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Total synthesis of both enantiomers of the biosurfactant aureosurfactin *via* bidirectional synthesis with a chiral Horner–Wittig building block†

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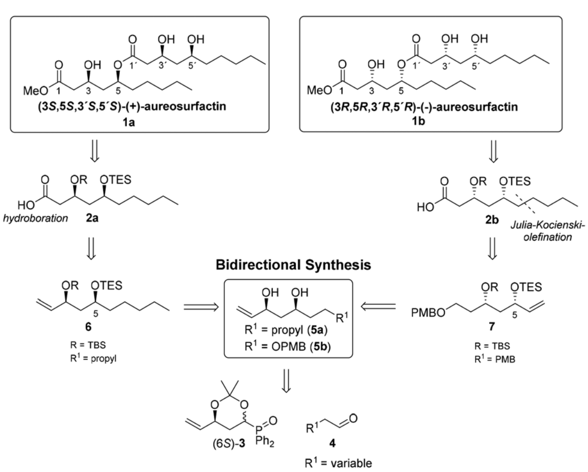
Aureosurfactin is a novel biosurfactant that exhibits similar surface tension activity to known biosurfactants. In this work, we now report a facile synthesis for aureosurfactin using a bidirectional synthetic strategy. Both enantiomers of the target compound were accessed from the (*S*)-building block, derived from the same chiral pool starting material.

Surfactants are distinguished by their amphiphilic nature:[1] their structure consists of both hydrophobic and hydrophilic moieties, enabling them to reduce surface and interfacial tension by accumulation of the respective hydro- or lipophilic parts on the surface of one phase of two immiscible fluids.[2–4] Surfactants are widely used in cosmetic, textile, pharmaceutical and food industries, making them indispensable for daily use.[5] However, the wide range of applications of mainly petroleum-based surfactants also contributes to environmental pollution, as they are typically not fully biodegradable.[6,7] As a result, biosurfactants gained in importance in recent years, and the investigation of non-toxic, biodegradable and thus environmentally friendly biosurfactants is currently of utmost interest for the respective chemical industries.[1b,8–10] In 2016, Yun *et al.* isolated the novel biosurfactant aureosurfactin (**1**) from *Aureobasidium pullulans*, with a surface tension activity similar to those of known biosurfactants with commercial potential such as rhamnolipid.[8,11] Aureosurfactin (**1**) was characterized as a methyl ester of an acyclic dimer of either (3*R*,5*R*)- or (3*S*,5*S*)-3,5-dihydroxydecanoic acid (Scheme 1). The relative stereochemistry of the natural product was determined by comparison of ^{13}C NMR spectra with those of (3*R*,5*R*)-3,5-dihydroxydecanoic acid, its trimer exophilin A[12] and the related halymecins.[13] The absolute configuration of **1** was not elucidated and no values for optical rotation were provided. However, based on the isolation of (3*R*,5*R*)-3,5-dihydroxy decanoic acid from *Aureobasidium pullulans*[14] and its abundance as structural unit of natural products such as (+)-(3*R*,5*R*)-3-hydroxy-5-decanolide,[15] exophilin A,[12] halymecins[13] and the cyclic dimer verbalactone[16] we consider the (3*R*,5*R*,3′*R*,5′*R*)-configuration of aureosurfactin (**1b**) as being the more likely one.

Due to the uncertainty with regard to the absolute configuration of the natural surfactant, we decided to develop a *de novo* synthesis for both enantiomers of aureosurfactin (**1**). We point out that several syntheses of (3*R*,5*R*)-3,5-dihydroxydecanoic acid have been described in connection with the synthetic entries toward verbalactone,[17] The synthesis of methyl (3*S*,5*S*)-3,5-dihydroxydecanoate has been reported by Mineeva.[18] For the construction of (3*S*,5*S*,3′*S*,5′*S*)- and (3*R*,5*R*,3′*R*,5′R)-aureosurfactin (**1**), respectively, we envisioned the protected 3,5-dihydroxydecanoic acids **2a** und **2b** as key intermediates where the 5-OH bears a triethylsilyl-(TES) group that can be selectively removed over the *tert*-butyldimethylsilyl-(TBS) group attached at the 3-OH, thus making the coupling of both frag-



Scheme 1 Access to both enantiomers of aureosurfactin (**1**) *via* bidirectional synthesis starting from a Horner–Wittig building block.

