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A DOUBLE HEMIKETAL FORMATION/HETERO-MICHAEL ADDITION APPROACH TO THE [6,5,5]-DISPIROKETAL SYSTEM OF SPIROLIDES†

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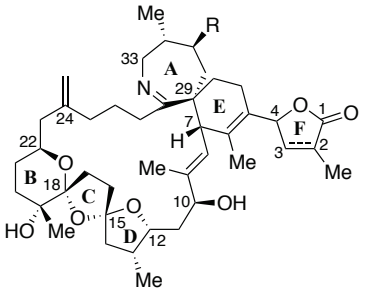
Abstract – An approach to the [6,5,5]-dispiroketal ring system of spirolides is described. It was found that *cisoid* isomers, which suffered from a destabilizing dipole–dipole interaction, were preferentially formed over *transoid* isomers by a double hemiketal formation/hetero-Michael addition sequence regardless of the reaction conditions used. However, the stereochemistry at C12 was controlled by the methyl group at C13, resulting in the preferential formation of undesired 12*S* isomers. As expected from precedents, the desired isomer could be obtained upon exposure of the 12*R* isomer, formed by the sequence, to TsOH in benzene, albeit in a ratio of 1:3 favoring its C15-epimer.

INTRODUCTION

In the mid-1990s, a number of polyether macrocyclic phycotoxins containing a spiro-linked cyclic imine moiety were isolated from a variety of shellfish species.[1] Although biological activities have been reported for some members of the family that includes pinnatoxins/pteriatoxins,[2] spirolides,[3] and gymnodimines,[4] the scarcity of a natural supply precluded mechanistic elucidation aiming to better understand their toxicity. This supply issue, in conjunction with the intriguing structures, has spurred considerable interest in the chemical community,[1b,5] culminating in the total syntheses of pinnatoxins,[6–9] pteriatoxins[10] and (–)-gymnodimine.[11] The synthetic material served to establish the mode of action of pinnatoxin A.[8b] Despite considerable efforts,[12,13] however, total synthesis of any member of the spirolide group has not been reported to date. Spirolides A–D, prominent members of this group isolated by Wright and co-

† Dedicated to Professor Masakatsu Shibasaki on the occasion of his 70th birthday

workers in 1995 from extracts of digestive glands of mussels and scallops,[3a] share a unique 23-membered carbocyclic backbone that is composed of a [6,5,5]-dispiroketal (BCD rings) and a 7-membered cyclic imine (A ring) spiro-linked to a cyclohexene (E) ring (Figure 1). While stereoselective syntheses of the [6,7]-spiroimine portion, an active pharmacophore in these molecules,[3b] have been achieved by several groups,[13] a stereocontrolled construction of the [6,5,5]-dispiroketal ring system presents a major challenge because the dispiroketal benefits from only a single anomeric effect. With regard to the equilibration of dispiroketal isomers, Ishihara and Hatakeyama and co-workers demonstrated that exposure of either the desired *cisoid* isomer or its C15-epimer (*transoid* isomer) to CSA in MeCN effected isomerization at C15, providing a mixture of isomers favoring the C15-epimer in a ratio of 2:1.[12c] Brimble and Meilert reported that a mixture of four unsaturated dispiroketal isomers underwent epimerization under epoxidation conditions, leading to the exclusive formation of the corresponding *transoid* C15-epimer.[12e,f] With these results in mind, Zakarian and co-workers suggested the difficulty of desired stereocontrol in the acyclic system.[12g]



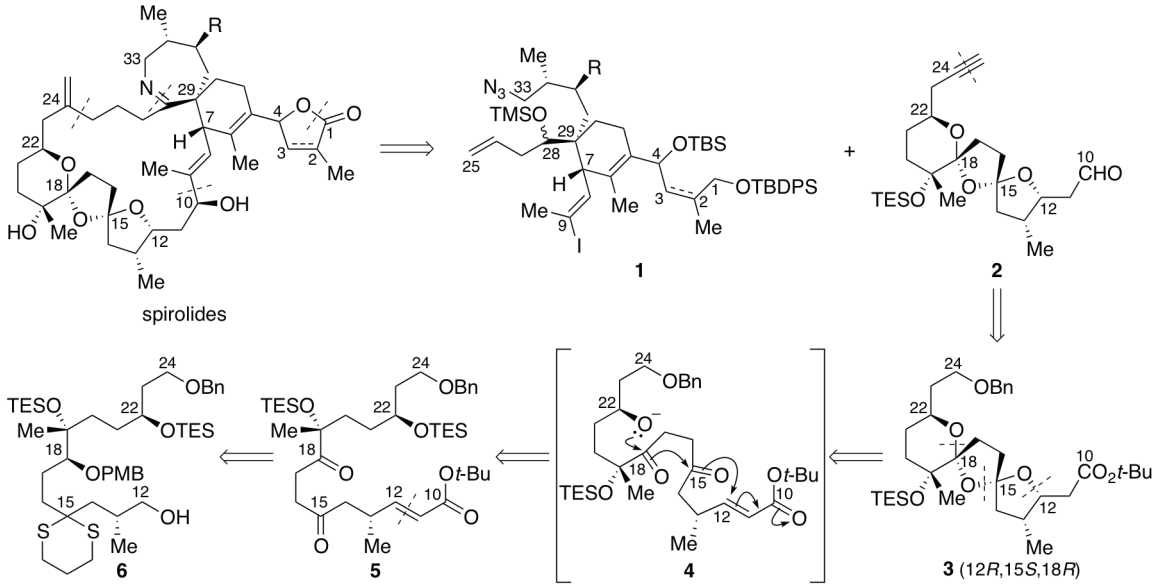
	R	C2–C3
spirolide A	H	Δ
spirolide B	H	–
spirolide C	Me	Δ
spirolide D	Me	–

Figure 1. Structures of spirolides A–D

During the course of our studies directed toward the total synthesis of pinnatoxin A, we have developed a tandem double hemiketal formation/hetero-Michael addition sequence for the construction of its [6,5,6]-dispiroketal ring system.[14] This method has the advantage of not only generating three stereocenters in a single operation but also allowing access to thermodynamically unstable isomers by appropriate choice of reaction conditions. We wondered whether the desired *cisoid* isomer could be obtained by the sequence under kinetic conditions. In this article, we present our studies aimed at gaining access to the desired *cisoid* isomer by the tandem reaction sequence.

RESULTS AND DISCUSSION

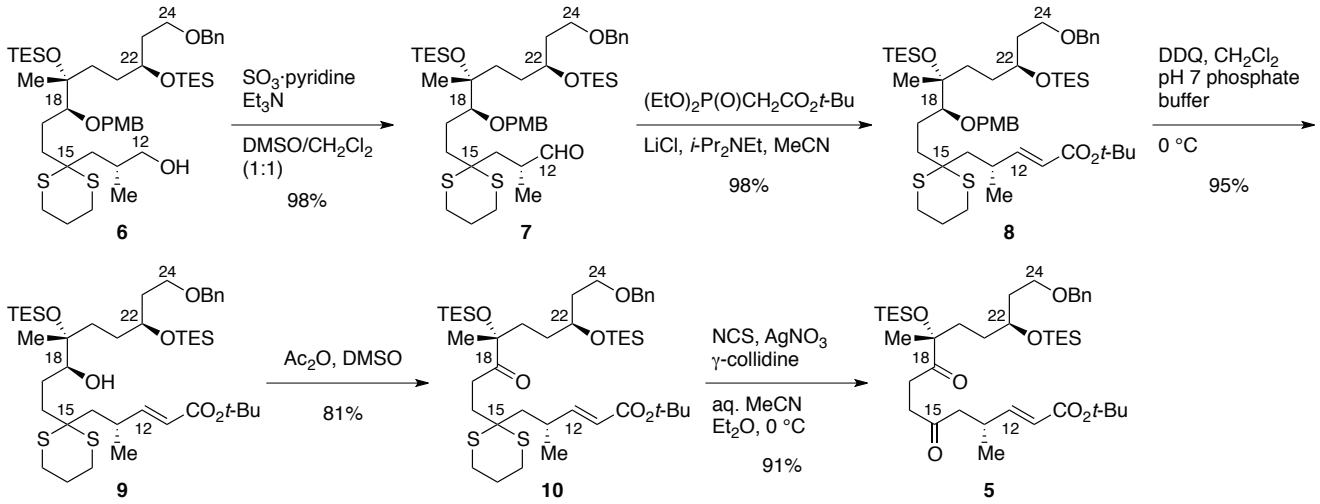
Our retrosynthetic analysis of spirolides is depicted in Scheme 1. We envisioned late-stage formation of the 7-membered cyclic imine by self-catalyzed dehydration and construction of the 23-membered carbocycle by Ru-catalyzed cycloisomerization, and the disconnection at C9–C10 divided the molecule into two fragments (**1** and **2**) of comparable complexity.[9] The [6,5,5]-dispiroketal in **2** would be constructed by removal of the C22 TES protecting group of open chain precursor **5** followed by the double hemiketal



