

# Total Synthesis of (+)-Tubelactomicin

## A. 1. Stereoselective Synthesis of the Lower-Half Segment by an Intramolecular Diels–Alder Approach

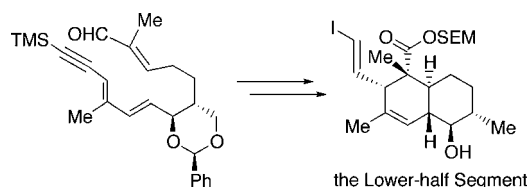
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### ABSTRACT



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  $\pi$ -facial selective intramolecular Diels–Alder reaction achieved using a trisubstituted methacrolein derivative tethering a 10-carbon dienyne unit at the  $\beta$ -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 *Nocardia*, which showed potent antimicrobial activity against acid-fast bacteria, including drug-resistant strains.<sup>1a</sup> 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.<sup>1b</sup> 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  $\alpha,\beta$ -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

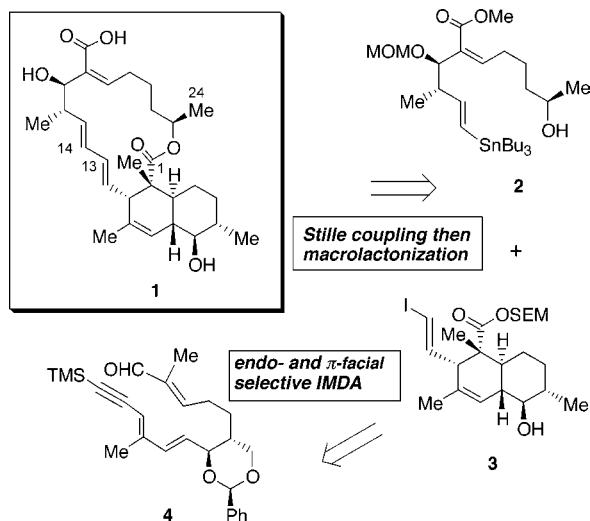
octahydronaphthalene-fused macrolides have been explored by many research groups in the past 2 decades.<sup>2</sup> The focus of our research has been the total synthesis of **1**, which was recently completed.

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.

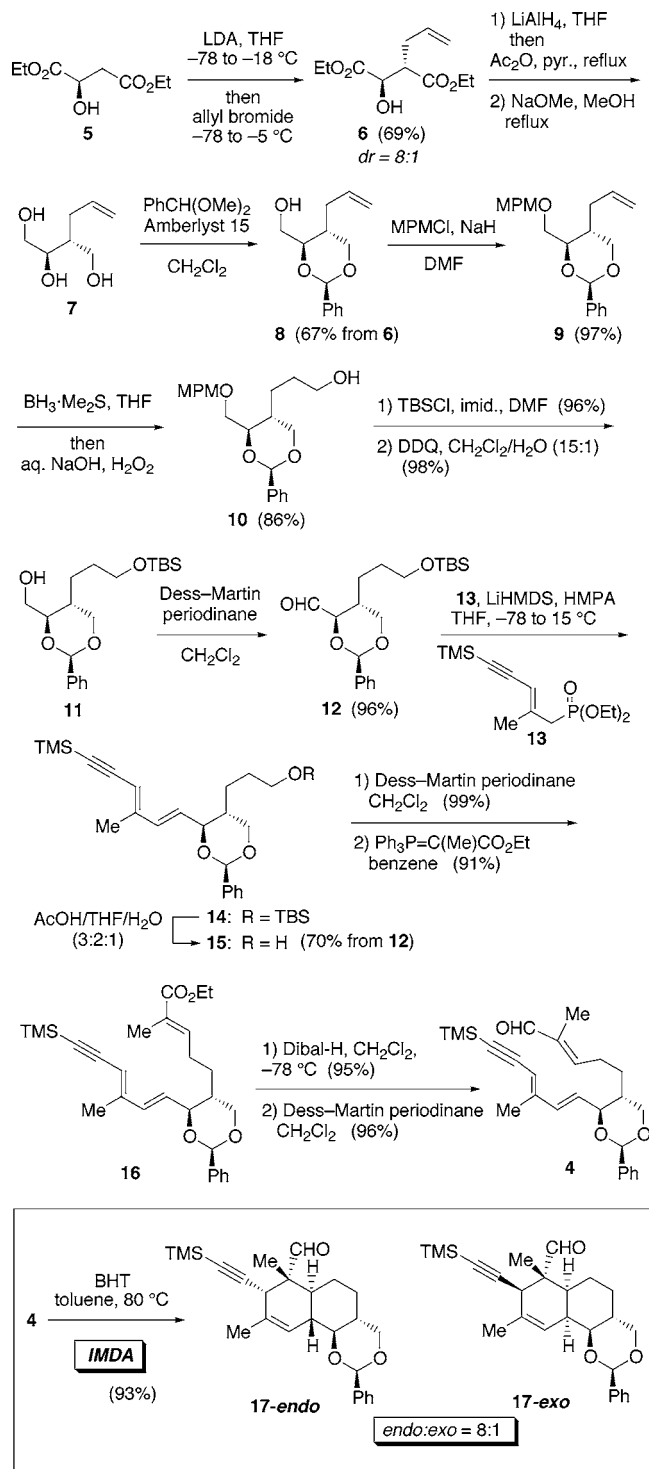
**Scheme 1.** Structure of (+)-Tubelactomicin A (**1**) and Retrosynthetic Analysis



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  $\pi$ -facial selective intramolecular Diels–Alder (IMDA) reaction of a  $\beta$ -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<sup>3</sup> using substrate **4**. In this Letter, we report a highly stereoselective synthesis of the lower-half segment **3**, starting with diethyl (*R*)-malate (**5**)<sup>4</sup> 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.<sup>5</sup>

Synthesis of the lower-half segment **3** is outlined in Schemes 2 and 3. According to Seebach's precedent,<sup>6</sup> 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)



(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.

