SYNTHESIS OF MEREMYCIN A TO D

MSc Dissertation report by:

SAIESH V. KORGAONKAR

20PO490044

SCHOOL OF CHEMICAL SCIENCES

GOA UNIVERSITY

GOA 403206

APRIL 2022

SYNTHESIS OF MEREMYCIN A TO D

Submitted in Partial Fulfillment

Of

The Degree Of M.Sc (Organic Chemistry)

By

Mast. SAIESH V. KORGAONKAR

To the

School Of Chemical Sciences

Goa University

Goa 403206

APRIL 2022

DECLARATION

I declare that the literature review titled "**SYNTHESIS OF MEREMYCIN A TO D"** has been carried out by me in the Chemistry Department, School Of Chemical Sciences, Goa University, The information derived from the literature has been duly acknowledged in the text and a list of references is provided.

Saiesh V. Korgaonkar

CERTIFICATE

This is to certify that the literature review entitled ““**SYNTHESIS OF MEREMYCIN A TO D”** submitted by the student is the record of research work carried out by the candidate during the academic year 2021-2022 under my supervision in the partial fulfillment of the requirements for the degree of Master of Science in Chemistry.

DR. Rupesh A. Kunkalkar
(project guide)

Prof.Vidhyadatta Verenkar
(Dean, of SCS, Goa University)

ACKNOWLEDGEMENT

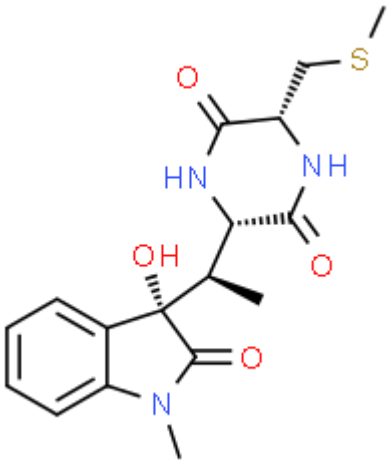
I would like to express my special thanks of gratitude to my teacher Dr Rupesh A. Kunkalkar as well as our dean prof. Vidhyadatta M. Shet Verenkar and vice-dean Dr Rajendra N.Sirsat who gave me the opportunity to this wonderful project on the topic'' **SYNTHESIS OF MEREMYCIN A TO D"**'' which also helped me in doing a lot of research and I came to know about so many new things I am really thankfull to them.

INDEX

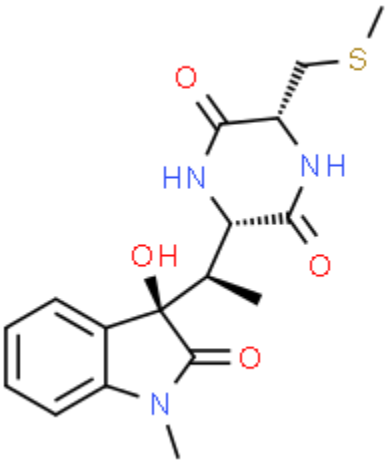
ABSTRACT

The total synthesis of maremycins A, B, C1/C2, D1, and D2 is achieved starting from the natural amino acids L-isoleucine and S-methyl-L-cysteine, in which the total synthesis of maremycins B, C1/C2, and D2 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 (2S,3S)-b-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. A concise synthesis of maremycins A and D1 has been accomplished via cycloaddition of a chiral cyclic nitrone with (E)-3-ethylidene-1- methylindolin-2-one as a key step. This synthesis clarifies the stereochemistry of the maremycins and is suitable for large-scale synthesis for biological screening.

