DOI: 10.1002/chem.200902544

A Selective 3-Acylation of Tetramic Acids and the First Synthesis of Ravenic Acid

Andrea Schlenk,[a] Randi Diestel,[b] Florenz Sasse,[b] and Rainer Schobert*[a]

Abstract: 3-Acyltetramic acids, including delicate 3-oligoenoyl derivatives, such as the *Penicillium* metabolite ravenic acid, were prepared in two high-yielding steps. Reaction of tetramic acids with the ylide Ph_3PCCO afforded exclusively the corresponding 3-acylylidenetetramic acids. These were amenable to Wittig olefinations with aliphatic, aromatic, saturated and unsaturated aldehydes after deprotonation with KO*t*Bu. Due to its simplicity, selectivity and tolerance of pH-sensitive groups this method is superior to the established acylation protocols by Jones and Yoshii. It is also applicable to the synthesis of 3-acyltetronic acids. The new 3-oligoenoyl tetramic acids exhibited structure-dependent antimicrobial and cytotoxic activity.

Keywords: acylation · antibiotics · ravenic acid · tetramic acids · ylides

Introduction

Tetramic acids (i.e., pyrrolidine-2,4-diones) and tetronic acids (i.e., dihydrofuran-2,4-diones) are widespread in nature.[1–3] They are produced by a variety of marine and terrestrial organisms including bacteria, algae, sponges, fungi and lichens. The 3-acyl-substituted derivatives are particularly often associated with biological activity. Various strategies exist for their synthesis. Among these, the base-induced Lacey–Dieckmann cyclisation[4] of *N*-(β-ketoacyl)-α-amino esters is the most widely adopted one,[5] since it directly affords the 3-acyltetramic acids. A potential drawback of this protocol is the frequently observed racemisation at C-5 of the pyrrolidine-2,4-dione core.[6] An alternative two-step approach first generates the tetramate by condensation of α-amino acids or esters with a dipolar C_2-building block, such as Meldrum's acid[7] or the stable ylide Ph_3PCCO (**1**).[8] The tetramic acids thus obtained are subsequently acylated at C-3 either with acyl chlorides and BF_3-diethyl etherate as demonstrated by Jones et al.[9] or with carboxylic acids and *N*,*N*-dicyclohexylcarbodiimide/4-dimethylaminopyridine as demonstrated by Yoshii et al.[10] Both acylation methods are tricky. The former is not compatible with acid-sensitive functionalities and skipped carbon–carbon double bonds, whereas the latter tends to fail erratically or to yield 4-*O*-acylated products instead. Herein, we report a new selective 3-acylation of tetramic and tetronic acids with ylide **1** and a downstream Wittig alkenation with the so-formed acyl ylides.

[a] A. Schlenk, Prof. Dr. R. Schobert
Organic Chemistry Laboratory, University of Bayreuth
Universitaetsstrasse 30/NW 1
95440 Bayreuth (Germany)
Fax: (+49) 921552671
E-mail: Rainer.Schobert@uni-bayreuth.de

[b] R. Diestel, Dr. F. Sasse
Helmholtz Centre for Infection Research (HZI)
Department of Chemical Biology, Inhoffenstrasse 7
38124 Braunschweig (Germany)

Results and Discussion

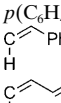
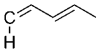
We had long since observed that tetronic acids, 4-hydroxycoumarins and pyrazol-5-ones, reacted with Ph_3PCCO (**1**) under mild, pH-neutral conditions to leave exclusively the corresponding 3-phosphoranylideneacyltetronic acids, 3-phosphoranylideneacyl-4-oxocoumarins or 4-phosphoranylideneacylpyrazol-5-ones, respectively.[11] Unfortunately, these products failed to undergo Wittig olefination with aldehydes, a reaction that would provide access to, for example, the 3-oligoenoyltetronic acid motif occurring in dozens of natural products. X-ray and NMR spectroscopic studies had revealed π-delocalisation, as well as H-chelate or even phosphonium salt character of the tricarbonyl ylide moiety in these compounds as a reason for their inactivity. Desultory attempts to "switch" them active by removal of the chelated proton with various bases were all unsuccessful. For a more systematic study, we now prepared the congenerous 3-acylylidic tetramic acids, for example, **3**, in virtually quantitative yield by treating the well-soluble *N*-*tert*-butoxycarbonyl

(Boc)-protected tetramic acids **2** with Ph_3PCCO. Next, we identified potassium *tert*-butoxide in THF as a base appropriate for the deprotonation/activation of ylides **3**. The resulting potassium salts were not normally isolated but reacted right away with the respective aldehyde as solutions in THF at reflux. This afforded the corresponding *N*-Boc-3-(α-hydroxydienyl)pyrrolidine-2,4-diones, which were not purified but treated with trifluoroacetic acid (TFA) to liberate the target compounds **4** in yields ranging from 60 to 80% (Table 1). The same conversion was possible with *N*-alkyl- and N,H-substituted tetramic acids, for example, **5**, and with tetronic acids, such as **7** (Scheme 1). All steps proceeded with retention of the configuration at C-5 of the starting tetramic or tetronic acids as determined by HPLC comparison with authentic racemic product samples. It is also worth noting that the *E*-configured C=C bond introduced in the course of the Wittig alkenation can be removed by catalytic hydrogenation without affecting the formal C=C bond at C-3.

The merits of this new acylation protocol are its regioselectivity and mildness of conditions that allow for the presence of acid-sensitive functionalities, such as conjugated C=C bonds. We demonstrate this by the first synthesis of ravenic acid (**4f**) that was originally obtained from a microfungus *Penicillium* sp. (MINAP9902) isolated from the interior of fruiting bodies of the myxomycete *Lycogala epidendrum* collected in south-east Queensland. Larger amounts of **4f** were later extracted from culture broths of this fungus. It was found to be active against methicillin-resistant *Staphylococcus aureus*.[12]

