JOC Article

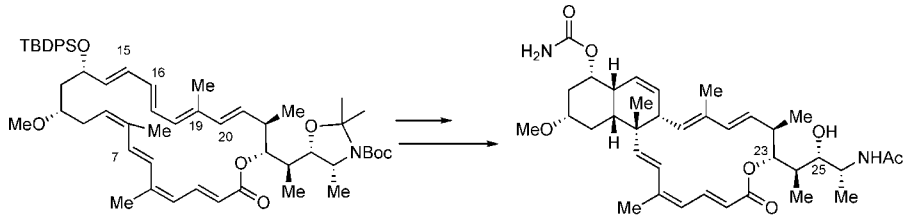
Total Synthesis of (+)-Superstolide A

Mariola Tortosa,[†] Neal A. Yakelis,[‡] and William R. Roush*,[†]

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458, and Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

roush@scripps.edu

Received August 13, 2008



A convergent and highly stereocontrolled total synthesis of the cytotoxic macrolide (+)-superstolide A is described. Key features of this synthesis include the use of bimetallic linchpin **36b** for uniting the C(1)−C(15) (**43**) and the C(20)−C(27) (**38**) fragments of the natural product, a late-stage Suzuki macrocyclization of **49**, and a highly diastereoselective transannular Diels−Alder reaction of macrocyclic octaene **4**. In contrast, the intramolecular Diels−Alder reaction of pentaenal **5** provided the desired cycloadduct with lower stereoselectivity (6:1:1).

Introduction

In 1994, Minale and co-workers reported the isolation and structural determination of superstolides A (**1**) and B (**2**) (Figure 1) from the New Caledonian sponge *Neosiphonia superstes*.[1,2] The superstolides are highly cytotoxic against several cancer cell lines including murine P388 leukemia cells (IC_{50} = 3 ng/mL for both **1** and **2**), human nasopharyngeal cells (IC_{50} = 5 ng/mL for **2**), and non-small cell lung carcinoma cells (IC_{50} = 4 ng/mL for both **1** and **2**). Due to their interesting chemical structures and potent biological properties, the superstolides have attracted considerable attention as synthetic targets. Efforts toward the C(21)−C(26) fragment have been reported by D'Auria,[3] Jin,[4] Romea and Urpi,[5] Paterson,[6] and Marshall[7] as well as our group.[8] In 1996, we published a highly diastereoselective synthesis of the *cis*-fused octahydronaphthalene nucleus,[9] and a few years later, Jin and co-workers reported a different approach toward this part of the molecule.[10] Recently, we reported the first total synthesis of (+)-superstolide A[11] by a route that proceeds via the transannular Diels−Alder reaction of macrocyclic octaene **4**, an element of the synthesis that is presumably biomimetic in nature.[12,13] We report herein a full account of the evolution of the synthetic strategy that led to the

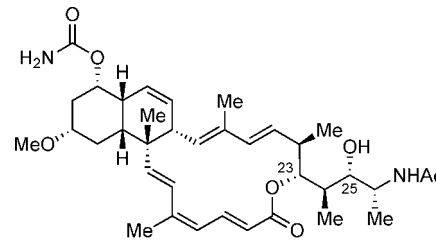


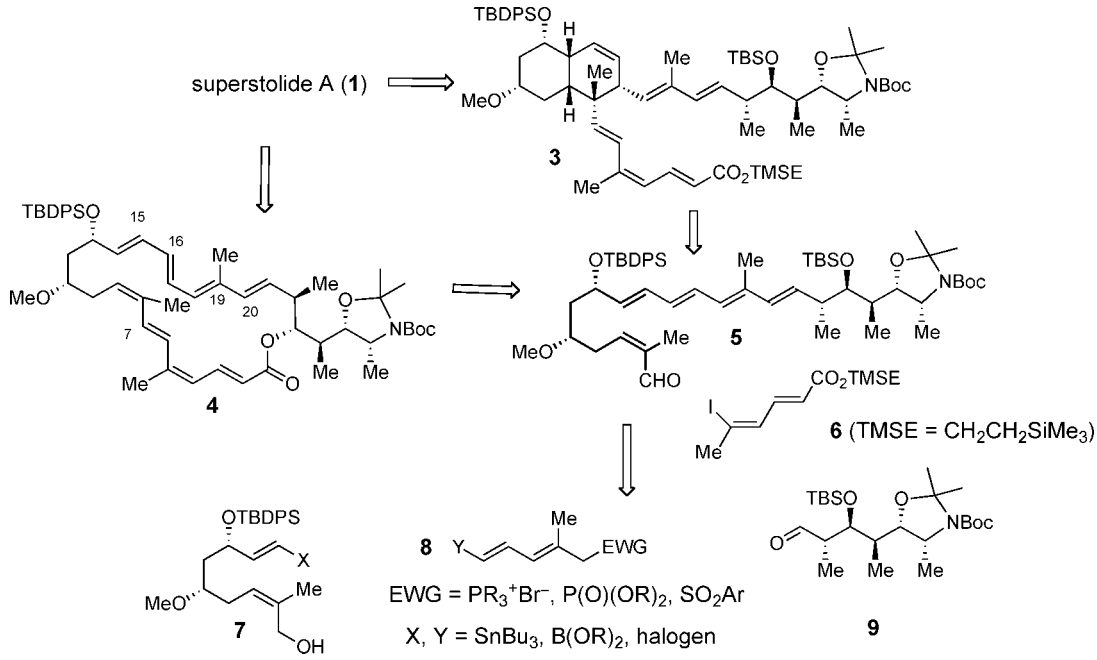
FIGURE 1. Superstolides A and B.

[†] Scripps Florida.
[‡] University of Michigan.

(1) D'Auria, M. V.; Debitus, C.; Paloma, L. G.; Minale, L.; Zampella, A. *J. Am. Chem. Soc.* **1994**, *116*, 6658.
(2) D'Auria, M. V.; Paloma, L. G.; Minale, L.; Zampella, A.; Debitus, C. *J. Nat. Prod.* **1994**, *57*, 1595.
(3) Zampella, A.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2001**, *12*, 1543.
(4) Yu, W.; Zhang, Y.; Jin, Z. *Org. Lett.* **2001**, *3*, 1447.
(5) Solsona, J. G.; Romea, P.; Urpi, F. *Org. Lett.* **2003**, *5*, 4681.
(6) Paterson, I.; Mackay, A. C. *Synlett* **2004**, 1359.
(7) Marshall, J. A.; Mulhearn, J. J. *Org. Lett.* **2005**, *7*, 1593.
(8) (a) Roush, W. R.; Hertel, L.; Schnaderbeck, M. J.; Yakelis, N. A. *Tetrahedron Lett.* **2002**, *43*, 4885. (b) Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 3838.
(9) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989.
(10) Hua, Z.; Yu, W.; Su, M.; Jin, Z. *Org. Lett.* **2005**, *7*, 1939.
(11) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 2722.
(12) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078.
(13) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321.

10.1021/jo801794s CCC: $40.75
Published on Web 10/29/2008

SCHEME 1. Retrosynthetic Analysis



successful synthesis of **1** and of the difficulties that were encountered along the way.

Synthetic Strategy

From the outset of our work on superstolide A, we intended to synthesize the highly substituted *cis*-octahydronaphthalene unit by a Diels−Alder reaction performed in either the intramolecular (IMDA)[9] or transannular (TDA) mode.[8a] We established in early studies that the IMDA reaction of a model substrate provided the *cis*-octahydronaphthalene nucleus with 6:1:1 selectivity.[9] Although this was a promising result, a plan to pursue a transannular Diels−Alder reaction of the 24-membered octaene **4** also seemed attractive since several TDA reactions are known to be much more stereoselective than analogous IMDA cyclizations.[14] We have successfully demonstrated this principle in several syntheses,[15,16] and superstolide A provided another challenging test case to explore the generality of this concept. We recognized that there were several possible TDA reactions that could occur within macrocycle **4**, however we anticipated that the proposed cyclization would predominate owing to the favorable kinetics of closure of a 6-membered ring at C(9)−C(14). While a 6-membered ring could also be closed by a TDA reaction of a C(2,3)-dienophile and a C(18−21)-diene, this cyclization would require the lactone to adopt a disfavored *s-cis* conformation. IMDA reactions of substrates with esters in the connecting chain are generally highly disfavored.[14,17] Although the proposed transannular cyclization offered potential advantages in terms of stereoselectivity, we were aware of the chemical sensitivity of the two conjugated tetraene units of **4**.

Therefore, we designed a strategy that would allow us to adjust the timing of the Diels−Alder reaction relative to the macrocyclization step late in the synthesis (i.e., use of **3** vs **4** as key intermediates, Scheme 1). On the basis of this analysis, we targeted functionalized pentaenal **5** as a common precursor to **3** and **4**. In the synthetic direction, the aldehyde unit of **5** could be transformed into a vinylmetal intermediate capable of being coupled with iodide **6**, either prior to or after the Diels−Alder reaction. Finally, pentaenal **5** could be assembled by coupling of suitably functionalized fragments **7**-**9**, via olefination of **8** and **9** followed by a metal catalyzed cross-coupling reaction with **7**.[18]

Results and Discussion

Synthesis of Allylic Alcohols 7a,b. The synthesis of allylic alcohols **7a**,**b** started with the asymmetric allylation (96:4 dr) of known aldehyde **10** using Brown's ^{d}Ipc$_2$Ballyl reagent under salt-free conditions (Scheme 2).[19] *O*-Methylation of the resulting secondary alcohol followed by ketal hydrolysis afforded diol **11** in 53% yield over three steps. Selective formation of the primary trityl ether followed by protection of the secondary hydroxyl group gave triether **12**. After ozonolysis of the double bond of **12**, the resulting aldehyde was subjected to Horner−Wadsworth−Emmons olefination according to the Still−Gennari[20] procedure, which afforded (*Z*)-enoate **13** in 74% over four steps. Deprotection of the primary trityl ether of **13** followed by oxidation of the resulting alcohol using Parikh−Doering conditions provided aldehyde **14** (90%).[21] This intermediate was elaborated to vinyl iodide **7a** (79%) and vinylboronate **7b** (89%) by using Takai[22] or modified Takai[23] conditions followed by DIBAL-H reduction of the ester.

