Front. Chem. Sci. Eng. 2021, 15(3): 595–601
https://doi.org/10.1007/s11705-020-1971-4

VIEWS & COMMENTS

2019 highlights of the structural revision of natural product *via* total synthesis

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For over a century, chemical synthesis has played an essential role in the structural assignment of natural products. With the development of characterization instrumentation and methods [1], such as nuclear magnetic resonance (NMR), high-resolution mass spectrometry, X-ray crystallography etc., natural product chemists view synthetic chemistry more as an assistive technology and less as a core competence. Contrary to this opinion, the development of synthetic chemistry will continue to be critical in the structural evaluation of natural products. Two comprehensive reviews on natural products with revised structures have already been published [2,3]. Many natural products had their structures reassigned, in particular their stereochemical configurations, by total synthesis in 2019 [4–13]. This paper covers some selected examples.

Monocillin VII. Monocillin VII was isolated in 2017 from the rice-grown cultures of a *Paecilomyces* sp. SC0924 [14]. Key structural elements include a β-resorcylate and a 12-membered macrolactone. The first total synthesis of the monocillin VII was completed by the Mohapatra's group [15] in which the proposed structure of the natural product was synthesized (Scheme 1). The approach included Sonogashira coupling between **1** and **2**, dicobaltization, which change geometry of alkyne and improve the macrolactonisation, and Au-catalyzed hydration, to form the proposed Monocillin VII (**4b**). Unexpectedly, the synthetic compound showed deviations from the product in the ^{1}H NMR and ^{13}C NMR spectra and optical rotation. They suggested a new revised structure and synthesized the 10′*S*-isomer by a similar route. Comparison of their ^{1}H and ^{13}C NMR data with the published data for the natural product allowed correction of the originally assigned structure.

Biemamides B and D. Biemamides B and D were isolated in 2018 from *Streptomyces* sp. [16]. These natural products contain a pyrimidine core. The structure was originally assigned at C5 to the *R* absolute configuration. The first synthesis was published by the Ha group [17] and the synthetic compounds were found to be enantiomeric to the natural products (Scheme 2). The route began with a regio- and stereo-selective ring opening of the azididine **5** followed by amidation, cyclization to give the pyrimidinedione **8**, which was reduced to free amide and converted to final product *ent*-**8a** and *ent*-**8b**. The specific rotation and the electronic circular dichroism spectrum of the synthetic compounds where opposite in sign to the natural products. This resulted in the revision of the absolute configuration to (–)-5*S* for both compounds.

Citrafungin A. The alkyl citrate natural product citrafungin A was first isolated in 2004 from the fungal sterile mycelium (MF6339) [18]. The absolute configuration of the core of the originally proposed structure was assigned as 3*R*, 4*R*, 6*R* and this was synthesized by several different groups [19–21]. However, the specific rotation $[\alpha]_D = +3.2$, (c = 0.25, MeOH) [20] did not match well to that reported and the configuration was then reassigned as 3*S*, 4*S*, 6*S* in line with all the other alkyl citrates [22]. Recently, Rizzacasa and co-workers reported the synthesis of the revised structure of citrafungin A (3*S*, 4*S*, 6*S*) and its degradation product **12** (Scheme 3) [23]. The synthesis involved a formal [2 + 2] cycloaddition and cascade rearrangement to rapidly access the citrate moiety. The spectral and chiroptical data of the diacid degradation product **12** matched that reported for the natural product and this proved those the absolute configuration of the core was opposite to that originally assigned. The intermediate **11** was then converted into the natural product **13a**.

