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The Stereochemical Outcome of Electrophilic Addition Reactions on the 5,6-Double Bond in the Spinosyns

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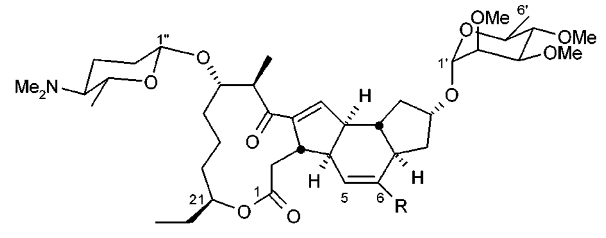
The electrophilic addition of reagents to the 5,6-double bond in spinosyn A and spinosyn D systems occurred with high π-diastereofacial selectivity. Addition occurred preferentially from the β face of the molecule with selectivities ranging from 5:1 to better than 30:1. Various NMR properties were investigated in order to distinguish the β and α isomers with the help of theoretical models of the products. These NMR properties include a ^{13}C γ effect to C-11 and vicinal coupling between H-4 and H-5. To help rationalize the selectivity, computational studies on the transition states for epoxidation were calculated using density functional theory. The results indicate that β epoxidation is favored and that the geometries of the transition structures are consistent with torsional steering being the source of the selectivity.

Introduction

The spinosyns,[1] as represented by spinosyn A (**1**) and spinosyn D (**2**), are natural products derived from *Saccharopolyspora spinosa* and were found to act as insect control agents. During the course of our structure−activity relationship work on the spinosyns,[2] it was found that a number of reactive functional groups on the molecule were amenable to modification. In particular, the 5,6-double bond is one of the most reactive groups within the molecule which, together with the forosamine nitrogen, represent the primary positions for electrophilic attack by reagents such as *m*-CPBA.



spinosyn A (**1**), R = H
spinosyn D (**2**), R = Me

One problem that arose in this work was the stereochemical assignment of products resulting from electrophilic addition to the 5,6-double bond. Although addition to the α face − which is less sterically crowded than the β face − was expected, preliminary NMR analysis of the epoxidation product indicated that β addition had occurred.[3] We report here the methods used for determining the configuration of the 5,6-epoxides of the spinosyns using NMR spectroscopy and molecular modeling. These methods are general and may also be applied to the identification of other products resulting from electrophilic addition to the 5,6-double bond. In addition, computational studies on the transition states for the epoxidation were calculated using density functional theory in order to rationalize the observed π-selectivity.

Results and Discussion

Epoxidation of the 5,6-double bond in spinosyn A (**1**) and spinosyn D (**2**) was accomplished with *m*-CPBA in

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10.1021/jo015830p CCC: $20.00

Scheme 1

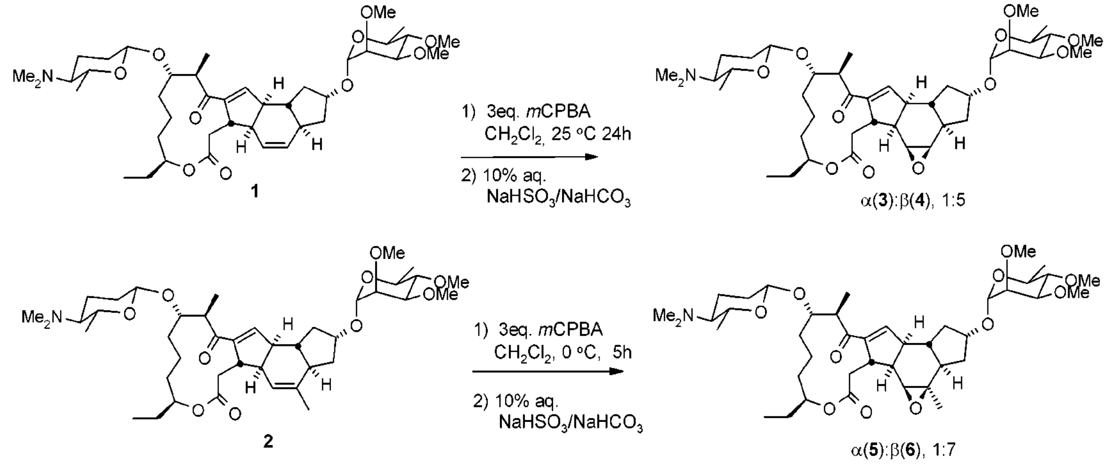

Table 1. ^{1}H and ^{13}C NMR[a] Chemical Shifts Differences for A and D Epoxides