Synthesis of Trienyl Iodide 20. Trienyl iodide **20** was synthesized from the known allylic alcohol **16**[24] as outlined in

(14) (a) Takao, K.-i.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779. (b) Deslongchamps, P. *Aldrichim. Acta* **1991**, *24*, 43. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 513−550. (d) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

(15) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502.

(16) (a) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11955. (b) Winbush, S. M.; Mergot, D. J.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1818.

(17) Boeckman, R. K., Jr.; Flann, C. J. *Tetrahedron Lett.* **1983**, *24*, 5035.

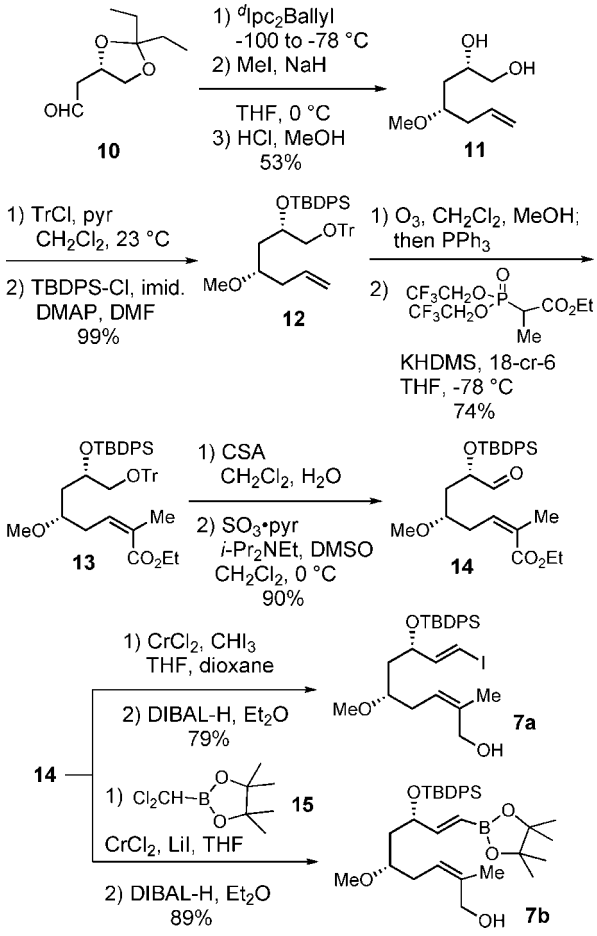
(18) Review of palladium-catalyzed cross-coupling reactions in total synthesis: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

(19) Smith, A. B.; Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 10935.

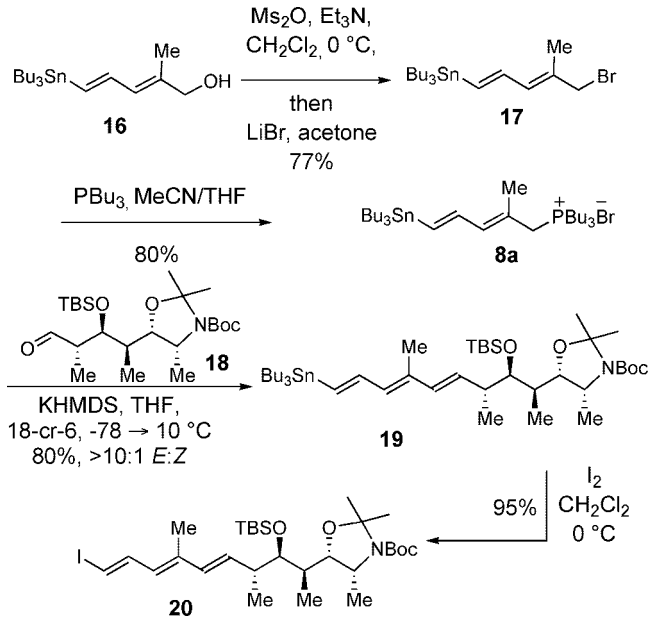
(20) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(21) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

SCHEME 2. Synthesis of Allylic Alcohols 7a,b

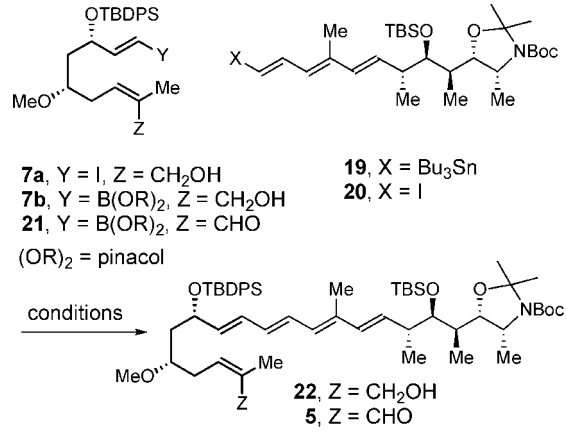


SCHEME 3. Synthesis of Trienyl Iodide 20



Scheme 3. Evans had previously reported the conversion of **16** to the dienylic bromide **17** using carbon tetrabromide and triphenylphosphine.[24] This reaction provided bromide **17** in variable yield and purity; therefore, a much cleaner method with higher and more reliable yields was developed. The dienylic mesylate was generated by treatment of **16** with methanesulfonic

SCHEME 4. Synthesis of the IMDA Precursor 22



		conditions	product
19	**7a**	Pd(PPh$_3$)$_4$ (cat) NMP, 23 °C	**22** (21%)
20	**7b**	Pd(PPh$_3$)$_4$ (cat) Tl$_2$CO$_3$, THF-H$_2$O, 23 °C	**22** (95%)
20	**21**	Pd(PPh$_3$)$_4$ (cat) Tl$_2$CO$_3$, THF, H$_2$O, 23 °C	—

anhydride and triethylamine in dichloromethane at 0 °C. The reaction was then diluted with acetone, and lithium bromide was added at 23 °C to effect S_N2 displacement giving dienylic bromide **17** in 77% yield. Treatment of **17** with PBu_3 in a mixture of CH_3CN and THF provided phosphonium salt **8a**. The Wittig reaction of the ylide generated from phosphonium salt **8a** and aldehyde **18**[8b] furnished trienyl stannane **19** in 80% yield with (*E*)-selectivity greater than 10:1. Initially, we had considered using Horner−Wadsworth−Emmons and Julia olefination sequences for the synthesis of trienyl stannane **19**. However, these strategies were ultimately abandoned due to the low yields and poor stereoselectivities realized in the synthesis of (*E*,*E*,*E*)-triene **19** by using these reactions.

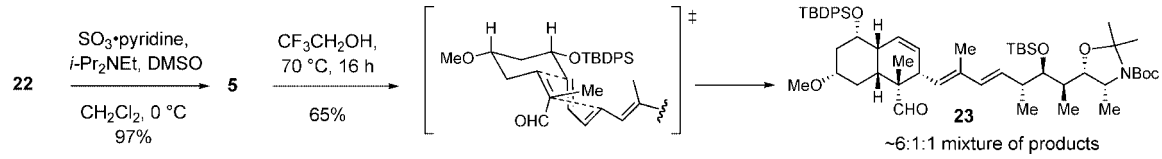
Trienylstannane **19** was a viable Stille cross-coupling partner for **7a**, but conversion to iodide **20** would be required for cross-coupling with vinylboronate **7b**. Careful titration of trienylstannane **19** with 1 equiv of iodine afforded **20** in 95% yield. Iodide **20** was found to be very sensitive, with olefin isomerization occurring if any excess of iodine was used in the reaction with **19**, and product decomposition occurred during attempted chromatographic purification of **20** on silica gel or alumina.

IMDA Approach: Initial Studies. With all the cross-coupling partners in hand, we looked for optimal conditions for the fragment assembly (Scheme 4). Treatment of a mixture of iodide **7a** and trienylstannane **19** with catalytic Pd(PPh$_3$)$_4$ furnished allylic alcohol **22** in low yield (21%).[25] In contrast, the Suzuki cross-coupling between **7b** and **20** in the presence of thallium(I) carbonate[26] gave **22** in excellent yield (95%). Hoping to minimize the manipulations of this sensitive intermediate, we attempted to use enal **21** in a Suzuki coupling with **20**, but unfortunately, this reaction was unsuccessful.

