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Total Synthesis of (+)-Tubelactomicin A. 1. Stereoselective Synthesis of the Lower-Half Segment by an Intramolecular Diels–Alder Approach

Toru Motozaki, Kiyoto Sawamura, Akari Suzuki, Keigo Yoshida, Tatsuo Ueki, Aiko Ohara, Ryosuke Munakata, Ken-ichi Takao, and Kin-ichi Tadano*

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

tadano@applc.keio.ac.jp

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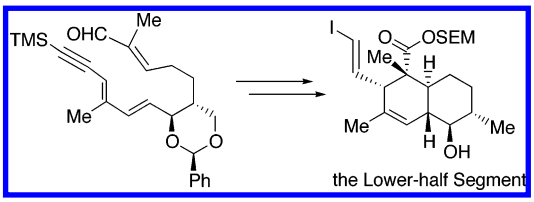
ABSTRACT



Starting from diethyl (*R*)-malate, synthesis of the lower-half segment of (+)-tubelactomicin A, a 16-membered macrolide antibiotic, has been achieved. The synthesis involved the highly *endo*- and π-facial selective intramolecular Diels–Alder reaction achieved using a trisubstituted methacrolein derivative tethering a 10-carbon dienyne unit at the β-carbon, which in turn was prepared from a known allylated malic acid derivative.

(+)-Tubelactomicin A (**1**) was isolated from the culture broth of an actinomycete strain designated MK703-102F1, a member of *Nacardia*, which showed potent antimicrobial activity against acid-fast bacteria, including drug-resistant strains.[1a] The structure of **1** was elucidated by extensive NMR analysis and confirmed by a single-crystal X-ray analysis of the carboxamide derivative with L-phenylalanine methyl ester; therefore, the absolute stereochemistry was established as shown in Scheme 1.[1b] The structure of **1** is characterized by a *trans*-fused octahydronaphthalene moiety possessing six contiguous stereogenic centers and a 16-membered macrolactone incorporating an (*E*,*E*)-conjugate diene and an α,β-disubstituted (*Z*)-acrylic acid moiety. So far, a number of macrolides, which consist of tricyclic structures similar to **1**, have been isolated as biologically intriguing natural products. In addition, synthetic studies directed at these octahydronaphthalene-fused macrolides have been explored by many research groups in the past 2 decades.[2] The focus of our research has been the total synthsis of **1**, which was recently completed.

In retrosynthetic consideration of the target natural product shown in Scheme 1, **1** was divided into two segment, **2** and **3**, i.e., an (*E*)-vinylstannane incorporating a C14−C24 chain as the upper-half segment and an octahydronaphthalene

(1) (a) Igarashi, M.; Hayashi, C.; Homma, Y.; Hattori, S.; Kinoshita, N.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **2000**, *53*, 1096−1101. (b) Igarashi, M.; Nakamura H.; Naganawa, H.; Takeuchi, T. *J. Antibiot*. **2000**, *53*, 1102−1107.

(2) For the total synthesis of (−)-chlorothricolide, see: (a) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 6457−6458. (b) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411−7419. For the total synthesis of (±)-24-*O*-methylchlorothricolide, see: (c) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431−3434. For the total synthesis of (+)-tetronolide, see: (d) Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. *Tetrahedron Lett.* **1991**, *32*, 4925−4928. For the formal synthesis of (+)-tetronolide, see: (e) Roush, W. R.; Reilly, M. L.; Koyama. K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708−8721. For synthetic studies of superstolide A, see: (f) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989−8992. (g) Yu, W.; Zhang, Y.; Jin Z. *Org. Lett.* **2001**, *3*, 1447−1450. (h) Zampella, A.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2001**, *12*, 1543−1545. (i) Roush, W. R.; Hertel, L.; Schnaderbeck, M. J.; Yakelis, N. A. *Tetrahedron Lett.* **2002**, *43*, 4885−4887. (j) Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 3838−3843.

