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Total synthesis of maremycins A, B, C_1/C_2, D_1, and D_2

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ABSTRACT

The total synthesis of maremycins A, B, C_1/C_2, D_1, and D_2 is achieved starting from the natural amino acids L-isoleucine and *S*-methyl-L-cysteine, in which the total synthesis of maremycins B, C_1/C_2, and D_2 is accomplished for the first time. The synthesis features a position-selective intramolecular bromination process for the synthesis of key chiral building block, a Pd-catalyzed indole synthesis for the preparation of (2*S*,3*S*)-β-methyltryptophan and hydroxylation of oxindoles by molecular oxygen. In addition, the protocol for conversion of maremycins A and B to maremycins C and D was improved.

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Maremycins A (**1**), B (**2**), C_1/C_2 (**3**/**4**), D_1 (**5**), and D_2 (**6**) have a 3-substituted-3-hydroxy-2-oxindole structural motif, which is present in many bioactive natural products and pharmaceutical lead compounds (Fig. 1).[1] Maremycins A and B were first isolated from the culture broth of *Streptomyces* species B 9173 by Laatsch and co-workers in 1995.[2] Maremycins C_1/C_2 (**3**/**4**) as well as D_1/D_2 (**5**/**6**) are diastereomers and were isolated as two inseparable mixtures from *Streptomyces* sp. (GT 051237) by Grabley and co-workers in 2001.[3] However, except maremycins B (**2**) and C (**3**/**4**) were reported to have a slight cytotoxicity to the L-929 mouse fibroblastoma cell line, K562 human leukemia cell line, and Hela human cervix carcinoma cell line (IC_{50} 50.0 μg/mL), these natural products have not been found with other potential bioactivity so far. In 2008, Tamura reported the first total synthesis of maremycins A and D_1 via [3+2] cycloaddition as the key step,[4] which confirmed the stereochemistry of the natural maremycins A and D_1 and also established the stereochemistry of **2**–**4**, and **6**.

With our ongoing study on the efficient synthesis of indole alkaloids,[5] we became interested in the synthesis of maremycins. Our synthesis was inspired by the proposed biosynthesis of the natural product and was based on biomimetic disconnections leading to two 'amino acid' subunits, L-cysteine and β-methyltryptophan (β-MeTrp) (Scheme 1). It was clear that one of the main issues was the synthesis of β-MeTrp. In fact, the synthesis of β-MeTrp has received extensive attention[6] since it is an important structural moiety of a variety of natural products such as telomycin,[7] chaetoglobisins,[8] and FR900452,[9] is known to be the biosynthetic precursor of both streptonigrin[10] and lavendomycin,[11] has been used as a bioisostere of amino acid residue of peptide mimetic compounds in the field of peptide-based drug design,[12] and has been used as a chiral catalyst for asymmetric Diels–Alder reaction.[13] Optically active β-MeTrp has been prepared by either resolution of enantiomers[14–16] or asymmetric synthesis.[17–20] The asymmetric synthesis includes (a) coupling indole with aziridine-2-carboxylate;[17] (b) using Evans' chiral auxiliaries;[18] (c) functionalization of the cyclic tryptophan tautomer;[19] (d) diastereoselective addition of the lithium salt of the Schöllkopf bis-lactim ether to indole derivatives.[20] Herein, we describe a new synthetic route for the synthesis of (2*S*,3*S*)-β-MeTrp by using the palladium-catalyzed indole synthesis as key step.[21] The (2*S*,3*S*)-β-MeTrp was successfully converted into maremycins A–D,

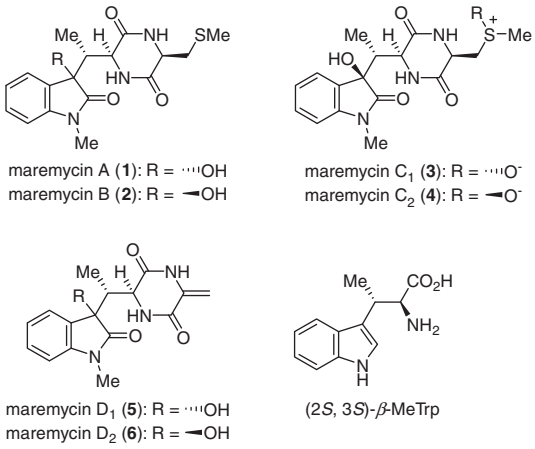

Figure 1. Structures of maremycins A–D.