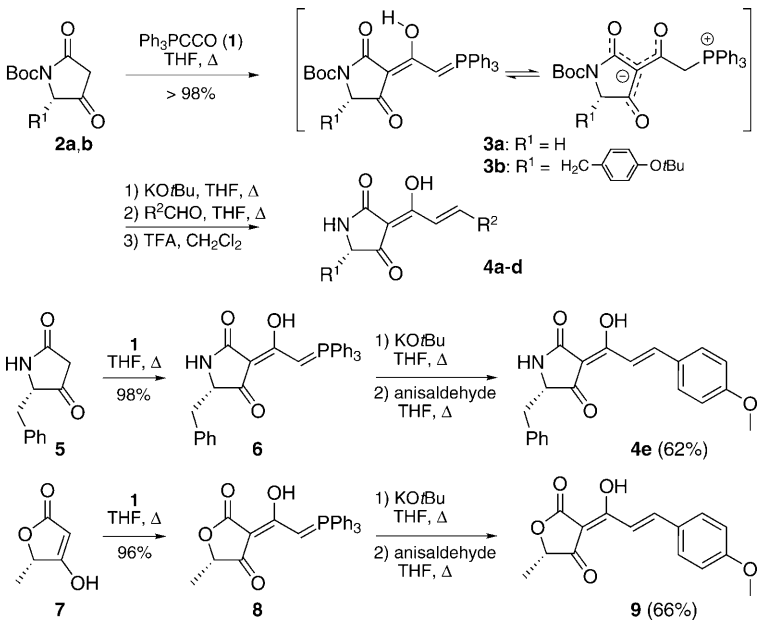
Ylide **3a**, accessible by acylation of *N*-Boc-pyrrolidine-2,4-dione (**2a**; $R^1=H$)[7b] with Ph_3PCCO in 98% yield, was first deprotonated with KO*t*Bu in THF and then treated with 2-methylocta-2*E*,4*E*,6*E*-trienal (**12**) to leave **4f** after deprotection with TFA (Scheme 2). HPLC purification eventually afforded an orange crystalline solid in 62% yield with respect to **2a**. Aldehyde **12** was readily prepared. An *E*-selective Horner–Emmons alkenation of sorbinaldehyde with the dianion of 2-diethoxyphosphorylpropionic acid (**10**)[13] gave 2-methylocta-2*E*,4*E*,6*E*-trienoic acid (**11**) in 72% yield. Acid **11** was treated with $SOCl_2$ in dichloromethane and the resulting crude acid chloride was immediately reduced with an excess of $LiAlH(OtBu)_3$ at −70 °C to afford aldehyde **12** in 50% yield after purification.

Table 1. 3-Alkenoyltetramic acids **4** by acylation with Ph_3PCCO (**1**)/aldehydes.

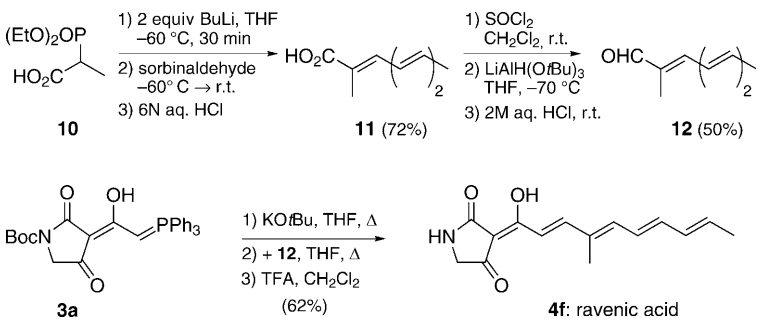
Compounds **4**	R^1	R^2	Yield [%]	Made via ylide
4a	H	$(CH_2)_8Me$	76	**3a**
4b	H	$p(C_6H_4)OMe$	84	**3a**
4c	H		78	**3a**
4d[a]	(5*S*)-*p*(OH)Bn		66	**3b**
4e	(5*S*)-CH_2Ph	$p(C_6H_4)OMe$	62	**6**

[a] Precursors **2b** and **3b**: $R^1=(5S)$-CH_2-$p(C_6H_4)O$*t*Bu.

Table 2 summarizes the results of agar diffusion assays with compounds **4**. In line with the original report,[12] we found antimicrobial activity for ravenic acid **4f** against



Scheme 1. Selective 3-acylation of tetronic and tetramic acids.



Scheme 2. Synthesis of ravenic acid (**4f**).

Table 2. Antibiotic activity[a] of tetramic acids **4** against selected Gram-positive bacteria.[b]

	4a	4c	4e	4f
Staphylococcus aureus	11	0	0	11
Micrococcus luteus	8	0	0	0
Mycobacterium phlei	11	8	9	9

[a] Agar plates inoculated with the respective microrganisms were incubated with 6 mm cellulose discs containing 20 μL of a methanolic solution (1 mg mL^{-1}) of the compounds tested. The diameters (in mm) of the resulting growth-inhibition zones were determined after 24 h of incubation at 30 °C and are cited here. [b] None of the compounds inhibited the growth of the Gram-negative bacteria *E. coli tolC* and *Klebsiella pneumoniae*. Compounds **4b**, **4d** and **9** were inactive in all tested bacteria.

Staphylococcus aureus. It was also active against *Mycobacterium phlei*. Analogue **4a** was equally active against *S. aureus* and even more active than **4f** against *Mycobacterium phlei* and *Micrococcus luteus*. A high degree of unsaturation of the side chain at C-3 seems not to be a prerequisite for antibiotic activity of 3-acyltetramic acids in these bacteria.

Some derivatives of **4** were also noticeably cytotoxic. For instance, in MTT tests compounds **4a** and **4e** exhibited an IC_{50}(48 h) value of <15 μM against HL-60 human leukemia cells. With an IC_{50}(48 h) value of 22 μM against multidrug-resistant KB-V1 human cervix carcinoma cells, compound **4e** even surpassed the efficacy of the clinical anticancer drug doxorubicin. This efficiency is not merely due to the detergent-like nature of compounds such as **4a** and **4e**. For instance, tetramic acid **4a**, while active also against primary human umbilical vein endothelial cells (HUVEC; from Lonza) with an IC_{50} of 9.3 μM, had a distinct impact on cellular membranes only at much higher concentrations. In hemolysis assays with red blood cells from sheep (from Fiebig Nährstofftechnik, Idstein-Niederauroff, Germany) we found an ED_{50} of 250 μM. In contrast, ravenic acid (**4f**) had little effect both on HUVEC and on erythrocyte membranes with IC_{50} and ED_{50} values of >100 μM. A detailed study including more 3-acyltetramic acids and tumour cell lines will be disclosed elsewhere.

