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Total Synthesis of Macquarimicins Using an Intramolecular Diels−Alder Approach Inspired by a Biosynthetic Pathway

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Abstract: A total synthesis of the macquarimicins A−C (**1**−**3**), novel natural products with intriguing tetra- or pentacyclic frameworks, has been achieved. The synthesis features an extensive investigation of the biosynthesis-based intramolecular Diels−Alder (IMDA) reactions of (*E*,*Z*,*E*)-1,6,8-nonatrienes. Considering possible biosynthetic sequences, four types of substrates were synthesized, and their IMDA reactions were examined. From one of the four substrates, the total synthesis was achieved via a transannular Diels−Alder reaction, which led to the stereoselective construction of the unique molecular framework. The convergent and efficient synthetic pathway afforded (+)-**1** in 27 linear steps with 4.3% and 9.9% overall yields from readily available ethyl (2*E*,4*S*)-4,5-(isopropylidene)dioxy-2-pentenoate (**22**) and (*R*)-epichlorohydrin (**30**), respectively. Furthermore, efficient syntheses of **2**, **3**, and the 9-*epi*-cochleamycins A (**57**) and B (**58**) were accomplished. Additionally, the present work established the absolute stereochemistry of macquarimicins and revised the C(2)−C(3) geometry of **1**.

Introduction

Background. The macquarimicins A−C (**1**−**3**, Figure 1) were isolated from *Micromonospora chalcea* by researchers at Abbott Laboratories in 1995.[1,2] Their planer structures and relative stereochemistry except for C(14) of **3** were elucidated on the basis of 1D- and 2D-NMR experiments and X-ray crystallography of **2**. The molecular architecture of macquarimicins is characterized by unique tetra- and pentacyclic frameworks, which share a *cis*-tetrahydroindanone ring (AB ring) and a β-keto-δ-lactone ring (D ring). Additionally, macquarimicin A (**1**) and macquarimicin B (**2**) contain a strained 10-membered carbocycle (C ring) in which a conjugated alkene is incorporated at the bridgehead position of the CD ring. On the other hand, the pentacyclic framework of macquarimicin C (**3**) contains a characteristic 2-oxabicyclo[2.2.2]octane substructure and an array of seven contiguous stereogenic centers, including one quaternary carbon center.

Initially, macquarimicin A (**1**) was isolated as a very weak antibacterial agent by the Abbott researchers, while macquarimicins B (**2**) and C (**3**) were found to exhibit cytotoxicity against the P388 leukemia cell line (IC_{50} 0.3 and 30.0 μg/mL, respectively).[1a] In 1999, researchers at Sankyo Co. disclosed that **1** is a selective inhibitor of membrane-bound neutral sphingomyelinase (N-SMase).[3] Recently, N-SMase has been emerging as an interesting pharmacological target, because ceramide, an important second messenger produced by sphingomyelinase, is involved in a variety of biological processes, particularly inflammation and apoptosis.[4] An improved understanding of SMase-dependent signaling may provide novel strategies for the treatment of diseases such as inflammatory and neurodegenerative diseases, as well as cancer. Thus, selective inhibitors of N-SMase could be used to gain insight into the enzyme mechanism, which is currently unknown, and more importantly into the experimental therapy of such diseases.[5] In fact, the Sankyo researchers have shown that some N-SMase inhibitors, including **1**, inhibit LPS-induced production

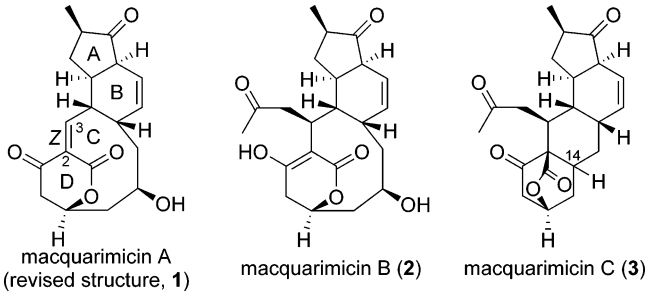


Figure 1. Structures of macquarimicins A−C (**1**−**3**).

(1) (a) Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Rasmussen, R. R.; Hensey, D. M.; Humphrey, P. E.; Swanson, S. J.; Barlow, G. J.; Premachandran, U.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 462−466. (b) Hochlowski, J. E.; Mullally, M. M.; Henry, R.; Whittern, D. M.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 467−470.

(2) The structure of macquarimicin A was originally reported to be its (*E*)-isomer concerning the C(2)−C(3) double bond. In this paper, however, we use the structure **1** shown in Figure 1 because we found that the (*Z*)-isomer **1** is the correct structure for macquarimicin A through this work. See also ref 28.

(3) Tanaka, M.; Nara, F.; Yamasato, Y.; Masuda-Inoue, S.; Doi-Yoshioka, H.; Kumakura, S.; Enokita, R.; Ogita, T. *J. Antibiot.* **1999**, *52*, 670−673.

(4) For applications of the N-SMase inhibitors, see: (a) Nara, F.; Tanaka, M.; Hosoya, T.; Suzuki-Konagai, K.; Ogita, T. *J. Antibiot.* **1999**, *52*, 531−535. (b) Wascholowski, V.; Giannis, A. *Drug News Perspect.* **2001**, *14*, 581−590. (c) Amtmann, E.; Baader, W.; Zoller, M. *Drug Exp. Clin. Res.* **2003**, *29*, 5−13.

10.1021/ja048320w CCC: $27.50

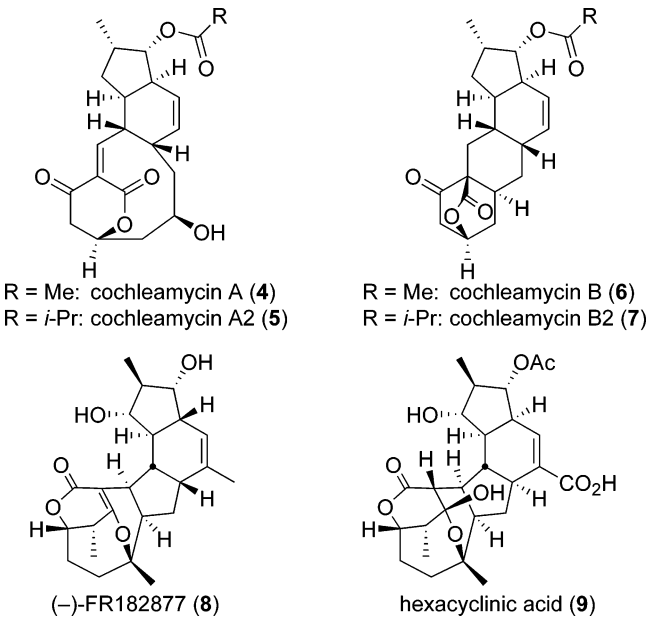


Figure 2. Structures of related natural products.

of IL-1β and PGE_2, the key inflammatory cytokines, and exhibit antiinflammatory activity in vivo by oral administration.[3,4a]

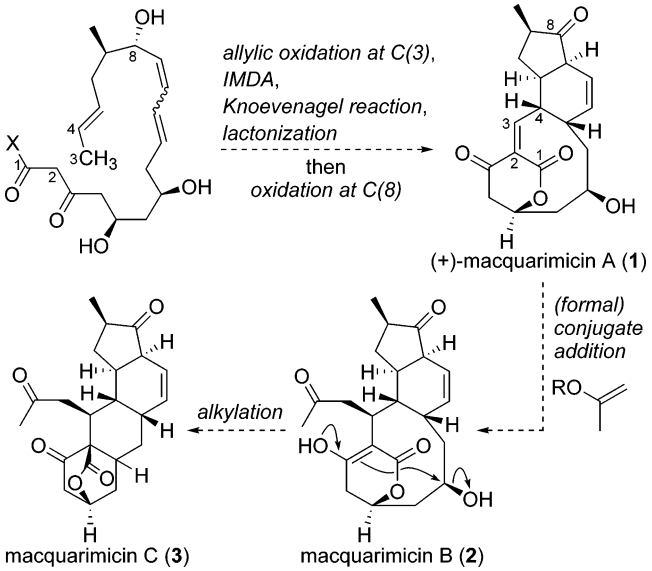
Closely related natural products, antitumor antibiotics, cochleamycin (**4**−**7**),[6] a microtubule-stabilizing agent FR182877 (**8**),[7,8] and hexacyclinic acid (**9**)[9] have been isolated (Figure 2). These natural products may share a biogenetic pathway that involves the intramolecular Diels−Alder (IMDA) reaction of polyketide intermediates.[6d,10,11] It has been proposed that Diels−Alder reactions may be involved in the biosynthesis of more than 100 natural products.[11b] However, to date, only three natural enzymes, solanapyrone synthase (SPS),[12] lovastatin nonaketide synthase (LNKS),[13] and macrophomate synthase (MPS),[14] have been shown to catalyze Diels−Alder reactions in purified or partially purified form. In 2003, the group of Tanaka and Oikawa elucidated the structure of Diels−Alderase for the first time by X-ray crystallography of MPS.[15] In this area, synthetic chemistry has been playing an important role. For example, the catalytic activities on the Diels−Alder reactions of all three enzymes were investigated using synthetically prepared substrates. Details of the biosyntheses of **1**−**9** are still unclear. Therefore, the development of a synthetic methodology may help to elucidate the details by supplying synthetic probes. This intriguing feature of this class of natural products, combined with biological activities and a formidable molecular architecture, makes them highly attractive targets for synthetic chemists.

In 1999, Sorensen and co-workers reported the first synthetic study of FR182877 (**8**) and proposed the biosynthetic pathway for the antibiotic.[10] Soon after, synthetic investigations of **8** and **9** were reported by the groups of Armstrong,[16] Sorensen,[17] Nakada,[18] Roush,[19] and Clarke.[20] In 2002, Sorensen and co-workers[21] and Evans and Starr[22] independently achieved enantioselective total syntheses of (+)- and (−)-**8**, respectively. Their elegant approaches featured a domino sequence of two transannular Diels−Alder (TADA) reactions that converted monocyclic substrates into pentacyclic cycloadducts with remarkable stereoselectivity.

The first report on the synthetic study of macquarimicins or cochleamycins was disclosed by our group in 2001.[23] Later, the groups of Paquette[24] and Roush[25] also reported their synthetic studies. All three studies concern the construction of the tetrahydroindane ring (AB ring) using the IMDA reaction of (*E*,*Z*,*E*)-1,6,8-nonatrienes as the key transformation. In 2003, Tatsuta and co-workers[26] disclosed the first total synthesis of (+)-**4** and established its absolute configuration. The Tatsuta synthesis also features the IMDA reaction of an (*E*,*Z*,*E*)-triene to form the AB ring, and they employed the SmI_2-mediated intramolecular Reformatsky reaction to construct the 10-membered carbocycle. Very recently, the Roush group has also accomplished their total synthesis of (+)-**4** using a TADA strategy.[27] In 2003, we reported the first total synthesis of (+)-**1** using a TADA reaction as the key step.[28] Through this work, we determined the absolute configuration of natural (+)-**1** and revised its proposed structure concerning the C(2)−C(3) geometry. Herein, we report a full account of the total synthesis

(5) For examples of N-SMase inhibitors, see: (a) Nara, F.; Tanaka, M.; Hosoya, T.; Suzuki-Konagai, K.; Ogita, T. *J. Antibiot.* **1999**, *52*, 525−530. (b) Uchida, R.; Tomoda, H.; Dong, Y.; Omura, S. *J. Antibiot.* **1999**, *52*, 572−574. (c) Tanaka, M.; Nara, F.; Yamasato, Y.; Ono, Y.; Ogita, T. *J. Antibiot.* **1999**, *52*, 827−830. (d) Uchida, R.; Tomoda, H.; Arai, M.; Omura, S. *J. Antibiot.* **2001**, *54*, 882−889. (e) Arenz, C.; Giannis, A. *Angew. Chem., Int. Ed.* **2000**, *35*, 1440−1442. (f) Hakogi, T.; Monden, Y.; Iwama, S.; Katsumura, S. *Org. Lett.* **2000**, *2*, 2627−2629. (g) Lindsey, C. C.; Gómez-Díaz, C.; Villalba, J. M.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 4559−4565.
(6) (a) Shindo, K.; Kawai, H. *J. Antibiot.* **1992**, *45*, 294−295. (b) Shindo, K.; Matsuoka, M.; Kawai, H. *J. Antibiot.* **1996**, *49*, 241−243. (c) Shindo, K.; Iijima, H.; Kawai, H. *J. Antibiot.* **1996**, *49*, 244−248. (d) Shindo, K.; Sakakibara, M.; Kawai, H.; Seto, H. *J. Antibiot.* **1996**, *49*, 249−252.
(7) (a) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123−130. (b) Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204−206. (c) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615−622; **2002**, *55*, C-1.
(8) Recently, carboxyesterase-1 inhibitory activity of **8** was reported: Adam, G. C.; Vanderwal, C. D.; Sorensen, E. J.; Cravatt, B. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5480−5484.
(9) Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3258−3261.
(10) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.* **1999**, *1*, 645−648. See also ref 21b.
(11) For reviews on the biosynthesis of Diels−Alder-type natural products, see: (a) Ichihara, A.; Oikawa, H. *Curr. Org. Chem.* **1998**, *2*, 365−394. (b) Ichihara, A.; Oikawa, H. In *Comprehensive Natural Products Chemistry*; Sankawa, U., Ed.; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Series Eds.; Elsevier: Oxford, 1999; Vol. 1, pp 367−408. (c) Williams, R. M.; Stocking, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078−3115.
(12) Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748−8756.
(13) Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D. J.; Vanden Heever, J. P.; Hutchinson, C. R.; Vederas, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11519−11520.
(14) Watanabe, K.; Mie, T.; Ichihara, A.; Oikawa, H.; Honma, M. *J. Biol. Chem.* **2000**, *275*, 38393−38401.
(15) Ose, T.; Watanabe, K.; Mie, T.; Honma, M.; Watanabe, H.; Yao, M.; Oikawa, H.; Tanaka, I. *Nature* **2003**, *422*, 185−189.
(16) Armstrong, A.; Goldberg, F. W.; Sandham, D. A. *Tetrahedron Lett.* **2001**, *42*, 4585−4587.
(17) Vanderwal, C. D.; Vosburg, D. A.; Sorensen, E. J. *Org. Lett.* **2001**, *3*, 4307−4310.
(18) Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2002**, *43*, 3263−3267.
(19) Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223−4226.
(20) (a) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commun.* **2003**, 1560−1561. (b) Clarke, P. A.; Grist, M.; Ebden, M. *Tetrahedron Lett.* **2004**, *45*, 927−929.
(21) (a) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552−4553. (b) The Sorensen group also has reported the total synthesis of natural (−)-FR182877: Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393−5407.
(22) (a) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787−1790. (b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531−13540.
(23) Munakata, R.; Ueki, T.; Katakai, H.; Takao, K.; Tadano, K. *Org. Lett.* **2001**, *3*, 3029−3032.
(24) Chang, J.; Paquette, L. A. *Org. Lett.* **2002**, *4*, 253−256.
(25) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4725−4728.
(26) Tatsuta, K.; Narazaki, F.; Kashiki, N.; Yamamoto, J.; Nakano, S. *J. Antibiot.* **2003**, *56*, 584−590.
(27) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004**, *6*, 2043−2046.
(28) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722−14723.

