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Formal synthesis of tubelactomicins via a transannular Diels–Alder approach

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Abstract—A formal synthesis of the antimicrobial tricyclic macrolides, tubelactomicins A and E, featured by a transannular Diels–Alder (TADA) approach, has been explored. The key issue for the transannular cyclization was the synthesis of a 24-membered macrolactone equipped with all the requisite functionalities, which has been achieved using an intramolecular Hiyama cross-coupling strategy. The Hiyama coupling reaction spontaneously triggered off the TADA reaction. From the *endo*-TADA adduct, formal syntheses of tubelactomicins A and E were achieved. The 24-membered macrolactone formation was also achieved via an intramolecular ring-closing metathesis approach.

The isolation and structure determination of (+)-tubelactomicin A (**1**) (Scheme 1) were reported by studies at the Institute of Microbial Chemistry in 2000.[1] This tricyclic 16-membered macrolide **1** showed potent antimicrobial activity against acid-fast bacteria, including drug-resistant strains. Following the isolation of **1**, the same group isolated and characterized structurally similar macrolides, tubelactomicins B (**2**), D (**3**), and E (**4**).[2] These antibiotics **2**–**4** also showed a broad range of antimicrobial activity. In 2005, we reported the total synthesis of **1**, thereby establishing the stereochemistry of the (+)-natural form.[3] Tatsuta and co-workers have also accomplished the total synthesis of **1**.[4] Recently, we also accomplished the total syntheses of **2**–**4** and established their unknown stereochemistries.[5] In the accomplished total synthesis of (+)-tubelactomicins, our group and Tatsuta's group utilized intramolecular Diels–Alder (IMDA) approaches for the construction of the octahydronaphthalene parts in **1**–**4**. On the other hand, it might be possible that the tricyclic structures of **1**–**4** are constructed by a transannular Diels–Alder (TADA) reaction of a 24-membered macrolactone equipped with all the requisite functionalities. Attracted by this hypothesis, we have explored the total synthesis of tubelactomicins using this plausible TADA approach as a key step.[6] Herein, we report the total syntheses of **1** and **4**, which were realized using the attempted TADA strategy. Our synthetic approach is summarized in Scheme 1. As substrates for the synthesis of the key 24-membered macrolactone such as **5**, we envisioned long-chained esters **6**, which incorporate with vinylstannane, vinylboronate, or vinylsilane and vinyl iodide functionalities at both terminals. These highly functionalized esters **6** would be obtained by the Wittig olefination of α-phosphonopropionyl ester **7** and (*E*,*E*,*E*)-undeca-6,8,10-trienal **9** (for **6** with M = trimethylsilyl = TMS). Ester **7** could be prepared from the previously reported vinylstannane **8**.[3b] On the other hand, (trienyl)trimethylsilane **9** could be obtained by the Horner–Wadsworth–Emmons (HWE) olefination of the known aldehyde **10**[3a] and (*E*,*E*)-pentadienyl phosphonate **11**. Along this synthetic plan, we started the synthesis of the 24-membered lactone **5**.

First, the α-phosphonopropionate **7** was synthesized from **8** via a two-step manipulation, that is, tin–iodine exchange, followed by esterificaton with commercially available **12** (Scheme 2). We initially explored the HWE olefination of **7** with aldehyde **13**,[3a] a synthetic intermediate of our previous total synthesis of **1**. This

