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A highly stereoselective synthesis of the C10–C31 (BCDEF ring) portion of pinnatoxin A

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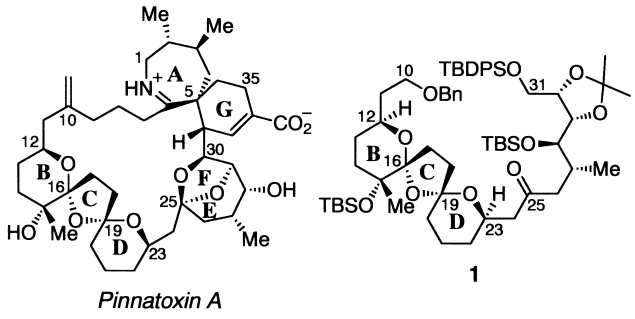
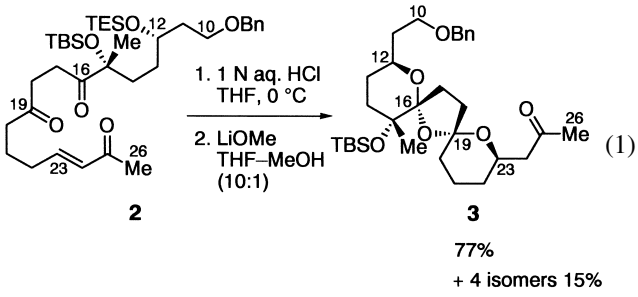
Abstract—An efficient, highly stereoselective synthesis of the C10–C31 (BCDEF ring) portion of pinnatoxin A has been achieved utilizing tandem double hemiketal formation/intramolecular hetero-Michael addition to construct the 6,5,6-dispiroketal (BCD ring) system and subsequent intramolecular ketalization to form the 5,6-bicycloketal (EF ring) system as key steps.

1. Introduction

In the preceding article,[1] a retrosynthetic analysis of pinnatoxin A was outlined, wherein the C10–C31 ketone fragment **1** became the first important target for our synthetic venture. In the synthesis of **1**, our strategic interest was centered on the construction of the 6,5,6-dispiroketal (BCD ring) system. We investigated the viability of the desired dispiroketalization via a tandem double hemiketal formation/intramolecular hetero-Michael addition process (Eq. (1)). Armed with positive results, we now embarked on the synthesis of the C10–C31 (BCDEF ring) portion of pinnatoxin A.[2]



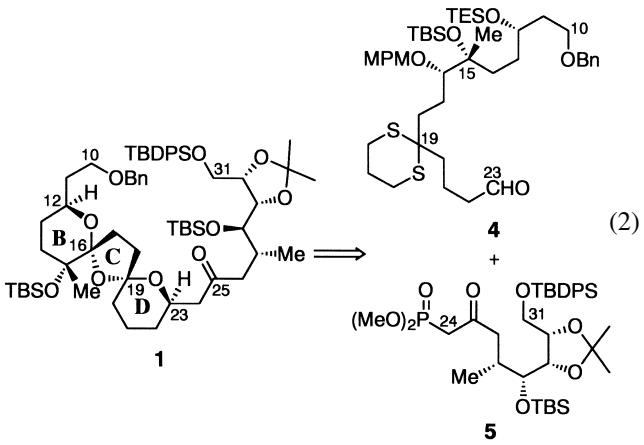


(1)

2. Results and discussions

2.1. Synthesis of the dispiroketalization precursor

According to the retrosynthetic analysis shown in the preceding paper, β-ketophosphonate **5** was initially chosen as the C24–C31 fragment (Eq. (2)). The synthesis of **5** was implemented as shown in Scheme 1. Protection of the known alcohol **6**[3] with TBSCl gave silyl ether **7** in 97% yield (Scheme 1). The benzyl group in **7** was removed by



(2)

Keywords: dispiroketal; hemiketal formation; hetero-Michael addition; internal ketalization.

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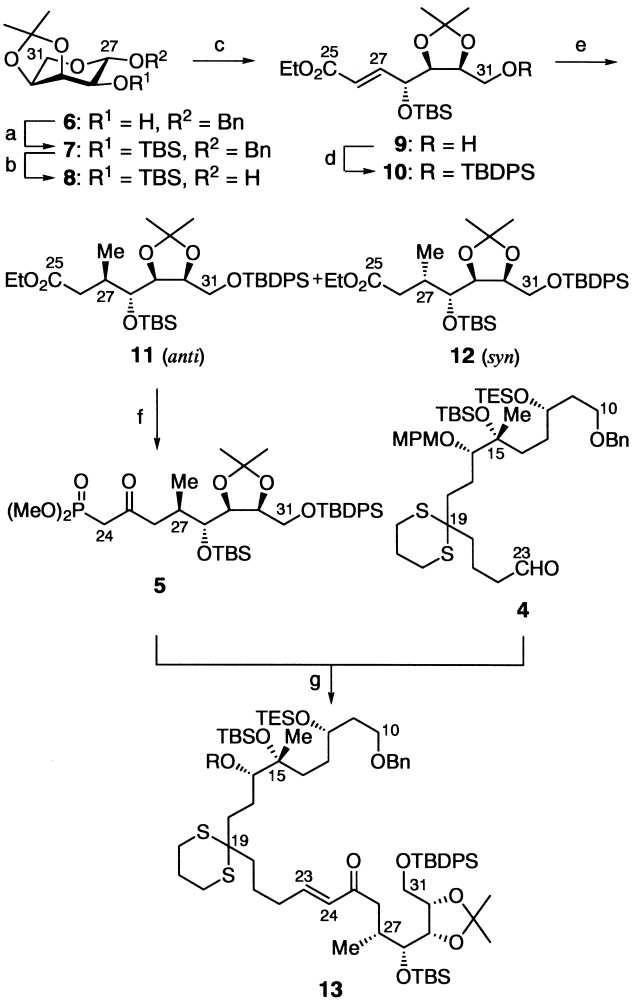
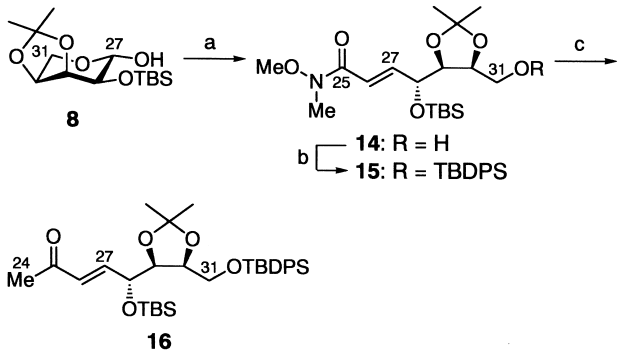


Scheme 1. *Reagents and conditions*: (a) TBSCl, imidazole, DMF, 16 h, 97%; (b) H_2, 20% $Pd(OH)_2$, EtOH, 48 h, 83%; (c) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 32 h, 98%; (d) TBDPSCl, imidazole, DMF, 13 h, 95%; (e) Me_2CuLi (10 equiv.), TMSCl (10 equiv.), THF, −20°C, 16 h, 71% of **11** and 15% of **12**; (f) $(MeO)_2P(O)CH_2Li$, THF, −78°C, 1 h, 80%; (g) LiCl, *i*-Pr_2NEt, CH_3CN, 20 h, 96%.

hydrogenolysis to afford the lactol **8**, which upon treatment with $Ph_3P{=}CHCO_2Et$ in refluxing benzene furnished (*E*) enoate **9** as a single stereoisomer in 81% yield. The resultant hydroxyl group was protected as its TBDPS ether (95%) to set up conjugate addition of methylcopper reagents to create the stereogenic center at C27. According to the Hanessian protocol[4] originally developed by Corey,[5] the crucial conjugate addition of Me_2CuLi to enoate **10** was achieved in the presence of TMSCl to provide a 4.5:1 mixture of adducts favoring the desired *anti* isomer **11** in 86% combined yield. After separation of the isomers, *anti* isomer **11** was converted to β-ketophosphonate **5** in 80% yield.[6] Horner–Wadsworth–Emmons olefination of the C10–C23 aldehyde fragment **4**[1] with **5** under Masamune conditions[7] proceeded uneventfully to furnish (*E*) enone **13** in 96% yield.

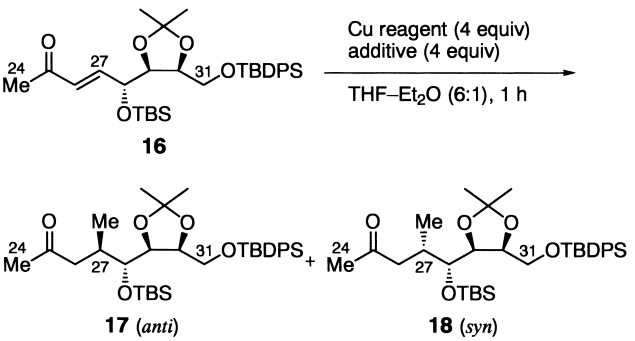
Although the synthesis of the C10–C31 enone fragment **13** was realized by the above route, this synthesis was far from optimal. The major drawback lay in the conjugate addition step. While the Hanessian conditions proved to be the only choice for this process, the conjugate addition to enoate **10** required a large (10-fold) excess of Me_2CuLi. Furthermore, this step involved a tedious chromatographic separation of *anti* isomer **11** from *syn* isomer **12** due to modest diastereoselectivity. Thus, we felt compelled to improve the efficiency of this step. We surmised that by replacing a less reactive enoate with a more reactive enone, a diversity of reaction conditions available would overcome these problems. In this scenario, the construction of the C23–C24 linkage relied on a fragment assembly aldol reaction.



Scheme 2. *Reagents and conditions*: (a) $Ph_3P{=}CHCON(OMe)Me$, benzene, reflux, 39 h, 90%; (b) TBDPSCl, imidazole, DMF, 12 h, 94%; (c) MeMgI, Et_2O, 0°C, 5 h, 94%.

Toward this end, we initiated the synthesis of (*E*) enone **16** with lactol **8** as shown in Scheme 2. An initial attempt to elaborate an enone moiety directly from **8** with $Ph_3P{=}CHCOMe$ proved to be unrewarding because of the propensity of the product to undergo an intramolecular hetero-Michael addition under Wittig conditions. We therefore adopted a stepwise approach. By treatment with a phosphorane carrying Weinreb's amide,[8] the lactol **8** was first converted to α,β-unsaturated amide **14** in 90% yield. Protection of the primary hydroxyl group as its TBDPS

Table 1. Conjugate addition of organocopper reagents to **16**



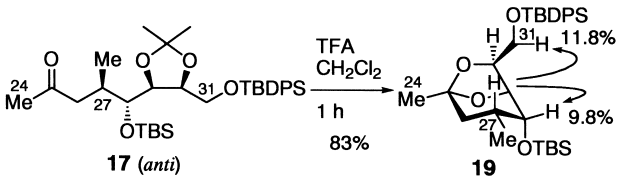
Entry	Organocopper reagents	Additive	Temperature (°C)	Yield (%)	**17**:**18**[a]
1	Me_2CuLi	–	0	83	74:26
2	Me_2CuLi	TMSCl	−78	83	95:5
3	Me_2CuLi	$BF_3{\cdot}OEt_2$	−78	54[b]	99:1
4	MeCu(CN)Li	$BF_3{\cdot}OEt_2$	−78	80	99:1
5	MeCu(CN)Li	TMSCl	−78	SM recovery	

[a] Determined by HPLC analysis (column, Zorbax® Sil, 4.6×250 mm; eluent, 9% AcOEt in hexane; flow rate 1.0 mL/min).
[b] 1,2-Adduct was obtained in 21% yield.

ether was followed by treatment with MeMgI[9] to afford the desired enone **16** in 88% yield.

