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# Total Syntheses of Natural Tubelactomicins B, D, and E: Establishment of Their Stereochemistries†

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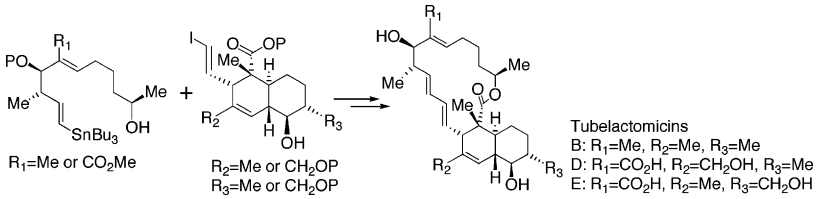


Total syntheses of the antimicrobial tricyclic 16-membered macrolides, (+)-tubelactomicin B, (+)-tubelactomicin D, and (+)-tubelactomicin E, have been accomplished for the first time with common synthetic approaches. These total syntheses established the relative and absolute configurations of the three tubelactomicins, for which planar structures had solely been reported. The total synthesis of (+)-tubelactomicin D included a newly developed stereoselective intramolecular Diels−Alder reaction for constructing the highly functionalized octahydronaphthalene substructures.

## Introduction

(+)-Tubelactomicin A (**1**) (Figure 1) was isolated from the culture broth of an actinomycete strain designated MK703-102F1, and its structure was determined by the researchers at the Institute of Microbial Chemistry in Japan.[1b] This tricyclic 16-membered macrolide **1** showed potent antimicrobial activity against acid-fast bacteria, including drug-resistant strains.[1a] Following the isolation of **1**, the same group isolated and characterized structurally similar macrolides, i.e., (+)-tubelactomicin B (**2**), (+)-tubelactomicin D (**3**), and (+)-tubelactomicin E (**4**), from the same microoganism.[2] These antibiotics **2**−**4** also showed a broad range of antimicrobial activity. The planar structures of **2**−**4** were determined on the basis of spectral analysis [UV, IR, $^1$H and $^{13}$C NMR]. Although their relative and absolute stereochemistries remained undetermined, it was considered that **2**−**4** possess the same stereochemistries as **1**. In 2005, we reported the total synthesis of **1**, thereby establishing the stereochemistry of the (+)-natural form.[3] Tatsuta and coworkers have also accomplished the total synthesis of **1**.[4] Herein, we report the total syntheses of three other tubelactomicins, **2**−**4**, thereby establishing their unknown relative and absolute stereochemistries as those depicted in Figure 1.

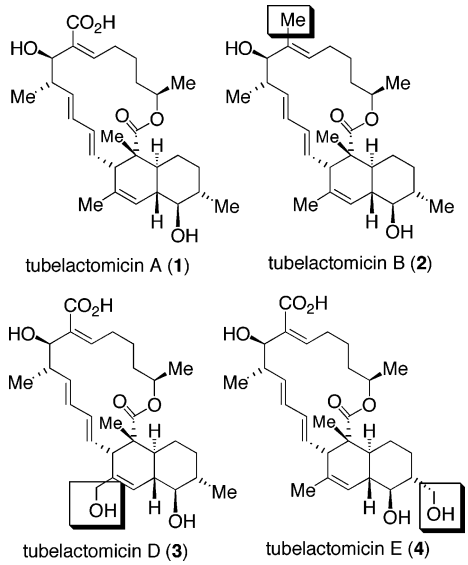


**FIGURE 1.** Structures of tubelactomicins.

† This paper is dedicated to the memory of the late Professor Yoshihiko Ito.

(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.; Takeuchi, T. *J. Antibiot.* **2000**, *53*, 1102−1107.

(2) Takeuchi, T.; Igarashi, M.; Naganawa, H.; Hamada, M. Japanese Patent JP2001-55386A, 2001.

(3) (a) Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.; Tadano, K. *Org. Lett.* **2005**, *7*, 2261−2264. (b) Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.; Tadano, K. *Org. Lett.* **2005**, *7*, 2265−2267.

