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Total Synthesis of Anachelin H

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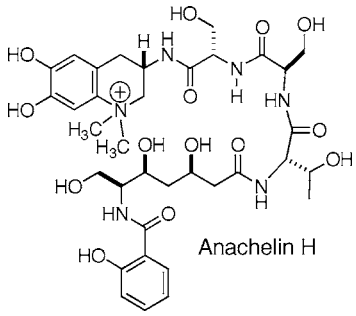
ABSTRACT



The first total synthesis of anachelin H is reported. Starting from L-Ser, a stereodivergent synthesis of the polyketide fragment resulting in all possible diastereoisomers is described. The alkaloid peptide fragment is prepared via a tellurium-mediated oxidative aza annulation as the key step. Coupling of the fragments gave synthetic anachelin H, which was found to be identical to a sample of the natural product, thus confirming the configuration by total synthesis.

The complex secondary metabolite anachelin was recently isolated from the freshwater cyanobacterium *Anabaena cylindrica*[1,2] and postulated to serve as a bacterial growth factor facilitating iron uptake (so-called *siderophore*).[3] The structure is characterized by a fascinating blend of polyketide, peptide, and alkaloid fragments. While Budzikiewicz, Walsby, and co-workers isolated both anachelin H (**1**) and anachelin-1 (**2**) and determined the constitution of the former,[1] Murakami et al. obtained anachelin-1 (**2**) and anachelin-2 (**3**) together with two related esters.[2] However, in all these studies the relative and absolute configuration of four stereogenic centers was left unassigned.[1,2] In addition, it is not clear which of these compounds **1**−**3** is biologically active, and also the mode of action remains unknown.

To investigate all these questions, we started a complex molecule synthesis program that resulted in the preparation of a diasteroisomer of anachelin, whose spectra did not match those of the natural product.[4] In paticular, major differences were detected for the protons attached to C(2), C(3), and C(5). These facts, combined with the unknown configuration

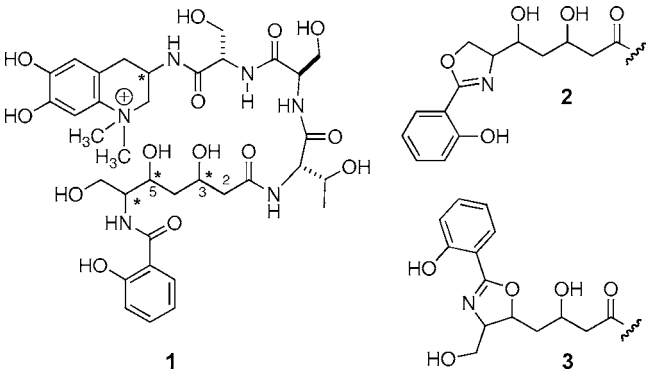


Figure 1. Anachelins **1**−**3**, isolated from *Anabaena cylindrica*, display an interesting structure featuring polyketide, peptide, and alkaloid fragments.

(1) Beiderbeck, H.; Taraz, K.; Budzikiewicz, H.; Walsby, A. E. *Z. Naturforsch.* **2000**, *55c*, 681−687. Beiderbeck, H. Ph.D. Dissertation, Universität zu Köln, Köln, 2000. Anachelin was probably isolated 30 years ago, but its constitution could not be elucidated; see: Walsby, A. E. *Br. Phycol. J.* **1974**, *9*, 383−391.

(2) Itou, Y.; Okada, S.; Murakami, M. *Tetrahedron* **2001**, *57*, 9093−9099.

(3) Reviews: Keller-Schierlein, W.; Prelog, V.; Zahner, H. *Fort. Chem. Org. Nat.* **1964**, *22*, 279−322. Raymond, K. N.; Muller, G.; Matzanke, B. F. *Top. Curr. Chem.* **1984**, *123*, 49−102. Drechsel, H.; Jung, G. *J. Pept. Sci.* **1998**, *4*, 147−181.