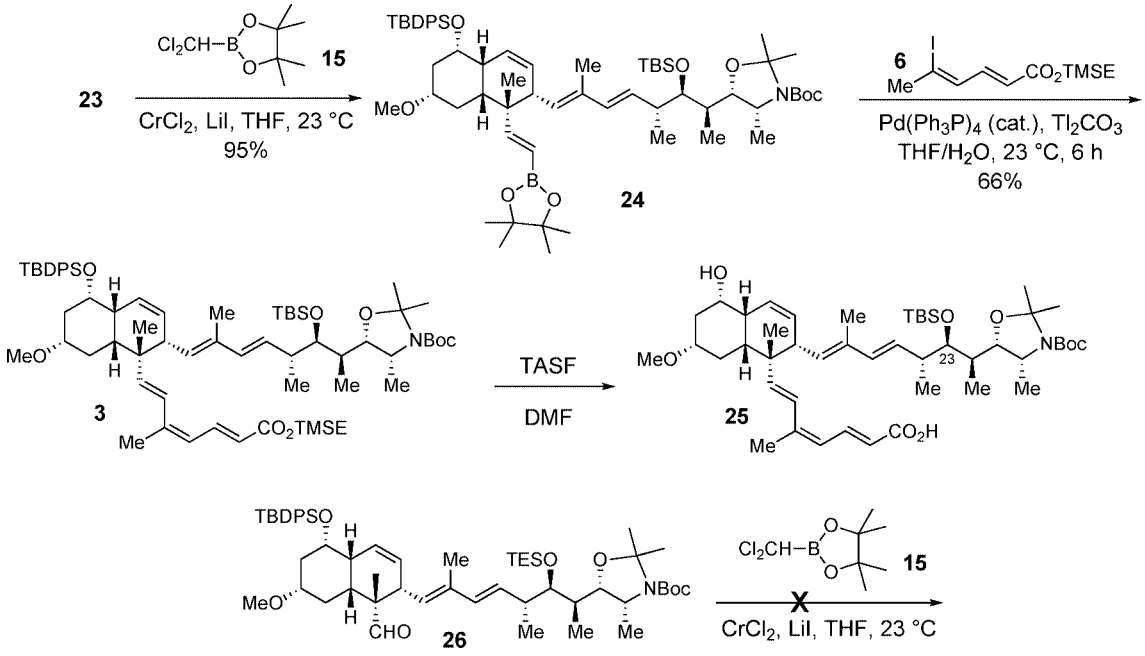
Oxidation of allylic alcohol **22** with SO_3-pyridine[21] afforded **5**, which was then subjected to the intramolecular Diels−Alder

(22) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(23) Takai, K.; Shinomiya, N.; Kaihara, H.; Yoshida, N.; Moriwake, T. *Synlett* **1995**, 963.
(24) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.
(25) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
(26) Markó, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2507.

SCHEME 5. IMDA of Pentaenal 5



SCHEME 6. Elaboration of the IMDA Adduct 23



reaction conditions previously developed in our group for the superstolide synthesis.[9] Specifically, heating a solution of **5** in 2,2,2-trifluoroethanol at 70 °C gave a ca. 6:1:1 mixture of products favoring the endo adduct **23** (65%) (Scheme 5).[27]

The relative stereochemistry of the *cis*-fused bicyclic octahydronaphthalene unit of **23** was assigned on the basis of NOE interactions between H(9), H(10), H(14), H(17), and Me(30) (Figure 2). This assignment is in agreement with the NOE's measured on the natural product[1] and the results observed in the intramolecular Diels–Alder studies of model substrates.[9]

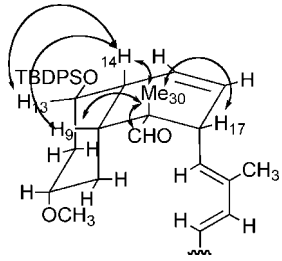
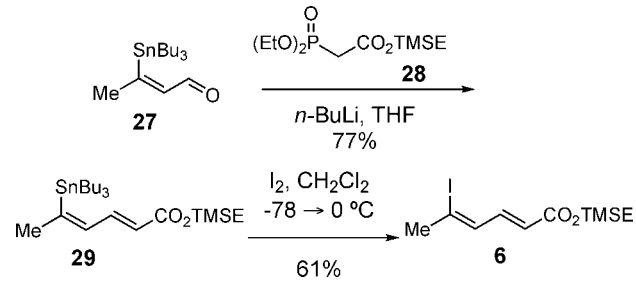


FIGURE 2. ^{1}H NOE interactions in the IMDA adduct **23**.

Aldehyde **23** was subjected to modified Takai conditions[23] using dichloromethylboronate **15**[28] to provide pinacol vinylboronate **24** in 95% yield (Scheme 6). With **24** in hand, we focused on the synthesis of its cross-coupling partner (Scheme 7). Aldehyde **27**[29] was subjected to Horner–Wadsworth–Emmons

SCHEME 7. Synthesis of Iodide 6



olefination using phosphonate **28**[30] to give enoate **29** (77%). Treatment of **29** with iodine in CH_2Cl_2 provided iodide **6** in 61% yield.

Treatment of a mixture of **24** and **6** in wet THF with thallium(I) carbonate[26] and catalytic $Pd(PPh_3)_4$ furnished the trienoate ester **3** in 66% yield (Scheme 6). We thought this intermediate would undergo global silyl deprotection upon treatment with a suitable fluoride source. However, treatment of **3** with TAS-F afforded **25** with a TBS ether remaining on C(23).[31] Unfortunately, further attempts to effect global deprotection with a model substrate failed under a variety of conditions. It was clear from these results that the macrocyclization substrate must have an easily removable protecting group on C(23)-OH. Accordingly, we decided to protect C(23)-

(27) IMDA cyclization of **5** was attempted in toluene at 70–80 °C, but ^{1}H NMR analysis showed lower conversion and decomposition of **5**.

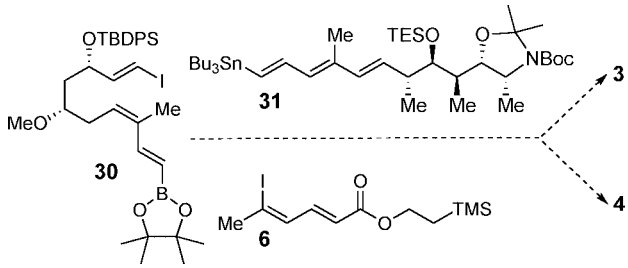
(28) Wuts, P. G.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137.

(29) Dominguez, B.; Pazos, Y.; de Lera, A. R. *J. Org. Chem.* **2000**, *65*, 5917.

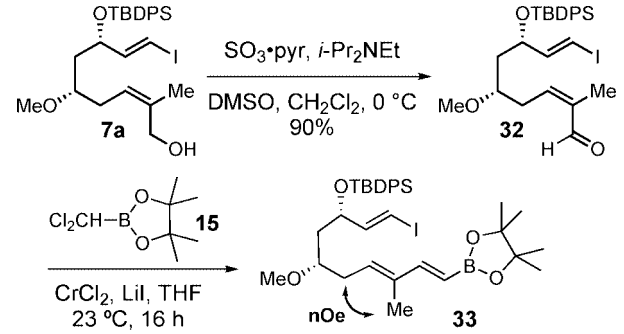
(30) Cushman, M.; Casimiro-Garcia, A.; Hejchman, E.; Ruell, J. A.; Huang, M.; Schaeffer, C. A.; Williamson, K.; Rice, W. G.; Buckheit, R. W. J. *J. Med. Chem.* **1998**, *41*, 2076.

(31) Compound **25** could not be fully characterized due to the small quantities obtained from these experiments, but ^{1}H NMR spectra showed a TBS ether on C(23).

SCHEME 8. Revision of the Synthetic Strategy



SCHEME 9. Unexpected *Z*/*E* Isomerization during Takai Olefination of 32



OH as a triethylsilyl ether. Aldehyde **26** was synthesized following the same sequence shown for the TBS ether **23**. However, despite considerable efforts, we were unable to accomplish the Takai olefination of this intermediate with **15** to give the corresponding pinacol vinylboronate.

Synthesis of Iodo Boronate 30. Due to the difficulties encountered in Scheme 6, we decided to install the vinylboronate unit prior to the IMDA cycloaddition. We thought **30** would be a suitable intermediate for joining the different fragments of the molecule (Scheme 8). Importantly, this modified strategy would still allow us to establish the octahydronaphthalene unit via an intramolecular or transannular Diels−Alder reaction.

Oxidation of alcohol **7a** under Parikh−Doering conditions[21] provided aldehyde **32** in 90% yield (Scheme 9). Surprisingly, the Takai olefination of **32** with dichloromethylboronate **15** resulted in complete *Z*/*E* isomerization of the (*Z*)-trisubstituted double bond to give (*E*)-**33** as a single isomer. Since only one boronic ester was isolated from the Takai olefination, this isomerization was not suspected in our initial trials, in which aldehyde **32** was used directly as the crude product from oxidation of **7a**. However, silica gel chromatographic purification of **32** provided material that was a 70:30 *Z*:*E* mixture of enals. When this mixture was subjected to Takai olefination with **16**, **33** was again obtained as a single (*E*) product, as determined by NOE analysis.

We also tried to introduce the vinylboronate moiety through a hydroboration reaction of an alkyne derived from **32**. However, despite extensive efforts to convert **32** to the requisite enyne (Seyferth−Gilbert,[32] trimethylsilyldiazomethane,[33] and Corey−Fuchs[34] conditions), we were unable to devise a high-yielding and highly stereoselective synthesis of the enyne, and this approach was ultimately abandoned. Here again, isomerization of the trisubstituted olefin was a significant complication.

Second Generation Strategy. At this point, it became apparent that a different strategy was required to construct the C(1)−C(7) fragment of superstolide A. The new approach was designed to proceed from the four building blocks **35**−**38** (Scheme 10). Again, we intended that the timing of the Diels−Alder reaction relative to the macrocyclization event could be adjusted late in the synthesis. We thought a Wittig reaction between phosphonium salt **35** and aldehyde **37** could avoid the isomerization of the labile (*Z*)-trisubstituted double bond C(8)−C(9) demonstrated in Scheme 9. Although we had already developed a synthesis of the Suzuki cross-coupling partner **20** (Scheme 3), the sequence proved not to be highly reproducible on a multigram scale. Therefore, use of the bifunctional linchpin **36** with orthogonal cross-coupling functional groups was considered for synthesis of the C(14)−C(21) tetraene.[35]

Development of a Bimetallic Diene Linchpin. The bifunctional linchpin **36** was designed such that the two termini would bear functional groups capable of undergoing sequential cross coupling reactions. Initially vinylsilane/vinylstannane **36a** and vinylboronate/vinylstannane **36b** were targeted (Scheme 11). Vinylsilane **36a** was prepared by olefination of **44**[29] using lithiated bis(trimethylsilyl)methane,[36] albeit in low yield. Other bases were screened for deprotonation of bis(trimethylsilyl)-methane (methyllithium, *tert*-butyllithium, TMEDA as additive) but with no improvement in reaction efficiency.