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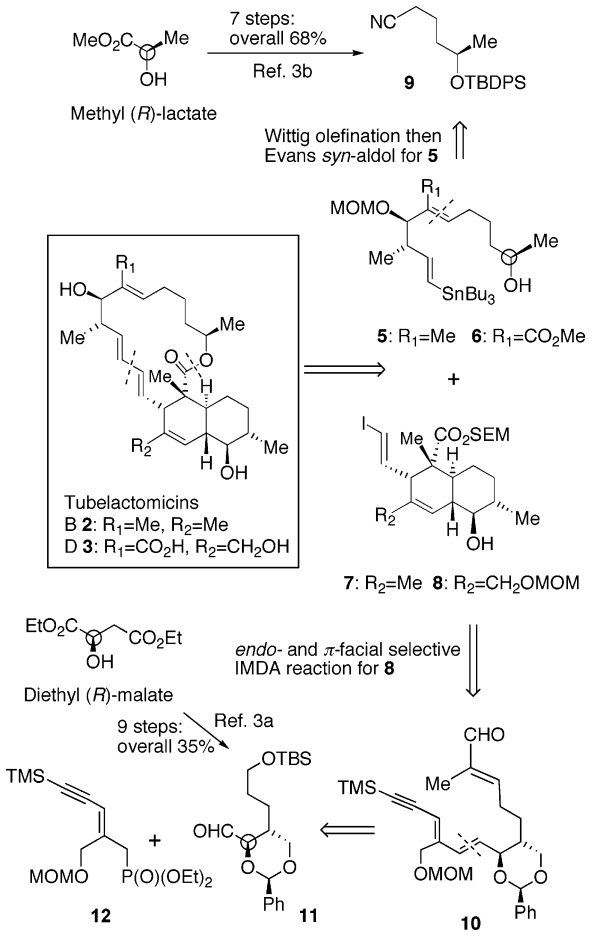
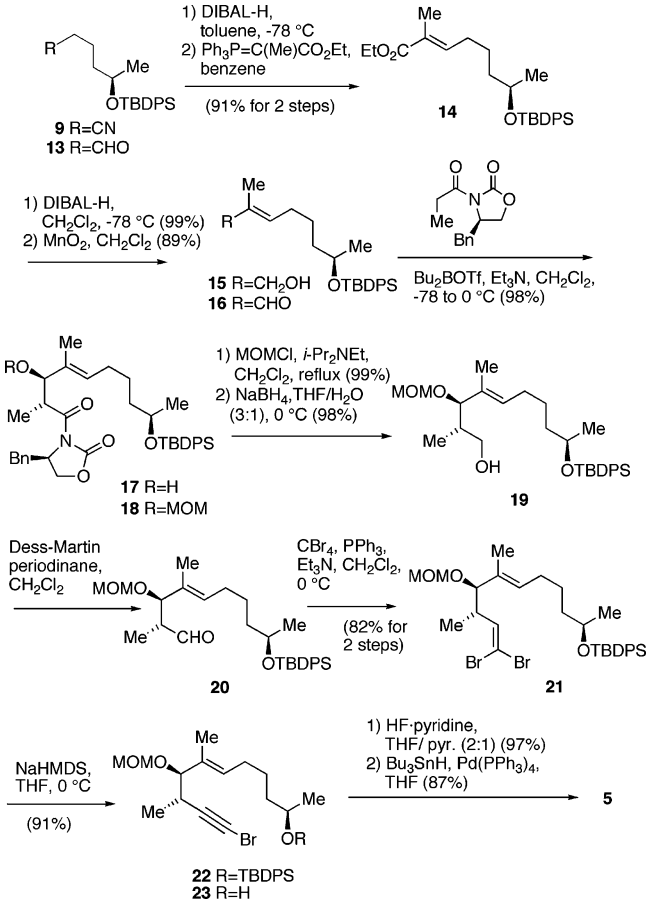
**SCHEME 1. Retrosynthetic Approach to Tubelactomicins B (2) and D (3)**




We envisioned that the total syntheses of **2**−**4** would be accomplished using convergent synthetic approaches similar to that used for the total synthesis of **1**. Therefore, the targeted macrolides **2** and **3** were divided into two segments, i.e., the upper-half segment **5** (for **2**) or **6**[3b] (for **3**) and the lower-half segment **7**[3a] (for **2**) or **8** (for **3**) as shown in Scheme 1. The novel upper-half segment **5** would be synthesized from **9**, which was prepared previously from methyl (*R*)-lactate,[3b] using the analogous carbon−carbon bond extension strategy including the Evans *syn*-aldol strategy[5] to that used for the synthesis of another upper-half segment **6**. The novel highly oxygenated octahydronaphthalene derivative **8**, as the lower-half segment of **3**, would be synthesized through an *endo*- and $\pi$-facial selective intramolecular Diels−Alder (IMDA) reaction[6] of unsaturated aldehyde carrying a dienyne segment, i.e., **10**. We previously observed that the structurally similar octahydronaphthalene derivative **7** was obtained stereoselectively by the IMDA

**SCHEME 2. Synthesis of the Upper-Half Segment 5**




reaction of the substrate with a methyl group instead of the (methoxymethoxy)methyl (MOM) group in **10**.[3a] This substrate **10** for the attempted IMDA reaction would be obtained by the (*E*)-selective Horner−Wadsworth−Emmons olefination of highly oxygenated hexanal **11** and a novel (*E*)-trisubstituted olefin **12**, which possesses a (trimethylsilyl)acetylene group, a diethyl methylphosphonate moiety, and an MOM-protected hydroxylmethyl group. The aldehyde **11** was previously prepared from diethyl (*R*)-malate[3a] via a stereoselective α-allylation developed by Seebach and co-workers.[7] As established in the case of the total synthesis of **1**,[3b] the upper- and lower-half segments, i.e., the combination of **5** and **7** or **6** and **8**, might be connected via a stereoselective $sp^2$−$sp^2$ coupling, followed by a 16-membered macrolactonization, to construct the entire framework of **2** or **3**, respectively. On the other hand, the known *trans*-fused octahydronaphthalene derivative,[3a] which was synthesized as a key intermediate for the total synthesis of **1**, could be used for the total synthesis of another macrolide **4** as the coupling partner of **6** (vide infra). Following these synthetic plans, we embarked on the total syntheses of **2**−**4**.

## Results and Discussion

The synthesis of **5** from the known **9** is summarized in Scheme 2. Compound **9** was converted to α-methylated α,$\beta$-unsaturated ester **14** by diisobutylaluminum hydride (DIBAL-H) reduction followed by a Wittig olefination of the

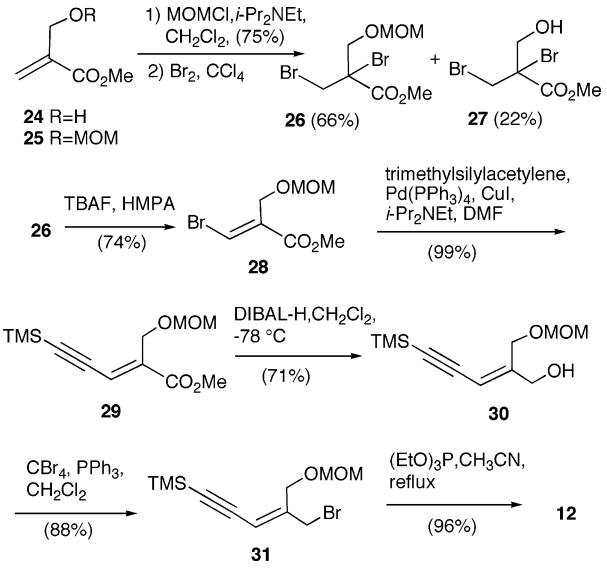
(4) Hosokawa, S.; Seki, M.; Fukuda, H.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 2439−2442.

