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Studies directed toward the total synthesis of pinnatoxin A: synthesis of the 6,5,6-dispiroketal (BCD ring) system by double hemiketal formation/hetero-Michael addition strategy

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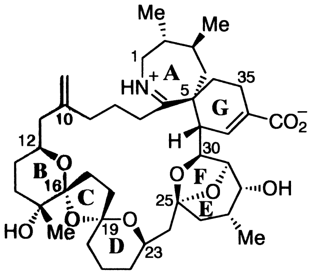
Abstract—An efficient, highly stereoselective synthesis of the C10–C26 portion of pinnatoxin A has been achieved, wherein the key step is a highly stereoselective construction of the 6,5,6-dispiroketal (BCD ring) system by an intramolecular hetero-Michael addition of a hemiketal alkoxide reversibly formed under the influence of lithium methoxide. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently, novel marine-derived polyether macrocycles such as pinnatoxins,[1] spirolides,[2] gymnodimine,[3] and spiro-prorocentrimine[4] containing a spiro-linked cyclic imine moiety have been isolated. These natural products have been considered as culprits in shellfish poisoning, and the majority of them have also been found to be Ca^{2+} channel activators.[2a,5] Pinnatoxins, the first and most prominent members of this class, were isolated from the shellfish *Pinna muricata* and characterized by Uemura and co-workers in 1995.[1a] Very recently, pteriatoxins have been isolated from the Okinawan bivalve *Pteria penguin* and characterized by the same group.[1e] Structurally, pinnatoxins and pteriatoxins share a unique 27-membered carbocyclic backbone which is composed of an unusual 6,7-spiro-linked imine moiety (AG ring), a 5,6-bicycloketal (EF ring), and a 6,5,6-dispiroketal (BCD ring), and represent variations in the substitution pattern at C21, C22, C28 and C33. Their unprecedented molecular architecture, coupled with the associated biological activity and scarcity of natural supply, renders them worthy targets for total synthesis.[6–8]



Pinnatoxin A (**1**)

With respect to a presumed biosynthetic pathway to these molecules, Uemura proposed that the 6,7-azaspirocyclic (AG ring) system would arise from a sequence of intramolecular Diels–Alder reaction and imine formation events or vice versa, which would lead to the concurrent assembly of a polyether macrocycle. In this context, a macrocyclization strategy via a biomimetic intramolecular Diels–Alder reaction, while its application remains to be explored, would provide one of the most concise and elegant solutions to the challenge posed by their molecular architecture. By employing this bold macrocyclization strategy followed by an ingenious imine formation, Kishi and co-workers accomplished the first total synthesis of (−)-pinnatoxin A in 1998, which also established the absolute stereochemistry of the natural (+)-pinnatoxin A, as shown in **1**.[6] The crucial biomimetic intramolecular Diels–Alder reaction in Kishi's landmark synthesis of (−)-**1** produced a 1.0:0.9:0.4 mixture of three out of the eight possible adducts, with the desired *exo* product favored. It is of interest to note that all three products possessed the correct regiochemistry, while there is room for improvement in the stereoselectivity.

In planning our synthesis of pinnatoxin A (**1**), we also were greatly intrigued by Uemura's biosynthetic proposal.[1a] Our synthetic strategy is outlined in Scheme 1. Standard retrosynthetic manipulation of **1** based on an intramolecular Diels–Alder transform dictated disconnections at the C9–C10, C5–C31, and C35–C39 linkages to reveal diene **2** as an advanced intermediate. We envisioned installation of the C31–C35 diene moiety exploiting Wittig olefination or a

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

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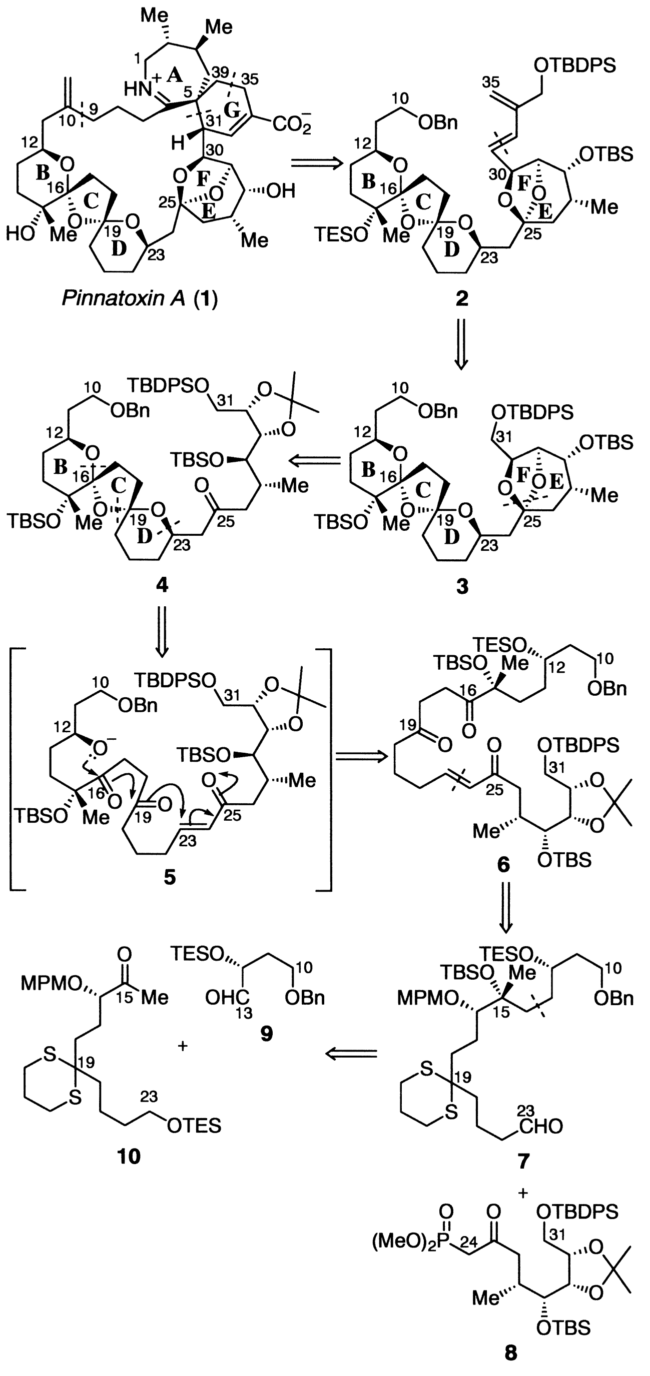
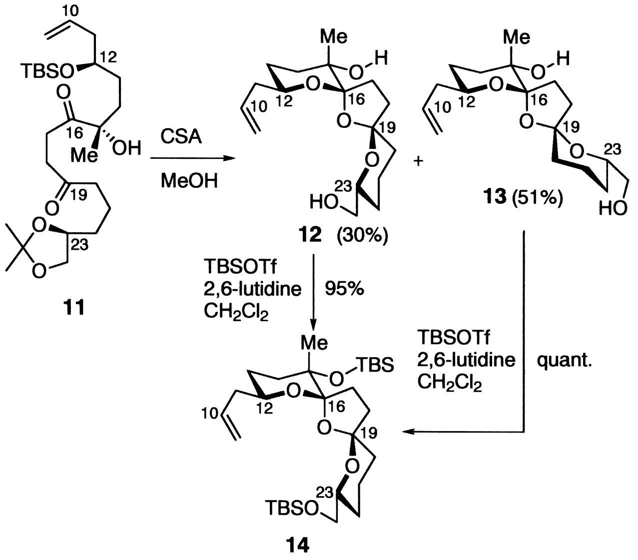
like process, which led back to the C10–C31 fragment **3**. The bicycloketal (EF) ring system in **3** could be constructed readily from ketone **4** by an intramolecular ketalization via C29,C30-diol. Consequently, the C10–C31 ketone fragment **4** became the first important target for our synthetic venture, wherein a strategic point lay in the construction of the 6,5,6-dispiroketal (BCD ring) system.

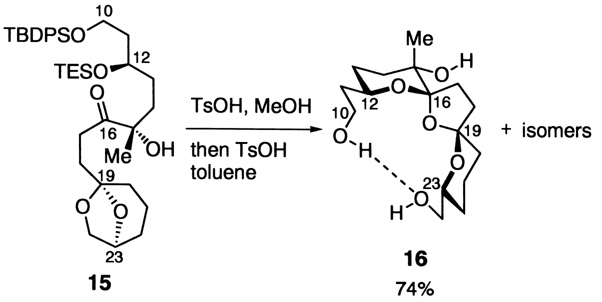


Scheme 1. Retrosynthetic analysis of pinnatoxin A.

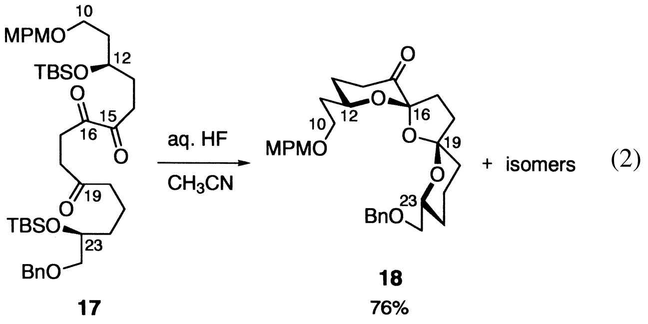


Scheme 2. Kishi's synthesis of the dispiroketal portion of (−)-pinnatoxin A.

Apart from the construction of the azaspirocyclic (AG ring) system, a stereocontrolled construction of the 6,5,6-dispiroketal (BCD ring) system presents a major challenge in the synthesis of **1** as mentioned by the Kishi,[6] Murai,[7] and Hirama[8] groups.[9] Although a number of methods have been developed to synthesize bicyclic spiroketal subunits,[10] the formation of tricyclic dispiroketals has been less thoroughly investigated.[11,12] The majority of reported synthetic strategies in either case rely on acid-catalyzed cyclization of open-chain hydroxyketones. An important consideration for dispiroketalization here is that the BCD ring system with a *cisoid* relationship about the spirocyclic centers benefits from two anomeric effects but experiences the dipole-dipole repulsion arising from the C16–O12 and C19–O23 bonds. Hence, it is uncertain whether the classic dispiroketalization strategy will result in high selectivity for the desired ketal configurations. In this context, Kishi and co-workers demonstrated that treatment of an appropriate tetrahydroxy diketone with CSA led to the formation of a 2:3 mixture of C19 epimeric dispiroketals, and the unwanted *transoid* isomer epimerized exclusively to the desired *cisoid* isomer under standard silylation conditions (Scheme 2).[6] In the same context, Hirama and co-workers found that the equilibrium ratio of C19 epimeric dispiroketals under thermodynamically controlled ketalization was greatly improved by use of toluene as a solvent, wherein it was suggested that an intramolecular hydrogen bond between the terminal C10,C24-dihydroxy groups might play an important role in the stereoselective formation of the desired isomer (Eq. (1)).[8a] On the other hand, Murai and Ishihara and co-workers reported that treatment of 1,12-bis(silyloxy)-4,5,8-triketone with aqueous HF in CH_3CN led to the preferential formation of the desired 6,5,6-dispiroketal out of the eight possible isomers in 76% yield, and suggested that the anomeric effect would be enhanced by a ketone carbonyl group adjacent to the spirocenter (Eq. (2)).[7a,b]



(1)



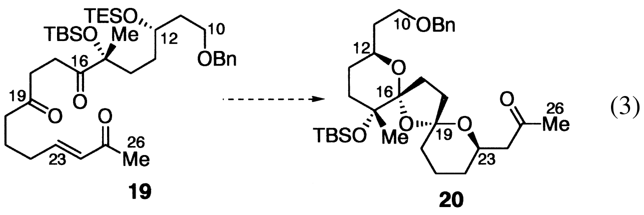
An alternative approach to spiroketals involves the hetero-Michael addition of a hemiketal alkoxide to an internal enone,[13] which has the advantage of generating a chiral center from an enone in the conjugate addition step as well as a chiral spirocenter. This elegant approach, however, has not yet been applied to the synthesis of dispiroketals. On inspection of a ketone carbonyl group at C25 of **4**, it was readily apparent that a strategy based on this approach would not only benefit from the construction of the BCD ring system but also from the direct assembly of the EF ring system. Some concern, however, arose over the formation of the C19,C23 epimeric dispiroketal with a *transoid* arrangement, which is not only stabilized by two anomeric effects like the desired *cisoid* isomer but also relieved of the dipole repulsion. Despite no clear thermodynamic preference for the desired isomer, we envisaged that the dispiroketal fragment **4** would be favorably derived from the tandem hemiketal formation/hetero-Michael reaction sequence shown in **5** by judicious choice of conditions. As a result, the C10–C31 enone fragment **6** was chosen as a precursor to **4**. After appropriate functional group manipulations, **6** could be disconnected at the C23–C24 double bond to give aldehyde **7** and β-ketophosphonate **8**. In turn the aldehyde **7** was envisioned to be obtained by aldol fragment coupling of aldehyde **9** and methyl ketone **10** followed by installation of the C15 methyl group.

In our initial studies directed toward the total synthesis of **1**, we felt it was prudent to test the viability of the key hemiketal formation/hetero-Michael reaction process to construct the BCD ring system. Herein, we describe the details of our model study and offer a mechanistic explanation for the stereochemical outcome observed in the present reaction.[14]

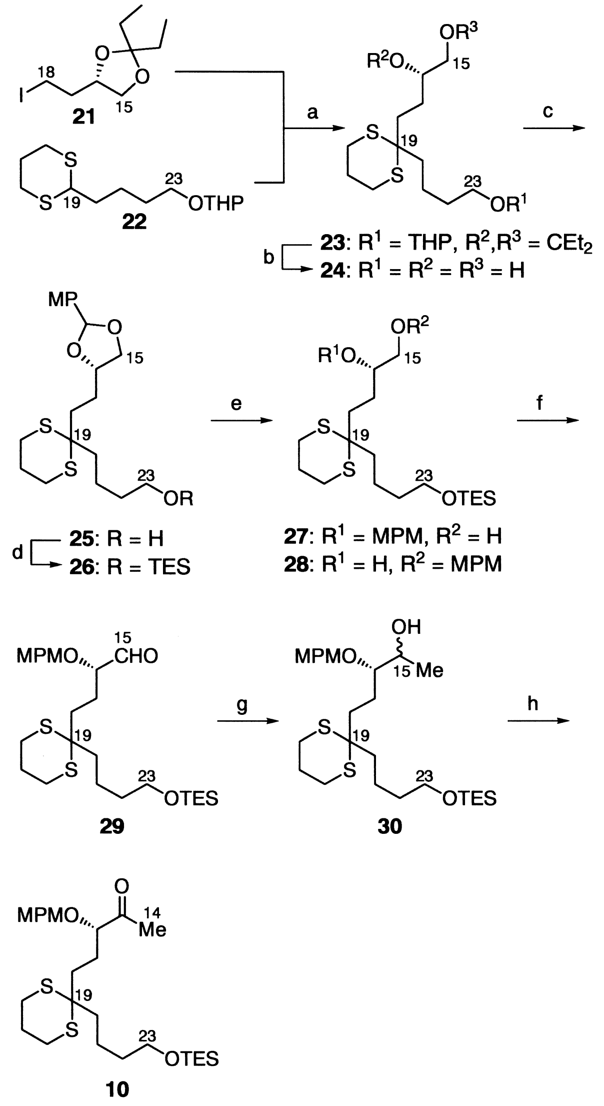
2. Results and discussions

2.1. Synthesis of the dispiroketalization precursor

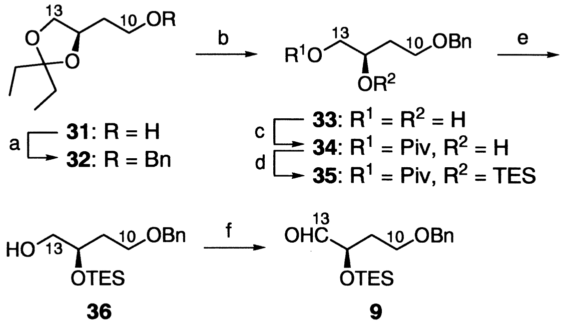
With the synthesis of halichondrin Bs, Kishi and co-workers achieved the novel construction of the fully functionalized 6,6-spiroketal system by exploiting tandem Bu_4NF-induced in situ desilylation/hemiketal formation/intramolecular hetero-Michael addition.[13d] Based on this precedent, triketone **19** corresponding to the C10–C26 portion of pinnatoxin A was chosen as a model substrate for the dispiroketalization studies. At this juncture, we envisaged that the assembly of the dispiroketal **20** would be triggered by selective desilylation of the C12 TES group in **19** with Bu_4NF (Eq. (3)).



To this end, the synthesis of the C14–C23 ketone fragment **10** commenced with alkylation of dithiane **22**[15] with iodide **21**[16] (Scheme 3). Lithiation of **22** followed by addition of iodide **21** furnished 2,2-disubstituted dithiane **23** in 95% yield. Exposure of **23** to TsOH in aqueous MeOH resulted in concurrent removal of the pentylidene ketal and the THP ether to give triol **24** (98%), which upon treatment with 4-methoxybenzaldehyde dimethyl acetal in the presence of a catalytic amount of PPTS provided alcohol **25** in 75%



Scheme 3. *Reagents and conditions*: (a) BuLi, THF/HMPA (10:1), −78°C, 1 h, 95%; (b) TsOH, MeOH/H_2O, 35 h, 98%; (c) anisaldehyde dimethyl acetal, PPTS, CH_2Cl_2, 6 h, 75%; (d) TESCl, imidazole, CH_2Cl_2, 2 h, 98%; (e) DIBAL-H, CH_2Cl_2, −78 to −20°C, 2 h, 87%; (f) SO_3·pyridine, Et_3N, DMSO, 1 h, 92%; (g) MeMgI, THF–Et_2O, −78 to −50°C, 2 h, 92%; (h) SO_3·pyridine, Et_3N, DMSO, 1 h, 93%.

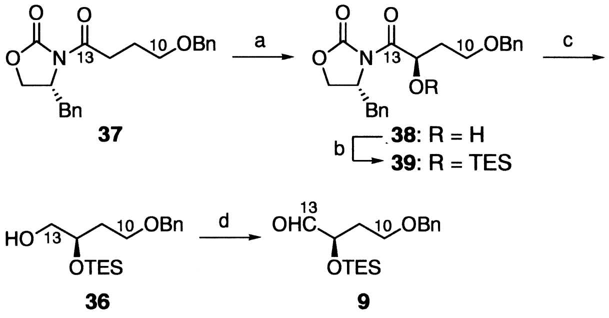


Scheme 4. *Reagents and conditions*: (a) NaH, BnBr, THF/HMPA (5:1), 10 h; (b) TsOH, THF/H_2O (10:1), 60°C, 5 h, 91% (two steps); (c) PivCl, pyridine, CH_2Cl_2, 0°C, 1 h, then rt, 1 h, 90%; (d) TESCl, Et_3N, CH_2Cl_2, 1 h, 97%; (e) DIBAL-H, CH_2Cl_2, −78°C, 1 h, 94%; (f) SO_3·pyridine, Et_3N, DMSO, 1 h, 97%.

yield. Silylation of the C23 hydroxyl group with TESCl was followed by reductive cleavage of the 4-methoxybenzylidene (MP) acetal with DIBAL-H[17] to afford primary alcohol **27** in 85% yield, along with 7% of its isomer **28**. Transformation of alcohol **27** to methyl ketone **10** was effected by sequential Parikh–Doering oxidation,[18] addition of MeMgI, and re-oxidation in 79% yield for the three-step process.

