110. Enzyme-Catalyzed Hydrolysis of Some Functionalized Dimethyl Malonates[1])

by **Marcel Luyten, Susanna Müller, Beat Herzog,** and **Reinhart Keese***

Institut für Organische Chemie, Universität Bern, Freiestrasse 3, CH-3012 Bern

(21.IV.87)

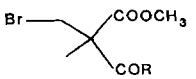
A method is described for the preparation of (+)-(*R*)-methyl hydrogen 2-(*tert*-butoxymethyl)-2-methylmalonate (**5e**) in synthetically useful amounts from readily available starting material.

Multifunctional, chiral compounds with known absolute configuration are valuable starting materials for synthetic purposes. They can be prepared by asymmetric synthesis [1] [2] or by enantioselective reactions with appropriate catalysts or enzymes [3]. The desired synthons can also be obtained from the chiral pool [4], although the necessary transformations might be a multistep task.

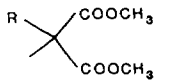
Enzymatic reactions, by now an established synthetic method in the organic laboratory [5], provide a wide range of useful chiral synthons from prochiral precursors. The success of this methodology stems from the fact that certain enzymes will accept a wide range of substrates while retaining a high enantioselectivity.

In cases, where the desired chiral compound is formed with small enantiomeric excess (e.e.), it might be possible to prepare the desired synthons in high chemical yield and e.e. *via* a masked or modified functionality. For synthesis of the functionalized malonate **6a** with high optical purity, the enantioselective hydrolysis of the prochiral malonates **4a–e** by pig-liver esterase (PLE) was investigated.

Results and Discussion. – In the course of preparation of optically active derivatives of 2-(bromomethyl)-2-methylmalonate **1a**, we noticed that **1b** was hydrolysed by PLE with a moderate e.e. of 46%. Similar results were obtained with **4a** and **4b**. It has been shown by *Björkling* that the optical purity as well as the chirality in the PLE-catalyzed hydrolysis of dialkylated malonates of type **2** depend strongly on the chain length and substituent patterns of an aromatic ring [6]: with $n = 2$–4, the acids formed had (*S*)-configuration, whereas with $n = 6$ and 7, the acids obtained with high e.e. had (*R*)-configuration.



1a R = C_2H_5S
b R = CH_3O

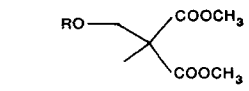


2 R = H–$(CH_2)_n$, n = 2–7
3 R = C_6H_5
R = C_6H_5–X–,
X = COO, O, CH_2, $(CH_2)_2$, CH_2O

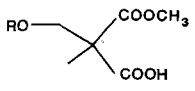
[1]) Presented at the meeting of the Swiss Chemical Society, Berne, October 10, 1986.

Schneider had reported that PLE hydrolyses exclusively the (*pro-S*)-methoxycarbonyl group in disubstituted malonates of type **3**, giving the acids with moderate to high e.e. [7]. An e.e. of 46% was observed in the hydrolysis of dimethyl 2-hydroxy-2-methylmalonate [8].

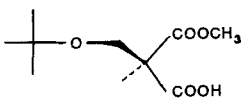
We argued that a bulky substituent containing a functionality which readily could be transformed into the desired hydroxymethyl group of **6a** might lead to highly selective hydrolysis of the (*pro-S*)-ester group. The desired malonates **4a–f** were prepared by alkylation of dimethyl methylmalonate (see *Exper. Part*). When the (*tert*-butyl)dimethylsilyl derivative **4c** of dimethyl 2-(hydroxymethyl)-2-methylmalonate (**4a**) was



