Total synthesis of (−)-spinosyn A

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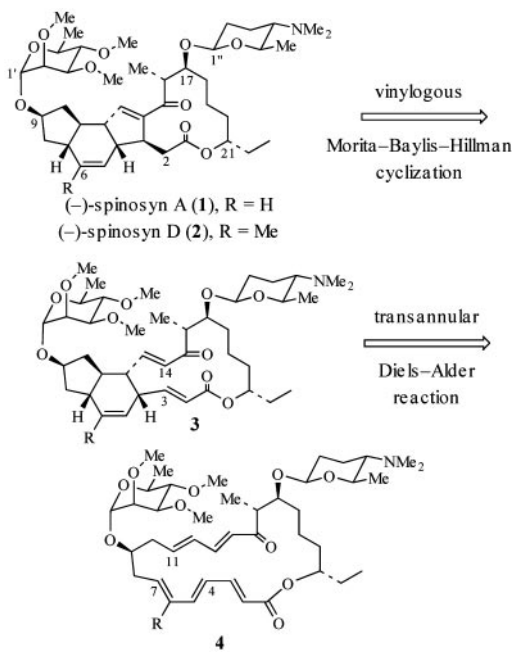
A convergent, highly stereoselective total synthesis of (−)-spinosyn A (1) is described. Key features of the synthesis include the transannular Diels–Alder reaction of macrocyclic pentaene 11 and the transannular Morita–Baylis–Hillman cyclization of 12 that generates tetracycle 26. The total synthesis of (−)-spinosyn A was completed by a sequence involving the highly β-selective glycosidation reaction of 13 and glycosyl imidate 30.

The spinosyns are a family of polyketide natural products that possess extraordinary insecticidal activity. The biosynthetic mixture, generated by *Saccharopolyspora spinosa*, comprises mostly spinosyn A (**1**) (Scheme 1) (≈85%) and spinosyn D (≈10–15%) (1–8). This mixture is currently marketed for use as an insecticide against a variety of insects (6). Total syntheses of spinosyn A have been reported by Evans and Black (9) and Paquette *et al.* (10, 11).

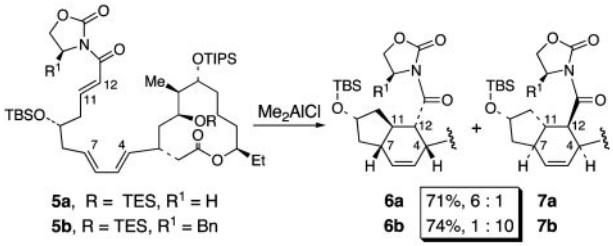


Scheme 1. Biomimetic strategy for synthesis of **1**.

Synthetic Strategy

Diels–Alder reactions have been proposed as key steps in the biogenesis of several natural products, including lovastatin, solanapyrone, nargenicin, and ikarugamycin (12). Kirst *et al.* (3) suggested that the biosynthesis of spinosyn A may involve a transannular Diels–Alder (TDA) (13) reaction of a macrocyclic pentaene to form the C(4)—C(12) and C(7)—C(11) bonds (see **4** → **3**; Scheme 1). Kirst also suggested that a transannular cyclization of a 1,3-dicarbonyl nucleophile may generate the C(3)—C(14) bond (3). Alternatively, we speculated that the C(3)—C(14) bond may be formed by a vinylogous Morita–Baylis–Hillman (MBH) reaction mediated by an enzymatic nucleophile (compare **3** → **1**; Scheme 1). Based on these biosynthetic considerations, we sought to assemble spinosyn A (**1**) via a TDA and MBH cyclization sequence of an appropriately functionalized macrocyclic pentaene **4**.

