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A Short Synthesis of the Mould Metabolite (*R*)-(+)-Carolinic Acid from (*S*)-Lactic Acid

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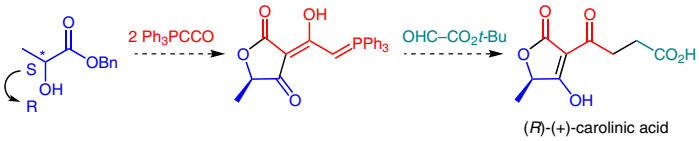

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Abstract (*R*)-(+)-Carolinic acid was prepared in seven steps and 59% yield from inexpensive benzyl L-lactate, the configuration of which was inverted by a Mitsunobu reaction with trifluoroacetate. The resulting benzyl D-lactate was cyclised by a domino addition–Wittig alkenation reaction with Ph_3PCCO. The product tetronic acid was acylated with a second equivalent of this ylide to give a 3-acylylidenetetronic acid, which was olefinated directly with *tert*-butyl glyoxylate. The product alkene was hydrogenated and deprotected to afford pure crystalline (*R*)-(+)-carolinic acid, which proved inactive against *Staphylococcus aureus* and *Escherichia coli* mutant D21f2.

Key words tetronic acids, carolinic acid, Wittig reaction, natural products, stereoinversion

Over 100 naturally occurring tetronic acids are known to date, a good deal of them featuring a 3-acyl residue and exhibiting biological activities associated with their metal affinity and stereoelectronic resemblance to inorganic phosphate.[1–5] Although tetronic acids have been known[6–8] since the 1880's they were not identified as part of natural products until 1934 when Clutterbuck et al. isolated five closely related 5-substituted derivatives from the mould *Penicillium charlesii* G. Smith grown on glucose.[9] Amongst them were carlosic acid (**1**),[10] which is also an intermediate in the biosynthesis of penicillic acid, as well as carolic acid (**2**)[11,12] and carolinic acid (**3**) (Figure 1). The absolute configuration of **2** and **3** was elucidated by Boll et al. in 1968.[13] Racemic carolinic acid **3** was synthesised by Haynes et al.,[14] Svendsen and Boll,[15] and Ley et al.[16] The first two syntheses cyclised a γ-halo-β-ketoester with the required succinyl residue already attached to the α-carbon atom, whereas the Ley group obtained **3** by Pd-catalysed succinylation of methyl 3-stannyltetronate.

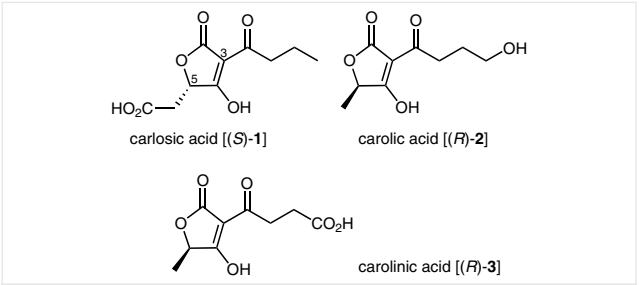
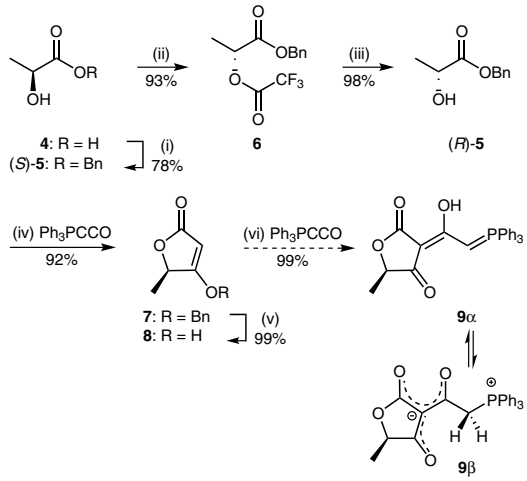


Figure 1 Tetronic acids produced by *Penicillium charlesii* G. Smith

Herein, we report an expeditious synthesis of the natural (*R*)-(+)-enantiomer of carolinic acid starting from inexpensive L-lactic acid, which utilises the cumulated ylide $Ph_3P{=}C{=}C{=}O$[17,18] for both the closure of the five-membered ring and the 3-acylation reaction.

