Studies on the Synthesis of (−)-Spinosyn A: Application of the Steric Directing Group Strategy to Transannular Diels−Alder Reactions

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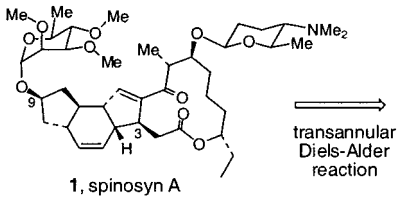
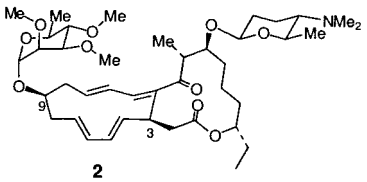
A highly diastereoselective and enantioselective synthesis of the decahydro-*as*-indacene nucleus **12** of (−)-spinosyn A (**1**) is reported. By implementing the steric directing group strategy, tricyclic lactone **37** was produced from a remarkably diastereoselective transannular Diels−Alder reaction of lactone **9**. The tricyclic core of the natural product was then obtained by using an Ireland−Claisen ring contraction of **37**. Reversal of the order of these two steps resulted in an almost complete loss of diastereoselectivity.

Introduction

Spinosyn A (**1**)[1−3] is a member of a group of natural products that possess perhydro-*as*-indacene ring systems.[4−7] The spinosyn family displays very potent insecticidal activity,[8,9] and the biosynthetic mixture (consisting of ca. 85% of **1**) is marketed for use against a wide variety of insects.[9,10] Although total syntheses of the (+)- and (−)-enantiomers of spinosyn A have been reported by Evans and Paquette,[11,12] these molecules remain as challenging targets for total synthesis. Our interest in the spinosyns was inspired by the hypothesis that these molecules are assembled biosynthetically by the transannular Diels−Alder reaction of an appropriately substituted (*E*,*E*,*E*)-cyclododeca-1,6,8-triene such as **2**.[2,13] Hirata has suggested that an analogous transannular Diels−Alder reaction may be involved in the biosynthesis of ikarugamycin.[4b]



1, spinosyn A



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Transannular Diels−Alder (TDA) reactions display significant advantages over conventional intramolecular Diels−Alder variants due to a lowered $\Delta G^{\ddagger}$ resulting from a decreased $\Delta S^{\ddagger}$.[14,15] As a result, cycloaddition reactions of (noncyclic) trienes that do not proceed efficiently in the intramolecular mode work smoothly in the transannular version,[16] sometimes with substantially improved diastereoselectivity.[17,18]

We established in earlier studies that the transannular Diels−Alder reactions of **4a** and **4b**, which were in situ generated by Ireland enolate Claisen ring contractions[19−21] of 16-membered lactones **3a** and **3b**, proceed readily at

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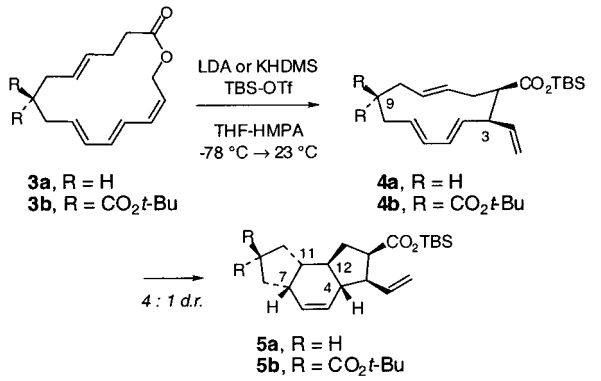
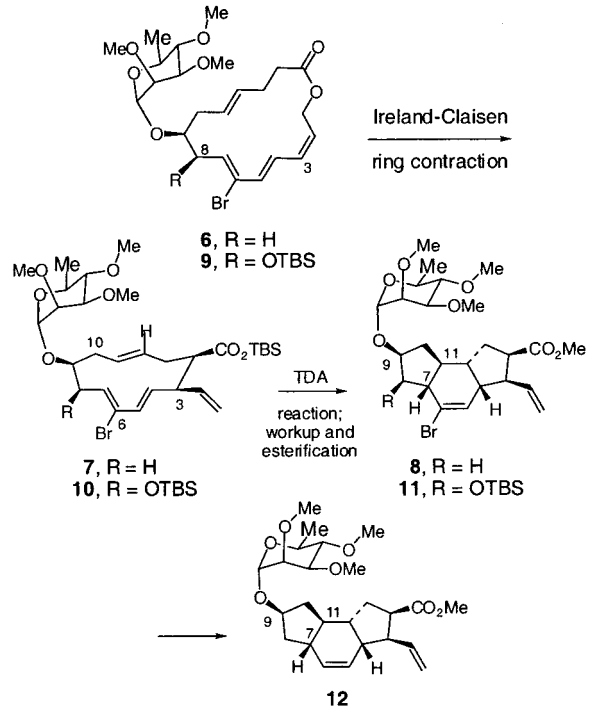
ambient temperature.[22,23] Other strategies for synthesis of the strained (*E*,*E*,*E*)-cyclododeca-1,6,8-triene systems have met with considerably greater difficulty.[24] The TDA reactions of **4** illustrate the great rate accelerations that can be achieved by working in the transannular Diels−Alder manifold, as analogous intramolecular Diels−Alder reactions of trienes with unactivated dienophiles require temperatures in excess of 150 °C for reaction to occur.[25−27] However, the diastereoselectivity of the cyclization reactions of **4a** and **4b** is incorrect for ultimate application to the synthesis of **1**, since the C(7)−C(11) and C(4)−C(12) ring fusions in the natural product are trans and cis, respectively, whereas these two relationships are reversed in tricycles **5a** and **5b**. Consequently, we decided to introduce additional stereochemical control elements into the macrocyclic triene substrate in order to induce the transannular Diels−Alder reaction to produce the stereoisomer required for use in a spinosyn A total synthesis.



