

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

Ji Yoon Kim, Geum-Sook Hwang,[†] Seung Min Lee, Jae Hyun Han, Eun Young Kim,[†] and Do Hyun Ryu*

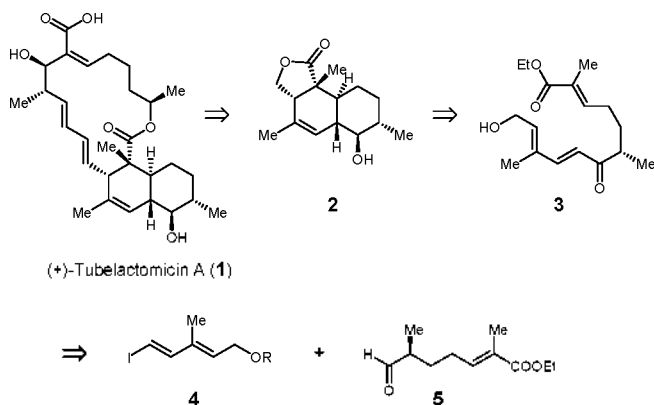
Department of Chemistry, Sungkyunkwan University, Suwon, Gyeonggi 440-746, Korea. *E-mail: dhryu@skku.edu

[†]Korea Basic Science Institute, 5St, Anam-Dong, Seongbuk-Gu, Seoul 136-713, Korea

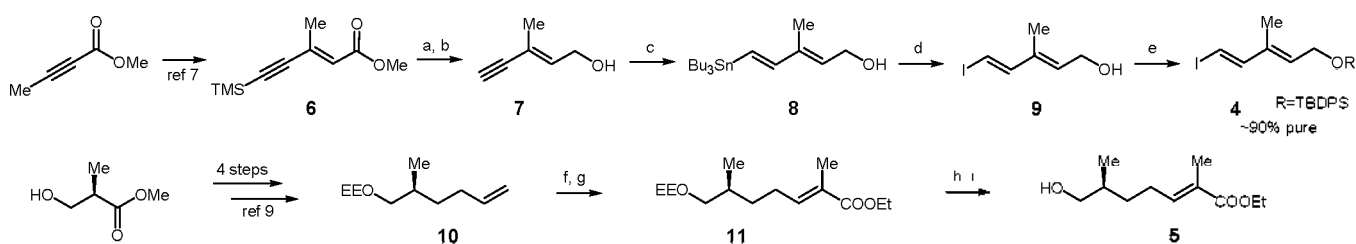
Received October 29, 2008, Accepted December 23, 2008

Key Words: Tubelactomicin A. Nozaki-Hiyama-Kishi reaction, Intramolecular Diels-Alder reaction, Octahydronaphthalene. Luche reduction

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 *Nocardia*.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 Tadano³ and Tatsuta⁴ 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**



Scheme 2. Reagents and conditions: a) DIBAL-H, PhMe, -78 °C, 95% b) *n*-Bu₄NF, THF, 0 °C, 93% c) *n*-Bu₃Sn(Bu)CuCNLi₂, THF, -78 °C to -30 °C, 86% d) I₂, CH₂Cl₂, 86% e) TBDPSCl, Et₃N, DMAP, r.t. f) O₃, MeOH, -78 °C g) Ph₃P=C(CH₃)CO₂Et, r.t., 92%, two steps h) 10% HCl, THF, 0 °C, 93% i) PCC, Celite, CH₂Cl₂, r.t., 85%.

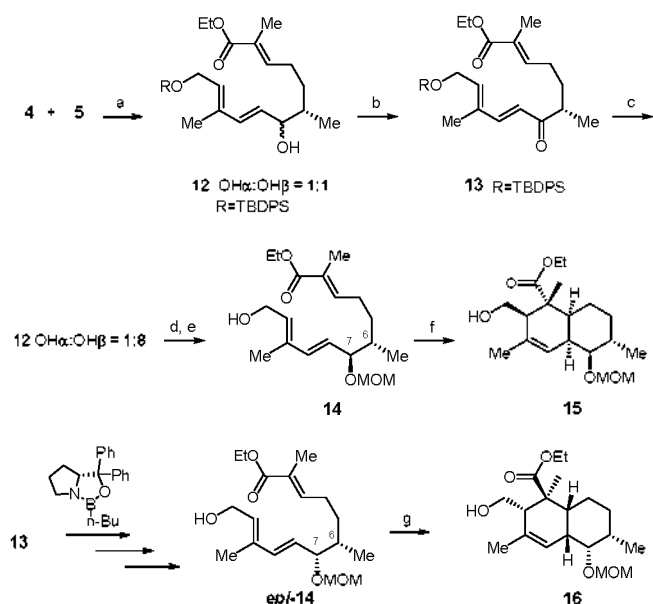
Herein, we report an efficient stereoselective synthesis of the southern domain of Tubelactomicin A (**2**), containing all requisite stereocenters and functional groups by a tandem intramolecular Diels-Alder (IMDA)/lactonization reaction and describe *endo* or *exo*-selective IMDA reaction.

