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Towards the total synthesis of the anti-trypanosomal macrolide, Actinoallolides: construction of a key linear intermediate

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ABSTRACT

Herein, we describe the synthesis of key intermediate (+)-**8** as an essential intermediate including full carbon framework for completing the convergent total synthesis of Actinoallolide A (**1**). (+)-**8** was obtained by Negishi and Stille cross coupling from (+)-**9**, (+)-**10** and (−)-**11**. Stereo-divergent preparation of two similar units, consisting of three consecutive stereocenters, facilitated the synthesis of (+)-**10** and (−)-**11**.

Actinoallolides A–E (**1**–**5**) are new 12-membered or 14-membered macrolides, isolated from a culture broth of *Actinoallomurus fulvus* MK10-036 during our program of physicochemical screening for metabolites[1] (Fig. 1). The absolute configuration of Actinoallolide A (**1**) was determined by detailed NMR analyses and single-crystal X-ray crystallography of its MTPA ester.[1] The structural features of **1** are as follows: (1) a 12-membered macrolactone possessing five-membered hemiacetal moiety inside the macrolactone ring, and (2) a side chain including consecutive asymmetric centers, which can be recognized by the similar repeating stereochemical triad (i.e., C1′–C3′ and C7′–C9′) embedded in the linear backbone.

Actinoallolides A–E were found to exhibit in vitro anti-trypanosomal activity against *Trypanosoma brucei brucei* GUTat 3.1 strain (the causative agent of Nagana disease in animals), *Trypanosoma brucei rhodesiense* STIB900 (causative agent of Human African Trypanosomiasis), *Trypanosoma cruzi* Tulahun C4C8 strain (causative agent of Chagas disease). Actinoallolide A (**1**) showed the most potent activity and specific selectivity (anti-trypanosomal activity; 0.0049 μg/mL against *T. b. brucei* GUTat 3.1 strain, 0.086 μg/mL against *T. b. rhodesiense* STIB900 strain, 0.226 μg/mL against *T. cruzi* Tulahun C4C8 strain, cytotoxicity; >100 μg/mL against MRC-5 cell, MIC; >10 μg/paper disk against Gram positive and Gram-negative bacteria).[1]

12-Membered macrolide antibiotics have been reported to have various biological activities, such as Methymycin (antibacterial activity),[2] Pladienolides (antitumor activity)[3] and NK30424-A, B (antineoplastic activity).[4] However, to our knowledge, Actinoallolides are the first example of anti-trypanosomal macrolides. In addition, all currently anti-trypanosomal drugs (such as Suramin, Pentamidine, Melarsoprol, and Eflornithine) are toxic, expensive, difficult to administer, and have difficulty in crossing the blood brain barrier, and parasite resistance to them is increasing. Actinoallolides would be expected to have a different mode of anti-trypanosomal action compared with all current drugs, due to the significant difference in chemical structures. Consequently, we attempted to facilitate the creation of promising lead compounds for possible anti-trypanosomal drug development by establishing the total synthesis of Actinoallolides.

Although 12-membered macrolide antibiotics (i.e., Methymycin,[5] Pladienolides,[6]) have been synthesized, synthesis of Actinoallolides has never been reported yet. In addition, since Actinoallolides have different frameworks (i.e., macrolactone and side chain) compared with other 12-membered macrolides, nothing is known about the relationship between the specific biological pattern in 12-membered macrolides and its functional groups on the ring and side chain.

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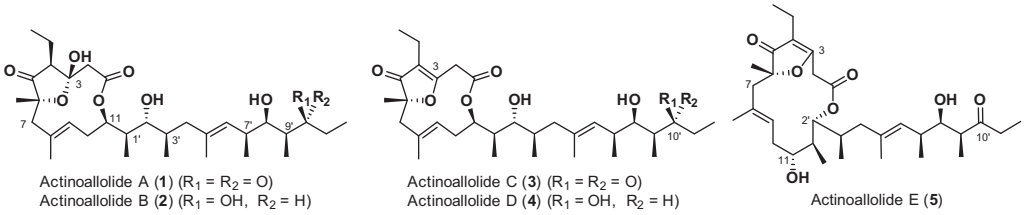


Figure 1. Structure of Actinoallolides.

