# Total Synthesis of Albicidin: A Lead Structure from *Xanthomonas albilineans* for Potent Antibacterial Gyrase Inhibitors \*\*

Julian Kretz, Dennis Kerwat, Vivien Schubert, Stefan Grätz, Alexander Pesic, Siamak Semsary, Stéphane Cociancich, Monique Royer, and Roderich D. Süssmuth\*

#### Dedicated to Professor Klaus Grohe

Abstract: The peptide antibiotic albicidin, which is synthesized by the plant pathogenic bacterium Xanthomonas albilineans, displays remarkable antibacterial activity against various Gram-positive and Gram-negative microorganisms. The low amounts of albicidin obtainable from the producing organism or through heterologous expression are limiting factors in providing sufficient material for bioactivity profiling and structure-activity studies. Therefore, we developed a convergent total synthesis route toward albicidin. The unexpectedly difficult formation of amide bonds between the aromatic amino acids was achieved through a triphosgene-mediated coupling strategy. The herein presented synthesis of albicidin confirms the previously determined chemical structure and underlines the extraordinary antibacterial activity of this compound. The synthetic protocol will provide multigram amounts of albicidin for further profiling of its drug properties.

Owing to the increasing development of antibiotic resistance by bacterial pathogens, there is an enormous need for new antibiotic lead structures. A major cause of concern are Gram-negative bacteria, which have an outer membrane as an additional protective barrier<sup>[1]</sup> that makes infections difficult to treat.<sup>[2]</sup> A prominent group of Gram-negative pathogens that cause serious infections are *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* (the ESKAPE group of bacteria),<sup>[3–5]</sup> which show rapid development of multi- or pan-drug-resistant<sup>[6,7]</sup> strains. Likewise, there is an increasing number of Gram-positive bacteria, like *Clostridium difficile*, which cause serious infections, partic-

[\*] J. Kretz, D. Kerwat, V. Schubert, S. Grätz, A. Pesic, S. Semsary, Prof. Dr. R. D. Süssmuth Institut für Organische Chemie, Technische Universität Berlin Straße des 17 Juni 124, 10623 Berlin (Germany) E-mail: suessmuth@chem.tu-berlin.de Homepage: http://www.biochemie.tu-berlin.de
S. Cociancich, M. Royer CIRAD, UMR BGPI 34398 Montpellier Cedex5 (France)
[\*\*\*] This work was supported by the Deutsche Forschungsgemeinschaft

(DFG; SU239/11-1 and SU239/18-1, Cluster of Excellence (UniCat)), by the Fonds der Chemischen Industrie (J.K.) and by the City of Berlin (Elsa-Neumann-Fellowship to D.K.).

Supporting information for this article (including experimental details) is available on the WWW under http://dx.doi.org/10.1002/anie.201409584.

towards identifying and developing new antibiotics, pathogenic bacteria have also been considered as sources of new drugs.<sup>[9]</sup> Such a bacterial strain is the plant pathogen *Xanthomonas albilineans*, which causes leaf scald disease in sugar cane,<sup>[10,11]</sup> thereby leading to significant economic damage through crop losses.<sup>[12]</sup> Albicidin, which is synthesized by *X. albilineans*, was first characterized in the early 1980s.<sup>[13,14]</sup> It displays strong antibacterial activity against Gram-positive and Gram-negative bacteria at nanomolar concentrations by acting as an inhibitor of DNA gyrase.<sup>[15]</sup> It took more than 30 years to elucidate the structure of albicidin (**1a**)<sup>[16]</sup> owing to its extremely low abundance in *X. albilineans* cultures and its oligo-aromatic character, which dramatically complicates its structure elucidation (Scheme 1).

ularly in a hospital-associated environment.<sup>[8]</sup> In our efforts

Heterologous production of albicidin in the host strain *X. axonopodis* pv. *vesicatoria* resulted in higher production yields,<sup>[17]</sup> thereby facilitating <sup>15</sup>N- and <sup>13</sup>C-labeling of albicidin for extensive electrospray ionization mass spectrometry (ESI-MS) and nuclear magnetic resonance (NMR) spectroscopy analysis.<sup>[16]</sup> As shown in Scheme 1, albicidin is an acyl pentapeptide composed of six building blocks of mainly



**Scheme 1.** Retrosynthetic Scheme for albicidin (**1a**) with strategic coupling sites (i) and (ii) to establish a convergent total synthesis from the three fragments **2**, **3**, and **4**, with their building blocks additionally labeled **A-F**.