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ments *via* ester formation possible. On the other hand, global removal of all remaining silylether protecting groups in one step, following the connection of the fragments, was also possible.

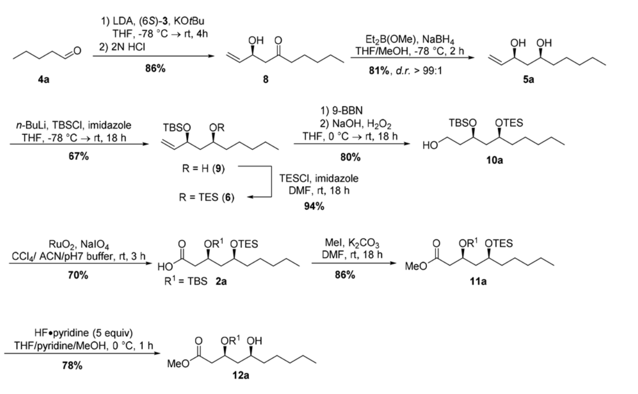
For the synthesis of both enantiomers **2a** and **2b** we selected our recently developed modular strategy for the diastereoselective synthesis of *syn*- and *anti*-1,3-polyol units based on the chiral diphenylphosphane oxide (6*S*)-**3** (Scheme 1),[19,20] which can be easily prepared from readily available and inexpensive 2-deoxy-D-ribose in seven steps.[21] A Horner–Wittig reaction with aldehydes **4a** (R = *n*Pr) and **4b** (R = OPMB), respectively, and a subsequent *syn*-reduction should provide the 1,3-diols **5a** and **5b**. The preparation of (3*S*,5*S*)-3,5-dihydroxydecaonic acid derivative **2a** should be obtained from **5a** *via* sequential silyl protection. The resulting alkene **6** should afford the carboxylic acid **2a** by hydroboration of the double bond and subsequent oxidation of the resulting primary alcohol. The retrosynthetic plan for the construction of the (3*R*,5*R*)-enantiomer **2b** included first a sequential silyl protection of **5b** to give the alkene **7**. The prolongation of the vinyl- to a 1-pentenyl side chain proceeded *via* Lemieux–Johnson oxidation and a subsequent Julia–Kocienski olefination. Following simultaneous hydrogenation of the olefinic double bond and PMB-deprotection, acid **2b** should be obtained by oxidation of the primary alcohol.

This synthetic strategy for the first total synthesis of (+)- and (−)-aureosurfactin (**1**), starting with a mutual chiral pool-derived building block (6*S*)-**3**, demonstrates another facet of how to easily access 1,3-polyol-containing structures with the use of Horner–Wittig methodologies: chiral diphenylphosphane oxide **3** is rapidly elaborated in both directions, thus providing a fully controlled entry to both enantiomeric series of the desired target compounds.