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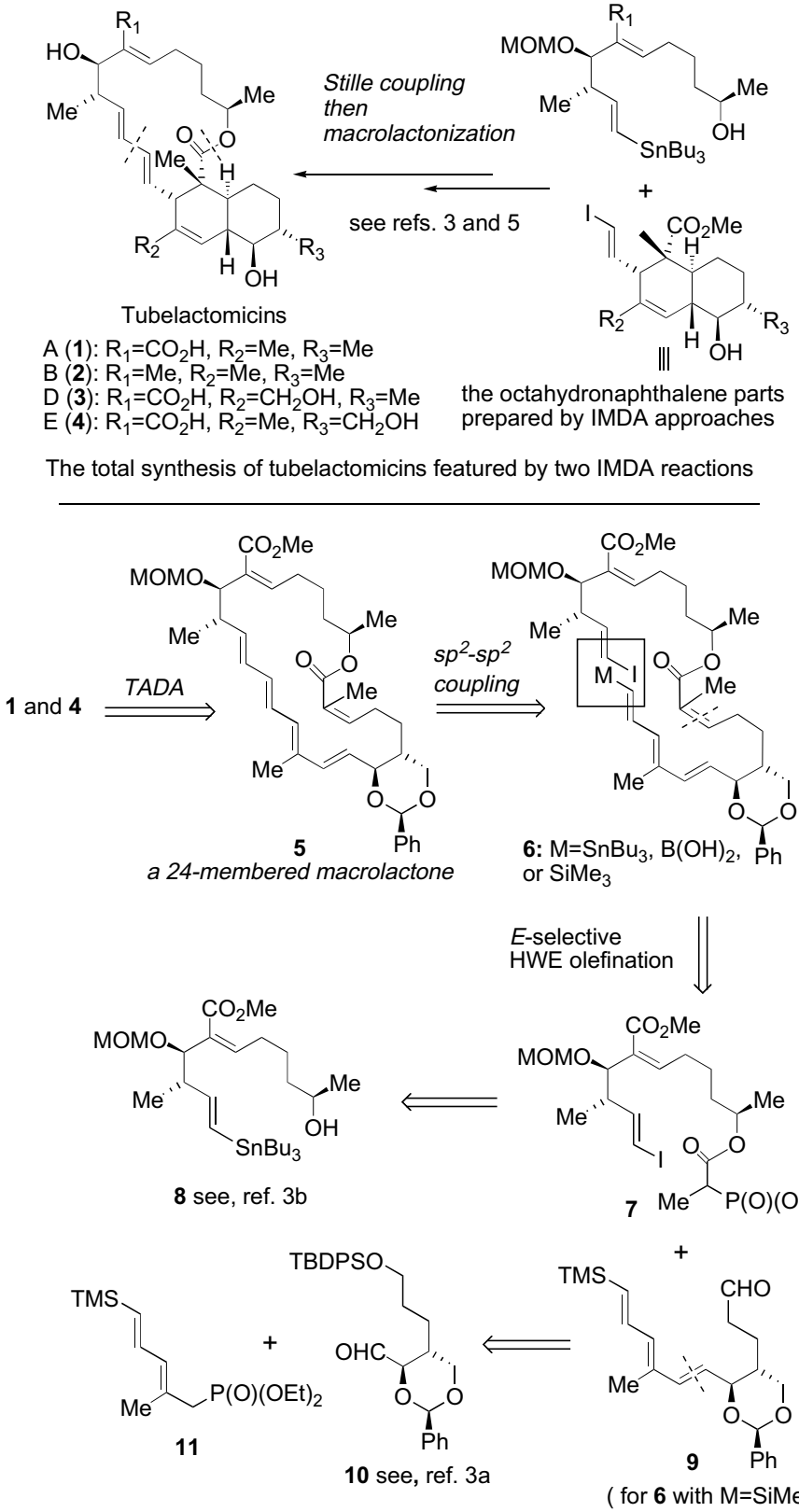
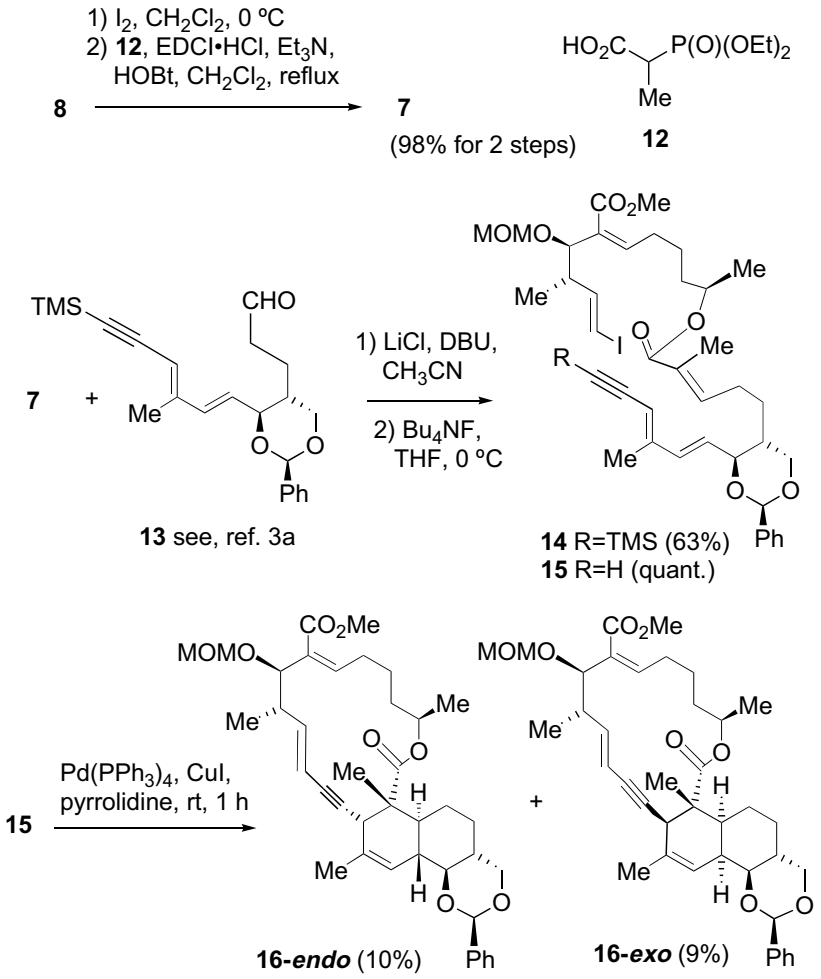


