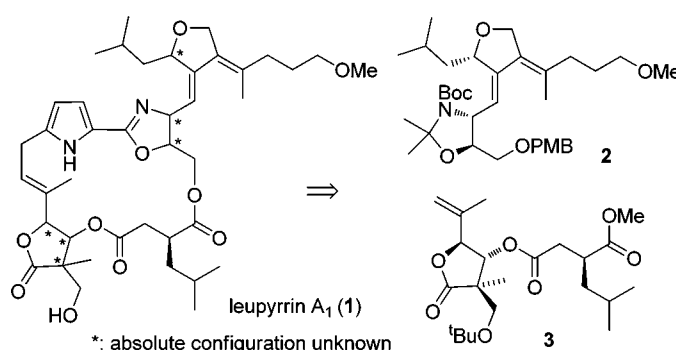# Stereoselective Synthesis of the Butyrolactone and the Oxazoline/Furan Fragment of Leupyrrin A₁

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ABSTRACT

Stereoselective syntheses of the Northern and the Southern fragments 2 and 3 of leupyrrin A₁ are reported. The convergent preparation of 2 is highlighted by a zirconocene-mediated one-pot cyclization–regioselective opening of an advanced diyne while the route to 3 involves a Krische allylation and a one-pot Sharpless dihydroxylation–cyclization. Comparison of the spectroscopic data with those reported for the natural product supports a relative stereochemical assignment within these heterocycles.

During the past decades, myxobacteria have proven to be a particularly rich source of structurally novel and diverse natural products with a broad range of biological activities.[1] The family of the leupyrrins was isolated as one of the main groups of secondary metabolites from *Sorangium cellulosum*, strains So ce705 and So ce690.[2] They demonstrate potent biological activities against various fungi and eukaryotic cells.[2] As shown in Scheme 1 for the main metabolite leupyrrin A₁ (**1**, Figure 1), their singular architectures are highlighted by a number of

structurally unusual motifs, including an unusually substituted γ-butyrolactone ring together with a pyrrole and an oxazoline ring which are embedded in a nonsymmetric macrodiolide core structure.[1] The side chain incorporates a unique unsymmetrically substituted furan ring with two alkyliden groups, one of them directly appending the chiral macrocyclic oxazoline. The potent biological properties and natural scarcity, coupled with their unique and intriguing molecular architectures, render the leupyrrins attractive synthetic targets. A synthesis is however severely hampered by the lack of full stereochemical knowledge, as merely one of the seven stereogenic centers (C-3′) has been rigorously assigned and only relative configurations have been tentatively proposed within the butyrolactone and the oxazoline fragments by conformational NMR studies.[2a]

As a prelude to devising a first total synthesis of the leupyrrins to unambiguously assign the stereochemistry and enhance the supply for biological evaluation, we report efficient syntheses of the Northern and the Southern fragments **2** and **3**. The concise routes proceed with high

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[†] Contributed to synthesis of **2** and **3**, including initial synthesis of **15a**.
[‡] Contributed to synthesis of **6** and large-scale synthesis of **15a**.
(1) For reviews, see: (a) Reichenbach, H.; Höfle, G. In *Drug Discovery from Nature*; Grabley, S., Thiericke, R., Eds.; Springer-Verlag: Berlin, 1999; pp 149–179. (b) Menche, D. *Nat. Prod. Rep.* **2008**, *25*, 905–918. (c) Weissman, K. J.; Müller, R. *Nat. Prod. Rep.* **2010**, *27*, 1276–1295.
(2) (a) Müller, R.; Bode, H. B.; Wenzel, S.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Nat. Prod.* **2003**, *66*, 1203–1206. (b) Bode, H. B.; Wenzel, S. C.; Irschik, H.; Höfle, G.; Müller, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4163–4167. (c) Kopp, M.; Irschik, H.; Gemperlein, K.; Buntin, K.; Meiser, P.; Weissman, K. J.; Bode, H. B.; Müller, R. *Mol. BioSyst.* **2011**, *7*, 1549–1563.

stereoselectivity and confirm the relative stereochemistry within the heterocyclic moieties.