compd	**1**	**3**	**4**	D (**3**−**1**)	D (**4**−**1**)	**2**	**6**	D (**6**−**2**)
H-11	0.90	0.80	1.33	−0.10	0.43	1.01	1.32	0.31
C-11	45.6	44.3	39.2	−1.3	−6.4	45.9	40.7	−5.2
H-12	2.87	2.53	2.57	−0.34	−0.30	2.78	2.54	−0.24
C-12	49.3	47.8	48.7	−1.5	−0.6	49.0	48.7	−0.3
H-3	3.00	3.25	3.50	0.25	0.50	2.97	3.45	0.48
H-7	2.16	1.65	2.05	−0.51	−0.11	2.19	1.95	−0.24
H13	6.76	6.72	6.58	−0.04	−0.18	6.76	6.58	−0.18

[a] Spectra taken in $CDCl_3$.

Table 2. Distance between Epoxide Oxygen and Indicated Hydrogen Atoms in the MM3-Minimized Structures

	distance (Å)	
position	*β* epoxide	α epoxide
3	2.600	4.074
8α	4.067	4.134
8*β*	3.095	4.192
11	2.604	3.816
12	4.058	3.266

dichloromethane (Scheme 1). The first equivalent of oxidizing agent reacted rapidly to form the *N*-oxide, which was then slowly epoxidized at the 5,6-double bond to give predominantly the *β* epoxide (ratio α/*β* < 1:5). While the *N*-oxide-5,6-epoxide may be isolated from the reaction mixture, it was most convenient to regenerate the free amine during workup by washing with 10% aqueous sodium bisulfite. In general, 6-methyl spinosyns (spinosyn D) reacted much faster than unsubstituted derivatives (spinosyn A), and the reaction could be conducted at lower temperatures giving greater *β* selectivity.

The α epoxide **3** was formed as the major product (ratio α/*β* > 10:1) in a two-step procedure, where formation of the bromohydrin was followed by intramolecular displacement with sodium hydride in THF. The hydroxybromination of **1** requires 1−2 equiv of strong mineral or organic acid (such as H_2SO_4 or CF_3CO_2H), which is needed to protonate the amine nitrogen, thus protecting it from reaction with bromonium ion. In the absence of acid, the amine reacted rapidly with *N*-bromosuccinamide and other electrophilic halogen sources to give monodemethylation of the nitrogen atom. NMR was used to deduce the configuration of the products from the oxidation. All molecules were assigned using ^{1}H and ^{13}C chemical shifts, and DEPT-, HMQC-, HMBC-, and TOCSY-based experiments. The key chemical shift differences between **1**, **3**, and **4** are shown in Table 1.

The assignment of configuration of epoxides **3** and **4** initially centered on the large upfield shift of C-11 in epoxide **4**, suggesting a *β* configuration. In polycyclic compounds bearing a six-membered ring, such as steroids[4] and diterpene epoxides,[5] characteristic upfield shifts of 5−6 ppm are observed in those *γ* carbons having an axial hydrogen syn relative to the epoxide (the so-called *γ* effect). To provide supporting data for the epoxide assignment, three-dimensional models of epoxides **3** and **4** were constructed using the X-ray crystal structure of **1** as a starting point and minimized with the MM3 force field.[6] Some of the atomic distances in the resulting models are shown in Table 2. The models clearly showed that in **4**, H-11 is axial and syn to the epoxide, while in the **3**, H-12 is axial and syn. While both isomers do exhibit upfield shifts relative to their corresponding olefins, the magnitude of the upfield shift is substantially larger in the *β* isomer (Table 1). This may be attributed to the shorter distance of the epoxide oxygen to H-11 in the *β* isomer (2.60 Å) compared to the distance of the epoxide oxygen to H-12 in the α isomer (3.26 Å, Table 2).

Recent ^{13}C NMR analyses of eudimane sesquiterpene lactone epoxides, however, indicate that upfield shifts in the *γ*-carbon bearing a syn axial hydrogen do not always predict epoxide configuration.[7] This is due to significant upfield shifts in the carbon signals that may also occur as a result of conformational changes in the epoxide in relation to the starting olefin. Therefore, additional NMR data were obtained in order to corroborate the initial assignment of epoxide configuration that was based solely on the *γ* effect.