Conclusion

We have developed a protocol for the synthesis of 3-acyltetramic acids based upon the regioselective C-3-acylation of tetramic acids with the phosphorus ylide Ph_3PCCO. The resulting 3-triphenylphosphoranylideneacyltetramic acids could be deprotonated with potassium *tert*-butoxide affording salts of yet unknown structure that underwent Wittig alkenations with various types of aldehydes. The conditions are mild enough to avoid racemisation of sensitive stereocentres and to allow the introduction of highly unsaturated side chains at C-3, which are prone to rearrangements and polymerisations under the acidic conditions of the Jones acylation protocol. If undesired, the newly formed C=C bond can be removed selectively by catalytic hydrogenation. The same protocol is applicable to the acylation of tetronic acids. We are currently applying it to the synthesis of more complex natural compounds and we also want to gain structural information on the potassium ylide salt intermediates to better understand the origin of their reactivity.

Experimental Section

General methods: Melting points were recorded on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrophotometer equipped with an ATR sampling unit. NMR spectra were recorded under conditions indicated on a Bruker Avance 300 spectrometer. Chemical shifts (δ) are given in parts per million downfield from TMS as an internal standard. Mass spectra were recorded by using a Varian MAT 311A (EI). Microanalyses were carried out with a Perkin–Elmer 2400 CHN elemental analyser. For column chromatography, Merck silica gel 60 (230–400 mesh) was used. TLC: silica gel 60 F254 (Merck). Optical rotations were recorded at 589 nm with a Perkin–Elmer polarimeter 241. A Knauer system with UV detector K-2000 and pump K-1800 was used for preparative HPLC. Analytical HPLC was performed on a Beckman system with solvent module 126 and a diode array detector 168 equipped with a Nucleodex CD-ß-PM column (Macherey–Nagel). Prontosil Solvents (HPLC grade) were purchased from Merck. THF was dried over a Na/K-alloy and CH_2Cl_2 was dried over P_2O_5. Starting compounds were prepared according to literature procedures or purchased from Fluka, Aldrich or Acros Organic and were used without further purification. The weak acid anion exchanger Dowex MPWA was bought from Aldrich.

Synthesis of 3-triphenylphosphoranylideneacetyltetramic acids 3 or 6—general procedure: Under an inert atmosphere, a solution of Ph_3PCCO (302 mg, 1.0 mmol) in dry THF (20 mL) was added dropwise over a period of 20 min to a refluxing solution of the respective pyrrolidine-2,4-dione **2** or **5** (1.0 mmol) in dry THF (60 mL). Heating was continued for another 16 h, then half of the solvent was evaporated, pentane was added to the remainder and the product was allowed to precipitate. It was collected by filtration, washed and dried or recrystallised.

1-*tert*-Butoxycarbonyl-3-[(triphenylphosphoranylidene)acetyl]pyrrolidine-2,4-dione (3a): White solid (495 mg, 98 %) from 1-*tert*-butoxycarbonylpyrrolidine-2,4-dione (**2a**)[7b] (199 mg); m.p. 194 °C; IR (ATR): $\tilde{\nu}$= 1751, 1620, 1557, 1436, 1328, 1153, 1103, 844, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2:1 mixture of ylide (a) and betaine (b): δ=1.45 (s, 9H; Me_3^b), 1.48 (s, 9H; Me_3^a), 3.77 (s, 2H; 5-H^b), 3.94 (s, 2H; 5-H^a), 5.12 (d, J= 12.5 Hz, 1H; CH_2P), 5.27 (d, J=20.5 Hz, 1H; P=CH), 7.47–7.74 (m, 15H; PPh_3), 12.38 ppm (brs., 1H; OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): ylide (two rotamers): δ=27.6 (Me_3), 51.2/54.0 (C-5), 55.7 (d, J_{PC}= 106.9 Hz; P=CH), 56.3 (d, J_{PC}=106.8 Hz; P=CH), 81.3/81.5 (*C*Me_3), 93.2/95.8 (C-3), 124.1 (d, J_{PC}=93.7 Hz; C^{ipso}), 150.7 (CO_2), 168.2 (C-2), 187.6 (C-1′), 191.9 ppm (C-4); betaine: δ=27.5 (Me_3), 35.1 (d; J_{PC}=52.8 Hz; P-CH_2), 52.4 (C-5), 81.1 (*C*Me_3), 103.4 (C-3), 119.8 (d, J_{PC}=88.5 Hz; C^{ipso}), 150.3 (CO_2), 172.2 (C-2), 178.7 (C-1′), 189.9 ppm (C-4); further unassignable phenyl signals of both isomers: 128.4, 128.5, 128.6, 129.3, 129.4, 129.7, 129.8, 129.9, 131.8, 131.9, 132.1, 133.0, 133.1, 133.2, 133.3, 133.8, 133.9, 134.4, 134.5 ppm; ^{31}P NMR (161.7 MHz, H_3PO_4/$_{ext}$, $CDCl_3$): δ= 15.6 (ylide), 22.8 ppm (betaine); MS (EI): *m*/*z* (%): 501 (8) $[M]^+$, 401 (10), 301 (100), 262 (20) $[PPh_3]^+$, 183 (35), 151 (15), 77 (30), 57 (29); elemental analysis calcd (%) for $C_{29}H_{28}NO_5P$: C 69.45, H 5.63, N 2.79; found: C 69.51, H 5.66, N 2.83.

(5*S*)-5-(4-*tert*-Butoxybenzyl)-1-(*tert*-butoxycarbonyl)-3-[(triphenylphosphoranylidene)acetyl]pyrrolidine-2,4-dione (3b): White solid (663 mg, 99 %) from (5*S*)-5-(4-*tert*-butoxybenzyl)-1-(*tert*-butoxycarbonyl)pyrrolidine-2,4-dione (**2b**)[14] (361 mg); m.p. >210 °C (decomp); $[\alpha]_D^{25}=-28$ (c= 1.0 in $CHCl_3$); IR (ATR): $\tilde{\nu}$=2976, 1750, 1692, 1624, 1505, 1333, 1154, 896, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1:0.3 mixture of ylide and betaine: δ= 1.26 (s, 9H; Me_3), 1.53 (s, 9H; Me_3), 2.54 (dd, J=3.2, 10.4 Hz, 1H; CH_2Ar), 3.24 (dd, J=3.2, 10.4 Hz, 1H; CH_2Ar), 3.94 (dd, J=3.2, 10.4 Hz, 1H; 5-H), 5.24 (d, J=19.4 Hz, 1H; P=CH), 6.76 (d, J=8.9 Hz, 2H; H^{ar}), 6.99 (d, J=8.9 Hz, 2H; H^{ar}), 7.48–7.72 (m, 15H; PPh_3), 12.20 ppm (brs,