Given that L-lactic acid **4** is much cheaper than its D-enantiomer, which is required for the synthesis of the natural (*R*)-carolinic acid **3**, we inverted the configuration of its benzyl ester (*S*)-**5** in two steps and 91% yield (Scheme 1). Mitsunobu esterification with trifluoroacetic acid afforded diester **6**, which was selectively hydrolysed with lithium carbonate in aqueous methanol to leave benzyl lactate (*R*)-**5**. This was cyclised with ketenylidenetriphenylphosphorane, Ph_3PCCO, under pH-neutral, non-racemizing conditions to furnish tetronate **7** in 92% yield. This domino reaction proceeds through addition of the OH-group of (*R*)-**5** across the C=C bond of the starting ylide to give a new stabilised ester ylide, which undergoes an intramolecular olefination of its ester carbonyl group.[18] Tetronic acid **8** was then liberated by catalytic hydrogenolysis of tetronate **7**. The 3-acylation of tetronic acids can be achieved in various ways, e.g., by reaction with the respective acyl chlorides and BF_3-diethyl etherate according to Jones,[19] or with carboxylic acids and various condensation agents according to

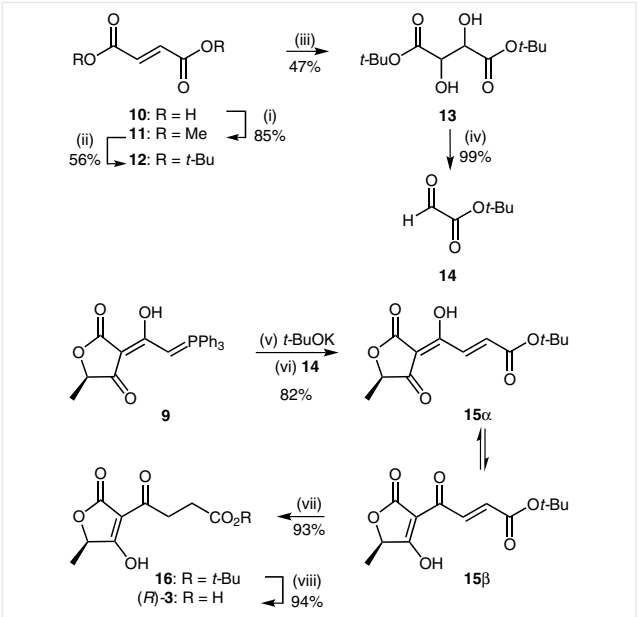
Yoshii,[20] Yoda,[21] or Moloney,[22] or with the ylide Ph_3PCCO.[23] In the latter case, stabilised phosphorus ylides such as **9** result in quantitative yield. They can be deprotonated by potassium *tert*-butoxide in tetrahydrofuran (THF) to give an anionic species that undergoes Wittig alkenation reactions with aldehydes.[24]



Scheme 1 Inversion of benzyl L-lactate **5** and synthesis of 3-[(triphenylphosphoranylidene)acetyl]tetronic acid **9**. *Reagents and conditions*: (i) (a) KOH, DMF, 100 °C, 1 h; (b) BnBr, DMF, 100 °C, 17 h; (ii) diisopropyl azodicarboxylate (DIAD), TFA, Ph_3P, THF, r.t., 7 h; (iii) Li_2CO_3, MeOH/H_2O (8:1), r.t., 20 min; (iv) Ph_3PCCO, benzoic acid, THF, reflux, 48 h; (v) 5% Pd/C, H_2 (1 bar), MeOH, r.t., 1.5 h; (vi) Ph_3PCCO, THF, reflux, 14 h.

To obtain carolinic acid in this way, ylide **9** was prepared in situ, deprotonated, and immediately reacted with *tert*-butyl glyoxylate **14**, which was accessible in four steps and 22% yield by an optimised literature procedure starting from fumaric acid **10** (Scheme 2).

