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Synthesis of the Bis-Spiroacetal Core of the Antimitotic Agent Spirastrellolide B

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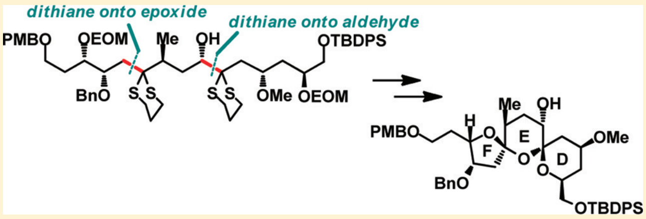
Ⓢ *Supporting Information*

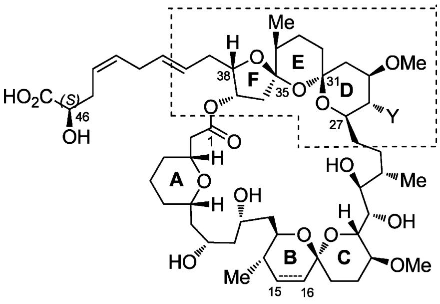
ABSTRACT: The spirastrellolides are a family of potent antimitotic agents isolated from the marine sponge *Spirastrella coccinea*. Synthetic studies toward the DEF bis-spiroacetal core of spirastrellolide B are reported. A modular approach was pursued by the use of two dithiane disconnections to enable a highly convergent synthesis. The ease of lithiation and nucleophilicity of these 2-substituted-1,3-dithianes were investigated during the course of the synthesis, and the alkylations were found to proceed most efficiently at elevated temperatures. Formation of the [5,6,6]-bis-spiroacetal ring system was achieved via a double dithiane deprotection/spiroacetalization strategy.



INTRODUCTION

The spirastrellolides are a family of polyketide macrolides isolated from the marine sponge *Spirastrella coccinea* that exhibit potent antimitotic activity.[1] The spirastrellolides exhibit this activity not by the disruption of tubulin/spindle formation like other sponges' macrolide antimitotics (e.g., the spongistatins and laulimalides), but by their potent inhibiton of Ser/Thr protein phosphatase PP2A (IC_{50} = 1 nM). PP2A is an enzyme involved in cellular signaling that is emerging as a novel medicinal target for the treatment of cancer.[2] The ability to synthesize the spirastrellolides is therefore important not only for its potential as a therapeutic agent but also for its use as a biological tool in the investigation of PP2A function.

Spirastrellolide A (**1**, Figure 1) was the first member of its family to be isolated in 2003[1c] and allowed the determination of the relative stereochemistry within each of the C3−C7 (A), C9−C24 (BC), and C27−C38 (DEF) fragments. The absolute configuration of the macrolide core was not determined until the availability of a crystalline derivative of spirastrellolide B (**2**) in 2007.[1b] Early synthetic strategies therefore relied on highly modular strategies, with disconnections made to isolate each of the regions of known relative stereochemistry. The complex structure of the spirastrellolides has generated a great deal of interest within the synthetic community,[3] and of particular interest to our research group is the intriguing DEF-bis-spiroacetal.[4] Our preliminary results on the use of a double dithiane deprotection/spiroacetalization strategy to construct the [5,6,6]-bis-spiroacetal core was described in a previous communication.[5] Herein, we disclose the full details of our synthetic efforts toward the DEF bis-spiroacetal of spirastrellolide B, in particular highlighting the two carefully optimized dithiane alkylations to construct our highly functionalized cyclization precursor.[6]



Spirastrellolide A (**1**): Y = Cl, $\Delta^{15,16}$
Spirastrellolide B (**2**): Y = H

Figure 1. Spirastrellolides A and B and the DEF bis-spiroacetal.

RESULTS AND DISCUSSION

We envisaged synthesis of the interesting [5,6,6]-bis-spiroacetal of spirastrellolide B using a highly convergent route involving two dithiane alkylations. Formation of the key tricyclic bis-spiroacetal would be achieved using a double dithiane deprotection/spiroacetalization strategy. The structure of the DEF bis-spiroacetal moiety benefits from full anomeric stabilization, and in addition, all of its substituents occupy equatorial positions. The desired configuration at C31 and C35 should therefore result from bis-dithiane deprotection of acyclic precursor **4** (Scheme 1) under equilibrating conditions to form the desired bis-spiroacetal **3**. Acyclic precursor **4** is accessible via alkylation of dithiane **6** with iodide **5**, which in turn is prepared via union of dithiane **7** with epoxide **8**. These two successive dithiane alkylations considerably simplify the carbon backbone of the target into three smaller fragments, thereby facilitating a highly convergent approach to DEF bis-spiroacetal **3**.

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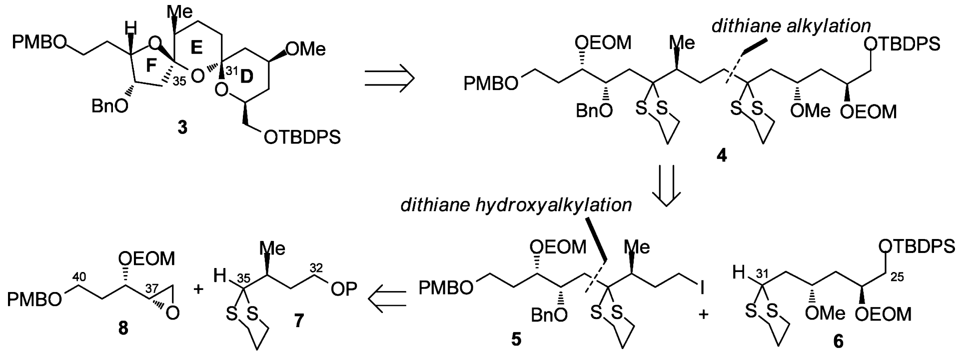
Scheme 1. Retrosynthesis of DEF Bis-Spiroacetal 3



The initial objective was to construct the dithiane C32−35 fragment **7** and investigate its use as an umpolung alkylating agent. Synthesis began with Sharpless epoxidation[7] of allylic alcohol **9** (Scheme 2), which was readily available from 1,3-propanediol in 58% yield over a four step sequence. Regioselective epoxide opening with trimethylaluminium[8] followed by oxidative cleavage then afforded aldehyde **10**. The lability of the PMB group precluded the conventional use of $BF_3 \cdot Et_2O$ after the installation of the dithiane moiety, which was successfully formed by the treatment of aldehyde **10** with 1,3-propanedithiol in the presence of $CoCl_2$.[9] Dithiane **11**, however, proved ineffective for subsequent alkylation reactions, and deuterium exchange experiments were conducted to investigate the ease of lithiation at C2 of the 1,3-dithiane. To our surprise, treatment of dithiane **11** with a variety of bases, with or without additives such as HMPA and DMPU, failed to give any significant metalation (see Table 1). This difficulty in lithiation may be due to donation of electron density from the π system of the PMB group to the C−S σ^* of the dithiane, thus reducing the ability of the σ^* to increase the acidity of the α-hydrogen (Figure 2).[10] Efforts were thus directed toward finding an alternative protecting group for dithiane fragment **11**.

Scheme 2. Synthesis of Dithiane Fragment 11

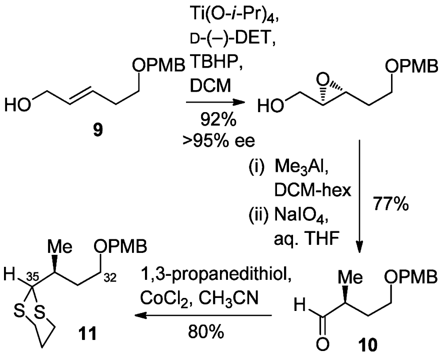
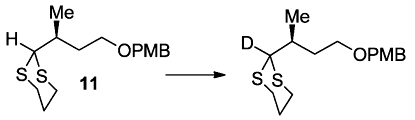


Table 1. Examination of Conditions for the Lithiation of Dithiane 11



	base used	additives	temp (°C)	time (min)	deuteration (%)
1	*t*-BuLi	none	−78	30	0
2	*t*-BuLi	10% HMPA	−78	60	<5
3	*s*-BuLi	none	−50	15	0
4	*s*-BuLi	DMPU/ TMEDA	−50	30	<5
5	*n*-BuLi	none	−20	60	<5
6	*n*-BuLi	none	rt	5	<5

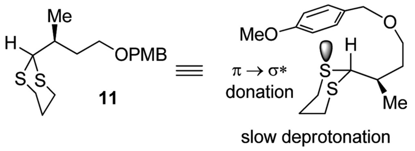
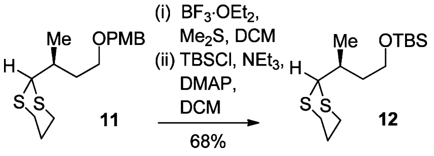


Figure 2. Proposed explanation for the slow deprotonation of dithiane **11**.

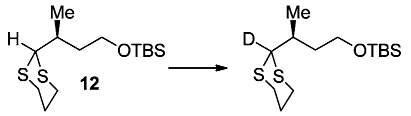
Scheme 3. Synthesis of Dithiane Fragment 12



Deprotection of the PMB ether was first attempted using DDQ but resulted in low yields of 20−50%. The use of $BF_3 \cdot Me_2S$ proved effective in removing the PMB ether, which was readily converted to TBS ether **12** in 68% yield over the two steps (Scheme 3). Lithiation of TBS-protected dithiane **12** was now readily achievable, though the results varied greatly with temperature. Although most dithiane alkylations are performed at temperatures of −20 °C or below, we found lithiation to be most efficient using *n*-BuLi at 0 °C or room temperature following short reaction times (entries 7−8, Table 2). The deuterium exchange experiments conducted using *n*-BuLi at −20 °C (entries 3−5, Table 2) initially revealed an increase and then a decrease in deuterium incorporation, which suggests the lithiated species has a limited lifetime in solution. The use of a 4:1 mixture of *n*-BuLi−Bu_2Mg[11] (entry 11, Table 2) was shown to greatly increase the lifetime of the metalated species.