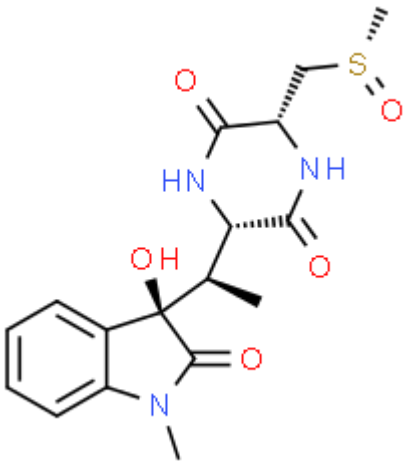
INTRODUCTION



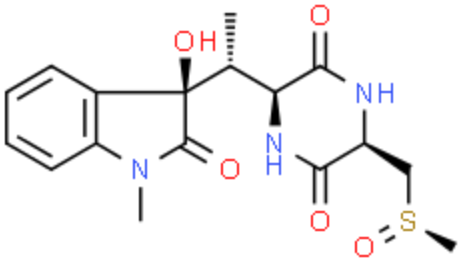
maremycin A



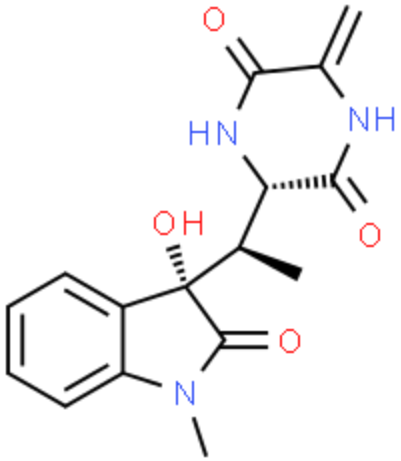
Maremycin B



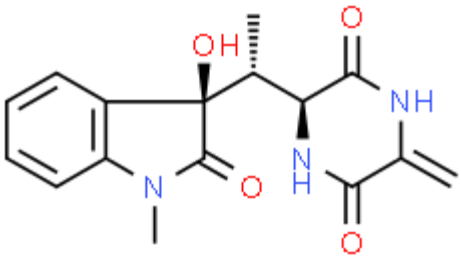
Maremycin C1



Maremycin C2



Maremycin D1



Maremycin D2

Figure 1- structures of maremycins A-D

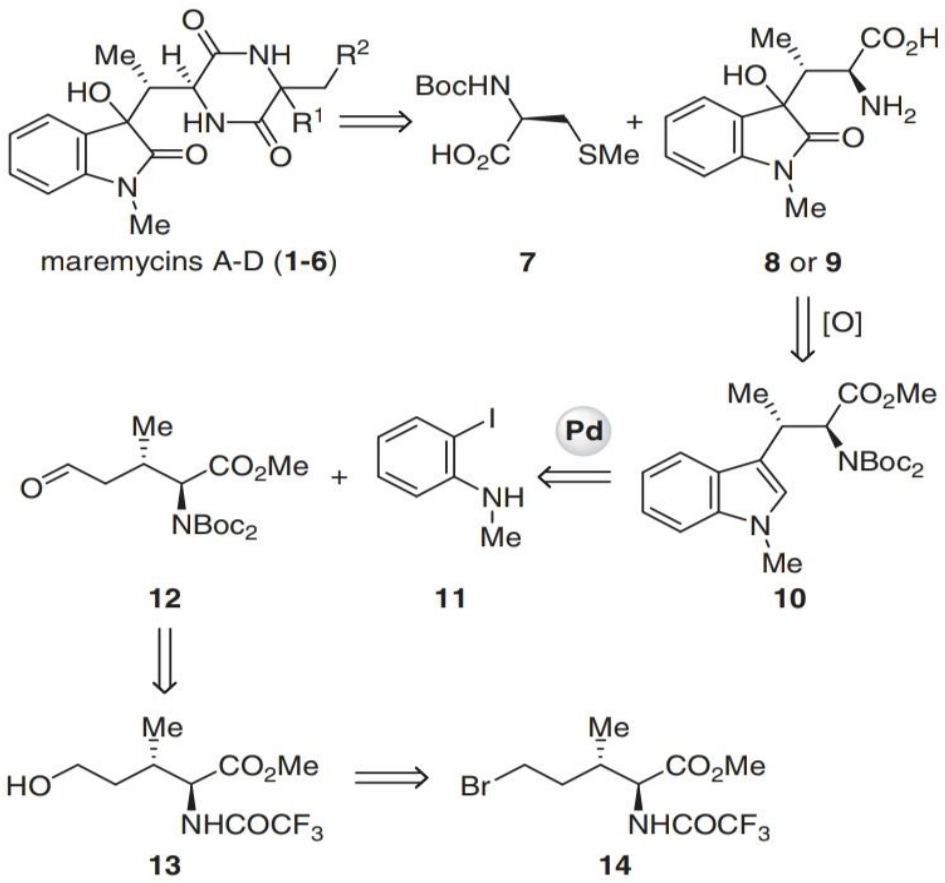
Maremycins A (1), B (2), C1/C2 (3/4), D1 (5), and D2 (6) have a 3- substituted-3-hydroxy-2-oxindole structural motif, which is present in many bioactive natural products and pharmaceutical lead compounds (Fig. 1)[1]. Maremycins A and B were first isolated from the culture broth of Streptomyces species B 9173 by Laatsch and coworkers in 1995[2].Maremycins C1/C2 (3/4) as well as D1/D2 (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 (IC50 50.0 lg/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 D1 via [3+2] cycloaddition as the key step[4] which confirmed the stereochemistry of the natural maremycins A and D1 and also established the stereochemistry of 2–4, and 6