1H; OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): ylide: δ=28.3 (Me_3), 28.7 (Me_3), 36.4 (CH_2Ar), 56.7 (d, J=108.6 Hz; P=CH), 63.0 (C-5), 78.2 (O*C*tBu), 81.6 (*C*Me_3), 98.2, 98.8 (each a d, J=12.1 Hz; C-3), 124.0 (d J=92.5 Hz; C^{ipso}), 149.7 (CO_2), 153.8 (O–C^{ipso}), 173.2 (C-2), 189.9 (C-1′), 193.2 ppm (C-4); betaine: δ=28.2 (Me_3), 28.5 (Me_3), 34.4 (d, J=50.6 Hz; P-CH_2), 36.0 (CH_2Ar), 61.5 (C-5), 77.8 (O*C*Me_3), 80.3 (*C*Me_3), 103.2 (C-3), 119.5 (d, J=88.4 Hz; C^{ipso}), 149.1 (CO_2), 153.5 (O–C^{ipso}), 168.6 (C-2), 179.2 (C-1′), 192.2 ppm (C-4); further unassignable phenyl signals of both isomers: 123.2, 123.4, 123.5, 123.6, 124.7, 128.4, 128.6, 128.7, 129.1, 129.2, 129.3, 129.4, 129.8, 129.9, 130.1, 130.2, 130.3, 130.4, 130.5, 130.6, 130.8, 131.9, 132.0, 132.1, 133.0, 133.1, 133.2, 133.3, 133.7, 133.8, 134.3, 134.4, 134.9 ppm; ^{31}P NMR (161.7 MHz, H_3PO_4/$_{ext}$, $CDCl_3$): δ=15.5/15.6 (ylide), 22.6 ppm (betaine); MS (EI): *m*/*z* (%): 663 (10) [*M*]$^+$, 563 (3), 400 (10), 205 (18), 183 (15), 107 (100); elemental analysis calcd (%) for $C_{40}H_{42}NO_6P$: C 72.38, H 6.38, N 2.11; found: C 72.37, H 6.44, N 2.14.

(5*S*)-5-Benzyl-3-[(triphenylphosphoranylidene)acetyl]pyrrolidine-2,4-dione (6): White solid (485 mg, 98%) from (5*S*)-5-benzylpyrrolidine-2,4-dione (**5**)[15] (189 mg); m.p. >200°C (decomp); $[\alpha]_D^{25}=-119$ (c=0.5 in $CHCl_3$); IR (ATR): $\tilde{\nu}$=1661, 1622, 1542, 1410, 1333, 1184, 1104, 742, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1:1 mixture of ylide (a) and betaine (b): δ=2.23–2.40 (m, 1H; CH_2Ar^b), 2.44–2.60 (m, 1H; CH_2Ar^a), 3.07–3.36 (m, 2H; CH_2Ar^{a+b}), 3.56–3.67 (m, 1H; 5-H^b), 3.76–3.79 (m, 1H; 5-H^a), 4.91–5.16 (m, 2H; CH_2P), 5.34 (d, J=20.3 Hz, 1H; P=CH), 7.02–7.26 (m, 5H; H^{ar}), 7.35–7.73 (m, 30H; PPh_3), 12.56 ppm (brs, 1H; OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): ylide: δ=38.9 (CH_2Ar), 53.6 (d, J_{PC}=108.6 Hz; P=CH), 62.4 (C-5), 90.4/94.0 (each a d, J_{PC}=12.1 Hz; C-3), 124.5 (d, J=92.1 Hz; P–C^{ipso}), 138.7 (C–*C*^{ipso}), 173.8 (C-2), 178.3 (C-1′), 195.0 ppm (C-4); betaine: δ=34.4 (d, J_{PC}=52.2 Hz; P–CH_2), 38.4 (CH_2Ar), 60.2 (C-5), 101.6 (C-3), 119.8 (d, J_{PC}=87.4 Hz; P–C^{ipso}), 138.5 (C–*C*^{ipso}), 173.1 (C-2), 177.8 (C-1′), 191.7 ppm (C-4); further unassignable phenyl signals of both isomers: 126.4, 127.0, 128.4, 128.5, 128.6, 129.1, 129.2, 129.4, 129.7, 129.9, 130.2, 130.3, 130.4, 130.5, 131.6, 131.7, 131.8, 131.9, 132.0, 132.1, 133.1, 133.2, 133.4, 133.9, 134.0, 134.4 ppm; ^{31}P NMR (161.7 MHz, H_3PO_4/$_{ext}$, $CDCl_3$): δ=15.5/15.8 (ylide), 22.9 ppm (betaine); MS (EI): *m*/*z* (%): 491 (5) [*M*]$^+$, 400 (10), 301 (25), 262 (15), 201 (35), 183 (35), 151 (20), 91 (100); elemental analysis calcd (%) for $C_{31}H_{26}NO_3P$: C 75.75, H 5.33, N 2.85; found: C 75.77, H 5.33, N 2.92.

Synthesis of (5*S*)-5-methyl-3-[(triphenylphosphoranylidene)acetyl]dihydrofuran-2,4-dione (8): Analogously to compounds **3**, lactone **8** was obtained as a white solid (400 mg, 96%) from (5*S*)-5-methyltetronic acid (**7**)[16] (114 mg, 1.0 mmol); m.p. >200°C (decomp); $[\alpha]_D^{25}=-8.9$ (c=1.0 in $CHCl_3$); IR (ATR): $\tilde{\nu}$=1732, 1657, 1622, 1433, 1108, 996, 745, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1:3 mixture of ylide (a) and betaine (b): δ=1.17 (d, J=6.7 Hz, 3H; Me^b), 1.33 (d, J=7.3 Hz, 3H; Me^a), 4.15 (q, J=6.7 Hz, 1H; 5-H^b), 4.41 (q, J=7.3 Hz, 1H; 5-H^a), 4.90 (d, J=14.2 Hz, 2H; PCH_2), 4.92–5.00 (m, 1H; P=CH), 7.38–7.68 (m, 15H; H^{ar}), 11.17 ppm (brs, 1H; OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): ylides: δ=17.6 (Me), 56.4 (d, J_{PC}=109.2 Hz; P=CH), 75.4 (C-5), 99.6 (C-3), 123.6 (d, J_{PC}=92.5 Hz; C^{ipso}), 175.3 (C-2), 185.3 (C-1′), 197.5 ppm (C-4); betaines: δ=17.2 (Me), 34.9 (d, J_{PC}=52.9 Hz; PCH_2), 76.1 (C-5), 96.0 (C-3), 119.2 (d, J_{PC}=87.9 Hz; C^{ipso}), 172.3 (C-2), 179.1 (C-1′), 192.1 ppm (C-4); further unassignable phenyl signals of both isomers: 128.4, 128.6, 129.3, 129.5, 129.8, 129.9, 130.4, 130.5, 130.6, 133.1, 133.3, 133.4, 133.8, 133.9, 134.6, 134.7 ppm; ^{31}P NMR (161.7 MHz, H_3PO_4/$_{ext}$, $CDCl_3$): δ=15.4 (ylide), 22.7 ppm (betaine); MS (EI): *m*/*z* (%): 416 (45) [*M*]$^+$, 316 (10), 301 (100), 262 (30), 201 (20), 183 (55), 77 (21); elemental analysis calcd (%) for $C_{25}H_{21}O_4P$: C 72.11, H 5.08; found: C 72.08, H 5.00.