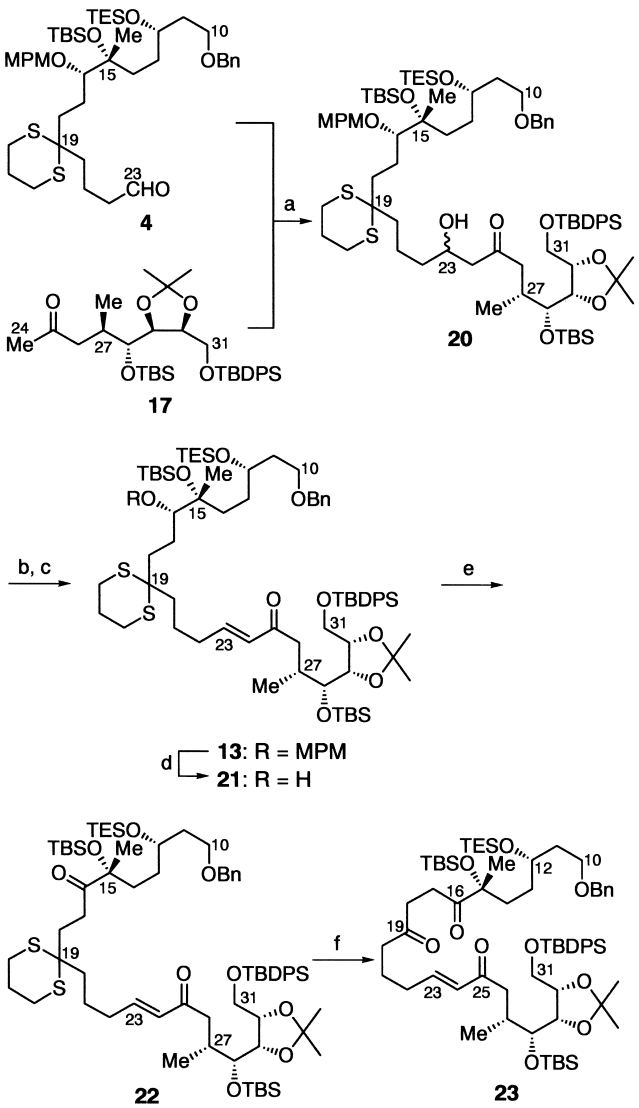
Although *anti*-selective conjugate addition reactions of methylcopper or dimethylcuprate reagents to γ-alkoxy-α,β-unsaturated esters have been extensively studied,[10] a limited number of examples for γ-alkoxy-α,β-enone system have been reported.[11–13] We initially examined conjugate addition of Me_2CuLi to the enone **16** (Table 1). It was found that the reaction with 4 equiv. of Me_2CuLi proceeded at 0°C to give a readily separable mixture of adducts in 83% yield with modest *anti*-selectivity (entry 1). It is well documented that an additive such as TMSCl or $BF_3{\cdot}OEt_2$ has a remarkable effect on the rate as well as the stereochemical outcome of conjugate addition of organocopper reagents to α,β-unsaturated carbonyl compounds.[14] Indeed the reaction of **16** with Me_2CuLi in the presence of TMSCl proceeded at −78°C to completion within an hour to afford, after acid hydrolysis, a 95:5 mixture of adducts favoring *anti*isomer **17** in 83% yield (entry 2). The use of $BF_3{\cdot}OEt_2$ exhibited much higher *anti*-selectivity (99:1), but the product yield was only 54% due to the formation of a 1,2-adduct (entry 3). We next examined the reaction with MeCu(CN)Li instead of Me_2CuLi. We found that conjugate addition of MeCu(CN)Li to **16** in the presence of $BF_3{\cdot}OEt_2$ at −78°C led to the virtually exclusive formation of *anti* adduct **17** in 80% yield (entry 4). On the other hand, the reaction with MeCu(CN)Li/TMSCl did not work (entry 5).

The stereochemistry at C27 of *anti* adduct **17** was established by ^1H NOE experiment of the bicycloketal **19** derived from **17** upon exposure to TFA in CH_2Cl_2 (Eq. (3)). C27–H showed significant NOE interactions with C28–H and C31–H, suggesting that C27–H was axially disposed.

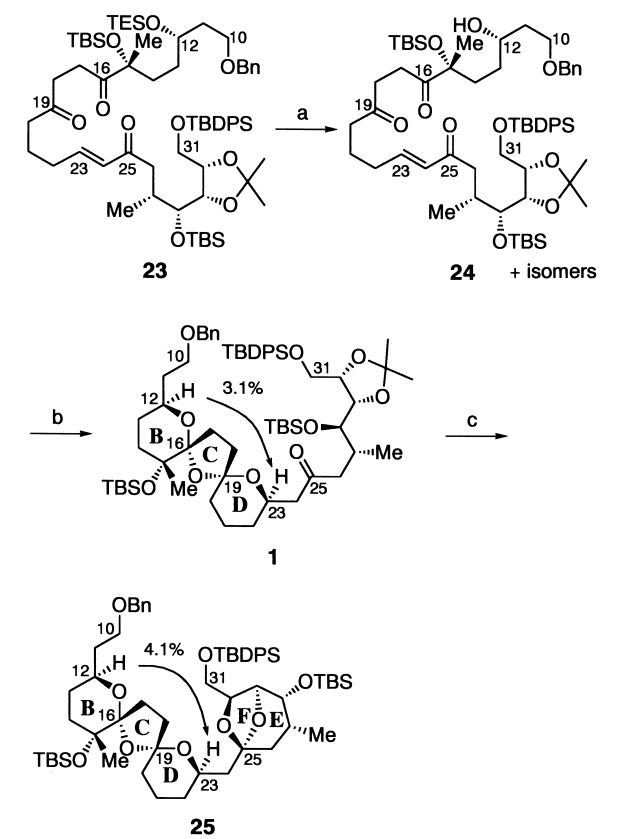


(3)

With the efficient synthesis of the C24–C31 ketone fragment **17** realized, the stage was now set for the aldol fragment coupling to construct the C23–C24 bond and the elaboration of the dispiroketalization precursor **23** (Scheme 3). The lithium enolate derived from methyl ketone **17** was allowed to react with the C10–C23 aldehyde fragment **4**, providing a mixture of diastereomeric aldol



Scheme 3. *Reagents and conditions*: (a) LiHMDS, THF, −78°C, then **4**, −78 to −50°C, 1.5 h, 88%; (b) Ac_2O, pyridine, DMAP, 16 h; (c) DBU, CH_2Cl_2, 1 h, 89% (two steps); (d) DDQ, CH_2Cl_2/pH 7 phosphate buffer (10:1), 1 h, 93%; (e) Dess–Martin periodinane, CH_2Cl_2/pyridine (5:1), 0°C, 1 h, 84%; (f) NCS, $AgNO_3$, γ-collidine, CH_3CN/H_2O (4:1), 87%.



Scheme 4. *Reagents and conditions*: (a) 1N aqueous HCl/THF (1:10), 0°C, 1 h; (b) LiOMe (1 equiv.), THF/MeOH (10:1), 4 h, 77% of **1** and 14% of other isomers (two steps); (c) CSA, CH_2Cl_2, 5 h, 62%.

adducts **20** in 88% yield. Acetylation of the hydroxyl group in **20** was followed by exposure to DBU to furnish enone **13** in 89% yield. Finally, the target triketone **23** was obtained by oxidative deprotection of MPM ether[15] followed by Dess–Martin oxidation[16] and oxidative hydrolysis of dithiane under standard Corey conditions[17] in 68% yield over three steps from **13**.

2.2. Construction of BCDEF ring system

Having successfully arrived at **23**, we were now ready for the key dispiroketalization via a tandem double hemiketal formation/hetero-Michael addition process (Scheme 4). Following the protocol developed in model studies,[1] we first submitted triketone **23** to 1N aqueous HCl. Gratifyingly, selective liberation of the C12 hydroxyl group resulted in the formation of an equilibrium mixture of hydroxytriketone **24** and hemiketals, which upon treatment with LiOMe in THF/MeOH (10:1) at room temperature afforded the desired dispiroketal **1** in 77% isolated yield, accompanied by 14% of other diastereomers. Finally, removal of the acetonide group in **1** with CSA in CH_2Cl_2 with concomitant bicycloketalization gave the C10–C31 fragment **25**, containing the BCDEF ring system of pinnatoxin A, as a single isomer in 62% yield.[18] The stereochemistries of **1** and **25** were verified by the diagnostic ^{1}H NOE correlation between C12–H and C23–H.[20]

3. Conclusion

We have achieved an efficient, highly stereoselective synthesis of the C10–C31 (BCDEF ring) portion of pinnatoxin A, wherein the key features involve (a) a stereocontrolled conjugate addition of MeCu(CN)Li in the presence of $BF_3{\cdot}OEt_2$ to establish the C27 stereogenic center, (b) a fragment assembly aldol reaction to join the C23–C24 bond, (c) a tandem double hemiketal formation/intramolecular hetero-Michael addition[2] to construct the 6,5,6-dispiroketal (BCD ring) system, and (d) an intramolecular ketalization to form the 5,6-bicycloketal (EF ring) system. Further efforts toward a total synthesis of pinnatoxin A are currently underway.

4. Experimental

4.1. General

For a description of general information, see the preceding paper.[1] *N*-Methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide was prepared according to the literature procedure.[8]

4.1.1. (3a*S*,6*S*,7*S*,7a*S*)-6-Benzyloxy-2,2-dimethyl-7-(*tert*-butyldimethylsilyl)oxy-tetrahydro-1,3-dioxolo[4,5-*c*]pyran (7). TBSCl (2.80 g, 18.6 mmol) was added to a stirred solution of alcohol **6** (4.73 g, 16.9 mmol) and imidazole (2.87 g, 42.2 mmol) in DMF (60 mL) at 0°C under an argon atmosphere. After stirring for 16 h, the reaction was quenched with three pieces of ice, and the mixture was partitioned between AcOEt (100 mL) and H_2O (40 mL). The organic layer was washed with brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (8.0 g, colorless oil), which was purified by column chromatography (silica gel 80 g, 20:1→16:1 *n*-hexane/acetone) to give silyl ether **7** (6.44 g, 97%) as a colorless oil: $[\alpha]_D^{24}=+97.2$ (*c* 1.19, $CHCl_3$); IR (neat) 2930, 1458, 1372, 1246, 1215, 1119, 1036, 839, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H, SiC*H*$_3$), 0.11 (s, 3H, SiC*H*$_3$), 0.90 (s, 9H, SiC (C*H*$_3$)$_3$), 1.35 (s, 3H, acetonide C*H*$_3$), 1.53 (s, 3H, acetonide C*H*$_3$), 3.57 (dd, *J*=3.8, 13.7 Hz, 1H, C31–*H*), 3.73–3.76 (m, 2H, C28–*H*, C31–*H*), 4.24 (m, 1H, C30–*H*), 4.41 (dd, *J*=3.1, 7.0 Hz, 1H, C29–*H*), 4.55 (d, *J*=11.2 Hz, 1H, C*H*Ph), 4.79–4.82 (m, 2H, C27–*H*, C*H*Ph), 7.27 (m, 1H, Ar*H*), 7.31–7.36 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.4, 18.3, 25.2, 25.8, 26.8, 62.8, 69.7, 70.7, 73.8, 75.2, 100.0, 109.7, 127.3, 127.7, 128.1, 137.8; FAB-HRMS *m*/*z* calcd for $C_{21}H_{33}O_5Si$ (M$^+$−H) 393.2097, found 393.2086; Anal. calcd for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.69, found: C, 63.77; H, 8.57.