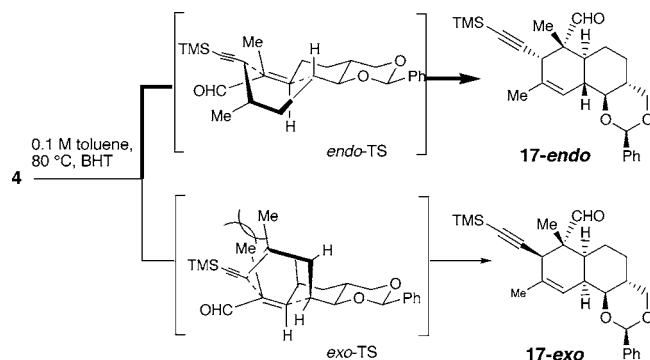
the diester **6**, followed by regioselective acetalization of the resulting triol **7** with benzaldehyde dimethylacetal, provided **8**.<sup>8</sup> Temporary protection of the primary hydroxyl group in

(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<sup>9</sup> of the liberated hydroxyl group, followed by the *E*-selective Horner–Emmons olefination of the resulting aldehyde **12** with phosphonate **13**,<sup>10</sup> 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  $\alpha,\beta$ -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**<sup>11</sup> with an 8:1 *endo:exo* ratio (<sup>1</sup>H NMR analysis) in a combined yield of 93%. As a result, the IMDA reaction of **4** proceeded with complete  $\pi$ -facial

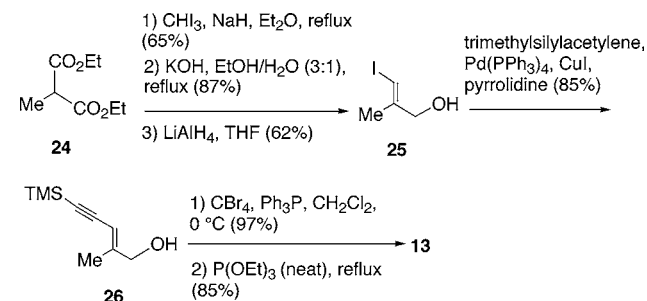


**Figure 1.** Plausible transition states for the IMDA of **4**.

selectivity. As shown in Figure 1, two chairlike transition

(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.; Spatore, 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**.



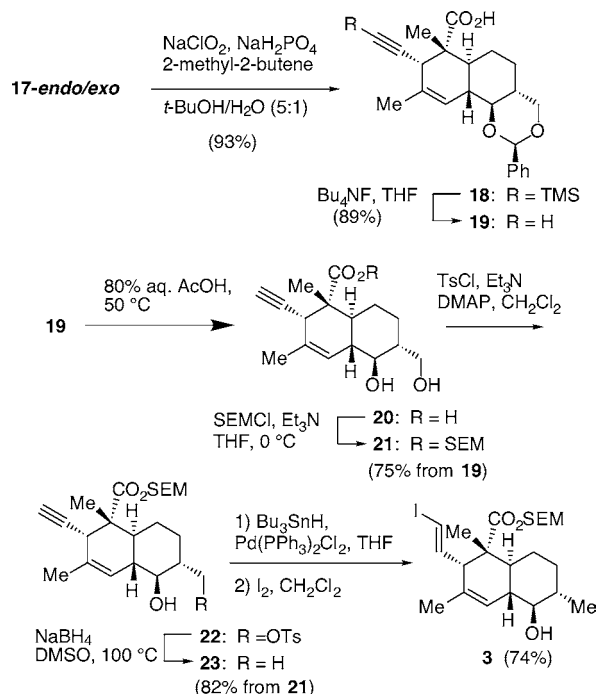
For preparation of **25**, see: Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47–65. For preparation of **26**, see: de Lera, A. R.; Iglesias, B.; Rodríguez, J.; Álvarez, R.; López, S.; Villanueva, X.; Padros, E. *J. Am. Chem. Soc.* **1995**, *117*, 8220–8231.

(11) The structure of the major adduct **17-endo** was confirmed on the basis of extensive <sup>1</sup>H NMR analysis.

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<sub>2</sub> oxidation of the aldehyde functionalities in the diastereomeric mixture **17-endo/exo**, followed by desilylation of the resulting **18**,<sup>12</sup> 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-(triethylsilyl)ethoxymethyl (SEM) ester, the primary hydroxyl group of the resulting **21** was selectively sulfonated, providing the tosyl ester **22**. The NaBH<sub>4</sub>-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 segment **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

(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  $^1\text{H}$  and  $^{13}\text{C}$  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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