An Efficient Synthesis of Carlosic Acid and Other 5-Carboxymethyltetronates from Malates

Rainer Schobert,* Carsten Jagusch

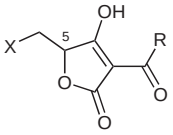
Organisch-chemisches Laboratorium der Universität Bayreuth, Gebäude NW I, 95440 Bayreuth, Germany
Fax +49(921)552671; E-mail: Rainer.Schobert@uni-bayreuth.de

Received 16 March 2005; revised 14 April 2005

Abstract: *S*-Carlosic acid was prepared in six steps and 32% yield from malic acid. Ring closure was effected by a domino addition–Wittig alkenation reaction with Ph_3PCCO. A variant employing resin-bound malates furnished immobilized 5-carboxymethyltetronates. It should be amenable to parallelization and automation.

Key words: domino reactions, solid-phase, lactones, natural products, bismuth triflate

Tetronic acids are rife in nature[1,2] and have been isolated from a broad range of predominantly lower organisms such as moulds, fungi, lichens and sponges. 3,5-Disubstituted derivatives are of particular medicinal interest due to their frequent biological activities.[3] Compounds **1** and **2** are typical examples of bioactive 3-acyltetronic acids bearing short hydrophilic hydroxymethyl or carboxymethyl residues at C-5. RK-682 5*R*-**1**[4] was isolated from the strains of *Actinomycetes* DSM 7357 and *Streptomyces* sp. AL-462 and was found to inhibit HIV-1 protease and various protein tyrosine phosphatases. Carlosic acid 5*S*-**2** (Figure 1) is an intermediate in the biosynthesis of penicillic acid. It was isolated from *Penicillium charlesii*[5] as early as 1934 but synthesized for the first time only in 1974 by Bloomer and Kappler.[6,7]

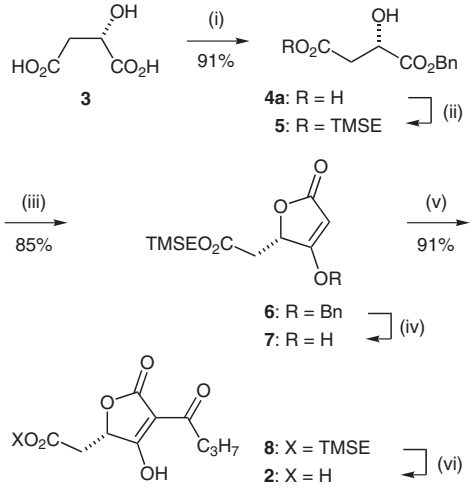


RK-682 (5*R*-**1**): R = $(CH_2)_{14}Me$; X = OH
Carlosic acid (5*S*-**2**): R = *n*-C_3H_7; X = CO_2H

Figure 1

Herein we report an efficient five-step solution-phase synthesis of carlosic acid from benzyl malate and a solid-phase variant thereof, which should be widely applicable to 5-carboxymethyl substituted tetronates in general, lending itself ideally to a combinatorial processing.

α-Hydroxyesters can be cyclized under pH-neutral, non-racemizing conditions to the corresponding tetronates with the cumulated phosphorus ylide (triphenylphosphoranylidene)ketene, $Ph_3P{=}C{=}C{=}O$.[8] This reaction commences with an addition of the OH-group across the C=C bond in the starting ylide to give a stabilized ester ylide which is not normally isolated but undergoes an intramolecular olefination of the ester C=O bond. The same approach was now pursued for the synthesis of carlosic acid from an appropriate malate (Scheme 1).



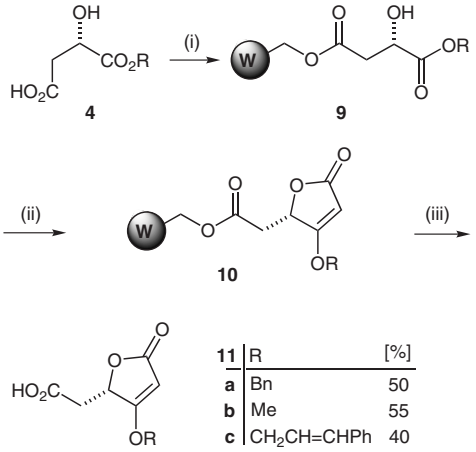
Scheme 1 Solution-phase synthesis of carlosic acid 5*S*-**2** from malate **5** and Ph_3PCCO. *Reagents and conditions*: (i) $(CF_3CO_2)_2O$, neat, r.t., 40 min; evaporation, then $PhCH_2OH$, r.t., 3 h; (ii) DCC, DMAP, $Me_3Si(CH_2)_2OH$=TMSEOH, CH_2Cl_2, 0 → 25 °C, 16 h, 50%; (iii) Ph_3PCCO, C_6H_6, reflux, 16 h; (iv) 5% Pd/C, H_2 (1 bar), MeOH, r.t., 1 h, 99%; (v) DCC, DMAP, Et_3N, $C_3H_7CO_2H$, CH_2Cl_2, 0 → 25 °C, 15 h; (vi) TBAF·$3H_2O$, THF, r.t., 2 h, 90%.