LITERATURE REVIEW

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 b-methyltryptophan (bMeTrp) (Scheme 1). It was clear that one of the main issues was the synthesis of b-MeTrp. In fact, the synthesis of b-MeTrp has

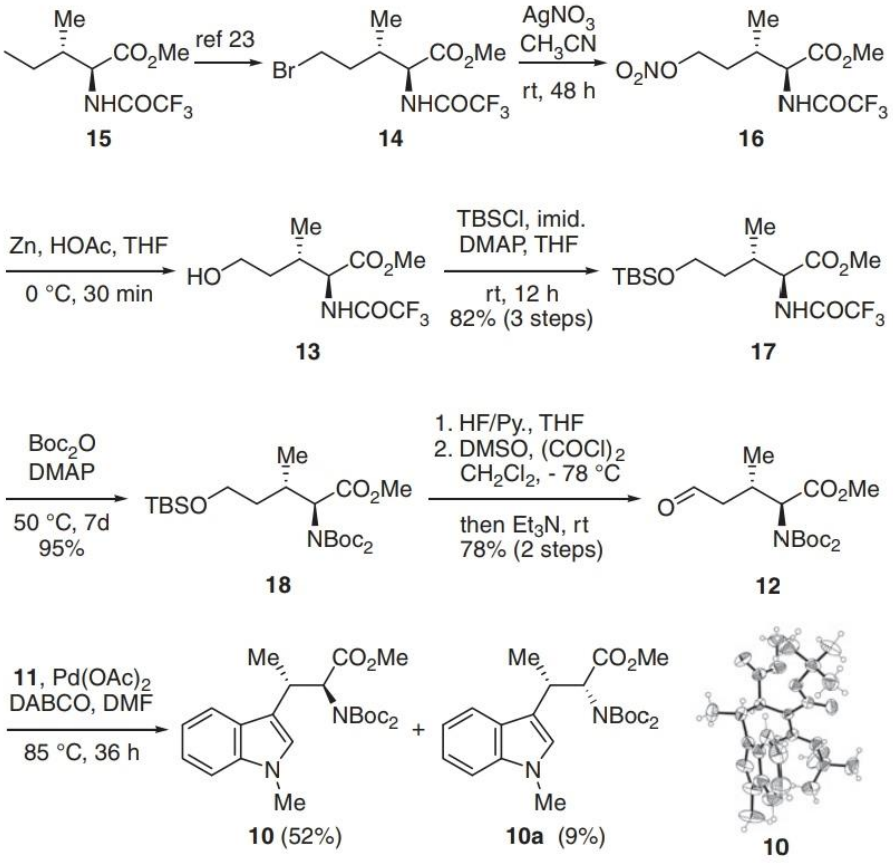
received extensive attention[6] since it is an important structural moiety of a variety of natural products such as telomycin[7], chaetoglobisins[8], and FR900452[9], is known to be the biosynthetic precursor of both streptonigrin[10] and lavendomycin,[11] has been used as a bioisostere of amino acid 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 bMeTrp has been prepared by either resolution of enantiomers or asymmetric synthesis[14,15]. The asymmetric synthesis includes (a) coupling indole with aziridine-2-carboxylate; (b) using Evans' chiral auxiliaries;[16] (c) functionalization of the cyclic tryptophan tautomer; (d) diastereoselective addition of the lithium salt of the Schöllkopf bis-lactim ether to indole derivatives.Herein, we describe a new synthetic route for the synthesis of (2S,3S)-b-MeTrp by using the palladium-catalyzed indole synthesis as key step. The (2S,3S)-b-MeTrp was successfully converted into maremycins A–D, in which the total synthesis of maremycins B, C1/C2, and D2 is accomplished for the first time.

