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SYNTHETIC STUDIES ON AZASPIRACID, A NOVEL SHELLFISH POISON: ATTEMPTS TO CONSTRUCT THE ABCD RING SYSTEM

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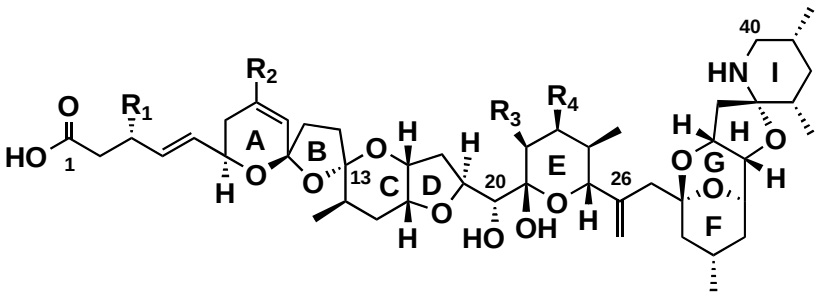
Abstract - Synthesis of the ABCD ring system of azaspiracid (**1**) was attempted. Construction of the highly substituted tetrahydrofuran (**9**) *via* the Pd(0)-mediated cyclization, followed by spirocyclization afforded trispiro-ring (**28**), carrying an unnatural ring-junctions. The BCD ring system of **1** was successfully produced by using the bridge of a sulfur atom between the B and C ring to control the spiroacetal center of the C13 position. The stereostructures were unambiguously determined by the NOE experiments.

INTRODUCTION

In 1995, human poisoning in the Netherlands was caused by the blue mussel *Mytilus edulis*, which was collected in Killary Harbor, Ireland.[1] Azaspiracid (**1**) and four congeners (**2**-**5**), novel shellfish poisons, were isolated as the causal toxin leading to the poisoning.[1a] Azaspiracids have fascinated many organic chemists for the bioactivity and unique structures, which possess an azaspiro ring, a 2,9-dioxabicyclo[3.3.1]nonane ring, and trispiro ring units in a molecule.[1] Furthermore the relative stereochemistry between the C1-C25 and the C28-C40 domains and the absolute configuration of the molecule have not been disclosed.[1a] Although many efforts were reported,[2] there has been no accomplishment of the total synthesis, the successfully investigation was the synthesis of proposed structure by Nicolaou's group.[3] Therefore, we initiated a synthetic investigation to determine the complete structure, and to understand the structure-activity relationship. Although several groups have

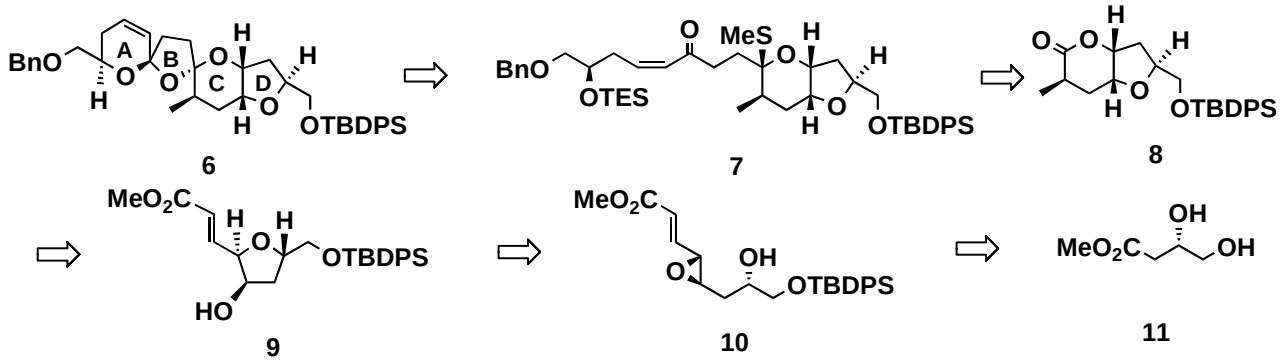
accomplished the synthesis of the FGHI ring part of **1** to date,[2i, j, l] construction of the ABCD ring system has been reported only by Nicolaou and co-workers.[2k] We describe herein our access to construction of the ABCD ring system of azaspiracid (**1**), along with our own thioether approach to the BCD ring system of **1** as a model study.[4]



		R_1	R_2	R_3	R_4
1	azaspiracid :	H	H	Me	H
2	azaspiracid-2 :	H	Me	Me	H
3	azaspiracid-3 :	H	H	H	H
4	azaspiracid-4 :	OH	H	H	H
5	azaspiracid-5 :	H	H	H	OH

RESULTS AND DISCUSSION

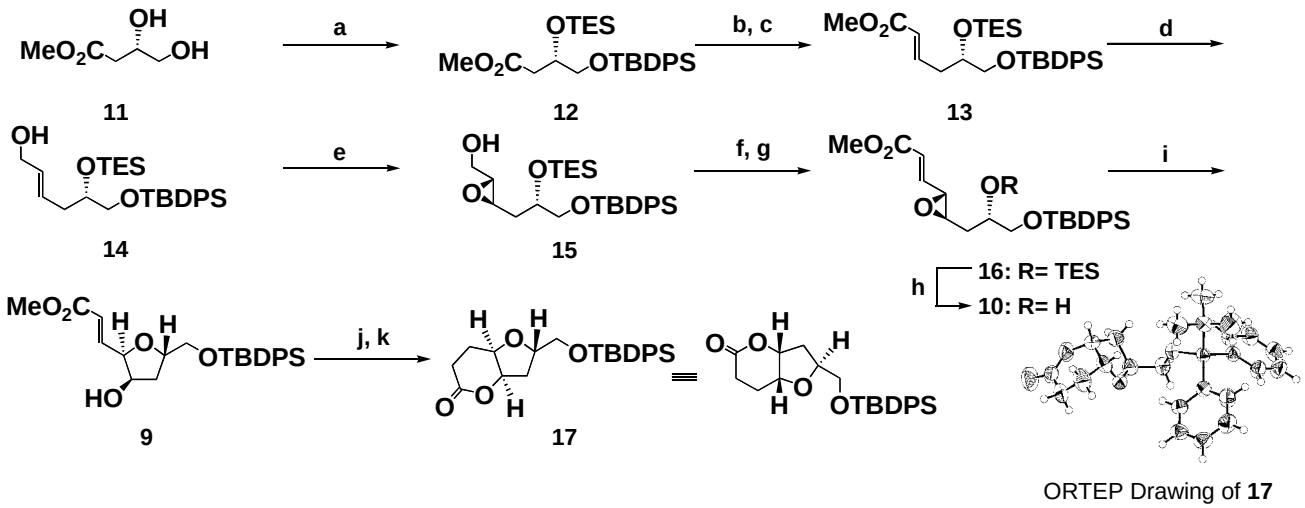
By our first retrosynthetic analysis of the ABCD ring system (**6**), the ABC rings structure would be constructed by the intramolecular acetalization of the thioacetal (**7**), which might be prepared from lactone (**8**) through tetrahydrofuran (**9**) (Scheme 1). The substituted tetrahydrofuran would be produced by the known procedure using **10**, easily prepared from L-malic acid.



Scheme 1. Retrosynthesis of the ABCD ring system of azaspiracid (**1**).

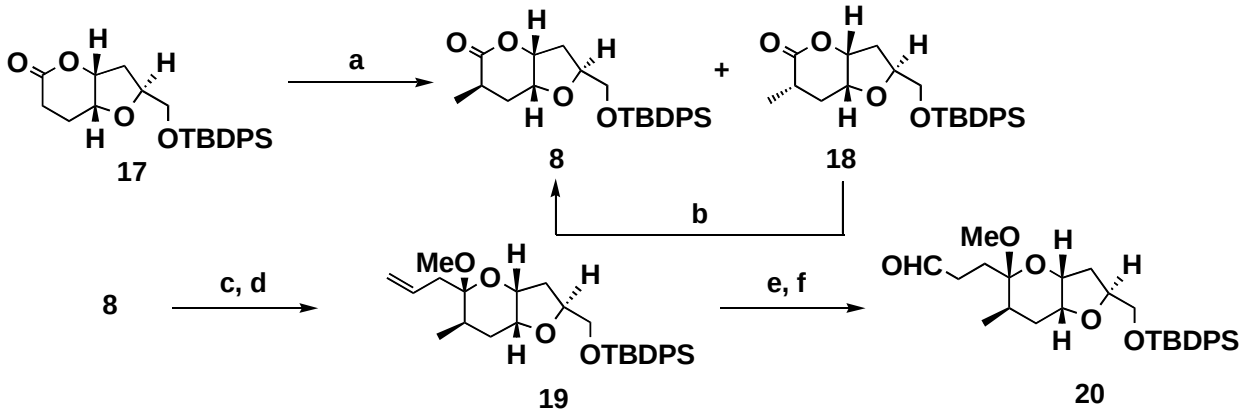
Along this line, two hydroxyl groups of **11**[5] were selectively protected to afford siloxy ether (**12**). Reduction of **12** and the following Wittig reaction gave α,β-unsaturated ester (**13**) in good yield, which was then reduced to allyl alcohol (**14**). Sharpless asymmetric epoxydation[6] provided epoxy alcohol (**15**) in 90% yield. Oxidation of **15** with SO_3•Py-DMSO, followed by the Wittig reaction yielded ester (**16**). Removal of a TES group under acidic conditions afforded **10** in 82% yield. At this stage, Hirama's

protocol[7] was employed to construct highly substituted tetrahydrofuran (**9**). Thus, treatment of **10** with $Pd_2(dba)_3$ and Ph_3P provided tetrahydrofuran (**9**) as a single isomer in 90% yield. After selective reduction of **9**, acidic treatment effected the desired lactonization to give **17** in 79% yield. The structure of lactone (**17**) was unambiguously determined by X-ray single crystallographic analysis (Scheme 2).[8]



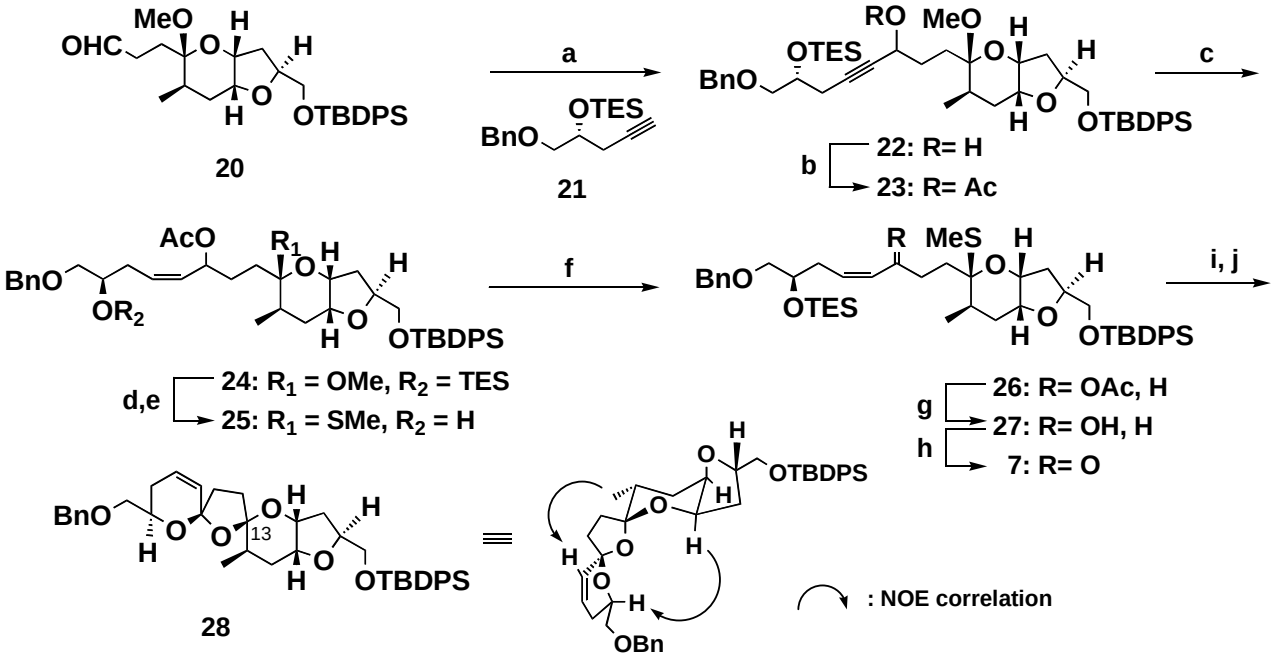
Scheme 2. *Reagents and conditions*: (a) TBDPSCl, Imid, then TESCl, 95%; (b) DIBAL, -78 ˚C; (c) $Ph_3P{=}CHCO_2Me$, 94% in 2 steps; (d) DIBAL-H, -78 ˚C, 95%; (e) $Ti(O\textit{i}\text{-}Pr)_4$, D-(-)-DET, TBHP, 90%; (f) SO_3•Py, DMSO, Et_3N; (g) $Ph_3P{=}CHCO_2Me$, 79% in 2 steps; (h) CSA, MeOH, 0 ˚C, 82%; (i) $Pd_2(dba)_3$•$CHCl_3$, Ph_3P, rt, 90%; (j) H_2, 10% Pd-C; (k) CSA, 79% in 2 steps.

