Natural Product Synthesis

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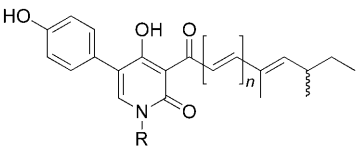
A Unified Approach for the Stereoselective Total Synthesis of Pyridone Alkaloids and Their Neuritogenic Activity**

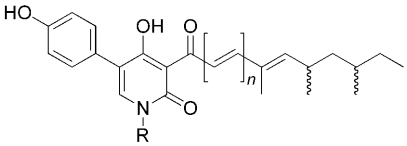
*Henning Jacob Jessen, Andreas Schumacher, Travis Shaw, Andreas Pfaltz, and Karl Gademann**

The enhancement of cognitive function, memory, and learning in healthy human subjects by application of chemical compounds is becoming more prevalent in our knowledge-focused society.[1] The use of such compounds also constitutes a promising approach to address the deleterious effects of neurodegenerative diseases.[2] In the search for novel lead structures traditional medicine is an important resource. For instance in China, entomopathogenic fungi such as *Cordyceps* and their extracts have been used for centuries to strengthen the immune system and improve cognitive function.[3] Many of these fungi contain pyridone alkaloids, for example, pretenellin B (**1**), tenellin (**2**), and bassianin (**4**).[4] A few years ago Hamburger and co-workers disclosed the structures of additional representatives isolated from the entomopathogenic fungi *Paecilomyces farinosus* and *Paecilomyces militaris*: the farinosones A (**5**) and B (**6**) as well as militarinone D (**9**).[5,6] Farinosone A (**5**) induces and enhances neurite outgrowth in the PC-12 cell line, which would be in line with the postulated positive effects on learning and cognition. However, it remains unclear, whether pyridone alkaloids—in particular (pre)-tenellin B, (pre)-bassianin, and militarinone D—generally display neuritogenic activity. To address this question, a unified synthetic approach towards the total synthesis of this family of natural products would be desirable and would also provide access to putative natural products such as pyridones **3**, **7**, and **8**.

Herein, we report a modular approach for the stereoselective total synthesis of the pyridone alkaloids pretenellin B (**1**), farinosone A (**5**), militarinone D (**9**), and the unknown precursor prebassianin B (**3**), as well as their respective enantiomers. In addition, we were able to assign the previously unknown absolute configuration of the natural products and evaluate their neuritogenic activity.



R = H; *n* = 1: pretenellin B (**1**)
R = OH; *n* = 1: tenellin (**2**)
R = H; *n* = 2: prebassianin B (**3**), unknown
R = OH; *n* = 2: bassianin (**4**)
R = H; *n* = 3: farinosone A (**5**)
R = OH; *n* = 3: farinosone B (**6**)



R = H; *n* = 1: **7**, unknown
R = OH; *n* = 1: **8**, unknown
R = H; *n* = 2: militarinone D (**9**)
R = OH; *n* = 2: **10** unknown

Since pyridone alkaloids generally feature structural differences in both the polyene chain and in the oxidation pattern of the ring system, a flexible route is required to introduce substituents onto the pyridone core. The aromatic group could be attached by a cross-coupling reaction and the polyene side chain could be introduced by a Horner–Wadsworth–Emmons (HWE) reaction[7] on a densely functionalized pyridone β-ketophosphonate, which should allow for high yields of the desired *E* isomers. To our knowledge, such an approach has never been applied in the numerous reported total syntheses of pyridone alkaloids, as surprisingly few pyridone core functionalizations have been reported in this context.[6]

The synthesis of the target natural products started with the preparation of the pyridone core **12**[8] on a 10 g scale from ethyl cyanoacetate (**11**, Scheme 1). Selective bromination of **12** with NBS gave bromopyridone **13**, which crystallized from toluene/ethyl acetate. The initial plan was to conduct cross-coupling reactions at this stage, but the reactivity of bromopyridone **13** proved to be too low regardless of the different reagents, catalysts, additives, temperatures, and solvents employed. This pyridone might inactivate the catalyst by complexation, and we therefore blocked the amide functionality with different protecting groups. The 2-trimethylsilylethoxymethyl group (SEM) was the most effective protecting group, although problems concerning N- and O-selectivity[9] were encountered that could not be solved by using different solvents and bases. However, the obtained (ca. 1:1) mixtures were amenable to Suzuki–Miyaura cross-coupling[10] and gave the *para*-methoxybenzyl(PMB)-protected pyridones in 95%