The regioselective monobenzylation of malic acid according to a literature method[9] gave the corresponding α-hydroxyester **4a**, the free β-carboxylic acid group of which was protected with a trimethylsilylethyl (TMSE)[10] group to give the diester **5**. Reaction of the latter with the ylide Ph_3PCCO under standard solution conditions furnished the benzyl tetronate **6** in a satisfactory 85% yield after purification by flash column chromatography on silica gel. The use of polystyrene-bound Ph_3PCCO, which became available recently,[11] is not necessary here and is generally advisable mainly in cases where the product alkenes are difficult to separate from the by-product phosphane oxide (e.g. tetramates).[12] There are several methods known for the downstream introduction of a 3-acyl residue into preformed tetronic acids under conditions not affecting the chirality center C-5, e.g. the protocol by Yoshii (RCO_2H, DCC, DMAP, Et_3N).[13] Hence tetronate **6** was first hydrogenolytically debenzylated using 5% Pd on charcoal as

SYNTHESIS 2005, No. 14, pp 2421–2425
Advanced online publication: 14.07.2005
DOI: 10.1055/s-2005-870018; Art ID: T03605SS

the catalyst. Treatment of the free tetronic acid **7** with butyric acid under Yoshii conditions led to the formation of the 3-butanoyltetronic acid **8** in excellent 91% yield. Compound **8** was finally deprotected with TBAF,[14] which must not be entirely water-free, to leave optically pure carlosic acid 5*S*-(–)-**2** in 32% overall yield with respect to malic acid.

Malic acid monoesters **4b**,**c** were then prepared analogously and immobilized as esters **9** by attachment of their free β-carboxylic acid function to Wang resin via a Mitsunobu esterification (Scheme 2).



11	R	[%]
a	Bn	50
b	Me	55
c	$CH_2CH{=}CHPh$	40

Scheme 2 Solid-phase synthesis of 5-carboxymethyltetronates **11** from malates **4**. *Reagents and conditions*: (i) Wang resin, PPh_3, DIAD, THF, –10 °C → r.t., 14 h; (ii) Ph_3PCCO, THF, 60 °C, 22 h; (iii) 0.05–0.3 mol% $Bi(OTf)_3$, H_3CCN, 100 °C, microwave, 1 h.

A twofold, easily recoverable excess of **4** was applied to ensure exhaustive loading of the resin. The hydroxyesters **9** were then cyclized with Ph_3PCCO under standard conditions to give the tetronates **10**. Their liberation by cleavage of the exocyclic ester bond turned out not to be a trivial problem. Saponification under basic conditions would endanger the integrity of the configuration at C-5 and also of the lactone bond. Acidic ester cleavage, e.g. with TFA more often than not also disrupts the 'internal' benzyl ether bond of the Wang linker.[15] Bismuth triflate, $Bi(OTf)_3$, was now found to be a highly efficacious though mild Lewis acid catalysts for the selective cleavage of the 5-methylenecarboxylate.[16] It was required in only 0.05–0.3 mol%, did not affect the configuration at C-5 and gave purer products and higher yields when compared to the more common cleavage with TFA/trialkylsilane. For allylic residues R (e.g. **11c**), downstream [3s,3s]-Claisen rearrangements were not induced unless microwave irradiation was maintained for a prolonged period in the presence of more than 0.4 equivalents of $Bi(OTf)_3$. The immobilized tetronic acid **10** (R = H) can be obtained by selective cleavage of a resin-bound tetronate with R = TMSE as described above for carlosic acid. It should be of interest as an entry point to libraries of immobilized tetronates with variable residues R (by 4-O-alkylation) and of 3-acyltetronic acids (by 3-C-acylation). Work to this end is currently underway.

