JOC Article

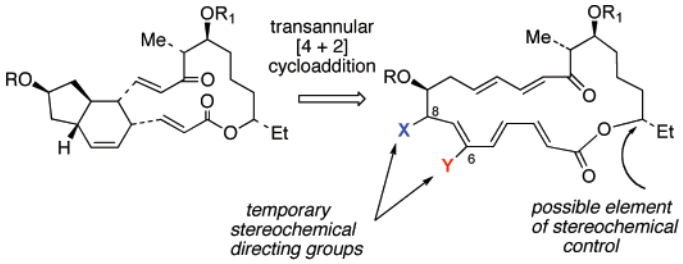
Total Synthesis of (−)-Spinosyn A: Examination of Structural Features That Govern the Stereoselectivity of the Key Transannular Diels−Alder Reaction

SusAnn M. Winbush,[†] Dustin J. Mergott,[‡,§] and William R. Roush*,[†]

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458, and Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48105

roush@scripps.edu

Received November 15, 2007



A study of elements of stereochemical control in transannular Diels−Alder reactions leading to the decahydro-*as*-indacene core of (−)-spinosyn A is described. Initial studies focused on macrocyclic pentaene **9**, which includes C(6)-Br and C(8)-OTBS substituents. Excellent selectivity (>95:5) was observed in the cycloaddition of **9** as a consequence of 1,3-allylic strain interactions involving the C(6) and C(8) substituents in the disfavored **TS-2**. The major cycloadduct **22** was used in a formal synthesis of (−)-spinosyn A. The TDA cyclizations of **12** (which lacks the C(8)-OTBS unit of **9**), **13** (which lacks the C(6)-Br substituent of **12**), and **14** (which lacks the C(6)-Br and C(21)-Et substituents of **12**) were also studied. Macrocycles **12** and **13** served as precursors to (−)-spinosyn A and the (−)-spinosyn A aglycon (**34**), respectively. It is striking that substrates **12**−**14** give very similar distributions of transannular Diels−Alder cycloadducts, indicating that the C(6)-Br and C(21)-stereocenter do not play a significant role in the diastereoselectivity of the TDA cycloaddition of spinosyn A precursor **12**. It is likely that some as yet unidentified conformational or structural features of macrocycles **12**−**14** contribute to the levels of diastereoselectivity achieved, since these TDA reactions are more selective for the C(7)−C(9) stereochemical relationship found in the natural product than are the IMDA reactions of trienes **4** and **7**.

Introduction

Spinosyn A (**1**), a polyketide natural product possessing potent insecticidal activity, is the major component of a biosynthetic mixture generated by the soil microbe *Saccharopolyspora* spinosa.[1a−c] The natural product mixture is currently marketed by Dow AgroSciences as an agricultural insecticide against a variety of insects.[1c−e] Among many attractive features of this highly active class of insecticides is their low toxicity to beneficial insects and rapid degradation in the environment.[1f] Total syntheses of spinosyn A have been reported by the laboratories of Evans[2] and Paquette,[3] in addition to our own.[4]

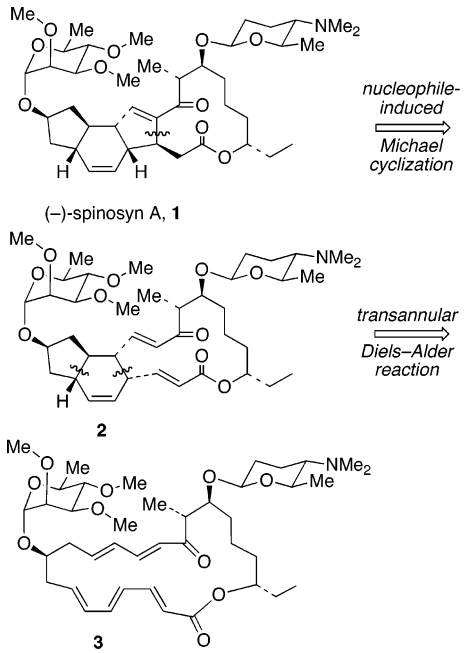
Our strategy for the synthesis of **1**, inspired by the proposed biogenesis[5,6] summarized in Scheme 1, involves the transannular Diels−Alder (TDA)[8,9] cycloaddition of an intermediate of type **3** followed by a nucleophile-induced Michael-type[7] ring closure of macrocycle **2**. Previous studies of the transannular variant

[†] Scripps Florida.
[‡] University of Michigan.
[§] Present address: Lilly Research Laboratories, Indianapolis, Indiana 46285.

(1) (a) Kirst, H. A.; Michel, K. H.; Martin, J. W.; Creemer, L. C.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Jones, N. D.; Thompson, G. D. *Tetrahedron Lett.* **1991**, *31*, 4839. (b) Kirst, H. A.; Michel, K. H.; Mynderase, J. S.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L. D.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Thompson, G. D. In *Fermentation-Derived Tetracyclic Macrolides* 1992; pp 214−225. (c) Creemer, L. C.; Kirst, H. A.; Paschal, J. W. *J. Antibiot.* **1998**, *51*, 795. (d) Sparks, T. C.; Crouse, G. D.; Durst, G. *Pest. Manage. Sci.* **2001**, *57*, 896. (e) Dagani, R. *Chem. Eng. News* **1999**, *77* (July 5), 30. (f) Tomkins, A. R.; Holland, P. T.; Thomson, C.; Wilson, D. J.; Malcolm, C. P. *Proc. 52nd N. A Plant Protection Conf.* **1999**, 94−97.

10.1021/jo7024515 CCC: $40.75
Published on Web 01/24/2008

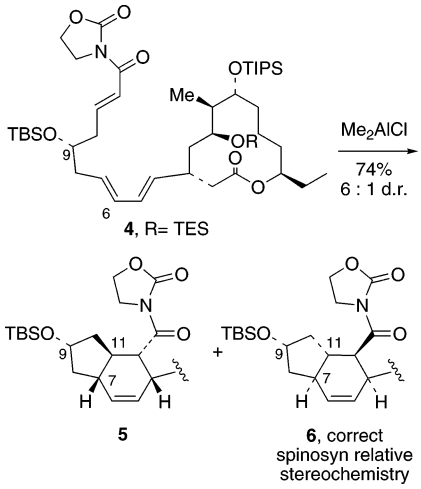
SCHEME 1. Proposed Biogenesis of (−)-Spinosyn A



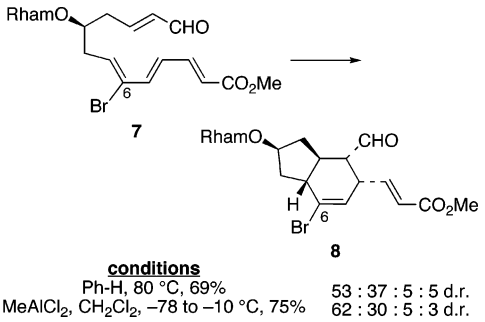
of the Diels−Alder reaction in our laboratory have demonstrated several cases of enhanced stereoselectivity compared to analogous intramolecular cycloadditions.[10,11] In these cases, the manner in which the diene and dienophile approach each other is restricted by conformational constraints which contributes to the level of diastereofacial selectivity observed.[8] At the outset of the (−)-spinosyn A synthesis, we hoped that the TDA reaction of **3**, or its synthetic equivalents, would similarly display enhanced diastereoselectivity compared to traditional intramolecular Diels−Alder substrates.

Initial design and selection of the substrate(s) for our synthetic studies were influenced by the work of Evans[2] (Scheme 2). Data reported for the Me_2AlCl-promoted intramolecular Diels−Alder (IMDA)[12] reaction of **4** indicated that a 6:1 mixture of **5** and **6** was obtained, favoring **5** with the incorrect diastereomeric

SCHEME 2. IMDA Reaction of 4 (work of Evans[2])



SCHEME 3. IMDA Cycloaddition of 7[15]

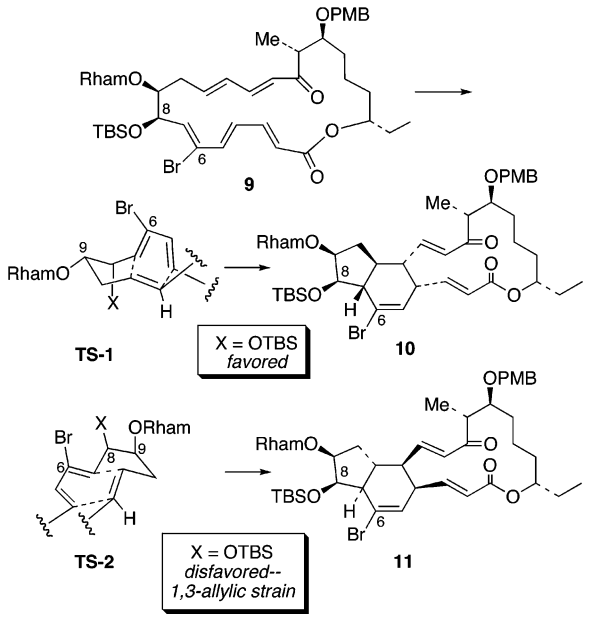


relationship between the C(9)-alkoxy group relative to the C(7)−C(11) ring fusion, opposite to what is needed for the indacene core of spinosyn A.