Further examination of the models revealed that the dihedral angle H-4 to H-5 may be used to distinguish between the two molecules using a representation of the Karplus equation.[8] For both molecules, the H-6 to H-7

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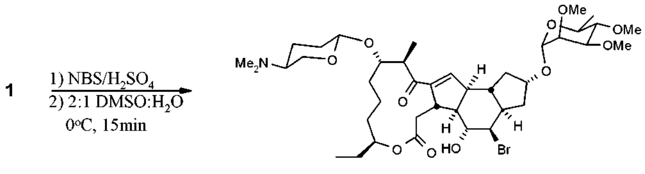
torsion angle is about 62−75°, giving rise to a small coupling constant (with respect to line width, and thus not resolved in the 1D experiment). For the α epoxide **3**, the H-4 to H-5 torsion is 80°, and so no coupling should be visible between H-4 and H-5. For the β compound, this torsion is 34°, which should result in a quantifiable coupling of about 4 Hz. While this coupling is not visible in the epoxides **3** and **4** due to signal overlap, a clear coupling constant of 3.4 Hz was measured for epoxide **6**. To measure the H-4 to H-5 coupling in epoxides **3** and **4**, the spectra were measured in benzene-d_6, which is known to induce shifts in proton resonances relative to chlorinated solvents for six membered ring epoxides.[9] The spectra clearly show that the signal for H-5 is coupled to H-4 with a coupling of 4.0 Hz in the β isomer, while in the α isomer, no coupling is observed. The assignment of α and β epoxides was confirmed by X-ray analysis on the crystalline derivative **6**.

Other electrophilic addition reactions to the 5,6-double bond also proceed stereoselectively favoring attack from the β face. Bromohydration and oxymercuration of **1** occur selectively via trans diaxial addition to the 5,6-double bond to give the nucleophile attached to C-5 with the α configuration and the electrophile attached to C-6 with the β configuration.



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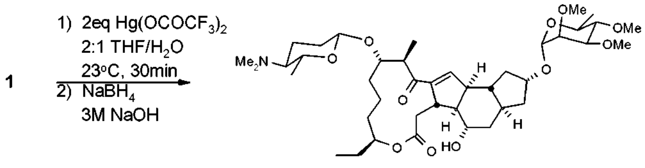

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This high regioselectivity in these transformations can be explained by the conformational constraints on the six-membered ring. After electrophilic addition preferentially on the β face, the nucleophile preferentially attacks at C-5, as this gives diaxial addition. Attack of the nucleophile at C-6 results in the less favored equatorial addition.

The assignment of product configuration was based on the coupling constants between H-4 to H-5 using the same analysis performed on the α and β epoxides. For the C-5 α configuration there will be no coupling (78° dihedral between H-4 and H-5) while for the β configuration there will be a 3−4 Hz coupling (42° dihedral angle between H-4 and H-5). No coupling was observed between H-4 and H-5 in compound **7** or **8**. Additionally, the bromohydrin **7** was converted into the α epoxide **3** by treatment with base.

Having established the configuration of the addition products to the 5,6-double bond, it was now left to explain the origin of the observed π-facial selectivity. The X-ray structure of spinosyn A (**1**) shows that the β face is more sterically hindered than the α face. Therefore, selectivity cannot be explained by steric arguments alone. Recent examples of epoxidation of polycyclic compounds with peracids from the more hindered face have been attributed to torsional steering[10] particularly in the absence of charged or highly polar groups[11] and may be used to explain the observed π-facial stereocontrol in the spinosyns. Torsional steering is especially pronounced when the C=C−C−H dihedral angle approximates 90°. Table 3 lists the dihedral angles around the cyclohexene ring in the MM3-minimized structures of **1** and **2**.