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**.

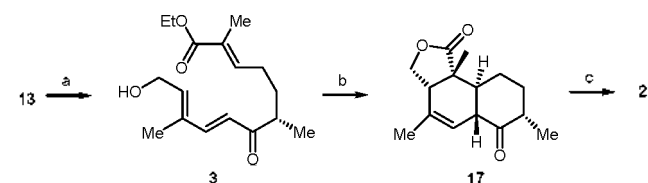
The synthesis of vinyl iodide **4** originates from ester **6**, conveniently prepared *via* 1 step from 3-methyl propionate by a known procedure.⁷ Diisobutylaluminium hydride (DIBAL-H) reduction of ester **6** and subsequent desilylation provided alcohol **7** in 88% yield in 2 steps. Treatment of **7** 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 **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 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**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 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, catecholborane, PhMe, -78 °C, 75%. d) MOMCl, *i*-Pr₂NEt, CH_2Cl_2 , reflux, 98%. e) *n*-Bu₄NF, 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 , NaBH₄, 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 ($\alpha\text{-OH}:\beta\text{-OH} = 1:1$) 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*)-oxaza-

borolidine (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.

Acknowledgments. This work was supported by a Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2005-070-C00073, KRF-2008-331-C00160) and by a Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MEST) (No. R01-2008-000-11094-0) and by KBSI grant (N28043) to G.-S. Hwang.

References and Notes

- Igarashi, M.; Hayashi, C.; Homma, Y.; Hattori, S.; Kinoshita, N.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **2000**, *53*, 1096.
- Igarashi, M.; Nakamura, H.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **2000**, *53*, 1102.
- Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.-I.; Tadano, K.-I. *Org. Lett.* **2005**, *7*, 2265.
- Hosokawa, S.; Seki, M.; Fukuda, H.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 2439.
- Sawamura, K.; Yoshida, K.; Suzuki, A.; Motozaki, T.; Kozawa, I.; Hayamizu, T.; Munakata, R.; Takao, K.-I.; Tadano, K.-I. *J. Org. Chem.* **2007**, *72*, 6143.
- (a) Couladouros, E. A.; Bouzas, E. A.; Magos, A. D. *Tetrahedron* **2006**, *62*, 5272. (b) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031.
- Trost, B. M.; Harms, A. E. *Tetrahedron Lett.* **1996**, *37*, 3971.
- Dominguez, B.; Iglesias, B.; Lera, A. R. *Tetrahedron* **1999**, *55*, 15071.
- (a) Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888. (b) Choi, J. Y.; Hwang, G.-S.; Senapati, B. K.; Ryu, D. H. *Bull. Korean Chem. Soc.* **2008**, *29*, 1879.
- Lee, M. Y.; Kim, K. H.; Jiang, S.; Jung, Y. H.; Sim, J. Y.; Hwang, G.-S.; Ryu, D. H. *Tetrahedron Lett.* **2008**, *49*, 1965.
- Sim, J. Y.; Hwang, G.-S.; Kim, K. H.; Ko, E. M.; Ryu, D. H. *Chem. Commun.* **2007**, 5064.
- Kramp, G. J.; Kim, M.; Gais, H.-J.; Vermeeren, C. *J. Am. Chem. Soc.* **2005**, *127*, 17910.
- (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. (b) Shon, J. K.; Sim, J. Y.; Thakur, S. S.; Ko, E. M.; Kong, S. S.; Choi, J. Y.; Kang, M.; Senapati, B. K.; Choi, D. S.; Ryu, D. H.; Kim, J. M. *Bull. Korean Chem. Soc.* **2008**, *29*, 1993.