Scheme 1. Retrosynthetic analysis

formation/hetero-Michael addition sequence. Enoate **5** could be elaborated from alcohol **6**, which would be readily prepared in analogy with our published procedure.[14]

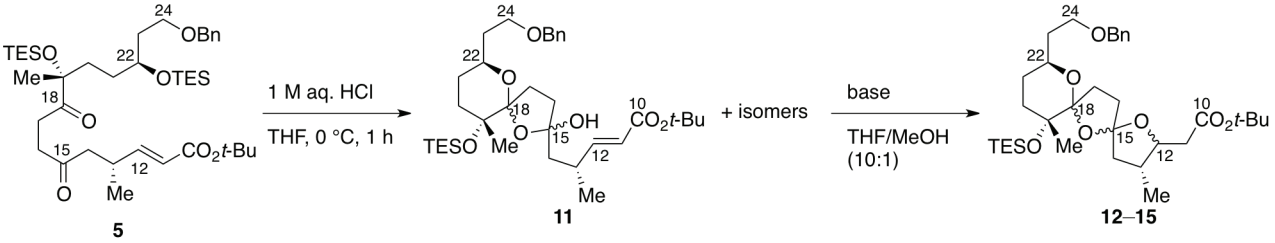
Synthesis of open chain precursor **5** began with Parikh–Doering oxidation[15] of alcohol **6**,[16] affording aldehyde **7** in 98% yield (Scheme 2). The α,β-unsaturated ester moiety was then stereoselectively installed by a Horner–Wadsworth–Emmons reaction with *tert*-butyl diethylphosphonoacetate under Masamune conditions[17] to give enoate **8** in 98% yield. Deprotection of the PMB ether with DDQ[18] followed by Albright–Goldman oxidation[19] provided ketone **10** in 77% yield for the two steps. Oxidative removal of the dithiane protective group under Corey conditions[20] furnished cyclization precursor **5** in 91% yield.



Scheme 2. Synthesis of cyclization precursor **5**

With the cyclization precursor **5** in hand, we then proceeded to investigate the key double hemiketal formation/hetero-Michael addition sequence. Exposure of bis-TES ether **5** to 1 M aqueous HCl effected

Table 1. Double hemiketal formation/hetero-Michael reaction



Entry	Base	Temp, °C	Time	Yield, %	**12**:**13**:**14**:**15**[a]	*cisoid*:*transoid*
1	NaOMe	–50	24 h	90	31:29:23:17	83:17
2	KOMe	–50	24 h	97	52:20:13:15	85:15
3	LiOMe	–30	24 h	98	4:48: 6:42	58:42
4	Triton B	–30	12 h	96	25:37:17:21	79:21
5	NaOMe	0	2 min	92	32:32:21:15	85:15
6	NaOMe	0	4 h	91	11:59: 3:27	73:27
7	NaOMe	0	48 h	87	3:65: 0:32	68:32
8	LiOMe	0	1 h	98	8:48: 7:37	63:37

[a] Determined by HPLC analysis (column, Zorbax® Sil, 4.6 × 250 mm; eluent, 6% AcOEt in *n*-hexane; flow rate, 1.0 mL/min).

selective deprotection of the secondary TES group to provide an equilibrium mixture of products **11**, the reaction of which with NaOMe in THF/MeOH (10:1) proceeded at –50 °C to give a mixture of four dispiroketal diastereomers out of the eight possible stereoisomers in 90% combined yield and a 31:29:23:17 ratio (Table 1, entry 1). The isomers were readily separated by column chromatography, and stereochemistries were confirmed by NOESY experiments (Figure 2). The NOE between C17-H_2 and C19-CH_3 allowed for the establishment of an 18*R* configuration of isomers **13** and **15**, whereas C17-*H* exhibited significant NOE interactions with C20-*H* and C22-*H* in isomers **12** and **14** with an 18*S* configuration. The *transoid* arrangement in isomer **15** was evident from the interaction of Si(CH_2CH$_3$)$_3$ with C11-*H*, and a NOE between Si(CH_2CH$_3$)$_3$ and C14-*H* established the *cisoid* arrangement in isomers **13** and **14**. Despite

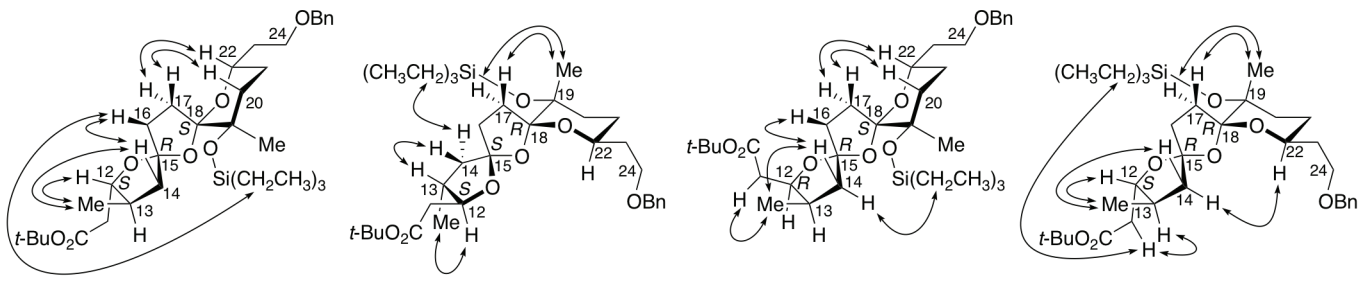
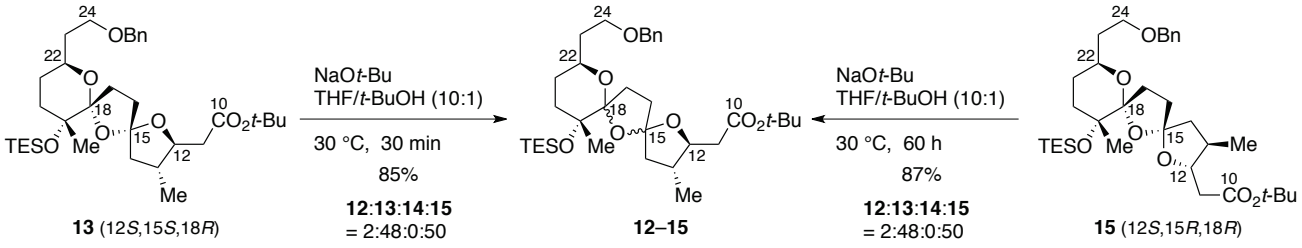