Table 3. Dihedral Angles about the Cyclohexene Ring in Spinosyn A and D

dihedral angle	spinosyn A (**1**)	spinosyn D (**2**)
C4−C5−C6−C7	−1.1	−0.7
C5−C6−C7−C11	26.5	25.2
C6−C7−C11−C12	−57.4	−56.7
C7−C11−C12−C4	62.7	62.7
C11−C12−C4−C5	−36.5	−37.3
C12−C4−C5−C6	6.5	7.2
C3−C4−C5−C6	−114.0	−113.5
H4−C4−C5−C6	125.0	125.5
C5−C6−C7−H7	−93.0	−94.0
C5−C6−C7−C8	142.7	141.6

The conformation of the cyclohexene ring in **1** and **2** is 1,2-diplanar[12] with C-12 almost in the plane of the C5−C6 double bond (dihedral angle 6.5°, Table 3). Experimental and theoretical studies on the conformations of cyclohexene rings show that the most stable conformation is the symmetrical half chair where the torsional angle between the double bond and the pseudoaxial hydrogen is 75−76°.[13] Consequently, face selection on the half chair form of cyclohexene and substituted cyclohexenes is expected to be poor as a result of internal compensation of opposite torsional effects. However, distortion of the symmetrical half-chair conformation of cyclohexenes to 1,2-diplanar forms can show good stereoselectivity as the opposing torsional effects will not be equal.[14a] In rigid polycyclic systems where the dihedral angle of the C=C double bond with the pseudoaxial hydrogen approches 90°, these torsional effects can be very significant. In **1**, the pseudoaxial H-7 substituent, located on the α face of the molecule, is almost perpendicular to the 5,6-double bond (dihedral angle −93°). There is no comparable perpendicular substituent on the β face of the cyclohexene ring in **1**. Since addition to the double bond must proceed antiperiplanar to pseudoaxial substituents in order to minimize torsional strain, β attack occurs preferentially

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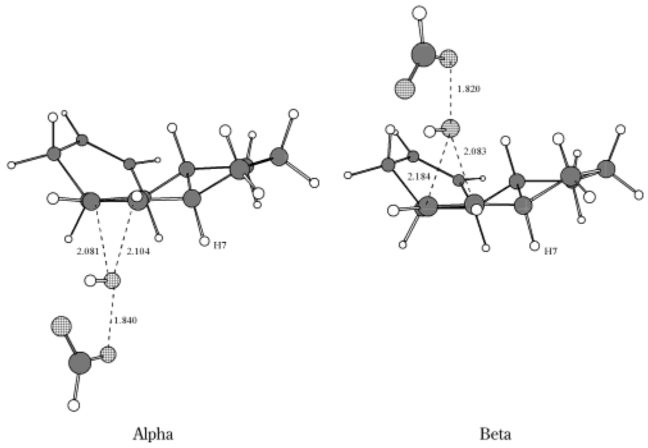

Figure 1. B3LYP/6-31G* transition-state structures for epoxidation.

in order to reduce the torsional stain with the H-7 substituent. This occurs despite the *β* face being more hindered.

To help explain the facial selectivity in the *m*-CPBA epoxidation of **1**, the α and *β* transition structures (TS) were located at the AM1 and subsequently the B3LYP/6-31G* level using the transition state optimization scheme in Gaussian 94.[14] The starting *Z*-matrixes were constructed according to the results by Bach[15] and Singleton[16] on the performic acid epoxidation of ethylene and propene at the MP2/6-31G* and B3LYP/6-31G* levels. They were able to reproduce experimental activation energies and kinetic isotope effects. Due to the size of the spinosyns, only the 3-fused ring system was considered and *m*-CPBA was modeled with performic acid.[17] Both TSs (α and *β*) were verified by normal-mode analysis at each level. Only one imaginary frequency existed for each, and this mode corresponded to oxygen transfer to the double bond.

The two B3LYP/6-31G* TSs (Figure 1) had geometries very similar to those calculated by Bach and Singleton. The experimental α/*β* ratio of epoxide products was found to be 1:5, suggesting that epoxidation from the seemingly more hindered face was preferred by about 1 kcal·mol^{-1} at 25 °C. The difference (i.e., $E_\alpha - E_\beta$) in the calculated TS energies is 1.3 kcal·mol^{-1} (B3LYP/6-31G*//B3LYP/6-31G* energies with zero-point energy correction included) corresponding to a marked *β* preference.