Wittig reaction affording 3-acyltetramic acids 4—general procedure: Under an inert atmosphere a solution of the respective ylide **3** or **6** (1.0 mmol) in dry THF (40 mL) was treated with potassium *tert*-butoxide (112 mg, 1.0 mmol) and the resulting mixture was heated at reflux for 20 min. A solution of the respective aldehyde (1.0 mmol) in dry THF (10 mL) was added dropwise and the mixture thus obtained was heated at reflux for another 6 h. The solution was chilled to room temperature and filtered through a column (2×5 cm) charged with Dowex MPWA anion exchanger resin to remove most of the byproduct phosphine oxide. The resin was rinsed several times with 50 mL each of ethyl acetate, methanol, THF and CH_2Cl_2. Finally, the product was recovered from the column by eluting it first with a mixture of 1 M aq. $KHSO_4$/methanol (1:1; 100 mL), then with neat methanol. The combined eluates were concentrated and the remaining aqueous phase was extracted several times with chloroform. The extracts were dried with $NaSO_4$, filtered and concentrated in vacuum to yield the crude 3-acyltetramic acids. The protecting groups of products **4a–d** were removed by treating their solutions in CH_2Cl_2 (1.0 mmol in 20 mL) with trifluoroacetic acid (TFA; 3 mL) and stirring them at room temperature for 30 min. Hexane (50 mL) was added and all volatiles were evaporated under reduced pressure. This operation was repeated twice. The resulting 3-acyltetramic acids **4** were purified by preparative HPLC (Prontosil column RP-18 250×20 mm, 5 μm; gradient: ascending from 30:70 MeCN/H_2O to 80:20 MeCN/H_2O over 35 min; flow rate: 20 mL min^{-1}).

3-[(*E*)-1-Hydroxydodec-2-enylidene]pyrrolidine-2,4-dione (4a): White solid (210 mg, 76%) from ylide **3a** (501 mg) and decanal (188 μL); m.p. 98–100°C (methanol/pentane 1:2); IR (ATR): $\tilde{\nu}$=3196, 2918, 2848, 1709, 1664, 1651, 1591, 1459, 1253, 980, 701 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$): δ=0.85 (t, J=6.6 Hz, 3H; Me), 1.18–1.40 (m, 12H; CH_2), 1.45–1.64 (m, 2H; CH_2), 2.30 (dt, J=13.3, 6.6 Hz, 2H; CH_2C=C), 3.77 (s, 2H; 5-H), 7.05 (d, J=15.4 Hz, 1H; 2′-H), 7.21–7.30 ppm (m, 1H; 3′-H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$): δ=13.9 (Me), 22.1 (*C*Me), 27.6, 29.0, 29.1, 29.2, 29.3, 29.4 (CH_2), 31.6 (*C*H_2C=C), 51.3 (C-5), 100.1 (C-3), 120.9 (C-2′), 149.7 (C-3′), 172.6 (C-2), 176.2 (C-1), 193.9 ppm (C-4); MS (EI): *m*/*z* (%): 279 (30) [*M*]$^+$, 180 (12), 152 (100); HRMS (EI): *m*/*z*: calcd for $C_{16}H_{24}NO_3^-$: 278.1756; found: 278.1751; calcd for $C_{16}H_{26}NO_3^+$: 280.1905; found: 280.1900; elemental analysis calcd (%) for $C_{16}H_{25}NO_3$: C 68.79, H 9.02, N 5.01; found: C 68.82, H 8.89, N 5.07.

3-[(*E*)-1-Hydroxy-3-(4-methoxyphenyl)allylidene]pyrrolidine-2,4-dione (4b): Yellow solid (220 mg, 84%) from ylide **3a** (501 mg) and anisaldehyde (136 μL); m.p. 119–121°C (methanol/pentane 1:2); IR (ATR): $\tilde{\nu}$=2976, 1660, 1635, 1600, 1581, 1511, 1335, 1263, 1161, 1036, 836, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=3.84 (brs, 5H; OMe, 5-H), 6.13 (brs, 1H; NH), 6.92 (d, J=9.1 Hz, 2H; H^{ar}), 7.62 (d, J=9.1 Hz, 2H; H^{ar}), 7.66 (d, J=15.5 Hz, 1H; =CH), 7.85 ppm (d, J=15.5 Hz, 1H; =CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=49.6 (Me), 51.6 (C-5), 92.0 (C-3), 113.7 (C^{ar}), 118.7 (C-2′), 128.6 (C^{ar}), 133.7 (C^{ipso}), 145.1 (C-3′), 162.4 (C^{ipso}), 174.9 (C-2), 176.7 (C-1′), 192.6 ppm (C-4); MS (EI): *m*/*z* (%): 259 (100) [*M*]$^+$, 216 (52), 201 (49), 161 (53), 133 (40), 103 (20), 89 (60); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{12}NO_4^-$: 258.0772; found: 258.0766; calcd for $C_{14}H_{14}NO_4^+$: 260.0917; found: 260.0923; elemental analysis calcd (%) for $C_{14}H_{13}NO_4$: C 64.86, H 5.05, N 5.40; found: C 64.86, H 5.09, N 5.44.