The homologation of aldehyde **44** to the vinylboronate **36b** was also problematic. Olefination under Takai conditions using pinacol dichloromethylboronate gave **36b** with no *Z*/*E* selectivity, and use of bis(1,3,2-dioxaborin-2-yl)methane[37] was hampered by the difficulty and unpredictability of its preparation.

We also hoped that homologation of aldehyde **44** to alkyne **45** would allow opportunities for hydrometalation (Scheme 12). Alkyne **45** was prepared from aldehyde **44** by treatment with lithiotrimethylsilyldiazomethane.[33] Unfortunately, attempted hydrozirconation of **45** using the Schwartz reagent[38] did not give the desired compound, and hydroboration with catechol or pinacol borane were also unsuccessful. Gratifyingly, hydroboration of **45** according to Snieckus' procedure[39] provided **36b** in good yield (50−67%).

Synthesis of Pentaenoate 43a. Phosphonium salt **35a** was synthesized from alcohol **7a** by conversion to the corresponding allylic bromide (98%) followed by treatment with PBu_3 (89%, Scheme 13). The synthesis of the aldehyde coupling partner **37a** started from hydroxybutenolide **39**.[40] Horner−Wadsworth−Emmons olefination of **39** with the β-phosphonoester **40** provided **41a** (88%). Reduction of the carboxylic acid via the mixed anhydride followed by oxidation of the primary alcohol using the Dess−Martin periodinane[41] gave **37a** in 68% yield. This aldehyde was then coupled with phosphonium salt **35a** to provide the isomerically pure pentaenoate **43a** in 81% yield.

Synthesis of the C(16)−C(27) Fragment 47. Vinylboronate **47** was synthesized starting from alcohol **46** (Scheme 14).[8b] Temporary protection of C(25)-OH of **46** as a TES ether

(32) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837.

(33) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721.

(34) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

(35) (a) Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, *7*, 2289. (b) Coleman, R. S.; Lu, X. *Chem. Commun.* **2006**, 423.

(36) Gröbel, B. T.; Seebach, D. *Chem. Ber.* **1977**, *110*, 852.

(37) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20.

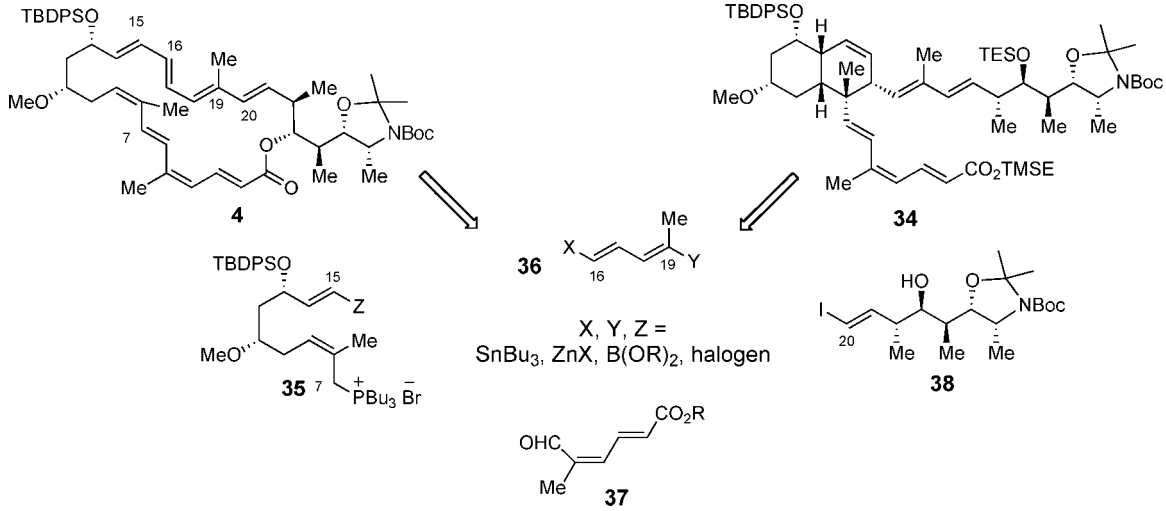
(38) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895.

(39) Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3349.

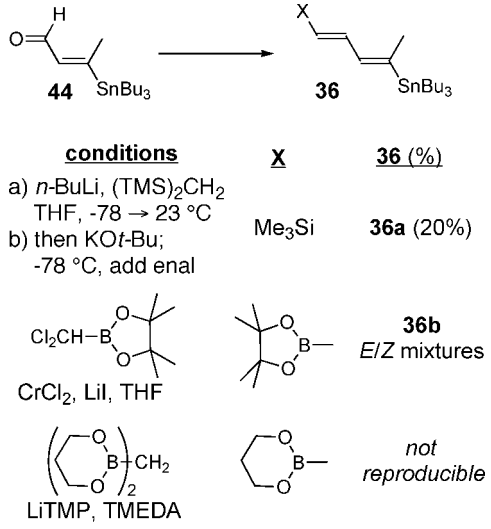
(40) Fell, S. C. M.; Harbridge, J. B. *Tetrahedron Lett.* **1990**, *31*, 4227.

(41) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

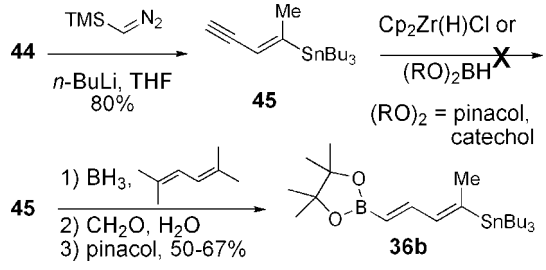
SCHEME 10. Second-Generation Retrosynthesis of Superstolide A



SCHEME 11. Studies on the Synthesis of a Bimetallic Linchpin



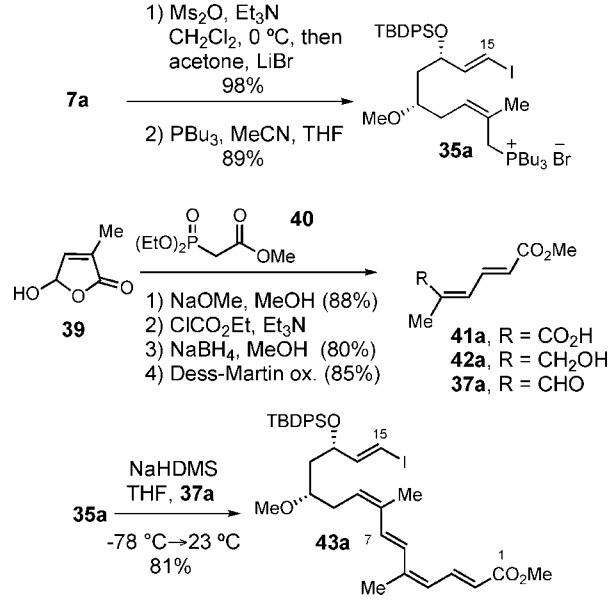
SCHEME 12. Synthesis of Bimetallic Linchpin 36b



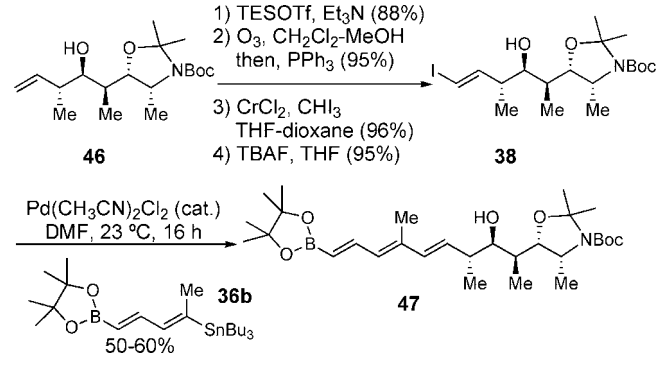
followed by ozonolysis of the alkene provided the corresponding aldehyde. Treatment of this intermediate with $CrCl_2-CHI_3$[22,42] and deprotection of C(25)-OH gave **38** in 76% yield over four steps. Attempted Stille cross-coupling reaction between **38** and bimetallic linchpin **36b**, using catalytic $Pd_2(dba)_3$ and $AsPh_3$ in THF at 50 °C,[43] gave only decomposition of the bimetallic fragment. However, treatment of **38** and **36b** with catalytic $Pd(CH_3CN)_2Cl_2$ in DMF afforded vinylboronic ester **47** in 50−60% overall yield.[44]

Fragment Assembly and Total Synthesis of Superstolide A. With tetraenoate **43a** and vinylboronic ester **47** in hand, we