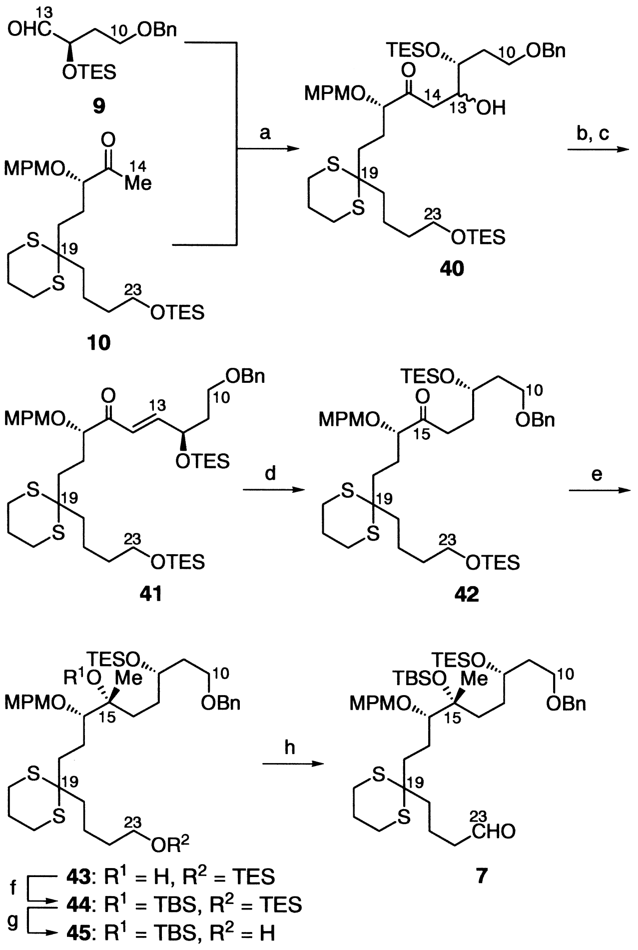
The synthesis of the C10–C13 aldehyde fragment **9** was initiated with benzylation of the known alcohol **31**, readily obtained from D-malic acid,[19] to provide benzyl ether **32**, which upon exposure to TsOH in aqueous THF afforded diol **33** in 91% yield (Scheme 4). Selective protection of the primary hydroxyl group with PivCl was followed by silylation with TESCl to give **35** in 87% yield. Deprotection of the C13 pivaloate ester with DIBAL-H provided alcohol **36** in 94% yield, which underwent Parikh–Doering oxidation to afford aldehyde **9** in 72% yield over six steps from alcohol **31**.

Although this route is amenable to a large supply of the aldehyde **9**, the overall length of this sequence from D-malic acid (11 steps, 47% overall yield) as well as the use of an expensive starting material prompted us to explore an alternative route to **9**. Since the length of the sequence was due to tedious protecting group interchanges, we turned our attention to the feasibility of Evans' diastereoselective α-hydroxylation methodology.[20] Reaction of the sodium enolate derived from the known carboximide **37**[21] with 2-(phenylsulfonyl)-3-phenyloxaziridine in THF at −90°C furnished alcohol **38** as a single diastereomer in 81% yield (Scheme 5). The resultant hydroxyl group was protected as its TES ether to give **39** in 89% yield. Reductive removal of the oxazolidinone auxiliary[22] proceeded without incident to afford optically pure (*R*)-alcohol **36** in 81% yield, accompanied by an 84% recovery of the auxiliary. This more practical sequence furnished aldehyde **9** in 52% yield over five steps from the reusable oxazolidinone auxiliary.

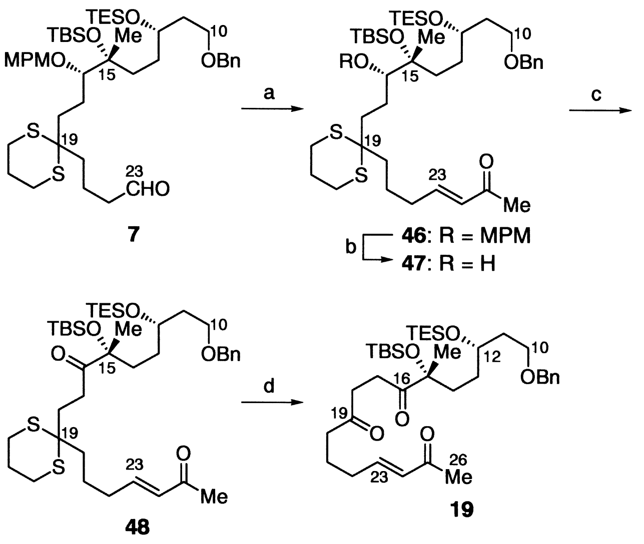


Scheme 5. *Reagents and conditions*: (a) NaHMDS, 2-(phenylsulfonyl)-3-phenyloxaziridine, THF, −90°C, 80%; (b) TESCl, imidazole, CH_2Cl_2, 1 h, 89%; (c) $LiBH_4$, H_2O, THF, 0°C, 1 h, 81%; (d) see Scheme 4.

With the C10–C13 aldehyde fragment **9** and the C14–C23 ketone fragment **10** in hand, the stage was now set for elaboration of the C10–C23 aldehyde **7** (Scheme 6). Aldol fragment coupling of **9** and **10** using LiHMDS–$ZnCl_2$ in THF furnished aldol adduct **40** in 98% yield. The superfluous C13 hydroxyl group was then removed by the elimination–hydrogenation sequence. Acetylation of alcohol **40** was followed by exposure to DBU to give enone **41** in 88% yield. Of various conditions surveyed,[23] conjugate reduction with the Stryker reagent[24] proved to be the optimal choice, affording ketone **42** in 91% yield. Stereoselective creation of the quaternary carbon center at C15 was well performed by chelation-controlled addition of MeMgI to ketone **42** in 95% yield. The resultant hydroxyl group in **43** was



Scheme 6. *Reagents and conditions*: (a) LiHMDS, $ZnCl_2$, THF, −78°C, then **9**, −78 to −50°C, 1.5 h, 98%; (b) Ac_2O, pyridine, DMAP, 20 h; (c) DBU, CH_2Cl_2, 0°C, 1 h, 88% (two steps); (d) $[(Ph_3P)CuH]_6$, benzene, 10 h, 91%; (e) MeMgI, Et_2O, −78°C, 1 h, 95%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 4 h, 93%; (g) Bu_4NF (1.05 equiv.), THF/AcOH (10:1), 0°C, 1 h, 88%; (h) SO_3·pyridine, Et_3N, DMSO, 1 h, 94%.



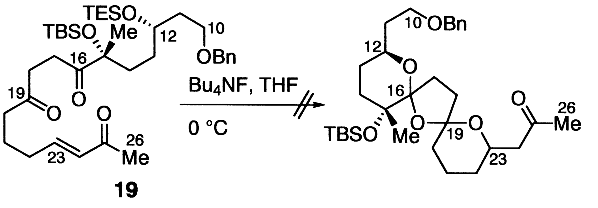
Scheme 7. *Reagents and conditions*: (a) Ph$_3$P=CHCOMe, benzene, reflux, 10 h, 98%; (b) DDQ, CH$_2$Cl$_2$/pH7 phosphate buffer (10:1), 20 min, 94%; (c) Dess–Martin periodinane, CH$_2$Cl$_2$/pyridine, 0°C, 1 h, 96%; (d) NCS, AgNO$_3$, γ-collidine, CH$_3$CN/H$_2$O (4:1), 93%.

protected as its TBS ether to give **44** in 93% yield. Selective deprotection of the primary TES ether was accomplished by treatment of **44** with Bu$_4$NF in THF/AcOH, providing alcohol **45** in 88% yield. Subsequent Parikh–Doering oxidation completed the synthesis of the C10–C23 aldehyde **7**, a key intermediate for the actual C10–C31 enone fragment **6** as well as for a model triketone **19**, in 94% yield.

The enone functionality was readily installed by Wittig olefination with Ph$_3$P=CHCOMe to give **46** in 98% yield (Scheme 7). Deprotection of the MPM ether with DDQ[25] followed by Dess–Martin oxidation[26] provided diketone **48** in 90% yield. Oxidative removal of the dithiane protective group under standard Corey conditions[27] furnished the target triketone **19** in 93% yield.

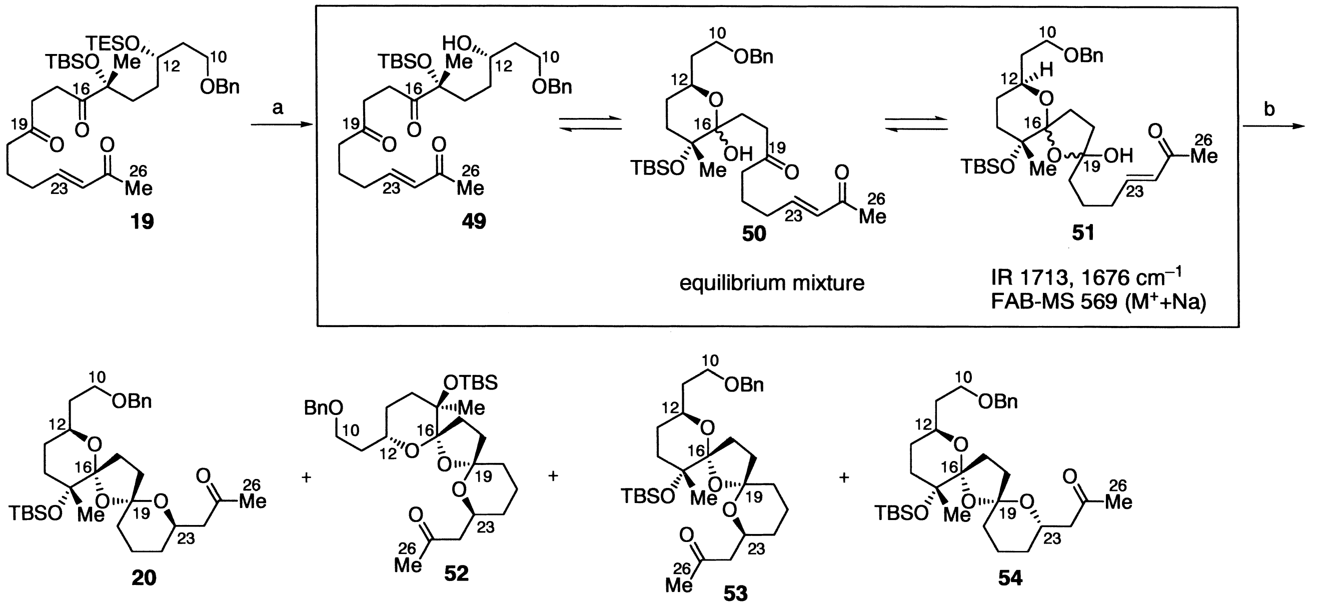
2.2. Dispiroketalization via double hemiketal formation/hetero-Michael addition process

With a viable route to the dispiroketal precursor **19** secured, the stage was now set for the tandem hemiketal formation/intramolecular hetero-Michael addition. As mentioned above, we initially explored a direct conversion of **19** to dispiroketals triggered by selective desilylation of the C12 TES group with Bu$_4$NF in THF. The reaction, however, met with failure (Eq. (4)). Therefore, we examined a stepwise procedure as follows (Scheme 8). Upon exposure of **19** to 1N aqueous HCl in THF, selective desilylation of the C12 TES ether provided an equilibrium mixture of products. While the NMR and mass spectra revealed the absence of a TES group, the complexity of the spectrum prevented the characterization of their components. In the infrared spectrum of the mixture, absorptions at 1713 and 1676 cm^{-1} indicated the presence of a nonconjugated ketone carbonyl and the preservation of an enone moiety, respectively. On the basis of these spectral characteristics, we eventually conjectured that hydroxytriketone **49** and stereoisomers of hemiketals **50** and **51** might be involved in the mixture under equilibrium. Aside from the structural confirmation, our attention was next focused on the base-promoted cyclization process.



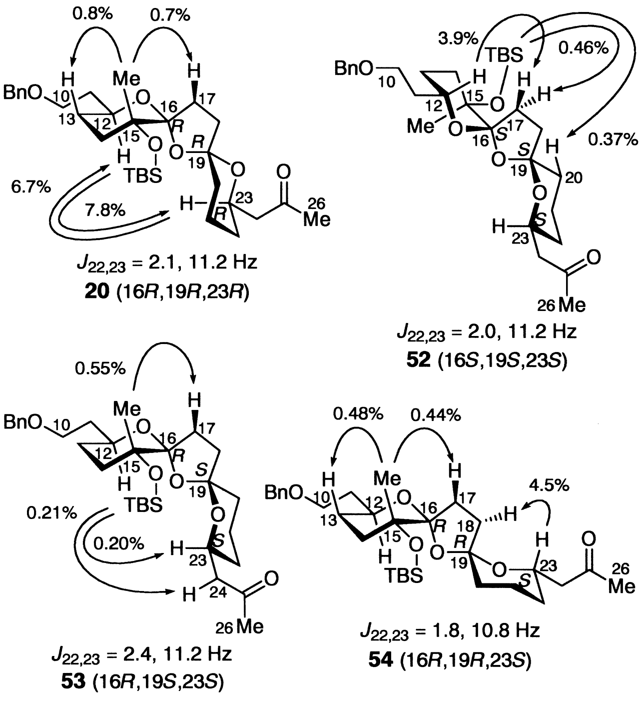
(4)

Submission of the equilibrium mixture to NaOMe (1.0 equiv.) in THF/MeOH (10:1) at 0°C resulted in the formation of four dispiroketal diastereomers out of the eight



Scheme 8. *Reagents and conditions*: (a) 1N aqueous HCl/THF, 0°C, 1 h; (b) NaOMe (1 equiv.), THF/MeOH (10:1), 0°C, 1 h, 91% (**20**/**52**/**53**/**54**=77:8:10:5).

possible stereoisomers in a 77:8:10:5 ratio in a total yield of 91% for the two-step sequence from triketone **19**. The dispiroketal isomers were readily separated by chromatography. Gratifyingly, the major product proved to be the desired dispiroketal **20** as follows. Stereochemical assignments of the four diastereomers followed from ^{1}H NOE experiments as shown in Fig. 1, which deserve some comments. Since the steric bulk of the C12 side-chain and the C15 TBS ether directs both C15–O and C12–C11 bonds to equatorial positions on the tetrahydropyran ring, the B ring of each isomer is presumed to adopt a chair conformation. On the other hand, homonuclear decoupling experiments established the vicinal coupling constants between the protons at C22 and C23 (**20**: 2.1, 11.2 Hz, **52**: 2.0, 11.2 Hz, **53**: 2.4, 11.2 Hz, **54**: 1.8, 10.8 Hz), the magnitude of which indicated that the D ring of each isomer would also adopt the chair conformation where C23–H was axially disposed. Based on these conformational analysis, the stereochemistry of the desired (16*R*,19*R*,23*R*)-dispiroketal **20** was verified by the diagnostic ^{1}H NOE correlation between C12–H and C23–H. This NOE is only possible in the desired dispiroketal with a *cisoid* arrangement as previously observed by the Murai[7a,c] and Hirama[8a] groups. The ^{1}H NOE between C17–H and C12–H allowed for the establishment of 16*S* configuration of **52**, whereas C17–H exhibited a significant ^{1}H NOE interaction with C15–CH_3 in dispiroketals **53** and **54** with 16*R* configuration. The 19*S* and 23*S* configurations of **52** were confirmed by the absence of an NOE between C23–H and C18–H in conjunction with an NOE between $SiC(CH_3)_3$ and C20–H. Thus, the stereochemistry of the newly formed chiral centers in **52** was established as 16*S*,19*S*,23*S*, which were totally opposite to those in **20**. Of the three possible isomers with 16*R* configuration, significant NOE interactions of $SiC(CH_3)_3$ with C23–H and C24–H in **53** and the absence of an NOE between $SiC(CH_3)_3$ and the C23 side-chain of **54** in conjunction with an NOE between C23–H and C18–H allowed us to assign the stereochemistries of **53** and **54** as 16*R*,19*S*,23*S*, and 16*R*,19*R*,23*S*, respectively.[28] Finally, the stereochemistry of all the stereogenic centers in the dispiroketal **20** was unambiguously established by X-ray crystallography of the derived semicarbazone *anti* **59** as shown in Fig. 2. The dispiroketal **20** was derivatized by the following five-step sequence of reactions to give *anti* **59** (Scheme 9): (1) reduction of the C25 carbonyl group with $NaBH_4$; (2) desilylation of the C15 hydroxyl group with Bu_4NF under reflux; (3) oxidation of the C25 hydroxyl group with SO_3·pyridine in DMSO; (4) debenzylation of the C10 hydroxyl group with $Pd(OH)_2$ under hydrogen; (5) semicarbazone formation.



$J_{22,23}$ = 2.1, 11.2 Hz
20 (16*R*,19*R*,23*R*)

$J_{22,23}$ = 2.0, 11.2 Hz
52 (16*S*,19*S*,23*S*)

$J_{22,23}$ = 2.4, 11.2 Hz
53 (16*R*,19*S*,23*S*)

$J_{22,23}$ = 1.8, 10.8 Hz
54 (16*R*,19*R*,23*S*)

Figure 1. Selected NOE interactions observed in the dispiroketals.

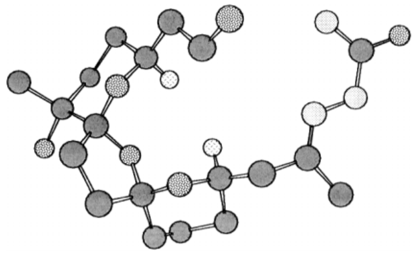
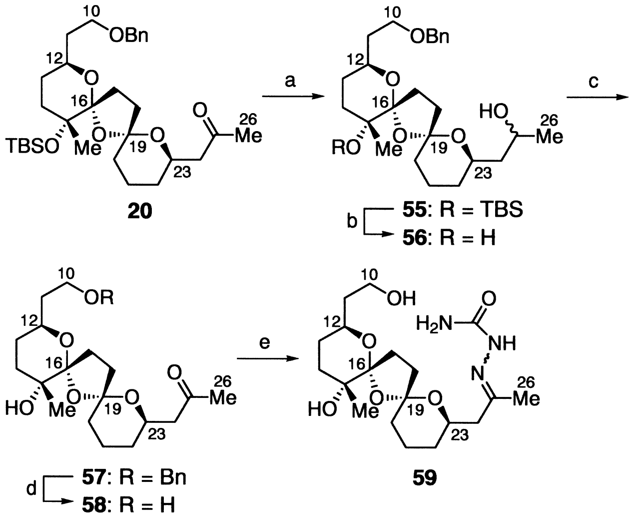


Figure 2. X-Ray crystal structure of *anti* **59**, rendered in Chem3D. For the purpose of clarity, only protons attached to stereogenic centers are shown.



20

55: R = TBS
56: R = H

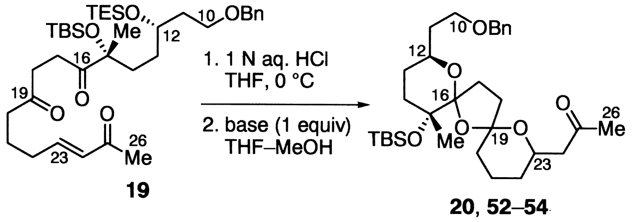
57: R = Bn
58: R = H

59

Scheme 9. *Reagents and conditions*: (a) $NaBH_4$, CH_2Cl_2/MeOH (4:1), 0°C, 2 h, 93%; (b) Bu_4NF, THF, reflux, 12 h, 91%; (c) SO_3·pyridine, Et_3N, DMSO, 2 h, 90%; (d) H_2, 20% $Pd(OH)_2$/C, AcOEt, 13 h, 92%; (e) $H_2NNHCONH_2$·HCl, NaOAc, EtOH/H_2O (5:1), 8 h, 98% (*syn*/*anti*=1:1.6).

Encouraged by these results, we next studied the effects of base to determine the optimal conditions for highest yield and stereoselectivity (Table 1). Of the alkaline metal methoxides screened, LiOMe was found to be the base of choice for this cyclization, providing the desired dispiroketal **20** in high yield and with the highest level of diastereoselectivity. The use of NaOMe or KOMe slightly decreased the diastereoselectivity as the formation of **53** increased, though similar ratios of **52** and **54** were observed as with the case of LiOMe. Addition of 12-crown-4 did not affect the outcome of the reaction with LiOMe (entry 4), suggesting that the stereoselectivity observed here would

Table 1. Double hemiketal formation/intramolecular hetero-Michael addition



Entry	Base	Temperature	Time	Yield (%)	**20/52/53/54**[a]
1	NaOMe	0°C	1 h	91	77:8:10:5
2	KOMe	0°C	2 h	90	74:9:12:5
3	LiOMe	0°C	24 h	87	85:8:2:5
4[b]	LiOMe	0°C	24 h	91	83:8:3:6
5	Triton B	0°C	5 h	86	77:7:11:5
6	LiOMe	rt	10 s	73	33:64:0:3
7	LiOMe	rt	5 min	88	50:46:0:4
8	LiOMe	rt	1 h	87	77:15:2:6
9	LiOMe	rt	4 h	92	84:8:3:5
10	LiOMe	rt	48 h	80	82:8:6:4
11	LiOMe	−50°C	8 h	89	20:80:0:0
12	NaOMe	−50°C	1.5 h	88	24:76:0:0
13	KOMe	−50°C	1.5 h	91	24:76:0:0

[a] Determined by HPLC analysis (column, Zorbax® Sil, 4.6×250 mm; eluent, 9% AcOEt in hexane; flow rate 1.0 mL/min).