This energy difference can be attributed to the torsional destabilization in the α TS from the nearly eclipsed arrangement of the transferred oxygen atom and the H-7 axial hydrogen (torsion $O-C_6-C_7-H = -13.2°$). The staggered arrangement that occurs in the *β* transition structure is more favored despite the additional crowding effects of the C-3 methine. This torsional effect also exists in the epoxide products where MM3 calculations show a difference in energy of 1.66 kcal·mol^{-1} in favor of the *β* epoxide. The preference for a staggered arrangement in the transition structures of addition reactions to olefins and carbonyl groups is well-known and has been reviewed by Houk and co-workers.[18]

In summary, additions to the 5,6-double bond of the spinosyns occur preferentially from the more sterically demanding *β* face. The assignment of configuration of the additional products can be made using the observed coupling constants between H-4 to H-5. For the C-5 α configuration, there will be no coupling (80° dihedral between H-4 and H-5) while for the *β* configuration there will be a 3−4 Hz coupling (40° dihedral angle). Computational studies on the epoxidation transition state suggest a nearly symmetrical transition state with the transferred oxygen atom approximately equidistant from C-5 and C-6. The transition structures provide evidence that the stereoselectivity of addition reactions to the 5,6-double bond of the spinosyns is controlled by torsional effects involving the pseudoaxial H-7 substituent on the α face and the incoming electrophile.

Experimental Section

General Methods. All NMR data were obtained at 400 MHz for proton and 100 MHz for carbon data, in chloroform-*d* or benzene-d_6 as indicated in the text, using TMS as an internal standard. Compounds were purified by HPLC as indicated in the experimental details.

Crystallographic Studies of Spinosyn A (1). A colorless plate, crystal size 0.38 × 0.28 × 0.17 mm, space group $P2_12_12_1$ (no. 19), $a = 9.5460(2)$ Å, $b = 12.7114(5)$ Å, $c = 34.2575(13)$ Å, $V = 4169.0(4)$ Å^3, $z = 4$, was used for data collection. The data were acquired on a Nonius KappaCCD spectrometer, using Mo Kα radiation at a temperature of 296 K. The structure was solved by direct methods using SIR97[19] and expanded using difference Fourier synthesis. The structure was refined on an AlphaServer 2100 using SHELX-97[20] using 5373 reflections and 479 variable parameters and gave $R = 0.052$ and $Rw = 0.126$. The goodness of fit value was 1.030.

Crystallographic Studies of 6. A colorless prism, crystal size 0.25 × 0.22 × 0.18 mm, space group $P2_12_12_1$ (no. 19), $a = 732660(21)$ Å, $b = 12.4551(14)$ Å, $c = 35.380(2)$ Å, $V = 4288.8(12)$ Å^3, $z = 4$, was used for data collection. The data were acquired on a Nonius KappaCCD spectrometer, using Mo Kα radiation at a temperature of 296 K. The structure was solved by direct methods using SIR97[18] and expanded using difference Fourier synthesis. The structure was refined on an AlphaServer 2100 using SHELX-97[19] using 4359 reflections and 498 variable parameters and gave $R = 0.068$ and $Rw = 0.139$. The goodness of fit value was 1.025.

General Procedure for Oxidation with *m*-CPBA. (5*S*,6*R*)-5,6-Epoxyspinosyn A (4). Spinosyn A (10.0 g, 13.7 mmol) was dissolved in dichloromethane (50 mL) and stirred at 0 °C under nitrogen. A solution of 50% *m*-CPBA (10.6 g, 30.9 mmol) in dichloromethane (70 mL) was added, and the reaction was stirred for 5 h at 0 °C and then at 23 °C for 16 h. The reaction mixture washed with 10% aqueous $NaHSO_3$ solution (3 × 50 mL), 10% aqueous $NaHCO_3$ solution (3 × 50 mL), and brine solution (50 mL), dried (anhydrous K_2CO_3), and concentrated to give a 5:1 mixture (by HPLC) of α **3** and *β* epoxides **4** as a white solid (6.89 g, 68%). The *β* epoxide **4** was purified by HPLC (C18, MeOH/0.02%NH_4OAc 90:10). (5*S*,6*R*)-5,6-Epoxyspinosyn A (**4**): partial ^{1}H NMR ($CDCl_3$) δ 6.57 (1H, t), 3.5 (1H, m), 3.4 (1H, m), 3.39 (1H, d), 3.38 (1H, t), 2.57 (1H, ddt), 2.05 (1H, m), 1.33 (1H, m); ^{13}C NMR 146.2, 54.8, 53.1, 48.7, 44.0, 41.6, 39.2, 39.0; MS *m*/*z* 148 (M + 1).

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(5*S*,6*R*)-5,6-epoxyspinosyn D (6) (82 mg; 30%): partial ^{1}H NMR δ 6.59 (1H, dd), 3.45 (1H, m), 3.4 (1H, ddd, $J = 9.1$, 9.1, 3.6), 3.18 (1H, d, $J = 3.6$), 2.54 (1H, ddt), 1.97 (1H, m), 1.40 (3H, s), 1.32 (1H,m).