Installation of a methyl group to **17** was carried out under LDA-MeI conditions. Although no stereochemical selectivity was observed in this reaction, the two diastereomers (**8** and **18**) were chromatographically separated. The undesired **18** was epimerized with DBU, according to Forsyth



Scheme 3. *Reagents and conditions*: (a) LDA, -78 ˚C, then MeI, 32% of **8** and 41% of **18**; (b) DBU, 60 ˚C, 36% of **8** and 58% of **18**; (c) allylmagnesium bromide, diethyl ether, -78 ˚C; (d) CSA, MeOH, 84% in 2 steps; (e) 9-BBN, then 3 M aq. NaOH, 35% aq. H_2O_2; (f) TPAP, NMO, MS4Å, 93% in 2steps.

protocol[2g] to afford a 1:2 mixture of **8** and **18**. Repetition of this method accumulatively afforded the desired **8** in 60% yield from **17** (Scheme 3).

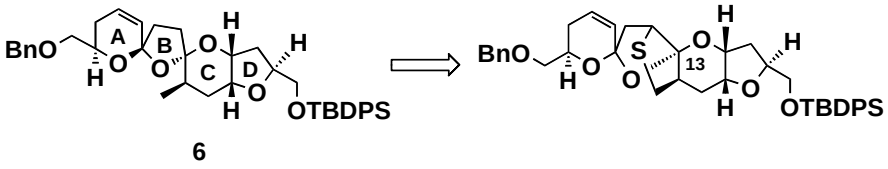


Scheme 4. *Reagents and conditions*: (a) EtMgBr, **21**, -60 ˚C, 53%; (b) Ac_2O, Py, 94%; (c) Lindlar cat., H_2, 99%; (d) $Zn(OTf)_2$, TMSSMe, 0 ˚C; (e) CSA, MeOH, 0 ˚C, 89% in 2 steps; (f) TESCl, Imid, 0 ˚C to rt, 98%; (g) DIBAL-H, -78 ˚C, 68%; (h) SO_3•Py, DMSO, Et_3N, rt, 95%; (i) TBAF, 0 ˚C; (j) MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, MS4Å, 0 ˚C to rt, 47% in 2 steps.

According to Forsyth protocol,[2g] treatment of **8** with allylmagnesium bromide, followed by acetalization, yielded methyl acetal (**19**). Hydroboration of **19** with 9-BBN afforded an alcohol, which on TPAP oxidation gave aldehyde (**20**). Upon addition of an acetylide prepared from **21**,[9] **20** provided alcohol (**22**) as a diastereomeric mixture (Scheme 4). Acetylation of **22** gave acetate (**23**), which was selectively reduced to afford olefin (**24**) in good yield. Thioacetalization of **24** with TMSSMe in the presence of $Zn(OTf)_2$, followed by acidic treatment provided thioacetal (**25**) in 89% yield, which was protected as a TES ether to give **26**. After reductive removal of an acetyl group, the resulted **27** was oxidized to give ketone (**7**).

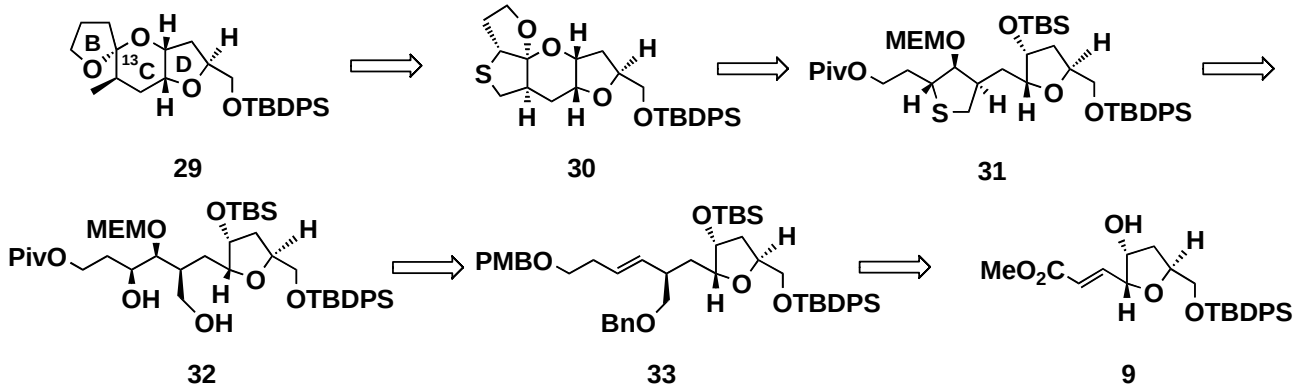
In the next stage, construction of the trispiro-ring of **6** was attempted by using ketone (**7**). Deprotection of **7** with TBAF afforded an acid-labile keto alcohol, which was treated with MeOTf[10] to provide **28** as a major product in 47% yield in 2 steps. However, the stereochemistry of this trispiro-ring (**28**) having the undesired configuration at the C13 spiroacetal center, was observed by the NOE experiments (Scheme 4).

Despite of detailed inspection of minor products, no desired product was observed, similar to results by the Forsyth group.[2g] All efforts for isomerization of **28** to **6** were unsuccessful.

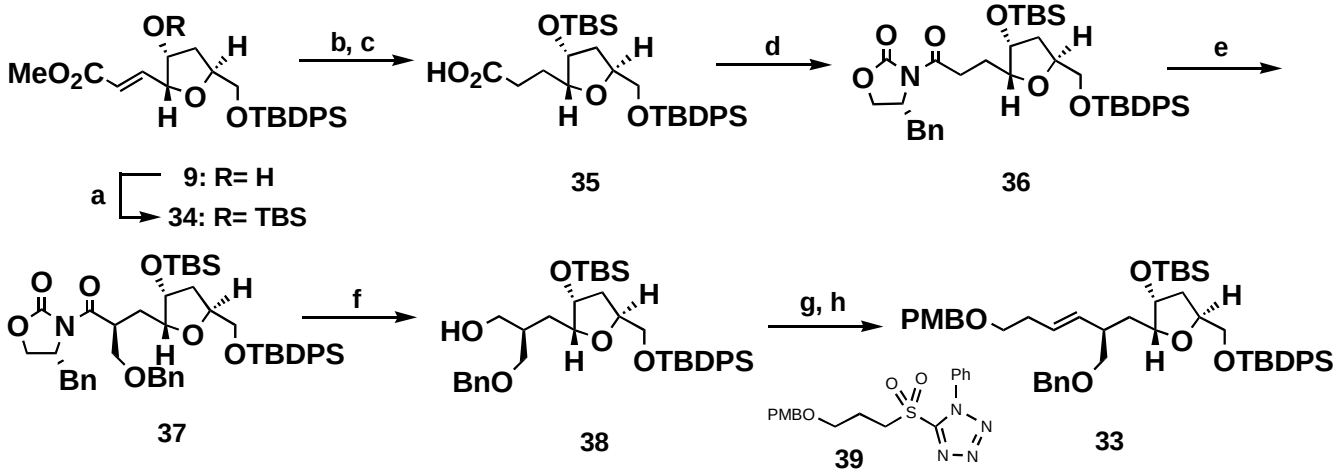


Scheme 5. The new synthetic strategy of the ABCD ring system**.**

Our attention turned to a new strategy for construction of the spirocenter (Scheme 5). Thus, the configuration at the C13 position would be controlled by a bridge using a sulfur atom. After acetalization, removal of the sulfur atom might afford the desired ABCD ring system (**6**). We attempted the synthesis of the BCD ring system to confirm efficiency of our strategy as a model study.



Scheme 6. Retrosynthesis of the BCD ring system.

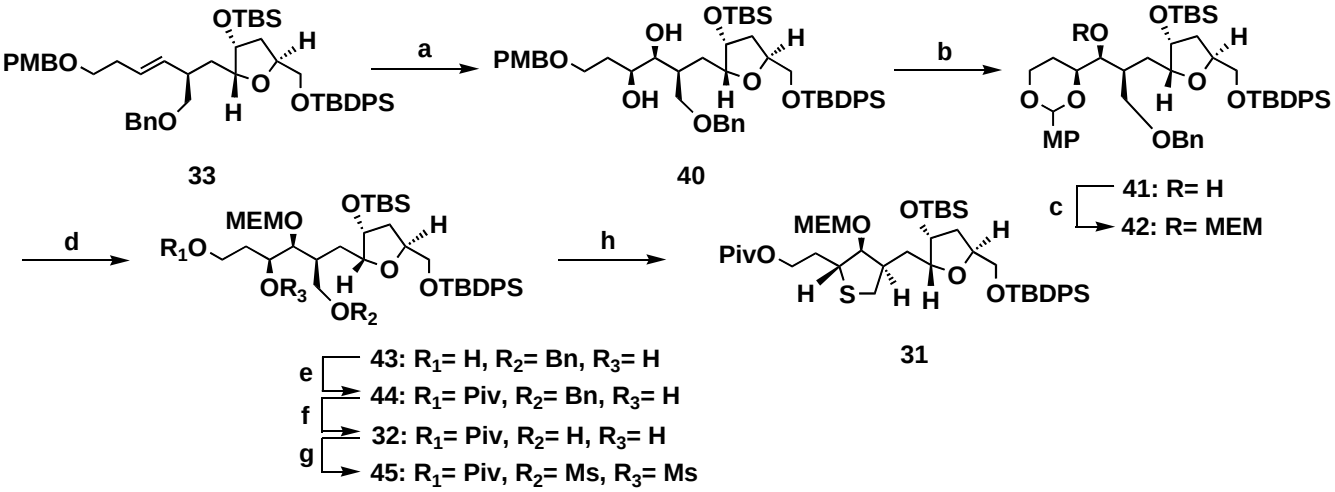


Scheme 7. *Reagents and conditions*: (a) TBSOTf, 2,6-lutidine, 86%; (b) H_2, 10% Pd-C; (c) LiOH, 98% in 2 steps; (d) PivCl, Et_3N, 0 ˚C, then (*R*)-4-benzyl-2-oxazolidinone, LiCl, 0 ˚C to rt, 88%; (e) LHMDS, -78 ˚C, then BOMCl, LiI, -78 ˚C to -50 ˚C, 78%; (f) $LiBH_4$, 91%; (g) TPAP, NMO, MS4Å; (h) **39**, LHMDS, -78 ˚C, 50% in 2 steps.

Spiroacetal (**29**), a model compound of the BCD ring system, would be obtained from acetal (**30**) by desulfurization (Scheme 6). Acetal (**30**) would be produced from olefin (**33**) through **32** and tetrahydrothiophene (**31**). Olefin (**33**) would be easily obtained from **9** (vide supra).

Protection of **9** as a TBS ether, followed by hydrogenation and saponification gave carboxylic acid (**35**) (Scheme 7). Compound (**35**) was condensed with the Evans's chiral auxiliary group,[11] followed by benzyloxymethylation of **36** to afford benzyl ether (**37**) as a single isomer in 78% yield. Reductive removal of the chiral auxiliary gave alcohol (**38**). Oxidation of **38** gave an aldehyde, which was reacted with sulfone (**39**) under the Julia olefination conditions,[12] to yield (*E*)-olefin (**33**) (50% in 2 steps) and (*Z*)-olefin (11% in 2 steps).

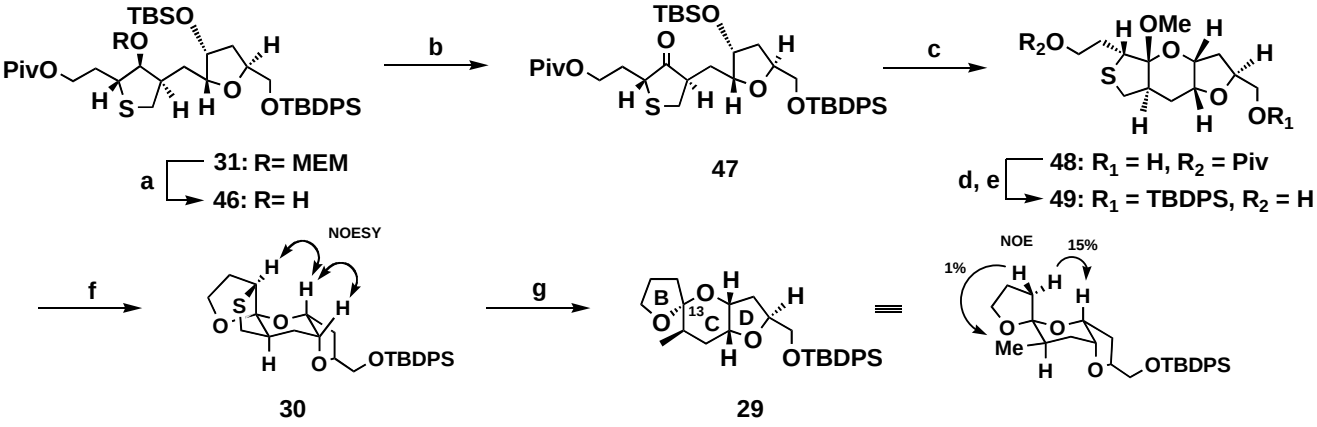
Introduction of a sulfur atom was shown in Scheme 8. Asymmetric dihydroxylation[13] of **33** afforded diol (**40**), which on DDQ oxidation and protection as a MEM ether gave **42**. Removal of an anisylidene acetal under acidic conditions and selective protection of a primary hydroxyl group, followed by hydrogenolysis afforded diol (**32**). After dimesylation, treatment with Na_2S gave tetrahydrothiophene (**31**) in 70% yield.



