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Preparation of the 5/5-Spiroketal of the Ritterazines

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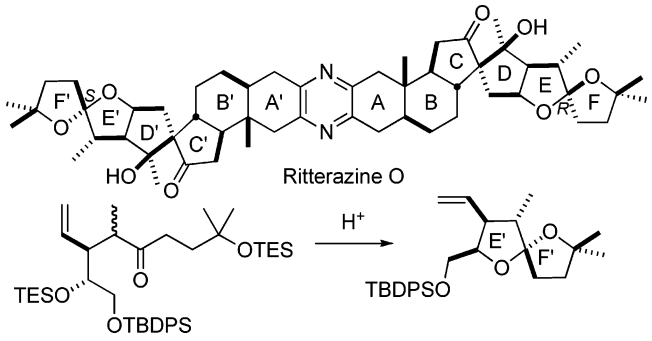
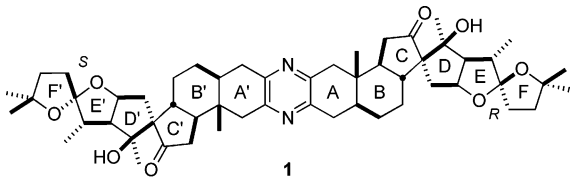


The enantiomerically pure 5/5-spiroketal required for the synthesis of the ritterazines has been prepared with high diastereocontrol by ring closure followed by equilibration.

Introduction

The ritterazines (represented by ritterazine O **1**), found in small quantities in the lipophilic extract of the tunicate *Ritterella tokioka*, induce apoptosis in apoptosis-resistant malignant cells.[1] With the closely related cephalostatins, which show the same activity, they form a unique class of trisdecacyclic molecules featuring a pyrazine as the core ring, steroid-related structures, and spiroketal edge rings (E and F). Partial syntheses from steroid precursors of several of the 6-6-6-5 cephalostatins and derivatives have been accomplished.[2] There has been no report of efforts other than our own toward the 6-6-5-5 ritterazines or cephalostatins. In a preceding paper,[3] we described the preparation of the A−B−C carbocyclic core of these ritterazines via an intramolecular diene cyclozirconation−carbonylation process. Here we present our synthesis of the 5/5-spiroketals (rings E and F, rings E′ and F′) of **1**.

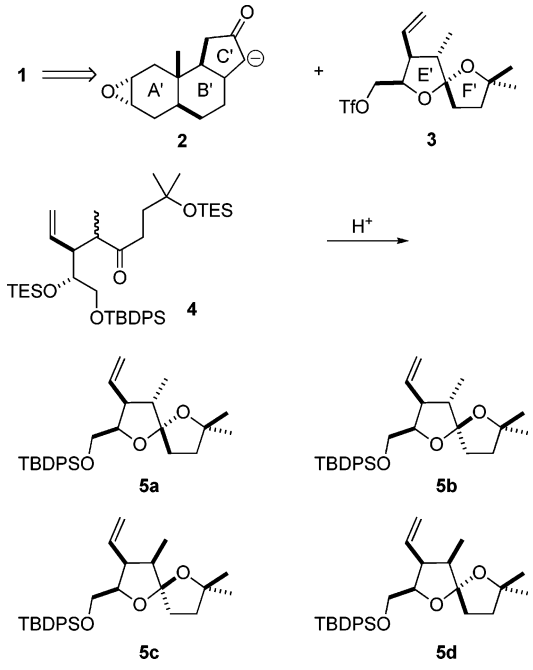


1

Ritterazine O

(1) For the isolation and activity of the ritterazines and cephalostatins, see: (a) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 4484. (b) Komiya, T.; Fusetani, N.; Matsunaga, S.; Kubo, A.; Kaye, F. J.; Kelley, M. J.; Tamura, K.; Yoshida, M.; Fukuoka, M.; Nakagawa, K. *Cancer Chemother. Pharmacol.* **2003**, *51*, 202. (c) Pettit, G. R.; Tan, R.; Xu, J.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 955.

