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A Convergent Synthesis of the Macrocyclic Core of Cytotrienins: Application of RCM for Macrocyclization

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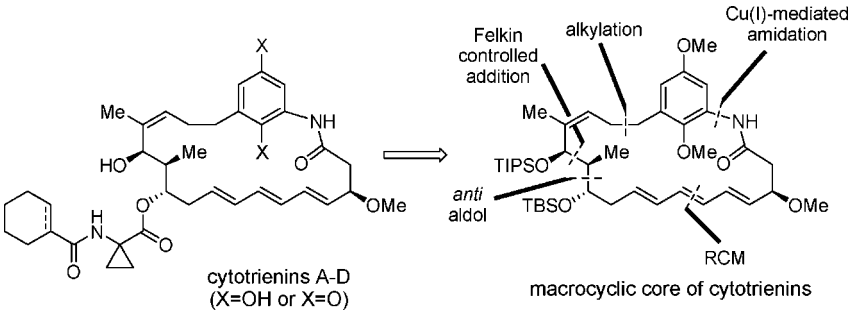
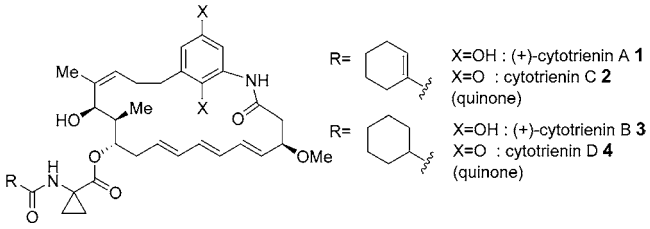
ABSTRACT



The asymmetric synthesis of the fully elaborated macrocyclic core of cytotrienins A−D, potent apoptosis-inducing agents, is described. Synthetic highlights include the construction of the aniline bond using a copper-mediated amidation and the use of a ring-closing metathesis (RCM) reaction to efficiently install the (*E*,*E*,*E*)-triene and simultaneously construct the macrocyclic lactam.

In the last two decades, a series of publications reported the isolation and structure elucidation of several members of a new class of ansamycin compounds, including mycotrienins (or ansatrienins),[1] trienomycins,[1c,2] and thiazinotrienomycins.[3] Common structural features of these compounds include a (*E*,*E*,*E*)-triene within a 21-membered lactam containing four stereocenters; functionalized side chains and aromatic cores differentiate the individual structures and play an important role in their biological activities. More recently, Osada and co-workers isolated four new members of this family of compounds, cytotrienins A−D **1**−**4** (Scheme 1), obtained from the fermentation broth of *Streptomyces* sp. RK95-74.[4] Those new ansamycins possess an unusual aminocyclopropane carboxylic acid side chain, and cytotrienins A and B were shown to induce apoptosis in human acute promyelotic

Scheme 1. Cytotrienins A−D



(1) (a) Sugita, M.; Natori, Y.; Sasaki, T.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1460−1466. (b) Sugita, M.; Sasaki, T.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot.* **1982**, *35*, 1467−1473. (c) Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Barbosa, J.; Funayama, S.; Komiyama, K, Omura, S. *J. Am. Chem. Soc.* **1996**, *118*, 8308−8315.

(2) (a) Funyama, S.; Okada, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1107−1109. (b) Funyama, S.; Okada, K.; Iwasaki, K.; Komiyama, K.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 1677−1683. (c) Nomoto, H.; Katsumata, S.; Takahashi, K.; Funayama, S.; Komiyama, K.; Umezawa, I.; Ōmura, S. *J. Antibiot.* **1989**, *42*, 479−481.

(3) (a) Hosokawa, N.; Naganawa, H.; Inuma, H.; Hamada, M.; Takeuchi, T.; Kanbe, T.; Hori, M. *J. Antibiot.* **1995**, *48*, 471−478. (b) Smith, A. B., III; Barbosa, J.; Hosokawa, N.; Naganawa, H.; Takeuchi, T. *Tetrahedron Lett.* **1998**, *39*, 2891−2894.

