Phosphorus Ylide Based Functionalizations of Tetronic and Tetramic Acids

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In memory of Hans-Jürgen Bestmann

Abstract: The versatility of the ylide (triphenylphosphoranylideneketene (Ph3P–C=O, 3) in the construction of tetronic and tetramic acids from various carboxylic acid derivatives is demonstrated by new reactions and extensions of known ones. With α-hydroxy or α-amino esters, 3 affords tetrates or tetramates. A two-step synthesis of (−)-epi-blastmycinolactol shows that allyl α-hydroxy esters can be domino Wittig–Claisen reacted to give 3-α-lactones. More extended Wittig–Claisen–Conia cascades can produce 3-alkylidendefuran-2,4-diones, the photooxygenation of which furnishes lactone endoperoxides with antiplasmodial potential. Tetronic acids can be acylated by 3 to give the corresponding 3-acyl compounds, e.g. the fungal metabolite pestethoxin. α-Hydroxy acids react with 3 to afford the corresponding 3-phosphorylidenefuran-2,4-diones. The antibiotic (R)-reutericyclin was built up from benzyl D-leucinate and 3 in four steps by downstream acylation first at C3, then at N1 without racemization.

Key words: domino reactions, phosphorus ylides, tetramic acids, lactones, reutericyclin

Introduction

Several hundred natural products containing either the 4-hydroxyfuran-2(5H)-one (also known as tetronic acid) or the pyrrolidine-2,4-dione (also known as tetronic acid) ring systems have been isolated from a variety of marine and terrestrial organisms, such as bacteria, moulds, algae, fungi, lichens, and sponges.1–4 Typical of these compounds, and of the 3-acyl derivatives in particular, is a high incidence of biological activity including antibiotic, antiviral, antineoplastic, and anticoagulant effects. This has been explained by their ability to chelate biologically important metal ions and to mimic phosphate groups in the binding sites of kinases. Prominent examples are the mould metabolite RK-682 (1),5,6 which inhibits HIV-1 protease and various dual specificity phosphatases, and the Lactobacillus reuteri metabolite reutericyclin (2),7 which inhibits Helicobacter pylori, the causative agent of stomach ulcers (Figure 1, top). Many more natural products are known where additional functional groups attached to positions C3, C5, or 4-O in tetronic acids, or to N1, C3, or C5 in tetramic acids confer further biological properties.8–10 Sometimes, these functional appendages are even more determinant for the chemical and physiological properties than the heterocyclic core itself. For example, the Streptomyces metabolite tetronasin is an ionophore antibiotic due to its extended polyether moiety attached at C3,11 and the yellow pigment physarorubinic acid, an antimicrobial metabolite of Physarum polycephalum,12 owes its color to the conjugated oligoenoyl side chain at C3. While the biosyntheses of such functionalized tetronic and tetramic acids are short and stereoselective, the total laboratory syntheses are often not. In the biosynthesis of tetronic acids, the segment N1–C5–C4 normally originates from the respective α-amino acids, e.g. leucine in reutericyclin, while the source of the C2–C3 segment as well as of potential 3-polyenoyl side chains has been found to be acetate in most cases.13–18 Usually, the preformed polyketides are then linked to the amino acid by peptide synthetases and the lactam ring is closed in the final step between C3 and C4 either enzymatically or spontaneously in the cytoplasm (Figure 1, bottom).

In contrast, total synthesis faces two intricate problems: 1. The ring-closure step. Conditions have to be mild enough not to cause racemization at C5. The hydrogen at C5 is relatively acidic due to the adjacent heteroatom and an inherent tendency to aromatize. In the widely used Lacey protocol,19 3-acyltetramic acids are obtained by alkaline Dieckmann condensation of N-(β-oxoacyl)-α-amino esters, frequently with (partial) racemization.
Although variants have been published where racemization could be suppressed by carefully controlled conditions,\textsuperscript{20-22} the method still lacks generality and predictability. Safer, truly pH-neutral, methods are few and far between. Jouin’s protocol\textsuperscript{23-26} condenses Meldrum’s acid with \(\alpha\)-hydroxy or \(\alpha\)-amino acids, respectively, in the presence of \(N,N’\)\textsuperscript{-dicyclohexylcarbodiimide} and 4-(dimethylamino)pyridine. Heating the intermediate \(\gamma\)-amino-\(\beta\)-oxo ester leads to the corresponding tetramic acid with concomitant formation of acetone and carbon dioxide. Effenberger cyclized chiral \(\gamma\)-hydroxy-\(\beta\)-oxo esters, as obtained by Blaise reaction of O-silylated cyanohydrins with Reformatsky reagents, under acidic conditions to afford enantiomerically pure tetronic acids.\textsuperscript{27}

2. Downstream 3-acylation. Its success very much depends on the system to be acylated. C5- or N1-unsubstituted tetramic acids are particularly hard to react. Another problem is the introduction of long-chain, conjugated polyunsaturated acyl residues. Each of the four most used methods has its shortcomings. The Jones acylation\textsuperscript{28} using acyl halides and boron trifluoride–diethyl ether complex

Biographical Sketches

**Rainer Schobert** studied chemistry at the University of Erlangen (Dipl.-Chem., 1982). He received his doctoral degree in 1985 for works on macrolide antibiotics under the guidance of Prof Hans-Jürgen Bestmann. After a postdoctoral project on organoiron chemistry with Prof Steve Ley, then at the Imperial College in London, he went back to Erlangen to finish his habilitation on early transition metalloccenes in 1993. Between 1999 and 2001 he was a senior lecturer at The Queen’s University Belfast. He currently holds the Chair of Organic Chemistry at the University of Bayreuth, Bavaria. His research interests span a wide range with a focus on the synthesis of bio-active natural and synthetic drugs and the development of new domino reactions and oligofunctional reagents.