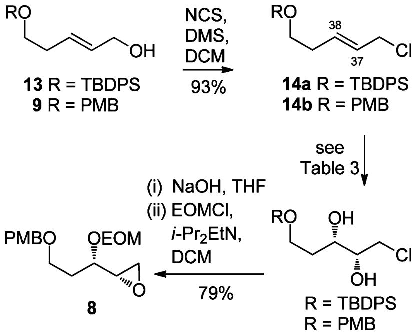
Synthesis of epoxide fragment **8** (Scheme 4) began with an investigation into the Sharpless dihydroxylation[12] of allylic chlorides **14a** and **14b**, both readily available from the corresponding allylic alcohol. Initial investigations were performed with TBDPS-protected allylic chloride **14a**, where the anthraquinone (AQN)[13] linker (90% *ee*) was found to be superior to both the phthalazine (PHAL) and pyrimidine

Table 2. Examination of Conditions for the Lithiation of Dithiane 12



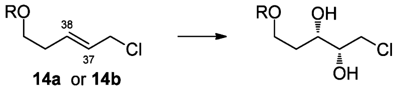
	base used	additives	temp (°C)	time (min)	deuteration (%)
1	t-BuLi	none	−78	30	15
2	t-BuLi	10% HMPA	−78	60	10
3	n-BuLi	none	−20	5	11
4	n-BuLi	none	−20	15	41
5	n-BuLi	none	−20	60	22
6	n-BuLi	none	0	5	44
7	n-BuLi	none	0	15	81
8	n-BuLi	none	rt	5	81
9	n-BuLi	TMEDA	−20	90	0
10	n-BuLi	DMPU	0	15	76
11	n-BuLi−B u$_2$Mg	none	rt	60	72

Scheme 4. Synthesis of Epoxide 8



(PYR) linkers (72−74% *ee*; entries 1−4, Table 3). Further improved results were achieved with PMB-protected **14b** as the substrate, which allowed access to the desired diol in 94% *ee*, superior to the previously reported example using PHAL (88% *ee*).[14] Subsequent treatment with NaOH to form the epoxy alcohol followed by protection as an ethoxymethyl (EOM) ether provided epoxide **8** in 72% over 4 steps.

Table 3. Asymmetric Dihydroxylation of Allylic Alcohol 14



	R	chiral ligand (ligand/mol %)	OsO$_4$ (mol %)	*ee* (%)
1	TBDPS	(DHQ)$_2$PHAL/5	1	72
2	TBDPS	(DHQ)$_2$PHAL/10	0.25	74
3	TBDPS	(DHQ)$_2$PYR/5	1	73
4	TBDPS	(DHQ)$_2$AQN/5	1	90
5	PMB	(DHQ)$_2$AQN/5	1	94

Union of dithiane **12** and epoxide **8** (Scheme 5) was efficiently achieved by treatment of dithiane **12** (1.6 equiv) with n-BuLi at room temperature, followed by the addition of epoxide **8**. The coupled product was isolated in quantitative yield, and excess dithiane **12** was fully recovered. Protection of the resulting secondary alcohol as a benzyl ether, followed by treatment with TBAF afforded primary alcohol **15** in 82% yield over the two steps. Attempts to convert alcohol **15** into the requisite iodide using either Appel or Finkelstein conditions only resulted in decomposition of the starting material. From the previous literature, it appears that in the presence of a proximal leaving group, 2,2-disubstituted dithianes readily undergo intramolecular alkylation to form unstable ring-expanded products.[15] To circumvent this problem, alcohol **15** was first oxidized using tetrapropyl ammonium perruthenate (TPAP)/NMO[16] and converted to *N*-TBS-tosylhydrazone **17** in order to attempt a Myers reductive coupling[17] to bring together fragments **17** and **6**.

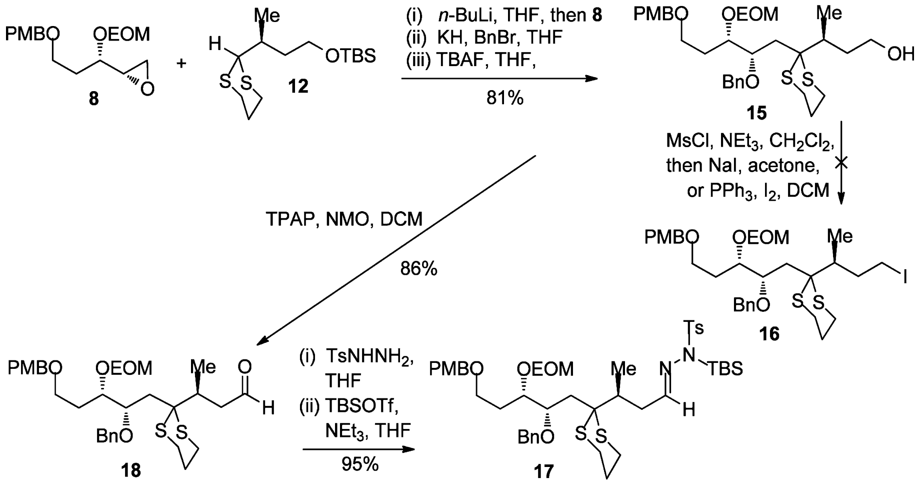
Synthesis of the dithiane C25−C31 fragment **6** utilized triol **19** (Scheme 6), which was derived from D-(+)-ribonic acid γ-lactone (**20**) in 45% over five steps.[18] Initial attempts to convert this 1,2,4-triol (**19**) into epoxide **21** via a two-step sulfonation/displacement sequence were met with difficulties. Following careful experimentation, it was discovered that the most efficient way to generate this epoxide and avoid side reactions was to treat triol **19** with potassium hexamethyldisilazide (KHMDS) for a short period of time at high dilution, followed immediately by the addition of *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole.[19] Following EOM protection, epoxide **21** was isolated in 53% yield over these two steps. Alkylation of epoxide **21** with lithiated-1,3-dithiane followed by methylation then provided the desired C25−C31 dithiane fragment **6**.

The lithiation of dithiane **6** was investigated using conditions successfully employed for the alkylation of dithiane C32−C35 fragment **12**. n-BuLi appeared sufficient to achieve lithiation using a short reaction time (entries 1−3, Table 4), but when these conditions were employed for the alkylation with model iodide **22** (entries 1−2, Table 5), no product was observed. Treatment of dithiane **6** with t-BuLi in 10% HMPA−THF achieved efficient lithiation at −78 °C (entry 5, Table 4) and was accompanied by a deep red coloration. Successful alkylation with model iodide **22** (entry 3, Table 5) was achieved under these conditions.

These latter conditions were next employed in the investigation of the reductive alkylation of **6** with *N*-TBS-tosylhydrazone **17**. Although we were able to demonstrate successful union of a model *N*-TBS-tosylhydrazone (**23**) with lithio-1,3-dithiane (Scheme 7), attempts to alkylate 2-substituted dithiane **6** with advanced *N*-TBS-tosylhydrazone **17** were unsuccessful (Scheme 8). Following several alkylation attempts, only full recovery of both starting materials was observed. Attention thus turned to the use of aldehyde **18** for later alkylations, with the hope that the resulting superfluous hydroxyl group formed could be readily removed via Barton−McCombie deoxygenation.[20]

Although the t-BuLi/HMPA conditions were suitable to achieve efficient alkylation of model iodide **22** with dithiane **6** (entry 3, Table 5), the same conditions failed to achieve alkylation of dithiane **6** with the required aldehyde **18** (Scheme 9). It is uncertain whether higher temperatures were needed for alkylation to proceed; however when n- or t-BuLi was used, higher temperatures resulted in rapid decomposition of the anion. An efficient way to generate the dithiane anion at a higher temperature was again found to involve the use of a 4:1 mixture of n-BuLi−Bu$_2$Mg (entry 6, Table 4). Under these conditions, the metalated anion as observed by the deep red coloration was maintained for over an hour at room temperature. Use of this mixed organometallic reagent finally allowed effective union of dithiane **6** and aldehyde **18** to afford

Scheme 5. Synthesis of N-TBS Hydrazone Derivative 17



Scheme 6. Synthesis of C25−C31 Dithiane Fragment 6

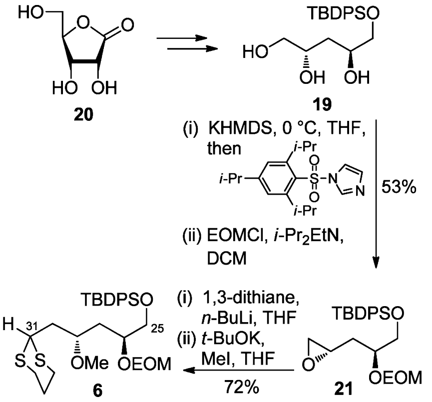
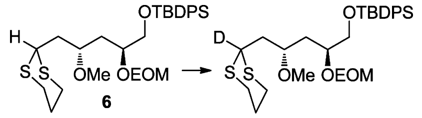


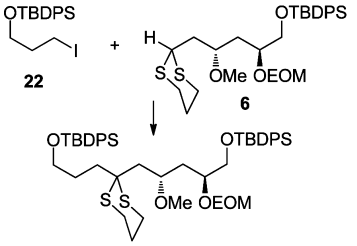
Table 4. Conditions Attempted for the Lithiation of Dithiane 6



	base used	additives	temp (°C)	time (min)	deuteration (%)
1	*n*-BuLi	none	rt	5	50
2	*n*-BuLi	none	−78	30	24
3	*n*-BuLi	none	−78 to −50	15	75
4	*t*-BuLi	10% HMPA	−78 to −50	30	39
5	*t*-BuLi	10% HMPA	−78	15	90
6	*n*-BuLi−Bu$_2$Mg	none	rt	5	85

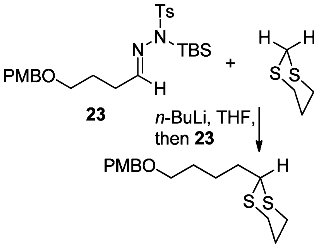
bis-dithiane **24** in 78% yield as a 3:2 mixture of diastereomers (Scheme 9). The epimeric alcohols **24** were separated by preparative TLC.

Table 5. Conditions Attempted for the Model Alkylation of Dithiane 6



	base used	additives	temp (°C)	time (min)	result (%)
1	*n*-BuLi	none	−78 to −50	15	no reaction
2	*n*-BuLi	DMPU (2 equiv)	−78 to −50	15	no reaction
3	*t*-BuLi	10% HMPA	−78	15	73

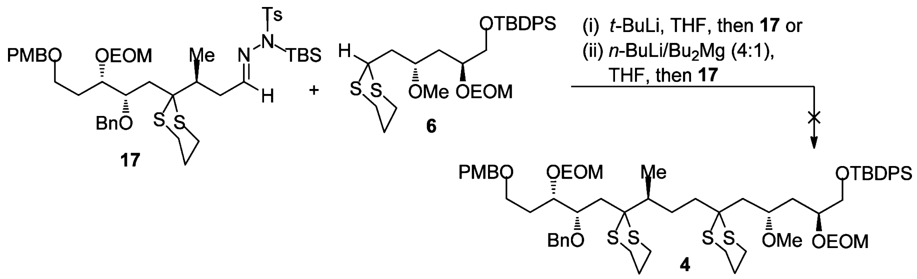
Scheme 7. Successful Union of a Model *N*-TBS-tosylhydrazone (23) with Lithio-1,3-dithiane



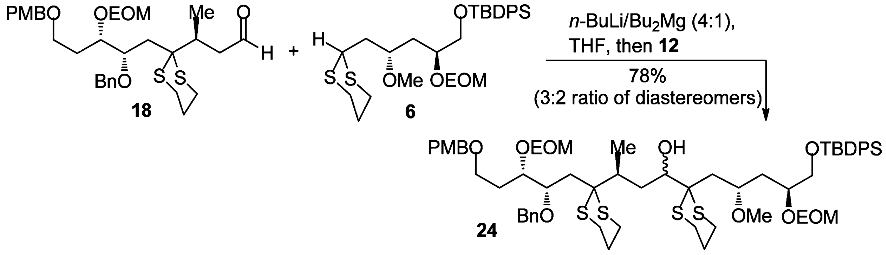
A large number of attempts to remove the superfluous hydroxyl group of alcohol **24** using Barton−McCombie, Martin's sulfurane,[21] chlorodiphenylsilane/InCl$_3$,[22] and mesylation/LiAlH$_4$ conditions were unsuccessful. At this point, it was postulated that the presence of the two dithiane moieties were impeding further functionalization of the alcohol. Thus it was decided to first investigate the crucial double dithiane deprotection/spiroacetalization sequence and to perform the deoxygenation following bis-spiroacetal formation.