Scheme 1. Plausible Biosynthetic Pathway of Macquarimicins



of the macquarimicins A−C (**1**−**3**) by employing the biosynthesis-based Diels−Alder strategy, in which the IMDA reactions of a variety of (*E*,*Z*,*E*)-1,6,8-nonatrienes are extensively investigated. The present synthesis also features an efficient and concise construction of the characteristic framework of macquarimicins.

Biosynthetic Hypothesis. In 1996, Shindo, Seto, and co-workers reported biosynthetic studies of cochleamycins using ^{13}C- and ^{2}H-labeled compounds, which revealed the polyketide origin of cochleamycins and their carbon skeletons consisting of eight acetate units and one propionate unit.[6d] In the study, they proposed a biosynthetic hypothesis in which the sequential IMDA reaction, the intramolecular Knoevenagel reaction, and reductive transannular alkylation take place to form the molecular architecture of cochleamycins. We supposed that **1** might be synthesized through the common pathway to **4** (Scheme 1). The order of the three cyclization reactions was unclear because the isotope-labeling study[6d] indicates only a linear structure of the polyketide precursor but not intermediates in the cyclization sequence. A conjugate addition or a hetero Diels−Alder reaction of an acetone equivalent to **1** followed by hydrolysis[29] would generate **2**. A dehydrative transannular alkylation of **2** as depicted would provide **3** with inversion of configuration.[30] To construct a tetrahydroindane ring with *cis-anti-cis* ring fusion in an IMDA reaction, the reaction of an (*E*,*Z*,*E*)-1,6,8-nonatriene has to proceed in *endo*-mode and the reaction of an (*E*,*E*,*Z*)-1,6,8-nonatriene had to proceed in *exo*-mode (Scheme 2). With these synthetic and stereochemical issues in mind, we embarked on the synthesis of a variety of IMDA substrates.

Results and Discussion

Synthetic Plan. As mentioned in ref 2, we assumed macquarimicin A has a C(2)−C(3) geometry opposite to that reported in the original literature.[1b] The following is our

Scheme 2. Possible IMDA Reactions Forming a *cis-anti-cis*-Tetrahydroindane

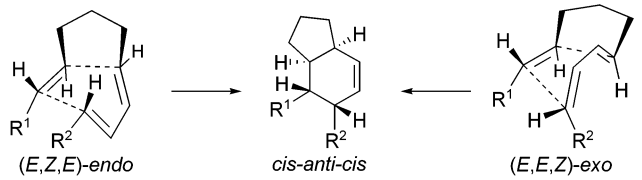
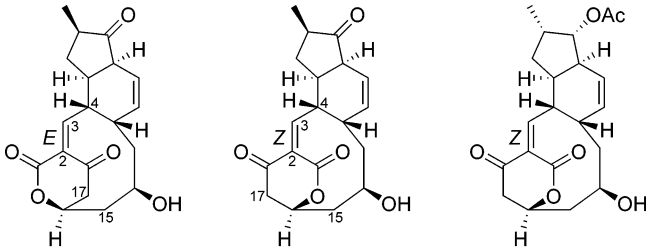


Table 1. Comparison of ^{1}H NMR Data Reported for Macquarimicin A to **4**



position[a]	macquarimicin A[b]	cochleamycin A[c]
3	6.78 (d, 11.1)[d]	6.77 (d, 11.3)
4	3.44 (ddd, 11.1, 6.1, 2.4)	3.30 (ddd, 11.3, 5.6, 2.4)
15	1.80 (dt, 15.4, 2.3)	1.78 (ddd, 15.5, 2.4, 2.4)
	2.49 (dddd, 15.4, 11.6, 4.7, 1.0)	2.48 (ddd, 15.5, 11.8, 4.5)
17	2.67 (dd, 18.8, 0.8)	2.66 (d, 19.0)
	3.14 (ddd, 18.8, 7.4, 1.0)	3.11 (dd, 19.0, 7.5)

[a] Macquarimicin numbering. [b] Cited from ref 1b. [c] Cited from ref 6c. [d] Coupling constants in J = Hz.

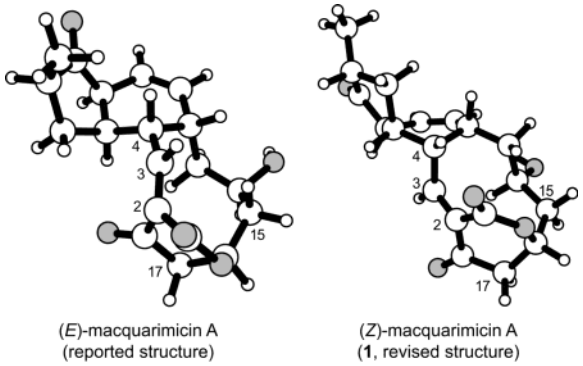


Figure 3. The most stable conformers for the C(2)−C(3) geometrical isomers of macquarimicin A.

evidence. As shown in Table 1, the reported ^{1}H NMR data for macquarimicin A and cochleamycin A (**4**) are in substantial agreement despite the opposite geometry at C(2)−C(3). On the other hand, a molecular modeling study suggested the significant conformational difference between each most stable conformer for the two geometrical isomers (Figure 3).[31] Thus, it might be considered that macquarimicin A has the same C(2)−C(3) geometry as that of **4**, the geometry of which was determined unambiguously by NOE experiments.[32,33]

The retrosynthetic analysis of macquarimicins (**1**−**3**) is outlined in Scheme 3. The core of our strategy was the

(29) Involvements of intermolecular hetero Diels−Alder reactions are suggested in biosyntheses of several natural products: (a) Seo, S.; Sankawa, U.; Ogihara, Y.; Itaka, Y.; Shibata, S. *Tetrahedron* **1973**, *29*, 3721−3726. (b) Baldwin, J. E.; Mayweg, A. V. W.; Neumann, K.; Pritchard, G. J. *Org. Lett.* **1999**, *1*, 1933−1935. (c) Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Williams, A. J.; Watkin, D. J. *Org. Lett.* **1999**, *1*, 1937−1939.

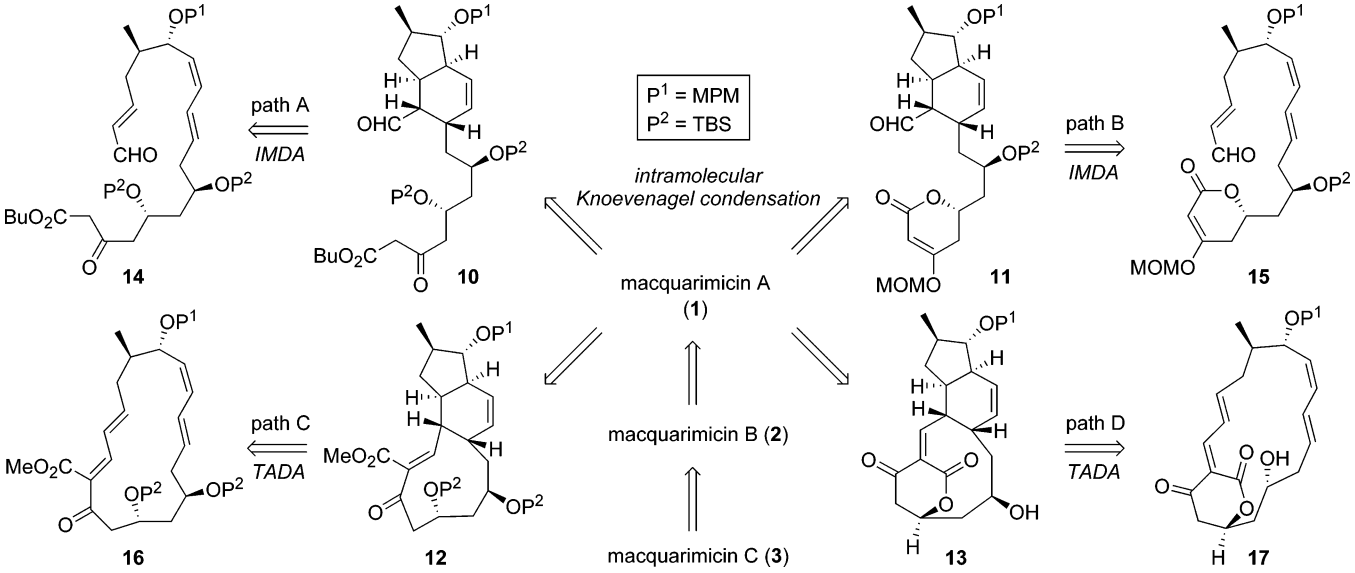
(30) Although the configuration of C(14) in **3** had not been determined, it was estimated to be the same as that of cochleamycin B (**6**).

(31) This calculation was performed with Spartan '02 for Windows.

(32) In 1992, Shindo and co-workers reported the structure of **4** to be its *E*-isomer (ref 6a), but they corrected it to the *Z*-isomer in a later report (ref 6c) based on a ^{13}C−{^{1}H} NOE experiment.

(33) Although the Shindo group and ours depicted the structure of macquarimicin A as its correct (*Z*)-isomer **1** (refs 6b and 23, respectively), the first mention of this geometry issue was made by the Sorensen group (ref 21b).

Scheme 3. Retrosynthetic Analysis of Macquarimicins



construction of the molecular framework using the IMDA reaction inspired by the proposed plausible biosynthesis.[34−36] We employed this [4+2] cycloaddition strategy because we were greatly interested in the possibility that the IMDA reaction of (*E*,*Z*,*E*)-1,6,8-nonatrienes could be involved in the biosynthesis of **1**. This type of IMDA reaction has been far less utilized in organic synthesis as compared to its (*E*,*E*,*E*)- and (*Z*,*E*,*E*)-counterparts due to its lower rate and possible side reactions such as olefin isomerization.[37,38] We anticipated that this study would help to enlarge the scope of this type of IMDA reaction, which had not been fully investigated.

On the basis of the biosynthetic hypothesis shown in Scheme 1, we considered macquarimicin A (**1**) to be a precursor of **2** and **3** (Scheme 3). We were especially interested in the stereochemical outcome of these transformations, which could disclose the intrinsic reactivity of these natural products to verify the proposed biosynthesis. Planning the synthesis of **1** featured by the biomimetic Diels−Alder reaction, we were not sure of the best structure of the substrate, due to the uncertain order of the three ring-forming reactions. We planned to synthesize four types of (*E*,*Z*,*E*)-substrates (**14**−**17**), considering possible cyclization sequences, to fully investigate the stereochemical outcome of the IMDA reactions. The IMDA reactions of the linear substrates **14** (path A) and **15** (path B) would provide cycloadducts **10** and **11**, respectively, bearing a β-ketoester or a β-keto-δ-lactone moiety as a nucleophilic part for the subsequent intramolecular Knoevenagel condensation. On the other hand, the IMDA reactions of **16** (path C) and **17** (path D), categorized as transannular Diels−Alder (TADA) reactions, would produce **12** and **13**, respectively, forming the 10-membered carbocycle simultaneously.[39,40] The cycloadduct **12** was expected to afford **1** by a δ-lactone formation, while the cycloadduct **13** already possesses the tetracyclic framework of **1**. These TADA approaches were especially of interest because no biomimetic total synthesis employing the TADA approach had been disclosed when we started this synthetic work.[41,42]

For the synthesis of these four types of IMDA substrates (**14**−**17**), we designed a convergent and flexible strategy to carry out the work efficiently (Scheme 4). First, the substrates (**14**−**17**) were dissected at C(10)−C(11). This sp^2−sp^2 bond connection would be realized by the Stille coupling reaction between

(34) For recent reviews on biomimetic syntheses, see: (a) Williams, R. M.; Cox, R. *Acc. Chem. Res.* **2003**, *36*, 127−139. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551−564. (c) Reference 11b. (d) de la Torre, M. C.; Sierra, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 160−181.

