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TETRAHEDRON

Enantioselective Synthesis of the Medium Ring Ethers, Tetrahydrooxepin, Oxocane and Hexahydrooxonin, of Ciguatoxin. Extensive Ring-Expansion and Chemoenzymatic Desymmetrization Strategy

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Abstract: The extensive ring-expansion strategy for the synthesis of tetrahydrooxepin, oxocane, and hexahydrooxonin, which correspond to the D(E), I and F rings of ciguatoxin (CTX1B, **1**), respectively, has been established. Chemoenzymatic acylation of the *meso* alcohols using a lipase provides an expeditious entry for the enantiomeric building blocks. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Ciguatera is a widespread human scale food poisoning that is caused by fishes dwelling in coral reefs in the tropics and subtropics.[1,2] The most potent is ciguatoxin (CTX1B, **1**),[3] regarded as the principal causative toxin of ciguatera, was isolated from the moray eel, *Gymnothorax javanicus*, and the absolute configuration was determined quite recently, as shown in Figure 1.[4,5] Synthesis of **1** has received considerable attention among synthetic chemists due to the striking structural and biological features of this toxin.[6-9] In the present synthetic study on **1**,[5,10] we describe a new enantiocontrolled strategy that is based on an extensive ring-expansion and chemoenzymatic desymmetrizaton for synthesizing tetrahydrooxepins, oxocanes, and hexahydrooxonins corresponding to the D(E), I, and F rings, respectively.[10b]

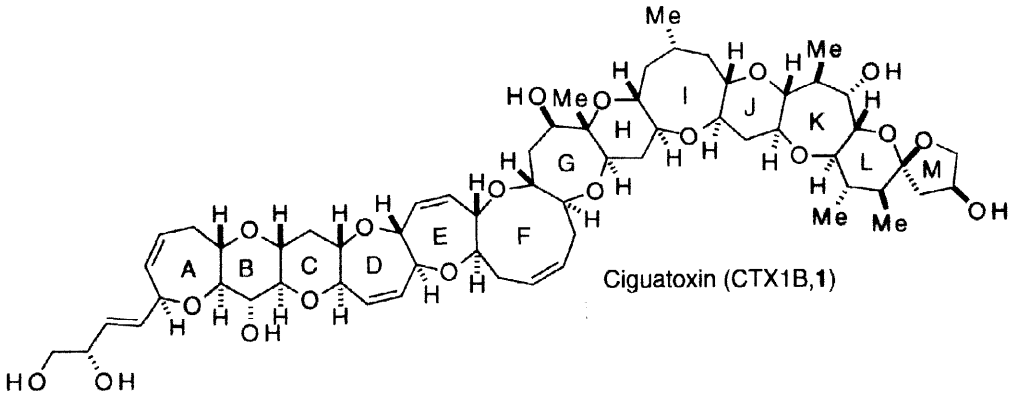

Figure 1. Structure of ciguatoxin (CTX1B, **1**).

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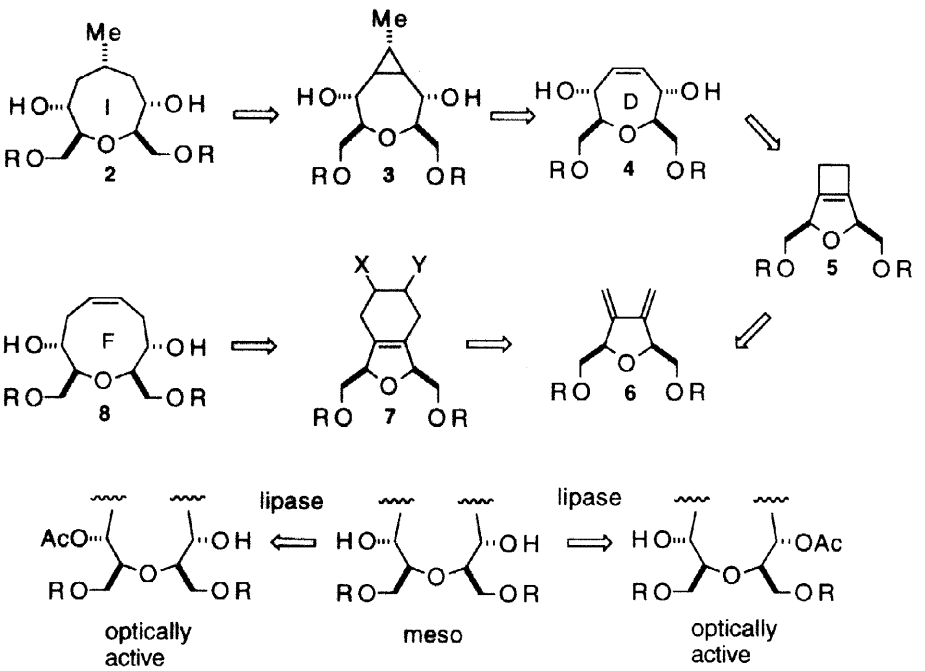
RESULTS AND DISCUSSION

Synthetic Strategy

A versatile route which would provide both enantiomers of **1** was planned, as outlined in Scheme 1, because the absolute configuration of **1** was not determined at the beginning of the present study. An *exo*-diene (**6**) was envisaged as a pivotal intermediate for the *meso* oxocane (**2**), tetrahydrooxepin (**4**), and hexahydrooxonin (**8**), which correspond to the I, D(E), and F ring moieties of **1**, respectively. The oxocane (**2**) would be synthesized starting with **6** via tetrahydrooxepin (**4**) through the successive ring expansion reaction of the 3-oxabicyclo[3.2.0]hept-1(5)-ene system (**5**) and the 4-oxabicyclo[5.1.0]octane system (**3**). The hexahydrooxonin (**8**) would also be constructed from **6** via the 3-oxabicyclo[4.3.0]non-1(5)-ene system (**7**). Desymmetrization of the *meso* diols (**2**, **4**, and **8**) may be realized by lipase-catalysts.[6c,11] The crucial steps of the present strategy include (i) stereoselective introduction of the secondary alcohols onto the medium ring ethers (**4** and **8**) and (ii) stereocontrol of the methyl group and regioselective cleavage of the cyclopropane ring of **3**.

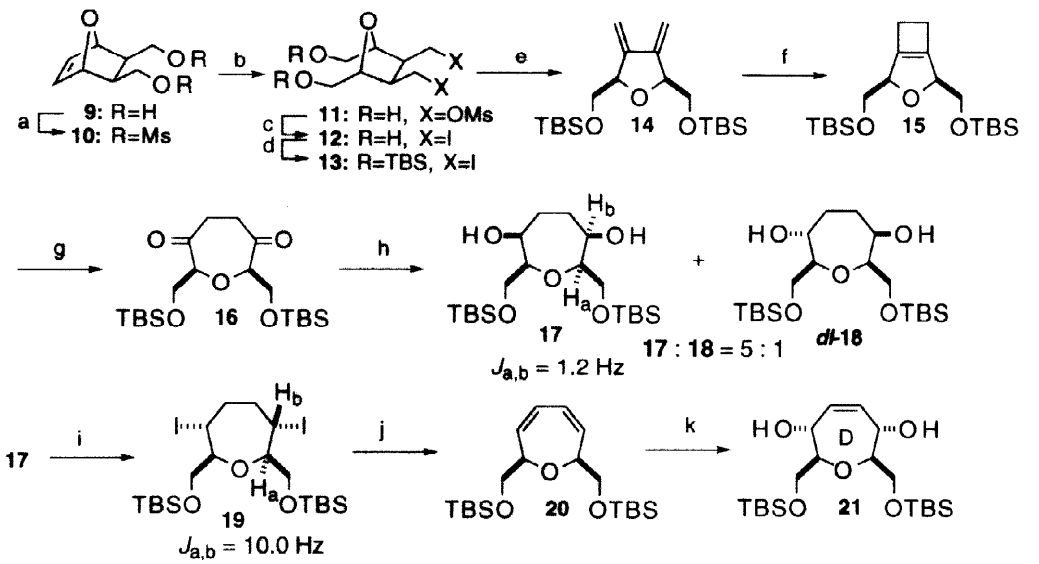


Scheme 1. Extensive ring-expansion and chemoenzymatic desymmetrization strategy.