SCHEME 1



Results and Discussion

Synthetic Approach: To prepare ritterazine O **1**, we planned to alkylate the ketone **2** with the triflate **3** (Scheme 1). We envisioned preparing **3** by the acid-catalyzed deprotection, cyclization, and equilibration of the ketone **4** to give **5a**. Although many 5/5-spiroketals have been prepared,[4] little is known about stereocontrol.[5] Under acid-catalyzed conditions,

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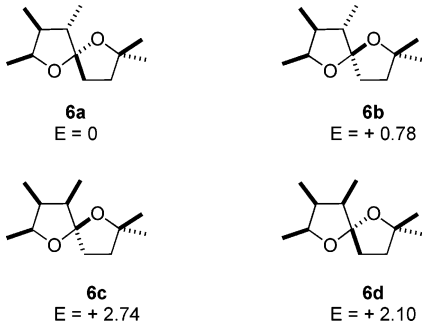
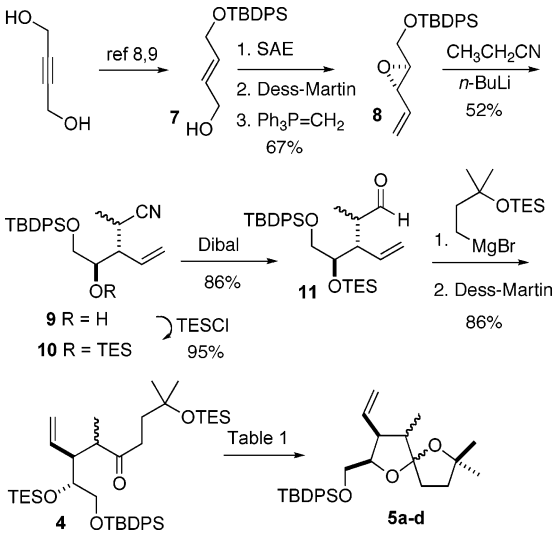


FIGURE 1. Calculated relative stabilities (MOPAC PM3, kcal/mol) of diastereomers **6a**−**6d**.

6/5- and 6/6-spiroketals generally equilibrate toward a particular diastereoisomer due to anomeric or substituent stabilization in the six-membered rings,[6] but 5/5-spiroketals typically equilibrate to nearly a 1:1 mixture of epimers.[4c] An advantage in the synthesis of **5a** is the presence of the methyl group adjacent to the spiro carbon, which we expected to exert significant stereocontrol. It was reasonable to expect that the methyl group on the E ring which is *cis* to the vinyl group in **5c** and **5d** would equilibrate to the *trans* form. MOPAC PM3 calculations[7] with model compounds **6a**−**6d** (Figure 1) further encouraged us to adopt this route to **5a**.

Preparation of the Spiroketal Precursor: The synthesis of **4** (Scheme 2) began with 2-butyne-1,4-diol, which was converted into enantiomerically pure **8** following literature precedents[8,9] and modifications thereof.[10a] Opening of epoxides is known to be particularly difficult with nitrile-stabilized anions,[11] but the presence of the vinyl group in **8** promoted attack by the propionitrile anion, leading to the desired alcohol **9**. Protection of the alcohol **9** was required, as addition of the side chain Grignard reagent to **9** led to lactone formation. Reduction of **10** to the aldehyde, Grignard addition,[12] and oxidation delivered the desired ketone **4**.

SCHEME 2



Spiroketal Formation and Equilibration: The crucial deprotection/cyclization of **4** was carried out with aqueous HCl in THF. The spiroketal **5a** was obtained along with notable amounts of the other diastereomers **5b**−**5d** (Table 1, entry 1). The four diastereomers were separable by silica gel chromatography, and their structures could be assigned spectroscopically.