Microwave irradiations were carried out in sealed vials in an MLS Microchemist system. Melting points were recorded in a Gallenkamp apparatus and are uncorrected. Optical rotations were recorded at 589 nm with a Perkin-Elmer polarimeter 241. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrophotometer equipped with an ATR sampling unit. NMR spectra were recorded under conditions as indicated on a Bruker Avance 300 spectrometer. Chemical shifts are given in ppm (δ) downfield from TMS as internal standard. Mass spectra were recorded using a Varian MAT 311A (EI, 70 eV). Microanalyses were carried out with a Perkin-Elmer 2400 CHN elemental analyzer. For flash chromatography Merck silica gel 60 (230–400 mesh) was used. Starting compounds were purchased from Fluka, Bachem and Novabiochem (Wang resin) and used as such without further purification.

Malic Acid Monoesters (4); Typical Procedure for (2*S*)-2-Hydroxysuccinic Acid 1-Benzyl Ester (4a)

Trifluoroacetic anhydride (45 mL) was added to L-malic acid (10.6 g, 79.2 mmol). After 40 min stirring of the mixture all volatiles were distilled off on a rotary evaporator at < 30 °C. Anhydrous benzyl alcohol (50 mL) was added to the white crystalline residue and the resulting mixture was stirred at r.t. for 3 h. The excess alcohol was distilled off and the crude remainder was purified by column chromatography on silica gel 60 to yield **4a** (16.2 g, 91%) as a colorless oil; R_f 0.25 (cyclohexane–EtOAc, 1:2); $[\alpha]_D^{25}$ –15.3 (*c* = 1, $CHCl_3$) {Lit.[17] $[\alpha]_D$ 16.7 (*c* = 1.6, $CHCl_3$) for *ent*-(**4a**)}.

IR (ATR): 3425, 1726, 1711, 1240 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.78 (dd, *J* = 16.6, 6.2 Hz, 1 H, CH_2), 2.94 (dd, *J* = 16.6, 4.5 Hz, 1 H, CH_2), 4.52 (dd, *J* = 6.2, 4.5 Hz, 1 H, CH), 5.17 (s, 2 H, OCH_2), 7.28–7.33 (m, 5 H, ar-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 38.2 (C3), 67.1 (C2), 67.6 (OCH_2), 128.3, 128.4, 128.5 (ar-CH), 134.8 (ar-C^q), 173.0 (C4), 175.2 (C1).

(2*S*)-2-Hydroxysuccinic Acid 1-Methyl Ester (4b)[18]

Yield: 3.3 g (86%) from malic acid (3.54 g, 26.3 mmol) and MeOH (15 mL); colorless oil; $[\alpha]_D^{25}$ –15.0 (*c* = 1, MeOH) {lit.[18] $[\alpha]_D$ –15.6 (*c* = 1.33, MeOH)}.

(2*S*)-2-Hydroxysuccinic Acid 1-Cinnamyl Ester (4c)

Yield: 6.2 g (32%) from malic acid (10.6 g, 26.3 mmol) and cinnamyl alcohol (10.6 mL, 79 mmol); colorless oil; R_f 0.37 (hexane–EtOAc, 1:1).

IR (ATR): 3402, 1727, 1717, 1695, 1205, 1110 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.83 (dd, *J* = 16.2, 6.0 Hz, 1 H, CH_2), 2.94 (dd, *J* = 16.2, 4.5 Hz, 1 H, CH_2), 4.52 (t, *J* = 4.5 Hz, 1 H, CH), 4.84 (d, *J* = 6.6 Hz, 2 H, OCH_2), 6.20–6.31 (m, 1 H, C*H*=CPh), 6.66 (d, *J* = 15.9 Hz, 1 H, C*H*Ph), 7.23–7.40 (m, 5 H, ar-CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 38.5 (C3), 66.8 (C1′), 67.2 (C2), 122.0 (C2′), 126.8, 128.4, 128.7 (ar-CH), 135.5 (C3′), 135.9 (C4′), 173.0 (C1), 175.8 (C4).

MS: *m*/*z* (%) = 250 (21) [M^+], 232 (9), 204 (6), 161 (13), 134 (29), 117 (100).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.36; H, 5.60.