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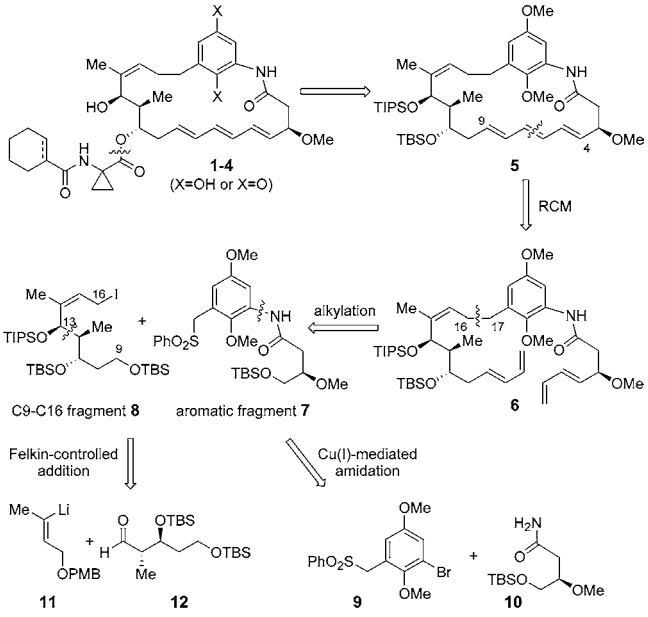
leukemia HL-60 cells with an ED_{50} value of 7.7 nM.[5] The absolute and relative stereochemistry of cytotrienins have yet to be determined but can be assumed to be identical to those of mycotrienins due to their structural similarities and biosynthetic pathway.[4a,6]

The biological activities and unique structures of these ansamycins have made them attractive targets for synthesis. Thus, several strategies have been used for the key macrocyclization step. The initial report by Smith for the synthesis of (+)-trienomycins A and F utilized a bis-Wittig olefination.[7] The synthesis of (+)-mycotrienin I incorporated a tandem inter-/intramolecular Stille coupling,[8] while (+)-thiazinotrienomycin E was constructed using macrolactamization.[9] Described herein is our approach to the fully elaborated macrocyclic core of cytotrienins, featuring a ring-closing metathesis (RCM) reaction for the key macrocyclization step.

From a retrosynthetic perspective, we envisioned installation of the side chain late in the synthesis, thereby permitting construction of cytotrienins A−D from the common advanced precursor **5** as depicted in Scheme 2. To

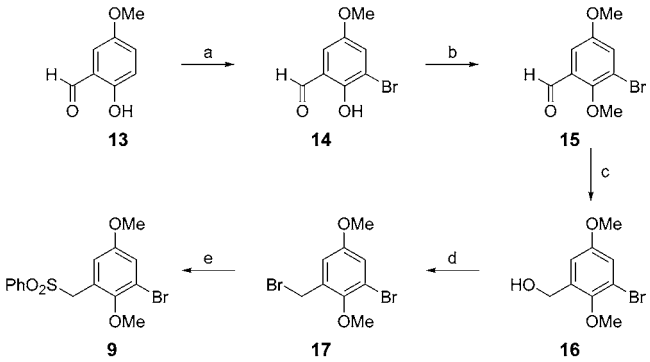
Scheme 2. Retrosynthetic Analysis of Cytotrienins A−D



install the C4−C9 (*E*,*E*,*E*)-triene and simultaneously effect macrocyclization, we decided to employ a challenging RCM[10] using the bis-1,3-diene **6** as the triene precursor. Further analysis of **6** suggested that it could be disconnected at the C16−C17 bond to give the aromatic **7** and the C9−C16 **8** fragments, which would be coupled by alkylation of the sulfone as previously documented.[7−9] The aromatic fragment **7** could be synthesized using Buchwald's copper-mediated amidation[11] of **9** with **10** while the C9−C16 fragment would derive from addition of lithium anion **11** onto aldehyde **12**, readily available via Abiko and Masamune's *anti*-aldol methodology.[12]

The synthesis of the aromatic fragment (Scheme 3) started with a regioselective bromination of commercially available

Scheme 3. Synthesis of the Aromatic Core[a]



[a] Reagents and conditions: (a) Br_2, AcONa, AcOH, 89%. (b) Me_2SO_4, K_2CO_3, DMF, 99%. (c) BH_3·THF, THF, quant. (d) PPh_3, CBr_4, THF, 96%. (e) $PhSO_2Na$, DMF, 86%.