Our retrosynthetic analysis of maremycins A–D (1–6) is illustrated in Scheme 1. Maremycins D1 and D2 could be obtained by syn-elimination of the sulfoxide of the corresponding maremycin A sulfoxide and maremycin C as reported by Tamura. Maremycins C1/C2 (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 (2S,3S)-b-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 .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. We envisioned that the key chiral building block aldehyde 12 could be derived from 13 by functional group transformation



Scheme 1 – Retrosynthesis analysisof maremycins A-D

Our synthesis commenced with the preparation of (2S,3S)-bMeTrp 10 as illustrated in Scheme 2. Bromide 14 was prepared from 15 following the Corey's protocol[17]. Corey's group reported that bromide 14 could be converted into alcohol 13 in a 91% yield by treatment with AgNO3 in THF/H2O (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[18]. 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[19] we next focused on the optimization of the synthesis of 16 from 14. Finally, under optimized conditions (AgNO3, anhydrous CH3CN), 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 Boc2O/DMAP in various solvents (THF, CH2Cl2 or CH3CN) failed even by prolonging the reaction time or raising the reaction

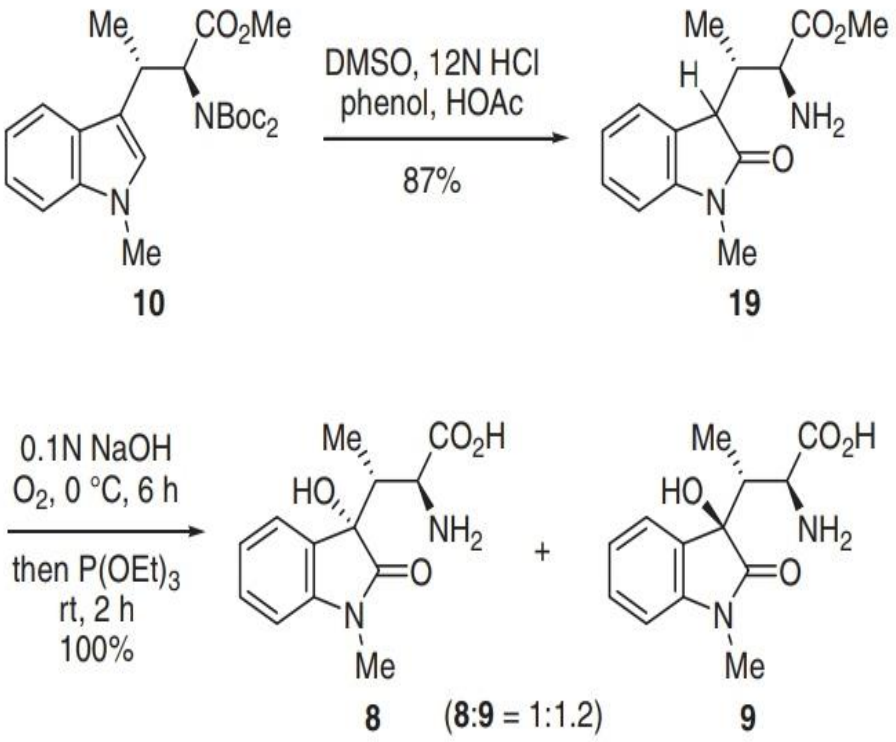


Scheme 2- synthesis of (2S,3S))-b–methyltryptophan.