As shown in Figure 1, these moieties may be disconnected from the natural product by an esterification, a ring-closing metathesis, and an oxazoline formation. At the beginning of our campaign the absolute configurations within the heterocycles were arbitrarily assigned while selection of the relative configurations was based on the proposal in the isolation paper.[2a] Finally, a modular synthetic route to set the stereogenic center at C-26 was pursued by late-stage diversification (*vide infra*).
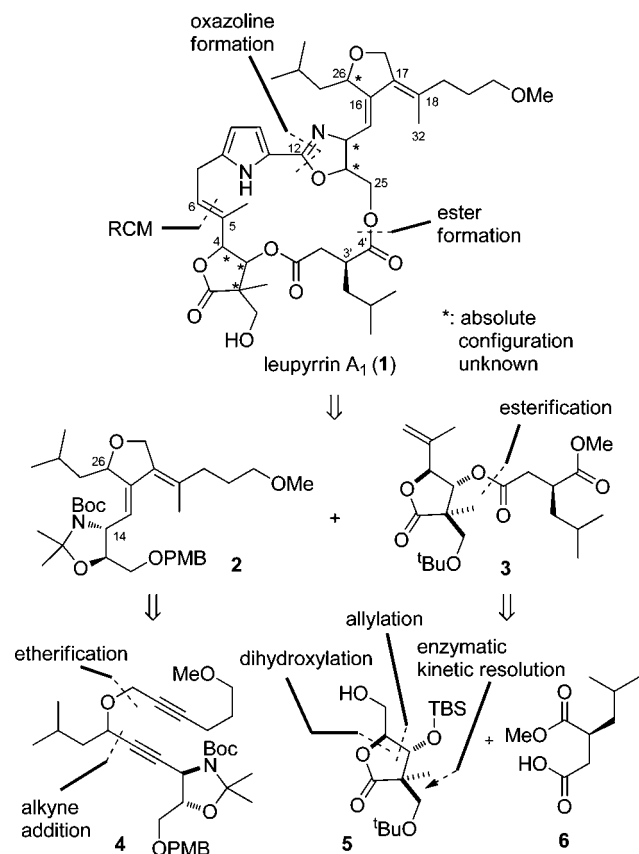

Figure 1. Synthetic approach to the Northern and Southern fragments of leupyrrin A$_1$ (**1**).

The synthesis of bis-alkylidene-substituted tetrahydrofuran of **2** should be accomplished by a Zr-mediated cyclization strategy, as recently developed in our group.[3] The required diyne **4** with either configuration at C-26 was to be synthesized from a stereodivergent alkyne addition and subsequent etherification. The γ-butyrolactone **3**, in turn, was envisioned to arise from an esterification of known acid **6** with fragment **5** whose *anti*-diol moiety was planned to arise from an asymmetric allylation and subsequent Sharpless' dihydroxylation and the quaternary

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stereocenter should be derived from an enzymatic diester hydrolysis catalyzed by PLE.[4]

As shown in Scheme 1, the synthesis of **3** started from known aldehyde **7**,[5] which was obtained in four steps from methyl dimethyl malonate.[4] Unfortunately, direct vinylation of **7** using different vinylating agents[6] resulted in either low conversion or poor diastereoselectivities. Instead, allylation following the protocol developed by Krische[7] afforded the homoallyl alcohol in good yield and excellent diastereoselectivity whose configuration was confirmed by Mosher ester analysis.[8]

Scheme 1. Synthesis of the Butyrolactone Fragment **3**
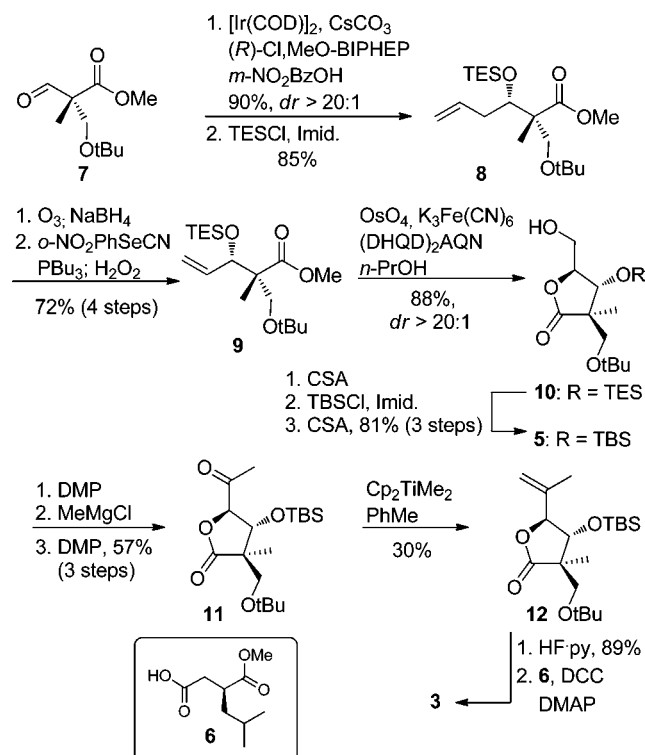
Subsequent TES-protection of the free alcohol afforded **8**, which was elaborated into **9** by ozonolysis, reductive workup, and subsequent elimination following the Grieco protocol.[9] Sharpless dihydroxylation[10] using the (DHQD)$_2$AQN ligand resulted in clean formation of the five-membered butyrolactone **10** as a single diastereomer