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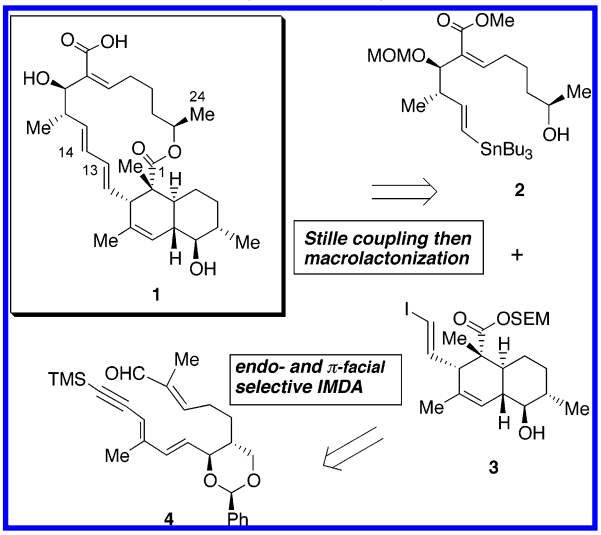
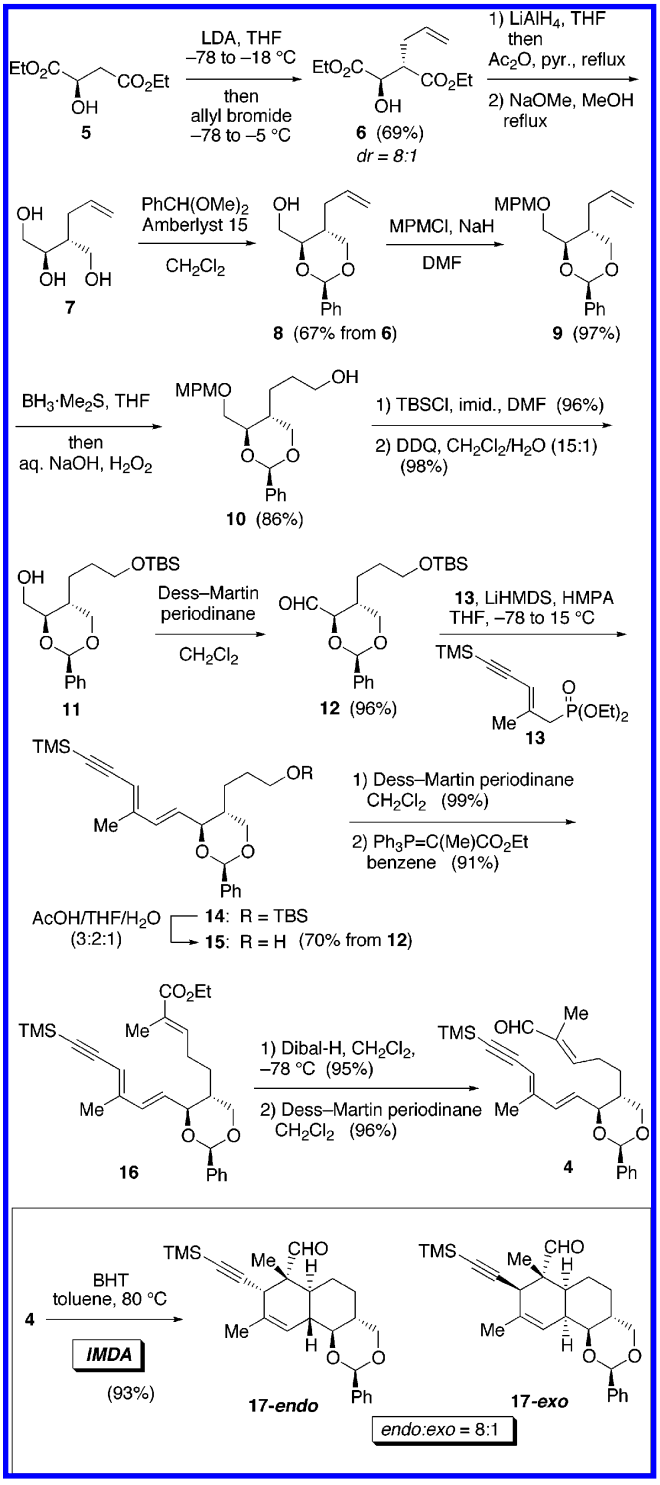
Scheme 1. Structure of (+)-Tubelactomicin A (**1**) and Retrosynthetic Analysis



carboxylic acid carrying an (*E*)-vinyl iodide as the lower-half (C1−C13) segment, respectively. These two segments could be connected sequentially in later synthetic stages by (1) sp^2-sp^2 Stille coupling to form a carbon−carbon bond between C13 and C14 and (2) intramolecular esterification at the C1 carboxylic acid and the C23 hydroxyl group to form the 16-membered macrolactone structure. The highly functionalized *trans*-fused octahydronaphthalene **3** could be synthesized through the *endo*- and π-facial selective intramolecular Diels−Alder (IMDA) reaction of a β-substituted (*E*)-methacrolein derivative **4** possessing a 10-carbon tether incorporating an (*E*,*E*)-dienyne terminal. One of the key issues for the total synthesis was the stereoselectivity of the IMDA reaction[3] using substrate **4**. In this Letter, we report a highly stereoselective synthesis of the lower-half segment **3**, starting with diethyl (*R*)-malate (**5**)[4] along this synthetic plan. The synthesis of the upper-half segment **2** and the completion of the total synthesis of **1** are described in the following paper.[5]

