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Macrocyclic skeletal modification approach to the anti-trypanosomal macrolides, actinoallolides†

Goh Sennari, Akito Watanabe, Takanori Ōno, Jun Oshita, Yoshihiko Noguchi, Tomoyasu Hirose* and Toshiaki Sunazuka*

Herein, we report the construction of 16-membered macrocycles that were designed as intermediates toward the unified synthesis of actinoallolides. Key to our synthesis was the use of Mitsunobu macrocyclization, followed by a sequence of Birch reduction and oxidative C–C cleavage to edit the macrocycle.

Polyketide natural products, in particular macrolides, represent a remarkable class of bioactive compounds with diverse therapeutic applications such as antibacterial, antifungal, and anticancer agents. Their complex architectures, often including multiple stereocenters and intrinsic macrocyclic ring systems, pose challenges in chemical synthesis.[1] Therefore, the development of new synthetic methodologies and strategies could contribute to the foundation of drug discovery research through efficient synthesis of these compounds and their analogs.[2]

Our group has had a long-standing interest in total synthesis and derivatization of macrolide natural products[3] in order to improve their functions as drug lead compounds.[4] In our structure–activity relationship (SAR) study through semi-synthesis of erythromycins, we revealed that translactonization of the 14-membered aglycon to form 12-membered ring systems attenuated the antibacterial activities but enhanced selective anti-inflammatory and/or immunomodulatory properties.[5] This approach led us to pursue a synthetic study of actinoallolides (*i.e.*, **1** and **2**) that were isolated as anti-trypanosomal 12- and 14-membered macrolides at our institute (Fig. 1).[6] Through the total synthesis campaign, we envisaged that access to the adjacent chemical space, which might not be otherwise explored using the naturally occurring products, would be beneficial to delving into further SAR studies.

In 2020, the Paterson group achieved the first total synthesis of actinoallolides using ring-closing metathesis to forge the macrocycle.[7] In addition, we previously reported the construction of a linear all-carbon framework of actinoallolides *via* divergent fragment synthesis, followed by Negishi and Stille cross-coupling reactions.[8] Herein, our efforts to elaborate the designed 16-membered macrocycle toward the total synthesis of actinoallolides are disclosed.

In the isolation study of actinoallolides,[6] the treatment of **1** with acidic conditions effected β-elimination and partial translactonization, affording the 14-membered natural congener **2**. Inspired by this reaction, our retrosynthesis hinged on the assertion that the actinoallolide family including both 12- and 14-membered macrolides might be prepared by translactonization(s) of a common 16-membered ring intermediate such as **4** *via* 14-membered macrolactone **3**, followed by installation of the side chain[8] using a cross-coupling reaction (Scheme 1). Not only could this allow access to all congeners and new chemical space in the macrolactone ring system, but it could also provide the opportunity to optimize the side chain structure that was suggested to be important for their biological activities in the preliminary SAR of the natural product.[6]

We envisioned that the β-ketolactone in **4** could be constructed by a skeletal modification of the macrocyclic aryl ether **6**.[9] In the

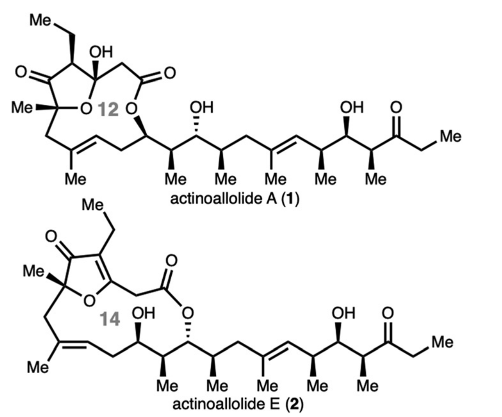

Fig. 1 Structures of actinoallolides A and E.

Ōmura Satoshi Memorial Institute and Graduate School of Infection Control Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

