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 (triphenylphosphoranylidene)ketene (Ph_3P=C=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 tetronates or tetramates. A two-step synthesis of (–)-*epi*-blastmycinolactol shows that allyl α-hydroxy esters can be domino Wittig–Claisen reacted to give 3-allyltetronic acids. More extended Wittig–Claisen–Conia cascades can produce 3-alkylidenefuran-2,4-diones, the photooxygenation of which furnishes lactone endoperoxides with antiplasmodial potential. Tetronic acids can be acylated by **3** at C3 to give the corresponding acyl ylides. Their saponification yields the respective 3-acetyl compounds, e.g. the fungal metabolite pesthetoxin. α-Hydroxy acids react with **3** to afford the corresponding 3-phosphoranylidenefuran-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(5*H*)-one (also known as tetronic acid) or the pyrrolidine-2,4-dione (also known as tetramic 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 tetramic 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).

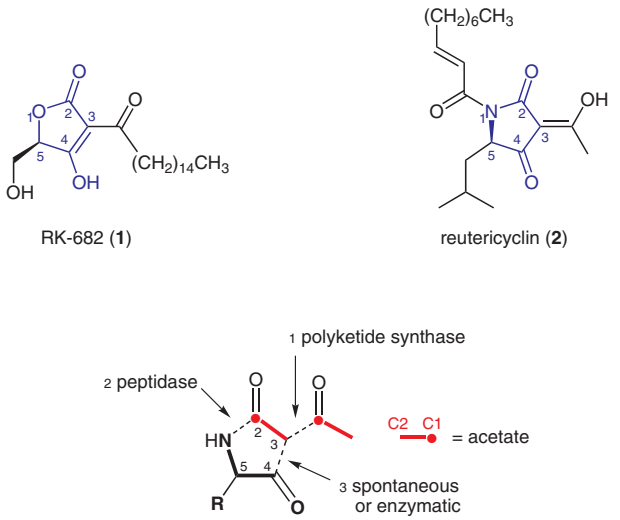

Figure 1 RK-682 (**1**) and reutericyclin (**2**) as typical natural tetronic and tetramic acids (top), and the general biosynthetic assembly of 3-acyltetramic acids (bottom).

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.

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Although variants have been published where racemization could be suppressed by carefully controlled conditions,[20–22] the method still lacks generality and predictability. Safer, truly pH-neutral, methods are few and far between. Jouin's protocol[23–26] condenses Meldrum's acid with α-hydroxy or α-amino acids, respectively, in the presence of *N*,*N*′-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine. Heating the intermediate γ-amino-β-oxo ester leads to the corresponding tetramic acid with concomitant formation of acetone and carbon dioxide. Effenberger cyclized chiral γ-hydroxy-β-oxo esters, as obtained by Blaise reaction of O-silylated cyanohydrins with Reformatsky reagents, under acidic conditions to afford enantiomerically pure tetronic acids.[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[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 metallocenes 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 bioactive natural and synthetic drugs and the development of new domino reactions and oligofunctional reagents.

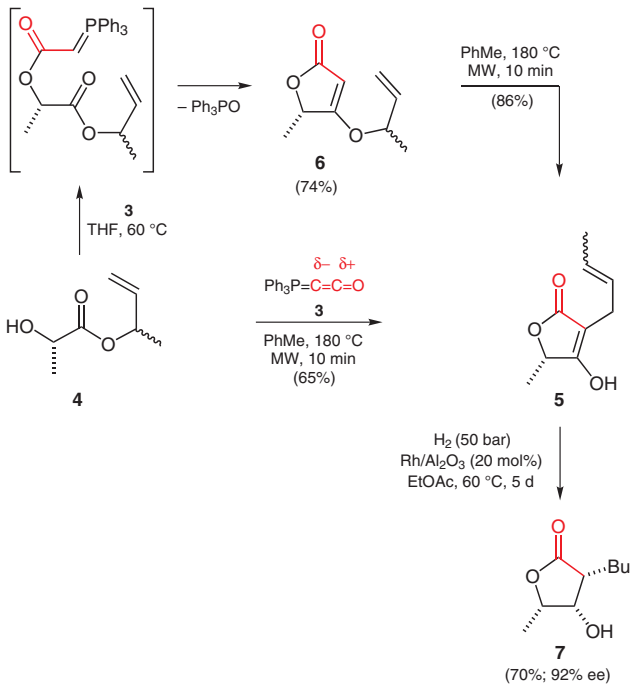
Matthias Dietrich was born in 1980 in Tirschenreuth, Bavaria. In 2001 he began his studies at the University of Bayreuth towards a qualification as a secondary level teacher of chemistry and biology on a concurrent route. Having just finished an optional third year project in chemistry on the synthesis 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,[29] 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 shift step 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.[30] Boeckman's approach[31] of introducing polyenoyl residues via Horner alkenation of 3-β-phosphonylacetyl tetramic 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.



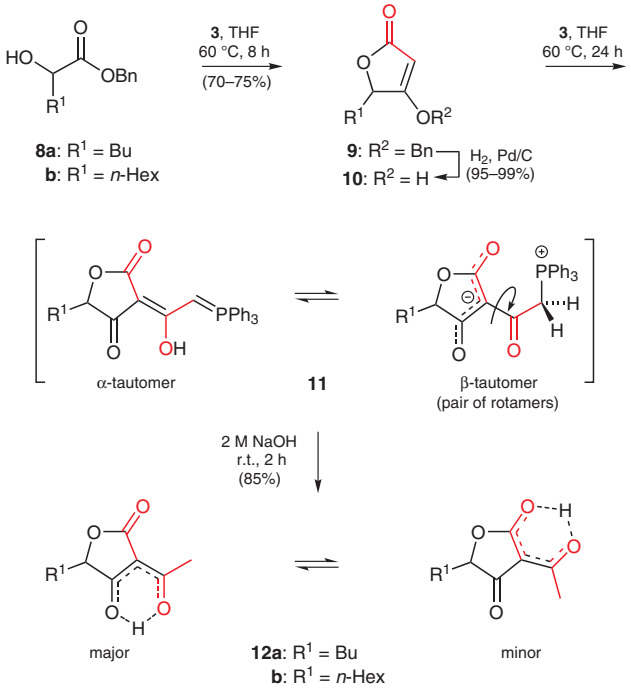
Scheme 1 A short synthesis of (–)-*epi*-blastmycinolactol (**7**) via domino addition–Wittig alkenation–Claisen rearrangement of methallyl lactate **4** with ylide **3**.

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 (triphenylphosphoranylidene)ketene (Ph_3P=C=C=O, **3**),[32] which is also available in a resin-bound form,[33] to give the corresponding tetronates or tetramates, respectively.[34] While not Wittig-active itself, **3** adds the OH or NRH groups of hydroxy and amino esters across its C=C bond to give acyl ylides that in turn undergo rapid ring-closing intra-Wittig alkenation. We have exploited this domino process for the construction of various optically pure natural products, e.g. **1**[35] or the sponge-produced cytotoxic melophlins.[36] In the case of allyl esters, further pericyclic reactions may follow the cyclization step, depending on the temperature and solvent polarity.[37] For example, one-pot reaction of methallyl (*S*)-lactate (**4**) and **3** in toluene under microwave irradiation (sealed vial, 180 °C, 10 min) afforded the 3-(but-2-enyl)-5-methyltetronic acid **5** in 65% yield. The reaction can also be carried out stepwise by first preparing the methallyl tetronate **6** in tetrahydrofuran and then rearranging it under microwave irradiation as above. Yields are similar but the byproduct triphenylphosphine oxide is more easily separated from **6** than from **5**. Simultaneous hydrogenation of both C–C double bonds with hydrogen gas (50 bar) using a rhodium/alumina catalyst (20 mol%) in analogy to Node et al.[38] afforded the natural γ-lactone (–)-3-*epi*-blastmycinolactol (**7**) with 92% ee (GC; Lipodex-E; comparison with base-line separated authentic racemate) (Scheme 1).