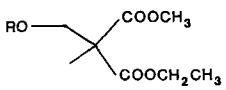
4a–f



5a–e



(+)-(*R*)-**5e**



6a, f

a R = H **d** R = $C_6H_5CH_2$
b R = CH_3 **e** R = *t*-Bu
c R = (*t*-Bu)$(CH_3)_2$Si **f** R = $CH_3C{=}O$

incubated with PLE, the acid **5c** was obtained with 96% e.e. However, the reaction was rather sluggish and gave **5c** only in moderate yield (49%). Although the benzyl-substituted methyl hydrogen malonate **5d** could be obtained from **4d** in high chemical yield, the e.e. was too low for our purposes *(cf. Table)*. High chemical yield (90%) and e.e. (96%) were obtained, when the (*tert*-butoxy)methyl derivative **4e** was hydrolyzed with PLE. This reaction proceeded repeatedly at a higher rate than with **4c**. A lower rate and an e.e. of 90% was observed when the reaction was scaled up to 0.04 mol. When dimethylsulfoxide (10%) was added to the reaction mixture, the rate was lower, while the e.e. remained high at 95% [9]. Addition of 10% (*v/v*) of MeOH gave **5e** in high chemical yield, but a low e.e. of 86%.

Table. *Hydrolysis of Malonates* **4a–e** (5 mmol) *by Pig-Liver Esterase*

4		**5**			
	R	Time[a]) [h]	Yield [%]	e.e. [%]	Configuration
a	H	46.5	37	6	*S*
b	CH_3	30[b])	86	21	*S*
c	(*t*-Bu)$(CH_3)_2$Si	67[c])	49	95	*R*
d	$C_6H_5CH_2$	20.5[d])	90	67	*R*
e	*t*-Bu	6.25	90	96	*R*

[a]) Uptake of 1 equiv. of NaOH in h.
[b]) Reaction started at 10°.
[c]) Reaction with 2.5 mmol of substrate for 28 h; then 2.5 mmol added; 200 µl of PLE added after 24 h and 44 h.
[d]) 200 µl of PLE added after 18 h.

It can be concluded, that PLE hydrolyzes 2,2-dialkylated dimethyl malonates with one bulky substituent which may contain an O-atom and attacks preferentially the (*pro-S*)-methoxycarbonyl group[2]). The absolute configuration of the (+)-acid **5c** was established by chemical correlation with (+)-(*S*)-α-methylserine [10]. The (+)-(*S*)-2-(hydroxymethyl)diester **6a**, prepared from (+)-(*R*)-acid **5c**, served as relais for the determination of the absolute configuration of (−)-(*S*)-acids **5a** and **5b** and the (+)-(*R*)-acids **5d** and **5e** *(cf. Exper. Part)*.

Conclusions. – Superior to the substrates **4a–d**, the readily available dimethyl 2-[(*tert*-butoxy)methyl]-2-methylmalonate (**4e**) is hydrolyzed by PLE to give the (+)-(*R*)-acid **5e** in high chemical yield and an e.e. of 96%. After protection of the acid group, the *t*-Bu group can be cleaved by treatment with HBr in CH_2Cl_2. Thus, the chiral trifunctional derivative **5e** of malonic acid is another compound of the rapidly increasing number of synthons which are readily accessible by enzyme reactions [3].

The support of this work by the *Swiss National Science Foundation* (project No. 2.236-0.84 and 2.016-0.86), the *Stipendienfonds der Basler Chemischen Industrie*, and the *Stiftung zur Förderung der Forschung an der Universität Bern* is gratefully acknowledged.

Experimental Part

General. See [11]. Pig-liver esterase (PLE; E.C. 3.1.1.1; suspension in 3.2M $(NH_4)_2SO_4$ soln., 130 U/mg) was purchased from *Fluka AG*.

General Procedure for Alkylation of Dimethyl 2-Methylmalonate. The malonate was deprotonated with NaH in THF and alkylated with the appropriate alkyl halide under reflux.

Dimethyl 2-(Methoxymethyl)-2-methylmalonate (**4b**). Yield 80%. R_f (pentane/Et_2O 1:1) 0.49. IR: 1750–1720, 1436, 1305, 1110. ^{1}H-NMR: 1.5 (*s*, 3 H); 3.32 (*s*, 3 H); 3.7 (*s*, 8 H). MS: 175 (2, $M^{+\cdot} - 15$), 131 (26), 99 (24), 45 (100).