Harziane diterpenoid. The unnamed harziane diterpenoid **19a** was isolated in 2014 from a *Trichoderma* symbiont of *Taxus baccata* [24]. The structural elements included the unique and caged 6-5-7-4 carbon skeleton. The first racemic total synthesis was completed by the Carreira group (Scheme 4) [25]. They also suggested that the original assignment at C9 of the natural product was incorrect and then completed an synthesis of the original

Received May 8, 2020; accepted June 10, 2020

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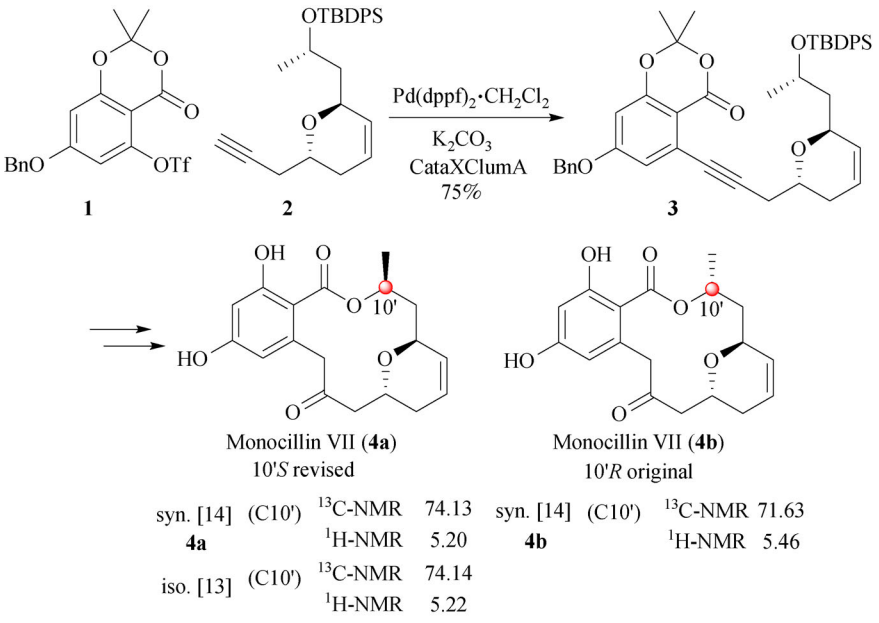
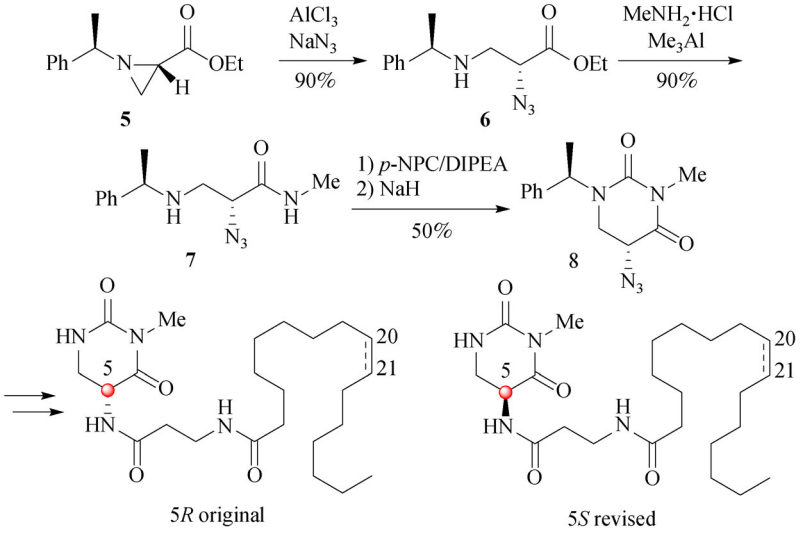