This approach is reminiscent of the biosynthesis of tetronic acids. Ylide **3** formally replaces acetate as the C_2O-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-*n*-alkyltetronic acids **10** were readily obtained in two steps from the corresponding benzyl 2-hydroxyalkanoates **8** and ylide **3** (Scheme 2). Remarkably, they exist as 3:2 mixtures of enol and keto forms in deuterochloroform, which are clearly discernable in the ^{1}H 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.[39] 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 phosphine oxide as the byproduct. The acyl ylides **11** exist as mixtures of an enol–ylide tautomer (α) and a prevailing oxo–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 ^{13}C and ^{31}P 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-enolate 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 pesthetoxin, a leaf necrosis inducing metabolite of the grey blight fungus *Pestalotiopsis theae* which regularly infects tea crops.[40] In solution, 3-

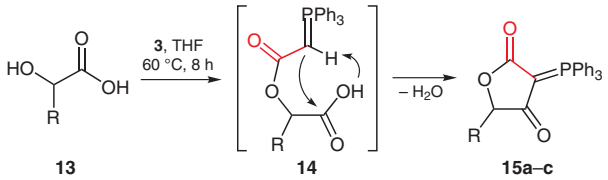
acetyltetronic acids **12**, like the acyl ylides **11**, exist as mixtures of two tautomers. In the case of **12** these tautomers differ in the ring-bound oxygen atom (2-O vs. 4-O) that forms a H-chelate with the exocyclic carbonyl oxygen atom. According to NMR, in the usual organic solvents the tautomer featuring a H-chelate between the exocyclic and the 4-carbonyl groups is dominant (e.g., by 1.6:1 in $CDCl_3$). Either tautomer 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-acyltetronic acids.[41]



Scheme 2 Synthesis of 3-acetyltetronic acids **12** from α-hydroxy esters **8** and two equivalents of ylide **3** as a C_2O source.

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-phosphoranylidenefuran-2,4-diones **15**[43] in good yields and without racemization; (*S*)-**15c** 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 bisacyl 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-Phosphoranylidenefuran-2,4-diones **15** from α-Hydroxy Acids **13** and Ylide **3**



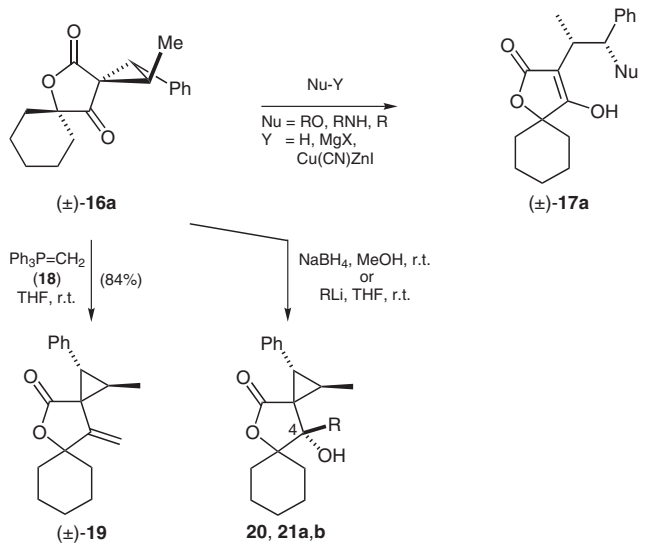
15	R	Yield (%)
a	Me	65
b	*n*-C_6H_{13}	67
c	Ph	72[a]

[a] (5*S*)-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 methylenetriphenylphosphorane ($Ph_3P{=}CH_2$, **18**), sodium borohydride, and alkyllithium compounds react with the 4-oxo group of diastereopure[37a] 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 methylide **18**, resembles the 4-methylene-3-spirocycloalkylfuran-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.



Scheme 3 4-Functionalization of 3-spirocyclopropylfuran-2,4-dione (±)-**16a**

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

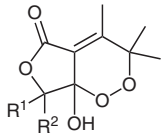
Product	R	Yield (%)
20	H	90[a]
21a	Me	90
21b	Ph	58

[a] Overall yield of a 3:2 mixture of diastereomers.

With one equivalent of methyllithium or 1.5 equivalents of phenyllithium in tetrahydrofuran at room temperature a single isomer was formed in good yield, which we ascribe the shown structures **21a**,**b** based on the NMR spectra. Similar yields and stereoselectivities were obtained in reactions with butyllithium and various alkynyllithium compounds. Analogues of **16** with residues other than spirocyclohexyl at C5 reacted equally well. The tertiary alcohols **21**, with adjacent carbonyl and spirocyclopropyl rings which are susceptible to attack by (bio-)nucleophiles, bear some resemblance to the natural antitumoral alkylants illudin M and S that were extracted from the Jack o'Lantern mushroom (*Omphalotus illudens*)[48] and to the carcinogen ptaquiloside, isolated from the fern *Pteridium aquilinum*.[49]

As reported previously, tetronates bearing 4-*O*-allyl residues with trisubstituted alkenes undergo an extended Claisen–Conia–retro-Conia–isomerization rearrangement to 3-alkylidenefuran-2,4-diones when heated. They are amenable to oxidation with singlet oxygen affording endoperoxide hemiketals **22** (Table 3);[50] some of these compounds were tested for antiplasmodial activity[51] and found to be as effective as the natural antimalarial lead artemisinin.[52]

Table 3 Structure of Endoperoxide Hemiketals **22**



22

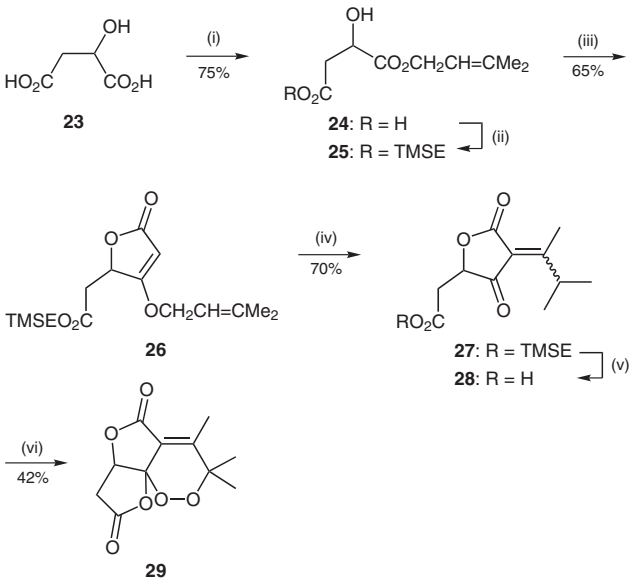
22	R^1	R^2	IC_{50}[a] (nM)
a	$-(CH_2)_5-$		3.9
b	$-(CH_2)_4-$		6.0
c	Ph	H	5.9

[a] Tested against *Plasmodium falciparum* POW according to the WHO protocol with artemisinin (IC_{50} 4.3 nM) as a standard.

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-alkylidenefuran-2,4-dione **27**. Desilylation with tetrabutylammonium 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,[53] 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.[54] 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.[7a,b] Like all 3-acyltetramic acids,[55,56] **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 $Me_2C{=}CHCH_2OH$, neat, r.t.; (ii) TMSEOH, DCC, THF, r.t. to 65 °C, 16 h, 60%; (iii) $Ph_3P{=}C{=}C{=}O$ (**3**), THF, 55 °C, 16 h; (iv) sealed glass tube, 170 °C, 24 h; (v) TBAF·$3H_2O$, THF, r.t., 2 h, 90%; (vi) O_3, CH_2Cl_2, PTSA, $CuSO_4$, hν, r.t., 1 h.

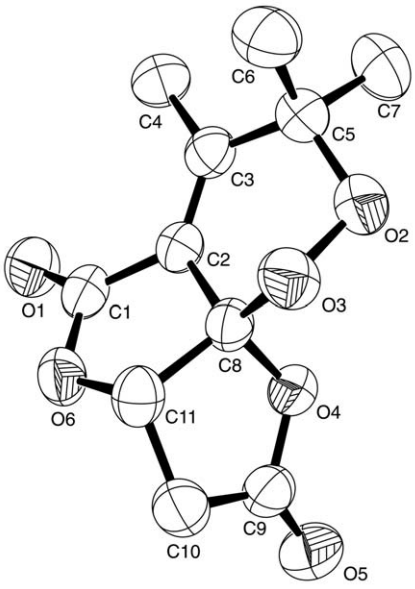
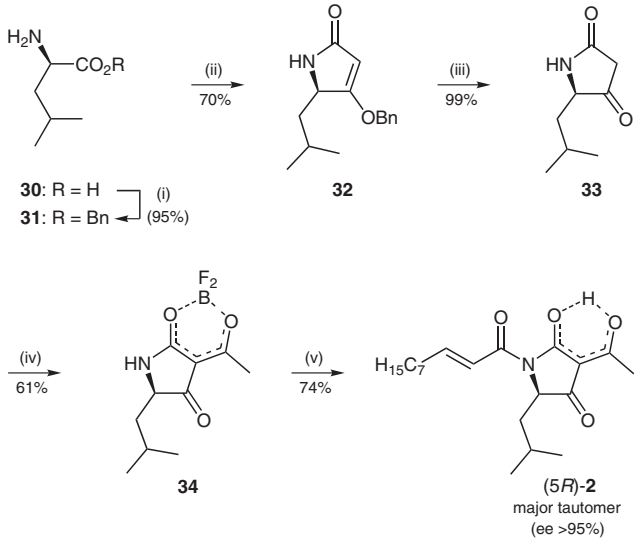