2-hydroxy-5-methoxybenzaldehyde **13** using standard conditions (Br_2, AcONa, AcOH). Methylation of the phenol with dimethyl sulfate and potassium carbonate followed by reduction of the aldehyde with BH_3·THF gave benzylic alcohol **16** in excellent yield (99% over two steps). At this stage, it was necessary to introduce the sulfone, which was effected by bromination of the benzylic alcohol with triphenylphosphine and carbon tetrabromide followed by displacement with sodium benzenesulfinate. This reaction sequence efficiently completed the synthesis of the first subunit **9** for the amidation reaction.

The synthesis of the chiral subunit **10**, required for this amidation reaction, is depicted in Scheme 4. Its preparation began with Jacobsen's hydrolytic kinetic resolution (HKR) of racemic epoxide (±)-**18** employing (*S*,*S*)-Co(salen).[13] This reaction provided enantiomerically pure diol **19** in multigram quantities and high enantiomeric purity. Selective protection of the primary alcohol of the diol **19** (TBSCl, imidazole,

(4) (a) Zhang, H. P.; Kakeya, H.; Osada, H. *Tetrahedron Lett.* **1997**, *38*, 1789−1792. (b) Osada, H.; Kakeya, H.; Zhang, H. P.; Kobinata, K. PCT Int. Appl. WO 9823594, 1998.

(5) Kakeya, H.; Zhang, H. P.; Kobinata, K.; Onose, R.; Onozawa, C.; Kudo, T.; Osada, H. *J. Antibiot.* **1997**, *50*, 370−372.

(6) Zhang, H. P.; Kayeka, H.; Osada, H. *Tetrahedron Lett.* **1998**, *39*, 6947−6948.

(7) Smith, A. B., III.; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 8316−8328.

(8) Masse, C. E.; Yang, M.; Solomon, J.; Panek, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4123−4134.

(9) Smith, A. B., III; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738−3753.

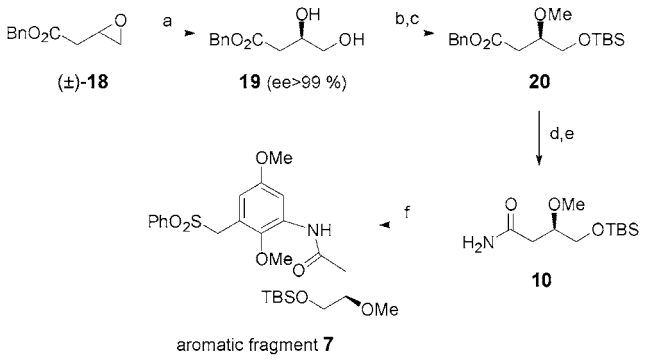
(10) For recent reviews, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(11) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428.

(12) (a) Abiko, A.; Liu, J. F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586−2587. (b) Inoue, T.; Liu, J. F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250−5256.

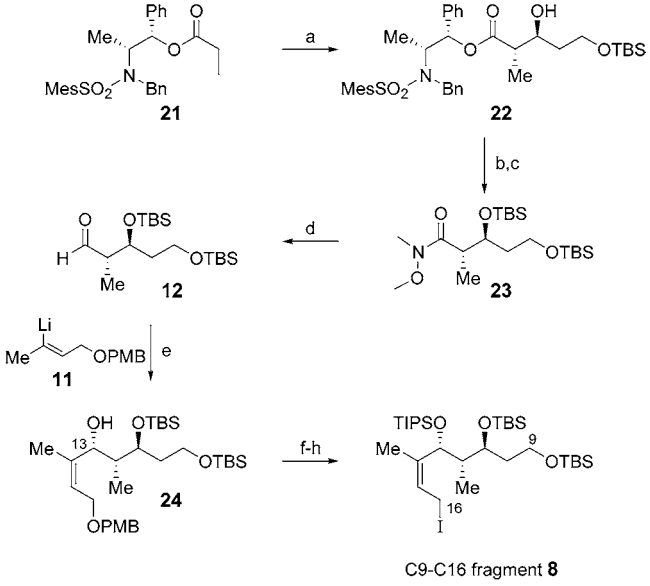
(13) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