Fumaric acid **10** was converted into its methyl ester **11**, which was transesterified with *n*-butyllithium and *tert*-butyl alcohol to afford di-*tert*-butyl ester **12**.[25,26] This was oxidised with $KMnO_4$ and the resulting tartrate **13** was treated with lead tetraacetate to furnish the Criegee cleavage product **14**.[27] Its Wittig olefination with the anion generated in situ by treating ylide **9**, freshly prepared from tetronic acid **8** and Ph_3PCCO, with potassium *tert*-butoxide, afforded 3-enoyltetronic acid **15** in 82% yield and as a mixture of isomers/tautomers, two of which were observable in the NMR spectra. Hydrogenation of the alkene **15** and subsequent cleavage of the product ester **16** left optically pure carolinic acid (*R*)-(+)-**3** in 59% overall yield with respect to starting benzyl L-lactate. Its specific optical rotation was $[\alpha]_D^{25}$ +23 (*c* 0.33, H_2O) and $[\alpha]_{546}^{25}$ +53 [Lit.[9] +60 (*c* 0.33, H_2O)]. The stereochemical purity of the synthesised product was additionally confirmed by chiral HPLC analysis. In preliminary tests, the synthetic (*R*)-(+)-carolinic acid proved inactive



Scheme 2 *Reagents and conditions*: (i) H_2SO_4, MeOH, reflux, 2 h; (ii) BuLi, *t*-BuOH, THF, r.t., 2.5 h; (iii) $KMnO_4$, *t*-BuOH, r.t., 0.5 h; (iv) $Pb(OAc)_4$, THF, r.t., 0.5 h; (v) *t*-BuOK, THF, reflux, 20 min; (vi) **14**, THF, reflux, 2 h; (vii) 5% Pd/C, H_2 (1 bar), EtOAc, r.t., 0.5 h; (viii) TFA, CH_2Cl_2, 0 °C, 6 h.

against Gram-positive *Staphylococcus aureus* (DSM346) and the drug-sensitive, Gram-negative *Escherichia coli* mutant D21f2 at concentrations as high as 20 µg/mL.

Melting points (uncorrected) were obtained with an Electrothermal 9100 apparatus. Optical rotations were obtained with a Perkin–Elmer polarimeter 241 (λ = 589 nm, 546 nm). IR spectra were obtained with a Perkin–Elmer Spectrum One FTIR spectrophotometer with ATR sampling unit. NMR spectra were obtained with a Bruker Avance 300 spectrometer, chemical shifts are reported in ppm (δ) downfield from TMS_{int}. Mass spectra were obtained with a Varian MAT 8500 (EI, 70 eV). High-resolution mass spectra were obtained with a Thermo Fisher Scientific Q Exactive in ESI^+ ESI^- mode. Chiral HPLC column was a Macherey-Nagel Nucleodex beta-OH. For flash chromatography Merck silica gel 40–60 (230–400 mesh) was used.

(*S*)-Benzyl 2-Hydroxypropionate [(*S*)-5]

A solution of L-(+)-lactic acid **4** (5.0 g, 55.5 mmol) in DMF (200 mL) was heated to 100 °C, treated with KOH (3.74 g, 66.6 mmol), and stirred for 1 h. Benzyl bromide (7.6 mL, 63.8 mmol) was added and the mixture was stirred and heated at 100 °C for another 16 h. After cooling to r.t., the solvent was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (200 mL), washed with H_2O (200 mL), and the aqueous phase was extracted with CH_2Cl_2 (200 mL). The combined organic phases were dried over $MgSO_4$ and the crude product was purified by column chromatography (silica gel 60; hexanes/EtOAc, 4:1) to give (*S*)-**5**.

Yield: 6.94 g (78%); colourless oil; R_f = 0.59 (hexanes/EtOAc, 2:1); $[\alpha]_D^{25}$ –14.4 (*c* 4.0, MeOH) [Lit.[28] –15.9 (*c* 4.0, MeOH)].

IR (ATR): 3424, 1731, 1198, 1122, 1043, 735, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.9 Hz, 3 H, CH_3), 3.45 (s, 1 H, OH), 4.19–4.30 (m, 1 H, CH), 5.10 (s, 2 H, OCH_2), 7.21–7.29 (m, 5 H, Ar-CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.0 (C3), 66.6 (C2), 66.7 (OCH_2), 127.9, 128.1, 128.3 (Ar-CH), 135.1 (Ar-C^q), 175.1 (C1).

MS (EI, 70 eV): *m*/*z* (%) = 180 (3) [M$^+$], 108 (4), 91 (100), 89 (3), 77 (6), 65 (12), 51 (2), 46 (3).

(*R*)-Benzyl 2-Trifluoroacetopropionate (6)

A solution of (*S*)-**5** (6.50 g, 36.07 mmol) in THF (150 mL) was treated with Ph_3P (11.35 g, 43.28 mmol), TFA (3.3 mL, 43.28 mmol), and DIAD (8.5 mL, 43.28 mmol), and stirred at r.t. for 7 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel 60; hexanes/EtOAc, 8:1) to give **6**.