While our premise was that conformational effects would contribute to a synthetically useful transannular cycloaddition of intermediates patterned after **3**, it was not obvious that these effects would counteract the stereochemical influence of the C(9)-substituent observed in the IMDA reaction of **4**. We chose, therefore, to employ a steric directing group strategy,[13,14] originally developed in our laboratory to effect stereochemical control in the intramolecular Diels−Alder reaction involving placement of a temporary substituent at C(6) of the diene so as to introduce nonbonded interactions in transition states we wished to disfavor.[14] On the basis of a series of preliminary studies, it was apparent that incorporation of a bromine atom at the C(6) position of tetraene **7** partially offset the intrinsic stereochemical directing influence offered by the resident C(9)-alkoxy function (Scheme 3). The stereoselectivity of the thermal IMDA cycloaddition of **7** was only 53:37:5:5 (ca. 1.5:1 dr with respect to the two most abundant diastereomers), whereas selectivities were only slightly better under Lewis acid promoted conditions (62:30:5:3 dr).[15] Therefore, we decided to introduce a second removable substituent at the C(8) position as illustrated in macrocycle **9** (Scheme 4). We anticipated this additional directing unit would introduce an allylic 1,3-strain[16] interaction

(2) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.
(3) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543.
(4) Mergott, D. J.; Frank. S. A.; Roush, W. R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 11955.
(5) (a) Kirst, H. A.; Michel, K. H.; Mynderse, J. S.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L. D.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Thompson, G. D. In *Synthesis and Chemistry of Agrochemicals III*; Baker, D. R., Fenyes, J. G., Steffens, J. J., Eds.; ACS Symp. Ser, No. 504; American Chemical Society: Washington, DC, 1992. (b) For a recent study on the biosynthesis of the spinosyns: Kim, H. J.; Pongdee, R.; Wu, Q.; Hong, L.; Liu, H.-w. *J. Am. Chem. Soc.* **2007**, *129*, 14582.
(6) Review of Diels−Alder reactions in biosynthesis: (a) Stockings, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078. (b) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321.
(7) Little, R. D.; Masjedizadeh, M. R.; Wllquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315.
(8) Review of transannular Diels−Alder reactions in total synthesis: Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243.
(9) Review of Diels−Alder reactions in natural product synthesis: (a) Nicolaou, K. C.; Synder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167.
(10) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502.
(11) Tortosa, M.; Yahekis, N. A.; Roush, W. R. *J. Am. Chem. Soc.* Submitted for publication.
(12) Roush, W. R. Intramolecular Diels−Alder reactions. *Comp. Org. Synth.* **1991**, *5*, 513.
(13) Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3423.
(14) (a) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327. (b) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192.
(15) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157.

SCHEME 4. Transition States for TDA Cycloaddition of 9



with the C(6)-Br atom, thus further destabilizing transition state 2 (**TS-2**) relative to transition state 1 (**TS-1**).[15]

During the course of this work, we synthesized and studied the transannular Diels−Alder reactions of macrocycles **9** and **12** (the latter is a key intermediate in our published total synthesis of **1**).[4] Macrocycles **13** and **14** were also constructed in an effort to elucidate the factors that control the diastereoselectivity of this pivotal transannular Diels−Alder reaction (Figure 1). The results of these studies are described herein.

Results and Discussion

Our initial approach to the synthesis of (−)-spinosyn A (**1**) targeted macrocycle **9**, with two directing groups, as the key cyclization substrate.[17] We envisaged that macrocycle **9** could be accessed through the Horner−Wadsworth−Emmons (HWE)[18] coupling of **15** and **16** (Scheme 5).

Assembly of macrocycle **9** commenced with the coupling of aldehyde **15** (which was prepared by Swern oxidation of the known allylic alcohol precursor—see the Supporting Information for details)[15,19] and known β-ketophosphonate **16** (Scheme 6).[4] Treatment of phosphonate **16** with activated barium hydroxide[20] followed by addition of aldehyde **15** afforded polyene **17** in 94% isolated yield. Treatment of triene **17** with aqueous acetic acid effected deprotection of the TES ether.[21,22] Acylation of the resulting alcohol with diethyl phosphonoacetic acid (**18**) provided phosphonate **19** in 81% yield. Suzuki[23,24] coupling of **19** with vinyl boronic acid **20**[25] then afforded the corresponding allylic alcohol in 63% yield. Subsequent oxidation of the primary alcohol by using the Parikh−Doering[26] protocol provided aldehyde **21**, which was used directly in the next step without purification.

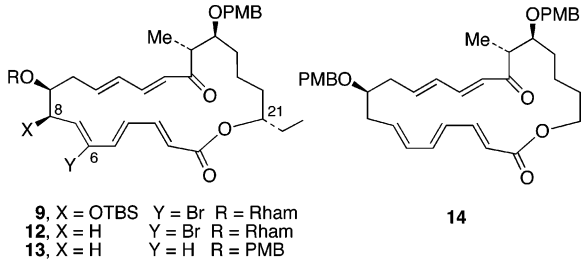
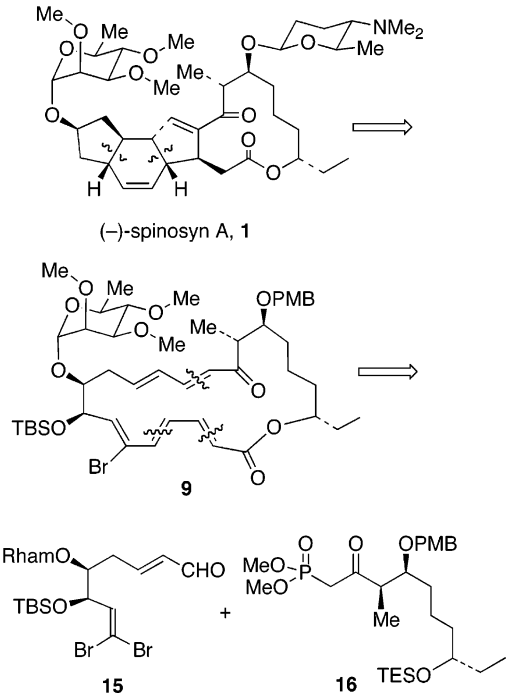


FIGURE 1. Macrocycles studied in this work.

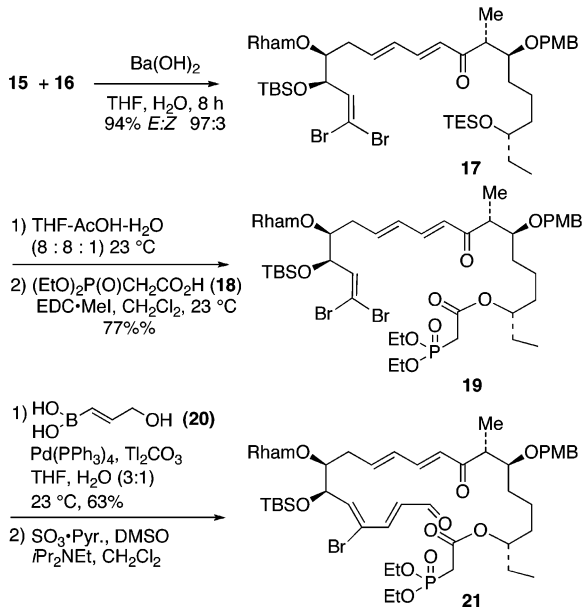
SCHEME 5. Strategy for Synthesis of (−)-Spinosyn A (1) via 9



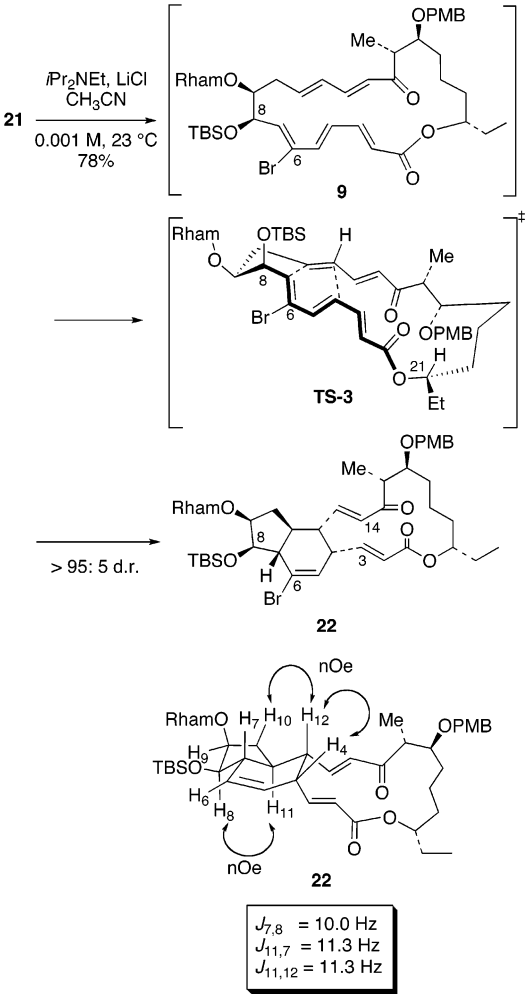
Treatment of **21** with lithium chloride[27] and diisopropylethylamine effected a tandem macrocyclization[28−30] and transannular Diels−Alder reaction, in which the undetected macrocycle **9** directly converts to cycloadduct **22** in 78% yield with >95:5 diastereoselectivity (Scheme 7). The stereochemistry of the adduct **22** was assigned based on 2D NOESY and coupling constant analysis. Key NOE cross-peaks observed in the NOESY spectrum include those between H(12) and both H(4) and H(7), which indicates these three protons reside on the same face of tricycle **22**. The large *J* values observed between H(8), H(7), and H(11) are consistent with a C(7)−C(11) trans-ring fusion, as are the NOE interactions observed for H(8) and H(11).[31]

(16) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(17) Mergott, D. J., 2004, Ph.D. Thesis, University of Michigan, Ann Arbor, MI.
(18) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.
(19) Frank, S. A.; Roush, W. R. *J. Org. Chem.* **2002**, *67*, 4316.
(20) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.
(21) Hart, T. W.; Metcalfe, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, *156*.
(22) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.
(23) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866.
(24) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691.
(25) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989.
(26) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(27) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(28) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.
(29) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010.
(30) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011.