Angew. Chem. Int. Ed. 2014, 53, 1-6

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

Wiley Online Library

### Angewandte Communications

aromatic character. The N-terminus of the unusual pentapeptide bears a *para*-hydroxy coumaric acid with an additional methyl group in the 3-position of the Michael acceptor system (MCA, **A**). The main portion of the peptide consists of  $\delta$ -type aromatic amino acids: two *para*-aminobenzoic acids (*p*ABA<sup>2/4</sup>, **B** and **D**), which are connected by the unusual amino acid  $\beta$ -L-cyanoalanine (L-Cya<sup>3</sup>, **C**), and a C-terminal dipeptide motif composed of two 4-amino-2-hydroxy-3methoxybenzoic acids (*p*MBA<sup>5/6</sup>, **E** and **F**).

Herein, we present the first total synthesis of albicidin, in which extensive use was made of triphosgene (BTC) as a coupling reagent to establish peptide couplings of the comparatively inert *p*-aminobenzoic acids. This work confirms the previous structural assignment<sup>[16]</sup> and facilitates extensive structure–activity relationship (SAR) studies.

In our retrosynthetic considerations, we aimed at a convergent synthesis (Scheme 1). Hence, the molecule was broken up into three fragments: the N-terminal coumaric acid residue **A**, a central tripeptide **B–C–D**, and a C-terminal dipeptide **E–F**. In the early stage of our studies, we noticed that the introduction of building block **A** into the growing peptide dramatically restricted its solubility and therefore the synthesis begins with the C-terminal **E–F** building block.

Subsequently, the protecting group strategy had to be deliberately chosen: A final deprotection step should release all of the protecting groups from the carboxylic acid and phenolic functional groups. Reducing conditions such as hydrogenolysis by H<sub>2</sub>/Pd could not be applied because of the expected sensitivity of the double bond of the N-terminal coumaric acid residue. Furthermore, we noticed that the nitrile function of  $\beta$ -cyanoalanine was readily hydrolyzed under basic conditions, for example, on applying LiOH. Attempts to install commonly used acid-labile protecting groups, such as tert-butyl ethers or esters was highly inefficient, particularly at the sterically demanding tetra-substituted pMBA. Finally, we chose the allyl group as the protecting group for the phenol and ester functionalities, mainly because it became evident that both protection and deprotection proceed under mild conditions and in good to excellent vields (Scheme 2). While Fmoc or Boc protecting groups are extremely useful for protecting amines in classical peptide synthesis, we employed the nitro group as a masking functionality for the aromatic amines, not least for reasons of atom economy. Importantly the nitro group can be reduced under very mild conditions in the presence of allyl groups by using SnCl<sub>2</sub>·2H<sub>2</sub>O, which is beneficial for the overall protection group strategy.<sup>[18]</sup>

Careful examination of the albicidin structure reveals similarities to the architectures of oligo-aromatic foldamers,<sup>[19]</sup> for which typical strong coupling reagents such as hydroxybenzotriazole (HOBt), N,N'-dicyclohexylcarbodiimide (DCC), N,N,N',N'-tetramethylfluoroformamidinium hexafluorophosphate (TFFH), or acid chlorides have to be applied for peptide bond formation, mainly due to the weak nucleophilicity of aromatic amines.<sup>[20-24]</sup> In a systematic study, we examined coupling conditions with *para*-coumaric acid and *p*ABA derivatives and noticed that with the exception of acid chlorides, commonly used protocols and reagents (HATU, Cl-HOBt/EDAC, DCC/4-DMAP) combined with



Scheme 2. Reagents and conditions: A) a) H-pABA-OtBu (6), DCC, DMF, RT, 64%, *ee* 96% b) HCl/dioxane (4 M), RT, quant.; c) O<sub>2</sub>N-pABA-OSu (9), NEt<sub>3</sub>, DMF, RT, 89%; B) d) Allyl bromide, K<sub>2</sub>CO<sub>3</sub>, DMF, RT, 88%; e) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 2-methyl-2-butene, *t*BuOH, H<sub>2</sub>O, RT, 92%; f) allyl bromide, K<sub>2</sub>CO<sub>3</sub>, DMF, RT, 93%; g) SnCl<sub>2</sub>·2H<sub>2</sub>O, EtOH, 60°C, 1 h, 86%; h) **12**, BTC, 2,4,6-collidine, DIPEA, THF, RT, 19 h, 91%; C) i) **14**, SnCl<sub>2</sub>·2H<sub>2</sub>O, EtOH, 60°C, 79%; j) BTC, 2,4,6-collidine, DIPEA, THF, RT, 91%, k) SnCl<sub>2</sub>·2H<sub>2</sub>O, EtOH, 60°C, 73%; l) **2**, BTC, 2,4,6-collidine, DIPEA, THF, RT, 91%, k) SnCl<sub>2</sub>·2H<sub>2</sub>O, EtOH, 60°C, 73%; l) **2**, BTC, 2,4,6-collidine, THF, 26%.