Synthesis of the lower-half segment **3** is outlined in Schemes 2 and 3. According to Seebach's precedent,[6] regio- and diastereoselective allylation of the lithium enolate generated from **5** predominantly provided the *anti*-allylated product **6** (8:1 diastereomeric ratio). Hydride reduction of

Scheme 2. Synthesis of the Upper-Half Segment (Part 1)



the diester **6**, followed by regioselective acetalization of the resulting triol **7**[7] with benzaldehyde dimethylacetal, provided **8**.[8] Temporary protection of the primary hydroxyl group in

(3) For reviews on IMDA reactions, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 153−550. (b) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 464−474. (c) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820−849. (d) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243−4260.

(4) Wipf, P.; Uto, Y.; Yoshimura, S. *Chem. Eur. J.* **2002**, *8*, 1670−1681.

(5) Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.-i.; Tadano, K.-i. *Org. Lett.* **2005**, *7*, 2265−2268.

(6) (a) Seebach, D,; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197−200. (b) Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1984**, *63*, 109−120.

(7) Owing to its highly polar nature, the reduction product was once acetylated. The peracetate was purified on silica gel and then deacetylated with a catalytic amount of NaOMe.

(8) For the synthesis of enantiomeric **8**, see: Morimoto, Y.; Mikami, A.; Kuwabe, S.; Shirahama, H. *Tetrahedron: Asymmetry* **1996**, *7*, 3371−3390.

8 as the MPM (methoxy-phenylmethyl) ether provided **9**. Regioselective hydroboration of **9**, followed by oxidative treatment, produced **10**. Silylation of the resulting primary hydroxyl group and deprotection of the MPM group provided **11**. Dess−Martin oxidation[9] of the liberated hydroxyl group, followed by the *E*-selective Horner−Emmons olefination of the resulting aldehyde **12** with phosphonate **13**,[10] predominantly provided (*E*,*E*)-conjugated dienyne **14**. Acidic deprotection of the TBS group in **14** provided **15**. Installation of the dienophile part into **15** was achieved through a Wittig olefination reaction of the aldehyde prepared from **15** by Dess−Martin oxidation, followed by a two-step reduction/oxidation protocol of the resulting α,*β*-unsaturated ester **16**, which eventually provided the unsaturated aldehyde **4**, the substrate for the aimed IMDA reaction.

The thermal IMDA reaction of **4** in toluene at 80 °C for 24 h proceeded stereoselectively to provide the desired *trans*-fused cycloadduct **17-*endo***[11] with an 8:1 *endo*:*exo* ratio (^{1}H NMR analysis) in a combined yield of 93%. As a result, the IMDA reaction of **4** proceeded with complete *π*-facial

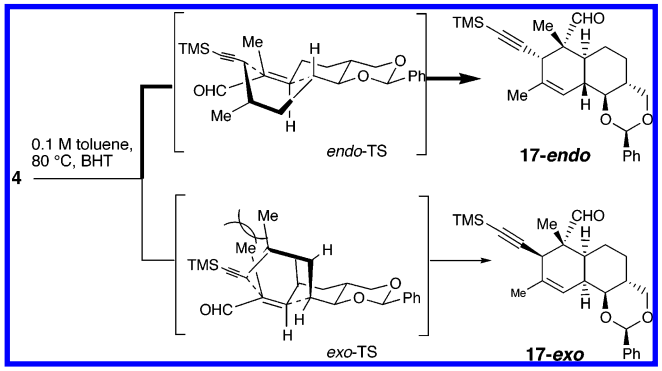
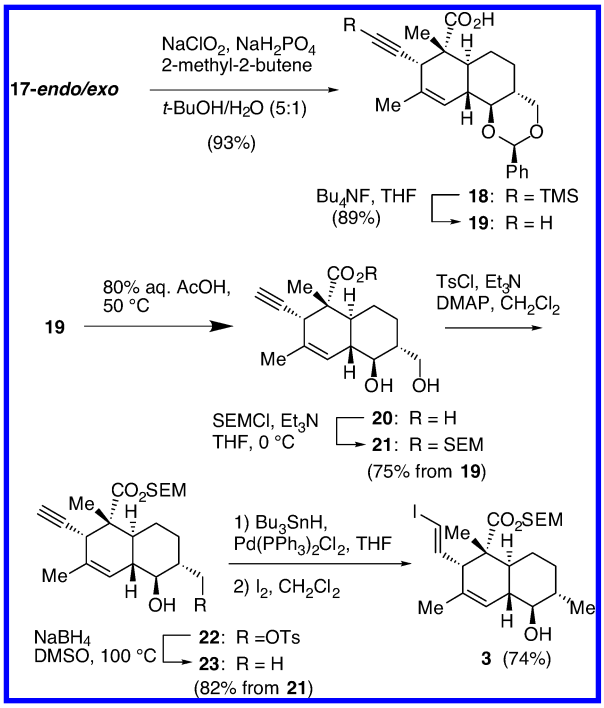


