

Synthetic Study of Macquarimicins: Highly Stereoselective Construction of the AB-Ring System

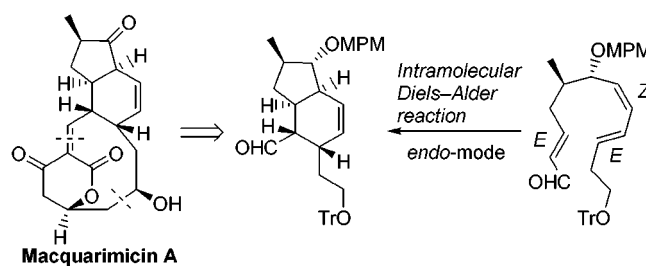
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ABSTRACT



The highly stereoselective synthesis of the AB-ring system of macquarimicins, a novel class of microbial metabolites with inhibitory activity for neutral sphingomyelinase, has been achieved. The present synthesis features the highly stereocontrolled construction of the *cis*-tetrahydroindan structure via the intramolecular Diels–Alder reaction of an (*E,Z,E*)-1,6,8-nonatriene derived from *D*-glyceraldehyde acetonide.

The macquarimicins A–C (**1–3**, Figure 1) were isolated from the fermentation broths of *Micromonospora chalcea* by a group at Abbott Laboratories in 1995.¹ Macquarimicins B and C were found to display cytotoxicity against the leukemia cell line P388. Later, researchers at Sankyo Co., Ltd. discovered that macquarimicin A is a selective inhibitor of membrane-bound neutral sphingomyelinase (N-SMase)

from rat brain.² Inhibitors of N-SMase recently have been stimulating considerable interest since it has been suggested that they might have clinical potential in pathologies such as inflammatory and autoimmune diseases.³ The unique structures of the macquarimicins comprise a *cis*-tetrahydroindanone ring, a β -keto- δ -lactone ring, and (for macquarimicins A and B) a 10-membered carbocycle (the CD-ring). Closely related antibiotics called cochleamycins have

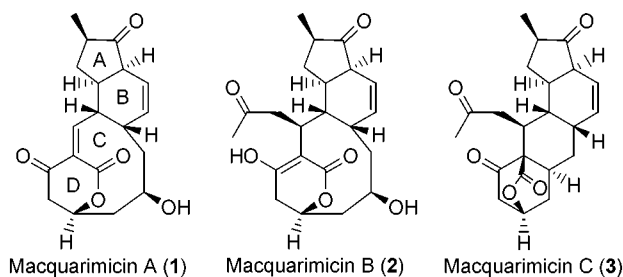


Figure 1. Structures of macquarimicins.

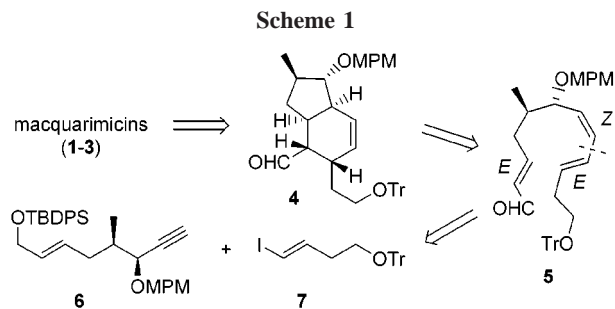
(1) (a) Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Rasmussen, R. R.; Hensey, D. M.; Humphrey, P. E.; Swanson, S. J.; Barlow, G. J.; Premachandran, U.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 462–466. (b) Hochlowski, J. E.; Mullally, M. M.; Henry, R.; Whittern, D. M.; McAlpine, J. B. *J.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

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

(3) (a) Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871–7892. (b) Nara, F.; Tanaka, M.; Masuda-Inoue, S.; Yamasato, Y.; Doi-Yoshioka, H.; Suzuki-Konagai, K.; Kumakura, S.; Ogita, T. *J. Antibiot.* **1999**, *52*, 531–535. (c) Uchida, R.; Tomoda, H.; Dong, Y.; Omura, S. *J. Antibiot.* **1999**, *52*, 572–574. (d) Tanaka, M.; Nara, F.; Yamasato, Y.; Ono, Y.; Ogita, T. *J. Antibiot.* **1999**, *52*, 827–830. (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.