**Matthias Dietrich** was born in 1980 in Tirschenreuth, Bavaria. In 2001 he began his studies at the University of Bayreuth towards a qualification as a secondary level teacher of chemistry and biology on a concurrent route. Having just finished an optional third year project in chemistry on the synthesis of endoperoxides, he decided to postpone his educational career and to continue his research as part of a Ph.D. project.

**Gillian Mullen** was born in 1980 in Co Down, Northern Ireland. She studied chemistry at The Queen’s University Belfast and graduated with a B.Sc. in 2001. Later that year she moved to Bayreuth with the Schobert group to explore new synthetic routes to natural tetramic acids. Since January 2006 she has been a research chemist with Pfizer in Cork, Ireland.

**Juan Manuel Urbina-Gonzalez** was born in 1974 in Pamplona, Colombia. He received his B.Sc. and M.Sc. degrees in Chemistry from the Universidad Industrial de Santander under the supervision of Prof Vladimir Kouznetsov. He then carried out his Ph.D. research at the University of Bayreuth under the supervision of Prof Schobert working on the synthesis of fused and spiro furanones.
does not work well for 5-unsubstituted tetramic and tetronic acids and is unsuitable for the introduction of Lewis acid sensitive highly unsaturated side arms. The Yoshii protocol, which works best for tetronic acids, employs free carboxylic acids and N,N'-dicyclohexylcarbodiimide/triethylamine. It is basically a domino sequence comprised of an initial 4-O acylation followed by a Fries-type 4-O→C3 acyl shift. It tends to fail erratically, mostly in the step shift and particularly in the case of unsubstituted systems. The high yielding palladium-catalyzed acylation of 3-stannyl-substituted tetronates requires harsh conditions during their preparation and has not yet been applied to C5-chiral tetronate targets.

Boeckman’s approach of introducing polyenoyl residues via Horner alkenation of 3-β-phosphonylacetyltetramic and tetronic acids also implies basic conditions both for the ring-closure and the phosphonate anion generation steps, which compromises potential stereocenters.

This paper presents some new approaches to bioactive tetramates and tetronates that exploit mild ring-closure methods and selective ways for the simultaneous generation or, at least facile downstream introduction, of frequently occurring functional groups. An emphasis will be laid on phosphorus ylide based domino reactions.

### 3- and 3,4-Functionalized Systems

The direct synthesis of 3-functionalized tetronic and tetramic acids from α-hydroxy or α-amino acid derivatives and phosphorus ylides is possible in different ways. Their esters react with the air-stable, pH-neutral (triphenylphosphorus ylides is possible in different ways. Their esters are similar but the byproduct triphenylphosphine oxide is ranging it under microwave irradiation as above. Yields the methallyl tetronate action can also be carried out stepwise by first preparing the construction of various optically pure natural products, e.g. 1 or the sponge-produced cytotoxic melophlins. In solution, 3-methoxytetronic acids and is unsuitable for the introduction of Lewis acid sensitive highly unsaturated side arms. The Yoshii protocol, which works best for tetronic acids, employs free carboxylic acids and N,N'-dicyclohexylcarbodiimide/triethylamine. It is basically a domino sequence comprised of an initial 4-O acylation followed by a Fries-type 4-O→C3 acyl shift. It tends to fail erratically, mostly in the step shift and particularly in the case of unsubstituted systems. The high yielding palladium-catalyzed acylation of 3-stannyl-substituted tetronates requires harsh conditions during their preparation and has not yet been applied to C5-chiral tetronate targets.

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### Scheme 1

A short synthesis of (−)-epi-blastmycinolactol (7) via domino addition–Wittig alkenation–Claisen rearrangement of methallyl lactate 4 with ylide 3.

This approach is reminiscent of the biosynthesis of tetronic acids. Ylide 3 formally replaces acetate as the C5-O-building block, and the ring gets closed between C3 and C4. Analogously, 3-acetyltetronic acids can be built up by using two equivalents of 3, one for the cyclization proper, and the other for attaching the 3-acetyl group. For example, the racemic 5-α-alkyltetronic acids 10 were readily obtained in two steps from the corresponding benzyl 2-hydroxalkanoates 8 and ylide 3 (Scheme 2). Remarkably, they exist as 3:2 mixtures of enol and keto forms in deuterchloroform, which are clearly discernable in the 1H NMR spectra. Tetronic acids 10 are also CH-acidic compounds and thus were amenable to acetylation at C3 with another equivalent of 3 in refluxing tetrahydrofuran. The resulting acyl ylides 11 can be isolated if desired, or hydrolyzed with aqueous sodium hydroxide at room temperature to leave the corresponding 3-acetyltetronic acids 12 and phosphate oxide as the byproduct. The acyl ylides 11 exist as mixtures of an enol–ylide tautomer (α) and a prevailing o xo–phosphonium tautomer (β) in the more common organic solvents. In dipolar, aprotic solvents such as dimethyl sulfoxide, only the β-tautomer is visible in the NMR. Low temperature 13C and 31P NMR studies revealed that the β-tautomer actually exists as a mixture of two distinct rotamers, presumably differing in the oxygen atom of the formal 1,3-dioxo-enate moiety that interacts with the phosphorus atom of the phosphonium group. At room temperature these rotamers interconvert too rapidly to be resolved by NMR. The hydrolysis product 12b is the natural phytotoxin pestethoxin, a leaf necrosis inducing metabolite of the grey blight fungus Pestalotiopsis theae which regularly infects tea crops. In solution, 3-
acetyltetronic acids 12, like the acyl ylides 11, exist as mixtures of two tautomers. In the case of 12 these tautomers differ in the ring-bound oxygen atom (2-O vs. 4-O) that forms a H-chelate with the exocyclic carbonyl oxygen atom. According to NMR, in the usual organic solvents the tautomer featuring a H-chelate between the exocyclic and the 4-carbonyl groups is dominant (e.g., by 1.6:1 in CDCl3). Either tautomers encompasses a subset of two so-called internal tautomeric forms with differently localized double bonds. However, these are interconverting too rapidly on the NMR time scale to be resolved, even at temperatures as low as –60 °C. This is in agreement with previous spectroscopic and ab initio studies of 3-acetyltetronic acids.41