[b] In the presence of 3 equiv. of 12-crown-4.

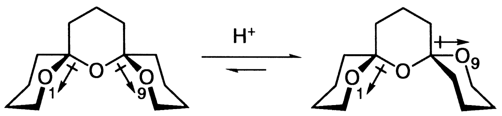
not arise from the chelation effect of the lithium cation. Ammonium hydroxide such as triton B also promoted the cyclization but was less effective in terms of diastereoselectivity (entry 5). While LiOMe-promoted cyclization of **19** at 0°C required a significantly longer time to reach completion compared with the cases of NaOMe and KOMe (entries 1 and 2 vs 3), the reaction at room temperature greatly shortened the reaction time to 4 h without affecting the product yield and diastereoselectivity (entry 9). Monitoring of this reaction by TLC and HPLC analyses showed that the intramolecular hetero-Michael addition took place immediately to predominantly form the undesired stereoisomer **52**, which was then slowly consumed to give the desired isomer **20** as a major product (entries 6–9). When the reaction time was prolonged (48 h), the ratio of **20** slightly diminished while the proportion of *transoid* isomer **53** doubled (entry 10). A similar process to form **20** as a major product via **52** was also observed with the use of NaOMe or KOMe (vide infra). At this point, we examined the effects of temperature on the isomerization process. We found that the reaction at −50°C proceeded smoothly to give an approximately 1:3 mixture of **20** and **52** regardless of the nature of metal methoxides employed, without any detection of the formation of **53** and **54** (entries 11–13). No isomerization was observed at this temperature. From these results, it is clear that the isomers **20** and **52** obtained here are the kinetically formed products. As expected, a 1:4 mixture of **20** and **52** formed with the use of LiOMe was smoothly isomerized at room temperature to give nearly the same ratio of products as that originally observed at room temperature. A similar isomerization process was also ascertained at 0°C with the case of NaOMe or KOMe (vide infra).

Finally, it should be noted that THF/MeOH (100:1–5:1) was the optimal solvent for the tandem hemiketal formation/intramolecular hetero-Michael addition process. While the reaction of **19** under the influence of LiOMe in THF proceeded smoothly at room temperature to give a mixture of **20** and **52**, it took 48 h to provide nearly the identical ratio of products observed with the reaction (4 h) in THF/MeOH (10:1). It was therefore suggested that MeOH as a co-solvent contributed not only to the dissolution of metal methoxides but also to the apparent accelaration of the isomerization reaction of **52** to **20**. This result might be ascribed to the nature of the enolate intermediates capable of internal chelation with the dispiroketal oxygen atoms. Somewhat surprisingly, the use of MeOH as the solvent resulted in a complex mixture of products.

2.3. Stereochemical models

2.3.1. Thermodynamic stability of the dispiroketals. In order to understand the observed stereochemical outcome of the reaction, we attempted to gain a mechanistic insight into the double hemiketal formation/hetero-Michael addition. Since the preferential formation of the desired isomer **20** was the result of some thermodynamic control, the thermodynamic stability of the dispiroketals was examined.

In general, three factors have been suggested to influence the thermodynamic stability of 1,7-dioxaspiro[5.5]undecanes, i.e. anomeric effects, steric influences, and intramolecular hydrogen bonding or other chelation effects.[10] To predict the stability of the dispiroketals, an additional factor, dipole–dipole interaction, should be taken into consideration. In this context, McGarvey and co-workers reported the stability of the *transoid* and *cisoid* isomers of 1,7,9-trioxadispiro[5.1.5.3]hexadecanes (Eq. (5)).[29] On the assumption that it has the all-chair conformations, the *cisoid* isomer **60**, wherein both O1 and O9 are axially disposed about the central ring, incorporates four stabilizing anomeric effects. On the other hand, the *transoid* isomer **61** embodies a maximum of three anomeric effects. However, **60** is estimated to be less stable by 0.3–0.7 kcal/mol than **61** because of the dipole–dipole repulsion of the two axial C–O bonds in **60**.

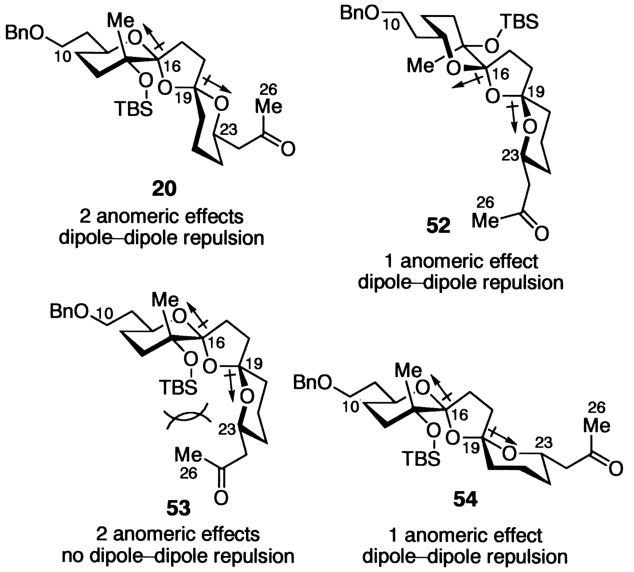


(5)

60
cisoid isomer
4 possible anomeric effects
dipole–dipole repulsion

61
transoid isomer
3 possible anomeric effects
no dipole–dipole repulsion

With these considerations in mind, we turned our attention to the actual dispiroketals (Fig. 3). Of the four dispiroketals obtained, isomers **20** and **53** appear to be more stable from two stabilizing anomeric effects compared to the other isomers **52** and **54** that benefit from only a single anomeric effect. While dispiroketal **20** is destabilized by the dipole–dipole repulsion between C16–O12 and C19–O23 bonds, dispiroketal **53** is relieved of the dipole-dipole destabilization, but suffered from the severe steric interaction between the C15 TBS ether and the C23 side-chain.



20
2 anomeric effects
dipole–dipole repulsion

52
1 anomeric effect
dipole–dipole repulsion

53
2 anomeric effects
no dipole–dipole repulsion

54
1 anomeric effect
dipole–dipole repulsion

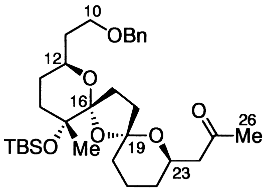
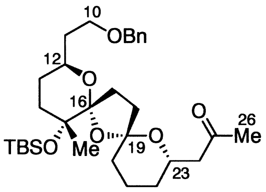
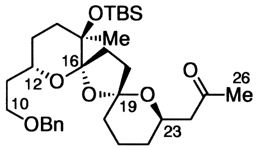
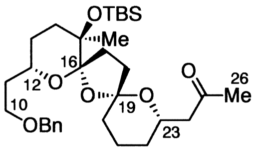
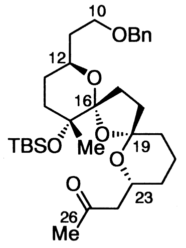
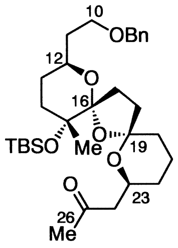
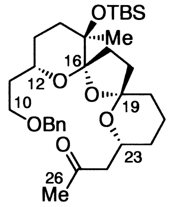
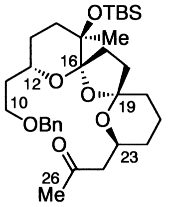
Figure 3. Steric and stereoelectronic effects that influence the thermodynamic stabilities of the four dispiroketals.

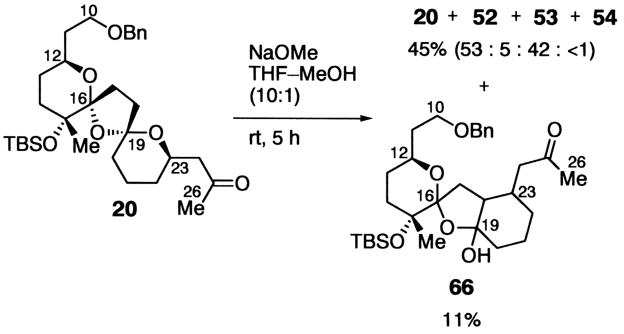
As a consequence, no clear thermodynamic preference for either of **20** and **53** was given.

To further examine this analysis, molecular mechanics calculations were carried out using the MM2* force field with Monte Carlo method on MacroModel 6.0.[30] The steric energies of the eight possible isomers relative to **20** are shown in Table 2. The calculations revealed that **53** was slightly more stable than **20** by 0.27 kcal/mol. While other isomers are less stable than **20**, it should be noted that the difference in energy between **52** and **20** is only 2.04 kcal/mol.

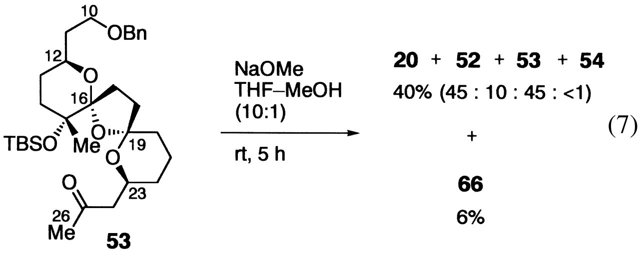
On the basis of these results, it is strongly suggested that interconversion of the dispiroketal isomers might not attain equilibrium under our dispiroketalization conditions (Table 1, entries 1–3, 9 and 10) where the second most stable, desired dispiroketal **20** was the major product, and the most stable isomer **53** was obtained as one of the minor products. In an effort to attain the equilibrium between these isomers, we separately submitted both isomers **20** and **53** to more harshly basic conditions (Eqs. (6) and (7)). We found that treatment of each isomer with NaOMe in THF/MeOH (10:1) at room temperature provided nearly identical ratios of the dispiroketal isomers **20**, **52**, and **53** at equilibrium (5 h). In the equilibrium mixture roughly equimolar amounts of **20** and **53** were formed as major products, though the combined yields of dispiroketals were less than 50% due to the formation of *C*-Michael product **66** and many decomposition products. These results are in good accordance with the foregoing speculation on the thermodynamic stability of the products. At this juncture, reasonable questions came to mind as to why **52** kinetically formed at an early stage isomerized smoothly to give the desired isomer **20** in preference to the most stable isomer **53**, and why the isomerization of **20** to **53** was so slow, particularly under the conditions with the use of LiOMe. Clearly, the diastereoselection observed in the present system is the result of both kinetic and thermodynamic control (vide infra).

Table 2. The relative steric energy calculated by MacroModel® MM2*

 **20** (desired isomer) 0.0 kcal/mol	 **54** (C23 isomer) +4.10 kcal/mol
 **62** (C16 isomer) +3.01 kcal/mol	 **65** (C16&C23 isomer) +7.61 kcal/mol
 **63** (C19 isomer) +3.16 kcal/mol	 **53** (C19&C23 isomer) –0.27 kcal/mol
 **64** (C16&C19 isomer) +5.70 kcal/mol	 **52** (C16&C19&C23 isomer) +2.04 kcal/mol



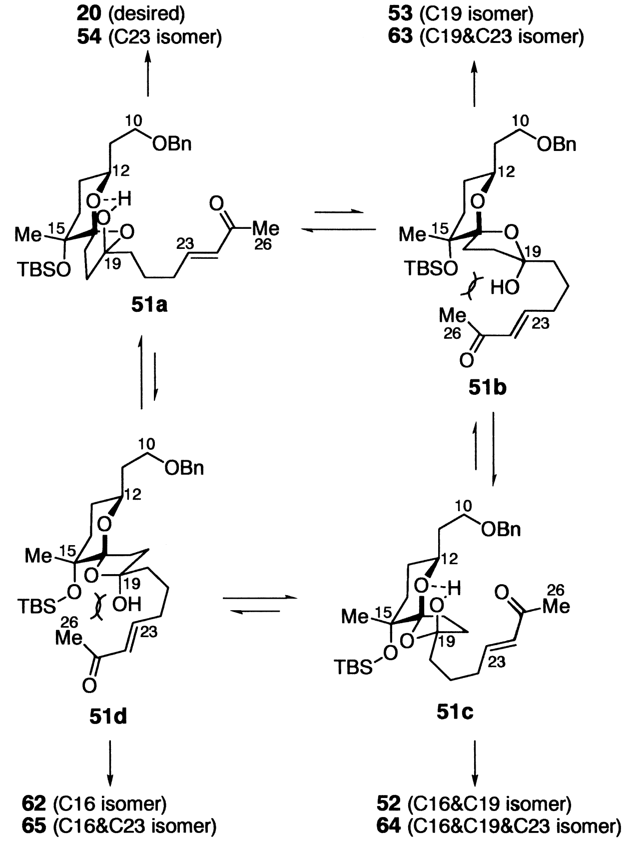
(6)



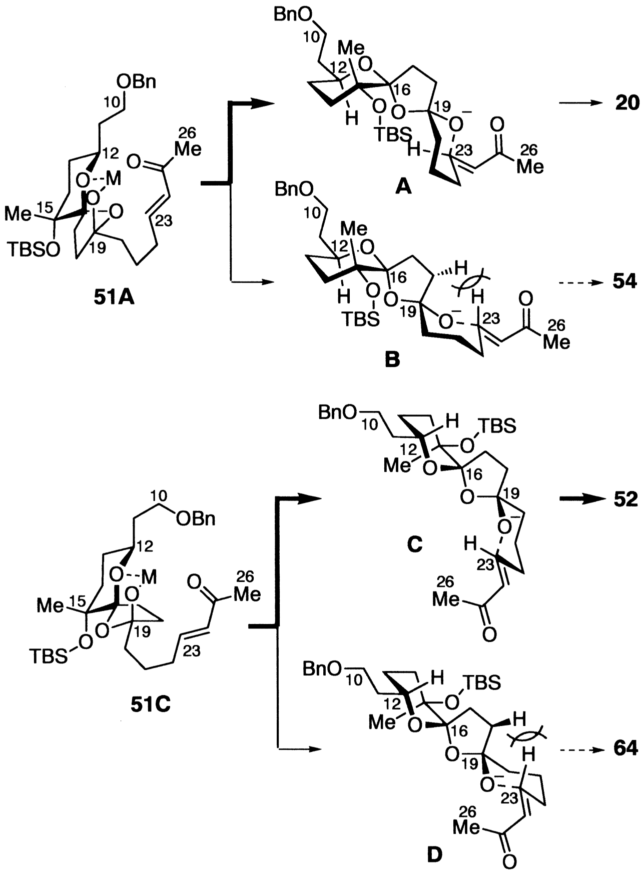
(7)

2.3.2. Origin of the kinetic preference for the formation of the isomer 52.

We have already mentioned that two isomers **20** and **52** in a ratio of 1:4–1:3 were predominantly obtained at −50°C regardless of the nature of metal methoxides, indicating that both isomers are the result of some kinetic control. Given the thermodynamic stability of the dispiroketal isomers, further discussions are required to account for the origin of the preference for the formation of the undesired isomer **52** as well as for that of the desired isomer **20**. To explain these results, not only the composition of the hemiketal mixture but also their stereochemistry should be taken into consideration. Judging from IR spectrum and ^{13}C NMR spectroscopy, it is conceivable that seven stereoisomers, i.e. **49**, two of **50**, and four of **51**, are involved in the mixture at equilibrium. However, assuming that equilibration of these isomers is rapid enough to interconvert each other, the problem could be reduced to the proportion of the four possible stereoisomers of hemiketal **51** and the facility of cyclization of each isomer.



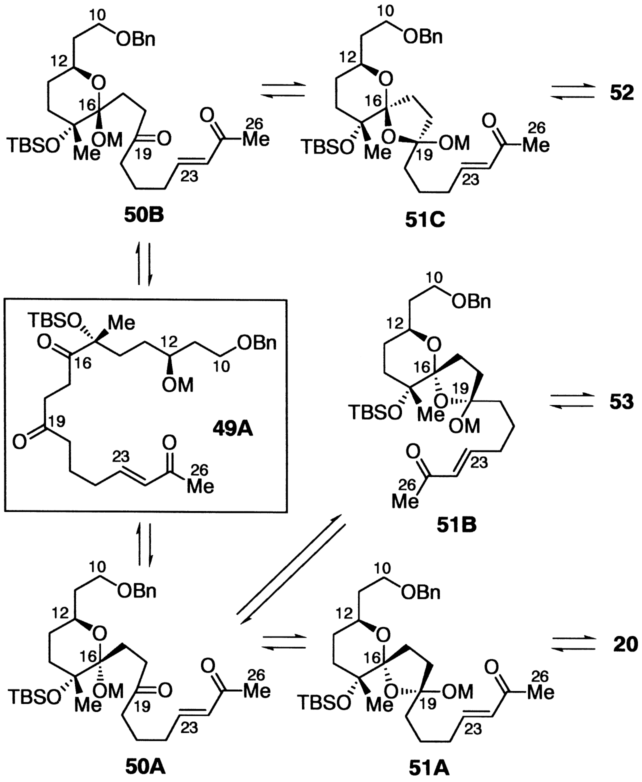
Scheme 10. Most stable conformations presumed for the four stereoisomers of hemiketal **51**.



Scheme 11. Transition state models for the hetero-Michael addition of **51A** and **51B**.

The proportion of the four stereoisomers of **51**, labeled as **51a–d**, depends on the thermodynamic stabilities of themselves. The most stable conformations of **51a–d** are presumed as presented in Scheme 10. On the assumption that the bulk of the C15 TBS ether and the C19 side-chain directs both C15–C16 and C19–C20 bonds to pseudo-equatorial positions on the tetrahydrofuran ring, the *cisoid* isomers **51a** and **51c** would benefit from the envelope geometry in the five-membered ring, wherein hydrogen bond between the hemiketal hydroxyl group and the B ring oxygen might function as a structure-stabilizing element. On the other hand, the *transoid* isomers **51b** and **51d** would adopt the half-chair geometry, wherein they suffer from the steric repulsion between the C15 TBS ether and the hemiketal hydroxyl group. These considerations suggest that the equilibrium between these isomers might heavily lie to **51a** and **51c**, wherein **51a** benefits from an anomeric stabilization. It is also suggested that the hindered nature of the hemiketal hydroxyl group in **51b** and **51d** would prevent the enone functionality from undergoing hetero-Michael addition.

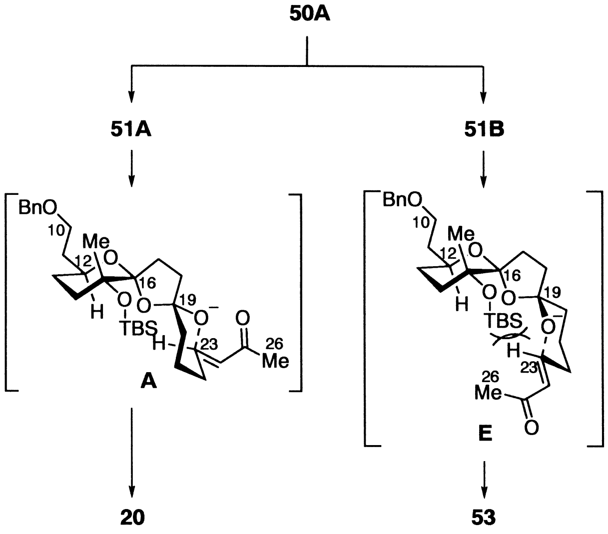
The formation of **20** and **52** from **51A** and **51C**, metalated derivatives of **51a** and **51c**, respectively, is well explained by invoking transition state models **A** and **C** rather than **B** and **D** as shown in Scheme 11. Of these models, **B** and **D** are



Scheme 12. Pathway for the isomerization of the dispiroketals.

disfavored by the severe repulsion between the hydrogens at C18 and C23. Compared with model **C**, model **A** seems energetically disadvantageous due to the weak steric interaction between the C12 and C23 side-chains. Provided that the system is under Curtin–Hammett control, this process leads to the predominant formation of **52** as observed early in the course of the dispiroketalization reaction.