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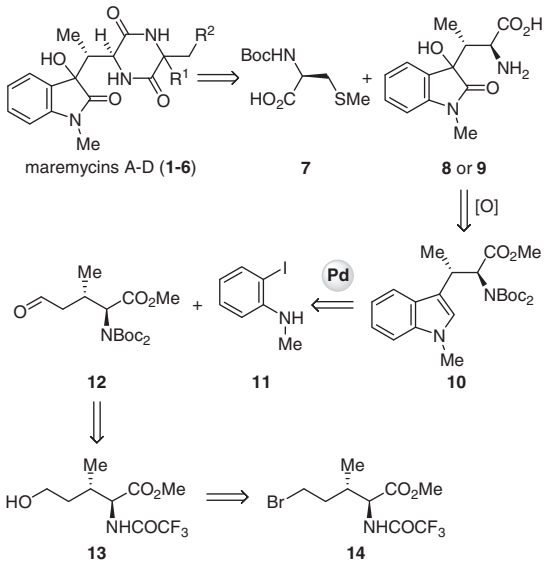
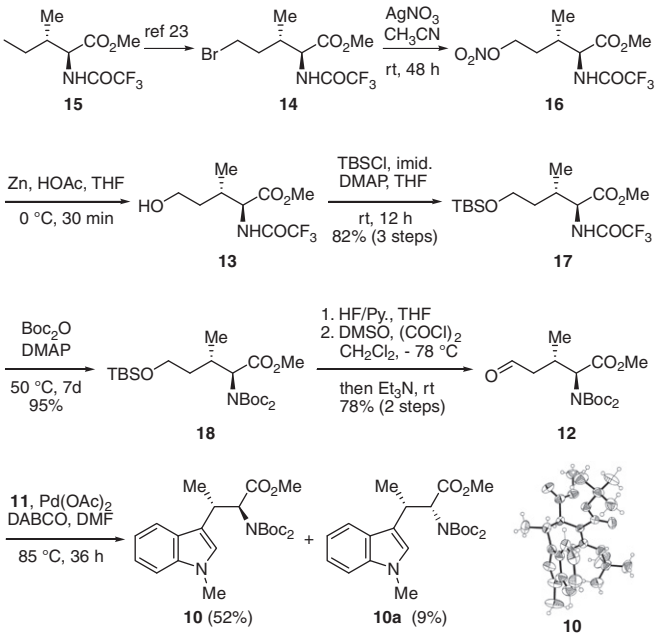


Scheme 1. Retrosynthetic analysis of maremycins A–D.



Scheme 2. Synthesis of (2*S*,3*S*)-β–methyltryptophan.

in which the total synthesis of maremycins B, C_1/C_2, and D_2 is accomplished for the first time.