(35) For recent reviews on the synthetic application of Diels−Alder reactions, see: (a) Brocksom, T. J.; Nakamura, J.; Ferreira, M. L.; Brocksom, U. *J. Braz. Chem. Soc.* **2001**, *12*, 597−622. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.

(36) For recent reviews on the IMDA reactions, see: (a) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 91−146. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 513−550. (d) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *42*, 14179−14233. (e) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 464−474. (f) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820−849.

(37) For reports on the IMDA reactions of (*E*,*Z*,*E*)-trienes, see: (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061−1970. (b) Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 6282−6284. (c) Boeckman, R. K., Jr.; Alessi, T. R. *J. Am. Chem. Soc.* **1982**, *104*, 3216−3217. (d) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719−5728. (e) Pyne, S. G.; Spellmeyer, D. C.; Chen, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5728−5740. (f) Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133−1135. (g) Wattanasin, S.; Kathawala, F. G.; Boeckman, R. K., Jr. *J. Org. Chem.* **1985**, *50*, 3810−3815. (h) Back, T. G.; Nava-Salgado, V. O.; Payne, J. E. *J. Org. Chem.* **2001**, *66*, 4361−4368. (i) Yakelis, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 957−960.

(38) For alkene isomerization of (*E*,*Z*)-1,3-dienes, see: (a) Matikainen, J.; Kalita, S.; Hämäläinen, M.; Hase, T. *Tetrahedron* **1997**, *53*, 4531−4538. (b) Diedrich, M. K.; Klärner, F.-G. *J. Am. Chem. Soc.* **1998**, *120*, 6212−6218. (c) Allen, A.; Gordon, D. M. *Indian J. Chem., Sect. B* **1999**, *38B*, 269−273.

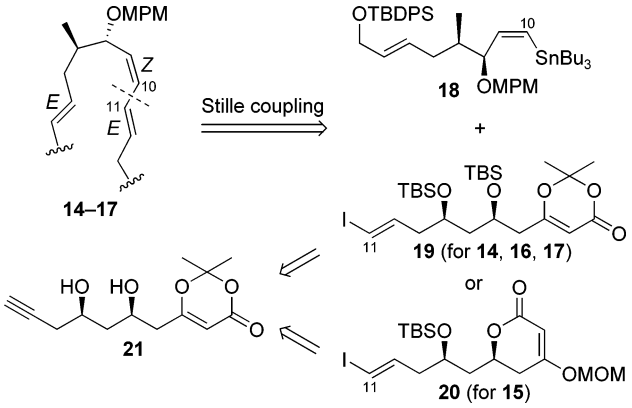
(39) For pioneering works on the TADA reaction, see: (a) Dauben, W. G.; Michno, D. M.; Olsen, E. G. *J. Org. Chem.* **1981**, *46*, 687−690. (b) Baettig, K.; Dallaire, C.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5249−5252. (c) Baettig, K.; Marinier, A.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5253−5254. (d) Bérubé, G.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5255−5258. (e) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J. *J. Am. Chem. Soc.* **1988**, *110*, 2674−2676.

(40) For a review on TADA, see: Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243−4260.

(41) For reports on the TADA-based total syntheses, see: (a) Shing, T. K. M.; Yang, J. *J. Org. Chem.* **1995**, *60*, 5785−5789. (b) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773−775. (c) Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5269−5278. (d) Bodwell, G. J.; Li, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3261−3262. (e) Soucy, P.; L'Heureux, A.; Toró, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 9983−9987. (f) Suzuki, T.; Usui, K.; Miyake, Y.; Namikoshi, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 553−556.

(42) To date, four TADA-based biomimetic total syntheses have been reported by the groups of Shair (ref 41b), Sorensen (ref 21), Evans (ref 22), and Deslongchamps (ref 41e).

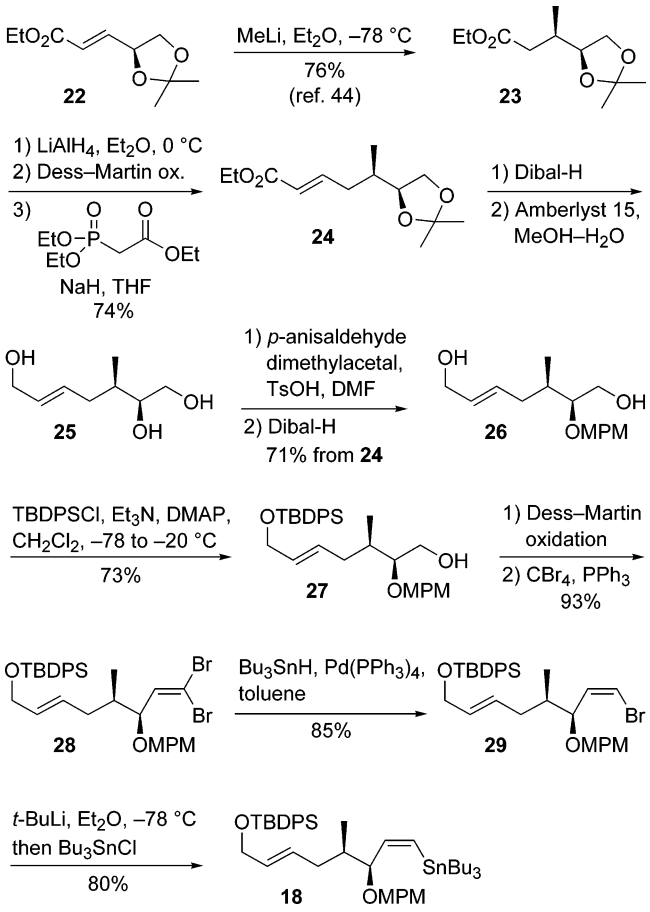
Scheme 4. Retrosynthetic Analysis of the IMDA Substrates



intermediates **18** and **19** or **20**. The iodoalkenes **19** and **20** would be, in turn, derived from **21**. This strategy seemed to be profitable for us because both **18** and **21** would serve as common precursors for all four types of IMDA substrates. As the absolute stereochemistry of the macquarimicins had not been established, we started from readily available enantiopure starting materials to synthesize **18** and **21**, hopeful that our choice would ultimately correspond to the absolute stereochemistry of the target.

Synthesis of the Coupling Substrates. The coupling substrate **18** was synthesized from known α,β-unsaturated ester **22**, which is readily available from D-mannitol[43] (Scheme 5). The diastereoselective conjugate addition of a methyl nucleophile to **22** was conducted as reported by Leonard and co-workers.[44] Thus, **22** was exposed to MeLi in diethyl ether at −78 °C to give *syn*-adduct **23** as a single diastereomer. The ester group in **23** was reduced with $LiAlH_4$, followed by Dess−Martin oxidation[45] and Horner−Wadsworth−Emmons olefination, providing (*E*)-unsaturated ester **24** with higher than 20:1 *E*-selectivity. Reduction of **24** with diisobutylaluminum hydride (Dibal-H) and deprotection of the acetonide gave triol **25**. The secondary hydroxyl group in **25** was selectively protected to provide the (4-methoxyphenyl)methyl (MPM) ether **26** by diol protection of **25** as the 4-methoxybenzylidene acetal,[46] followed by regioselective reductive cleavage of the acetal with Dibal-H.[47] The less-hindered allylic alcohol in **26** was selectively protected as a *tert*-butyldiphenylsilyl (TBDPS) ether to afford **27** in 73% yield, with 13% of recovered **26**. Dess−Martin oxidation of **27** and subjection of the resultant aldehyde to Corey−Fuchs conditions[48] provided dibromoalkene **28**. The application of Uenishi's method[49] to **28** afforded (*Z*)-bromoalkene **29** exclusively.[50] The halogen−lithium exchange of **29**, followed by treatment with Bu_3SnCl, produced (*Z*)-stannylalkene **18**.

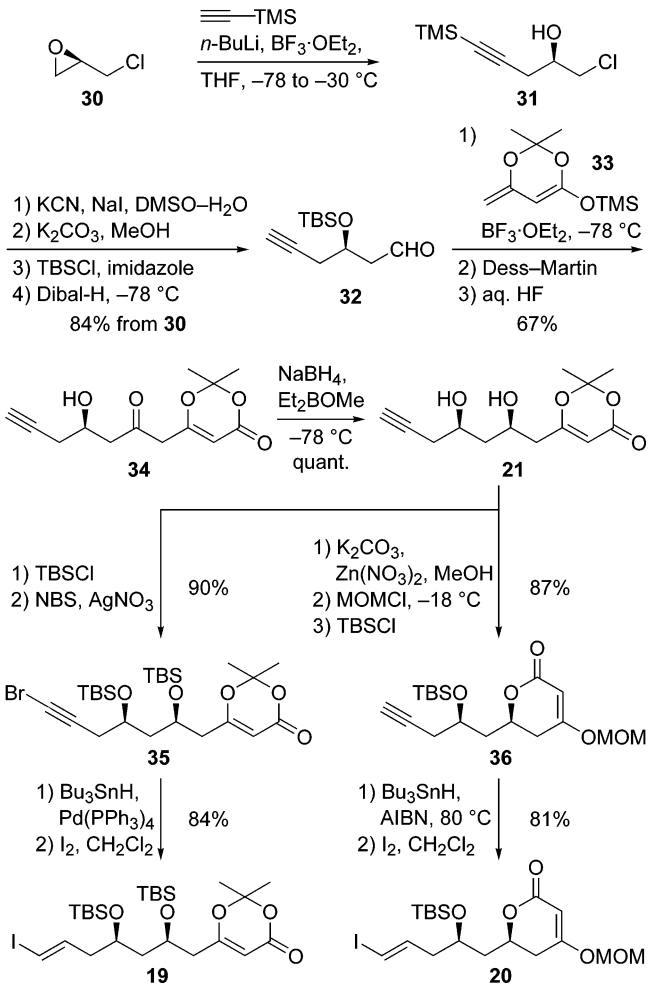
Scheme 5. Synthesis of (*Z*)-Stannylalkene **18**



The synthesis of the other coupling substrates **19** and **20** started from (*R*)-epichlorohydrin (**30**) via known acetylenic compound **31**[51] (Scheme 6). The conversion of **31** to aldehyde **32** was conducted in a straightforward manner and proceeded in an overall yield of 84% from **30**.[52] The $BF_3{\cdot}OEt_2$-mediated vinylogous Mukaiyama aldol reaction between **32** and **33**,[53] prepared from 2,2,6-trimethyl-1,3-dioxin-4-one, proceeded smoothly to give a 1:1 diastereomeric mixture of the adducts, which was converted into β-hydroxyketone **34** in two additional steps. The diastereoselective carbonyl reduction of **34**, according to Prasad's procedure,[54] gave the desired *syn*-1,3-diol **21** exclusively.[55] From the common intermediate **21**, the coupling substrates **19** and **20** were synthesized as follows. Protection of the two hydroxyl groups in **21** and conversion of the resultant disilylated product to bromoalkyne **35**, followed by one-pot

(43) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, 403−406.
(44) Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Swain, P. A. *Tetrahedron* **1995**, *51*, 12843−12858.
(45) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (d) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.
(46) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371−2374.
(47) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593−1596.
(48) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769−3772.
(49) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965−8975.
(50) The Wittig reaction of aldehyde derived from **27** using $Ph_3PCH_2I_2$ and NaHMDS as base gave a mixture of *Z*/*E* iodoalkene (ca. 5:1). See: Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173−2174.
(51) Takano, S.; Kamikubo, T.; Sugihara, T.; Suzuki, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1993**, *4*, 201−204.
(52) In the reaction of **31** with KCN to form the corresponding nitrile, the use of aqueous DMSO, instead of dry DMSO, prevented the formation of the TMS ether, which was generated as a result of migration of the alkynyl TMS group to the secondary alcohol.
(53) Grunwell, J. R.; Karapides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91−95.
(54) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158.
(55) The *syn*-stereochemistry of **21** was confirmed on the basis of ^{13}C NMR chemical shifts of the corresponding 1,3-diol acetonide using the well-recognized empirical rule of Rychnovsky et al.: Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515. See Supporting Information for details.

Scheme 6. Synthesis of the (*E*)-Iodoalkenes **19** and **20**



hydrostannylation-iodination,[56] afforded (*E*)-iodoalkene **19**. On the other hand, treatment of **21** under modified Sato and Kaneko's conditions reported by Carreira[57] gave a transient β-keto-δ-lactone, in which the keto carbonyl and the hydroxyl group were protected as a methoxymethyl enol ether and as a TBS ether, respectively, to produce **36** efficiently. Hydrostannylation of **36** under radical conditions using AIBN as an initiator and subsequent treatment of the resultant (*E*)-stannylalkene with I_2 produced the (*E*)-iodoalkene **20**.