Scheme 4. Completion of the Aromatic Fragment[a]



[a] Reagents and conditions: (a) (*S*,*S*)-Co(salen), AcOH, H_2O, THF, 50% conversion, 47%. (b) TBSCl, imidazole, THF, 0 °C, 96%. (c) Me_3OBF_4, 4 Å MS, proton sponge, CH_2Cl_2, 96%. (d) H_2, Pd/C, MeOH, quant. (e) EtOCOCl, Et_3N, CH_2Cl_2, −20 °C then NH_3 gas 91%. (f) **9** (1.0 equiv), 20 mol % CuI, 40 mol % *N*,*N*′-dimethylethylenediamine, K_2CO_3, toluene, 110 °C, 82%.

Scheme 5. Synthesis of the C9−C16 Fragment[a]



[a] Reagents and conditions: (a) Cy_2BOTf, Et_3N, CH_2Cl_2 −78 °C then $CHOCH_2CH_2OTBS$, −78 °C to room temperature, 94%, dr > 30:1. (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 96%. (c) Me(MeO)NH·HCl, ^{i}PrMgCl, THF, −20 to 5 °C, 87%. (d) DibalH, THF, −78 °C. (e) **11**, THF, −78 °C, 73% (two steps), dr = 6.5:1. (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 98%. (g) DDQ, CH_2Cl_2/H_2O (10/1), 0 °C, 94%. (h) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, 88%.

THF) allowed for the methylation of the secondary hydroxyl group with Meerwein's reagent in excellent overall yield (92% over two steps). Subsequent debenzylation of the ester **20** by hydrogenolysis followed by amidation in a two-step, one-pot procedure via a mixed anhydride provided the desired amide **10** in good yield.

To undertake the assembly of the aromatic fragment **7**, a copper-mediated amidation between aryl bromide **9** and amide **10** was investigated. After screening several reaction conditions,[11] it was determined that this coupling was best effected using 20 mol % CuI, 40 mol % *N*,*N*′-dimethylethylenediamine, and potassium carbonate as a base in toluene at 110 °C and using a slight excess (1.2 equiv) of the amide **10**. Under these conditions, amidation product **7** was obtained in 84% yield. Moreover, we found that a 1:1 ratio of bromide **9** and amide **10** did not significantly decrease the yield of this reaction since the aromatic fragment could be obtained in 82% yield and in multigram quantities.

The synthesis of the C9−C16 fragment is outlined in Scheme 5. *anti*-Aldol condensation of **21**[12] with *tert*-butyldimethylsilyloxypropionaldehyde furnished aldol adduct **22** as a single diastereoisomer (94% yield). Protection of the resulting alcohol as a TBS ether (TBSOTf, 2,6-lutidine, CH_2Cl_2) followed by removal of the chiral auxiliary afforded the Weinreb amide **23**. This last step proved to be quite challenging and required harsh conditions: while most common methods[14] failed to efficiently cleave the bulky auxiliary, we found after considerable experimentation that exposure of **22** to 10 equiv of Me(MeO)NMgCl[15] from −20 to 5 °C gave the desired amide **23** in 87% yield. Conversion of amide **23** to C9−C16 fragment **8** entailed installation of the C13 stereocenter and the trisubstituted (*Z*)-olefin. To this end, amide **23** was reduced to aldehyde **12** using DibalH in THF. Subsequent treatment of **12** at −78 °C with vinyllithium **11** provided the secondary alcohol **24** with a good overall yield (73% over two steps) and reasonable selectivity (Felkin:anti-Felkin = 6.5:1). The stereochemical outcome of this reaction can be rationalized using a Felkin−Ahn model, and the stereochemistry at C13 was unambiguously assigned using ^{13}C NMR chemical shift analysis of the acetonide derived from the 1,3-diol.[16] The completion of **8** was effected by protection of the emerged alcohol as its triisopropylsilyl ether, DDQ deprotection of the PMB ether, and conversion of the allylic alcohol to the iodide using a buffered solution of triphenylphosphine and iodine, which afforded the C9−C16 fragment **8** in 81% yield over the last three steps.