Dimethyl 2-(Acetoxymethyl)-2-methylmalonate (**4f**). A mixture of **4b** and HBr in AcOH to which NaI and 15% (*v/v*) of Ac_2O had been added was stirred overnight and gave, after workup, **4f** in 91% yield. R_f (hexane/Et_2O 2:1) 0.26. IR: 1735, 1240. ^{1}H-NMR: 1.5 (*s*, 3 H); 2.03 (*s*, 3 H); 3.73 (*s*, 6 H); 4.45 (*s*, 2 H).

Dimethyl 2-(Hydroxymethyl)-2-methylmalonate (**4a**). A soln. of 18.74 g (86 mmol) of **4f** in 200 ml of MeOH and 1 ml of conc. HCl was stirred for 4 days. After removal of 100 ml of MeOH and workup, 11.5 g (76%) of **4a** were isolated in 94% purity. R_f (hexane/Et_2O 2:1) 0.13. IR: 3700, 1730, 1300–1270, 1120, 1050. ^{1}H-NMR: 1.43 (*s*, 3 H); 3.73 (*s*, 6 H); 3.85 (*s*, 2 H). MS: 161 (3, $M^{+\cdot} - 15$), 146 (73), 145 (24), 117 (29), 115 (40), 114 (100), 86 (69), 85 (71), 83 (43), 59 (32), 57 (32).

*Dimethyl 2-{[(*tert*-Butyl)dimethylsilyl]oxymethyl}-2-methylmalonate* (**4c**). In MeCN, 4 g (23 mmol) of **4a** was reacted with 4.07 g (27 mmol) of (*tert*-butyl)chlorodimethylsilane in the presence of 3.53 g (54 mmol) of imidazole: 6.29 g (94%) of **4c**. R_f (hexane/Et_2O 1:1) 0.54. IR: 2960, 1730, 1260, 1100, 1008, 840. ^{1}H-NMR: 0.1 (*s*, 6 H); 0.9 (*s*, 8 H); 1.55 (*s*, 3 H); 3.78 (*s*, 6 H); 4.0 (*s*, 2 H). MS: 275 (1, $M^{+\cdot} - 15$), 233 (59), 203 (29), 119 (65), 89 (100).

Dimethyl 2-[(Benzyloxy)methyl]-2-methylmalonate (**4d**). Yield 82%. R_f (pentane/Et_2O 1:1) 0.51. IR: 1730, 1455, 1437, 1300, 1265, 1125, 1100. ^{1}H-NMR: 1.52 (*s*, 3 H); 3.68 (*s*, 6 H); 3.78 (*s*, 2 H); 4.5 (*s*, 2 H); 7.29 (*s*, 5 H). MS: 266 (2, $M^{+\cdot}$), 128 (81), 101 (20), 91 (100). HR-MS: 266.11512 ($C_{14}H_{18}O_5$, calc. 266.11399).

---

[2]) The following compounds of type **2** are also hydrolyzed in high chemical yield (%) with the enantiomeric excess (e.e.) indicated ($[\alpha]_D$ at r.t. in $CHCl_3$): R = $(CH_3)_2CH$, 87%, $[\alpha]_D = -0.55°$ (*c* = 3.29), e.e. = 19%; R = $C_6H_5(CH_2)_2$, 76%, $[\alpha]_D = +3.2°$ (*c* = 3.08), e.e. 84%; R = $C_6H_5(CH_2)_3$, 81%, $[\alpha]_D = +1.3°$ (*c* = 3.4), e.e. 87%; R = $(CH_3)_3C(CH_2)_2$, 95%, $[\alpha]_D = +0.85°$ (*c* = 3.03), e.e. 96%; no hydrolysis was observed with dimethyl 2-isopropyl-2-(phenylethyl)malonate.

tert-*Butyl Chloromethyl Ether* [12]. A soln. of 14.46 g (164 mmol) of *tert*-butyl methyl ether and 27.2 g mmol) of *N*-chlorosuccinimide in 250 ml of $CFCl_3$ was irradiated in a quartz vessel (reflux condenser) with a low-pressure lamp for 7 h. After filtration over *Celite* under N_2 and addition of 70 ml of abs. THF, the soln. was concentrated to $\frac{1}{3}$ of its volume and immediately used for alkylations.