In our earlier synthetic work conducted using compounds with the β-keto-δ-lactone structure, protection of the keto carbonyl was required due to the highly acidic and reactive nature of cyclic 1,3-dicarbonyl compounds.[58] To the best of our knowledge, no practical procedure for the protection of β-keto-δ-lactone has been reported.[59] We conducted a search to seek the most suitable protecting group for our case and found a methoxymethyl (MOM) group to be the best choice.[60] Therefore, the β-keto-δ-lactone generated from **21** was selectively protected as MOM enol ether (not shown) at −18 °C.[61] We also searched for deprotection conditions for the resultant MOM enol ether and found that treatment with $MgBr_2 \cdot OEt_2$ and EtSH in Et_2O at room temperature cleanly regenerated the starting β-keto-δ-lactone.[62] For example, the MOM group in the coupling substrate **20** was deprotected under these conditions in 98% yield. The present protection/deprotection methodology will enhance the synthetic flexibility for compounds involving β-keto-δ-lactones, which are frequently utilized as intermediates in natural product synthesis[63] and medicinal chemistry,[64] as in the synthesis of HIV protease inhibitor tipranavir.[64b]

Stille Coupling. With stannane **18** and iodides **19** and **20** in hand, we examined the Stille coupling reaction to combine them.[65] To probe the viability of the reaction, we conducted a preliminary study using several compounds related to **18** with the TBS ether of (*E*)-4-iodo-3-propen-1-ol or (*E*)-4-tributylstannyl-3-propen-1-ol as a coupling partner (Scheme 7). The results on the Stille coupling reactions using (*Z*)-bromoalkenes or -iodoalkenes, carrying an aldehyde or a hydroxymethyl group

(56) For hydrostannylation of 1-bromoalkynes, see: Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417−2419.

(57) (a) Sato, M.; Sakai, J.; Sugita, Y.; Yasuda, S.; Sakoda, H.; Kaneko, C. *Tetrahedron* **1991**, *47*, 5689−5708. (b) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360−12361.

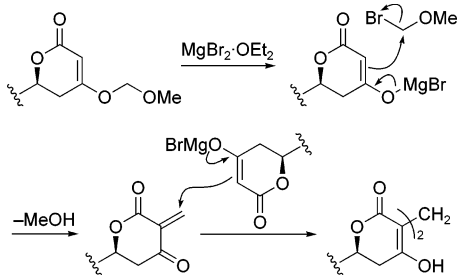
(58) For example, the acidity of δ,δ-dimethyl-β-keto-δ-lactone (2,2-dimethylpyran-4,6-dione, $pK_a = 10.5$) is between those of Meldrum's acid ($pK_a = 7.3$) and dimedone ($pK_a = 11.2$) in DMSO, which is stronger than acetic acid ($pK_a = 12.3$). The pK_a values are cited from the following references: (a) Arnett, E. M.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 809−812. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(59) Although a number of β-keto-δ-lactone equivalents have been synthesized, studies in the context of protection/deprotection have not been reported. See: (a) Nakata, T.; Takao, S.; Fukui, M.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 3873−3876. (b) Dziadulewicz, E.; Giles, M.; Moss, W. O.; Gallagher, T.; Harman, M.; Hursthouse, M. B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1793−1798. (c) D'Angelo, J.; Gomez-Pardo, D. *Tetrahedron Lett.* **1991**, *32*, 3063−3066. (d) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046. (e) Brandänge, S.; Färnbäck, M.; Leijonmarck, H.; Sundin, A. *J. Am. Chem. Soc.* **2003**, *125*, 11942−11955.

(60) Other protecting groups such as TBS, pivaloyl, and Boc were found to be too labile, while the *N*,*N*-dimethylcarbamoyl and 2,4,6-trimethylbenzoyl (mesitoyl) groups were too robust. The difficulty in enol-type protections arises from the vinylogous carbonate substructure making protecting groups labile and the β-acyloxyketone substructure leading to an easy elimination reaction. Ketal-type protecting groups such as dithiolane or dioxolane were also examined, but the protection and/or deprotection were less efficient.

(61) Neither MOM etherification of the secondary alcohol nor *C*-alkylation at the α-position of the β-keto-δ-lactone was observed under these conditions.

(62) Without EtSH, the scavenger for forming the formaldehyde equivalent, the yield of the deprotection dropped significantly due to the formation of a methylene-tethered dimer via the Knoevenagel−Michael reaction sequence shown below.



(63) (a) Ohmori, K.; Suzuki, T.; Miyazawa, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1993**, *34*, 4981−4984. (b) Spino, C.; Mayes, N.; Desfosses, H.; Sotheeswaran, S. *Tetrahedron Lett.* **1996**, *37*, 6503−6506. (c) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357−2384. (d) Paterson, I.; Luckhurst, C. A. *Tetrahedron Lett.* **2003**, *44*, 3749−3754.

(64) (a) Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 31−38. (b) Turner, S. R.; Strohbach, J. W.; Tommasi, R. A.; Aristoff, P. A.; Johnson, P. D.; Skulnick, H. I.; Dolak, L. A.; Seest, E. P.; Tomich, P. K.; Bohanon, M. J.; Horng, M.-M.; Lynn, J. C.; Chong, K.-T.; Hinshaw, R. R.; Watenpaugh, K. D.; Janakiraman, M. N.; Thaisrivongs, S. *J. Med. Chem.* **1998**, *41*, 3467−3476. (c) Boyer, F. E.; Vara Prasad, J. V. N.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hagen, S. E.; Markoski, L. J.; Tait, B. D.; Lunney, E. A.; Palovsky, A.; Ferguson, D.; Graham, N.; Holler, T.; Hupe, D.; Nouhan, C.; Tummino, P. J.; Urumov, A.; Zeikus, E.; Zeikus, G.; Gracheck, S. J.; Sanders, J. M.; VanderRoest, S.; Brodfuehrer, J.; Iyer, K.; Sinz, M.; Gulnik, S. V.; Erickson, J. W. *J. Med. Chem.* **2000**, *43*, 843−858.

(65) For reviews of the Stille coupling reaction, see: (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771−1780. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (c) Mitchell, T. N. *Synthesis* **1992**, 803−815. (d) Farina, V.; Krishnamurphy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652. (e) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235−1246.

Scheme 7. Mizorogi−Heck-type Cyclization of (*Z*)-Alkene Derivatives

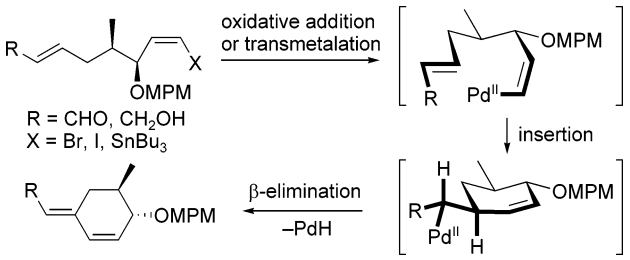
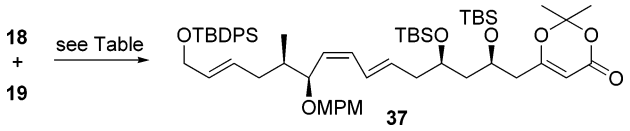


Table 2. Optimization of the Conditions for the Stille Coupling Reaction of **18** and **19**[a]



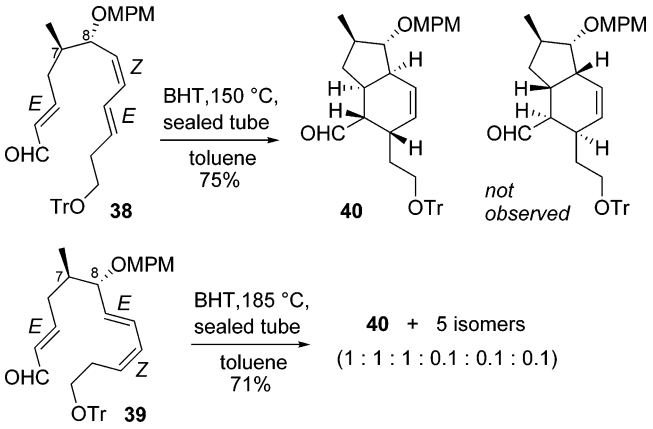
entry	catalyst	CuX	solvent	yield (%)[b]
1	$PdCl_2(MeCN)_2$	CuI	DMF	14
2	$PdCl_2(MeCN)_2$	CuBr	DMF	30
3	$PdCl_2(MeCN)_2$	CuCl	DMF	34
4	$PdCl_2(MeCN)_2$	CuCl	DMSO	59
5	$PdCl_2(MeCN)_2$	CuCl	DMSO−THF (1:1)	70
6	$Pd(PPh_3)_4$	CuCl	DMSO−THF (1:1)	72
7[c]	$Pd(PPh_3)_4$	CuCl	DMSO−THF (1:1)	97

[a] Reactions were conducted using 10 mol % of Pd catalyst and 1 equiv of CuX unless otherwise noted. [b] The yield from **19**. [c] 6 mol % of Pd catalyst was used.

as the left-hand terminal, were unsatisfactory due to the predominant occurrence of an intramolecular Mizorogi−Heck-type cyclization to give cyclohexene derivatives through the mechanism shown. Furthermore, an *O*-unprotected (*Z*)-stannylalkene and an *O*-TBDPS-protected (*Z*)-haloalkene again gave the corresponding cyclohexene derivatives as the predominant product.[66] Consequently, the use of a left-hand-protected (*Z*)-stannylalkene such as **18** was inevitable. Establishing **18** as the optimal substrate, we explored the Stille coupling reaction of **18** and **19**.

The results of the targeted Stille coupling are shown in Table 2. First, we examined standard conditions using 10 mol % of $PdCl_2(MeCN)_2$ and a stoichiometric amount of cuprous halide in DMF (entries 1−3).[67,68] The reaction was promoted most effectively with CuCl (entry 3), although the yield was still insufficient (34%). The reaction rate increased in the following order: CuI < CuBr < CuCl. Establishing CuCl as the optimal promoter, we next examined the effect of reaction solvents. Substantial improvement was achieved by using DMSO (59%, entry 4), and a further increase in yield was accomplished using a 1:1 DMSO−THF mixed solvent system (entry 5), which afforded a 70% yield of **37**.[69] We then optimized the palladium catalyst. We found that the use of $Pd(PPh_3)_4$ reduces undesired byproducts to provide a 72% yield of **37** (entry 6).[70] After optimization of the catalyst loading, we finally found that the optimal conditions involve the use of a smaller amount (6 mol %) of $Pd(PPh_3)_4$ in THF with the slow addition to the mixture of **18**, **19**, and CuCl in DMSO−THF. The coupling reaction proceeded reproducibly to provide **37** in 97% (entry 7).[71]

Scheme 8. Model IMDA Studies with (*E*,*Z*,*E*)- and (*E*,*E*,*Z*)-1,6,8-Nonatrienes **38** and **39**



The Intramolecular Diels−Alder (IMDA) Reactions. After optimizing the Stille coupling conditions, we investigated the key IMDA reaction. Prior to carrying out the IMDA reactions of **14**−**17**, we conducted a study using a model substrate **38**, which possesses the same substitution pattern on C(7) and C(8) as that in **14**−**17**, to test the reactivity of (*E*,*Z*,*E*)-1,6,8-nonatriene (Scheme 8).[23] In addition, we conducted the IMDA reaction of (*E*,*E*,*Z*)-1,6,8-nonatriene **39**, another candidate involved in the proposed biosynthesis of the macquarimicins and cochleamycins[6b] (Schemes 1 and 2). There have been no reports to date concerning the construction of a tetrahydroindane ring by the IMDA reaction of (*E*,*E*,*Z*)-1,6,8-nonatriene.

The IMDA reaction of (*E*,*Z*,*E*)-triene **38**[72] proceeded at 150 °C (5 h) in the presence of BHT (2,6-di-*tert*-butyl-4-methylphenol) in a sealed tube to afford the desired cycloadduct **40** in 75% yield with a selectivity of >20:1.[73,74] In this reaction, isomerization of the diene moiety was not observed. On the other hand, the IMDA reaction of (*E*,*E*,*Z*)-triene **39**[72] did not

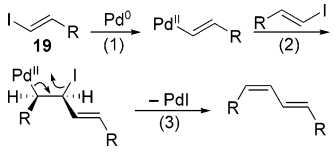
(66) Recently a Mizorogi−Heck-type reaction using organostannanes was reported: Hirabayashi, K.; Ando, J.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1409−1417.

(67) Conditions using a palladium catalyst solely did not afford the desired product **37**, presumably due to a slow transmetalation step caused by steric hindrance around the stannylalkene part in **18**. Also, the stoichiometric amount of CuCl was essential to promote the reaction effectively.

(68) For discussions on the copper effect in the Stille reaction, see: (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364. (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911. (c) Casado, A.; Espinet, P. *Organometallics* **2003**, *22*, 1305−1309.

(69) We examined the DMSO−THF mixed solvent due to the low solubility of substrates to DMSO alone.