Ylide-based cyclization of α-hydroxycarboxylic acid derivatives is also possible with retention of the phosphorus ylide functionality at C3. While the reaction of cumulated ylide 3 with free carboxylic acids leads to highly reactive anhydride ylides that are prone to decomposition yielding mixtures of various phosphorus containing species,42 the reaction of 3 with α-hydroxy acids 13 took an unexpectedly clear-cut course producing 3-phosphorylidenefurans-2,4-diones 1533 in good yields and without racemization; (S)-15a was obtained in 95% ee according to chiral HPLC from L-(+)-mandelic acid (Table 1). The reaction presumably starts with the addition of the alcohol group across the C=C bond of 3 to give an ester ylide 14. In contrast to the reaction of α-hydroxy esters with 3, this intermediate ylide now eliminates water rather than undergoing an intra-Wittig alkenation. The product bisacetyl ylides 15 are very stable and so do not react further with the byproduct water. Amazingly, even aqueous solutions of lactic acid reacted with the water-sensitive ylide 3 to afford 15a, if a drying agent, e.g. sodium sulfate, was added to the mixture in refluxing tetrahydrofuran. This leaves room for the extension of this chemistry to carbohydrate derivatives such as uronic acids with unprotected remote hydroxy groups.

**Table 1** Synthesis of 3-Phosphorylidenefurans-2,4-diones 15 from α-Hydroxy Acids 13 and Ylide 3

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
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<tr>
<td>a</td>
<td>65</td>
</tr>
<tr>
<td>b</td>
<td>67</td>
</tr>
<tr>
<td>c</td>
<td>72*</td>
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* (5S)-Enantiomer (95% ee) from L-(+)-mandelic acid.

Although ylides 15 are too stable to undergo Wittig alkenations under any conditions they should be amenable to follow-up reactions. Those reactions replacing the entire triphenylphosphine group would be most attractive. For instance, their oxidation with ozone, dimethyldioxirane, or oxaziridines should lead to the corresponding furan-2,3,4-triones, which are valuable building blocks for the construction of diverse heterocycles.44

We had already reported that 4-O-allyltetronates can be rearranged under forced conditions to the corresponding 3-spirocyclopropylfuran-2,4-diones 16 by a sequence comprised of a Claisen rearrangement to give the respective 3-allyltetronic acid and a Conia oxaene reaction of the latter.37 The compounds 16 had proved quite useful. A wide range of carbon and heteroatom nucleophiles opened the three-membered ring in such a way as to produce 3- (syn-1,2-disubstituted-alkyl)tetronic acids 17.37,45 Now we have found that some nucleophiles such as ylides like methyltriphenylphosphorane (Ph3P=CH2, 18), sodium borohydride, and alkylithium compounds react with the 4-oxo group of diastereopure7a racemic (+)-16a while leaving the cyclopropane ring unaffected (Scheme 3, Table 2). The resulting 3,4-difunctionalized furan-2-ones represent structural patterns occurring in bioactive natural products. For example, alkene (+)-19, obtained in over 80% yield from reaction of 16a with freshly prepared methyldie 18, resembles the 4-methylene-3-spirocycloylalkylfuran-2-one core of the bakkenolide family of sesquiterpenes.46,47 The reduction of diastereopure (±)-16a with 1.5 equivalents of sodium borohydride in methanol gave an easy to separate 3:2 mixture of diastereomeric alcohols 20 in 90% overall yield. The shown structure was tentatively assigned to the major isomer as it results from attack of hydride from the least hindered side. The 1H
NMR signal of its proton H4 peaks at a normal δ = 3.92, while the analogous signal of the minor isomer is distinctly high-field shifted to δ = 3.35 presumably due to a shielding by the nearby phenyl ring. The reaction with alkyllithium compounds is more diastereoselective.

With one equivalent of methylthiolium or 1.5 equivalents of phenyllithium in tetrahydrofuran at room temperature a single isomer was formed in good yield, which we ascribe based on the NMR spectra. Similar yields and stereoselectivities were obtained in reactions with butyllithium and various alkyllithium compounds. Analogues of 16 with residues other than spirocyclopropyl rings which are susceptible to attack by (bio-)nucleophiles, bear some resemblance to the natural antitumoral rings which are susceptible to attack by (bio-)nucleophiles.

Table 2 Structures and Yields for Products 20, 21a,b

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Yield (%)</th>
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<tr>
<td>20</td>
<td>H</td>
<td>90(^a)</td>
</tr>
<tr>
<td>21a</td>
<td>Me</td>
<td>90</td>
</tr>
<tr>
<td>21b</td>
<td>Ph</td>
<td>58</td>
</tr>
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</table>

\(^a\) Overall yield of a 3:2 mixture of diastereomers.