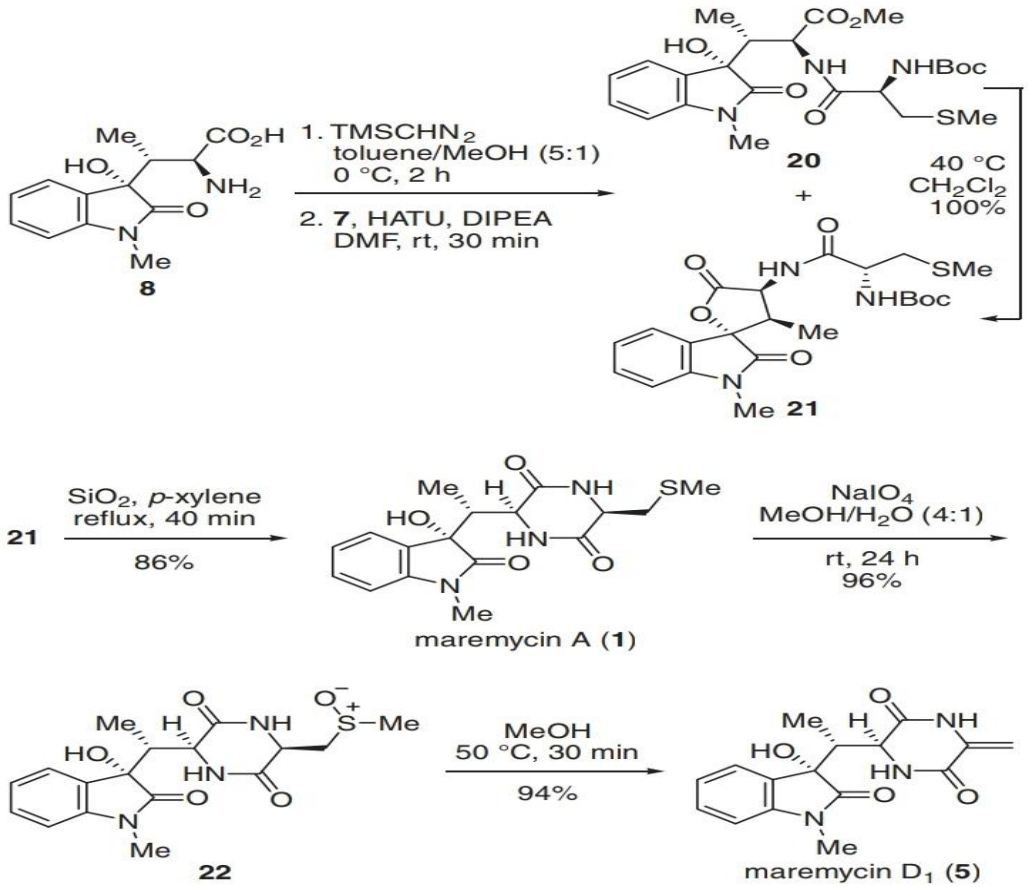
temperature. We speculated that the steric hindrance of b-methyl group may influence the reaction. Gratefully, when the reaction was carried out under solvent-free condition, it succeeded to afford 18 in a 95% yield. Desilylation of the TBS ether 18 with HF/Py in THF followed by Swern oxidation provided 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 (2S,3S)-b-MeTrp 10 in only a 30% yield. Comparing with the known substrates, the steric hindrance of b-methyl group would be responsible for the low yield. After extensive optimization of the reaction conditions, we found that removal of H2O 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 (2S,3S). It is noteworthy that (2R,3S)-b-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 bmethyl group (Scheme 3).27 According to the reported protocol, a variety of oxidants such as IBX/$CeCl_3$, DMDO[20], m-CPBA, NBS/tBuOH, and DMSO/(CH3SO2)2O32 were investigated. However, no desired product was obtained. Therefore, we started to explore the indirect strategy. Treatment of 10 with DMSO/HCl (12 N) resulted in the oxidation of indole along with deprotection of the two Boc groups to afford the oxindole 19 as a 1.5:1 diasterisomer mixture in an 87% yield. Oxidation of oxindole 19 in an alkaline solution with O2 at 0˚ C in the presence of P(OEt)3 proceeded cleanly and afforded the compounds 8 and 9 in 45% and 55% yields, respectively. The diastereoisomers 8 and 9 were separated by reversedphase column chromatography. Compound 8 has a higher polarity and its spectroscopic and physical properties (1 H and 13C NMR, ½a25 D were identical in all respects to the data of the key intermediate reported by Tamura.



