

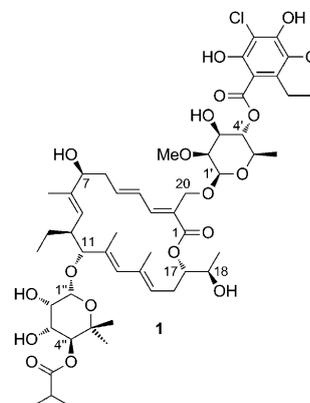
Total Synthesis of the Tiacumicin B (Lipiarmycin A3/Fidaxomicin) Aglycone**

Florian Glaus and Karl-Heinz Altmann*

Abstract: Tiacumicin B (lipiarmycin A3, fidaxomicin) is an atypical macrolide antibiotic which is used for the treatment of *Clostridium difficile* infections. Tiacumicin B is also a potent inhibitor of *Mycobacterium tuberculosis*, but due to its limited oral bioavailability is unsuitable for systemic therapy. To provide a basis for structure–activity studies that might eventually lead to improved variants of tiacumicin B, we have developed an efficient approach to the synthesis of the tiacumicin B aglycone. The synthesis features a high-yielding intramolecular Suzuki cross-coupling reaction to effect macrocyclic ring closure. Key steps in the synthesis of the macrocyclization precursor were a highly selective, one-pot Corey–Peterson olefination and an ene–diene cross-metathesis reaction. Depending on the reaction conditions, the final deprotection delivered either the fully deprotected tiacumicin B aglycone or partially protected versions thereof.

In 1987 researchers at Abbott Laboratories described the isolation of the glycosylated macrolide tiacumicin B (**1**) as the major antibacterial constituent of the soil bacterium *Dactylosporangium aurantiacum*.^[1,2] The compound was found to be identical^[1b] to lipiarmycin, which had already been isolated in 1975 from *Actinoplanes deccanensis*,^[3] and to clostomicin B1, isolated from *Micromonospora echinospora* in 1986.^[4] The original preparation of lipiarmycin^[3] was later discovered to be a ca. 3:1 mixture of two closely related macrolides, lipiarmycin A3 and lipiarmycin A4, whose gross chemical structures were determined in 1987.^[5] The complete relative and absolute configuration of **1** (from *Dactylosporangium aurantiacum*) was elucidated in 2005 by X-ray crystallographic analysis;^[6] importantly, most recently, **1** has been shown to be identical to lipiarmycin A3.^[7]

The structure of tiacumicin B (**1**) features an 18-membered macrolactone core with four chiral centers and a high degree of unsaturation; an additional, hydroxy-bearing ste-



reogenic center is present in the short side chain attached to C17. The aglycone core is connected via glycosidic linkages to 4-*O*-isobutyryl-5-methyl- β -D-rhamnose (at C11) and to 2-*O*-methyl- β -D-rhamnose (at C20), with the latter being esterified at C4 with dichlorohomoserine.

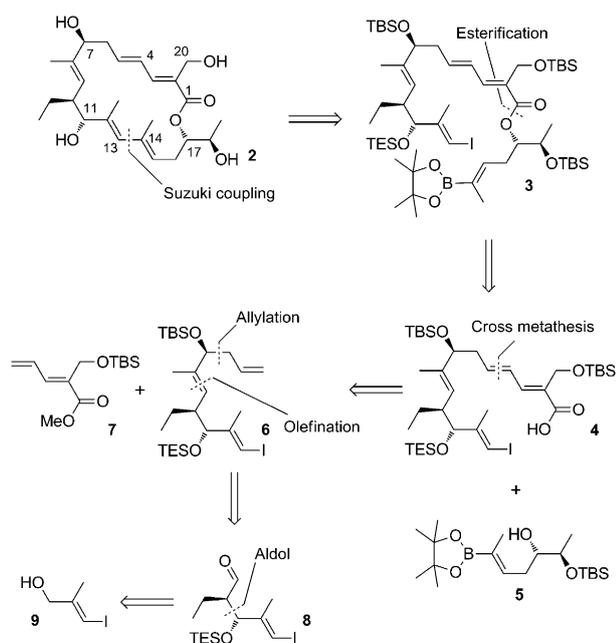
Tiacumicin B (**1**) is an inhibitor of bacterial RNA polymerase^[8] and it exhibits significant antibacterial activity against a range of Gram-positive organisms^[9] and also against *Mycobacterium tuberculosis*.^[10] At the same time, the compound is not susceptible to cross-resistance with rifamycin-type antibiotics,^[10] which were the only class of bacterial RNA polymerase inhibitors of clinical significance before 2011 (vide infra). Notably, **1** shows only minimal oral bioavailability,^[11] which limits its utility for the treatment of systemic infections, but renders it highly useful for the elimination of pathogens confined to the gastrointestinal tract. In 2011, tiacumicin B (**1**), under the generic name fidaxomicin (trade names Difcid (U.S.) and Dificlir (Europe)), was approved for the treatment of infections with the opportunistic pathogen *Clostridium difficile*, which is the most frequent cause of nosocomial diarrhea infections in the developed world.^[12]