Figure 2 Molecular structure of **29** (ORTEP representation, 50% probability ellipsoids); hydrogen atoms are omitted; selected bond lengths [Å] and dihedral angles [°]: C1–C2 1.471(3), C2–C3 1.334(3), C3–C5 1.521(3), C2–C8 1.487(3), C5–O2 1.443(3), O2–O3 1.481(2), C8–O3 1.389(3), C8–O4 1.441(2), C5–O2–O3–C8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

cations in the range of siderophores.[57–61] The proton-ionophoric properties were also drawn on to explain the bioactivity of **2**.[62] 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 one[7c] submitted an *N*-dec-2-enoylleucine 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 second[7d] synthesis of **2**, *N*-acetoacetylleucinate was cyclized under basic Lacey–Dieckmann conditions.[19] The resulting 3-acetyl-5-isobutyltetramic acid was finally deprotonated with butyllithium and N-acylated with (*E*)-dec-2-enoyl chloride to give (5*R*)-**2** with 80% ee. It remained unclear which one of the two basic steps, Dieckmann condensation or N1-deprotonation/acylation, had proceeded with partial racemization.[63]

We have now developed an alternative four-step synthesis of (5*R*)-**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,[28] i.e. employing acetyl chloride/boron trifluoride–diethyl ether complex, then at N1 using sodium hexamethyldisilazanide/(*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 tetramic 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 hexamethyldisilazanide 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 (5*S*)-enantiomer (i.e. >95% ee) as to chiral HPLC on permethylated β-cyclodextrin when compared with an authentic racemic sample. This and the optical rotation of $[\alpha]_D^{25}$ +18 (*c* 3.0, EtOH) are in keeping with the data reported[7d] by the Jung group for the product of their most recent synthesis [80% ee, $[\alpha]_D^{25}$ +13 (*c* 0.29, EtOH)]. NMR spectra in acetonitrile-d_3 revealed the presence of two, very likely external, tautomers in ca. 3:2 ratio.



Scheme 5 Synthesis of reutericyclin [(5*R*)-**2**]. *Reactions and conditions*: (i) BnOH, PTSA, benzene, reflux, 16 h; (ii) $Ph_3P{=}C{=}C{=}O$ (**3**), $PhCO_2H$ (cat), THF, 60 °C, 16 h; (iii) H_2 (1 bar), Pd/C (5%), MeOH, r.t., 1 h, (iv) $BF_3{\cdot}OEt_2$ (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 $KHSO_4$.

Conclusions

The cumulated ylide (triphenylphosphoranylidene)ketene (Ph_3PCCO, **3**) is a versatile C_2O building block for the construction of differently functionalized tetronates and tetramates 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 tetronic and tetramic acids are acylated by **3** at C3 to give the corresponding acyl ylides, which can be saponificated to the respective 3-acetyl systems. Even unprotected α-hydroxy acids react with **3** to afford the corresponding 3-phosphoranylidenefuran-2,4-diones. The downstream acylation at C3 of tetronic acids and of N1 and C3 of tetramic acids 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 tetramates 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 countercation that replaces hydrogen in these chelates. Work towards this end is underway in our laboratory.

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 using TMS as internal standard. The assignments of 1D NMR signals were verified with the aid of 2D spectra (HH-COSY, HETCOR–HSQC). In ^{1}H NMR spectra of isomeric mixtures, the quoted signal integrations refer to the hypothetically pure individual isomers. MS were recorded using a Varian MAT 311A (EI, 70 eV). Microanalyses were carried out with a Perkin-Elmer 2400 CHN elemental analyzer. Analytical chromatography of nonracemic samples was conducted on chiral permethylated β-cyclodextrin (HPLC) or Lipodex-E (GC) columns from Macherey–Nagel. For flash chromatography, Merck silica gel 60 (230–400 mesh) was used. Starting compounds were prepared according to literature procedures or purchased from Fluka and Aldrich and used as such without further purification.

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

A soln of **4**[34b] (144 mg, 1.0 mmol) and **3** (330 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 CH_2Cl_2 to remove Ph_3PO, then with neat Et_2O; R_f = 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}.

^{1}H NMR ($CDCl_3$): δ = 1.46 (d, *J* = 6.7 Hz, 3 H, 5-Me^E), 1.47 (d, *J* = 6.7 Hz, 3 H, 5-Me^Z), 1.60 (d, *J* = 4.8 Hz, 3 H, =CMe^Z), 1.66 (d, *J* = 6.4 Hz, 3 H, =CMe^E), 2.86 (d, *J* = 5.0 Hz, 2 H, CH_2^Z), 2.94 (d, *J* = 6.7 Hz, 2 H, CH_2^E), 4.80 (q, *J* = 6.7 Hz, 1 H, H5^{E+Z}), 5.30–5.60 (m, 2 H, =CH^{E+Z}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.7/17.7 (Me), 17.70/17.75 (Me), 19.2/24.0 (CH_2), 75.3 (CH), 99.2/99.4 (C^q), 125.8/126.2 (CH), 126.4/126.6 (CH), 177.0/177.1 (C^q), 177.2/177.5 (C^q).

MS: *m*/*z* (%) = 168 (24) [M$^+$], 150 (39), 127 (25), 114 (53), 95 (61), 81 (100).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.3; H, 7.2. Found: C, 64.0; H, 7.0.

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

A soln of **4**[34b] (2.41 g, 16.7 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–Et_2O, 1:1, R_f = 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}.

^{1}H NMR ($CDCl_3$), mixture of diastereomers *a* and *b*: δ = 1.39 (d, *J* = 6.8 Hz, 3 H, 5-Me), 1.40/1.41 (d, *J* = 6.4 Hz, 3 H, 1′-Me), 4.60 (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, =CH^E), 5.33 (dd, *J* = 10.4, 1.1 Hz, 1 H, =CH^Z), 5.50/5.80 (ddd, *J* = 17.4, 10.4, 6.5 Hz, 1 H, =CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): 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_2), 135.9 (CH), 172.7 (C^q), 181.0 (C^q).

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

Anal. Calcd for $C_9H_{12}O_3$: C, 64.3; H, 7.2. Found: C, 64.5; H, 7.4.

(3*R*,4*S*,5*S*)-3-Butyl-4-hydroxy-5-methyldihydrofuran-2(3*H*)-one [(–)-*epi*-Blastmycinolactol, 7]

A mixture of **5** (252 mg, 1.5 mmol), 5% Rh/Al_2O_3 catalyst (100 mg; 20 mol%), EtOAc (20 mL), and AcOH (10 mL) was placed in an autoclave and stirred at 60 °C for 5 d pressurized with H_2 gas (50 bar). The mixture was filtered through Celite and the filtrate was concentrated and purified by column chromatography (silica gel, Et_2O, R_f = 0.76) to give colorless crystals; yield: 181 mg (70%); 92% ee (GC; Lipodex-E); mp 97 °C (Lit.[38] 101–102 °C); $[\alpha]_D^{25}$ –82 (*c* 0.6, MeOH) [Lit.[38] $[\alpha]_D^{25}$ –84.8 (*c* 0.66, MeOH)].

IR (ATR): 3427, 2959, 1741, 1187, 1063 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H, Me), 1.30–1.41 (m, 2 H, CH_2), 1.39 (d, *J* = 6.5 Hz, 3 H, 5-Me), 1.35–1.44 (m, 2 H, CH_2), 1.53–1.69 (m, 1 H, 3-C*H*H), 1.69–1.84 (m, 1 H, 3-CH*H*), 2.53 (dt, *J* = 10.0, 4.9 Hz, 1 H, H3), 2.84 (br s, 1 H, OH), 4.28 (dd, *J* = 4.9, 3.0 Hz, 1 H, 4H), 4.43 (dq, *J* = 6.5, 3.0 Hz, 1 H, H5).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.6 (Me), 13.8 (Me), 22.5 (CH_2), 22.9 (CH_2), 29.7 (CH_2), 47.6 (CH), 71.1 (CH), 79.2 (CH), 178.3 (C^q).

MS: *m*/*z* (%) = 172 (2) [M^+], 155 (8), 116 (87), 99 (69), 85 (37), 57 (100).

4-(Benzyloxy)-5-butylfuran-2(5*H*)-one (9a)

Colorless oil from **8a**[64] (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%); R_f = 0.62 (Et_2O–*n*-pentane, 2:1).