(5) (a) Evans, D. A.; Bartroli, J.; Shih, T. L *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Gage J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77−82 and 83−91.

(6) 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, UK, 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. (e) For a recent review on this subject, see: Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779−4807.

(7) (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.

**SCHEME 3. Synthesis of the Allylic Phosphonate 12**

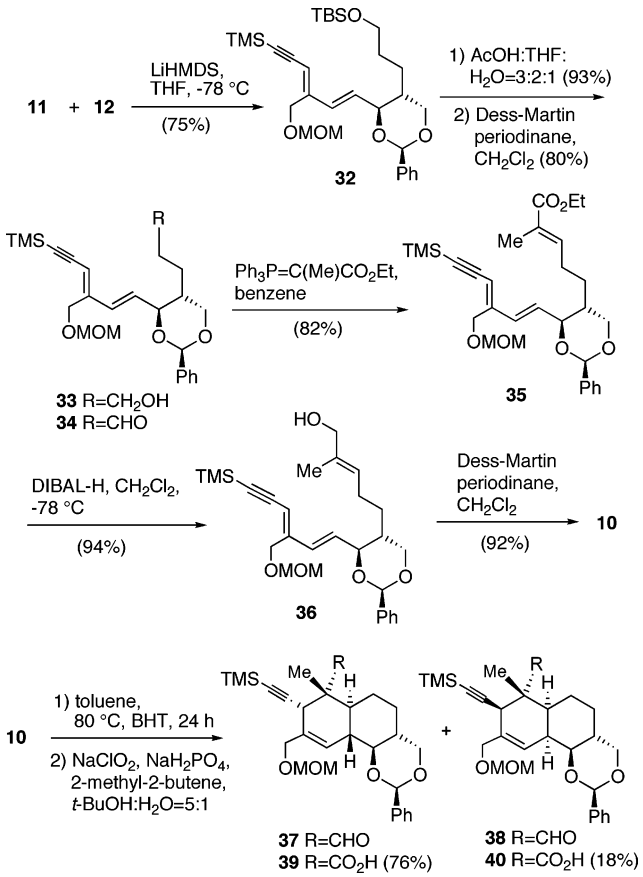



resulting aldehyde **13**. The ester **14** was converted to unsaturated aldehyde **16** by a reduction−oxidation protocol via allylic alcohol **15**. The highly *syn*-selective boron-mediated Evans aldol reaction of **16** and an *N*-propionyl Evans chiral oxazolidinone[5] produced the *syn*-adduct **17** with excellent stereoselection.[3b] The hydroxyl group in the aldol product **17** was protected as the MOM ether, and the chiral auxiliary was reductively removed from the resulting **18** to produce the primary alcohol **19**. Oxidation of **19** with Dess−Martin periodinane (DMP),[8] followed by Corey−Fuchs dibromoolefin formation[9] of the resulting aldehyde **20**, produced α,α-dibromoethylene derivative **21** efficiently. Base-induced elimination of hydrogen bromide from **21** provided bromoalkyne **22**. Deprotection of the *tert*-butyldiphenylsilyl (TBDPS) group in **22** with HF·pyridine, followed by treatment of the resulting **23** with tributylstannane in the presence of a catalytic amount of $Pd(PPh_3)_4$,[10] provided (*E*)-vinylstannane **5** stereoselectively.

For the synthesis of the lower-half segment **8**, we first prepared allylic phosphonate **12** from the α-hydroxymethylated methyl acrylate **24**,[11] the Morita−Baylis−Hillman product of methyl acrylate and *p*-formaldehyde. The synthesis of **12** from **24** is shown in Scheme 3. The allylic alcohol **24** was protected as the MOM ether. The addition of bromine to the MOM ether **25** produced dibromide **26** in 66% yield. The de-*O*-MOM derivative **27** was also produced, which was readily separated from **26**.

Treatment of **26** with tetrabutylammonium fluoride (TBAF) in HMPA provided (*E*)-bromoalkene **28** stereoselectively as a result of hydrogen bromide elimination from **26**. The Pd (0)-catalyzed Sonogashira coupling of **28** and (trimethylsilyl)-acetylene in the presence of CuI and *i*-$Pr_2NEt$[12] produced enyne ester **29** in high yield. The DIBAL-H reduction of **29** and allylic

**SCHEME 4. Synthesis of the Substrate 10 and the IMDA Reaction**




bromination of the resulting allylic alcohol **30** with carbon tetrabromide in the presence of triphenylphosphine provided allylic bromide **31**. The Arbusov rearrangement of **31** with triethyl phosphite produced functionalized diethyl allylphosphonate **12**.

The synthesis of **8**, commencing with the Horner−Wadsworth−Emmons reaction of the known aldehyde **11**[3a] and allylphosphonate **12**, is shown in Schemes 4 and 5. From the coupling of **11** and **12**, the (*E*,*E*)-dienyne-type adduct **32** was obtained stereoselectively. Acid hydrolysis of the silyl ether in **32**, oxidation of the resulting **33** with DMP, followed by the olefination of aldehyde **34** with $Ph_3P{=}C(Me)CO_2Et$ produced α,*β*-unsaturated ester **35** with exclusive (*E*)-selectivity. The (*E*)-geometry of the unsaturated ester moiety of **35** was secured by NOE experiment in the $^1H$ NMR analysis of **35**. Thus a 10% signal enhancement of the α-methyl group in the α,*β*-unsaturated ester in **35** was observed when one of the allylic methylene protons was irradiated. A reduction−oxidation strategy was used for the conversion of **35** to the IMDA substrate **10**. Thus, the DIBAL-H reduction of **35** provided allylic alcohol **36**, which was oxidized with DMP to produce **10**. The attempted IMDA reaction of **10** proceeded at 80 °C in toluene, as observed in the IMDA reaction of the less congested substrate, which possessed a methyl group instead of the $MOMOCH_2$ group in the diene part of **10**.[3a] The IMDA reaction produced two adducts **37** and **38** as an inseparable mixture. Thus, the mixture was further oxidized to the respective carboxylic acids **39** and **40** by a perchlorite oxidation. The carboxylic acids **39** and **40** were cleanly separated by chromatography on silica gel in 76% and 18% yield, respectively, for the two steps. The stereochemistry

(8) (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.

