

Total Synthesis of (+)-Tubelactomicin

A. 2. Synthesis of the Upper-Half Segment and Completion of the Total Synthesis

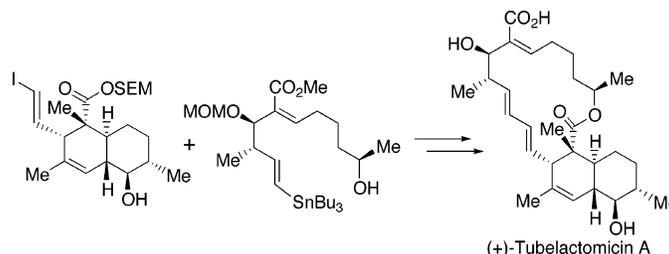
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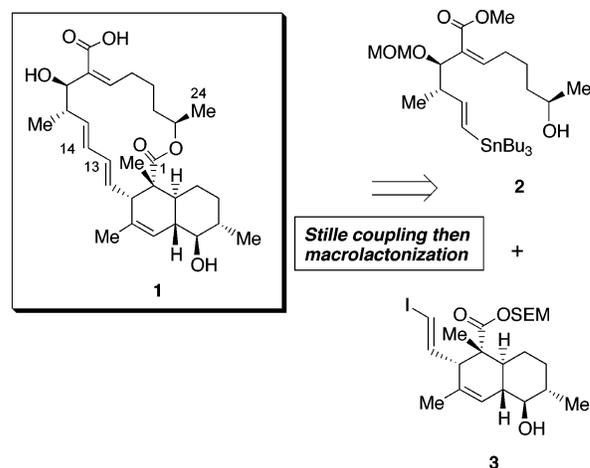
ABSTRACT



We have completed the total synthesis of natural (+)-tubelactomicin A (**1**), a 16-membered macrolide antibiotic. This Letter presents a highly efficient synthesis of the upper-half segment (C14–C24) and the completion of the total synthesis featuring a high-yielding Stille coupling for the connection of the upper-half and lower-half segments and Mukaiyama macrolactonization for the construction of the entire structure of **1**.

The biological properties^{1a} and structural uniqueness^{1b} of (+)-tubelactomicin A (**1**) (Scheme 1), isolated recently from the culture broth of an actinomycete strain designated MK703-102F1, prompted us to attempt its total synthesis. Along the retrosynthetic analysis shown in Scheme 1, we describe in the preceding paper² the stereoselective synthesis of the lower-half segment (C1–C13), a highly functionalized *trans*-fused octahydronaphthalene carboxylic acid **3**, based on the intramolecular Diels–Alder strategy. In this Letter, we describe a synthesis of the upper-half (C14–C24) segment **2**, an (*E*)-vinylstannane including an α,β -disubstituted (*Z*)-acrylic acid part, and the connection of the upper-half segment **2** and lower-half segment **3**. These two segments

Scheme 1. Retrosynthetic Analysis of **1**



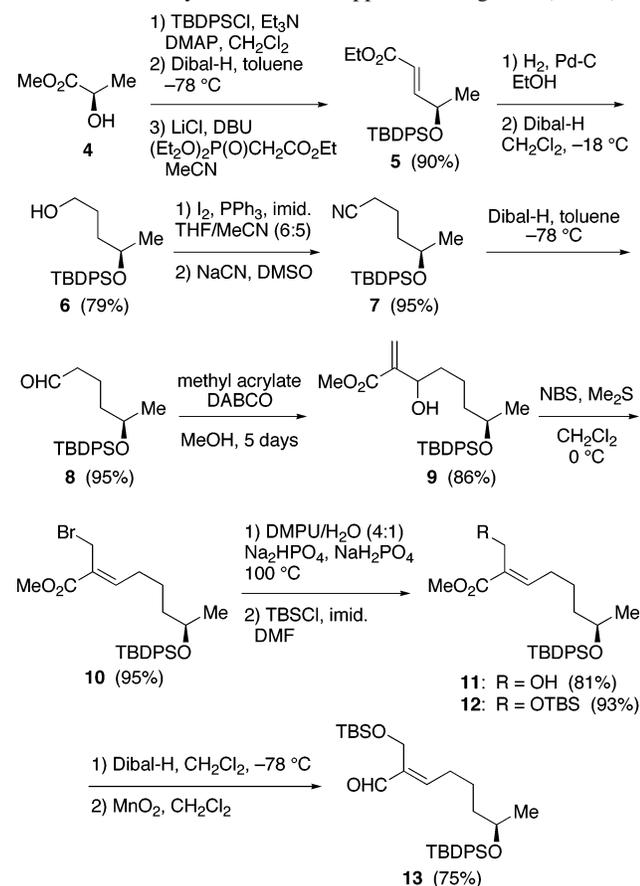
(1) (a) Igarashi, M.; Hayashi, C.; Homma, Y.; Hattori, S.; Kinoshita, N.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **2000**, *53*, 1096–1101. (b) Igarashi, M.; Nakamura H.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **2000**, *53*, 1102–1107.