Synthesis of the Tetrahydrooxepin

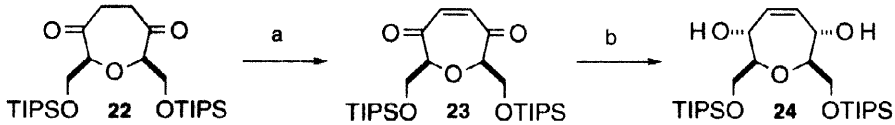
Synthesis of the *exo*-diene (**6**: R=TBS, **14**) and tetrahydrooxepin (**4**: R=TBS, **21**) is shown in Scheme 2. Readily available diol (**9**)[12] was mesylated. Ozonolysis of **10** followed by reduction with $NaBH_4$ gave diol (**11**) in 74% overall yield. Displacement of the mesylate groups of **11** with iodides and protection of the primary alcohols as *tert*-butyldimethysilyl (TBS) ethers furnished **13**. Diiodide (**13**) underwent a clean elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give **14**, whereas the elimination reaction of the corresponding dimesylate was sluggish under the same reaction conditions. Photoelectrocyclic reaction of the diene (**14**) resulted in the formation of cyclobutene (**15**), which was immediately subjected to ozonolysis followed by reduction with Ph_3P to give diketone (**16**) in 47% overall yield from **13**. Although reduction of **16** with $NaBH_4$ was not stereoselective, diisobutylaluminum hydride (DIBAL) reduction proceeded stereoselectively to yield *meso-cis*-diol (**17**) as a major product concomitant with the diastereomer (***dl*-18**) in a 5:1 ratio. The next task was the regioselective preparation of diene (**20**) from **17**. The diol (**17**) was converted to iodide (**19**) by

stereochemical inversion,[13] and treatment of **19** with DBU resulted in the exclusive formation of the conjugated diene (**20**) in 84% overall yield from **17**. Other stereoisomer derived from ***dl*-18** gave a mixture of the positional isomers of the dienes. The diene (**20**) was transformed to the diol (**21**) using the procedure reported by Martín.[6c]



Scheme 2. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0°C, 80%. (b) O_3, CH_2Cl_2, MeOH, -78°C then $NaBH_4$, 93%. (c) NaI, acetone, reflux. 89%. (d) TBSCl, Imidazole, DMF, 97%. (e) DBU, THF, reflux, 90%. (f) hν (low pressure mercury lamp), hexane, EtOH, 90%. (g) O_3, CH_2Cl_2, -78°C then Ph_3P, 58%. (h) DIBAL, CH_2Cl_2, -78°C, 52%. (i) I_2, Ph_3P, imidazole, benzene, 87%. (j) DBU, THF, reflux, 97%. (k) O_2, 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP), hν (high pressure mercury lamp), $CHCl_3$, 0°C then H_2, Lindlar catalyst, MeOH, 48%.

A more straightforward synthesis of the tetrahydrooxepin (**4**: R=TIPS, **24**) is shown in Scheme 3. Triisopropylsilyl (TIPS) ether (**22**) was prepared from **12** in an analogous sequence using TIPSOTf rather than TBSCl. Formation of the bis-silylenol ether from **22** followed by treatment with *N*-bromosuccinimide (NBS) gave enone (**23**). Whereas 1,2-reduction of **23** with $CeCl_3$•$7H_2O$-$NaBH_4$ gave a mixture of the diol (**24**) and the diastereomer (**25**) in a 63 : 37 ratio (Table 1, entry 1), highly stereoselective reduction was achieved using $TiCl_4$-Et_3SiH (94.5 : 5.5, entry 2). The stereochemistry was determined by ^1H NMR analysis of **24** ($J_{a,b}$=8.6 Hz) and the corresponding acetonide (**26**) ($J_{a,b}$=8.8 Hz). The stereochemical outcome can be explained based on Cieplak's hypothesis (Figure 2).[14] The hydride is thought to preferentially attack anti to the neighboring σ_{CH} rather than the σ_{CC} because of the higher electron donating ability of σ_{CH}. Therefore, axial attack of the hydride to the intermediate A and C resulted in the formation of the equatorial diol (**24**) (path a). The formation of a considerable amount of **25** associated with the use of $CeCl_3$•$7H_2O$-$NaBH_4$ may be attributed to competitive intramolecular hydride delivery via intermediate D (path b).



Scheme 3. Reagents and conditions: (a) TMSCl, LDA, THF, then NBS, propylene oxide, 81%; (b) See Table 1.

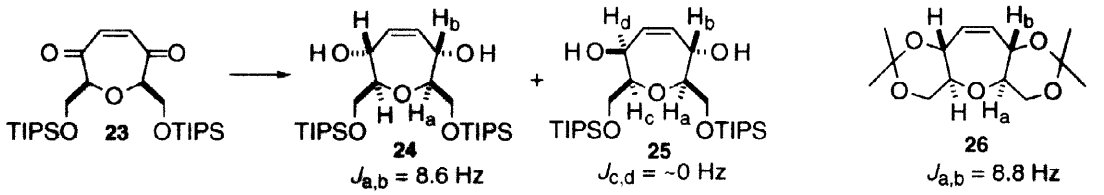


Table 1. Stereoselective reduction of the diketone **23**.

entry	reagent (mol eq.)	solvent	temp./°C	ratio (**24**:**25**)[a]	yield/%
1	$NaBH_4$ (10), $CeCl_3 \cdot 7H_2O$ (10)	MeOH	-70	63 : 37	43
2	Et_3SiH (10), $TiCl_4$ (2.4)	$_2Cl_2$	-78~-40	94.5 : 5.5	48

[a] The ratio was determined by HPLC analysis.

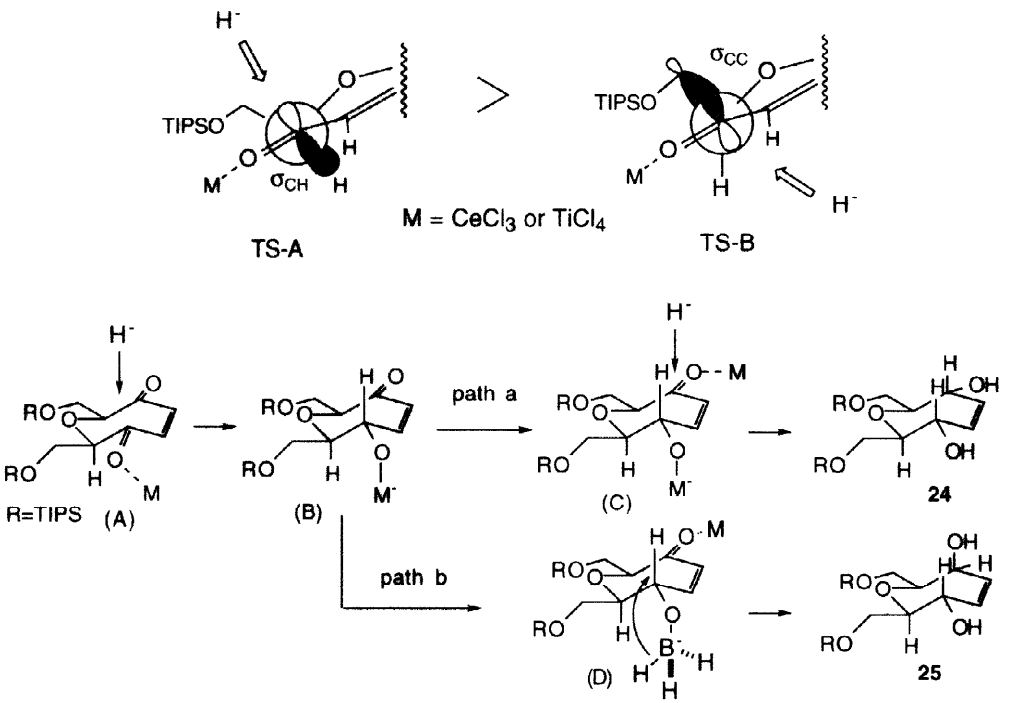
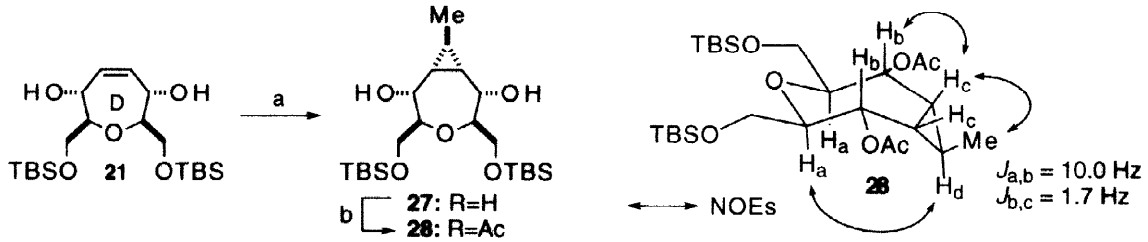


Figure 2. A hypothetical model of the stereoselective reduction of **23**.