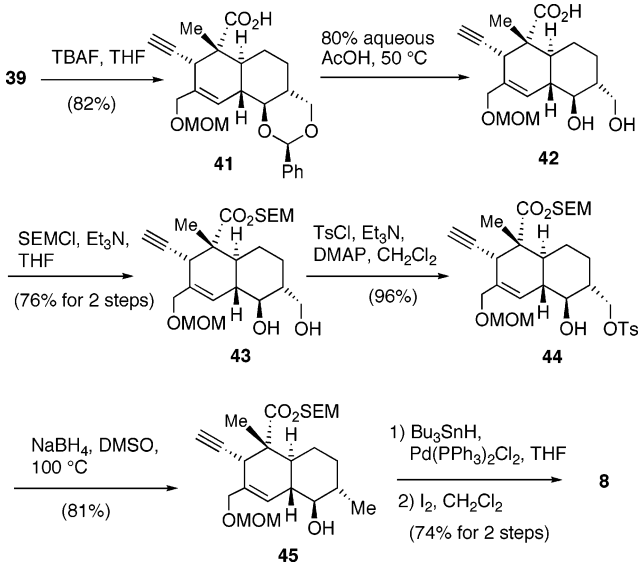
(9) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769−3772.

(10) Boden, C. D. J.; Pattenden, G.; Ye. T. *J. Chem. Soc., Perkin Trans. I* **1996**, 2417−2419.

(11) For the preparation of **24** and bromine addition to **24**, see: Ben Ayed, T.; Amri, H.; El Gaied, M. M. *Tetrahedron* **1991**, *47*, 9621−9628.

(12) de Lera, A. R.; Iglesias, B.; Rodriguez, J.; Alvarez, R.; Lopez, S.; Villanueva, X.; Padros, E. *J. Am. Chem. Soc.* **1995**, *117*, 8220−8231.

**SCHEME 5. Conversion of 39 to the Lower-Half Segment 8**

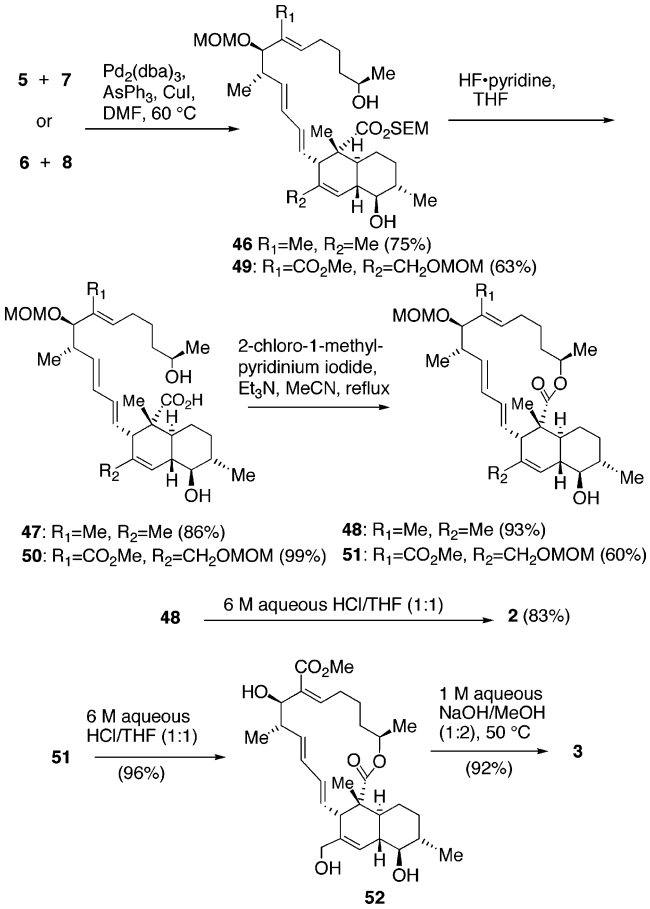



of the major product **39** was determined to be the desired *endo*-adduct unambiguously by $^1$H NMR analysis including detailed NOE experiments. For the stereochemistry of the minor product **40**, we assigned the *exo*-stereochemistry as depicted in Scheme 4 on the basis of our previous result experienced for the total synthesis of **1**.[3a] In the previous case,[3a] the ratio of the *endo*- and *exo*-adduct was approximately 8 to 1. In the present case, the *endo*/*exo* selectivity of the IMDA reaction of **10** was estimated to be approximately 4:1. It is apparent that the bulkiness of the more congested group in the diene part diminishes the *endo*/*exo* ratio of the IMDA reaction. As we observed in the case of **1**, the $\pi$-facial selectivity in the IMDA reaction of **10** was completely controlled.

Having achieved the synthesis of the desired IMDA adduct **39**, we explored the conversion of **39** to the lower-half segment **8** as shown in Scheme 5. Protodesilylation of the *C*-TMS group in **39** with TBAF and hydrolytic de-*O*-benzylidenation, followed by (2-trimethylsilylethoxy)methyl (SEM) ester formation, provided **43** via **41** and **42**. Selective tosylation of diol **43** and deoxygenation of the resulting primary tosylate **44** with $NaBH_4$ in hot DMSO provided **45**. Regio- and *cis*-selective palladium-catalyzed hydrostannylation of the acetylene functionality in **45** and subsequent metal−iodine exchange of the resulting vinylstannane provided the lower-half segment **8** in good overall yield.