2.3.3. Rationalization for the predominant formation of the desired isomer 20. With an explanation for the significant kinetic preference for the formation of **52** offered, we now address a rationalization for a high level of stereoselectivity for the desired isomer **20** under LiOMe-mediated dispiroketalization conditions. Since the stereochemistries of the newly formed chiral centers in **20** were totally opposite to those in **52**, it is obvious that the isomerization of **52** to **20** proceeded via the reaction sequence of retro-Michael reaction, dissociation to **49A**, double hemiketalization, and hetero-Michael addition (Scheme 12). As shown in Table 2, the dispiroketal **52** is the most stable isomer of the six isomers other than two isomers **20** and **53** with little difference in energy. Theoretically, **54** and the four possible isomers **62**–**65** could equilibrate with the more stable isomers **20** and **53** under the conditions where **52** undergoes isomerization. Since **20** and **53** have the same configuration at C16, a prime requirement for the preferential formation of **20** over **53** would be a much more facile hetero-Michael reaction of **51A** relative to that of **51B** as well as an energy barrier high enough to suppress the retro-Michael reaction from **20** to **51A**. This explanation can be rationalized by considering that the formation of **53** from **51B** is particularly disfavored by the hindered nature of the hemiketal alkoxide in **51B** which would prevent the enone functionality from undergoing hetero-Michael addition (vide supra), whereas **20** can be smoothly formed from **51A** (Scheme 13). While the pK_b of LiOMe is unknown, the choice of this base, which is weaker than NaOMe or KOMe, is crucial to the success of the present tandem double hemiketal formation/hetero-Michael addition process simply because its basicity is weak enough to prevent the desired isomer **20** from undergoing retro-Michael reaction even at room temperature.



Scheme 13. Transition state models for the formation of **20** and **53**.

3. Conclusion

We have developed an efficient, highly stereoselective method for the construction of the 6,5,6-dispiroketal (BCD) ring system of pinnatoxin A, which is based on an intramolecular hetero-Michael addition of a hemiketal alkoxide reversibly formed under the influence of lithium methoxide. We have also offered a mechanistic explanation for the observed stereochemical outcome. This novel process should be useful in the construction of other dispiroketals. In the following article, we describe the stereoselective synthesis of the C10–C31 (BCDEF ring) portion of pinnatoxin A utilizing this methodology.

4. Experimental

4.1. General

Melting points were determined on a Büchi 535 digital melting point apparatus and were uncorrected. Optical rotations were recorded on a JASCO P-1030 digital polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrophotometer and absorbance bands were reported in wavenumber (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JEOL EX270 (270 MHz), JEOL AL400 (400 MHz) or Bruker ARX500 (500 MHz) spectrometers, with tetramethylsilane (δ_H 0.00) or C_6H_6 (δ_H 7.20) as an internal standard. Coupling constants (J) are reported in hertz (Hz). Abbreviations of multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data are presented as follows: chemical shift, multiplicity, coupling constants, integration, and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on JEOL EX270 (67.8 MHz), JEOL AL400 (100.6 MHz) or Bruker ARX500 (125.8 MHz) spectrometers, with $CDCl_3$ (δ_C 77.0) or C_6D_6 (δ_C 128.0) as an internal standard. Electron ionization (EI) mass spectra were recorded on JEOL JMS-DX303 or JEOL FABmate spectrometer, operating with an ionization energy of 70 eV. Fast atom bombardment (FAB) mass spectra were recorded on a JEOL JMS HX110 spectrometer.

Column chromatography was carried out on Merck Kieselgel 60 (63–200 μm or 40–63 μm), Wakogel C-200 (75–150 μm) or Kanto Silica gel 60 N (63–210 μm). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. HPLC analyses were performed on a JASCO PU-980 and UV-970 (detector, λ=254 nm). Retention times (t_R) and peak ratios were determined with a Shimadzu Chromatopac C-R6A. Hexane was of HPLC grade, and filtered and degassed before use.

Reagents and solvents were purified by standard means or used as received otherwise noted. Dehydrated stabilizer free THF was purchased from Kanto Chemical Co., Inc. 2-(Phenylsulfonyl)-3-phenyloxaziridine,[31] Stryker reagent[32] and Dess–Martin periodinane[33] were prepared according to literature procedures.

4.1.1. (*S*)-2,2-Diethyl-5-(2-{2-[4-(tetrahydropyran-2-yloxy)butyl]-1,3-dithian-2-yl}ethyl)-1,3-dioxolane (23). Butyllithium in *n*-hexane (2.6 M, 16.6 mL, 43.2 mmol) was added to a solution of dithiane **22** (12.4 g, 44.9 mmol) in THF (100 mL)–HMPA (10 mL) at −78°C under an argon atmosphere. After 30 min, a solution of iodide **21** (10.2 g, 35.9 mmol) in THF (12 mL) was added, and the mixture was stirred at −78°C for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the whole was extracted with AcOEt (2×80 mL). The organic extract was washed with brine (2×50 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (21.5 g, yellow oil), which was purified by column chromatography (silica gel 200 g, 8:1 *n*-hexane/AcOEt) to give dithiane **23** (14.7 g, 95%) as a colorless oil: $[\alpha]_D^{23}=-3.61$ (*c* 2.32, EtOH); IR (neat) 2942, 2872, 1454, 1354, 1275, 1173, 1123, 1078, 1034, 920 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88–0.92 (m, 6H, pentylidene CH_3×2), 1.52–1.96 (m, 21H, C17–H_2, C18–H, C20–H_2, C21–H_2, C22–H_2, SCH_2CH_2, pentylidene CH_2×2, THP CH_2×3), 2.12 (m, 1H, C18–H), 2.79–2.83 (m, 4H, SCH_2×2), 3.40 (m, 1H, THP OCH), 3.49–3.53 (m, 2H, C15–H, C23–H), 3.76 (m, 1H, THP OCH), 3.87 (m, 1H, C23–H), 4.05–4.10 (m, 2H, C15–H, C16–H), 4.58 (m, 1H, THP OCHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.7, 7.9, 19.3, 20.4, 25.1, 25.2, 25.6, 25.7, 28.3, 29.3, 29.5, 29.6, 30.4, 33.8, 37.9, 52.6, 61.9, 66.8, 69.7, 75.8, 98.45, 98.46, 112.4; FAB-HRMS *m/z* calcd for $C_{22}H_{40}O_4S_2$ (M^+) 432.2368, found 432.2375.

4.1.2. (*S*)-4-[2-(4-Hydroxybutyl)-1,3-dithian-2-yl]-butane-1,2-diol (24). *p*-Toluenesulfonic acid monohydrate (1.00 g, 5.3 mmol) was added to a stirred solution of acetal **23** (26.1 g, 60.3 mmol) in MeOH (120 mL)–H_2O (10 mL) at room temperature. After stirring for 35 h, the reaction was quenched with Et_3N (4.1 mL). The solvent was removed in vacuo, and the residual yellow oil (26.3 g) was purified by column chromatography (silica gel 100 g, 1:1 *n*-hexane/AcOEt→1:4 AcOEt/acetone) to give triol **24** (16.6 g, 98%) as a colorless syrup: $[\alpha]_D^{25}=-4.94$ (*c* 1.11, $CHCl_3$); IR (neat) 3385, 2938, 1422, 1275, 1069, 909, 868, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.66 (m, 6H, C17–H_2, C21–H_2, C22–H_2), 1.85–2.00 (m, 8H, OH×3, C18–H, C20–H_2, SCH_2CH_2), 2.16 (m, 1H, C18–H), 2.77–2.88 (m, 4H, SCH_2×2), 3.49 (dd, *J*=7.2, 11.0 Hz, 1H, C15–H), 3.66–3.72 (m, 4H, C15–H, C16–H, C23–H_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 25.4, 25.9, 27.6, 32.3, 33.8, 37.7, 52.8, 61.8, 66.4, 72.1; FAB-HRMS *m/z* calcd for $C_{12}H_{24}O_3S_2Na$ (M^++Na) 303.1064, found 303.1068.

4.1.3. (*S*)-4-(2-{2-[2-(4-Methoxyphenyl)-1,3-dioxolan-4-yl]ethyl}-1,3-dithian-2-yl)-1-butanol (25). Pyridinium *p*-toluenesulfonate (1.0 g, 3.98 mmol) was added to a stirred solution of triol **24** (20.3 g, 72.4 mmol) and *p*-anisaldehyde dimethyl acetal (19.7 g, 108.1 mmol) in CH_2Cl_2 (150 mL) at room temperature under an argon atmosphere. After stirring for 6 h, Et_3N (3 mL) was added to the reaction mixture. The solvent was removed in vacuo, and the residual yellow oil (40.6 g) was purified by column chromatography (silica gel 150 g, 4:1→2:1 *n*-hexane/AcOEt) to give acetal **25** (21.7 g, 75%) as a colorless syrup: $[\alpha]_D^{25}=-9.25$ (*c* 1.15, $CHCl_3$); IR (neat) 3445, 2938, 1615, 1516, 1454, 1304, 1284, 1173, 1076, 909, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (brs, 1H, OH), 1.49–1.67 (m, 4H, C21–H_2, C22–H_2), 1.69–1.98 (m, 7H, C17–H_2, C18–H, C20–H_2, SCH_2CH_2), 2.19 (m, 1H, C18–H), 2.73–2.87 (m, 4H, SCH_2×2), 3.62–3.65 (m, 2.5H, C15–H, C23–H_2), 3.73 (m, 0.5H, C15–H), 3.81 (s, 3H, $C_6H_4OCH_3$), 4.10 (m, 0.5H, C15–H), 4.18–4.29 (m, 1.5H, C15–H, C16–H), 5.76 (s, 0.5H, ArCH), 5.88 (s, 0.5H, ArCH), 6.90 (m, 2H, ArH), 7.39–7.43 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 20.2, 25.1, 25.7, 28.1, 28.6, 32.5, 33.8, 38.05, 38.10, 52.6, 52.7, 55.1, 62.03, 62.04, 69.7, 70.4, 76.0, 76.5, 102.7, 103.7, 113.38, 113.41, 127.5, 127.8, 129.4, 130.0, 159.9, 160.0; FAB-HRMS *m/z* calcd for $C_{20}H_{30}O_4S_2$ (M^+) 398.1586, found 398.1563.

4.1.4. (*S*)-2-{2-[2-(4-Methoxyphenyl)-1,3-dioxolan-4-yl]-ethyl-2-[4-(triethylsilyloxy)butyl]-1,3-dithiane (26). TESCl (3.27 mL, 19.5 mmol) was added to a stirred solution of alcohol **25** (7.02 g, 17.6 mmol) and imidazole (3.00 g, 44.0 mmol) in CH_2Cl_2 (60 mL) at 0°C under an argon atmosphere. After stirring at room temperature for 2 h, the reaction was quenched by addition of ice, and the whole mixture was partitioned between AcOEt (100 mL) and saturated aqueous NH_4Cl (40 mL). The organic layer was washed with brine (40 mL), and dried over Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (10.5 g), which was purified by column chromatography (silica gel 80 g, 10:1 *n*-hexane/AcOEt) to give TES ether **26** (8.83 g, 98%) as a colorless oil: $[\alpha]_D^{24}=-7.12$ (*c* 2.21, $CHCl_3$); IR (neat) 2951, 2876, 1615, 1516, 1458, 1379, 1304, 1248, 1171, 1092, 1036, 1011, 829, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.57–0.62 (m, 6H, $Si(CH_2CH_3)_3$), 0.94–0.99 (m, 9H, $Si(CH_2CH_3)_3$), 1.47–1.54 (m, 4H, C21–H_2, C22–H_2), 1.68–1.96 (m, 7H, C17–H_2, C18–*H*, C20–H_2, SCH_2CH_2), 2.20 (m, 1H, C18–*H*), 2.73–2.87 (m, 4H, SCH_2×2), 3.60–3.64 (m, 2.5H, C15–*H*, C23–H_2), 3.73 (m, 0.5H, C15–*H*), 3.81 (s, 3H, $C_6H_4OCH_3$), 4.10 (m, 0.5H, C15–*H*), 4.18–4.28 (m, 1.5H, C15–*H*, C16–*H*), 5.76 (s, 0.5H, ArC*H*), 5.87 (s, 0.5H, ArC*H*), 6.90 (m, 2H, Ar*H*), 7.39–7.43 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.4, 6.7, 20.3, 25.3, 25.9, 28.3, 28.7, 32.9, 33.9, 34.1, 38.3, 52.8, 55.2, 62.5, 69.9, 70.6, 76.2, 76.8, 102.9, 103.0, 103.97, 104.03, 113.6, 127.7, 128.0, 129.8, 130.4, 160.2, 160.3; EI-LRMS *m/z* 512 (M^+), 241 (bp); EI-HRMS *m/z* calcd for $C_{26}H_{44}O_4S_2Si$ (M^+) 512.2450, found 512.2455; Anal calcd for $C_{26}H_{44}O_4S_2Si$: C, 60.89; H, 8.65; S, 12.50, found C, 60.66; H, 8.70; S, 12.64.

4.1.5. (*S*)-2-(4-Methoxybenzyl)oxy-4-{2-[4-(triethylsilyloxy)butyl]-1,3-dithian-2-yl}-1-butanol (27). Diisobutylaluminum hydride in *n*-hexane (1.01 M, 93.9 mL, 94.8 mmol) was added to a stirred solution of *p*-methoxybenzylidene acetal **26** (19.4 g, 37.9 mmol) in CH_2Cl_2 (250 mL) at −78°C under an argon atmosphere. After stirring at −20°C for 2 h, the reaction was quenched with methanol (5 mL), and 1 M aqueous sodium potassium tartrate (400 mL) was added to the solution. The mixture was stirred vigorously at room temperature for 3 h, and extracted with AcOEt (2×400 mL). The combined organic extracts were washed with brine (200 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (23.2 g), which was purified by column chromatography (silica gel 400 g, 8:1→6:1 *n*-hexane/AcOEt) to give alcohol **27** (17.1 g, 87%) as a colorless oil, along with isomer **28** (1.40 g, 7%) as a colorless oil: $[\alpha]_D^{22}=+12.9$ (*c* 2.23, $CHCl_3$); IR (neat) 3447, 2951, 1514, 1284, 1096, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$), 0.96 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 1.45–1.56 (m, 4H, C21–H_2, C22–H_2), 1.71 (m, 2H, C17–H_2), 1.84–2.00 (m, 7H, O*H*, C18–H_2, C20–H_2, SCH_2CH_2), 2.77–2.80 (m, 4H, SCH_2×2), 3.49–3.56 (m, 2H, C15–*H*, C16–*H*), 3.62 (m, 2H, C23–H_2), 3.66 (m, 1H, C15–*H*), 3.81 (s, 3H, $C_6H_4OCH_3$), 4.49 (d, *J*=11.3 Hz, 1H, OC*H*Ar), 4.58 (d, *J*=11.3 Hz, 1H, OC*H*Ar), 6.89 (d, *J*=8.6 Hz, 2H, Ar*H*), 7.28 (d, *J*=8.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.2, 6.5, 20.2, 25.2, 25.3, 25.7, 38.0, 52.9, 54.9, 55.0, 62.3, 63.9, 70.9, 78.9, 113.5, 129.1, 130.2, 159.0; EI-LRMS *m/z* 514 (M^+), 121 (bp); EI-HRMS *m/z* calcd for $C_{26}H_{46}O_4S_2Si$ (M^+) 514.2607, found 514.2608; Anal calcd for $C_{26}H_{46}O_4S_2Si$: C, 60.65; H, 9.01; S, 12.46, found C, 60.52; H, 8.99; S, 12.50.

Data for **28**: $[\alpha]_D^{21}=-1.48$ (*c* 2.3, $CHCl_3$); IR (neat) 3455, 2951, 1613, 1514, 1458, 1248, 1096, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$), 0.95 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 1.48–1.60 (m, 6H), 1.82–1.94 (m, 5H), 2.10 (m, 1H), 2.35 (brs, 1H, O*H*), 2.74–2.87 (m, 4H), 3.31 (dd, *J*=8.0, 9.2 Hz, 1H, C15–*H*), 3.49 (dd, *J*=3.2, 9.2 Hz, 1H, C15–*H*), 3.61 (m, 2H, C23–H_2), 3.78–3.81 (m, 4H, C16–*H*, $C_6H_4OCH_3$), 4.48 (s, 2H, OCH_2Ar), 6.89 (d, *J*=8.8 Hz, 2H, Ar*H*), 7.26 (d, *J*=8.8 Hz, 2H, Ar*H*); ^{13}C NMR (68 MHz, $CDCl_3$) δ 4.4, 6.7, 20.3, 25.4, 25.9, 28.0, 33.0, 33.8, 38.3, 53.1, 55.2, 62.6, 70.4, 73.0, 74.2, 113.8, 129.4, 130.0, 159.3; EI-LRMS *m/z* 514 (M^+), 121 (bp); EI-HRMS *m/z* calcd for $C_{26}H_{46}O_4S_2Si$ (M^+) 514.2607, found 514.2604.

4.1.6. (*S*)-2-(4-Methoxybenzyl)oxy-4-{2-[4-(triethylsilyloxy)butyl]-1,3-dithian-2-yl}butyraldehyde (29). Sulfur trioxide pyridine complex (4.64 g, 29.2 mmol) was added over 15 min to a stirred solution of alcohol **27** (5.03 g, 9.77 mmol) and Et_3N (8.1 mL, 58.1 mmol) in DMSO (60 mL) under an argon atmosphere. After stirring at room temperature for 1 h, the mixture was diluted with Et_2O (50 mL) and poured into saturated aqueous NH_4Cl (50 mL) and H_2O (20 mL) at 0°C. The whole was extracted with AcOEt (2×80 mL), and the organic layer was washed successively with saturated aqueous NH_4Cl (40 mL) and brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (6 g, orange oil), which was purified by column chromatography (silica gel 60 g, 8:1 *n*-hexane/AcOEt) to give aldehyde **29** (4.62 g, 92%) as a colorless oil: $[\alpha]_D^{22}=-26.3$ (*c* 2.01, $CHCl_3$); IR (neat) 2951, 1732, 1613, 1514, 1284, 1098, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$), 0.96 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 1.47–1.55 (m, 4H, C21–H_2, C22–H_2), 1.80–1.95 (m, 8H, C17–H_2, C18–H_2, C20–H_2, SCH_2CH_2), 2.74–2.81 (m, 4H, SCH_2×2), 3.61 (m, 2H, C23–H_2), 3.75 (m, 1H C16–*H*), 3.81 (s, 3H, $C_6H_4OCH_3$), 4.53 (d, *J*=11.5 Hz, 1H, OC*H*Ar), 4.58 (d, *J*=11.5 Hz, 1H, OC*H*Ar), 6.89 (d, *J*=8.5 Hz, 2H, Ar*H*), 7.28 (d, *J*=8.5 Hz, 2H, Ar*H*), 9.62 (d, *J*=2.0 Hz, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.4, 6.7, 20.2, 25.0, 25.16, 25.23, 25.9, 32.6, 32.9, 38.4, 52.8, 55.2, 62.5, 72.1, 82.7, 113.9, 129.2, 129.6, 159.5, 203.2; EI-LRMS *m/z* 512 (M^+), 121 (bp); EI-HRMS *m/z* calcd for $C_{26}H_{44}O_4S_2Si$ (M^+) 512.2450, found 512.2471; Anal calcd for $C_{26}H_{44}O_4S_2Si$: C, 60.89; H, 8.65; S, 12.50, found C, 60.86; H, 8.62; S, 12.70.

4.1.7. (3*S*)-3-(4-Methoxybenzyl)oxy-5-{2-[4-(triethylsilyl)oxybutyl]-1,3-dithian-2-yl}-2-pentanol (30). MeI (1.25 mL, 20.0 mmol) in Et_2O (2 mL) was added over 30 min to a suspension of magnesium tuning (510.3 mg, 21.0 mmol) in Et_2O (4 mL) under an argon atmosphere. After refluxing for 30 min, the solution was cooled to room temperature, and diluted with THF (15 mL). The mixture was cooled to −78°C, and a solution of aldehyde **29** (2.05 g, 4.00 mmol) in THF (3 mL) was added. After stirring at −78°C for 1 h and at −50°C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (40 mL), and the whole was extracted with AcOEt (80 mL and 40 mL). The combined organic extracts were washed successively with saturated aqueous NH_4Cl (40 mL) and brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (2.4 g), which was purified by column chromatography (silica gel 20 g, 4:1 *n*-hexane/ AcOEt) to give alcohol **30** (1.94 g, 92%) as a colorless oil: $[\alpha]_D^{22}=+18.8$ (*c* 2.06, $CHCl_3$); IR (neat) 3461, 2951, 1613, 1514, 1456, 1248, 1094, 820, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$), 0.95 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 1.17 (d, *J*=6.3 Hz, 3H, C14–H_3), 1.47–1.65 (m, 4H, C21–H_2, C22–H_2), 1.81–2.05 (m, 8H, C17–H_2, C18–H_2, C20–H_2, SCH_2CH_2), 2.47 (d, *J*=3.0 Hz, 1H, O*H*), 2.74–2.84 (m, 4H, SCH_2×2), 3.23–3.32 (m, 1H, C15–*H*), 3.60–3.63 (m, 2H, C23–H_2), 3.75 (m, 1H, C16–H), 3.81 (s, 3H, $C_6H_4OCH_3$), 4.48 (d, J=10.9 Hz, 0.5H, OCHAr), 4.53 (s, 1H, OCHAr), 4.63 (d, J=11.5 Hz, 0.5H, OCHAr), 6.89 (d, J=8.5 Hz, 2H, ArH), 7.28 (d, J=8.5 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.4, 6.8, 18.1, 18.7, 20.37, 20.41, 23.6, 24.1, 25.4, 25.86, 25.91, 32.2, 32.95, 32.98, 33.7, 38.15, 38.18, 53.1, 53.2, 55.1, 62.47, 62.54, 67.9, 68.5, 71.5, 71.7, 82.2, 83.2, 113.6, 113.7, 129.3, 129.4, 130.0, 130.3, 159.0, 159.1; FAB-HRMS *m/z* calcd for $C_{27}H_{48}O_4S_2Si$ (M^+) 528.2764, found 528.2778.