3-[(2*E*,4*E*)-1-Hydroxy-5-phenylpenta-2,4-dienylidene]pyrrolidine-2,4-dione (4c): Orange solid (200 mg, 78%) from ylide **3a** (501 mg) and cinnamic aldehyde (82 μL); m.p. 118–119°C (methanol/pentane 1:2); IR (ATR): $\tilde{\nu}$=3204, 1664, 1621, 1609, 1558, 1456, 1244, 990, 749 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$): δ=3.79 (s, 2H; 5-H), 7.22–7.25 (m, 2H; 2′-H, 3′-H), 7.29–7.46 (m, 5H; H^{ar}), 7.59–7.62 (m, 2H; 4′-H, 5′-H), 8.77 ppm (brs; NH); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$): δ=51.4 (C-5), 100.5 (C-3), 121.0 (C-2′), 127.4 (C-4′), 127.7, 128.2, 128.9, 129.5, 135.9 (C^{ipso}), 142.8 (C-3′), 143.9 (C-5′), 172.4 (C-2), 175.6 (C-1′), 193.3 ppm (C-4); MS (EI): *m*/*z* (%): 255 (100) [*M*]$^+$, 226 (60), 197 (40), 141 (42), 127 (100), 99 (65), 77 (35); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{12}NO_3^-$: 254.0823; found: 254.0817; calcd for $C_{15}H_{14}NO_4^+$: 256.0968; found: 256.0974; elemental analysis calcd (%) for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49; found: C 70.56, H 5.14, N 5.55.

(*S*)-5-(4-Hydroxybenzyl)-3-[(2*E*,4*E*,6*E*)-1-hydroxyocta-2,4,6-trienylidene]pyrrolidine-2,4-dione (4d): Yellow solid (211 mg, 66%) from ylide **3b** (633 mg) and sorbinaldehyde (96 μL); m.p. 169–170°C; $[\alpha]_D^{25}=-15$ (c=0.05 in $CHCl_3$); IR (ATR): $\tilde{\nu}$=3257, 1643, 1617, 1593, 1515, 1203, 1175, 1024, 814, 721 cm^{-1}; ^{1}H NMR (MeOD): δ=1.84 (d, J=6.9 Hz, 3H; Me), 2.85 (dd, J=9.5, 5.4 Hz, 1H; 5-CH_2), 2.99 (dd, J=9.5, 5.4 Hz, 1H; 5-CH_2), 4.05 (q, J=6.9 Hz, 1H; 5-H), 6.09 (dq, J=15.2, 6.9 Hz, 1H; MeC*H*), 6.20–6.47 (m, 2H; C*H*, 5′-H, 6′-H), 6.66 (d, J=7.7 Hz, 2H; H^{ar}), 6.70–6.88 (m, 1H; 4′-H), 6.98 (d, J=7.7 Hz, 2H; H^{ar}), 7.07 (d, J=15.4 Hz, 1H; 2′-H), 7.41–7.49 ppm (m, 1H; 3′-H); ^{13}C NMR (75.5 MHz, MeOD): δ=17.5 (Me), 36.2 (5-CH_2), 53.9 (C-5), 102.2 (C-3), 114.7 (C^{ar}), 115.5 (C-2′), 126.4 (C-4′), 128.5 (C^{ipso}), 130.2 (C-6′), 130.4 (C^{ar}), 131.6 (C-7′), 137.0 (C-5′), 144.1 (C-3′), 155.9 (O–C^{ipso}), 170.0 (C-2), 173.7 (C-1′),

195.8 ppm (C-4); MS (EI): *m/z* (%): 325 (10) $[M]^+$, 262 (12), 107 (100), 91 (43); HRMS (EI): *m/z*: calcd for $C_{19}H_{18}NO_4^-$: 324.1241; found: 324.1236; calcd for $C_{19}H_{20}NO_4^+$: 326.1387; found: 326.1392; elemental analysis calcd (%) for $C_{19}H_{19}NO_4$: C 70.14, H 5.89, N 4.31; found: C 70.21, H 5.88, N 4.33.

(*S*)-5-Benzyl-3-[(*E*)-1-hydroxy-3-(4-methoxyphenyl)allylidene]pyrrolidine-2,4-dione (4e): Yellow solid (219 mg, 62%) from ylide **6** (491 mg) and anisaldehyde (136 μL); m.p. 158–160°C (methanol/pentane 1:2); $[\alpha]_D^{25}=44$ ($c=0.05$ in $CHCl_3$); IR (ATR): $\tilde{\nu}=3185$, 1661, 1630, 1553, 1421, 1252, 1171, 977, 824, 698 cm^{-1}; ^1H NMR ($(CD_3)_2SO$): $\delta=2.95$–2.98 (m, 2H; 5-CH_2), 3.83 (s, 3H; Me), 4.21 (t, $J=6.0$ Hz, 1H; 5-H), 7.04 (d, $J=8.4$ Hz, 2H; H^{ar}), 7.11–7.28 (m, 5H; H^{ar}), 7.47 (d, $J=15.6$ Hz, 1H; 2′-H), 7.66 (d, $J=8.4$ Hz, 2H; H^{ar}), 7.75 (d, $J=15.6$ Hz, 1H; 3′-H), 8.92 ppm (s, 1H; NH); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$): $\delta=36.7$ (5-CH_2), 55.5 (Me), 103.5 (C-3), 114.8 (C-2′), 114.9 (C^{ar}), 126.6, 126.8 (C^{ipso}), 128.1 (C^{ar}), 129.7, (C^{ar}), 130.7, 136.0 (C^{ipso}), 143.4 (C-3′), 162.0 (OC^{ipso}), 173.0 (C-2), 175.1 (C-1′), 194.9 ppm (C-4); MS (EI): *m/z* (%): 349 (100) $[M]^+$, 258 (100), 201 (12), 161 (80), 133 (19), 91 (48); HRMS (EI): *m/z* calcd for $C_{21}H_{18}NO_4^-$: 348.1236; found: 348.1236; calcd. for $C_{21}H_{20}NO_4^+$; 350.1507; found: 350.1502; elemental analysis calcd (%) for $C_{21}H_{19}NO_4$: C 72.19, H 5.48, N 4.01; found: C 72.22, H 5.52, N 3.98.