Diastereoselectivity of the Diels–Alder Reaction. Paramount to the success of this synthetic strategy is the control of the diastereoselectivity of the TDA reaction (**4** → **3**). It is known from the work of Evans and Black (9) that the intrinsic diastereofacial selectivity of the intramolecular Diels–Alder (IMDA) reaction of **5a** favors the incorrect C(7)—C(11) trans-fused diastereomer **6a** with 6:1 selectivity (Scheme 2). Although Evans and Black (9) addressed this issue by incorporating a chiral auxiliary (13) in the dienophile (see **5b** → **7b**), we would not have recourse to this strategy for the TDA cyclization of **4**. Thus, some means for controlling the stereochemistry at the C(7)—C(11) ring fusion relative to the C(9)—alkoxy substituent in the Diels–Alder reaction was required.



Scheme 2. Results of IMDA reactions of trienes **5a** and **5b** (9).

We initially hoped to use the steric directing-group strategy to control the diastereoselectivity of the Diels–Alder reaction (15–17), which could involve appending a bromine steric directing group at C(6) of the IMDA or TDA substrate to control the stereochemical outcome of the cycloaddition, leading to the desired C(7)—C(11) trans-fused diastereomer. It was anticipated that **TS2**, which leads to the undesired C(7)—C(11) trans-fused isomer **10** and is favored in the absence of the C(6)—Br steric directing group, may be destabilized relative to **TS1** by a steric interaction between C(6)—Br and the C(9)—alkoxy substituent (Scheme 3). However, the IMDA reaction of **8** under Lewis acid catalysis provides only an ≈2:1 mixture of C(7)—C(11) trans-fused diastereomers **9** and **10** (18).‡ Thus, although the presence of the C(6)—Br directing group in **8** counteracts the intrinsic diastereofacial bias imparted by the C(9) alkoxy substituent in **5a**, it was apparent that some additional means of increasing the diastereoselectivity of the TDA reaction of **4** would be required.

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Abbreviations: TDA, transannular Diels–Alder; MBH, Morita–Baylis–Hillman; IMDA, intramolecular Diels–Alder; TBS, *tert*-butyldimethylsilyl; PMB, *p*-methoxybenzyl; AIBN, azobisisobutyronitrile; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; THF, tetrahydrofuran; DMAP, dimethylaminopyridine; Rham, rhamnopyranosyl.

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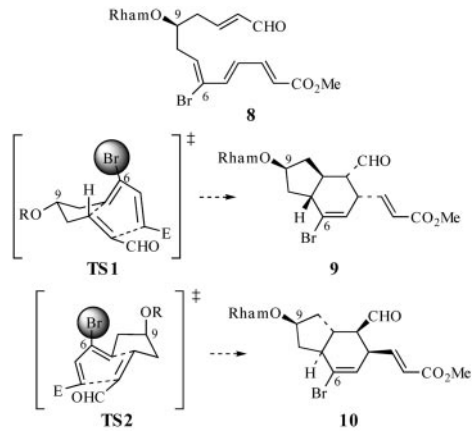
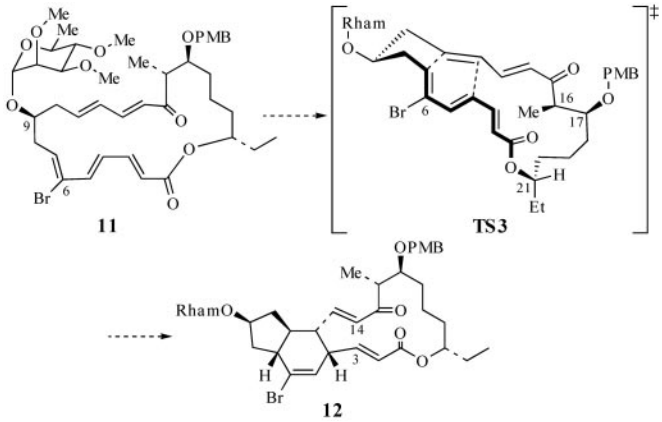
‡Diastereomers **9** and **10** were inseparable by HPLC. Consequently, the stereochemistry of **9** and **10** was not rigorously established.



Scheme 3. Transition states for the IMDA reaction of **8**.