Scheme 8. *Reagents and conditions*: (a) AD-mix-α, $MeSO_2NH_2$, 95%; (b) DDQ, MS4Å, 61%; (c) MEMCl, *i*-Pr_2NEt, 91%; (d) 80% aq.AcOH, rt, 91%; (e) PivCl, Py, 0 ˚C to rt, 88%; (f) H_2, 20% $Pd(OH)_2$-C, 77%; (g) MsCl, Et_3N, 95%; (h) Na_2S, 100˚C, 79%.

Deprotection of a MEM group[14] and oxidation gave ketone (**47**) (Scheme 9). Similar to the first acetalization to produce the C ring, treatment of **47** with CSA in MeOH provided methyl acetal (**48**) in 86% yield. Reprotection by a TBDPS group and removal of a pivalate group gave alcohol (**49**) as a

precursor of the BCD ring system. Thus, treatment of **49** with $Yb(OTf)_3$[15] in MeCN afforded acetal (**30**) in 98% yield, carrying the desired configuration at the C13 position. The stereochemistry was confirmed by the NOESY experiments (Scheme 9). Finally, desulfurization of **30** with Raney Ni W-4 gave the BCD ring system (**29**) in 95% yield, without epimerization at the spiroacetal center. The BCD ring system (**29**) was confirmed by NOE correlation (Scheme 9).



Scheme 9. *Reagents and conditions*: (a) $ZnBr_2$, 83%; (b) SO_3•Py, DMSO, *i*-Pr_2NEt, 89%; (c) CSA, MeOH, 86%; (d) TBDPSCl, Et_3N, DMAP; (e) DIBAL, -78 ˚C, 79% in 2 steps; (f) $Yb(OTf)_3$, rt, 97%; (g) Raney Ni W-4, reflux, 95%.

In conclusion, we have synthesized the trispiro-ring (**28**) *via* the Pd(0)-mediated cyclization and acetalization, starting from diol (**11**). Compound (**28**) possessed the unnatural stereochemistry at the C13 spiroacetal center. The structural control of the C13 spiroacetal center was carried out by a new strategy, based on connection between the B and C rings with a sulfur atom. Manipulation of this strategy effected synthesis of the BCD ring system (**29**) of azaspiracid (**1**) was accomplished.

EXPERIMENTAL

General. All reactions were carried out under an argon atmosphere unless otherwise noted. All melting points were measured on a Yanaco MP-S3 and uncorrected. Optical rotations were measured on a JASCO DIR-360 digital polarimeter with sodium (D line) lamp. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H-NMR spectra and ^{13}C-NMR spectra were obtained on JNM-EX270 and JNM-GX400 spectrometers in deuteriochloroform solvent using tetramethylsilane as an internal standard, otherwise stated. HRMS spectra were obtained on Hitachi M-80B GC-MS operating at the ionization energy of 70 eV or JEOL JMS-700 spectrometers. Preparative and analytical TLC were

carried out on silica gel plate (Kieselgel 60 F254, E. Merck AG., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto Chemical Silica 60N (spherical, neutral, 63-210 μm) was used for column chromatography.

*Methyl (3S)-4-tert-butyldiphenylsiloxy-3-triethylsiloxybutanoate (**12**)*

To a solution of **11** (1.0 g, 7.5 mmol) in DMF (40 mL) were added imidazole (2.00 g, 29.4 mmol) and TBDPSCl (1.9 mL, 7.3 mmol) at 0 ˚C. After being stirred at rt for 20 min, the reaction mixture was recooled to 0 ˚C, and TESCl (1.5 mL, 9.0 mmol) was added. After kept at the same temperature for 20 min, the mixture was poured into H_2O, then extracted with 50% EtOAc / hexane (3×). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5% EtOAc in hexane) to give **12** (3.45 g, 95%) as a colorless oil: $[\alpha]^{21}_D$ –26.3˚ (*c* 1.0, $CHCl_3$); IR (film) ν 2954, 1741 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.66 (complex, 4H), 7.45-7.37 (complex, 6H), 4.20 (m, 1H), 3.67 (s, 3H), 3.61 (dd, 1H, *J*= 9.8, 4.9 Hz), 3.46 (dd, 1H, *J*= 9.8, 7.3 Hz), 2.81 (dd, 1H, *J*= 4.3, 15 Hz), 2.43 (dd, 1H, *J*= 8.3, 15 Hz), 1.04 (s, 9H), 0.85 (t, 9H, *J*= 7.8 Hz), 0.48 (q, 6H, *J*= 7.8 Hz); ^{13}C-NMR (100 MHz) δ 172.3, 135.5, 133.2, 129.6, 127.6, 69.9, 67.4, 51.5, 40.2, 26.8, 19.2, 6.8, 4.8. HREIMS calcd for $C_{26}H_{39}O_3Si_2$ (M^+-OMe) 455.2435, found: *m/z* 455.2434.

*Methyl (2E,5S)-6-tert-butyldiphenylsiloxy-5-triethylsiloxyhex-2-enoate (**13**)*

To a solution of **12** (1.85 g, 3.8 mmol) in toluene (40 mL) was added DIBAL-H (1.0 M solution in toluene, 4.2 mL, 4.2 mmol) at –78 ˚C. After 1 h, the mixture was diluted with sat. aq. NH_4Cl (1.5 mL) and Et_2O. After the addition of $MgSO_4$, the mixture was filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. A mixture of the residue and $Ph_3P{=}CHCO_2Me$ (2.54 g, 7.6 mmol) in benzene (40 mL) was stirred at rt for 8 h, then concentrated *in vacuo*. Purification by silica gel column chromatography (5% EtOAc in hexane) gave **13** (1.83 g, 94%) as a colorless oil: $[\alpha]^{19}_D$ –7.5˚ (*c* 1.0, $CHCl_3$); IR (film) ν 2954, 1728 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.66 (complex, 4H), 7.43-7.36 (complex, 6H), 7.01 (m, 1H), 5.89 (d, 1H, *J*= 16 Hz), 3.80 (m, 1H), 3.73 (s, 3H), 3.56 (dd, 1H, *J*= 10, 4.8 Hz), 3.46 (dd, 1H, *J*= 10, 7.6 Hz), 2.61 (m, 1H), 2.40 (m, 1H), 1.04 (s, 9H), 0.86 (t, 9H, *J*= 8.0 Hz), 0.48 (q, 6H, *J*= 8.0 Hz); ^{13}C-NMR (100 MHz) δ 172.3, 146.1, 135.5, 133.2, 129.6, 127.6, 123.0, 67.2, 67.2, 51.4, 37.5,

26.9, 19.2, 6.8, 4.8. HREIMS calcd for $C_{29}H_{45}O_4Si_2$ (M^++H) 513.2854, found: *m/z* 513.2844.

*(2E,5S)-6-tert-Butyldiphenylsiloxy-5-triethylsiloxyhex-2-en-1-ol (**14**)*

To a solution of **13** (1.83 g, 3.57 mmol) in CH_2Cl_2 (35 mL) was added DIBAL-H (1.0 M solution in toluene, 11 mL, 11 mmol) at –78 ˚C. After 10 min, the mixture was treated with essentially the same procedure as in the case of **12** to give **14** (1.64 g, 95%) as a colorless oil: $[\alpha]^{20}_D$ –5.2˚ (*c* 1.0, $CHCl_3$); IR (film) ν 3348, 2954 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.67 (complex, 4H), 7.45-7.36 (complex, 6H), 5.69 (m, 2H), 4.06 (br d, 2H, *J*= 4.0 Hz), 3.75 (m, 1H), 3.56 (dd, 1H, *J*= 10, 5.2 Hz), 3.48 (dd, 1H, *J*= 10, 7.2 Hz), 2.43 (m, 1H), 2.25 (m, 1H), 1.04 (s, 9H), 0.89 (t, 9H, *J*= 8.0 Hz), 0.53 (q, 6H, *J*= 8.0 Hz); ^{13}C-NMR (67.8 MHz) δ 135.5, 135.4, 133.5, 133.4, 131.4, 129.5, 129.0, 127.5, 72.4, 67.1, 63.7, 37.3, 26.9, 19.3, 6.9, 4.9. HREIMS calcd for $C_{24}H_{35}O_3Si_2$ (M^+-*t*-Bu) 427.2123, found: *m/z* 427.2123.

*{3-[(2S)-3-tert-Butyldiphenylsiloxy-2-triethylsiloxypropyl](2S,3R)oxiran-2-yl}methanol (**15**)*

To a solution of Ti(O*i*-Pr)$_4$ (8.4 mL, 29 mmol) in CH_2Cl_2 (270 mL) was added (-)-diethyl D-tartrate (8.1 g, 34.6 mmol) at –20 ˚C, and the resultant mixture was stirred for 10 min. A solution of **14** (14 g, 29 mmol) in CH_2Cl_2 (30 mL) was then added, and stirring was continued for 10 min prior to the addition of anhydrous TBHP (5.1 M in isooctane, 14 mL, 72 mmol). After being stirred at the same temperature for 5 h, aq. 10% L-(+)-tartaric acid was added. The organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in Et_2O (200 mL) and 1 M aq. NaOH (100 mL) was added to the solution at 0 ˚C. After being stirred at the same temperature for 30 min, the organic layer was separated and the aqueous layer was extracted with Et_2O (2×). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20% EtOAc in hexane) to afford **15** (13.1 g, 90%) as a colorless oil: $[\alpha]^{19}_D$ –0.5˚ (*c* 1.0, $CHCl_3$); IR (film) ν 3442, 2954 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.43-7.36 (complex, 6H), 3.88 (complex, 2H), 3.63 (dd, 1H, *J*= 10.3, 4.9 Hz), 3.56 (complex, 2H), 3.63 (dt, 1H, *J*= 5.9, 2.4 Hz), 2.91 (m, 1H), 1.92-1.81 (complex, 2H), 1.05 (s, 9H), 0.88 (t, 9H, *J*= 8 Hz), 0.51 (q, 6H, *J*= 8 Hz); ^{13}C-NMR (100 MHz) δ 135.5, 133.4, 129.6, 127.6, 70.7, 67.4, 61.7, 58.4, 53.2, 36.8, 26.9, 19.2, 6.9, 4.8. HREIMS calcd for $C_{28}H_{45}O_4Si_2$ (M^++H) 501.2853, found: *m/z*

501.2837.

*Methyl (2E)-3-{3-[(2S)-3-tert-butyldiphenylsiloxy-2-triethylsiloxypropyl](2S,3R)oxiran-2-yl}prop-2-enoate (**16**)*

To a solution of **15** (1.41 g, 2.8 mmol) in CH_2Cl_2 (18 mL) were added DMSO (9 mL), Et_3N (9 mL) and SO_3• Py (2.6 g, 16 mmol) at rt. The reaction mixture was stirred for 2 h, and then poured into H_2O. The organic phase was separated and the aqueous phase was extracted with Et_2O (2×). The combined organic extracts were washed sat. aq. NH_4Cl, H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was treated with $Ph_3P{=}CHCO_2Me$ (1.9 g, 5.7 mmol) in benzene (30 mL) as in the case of **13** to give **16** (1.23 g, 79%) as a colorless oil: $[\alpha]^{20}_D$ –7.6˚ (*c* 1.0, $CHCl_3$); IR (film) ν 2954, 1730, 1658 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.66 (complex, 4H), 7.45-7.36 (complex, 6H), 6.66 (dd, 1H, *J*= 15.6, 7 Hz), 6.10 (d, 1H, *J*= 15.6 Hz), 3.88 (m, 1H), 3.75 (s, 3H), 3.63 (dd, 1H, *J*= 10, 4 Hz), 3.55 (dd, 1H, *J*= 10, 7 Hz), 3.21 (br d, 1H, *J*= 7 Hz), 3.01 (br t, 1H, *J*= 6 Hz), 1.97-1.86 (complex, 2H), 1.05 (s, 9H), 0.87 (t, 9H, *J*= 8.0 Hz), 0.49 (q, 6H, *J*= 8.0 Hz); ^{13}C-NMR (100 MHz) δ 166.0, 145.0, 135.5, 135.4, 133.3, 133.1, 129.6, 127.6, 123.0, 70.5, 67.2, 58.6, 56.1, 51.7, 37.0, 26.9, 19.2, 6.9, 4.8. HREIMS calcd for $C_{31}H_{47}O_5Si_2$ (M^++H) 555.2959, found: *m/z* 555.2959.