TABLE 1. Equilibration of Diastereomers 5a−d

			Yield (%)			
entry	from	conditions	**5a**	**5b**	**5c**	**5d**
1	**4**	A[a]	37[d]	3[d]	33[d]	15[d]
2	entry 1 mix	B[c]	74[b]	17[b]	of **5b-d**	
3	**5c**:**5d** = 71:29	B	62[b]	3[d]	8[d]	3[d]
4	**5a**	B	81[b]	6[b]	3[b]	1[b]
5	**5c**	C[e]	0[f]	0[f]	54[f]	46[f]
6	**5d**	C	0[f]	0[f]	40[f]	60[f]

[a] Aqueous 1 M HCl/THF (1:4), rt, 3 h. [b] Isolated yield. [c] PPTS (0.1 M), CH_2Cl_2, 80 °C (sealed flask), 5−7 h. [d] Determined by NMR ratios from partially separated mixtures. [e] In $CDCl_3$ for 4 weeks. [f] NMR ratio.

Further equilibration of the mixture of **5a**−**5d** obtained in entry 1 was observed when the reaction time was prolonged, but this also led to decomposition. It was better to equilibrate the mixture with PPTS in CH_2Cl_2 (entry 2), which delivered **5a** in 74% yield accompanied by 17% of a mixture of the other three diastereomers. The recovered mixture of ketals **5b**−**5d** could be subjected again to equilibration. For example (entry 3), under PPTS-catalyzed conditions, a mixture of **5c** and **5d** can be converted to **5a** in 70% yield, based on starting material not recovered. Entries 5 and 6 show that, under careful acid-catalyzed conditions, **5c** and **5d** can be equilibrated, without going on to **5a**. This can be rationalized by a low activation barrier for the inversion at the spiro center. By contrast, the inversion of the methyl substituent requires more drastic conditions. Entry 4 shows the result of a PPTS-catalyzed equilibration that started from pure **5a**.

Structure Assignments: The relative configurations of the secondary methyl groups of **5a**−**5d** were assigned unambiguously using NMR NOE techniques, which showed clear correlations between this methyl and the methine proton of the

(2) For leading references, see: (a) Lee, J. S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2005**, *127*, 13122. (b) Nawasreh, M.; Winterfeldt, E. *Curr. Org. Chem.* **2003**, *7*, 649.

(3) Taber, D. F.; Taluskie, K. V. *J. Org. Chem.* **2006**, *71*, 2797.

(4) For a review, see: (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. For a selection of recent work on 5/5-spiroketals, see: (b) Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 857. (c) Doubský, J.; Streinz, L.; Šaman, D.; Zedník, J.; Koutek, B. *Org. Lett.* **2004**, *6*, 4909.

(5) For stereoselective 5/5-spiroketal formation, see: (a) Sharma, G. V. M.; Subash Chander, A.; Goverdan Reddy, V.; Krishnudu, K.; Ramana Rao, M. H. V.; Kunwar, A. C. *Tetrahedron Lett.* **2000**, *41*, 1997. (b) Betancor, C.; Freire, R.; Pérez-Martin, I.; Prangé, T.; Suárez, E. *Org. Lett.* **2002**, *4*, 1295. (c) Lee, S.; LaCour, T. G.; Lantrip, D.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 313. (d) Lee, J. S.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2247. (e) Sartillo-Piscil, F.; Vargas, M.; Anaya de Parrodi, C.; Quintero, L. *Tetrahedron Lett.* **2003**, *44*, 3919. (f) Jeong, J. U.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, *35*, 5385.

(6) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983.

(7) Structures **6a**−**6d** were first minimized with Mechanics before they were evaluated with MOPAC PM3. Both Mechanics and MOPAC PM3 were used as implemented on the Fujitsu CAChe workstation.

(8) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959.