It is well established that conformational preferences of macrocyclic systems can be used to control the stereochemical outcome of synthetic transformations (19–26). In this connection, we anticipated that the C(21) stereocenter, adjacent to the macrolactone carbonyl, might be a stereochemical control element capable of enhancing the diastereoselectivity of the TDA reaction (**11** → **12**; Scheme 4). In the preferred conformation of the macrolactone linkage, C(21)—H should eclipse the carbonyl group (27). Analysis of the transition states of the TDA reaction of **11** indicates that the macrolactone linkage would possess this favorable conformation in **TS3**, which leads to the desired cycloadduct **12** (Scheme 4).

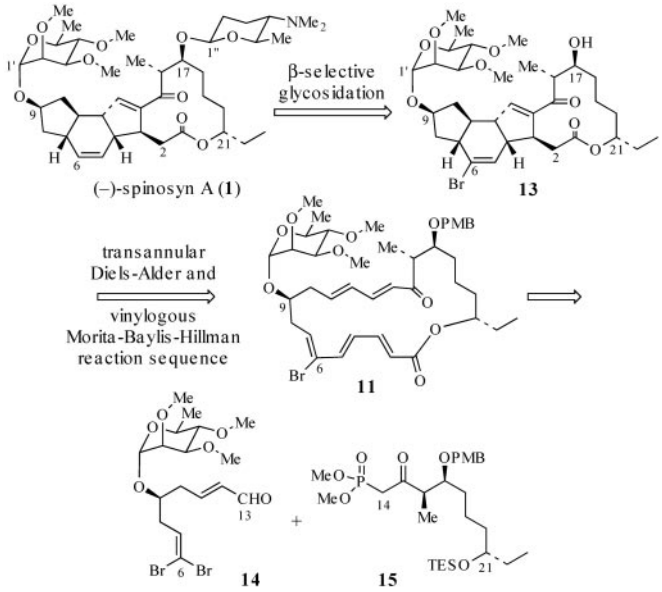


Scheme 4. Transition-state analysis of the TDA reaction of **11**.

Based on this analysis, we targeted macrocyclic pentaene **11** as a substrate for the assembly of spinosyn A (Scheme 5). It was envisaged that **11** would be accessible via Horner–Wadsworth–Emmons coupling of aldehyde **14** and β-ketophosphonate **15**. A TDA and transannular MBH reaction sequence from **11** should lead to **13**. Installation of the forosamine unit then should afford the natural product. We report herein the successful application of this strategy to the total synthesis of (−)-spinosyn A (**1**).

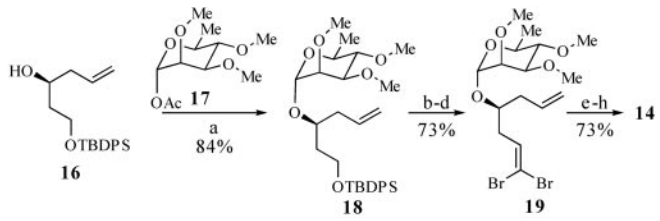
Chemistry

Synthesis of Aldehyde 14. The synthesis of **14** began with readily available alcohol **16** (28) (Scheme 6). Glycosidation of **16** with α-L-rhamnopyranosyl (Rham) acetate **17** (29) in the presence of *tert*-butyldimethylsilyl (TBS) trifluoromethanesulfonate afforded the α-glycoside **18** in 84% yield. Removal of the *tert*-butyldiphe-



Scheme 5. Retrosynthetic strategy for synthesis of **1**.