been discovered, and their biosynthesis via an intramolecular Diels–Alder (IMDA) reaction has been proposed.⁴ The intriguing biological activity and structures of macquarimicins have prompted us to work toward their total synthesis and determination of their unknown absolute configuration. Herein, we report the synthesis of the AB-ring system of macquarimicins, featuring the highly stereoselective construction of the framework through the IMDA reaction of an (*E,Z,E*)-1,6,8-nonatriene derivative. Compared to (*E,E,E*)- or (*Z,E,E*)-trienes, (*E,Z,E*)-trienes have been far less utilized in IMDA reactions due to their lower reactivity and the possibility of a side reaction such as olefin isomerization.^{5,6} Despite these drawbacks, we considered the IMDA reactions of (*E,Z,E*)-trienes to be synthetically valuable as they are known to attain only the *endo*-transition state, leading to *cis*-fused cycloadducts.⁷ In our study, we anticipated that the reaction would be effected by designing appropriate substrates.

Our retrosynthetic analysis for macquarimicins is shown in Scheme 1. It was expected that **4**, an advanced intermedi-



ate for the macquarimicin synthesis, would be synthesized through the diastereoselective IMDA reaction of (*E,Z,E*)-triene **5**. The triene **5** could become available from alkyne **6** and (*E*)-vinyl iodide **7** via Sonogashira coupling followed by semi-hydrogenation of the triple bond.

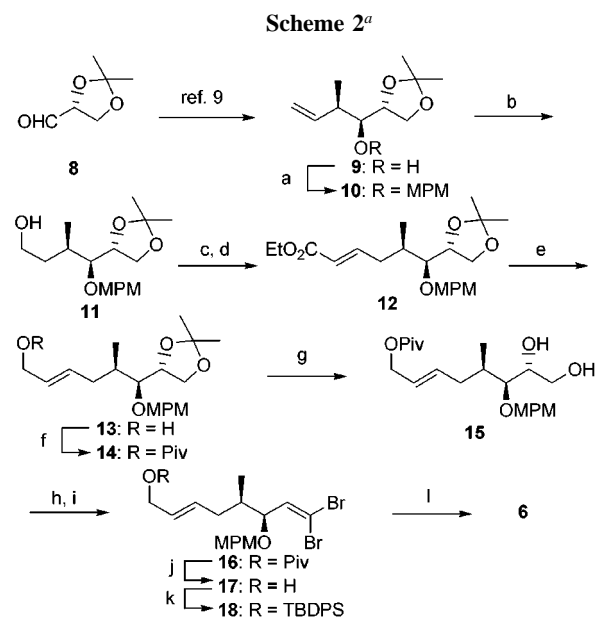
(4) (a) Shindo, K.; Matsuoka, M.; Kawai, H. *J. Antibiot.* **1996**, *49*, 241–243. (b) Shindo, K.; Iijima, H.; Kawai, H. *J. Antibiot.* **1996**, *49*, 244–248. (c) Shindo, K.; Sakakibara, M.; Kawai, H. *J. Antibiot.* **1996**, *49*, 249–252.

(5) For some 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**, *53*, 14179–14233. (e) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 464–474.

(6) For some IMDA reactions using (*E,Z,E*)-trienes, see: (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061–1070. (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) Yoshioka, M.; Nakai, H.; Ohno, M. *J. Am. Chem. Soc.* **1984**, *106*, 1133–1135. (f) Wattanasin, S.; Kathawala, F. G.; Boeckman, R. K., Jr. *J. Org. Chem.* **1985**, *50*, 3810–3815. (g) Diedrich, M. K.; Klärner, F.-G. *J. Am. Chem. Soc.* **1998**, *120*, 6212–6218. (h) Back, T. G.; Payne, J. E. *Org. Lett.* **1999**, *1*, 663–665. (i) Back, T. G.; Nava-Salgado, V. O.; Payne, J. E. *J. Org. Chem.* **2001**, *66*, 4361–4368.

(7) Very recently, effective utilization of Lewis acid catalysts in the IMDA reactions of (*Z*)-substituted diene has been reported, see: Yakelis, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 957–960.