In 1985, Boeckman and our group introduced the steric directing group strategy for controlling the diastereoselectivity of intramolecular Diels−Alder reactions.[28,29] We have used this technology to considerable advantage in our total synthesis of chlorothricolide[28,30,31] and in the synthesis of the bottom half fragments of kijanolide and tetronolide.[32] In all of the examples studied to date, introduction of a removable steric directing group at C(6) of the triene substrate led to a substantial increase in selectivity for formation of the trans-ring fusion at the adjacent position (e.g., at C(7)−C(11) in **8**), even in cases where the cis-ring fusion is favored in the absence of the steric directing group substituent.[28,30,31] Accordingly, we anticipated that the diastereoselectivity of the cyclizations of **4** could be reversed by use of a C(6)-substituted triene such as **7** as the transannular Diels−Alder substrate. However, MM2 analysis[33] of transition states of the TDA cyclization of **7** led us to suspect that control of the stereochemical relationship between the C(7)−C(11) trans-fusion and the preexisting C(9)-alkoxy substituent would be poor. Therefore, we also decided to introduce a C(8)−OTBS unit in the Diels−Alder substrate (cf., **10**) in order to better control the transmission of stereochemical information from C(9) to the developing trans-ring fusion in the Diels−Alder reaction. Minimization of potential allylic strain interactions leads to the conclusion that the preferred product of the Diels−Alder reaction of **10** should have the stereostructure depicted in **11**.[31,34] We also anticipated, based on MM2 analysis of possible transition states, that the C(9)-alkoxy group might help to control the stereochemistry of the Ireland enolate Claisen ring contraction of macrocyclic precursor **9** (cf. for control of the C(3)−C(9) stereochemical relationship in **10**).[33]



We describe herein a synthesis of the spinosyn A tricycle **12** by a route involving the tandem ring contraction−transannular Diels−Alder reaction of macrocycle **9**. A second-generation synthesis of intermediate **12** by the transannular Diels−Alder reaction of **9** followed by the Ireland enolate Claisen ring contraction of the initial TDA product is also described.

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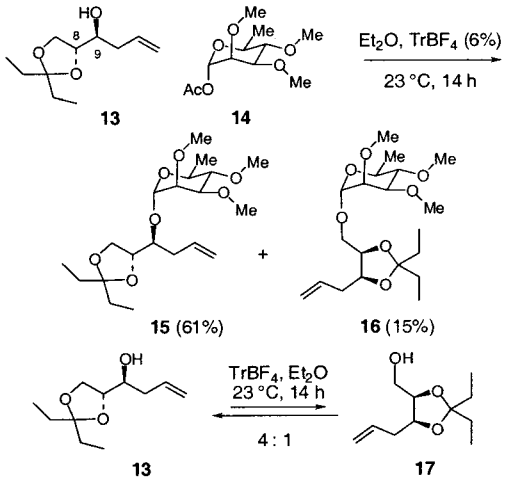
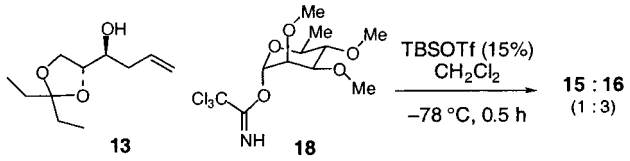
Results and Discussion

Synthesis of Lactone 9. We elected to use the readily available alcohol **13**[35] as the starting material for the synthesis of **12**. The free hydroxyl group of **13** was destined to become the C(9)-substituent of **9**−**12**, while the second stereocenter of **13** would serve as a precursor to the C(8)−OTBS substituent of **9**−**11**. Another key strategic decision on our part was to install the rhamnosyl unit at the very beginning of the synthesis, so as to avoid protection/deprotection sequences for C(9) throughout the synthesis.

Alcohol **13** is easily prepared in excellent yield and with high diastereoselectivity by the asymmetric allylboration of D-glyceraldehyde pentylidene ketal[36] by using the diisopropyl (*R*,*R*)-tartrate modified allylboronate reagent.[37,38] Treatment of **13** with 1.2 equiv of tri-*O*-methyl-α-L-rhamnopyranosyl acetate **14**[39] in Et_2O in the presence of catalytic amounts (6%) of trityl tetrafluoroborate ($TrBF_4$)[40] afforded the desired α-glycoside **15** in 61% yield after chromatographic purification. Also isolated was the regioisomeric glycoside **16** (15% yield). Glycoside **16** results from isomerization of the pentylidene group to the internal diol unit and glycosidation of the primary alcohol.[41] Control experiments showed that treatment of an Et_2O solution of **13** with $TrBF_4$ (0.1 equiv) and AcOH (1 equiv) rapidly produced a 4:1 equilibrium mixture of **13** and the migrated ketal isomer **17**. Apparently, as the glycosidation reaction progresses, an equilibrium is set up between **13** and **17**, and both isomers undergo glycosidation with donor **14**.



Several attempts to suppress the formation of the unwanted glycoside **17** were unsuccessful. Performing the glycosidation reaction in toluene or CH_2Cl_2 gave diminished ratios of **15** with respect to **16** (2:1). Subsequent control experiments established that the equilibrium mixture of **13** and **17** was reached in 1.5 h in toluene under the conditions of the glycosidation reaction (23 °C). Attempts to perform the glycosidation by using TBS−OTf as the promoter[42] gave results similar results to those for the $TrBF_4$-catalyzed procedure (56% isolated yield of **15**). We also prepared a cyclohexylidene ketal protected analogue of **13**, and this presumably more stable acceptor gave identical results in the glycosidation reaction. Attempts to use the much more reactive trichloroacetimidate **18** as the donor, using catalytic TBS−OTf (15%) as the promoter, also provided a 1:3 mixture of **15** and **16**, even though this reaction was complete within 30 min at −78 °C.[43] Because ketal equilibration (**13** to **17**) should not occur rapidly at −78 °C, we suspect that **16** arises by attack of the relatively unhindered primary ether oxygen atom of **13** on the activated glycosyl donor, followed by ketal migration.