The C32 secondary alcohol was first protected as a methyl ether to allow investigation of the bis-dithiane deprotection−bis-spiroacetalization sequence (Scheme 10).[23] Several methods were examined for the double EOM deprotection, with best results found to be the use of PPTS in *t*-BuOH[24] to furnish the corresponding diol in 66% yield. Gratifyingly, the bis-dithiane deprotection step was accomplished by treatment of the diol with HgCl$_2$, resulting in concomitant bis-spiroacetalization to generate the desired bis-spiroacetal **26** as a single diastereoisomer in 62% yield. The double anomerically stabilized

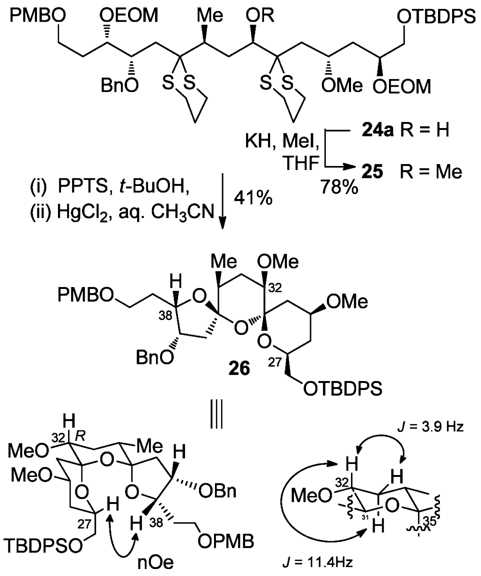
Scheme 8. Unsuccessful Alkylation of 2-Substituted Dithiane **6** with Advanced *N*-TBS-tosylhydrazone **17**



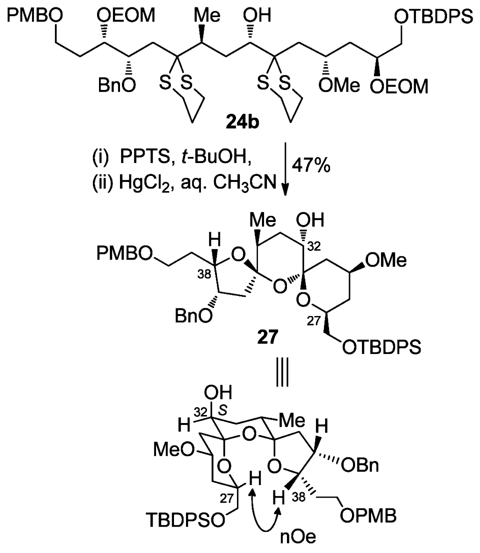
Scheme 9. Synthesis of Bis-Dithiane **24**



Scheme 10. Synthesis of Bis-Spiroacetal **26**



Scheme 11. Synthesis of Bis-Spiroacetal **27**



configuration was confirmed by a strong NOE correlation between the C_{27} and C_{38} methine protons, and the *R* stereochemistry at C_{32} was established by analysis of coupling constants.

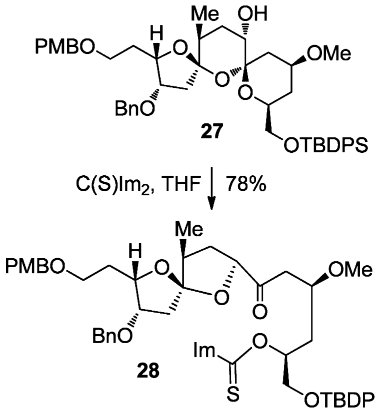
Following successful demonstration of the bis-dithiane deprotection−tandem spiroacetalization methodology, further synthetic efforts were undertaken to investigate the late-stage deoxygenation step. Treatment of unprotected alcohol **24b** with PPTS in *t*-BuOH at 85 °C provided the corresponding triol (Scheme 11). Upon addition of $HgCl_2$, the desired bis-spiroacetal **27** was formed in 74% yield as a single diastereomer, with no sign of competing cyclizations. The stereochemistry of this fully anomerically stabilized bis-spiroacetal was also confirmed by analysis of NOE correlations.

Attempts to form the xanthate and phenoxythiocarbonyl derivatives of bis-spiroacetal **27** were met with disappointment, and efforts to form the thiocarbonylimidazole derivative resulted in the formation of ring-opened derivative **28**[25] (Scheme 12), the structure of which was confirmed by the presence of characteristic carbonyl carbon at δ 211.9 in the ^{13}C NMR spectrum. These results demonstrate the highly sterically hindered nature of the C32 hydroxyl group. Attempts to use Martin's sulfurane and mesylation/$LiAlH_4$ conditions were also unsuccessful. It was therefore concluded that in spite of our earlier misleading communication,[5] deoxygenation of alcohol **27** could not be achieved. Similar difficulties were also experienced using the epimeric equatorial C32 alcohol. Attempts to effect mesylation of alcohol **27** and subsequent elimination to an alkene that could be reduced also met with no success.

■ CONCLUSION

In summary, we have shown that the core of the DEF bis-spiroacetal ring system of spirastrellolide B can be accessed using a double dithiane deprotection/spiroacetalization strategy. Synthesis of the acyclic precursor required careful

Scheme 12. Attempts to Form the Thiocarbonylimidazole Derivative of Bis-Spiroacetal 27



optimization of the dithiane alkylation conditions. Although dithiane alkylations are conventionally performed at low temperatures, the best results for our substrates were obtained at room temperature following short reaction times. These alkylations include the alkylation of 2-substituted-1,3-dithianes with an epoxide and an aldehyde. The latter method required the use of the mixed organometallic reagent *n*-BuLi–Bu_2Mg to prolong the lifetime of the lithiated anion in order to facilitate nucleophilic attack. Efforts are ongoing to improve the current synthesis and to construct the DEF bis-spiroacetal without the extraneous C32 hydroxyl group. In the meantime, the current synthetic route can be used to access C32 oxygenated analogues of the DEF bis-spiroacetal in order to investigate their PP2A activity.

■ EXPERIMENTAL SECTION

Synthesis of Dithiane C32–C35 Fragment 7. *(2S,3S)-5-(4-Methoxybenzyloxy)-3-methylpentane-1,2-diol.*[26] To a stirred solution of the epoxy alcohol (1.98 g, 8.31 mmol) in CH_2Cl_2 (35 mL) and hexanes (16 mL) was added dropwise trimethylaluminium (18.3 mL, 2.0 M in hexanes, 35.6 mmol) at 0 °C, and the mixture was allowed to warm to rt and stirred overnight. The reaction mixture was diluted with Et_2O (60 mL), H_2O (1.4 mL) was added, and the mixture was stirred vigorously at rt until a white gelatinous precipitate formed. To the mixture was added 1.3 M NaOH (4.2 mL), and the mixture was stirred vigorously until a white gel formed on the surface of the flask and the bulk of the solution became clear. The liquid was decanted, and the white solid gel was extracted with Et_2O (2 × 60 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (hexanes/EtOAc 1:9) to afford the title compound (1.64 g, 6.46 mmol, 78%) as a colorless oil.

*(S)-4-(4-Methoxybenzyloxy)-2-methylbutanal (**10**).* To a stirred solution of sodium periodate (1.50 g, 6.99 mmol) in a 1:1 mixture of THF–H_2O (26 mL) was added dropwise a solution of the diol (1.62 g, 6.36 mmol) in THF (10 mL), and the mixture was stirred at rt for 15 min. To the resulting cloudy solution was added a 2:1 mixture of PhH–Et_2O (75 mL), and the organic layer was washed with H_2O (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude aldehyde **10** (1.40 g, 6.29 mmol, 99%) was isolated as a colorless oil and used in the next reaction without further purification. A sample of the product was purified by flash chromatography (hexanes/EtOAc 9:1) for spectroscopic analysis: R_f (hexanes/EtOAc 9:1) = 0.26; $[\alpha]_D^{18}$ = +14.3 (*c* 0.78, $CHCl_3$); HRMS found (FAB) M^+, 222.1259, $C_{13}H_{18}O_3$ requires 222.1256; IR (film) 2934, 2860, 2717, 1723, 1613, 1513, 1247, 1174, 1097, 1034, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, 1H, J = 2.0 Hz), 7.23 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 4.40 (s, 2H), 3.79 (s, 3H), 3.54–3.45 (m, 2H), 2.56–2.48 (m, 1H), 2.07–1.98 (m, 1H), 1.71–1.63 (m, 1H), 1.09 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 159.1, 130.2, 129.2, 113.7, 72.6, 67.0, 55.2, 43.7, 30.8, 13.2; *m/z* (EI) 222 (M^+, 1%), 152 (6), 137 (62), 121 (100), 107 (4), 91 (4), 85 (3), 77 (9).

*(S)-2-(4-(4-Methoxybenzyloxy)butan-2-yl)-1,3-dithiane (**11**).* To a solution of aldehyde **10** (446 mg, 2.01 mmol) in CH_3CN (10 mL) was added 1,3-propanedithiol (0.242 mL, 2.41 mmol) followed by a catalytic amount of $CoCl_2 \cdot 6H_2O$ (23.9 mg, 0.100 mmol), and the mixture was stirred at rt for 2 h. The reaction mixture was then concentrated and purified by flash chromatography (hexanes/EtOAc 9:1) to afford the title compound **11** (504 mg, 1.61 mmol, 80%) as a colorless oil: R_f (hexanes/EtOAc 3:1) = 0.42; $[\alpha]_D^{23}$ = +6.3 (*c* 0.80, $CHCl_3$); HRMS found (EI) M^+, 312.1223, $C_{16}H_{24}O_2S_2$ requires 312.1218; IR (film) 2954, 2931, 2899, 2859, 1611, 1511, 1239, 1172, 1089, 1032, 818, 753, 518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.43 (s, 2H), 4.11 (d, 1H, J = 4.0 Hz), 3.80 (s, 3H), 3.56–3.44 (m, 2H), 2.94–2.80 (m, 4H), 2.16–2.04 (m, 2H, 2-H), 2.01–1.90 (m, 1H), 1.89–1.74 (m, 1H), 1.59 (ddt, 1H, J = 14.1, 8.2, 6.0 Hz), 1.08 (d, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.7, 129.2, 113.8, 72.4, 67.7, 55.3, 55.3, 35.4, 33.8, 31.1, 30.8, 26.4, 17.0; *m/z* (EI) 312 (M^+, 3.5%), 191 (100), 173 (10), 121 (90), 119 (35), 107 (6), 85 (17), 41 (10).