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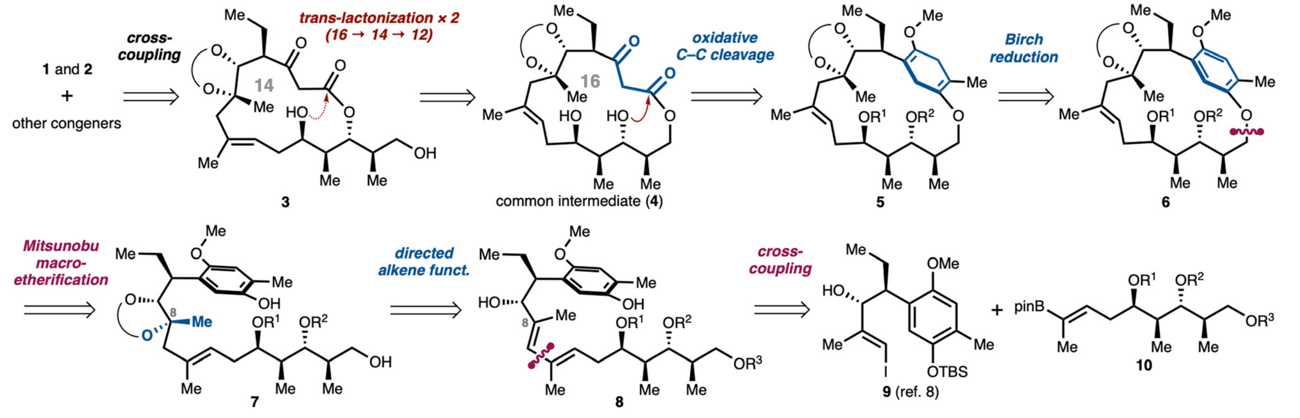
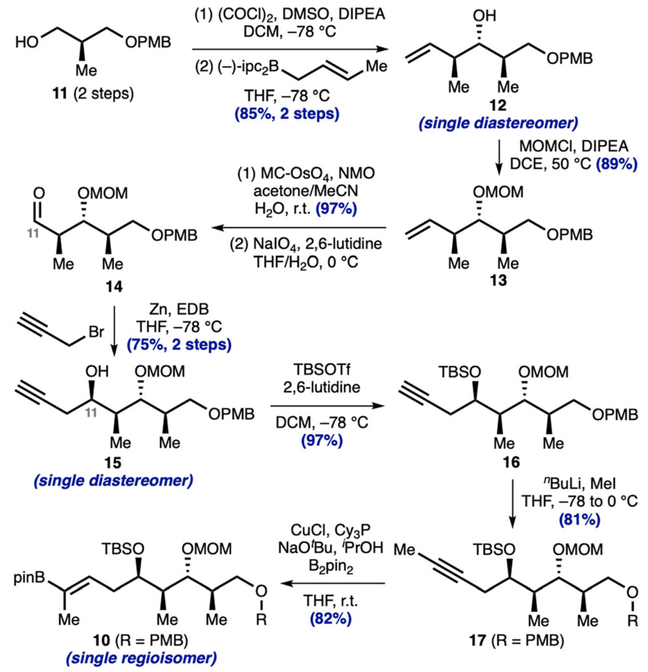


Scheme 1 Our retrosynthesis of the actinoallolide family.

forward sense, Birch reduction of the substituted benzene ring in **6** and subsequent oxidative C–C cleavage of skipped diene **5** would provide the common intermediate. The macrocycle **6** could arise from phenol **7** by an intramolecular Mitsunobu etherification, leveraging preorganization effect using a cyclic protecting group as the turn-inducer.[10] This strategy could allow us to handle the generally reactive β-ketoester functionality as stable arene precursors through the synthesis sequence. Additionally, it could serve as an alternative approach for macrolide syntheses that have relied on macrocyclization by macrolactonization or ring-closing metathesis.[11]

Key to the preparation of **7** would be the construction of the tetrasubstituted carbon center at C8. We envisaged that neighboring participation of the hydroxy group could induce the requisite stereochemistry, tracing back diene **8** as its precursor. Disconnection of the diene moiety in **8** divided the molecule into two fragments, vinyl iodide **9** and vinylboronic ester **10**, which could be stitched together by a Suzuki–Miyaura cross-coupling reaction.[12] In our previous work,[8] an analogous diene with an all-carbon framework was prepared by Stille coupling of a vinyl stannane derived from **9** with the corresponding vinyl iodide (Schemes S1 and S2 in the ESI†). Due to the regioselectivity issue in preparing the electrophile and low-yielding Stille coupling, we sought a different approach to construct the diene moiety. Because we have reported the synthesis of vinyl iodide **9** over 12 steps,[8] this work commenced with investigation to synthesize vinylboronic ester **10**.

