



Total Synthesis Hot Paper

The Total Synthesis of Chondrochloren A

Yannick Linne, Elisa Bonandi, Christopher Tabet, Jan Geldsetzer, and Markus Kalesse*

In memory of Professor Wittko Francke (1940–2020)

Abstract: The first total synthesis of chondrochloren A is accomplished using a 1,2-metallate rearrangement addition as an alternative for the Nozaki-Hiyama-Kishi reaction. This transformation also avoids the inherent challenges of this polyketide segment and provides a new, unprecedented strategy to assemble polyketidal frameworks. The formation of the *Z*-enamamide is accomplished using a *Z*-selective cross coupling of the corresponding amide to a *Z*-vinyl bromide.

The chondrochlorens A and B were isolated during a screening campaign for biologically active natural products from myxobacterium *Chondromyces crocatus* (Cmc5) by the groups of Höfle and Reichenbach in 2003 (Figure 1).^[1] The antibiotic potential of the chondrochlorens is barely tapped. So far, only agar diffusion tests were reported disclosing only weak antibiotic activity against *Micrococcus luteus*, and *Schizosaccharomyces bombe*. Only traces of inhibition against *B. subtilis*, and *Staphylococcus aureus* were observed.^[1]

Due to our interest in polyketide-peptide hybrids^[2] we initiated the synthesis of chondrochloren A (1) as it exhibits three distinct segments with synthetically challenging sub-units. One can envision the synthesis of the *Z*-enamamide moiety through a *Z*-selective Buchwald-type cross coupling^[3] using the corresponding amide and *Z*-vinyl bromide and the middle triol segment to be derived from ribonolactone (Figure 1). However, the western polyketide segment (C7 to C14) which looks as if it could be easily made accessible through

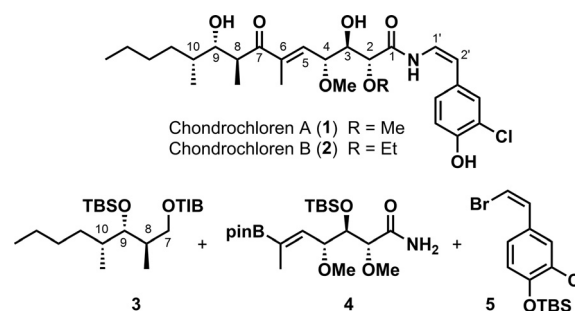


Figure 1. Structures of chondrochloren A and B and their retrosynthetic analysis. TBS = *tert*-butyldimethylsilyl, TIB = 2,4,6-triisopropylbenzoyl, pin = pinacolato.

established aldol chemistry,^[4] proved synthetic challenges which we solved using a 1,2-metallate rearrangement. Here this strategy was employed for the first time and its incorporation into a successful total synthesis proves it to be a powerful alternative to the Nozaki-Hiyama-Kishi reaction.^[5]

The challenge of generating polyketide fragments of this kind was already described by Evans and co-workers in 1991.^[4] They described different *E*- and *Z*-enolates of alpha-chiral ethyl ketones and their stereochemical outcome in aldol reactions. As shown in Scheme 1, both the *Z* and *E*-enolate generate the product with the methyl groups on both sides of the keto group *syn* to each other. This analysis would therefore exclude constructing this fragment through an aldol reaction as shown below.

Equally, an aldol disconnection between C8 and C9 would not provide the desired isomer as it would require an *E*-enolate, which is disfavored due to the allylic strain situation. Both disconnections were investigated in the course of our synthetic endeavors and did not yield any useful yield and/or selectivities (Scheme 2).

Being aware of these analyses and having them confirmed by not being able to establish either one of these aldol disconnections in our laboratories, we turned our focus to 1,2-metallate transformations that were developed by Matteson and Hoppe^[6] and brought to a new level of applications by Aggarwal.^[7] It should be pointed out that this 1,2-metallate rearrangement serves as an attractive alternative to the Nozaki-Hiyama-Kishi reaction^[5] and can be performed in a stereoselective manner. It provides the additional advantage that one would be able to add the completely established polyketide segment without the necessity to adjust oxidation states later on as was required for the disconnection depicted in Scheme 3.