4.1.2. Ethyl (2*E*,4*R*,5*S*,6*S*)-4-(*tert*-butyldimethylsilyl)-oxy-5,6-(dimethylmethylenedioxy)-7-hydroxy-2-heptenoate (9). To a solution of benzyl acetal **7** (3.45 g, 8.7 mmol) in EtOH (30 mL) was added 20% $Pd(OH)_2$ (246 mg), and the mixture was vigorously stirred for 2 days under a hydrogen atmosphere. The catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo to furnish the crude product (2.7 g, colorless oil), which was purified by column chromatography (silica gel 80 g, 4:1 *n*-hexane/AcOEt) to give lactol **8** (2.22 g, 83%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 3H, SiC*H*$_3$), 0.15 (s, 3H, SiC*H*$_3$), 0.93 (s, 9H, SiC(C*H*$_3$)$_3$), 1.34 (s, 3H, acetonide C*H*$_3$), 1.52 (s, 3H, acetonide C*H*$_3$), 3.00 (d, *J*=3.0 Hz, 1H, O*H*), 3.56 (dd, *J*=4.0, 12.6 Hz, 1H, C31–*H*), 3.66 (dd, *J*=3.2, 6.6 Hz, 1H, C28–*H*), 3.80 (dd, *J*=3.6, 12.6 Hz, 1H, C31–*H*), 4.25 (m, 1H, C30–*H*), 4.40 (dd, *J*=3.2, 6.6 Hz, 1H, C29–*H*), 5.01 (dd, *J*=3.0, 6.6 Hz, 1H, C27–*H*).

A solution of ethyl (triphenylphosphoranylidene)acetate (1.04 g, 2.97 mmol) and hemiacetal (603.2 mg, 1.98 mmol) in benzene (40 mL) was heated at reflux for 32 h. The solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel 50 g, 8:1→4:1 *n*-hexane/AcOEt) to give enoate **9** (727 mg, 98%) as a colorless syrup: $[\alpha]_D^{22}=-22.6$ (*c* 1.03, $CHCl_3$); IR (neat) 3499, 2934, 2861, 1723, 1471, 1369, 1258, 1167, 1078, 1040, 839 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H, SiC*H*$_3$), 0.13 (s, 3H, SiC*H*$_3$), 0.92 (s, 9H, SiC(C*H*$_3$)$_3$), 1.30 (t, *J*=7.3 Hz, 3H, OCH$_2$C*H*$_3$), 1.35 (s, 3H, acetonide C*H*$_3$), 1.47 (s, 3H, acetonide C*H*$_3$), 2.49 (dd, *J*=6.4, 7.1 Hz, 1H, O*H*), 3.68 (m, 2H, C31–*H*), 4.12 (m, 1H, C29–*H*), 4.19–4.23 (m, 3H, C30–*H*, OC*H*$_2$CH$_3$), 4.64 (m, 1H, C28–*H*), 6.04 (d, *J*=15.7 Hz, 1H, C26–*H*), 6.89 (dd, *J*=5.7, 15.7 Hz, 1H, C27–*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.1, 14.2, 18.1, 25.4, 25.8, 27.6, 60.5, 61.5, 70.8, 77.7, 78.5, 108.2, 122.8, 146.1, 165.6; EI-LRMS *m*/*z* 359 (M$^+$−CH$_3$), 75 (bp); EI-HRMS *m*/*z* calcd for $C_{17}H_{31}O_6Si$ (M$^+$−CH$_3$) 359.1890, found 359.1893; Anal. calcd for $C_{18}H_{34}O_6Si$: C, 57.72; H, 9.15, found: C, 57.54; H, 9.13.

4.1.3. Ethyl (2*E*,4*R*,5*S*,6*S*)-4-(*tert*-Butyldimethylsilyl)-oxy-7-(*tert*-butyldiphenylsilyl)oxy-5,6-(dimethylmethylene-dioxy)-2-heptenoate (10). TBDPSCl (0.54 mL, 2.10 mmol) was added to a stirred solution of alcohol **9** (654.0 mg, 1.75 mmol) and imidazole (297.6 mg, 4.38 mmol) in DMF (20 mL) at 0°C under an argon atmosphere. After stirring at room temperature for 13 h, the reaction was quenched by addition of crushed ice, and the whole was partitioned between AcOEt (50 mL) and H_2O (30 mL). The aqueous layer was extracted with AcOEt (50 mL), and the combined organic extracts were washed with brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.3 g), which was purified by column chromatography (silica gel 30 g, 20:1 *n*-hexane/acetone) to give TBDPS ether **10** (1.02 g, 95%) as a colorless syrup: $[\alpha]_D^{22}=-6.70$ (*c* 1.27, $CHCl_3$); IR (neat) 2934, 2859, 1728, 1661, 1472, 1370, 1258, 1169, 980 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.13 (s, 3H, SiCH_3), −0.06 (s, 3H, SiCH_3), 0.75 (s, 9H, SiC(CH_3)$_3$), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.29 (t, *J*=7.1 Hz, 3H, OCH$_2$CH_3), 1.34 (s, 3H, acetonide CH_3), 1.42 (s, 3H, acetonide CH_3), 3.77 (dd, *J*=7.8, 11.2 Hz, 1H, C31−*H*), 3.90 (dd, *J*=3.3, 11.2 Hz, 1H, C31−*H*), 4.06 (m, 1H, C29−*H*), 4.19 (q, *J*=7.1 Hz, 3H, OCH_2CH$_3$), 4.30 (m, 1H, C30−*H*), 4.45 (m, 1H, C28−*H*), 5.91 (dd, *J*=1.1, 15.6 Hz, 1H, C26−*H*), 6.85 (dd, *J*=5.8, 15.6 Hz, 1H, C27−*H*), 7.35−7.43 (m, 6H, Ar*H*), 7.67−7.72 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.0, 14.3, 18.0, 19.3, 25.4, 25.8, 26.9, 27.5, 60.4, 63.7, 70.9, 78.6, 79.1, 108.4, 122.6, 127.46, 127.53, 129,48, 129.49, 133.3, 133.5, 135.5, 135.7, 147.0, 165.8; FAB-HRMS *m*/*z* calcd for $C_{34}H_{52}O_6Si_2Na$ (M^++Na) 635.3200, found 635.3218.

4.1.4. Ethyl (3*R*,4*R*,5*S*,6*S*)-4-(*tert*-butyldimethylsilyl)-oxy-7-(*tert*-butyldiphenylsilyl)oxy-5,6-(dimethylmethylenedioxy)-3-methylheptanoate (11). Methyllithium in Et_2O (1.14 M, 19.0 mL, 21.7 mmol) was added to a suspension of CuI (2.06 g, 10.85 mmol) in THF (35 mL) at −78°C under an argon atmosphere, and the resulting mixture was stirred at 0°C for 20 min to form a clear, colorless solution. After cooling to −78°C, TMSCl (1.38 mL, 10.85 mmol) was added, and the mixture was stirred at this temperature for 5 min. A solution of enoate **10** (665.0 mg, 1.08 mmol) in THF (5.0 mL) was added, and the mixture was stirred at −20°C for 16 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL), and the mixture was stirred at room temperature for 1 h. The whole mixture was extracted with AcOEt (2×50 mL), and the combined organic extracts were washed with brine (2×20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (yellow oil), which was purified by column chromatography (silica gel 50 g, 16:1 *n*-hexane/AcOEt) to give *anti* adduct **11** (479.2 mg, 71%) as a colorless syrup, along with its stereoisomer **12** (105.2 mg, 15%); $[\alpha]_D^{24}=-33.5$ (*c* 1.04, $CHCl_3$); IR (neat) 2934, 2859, 1736, 1460, 1377, 1254, 1181, 1090, 837, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.16 (s, 3H, SiCH_3), −0.02 (s, 3H, SiCH_3), 0.77 (s, 9H, SiC(CH_3)$_3$), 0.96 (d, *J*=6.4 Hz, 3H, C36−H_3), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.21 (t, *J*=7.3 Hz, 3H, OCH$_2$CH_3), 1.35 (s, 3H, acetonide CH_3), 1.40 (s, 3H, acetonide CH_3), 2.17−2.24 (m, 2H, C26−*H*, C27−*H*), 2.54 (dd, *J*=9.6, 20.4 Hz, 1H, C26−*H*), 3.64 (dd, *J*=7.9, 10.8 Hz, 1H, C31−*H*), 3.71 (dd, *J*=2.3, 7.3 Hz, 1H, C28−*H*), 3.80 (dd, *J*=2.6, 10.8 Hz, 1H, C31−*H*), 4.06−4.11 (m, 3H, C29−*H*, OCH_2CH$_3$), 4.25 (m, 1H, C30−*H*), 7.34−7.42 (m, 6H, Ar*H*), 7.68−7.73 (m, 4H, Ar*H*); FAB-HRMS *m*/*z* calcd for $C_{35}H_{56}O_6Si_2Na$ (M^++Na) 651.3513, found 651.3516.

Data for **12**: $[\alpha]_D^{24}=-30.9$ (*c* 1.01, $CHCl_3$); IR (neat) 2934, 2859, 1736, 1464, 1427, 1370, 1254, 1179, 1111, 835, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.17 (s, 3H, SiCH_3), −0.06 (s, 3H, SiCH_3), 0.77 (s, 9H, SiC(CH_3)$_3$), 0.94 (d, *J*=6.8 Hz, 3H, C36−H_3), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.23 (t, *J*=7.0 Hz, 3H, OCH$_2$CH_3), 1.32 (s, 3H, acetonide CH_3), 1.41 (s, 3H, acetonide CH_3), 2.14 (dd, *J*=10.3, 14.6 Hz, 1H, C26−*H*), 2.22 (m, 1H, C27−*H*), 2.43 (dd, *J*=3.8, 14.6 Hz, 1H, C26−*H*), 3.64 (dd, *J*=8.0, 10.9 Hz, 1H, C31−*H*), 3.72 (dd, *J*=2.6, 7.9 Hz, 1H, C28−*H*), 3.79 (dd, *J*=1.9, 10.9 Hz, 1H, C31−*H*), 3.99 (m, 1H, C29−*H*), 4.11 (q, *J*=7.0 Hz, 2H, OCH_2CH$_3$), 4.25 (m, 1H, C30−*H*), 7.34−7.42 (m, 6H, Ar*H*), 7.68−7.74 (m, 4H, Ar*H*); FAB-HRMS *m*/*z* calcd for $C_{35}H_{56}O_6Si_2Na$ (M^++Na) 651.3513, found 651.3520.

4.1.5. Dimethyl (4*R*,5*R*,6*S*,7*S*)-5-(*tert*-butyldimethylsilyl)oxy-8-(*tert*-butyldiphenylsilyl)oxy-6,7-(dimethylmethylenedioxy)-4-methyl-2-oxopentylphosphonate (5). Butyllithium in *n*-hexane (1.54 M, 0.31 mL, 0.477 mmol) was added to a solution of dimethyl methylphosphonate (59.4 mg, 0.479 mmol) in THF (5 mL) at −78°C under an argon atmosphere. After stirring for 50 min, a solution of ester **11** (100.0 mg, 0.159 mmol) in THF (2 mL) was added, and the mixture was stirred at −78°C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the whole was extracted with AcOEt (2×25 mL). The combined organic extracts were washed successively with brine (2×10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel 10 g, 1:4 *n*-hexane/AcOEt) to give phosphonate **5** (89.7 mg, 80%) as a colorless syrup: $[\alpha]_D^{22}=-34.5$ (*c* 1.20, $CHCl_3$); IR (neat) 2955, 2857, 1715, 1472, 1372, 1260, 1032, 897, 835, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.15 (s, 3H, SiCH_3), −0.01 (s, 3H, SiCH_3), 0.79 (s, 9H, SiC(CH_3)$_3$), 0.92 (d, *J*=7.0 Hz, 3H, C36−H_3), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.35 (s, 3H, acetonide CH_3), 1.38 (s, 3H, acetonide CH_3), 2.31 (m, 1H, C27−*H*), 2.52 (dd, *J*=8.3, 18.0 Hz, 1H, C26−*H*), 2.83 (dd, *J*=4.8, 18.0 Hz, 1H, C26−*H*), 2.97 (dd, *J*=13.9, 22.6 Hz, 1H, C24−*H*), 3.08 (dd, *J*=13.9, 22.7 Hz, 1H, C24−*H*), 3.61 (dd, *J*=7.7, 10.8 Hz, 1H, C31−*H*), 3.67 (dd, *J*=2.9, 7.4 Hz, 1H, C28−*H*), 3.73 (d, *J*=11.2 Hz, 3H, POCH_3), 3.74 (d, *J*=11.2 Hz, 3H, POCH_3), 3.78 (dd, *J*=2.8, 10.8 Hz, 1H, C31−*H*), 4.07 (dd, *J*=6.3, 7.4 Hz, 1H, C29−*H*), 4.25 (m, 1H, C30−*H*), 7.34−7.42 (m, 6H, Ar*H*), 7.67−7.72 (m, 4H, Ar*H*); FAB-HRMS *m*/*z* calcd for $C_{36}H_{59}O_8PSi_2Na$ (M^++Na) 729.3384, found 729.3378.