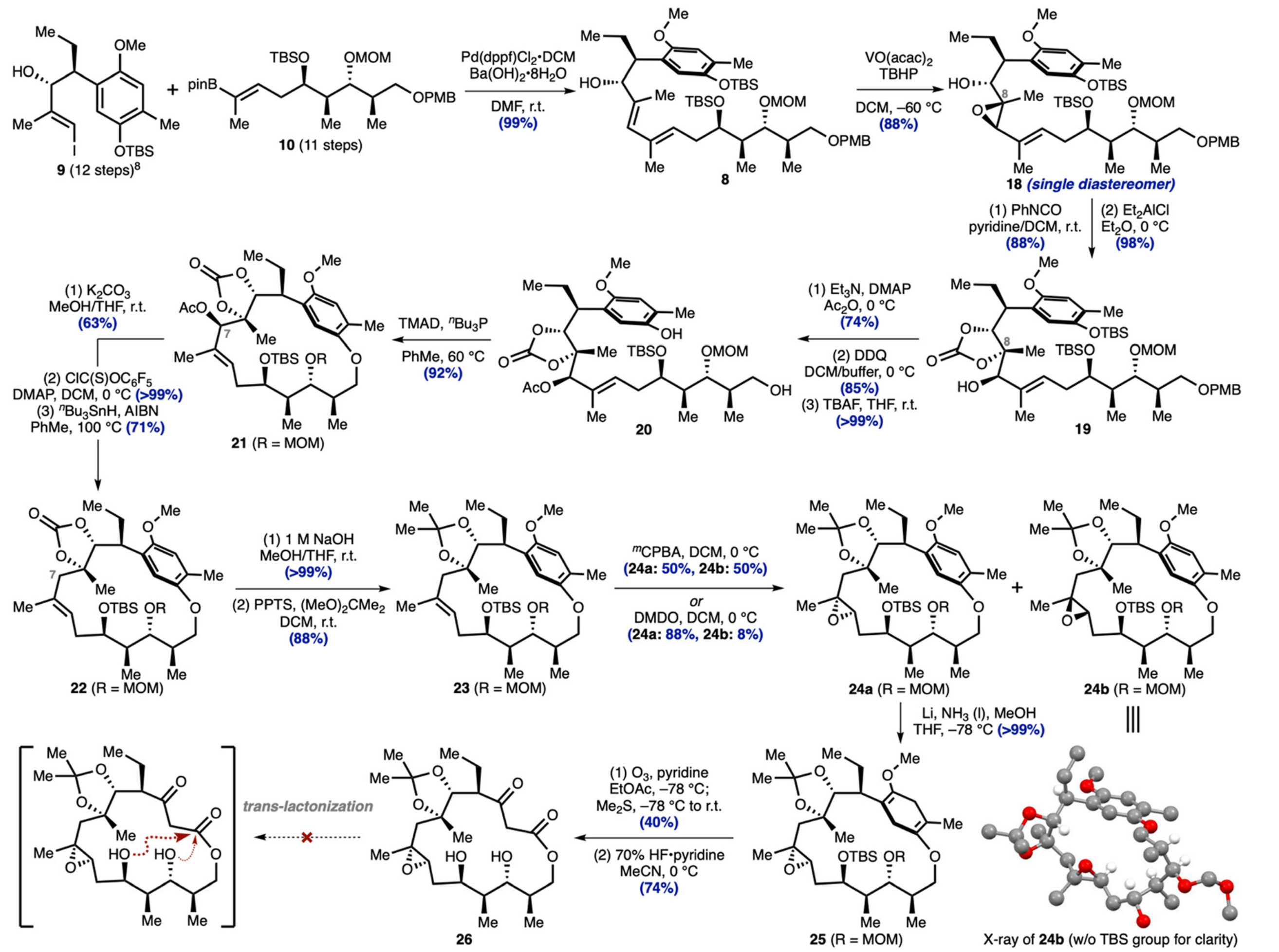
Based on the previous work,[8] known alcohol **11** was prepared from (*R*)-Roche ester over two steps.[13] Considering scalability of the previously employed Krische crotylation[14] that required a sealed tube, we sought an alternative to prepare known alcohol **12** (Scheme 2).[15] Thus, treatment of **11** with Swern oxidation conditions afforded the corresponding aldehyde, which was followed by a Brown crotylation, providing **12** in excellent yield and diastereoselectivity. Protection of **12** with a MOM group under thermal conditions afforded acetal **13** in 89% yield. Because ozonolysis of **13** was somehow capricious, presumably due to competitive oxidation of the acetal and/or PMB moieties, two-step Malaprade–Lemieux–Johnson oxidation was used for this purpose. Subjection of **13** to modified



Scheme 2 Selective fragment synthesis.

dihydroxylation conditions using micro-encapsulated (MC) osmium tetroxide[16] gave the corresponding diols as a mixture of diastereomers in 97% yield. Subsequent oxidative cleavage in the presence of 2,6-lutidine reproducibly provided aldehyde **14**. With the reliable route to aldehyde **14**, we investigated propargylation reactions to set the requisite stereochemistry at C11.

Although previous propargylation was not stereoselective,[8] we found that treatment of **14** with propargyl bromide in the presence of zinc and 1,2-dibromoethane (EDB)[17] as a crucial additive gave rise to alcohol **15** in 75% yield over two steps as a single diastereomer. We later confirmed the stereochemistry by a single-crystal X-ray diffraction (*vide infra*). The resulting hydroxy group in **15** was protected with a TBS group, which was followed by methylation of the terminal alkyne, affording propyne **17** in 81% yield. To our delight, the internal alkyne



Scheme 3 Cross-coupling, macro-etherification and skeletal modification to elaborate 16-membered macrocycles.

moiety in **17** was engaged regioselectively in a copper-catalyzed hydroboration[18] to provide **10** in 82% yield as a single isomer. Consequently, we prepared the fragment in a highly selective manner over 11 steps from the commercial material.