Ravenic acid (4f): Tangerine solid (160 mg, 62%) from ylide **3a** (501 mg) and (2*E*,4*E*,6*E*)-2-methylocta-2,4,6-trienal (**12**) (136 mg); m.p. 133–136°C; IR (ATR): $\tilde{\nu}=3238$, 1662, 1616, 1557, 1440, 1252, 1096, 1024, 798 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.86$ (d, $J=6.9$ Hz, 3H; CHCH_3), 2.03 (s, 3H; CH_3), 3.84 (s, 2H; 5-H), 5.95 (dq, $J=15.1$, 6.9 Hz, 1H; C*H*CH_3), 6.23 (ddd, $J=15.1$, 10.4, 1.7 Hz, 1H; 8′-H), 6.45–6.55 (m, 2H; 6′-H, 7′-H), 6.56 (d, $J=11.1$ Hz, 1H; 5′-H), 7.19 (d, $J=15.2$ Hz, 1H; 2′-H), 7.59 ppm (d, $J=15.2$ Hz, 1H; 3′-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=12.5$ (4′-Me), 18.7 (CH*Me*), 51.5 (C-5), 99.7 (C-3), 116.4 (C-2′), 126.4 (C-6′), 132.1 (C^q-4′), 134.5 (C-9′), 139.5 (C-7′), 142.6 (C-3′), 174.6 (C-2), 176.7 (C-1′), 192.5 ppm (C-4); MS (EI): *m/z* (%): 259 (25) $[M]^+$, 241 (10), 149 (10), 126 (42), 44 (100); HRMS (EI): *m/z*: calcd for $C_{15}H_{16}NO_3^-$: 258.1136; found: 258.1130; calcd for $C_{15}H_{18}NO_3^+$: 260.1281; found: 260.1287; elemental analysis calcd (%) for $C_{15}H_{17}NO_3$: C 69.48, H 6.61, N 5.40; found: C 69.50, H 6.66, N 5.48.

(2*E*,4*E*,6*E*)-2-Methylocta-2,4,6-trienoic acid (11): Compound **11** was obtained from 2-diethoxyphosphorylpropionic acid (**10**) (4.20 g, 20.0 mmol) and sorbinaldehyde (2.10 mL, 20.0 mmol) according to a general literature procedure.[13b] Recrystallisation from hexane/diethyl ether (2:1) left a white solid of m.p. 125–130°C; yield: 2.17 g (72%); IR (ATR): $\tilde{\nu}=$ 2999, 2520, 1675, 1600, 1418, 1267, 988, 923, 749 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.81$ (d, $J=7.0$ Hz, 3H; CHCH_3), 1.93 (s, 3H; CH_3), 5.92 (dq, $J=15.1$, 7.0 Hz, 1H; 7-H), 6.20 (dd, $J=15.1$, 10.4 Hz, 1H; 6-H), 6.35 (dd, $J=14.8$, 11.5 Hz, 1H; 4-H), 6.52 (dd, $J=14.8$, 10.4 Hz, 1H; 5-H), 7.30 ppm (d, $J=$ 14.8 Hz, 1H; 3-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=12.8$ (Me), 18.7 (Me), 126.7 (C-3), 127.2 (C-2), 133.2 (C-5), 135.1 (C-4), 140.4 (C-6), 141.4 (C-7), 172.1 ppm (C-1); MS (EI): *m/z* (%): 152 (50) $[M]^+$, 137 (10), 107 (100), 105 (18), 91 (75), 79 (36), 77 (23), 65 (19); HRMS (EI): *m/z*: calcd for $C_9H_{12}O_2$: 152.08373; found: 152.08370; elemental analysis calcd (%) for $C_9H_{12}O_2$: C 71.03, H 7.95; found: C 70.88, H 7.89.

(2*E*,4*E*,6*E*)-2-Methylocta-2,4,6-trienal (12): Under an inert atmosphere a mixture of acid **11** (3.04 g, 20.0 mmol), freshly distilled $SOCl_2$ (3.0 mL, 42 mmol), dry CH_2Cl_2 (50 mL) and two drops of dry DMF was stirred at room temperature overnight. All volatiles were removed and the crude acid chloride was redissolved in THF (70 mL). The resulting solution was chilled to −70°C and treated dropwise with a 1 M solution of LiAlH(*O*t*Bu*)$_3$ in THF (1.5 equiv, 30 mL, 30.0 mmol). Stirring was continued at this temperature for a further 2 h, then 2 M aq. HCl (25 mL) was added and the mixture was allowed to warm to room temperature. The aqueous layer was extracted with diethyl ether (3×25 mL), the combined organic layers were washed with 2×25 mL each of saturated aq. $NaHCO_3$, saturated aq. NaCl and water. After drying with $NaSO_4$ the solvent was removed and the crude product was purified by column chromatography on silica gel to give aldehyde **12** (1.36 g, 50%) as a colourless oil; $R_f=$ 0.44 (hexane/diethyl ether 2:1); IR (ATR): $\tilde{\nu}=2927$, 2715, 1782, 1675, 1662, 1605, 1240, 1192, 996, 985 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.81$ (d, $J=$ 7.0 Hz, 3H; CHCH_3), 1.93 (s, 3H; CH_3), 5.94 (dq, $J=15.1$, 7.0 Hz, 1H; 7-H), 6.21 (dd, $J=15.1$, 10.4 Hz, 1H; 6-H), 6.53 (dd, $J=14.8$, 10.4 Hz, 1H; 4-H), 6.81 (dd, $J=14.8$, 10.4 Hz, 1H; 5-H), 7.31 (d, $J=14.8$ Hz, 1H; 3-H), 9.41 ppm (s, 1H; CHO); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=13.8$ (Me), 18.6 (Me), 126.8 (C-3), 127.1 (C-2), 131.6 (C-5), 136.0 (C-4), 141.7 (C-6), 148.9 (C-7), 194.5 ppm (C-1); MS (EI): *m/z* (%): 136 (100) $[M]^+$, 121 (40), 107 (36), 93 (62), 91 (78), 77 (58), 65 (26); HRMS (EI): *m/z*: calcd for $C_9H_{12}O_2$: 136.08882; found: 136.08880; elemental analysis calcd (%) for $C_9H_{12}O$: C 79.37, H 8.88; found: C 79.30, H 8.78.