(2*S*)-1-Benzyl-4-trimethylsilylethyl Malate (5)

Ester **4a** (2.24 g, 10.0 mmol) in CH_2Cl_2 (20 mL) was treated with DMAP (50 mg) and trimethylsilylethanol (1.57 mL, 11.0 mmol), the resulting mixture was cooled to 0 °C and dicyclohexylcarbodiimide (DCC; 2.27 g, 11.0 mmol) was added portionwise. The reaction mixture was stirred at r.t. for 16 h, the precipitated dicyclohexylurea was filtered off, the filtrate was concentrated and the crude product was purified by column chromatography on silica

gel to yield **5** (1.61 g, 50%) as a colorless oil; R_f 0.31 (hexane–EtOAc, 4:1); $[\alpha]_D^{25}$ –15.9 (*c* = 1, $CHCl_3$).

IR (ATR): 3451, 1738, 1248, 858, 832 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.0 (s, 9 H, $SiMe_3$), 0.90–0.96 (m, 2 H, CH_2Si), 2.73 (dd, *J* = 16.3, 5.8 Hz, 1 H, CH_2), 2.83 (dd, *J* = 16.3, 4.7 Hz, 1 H, CH_2), 4.09–4.17 (m, 2 H, CH_2CH_2Si), 4.50 (dd, *J* = 5.8, 4.7 Hz, 1 H, H-5), 5.20 (s, 2 H, OCH_2), 7.30–7.37 (m, 5 H, ar-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = –1.6 ($SiMe_3$), 17.2 (CH_2Si), 38.7 (C3), 63.3 (CH_2CH_2Si), 67.3 (C2), 67.6 (OCH_2), 128.3, 128.5, 128.6 (ar-CH), 135.0 (ar-C^q), 170.5 (C4), 173.2 (C1).

Anal. Calcd for $C_{16}H_{24}O_5Si$: C, 59.23; H, 7.46. Found: C, 59.36; H, 7.37.

(5*S*)-4-Benzyloxy-5-trimethylsilylethylcarboxymethyl[5*H*]furan-2-one (6)

Compound **5** (650 mg, 2.0 mmol), Ph_3PCCO (786 mg, 2.6 mmol), and catalytic amounts of benzoic acid were dissolved in benzene (15 mL) and heated under reflux for 16 h or irradiated for 1 h at 100 °C in a microwave oven. The solvent was evaporated and the crude product was purified by column chromatography to leave **6** (591 mg, 85%) as a colorless oil; R_f 0.37 (hexane–EtOAc, 2:1); $[\alpha]_D^{25}$ –15.1 (*c* = 1, $CHCl_3$).

IR (ATR): 3120, 3066, 1760, 1730, 1628, 1248, 1166, 1152, 858, 832 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.0 (s, 9 H, $SiMe_3$), 0.90–0.96 (m, 2 H, CH_2Si), 2.59 (dd, *J* = 16.1, 8.1 Hz, 1 H, CH_2), 2.83 (dd, *J* = 16.2, 4.3, 1 H, CH_2), 4.10–4.17 (m, 2 H, CH_2CSi), 5.04 (s, 2 H, OCH_2), 5.13 (s, 1 H, H-3), 5.20 (dd, *J* = 8.1, 4.3 Hz, 1 H, H-5), 7.31–7.39 (m, 5 H, ar-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = –1.6 ($SiMe_3$), 17.2 (CH_2Si), 37.2 (CH_2CO_2), 63.5 (*C*CSi), 74.6 (CH_2Ph), 75.1 (C5), 89.9 (C3), 127.9, 128.8, 129.1 (ar-CH), 133.6 (ar-C^q), 168.8 (CO_2TMSE), 171.7 (C2), 179.7 (C4).

MS: *m*/*z* (%) = 348 (7) [M^+], 186 (7), 132 (7), 101 (6), 91 (100), 73 (75), 65 (15), 45 (20).

Anal. Calcd for $C_{18}H_{24}O_5Si$: C, 62.04; H, 6.94. Found: C, 62.16; H, 6.90.

(5*S*)-5-Trimethylsilylethylcarboxymethyldihydrofuran-2,4-dione (7)

Compound **6** (348 mg, 1.0 mmol) was dissolved in MeOH (20 mL) and treated with 5% Pd on charcoal (25 mg). The reaction vessel was repeatedly evacuated and flushed with hydrogen gas and left to stir at r.t. for 1 h, pressurized with 1 atm of H_2. The resulting reaction mixture was filtered through a short plug of celite, which was washed with MeOH (40 mL). The filtrate was concentrated on an oil pump to give pure tetronic acid **7** (250 mg, 99%) as a yellowish solid; mp 80–81 °C; R_f 0.24 (hexane–EtOAc, 1:1); $[\alpha]_D^{25}$ –19.4 (*c* = 1, MeOH).