[*] Y. Linne, Dr. E. Bonandi, C. Tabet, Prof. Dr. M. Kalesse

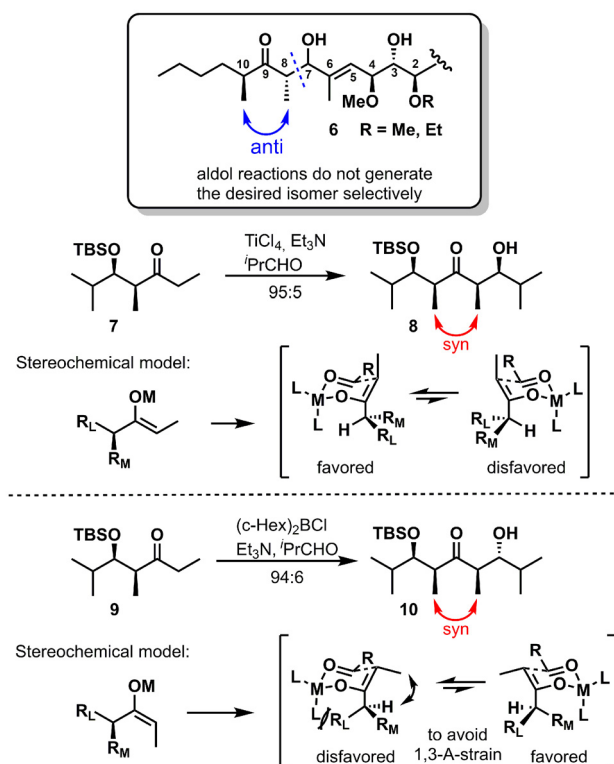
Institute for Organic Chemistry
Gottfried Wilhelm Leibniz Universität Hannover
Schneiderberg 1B, 30167 Hannover (Germany)
E-mail: markus.kalesse@oci.uni-hannover.de

Prof. Dr. M. Kalesse
Centre of Biomolecular Drug Research (BMWZ)
Gottfried Wilhelm Leibniz Universität Hannover
Schneiderberg 38, 30167 Hannover (Germany)

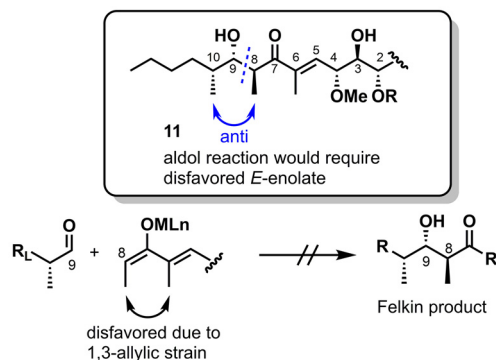
Dr. J. Geldsetzer, Prof. Dr. M. Kalesse
Helmholtz Centre for Infection Research (HZI)
Inhoffenstrasse 7, 38124 Braunschweig (Germany)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/anie.202016072>.

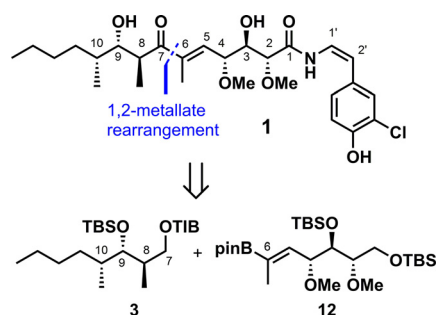
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Scheme 1. Retrosynthetic analysis of the C7 to C14 aldol segment.