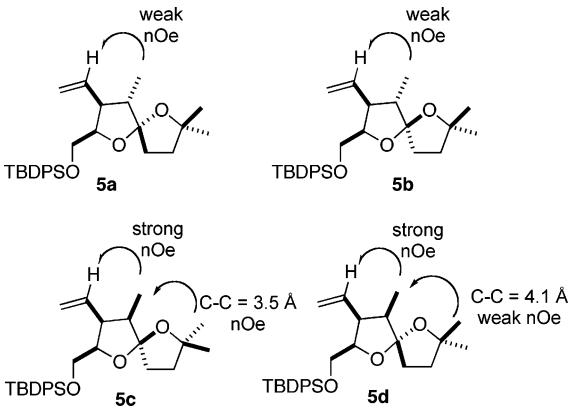
(9) Mori, Y.; Asai, M.; Kawade, J.-i.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5315.

(10) (a) Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1638. (b) Nacro, K.; Zedde, C.; Escudier, J.-M.; Baltas, M.; Gorrichon, L.; Neier, R. *Chirality* **1998**, *10*, 804.

(11) (a) Larchevêque, M.; Debal, A. *Synth. Commun.* **1980**, *10*, 49. (b) Taylor, S. K.; DeYoung, D.; Simons, L. J.; Vyvyan, J. R.; Wemple, M. A.; Wood, N. K. *Synth. Commun.* **1998**, *28*, 1691.

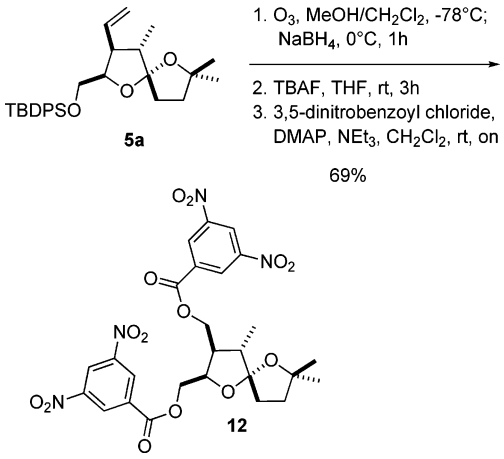
(12) Andrews, D. R.; Barton, D. H. R.; Hesse, R. H.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 4819.

SCHEME 3



vinyl group for **5c** and **5d** (Scheme 3). A NOE between the methyl group of the E ring and the nearest methyl in the F ring was observed in **5c** and was very weak in **5d**. The calculated distances between the carbons of those methyls were 3.5 and 4.1 Å, respectively, which allowed unequivocal assignment of **5c** and **5d**. The differentiation of **5a** and **5b** was less clear, so we converted **5a** into the crystalline bis-dinitrobenzoate **12** under careful nonacidic conditions (Scheme 4). This derivative delivered a crystal that was suitable for X-ray analysis (Figure 2).

SCHEME 4



The three-dimensional structure of **12** was instructive. The more highly substituted five-membered ring adopts a half-chair conformation. Following the expected anomeric affect,[6] the more stable diastereomer **5a** of the spiroketal then has the oxygen branch, rather than the carbon branch, axial on that half chair. This may be a general principle contributing to conformational preferences in five-membered ring spiroketals.

Conclusion

The preparation of the key building block **5a** has been accomplished, using a δ,δ'-dihydroxyketone spiroketalization as the key step, followed by equilibration. These results make the enantiomerically pure spiroketal **5a** available in sufficient quantity to support our efforts toward the total synthesis of the ritterazines. The correlation between the experimental results and the MOPAC PM3 calculations is encouraging.

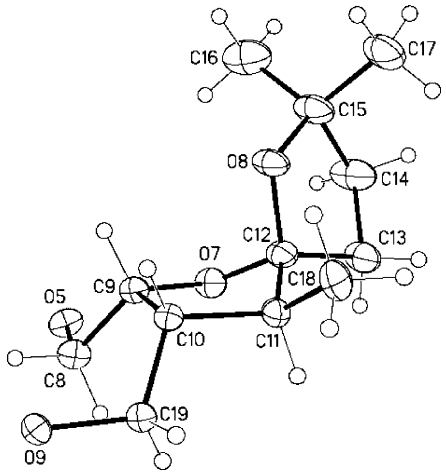


FIGURE 2. Molecular structure of compound **12**. The dinitrobenzoyl groups have been omitted for clarity. ORTEP drawings are shown at the 50% probability level.

