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## COMMUNICATION

## Synthesis of the C50 Diastereomers of the C33–C51 Fragment of Stambomycin D

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**As products of genome mining, the stereochemical assignment of the macrolide antibiotics stambomycins A–D has been made on the basis of sequence analysis of the associated polyketide synthase, aside from two stereocentres at C28 and C50. Here we describe syntheses of two C50 diastereomers of the C33–C51 region of the stambomycins, which support the PKS-based configurational assignment, and establish a strategy suitable for access to the extended stambomycin framework.**

The stambomycins are a family of macrolide natural products discovered and isolated from *Streptomyces ambofaciens* by Challis, Aigle and co-workers using a genome mining approach (Figure 1a).<sup>1–4</sup> Differing only in the nature of their C26 alkyl sidechains, these molecules exhibit potent anti-tumour and anti-bacterial activities. The connectivity, and the identity of the majority of the stereocentres of the natural product framework, could be predicted by sequence analysis of the polyketide synthases responsible for its assembly,<sup>5–8</sup> with the exception of the stereocentres at C28 and C50 which are installed by cytochrome P450-catalyzed oxidations.<sup>9</sup> While an unequivocal validation of stereochemistry remains to be achieved, confirmation of the sequence analysis predicted stereostructure would underline the value of this method,<sup>10–14</sup> compared to other structural assignment techniques such as NMR spectroscopy<sup>15–18</sup> (including associated computational analysis),<sup>19–24</sup> which can be ambiguous for molecules of such complexity.<sup>25–28</sup>

We recently described a synthesis of the C1–C27 region of stambomycin D, in which the spectroscopic data of the synthetic truncate showed a good match with that of the

natural product.<sup>29</sup> Continuing from that work, we report here the synthesis of two C50 diastereomers of the C33–C51 segment of the stambomycins, and comparison of the associated spectroscopic data with the natural product, which further supports the sequence analysis based stereochemical prediction. This study also identifies suitable conditions for deprotection of the target fragments, bearing in mind the potential sensitivities in these molecules (specifically the C50 allylic oxygen functionality) and, for future work, compatibility

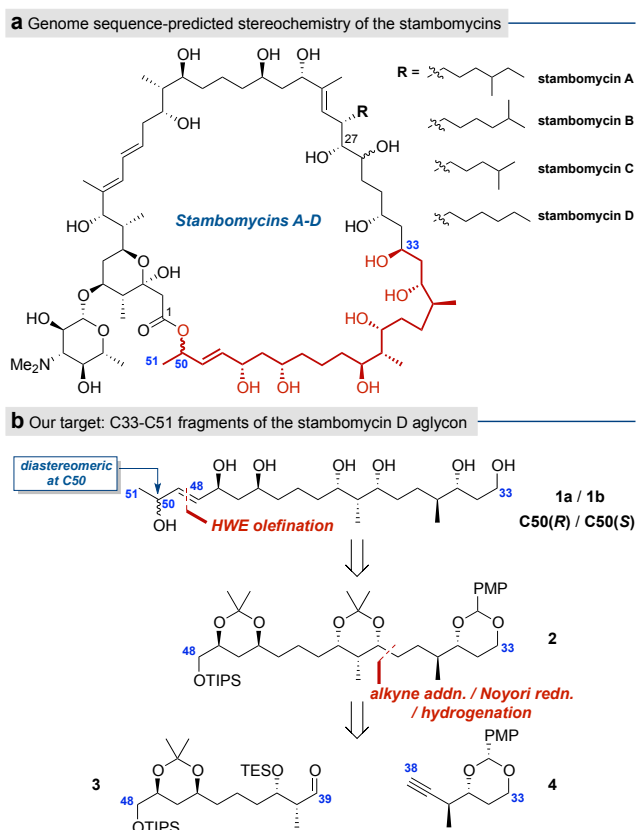


Figure 1. (a) Stambomycins A–D; (b) the C50 diastereomeric C33–C51 fragments **1a** and **1b**, and planned retrosynthesis.