(S)-2-(1,3-Dithian-2-yl)butan-4-ol. To a stirred solution of $BF_3 \cdot OEt_2$ (0.493 mL, 6.64 mmol) in CH_2Cl_2 (5 mL) was added Me_2S (0.493 mL, 6.64 mmol), and the mixture was stirred at rt for 20 min. A solution of PMB ether **11** (217 mg, 0.694 mmol) in CH_2Cl_2 (2 mL) was added, and the mixture was stirred at rt for a further 20 min. The reaction was quenched by the addition of saturated aq $NaHCO_3$ (10 mL) and stirred at rt for 20 min. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 1:1) afforded the title compound (107 mg, 0.556 mmol, 80%) as a colorless oil: R_f (hexanes/EtOAc 1:1) = 0.39; $[\alpha]_D^{24}$ = −3.6 (*c* 0.72, $CHCl_3$); HRMS found (ESI) M^+ + Na, 215.0527, $C_8H_{16}NaOS_2$ requires 215.0535; IR (film) 3368 br, 2930, 2896, 1454, 1422, 1379, 1276, 1084, 1053, 1009, 907, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (d, 1H, J = 4.2 Hz), 3.80–3.63 (m, 2H), 2.97–2.81 (m, 4H), 2.17–2.03 (m, 2H, 2-H), 1.97–1.76 (m, 3H), 1.60 (ddt, 1H, J = 14.0, 8.1, 6.0 Hz), 1.69 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.8, 55.3, 36.9, 35.3, 31.0, 30.8, 26.3, 17.1; *m/z* (ESI) 215 (M^+ + Na, 100%), 188 (28), 171 (61), 143 (10), 126 (13), 100 (22).

*(S)-2-(4-(tert-Butyldimethylsilyloxy)butan-2-yl)-1,3-dithiane (**12**).*[5] To a stirred solution of the alcohol (312 mg, 1.63 mmol) in CH_2Cl_2 (16 mL) at rt were added triethylamine (0.679 mL, 4.88 mmol), *tert*-butyldimethylsilyl chloride (367 mg, 2.44 mmol), and *N,N*-dimethyl-4-aminopyridine (20 mg, 0.16 mmol), and the mixture was stirred for 2.5 h at this temperature. Saturated aq NH_4Cl (10 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined,

washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 30:1) afforded the title compound **12** (423 mg, 1.38 mmol, 85%) as a colorless oil.

Synthesis of epoxide C36–C40 fragment 8. *(E)-5-(tert-Butyldiphenylsilyloxy)-1-chloropent-2-ene (14a).* To a stirred solution of *N*-chlorosuccinimide (2.39 g, 17.9 mmol) in CH_2Cl_2 (30 mL) was added Me_2S (1.32 mL, 17.9 mmol) at 0 °C, and the mixture was stirred at rt for 1.5 h. The mixture was cooled to −20 °C, and a solution of allylic alcohol **13** (2.03 g, 5.96 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 30 min at 0 °C, the mixture was warmed to rt and stirred for a further 2 h. H_2O (15 mL) was added, the layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 20:1) afforded the title compound **14a** (2.02 g, 5.63 mmol, 94%) as a colorless oil: R_f (hexanes/EtOAc 20:1) = 0.38; HRMS found (FAB) MH$^+$ 359.1598 and (M + 2)H$^+$ 361.1558, $C_{21}H_{28}{}^{35}ClOSi$ requires 359.1598 and $C_{21}H_{28}{}^{37}ClOSi$ requires 361.1569; IR (film) 3071, 2956, 2930, 2857, 1472, 1427, 1111, 966, 823, 737, 701, 687, 613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H), 7.42–7.34 (m, 6H), 5.80 (dtd, 1H, J = 15.2, 6.8, 0.8 Hz), 5.68 (dtt, 1H, J = 15.2, 6.8, 1.1 Hz), 4.02 (dd, 2H, J = 6.8, 0.8 Hz), 3.73 (t, 2H, J = 6.5 Hz), 2.33 (dtd, 2H, J = 6.8, 6.5, 1.1 Hz), 1.05 (s, 9H, OSi^t*Bu*Ph$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.8, 132.5, 129.6, 127.8, 127.6, 63.1, 45.2, 35.4, 26.8, 19.2; *m/z* (EI) 301 (7%), 265 (11), 247 (58), 217 (100), 181 (17), 135 (16), 91 (39).

(2R,3S)-5-(tert-Butyldiphenylsilyloxy)-1-chloropentane-2,3-diol. A stirred solution of dihydroquinine $(DHQ)_2AQN$ (92 mg, 0.11 mmol), osmium tetroxide (0.30 mL; 2.5 wt % solution in *t*-butanol, 0.021 mmol), $K_3[Fe(CN)_6]$ (2.09 g, 6.35 mmol), K_2CO_3 (877 mg, 6.35 mmol), $NaHCO_3$ (531 mg, 6.32 mmol), and methanesulfonamide (205 mg, 2.16 mmol) in *t*-butanol/H_2O (1:1) (11 mL) was treated with a solution of allylic halide **14a** (767 mg, 2.14 mmol) in *t*-butanol (2 mL), and the mixture was stirred at 0 °C for 2 d. $Na_2S_2O_5$ (2.02 g) was added portionwise over 30 min with vigorous bubbling, and the mixture was stirred at rt for 1 h. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 1 M KOH (8 mL), 1 M HCl (8 mL), and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 7:3) afforded the title compound (840 mg, 2.14 mmol, 91%, 90% *ee*) as a colorless oil that solidified on standing in vacuo overnight to form a colorless solid (mp 50–53 °C): R_f (hexanes/EtOAc 7:3) = 0.27; $[\alpha]_D^{26}$ = +8.35 (*c* 0.80, $CHCl_3$); HRMS found (FAB) MH$^+$ 393.1655 and (M + 2)H$^+$ 395.1631, $C_{21}H_{30}{}^{35}ClO_3Si$ requires 393.1653 and $C_{21}H_{30}{}^{37}ClO_3Si$ requires 395.1623; IR (film) 3417 br, 3071, 2958, 2931, 2858, 1472, 1427, 1112, 922, 757, 702, 614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (m, 4H), 7.47–7.38 (m, 6H), 4.10–4.06 (m, 1H), 3.91–3.89 (m, 2H), 3.70–3.64 (m, 2H), 3.61–3.56 (m, 1H), 3.48 (d, 1H, J = 3.5 Hz), 2.89 (d, 1H, J = 6.3 Hz), 1.97–1.88 (m, 1H), 1.72–1.64 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 132.7, 129.9, 127.8, 74.0, 70.6, 62.7, 45.7, 35.0, 26.8, 19.0; *m/z* (EI) 317 (1%), 257 (21), 227 (27), 199 (100), 181 (14), 139 (18), 135 (17), 91 (34).

(E)-1-Chloro-5-(4-methoxybenzyloxy)pent-2-ene (14b). To a stirred solution of *N*-chlorosuccinimide (784 mg, 5.87 mmol) in CH_2Cl_2 (15 mL) was added dimethyl sulfide (0.434 mL, 5.87 mmol) at 0 °C, and the mixture was stirred at rt for 1 h. The mixture was cooled to −20 °C, and a solution of allylic alcohol **9** (1.03 g, 4.63 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After stirring for 30 min at 0 °C, the mixture was warmed to rt and stirred overnight. H_2O (10 mL) was added, the layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 9:1) afforded the title compound **14b** (1.04 g, 4.31 mmol, 93%) as a light yellow oil: R_f (hexanes/EtOAc 9:1) = 0.33; HRMS found (ESI) (M + Na)$^+$ 263.0803 and [(M + 2) + Na]$^+$ 265.0775, $C_{13}H_{17}{}^{35}ClNaO_2$ requires 263.0809 and $C_{13}H_{17}{}^{37}ClNaO_2$ requires 265.0780; IR (film) 2950, 2935, 2904, 2856, 1612, 1512, 1464, 1441, 1361, 1302, 1245, 1172, 1094, 1033, 966, 815, 672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, 2H, J = 8.7 Hz), 6.89 (d, 2H, J = 8.7 Hz), 5.82 (dt, 1H, J = 15.2, 6.5 Hz), 5.74–5.64 (m, 1H), 4.45 (s, 2H), 4.04 (dd, 2H, J = 6.8, 0.7 Hz), 3.81 (s, 3H), 3.51 (t, 2H, J = 6.6 Hz), 2.38 (dtd, 2H, J = 6.6, 6.6, 0.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 132.3, 130.3, 129.2, 127.6, 113.7, 72.5, 68.9, 55.2, 45.1, 32.5; *m/z* (ESI) 263 (M$^+$ + Na, 5%), 227 (12), 137 (25), 121 (100).

(2R,3S)-1-Chloro-5-(4-methoxybenzyloxy)pentane-2,3-diol. A solution of $(DHQ)_2AQN$ (36 mg, 0.042 mmol), osmium tetroxide (0.14 mL; 2.5 wt % solution in *t*-butanol, 0.010 mmol), $K_3[Fe(CN)_6]$ (2.05 g, 6.23 mmol), K_2CO_3 (861 mg, 6.23 mmol), $NaHCO_3$ (523 mg, 6.23 mmol), and methanesulfonamide (174 mg, 2.08 mmol) in a 1:1 mixture of *t*-butanol–H_2O (12.5 mL) was treated with a solution of allylic halide **14b** (509 mg, 2.11 mmol) in *t*-butanol (2 mL), and the mixture was stirred at 0 °C for 14 h. $Na_2S_2O_5$ (1.98 g) was added portionwise over 30 min with vigorous bubbling, and the mixture was stirred at rt for 1 h. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 1 M aq KOH (8 mL), 1 M aq HCl (8 mL), and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 2:3) afforded the title compound (560 mg, 2.07 mmol, 81%, 94% *ee*) as a colorless oil: R_f (hexanes/EtOAc 2:3) = 0.36; $[\alpha]_D^{17}$ = +15.0 (*c* 0.99, $CHCl_3$); HRMS found (ESI) (M + Na)$^+$ 297.0863 and [(M + 2) + Na]$^+$ 299.0836, $C_{13}H_{19}{}^{35}ClNaO_4$ requires 297.0864 and $C_{13}H_{17}{}^{37}ClNaO_2$ requires 299.0834; IR (film) 3312 br (OH), 2954, 2924, 2906, 2870, 1614, 1517, 1453, 1430, 1305, 1255, 1179, 1163, 1129, 1074, 1054, 1033, 1008, 990, 927, 850, 810, 760, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 2H, J = 8.7 Hz), 6.89 (d, 2H, J = 8.7 Hz), 4.46 (s, 2H), 3.97 (dt, 1H, J = 8.8, 2.8 Hz), 3.81 (s, 3H), 3.73–3.53 (m, 5H), 3.27 (br s, 1H), 2.91 (br s, 1H), 2.03–1.90 (m, 1H), 1.76 (dddd, 1H, J = 14.7, 5.0, 3.6, 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 129.6, 129.4, 113.9, 74.0, 73.1, 70.6, 68.1, 55.3, 45.8, 33.1; *m/z* (ESI) 297 (M$^+$ + Na, 4%), 195 (9), 177 (5), 121 (100).