The synthesis of alkyne **6** was accomplished as illustrated in Scheme 2.⁸ The crotylboration of *D*-glyceraldehyde



^a Reagents and conditions: (a) MPMCl, NaH, DMF (93%); (b) $\text{BH}_3 \cdot \text{SMe}_2$, THF, then H_2O_2 , aqueous NaOH (77%); (c) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78°C to room temperature; (d) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, benzene (84% for 2 steps); (e) DIBALH, CH_2Cl_2 , -78°C (97%); (f) PivCl, Et_3N , pyr. (97%); (g) $\text{AcOH}-\text{THF}-\text{H}_2\text{O}$ (3:1:1), 40°C (95%); (h) NaIO_4 , $\text{MeOH}-\text{H}_2\text{O}$ (2:1); (i) CBr_4 , PPh_3 , CH_2Cl_2 , -78°C (82% for 2 steps); (j) DIBALH, CH_2Cl_2 , -78°C (97%); (k) TBDPSCl, imidazole, DMF (97%); (l) BuLi , THF, -78°C (80%).

acetone **8** with pinacol (*Z*)-crotylboration was conducted as described by Roush et al.,⁹ affording **9** diastereoselectively. The alcohol **9** was protected as a (4-methoxyphenyl)methyl (MPM) ether, giving **10**. Treatment of **10** with borane– Me_2S followed by oxidation with H_2O_2 provided **11** regioselectively.¹⁰ The Swern oxidation of **11** and the Wittig olefination of the resultant aldehyde provided the α,β -unsaturated ester **12**. Reduction of **12** with diisobutylaluminum hydride (DIBALH) followed by esterification of the resultant allylic alcohol (**13**) provided pivalate **14**. The acetal group in **14** was then deprotected by acidic hydrolysis to afford diol **15**. The oxidative cleavage of the diol in **15** with sodium periodate and the Corey–Fuchs homologation¹¹ of the resultant aldehyde provided dibromoalkene **16**. Reductive removal of the pivaloyl group in **16** with DIBALH provided **17**, which was protected as a *tert*-butyldiphenylsilyl (TBDPS) ether, giving **18**.¹² Treatment of **18** with BuLi ¹¹ afforded the alkyne **6**, the substrate for the Sonogashira coupling.

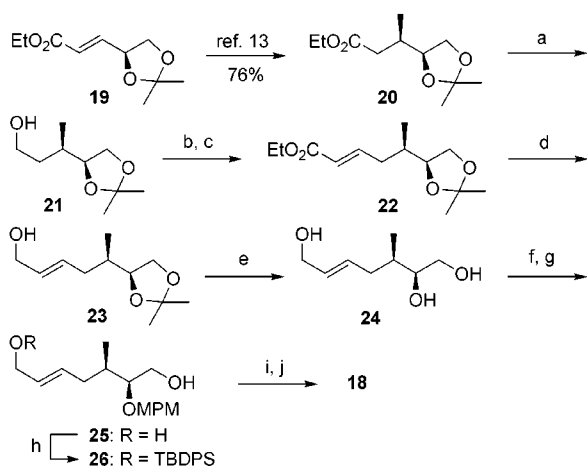
We investigated another synthetic route to the alkyne **6** (Scheme 3). The second-generation synthesis of **6** com-

(8) All new compounds were characterized by ^1H and ^{13}C NMR, IR, and HRMS. Yields refer to isolated, chromatographically purified products.

(9) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422–3434.

(10) A diastereomeric mixture (1:1) of the secondary alcohols was also isolated (10%).

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

Scheme 3^a

^a Reagents and conditions: (a) LiAlH_4 , Et_2O , 0°C (96%); (b) PCC, NaOAc, MS4A, CH_2Cl_2 (76%); (c) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, NaH, THF (80%); (d) DIBALH, CH_2Cl_2 , -78°C ; (e) Amberlyst 15, $\text{MeOH}-\text{H}_2\text{O}$ (1:1), 40°C ; (f) *p*-anisaldehyde dimethyl acetal, TsOH· H_2O , DMF, reduced pressure; (g) DIBALH, CH_2Cl_2 , -78°C (80% for 4 steps); (h) TBDPSCl, Et_3N , DMAP, CH_2Cl_2 , -78°C to -20°C (73%); (i) Dess–Martin periodinane, CH_2Cl_2 ; (j) CBr_4 , PPh_3 , CH_2Cl_2 , -78°C (77% for 2 steps).