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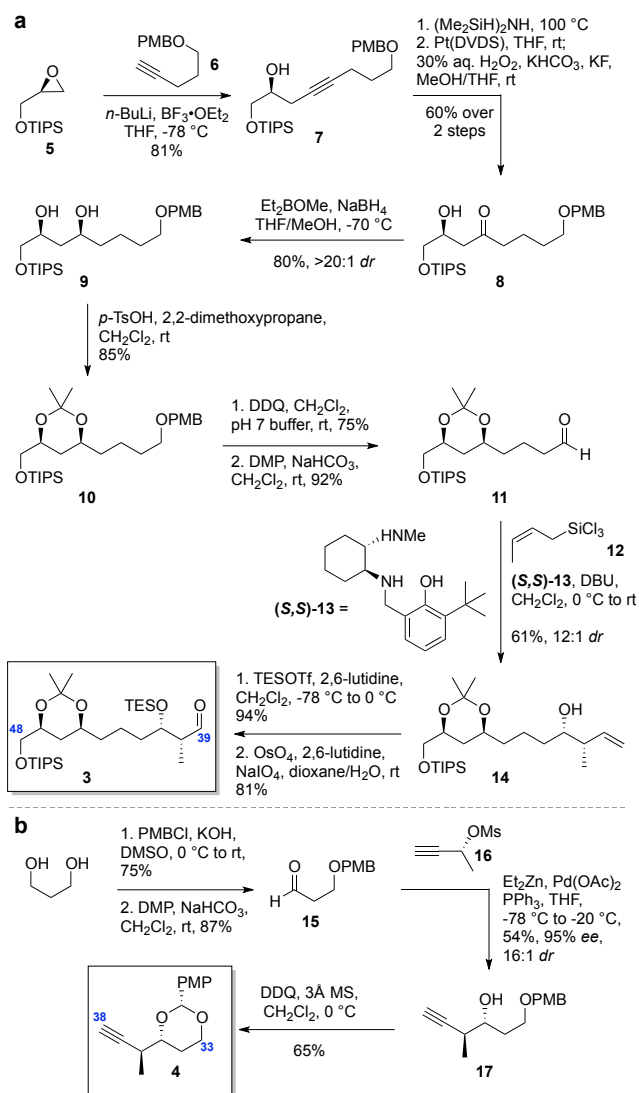
with the previously synthesized C10–C13 diene. In doing so, we demonstrate the ability to install either stereochemistry at C50 at a late synthetic stage, thus laying the groundwork for further studies on the full-length natural product.

Our retrosynthetic analysis of the C33–C51 fragments **1a** and **1b** is shown in Figure 1b. This commences with a late-stage Horner-Wadsworth-Emmons (HWE) olefination / asymmetric reduction at C48 on the C33–C48 motif **2**. Further disconnection at the centre of this unit reveals the C39–C48 aldehyde **3** and C33–C38 alkyne **4**; the union of these two fragments could potentially be achieved by addition of an acetylide derived from **4** to aldehyde **3**, followed by an oxidation / asymmetric reduction / hydrogenation sequence to install the required C39 stereochemistry and C37–C38 saturation.

Synthesis of the C39–C48 aldehyde **3** (Scheme 1a) commenced with addition of alkyne **6** to TIPS-protected (*R*)-glycidol **5**, which afforded homopropargylic alcohol **7** in 81% yield. **7** was treated with 1,1,3,3-tetramethyldisilazane as a prelude to intramolecular hydrosilylation<sup>30, 31</sup> catalyzed by platinum(0) 1,3-divinyl-1,1,3,3-tetramethyldisiloxane,<sup>32</sup> with Tamao oxidation of the intermediate cyclic siloxane furnishing hydroxyketone **8** in good yield (60%). Subsequent Narasaka-Prasad diastereoselective reduction<sup>33</sup> of **8** with diethylmethoxyborane and sodium borohydride gave 1,3-*syn* diol **9** in excellent yield and stereoselectivity (80%, >20:1 *dr*). Treatment of this diol with 2,2-dimethoxypropane and *p*-TsOH afforded acetonide **10** (85%), which enabled confirmation of the relative stereochemistry of the *syn* diol through the Rychnovsky method.<sup>34,35</sup> Deprotection of the PMB ether in **10** (DDQ, 75%) followed by Dess-Martin oxidation afforded aldehyde **11** (92%). To install the next two adjacent stereocentres, a Leighton crotylation<sup>36</sup> was performed on **11**, which proceeded with excellent diastereoselectivity; the stereochemistry of the newly-introduced hydroxyl-bearing stereocentre was confirmed by Mosher ester analysis.<sup>37, 38</sup> Alcohol **14** was then treated with TES triflate and 2,6-lutidine to generate the corresponding TES ether in high yield (94%). Finally, oxidative cleavage of the terminal alkene<sup>39</sup> afforded the C39–C48 aldehyde **3** (81%).

Preparation of the C33–C38 alkyne **4** (Scheme 1b) began with mono-PMB protection of propane-1,3-diol (75%), followed by Dess-Martin oxidation to aldehyde **15** (87%). Enantio- and diastereoselective allenylzinc addition<sup>40–42</sup> of propargylic mesylate **16** to aldehyde **15** gave propargylic alcohol **17** in 54% yield (95% *ee*, 16:1 *dr*), with the stereochemistry of the newly-installed alcohol confirmed by Mosher ester analysis. Treatment of **17** with DDQ in dry CH<sub>2</sub>Cl<sub>2</sub><sup>43</sup> effected oxidation to the PMP acetal **4** (65%).

