DOI: 10.1002/ejoc.200900409

Natural Product Synthesis Featuring Intramolecular Diels–Alder Approaches – Total Syntheses of Tubelactomicins and Spiculoic Acid A

Kin-ichi Tadano*[a]

Keywords: Intramolecular Diels–Alder reaction / Natural products / Total synthesis / Cycloaddition / Tubelactomicins / Spiculoic acid A

We have recently accomplished the total syntheses of the antimicrobial tricyclic 16-membered macrolides (+)-tubelactomicin A, B, D, and E by common synthetic approaches based on intramolecular Diels–Alder (IMDA) reactions. These total syntheses established the relative and absolute configurations of three antibiotics – (+)-tubelactomicins B, D, and E – for which only planar structures had been previously reported. In addition, we have very recently accomplished the total synthesis of a marine natural product, (+)-spiculoic acid A, by an IMDA strategy. This Microreview summarizes our total syntheses of the four tubelactomicns and the total synthesis of (+)-tubelactomicin A by Tatsuta et al. Both approaches were based on the use of stereoselective IMDA reactions for the construction of the lower-half segments of the antibiotics. Total syntheses of the unnatural (–) and natural (+) enantiomers of spiculoic acid A, the former achieved by Baldwin and Lee's group and the latter achieved by the author's group, are also summarized.

[a] Department of Applied Chemistry, Keio University, 3-14-1, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan
E-mail: tadano@applc.keio.ac.jp

1. Introduction

As a representative highly stereoselective cycloaddition reaction, the Diels–Alder reaction is the most widely explored pericyclic reaction for the construction of functionalized six-membered carbocyclic and heterocyclic compounds. In addition to the construction of monocyclic six-membered systems, polycyclic compounds containing a variety of functionalities are also available by Diels–Alder approaches. The remarkable usefulness of Diels–Alder reactions has been validated in many instances through the syntheses of structurally complex natural products.[1] The intramolecular version of the Diels–Alder (IMDA) reaction is a valuable synthetic tool for the synthesis of structurally intriguing natural products and has been widely explored in recent years.[2] In the past two decades, the author's group has been actively involved in the total synthesis of biologically important natural products by a variety of IMDA approaches.[3] In this Microreview, the author sum-

Kin-ichi Tadano was born in Chiba Prefecture, Japan in 1948. In 1977 he received his Ph.D. degree from Keio University in synthetic studies of carbocylclic nucleosides under the supervision of Professor Tetsuo Suami. He started his academic career in 1973 as an instructor in the Department of Applied Chemistry, Keio University. From 1977 to 1979 he was a research associate at the laboratory led by Professor Kenneth L. Rinehart at the University of Illinois at Urbana–Champaign, USA. He then returned to Keio University to resume his position at the faculty. He was promoted to Assistant Professor (1982), to Associate Professor (1988), and then to Professor (1994). His principle scientific concerns are synthetic studies of biologically important and structurally unique natural products and the development of asymmetric synthesis using sugars as a chiral environment.

marizes the total syntheses of a family of tubelactomicins – (+)-tubelactomicins A, B, D, and E – achieved for the first time by the author's group. The total synthesis of (+)-tubelactomicin A by Tatsuta et al. is also described. In addition, the total syntheses of (–)- and (+)-spiculoic acid A, accomplished by Baldwin and Lee's group and by the author's group, respectively, are summarized. All of the synthetic approaches to these biologically intriguing natural products were achieved by the use of IMDA reactions for the construction of the core structures of the target molecules.

2. Total Synthesis of (+)-Tubelactomicins

(+)-Tubelactomicin A (**1**, Figure 1) was isolated in 2000 from the culture broth of an actinomycete strain designated MK703-102F1, a member of *Nocardia*, by Igarashi et al. at the Institute of Microbial Chemistry in Japan.[4] The relative and absolute stereochemistries of **1** were determined by the Igarashi group after extensive spectroscopic analysis and were finally confirmed by X-ray crystallographic analysis of the carboxamide derivative with l-phenylalanine methyl ester.[4b] The structural characteristics of **1** are (1) a *trans*-fused octahydronaphthalene moiety possessing six contiguous stereogenic carbon centers, and (2) a 16-membered macrolactone incorporating an (*E*,*E*)-conjugate diene and an α,β-disubstituted (*Z*)-acrylic acid moiety. This tricyclic 16-membered macrolide **1** showed potent antimicrobial activity against acid-fast bacteria, including drug-resistant strains.[4a] After the isolation of **1**, the same group isolated and characterized closely related macrocyclic compounds, designated (+)-tubelactomicin B (**2**), D (**3**), and E (**4**), from the same microorganism.[5] These antibiotics **2**–**4** also showed broad ranges 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 most likely that compounds **2**–**4** possessed the same relative and absolute stereochemistries as **1** in that these natural products were isolated from the same culture broth as **1**.

So far, a number of macrolides with tricyclic structures similar to that of **1** have been isolated and characterized. Synthetic studies directed towards these octahydronaphthalene-fused macrolides have been explored by several research groups in the past two decades.[6] In 2005, we reported the total synthesis of **1**, thereby confirming the stereochemistry of the (+) natural form.[7] In 2006, Tatsuta et al. also reported the total synthesis of **1**.[8] Later, we accomplished the total syntheses of tubelactomicins **2**–**4** by synthetic approaches slightly modified from that used for the total synthesis of **1**.[9] As a result, we established the unknown relative and absolute stereochemistries of **2**–**4** as those depicted in Figure 1. Recently, we also reported the total syntheses of **1** and **4** by a transannular Diels–Alder approach, a variant of the IMDA reaction.[10]

2.1 Total Syntheses of (+)-Tubelactomicins A, B, D, and E by the Tadano Group

Aiming at the total syntheses of tubelactomicins **1**–**4**, all in enantiomerically pure forms, we envisioned that these total syntheses should be accomplishable by convergent synthetic approaches similar to those shown in Scheme 1. These common synthetic strategies for obtaining the tricyclic skeletons of **1**–**4** were based on the assembly of upper-half segments such as **5** or **6** and of lower-half segments such as **7**–**9** by transition-metal-catalyzed cross-coupling such as Stille coupling,[11] followed by lactonization to form the 16-membered macrolide structures. The upper-half segments **5** ($R^1 = CO_2R$) and **6** (R^1 = Me) should be synthesizable from **10** ($R^1 = CH_2OP$) and **11** (R = Me), respectively, by an identical carbon–carbon bond extension strategy involving the Evans *syn*-aldol approach.[12] The three lower-half segments **7**–**9**, all highly functionalized 1,1,2,3,5,6-hexasubstituted octahydronaphthalene derivatives, should be synthesizable through stereoselective (*endo*-selective and π-facial-selective) IMDA reactions of unsaturated aldehydes **12** (R^2 = Me) or **13** ($R^2 = CH_2OP$), each carrying a terminal conjugated dienyne part. The intermediates **10** and **11** should be accessible from methyl (*R*)-lactate (**14**) through a series of standard carbon-chain elongations. On the other hand, the IMDA substrates **12** and **13** should be available from diethyl (*R*)-malate (**15**) through a conventional carbon-elongation approach for the introduction of the terminal trimethylsilylated dienyne part as a 4π system and the α-methylated unsaturated aldehyde part as a 2π system. Following these synthetic schemes, we eventually completed the total syntheses of the four tubelactomicins **1**–**4** as described below.

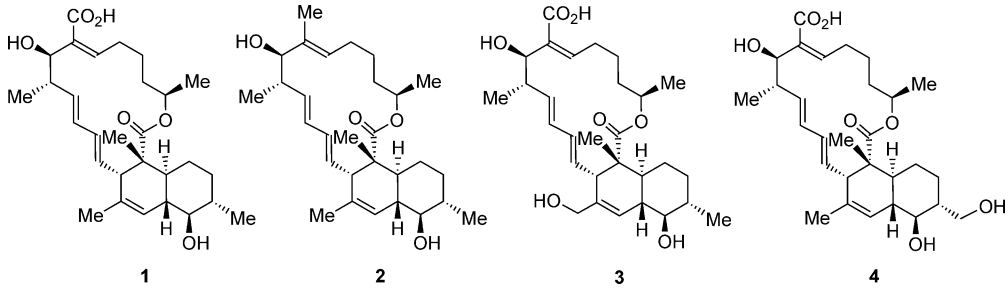
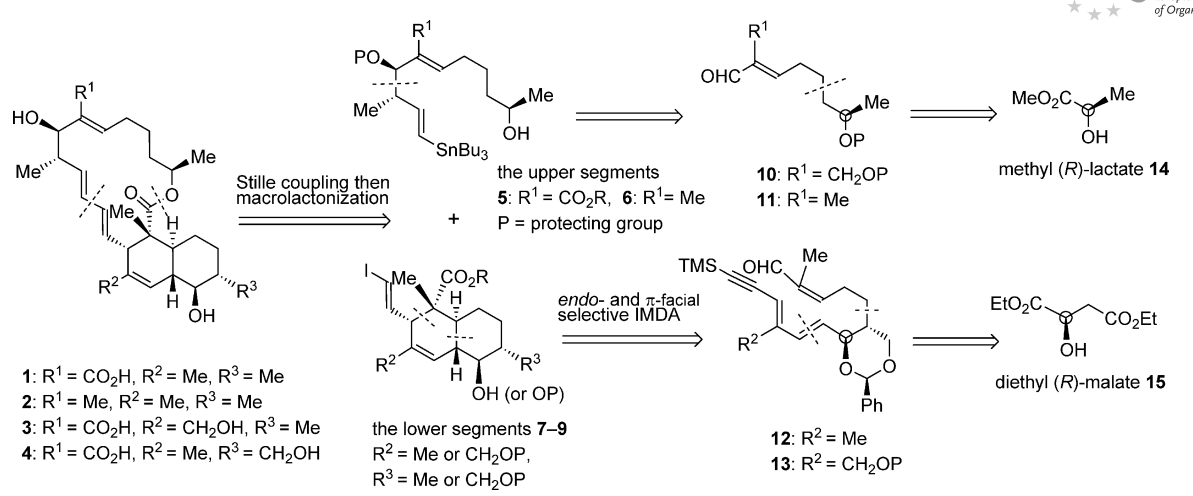
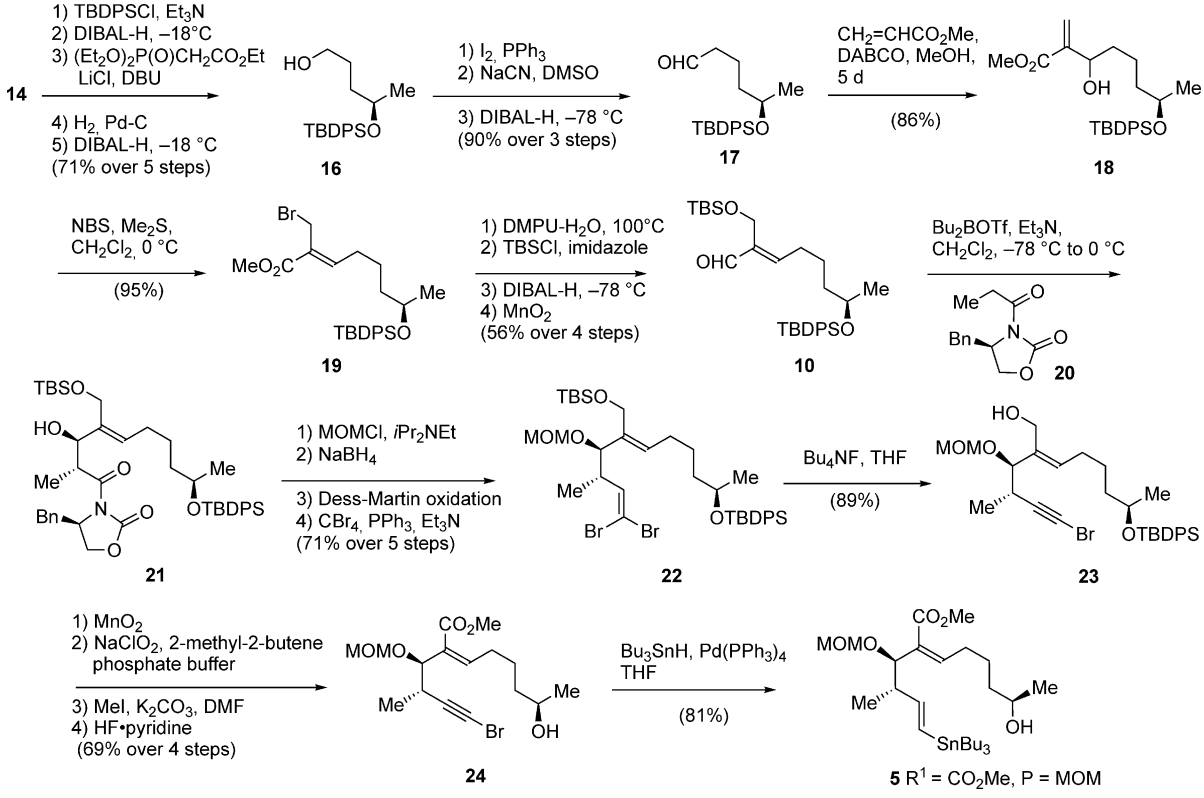