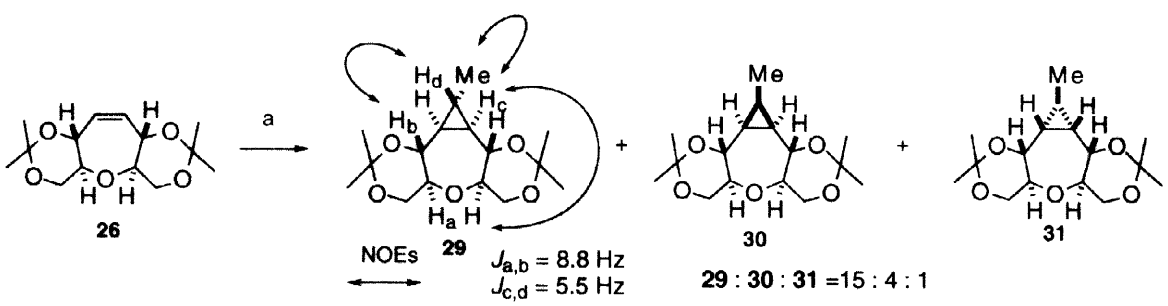
Synthesis of Oxocane

Having completed the synthesis of the tetrahydrooxepin (**4**: R=TBS, **21**), we examined the synthesis of oxocane (**2**: R=TBS) via cyclopropane (**3**: R=TBS), which was obtained by Simmons-Smith reaction (Scheme 4). Treatment of the tetrahydrooxepin (**21**) using Et_2Zn and CH_3CHI_2 resulted in the formation of methylcyclopropane (**27**) in 36% yield as a single stereoisomer. Unfortunately, **27** was an undesired diastereomer with respect to the methyl group of which the structure was determined by ^1H NMR analysis of the corresponding acetate (**28**).



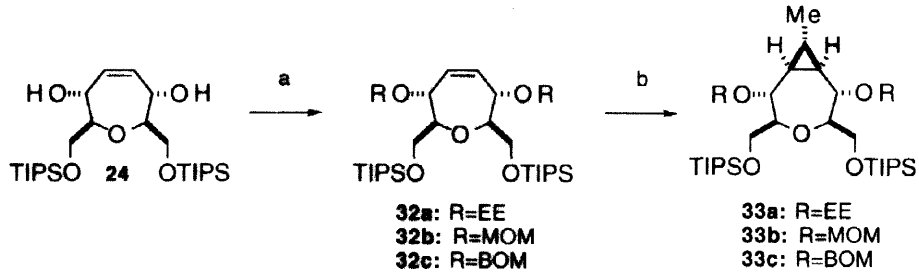
Scheme 4. Reagents and conditions: (a) Et_2Zn, CH_3CHI_2, benzene, reflux, 22h, 36% (recovery of **21**, 38%). (b) Ac_2O, Py.

Alternatively, the carbenoid addition reaction was examined (Scheme 5).[15] Treatment of **26** with CH_3CHN_2 using $Pd(OAc)_2$ in Et_2O resulted in the formation of a diastereomeric mixture of methylcyclopropanes **29**, **30**, and **31** in a 15 : 4 : 1 ratio. The low yield of the products (38%) was presumably due to the steric bulkiness of the carbenoid complex generated from CH_3CHN_2 because the reaction with CH_2N_2 proceeded smoothly to give the corresponding cyclopropane in 90% yield. $Rh_2(OAc)_4$, $PdCl_2(CH_3CN)_2$, and $Cu(OTf)_2$ were ineffective, and other solvents were not suitable for this reaction, except for ethyl acetate which increased the solubility of $Pd(OAc)_2$.



Scheme 5. Reagents and conditions: (a) CH_3CHN_2, $Pd(OAc)_2$, Et_2O, 38% (recovery of **26**, 62%).

In an attempt to improve the stereoselectivity, we examined the effect of protecting groups using **32a~c** prepared from **24** (Scheme 6, Table 2). Although the use of ethoxyethyl (EE) ether (**32a**) did not improve the selectivity (run 1), that of the methoxymethyl (MOM) ether (**32b**) resulted in better selectivity than **26** (run 2). Highly stereoselective methylcyclopropanation was realized using benzyloxymethyl (BOM) ether (**32c**) giving **33c** in a 24 : 1 ratio (run 3). Although the reaction did not reach completion, even when excess reagents were added, recycling of the recovered **32c** and repetition of this procedure three times gave an 90% yield of **33c** (run 4). High stereoselectivity using **32c** can be rationalized as shown in Figure 3. The BOM groups of **32c** effectively block the α-side of the olefin; therefore, carbenoid addition occurred from the less-hindered β-side via the transition state, in which the methyl group takes on equatorial orientation due to steric hindrance.



Scheme 6. Reagents and conditions: (a) ethyl vinyl ether, PPTS, 90% (for **32a**); MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 56% (for **32b**); BOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, quant. (for **32c**); (b) See, Table 2.

Table 2. Carbenoid addition reaction of **32**.[a]

run	substrate	product	ratio[b]	yield/%[c]
1	**32a** (R=EE)	**33a**	2.5 : 1	33 (65)
2	**32b** (R=MOM)	**33b**	6 : 1	37 (63)
3	**32c** (R=BOM)	**33c**	24 : 1	45 (53)
4	**32c** (R=BOM)	**33c**	24 : 1	90[d] (0)

[a]Reaction was carried out using 30 mol% of $Pd(OAc)_2$ at room temperature in EtOAc and Et_2O. [b]The ratio of the product **33** and other isomers. [c]In parenthesis indicate the recovered yields of **32**. [d]Yield after three times repetition.

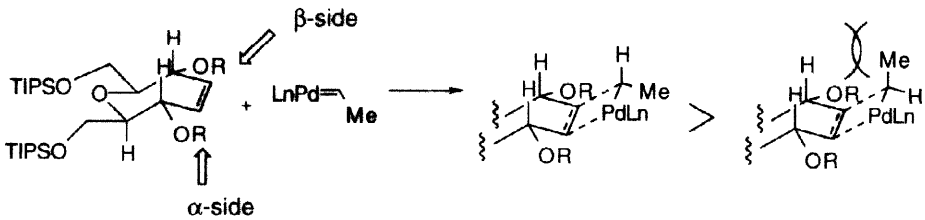
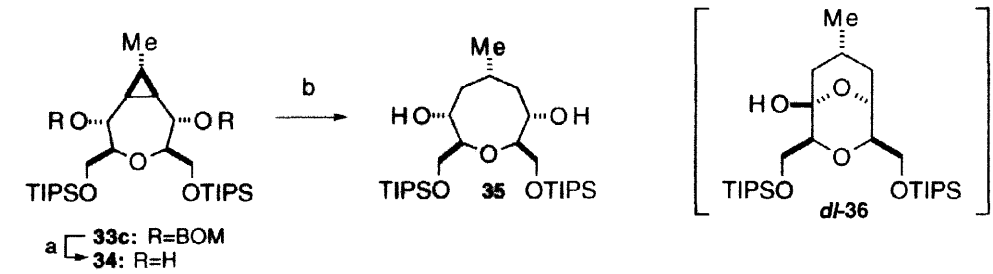


Figure 3. A transition state model of the stereoselective carbenoid addition.

The next crucial step is a regioselective reductive-opening of the cyclopropane ring of **33c**. Although cleavage of the reactive cyclopropanes (such as vinylcyclopropanes or cyclopropanols) occurs easily under reductive or acidic conditions, cleavage of the inactivated cyclopropanes appeareded to be problematic. Hydrogenation of **33c** using $Pd(OH)_2/C$ did not induce ring-opening of the cyclopropane. Rather, this resulted in the removal of the BOM groups (Scheme 7). After numerous experiments using various substrates (**29**, **33** and other derivatives) under various conditions, we found that hydrogenation of **34** using Rh/Al_2O_3 catalyst in cyclohexane at room temperature proceeded regioselectively to give oxocane (**35**) as a single isomer. The choice of the substrate and reaction conditions was crucial in this reaction. For instance, the reaction did not proceed when the secondary hydroxy groups of **34** were protected, or when MeOH and Rh/C were used as a solvent and catalyst, respectively. Furthermore, a higher reaction temperature (60°C) resulted in the formation of by-product (**36**). These results suggest that the regioselectivity in the cleavage of the cyclopropane ring occurred due to the followings. The hydroxy groups facilitate the adsorption of **34** onto the surface of the Al_2O_3 (Figure 4). Insertion of Rh-H to the carbon-carbon bond from the same side of the hydroxy groups followed by reductive elimination gave **35**. The by-product (**36**) is thought to have formed via β-hydride elimination from the intermediate B. Thus, synthesis of oxocane (**35**) was achieved in four steps from tetrahydrooxepin (**24**) in 50% overall yield.



