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Solid-phase domino syntheses of functionalized tetronates with $Ph_3P{=}C{=}C{=}O$

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Abstract—Domino addition–Wittig olefination reactions of α-hydroxy esters immobilized on polystyrene with $Ph_3P{=}C{=}C{=}O$ to give resin-bound tetronates proceed as readily as in solution. α-Hydroxy allyl esters can react to give either supported allyl tetronates or the corresponding Claisen-rearranged 3-allyltetronic acids, depending on conditions.

3,5-Disubstituted tetronic acids are of medical interest as potential antibiotic, antiviral, antineoplastic and herbicidal agents.[1] We have previously reported an expeditious domino synthesis from α-hydroxy allyl esters and the cumulated phosphorus ylide $Ph_3P{=}C{=}C{=}O$.[2] This proceeds via a controlable sequence of addition of the alcohol onto the ylidic C=C bond, intramolecular Wittig alkenation and Claisen rearrangement to give 3-allyl substituted tetronic acids. More recently we have published cascades extended by Conia-type oxa-ene reactions and further steps that eventually led to tetronic acids with flexibly functionalized 3-alkyl residues.[3] For the parallel synthesis of larger ensembles of potentially bioactive derivatives of such tetronic acids, conditions and limitations of reacting immobilized hydroxy esters with Ph_3PCCO have now been evaluated.

Immobilized α-hydroxy esters of type **3** could be obtained from ring-opening of glycidyl esters **2** by OH-, NH_2–, or SH-terminal polystyrenes **1**[4] of the Merryfield (**1a**,**b**) or the Wang-type (**1c**) (Scheme 1). An efficacious Lewis-acid catalyst for the epoxide opening by polymer-bound alcohol **1c** was found in lithium perchlorate,[5] whereas zinc chloride in DMF/methanol promoted best the reaction of **2** with thiol **1b**. Reaction times can be cut down to less than 1 h by applying microwave irradiation. Ring-opening of **2** to give **3** (X = NH) by the immobilized benzylamine **1a** has been achieved following its deprotonation with $LiN(SO_2CF_3)_2$.[6] In each case the yield (ca. 90%) of the conversion **2**→**3** was estimated on grounds of the weight increase. Complete consumption of the starting nucleophile was ascertained in the case of **1a** by a negative Kaiser staining test.[7] The tandem addition–intra Wittig alkenation reaction of hydroxyesters **3** with cumulated ylide Ph_3PCCO was carried out in THF under microwave conditions with a little benzoic acid added as a catalyst.[8] At 80°C formation of the tetronates **4** was complete after 20 min as to the IR spectra (indicative bands: **3**: 1732–1737 cm^{-1}; **4**: 1725–1730 cm^{-1}) and a negative staining test[9] for free OH-groups. Selective and quantitative benzyl ether cleavage of the linkers in tetronates **4a**–**c** with TFA/DCM (1:1) for 2 h at room temperature in each case afforded exclusively the corresponding 5-hydroxymethylenetetronate which was characterized by ESI mass spectrometry. Allyl esters **3** [$R^2 = CH_2C(R^3){=}CH_2$] could be converted not only to the respective tetronates **4** under these conditions but also directly to the Claisen-rearranged 3-allyltetronic acids **5** by maintaining 120°C in the microwave oven for 1 h.[10]

The liberation of the tetronic acids from the resin in **5**, analogously to that of **4a**–**c**, met with unexpected difficulties. Other customary reagents such as DDQ (0.1 M in CH_2Cl_2) or HF·py failed likewise. As prolonged exposure to TFA only led to cleavage of the 'internal' benzyl ether bond of the Wang linker we assumed that compounds **5** predominantly exist as H-chelates **5′**, the ether-O of which is less basic and less accessible to electrophilic cleaving reagents. Hence we benzylated **5** selectively at O-4 using our isourea method[11] to obtain the non-chelated polymer-bound benzyl 3-allyltetronates **6**.[12] These could then be detached from the resin under standard conditions (TFA/DCM, 9:1), conveniently with concomitant cleavage of the 'protect-