To more closely mimic the tetracyclic framework and the presence of a full ketal in artemisinin we now prepared the tricyclic bislactone endoperoxide ketal 29 as outlined in Scheme 4. The 4-O-(3-methylbut-2-enyl) tetronate 26 was readily accessible by sequential esterification of malic acid first with 3-methylbut-2-ene-1-ol then with trimethylsilylethanol (TMSEOH), followed by Wittig cyclization of hydroxy ester 25 with ylide 3. It was submitted to a thermal cascade conversion to give the corresponding 3-alkylidene furan-2,4-dione 27. Desilylation with tetramethylammonium fluoride provided furan-2,4-dione 28, which upon photooxygenation in the presence of 4-toluenesulfonic acid cyclized directly to product 29. However, contrary to the reports by other groups on similar couples of hemiketal/full ketal endoperoxides, compound 29 proved to be not more active than 22 but virtually inactive against *Plasmodium falciparum*. Figure 2 depicts the molecular structure of 29 as obtained from a single-crystal X-ray structural analysis. It demonstrates that steric congestion around the O–O bond is probably not responsible for this lack of activity. The cleavage of this labile bond by contact with heme molecules, which originate from the decay of parasite-infested erythrocytes, is thought to be crucial for antimalarial activity.

1,3-Difunctionalized Systems: Reutericyclin

The 1,3-bisacyl-substituted tetramic acid reutericyclin \([(5R)-2]\) exhibits antibiotic activity against a wide variety of Gram-positive bacteria, including common sourdough lactic acid bacteria. It was first obtained from a sourdough isolate of *Lactobacillus reuteri* by Jung et al.\(^a,b\) Like all 3-acyltetramic acids, \(^{25,56}\) 2 usually exists as a mixture of various tautomers the ratio of which is dependent mainly on the solvent polarity. Some of these tautomers are strong chelate ligands with binding constants for various metal...
Scheme 4  Synthesis of bislactone endoperoxide ketal 29. Reactions and conditions: (i) TFAA, then Me2C=CHCH2OH, neat, r.t.; (ii) TMSEOH, DCC, THF, r.t. to 65 °C, 16 h, 60%; (iii) Ph3P=C=C=O (ORTEP representation, 50% probability ellipsoids); hydrogen atoms are omitted; selected bond lengths [Å] and dihedral angles [°]: C1–C2 1.471(3), C2–C3 1.334(3), C3–C5 1.521(3), C2–C8 1.487(3), C5–C2 1.443(3), O2–O3 1.443(3), O2–O3 1.334(3), C3–C5 1.521(3), C2–C8 1.487(3), C5–O2–O3–C8 75.00(19), C3–C2–C8–O4 –103.8(2), O3–C8–C11–C10 –99.5(2).

Figure 2  Molecular structure of 29 (ORTEP representation, 50% probability ellipsoids); hydrogen atoms are omitted; selected bond lengths [Å] and dihedral angles [°]: C1–C2 1.471(3), C2–C3 1.334(3), C3–C5 1.521(3), C2–C8 1.487(3), C5–O2 1.443(3), O2–O3 1.481(2), C8–O3 1.389(3), O3–O4 1.441(2), C5–O2–O3–C8 75.00(19), C3–C2–C8–O4 –103.8(2), O3–C8–C11–C10 –99.5(2).

The proton-ionophoric properties were also drawn on to explain the bioactivity of 2. Synthetic approaches towards 2 have to sort out the optimum order and methods of attaching the two acyl residues at N1 and C3 with the additional challenge of avoiding racemization at C5. The Jung group published two syntheses of 2, which differ in the procedure of the ring closure and in the order of introduction of the acyl residues at N1 and C3. The first one25 submitted an N-dec-2-enoyllecine to the condensation–cyclization reaction with Meldrum’s acid as described by Jouin et al.23 The 3-acetyl group was introduced last with acetyl chloride and catalytic amounts of titanium(IV) chloride and this led to racemization at C5. In the second18 synthesis of 2, N-acetoacetylleucinate was cyclized under basic Lacey–Dieckmann conditions.19 The resulting 3-acetyl-5-isobutyrtetramic acid was finally deprotonated with butyllithium and N-acylated with (E)-dec-2-enoyl chloride to give (5R)-2 with 80% ee. It remained unclear which one of the two basic steps, Dieckmann condensation or N1-deprotonation/acetylation, had proceeded with partial racemization.63