4.1.6. [1*R*,1(4*S*,5*S*),2*R*,5*E*,9(3*S*,4*R*,7*S*)]-9-{2-[9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-3-(4-methoxybenzyl)-oxy-4-methyl-7-(triethylsilyl)oxynonyl]-1,3-dithian-2-yl}-1-(*tert*-butyldimethylsilyl)oxy-1-[5-(*tert*-butyldiphenylsilyl)oxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methyl-5-nonen-4-one (13). To a solution of phosphonate **5** (242.1 mg, 0.34 mmol) and LiCl (42.0 mg, 0.99 mmol) in

CH_3CN (5 mL) was added *i*-Pr_2NEt (0.34 mL, 1.95 mmol), followed by addition of a solution of aldehyde **4** (274.1 mg, 0.33 mmol) in CH_3CN (1 mL) under an argon atmosphere. After stirring for 37 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the whole was extracted with AcOEt (40 mL). The organic extract was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel 50 g, 12:1 *n*-hexane/AcOEt) to give enone **13** (444.4 mg, 96%) as a colorless syrup: $[\alpha]_D^{25}=-17.5$ (*c* 1.17, $CHCl_3$); IR (neat) 2953, 1698, 1671, 1615, 1514, 1462, 1370, 1250, 1092, 835, 775, 739, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.17 (s, 3H, SiCH_3), −0.01 (s, 3H, SiCH_3), 0.08 (s, 6H, SiCH_3×2), 0.58 (q, *J*=7.9 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.77 (s, 9H, SiC(CH_3)$_3$), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.91 (d, *J*=7.0 Hz, 3H, C36−H_3), 0.92 (t, *J*=7.9 Hz, 9H, Si(CH$_2$CH_3)$_3$), 1.05 (s, 9H, SiC(CH_3)$_3$), 1.21 (s, 3H, C37−H_3), 1.35 (s, 3H, acetonide CH_3), 1.40 (s, 3H, acetonide CH_3), 1.53–1.61 (m, 6H, C13−H_2, C14−H_2, C17−H_2), 1.71–1.88 (m, 9H, C11−H_2, C18−*H*, C20−H_2, C21−H_2, SCH$_2$CH_2), 2.10–2.17 (m, 3H, C18−*H*, C22−H_2), 2.33 (m, 1H, C27−*H*), 2.39 (dd, *J*=8.7, 16.1 Hz, 1H, C26−*H*), 2.64–2.74 (m, 5H, C26−*H*, SCH_2×2), 3.16 (brd, *J*=7.9 Hz, 1H, C16−*H*), 3.49–3.57 (m, 2H, C10−H_2), 3.60 (dd, *J*=7.9, 10.8 Hz, 1H, C31−*H*), 3.66 (dd, *J*=2.7, 7.6 Hz, 1H, C28−*H*), 3.76–3.79 (m, 5H, C12−*H*, C31−*H*, C_6H_4OCH_3), 4.08 (m, 1H, C29−*H*), 4.25 (m, 1H, C30−*H*), 4.43–4.50 (m, 3H, OC*H*Ar, OCH_2Ph), 4.58 (d, *J*=11.0 Hz, 1H, OC*H*Ar), 6.05 (d, *J*=15.9 Hz, 1H, C24−*H*), 6.76 (m, 1H, C23−*H*), 6.84 (d, *J*=8.5 Hz, 2H, Ar*H*), 7.23–7.28 (m, 3H, Ar*H*), 7.31–7.42 (m, 10H, Ar*H*), 7.67–7.72 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −4.1, −2.1, −1.9, 4.9, 6.8, 14.4, 17.8, 18.1, 18.8, 22.4, 23.2, 25.0, 25.1, 25.5, 25.6, 25.7, 25.9, 26.7, 27.7, 31.4, 32.1, 33.9, 35.4, 36.4, 37.2, 37.8, 42.8, 53.0, 54.7, 63.7, 66.7, 69.8, 72.4, 72.6, 73.8, 77.2, 78.0, 78.6, 84.5, 107.7, 113.4, 127.1, 127.2, 127.3, 127.9, 128.6, 129.25, 129.29, 130.8, 133.1, 133.3, 135.4, 135.6, 138.3, 145.5, 158.8, 199.2; FAB-HRMS *m/z* calcd for $C_{79}H_{128}O_{10}S_2Si_4Na$ (M^++Na) 1435.7923, found 1435.7960.

4.1.7. (2*E*,4*R*,5*S*,6*S*)-*N*-Methoxy-*N*-methyl-4-(*tert*-butyldimethylsilyl)oxy-5,6-(dimethylmethylenedioxy)-7-hydroxy-2-heptenamide (14). A solution of *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (17.9 g, 68.0 mmol) and lactol **8** (11.6 g, 38.1 mmol) in benzene (120 mL) was refluxed for 39 h. The solvent was evaporated in vacuo and the residue (31 g, brown solid) was purified by column chromatography (silica gel 300 g, 8:1→4:1 *n*-hexane/acetone) to give amide **14** (13.3 g, 90%) as a colorless syrup: $[\alpha]_D^{22}=-31.8$ (*c* 1.30, $CHCl_3$); IR (neat) 3463, 2934, 1667, 1636, 1464, 1418, 1383, 1254, 1217, 1171, 1078, 837, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H, SiCH_3), 0.16 (s, 3H, SiCH_3), 0.95 (s, 9H, SiC(CH_3)$_3$), 1.35 (s, 3H, acetonide CH_3), 1.48 (s, 3H, acetonide CH_3), 2.59 (m, 1H, O*H*), 3.26 (s, 3H, NCH_3), 3.70 (m, 5H, C31−H_2, NOCH_3), 4.17–4.19 (m, 2H, C29−*H*, C30−*H*), 4.75 (m, 1H, C28−*H*), 6.71 (d, *J*=15.5 Hz, 1H, C26−*H*), 6.93 (dd, *J*=4.7, 15.5 Hz, 1H, C27−*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 18.0, 25.2, 25.6, 27.4, 32.1, 61.4, 61.6, 70.9, 77.7, 78.3, 107.8, 119.8, 144.3, 165.5; FAB-HRMS *m/z* calcd for $C_{18}H_{36}NO_6Si$ (M^++H) 390.2312, found 390.2282; Anal. calcd for $C_{18}H_{35}NO_6Si$: C, 55.50; H, 9.06; N, 3.60, found: C, 55.42; H, 8.92; N, 3.62.

4.1.8. (2*E*,4*R*,5*S*,6*S*)-*N*-Methoxy-*N*-methyl-4-(*tert*-butyldimethylsilyl)oxy-7-(*tert*-butyldiphenylsilyl)oxy-5,6-(dimethylmethylenedioxy)-2-heptenamide (15). TBDPSCl (1.70 mL, 6.53 mmol) was added to a stirred solution of alcohol **14** (2.32 g, 5.94 mmol) and imidazole (1.01 g, 14.9 mmol) in DMF (20 mL) at 0°C under an argon atmosphere. After stirring at room temperature for 12 h, the reaction was quenched by addition of crushed ice, and the whole was partitioned between AcOEt (80 mL) and H_2O (30 mL). The organic layer was washed with brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel 50 g, 6:1→4:1 *n*-hexane/AcOEt) to give TBDPS ether **15** (3.49 g, 94%) as a colorless syrup: $[\alpha]_D^{25}=-11.5$ (*c* 1.12, $CHCl_3$); IR (neat) 2932, 1669, 1634, 1470, 1427, 1385, 1256, 1107, 837, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.11 (s, 3H, SiCH_3), −0.05 (s, 3H, SiCH_3), 0.76 (s, 9H, SiC(CH_3)$_3$), 1.05 (s, 9H, SiC(CH_3)$_3$), 1.34 (s, 3H, acetonide CH_3), 1.42 (s, 3H, acetonide CH_3), 3.23 (s, 3H, NCH_3), 3.55 (s, 3H, NOCH_3), 3.81 (dd, *J*=8.0, 11.2 Hz, 1H, C31−*H*), 3.91 (dd, *J*=2.7, 11.2 Hz, 1H, C31−*H*), 4.12 (m, 1H, C29−*H*), 4.30 (m, 1H, C30−*H*), 4.56 (m, 1H, C28−*H*), 6.55 (d, *J*=15.4 Hz, 1H, C26−*H*), 6.88 (dd, *J*=5.1, 15.4 Hz, 1H, C27−*H*), 7.34–7.41 (m, 6H, Ar*H*), 7.66–7.71 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.5, 17.8, 19.0, 25.2, 25.5, 26.7, 27.3, 31.9, 61.3, 63.8, 71.0, 78.6, 107.8, 119.7, 127.2, 127.3, 129.15, 129.17, 133.2, 133.3, 135.2, 135.4, 144.9, 165.5; FAB-HRMS *m/z* calcd for $C_{34}H_{54}NO_6Si_2$ (M^++H) 628.3490, found 628.3442; Anal. calcd for $C_{34}H_{53}NO_6Si_2$: C, 65.03; H, 8.51; N, 2.23, found: C, 64.72; H, 8.51; N, 2.12.

4.1.9. (3*E*,5*R*,6*S*,7*S*)-5-(*tert*-Butyldimethylsilyl)oxy-8-(*tert*-butyldiphenylsilyl)oxy-5,6-(dimethylmethylenedioxy)-3-octen-2-one (16). A solution of MeI (2.25 mL, 36.1 mmol) in Et_2O (10 mL) was added over 30 min to a suspension of magnesium tuning (877.5 mg, 36.1 mmol) in Et_2O (11 mL) under an argon atmosphere. After refluxing for 30 min, the solution was cooled to room temperature, and added to a stirred solution of amide **15** (4.53 g, 7.21 mmol) in Et_2O (60 mL) at 0°C under an argon atmosphere. After stirring at 0°C for 5 h, the mixture was poured into saturated aqueous NH_4Cl (60 mL), and the whole was extracted with AcOEt (2×50 mL). The combined organic extracts were washed with brine (2×40 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (5 g), which was purified by column chromatography (silica gel 100 g, 12:1→8:1 *n*-hexane/AcOEt) to give enone **16** (3.94 g, 94%) as a colorless oil: $[\alpha]_D^{23}=+3.1$ (*c* 1.06, C_6H_6); IR (neat) 2932, 2859, 1682, 1634, 1472, 1427, 1362, 1256, 1111, 984, 837, 779, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.14 (s, 3H, SiCH_3), −0.07 (s, 3H, SiCH_3), 0.76 (s, 9H, SiC(CH_3)$_3$), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.33 (s, 3H, acetonide CH_3), 1.42 (s, 3H, acetonide CH_3), 2.20 (s, 3H, C24−H_3), 3.78 (dd, *J*=7.6, 11.2 Hz, 1H, C31−*H*), 3.89 (dd, *J*=3.5, 11.2 Hz, 1H, C31−*H*), 4.06 (m, 1H, C29−*H*), 4.30 (m, 1H, C30−*H*), 4.44 (m, 1H, C28−*H*), 6.13 (d, *J*=16.0 Hz, 1H, C26−*H*), 6.44 (dd, *J*=6.0, 16.0 Hz, 1H, C27−*H*), 7.35–7.47 (m, 6H, Ar*H*),

7.67–7.71 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −3.9, 18.0, 19.2, 25.3, 25.8, 26.9, 27.3, 27.5, 63.5, 71.1, 78.5, 79.2, 108.4, 127.48, 127.54, 129.5, 129.6, 131.4, 133.1, 133.4, 135.5, 135.7, 145.9, 197.7; FAB-HRMS *m/z* calcd for $C_{33}H_{50}O_5Si_2Na$ (M^++Na) 605.3094, found 605.3076.