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(8) Interestingly, use of the (*S*)-Cl,MeO-BIPHEP ligand enabled access to the diastereomeric homoallylic alcohol in excellent diastereoselectivity, suggesting that substrate control is completely overridden by the catalyst.

in 88% yield without isolation of the intermediary diol due to the basic reaction conditions employed.[11] At this stage, it became necessary to transform **10** into its more stable TBS-congener **5** to secure reproducibly high yields for the ensuing introduction of the methylene unit. To this end, **5** was oxidized to an aldehyde and treated with MeMgCl to give a 1:1 diastereomeric mixture of the secondary alcohols which were directly oxidized to methyl ketone **11**. Next, installation of the required methylene group was examined which proved to be troublesome. None of the standard methylenation methods, such as Wittig,[12] Tebbe,[13] Peterson,[14] or Takai–Lombardo olefination[15] resulted in the formation of olefin **12**, presumably due to steric hindrance or inherent enolate formation under the basic reaction conditions. Trapping of the enolate as the corresponding vinyl triflate for a cross-coupling reaction also remained unsuccessful. Finally, base-free conditions using the Petasis reagent[16] gave rise to **12**, yet in only moderate yields (30%). Deprotection of the TBS-group with HF·py and subsequent esterification with acid **6**[17] proceeded uneventfully to give the fully elaborated fragment **3**.

We then turned our attention to the synthesis of Northern fragment **2**. As shown in Scheme 2, our route started from known aldehyde **13**, which was prepared in seven steps following a route developed by McLeod et al.[18] Introduction of the alkyne,[19] reduction of the ester with LAH, and subsequent PMB-protection proceeded smoothly giving **14** in 61% overall yield. Next, a modular construction of the stereogenic center at C-26 was pursued. While asymmetric alkyne addition to isovaleraldeyde

proved not feasible,[20] a chromatographically separable 1:1 mixture of **15a** and **15b** was obtained from addition of lithiated **14**. Diastereomerically enriched **15b** can be directly obtained from this mixture following an oxidation/reduction sequence. In detail, CBS-reduction[21] using the (*R*)-CBS oxazaborolidine afforded (26*R*)-configured **15b** in excellent yield and a preparatively useful diastereomeric ratio of 6:1.[22] Epimeric **15a**, in turn, may be selectively accessed by a Mitsunobu inversion from **15b**.[23]

Scheme 2. Joint Synthesis of **15a** and **15b** by a Late Stage Diversification Strategy
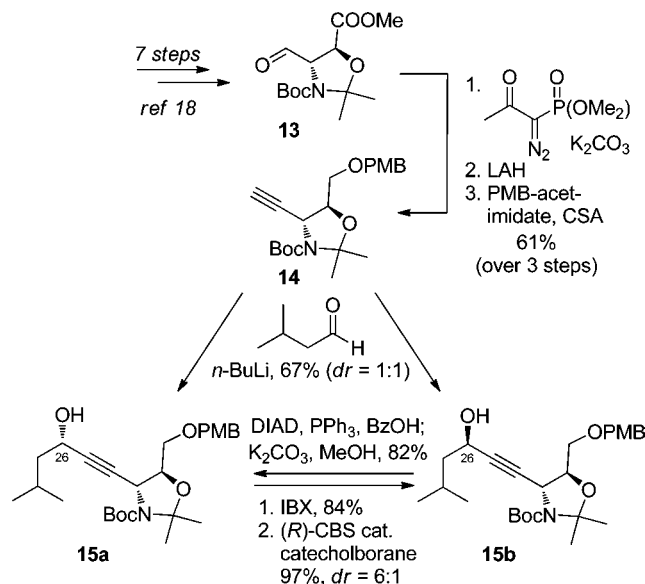
Isomer **15a** was then further homologated with tosylate **16** to access diyne **4**. Efforts were directed to apply our key Zr-mediated cyclization/regioselective opening sequence to access the furan core of leupyrrin A$_1$ (Scheme 3) following a sequence previously developed in our group.[3] To this end, **4** was subjected to a freshly prepared zirconocene solution[24] at −78 °C. The mixture was then allowed to warm to room temperature, and the reaction progress was monitored by TLC. After conversion to zirconacyclopentadiene **17** was complete, regioselective opening was accomplished *in situ* by addition of 2.00 equiv of NBS at −78 °C. Gratifyingly, bromide **18** was obtained as a single regioisomer with the desired constitution in 88% yield, in

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(11) It should be noted that the use of (DHQ)₂AQN also resulted in the formation of the C3−C4 antidisubstitued butyrolactone as the only diastereomer, assuming that, in this case, substrate control was stronger than the influence of the catalyst.