(2S,3S)-1,2-Epoxy-5-(4-methoxybenzyloxy)-3-pentanol. To a stirred solution of the chlorodiol (517 mg, 1.88 mmol) in THF (3.5 mL) was added pulverized NaOH (188 mg, 4.71 mmol) at 0 °C. After stirring for 1.5 h, Et_2O (20 mL) and H_2O (5 mL) were added, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated aq NH_4Cl (10 mL) and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 2:3) afforded the title compound (406 mg, 1.70 mmol, 91%) as a colorless oil: R_f (hexanes/EtOAc 2:3) = 0.32; $[\alpha]_D^{19}$ = +3.6 (*c* 1.10, $CHCl_3$); HRMS found (ESI) (M + Na)$^+$ 261.1093,

$C_{13}H_{18}NaO_4$ requires 261.1097; IR (film) 3423 br, 2935, 2856, 1612, 1512, 1302, 1244, 1174, 1087, 1030, 910, 814, 755 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.24 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 4.47 (d, 1H, J = 11.5 Hz), 4.42 (d, 1H, J = 11.5 Hz), 3.79 (s, 3H), 3.73–3.59 (m, 3H), 2.99 (ddd, 1H, J = 4.7, 4.0, 2.8 Hz), 2.76 (dd, 1H, J = 5.0, 4.0 Hz), 2.70 (dd, 1H, J = 5.0, 2.8 Hz), 1.88 (q, 2H, J = 6.0 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 159.2, 130.0, 129.2, 113.7, 72.8, 69.9, 67.1, 55.2, 55.1, 44.5, 33.8; m/z (ESI) 261 (M$^+$ + Na, 100%), 251 (12), 145 (8), 135 (8), 121 (24).

*(2S,3S)-1,2-Epoxy-3-(ethoxymethoxy)-5-(4-methylbenzyloxy)pentane (**8**).*[5] To a stirred solution of the epoxy alcohol (183 mg, 0.77 mmol) and diisopropylethylamine (0.535 mL, 3.07 mmol) in CH$_2$Cl$_2$ (7.5 mL) was added ethoxymethyl chloride (0.142 mL, 1.54 mmol) at rt. The mixture was allowed to stir for 2 d before saturated aq NH$_4$Cl (15 mL) was added. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, concentrated in vacuo, and purified by flash chromatography (hexanes/EtOAc 3:1 to 1:1) to afford the title compound **8** (197 mg, 0.67 mmol, 87%) as a colorless oil.

First Coupling and Elaboration. *(S)-1-(tert-Butyldimethylsilyloxy)-3-(2-((2′S,3′S)-3′-(ethoxymethoxy)-2′-hydroxy-5′-(4-methoxybenzyloxy)pentan-1′-yl)-1,3-dithian-2-yl)-butane.*[5] To a stirred solution of dithiane **8** (319 mg, 1.04 mmol) in THF (10 mL) was added *n*-BuLi (0.65 mL; 1.6 M in hexanes, 1.04 mmol) at rt under N$_2$, and the mixture was stirred for 5 min at this temperature. A solution of epoxide **12** (193 mg, 0.65 mmol) was added, and the mixture was stirred for 10 min at rt before being quenched by the addition of saturated aq NH$_4$Cl (5 mL). EtOAc (10 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, concentrated in vacuo, and purified by flash chromatography (hexanes/EtOAc 3:1) to afford the title compound (385 mg, 0.64 mmol, 98%) as a colorless oil.

(S)-3-(2-((2′S,3′S)-2′-(Benzyloxy)-3′-(ethoxymethoxy)-5′-(4-methoxybenzyloxy)pentan-1′-yl)-1,3-dithian-2-yl)-1-(tert-butyldimethylsilyloxy)butane. To a stirred solution of the secondary alcohol (334 mg, 0.55 mmol) in THF (5.6 mL) at rt under N$_2$ was added benzyl bromide (0.390 mL, 3.32 mmol) followed by KH (148 mg; 30 wt % dispersion in mineral oil, 1.11 mmol). The mixture was stirred for 5 h before being quenched with saturated aq NH$_4$Cl (5 mL). EtOAc (10 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. Purification by flash chromatography (100% hexanes to hexanes/EtOAc 9:1) afforded the title compound (326 mg, 0.47 mmol, 85%) as a colorless oil: R_f (100% hexanes to hexanes/EtOAc 9:1) = 0.23; $[\alpha]_D{}^{17}$ = −48.6 (c 0.91, CHCl$_3$); HRMS found (ESI) MH$^+$, 693.3686, $C_{37}H_{61}O_6S_2Si$ requires 693.3673; IR (film) 2950, 2928, 2885, 2855, 1613, 1513, 1463, 1388, 1361, 1247, 1089, 1033, 903, 833, 775, 735, 698 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35–7.21 (m, 7H), 6.86 (d, 2H, J = 8.8 Hz), 4.76 (d, 1H, J = 7.0 Hz), 4.67 (d, 1H, J = 7.0 Hz), 4.64 (d, 1H, J = 10.9 Hz), 4.56 (d, 1H, J = 10.9 Hz), 4.42 (s, 2H), 4.04–3.98 (m, 2H), 3.80 (s, 3H), 3.74–3.50 (m, 6H), 2.90–2.66 (m, 4H), 2.45–2.23 (m, 3H), 2.14–1.87 (m, 4H), 1.75–1.65 (m, 1H), 1.37–1.26 (m, 1H), 1.22 (t, 3H, J = 7.1 Hz), 1.11 (d, 3H, J = 6.7 Hz), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 159.1, 138.7, 130.7, 129.2, 128.1, 128.0, 127.3, 113.7, 94.3, 76.9, 72.9, 72.4, 71.6, 67.1, 63.6, 61.9, 59.2, 55.3, 35.4, 35.1, 34.6, 29.6, 26.0, 25.7, 25.5, 25.3, 18.3, 15.1, 14.5, −5.3, −5.3; m/z (ESI) 715 (M$^+$ + Na, 100%), 649 (3), 541 (5), 419 (4), 299 (5), 121 (9).

*(S)-3-(2-((2′S,3′S)-2′-(Benzyloxy)-3′-(ethoxymethoxy)-5′-(4-methoxybenzyloxy)pentan-1′-yl)-1,3-dithian-2-yl)butan-1-ol (**15**).* To the neat silyl protected ether (326 mg, 0.47 mmol) was added a solution of TBAF (5.0 mL; 1.0 M in THF, 5.0 mmol) at rt, and the mixture was stirred at this temperature overnight. Saturated aq NaHCO$_3$ (10 mL) was added, the layers were separated, and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 15 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated to a volume of ∼5 mL before being purified by flash chromatography (hexanes/EtOAc 3:2) to afford the title compound (265 mg, 0.46 mmol, 97%) as a colorless oil: R_f (hexanes/EtOAc 1:1) = 0.27; $[\alpha]_D{}^{16}$ = −49.3 (c 0.58, CHCl$_3$); HRMS found (ESI) (M + Na)$^+$, 601.2636, $C_{31}H_{46}NaO_6S_2$ requires 601.2628; IR (film) 2930, 2876, 1612, 1513, 1454, 1364, 1302, 1246, 1180, 1093, 1029, 819, 743, 698 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.34–7.22 (m, 7H), 6.86 (d, 2H, J = 8.7 Hz), 4.76 (d, 1H, J = 6.9 Hz), 4.67 (d, 1H, J = 6.9 Hz), 4.58 (s, 2H), 4.43 (s, 2H), 4.05–3.96 (m, 2H), 3.80 (s, 3H), 3.73 (ddd, 1H, J = 10.6, 6.9, 4.5 Hz), 3.63 (q, 2H, J = 7.0 Hz), 3.59–3.50 (m, 3H), 2.93–2.64 (m, 4H), 2.39–2.29 (m, 2H), 2.25–2.15 (m, 1H), 2.14–2.02 (m, 2H), 2.00–1.80 (m, 2H), 1.70 (dddd, 1H, J = 14.2, 8.8, 5.4, 5.4 Hz), 1.42 (dddd, 1H, 13.8, 9.7, 5.6, 4.5 Hz), 1.22 (t, 3H, J = 7.0 Hz), 1.12 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.1, 138.5, 130.6, 129.2, 128.2, 128.0, 127.4, 113.7, 94.4, 77.0, 72.9, 72.4, 71.7, 67.0, 63.7, 61.7, 59.0, 55.3, 35.6, 35.4, 34.6, 29.6, 25.8, 25.4, 25.3, 15.1, 14.7; m/z (ESI) 601 (M$^+$ + Na, 100%), 493 (48), 385 (24), 347 (24), 313 (36), 217 (12), 121 (90).

*(S)-3-(2-((2′S,3′S)-2′-(Benzyloxy)-3′-(ethoxymethoxy)-5′-(4-methoxybenzyloxy)pentan-1′-yl)-1,3-dithian-2-yl)butanal (**18**).*[5] To a stirred solution of alcohol **15** (64 mg, 0.11 mmol) in CH$_2$Cl$_2$ (2 mL) were added 4 Å MS (50 mg), *N*-methylmorpholine-*N*-oxide (22 mg, 0.19 mmol), and tetra-*n*-propylammonium perruthenate (4 mg, 0.011 mmol), and the mixture was stirred at rt. After 20 min, the mixture was quickly filtered through a plug of silica (2 cm), and the silica was flushed with hexanes/EtOAc 2:1 (5 mL). The filtrate was concentrated in vacuo to afford pure title compound **18** (55 mg, 0.10 mmol, 86%) as a colorless oil.