Figure 2. Relevant NOESY data for dispiroketal products **12**–**15**

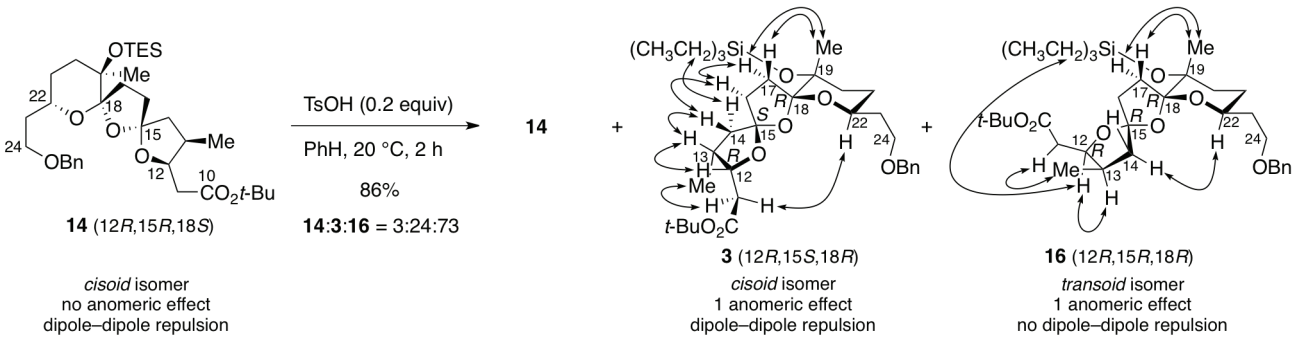
the absence of the diagnostic NOE between Si(CH_2CH_3)$_3$ and C14-*H*, interactions of C16-*H* with C14-*H* and Si(CH_2CH_3)$_3$ allowed us to assign dispiroketal **12** as a *cisoid* isomer. The 12*S* configuration of isomers **12**, **13** and **15** was confirmed by a NOE interaction of C13-CH_3 with C12-*H*, and a NOE between C13-CH_3 and C11-*H* supported the stereochemical assignment of the 12*R* configuration of isomer **14**. In general, anomeric effects, steric influences, intramolecular hydrogen bonding or other chelation effects, and dipole–dipole interaction have been suggested to influence the thermodynamic stability of dispiroketals.[21] An inspection of the structure of four dispiroketals **12**–**15** reveals that isomers **13** and **15** appear to be more stable from a stabilizing anomeric effect compared to isomers **12** and **14**.[22] Isomer **15** is the only compound that is relieved of the dipole–dipole destabilization between C15–O12 and C18–O22 bonds.

Although *cisoid* isomers were preferentially formed (*cisoid*:*transoid* = 83:17) by the action of NaOMe at a low temperature (Table 1, entry 1), the fact that desired isomer **3** could not be obtained prompted us to investigate the reaction conditions. Unfortunately, however, dispiroketal products other than isomers **12**–**15** could not be obtained regardless of the reaction conditions surveyed (Table 1, entries 2–8). The 18*S* isomer **12** was formed with enhanced diastereoselectivity (dr = 52:20:13:15) by the use of KOMe instead of NaOMe (entry 2). The temperature limit for the LiOMe-mediated reaction was –30 °C, at which thermodynamically favored 18*R* isomers **13** and **15** were obtained as major products in a ratio of *ca*. 1:1 (entry 3). Similar diastereoselectivity was observed by changing the base from NaOMe to Triton B (entry 4).[23] Raising the temperature to 0 °C in the reaction with NaOMe caused isomerization, 12*S* isomer **13** being formed as a major product (entries 5–7), whereas isomerization did not occur at 0 °C with the aid of LiOMe (entry 8). Since independent submission of thermodynamically favored 18*R* isomers **13** and **15** to NaO*t*-Bu at a higher temperature (30 °C) provided identical ratios of dispiroketal isomers **12**–**15** at equilibrium (Scheme 3),[24,25] the diastereoselection observed with NaOMe would be the result of both kinetic and thermodynamic control.



Scheme 3. Equilibration under basic conditions

With 12*R* isomer **14** in hand, we therefore attempted an isomerization under acidic conditions so as to confirm the stereochemical assignment at C12. Exposure of isomer **14** to TsOH in benzene at 20 °C for 2 h resulted in the formation of only two new dispiroketal isomers, the stereochemistries of which were



Scheme 4. Equilibration under acidic conditions

assigned by the key NOE interactions depicted in Scheme 4. This experiment unambiguously reveals that the C12 configurations of isomers **14**, **3** and **16** are the same but opposite to those of isomers **12**, **13** and **15**[26] and that the thermodynamic preference for formation of 15*R* isomer **16** is in good agreement with the Ishihara/Hatakeyama observations.[12c]

In conclusion, we have demonstrated that *cisoid* isomers, destabilized by dipole–dipole repulsion between C15–O12 and C18–O22 bonds, were preferentially formed when the double hemiketal formation/hetero-Michael addition sequence was applied for the construction of a [6,5,5]-dispiroketal ring system. While overriding the facial bias conferred on the olefin moiety by the methyl group at C13 proved difficult in the present system, the preference of this sequence for *cisoid* isomers would find application in organic synthesis.

EXPERIMENTAL

[2*R*,3(3*S*,4*R*,7*S*)]-3-[2-[9-Benzyloxy-3-(4-methoxybenzyloxy)-4-methyl-4,7-bis(triethylsilyloxy)nonyl]-1,3-dithian-2-yl]-2-methylpropanal (7). Sulfur trioxide pyridine complex (271 mg, 1.70 mmol) was added over 30 min to an ice-cooled (0 °C) mixture of alcohol **6** (473 mg, 0.556 mmol) and Et_3N (0.39 mL, 2.83 mmol) in DMSO/CH_2Cl_2 (1:1, 7.6 mL). After 30 min of stirring at room temperature, the reaction was quenched with H_2O (5 mL), and the resulting mixture was partitioned between AcOEt (30 mL) and saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with AcOEt (30 mL), and the combined organic extracts were washed with brine (2 × 10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (507 mg, pale yellow oil), which was purified by column chromatography (silica gel 10 g, 10:1 *n*-hexane/AcOEt) to give aldehyde **7** (460 mg, 98%) as a colorless oil. R_f 0.55 (3:1 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ –1.49 (*c* 1.03, $CHCl_3$); IR (neat) 2952, 2874, 1724, 1514, 1456, 1248, 1092, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (q, J = 8.0 Hz, 6H, Si(CH_2CH_3)$_3$), 0.62 (q, J = 8.0 Hz, 6H, Si(CH_2CH_3)$_3$), 0.946 (t, J = 8.0 Hz, 9H, Si(CH_2CH_3)$_3$), 0.952 (t, J = 8.0 Hz, 9H, Si(CH_2CH_3)$_3$), 1.09 (d, J = 7.3 Hz, 3H, C13-CH_3), 1.20 (s, 3H, C19-CH_3), 1.42–2.10 (m, 13H), 2.57–2.88 (m, 6H, C13-*H*, one of CH_2, 2 × SCH_2), 3.17 (dd, J = 1.9, 8.8 Hz, 1H, C18-*H*), 3.54 (m, 2H, C24-H_2),

3.78 (s, 3H, OCH_3), 3.79 (m, 1H, C22-*H*), 4.45 (d, *J* = 11.8 Hz, 1H, one of OCH_2Ph), 4.46 (d, *J* = 10.9 Hz, 1H, one of OCH_2PMP), 4.49 (d, *J* = 11.8 Hz, 1H, one of OCH_2Ph), 4.62 (d, *J* = 10.9 Hz, 1H, one of OCH_2PMP), 6.86 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.24–7.35 (m, 7H, Ar*H*), 9.69 (d, *J* = 1.9 Hz, 1H, C12-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (CH_2), 6.96 (CH_2), 6.97 (CH_3), 7.3 (CH_3), 16.2 (CH_3), 24.1 (CH_3), 24.8 (CH_2), 25.1 (CH_2), 25.9 (CH_2), 26.1 (CH_2), 31.7 (CH_2), 35.8 (CH_2), 36.9 (CH_2), 37.2 (CH_2), 39.9 (CH_2), 42.7 (CH), 53.0 (C), 55.2 (CH_3), 67.1 (CH_2), 70.0 (CH), 72.9 (CH_2), 74.0 (CH_2), 78.1 (CH), 85.1 (C), 113.6 (CH), 127.4 (CH), 127.6 (CH), 128.3 (CH), 129.1 (CH), 131.3 (C), 138.5 (C), 159.0 (C), 203.4 (C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{45}H_{76}O_6S_2Si_2Na$ 855.4520; found 855.4518.