SCHEME 6. Synthesis of Macrocyclization Precursor 21



SCHEME 7. Transannular Diels−Alder Reaction of 9



We developed the vinylogous Morita−Baylis−Hillman (MBH)[32−34] reaction specifically for use in constructing the C(3)−C(14) bond of tetracycle **23.** Treatment of transannular cycloadduct **22** with Me_3P in *tert*-amyl alcohol provided

SCHEME 8. Vinylogous Morita−Baylis−Hillman Cyclization of 22

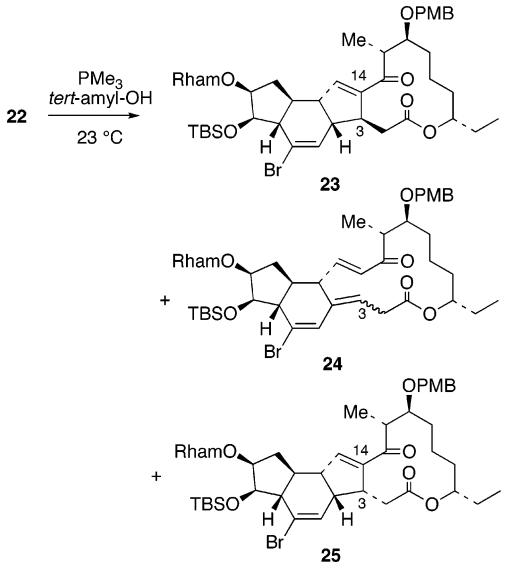


TABLE 1. Vinylogous Morita−Baylis−Hillman Reaction of 22

entry	PMe_3 (equiv)	concn (M)	ratio (**23**:**24**:**25**)	yield (%)
1[a]	1.5	0.05	79:15:6	91
2[b]	1.5	0.05	58:38:4	95
3[c]	0.6	0.05	51:45:4	96
4[d]	8.0	0.005	91:4:5	90
5[e]	8.0	0.005	81:11:8	80

[a] Conducted on 0.001 mmol scale. [b] Conducted on 0.024 mmol scale. [c] Conducted on 0.052 mmol scale. [d] Conducted on 0.002 mmol scale. [e] Conducted on 0.16 mmol scale.

tetracycle **23** as the major component of a 79:15:6 product mixture, along with olefin migration product **24** (whose olefin geometry was not rigorously assigned) and C(3)-diastereomer **25** (Scheme 8). Subsequent experiments with **22**, conducted on a larger scale, however, afforded the desired tetracycle **23** in a 58:38:4 ratio along with **24** and **25** (entry 2, Table 1).

Based on the assumption that the olefin migration is initiated by deprotonation of the allylic C(4)-H of **22**, attempts were made to minimize formation of **24** by modification of the cyclization conditions. While it seemed unlikely that trimethylphosphine ($pK_a = 9$)[35] could be responsible for promoting the olefin migration via direct deprotonation of the C(4)-H, it was found that the amount of **24** increased when Me_3P (0.6 equiv) was added portion-wise to a solution of **22** in *tert*-amyl alcohol (entry 3, Table 1).

Ketone and ester enolates are intermediates along the vinylogous Morita−Baylis−Hillman reaction pathway (Scheme 9). In the presence of an alcoholic solvent, such as *tert*-amyl alcohol, it is probable that some alkoxide ion is also generated by protonation of the enolates (see **27** to **28**).[36] This alkoxide should be capable of initiating olefin migration via deprotonation

(31) Pretsch, E.; Bühlmann, P.; Affolter, C. ^{1}H-NMR Spectroscopy. In *Structure Determination of Organic Compounds*, 3rd ed.; Springer: New York, 2000.

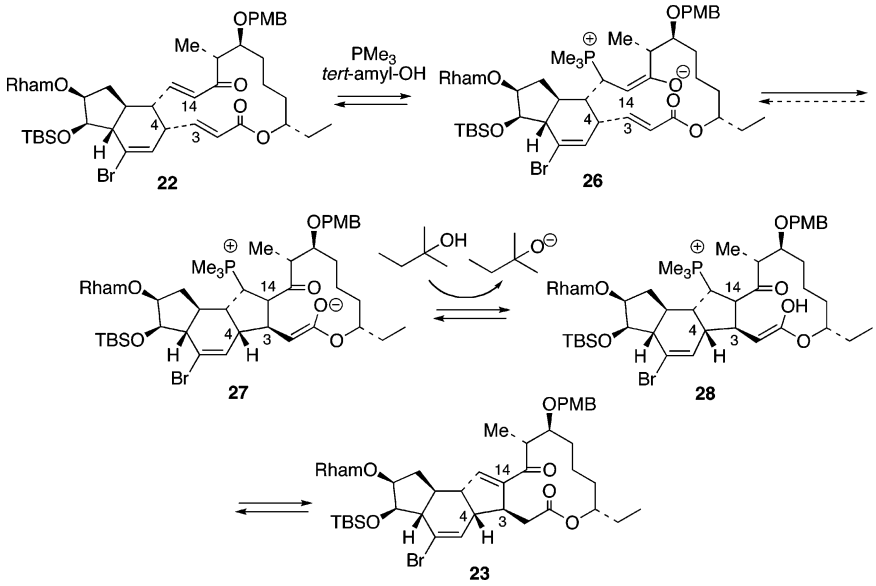
(32) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.

(33) Wang, L. C.; Luis, A. L.; Agaplou, K.; Jang, H. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402.

(34) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404.

(35) Henderson, Wm. A.; Streuli, C. A. *J. Am. Chem. Soc.* **1960**, *82*, 5791.

SCHEME 9. Reaction Pathway for the Vinylogous MBH Reaction of 22

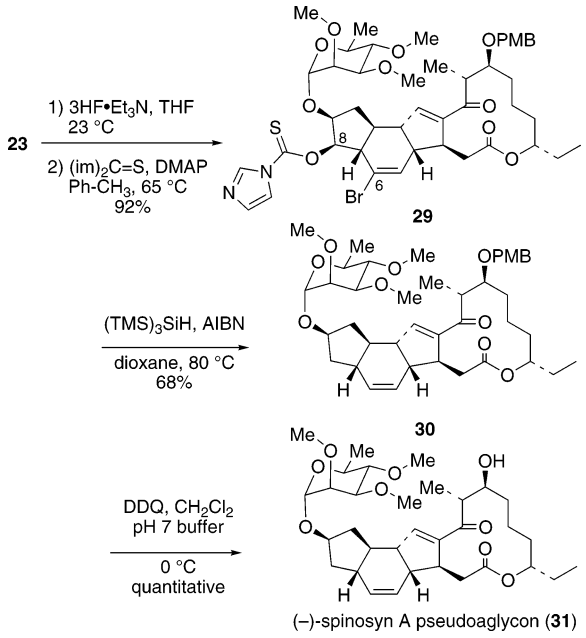


of the C(4)-H of **22**. As this deprotonation is an intermolecular process, it was reasoned that carrying out the reaction under high dilution conditions would suppress the C(2)−C(3) olefin migration. Indeed, when **22** was treated with Me_3P (8 equiv added in 3 portions) in *tert*-amyl alcohol at 0.005 M (a 10-fold dilution over previous experiments) the desired MBH product **23** was obtained in 90% yield as a 91:4:5 mixture with diastereomer **25** and olefin migration product **24** (entry 4, Table 1). When this experiment was performed on a larger scale (entry 5) the ratio dropped somewhat (81:11:8); however, **23** was still obtained in 80% yield. It is conceivable that the large excess of Me_3P used in the experiments leads to very high conversion of **22** to **26**, thereby minimizing the amount of **22** available for the alkoxide-induced deconjugation reaction.

With the steric directing groups having served their purpose in inducing excellent selectivity in the transannular cycloaddition of **9**, it was necessary to excise both units for elaboration of **23** to the natural product. Deprotection of the TBS ether was accomplished in 92% yield by treatment of tetracycle **23** with $Et_3N{\cdot}3HF$.[37] Acylation of the resultant alcohol with thiocarbonyldiimidazole gave thioester **29** in quantitative yield.[38] Exposure of **29** to $(TMS)_3SiH$[39,40] and AIBN at 80 °C effected clean reductive removal of the thiocarbonyloxy and bromine substituents, providing tetracycle **30** in 68% yield. Finally, removal of the PMB group from **30** with DDQ afforded the spinosyn A pseudoaglycon **31** quantitatively (Scheme 10). This material was identical in all respects to natural samples generously provided by both Paquette and Kirst. Synthetic **31** also matched material synthesized in our laboratory from **33**, which was subsequently converted to (−)-spinosyn A (Scheme 11).[4]

It is instructive to compare the stereoselectivity of the transannular Diels−Alder reaction of **9** (Scheme 7) with that of our previously published spinosyn A precursor **12** (Scheme 11).[4] The tandem HWE cyclization of **32** and transannular

SCHEME 10. Synthesis of the Spinosyn A Pseudoglycon (31): Formal Synthesis of (−)-Spinosyn A

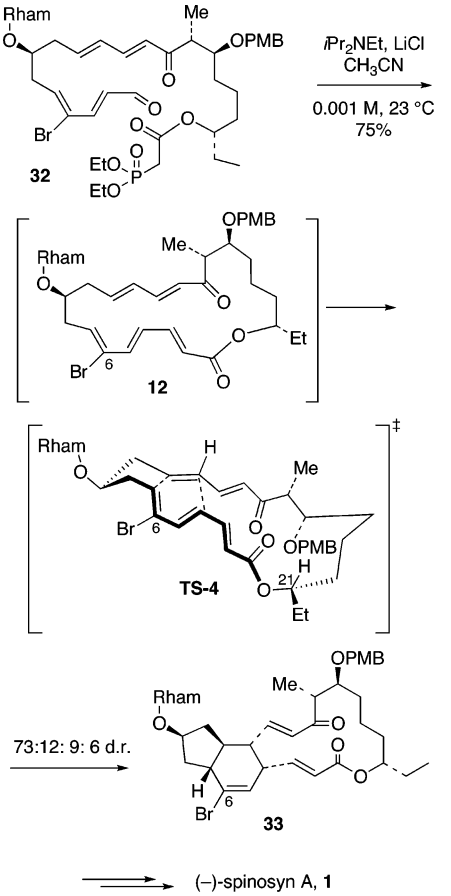


Diels−Alder reaction of macrocycle **12** provided a 73:12:9:6 mixture of four cycloadducts, from which tricycle **33** was isolated as the major diastereomer. Given the selectivity of the conversion of **12** to **33** is lower than that for the conversion of **9** to **22**, it is apparent that the C(8)-OTBS unit of **9** plays a beneficial role in enhancing the stereoselectivity of the TDA reaction of **9** (>95:5 dr). Nevertheless, the selectivity of the **12** to **33** cycloaddition (ca. 6:1 dr) is synthetically useful (as evidenced by our use of **33** in our total synthesis of (−)-spinosyn A),[4] and the synthesis of **12** is several steps shorter than the synthesis of **9**. The conversion of **12** to **33** is also more selective than the ca. 1.5−2:1 selectivity achieved in the IMDA reaction of **7** (Scheme 3).[4,15]