As previously reported,[7−9] union of fragments **7** and **8** was effected by alkylation of the sulfone **7** with the iodide **8** (Scheme 6). Deprotonation of the latter with LiHMDS in THF at −78 °C followed by addition of **8** gave a coupling product, which was subjected to treatment with sodium mercury amalgam in buffered methanol, providing the desulfonylated intermediate **25**.

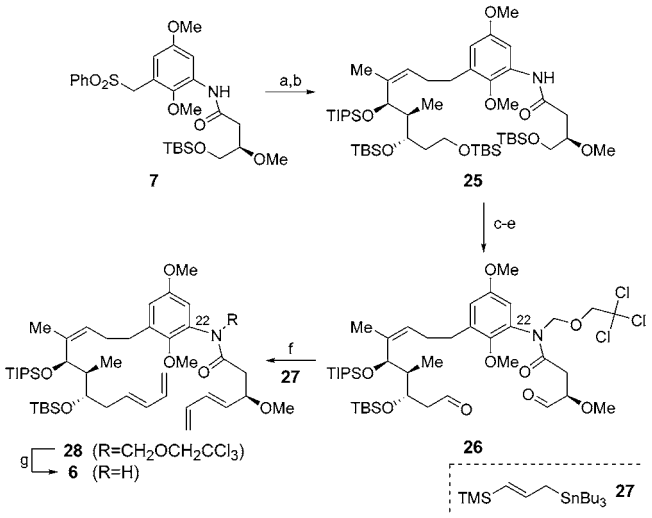
At this stage, we initiated the construction of the key (*E*,*E*)-bis-1,3-diene for macrocyclization by RCM. To prevent any complications due to cyclization of the amide to an *N*-acylhemiaminal in a subsequent step, the amide was protected as a 2,2,2-trichloroethylaminal, as previously discussed by

(14) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993. (b) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, 38, 2685−2688. (c) Huang, P. Q.; Zheng, X.; Deng, X. M. *Tetrahedron Lett.* **2001**, *42*, 9039−9041.

(15) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461−5464.

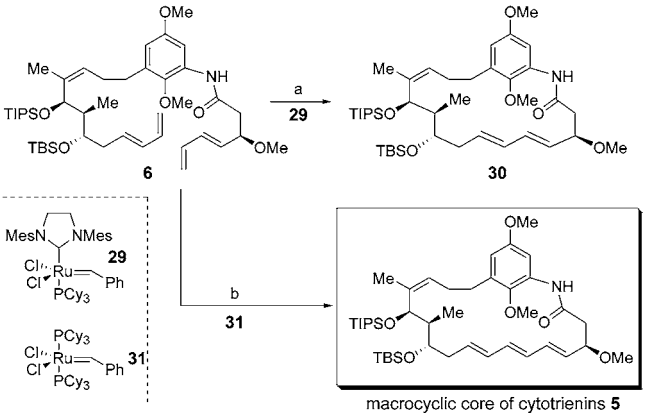
(16) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100.

Scheme 6. Fragment Coupling: Installation of the Bis-1,3-diene[a]



[a] Reagents and conditions: (a) LiHMDS (2.2 equiv), −78 °C then **8**, −78 to −30 °C, 73%. (b) Na(Hg), Na_2HPO_4, MeOH, −20 °C, 96%. (c) KH, THF, 0 °C then $ClCH_2OCH_2CCl_3$, rt, 95%. (d) HF·pyr, pyr, THF, 0 °C, 91%. (e) pyr·SO_3, Et_3N, DMSO, 91%. (f) (i) **27**, BF_3·OEt_2, CH_2Cl_2, −78 to −50 °C; (ii) ^{t}BuOK, THF, 61% (two steps). (g) Na(Hg), Na_2HPO_4, MeOH, −20 °C, 75%.