(4) Gademann, K.; Bethuel, Y. *Angew. Chem.* **2004**, *116*, 3389−3391; *Angew. Chem., Int. Ed.* **2004**, *43*, 3327−3329.

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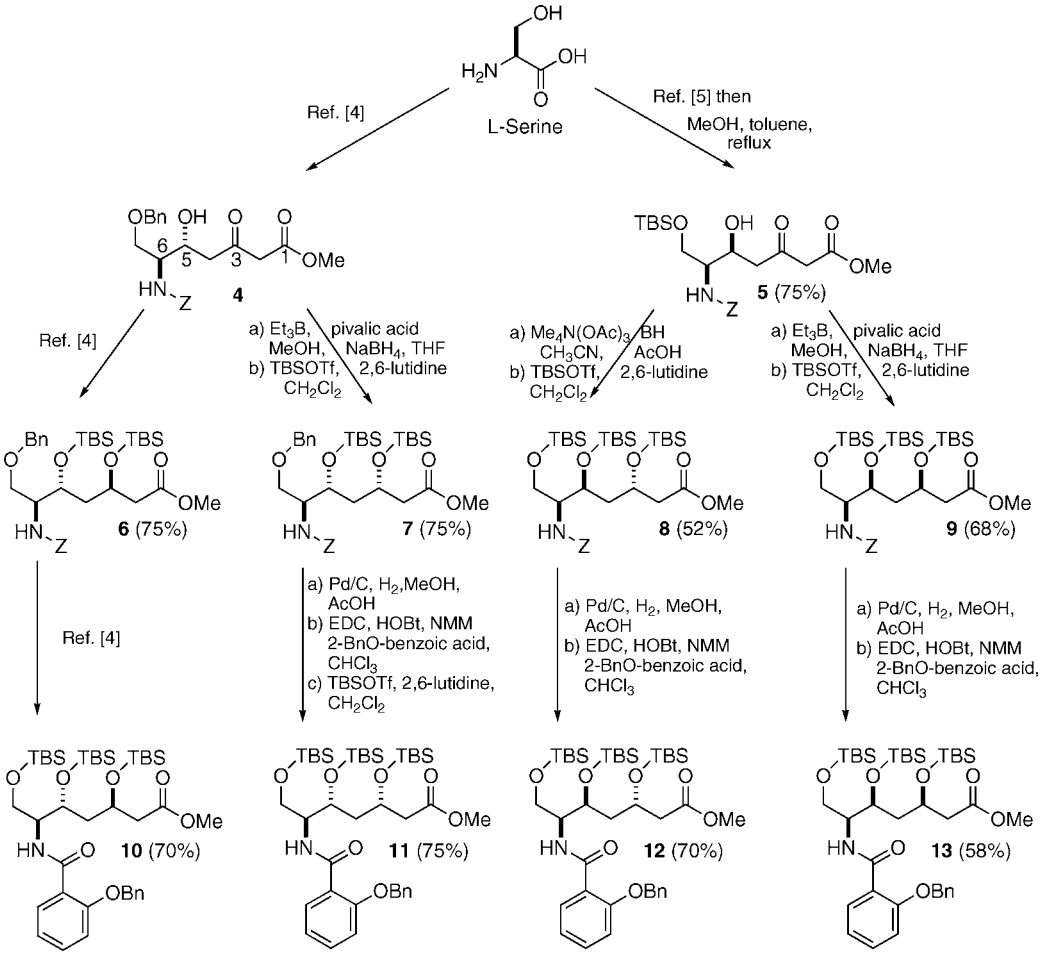
Scheme 1. Stereodivergent Synthesis of All Possible Diastereoisomers of the Polyketide Fragment



at four stereogenic centers, forced us to prepare all diastereoisomers of the polyketide part in order to establish the unknown stereochemistry. In this communication, we report the stereodivergent synthesis of all possible diastereoisomers of the polyketide fragment resulting in the total synthesis of anachelin H, thus ultimately proving the relative configuration of the natural product. When this work was being finished, a report from Okada and co-workers appeared, where the absolute and relative configuration was independently determined by degradation of the natural product.[5]