Figure 1. Structures of (+)-tubelactomicins A (**1**), B (**2**), D (**3**), and E (**4**).



Scheme 1. Retrosynthetic analysis for the total syntheses of (+)-tubelactomicins A (**1**), B (**2**), D (**3**), and E (**4**).

The synthesis of the upper-half segment **5** starting from **14** is summarized in Scheme 2. A five-step standard functional-group manipulation from **14**, including the Roush–Masamune variant of Horner–Wadsworth–Emmons olefination,[13] provided a two-carbon-elongated alcohol **16**. The further one-carbon extension of **16**, including two substitution reactions via the iodide and then the cyanide, followed by subsequent diisobutylaluminium hydride (DIBAL-H) reduction, provided the δ-hydroxylated hexanal derivative **17**. After some unsuccessful trials, the stereoselective construction of the (*Z*)-trisubstituted olefin moiety in **5** was efficiently achieved through a Morita–Baylis–Hillman reaction[14] between aldehyde **17** and methyl acrylate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in MeOH.[15] The 1:1 diastereomeric mixture of the α-substituted acrylic acids **18** was treated with *N*-bromosuccinimide (NBS) in the presence of Me_2S, efficiently providing the (*Z*)-trisubstituted allylic bromide **19** by a highly stereoselective S_N2' mechanism.[16] The allylic bromide **19** was converted into the unsaturated aldehyde **10** (R^1 = CH_2OTBS) by a four-step reaction sequence, involving substitution of the bromine group by a hydroxy group by treatment with aqueous 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU)[17] and a two-step reduction/



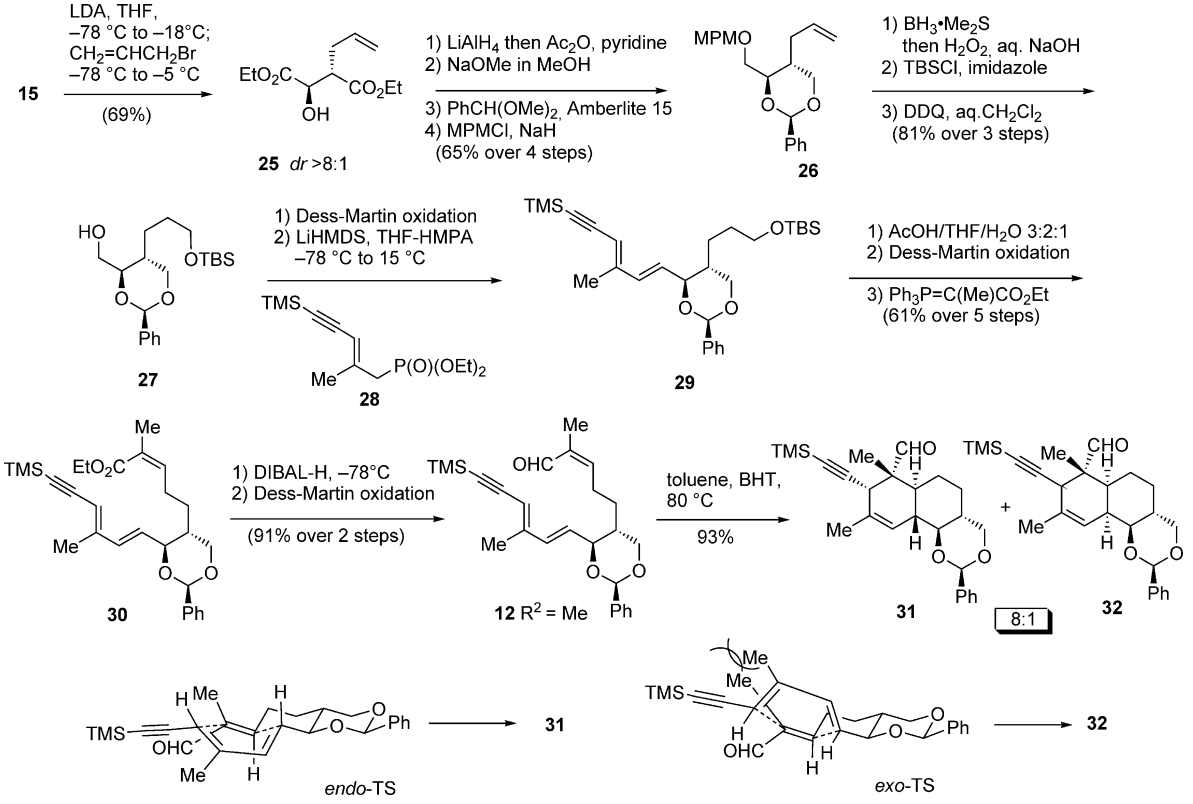
Scheme 2. Synthesis of the upper-half segment **5** from methyl (*R*)-lactate (**14**).

oxidation of the ester functionality. The stereoselective introduction of the vicinal *syn*-methyl/hydroxy unit was well achieved by an Evans-type chiral-auxiliary-based aldol approach using (4*R*)-4-benzyl-3-propionyloxazolidin-2-one (**20**).[12] This aldol reaction provided the desired *syn* adduct **21** exclusively.

Protection of the resulting aldol **21**, reductive removal of the chiral auxiliary, Dess–Martin oxidation[18] of the resulting primary alcohol, and a Corey–Fuchs α,α-dibromoolefination[19] of the resulting aldehyde eventually provided **22**. De-*O*-silylation of the TBS ether **22** by treatment with Bu_4NF, accompanied by simultaneous elimination of HBr, provided the bromoalkyne **23**. The allylic alcohol part in **23** was then converted into the unsaturated ester **24** by two-step oxidation and esterification, and subsequent de-*O*-silylation. Regio- and stereoselective hydrostannylation of the bromoalkyne **24**, as in Pattenden's report,[20] provided the upper-half segment **5** in high yield.

The synthesis of the lower-half segment **7** [R^2, R^3 = Me, R = (2-trimethylsilyl)ethoxymethyl (SEM)] from diethyl (*R*)-malate (**15**) through the IMDA reaction of **12** (R^2 = Me) is summarized in Schemes 3 and 4. Regio- and diastereoselective allylation of the lithium enolate generated from **15** by Seebach's procedure[21] predominantly provided the *anti*-allylated product **25** (*dr* > 8:1) in a combined yield of 69%. A standard carbon-chain elongation approach was applied to **25** for introduction of both the diene and the dienophile units in the IMDA substrate **12** as follows. Hydride reduction of the esters in **25** and regioselective acetalization of the resulting triol with benzaldehyde dimethylacetal, followed by (4-methoxyphenyl)methyl (MPM) protection of the remaining hydroxy group, provided **26**. For purification of the intermediary triol derivative, an acetylation/deacetylation step was required. Regioselective hydroboration of the vinyl group in **26**, followed by workup with alkaline hydrogen peroxide, provided the primary alcohol, which was protected with TBSCl. The MPM group in the resulting TBS ether was deprotected to provide **27**.

Dess–Martin oxidation of **27** and treatment of the resulting aldehyde with the conjugated enyne phosphonate **28** was next explored. The allylic phosphonate **28** was synthesized from diethyl methylmalonate by reported procedures.[22] This Horner–Wadsworth–Emmons reaction efficiently provided the (*E*,*E*)-conjugated dienyne **29** as the sole adduct. By a three-step standard manipulation, including a highly stereoselective Wittig olefination, **29** was converted into the α-methylated α,β-unsaturated ester **30**, which was further converted into the IMDA substrate **12** by a reduction/oxidation procedure. We expected that the unsaturated aldehyde **12** might be a more highly activated substrate for the attempted IMDA reaction than the unsaturated ester **30**. Gratifyingly, the IMDA reaction of **12** had proceeded to completion at 80 °C (toluene) after 24 h with high stereoselectivity, resulting in the formation of an approximately 8:1 inseparable mixture of the desired *trans*-fused *endo* adduct **31** and the *cis*-fused *exo* adduct **32** in a high combined yield of 93%. In this IMDA reaction, π-facial selectivity was completely controlled and can be ex-



Scheme 3. Synthesis of the IMDA substrate **12** from diethyl (*R*)-malate (**15**) and the subsequent IMDA reaction.