IR (ATR): 3126, 1762, 1726, 1618, 1249, 1168, 858, 832 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.0 (s, 9 H, $SiMe_3$), 0.80–0.92 (m, 2 H, CH_2Si), 3.04 (s, 2 H, H-3), 3.12 (d, *J* = 22.1 Hz, 1 H, CH_2), 3.38 (d, *J* = 22.1 Hz, 1 H, CH_2), 4.04–4.13 (m, 2 H, CH_2CSi), 4.77 (s, 1 H, H-5).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = –1.6 ($SiMe_3$), 17.2 (CH_2Si), 36.4 (CH_2CO_2), 37.8 (C3), 64.2 (CH_2CSi), 81.1 (C5), 169.4 (CO_2TMSE), 170.5 (C2), 205.2 (C4).

MS: *m*/*z* (%) = 258 (5) [M^+], 243 (15), 215 (25), 173 (15), 145 (20), 129 (50), 117 (10), 101 (100), 73 (100).

Anal. Calcd for $C_{11}H_{18}O_5Si$: C, 51.14; H, 7.02. Found: C, 51.28; H, 6.95.

(5*S*)-3-Butanoyl-5-trimethylsilylethylcarboxymethyldihydrofuran-2,4-dione (8)

Et_3N (0.15 mL, 1.1 mmol) was added at 0 °C to a stirred suspension of tetronic acid **7** (258 mg, 1.0 mmol) in anhyd CH_2Cl_2 (10 mL). To the resulting homogeneous solution was added in succession DMAP (36 mg, 0.3 mmol), butyric acid (97 mg, 1.1 mmol) and DCC (2.47 mg, 1.2 mmol) in three portions. The mixture was stirred for 10 min at 0 °C, the cooling bath was removed, and stirring continued for 15 h at r.t. The precipitate *N*,*N*′-dicyclohexylurea was filtered off over a short plug of celite which was washed with EtOAc. The combined filtrates were washed with 5% HCl, dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by chromatography on silica gel to leave **8** (300 mg, 91%) as orange crystals; mp 86–88 °C; $[\alpha]_D^{25}$ –28.0 (*c* = 0.5, MeOH).

IR (ATR): 3380, 1726, 1633, 1465, 1249, 1167, 858, 832 cm^{-1}.

^1H NMR (CD_3OD): δ = 0.05 (s, 9 H, $SiMe_3$), 0.94 (t, *J* = 7.55 Hz, 3 H, CCH_3), 0.99 (t, *J* = 8.4 Hz, 2 H, CH_2Si), 1.50–1.59 (m, 2 H, CH_2CH_3), 2.54 (dd, *J* = 16.2, 7.0 Hz, 1 H, CH_2), 2.76 (t, *J* = 7.0 Hz, 2 H, $COCH_2$), 2.92 (d, *J* = 16.2 Hz, 1 H, CH_2), 4.19 (t, *J* = 8.4 Hz, 2 H, OCH_2), 4.73 (s, 1 H, H-5), 9.52 (br, 1 H, OH).

MS: *m*/*z* (%) = 328 (5) [M^+], 313 (15), 285 (50), 257 (20), 239 (30), 167 (20), 151 (10), 123 (20), 101 (15), 84 (15), 73 (100).

Anal. Calcd for $C_{15}H_{24}O_6Si$: C, 54.85; H, 7.37. Found: C, 54.69; H, 7.30.

(5*S*)-Carlosic Acid (2)

A solution of **8** (157 mg, 0.5 mmol) in THF (4 mL) was treated with $TBAF{\cdot}3H_2O$ (480 mg, 1.5 mmol) in one portion. After stirring of the mixture at r.t. for 2 h Et_2O (5 mL) and water (5 mL) were added and stirring was continued for 10 min. The layers were separated and the aqueous one was extracted with Et_2O to remove organic impurities. Carlosic acid **2** was extracted from the clear aqueous phase with hot benzene (3 × 50 mL). The combined organic layers were dried and evaporated to leave yellowish crystals (103 mg, 90%); mp 175 °C (lit.[19] 176–177 °C); $[\alpha]_D^{25}$ –125.0 (*c* = 0.25, H_2O) {Lit.[7e] $[\alpha]_D$ –125.0 (*c* = 0.28, H_2O)}.