(S)-3-(2-((2′S,3′S)-2′-(Benzyloxy)-3′-(ethoxymethoxy)-5′-(4-methoxybenzyloxy)pentan-1′-yl)-1,3-dithian-2-yl)butanal toluenesulfonylhydrazone. To a stirred solution of aldehyde **18** (15 mg, 0.026 mmol) in THF (1 mL) was added tosylhydrazine (5 mg, 0.026 mmol) at rt, and the solution was stirred for 20 min. Concentration and purification by flash chromatography (hexanes/EtOAc 1:2) afforded the title compound (19 mg, 0.025 mmol, 95%) as a colorless oil: R_f (hexanes/EtOAc 1:1) = 0.20; $[\alpha]_D{}^{16}$ = −47.2 (c 0.95, CHCl$_3$); HRMS found (ESI) (M + Na)$^+$, 767.2837, $C_{38}H_{52}N_2NaO_7S_3$ requires 767.2829; IR (film) 3203, 3065, 3034, 2927, 2857, 1612, 1513, 1453, 1361, 1247, 1166, 1093, 1030, 813, 701, 669; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22 (d, J = 8.5 Hz, 2H), 7.54 (br s, 1H), 7.30–7.22 (m, 9H), 7.05 (dd, J = 6.2, 4.3 Hz, 1H), 7.85 (d, J = 8.5 Hz, 2H), 4.72 (d, J = 6.9 Hz, 1H), 4.64 (d, J = 6.9 Hz, 1H), 4.56 (d, J = 11.1 Hz, 1H), 4.52 (d, J = 11.1 Hz, 1H), 4.42 (s, 3H), 4.02–3.98 (m, 1H), 3.95–3.92 (m, 1H), 3.79 (s, 3H), 3.64–3.50 (m, 4H), 2.92–2.78 (m, 2H), 2.73–

2.59 (m, 2H), 2.40 (s, 3H), 2.33−2.12 (m, 3H), 2.09−1.88 (m, 3H), 1.86−1.77 (m, 1H), 1.70−1.61 (m, 1H), 1.20 (t, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.1, 152.8, 150.0, 144.0, 138.4, 135.3, 130.6, 129.6, 129.2, 128.2, 128.0, 127.9, 127.6, 127.4, 113.7, 94.4, 77.0, 72.7, 72.4, 71.6, 67.0, 63.6, 58.3, 55.3, 37.1, 35.5, 34.6, 29.5, 25.7, 25.5, 25.1, 21.5, 15.1, 14.4; *m*/*z* (ESI) 767 (M$^+$ + Na, 100%), 611 (6), 583 (20), 557 (8), 347 (20), 303 (12), 121 (12). To form the *N*-TBS hydrazone derivative (**17**), a solution of the above tosyl hydrazone (19 mg, 0.025 mmol) in THF (0.5 mL) at −78 °C was treated with NEt$_3$ (5 mg, 0.05 mmol) followed by TBSOTf (9.8 mg, 0.035 mmol) and stirred for 20 min. The reaction was quenched with MeOH, diluted with hexanes, washed with saturated NaHCO$_3$ and brine, dried over MgSO$_4$, filtered, and concentrated to afford **17**, which was used without further purification.

Synthesis of Dithiane C25−C31 Fragment 6. *(2S,4S)-1-(tert-Butyldiphenylsilyloxy)-2-(ethoxymethoxy)-4,5-epoxypentane (**21**).* To a stirred solution of triol **19** (998 mg, 2.66 mmol) in THF (120 mL) was added KHMDS (6.90 mL, 0.5 M solution in toluene, 3.46 mmol) at rt, and the solution was stirred for 5 min. 1-(2,4,6-Triisopropyltoluenesulfonyl)-imidazole (1.16 g, 3.46 mmol) was added in one portion, and the reaction was stirred for 1 h at rt. Saturated aq NH$_4$Cl (10 mL) was added, the layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was taken up in CH$_2$Cl$_2$ (30 mL), and to the mixture were added triethylamine (2.80 mL, 16.0 mmol) and ethoxymethyl chloride (0.724 mL, 8.00 mmol). This mixture was allowed to stir at rt for 2 d before the addition of saturated aq NH$_4$Cl (15 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, concentrated in vacuo, and purified by flash chromatography (hexanes/EtOAc 3:1) to afford the title compound **21** (582 mg, 1.40 mmol, 53% over the two steps) as a colorless oil: R_f (hexanes/EtOAc 3:1) = 0.43; $[\alpha]_D^{18}$ = −25.9 (*c* 1.10, CHCl$_3$); HRMS found (FAB) MH$^+$, 415.2296, C$_{24}$H$_{35}$O$_4$Si requires 415.2305; IR ν_{max} (film) 2927, 2856, 1472, 1427, 1390, 1184, 1110, 1029, 822, 740, 697, 613, 518 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68−7.65 (m, 4H), 7.46−7.35 (m, 6H), 4.78 (d, 1H, *J* = 6.8 Hz), 4.72 (d, 1H, *J* = 6.8 Hz), 3.91 (dddd, 1H, *J* = 7.9, 5.3, 5.3, 4.8 Hz), 3.74−3.52 (m, 4H), 3.08−3.02 (m, 1H), 2.77 (dd, 1H, *J* = 5.1, 4.0 Hz), 2.49 (dd, 1H, *J* = 5.0, 2.7 Hz), 1.85−1.68 (m, 2H), 1.15 (t, 3H, *J* = 7.1 Hz), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 135.6, 133.4, 129.7, 127.7, 94.7, 75.5, 66.1, 63.4, 49.5, 47.6, 35.4, 26.8, 19.2, 15.0; *m*/*z* (EI) 357 (M$^+$ − ^{t}Bu, 2.5%), 327 (6), 281 (12), 241 (40), 227 (19), 199 (26), 183 (27), 163 (37), 135 (25), 91(31), 59 (100), 41 (18).

(2S,4S)-1-(tert-Butyldiphenylsilyloxy)-5-(1,3-dithian-2-yl)-2-(ethoxymethoxy)-4-pentanol. To a stirred solution of 1,3-dithiane (1.14 g, 9.47 mmol) in THF (16 mL) under N$_2$ at −20 °C was added *n*-BuLi (5.92 mL; 1.6 M in hexanes, 9.47 mmol), and the mixture was stirred for 30 min. To this mixture was added a solution of epoxide **21** (1.31 mg, 3.16 mmol) in THF (3.5 mL), and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of saturated aq NH$_4$Cl (5 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and purified by flash chromatography (hexanes/EtOAc 3:1) to afford the title compound (1.48 g, 2.77 mmol, 88%) as a colorless oil: R_f (hexanes/EtOAc 3:1) = 0.28; $[\alpha]_D^{20}$ = −30.2 (*c* 1.96, CHCl$_3$); HRMS found (EI) M$^+$, 534.2303, C$_{28}$H$_{42}$O$_4$S$_2$Si requires 534.2294; IR (film) 3461br, 2931, 2899, 2857, 1472, 1427, 1390, 1104, 1028, 823, 752, 697, 666, 613 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68−7.65 (m, 4H), 7.45−7.36 (m, 6H), 4.83 (d, 1H, *J* = 6.8 Hz), 4.73 (d, 1H, *J* = 6.8 Hz), 4.30 (dd, 1H, *J* = 9.9, 4.8 Hz), 4.24−4.14 (m, 1H), 3.99−3.91 (m, 1H), 3.79−3.44 (m, 4H), 2.96−2.77 (m, 4H), 2.16−2.04 (m, 1H), 1.97−1.73 (m, 3H), 1.59−1.54 (m, 2H), 1.20 (t, 3H, *J* = 7.2 Hz), 1.05 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 135.5, 133.2, 129.7, 127.7, 96.0, 76.5, 66.8, 64.1, 64.1, 44.0, 42.6, 38.8, 30.3, 29.9, 26.8, 26.0, 19.1, 15.0; *m*/*z* (EI) 534 (M$^+$, 0.2%), 516 (M$^+$ − H$_2$O, 0.1), 431 (23), 293 (10), 267 (11), 241 (91), 207 (30), 199 (100), 163 (46), 135 (33), 119 (62), 59 (39), 44 (99).

*(2S,4S)-1-(tert-Butyldiphenylsilyloxy)-5-(1,3-dithian-2-yl)-2-(ethoxymethoxy)-4-methoxypentane (**6**).*[5] To a stirred solution of the secondary alcohol (314 mg, 0.59 mmol) in THF (6 mL) at rt was added methyl iodide (0.110 mL, 1.76 mmol), followed by potassium *tert*-butoxide (99 mg, 0.88 mmol) in one portion. The reaction was quenched after 10 min by the addition of saturated aq NH$_4$Cl (2 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc 9:1) afforded the title compound **6** (263 mg, 0.48 mmol, 82%) as a colorless oil.

Final Coupling and Elaboration. *(2S,4S)-1-(tert-Butyldiphenylsilyloxy)-5-(2-(3′-(tert-butyldiphenylsilyloxy)propan-1′-yl)-1,3-dithian-2-yl)-2-(ethoxymethoxy)-4-methoxypentane.* To a stirred solution of dithiane **6** (20 mg, 0.036 mmol) in a 10:1 mixture of THF−HMPA (0.3 mL) at −78 °C was added *t*-BuLi (0.023 mL; 1.7 M solution in heptane, 0.038 mmol), and the mixture was stirred at this temperature for 15 min. To this mixture was added a solution of iodide **22** (7.8 mg, 0.018 mmol) in THF−HMPA (10:1; 0.2 mL), and the mixture was stirred at −78 °C for 30 min before being quenched by the addtion of saturated aq NH$_4$Cl (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layers were combined, washed with brine, dried over MgSO$_4$, and concentrated in vacuo. Purification by flash chromatography (hexane/EtOAc 9:1) afforded the title compound (11.3 mg, 0.013 mmol, 73%) as a colorless oil: R_f (hexanes/EtOAc 9:1) = 0.25; $[\alpha]_D^{22}$ = −10.2 (*c* 0.53, CHCl$_3$); HRMS found (ESI) (M + Na)$^+$, 867.3944, C$_{48}$H$_{68}$NaO$_5$S$_2$Si$_2$ requires 867.3939; IR (film) 2930, 2900, 1472, 1427, 1389, 1106, 1031, 823, 755, 740, 700, 613 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70−7.66 (m, 8H), 7.43−7.35 (m, 12H), 4.80 (d, 1H, *J* = 6.8 Hz), 4.71 (d, 1H, *J* = 6.8 Hz), 3.84−3.79 (m, 1H), 3.73−3.60 (m, 6H), 3.57−3.50 (m, 1H), 3.30 (s, 3H), 2.88−2.67 (m, 4H), 2.12−2.02 (m, 3H), 1.99−1.86 (m, 3H), 1.85−1.68 (m, 4H), 1.13 (t, 3H, *J* = 7.0 Hz), 2 × 1.05 (s, 9 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 135.6, 133.5, 129.6, 127.6, 95.1, 75.7, 75.0, 66.7, 63.9, 56.1, 52.5, 44.1, 38.4, 35.5, 27.9, 26.9, 26.8, 26.1, 25.2, 19.2, 15.1.