Scheme 7. Reagents and conditions: (a) 10%$Pd(OH)_2$/C, H_2, EtOAc, 75%; (b) Rh/Al_2O_3, H_2 (5kg/cm^2), cyclohexane, 6 days, 82%.

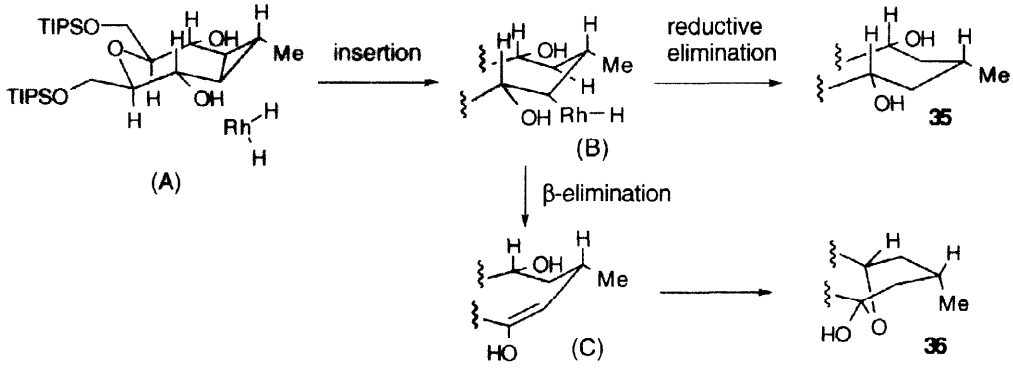
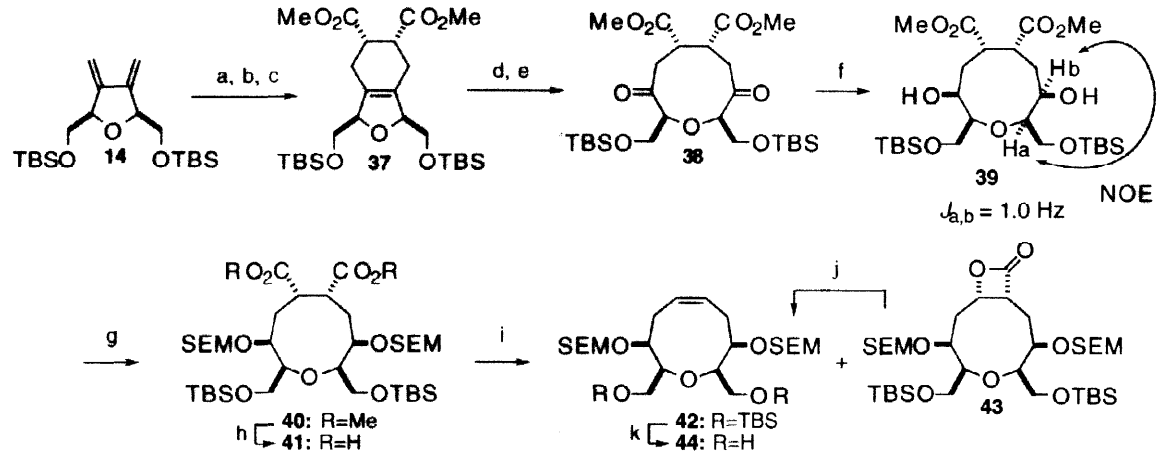


Figure 4. A plausible mechanism for the formation of **35** and **36**.

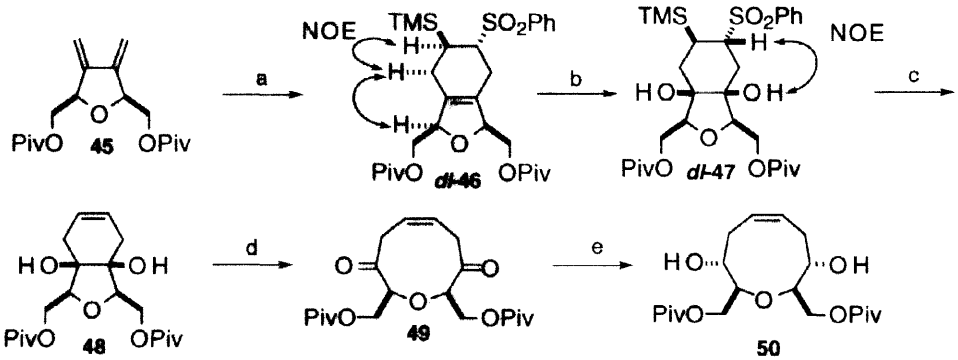
Synthesis of the Hexahydrooxonin

Synthesis of the hexahydrooxonin (**8**) from *exo*-diene (**6**) was examined (Scheme 8). The Diels-Alder reaction of **14** with maleic anhydride, followed by hydrolysis and methylation, gave diester (**37**) as a single stereoisomer in 81% yield from **14**. Whereas oxidative cleavage of the double bond of **37** by ozonolysis was unsuccessful, dihydroxylation of **37** and treatment of the resulting glycol using $Pb(OAc)_4$ gave diketone (**38**). Reduction of **38** with $NaBH_4$ proceeded stereoselectively to give diol (**39**) as a single isomer in 83% overall yield. Although the stereochemistry of the resulting secondary alcohol was the opposite to that desired, the synthesis was carried out because the stereochemistry can be inverted readily at a later stage. Protection of the hydroxy groups of **39** as trimethylsilylethoxymethyl (SEM) ethers (89%) followed by saponification of diesters (95%) gave dicarboxylic acid (**41**). Introduction of the double bond was attempted using Barton's decarboxylation method.[16] However, preparation of the bis-acyl chloride from **41** failed due to the formation of the corresponding anhydride. In contrast, treatment of **41** with $Pb(OAc)_4$[17] under irradiation by a tungsten lamp resulted in the formation of the hexahydrooxonin (**42**) in 35% yield concomitant with β-lactone (**43**) (40%). The lactone (**43**) was readily converted to **42** by heating in the presence of silica gel (75%).[18] The stereoochemistry of the *meso* olefin (**42**) was ambiguous at this stage, the *Z*-geometry was confirmed by ^{1}H NMR analysis after the desymmetrization of **42** (*vide post*). Selective desilylation of the TBS groups of **42** with tetrabutylammonium fluoride (TBAF) yielded diol (**44**). Since this method has drawbacks in that inversion of the alcohol stereochemistry is requisite and introduction of the double bond is inefficient, an alternative method was investigated.



Scheme 8. Reagents and conditions: (a) maleic anhydride, Et_2O, reflux; (b) H_2O, THF; (c) CH_2N_2, Et_2O, 0°C, 81% (3 steps); (d) OsO_4, *N*-methylmorphorine *N*-oxide, 1,4-dioxane, H_2O, 75°C, 94%; (e) $Pb(OAc)_4$, Py, 94%; (f) $NaBH_4$, MeOH, 0°C, 94%; (g) SEMCl, $^iPr_2NEt$, Bu_4NI, 89%; (h) LiOH, Bu_4NBr, ^tBuOH, H_2O, 95%; (i) $Pb(OAc)_4$, benzene, hv (tungsten lamp), 35% (**43**; 40%); (j) silica gel, toluene, 70°C, 75%; (k) TBAF, THF, 0°C~rt, 86%.

New synthesis of hexahydrooxonin (**50**) from *exo*-diene (**45**) is shown in Scheme 9. The Diels-Alder reaction[19] of **45** with (*E*)-2-trimethylsilylvinyl phenylsulfone[20] resulted in the formation of racemic ***dl*-46** as a single diastereomer. Although dihydroxylation of the hindered olefin (***dl*-46**) under standard conditions was too sluggish (Table 3, entry 1, 2),[21,22] the reaction under Tsuji's conditions[23] using diazabicyclo[2.2.2]octane (DABCO) and $K_3Fe(CN)_6$ proceeded smoothly to give diol (***dl*-47**) as a single diastereomer (entry 3, 4). Introduction of the *cis*-double bond was successfully achieved by treatment of ***dl*-47** with TBAF in THF at 40°C to give the olefin (**48**) smoothly in good yield (88%).[22] Oxidative cleavage of the glycol with $Pb(OAc)_4$ gave diketone (**49**). Stereoselective reduction of the diketone (**49**) was examined next (Table 4). Reduction of **49** with $NaBH_4$ resulted in the formation of the three possible diastereomers **50**, **51**, and **52** in a 25 : 53 : 22 ratio. The ratio of the equatorial alcohols was improved with $CeCl_3 \cdot 7H_2O$-$NaBH_4$, and reduction of **49** with $TiCl_4$-Et_3SiH at -78 to -15°C gave the desired **50** as a single isomer in 86% yield. A plausible mechanism of the stereoselective reduction of the diketone (**49**) in comparison with **38** was depicted in Figure 5. The hexahydrooxonin (**49**) should exist as an equiriblium mixture of the conformers (A and B) based on the similarity with the other hexahydrooxonin system.[3,7c] The hydride can attack from both sides of the carbonyl groups of A and B resulting in the formation of the diastereomeric mixture. In the presence of Lewis acid, C is presumed to be a stable conformation, and hydride should preferencially attack anti to the neighboring σ_{CH} based on Cieplak's hypothesis.[14] Formation of a considerable amount of **51** with $CeCl_3 \cdot 7H_2O$-$NaBH_4$ may be attributed to the competitive intramolecular hydride delivery via intermediate D. However, conformer F of the oxocane (**38**) should be more stable than E due to steric hindrance, and the hydride should attack from the less hindered side giving axial diol (**39**) exclusively. Thus, synthesis of hexahydrooxonin (**50**) was achieved in five steps from *exo*-diene (**45**) in 46% overall yield.