*Methyl (2E)-3-{3-[(2S)-3-tert-butyldiphenylsiloxy-2-hydroxypropyl](2S,3R)-oxiran-2-yl}prop-2-enoate (**10**)*

A mixture of **16** (1.23 g, 2.22 mmol) and a catalytic amount of CSA in MeOH (25 mL) was stirred at 0 °C for 5 min; the reaction was quenched by the addition of sat. aq. $NaHCO_3$. Usual work-up and purification by silica gel column chromatography (5→25% EtOAc in hexane) gave **10** (0.80 g, 82%) as a colorless oil: $[\alpha]^{20}_D$ +3.3˚ (*c* 1.0, $CHCl_3$); IR (film) ν 3502, 2931, 1726 cm^{-1}; ^{1}H-NMR (270 MHz) δ 7.65 (complex, 4H), 7.47-7.38 (complex, 6H), 6.64 (dd, 1H, *J*= 15, 7 Hz), 6.10 (d, 1H, *J*= 15 Hz), 3.91 (m, 1H), 3.75 (s, 3H), 3.67 (dd, 1H, *J*= 10.3, 4 Hz), 3.58 (dd, 1H, *J*= 10.3, 7 Hz), 3.25 (dd, 1H, *J*= 7, 2 Hz), 3.00 (dt, 1H, *J*= 6, 2 Hz), 2.56 (d, 1H, *J*= 4 Hz), 1.78 (complex, 2H), 1.07 (s, 9H); ^{13}C-NMR (100 MHz) δ 165.9, 144.5, 135.4, 132.8, 129.8, 127.7, 123.2, 69.4, 67.3, 58.6, 55.8, 51.7, 35.0, 26.9, 19.3. HREIMS calcd for $C_{31}H_{47}O_5Si_2$ (M^+-OH) 423.1990, found: *m/z* 423.2019.

*Methyl (2E)-3-[(2R,3R,5S)-5-tert-butyldiphenylsiloxymethyl-3-hydroxyoxolan-2-yl]prop-2-enoate (**9**)*

A mixture of **10** (0.80 g, 1.8 mmol), Ph_3P (0.10 g, 0.38 mmol), and $Pd_2(dba)_3$•$CHCl_3$ (18.3 mg, 18 μmol) in CH_2Cl_2 (18 mL) was stirred at rt for 5 min. After evaporation, the residue was purified by silica gel column chromatography (25→33% EtOAc in hexane) to give **9** (0.72 g, 90%) as a colorless oil: $[\alpha]^{20}_D$ –26.0˚ (*c* 1.0, $CHCl_3$); IR (film) ν 3440, 2931, 1724 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.44-7.35 (complex, 6H), 6.99 (dd, 1H, *J*= 15.6, 4.4 Hz), 6.20 (dd, 1H, *J*= 15.6, 1.5 Hz), 4.58 (m, 1H), 4.46-4.41 (complex, 2H), 3.81 (dd, 1H, *J*= 11, 4 Hz), 3.74 (s, 3H), 3.64 (dd, 1H, *J*= 11, 4 Hz), 2.21 (ddd, 1H, *J*= 13, 8, 5 Hz), 2.06 (br dd, 1H, *J*= 13, 6 Hz), 1.05 (s, 9H); ^{13}C-NMR (100 MHz) δ 166.6, 143.7, 135.5, 133.3, 133.2, 129.6, 127.6, 122.5, 82.0, 78.3, 74.1, 65.9, 51.7, 36.8, 26.9, 19.3. HREIMS calcd for $C_{21}H_{23}O_5Si$ (M^+-*t*-Bu) 383.1313, found: *m/z* 383.1332.

*(1R,6R,8S)-8-tert-Butyldiphenylsiloxymethyl-2,7-dioxabicyclo[4.3.0]nonan-3-one (**17**)*

A mixture of **9** (4.34 g, 9.9 mmol) and a catalytic amount of 10% Pd-C in EtOH (100 mL) was stirred at rt under hydrogen atmosphere for 1 h. The mixture was filtrated through Celite pad and the filtrate was concentrated *in vacuo*. The residue was dissolved in benzene (100 mL) and a catalytic amount of CSA was added. After being stirred at reflux temperature for 3 h, the mixture was cooled to 0 °C and diluted with sat. aq. $NaHCO_3$. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (50% EtOAc in hexane) gave a crystalline residue. Recrystallization from Et_2O afforded **17** (3.21 g, 79%) as colorless needles: mp 100.8-101.2 ˚C; $[\alpha]^{25}_D$ –5.8˚ (*c* 1.00, $CHCl_3$); IR (film) ν 2930, 1745 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.67 (complex, 4H), 7.43-7.37 (complex, 6H), 4.95 (t, 1H, *J*= 4 Hz), 4.33 (complex, 2H), 3.82 (dd, 1H, *J*= 11, 4 Hz), 3.64 (dd, 1H, *J*= 11, 4 Hz), 2.63 (m, 1H), 2.43-2.24 (complex, 3H), 2.13-2.04 (complex, 2H), 1.06 (s, 9H); ^{13}C-NMR (100 MHz) δ 170.9, 135.5, 133.2, 133.1, 129.7, 129.6, 127.7, 127.6, 127.5, 82.9, 78.7, 73.9, 65.8, 36.0, 26.9, 25.2, 23.7, 19.3. HREIMS calcd for $C_{24}H_{30}O_4Si$ (M^+) 410.1901, found: *m/z* 410.1911. Anal. Calcd for $C_{24}H_{30}O_4Si$: C, 70.21; H, 7.36. Found: C, 70.05; H, 7.30.

*(1R,4R,6R,8S)-8-tert-Butyldiphenylsiloxymethyl-4-methyl-2,7-dioxabicyclo[4.3.0]nonan-3-one (**8**) and (1R,4S,6R,8S)-8-tert-butyldiphenylsiloxymethyl-4-methyl-2,7-dioxabicyclo[4.3.0]nonan-3-one (**18**)*

To a solution of *i*-Pr_2NH (1.1 mL, 7.8 mmol) in THF (80 mL) at 0 °C was added *n*-BuLi (1.59 M solution

in hexane, 4.4 mL, 7.0 mmol). After 1 h, the solution was cooled to -78 °C and a solution of **17** (2.64 g, 6.43 mmol) in THF (12 mL) was added. The reaction mixture was stirred at the same temperature for 1 h, and then MeI (0.80 mL, 12.9 mmol) was added. After being stirred for 2 h, the reaction was quenched by sat. aq. NH_4Cl. The resultant mixture was diluted with Et_2O. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (2% EtOAc in hexane) to give **8** (0.89 g, 32%) and **18** (1.11 g, 41%) as colorless oils: **8**: $[\alpha]^{21}_D$ –8.9˚ (*c* 4.7, $CHCl_3$); IR (film) ν 2931, 1740 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.67(complex, 4H), 7.46-7.37 (complex, 6H), 5.03 (br t, 1H, *J*= 4 Hz), 4.35-4.27 (complex, 2H), 3.82 (dd, 1H, *J*= 11, 3 Hz), 3.63 (dd, 1H, *J*= 11, 4 Hz), 2.78 (m, 1H), 2.40-2.21 (complex, 3H), 1.79 (m, 1H), 1.27 (d, 3H, *J*= 7.2 Hz), 1.05 (s, 9H); ^{13}C-NMR (100 MHz) δ 173.7, 135.4, 133.0, 129.7, 127.7, 83.3, 78.8, 74.4, 65.9, 36.5, 32.1, 29.4, 26.8, 19.2, 15.9; HREIMS calcd for $C_{25}H_{32}O_4Si$ (M^+) 424.2067, found: *m/z* 424.2040. **18**: $[\alpha]^{22}_D$ +35.5˚ (*c* 1.0, $CHCl_3$); IR (film) ν 2931, 1749 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.67 (complex, 4H), 7.45-7.36 (complex, 6H), 4.83 (br t, 1H, *J*= 4 Hz), 4.48 (m, 1H), 4.35 (m, 1H), 3.80 (dd, 1H, *J*= 11, 3 Hz), 3.63 (dd, 1H, *J*= 11, 4 Hz), 2.43-2.22 (complex, 3H), 1.64 (m, 1H), 1.23 (d, 3H, *J*= 6.4 Hz), 1.05 (s, 9H); ^{13}C-NMR (67.8 MHz) δ 175.5, 135.4, 133.1, 129.6, 127.6, 80.7, 78.2, 76.2, 65.7, 34.6, 33.3, 32.5, 26.9, 19.3, 15.4. HREIMS calcd for $C_{25}H_{32}O_4Si$ (M^+) 424.2068, found: *m/z* 424.2075.

*Isomerization from **18** to **8***

To a solution of **18** (1.11 g, 2.6 mmol) in MeCN (40 mL) at rt was added DBU (0.39 mL, 2.6 mmol). After being stirred at 60 ˚C for 11 h, the mixture was cooled to 0 ˚C and then added sat. aq. NH_4Cl and Et_2O. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20→33% EtOAc in hexane) to give **8** (0.40 g, 36%) and **18** (0.64 g, 58%) as colorless oils.

*(1R,3S,4R,6R,8S)-8-tert-Butyldiphenylsiloxymethyl-3-methoxy-4-methyl-3-(prop-2-enyl)-2,7-dioxabicyclo [4.3.0]nonane (**19**)*

To a solution of **8** (0.43 g, 1.0 mmol) in Et_2O (35 mL) at -78 °C was added allylmagnesium bromide (1.0 M solution in Et_2O, 1.0 mL, 1 mmol). After being stirred at the same temperature for 30 min, the reaction was quenched by sat. aq. NH_4Cl, and diluted with EtOAc. The organic extracts were washed

with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL) and MeOH (10 mL) and CSA (cat.) were added at 0 °C. The reaction mixture was allowed to warm to rt. After 1 h, sat. aq. $NaHCO_3$ was added, and then the mixture was concentrated *in vacuo*, and the residue was diluted with Et_2O and H_2O. The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (7% EtOAc in hexane) gave **19** (0.41 g, 84%) as a colorless oil: $[\alpha]^{22}_D$ +83.6˚ (*c* 0.4, $CHCl_3$); IR (film) ν 2929, 1429 cm^{-1}; ^{1}H-NMR (270 MHz) δ 7.69 (complex, 4H), 7.45-7.35 (complex, 6H), 5.77 (m, 1H), 5.07 (br d, 1H, *J*= 15 Hz), 5.02 (br d, 1H, *J*= 8 Hz), 4.32 (m, 1H), 4.06 (m, 1H), 3.94 (m, 1H), 3.78 (dd, 1H, *J*= 11, 4.3 Hz), 3.68 (dd, 1H, *J*= 11, 3.5 Hz), 3.26 (s, 3H), 2.57 (dd, 1H, *J*= 14, 5.1 Hz), 2.25 (dd, 1H, *J*= 14, 9.2 Hz), 2.11-1.97 (complex, 3H), 1.78-1.73 (complex, 2H), 1.18 (s, 9H), 0.84 (d, 3H, *J*= 6.8 Hz). HREIMS calcd for $C_{28}H_{37}O_3Si$ (M^+-OMe) 449.2510, found: *m/z* 449.2540.

*3-{(1R,3S,4R,6R,8S)-8-tert-Butyldiphenylsiloxymethyl-3-methoxy-4-methyl-2,7-dioxabicyclo[4.3.0]non-3-yl}propanal (**20**)*

To a solution of **19** (94.0 mg, 0.20 mmol) in THF (11 mL) at 0 °C was added 9-BBN (0.5 M solution in THF, 2.3 mL, 12 mmol); the mixture was stirred at the same temperature for 1 h. After being stirred at rt for another 1h, the mixture was recooled to 0 °C and 3 M aq. NaOH (4 mL) and aq. 35% H_2O_2 (3 mL) were added to the solution. After being stirred at rt for further 2 h, the mixture was diluted with sat. aq. $NaHCO_3$ and EtOAc. Usual work-up gave a crude alcohol (110.3 mg). To a solution of the alcohol in CH_2Cl_2 (12 mL) were added powdered MS4Å (110 mg), tetra-*n*-propylammonium perruthenate (10 mg, 0.028 mmol), and NMO (80 mg, 0.68 mmol) at rt. After being stirred for 10 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (11% EtOAc in hexane) to give **20** (90.8 mg, 93%) as a colorless oil: $[\alpha]^{22}_D$ +39.1˚ (*c* 1.0, $CHCl_3$); IR (film) ν 2929, 1726 cm^{-1}; ^{1}H-NMR (400 MHz) δ 9.75 (t, 1H, *J*= 2 Hz), 7.68 (complex, 4H), 7.44-7.35 (complex, 6H), 4.27 (m, 1H), 4.04 (m, 1H), 3.93 (m, 1H), 3.79 (dd, 1H, *J*= 11, 4 Hz), 3.66 (dd, 1H, *J*= 11, 3.5 Hz), 3.27 (s, 3H), 2.52-2.43 (complex, 2H), 2.21-2.05 (complex, 2H), 1.99-1.94 (complex, 2H), 1.82-1.75 (complex, 3H), 1.05 (s, 9H), 0.85 (d, 3H, *J*= 6.8 Hz); 13C-NMR (100 MHz) δ 201.9, 135.5, 133.5, 129.5, 127.6, 100.4, 78.6, 76.6, 72.5, 66.1, 47.9, 39.1, 35.6, 29.6, 26.9, 25.9, 19.3, 15.4. HREIMS calcd for $C_{28}H_{37}O_4Si$ (M^+-OMe) 465.2458, found: *m/z* 465.2444.

*Synthesis of alcohol (**22**)*

To a solution of **21** (0.17 g, 0.56 mmol) in THF (3 mL) at 0 °C was added EtMgBr (0.96 M solution in THF, 0.52 mL, 0.50 mmol); the solution was stirred for 30 min, then warmed to rt. After 1 h, the mixture was recooled to -60 °C and a solution of **20** (90.8 mg, 0.183 mmol) in THF (2 mL) was added. After 1 h, sat. aq. $NaHCO_3$ was added, and usual work-up gave a diasteromeric mixture (**22**) (78.2 mg, 53%) as a colorless oil. HREIMS calcd for $C_{46}H_{65}O_6Si_2$ (M^+-OMe) 769.4315, found: *m/z* 769.4304.