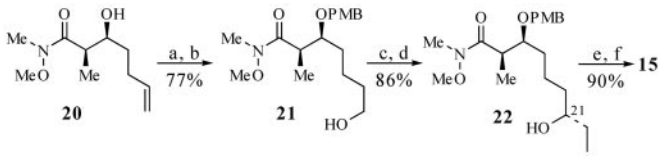
nylsilyl group with tetrabutylammonium fluoride proceeded in 84% yield, and oxidation of the resulting alcohol under Dess–Martin conditions afforded the corresponding aldehyde in 92% yield (30, 31). Treatment of this aldehyde with Ph_3P and CBr_4 then afforded 1,1-dibromoolefin **19** in 94% yield (32). Selective ozonolysis of the primary olefin (33) and Wittig olefination of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ generated the unsaturated ester with the required (*E*)-configuration in 82% yield and with ≥95:5 selectivity. Reduction of the ester with diisobutylaluminum hydride and oxidation of the allylic alcohol with SO_3·pyridine then provided aldehyde **14** (34).



Scheme 6. Synthesis of aldehyde **14**. a, TBS trifluoromethanesulfonate, 4 Å MS, CH_2Cl_2, 23°C, 15 min, 84%; b, tetrabutylammonium fluoride, THF, 0°C → 23°C, 1.5 h, 84%; c, Dess–Martin periodinane, pyridine, wet CH_2Cl_2, 0°C → 23°C, 2.5 h, 92%; d, CBr_4, Ph_3P, CH_2Cl_2, 0°C → 23°C, 30 min, 94%; e, O_3, 4:1 CH_2Cl_2/MeOH, $KHCO_3$, −78°C → 23°C, 3 h; f, $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 23°C, 12 h, 82% from **19**, ds = 95:5; g, diisobutylaluminum hydride, CH_2Cl_2, −78°C → 0°C, 1.25 h, 89%; h, SO_3·pyridine, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 0°C, 20 min.

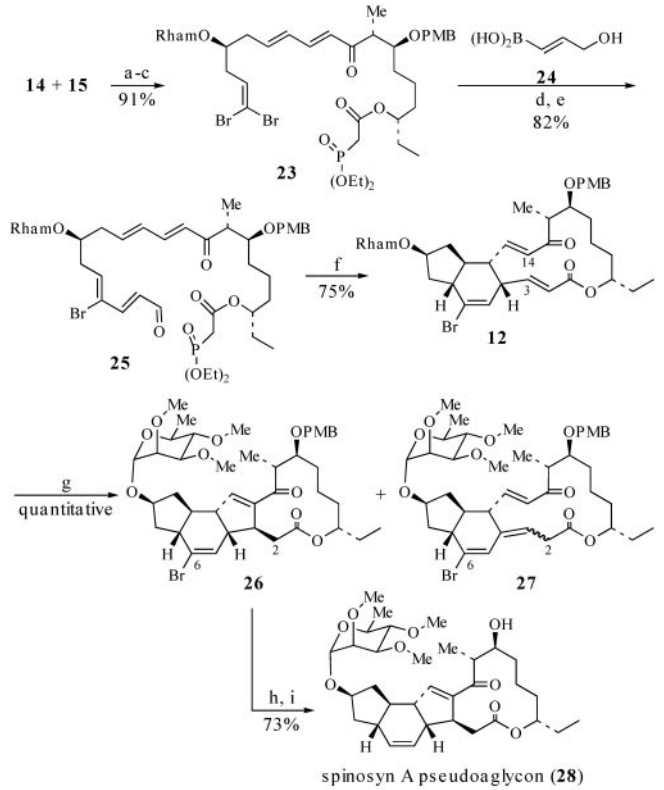
Synthesis of β-Ketophosphonate 15. We elected to use readily available alcohol **20** (9) as the starting material for the synthesis of β-ketophosphonate **15** (Scheme 7). Treatment of **20** with potassium hexamethyldisilazane and *p*-methoxybenzyl bromide (PMB—Br) afforded the PMB ether in 91% yield. Hydroboration of the olefin with disiamylborane then provided primary alcohol **21** in 85% yield. Oxidation of **21** with SO_3·pyridine gave the corresponding aldehyde in 91% yield (34). Treatment of this aldehyde with diethylzinc in the presence of (−)-*N*,*N*-dibutylnorephedrine then gave the C(21) alcohol **22** as a 9:1 mixture of diastereomers in 94% yield (35–37). Protection of

alcohol **22** as the triethylsilyl ether proceeded in 94% yield. Exposure of this triethylsilyl ether to dimethyl lithiomethylphosphonate then afforded β-ketophosphonate **15** (25, 38).