***tert*-Butyl [2*E*,4*R*,5(3*S*,4*R*,7*S*)]-5-[2-[9-Benzyloxy-3-(4-methoxybenzyloxy)-4-methyl-4,7-bis(triethylsilyloxy)nonyl]-1,3-dithian-2-yl]-4-methyl-2-pentenoate (8).** To an ice-cooled (0 °C) mixture of aldehyde **7** (649 mg, 0.779 mmol) and *tert*-butyl diethylphosphonoacetate (394 mg, 1.56 mmol) in MeCN (8 mL) was added *N*,*N*-diisopropylethylamine (0.27 mL, 1.56 mmol), followed by addition of LiCl (132 mg, 3.12 mmol). The reaction mixture was stirred at room temperature for 8 h, after which an additional *tert*-butyl diethylphosphonoacetate (197 mg, 0.781 mmol), *N*,*N*-diisopropylethylamine (0.14 mL, 0.781 mmol) and LiCl (66 mg, 1.56 mmol) were added at 0 °C. After 17 h of stirring at room temperature, the reaction mixture was diluted with Et_2O (4 mL), and saturated aqueous $NaHCO_3$ (2 mL) and H_2O (1 mL) were added. The resulting mixture was extracted with AcOEt (3 × 20 mL), and the combined organic extracts were washed with brine (6 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.47 g, pale yellow oil), which was purified by column chromatography (silica gel 40 g, 15:1 *n*-hexane/AcOEt) to give enoate **8** (710 mg, 98%) as a colorless oil. R_f 0.56 (4:1 *n*-hexane/AcOEt); $[\alpha]_D^{27}$ –17.7 (*c* 1.02, $CHCl_3$); IR (neat) 2953, 2874, 1713, 1649, 1612, 1514, 1456, 1416, 1366, 1302, 1248, 1157, 1142, 1094, 1040, 1009 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.9 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.61 (q, *J* = 7.9 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.94 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$CH_3)$_3$), 0.95 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$CH_3)$_3$), 1.10 (d, *J* = 6.8 Hz, 3H, C13-CH_3), 1.19 (s, 3H, C19-CH_3), 1.43–1.89 (m, 12H, 6 × CH_2), 1.47 (s, 9H, CO$_2$C(CH_3)$_3$), 2.03 (dd, *J* = 6.4, 14.9 Hz, 1H, one of C14-H_2), 2.16 (m, 1H, one of CH_2), 2.61–2.77 (m, 5H, C13-*H*, 2 × SCH_2), 3.18 (dd, *J* = 2.5, 8.9 Hz, 1H, C18-*H*), 3.54 (m, 2H, C24-H_2), 3.78 (s, 3H, OCH_3), 3.79 (m, 1H, C22-*H*), 4.45 (d, *J* = 11.9 Hz, 1H, one of OCH_2Ph), 4.46 (d, *J* = 11.0 Hz, 1H, one of OCH_2PMP), 4.48 (d, *J* = 11.9 Hz, 1H, one of OCH_2Ph), 4.62 (d, *J* = 11.0 Hz, 1H, one of OCH_2PMP), 5.69 (dd, *J* = 1.0, 15.7 Hz, 1H, C11-*H*), 6.85 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.87 (dd, *J* = 8.0, 15.7 Hz, 1H, C12-*H*), 7.23–7.33 (m, 7H, Ar*H*); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 5.0 (CH_2), 6.89 (CH_3), 6.92 (CH_2), 7.2 (CH_3), 21.8 (CH_3), 24.1 (CH_3), 25.0 (CH_2), 25.5 (CH_2), 25.9 (CH_2), 26.0 (CH_2), 28.0 (CH_3), 31.6 (CH_2), 32.6 (CH), 35.7 (CH_2), 36.0 (CH_2), 37.2 (CH_2), 44.5 (CH_2), 53.7 (C), 55.1 (CH_3), 67.0 (CH_2), 70.0 (CH), 72.8 (CH_2), 73.9 (CH_2), 78.2 (C), 79.7 (C), 85.2 (CH), 113.5 (CH), 120.8 (CH), 127.3 (CH), 127.5 (CH), 128.2 (CH), 129.0 (CH), 131.3 (C), 138.4 (C), 153.6 (CH), 158.9 (C),

166.1 (C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{51}H_{86}O_7S_2Si_2Na$ 953.5251; found 953.5247; Anal. Calcd for $C_{51}H_{86}O_7S_2Si_2$: C, 65.76; H, 9.31. Found: C, 65.57; H, 9.18.

***tert*-Butyl [2*E*,4*R*,5(3*S*,4*R*,7*S*)]-5-[2-[9-Benzyloxy-3-hydroxy-4-methyl-4,7-bis(triethylsilyloxy)nonyl]-1,3-dithian-2-yl]-4-methyl-2-pentenoate (9).** 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (207 mg, 0.914 mmol) was added to an ice-cooled (0 °C) mixture of PMB ether **8** (710 mg, 0.762 mmol) in CH_2Cl_2/pH 7 phosphate buffer (5:1, 7.8 mL). After 50 min of stirring, the reaction was quenched with a mixture of saturated aqueous $NaHCO_3$ (2 mL) and 1 M aqueous $Na_2S_2O_3$ (2 mL), and the resulting mixture was filtered through a Celite pad. The filtrate was extracted with AcOEt (2 × 20 mL), and the combined organic extracts were successively washed with saturated aqueous $NaHCO_3$ (6 mL) and brine (8 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (768 mg, brown oil), which was purified by column chromatography (silica gel 20 g, toluene → 8:1 *n*-hexane/AcOEt) to give alcohol **9** (588 mg, 95%) as a colorless oil. R_f 0.47 (4:1 *n*-hexane/AcOEt); $[\alpha]_D^{27}$ –19.2 (*c* 1.00, $CHCl_3$); IR (neat) 3545, 2955, 2876, 1713, 1649, 1456, 1416, 1368, 1288, 1238, 1159, 1092, 1007 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.9 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.61 (q, *J* = 7.9 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.95 (t, *J* = 7.9 Hz, 18H, 2 × Si(CH$_2$C*H*$_3$)$_3$), 1.14 (d, *J* = 6.8 Hz, 3H, C13-C*H*$_3$), 1.20 (s, 3H, C19-C*H*$_3$), 1.39–1.48 (m, 2H, C*H*$_2$), 1.47 (s, 9H, CO$_2$C(C*H*$_3$)$_3$), 1.54–1.64 (m, 4H, 2 × C*H*$_2$), 1.74–1.94 (m, 6H, 3 × C*H*$_2$), 2.05 (dd, 1H, *J* = 8.1, 15.6 Hz, one of C14-*H*$_2$), 2.37 (ddd, 1H, *J* = 4.3, 12.1, 14.5 Hz, one of C*H*$_2$), 2.54 (d, 1H, *J* = 3.6 Hz, C18-O*H*), 2.69–2.88 (m, 5H, C13-*H*, 2 × SC*H*$_2$), 3.28 (ddd, 1H, *J* = 1.5, 3.6, 10.4 Hz, C18-*H*), 3.54 (m, 2H, C24-*H*$_2$), 3.82 (m, 1H, C22-*H*), 4.47 (d, *J* = 11.9 Hz, 1H, one of OC*H*$_2$Ph), 4.51 (d, *J* = 11.9 Hz, 1H, one of OC*H*$_2$Ph), 5.74 (dd, *J* = 0.9, 15.6 Hz, 1H, C11-*H*), 6.87 (dd, *J* = 8.1, 15.6 Hz, 1H, C12-*H*), 7.25–7.36 (m, 5H, Ar*H*); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 5.0 (CH_2), 6.7 (CH_2), 6.9 (CH_3), 7.1 (CH_3), 21.8 (CH_3), 24.2 (CH_3), 25.1 (CH_2), 25.9 (2 × CH_2), 26.0 (CH_2), 28.1 (CH_3), 31.4 (CH_2), 32.6 (CH), 32.7 (CH_2), 35.7 (CH_2), 37.1 (CH_2), 44.4 (CH_2), 53.5 (C), 67.0 (CH_2), 69.8 (CH), 72.9 (CH_2), 78.16 (CH), 78.23 (C), 79.8 (C), 120.9 (CH), 127.4 (CH), 127.6 (CH), 128.2 (CH), 138.4 (C), 153.5 (CH), 166.1 (C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{43}H_{78}O_6S_2Si_2Na$ 833.4676; found 833.4675; Anal. Calcd for $C_{43}H_{78}O_6S_2Si_2$: C, 63.65; H, 9.69. Found: C, 63.42; H, 9.50.