*Synthesis of acetate (**23**)*

A solution of **22** (26.2 mg, 33 μmol) in pyridine (0.5 mL) and Ac_2O (0.3 mL) was stirred at rt for 4 h, and then concentrated *in vacuo* to give diastereomeric mixture (**23**) (26.0 mg, 94%) as a colorless oil. HREIMS calcd for $C_{45}H_{61}O_8Si_2$ (M^+-*t*-Bu) 785.3901, found: *m/z* 785.3911.

*Reduction of **23** into olefin (**24**)*

A solution of **23** (73.0 mg, 87 μmol) in benzene (1 mL) in the presence of Lindlar cat. (20 mg) was stirred at rt under a hydrogen atmosphere for 4 h. Usual work-up gave diastereomeric mixture (**24**) (72.1 mg, 99%) as a colorless oil. HREIMS calcd for $C_{48}H_{69}O_7Si_2$ (M^+-OMe) 813.4578, found: *m/z* 813.4550.

*Synthesis of thioketal (**25**)*

To a solution of **24** (72.1 mg, 85.3 μmol) in CH_2Cl_2 (1 mL) were added TMSSMe (0.12 mL, 0.85 mmol) and $Zn(OTf)_2$ (31 mg, 85 μmol) at 0 °C. After 20 min, the solution was diluted with H_2O and CH_2Cl_2. The organic layers were washed with sat. aq. $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. A mixture of the residue and a catalytic amount of CSA in MeOH (1 mL) was stirred at 0 °C for 5 min, then sat. aq. $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3×), the crude product was purified by silica gel column chromatography (11→25% EtOAc in hexane) to give a diastereomeric mixture **(25)** (56.6 mg, 89%) as a colorless oil. HREIMS calcd for $C_{42}H_{55}O_6Si$ (M^+-OMe) 699.3714, found: *m/z* 699.3697.

*Protection of **25** with a TES group into alcohol (**27**)*

To a solution of **25** (56.6 mg, 75.8 μmol) in DMF (1 mL) were added imidazole (31 mg, 0.91 mmol) and TESCl (50 μL, 0.30 mmol) at 0 °C. After being stirred at rt for 2 h, usual work-up gave **26** (64.2 mg,

98%) as a colorless oil. To a solution of **26** (9.7 mg, 11 μmol) in CH_2Cl_2 (0.5 mL) was added DIBAL-H (1.0 M solution in toluene, 0.1 mL, 0.1 mmol) at –78 °C. After being stirred at the same temperature for 15 min, usual work-up gave a diastereomeric mixture (**27**) (6.3 mg, 68%) as a colorless oil.

*(7R)-1-[(1R,3R,4R,6R,8S)-8-tert-Butyldiphenylsiloxymethy-3-methylthio-4-methyl-2,7-dioxabicyclo[4.3.0]non-3-yl](4Z)-7-triethylsiloxy-8-phenylmethoxyoct-4-en-3-one (**7**)*

Alcohol (**27**) (6.3 mg, 7.7 μmol) was oxidized with SO_3•Py (30 mg, 0.19 mmol), Et_3N (0.1 mL) and DMSO (0.4 mL), as in the case of **15** to give **7** (6.0 mg, 95%) as a colorless oil: $[\alpha]^{22}_D$ +6.5˚ (*c* 0.13, $CHCl_3$); IR (film) ν 2929, 1693, 1617 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.42-7.31 (complex, 11H), 6.21 (complex, 2H), 4.50 (s, 2H), 4.29 (m, 1H), 4.23 (m, 1H), 3.98-3.94 (complex, 2H), 3.78 (dd, 1H, *J*= 11, 4 Hz), 3.65 (dd, 1H, *J*= 11, 3 Hz), 3.40-3.38 (complex, 2H), 2.88-2.87 (complex, 2H), 2.58-2.50 (complex, 2H), 2.29 (m, 1H), 2.19-2.10 (complex, 3H), 2.00 (m, 1H), 1.96 (s, 3H), 1.89-1.85 (complex, 2H), 1.05 (s, 3H), 0.90 (t, 9H, *J*= 8.0 Hz), 0.58 (q, 6H, *J*= 8.0 Hz). HREIMS calcd for $C_{47}H_{68}O_6SSi_2$ (M^+) 816.4270, found: *m/z* 816.4233. This compound was used for the next reaction without further characterization.

*{(2R,11S,12R,14R,15R,17R,19S)-19-tert-Butyldiphenylsiloxymethyl-15-methyl-13,18-dioxadispiro-[2H-3,6-dihydropyran-6,5'-oxolane-2',3''-bicyclo[4.3.0]nonane]-2-yl}phenylmethoxymethane (**28**)*

To a solution of **7** (9.1 mg, 11 μmol) in THF (0.4 mL) at 0 °C was added TBAF (1.0 M solution in THF, 30 μL, 30 μmol). After 1 h, the mixture was diluted with H_2O and EtOAc. The organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (silica gel, 14→33% EtOAc in hexane) to give a keto alcohol (6.6 mg) as a colorless oil.

A mixture of the keto alcohol (6 mg, 9 μmol), powdered MS4Å (40 mg) and 2,6-di-*tert*-butyl-4-methylpyridine (20 mg, 97 μmol), methyl trifluoromethanesulfonate (5 μL, 4 μmol) in MeCN (0.5 mL) was stirred at rt for 3 h, and then diluted with sat. aq. $NaHCO_3$ and EtOAc. The organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC (25% EtOAc in hexane) to afford **28** (3.4 mg, 47% in 2 steps) as a colorless oil: $[\alpha]^{21}_D$ +41.4˚ (*c* 0.22, $CHCl_3$); IR (film) ν 2929, 1589 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.41-7.22 (complex, 11H), 5.95 (m, 1H), 5.61 (d, 1H, *J*= 10.4 Hz), 4.63 (s, 2H), 4.38 (m, 1H), 4.32 (m,

1H), 4.22 (m, 1H), 3.88 (d, 1H, *J*= 2.5 Hz), 3.62 (dd, 1H, *J*= 10.8, 4.4 Hz), 3.56 (dd, 1H, *J*= 10.8, 4.4 Hz), 3.53 (dd, 1H, *J*= 10.3, 5.4 Hz), 3.46 (dd, 1H, *J*= 10.3, 5.4 Hz), 2.19-2.14 (complex, 3H), 2.03 (t, 2H, *J*= 7.6 Hz), 1.94-1.92 (complex, 3H), 1.85-1.79 (complex, 3H), 1.76-1.70 (complex, 2H), 0.97 (s, 9H), 0.79 (d, 3H, *J*= 6.8 Hz); ^{13}C-NMR (100 MHz) δ 138.5, 135.6, 135.5, 133.7, 129.5, 128.5, 128.2, 127.5, 127.4, 127.3, 109.3, 104.9, 78.6, 77.2, 76.6, 73.3, 72.7, 69.2, 66.4, 37.4, 35.9, 35.0, 31.2, 31.1, 29.8, 26.9, 19.4, 15.9. HREIMS calcd for $C_{40}H_{50}O_6Si$ (M^+) 654.3373, found: *m/z* 654.3370.

*Methyl (2E)-3-[(2R,3R,5S)-5-tert-Butyldiphenylsiloxymethyl-3-tert-butyldimethylsiloxyoxolan-2-yl]prop-2-enoate (**34**)*

To a solution of **9** (8.21 g, 19 mmol) in CH_2Cl_2 (180 mL) were added 2,6-lutidine (7.4 mL, 64 mmol) and TBSOTf (5.9 mL, 26 mmol) at 0 ˚C. After being stirred at the same temperature for 30 min, the mixture was poured into H_2O, and extracted with EtOAc (3×) to give a crude product, which was purified by silica gel column chromatography (5→9% EtOAc in hexane) to afford 34 (9.2 g, 86%) as a colorless oil: $[\alpha]^{22}_D$ –7.7˚ (c 1.0, CHCl3); IR (film) ν 2929, 1728 cm$^{-1;}$ ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.45-7.36 (complex, 6H), 6.99 (dd, 1H, *J*= 15, 5 Hz), 6.20 (br d, 1H, *J*= 15 Hz), 4.52 (complex, 2H), 4.39 (m, 1H), 3.81 (dd, 1H, *J*= 10.9, 4 Hz), 3.75 (s, 3H), 3.66 (dd, 1H, *J*= 10.9, 4 Hz), 2.14 (ddd, 1H, *J*= 12.6, 8, 5 Hz), 1.92 (ddd, 1H, *J*= 12.6, 7, 3 Hz), 1.07 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (100 MHz) δ 166.5, 145.8, 135.5, 133.4, 133.3, 129.5, 127.5, 121.3, 82.1, 78.5, 74.8, 66.0, 51.5, 37.4, 26.9, 25.7, 19.3, 18.1, -4.6, -4.9. HREIMS calcd for $C_{30}H_{43}O_4Si$ (M^+-OMe) 523.2697, found: *m/z* 523.2684.

*3-[(2R,3R,5S)-5-tert-Butyldiphenylsiloxymethyl-3-tert-butyldimethylsiloxyoxolan-2-yl]propanoic acid (**35**)*

A mixture of **34** (9.2 g, 17 mmol) and a catalytic amount of 10% Pd-C in EtOH (170 mL) was stirred at rt under a hydrogen atmosphere for 2 h. After filtration, the filtrate was concentrated *in vacuo*. A mixture of the residue and LiOH•H_2O (7.0 g, 0.17 mol) in H_2O (40 mL), MeOH (80 mL), and THF (40 mL) was stirred at rt for 2 h, and then sat. aq. NH_4Cl was added. Usual work-up gave **35** (8.82 g, 98%) as a colorless oil: $[\alpha]^{20}_D$ –6.8˚ (*c* 1.0, $CHCl_3$); IR (film) ν 3072, 2929, 1711 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.44-7.35 (complex, 6H), 4.35-4.29 (complex, 2H), 3.93 (dt, 1H, *J*= 9, 4 Hz), 3.77 (dd, 1H, *J*= 11, 4 Hz), 3.61 (dd, 1H, *J*= 11, 4 Hz), 2.54 (t, 1H, *J*= 7 Hz), 2.12 (ddd, 1H, *J*= 13, 8.8, 4.4 Hz),

1.99-1.78 (complex, 3H), 1.04 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (100 MHz) δ 179.2, 135.5, 135.5, 133.5, 133.3, 129.5, 127.6, 82.1, 77.6, 73.7, 66.0, 37.5, 31.2, 26.8, 25.8, 24.9, 19.3, 18.1, -4.5, -4.9. HREIMS calcd for $C_{26}H_{54}O_5Si_2$ (M^+-*t*-Bu) 485.2187, found: *m/z* 485.2176.

*(4R)-3-{3-[(2R,3R,5S)-5-tert-Butyldiphenylsiloxymethyl-3-tert-butyldimethylsiloxyoxolan-2-yl]propanoyl }-4-benzyl-1,3-oxazolidin-2-one (**36**)*

To a solution of **35** (1.75 g, 3.2 mmol) in THF (30 mL) were added Et_3N (1.4 mL, 10 mmol) and PivCl (0.59 mL, 4.8 mmol) at 0 ˚C. After 45 min, LiCl (0.68 g, 16 mmol) and (*R*)-4-benzyl-2-oxazolidinone (0.86 g, 4.9 mmol) were added, and then the mixture was stirred at rt for 2 h. Usual work-up and purification by silica gel column chromatography (9→17% EtOAc in hexane) afforded **36** (1.99 g, 88%) as a colorless oil: $[\alpha]^{23}_D$ –25.3˚ (*c* 0.92, $CHCl_3$); IR (film) ν 2929, 1784, 1701 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.41-7.27 (complex, 9H), 7.18 (complex, 2H), 4.63 (ddd, 1H, *J*= 13.2, 6.8, 3.4 Hz), 4.36 (m, 1H), 4.29 (m, 1H), 4.16-4.08 (complex, 2H), 4.44 (br dt, 1H, *J*= 7.3, 3.4 Hz), 3.74 (dd, 1H, *J*= 10.7, 4.3 Hz), 3.63 (dd, 1H, *J*= 10.7, 3.4 Hz), 3.25 (dd, 1H, *J*= 13, 3.4 Hz), 3.14-3.01 (complex, 2H), 2.63 (dd, 1H, *J*= 13, 9.8 Hz), 2.12 (m, 1H), 2.04-1.88 (complex, 2H), 1.04 (s, 9H), 0.91 (s, 9H), 0.10 (s, 6H);^{13}C-NMR (100 MHz) δ 173.0, 153.3, 135.5, 135.3, 133.4, 129.5, 129.3, 128.8, 127.6, 127.2, 82.0, 77.4, 73.7, 66.2, 66.1, 55.2, 37.9, 37.6, 32.5, 26.9, 25.9, 24.5, 19.3, 18.2, -4.4, -4.9. HREIMS calcd for $C_{36}H_{46}NO_6Si_2$ (M^+-*t*-Bu) 644.2864, found: *m/z* 644.2854.