4.1.10. (4*R*,5*R*,6*S*,7*S*)-5-(*tert*-Butyldimethylsilyl)oxy-8-(*tert*-butyldiphenylsilyl)oxy-5,6-(dimethylmethylenedioxy)-4-methylocten-2-one (17). Methyllithium in Et_2O (1.14 M, 3.6 mL, 4.12 mmol) was added to a suspension of CuCN (369.1 mg, 4.12 mmol) in THF (15 mL) at −78°C under an argon atmosphere, and the resulting mixture was stirred at 0°C for 10 min to form a clear, colorless solution. After cooling to −78°C, $BF_3{\cdot}OEt_2$ (0.52 mL, 4.12 mmol) was added, and the mixture was stirred at this temperature for 5 min. A solution of enone **16** (600.0 mg, 1.03 mmol) in THF (3 mL) was added, and the mixture was stirred at −78°C for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (9 mL) and 28% aqueous NH_3 (3 mL), and the mixture was diluted with Et_2O (10 mL). After stirring at room temperature for 20 min, the whole was extracted with AcOEt (50 mL). The organic extract was washed successively with 3% aqueous HCl (2×20 mL), H_2O (20 mL), saturated aqueous $NaHCO_3$ (2×20 mL) and brine (2×20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (603.8 mg, slightly yellow oil), which was purified by column chromatography (silica gel 15 g, 20:1 *n*-hexane/AcOEt) to give ketone **17** (490.8 mg, 80%) as a colorless syrup: $[\alpha]_D^{25}$=−39.0 (*c* 1.06, $CHCl_3$); IR (neat) 2934, 2859, 1719, 1472, 1427, 1370, 1254, 1217, 1088, 897, 837, 777, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.13 (s, 3H, SiC*H*$_3$), 0.04 (s, 3H, SiC*H*$_3$), 0.79 (s, 9H, SiC(C*H*$_3$)$_3$), 0.92 (d, *J*=6.4 Hz, 3H, C36–*H*$_3$), 1.07 (s, 9H, SiC(C*H*$_3$)$_3$), 1.35 (s, 3H, acetonide C*H*$_3$), 1.40 (s, 3H, acetonide C*H*$_3$), 2.06 (s, 3H, C24–*H*$_3$), 2.26–2.31 (m, 2H, C26–*H*$_2$), 2.72 (m, 1H, C27–*H*), 3.63 (dd, *J*=7.7, 10.8 Hz, 1H, C31–*H*), 3.69 (dd, *J*=2.4, 7.4 Hz, 1H, C28–*H*), 3.80 (dd, *J*=2.7, 10.8 Hz, 1H, C31–*H*), 4.08 (m, 1H, C29–*H*), 4.25 (m, 1H, C30–*H*), 7.35–7.42 (m, 6H, Ar*H*), 7.69–7.74 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −3.9, 14.8, 18.1, 19.1, 25.7, 25.9, 26.9, 27.9, 30.3, 33.6, 46.6, 63.8, 72.5, 77.4, 78.8, 108.0, 127.4, 127.5, 129.39, 129.43, 133.3, 133.4, 135.6, 135.7, 208.0; FAB-HRMS *m/z* calcd for $C_{34}H_{54}O_5Si_2Na$ (M^++Na) 621.3408, found 621.3379; Anal. calcd for $C_{34}H_{54}O_5Si_2$: C, 68.07; H, 9.09, found: C, 68.18; H, 9.00.

Data for *syn*-isomer **18**: $[\alpha]_D^{24}$=−30.4 (*c* 0.82, $CHCl_3$); IR (neat) 2932, 2859, 1719, 1472, 1427, 1368, 1254, 1217, 1111, 835, 777, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.16 (s, 3H, SiC*H*$_3$), −0.07 (s, 3H, SiC*H*$_3$), 0.76 (s, 9H, SiC(C*H*$_3$)$_3$), 0.89 (d, *J*=6.7 Hz, 3H, C36–*H*$_3$), 1.07 (s, 9H, SiC(C*H*$_3$)$_3$), 1.36 (s, 3H, acetonide C*H*$_3$), 1.41 (s, 3H, acetonide C*H*$_3$), 2.10 (s, 3H, C24–*H*$_3$), 2.24–2.29 (m, 2H, C26–*H*, C27–*H*), 2.50 (m, 1H, C26–*H*), 3.65 (dd, *J*=7.8, 11.0 Hz, 1H, C31–*H*), 3.70 (dd, *J*=2.5, 7.5 Hz, 1H, C28–*H*), 3.80 (dd, *J*=2.3, 11.0 Hz, 1H, C31–*H*), 3.99 (m, 1H, C29–*H*), 4.24 (m, 1H, C30–*H*), 7.34–7.42 (m, 6H, Ar*H*), 7.68–7.74 (m, 4H, Ar*H*); FAB-HRMS *m/z* calcd for $C_{34}H_{55}O_5Si_2$ (M^++H) 599.3588, found 599.3581.

Data for 1,2-adduct: $[\alpha]_D^{22}$=−5.91 (*c* 2.10, $CHCl_3$); IR (neat) 3455, 2932, 2859, 1472, 1427, 1372, 1252, 1219, 1111, 835, 777, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.15 (s, 3H, SiC*H*$_3$), −0.08 (s, 3H, SiC*H*$_3$), 0.73 (s, 9H, SiC(C*H*$_3$)$_3$), 1.07 (s, 9H, SiC(C*H*$_3$)$_3$), 1.246 (s, 3H, C(C*H*$_3$)$_2$), 1.254 (s, 3H, C(C*H*$_3$)$_2$), 1.34 (s, 3H, acetonide C*H*$_3$), 1.41 (s, 3H, acetonide C*H*$_3$), 3.79 (dd, *J*=8.2, 11.1 Hz, 1H, C31–*H*), 3.94 (dd, *J*=2.9, 11.1 Hz, 1H, C31–*H*), 3.97 (t, *J*=6.2 Hz, 1H, C29–*H*), 4.24 (dd, *J*=6.2, 7.0 Hz, 1H, C28–*H*), 4.30 (m, 1H, C30–*H*), 5.53 (dd, *J*=7.0, 15.7 Hz, 1H, C27–*H*), 5.68 (d, *J*=15.7 Hz, 1H, C26–*H*), 7.34–7.42 (m, 6H, Ar*H*), 7.68–7.74 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −3.5, 17.9, 19.2, 25.5, 25.8, 26.9, 27.7, 29.2, 29.5, 63.8, 70.3, 72.0, 79.0, 79.6, 108.1, 126.6, 127.5, 127.6, 129.5, 133.5, 133.9, 135.7, 135.8, 140.7; FAB-HRMS *m/z* calcd for $C_{34}H_{54}O_5Si_2Na$ (M^++Na) 621.3408, found 621.3412.

4.1.11. (1*S*,2*R*,3*R*,5*S*,7*S*)-2-(*tert*-Butyldimethylsilyl)oxy-7-(*tert*-butyldiphenylsilyloxy)methyl-3,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (19). TFA (0.05 mL, 0.65 mmol) was added to a stirred solution of ketone **17** (165.1 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) at room temperature. After stirring for 1 h, Et_3N (0.5 mL) was added to the slightly pink solution. The resultant solution was poured into a two-layer mixture of Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (20 mL), and the layers were separated. The aqueous layer was extracted with AcOEt (2×20 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 (176.9 mg, slightly yellow oil), which was purified by column chromatography (silica gel 10 g, 20:1 *n*-hexane/AcOEt) to give acetal **19** (123.1 mg, 83%) as a colorless oil: $[\alpha]_D^{25}$=+38.8 (*c* 1.01, $CHCl_3$); IR (neat) 2957, 2859, 1471, 1429, 1385, 1252, 1206, 1107, 1069, 1007, 835, 775, 739, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 3H, SiC*H*$_3$), 0.09 (s, 3H, SiC*H*$_3$), 0.83 (d, *J*=6.8 Hz, 3H, C36–*H*$_3$), 0.93 (s, 9H, SiC(C*H*$_3$)$_3$), 1.06 (s, 9H, SiC(C*H*$_3$)$_3$), 1.42 (s, 3H, C24–*H*$_3$), 1.47–1.51 (m, 2H, C26–*H*$_2$), 1.95 (m, 1H, C27–*H*), 3.65 (dd, *J*=1.8, 3.9 Hz, 1H, C28–*H*), 3.80 (m, 1H, C31–*H*), 3.96 (dd, *J*=5.7, 10.4 Hz, 1H, C31–*H*), 4.19 (m, 1H, C30–*H*), 4.36 (dd, *J*=1.8, 4.5 Hz, 1H, C29–*H*), 7.36–7.46 (m, 6H, Ar*H*), 7.63–7.66 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.4, 16.8, 18.2, 19.1, 24.4, 25.9, 26.8, 29.8, 40.3, 61.4, 67.6, 80.9, 107.3, 127.7, 127.7, 129.81, 129.83, 132.8, 133.1, 135.4, 135.6; FAB-HRMS *m/z* calcd for $C_{31}H_{49}O_4Si_2$ (M^++H) 541.3170, found 541.3163.

4.1.12. [1*R*,1(4*S*,5*S*),2*R*,9(3*S*,4*R*,7*S*)]-9-{2-[9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-3-(4-methoxybenzyl)oxy-4-methyl-7-(triethylsilyl)oxynonyl]-1,3-dithian-2-yl}-1-(*tert*-butyldimethylsilyl)oxy-1-[5-(*tert*-butyldiphenylsilyl)oxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-6-hydroxy-2-methylnonan-4-one (20). Butyllithium in *n*-hexane (1.56 M, 0.47 mL, 0.73 mmol) was added to a solution of HMDS (0.16 mL, 0.76 mmol) in THF (2 mL) at 0°C under an argon atmosphere. After 10 min at 0°C, the solution was cooled to −78°C, and a solution of ketone **17** (323.0 mg, 0.606 mmol) in THF (1 mL) was added. After 30 min, a solution of aldehyde **4** (336.5 mg, 0.404 mmol) in THF (1 mL) was added, and the mixture was stirred at −78°C for 1 h and at −50°C for 30 min. The reaction was