The hydroxyketone **4** bearing the 5,6-anti-configuration was accessed on a large scale using a biomimetic C_2 elongation/reduction strategy.[4] The other 5,6-syn-diastereoisomer **5** was prepared by a catalytic asymmetric vinylogous Mukaiyama aldol reaction according to Moreau and Campagne.[6] These hydroxyketones **4** and **5** set the starting point for our stereodivergent synthesis of the polyketide fragment. A directed hydride transfer following the method of Evans gave access to the corresponding 3,5-anti-diastereoisomers.[7] Thus, separate treatment of each hydroxyketone **4** and **5** with $BH(OAc)_3$ at −20 °C resulted in the clean formation of the (3*R*,5*R*,6*S*)-diastereoisomer **6** as well as the (3*S*,5*S*,6*S*)-counterpart **8** in high yield and diastereoselectivity after TBS protection.[8] Flash chromatography[9] provided the diastereomerically pure compounds.

The corresponding 3,5-syn reduction was addressed next. We anticipated that the usual reduction protocols following Narasaka et al.[10] or Prasad et al.[11] might be incompatible with the functionalities present in the molecule. In fact, the addition of pivalic acid in the course of elaborating the borane chelating agent was found to be crucial for a successful and selective reaction.[12] Thus, hydroxyketones **4** and **5** were reduced smoothly by $NaBH_4$ after precomplexation of the substrate with Et_2BOMe, preformed from Et_3B, pivalic acid,

(5) Ito, Y.; Ishida, K.; Okada, S.; Murakami, M. *Tetrahedron* **2004**, *60*, 9075−9080.

(6) Moreau, X.; Campagne, J.-M. *Tetrahedron Lett.* **2001**, *42*, 4467−4469.

(7) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

(8) Diastereoisomeric ratios were greater than 95:5 for **6** and greater than 97:3 for **8** as determined by analysis of the crude reaction product by ^{1}H NMR.

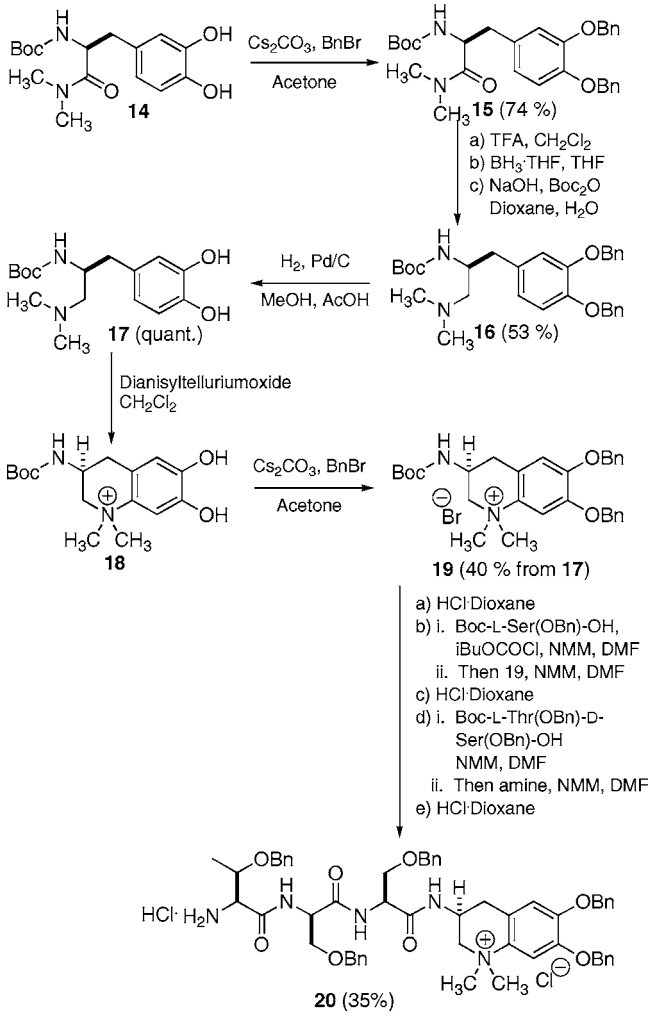
(9) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(10) Narasaka, K.,; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233−2238.