Experimental Section

(3*S*)-3-((*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-hydroxyethyl)-2-methyl-4-pentenenitrile (9). To a solution of propionitrile (2.24 g, 40.6 mmol) in THF (57 mL) was added *n*-BuLi (1.9 M, 19 mL) at −78 °C. After this solution was stirred for 1 h at −78 °C, a solution of epoxide **8** (2.75 g, 8.12 mmol) in THF (10 mL) was added over 3 min at −78 °C. The temperature of the solution was progressively increased over 2 h, and when it reached −10 °C, the reaction was quenched with saturated aqueous NH_4Cl (40 mL). The mixture was partitioned between ether and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the alcohol **9** as a mixture of two diastereomers as a colorless oil (1.66 g, 52% yield in a ratio of 54:46): TLC R_f (MTBE/PE = 40:60) = 0.84 and 0.62; ^{1}H NMR of mixture δ 1.06 (s), 1.07 (s), 1.25 (d, J = 7.2 Hz), 1.29 (d, J = 7.1 Hz), 2.10−2.21 (m, 1H), 2.36 (br s), 2.43 (br s), 2.78−2.95 (m, 1H), 3.52−3.70 (m, 2H), 3.81−3.87 (m), 4.14−4.23 (m), 5.03 (dd, J = 17.2, 1.4 Hz), 5.16 (dd, J = 17.1, 1.4 Hz), 5.18 (dd, J = 10.2, 1.6 Hz), 5.30 (dd, J = 10.2, 1.5 Hz), 5.61 (dd, J = 17.2, 10.0 Hz), 5.82 (dd, J = 17.1, 10.0 Hz), 7.37−7.49 (m, 6H), 7.61−7.68 (m, 4H); ^{13}C NMR[13] of mixture δ u 132.9, 132.9, 132.8, 122.3, 121.8, 121.0, 120.7, 66.4, 65.9, 19.2, 19.2, d 135.5, 133.0, 132.8, 130.0, 129.9, 129.9, 127.9, 127.8, 127.8, 127.8, 71.6, 71.1, 49.5, 49.5, 27.0, 26.8, 26.8, 26.7, 16.5, 16.2; IR of mixture (cm^{-1}) 3454 (br), 2929, 2857, 2240, 1113; MS *m*/*z* (%) 394 (M + H, 100), 362 (13), 307 (11); HRMS calcd for $C_{24}H_{31}NO_2SiNa$ (M + Na) 416.2022, obsd 416.2032.

(3*S*)-3-((*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-(triethylsilyloxy)-ethyl)-2-methyl-4-pentenenitrile (10). To a solution of the alcohol **9** (1.56 g, 3.96 mmol) in pyridine (20 mL) were added DMAP (97 mg, 0.79 mmol) and triethylsilyl chloride (2.0 mL, 11.9 mmol) at rt. The reaction mixture was stirred at rt for 20 h, then partitioned between ether, and sequentially a 1:1 mixture of water and saturated aqueous NH_4Cl and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the nitrile **10** as a mixture of two diastereomers as a slightly yellow oil (1.90 g, 95% yield): TLC R_f (MTBE/PE = 5:95) = 0.53 and 0.41; ^{1}H NMR of mixture δ 0.39−0.49 (m, 6H), 0.79−0.86 (m, 9H), 1.05 (s, 9H), 1.30 (d, J = 7.1 Hz), 1.33 (d, J = 7.1 Hz), 2.44−2.50 (m), 2.54−2.62 (m), 2.68−2.77 (m), 2.80−2.89 (m), 3.44−3.59 (m, 2H), 3.74−3.80 (m), 4.09−4.15 (m), 5.16−5.35 (m, 2H), 5.49−5.60 (m), 5.77−5.88 (m), 7.33−7.47 (m, 6H),

(13) ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u".