quenched with saturated aqueous NH_4Cl (15 mL), and the whole was extracted with AcOEt (2×40 mL). The combined organic extracts were washed successively with saturated aqueous NH_4Cl (20 mL) and brine (2×20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (748.0 mg, slightly yellow oil), which was purified by column chromatography (silica gel 15 g, 4:1→3:1 *n*-hexane/Et_2O) to give β-hydroxyketone **20** (508.9 mg, 88%) as a colorless oil: $[\alpha]_D^{25}=-17.7$ (*c* 1.10, $CHCl_3$); IR (neat) 3509, 2955, 1707, 1613, 1514, 1462, 1427, 1370, 1250, 1090, 835, 775, 741, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.16 to −0.15 (m, 3H, SiCH_3), −0.01 (m, 3H, SiCH_3), 0.09 (s, 6H, SiCH_3×2), 0.58 (q, *J*=7.9 Hz, 6H, Si(CH_2CH_3)$_3$), 0.78 (s, 9H, SiC(CH_3)$_3$), 0.86 (s, 9H, SiC(CH_3)$_3$), 0.90 (d, *J*=6.2 Hz, 3H, C36−H_3), 0.94 (t, *J*=7.9 Hz, 9H, Si(CH_2CH_3)$_3$), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.21 (s, 3H, C37−H_3), 1.31–1.34 (m, 4H, C22−*H*, acetonide CH_3), 1.39 (s, 3H, acetonide CH_3), 1.42–1.47 (m, 2H, C22−*H*, C14−*H*), 1.53–1.64 (m, 6H, C13−H_2, C14−*H*, C17−*H*, C21−H_2), 1.69–1.89 (m, 8H, C11−H_2, C17−*H*, C18−*H*, C20−H_2, SCH_2CH_2), 2.15 (m, 1H, C18−*H*), 2.27–2.33 (m, 2H, C26−*H*, C27−*H*), 2.37–2.43 (m, 1H, C24−*H*), 2.47–2.52 (m, 1H, C24−*H*), 2.63–2.77 (m, 5H, C26−*H*, SCH_2×2), 2.98 (d, *J*=3.0 Hz, 0.5H, O*H*), 3.03 (d, *J*=3.0 Hz, 0.5H, O*H*), 3.16 (m, 1H, C16−*H*), 3.47–3.57 (m, 2H, C10−H_2), 3.62 (m, 1H, C31−*H*), 3.66 (dd, *J*=2.3, 7.4 Hz, 1H, C28−*H*), 3.77–3.79 (m, 5H, C12−*H*, C31−*H*, $C_6H_4OCH_3$), 3.98 (m, 1H, C23−*H*), 4.06 (m, 1H, C29−*H*), 4.24 (m, 1H, C30−*H*), 4.43–4.51 (m, 3H, OC*H*Ar, OCH_2Ph), 4.58 (d, *J*=11.0 Hz, 1H, OC*H*Ar), 6.83–6.85 (m, 2H, Ar*H*), 7.23–7.27 (m, 3H, Ar*H*), 7.32–7.41 (m, 10H, Ar*H*), 7.68–7.72 (m, 4H, Ar*H*); FAB-HRMS *m/z* calcd for $C_{79}H_{130}O_{11}S_2Si_4Na$ (M^++Na) 1453.8028, found 1453.8100.

4.1.13. [1*R*,1(4*S*,5*S*),2*R*,5*E*,9(3*S*,4*R*,7*S*)]-9-{2-[9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-3-(4-methoxybenzyl)oxy-4-methyl-7-(triethylsilyl)oxynonyl]-1,3-dithian-2-yl}-1-(*tert*-butyldimethylsilyl)oxy-1-[5-(*tert*-butyldiphenylsilyl)oxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methyl-5-nonen-4-one (13). Acetic anhydride (0.05 mL, 0.538 mmol) was added to a stirred solution of alcohol **20** (428.8 mg, 0.299 mmol) and DMAP (3.6 mg, 29 μmol) in pyridine (1.5 mL) under an argon atmosphere. After stirring at room temperature for 16 h, H_2O (10 mL) was added, and the whole was extracted with AcOEt (2×40 mL). The combined organic extracts were washed successively with 1% aqueous HCl (2×20 mL), H_2O (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (2×20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (504.4 mg, yellow oil), which was used without further purification.

DBU (75 μL, 0.449 mmol) was added to a stirred solution of the crude acetate (504.4 mg) in CH_2Cl_2 (1.5 mL) at room temperature. After stirring for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the whole was extracted with AcOEt (2×40 mL). The combined organic extracts were washed successively with saturated aqueous NH_4Cl (20 mL) and brine (2×20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (534.4 mg, yellow oil), which was purified by column chromatography (silica gel 10 g, 12:1→10:1 *n*-hexane/AcOEt) to give enone **13** (375.4 mg, 89% (two steps)) as a colorless syrup. The spectral data of this material were identical with those of a sample obtained from aldehyde **4** and β-ketophosphonate **5** as described above.

4.1.14. [1*R*,1(4*S*,5*S*),2*R*,5*E*,9(3*S*,4*R*,7*S*)]-9-{2-[9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-3-hydroxy-4-methyl-7-(triethylsilyl)oxynonyl]-1,3-dithian-2-yl}-1-(*tert*-butyldimethylsilyl)oxy-1-[5-(*tert*-butyldiphenylsilyl)oxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methyl-5-nonen-4-one (21). To a solution of MPM ether **13** (601.0 mg, 0.425 mmol) in CH_2Cl_2 (8 mL)-pH 7 phosphate buffer (0.8 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (115.6 mg, 0.509 mmol) at room temperature. After stirring for 1 h, saturated aqueous $NaHCO_3$ (20 mL) was added, and the whole was extracted with AcOEt (2×40 mL). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (3×30 mL), H_2O (30 mL) and brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (626.1 mg), which was purified by column chromatography (silica gel 10 g, 10:1 *n*-hexane/AcOEt) to give alcohol **21** (512.7 mg, 93%) as a colorless oil: $[\alpha]_D^{25}=-19.1$ (*c* 1.15, $CHCl_3$); IR (neat) 3491, 2932, 1696, 1669, 1632, 1462, 1427, 1372, 1254, 1101, 837, 775, 741, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.15 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3), 0.11 (s, 6H, SiCH_3×2), 0.59 (q, *J*=8.0 Hz, 6H, Si(CH_2CH_3)$_3$), 0.78 (s, 9H, SiC(CH_3)$_3$), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.91 (d, *J*=6.8 Hz, 3H, C36−H_3), 0.95 (t, *J*=8.0 Hz, 9H, Si(CH_2CH_3)$_3$), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.21 (s, 3H, C37−H_3), 1.36 (s, 3H, acetonide CH_3), 1.40 (s, 3H, acetonide CH_3), 1.43–1.48 (m, 3H, C13−*H*, C17−H_2), 1.56–1.63 (m, 5H, C13−*H*, C14−H_2, C21−H_2), 1.72–1.95 (m, 7H, C11−H_2, C18−*H*, C20−H_2, SCH_2CH_2), 2.15–2.17 (m, 2H, C22−H_2), 2.27–2.42 (m, 4H, C18−*H*, C26−*H*, C27−*H*, O*H*), 2.71–2.86 (m, 5H, C26−*H*, SCH_2×2), 3.30 (dd, *J*=3.6, 10.2 Hz, 1H, C16−*H*), 3.52–3.55 (m, 2H, C10−H_2), 3.62 (dd, *J*=7.9, 10.9 Hz, 1H, C31−*H*), 3.68 (dd, *J*=2.8, 7.5 Hz, 1H, C28−*H*), 3.78–3.83 (m, 2H, C12−*H*, C31−*H*), 4.09 (m, 1H, C29−*H*), 4.26 (m, 1H, C30−*H*), 4.47 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.50 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 6.06 (d, *J*=15.7 Hz, 1H, C24−*H*), 6.77 (m, 1H, C23−*H*), 7.27 (m, 1H, Ar*H*), 7.32–7.42 (m, 10H, Ar*H*), 7.68–7.73 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −4.0, −2.2, −2.1, 4.9, 6.8, 14.6, 17.9, 18.1, 19.0, 22.6, 23.7, 25.2, 25.6, 25.8, 26.8, 27.8, 31.1, 32.3, 33.4, 33.9, 35.4, 36.9, 38.1, 42.9, 53.0, 63.8, 66.7, 69.7, 72.7, 72.8, 77.2, 77.3, 77.4, 78.2, 78.8, 107.9, 127.31, 127.33, 127.4, 127.5, 128.1, 129.35, 129.39, 130.9, 133.3, 133.4, 135.5, 135.7, 138.2, 145.8, 199.6; FAB-HRMS *m/z* calcd for $C_{71}H_{120}O_9S_2Si_4Na$ (M^++Na) 1315.7348, found 1315.7340.

4.1.15. [1*R*,1(4*S*,5*S*),2*R*,5*E*,9(4*R*,7*S*)]-9-{2-[9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-4-methyl-3-oxo-7-(triethylsilyl)oxynonyl]-1,3-dithian-2-yl}-1-(*tert*-butyldimethylsilyl)oxy-1-[5-(*tert*-butyldiphenylsilyl)oxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methyl-5-nonen-4-one (22). Dess–Martin periodinane (607 mg, 1.43 mmol) was added to a solution of alcohol **21** (1.03 g, 0.795 mmol) in CH_2Cl_2 (10 mL)–pyridine (2 mL) at 0°C under an argon atmosphere. After stirring at 0°C for 1 h, the reaction was

quenched with saturated aqueous $NaHCO_3$ (5 mL) and 1 M $Na_2S_2O_3$ (5 mL), and the whole was extracted with AcOEt (2×50 mL). The combined organic extracts were washed successively with 0.5% aqueous HCl (3×20 mL), saturated aqueous $NaHCO_3$ (2×20 mL) and brine (2×20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.14 g, slightly yellow oil), which was purified by column chromatography (silica gel 20 g, 16:1→12:1 *n*-hexane/AcOEt) to give ketone **22** (867.5 mg, 84%) as a colorless oil: $[\alpha]_D^{24}=-10.1$ (*c* 1.02, $CHCl_3$); IR (neat) 2953, 1715, 1672, 1630, 1462, 1427, 1368, 1254, 1215, 1090, 1007, 835, 775, 739, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.15 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3), 0.13 (s, 6H, SiCH_3×2), 0.57 (q, *J*=7.9 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.78 (s, 9H, SiC(CH_3)$_3$), 0.91–0.95 (m, 21H, C36–H_3, Si(CH$_2$CH_3)$_3$, SiC(CH_3)$_3$), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.23 (m, 1H, 13–*H*), 1.33 (s, 3H, C37–H_3), 1.36 (s, 3H, acetonide CH_3), 1.40 (s, 3H, acetonide CH_3), 1.49–1.79 (m, 9H, C11–H_2, C13–*H*, C14–H_2, C20–H_2, C21–H_2), 1.83–1.97 (m, 2H, SCH$_2$CH_2), 2.15–2.17 (m, 4H, C18–H_2, C22–H_2), 2.34 (m, 1H, C27–*H*), 2.40 (dd, *J*=8.7, 16.1 Hz, 1H, C26–*H*), 2.66–2.89 (m, 7H, C17–H_2, C26–*H*, SCH_2×2), 3.47–3.55 (m, 2H, C10–H_2), 3.62 (dd, *J*=7.8, 10.8 Hz, 1H, C31–*H*), 3.68 (dd, *J*=2.8, 7.5 Hz, 1H, C28–*H*), 3.78–3.82 (m, 2H, C12–*H*, C31–*H*), 4.09 (m, 1H, C29–*H*), 4.26 (m, 1H, C30–*H*), 4.45 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.49 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 6.06 (d, *J*=15.7 Hz, 1H, C24–H), 6.76 (m, 1H, C23–H), 7.27 (m, 1H, ArH), 7.31–7.42 (m, 10H, ArH), 7.68–7.73 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −3.9, −2.19, −2.17, 5.0, 6.9, 14.7, 18.0, 19.1, 22.7, 25.1, 25.7, 25.86, 25.93, 26.9, 27.9, 31.3, 31.7, 32.4, 33.4, 34.0, 36.9, 37.1, 39.0, 43.0, 52.7, 63.9, 66.9, 69.2, 72.8, 72.9, 77.2, 77.5, 78.2, 78.9, 82.7, 108.0, 127.38, 127.43, 127.52, 127.54, 128.2, 129.4, 129.5, 131.1, 133.4, 133.5, 135.7, 135.8, 138.4, 145.7, 199.8, 214.6; FAB-HRMS *m/z* calcd for $C_{71}H_{118}O_9S_2Si_4Na$ (M^++Na) 1313.7191, found 1313.7170.