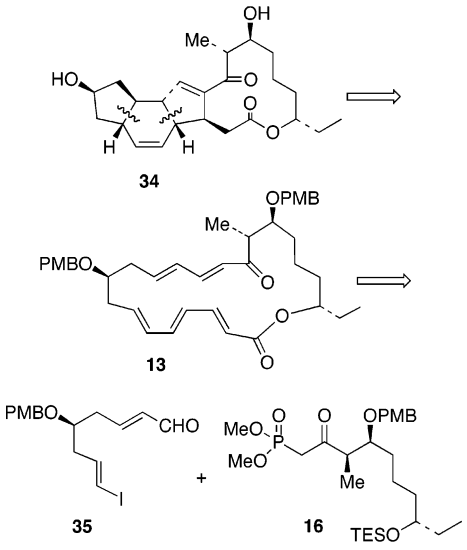
The fact that the transannular cycloaddition of **12** (Scheme 11) is more selective than the IMDA reaction of **7** (Scheme 3) suggests that some additional factors contribute to stereochem-

(36) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.
(37) McClinton, M. A. *Aldrichim. Acta* **1995**, *28*, 31.
(38) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.
(39) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678.
(40) Chargilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

SCHEME 11. Transannular Diels−Alder Reaction of 12[4]

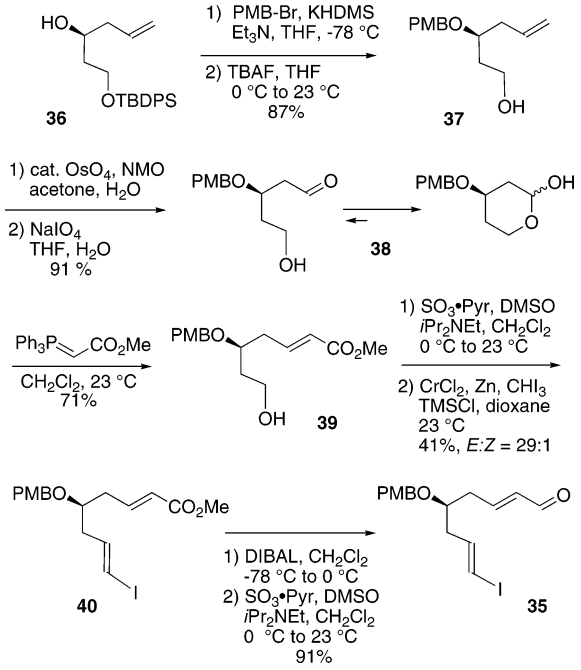


SCHEME 12. Strategy for Synthesis of (−)-Spinosyn A Aglycon 34 via 13

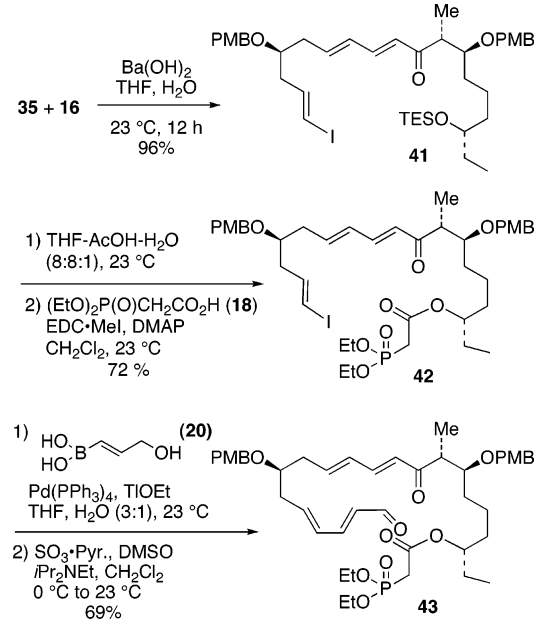


ical control of the transannular event. We speculated the C(21)-stereocenter, adjacent to the macrolactone carbonyl, might be a conformational control element capable of enhancing the diastereoselectivity of the TDA reaction (Scheme 11).[4] In the energetically preferred conformation of the macrolactone linkage, C(21)-H eclipses the C(1)-carbonyl group, allowing the ethyl chain to extend into a sterically unencumbered region.[16] The C(21)-stereocenter thus dictates the face of the diene that the dienophile may approach, by serving as a "turning point"

SCHEME 13. Synthesis of Aldehyde 35



SCHEME 14. Synthesis of Macrocyclization Precursor 43

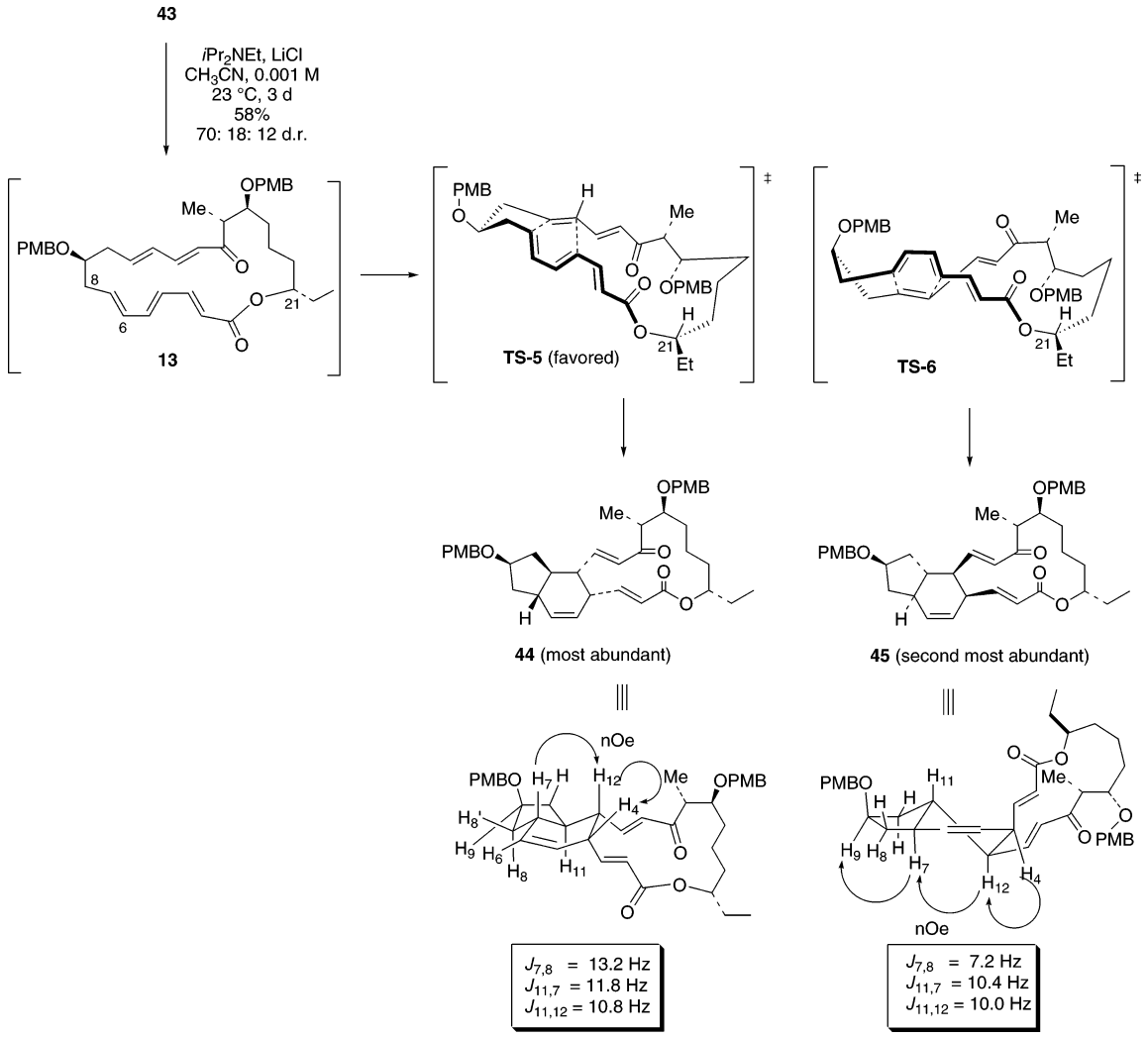


in the macrocycle. Based on the expectation that the C(6)-Br group was playing a beneficial role in **TS-4**, we surmised that the conformational preferences induced by C(21) served to reinforce the (assumed) favorable effects of the C(6)-Br in **TS-4** leading to enhanced selectivity compared to the model intramolecular Diels−Alder substrate **7** (Scheme 3).[4,15]

Based on this analysis, we elected to study the transannular cycloaddition of a substrate lacking any stereochemical directing groups. Accordingly, we targeted the synthesis of (−)-spinosyn A aglycon **34** by way of macrocyclic pentaene **13**. Our strategy to prepare macrocycle **13** closely mimicked that used to access **9** and **12**, with appropriate modifications of precursor **35** (Scheme 12).

The synthesis of vinyl iodide **35** began with enantiomerically enriched alcohol **36**,[41] which is readily available in three steps

SCHEME 15. Transannular Diels−Alder Reaction of 13



with 94% ee from commercially available propane 1,3-diol. Protection of **36** as a *p*-methoxybenzyl (PMB) ether followed by deprotection of the TBDPS ether gave alcohol **37**.[21,22] Olefin dihydroxylation of **37**, followed by oxidative cleavage of the resultant diol afforded hemiacetal **38**.[42] Hemiacetal **38** was treated with $Ph_3P{=}CHCO_2Me_3$ to give **39**. Oxidation of alcohol **39** followed by the application of the catalytic Takai−Utimoto olefination[43] led to vinyl iodide **40** with an optimized *E*:*Z* ratio of 29:1. Reduction of the methyl ester to the primary alcohol and subsequent oxidation of the allylic alcohol to the enal completed the synthesis of fragment **35** (Scheme 13).