(1R,3S)-3-(2-((2′S,3′S)-2′-(Benzyloxy)-3′-(ethoxymethoxy)-5′-(4-methoxybenzyloxy)pentan-1′-yl)-1,3-dithian-2-yl)-1-(2-((2″S,4″S)-5″-(tert-butyldiphenylsilyloxy)-4″-(ethoxymethoxy)-2″-methoxypentan-1″-yl)-1,3-dithian-2-yl)butan-1-ol (24a) and (1S,3S)-3-(2-((2′S,3′S)-2′-(Benzyloxy)-3′-(ethoxymethoxy)-5′-(4-methoxybenzyloxy)-pentan-1′-yl)-1,3-dithian-2-yl)-1-(2-((2″S,4″S)-5″-(tert-butyldiphenylsilyloxy)-4″-

*(ethoxymethoxy)-2″-methoxypentan-1″-yl)-1,3-dithian-2-yl)butan-1-ol (**24b**).*[5] To a stirred solution of dithiane **6** (138 mg, 0.25 mmol) in THF (4 mL) were added a premixed solution of *n*-BuLi (0.126 mL; 1.6 M in hexane, 0.202 mmol) and di-*n*-butylmagnesium (0.050 mL; 1.0 M solution in heptane, 0.050 mmol), and the mixture was stirred for 20 min at rt. To this mixture was added a solution of aldehyde **18** (55 mg, 0.10 mmol) in THF (1 mL), and the resulting mixture was stirred for 10 min before being quenched by saturated aq NH_4Cl (5 mL). EtOAc (10 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (hexanes/EtOAc 9:1 to 3:1) to afford a 3:2 ratio of diastereomeric alcohols **24a** and **24b** (84 mg, 0.08 mmol, 78%) as a colorless oil and recovered dithiane **6** (85 mg, 0.16 mmol) also as a colorless oil. For characterization purposes, the diastereomeric alcohols were separated by preparative thin layer chromatography (PTLC) (hexanes/EtOAc 3:1) to separately afford alcohols **24a** (48 mg, 0.043 mmol) and **24b** (32 mg, 0.028 mmol), both as colorless oils. Bisdithiane **24a**: R_f (hexanes/EtOAc 3:1) = 0.25; $[\alpha]_D^{20}$ = −29.8 (*c* 1.07, $CHCl_3$); HRMS found (ESI) $(M + Na)^+$, 1147.4917, $C_{60}H_{88}NaO_{10}S_4Si$ requires 1147.4922; IR (film) 2930, 2889, 2857, 1725, 1612, 1513, 1461, 1427, 1390, 1362, 1276, 1247, 1180, 1095, 1031, 823, 751, 701, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.45−7.23 (m, 13H), 6.86 (d, 2H, *J* = 8.6 Hz), 4.78 (d, 1H, *J* = 7.0 Hz), 4.77 (d, 1H, *J* = 7.0 Hz), 4.72 (d, 1H, *J* = 7.0 Hz), 4.67 (d, 1H, *J* = 7.0 Hz), 4.60 (s, 2H), 4.42 (s, 2H), 4.06−4.03 (m, 2H), 3.89−3.73 (m, 7H), 3.70−3.50 (m, 8H), 3.29 (s, 3H), 2.92−2.59 (m, 9H), 2.41 (d, 1H, *J* = 15.6 Hz), 2.34−2.26 (m, 1H), 2.25 (dd, 1H, *J* = 15.6, 7.5 Hz), 2.17−1.84 (m, 8H), 1.80−1.65 (m, 2H), 1.43−1.33 (m, 1H), 1.27 (d, 3H, *J* = 6.5 Hz), 1.21 (t, 3H, *J* = 7.1 Hz), 1.14 (t, 3H, *J* = 7.1 Hz), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 138.6, 135.6, 133.4, 130.7, 129.7, 129.2, 128.2, 127.9, 127.7, 127.3, 113.7, 94.8, 94.3, 77.3, 75.8, 75.7, 75.4, 72.7, 72.4, 71.7, 67.1, 66.3, 63.6, 63.4, 60.1, 58.6, 55.6, 55.3, 40.0, 39.7, 37.0, 34.8, 34.5, 29.6, 26.9, 26.1, 25.9, 25.6, 25.4, 25.4, 24.9, 19.2, 16.7, 15.1, 15.1; *m*/*z* (ESI) 1147 (M^+ + Na, 100%), 1039 (92), 931 (73), 857 (38), 599 (37), 495 (25), 423 (33).

*(1R,3S)-3-(2-((2′S,3′S)-2′-(Benzyloxy)-3′-(ethoxymethoxy)-5′-(4-methoxybenzyloxy)pentan-1′-yl)-1,3-dithian-2-yl)-1-(2-((2″S,4″S)-5″-(tert-butyldiphenylsilyloxy)-4″-(ethoxymethoxy)-2″-methoxypentan-1″-yl)-1,3-dithian-2-yl)-1-methoxybutane (**25**).* To a stirred solution of alcohol **24a** (29 mg, 0.026 mmol) and methyl iodide (0.2 mL, 3.21 mmol) in THF (1 mL) was added KH (35 mg; 30 wt % dispersion in mineral oil, 0.26 mmol) at rt, and the mixture was stirred overnight under N_2. Saturated aq NH_4Cl was added (4 mL), followed by EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by PTLC (hexanes/EtOAc 4:1) afforded the title compound **25** (26 mg, 0.023, 89%) as a colorless oil: R_f (hexanes/EtOAc 3:1) = 0.38; $[\alpha]_D^{20}$ = −41.9 (*c* 0.67, $CHCl_3$); HRMS found (ESI) $(M + Na)^+$, 1161.5081, $C_{61}H_{90}NaO_{10}S_4Si$ requires 1161.5078; IR (film) 2960, 2927, 2857, 1727, 1613, 1513, 1463, 1454, 1427, 1391, 1362, 1247, 1178, 1092, 1032, 822, 740, 701, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.43−7.35 (m, 6H), 7.33−7.22 (m, 7H), 6.85 (d, 2H, *J* = 8.5 Hz), 4.86 (d, 1H, *J* = 6.9 Hz), 4.78 (d, 1H, *J* = 6.9 Hz), 4.77 (d, 1H, *J* = 6.8 Hz), 4.66 (d, 1H, *J* = 6.8 Hz), 4.64 (d, 1H, *J* = 11.3 Hz), 4.57 (d, 1H, *J* = 11.3 Hz), 4.41 (s, 2H), 4.09−4.03 (m, 2H), 3.90−3.82 (m, 2H), 3.80 (s, 3H), 3.75−3.50 (m, 9H), 3.44 (s, 3H), 3.33 (s, 3H), 3.05−2.56 (m, 9H), 2.48 (d, 1H, *J* = 15.4 Hz), 2.24 (dd, 1H, *J* = 15.5, 4.8 Hz), 2.19−2.04 (m, 3H), 2.02−1.82 (m, 5H), 1.78−1.67 (m, 3H), 1.43 (dt, 1H, *J* = 14.5, 8.0 Hz), 1.24 (d, 3H, *J* = 6.8 Hz), 1.21 (t, 3H, *J* = 7.1 Hz), 1.16 (t, 3H, *J* = 7.1 Hz), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 138.7, 135.7, 133.6, 130.7, 129.6, 129.2, 128.2, 127.6, 127.3, 127.2, 113.7, 95.3, 94.3, 87.4, 77.6, 76.0, 75.1, 72.4, 72.4, 71.4, 67.1, 67.1, 63.6, 63.3, 60.8, 60.4, 57.5, 55.9, 55.3, 40.5, 39.1, 39.1, 35.7, 34.5, 29.6, 26.9, 26.7, 26.4, 25.9, 25.6, 25.5, 24.7, 19.2, 16.5, 15.1, 15.1; *m*/*z* (ESI) 1162 (M^+ + Na, 100%), 1055 (23), 963 (7), 873 (7), 731 (8), 657 (7), 583 (14), 495 (15), 423 (12).

(1R,3S)-3-(2-((2′S,3′S)-2′-(Benzyloxy)-3′-hydroxy-5′-(4-methoxybenzyloxy)pentan-1′-yl)-1,3-dithian-2-yl)-1-(2-((2″S,4″S)-5″-(tert-butyldiphenylsilyloxy)-4″-hydroxy-2″-methoxypentan-1″-yl)-1,3-dithian-2-yl)-1-methoxybutane. To a stirred solution of bisdithiane **25** (21.5 mg, 0.019 mmol) in *t*-butanol (0.6 mL) was added pyridinium *p*-toluenesulfonate (46 mg, 0.18 mmol), and the mixture was heated at reflux for 5.5 h. To the solution was added CH_2Cl_2 (0.2 mL), and the mixture was introduced directly onto the PTLC plate and purified by PTLC (hexanes/EtOAc 3:1) to afford the title compound (12.9 mg, 0.013 mmol, 66%) as a colorless oil: R_f (hexanes/EtOAc 2:1) = 0.19; $[\alpha]_D^{17}$ = −23.8 (*c* 0.75, $CHCl_3$); HRMS found (ESI) $(M + Na)^+$, 1045.4233, $C_{55}H_{78}NaO_8S_4Si$ requires 1045.4241; IR (film) 2925, 2856, 1732, 1612, 1513, 1462, 1427, 1361, 1247, 1088, 1035, 909, 822, 737, 702, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.46−7.35 (m, 6H), 7.32−7.23 (m, 7H), 6.88 (d, 2H, *J* = 8.7 Hz), 4.71 (d, 1H, *J* = 11.4 Hz), 4.60 (d, 1H, *J* = 11.4 Hz), 4.45 (s, 2H), 4.09−3.91 (m, 4H), 3.81 (s, 3H), 3.73 (dt, 1H, *J* = 9.2, 4.8 Hz), 3.68−3.55 (m, 4H), 3.47 (s, 3H), 3.36 (s, 3H), 3.08−2.61 (m, 9H), 2.53 (d, 1H, *J* = 15.4 Hz), 2.30 (dd, 1H, *J* = 15.5, 5.4 Hz), 2.29−2.20 (m, 1H), 2.11 (dd, 1H, *J* = 15.4, 7.5 Hz), 1.99−1.78 (m, 8H), 1.60 (ddd, 1H, *J* = 14.7, 6.8, 2.8 Hz), 1.44 (dt, 1H, *J* = 14.9, 8.2 Hz), 1.27 (d, 3H, *J* = 6.2 Hz), 1.07 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 138.8, 135.6, 133.4, 130.1, 129.7, 129.4, 128.3, 127.7, 127.4, 127.3, 113.9, 87.3, 79.6, 77.2, 73.1, 72.0, 71.9, 69.7, 69.5, 68.2, 61.0, 60.0, 57.6, 56.6, 55.3, 40.4, 39.0, 38.5, 35.5, 34.9, 31.3, 26.9, 26.7, 26.4, 26.0, 25.7, 25.3, 24.7, 19.3, 16.7; *m*/*z* (ESI) 1045 (M^+ + Na, 98%), 937 (100), 907 (10), 829 (55), 715 (32), 607 (48), 525 (12), 437 (12), 365 (13).