***tert*-Butyl [2*E*,4*R*,5(4*R*,7*S*)]-5-[2-[9-Benzyloxy-4-methyl-3-oxo-4,7-bis(triethylsilyloxy)nonyl]-1,3-dithian-2-yl]-4-methyl-2-pentenoate (10).** Acetic anhydride (0.31 mL, 3.25 mmol) was added to a stirred solution of alcohol **9** (659 mg, 0.812 mmol) in DMSO (10 mL). The reaction mixture was stirred for 28 h, after which an additional acetic anhydride (0.46 mL, 4.88 mmol) was added. After another 28 h of stirring, the reaction mixture was diluted with Et_2O (10 mL) and poured into an ice-cooled (0 °C) saturated aqueous $NaHCO_3$ (20 mL). After 1 h of stirring at room temperature, the resulting mixture was extracted with *n*-hexane/AcOEt (1:2, 2 × 125 mL). The combined organic extracts were successively washed with saturated aqueous $NaHCO_3$ (40 mL), H_2O (40 mL), saturated aqueous NH_4Cl (40 mL) and brine (2 × 40 mL),

and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (926 mg, yellow oil), which was purified by column chromatography (silica gel 35 g, 15:1 *n*-hexane/AcOEt) to give ketone **10** (530 mg, 81%) as a colorless oil. R_f 0.56 (4:1 *n*-hexane/AcOEt); $[\alpha]_D^{18}$ –10.4 (*c* 1.01, benzene); IR (neat) 2955, 2876, 1715, 1653, 1649, 1456, 1366, 1290, 1238, 1159, 1094, 1009, 978 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.58 (q, J = 8.0 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.64 (q, J = 8.0 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.94 (t, J = 8.0 Hz, 9H, Si(CH$_2$CH_3)$_3$), 0.99 (t, J = 8.0 Hz, 9H, Si(CH$_2$CH_3)$_3$), 1.13 (d, J = 6.8 Hz, 3H, C13-CH_3), 1.26 (m, 1H, one of C21-H_2), 1.32 (s, 3H, C19-CH_3), 1.47 (s, 9H, CO$_2$C(CH_3)$_3$), 1.50–1.59 (m, 2H, CH_2), 1.65–1.79 (m, 3H, 1.5 × CH_2), 1.77 (dd, J = 4.8, 15.0 Hz, 1H, one of C14-H_2), 1.83–1.96 (m, 2H, CH_2), 1.99 (dd, J = 6.0, 15.0 Hz, 1H, one of C14-H_2), 2.19 (m, 2H, CH_2), 2.65–2.77 (m, 4H, C13-H, one of C17-H_2, SCH_2), 2.82–2.92 (m, 3H, one of C17-H_2, SCH_2), 3.51 (m, 2H, C24-H_2), 3.80 (m, 1H, C22-H), 4.45 (d, J = 11.9 Hz, 1H, one of OCH_2Ph), 4.49 (d, J = 11.9 Hz, 1H, one of OCH_2Ph), 5.72 (dd, J = 1.1, 15.6 Hz, 1H, C11-H), 6.86 (dd, J = 7.9, 15.6 Hz, 1H, C12-H), 7.28–7.35 (m, 5H, ArH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 5.0 (CH_2), 6.8 (CH_2), 7.0 (CH_3), 7.2 (CH_3), 21.9 (CH_3), 24.9 (CH_2), 25.8 (CH_3), 26.12 (CH_2), 26.13 (CH_2), 28.1 (CH_3), 31.7 (CH_2), 31.8 (CH_2), 32.6 (CH), 33.2 (CH_2), 37.02 (CH_2), 37.03 (CH_2), 45.5 (CH_2), 53.3 (C), 67.0 (CH_2), 69.2 (CH), 73.0 (CH_2), 80.0 (C), 82.5 (C), 121.1 (CH), 127.5 (CH), 127.7 (CH), 128.3 (CH), 138.5 (C), 153.3 (CH), 166.2 (C), 214.8 (C); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{43}H_{76}O_6S_2Si_2Na$ 831.4520; found 831.4518; Anal. Calcd for $C_{43}H_{76}O_6S_2Si_2$: C, 63.81; H, 9.47. Found: C, 63.51; H, 9.48.

***tert*-Butyl (2*E*,4*R*,10*R*,13*S*)-15-Benzyloxy-4,10-dimethyl-6,9-dioxo-10,13-bis(triethylsilyloxy)-2-pentadecenoate (5).** A solution of dithioacetal **10** (368 mg, 0.455 mmol) in Et_2O (12 mL) was added to an ice-cooled (0 °C) mixture of $AgNO_3$ (487 mg, 2.87 mmol), *N*-chlorosuccinimide (364 mg, 2.73 mmol) and γ-collidine (0.72 mL, 5.46 mmol) in 80% aqueous MeCN (28.7 mL). After 10 min of stirring at 0 °C, the reaction was quenched with a mixture of saturated aqueous $NaHCO_3$ (15 mL) and 1 M aqueous $Na_2S_2O_3$ (15 mL), and the resulting mixture was extracted with AcOEt (20 mL and 40 mL). The combined organic extracts were washed with brine (30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (936 mg, yellow oil), which was purified by column chromatography (silica gel 25 g, 15:1 *n*-hexane/AcOEt) to give diketone **5** (299 mg, 91%) as a colorless oil. R_f 0.58 (4:1 *n*-hexane/AcOEt); $[\alpha]_D^{30}$ –12.5 (*c* 2.63, benzene); IR (neat) 2957, 2876, 1715, 1649, 1458, 1368, 1155, 1094, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.57 (q, J = 8.0 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.64 (q, J = 8.0 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.94 (t, J = 8.0 Hz, 9H, Si(CH$_2$CH_3)$_3$), 0.98 (t, J = 8.0 Hz, 9H, Si(CH$_2$CH_3)$_3$), 1.05 (d, J = 6.8 Hz, 3H, C13-CH_3), 1.25 (m, 1H, one of C21-H_2), 1.32 (s, 3H, C19-CH_3), 1.44–1.60 (m, 2H, one of C20-H_2, one of C21-H_2), 1.47 (s, 9H, CO$_2$C(CH_3)$_3$), 1.66–1.78 (m, 3H, one of C20-H_2, C23-H_2), 2.46 (dd, 1H, J = 7.9, 16.8 Hz, one of C14-H_2), 2.53–2.61 (m, 2H, CH_2CO), 2.61 (dd, J = 5.8, 16.8 Hz, 1H, one of C14-H_2), 2.82–2.99 (m, 3H, C13-H, CH_2CO), 3.48–3.57 (m, 2H, C24-H_2),

3.79 (m, 1H, C22-*H*), 4.46 (d, *J* = 11.9 Hz, 1H, one of OC*H*$_2$Ph), 4.49 (d, *J* = 11.9 Hz, 1H, one of OC*H*$_2$Ph), 5.71 (dd, *J* = 1.1, 15.7 Hz, 1H, C11-*H*), 6.78 (dd, *J* = 6.9, 15.7 Hz, 1H, C12-*H*), 7.26–7.34 (m, 5H, Ar*H*); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 5.0 (CH_2), 6.7 (CH_2), 6.9 (CH_3), 7.1 (CH_3), 18.9 (CH_3), 25.9 (CH_3), 28.1 (CH_3), 31.3 (CH), 31.5 (CH_2), 31.9 (CH_2), 36.3 (CH_2), 36.99 (CH_2), 37.00 (CH_2), 48.4 (CH_2), 67.0 (CH_2), 69.2 (CH), 73.0 (CH_2), 80.1 (C), 82.4 (C), 121.6 (CH), 127.4 (CH), 127.6 (CH), 128.3 (CH), 138.6 (C), 151.3 (CH), 166.1 (C), 207.2 (C), 214.6 (C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{40}H_{70}O_7Si_2Na$ 741.4558; found 741.4556; Anal. Calcd for $C_{40}H_{70}O_7Si_2$: C, 66.81; H, 9.81. Found: C, 66.57; H, 9.56.