Synthesis of TDA cyclization precursor **43** proceeded via the adjoining of fragments **35** and **16** by treatment with $Ba(OH)_2$,[20] followed by a series of standard functional group manipulations depicted in Scheme 14.

Treatment of **43** with LiCl and *i*Pr_2NEt in CH_3CN[27] at ambient temperature over 3 days led to a mixture of cycloadducts (58% yield, combined) from which the major cycloadduct **44** was obtained in 34% yield. Two minor diastereomers of which adduct **45** was the second most abundant were also obtained; the third minor product could not be isolated in sufficient quantity or purity for complete structural characterization.[44] The diastereoselectivity for the conversion of **13** to **44** was 70:18:12, as determined by HPLC analysis of reaction mixtures (Scheme 15).[45]

Macrocycle **13** was not detected at any stage of the reaction, as it spontaneously underwent cycloaddition under conditions of the intramolecular HWE reaction. However, small amounts of material believed to be the macrocyclic (*Z*)-enoate **46** ($J_{2,3}$ = 11. 6 Hz) were isolated and observed to undergo cycloaddition, either at ambient temperature or more rapidly upon mild heating (Scheme 16). Characterization of **46** was complicated by its tendency to cyclize to a mixture of adducts **47** during all manipulations at ambient temperature (including attempted chromatographic purification). Attempts to purify and assign stereochemistry to the cycloadducts produced from **46** were not performed owing to the limited quantities of **46** that were available.

(41) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102.

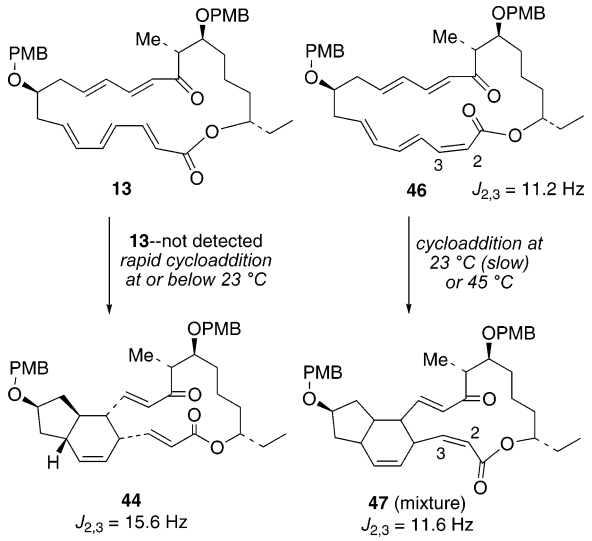
(42) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.

(43) Takai, K.; Ichiguchi, T.; Hikasa, S. *Synlett* **1999**, *8*, 1268.

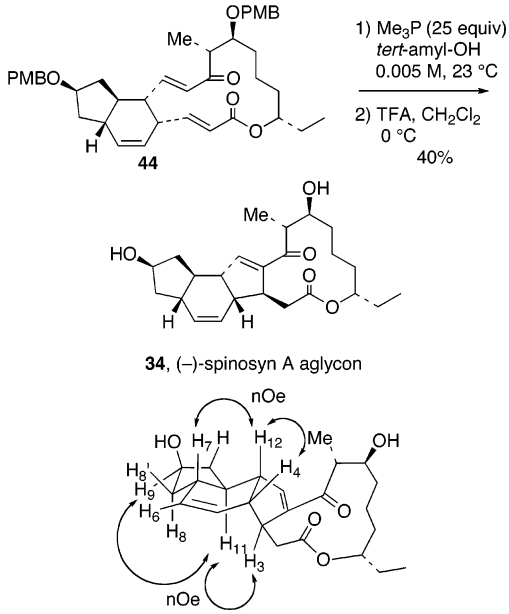
(44) The HWE-TDA cyclization of **43** was also performed with NaH in THF at 23 °C over 5−10 h (51% yield). However, while product yields were comparable, the NaH-promoted HWE reaction mixture contained more byproducts than did the LiCl-*i*Pr_2NEt reaction mixtures.

(45) Diastereomer ratio determined by analytical reverse-phase HPLC (acetonitrile:water:trifuloroacetic acid) with C-18 OD column UV detection at λ = 215, 230, 254, 280, and 420 nm.

SCHEME 16. TDA Cycloaddition of Isomeric Macrocycles 13 and 46



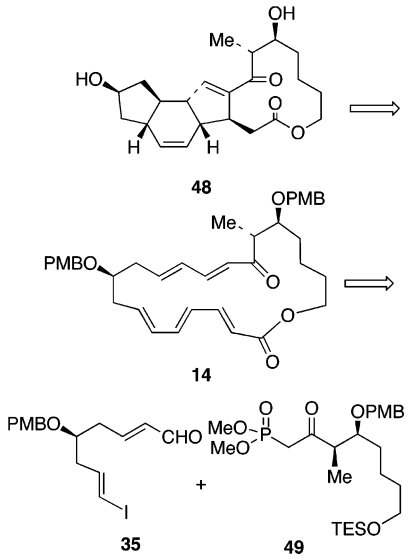
SCHEME 17. Synthesis of (−)-Spinosyn A Aglycon 34



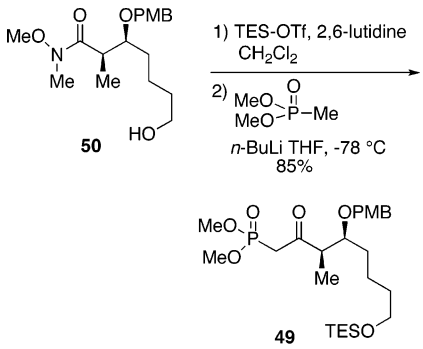
Partial stereochemical assignment of **44** was based on the ^{1}H NOE interactions summarized in Scheme 15. In these stereochemical assignments, the C(9) stereocenter served as an important reference point, as its configuration was determined with confidence as it was installed through the highly enantioselective asymmetric Brown allylation reaction.[46] However, it was difficult to observe the expected H(9)−H(11) cross-peak, since H(11) is buried in the hydrocarbon region of the ^{1}H NMR spectrum of **44**. We opted to convert **44** to the spinosyn aglycon **34** through a vinylogous Morita−Baylis−Hillman cyclization,[32−34] followed by deprotection of the PMB ethers (Scheme 17).

Spectroscopic data obtained for synthetic aglycon **34** compared favorably with the literature data for the natural (−)-spinosyn A aglycon (^{1}H NMR, ^{13}C NMR, HRMS).[1] Further, through a series of 2D NOESY and 1D NOE experiments, NOE cross-peaks were observed between H(9) and H(11), H(3) and H(11), and H(12) with both H(7) and H(4), as indicated in the three-dimensional representation of **34** in Scheme 17.

SCHEME 18. Strategy for Synthesis of 48 via Macrocycle 14



SCHEME 19. Synthesis of β-Ketophosphonate 49



Remarkably, the diastereoselectivity of the transannular cycloaddition of **13** to **44** is quite similar to that observed for the conversion of **12** to **33**, suggesting the C(6)-bromine directing group is not a significant element of stereocontrol in the transannular Diels−Alder reaction of **12**. The carbocyclic framework of macrocycle **13** alone must be responsible for the favorable stereochemical outcome of this cycloaddition.

The final series of experiments in this study were designed to probe our hypothesis that the C(21)-stereocenter might be a stereochemical control element for these transannular Diels−Alder reactions. Specifically, we decided to study the TDA cyclization of macrocycle **14**, lacking the C(21)-stereocenter (see Scheme 18).

The synthesis of β-ketophosphonate **49** (Scheme 19) proceeded by way of the known intermediate **50**,[4] which was protected as a TES ether before conversion of the Weinreb amide unit to the β-ketophosphonate functionality of **49**.[47]

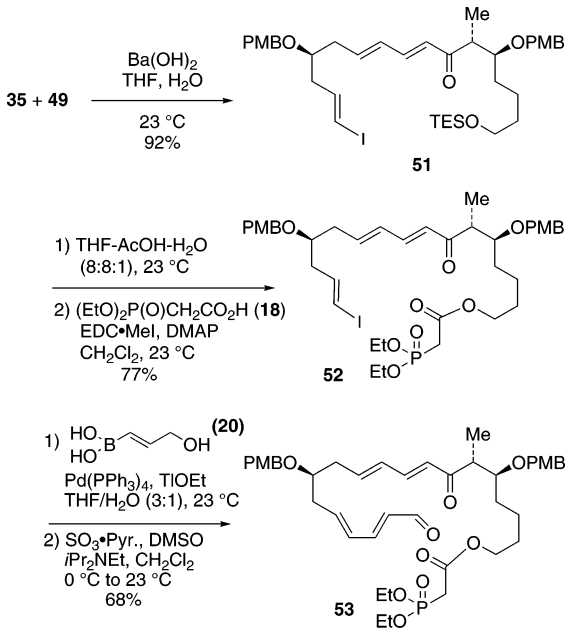
The Horner−Wadsworth−Emmons coupling of **35** and **49** led to the isolation of polyene **51** in 92% yield.[20] Intermediate **51** was then converted to macrocyclization substrate **53** through the series of transformations shown in Scheme 20.

Following the protocol for the macrocyclization reactions of **21**, **32**, and **43**, intermediate **53** was initially subjected to the

(46) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

(47) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374.