SCHEME 13. Synthesis and Wittig Coupling of 35a and Aldehyde 37a

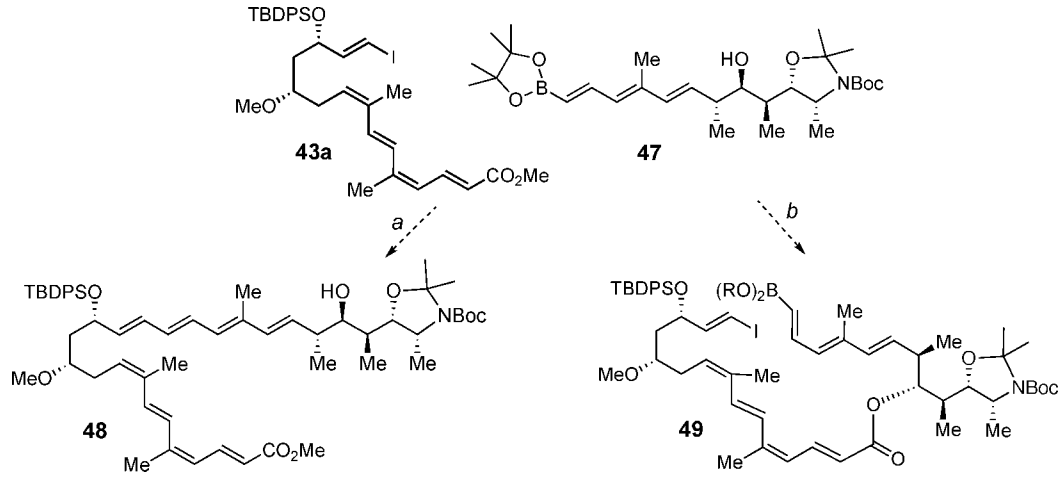


SCHEME 14. Synthesis of the C(16)−C(27) Fragment 47

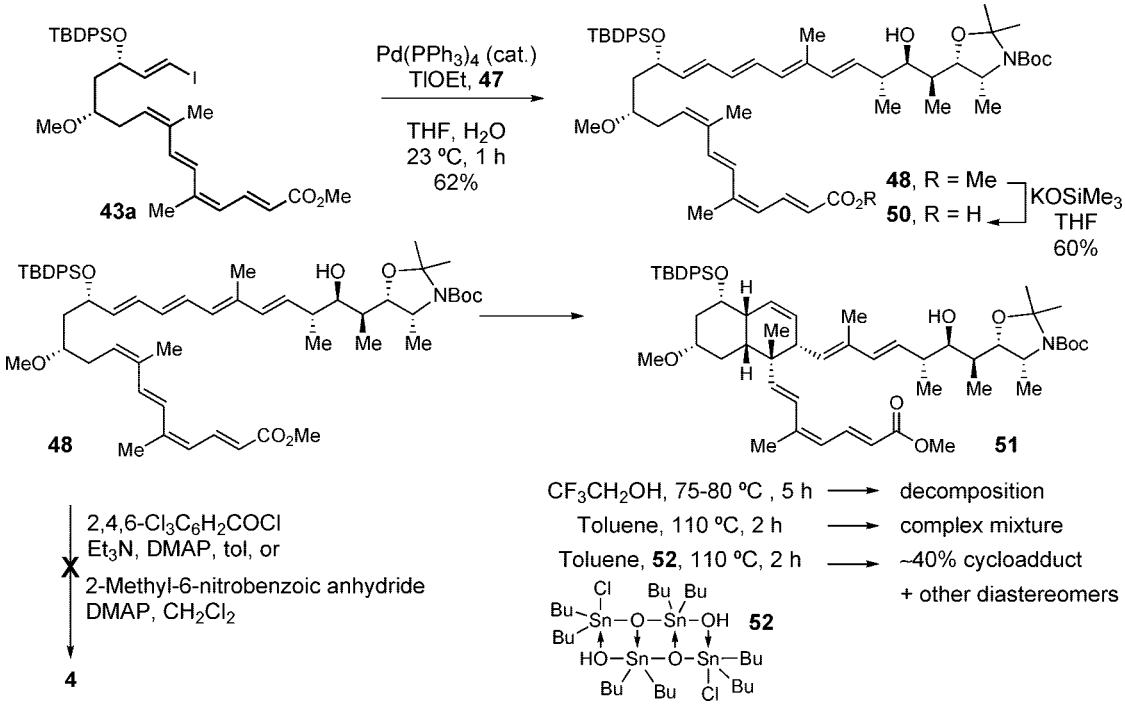


envisioned two possible ways to combine the two fragments: a Suzuki cross-coupling reaction followed by a macrolactonization (path *a*, Scheme 15) or a cross-esterification prior to the Suzuki reaction (path *b*, Scheme 15). Path *a* initially seemed more attractive to us since intermediate **48** would be a suitable

SCHEME 15. Fragment Assembly Strategies



SCHEME 16. Macrolactonization Pathway for Superstolide Synthesis



precursor to test both the intramolecular and transannular Diels−Alder cycloadditions.

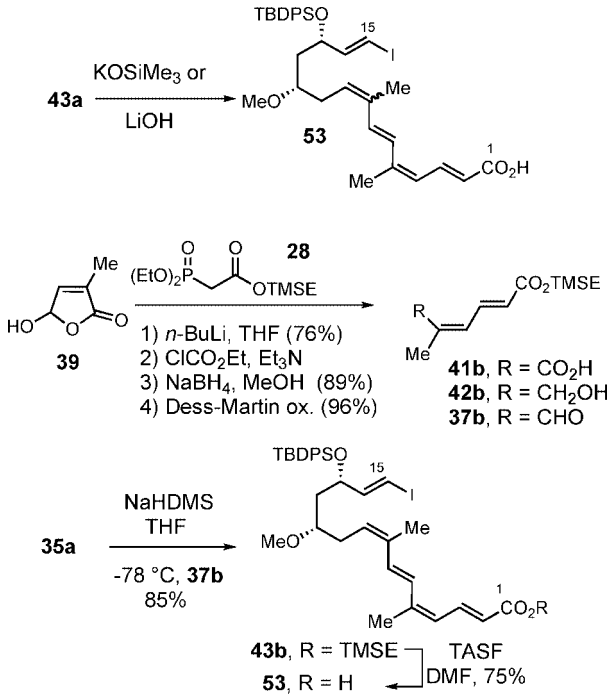
Treatment of **43a** and **47** in wet THF with TlOEt and catalytic $Pd(PPh_3)_4$ provided isomerically pure polyunsaturated ester **48** in 62% yield (Scheme 16).[45] Heating a solution of **48** in CF_3CH_2OH resulted in decomposition probably due to acidity of the solvent. When the IMDA reaction of **48** was attempted in toluene, the ^1H NMR spectrum of the crude product showed low conversion and decomposition of **48**. Slightly better results (ca. 40% of a mixture of diastereomers) were obtained by treatment of **48** with Otera's catalyst **52,**[46] but there was evidence that **48** decomposed upon heating.

Deprotection of the methyl ester of **48** by treatment with $KOSiMe_3$ gave seco acid **50**.[47] Although in some trials we could obtain isomerically pure **50**, this reaction was not reproducible, and inseparable mixtures of compounds derived from isomerization of the labile C(2)−C(9) tetraenoate unit were usually obtained. Pure carboxylic acid **50** was subjected to macrolactonization conditions. Unfortunately, treatment of **50** under Yamaguchi conditions[48,49] or with 2-methyl-6-nitrobenzoic anhydride[50] gave a complex mixture of products.

After this result, we turned our attention to the approach shown in path *b*. Not surprisingly after the difficulties encountered with **48**, attempted deprotection of methyl ester **43a** was problematic (Scheme 17). Under various ester cleavage conditions, we obtained **50** as mixtures of *E*/*Z* isomers at the

(42) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.
(43) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(44) Bimetallic linchpin **36** provided an alternative route to access IMDA precursors analogous to **22** and **5** for the synthesis of IMDA adduct **26** (see the Supporting Information). This sequence was more reliable than that previously described in Schemes 3 and 4.
(45) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691.
(46) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.
(47) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.
(48) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(49) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7.
(50) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535.

SCHEME 17. Synthesis of Carboxylic Acid 53



C(8)−C(9)-trisubstituted alkene. It was clear that synthesis of this sensitive substrate would require a different protecting group strategy for the carboxylic acid of immediate precursors. Accordingly, we elected to use a β-trimethylsilylethyl ester. Horner−Wadsworth−Emmons olefination of hydroxybutenolide **39**[40] and β-phosphonoester **28**[30] afforded **41b** in 76% yield. Reduction of the carboxylic acid via the mixed anhydride followed by oxidation of the dienylic alcohol using Dess−Martin conditions[41] provided aldehyde **37b** in 85% yield. Wittig olefination of this aldehyde using phosphonium salt **35a** provided ester **43b** (85%). Selective deprotection of the ester by treatment with TASF in DMF gave carboxylic acid **53** as a single isomer in 75% yield.[51]

Coupling of the carboxylic acid **53** and alcohol **47** by using the Yamaguchi esterification procedure[48,49] (**53**, trichlorobenzoyl chloride, Et_3N, then **47** and DMAP) gave ester **49** in 65% yield (Scheme 18). Treatment of a 0.001 M solution of **49** in wet THF with TlOEt and catalytic $P(PPh_3)_4$ effected an intramolecular Suzuki reaction that provided the macrocyclic octaene **4** (35−40%).[52] We also isolated products believed to arise from bimolecular cross coupling of **49**. Gratifyingly, macrocycle **4** underwent a highly diastereoselective transannular Diels−Alder cyclization at 23 °C over 5 days, or in 2 h at 80 °C, to give **54** as the only observed cycloadduct in 30−35% overall yield (two steps from **49**). Interestingly, ^{1}H NMR analysis of **54** at 23 °C showed doubling of the ^{1}H resonances for many protons in the vicinity of the *N*-Boc unit, but also distal protons including H(3) and H(6). This observation suggested that **54** exists as a dynamic mixture of *N*-Boc rotamers along with conformational isomers within the newly formed 16-membered ring; this deduction was confirmed by variable temperature ^{1}H NMR studies.