Rather surprisingly, despite their intriguing structures and biological profiles, no total synthesis of any member of the tiacumicin/lipiarmycin/clostomicin family (or the corresponding aglycones) has been reported in the literature to date. In the context of our work on new drugs against tuberculosis,^[13] we have thus embarked on the total synthesis of the tiacumicin B aglycone (**2**; Scheme 1), in order to provide a basis for structure–activity relationship (SAR) studies.^[14] Ultimately, this work aims to identify tiacumicin B analogues with improved biopharmaceutical properties. Alternative approaches to the synthesis of the tiacumicin B aglycone (**2**) and its 18S isomer are described in two concurrent papers in this issue by the groups of Gademann and Zhu, respectively.^[32]

[*] M. Sc. F. Glaus, Prof. K.-H. Altmann
Swiss Federal Institute of Technology (ETH) Zürich
Department of Chemistry and Applied Biosciences
Institute of Pharmaceutical Sciences, HCI H405
Vladimir-Prelog-Weg 4, 8093 Zürich (Switzerland)
E-mail: karl-heinz.altmann@pharma.ethz.ch

[**] This work was supported by the European Union as part of the EU FP7 programme “More Medicines for Tuberculosis” (MM4TB), grant agreement no. 260872. We are indebted to Dr. Bernhard Pfeiffer and Leo Betschart for NMR support, to Dr. Michael Wörle, Dr. Nils Trapp, and Michael Solar for X-ray crystallographic analysis, and to Dr. Xiangyang Zhang, Louis Bertschi, Rolf Häfliger, and Oswald Greter for mass spectra.

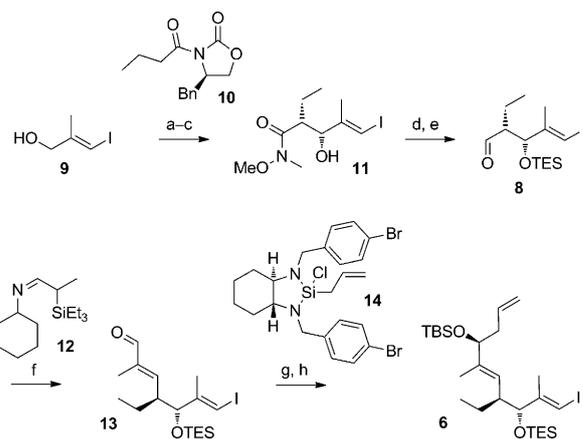
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201409510>.



Scheme 1. Retrosynthesis of the tiacumicin B aglycone (**2**). TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

As illustrated in Scheme 1, one of the central elements of our projected synthesis of **2** was the use of an intramolecular Suzuki cross-coupling reaction to effect macrocyclic ring closure. The requisite macrocyclization precursor **3** could be disconnected into acid **4** and alcohol **5**; the former was to be obtained by ene–diene cross-metathesis between olefin **6** and diene **7**,^[15] followed by ester saponification. While olefin–olefin cross-metathesis has found numerous applications in organic synthesis, reactions involving conjugated dienes such as **7** have been investigated only scarcely.^[16] The terminal olefin **6** was envisioned to be synthesized from the known alcohol **9**^[17] by a sequence of oxidation, stereoselective aldol reaction, olefination, and stereoselective allylation. Finally, protecting groups were chosen such as to allow for stepwise selective deprotection of the C11 and C20 hydroxy groups, in order to enable subsequent independent derivatization at these positions for analogue synthesis (or the synthesis of the natural product **1**).