Typical Procedure for the Double Hemiketal Formation/Hetero-Michael Addition Sequence. To an ice-cooled (0 °C) solution of TES ether **5** (20.8 mg, 28.9 μmol) in THF (0.3 mL) was added 1 M aqueous HCl (0.03 mL). After 1 h of stirring, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL), and the resulting mixture was partitioned between AcOEt (15 mL) and H_2O (5 mL). The aqueous layer was extracted with AcOEt (15 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (20.2 mg, colorless oil), which was used without further purification.

NaOMe in MeOH (1 M, 0.03 mL, 0.03 mmol) was added to a cooled (–50 °C) solution of the equilibrium mixture in THF (0.3 mL). After 24 h of stirring, the reaction was quenched with saturated aqueous NH_4Cl (5 mL), the resulting mixture was partitioned between AcOEt (15 mL) and H_2O (5 mL). The aqueous layer was extracted with AcOEt (15 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (18.3 mg, colorless oil), which was purified by column chromatography (silica gel 6 g, 6:1 *n*-hexane/AcOEt) to give a mixture of dispiroketals **12**–**15** (15.8 mg, 90%) as a colorless oil. The ratio of isomers (**12**/**13**/**14**/**15** = 31:29:23:17) was determined by HPLC analysis (column, Zorbax® Sil, 4.6 × 250 mm; eluent, 6% AcOEt in *n*-hexane; flow rate, 1.0 mL/min; detection, 254 nm, t_R (**12**) = 36.2 min, t_R (**13**) = 18.2 min, t_R (**14**) = 74.8 min, t_R (**15**) = 15.2 min). The isomers **12**–**15** could be separated by flash column chromatography (50:1 → 30:1 toluene/AcOEt).

***tert*-Butyl (2*S*,3*R*,5*R*,7*S*,9*S*,12*R*)-[9-(2-Benzyloxyethyl)-3,12-dimethyl-12-triethylsilyloxy-1,6,8-trioxadispiro[4.1.5.2]tetradecan-2-yl]acetate (12).** R_f 0.41 (6:1 *n*-hexane/AcOEt); $[\alpha]_D^{20}$ +54.0 (*c* 0.991, benzene); IR (neat) 2951, 2874, 1728, 1458, 1368, 1175, 1140, 1101, 1061, 1007, 977 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.56 (dq, *J* = 15.0, 8.0 Hz, 3H, Si(CH*H*CH$_3$)$_3$), 0.59 (dq, *J* = 15.0, 8.0 Hz, 3H, Si(CH*H*CH$_3$)$_3$), 0.93 (d, *J* = 6.6 Hz, 3H, C13-C*H*$_3$), 1.01 (t, *J* = 8.0 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 1.22 (m, 2H, C21-*H*$_2$), 1.38 (s, 9H, $CO_2C(CH_3)_3$), 1.43 (s, 3H, C19-C*H*$_3$), 1.48 (dd, *J* = 11.0, 11.8 Hz, 1H, one of C14-*H*$_2$), 1.55 (m, 2H, C20-*H*$_2$), 1.76 (m, 2H, C23-*H*$_2$), 1.97 (m, 1H, one of C16-*H*$_2$), 2.09–2.16 (m, 2H, one of C16-*H*$_2$, one of C17-*H*$_2$), 2.23–2.30 (m, 2H, one of C14-*H*$_2$, one of C17-*H*$_2$), 2.36 (m, 1H, C13-*H*), 2.67

(dd, *J* = 6.2, 15.4 Hz, 1H, one of C11-H_2), 2.92 (dd, *J* = 6.7, 15.4 Hz, 1H, one of C11-H_2), 3.60 (dt, *J* = 8.8, 4.9 Hz, 1H, one of C24-H_2), 3.66 (m, 1H, C22-*H*), 3.78 (dt, *J* = 5.5, 8.8 Hz, 1H, one of C24-H_2), 4.22 (ddd, *J* = 6.2, 6.5, 6.7 Hz, 1H, C12-*H*), 4.49 (d, *J* = 11.9 Hz, 1H, one of OCH_2Ph), 4.54 (d, *J* = 11.9 Hz, 1H, one of OCH_2Ph), 7.12 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.23 (t, *J* = 7.4 Hz, 2H, Ar*H*), 7.43 (d, *J* = 7.4 Hz, 2H, Ar*H*); ^{13}C NMR (125.7 MHz, C_6D_6) δ 7.2 (CH_2), 7.5 (CH_3), 17.9 (CH_3), 21.8 (CH_3), 28.2 (CH_3), 30.08 (CH_2), 30.10 (CH_2), 36.1 (CH_2), 36.4 (CH_2), 38.0 (CH_2), 38.9 (CH), 43.3 (CH_2), 45.0 (CH_2), 67.4 (CH_2), 70.1 (CH), 73.4 (CH_2), 75.0 (C), 79.6 (C), 83.0 (CH), 111.8 (C), 115.5 (C), 127.5 (CH), 127.9 (CH), 128.5 (CH), 139.9 (C), 170.9 (C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{34}H_{56}O_7SiNa$ 627.3688; found 627.3669.

***tert*-Butyl (2*S*,3*R*,5*S*,7*R*,9*S*,12*R*)-[9-(2-Benzyloxyethyl)-3,12-dimethyl-12-triethylsilyloxy-1,6,8-trioxadispiro[4.1.5.2]tetradecan-2-yl]acetate (13).** R_f 0.51 (6:1 *n*-hexane/AcOEt); $[\alpha]_D^{21}$ –10.1 (*c* 0.662, benzene); IR (neat) 2953, 2876, 1732, 1454, 1368, 1153, 1101, 1016, 974 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.56 (q, *J* = 7.9 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.94 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$CH_3)$_3$), 1.12 (d, *J* = 6.7 Hz, 3H, C13-CH_3), 1.28 (s, 3H, C19-CH_3), 1.442 (s, 9H, $CO_2C(CH_3)_3$), 1.443 (m, 1H, one of C21-H_2), 1.54–1.59 (m, 2H, one of C20-H_2, one of C21-H_2), 1.67–1.81 (m, 3H, one of C17-H_2, C23-H_2), 1.85 (dd, *J* = 5.7, 12.7 Hz, 1H, one of C14-H_2), 1.91 (m, 1H, one of C16-H_2), 2.00 (m, 1H, C13-*H*), 2.08–2.21 (m, 4H, one of C14-H_2, one of C16-H_2, one of C17-H_2, one of C20-H_2), 2.34 (dd, *J* = 6.9, 14.7 Hz, 1H, one of C11-H_2), 2.46 (dd, *J* = 5.7, 14.7 Hz, 1H, one of C11-H_2), 3.55 (q, *J* = 8.3 Hz, 1H, one of C24-H_2), 3.57 (dt, *J* = 5.8, 8.3 Hz, 1H, one of C24-H_2), 3.99 (ddd, *J* = 5.7, 6.3, 6.9 Hz, 1H, C12-*H*), 4.02 (m, 1H, C22-*H*), 4.48 (d, *J* = 11.9 Hz, 1H, one of OCH_2Ph), 4.53 (d, *J* = 11.9 Hz, 1H, one of OCH_2Ph), 7.26 (m, 1H, Ar*H*), 7.31–7.35 (m, 4H, Ar*H*); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 6.8 (CH_2), 7.1 (CH_3), 18.2 (CH_3), 24.4 (CH_3), 28.1 (CH_3), 30.4 (CH_2), 31.0 (CH_2), 34.6 (CH_2), 35.5 (CH_2), 35.9 (CH_2), 38.1 (CH), 41.0 (CH_2), 44.6 (CH_2), 67.5 (CH), 67.9 (CH_2), 72.9 (CH_2), 73.0 (C), 80.4 (C), 81.8 (CH), 110.0 (C), 116.0 (C), 127.3 (CH), 127.6 (CH), 128.3 (CH), 138.9 (C), 170.5 (C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{34}H_{56}O_7SiNa$ 627.3688; found 627.3684.