Scheme 7. Synthesis of β-ketophosphonate **15**. a, PMB—Br, Et_3N, potassium hexamethyldisilazane, THF, −78°C → 23°C, 13 h, 91%; b, BH_3·SMe_2, 2-methyl-2-butene, THF, 0°C, 5 h, then H_2O_2, $NaHCO_3$, 85%; c, SO_3·pyridine, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 0°C, 30 min, 91%; d, Et_2Zn (1 M in hexanes), (−)-*N*,*N*-dibutylnorephedrine, toluene, 0°C → 23°C, 76 h, 94%, ds = 90:10; e, triethylsilyltrifluoromethanesulfonate, 2,6-lutidine, CH_2Cl_2, 0°C, 1 h, 94%; f, $(MeO)_2P(O)CH_3$, BuLi, THF, −78°C, 30 min, 96%.

Synthesis of Pseudoaglycon 28. Aldehyde **14** and β-ketophosphonate **15** were coupled by treatment of **15** with activated $Ba(OH)_2$ followed by the addition of **14** (39) (Scheme 8), which afforded the corresponding triene in 93% yield over two steps. Removal of the C(21)—triethylsilyl group and acylation of the resulting alcohol with diethyl phosphonoacetic acid then generated phosphonate **23** in 98% yield. Suzuki coupling of **23** with vinyl boronic acid **24** (40) provided the allylic alcohol in 82% yield. Oxidation of this alcohol with SO_3·pyridine provided the aldehyde **25** (34). We anticipated that macrocyclization of **25** would give macrocycle **11** (41–43); however, treatment of **25** with *i*-Pr_2NEt and LiCl in CH_3CN (44) directly afforded Diels–Alder cycloadduct **12** in 75% yield (over two steps) as a 73:12:9:6 mixture of two trans- and two cis-fused diastereomers. Cycloadduct **12** presumably arises from a tandem macrocyclization and TDA reaction sequence (**25** → **11** → **12**). Based on the observation that the TDA reaction of macrocycle **11** (**11** → **12**) is more diastereoselective than the corresponding IMDA reaction of triene **8** (**8** → **9**), it seems that conformational preferences of **11** play a role in determining the stereoselectivity of the TDA reaction, as predicted in **TS3** (Scheme 4). To establish the stereochemistry of the major cycloadduct **12**, this intermediate was converted to the spinosyn A pseudoaglycon **28**. Thus, treatment of **12** with Me_3P effected the vinylogous MBH cyclization (18, 45, 46) and provided an 88:7:5 mixture of the desired product **26**, the olefin migration product **27**, and the C(3) epimer of **26** (structure not shown) in quantitative yield. After HPLC purification of **26**, reductive removal of the C(6)—Br directing group was accomplished by treatment of **26** with (tristrimethylsilyl)silane and azobisisobutyronitrile (AIBN) (47, 48). Finally, removal of the PMB group with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ) afforded the spinosyn A pseudoaglycon **28**, which was identical in all respects to natural **28**. Because the published syntheses of (−)-spinosyn A (**1**) by Paquette *et al*. (10, 11) and (+)-spinosyn A by Evans and Black (9) proceed by way of the pseudoaglycon **28** (or *ent*-**28** in the case of Evans and Black), this synthesis of **28** constitutes a formal synthesis of (−)-spinosyn A (**1**).