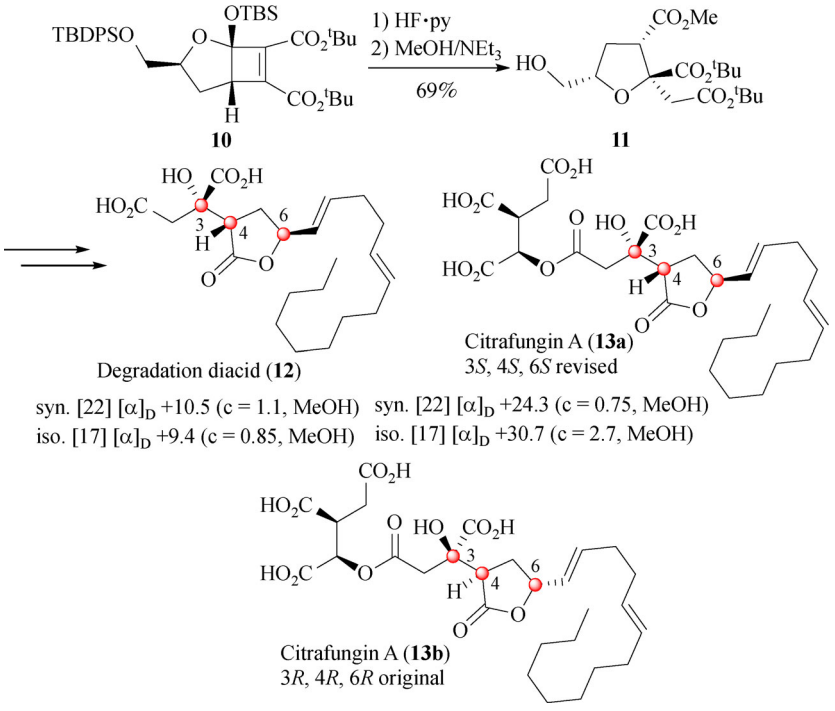
Scheme 1 Onogashira coupling and revised structure of monocillin VII (**4a**) [15].



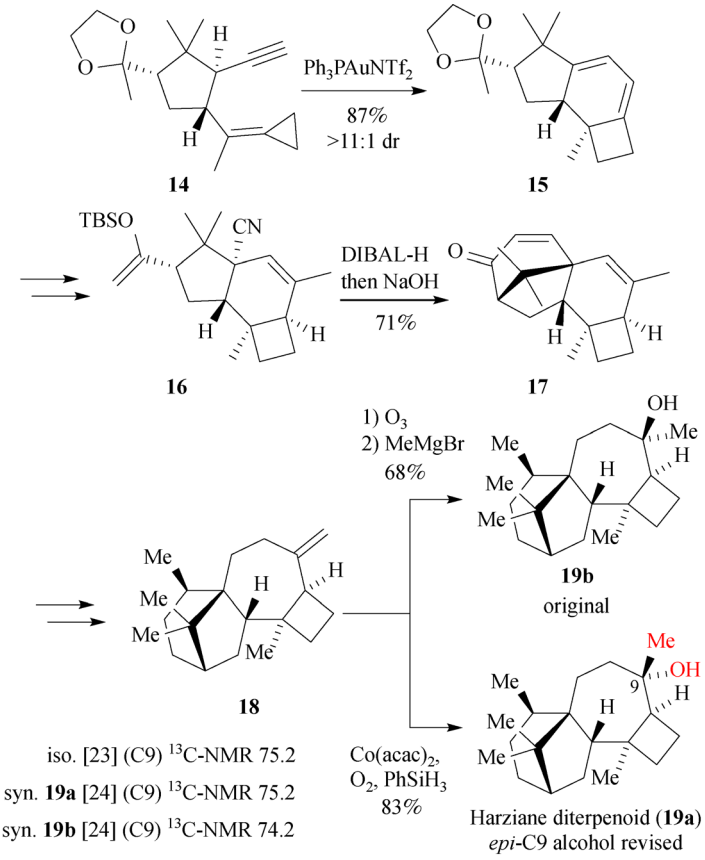
Scheme 2 Synthesis of pyrimidinedione 2d and revised structure of biemamides B (**9a**) and B (**9b**) [17].

19b and revised structure **19a** to support this reassignment. The carbon skeleton was formed by a sequential Au-catalyzed cycloisomerization to give the cyclobutane **15**, intramolecular imine aldol condensation of **16** and ketoaldehyde ring expansion. The late-stage addition or Mukaiyama hydration at C9 led to the two different epimers at C9. The comparison of the spectral data proved that the *epi*-C9 alcohol **19a** is the correct structure.