(2) Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.-i.; Tadano, K.-i. *Org. Lett.* **2005**, *7*, 2261–2264.

could be connected sequentially by sp^2 - sp^2 Stille coupling to form a single bond between C13 and C14 and then by intramolecular esterification at the carboxylic acid (C1) and a hydroxyl group at C23 to form the 16-membered macrolactone structure, providing a protected form of tubelactomicin A. Deprotection would complete the total synthesis.

The synthesis of the upper-half segment **2** is outlined in Schemes 2 and 3. Methyl (*R*)-lactate (**4**) was converted into

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

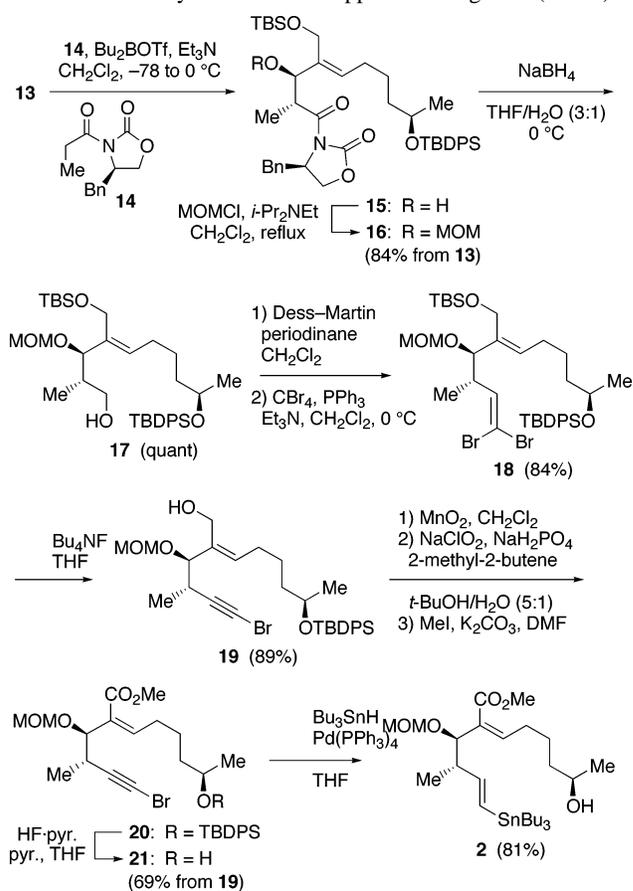


ethyl (2*E*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)-2-pentenoate (**5**) using the Roush–Masamune variant³ of Horner–Emmons elongation. The unsaturated ester part in **5** was reduced, providing a partially protected 1,4-pentanediol **6** by hydrogenation, followed by diisobutylaluminum hydride (Dibal-H) reduction. The hydroxyl group in **6** was replaced by a cyano group via the iodo derivative, providing a hexanenitrile derivative **7**. Dibal-H reduction of **7** gave aldehyde **8**, which was subjected to a Morita–Baylis–Hillman reaction⁴ with methyl acrylate and 1,4-diazabicyclo[2.2.2]octane (DABCO)

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(4) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1, 2815. (b) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q. For a recent review on this subject, see: Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891.

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



in the presence of MeOH.^{5,6} The resulting α -substituted acrylic acid ester **9** was obtained as a 1:1 diastereomeric mixture (¹H NMR analysis). Treatment of the mixture **9** with NBS and Me₂S provided the (*Z*)-acryloyl ester **10** stereoselectively, which bears a bromomethyl group at the α -position, as a result of an S_N2' substitution of a bromide ion.⁷ The allylic bromide **10** was converted into the allylic alcohol **11** by hydrolysis in aqueous 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) under buffered conditions.⁸ A two-step reduction/oxidation applied to the ester functionality in **12**, the *tert*-butyldimethylsilyl (TBS) ether of **11**, provided the unsaturated aldehyde **13**.⁹

Next, the contiguous stereogenic centers at C16 and C17 were introduced by a boron-mediated *syn*-stereoselective

(5) Although a higher yield (92%) was realized when this reaction was carried out in neat DABCO, the reaction was completed after 30 days at room temperature. The coexistence of MeOH remarkably reduced the reaction time. We confirmed that 3-hydroxyquinuclidine (neat) also accelerates the reaction without a loss of the yield of **9**.

(6) For the acceleration of the Baylis–Hillman reaction in the presence of MeOH, see: Aggarwal, V. K.; Mereu, G. T.; Tarver, R.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183–7189 and references therein.

(7) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849–3859.