Yield: 9.18 g (93%); colourless oil; R_f = 0.53 (hexanes/EtOAc, 6:1); $[\alpha]_D^{25}$ +38 (*c* 1.0, MeOH).

IR (ATR): 1790, 1749, 1672, 1547, 1199, 1151, 1125, 1090, 734, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (d, *J* = 7.2 Hz, 3 H, CH_3), 5.23 (s, 2 H, OCH_2), 5.32 (q, *J* = 7.2 Hz, 1 H, CH), 7.32–7.44 (m, 5 H, Ar-CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.4 (C3), 67.7 (OCH_2), 71.7 (C2), 114.2 (q, *J* = 283.8 Hz, CF_3), 128.4, 128.5 (Ar-CH), 134.7 (Ar-C^q), 156.8 (q, *J* = 42.5 Hz, CCF_3), 168.2 (C1).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{12}H_{11}F_3O_4$: 276.0609; found: 276.0607.

(*R*)-Benzyl 2-Hydroxypropionate [(*R*)-5]

A solution of Li_2CO_3 (23 mg, 0.31 mmol) in H_2O (5 mL) was added to a solution of **6** (1.09 g, 3.93 mmol) in MeOH (40 mL). After stirring for 20 min at r.t., the mixture was washed with brine, extracted with EtOAc (3 × 50 mL) and dried over $MgSO_4$. The organic phase was concentrated to give (*R*)-**5**.

Yield: 641 mg (98%); colourless oil; R_f = 0.36 (hexanes/EtOAc, 4:1); $[\alpha]_D^{25}$ +13.3 (*c* 0.72, MeOH) [Lit.[29] +13.2 (*c* 0.72, MeOH)].

IR (ATR): 3440, 1732, 1199, 1122, 1043, 735, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.9 Hz, 3 H, CH_3), 3.51 (s, 1 H, OH), 4.32 (q, *J* = 6.9 Hz, 1 H, CH), 5.21 (s, 2 H, OCH_2), 7.33–7.40 (m, 5 H, Ar-CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.3 (C3), 66.9 (C2), 67.2 (OCH_2), 128.2, 128.5, 128.6 (Ar-CH), 135.3 (Ar-C^q), 175.5 (C1).

MS (EI, 70 eV): *m*/*z* (%) = 180 (2) [M$^+$], 108 (3), 91 (100), 89 (4), 77 (6), 65 (15), 51 (2), 46 (3).

(*R*)-4-Benzyloxy-5-methylfuran-2(5*H*)-one (7)

A mixture of (*R*)-**5** (2.17 g, 12.05 mmol), anhydrous THF (60 mL), Ph_3PCCO (4.74 g, 15.67 mmol), and a catalytic amount of benzoic acid was heated to reflux for 48 h. The volatiles were removed in vacuo and the residue was purified by column chromatography (silica gel 60; hexanes/EtOAc, 3:1) to give **7**.

Yield: 2.04 g (92%); white solid; mp 74 °C [Lit.[30] 84 °C for enantiomer]; R_f = 0.65 (hexanes/EtOAc, 2:1); $[\alpha]_D^{25}$ +11.8 (*c* 1.33, $CHCl_3$).

IR (ATR): 3122, 1745, 1617, 1349, 1294, 1235, 1162, 1077, 1059, 943, 916, 902, 858, 815, 757, 709, 699, 659 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 7.0 Hz, 3 H, CH_3), 4.85 (q, *J* = 7.0 Hz, 1 H, $CHCH_3$), 5.04 (s, 2 H, OCH_2), 5.10 (s, 1 H, 3-H), 7.31–7.43 (m, 5 H, Ar-CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.8 (5-Me), 74.3 (OCH_2), 75.4 (C5), 89.0 (C3), 127.8, 128.7, 128.9 (Ar-CH), 133.8 (Ar-C^q), 172.3 (C2), 182.0 (C4).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}O_3$: 205.08592; found: 205.08575.

(*R*)-4-Hydroxy-5-methylfuran-2(5*H*)-one (8)

Compound **7** (2.03 g, 9.94 mmol) was dissolved in MeOH (50 mL), 5% Pd on charcoal (102 mg) was added, and the resulting mixture was purged with hydrogen gas and kept under an H_2 atmosphere (1 bar) for 1.5 h while stirring. After filtration over a pad of Celite, the solvent was removed in vacuo to leave **8** as a 85:15 mixture of enol and diketo tautomers.