*(4R)-3-{(2S)-3-[(2R,3R,5S)-5-tert-Butyldiphenylsiloxymethyl-3-tert-butyldimethylsiloxyoxolan-2-yl]-2-phenylmethoxymethylpropanoyl}-4-benzyl-1,3-oxazolidin-2-one (**37**)*

To a solution of **36** (9.02 g, 12.8 mmol) in THF (100 mL) at -78 ˚C was added LHMDS (1.0 M solution in THF, 25 mL, 25 mmol). After 45 min, BOMCl (5.9 mL, 39 mmol) and a solution of LiI (6.7 g, 50 mmol) in THF (20 mL) were added. The mixture was stirred at -50 ˚C for 1 h, and diluted with 2 M aq. HCl and EtOAc. The organic extracts were washed with aq. $Na_2S_2O_3$ (2×), H_2O, sat. aq. $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (6→9% EtOAc in hexane) to give **37** (8.28 g, 78%) as a colorless oil: $[\alpha]^{23}_D$ –20.8˚ (*c* 1.00, $CHCl_3$); IR (film) ν 2929, 1780, 1697 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.63 (complex, 4H), 7.33 (complex, 10H), 7.24 (complex, 4H), 7.15 (complex, 2H), 4.53 (complex, 4H), 4.33 (br dd, 1H, *J*= 9.8, 4 Hz), 4.13 (m, 1H), 3.97 (br dt, 1H, *J*= 9.8, 3.9 Hz), 3.89 (dd, 1H, *J*= 9, 2.9 Hz), 3.83 (br d, 1H, *J*=

8.8 Hz), 3.78 (br d, 1H, *J*= 8.8 Hz), 3.62 (dd, 1H, *J*= 9, 5 Hz), 3.57 (dd, 1H, *J*= 10.3, 4.3 Hz), 3.52 (dd, 1H, *J*= 10.3, 4.3 Hz), 3.13 (dd, 1H, *J*= 13.7, 3.4 Hz), 2.66 (dd, 1H, *J*= 13.7, 9.3 Hz), 2.00-1.97 (complex, 2H), 1.87 (m, 1H), 1.71 (dt, 1H, *J*= 14, 3.9 Hz), 1.01 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C-NMR (100 MHz) δ 175.5, 153.4, 138.6, 135.5, 135.4, 133.5, 133.2, 129.5, 129.4, 129.3, 128.7, 128.2, 127.6, 127.5, 127.4, 127.0, 81.0, 73.4, 73.0, 72.2, 66.6, 65.5, 55.3, 40.6, 38.0, 37.2, 29.8, 26.9, 26.4, 25.9, 19.3, 18.1, -4.5, -4.9. HREIMS calcd for $C_{44}H_{54}NO_7Si_2$ (M^+-*t*-Bu) 764.3436, found: *m/z* 764.3459.

*(2R)-3-[(2R,3R,5S)-5-tert-Butyldiphenylsiloxymethyl-3-tert-butyldimethylsiloxyoxolan-2-yl]-2-phenylmethoxymethylpropan-1-ol (**38**)*

A mixture of **37** (8.28 g, 10 mol) and $LiBH_4$ (2.2 g, 0.1 mol) in EtOH (50 mL), THF (30 mL), and H_2O (20 mL) was stirred at 0 ˚C for 2 h, and sat. aq. NH_4Cl was added. Usual work-up afforded **38** (5.97 g, 91%) as a colorless oil: $[\alpha]^{22}_D$ –5.7˚ (*c* 1.00, $CHCl_3$); IR (film) ν 3450, 2929 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.42-7.27 (complex, 11H), 4.48 (s, 2H), 4.33 (m, 1H), 4.27 (m, 1H), 3.95 (br dt, 1H, *J*= 9.3, 2.9 Hz), 3.75 (complex, 2H), 3.68 (m, 1H), 3.62 (dd, 1H, *J*= 11, 4 Hz), 3.47 (complex, 2H), 2.11-1.99 (complex, 2H), 1.87 (ddd, 1H, *J*= 12.7, 6.4, 1.5 Hz), 1.67 (ddd, 1H, *J*= 14, 5.4, 2.9 Hz), 1.56 (m, 1H), 1.04 (s, 9H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C-NMR (100 MHz) δ 138.2, 135.5, 135.4, 129.6, 128.3, 127.6, 127.5, 82.2, 77.9, 74.5, 73.3, 66.0, 65.3, 40.1, 37.5, 29.9, 26.8, 25.9, 19.3, 18.2, -4.5, -4.8. HREIMS calcd for $C_{38}H_{57}O_5Si_2$ (M^++H) 649.3741, found: *m/z* 649.3711.

*(3E)(5R)-6-[(2R,3R,5S)-3-tert-Butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]-1-(4-methoxyphenylmethoxy)-5-phenylmethoxymethylhex-3-ene (**33**)*

Oxidation of **38** (1.50 g, 2.3 mmol) with tetra-*n*-propylammonium perruthenate (81 mg, 0.23 mmol), NMO (0.81 g, 6.9 mmol), and powdered MS4Å (1.3 g) in CH_2Cl_2 (20 mL) gave an aldehyde as in the case of **20**.

To a solution of **39** (0.21 g, 0.53 mmol) in THF (20 mL) at -78 ˚C was added LHMDS (1.0 M solution in THF, 2.4 mL, 2.4 mmol). After 1 h, the reaction mixture was added to a solution of the aldehyde in THF (8 mL). After being stirred at the same temperature for 1 h, the reaction mixture was diluted with sat. aq. NH_4Cl and EtOAc. The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (17% EtOAc in hexane) to afford **33** (0.93 g, 50% in 2 steps) and the corresponding (*Z*)-olefin (0.20 g, 11% in 2 steps) as

colorless oils: (*E*)-Form **33**; $[\alpha]^{22}_{D}$ –18.1˚ (*c* 1.00, $CHCl_3$); IR (film) ν 2856 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.42-7.34 (complex, 6H), 7.28 (complex, 5H), 7.23 (d, 2H, *J*= 8.3 Hz), 6.85 (d, 2H, *J*= 8.3 Hz), 5.49-5.45 (complex, 2H), 4.47 (d, 1H, *J*= 12.2 Hz), 4.43 (d, 1H, *J*= 12.2Hz), 4.39 (s, 2H), 4.27-4.24 (complex, 2H), 3.87 (dt, 1H, *J*= 7, 2.9 Hz), 3.78 (s, 3H), 3.72 (dd, 1H, *J*= 10.7, 4.4 Hz), 3.61 (dd, 1H, *J*= 10.7, 4 Hz), 3.44-3.39 (complex, 4H), 2.41 (m, 1H), 2.31 (br d, 1H, *J*= 6.8 Hz), 2.28 (br d, 1H, *J*= 6.8 Hz), 2.04 (ddd, 1H, *J*= 12.7, 9, 4.4 Hz), 1.88 (dd, 1H, *J*=12.5, 6 Hz), 1.79 (ddd, 1H, *J*= 13.7, 6.8, 6.4 Hz), 1.57 (m, 1H), 1.03 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (100 MHz) δ 158.9, 138.6, 135.5, 134.0, 133.6, 133.4, 130.5, 129.5, 129.1, 128.1, 127.5, 127.4, 127.2, 127.1, 113.6, 81.0, 77.2, 73.8, 73.2, 72.8, 72.5, 70.0, 66.1, 55.2, 40.0, 37.8, 33.2, 31.0, 26.8, 25.8, 19.3, 18.1, -4.3, -4.8. HREIMS calcd for $C_{49}H_{69}O_6Si_2$ (M^++H) 809.4628, found: *m/z* 809.4610. (*Z*)-olefin; $[\alpha]^{23}_{D}$ –12.6˚ (*c* 1.00, $CHCl_3$); IR (film) ν 2929 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.42-7.27 (complex, 11H), 7.22 (d, 2H, *J*= 8.3 Hz), 6.84 (d, 2H, *J*= 8.3 Hz), 5.46 (dt, 1H, *J*= 10.7, 7.3 Hz), 5.36 (br t, 1H, *J*= 10.7 Hz), 4.44 (s, 2H), 4.39 (s, 2H), 4.27-4.22 (complex, 2H), 3.85 (m, 1H), 3.78 (s, 3H), 3.72 (dd, 1H, *J*= 10.7, 4.4 Hz), 3.61 (dd, 1H, *J*= 10.7, 4 Hz), 3.44-3.33 (complex, 4H), 2.76 (m, 1H), 2.44-2.31 (complex, 2H), 2.00 (ddd, 1H, *J*= 13.2, 9, 4.4 Hz), 1.89-1.82 (complex, 2H), 1.54 (m, 1H), 1.03 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (100 MHz) δ 158.9, 138.6, 135.5, 134.7, 133.6, 133.5, 130.5, 129.6, 129.1, 128.1, 127.5, 127.3, 127.2, 126.8, 113.6, 81.1, 77.2, 73.9, 73.3, 72.8, 72.5, 69.7, 66.2, 55.2, 37.8, 35.0, 31.3, 28.5, 26.9, 25.8, 19.3, 18.1, -4.3, -4.8. HREIMS calcd for $C_{42}H_{61}O_6Si_2$ (M^+-Bn) 717.4003, found: *m/z* 717.3975.

*(2S,3S,4S)-1-[(2R,3R,5S)-3-tert-Butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]-6-(4-methoxyphenylmethoxy)-2-phenylmethoxymethylhexane-3,4-diol (**40**)*

To a solution of AD-mix-α (3.2 g) and methanesulfonamide (0.22 g, 2.3 mmol) in *t*-BuOH-H_2O (1:1, 14 mL) at 0 ˚C was added a solution of **33** (0.93 g, 1.1 mmol) in *t*-BuOH (4 mL); the mixture was stirred at rt for 2 days. After addition of Na_2SO_3, the mixture was diluted with EtOAc. The organic extracts were washed with 2 M aq. NaOH, and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20→33% EtOAc in hexane) to give **40** (0.92 g, 95%) as a colorless oil: $[\alpha]^{22}_{D}$ –2.1˚ (*c* 0.77, $CHCl_3$); IR (film) ν 3458, 2929, 1612, 1513 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.39 (complex, 6H), 7.32-7.22 (complex, 6H), 6.84 (d, 2H, *J*= 8.3 Hz), 4.45 (d, 1H, *J*= 11.2 Hz), 4.42 (s, 2H), 4.40 (d, 1H, *J*= 11.2 Hz), 4.29 (m, 1H), 4.23 (m, 1H), 3.93-3.86

(complex, 2H), 3.78 (s, 3H), 3.74 (dd, 1H, *J*= 10.7, 3.9 Hz), 3.66 (dd, 1H, *J*= 9, 6 Hz), 3.62-3.46 (complex, 6H), 3.29 (d, 1H, *J*= 7 Hz), 2.07 (complex, 2H), 1.89-1.81 (complex, 4H), 1.65 (m, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (100 MHz) δ 158.9, 137.8, 135.5, 133.5, 133.4, 130.5, 129.5, 129.2, 129.1, 128.3, 127.6, 113.7, 81.4, 77.6, 76.5, 74.3, 73.3, 72.7, 70.7, 69.8, 67.5, 66.0, 55.2, 38.8, 37.5, 33.6, 29.4, 26.9, 25.9, 19.3, 18.2, -4.5, -4.8. HREIMS calcd for $C_{45}H_{61}O_8Si_2$ (M^+-*t*-Bu) 785.3901, found: *m/z* 785.3896.

*(1S,2S)-1-[(4S)-2-(4-Methoxyphenyl)1,3-dioxan-4-yl]-3-[(2R,3R,5S)-3-tert-butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]-2-phenylmethoxymethylpropan-1-ol (**41**)*

To a solution of **40** (1.89 g, 2.2 mmol) and MS4Å (1.1 g) in CH_2Cl_2 (22 mL) was added DDQ (1.03 g, 4.5 mmol) at rt. After being stirred for 15 min, the mixture was diluted with sat. aq. $NaHCO_3$ and EtOAc. The organic extracts were washed with sat. aq. $NaHCO_3$, H_2O, and brine, dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (16→20% EtOAc in hexane) to afford **41** (1.15 g, 61%) as a colorless oil: $[\alpha]^{20}_D$ +6.9˚ (*c* 1.00, $CHCl_3$); IR (film) ν 3483, 2929 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.41-7.33 (complex, 10H), 7.27 (complex, 3H), 6.84 (d, 2H, *J*= 8.8 Hz), 5.44 (s, 1H), 4.39 (br s, 2H), 4.31-4.20 (complex, 3H), 4.02 (br dd, 1H, *J*= 9.3, 6.4 Hz), 3.95 (br d, 1H, *J*= 9.3 Hz), 3.84 (dd, 1H, *J*= 11.7, 2.4 Hz), 3.78 (s, 3H), 3.74-3.67 (complex, 4H), 3.62-3.57 (complex, 2H), 2.90 (d, 1H, *J*= 4.9 Hz), 2.15-2.08 (complex, 2H), 1.95-1.76 (complex, 3H), 1.70 (m, 1H), 1.59 (m, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (100 MHz) δ 159.6, 138.3, 135.4, 133.4, 131.1, 129.5, 129.4, 128.1, 127.5, 127.4, 127.3, 113.3, 100.9, 80.9, 78.9, 77.4, 76.0, 74.2, 73.1, 69.7, 66.6, 66.0, 55.2, 37.5, 37.2, 29.7, 27.3, 26.8, 25.8, 19.3, 18.1, -4.5, -4.8. HREIMS calcd for $C_{49}H_{69}O_8Si_2$ (M^++H) 841.4527, found: *m/z* 841.4539.