(70) The substantial byproduct was a dimeric (*E*,*Z*)-diene generated from **19**. The corresponding (*E*,*E*)-diene was not observed. Stereospecific formation of the (*E*,*Z*)-dimer can be explained by an intermolecular Mizorogi−Heck-type mechanism, which involves three elemental steps as shown below: (1) oxidative addition of **19** to Pd(0), (2) insertion of another molecule of **19**, and (3) the *syn* elimination of *β*-iodide, instead of the usual *β*-hydride, to give the dimeric (*E*,*Z*)-diene. For examples of similar reactions involving *β*-bromide elimination, see: (a) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 2049−2054. (b) Edvardsen, K. R.; Benneche, T.; Tius, M. A. *J. Org. Chem.* **2000**, *65*, 3085−3089.



(71) Corey et al. have reported the utility of the CuCl/LiCl/$Pd(PPh_3)_4$/DMSO system in Stille coupling: Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605.

(72) For the syntheses of model substrates **38** and **39**, see the Supporting Information.

(73) The diastereomers of **40** were not found.

(74) The stereochemistry of the predominant product was unambiguously determined by analysis of the ^1H NMR spectrum and NOE experiments. For details, see the Supporting Information.

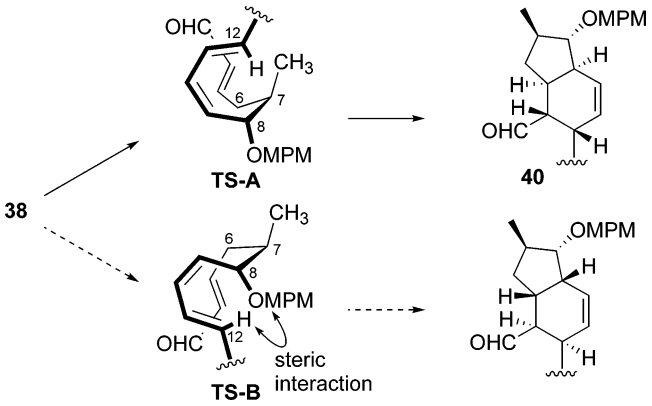


Figure 4. Plausible mechanism for the stereoselectivity in the IMDA reaction of **38**.

take place at 150 °C but proceeded slowly at 185 °C (11 days). This reaction produced a mixture of six cycloadducts in a ratio of 1:1:1:0.1:0.1:0.1.[75] One of the three major cycloadducts proved to be identical to the cycloadduct **40**, which might have been generated via an *exo* transition state. Theoretically, the IMDA reaction of (*E*,*E*,*Z*)-triene **39** provides four cycloadducts at most when the reaction proceeds concertedly, as is usually accepted. Therefore, alkene isomerization of **39** was probably involved in the formation of the other two cycloadducts.[76]

The stereochemical result from the IMDA reaction of **38** is rationalized by considering the two transition states illustrated in Figure 4. As it is generally accepted that *exo* transition states are unlikely to be accessible because the reaction sites do not approach each other closely enough to react in the IMDA reaction of a (*E*,*Z*,*E*)-nonatriene, only two *endo* transition states, **TS-A** or **TS-B**, are possible. As compared with **TS-B**, **TS-A** leading to **40** seems to be substantially more favorable because a severe steric interaction between the (4-methoxyphenyl)-methoxy group and vinylic hydrogen exists in **TS-B**. Consequently, the configuration at C(8) attaching the OMPM group should significantly affect the π-facial selection of the cycloaddition.[77] By comparison of the result obtained from the IMDA of **38** with Paquette's observation,[24,78] it is obvious that the diastereocontrol induced by the C(8)-substituent is superior to that by the C(7)-substituent. Meanwhile, the effect of substituents at C(6) and C(7) (macquarimicin numbering) on stereoselectivity in the IMDA reaction of (*E*,*Z*,*E*)-1,6,8-nonatrienes has not been investigated systematically. Further investigations are required for a more precise account of the diastereoselectivity to enhance the synthetic value of the IMDA reaction of (*E*,*Z*,*E*)-1,6,8-nonatrienes.

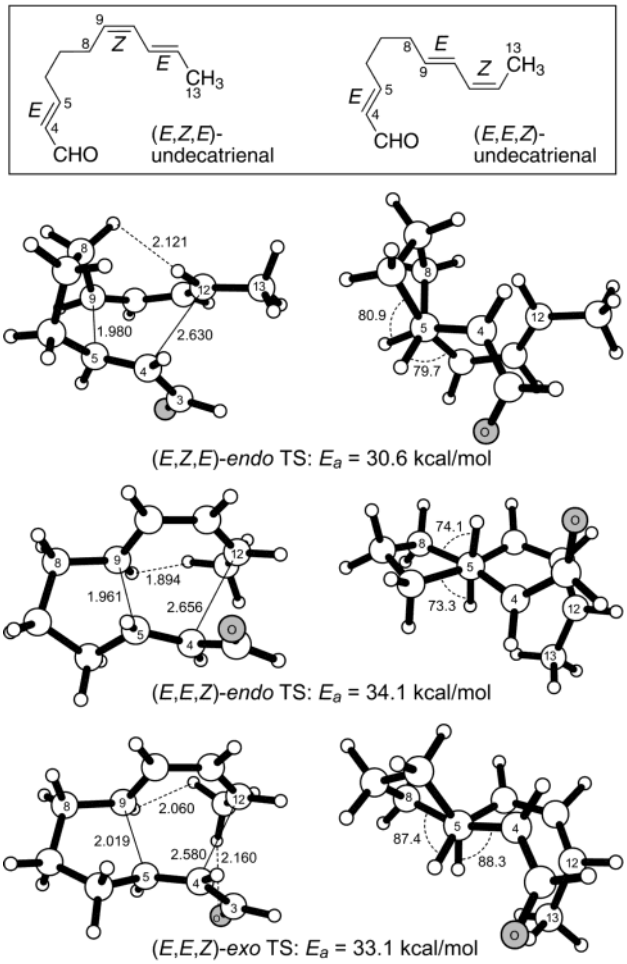
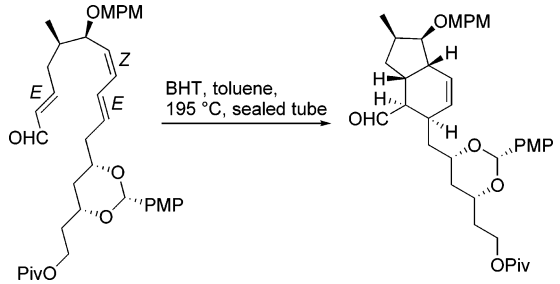


Figure 5. Transition structures for the IMDA reaction of (*E*,*Z*,*E*)- and (*E*,*E*,*Z*)-undecatrienals. Units are in Å (length) or deg (angle). Atom numbers correspond to those of macquarimicins.

To synthesize a tetrahydroindane framework with *cis-anti-cis* ring fusion, the results depicted in Scheme 8 imply that (*E*,*Z*,*E*)-nonatrienes are apparently more useful than (*E*,*E*,*Z*)-nonatrienes in regard to both reactivity and stereoselectivity. To obtain a deep insight into the origin of the observed significant reactivity difference, transition structures (TSs) of the IMDA reactions of (*E*,*Z*,*E*)- and (*E*,*E*,*Z*)-undecatrienal have been theoretically studied by means of DFT (B3LYP) calculations (Figure 5).[31,79]

Electronic energies of transition structures relative to ground states were calculated to be 30.6, 34.1, and 33.1 kcal/mol for (*E*,*Z*,*E*)-*endo*, (*E*,*E*,*Z*)-*endo*, and (*E*,*E*,*Z*)-*exo* TS, respectively.[80] The lower activation barrier for the (*E*,*Z*,*E*)-undecatrienal agrees with experimentally observed higher reactivity of (*E*,*Z*,*E*)-triene **38** as compared with the (*E*,*E*,*Z*)-isomer **39**. On the basis of transition structures shown in Figure 5, we consider that the

(75) The ratio was determined by ^{1}H NMR analysis taken for partly purified mixtures of the cycloadducts.
(76) Two types of isomerization reactions, *E*/*Z* isomerization and a [1,5]-hydrogen shift, are probably involved. The former generates an (*E*,*E*,*E*)-1,6,8-nonatriene to give diastereomeric tetrahydroindanes, while the latter generates an (*E*,*Z*,*E*)-1,7,9-decatriene to give octahydronaphthalenes. The combination of the two isomerization processes, which produces an (*E*,*E*,*E*)-1,7,9-decatriene, is also possible.
(77) For previous discussions on this diastereoselectivity, see ref 37d−f.
(78) Chang and Paquette (ref 24) reported the result shown below. In their study, the formation of another diastereomer was not observed.

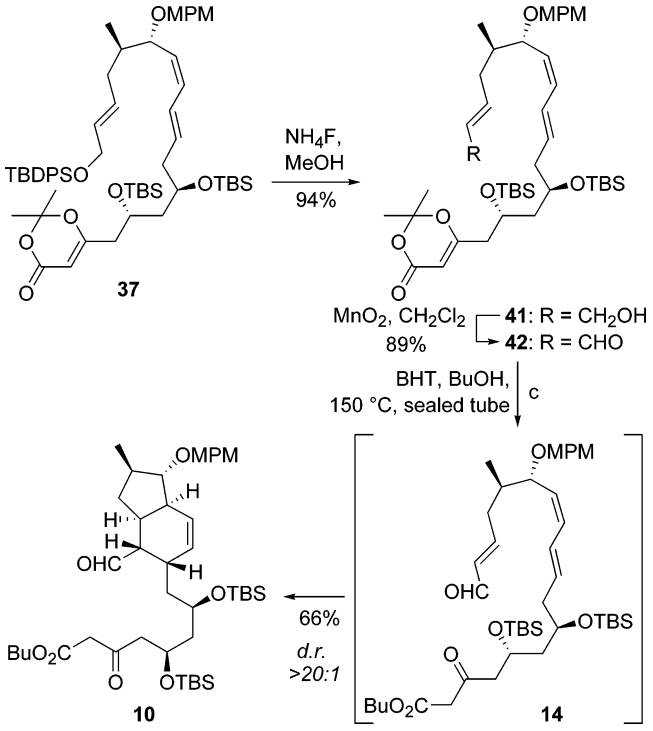


(79) The calculation was carried out using the B3LYP/6-31G(d) level of theory. Vibrational frequency calculations were carried out to ensure the authenticity of the transition structures. The vibration associated with the imaginary frequency was checked to correspond with a movement in the direction of the reaction coordinate.
(80) Energies include zero-point energy corrections.

lower reactivity of (*E*,*E*,*Z*)-triene **39** is predominantly attributable to steric interactions. A nonbonding interaction between H(8)−H(12) [for the (*E*,*Z*,*E*)-isomer] or H(9)−H(13) [for the (*E*,*E*,*Z*)-isomer] exists because of the *s-cis* conformation of the (*E*,*Z*)-diene, which makes the distance between two hydrogen atoms shorter than the sum of van der Waals radii (2.4 Å). This is most prominent in the case of the (*E*,*E*,*Z*)-*endo* TS. In the (*E*,*E*,*Z*)-*exo* TS, the repulsion is somewhat released by rotation around C(12)−C(13), which is not available in the (*E*,*E*,*Z*)-*endo* TS due to another steric interaction between H(4)−H(13). The longer H(8)−H(12) distance in the (*E*,*Z*,*E*)-*endo* TS reduces the steric repulsion, making it the most favorable transition state. An additional nonbonding interaction exists in the (*E*,*E*,*Z*)-*exo* TS between H(13) and the C(3) carbonyl oxygen. In this case, the distance between the two atoms (2.16 Å) is remarkably shorter than the sum of van der Waals radii (2.6 Å).[81] Strains in the forming cyclopentane ring do not seem to be the determining factor because Newman projections of a C(5)−C(9)-forming bond suggest a twist-mode asynchronicity[82,83] of (*E*,*E*,*Z*)-TSs similar to that of (*E*,*E*,*E*)-counterparts.[84] For example, Roush and co-workers reported two examples of IMDA reactions in which (*E*,*E*,*E*)-1,6,8-nonatrienes possessing a similar substitution pattern to **39** reacted at 85 and 110 °C.[85] Considering the above discussions together, the reactivity difference between **38** and **39** seems to originate from the steric repulsions in the transition states, although further experimentation is required to confirm the generality of the reactivity order.

Confirming the feasibility of the IMDA reaction using (*E*,*Z*,*E*)-trienes, we advanced to the IMDA substrates **14**−**17**. The case of **14**, the IMDA substrate in path A (Scheme 3), is depicted in Scheme 9. The Stille coupling product **37** was treated with ammonium fluoride in MeOH[86] to remove the TBDPS group selectively. The resultant primary alcohol **41** was oxidized with MnO_2 in CH_2Cl_2 to give α,β-unsaturated aldehyde **42**. Heating of **42** at 150 °C in 1-butanol in a sealed tube for 6 h resulted in the formation of cycloadduct **10**[74] through the IMDA reaction of transient **14**, generated by thermolysis of the dioxinone ring in **42** via a retro hetero Diels−Alder reaction.[87]

Scheme 9. Intramolecular Diels−Alder Reaction of **14**



Although the yield of the cycloaddition was moderate (66%) due to the instability of the β-ketoester moiety,[88] the reaction proceeded with a diastereoselectivity higher than 20:1.[89]

We next examined the IMDA reaction corresponding to path B in Scheme 3. To synthesize the IMDA substrate **15**, the Stille coupling of (*Z*)-stannylalkene **18** and (*E*)-iodoalkene **20** was undertaken (Scheme 10).[90] Subsequent removal of the TBDPS group in the coupling product and oxidation of the resultant allylic alcohol **43** with MnO_2 provided the IMDA substrate **15**. The IMDA reaction of **15** occurred at 150 °C, providing four cycloadducts. The major cycloadduct was characterized to be **11**[74] (81%), and one of the other cycloadducts was found to be diastereomer **44**[74] (6%). Interestingly, the other product proved to be a mixture of hetero Diels−Alder cycloadducts **45** (9% as a 3:2 mixture of diastereomers). Although a large number of reports on the intramolecular hetero Diels−Alder reaction have been reported,[91] to the best of our knowledge, this is the first example of the isolation of a hetero cycloadduct as a byproduct in the "normal" IMDA reaction of 1,6,8-nonatrienes or 1,7,9-decatrienes.