General Procedure for Oxidation with *N*-Bromosuccinamide. (5*R*,6*R*)-5-Hydroxy-6-bromospinosyn A (7) and (5*R*,6*S*)-5,6-Epoxyspinosyn A (3). Spinosyn A (1.33 g, 1.82 mmol) was suspended in dimethyl sulfoxide (15 mL), and water (5 mL) was added. To this suspension was added concentrated H_2SO_4 (1.80 mmol), which gave a colorless solution. The solution was cooled to 0 °C, *N*-bromosuccinamide (322 mg, 1.80 mmol) was added, and the reaction was stirred for 10 min. The reaction was added to 10% aqueous $NaHCO_3$ (50 mL) and extracted with ether (3 × 25 mL). The ether extracts were combined, washed with brine solution (25 mL), dried (K_2CO_3), and concentrated to give the intermediate bromohydrin as a white solid (1.3 g, 86%). (5*R*,6*R*)-5-Hydroxy-6-bromospinosyn A (**7**): partial ^{1}H NMR δ 6.69 (1H, bs), 4.43 (1H, d), 3.97 (1H, m), 3.34 (1H, m), 3.11 (m, 1H), 3.00 (1H, dd), 2.83 (1H, m), 2.50−2.35 (2H, m). The bromohydrin **7** (161 mg, 0.195 mmol) was dissolved in tetrahydrofuran (5 mL) under nitrogen and sodium hydride (12.5 mg as 60% dispersion, 0.312 mmol) added. After the gas evolution ceased (5 min), the reaction was stirred for 30 min, added to 10% aqueous $NaHCO_3$ (25 mL), and extracted with ether (2 × 25 mL). The ether extracts were combined, washed with brine (25 mL), dried (K_2CO_3), and concentrated to give the α epoxide **3** as white solid (0.14 g, 96%). (5*R*,6*S*)-Epoxyspinosyn A (**3**): partial ^{1}H NMR δ 6.7 (1H, $J =$ t, 2.2, 2.2), 3.45 (1H, m), 3.19 (1H, dd, $J = 4.0$, 1.5), 3.12 (1H, m), 3.05 (1H, d, $J = 4$), 2.53 (1H, ddt), 1.61 (1H, m), 0.8 (1H, m); partial ^{13}C NMR δ 147.1, 55.8, 53.5, 47.8, 44.3, 43.7, 42.0, 39.7; MS *m*/*z* 748 (M + 1).

(5*S*)-5,6-Dihydro-5-hydroxyspinosyn A (8). Mercuric trifluoroacetate (1.12 g, 2.62 mmol) was suspended in 30 mL of THF/water (2:1, v/v). To this yellow suspension was added spinosyn A (0.98 g, 1.34 mmol), and the reaction was stirred at 23 °C for 30 min. The reaction was treated with 7 mL of 1 N NaOH followed by 2.5 mL of $NaBH_4$ (60.5 M solution in 3 M NaOH). The reaction turned black supporting a precipitate, stirring was halted, and the solids were allowed to settle to the bottom of flask. The supernatant was diluted with ether (50 mL). The layers were separated, and the aqueous layer was further extracted with ether (2 × 25 mL). The ether extracts were combined, washed with 10% aqueous $NaHCO_3$ (30 mL), dried over K_2CO_3, and concentrated. The residue was purified by medium-pressure liquid chromatography (230−400 mesh $Si(O_2)$, CH_2Cl_2/MeOH 95:5, v/v) to give a white solid (5*S*)-5,6-dihydro-5-hydroxyspinosyn A (**8**) (349.7 mg, 30.4%): partial ^{1}H NMR δ 6.84 (1H, bs), 4.07 (1H, bs), 3.30 (1H, m), 3.15 (1H, dd), 3.11 (1H, t), 3.02 (1H, m), 2.91−2.76 (2H, m); partial ^{13}C NMR δ 148.6, 67.4, 48.3, 48.2, 47.5, 45.8, 43.01, 35.2.

Supporting Information Available: NMR data for **1**−**4** and **6**, X-ray experimental data and ORTEP diagrams for the crystal structures of **1** and **6**, and *Z*-matrixes on the theoretical studies outlined in Figure 1 with computed total energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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