IR (ATR): 3119, 3035, 2957, 2872, 1755, 1629, 1230, 1016 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H, Me), 1.32–1.43 (m, 4 H, CH_2), 1.57–1.66 (m, 1 H, 5-CH*H*), 1.88–1.97 (m, 1 H, 5-C*H*H), 4.77–4.80 (m, 1 H, H5), 5.04 (2 d, *J* = 16.5 Hz, 2 H, OCH_2), 5.12 (s, 1 H, H3), 7.35–7.43 (m, 5 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.7 (Me), 22.2 (CH_2), 26.2 (CH_2), 31.4 (CH_2), 74.2 (CH_2), 78.9 (CH), 90.0 (CH), 127.8, 128.7, 128.9 (ar-CH), 133.9 (ar-C^q), 172.6 (C^q), 181.0 (C^q).

MS: *m*/*z* (%) = 246 (3) [M^+], 212 (4), 189 (8), 132 (20), 105 (11), 91 (100).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.1; H, 7.4. Found: C, 72.8; H, 7.0.

4-(Benzyloxy)-5-hexylfuran-2(5*H*)-one (9b)

Colorless oil from **8b**[65] (4.27 g, 17.1 mmol) and **3** (5.42 g, 17.9 mmol) in THF (150 mL), reflux for 8–16 h; yield: 3.50 g (75%); R_f = 0.42 (Et_2O–*n*-hexane, 3:2).

IR (ATR): 2928, 1752, 1625, 1300, 1155 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3 H, Me), 1.15–1.45 (m, 8 H, CH_2), 1.51–1.66 (m, 1 H, 5-CH*H*), 1.80–1.96 (m, 1 H, 5-C*H*H), 4.76 (ddd, *J* = 7.7, 3.7, 1.0 Hz, 1 H, H5), 4.99 (d, *J* = 11.6 Hz, 1 H, 4-OCH), 5.04 (d, *J* = 11.6 Hz, 1 H, 4-OCH), 5.09 (d, *J* = 1.0 Hz, 1 H, H3), 7.30–7.42 (m, 5 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.9 (Me), 22.4 (CH_2), 24.0 (CH_2), 28.8 (CH_2), 31.4 (CH_2), 31.7 (CH_2), 79.0 (CH), 89.5 (CH), 127.8, 128.7, 128.9 (ar-CH), 133.9 (ar-C^q), 172.6 (C^q), 181.0 (C^q).

MS: *m*/*z* (%) = 274 (2) [M^+], 256 (1), 190 (5), 91 (100).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.4; H, 8.1. Found: C, 74.7; H, 8.0.

5-Butyl-4-hydroxyfuran-2(5*H*)-one (10a); Typical Procedure

White solid from **9a** (984 mg, 4.0 mmol) upon hydrogenation with 10% Pd/C (150 mg) as a catalyst in MeOH and H_2 (1 atm) for 12 h followed by filtration through a short plug of Celite and recrystallization (Et_2O); yield: 587 mg (95%); mp 79–80 °C.

IR (KBr): 3443, 2959, 2931, 1719, 1623, 1458, 1275 cm^{-1}.

^1H NMR ($CDCl_3$), 3:2 mixture of enol and keto tautomers: δ = 0.91 (t, *J* = 7.2 Hz, 3 H, Me), 1.35–1.46 (m, 4 H, CH_2), 1.61–1.68 (m, 1 H, 5-C*H*H), 1.93–1.99 (m, 1 H, 5-CH*H*), 3.20 (d, *J* = 6.6 Hz, 2 H, $H3^{keto}$), 4.76–4.79 (m, 1 H, $H5^{keto}$), 4.80–4.83 (m, 1 H, $H5^{enol}$), 5.04 (s, 1 H, $H3^{enol}$).

^{13}C NMR (75.5 MHz, $CDCl_3$): enol: δ = 13.8 (Me), 22.3 (CH_2), 26.2 (CH_2), 31.1 (CH_2), 80.7 (CH), 88.7 (CH), 177.7 (C^q), 184.0 (C^q); keto: δ = 13.6 (Me), 22.1 (CH_2), 26.5 (CH_2), 31.0 (CH_2), 37.5 (CH_2), 86.5 (CH), 169.9 (C^q), 205.6 (C^q).

MS: *m*/*z* (%) = 156 (2) [M^+], 128 (4), 100 (72), 86 (41), 43 (100).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 61.5; H, 7.4.

5-Hexyl-4-hydroxyfuran-2(5*H*)-one (10b)

White solid from **9b** (3.48 g, 12.7 mmol), analogously to the synthesis of **10a**; yield: 2.38 g (99%); mp 99 °C [Lit.[66] 101–103 °C].

IR (ATR): 3129, 2926, 1692, 1567, 1277 cm^{-1}.

^1H NMR ($CDCl_3$), 3:2 mixture of enol and keto tautomers: δ = 0.92 (t, *J* = 7.2 Hz, 3 H, Me), 1.35–1.54 (m, 8 H, CH_2), 1.61–1.68 (m, 1 H, 5-C*H*H), 1.90–1.97 (m, 1 H, 5-CH*H*), 3.22 (d, *J* = 6.6 Hz, 2 H, $H3^{keto}$), 4.76–4.80 (m, 1 H, $H5^{keto}$), 4.80–4.83 (m, 1 H, $H5^{enol}$), 5.04 (s, 1 H, $H3^{enol}$).

MS: *m*/*z* (%) = 184 (6) [M^+], 156 (1), 142 (2), 114 (12), 100 (100).

5-Butyl-4-hydroxy-3-[1-oxo-2-(triphenylphosphoranyl)ethyl]furan-2(5*H*)-one (11a)

A soln of **3** (2.00 g, 6.6 mmol) and **10a** (0.80 g, 5.1 mmol) in THF (20 mL) was refluxed for 12 h. Upon cooling, colorless crystals of **11a** precipitated; yield: 1.87 g (80%); mp >192 °C (dec.). In soln, mixture of enol–ylide (α) and two rotameric oxo–phosphonium (β) tautomers, the latter only discernable at low temperature:

^{13}C NMR (125.7 MHz, $CDCl_3$, –58 °C); tautomer α: δ = 14.12 (Me), 22.29 (CH_2, CMe), 26.80 (CH_2, *C*CMe), 31.01 (CH_2; 5-C), 56.01 (d, $^1J_{PC}$ = 107.51 Hz, P=CH), 83.26 (CH, C5), 89.26 (C^q, C3), 122.61 (d, $^1J_{PC}$ = 92.03 Hz, C-ipso), 129.23 (d, $^3J_{PC}$ = 12.70 Hz, C-meta), 132.82 (d, $^2J_{PC}$ = 10.81 Hz, C-ortho), 133.29 (C-para), 171.78, 176.74, 196.38 (C^q, 3-C, C2, C4); tautomer β: δ = 14.00/14.04 (Me), 22.35/22.39 (CH_2, *C*Me), 26.39/26.69 (CH_2, *C*CMe), 31.23/31.34 (CH_2, 5-C), 34.58/34.60 (each d, $^1J_{PC}$ = 51.06/52.02 Hz, P-CH_2), 80.33/80.64 (CH, C5), 96.83/97.29 (C^q, C3), 118.59/118.20 (each d, $^1J_{PC}$ = 88.90/88.53 Hz, C-ipso), 129.68/129.74 (each d, $^3J_{PC}$ = 12.83/12.70 Hz, C-meta), 133.50/133.61 (each d, $^2J_{PC}$ = 11.82/11.44 Hz, C-ortho), 134.43/134.54 (C-para), 173.32/173.55, 179.33/179.64, 197.63/197.81 (C^q, 3-C, C2, C4).

^{31}P NMR (202.4 MHz, H_3PO_4 ext., $CDCl_3$, –58 °C): δ = 16.87 (α), 23.70/23.93 (β).

^{31}P NMR (121.4 MHz, H_3PO_4 ext., DMSO-d_6, 32 °C): δ = 23.93 (tautomer β only).

MS: *m*/*z* (%) = 458 (24) [M^+], 415 (4), 402 (17), 301 (19), 277 (100), 262 (32), 201 (24), 183 (41).

Anal. Calcd for $C_{28}H_{27}O_4P$: C, 73.4; H, 5.9. Found: C, 73.0; H, 5.6.

3-Acetyl-5-butyl-4-hydroxyfuran-2(5*H*)-one (12a) from 10a; Typical Procedure

A soln of **3** (0.97 g, 3.2 mmol) and **10a** (0.46 g, 2.9 mmol) in THF (50 mL) was heated under reflux for 24 h. After cooling to r.t. the resulting mixture was treated dropwise with aq 2 M NaOH (20 mL). Stirring was continued at r.t. for 2 h, then 47% aq HBr soln was added carefully until the volume was twice the original. This mixture was extracted with Et_2O (3 × 20 mL), the combined organic phases were washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. Sublimation of the residue at 80 °C/6.7 mbar afforded white crystals; yield: 495 mg (85%); mp 54 °C.

IR (ATR): 3079, 2958, 2923, 1746, 1666, 1597, 1165, 1012 cm^{-1}.