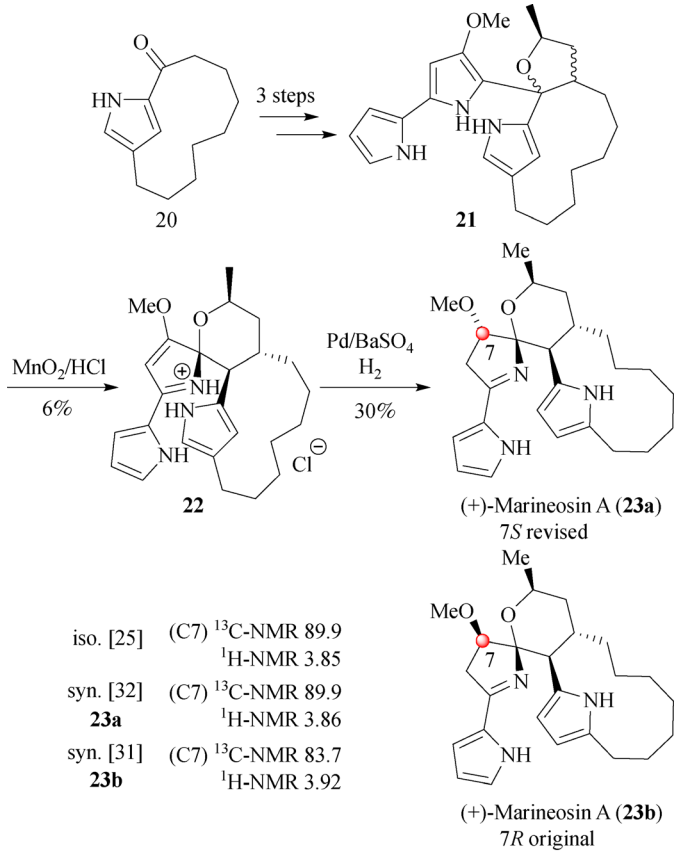
(+)-Marineosin A. Marineosin A was isolated from a marine-derived *Streptomyces* sp. CNQ-617 in 2008 [26]. Due to its novel structure and biological activity, several groups published synthetic studies [27–32] and Shi with co-workers completed the synthesis of the proposed structure [32]. The structure of the synthetic material was confirmed by X-ray crystallography; however, the spectroscopic data differed to that reported for the natural product. Recently, Harran and co-workers reported an eight-step synthesis and stereochemical reassignment of (+)-mar-



Scheme 3 Cascade rearrangement and revised structure of citrafungin A (**13a**) [23].



Scheme 4 Cycloisomerization and revised structure of harziane diterpenoid (**19a**) [25].