Scheme 9. Reagents and conditions: (a) (*E*)-2-trimethylsilylvinyl phenylsulfone, toluene, 75%; (b) See; Table 3; (c) TBAF, THF, 40°C, 88%; (d) $Pb(OAc)_4$, Py, 95%; (e) See; Table 4.

Table 3. Dihydroxylation of the olefin **46**.[a]

entry	reagent (mol eq.)	solvent	temp./°C	time/d	yield/%[b]
1	*N*-methylmorphorine *N*-oxide (5)	dioxane-H_2O (1:1)	75~80	7	4 (70)
2	trimethylamine *N*-oxide (5)	dioxane-H_2O (1:1)	80~90	7	20 (70)
3	$K_3Fe(CN)_6$ (10), K_2CO_3 (10), DABCO (1)	^tBuOH-H_2O (1:1)	40~45	1	56 (38)
4	$K_3Fe(CN)_6$ (10), K_2CO_3 (10), DABCO (0.25)	^tBuOH-H_2O (1:1)	40~45	1	88 (0)

[a] Reaction was carried out using 0.5 mol% of OsO_4. [b] In parentheses indicate the recovered yields of **46**.

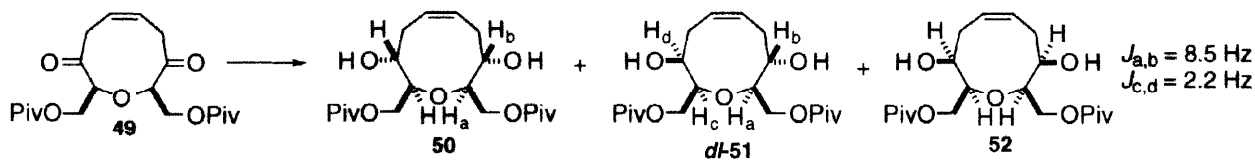


Table 4. Reduction of the diketone **49**.

entry	reagent (mol eq.)	solvent	temp./°C	ratio (**50**:**51**:**52**)[a]	yield/%
1	$NaBH_4$ (2.5)	MeOH	0	25 : 53 : 22	68
2	$NaBH_4$ (3), $CeCl_3$•$7H_2O$ (3)	EtOH	-78~13	35 : 65 : 0	72
3	Et_3SiH (10), $TiCl_4$ (3)	CH_2Cl_2	-78~-15	100 : 0 : 0	86

[a] The ratio of the diastereomers was determined by HPLC analysis.

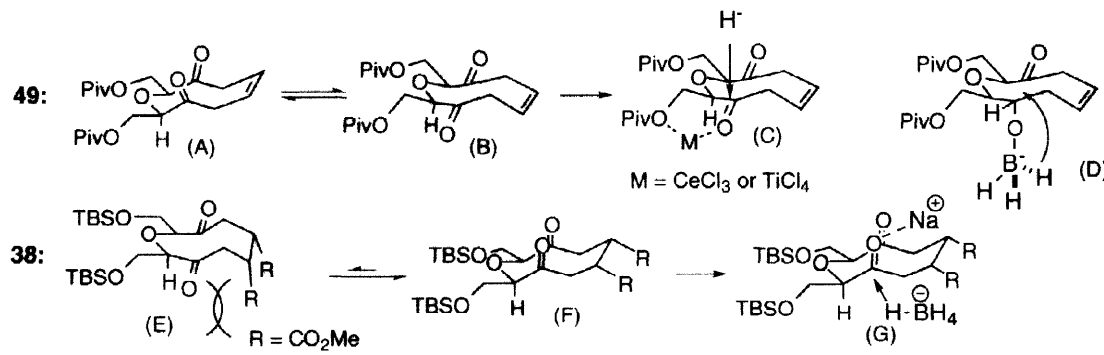
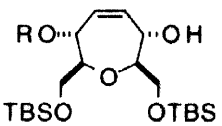


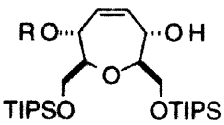
Figure 5. A plausible mechanism of the stereoselective reduction of **38** and **49**.

Chemoenzymatic Desymmetrization

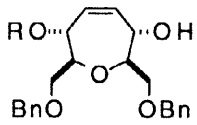
Chemoenzymatic desymmetrization of the *meso* cyclic ethers obtained was then examined. Asymmetric monoacylation of the tetrahydrooxepins using lipases and vinyl acetate is shown in Table 5. The reaction of TBS ether (**21**) proceeded highly stereoselectivly to give mono acetate (**54**) in >96% ee (run 1~6). The solvent effect was hardly observable using both lipases AK and PS, whereas the rate for AK is faster than that for PS (Amano). Although the reaction of TIPS ether (**24**) was sluggish under the same conditions, the reaction rate and yield were increased using vinyl acetate as a solvent (run 7). It is noteworthy that the reaction of benzyl ether (**53**), prepared from **24** (desilylation and selective protection of the primary alcohol), was much faster than **24** to give mono acetate (**56**) with excellent enantioselectivity in >99% ee (run 8).



21: R=H
54: R=Ac



24: R=H
55: R=Ac



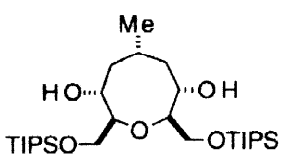
53: R=H
56: R=Ac

Table 5. Chemoenzymatic asymmetric acylation of tetrahydrooxepins.

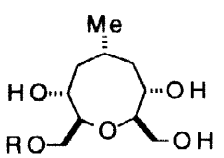
run	substrate	product	lipase (%w/w)	solvent	temp./°C	time/d	yield/%[a]	ee/%[b]
1	**21**	**54**	PS (100)	benzene	30	8	50 (23)	>99
2	**21**	**54**	PS (100)	CH_3CN	30	8	58 (42)	>99
3	**21**	**54**	PS (100)	^tBuOMe	30	6	12 (85)	97
4	**21**	**54**	AK (100)	benzene	30	6	70 (30)	98
5	**21**	**54**	AK (100)	CH_3CN	30	6	65 (35)	>99
6	**21**	**54**	AK (100)	^tBuOMe	30	6	60 (6)	96
7	**24**	**55**	AK (40)	-[c]	25	5	77	>99
8	**53**	**56**	AK (4)	-[c]	30	2	81	>99

[a]In parentheses indicate the recovered yields of **21**. [b]Determined by HPLC analysis of the corresponding benzoate (CHIRALCEL OD). [c]Vinyl acetate was used as a solvent.

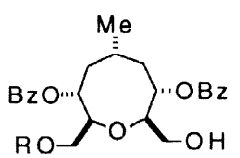
The results of the desymmetrization of oxocanes are summarized in Table 6. Whereas asymmetric acylation of oxocane (**35**) using lipase AK was sluggish compared to tetrahydrooxepin (**24**), that of the corresponding tetraol (**57**) derived from **35** by desilylation proceeded smoothly to give the mono acetate (**58**) in good yields but in moderate selectivity (55% ee, run 1). The addition of triethylamine not only increased the reaction rate[11e] but also caused a reversal of enantioselectivity (run 2). Lipases PS and PPL (Sigma) were not suitable for **57** (run 3,4). However, dibenzoate (**59**), derived from **35** via benzoylation and desilylation, gave mono acetate (**60**) in high enantiomeric excess (93% ee, run 5). Chemical yield of **60** was improved up to 94% without loss of the optical purity by using vinyl acetate as a solvent (run 6).