4.1.8. (*S*)-3-(4-Methoxybenzyl)oxy-5-{2-[4-(triethylsilyl)-oxybutyl]-1,3-dithian-2-yl}pentan-2-one (10). Sulfur trioxide pyridine complex (3.17 g, 19.9 mmol) was added over 15 min to a stirred solution of alcohol **30** (3.50 g, 6.62 mmol) and Et_3N (5.5 mL, 39.7 mmol) in DMSO (30 mL) at room temperature under an argon atmosphere. After stirring at room temperature for 1 h, the mixture was diluted with Et_2O (60 mL) and poured into saturated aqueous NH_4Cl (60 mL) at 0°C. The whole was extracted with AcOEt (2×50 mL), and the organic extract was washed with H_2O (2×30 mL), and brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (3.6 g, orange oil), which was purified by column chromatography (silica gel 40 g, 10:1 *n*-hexane/AcOEt) to give ketone **10** (3.25 g, 93%) as a colorless oil: $[\alpha]_D^{25}=-24.1$ (c 0.98, $CHCl_3$); IR (neat) 2951, 1715, 1613, 1514, 1458, 1418, 1354, 1302, 1248, 1284, 1175, 1098, 1036, 822, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, J=8.0 Hz, 6H, Si($CH_2CH_3)_3$), 0.95 (t, J=8.0 Hz, 9H, Si($CH_2CH_3)_3$), 1.44–1.56 (m, 4H, C21–H_2, C22–H_2), 1.79–2.05 (m, 8H, C17–H_2, C18–H_2, C20–H_2, SCH_2CH_2), 2.18 (s, 3H, C14–H_3), 2.70–2.84 (m, 4H, SCH_2×2), 3.59–3.62 (m, 2H, C23–H_2), 3.75 (m, 1H, C16–H), 3.81 (s, 3H, $C_6H_4OCH_3$), 4.40 (d, J=11.5 Hz, 1H, OCHAr), 4.52 (d, J=11.5 Hz, 1H, OCHAr), 6.89 (d, J=8.5 Hz, 2H, ArH), 7.27 (d, J=8.5 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.4, 6.8, 20.3, 25.3, 25.5, 25.87, 25.90, 26.7, 33.0, 38.5, 52.8, 55.2, 62.5, 71.9, 84.1, 113.7, 129.3, 129.4, 159.2, 210.6; FAB-HRMS *m/z* calcd for $C_{27}H_{46}O_4S_2Si$ (M^+) 526.2607, found 526.2623; Anal calcd for $C_{27}H_{46}O_4S_2Si$: C, 61.55; H, 8.80; S, 12.17, found C, 61.27; H, 8.76; S, 12.41.

4.1.9. (*R*)-4-(Benzyloxy)butane-1,2-diol (33). To a solution of alcohol **31** (4.11 g, 23.5 mmol) in THF (50 mL)–HMPA (10 mL) at 0°C was added NaH (620 mg, 25.8 mmol), followed by addition of BnBr (3.4 mL, 28.2 mmol). After stirring at room temperature for 10 h, the reaction was quenched with MeOH (3 mL), and the whole was partitioned between AcOEt (100 mL) and saturated aqueous NH_4Cl (30 mL). The aqueous layer was extracted with AcOEt (50 mL), and 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, which was used without further purification.

p-Toluenesulfonic acid monohydrate (500 mg, 2.63 mmol) was added to a stirred solution of the crude acetal in THF (60 mL)-H_2O (6 mL) at room temperature, and the mixture was stirred at 60°C for 5 h. After cooling, the reaction was quenched with Et_3N (3 mL), and the solvent was removed in vacuo. The yellow residue was purified by column chromatography (silica gel 80 g, 1:1 *n*-hexane/AcOEt) to give diol **33** (4.20 g, 91%) as a colorless syrup: $[\alpha]_D^{23}=-4.81$ (c 1.33, $CHCl_3$); IR (neat) 3387, 2934, 2866, 1454, 1366, 1096, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (m, 1H, C11–H), 1.84 (m, 1H, C11–H), 2.34 (brs, 1H, OH), 3.15 (brs, 1H, OH), 3.50 (m, 1H, C13–H), 3.63 (m, 1H, C13–H), 3.65–3.74 (m, 2H, C10–H), 3.92 (m, 1H, C12–H), 4.53 (s, 2H, OCH_2Ph), 7.29–7.37 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6, 66.0, 67.0, 69.7, 72.5, 127.1, 127.8, 137.6; EI-LRMS *m/z* 196 (M^+), 91 (bp); EI-HRMS *m/z* calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099, found 196.1089.

4.1.10. (*R*)-4-Benzyloxy-1-(pivaloyl)oxy-2-butanol (34). Trimethylacetyl chloride (3.19 mL, 25.9 mmol) was added to a stirred solution of diol **33** (4.85 g, 24.7 mmol) in CH_2Cl_2 (20 mL)–pyridine (20 mL) at 0°C under an argon atmosphere. After stirring at 0°C for 1 h and at room temperature for 1 h, the reaction was quenched with crushed ice, and the whole was partitioned between AcOEt (100 mL) and 10% aqueous HCl (40 mL). The aqueous layer was extracted with AcOEt (80 mL), and the combined organic extracts were washed successively with H_2O (40 mL), saturated aqueous $NaHCO_3$ (2×40 mL) and brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (8.2 g), which was purified by column chromatography (silica gel 100 g, 6:1→4:1 *n*-hexane/AcOEt) to give ester **34** (6.25 g, 90%) as a colorless oil: $[\alpha]_D^{25}=-2.37$ (c 3.35, $CHCl_3$); IR (neat) 3472, 2971, 2872, 1728, 1481, 1456, 1366, 1285, 1163, 1001, 1032, 739, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 9H, C($CH_3)_3$), 1.79–1.82 (m, 2H, C11–H), 2.98 (brs, 1H, OH), 3.66 (m, 1H, C10–H), 3.73 (m, 1H, C10–H), 4.03–4.12 (m, 3H, C12–H, C13–H_2), 4.53 (s, 2H, OCH_2Ph), 7.28–7.37 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 32.9, 38.4, 67.2, 67.70, 67.74, 72.7, 127.1, 127.2, 127.9, 137.6, 177.9; FAB-HRMS *m/z* calcd for $C_{16}H_{25}O_4$ (M^++H) 281.1796, found 281.1736.

4.1.11. (*R*)-4-Benzyloxy-1-(pivaloyl)oxy-2-(triethylsilyl)-oxybutane (35). TESCl (4.13 mL, 24.3 mmol) was added to a stirred solution of alcohol **34** (6.20 g, 22.1 mmol) and imidazole (3.76 g, 55.3 mmol) in CH_2Cl_2 (50 mL) at 0°C under an argon atmosphere. After stirring at room temperature for 1 h, the reaction was quenched with crushed ice, and the mixture was partitioned between AcOEt (100 mL) and H_2O (80 mL). The aqueous layer was extracted with AcOEt (80 mL), and the combined organic extracts were washed successively with H_2O (40 mL), and brine (2×30 mL), and dried over Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (9.2 g, a colorless oil), which was purified by column chromatography (silica gel 100 g, 10:1→8:1 *n*-hexane/AcOEt) to give TES ether **35** (8.46 g, 97%) as a colorless oil: $[\alpha]_D^{23}=+8.29$ (c 3.29, $CHCl_3$); IR (neat) 2957, 2878, 1732, 1480, 1456, 1366, 1283, 1238, 1161, 1123, 1009, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69 (q, J=8.1 Hz, 6H, Si($CH_2CH_3)_3$), 0.95 (t, J=8.1 Hz, 9H, Si($CH_2CH_3)_3$), 1.20 (s, 9H, C($CH_3)_3$), 1.77 (m, 1H, C11–H), 1.85 (m, 1H, C11–H), 3.54–3.61 (m, 2H, C10–H_2), 3.99–4.00 (m, 2H, C13–H_2), 4.07 (m, 1H, C12–H), 4.48 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.51 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 7.29 (m, 1H, Ar*H*), 7.32–7.35 (m, 4H, Ar*H*); FAB-HRMS *m*/*z* calcd for $C_{22}H_{39}O_4Si$ (M^++H) 395.2618, found 395.2608.

4.1.12. (*R*)-4-Benzyloxy-2-(triethylsilyl)oxy-1-butanol (36). Diisobutylaluminum hydride in *n*-hexane (1.01 M, 41.8 mL, 42.2 mmol) was added to a stirred solution of ester **35** (8.34 g, 21.13 mmol) in CH_2Cl_2 (120 mL) at −78°C under an argon atmosphere. After stirring at −78°C for 1 h, the reaction was quenched with MeOH (10 mL), and 10% aqueous potassium sodium tartrate (100 mL) was added. The mixture was stirred vigorously at room temperature for 2 h, and the whole was extracted with AcOEt (2×150 mL). The combined organic extracts were washed with brine (60 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 100 g, 6:1 *n*-hexane/AcOEt) to give alcohol **36** (6.15 g, 94%) as a colorless oil: $[\alpha]_D^{23}=+4.49$ (*c* 3.08, C_6H_6); IR (neat) 3445, 2955, 2876, 1456, 1414, 1364, 1238, 1096, 1007, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.61 (q, *J*=8.0 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.96 (t, *J*=8.0 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 1.80–1.88 (m, 2H, C11–*H*$_2$), 2.29 (brs, 1H, O*H*), 3.47–3.59 (m, 4H, C10–*H*$_2$, C13–*H*$_2$), 3.95 (m, 1H, C12–*H*), 4.48 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.51 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 7.27–7.36 (m, 5H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.9, 6.8, 34.3, 66.4, 66.5, 70.2, 73.0, 127.55, 127.62, 128.3, 138.1; FAB-HRMS *m*/*z* calcd for $C_{17}H_{31}O_3Si$ (M^++H) 311.2043, found 311.2035; Anal. calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74, found: C, 65.51; H, 9.68.

4.1.13. (*R*)-4-Benzyloxy-2-(triethylsilyl)oxybutanal (9). Sulfur trioxide pyridine complex (3.59 g, 22.5 mmol) was added over 15 min to a stirred solution of alcohol **36** (3.50 g, 11.27 mmol) and Et_3N (9.4 mL, 67.6 mmol) in DMSO (20 mL) under an argon atmosphere. After stirring for 1 h, the mixture was diluted with Et_2O (50 mL), and poured into saturated aqueous NH_4Cl (40 mL) and H_2O (20 mL) at 0°C. The whole was extracted with AcOEt (2×80 mL), and the combined organic extracts were washed with saturated aqueous NH_4Cl (2×40 mL) and brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (4.9 g, orange oil), which was purified by column chromatography (silica gel 50 g, 8:1 *n*-hexane/AcOEt) to give aldehyde **9** (3.39 g, 97%) as a colorless oil: $[\alpha]_D^{23}=+2.25$ (*c* 3.11, $CHCl_3$); IR (neat) 2957, 2878, 1736, 1456, 1416, 1240, 1117, 1015, 835, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.62 (q, *J*=7.8 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.95 (t, *J*=7.8 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 1.96 (m, 2H, C11–*H*$_2$), 3.56 (m, 1H, C10–*H*), 3.65 (m, 1H, C10–*H*), 4.19 (m, 1H, C12–*H*), 4.46 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.49 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 7.27–7.36 (m, 5H, Ar*H*), 9.63 (d, *J*=1.1 Hz, 1H, C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.7, 6.6, 33.4, 64.8, 72.8, 74.7, 127.4, 127.5, 128.2, 138.1, 203.5; FAB-HRMS *m*/*z* calcd for $C_{17}H_{29}O_3Si$ (M^++H) 309.1886, found 309.1877.

4.1.14. [3(2*R*),4*R*]-4-Benzyl-3-(4-benzyloxy-2-hydroxybutyryl)-2-oxazolidinone (38). A solution of imide **37** (15.0 g, 42.4 mmol) in THF (75 mL) was added to a solution of NaHMDS (1.0 M in THF, 50.9 mL, 50.9 mmol) at −78°C under an argon atmosphere. After stirring at −78°C for 30 min, the solution was cooled to −90°C, and a solution of 2-(phenylsulfonyl)-3-phenyloxaziridine (16.8 g, 63.6 mmol) in THF (50 mL) was added. Upon completion of the addition, the reaction was quenched by addition of AcOH (15 mL) in THF (30 mL), and the mixture was partitioned between AcOEt (150 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with AcOEt (100 mL), and the combined organic extracts were washed successively with saturated aqueous Na_2SO_3 (100 mL), 1 M aqueous $NaHSO_4$ (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (33.6 g, a yellow oil), which was purified by column chromatography (silica gel 500 g, 4:1 *n*-hexane/AcOEt) to give alcohol **38** (12.6 g, 80%) as a colorless oil: $[\alpha]_D^{26}=-80.4$ (*c* 2.16, $CHCl_3$); IR (neat) 3493, 3030, 2926, 2865, 1780, 1696, 1497, 1454, 1391, 1354, 1292, 1213, 1121, 1014, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.12 (m, 1H, C11–*H*), 2.20 (m, 1H, C11–*H*), 2.74 (dd, *J*=9.6, 13.6 Hz, 1H, C*H*Ph), 3.25 (dd, *J*=3.2, 13.6 Hz, 1H, C*H*Ph), 3.64–3.72 (m, 2H, C10–*H*$_2$), 3.79 (dd, *J*=7.8, 8.9 Hz, 1H, C*H*O), 4.00 (dd, *J*=2.3, 8.9 Hz, 1H, C*H*O), 4.24 (dddd, *J*=2.3, 3.2, 7.8, 9.6 Hz, 1H, NC*H*), 4.38 (d, *J*=11.1 Hz, 1H, OC*H*Ph), 4.44 (d, *J*=11.1 Hz, 1H, OC*H*Ph), 5.18 (t, *J*=4.9 Hz, 1H, C12–*H*), 7.13 (m, 2H, Ar*H*), 7.22 (m, 1H, Ar*H*), 7.26–7.34 (m, 7H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 33.7, 37.3, 55.4, 65.6, 66.6, 68.1, 73.1, 127.2, 127.6, 127.9, 128.1, 128.7, 129.2, 134.9, 138.1, 153.2, 174.6; FAB-HRMS *m*/*z* calcd for $C_{21}H_{24}NO_5$ (M^++H) 370.1655, found 370.1652; Anal. calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79, found: C, 68.28; H, 6.40; N, 3.81.

4.1.15. [3(2*R*),4*R*]-4-Benzyl-3-[4-benzyloxy-2-(triethylsilyl)oxybutyryl]-2-oxazolidinone (39). TESCl (6.6 mL, 39.3 mmol) was added to a solution of alcohol **38** (13.2 g, 35.7 mmol) and imidazole (6.1 g, 89.4 mmol) in CH_2Cl_2 (100 mL) at 0°C under an argon atmosphere. After stirring at room temperature for 1 h, the reaction was quenched with H_2O (50 mL), and the whole was extracted with AcOEt (200 mL). The organic extract was washed with brine (100 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (17.5 g), which was purified by column chromatography (silica gel 150 g, 8:1 *n*-hexane/AcOEt) to give TES ether **39** (15.4 g, 89%) as a colorless oil; $[\alpha]_D^{21}=-43.4$ (*c* 0.99, $CHCl_3$): IR (neat) 2955, 2876, 1780, 1715, 1454, 1389, 1350, 1211, 1136, 1103, 1015, 972, 733, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.65 (q, *J*=8.0 Hz, 6H, Si(C*H*$_2$CH$_3$)$_3$), 0.97 (t, *J*=8.0 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$), 2.09 (q, *J*=5.3 Hz, 2H, C11–*H*$_2$), 2.64 (dd, *J*=10.3, 13.3 Hz, 1H, C*H*Ph), 3.31 (dd, *J*=3.1, 13.3 Hz, 1H, C*H*Ph), 3.64–3.72 (m, 3H, C10–*H*$_2$, C*H*O), 3.94 (dd, *J*=2.3, 8.9 Hz, 1H, C*H*O), 4.25 (m, 1H, NC*H*), 4.41 (s, 2H, OC*H*$_2$Ph), 5.55 (t, *J*=5.3 Hz, 1H, C12–*H*), 7.15 (m, 2H, Ar*H*), 7.20 (m, 1H, Ar*H*), 7.25–7.33 (m, 7H, Ar*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 4.6, 6.7, 35.6, 37.7, 55.6, 65.9, 66.3, 68.3, 72.9, 127.1, 127.5, 127.8, 128.1, 128.8, 129.3, 135.4, 138.4, 153.3, 173.7; FAB-HRMS *m*/*z* calcd for $C_{27}H_{38}NO_5Si$ (M^++H) 484.2519, found 484.2538; Anal. calcd for $C_{27}H_{37}NO_5Si$: C, 67.05; H, 7.71; N, 2.89, found: C, 67.09; H, 7.75; N, 2.88.

4.1.16. (*R*)-4-Benzyloxy-2-(triethylsilyl)oxy-1-butanol (36). Lithium borohydride in THF (0.65 M, 16.9 mL, 11.0 mmol) was added to a stirred solution of oxazolidinone **39** (4.07 g, 8.41 mmol) in THF (40 mL)–H_2O (0.22 mL, 12.2 mmol) at 0°C under an argon atmosphere. After stirring at 0°C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (40 mL), and the whole was extracted with AcOEt (2×50 mL). The organic extract was washed with brine (30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (4.34 g), which was purified by column chromatography (silica gel 80 g, 6:1→1:1 *n*-hexane/AcOEt) to give alcohol **36** (2.10 g, 81%) as a colorless oil, along with recovered auxiliary (1.25 g, 84%) as a colorless solid. The spectral data of this material were identical with those of a sample obtained from **31** as described above.