With both vinyl iodide **9** and boronic ester **10** in hand, we investigated Suzuki–Miyaura cross-coupling. In the event, treatment of **9** and **10** with the palladium precatalyst in the presence of barium hydroxide provided diene **8** (Scheme 3). Importantly, this coupling reaction proceeded in excellent yield with a slight excess amount of **10** (1.1 equiv.) on a multi-gram scale, setting the stage to manipulate the diene moiety. It turned out that chemo-, regio- and stereo-selective manipulation of the diene in **8** was quite challenging using a variety of hydroalkoxylation conditions.[19] Therefore, we sought an alcohol-directed transformation to construct the requisite tetrasubstituted carbon center. To this end, we found that vanadium-catalyzed epoxidation in the presence of TBHP[20] effected chemo- and stereo-selective epoxidation to give rise to epoxide **18** in 88% yield as a single diastereomer. Treatment of **18** with phenyl isocyanate provided the corresponding phenylcarbamate in 88% yield, which was followed by epoxide ring-opening involving intramolecular cyclization,[21] affording cyclic carbonate **19** in 98% yield. Although the resulting hydroxy group needed to be removed in downstream transformations, this three-step sequence allowed us to construct the challenging tetrasubstituted carbon in a highly selective and scalable manner.

Because the cyclic carbonate group that was necessary to set the stereochemistry at C8 could induce the templated preorganization for macrocyclization,[10] we turned our attention to the planned Mitsunobu macro-etherification. In this regard, allylic alcohol **19** was first protected with an acetyl group (74% yield), and subsequent cleavage of the PMB group provided the corresponding alcohol in 85% yield. Selective deprotection of the phenol was achieved by treatment with TBAF to afford **20** quantitatively. To our delight, Mitsunobu 16-membered cyclization proceeded smoothly using TMAD and Bu_3P under thermal conditions to give macrocycle **21** in 92% yield. After removal of the acetyl group, Barton–McCombie deoxygenation using a perfluorophenyl thiocarbonate group[22] to suppress the undesired sigmatropic rearrangement furnished the product **22** in 71% yield. In this way, the stage was set for our key skeletal modification of the macrocycle.

Our preliminary efforts to effect Birch reduction using **22** proved unsuccessful due to the competitive reactivity of the cyclic carbonate moiety. In addition, the trisubstituted alkene moiety was not compatible under ozonolysis conditions despite the excess substituents on the arene ring that were installed to make the corresponding skipped diene moiety more electron rich.[23] These observations necessitated us to implement the following three-step transformation. After hydrolysis of **22** and subsequent protection to provide acetonide **23**, we attempted protection of the alkene group with an epoxide ring. For this purpose, treatment of **23** with *m*-CPBA gave rise to epoxides **24a** and **24b** as a separable 1 : 1 mixture in quantitative yield. We determined the structure of **24b** unambiguously by X-ray crystallographic analysis.

After a survey of reaction conditions, we found that DMDO-mediated epoxidation selectively provided **24a** in 88% yield. Gratifyingly, subjection of **24a** to Birch reduction conditions converted the arene ring to skipped diene **25**, followed by ozonolysis to construct the desired β-ketolactone in 40% yield. To the best of our knowledge, this is the first example of the sequence applying to a multi-functional macrocyclic scaffold, demonstrating the power of this strategy in a complex system.

In order to implement translactonization, global deprotection provided diol **26** in 74% yield. Unfortunately, our extensive efforts to effect the planned translactonization proved difficult due to competitive side reactions. This suggests that direct 12-membered macrocyclization would be desirable to elaborate this class of molecules. Nevertheless, our current results underscore the utility of the skeletal modification approach to convert the aryl ether to the β-ketolactone in the context of a complex natural product synthesis.

In conclusion, we demonstrated macro-etherification using a Mitsunobu reaction to forge the designed 16-membered macrocycle *en route* to actinoallolides. We showcased that the key macrocyclic carbon skeletal editing of the aryl ether to β-ketolactone was achieved by Birch reduction, followed by oxidative C–C cleavage of the skipped diene. We believe that this study should inform future synthetic design plans to elaborate this class of molecules as well as to adopt the core modification approach in total synthesis. Additional efforts toward the interception of the desired 12- and 14-membered macrolactones are currently underway in our laboratory.

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Data availability

Crystallographic data for **24b** has been deposited at CCDC under 2453344† and can be obtained from https://doi.org/DOI:10.5517/ccdc.csd.cc2md85h.

Conflicts of interest

There are no conflicts to declare.

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