[*] Dr. H. J. Jessen, A. Schumacher, T. Shaw,[+] Prof. Dr. A. Pfaltz, Prof. Dr. K. Gademann
Department Chemie, Universität Basel
4056 Basel (Switzerland)
Fax: (+41) 61-267-1103
E-mail: karl.gademann@unibas.ch
Homepage: http://www.chemie.unibas.ch/~gademann

[+] Current address: Department of Chemistry
Princeton University, Princeton, NJ 08544 (USA)

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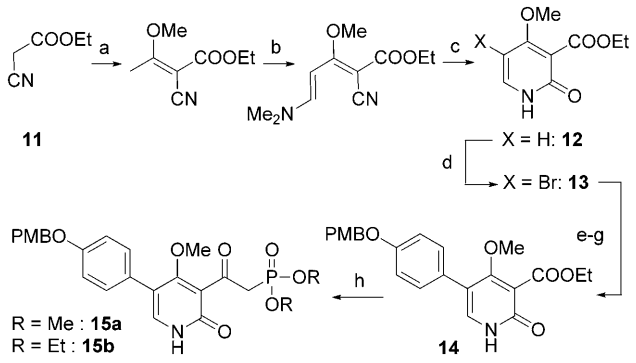
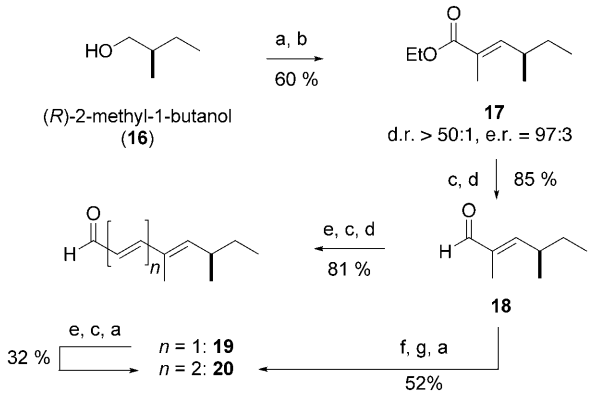


Scheme 1. a) $CH_3C(OCH_3)_3$, reflux; b) DMF/dimethyl acetal, reflux; c) aq AcOH, reflux, 41%, 3 steps; d) NBS, NH_4NO_3, CH_3CN, reflux, 90%; e) SEM-Cl, Et_3N, CH_2Cl_2, 0°C; f) $[Pd(PPh_3)_4]$, K_2CO_3, (4-[{4-methoxybenzyl}oxy]phenyl)boronic acid, DME/H_2O/DMF, 60°C; g) for *N*-SEM pyridone: TBAF, THF, 60°C, 95%, 3 steps; for *O*-SEM pyridine: TFA, 95%, 3 steps; h) $MeP(O)(OR)_2$, *n*BuLi, −78°C, THF, quant. Abbreviations: AcOH = acetic acid, DME = 1,2-dimethoxyethane, DMF = dimethylformamide, NBS = *N*-bromosuccinimide, PMB = *para*-methoxybenzyl, SEM-Cl = (trimethylsilyl)ethoxymethyl chloride, TBAF = tetrabutylammonium fluoride, TFA = trifluoroacetic acid.

yield, which were then readily separated. In both cases, subsequent removal of the SEM group gave phenylpyridone **14**, which was quantitatively transformed on a gram scale into the corresponding β-ketophosphonates **15a/b** by using three equivalents of lithiated methyl phosphonate (X-ray crystal structure analysis in the Supporting Information).