Based on the above retrosynthetic considerations, the synthesis commenced with the MnO₂-mediated allylic oxidation of **9** (Scheme 2). The resulting volatile aldehyde was not isolated, but the reaction mixture was filtered through celite and the concentrated filtrate was treated directly with the boron enolate of **10**;^[18] this protocol gave the desired *syn*-aldol product with excellent diastereoselectivity (d.r. > 20:1). Separation of the aldol product from unreacted **10** proved to be difficult and thus was not attempted for multigram-scale reactions. Rather, the mixture, after aqueous workup and filtration through silica, was treated with AlMe₃/MeONH-Me-HCl to provide Weinreb amide **11** in 53% overall yield for the three-step sequence from **9**. The absolute configuration of **11** was secured by X-ray crystallography (see the Supporting Information for details).^[19] TES protection of the secondary hydroxy group followed by reduction of the Weinreb amide

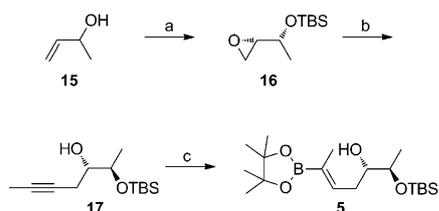


Scheme 2. a) MnO₂, 3 Å molecular sieves, CH₂Cl₂, RT, 75 min; b) **10**, Bu₂BOTf, NEt₃, CH₂Cl₂, –78 °C, 2.5 h; then 0 °C, 1.5 h; then pH 7 buffer, MeOH, H₂O₂, 0 °C, 1 h; c) MeONHMe-HCl, AlMe₃, THF, 0 °C, 2 h, 53% (three steps); d) TESCl, imidazole, CH₂Cl₂, RT, 30 min, 94%; e) DIBAL-H, THF, –30 °C, 1 h; then –20 °C, 1 h, 94%; f) **12**, sBuLi, THF, –20 °C, 2 h; then PhSH, –20 °C, 2 h; then sat. aq. NaH₂PO₄, RT, 4 h, *E/Z* 20:1, 81% (ca. 95% pure); g) **14**, Sc(OTf)₃, CH₂Cl₂, –35 °C to –20 °C, 30 min; then –20 °C, 2.5 h; then 1 M HCl, RT, 7 min, 83%, d.r. > 20:1; h) TBSCl, imidazole, CH₂Cl₂, RT, 22 h, 93%. OTf = trifluoromethanesulfonate, DIBAL-H = diisobutylaluminum hydride, THF = tetrahydrofuran.

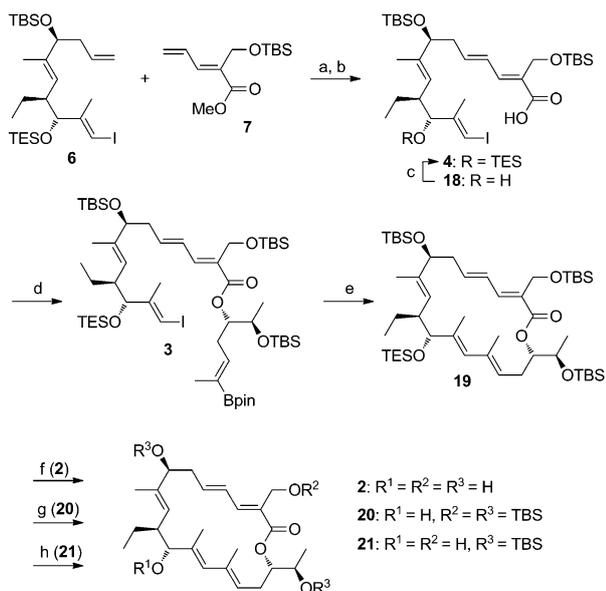
functionality with DIBAL-H then furnished aldehyde **8**. Aldehyde **8** was then transformed into enal **13** by a newly developed variant of the Corey–Peterson olefination reaction,^[20] which employed thiophenol (rather than the commonly used trifluoroacetic acid)^[21] to isomerize the *E/Z* mixture of aldimines formed upon addition of the anion of α -silylimine **12** to aldehyde **8**. Treatment of the aldimine mixture (*E/Z* ca. 1:3) with thiophenol in situ induced rapid *Z* to *E* isomerization, yielding imine mixtures with *E/Z* ratios of between 15:1 and 22:1 within two hours;^[21] hydrolysis of the imine moiety then afforded enal **13** in 81% yield and 95% purity. Allylation of **13** with Leighton's strained silacycle **14**^[22] in the presence of Sc(OTf)₃^[23] set the C7 stereocenter (tiacumicin numbering) with excellent selectivity (d.r. > 20:1) and in high yield (83%).^[24] TBS protection of the secondary hydroxy group then furnished the desired building block **6**.

