Stereoselective Synthesis of the Southern Domain of Tubelactomicin A by a Tandem Intramolecular Diels-Alder/Lactonization Reaction

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As part of a program aimed at the discovery of new antimicrobial natural products, Igarashi and co-workers isolated Tubelactomicin A (1) from the culture broth of an actinomycete strain designated MK 703-102F1, a member of *Narcardia*. Tubelactomicin A showed strong activity against acid-fast bacteria, including drug-resistant strains, and was suggested as a lead for the development of novel type of antitubercular drugs. The structure of 1 was assigned by spectroscopic analysis and the absolute configuration determined by X-ray crystallographic analysis to be a 16-membered macrolactone of which the southern portion is the trans-fused decaline moiety possessing 6 contiguous stereogenic centers as shown in Scheme 1.2 Due to its interesting biological activity and structural complexity, Tubelactomicin A has been an attractive target molecule for organic chemists. Thus far, the Tadano3 and Tatsuta4 groups have reported on the total synthesis of 1. Recently, the Tanano group also reported Tubelactomincins B, D, and E.5

Herein, we report an efficient stereoselective synthesis of the southern domain of Tubelactomicin A (2), containing all requisite stereocenters and functional groups by a tandem intramolecular Diels-Alder (IMDA)/lactonization reaction and describe endo or exo-selective IMDA reaction.

As shown in Scheme 1, we envisioned that the southern domain, 2 could be achieved by IMDA reaction and selective reduction of its precursor 3, while 3 could be formed by a Nozaki-Hiyama-Kishi reaction6 of vinyl iodide 4 and aldehyde 5.

The synthesis of vinyl iodide 4 originates from ester 6, conveniently prepared via 1 step from 3-methyl propiolate by a known procedure.7 Diisobutylaluminium hydride (DIBAL-H) reduction of ester 6 and subsequent desilylation provided alcohol 7 in 88% yield in 2 steps. Treatment of 7 with tributyltin hydride and copper cyanide in THF exclusively afforded the (E)-vinyl stannane compound in 86% yield.8 After iodination of 8 in 86% yield, the alcohol was protected with several different groups, such as TBDPS, THP, or TBS. However, it was found out that the TBDPS-protected alcohol of 9 was the most stable and thus used without silica gel column purification.

As shown in Scheme 2, the synthesis of 5 could be achieved from compound 10, which is easily prepared in 4 steps from commercially available (R)-methyl 3-hydroxy-2-methylpropionate.9 Ozonolysis of the vinyl group of 10 and a subsequent Wittig reaction10 using Ph3P=C(CH3)CO2Et provided E-olefin 11 in 92% yield in 2 steps. The E-configuration of 11 was confirmed by 1H-NMR studies. After deprotection of the ethyl vinyl ether group under acidic conditions, the resulting alcohol was oxidized with pyridinium chlorochromate to give aldehyde 5 in 79% yield in 2 steps.

With the required components of 4 and 5 in hand, we examined several reaction conditions for the Nozaki-Hiyama-Kishi reaction.
under thermal IMDA conditions provided the undesired coupled alcohol in 93% yield along with 15% of recovered epimer at -78 °C afforded the desired aldehyde 3 with 98% yield. It is noteworthy that the ratio of DMSO and THF in the presence of chromium triflate in toluene, reflux, furnished desired alcohol 13, 52% yield with a ratio of 8:1. Protection of the methoxy group followed by removal of the TBDPS group using TBAF led to the precursor for the IMDA reaction.

Kishi reaction between vinyl iodide 4 and aldehyde 5. Using 1 equivalent of nickel chloride in the presence of chromium chloride in a mixture of DMSO and THF (2:3:1) at ambient temperature, a satisfying result could be obtained with the desired coupled alcohol 12 as a mixture (α-OH:β-OH = 1:1) in 98% yield. It is noteworthy that the ratio of DMSO and THF is crucial for a high yield. Use of an inverse mixture of DMSO and THF (1:2.3) or only DMSO afforded 12 in 45% or 70% yield, respectively.

Alcohol 12 was then subjected to Dess-Martin oxidation to give ketone 13 in 93% yield. CBS reduction of ketone 13 furnished desired alcohol 14 as the major product in 90% yield with a ratio of 8:1. Protection of the methoxy methyl ether group followed by removal of the TBDPS group in 14 using TBAF led to the precursor for the IMDA reaction. In contrast to the Todano group’s result. Treatment of 14 under thermal IMDA conditions provided the undesired exo-mode cyclized cis-adduct, 15, as a single product in 86% yield. In order to investigate the stereochemistry effect of 7-alcohol, the β-hydroxy epimer of 14, epimer-14 was prepared by following the same sequence from 13 using (R)-oxazaborolidine (Scheme 3). Interestingly, IMDA reaction of epimer-14 also afforded 60% of cis-fused adduct 16 and 10% of recovered epimer-14 by exo-mode cyclization.13

On the other hand, TBDPS-deprotected ketone 3 was cyclized under similar conditions via a tandem IMDA/lactonization reaction to give desired endo-cyclized trans-adduct 17 as a single product in 52% yield along with 15% of recovered 3. Finally, stereoselective Luche reduction of ketone at -78 °C afforded the desired stereochemistry of alcohol 2 (> 20:1) in 83% yield.

In conclusion, an efficient synthetic route for the southern domain of Tubulactomicin A, 2, has been developed. The key steps include: a Nozaki-Hiyama-Kishi reaction of vinyl iodide 4 and aldehyde 5 a tandem IMDA/lactonization reaction, and stereoselective Luche reduction to construct all 6 stereocenters and functional groups. Further studies of exo or endo selective IMDA reactions will be reported in due course.

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References and Notes