We then explored the Stille coupling[13] of **5** and **7** and also that of **6** and **8** for the total syntheses of **2** and **3**, respectively. The reaction conditions and results of the Stille couplings and transformation of the coupling products **46** and **49** into **2** and **3**, respectively, are summarized in Scheme 6. The palladium-catalyzed Stille coupling of **5** and **7** proceeded with CuI in the presence of $AsPh_3$ in DMF,[14] providing (*E*,*E*)-diene **46** efficiently. Deprotection of the SEM ester in **46** with HF·pyridine and lactonization of the resulting seco acid **47** under the Mukaiyama conditions (2-chloro-1-methylpyridinium iodide and triethylamine)[15] provided 16-membered macrolactone **48** in an

**SCHEME 6. Completion of the Total Syntheses of 2 and 3**




excellent yield of 93%. Finally, acid hydrolysis of the MOM group in **48** provided (+)-tubelactomicin B (**2**), which was found to be identical with a natural sample by comparison of spectra ($^1$H and $^{13}$C NMR, IR), $[\alpha]_D$, and TLC behavior. The dextrorotatory property of synthetic **2** proved that the absolute stereochemistry of natural **2** was as depicted. Similarly, the Stille coupling of **6** and **8** provided (*E*,*E*)-diene **49** under the same conditions as those used for the coupling of **5** and **7**. The Mukaiyama macrolactonization of the seco acid **50** derived from **49** provided **51** with a lower yield of 59% for two steps. The two-step deprotection of **51** via **52** eventually provided (+)-tubelactomicin D (**3**), which was identical with a natural sample ($[\alpha]_D$, $^1$H and $^{13}$C NMR, IR, and TLC behavior), establishing the absolute configuration of **3**.

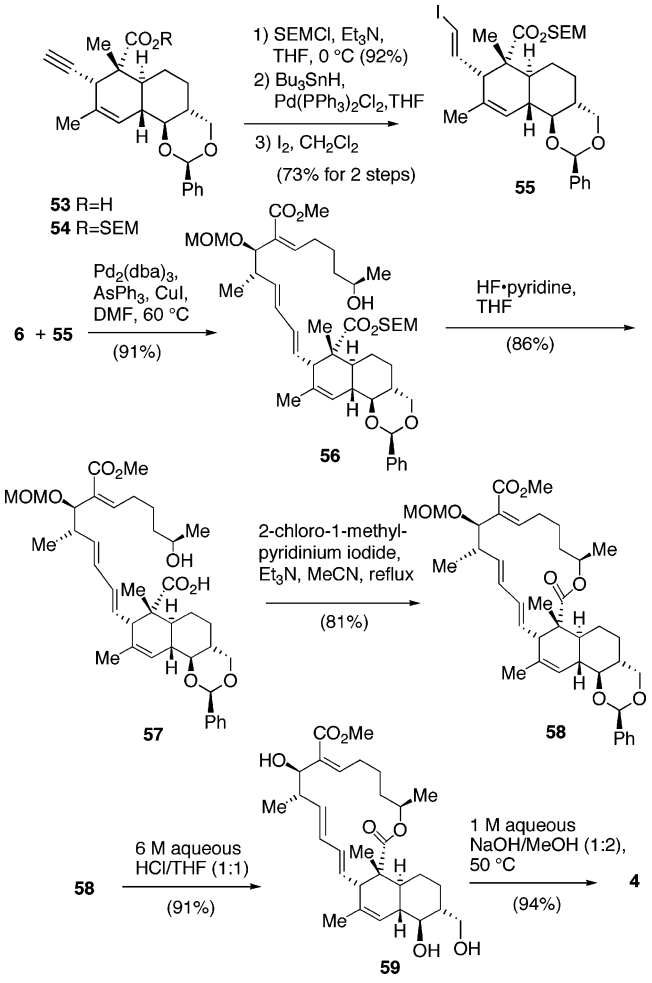
The total synthesis of (+)-tubelactomicin E (**4**) was started with the previously reported intermediate **53**[3a] used for the total synthesis of **1**. The total synthesis of **4** from **53** is shown in Scheme 7. The octahydronaphthalene derivative **53** was in turn synthesized featuring an *endo*- and $\pi$-facial selective IMDA reaction of a D-malic acid-derived substrate. According to the conversion of **45** to **8**, the carboxylic acid **53** was esterified with SEMCl, and the resulting SEM ester **54** was subjected to the palladium-catalyzed hydrostannylation, followed by tin−iodine exchange, providing **55**. The palladium-catalyzed Stille coupling of the upper-half segment **6**[3b] and vinyl iodide **55** provided conjugated (*E*,*E*)-diene **56**. Deprotection of the SEM group in **56** and the Mukaiyama macrolactonization of the resulting seco acid **57** provided **58**, from which (+)-tubelacto-

(13) For some reviews on Stille coupling, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Espinet, P.; Echavarren, A. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704−4734.

(14) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911.

(15) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49−50.

**SCHEME 7. Total Synthesis of (+)-Tubelactomicin E (4)**




micin E (**4**) was synthesized by a two-step deprotection via **59**. The synthetic **4** was identical with a natural sample ($[\alpha]_D$, $^1$H and $^{13}$C NMR, IR, and TLC behavior).

In conclusion, we have completed the total syntheses of natural (+)-tubelactomicins B (**2**), D (**3**), and E (**4**) for the first time. These total syntheses also established the relative and absolute stereochemistries of these natural products, which had not been determined.