7.61−7.70 (m, 4H); ^{13}C NMR of mixture δ u 133.2, 133.1, 122.4, 122.4, 120.7, 120.5, 65.2, 64.7, 19.1, 4.9, 4.8, d 135.6, 135.5, 135.5, 133.5, 133.3, 129.8, 129.8, 129.6, 129.5, 127.7, 127.7, 127.7, 127.7, 72.7, 72.2, 50.3, 50.2, 27.2, 26.8, 16.8, 6.8, 6.7; IR of mixture (cm^{-1}) 2956, 2934, 2877, 2859, 2239, 1472, 1462, 1428, 1113; MS *m*/*z* (%) 508 (M + H, 100), 462 (18), 394 (13); HRMS calcd for $C_{30}H_{45}NO_2Si_2Na$ (M + Na) 530.2887, obsd 530.2890.

(3*S*)-3-((*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-(triethylsilyloxy)-ethyl)-2-methyl-4-pentenal (11). To a solution of the nitrile **10** (2.00 g, 3.93 mmol) in toluene (25 mL) was added a 20 wt % solution of Dibal in toluene (10.2 mmol, 8.4 mL) at −78 °C. The temperature of the solution was progressively increased over 2.5 h, and when it reached −5 °C, the reaction was poured in a well-stirred mixture of saturated aqueous NH_4Cl (100 mL) and ether (500 mL). After partition, the aqueous phase was re-extracted with ether (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the aldehyde **11** as a mixture of two diastereomers as a slightly yellow oil (1.72 g, 86% yield): TLC R_f (MTBE/PE = 4:96) = 0.51 and 0.46; ^{1}H NMR of mixture δ 0.37−0.78 (m, 6H), 0.79−0.86 (m, 9H), 1.02−1.13 (m, 12H), 2.51−2.65 (m), 2.74−2.82 (m), 3.43−3.58 (m), 3.73−3.79 (m), 3.82−3.88 (m), 5.09−5.25 (m, 2H), 5.68−5.69 (m, 1H), 7.34−7.47 (m, 6H), 7.60−7.68 (m, 4H), 9.63−9.66 (m, 1H); ^{13}C NMR of mixture δ u 133.4, 133.3, 119.2, 188.7, 65.2, 64.7, 19.2, 19.1, 4.9, 4.9, d 205.5, 205.3, 135.5, 135.5, 135.5, 129.8, 129.7, 129.7, 129.6, 127.7, 127.0, 73.2, 72.3, 49.0, 48.4, 47.1, 4.9, 26.8, 26.8, 12.7, 12.6, 6.7; IR of mixture (cm^{-1}) 3072, 2957, 2876, 2858, 1726, 1428, 1112; MS *m*/*z* (%) 511 (M + H, 13), 333 (100); HRMS calcd for $C_{30}H_{46}O_3Si_2Na$ (M + Na) 533.2883, obsd 533.2866.