Yield: 1.12 g (99%); yellow solid; mp 107 °C [Lit.[30] 118 °C for enantiomer of unspecified enol/diketo ratio]; R_f = 0.38 tailing (acetone/CH_2Cl_2, 1:1); $[\alpha]_D^{25}$ +10.8 (*c* 1.22, MeOH) [Lit.[30] +20.4 (*c* 1.22, MeOH) for enantiomer of unspecified enol/diketo ratio].

IR (ATR): 2940, 2689, 1704, 1587, 1235, 1163, 1074, 1046, 960, 905, 807 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 1.41 (d, *J* = 6.2 Hz, 3 H, CH_3), 4.86 (q, *J* = 6.2 Hz, 1 H, $CHCH_3$), 4.91 (s, 1 H, 3-H), 11.14 (s, 1 H, OH). *Diketone*: 1.41 (d, *J* = 6.2 Hz, 3 H, CH_3), 3.27–3.34 (m, 2 H, CH_2), 4.91 (q, *J* = 6.2 Hz, 1 H, $CHCH_3$).

^{13}C NMR (75.5 MHz, acetone-d_6): δ = 18.1 (CH_3), 75.9 (C5), 89.0 (C3), 168.4 (C4), 182.9 (C2).

MS (EI, 70 eV): *m*/*z* (%) = 114 (14) [M$^+$], 86 (14), 43 (100).

Dimethyl Fumarate (11)

A mixture of fumaric acid **10** (5.0 g, 43.08 mmol), MeOH (70 mL), and H_2SO_4 (1.72 mL, 32.31 mmol) was stirred and heated to reflux for 2 h, then cooled to r.t., and neutralized with 10% aq Na_2CO_3 solution. The precipitate was filtered off to give **11**.

Yield: 5.24 g (85%); white solid; mp 102 °C [Lit.[25] 102 °C]; R_f = 0.37 (hexanes/EtOAc, 95:5).

IR (ATR): 3077, 2964, 1706, 1439, 1295, 1154, 990, 881, 774, 672 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 6 H, OCH_3), 6.86 (s, 2 H, CH).

^{13}C NMR (75.5 Hz, $CDCl_3$): δ = 52.5 (OCH_3), 133.7 (CH), 165.5 (CO).

Di-*tert*-butyl Fumarate (12)

A mixture of *t*-BuOH (1.30 mL) and THF (20 mL) was cooled to 0 °C and treated first dropwise with BuLi (5.55 mL, 13.88 mmol), and after 15 min with **11** (1.00 g, 6.94 mmol). Stirring was continued for 1 h at 0 °C and then at r.t. for 1 h. The reaction was quenched with NH_4Cl and the mixture was extracted with EtOAc (3 × 50 mL). The organic phases were washed with brine, dried over $MgSO_4$ and purified by column chromatography (silica gel 60; hexanes/EtOAc, 19:1) to give **12**.

Yield: 886 mg (3.88 mmol); white solid; mp 69 °C [Lit.[26] 69 °C]; R_f = 0.88 (hexanes/EtOAc, 8:1).

IR (ATR): 2982, 2940, 1703, 1368, 1138, 974, 846, 777, 767, 673 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 18 H, CH_3), 6.67 (s, 2 H, CH).

^{13}C NMR (75.5 Hz, $CDCl_3$): δ = 28.1 (CH_3), 81.6 ($C(CH_3)_3$), 134.7 (CH), 164.7 (CO).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{20}O_4Na$: 251.12521; found: 251.12538.

Di-*tert*-butyl Tartrate (13)

A solution of **12** (5.15 g, 22.55 mmol) in *t*-BuOH (100 mL) was treated with a solution of $KMnO_4$ (5.35 g, 33.83 mmol) in H_2O (100 mL). The mixture was stirred for 30 min and then extracted with Et_2O (3 × 100 mL). The organic phases were washed with H_2O (3 × 60 mL), dried over $MgSO_4$, and diluted with *n*-hexane to precipitate **13**.

Yield: 2.74 g (10.45 mmol); colourless needles; mp 83 °C [Lit.[27] 84–85 °C]; R_f = 0.49 (hexanes/EtOAc, 5:1).