***tert*-Butyl (2*R*,3*R*,5*R*,7*S*,9*S*,12*R*)-[9-(2-Benzyloxyethyl)-3,12-dimethyl-12-triethylsilyloxy-1,6,8-trioxadispiro[4.1.5.2]tetradecan-2-yl]acetate (14).** R_f 0.33 (6:1 *n*-hexane/AcOEt); $[\alpha]_D^{21}$ +72.8 (*c* 0.460, benzene); IR (neat) 2951, 2876, 1732, 1458, 1368, 1148, 1101, 1055, 1007, 897 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.58 (dq, *J* = 14.9, 7.9 Hz, 3H, Si(CH*H*CH$_3$)$_3$), 0.61 (dq, *J* = 14.9, 7.9 Hz, 3H, Si(CH*H*CH$_3$)$_3$), 0.74 (d, *J* = 7.0 Hz, 3H, C13-CH_3), 1.02 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$CH_3)$_3$), 1.25 (m, 2H, C21-H_2), 1.37 (s, 9H, $CO_2C(CH_3)_3$), 1.47 (s, 3H, C19-CH_3), 1.50 (dd, *J* = 7.0, 12.9 Hz, 1H, one of C14-H_2), 1.58 (m, 2H, C20-H_2), 1.73 (m, 1H, one of C23-H_2), 1.81 (m, 1H, one of C23-H_2), 2.01 (m, 1H, one of C16-H_2), 2.10–2.18 (m, 2H, one of C16-H_2, one of C17-H_2), 2.30 (m, 1H, one of C17-H_2), 2.31 (dd, *J* = 7.4, 15.2 Hz, 1H, one of C11-H_2), 2.37 (dd, *J* = 7.5, 12.9 Hz, 1H, one of C14-H_2), 2.53 (dd, *J* = 7.1,

15.2 Hz, 1H, one of C11-H_2), 2.55 (dsext, J = 7.5, 7.0 Hz, 1H, C13-*H*), 3.58 (dt, J = 8.9, 5.3 Hz, 1H, one of C24-H_2), 3.66 (m, 1H, C22-*H*), 3.75 (dt, J = 5.2, 8.9 Hz, 1H, one of C24-H_2), 4.44 (d, J = 11.9 Hz, 1H, one of OCH_2Ph), 4.50 (d, J = 11.9 Hz, 1H, one of OCH_2Ph), 4.76 (ddd, J = 7.0, 7.1, 7.4 Hz, 1H, C12-*H*), 7.12 (t, J = 7.5 Hz, 1H, Ar*H*), 7.22 (t, J = 7.5 Hz, 2H, Ar*H*), 7.41 (d, J = 7.5 Hz, 2H, Ar*H*); ^{13}C NMR (125.7 MHz, C_6D_6) δ 7.3 (CH_2), 7.5 (CH_3), 14.7 (CH_3), 22.0 (CH_3), 28.1 (CH_3), 30.0 (CH_2), 30.3 (CH_2), 34.6 (CH), 36.4 (CH_2), 37.4 (CH_2), 37.8 (CH_2), 37.9 (CH_2), 44.2 (CH_2), 67.5 (CH_2), 70.3 (CH), 73.3 (CH_2), 75.1 (C), 77.5 (CH), 79.7 (C), 111.6 (C), 114.6 (C), 127.5 (CH), 128.0 (CH), 128.5 (CH), 139.9 (C), 170.3 (C); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{34}H_{56}O_7SiNa$ 627.3688; found 627.3667.

***tert*-Butyl (2*S*,3*R*,5*R*,7*R*,9*S*,12*R*)-[9-(2-Benzyloxyethyl)-3,12-dimethyl-12-triethylsilyloxy-1,6,8-trioxadispiro[4.1.5.2]tetradecan-2-yl]acetate (15).** R_f 0.55 (6:1 *n*-hexane/AcOEt); $[\alpha]_D^{21}$ +49.6 (*c* 0.270, benzene); IR (neat) 2953, 2874, 1734, 1458, 1368, 1165, 1099, 1020, 964 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.73 (dq, J = 15.2, 8.0 Hz, 3H, Si(CH*H*CH_3)$_3$), 0.79 (dq, J = 15.2, 8.0 Hz, 3H, Si(CH*H*CH_3)$_3$), 0.80 (d, J = 6.6 Hz, 3H, C13-CH_3), 1.16 (t, J = 8.0 Hz, 9H, Si($CH_2C H_3$)$_3$), 1.29–1.36 (m, 2H, C21-H_2), 1.34 (s, 3H, C19-CH_3), 1.422 (m, 1H, one of C14-H_2), 1.423 (s, 9H, CO_2C(CH_3)$_3$), 1.50 (dt, J = 11.9, 3.4 Hz, 1H, one of C20-H_2), 1.63–1.75 (m, 3H, one of C17-H_2, C23-H_2), 2.03–2.17 (m, 3H, C13-*H*, C16-H_2), 2.18–2.26 (m, 2H, one of C14-H_2, one of C20-H_2), 2.44 (dt, J = 8.7, 11.7 Hz, 1H, one of C17-H_2), 2.56 (dd, J = 5.2, 15.7 Hz, 1H, one of C11-H_2), 2.81 (dd, J = 7.3, 15.7 Hz, 1H, one of C11-H_2), 3.41 (dt, J = 9.1, 4.9 Hz, 1H, one of C24-H_2), 3.57 (dt, J = 4.9, 9.1 Hz, 1H, one of C24-H_2), 4.03–4.11 (m, 2H, C12-*H*, C22-*H*), 4.31 (d, J = 12.4 Hz, 1H, one of OCH_2Ph), 4.33 (d, J = 12.4 Hz, 1H, one of OCH_2Ph), 7.09 (t, J = 7.4 Hz, 1H, Ar*H*), 7.18 (t, J = 7.4 Hz, 2H, Ar*H*), 7.31 (d, J = 7.4 Hz, 2H, Ar*H*); ^{13}C NMR (125.7 MHz, C_6D_6) δ 7.5 (CH_2), 7.7 (CH_3), 16.4 (CH_3), 25.2 (CH_3), 28.2 (CH_3), 30.6 (CH_2), 31.1 (CH_2), 34.7 (CH_2), 35.2 (CH_2), 36.5 (CH_2), 38.7 (CH), 42.2 (CH_2), 47.4 (CH_2), 66.0 (CH), 67.2 (CH_2), 72.8 (C), 73.0 (CH_2), 79.8 (C), 82.6 (CH), 110.3 (C), 115.4 (C), 127.62 (CH), 127.63 (CH), 128.6 (CH), 139.4 (C), 170.7 (C); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{34}H_{56}O_7SiNa$ 627.3688; found 627.3694.

Typical Procedure for the Equilibration under Basic Conditions. NaO*t*-Bu (2.1 mg, 22 μmol) was added to an ice-cooled (0 °C) solution of dispiroketal **13** (4.6 mg, 7.6 μmol) in THF/*t*-BuOH (10:1, 0.33 mL). After 30 min of stirring at 30 °C, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), and the resulting mixture was partitioned between AcOEt (10 mL) and H_2O (5 mL). The aqueous layer was extracted with AcOEt (10 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (6.9 mg, pale yellow oil), which was purified by flash column chromatography (silica gel 5 g, 9:1 *n*-hexane/AcOEt) to give a mixture of dispiroketals **12**–**15** (3.9 mg, 85%) as a colorless oil. The ratio of isomers (**12**/**13**/**14**/**15** = 2:48:0:50) was determined by HPLC analysis (column, Zorbax® Sil, 4.6 × 250 mm; eluent, 6% AcOEt in *n*-hexane; flow rate, 1.0 mL/min; detection, 254 nm).