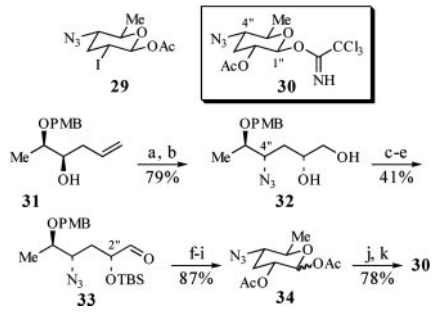


Scheme 8. Synthesis of pseudoaglycon **28**. a, $Ba(OH)_2$, 40:1 THF/H_2O, 23°C, 8 h, 93% over two steps; b, 8:8:1 THF/HOAc/H_2O, 23°C, 4 h, quantitative; c, $(EtO)_2P(O)CH_2CO_2H$, *N*-ethyl, *N*′-(3-dimethylaminopropyl)-carbodiimide·MeI, DMAP, CH_2Cl_2, 23°C, 1.5 h, 98%; d, **24**, $Pd(PPh_3)_4$, Tl_2CO_3, 3:1 THF/H_2O, 2 h, 82%; e, SO_3·pyridine, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 0°C, 30 min; f, *i*-Pr_2NEt, LiCl, CH_3CN (1 mM), 23°C, 19 h, 75%, (*E*)/(*Z*) = ≥95:5, ds = 73:12:9:6; g, Me_3P (8 eq), *tert*-amyl alcohol (0.005 M), 23°C, 6 h, quantitative; h, $(trimethylsilyl)_3SiH$, AIBN, dioxane, 80°C, 1.5 h; i, DDQ, CH_2Cl_2/pH 7 buffer, 0°C, 3 h, 73%.

Synthesis of Glycosyl Donor 30. The remaining challenge in completing a total synthesis of (−)-spinosyn A was the installation of the forosamine unit at C(17)—OH. This glycosidation proved to be a significant problem in the syntheses of spinosyn A by both Evans and Black (9) and Paquette *et al*. (11). Evans and Black obtained a 70% yield for the installation of the forosamine unit in their synthesis; however, the selectivity for the formation of the required β-glycoside was 1:6 β/α. In the synthesis of spinosyn A by Paquette *et al*., installation of the forosamine unit proceeded in 17% yield and with 2:3 β/α selectivity. Thus, both the efficiency and selectivity of this glycosidation step needed to be addressed.

Highly selective methods for the synthesis of 2-deoxy-β-glycosides by using 2-iodo-glycosyl acetate, trichloroacetimidate, and fluoride donors were recently reported from this laboratory (49–53). These glycosidation reactions afford the β-glycosides in high yield and with excellent β-selectivity. We considered applying this technology to the installation of the forosamine unit in the present work; however, we recognized that stereoselective preparation of the requisite 2-iodo-glycosyl acetate donor **29** would be difficult. Therefore, we elected to target glycosyl imidate (54, 55) **30**, which contains a C(2″)—OAc directing group for stereocontrol of the glycosidation step (56–60) and a C(4″)—N_3 for protection of the amino functionality (61) (Scheme 9).

The synthesis of **30** began with homoallylic alcohol **31** (62). A Mitsunobu reaction of **31** with diphenylphosphoryl azide was used to install the C(4″)—N_3 (63, 64). Sharpless asymmetric dihydroxylation of the terminal olefin then afforded diol **32** in 96% yield as an 86:14 mixture of inseparable diastereomers (65). Silylation of the diol mixture with TBSCl followed by treatment of the resulting bis-silyl ether with aqueous acetic acid (1:3) in tetrahydrofuran afforded the corresponding primary alcohol in 62% yield over two steps. Oxidation of this alcohol with SO_3·pyridine (34) then gave the aldehyde **33** in 66% yield after HPLC purification. Purified **33** had diastereomeric purity of 93:7. Deprotection of the PMB ether with DDQ afforded the