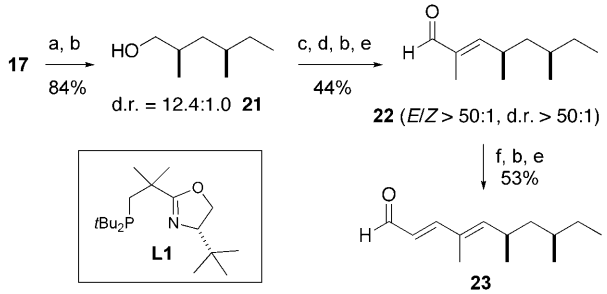
The syntheses of the different aldehydes for the HWE reactions are summarized in Scheme 2. The stereogenic center of the *R*-configured aldehydes was established in high diastereomeric excess (> 50:1) by stereoselective enolate alkylation according to a procedure published by Myers et al.[11] Reductive cleavage of the auxiliary with lithium amidotrihydridoborate released (*R*)-2-methyl-1-butanol (**16**) in 79% yield (two steps) with e.r. > 98:2, whereas (*S*)-2-methyl-1-butanol (*ent*-**16**) is commercially available. Because



Scheme 2. a) TPAP, NMO, CH_2Cl_2, 0°C; b) ethyl 2-(triphenylphosphoranylidene)propanoate, CH_2Cl_2, 35°C; c) DIBAH, CH_2Cl_2, −78°C; d) MnO_2, CH_2Cl_2; e) methyl 2-(diethoxyphosphoryl)acetate, LiCl, DBU, CH_3CN, 0°C; f) $CrCl_2$, CHI_3, 0°C; g) (*E*)-3-(tributylstannyl)prop-2-en-1-ol, $[Pd(CH_3CN)_2Cl_2]$, *N*-methyl-2-pyrrolidinone. Abbreviations: DIBAH = diisobutylaluminum hydride, NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate.

of the high volatility of the corresponding aldehydes after oxidation with TEMPO/$PhI(OAc)_2$, a HWE reaction under Masamune–Roush conditions[12a] was carried out directly after aqueous workup. Unfortunately, these conditions led to partial racemization (e.r. 83:17),[12b–d] which was also the case when lithium hexafluoroisopropoxide[13] or barium hydroxide[14] were employed. Further optimization supported by GC analysis on a chiral stationary phase revealed TPAP/NMO[15] as a suitable oxidant, followed by condensation with the less basic Wittig reagent at 35°C (completely *E*-selective, e.r. 97:3).[16] After reduction with DIBAH followed by oxidation with activated MnO_2, aldehyde **18** was obtained in 85% yield (two steps). This aldehyde was not only the starting material for the synthesis of pretenellin B (**1**) but also useful in obtaining the homologous aldehyde **19** for the synthesis of prebassianin B (**3**). In this case, the HWE reaction under Masamune–Roush conditions gave selectively the homologous *E*-configured ester without racemization. Reduction and oxidation resulted in dienal **19**. Repetition of this sequence resulted in the C_2-homologated aldehyde **20**, with high *E*-selectivity and no observed racemization. This trienal **20** was required for the preparation of farinosone A (**5**). As the final steps proceeded in only moderate yield, an alternative sequence was explored: a Takai reaction[17] (*E*/*Z* 4:1) was followed by a Stille coupling,[18] and subsequent oxidation directly yielded trienal **20**. At this stage, the minor *Z* isomer was removed by flash chromatography. In summary, the described protocols provided the required series of *R*- and *S*-configured *all-E* unsaturated aldehydes efficiently and stereoselectively.

The synthesis of militarinone D (**9**) required aldehyde **23**, which was obtained by diastereoselective hydrogenation under catalyst control (Scheme 3). The reliable generation