^{1}H NMR ($CDCl_3$), 1.6:1 mixture of two tautomers a/b: δ = 0.84 (t, *J* = 7.3 Hz, 3 H, Me^b), 0.85 (t, *J* = 7.1 Hz, 3 H, Me^a), 1.20–1.45 (m, 4 H, CH_2), 1.57–1.74 (m, 1 H, 5-C*H*H), 1.82–1.96 (m, 1 H, 5-CH*H*), 2.48 (s, 3 H, MeCO), 4.55 (dd, *J* = 8.0, 4.2 Hz, 1 H, H5^b), 4.68 (dd, *J* = 8.0, 4.4 Hz, 1 H, H5^a), 10.9 (br s, 1 H, OH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.7 (Me), 19.5 (Me^b), 22.2 (CH_2), 22.4 (Me^a), 26.4 (CH_2^a), 26.5 (CH_2^b), 30.9 (CH_2^b), 31.0 (CH_2^a), 80.0 (CH^a), 85.6 (CH^b), 97.8 (C^{qb}), 100.7 (C^{qa}), 167.9 (C^{qa}), 175.9 (C^{qb}), 188.1 (C^{qb}), 194.3 (C^{qa}), 194.9 (C^{qb}), 199.8 (C^{qa}).

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

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1. Found: C, 60.5; H, 7.1.

3-Acetyl-5-hexyl-4-hydroxyfuran-2(5*H*)-one (Pesthetoxin, 12b) from 10b

From **3** (0.63 g, 2.1 mmol) and **10b** (0.35 g, 1.8 mmol) analogously to the synthesis of **12a**; yield: 359 mg (85%); mp 58 °C [Lit.[40] no mp reported].

IR (ATR): 3078, 1747, 1665, 1601, 1581, 1166, 1078 cm^{-1}.

^{1}H NMR ($CDCl_3$), 1.6:1 mixture of two tautomers a/b: δ = 0.84 (t, *J* = 6.7 Hz, 3 H, Me), 1.17–1.36 (m, 6 H, CH_2), 1.36–1.52 (m, 2 H, CH_2), 1.61–1.77 (m, 1 H, 5-C*H*H), 1.83–1.98 (m, 1 H, 5-CH*H*), 2.51 (s, 3 H, COMe^b), 2.52 (s, 3 H, COMe^a), 4.59 (dd, *J* = 8.0, 4.3 Hz, 1 H, H5^b), 4.71 (dd, *J* = 7.7, 4.5 Hz, 1 H, H5^a), 12.5 (br s, 1 H, OH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (Me^{a+b}), 19.5 (Me^b), 22.4 (Me^a), 22.5 (CH_2^{a+b}), 24.3 (CH_2^a), 24.4 (CH_2^b), 28.7 (CH_2^a), 28.8 (CH_2^b), 31.2 (CH_2^b), 31.3 (CH_2^a), 31.4 (CH_2^{a+b}), 80.0 (CH^a), 85.6 (CH^b), 97.8 (C^{qb}), 100.7 (C^{qa}), 167.9 (C^{qa}), 175.9 (C^{qb}), 188.0 (C^{qb}), 194.3 (C^{qa}), 194.9 (C^{qb}), 199.8 (C^{qa}).

MS: *m*/*z* (%) = 227 (2), 226 (9) [M$^+$], 155 (23), 142 (100).

3-(Triphenylphosphoranylidene)furan-2,4(3*H*,5*H*)-diones 15; General Procedure

A mixture of ylide **3** (6.00 g, 19.8 mmol), α-hydroxycarboxylic acid **13** (22.5 mmol), and THF (150 mL) was heated under gentle reflux for ca. 8 h. When employing aqueous solns of lactic acid, some drying agent (Na_2SO_4, ca. 3–5 g) was also added. After cooling to r.t. the mixture was concentrated and the remainder was purified by column chromatography (silica gel).

5-Methyl-3-(triphenylphosphoranylidene)furan-2,4(3*H*,5*H*)-dione (15a)

From DL-lactic acid (2.02 g, 22.5 mmol); chromatography (THF–CH_2Cl_2, 1:2) gave **15a** as colorless crystals; yield: 4.82 g (65%); mp 113–115 °C.

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

^{1}H NMR ($CDCl_3$): δ = 1.44 (d, *J* = 6.8 Hz, 3 H, Me), 4.58 (q, *J* = 6.8 Hz, 1 H, CH), 7.45–7.65 (m, 15 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.9, 60.5 (d, $^1J_{PC}$ = 125 Hz), 79.4, 121.3 (d, $^1J_{PC}$ = 93 Hz), 128.0, 133.1, 133.8, 174.6, 198.0.

^{31}P NMR (121.4 MHz, H_3PO_4 ext., $CDCl_3$): δ = 11.62.

MS: *m*/*z* (%) = 374 (27), 301 (52), 275 (76), 262 (100), 183 (50).

Anal. Calcd for $C_{23}H_{19}O_3P$: C, 73.8; H, 5.1. Found: C, 73.7; H, 5.2.

5-Hexyl-3-(triphenylphosphoranylidene)furan-2,4(3*H*,5*H*)-dione (15b)

From **13b** (3.61 g, 22.5 mmol); chromatography (hexane–Et_2O, 3:2) gave **15b** as a colorless solid; yield: 5.90 g (67%); mp 80 °C.

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

^{1}H NMR ($CDCl_3$): δ = 0.83 (t, *J* = 6.7 Hz, 3 H, Me), 1.16–1.35 (m, 6 H, CH_2), 1.40–1.54 (m, 2 H, CH_2), 1.62–1.72 (m, 1 H, 5-CH), 1.84–1.98 (dd, *J* = 3.8, 7.5 Hz, 1 H, 5-CH), 4.52 (m, 1 H, H5), 7.44–7.63 (m, 15 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.9, 22.3, 24.5, 28.9, 31.5, 31.8, 61.2 (d, $^1J_{PC}$ = 122 Hz), 83.3, 121.6 (d, $^1J_{PC}$ = 94 Hz), 128.9, 133.2, 133.9, 175.0, 197.4.

^{31}P NMR (121.4 MHz, H_3PO_4 ext., $CDCl_3$): δ = 11.56.

MS: *m*/*z* (%) = 444 (38), 373 (16), 360 (100), 301 (40), 262 (51), 183 (34).

Anal. Calcd for $C_{28}H_{29}O_3P$: C, 75.7; H, 6.6. Found: C, 75.7; H, 6.3.

5-Phenyl-3-(triphenylphosphoranylidene)furan-2,4(3*H*,5*H*)-dione (15c)

From DL-mandelic acid (3.42 g, 22.5 mmol); chromatography (cyclohexane–EtOAc, 1:5) gave (±)-**15c** as colorless crystals; yield: 6.22 g (72%); mp 178–180 °C. L-(+)-Mandelic acid gave (+)-**15c**; 95% ee; $[\alpha]_D^{25}$ +58 (*c* 1.2, $CHCl_3$).

IR (ATR): 3056, 1726, 1626, 1435, 1347, 722, 688 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.48 (s, 1 H, H5), 7.25–7.60 (m, 20 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 61.3 (d, $^1J_{PC}$ = 122 Hz), 84.1, 121.5 (d, $^1J_{PC}$ = 94 Hz), 125.7, 127.9, 128.3, 129.2, 133.4, 134.1, 136.5, 175.2, 194.8.

^{31}P NMR (121.4 MHz, H_3PO_4 ext., $CDCl_3$): δ = 11.99.

Anal. Calcd for $C_{28}H_{21}O_3P$: C, 77.1; H, 4.8. Found: C, 76.8; H, 4.6.

(±)-1-Methyl-4-methylene-2-phenyl-11-oxadispiro[2.1.5.2]dodecan-12-one [(±)-19]

To a slurry of methyltriphenylphosphonium bromide (750 mg, 2.11 mmol) in THF (20 mL), 1.6 M BuLi in hexane (1.3 mL, 2.08 mmol) was slowly added. The dark orange soln was stirred at r.t. for 30 min and then treated with a soln of diastereopure racemic (±)-**16a**[37a] (500 mg, 1.76 mmol) in THF (10 mL). After stirring for a further 4 h the resulting mixture was filtered through a small plug of silica gel, the filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel; Et_2O–hexane, 1:1, R_f = 0.78) to give colorless solid **19**; yield: 422 mg (84%).

IR (ATR): 2931, 1753, 1315, 1267, 1127, 968 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.18–1.88 (m, 10 H, CH_2), 1.59 (d, *J* = 6.3 Hz, 3 H, Me), 1.96 (dq, *J* = 8.5, 6.3 Hz, 1 H, *H*CMe), 3.12 (d, *J* = 8.5 Hz, 1 H, *H*CPh), 3.69 (d, *J* = 1.1 Hz, 1 H, =CH*H*), 4.39 (d, *J* = 1.1 Hz, 1 H, =C*H*H), 7.12–7.33 (m, 5 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.9, 21.9, 22.1, 25.0, 33.0, 34.7, 37.4, 37.7, 45.6, 86.7, 101.6, 127.3, 128.2, 129.9, 134.2, 150.6, 175.8.