## Experimental Section

**(1*E*,3*S*,4*R*,5*E*,10*R*)-10-Hydroxy-4-methoxymethoxy-3,5-dimethyl-1-(tributylstannyl)undeca-1,5-diene (5).** The following reaction was carried out under argon. To a stirred solution of **23** (353 mg, 1.06 mmol) in THF (7 mL) were added $Pd(PPh_3)_4$ (123 mg, 0.10 mmol) and $Bu_3SnH$ (0.85 mL, 3.16 mmol). The reaction mixture was stirred for 10 min and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4 doped with $Et_3N$) to give 504 mg (87%) of **5** as a colorless oil. $^1$H NMR analysis revealed the product contained approximately 9% of the *Z*-isomer. This mixture was used for subsequent steps without separation. Compound **5**: TLC, $R_f$ 0.48 (EtOAc/hexane, 1:2); $[\alpha]^{22.5}_D$ +58.7 (*c* 0.85, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ 0.78−0.95 (m, 15H), 1.11 (d, $J$ = 6.6 Hz, 3H), 1.18 (d, $J$ = 6.6 Hz, 3H), 1.22−1.38, 1.40−1.54 (m, 12H), 1.22−1.54 (m, 4H), 1.48 (s, 3H), 1.60 (s, 1H), 1.88 (m, 2H), 2.41 (ddq, $J$ = 7.1, 9.0, 6.2 Hz, 1H), 3.38 (s, 3H), 3.63 (d, $J$ = 9.0 Hz, 1H), 3.84 (m, 1H), 4.45 (d, $J$ = 6.6 Hz, 1H), 4.62 (d, $J$ = 6.6 Hz, 1H), 5.32 (t, $J$ = 6.6 Hz, 1H), 5.71 (dd, $J$ = 7.1, 19.0 Hz, 1H), 5.87 (d, $J$ = 19.0 Hz, 1H); $^{13}$C NMR (68 MHz) $\delta$ 9.4 × 3, 11.4, 13.7 × 3, 17.1, 23.4, 25.7, 27.2, 27.4 × 3, 29.1 × 3, 39.1, 44.2, 55.6, 67.9, 85.8, 93.0, 126.5, 130.3, 132.9, 150.9; IR (neat) 3400, 2960, 1600, 1460 cm$^{-1}$; HRMS calcd for $C_{23}H_{45}O_3Sn$ ($M^+$− Bu) *m*/*z* 489.2391, found 489.2392.

**2-(Trimethylsilyl)ethoxymethyl (1*R*,2*S*,4a*R*,5*R*,6*S*,8a*S*)-5-Hydroxy-2-[(1*E*,3*E*,5*S*,6*R*,7*E*,12*R*)-12-hydroxy-6-methoxymethoxy-5,7-dimethyltrideca-1,3,7-trienyl]-1,3,6-trimethyl-1,2,4a,5,6,7,8,-8a-octahydronaphthalene-1-carboxylate (46).** The following reaction was carried out under argon. To a stirred solution of **5** (55.4 mg, 102 mmol) and **7**[3a] (38.5 mg, 74.0 mmol) in degassed DMF (1 mL) was added a solution of $Pd_2(dba)_3$ (3.5 mg, 3.8 mmol), $AsPh_3$ (9.3 mg, 30 mmol), and CuI (2.9 mg, 15 mmol) in degassed DMF (0.25 mL). The mixture was stirred for 45 min and then heated at 60 °C for 2 h. After being cooled to room temperature, the mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried and concentrated with the aid of toluene. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5 to 1:3) to give 35.8 mg (75%) of **46** as a colorless oil: TLC, $R_f$ 0.66 (EtOAc/hexane, 2:1); $[\alpha]^{26.5}_D$ +216 (*c* 0.55, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ 0.03 (s, 9H), 0.96 (t, $J$ = 8.3 Hz, 2H), 1.05 (d, $J$ = 6.4 Hz, 3H), 1.10 (d, $J$ = 6.6 Hz, 3H), 1.16 (s, 3H), 1.18 (d, $J$ = 6.2 Hz, 3H), 1.32−1.51 (m, 5H), 1.49 (s, 3H), 1.62 (s, 3H), 1.60−1.83 (m, 6H), 1.96−2.09 (m, 2H), 2.35 (d, $J$ = 9.6 Hz, 1H), 2.30−2.47 (m, 1H), 2.91 (m, 1H), 3.37 (s, 3H), 3.57 (d, $J$ = 9.0 Hz, 1H), 3.68 (t, $J$ = 8.3 Hz, 2H), 3.78 (m, 1H), 4.44, 4.60 (2d, $J$ = 6.6 Hz, 1H × 2), 5.10, 5.21 (2d, $J$ = 6.0 Hz, 1H × 2), 5.28 (m, 1H), 5.29 (t, $J$ = 6.8 Hz, 1H), 5.44 (m, 1H), 5.76 (s, 1H), 5.82−5.98 (m, 2H); $^{13}$C NMR (68 MHz) $\delta$ −1.4 × 3, 11.3, 16.5, 16.8, 18.0, 18.7, 22.6, 23.5, 25.6, 27.0, 27.4, 33.3, 37.7, 39.0, 40.8. 45.5, 49.7, 54.3, 55.6, 67.8, 67.9, 79.5, 85.8, 89.5, 93.0, 121.0, 128.9, 130.6, 131.3, 132.4, 132.6, 133.0, 135.6, 175.1; IR (neat) 3420, 2950, 2930, 2880, 1730, 1710, 1460 cm$^{-1}$; HRMS calcd for $C_{37}H_{64}O_7Si$ ($M^+$) *m*/*z* 648.4421, found 648.4419.