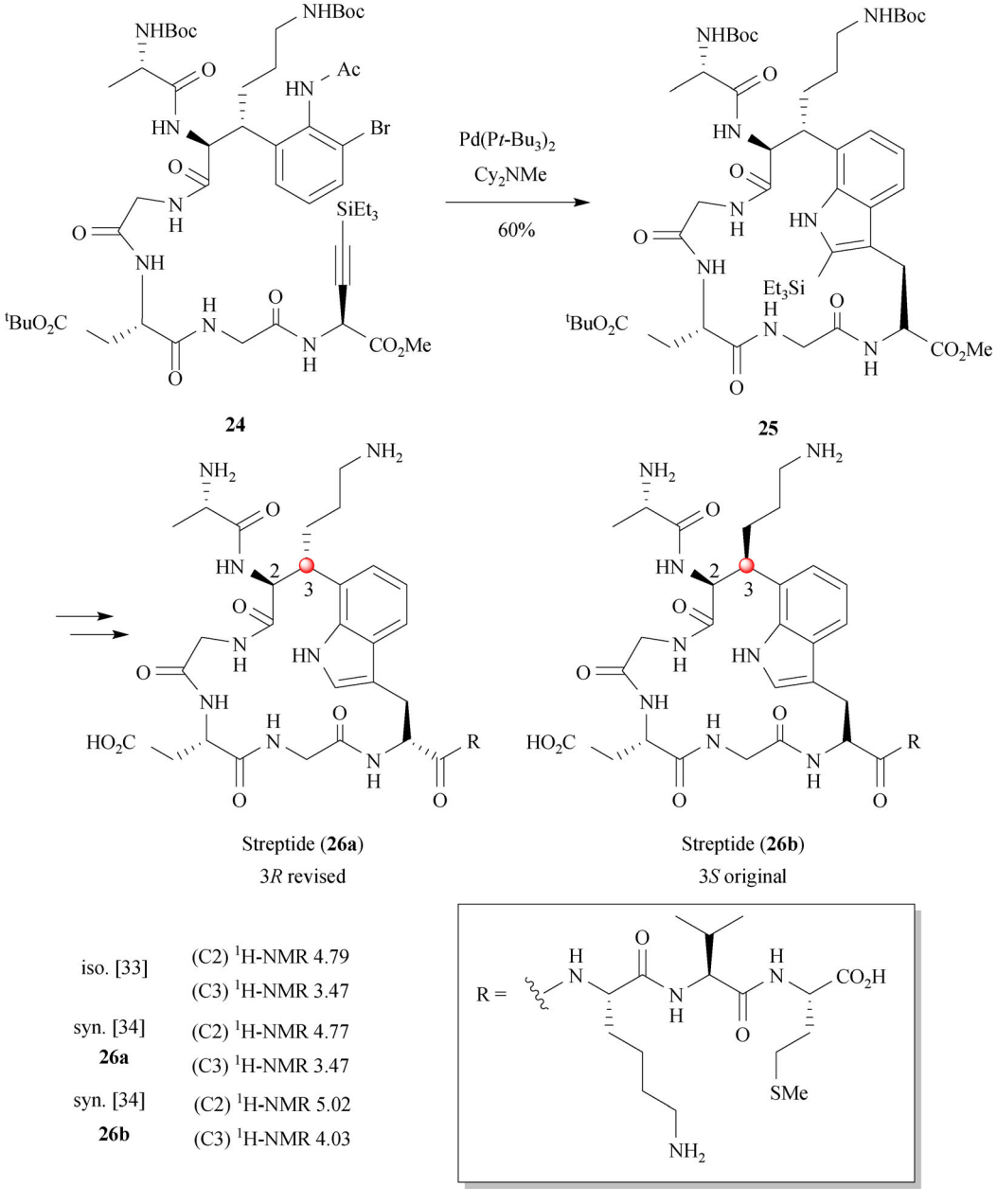
Scheme 5 Redox reaction and revised structure of (+)-marineosin A (**23a**) [33].

ineosin A (Scheme 5) [33]. Their route started with the synthesis of ketopyrrolophane **20** in three steps including a flow photochemical step. After conversion to compound **21**, oxidation using special "acidic" MnO_2 gave only a low yield of **22** (6%), which was unstable. Fortunately, the reduction gave a stable final product marineosin A (**23**), which matched the reported data. This allowed for the revision of the stereochemistry as 7*S*.