Scheme 1. Attempted TADA approaches.

olefination provided **14** in a yield of 63%, which was de-C-silylated with Bu_4NF, providing **15**. As a model experiment, we explored the macrolactone formation using **15** via an intramolecular sp–sp^2 cross-coupling strategy. Thus, the Pd-catalyzed intramolecular Sonogashira coupling of **15** was explored using pyrrolidine

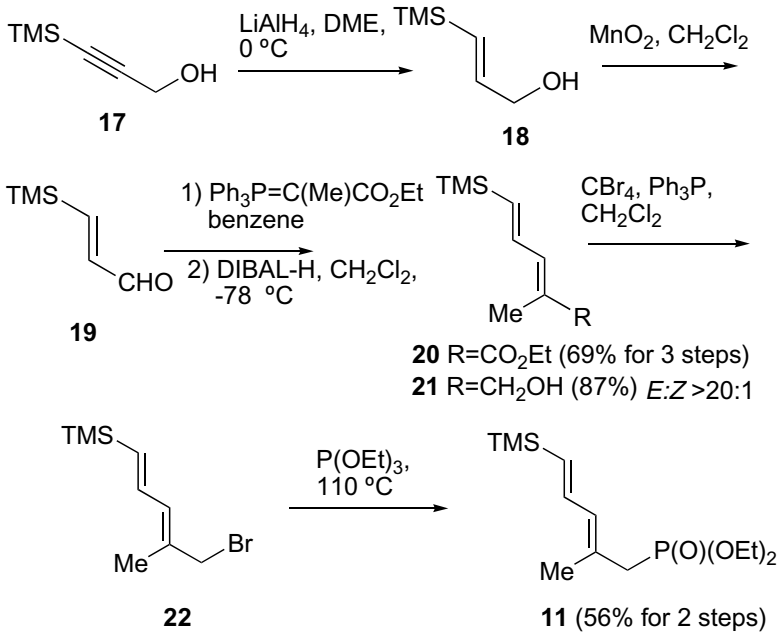


Scheme 2. The Sonogashira coupling/TADA reaction of **15**.