*(2S,3S,5R,7S,9S,11S,13R,15S)-3-(Benzyloxy)-9-((tert-butyldiphenylsilyloxy)methyl)-2-(1′-(4-methoxybenzyloxy)-ethan-2′-yl)-11-methoxy-13-methoxy-15-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadecane (**26**).* To a stirred solution of the diol (9.6 mg, 0.0094 mmol) in a 4:1 mixture of $CH_3CN−H_2O$ (0.5 mL) was added $HgCl_2$ (15 mg, 0.055 mmol), and the resulting mixture was stirred at 0 °C for 5 h. The reaction was quenched by the addition of saturated aq $NaHCO_3$ (2 mL), and the resulting mixture was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (hexanes/EtOAc 4:1) to afford the title compound **26** (4.8 mg, 0.0058 mmol, 62%) as a colorless oil: R_f (hexanes/EtOAc 3:1) = 0.38; $[\alpha]_D^{20}$ = +6.7 (*c* 0.32, EtOAc); HRMS found (ESI) $(M + Na)^+$, 847.4214, $C_{49}H_{64}NaO_9Si$ requires 847.4212; IR (film) 2955, 2927, 1728,

1613, 1587, 1513, 1463, 1456, 1428, 1380, 1360, 1247, 1110, 1095, 1072, 1010, 951, 822, 739, 701, 606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.67 (m, 4H), 7.40−7.26 (m, 11H), 7.11 (d, 2H, J = 8.6 Hz), 6.79 (d, 2H, J = 8.6 Hz), 4.52 (d, 1H, J = 11.9 Hz), 4.34 (d, 1H, J = 11.9 Hz), 4.24−4.18 (m, 1H), 4.19 (d, 1H, J = 11.6 Hz), 4.14 (d, 1H, J = 11.6 Hz), 4.09−4.04 (m, 1H), 3.89−3.76 (m, 5H), 3.73−3.63 (m, 2H), 3.49−3.36 (m, 2H), 3.37 (s, 3H), 3.35 (s, 3H), 3.03 (dd, 1H, J = 11.4, 3.9 Hz), 2.25 (br d, 1H, J = 11.8 Hz), 2.18−2.16 (m, 2H), 2.01−1.76 (m, 5H), 1.67 (dt, 1H, J = 11.6, 3.5 Hz), 1.35−1.22 (m, 2H), 1.05 (s, 9 H), 0.95 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 138.4, 135.9, 135.7, 134.0, 133.5, 130.8, 129.5, 129.1, 128.3, 127.6, 127.6, 127.4, 127.3, 113.6, 107.8, 99.7, 81.8, 79.9, 78.3, 73.6, 72.3, 71.1, 69.6, 67.6, 66.5, 57.2, 2 × 55.3, 63.7, 38.1, 37.9, 34.0, 29.2, 27.3, 26.9, 19.3, 16.4; m/z (ESI) 847 (M^+ + Na, 29%), 739 (100), 721 (13), 551 (8), 479 (17), 451 (31), 425 (33), 121 (15).

(1S,3S)-3-(2-((2′S,3′S)-2′-(Benzyloxy)-3′-hydroxy-5′-(4-methoxybenzyloxy)-pentan-1′-yl)-1,3-dithian-2-yl)-1-(2-((2″S,4″S)-5″-(tert-butyldiphenylsilyloxy)-4″-hydroxy-2″-methoxypentan-1″-yl)-1,3-dithian-2-yl)-butan-1-ol.[5] To a stirred solution of bisdithiane **24b** (8.2 mg, 0.007 mmol) in *t*-butanol (0.4 mL) was added pyridinium *p*-toluenesulfonate (17 mg, 0.068 mmol), and the mixture was heated at reflux for 2 h. To the solution was added CH_2Cl_2 (0.2 mL), and the mixture was introduced directly onto the PTLC plate and purified by PTLC (hexanes/EtOAc 3:1) to afford the title compound (4.6 mg, 0.004 mmol, 63%) as a colorless oil.

*(2S,3S,5R,7S,9S,11S,13S,15S)-3-(Benzyloxy)-9-((-butyldiphenylsilyloxy)methyl)-2-(1′-(4-methoxybenzyloxy)-ethan-2′-yl)-13-hydroxy-11-methoxy-15-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadecane (**27**).*[5] To a stirred solution of the triol (4.4 mg, 0.004 mmol) in a 4:1 mixture of CH_3CN-H_2O (0.5 mL) was added $HgCl_2$ (15 mg, 0.055 mmol), and the resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched by the addition of saturated aq $NaHCO_3$ (2 mL), and the resulting mixture was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (hexanes/EtOAc 4:1) to afford the title compound **27** (2.7 mg, 0.003 mmol, 74%) as a colorless oil.

*(2S,4S)-6-((2S,4S,5R,7S,8S)-8-(Benzyloxy)-7-(2-((4-methoxybenzyl)oxy)ethyl)-4-methyl-1,6-dioxaspiro[4.4]-nonan-2-yl)-1-((tert-butyldiphenylsilyl)oxy)-4-methoxy-6-oxohexan-2-yl 1H-imidazole-1-carbothioate (**28**).*[25] To a stirred solution of alcohol **27** (1.7 mg, 2.1 μmol) in THF (0.6 mL) was added 1,1′-thiocarbonyldiimidazole (9 mg, 0.050 mmol), and the mixture was heated at reflux for 48 h. The mixture was then introduced directly onto the PTLC plate and purified by PTLC (hexanes/EtOAc 2:1) to afford the title compound **28** (1.5 mg, 1.6 μmol, 78%) as a colorless oil: R_f (hexanes/EtOAc 2:1) = 0.19; $[\alpha]_D^{20}$ = −26.5 (c 0.10, $CHCl_3$); HRMS found (ESI) MH^+, 921.4171, $C_{52}H_{65}N_2O_9SSi$ requires 921.4175; IR ν_{max} (film) 2961, 2929, 2857, 1710, 1615, 1514, 1463, 1386, 1284, 1247, 1096, 1027, 969, 824, 741, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (br s), 7.63−7.55 (m, 5H), 7.43−7.25 (m, 11H), 7.20 (d, 2H, J = 8.8 Hz), 7.04 (br s, 1H), 6.82 (d, 2H, J = 8.8 Hz), 5.89−5.82 (m, 1H), 4.53 (d, 1H, J = 12.1 Hz), 4.42−4.24 (m, 5H), 4.11−4.06 (m, 1H), 3.96 (dd, 1H, J = 11.6, 3.5 Hz), 3.79 (dd, 1H, J = 11.6, 4.7 Hz), 3.77 (s, 3H), 3.74−3.65 (m, 1H), 3.56−3.49 (m, 2H), 3.22 (s, 3H), 2.99 (dd, 1H, J = 17.6, 4.8 Hz), 2.75 (dd, 1H, J = 17.6, 7.3 Hz), 2.36−2.27 (m, 2H), 2.18−2.04 (m, 3H), 2.01−1.93 (m, 1H), 1.88−1.69 (m, 2H), 1.26−1.24 (m, 1H), 1.03−1.00 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 159.0, 137.8, 136.9, 135.5, 132.9, 129.8, 129.1, 128.3, 128.1, 127.8, 127.7, 127.5, 127.3, 115.4, 113.7, 82.5, 81.7, 78.8, 78.1, 73.2, 72.5, 71.1, 67.3, 64.4, 57.2, 55.3, 41.5, 40.9, 39.9, 36.1, 35.5, 29.7, 26.7, 19.2, 12.1; m/z (ESI) 921 (MH^+, 0.5%), 397 (18), 259 (49), 189 (19), 139 (73), 121 (100).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Warabi, K.; Williams, D. E.; Patrick, B. O.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 508. (b) Williams, D. E.; Keyzers, R. A.; Warabi, K.; Desjardine, K.; Riffell, J. L.; Roberge, M.; Andersen, R. J. *J. Org. Chem.* **2007**, 72, 9842. (c) Williams, D. E.; Roberge, M.; Soest, R. V.; Andersen, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 5296.

(2) McCluskey, A.; Sim, A. T. R.; Sakoff, J. A. *J. Med. Chem.* **2002**, *45*, 1151.

(3) (a) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4121. (b) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4125. (c) Liu, J.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 2273. (d) Pan, Y.; De Brabander, J. K. *Synlett* **2006**, 853. (e) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Maltas, P.; Moessner, C. *Chem. Commun.* **2006**, 4186. (f) Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997. (g) Liu, J.; Yang, J. H.; Ko, C.; Hsung, R. P. *Tetrahedron Lett.* **2006**, *47*, 6121. (h) Fürstner, A.; Fenster, M. D. B.; Fasching, B.; Godbout, C.; Radkowski, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 5506. (i) Fürstner, A.; Fenster, M. D. B.; Fasching, B.; Godbout, C.; Radkowski, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 5510. (j) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Genovino, J.; Lim, J. H.; Moessner, C. *Chem. Commun.* **2007**, 1852. (k) Smith, A. B. III; Kim, D.-S. *Org. Lett.* **2007**, *9*, 3311. (l) Wang, C.; Forsyth, C. J. *Heterocycles* **2007**, *72*, 621. (m) Fürstner, A.; Fasching, B.; O'Neil, G. W.; Fenster, M. D. B.; Godbout, C.; Ceccon, J. *Chem. Commun.* **2007**, 3045. (n) Keaton, K. A.; Phillips, A. J. *Org. Lett.* **2008**, *10*, 1083. (o) Chandrasekhar, S.; Rambabu, C.; Reddy, A. S. *Org. Lett.* **2008**, *10*, 4355. (p) Yang, J.-H.; Liu, J.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 2525. (q) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3016. (r) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3021. (s) O'Neil, G. W.; Ceccon, J.; Benson, S.; Collin, M.-P.; Fasching, B.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9940. (t) Benson, S.; Collin, M.-P.; O'Neil, G. W.; Ceccon, J.; Fasching, B.; Fenster, M. D. B.; Godbout, C.; Radkowski, K.; Goddard, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9946. (u) Paterson, I.; Dalby, S. M. *Nat. Prod. Rep.* **2009**, *26*, 865. (v) Sabitha, G.; Rao, A. S.; Yadav, J. S. *Synthesis* **2010**, 505. (w) Smith, A. B. III; Smits, H.; Kim, D.-S. *Tetrahedron* **2010**, *66*, 6597. (x) Benson, S.; Collin, M.-P.; Arlt, A.; Gabor, B.; Goddard, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2011**, No. 10.1002/anie.201103270.

(4) Brimble, M. A.; Fares, F. A. *Tetrahedron* **1999**, *55*, 7661.

(5) Chen, J. L.-Y.; Brimble, M. A. *Chem. Commun.* **2010**, *46*, 3967.

(6) (a) Smith, A. B. III; Wuest, W. M. *Chem. Commun.* **2008**, 5883. (b) Smith, A. B. III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365. (c) Yus, M. Y.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147. (d) Smith, A. B. III; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35.

(7) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(8) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.

(9) De, S. K. *Tetrahedron Lett.* **2004**, *45*, 1035.

(10) Smith, A. B. III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468.

(11) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491.

(12) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(13) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 448.

(14) Pearson, W. H.; Lian, B. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1724.

(15) Smith, A. B. III; Condon, S. M.; McCauley, J. A.; Leazer, J. L. Jr.; Leahy, J. W.; Maleczka, R. E. Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947.

(16) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(17) Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891.

(18) Attwood, S. V.; Barrett, A. G. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1315.

(19) Corey, E. J.; Weigel, L. O.; Chanberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439.

(20) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(21) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 2339–2341.

(22) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741.

(23) Steric hindrance at the C32 alcohol prevented introduction of bulky protecting groups capable of withstanding the acidic conditions required for removal of the EOM groups. As a result, alcohol **24a** was methylated.

(24) Monti, H.; Leandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021.

(25) This compound was incorrectly assigned in our original communication as the thiocarbonyl derivative of the bis-spiroacetal **27**.

(26) Hara, A.; Morimoto, R.; Ishikawa, Y.; Nishiyama, S. *Org. Lett.* **2011**, *13*, 4036.