4.1.17. (3*S*,7*R*)-9-Benzyloxy-6-hydroxy-3-(4-methoxybenzyl)oxy-7-(triethylsilyl)oxy-1-{2-[4-(triethylsilyl)oxybutyl]-1,3-dithian-2-yl}nonan-4-one (40). Butyllithium in *n*-hexane (1.56 M, 11.1 mL, 17.32 mmol) was added to a solution of HMDS (3.7 mL, 17.54 mmol) in THF (40 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 **10** (6.96 g, 13.23 mmol) in THF (20 mL) was added dropwise over 30 min. After stirring at −78°C for 30 min, a solution of $ZnCl_2$ (4.72 g, 34.62 mmol) in THF (20 mL) was added, and the mixture was stirred for 30 min. A solution of aldehyde **9** (3.49 g, 11.31 mmol) in THF (10 mL) was added to the mixture at −78°C. After stirring at −78°C for 1 h and then at −50°C for 30 min, the mixture was quenched with saturated aqueous NH_4Cl (100 mL), and the whole was extracted with AcOEt (2×150 mL). The combined organic extracts were washed successively with saturated aqueous NH_4Cl (100 mL) and brine (2×50 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (11.9 g, slightly yellow oil), which was purified by column chromatography (silica gel 100 g, 6:1 *n*-hexane/AcOEt) to give β-hydroxy ketone **40** (9.26 g, 98%) as a colorless oil: $[\alpha]_D^{26}=-21.4$ (*c* 1.19, $CHCl_3$); IR (neat) 3493, 2953, 2876, 1715, 1612, 1514, 1456, 1416, 1248, 1096, 1011, 822, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.57–0.63 (m, 12H, $\mathrm{Si(C}H_2\mathrm{CH_3)_3}\times 2$), 0.93–0.97 (m, 18H, $\mathrm{Si(CH_2C}H_3\mathrm{)_3}\times 2$), 1.44–1.55 (m, 4H, C21–H_2, C22–H_2), 1.68–2.05 (m, 10H, C11–H_2, C17–H_2, C18–H_2, C20–H_2, $\mathrm{SCH_2C}H_2$), 2.58–2.88 (m, 6H, C14–H_2, $\mathrm{SC}H_2\times 2$), 3.04 (d, *J*=3.5 Hz, 1H, O*H*), 3.53–3.65 (m, 4H, C10–H_2, C23–H_2), 3.79–3.85 (m, 5H, C12–*H*, C16–*H*, $\mathrm{C_6H_4OC}H_3$), 4.07 (m, 1H, C13–*H*), 4.35–4.39 (m, 1H, OC*H*Ar), 4.50 (s, 2H, $\mathrm{OC}H_2\mathrm{Ph}$), 4.56 (m, 1H, OC*H*Ar), 6.87 (d, *J*=8.5 Hz, 2H, Ar*H*), 7.24–7.31 (m, 3H, Ar*H*), 7.33–7.35 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.3, 4.9, 6.7, 6.8, 20.2, 25.2, 25.77, 25.80, 26.4, 26.5, 32.9, 33.0, 33.3, 38.5, 40.3, 41.3, 52.9, 55.1, 62.5, 66.2, 66.5, 69.6, 70.4, 71.7, 72.0, 72.4, 72.9, 73.0, 83.8, 84.1, 113.7, 127.4, 127.56, 127.60, 128.20, 128.22, 129.4, 129.5, 138.0, 138.1, 159.3, 212.1, 212.5; FAB-HRMS *m/z* calcd for $C_{44}H_{75}O_7S_2Si_2$ (M^++H) 835.4493, found 835.4485; Anal. calcd for $C_{44}H_{74}O_7S_2Si_2$: C, 63.26; H, 8.93; S, 7.68, found: C, 63.29; H, 8.91; S, 7.86.

4.1.18. (3*S*,7*R*)-9-Benzyloxy-3-(4-methoxybenzyl)oxy-7-(triethylsilyl)oxy-1-{2-[4-(triethylsilyl)oxybutyl]-1,3-dithian-2-yl}-5-nonen-4-one (41). Acetic anhydride (0.52 mL, 5.56 mmol) was added to a stirred solution of alcohol **40** (2.32 g, 2.78 mmol) and DMAP (20.4 mg, 0.16 mmol) in pyridine (20 mL) under an argon atmosphere. After stirring at room temperature for 20 h, the reaction was quenched by addition of H_2O (20 mL), and the whole was extracted with AcOEt (2×60 mL). The combined organic extracts were washed successively with 0.1% aqueous HCl (2×50 mL), H_2O (40 mL), saturated aqueous $NaHCO_3$ (40 mL) and brine (2×20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (3.7 g, yellow oil), which was used without further purification.

DBU (0.50 mL, 3.34 mmol) was added to a stirred solution of the crude acetate (3.7 g) in CH_2Cl_2 (15 mL) at 0°C under an argon atmosphere. After stirring at 0°C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the mixture was extracted with AcOEt (60 mL). The organic layer was 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 (2.8 g), which was purified by column chromatography (silica gel 20 g, 10:1→8:1 *n*-hexane/AcOEt) to give enone **41** (2.01 g, 88% (two steps)) as a colorless oil: $[\alpha]_D^{28}=-27.8$ (*c* 2.17, $CHCl_3$); IR (neat) 2953, 2876, 1694, 1630, 1514, 1456, 1416, 1302, 1248, 1096, 1038, 1011, 820, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.56–0.61 (m, 12H, $\mathrm{Si(C}H_2\mathrm{CH_3)_3}\times 2$), 0.92–0.97 (m, 18H, $\mathrm{Si(CH_2C}H_3\mathrm{)_3}\times 2$), 1.44–1.55 (m, 4H, C21–H_2, C22–H_2), 1.75–1.96 (m, 9H, C11–H_2, C17–H_2, C18–*H*, C20–H_2, $\mathrm{SCH_2C}H_2$), 2.06 (m, 1H, C18–*H*), 2.66–2.83 (m, 4H, $\mathrm{SC}H_2\times 2$), 3.51 (m, 1H, C10–*H*), 3.58–3.62 (m, 3H, C10–*H*, C23–H_2), 3.80 (s, 3H, $\mathrm{C_6H_4OC}H_3$), 3.89 (m, 1H, C16–*H*), 4.31 (d, *J*=11.5 Hz, 1H, OC*H*Ar), 4.46 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.50 (d, *J*=11.8 Hz, 1H, OC*H*Ph) 4.52–4.57 (m, 2H, C12–*H*, OC*H*Ar), 6.68 (dd, *J*=1.3, 15.6 Hz, 1H, C14–*H*), 6.85–6.88 (m, 2H, Ar*H*), 7.04 (dd, *J*=4.7, 15.6 Hz, 1H, C13–*H*), 7.23–7.30 (m, 3H, Ar*H*), 7.31–7.36 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.4, 4.7, 6.7, 6.8, 20.2, 25.2, 25.8, 27.2, 33.0, 33.1, 37.5, 38.4, 52.8, 55.0, 62.5, 65.9, 68.9, 71.4, 72.8, 83.3, 113.6, 122.4, 127.3, 127.4, 128.1, 129.1, 129.4, 138.1, 150.4, 159.1, 200.4; FAB-HRMS *m/z* calcd for $C_{44}H_{72}O_6S_2Si_2Na$ (M^++Na) 839.4207, found 839.4216; Anal. calcd for $C_{44}H_{72}O_6S_2Si_2$: C, 64.66; H, 8.88; S, 7.85, found: C, 64.59; H, 8.86; S, 7.97.

4.1.19. (3*S*,7*S*)-9-Benzyloxy-3-(4-methoxybenzyl)oxy-7-(triethylsilyl)oxy-1-{2-[4-(triethylsilyl)oxybutyl]-1,3-dithian-2-yl}nonan-4-one (42). Stryker reagent (3.89 g, 1.98 mmol) was added to a solution of enone **41** (2.03 g, 2.48 mmol) in wet benzene (21 mL) at room temperature under an argon atmosphere. After stirring of the dark brown solution at room temperature for 10 h, the solvent was removed in vacuo. The crude product (6.1 g) was purified by column chromatography (silica gel 30 g, 20:1→8:1 *n*-hexane/AcOEt) to give ketone **42** (1.85 g, 91%) as a colorless oil: $[\alpha]_D^{25}=-16.4$ (*c* 1.10, $CHCl_3$); IR (neat) 2953, 2876, 1715, 1613, 1514, 1456, 1416, 1302, 1248, 1175, 1098, 1038, 1011, 820, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.56–0.61 (m, 12H, $\mathrm{Si(C}H_2\mathrm{CH_3)_3}\times 2$), 0.92–0.97 (m, 18H, $\mathrm{Si(CH_2C}H_3\mathrm{)_3}\times 2$), 1.44–1.55 (m, 4H, C21–H_2, C22–H_2), 1.66–2.02 (m, 12H, C11–H_2, C13–H_2, C17–H_2, C18–H_2, C20–H_2, SCH$_2$CH_2), 2.58–2.83 (m, 6H, C14–H_2, SCH_2×2), 3.49–3.56 (m, 2H, C10–H_2), 3.58–3.61 (m, 2H, C23–H_2), 3.77 (m, 1H, C16–*H*), 3.80 (s, 3H, C$_6$H$_4$OCH_3), 3.91 (m, 1H, C12–*H*), 4.37 (d, *J*=11.4 Hz, 1H, OC*H*Ar), 4.45–4.51 (m, 3H, OC*H*Ar, OCH_2Ph), 6.87 (d, *J*=8.5 Hz, 2H, Ar*H*), 7.25–7.30 (m, 3H, Ar*H*), 7.32–7.36 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ 4.5, 5.0, 6.8, 6.9, 20.3, 25.3, 25.86, 25.91, 26.8, 30.5, 33.0, 33.1, 33.6, 37.0, 38.5, 52.9, 62.5, 66.9, 68.5, 71.8, 72.9, 83.9, 113.7, 127.3, 127.5, 128.1, 129.3, 129.4, 138.3, 159.2, 212.2; FAB-HRMS *m/z* calcd for $C_{44}H_{73}O_6S_2Si_2$ (M$^+$−H) 817.4387, found 817.4401; Anal. calcd for $C_{44}H_{74}O_6S_2Si_2$: C, 64.50; H, 9.10; S, 7.83, found: C, 64.74; H, 8.94; S, 7.82.

4.1.20. (3*S*,4*R*,7*S*)-9-Benzyloxy-3-(4-methoxybenzyl)oxy-4-methyl-7-(triethylsilyl)oxy-1-{2-[4-(triethylsilyl)oxybutyl]-1,3-dithian-2-yl}nonan-4-ol (43). A solution of ketone **42** (630.7 mg, 0.77 mmol) in Et$_2$O (2 mL) was added to a solution of MeMgI (prepared from MeI (0.24 mL, 3.86 mmol) and magnesium tuning (93.4 mg, 3.84 mmol)) in Et$_2$O (8 mL) at −78°C under an argon atmosphere. After stirring at −78°C for 1 h, the reaction was quenched with saturated aqueous NH$_4$Cl (20 mL), and the whole was extracted with AcOEt (50 mL). The organic layer was washed with brine (20 mL), and dried over anhydrous Na$_2$SO$_4$. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel 10 g, 6:1 *n*-hexane/AcOEt) to give alcohol **43** (611.6 mg, 95%) as a colorless oil: $[\alpha]_D^{25}$=+1.25 (*c* 1.12, C$_6$H$_6$); IR (neat) 3486, 2953, 2876, 1613, 1514, 1456, 1416, 1372, 1248, 1094, 1011, 822, 739 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.57–0.62 (m, 12H, Si(CH_2CH$_3$)$_3$×2), 0.93–0.97 (m, 18H, Si(CH$_2$CH_3)$_3$×2), 1.14 (s, 3H, C37–H_3), 1.42–1.68 (m, 9H, C13–H_2, C14–H_2, C17–*H*, C21–H_2, C22–H_2), 1.70–1.91 (m, 8H, C11–H_2, C17–*H*, C18–*H*, C20–H_2, SCH$_2$CH_2), 2.17 (m, 1H, C18–*H*), 2.26 (brs, 1H, O*H*), 2.70–2.80 (m, 4H, SCH_2×2), 3.20 (dd, *J*=3.0, 8.0 Hz, 1H, C16–*H*), 3.51–3.55 (m, 2H, C10–H_2), 3.59–3.62 (m, 2H, C23–H_2), 3.80 (s, 3H, C$_6$H$_4$OCH_3), 3.86 (m, 1H, C12–*H*), 4.46 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.50 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.55 (d, *J*=11.0 Hz, 1H, OC*H*Ar), 4.63 (d, *J*=11.0 Hz, 1H, OC*H*Ar), 6.87 (d, *J*=8.6 Hz, 2H, Ar*H*), 7.26–7.33 (m, 7H, Ar*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ 4.4, 5.0, 6.8, 7.0, 20.5, 23.6, 25.4, 25.5, 25.9, 30.8, 32.2, 33.0, 35.3, 37.1, 38.2, 53.3, 55.1, 62.6, 66.9, 69.8, 72.8, 74.2, 74.8, 86.8, 113.6, 127.3, 127.4, 128.1, 129.1, 130.5, 138.3, 159.0; FAB-HRMS *m/z* calcd for $C_{45}H_{78}O_6S_2Si_2Na$ (M$^+$+Na) 857.4676, found 857.4702; Anal. calcd for $C_{45}H_{78}O_6S_2Si_2$: C, 64.70; H, 9.41; S, 7.68, found: C, 64.73; H, 9.24; S, 7.78.

4.1.21. 2-[(3*S*,4*R*,7*S*)-9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-3-(4-methoxybenzyl)oxy-4-methyl-7-(triethylsilyl)oxynonyl]-2-[4-(triethylsilyl)oxybutyl]-1,3-dithiane (44). TBSOTf (0.25 mL, 1.09 mmol) was added to a stirred solution of alcohol **43** (590.6 mg, 0.707 mmol) and 2,6-lutidine (0.41 mL, 3.54 mmol) in CH$_2$Cl$_2$ (5 mL) at 0°C under an argon atmosphere. After stirring at room temperature for 4 h, the reaction was quenched with H$_2$O (10 mL), and the whole mixture was partitioned between AcOEt (50 mL) and 0.1% aqueous HCl (40 mL). The organic layer was washed successively with 0.1% aqueous HCl (2×40 mL), H$_2$O (10 mL), saturated aqueous NaHCO$_3$ (2×10 mL) and brine (2×10 mL), and dried over anhydrous Na$_2$SO$_4$. Filtration and evaporation in vacuo furnished the crude product (818 mg, yellow oil), which was purified by column chromatography (silica gel 10 g, 16:1 *n*-hexane/AcOEt) to give silyl ether **44** (626.3 mg, 93%) as a colorless oil: $[\alpha]_D^{24}$=−4.09 (*c* 2.25, CHCl$_3$); IR (neat) 2953, 2876, 1613, 1514, 1460, 1416, 1372, 1250, 1096, 1007, 835, 774, 741 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.09 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3), 0.56–0.61 (m, 12H, Si(CH_2CH$_3$)$_3$×2), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.92–0.97 (m, 18H, Si(CH$_2$CH_3)$_3$×2), 1.21 (s, 3H, C37–H_3), 1.46–1.64 (m, 9H, C13–H_2, C14–H_2, C17–*H*, C21–H_2, C22–H_2), 1.69–1.90 (m, 8H, C11–H_2, C17–*H*, C18–*H*, C20–H_2, SCH$_2$CH_2), 2.15 (m, 1H, C18–*H*), 2.67–2.78 (m, 4H, SCH_2×2), 3.17 (dd, *J*=2.0, 9.1 Hz, 1H, C16–*H*), 3.49–3.56 (m, 2H, C10–H_2), 3.57–3.60 (m, 2H, C23–H_2), 3.78–3.79 (m, 4H, C12–*H*, C$_6$H$_4$OCH_3), 4.43–4.52 (m, 3H, OC*H*Ar, OCH_2Ph), 4.57 (d, *J*=10.9 Hz, 1H, OC*H*Ar), 6.85 (m, 2H, Ar*H*), 7.24–7.28 (m, 3H, Ar*H*), 7.31–7.33 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, CDCl$_3$) δ −1.8, −1.7, 4.4, 5.1, 6.8, 6.9, 18.4, 20.4, 23.4, 25.3, 25.5, 25.88, 25.93, 26.1, 31.6, 33.1, 35.5, 36.6, 37.4, 38.3, 53.5, 55.2, 62.7, 67.1, 70.1, 72.9, 73.9, 78.2, 85.0, 113.6, 127.4, 127.6, 128.2, 128.9, 131.3, 138.5, 158.9; FAB-HRMS *m/z* calcd for $C_{51}H_{91}O_6S_2Si_3$ (M$^+$−H) 947.5565, found 947.5565; Anal. calcd for $C_{51}H_{92}O_6S_2Si_3$: C, 64.50; H, 9.76; S, 6.75, found: C, 64.48; H, 9.61; S, 6.71.

4.1.22. 4-{2-[(3*S*,4*R*,7*S*)-9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-3-(4-methoxybenzyl)oxy-4-methyl-7-(triethylsilyl)oxynonyl]-1,3-dithian-2-yl}butan-1-ol (45). Bu$_4$NF in THF (1.0 M, 7.76 mL, 7.76 mmol) was added to a stirred solution of tris-silyl ether **44** (7.02 g, 7.39 mmol) in THF (70 mL)–AcOH (7 mL) at 0°C. After stirring at 0°C for 1 h, saturated aqueous NaHCO$_3$ (20 mL) was added, and the whole was extracted with AcOEt (2×150 mL). The combined organic extracts were washed successively with saturated aqueous NaHCO$_3$ (2×40 mL), H$_2$O (40 mL) and brine (2×40 mL), and dried over anhydrous Na$_2$SO$_4$. Filtration and evaporation in vacuo furnished the crude product (7.1 g, colorless oil), which was purified by column chromatography (silica gel 150 g, 6:1→4:1→1:2 *n*-hexane/AcOEt) to give alcohol **45** (5.44 g, 88%) as a colorless oil, along with diol (506.7 mg, 9%) as a colorless syrup: $[\alpha]_D^{25}$=−6.02 (*c* 1.19, CHCl$_3$); IR (neat) 3463, 2953, 2876, 1613, 1514, 1460, 1370, 1250, 1092, 1036, 835, 774, 741 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.09 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3), 0.58 (q, *J*=8.1 Hz, 6H, Si(CH_2CH$_3$)$_3$), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.94 (t, *J*=8.1 Hz, 9H, Si(CH$_2$CH_3)$_3$), 1.22 (s, 3H, C37–H_3), 1.46–1.62 (m, 10H, C13–H_2, C14–H_2, C17–*H*, C21–H_2, C22–H_2, O*H*), 1.69–1.90 (m, 8H, C11–H_2, C17–*H*, C18–*H*, C20–H_2, SCH$_2$CH_2), 2.16 (m, 1H, C18–*H*), 2.67–2.79 (m, 4H, SCH_2×2), 3.16 (dd, *J*=2.0, 9.2 Hz, 1H, C16–*H*), 3.50–3.56 (m, 2H, C10–H_2), 3.59–3.61 (m, 2H, C23–H_2), 3.79 (m, 4H, C12–*H*, C$_6$H$_4$OCH_3), 4.44–4.50 (m, 3H, OC*H*Ar, OCH_2Ph), 4.59 (d, *J*=10.8 Hz, 1H, OC*H*Ar), 6.84–6.87 (m, 2H, Ar*H*), 7.24–7.30 (m, 3H, Ar*H*), 7.31–7.33 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, CDCl$_3$) δ −1.9, −1.8, 5.1, 6.9, 18.3, 20.2, 23.5, 25.2, 25.4, 25.85, 25.88, 26.1, 31.7, 32.7, 35.3, 36.6, 37.3, 38.1, 53.4, 55.2, 62.4, 67.1, 70.1, 72.9, 74.0, 78.2, 85.0, 113.6, 127.4, 127.6, 128.2, 128.9, 131.2, 138.4, 158.9; FAB-HRMS *m/z* calcd for $C_{45}H_{78}O_6S_2Si_2Na$ (M^++Na) 857.4676, found 857.4689; Anal. calcd for $C_{45}H_{78}O_6S_2Si_2$: C, 64.70; H, 9.41; S, 7.68, found: C, 64.68; H, 9.54; S, 7.63.

4.1.23. 4-{2-[(3*S*,4*R*,7*S*)-9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-3-(4-methoxybenzyl)oxy-4-methyl-7-(triethylsilyl)oxynonyl]-1,3-dithian-2-yl}butyraldehyde (7). Sulfur trioxide pyridine complex (1.26 g, 7.94 mmol) was added over 30 min to a stirred solution of alcohol **45** (2.21 g, 2.65 mmol) and Et_3N (2.2 mL, 15.9 mmol) in DMSO (25 mL) under an argon atmosphere. After stirring at room temperature for 1 h, the mixture was diluted with Et_2O (30 mL), and poured into saturated aqueous NH_4Cl (50 mL) at 0°C. The whole mixture was extracted with AcOEt (2×80 mL). The combined organic extracts were washed successively with 0.5 M aqueous $NaHSO_4$ (2×30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (2×30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (2.25 g, slightly yellow oil), which was purified by column chromatography (silica gel 50 g, 10:1→8:1 *n*-hexane/AcOEt) to give aldehyde **7** (2.07 g, 94%) as a colorless oil: $[\alpha]_D^{25}$=−6.15 (*c* 1.04, $CHCl_3$); IR (neat) 2953, 2878, 1726, 1613, 1514, 1458, 1370, 1250, 1094, 1007, 835, 774, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.58 (q, J=8.0 Hz, 6H, $Si(CH_2CH_3)_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.94 (t, J=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 1.22 (s, 3H, C37–H_3), 1.53–1.64 (m, 5H, C13–H_2, C14–H_2, C17–H), 1.69–1.91 (m, 10H, C11–H_2, C17–H, C18–H, C20–H_2, C21–H_2, SCH_2CH_2), 2.12 (m, 1H, C18–H), 2.40–2.43 (m, 2H, C22–H_2), 2.73–2.75 (m, 4H, SCH_2×2), 3.17 (m, 1H, C16–H), 3.49–3.58 (m, 2H, C10–H_2), 3.78 (m, 4H, C12–H, $C_6H_4OCH_3$), 4.44–4.50 (m, 3H, OCHAr, OCH_2Ph), 4.59 (d, J=10.9 Hz, 1H, OCHAr), 6.84–6.86 (m, 2H, ArH), 7.24–7.29 (m, 3H, ArH), 7.31–7.33 (m, 4H, ArH), 9.73 (t, J=1.3 Hz, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.8, −1.7, 5.1, 6.9, 17.0, 18.4, 23.4, 25.2, 25.3, 25.9, 26.1, 31.7, 35.6, 36.6, 37.4, 37.6, 43.6, 53.2, 55.2, 67.1, 70.1, 72.9, 74.0, 78.3, 84.9, 113.6, 127.4, 127.6, 128.2, 128.9, 131.2, 138.5, 159.0, 201.7; FAB-HRMS *m/z* calcd for $C_{45}H_{76}O_6S_2Si_2Na$ (M^++Na) 855.4519, found 855.4564; Anal. calcd for $C_{45}H_{76}O_6S_2Si_2$: C, 64.85; H, 9.19; S, 7.70, found: C, 64.69; H, 9.00; S, 7.63.