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(20) (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688. (b) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760–13761. (c) Trost, B. M.; Sieber, J. D.; Qian, W.; Dhawan, R.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 5478–5481.
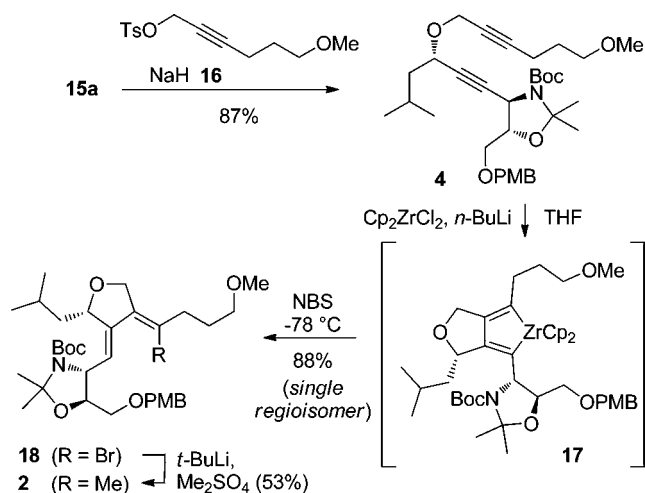
(21) (a) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863. (b) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606–1608. (c) Mazur, P.; Nakanishi, K. *J. Org. Chem.* **1992**, *57*, 1047–1051. (d) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.

(22) In contrast, asymmetric reduction of the ynone leading also directly to (26*S*)-configured **15a** failed, possibly due to steric shielding of the *re*-face of the ketone by the bulky Boc-group.

(23) For a review on the Mitsunobo reaction, see: Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551–2651.

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Scheme 3. Zr-Mediated Oxidative Cyclization of **4** Leading to the Furan Core of the Leupyrrins

Figure 2. Selected NMR data determined for the Southern (a) and Northern fragment (b).

agreement with our previously developed mechanistic proposal based on a remote coordination in such type of oxidative ring cleavages.[3] The following halogen−lithium exchange was then initiated by reaction with *t*-BuLi and addition of Me_2SO_4 leading to the formation of the targeted C-18 methyl-substituted diene **2**.[25]

Importantly, the NMR data of both synthetic fragments were closely related to those reported for the natural product.[2] As exemplarily shown for **5** in Figure 2a, all butyrolactone moieties displayed similar sets of NOE correlations as those reported for natural leupyrrin A_1, *i.e.* from H-4 to both Me-2 and from H-3 to both H-22 and Me-5. In a similar fashion, also synthetic **2** resided in a closely related conformation to that reported for natural **1**, as indicated by a similar set of coupling constants (Figure 2b).[26] These data confirm both the constitution and relative configuration within these segments of the natural product as originally proposed by the Müller group.[2]

In summary, we have devised efficient stereoselective syntheses of the fully functionalized Northern and Southern fragments **2** and **3** of the leupyrrins. Preparation of the highly substituted butyrolactone **3** was based on a

stereoselective allylation and dihydroxylation to install the C3/C4 stereocenters with high selectivity, while synthesis of **2** relied on a one-pot zirconocene-mediated diyne cyclization−regioselective opening, which proceeds with excellent and predictable regioselectivities. Notably, this presents one of the most advanced applications of Zr-mediated oxidative cyclization in complex target synthesis. Importantly, the stereogenic center at C-26 may be set with either configuration by a late stage diversification strategy adding considerable flexibility to the route. The close spectroscopic similarity of these fragments with the data reported for the natural products supports the assignment of the relative configuration as shown. With this stereochemical confirmation in hand efforts can now be directed toward the development of a modular synthetic strategy to enable a first total synthesis of the leupyrrins.

Supporting Information Available. Experimental details, spectral data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Diene **2** was obtained as a 4:1 mixture of **2** and the corresponding diene which was formed by hydrolysis of lithiated **18**. See Supporting Information for further details.

(26) A characteristic NOE correlation from H-14 to H-26 was also observed, which has not been mentioned in the isolation manuscript. This may suggest the configuration at C-26 of *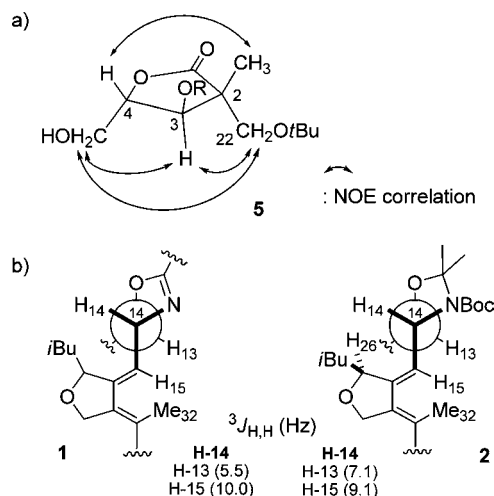*2** could be opposite to that in the natural product.