The synthesis of building block **5** departed from racemic but-3-en-2-ol (**15**), which was subjected to Sharpless kinetic resolution, affording, after in situ protection of the hydroxy group, **16** in 21% yield (compare to a maximum yield of 45%) (Scheme 3).^[25] The epoxide ring in **16** was then smoothly opened with the anion of propyne to provide **17** in 75% yield. Cu^I-catalyzed formal hydroboration^[26,27] then afforded *Z*-vinyl boronic ester **5** with superb regio- (> 20:1) and stereoselectivity (*Z/E* > 20:1) in 79% yield.

With all fragments in hand, the assembly of the tiacumicin B aglycone (**2**) was investigated, with the initial focus on the crucial cross-metathesis step (Scheme 4). These experiments revealed a pronounced tendency of diene **7** towards rapid homodimerization, regardless of the catalyst used (Grubbs I, II, and III; Hoveyda–Grubbs I and II, Piers–Grubbs),^[28] solvent (toluene, CH₂Cl₂, Et₂O, EtOAc, THF,



Scheme 3. a) $\text{Ti}(\text{OiPr})_4$, (–)-DIPT, $t\text{BuOOH}$ (0.45 equiv), 3 Å molecular sieves, CH_2Cl_2 , -20°C , 39 h; then TBSCl, imidazole, CH_2Cl_2 , -20°C to RT; then RT, 16 h, 21%; b) $n\text{BuLi}$, propyne, $\text{BF}_3\cdot\text{OEt}_2$, THF, -78°C , 3.5 h, 75%, 18% recovered **16**; c) bis(pinacolato)diboron, CuCl (5 mol%), KOtBu (20 mol%), PPh_3 (6 mol%), THF/MeOH, RT, 3.5 h, 79%. (–)-DIPT = (–)-diisopropyl *D*-tartrate.



Scheme 4. a) Hoveyda–Grubbs II (15 mol%), EtOAc, RT, 3.5 h, 56%, *E/Z* 6.7:1 at C4–C5, 27% recovered **6**; b) LiOH, $t\text{BuOH}/\text{H}_2\text{O}$ 3:1, 33°C , 48 h, 69% (**4**), 16% (**18**); c) 1. TSCl, imidazole, CH_2Cl_2 , RT, 14 h; 2. K_2CO_3 , MeOH, RT, 10 min, 84% (two steps); d) **5**, 2,4,6- $\text{Cl}_3\text{H}_2\text{C}_6\text{COCl}$, NEt_3 , DMAP, toluene, RT, 5.5 h, 81%; e) $[\text{Pd}(\text{PPh}_3)_4]$ (20 mol%), TIOEt, THF/ H_2O 3:1, RT, 25 min, 73%; f) $\text{NEt}_3\cdot 3\text{HF}$, CH_3CN , 0°C to RT, 1 h; then RT, 8 h; then 50°C , 86 h, 47% after HPLC purification; g) $\text{NEt}_3\cdot 3\text{HF}$, $\text{CH}_3\text{CN}/\text{THF}$ 7:3, -15°C , 4 h; then -25°C , 15 h; then -15°C , 7 h, 70% (**20**), 22% (**19**); h) $\text{NEt}_3\cdot 3\text{HF}$, $\text{CH}_3\text{CN}/\text{THF}$ 6:4, -15°C to 5°C , 2 h; then 5°C , 5 h; then 15°C , 27 h, 54%. Bpin = pinacolatoboron, DMAP = 4-dimethylaminopyridine.

dioxane, and C_6F_6 were investigated), and temperature (0°C to 80°C). In addition, rapid catalyst deactivation was noticed in all cases. In general, second-generation Grubbs and Hoveyda–Grubbs catalysts gave better conversions and higher *E/Z* ratios for the newly formed C4–C5 double bond than first- and third-generation catalysts. Best results were obtained when separate solutions of **7** and Hoveyda–Grubbs II catalyst in EtOAc were added simultaneously to a solution of **6** in EtOAc at room temperature (syringe pump addition). Following this protocol, the desired cross-metathesis product could be isolated in 56% yield as an inseparable 6.7:1 mixture of *E/Z* isomers at C4–C5; at the same time, 27% of the more valuable fragment **6** could be re-isolated.