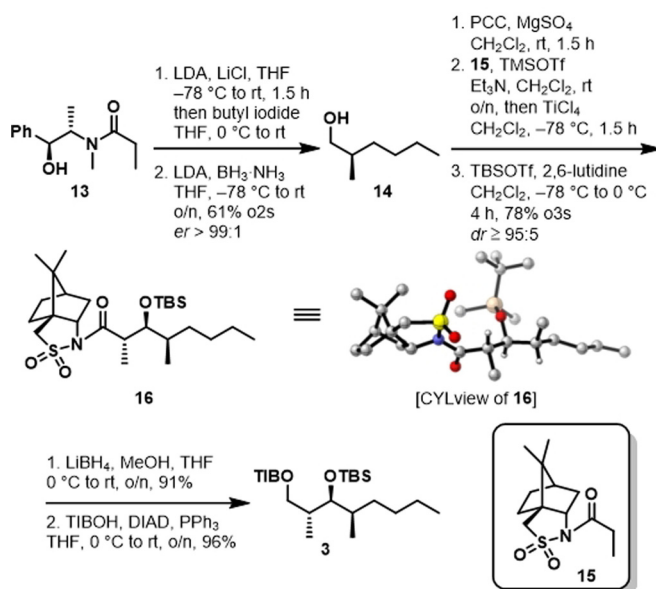


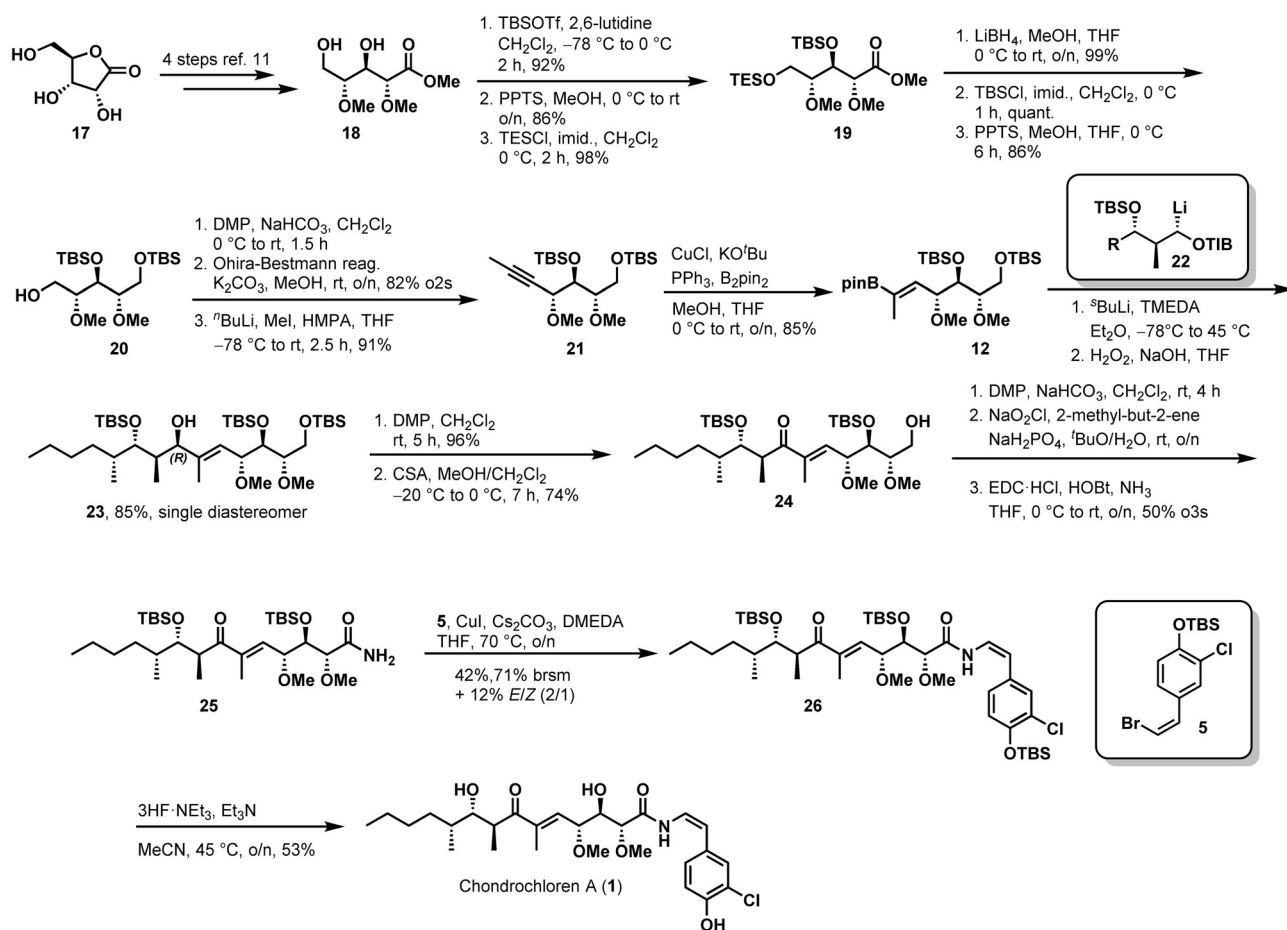
Scheme 2. Retrosynthetic analysis of the C8 to C9 aldol disconnection.