In previous our isolation study and structural analysis of Actinoallolides,[1] the structure of **1**, together with structural information of related compounds and observation of naturally occurring **1**, indicated that the hemiacetal moiety would easily undergo β-elimination of the hydroxy group at the C-3 position under acidic conditions to afford enone-type Actinoallolides C (**3**) and D (**4**).[1] In addition, the acid-sensitive hemiacetal moiety could be led from the β-ketoester precursor, which is highly reactive moiety under acidic and basic conditions.

Hence, we needed to develop selective preparation of the hemiacetal moiety from a β-ketoester at the late stage to complete the total synthesis. From the remark mentioned above, we envisaged that utilizing a phenolether (**7**) as a key precursor for construction of a highly reactive hemiacetal moiety could overcome possible instability toward the total synthesis of **1** (Scheme 1). The hemiacetal moiety would, accordingly, be constructed in the late stage of the total synthesis as a key conversion by a Birch reduction of **7** and subsequent chemoselective oxidative cleavage of cyclohexadiene (**6**),[7] which could be accomplished by introduction of substituents on the benzene ring of **7** to heighten the electron density of the olefins compared with others (i.e., C8–C9, C5′–C6′) (Scheme 1).[8] The disconnection of **7** into three distinct parts (the Left (**9**), Center (**10**), and Right parts (**11**)) at the phenolether bond and the two tri-substituted olefin sites through Mitsunobu macroetherification, Negishi[9] and Stille[10] coupling could allow the convergent synthetic route, not merely for total synthesis but also to enable the synthesis of several derivatives. The similarity of the stereo-chemical triad of **10** and **11** suggested use of a common intermediate (**12**), which could be efficiently afforded by construction of its stereocenters.[11] As stated above, we envisioned the convergent total synthetic route of **1** would also furnish a range of derivatives.

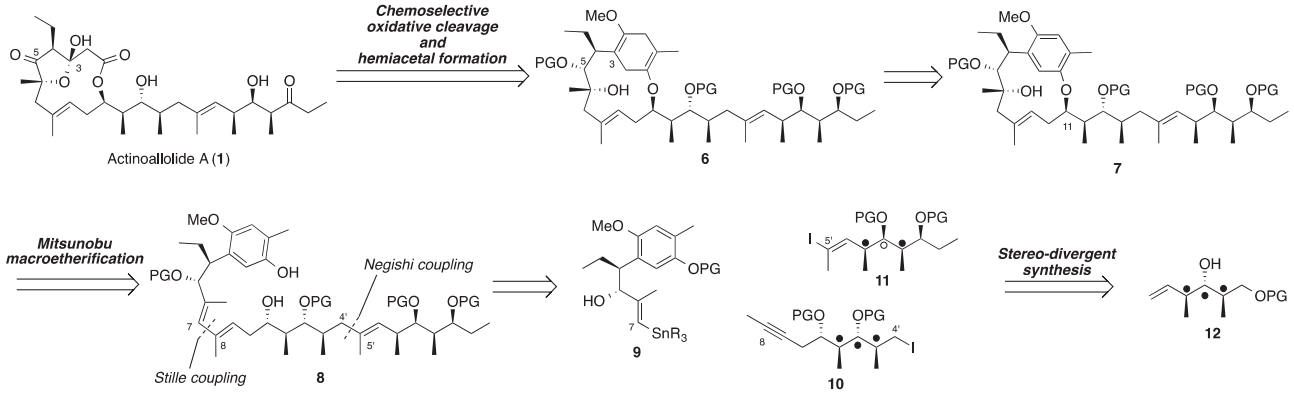
Herein, we report the synthesis of key intermediate **8** as an essential intermediate including full carbon framework for completing the convergent total synthesis of Actinoallolide A (**1**). In synthesis of the Left part **9**, we utilized Hartwig's α-arylation and kinetic resolution of the racemic allyl alcohol using Sharpless asymmetric epoxidation to achieve our goal. We also employed a new stereoselective reduction of 3-alkoxyketone using Schwartz's reagent and Lewis acid combination. We further developed a stereo-divergent synthesis of both Center part **10** and Right part **11** using a common intermediate **12** origin.