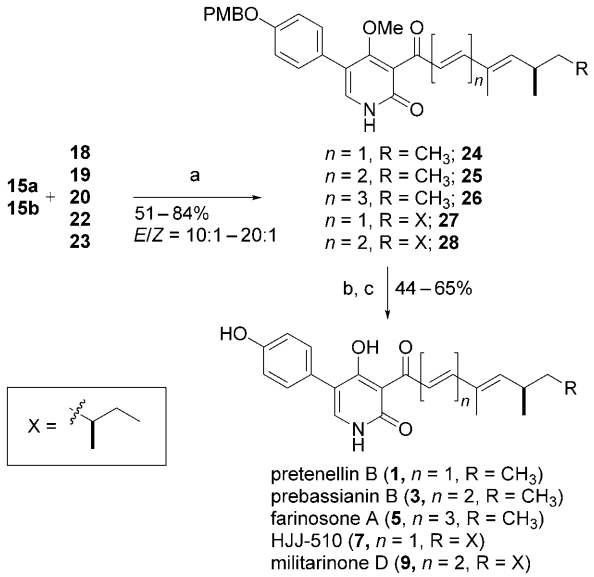


Scheme 3. a) 2 mol% [Ir(**L1**)cod]BAr^F_4, 50 bar H_2, 7°C, CH_2Cl_2, 4 h; b) DIBAH, CH_2Cl_2, −78°C; c) TPAP, NMO, CH_2Cl_2, 0°C; d) ethyl 2-(triphenylphosphoranylidene)propanoate, CH_2Cl_2, 35°C; e) MnO_2, CH_2Cl_2; f) methyl 2-(diethoxyphosphoryl)acetate, LiCl, DBU, CH_3CN, 0°C. Abbreviations: Ar^F = 3,5-bis(trifluoromethyl)phenyl, cod = cyclooctadiene.

of 1,3-*syn*-methyl arrays can be achieved by repeated stereoselective enolate alkylations according to Myers.[11] Other interesting approaches have been published, for example, by the research groups of Breit,[19a] Feringa/Minnaard,[19b] Negishi,[19c] and Burgess.[16c] As a streamlined alternative, the iridium-catalyzed diastereoselective hydrogenation of intermediate ester **17** under catalyst con-

trol[16c,d,19d] would directly confer the *syn* or *anti* configuration of the two methyl groups in a single step. After extensive screening (see the Supporting Information) of different oxazoline- and pyridine-derived N,P ligands,[19e] we found that the NeoPHOX ligand **L1** can be used to generate the *syn*-dimethyl configuration under optimized conditions in good diastereoselectivity (>99% conversion, d.r. = 12.4:1.0). Further enrichment of the diastereomeric mixture to d.r. > 50:1 (after reduction to alcohol **21**) was feasible with standard flash chromatography.[19c]

The coupling of phosphonates **15a** and **15b** with the corresponding aldehydes was addressed next. Diethylphosphonate **15b** generally gave better *E*/*Z* ratios; however, this derivative was not reactive enough to couple with the α-branched aldehydes **18** and **22**. In these cases, dimethylphosphonate **15a** was utilized as an efficient substitute (Scheme 4). The phosphonates were prone to a range of



Scheme 4. a) LiOH, H_2O/THF; b) LiI, pyridinium chloride, THF, microwave irradiation, 60 °C, 4 h; c) 2.5% TFA in CH_2Cl_2, 5 min.

side reactions, and careful optimization of the reaction parameters provided conditions under which the formation of by-products was almost completely suppressed. Finally, 2 equivalents of LiOH in a degassed THF/water (5:1) mixture under exclusion of light and with a 1:1.2 ratio of phosphonate to aldehyde furnished the protected natural products after 1–4 days with yields ranging from 51 to 84% and in good selectivities (*E*/*Z* 10:1 to 20:1). The subsequent cleavage of the protecting groups generated additional problems; despite the lability of the methyl ether, which was readily cleaved by heating in the presence of 10 equivalents of sodium chloride, we always observed partial isomerization of the α,β double bond of the polyene system (6:1 in the case of pretenellin B, 2.5:1 in the case of farinosone A). The best ratios were obtained by deprotection with freshly crystallized LiI in degassed THF in the presence of pyridinium hydrochloride under microwave irradiation. The *E*/*Z* mixtures of the synthetic compounds were not separable by either standard flash chromatography or by HPLC on a RP-18 column. Gratifyingly, the *E*/*Z* isomers showed pronounced differences in their retention times in HPLC on amyolse- or cellulose-derived chiral stationary phases. HPLC separations were conducted on a semipreparative scale with the UV detector switched off, as otherwise again isomerization occurred. After removal of the PMB group, the corresponding synthetic natural products were isolated in multi-milligram quantities with high enantiomeric purity and *all-E* configuration.