We have now developed an alternative four-step synthesis of (5R)-2 from D-leucine benzyl ester comprised of our pH-neutral domino N-acylation–Wittig cyclization with ylide 3, and subsequent stepwise nonracemizing acylations, first at C3 under Jones’ conditions,26 i.e. employing acetyl chloride/boron trifluoride–diethyl ether complex, then at N1 using sodium hexamethyldisilazane/(E)-dec-2-enoyl chloride at low temperature (Scheme 5). Benzyl D-leucinate (31), which is available in near quantitative yield from D-leucine (30) and benzyl alcohol, was cyclized with ylide 3 to give the 4-O-benzyltetramate 32 in 70% yield. Hydrogenolytic debenzylation of the latter afforded the rather polar and delicate tietramic acid 33 that crystallized from ethyl acetate as the pure keto tautomer shown in Scheme 5. Compound 33 was then treated with an excess of both boron trifluoride–diethyl ether complex and acetyl chloride to give the difluoroboryl-chelate complex 34 of the corresponding 3-acetyltetramic acid. Complex 34 was stable and sufficiently unpolar to allow for its purification by column chromatography on silica gel. In solution it may exist as a mixture of tautomers. Conveniently, it is also stable to base with the difluoroboryl chelate acting as a built-in protecting group for the acetyl residue. Hence compound 34 could be deprotonated/acylated at N1 right away. To safely circumvent racemization at C5 in the course of this procedure some experimentation was necessary. We found that deprotonation at N1 by treatment of 34 with sodium hexamethyldisilazane for five minutes at –78 °C in tetrahydrofuran solution followed by immediate quenching with (E)-dec-2-enoyl chloride and final aqueous workup produced a sample of reutericyclin virtually void of the (5S)-enantiomer (i.e. >95% ee) as to chiral HPLC on permethylated dextrin when compared with an authentic racemic sample. This and the optical rotation of [α]D25 +18 (c 3.0, EtOH) are in keeping with the data reported7d by the Jung group for the product of their most recent synthesis [80% ee, [α]D25 +13 (c 0.29, EtOH)]. NMR spectra in acetonitrile- d3 revealed the presence of two, very likely external, tautomers in ca. 3:2 ratio.
Scheme 5  Synthesis of reutericyclin [(5S)-2].  *Reactions and conditions:* (i) BnOH, PTSA, benzene, reflux, 16 h; (ii) Ph3P=CH=O (3), PhCO2H (cat), THF, 60 °C, 16 h; (iii) 3 (1 bar), Pd/C (5%), MeOH, r.t., 1 h, (iv) BF3·OEt2 (excess), AcCl (8 equiv), 70 °C, 8 h; (v) (a) NaHMDS, THF, −78 °C, 5 min, (b) (E)-dec-2-enoyl chloride, −65 °C, 1 h, (c) aq 1 M KHSO4.

Conclusions

The cumulated ylide (triphenylphosphoranylidene)ketene (Ph3PCCO, 3) is a versatile C2O building block for the construction of differently functionalized tetrates and tetrates and close derivatives thereof. Esters of α-hydroxy and α-amino acids can be cyclized to the corresponding 4-O-alkyl systems without racemization of positions bearing acidic hydrogen atoms. Multiple use of ylide 3 is also possible and particularly economic. Free tetratomic and tricatomic acids are acylated by 3 at C3 to give the corresponding acyl ylides, which can be saponified to the respective 3-acyl systems. Even unprotected α-hydroxy acids react with 3 to afford the corresponding 3-phosphorylidenefuran-2,4-diones. The downstream acylation at C3 of tetratomic acids and of N1 and C3 of tetric acid is also possible by various means and methods without racemization. Hence we are now able to attach certain types of residues to any and all positions. Where do conceivable and desirable extensions of this methodology lie? The C3 acylation of N- and C5-unsubstituted tetrates is still problematic as is the C3 acylation with highly unsaturated residues in general. Neither Jones’ nor Yoshii’s protocols work well in these cases, if at all. A way out of this predicament could be to switch 3-acyl ylides akin to **11** ‘Wittig-active’ and have them alkenate unsaturated aldehydes. Ylides like **11** are unreactive, very likely due to H-chelate formation, which, we hope, can be broken up by deprotonation with a mild base that does not provide a counteraction that replaces hydrogen in these chelates. Work towards this end is underway in our laboratory.

(5S)-3-(But-2-eny)-4-hydroxy-5-methylfuran-2(5H)-one (5)

A soln of 4 (144 mg, 1.0 mmol) and 3 (300 mg, 1.1 mmol) in toluene (5 mL) was placed in a sealed glass vial and irradiated in the microwave oven at 180 °C for 10 min. The resulting mixture was concentrated and the residue was purified by column chromatography (silica gel, first with neat CH2Cl2 to remove Ph3PO, then with neat EtO; Rf = 0.54). Evaporation of the second eluate afforded 5 as a colorless oil; yield: 109 mg (65%); ratio E/Z 2.3:1.

IR (ATR): 3191, 2709, 1719, 1631, 1057, 964, 732 cm⁻¹.

1H NMR (CDCl3): δ = 1.46 (d, J = 6.7 Hz, 3 H, 5-Me), 1.47 (d, J = 6.7 Hz, 3 H, 5-Me), 1.60 (d, J = 4.8 Hz, 3 H, =CMe2), 1.66 (d, J = 6.4 Hz, 3 H, =CMe2), 2.86 (d, J = 5.0 Hz, 2 H, CH2), 2.94 (d, J = 6.7 Hz, 2 H, CH2), 4.80 (q, J = 6.7 Hz, 1 H, H5=CH), 5.30–5.60 (m, 2 H, −CH2=). 13C NMR (75.5 MHz, CDCl3): δ = 12.7/17.7 (Me), 17.1/17.75 (Me), 19.2/24.0 (CH2), 75.3 (CH), 99.2/99.4 (C), 125.8/126.2 (CH), 126.4/126.6 (CH), 177.0/177.1 (C), 177.2/177.5 (C). MS: m/z (%) = 168 (24) [M]+, 159 (39), 127 (25), 114 (53), 95 (61), 81 (100).

Anal. Calcld for C9H12O3: C, 64.5; H, 7.4. Found: C, 64.0; H, 7.0.

(5S)-5-Methyl-4-(1-methylallyloxy)furan-2(5H)-one (6): Typical Procedure

A soln of 3 (4.1 mg, 16.5 mmol), 3 (5.59 g, 18.5 mmol), and benzoic acid (100 mg, 0.8 mmol) in THF (100 mL) was heated under gentle reflux for 16 h. The resulting mixture was concentrated and the residue was purified by column chromatography (silica gel, hexane–EtO; 1:1, Rf = 0.35). Evaporation of the eluate afforded 6 as a colorless oil; yield: 2.10 g (74%); 1:1 mixture of diastereomers.