Synthesis of Left part

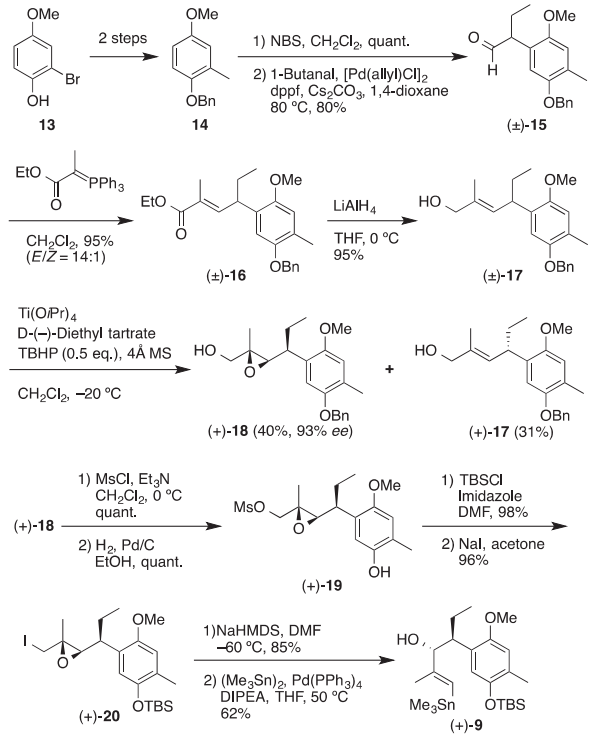
Synthesis of Left part (**9**) was accomplished using commercially available mono-methylhydroquinone (**13**), following the known protocol[12] to provide **14**. Subsequently, *ortho*-bromination using *N*-bromosuccinimide and Hartwig's α-arylation[13] of aldehyde was carried out to furnish the homobenzaldehyde (±)-**15** (Scheme 2). This was transformed into α,β-unsaturated ester (±)-**16** under the Wittig condition, followed by reduction of the ester moiety to afford racemic allyl alcohol (±)-**17**. Simultaneously, we attempted kinetic resolution of (±)-**17**, which was separated by Sharpless asymmetric epoxidation to afford the optically-active epoxy alcohol in 93% ee.[14] In the next four steps, the hydroxy group of (+)-**18** was mesylated, followed by deprotection of benzyl group to yield phenol (+)-**19**. Subsequently, protection of the phenolic-OH with a TBS group, followed by Finkelstein reaction provided iodo-epoxide (+)-**20**. Selective deprotonation of the methylene proton from (+)-**20** enabled opening of the epoxy ring via anti-elimination to provide the *E*-vinyl iodide.[15] Finally, iodine–tin exchange using $Pd(PPh_3)_4$ and hexamethylditin produced *E*-vinyl stannane (+)-**9** in good yield.

Synthesis of Center part

The stereo-divergent synthesis of Center part (**10**) began with common intermediate (−)-**12**, which was easily prepared from commercial methyl (*R*)-(+)-3-hydroxy-2-methylpropionate (**21**) using the known procedure[16] and Krische's catalytic asymmetric crotylation[17] (Scheme 3). With common intermediate (−)-**12** in hand, synthesis of the Center part began with acetalization of (−)-**12** to provide the PMP acetal in good yield. PMP acetal was then converted to aldehyde (−)-**23** using ozonolysis, followed by the nucleophilic addition of allenyl zinc species,[18] to afford homopropargyl alcohol (+)-**24** and (−)-**25** as a separable diastereomer



Scheme 1. Retrosynthetic analysis of Actinoallolide A (**1**).



Scheme 2. Synthesis of Left part (+)-**9**.