**(1*R*,2*S*,4a*R*,5*R*,6*S*,8a*S*)-5-Hydroxy-2-[(1*E*,3*E*,5*S*,6*R*,7*E*,12*R*)-12-hydroxy-6-methoxymethoxy-5,7-dimethyltrideca-1,3,7-trienyl]-1,3,6-trimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic Acid (47).** To a cooled (0 °C), stirred solution of **46** (35.5 mg, 54.7 mmol) in THF (1 mL) was added HF•pyridine complex (0.2 mL). The mixture was stirred for 21 h and quenched with saturated aqueous $NaHCO_3$ (4 mL) at 0 °C. This was diluted with saturated aqueous $NaHCO_3$ (16 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried and concentrated with the aid of toluene. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give 24.3 mg (86%) of **47** as a colorless oil: TLC, $R_f$ 0.51 (EtOAc/hexane, 2:1); $[\alpha]^{25}_D$ +198 (*c* 1.02, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ 1.04 (d, $J$ = 6.4 Hz, 3H), 1.14 (d, $J$ = 6.8 Hz, 3H), 1.15 (s, 3H), 1.19 (d, $J$ = 6.2 Hz, 3H), 1.31−1.49 (m, 5H), 1.51 (s, 3H), 1.63 (s, 3H), 1.55−1.83 (m, 6H), 1.93−2.13 (m, 2H), 2.38 (d, $J$ = 9.4 Hz, 1H), 2.32−2.49 (m, 1H), 2.91 (m, 1H), 3.37 (s, 3H), 3.57 (d, $J$ = 9.4 Hz, 1H), 3.77−3.92 (m, 1H), 4.44, 4.60 (2d, $J$ = 6.7 Hz, 1H × 2), 5.28−5.52 (m, 3H), 5.75 (s, 1H), 5.85−6.02 (m, 2H); $^{13}$C NMR (68 MHz) $\delta$ 11.3, 16.6, 16.7, 18.7, 22.8, 23.1, 25.3, 26.8, 27.1, 33.5, 37.6, 38.3, 38.4, 40.8, 45.7, 49.0, 53.9, 55.6, 68.3, 79.5, 86.2, 92.9, 120.9, 129.3, 130.8, 131.5, 132.4, 132.6, 133.2, 134.7, 178.3; IR (neat) 3420, 2970, 2930, 2880, 1710, 1690, 1460, 1450 cm$^{-1}$.

**(1*S*,2*E*,4*E*,6*S*,7*R*,8*E*,13*R*,16*R*,17*S*,20*S*,21*R*,22*R*)-21-Hydroxy-7-methoxymethoxy-6,8,13,16,20,24-hexamethyl-14-oxatricyclo-[14.8.0.0$^{17,22}$]tetracosa-2,4,8,23-tetraene-15-one (48).** A solution of **47** (20.2 mg, 38.9 $\mu$mol) in MeCN (24 mL) was added to a refluxing solution of 2-chloro-1-methylpyridinium iodide (50.1 mg, 0.196 mmol) and $Et_3N$ (0.055 mL, 0.40 mmol) in MeCN (12 mL) over 2.5 h by an addition funnel. The addition funnel was rinsed with 3.5 mL of MeCN and the washing was added to the reaction mixture. The mixture was refluxed for an additional 3.5 h. After being cooled to room temperature, the mixture was concentrated

in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 18.2 mg (93%) of **48** as a colorless oil: TLC, $R_f$ 0.76 (EtOAc/hexane, 1:1); $[\alpha]^{26}_D$ +182 (*c* 0.875, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ 0.83−0.98 (m, 2H), 1.04 (d, $J$ = 6.2 Hz, 3H), 1.12 (s, 3H), 1.16−1.29 (m, 6H), 1.34−1.50 (m, 2H), 1.52 (s, 3H), 1.57−1.60 (m, 7H), 1.63 (s, 3H), 1.96−2.24 (m, 2H), 2.34 (d, $J$ = 10.2 Hz, 1H), 2.39−2.51 (m, 1H), 2.92 (m, 1H), 3.37 (s, 3H), 3.48 (d, $J$ = 9.6 Hz, 1H), 4.44, 4.58 (2d, $J$ = 6.4 Hz, 1H × 2), 4.62−4.76 (m, 1H), 5.09 (m, 1H), 5.31 (dd, $J$ = 14.1, 10.2 Hz, 1H), 5.47 (dd, $J$ = 14.9, 6.5 Hz, 1H), 5.73 (s, 1H), 5.81−6.10 (m, 2H); $^{13}$C NMR (68 MHz) $\delta$ 11.2, 15.7, 16.7, 18.7, 19.2, 22.6, 25.3, 26.4, 26.8, 33.3, 34.8, 36.7, 38.1, 40.9, 45.6, 48.5, 54.3, 55.5, 71.2, 79.6, 88.1, 93.0, 120.5, 127.8, 130.9, 131.8, 132.8, 133.4 × 2, 135.5, 174.2; IR (neat) 3490, 2980, 2930, 2880, 1720, 1460 cm$^{-1}$; HRMS (FAB) calcd for $C_{31}H_{48}O_5$ ($M^+$) $m/z$ 500.3502, found 500.3505.

**(+)-Tubelactomicin B (2).** To a cooled (0 °C), stirred solution of **48** (17.5 mg, 34.9 $\mu$mol) in THF (0.5 mL) was added 6 M aqueous HCl (0.5 mL). The mixture was stirred for 11 h and then additional 6 M aqueous HCl (0.25 mL) and THF (0.5 mL) were added. The mixture was stirred for an additional 6 h and neutralized with saturated aqueous $NaHCO_3$ (15 mL) at 0 °C. This was extracted with $CH_2Cl_2$ (3 × 8 mL). The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give 13.3 mg (83%) of **2** as a colorless solid: TLC, $R_f$ 0.58 ($CHCl_3$/MeOH, 10:1), $R_f$ 0.62 (EtOAc/hexane, 1:1); $[\alpha]^{24.5}_D$ +101(*c* 0.60, MeOH); $^1$H NMR (300 MHz) $\delta$ 0.83−1.00 (m, 2H), 1.04 (d, $J$ = 6.2 Hz, 3H), 1.12 (s, 3H), 1.18 (d, $J$ = 6.8 Hz, 3H), 1.21 (d, $J$ = 6.2 Hz, 3H), 1.32−1.51 (m, 2H), 1.60 (s, 3H), 1.61−1.88 (m, 7H), 1.63 (s, 3H), 1.93−2.20 (m, 2H), 2.32−2.45 (m, 1H), 2.35 (d, $J$ = 10.2 Hz, 1H), 2.92 (m, 1H), 3.57 (d, $J$ = 9.0 Hz, 1H), 4.68 (m, 1H), 5.06 (m, 1H), 5.31 (dd, $J$ = 14.0, 10.2 Hz, 1H), 5.48 (dd, $J$ = 15.0, 6.4 Hz, 1H), 5.73 (s, 1H), 5.81−5.99 (m, 2H); $^{13}$C NMR (68 MHz) $\delta$ 11.1, 15.5, 16.7, 18.7, 19.2, 22.6, 25.3, 26.3, 26.8, 33.3, 34.8, 38.1, 40.9, 45.6, 48.5, 54.3, 71.3, 79.6, 85.3, 120.5, 127.6, 129.2, 130.8, 133.3, 133.4, 135.5, 136.2, 174.3; IR (KBr) 3420, 2980, 2930, 2880, 1720, 1705, 1460 cm$^{-1}$; HRMS calcd for $C_{29}H_{44}O_4$ ($M^+$) $m/z$ 456.3240, found 426.3234.