We then investigated the behavior of the mixture **45** under the same thermal conditions because this compound implies the

(81) Even though this interaction is absent in the *s-trans* conformation for the (*E*,*E*,*Z*)-*exo* TS, the *s-cis* conformation was proved to have lower energy, reflecting the general *s-cis* preference in the Diels−Alder reactions. For example, in the Diels−Alder reaction of butadiene and acrolein, it is reported that the *s-cis* conformation is preferred to the *s-trans* conformation in either the *endo* or the *exo* transition state by 1.3 or 1.8 kcal mol^{-1}, respectively (B3LYP/6-31G(d)): (a) García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415−2420. (b) Kong, S.; Evenseck J. D. *J. Am. Chem. Soc.* **2000**, *122*, 10418−10427.

(82) In the early 1980s, the importance of asynchronous transition states was proposed for interpreting the *endo*-selectivity of the IMDA reactions of (*E*,*E*,*E*)-nonatrienes: (a) Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696−6704. (b) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273−2280. (c) Taber, D. F.; Campbell, C.; Gunn, B. P.; Chiu, I.-C. *Tetrahedron Lett.* **1981**, *22*, 5141−5144.

(83) Houk and Brown introduced the concept of the "twist-asynchronous" model, in which a torque applied to the forming bond by the connecting chain plays an important role: Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297−2300. See also: (a) Lin, Y.-T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2269−2272. (b) Wu, T.-C.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2293−2296. (c) Lin, Y.-T.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2517−2520.

(84) (a) Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796−4804. (b) Brown, F. K.; Raimondi, L.; Houk, K. N.; Bock, C. W. *J. Org. Chem.* **1992**, *57*, 4862−4869.

(85) (a) Roush, W. R.; Wada, C. K. *J. Am. Chem. Soc.* **1994**, *116*, 2151−2152. (b) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S. *Tetrahedron Lett.* **1987**, *28*, 2447−2450.

(86) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177−1180.

(87) (a) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105−5108. (b) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431−2435. (c) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360−12361.

(88) The major side reaction was the formation of a methyl ketone, resulting from the loss of the butoxycarbonyl group in **10**.

(89) A cycloadduct, likely to be a diastereomer, was also isolated in a smaller amount of 2%. However, we were not able fully to characterize this minor product due to the contamination of another byproduct, which was hardly removed by silica gel chromatography.

(90) This reaction was conducted prior to the optimization of the Stille coupling conditions.

(91) For some examples of the construction of the 5-6 bicyclic system by an intramolecular hetero Diels−Alder reaction, see: (a) Schreiber, S. L.; Meyers, H. B. *J. Am. Chem. Soc.* **1988**, *110*, 5198−5200. (b) Tietze, L. F.; Denzer, H.; Hodgrün, X.; Neumann, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1295−1297. (c) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467−6471. (d) Takano, S.; Ohkawa, T.; Tamori, S.; Satoh, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 189−191. (e) Tietze, L. F.; Brumby, T.; Pfeiffer, T. *Liebigs Ann. Chem.* **1988**, 9−12. (f) Shrestha, K. S.; Honda, K.; Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 73−83.

Scheme 10. Intramolecular Diels–Alder Reaction of **15**

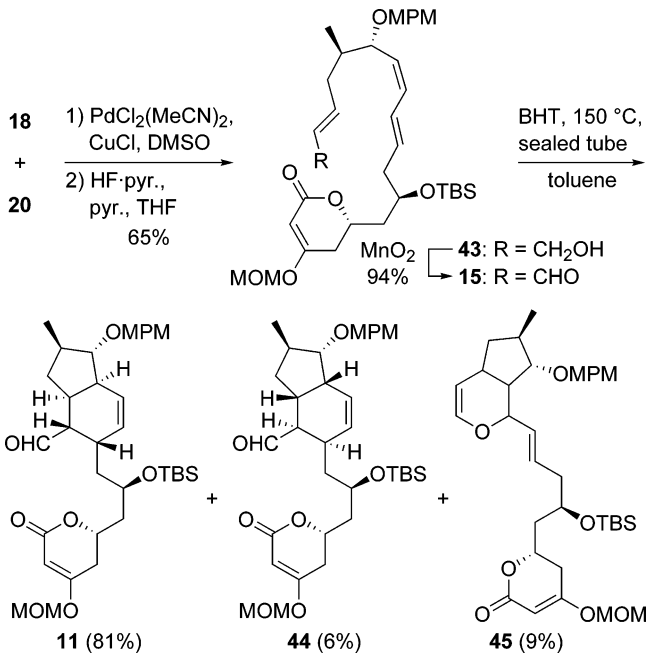
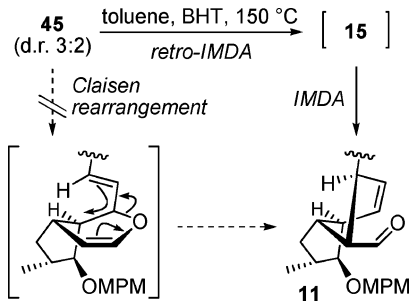


Table 3. Thermal Conversion of **45** to **11**



	ratio[a]		
time (h)	**45**	**15**	**11**
0	100	0	0
9	87	8	5
34	43	3	54
60	19	4	77

[a] Determined by ^{1}H NMR analysis of the reaction mixture.

possible involvement of the hetero IMDA/Claisen rearrangement pathway[92] in the conversion of **15** to **11** or **44** (Table 3). The results shown in Table 3 suggest the direct formation of both **11** and **44** from **15** but not via **45**. On heating of **45** at 150 °C, formation of the cycloadduct **11** and the IMDA substrate **15** was indeed observed. Although **45** was a 3:2 diastereomeric mixture, **11** was formed stereoselectively, and only a trace amount of **44** was observed in the ^{1}H NMR analysis of the crude mixture. Considering the formation of **15** and the diastereoselectivity, it is reasonable to conclude that the conversion of **45** to **11** proceeds via the retro hetero IMDA/IMDA sequence but not via Claisen rearrangement.[93] Additionally, as the reaction of **15** leading to **11** (8 h) is much faster than that of **45** to **11**, the latter is unlikely to be the primary pathway of the former reaction.

Next, we examined the IMDA reaction via path C in Scheme 3, the TADA of **16**. In addition to the substrate **16**, we prepared another substrate **49**, which bears MOM groups for the protection of the 1,3-diol part (Scheme 11). Thus, the primary alcohol **41** was converted into methyl carbonate **46**. From **46**, the TADA substrates **16** and **49** were synthesized independently. Thermolysis of **46** in the presence of MeOH afforded β-keto ester **47a** in nearly quantitative yield. Alternatively, two TBS groups in **46** were removed with HF·pyr., and the resultant diol was protected as di-MOM ether. Thermolysis of this compound as conducted for **46** gave another β-keto ester **47b**. The Pd(0)-catalyzed macrocyclization[94,95] of allyl carbonate **47a** or **47b** was successfully carried out to form the desired 17-membered macrocycles **48a** or **48b** (both as ca. 3:2 diastereomeric mixtures), respectively, using $Pd(PPh_3)_4$/dppe (1:1) as a catalyst.[96] Introduction of a conjugate double bond into **48a** or **48b** was then successfully carried out by a phenylselenenylation-oxidation sequence[97,98] to give the TADA substrate **16** or **49**, respectively, with a high geometric ratio (>20:1) in favor of the desired (*Z*)-isomer.[74,99]

The TADA reactions of **16** and **49** proceeded at 130 °C. In contrast to the IMDA reactions of **14** and **15**, both **16** and **49** gave mixtures of at least five cycloadducts without remarkable stereoselectivity and in unpractical yields.[100] As mentioned above, theoretically, the (*E*,*Z*,*E*)-trienes only attain *endo* transition states affording two diastereomers. Thus, an alkene isomerization or regioisomeric IMDA reaction must be involved in the TADA reactions of **16** and **49**. Inspection of ^{1}H NMR spectra suggested that most of the cycloadducts possess newly formed carbon–carbon bonds between C(4)–C(12) and C(5)–C(9). Thus, the minor products probably arose from alkene isomerization of the substrates. Although isolation and characterization of all of the products were quite difficult, we were able to elucidate the stereochemistry of the major cycloadducts obtained in both TADA reactions. In the case of **16**, the desired cycloadduct **12** was not obtained. The diastereomer **51a**[74] and

(92) For examples of Claisen rearrangement in related systems, see: (a) Büchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126–3133. (b) Ireland, R. E.; Godfrey, J. D.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1981**, *103*, 2446–2448. (c) Childers, W. E., Jr.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 5277–5279. (d) Turos, E.; Audia, J. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8231–8236. (e) Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343–1345.

(93) Burke and co-workers have reported a retro hetero IMDA/IMDA reaction in an attempted Claisen rearrangement: Burke, S. D.; Armistead, D. M.; Shankaran, K. *Tetrahedron Lett.* **1986**, *27*, 6295–6298.

(94) (a) Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3864–3867. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867–3868. (c) Trost, B. M.; Ohmori, M.; Boyd, S. A.; Okawara, H.; Brickner, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8281–8284. (d) Review: Trost, B. M. *Anvew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173–1192.

(95) For recent applications, see: (a) Reference 21. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825. (c) Hoffmann, H. M. R.; Pohlmann, J. *Tetrahedron Lett.* **1998**, *39*, 7085–7088. (d) Fürstner, A.; Krause, H. *J. Org. Chem.* **1999**, *64*, 8281–8286. (e) Yuasa, H.; Makado, G.; Fukuyama, Y. *Tetrahedron Lett.* **2003**, *44*, 6235–6239.

(96) The use of the corresponding acetate instead of the carbonate **47a** also afforded macrocycle **48a** ($Pd(PPh_3)_4$, dppe, BSA, THF, reflux). However, the yield was capricious (51–86%) due to the formation of a terminal diene, which was formed via the β-hydride elimination of the intermediary π-allylpalladium complex. For the use of carbonates in Pd-catalyzed allylic alkylation, see: Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523–1529.

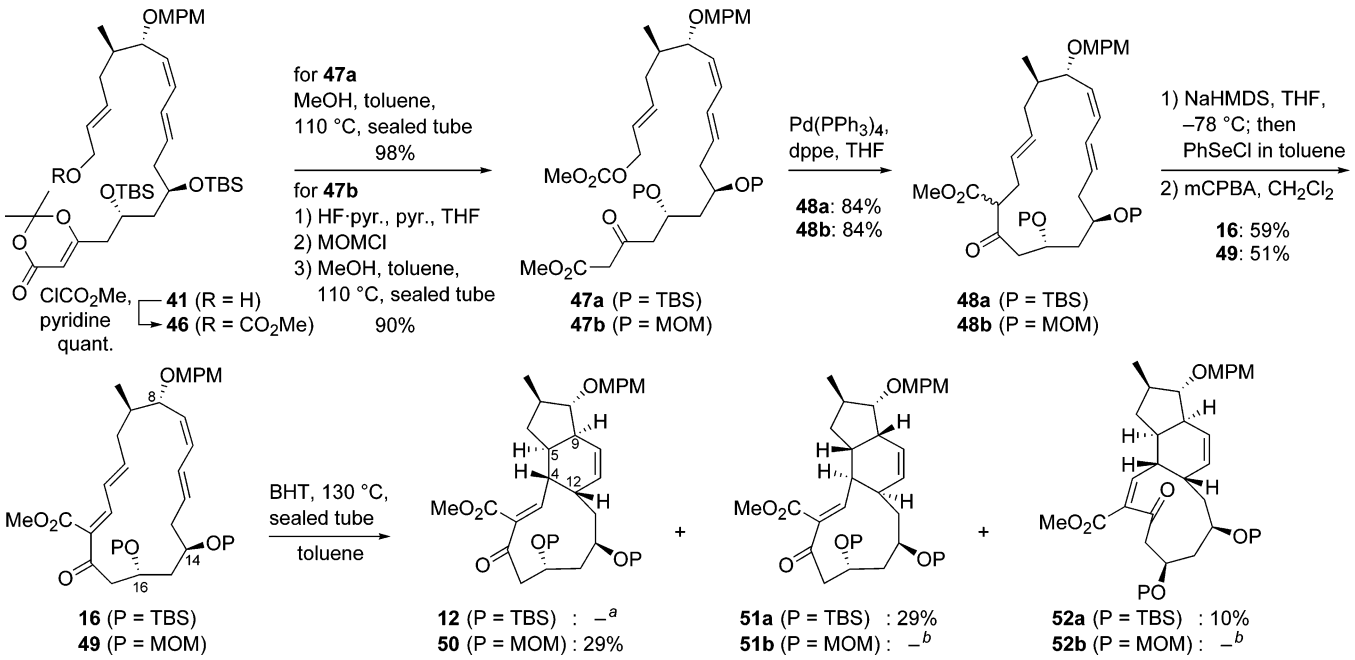
(97) In the selenenylation reaction, addition of PhSeCl as a toluene solution, not a THF solution, was essential for maintaining reproducibility.