The pentylidene ketal protecting group of **15** was hydrolyzed by using an excess of *p*-toluenesulfonic acid in a 1:1 mixture of THF and water at 65 °C, thereby giving the corresponding diol in 96% yield. The diol was then treated with excess TBS−OTf in the presence of 2,6-lutidine to provide the bis-TBS ether **19** in 88% yield after chromatographic purification. Selective removal of the primary TBS ether was achieved by treatment of **19** with PTSA (10%) in MeOH for 3 h.[44] This provided the mono-TBS ether **20** in 71% yield along with 25% of recovered **19**. It was necessary to stop this deprotection reaction short of completion in order to prevent competitive hydrolysis of the secondary TBS ether. Accordingly, resubjection of recovered **19** to the deprotection conditions provided additional quantities of **20**; the yield of **20** was 88% after one such recycle step.

Oxidation of alcohol **20** to the corresponding aldehyde was effected by using the Dess−Martin periodinane reagent.[45] Treatment of the crude aldehyde with a premixed solution of Ph_3P and CBr_4 gave dibromoolefin **21** in 97% yield after chromatographic purification.[46] Selective ozonolysis of the vinyl group was achieved in a 4:1 CH_2Cl_2−MeOH solvent system containing $KHCO_3$ at −78 °C, without special precaution for ozone stoichiometry, since deactivated, halogen-substituted olefins undergo ozonolysis at considerably slower rates.[47] The resulting aldehyde, obtained in 96% yield after the intermediate α-methoxy hydroperoxide was reduced with triphenylphosphine, was treated with 1.4 equiv of vinylmagnesium bromide to give a 2:1 mixture of allylic alcohols **22**. These alcohols, without separation of the diastereomers, were then subjected to the Johnson orthoester Claisen protocol, thereby providing **23** in 94% yield as a single olefin isomer.[48] The importance of stereocontrol for this step is paramount, as this olefin

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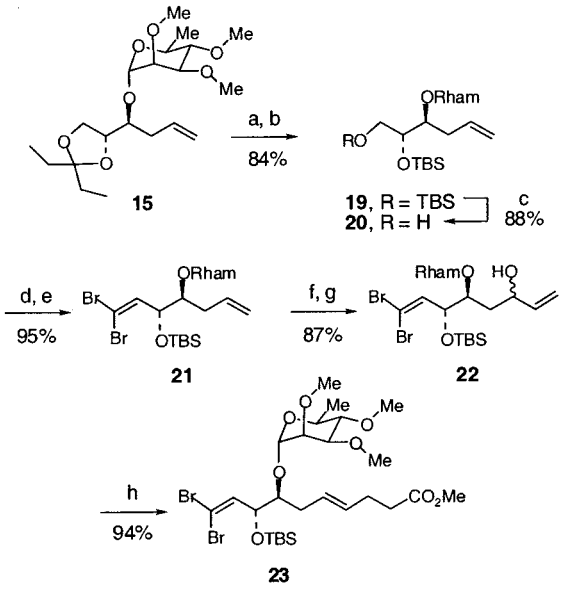
Scheme 1[a]



[a]Key: (a) *p*-TsOH, 1:1 THF, H_2O, 65 °C, 1 h, 96%; (b) TBS-OTf, CH_2Cl_2 2,6-lutidine, 0−23 °C, 88%; (c) *p*-TsOH, MeOH, 0∠23 °C, 3 h, 88% after one recycle of recovered **19**; (d) Dess−Martin periodinane, wet CH_2Cl_2, pyridine; (e) Ph_3P, CBr_4, CH_2Cl_2, 0−23 °C, 0.5 h, 95% from **20**; (f) O_3, 4:1 CH_2Cl_2−MeOH, $KHCO_3$, −78 °C, then Ph_3P, −78 to +23 °C, 96%; (g) $H_2C{=}CHMgBr$, THF, −78 to +23 °C, 91%; (h) $CH_3C(OMe)_3$, $EtCO_2H$, toluene, 110 °C, 72 h, 94%.

serves as the dienophilic segment of the transannular Diels−Alder substrate **10** (Scheme 1).

Vinylboronic acid **25**, needed for the subsequent Suzuki cross-coupling reaction[49,50] with **23**, was prepared in 81% yield by hydroboration of the readily available acetylene **24**[51] with 2.2 equiv of catecholborane.[52,53] Because vinylboronic acid **25** is quite unstable (substantial amounts of intractable material were produced when **25** was stored neat), this material generally was used in the cross coupling reaction with **23** immediately following its preparation. The Pd(0)-catalyzed cross coupling reactions of 1,1-dibromoolefins and vinylboronic acids are known to produce 2-bromo (*Z*)-1,3-dienes with excellent selectivity.[54,55] The efficiency of these reactions is greatly enhanced when performed using thallium hydroxide as the base, which enhances the rate of cross-coupling at the expense of competitive dehydrohalogenation reactions.[55,56] We recently introduced the use of thallium ethoxide in these reactions, owing to problems with the availability and shelf life of TlOH.[57] Accordingly, treatment of dibromoolefin **23** with 3 equiv of **25**, 1.8 equiv of TlOEt, and catalytic amounts of $(Ph_3P)_4Pd$ in aqueous THF (3:1) provided the desired conjugated triene **26** in 75−87% yield.