**(+)-Tubelactomicin D (3).** To a stirred solution of **52** (40.1 mg, 77.6 $\mu$mol) in MeOH (3 mL) was added 1 M aqueous NaOH (1.5 mL). The mixture was heated at 50 °C with stirring for 6.5 h. After being cooled to 0 °C, the mixture was acidified with 1 M aqueous HCl to pH 2. This was diluted with $H_2O$ (4 mL) and extracted with $CH_2Cl_2$ (3 × 3 mL). The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/acetone, 2:1) to give **3** (36.0 mg, 92%) as a colorless oil: TLC, $R_f$ 0.22 ($CHCl_3$/MeOH, 10:1 containing 1% AcOH); $[\alpha]^{24.5}_D$ +95.7 (*c* 0.14, $CHCl_3$); $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 1.03 (d, $J$ = 6.4 Hz, 3H), 1.12 (s, 3H), 1.15 (d, $J$ = 6.0 Hz, 3H), 1.21 (d, $J$ = 7.3 Hz, 3H), 1.27−1.33 (m, 3H), 1.34−1.71 (m, 3H), 1.60−1.78 (m, 4H), 1.84−1.88 (m, 1H), 2.40−2.60 (m, 2H), 2.72 (d, $J$ = 10 Hz, 2H), 2.84 (t, $J$ = 9.0 Hz, 2H), 3.89−3.93 (m, 5H), 4.71 (m, 1H), 5.28 (dd, $J$ = 10, 14 Hz, 1H), 5.72 (dd, $J$ = 5.7, 14 Hz, 1H), 5.81 (dd, $J$ = 4.6, 8.3 Hz, 1H), 5.89−6.00 (m, 2H), 6.09 (br s, 1H); $^{13}$C NMR (75 Hz, acetone-$d_6$) $\delta$ 15.9, 17.1, 19.4, 19.5, 26.1, 27.8, 29.0, 34.4, 35.9, 39.6, 41.2, 41.9, 46.5, 48.9, 50.5, 65.1, 71.4, 79.4, 81.8, 122.9, 128.7, 131.7, 134.3, 134.7, 137.0, 137.7, 144.7, 168.6, 174.4; IR (neat) 3600, 3500, 2980, 1740, 1680, 1650, 1460 cm$^{-1}$; HRMS calcd for $C_{29}H_{42}O_7$ ($M^+$) $m/z$ 502.2930, found 502.2929.

**(+)-Tubelactomicin E (4).** To a stirred solution of **59** (9.9 mg, 19 $\mu$mol) in MeOH (1 mL) was added 1 M aqueous NaOH (0.5 mL). The mixture was heated to 50 °C for 3 h. After being cooled to room temperature, the mixture was acidified with 1 M aqueous HCl to pH 2 at 0 °C. This was diluted with 1 M aqueous HCl (10 mL) and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/hexane, 1:1 containing 1% AcOH) to give 9.1 mg (94%) of **4** as a colorless solid: TLC, $R_f$ 0.27 ($CHCl_3$/MeOH, 10:1 containing 1% AcOH), 0.36 (acetone/hexane, 1:1 containing 1% AcOH); $[\alpha]^{23.5}_D$ +94.9 (*c* 0.23, MeOH); $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 1.01−1.76 (m, 10H), 1.13 (s, 3H), 1.15 (d, $J$ = 6.0 Hz, 3H), 1.23 (d, $J$ = 6.3 Hz, 3H), 1.61 (s, 3H), 1.84 (m, 1H), 2.40 (d, $J$ = 10.0 Hz, 1H), 2.47−2.57 (m, 2H), 2.60−2.73 (m, 1H), 3.22 (dd, $J$ = 9.3, 9.3 Hz, 1H), 3.65 (dd, $J$ = 10.5, 6.6 Hz, 1H), 3.72 (dd, $J$ = 10.5, 5.1 Hz, 1H), 3.94 (d, $J$ = 8.4 Hz, 1H), 4.71 (m, 1H), 5.29 (dd, $J$ = 13.9, 10.0 Hz, 1H), 5.70 (dd, $J$ = 14.6, 6.2 Hz, 1H), 5.83 (s, 1H), 5.83−6.00 (m, 3H); $^{13}$C NMR (75 MHz, acetone-$d_6$) $\delta$ 16.1, 17.2, 19.4, 22.9, 26.0, 27.2, 28.1, 35.8, 38.5, 41.9, 46.5, 48.1, 49.1, 55.1, 67.1, 71.4, 77.4, 81.3, 122.3, 128.9, 131.8, 133.0, 134.2, 134.9, 136.9, 144.4, 168.6, 174.4 (solvent peak overlapped one carbon peak, so one carbon was not detected); IR (KBr) 3420, 2930, 2860, 1720, 1700, 1460 cm$^{-1}$; HRMS calcd for $C_{29}H_{42}O_7$ ($M^+$) $m/z$ 502.2930, found 502.2930.

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**Supporting Information Available:** Experimental procedures and full spectroscopic data for all new compounds described herein and copies of $^1$H and $^{13}$C NMR spectra for all new compounds, synthetic and natural tubelactomicins B, D, and E. This material is available free of charge via the Internet at http://pubs.acs.org.

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