(98) Although the intermediary selenide was a diastereomeric mixture (ca. 2:1), virtually one geometrical isomer was formed through the oxidation/*syn*-elimination process.

(99) We explored the synthesis of **16** from the aforementioned linear α,β-unsaturated aldehyde **14** in a more straightforward manner by employing the intramolecular Knoevenagel reaction. However, the desired 17-membered carbocycle was not obtained despite extensive exploration.

(100) In addition to **16** and **49**, we also examined a TADA substrate without protecting groups for the 1,3-diol moiety. However, the TADA substrate in this case decomposed under the thermal conditions (150 °C).

Scheme 11. Synthesis and Transannular Diels–Alder Reaction of **16** and **49**[a]



[a] (a) Not observed. (b) A small amount (<10%) of these products might be generated.

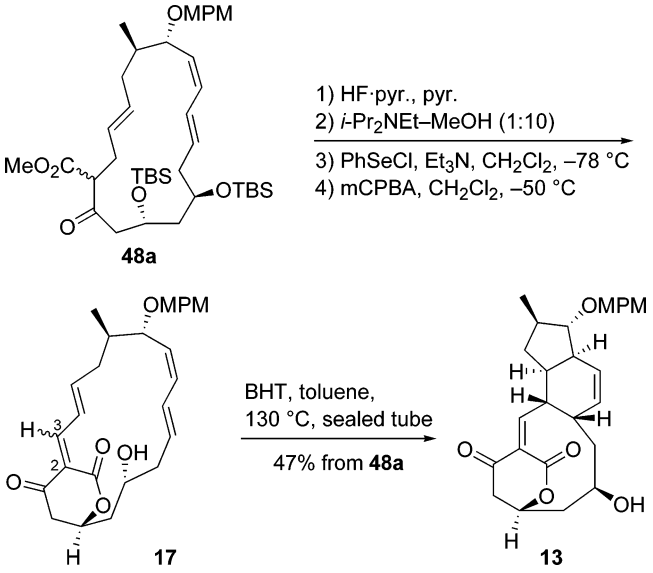
geometrical isomer **52a**[74] were isolated as the major products. On the other hand, the TADA reaction of the MOM-protected substrate **49** provided the desired **50**[74] as the major product despite a low yield of 29%. Small amounts of isomeric cycloadducts, presumably **51b** and **52b**, were formed, although we were not able to isolate them in pure form.

The unsuccessful results obtained from the TADA reactions using the substrates **16** and **49** are considered to be attributable to easy alkene isomerization. Regarding the TADA substrates **16** and **49**, their macrocyclic structure seems to accelerate undesired side reactions such as alkene isomerization. In fact, **16** and **49** isomerized at 130 °C, while the linear IMDA substrates **14**, **15**, and **38** successfully afforded the corresponding cycloadducts even at a higher reaction temperature (150 °C). These phenomena are not in accord with the generally accepted recognition that the TADA reaction using (*E*,*Z*)-dienes proceeds more efficiently than the IMDA counterpart.[40]

Although the yields were disappointing, we were interested in the stereochemical outcome of these TADA reactions. As in the case of **38** (Figure 4), the diastereocontrol induced by the C(8) stereogenic center in **16** and **49** may make the transition states leading to **12** and **50** favorable. However, the TADA substrates **16** and **49** preferably provided the cycloadducts **51a** and **50**, respectively. These results could be explained by considering the following two competing steric interactions. In the case of the TADA reaction of **16**, the diastereocontrol induced by the bulky OTBS groups at C(14) and C(16) probably exceeded that induced by the C(8) substituent, resulting in the formation of the undesired cycloadduct **51a**. On the other hand, the smaller OMOM groups in **49** might have decreased the unfavorable steric interaction, resulting in the formation of **50** under the diastereocontrol induced by the C(8) OMPM group.

Finally, we examined the IMDA reaction of substrate **17**, indicated as path D in Scheme 3 (Scheme 12). The substrate **17** was synthesized from **48a** in a three-step sequence: (1) deprotection of the TBS groups, (2) lactonization under basic

Scheme 12. Transannular Diels–Alder Reaction of **17**



conditions,[101] and (3) introduction of the C(2)–C(3) double bond.[102] The TADA substrate **17** showed a complicated ^{1}H NMR spectrum, making determination of the *E*/*Z* ratio extremely difficult. We attribute this complication to the presence of tautomers such as a hemiketal form and/or rotamers, in addition to geometrical isomers about the C(2)–C(3) double bond. By heating the macrocycle **17** to 130 °C, the desired tetracyclic compound **13**[74] was obtained as a sole cycloadduct in an overall yield of 47% from **48a**. No diastereomer or geometrical isomer was obtained. Contrary to the TADA reactions of the macro-

(101) Under acidic conditions, the desired δ-lactone was not obtained; however, β-elimination of the C(16)–OH occurred to form a (*Z*)-α,β-unsaturated ketone substructure.

(102) We also investigated the synthesis of **17** through a macroallylation strategy applied to an allyl acetate or carbonate bearing the preexisting β-keto-δ-lactone ring, but the yield of the macroallylation product was lower (ca. 30%) as compared to that obtained from the corresponding β-ketoester derivative **47a** (84%).

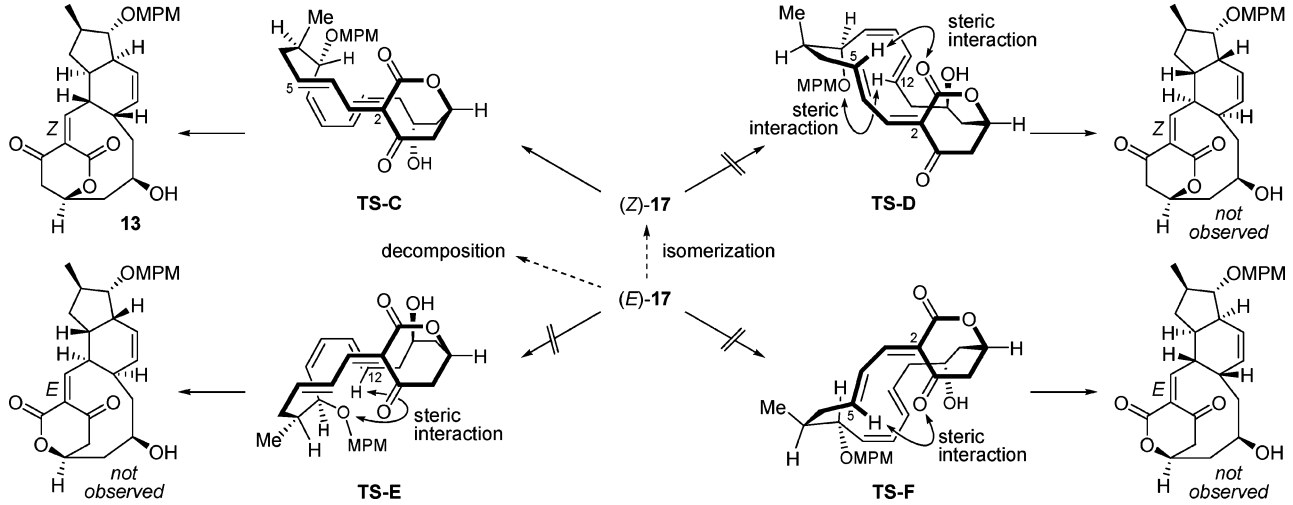


Figure 6. Plausible mechanisms for the stereoselectivity in the TADA of **17**.

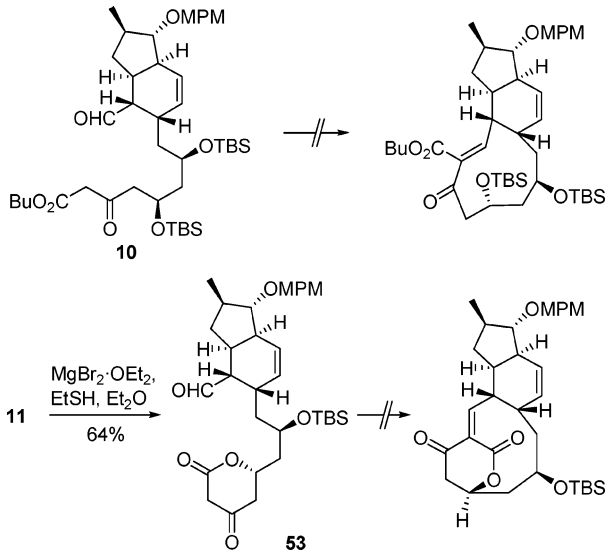
cycles **16** or **49**, the TADA reaction of **17** proceeded successfully to give **13** highly stereoselectively.

The stereochemical outcome observed in the TADA reaction of **17** can be rationalized as follows (Figure 6). Considering the (2*Z*)-isomer (*Z*)-**17**, two *endo* transition states, **TS-C** with *s-trans* conformation through C(2)−C(5) and **TS-D** (with *s-cis*), are possible. Comparing the two transition states, **TS-C** seems to be considerably more favorable, considering that two severe steric interactions are present in **TS-D**. One is a repulsion generated between the OMPM group and H(12) as explained for the stereoselectivity observed in the IMDA reactions of **14**, **15**, and **38** (Figure 4). The other is a repulsion between H(5) and the lactone carbonyl oxygen. The cycloadducts derived from the (2*E*)-isomer, (*E*)-**17**, were not observed. Each *endo* transition state from (*E*)-**17**, **TS-E** or **TS-F**, suffers from one of the two steric interactions present in **TS-D**. As both TADA transition states seem to be disfavored, the (*E*)-**17**, if it existed, might isomerize to its (*Z*)-isomer rather easily or decompose under the reaction conditions.

The IMDA reactions of **14**−**17** proceeded at 130 °C or higher temperatures. The low reactivity of these substrates contrasts with the facts reported by the groups of Sorensen[21] and Evans[22] regarding their total synthesis of FR182877. In their cases, a tandem transannular Diels−Alder sequence proceeded at 40 and 50 °C, respectively. On the basis of these observations, the two groups indicated the possibility that FR182877 is biosynthesized spontaneously from a monocyclic precursor through the cycloaddition cascade. Assuming the involvement of an IMDA reaction in the biosynthesis of macquarimicins and cochleamycins, a spontaneous cycloaddition at ambient temperature seems to be difficult considering the lower reactivity of (*E*,*Z*,*E*)- or (*E*,*E*,Z)-1,6,8-nonatrienes observed in this study. Although we still have no evidence, some kind of acceleration may participate in the biosynthetic IMDA process for the macquarimicin and cochleamycin cases.

Completion of the Total Synthesis. To achieve the total synthesis of macquarimicins, transformations of the aforementioned cycloadducts were investigated. As summarized in Scheme 3, we first explored the intramolecular Knoevenagel reaction for **10** and **11** to construct the 10-membered carbocycle (C-ring) of **1** (Scheme 13). The exposure of **10** or **53**, the latter

Scheme 13. Examination of the Intramolecular Knoevenagel Reaction for **10** and **53**



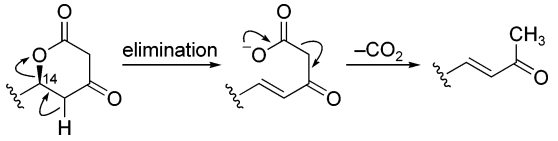
prepared from **11** by removal of the MOM group with $MgBr_2 \cdot OEt_2$ and EtSH in Et_2O,[103] to a variety of conditions[104] provided none of the desired cyclized products. The β-keto-δ-lactone moiety in **53** proved to be labile under the conditions employed, resulting in the formation of an α,β-unsaturated methyl ketone.[105]

Our attention was next focused on the construction of the tetracyclic framework of **1** from the TADA cycloadduct **50**. The MPM group in **50** was first removed with DDQ, and the

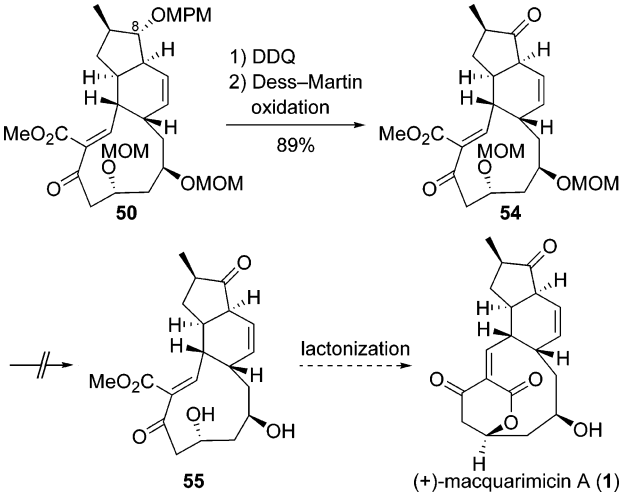
(103) The deprotection, proceeding in 64% yield, accompanied the formation of a dithioacetal.