Table 1. Synthesis of Macrolactone 9 by Cyclization of Seco Acid 27

conditions[a]	*T* (°C)	yield[b] (%)
2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2	45	33
2,4,6-trichlorobenzoyl chloride, DMAP, toluene	65	38
Ph_3P, DEAD, THF	45	54
Ph_3P, DIAD, THF	45	48
PyBrOP, DMAP, CH_2Cl_2	23	37
PyBOP, DMAP, CH_2Cl_2	23	70

[a] All reactions were performed by addition of **27** to the reaction mixtures over 8−12 h. The final concentration of **27** in all cases was 0.003 M. [b] Yields are of chromatographically purified **9**.

Saponification of **26** afforded *seco*-acid **27** in 87% yield, thereby setting the stage for the key macrolactonization experiment (see Table 1).[58] Initial attempts to effect the macrocyclization of **27** by using Mukaiyama conditions (2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, 45 °C)[59] provided the desired lactone **9** in only 33% yield. We observed a dienyl acetylene, resulting from dehydrobromination of **26**, in the ^1H NMR spectrum of the crude reaction product; however, we were unable to isolate the dienyne product owing to its apparent decomposition on silica gel. Use of less basic reaction conditions, such as the Yonemitsu variant[60] of the Yamaguchi macrolactonization procedure,[61] gave only a slight improvement in the isolated yield of **9** (38%). A significant improvement (54% isolated yield of **9**) was achieved when Mitsunobu conditions were employed.[62] However, substantial amounts of the hydrazide coupling product **28** were also obtained, a side product that is known to occur when the concentration of the acid coupling partner is low with respect to the alcohol.[63] All attempts to minimize the formation of **28** by modification of reaction conditions were unsuccessful. Replacement of diethyl azodicarboxylate in the Mitsunobu protocol with the more sterically hindered diisopropyl azodicarboxylate, which has been used previously to suppress formation of hydrazide substitution products,[64] led to the formation of **9** in only 48% yield. Ultimately, the best results were obtained when the macrolactonization of **27** was performed by using the peptide coupling agent benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP).[65] Indeed, we were delighted to discover that slow addition of **27** to a CH_2Cl_2 solution of PyBOP and DMAP provided **9** in 70% yield. However, use of the related peptide coupling agent PyBrOP provided **9** in only 37% yield.[66]

Ring Contraction and Cycloaddition of 9. Treatment of lactone **9** with KHMDS and TBS−OTf in 4:1 THF−HMPA at −78 °C followed by heating the intermediate silyl ketene acetal at 140 °C overnight afforded a mixture of tricyclic adducts. The mixture was subjected to an aqueous workup to hydrolyze the TBS esters, followed by esterification of the mixture of carboxylic acids with $TMSCHN_2$, thereby giving a mixture of four diastereomeric methyl esters as determined by ^1H NMR analysis. Partial separation of two of the diastereomers, **30** and **31**, was achieved by column chromatography; **30** was isolated in 23% yield while **31** was obtained in 10% yield. The two remaining cycload-

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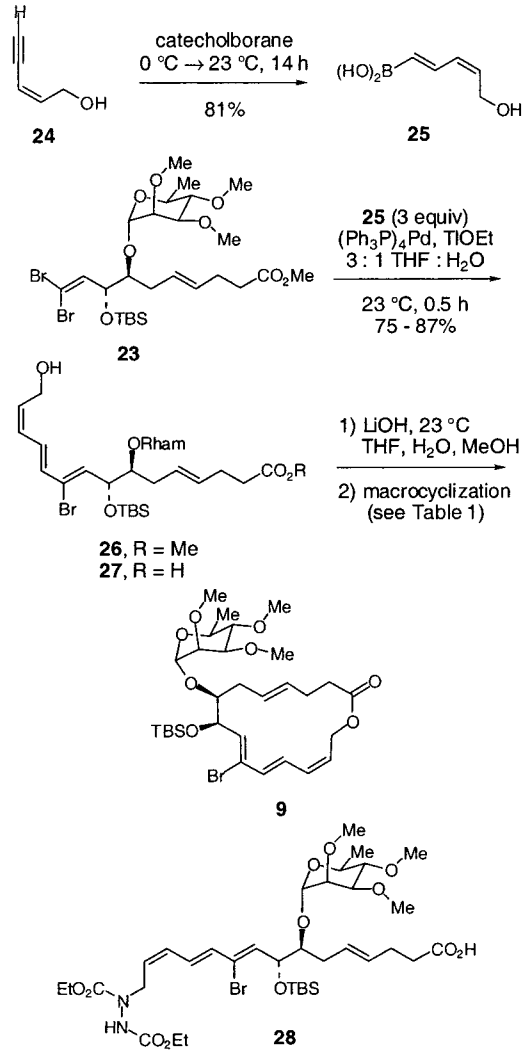
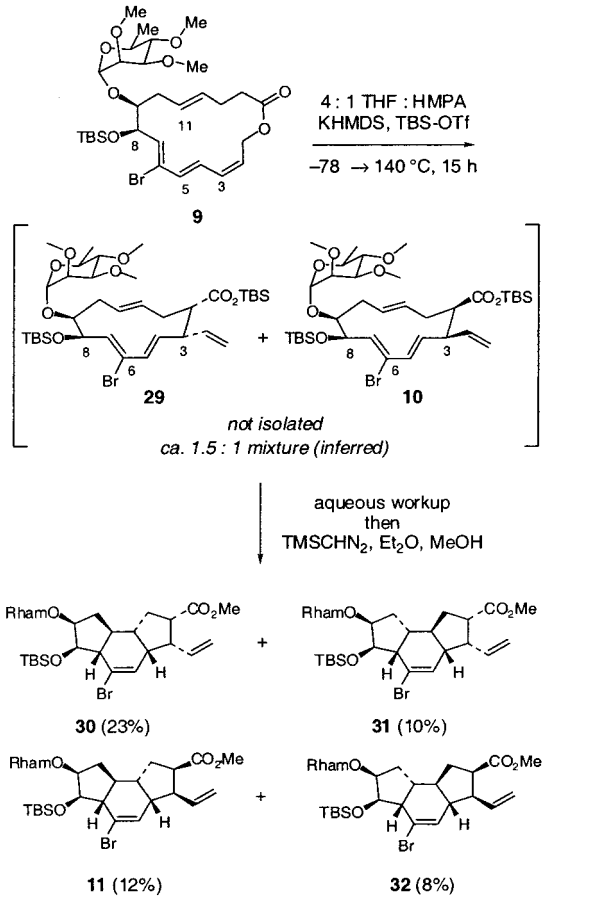
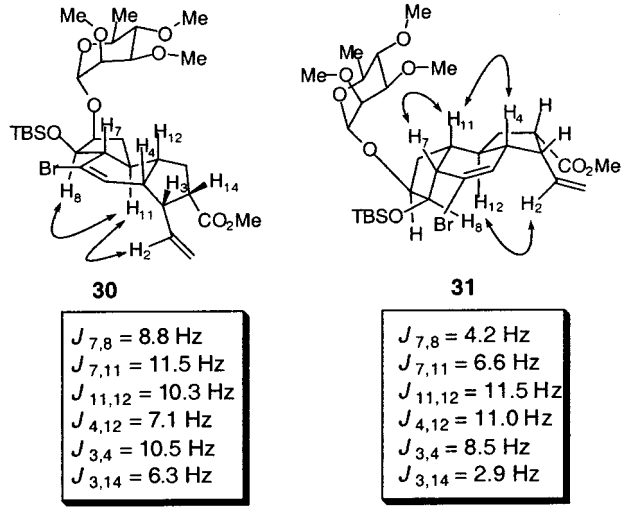