IR (ATR): 3481, 2975, 1731, 1367, 1248, 1091, 853, 755, 603 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 18 H, CH_3), 3.08 (d, *J* = 7.0 Hz, 2 H, C*H*OH), 4.37 (d, *J* = 7.0 Hz, 2 H, OH).

^{13}C NMR (75.5 Hz, $CDCl_3$): δ = 28.1 (CH_3), 72.5 (CH), 83.6 (*C*CH_3), 171.1 (CO).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{22}O_6Na$: 285.13086; found: 285.13043.

***tert*-Butyl 2-Oxoacetate (14)**

A mixture of **13** (147 mg, 0.56 mmol), THF (6 mL), and $Pb(OAc)_4$ (274 mg, 0.62 mmol) was stirred at r.t. for 30 min. The reaction mixture was passed through a syringe filter and the filtrate was used directly for the next reaction step without further purification; R_f 0.28 (hexanes/EtOAc, 3:1).[31,32]

(*R*)-3-[3′-(*tert*-Butoxycarbonyl)prop-(2′*E*)-enoyl]-5-methyltetronic Acid (15)

A boiling solution of tetronic acid **8** (277 mg, 2.43 mmol) in THF (20 mL) was slowly treated over 20 min with a solution of Ph_3PCCO (733 mg, 2.43 mmol) in the same solvent (7 mL). Heating was continued for a further 14 h, then *t*-BuOK (269 mg, 2.40 mmol) was added and heating to reflux was continued for 30 min. *tert*-Butyl glyoxylate **14** (236 mg; 1.441 mmol), as obtained from the Criegee cleavage of **13**, was added dropwise by using a syringe and the reaction mixture was stirred until completeness was indicated by ^{31}P NMR spectroscopic analysis (ca. 2 h). The reaction was quenched with $KHSO_4$ and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (60 mL) and the pH was adjusted to 8.5 with aq $NaHCO_3$ to allow the tetronate salt to accumulate in the aqueous layer. After separation of the phases, the aqueous layer was acidified with 1 M HCl to liberate the tetronic acid, which was extracted with several portions of diethyl ether (70 mL). These extracts were dried with $MgSO_4$ and concentrated in vacuum to afford **15**.

Yield: 524 mg (82%); yellow solid; 1:1 mixture of diketo and enol tautomers; mp 80 °C; R_f = 0.29 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{25}$ +11.5 (*c* 1.0, MeOH).

IR (ATR): 3090, 3057, 2988, 2940, 1761, 1670, 1652, 1571, 1390, 1369, 1311, 1154, 1087, 1051, 1026, 1000, 810, 690, 599 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.53 [s, 9 H, $C(CH_3)_3$], 1.55 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 4.77 (q, *J* = 6.8 Hz, 1 H, C*H*CH_3), 7.00 (d, *J* = 15.7 Hz, 1 H, C*H*COO), 7.94 (d, *J* = 15.7 Hz, 1 H, C*H*CHCOO). δ (*enol*) = 1.53 [s, 9 H, $C(CH_3)_3$], 1.54 (d, *J* = 7.2 Hz, 3 H, CHC*H*$_3$), 4.85 (q, *J* = 7.2 Hz, 1 H, C*H*CH_3), 7.02 (d, *J* = 15.8 Hz, 1 H, C*H*CHOO), 7.95 (d, *J* = 15.8 Hz, 1 H, C*H*CHCOO).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.7 (5-Me), 27.9 [$C(CH_3)_3$], 82.1 (C5), 82.5 [*C*$(CH_3)_3$], 98.0 (C3), 130.3 (=*C*HCO_2), 136.4 (*C*H=CHCO_2), 163.3 (=CH*C*O_2), 174.0 (COH), 175.3 (C2), 194.5 (C4). δ (*enol*) = 16.7 (5-Me), 27.9 [$C(CH_3)_3$], 77.8 (C5), 82.5 [*C*$(CH_3)_3$], 99.9 (C3), 130.7 (*C*H=CHCO_2), 136.9 (=*C*HCO_2), 166.5 (=CH*C*O_2), 175.3 (C2), 177.8 (CCOC), 203.6 (C4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}O_6Na$: 291.08391; found: 291.08352.