MS: *m*/*z* (%) = 283 (17), 282 [M$^+$] (100), 267 (11), 237 (34), 195 (22), 115 (23), 105 (46).

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.8; H, 7.9. Found: C, 80.4; H, 7.6.

4-Hydroxy-1-methyl-2-phenyl-11-oxadispiro[2.1.5.2]dodecan-12-one (20)

A soln of (±)-**16a** (290 mg, 1.0 mmol) in MeOH (20 mL) was chilled to 0 °C and slowly treated with $NaBH_4$ (65 mg, 1.7 mmol). After stirring at r.t. for 24 h, the mixture was quenched with sat. aq $NaHCO_3$ soln to pH 8–9 and then repeatedly extracted with CH_2Cl_2. The combined extracts were dried, concentrated, and purified by chromatography (silica gel, hexane–Et_2O, 3:1) to give **20** as a colorless solid; yield: 263 mg (90%); 3:2 mixture of diastereomers; mp 201 °C. The diastereomers were separated by column chromatography (hexane–Et_2O, 1:1); R_f = 0.30 and 0.43.

Minor Isomer

IR (ATR): 3394, 2933, 1735, 1499, 1197, 1028, 952 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.15–1.80 (m, 10 H, CH_2), 1.49 (d, *J* = 6.3 Hz, 3 H, Me), 1.50 (d, *J* = 6.8 Hz, 1 H, OH), 2.25 (dq, *J* = 7.8, 6.3 Hz, 1 H, *H*CMe), 2.74 (d, *J* = 7.8 Hz, 1 H, *H*CPh), 3.39 (d, *J* = 6.8 Hz, 1 H, H4), 7.11–7.35 (m, 5 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.5, 21.8, 22.0, 22.8, 24.9, 30.3, 35.5, 38.6, 39.0, 74.1, 86.1, 127.2, 128.1, 128.6, 135.8, 175.3.

MS: *m*/*z* (%) = 286 [M^+], 268 (55), 257 (80), 223 (62), 181 (31), 118 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{18}H_{22}O_3$: 286.15689; found: 286.15690.

(±)-4-Hydroxy-1,4-dimethyl-2-phenyl-11-oxa-dispiro[2.1.5.2]dodecan-12-one (21a)

A soln of (±)-**16a** (300 mg, 1.06 mmol) in THF (20 mL) was slowly treated at r.t. with 1.6 M MeLi in Et_2O (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, Et_2O–hexane, 1:1) left pure crystalline **21a**; yield: 288 mg (90%); mp 190 °C.

IR (KBr): 3423, 1724, 961 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.79 (s, 3 H, Me), 1.34 (d, *J* = 6.3 Hz, 3 H, Me), 1.38–1.78 (m, 11 H), 2.09–2.16 (m, 1 H), 2.89 (d, *J* = 7.8 Hz, 1 H, *H*CPh), 7.23–7.34 (m 5 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.8, 20.5, 21.2, 21.5, 25.0, 25.3, 27.2, 33.3, 34.8, 42.0, 80.0, 89.2, 127.1, 127.6, 128.1, 128.6, 134.6, 175.2.

MS: *m*/*z* (%) = 301 (1), 300 [M^+] (6), 283 (13), 282 (44), 237 (22), 194 (27), 117 (51), 43 (100).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{19}H_{24}O_3$: 300.17255; found: 300.17258.

(±)-4-Hydroxy-1-methyl-2,4-diphenyl-11-oxa-dispiro[2.1.5.2]dodecan-12-one (21b)

Analogously to the synthesis of **21a**, **21b** was obtained from (±)-**16a** (150 mg, 0.5 mmol) and 1.6 M PhLi in toluene (0.60 mL, 1.0 mmol). Chromatography (silica gel 60, Et_2O–hexane, 1:4) gave **21b** as a white solid; yield: 110 mg (58%); mp 183 °C.

IR (KBr): 3429, 2932, 1732, 1447, 1274, 1101, 766 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.33 (d, *J* = 6.5 Hz, 3 H, Me), 1.04–1.96 (m, 10 H), 2.11 (d, *J* = 8.2 Hz, 1 H, *H*CPh), 2.39 (dq, *J* = 8.2, 6.5 Hz, 1 H, *H*CMe), 2.85 (s, 1 H, OH), 7.09–7.85 (m, 10 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.5, 21.1, 21.3, 24.7, 26.4, 32.8, 34.4, 45.1, 50.0, 83.2, 126.8, 126.9, 127.0, 127.7, 128.3, 128.5, 135.4, 142.6, 175.5.

MS: *m*/*z* (%) = 344 [$M^+ - H_2O$] (14), 264 (12), 255 (100), 173 (19), 105 (74), 77 (15).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{24}H_{26}O_3$: 362.46144; found: 362.46138.

3-Hydroxy-4-(3-Methylbut-2-enyl)oxybutanoic acid (24)

A mixture of malic acid (**23**, 5.43 g, 40.5 mmol) and TFAA (34.00 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, 5:2:1); R_f = 0.26 (cyclohexane–EtOAc, 1:1). The eluate was evaporated and residual TFA was removed azeotropically with toluene (3 × 5 mL); yield: 6.13 g (75%).

IR (ATR): 3441, 3207, 1715, 1263, 1180, 1101 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.64 (s, 3 H, Me), 1.68 (s, 3 H, Me), 2.75 (dd, *J* = 16.6, 6.6 Hz, 1 H, *H*HCC=O), 2.85 (dd, *J* = 16.6, 4.4 Hz, 1 H, H*H*CC=O), 4.47 (dd, *J* = 6.6, 4.4 Hz, 1 H, *H*COH), 4.63 (d, *J* = 7.3 Hz, 2 H, H_2C-O), 5.23–5.35 (m, 1 H, =CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.9, 25.6, 38.5, 62.8, 67.2, 117.7, 140.2, 173.3, 175.5.

MS: *m*/*z* (%) = 202 (2), 187 (1), 85 (60), 71 (14), 69 (100).

Anal. Calcd for $C_9H_{14}O_5$: C, 53.5; H, 6.9. Found: C, 53.7; H, 6.7.

1-(3-Methylbut-2-enyl) 4-[2-(Trimethylsilyl)ethyl] 2-Hydroxybutanedioate (25)

A mixture of DCC (5.19 g, 25.2 mmol), 2-(trimethylsilyl)ethanol (3.70 g, 25.0 mmol), and a catalytic amounts of $CuCl_2$ was stirred at r.t. for 6 h. Then a soln 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, 5:1); yield: 4.40 g (60%).

IR (ATR): 3491, 1734, 1249, 1165 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.03 (s, 9 H, SiMe), 0.87–0.97 (m, 2 H, $SiCH_2$), 1.65 (s, 3 H, Me), 1.69 (s, 3 H, Me), 2.68 (dd, *J* = 16.3, 6.2 Hz, 1 H, *H*HCC=O), 2.76 (dd, *J* = 16.3, 4.5 Hz, 1 H, H*H*CC=O), 3.32 (s, 1 H, OH), 4.07–4.17 (m, 2 H, OCH_2), 4.36–4.44 (m, 1 H, *H*COH), 4.62 (d, *J* = 7.3 Hz, 2 H, H_2CO), 5.27 (t, *J* = 7.3 Hz, 1 H, =CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = –1.6, –1.5, 17.2, 18.0, 25.7, 38.8, 62.7, 63.2, 67.2, 117.7, 140.0, 169.3, 173.3.

MS: *m*/*z* (%) = 302 [M^+] (1), 217 (1), 173 (18), 131 (27), 73 (100).

Anal. Calcd for $C_{14}H_{26}O_5Si$: C, 55.6; H, 8.6. Found: C, 55.7; H, 8.4.

4-(3-Methylbut-2-enyloxy)-5-({[2-(trimethylsilyl)ethoxy]carbonyl}methyl)furan-2(5*H*)-one (26)

A mixture of **3** (2.12 g, 7.0 mmol), **25** (1.65 g, 5.5 mmol), benzoic acid (133 mg, 1.1 mmol), and THF (50 mL) was heated at 55 °C for 16 h. All volatiles were removed and the residue was purified by column chromatography (silica gel, cyclohexane–EtOAc 3:1). Concentration of the eluate left tetronate **26** as a colorless oil; yield: 1.23 g (65%).