IR (ATR): 3133 (br), 1745, 1707, 1662, 1604, 1016 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 0.88 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.50–1.57 (m, 2 H, CH_2CH_3), 2.56 (dd, *J* = 16.7, 7.3 Hz, 1 H, CH_2), 2.73 (t, *J* = 7.0 Hz, 2 H, $COCH_2$), 2.83 (dd, *J* = 16.7, 3.5 Hz, 1 H, CH_2), 4.83 (dd, *J* = 7.3, 3.5 Hz, 1 H, H-5), 9.52 (br, 2 H, OH).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 13.7 (Me), 18.3 (CH_2Me), 36.2 (CH_2CO_2), 38.7 ($COCH_2$), 75.8 (C5), 98.2 (C3), 170.5 (CO_2H), 170.8 (C2), 192.1 ($COCH_2$), 192.3 (C4).

MS: *m*/*z* (%) = 228 (5) [M^+], 210 (35), 192 (25), 183 (15), 167 (50), 151 (30), 139 (20), 97 (40), 84 (100).

Immobilized Malates (9); General Procedure

Under a blanket of anhyd Ar Wang resin (1.0 g, loading 1.2 mmol/g, 100–200 mesh, 1% DVB) was suspended in anyhd THF (12 mL) and allowed to swell for 30 min. Malate **4** (2.4 mmol) and Ph_3P (0.65 g, 2.4 mmol) were added, the mixture was chilled to –10 °C and gently shaken and then treated dropwise with a 2 M solution of DIAD (0.47 mL, 2.4 mmol) in anhyd THF (1.2 mL). The mixture was allowed to warm up to r.t. overnight and shaken at this temperature for a further 14 h. The colorless resin was collected on a sintered frit, rinsed in turn with THF (2 × 20 mL), CH_2Cl_2 (2 × 20 mL), CH_2Cl_2 (3 × 20 mL), MeOH (3 × 20 mL) and Et_2O (2 × 20 mL), and dried on an oil pump. Completeness was ascertained by weight increase.

9a

Yield: 1.24 g from **4a** (0.54 g = twofold excess).

IR (ATR): 3505 (br), 1737, 1167 cm^{-1}.

9b
Yield: 1.16 g from **4b** (0.36 g = twofold excess).

IR (ATR): 3507 (br), 1736, 1170 cm^{-1}.

9c
Yield: 1.28 g from **4c** (0.6 g = twofold excess).

IR (ATR): 3504 (br), 1736, 1168 cm^{-1}.

Immobilized Tetronates (10); General Procedure
Under a blanket of anhyd Ar resin-bound malate **9** (1.2 mmol) was suspended in anhyd THF (10 mL) and treated with Ph_3PCCO (480 mg, 1.6 mmol) and benzoic acid (10 mg). The mixture was gently shaken at 60 °C for 22 h. At r.t. the light brown resin was collected on a sintered frit, washed in turn with THF (2 × 20 mL), DMF (2 × 20 mL), CH_2Cl_2 (3 × 20 mL), MeOH (3 × 20 mL), toluene (2 ×20 mL) and Et_2O (2 × 20 mL) and dried in vacuum. Completeness was ascertained by the weight increase and the disappearance of the OH-band of **9** in the IR spectra.

10a
IR (ATR): 1761, 1738, 1631 cm^{-1}.

10b
IR (ATR): 1760, 1736, 1636 cm^{-1}.

10c
IR (ATR): 1754, 1738, 1629 cm^{-1}.

Tetronates 11 from Cleavage of 10 with $Bi(TfO)_3$; Typical Procedure for (5*S*)-4-Benzyloxy-5-carboxymethyl[5*H*]furan-2-one (11a)
Under a blanket of anhyd Ar bismuth triflate (196 mg, 0.3 mmol) was added to a suspension of **10a** (1.3 g, 1.2 mmol) in MeCN (10 mL). The mixture was irradiated in a microwave oven at 100 °C for 1 h and then filtered at r.t. over a fritted funnel. The yellow resin was washed with THF (2 × 20 mL), DMF (2 × 20 mL), CH_2Cl_2 (3 × 20 mL), MeOH (3 × 20 mL), toluene (2 × 20 mL) and Et_2O (2 × 20 mL). The combined filtrates were concentrated and the residue purified by column chromatography on silica gel 60 to yield **11a** (150 mg, 50%) as white crystals; mp 128–130 °C; R_f 0.41 (hexane–EtOAc, 1:2); $[\alpha]_D^{25}$ –10.8 (*c* = 1, MeOH).