various solvents (DMF, NMP, THF, DMF) mostly failed (HPLC-MS control).

Among the coupling agents that form an acid chloride from a benzoic acid precursor, we identified triphosgene

www.angewandte.org

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!

(BTC), established by Jung et al.,  $^{[25,26]}$  as a superior coupling agent. Other methods to generate acid chlorides with reagents such as thionyl chloride or cyanuric chloride resulted in lower yields or extended reaction times (>7 d).

With these general considerations, we set out to assemble albicidin: The coumaric acid building block A (2) was synthesized in two steps with 89% yield, mainly according to literature procedures.<sup>[27]</sup> Initially, for assembly of the central tripeptide 3 (Scheme 2A), the required Boc- $\beta$ -CyapABA-OtBu dipeptide (7) was synthesized through condensation of Boc-protected β-cyanoalanine with H-pABA-OtBu in a two-step sequence.<sup>[28]</sup> However, the resulting dipeptide 7 was obtained in low yields and we therefore sought to shorten this reaction sequence by making use of a known side reaction of unprotected Asn in peptide chemistry, namely, nitrile formation under amide bond coupling conditions.<sup>[29]</sup> Since cyclic intermediates resulting from this dehydration are sensitive to racemization,<sup>[30,31]</sup> we had to study this key reaction in more detail. Various coupling conditions were examined and HATU/DIPEA were found to produce a high degree of racemization, whereas carbodiimides (EDC, DIC and DCC) without the addition of bases<sup>[32]</sup> gave excellent enantiomeric excess (ee = 96%), albeit with low yields (13%). Through variation of the reaction conditions, we improved the yield of this one pot reaction to 64% with almost negligible racemization (< 4%).

Having established a smooth access to dipeptide **7**, the acid-labile Boc and *t*Bu-ester protecting groups were removed with HCl/dioxane (4M) to quantitatively obtain dipeptide **8**. Most importantly, this deprotection approach prevents rehydration of the nitrile of  $\beta$ -cyanoalanine.<sup>[29]</sup> Subsequently, dipeptide **8** was converted into the central tripeptide **3** by using an activated succinimide ester of 4-nitrobenzoic acid and triethylamine as a base in yields of 89 %.<sup>[33]</sup>

The synthesis of the C-terminal fragment E-F (4) is illustrated in Scheme 2B. An important prerequisite for successful assembly, building block 10, is available from ortho-vanillin.<sup>[34,35]</sup> Further derivatization into key building blocks 12 and 13 required an allyl protecting group, which was introduced in yields of 88% with K<sub>2</sub>CO<sub>3</sub>/allyl bromide. For oxidation of the aldehyde functionality of compound 11 to carboxylic acid 12, we chose mild conditions to keep the potentially vulnerable double bond of the allyl protection group intact. Compound 12 was obtained in a yield of 92%. After protection of the C-terminus of 12, free amine 13 was obtained after reduction of the nitro group under mild conditions with SnCl<sub>2</sub>·2H<sub>2</sub>O (EtOH/60°C) in yields of 86%.<sup>[18]</sup> With the aromatic building blocks 12 and 13 in hand, fragment E-F (4) was assembled through BTCmediated peptide coupling. As mentioned above, commonly used peptide coupling reagents, for example T3P, failed in our studies with substrates that have a high steric demand and bear aromatic amines. The method by Jung et al.<sup>[25,26]</sup> resulted in satisfying yields and often shorter reaction times. The dipeptide 14 was synthesized in a yield of 91 % (BTC, 2,4,6collidine, DIPEA, THF) and after reduction of the nitro functionality with SnCl<sub>2</sub>·2H<sub>2</sub>O, we obtained the last building block **4** for the total synthesis of albicidin in a yield of 79%. Finally, fully protected albicidin **17** was assembled from the three fragments (**2**, **3** and **4**). Coupling of central tripeptide **3** and C-terminal fragment **4** was achieved by applying the BTC-mediated peptide coupling conditions,<sup>[25]</sup> which resulted in pentapeptide **15** in 91 % yield (Scheme 2 C). The reduction of the N-terminal nitro group of compound **15** to obtain pentapeptide **16** was followed by a quantitative BTC-mediated coupling with coumaric acid derivative **2**. Global allyl deprotection of fully protected albicidin **17** with Pd(PPh<sub>3</sub>)<sub>4</sub> and phenylsilane as a scavenger resulted in albicidin, which was purified by preparative reversed-phase HPLC. Comparison of the analytical data with those obtained for the natural product were in excellent accordance, thus confirming the structure of albicidin (see the Supporting Information).<sup>[16]</sup>