35



57: R=H
58: R=Ac



59: R=H
60: R=Ac

Table 6. Chemoenzymatic asymmetric acylation of oxocanes.

run	substrate	product	lipase (w/w%)	solvent	temp./°C	time/h	yield/%[c]	ee/%
1	**57**	**58**	AK (100)	CH_3CN	30	22	quant.	55[d]
2	**57**	**58**	AK (100)	CH_3CN[a]	30	9	quant.	39[d,e]
3	**57**	**58**	PS (100)	CH_3CN	30	84	quant.	32[d]
4	**57**	**58**	PPL (100)	CH_3CN	37	24	5 (90)	5[d]
5	**59**	**60**	AK (110)	benzene	30	192	50 (50)	93[f]
6	**59**	**60**	AK (110)	–[b]	30	144	92	92[f]

[a]Triethylamine was used as a cosolvent. [b]Vinyl acetate was used as a solvent. [c]In parentheses indicate recovered yields of the starting materials. [d]Determined by HPLC analysis of the corresponding benzoate derivative **67** (CHIRALCEL OD). See; Scheme 10. [e]The enantiomeric excess of the antipode. [f]Determined by HPLC analysis (CHIRALCEL OD).

Next, asymmetric acylation of hexahydrooxonins was examined (Table 7). Although asymmetric acylation of the diol (**44**) was too sluggish, that of tetraol (**61**), prepared from **44** by desilylation, proceeded smoothly to give monoacetate (**62**) in 83% ee together with a small amount of diacetate (run 1). The reaction of the diol (**50**) was also too sluggish, and that of tetraol (**63**) gave not only a monoacetate, but also a mixture of diacetates and triacetates, unlike the *cis,syn,cis*- hexahydrooxonin (**61**) (run 2). Then, asymmetric acylation of *p*-methoxybenzyl (MPM) ether (**64**) prepared from **50** was examined using various solvents. The reaction in aceonitrile, benzene, and vinyl acetate gave excellent enantiomeric excess (>94% ee, run 4, 7, and 8), and the vinyl acetate is suitable both in yield and selectivity.

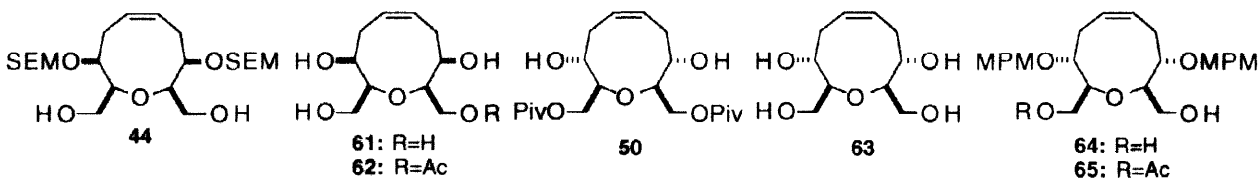
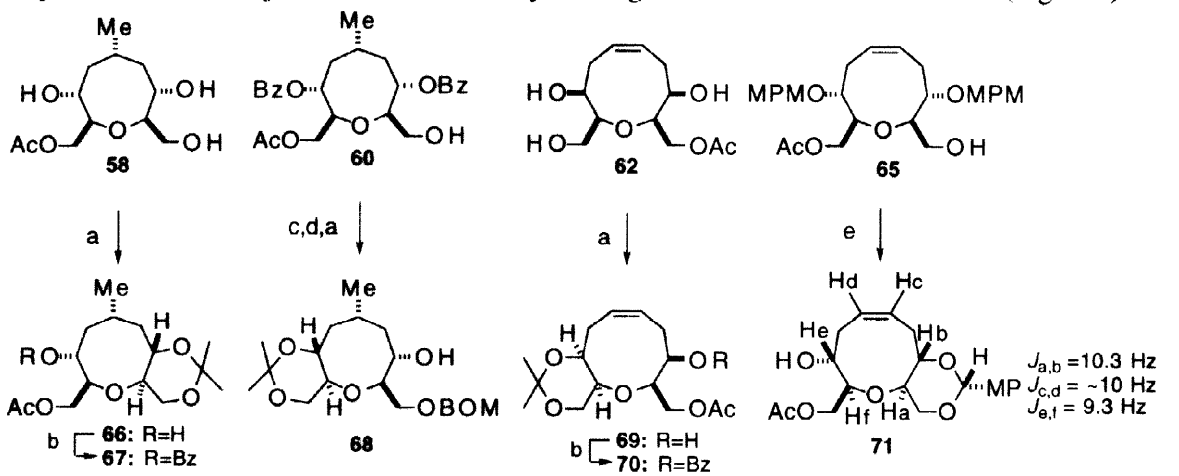


Table 7. Chemoenzymatic asymmetric acylation of hexahydrooxonins.

run	substrate	product	lipase (w/w%)	solvent	temp./°C	time/d	yield/%[a]	ee/%
1	**61**	**62**	AK (66)	benzene	30	0.7	54 (32)[c]	83[e]
2	**61**	**62**	AK (29)	CH_3CN	30	5	91	82[e]
3	**61**	**62**	PS (200)	CH_3CN	30	21	60 (9)[d]	14[e]
4	**64**	**65**	AK (20)	CH_3CN	37	5	55 (45)	96[f]
5	**64**	**65**	AK (20)	THF	37	5	11 (89)	84[f]
6	**64**	**65**	AK (20)	toluene	37	5	44 (56)	85[f]
7	**64**	**65**	AK (20)	benzene	37	5	68 (31)	95[f]
8	**64**	**65**	AK (20)	–[b]	37	5	76 (23)	94[f]

[a]In parentheses indicate the recovered yields of the starting materials. [b]Vinyl acetate was used as a solvent. [c]Diacetetes were obtained in 9% yield. [d]Diacetetes were obtained in 31% yield. [e]Determined by HPLC analysis (CHIRALCEL OD) of the corresponding benzoate derivative **70**. See; Scheme 10. [f]Determined by HPLC analysis (CHIRALCEL OD).

The absolute configurations of these monoacetates were determined by modified Mosher's method.[24] The secondary alcohols (**55** and **56**) were directly converted to the corresponding (*S*)- and (*R*)-α-methoxy-α-trifluoromethylphenylacetyl (MTPA) esters. The triols, **58** and **62**, and primary alcohols, **60** and **65**, were converted to the corresponding acetals, **66**, **69**, **68**, and **71**, respectively (Scheme 10), and the resulting secondary alcohols were subjected to ^{1}H NMR analysis using the modified Mosher's method (Figure 6).



Scheme 10. Reagents and conditions: (a) 2,2-dimethoxypropane, PPTS, CH_3CN. (b) BzCl, DMAP, Py. (c) BOMCl, $^iPr_2NEt$, CH_2Cl_2. (d) K_2CO_3, MeOH. (e) DDQ, CH_2Cl_2, then H_2O.

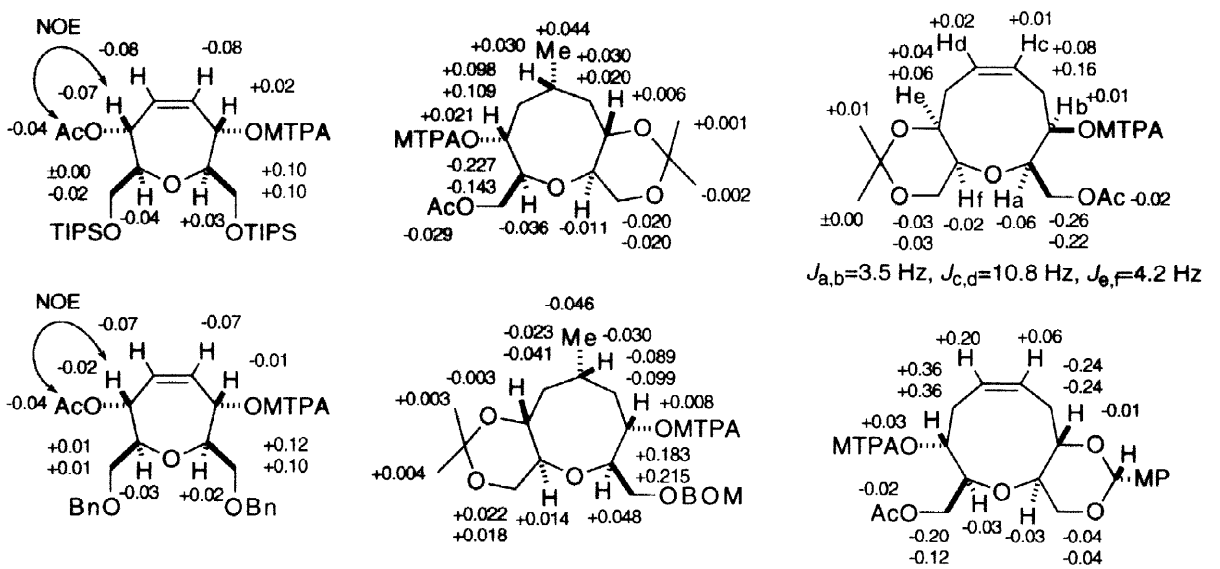


Figure 6. Determination of the absolute configurations of **55**, **56**, **66**, **68**, **69**, and **71** by modified Mosher's method.