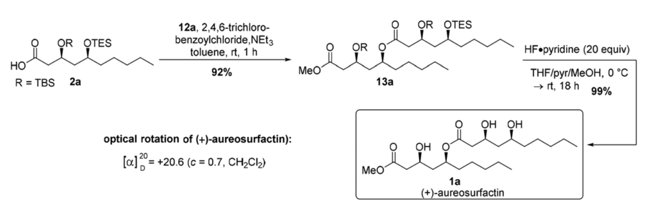
The synthesis of (3*S*,5*S*,3′*S*,5′*S*)-aureosurfactin (**1a**) started with the Horner–Wittig reaction of valeraldehyde **4a** and chiral building block (6*S*)-**3** to obtain β-hydroxyketone **8** in 86% yield (Scheme 2). Subsequent Narasaka–Prasad reduction[22] furnished *syn*-diol **5a** in 81% yield with an excellent diastereoselectivity (d.r. >99 : 1), after purification. Selective TBS-protection of the allylic alcohol gave rise to silyl ether **9** in 67% yield.[23] Protection of the remaining secondary alcohol using TESCl yielded silyl ether **6**, and hydroboration of the double bond followed by oxidation then provided the primary alcohol **10** in 75% over two steps. We then used an oxidation method developed by Paterson *et al.*[24] to obtain the carboxylic acid **2a** in 70% yield in one step from alcohol **10a**, employing ruthenium dioxide and sodium periodate. Subsequent methylation with iodomethane and potassium carbonate following the protocol of Nakata *et al.*[25] gave methyl ester **11a** in high yield. Next, we explored different conditions for the selective TES-deprotection: the use of standard conditions like PPTS, CSA or TFA led only to undesired cyclization products, while using 5 equivalents of the less acidic HF·pyridine complex[26] at 0 °C gave the desired product **12a** in excellent 94% yield (Scheme 2).

With acid **2a** and alcohol **12a** in hand, we planned to connect the fragments with classical Yamaguchi esterification conditions.[27] Gratifyingly, the reaction proceeded smoothly to provide the envisaged ester product **13a** in 92% yield (Scheme 3). The following global deprotection of the silyl ethers with 20 equivalents of HF·pyridine complex[26] gave the desired (3*S*,5*S*,3′*S*,5′*S*)-(+)-aureosurfactin (**1a**) in almost quantitative yield. Hence, we were able to synthesize 39 mg of **1a**, with an overall yield of 15% through the longest linear sequence of 10 steps (Scheme 3).

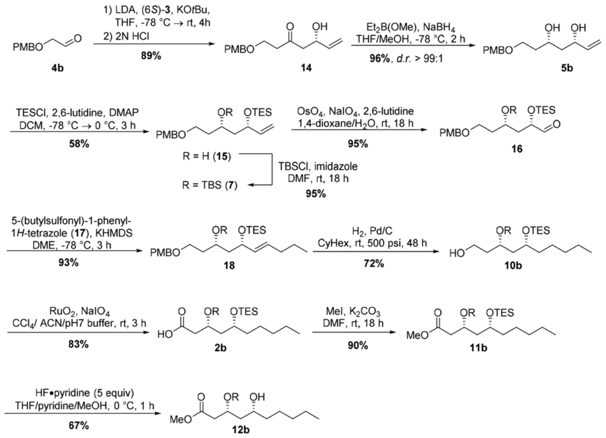
Next, we envisaged the total synthesis of the other enantiomer, (3*R*,5*R*,3′*R*,5′*R*)-aureosurfactin (**1b**). A corresponding synthesis using the respective (6*R*)-enantiomer of building block **3** was inapplicable, due to the high costs for 2-deoxy-L-ribose that would be required as starting material for building block synthesis. Instead, our retrosynthetic approach for (3*R*,5*R*,3′*R*,5′*R*)-**1** envisioned the above-described bidirectional synthesis involving a Horner–Wittig reaction of (6*S*)-**3** with 2-((4-methoxybenzyl)-oxy)-acetaldehyde (**4b**),[28] which gave rise to the β-hydroxyketone **14** in 89% yield (Scheme 4). Subsequent reduction of **14** by employing Narasaka-Prasad conditions yielded *syn*-diol **5b** in 96% yield and with good diastereoselectivity (d.r. >99 : 1). The following selective TES-protection of the allylic alcohol was accomplished in moderate 58% yield with TESCl in the presence of 2,6-lutidine and DMAP.[29] After TBS-protection, Lemieux–Johnson oxidation of the resulting silyl ether **7** gave the aldehyde **16** in 90% yield over two steps. Julia–Kocienski olefination with sulfone **17**, which was generated over two steps starting from *n*-butanol (see ESI†), and subsequent hydrogenation gave primary alcohol **10b** in 67% over



Scheme 2 Synthesis of the intermediates **2a** and **12a** of (+)-aureosurfactin (**1a**).