IR (ATR): 2986, 1753, 1617, 1292, 1083, 954 cm⁻¹.

1H NMR (CDCl3), mixture of diastereomers a and b: δ = 1.39 (d, J = 6.8 Hz, 3 H, 3-Me), 1.72 (d, J = 6.4 Hz, 3 H, 1-Me), 4.00 (m, 1 H, H1'), 4.73 (dq, J = 6.8, 1.0 Hz, 1 H, H5), 4.91/4.92 (d, J = 1.0 Hz, 1 H, H3), 5.23 (dd, J = 17.4, 1.1 Hz, 1 H, =CH2), 5.33 (dd, J = 10.4, 1.1 Hz, 1 H, =CH2), 5.50/5.80 (ddd, J = 17.4, 10.4, 6.5 Hz, 1 H, =CH).

13C NMR (75.5 MHz, CDCl3): δ = 17.7 (Me), 20.1/20.3 (Me), 75.4 (CH), 80.0/80.2 (CH), 88.70/88.75 (CH), 117.6/117.8 (CH), 135.9 (CH), 172.7 (C), 181.0 (C).

MS: m/z (%) = 168 (14) [M]+, 150 (25), 114 (33), 95 (31), 81 (53), 55 (100).

Anal. Calcld for C9H10O2: C, 64.3; H, 7.2. Found: C, 64.5; H, 7.4.
Tetronic and Tetrameric acids

3909

4-(Benzoyl)-5-butyrfuran-2(5H)-one (9a)

Colorless oil from 8a (2.22 g, 10.0 mmol) and 3 (3.90 g, 13.0 mmol) in THF (50 mL), reflux for 8 h, analogously to the synthesis of 6; yield: 1.72 g (70%); Rf = 0.62 (EtOAc–pentane, 2:1).

IR (ATR): 3079, 2958, 2923, 1746, 1666, 1597, 1165, 1012 cm–1.

3-Acetyl-5-butyl-4-hydroxyfuran-2(5H)-one (10a); Typical Procedure

A soln of 9b (0.46 g, 2.9 mmol) in THF (20 mL) was refluxed for 12 h. Upon cooling, colorless crystals of 10a precipitated; yield: 1.72 g (85%); mp 110–112 °C. Anal. Calcd for C15H18O3: C, 73.1; H, 7.4. Found: C, 72.8; H, 7.0.

IR (ATR): 3119, 3035, 2957, 2872, 1755, 1629, 1230, 1016 cm–1.

3-Acetyl-5-butyl-4-hydroxyfuran-2(5H)-one (10b)

A soln of 3.48 g, 12.7 mmol), analogously to the synthesis of 10a; yield: 2.38 g (99%); mp 99 °C (Lit.38 101–102 °C); [α]D = 0.76) to give colorless crystals; yield: 181 mg (70%); 92% ee (3).

IR (ATR): 2928, 1752, 1625, 1300, 1155 cm–1.

3-Acetyl-5-butyl-4-hydroxyfuran-2(5H)-one (10b)

A soln of 3.48 g, 12.7 mmol), analogously to the synthesis of 10a; yield: 2.38 g (99%); mp 99 °C (Lit.38 101–102 °C); [α]D = 0.76) to give colorless crystals; yield: 181 mg (70%); 92% ee (3).

IR (ATR): 2928, 1752, 1625, 1300, 1155 cm–1.

3-Acetyl-5-butyl-4-hydroxyfuran-2(5H)-one (10b)

A soln of 3.48 g, 12.7 mmol), analogously to the synthesis of 10a; yield: 2.38 g (99%); mp 99 °C (Lit.38 101–102 °C); [α]D = 0.76) to give colorless crystals; yield: 181 mg (70%); 92% ee (3).

IR (ATR): 2928, 1752, 1625, 1300, 1155 cm–1.

3-Acetyl-5-butyl-4-hydroxyfuran-2(5H)-one (10b)

A soln of 3.48 g, 12.7 mmol), analogously to the synthesis of 10a; yield: 2.38 g (99%); mp 99 °C (Lit.38 101–102 °C); [α]D = 0.76) to give colorless crystals; yield: 181 mg (70%); 92% ee (3).

IR (ATR): 2928, 1752, 1625, 1300, 1155 cm–1.
1H NMR (CDCl3): 1.6:1 mixture of two tautomers a/b: \( \delta = 0.84 \) (t, \( J = 7.3 \) Hz, 3 H, Me\( \beta \)), 1.61 (s, \( J = 7.1 \) Hz, 3 H, Me\( \alpha \)), 1.20–1.45 (m, 4 H, CH\( \beta \)), 1.57–1.74 (m, 1 H, 5-C\( \alpha \)), 1.82–1.96 (m, 1 H, 5-C\( \beta \)). 2.48 (s, 3 H, MeCO), 4.55 (dd, \( J = 8.0, 4.2 \) Hz, 1 H, H5\( \beta \)), 4.68 (dd, \( J = 8.0, 4.4 \) Hz, 1 H, H5\( \alpha \)), 10.9 (br s, 1 H, OH).

IR (ATR): 2921, 1708, 1637, 1588, 1437, 1183, 1119, 719 cm\(^{-1}\).

13C NMR (CDCl3): \( \delta = 13.7 \) (Me\( \beta \)), 19.5 (Me\( \beta \)), 22.2 (CH\( \beta \)), 22.4 (Me\( \beta \)), 26.4 (CH\( \beta \)), 26.5 (CH\( \alpha \)), 30.9 (CH\( \alpha \)), 31.0 (CH\( \alpha \)), 80.0 (CH\( \beta \)), 85.6 (CH\( \beta \)), 97.8 (C\( \beta \)), 100.7 (C\( \alpha \)), 167.9 (C\( \alpha \)), 175.9 (C\( \alpha \)), 188.1 (C\( \alpha \)), 194.3 (C\( \alpha \)), 194.9 (C\( \alpha \)), 199.8 (C\( \alpha \)).