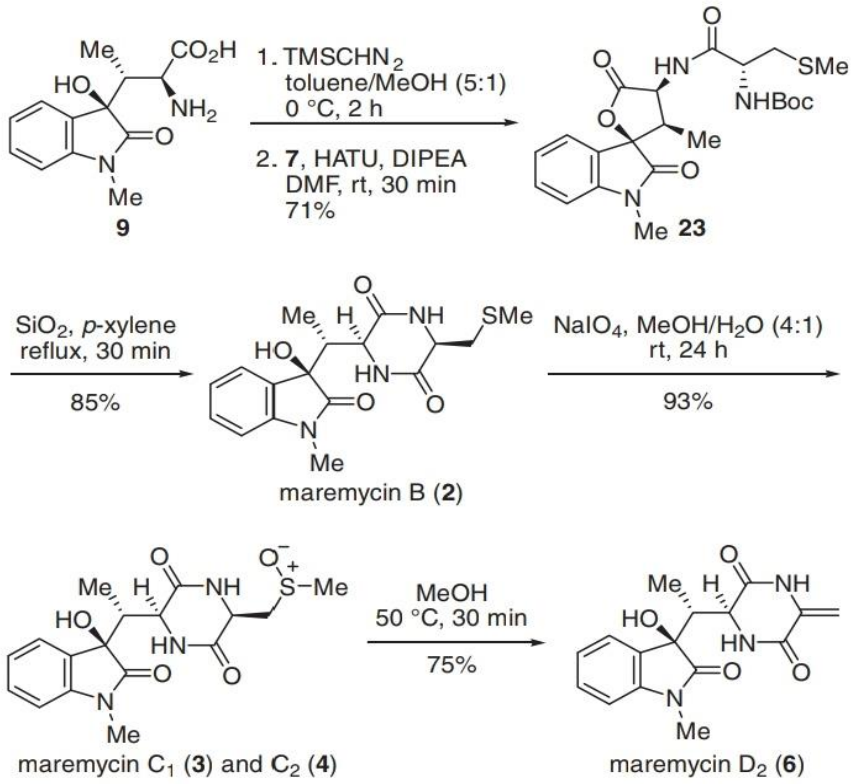
Scheme 3- . Synthesis of 3-hydroxy-2-oxindole.



Scheme 4- Synthesis of maremycins A (1) and D1 (5).

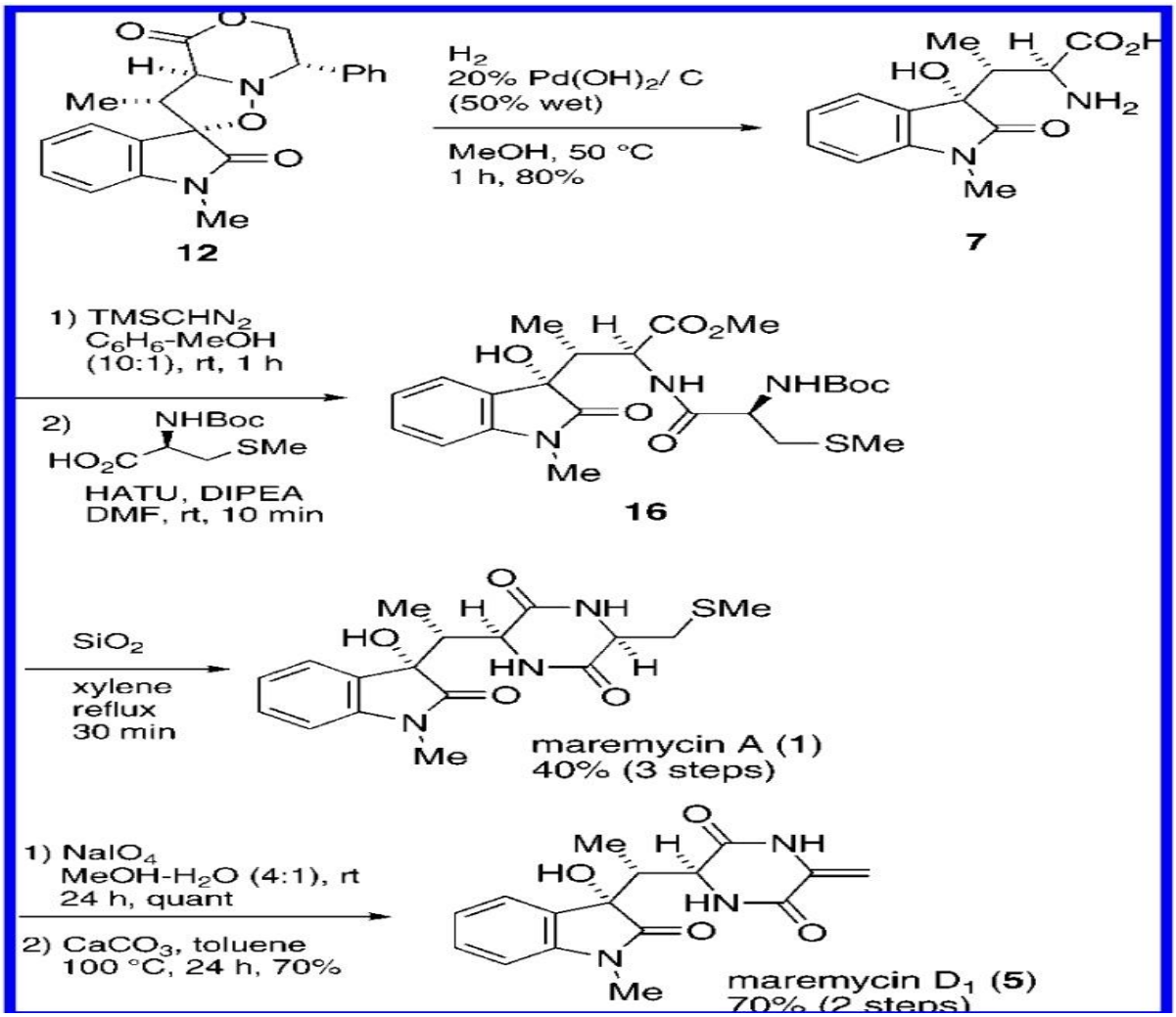
Conversion of 8 to maremycin A (1) and D1 (5) was successfully carried out, and we made interesting observations (Scheme 4). Treatment of amino acid 8 with TMSCHN2 followed by condensation with N-Boc-S-methyl-L-cysteine (7) gave not only the desired methyl ester 20 but also the lactone 21. In fact, ester 20 is unstable and easily converted into lactone 21 under a variety of conditions. Fortunately, lactone 21 could also be converted into maremycin A (1) in an 86% yield following the same protocol (silica gel in boiling p-xylene) as reported for methyl ester 20. Although thermal elimination of sulfoxide from 22 in the presence of CaCO3 in refluxing toluene for 24 h could afford maremycin D1 (5) in a 70% yield (brsm), we found that the presence of CaCO3 is not necessary when methanol was used as the solvent, probably due to the poor solubility and reactivity of 22 in toluene. The reaction was completed in methanol at 50°C in 30 min and provided 5 in a 94% yield. The