Elaboration of **54** to superstolide A proceeded smoothly (Scheme 18). Removal of the TBDPS ether by treatment with TBAF followed by treatment of the resulting alcohol with trichloroacetyl isocyanate[53] installed the carbamate moiety at C(13) in 65% yield from **54**. Finally, treatment of the resulting carbamate with TFA, to remove the Boc and acetonide protecting groups, followed by addition of Ac_2O and Et_3N provided synthetic (+)-superstolide in 42% yield from **54**. Comparison of the ^{1}H and ^{13}C NMR data of synthetic and natural superstolide A showed excellent agreement.[1]

Summary

We have achieved the first total synthesis of (+)-superstolide A by a convergent and highly stereoselective sequence. Highlights of this work include an intramolecular Suzuki coupling reaction and a highly stereoselective transannular Diels−Alder cycloaddition of **4** to assemble the tricyclic skeleton of superstolide A. This work demonstrates that conformational preferences imposed by the macrocycle improve the stereoselectivity of the key Diels−Alder step, since conventional intramolecular Diels−Alder cycloaddition of **5** gives a 6:1:1 mixture of three cycloadducts. Additionally, the example described herein expands the number of successful applications of Suzuki macrocyclizations to highly functionalized late-stage intermediates in the total synthesis of complex natural products.[52]

A significant part of our efforts in this synthetic venture concerned the efficient and stereoselective synthesis of polyene fragments. Many of the late-stage intermediates were extremely sensitive toward acid, base, or even storage which required the optimization of each individual transformation to avoid isomerization of the double bonds. The solutions found, as well as the synthetic strategies described herein, should be useful for the synthesis of superstolide analogs and other polyene-containing macrolactones.

Experimental Section[54]

Synthesis of Ester 49. To a 0 °C solution of vinyl iodide **43b** (167 mg, 0.217 mmol) in anhydrous DMF (2 mL) was added TAS-F (0.62 mL of a 0.5 M solution in DMF freshly prepared, 0.31 mmol). The mixture was stirred at room temperature for 1 h and quenched with 10% aq $NaHCO_3$ (0.5 mL). Water (2 mL) and EtOAc (5 mL) were added. The organic phase was washed with water (2 × 2 mL) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford carboxylic acid **53** (109 mg, 0.163 mmol, 75%) as a colorless oil, which was immediately used in the next reaction.

To a solution of the crude acid **53** (133 mg, 0.198 mmol) in THF (2 mL) was added triethylamine (0.14 mL, 0.99 mmol) followed by 2,4,6-trichlorobenzoyl chloride (50 μL, 0.32 mmol). The mixture was stirred for 1 h at room temperature. Hexanes (3 mL) were added, and the slurry was filtered through Celite and concentrated. The crude product was dissolved in toluene (2 mL) and was added to a solution of alcohol **47** (93 mg, 0.18 mmol) and DMAP (98 mg, 0.80 mmol) in toluene (2 mL). The reaction mixture was stirred for 12 h at room temperature, diluted with EtOAc (4 mL), and poured into water (4 mL). The aqueous phase was extracted with EtOAc (3 × 4 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered,

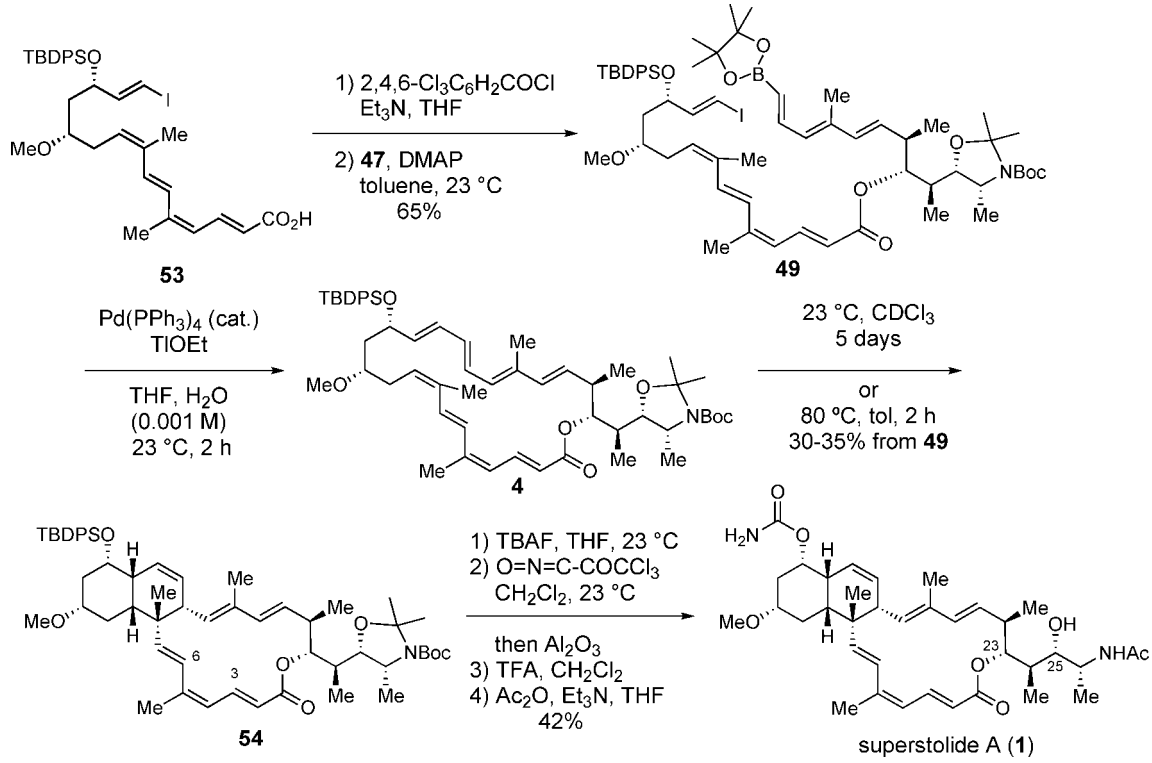
(51) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

(52) (a) For recent examples of Suzuki macrocyclization reactions, see: Jia, Y.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2007**, *9*, 2401. (b) Wu, B.; Liu, Q.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6673. (c) Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313.

(53) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

(54) The spectroscopic and physical properties (e.g., ^{1}H NMR, ^{13}C NMR, IR, mass spectrum, and/or C,H analysis) of all new compounds were fully consistent with the assigned structures. Yields refer to chromatographically and spectroscopically homogeneous materials (unless noted otherwise). Experimental procedures and tabulated spectroscopic data for other new compounds are provided in the Supporting Information.

SCHEME 18. Completion of the Total Synthesis of Superstolide A



and concentrated. Purification by flash chromatography (1 g of Davisil, 5% EtOAc/hexanes) afforded ester **49** (128 mg, 0.109 mmol, 61%) as a yellow oil. The isolated product was contaminated with a small amount of **47** and was immediately used in the next reaction without further purification: ^{1}H NMR (400 MHz, C_6D_6) δ 7.76 (ddd, J = 14.4, 12.2, 2.0 Hz, 1H), 7.63−7.59 (m, 4H), 7.43−7.30 (m, 7H), 6.87 (d, J = 15.6 Hz, 1H), 6.70 (d, J = 15.6 Hz, 1H), 6.48 (dd, J = 14.4, 7.2 Hz, 2H), 6.09 (d, J = 15.6 Hz, 1H), 6.07 (d, J = 12.4 Hz, 1H), 6.02 (d, J = 11.2 Hz, 1H), 5.78 (d, J = 14.8 Hz, 1H), 5.76−5.69 (m, 1H), 5.51 (d, J = 17.6 Hz, 1H), 5.39 (t, J = 7.4 Hz, 1H), 5.24 (td, J = 7.5, 2.8 Hz, 1H), 4.26 (m, 1H), 3.98−3.95 and 3.81−3.78 (2 m, 1H combined), 3.68 (ddd, J = 10.0, 8.1, 4.7 Hz, 1H), 3.32−3.27 (m, 1H), 3.19 (s, 3H), 2.63−2.55 (m, 1H), 2.40−2.25 (m, 2H), 2.07−2.00 (m, 1H), 2.00 (s, 3H), 1.91 (s, 3H), 1.88 (s, 3H), 1.79−1.72 (m, 1H), 1.60−1.50 (m, 1H), 1.57 and 1.52 (2 s, 3H combined), 1.47 and 1.41 (2 s, 3H combined), 1.45 and 1.44 (2 s, 9H combined), 1.26 (s, 3H), 1.11 and 1.07 (2 d, J = 6.3 Hz, 3H combined), 1.07−1.04 (m, 3H overlapped), 1.05 (s, 9H), 0.91 and 0.88 (m, 3H); ^{13}C NMR (400 MHz, C_6D_6) δ 166.2, 151.7, 151.4, 148.5, 146.4, 142.6, 139.2, 139.0, 138.9, 136.2, 136.1, 135.6, 135.5, 134.4, 134.1, 134.0, 133.8, 132.2, 130.1, 129.3, 129.0, 128.5, 124.9, 121.1, 121.0, 93.3, 92.5, 82.9, 79.2, 78.8, 77.7, 77.3, 77.0, 76.9, 75.6, 75.5, 74.2, 56.0, 54.9, 54.7, 42.2, 41.2, 41.1, 34.4, 34.2, 31.6, 30.1, 28.6, 28.4, 27.6, 27.2, 25.1, 24.95, 24.91, 23.9, 21.0, 20.3, 19.5, 17.5, 17.4, 14.1, 13.4, 12.9, 9.8, 9.5 [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]; IR (neat) 2977, 2934, 2280, 1698, 1609, 1455, 1428, 1391, 1342, 1254, 1145, 1106, 993, 703 cm^{-1}; HRMS (ESI) m/z for $C_{63}H_{91}BINO_9SiNa$ [M + Na]$^+$ calcd 1194.5504, found 1194.5502.