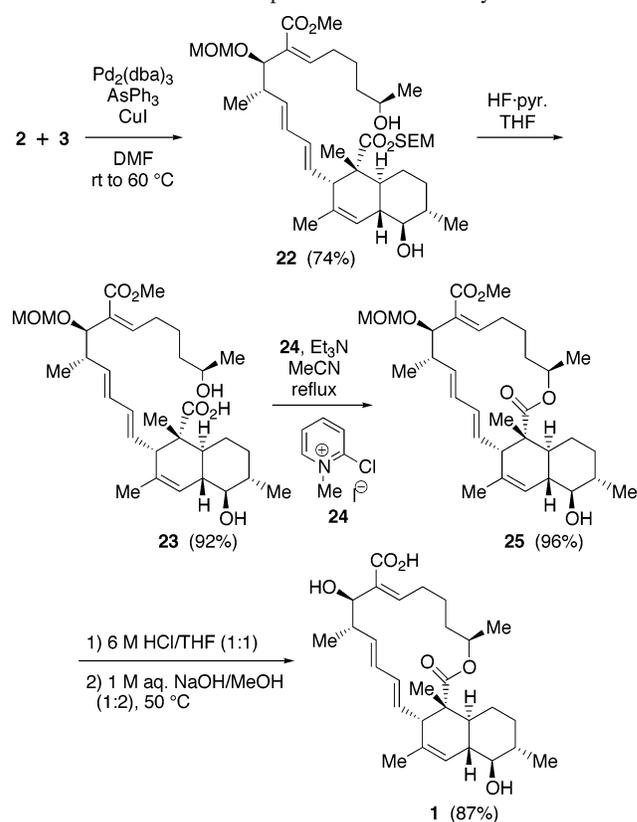
(8) In place of DMPU, HMPA was also effective, although the yield of **11** was somewhat reduced. The phosphate-buffered solution was crucial to sustain the silyl protecting group. For the effect of the polar aprotic solvents, see: Hutchins, R. O.; Taffer, I. M. *J. Org. Chem.* **1983**, *48*, 1360–1362.

(9) In the NOE experiment of **13**, a remarkable (22%) signal enhancement of the CHO proton was observed when the β -vinyl proton was irradiated. Thus, the geometrical structures of **11**–**13** were ascertained.

Evans aldol reaction¹⁰ using (4*R*)-4-benzyl-3-propionyl-2-oxazolidinone **14**.¹¹ Protection of the hydroxyl group in the aldol adduct **15**, which was followed by the reductive removal of the chiral auxiliary in the resulting MOM ether **16**, provided **17**. The synthesis of the upper-half segment **2** from **17** was achieved uneventfully by the following reaction sequence: (1) conversion of **17** into α,α -dibromoalkene **18** via Dess–Martin oxidation¹² and Corey–Fuchs dibromoolefination¹³ of the resulting aldehyde, followed by Bu₄NF-mediated simultaneous desilylation of the TBS ether and dehydrobromination; (2) two-step oxidation of the resulting primary hydroxyl group in the bromoalkyne **19** to the carboxylic acid and successive esterification; (3) desilylation of the TBDPS group in the resulting **20**, which regenerates the secondary hydroxyl group; and (4) regioselective hydrostannylation of **21** according to Pattenden's procedure.¹⁴

With the upper-half segment **2** in hand, we explored the assembly of **2** and **3**, taking advantage of a Stille coupling protocol¹⁵ for the formation of the (*E,E*)-conjugate diene part in **1** (Scheme 4). Treatment of **2** and **3** in the presence of Pd₂(dba)₃ (5% molar equiv), AsPh₃ (40% molar equiv), and CuI (20% molar equiv) at 60 °C in DMF¹⁶ provided the coupling product **22** in 74% yield. The HF·pyridine-mediated deprotection of the SEM ester, followed by the macrolactonization of the resulting seco-acid **23** under Mukaiyama conditions,¹⁷ using 2-chloro-1-methyl-pyridinium iodide **24** and Et₃N in refluxing MeCN, provided **25** in excellent yield. Finally, acidic removal of the MOM group in **25**, followed by alkaline hydrolysis, provided **1**. A comparison of the spectral data of synthetic **1** (¹H, ¹³C NMR, IR, and TLC behaviors in two solvent systems) with those of a natural specimen revealed that they were identical. The optical rotation of synthetic **1** [$[\alpha]^{20.5}_{\text{D}} +101$ (*c* 0.63, MeOH)] coincided with that of the natural product [$[\alpha]^{25}_{\text{D}} +103$ (*c* 0.64, MeOH)].

Scheme 4. Completion of the Total Synthesis



In conclusion, we have completed the first total synthesis of natural (+)-tubelactomicin A (**1**). The total synthesis of **1** was achieved with 54 total steps and 30 or 29 linear steps from methyl (*R*)-lactate (**4**) or from diethyl (*R*)-malate in 6.2% or 4.1% overall yields, respectively.

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

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