IR (ATR): 3112 (br), 1722, 1713, 1620, 1584 cm^{-1}.

^{1}H NMR (CD_3OD): δ = 2.57 (dd, *J* = 16.5, 8.2 Hz, 1 H, CH_2CO_2), 2.89 (dd, *J* = 16.5, 3.8 Hz, 1 H, CH_2CO_2), 5.19 (s, 2 H, OCH_2), 5.19 (dd, *J* = 8.2, 3.8 Hz 1 H, H-5), 5.33 (s, 1 H, H-3), 7.35–7.52 (m, 5 H, ar-H).

^{13}C NMR (75.5 MHz, CD_3OD): δ = 38.1 (CH_2CO_2), 76.1 (OCH_2), 77.4 (C5), 90.5 (C3), 129.3, 129.9, 130.0 (ar-CH), 136.0 (ar-C^q), 172.7 (COOH), 175.2 (C2), 182.8 (C4).

MS: *m*/*z* (%) = 248 (10) [M^+], 132 (10), 91 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{12}O_5$: 248.06847; found: 248.06840.

(5*S*)-5-Carboxymethyl-4-methoxy[5*H*]furan-2-one (11b)
Yield: 113 mg (55%) from **10b** (1.2 g); colorless oil; R_f 0.19 (hexane–EtOAc, 1:1).

IR (ATR): 3328 (br), 1728, 1626, 1516 cm^{-1}.

^{1}H NMR (CD_3OD): δ = 2.56 (dd, *J* = 16.6, 8.2 Hz, 1 H, CH_2CO_2), 2.91 (dd, *J* = 16.6, 3.8 Hz, 1 H, CH_2CO_2), 3.74 (s, 3 H, OMe), 5.22 (ddd, *J* = 8.2, 3.8, 1.1 Hz, 1 H, H-5), 5.27 (dd, *J* = 1.1 Hz, 1 H, H-3).

^{13}C NMR (75.5 MHz, CD_3OD): δ = 37.7 (CH_2CO_2H), 60.8 (OMe), 77.2 (C5), 89.6 (C3), 172.6 (CO_2H), 175.2 (C2), 184.2 (C4).

Anal. Calcd for $C_7H_8O_5$: C, 48.84; H, 4.68. Found: C, 48.79; H, 4.60.

(5*S*)-5-Carboxymethyl-4-cinnamyloxy[5*H*]furan-2-one (11c)
Yield: 63 mg (40%) from **10c** (400 mg); colorless oil; R_f 0.32 (hexane–EtOAc, 1:2).

^{1}H NMR (CD_3OD): δ = 2.65 (d, *J* = 16.1 Hz, 1 H, CH_2CO_2), 2.93 (d, *J* = 16.1 Hz, 1 H, CH_2CO_2), 4.56 (d, *J* = 5.6 Hz, 3 H, OMe), 5.10 (s, 1 H, 3-H), 5.19 (dd, *J* = 7.9, 3.3 Hz, 1 H, OCH), 5.40 (d, *J* = 10 Hz, 1 H, C*H*Ph), 5.87–6.01 (m, 1 H, C*H*=CPh), 7.46–7.68 (m, 5 H, ar-H).

^{13}C NMR (75.5 MHz, CD_3OD): δ = 36.8 (CH_2COOH), 73.4 (OCH_2C=), 75.0 (C5), 89.7 (C3), 120.4 (=*C*HPh), 128.6 (ar-CH), 130.0 (*C*H=CPh), 132.1 (ar-CH), 135.9 (ar-C^q), 162.1 (C2), 172.0 (CO_2H), 179.6 (C4).

Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.69; H, 5.21.

Acknowledgment

Generous financial support from the Deutsche Forschungsgemeinschaft (Grant Scho 402/7-2) and Bayer CropScience is gratefully acknowledged. We thank Daniel Gunzelmann for his practical contributions during his 3rd year's project.