Scheme 3. Formation of the C6-C7 carbon bond through 1,2-metallate rearrangement. TBS = *tert*-butyldimethylsilyl, TIB = 2,4,6-triisopropylbenzoyl, pin = pinacolato.

The synthesis of the polyketide segment **3** starts with a Myers alkylation.^[8] Reduction of the so-obtained product provides alcohol **14** which was oxidized using PCC to obtain its corresponding aldehyde. The desired stereotriade was generated through an Oppolzer aldol reaction with TiCl₄ as the Lewis acid.^[9] The configuration was confirmed at this point through an X-ray analysis of the TBS-protected secondary alcohol **16**. Reductive removal of the chiral auxiliary and introduction of the TIB-group via a Mitsunobu reaction^[10] provides the C7-C14 segment (**3**) of chondrochloren A (**1**) in 42% yield over 7 steps ready to undergo a 1,2-metallate rearrangement for coupling with the middle segment **12** (Scheme 4).

The synthesis of the polyoxygenated middle fragment commenced with a known four-step sequence starting from ribonolactone (**17**) (Scheme 5).^[11] Ester **18** was double TBS-protected and the primary hydroxy group liberated by treatment with PPTS in MeOH at room temperature. The primary OH group was then TES protected in order to have it later selectively liberated for the alkyne formation. A three-step sequence of reduction, TBS protection and selective TES deprotection generated pentaol **20** with one primary hydroxyl available for the aforementioned alkyne formation. This was achieved using the Ohira-Bestmann protocol.^[12] Finally, the alkyne was methylated with *n*BuLi and MeI in THF-HMPA. For the hydroboration we relied on a copper-mediated hydroboration using bis(pinacolato)diboron^[13] to provide vinyl boronic ester **12** in 42% over 10 steps starting from literature known ester **18**.^[11] This set the stage for the 1,2-metallate rearrangement with TIB ester **3**. We deliberately chose this bond for the pivotal disconnection as one would not have to control the configuration at C7 since this center would be oxidized in the course of the synthesis. As we will describe