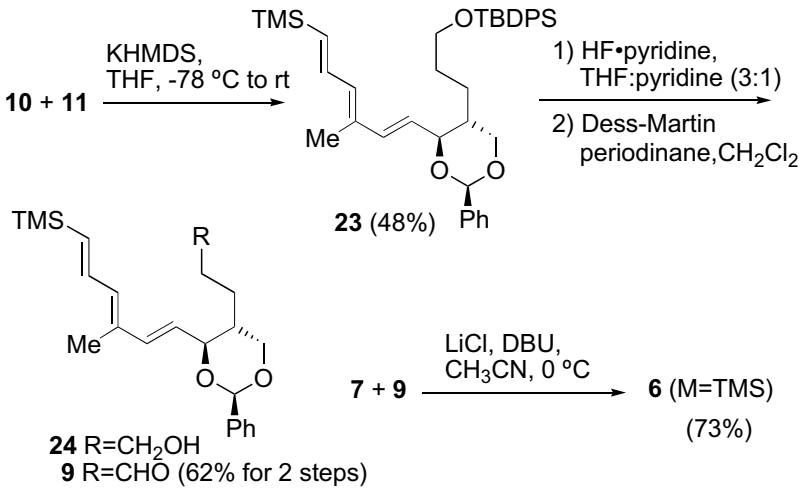
as a base at room temperature. After 1 h, this coupling produced two products. Interestingly, these products were identified to be an *endo*-TADA adduct **16-*endo*** and an *exo*-TADA one **16-*exo***, which were isolated in 10% and 9% yields, respectively. Neither the Sonogashira coupling product nor other by-products were isolated from the reaction mixture. We consider that the low yields of **16-*endo*** and **16-*exo*** are mainly due to the difficulty in the formation of 24-membered intermediate in the intramolecular cyclization step. On the other hand, we conclude that the TADA reaction occurred instantly after the Sonogashira coupling product was formed. It should be emphasized that the IMDA reaction of **15** was not the first event. This was evidenced by the fact that the IMDA reaction of **14** started by heating **14** at 80 °C and completed after 4 days, providing an approximately 1:2 mixture (^{1}H NMR analysis) of *endo*- and *exo*-adducts (not shown) in a combined yield of 93%. We then focused our efforts on the synthesis of substrates **6** (R = $SnBu_3$ or $B(OH)_2$) via the functionalization of the acetylene moiety in **15**. Despite extensive efforts,[7] however, we could not find efficient conditions for the synthesis of these terminally metalated olefins as the substrates for the attempted intramolecular Stille or Suzuki–Miyaura coupling reaction.

Next, we explored the synthesis of vinylsilane **6** (M = $SiMe_3$) as the substrate for intramolecular Hiyama cross-coupling.[8] The synthesis of **6** was expected to be achieved by the HWE reaction of **7** and aldehyde **9** with an (*E*,*E*,*E*)-trienyl trimethylsilane moiety. For the synthesis of **9**, we explored the synthesis of pentadienyl phosphonate **11** as the HWE reaction partner of the previously reported aldehyde **10**.[3a] The synthesis of **11** was achieved as shown in Scheme 3. Thus, the $LiAlH_4$ reduction of commercially available C-silylated propargylic alcohol **17** provided *trans*-allylic alcohol **18**,[9] which was converted into unsaturated aldehyde **19** with MnO_2.[10] The Wittig reaction of **19** with $Ph_3P=C(Me)$-CO_2Et provided the α,β:γ,δ-unsaturated ester **20**. The diisobutylaluminum hydride (DIBAL-H) reduction of **20** provided pentadienyl alcohol **21** (*E*:*Z* = >20:1). Bromination of **21** with a mixture of CBr_4 and Ph_3P, followed by a thermal Arbusov rearrangement of the resulting bromide **22** with triethyl phosphite, eventually produced **11**.