ducts, **11** and **32**, were inseparable by HPLC and therefore were obtained as a mixture (20% yield, combined). Tricycle **11** was subsequently prepared by an alternative route (vide infra), and the stereochemistry of this compound was assigned at that time. The stereostructural assignment of **32** is tentative and is based upon correlation of the ^{1}H NMR resonances for C(7)−H, C(11)−H, and C(14)−H with the same protons in the ^{1}H NMR spectrum of **11**.

The stereostructures of **30** and **31** were assigned on the basis of the ^{1}H NMR data summarized below. 1H NOESY experiments established NOE contacts between H(11) and H(8) and between H(11) and H(2) in diastereomer **30**. These data, together with the coupling constant data that indicate trans relationships between H(7)−H(8), H(7)−H(11), and H(11)−H(12), are uniquely consistent with the stereochemistry depicted for **30**. Key NOE and coupling constant data similarly highlighted for structure **31** establish that H(7), H(11) and H(4) are cis; that H(12) and the vinyl group are on the same side of the molecule, and that H(4) and H(12) are trans.



The fact that the two major products (**30** and **31**) of the tandem ring contraction-transannular Diels−Alder reaction of **9** have incorrect stereochemistry at C(3) indicates that the Claisen ring contraction step provided a ca. 1.5:1 mixture of isomeric cyclododecatrienes **29** and **10**, presumably by way of transition states **A** and **B**. On the basis of our earlier studies,[23] we anticipated that the Claisen ring contraction would proceed by way of the Z(O)-silyl ketene acetal, but we were unable to isolate or characterize this intermediate in the present instance.

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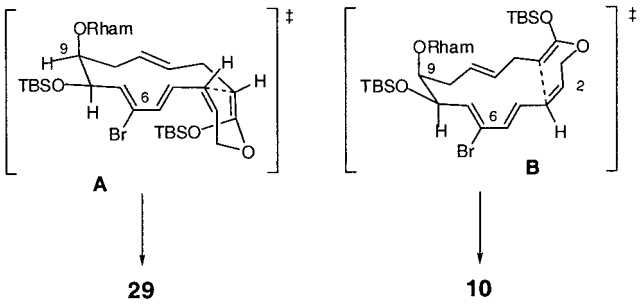
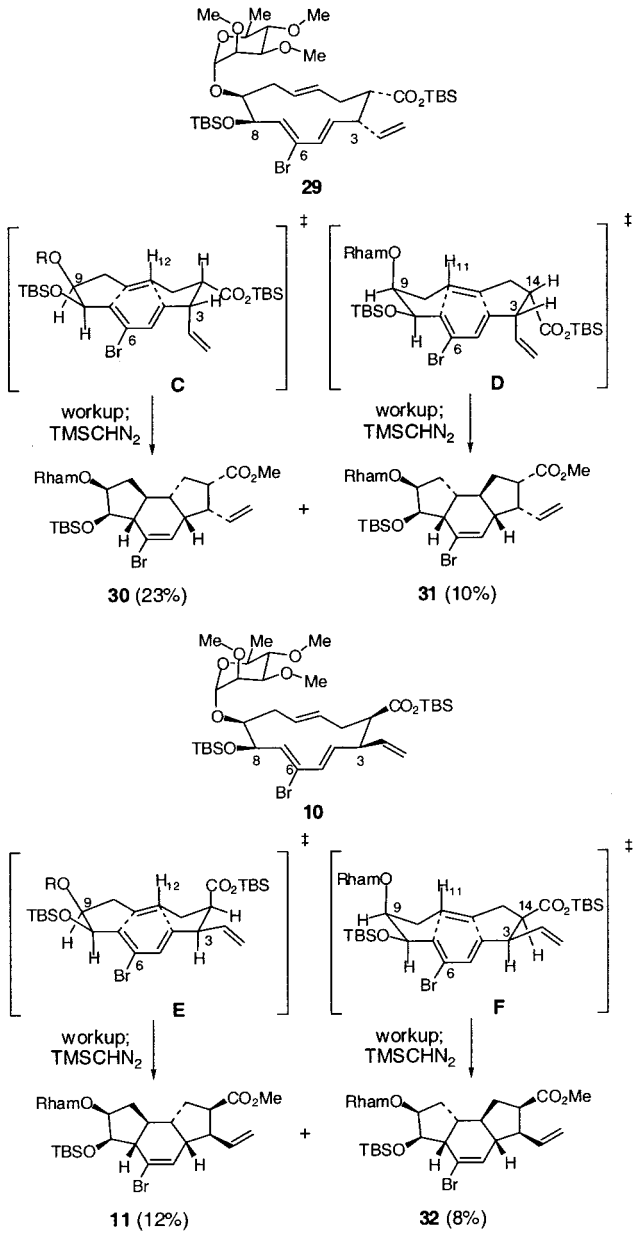
MM2 calculations of possible transition states had led us to expect that the Claisen ring contraction would occur preferentially via by way of transition state B, with an extended conformation of the conjugated triene. Our modeling studies also predicted that the alternative, isomeric *E*(O)-silyl ketene acetal (not shown) also should cyclize to provide **10** preferentially, although the transition states in this case were predicted to be much higher in energy than either A or B. Nevertheless, the results clearly indicate that the two predominant Diels−Alder adducts derive from **29**, which implicates transition state A as being the lowest energy pathway for the Claisen ring-contraction step.