Since albicidin has only one stereocenter (L-Cya), we intended to briefly assess the influence of the configuration of Cya on its antibacterial activity. Therefore, *ent*-albicidin (**1b**) was synthesized. The circular dichroism (CD) spectrum of the natural product shows the same Cotton effect<sup>[36,37]</sup> as synthetic (*S*)-configured albicidin (see the Supporting Information). By contrast, *ent*-albicidin reveals virtually the inverted CD spectrum, as expected for the (*R*) configuration of Cya.

Subsequently we performed activity studies on the molecular target DNA gyrase from *E. coli* with both albicidin enantiomers. Gyrase is also the major target of quinolone antibiotics, for example, ciprofloxacin,<sup>[38]</sup> which is still considered the gold standard for gyrase inhibition.<sup>[39]</sup> A previously established protocol was employed to estimate the half maximal inhibitory concentration  $(IC_{50})^{[15,40]}$  and adequately compare it with published values. As shown in Figure 1 A, the IC<sub>50</sub> value for synthetic albicidin is approximately 40 nm, which is in excellent accordance the value reported for the natural product.<sup>[15]</sup> Intriguingly, the IC<sub>50</sub> for *ent*-albicidin was determined to be approximately 40 nm as well (Figure 1 B).



**Figure 1.** Inhibition assay of DNA gyrase supercoiling activity (*E. coli*) for determination of the half maximal inhibitory concentration ( $IC_{so}$ ) values of albicidin (A) and *ent*-albicidin (B). The control experiment without enzyme and drug (lane c) shows relaxed DNA (re), and the addition of enzyme (lane 0) results in supercoiled DNA (sc). The other lanes represent the reaction with enzyme and increasing concentrations of the corresponding drug (30–200 nm).

www.angewandte.org

## Angewandte Communications

The  $IC_{50}$  for ciprofloxacin was determined to be approximately 200 nm, (see the Supporting Information), which clearly underlines the remarkable gyrase-inhibiting potential of albicidin.

Finally, the antibacterial activity of synthetic albicidin, as well as of *ent*-albicidin, was determined against a set of mostly Gram-negative bacteria (Table 1). Albicidin showed excellent minimum inhibitory concentration (MIC) values between 1 and  $0.031 \,\mu\text{gmL}^{-1}$ , comparable to those for ciprofloxacin.

**Table 1:** Antibacterial activity of albicidin (**1** a), *ent*-albicidin (**1** b), and ciprofloxacin against various bacterial strains.

Strain <sup>[a]</sup>			
	Albicidin	ent-Albicidin	Ciprofloxacin
E. coli <sup>[c]</sup>	0.031	0.063	0.015
E. coli <sup>[c]</sup>	0.063	0.5	32
E. coli <sup>[d]</sup>	0.5	>64	>64
S. enteritidis <sup>[b]</sup>	0.5	>64	0.031
P. aeruginosa <sup>[b]</sup>	1	>64	0.5
S. aureus <sup>[b]</sup>	16	>64	0.5
M. luteus <sup>[b]</sup>	1	8	n.d. <sup>[e]</sup>

[a] For strain numbers, see the Supporting Information. [b] Fluoroqui-

nolone sensitive. [c] Fluoroquinolone resistant (*qnrA1* mutation).<sup>[41]</sup> [d] Fluorquinolone resistant (*gyrA* mutation). [e] n.d. = not determined.