4.1.16. [1*R*,1(4*S*,5*S*),2*R*,5*E*,14*R*,17*S*]-19-Benzyloxy-1,14-bis(*tert*-butyldimethylsilyl)oxy-1-[5-(*tert*-butyldiphenylsilyl)oxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2,14-dimethyl-17-(triethylsilyl)oxy-5-nonadecene-4,10,13-trione (23). A solution of dithioacetal **22** (181.9 mg, 0.140 mmol) in Et_2O (0.5 mL) was added to a solution of $AgNO_3$ (143.5 mg, 0.845 mmol), *N*-chlorosuccinimide (121.5 mg, 0.91 mmol) and 2,4,6-collidine (0.1 mL, 0.757 mmol) in 80% aqueous CH_3CN (3 mL) at room temperature. After stirring for 20 min, saturated aqueous Na_2SO_3 (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL) were added to the mixture. The mixture was filtered through a Celite pad, and the filtrate was extracted with AcOEt (2×40 mL). The combined organic extracts were washed successively with 0.5% aqueous HCl (2×30 mL), H_2O (20 mL), saturated aqueous $NaHCO_3$ (2×30 mL) and brine (2×20 mL), and dried over Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (229.6 mg), which was purified by column chromatography (silica gel 10 g, 16:1 *n*-hexane/AcOEt) to give triketone **23** (145.8 mg, 87%) as a colorless oil: $[\alpha]_D^{25}=-13.1$ (*c* 1.05, $CHCl_3$); IR (neat) 2955, 1715, 1672, 1630, 1462, 1370, 1254, 1215, 1090, 1007, 837, 777, 739, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −1.64 (s, 3H, SiCH_3), −0.01 (s, 3H, SiCH_3), 0.13 (s, 3H, SiCH_3), 0.14 (s, 3H, SiCH_3), 0.58 (q, *J*=7.9 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.77 (s, 9H, SiC(CH_3)$_3$), 0.91–0.96 (m, 21H, C36–H_3, Si(CH$_2$-CH_3)$_3$, SiC(CH_3)$_3$), 1.05 (s, 9H, SiC(CH_3)$_3$), 1.23 (m, 1H, C13–*H*), 1.33 (s, 3H, C37–H_3), 1.36 (s, 3H, acetonide CH_3), 1.40 (s, 3H, acetonide CH_3), 1.47–1.64 (m, 2H, C13–*H*, C14–*H*), 1.67–1.78 (m, 5H, C11–H_2, C14–*H*, C21–H_2), 2.13–2.17 (m, 2H, C22–H_2), 2.32 (m, 1H, C27–*H*), 2.39 (dd, *J*=8.5, 16.1 Hz, 1H, C26–*H*), 2.46–2.62 (m, 4H, C18–H_2, C20–H_2), 2.76–2.82 (m, 2H, C17–*H*, C26–*H*), 2.97 (ddd, *J*=5.1, 7.4, 19.4 Hz, 1H, C17–*H*), 3.48–3.56 (m, 2H, C10–H_2), 3.61 (dd, *J*=7.7, 10.8 Hz, 1H, C31–*H*), 3.67 (dd, *J*=2.7, 7.5 Hz, 1H, C28–*H*), 3.76–3.82 (m, 2H, C12–*H*, C31–*H*), 4.09 (dd, *J*=6.2, 7.5 Hz, 1H, C29–*H*), 4.25 (m, 1H, C30–*H*), 4.45 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.49 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 6.05 (d, *J*=16.0 Hz, 1H, C24–*H*), 6.74 (m, 1H, C23–*H*), 7.27 (m, 1H, Ar*H*), 7.31–7.42 (m, 10H, Ar*H*), 7.67–7.73 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −3.9, −2.22, −2.15, 5.0, 6.9, 14.7, 18.0, 18.3, 19.1, 22.0, 25.7, 25.86, 25.93, 26.1, 26.9, 27.9, 31.47, 31.54, 32.2, 34.0, 35.8, 36.8, 37.0, 41.8, 43.0, 63.9, 66.9, 69.2, 72.7, 72.9, 77.5, 78.9, 82.7, 108.0, 127.35, 127.43, 127.5, 128.2, 129.45, 129.50, 131.1, 133.4, 133.5, 135.7, 135.8, 138.5, 145.7, 199.9, 208.3, 214.2; FAB-HRMS *m/z* calcd for $C_{68}H_{112}O_{10}Si_4Na$ (M^++Na) 1223.7230, found 1223.7270.

4.1.17. [1(2*R*,6*R*,8*R*,10*S*,13*R*),4*R*,5*R*,5(4*S*,5*S*)]-1-[10-(2-Benzyloxy)ethyl-13-(*tert*-butyldimethylsilyl)oxy-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-5-(*tert*-butyldimethylsilyl)oxy-5-[5-(*tert*-butyldiphenylsilyl)oxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylpentan-2-one (1). To a solution of TES ether **23** (554.2 mg, 0.46 mmol) in THF (7 mL) at 0°C was added 1N aqueous HCl (0.7 mL). After stirring at 0°C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and the whole was extracted with AcOEt (50 mL). The organic extract was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (539.8 mg), which was used without further purification.

LiOMe (17.6 mg, 0.46 mmol) was added to a stirred solution of the equilibrium mixture (539.8 mg) in THF (5 mL)–MeOH (0.5 mL) at 0°C under an argon atmosphere. After stirring at room temperature for 4 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL), and the mixture was partitioned between AcOEt (50 mL) and H_2O (10 mL). The organic extract was washed with brine (10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (524.2 mg, yellow oil), which was purified by flash column chromatography (silica gel 30 g, 12:1→8:1 *n*-hexane/Et_2O) to give dispiroketal **1** (387.3 mg, 77%) as a colorless oil, along with isomers (one less polar isomer (29.4 mg, 6%) and two more polar isomers (40.8 mg, 8%)) as a colorless oil: $[\alpha]_D^{24}=-22.9$ (*c* 0.46, $CHCl_3$); IR (neat) 2934, 2859, 1713, 1462, 1370, 1254, 1223, 1088, 976, 835, 775, 737, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.17 (s, 3H, SiCH_3), −0.02 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.76 (s, 9H, SiC(CH_3)$_3$), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.87 (d, *J*=6.7 Hz, 3H, C36–H_3), 1.01 (m, 1H, C22–*H*), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.28 (s, 3H, C37–H_3), 1.33 (s, 3H, acetonide CH_3), 1.37 (s, 3H, acetonide

CH_3), 1.39–1.51 (m, 3H, C13–*H*, C20–*H*, C21–*H*), 1.59–1.61 (m, 3H, C13–*H*, C14–*H*, C22–*H*), 1.67–1.83 (m, 5H, C11–H_2, C17–*H*, C18–*H*, C20–*H*), 1.88 (m, 1H, C21–*H*), 2.02 (m, 1H, C18–*H*), 2.08–2.29 (m, 4H, C14–*H*, C17–*H*, C26–*H*, C27–*H*), 2.38 (dd, *J*=8.2, 16.0 Hz, 1H, C24–*H*), 2.50 (dd, *J*=5.1, 16.0 Hz, 1H, C24–*H*), 2.66 (dd, *J*=5.0, 16.7 Hz, 1H, C26–*H*), 3.48 (m, 1H, C10–*H*), 3.56–3.61 (m, 3H, C10–*H*, C28–*H*, C31–*H*), 3.76 (dd, *J*=2.4, 10.8 Hz, 1H, C31–*H*) 3.94 (m, 1H, C12–*H*), 4.04 (dd, *J*=6.2, 7.5 Hz, 1H, C29–*H*), 4.23–4.30 (m, 2H, C23–*H*, C30–*H*), 4.44 (s, 2H, OCH_2Ph), 7.23 (m, 1H, Ar*H*), 7.29–7.41 (m, 10H, Ar*H*), 7.67–7.72 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.0, −3.8, −1.93, −1.90, 14.4, 18.1, 19.1, 19.4, 24.4, 25.8, 25.9, 28.1, 30.2, 30.6, 30.8, 33.5, 34.2, 34.5, 35.8, 37.5, 47.3, 49.8, 63.9, 67.8, 68.0, 68.9, 72.2, 72.7, 73.4, 77.3, 79.0, 107.9, 108.1, 110.5, 127.3, 127.4, 127.5, 127.6, 128.2, 129.5, 129.6, 133.5, 133.6, 135.7, 135.9, 138.7, 208.7; FAB-HRMS *m/z* calcd for $C_{62}H_{98}O_{10}Si_3Na$ (M^++Na) 1109.6365, found 1109.6440; Anal. calcd for $C_{62}H_{98}O_{10}Si_3$: C, 68.46; H, 9.08, found: C, 68.06; H, 9.00.

4.1.18. [2*S*,5*R*,6*R*,8*R*,10*R*,10(1*S*,2*R*,3*R*,5*R*,7*S*)]-2-[2-(Benzyloxy)ethyl]-5-(*tert*-butyldimethylsilyl)oxy-10-[2-(*tert*-butyldimethylsilyl)oxy-7-(*tert*-butyldiphenylsilyl)-oxymethyl-3-methyl-6,8-dioxabicyclo[3.2.1]oct-5-ylmethyl]-5-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadecane (25). To a solution of ketone **1** (48.0 mg, 44.1 μmol) in CH_2Cl_2 (0.5 mL) was added CSA (10.3 mg, 44.1 μmol), and the solution was stirred for 5 h. The mixture was poured into a two-layer mixture of saturated aqueous $NaHCO_3$ (5 mL) and Et_2O (5 mL), and the whole was extracted with AcOEt (2×15 mL). 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 (slightly yellow oil), which was purified by column chromatography (silica gel 15 g, 16:1 *n*-hexane/AcOEt) and preparative thin layer chromatography (20:1 CH_2Cl_2/AcOEt) to give bicycloketal **25** (28.1 mg, 62%) as a colorless oil: $[\alpha]_D^{21}$=+9.81 (*c* 1.65, $CHCl_3$); IR (neat) 2953, 2859, 1462, 1364, 1252, 1138, 1103, 1049, 1005, 976, 835, 774, 702 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.13 (s, 6H, SiCH_3), 0.17 (s, 3H, SiCH_3), 0.18 (s, 3H, SiCH_3), 0.94 (d, *J*=6.7 Hz, 3H, C36–H_3), 1.01 (s, 9H, SiC(CH_3)$_3$), 1.07 (s, 9H, SiC(CH_3)$_3$), 1.19 (s, 9H, SiC(CH_3)$_3$), 1.34 (s, 3H, C37–H_3), 1.37 (m, 1H, C22–*H*), 1.46–1.53 (m, 3H), 1.57 (m, 1H), 1.64 (m, 1H), 1.72 (t, *J*=12.5 Hz, 1H, C26–*H*), 1.81–1.87 (m, 2H), 1.89–2.00 (m, 3H), 2.02–2.21 (m, 6H), 2.27–2.38 (m, 3H), 3.75 (m, 1H, C10–*H*), 3.79 (t, *J*=1.5 Hz, 1H, C28–*H*), 3.83 (m, 1H, C10–*H*), 4.00 (dd, *J*=9.3, 10.4 Hz, 1H, C31–*H*), 4.21 (dd, *J*=5.5, 10.4 Hz, 1H, C31–*H*), 4.27 (m, 1H, C12–*H*), 4.43 (m, 1H, C30–*H*), 4.43 (d, *J*=12.3 Hz, 1H, OC*H*Ph), 4.47 (d, *J*=12.3 Hz, 1H, OC*H*Ph), 4.50 (m, 1H, C23–*H*), 4.56 (dd, *J*=1.5, 4.3 Hz, 1H, C29–*H*), 7.13 (m, 1H, Ar*H*), 7.18–7.23 (m, 2H, Ar*H*), 7.26–7.29 (m, 6H, Ar*H*), 7.35–7.38 (m, 2H, Ar*H*), 7.76–7.78 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.3, −1.88, −1.86, 16.9, 18.1, 18.3, 19.2, 19.7, 24.4, 25.89, 25.92, 26.8, 29.6, 30.1, 30.6, 32.3, 34.3, 34.6, 35.7, 37.6, 39.4, 44.7, 61.5, 67.8, 67.9, 68.0, 68.8, 72.7, 73.5, 78.0, 80.2, 107.9, 108.0, 110.3, 127.2, 127.4, 127.7, 127.8, 128.2, 129.8, 133.0, 133.2, 135.5, 135.6, 138.8; FAB-HRMS *m/z* calcd for $C_{59}H_{92}O_9Si_3Na$ (M^++Na) 1051.5946, found 1051.5980.