(3*S*)-3-((*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-(triethylsilyloxy)-ethyl)-4,8-dimethyl-8-(triethylsilyloxy)1-nonen-5-one (4). A solution of $BrCH_2CH_2C(CH_3)_2OTES$ (2.10 g, 7.5 mmol) and iodine (17 mg) in THF (19 mL) was added to magnesium turnings (200 mg, 8.25 mmol) over 10 min at rt.[12] Stirring was continued for an additional 2.5 h at rt. The resulting Grignard solution was cooled to 0 °C, then cannulated over 5 min into a solution of the preceding aldehyde (1.28 g, 2.5 mmol) in THF (5 mL) at 0 °C. After 10 min, the mixture was partitioned between ether (50 mL) and saturated aqueous NH_4Cl (10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2 (30 mL) and the Dess−Martin reagent (3.18 g, 7.5 mmol) was added. After 2 h at rt, the mixture was poured into a 1:1 mixture of 20 wt % aqueous $Na_2S_2O_3$ (50 mL) and saturated aqueous NH_4Cl (50 mL) and stirred at rt for 5 min. This mixture was then partitioned with ether (100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the ketone **4** as a mixture of two diastereomers as a slightly yellow oil (1.54 g, 86% yield): TLC R_f (MTBE/PE = 3:97) = 0.37 and 0.23; ^{1}H NMR of mixture δ 0.37−0.49 (m, 6H), 0.51−0.62 (m, 6H), 0.78−0.88 (m, 9H), 0.90−0.98 (m, 9H), 1.01−1.13 (m, 12H), 1.16−1.24 (m, 3H), 1.58−1.75 (m, 2H), 2.43−2.86 (m, 4H), 3.38−3.53 (m, 2H), 3.65−3.71 (m), 3.81−3.88 (m), 4.95−5.18 (m, 2H), 5.57−5.77 (m, 1H), 7.33−7.46 (m, 6H), 7.60−7.69 (m, 4H); ^{13}C NMR of mixture δ u 214.8, 214.3, 133.6, 133.6, 133.5, 118.5, 118.4, 72.6, 72.5, 65.8, 65.2, 38.4, 38.2, 37.7, 36.7, 19.2, 19.2, 6.7, 5.2, 5.1, d 135.7, 135.6, 135.6, 135.6, 135.5, 129.7, 129.7, 129.6, 129.6, 127.7, 127.7, 127.6, 73.5, 71.2, 49.5, 48.7, 47.1, 46.6, 30.0, 29.9, 29.8, 26.9, 16.2, 15.0; IR of mixture (cm^{-1}) 2957, 2934, 2911, 2876, 1715, 1113; MS *m*/*z* (%) 579 (52), 447 (100), 387 (46); HRMS calcd for $C_{42}H_{70}O_4Si_3$ (M + H) 711.4660, obsd 711.4640.

Spiroketals 5a−d. A solution of the ketone **4** (4.28 g, 6.02 mmol) in aqueous HCl (48 mL, 1 M) and THF (190 mL) was stirred at rt for 3 h. The solution was then partitioned between ether (500 mL) and sequentially saturated aqueous $NaHCO_3$ (120 mL), water (120 mL), and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the spiroketals **5a−5d** as a mixture of four diastereomers as a colorless oil (2.44 g, 87% yield).

(2*R*,3*S*,4*S*,5*S*)-2-*tert*-Butyldiphenylsilyloxymethyl-3-ethenyl-4,7,7-trimethyl-1,6-dioxaspiro[4.4]nonane (5a): TLC R_f (MTBE/PE = 5:95) = 0.48; ^{1}H NMR δ 0.92 (d, J = 6.8 Hz, 3H), 1.04 (s, 9H), 1.18 (s, 3H), 1.39 (s, 3H), 1.67−1.76 (m, 1H), 1.95−2.20 (m, 4H), 2.72−2.83 (m, 1H), 3.61 (dd, J = 11.1, 3.0 Hz, 1H), 3.76 (dd, J = 11.3, 3.5 Hz, 1H), 4.10−4.16 (m, 1H), 5.05−5.13 (m, 2H), 5.89−6.00 (m, 1H), 7.32−7.44 (m, 6H), 7.66−7.78 (m, 4H); ^{13}C NMR δ u 133.7, 133.5, 81.7, 64.4, 37.4, 34.0, 19.2, d 137.4, 135.8, 135.7, 129.6, 129.5, 127.6, 127.5, 79.4, 52.5, 44.8, 29.8, 28.3, 26.8, 11.7; IR (cm^{-1}) 2963, 2930, 2858, 1112; MS *m*/*z* (%) 387 (100), 309 (10); HRMS calcd for $C_{29}H_{40}O_3SiNa$ (M + Na) 487.2644, obsd 487.2658; $[\alpha]_D$ −77 (*c* 1.00, CH_2Cl_2).