Remarkably, albicidin shows unaltered activity against ciprofloxacin-resistant strains, for example, *E. coli qnrA1*, with a mutation in *qnrA1*, a member of the pentapeptide repeat protein (PRP) family,<sup>[41]</sup> or *E. coli gyrA*, which has a mutation in the GyrA subunit. Interestingly, for some strains, *ent*albicidin shows comparable activity, thus indicating that the stereocenter of albicidin is of minimal significance for the antibacterial activity. This effect will be examined in more detail in future studies.

In summary, we have established the first total synthesis route to the novel antibacterial drug albicidin. BTC proved superior to other peptide coupling reagents, including those which are commonly used for challenging sequences. The racemization-free synthesis is convergent and easy to scale up. The synthesis of albicidin in multigram amounts will enable further pharmacological profiling, as well as the investigation of its structure–activity relationships (SAR) through the synthesis of derivatives. The microbiological data indicate strong antibacterial activity with low MIC values, including against quinolone resistant strains, thus demonstrating the resistance-breaking potential of albicidin. These promising results provide the basis for the assessment of albicidin as a lead structure for antibacterial drug development.

Received: September 29, 2014 Published online:

**Keywords:** albicidin · gyrase · *para*-aminobenzoic acid · peptides · total synthesis

- [1] T. J. Beveridge, J. Bacteriol. 1999, 181, 4725-4733.
- [2] P. D. Tamma, S. E. Cosgrove, L. L. Maragakis, *Clin. Microbiol. Rev.* 2012, 25, 450–470.

- [3] H. W. Boucher, G. H. Talbot, D. K. Benjamin, J. Bradley, R. J. Guidos, R. N. Jones, B. E. Murray, R. A. Bonomo, D. Gilbert, *Clin. Infect. Dis.* 2013, 56, 1685–1694.
- [4] L. B. Rice, J. Infect. Dis. 2008, 197, 1079-1081.
- [5] H. W. Boucher, G. H. Talbot, J. S. Bradley, J. E. Edwards, D. Gilbert, L. B. Rice, M. Scheld, B. Spellberg, J. Bartlett, *Clin. Infect. Dis.* 2009, 48, 1–12.
- [6] M. E. Falagas, P. K. Koletsi, I. A. Bliziotis, J. Med. Microbiol. 2006, 55, 1619–1629.
- [7] M. E. Falagas, I. A. Bliziotis, Int. J. Antimicrob. Agents 2007, 29, 630–636.
- [8] L. R. Peterson, Clin. Infect. Dis. 2009, 49, 992-993.
- [9] S. Müller, E. Garcia-Gonzalez, A. Mainz, G. Hertlein, N. C. Heid, E. Mösker, H. van den Elst, H. S. Overkleeft, E. Genersch, R. D. Süssmuth, *Angew. Chem. Int. Ed.* 2014, *53*, 10821–10825; *Angew. Chem.* 2014, *126*, 10998–11002.
- [10] R. G. Birch, S. S. Patil, Physiol. Mol. Plant Pathol. 1987, 30, 199– 206.
- [11] R. G. Birch, S. S. Patil, Physiol. Mol. Plant Pathol. 1987, 30, 207– 214.
- [12] P. Rott, D. Soupa, Y. Brunet, P. Feldmann, P. Letourmy, *Plant Pathol.* **1995**, *44*, 1075–1084.
- [13] R. G. Birch, S. S. Patil, J. Gen. Microbiol. 1985, 131, 1069-1075.
- [14] "Antibiotic and Process for the Production Thereof": R.G. Birch, S. S. Patil, US4525354 (A), 1985.
- [15] S. M. Hashimi, M. K. Wall, A. B. Smith, A. Maxwell, R. G. Birch, Antimicrob. Agents Chemother. 2007, 51, 181–187.
- [16] S. Cociancich, A. Pesic, D. Petras, S. Uhlmann, J. Kretz, V. Schubert, L. Vieweg, S. Duplan, M. Marguerettaz, J. Noëll, I. Pieretti, M. Hügelland, S. Kemper, A. Mainz, P. Rott, M. Royer, R. D. Süssmuth, *Nat. Chem. Biol.*, DOI: 10.1038/nchembio.1734, in press.
- [17] E. Vivien, D. Pitorre, S. Cociancich, I. Pieretti, D. W. Gabriel, P. C. Rott, M. Royer, *Antimicrob. Agents Chemother.* 2007, *51*, 1549–1552.
- [18] F. D. Bellamy, K. Ou, Tetrahedron Lett. 1984, 25, 839-842.
- [19] I. Huc, Eur. J. Org. Chem. 2004, 17-29.
- [20] D.-W. Zhang, X. Zhao, J.-L. Hou, Z.-T. Li, Chem. Rev. 2012, 112, 5271–5316.
- [21] B. Gong, Chem. Eur. J. 2001, 7, 4336-4342.
- [22] J. Zhu, R. D. Parra, H. Zeng, E. Skrzypczak-Jankun, X. C. Zeng, B. Gong, J. Am. Chem. Soc. 2000, 122, 4219–4220.
- [23] J. T. Ernst, J. Becerril, H. S. Park, H. Yin, A. D. Hamilton, Angew. Chem. Int. Ed. 2003, 42, 535–539; Angew. Chem. 2003, 115, 553–557.
- [24] Y. Hamuro, S. J. Geib, A. D. Hamilton, J. Am. Chem. Soc. 1996, 118, 7529-7541.
- [25] B. Thern, J. Rudolph, G. Jung, *Tetrahedron Lett.* 2002, 43, 5013– 5016.
- [26] B. Thern, J. Rudolph, G. Jung, Angew. Chem. Int. Ed. 2002, 41, 2307–2309; Angew. Chem. 2002, 114, 2401–2403.
- [27] A. Yamamoto, K. Nakamura, K. Furukawa, Y. Konishi, T. Ogino, K. Higashiura, H. Yago, K. Okamoto, M. Otsuka, *Chem. Pharm. Bull.* 2002, 50, 47-52.
- [28] D. L. Boger, R. M. Borzilleri, S. Nukui, R. T. Beresis, J. Org. Chem. 1997, 62, 4721-4736.
- [29] S. Mojsov, A. R. Mitchell, R. B. Merrifield, J. Org. Chem. 1980, 45, 555-560.
- [30] R. Paul, A. S. Kende, J. Am. Chem. Soc. 1964, 86, 4162-4166.
- [31] J. L. Radkiewicz, H. Zipse, S. Clarke, K. N. Houk, J. Am. Chem. Soc. 1996, 118, 9148–9155.
- [32] A. Dutt Konar, J. Mol. Struct. 2013, 1036, 350-360.
- [33] M. Adamczyk, J. R. Fino, Org. Prep. Proced. Int. 1996, 28, 470– 474.
- [34] S. Kato, T. Morie, J. Heterocycl. Chem. 1996, 33, 1171-1178.
- [35] M. S. Tichenor, D. B. Kastrinsky, D. L. Boger, J. Am. Chem. Soc. 2004, 126, 8396-8398.