menced with the diastereoselective conjugate addition of MeLi to **19**, as reported by Leonard et al.¹³ Thus, the known α,β -unsaturated ester **19**¹⁴ was exposed to MeLi in diethyl ether at -78°C to give the *syn*-adduct **20** as a single diastereomer.¹⁵ The ester group in **20** was reduced with LiAlH_4 , giving the primary alcohol **21**.¹⁶ Oxidation of **21** with pyridinium chlorochromate (PCC), followed by Horner–Wadsworth–Emmons olefination, provided the unsaturated ester **22** with an *E*-selectivity greater than 20:1. Reduction of **22** with DIBALH gave allylic alcohol **23**. Through the following conventional steps, **23** was converted into **26**. Namely, the acetonide in **23** was hydrolyzed to give triol **24**, in which the secondary alcohol was selectively protected as an MPM ether, giving **25** by the formation of methoxybenzylidene acetal¹⁷ followed by regioselective cleavage with DIBALH.¹⁸ The less-hindered primary allylic alcohol in **25** was selectively protected with 0.85 equiv of TBDPSCl to afford **26** in a 73% yield with 13% of recovered **25**.¹⁹ The oxidation of primary alcohol **26** with Dess–Martin

(12) Hydrolytic removal of the isopropylidene group in the TBDPS ether derived from **13** provided the corresponding diol in an unacceptable low yield.

(13) Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Swain, P. A. *Tetrahedron* **1995**, *51*, 12843–12858.

(14) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, 403–406.

(15) In our hands, the yield of **20** increased when the reaction was conducted on a larger scale. Consequently, we were able to prepare **20** on a 15 g scale with complete diastereoselectivity.

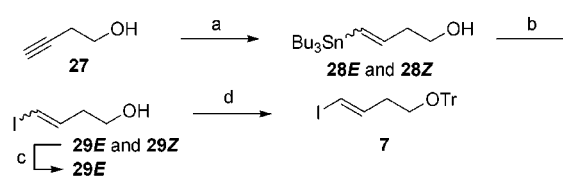
(16) Compound **21** had been synthesized by Boeckman et al. using a different route, see: Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1991**, *113*, 5337–5353.

(17) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371–2374.

(18) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593–1596.

periodinane²⁰ and the treatment of the resultant aldehyde with Corey–Fuchs conditions¹¹ provided the dibromoalkene **18**, the precursor of the alkyne **6**, as shown in Scheme 2.²¹

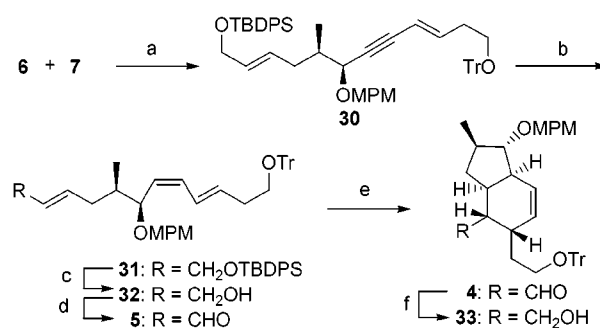
The vinyl iodide **7**, a coupling partner of the expected Sonogashira reaction, was derived from the known compound **29E**²² (Scheme 4). We developed a modified proce-

Scheme 4^a

^a Reagents and conditions: (a) Bu_3SnH , AIBN, benzene, 80°C ; (b) I_2 , CH_2Cl_2 , 0°C ; (c) MeONa, MeOH, reflux (74% for 3 steps); (d) TrCl , DMAP, pyr., 60°C (100%).

cedure for a more convenient way to prepare **29E**.²³ Thus, 3-butyn-1-ol (**27**) was hydrostannylated to give a mixture of **28E** and **28Z**.^{22b} The mixture was immediately treated with iodine in CH_2Cl_2 to give a mixture of vinyl iodide **29E** and **29Z**. After most tin byproducts were separated by an aqueous KF workup, the mixture of **29E** and **29Z** was treated with MeONa (1.5 molar equiv) in refluxing MeOH. Under these conditions, only the *Z*-isomer was susceptible to an elimination reaction, which gave **27**.²⁴ Isomerically pure **29E** was obtained in an overall yield of 74% from **27**. The vinyl iodide **29E** was treated with trityl chloride in pyridine to give trityl ether **7**.

The desired AB-ring was constructed as illustrated in Scheme 5. The Sonogashira coupling between **6** and **7** was

Scheme 5^a

^a Reagents and conditions: (a) $\text{Pd}(\text{PPh}_3)_4$, CuI, Et_3N (91%); (b) H_2 , Lindlar catalyst, quinoline, 1-hexene (66%, 31% recovery of **30**); (c) Bu_4NF , THF (100%); (d) MnO_2 , CH_2Cl_2 (83%); (e) 0.01 M, toluene, BHT (catalytic), 150°C , in a sealed tube (75%); (f) NaBH_4 , EtOH (99%).

conducted in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ and CuI in triethylamine, efficiently providing **30** in 91% yield. Semi-hydrogenation of **30** in 1-hexene with Lindlar catalyst²⁵ afforded **31** in a 66% yield, along with recovered

30 (31%). Treatment of **31** with Bu_4NF in THF gave primary allylic alcohol **32**, which was oxidized with MnO_2 , affording **5**, the substrate for the IMDA reaction. On heating to 150°C in a sealed tube, the IMDA reaction of **5** proceeded smoothly, without isomerization of the diene moiety, to produce the desired cycloadduct **4** in a 75% yield as a single isomer.