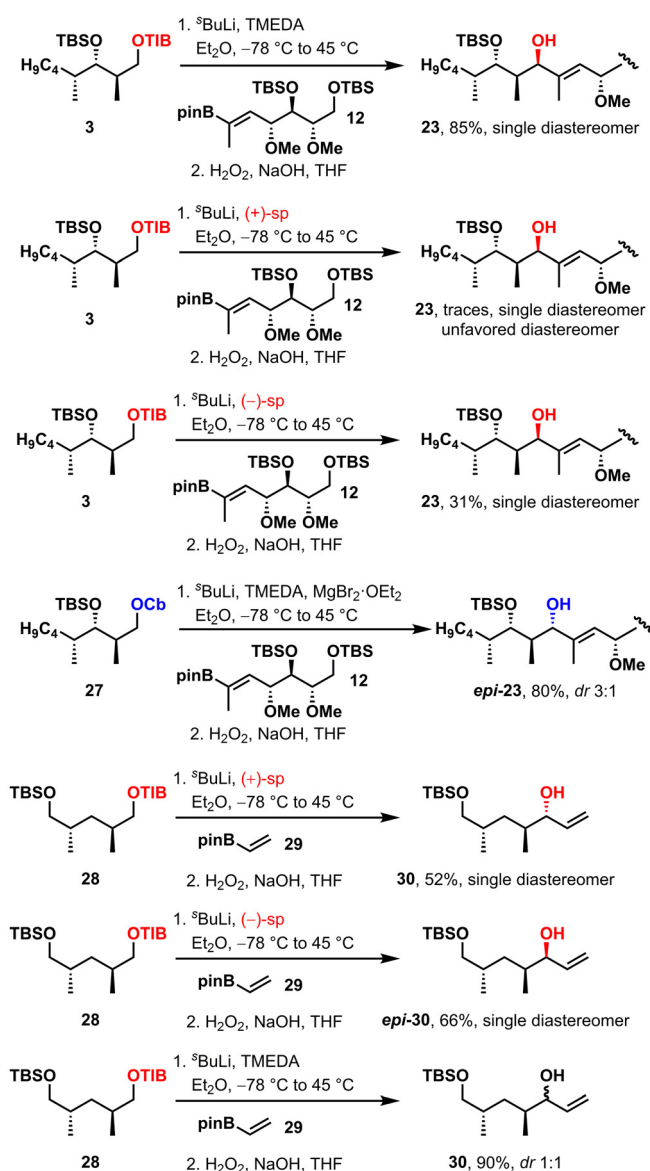
Scheme 4. Synthesis of the C7 to C14 segment (**3**).^[18] DIAD = diisopropyl azodicarboxylate, PCC = pyridinium chlorochromate, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TIB = 2,4,6-triisopropylbenzoyl, o/n = overnight, o2s = over two steps, o3s = over three steps.



Scheme 5. Synthesis of chondrochloren A (1). CSA = camphor-10-sulfonic acid, DMEDA = *N,N'*-dimethylethylenediamine, DMP = Dess–Martin periodinane, EDC = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, HMPA = hexamethylphosphoramide, HOBT = 1-hydroxybenzotriazole, pin = pinacolato, PPTS = pyridinium *p*-toluenesulfonate, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TIB = 2,4,6-triisopropylbenzoyl, TMEDA = *N,N,N',N'*-tetramethylethylenediamine, o/n = overnight, o2s = over two steps, o3s = over three steps.

in detail below, standard protocol with sparteine^[6,7] gave only poor yields. On the other hand, deprotonation of **3** with *s*BuLi in the presence of TMEDA provided the lithiated species **22** and subsequent treatment with vinyl boronic ester **12** afforded the 1,2-rearranged product **23**. Unexpectedly, it provided the desired product in very good yields (85%) and as a single stereoisomer. With compound **23** in hand, the synthesis continued with the aforementioned oxidation of the secondary alcohol and liberation of the primary hydroxy group, which was oxidized to its corresponding acid.^[14] Amide formation to give **25** was achieved with EDC, HOBT and NH₃.^[15] This set the stage for the endgame of the synthesis. Using *Z*-vinyl bromide **5**^[11] and CuI, DMEDA and Cs₂CO₃ led to the envisioned Buchwald coupling.^[3] In contrast to previous model studies, we observed the emergence of the *E*-isomer.^[11] We believe that this is due to subsequent isomerization as we observe varying amounts of the isomers on different reaction times and in samples of the authentic material. Finally, the synthesis of chondrochloren A (**1**) (23 linear steps from ribonolactone (**17**), 0.8% yield) was enabled by a global TBS-deprotection with HF·NEt₃.