Conclusion

The higly stereoselective synthesis of the D(E), I, and F rings of **1** was achieved. The extensive ring-expansion and chemoenzymatic desymmetrization method described in the present paper also provide key chiral building blocks that should be useful for the synthesis of other polyether marine toxins. Further studies directed toward the total synthesis of **1** are currently in progress in our laboratory.

EXPERIMENTAL SECTION

General methods ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 (200 MHz), a Mercury 2000 (200 MHz), an INOVA 500 (500 MHz), a JEOL GX-400 (400 MHz), an Alpha-500 (500 MHz), or a Brucker AM-600 (600 MHz) spectrometer. Chemical shifts are reported in δ (ppm) using chloroform as an internal standard of δ 7.26 and δ 77.00 for ^1H and ^{13}C NMR, respectively. IR spectra were recorded on a JASCO FT/IR-7000, or a Perkin-Elmer Spectrum BX FT-IR spectrometer. Low- and high-resolution mass spectra (MS, HRMS) were recorded on a JEOL HX-110, a JMS-DX303, a JMS-AX500, or a HITACHI M-2500-S instrument. MALDI-TOF MS was recorded on a PerSeptive Biosystem Voyager DE STR SI-3 instrument. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter. Elemental analysis was conducted with a Yanako CHN corder MT-5. Melting points were measured on Ynanagimoto micro-melting point apparatus, and were not corrected. Tetrahydrofuran (THF) was distilled from benzophenone ketyl just prior to use. Dichloromethane (CH_2Cl_2), benzene, toluene, and pyridine were distilled from calcium hydride. Flash column chromatography was performed using E. Merck silica gel 60 (230-400 mesh).

***exo*-6,7-Bis(methanesulfonyloxymethyl)-2-oxabicyclo[2.2.1]hept-4-ene (10).** To a stirred solution of **9** (40.4 g, 0.259 mol) and Et_3N (108 mL, 0.777 mol) in CH_2Cl_2 (500 mL) at 0°C was added dropwise a solution of MsCl (50.1 mL, 0.647 mol) in CH_2Cl_2 (100 mL) over a 80 minutes period, and additional stirring for 30 minutes. The reaction was quenched with saturated aqueous NH_4Cl, and the organic phase was washed with water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by recrystallization from hexane/CH_2Cl_2 to give 64.5 g (0.206 mol, 80%) of **10** as colorless prisms, mp 116-117°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.66-2.85 (2H, m), 3.24 (6H, s), 3.61 (2H, dd, *J*=12.3, 5.3 Hz), 3.76 (2H, dd, *J*=12.3, 3.5 Hz), 3.98-4.10 (2H, m), 4.36-4.62 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.10, 43.49, 65.32, 71.19, 84.03; IR (KBr) ν 3038, 3022, 2978, 2944 cm^{-1}; MS (EI, 70 eV) m/z (%) 312 (M^+, 7), 148 (100); Anal. Calcd for $C_{10}H_{16}O_7S_2$: C, 38.45: H, 5.16: S, 20.53. Found: C, 38.30; H, 5.14; S, 20.69.

(2*R,3*S**,4*R**,5*S**)-3,4-Bis(methanesulfonyloxymethyl)tetrahydrofuran-2,5-dimethanol (11).** Ozone was passed through a stirred solution of **10** (12.0 g, 38.4 mmol) in CH_2Cl_2 (700 mL) and MeOH (140 mL) at -78°C over 100 minutes until a blue coloration persisted. The excess ozone was removed with a stream of nitrogen for 30 minutes. $NaBH_4$ (7.27 g, 0.192 mol) was added to the reaction mixture at -78°C, and the cooling bath was removed. The reaction mixture was slowly warmed to room temperature, and then quenched with 2N HCl (100 mL), and then neutralized with saturated aqueous $NaHCO_3$ (15 mL) at 0°C. The organic layer was separated and the aqueous layer was concentrated under reduced pressure. The residue was purified by recrystallization from water to give 12.4 g (35.6 mmol, 93%) of **11** as colorless prisms, mp 92-94 °C; ^1H NMR (200 MHz, D_2O) δ 2.66-2.85 (2H, m), 3.24 (6H, s), 3.61 (2H, dd, *J*=12.3, 5.3 Hz), 3.76 (2H, dd, *J*=12.3, 3.5 Hz), 3.98-4.10 (2H, m), 4.36-4.62 (4H, m); ^{13}C NMR (50 MHz, D_2O) δ 39.10, 43.49, 65.32, 71.19, 84.03; IR (KBr) ν 3276, 3048, 2952, 2920, 2886 cm^{-1}.

(2*R,3*R**,4*S**,5*S**)-3,4-Bis(iodomethyl)tetrahydrofuran-2,5-dimethanol (12).** A solution of **11** (37.4 g, 0.107 mol) and NaI (63.9 g, 0.429 mol) in acetone (1500 mL) was stirred at reflux for 24 hours. The resulting white precipitates were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by recrystallization from EtOAc to give 39.2 g (95.1 mmol, 89%) of **12** as colorless prisms, mp 97-99°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.66-2.86 (2H, m), 3.14 (2H, dd, *J*=9.9, 7.4 Hz), 3.28 (2H, dd, *J*=9.9, 7.1 Hz), 3.57 (2H, dd, *J*=12.1, 4.0 Hz), 3.84 (2H, dd, *J*=12.1, 2.6 Hz), 3.90-4.00 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 2.24, 46.50, 63.40, 83.51; IR (KBr) ν 2920, 2888, 2838 cm^{-1}; MS (EI, 70 eV)

m/z (%) 412 (M^+, 0.3), 381 (87), 285 (22), 253 (100), 209 (21), 197 (20); Anal. Calcd for $C_8H_{14}O_3I_2$: C, 23.32; H, 3.42; I, 61.60. Found: C, 23.08; H, 3.35; I, 61.23.

(2*R,3*R**,4*S**,5*S**)-2,5-Bis(*tert*-butyldimethylsilyloxymethyl)-3,4-bis(iodomethyl)-tetrahydrofuran (13).** A solution of **12** (31.3 g, 76.0 mmol) in DMF (50 mL) was added imidazole (15.5 g, 0.228 mol) and TBSCl (24.0 g, 0.160 mol), and stirred for an hour. The reaction was added water and extracted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl (15 mL) and saturated aqueous $NaHCO_3$ (15 mL), and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 47.1 g (73.5 mol, 97%) of **13** as colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (12H, s), 0.90 (18H, s), 2.60-2.78 (2H, m), 3.18-3.32 (4H, m), 3.58 (2H, dd, *J*=10.5, 5.5 Hz), 3.67 (2H, dd, *J*=10.5, 4.2 Hz), 3.88 (2H, dd, *J*=5.5, 4.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.39, 3.14, 18.31, 25.96, 48.35, 65.37, 82.86; IR (film) ν 2958, 2932, 2898, 2860 cm^{-1}; MS (EI, 70 eV) m/z (%) 583 (M^+-^{t}Bu, 4), 582 (11), 455 (11), 450 (15), 328 (23), 327 (71), 311 (12), 297 (41); Anal. Calcd for $C_{20}H_{42}O_3I_2Si_2$: C, 37.50; H, 6.61; I, 39.62. Found: C, 37.76; H, 6.40; I, 39.76.

(2*R,5*S**)-2,5-Bis(*tert*-butyldimethylsilyloxymethyl)-3,4-dimethylene-2,5-dihydrofuran (14).** A solution of **13** (6.47 g, 10.1 mmol) and DBU (4.53 mL, 30.3 mmol) in THF (100 mL) was stirred at reflux for 2 hours. The resulting precipitates were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by florisil column chromatography (hexane/EtOH=20/1) to give 3.14 g (9.1 mmol, 90%) of **14** (To prevent polymerization of diene **14**, the elute of the chromatography was directly subjected to following photo-reaction) as colorless oil; UV (hexane) λmax 245nm (ε 6800); ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (12H, s), 0.90 (18H, s), 3.65 (2H, dd, *J*=10.4, 5.3 Hz), 3.73 (2H, dd, *J*=10.4, 5.3 Hz), 4.50-4.64 (2H, m), 5.02 (4H, d, *J*=1.8 Hz), 5.46 (4H, d, *J*=2.4Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.30, 18.42, 25.96, 66.92, 81.91, 103.88, 146.16; IR (film) ν 2960, 2932, 2888, 2862, 1473, 1464, 1427 cm^{-1}; MS (EI, 70 eV) m/z(%) 384 (M^+, 3), 327 (100), 235 (12), 195 (52), 165 (15), 147 (17), 115 (10); HRMS (EI, 70 eV) calcd for $C_{20}H_{40}O_3Si_2$ (M^+) 384.2516, found 384.2521.