SCHEME 20. Synthesis of Precursor 53

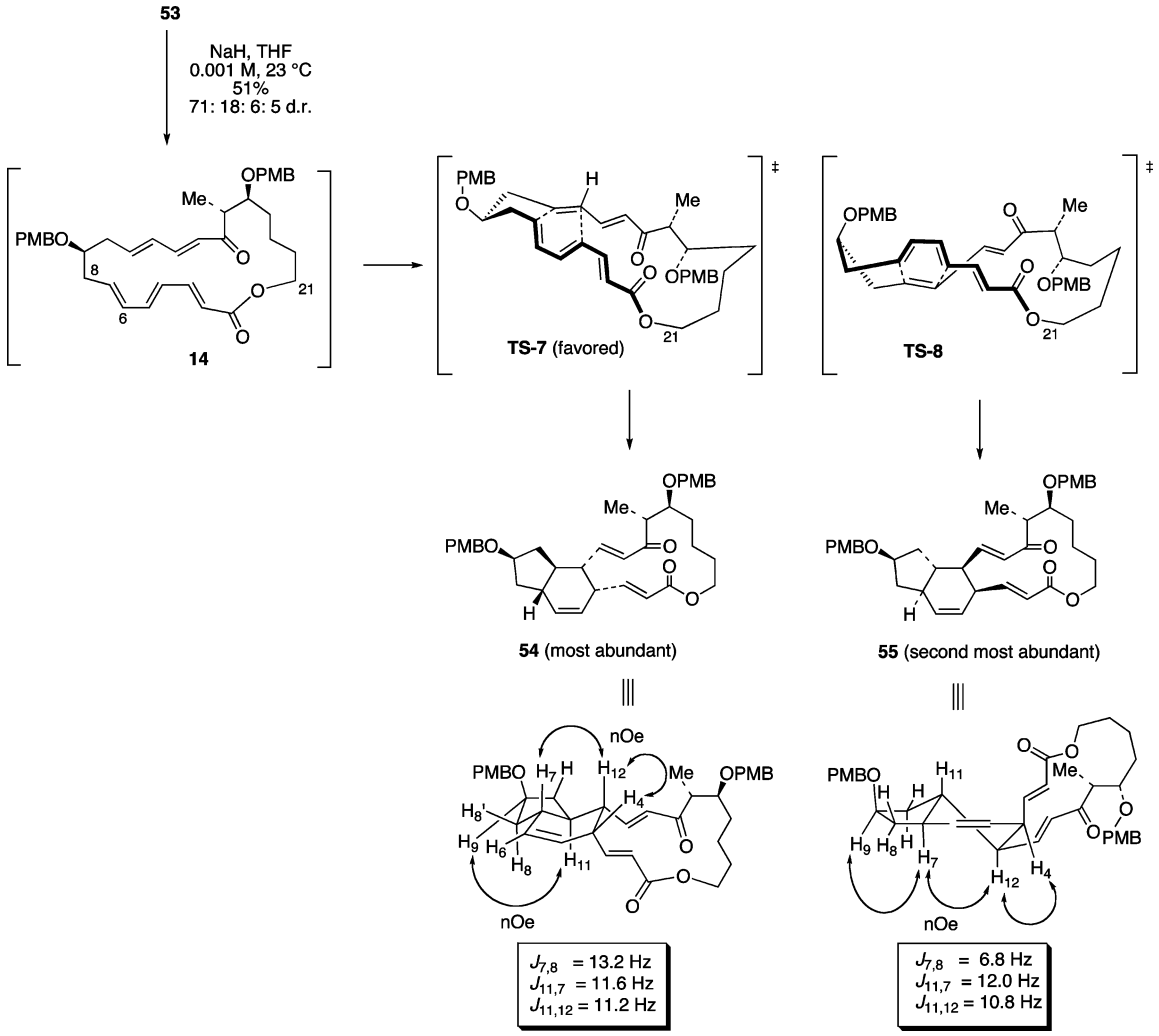


Masamune[27] conditions for HWE olefination; however, treatment of **53** with an excess of lithium chloride and diisopropylethylamine did not result in macrocyclization; only products of hydrolysis of the C(21) O-acyl group were observed. Gratifyingly, treatment of **53** with NaH in THF at 0.001 M concentration led to the isolation of adduct **54**.[48,49] The diastereoselectivity for this one-pot cyclization was 71:18:16:5 (as determined by HPLC analysis),[45] of which **54** and **55** were identified as the two most abundant cycloadducts (Scheme 21).

The stereochemical arrangement about the newly generated tricyclic core of the two major adducts **54** and **55** was established through ^{1}H NOE studies (see Scheme 21). The crucial H(9)−H(11) cross-peak for the most abundant diastereomer **54**, together with $J_{7,11}$ = 11.6 Hz, confirmed that **54** has the appropriate trans-fused C(7)−C(11) configuration, as in the case of (−)-spinosyn A (**1**). Stereoisomer **55** displayed an NOE cross-peak between H(9) and H(7) together with $J_{7,11}$ = 12.0 Hz, indicating that **55** has the relative stereochemistry shown, opposite to the natural product (**1**).

The stereochemical assignment of the most abundant diastereomer **54** was further supported by extensive ^{1}H NOE studies performed on tetracycle **56**, which was generated as shown in Scheme 22 by the Me_3P-mediated vinylogous MBH cyclization. 2D NOESY data obtained for **56** suggest diastereomer **54** has the same stereochemistry about the indacene core as the natural product (**1**).

SCHEME 21. Cycloaddition of 14 and Assignment of Stereochemistry of Two Major Adducts 54 and 55



SCHEME 22. Synthesis of Tetracycle 56 To Confirm Stereochemical Assignment of 54

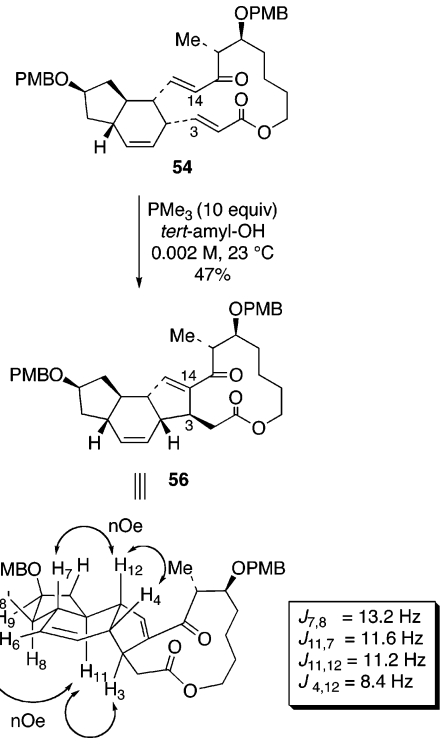


TABLE 2. Summary of TDA Diastereoselectivities

conversion	diastereoselectivity
9 to **22**	>95:5
12 to **33**	73:12:9:6
13 to **44**	70:18:12
14 to **54**	71:18:6:5

It is striking that the diastereoselectivity of the TDA cycloadditions of **12**, **13**, and **14** are very similar (Table 2). Clearly, neither the C(21)-Et substituent nor the C(6)-Br steric directing group contribute substantially to the diastereoselectivity of the TDA cyclization of **12**. That the TDA events of all three substrates are more selective than the IMDA reaction of **7** (Scheme 3),[4,15] and are considerably more selective for the correct C(7)−C(9) stereochemistry than is the IMDA reaction of **4** (Scheme 2),[2] remains suggestive that some conformational feature of the 22-membered ring of **9**, **12**, and **13** is responsible for the enhanced, and more favorable, diastereoselectivity of these TDA reactions. However, it has not been possible to identify the factor (or factors) that is responsible for this enhanced selectivity owing to the conformational flexibility (i.e., multiple conformations) of the developing 15-membered ring in the competing TDA transition states (**TS-5** and **TS-6** in Scheme 15, and **TS-7** and **TS-8** in Scheme 21).

Conclusion

We have studied potential elements of stereochemical control in transannular Diels−Alder (TDA) reactions leading to the perhydroindacene ring system of (−)-spinosyn A (**1**). It is striking that the stereoselectivities of TDA cycloadditions of **12**, **13** (which lacks the C(6)-Br unit of **12**), and **14** (which lacks the C(6)-Br and C(21)-Et substituents of **12**) are very similar (Table 2). Given that the cycloadditions of **12**−**14** are more selective for the C(7)−C(9) stereochemical relationship found in the spinosyns than the IMDA reactions of **4** (Scheme 2)[2] or **7** (Scheme 3),[4,15] we conclude that some as yet unidentified conformational preference of the macrocycles in the competing transition states **TS-5** and **TS-6** (Scheme 15) and **TS-7** and **TS-8** (Scheme 21) contributes to the enhanced diastereoselectivity of the transannular cyclizations. In contrast, the TDA cycloaddition of **9**, which possesses an extra C(8)-OTBS substituent compared to **12**, undergoes a highly diastereoselective transannular cyclization (>95:5 dr). The latter result is attributed to 1,3-allylic strain interactions involving C(6)-Br and C(8)-OTBS in the disfavored **TS-2**.