The two major tricycloadducts **30** and **31** arise from **29** through the transannular Diels−Alder transition states C and D, respectively. It is interesting that the H(7)−H(8) stereochemistry is trans in all four of the tricyclic products, indicating that the C(6)−Br steric directing group was effective in controlling this relationship in all four of the transannular Diels−Alder transition states. The C(6)−Br steric directing group also played the anticipated role[28,30] in inducing a C(7)−C(11) trans-ring fusion in **30**, although the ratio of C(7)−C(11) trans/cis ring fusion isomers (**30**/**31**) was only 2:1 in this series. In the absence of the steric directing group, the transannular Diels−Alder reactions of **4a** and **4b** proceeded with ca. 4:1 selectivity toward tricycles **5a** and **5b** with C(7)−C(11) cis ring fusions.[22,23]

The two remaining tricycles, **11** and **32**, derive from the originally targeted cyclododecatriene **10** via transition states E and F. Although *A*(1,3) interactions between the C(3)-vinyl group and the C(4)−C(5) olefin that are present in transition states C and D are absent in E and F, the ratio of C(7)−C(11) trans/cis ring fusion isomers (**11** and **32**, respectively) in this series is approximately 1.5:1, roughly comparable (within the experimental error of our measurements) of the ratio of the cycloadducts **30** and **31** deriving from the isomeric cyclododecatriene **29**.

While we were disappointed that the Claisen ring contraction of **9** did not proceed with better stereoselectivity, we were modestly encouraged that the C(6)−Br steric directing group had reversed the stereochemicalpreference of the transannular Diels−Alder reaction compared to the results of our earlier investigations of **4a** and **4b**.[22,23] Because earlier studies had established that a C(6)−$SiMe_3$ steric directing group is capable of exerting a larger influence on the stereochemical course



of intramolecular Diels−Alder reactions than the C(6)−Br directing group,[28−30] we also synthesized and examined the ring contraction-transannular Diels−Alder reaction of **33**. Lactone **33** was converted to the corresponding ketene silyl acetal by using the procedure developed for **9**, and the silyl ketene acetal was then heated at 140 °C to effect the Ireland-Claisen ring contraction. Acidic hydrolysis of the reaction mixture followed by esterification of the crude carboxylic acids afforded a mixture of three tricyclic products **34**−**36**. These isomers were purified by HPLC and characterized by ^{1}H NMR analysis. Once again, the major product **34** (obtained in 18% yield) possessed the incorrect stereochemistry at C(3), indicating that the Claisen ring contraction step had occurred with poor diastereoselectivity. Tricycles **35** and **36**, obtained in 12% and 10% yield respectively, have the desired C(3)−C(8) stereochemical relationship. However, the fact that a ca. 1:1 mixture of the two was obtained indicated that the C(6)-TMS steric directing group underperformed our expectations,[29,30] and did not adequately control the stereochemical course of the transannular Diels−Alder reaction.

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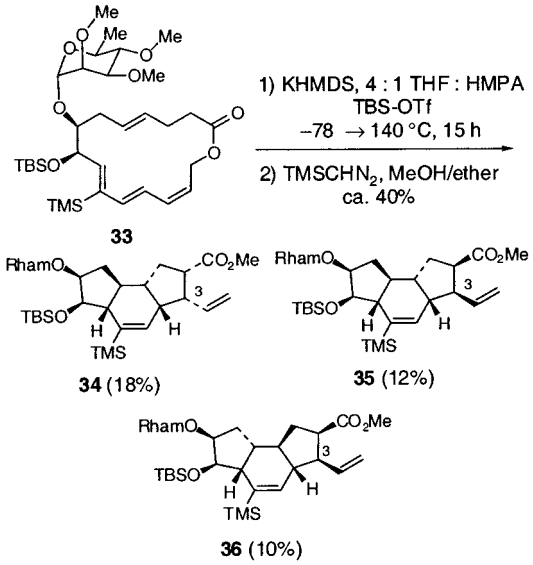
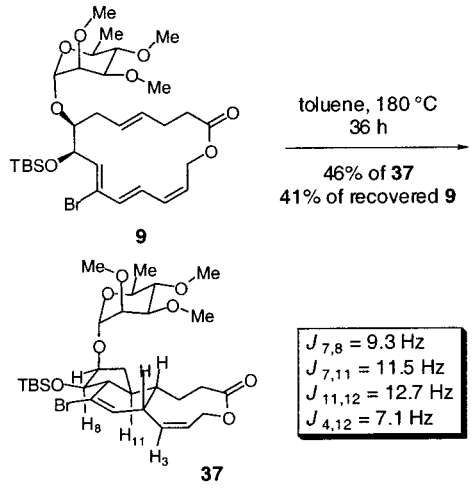