*(1S,2S)-{1-[(4S)-2-(4-Methoxyphenyl)1,3-dioxan-4-yl]-3-[(2R,3R,5S)-3-tert-butyldimethylsiloxy-5-tert-butyl-diphenylsiloxymethyloxolan-2-yl]-2-phenylmethoxymethylpropoxy}-2-methoxyethoxymethane (**42**)*

A mixture of **41** (0.43 g, 0.51 mmol), *i*-Pr_2NEt (1.1 mL, 6.4 mmol), and MEMCl (0.24 mL, 2.1 mmol) in CH_2Cl_2 (5 mL) was stirred at refluxing temperature for 40 h, and then poured into H_2O. Usual work-up afforded **42** (0.43 g, 91%) as a colorless oil: $[\alpha]^{20}_D$ +5.2˚ (*c* 1.00, $CHCl_3$); IR (film) ν 2929 1616, 1518 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.37 (complex, 9H), 7.30 (complex, 4H), 6.83 (d, 2H, *J*= 8.8 Hz), 5.39 (s, 1H), 4.90 (d, 1H, *J*= 6.4 Hz), 4.86 (d, 1H, *J*= 6.4 Hz), 4.43 (d, 1H, *J*= 11.7 Hz), 4.39

(d, 1H, *J*= 11.7 Hz), 4.27 (complex, 2H), 4.20-4.13 (complex, 2H), 4.00 (m, 3H), 3.78 (s, 3H), 3.73-3.67 (complex, 5H), 3.62 (dd, 1H, *J*= 10.7, 3.9 Hz), 3.44 (dd, 1H, *J*= 9.3, 4.4 Hz), 3.40 (complex, 2H), 3.30 (s, 3H), 2.22 (m, 1H), 2.07 (m, 1H), 1.89-1.77 (complex, 3H), 1.65-1.58 (complex, 2H), 1.04 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (100 MHz) δ 159.5, 138.5, 135.5, 135.4, 133.5, 133.4, 131.3, 129.5, 128.1, 127.6, 127.3, 127.2, 113.3, 100.9, 97.6, 82.2, 81.2, 79.8, 77.2, 73.9, 73.0, 71.7, 69.9, 67.7, 66.6, 66.2, 58.9, 55.2, 37.5, 36.9, 29.6, 27.8, 26.8, 25.8, 19.3, 18.1, -4.5, -4.8. HRFABMS calcd for $C_{53}H_{76}O_{10}Si_2Na$ ($M+Na^+$) 951.4874, found: *m/z* 951.4866.

*(3S,4S,5S)-6-[(2R,3R,5S)-3-tert-Butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]-4-(2-methoxyethoxymethoxy)-5-(phenylmethoxymethyl)hexane-1,3-diol (**43**)*

A mixture of **42** (0.43 g, 0.46 mmol) in 80% aq. AcOH (10 mL) was stirred at rt for 1 h to give **43** (0.34 g, 91%) as a colorless oil: $[\alpha]^{20}_D$ +12.9˚ (*c* 1.00, $CHCl_3$); IR (film) ν 3452, 2929 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.38 (complex, 6H), 7.27 (complex, 5H), 4.82 (d, 2H, *J*= 7 Hz), 4.79 (d, 2H, *J*= 7 Hz), 4.40 (s, 2H), 4.31-4.23 (complex, 3H), 3.96 (complex, 2H), 3.84 (m, 1H), 3.76-3.73 (complex, 3H), 3.67-3.56 (complex, 3H), 3.53 (complex, 2H), 3.40 (dd, 1H, *J*= 9.3, 5.4 Hz), 3.36 (s, 3H), 2.19 (m, 1H), 2.10 (ddd, 1H, *J*= 13.2, 8.8, 4.4 Hz), 1.86 (dd, 1H, *J*= 12.7, 6.4 Hz), 1.78-1.65 (complex, 3H), 1.57 (ddd, 1H, *J*= 14.2, 7.3, 2.9 Hz), 1.04 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (100 MHz) δ 138.1, 135.5, 135.4, 133.4, 133.3, 129.5, 128.2, 127.7, 127.6, 127.4, 98.1, 87.8, 81.9, 77.6, 74.3, 73.0, 72.9, 71.6, 69.7, 67.9, 66.0, 61.9, 59.0, 38.5, 37.5, 34.6, 29.8, 26.8, 25.8, 19.3, 18.1, -4.5, -4.8. HREIMS calcd for $C_{45}H_{71}O_9Si_2$ (M^++H) 811.4631, found: *m/z* 811.4627.

*(3S,4S,5S)-6-[(2R,3R,5S)-3-tert-Butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]-3-hydroxy-4-(2-methoxyethoxymethoxy)-5-(phenylmethoxymethyl)hexyl 2,2-dimethylpropanoate (**44**)*

A mixture of **43** (0.90 g, 1.1 mmol) and PivCl (0.30 mL, 2.4 mmol) in pyridine (1.6 mL) and CH_2Cl_2 (10 mL) was stirred at rt for 6 h, and then poured into H_2O. Usual work-up afforded **44** (0.87 g, 88%) as a colorless oil: $[\alpha]^{20}_D$ +5.5˚ (*c* 1.00, $CHCl_3$); IR (film) ν 3481, 2929, 1726 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.41-7.36 (complex, 6H), 7.31-7.24 (complex, 5H), 4.80 (s, 2H), 4.43 (d, 1H, *J*= 12.2 Hz), 4.39 (d, 1H, *J*= 12.2 Hz), 4.25-4.18 (complex, 4H), 3.94 (br d, 1H, *J*= 9.8 Hz), 3.81 (complex, 2H), 3.73 (complex, 2H), 3.67-3.55 (complex, 4H), 3.52 (complex, 2H), 3.44 (dd, 1H, *J*= 9.3, 4.9 Hz), 3.35 (s, 3H), 2.21 (m, 1H), 2.09 (ddd, 1H, *J*= 13.2, 8.3, 4.9 Hz), 1.88-1.79 (complex, 3H), 1.70 (m, 1H),

1.61 (ddd, 1H, *J*= 14.2, 7.3, 2.9 Hz), 1.16 (s, 9H), 1.04 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (100 MHz) δ 178.2, 138.2, 135.5, 135.4, 133.4, 133.3, 129.5, 128.1, 127.7, 127.5, 127.4, 127.3, 97.7, 86.3, 81.9, 77.2, 74.3, 73.0, 71.6, 69.7, 68.4, 67.8, 66.0, 61.9, 58.9, 38.6, 37.4, 32.7, 29.4, 27.2, 26.8, 25.8, 19.2, 18.1, -4.5, -4.9. HREIMS calcd for $C_{46}H_{69}O_{10}Si_2$ (M^+-*t*-Bu) 837.4425, found: *m/z* 837.4392.

*(3S,4S,5S)-5-{[(2R,3R,5S)-3-tert-Butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]methyl}-3,6-dihydroxy-4-(2-methoxyethoxymethoxy)hexyl 2,2-dimethylpropanoate (**32**)*

A mixture of **44** (0.87 g, 0.97 mmol) and a catalytic amount of 20% $Pd(OH)_2$-C was stirred in EtOAc (10 mL) at rt under a hydrogen atmosphere for 13 h. Usual work-up afforded **32** (0.60 g, 77%) as a colorless oil: $[\alpha]^{20}_D$ –4.2˚ (*c* 0.74, $CHCl_3$); IR (film) ν 3454, 2929, 1728 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.66 (complex, 4H), 7.41-7.35 (complex, 6H), 4.85 (d, 1H, *J*= 6.8 Hz), 4.80 (d, 1H, *J*= 6.8 Hz), 4.31-4.24 (complex, 4H), 4.01 (m, 1H), 3.88-3.71 (complex, 5H), 3.63 (complex, 2H), 3.54 (complex, 3H), 3.37 (s, 3H), 2.12-2.04 (complex, 2H), 1.90-1.79 (complex, 3H), 1.69 (complex, 2H), 1.18 (s, 9H), 1.04 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (100 MHz) δ 178.4, 135.5, 133.5, 133.4, 129.6, 127.6, 98.4, 88.2, 81.0, 77.7, 74.4, 71.6, 68.5, 68.2, 66.1, 61.6, 59.0, 39.4, 38.8, 37.7, 32.8, 29.3, 27.3, 26.9, 25.9, 19.3, 18.2, -4.5, -4.8. HREIMS calcd for $C_{43}H_{71}O_9Si_2$ (M^+-OH) 787.4632, found: *m/z* 787.4622.

*(3S,4S,5S)-5-{[(2R,3R,5S)-3-tert-Butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]-methyl}-3,6-bis(methanesulfonyloxy)-4-(2-methoxyethoxymethoxy)hexyl 2,2-dimethylpropanoate (**45**)*

To a solution of **32** (0.60 g, 0.75 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (4.2 mL, 17 mmol) and MsCl (0.69 mL, 12 mmol) at 0 ˚C. After being stirred at the same temperature for 30 min, the reaction mixture was poured into H_2O. Usual work-up gave **45** (0.68 g, 95%) as a colorless oil: $[\alpha]^{27}_D$ –7.9˚ (*c* 1.00, $CHCl_3$); IR (film) ν 2931, 1728 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.66 (complex, 4H), 7.40 (complex, 6H), 4.98 (m, 1H), 4.87 (d, 1H, *J*= 13.7 Hz), 4.83 (d, 1H, *J*= 13.7 Hz), 4.44 (dd, 1H, *J*= 9.8, 4.9 Hz), 4.34 (complex, 2H), 4.25-4.16 (complex, 3H), 3.99 (br d, 1H, *J*= 11.2 Hz), 3.86 (dd, 1H, *J*= 6.3, 4.9 Hz), 3.75 (complex, 2H), 3.70 (dd, 1H, *J*= 11, 4.4 Hz), 3.61 (dd, 1H, *J*= 11, 4.4 Hz), 3.53 (complex, 2H), 3.35 (s, 3H), 3.04 (s, 3H), 2.98 (s, 3H), 2.29 (m, 1H), 2.17 (m, 1H), 2.06 (complex, 2H), 1.90 (complex, 2H), 1.52 (m, 1H), 1.19 (s, 9H), 1.05 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (100 MHz) δ 178.2, 135.5, 135.4, 133.5, 133.4, 129.6, 127.6, 97.6, 80.0, 79.7, 79.3, 77.6, 73.9, 71.7, 68.4, 68.3, 66.3, 59.9,

59.0, 38.8, 38.6, 37.5, 37.3, 37.2, 31.6, 30.0, 27.2, 26.9, 25.9, 19.3, 18.1, -4.6, -4.7. HRFABMS calcd for $C_{45}H_{76}O_{14}S_2Si_2Na$ ($M+Na^+$) 983.4113, found: *m/z* 983.4143.

*(2R,3S,4R)-2-{4-[[(2R,3R,5S)-3-tert-Butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]methyl]-3-(2-methoxyethoxymethoxy)thiolan-2-yl}ethyl 2,2-dimethylpropanoate (**31**)*

A mixture of **45** (51.7 mg, 53.8 μmol) and $Na_2S•9H_2O$ (79.9 mg, 0.33 mmol) in DMF (1 mL) was stirred at 100 ˚C for 5 min, and then partitioned between H_2O and EtOAc. Usual work-up afforded **31** (34.3 mg, 79%) as a colorless oil: $[\alpha]^{25}_D$ +16.9˚ (*c* 1.00, $CHCl_3$); IR (film) ν 2929, 1730 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.44-7.35 (complex, 6H), 4.86 (d, H, *J*= 7 Hz), 4.84 (d, H, *J*= 7 Hz), 4.28 (complex, 2H), 4.17 (m, 1H), 4.11 (m, 1H), 4.06 (m, 1H), 3.88 (br d, H, *J*= 10.3 Hz), 3.77 (dd, 1H, *J*= 10.8, 3.9 Hz), 3.71 (m, 1H), 3.62 (dd, 1H, *J*= 10.8, 3.4 Hz), 3.52 (m, 1H), 3.42 (m, 1H), 3.36 (s, 3H), 2.94 (dd, 1H, *J*= 9.8, 6.8 Hz), 2.67 (dd, 1H, *J*= 10.3, 9.8 Hz), 2.51 (m, 1H), 2.17-2.05 (complex, 2H), 1.98 (m, 1H), 1.89 (dd, 1H, *J*= 12.7, 6.3 Hz), 1.62 (m, 1H), 1.19 (s, 9H), 1.04 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (100 MHz) δ 178.2, 135.5, 134.7, 133.5, 133.4, 129.6, 129.5, 127.6, 127.5, 94.4, 86.3, 81.6, 77.6, 74.3, 71.7, 67.2, 66.1, 62.7, 59.0, 48.8, 43.0, 38.7, 37.7, 36.0, 33.3, 28.7, 27.2, 26.9, 25.8, 19.3, 18.1, -4.5, -4.8. HREIMS calcd for $C_{42}H_{67}O_7SSi_2$ (M^+-OMe) 771.4142, found: *m/z* 771.4134.

