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

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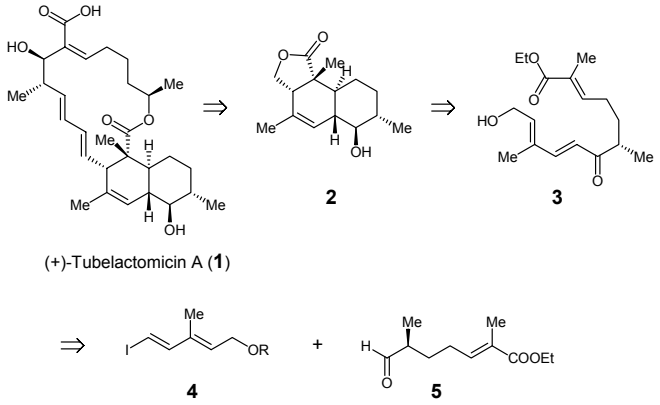
As part of a program aimed at the discovery of new antimicrobial natural products, Igarashi and co-workers isolated Tubelactomicin A (**1**) from the culture broth of an actinomycete strain designated MK 703-102F1, a member of *Narcardia*.[1] Tubelactomicin A showed strong activity against acid-fast 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 Tadano[3] and Tatsuta[4] groups have reported on the total synthesis of **1**. Recently, the Tanano group also reported Tubelactomicins B, D, and E.[5]



Scheme 1. Retrosynthetic analysis of **2**

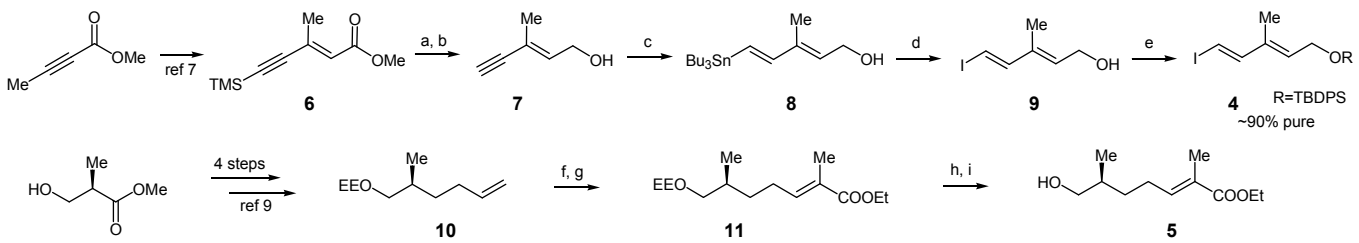
Herein, we report an efficient stereoselective synthesis of the southern domain of Tubelactomicin A (**2**), containing all requisite stereocenters and functional groups by a tandem intramolecular Diels-Alder (IMDA)/lactonization reaction and describe *endo* or *exo*-selective IMDA reaction.

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 reaction[6] of vinyl iodide **4** and aldehyde **5**.

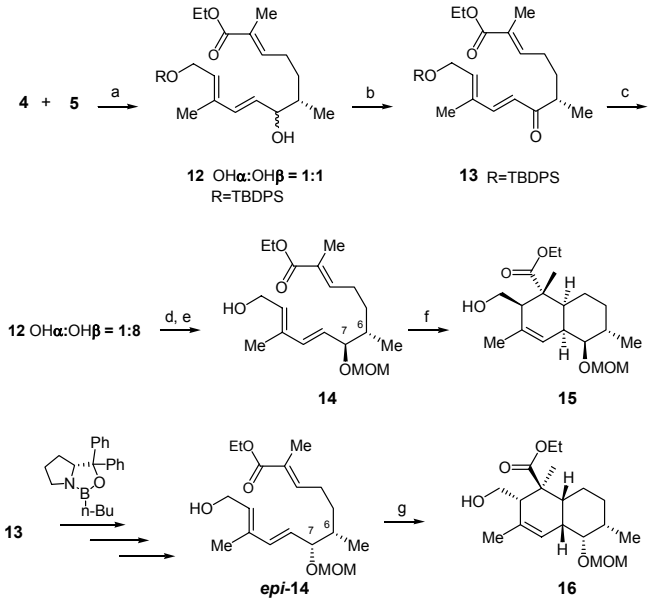
The synthesis of vinyl iodide **4** originates from ester **6**, conveniently prepared *via* 1 step from 3-methyl propiolate by a known procedure.[7] Diisobutylaluminium hydride (DIBAL-H) reduction of ester **6** and subsequent desilylation provided alcohol **7** in 88% yield in 2 steps. Treatment of **7** with tributyltin hydride and copper cyanide in THF exclusively afforded the (*E*)-vinyl stanne 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 **4** 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-methylpropanoate.[9] Ozonolysis of the vinyl group of **10** and a subsequent Wittig reaction[10] using $Ph_3P{=}C(CH_3)CO_2Et$ provided *E*-olefin **11** in 92% yield in 2 steps. The *E*-configuration of **11** was confirmed by ^{1}H-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**[11] in 79% yield in 2 steps.

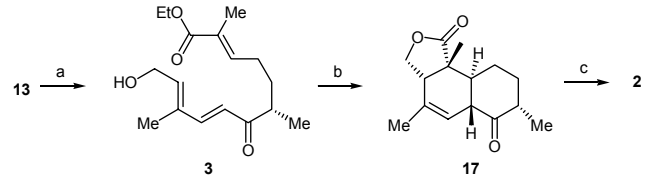
With the required components of **4** and **5** in hand, we examined several reaction conditions for the Nozaki-Hiyama-



Scheme 2. Reagents and conditions: a) DIBAL-H, PhMe, -78 °C, 95% b) *n*-Bu_4NF, THF, 0 °C, 93% c) *n*-$Bu_3Sn(Bu)CuCNLi_2$, THF, -78 °C to -30 °C, 86% d) I_2, CH_2Cl_2, 86% e) TBDPSCl, Et_3N, DMAP, r.t. f) O_3, MeOH, -78 °C g) $Ph_3P{=}C(CH_3)CO_2Et$, r.t., 92%, two steps h) 10% HCl, THF, 0 °C, 93% i) PCC, Celite, CH_2Cl_2, r.t., 85%.



Scheme 3. Reagents and conditions: a) $NiCl_2$, $CrCl_2$, THF: DMSO =1:2.25, r.t., 98%. b) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 93%. c) (s)-oxazaborolidine, catecolborane, PhMe, -78 °C, 75%. d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, reflux, 98%. e) *n*-Bu_4NF, THF, r.t., 92%. f) BHT, toluene, 130 °C, 24h, 89%. g) BHT, toluene, 130 °C, 24h, 60%.



Scheme 4. Reagents and conditions: a) HF-Pyridine, THF: pyridine=2:1, 0 °C, 80%. b) BHT, toluene, 130 °C, 24h, 52% c) $CeCl_3$, $NaBH_4$, MeOH, -78 °C, 83%.

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 to 1.[12] Protection of the methoxy methylether group followed by removal of the TBDPS group in **14** using TBAF led to the precursor for the IMDA reaction. In contrast to the Tadano group's result.[3] 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, *epi*-14** was prepared by following the same sequence from **13** using (*R*)-oxazaborolidine (Scheme 3). Interestingly, IMDA reaction of ***epi*-14** also afforded 60% of *cis*-fused adduct **16** and 10% of recovered ***epi*-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 requisite stereochemistry of alcohol **2** (> 20:1) in 83% yield.

In conclusion, an efficient synthetic route for the southern domain of Tubelactomicin 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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