*Dimethyl 2-[(*tert*-Butoxy)methyl]-2-methylmalonate* (**4e**). Before addition of the *tert*-butyl chlormethyl ether, 1 mol-equiv. of $(C_2H_5)_3N$ was added to the deprotonated malonate. Yield 71%. R_f (hexane/Et_2O 4:1) 0.31. IR: 1730, 1435, 1365, 1085. ^{1}H-NMR: 1.04 (*s*, 9 H); 1.4 (*s*, 3 H); 3.63 (*s*, 8 H). MS: 217 (7, $M^{+\cdot} - 15$), 175 (67), 159 (89), 115 (80), 75 (22), 57 (100).

General Procedure for the Hydrolysis with PLE. To the 2,2-dialkylated dimethyl malonate **4a–e** (5 mmol) suspended in 50 ml of a 0.1N phosphate-buffer soln. at pH 7, 200 µl of PLE (260 U) were added. The addition of 1M NaOH monitored by a pH-stat *(Metrohm AG)* proceeded until 1 equiv. of base had been consumed. Base was added to the mixture and by-products removed with Et_2O. Upon acidification with H_3PO_4, the 2,2-dialkylated methyl hydrogen malonate **5a–e**, extracted with Et_2O, was obtained in a purity > 90%. The enantiomeric excess (e.e.) was determined by ^{1}H-NMR (400 MHz) of the ammonium salt of **5a–e** with (+)-(*R*)-phenylethylamine. In cases with high e.e. (**5c**, **5e**), the relevant ^{1}H-NMR signals were identified in the ammonium salts prepared from racemic methyl hydrogen malonate (saponification with 1 mol-equiv. of KOH).

Methyl Hydrogen 2-(Methoxymethyl)-2-methylmalonate (**5b**). Yield 86%. $[\alpha]_D^{r.t.} = -0.99°$ (c = 3.2, CH_3OH); e.e. = 21% (*S*). IR: 1710, 1445, 1110, 1106. ^{1}H-NMR: 1.5 (*s*, 3 H); 3.36 (*s*, 5 H); 3.73 (*s*, 3 H); 7.7 (*s*, 1 H). MS: 176 (1, $M^{+\cdot}$), 146 (2), 100 (13), 99 (14), 69 (46), 45 (100).

Methyl Hydrogen 2-(Hydroxymethyl)-2-methylmalonate (**5a**). Yield 37%. $[\alpha]_D^{r.t.} = -0.35°$ (c = 3.1, CH_3OH); e.e. = 6.5% (*S*). IR: 1750–1710, 1270, 1125. ^{1}H-NMR: 1.47 (*s*, 3 H); 3.77 (*s*, 3 H); 3.90 (*s*, 2 H); 7.30 (*s*, 2 H); impurities at 1.0–1.3, 3.2–3.6. MS: 161 (1, $M^{+\cdot} - 1$), 146 (12), 132 (16), 110 (43), 101 (46), 86 (29), 85 (30), 69 (42), 59 (69), 57 (57), 56 (90), 29 (100).

*Methyl Hydrogen 2-{[(*tert*-Butyl)dimethylsilyl]oxymethyl}-2-methylmalonate* (**5c**). Yield 49%. $[\alpha]_D^{r.t.} = +5.33°$ (c = 3.26, CH_3OH); e.e. 96% (*R*). IR: 1760–1700, 1470, 1465, 1260, 1100, 840. ^{1}H-NMR: 0.1 (*s*, 6 H); 0.9 (*s*, 9 H); 1.5 (*s*, 3 H); 3.7 (*s*, 3 H); 3.9 (*s*. 2 H); 10.48 (*s*, 1 H). MS: 219 (20), 189 (23), 143 (32), 105 (19), 94 (22), 75 (100).

Methyl Hydrogen 2-[(Benzyloxy)methyl]-2-methylmalonate (**5d**). Yield 90%. $[\alpha]_D^{r.t.} = +6.13°$ (c = 2.94, CH_3OH); e.e. = 67% (*R*). IR: 1760–1710, 1455, 1437, 1300, 1265, 1248, 1095, 700. ^{1}H-NMR: 1.5 (*s*, 3 H); 3.67 (*s*, 3 H); 3.72 (*s*, 2 H); 4.45 (*s*, 2 H); 7.17 (*s*, 5 H); 10.83 (*s*, 1 H). MS: 252 (3, $M^{+\cdot}$), 146 (11), 128 (28), 108 (22), 107 (39), 92 (10), 91 (100).