The stereochemistry of **4** was determined by NOE experiments of **4** and **33** as shown in Figure 2. Compound **33** was

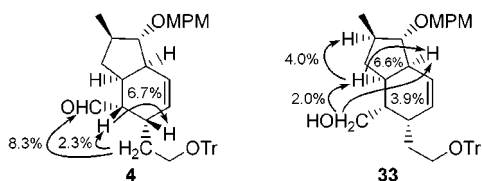


Figure 2. NOE experiments on **4** and **33**.

obtained by NaBH_4 reduction of **4**. The stereochemical outcome of the IMDA reaction is rationalized by considering the transition states illustrated in Figure 3. Since the *exo*-mode is sterically inaccessible in the IMDA reactions of (*E,Z,E*)-1,6,8-nonatrienes, only two endo-transition states, **A** or **B**, are possible. Compared with **B**, transition state **A**, which leads to **4**, seems to be substantially more favorable

(19) The reductive opening of the TBDPS-protected acetal, prepared from **24** [(1) MPM acetal formation, (2) silyl ether (OTBDPS) formation], with DIBALH was accompanied by cleavage of the silyl ether.

(20) (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.

(21) The overall yield of **6** from **8** was 23% and that from **19** was 16%. We prefer the second route because the isolation of **9** from other diastereomers by chromatographic separation on silica gel was problematic in our case on a large-scale experiment.

(22) (a) Nicolaou, K. C.; Stylianides, N. A.; Ramphal, J. Y. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2131–2132. (b) Pilli, R. A.; de Andrade, C. K. Z.; Souto, C. R. O.; de Meijere, A. *J. Org. Chem.* **1998**, *63*, 7811–7819. (c) Chong, J. M.; Heuft, M. A. *Tetrahedron* **1999**, *55*, 14243–14250. (d) Germain, J.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 4051–4054.

(23) During a large-scale preparation of **29E**, we encountered a tedious chromatographic separation of **28E** and **28Z**.

(24) Schlosser, M.; Ladenberger, V. *Chem. Ber.* **1971**, *104*, 2873–2884.

(25) Ho, T.-L.; Liu, S.-H. *Synth. Commun.* **1987**, *17*, 969–973.

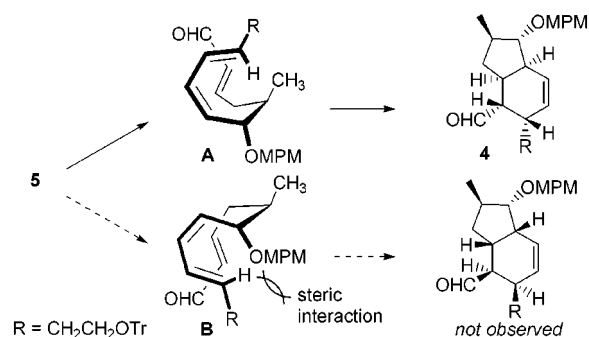


Figure 3. Plausible mechanism for diastereoselection.

because of the severe steric interaction between the (4-methoxyphenyl)methoxy group and the vinylic hydrogen atom existing in transition state **B**. Consequently, the configuration of the MPMO group is believed to affect significantly the π -facial selection of the cycloaddition.

In conclusion, a stereoselective synthesis of the AB-ring system of macquarimicins using an IMDA approach has been achieved. The present work has demonstrated the effectiveness of the use of an (*E,Z,E*)-1,6,8-nonatriene as the substrate for an IMDA reaction. The key steps in the present work are the Sonogashira coupling of the alkyne **6** derived from D-glyceraldehyde acetonide and (*E*)-vinyl iodide **7**, as well as the highly diastereoselective IMDA reaction of the (*E,Z,E*)-triene **5**. We are currently investigating the total synthesis of macquarimicins.

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Supporting Information Available: Experimental procedures and spectroscopic characterization (^1H and ^{13}C NMR, IR, and HRMS) of all new compounds. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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