References

(1) (a) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551. (b) Bergquist, P. R.; Wells, R. J. In *Marine Natural Products*, Vol. V; Academic Press: New York, **1983**, 1. (c) Pattenden, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 133. (d) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (e) Keller-Schierlein, W.; Muntwyler, R.; Pache, W.; Zähner, H. *Helv. Chim. Acta* **1969**, *52*, 127. (f) Haynes, L. J.; Plimmer, J. R. *Q. Rev. Chem. Soc.* **1960**, *14*, 292.
(2) For a recent review of syntheses see: Tejedor, D.; Garcia-Tellado, F. *Org. Prep. Proced. Int.* **2004**, *36*, 35.
(3) (a) Rehse, K.; Wagenknecht, J. *Arch. Pharm.* **1979**, *312*, 164. (b) Arai, K. *Chem. Pharm. Bull.* **1989**, *37*, 3229. (c) Roggo, B. E.; Petersen, F.; Delmendo, R.; Jenny, H.-B.; Peter, H. H.; Roesel, J. *J. Antibiot.* **1994**, *47*, 136. (d) Lang, M.; Roesel, J. *Arch. Pharm.* **1993**, *326*, 921. (e) Sodeoka, M.; Sampe, R.; Kagamizono, T.; Osada, H. *Tetrahedron Lett.* **1996**, *37*, 8775. (f) Grandjean, J.; Laszlo, P. *Tetrahedron Lett.* **1983**, *24*, 3319.
(4) (a) Roggo, B. E.; Hug, P.; Moss, S.; Raschdorf, F.; Peter, H. H. *J. Antibiot.* **1994**, *47*, 143. (b) Mittra, A.; Yamashita, M.; Kawasaki, I.; Murai, H.; Yoshioka, T.; Ohta, S. *Synlett* **1997**, 909.
(5) (a) Clutterbuck, P. W.; Haworth, W. N.; Raistrick, H.; Smith, G.; Stacey, M. *Biochem. J.* **1934**, *28*, 94. (b) For the biosynthesis see: Bentley, R.; Bhate, D. S.; Keil, J. G. *J. Biol. Chem.* **1962**, *237*, 859.
(6) Bloomer, J. L.; Kappler, F. E. *J. Org. Chem.* **1974**, *39*, 113.
(7) For other syntheses of **2** also see: (a) Svendsen, A.; Boll, P. M. *J. Org. Chem.* **1975**, *40*, 1927. (b) Svendsen, A.; Boll, P. M. *Tetrahedron Lett.* **1974**, *15*, 2821. (c) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *Tetrahedron Lett.* **1983**, *24*, 5143. (d) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 121. (e) Mitsos, C. A.; Zografos, A. L.; Igglessi-Markopoulou, O. *J. Org. Chem.* **2000**, *65*, 5852.
(8) (a) Löffler, J.; Schobert, R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2799. (b) Schobert, R.; Gordon, G. J. *Curr. Org. Chem.* **2002**, *6*, 1181.

(9) Danielmeier, K.; Steckhan, E. *Tetrahedron: Asymmetry* **1995**, *6*, 1181.
(10) Bourne, G.; Horwell, T.; David, C.; Pritchard, M. C. *Tetrahedron* **1991**, *47*, 4763.
(11) Schobert, R.; Jagusch, C.; Melanophy, C.; Mullen, G. *Org. Biomol. Chem.* **2004**, *2*, 3524.
(12) Schobert, R.; Jagusch, C. *Tetrahedron* **2005**, *61*, 2301.
(13) (a) Nomura, K.; Hori, K.; Arai, M.; Yoshii, E. *Chem. Pharm. Bull.* **1986**, *34*, 5188. (b) Pashkovskii, F. S.; Katok, Y. M.; Khlebnikova, T. S.; Koroleva, E. V.; Lakhvich, F. A. *Russ. J. Org. Chem.* **2003**, *7*, 998.
(14) Willson, T.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Campbell, S. F.; Bordner, J. *Tetrahedron* **1990**, *46*, 1757.
(15) Schobert, R.; Jagusch, C. *Tetrahedron Lett.* **2003**, *44*, 6449.
(16) (a) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517. (b) Sreedhar, B.; Swapna, V.; Sridnar, C. *Synth. Commun.* **2004**, *34*, 1433.
(17) Sutton, A. E.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9935.
(18) Hayashi, Y.; Yamaguchi, J.; Shoji, M. *Tetrahedron* **2002**, *58*, 9839.
(19) Sato, M.; Sakaki, J.-I.; Takayama, K.; Kobayashi, S.; Suzuki, M.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 94.