As mentioned above, our early attempts on the synthesis of this natural product used aldol strategies, which failed miserably (see Supporting Information). We were therefore very pleased to notice that the 1,2-metallate rearrangement worked so well and can be used as a powerful tool for setting up C–C bonds. This transformation is widely underexploited and can serve as a valuable alternative to the Nozaki-Hiyama-Kishi reaction,^[5] in particular as it can be performed in a stereoselective manner. To investigate this in more detail we performed this particular C–C bond formation in the presence of sparteine and with the Cb group instead of TIB. Surprisingly, in the presence of (+)-sparteine, only traces of the rearranged product were observed and switching the TIB to a Cb group led to the opposite stereoisomer. The sense of chirality generally induced by (+)-sparteine is opposite to the one observed in the transformation of **3** to **23** (Scheme 6). Obviously, the inherent selectivity overrules the stereocontrolling properties of (+)-sparteine which is supported by the higher yields of the same transformation (**3**→**23**) using (–)-sparteine. The low yields are therefore the consequence of the mismatched situation for this substrate. Hoppe already reported selected examples in which a diastereoselective



Scheme 6. Diastereomeric selectivities of the 1,2-metallate rearrangement. Cb = *N,N*-diisopropylcarbamoyl, pin = pinacolato, TBS = *tert*-butyldimethylsilyl, TIB = 2,4,6-triisopropylbenzoyl, TMEDA = *N,N,N',N'*-tetramethylethylenediamine, sp = sparteine.

metallate rearrangement was observed even in the absence of sparteine.^[16] To further explore this transformation as an alternative to the Nozaki-Hiyama-Kishi reaction TIB ester **28**^[17] was subjected to 1,2-metallate rearrangements and different conditions with vinylboronic acid pinacol ester **29**. Gratifyingly, both enantiomers of sparteine accomplished a stereoselective metallate rearrangement and the corresponding allylic alcohols **30** and **epi-30** were obtained as single isomers (Scheme 6). These findings further support this strategy as an alternative to the NHK-reaction. On the other hand, the absence of sparteine lead to a 1:1 diastereomeric mixture of isomers which indicated that the chiral induction observed for compound **3** requires a β -chiral center. Even more remarkably, here we show in the context of a polyketide synthesis for the first time the switch of

selectivity by changing from a TIB to a Cb group. As this serves as an alternative for the Nozaki-Hiyama-Kishi reaction,^[5] the generation of diastereomeric alcohols through alteration of the carbanion-stabilizing group holds the potential to become a new highly valuable tool for total synthesis. The scope and limitations of this protocol with other substrates will be reported in due course.

In summary, we have accomplished the first total synthesis of chondrochloren A (**1**), a complex secondary metabolite from myxobacteria. The synthesis relied on a 1,2-metallate rearrangement in one of the key steps in order to overcome the inherent selectivity problems of the polyketide portion. The endgame of the synthesis used a *Z*-selective Buchwald-type of cross coupling to complete the first total synthesis of this natural product.

Acknowledgements

We are very grateful to Dr. Rolf Jansen (HZI) for authentic chondrochloren A. A generous gift of B_2pin_2 from Allychem is also appreciated. We thank Dr. J. Fohrer, M. Rettstadt and D. Körtje for detailed NMR analysis, A. Schulz and R. Reichel for mass spectra and Dr. G. Dräger for X-ray analysis. In terms of preparation of this manuscript, we thank Alina Eggert, Giada Tedesco and Daniel Lücke. Open access funding enabled and organized by Projekt DEAL.

Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,2-metallate rearrangement · chondrochloren · Hoppe anion · natural product synthesis · polyketides

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- [18] Deposition Number 2046919 (for **16**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Manuscript received: December 2, 2020

Revised manuscript received: January 13, 2021

Accepted manuscript online: January 15, 2021

Version of record online: February 25, 2021