4.1.24. 1-[2-[(3*S*,4*R*,7*S*)-9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-3-(4-methoxybenzyl)oxy-4-methyl-7-(triethylsilyl)oxy]nonyl-1,3-dithian-2-yl]-4-hepten-6-one (46). To a solution of aldehyde **7** (592.2 mg, 0.71 mmol) in benzene (10 mL) was added 1-triphenylphosphoranylidene-2-propanone (407.0 mg, 1.28 mmol), and the mixture was refluxed for 10 h. After cooling, the solvent was removed in vacuo, and the residue (1.42 g, yellow solid) was purified by column chromatography (silica gel 20 g, 8:1 *n*-hexane/AcOEt) to give enone **46** (611.2 mg, 98%) as a colorless oil: $[\alpha]_D^{21}$=−5.89 (*c* 2.04, $CHCl_3$); IR (neat) 3485, 2953, 1678, 1615, 1514, 1460, 1362, 1252, 1094, 835, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 6H, $Si(CH_3)_2$), 0.58 (q, J=7.9 Hz, 6H, $Si(CH_2CH_3)_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.94 (t, J=7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 1.22 (s, 3H, C37–H_3), 1.56–1.65 (m, 6H, C13–H_2, C14–H_2, C17–H_2), 1.72–1.90 (m, 9H, C11–H_2, C18–H, C20–H_2, C21–H_2, SCH_2CH_2), 2.24 (m, 1H, C18–H), 2.19–2.22 (m, 5H, C22–H_2, C26–H_3), 2.67–2.79 (m, 4H, SCH_2×2), 3.17 (dd, J=1.6, 8.7 Hz, 1H, C16–H), 3.51–3.56 (m, 2H, C10–H_2), 3.78–3.79 (m, 4H, C12–H, $C_6H_4OCH_3$), 4.46–4.50 (m, 3H, OCHAr, OCH_2Ph), 4.59 (d, J=10.9 Hz, 1H, OCHAr), 6.09 (d, J=16.0 Hz, 1H, C24–H), 6.75 (m, 1H, C23–H), 6.85 (d, J=8.5 Hz, 2H, ArH), 7.23–7.26 (m, 3H, ArH), 7.32–7.33 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.9, −1.7, 5.0, 6.9, 18.3, 22.6, 23.3, 25.2, 25.3, 25.8, 26.0, 26.7, 31.6, 32.4, 35.4, 36.5, 37.3, 37.8, 53.1, 55.0, 66.9, 69.9, 72.8, 73.9, 78.0, 84.7, 113.4, 127.2, 127.4, 128.0, 128.7, 130.9, 131.4, 138.2, 147.2, 158.7, 198.0; FAB-HRMS *m/z* calcd for $C_{48}H_{80}O_6S_2Si_2Na$ (M^++Na) 895.4832, found 895.4851; Anal. calcd for $C_{48}H_{80}O_6S_2Si_2$: C, 66.01; H, 9.23; S, 7.34, found: C, 65.86; H, 9.30; S, 7.44.

4.1.25. 1-[2-[(3*S*,4*R*,7*S*)-9-Benzyloxy-4-(*tert*-butyldimethylsilyl)oxy-3-hydroxy-4-methyl-7-(triethylsilyl)oxy]nonyl-1,3-dithian-2-yl]-4-hepten-6-one (47). To a solution of MPM ether **46** (571.2 mg, 0.649 mmol) in CH_2Cl_2 (10 mL)–pH 7 phosphate buffer (1 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (176.9 mg, 0.779 mmol) at room temperature. After stirring for 20 min, saturated aqueous $NaHCO_3$ (10 mL) was added, and the whole was extracted with AcOEt (2×50 mL). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (2×20 mL), H_2O (20 mL) and brine (2×20 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 30 g, 4:1 *n*-hexane/Et_2O) to give alcohol **47** (459.4 mg, 94%) as a colorless oil: $[\alpha]_D^{21}$=−7.81 (*c* 2.01, $CHCl_3$); IR (neat) 3480, 2953, 2878, 1676, 1628, 1456, 1418, 1362, 1254, 1091, 1007, 835, 774, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.59 (q, J=7.9 Hz, 6H, $Si(CH_2CH_3)_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.95 (t, J=7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 1.21 (s, 3H, C37–H_3), 1.39–1.48 (m, 3H, C13–H, C17–H_2), 1.54–1.73 (m, 5H, C13–H, C14–H_2, C21–H_2), 1.75–1.78 (m, 2H, C11–H_2), 1.88–2.00 (m, 5H, C18–H, C20–H_2, SCH_2CH_2), 2.21–2.26 (m, 5H, C22–H_2, C26–H3), 2.31 (m, 1H, C18–H), 2.44 (d, J=4.8 Hz, 1H, OH), 2.72–2.77 (m, 2H, SCH_2), 2.83–2.89 (m, 2H, SCH_2), 3.30 (m, 1H, C16–H), 3.52–3.55 (m, 2H, C10–H_2), 3.83 (m, 1H, C12–H), 4.47 (m, J=11.9 Hz, 1H, OCHPh), 4.50 (m, J=11.9 Hz, 1H, OCHPh), 6.09 (dd, J=16.0 Hz, 1H, C24–H), 6.78 (m, 1H, C23–H), 7.28 (m, 1H, ArH), 7.32–7.36 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.23, −2.18, 4.9, 6.8, 18.1, 22.5, 23.6, 25.2, 25.6, 25.7, 26.6, 31.1, 32.3, 33.3, 35.3, 36.8, 37.9, 52.9, 66.7, 69.7, 72.8, 78.2, 127.3, 127.4, 128.1, 131.4, 138.2, 147.2, 198.0; FAB-HRMS *m/z* calcd for $C_{40}H_{72}O_5S_2Si_2Na$ (M^++Na) 775.4257, found 775.4194; Anal. calcd for $C_{40}H_{72}O_5S_2Si_2$: C, 63.78; H, 9.63; S, 8.51, found: C, 63.69; H, 9.51; S, 8.64.

4.1.26. 1-[2-[(4*R*,7*S*)-9-Benzyl-4-(*tert*-butyldimethylsilyl)oxy-4-methyl-3-oxo-7-(triethylsilyl)oxy]nonyl-1,3-dithian-2-yl]-4-hepten-6-one (48). Dess–Martin periodinane (338.2 mg, 0.797 mmol) was added over 10 min to a solution of alcohol **47** (241.0 mg, 0.319 mmol) in CH_2Cl_2 (100 mL)–pyridine (5 mL) at 0°C under an argon atmosphere. After stirring at 0°C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL) and 1 M $Na_2S_2O_3$ (25 mL), and the whole was extracted with Et_2O (2×80 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 (272.0 mg, yellow oil), which was purified by column chromatography (silica gel 15 g, 8:1 *n*-hexane/AcOEt) to give ketone **48** (230.2 mg, 96%) as a colorless oil: $[\alpha]^{22}_{D}=+10.3$ (*c* 2.27, $CHCl_3$); IR (neat) 2953, 2878, 1715, 1678, 1628, 1456, 1418, 1362, 1254, 1096, 1007, 835, 775, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 6H, $Si(CH_3)_2$), 0.57 (q, J=8.0 Hz, 6H, $Si(CH_2CH_3)_3$), 0.92–0.95 (m, 18H, $Si(CH_2CH_3)_3$, $SiC(CH_3)_3$), 1.24 (m, 1H, C13–*H*), 1.33 (s, 3H, C37–H_3), 1.50–1.80 (m, 9H, C11–H_2, C13–*H*, C14–H_2, C20–H_2, C21–H_2), 1.86–1.97 (m, 2H, SCH_2CH_2), 2.14–2.24 (m, 7H, C18–H_2, C22–H_2, C26–H_3), 2.68–2.78 (m, 3H, C17–*H*, SCH_2), 2.80–2.90 (m, 3H, C17–*H*, SCH_2), 3.47–3.55 (m, 2H, C10–H_2), 3.79 (m, 1H, C12–*H*), 4.45 (d, J=11.9 Hz, 1H, OC*H*Ph), 4.49 (d, J=11.9 Hz, 1H, OC*H*Ph), 6.09 (d, J=15.8 Hz, 1H, C24–*H*), 6.77 (m, 1H, C23–*H*), 7.28 (m, 1H, Ar*H*), 7.32–7.34 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.4, −2.3, 4.8, 6.8, 18.2, 22.5, 25.0, 25.7, 25.8, 26.6, 31.0, 31.5, 32.3, 33.3, 36.8, 36.9, 38.7, 52.5, 66.7, 68.9, 72.8, 82.5, 127.3, 127.4, 128.1, 131.5, 138.2, 147.0, 198.0, 214.6; FAB-HRMS *m/z* calcd for $C_{40}H_{70}O_5S_2Si_2Na$ (M^++Na) 773.4101, found 773.4061; Anal. calcd for $C_{40}H_{70}O_5S_2Si_2$: C, 63.95; H, 9.39; S, 8.54, found: C, 63.75; H, 9.42; S, 8.66.

4.1.27. (3*E*,12*R*,15*S*)-17-Benzyloxy-12-(*tert*-butyldimethylsilyl)oxy-8,11-dioxo-12-methyl-15-(triethylsilyl)-oxy-3-heptadecen-2-one (19). A solution of dithioacetal **48** (258.0 mg, 0.343 mmol) in Et_2O (3 mL) was added to a solution of $AgNO_3$ (350 mg, 2.06 mmol), *N*-chlorosuccinimide (297.7 mg, 2.23 mmol) and 2,4,6-collidine (0.4 mL) in 80% aqueous CH_3CN (10 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. The mixture was filtered through a Celite pad and the filtrate was extracted with AcOEt (2×50 mL). The combined organic extracts were washed successively with 0.3% aqueous HCl (5×30 mL), H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (280.4 mg), which was purified by column chromatography (silica gel 15 g, 4:1 *n*-hexane/AcOEt) to give triketone **19** (209.9 mg, 93%) as a colorless oil: $[\alpha]^{25}_{D}=+9.33$ (*c* 1.07, $CHCl_3$); IR (neat) 2955, 2878, 1715, 1678, 1630, 1454, 1362, 1254, 1094, 1007, 835, 775, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 6H, $Si(CH_3)_2$), 0.55 (q, J=7.5 Hz, 6H, $Si(CH_2CH_3)_3$), 0.90–0.94 (m, 18H, $Si(CH_2CH_3)_3$, $SiC(CH_3)_3$), 1.23 (m, 1H, C13–*H*), 1.31 (s, 3H, C37–H_3), 1.49–1.61 (m, 2H, C13–*H*, C14–*H*), 1.67–1.78 (m, 5H, C11–H_2, C14–*H*, C21–H_2), 2.18–2.22 (m, 5H, C22–H_2, C26–H_3), 2.47–2.50 (m, 2H, C20–H_2), 2.53–2.57 (m, 2H, C18–H_2), 2.79 (m, 1H, C17–*H*), 2.92 (m, 1H, C17–*H*), 3.48–3.52 (m, 2H, C10–H_2), 3.77 (m, 1H, C12–*H*), 4.43 (d, J=11.2 Hz, 1H, OC*H*Ph), 4.47 (d, J=11.2 Hz, 1H, OC*H*Ph), 6.05 (d, J=16.2 Hz, 1H, C24–*H*), 6.73 (m, 1H, C23–*H*), 7.25 (m, 1H, Ar*H*), 7.30–7.31 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.4, −2.3, 4.8, 6.8, 18.2, 21.7, 25.8, 26.0, 26.7, 31.3, 31.5, 32.2, 35.7, 36.7, 36.9, 41.6, 66.8, 69.0, 72.8, 82.5, 127.3, 127.4, 128.1, 131.5, 138.3, 147.1, 198.2, 208.3, 214.3; FAB-HRMS *m/z* calcd for $C_{37}H_{64}O_6Si_2Na$ (M^++Na) 683.4139, found 683.4113; Anal. calcd for $C_{37}H_{64}O_6Si_2$: C, 67.22; H, 9.74, found: C, 67.10; H, 9.84.

4.1.28. Double hemiketal formation/intramolecular hetero-Michael addition. To a solution of TES ether **19** (100.6 mg, 0.15 mmol) in THF (1 mL) at 0°C was added 1N aqueous HCl (0.1 mL). After stirring at 0°C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), and the mixture was partitioned between AcOEt (20 mL) and H_2O (5 mL). The organic extract was washed with brine (2×10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product, which was used without further purification.

NaOMe (1 M in MeOH, 0.15 mL, 0.15 mmol) was added to a stirred solution of the equilibrium mixture in THF (1.5 mL) at 0°C under an argon atmosphere. After stirring at 0°C for 1 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL), and the whole was extracted with AcOEt (2×20 mL). 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 (93.5 mg), which was purified by column chromatography (silica gel 5 g, 12:1→8:1 *n*-hexane/AcOEt) to give a mixture of dispiroketals (75.6 mg, 91%, **20**/**52**/**53**/**54**=77:8:10:5) as a colorless oil. The ratio of isomers was determined by HPLC analysis (column, Zorbax® sil, 4.6×250 mm; eluent, 10:1 *n*-hexane/AcOEt; flow rate, 1.0 mL/min; detection, 254 nm, t_R (**53**)=11.6 min, t_R (**20**)=22.3 min, t_R (**52**)=34.5 min, t_R (**54**)=38.4 min). The isomers could be readily separated by column chromatography (silica gel 20 g, 12:1→8:1 *n*-hexane/AcOEt) to afford **20** (53.3 mg, 64%), along with isomers **52** (5.8 mg, 7%), **53** (7.3 mg, 9%) and **54** (3.6 mg, 4%).

4.1.29. 1-[(2*R*,6*R*,8*R*,10*S*,13*R*)-10-(2-Benzyloxy)ethyl-13-(*tert*-butyldimethylsilyloxy)-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-2-propanone (20). $[\alpha]^{23}_{D}=-4.70$ (*c* 1.02, $CHCl_3$); IR (neat) 2953, 2857, 1717, 1456, 1364, 1252, 1225, 1103, 1042, 870, 774, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.17 (m, 1H, C22–*H*), 1.29 (s, 3H, C37–H_3), 1.40–1.49 (m, 2H, C13–*H*, C20–*H*), 1.58–1.87 (m, 9H, C11–H_2, C13–*H*, C14–*H*, C17–*H*, C18–*H*, C20–*H*, C21–*H*, C22–*H*), 1.91 (m, 1H, C21–*H*), 2.04 (m, 1H, C18–*H*), 2.09–2.19 (m, 5H, C14–*H*, C17–*H*, C26–H_3), 2.41 (dd, J=6.9, 15.2 Hz, 1H, C24–*H*), 2.56 (dd, J=6.1, 15.2 Hz, 1H, C24–*H*), 3.51 (m, 1H, C10–*H*), 3.59 (m, 1H, C10–*H*), 3.94 (m, 1H, C12–*H*), 4.28 (m, 1H, C23–*H*), 4.48 (s, 2H, OCH_2Ph), 7.26 (m, 1H, Ar*H*), 7.32–7.33 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.93, −1.91, 18.0, 19.4, 24.4, 25.9, 30.1, 30.6, 30.8, 31.3, 34.1, 34.3, 35.9, 37.5, 50.3, 67.6, 67.9, 69.2, 72.7, 73.5, 107.9, 110.5, 127.3, 127.5, 128.3, 138.7, 207.6; TLC R_f=0.51 (3:1 *n*-hexane/AcOEt); FAB-HRMS *m/z* calcd for $C_{31}H_{50}O_6SiNa$ (M^++Na) 569.3274, found 569.3267; Anal. calcd for $C_{31}H_{50}O_6Si$: C, 68.09; H, 9.22, found: C, 68.22; H, 9.17.

4.1.30. 1-[(2*S*,6*S*,8*S*,10*S*,13*R*)-10-(2-Benzyloxy)ethyl-13-(*tert*-butyldimethylsilyloxy)-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-2-propanone (52). $[\alpha]_D^{29}$=+38.6 (*c* 1.06, $CHCl_3$); IR (neat) 2930, 2857, 1715, 1456, 1362, 1252, 1176, 1138, 1098, 1049, 835, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3), 0.86 (s, 9H, SiC(CH_3)$_3$), 1.21 (m, 1H, C22–*H*), 1.35–1.43 (m, 4H, C13–*H*, C37–H_3), 1.49–1.55 (m, 2H, C13–*H*, C20–*H*), 1.63–1.73 (m, 5H, C11–*H*, C14–*H*, C20–*H*, C21–*H*, C22–*H*), 1.75–1.81 (m, 2H, C11–*H*, C14–*H*), 1.84–1.98 (m, 3H, C17–*H*, C18–*H*, C21–*H*), 2.02 (m, 1H, C17–*H*), 2.19 (s, 3H, C26–H_3), 2.29 (ddd, *J*=7.1, 8.9, 12.5 Hz, 1H, C18–*H*), 2.42 (dd, *J*=5.7, 14.6 Hz, 1H, C24–*H*), 2.47 (dd, *J*=7.6, 14.6 Hz, 1H, C24–*H*), 3.50–3.58 (m, 2H, C10–H_2), 3.62 (m, 1H, C12–*H*), 4.35 (m, 1H, C23–*H*), 4.49 (s, 2H, OCH_2Ph), 7.27 (m, 1H, Ar*H*), 7.33–7.34 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, C_6D_6) δ -1.7, 18.4, 20.3, 21.7, 26.2, 28.6, 29.9, 30.2, 31.2, 34.1, 36.4, 37.8, 38.6, 51.1, 67.2, 68.3, 70.8, 73.2, 75.2, 107.1, 112.5, 127.6, 127.8, 128.6, 139.5, 205.4; TLC R_f=0.45 (3:1 *n*-hexane/ AcOEt); FAB-HRMS *m/z* calcd for $C_{31}H_{50}O_6SiNa$ (M^++Na) 569.3274, found 569.3278; Anal. calcd for $C_{31}H_{50}O_6Si$: C, 68.09; H, 9.22, found: C, 68.06; H, 9.19.

4.1.31. 1-[(2*S*,6*S*,8*R*,10*S*,13*R*)-10-(2-Benzyloxy)ethyl-13-(*tert*-butyldimethylsilyloxy)-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-2-propanone (53). $[\alpha]_D^{24}$=+28.5 (*c* 0.45, $CHCl_3$); IR (neat) 2949, 2857, 1721, 1454, 1362, 1252, 1184, 1146, 1049, 868, 835, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3), 0.86 (s, 9H, SiC(CH_3)$_3$), 1.09 (m, 1H, C22–*H*), 1.30 (s, 3H, C37–H_3), 1.43 (m, 1H, C13–*H*), 1.50–1.65 (m, 6H, C13–*H*, C14–*H*, C18–*H*, C20–H_2, C21–*H*), 1.66–1.76 (m, 3H, C11–H_2, C22–*H*), 1.84–2.00 (m, 3H, C17–*H*, C18–*H*, C21–*H*), 2.12 (m, 3H, C26–H_3), 2.19 (m, 1H, C14–*H*), 2.27 (m, 1H, C17–*H*), 2.53 (dd, *J*=9.3, 16.2 Hz, 1H, C24–*H*), 2.62 (dd, *J*=3.3, 16.2 Hz, 1H, C24–*H*), 3.49–3.57 (m, 2H, C10–H_2), 3.97 (m, 1H, C12–*H*), 4.28 (m, 1H, C23–*H*), 4.43 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 4.48 (d, *J*=11.8 Hz, 1H, OC*H*Ph), 7.28 (m, 1H, Ar*H*), 7.30–7.35 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.0, 18.1, 20.0, 24.6, 25.9, 29.3, 30.5, 30.6, 31.0, 34.4, 36.1, 36.2, 37.0, 50.5, 66.2, 67.1, 67.5, 72.8, 72.9, 107.5, 110.6, 127.5, 127.6, 128.3, 138.5, 207.0; TLC R_f=0.59 (3:1 *n*-hexane/ AcOEt); FAB-HRMS *m/z* calcd for $C_{31}H_{50}O_6SiNa$ (M^++Na) 569.3274, found 569.3256; Anal. calcd for $C_{31}H_{50}O_6Si$: C, 68.09; H, 9.22, found: C, 68.17; H, 9.19.