Equilibration under Acidic Conditions. *p*-Toluenesulfonic acid (0.5 mg, 2.8 μmol) was added to a stirred solution of dispiroketal **14** (8.5 mg, 14 μmol) in benzene (0.47 mL). After 2 h of stirring, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), and the resulting mixture was partitioned between AcOEt (15 mL) and H_2O (2 mL). The aqueous layer was extracted with AcOEt (15 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (7.9 mg, colorless oil), which was purified by column chromatography (silica gel 6 g, 6:1 *n*-hexane/AcOEt) to give a mixture of dispiroketals **14**, **3** and **16** (7.3 mg, 86%) as a colorless oil. The ratio of isomers (**14**/**3**/**16** = 3:24:73) was determined by HPLC analysis (column, Zorbax® Sil, 4.6 × 250 mm; eluent, 9% AcOEt in *n*-hexane; flow rate, 1.0 mL/min; detection, 254 nm, t_R (**14**) = 25.7 min, t_R (**3**) = 12.5 min, t_R (**16**) = 7.8 min).

***tert*-Butyl (2*R*,3*R*,5*S*,7*R*,9*S*,12*R*)-[9-(2-Benzyloxyethyl)-3,12-dimethyl-12-triethylsilyloxy-1,6,8-trioxadispiro[4.1.5.2]tetradecan-2-yl]acetate (3).** R_f 0.48 (6:1 *n*-hexane/AcOEt); $[\alpha]_D^{21}$ –8.5 (*c* 0.094, benzene); IR (neat) 2953, 2876, 1730, 1458, 1368, 1152, 1099, 1040, 1015, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.61 (q, *J* = 8.0 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 1.04 (t, *J* = 8.0 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 1.07 (d, *J* = 7.1 Hz, 3H, C13-C*H*$_3$), 1.30 (s, 3H, C19-C*H*$_3$), 1.35–1.40 (m, 2H, C21-*H*$_2$), 1.38 (s, 9H, $CO_2C(CH_3)_3$), 1.46 (m, 1H, one of C20-*H*$_2$), 1.76–1.87 (m, 3H, one of C16-*H*$_2$, one of C17-*H*$_2$, one of C23-*H*$_2$), 1.91 (dd, *J* = 7.9, 13.0 Hz, 1H, one of C14-*H*$_2$), 1.98 (m, 1H, one of C23-*H*$_2$), 1.99 (dd, *J* = 5.2, 13.0 Hz, 1H, one of C14-*H*$_2$), 2.10–2.20 (m, 2H, one of C17-*H*$_2$, one of C20-*H*$_2$), 2.25 (dddq, *J* = 5.2, 6.4, 7.9, 7.1 Hz, 1H, C13-*H*), 2.37 (dt, *J* = 8.6, 12.1 Hz, 1H, one of C16-*H*$_2$), 2.58 (dd, *J* = 7.9, 15.8 Hz, 1H, one of C11-*H*$_2$), 2.78 (dd, *J* = 6.4, 15.8 Hz, 1H, one of C11-*H*$_2$), 3.74 (m, 2H, C24-*H*$_2$), 4.22 (m, 1H, C22-*H*), 4.45 (d, *J* = 12.1 Hz, 1H, one of OC*H*$_2$Ph), 4.53 (d, *J* = 12.1 Hz, 1H, one of OC*H*$_2$Ph), 4.62 (dt, *J* = 7.9, 6.4 Hz, 1H, C12-*H*), 7.11 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.22 (t, *J* = 7.6 Hz, 2H, Ar*H*), 7.39 (d, *J* = 7.6 Hz, 2H, Ar*H*); ^{13}C NMR (125.7 MHz, C_6D_6) δ 7.3 (CH_2), 7.5 (CH_3), 14.6 (CH_3), 24.7 (CH_3), 28.1 (CH_3), 30.8 (CH_2), 31.3 (CH_2), 35.2 (CH_2), 35.8 (CH), 36.7 (CH_2), 36.9 (CH_2), 38.2 (CH_2), 45.1 (CH_2), 67.8 (CH), 68.1 (CH_2), 73.1 (CH_2), 73.5 (C), 79.2 (CH), 79.8 (C), 110.3 (C), 116.5 (C), 127.4 (CH), 127.8 (CH), 128.5 (CH), 139.9 (C), 170.7 (C); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{34}H_{56}O_7SiNa$ 627.3688; found 627.3704.

***tert*-Butyl (2*R*,3*R*,5*R*,7*R*,9*S*,12*R*)-[9-(2-Benzyloxyethyl)-3,12-dimethyl-12-triethylsilyloxy-1,6,8-trioxadispiro[4.1.5.2]tetradecan-2-yl]acetate (16).** R_f 0.57 (6:1 *n*-hexane/AcOEt); $[\alpha]_D^{21}$ +71.9 (*c* 0.163, benzene); IR (neat) 2955, 2874, 1732, 1458, 1368, 1150, 1101, 1028, 962 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.68 (d, *J* = 7.0 Hz, 3H, C13-C*H*$_3$), 0.73 (dq, *J* = 14.8, 7.9 Hz, 3H, Si(CH*H*CH$_3$)$_3$), 0.80 (dq, *J* = 14.8, 7.9 Hz, 3H, Si(CH*H*CH$_3$)$_3$), 1.17 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 1.28–1.39 (m, 2H, C21-*H*$_2$), 1.34 (s, 3H, C19-C*H*$_3$), 1.42 (m, 1H, one of C14-*H*$_2$), 1.43 (s, 9H, $CO_2C(CH_3)_3$), 1.53 (ddd, *J* = 3.0, 4.0, 11.9 Hz, 1H, one of C20-*H*$_2$), 1.66–1.77 (m, 3H, one of C17-*H*$_2$, C23-*H*$_2$), 2.03 (dd, *J* = 7.8, 12.1 Hz, 1H, one of C16-*H*$_2$), 2.16–2.26 (m, 4H, one of C11-*H*$_2$, one of C14-*H*$_2$, one of C16-*H*$_2$, one of C20-*H*$_2$), 2.40 (dd, *J*

= 7.5, 14.6 Hz, 1H, one of C11-H_2), 2.49 (dt, J = 7.8, 12.1 Hz, 1H, one of C17-H_2), 2.61 (m, 1H, C13-*H*), 3.44 (dt, J = 8.9, 5.3 Hz, 1H, one of C24-H_2), 3.58 (dt, J = 5.2, 8.9 Hz, 1H, one of C24-H_2), 4.10 (m, 1H, C22-*H*), 4.35 (s, 2H, OCH_2Ph), 4.73 (q, J = 7.5 Hz, 1H, C12-*H*), 7.09 (t, J = 7.4 Hz, 1H, Ar*H*), 7.18 (t, J = 7.4 Hz, 2H, Ar*H*), 7.32 (d, J = 7.4 Hz, 2H, Ar*H*); ^{13}C NMR (125.7 MHz, C_6D_6) δ 7.4 (CH_2), 7.6 (CH_3), 14.2 (CH_3), 25.2 (CH_3), 28.2 (CH_3), 30.8 (CH_2), 31.0 (CH_2), 34.6 (CH), 35.1 (CH_2), 35.2 (CH_2), 36.5 (CH_2), 38.0 (CH_2), 45.1 (CH_2), 66.2 (CH), 67.3 (CH_2), 72.7 (C), 73.1 (CH_2), 78.2 (CH), 79.7 (C), 110.4 (C), 114.9 (C), 127.6 (CH), 127.7 (CH), 128.5 (CH), 139.4 (C), 170.5 (C); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{34}H_{56}O_7SiNa$ 627.3688; found 627.3680.

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24. The use of NaOMe/MeOH instead of NaO*t*-Bu/*t*-BuOH caused partial transesterification.
25. Formation of a small amount of 12*R* isomers **3** and **16** was observed under these conditions.
26. Exposure of isomer **12** to TsOH in benzene at 20 °C for 3 d gave a 6:49:45 mixture of isomers **12**, **13** and **15** in 96% yield. The ratio of the three 12*S* isomers is nearly identical to that obtained by the LiOMe-mediated reaction as shown in entry 3, Table 1, although the reason is not clear at present.