Suzuki Macrocyclization of 49 and Transannular Diels−Alder Reaction of 4: Synthesis of Cycloadduct 54. To a solution of ester **49** (120 mg, 0.102 mmol) in degassed THF/H_2O (3:1) (100 mL, three freeze−pump−thaw cycles) was added a solution of $Pd(PPh_3)_4$ (17 mg, 0.01 mmol) in THF (1 mL) followed by TlOEt (14 μL, 0.20 mmol). The mixture was stirred for 2 h and then was filtered through Celite and poured into water (20 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was filtered through a short pad of Davisil (5% EtOAc−hexane, with 2% Et_3N) to afford macrocyclic octaene **4**, which was immediately used in the next reaction without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.60 (m, 4H), 7.45−7.30 (m, 6H), 6.60 (d, J = 15.8 Hz, 1H), 6.52 (d, J = 15.8 Hz, 1H), 6.21 (dd, J = 14.8, 11.5 Hz, 1H), 6.02 (dd, J = 15.3, 12.2 Hz, 1H), 5.87 (d, J = 15.4 Hz, 1H), 5.78 (dd, J = 17.1, 14.3 Hz, 1H), 5.77 (d, J = 14.8 Hz, 1H), 5.65 (d, J = 11.1 Hz, 1H), 5.55 (app td, J = 15.3, 2.0 Hz, 1H), 5.47−5.32 (m, 3H), 5.06 and 5.04 (2 dd, J = 7.7, 1.6 Hz, 1H combined), 4.07 (m, 1H), 3.99 and 3.83 (2 m, 1H combined), 3.71 (m, 1H), 3.04 (s, 3H), 2.97 (m, 1H), 2.33 (m, 2H), 2.18 (m, 1H), 2.00 (m, 2H), 1.96 (s, 3H), 1.77 (s, 3H), 1.75 (s, 3H), 1.56 and 1.51 (2 s, 3H combined), 1.45 (m, 1H overlapped), 1.45−1.43 (2 s, 9H combined), 1.38 and 1.35 (2 s, 3H combined), 1.14 and 1.12 (2 d, J = 6.2 Hz, 3H combined), 1.08−1.03 (m, 3H), 0.95 and 0.93 (2 d, J = 7.1 Hz, 3H combined).

A solution of the crude macrolactone **4** and BHT (one crystal) in toluene (54 mL, 0.001 M) was degassed (three freeze−pump−thaw cycles), heated at 80 °C for 2 h, and then concentrated in vacuo. Purification of the crude product by flash chromatography (0−5% EtOAc−CH_2Cl_2) afforded **54** (31 mg, 0.034 mmol, 33% two steps) as a colorless oil: $[\alpha]^{25}_D$ = +58.0 (c 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (m, 4H), 7.44−7.35 (m, 6H), 7.06 and 7.05 (2 dd, J = 15.5, 10.4 Hz, 1H combined), 6.60 and 6.59 (2 d, J = 16.4 Hz, 1H combined), 6.10 and 6.09 (2 d, J = 15.3 Hz, 1H combined), 6.00 (d, J = 10.5 Hz, 1H), 5.86 (d, J = 10.6 Hz, 1H), 5.73 and 5.72 (2 d, J = 15.3 Hz, 1H combined), 5.64 (d, J = 10.7 Hz, 1H), 5.57 and 5.56 (2 d, J = 16.4 Hz, 1H), 5.51 (dt, J = 10.3, 3.4 Hz, 1H), 5.37 and 5.34 (2 dd, J = 15.3, 9.7 Hz, 1H combined), 4.96 and 4.95 (2 dd, J = 10.5, 3.6 Hz, 1H combined), 3.95 and 3.79 (2 qd, J = 6.0, 4.6 Hz, 1H combined), 3.88 and 3.85 (2 dd, J = 10.5, 4.5 Hz, 1H combined), 3.69 (dt, J = 11.6, 4.9 Hz, 1H), 3.18 (s, 3H), 3.06 (br d, J = 10.0 Hz, 1H), 2.77 (tt, J = 11.1, 3.7 Hz, 1H), 2.49−2.39 (m, 2H), 2.03−1.92 (m, 2H), 1.83 (s, 3H), 1.77 (s, 3H), 1.63 (m, 1H), 1.58 and 1.53 (2 s, 3H combined), 1.49 and 1.47 (2 s, 3H combined), 1.48−1.46 (m, 1H), 1.47 and 1.45 (2

s, 9H combined), 1.39−1.26 (m, 2H), 1.15 and 1.12 (2 d, J = 6.3 Hz, 3H combined), 1.09 (s, 9H), 1.08 and 1.07 (2 d, J = 7.0 Hz, 3H combined), 0.86 and 0.85 (2 d, J = 6.8 Hz, 3H combined); ^{1}H NMR (400 MHz, C_6D_6) δ 7.85−7.82 (m, 4H), 7.35 (dd, J = 15.3, 10.6 Hz, 1H), 7.26−7.22 (m, 6H), 6.78 and 6.77 (2 d, J = 16.4 Hz, 1H combined), 6.28 (d, J = 10.2 Hz, 1H), 5.96 and 5.93 (2 d, J = 10.0 Hz, 1H combined), 5.94 and 5.90 (2 d, J = 15.5 Hz, 1H combined), 5.81−5.77 (m, 2H), 5.63 (br d, J = 10.0 Hz, 1H), 5.57 and 5.56 (2 d, J = 16.4 Hz, 1H combined), 5.29 and 5.28 (2 dd, J = 15.3, 9.7 Hz, 1H combined), 5.30 (d, J = 10.1 Hz, 1H), 4.10 and 3.87 (2 m, 1H combined), 4.02 and 3.96 (2 dd, J = 10.6, 4.5 Hz, 1H combined), 3.84 (m, 1H), 3.11 (br d, J = 10.0 Hz, 1H), 3.00 and 2.99 (2 s, 3H combined), 2.71−2.61 (m, 2H), 2.31−2.21 (m, 2H), 1.96−1.89 (m, 1H), 1.87 (s, 3H), 1.84 (m, 1H), 1.72 and 1.69 (2 s, 3H combined), 1.68 and 1.65 (2 s, 3H combined), 1.65 (s, 3H), 1.64 (m, 1H overlapped), 1.50 and 1.45 (2 s, 9H combined), 1.44 (m, 1H overlapped), 1.22 (s, 9H), 1.20−1.16 (2 d, J = 6.2 Hz, 3H combined), 0.98 (s, 3H), 0.92 and 0.91 (2 d, J = 6.7 Hz, 3H combined), 0.64 and 0.63 (2 d, J = 7.0 Hz, 3H combined); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 167.3, 151.9, 151.5, 142.5, 141.8, 138.2, 135.6, 135.4, 135.3, 134.2, 134.1, 132.7, 132.6, 132.2, 130.8, 129.7, 129.6, 129.5, 127.61, 127.57, 125.80, 125.77, 125.32, 125.28, 122.2, 122.0, 92.7, 92.3, 79.6, 79.0, 77.7, 77.2, 77.0 (overlapping w/ chloroform), 75.7, 75.6, 71.5, 55.7, 54.5, 43.3, 41.6, 41.52, 41.48, 41.47, 41.4, 41.3, 38.6, 37.1, 34.3, 34.1, 30.81, 30.77, 30.0, 29.9, 28.6, 28.5, 28.2, 27.3, 27.0, 24.7, 23.5, 21.1, 19.3, 17.6, 17.5, 13.7, 13.0, 11.99, 11.97, 9.3, 9.2; IR (neat) 2929, 1695, 1388, 1258, 1110, 1003, 867, 820 cm^{-1}; HRMS (ESI) m/z for $C_{57}H_{79}NO_7SiNa$ [M + Na]$^+$ calcd 940.5518, found 940.5517. [Note: compound **54** exhibited coalescence of ^{1}H NMR signals at 50 °C in C_6D_6. See the Supporting Information (2).]