4.1.19. (2*R*,3*S*,4*S*)-2-(*tert*-Butyldimethylsilyl)oxy-5-(*tert*-butyldiphenylsilyl)oxy-3,4-(dimethylmethylene)dioxypentanal (26). Ozone gas was bubbled through a stirred solution of enoate **10** (100.4 mg, 0.164 mmol) in CH_2Cl_2 (20 mL) at −78°C until the solution turned pale blue. After stirring at −78°C for 15 min, Me_2S (5 mL) was added, and the mixture was stirred at room temperature for 10 h. Evaporation in vacuo furnished the crude product (108 mg, slightly yellow oil), which was purified by column chromatography (silica gel 15 g, 20:1 *n*-hexane/AcOEt) to give aldehyde **26** (74.3 mg, 83%) as a colorless oil: $[\alpha]_D^{26}$=−4.7 (*c* 1.13, $CHCl_3$); IR (neat) 2932, 2859, 1738, 1472, 1427, 1383, 1256, 1111, 837, 781, 704 cm^{-1}; ^{1}H NMR (270 MHz, $CHCl_3$) δ −0.08 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3), 0.81 (s, 9H, SiC(CH_3)$_3$), 1.06 (s, 9H, SiC(CH_3)$_3$), 1.33 (s, 3H, acetonide CH_3), 1.42 (s, 3H, acetonide CH_3), 3.77 (dd, *J*=5.9, 10.5 Hz, 1H, C31–*H*), 3.97 (dd, *J*=4.6, 10.5 Hz, 1H, C31–*H*), 4.25–4.31 (m, 3H, C28–*H*, C29–*H*, C30–*H*), 7.37–7.44 (m, 6H, Ar*H*), 7.67–7.70 (m, 6H, Ar*H*), 9.58 (d, *J*=2.0 Hz, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.5, 18.0, 19.2, 24.9, 25.7, 26.9, 27.1, 63.3, 76.6, 77.4, 77.9, 108.7, 127.6, 127.7, 129.65, 129.67, 133.2, 133.4, 135.6, 135.7, 201.4; FAB-HRMS *m/z* calcd for $C_{48}H_{80}O_6S_2Si_2Na$ (M^++Na) 895.4832, found 895.4851.

4.1.20. [1(2*R*,6*R*,8*R*,10*S*,13*R*),5*R*,5(4*S*,5*S*)]-1-[10-(2-Benzyloxy)ethyl-13-(*tert*-butyldimethylsilyl)oxy-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-5-(*tert*-butyldimethylsilyl)oxy-5-[5-(*tert*-butyldiphenylsilyl)oxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3-penten-2-one (28). To a solution of LiHMDS (prepared from HMDS (10 μL, 47.4 μmol) and butyllithium in *n*-hexane (1.56 M, 28 μL, 43.7 μmol)) in THF (0.25 mL) was added a solution of methyl ketone **3** (20.0 mg, 36.6 μmol) in THF (0.1 mL) at −78°C under an argon atmosphere. After stirring at this temperature for 1 h, aldehyde **26** (23.8 mg, 43.9 μmol) in THF (0.15 mL) was added, and the resulting mixture was stirred at −78°C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (1 mL), and the mixture was partitioned between Et_2O (3 mL) and H_2O (3 mL). The aqueous layer was extracted with AcOEt (2×10 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 (46.1 mg), which was used without further purification.

Ac_2O (10 μL, 0.11 mmol) was added to a stirred solution of the aldol adduct (46.1 mg) in pyridine (0.3 mL) under an argon atmosphere. After stirring for 5 h, the solution was poured into a two-layer mixture of AcOEt (5 mL) and H_2O (1 mL), and the whole was extracted with AcOEt (5 mL). The organic extract was washed successively with 3% aqueous HCl (3×3 mL), H_2O (3 mL), saturated aqueous $NaHCO_3$ (3 mL) and brine (2×3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (48.4 mg), which was used without further purification.

DBU (10 μL, 66.9 μmol) was added to a solution of the acetate (48.4 mg) in CH_2Cl_2 (0.3 mL) at 0°C under an argon atmosphere. After stirring for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (0.5 mL), and the

whole was partitioned between AcOEt (5 mL) and H_2O (1 mL). The organic extract was washed with brine (2×2 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (47.3 mg), which was purified by column chromatography (silica gel 15 g, 60:1 benzene/acetone) to give enone **28** (9.6 mg, 24%) as a colorless oil, along with recovered ketone **3** (10.9 mg, 56%): $[\alpha]_D^{21}=-3.8$ (*c* 0.25, C_6H_6); IR (neat) 2932, 2857, 1698, 1674, 1634, 1462, 1370, 1254, 1223, 1111, 978, 835, 775, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.18 (s, 3H, SiCH_3), −0.10 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.73 (s, 9H, SiC(CH_3)$_3$), 0.85 (s, 9H, SiC(CH_3)$_3$), 1.06 (9H, SiC(CH_3)$_3$), 1.09–1.18 (m, 1H, C22–*H*), 1.28 (s, 3H, C37–H_3), 1.30 (s, 3H, acetonide CH_3), 1.39 (s, 3H, acetonide CH_3), 1.41–1.49 (m, 2H, C13–*H*, C20–*H*), 1.56–1.86 (m, 9H, C11–H_2, C13–*H*, C14–*H*, C17–*H*, C18–*H*, C20–*H*, C21–*H*, C22–*H*), 1.90 (m, 1H, C21–*H*), 1.99–2.18 (m, 3H, C14–*H*, C17–*H*, C18–*H*), 2.59 (dd, *J*=7.9, 15.5 Hz, 1H, C24–*H*), 2.64 (dd, *J*=5.1, 15.5 Hz, 1H, C24–*H*), 3.49 (m, 1H, C10–*H*), 3.59 (m, 1H, C10–*H*), 3.75 (dd, *J*=8.0, 11.2 Hz, 1H, C31–*H*), 3.87 (dd, *J*=3.0, 11.2 Hz, 1H, C31–*H*), 3.96 (m, 1H, C12–*H*), 4.00 (m, 1H, C29–*H*), 4.28 (m, 1H, C30–*H*), 4.34–4.39 (m, 2H, C23–*H*, C28–*H*), 4.43 (s, 2H, OCH_2Ph), 6.16 (d, *J*=15.7 Hz, 1H, C26–*H*), 6.66 (dd, *J*=6.0, 15.7 Hz, 1H, C27–*H*), 7.23 (m, 1H, Ar*H*), 7.28–7.42 (m, 10H, Ar*H*), 7.67–7.71 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −3.8, −1.92, −1.88, 17.9, 18.7, 19.2, 19.5, 24.4, 25.4, 25.7, 25.9, 26.9, 27.6, 29.7, 30.2, 30.5, 30.6, 34.2, 34.5, 35.9, 37.5, 47.3, 63.7, 67.8, 68.0, 69.4, 71.1, 72.8, 73.4, 78.7, 79.3, 108.0, 108.5, 110.5, 127.3, 127.6, 127.7, 128.2, 129.59, 129.63, 131.3, 133.4 133.6, 135.6, 135.7, 135.8, 138.7, 145.4, 198.0; FAB-HRMS *m/z* calcd for $C_{61}H_{94}O_{10}Si_3Na$ (M^++Na) 1093.6052, found 1093.6040.

4.1.21. [1(2*R*,6*R*,8*R*,10*S*,13*R*),4*R*,5*R*,5(4*S*,5*S*)]-1-[10-(2-Benzyloxy)ethyl-13-(*tert*-butyldimethylsilyl)oxy-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-5-(*tert*-butyldimethylsilyl)oxy-5-[5-(*tert*-butyldiphenylsilyl)-oxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methyl-pentan-2-one (1). Methyllithium in Et_2O (1.14 M, 0.16 mL, 0.18 mmol) was added to a suspension of CuCN (16.0 mg, 0.18 mmol) in THF (1 mL) at −78°C under an argon atmosphere, and the resulting mixture was stirred at 0°C for 10 min to form a clear, colorless solution. After cooling to −78°C, $BF_3{\cdot}OEt_2$ (24 μL, 0.19 mmol) was added, and the mixture was stirred at this temperature for 5 min. A solution of enone **28** (12.0 mg, 11.2 μmol) in THF (0.5 mL) was added, and the mixture was stirred at −78°C for 2 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL) and 28% aqueous NH_3 (1 mL), and the mixture was diluted with Et_2O (5 mL). After stirring at room temperature for 20 min, the whole was extracted with AcOEt (15 mL). The organic extract was washed successively with 3% aqueous HCl (5 mL), H_2O (10 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel 5 g, 12:1 *n*-hexane/AcOEt) to give ketone **1** (8.9 mg, 73%) as a colorless syrup. The spectral data of this material were identical with those of a sample obtained from triketone **23** as described above.

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18. The isomerization of **25** to its C19 epimer, if any, could not be found under the ketalization conditions (CSA in CH_2Cl_2). In this respect, Murai and co-workers reported that the C19 epimer of the closely related dispiroketal compound isomerized under the similar conditions to give a 4.3:1 equilibrium mixture of C19 epimeric dispiroketals, with the undesired configuration favored.[19] However, they did not mention the result of epimerization of the desired isomer.
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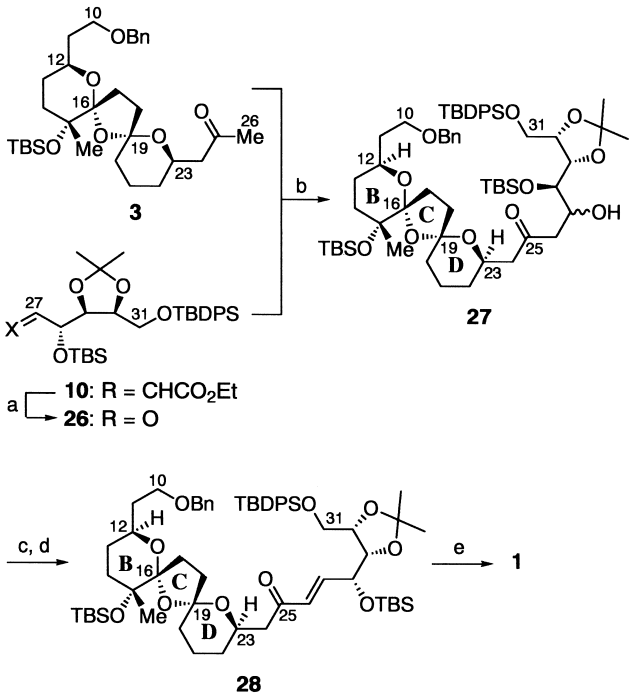
20. To further ascertain the stereochemical assignment of the products, an alternative route to the dispiroketal **1** from **3**, the stereochemistry of which was unambiguously established by a single-crystal X-ray analysis,[1] was explored (Scheme 5). The reaction of the lithium enolate derived from methyl ketone **3** with aldehyde **26**, which was obtained by the ozonolysis of enoate **10** in 83% yield, stopped at ca. 40% conversion of **3** to afford an inseparable mixture of aldol adduct **27** and unreacted ketone **3**. Treatment of the mixture with Ac_2O followed by exposure to DBU gave enone **28** in 24% overall yield for the three steps, along with 56% recovery of ketone **3**. Installation of the C27 methyl group under the foregoing conditions furnished **1** in 73% yield, which was identical in all respects with the material derived from an equilibrium mixture of hydroxytriketone **24** and hemiketals.



Scheme 5. *Reagents and conditions*: (a) O_3, CH_2Cl_2, −78°C, 15 min, then Me_2S, rt, 10 h, 83%; (b) LiHMDS, THF, −78°C, 1 h, then **26**, −78°C, 2 h; (c) Ac_2O, pyridine, 5 h; (d) DBU, CH_2Cl_2, 0°C, 2 h, 24% (three steps); (e) MeCu(CN)Li, $BF_3{\cdot}OEt_2$, THF/Et_2O (11:1), −78°C, 2 h, 73%.