Careful saponification of the ester group in the metathesis product with LiOH in $t\text{BuOH}/\text{H}_2\text{O}$ at slightly elevated temperature (33°C) afforded acid **4** in 69% yield together with some TES-protected material (**18**); the latter could be readily converted into **4** by reaction with an excess of TSCl.^[31] Esterification of **4** with alcohol **5** (Scheme 4) using a Yamaguchi protocol^[29] then provided **3**, as the requisite precursor for the projected Suzuki macrocyclization. Ring closure was effected by treating **3** with $[\text{Pd}(\text{PPh}_3)_4]$ followed by TIOEt in a mixture of THF and water.^[30] Remarkably, under these conditions the reaction was usually complete in less than 30 min at room temperature and furnished the desired macrocycle **19** in 73% yield as a 9.5:1 mixture of *E/Z* isomers at C4–C5.^[31]

While **19** was not crystalline, a differently protected version of the compound (i.e. **22**, Figure 1) afforded crystals suitable for X-ray analysis,^[19] which confirmed the correct configurations of all stereocenters and double bonds (for details see the Supporting Information). Importantly, **22** was

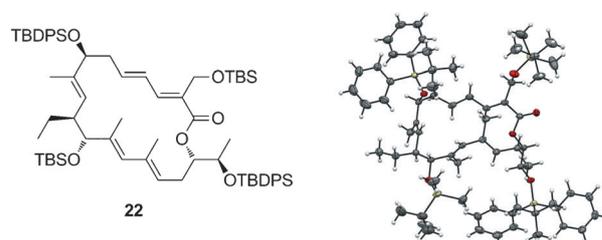


Figure 1. Structural formula and ORTEP representation of **22**; thermal ellipsoids drawn at 50% probability. Disorders were omitted (see the Supporting Information for details). TBBDPS = *tert*-butyldiphenylsilyl.

obtained from **9** by the same route as **19** (except for the introduction of protecting groups). Global desilylation of **19** was best achieved with $\text{NEt}_3\cdot 3\text{HF}$, which provided **2** in 47% yield after purification by preparative HPLC (Scheme 4).^[31] When the reaction temperature was lowered from 55°C to 15°C or -15°C , it was possible to use the same reagent to remove the secondary TES group (\rightarrow **20**) with reasonable selectivity, or selectively cleave the TES ether and the primary TBS ether simultaneously (\rightarrow **21**), thus generating substrates suitable for further functionalization, including the synthesis of tiacumicin B (**1**).

In conclusion, we have developed an efficient synthesis of the tiacumicin B aglycone (**2**). The synthesis comprises 12 linear steps from alcohol **9** to the fully protected aglycone **19**. Key steps are a modified Corey–Peterson olefination, which allowed for the one-pot formation of *E*- α -methyl α,β -unsaturated aldehyde **13**, a cross-metathesis reaction between **6** and **7**, and a highly efficient intramolecular TIOEt-promoted Suzuki coupling as the macrocyclization step. Based on the chemistry presented in this paper, current work in our laboratory focuses on the synthesis of tiacumicin analogues and their biological evaluation.

Received: September 26, 2014

Published online: ■■■■■, ■■■■■

Keywords: Corey–Peterson olefination · macrolides · Suzuki coupling · tiacumicin · total synthesis