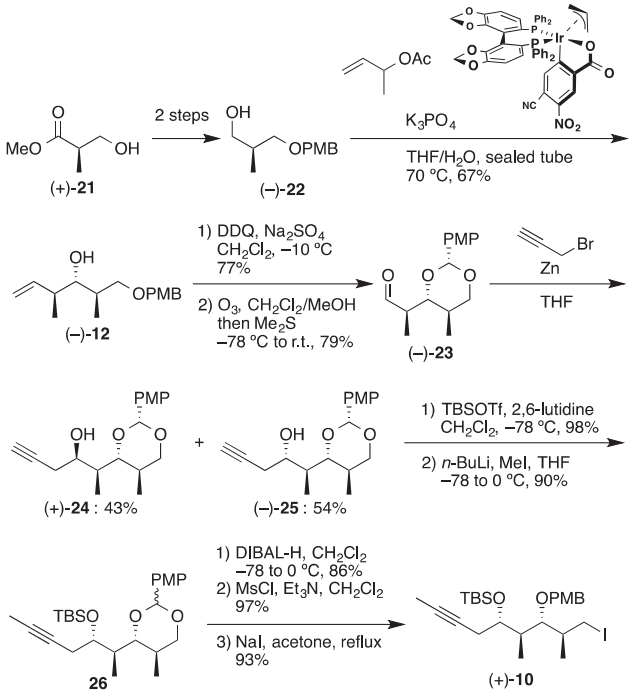
(1:1); the stereochemistry of (+)-**24** and (−)-**25** was determined by the modified Mosher method.[19] Provided with desired alcohol (−)-**25** and a hydroxyl group protected with a TBS group, the PMP acetal moiety epimerized, with subsequent C-methylation of the alkyne group to afford di-substituted alkyne (**26**). PMP acetal (**26**) was then converted to the PMB ether by reductive cleavage, followed by mesylation of the primary alcohol and subsequent iodination to afford desired Center part (+)-**10** in excellent yield.

Synthesis of Right part

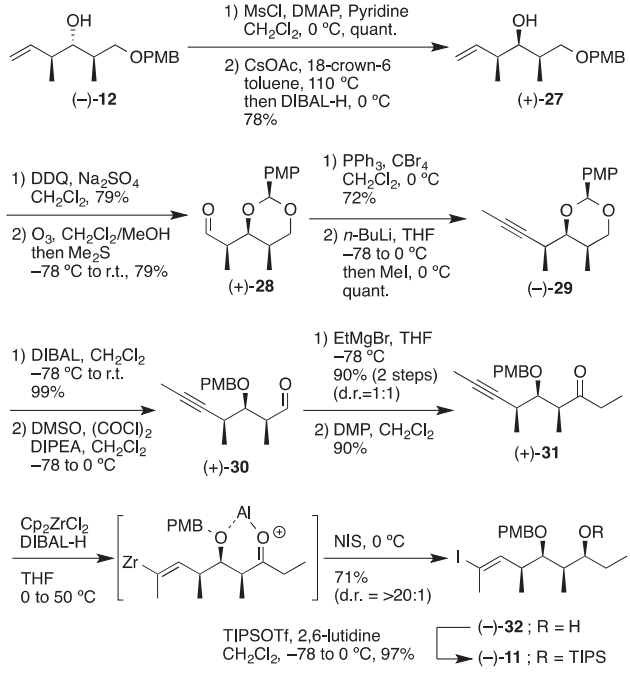
We attempted to invert the (*S*)-hydroxyl group of (−)-**12** to the (*R*)-configuration but Mitsunobu inversion[20] proved unsuccessful. We concluded that there was a hydroxyl group creating steric hindrance position on (−)-**12**. Therefore, (−)-**12** was converted to the corresponding mesylate, which was exposed to cesium acetate in the presence of 18-crown-6, followed by reduction with DIBAL-H to afford the desired chiral alcohol (+)-**27** in a one-pot process with the inversion of the stereochemistry[21] (Scheme 4). Following the same reaction sequence as in the synthesis of (−)-**23** produced (+)-**28** in good yield. This was transformed to alkyne (−)-**29** by using Corey–Fuchs preparation and subsequent regioselective PMP acetal opening to produce primary alcohol. After 3-step preparation of ketone (+)-**31** from the primary alcohol, we attempted preparation of the vinyl iodide from (+)-**31** using the Negishi's method.[22] As a result of hydrozirconation of (+)-**31**, chiral alcohol (−)-**32** was given as a single diastereomer. In general, the Schwartz's reagent does not reduce the carbonyl group. However, in situ generated diisobutyl aluminum chloride activated and reduced the carbonyl group through a six-member transition state which can control the stereochemistry of the hydroxyl group. Finally, protection of the hydroxyl group with a TIPS group afforded desired Right part (−)-**11**.