(*R*)-3-[3′-(*tert*-Butoxycarbonyl)propanoyl]-5-methyltetronic Acid (16)

Compound **15** (832 mg, 3.10 mmol) was dissolved in anhydrous EtOAc (30 mL), 5 % Pd on charcoal (42 mg) was added, and the resulting mixture was purged with hydrogen gas and kept under a H_2 atmosphere (1 bar) for 30 min while stirring. After filtration over a pad of Celite, the solvent was removed in vacuo to give **16**.

Yield: 778 mg (93%); yellow oil; R_f = 0.29 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{25}$ +6.3 (*c* 1.0, MeOH).

IR (ATR): 2980, 1762, 1726, 1653, 1599, 1366, 1236, 1148, 1047, 1005, 845 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 [s, 9 H, $(CH_3)_3$], 1.53 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$), 2.61 (t, *J* = 6.2 Hz, 2 H, CH_2CO_2), 3.18 (t, *J* = 6.2 Hz, 2 H, C*H*$_2$-CH_2CO_2), 4.88 (q, *J* = 7.0 Hz, 1 H, C*H*CH_3), 11.78 (br. s, 1 H, OH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.1 (5-Me), 28.1 [$(CH_3)_3$], 29.0 (*C*H$_2$-CH_2CO_2), 32.6 (*C*H$_2$CO$_2$), 75.2 (C5), 81.2 [*C*$(CH_3)_3$], 100.7 (C3), 167.8 (CH_2CO_2), 171.2 (C2), 196.7 [3-*C*(O)CH_2], 198.1 (C4).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}O_6Na$: 293.09956; found: 293.09877.

(*R*)-(+)-Carolinic Acid [(*R*)-3]

A solution of ester **16** (176 mg, 0.65 mmol) in CH_2Cl_2 (12 mL) was cooled to 0 °C and treated with TFA (1.3 mL). After stirring for 6 h, the solvent was removed at 0 °C in vacuo to leave (*R*)-(+)-carolinic **3** acid as a light-yellow solid.

Yield: 131 mg (94%); recrystallised from acetonitrile to afford white crystals; mp 141 °C (Lit.[15] 141–142 °C); R_f = 0.20 (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{25}$ +23 / $[\alpha]_{546}^{25}$ +53 (*c* 0.33, H_2O) [Lit.[9] $[\alpha]_{546}$ +60 (*c* 0.33, H_2O)].

IR (ATR): 3279, 2443, 1745, 1729, 1652, 1594, 1374, 1229, 1158, 1056, 1021, 954, 825, 793, 771, 671, 588 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.35 (d, *J* = 6.8 Hz, 3 H, 5-Me), 2.43 (t, *J* = 6.8 Hz, 2 H, $CH_2CH_2CO_2$), 2.96 (t, *J* = 6.8 Hz, 2 H, C*H*$_2$$CH_2CO_2$), 4.81 (q, *J* = 6.8 Hz, 1 H, 5-H).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 17.5 (5-Me), 27.6 ($CH_2CH_2CO_2$), 35.0 ($CH_2CH_2CO_2$), 74.1 (C5), 98.9 (C3), 170.4 (C2), 174.0 ($CH_2CH_2CO_2$), 190.5 [3-*C*(O)CH_2], 193.0 (C4).

HRMS: *m*/*z* [M–H]$^-$ calcd for $C_9H_9O_6$: 213.03936; found: 213.03999.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562625.

References

(1) Haynes, L. J.; Plimmer, J. R. *Q. Rev., Chem. Soc.* **1960**, *14*, 292.
(2) Tejedor, D.; Garcia-Tellado, F. *Org. Prep. Proced. Int.* **2004**, *36*, 35.
(3) Zografos, A. L.; Georgiadis, D. *Synthesis* **2006**, 3157.
(4) Schobert, R.; Schlenk, A. *Bioorg. Med. Chem.* **2008**, *16*, 4203.
(5) Georgiadis, D. *Tetronic Acids*, In *Natural Lactones and Lactams*; Janecki, T., Ed.; Wiley-VCH: Weinheim, **2013**.