*(2R,3S,4R)-2-{4-[[(2R,3R,5S)-3-tert-Butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]methyl]-3-hydroxythiolan-2-yl}ethyl 2,2-dimethylpropanoate (**46**)*

A mixture of **31** (34.8 mg, 43 μmol) and $ZnBr_2$ (0.20 g, 0.89 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 8 h, and then diluted with sat. aq. $NaHCO_3$. The mixture was extracted with EtOAc (3x), the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purıfied by silica gel column chromatography (5→6% EtOAc in benzene) to afford **46** (25.4 mg, 83%) as a colorless oil: $[\alpha]^{26}_D$ +25.5˚ (*c* 1.00, $CHCl_3$); IR (film) ν 3485, 2929, 1730 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.67 (complex, 4H), 7.43-7.37 (complex, 6H), 4.34 (m, 1H), 4.27 (m, 1H), 4.22 (m, 1H), 4.20-4.04 (complex, 2H), 3.95 (br d, H, *J*= 11 Hz), 3.78 (dd, 1H, *J*= 11, 3.4 Hz), 3.61 (dd, 1H, *J*= 11, 3.9 Hz), 3.37 (br dd, 1H, *J*= 10.2, 3.4 Hz), 2.90 (dd, 1H, *J*= 10.2, 6.8 Hz), 2.72 (t, 1H, *J*= 10.2 Hz), 2.28 (m, 1H), 2.07 (complex, 2H), 1.89 (complex, 2H), 1.71-1.59 (complex, 2H), 1.19 (s, 9H), 1.05 (s, 9H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C-NMR (100 MHz) δ 178.2, 135.5, 134.7, 133.4, 133.3, 129.6, 129.5, 127.6, 82.8,

80.5, 78.1, 74.6, 65.8, 62.6, 51.6, 45.7, 38.7, 37.5, 36.0, 34.2, 29.9, 27.2, 26.8, 26.6, 25.8, 19.3, 18.2, -4.5, -4.8. HREIMS calcd for $C_{39}H_{61}O_5SSi_2$ (M^+-OH) 697.3774, found: *m/z* 697.3763.

*2-{(2R,4R)-4-[[(2R,3R,5S)-3-tert-Butyldimethylsiloxy-5-tert-butyldiphenylsiloxymethyloxolan-2-yl]methyl]-3-oxo-2-(2,4,5-trihydrothienyl)}ethyl 2,2-dimethylpropanoate (**47**)*

A mixture of **46** (13.6 mg, 19 μmol), SO_3•Py (38.5 mg, 0.24 mmol), *i*-Pr_2NEt (0.2 mL), and DMSO (0.3 mL) in CH_2Cl_2 (0.3 mL) was stirred at rt for 20 min. Usual work-up afforded **47** (12.5 mg, 89%) as a colorless oil: $[\alpha]^{26}_D$ +54.9˚ (*c* 1.00, $CHCl_3$); IR (film) ν 2929, 1732 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.43-7.36 (complex, 6H), 4.31 (m, 1H), 4.27 (m, 1H), 4.17 (t, 2H, *J*= 6.3 Hz), 3.91 (dt, 1H, *J*= 10.2, 3.4 Hz), 3.77 (dd, 1H, *J*= 11, 3.4 Hz), 3.59 (dd, 1H, *J*= 11, 3.4 Hz), 3.44 (dd, 1H, *J*= 9, 4.4 Hz), 3.12 (dd, 1H, *J*= 10, 7 Hz), 2.75 (complex, 2H), 2.34 (m, 1H), 2.22 (ddd, 1H, *J*= 14, 10, 3.9 Hz), 2.14 (ddd, 1H, *J*= 13, 8, 4 Hz), 1.98-1.86 (complex, 2H), 1.46 (ddd, 1H, *J*= 14, 9, 3 Hz), 1.19 (s, 9H), 1.04 (s, 9H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C-NMR (100 MHz) δ 214.4, 178.2, 133.5, 134.7, 133.5, 133.4, 129.6, 129.5, 127.6, 127.5, 79.9, 77.6, 74.2, 66.0, 62.2, 49.4, 47.6, 38.7, 37.3, 31.6, 30.6, 30.2, 27.2, 26.8, 26.6, 25.8, 19.3, 18.2, -4.5, -4.9. HREIMS calcd for $C_{39}H_{60}O_6SSi_2$ (M^+) 712.3645, found: *m/z* 712.3642.

*2-[(1R,3S,4R,7R,9R,11S)-11-Hydroxymethyl-3-methoxy-2,10-dioxa-5-thiatricyclo[7.3.0.0^{3,7}]dodec-4-yl]ethyl 2,2-dimethylpropanoate (**48**)*

To a solution of **47** (4.0 mg, 5.6 μmol) in MeOH (1 mL) was added a catalytic amount of CSA at rt. After being stirred for 3 h, usual work-up afforded **48** (1.8 mg, 86%) as a colorless oil: $[\alpha]^{23}_D$ +104.4˚ (*c* 1.00, $CHCl_3$); IR (film) ν 3444, 2937, 1728 cm^{-1}; ^{1}H-NMR (400 MHz) δ 4.32 (m, 1H), 4.24 (ddd, 1H, *J*= 11, 7, 5 Hz), 4.15 (m, 1H), 4.11 (m, 1H), 3.98 (d, 1H, *J*= 2.4 Hz), 3.77 (br d, 1H, *J*= 11 Hz), 3.52 (dd, 1H, *J*= 11, 5.4 Hz), 3.46 (dd, 1H, *J*= 10, 4.5 Hz), 3.27 (s, 3H), 2.70 (dd, 1H, *J*= 9.3, 7 Hz), 2.56 (dd, 1H, *J*= 12, 9.3 Hz), 2.35 (dddd, 1H, *J*= 12, 12, 7, 4 Hz), 2.21 (m, 1H), 2.08 (dd, 1H, *J*= 13, 6.4 Hz), 2.01-1.93 (complex, 4H), 1.58 (m, 1H), 1.20 (s, 9H); ^{13}C-NMR (100 MHz) δ 178.2, 106.1, 79.1, 75.6, 74.3, 64.7, 62.5, 47.9, 43.5, 38.7, 37.2, 35.0, 34.1, 30.9, 27.2, 27.1, 26.4. HREIMS calcd for $C_{18}H_{29}O_5S$ (M^+-OH) 357.1736, found: *m/z* 357.1735.

*2-[(1R,3S,4R,7R,9R,11S)-11-tert-Butyldiphenylsiloxymethyl-3-methoxy-2,10-dioxa-5-thiatricyclo-[7.3.0.0^{3,7}]dodec-4-yl]ethan-1-ol (**49**)*

A mixture of **48** (75.4 mg, 0.20 mmol), TBDPSCl (0.4 mL), Et_3N (0.6 mL), and DMAP (25.4 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 18 h to give a colorless oil.

A mixture of the crude and DIBAL-H (1.0 M solution in toluene, 1 mL, 1 mmol) was stirred at –78 ˚C for 10 min to give **49** (84.2 mg, 79%) as a colorless oil: $[\alpha]^{26}_D$ +74.2˚ (*c* 1.00, $CHCl_3$); IR (film) ν 3440, 2931 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.69 (complex, 4H), 7.44-7.35 (complex, 6H), 4.31 (m, 1H), 4.17 (dd, 1H, *J*= 4, 2 Hz), 4.17 (br d, 1H, *J*= 2 Hz), 3.80 (dd, 1H, *J*= 10.7, 3.9 Hz), 3.77 (m, 1H), 3.70 (m, 1H), 3.66 (dd, 1H, *J*= 10.7, 3.9 Hz), 3.52 (dd, 1H, *J*= 9, 5 Hz), 3.30 (s, 3H), 2.72 (dd, 1H, *J*= 9, 6.8 Hz), 2.56 (dd, 1H, *J*= 12.2, 9 Hz), 2.39 (ddd, 1H, *J*= 12, 7, 5 Hz), 2.22-2.13 (complex, 2H), 2.07-1.94 (complex, 4H), 1.56 (m, 1H), 1.05 (s, 9H); ^{13}C-NMR (100 MHz) δ 135.5, 135.4, 133.4, 133.3, 129.5, 129.4, 127.5, 106.1, 78.6, 75.6, 74.6, 645.9, 61.3, 48.0, 44.6, 37.8, 37.2, 35.2, 31.0, 26.9, 26.4, 19.3. HREIMS calcd for $C_{25}H_{31}O_5SSi$ (M^+-*t*-Bu) 471.1660, found: *m/z* 471.1680.

*{(1S,3R,5S,7R,9R,12R)-2,6,15-Trioxa-11-thiatetracyclo[7.6.0.0^{1,12}.0^{3,7}]pentadec-5-yl}tert-butyldiphenylsiloxymethane (**30**)*

To a solution of **49** (6.8 mg, 13 μmol) in MeCN (0.5 mL) was added $Yb(OTf)_3$ (4.5 mg, 7.3 μmol) at 0 ˚C. After being stirred at rt for 1 h, the mixture was diluted with sat. aq. $NaHCO_3$ and EtOAc. The organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20% EtOAc in hexane) to afford **30** (6.2 mg, 97%) as a colorless oil: $[\alpha]^{24}_D$ –3.4˚ (c 0.28, $CHCl_3$); IR (film) ν 2929 cm^{-1}; 1H-NMR (400 MHz) δ 7.68 (complex, 4H), 7.44-7.35 (complex, 6H), 4.46 (m, 1H), 4.26 (dt, 1H, J= 8.3, 2 Hz), 4.22 (m, 1H), 4.18 (m, 1H), 3.97 (br d, 1H, *J*= 2.4 Hz), 3.83 (br d, 1H, *J*= 5.4 Hz), 3.79 (dd, 1H, *J*= 10.7, 3.9 Hz), 3.64 (dd, 1H, *J*= 10.7, 3.9 Hz), 3.23 (dd, 1H, *J*= 10.2, 5.4 Hz), 2.62 (dt, 1H, *J*= 12.2, 5.4 Hz), 2.38 (m, 1H), 2.32 (d, 1H, *J*= 10.2 Hz), 2.19-2.05 (complex, 5H), 1.04 (s, 9H); ^{13}C-NMR (100 MHz) δ 135.6, 133.5, 129.6, 129.5, 127.6, 118.5, 78.6, 76.8, 75.2, 68.7, 66.2, 44.7, 37.6, 35.9, 34.0, 32.0, 29.1, 26.9, 19.3. HREIMS calcd for $C_{24}H_{27}O_4SSi$ (M^+-*t*-Bu) 439.1397, found: *m/z* 439.1389.

*{(1R,6R,8S,14R)-2,7-Dioxaspiro[bicyclo[4.3.0]nonane-3,5'-oxolane]-8-yl}tert-butyldiphenyl-siloxymethane (**29**)*

A mixture of **30** (3.6 mg, 7.2 μmol) and Raney Ni (0.3 mL) in EtOH (0.5 mL) was stirred at reflux temperature for 1 h. After filtration with Celite, the filtrate was concentrated *in vacuo*. The residue

was purified by preparative TLC (33% EtOAc in hexane) to afford **29** (3.2 mg, 95%) as a colorless oil: $[\alpha]^{23}_{D}$ –16.0˚ (*c* 0.37, $CHCl_3$); IR (film) ν 2929 cm^{-1}; ^{1}H-NMR (400 MHz, C_6D_6) δ 7.82 (complex, 4H), 7.23 (complex, 6H), 4.56 (m, 1H), 4.02 (ddd, 1H, *J*= 8.3, 7.8, 5.4 Hz), 3.76 (dd, 1H, *J*= 10.8, 3.9 Hz), 3.75 (brs, 1H), 3.70 (br d, 1H, *J*= 2.4 Hz), 3.67 (m, 1H), 3.55 (dd, 1H, *J*= 10.8, 4.4 Hz), 2.54 (ddd, 1H, 13, 6.8, 4 Hz), 2.09-2.03 (complex, 2H), 1.91 (ddd, 1H, *J*= 12.7, 9.3, 4.4 Hz), 1.75 (m, 1H), 1.61 (ddd, 1H, *J*= 12.7, 7.9, 3.4 Hz), 1.45 (m, 1H), 1.31 (m, 1H), 1.17 (s, 1H), 1.13 (m, 1H), 0.31 (d, 1H, *J*= 6.8 Hz); ^{13}C-NMR (100 MHz, C_6D_6) δ 136.1, 134.2, 129.9, 128.5, 110.5, 79.2, 76.3, 76.1, 67.8, 66.8, 36.5, 34.5, 31.0, 27.2, 25.4, 24.5, 19.7, 15.9. HREIMS calcd for $C_{28}H_{38}O_4Si$ (M^+) 466.2536, found: *m/z* 466.2530.

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8. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 219836. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
9. Alkyne (**21**) was prepared from benzyl (*R*)-(-)-glycidyl ether in 2 steps: (a) lithium acetylide, ethylenediamine complex, DMSO; (b) TESCl, Imid, DMF. **21**: $[\alpha]^{21}_{D}$ –2.2° (*c* 1.0, $CHCl_3$); IR (film) ν 3311, 2954 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.34 (complex, 5H), 4.55 (s, 2H), 3.61 (m, 1H), 3.50 (m, 2H), 2.50 (ddd, 1H, *J*= 17, 6.3, 2.4 Hz), 2.38 (ddd, 1H, *J*= 17, 6, 3 Hz), 1.95 (t, 1H, *J*= 2.4 Hz), 0.95 (t, 9H, *J*= 8 Hz), 0.62 (q, 6H, *J*= 8 Hz); ^{13}C-NMR (100 MHz) δ 138.2, 128.2, 127.5, 127.4, 81.7, 73.3, 70.0, 69.9, 24.7, 6.8, 4.9. HREIMS calcd for $C_{18}H_{28}O_2Si$ (M^+) 304.1857, found: *m/z* 304.1860.
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