Scheme 9. Synthesis of glycosyl imidate donor **30**. a, $(PhO)_2P(O)N_3$, Ph_3P, diethyl azodicarboxylate, THF, 0°C, 2 h, 82%; b, $K_2OsO_4(OH)_2$, (dihydroquinidine)$_2$-pyr, $K_3Fe(CN)_6$, K_2CO_3, 0°C, 7.5 h, 96%, ds = 86:14; c, TBSCl, imidazole, dimethylformamide, 4 h; d, HOAc/THF/H_2O (3:3:1), 23°C, 55 h, 62%; e, SO_3·pyridine, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 0°C, 15 min, 66%; f, DDQ, CH_2Cl_2/pH 7 buffer, 0°C, 4 h; g, Ac_2O, Et_3N, DMAP, CH_2Cl_2; h, tetrabutylammonium fluoride, THF, 0°C, 2 h; i, Ac_2O, Et_3N, DMAP, CH_2Cl_2, 87% from **33**, 1.3:1 β/α; j, ethylenediamine, HOAc, THF, 23°C, 24 h, 78%; k, 1,8-diazabicyclo[5.4.0]undec-7-ene, CH_2Cl_2/Cl_3CCN (1:1), 0°C, 1.5 h, 5:1 β/α.

lactol, which then was acylated with acetic anhydride. Removal of the C(2″) TBS ether and acylation of the resulting alcohol with Ac_2O provided glycosyl acetate **34** in 87% yield from **33**. Removal of the anomeric acetate with ethylenediamine and HOAc in THF gave the corresponding lactol in 78% yield (66). Finally, treatment of the lactol with 1,8-diazabicyclo[5.4.0]undec-7-ene in Cl_3CCN/CH_2Cl_2 (1:1) afforded trichloroacetimidate donor **30** with >95:5 diastereomeric purity at C(2″) (55).

Because of its instability, **30** was used immediately in the glycosidation reaction with acceptor **13**, itself prepared from **26** in quantitative yield via removal of the PMB group with DDQ (Scheme 10). Treatment of **13** with 2.1 eq of **30** in the presence of trimethylsilytrifluoromethanesulfonate afforded the β-glycoside **35** in 90–97% yield. The stereochemistry of **35** was assigned based on the observed $J_{1''\text{-}2''}$ coupling constant of 7.8 Hz.

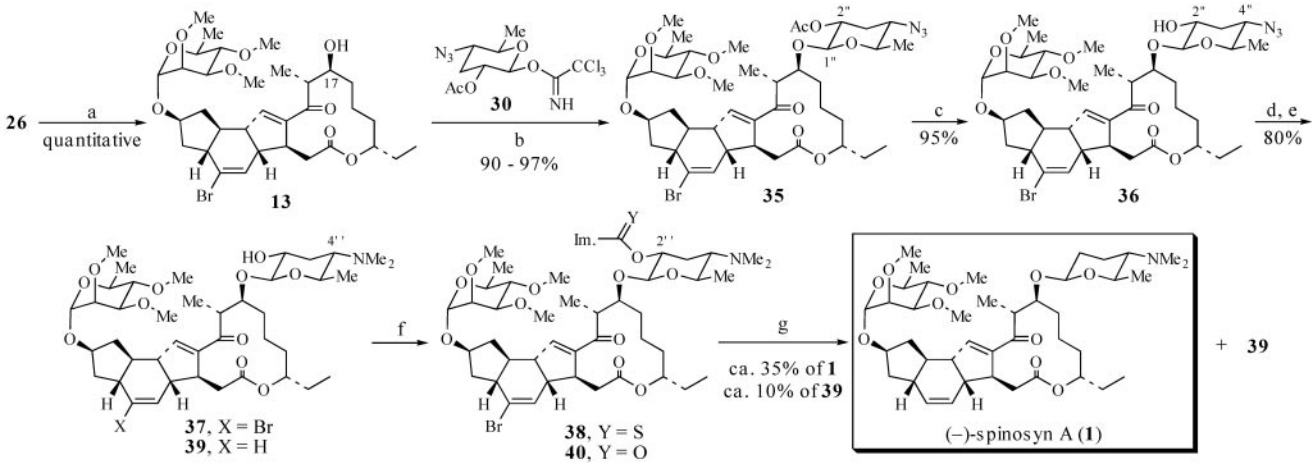
Completion of the Total Synthesis of 1. Deoxygenation at C(2″) and conversion of the C(4″)—N_3 to the C(4″)—NMe_2 of glycoside **35** were now required to complete a synthesis of **1**. The C(2″)—OAc was removed by treatment of **35** with guanidinium nitrate (67), which afforded alcohol **36** in 95% yield (Scheme 10). Deoxygenation at C(2″) was attempted first. Conversion of **36** to the corresponding thioimidazolide was accomplished by treatment with thiocarbonyldiimidazole (68); however, exposure of the thioimidazolide to $(trimethylsilyl)_3SiH$ (47, 48) and AIBN in dioxane at 80°C afforded only products in which the azide had been reduced to the primary amine.