In addition to the natural products, their enantiomers (and some additional *Z* isomers) were also isolated in relevant amounts and evaluated in neurite outgrowth assays. The absolute configuration of the natural products was determined by comparison of optical rotation values. In the case of militarinone D (**9**), the synthetic product was mixed with an authentic sample and analyzed by NMR spectroscopy.[20] The absolute configuration of militarinone D (**9**) was established as *R*,*R* and the absolute configuration of pretenellin B (**1**) and farinosone A (**5**) was established as *R*. As pretenellin B (**1**) was shown to be the direct precursor in the biosynthesis of tenellin (**2**), the *R* configuration would also be expected for **2**, and most likely also for natural bassianin (**4**) and farinosone B (**6**). In this context, the N-oxidation[21] of *rac*-pretenellin B (**1**) has been described in the literature[22] and was identified as the last step in the biosynthesis in a CYP-dependent oxidation.[23]

All compounds were evaluated in a standardized assay in PC-12 cells[24] (rat *pheochromocytoma*) to assess their neuritogenic potential. To this end, cells were grown on collagen-coated 24-well plates and incubated for 2 days with the compounds ($c = 20\ \mu M$) in "Dulbecco's modified Eagle medium" (DMEM), then fixed, stained with Giemsa, and examined under a microscope. The ratio of differentiated cells (at least one neurite with a length equal to one cell diameter) to total cells per area was determined (Figure 1). In control experiments, the effect of DMSO (0.1%) and nerve growth factor (NGF 7S, 10 ng mL^{-1}) was measured on each plate. At

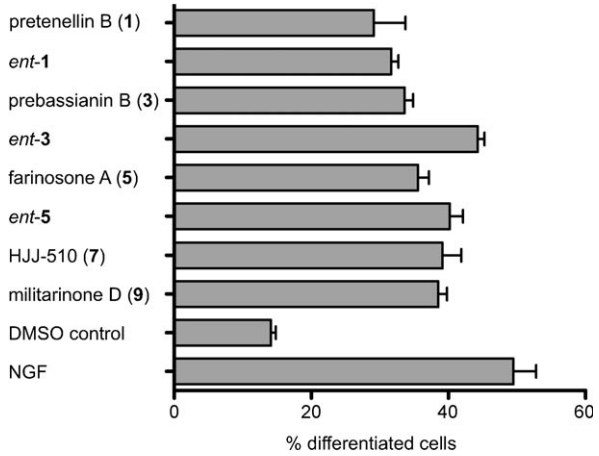


Figure 1. Neuritogenic activity of the pyridones in the PC-12 assay. All values were determined at $c = 20\ \mu M$. Nerve growth factor (NGF) control: 10 ng mL^{-1}. DMSO control: 0.1%. Incubation period 2 days. Number of counted cells >500. Error bars denote SEM.

least three areas with a combined minimal cell count of 500 were evaluated for each compound.

The data obtained (Figure 1) reveal the general neuritogenic activity of pyridone alkaloids in the PC-12 cell model. Only little influence on the activity appears to arise from the length of the side chain and the absolute configuration. Thus, this structural part does not appear to be essential to the pharmacophore. Furthermore, this study constitutes the first report on the neuritogenic activity of pretenellin B (**1**) and militarinone D (**9**), as well as the putative natural products prebassianin B (**3**) and HJJ-510 (**7**). This general activity might render 2-pyridones valuable lead structures for the development of modulators of neurite outgrowth. In addition, N-oxidation would lead to the corresponding hydroxamic acids such as tenellin (**2**), which might be of interest as phosphatase inhibitors.[25] Furthermore, Diels–Alder reactions have been shown to be suitable to cyclize different side chains on pyridones to access natural products with even more structural diversity (e.g. the synthesis of ilicicolin H[26]).

In summary, we have reported a modular assembly for the efficient stereoselective total synthesis of a whole family of sensitive polyene pyridone natural products. Notable steps in this convergent route include: 1) functionalization of a densely substituted pyridone core structure by cross-coupling reactions, 2) assembly of the polyenes under modified HWE conditions, and 3) diastereoselective synthesis of the *syn*-dimethyl array in **21** by iridium-catalyzed, stereoselective hydrogenation. Furthermore, we were able to show that these pyridone polyenes display general neuritogenic activity in the PC-12 cell model. Detailed studies on the mechanism of action of these natural products and the consequences of these results on the stimulation of cognitive processes will be carried out in our laboratories.