- [1] a) R. J. Theriault, J. P. Karwowski, M. Jackson, R. L. Girolami, G. N. Sunga, C. M. Vojtko, L. J. Coen, *J. Antibiot.* **1987**, *40*, 567–574; b) J. E. Hochlowski, S. J. Swanson, L. M. Ranfranz, D. N. Whittern, A. M. Buko, J. B. McAlpine, *J. Antibiot.* **1987**, *40*, 575–588.
- [2] For a review on tiacumicins see: W. Erb, J. Zhu, *Nat. Prod. Rep.* **2013**, *30*, 161–174.
- [3] a) F. Parenti, H. Pagani, G. Beretta, *J. Antibiot.* **1975**, *28*, 247–252; b) C. Coronelli, R. J. White, G. C. Lancini, F. Parenti, *J. Antibiot.* **1975**, *28*, 253–259; c) S. Sergio, G. Pirali, R. White, F. Parenti, *J. Antibiot.* **1975**, *28*, 543–549.
- [4] a) S. Ōmura, N. Imamura, R. Ōiwa, H. Kuga, R. Iwata, R. Masuma, Y. Iwai, *J. Antibiot.* **1986**, *39*, 1407–1412; b) Y. Takahashi, Y. Iwai, S. Ōmura, *J. Antibiot.* **1986**, *39*, 1413–1418.
- [5] a) A. Arnone, G. Nasini, B. Cavalleri, *J. Chem. Soc. Perkin Trans. I* **1987**, 1353–1359; b) E. Martinelli, L. Faniuolo, G. Tuan, G. G. Gallo, B. Cavalleri, *J. Antibiot.* **1983**, *36*, 1312–1322.
- [6] Y.-K. Shue, F. K. Babakhani, F. W. Okumu, P. S. Sears, S. L. Miller-Shangle, R. B. Walsh, PCT application WO 2005/112990 A2, **2005**. See also PCT application WO 2006/085838 A1, **2006** and US patent application US 2008/0269145 A1, **2008**.
- [7] A. Bedeschi, P. Fonte, G. Fronza, C. Fuganti, S. Serra, *Nat. Prod. Commun.* **2014**, *9*, 237–240.
- [8] I. Artsimovitch, J. Seddon, P. Sears, *Clin. Infect. Dis.* **2012**, *55*, S127–S131. RNA polymerase inhibition by tiacumicin-type structures was first demonstrated in Ref. [3c] for lipiarmycin, the 3:1 mixture of tiacumicin B (lipiarmycin A3) and lipiarmycin A4.
- [9] E. J. C. Goldstein, F. Babakhani, D. M. Citron, *Clin. Infect. Dis.* **2012**, *55*, S143–S148.
- [10] M. Kurabachew, S. H. J. Lu, P. Krastel, E. K. Schmitt, B. L. Suresh, A. Goh, J. E. Knox, N. L. Ma, J. Jiricek, D. Beer, M. Cynamon, F. Petersen, V. Dartois, T. Keller, T. Dick, V. K. Sambandamurthy, *J. Antimicrob. Chemother.* **2008**, *62*, 713–719.
- [11] P. Sears, D. W. Crook, T. J. Louie, M. A. Miller, K. Weiss, *Clin. Infect. Dis.* **2012**, *55*, S116–S120.
- [12] a) J. Lucado, C. Gould, A. Elixhauser, HCUP Statistical Brief #124, **2012**, <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf> (accessed August **2014**); b) M. J. T. Crobach, O. M. Dekkers, M. H. Wilcox, E. J. Kuijper, *Clin. Microbiol. Infect.* **2009**, *15*, 1053–1066.
- [13] a) F. Glaus, K.-H. Altmann, *Angew. Chem. Int. Ed.* **2012**, *51*, 3405–3409; *Angew. Chem.* **2012**, *124*, 3461–3465; b) O. P. Horlacher, R. C. Hartkoorn, S. T. Cole, K.-H. Altmann, *ACS Med. Chem. Lett.* **2013**, *4*, 264–268; c) R. C. Hartkoorn, F. Pojer, J. A. Read, H. Gingell, J. Neres, O. P. Horlacher, K.-H. Altmann, S. T. Cole, *Nat. Chem. Biol.* **2014**, *10*, 96–98.
- [14] The currently available SAR information on tiacumicins is solely derived from naturally occurring variants and analogues that are accessible by metabolic engineering: a) J. E. Hochlowski, M. Jackson, R. R. Rasmussen, A. M. Buko, J. J. Clement, D. N. Whittern, J. B. McAlpine, *J. Antibiot.* **1997**, *50*, 201–205; b) Y. Xiao, S. Li, S. Niu, L. Ma, G. Zhang, H. Zhang, G. Zhang, J. Ju, C. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 1092–1105; c) S. Niu, T. Hu, S. Li, Y. Xiao, L. Ma, G. Zhang, H. Zhang, X. Yang, J. Ju, C. Zhang, *ChemBioChem* **2011**, *12*, 1740–1748. See also Ref. [1a].
- [15] The synthesis of a TIPS-protected variant of this diene has been described: A. B. Charette, B. Côté, S. Monroc, S. Prescott, *J. Org. Chem.* **1995**, *60*, 6888–6894, and references therein.