4.1.32. 1-[(2*S*,6*R*,8*R*,10*S*,13*R*)-10-(2-Benzyloxy)ethyl-13-(*tert*-butyldimethylsilyloxy)-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-2-propanone (54). $[\alpha]_D^{21}$=+33.7 (*c* 0.49, $CHCl_3$); IR (neat) 2928, 2855, 1721, 1462, 1370, 1256, 1041, 835, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 6H, SiCH_3), 0.84 (s, 9H, SiC(CH_3)$_3$), 1.26–1.28 (m, 4H, C22–*H*, C37–H_3), 1.45 (m, 1H, C13–*H*), 1.53–1.83 (m, 11H, C11–*H*, C13–*H*, C14–*H*, C17–*H*, C18–*H*, C20–*H*, C21–*H*, C22–*H*), 2.01–2.21 (m, 6H, C14–*H*, C17–*H*, C18–*H*, C26–H_3), 2.43 (dd, *J*=5.4, 16.0 Hz, 1H, C24–*H*), 2.68 (dd, *J*=7.3, 16.0 Hz, 1H, C24–*H*), 3.50–3.58 (m, 2H, C10–H_2), 3.91 (m, 1H, C23–*H*), 4.00 (m, 1H, C12–*H*), 4.48 (s, 2H, OCH_2Ph), 7.26 (m, 1H, Ar*H*), 7.32–7.33 (m, 4H, Ar*H*); TLC R_f=0.43 (3:1 *n*-hexane/AcOEt); FAB-HRMS *m/z* calcd for $C_{31}H_{50}O_6SiNa$ (M^++Na) 569.3274, found 569.3299.

4.1.33. 1-[(2*R*,6*R*,8*R*,10*S*,13*R*)-10-(2-Benzyloxyethyl)-13-hydroxy-13-(*tert*-butyldimethylsilyl)oxy-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-2-propanol (55). A solution of ketone **20** (50.5 mg, 0.092 mmol) in CH_2Cl_2 (8 mL) was added to a solution of $NaBH_4$ (7.0 mg, 0.18 mmol) in MeOH (2 mL) at 0°C. After stirring at 0°C for 2 h, the mixture was poured into saturated aqueous NH_4Cl (4 mL), and the whole was extracted with AcOEt (2×15 mL). 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, which was purified by column chromatography (silica gel 5 g, 8:1 *n*-hexane/AcOEt) to give alcohol **55** (47.0 mg, 93%) as a colorless oil: $[\alpha]_D^{22}$=−6.27 (*c* 1.11, $CHCl_3$); IR (neat) 3520, 2934, 2859, 1456, 1370, 1252, 1225, 1175, 1140, 1036, 970, 870, 835, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CHCl_3$) δ 0.08 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3), 0.85 (s, 9H, SiC(CH_3)$_3$), 1.09 (d, *J*=6.2 Hz, 1.5H, C26–H_3), 1.11 (d, *J*=6.2 Hz, 1.5H, C26–H_3), 1.22–1.30 (m, 4H, C22–*H*, C37–H_3), 1.35 (m, 1H, C13–*H*), 1.46–2.09 (m, 14H, C11–H_2, C13–*H*, C14–*H*, C17–*H*, C18–H_2, C20–H_2, C21–H_2, C22–*H*, C24–H_2), 2.12–2.22 (m, 2H, C14–*H*, C17–*H*), 3.47–3.64 (m, 2.5H, C10–*H*, O*H*), 3.82 (brs, 0.5H, O*H*), 3.98–4.23 (m, 3H, C12–*H*, C23–*H*, C25–*H*), 4.49 (s, 1H, OC*H*Ph), 4.51 (s, 1H, OC*H*Ph), 7.29 (m, 1H, Ar*H*), 7.33–7.35 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.93, −1.92, 18.0, 19.5, 19.7, 23.4, 24.0, 24.37, 24.40, 25.9, 29.5, 29.6, 30.69, 30.73, 30.8, 31.4, 33.8, 33.9, 34.1, 34.4, 35.6, 35.8, 37.6, 37.8, 44.5, 44.8, 63.5, 66.8, 67.2, 67.7, 67.8, 68.5, 69.8, 72.7, 72.8, 73.6, 73.7, 107.7, 107.8, 110.4, 110.9, 127.3, 127.4, 127.5, 127.8, 128.2, 128.3, 138.2, 138.7; FAB-HRMS *m/z* calcd for $C_{31}H_{52}O_6SiNa$ (M^++Na) 571.3431, found 571.3408.

4.1.34. 1-[(2*R*,6*R*,8*R*,10*S*,13*R*)-10-(2-Benzyloxyethyl)-13-hydroxy-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-2-propanol (56). Bu_4NF in THF (1 M, 0.55 mL, 0.55 mmol) was added to a solution of TBS ether **55** (60.3 mg, 0.11 mmol) in THF (1 mL), and the mixture was refluxed for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (3 mL), and the whole was extracted with AcOEt (2×10 mL). The combined organic extracts were washed successively with water (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration in vacuo furnished the crude product, which was purified by column chromatography (silica gel 8 g, 2:1 *n*-hexane/AcOEt) to give alcohol **56** (43.2 mg, 91%) as a colorless oil: $[\alpha]_D^{24}$=−6.93 (*c* 0.75, $CHCl_3$); IR (neat) 3505, 2938, 2868, 1454, 1227, 1086, 1028, 968, 868, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CHCl_3$) δ 1.09–1.11 (m, 3H, C26–H_3), 1.22 (s, 1.5H, C37–H_3), 1.24 (s, 1.5H, C37–H_3), 1.30 (m, 1H, C22–*H*), 1.45–2.05 (m, 16H, C11–H_2, C13–H_2, C14–H_2, C17–*H*, C18–*H*, C20–H_2, C21–H_2, C22–*H*, C24–H_2, O*H*), 2.10–2.24 (m, 2H, C17–*H*, C18–*H*), 3.44–3.62 (m, 3H, C10–H_2, O*H*), 3.96–4.23 (m, 3H, C12–*H*, C23–*H*, C25–*H*), 4.50 (s, 1H, OC*H*Ph), 4.52 (s, 1H, OC*H*Ph), 7.28 (m, 1H, Ar*H*), 7.32–7.35 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CHCl_3$) δ 19.5, 19.8, 21.0, 21.2, 23.4, 24.2, 29.5, 29.7, 30.70, 30.74, 30.8, 31.2, 34.4, 34.7, 35.4, 35.6, 35.7, 35.8, 37.6, 37.9, 44.6, 44.7, 63.2, 66.5, 67.1, 67.7, 67.9, 69.0, 69.7, 69.9, 70.0, 72.8, 72.9, 73.9, 107.8, 108.0, 110.6, 111.2, 127.4, 127.5, 127.7, 127.9, 128.2, 128.3, 137.9, 138.6; FAB-HRMS *m/z* calcd for $C_{25}H_{39}O_6$ (M^++H) 435.2747, found 435.2725.

4.1.35. 1-[(2*R*,6*R*,8*R*,10*S*,13*R*)-10-(2-Benzyloxyethyl)-13-hydroxy-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-2-propanone (57). Sulfur trioxide pyridine complex (46.3 mg, 0.291 mmol) was added to a solution of alcohol **56** (42.2 mg, 97.1 μmol) and Et_3N (0.1 mL, 0.71 mmol) in DMSO (3 mL) under an argon atmosphere. After stirring for 2 h, saturated aqueous NH_4Cl (2 mL) was added, and the resulting mixture was partitioned between water (5 mL) and AcOEt (15 mL). The aqueous layer was extracted with AcOEt (5 mL), and the combined organic extracts were washed with brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (43.5 mg, slightly yellow oil), which was purified by column chromatography (silica gel 5 g, 6:1→4:1 *n*-hexane/AcOEt) to give ketone **57** (37.6 mg, 90%) as a colorless oil: $[\alpha]_D^{23}=-6.69$ (*c* 1.21, $CHCl_3$); IR (neat) 3571, 2940, 2866, 1715, 1454, 1362, 1076, 1001, 953, 868, 739, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19–1.21 (m, 4H, C22–*H*, C37–H_3), 1.45–1.55 (m, 2H, C13–*H*, C20–*H*), 1.62–1.75 (m, 6H, C11–*H*, C13–*H*, C14–*H*, C20–*H*, C21–*H*, C22–*H*), 1.77–1.90 (m, 6H, O*H*, C11–*H*, C14–*H*, C17–*H*, C18–*H*, C21–*H*), 2.09 (s, 3H, C26–H_3), 2.11–2.19 (m, 2H, C17–*H*, C18–*H*), 2.42 (dd, *J*=6.6, 15.3 Hz, 1H, C24–*H*), 2.58 (dd, *J*=6.2, 15.3 Hz, 1H, C24–*H*), 3.53 (m, 1H, C10–*H*), 3.59 (m, 1H, C10–*H*), 3.88 (m, 1H, C12–*H*), 4.29 (m, 1H, C23–*H*), 4.49 (s, 2H, OCH_2Ph), 7.27 (m, 1H, Ar*H*), 7.32–7.33 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 21.0, 30.2, 30.6, 30.7, 31.3, 34.5, 35.7, 35.9, 37.5, 50.1, 67.4, 68.4, 69.5, 69.7, 108.1, 110.7, 127.4, 127.5, 128.3, 138.7, 207.3; FAB-HRMS *m/z* calcd for $C_{25}H_{37}O_6$ (M^++H) 433.2590, found 433.2583.

4.1.36. 1-[(2*R*,6*R*,8*R*,10*S*,13*R*)-13-Hydroxy-10-(2-hydroxyethyl)-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-2-propanone (58). Palladium hydroxide on carbon (20%, 5.6 mg) was added to a solution of benzyl ether **57** (34.6 mg, 80 μmol) in AcOEt (0.5 mL), and the flask was fitted with a hydrogen balloon and purged with hydrogen. After stirring for 13 h, the catalyst was filtered through a Celite pad, and the filtrate was evaporated in vacuo. The crude product (30.2 mg) was purified by column chromatography (silica gel 5 g, 1:2 *n*-hexane/AcOEt) to give alcohol **58** (25.2 mg, 92%) as a colorless oil: $[\alpha]_D^{24}=-7.68$ (*c* 0.50, $CHCl_3$); IR (neat) 3482, 2940, 1713, 1439, 1362, 1227, 1140, 1074, 1022, 955, 868 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21–1.25 (m, 4H, C22–*H*, C37–H_3), 1.46–1.58 (m, 2H, C13–*H*, C20–*H*), 1.63–1.76 (m, 7H, O*H*, C11–*H*, C13–*H*, C14–*H*, C20–*H*, C21–*H*, C22–*H*), 1.79–1.92 (m, 5H, C11–*H*, C14–*H*, C17–*H*, C18–*H*, C21–*H*), 2.08–2.23 (m, 5H, C17–*H*, C18–*H*, C26–H_3), 2.49 (dd, *J*=6.8, 16.0 Hz, 1H, C24–*H*), 2.82 (dd, *J*=5.9, 16.0 Hz, 1H, C24–*H*), 3.03 (brs, 1H, O*H*), 3.62 (m, 1H, C10–*H*), 3.77 (m, 1H, C10–*H*), 4.07 (m, 1H, C12–*H*), 4.38 (m, 1H, C23–*H*); ^{13}C NMR (125 MHz, C_6D_6) δ 19.8, 21.8, 30.7, 31.15, 31.21, 31.3, 34.8, 36.5, 38.2, 38.4, 49.8, 60.4, 69.8, 69.9, 108.3, 111.3, 206.3; FAB-HRMS *m/z* calcd for $C_{18}H_{31}O_6$ (M^++H) 343.2121, found 343.2137.

4.1.37. 1-[(2*R*,6*R*,8*R*,10*S*,13*R*)-13-Hydroxy-10-(2-hydroxy)ethyl-13-methyl-1,7,9-trioxadispiro[5.1.5.2]pentadec-2-yl]-2-propanone Semicarbazone (59). A solution of semicarbazide hydrochloride (23.7 mg, 0.21 mmol) and sodium acetate (24.5 mg, 0.42 mmol) in H_2O (0.1 mL) was added to a stirred solution of ketone **58** (14.6 mg, 42.63 μmol) in EtOH (0.5 mL) at room temperature. After stirring for 8 h, the mixture was partitioned between Et_2O (2 mL) and H_2O (2 mL), and the aqueous layer was extracted with AcOEt (2×10 mL). The combined organic extracts were washed with brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and concentration in vacuo furnished the crude product, which was purified by column chromatography (silica gel 5 g, 20:1→10:1 CH_2Cl_2/MeOH) to give semicarbazone **59** (16.6 mg, 98%) as a white solid. The isomers could be separated by column chromatography (silica gel 5 g, 1:4 acetone/AcOEt) to afford *anti* **59** (8.8 mg, 52%), along with *syn* **59** (5.7 mg, 33%): data for *anti* isomer; mp 139–140°C (hexane/Et_2O); IR (nujol) 3478, 3345, 2942, 1682, 1580, 1441, 1379, 1227, 1136, 1020, 868, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24–1.31 (m, 4H, C22–*H*, C37–H_3), 1.47–1.59 (m, 2H, C13–*H*, C20–*H*), 1.60–1.95 (m, 11H, C11–H_2, C13–*H*, C14–H_2, C17–*H*, C18–*H*, C20–*H*, C21–H_2, C22–*H*), 1.90 (s, 3H, C26–H_3), 2.10–2.23 (m, 2H, C17–*H*, C18–*H*), 2.41 (dd, *J*=6.2, 14.0 Hz, 1H, C24–*H*), 2.49 (dd, *J*=5.8, 14.0 Hz, 1H, C24–*H*), 2.63 (s, 1H, O*H*), 2.89 (brs, 1H, O*H*), 3.64 (m, 1H, C10–*H*), 3.77 (m, 1H, C10–*H*), 3.99 (m, 1H, C12–*H*), 4.14 (m, 1H, C23–*H*), 7.90 (s, 1H, N*H*); FAB-HRMS *m/z* calcd for $C_{19}H_{34}N_3O_6$ (M^++H) 400.2448, found 400.2422.

4.1.38. Typical procedure for the double hemiketal formation/intramolecular hetero-Michael addition (Table 1, entry 3). To a solution of TES ether **19** (20.0 mg, 30 μmol) in THF (0.3 mL) at 0°C was added 1N aqueous HCl (0.03 mL). After stirring at 0°C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL), and the mixture was poured into a two-layer mixture of Et_2O (5 mL) and H_2O (5 mL). The whole was extracted with AcOEt (2×10 mL), and the combined organic extracts were washed with brine (2×5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product, which was used without further purification.

LiOMe (1 M in MeOH, 30 μL, 30 μmol) was added to a stirred solution of the equilibrium mixture in THF (0.3 mL) at room temperature under an argon atmosphere. After stirring at room temperature for 4 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL), and the whole was extracted with AcOEt (2×10 mL). The combined organic extracts were washed with brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (18.5 mg), which was purified by column chromatography (silica gel 5 g, 12:1→8:1 *n*-hexane/AcOEt) to give a mixture of dispiroketals (15.2 mg, 92%, **20**/**52**/**53**/**54**=84:8:3:5) as a colorless oil. The ratio of isomers was determined by HPLC analysis (column, Zorbax® sil, 4.6×250 mm; eluent, 10:1 hexane/AcOEt; flow rate, 1.0 mL/min; detection, 254 nm, t_R (**53**)=11.6 min, t_R (**20**)=22.3 min, t_R (**52**)=34.5 min, t_R (**54**)=38.4 min).

4.1.39. Equilibration under basic conditions. *(i) Reaction of* ***20*** *with NaOMe*. NaOMe (1 M in MeOH, 45 μL, 45 μmol) was added to a stirred solution of **20** (24.5 mg, 44.8 μmol) in THF (0.5 mL) under an argon atmosphere. After stirring for 5 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL), and the whole was extracted with AcOEt (2×10 mL). The combined organic extracts were washed with 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→8:1 *n*-hexane/AcOEt) to give a mixture of dispiroketals (11.0 mg, 45%, **20/52/53/54**=53:5:42:<1) as a colorless oil, along with *C*-Michael product **66** (2.7 mg, 11%): data for *C*-Michael product **66**: $[\alpha]_D^{22}=+30.7$ (*c* 0.68, $CHCl_3$); IR (neat) 3466, 2928, 2857, 1717, 1460, 1362, 1258, 1134, 1096, 1026, 953, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 3H, SiCH_3), 0.19 (s, 3H, SiCH_3), 0.90 (s, 9H, Si$C(CH_3)_3$), 1.36 (s, 3H, C37–H_3), 1.43 (m, 2H), 1.54–1.73 (m, 10H), 2.02–2.36 (m, 7H), 2.47 (dd, *J*=2.2, 15.7 Hz, 1H), 2.52 (dd, *J*=6.9, 13.3 Hz, 1H), 3.59 (m, 1H, C10–*H*), 3.66 (m, 1H, C10–*H*), 4.05 (brs, 1H, O*H*), 4.17 (m, 1H, C12–*H*), 4.52 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 4.58 (d, *J*=11.9 Hz, 1H, OC*H*Ph), 7.27 (m, 1H, Ar*H*), 7.31–7.37 (m, 4H, Ar*H*); FAB-HRMS *m/z* calcd for $C_{31}H_{50}O_6SiNa$ (M^++Na) 569.3274, found 569.3264.

(ii) Reaction of ***53*** *with NaOMe*. NaOMe (1 M in MeOH, 55 μL, 55 μmol) was added to a stirred solution of **53** (30.0 mg, 54.9 μmol) in THF (0.5 mL) under an argon atmosphere. After stirring for 3 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL), and the whole was extracted with AcOEt (2×10 mL). The combined organic extracts were washed with brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (18.5 mg), which was purified by column chromatography (silica gel 5 g, 12:1→8:1 *n*-hexane/AcOEt) to give a mixture of dispiroketals (12.1 mg, 40%, **20/52/53/54**=45:10:45:<1) as a colorless oil, along with *C*-Michael product **66** (1.8 mg, 6%).

4.1.40. Equilibration under acidic conditions. *(i) Reaction of* ***52*** *with CSA*. CSA (12.9 mg, 0.056 mmol) was added to a stirred solution of **52** (10.1 mg, 0.018 mmol) in CH_2Cl_2 (0.2 mL) under an argon atmosphere. After stirring for 2 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 mL), and the whole was extracted with AcOEt (10 mL). The organic extract was washed with brine (3 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, 10:1→8:1 *n*-hexane/AcOEt) to give a mixture of dispiroketals (9.5 mg, 94%, **52/53/54**=19:68:13) as a colorless oil.

(ii) Reaction of ***53*** *with CSA*. CSA (16.4 mg, 0.071 mmol) was added to a stirred solution of **53** (12.9 mg, 0.024 mmol) in CH_2Cl_2 (0.2 mL) under an argon atmosphere. After stirring for 2 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 mL), and the whole was extracted with AcOEt (10 mL). The organic extract was washed with brine (3 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, 10:1→8:1 *n*-hexane/AcOEt) to give a mixture of dispiroketals (12.3 mg, 95%, **52/53/54**= 22:64:14) as a colorless oil.

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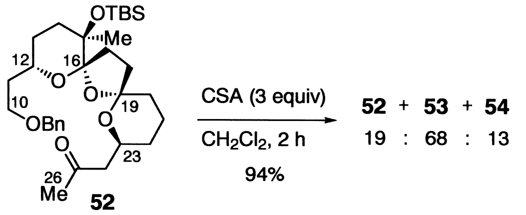

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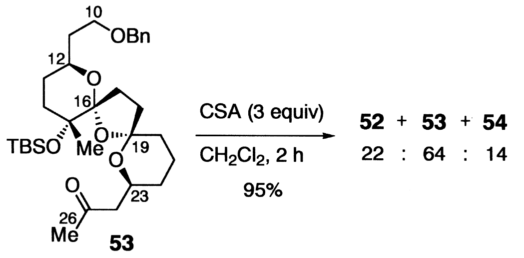
(8)



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(9)

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