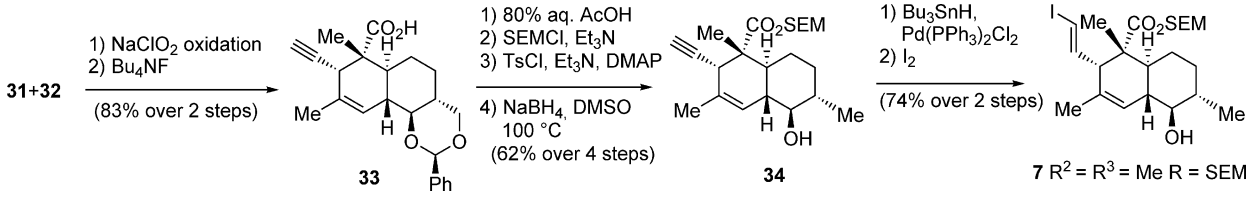
plained by use of the two transition-state (TS) models shown in Scheme 3. In each TS the diene approached the *Si*-face of the α-carbon atom in the α,β-unsaturated aldehyde moiety because the *trans*-fused benzylidene acetal locked both TSs into *trans*-decaline-like chair conformations, as depicted for the *endo* and *exo* TSs. Furthermore, a severe non-bonded interaction apparently existed between the methyl substituent in the diene part and the dienophile methyl terminal in the *exo* TS, making the *exo* TS significantly unfavorable. As a result, the IMDA reaction preferentially proceeded through the *endo* TS, leading to the desired adduct **31**. It should be emphasized that the benzylidene acetal plays a critical role in this stereoselective IMDA reaction by fixing the conformations of the *endo* and *exo* transition states.

The conversion of the 8:1 mixture of **31**/**32** into the lower-half segment **7** is summarized in Scheme 4. $NaClO_2$ oxidation[23] of the IMDA adducts, followed by protodesilylation of the TMS group in the acetylene moiety, provided the carboxylic acid **33**. At this stage, the compound derived from the minor *exo* adduct **32** (not shown) was cleanly removed from the major product **33** derived from **31**. Acid hydrolysis of the benzylidene acetal in **33**, esterification with [2-(triethylsilyl)ethoxy]methyl chloride (SEMCl), and selective tosylation of the diol, followed by deoxygenation of the resulting primary tosylate by $NaBH_4$ reduction in hot DMSO, eventually provided **34**. The acetylene moiety in **34** was converted into the (*E*)-vinyl iodide by regio- and stereoselective hydrostannylation and successive metal/iodine exchange. The lower-half segment **7** was thus obtained efficiently from **15** after a 24-step reaction sequence.

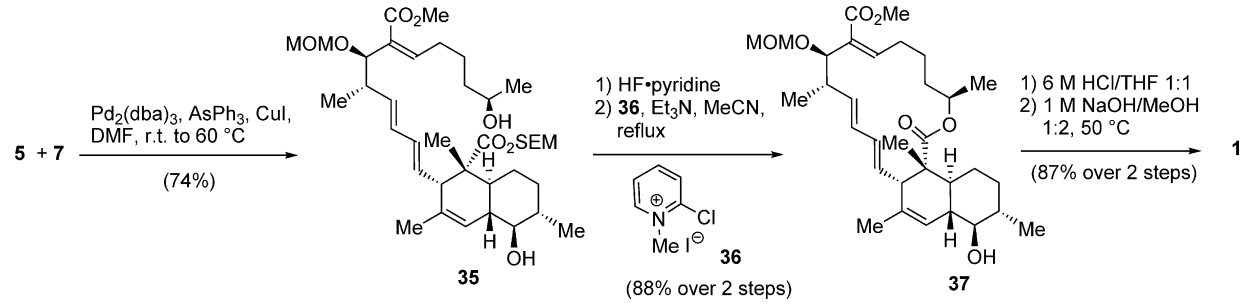
With the upper-half segment **5** and the lower-half segment **7** to hand, their assembly was explored in order to achieve the total synthesis of **1**, which was performed as depicted in Scheme 5. Stille coupling of **5** and **7** under Liebeskind-modified Pd-catalyzed conditions[24] provided the (*E*,*E*)-conjugate diene **35** uneventfully and in a good yield of 74%. The use of $AsPh_3$ and CuI was essential for the effectiveness of this Stille coupling. HF-mediated removal of the SEM group in ester **35** and subsequent lactonization of the resulting *seco*-acid with Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide, **36**[25]) in acetonitrile at reflux in the presence of Et_3N proceeded smoothly to provide the 16-membered macrolide **37** in a high yield of 88% from **35**. Finally, removal of the protecting groups in **37** by acidic hydrolysis, followed by alkaline hydrolysis, provided (+)-tubelactomicin A (**1**), which was identical in all aspects to the natural specimen, including its dextrorotatory properties.

The total synthesis of (+)-tubelactomicin B (**2**) is summarized in Scheme 6. The already described aldehyde **17** was elongated through a Wittig reaction with $Ph_3P{=}C(Me)$-CO_2Et. The resulting (*E*)-unsaturated ester was converted into **38** by a reduction/oxidation process. The unsaturated aldehyde **38** was subjected to Evans' *syn*-aldol strategy under the same reaction conditions as had been applied to the conversion of **10** into **21**. Further functional-group manipulations from the *syn*-aldol product **39** through the same reaction sequence as used for the synthesis of **23** from **21** provided bromoalkyne **41** via **40**. In this series, treatment of the Corey–Fuchs dibromoolefin-type intermediate with NaHMDS provided **41**. De-*O*-silylation of **41**, followed by stereoselective hydrostannylation, provided the upper-half segment **6** of compound **2**.

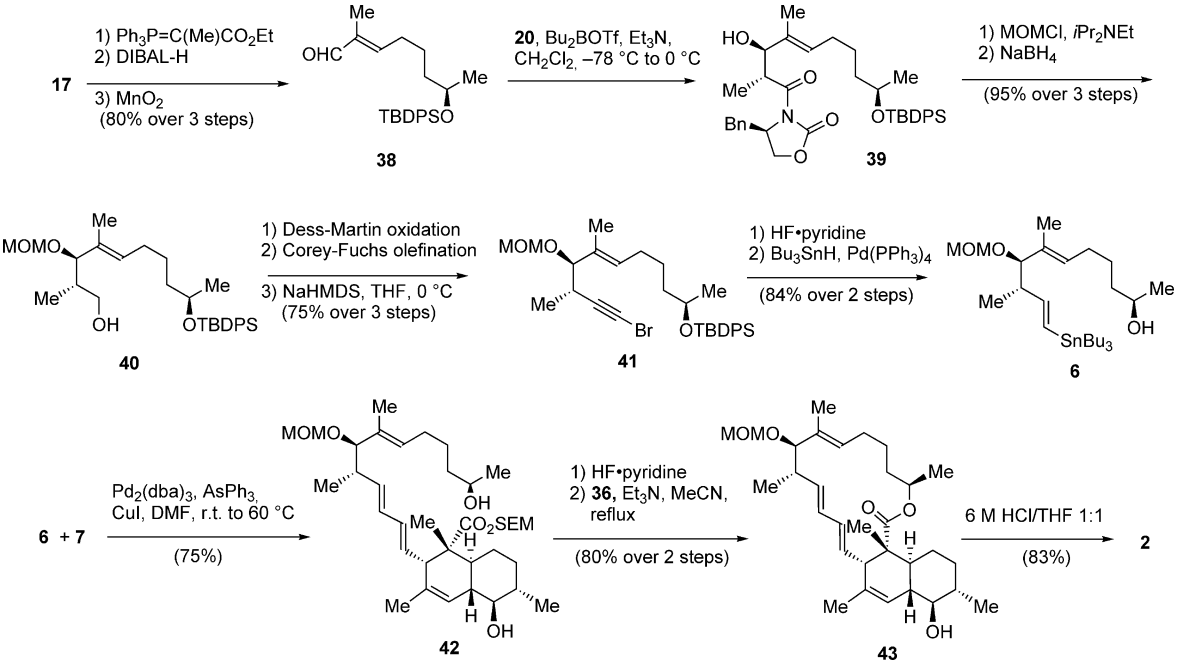
Stille coupling of **6** with the already described lower-half segment **7**, under the same conditions as had been used for the coupling of **5** and **7**, provided **42** in a practical yield of 75%. Removal of the SEM group and Mukaiyama lactonization of the resulting *seco*-acid provided the protected form **43** of **2**. The acidic removal of the MOM group in **43**



Scheme 4. Synthesis of the lower-half segment **7** from the mixture of the IMDA adducts **31** and **32**.



Scheme 5. Completion of the total synthesis of **1**.



Scheme 6. Total synthesis of (+)-tubelactomicin B (**2**).

eventually provided (+)-tubelactomicin B (**2**). The synthetic **2** was identical to the natural product in all aspects, thereby establishing the previously undetermined relative and absolute stereochemistries of **2**.

The total synthesis of (+)-tubelactomicin D (**3**) is summarized in Scheme 7. The synthesis of the lower-half segment of **3** required a more oxygenated substrate, such as **50**, for the attempted IMDA reaction. We thus synthesized the ynene phosphonate **47** for Horner–Wadsworth–Emmons olefination with the aldehyde derived from **27** in place of the phosphonate **28**. The known α-hydroxymethylated acrylic acid ester **44**,[26] the Morita–Baylis–Hillman product of methyl acrylate and *p*-formaldehyde, was converted into **47** by (1) MOM protection, (2) bromine addition followed by HBr elimination [to give the (*E*)-bromoalkene **45**], (3) Sonogashira coupling with (trimethylsilyl)acetylene[22] (to give the enyne **46**), (4) DIBAL reduction, (5) allylic bromination, and (6) Arbuzov rearrangement with $(EtO)_3P$. A Horner–Wadsworth–Emmons reaction between the aldehyde derived from **27** and **47** provided **48**. The desired IMDA substrate **50** (= **13**: $R^2 = CH_2OMOM$) was synthesized efficiently by an additional five-step manipulation from **48** via **49**. The IMDA reaction of **50** was completed at 80 °C. After $NaClO_2$ oxidation of the aldehyde functionalities in the resulting diastereomeric mixture of the IMDA adducts, the desired *endo* adduct **51** was isolated in 76% yield, accompanied by the *exo* adduct **52** (18%). The *endo*/*exo* selectivity of the IMDA reaction with the substrate **50** was thus approximately 4:1.