Stereoselective Synthesis of the Decahydro-*as*-indacene Core Structure of 1. At this stage, we elected to reorder the pericyclic steps leading from lactone **9** to tricycle **11**. We anticipated that if the Diels–Alder reaction of **9** was performed before the Ireland–Claisen ring contraction step, then it might be possible to control the stereochemistry of the C(3) vinyl substituent in the targeted tricycle **11** owing to the geometrical constraints of the nine-membered lactone unit of **37**.[20,21,67] The key would be to achieve high selectivity in the transannular Diels–Alder reaction of **9**.[15]

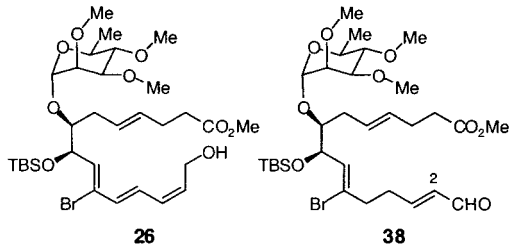
We were very pleased to find that heating a degassed solution of **9** in toluene at 180 °C for 36 h provided a single tricyclic product **37** in 46% yield; 41% of **9** was recovered and could be recycled to produce additional quantities of **37**. ^{1}H NMR analysis of the reaction mixtures failed to detect any other diastereomers of **37** in these experiments. No reaction was observed when the transannular Diels–Alder reaction was attempted at 140 °C. The stereochemistry indicated for **37** was assigned on the basis of NOE interactions observed between H(11) and H(3), and between H(11) and H(8), which indicates that these three units are positioned on the same face of the molecule. The large coupling constants observed between H(7)–H(8), H(7)–H(11), and H(11)–H(12) indicate that H(7), H(8), H(11), and H(12) are trans-diaxial. These data are uniquely consistent with the stereochemistry depicted for **37**. It is tempting to attribute the exquisite diastereoselectivity of the transannular Diels–Alder reaction of **9** to the C(6)-bromine steric directing group,[28–30] but until the TDA reaction of the analogous C(6)–H substituted triene is performed this conclusion is speculative.

We were unsuccessful in our attempts to drive the Diels–Alder reaction of **9** to completion, as starting material was consistently recovered after the reaction mixture was heated at 180 °C for several days in a sealed tube, or for several days in higher boiling solvents (e.g., decalin or triisopropylbenzene). Control experiments established that the formation of **37** is kinetically controlled, as **37** does not revert to **9** at 180 °C.

Interestingly, attempts to effect a conventional intramolecular Diels–Alder cyclization of seco ester **26** failed to give any Diels–Alder products when this compound was heated to 195 °C. Under these conditions,



the only products that were observed were the C(2)-(*E*)-isomer of **26** and trienal **38** resulting from a 1,5-hydrogen shift pathway. Consequently, the successful TDA reaction of **9** adds to the list of examples of Diels–Alder reactions that are successful in the transannular mode, but which fail altogether in the IMDA manifold.[14–16]



We next turned our attention to the Ireland enolate Claisen ring contraction of **37**. As we had anticipated, the cis C(4)–C(12) ring fusion of **37** indeed proved effective in controlling the diastereoselectivity of the Claisen rearrangement leading to the targeted tricycle **11**. Best results, at least initially, were obtained when **37** was treated with LiHDMS and TIPS–OTf in THF at –78 °C with warming to ambient temperature to promote the Ireland Claisen rearrangement step.[68] This reaction provided the targeted tricycle **11** in 48% yield after hydrolysis of the TIPS ester and esterification of the crude carboxylic acid with TMSCHN$_2$. However, significant quantities of the cycloheptene product **39** (15% yield) resulting from a competitive [1,3]-Claisen ring contraction process were also obtained. Products of [1,3]-Claisen rearrangements have been observed previously in ring contraction experiments.[69]

The stereochemistry of **11** was easily assigned based on the coupling constant data provided with the three-dimensional structure. This assignment was confirmed by an NOE experiment, which established that H(3) and H(11) are on the same face of the molecule.