The HWE olefination of **10**[3a] and **11** using potassium hexamethyldisilazide (KHMDS) as the base provided (*E*,*E*,*E*)-triene **23** (Scheme 4). Deprotection of the TBDPS (*t*-$BuPh_2Si$) group in **23**, followed by



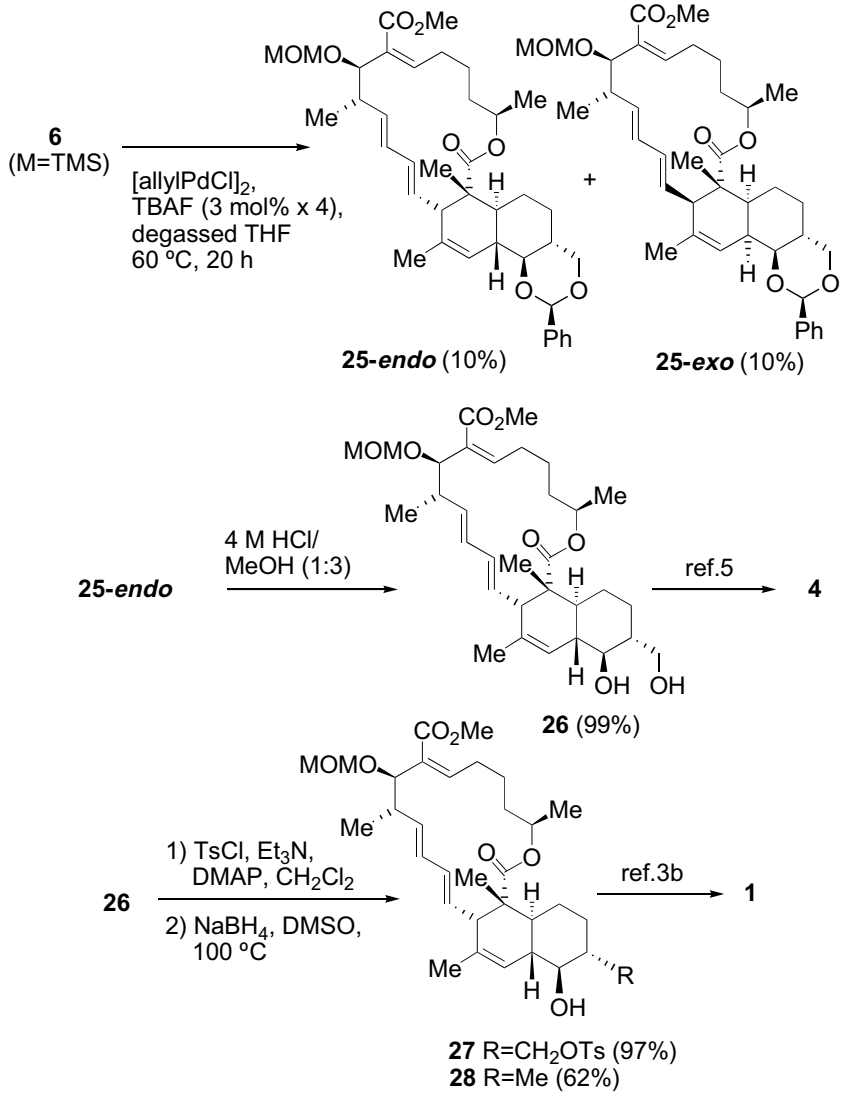
Scheme 3. Synthesis of pentadienyl phosphonate **11**.



Scheme 4. Synthesis of pentadienyl trimethysilane **6**.

Dess–Martin oxidation[11] of the resulting primary alcohol **24**, provided aldehyde **9**. Then, the HWE coupling of **7** and **9** smoothly provided **6** (M = TMS), the substrate for the intramolecular Hiyama cross-coupling.