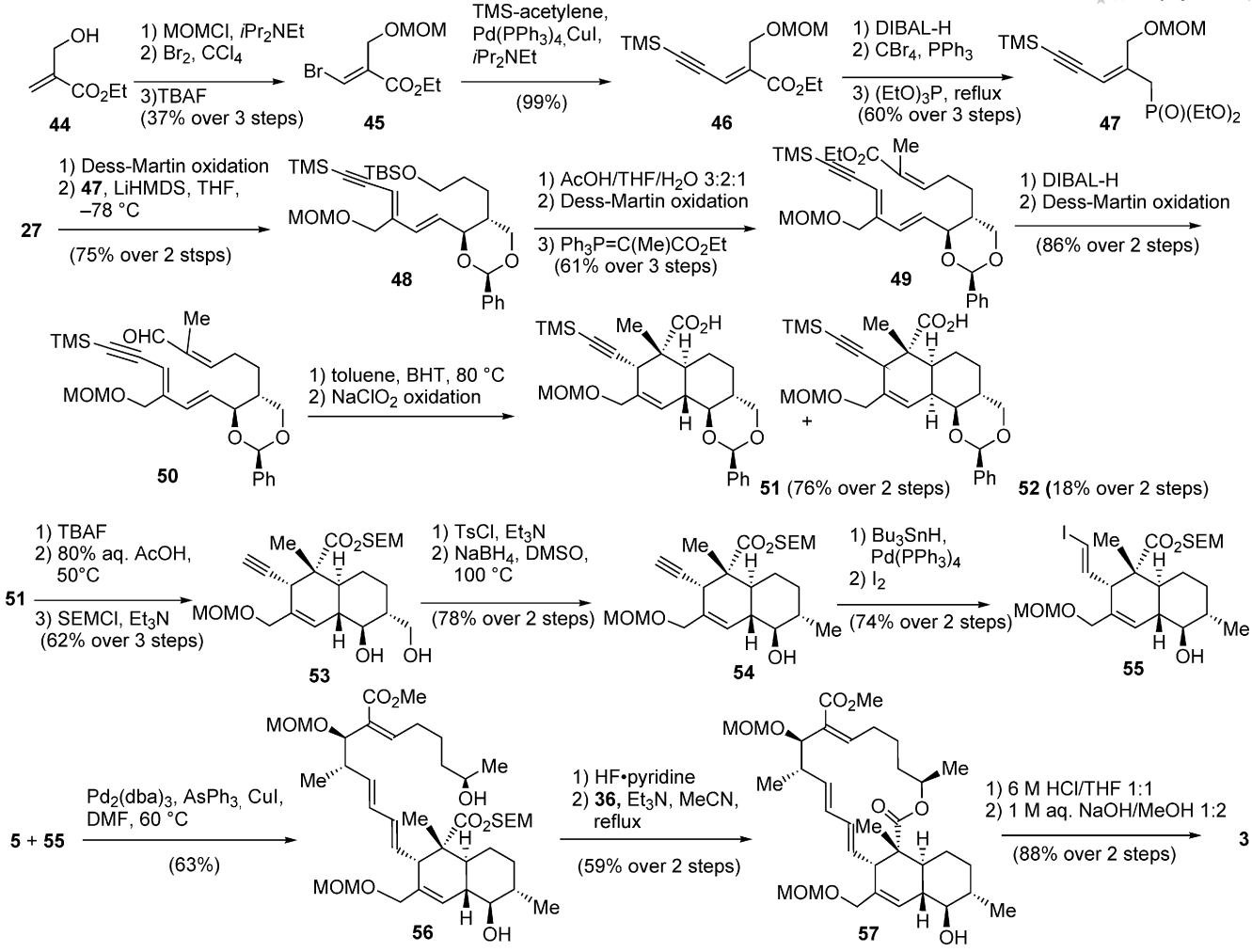
The *endo* adduct **51** was converted into **55**, the lower-half segment of **3** (= **8**: $R^2 = CH_2OMOM$, R^3 = Me, R = SEM), by a reaction sequence analogous to that used for the conversion of **33** into **7**, via **53** and **54**. Stille coupling of the upper-half segment **5** with the thus-obtained **55** (to give **56**) and Mukaiyama lactonization (to give **57**) proceeded uneventfully as in the cases of **35** and **42**. Total deprotection of **57** finally provided (+)-tubelactomicin D (**3**), thereby establishing the relative and absolute stereochemistry of the natural product.

The total synthesis of (+)-tubelactomicin E (**4**) is summarized in Scheme 8. The (*E*)-iodoalkene **58** (= **9**: R^2 = Me, R^3 = isopropylidene, R = SEM) was synthesized from the carboxylic acid **33** described above by a reaction sequence analogous to that used in the case of the total synthesis of **1**. Stille coupling of **5** with the thus-obtained **58** provided **59**. The Mukaiyama lactonization strategy used for the total syntheses of **1**–**3** was also quite effective for the *seco*-acid derived from **59**. Final deprotection of all the protecting groups provided (+)-tubelactomycin E (**4**) uneventfully.

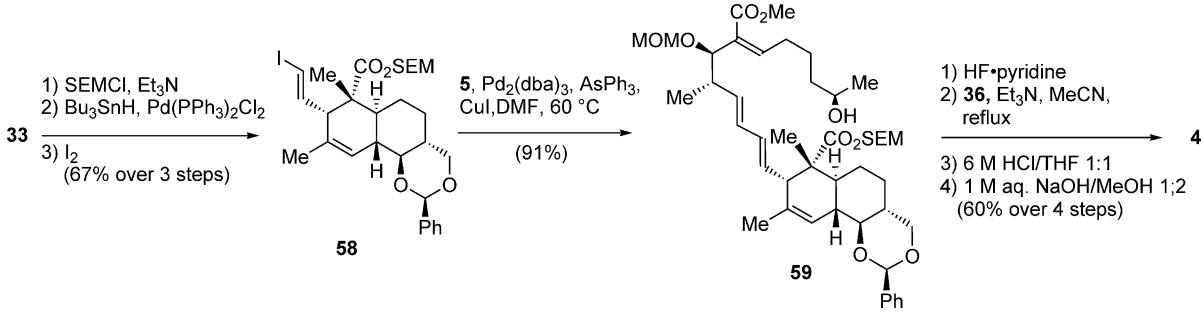
We have also accomplished the formal synthesis of (+)-tubelactomicins A (**1**) and E (**4**) by a transannular Diels–Alder approach, summarized in Scheme 9. For this purpose, the synthesis of the TMS-protected (*E*,*E*)-pentadienyl phosphonate **63** was first executed. The commercially available *C*-TMS-protected propargylic alcohol **60** was converted into the dienyl ester **61** by $LiAlH_4$-mediated reduction,[27] MnO_2 oxidation,[28] and Wittig olefination. Compound **63** was then synthesized via the pentadienyl bromide **62**, including an Arbuzov rearrangement.

Separately, the alcohol **27** described above was oxidized and the resulting aldehyde was then subjected to a Horner–Wadsworth–Emmons reaction with **63**, providing the (*E*,*E*,*E*)-triene **64**. A further two-step reaction from **64** provided the aldehyde **65**.

Independently, the upper-half segment **5** was first treated with iodine for metal/halogen exchange to provide an iodoalkene, which was acylated with the α-phosphonylated propionyl acid **66** under the standard coupling conditions



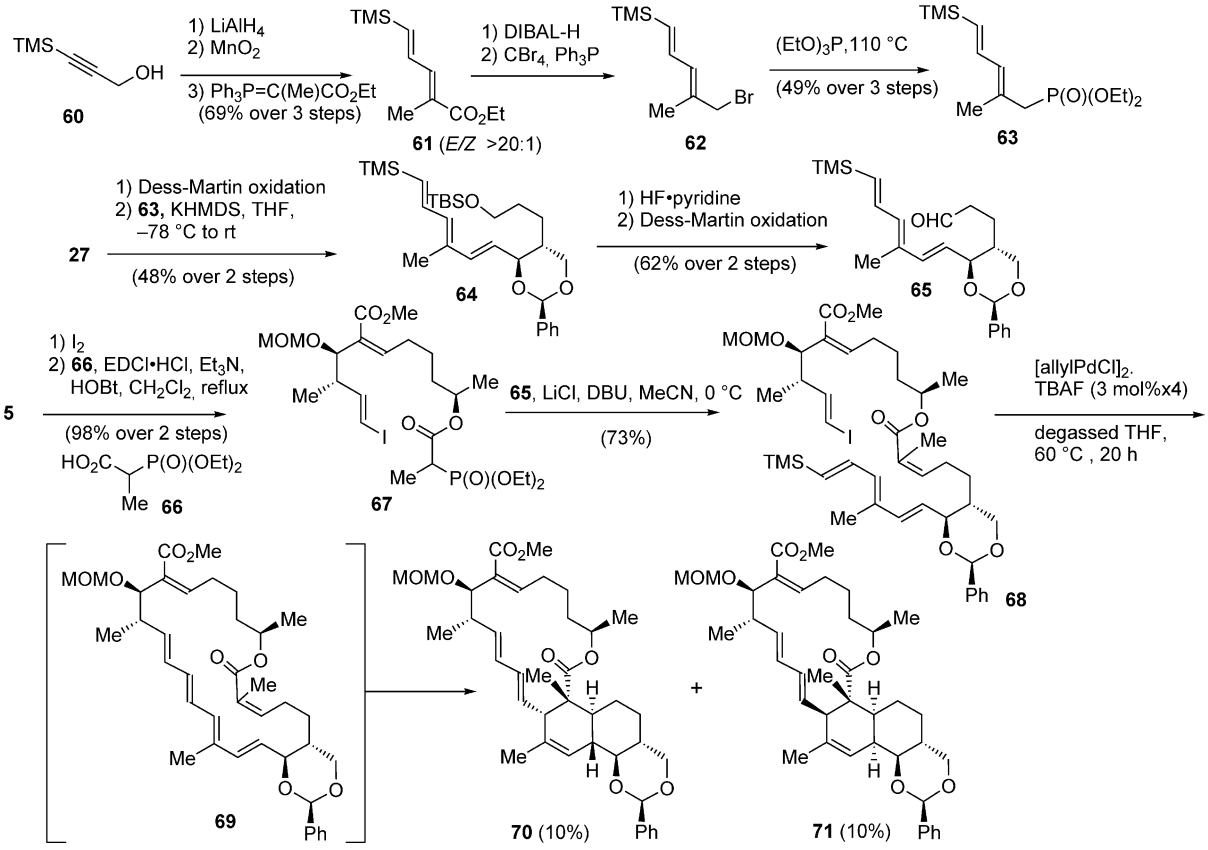
Scheme 7. Total synthesis of (+)-tubelactomicin D (**3**).