physical properties (1 H and 13C NMR, ½a25 D of the synthesized maremycins A (1) and D1 (5) matched those reported for the natural products. Similarly, conversion of 9 to maremycins B, C, and D2 was shown in Scheme 5. Interestingly, treatment of compound 9 with TMSCHN2 followed by condensation with N-Boc-S-methyl-L-cysteine gave only lactone 23 in a 71% yield. Lactone 23 was readily converted into maremycin B (2) and maremycins C1/C2 (3/4), which was further transformed to maremycin D2 in methanol in a 75% yield. However, thermal elimination of maremycins C1/C2 (3/4) under the Tamura's conditions (CaCO3 in toluene, reflux for 2 days), maremycin D2 was only obtained in less than a 10% yield. The spectroscopic and physical data of 2, 3, 4, and 6 were identical in all respects to the data reported in the literature, except the optical rotation of maremycin B (2). The optical rotation of synthetic 2 was ½a25 D = +78.3 (c 0.28, MeOH), while natural 2 was ½a25 D = +2.9 (c 0.21, MeOH). In summary, we have accomplished the asymmetric total synthesis of maremycins A, B, C1/C2, D1, and D2 from the same precursor (2S,3S)-b-methyltryptophan, in which the total synthesis of maremycins B, C1/C2, and D2 is accomplished for the first time. The synthesis features using three new synthetic methodologies, involving position-selective intramolecular bromination process for the synthesis of key chiral building block, the Pd-catalyzed indole synthesis for the preparation of b-methyl tryptophan and hydroxylation of oxindoles by molecular oxygen. In addition, the protocol for conversion of maremycins A and B to maremycins C and D**CONC** was improved.



Scheme 5- Synthesis of maremycins B (2), C1/C2 (3/4), and D2

Synthesis of Maremycins A and D1 via Cycloaddition of a Nitrone with (E)-3-Ethylidene-1-methylindolin-2-one



Scheme6- Synthesis of maremycin A and D1

A concise synthesis of maremycins A and D1 has been accomplished via cycloaddition of a chiral cyclic nitrone with (E)-3-ethylidene-1- methylindolin-2-one as a key step. This synthesis clarifies the stereochemistry of the maremycins and is suitable for large-scale synthesis for biological screening.