(104) We examined a variety of reagents such as amino acids (β-alanine, L-proline), amines (piperidine, pyrrolidine), ammonium salts (ethylenediamine diacetate, piperidinium acetate), and combinations of a Lewis acid and an amine ($TiCl_4$/pyridine, $MgBr_2 \cdot OEt_2$/lutidine).

(105) The α,β-unsaturated ketone might be produced by sequential β-elimination and decarboxylation as shown below.



Scheme 14. Attempt To Convert the Cycloadduct **50** to Macquarimicin A (**1**)



resultant C(8)−OH was oxidized with Dess−Martin periodinane to give ketone **54** (Scheme 14). Deprotection of two MOM groups in **54** would provide diol **55**, which would be followed by lactonization to afford, eventually, macquarimicin A (**1**). Unfortunately, treatment of **54** with Brønsted or Lewis acid (HCl, CF_3CO_2H, *B*-bromocatecholborane, TMSBr, or BBr_3) provided neither diol **55** nor **1**. We did not conduct further exploration using **50** due to its low yield observed in the TADA reaction of **49**.

Finally, the total synthesis of **1** from **13**, the TADA cycloadduct equipped with the ABCD ring, was investigated. Protection of the C(14)−OH in **13** as a TES ether, followed by removal of the MPM group, gave **56** (Scheme 15). Dess−Martin oxidation of **56** and subsequent PPTS-catalyzed cleavage of the TES ether afforded (+)-macquarimicin A (**1**) uneventfully. The spectral properties (^{1}H and ^{13}C NMR and IR) of synthetic (+)-**1** were completely identical to those of a natural sample, and optical rotation of synthetic (+)-**1** ($[\alpha]^{23}_D = +270$; *c* 0.20, MeOH) established the absolute configuration of natural (+)-**1** ($[\alpha]^{25}_D = +285.6$; *c* 0.2, MeOH).[3] Furthermore, extensive NOE experiments on synthetic (+)-**1** revealed that the C(2)−C(3) geometry must be *Z* but not *E* as was originally reported[1b,106] (Figure 7).

To complete the total synthesis of other members of macquarimicins, the conversion of macquarimicin A (**1**) into macquarimicin B (**2**) and then C (**3**) was attempted. On treatment of **1** with 2-methoxypropene in THF−H_2O, the expected intermolecular hetero Diels−Alder reaction took place smoothly, and then spontaneous hydrolysis of the transient cycloadduct occurred to provide **2** in a good yield of 83%. To convert **2** to **3**, a dehydrative transannular alkylation is required. Assuming that C(14) of **3** has the same stereochemistry as cochleamycin B (**6**), the configuration of C(14) in **2** must be inverted through the cyclization. In fact, the desired transformation was effected by treatment of **2** with CSA in dichloromethane to produce **3** quantitatively. The stereoselectivity of the two reactions from **1** to **3** is well explained as depicted in Figure 8. In the hetero

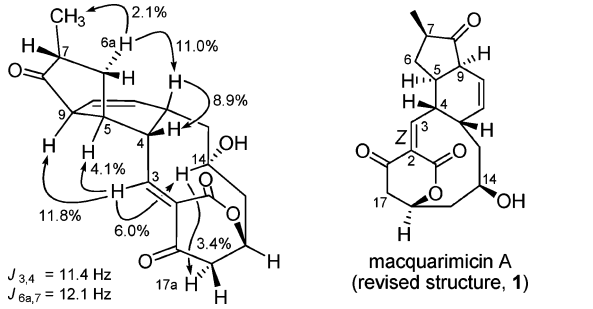
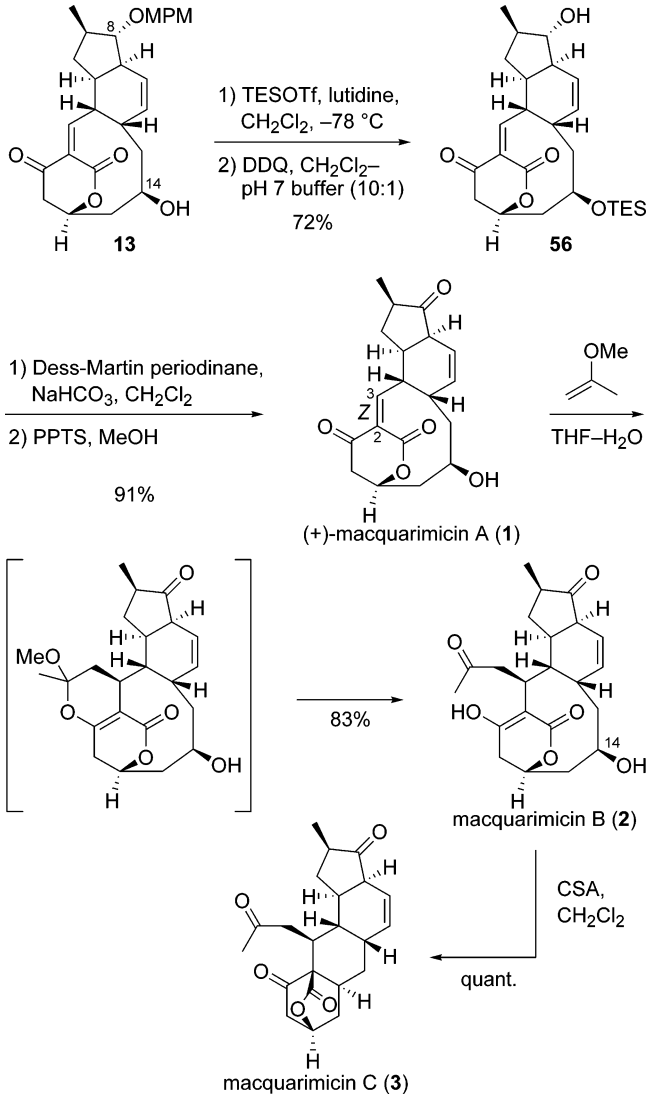


Figure 7. NOE experiments of **1**.

Scheme 15. Total Synthesis of Macquarimicins



Diels−Alder reaction of **1** with 2-methoxypropene,[107] the dienophile approaches from the outer side of the C ring in **1**, and this means the stereochemistry at C(3) in **2** is the same as the natural product. As an AM1 calculation[31] suggests the efficient overlap of $\pi(C_2-C_{18})$ and $\sigma^*(C_{14}-OH_2^+)$ orbitals in

(106) As shown in Figure 7, irradiations at H(3) and H(14) led to the enhancement of the signals of H(14) and H(17a), respectively. These results indicate that the three hydrogen atoms are located on the same side of the 10-membered ring. Therefore, the C(2)−C(3) geometry was determined to be *Z*.

(107) For examples of hetero Diels−Alder reactions using 2-methoxypropene as a dienophile, see: (a) Sato, M.; Kano, K.; Kitazawa, N.; Hisamichi, H.; Kaneko, C. *Heterocycles* **1990**, *31*, 1229−1232. (b) Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 707−709. (c) Nair, V.; Tressa, P. M. *Tetrahedron Lett.* **2001**, *42*, 4549−4551.

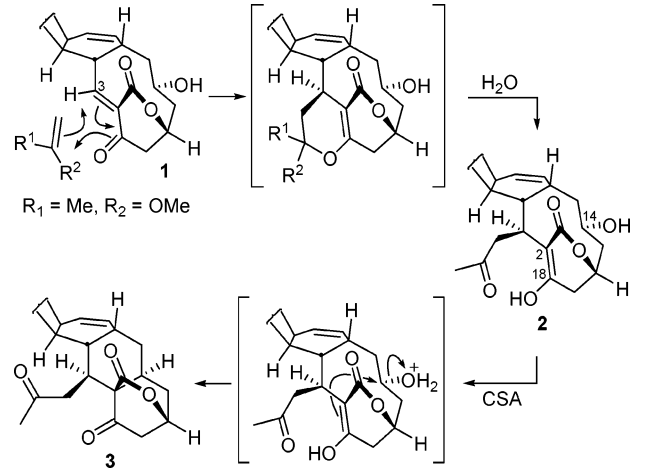
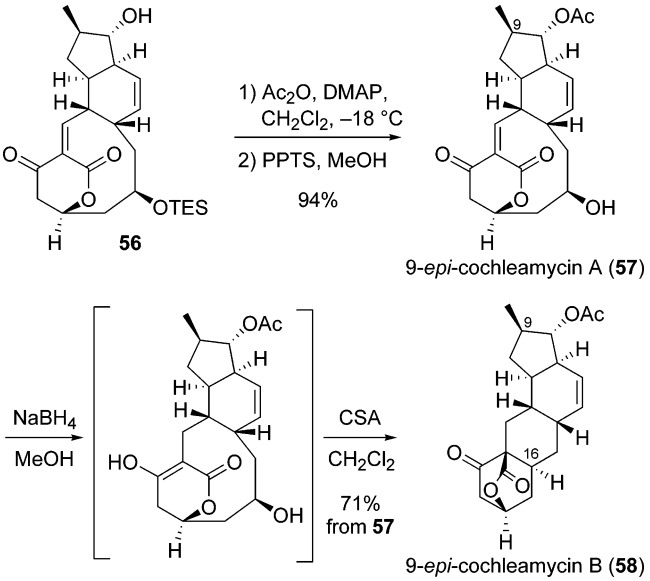


Figure 8. Plausible mechanism of the stereoselectivity observed in the transformation of **1** to **3**.

Scheme 16. Synthesis of 9-*epi*-Cochleamycins



protonated **2**, the transannular alkylation proceeds in an S_N2 manner to produce **3** with complete inversion of the configuration as shown in the second brackets.

To test the applicability of the transformation of **1** to **3** developed above, we explored the synthesis of the 9-*epi* series of cochleamycin (Scheme 16). The hydroxyl group in **56** was acetylated using Ac_2O and DMAP in CH_2Cl_2.[108] The TES group of the resultant acetate was removed with PPTS in MeOH to produce 9-*epi*-cochleamycin A (**57**). The ^1H NMR spectrum of **57** showed a pattern similar to that of cochleamycin A (**4**) except signals for the A-ring. The 1,4-hydride addition to **57** with $NaBH_4$ produced a transient β-keto-δ-lactone derivative, which was immediately converted into 9-*epi*-cochleamycin B (**58**) with CSA in 71% yield from **57**.

The stereochemistries of C(14) of **3** and C(16) of **58** were both determined to be *S* based on NOE difference experiments as shown in Figure 9. Thus, it was established that **3** has the same stereochemistry as cochleamycin B (**6**) and B2 (**7**). From these results, **6** and **7** might be synthesized stereoselectively

(108) The use of usual conditions such as Ac_2O/pyridine or AcCl/Et_3N/CH_2Cl_2 led to complex mixtures.

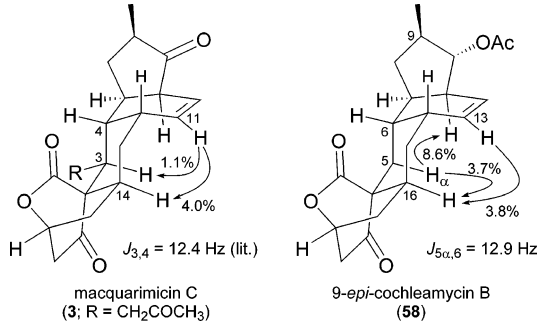


Figure 9. NOE experiments on **3** and **58**.

from cochleamycin A (**4**) and A2 (**5**), respectively, by employing the conditions developed for the transformation of **57** into **58**.

Conclusion

The first total syntheses of the macquarimicins A−C (**1**−**3**) and unnatural 9-*epi*-cochleamycins A (**57**) and B (**58**) have been accomplished. The key step in their total syntheses is the construction of the unique polycyclic molecular framework by a biosynthesis-based intramolecular Diels−Alder reaction. To synthesize the IMDA substrates (**14**−**17**) with the (*Z*,*E*)-diene moiety, a convergent union of a variety of intermediates by a modified Stille coupling strategy was successfully applied. The IMDA reactions including TADA reactions conducted using (*E*,*Z*,*E*)-1,6,8-nonatrienes are quite beneficial in the field of complex natural product synthesis. A model study comparing the reactivity of (*E*,*Z*,*E*)- and (*E*,*E*,*Z*)-1,6,8-nonatrienes was performed. It implied the potential advantage of the (*E*,*Z*,*E*)-trienes for the construction of *cis*-*anti*-*cis* tetrahydroindanes. In the present synthesis, (+)-macquarimicin A (**1**) was synthesized with 40 total steps and 27 linear steps from either **22** or **30** in 4.3% or 9.9% overall yields, respectively (92% or 89% average yield per step, respectively). Macquarimicins B (**2**) and C (**3**) were also synthesized from **1** in one or two more steps, respectively, guided by a hypothetical biosynthetic pathway. The present total synthesis reveals the intrinsic reactivity of these natural products. The seven to nine stereogenic centers in the macquarimicins and 9-*epi*-cochleamycins were constructed by five diastereoselective transformations in a completely stereoselective manner, utilizing the two stereogenic centers in the starting materials **22** and **30**. In addition, the present work established the absolute configuration of (+)-**1** and the relative configuration of **3** and revised the C(2)−C(3) geometry of **1**.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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