IR (ATR): 1762, 1735, 1628, 1312, 1249, 1166, 1151, 1040, 858 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.08 (s, 9 H, SiMe), 0.80–0.92 (m, 2 H, $SiCH_2$), 1.60 (s, 3 H, Me), 1.67 (s, 3 H, Me), 2.43 (dd, *J* = 16.3, 8.4 Hz, 1 H, *H*HCC=O), 2.71 (dd, *J* = 16.3, 4.0 Hz, 1 H, H*H*CC=O), 4.03–4.12 (m, 2 H, OCH_2), 4.44 (d, *J* = 7.1 Hz, 2 H, $=CCH_2$), 4.96 (s, 1 H, H3), 4.99–5.05 (m, 1 H, H5), 5.23–5.32 (t, *J* = 7.1 Hz, 1 H, =CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = –2.2, –2.0, –1.9, 17.0, 17.8, 25.4, 37.0, 63.1, 69.3, 74.8, 88.8, 116.6, 140.9, 168.0, 171.7, 179.8.

MS: *m*/*z* (%) = 326 [M^+] (1), 283 (38), 235 (14), 239 (22), 208 (42), 181 (26), 164 (42), 149 (62), 137 (23), 95 (23), 73 (100).

Anal. Calcd for $C_{16}H_{26}O_5Si$: C, 58.9; H, 8.0. Found: C, 59.1; H, 7.8.

3-(1,2-Dimethylpropylidene)-5-({[2-(trimethylsilyl)ethoxy]carbonyl}methyl)furan-2,4(3*H*,5*H*)-dione (27)

A soln of **26** (307 mg, 0.94 mmol) in toluene (10 mL), placed in a sealed glass bomb tube, was heated at 170 °C for 24 h. The resulting yellow to brownish soln was concentrated in vacuo and the oily residue was purified by column chromatography (silica gel, cyclohexane–EtOAc 5:1). Evaporation of the eluate afforded **27** as a faintly yellow oil as an *Z*/*E* mixture; yield: 214 mg (70%).

IR (ATR): 1767, 1714, 1609, 1249, 1208, 1170, 1070, 858 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = –0.03 (s, 9 H, SiMe), 0.86–0.93 (m, 2 H, $SiCH_2$), 1.07/1.11 (d, *J* = 6.9 Hz, 6 H, $HCMe_2$), 2.43/2.46 (s, 3 H,

MeC=), 2.89–2.95 (m, 2 H, H_2CC=O), 4.06–4.15 (m, 2 H, OCH_2), 4.38 (sept, J = 6.9 Hz, 1 H, C*H*Me_2), 4.65–4.71 (m, 1 H, H5).

^{13}C NMR (75.5 MHz, $CDCl_3$): 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), 311 (2), 238 (39), 239 (25), 208 (40), 181 (25), 164 (45), 149 (67), 95 (32), 73 (100).

Anal. Calcd for $C_{16}H_{26}O_5Si$: C, 58.9; H, 8.0. Found: C, 58.8; H, 8.2.

5-(Carboxymethyl)-3-(1,2-dimethylpropylidene)furan-2,4(3*H*,5*H*)-dione (28)

A soln of **27** (382 mg, 1.2 mmol) in THF (20 mL) was treated with 1 M TBAF in THF (4.70 mL, 4.7 mmol) and the resulting mixture was stirred at r.t. until all starting material had gone by TLC (ca. 2 h). All volatiles were removed in vacuo and the remainder was partitioned between H_2O (40 mL) and Et_2O (20 mL). The ethereal phase was discarded, the aqueous one was adjusted to a pH of 3 by addition of 7% aq HCl. It was then extracted with EtOAc (2 × 80 mL), the combined extracts were washed with brine and dried (Na_2SO_4). Evaporation in vacuo left **28** as a colorless oil as an *E*/*Z* mixture; yield: 237 mg (90%).

IR (ATR): 3225, 2931, 1709, 1645, 1605, 1208, 1171, 1069 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.08/1.10 (d, J = 6.9 Hz, 6 H, HC*Me*$_2$), 2.45/2.47 (s, 3 H, MeC=), 2.95–3.03 (m, 2 H, H_2CC=O), 4.38/4.39 (sept, J = 6.9 Hz, 1 H, C*H*Me_2), 4.68–4.75 (m, 1 H, H5).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.9, 16.1, 19.7, 19.9, 20.0, 20.1, 31.0, 31.2, 35.6, 77.3, 115.4, 115.6, 174.2, 190.8, 191.4, 196.6, 201.1.

MS: *m*/*z* (%) = 226 [M^+] (13), 208 (100), 193 (43), 181 (64), 164 (24), 149 (69), 137 (29), 95 (65).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.4; H, 6.2. Found: C, 58.5; H, 6.2.

4,4,5-Trimethyl-2,3,8,12-tetraoxatricyclo[7.3.0.0^{1,6}]dodec-5-en-7,11-dione (29)

Under an atmosphere of N_2, a flame-dried Schlenk tube was charged with **28** (185 mg, 0.82 mmol), CH_2Cl_2 (60 mL), anhyd $CuSO_4$ (12 mg) and PTSA (29 mg, 0.18 mmol), stoppered and then pressurized with dry O_2 (10 mL). It was placed ca. 8 cm from a glass-jacketed Heraeus low-pressure Hg lamp within a shared cooling bath kept at r.t. and entirely wrapped in aluminum foil and irradiated for 1 h while vigorously stirring. The resulting yellow mixture was filtered over a fritted Schlenk-type funnel and the filtrate was concentrated in vacuo at r.t. to give a yellow crude oil. This was purified by column chromatography [1 × 15 cm, silica gel 60 (5% H_2O); cyclohexane–THF, 1:1], R_f = 0.75 (cyclohexane–THF, 1:2) to give a colorless viscous oil which solidified upon standing; yield: 82 mg (42%); mp 120 °C ($CHCl_3$–hexane, dec.).

IR (ATR): 1772, 1762, 1685, 1242, 1062, 1016, 955 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 3 H, Me), 1.50 (s, 3 H, Me), 2.25 (s, 3 H, Me), 2.98–3.00 (m, 2 H, CH_2), 4.72–4.75 (m, 1 H, CH).

^{13}C JMOD NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (Me), 21.3 (Me), 23.2 (Me), 34.4 (CH_2), 76.6 (CH), 81.4 (C^q), 105.6 (C^q), 115.6 (C^q), 158.9 (C^q), 164.4 (C^q), 171.3 (C^q).

MS: *m*/*z* (%) = 240 [M^+] (3), 208 (32), 193 (12), 169 (13), 165 (13), 153 (10), 137 (22), 67 (19), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{12}O_6$: 240.06339; found: 240.06340.

Crystal data: Clear, colorless crystals from $CHCl_3$–hexane upon cooling. Empirical formula $C_{11}H_{12}O_6$, M = 240.21, monoclinic, space group $P2(1)/c$, crystal size 0.28 × 0.24 × 0.18 mm^3, a = 7.2615(15), b = 9.6131(19), c = 16.433(3) Å, α = 90°, β = 102.10(3)°, γ = 90°, V = 1121.6(4) $Å^3$, Z = 4, θ-range 2.47–26.01°, ω/θ-scans, index ranges –8 < h < 8, –11 < k < 11, –20 < l < 17; μ = 0.117 mm^{-1}; Siemens P4 diffractometer, 7370 unique reflections, 2067 with I > 2σ(I), 154 refined parameters. Structure solution: direct methods (SHELXS97); structure refinement: full-matrix least squares on F^2 (SHELXL97); $R1$ = 0.0414, $wR2$ = 0.0938. CCDC reference number 616240.

Benzyl D-Leucinate (31)

A mixture of D-leucine (**30**, 2.62 g, 20.0 mmol), BnOH (8.64 g, 80.0 mmol), PTSA·H_2O (4.96 g, 26.0 mmol), and benzene (150 mL) was stirred for 16 h with azeotropic removal of H_2O. The benzene was finally distilled off until approx. 30 mL remained. The residue was poured into vigorously stirred precooled Et_2O. The ammonium ester salt precipitated and was collected and washed with Et_2O (3 × 30 mL) in a filter funnel. The solid was dried on an oil pump, dissolved in CH_2Cl_2 and shaken with an excess of aq 1 M Na_2CO_3. The organic phase was separated, shaken with brine, separated, and dried (Na_2SO_4). Drying in vacuo gave **31**; yield: 4.33 g (95%).

IR (ATR): 3383, 2955, 1731, 1164, 1140, 696 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 6.5 Hz, 6 H, Me), 1.40 (ddd, J = 13.5, 8.6, 6.2 Hz, 1 H, *H*CCMe$_2$), 1.54 (ddd, J = 13.5, 8.0, 5.2 Hz, 1 H, *H*CCMe$_2$), 1.73 (m, 1 H, *H*CMe$_2$), 1.81 (s, 2 H, NH_2), 3.48 (dd, J = 8.6, 5.7 Hz, 1 H, HCN), 5.10 (s, 2 H, OCH_2), 7.27–7.33 (m, 5 H, ar-H).