MS: m/z (%) = 199 (1), 198 (8) [M\(^+\)]. 155 (14), 142 (100).

Anal. Caled for C\(_{19}\)H\(_{22}\)O\(_2\): C, 80.8; H, 7.9. Found: C, 80.4; H, 7.6.

3-Acetyl-5-hexyl-4-hydroxyfuran-2(5H)-one (Pesthetoxin, 12b)

From DL-lactic acid (2.02 g, 22.5 mmol); chromatography (THF–Et\(_2\)O, 3:2) to the synthesis of 12a; yield: 359 mg (85%); mp 58 °C [Lit.\(^{29}\) no mp reported].

IR (ATR): 2925, 1717, 1632, 1343, 1107, 998, 748 cm\(^{-1}\).

3\(
\begin{array}{l}
\text{H NMR (CDCl3):} \\
\text{13C NMR (75.5 MHz, CDCl3):} \\
\text{MS: m/z (%) = 227 (2), 226 (9) [M\(^+\)]. 155 (23), 142 (100).}
\end{array}
\)
3-Hydroxy-1,4-dimethyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecan-12-one (21b) was obtained from (±)-16a (300 mg, 1.06 mmol) in THF (20 mL) was slowly treated at r.t. with 1.6 M McLi in Et2O (0.75 mL, 1.20 mmol). The resulting mixture was stirred for a further 16 h and then filtered through a small plug of silica gel. Evaporation of the filtrate and column chromatography of the residue (silica gel 60, Et2O–hexane, 3:1) gave 21b as a white solid; yield: 110 mg (58%); mp 183 °C.


1-(3-Methylbut-2-en-1-yl)-2-hydroxybutan-2-one (24) is a mixture of DCC (5.19 g, 25.2 mmol), 2-(trimethylsilyl)ethanol (3.70 g, 25.0 mmol), and a catalytic amounts of CuCl2 was stirred at r.t. for 6 h. Then a solution of 24 (4.95 g, 24.5 mmol) in THF (50 mL) was added and the resulting mixture was heated under reflux for 16 h. Byproduct urea was precipitated in a fridge and removed by filtration. The filtrate was concentrated in vacuo and the remainder was purified by chromatography (silica gel; cyclohexane–EtOAc, 1:4); yield: 4.40 g (60%).

IR (ATR): 3491, 1734, 1249, 1165 cm⁻¹.


3-Hydroxy-4-(3-Methylbut-2-enyloxy)butanoic acid (26) is a mixture of mcl (23.5 g, 40.5 mmol) and TFAA (34.0 g, 161.9 mmol) was stirred at r.t. for 90 min and then concentrated in vacuo to give a precipitate of the mixed anhydride. This was treated with 3-methylbut-2-en-1-ol (10.49 g, 122.0 mmol), the resulting mixture was stirred at r.t. for 3.5 h and then evaporated to leave an oil. This was purified by column chromatography (silica gel, cyclohexane–EtOAc–AcOH, 1:1). The eluate was evaporated and residual TFAA was removed azetroponically with toluene (3 × 5 mL); yield: 6.13 g (75%).

IR (ATR): 3441, 3207, 1715, 1263, 1180, 1101 cm⁻¹.


3-(1,2-Dimethylpropylidene)-5-{[2-(trimethylsilyl)ethoxy]carbonyl}methyl)furan-2,4(3H,5H)-dione (27) is a mixture of mcl (23.5 g, 40.5 mmol) and TFAA (34.0 g, 161.9 mmol) was stirred at r.t. for 90 min and then concentrated in vacuo to give a precipitate of the mixed anhydride. This was treated with 3-methylbut-2-en-1-ol (10.49 g, 122.0 mmol), the resulting mixture was stirred at r.t. for 3.5 h and then evaporated to leave an oil. This was purified by column chromatography (silica gel, cyclohexane–EtOAc–AcOH, 1:1). The eluate was evaporated and residual TFAA was removed azetroponically with toluene (3 × 5 mL); yield: 6.13 g (75%).

IR (ATR): 3441, 3207, 1715, 1263, 1180, 1101 cm⁻¹.

MeC=C), 2.89–2.95 (m, 2 H, H₂CC=O), 4.06–4.15 (m, 2 H, OCH₂), 4.38 (s, q, J = 6.9 Hz, 1 H, C=CH₂Me), 4.65–4.71 (m, 1 H, H₅).

¹³C NMR (75.5 MHz, CDCl₃): δ = −1.7, 15.7, 17.1, 19.7, 19.9, 20.0, 30.1, 31.4, 35.9, 63.6, 77.6, 115.3, 168.9, 189.5, 190.0, 196.9, 201.1.

MS: m/z (%) = 326 [M⁺] (1), 291 (7), 276 (8), 251 (32), 226 (64), 208 (100), 193 (43), 181 (64), 153 (351), 149 (495), 137 (29), 127 (40), 107 (9), 95 (100).

Anal. Caled for C₁₆H₂₆O₅Si: C, 58.9; H, 8.0. Found: C, 58.8; H, 8.2.

1H NMR (CDCl₃): δ = 0.87 (q, J = 6.6 Hz, 3 H, Me), 1.35 (ddd, J = 9.4, 4.4, 5.5 Hz, 1 H, H₅).