As shown in Scheme 5, the Pd-catalyzed intramolecular Hiyama cross-coupling of **6** was examined in the presence of semi-catalytic amount of tetrabutylammonium fluoride (TBAF, four-times addition of each 3 mol % amount) at 60 °C for 20 h. As a result, two TADA adducts **25-*endo*** and **25-*exo*** were obtained. The structures of these two adducts were determined by extensive ^{1}H NMR analysis. Furthermore, one of the adducts, that is, **25-*endo***, was identified with a synthetic intermediate in the previous total synthesis of **4**.[5] Although the yields of **25-*endo*** and **25-*exo*** were not necessarily remarkable, neither the intermediary Hiyama cross-coupling product **5** nor other isolable products were found in the reaction mixture. We consider that the rather low yields of the TADA adducts were the result from the instability of the poly-unsaturated nature of substrate **6** under the transition-metal-catalyzed reaction conditions. In fact, a number of high-polar materials were found in the reaction mixture (TLC monitoring) during the Hiyama cross-coupling/TADA event. We could not isolate or identify these products. Compared to the previous results obtained from the stereoselective (*endo*- and π-facial) and high-yielding IMDA reactions realized in the total synthesis of tubelactomicins,[3,5] the *endo*/*exo*-selectivity observed in the Hiyama coupling/TADA reaction of **6** was low.[12] As expected from the result of the Sonogashira coupling/TADA reaction of **15**, however, it should be emphasized that the sequential intramolecular cyclization reactions of **6** proceeded with

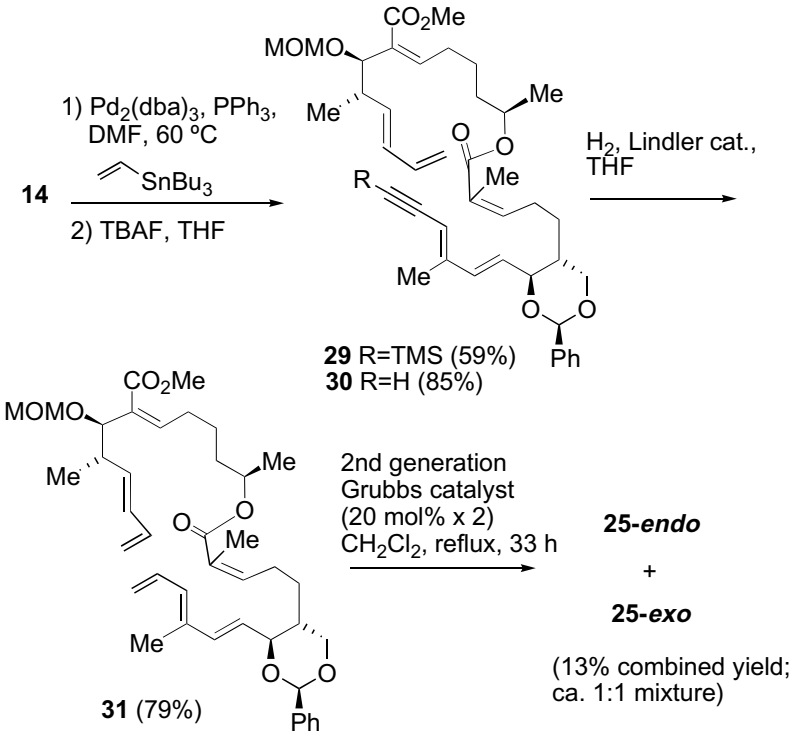


Scheme 5. The Hiyama coupling/TADA reaction of **6** and formal syntheses of **1** and **4**.

complete π-facial selectivity to provide the expected two adducts. The adduct **25-*endo*** was converted into (+)-tubelactomicin E (**4**) previously.[5] On the other hand, de-*O*-benzylidene product **26**, prepared from **25-*endo***, was selectively tosylated. Deoxygenation of the resulting primary tosylate **27** with $NaBH_4$ in hot DMSO provided **28**,[3b] from which (+)-tubelactomicin A (**1**) was synthesized previously.[3b]