(6) Demarcay, E. *Ann. Chim. Phys.* **1880**, *20*, 422.
(7) Wolff, L. *Justus Liebigs Ann. Chem.* **1896**, *291*, 226.
(8) Benary, E. *Ber. Dtsch. Chem. Ges.* **1907**, 1079.
(9) (a) Clutterbuck, P. W.; Haworth, W. N.; Raistrick, H.; Smith, G.; Stacey, M. *Biochem. J.* **1934**, *28*, 94. (b) Clutterbuck, P. W.; Raistrick, H.; Reuter, F. *Biochem. J.* **1935**, *29*, 300.
(10) For syntheses of carlosic acid, see: (a) Bloomer, J. L.; Kappler, F. E. *J. Org. Chem.* **1974**, *39*, 113. (b) Svendsen, A.; Boll, P. M. *J. Org. Chem.* **1975**, *40*, 1927. (c) Svendsen, A.; Boll, P. M. *Tetrahedron Lett.* **1974**, 2821. (d) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *Tetrahedron Lett.* **1983**, *24*, 5143. (e) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 121. (f) Mitsos, C. A.; Zografos, A. L.; Igglessi-Markopoulou, O. *J. Org. Chem.* **2000**, *65*, 5852. (g) Schobert, R.; Jagusch, C. *Synthesis* **2005**, 2421.
(11) For a structural elucidation of carolic acid, see: Simonsen, O.; Reffstrup, T.; Boll, P. M. *Tetrahedron* **1979**, *36*, 795.
(12) For the biosynthesis of **1** and **2**, see also: Bentley, R.; Bhate, D. S.; Keil, J. G. *J. Biol. Chem.* **1962**, *237*, 859.
(13) Boll, P. M.; Sorensen, E.; Balieu, E. *Acta Chem. Scand.* **1968**, *22*, 3251.
(14) (a) Haynes, L. J.; Plimmer, J. R.; Stanners, A. H. *J. Chem. Soc.* **1956**, 4661. (b) Haynes, L. J.; Plimmer, J. R. *Chem. Ind.* **1954**, *37*, 1147.
(15) Svendsen, A.; Boll, P. M. *Tetrahedron* **1973**, *29*, 4251.
(16) Ley, S. V.; Trudell, M. L.; Wadsworth, D. J. *Tetrahedron* **1991**, *47*, 8285.
(17) Bestmann, H. J.; Sandmeier, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 634.
(18) (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. (c) Schobert, R.; Boeckman, R. K. Jr.; Pero, J. E. *Org. Synth.* **2005**, *82*, 140.
(19) Jones, R. C. F.; Begley, M. J.; Peterson, G. E.; Sumaria, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1959.
(20) Hori, K.; Arai, M.; Nomura, K.; Yoshii, E. *Chem. Pharm. Bull.* **1987**, *35*, 4368.
(21) Sengoku, T.; Wierzejska, J.; Takahashi, M.; Yoda, H. *Synlett* **2010**, 2944.
(22) Jeong, Y.-C.; Moloney, M. G. *J. Org. Chem.* **2011**, *76*, 1342.
(23) Schobert, R.; Siegfried, S.; Nieuwenhuyzen, M.; Milius, W.; Hampel, F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1723.
(24) (a) Schlenk, A.; Diestel, R.; Sasse, F.; Schobert, R. *Chem. Eur. J.* **2010**, *16*, 2599. (b) Harras, M.; Bauer, T.; Kempe, R.; Schobert, R. *Tetrahedron* **2013**, *69*, 3677.
(25) Tapaswi, P. K.; Choi, M.-C.; Jung, Y. S.; Cho, H. J.; Seo, D. J.; Ha, C.-S. *J. Polym. Sci., Part A: Polym. Chem.* **2014**, *52*, 2316.
(26) Geny, A.; Agenet, N.; Iannazzo, L.; Malacria, M.; Aubert, C.; Gandon, V. *Angew. Chem. Int. Ed.* **2009**, *48*, 1810.
(27) Blake, J.; Tretter, J. R.; Juhasz, G. J.; Bonthrone, W.; Rapoport, H. *J. Org. Chem.* **1966**, 4061.
(28) Shin, I.; Lee, J.; Jung, M.; Lee, W.; Yoon, J. *J. Org. Chem.* **2000**, *65*, 7667.
(29) Zhu, S.-F.; Chen, C.; Cai, Y.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2008**, *47*, 932.
(30) Schobert, R.; Stehle, R.; Walter, H. *Tetrahedron* **2008**, *64*, 9401.
(31) For the synthesis of **14** by means of periodate, see: Våbenø, J.; Brisander, M.; Lejon, T.; Luthman, K. *J. Org. Chem.* **2002**, *67*, 9186.
(32) For a synthesis of **14** through ozonolysis, see: Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 5079.