Synthesis of the linear intermediate

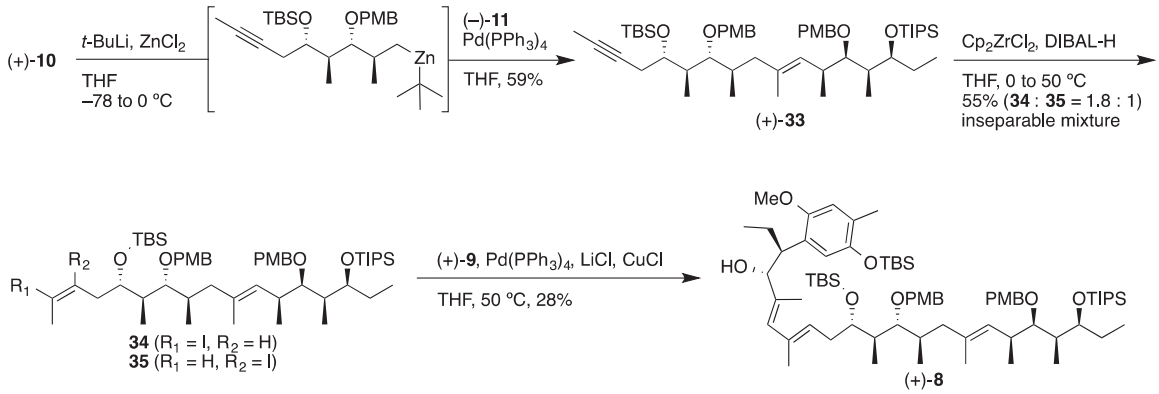
With Left part (+)-**9**, center part (+)-**10**, and right part (−)-**11** in hand, we examined the connection between each part (Scheme 5). At first, Negishi cross coupling[9] with (+)-**10** and (−)-**11** furnished a coupling product (+)-**33** in 59% yield. Subsequently, (+)-**33** was transformed to vinyl iodide (**34**) by using hydrozirconation condition[22] along with regioisomer (**35**) as inseparable mixture; since there was no functional group at the α-position of the alkyne moiety, steric effects were less compared with the synthesis of (+)-**32**. Finally, Stille coupling[10] with (+)-**9** and the mixture of **34**/**35** provided crucial linear compound (+)-**8** in 28% yield, together with non-reacted **35** recovered from the coupling reaction.



Scheme 3. Synthesis of Center part (+)-**10**.



Scheme 4. Synthesis of Right part (−)-**11**.



Scheme 5. Synthesis of key linear intermediate (+)-**8**.

In conclusion, we have achieved the synthesis of an essential intermediate including full carbon framework in the total synthesis of Actinoallolide A (**1**), consisting of three specific components (the Left part, (+)-**9**; Center part, (+)-**10**; and Right part, (+)-**11**) using Negishi and Stille reactions as key steps to connect each fragment. In synthesis of the Left part, we utilized Hartwig's α-arylation and kinetic resolution of the racemic allyl alcohol using Sharpless asymmetric epoxidation to achieve our goal. We also employed a new stereoselective reduction of the β-alkoxyketone using the Schwartz's reagent and Lewis acid combination. We further developed a stereo-divergent synthesis of both Center part (+)-**10** and Right part (−)-**11** with the common intermediate (−)-**12** origin. Further studies toward the total synthesis of **1** are now in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.022.

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