(11) Chen, K.-M.; Hardtmann, G. E.; Prasad, G. E.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158. See also: Sletzinger, M.; Verhoeven, T. R.; Volante, R. P.; McNamara, J. M.; Corley, E. G.; Liu, T. M.H. *Tetrahedron Lett.* **1985**, *26*, 2951−2954.

(12) Lee, H. T.; Woo, P. W. K. *J. Labelled Cpd. Radiopharm.* **1999**, *42*, 129−133.

Scheme 2. Synthesis of the Alkaloid Peptide Fragment **20**



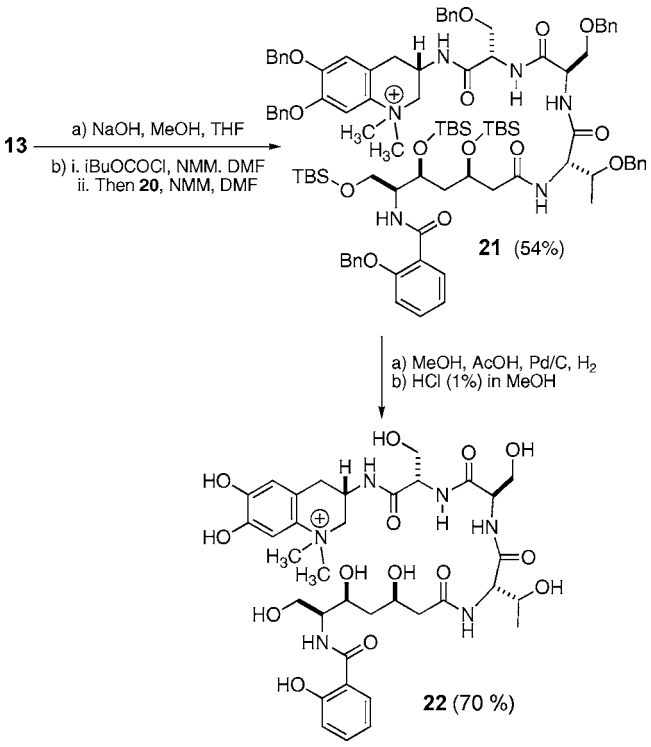
and MeOH. Both 3,5-syn compounds **7** and **9** could thus be isolated in good yield and high diastereoselectivity[13] after TBS protection and flash chromatography.

At this stage, we had one enantiomeric series of all possible diastereoisomers in hand. The four isomers **6**−**9** were then elaborated by cleavage of the Z group and condensation with O-Bn-protected salicylic acid to give compounds **12** and **13**. Compounds **10** and **11** were obtained after an additional introduction of a silyl ether protecting the primary hydroxy group (TBSCl, imidazole). Each of the four diastereoisomers **10**−**13** was thus obtained in 9−11 steps starting from Ser. In addition, *ent*-**12** and *ent*-**13** were also prepared starting from D-Ser.[14] Analysis of the NMR spectra of these compounds **10**−**13** revealed interesting patterns: In the natural product, the H(3) and H(5) resonances of the polyketide fragment appear at 4.09 and 4.06 ppm in D_2O, whereas the H(6) peak is observed at 4.21 ppm. Of all four isomers **10**−**13**, only compound **13** showed a similar pattern of peaks as observed in spectra of the natural product, although the resonances were shifted to lower field.[15] These spectroscopic arguments indicated the relative configuration to be (3*R**,5*S**,6*S**), and therefore, we advanced this diastereoisomer further.