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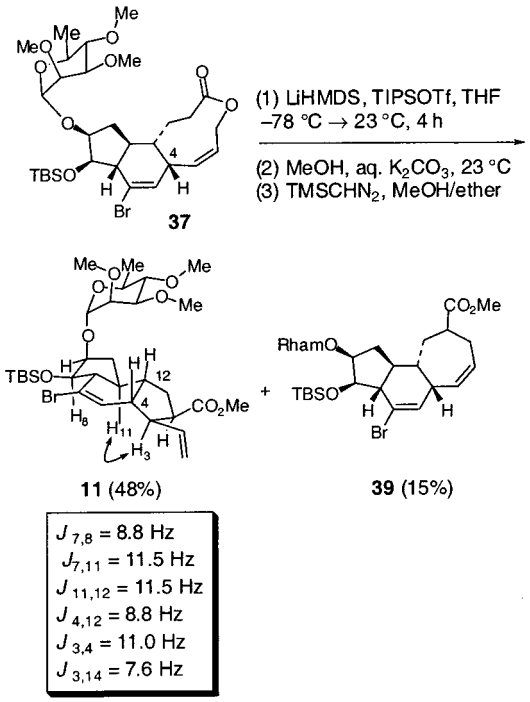
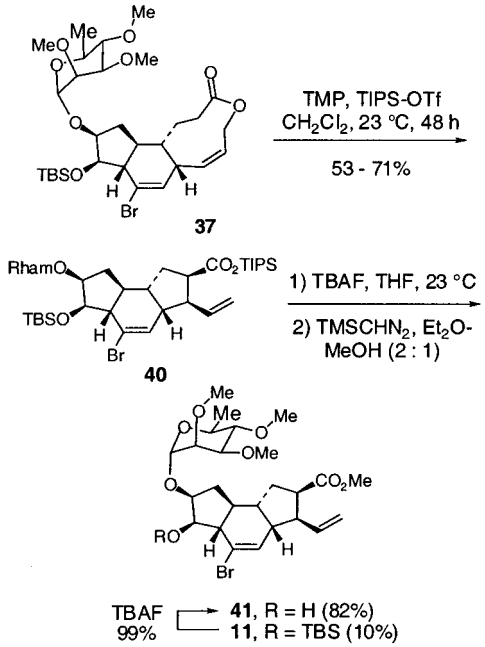
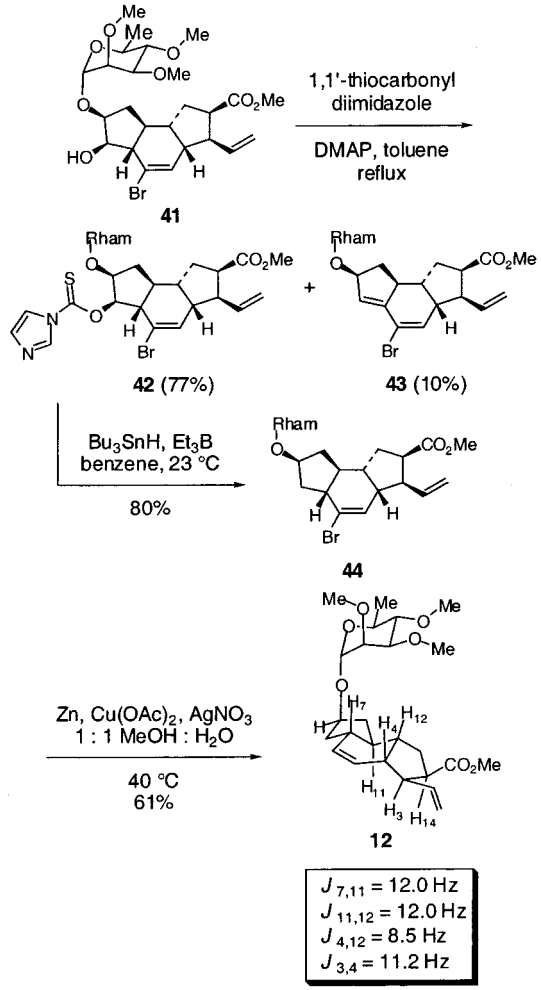


Attempts to perform the ring contraction of **37** by using KHDMS and TBS−OTf in THF−HMPA, LDA and TBS−Cl in THF−HMPA, or LiHMDS and TBS−OTf in THF were unsuccessful. However, treatment of **37** with 2,2,6,6-tetramethylpiperidine (TMP) and triisopropylsilyl triflate (TIPS−OTf) in CH_2Cl_2 at ambient temperature for 48 h provided the chromatographically stable TIPS ester **40** in up to 71% yield, with 10−19% of recovered **37**. Fortunately, products of the [1,3]-rearrangement were not observed. Simultaneous removal of the TIPS and TBS groups was accomplished by exposure of **40** to 3.5 equiv of TBAF in THF at ambient temperature. After esterification of the carboxylic acid with $TMSCHN_2$, tricyclic alcohol **41** was obtained in 82% yield, together with 10% of **11**. Treatment of **11** with TBAF in THF provided **41** in 99% yield.



Completion of the synthesis of the spinosyn tricyclic nucleus **12** involved reductive removal of the C(6)-bromide and C(8)-hydroxyl substituents. This was accomplished by treatment of **41** with 1,1-thiocarbonyldiimidazole and DMAP in toluene at reflux for 24 h to give the thiocarbonyl derivative **42** in 77% yield.[70] The hydroxyl group of **41** is relatively hindered, and it was necessary to use 3 equiv. of the thiocarbonyl diimidazole reagent for the reaction to go to completion. Under these conditions, 10% of the elimination product **43** was also obtained. Diene **43** presumably derives from a thermal syn elimination pathway.[71]

We anticipated at the outset that treatment of **42** with Bu_3SnH and AIBN would effect reduction of both the vinylbromide and thiocarbonyl derivatives.[70,72] However, heating a mixture of **42**, Bu_3SnH and AIBN in benzene at reflux led to substantial decomposition. Alternatively, when a benzene solution of **42** was treated with Bu_3SnH and Et_3B at ambient temperature in the presence of a catalytic amount of air, C(8) deoxygenation occurred smoothly and **44** was obtained in 80% yield.[73] It was necessary to exercise careful control over the stoichiometry of this reaction in order to minimize formation of alcohol **41** by reduction of the intermediate thioketal radical by excess Bu_3SnH.[74] However, owing to the relatively low temperature of this reaction, the C(6)-bromine substituent was not reduced.



Surprisingly, treatment of **44** with Bu_3SnH and AIBN in refluxing benzene gave products of hydrostannylation

of the vinyl group. Accordingly, the C(6)−Br was removed by reduction of **44** with a zinc amalgam generated from Zn, $Cu(OAc)_2$ and $AgNO_3$,[75] which provided the targeted tricycle **12** in 61% yield. This final reduction could also be accomplished by using 5% Na(Hg) in methanol, but products of ester hydrolysis and epimerization of the C(14) stereocenter were also observed.

Conclusion

In summary, we have developed a highly diastereoselective, 19-step synthesis of the perhydro-*as*-indacene nucleus **12** of spinosyn A. The transannular Diels−Alder reaction of **9** represents the first successful application of the steric directing group strategy to the transannular Diels−Alder reaction. Another attractive feature of this synthesis is that the rhamnosyl substituent is introduced at the very beginning, thereby minimizing protecting group manipulations as the synthesis progresses. Further progress toward completion of a total synthesis of spinosyn A will be reported in due course.

Acknowledgment. Financial support provided by the National Institute of General Medical Sciences (GM 26782) is gratefully acknowledged.

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

JO025580S

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