Scheme 3 Final steps of the total synthesis of (+)-aureosurfactin (**1a**).

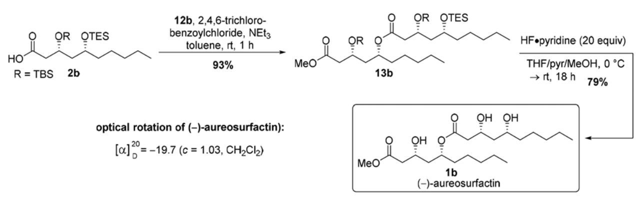


Scheme 4 Synthesis of the intermediates **2b** and **12b** of (−)-aureosurfactin (**1b**).

two steps. Oxidation of the hydroxy group using ruthenium dioxide and sodium periodate afforded carboxylic acid **2b** in high yield. In analogy to the other enantiomer the methyl ester fragment **12b** of (3*R*,5*R*,3′*R*,5′*R*)-**1b** was obtained *via* methylation of the acid with iodomethane and potassium carbonate and a selective TES-deprotection with five equivalents of HF·pyridine complex[26] at 0 °C.

After Yamaguchi esterification[27] of carboxylic acid **2b** with alcohol **12b** and global deprotection with HF·pyridine complex,[26] we obtained 50 mg of the desired product (3*R*,5*R*,3′*R*,5′*R*)-(−)-aureosurfactin (**1b**) in 73% over two steps (Scheme 5). In total, (−)-aureosurfactin (**1b**) was successfully obtained in an overall yield of 11% through the longest linear sequence of 12 steps.

In a simple experimental setting, we verified the described surface tension activity of aureosurfactin (**1**): to this end, the synthetic compound was dissolved in distilled water at a concentration of 1 mg per 100 mL, and 50 µL of the resulting solution were carefully placed on Parafilm and the degree of spreading was measured across the diameter (Fig. 1; 50 µL of distilled water were used as control). The reproducible results showed that the solutions containing either enantiomer have indeed a lower surface tension than the water.[11] Surprisingly for us, the racemic mixture of the two aureosurfactin enantiomers disrupts the surface tension of water to an even greater extent, an effect that may be further studied by others.



Scheme 5 Final steps of the total synthesis of (−)-aureosurfactin (**1b**).

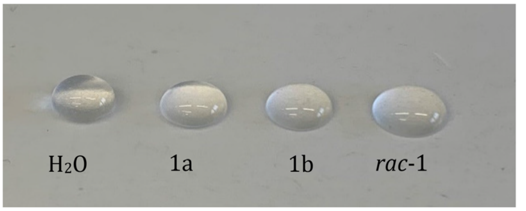


Fig. 1 First studies for the comparison of surface tension activity of **1a** and **1b** and the racemic mixture of **1**.

Conclusions

In conclusion, we have described a bidirectional synthesis of both enantiomers of aureosurfactin (**1**), starting from the chiral Horner–Wittig building block (6*S*)-**3**. While (3*S*,5*S*,3′*S*,5′*S*)-(+)-**1a** could be synthesized in a ten-step sequence from valeraldehyde, with an overall yield of 18%, the synthesis of (3*R*,5*R*,3′*R*,5′*R*)-(−)-**1b** required 12 synthetic steps with an overall yield of 13.5%. The structure and the relative stereochemistry proposed by Yun *et al.*[11] were confirmed, making both enantiomers accessible through *de novo*-synthesis.

Conflicts of interest

There are no conflicts to declare.

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