Benzyl d-Leucinate (33)

Benzyl d-leucinate (33, 33.2 g, 15.0 mmol) was dissolved in THF (50 mL), treated with 3 (4.35 g, 15 mmol) and benzoic acid (0.36 g, 3 mmol) and the mixture was stirred at 60 °C for 1 h. The solvent was removed and the remainder was purified by column chromatography (silica gel). Eluting first with 5% acetonitrile–CH₂Cl₂ gave the byproduct Ph₂PO, then eluting with 25% acetonitrile–CH₂Cl₂ gave 32 as a white solid; yield: 2.57 g (70%); mp 86–88 °C; [α]D₂⁵ +8.5 (c 3, CHCl₃).

IR (ATR): 1678, 1620, 1534, 1354, 1219 cm⁻¹.

MS: m/z (%) = 245 [M⁺] (5), 228 (2), 217 (5), 202 (4), 189 (57), 161 (13), 143 (18), 117 (33), 95 (100).

Anal. Caled for C₁₃H₁₈NO₂: C, 73.4; H, 7.8; N, 5.7. Found: C, 73.3; H, 7.7; N, 5.8.

(5R,4′-Benzoxyl)-5-isobutyl-1,5-dihydro-2H-pyrrrol-2-one (32)

Benzyl d-leucinate (31, 3.32 g, 15.0 mmol) was dissolved in THF (50 mL), treated with 3 (4.35 g, 15 mmol) and benzoic acid (0.36 g, 3 mmol) and the mixture was stirred at 60 °C for 1 h. The solvent was removed and the remainder was purified by column chromatography (silica gel). Eluting first with 5% acetonitrile–CH₂Cl₂ gave the byproduct Ph₂PO, then eluting with 25% acetonitrile–CH₂Cl₂ gave 32 as a white solid; yield: 2.57 g (70%); mp 86–88 °C; [α]D₂⁵ +8.5 (c 3, CHCl₃).

IR (ATR): 1678, 1620, 1534, 1354, 1219 cm⁻¹.

MS: m/z (%) = 245 [M⁺] (5), 228 (2), 217 (5), 202 (4), 189 (57), 154 (8), 132 (7), 92 (22), 91 (100).

Anal. Caled for C₁₃H₁₈NO₂: C, 73.4; H, 7.8; N, 5.7. Found: C, 73.3; H, 7.7; N, 5.8.

(5R)-5-Isobutylpyrrolidin-2,4-dione (33)

Dihydro-2H-pyrrrol-2-one (32, 490 mg, 2.0 mmol) was dissolved in MeOH (50 mL) and treated with 5% Pd/C (40 mg). The reaction vessel was repeatedly evacuated and flushed with H₂, and left to stir at t.r. for 1 h, pressurized with 1 atm of H₂. The resulting mixture was filtered through a short plug of Celite which was washed with MeOH (150 mL) and EtOAc (50 mL). The combined filtrates were concentrated on an oil pump and the remainder recrystallized (EtOAc) to give the pure keto tautomer of 33 as a yellowish solid; yield: 307 mg (99%); mp 106 °C [Lit.²⁵ 114–116 °C for rac-33]; [α]D₂⁵ +52 (c 1, CHCl₃) [Lit.²⁵ 55–57 (c 0.87, CHCl₃) for ent-33].

IR (KB): 3176, 1769, 1628, 1288, 797 cm⁻¹.

¹H NMR (CDCl₃): δ = 0.90 (d, J = 6.5 Hz, 3 H, Me), 0.91 (d, J = 6.5 Hz, 3 H, Me), 1.45 (ddd, J = 13.7, 9.4, 4.5 Hz, 1 H, HC=CH₂Me), 1.60 (dd, J = 13.7, 8.9, 4.4 Hz, 1 H, HC=CH₂Me), 1.70–1.77 (m, 1 H, H₂CMe₂), 2.98 (s, 2 H, H₃), 3.98 (dd, J = 9.4, 4.4 Hz, 1 H, H₅).

SCHRÖDER ET AL. FEATURE ARTICLE

Synthesis 2006, No. 22, 3902–3914 © Thieme Stuttgart · New York
3-[1-(Difluoroboryloxy)ethyldiene]-5-isobutylpyrrolidine-2,4-dione (34)

To a stirred soln of 33 (0.30 g, 1.9 mmol) in ethereal BF₃·OEt₂ (2 mL) was added AcCl (0.61 g, 7.8 mmol). After heating the mixture at 70 °C for 4 h, further AcCl (0.61 g, 7.8 mmol) was added and heating was continued for a further 4 h at the same temperature. The cooled mixture was then treated with sat. aq NH₄Cl (20 mL) and immediately extracted with EtOAc (3 × 20 mL). The combined extracts were dried (Na₂SO₄) and evaporated to yield an oil, which was purified by column chromatography (silica gel; hexane–EtOAc, 60:40, 254). After stirring for 5 min, (E)-2-ethylchloride (105 mg, 0.55 mmol) was added slowly to maintain the low temperature and monitoring the reaction progress by TLC. The reaction was stopped after 1 h by addition of 1 M aq KH₂SO₄ (20 mL) and the pH value was measured to ensure the base had been neutralized. EtOAc (50 mL) was added and the organic phase was separated from the aqueous layer. The latter was extracted with EtOAc (25 mL) and the combined extracts were dried (Na₂SO₄) and evaporated to yield an oil, which was purified by column chromatography (silica gel, hexane–EtOAc, 60:40, 254) to give yellow crystals; yield: 290 mg (61%); mp 116 °C.

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References

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(53) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC number 616240). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033, e-mail: teched@chemcrys.cam.ac.uk].