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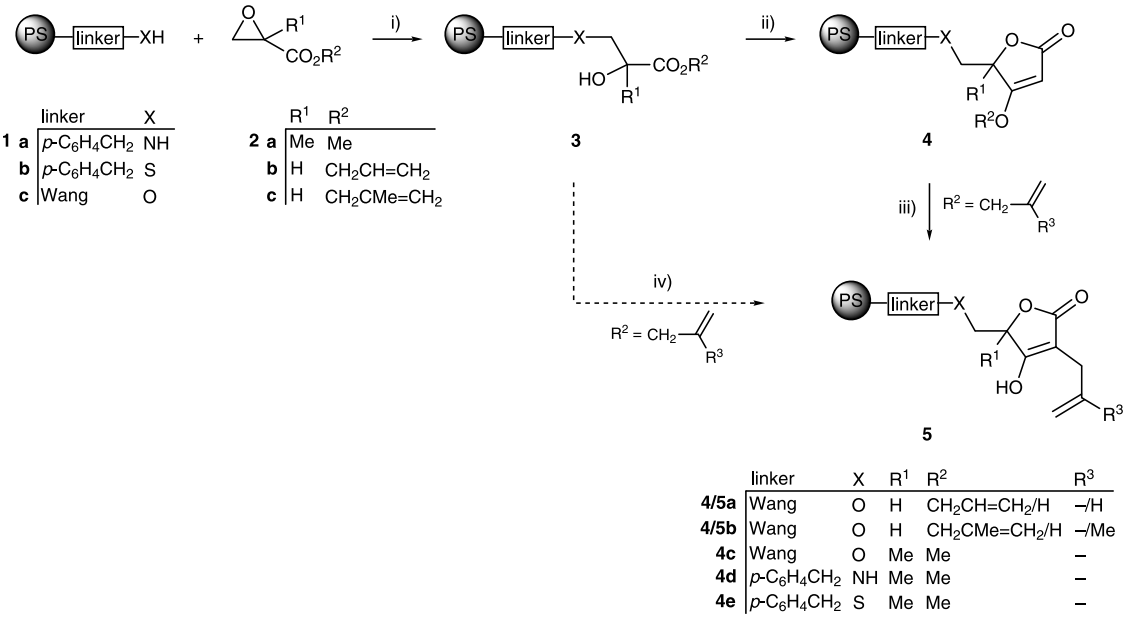
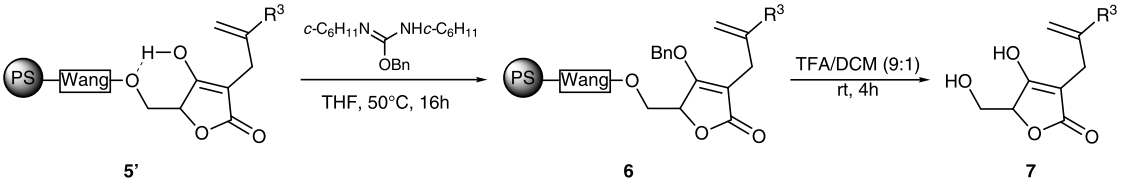


Scheme 1. *Reagents and conditions*: (i) X = O: $LiClO_4$ (1 equiv.), DMF, 85°C, 30 min, microwave (MW) (100 W); X = NH: $LiNTf_2$, CH_2Cl_2, 25°C, 3 days; X = S: $ZnCl_2 \cdot Et_2O$ (0.5 equiv.), DMF/MeOH 9:1, 60°C, 4 days; (ii) Ph_3PCCO (1.3 equiv.), cat. $PhCO_2H$, THF, 80°C, 20 min, MW; (iii) 120°C, 1 h, MW or toluene, reflux, 48 h; (iv) Ph_3PCCO (1.3 equiv.), cat. $PhCO_2H$, THF, 120°C, 1 h, MW.



Scheme 2. Liberation of 3-allyl-5-hydroxymethylenetetronic acids **7**.

ing' benzyl group. The 3,5-disubstituted tetronic acids **7** were obtained almost quantitatively (with respect to **5**) and were characterized by ESI-MS[13] (Scheme 2).

In conclusion we have demonstrated that domino Wittig–pericyclic reaction sequences can be ported to the solid-phase thus opening access to libraries of potentially bioactive heterocycles. Microwave irradiation was found especially conducive to a time-saving automatable processing.