Experimental Section

(1*R*,2*S*,3a*S*,4*S*,5*E*,8*R*,9*S*,13*S*,16*E*,18*R*,20a*S*)-20-Bromo-1-(*tert*-butyldimethylsiloxy)-13-ethyl-9-(4-methoxybenzyloxy)-8-methyl-2-[(6-deoxy-2,3,4-trimethyl-*O*-methyl-α-L-mannopyranosyl)oxy]-2,3,3a,4,18,20a-hexahydro-1*H*-indeno[5,4-*e*]oxacyclopentadeca-5,16-diene-7,15-dione (22). THF and H_2O were degassed separately via the freeze−pump−thaw method (3 cycles, vent to argon). Vinyl boronic acid **20** (190 mg, 1.9 mmol) was transferred in MeOH to a flask containing **19** (370 mg, 0.34 mmol) and this mixture was concentrated under reduced pressure, placed under high vacuum, and vented to argon. The evacuate/vent cycle was repeated three times and then degassed THF (9 mL) was added followed by degassed H_2O (3 mL). $Pd(PPh_3)_4$ (275 mg, 0.24 mmol) was added and the resulting yellow suspension was stirred for 5 min at which point Tl_2CO_3 (320 mg, 0.68 mmol) was added.[6] The resulting yellow, heterogeneous reaction was protected from light with aluminum foil and stirred under argon for 50 min. At this point, additional $Pd(PPh_3)_4$ (120 mg, 0.10 mmol) and a small amount of Tl_2CO_3 were added. Stirring was continued for an additional 1 h at which point phosphonate **19** was consumed as judged by TLC analysis. The pale yellow reaction mixture was diluted with Et_2O followed by 1 M $NaHSO_4$. The resulting bright yellow biphasic mixture was stirred vigorously for 10 min and then filtered through Celite, rinsing with Et_2O and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated yielding a yellow solid. Purification of this material by column chromatography (40 × 140 mm silica, 1:1 hexanes:acetone) afforded the allylic alcohol **SI-3** (231 mg, 63%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.21 (m, 2 H), 7.15 (dd, J = 15.1, 9.8 Hz, 1 H), 6.88−6.84 (m, 2 H), 6.32−6.15 (m, 5 H), 5.91 (d, J = 8.3 Hz, 1 H), 5.03 (d, J = 1.2 Hz, 1 H), 4.83−4.77 (m, 1 H), 4.64 (dd, J = 8.3, 4.2 Hz, 1 H), 4.47 (d, A of AB system, J = 11.0 Hz, 1 H), 4.41 (d, B of AB system, J = 11.0 Hz, 1 H), 4.31−4.27 (m, 2 H), 4.18−4.11 (m, 4 H), 3.79 (s, 3 H), 3.79−3.76 (m, 1 H), 3.65−3.60 (m, 1 H), 3.57 (dd, J = 9.5, 6.4 Hz, 1 H), 3.55−3.53 (m, 1 H), 3.51 (s, 3 H), 3.48 (s, 3 H), 3.43 (s, 3 H), 3.41 (dd, J = 9.8, 3.2 Hz, 1 H), 3.09 (t, J = 9.3 Hz, 1 H), 2.95−2.89 (m, 1 H), 2.92 (dd, J = 21.5, 3.2 Hz, 2 H), 2.47−2.36 (m, 2 H), 2.30−2.20 (m, 1 H), 1.58−1.41 (m, 8 H), 1.32 (t, J = 7.1 Hz, 6 H), 1.20 (d, J = 6.4 Hz, 3 H), 1.15 (d, J = 6.8 Hz, 3 H), 0.88 (m, 3 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 165.5 (d, J = 6.6 Hz), 159.1, 142.4, 141.3, 132.0, 131.1, 130.4, 129.4, 128.5, 128.4, 127.5, 125.4, 113.7, 97.9, 81.9, 81.1, 80.9, 80.0, 77.4, 74.5, 72.1, 68.2, 62.5 (d, J = 1.8 Hz), 60.7, 58.9, 57.6, 55.2, 48.7, 35.2, 34.9, 33.8, 33.3, 32.6, 26.7, 25.7, 21.4, 17.9, 17.6, 16.3 (d, J = 6.1 Hz), 12.8, 9.4, −4.3, −5.0; $[\alpha]^{26.8}_D$ −41.8 (*c* 9.5, $CHCl_3$); IR (thin film) 3402, 2932, 2858, 1732, 1683, 1656, 1636, 1612, 1593, 1514, 1463, 1441, 1389, 1368, 1251, 1198, 1174, 1118, 1055, 966, 914, 838, 779, 756, 723, 696, 666 cm^{-1};

(48) Stocksdale, M. G.; Ramurthy, S.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 1221.

(49) Menche, D.; Hassfeld, J.; Li, J.; Rudolph, S. *J. Am. Chem. Soc.* **2007**, *129*, 6100.

HRMS (ES) calcd for $C_{51}H_{84}BrO_{15}PSi$ $[M + H]^+$ *m/z* 1077.4398, found 1077.4399.

The above allylic alcohol (231 mg, 0.21 mmol) was azeotropically dried by coevaporation from benzene and then dissolved in CH_2Cl_2 (10.5 mL). *i*-Pr_2NEt (0.26 mL, 1.5 mmol) was added followed by DMSO (0.13 mL, 1.8 mmol). The reaction mixture was cooled to 0 °C and SO_3·pyr (140 mg, 0.88 mmol) was added. The resulting reaction mixture was stirred at 0 °C for 25 min at which point TLC analysis indicated the disappearance of **SI-3**. The reaction mixture was diluted with saturated $NaHCO_3$ (~7 mL), the ice bath was removed, and the biphasic mixture was stirred vigorously for 5 min. This mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated yielding a yellow oil. Residual pyridine was removed by coevaporation from benzene and the resulting aldehyde **21** was used directly in the next reaction.

The crude aldehyde **21** from the preceding experiment (theoretically, 0.21 mmol) was dissolved in CH_3CN (210 mL) under argon. Dry LiCl (340 mg, 8.0 mmol) was added and the resulting heterogeneous mixture was stirred slowly for 5 min to allow the stir bar to grind up the LiCl. *i*-Pr_2NEt (1.25 mL, 7.2 mmol) was added and the mixture was slowly stirred until the LiCl was very finely ground. The stirring velocity was then increased and the reaction mixture was stirred for 12 h at which point ESMS analysis indicated that the starting aldehyde **21** had been consumed. The reaction mixture was poured into a biphasic mixture of EtOAc (300 mL) and 1 M $NaHSO_4$ (100 mL). The reaction flask was rinsed with EtOAc (100 mL) and this rinse was added to the biphasic mixture. The mixture was agitated, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated yielding the crude product (≥95:5 mixture of cycloadducts). Purification of this material by column chromatography (35 × 70 mm silica, 3:2 hexanes:EtOAc) afforded **22** (150 mg, 78%) as a yellow foam. An analytical sample of **22** was prepared by preparative HPLC (3:2 hexanes:EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.23 (m, 2 H), 6.90−6.86 (m, 2 H), 6.62 (dd, J = 16.6, 4.9 Hz, 1 H), 6.45 (dd, J = 15.6, 9.3 Hz, 1 H), 6.05 (dd, J = 16.6, 1.7 Hz, 1 H), 5.83 (dd, J = 4.4, 2.7 Hz, 1 H), 5.71 (dd, J = 15.4, 0.5 Hz, 1 H), 4.91 (d, J = 1.7 Hz, 1 H), 4.90−4.85 (m, 1 H), 4.48 (d, A of AB system, J = 11.0 Hz, 1 H), 4.42 (d, B of AB system, J = 10.7 Hz, 1 H), 3.98 (app dt, J = 6.4, 3.9 Hz, 1 H), 3.91 (dd, J = 9.8, 5.9 Hz, 1 H), 3.81 (s, 3 H), 3.65 (dd, J = 3.2, 1.7 Hz, 1 H), 3.55 (s, 3 H), 3.50−3.46 (m, 1 H), 3.49 (s, 3 H), 3.48 (s, 3 H), 3.46 (dd, J = 9.3, 3.2 Hz, 1 H), 3.34−3.29 (m, 1 H), 3.13 (t, J = 9.5 Hz, 1 H), 3.04 (app quint., J = 7.1 Hz, 1 H), 2.79−2.73 (m, 1 H), 2.67−2.61 (m, 1 H), 2.52 (app quint., J = 7.3 Hz, 1 H), 1.76 (app dq, J = 11.2, 7.6 Hz, 1 H), 1.64−1.24 (m, 10 H), 1.25 (d, J = 6.1 Hz, 3 H), 1.17 (d, J = 6.8 Hz, 1 H), 0.97 (s, 9 H), 0.88 (t, J = 7.3 Hz, 3 H), 0.19 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6, 165.2, 159.2, 145.0, 144.7, 131.3, 130.4, 130.3, 129.5, 123.8, 123.6, 113.8, 99.0, 82.2, 81.3, 81.1, 78.0, 76.6, 76.1, 71.9, 68.6, 61.1, 59.3, 57.8, 55.3, 51.5, 46.8, 45.1, 43.8, 37.5, 35.2, 33.4, 32.2, 27.5, 26.2, 21.1, 17.9, 17.7, 15.2, 9.9, −3.3, −4.5; $[\alpha]^{26.8}_D$ −150.0 (*c* 0.2, $CHCl_3$); IR (thin film) 2930, 2857, 1713, 1664, 1614, 1514, 1462, 1361, 1250, 1123, 1143, 1119, 1104, 1057, 1035, 863, 839, 774, 680 cm^{-1}; HRMS (ES) calcd for $C_{47}H_{71}BrO_{11}Si$ $[M + Na]^+$ *m/z* 941.3847, found 941.3847.

(2*R*,3a*S*,5a*S*,6*E*,10*S*,14*S*,15*R*,17*E*,18a*S*,18b*R*)-10-Ethyl-2,14-bis(4-methoxybenzyloxy)-15-methyl-3,3a,10,11,12,13,14,15,18a,-18b-decahydro-1*H*-indeno[5,4-*e*][1]oxacyclopentadecine-8,16-(2*H*,5a*H*)-dione (44). Method A: To a solution of dienal **43** (20 mg, 0.25 mmol, 1.0 equiv) in CH_3CN (25 mL) was added LiCl (39 mg, 0.93 mmol, 34 equiv; stored in a glovebox and flame dried under vacuum prior to use). Distilled diisopropylethylamine (0.15 mL, 0.85 mmol, 34 equiv) was added to the mixture, and the reaction was stirred for 3 days. The reaction was quenched with 1 N $KHSO_4$ (1 mL), then diluted with EtOAc and H_2O. The aqueous layer was extracted three times with EtOAc. The organic layers were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude mixture (a 70:18:12 mixture of cycloadducts; HPLC analysis) by silica gel column chromatography (4:1 hexanes:ethyl acetate) allowed for the isolation of **44** (5.6 mg, 35%, colorless oil) as the most abundant diastereomer, along with an inseparable mixture of minor diastereomers (overall 9.4 mg, 58% total product). The mixture of minor diastereomers was then subjected to normal phase HPLC (4:1 hexanes:ethyl acetate) allowing for partial separation to provide diastereomer **45** as the second most abundant reaction product. The ratio of diastereomers was determined by reverse-phase analytical HPLC (C-18 OD column 65:35:0.01 acetonitrile:water:trifluoroacetic acid) at simultaneous UV detection of λ = 215, 230, 254, 280, and 450 nm.