Figure 1. Plausible transition states for the IMDA of **4**.

selectivity. As shown in Figure 1, two chairlike transition states (*endo*-TS and *exo*-TS) were conformationally locked by the presence of the *trans*-oriented benzylidene acetal. In the two TSs, a severe nonbonded interaction occurred between the methyl substituent in the diene part and the dienophile terminal, apparently making the *exo*-TS unfavorable. Therefore, the IMDA reaction proceeds through the *endo*-TS, leading to the predominant formation of the desired **17-*endo***. It is apparent that the existence of the benzylidene acetal plays a critical role in the IMDA reaction.

The $NaClO_2$ oxidation of the aldehyde functionalities in the diastereomeric mixture **17-*endo/exo***, followed by desilylation of the resulting **18**,[12] provided **19** (Scheme 3). Acid

Scheme 3. Synthesis of the Upper-Half Segment (Part 2)

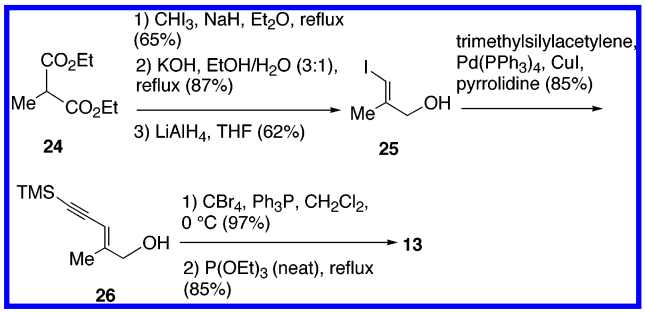


hydrolytic removal of the benzylidene acetal provided **20**. After protection of the carboxylic acid in **20** as the 2-(trimethylsilyl)ethoxymethyl (SEM) ester, the primary hydroxyl group of the resulting **21** was selectively sulfonylated, providing the tosyl ester **22**. The $NaBH_4$-reduction of the tosyloxy group in **22** in hot DMSO provided deoxygenated derivative **23**. The acetylene terminal was then hydrostannylated regio- and stereoselectively. The resulting (*E*)-vinylstannane was treated with iodine to provide the lower-half segment **3**.

In conclusion, we have achieved a stereoselective synthesis of the lower-half segement **3** for the total synthesis of **1**. Access to **3** features (1) the stereoselective IMDA of **4** for efficient construction of the highly functionalized *trans*-fused octahydronaphthalene derivative **17-*endo*** and (2) regio- and stereoselective hydrostannylation followed by iodination for

(9) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (c) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

(10) Phosphonate **13** was prepared from the known (*E*)-2-methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol **26**, which in turn was prepared from diethyl methylmalonate (**24**) via **25**.



For preparation of **25**, see: Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47−65. For preparation of **26**, see: de Lera, A. R.; Iglesias, B.; Rodriguez, J.; Alvarez, R.; Lopez, S.; Villanueva, X.; Padros, E. *J. Am. Chem. Soc.* **1995**, *117*, 8220−8231.

(11) The structure of the major adduct **17-*endo*** was confirmed on the basis of extensive ^{1}H NMR analysis.

(12) At this stage, the compound (not shown) derived from the minor *exo*-adduct of the IMDA reaction could be removed.

the conversion of the acetylenic part in **23** into the *trans*-vinyl iodide part.

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Supporting Information Available: Experimental procedures and characterization data, including ^{1}H and ^{13}C NMR spectra for all new synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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