*Methyl Hydrogen 2-[(*tert*-Butoxy)methyl]-2-methylmalonate* (**5e**). Yield 90%. M.p. 45–47°. $[\alpha]_D^{r.t.} = +6.78°$ (c = 3.11, CH_3OH); e.e. = 96% (*R*). IR: 1755, 1740, 1718, 1270, 1195, 1088. ^{1}H-NMR: 1.14 (*s*, 9 H); 1.47 (*s*, 3 H); 3.73 (*s*, 5 H); 10.4 (*s*, 1 H). MS: 203 (13, $M^{+\cdot} - 15$), 161 (31), 145 (65), 118 (10), 115 (27), 100 (19), 85 (22), 59 (60), 57 (100).

Absolute Configuration: α-Methylserine from **5c**. Reaction of **5c** (0.2 g, 72 mmol) in 0.5 ml of acetone first with ethyl chloroformiate (0.14 ml, 1.12 mmol) in the presence of Et_3N (0.12 ml, 0.86 mmol), then with NaN_3 (0.073 g, 1.12 mmol) in 0.5 ml of H_2O gave the azide which, after workup, was slowly heated in toluene [6a]. The isocyanate obtained (0.18 g) was refluxed in 4 ml of 20% HCl soln. for 3 h and yielded 0.086 g of crude α-methylserine, which was purified by ion-exchange chromatography (*Dowex 50 WX8*, 1M aq. NH_3): 0.052 g (60%). Crystallisation from H_2O/EtOH and a small amount of acetone gave white needles. M.p. 258–264° ([9]: 260–265°). $[\alpha]_D^{r.t.} = +5.45°$ (c = 2.02, H_2O), corresponds to (*S*)-configuration [10]. IR (KBr): 1650, 1615, 1570, 1540, 1410, 1353, 1070, 1060. ^{1}H-NMR (D_2O): 1.42 (*s*, 3 H); 3.67 (*d*, J = 12, 1 H); 3.92 (*d*, J = 12, 1 H); 4.78 (*s*, 4 H). ^{13}C-NMR: 21.0, 65.0, 67.3, 177.9. MS: 120 (1, $M^{+\cdot} + 1$), 89 (8), 88 (100), 74 (57).

Ethyl Methyl 2-(Hydroxymethyl)-2-methylmalonate (**6a**). *From* **5c**. Acid **5c** (0.173 g, 0.63 mmol) was esterified according to [13], filtered through silica gel, and treated with Bu_4NF in THF/H_2O 10:1 first at r.t. (1 h), then at reflux (1 h). After chromatography with hexane/Et_2O 2:1, then hexane/Et_2O 1:1 and a bulb-to-bulb distillation, **6a** was obtained as colourless oil. Yield 0.044 g (37%). R_f (Et_2O) 0.58. $[\alpha]_D^{r.t.} = +0.95°$ (c = 2.2, CH_3OH). ^{1}H-NMR: identical with that given below (from **5e**).

From **5d**. Acid **5d** (0.09 g, 0.36 mmol) was treated with diazoethane and hydrogenated with 10% Pd/C in AcOEt. The crude **6a** (0.065 g, 95%) was purified by *Lobar* chromatography with pentane/Et_2O 2:3. $[\alpha]_D^{r.t.} = -2.15°$ (c = 1.16, $CHCl_3$). ^{1}H-NMR: identical with that given below (from **5e**).