CONCUSION

. In conclusion, we have accomplished the first synthesis of maremycins A and D1 , featuring cycloaddition of cyclic nitrone 10 with (E)-3-ethylidene-1-methylindolin-2-one (9), and thereby conclusively determined the stereochemistries of the natural products 1 and 5. In addition, 5 has been fully characterized for the first time. This shortstep synthesis is expected to be suitable for obtaining large amounts of the natural products for biological screening.

BIBLIOGRAPHY

1. Fischer, C. & Koenig, B. Palladium- and copper-mediated N-aryl bond formation reactions for the synthesis of biological active compounds. *Beilstein J. Org. Chem.* **7**, 59–74 (2011).

2. Balk-Bindseil, W., Helmke, E., Weyland, H. & Laatsch, H. Marine bacteria, VIII. Maremycin A and B, new diketopiperazines from a marine Streptomyces sp. *Liebigs Ann.* **1995**, 1291–1294 (1995).

3. Tang, Y. Q., Sattler, I., Thiericke, R., Grabley, S. & Feng, X. Z. Maremycins C and D, new diketopiperazines, and maremycins E and F, novel polycyclic spiro-indole metabolites isolated from Streptomyces sp. *European J. Org. Chem.* 261–267 (2001) doi:10.1002/1099-0690(200101)2001:2<261::AID-EJOC261>3.0.CO;2-6.

4. Lan, Y. *et al.* Indole methylation protects diketopiperazine configuration in the maremycin biosynthetic pathway. *Sci. China Chem.* **59**, 1224–1228 (2016).

5. Xu, Z., Hu, W., Liu, Q., Zhang, L. & Jia, Y. Total synthesis of clavicipitic acid and aurantioclavine: Stereochemistry of clavicipitic acid revisited. *J. Org. Chem.* **75**, 7626–7635 (2010).

6. Cheng, C. C. & Robins, R. K. Potential Purine Antagonists. VI. Synthesis of 1-alkyl- and 1-aryl-4-Substituted Pyrazolo[3,4-d]Pyrimidines. *J. Org. Chem.* **21**, 1240–1256 (1956).

7. Gorres, K. L. & Raines, R. T. *Prolyl 4-hydroxylase*. *Critical Reviews in Biochemistry and Molecular Biology* vol. 45 (2010).

8. Cutler, H. G. *et al.* Chaetoglobosin K: A New Plant Growth Inhibitor And Toxin From Diplodia Macrospora. *J. Agric. Food Chem.* **28**, 139–142 (1980).

9. Liu, C. *et al.* Community structures and antifungal activity of root-associated endophytic actinobacteria of healthy and diseased soybean. *Microorganisms* **7**, 1–15 (2019).

10. Doyle, T. W. *et al.* Structure determination of lavendamycin- a new antitumor antibiotic from streptomyces lavendulae. *Tetrahedron Lett.* **22**, 4595–4598 (1981).

11. Liu, Y., Zhang, L. & Jia, Y. Total synthesis of maremycins A, B, C 1/C 2, D 1, and D 2. *Tetrahedron Lett.* **53**, 684–687 (2012).

12. Duncan, J. Design and Synthesis and Testing of Conformationally Constrained Peptidomimetics. (2013).

13. Corey, E. J. & Loh, T. P. First Application of Attractive Intramolecular Interactions to the Design of Chiral Catalysts for Highly Enantioselective Diels-Alder Reactions. *J. Am. Chem. Soc.* **113**, 8966–8967 (1991).

14. 国光、古荘、梶谷. NII-Electronic Library Service. *Chem. Pharm. Bull.* 2091 (2002).

15. Liao, S. & Hruby, V. J. Asymmetric synthesis of optically pure β-isopropylphenylalanine: A new β-branched unusual amino acid. *Tetrahedron Lett.* **37**, 1563–1566 (1996).

16. Manuscript, A. & Chemistry, O. Eyes of Collaboration. **74**, 9245–9264 (2011).

17. Li, J. & Sha, Y. A Convenient Synthesis of Amino Acid Methyl Esters. 1111–1119 (2008) doi:10.3390/molecules13051111.

18. Gm-, G. & Medical, G. Synthesis and 0-Lactamase Inhibitory Properties of. 518–522 (1985).

19. Morais, G. R. *et al.* C7-Substituted Estranes and Related Steroids. 229–251 (2006).

20. Joel, L., Romero, O., Jua, J. R. & Mendoza, A. supporting information. 6–12 (2012) doi:10.1107/S1600536812028450.