(5*R*)-4-(Benzyloxy)-5-isobutyl-1,5-dihydro-2*H*-pyrrol-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 16 h. The solvent was removed and the remainder was purified by column chromatography (silica gel). Eluting first with 5% acetone–CH_2Cl_2 gave the byproduct Ph_3PO, then eluting with 25% acetone–CH_2Cl_2 gave **32** as a white solid; yield: 2.57 g (70%); mp 86–88 °C; $[\alpha]_D^{25}$ +8.5 (*c* 3, $CHCl_3$).

IR (ATR): 1678, 1620, 1354, 1219 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.79 (d, J = 6.6 Hz, 3 H, Me), 0.80 (d, J = 6.6 Hz, 3 H, Me), 1.35 (ddd, J = 13.5, 9.8, 4.9 Hz, 1 H, *H*CCMe$_2$), 1.59 (ddd, J = 13.5, 9.3, 3.7 Hz, 1 H, *H*CCMe$_2$), 1.75 (m, 1 H, *H*CMe$_2$), 4.14 (m, 1 H, H5), 4.89 (s, 2 H, OCH_2), 4.92 (s, 1 H, H3), 7.18–7.23 (m, 5 H, ar-H), 7.77 (s, 1 H, NH).

^{13}C JMOD NMR (75.5 MHz, $CDCl_3$): δ = 21.6 (Me), 23.5 (Me), 25.1 (*C*Me$_2$), 41.4 (*C*CMe$_2$), 56.3 (C5), 72.9 (OCH_2), 94.2 (C3), 127.6, 128.5, 128.6, 134.9 (ar-C), 174.8 (C2), 177.6 (C4).

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

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.8; N, 5.7. Found: C, 73.3; H, 7.7; N, 5.8.

(5*R*)-5-Isobutylpyrrolidine-2,4-dione (33)

Dihydro-2*H*-pyrrol-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 H_2 and left to stir at r.t. for 1 h, pressurized with 1 atm of H_2. 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.[67] 114–116 °C for *rac*-**33**]; $[\alpha]_D^{25}$ 52 (*c* 1, CH_2Cl_2) [Lit.[68] –55 (*c* 0.87, CH_2Cl_2) for *ent*-**33**].

IR (KBr): 3176, 1769, 1682, 1288, 797 cm^{-1}.

^{1}H NMR ($CDCl_3$): 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, 5.5 Hz, 1 H, *H*CCMe$_2$), 1.60 (ddd, J = 13.7, 8.9, 4.4 Hz, 1 H, *H*CCMe$_2$), 1.70–1.77 (m, 1 H, *H*CMe$_2$), 2.98 (s, 2 H, H3), 3.98 (dd, J = 9.4, 4.4 Hz, 1 H, H5).

^{13}C JMOD NMR (75.5 MHz, $CDCl_3$): δ = 21.3 (Me), 23.1 (Me), 24.8 (*C*Me$_2$), 40.5 (C3), 41.2 (*C*CMe$_2$), 62.8 (C5), 171.7 (C2), 208.0 (C4).

3-[1-(Difluoroboryloxy)ethylidene]-5-isobutylpyrrolidine-2,4-dione (34)

To a stirred soln of **33** (0.30 g, 1.9 mmol) in ethereal BF_3·OEt_2 (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 NH_4Cl (20 mL) and immediately extracted with EtOAc (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated to yield an oil, which was purified by column chromatography (silica gel) R_f = 0.72 (hexane–EtOAc, 1:1) to give yellow crystals; yield: 290 mg (61%); mp 116 °C.

IR (KBr): 1704, 1648, 1026, 878, 686 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.97 (d, *J* = 6.4 Hz, 3 H, Me), 0.98 (d, *J* = 6.4 Hz, 3 H, Me), 1.53–1.56 (m, 1 H, *H*CCMe$_2$), 1.76–1.81 (m, 2 H, *H*CCMe$_2$ and *H*CMe$_2$), 2.53 (s, 3 H, H$_3$C-C=), 4.07 (m, 1 H, H5), 7.14 (s, 1 H, NH).

^{13}C JMOD NMR (75.5 MHz, $CDCl_3$): δ = 21.2 (Me), 21.5 (Me), 23.1 (Me), 25.3 (*C*Me$_2$), 39.9 (*C*CMe$_2$), 63.3 (C5), 99.2 (C3), 173.4 (C2), 187.4 (O-C=), 191.4 (C4).

Anal. Calcd for $C_{10}H_{14}BF_2NO_3$: C, 49.0; H, 5.8; N, 5.7. Found: C, 49.2; H, 5.7; N, 5.8.

(5*R*)-Reutericyclin {(5*R*)-3-Acetyl-1-[(*E*)-dec-2-enoyl]-4-hydroxy-5-isobutyl-1,5-dihydro-2*H*-pyrrol-2-one} (2)

Compound **34** (123 mg, 0.50 mmol) was placed in a Schlenk tube and dissolved in anhyd THF (25 mL). The soln was blanketed with argon, cooled to –78 °C and slowly treated with a 1 M NaHMDS in THF (0.55 mL, 0.55 mmol) while the temperature was kept below –65 °C. After stirring for 5 min, (*E*)-dec-2-enoyl chloride (105 mg, 0.55 mmol) was added slowly maintaining the low temperature and monitoring the reaction progress by TLC. The reaction was stopped after 1 h by addition of 1 M aq $KHSO_4$ (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 organic layers were dried (Na_2SO_4). After removal of the solvent, the crude product was purified by column chromatography (silica gel, hexane–EtOAc, 60:40, R_f = 0.43) to give a yellowish, sticky solid; yield: 129 mg (74%); melting range 150–157 °C [Lit.[7d] 161–164 °C]; $[\alpha]_D^{25}$ 18 (*c* 3, EtOH) [Lit.[7d] $[\alpha]_D^{13}$ (*c* 0.29, EtOH)]; >95% ee (chiral HPLC on permethylated β-cyclodextrin; MeCN–0.3% TEAA in H_2O, 40:60) when compared with an authentic racemic sample.

IR (KBr): 2956, 2926, 2856, 1715, 1635, 1518, 1466, 1349, 1325, 1225, 1155, 1128, 1041, 980, 893, 716 cm^{-1}.

^{1}H NMR (CD_3CN), 3:2 mixture of tautomers *a*/*b*: δ = 0.86–0.93 (m, 9 H^{a+b}, Me$_2$C, *Me*CH$_2$), 1.23–1.35 (m, 8 H^{a+b}, CH$_2$), 1.40–1.51 (m, 2 H^{a+b}, C*H*$_2$CMe$_2$), 1.74–1.83 (m, 1 H^{a+b}, C*H*Me$_2$), 2.24 (q, *J* = 7.1 Hz, 2 H^{a+b}, H$_2$CC=C), 2.45 (s, 3 H^{a+b}, MeCO), 4.21 (dd, *J* = 6.2, 4.4 Hz, 1 H, 5-H^b), 4.30 (t, *J* = 5.6 Hz, 1 H, 5-H^a), 6.93–7.00 (m, 1 H^{a+b}, HC=CCO), 7.33 (d, *J* = 15.4 Hz, 1 H, C=CH^{b}CO), 7.36 (d, *J* = 15.4 Hz, 1 H, C=CH^{a}CO), 9.67 (br s, 1 H$^{a/b}$, OH), 10.23 (br s, 1 H$^{b/a}$, OH).

^{13}C JMOD NMR (75.5 MHz, CD_3CN), mixture of tautomers *a*/*b*: δ = 13.4 (Me), 20.1/20.9 (Me), 21.9/22.0 (Me), 23.0 (Me), 24.1/24.2 (CH$_2$), 28.0 (CH$_2$), 28.8 (CH$_2$), 28.9 (CH$_2$), 31.5 (CH$_2$), 32.2 (CH$_2$), 39.1/39.2 (CH$_2$), 60.5/61.6 (CH), 95.4/96.4 (C^q), 124.0/124.2 (CH), 147.9/148.3 (CH), 164.7/165.0 (C^q), 169.3/172.1 (C^q), 171.4/171.9 (C^q), 194.1/197.0 (C^q).

MS (EI): *m*/*z* (%) = 350 [M$^+$ + 1] (2), 349 [M$^+$] (9), 348 [M$^+$ – H] (32), 333 (3), 319 (4), 305 (10), 293 (18), 292 (96), 277 (12), 263 (9), 249 (18), 221 (10), 207 (15), 193 (9), 182 (20), 153 (27), 141 (7), 140 (100), 139 (12), 112 (11), 84 (11), 69 (18).

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