From **5e**. After esterification of 0.20 g (0.9 mmol) of **5e** with diazoethane and filtration through silica gel, the diester was treated with HBr in CH_2Cl_2 at 0°. The crude **6a** was purified by filtration through silica gel and a bulb-to-bulb distillation to give 0.131 g (76.6%) of **6a** in a purity of 95%. $[\alpha]_D^{r.t.} = -2.67°$ (c = 3.07, $CHCl_3$); +1.58° (c = 2.4, CH_3OH). IR: 3575, 1725, 1465, 1300, 1270, 1120, 1050. ^{1}H-NMR: 1.25 (*t*, J = 7.0, 3 H); 1.43 (*s*, 3 H); 3.02

(*t*, *J* = 7.0, 1 H); 3.73 (*s*, 3 H); 3.85 (*d*, *J* = 7.0, 2 H); 4.21 (*q*, *J* = 7.0, 2 H). MS: 190 (1, $M^{+\cdot}$), 160 (66), 145 (22), 128 (56), 117 (20), 115 (61), 114 (59), 110 (10), 100 (40), 86 (60), 85 (100), 83 (46).

Ethyl Methyl 2-(Acetoxymethyl)-2-methylmalonate (**6f**). a) The ester obtained from 0.10 g (0.57 mmol) of (–)-acid **5b** with diazoethane was treated as described above for the preparation of **4f** from **4b** and gave 0.047 g (77%) of crude **6f**, which was purified by bulb-to-bulb distillation (b.p. 110–120°/0.1 Torr). $[\alpha]_D^{r.t.} = +0.59°$ (*c* = 2.54, $CHCl_3$).

b) A sample of 0.045 g (0.24 mmol) of **6a** (prepared from **5c**), was acetylated with Ac_2O in pyridine for 6 h and gave (–)-(*S*)-ester **6f** (0.020 g, 36%). $[\alpha]_D^{r.t.} = -2.27°$ (*c* = 1.19, $CHCl_3$). IR: 1744, 1733, 1303, 1245, 1145, 1127, 1045. ^{1}H-NMR: 1.19 (*t*, *J* = 7.5, 3 H); 1.43 (*s*, 3 H); 1.98 (*s*, 3 H); 3.67 (*s*, 3 H); 4.15 (*q*, *J* = 7.5, 2 H); 4.38 (*s*, 2 H). MS: 232 (2, $M^{+\cdot}$), 189 (24), 187 (32), 160 (70), 132 (59), 128 (32), 114 (23), 100 (48), 43 (100).

REFERENCES

[1] D. Enders, R. W. Hoffmann, *Chemie in unserer Zeit* **1985,** *19,* 177.
[2] J. D. Morrison, Ed., 'Asymmetric Synthesis', Academic Press, Orlando, Vol. 1–5.
[3] J. B. Jones, Tetrahedron Report No. 203, *Tetrahedron* **1986,** *42,* 3351.
[4] D. Seebach, H.-O. Kalinowski, *Nachr. Chem. Techn. Lab.* **1976,** *24,* 415.
[5] M. P. Schneider, Ed., 'Enzymes as Catalysts in Organic Synthesis', D. Reidel + Publ. Comp., Dordrecht, 1986.
[6] a) F. Björkling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, P. Szumlik, *Tetrahedron* **1985,** *41,* 1347; b) F. Björkling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, *Tetrahedron Lett.* **1985,** *26,* 4957.
[7] a) M. Schneider, N. Engel, H. Boensmann, *Angew. Chem.* **1984,** *96,* 54; *ibid. Int. Ed.* **1984,** *23,* 66; b) M. Schneider, personal communication (FB 9-Organische Chemie der Universität-GH, Gaußstrasse 20, D–5600 Wuppertal 1), Sept. 8, 1986.
[8] P. Mohr, N. Waespe-Šarčević, C. Tamm, K. Gawronska, J. K. Gawronski, *Helv. Chim. Acta* **1983,** *66,* 2501.
[9] F. Björkling, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, P. Szmulik, *Bioorg. Chem.* **1986,** *14,* 176.
[10] N. Takamura, S. Tetashima, K. Achiwa, S. Yamada, *Chem. Pharm. Bull.* **1967,** *15,* 1776.
[11] M. Luyten, R. Keese, *Tetrahedron* **1986,** *42,* 1687.
[12] H. W. Pinnick, N. H. Lajis, *J. Org. Chem.* **1978,** *43,* 3964.
[13] B. Neises, W. Steglich, *Angew. Chem.* **1978,** *90,* 556; *ibid. Int. Ed.* **1978,** *17,* 522.