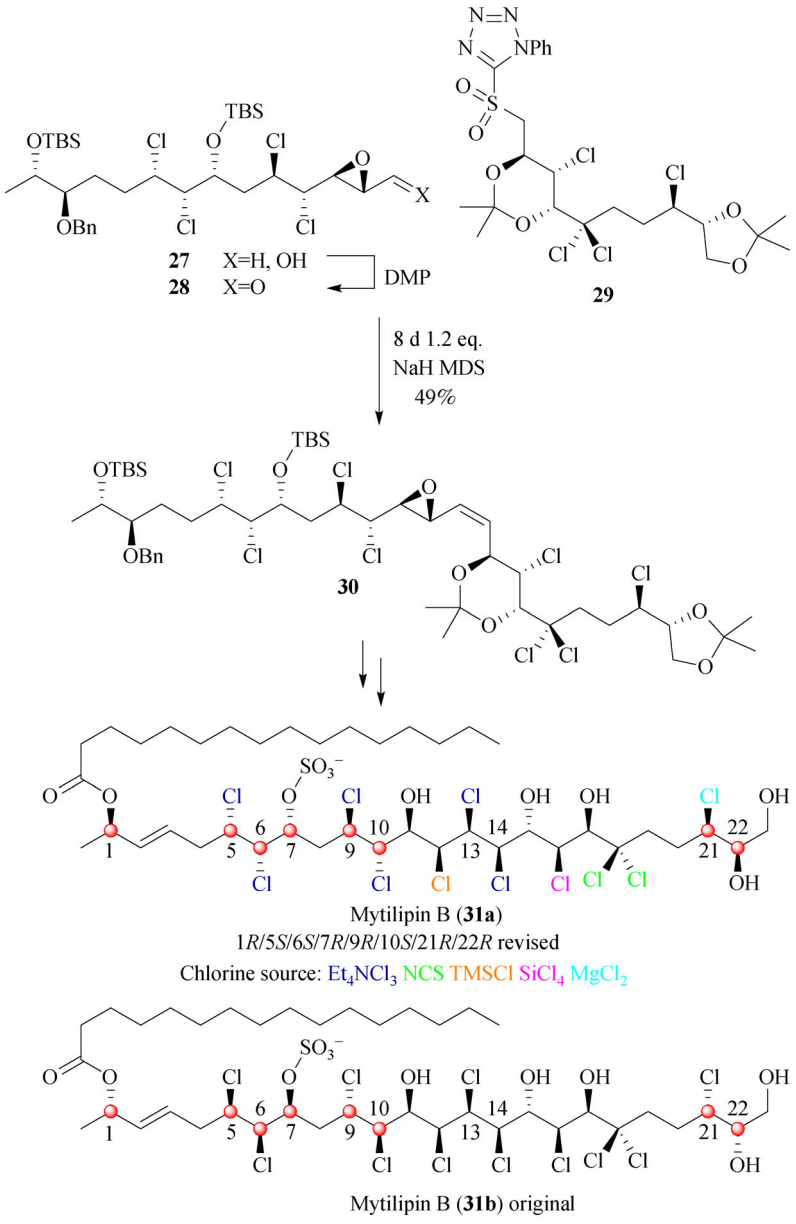
Streptide. Streptide was first isolated in 2015 from *Streptococcus thermophilus* [34]. The compound was identified as a 20-membered macrocyclic peptide with a novel lysine-tryptophan crosslink. The first total synthesis was competed by Boger and co-workers (Scheme 6) [35]. The key steps in the synthesis were a Pd-catalyzed indole macrocyclization to form indole **25** and diastereoselective C–H activation/β-arylation of a lysine derivative. Notably, both C3 diastereomers were carried through the similar route and afforded the same yield (60%) in the macrocyclization reaction. The ^{1}H NMR spectrum of the α/β proton in the crosslinked lysine shown a distinguishable difference between two diastereomers, only 3*R* matched the natural product. The isolated compound co-eluted on high performance liquid chromatography with streptide-3*R* diastereomer **26a** and so the stereochemistry of streptide was reassigned to 3*R*.

Mytilipin B. Mytilipin B is one of the most complex chlorosulfolipids. It was isolated in 2002 from a culinary mussel *Mytilus galloprovinvialis* [36]. This family of natural products contains a complex array of secondary chlorides and alcohols. The proposed structure was synthesised by Carreira's group in 2011 [37]. However, the spectral data of the synthetic compound showed deviations from those reported for the natural product. Recently, the same group published a paper that combined NMR analysis and chemical synthesis to revise the configuration (Scheme 7) [38]. The key C13-C14 bond was formed via a Julia olefination. Another highlight in this synthesis was the choice of different reagents (Et_4NCl_3, NCS, TMSCl/HCl, $SiCl_4$, $MgCl_2$) to achieve the required selective chlorinations. Eventually, four diastereomers were synthesized and compared with the natural product. The final structure resulted in revision of configuration at eight stereocenters.

Even with modern spectroscopic and computational techniques, the structures of many natural products are often incorrectly assigned. However, one can still turn to



Scheme 6 Indole macrocyclization and revised structure of streptide (**26**) [35].



Scheme 7 Julia olefination and revised structure of mytilipin B (**31**) [38].

synthetic chemistry to reveal the true structure of many natural products, especially those containing complex stereochemistry.

Acknowledgements We thank the Australian Research Council Discovery Grants Scheme and the University of Melbourne Research Grants Support Scheme for funding.

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