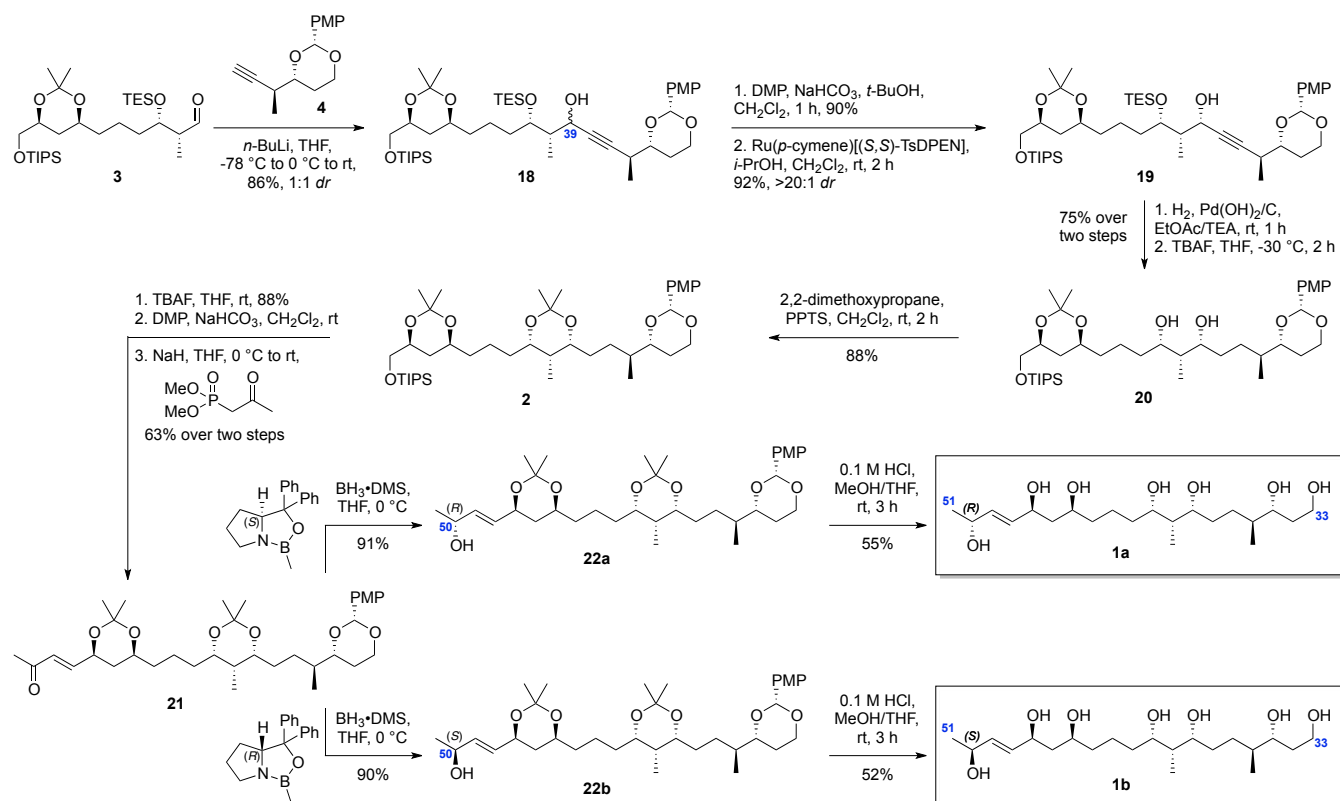
With fragments **3** and **4** in hands, attention turned to construction of the C33–C48 skeleton (Scheme 2). The union of **3** and **4** was achieved using *n*-BuLi, which gave a 1:1 mixture of the two diastereomeric propargylic alcohols **18** in 86% yield. To install the required stereocentre at C39, these diastereomers were oxidized (Dess-Martin periodinane, 90%), then reduced using Noyori asymmetric transfer hydrogenation,<sup>44</sup> which gave propargylic alcohol **19** in excellent yield and diastereoselectivity (92%, >20:1 *dr*). Hydrogenation of the triple bond in **19**



Scheme 1. (a) Synthesis of C39–C48 aldehyde **3**; and (b) synthesis of C33–C38 alkyne **4**.

proceeded smoothly in the presence of triethylamine, which suppressed unwanted deprotection of the TES ether and PMP acetal. The crude residue was directly reacted with TBAF to obtain diol **20** in 75% yield over two steps. Protection of **20** as an acetonide gave the C33–C48 fragment **2** in 87% yield; at this point the stereochemistry at C39 was confirmed by the Rychnovsky-Evans method.<sup>45,35</sup>