(2*R*,3*S*,4*S*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-3-ethenyl-4,7,7-trimethyl-1,6-dioxaspiro[4.4]nonane (5b): TLC R_f (MTBE/PE = 5:95) = 0.60. Although **5b** could be separated from the other diastereomers, its conversion to **5a** in $CDCl_3$ or in a PE/MTBE mixture was fast. Selection of ^{1}H NMR signals: δ 0.94 (d, J = 8.1 Hz, 3H), 1.04 (s, 9H), 1.16 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ u 133.9, 133.7, 117.3, 116.5, 81.0, 64.6, 36.9, 32.3, 19.2, d 137.0, 135.8, 135.7, 129.4, 127.5, 127.5, 117.3, 116.5, 79.3, 53.2, 43.8, 29.8, 28.6, 26.8, 13.8.

(2*R*,3*S*,4*R*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-3-ethenyl-4,7,7-trimethyl-1,6-dioxaspiro[4.4]nonane (5c): TLC R_f (MTBE/PE = 5:95) = 0.71; ^{1}H NMR δ 0.86 (d, J = 7.0 Hz, 3H), 1.03 (s, 9H), 1.09 (s, 3H), 1.27 (s, 3H), 1.60−1.68 (m, 1H), 1.84−2.02 (m, 4H), 2.19−2.29 (m, 1H), 2.69−2.79 (m, 1H), 3.64−3.75 (m, 2H), 4.04−4.13 (m, 1H), 4.95−5.04 (m, 2H), 5.92−6.04 (m, 1H), 7.31−7.42 (m, 6H), 7.65−7.71 (m, 4H); ^{13}C NMR δ u 134.1, 134.0, 116.9, 115.3, 82.0, 64.7, 37.0, 35.6, 19.3, d 135.9, 135.7, 135.7, 129.4, 127.5, 81.0, 50.6, 43.4, 30.1, 28.2, 26.8, 10.4; IR (cm^{-1}) 2965, 2930, 2857, 1112; MS *m*/*z* (%) 387 (100), 309 (11); $[\alpha]_D$ +8 (*c* 1.00, CH_2Cl_2).

(2*R*,3*S*,4*R*,5*S*)-2-*tert*-Butyldiphenylsilyloxymethyl-3-ethenyl-4,7,7-trimethyl-1,6-dioxaspiro[4.4]nonane (5d): TLC R_f (MTBE/PE = 5:95) = 0.54; ^{1}H NMR δ 0.89 (d, J = 7.4 Hz, 3H), 1.02 (s, 9H), 1.19 (s, 3H), 1.37 (s, 3H), 1.68−1.86 (m, 2H), 1.91−2.06 (m, 2H), 2.40−2.49 (m, 1H), 2.86−2.94 (m, 1H), 3.60−3.70 (m, 2H), 4.21−4.27 (dd, J = 11.5, 5.7 Hz, 1H), 5.00−5.04 (m, 1H), 5.04−5.08 (m, 1H), 5.55−5.67 (m, 1H), 7.30−7.44 (m, 6H), 7.64−7.75 (m, 4H); ^{13}C NMR δ u 134.0, 133.8, 117.9, 116.7, 80.4, 64.3, 37.5, 33.7, 19.2, d 135.7, 135.0, 134.3, 129.4, 127.5, 127.5, 79.3, 50.2, 44.5, 29.8, 28.8, 26.7, 12.2; IR (cm^{-1}) 2964, 2931, 2858, 1112; MS *m*/*z* (%) 387 (100), 309 (12); $[\alpha]_D$ −40 (*c* 1.00, CH_2Cl_2).

Procedure for the Equilibration of the Spiroketals. A solution of the mixed spiroketals **5a−5d** (1.24 g, 2.67 mmol) and PPTS (338 mg, 1.33 mmol) in CH_2Cl_2 (13.3 mL) was stirred at 80 °C in a sealed flask for 5 h. To the reaction mixture was added 8 g of silica gel. The solvent was evaporated, and the residue was chromatographed directly to give spiroketals **5a** (920 mg, 74%) and **5b−5c** (206 mg, 17%).

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Supporting Information Available: General experimental procedures, ^{1}H and ^{13}C spectra, X-ray data for **12**, and other data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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