reactions described. Thus, axial attack of electrophiles on the double bond of enol derivatives such as **2** and **6** might have been expected to occur on the diastereotopic face *cis* to the CH₃ and *t*-Bu groups [22]. Also, the exclusive cuprate additions to the 1,3-dioxinone **10**, containing only one sp³

⁹⁾ It is necessary to use HMPT or DMPU as co-solvent [19], otherwise no alkylation takes place. As in many other cases, DMPU has the same effect as HMPT [20].

¹⁰⁾ We did not find any product monoalkylated in the 5-position of the heterocycle. *Smith and Scarborough* [14] reported that the acetonide derivative yields the γ - and the α -alkylated products in a ratio of 2:1.

¹¹⁾ The (–)-menthone acetate of aceto-acetic acid was also investigated in the *deMayo*-type photoaddition. We thank Dr. *Demuth*, *Max-Planck-Institut*, D-4330 Müllheim a.d.R., for sending us his manuscript prior to publication [21].

¹²⁾ The acetals of the β -hydroxyamino acids (serine, threonine, phenylserine) are potential precursors of chiral 1,3-dioxinones of type **17** where R² = H, CH₃, or C₆H₅ and R³ = NR₂ or H.

C-atom in the ring, from the diastereotopic face *trans* to the *t*-Bu group is surprising. As we conclude from the crystal structure of a benzodioxinone [23], the ring should have a 'Sofa' conformation, with all atoms except the tetrasubstituted C-atom in a common plane. If the *t*-Bu group would occupy a *quasi*-equatorial position in such a conformer, the nucleophilic attack should occur *cis* to that group for steric reasons. An evaluation of the role, which the involved metals might play, and of possible stereoelectronic effects does not appear reasonable to us at this stage of the investigations.

We thank Dr. J. Winkler (University of Chicago, USA) for inspiring discussions about *deMayo* reactions with aceto-acetic-acid enol-acetal derivatives (achiral and racemic dioxinones of type **17**), and we gratefully acknowledge the receipt of a manuscript in which a chiral, menthone-derived dioxinone is used for a *deMayo* annelation¹¹⁾ [21].

Experimental Part

The ratios of diastereoisomers were determined from the ¹H-NMR spectra (300 MHz) of the crude products, > 95% ds indicates that no other isomer was detected. Unless otherwise stated, the acetals **1** and **3** were deprotonated at – 75° with LDA in THF. The neat electrophile was added, and the mixture was stirred overnight at – 75°. The oxidation and elimination of the phenylseleno acetal **9** were carried out in CH₂Cl₂ at r.t. The *Michael* additions were performed using dialkyl cuprates in THF at – 75° with NH₃/NH₄Cl quenching. The dienolate from **10** was prepared by treatment with LDA/DMPU (15%-vol. of solvent) at – 75° in THF. The neat electrophile was added, and the temp. allowed to rise to 0° overnight. Hydrogenation of **10** was performed using H₂ (30 at) and PtO₂ as catalyst in AcOEt. The following list contains some experimental details and characteristic data of the compounds prepared (y = yield; ds = content of major diastereoisomer). All spectra are in agreement with the proposed structures. All [α]_D values refer to r.t., CHCl₃ soln., and c = 1–2 g/100 ml. The NMR data refer to CDCl₃ solns.

1a: From tech.-grade pivalaldehyde (containing *t*-BuOH) and (*R*)-3-hydroxybutyric acid [**4**]¹³⁾ (CH₂Cl₂, Dowex 50 W, azeotropic removal of H₂O), 55% y, m.p. 82.5°, [α]_D = – 56.6° [6].

3a: From **1** and MeI (excess), 94% y, > 95% ds, m.p. 67.0–67.5°. ¹H-NMR: 2.35 (*qd*, *J* = 7.2, 10.4, H–C(5)); 3.62 (*qd*, *J* = 6.1, 10.5, H–C(6)).

3b: From **1** and CH₂CHCH₂Br, 85% y, > 95% ds, [α]_D = – 62.5°. ¹H-NMR: 1.34 (*d*, *J* = 6.08, CH₃); 3.82 (*qd*, *J* = 6.08, 10.13, H–C(6)).

3c: From **1** and C₆H₅CH₂Br, 80% y, > 95% ds, m.p. 63.0–64.0°, [α]_D = – 52.9°.

4: From **1** and benzaldehyde, 68% y (crude), separation of one diastereoisomer by flash chromatography (SiO₂, hexane/Et₂O 2:1). **4a**: ¹H-NMR: 0.84 (*d*, *J* = 6.1, CH₃); 2.82 (*dd*, *J* = 3.3, 9.1, H–C(5)); 4.0 (*qd*, *J* = 6.2, 9.1, H–C(6)); 5.43 (*d*, *J* = 3.3, H–C(1')).

5: From **3a** (LDA, then Me₃SiCl (excess) (→**6**), then aq. NH₄F, *in situ*), 93% y (crude), 85% ds. ¹H-NMR: 2.7 (*qd*, *J* = 7.23, 4.78, H–C(5)); 4.18 (*qd*, *J* = 6.41, 4.78, H–C(6)).