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[1] a) J. Harris, R. C. Kessler, M. Gazzaniga, P. Campbell, M. J. Farah, *Nature* **2008**, *456*, 702–705; b) M. J. Farah, J. Illes, R. Cook-Deegan, H. Gardner, E. Kandel, P. King, E. Parens, B. Sahakian, P. R. Wolpe, *Nat. Rev. Neurosci.* **2004**, *5*, 421–425.

[2] Reviews: a) R. M. Wilson, S. J. Danishefsky, *Acc. Chem. Res.* **2006**, *39*, 539–549; b) C. Tohda, T. Kuboyama, K. Komatsu, *Neurosignals* **2005**, *14*, 34–45.

[3] a) T. B. Ng, H. X. Wang, *J. Pharm. Pharmacol.* **2005**, *57*, 1509–1519; b) T. Chiba, M. Yamada, K. Torii, M. Suzuki, J. Sasabe, M. Ito, K. Terashita, S. Aiso, *J. Receptor Ligand Channel Res.* **2010**, *2010:3*, 97–104; c) I. K. Hwang, S. S. Lim, K.-Y. Yoo, Y. S. Lee, H. G. Kim, I.-J. Kang, H. J. Kwon, J. Park, S. Y. Choi, M.-H. Won, *Planta Med.* **2008**, *74*, 114–119; d) D. B. Ji, J. Ye, C. L. Li, Y. H. Wang, J. Zhao, S. Q. Cai, *Phytother. Res.* **2009**, *23*, 116–122.

[4] a) S. H. El Basyouni, D. Brewer, L. C. Vining, *Can. J. Bot.* **1968**, *46*, 441–448; b) A. G. McInnes, D. G. Smith, Chi-Kit Wat, L. C. Vining, J. L. C. Wright, *J. Chem. Soc. Chem. Commun.* **1974**, 281–282; c) L. M. Halo, M. N. Heneghan, A. A. Yakasai, Z. Song, K. Williams, A. M. Bailey, R. J. Cox, C. M. Lazarus, T. J. Simpson, *J. Am. Chem. Soc.* **2008**, *130*, 17988–17996; d) L. B. Jeffs, G. G. Khachatourians, *Toxicon* **1997**, *35*, 1351–1356; e) D. R. Williams, S.-Y. Sit, *J. Org. Chem.* **1982**, *47*, 2846–2851.

[5] a) Y. Cheng, B. Schneider, U. Riese, B. Schubert, Z. Li, M. Hamburger, *J. Nat. Prod.* **2004**, *67*, 1854–1858; b) Y. Cheng, B. Schneider, U. Riese, B. Schubert, Z. Li, M. Hamburger, *J. Nat. Prod.* **2006**, *69*, 436–438; c) K. Schmidt, U. Riese, Z. Li, M. Hamburger, *J. Nat. Prod.* **2003**, *66*, 378–383; d) K. Schmidt, W. Günther, S. Stoyanova, B. Schubert, Z. Li, M. Hamburger, *Org. Lett.* **2002**, *4*, 197–199.

[6] Review: H. J. Jessen, K. Gademann, *Nat. Prod. Rep.* **2010**, *27*, 1168–1185.

[7] W. D. Horner, W. S. Wadsworth, *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.

[8] B. Kasum, R. H. Prager, *Aust. J. Chem.* **1983**, *36*, 1455–1467.

[9] M. Breugst, H. Mayr, *J. Am. Chem. Soc.* **2010**, *132*, 15380–15389.

[10] N. Miyaura, A. Suzuki, *J. Chem. Soc. Chem. Commun.* **1979**, 866–867.

[11] A. Myers, B. Yang, H. Chen, L. McKinstry, D. Kopecky, J. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

[12] a) M. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186; b) G. Ramamoorthy, C. M. Acevedo, E. Alvira, M. A. Lipton, *Tetrahedron: Asymmetry* **2008**, *19*, 2546–2554. In the total synthesis of pyridovericin, Swern oxidation followed by Wittig olefination led to racemization. This underscores the sensitivity under these conditions: c) Q. Zhang, A. Rivkin, D. P. Curran, *J. Am. Chem. Soc.* **2002**, *124*, 5774–5781. In the synthesis published by Kane et al., oxidation with PDC followed by refluxing with Wittig reagent (see also Ref. [12c]); d) D. E. Kane, F. Kudo, K. Kinoshita, C. Khosla, *Chem. Biol.* **2002**, *9*, 131–142.