(*S*)-3-[(*E*)-1-Hydroxy-3-(4-methoxyphenyl)allylidene]-5-methyldihydrofuran-2,4-dione (9): Analogously to compounds **4**, lactone **9** was obtained as a yellow solid (180 mg, 66%) from ylide **8** (416 mg, 1.0 mmol) and anisaldehyde (136 μL); m.p. 97–98°C; $[\alpha]_D^{25}=-56$ ($c=0.1$ in $CHCl_3$); IR (ATR): $\tilde{\nu}=2933$, 1753, 1683, 1624, 1593, 1576, 1512, 1375, 1259, 1171, 1020 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.45$ (d, $J=6.9$ Hz, 3H; Me), 3.80 (s, 3H; OMe), 4.57–4.75 (m, 1H; 5-H), 6.86 (d, $J=8.9$ Hz, 2H; H^{ar}), 7.51 (d, $J=15.2$ Hz, 1H; 2′-H), 7.58 (d, $J=8.9$ Hz, 2H; H^{ar}), 7.92 (d, $J=15.2$ Hz, 1H; 3′-H), 10.45 ppm (brs, 1H; OH); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=$ 16.6 (Me), 55.3 (OMe), 81.2 (C-5), 96.3 (C-3), 113.6 (C-2′), 114.5 (C^{ar}), 126.6 (C^{ipso}), 131.6 (C^{ar}), 147.7 (C-3′), 163.0 (C^{ipso}), 176.6 (C-2), 181.2 (C-1′), 203.9 ppm (C-4); MS (EI): *m/z* (%): 274 (100) $[M]^+$, 245 (12), 201 (50), 174 (73), 131 (40), 77 (30); HRMS: *m/z*: calcd for $C_{15}H_{13}O_5^-$: 273.0768; found: 273.0763; calcd for $C_{15}H_{15}O_5^+$: 275.0914; found: 275.0919; elemental analysis calcd (%) for $C_{15}H_{14}O_5$: C 65.69, H 5.15; found: C 65.73, H 5.15.

Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft for financial support (grants Scho 402/9–1 and Sa 365/3–1) and to Miroslava Zoldakova for running MTT tests.

[1] For reviews on tetramic acids, see: a) H.-G. Henning, A. Gelbin, *Adv. Heterocycl. Chem.* **1993**, *57*, 139–185; b) B. J. L. Royles, *Chem. Rev.* **1995**, *95*, 1981–2001; c) E. L. Ghisalberti in *Studies in Natural Products Chemistry, Vol. 28/1* (Ed.: Atta-ur-Rahman), Elsevier, **2003**, pp. 109–163; d) monopyrrolic natural compounds including tetramic acid derivatives A. Gossauer in *Progress in the Chemistry of Organic Natural Products, Vol. 86* (Eds.: W. Herz, H. Falk, G. W. Kirby), Springer, New York, **2003**, pp. 1–188.

[2] For reviews on tetronic acids, see: a) D. Tejedor, F. Garcia-Tellado, *Org. Prep. Proced. Int.* **2004**, *36*, 33–59; b) A. L. Zografos, D. Georgiadis, *Synthesis* **2006**, 3157–3188.

[3] For reviews on tetramic and tetronic acids, see: a) R. Schobert, *Naturwissenschaften* **2006**, *94*, 1–11; b) R. Schobert, A. Schlenk, *Bioorg. Med. Chem.* **2008**, *16*, 4203–4221.

[4] R. N. Lacey, *J. Chem. Soc.* **1954**, 850–854.

[5] a) R. K. Boeckman, C. H. Weidner, R. B. Perni, J. J. Napier, *J. Am. Chem. Soc.* **1989**, *111*, 8036; b) L. A. Paquette, D. MacDonald, L. G. Anderson, J. Wright, *J. Am. Chem. Soc.* **1989**, *111*, 8037; c) S. V. Ley, S. C. Smith, P. R. Woodward, *Tetrahedron* **1992**, *48*, 1145–1174; d) Y. Iwata, N. Maekawara, K. Tanino, M. Miyashita, *Angew. Chem.* **2005**, *117*, 1556–1560; *Angew. Chem. Int. Ed.* **2005**, *44*, 1532–1536; e) L. Burke, D. Dixon, S. V. Ley, F. Rodríguez, *Org. Lett.* **2000**, *2*, 3611–3613; f) A. C. Hart, A. J. Phillips, *J. Am. Chem. Soc.* **2006**, *128*, 1094–1095; g) R. Böhme, G. Jung, E. Breitmaier, *Helv. Chim. Acta* **2005**, *88*, 2837–2841.

[6] J. Poncet, P. Jouin, B. Castro, L. Nicolas, M. Boutar, A. Gaudemer, *J. Chem. Soc. Perkin Trans. 1* **1990**, 611.

[7] a) P. Jouin, B. Castro, D. Nisato, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1177–1182; b) S. Hamilakis, D. Kontonassios, C. Sandris, *J. Heterocycl. Chem.* **1996**, *33*, 825–829; c) B. Q. Li, R. W. Franck, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2629–2634; d) Z. Liu, X. Ruan, X. Huang, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2505–2507.

[8] a) R. Schobert, C. Jagusch, C. Melanophy, G. Mullen, *Org. Biomol. Chem.* **2004**, *2*, 3524–3529; b) R. Schobert, C. Jagusch, *Tetrahedron* **2005**, *61*, 2301–2307; c) R. Schobert, M. Dietrich, G. Mullen, J.-M.

Urbina-Gonzalez, *Synthesis* **2006**, 3902–3914; d) B. Biersack, R. Diestel, C. Jagusch, G. Rapp, F. Sasse, R. Schobert, *Chem. Biodiversity* **2008**, *5*, 2423–2430.

[9] a) H. Kohl, S. V. Bhat, J. R. Patell, N. M. Ghandi, J. Nazareth, P. V. Divekar, N. J. de Souza, H. G. Berscheid, H.-W. Fehlhaber, *Tetrahedron Lett.* **1974**, *15*, 983–986; b) R. C. F. Jones, M. J. Begley, G. E. Peterson, S. Sumaria, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1959–1968.

[10] K. Hori, M. Arai, K. Nomura, E. Yoshii, *Chem. Pharm. Bull.* **1987**, *35*, 4368–4371.

[11] R. Schobert, S. Siegfried, M. Nieuwenhuyzen, W. Milius, F. Hampel, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1723–1730.

[12] A. P. Michael, E. J. Grace, M. Kotiw, R. A. Barrow, *J. Nat. Prod.* **2002**, *65*, 1360–1362.

[13] a) P. Coutrot, A. Ghribi, *Synthesis* **1986**, 661; b) P. Coutrot, A. Ghribi, *Synthesis* **1986**, 790–792.

[14] M. Storgaard, F. Zaragoza Doerwald, B. Peschke, D. Tanner, *J. Org. Chem.* **2009**, *74*, 5032–5040.

[15] M. Hosseini, H. Kringelum, A. Murray, J. E. Tonder, *Org. Lett.* **2006**, *8*, 2103–2106.

[16] R. Schobert, R. Stehle, H. Walter, *Tetrahedron* **2008**, *64*, 9401–9407.

Received: September 15, 2009
Revised: November 24, 2009
Published online: January 11, 2010