Scheme 7. RCM Studies: Effect of Catalyst on Macrocyclization[a]



[a] Reagents and conditions: (a) 10 mol % **29**, CH_2Cl_2, reflux, 47%. (b) 2 × 10 mol % **31**, CH_2Cl_2, reflux, 73% (83% based on recovered **6**).

Smith and co-workers in their synthesis of trienomycins.[7] Thus, treatment of **25** with potassium hydride and chloromethyl 2,2,2-trichloroethyl ether in THF gave the protected amide as a mixture of atropoisomers at the C22−N aniline bond (Scheme 6). Selective deprotection of the two primary TBS ethers using a buffered solution of HF·pyridine, followed by a double Parikh−Doering oxidation, afforded the bis-aldehyde **26**.

Transformation of this bis-aldehyde **26** to the bis-1,3-diene **28** (Scheme 6) turned out to be unexpectedly difficult. After considerable experimentation with conventional procedures using phosphorus-based olefination reagents, we eventually turned to an under-utilized reaction previously reported by Yamamoto[17] and modified by Keck.[18] Following this procedure, bis-aldehyde **26** was reacted with allyltin **27** in the presence of BF_3·OEt_2 to give a complex diastereoisomeric and atropoisomeric mixture of α-hydroxysilanes. Exposure of this mixture to catalytic potassium *tert*-butoxide in THF resulted in the formation of the Peterson elimination product **28** (Scheme 6).[19] Finally, deprotection of the amide with sodium mercury amalgam in buffered methanol provided the free amide **6** in 75% yield.

This set the stage for the crucial macrocyclization and formation of the (*E*,*E*,*E*)-triene by RCM.[20] Reaction of **6** with ruthenium catalyst **29** unexpectedly gave diene **30**,[21] presumably resulting from an unusual initiation of the RCM at the internal bond of one of the 1,3-dienes (Scheme 7).[22] To overcome this problem and initiate the RCM at one of the terminal olefins, **6** was exposed to the less reactive catalyst **31** in refluxing dichloromethane. Use of these conditions afforded the expected (*E*,*E*,*E*)-triene **5**[23] with excellent selectivity and yield.

In conclusion, we have described a convergent synthesis of the highly functionalized macrocyclic core of the cytotrienins. Synthetic highlights include an efficient synthesis of the aromatic fragment through the use of a copper-mediated amidation reaction, a modified Peterson olefination to install the bis-1,3-diene, and a macrocyclization by RCM to complete the assembly of the carbon framework of cytotrienins. Studies toward the completion of cytotrienins A−D are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311−318.

(18) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083−6089.

(19) The (*E*,*E*) stereochemistry of **28** was demonstrated by correlation with the product obtained from bis-aldehyde **26** using the following sequence: (i) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, (ii) DibalH, THF, (iii) Swern oxidation, (iv) $Ph_3P^+CH_3Br^-$, ^{n}BuLi, THF.

(20) (a) For construction of a conjugated, macrocyclic (*E*,*Z*,*Z*)-triene using RCM, see: Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040−6041. (b) For an attempt to construct a conjugated, macrocyclic triene using RCM, see: Wagner, J.; Cabrejas, L. M. M.; Grossmith, C. E.; Papageorgiou, C.; Senia, F.; Wagner, D.; France, J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 9255−9260.

(21) The (*E*,*E*) stereochemistry of the diene **30** was assigned on the basis of the coupling constants.

(22) For a precedent of formation of a diene starting from a bis-1,3-diene by RCM, see ref 20a.

(23) The (*E*,*E*,*E*) stereochemistry of the triene **5** was assigned on the basis of the coupling constants between the two protons of the newly created olefin.