Finally, we were interested in the 24-membered lactone formation via a ring-closing olefin metathesis (RCM) approach.[13] As summarized in Scheme 6, we synthesized linear heptaene **31** from the aforementioned vinyl iodide **14**. Thus, the Stille coupling of **14** and vinyltributylstannane provided conjugated diene **29** in a moderate yield of 59%. Protodesilylation of the TMS group in **29** provided **30**. The hemi-hydrogenation of the triple bond in **30** was achieved efficiently using a Lindler catalyst to provide **31**, the substrate for the attempted RCM approach. After some experimentation, we found that the second-generation Grubbs catalyst[14] was solely effective for the RCM of **31**,[15] which provided the TADA adducts **25-*endo*** and **25-*exo*** as an approximately 1:1 mixture in a combined yield of 13%. As the case of the intramolecular Hiyama cross-coupling applied to **6**, the initially formed RCM product **5** was not found in the reaction mixture. The TADA reaction of **5**, which was produced by the RCM of **31**, proceeded at a lower temperature compared to the case of the Hiyama coupling/TADA reaction of **6**. Although the π-facial selectivity of the TADA reaction was again complete, the *endo*/*exo*-selectivity was almost the same as the result obtained from the sequential cyclization achieved using **6**. Furthermore, another RCM product corresponding to **5**, which possesses a newly introduced *Z*-olefin part, was not found in the reaction mixture. We did not explore further for the improvement of the yields and selectivity of this RCM/TADA reaction.

In conclusion, we have accomplished the formal syntheses of tubelactomicins A and E via a TADA approach. Substrate **5** for the TADA reaction, that is, a highly functionalized 24-membered macrolactone equipped with an all-*E* conjugated tetraene part, was synthesized



Scheme 6. The metathesis approach to the TADA adducts.

by a Hiyama cross-coupling or a ring-closing olefin metathesis. Furthermore, these 24-membered macrolactone forming reactions triggered off a spontaneous TADA reaction.

Acknowledgments

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Supplementary data

The experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.002.

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6. We have accomplished the total synthesis of macquarimicins using a TADA approach, see Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2004**, *126*, 11254–11267.
7. We examined the following conditions for **15**: (1) Bu_3SnH/BuLi/CuCN/THF/−78 °C (complex mixture); (2) catechol-borane/cat.9-BBN/THF/0 °C and then H_2O workup (partial decomposition of **15** and 43% recovery of **15**); (3) catecholborane/$Cp_2Zr(H)Cl$/benzene/rt and then H_2O workup (partial decomposition of **15** and 44% recovery of **15**). For Lipshutz reagent in condition (1), see Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065–2068.
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12. Regarding the low *endo*/*exo*-selectivities observed in the TADA reactions of **15**, **6**, and **31** (in Scheme 6), we do not have reasonable explanation. On the other hand, we

previously found the following experimental result during studies on the IMDA reactions for the stereoselective construction of the octahydronaphthalene part. Thus, when the bulkiness of the dienophile part increased, the *endo*/*exo*-selectivity of the IMDA reaction reduced remarkably. In the case of the substrate possessing a CH=CHCOOR dienophile part in place of a CH=CHCHO functionality, the IMDA reaction provided a mixture of *endo*/*exo*-adducts in a 1:2 ratio. We speculate that this lack of the *endo*/*exo*-selectivity may arise from less effective secondary orbital interactions and/or increasing steric hindrances of the dienophile part in the transition-state of the IMDA reactions.

13. (a) For reviews on olefin metathesis, see *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527; For a recent paper on the 12-membered macrolactone formation using RCM, see Kanda, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotaka, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4350–4355.
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15. To maintain the reproducibility of the TADA reaction, it is important to add the Grubbs catalyst (each 20 mol %) for two times.