Scheme 8. Total synthesis of (+)-tubelactomicin E (**4**).

to provide **67**. A modified Horner–Wadsworth–Emmons olefination[13] of aldehyde **65** and phosphonate **67** efficiently (73%) provided **68**. The intramolecular Hiyama cross-coupling[29] of **68** proceeded smoothly under the standard conditions as shown in Scheme 9, providing two IMDA adducts, **70** and **71**, in almost equal amounts, although in a less satisfactory combined yield of 20%. Interestingly, the intermediately formed 24-membered macrocyclic compound **69** was not isolated; the formation of **69** spontaneously triggered the transannular Diels–Alder reaction. Unfortunately, the *endo*/*exo* selectivity of the transannular Diels–Alder process was significantly diminished in relation to those obtained in the cases of the substrates **12** and **50**. The *endo* adduct **70** was further elaborated to the key intermediates for **1** and **4**.

We also explored the formation of the 24-membered macrocyclic substrate **69** for the transannular Diels–Alder reaction through a ring-closing metathesis approach, which again provided a 1:1 mixture of **70**/**71** in a less practical combined yield of 13%.[10]



Scheme 9. Synthesis and intramolecular Hiyama cross-coupling of substrate **68**, followed by the transannular Diels–Alder reaction.

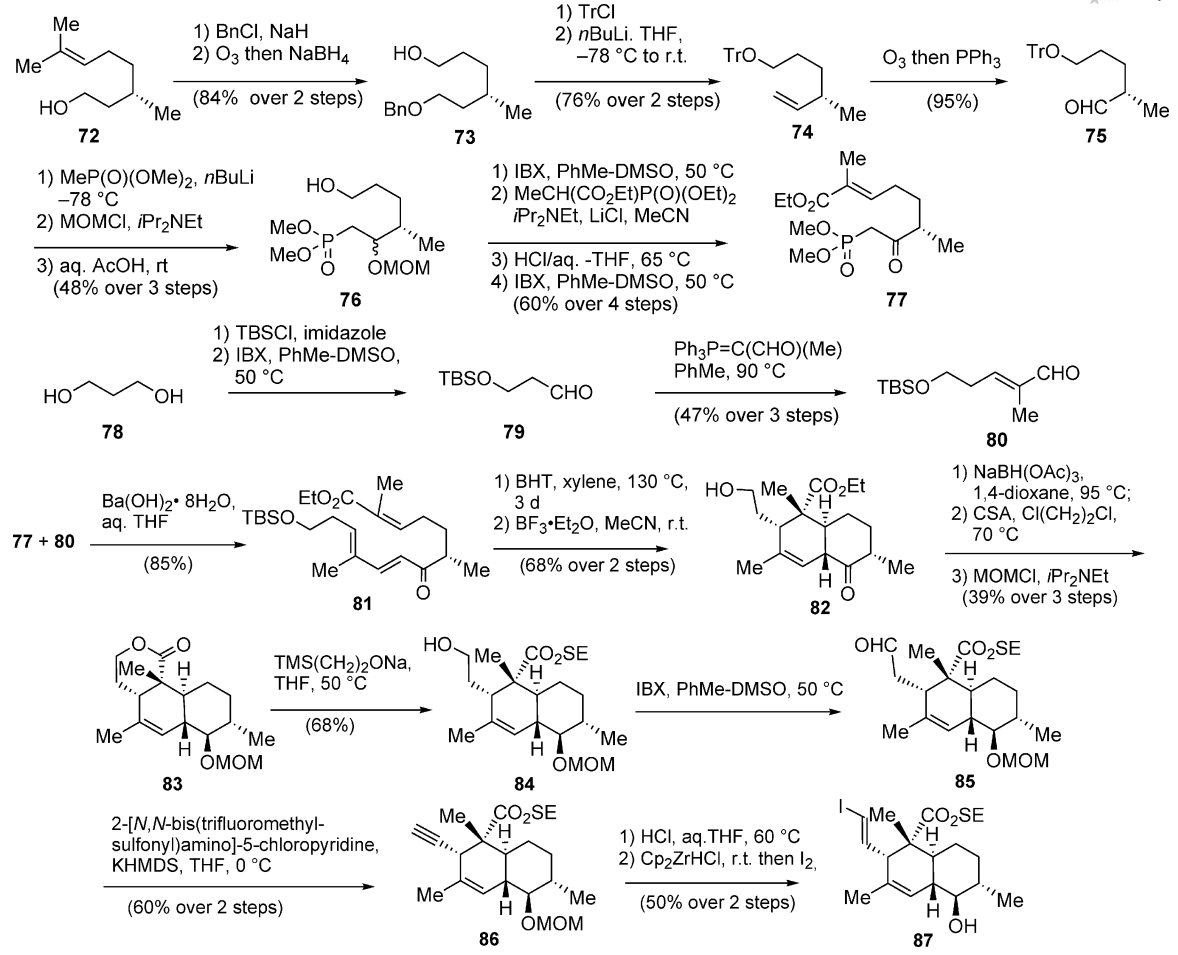
2.2 Total Synthesis of (+)-Tubelactomicin A by the Tatsuta Group

In 2006, Tatsuta et al. reported their total synthesis of (+)-tubelactomicin A (**1**).[8] Their total synthesis was also based on an IMDA approach to provide the lower-half octahydronaphthalene moiety in **1**. Their synthesis of the octahydronaphthalene moiety **87**, incorporating an (*E*)-alkenyl iodide side chain, started with (*S*)-citronellol (**72**). As shown in Scheme 10, compound **72** was converted into the chiral mono-*O*-protected diol **73** by a series of standard functional-group transformations. The enantiomeric α-methylpentanal derivative **75** was obtained via the hex-1-ene derivative **74** through three well-established transformations from **73**.[30] A nucleophilic attack of the anion generated from dimethyl methylphosphonate on **75** provided the β-hydroxyphosphonate, which was protected as the MOM ether. De-*O*-tritylation of this MOM ether provided **76**. Iodoxybenzoic acid mediated (IBX-mediated) oxidation of **76**, Horner–Wadsworth–Emmons olefination of the resulting aldehyde, de-*O*-methoxymethylation of the resulting α,β-unsaturated ester, and oxidation of the secondary hydroxy group provided the β-oxo phosphonate **77**.

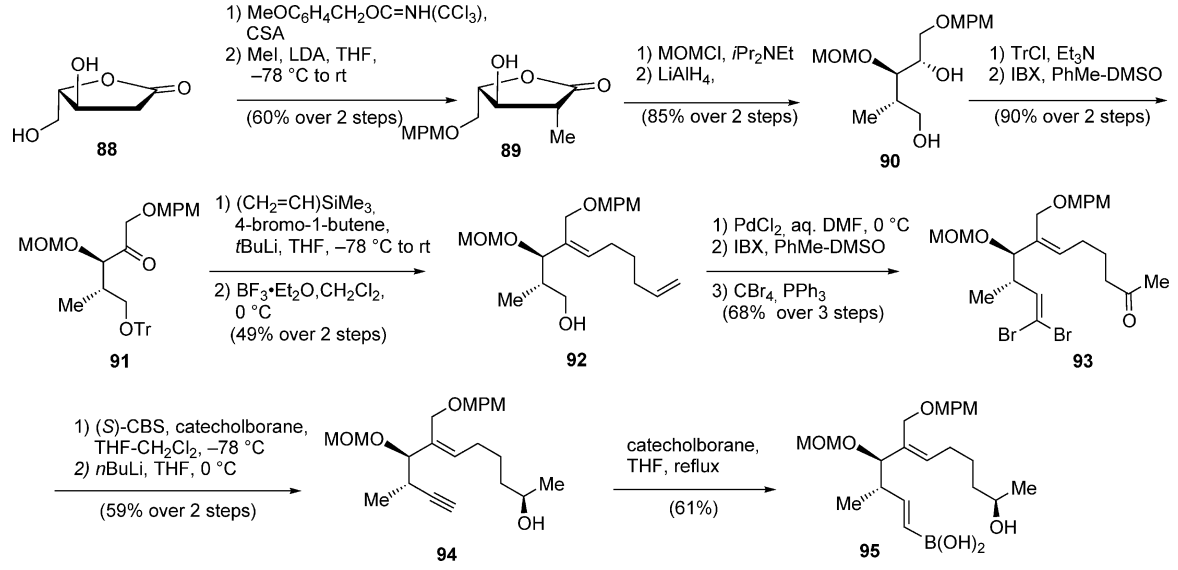
Independently, propane-1,3-diol (**78**) was converted into the α-methylated α,β-unsaturated aldehyde **80** via the β-silyloxypropanal **79**. $Ba(OH)_2$-promoted coupling[31] of **77** and **80** then efficiently produced the (*E*,*E*)-diene **81**, the substrate of the attempted IMDA reaction.

The IMDA reaction of **81** (130 °C for 3 d) proceeded stereoselectively to provide the desired *endo* adduct **82** as the sole product in 68% yield, after removal of the TBS group through the action of $BF_3{\cdot}Et_2O$. Highly stereoselective reduction of the oxo carbonyl group in **82**, acid-promoted δ-lactone formation, and protection of the secondary hydroxy group provided **83**. Ring-opening of the lactone moiety in **83** was accomplished by treatment of **83** with sodium (trimethylsilyl)ethoxide, providing the ester **84**. IBX-mediated oxidation of **84** provided the aldehyde **85**, which was treated with Comins' reagent[32] in the presence of KHMDS to introduce an acetylene unit, providing **86**. Removal of the MOM group in **86**, regio- and stereoselective hydrozirconation,[33] followed by metal/halogen exchange, eventually provided the lower-half segment of **1** (the vinyl iodide **87**) as the partner for the Suzuki–Miyaura coupling.

The synthesis of the upper-half segment **95**, a vinylboronic acid as the Suzuki–Miyaura coupling partner for the lower-half segment **87**, is summarized in Scheme 11. The synthesis of **95** commenced with 2-deoxy-L-ribonolactone (**88**). Selective protection of the primary hydroxy group in **88** and subsequent *C*-methylation of the resulting MPM ether by Tatsuta's previously reported procedure[34] stereoselectively provided the α-methylated γ-lactone **89**. Protection of the remaining hydroxy group in **89** and hydride-mediated γ-lactone opening produced **90**. Selective tritylation of **90**, followed by oxidation with IBX, produced ketone **91**.