We also developed an improved synthesis of the anachelin chromophore fragment (Scheme 2). Whereas in our previous route the diamine precursor **17** was prepared using a minimal protecting group strategy with free OH groups,[4] we found that protection of the hydroxy groups of the DOPA amide **14**[16] with Bn-groups, subsequent borane reduction of **15**, and deprotection of **16** proved by far superior. This diamine **17** was then converted via an oxidative aza annulation reaction using dianisyltelluriumoxide[17] to the tetrahydroquinolinium derivative **18**, which was again Bn protected under standard conditions. To this compound **19**, protected serine followed by a protected Thr−Ser dipeptide were condensed using the mixed anhydride method, which has proven superior to more elaborate coupling reagents with respect to ease of synthesis and purification. It must be pointed out that compounds such as **19** can be easily purified by flash chromatography on silica gel using CH_2Cl_2/MeOH as a solvent. The Boc-group was removed by HCl in dioxane to give the fragment **20** ready for coupling.

It was now time to merge the two fragments; therefore, the fully protected polyketide fragment **13** was saponified,[18] converted to the mixed anhydride, and coupled to the deprotected chromophore fragment **20** (Scheme 3). The fully

Scheme 3. Coupling of the Fragments to Synthetic Anachelin H



protected anachelin **21** was again obtained after FC in good yield. A two-step deprotection sequence of compound **21**, first by Pd/C and H_2 in a AcOH/MeOH mixture followed

(13) Diastereoselectivities were greater than 96:4 for **7** and greater than 97:3 for **9**.

by treatment with 1% HCl in methanol, gave synthetic anachelin H (**22**), whose physical data (NMR, MS, HPLC coinjection) were found to be identical to those of an authentic sample of the natural product.[19] Interestingly, whereas the HPLC analysis only shows the presence of **22**, the NMR spectrum reveals a minor derivative (less than 10%) of **22** which is in reversible equilibrium with anachelin H upon change of pH. As several congeners of anachelin have been isolated and partially shown to be equilibrated by acid,[1,2] this observation might help to clarify such biogenetic issues.[20] Spectroscopic investigations combined with the synthesis of these congeners are carried out and will be reported in the context of a full publication.

In conclusion, we have prepared synthetic anachelin H. Key features of this total synthesis include a stereodivergent preparation of all possible diastereoisomers of the polyketide fragment as well as a rapid entry into the tetrahydroquinolinium ring system using a tellurium-mediated oxidative aza annulation. This work now finally confirmed the relative and absolute configuration of four stereogenic centers of the polyketide alkaloid anachelin H by total synthesis.

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Supporting Information Available: Analytical data and experimental procedures for all new compounds as well as copies of spectra of intermediates and anachelin. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See Supporting Information for procedures and analytical data of all new compounds.

(15) See Supporting Information for the corresponding spectra.

(16) This compound is readily available from L-DOPA in two steps; see ref 4.

(17) Ley, S. V.; Meerholz, C. A.; Barton, D. H. R. *Tetrahedron* **1981**, *37*, 213−223. For a related application, see: Clews, J.; Cooksey, C. J.; Garratt, P. J.; Land, E. J.; Ramsden, C. A.; Riley, P. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4306−4315.

(18) Interestingly, both the methyl ester **13** as well as the derived acid display very similar R_f values on TLC.

(19) We thank Prof. Dr. H. Budzikiewicz for an authentic sample of Anachelin H.

(20) A change in pH could also induce other structural changes such as different protonation state or a change in conformation. For the solution structure of anachelin H, see: Gademann, K.; Budzikiewicz, H. *Chimia* **2004**, *58*, 212−214.