www.angewandte.org

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

These are not the final page numbers!



- [36] N. S. Simmons, C. Cohen, A. G. Szent-Gyorgyi, D. B. Wetlaufer, E. R. Blout, J. Am. Chem. Soc. 1961, 83, 4766–4769.
- [37] J. A. Schellman, P. Oriel, J. Chem. Phys. 1962, 37, 2114-2124.
- [38] A. Mustaev, M. Malik, X. Zhao, N. Kurepina, G. Luan, L. M. Oppegard, H. Hiasa, K. R. Marks, R. J. Kerns, J. M. Berger, et al., *J. Biol. Chem.* **2014**, 289, 12300–12312.
- [39] C. C. Sanders, Rev. Infect. Dis. 1988, 10, 516-527.
- [40] R. H. Flatman, A. J. Howells, L. Heide, H.-P. Fiedler, A. Maxwell, Antimicrob. Agents Chemother. 2005, 49, 1093-1100.
- [41] P. Nordmann, L. Poirel, J. Antimicrob. Chemother. 2005, 56, 463 469.

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

#### Angewandte Communications

## Communications



#### Natural Product Synthesis

J. Kretz, D. Kerwat, V. Schubert, S. Grätz, A. Pesic, S. Semsary, S. Cociancich, M. Royer, R. D. Süssmuth\* \_\_\_\_\_

Total Synthesis of Albicidin: A Lead Structure from *Xanthomonas albilineans* for Potent Antibacterial Gyrase Inhibitors



New antibiotics are urgently needed in view of bacterial resistance to established drugs. Albicidin shows activity against various Gram-negative and Gram-positive bacteria, thus making it a promising lead candidate for drug development. The first total synthesis of albicidin was achieved through a convergent synthetic approach that is applicable to the production of derivatives for structure– activity studies.

6 www.angewandte.org

These are not the final page numbers!