Method B: To a solution of dienal **43** (12.2 mg, 0.0153 mmol, 1.0 equiv) in THF (15 mL) was added NaH (1.8 mg, 0.075 mmol, 5.0 equiv) 95% in oil dispersion. The reaction was stirred 5 h at ambient temperature, at which point aqueous saturated NH_4Cl (1 mL) solution was added to quench the reaction. The mixture was diluted with Et_2O and H_2O. The aqueous layer was extracted with Et_2O three times. The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the mixture (see method A) allowed for the isolation of **44** (0.0028 mg, 35%, colorless oil) as the most abundant diastereomer, along with an inseparable mixture of minor diastereomers (overall 0.005 mg, 51% total product). Data for **44**: $[\alpha]^{23.7}_D$ −62.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.22 (m, 4H), 6.89−6.85 (m, 4H), 6.73 (dd, J = 16.6, 4.2 Hz, 1H), 6.51 (dd, J = 15.8, 9.4 Hz, 1H), 6.12 (dd, J = 16.6, 1.8 Hz, 1H), 5.96 (d, J = 9.6 Hz, 1H), 5.71 (d, J = 15.6 Hz, 1H), 5.38 (dt, J = 9.6, 3.4 Hz, 1H), 4.91−4.83 (m, 1H), 4.49 (d, J = 10.8 Hz, 1H), 4.41 (d, J = 10.8 Hz, 1H), 4.39 (br s, 2H), 4.16−4.11 (m, 1H), 3.80 (s, 6H), 3.55−3.50 (m, 1H), 3.35−3.27 (m, 1H), 3.09 (dq, J = 6.8, 1.6 Hz, 1H), 2.85−2.78 (m, 1H), 2.60 (ddd, J = 6.4, 6.4, 6.4 Hz, 1H), 2.38−2.27 (m, 1H), 2.04 (dd, J = 13.0, 6.6 Hz,1H), 1.64−1.35 (m, 11H), 1.19 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 165.6, 159.2, 147.4, 131.1, 130.8, 130.5, 129.5, 129.3, 127.8, 122.9, 113.8, 81.4, 78.1, 76.4, 71.9, 70.5, 55.3, 46.3, 44.3, 42.8, 42.3, 41.3, 37.4, 36.7, 33.6, 32.2, 27.6, 21.1, 15.5, 9.9; IR (thin film, NaCl) 2918, 2850, 1710, 1660, 1586, 1513, 1462, 1355, 1301, 1248, 1207, 1173, 1109, 1060, 1034, 982, 821, 752 cm^{-1}; HRMS (ESI) *m/z* 665.3476 [calcd M + Na^+ $C_{40}H_{50}O_7Na$ 665.3449].

Data for 45: (2*R*,3a*R*,5a*R*,6*E*,10*S*,14*S*,15*R*,17*E*,18a*R*,18b*S*)-10-Ethyl-2,14-bis(4-methoxybenzyloxy)-15-methyl-3,3a,10,11,-12,13,14,15,18a,18b-decahydro-1*H*-indeno[5,4-*e*][1]-oxacyclopentadecine-8,16(2*H*,5a*H*)-dione (45). $[\alpha]^{24.3}_D$ −9.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.21 (m, 4H), 6.91−6.84 (m, 4H), 6.75 (dd, J = 15.4, 10.2 Hz, 1H), 6.64 (dd, J = 15.2, 11.2 Hz, 1H), 6.25 (d, J = 14.8 Hz, 1H), 6.19 (dt, J = 9.0, 3.0 Hz, 1H), 5.80 (dt, J = 9.2, 2.8 Hz, 1H), 5.58 (d, J = 15.6 Hz, 1H), 4.92−4.83 (m, 1H), 4.59 (d, A of AB system, J = 11.2 Hz, 1H), 4.45 (d, B of AB system, J = 11.2 Hz, 1H), 4.20−4.06 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.32−3.28 (m, 1H), 2.87 (qd, J = 6.8, 6.2 Hz, 1H), 2.56 (app t, J = 10.0 Hz, 1H), 2.48 (dt, J = 13.2, 7.2 Hz, 1H), 2.16 (app q, J = 10.0 Hz, 1H), 2.00−1.95 (m, 1H), 1.81−1.11 (m, 12H), 1.08 (d, J = 6.8 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 166.2, 159.1, 147.3, 143.7, 135.2, 131.6, 130.5, 129.4, 129.2, 129.1, 128.3, 128.1, 124.3, 113.8, 82.1, 78.9, 71.2, 70.5, 55.3, 49.1, 44.6, 43.8, 43.6, 41.1, 36.9, 34.5, 32.5 (app d), 27.8, 23.0, 13.71, 9.72; IR (thin film, NaCl) 2920, 2851, 1714, 1657, 1586, 1513, 1463, 1377, 1302, 1248, 1172, 1035, 888, 821, 760, 720 cm^{-1}; HRMS (ESI) *m/z* 665.3403 [calcd M + Na^+ $C_{40}H_{50}O_7Na$ 665.3449].

(2*R*,3a*S*,5a*S*,6*E*,14*S*,15*R*,17*E*,18a*S*,18b*R*)-2,14-Bis(4-methoxybenzyloxy)-15-methyl-3,3a,10,11,12,13,14,15,18a,18b-decahydro-1*H*-indeno[5,4-*e*][1]oxacyclopentadecine-8,16(2*H*,5a*H*)-dione (54). To a solution of dienal **53** (50 mg, 0.066 mmol, 1.0 equiv) in THF

(13 mL) was added NaH (7 mg, 0.292 mmol, 4.4 equiv) 95% in oil dispersion. The reaction was stirred for 23 h at ambient temperature, at which point aqueous saturated NH_4Cl (1 mL) solution was added. The mixture was diluted with Et_2O and H_2O. The aqueous layer was extracted three times with Et_2O. The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude mixture (a 71 : 18 6 5 mixture of cycloadducts by HPLC analysis) by normal phase HPLC (3:1 hexanes:ethyl acetate) led to the isolation of **54** (16.2 mg, 40% overall mixture, colorless oil) as the most abundant diastereomer, along with a mixture of partially separable minor diastereomers of which **55** proved to be the second most abundant. Data for **54**: $[\alpha]^{25.2}_D$ −91.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.22 (m, 4H), 6.90−6.85 (m, 4H), 6.81−6.74 (m, 1H), 6.07 (dd, J = 16.8, 1.6 Hz, 1H), 6.02 (app d, J = 10.0 Hz, 1H), 5.66 (dd, J = 15.6, 1.2 Hz, 1H), 5.45 (dt, J = 10.0, 3.4 Hz, 1H), 4.52 (d, J = 3.2 Hz, 2H), 4.38 (s, 2H), 4.26−4.20 (m, 1H), 4.13−4.05 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.52−3.45 (m, 1H), 3.32−3.25 (m, 1H), 3.14 (dq, J = 16.8, 1.2 Hz, 1H), 2.88−2.82 (m, 1H), 2.52−2.46 (m, 1H), 2.34−2.25 (m, 1H), 2.03 (dd, J = 13.0, 6.6 Hz, 1H), 1.70−1.34 (m, 8H), 1.29 (dd, J = 12.6, 4.6 Hz, 1H), 1.22 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 165.7, 159.3, 159.2, 149.1, 147.3, 131.7, 130.9, 130.5 (app d), 129.4 (app d), 126.5, 123.2, 113.9 (app d), 82.0, 78.2, 72.7, 70.6, 65.1, 55.3 (app d), 47.3, 45.1, 42.5, 41.8, 40.6, 37.0, 36.7, 33.8, 28.0, 23.8, 15.1; IR (thin film, NaCl) 2929, 1714, 1658, 1613, 1586, 1513, 1456, 1353, 1302, 1247, 1172, 1034, 986, 912, 822, 754, 666 cm^{-1}; HRMS (ESI) *m*/*z* 637.3132 [calcd M + Na^+ $C_{38}H_{46}O_7Na$ 637.3136].

Data for 55: (2*R*,3a*R*,5a*R*,6*E*,14*S*,15*R*,17*E*,18a*R*,18b*S*)-2,14-Bis(4-methoxybenzyloxy)-15-methyl-3,3a,10,11,12,13,14,15,18a,-18b-decahydro-1*H*-indeno[5,4-*e*][1]oxacyclopentadecine-8,16-(2*H*,5a*H*)-dione (55). $[\alpha]^{24.4}_D$ + 45.2 (*c* 0.46, $CHCl_3$); ^{1}H NMR δ 7.29−7.21 (m, 4H), 6.90−6.85 (m, 4H), 6.76 (ddd, J = 15.6, 7.2, 2.8 Hz, 1H), 6.14 (d, J = 16.4 Hz, 1H), 6.02 (d, J = 10.0, 3.4 Hz, 1H), 5.68 (dd, J = 15.6, 0.8 Hz, 1H), 4.52−4.35 (m, 4H), 4.25−4.19 (m, 1H), 4.15−4.05 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.59−3.54 (m, 1H), 3.31−3.25 (m, 1H), 3.07 (dq, J = 7.2, 1.2 Hz, 1H), 2.71 (app dt, J = 10.8, 7.2 Hz, 1H), 2.41−2.34 (m, 1H), 1.96−1.28 (m, 7H), 1.17 (d, J = 6.8 Hz, 3H), 1.13 (dd, J = 6.8, 3.2 Hz, 2H); ^{13}C NMR δ 203.0, 165.5, 159.2, 148.6, 148.2, 131.4, 130.9, 130.7, 130.4, 129.4, 129.3, 129.1, 126.6, 123.3, 113.8 (app d), 80.7, 78.3, 72.0, 70.7, 64.6, 55.3, 47.6, 45.4, 43.4, 42.3, 40.0, 37.9, 36.2, 32.1, 28.1, 22.4, 15.0; IR (thin film, NaCl) 2934, 1715, 1613, 1513, 1455, 1302, 1248, 1173, 1035, 821, 731 cm^{-1}; HRMS (ESI) *m*/*z* 637.3093 [calcd M + Na^+ $C_{38}H_{46}O_7Na$ 637.3135].

Acknowledgment. Financial support provided by the National Institutes of Health (GM 26782) is gratefully acknowledged. We thank Dr. Ted Kamenecka for assistance with HPLC analysis of the TDA cycloadducts.

Supporting Information Available: Complete experimental details and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7024515