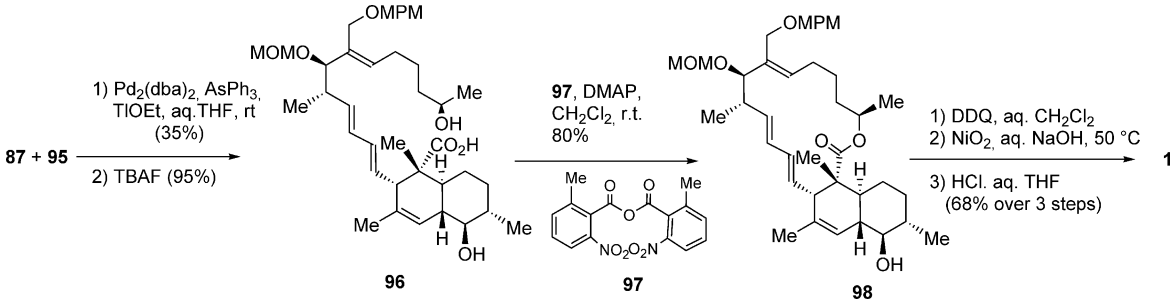


Scheme 10. Synthesis of the lower-half octahydronaphthalene derivative **87** by Tatsuta's group.



Scheme 11. Synthesis of the upper-half vinylboronic acid **95** by Tatsuta's group.

Installation of the trisubstituted olefin part in the upper-half segment was accomplished as follows. Treatment of ketone **91** with trimethyl(vinyl)silane and 4-bromobut-1-ene in the presence of *t*BuLi introduced a 1-(trimethylsilyl)hex-5-ene group into **91** through the addition of an α-silyl-stabilized carbanion onto the oxo carbonyl group in 65% yield. The resulting adduct was treated with BF_3·Et_2O to eliminate a trimethylsilanol, providing the (*E*)-trisubstituted olefin



Scheme 12. Completion of the total synthesis of **1** by Tatsuta's group.

92 with high geometrical selectivity.[35] A Wacker oxidation of the terminal double bond in **92**, IBX oxidation of the primary hydroxy group, and a Corey–Fuchs dibromoolefination of the resulting aldehyde provided **93**. Diastereoselective (*S*)-CBS-mediated catecholborane attack[36] at the methyl ketone in **93**, treatment of the α,α-dibromoolefin moiety in the resulting carbinol with *n*BuLi, and subsequent hydroboration of the resulting acetylene **94** in THF at reflux, followed by hydrolysis on silica gel, eventually provided the (*E*)-alkenylboronic acid **95**.

As shown in Scheme 12, Suzuki–Miyaura cross-coupling[37] of the lower-half segment **87** and the upper-half segment **95** in the presence of $Pd_2(dba)_3$, $AsPh_3$, and TlOEt, followed by removal of the SE group, provided the *seco*-acid **96** in a yield of 33% over two steps. The lactonization of **96** by use of Shiina's reagent **97**[38] efficiently produced the 16-membered macrolide **98**. Removal of the MPM group in **98** with DDQ, NiO_2-mediated oxidation of the resulting allylic alcohol to the carboxylic acid,[39] and acid hydrolysis of the MOM ether finally provided (+)-tubelactomycin A (**1**).

3. Total Synthesis of Spiculoic Acid A

(+)-Spiculoic acid A (**99**, Figure 2) is a secondary metabolite of polyketide origin, isolated in 2004 from methanol extracts of the Caribbean marine sponge *Plakortis angulospiculatus* (Carter) by Andersen et al.[40] This marine natural product showed in vitro cytotoxicity against human breast cancer MCF-7 cells. The relative stereochemistry of **99** was determined by Andersen's group on the basis of extensive NMR analysis. At the same time, Andersen's group isolated and characterized a closely related spiculane-type compound: spiculoic acid B (**100**), which showed no in vitro cytotoxicity against human breast cancer MCF-7 cells.[40] Later, a number of structurally related spiculane-type natural products were isolated from another marine sponge, *Plakortis zyggompha*, and their interesting biological activities have been reported.[41,42] Andersen et al. have proposed that **99** might be produced biosynthetically through an enzyme-catalyzed IMDA reaction of a linear triene containing all the functionalities in **99**, including a conjugated diene (4π) and a terminal unsaturated ester (2π). Synthetic studies of **99** have been explored by several groups.[43–45] In 2006, Baldwin and Lee's group reported the total synthesis of unnatural (–)-spiculoic acid A, thereby establishing the absolute stereochemistry of **99** as depicted.[43a] Their total synthesis of (–)-spiculoic acid A was achieved through the IMDA reaction of a linear conjugate diene with a terminal unsaturated ester functionality for the stereoselective construction of the bicyclic core structure. Independently, we have accomplished the total synthesis of natural (+)-enantiomer **99**.[46] These total syntheses of (–)- and (+)-spiculoic acid A are summarized in this Microreview.

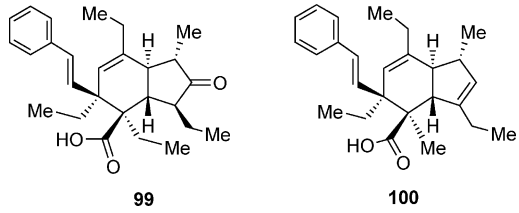
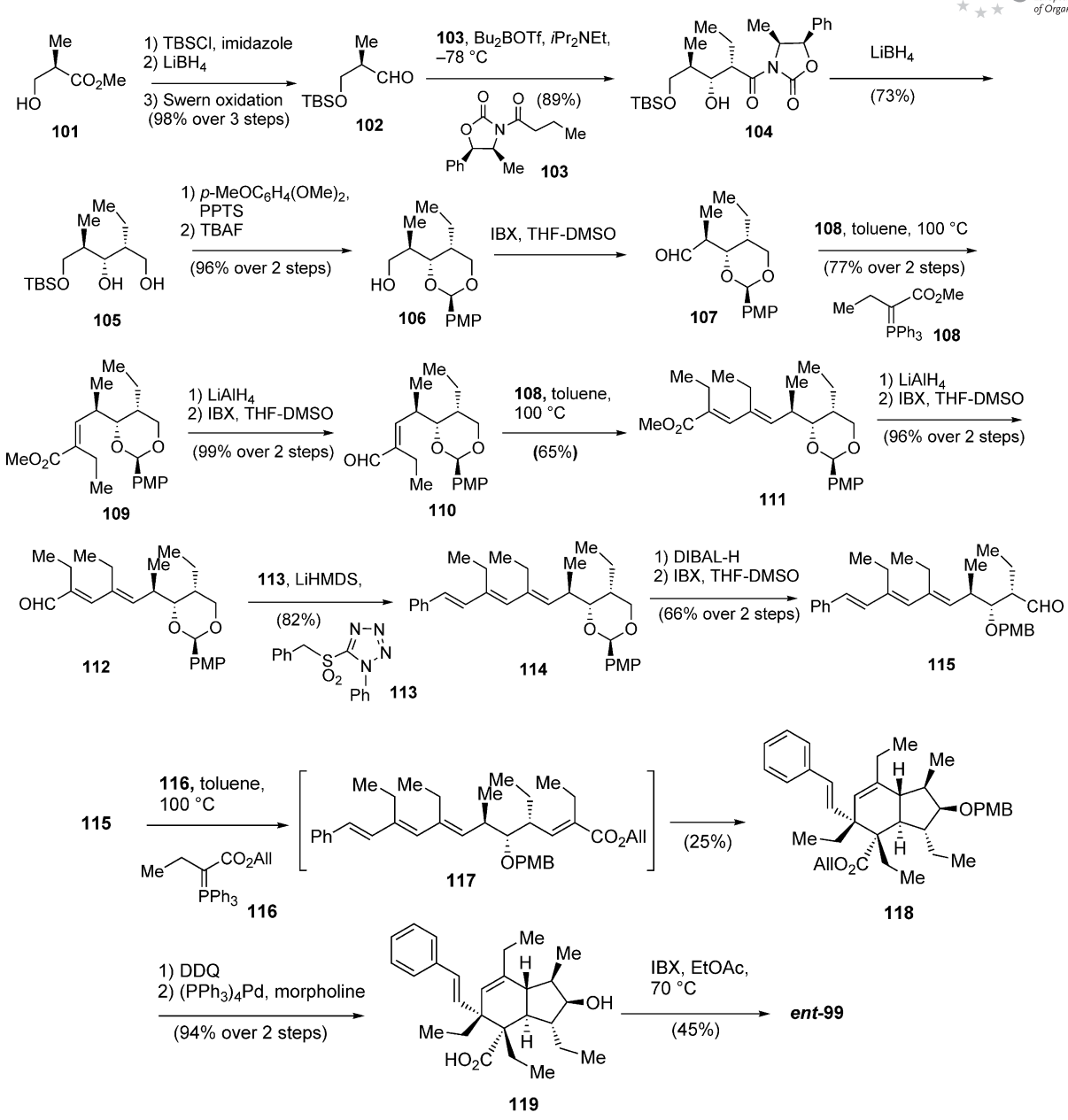


Figure 2. Structures of (+)-spiculoic acid A (**99**) and spiculoic acid B (**100**).

3.1 Total Synthesis of (–)-Spiculoic Acid A by the Baldwin/Lee Group

For their total synthesis of the (–) enantiomer of spiculoic acid A, the Baldwin/Lee group started with Roche ester **101**, as summarized in Scheme 13. Protection of the primary alcohol in **101** and hydride reduction of the ester followed by Swern oxidation provided aldehyde **102**. An Evans aldol reaction[47] between **102** and the chiral *N*-butyroyloxazolidinone **103**[48] stereoselectively provided the *syn* adduct in an excellent yield of 89%. $LiBH_4$-mediated removal[49] of the auxiliary from **104** provided the diol **105**. Protection of the diol **105** as a *p*-methoxybenzylidene (MPM) acetal and subsequent de-*O*-silylation provided **106**. IBX oxidation of **106** and Wittig olefination of the resulting aldehyde **107** with the stabilized ylide **108** provided the α-ethylated acrylic acid ester **109** with high (*E*) selectivity. Reduction/oxidation of the ester part in **109** provided the unsaturated aldehyde **110**. A second Wittig olefination, between **110** and **108**, provided the (*E*,*E*) doubly conjugated ester **111**. Further reduction/oxidation of **111** provided the α,β:γ,δ-unsaturated aldehyde **112**, which was subjected to Julia–Kocienski olefination[50] with the benzyl sulfone **113**[51] in the presence of lithium hexamethyldisilazide (LiHMDS) as a base, providing an (*E*,*E*,*E*)-triene **114** bearing a styryl moiety. Regiose-



Scheme 13. Total synthesis of unnatural (–)-spiculoic acid A by the Baldwin/Lee group.

lective reductive ring-opening of the *p*-methoxybenzylidene acetal in **114**, followed by IBX oxidation of the resulting primary alcohol, provided the aldehyde **115**, which was subjected to a final Wittig olefination with another stabilized allyl ester type ylide **116**. Interestingly, the Wittig product **117**, the IMDA substrate for constructing the bicyclic structure in spiculioc acid A, spontaneously underwent the IMDA reaction under the Wittig reaction conditions, providing the *endo* adduct **118** in a yield of 25% from **115**. Although both *endo* and π-facial stereoselectivities were complete, the Wittig reaction conditions were accompanied by the β-elimination of the (*p*-methoxybenzyl)oxy group in **115**, resulting in reduced formation of the desired **117**. Removal of the *p*-methoxybenzyl group in **118** with DDQ, followed by Pd^0-mediated removal of the allyl group in the presence of morpholine,[52] provided **119**. Lastly, IBX oxidation of **119** provided (–)-spiculoic acid A in 45% yield, thereby establishing the previously undetermined absolute stereochemistry of natural (+)-spiculoic acid A.