7a: From **3a** and MeI (excess), 90% y, m.p. 38.0–39.0°, [α]_D = + 28.7°.

7b: From **3c** and MeI (excess), 63% y, > 95% ds, m.p. 90.0–91.0°. ¹H-NMR: 1.26 (*d*, *J* = 6, CH₃); 1.38 (*s*, CH₃); 4.6 (*s*, H–C(2)).

8 (R¹ = C₆H₅CH₂, R² = H): From **3c** (95% EtOH/H₂O, r.t., Dowex 50 W), 97% y, m.p. 123.0–124.0°, for configuration, see Footnote 7.

9: From **1a** and C₆H₅SeCl (addition of the enolate soln. to selenyl chloride, – 75°), variable mixture of diastereoisomers, 83% y, separation from starting material possible by flash column chromatography.

10: From mixture of diastereoisomers **9**, H₂O₂ (30%), pyridine in CH₂Cl₂, (0° with > 50 mmol runs), 82% y, m.p. 48.5°, [α]_D = – 217.7°. ¹H-NMR: 1.05 (*s*, *t*-Bu); 2.05 (*s*, CH₃); 5.0 (*s*); 5.35 (*s*).

11a: From **10** and (C₅H₇)₂CuLi, > 95% ds. ¹H-NMR: 4.92 (*s*, H–C(2)).

11b: From **10** and (C₄H₉)₂CuLi (1.1 equiv.), 85% y, > 95% ds. ¹H-NMR: 1.24 (*s*, CH₃); 2.48 (*d*, *J* = 15.9, H–C(5)); 2.65 (*d*, *J* = 15.9, H–C(5)); 4.92 (*s*, H–C(2)). For configuration, see Footnote 8.

11c: From **10** and (C₅H₁₇)₂CuLi (3.5 equiv.), 66% y, > 95% ds, [α]_D = + 2.4°.

13a: From **10** and MeI (excess), 55% y after chromatographic separation from **14a** (ratio 5:1). ¹H-NMR: 1.05 (*s*, *t*-Bu); 1.14 (*t*, CH₃); 2.31 (*q*, CH₂); 5.02 (*s*); 5.28 (*s*).

¹³⁾ Available from *Marlborough Biopolymers Ltd.*, Elta House, Yarm Road, GB-Stockton-on-Tees, Cleveland TS18 3RX.

13b: From **10** and $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$, 58% y. $^1\text{H-NMR}$: 1.06 (s, *t*-Bu); 2.46–2.96 (*m*, CH_2CH_2); 4.90 (*s*); 5.18 (*s*); 7.0–7.3 (*m*, arom. H).

14a (By-product of **13a**): 12.5% y. $^1\text{H-NMR}$: 1.05 (*s*, *t*-Bu); 1.14 (*t*, CH_3); 1.82 (*s*, CH_3); 2.38 (*m*, CH_2); 4.95 (*s*, H–C(2)).

15: From **10** and $\text{C}_6\text{H}_5\text{CHO}$, 60% y, 70% ds. $^{13}\text{C-NMR}$ (major (minor) diastereoisomer): 23.77; 34.12; 42.52 (42.81); 71.11; 96.77 (97.06); 105.89 (106.13); 125.53 (125.62); 127.92 (128.01); 128.50; 142.51; 163.1; 171.76.

16: By irradiation (450-W Hg low-pressure lamp) of a 0.05M soln. of **10** in hexane with cyclohexene (4 equiv.), 74% y, mixture of diastereoisomers, acetal H-atoms (H–C(2)) in $^1\text{H-NMR}$: 4.88, 5.23, 5.36, and 5.57 ppm.

18¹⁴): From commercial *N*-benzyloxycarbonyl-protected (*S*)-serine and pivalaldehyde (C_6H_6 , pyridinium (*p*-toluenesulfonate), azeotropic removal of H_2O), 30% y, 75% ds, major diastereoisomer (crystallization from Et_2O), m.p. 106.0°, $[\alpha]_{\text{D}} = +8.7^\circ$.

19¹⁴): From commercially available ethyl (*S*)-3-hydroxy-2-methylpropionate (hydrolysis to acid *cf.* [4]) and acetalization with pivalaldehyde (C_6H_6 , pyridinium (*p*-toluenesulfonate), azeotropic removal of H_2O , *cf.* [6]). **19a**: 28% y, m.p. 42.0–45.0°. $^1\text{H-NMR}$: 1.35 (*d*, CH_3); 2.80 (*m*, H–C(5)); 4.95 (*s*, H–C(2)). **19b**: 32% y, m.p. 71.0–73.0°. $^1\text{H-NMR}$: 1.15 (*d*, CH_3); 2.60 (*m*, H–C(5)); 4.85 (*s*, H–C(2)). Assignment by NOE-NMR measurements.

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¹⁴) We thank U. Gysel and B. Giesinger for experimental assistance.