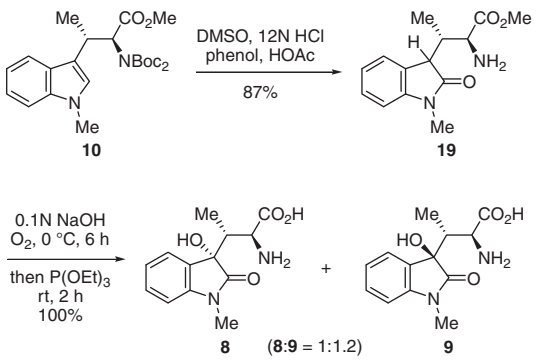
Our retrosynthetic analysis of maremycins A–D (**1**–**6**) is illustrated in Scheme 1. Maremycins D_1 and D_2 could be obtained by *syn*-elimination of the sulfoxide of the corresponding maremycin A sulfoxide and maremycin C as reported by Tamura. Maremycins C_1/C_2 (**3**/**4**) could be obtained by oxidation of maremycin B. In the forward sense, the formation of diketopiperazine ring of maremycins A and B could be obtained by the coupling of *S*-methyl-L-cysteine (**7**) and the derivative of tryptophan (**8** or **9**) followed by intramolecular cyclization. Both amino acids **8** and **9** would be available by the oxidation of (2*S*,3*S*)-β-MeTrp **10**, which could be prepared by the palladium-catalyzed annulation of *N*-methyl 2-iodoaniline (**11**) and aldehyde (**12**). The synthesis of similar chiral aldehyde **12** has been reported by many other groups.[22] However, all the existing methods have limitations because of the complicated operational procedures and low yields. In 2006, Corey and co-workers reported the synthesis of 5-hydroxy-isoleucine derivative **13** from 5-bromo-L-isoleucine derivative **14**, which was prepared by using a light-initiated position-selective intramolecular bromination procedure as key step.[23] We envisioned that the key chiral building block aldehyde **12** could be derived from **13** by functional group transformation.

Our synthesis commenced with the preparation of (2*S*,3*S*)-β-MeTrp **10** as illustrated in Scheme 2. Bromide **14** was prepared from **15** following the Corey's protocol.[24] Corey's group reported that bromide **14** could be converted into alcohol **13** in a 91% yield by treatment with $AgNO_3$ in THF/H_2O (1:1). However, in our hand, treatment of **14** under the same reaction condition provided the desired alcohol **13** in only a 10% yield, together with the nitrate **16** in a 50% yield.[25] The attempts to perform the direct conversion of **14** to **13** with acceptable yield were not successful even after screening many reaction conditions. Since reduction of **16** with Zn dust/HOAc could afford the alcohol **13** in nearly quantitative yield,[26] we next focused on the optimization of the synthesis of **16** from **14**. Finally, under optimized conditions ($AgNO_3$, anhydrous CH_3CN), **16** was obtained as the sole product in a 96% yield. The unstable alcohol **13** was protected as its TBS ether to provide **17** (82%, three steps).

Attempts to convert compound **17** into *N*,*N*-diBoc **18** with Boc_2O/DMAP in various solvents (THF, CH_2Cl_2 or CH_3CN) failed even by prolonging the reaction time or raising the reaction temperature. We speculated that the steric hindrance of β-methyl group may influence the reaction. Gratefully, when the reaction was carried out under solvent-free condition, it succeeded to afford **18** in a 95% yield. Desilylation of the TBS ether **18** with HF/Py in THF followed by Swern oxidation provided the desired aldehyde **12** in a 78% yield.

Having succeeded in the synthesis of key chiral aldehyde **12**, the stage was set for the Pd-catalyzed indole synthesis to construct the indole core. Treatment of **12** and *N*-methyl 2-iodoaniline (**11**) under standard conditions provided the desired (2*S*,3*S*)-β-MeTrp **10** in only a 30% yield. Comparing with the known substrates,[21] the steric hindrance of β-methyl group would be responsible for the low yield. After extensive optimization of the reaction conditions, we found that removal of H_2O produced during the formation of enamine (see Supplementary data) and the use of anhydrous DABCO were crucial to obtain higher yield (52%). X-ray analysis of crystalline **10** secured its absolute configurational assignment as (2*S*,3*S*). It is noteworthy that (2*R*,3*S*)-β-MeTrp **10a**, the epimer of **10**, was also obtained in a 9% yield, which was produced due to the long reaction time in the presence of base.[21b]

The direct oxidation of indole **10** to the 3-hydroxy-2-oxindole turned out to be challenging due to the steric hindrance of the β-methyl group (Scheme 3).[27] According to the reported protocol, a



Scheme 3. Synthesis of 3-hydroxy-2-oxindole.

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