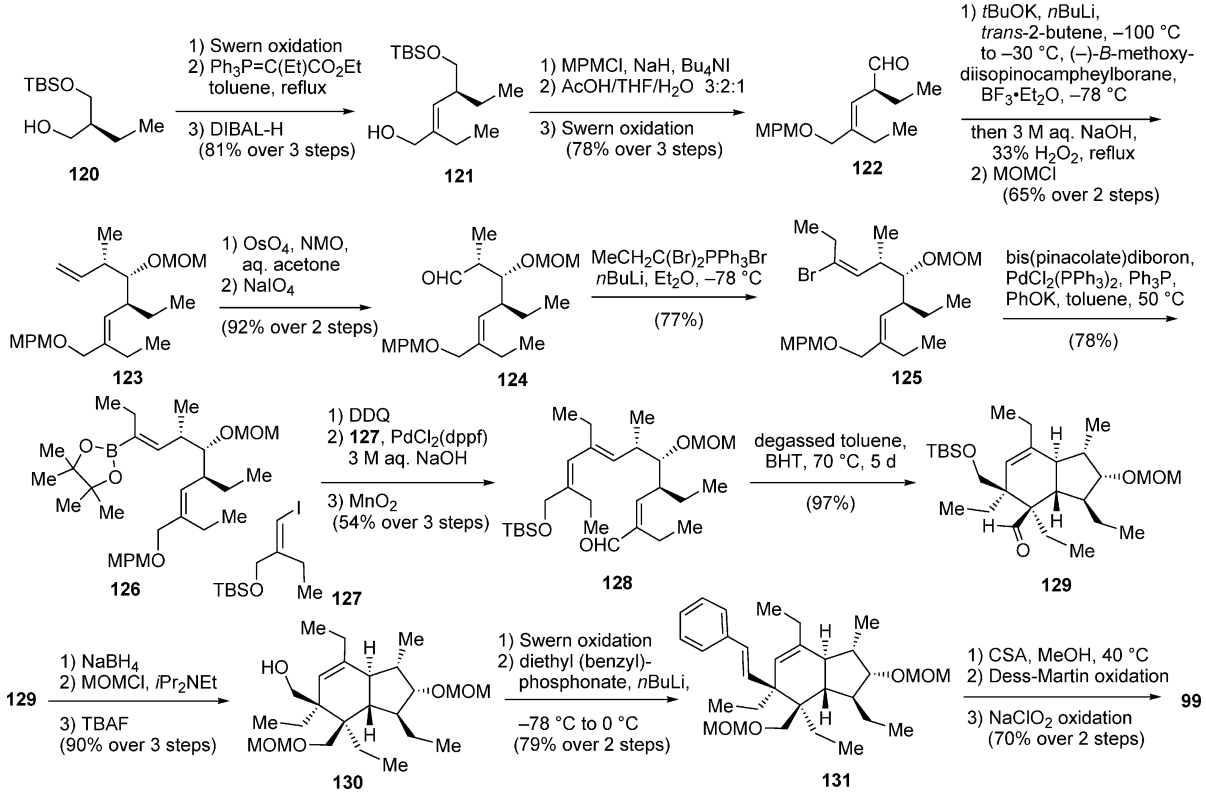
3.2 Total Synthesis of (+)-Spiculoic acid A by the Tadano Group.

We started our total synthesis of natural (+)-spiculoic acid A (**99**) with the known chiral building block **120**. This starting material **120** was synthesized according to Fukumoto's approach,[53] based on Evans' asymmetric alkylation.

As summarized in Scheme 14, the mono-*O*-protected diol **120** was converted into a trisubstituted allylic alcohol **121** by a standard three-step functional group transformation. Protection of **121** with MPM chloride and removal of the TBS group by acid hydrolysis, followed by Swern oxidation, provided the aldehyde **122**. The stereoselective introduction of an *anti*-β-methylhomoallylic alcohol moiety was achieved by the well-known Brown crotylboration protocol[54] with (–)-*B*-methoxydiisopinocampheylborane and the potassium salt of *trans*-but-2-ene. As a result, the desired *anti* adduct **123** was obtained after MOM protection of the resulting homoallylic alcohol in a practical yield of 65% from **122**. The diastereomeric ratio of two *anti* products in this crotylboration was approximately 3:1 in favor of the formation of **123**. A two-step oxidative carbon–carbon bond cleavage of **123** provided the aldehyde **124**, which was subjected to Wittig olefination with (1,1-dibromopropyl)triphenylphosphonium bromide[55] in the presence of a base (*n*BuLi). As a result, the (*E*)-trisubstituted alkene **125** was obtained stereoselectively [(*E*)/(*Z*) > 20:1]. Treatment of the vinyl bromide **125** with bis(pinacolato)diboron[56] in the presence of $PdCl_2(PPh_3)_2$, PPh_3, and PhOK in toluene provided the vinylboronate **126** in a good yield of 78%. After removal of the MPM group in **126**, the resulting allylic alcohol was subjected to Suzuki–Miyaura cross-coupling with the (*E*)-vinyl iodide **127**, synthesized from diethyl ethylmalonate by the reported procedures,[22a] under standard Pd^0-catalyzed conditions. The coupling product was then oxidized with MnO_2 to provide the unsaturated aldehyde **128**, the substrate for the IMDA reaction for construction of the bicyclic skeleton in **99**.

The IMDA reaction of **128** proceeded slowly but cleanly at 70 °C. After 5 d at 70 °C, the desired *endo* adduct **129** was obtained, with complete π-facial and *endo*/*exo* selectivity, in an excellent yield of 97%. No other adduct was found in the reaction mixture. This achievement of exclusive π-facial and *endo* selectivities can reasonably be explained in terms of the presence or absence of allylic strain ($A^{1,3}$ strain) occurring in the *endo* or *exo* transition states. Consequently, we had achieved remarkably efficient access to the bicyclic core structure of (+)-spiculoic acid A.

The remaining step toward the targeted natural product was the incorporation of the styryl side chain into the IMDA adduct **129**. $NaBH_4$-mediated reduction of **129**, MOM protection of the resulting primary hydroxy group, and subsequent de-*O*-silylation provided **130**. Swern oxidation and successive Horner–Wadsworth–Emmons olefination of the resulting aldehyde with the anion generated from diethyl benzylphosphonate provided the desired styryl derivative **131** in a good yield of 79%. Removal of both MOM groups in **131** and Dess–Martin oxidation of the resulting diol provided the oxo-aldehyde intermediate, which was further oxidized by Kraus–Pinnick oxidation[23] to provide (+)-spiculoic acid A (**99**), which by spectral comparison was identical to the natural product in all aspects.



Scheme 14. Total synthesis of natural (+)-spiculoic acid A (**99**) by the Tadano group.

4. Summary and Outlook

This Microreview summarizes the total synthesis of some natural products completed recently by the author's group through the design of efficient intramolecular Diels–Alder (IMDA) approaches as a key means of access to the construction of central carbon skeletons of the targeted molecules. These natural products are the tricyclic 16-membered macrolides (+)-tubelactomicins A, B, D, and E, and also the novel polyketide-derived marine natural product (+)-spiculoic acid A. Our total syntheses of these natural products are compared with the achievements of the Tatsuta group [for the synthesis of (+)-tubeactomicin A] and of the Baldwin/Lee group [for the synthesis of (–)-spiculoic acid A], respectively. All of the total syntheses cited in this Microreview are apparently notable examples of current total syntheses of structurally complex natural products that demonstrate the synthetic potency of the IMDA approach.

In the progress of modern organic synthesis, exemplified by the field of natural products synthesis, the power of Diels–Alder reactions for feasible access to mono- or polycyclic carbon frameworks is significant. As evidenced by a large number of reports, the incorporation of Diels–Alder reactions into a planned synthetic scheme makes synthetic manipulation facile and concise. In general, an intramolecular variant of this [4+2] cycloaddition approach is not necessarily as easy to carry out as an intermolecular Diels–Alder reaction, and also is not necessarily predictable enough for control over the stereoselectivities of cycloaddition such as regioselectivity, *endo*/*exo* selectivity, and/or π-facial selectivity. Nevertheless, a large number of products achieved through natural product synthesis have been the result of well-designed IMDA reaction approaches for the stereoselective construction of the formidable core skeletons found in a variety of natural products. Such impressive and sophisticated natural products synthesis will continue to attract the interest of synthetic organic chemists. The author believes confidently that a variety of IMDA approaches toward natural products synthesis will further show their inestimable value in the future.

Acknowledgments

The author wishes to thank his collaborators, whose names appear in the references cited and whose contributions made possible all the total syntheses described here. The total syntheses of (+)-tubelactomicins and (+)-spiculoic acid A accomplished in the author's group were supported by a Grant-in-Aid for Scientific Research on Priority Area (A) "Creation of Biologically Functional Molecules (18032069)" and in part by a Grant-in-Aid for the 21st Century COE program "Keio LCC" from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. The author thanks Dr. Masayuki Igarashi (Institute of Microbial Chemistry) for supplying the samples and spectral copies of natural tubelactomicins.

[1] Representative reviews published during this decade: a) P. Buonora, J.-C. Olsen, T. Oh, *Tetrahedron* **2001**, *57*, 6099–6138; b) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698; c) E. M. Stocking, R. M. Williams, *Angew. Chem. Int. Ed.* **2003**, *42*, 3078–3115; d) H. Oikawa, T. Tokiwano, *Nat. Prod. Rep.* **2004**, *21*, 321–352.