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References

1. (a) Pattenden, G. *Fortsch. Chem. Org. Naturst.* **1978**, *35*, 133–198; (b) Rehse, K.; Wagenknecht, J. *Arch. Pharm.* **1979**, *312*, 164–168; (c) Arai, K. *Chem. Pharm. Bull.* **1989**, *37*, 3229–3235; (d) Roggo, B. E.; Petersen, F.; Delmendo, R.; Jenny, H.-B.; Peter, H. H.; Roesel, J. *J. Antibiot.* **1994**, *47*, 143–147; (e) Lang, M.; Roesel, J. *Arch. Pharm.* **1993**, *326*, 921–924; (f) Sodeoka, M.; Sampe, R.; Kagamizono, T.; Osada, H. *Tetrahedron Lett.* **1996**, *37*, 8775–8778.
2. (a) Löffler, J.; Schobert, R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2799–2802; (b) Schobert, R.; Gordon, G. J. *Curr. Org. Chem.* **2002**, *6*, 1181–1196.
3. (a) Schobert, R.; Siegfried, S.; Gordon, G. J.; Mulholland, D.; Nieuwenhuyzen, M. *Tetrahedron Lett.* **2001**, *42*, 4561–4564; (b) Schobert, R.; Siegfried, S.; Gordon, G. J.; Nieuwenhuyzen, M.; Allenmark, S. *Eur. J. Org. Chem.* **2001**, 1951–1958.
4. Aminomethylpolystyrene **1a** (Novabiochem), cross-linked with 1% divinylbenzene (DVB), 100–200 mesh, loading 0.9 mmol/g; mercaptomethylpolystyrene **1b** (Novabiochem), cross-linked with 2% DVB, 100–200 mesh, loading 4 mmol/g; Wang resin **1c** (Novabiochem), cross-linked with 1% DVB, 100–200 mesh, loadings 1.8 and 2.9 mmol/g.
5. *General procedure for the generation of α-hydroxy esters **3** from **1c***: Wang resin **1c** (0.5 g; loading 2.9 mmol/g) was placed in a vial and pre-swollen for 15 min in DMF (3 mL). Glycidyl ester (2.9 mmol) and $LiClO_4$ (1.45 mmol; 0.484 mL of a 3.0 M solution in ethyl acetate) were added under Ar and the vial was sealed and exposed to microwaves at 85°C for 30 min. [**Warning!** *Lithium per-*

chlorate in an organic solvent is a potential dangerous explosive. The scale of operations should be limited and all precautionary measures should be taken.] Another equivalent of $LiClO_4$ (1.45 mmol) was added and the mixture exposed to microwaves at 85°C for a further 30 min. The golden-brownish resin was filtered and washed thoroughly with DMF (3×10 mL), MeOH (3×10 mL), THF (3×10 mL) and DCM (3×10 mL) and dried in vacuo. The degree of conversion was determined by the increase of the weight of the resin and found to be 80–90%. No more starting materials were detectable. FT-IR (KBr): 1733–1737 cm^{-1} (C=O).

6. Cossy, J.; Bellosta, V.; Hamoir, C.; Desmours, J.-R. *Tetrahedron Lett*. **2002**, *43*, 7083–7086.
7. Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem*. **1970**, *34*, 595.
8. *General procedure for the synthesis of tetronates* ***4***: **3** (1.45 mmol) was pre-swollen in THF (10 mL) while stirring and excluding air and moisture. Keteneylidenetriphenylphosphorane (1.89 mmol) and a catalytic amount of benzoic acid were added and the resulting mixture was heated under reflux for 20 h. The resin was filtered and washed with THF (2×20 mL), Et_2O (2×20 mL), MeOH (2×20 mL) and DCM (2×20 mL) and dried in vacuo. FT-IR (KBr): 1740–1733 cm^{-1} (C=O), 1640–1611 cm^{-1}.
9. Burkett, B. A.; Brown, R. C. D.; Meloni, M. M. *Tetrahedron Lett*. **2001**, *42*, 5773–5775.
10. *General procedure for the microwave-assisted synthesis of tetronic acids* ***5*** *on Wang resin from* ***3***: The immobilised α-hydroxy ester **3** (1.45 mmol) was pre-swollen in THF (5 mL) while stirring and excluding air and moisture. Keteneylidenetriphenylphosphorane (1.89 mmol) and a catalytic amount of benzoic acid were added and the resulting mixture, placed in a sealed vial, was exposed to microwaves at 120°C for 60 min. The resin was filtered and washed with THF (2×20 mL), Et_2O (2×20 mL), MeOH (2×20 mL) and DCM (2×20 mL) and dried in vacuo. FT-IR (KBr): 1710–1720 cm^{-1} (C=O), 1640–1611 cm^{-1}.
11. Schobert, R.; Siegfried, S. *Synlett* **2000**, 686–688.
12. *General procedure for the benzylation of tetronic acids to give* ***6***: **5** (1.25 mmol) was suspended in THF (5 mL) and *O*-benzyl-*N*,*N*′-dicyclohexylisourea (0.5 g, 1.3 equiv.) was added. The mixture was shaken for 16 h at 50–60°C. The resin was washed thoroughly with DMF (2×10 mL), THF (2×10 mL), MeOH (2×10 mL) and DCM (2×10 mL) and dried in vacuo.
13. *Cleavage of* ***6*** *to give* ***7***: Benzyl tetronate **6** (1.25 mmol) was swollen in DCM (5 mL) for 30 min and finally filtered. 10 mL of the cleavage solution (TFA/DCM 9:1) and 5% triisopropylsilane (0.5 mL) were added and the mixture was shaken for 4 h at rt. The resin was filtered and washed twice with 5 mL of DCM. The filtrate was evaporated to dryness. Quantitative conversion was found by weighing the crude and the identity of the products was determined by ESI-MS, NMR and IR.