Consequently, reduction of the azide before radical deoxygenation was explored next. Exposure of the azide to Me_3P or Ph_3P in THF followed by the addition of water did not afford the primary amine; only decomposition of **36** was observed (69–71). Fortunately, reduction of the azide could be accomplished with $SnCl_2$ in the presence of PhSH and Et_3N (72, 73). This reduction protocol gave the amine in 92% yield. Reductive amination with formaldehyde then afforded dimethylamine **37** in 87% yield (9).

Conversion of alcohol **37** to thioimidazolide **38** proceeded smoothly in the presence of thiocarbonyldiimidazole and dimethylaminopyridine (DMAP); however, reduction of **38** with $(trimethylsilyl)_3SiH$ and AIBN was unsuccessful. The major products observed under these conditions were alcohol **37**, desbromo alcohol **39**, and imidazolide **40** resulting from an unexpected thiocarbonyl-to-carbonyl exchange. Attempted deoxygenation of the thionochloroformate and xanthate derivatives of **37** gave similar results (68). Fortunately, treatment of **38** with the more reactive hydrogen atom donor Bu_3SnH (25 eq) and AIBN in dioxane afforded ≈3:1 mixture of (−)-spinosyn A (**1**) and alcohol **39**. The isolated yield of synthetic (−)-spinosyn A (**1**) was ≈35% (from **37**) after reverse-phase HPLC purification. The yield of recovered alcohol **39** was ≈10%. Synthetic (−)-spinosyn A was identified by comparison to a sample of natural (−)-**1** by ^1H NMR, IR, high-resolution MS, optical rotation, and TLC mobility.

Conclusions

This synthesis of (−)-spinosyn A features a tandem macrocyclization and TDA reaction in addition to a complex application of the vinylogous MBH reaction for construction of the spinosyn A pseudoaglycon **28**. Installation of the forosamine sugar was accomplished by means of a highly β-selective glycosidation of C(6)—bromo pseudoaglycon **13** with glycosyl imidate **30**. Conditions then were developed for removal of the C(6) and C(2″) directing groups and the installation of the C(4″) tertiary amine functionality from **35**. This synthesis of (−)-spinosyn A involved 23 steps in the longest linear sequence (31 steps total) and proceeded in 3% overall yield. Full experimental details are provided in the supporting information, which is published on the PNAS web site.



Scheme 10. Completion of the total synthesis of (−)-spinosyn A (**1**). a, DDQ, CH_2Cl_2/pH 7 buffer, 0°C, 4 h, quantitative; b, **30** (2.1 eq), trimethylsilytrifluoromethanesulfonate (30 mol %), CH_2Cl_2, −78°C, 1 h, 90–97%; c, guanidinium nitrate, NaOMe, MeOH, CH_2Cl_2, 2 h, 95%; d, $SnCl_2$, PhSH, Et_3N, THF, 15 min, 92%; e, $NaBH_3CN$, CH_2O, MeOH, HOAc, NaOAc, 87%; f, thiocarbonyldiimidazole, DMAP, Ph—CH_3, 65°C, 2 h; g, Bu_3SnH (25 eq), AIBN, dioxane, 100°C, 20 min, ≈35% of **1**, ≈10% of **39** after HPLC.

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