[2] Representative reviews published during this decade: a) A. G. Fallis, *Acc. Chem. Res.* **1999**, *32*, 464–474; b) B. R. Bear, S. M. Sparks, K. J. Shea, *Angew. Chem. Int. Ed.* **2001**, *40*, 820–849; c) E. Marsault, A. Toró, P. Nowak, P. Deslongchamps, *Tetrahedron* **2001**, *57*, 4243–4260; d) Y. Suzuki, T. Murata, K. Takao, K. Tadano, *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 679–690; e) A. Padwa, *Pure Appl. Chem.* **2004**, *76*, 1933–1952; f) L. F. Tietze, N. Rackelmann, *Pure Appl. Chem.* **2004**, *76*, 1967–1983; g) G. R. Heintzelman, I. R. Meigh, Y. R. Mahajan, S. M. Weinreb, *Org. React.* **2005**, *65*, 141–599; h) F. I. Zubkov, E. V. Nikitina, A. V. Variamov, *Russ. Chem. Rev.* **2005**, *74*, 639–669; i) K. Takao, R. Munakata, K. Tadano, *Chem. Rev.* **2005**, *105*, 4779–4807; j) W. L. Kelly, *Org. Biomol. Chem.* **2008**, *6*, 4483–4496.

[3] For the total synthesis of (–)-PI-201, see: a) K. Tadano, T. Murata, T. Kumagai, S. Ogawa, *Tetrahedron Lett.* **1993**, *34*, 7279–7282; b) T. Murata, T. Kumagai, M. Ishikawa, K. Tadano, S. Ogawa, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 3551–3561. For the total synthesis of (–)-mniopetals, see: c) T. Murata, M. Ishikawa, R. Nishimaki, K. Tadano, *Synlett* **1997**, 1291–1293; d) Y. Suzuki, R. Nishimaki, M. Ishikawa, T. Murata, K. Takao, K. Tadano, *Tetrahedron Lett.* **1999**, *40*, 7835–7838; e) Y. Suzuki, R. Nishimaki, M. Ishikawa, T. Murata, K. Takao, K. Tadano, *J. Org. Chem.* **2000**, *65*, 8595–8607; f) Y. Suzuki, A. Ohara, K. Sugaya, K. Takao, K. Tadano, *Tetrahedron* **2001**, *57*, 7291–7301; g) Y. Suzuki, K. Takao, K. Tadano in *Studies in Natural Products Chemistry* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **2003**, vol. 29, pp. 127–167. For the total synthesis of (+)-macquarimicins, see: h) R. Munakata, T. Ueki, H. Katakai, K. Takao, K. Tadano, *Org. Lett.* **2001**, *3*, 3029–3032; i) R. Munakata, H. Katakai, T. Ueki, J. Kurosaka, K. Takao, K. Tadano, *J. Am. Chem. Soc.* **2003**, *125*, 14722–14723; j) R. Munakata, H. Katakai, T. Ueki, J. Kurosaka, K. Takao, K. Tadano, *J. Am. Chem. Soc.* **2004**, *126*, 11254–11267.

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

[5] T. Takeuchi, M. Igarashi, H. Naganawa, M. Hamada, Japanese Patent JP2001-55386A, **2001**.

[6] For the total synthesis of (–)-chlorothricolide, see: a) W. R. Roush, R. J. Sciotti, *J. Am. Chem. Soc.* **1994**, *116*, 6457–6458; b) W. R. Roush, R. J. Sciotti, *J. Am. Chem. Soc.* **1998**, *120*, 7411–7419. For the total synthesis of racemic 24-*O*-methylchlorothricolide, see: c) K. Takeda, Y. Igarashi, K. Okazaki, E. Yoshii, K. Yamaguchi, *J. Org. Chem.* **1990**, *55*, 3431–3434. For the total synthesis of (+)-tetronolide, see: d) K. Takeda, E. Kawanishi, H. Nakamura, E. Yoshii, *Tetrahedron Lett.* **1991**, *32*, 4925–4928. For the formal synthesis of (+)-tetronolide, see: e) W. R. Roush, M. L. Reilly, K. Koyama, B. B. Brown, *J. Org. Chem.* **1997**, *62*, 8708–8721. For the total synthesis of (+)-superstolide A, see: f) M. Tortosa, N. A. Yakelis, W. R. Roush, *J. Am. Chem. Soc.* **2008**, *130*, 2722–2723; g) M. Tortosa, N. A. Yakelis, W. R. Roush, *J. Org. Chem.* **2008**, *73*, 9657–9667.

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

[8] S. Hosokawa, M. Seki, H. Fukuda, K. Tatsuta, *Tetrahedron Lett.* **2006**, *47*, 2439–2442.

[9] K. Sawamura, K. Yoshida, A. Suzuki, T. Motozaki, I. Kozawa, T. Hayamizu, R. Munakata, K. Takao, K. Tadano, *J. Org. Chem.* **2007**, *72*, 6143–6148.

[10] T. Anzo, A. Suzuki, K. Sawamura, T. Motozaki, M. Hatta, K. Takao, K. Tadano, *Tetrahedron Lett.* **2007**, *48*, 8442–8444.

[11] Recent reviews on the mechanism and application of Stille coupling: a) P. Espinet, A. Echavarren, *Angew. Chem. Int. Ed.*

2004, *43*, 4704–4734; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.
[12] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
[13] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
[14] For a recent review on the Morita–Baylis–Hillman reaction, see: D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–891.
[15] V. K. Aggarwal, G. T. Mereu, R. Tarver, R. McCague, *J. Org. Chem.* **1998**, *63*, 7183–7189.
[16] H. M. R. Hoffmann, J. Rabe, *J. Org. Chem.* **1985**, *50*, 3849–3859.
[17] R. O. Hutchins, I. M. Taffer, *J. Org. Chem.* **1983**, *48*, 1360–1362.
[18] a) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; b) R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899.
[19] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.
[20] C. D. J. Boden, G. Pattenden, T. Ye, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2417–2419.
[21] a) D. Seebach, D. Wasmuth, *Helv. Chim. Acta* **1980**, *63*, 197–200; b) D. Seebach, J. Aebi, D. Wasmuth, *Org. Synth.* **1984**, *63*, 109–120.
[22] a) R. Baker, J. L. Castro, *J. Chem. Soc. Perkin Trans. 1* **1990**, 47–65; b) A. R. de Lera, B. Iglesias, J. Rodriguez, R. Alvarez, S. Lopez, X. Villanueva, E. Padros, *J. Am. Chem. Soc.* **1995**, *117*, 8220–8231.
[23] a) G. A. Kraus, B. Roth, *J. Org. Chem.* **1980**, *45*, 4825–4830; b) B. S. Bal, W. E. Childers Jr, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096.
[24] V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905–5911.
[25] T. Mukaiyama, M. Usui, K. Saigo, *Chem. Lett.* **1976**, 49–50.
[26] T. Ben Ayed, H. Amri, M. M. El Gaied, *Tetrahedron* **1991**, *47*, 9621–9628.
[27] S. E. Denmark, T. K. Jones, *J. Org. Chem.* **1982**, *47*, 4595–4597.
[28] M. J. Carter, I. Fleming, A. Percival, *J. Chem. Soc. Perkin Trans. 1* **1981**, 2415–2435.
[29] Review on the Hiyama cross-coupling: T. Hiyama in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 421–453.
[30] M. Matsushita, Y. Nagaoka, H. Hioki, Y. Fukuyama, M. Kodama, *Chem. Lett.* **1996**, 1039–1040.
[31] a) C. Alvarez-Ibarra, S. Arias, G. Banon, M. J. Fernandez, M. Rodriguez, V. Sinisterra, *J. Chem. Soc., Chem. Commun.* **1987**, 1509–1510; b) I. Paterson, K.-S. Yeung, *Tetrahedron Lett.* **1993**, *34*, 5347–5350.
[32] D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
[33] J. Schwartz, J. A. Labinger, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 333–340.
[34] K. Tatsuta, S. Yasuda, K. Kurihara, K. Tanabe, R. Shinei, T. Okonogi, *Tetrahedron Lett.* **1997**, *38*, 1439–1442.
[35] P. F. Hudrlik, D. Peterson, *J. Am. Chem. Soc.* **1975**, *97*, 1464–1468.
[36] E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.
[37] Prominent review on Suzuki–Miyaura cross-coupling: N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.
[38] I. Shiina, M. Kubota, R. Ibuka, *Tetrahedron Lett.* **2002**, *43*, 7535–7539.
[39] K. Nakagawa, R. Konaka, T. Nakata, *J. Org. Chem.* **1962**, *27*, 1597–1601.
[40] X.-H. Huang, R. van Soest, M. Roberge, R. J. Andersen, *Org. Lett.* **2004**, *6*, 75–78.
[41] F. Berrué, O. P. Thomas, R. Fernández, P. Amade, *J. Nat. Prod.* **2005**, *68*, 547–549.
[42] F. Berrué, O. P. Thomas, R. Laville, S. Prabo, J. Golebiowski, R. Fernández, P. Amade, *Tetrahedron* **2007**, *63*, 2328–2334.
[43] a) J. E. D. Kirkham, V. Lee, J. E. Baldwin, *Chem. Commun.* **2006**, 2863–2865. The Baldwin/Lee group pointed out the structural misassignment of synthetic intermediates described in Mehta and Kundu's publication:[44] b) J. E. D. Kirkham, V. Lee, J. E. Baldwin, *Org. Lett.* **2006**, *8*, 5537–5540.
[44] G. Mehta, U. K. Kundu, *Org. Lett.* **2005**, *7*, 5569–5572.
[45] J. S. Crossman, M. V. Perkins, *Tetrahedron* **2008**, *64*, 4852–4867.
[46] D. Matsumura, T. Toda, T. Hayamizu, K. Sawamura, K. Takao, K. Tadano, *Tetrahedron Lett.* **2009**, *50*, 3356–3358.
[47] D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.
[48] M. A. Brimble, *Aust. J. Chem.* **1990**, *43*, 1035–1046.
[49] T. D. Penning, S. W. Djuric, R. A. Haack, V. J. Kalish, J. M. Miyashiro, B. W. Rowell, S. S. Yu, *Synth. Commun.* **1990**, *20*, 307–312.
[50] a) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26–29; b) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585.
[51] H. Hilpert, B. Wirz, *Tetrahedron* **2001**, *57*, 681–694.
[52] S. Friedrich-Bochnitschek, H. Waldmann, H. Kunz, *J. Org. Chem.* **1989**, *54*, 751–756.
[53] M. Ihara, F. Setsu, M. Shoda, N. Taniguchi, Y. Tokunaga, K. Fukumoto, *J. Org. Chem.* **1994**, *59*, 5317–5323.
[54] H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923.
[55] R. H. Smithers, *J. Org. Chem.* **1978**, *43*, 2833–2838.
[56] J. Takagi, K. Takahashi, T. Ishiyama, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006.

Received: April 15, 2009
Published Online: June 30, 2009