Synthesis of (+)-Superstolide A from Cycloadduct 54. To a 0 °C solution of **54** (20.0 mg, 0.022 mmol) in THF (1 mL) was added TBAF (0.13 mL of a 0.5 M solution in THF, freshly prepared, 0.066 mmol). The reaction mixture was stirred at room temperature for 12 h, diluted with EtOAc (3 mL), and poured into water (2 mL). The aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash chromatography (30−50% EtOAc−hexanes) afforded the C(13)-alcohol (designated **SI-11**, 11 mg, 0.016 mmol, 73%) as a white foam: $[\alpha]^{25}_D$ = +76.5 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 and 7.07 (2 dd, J = 15.5, 10.5 Hz, 1 H combined), 6.67 and 6.65 (2 d, J = 16.3 Hz, 1H combined), 6.11 (2 d, J = 15.3 Hz, 1H combined), 5.89 (d, J = 10.7 Hz, 1H), 5.76 (d, J = 10.4 Hz, 1H), 5.75 and 5.74 (2 d, J = 15.3 Hz, 1H combined), 5.67 (2 d, 2H overlapped), 5.54 (dt, J = 10.2, 3.5 Hz, 1H), 5.39 and 5.38 (2 dd, J = 15.3, 9.7 Hz, 1H combined), 4.97 and 4.96 (2 d, J = 11.1 Hz, 1H combined), 3.95 and 3.78 (qd and m, J = 6.4, 4.9 Hz, 1H combined), 3.88 and 3.85 (2 dd, J = 10.5, 4.6 Hz, 1H combined), 3.82−3.75 (m, 1H), 3.34 (s, 3H), 3.12 (br d, J = 10.0 Hz, 1H), 3.06 (m, 1 H), 2.74 (br s, 1H), 2.44 (m, 1H), 2.17 (br d, J = 11.8 Hz, 1H), 1.97 (m, 1H), 1.88 (s, 3H), 1.78 (s, 3H), 1.77 (m, 1H), 1.58 and 1.53 (2 s, 3H combined), 1.50 and 1.47 (2 s, 3H combined), 1.47 and 1.45 (2 s, 9H combined), 1.44−1.40 (m, 2H), 1.25 (m, 1H), 1.18 (s, 3H), 1.12 and 1.09 (2 d, J = 6.2 Hz, 3H combined), 1.08 and 1.07 (2 d, J = 6.7 Hz, 3H combined), 0.87 and 0.85 (2 d, J = 6.8 Hz, 3H combined); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 167.3, 151.9, 151.5, 142.3, 141.8, 138.1, 135.32, 135.28, 132.9, 132.8, 132.0, 131.0, 130.25, 130.23, 126.04, 126.01, 125.45, 125.43, 121.3, 120.9, 92.7, 92.3, 79.7, 79.0, 77.8, 77.1, 76.9, 75.70, 75.66, 70.3, 55.9, 54.51, 54.50, 43.4, 41.9, 41.8, 41.5, 41.4, 41.3, 38.6, 36.73, 36.69, 34.2, 34.0, 31.0, 30.9, 30.2, 30.1, 28.6, 28.5, 28.2, 27.3, 24.7, 23.5, 21.1, 17.55, 17.52, 13.7, 13.0, 12.02, 12.00, 9.3, 9.2; IR (neat) 3460, 2977, 2934, 2873, 1737, 1698, 1456, 1392, 1375, 1253, 1176, 1113, 1052, 1003, 738 cm^{-1}; HRMS (ESI) m/z for $C_{41}H_{61}NO_7Na$ [M + Na]$^+$ calcd 702.4340, found 702.4405.

To a solution of the C(13)-alcohol (**SI-11**, 11.0 mg, 0.016 mmol) in CH_2Cl_2 (0.5 mL) was added trichloroacetyl isocyanate (6.0 μL, 0.05 mmol). The solution was stirred at room temperature for 30 min and then loaded directly onto neutral Al_2O_3 and allowed to stand for 4 h. The product was flushed from the neutral Al_2O_3 with EtOAc, and the filtrate was concentrated in vacuo. Purification of the crude product by flash chromatography (30−50% EtOAc/hexanes) afforded the C(13)-carbamate (**SI-12**, 9.0 mg, 0.012 mmol, 76%) as a white foam: $[\alpha]^{25}_D$ = +64.9 (c 0.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 and 7.06 (2 dd, J = 15.3, 10.6 Hz, 1H combined), 6.67 and 6.65 (2 d, J = 16.3 Hz, 1H combined), 6.11 (d, J = 15.3 Hz, 1H), 5.90 (d, J = 10.7 Hz, 1H), 5.75 and 5.74 (2 d, J = 15.3 Hz, 1H combined), 5.66 (m, 3H), 5.53 (dt, J = 10.3, 4.5 Hz, 1H), 5.39 and 5.38 (2 dd, J = 15.4, 9.7 Hz, 1H combined), 4.97 and 4.96 (2 d, J = 10.5 Hz, 1H combined), 4.76 (dt, J = 12.5, 4.8 Hz, 1H), 4.65 (br s, 2H), 3.96 and 3.79 (2 m, 1H combined), 3.88 and 3.86 (2 dd, J = 10.7, 4.5 Hz, 1H combined), 3.34 (s, 3H), 3.14−3.06 (m, 2H), 2.87 (br s, 1H), 2.44 (m, 1H), 2.25 (br d, J = 11.4 Hz, 1H), 1.97 (m, 1 H), 1.89 (s, 3H), 1.79 (s, 3H), 1.58 and 1.53 (2 s, 3H combined), 1.50 and 1.47 (2 s, 3H combined), 1.50−1.40 (m, 2H overlapped), 1.47 and 1.45 (2 s, 9H combined), 1.30 (m, 1H), 1.17 (s, 3H), 1.12 and 1.09 (2 d, J = 6.3 Hz, 3H combined), 1.08 and 1.07 (2 d, J = 6.7 Hz, 3H combined), 0.87 and 0.85 (2 d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 167.3, 156.0, 151.9, 151.5, 142.0, 141.8, 138.2, 135.3, 135.2, 133.0, 132.9, 131.8, 131.1, 130.51, 130.50, 126.13, 126.09, 125.51, 125.47, 121.3, 121.1, 92.7, 92.3, 79.7, 79.0, 77.5, 77.1, 77.0 (overlapping w/ chloroform), 75.7, 75.6, 72.9, 56.0, 54.5, 43.2, 41.53, 41.51, 41.44, 41.39, 41.3, 36.1, 34.3, 34.0, 33.6, 31.1, 31.0, 30.2, 30.1, 28.6, 28.5, 28.2, 27.3, 24.7, 23.5, 21.1, 17.55, 17.51, 13.7, 13.0, 12.03, 12.01, 9.3, 9.2; IR (neat) 3422, 2977, 1681, 1673, 1632, 1391, 1257, 1112, 1054, 1003, 867 cm^{-1}; HRMS (ESI) m/z for $C_{42}H_{62}N_2O_8Na$ [M + Na]$^+$ calcd 745.4398, found 745.4439.

To a solution of carbamate **SI-12** (6 mg, 0.008 mmol) in wet CH_2Cl_2 (20 μL of water in 0.80 mL of CH_2Cl_2) was added trifluoroacetic acid (0.4 mL). The reaction mixture was stirred for 30 min at room temperature and then concentrated in vacuo. Toluene (1 mL) was added, and the solution was concentrated (×3, to remove all trifluoroacetic acid). The residue was diluted in THF (0.8 mL), and triethylamine (12 μL, 0.083 mmol) was added followed by acetic anhydride (3 μL, 0.03 mmol). The mixture was stirred overnight at room temperature and then concentrated. Purification of the crude product by flash chromatography (50−100% EtOAc/hexanes) afforded totally synthetic (+)-superstolide A (**1**) (4 mg, 0.006 mmol, 75%) as an amorphous white solid: $[\alpha]^{25}_D$ = +84.0 (c 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 15.2, 11.0 Hz, 1H, H-3), 6.87 (d, J = 16.4 Hz, 1H, H-6), 6.29 (d, J = 15.2 Hz, 1H, H-20), 6.23 (d, J = 8.8 Hz, 1H, NH), 5.91 (d, J = 11.0 Hz, 1H, H-4), 5.79 (d, J = 10.7 Hz, 1H, H-18), 5.70 (d, J = 14.9 Hz, 1H, H-2), 5.68 (d, J = 9.6 Hz, 1H, H-16), 5.60 (d, J = 16.4 Hz, 1H, H-7), 5.52 (dt, J = 10.1, 3.3 Hz, 1H, H-15), 5.32 (dd, J = 15.2, 9.6 Hz, 1H, H-21), 4.79 (d, J = 10.5 Hz, 1H, H-23), 4.77 (m, 1H, H-13), 4.63 (br s, 2H, NH_2), 4.19 (m, 1H, H-26), 3.35 (s, 3H, MeO), 3.33 (br s, 1H, OH-25, overlapped), 3.16 (dd, J = 10.5, 2.4 Hz, 1H, H-25), 3.10 (m, 1H, H-11), 2.89 (br s, 1H, H-14), 2.71 (m, 1H, H-22), 2.24 (br d, J = 10.5 Hz, 1H, H-12), 1.97 (s, 3H, Me-28), 1.92 (s, 3H, Me-29), 1.80 (m, 2H, H-10, H-24), 1.77 (s, 3H, Me-32), 1.48 (m, 1H, H-9), 1.45 (m, 1H, H-10), 1.30 (m, 1H, H-12), 1.15 (s, 3H, Me-30), 1.08 (d, J = 6.8 Hz, 3H, Me-33), 1.05 (d, J = 6.9 Hz, 3H, Me-35), 0.90 (d, J = 6.8 Hz, 1H, Me-34); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.0, 156.1, 142.7, 142.6, 139.3, 137.1, 133.1, 132.4, 130.2, 129.4, 125.8, 125.5, 121.3, 120.3, 77.0 (2C overlapping w/ chloroform), 73.1, 72.8, 56.1, 45.5, 42.9, 41.8, 40.9, 40.4, 37.6, 36.0, 33.7, 31.3, 30.8, 23.5, 20.7, 18.0, 12.6, 12.0, 8.8; IR (neat) 3434, 3351, 2961, 2927, 1716, 1692, 1528, 1451, 1376, 1331, 1261, 1100, 1059, 981 cm^{-1}; HRMS (ESI) m/z for $C_{36}H_{52}N_2O_7Na$ [M + Na]$^+$ calcd 647.3667, found 647.3666.

When making a detailed comparison of the carbon spectrum of the synthetic sample of (+)-superstolide A with that from the

isolation paper, we noticed that the peak for the ester carbon of the macrolactone in our spectrum was significantly smaller than that in the isolation paper. Numerous experiments (increased number of scans, increased relaxation time, increased temperature) were tried in order to minimize this difference, but without success. However, from the proton spectrum it was clear that the isolation sample had much more water present than the synthetic sample. Remarkably, addition of 1 μL of water to the NMR sample of synthetic (+)-superstolide A provided a ^{13}C NMR spectrum that perfectly matched the ^{13}C NMR spectrum available in the literature for natural superstolide A.

Acknowledgment. Financial support provided by the National Institutes of Health (GM026782) is gratefully acknowledged. We also acknowledge Ministerio de Educación y Ciencia, Spain, for a postdoctoral fellowship to M.T.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801794S