- [16] For a review see: A. Wojtkielewicz, *Curr. Org. Synth.* **2013**, *10*, 43–66.
- [17] R. Baker, J. L. Castro, *J. Chem. Soc. Perkin Trans. I* **1990**, 47–65.
- [18] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
- [19] CCDC 1025575 (**22**) and CCDC 1025576 (**11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [20] a) E. J. Corey, D. Enders, M. G. Bock, *Tetrahedron Lett.* **1976**, *17*, 7–10; b) R. H. Schlessinger, M. A. Poss, S. Richardson, P. Lin, *Tetrahedron Lett.* **1985**, *26*, 2391–2394; c) R. Desmond, S. G. Mills, R. P. Volante, I. Shinkai, *Tetrahedron Lett.* **1988**, *29*, 3895–3898.
- [21] TFA-mediated isomerization of the aldimine mixture derived from **8** was not investigated, as prior experiments with a TBS-protected analogue of **8** had led to only moderate *E/Z* ratios of 3:1 to 5:1 for the corresponding enal. In addition, the isomerization was slow, which gave rise to the formation of (unidentified) side products.
- [22] K. Kubota, J. L. Leighton, *Angew. Chem. Int. Ed.* **2003**, *42*, 946–948; *Angew. Chem.* **2003**, *115*, 976–978.
- [23] H. Kim, S. Ho, J. L. Leighton, *J. Am. Chem. Soc.* **2011**, *133*, 6517–6520.
- [24] The absolute configuration of the newly formed stereocenter was determined by Mosher ester analysis, according to the protocol described in: T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451–2458.
- [25] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, B. K. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
- [26] M. J. Hesse, C. P. Butts, C. L. Willis, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2012**, *51*, 12444–12448; *Angew. Chem.* **2012**, *124*, 12612–12616.
- [27] A. L. Moure, R. Gómez Arrayás, D. J. Cárdenas, I. Alonso, J. C. Carretero, *J. Am. Chem. Soc.* **2012**, *134*, 7219–7222.
- [28] A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243–251.
- [29] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
- [30] S. A. Frank, H. Chen, R. K. Kunz, M. J. Schnaderbeck, W. R. Roush, *Org. Lett.* **2000**, *2*, 2691–2694.
- [31] The C4–C5 *Z* isomer is derived from the minor isomer formed in the cross-metathesis reaction. Further purification of the mixture by flash chromatography in an alternative solvent system (see the Supporting Information) allowed the isolation of **19** as a single isomer. Only fractions containing pure **19** were collected in this process and no attempts were made at the exhaustive recovery of material by repeated chromatography of mixed fractions. All desilylation reactions were carried out with pure **19**.
- [32] H. Miyatake-Ondoabál, E. Kaufmann, K. Gademann, *Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201409464; *Angew. Chem.*, DOI: 10.1002/ange.201409464; W. Erb, J.-M. Grassot, D. Linder, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201409475; *Angew. Chem.*, DOI: 10.1002/ange.201409475.

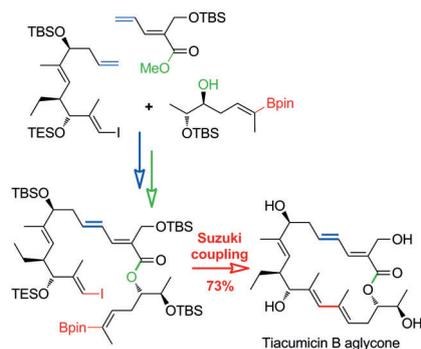
Communications



Natural Product Synthesis

F. Glaus, K.-H. Altmann* — ■■■■-■■■■

Total Synthesis of the Tiacumicin B
(Lipiarmycin A3/Fidaxomicin) Aglycone



The crucial ring closure in the title total synthesis is effected by an intramolecular Suzuki cross-coupling. Key steps in the assembly of the linear macrocyclization precursor are a highly selective one-pot Corey–Peterson olefination, which is based on a new thiophenol-mediated $Z \rightarrow E$ isomerization of an α,β -unsaturated aldimine, and an ene–diene cross-metathesis reaction.