[13] L. K. Blasdel, A. G. Myers, *Org. Lett.* **2005**, *7*, 4281–4283.

[14] I. Paterson, K.-S. Yeung, J. B. Smaill, *Synlett* **1993**, 774–776.

[15] W. P. Griffith, S. V. Ley, G. P. Withcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, 1625–1627.

[16] Published accordingly with a different oxidation method: a) S. V. Ley, A. Armstrong, D. Díez-Martín, M. J. Ford, P. Grice, J. G. Knight, H. C. Kolb, A. Madin, C. A. Marby, S. Mukherjee, A. N. Shaw, A. M. Z. Slawin, S. Vile, A. D. White, D. J. Williams, M. Woods, *J. Chem. Soc. Perkin Trans. 1* **1991**, 667–692; the published value for the optical rotation $[\alpha]_D = +23°$ differs markedly from our measured value $[\alpha]_D = +35°$. For a similar substrate: b) D. R. Williams, R. A. Turske, *Org. Lett.* **2000**, *2*, 3217–3220. With a different Wittig reagent: c) J. Zhou, J. W. Ogle, Y. Fan, V. Banphavichit, Y. Zhu, K. Burgess, *Chem. Eur. J.* **2007**, *13*, 7162–7170; d) J. Zhou, K. Burgess, *Angew. Chem.* **2007**, *119*, 1147–1149; *Angew. Chem. Int. Ed.* **2007**, *46*, 1129–1131.

[17] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.

[18] M.-T. Lai, D. Li, E. Oh, H.-W. Liu, *J. Am. Chem. Soc.* **1993**, *115*, 1619–1628.

[19] a) T. Reiss, B. Breit, *Chem. Eur. J.* **2009**, *15*, 6345–6348; b) R. Des Mazery, M. Pullez, F. Lopez, S. R. Harutyunyan, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2005**, *127*, 9966–9967; c) E. Negishi, Z. Tan, B. Liang, T. Novak, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5782–5787; d) M. G. Schrems, A. Pfaltz, *Chem. Commun.* **2009**, 6210–6212; e) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402–1411.

[20] We thank Professor Hamburger for an authentic sample and Dr. Melanie Quitschau for the spectroscopic analysis.

[21] E. Vedejs, S. Larsen, *Org. Synth.* **1987**, *64*, 127–137.

[22] J. H. Rigby, M. Qabar, *J. Org. Chem.* **1989**, *54*, 5852–5853.

[23] Reports on the biosynthesis: a) K. L. Eley, L. M. Halo, Z. Song, H. Powles, R. J. Cox, A. M. Bailey, C. M. Lazarus, T. J. Simpson, *ChemBioChem* **2007**, *8*, 289–297; b) S. Bergmann, J. Schümann,

K. Scherlach, C. Lange, A. Brakhage, C. Hertweck, *Nat. Chem. Biol.* **2007**, *3*, 213 – 217. See also Ref. [4c].

[24] a) L. A. Greene, A. S. Tischler, *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 2424 – 2428; b) I. Dikic, J. Schlessinger, I. Lax, *Curr. Biol.* **1994**, *4*, 702 – 708; c) Y. Obara, T. Aoki, M. Kusano, Y. Ohizumi, *J. Pharmacol. Exp. Ther.* **2002**, *301*, 803 – 811; d) H. J. Jessen, D. Barbaras, M. Hamburger, K. Gademann, *Org. Lett.* **2009**, *11*, 3446 – 3449; e) U. Riese, E. Ziegler, M. Hamburger, *FEBS Lett.* **2004**, *577*, 455 – 459.

[25] Reports on hydroxamic acids as selective phosphatase inhibitors: a) A. Fürstner, F. Feyen, H. Prinz, H. Waldmann, *Angew. Chem.* **2003**, *115*, 5519 – 5522; *Angew. Chem. Int. Ed.* **2003**, *42*, 5361 – 5364; b) A. Fürstner, F. Feyen, H. Prinz, H. Waldmann, *Tetrahedron* **2004**, *60*, 9543 – 9558.

[26] D. R. Williams, M. L. Bremmer, D. L. Brown, J. D'Antuono, *J. Org. Chem.* **1985**, *50*, 2809 – 2810.