Completion of the C33–C51 fragments began with deprotection of the TIPS ether in **2** (88%), followed by oxidation and HWE olefination to form enone **21** in 63% yield over two steps. Due to the stereochemical uncertainty at C50, **21** was treated with both (*S*)- and (*R*)-CBS reagents to afford the C50-(*R*)-enol **22a** (91%) and the C50-(*S*)-enol **22b** (90%) respectively, ready for the final deprotection. This proved challenging, as under acid conditions typically required to deprotect 1,3-*syn*-acetonides (e.g. 1 M HCl, 80% AcOH, or cat. TsOH), the C50 allylic alcohol proved susceptible to degradation (for example by ionization / elimination or ionization / cyclization), while milder conditions led to only partial deprotection and degradation on extended reaction times. After significant

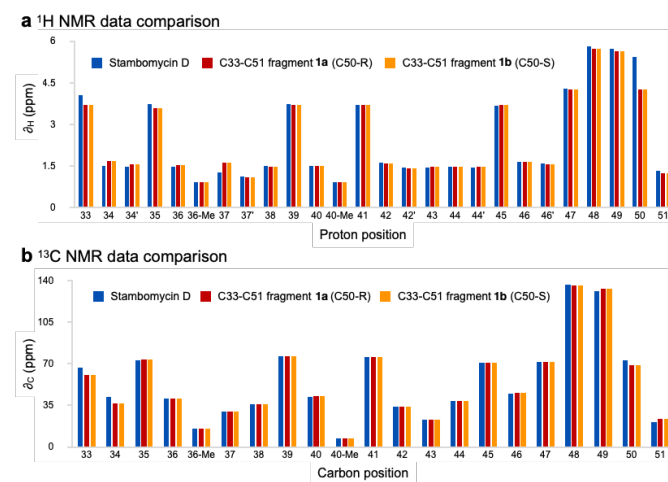
Scheme 2. Synthesis of the C33–C51 Fragments **1a** (C50(*R*)) and **1b** (C50(*S*))

exploration, we found that treatment of **22a** with 0.1 M HCl in 2:1 MeOH/THF for 3 h at ambient temperature afforded **1a** in a pleasing 55% yield. These conditions are particularly appealing, as they were also those optimized for deprotection of the C1–C27 fragment in our previous work.<sup>29</sup> Application of these conditions to the epimer **22b** gave **1b** in 52% yield. Purification of **1a** and **1b** proved non-trivial due to their extremely high polarity: normal phase chromatography was unsuitable, but high purity samples could be obtained using reversed phase HPLC.

With heptaols **1a** and **1b** in hands, we set about comparing their NMR spectroscopic data with that of stambomycin D (Figure 2). Although the synthesized and natural materials are cyclic and acyclic respectively, the conformational flexibility of the stambomycin D macrocycle likely confers the ability to adopt ‘acyclic-like’ conformations in local regions of structure, rendering such comparison informative if not definitive.<sup>46</sup> In the event, the <sup>1</sup>H and <sup>13</sup>C NMR spectra of the synthetic and natural materials showed a good match, with the expected exceptions of C50 which is incorporated into the macrolactone in the natural product but is a free alcohol in **1a** and **1b**, and at the point of truncation (C33–C35). It is worth noting that the most significant chemical shift difference of the synthetic fragments lay at C49 ( $\Delta\delta(^{13}\text{C}) = 0.04$  ppm); this suggests that with authentic and synthetic full-length materials in hand, the identification of the C50 stereocentre is likely to be achievable, and underlines the sensitivity of NMR spectroscopy in the discrimination of subtle stereochemical differences. A further discrepancy was

noted at C37, where the synthetic fragments showed distinct environments for the diastereotopic protons (as observed by HSQC). This suggested that a minor reassignment of the <sup>1</sup>H NMR data for the natural product may be required, which was confirmed by re-examination of the original HSQC data for the stambomycins. In general, our synthetic C33–C51 fragments show good agreement with stambomycin D, particularly in the central region (C36–C45), further validating the predicted stereochemistry of the natural product.

In conclusion, we have synthesized two diastereomers of the ‘southern’ C33–C51 region of stambomycin D, which

Figure 2. Comparison of <sup>1</sup>H and <sup>13</sup>C NMR Data of **1a** and **1b** with Stambomycin D.

displayed a good match of spectroscopic data with the natural product, particularly in the central region (C36–C45) of the fragments. This work further supports the sequence-predicted stereochemical assignment of the stambomycins. Importantly, the deprotection conditions applied to these fragments correlate with those employed for the C1–C27 segment, laying the groundwork for global deprotection of the entire C1–C51 framework. Efforts towards this goal will be reported in due course.

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### Conflicts of interest

There are no conflicts to declare.

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\*These authors contributed equally to this work.

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