(2*S,4*R**)-2,4-Bis(*tert*-butyldimethylsilyloxymethyl)-3-oxabicyclo[3.2.0]hept-1(5)-ene (15).** A solution of **14** (ca. 10.1 mmol) in hexane-EtOH (20:1, 800mL) was transferred into the quartz vessel, which was irradiated by a low pressure mercury lamp (160W) for 15 hours with a stream of nitrogen at room temperature. The residue was purified by florisil column chromatography to give 3.50 g (9.09 mmol, 90%) of **15** as colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (12H, s), 0.89 (18H, s), 2.70 (4H, d, *J*=1.4 Hz), 3.57 (2H, dd, *J*=10.2, 5.4 Hz), 3.69 (2H, dd, *J*=10.2, 5.2 Hz), 4.63-4.76 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.34, 18.29, 25.88, 27.07, 66.13, 84.21, 147.97; IR (film) ν 2960, 2932, 2888, 2862 cm^{-1}; MS (EI, 70eV) m/z (%) 327 (M^+-^{t}Bu, 6), 239 (16), 211 (4), 195 (15), 147 (13); Anal. Calcd for $C_{20}H_{40}O_3Si_2$: C, 62.44; H, 10.48. Found: C, 62.02; H, 10.08.

(2*S,7*R**)-2,7-Bis(*tert*-butyldimethylsilyloxymethyl)oxepan-3,6-dione (16).** Ozone was passed through a stirred solution of **15** (3.50 g, 9.10 mmol) in CH_2Cl_2 (90 mL) at -78°C over 15 minutes until a blue coloration persisted. The excess ozone was removed with a stream of nitrogen for 10 minutes. The reaction mixture was added Ph_3P (3.58 g, 0.136 mmol) at -78°C, and the cooling bath was removed. The reaction mixture was warmed to room temperature with stirring, concentrated under reduced pressure. The residue was purified by florisil column chromatography (hexane/EtOAc=20/1) to give 2.20 g (5.28 mmol, 58%) of **16** as colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.06 (6H, s), 0.86 (18H, s), 2.30-2.52 (2H, m, AA'BB'), 3.15-3.35 (2H, m, AA'BB'), 3.86-4.02 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.57, -5.38, 18.25, 25.79, 37.49, 65.00, 88.22, 212.13; IR (film) 2958, 2932, 2888, 2862, 1731, 1717 cm^{-1}; MS (EI, 70

eV) m/z (%) 359 (M^+-^{t}Bu, 20), 341 (3), 329 (4), 315 (5), 267 (6), 201 (25), 171 (30), 157 (11); HRMS (EI, 70 eV) calcd for $C_{16}H_{31}O_5Si_2$ (M^+-^{t}Bu, 20) 359.1708, found 359.1707.

(2*S,3*S**,6*R**,7*R**)-2,7-Bis(*tert*-butyldimethylsilyloxymethyl)oxepan-3,6-diol (17).** To a stirred solution of DIBAL in hexane (1.7 M, 288 μL) was added in dropwise a solution of **16** (40.0 mg, 96 μmol) in CH_2Cl_2 (1.6 mL) at -78°C and stirred for 30 minutes. The reaction was quenched with MeOH and saturated aqueous Rochelle salt (1 mL), then extracted with EtOAc. The organic phase was washed with brine and dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography to give 21.0mg (49.9 μmol, 52%) of **17** and its diastereomer ***dl*-18** 4.4 mg (10.6 μmol, 11%) as colorless feathers (hexane), mp 86°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (12H, s), 0.89 (18H, s), 1.70-1.92 (2H, m), 1.94-2.15 (2H, m), 3.42 (2H, ddd, *J*=5.5, 4.8, 1.2 Hz), 3.65 (2H, d, *J*=6.6 Hz), 3.76 (2H, dd, *J*=10.0, 4.8 Hz), 3.81 (2H, dd, *J*=10.0, 5.5 Hz), 4.00-4.10 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.49, 18.17, 25.78, 29.51 , 64.94, 70.26, 82.43; IR (KBr) ν 3448, 2932, 2862 cm^{-1}; MS (EI, 70 eV) m/z (%) 421 (M^+, 1), 405 (M^+-CH_3, 4), 365 (13), 364 (31), 363 (100), 327 (16), 213 (17), 195 (23), 187 (38), 169 (14), 157 (53), 143 (16); Anal. Calcd for $C_{20}H_{44}O_5Si_2$: C, 57.10; H, 10.54. Found C, 56.91; H, 10.25. ***dl*-18:** colorless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.068 (6H, s), 0.083 (3H, s), 0.088 (3H, s), 0.89 (9H, s), 0.90 (9H, s), 1.58-1.64 (1H, m), 1.67-1.73 (1H, m), 2.05-2.20 (2H, m), 2.40 (2H, d, *J*=6.5 Hz), 2.96-2.98 (1H, m), 3.38 (1H, ddd, *J*=5.0, 4.5, 3.0 Hz), 3.58-3.61 (2H, m), 3.71 (1H, dd, *J*=5.5, 3.0 Hz), 3.75 (1H, dd, *J*=5.5, 3.0Hz), 3.86 (1H, dd, *J*=5.0, 3.0 Hz), 3.87-3.90 (1H, m), 4.00-4.02 (1H, m); IR (KBr) ν 3450, 2932, 2862 cm^{-1}.

(2*S,3*R**,6*S**,7*R**)-2,7-Bis(*tert*-butyldimethylsilyloxymethyl)-3,6-diiodooxepane (19).** To a stirred solution of **17** (232 mg, 0.552 mmol), Ph_3P (582 mg, 2.22 mmol), and imidazole (189 mg, 2.78 mmol) in benzene (3 mL) was added in dropwise a solution of I_2 (704 g, 2.78 mmol) in toluene (3 mL) over 10 minutes at room temperature and stirred for 30 minutes. The resulting precipitates were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 308 mg (0.481 mmol, 87%) of **19** as colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (12H, s), 0.89 (18H, s), 2.15-2.47 (4H, m), 3.75 (2H, ddd, *J*=10.0, 4.4, 2.2 Hz), 3.85 (2H, dd, *J*=10.9, 4.4 Hz), 3.81 (2H, dd, *J*=10.9, 2.2 Hz), 4.25-4.45 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.33, -5.19, 18.35, 25.93, 30.50, 37.14, 64.34, 89.68; IR (film) ν 2930, 2860 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{32}O_3Si_2I_2$ (M^+-^{t}Bu) 581.9980, found 581.9987.

(2*R,7*S**)-2,7-Bis(*tert*-butyldimethylsilyloxymethyl)-2,7-dihydrooxepine (20).** A solution of **19** (1.48 g, 2.31 mmol) and DBU (1.38 mL, 9.22 mmol) in THF (25 mL) was refluxed for 2 hours. The resulting precipitates were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 860 mg (2.24 mmol, 97%) of **20** as colorless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.05 (12H, s), 0.88 (18H, s), 3.54 (2H, dd, *J*=10.0, 7.1 Hz), 3.81 (2H, dd, *J*=10.0, 6.5 Hz), 4.40 (2H, bt, *J*=7.0 Hz), 5.83-6.00 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.33, -5.23, 18.31, 25.89, 65.17, 80.69, 125.58, 135.92; IR (film) ν 2958, 2932, 2888, 2862 cm^{-1}; MS (EI, 70 eV) m/z (%) 384 (M^+, 4), 327 (100), 195 (66), 171 (30), 169 (22), 147 (37); HRMS (EI, 70 eV) calcd for $C_{20}H_{40}O_3Si_2$ (M^+) 384.2516, found 384.2512.

(2*S,3*R**,6*S**,7*R**)-2,7-Bis(*tert*-butyldimethylsilyloxymethyl)-2,3,6,7-tetrahydrooxepin-3,6-diol (21).** A solution of **20** (860 mg, 2.24 mmol) and TPP (14 mg, 22.8 μmol) in $CHCl_3$ (400 mL) was irradiated by a high pressure mercury lamp (200W) for 1.5 hours with a stream of oxygen at 0°C. The reaction mixture was concentrated under reduced pressure, and the residue was purified by florisil column chromatography to give endo-peroxide. The endo-peroxide was dissolved in MeOH (25 mL) and hydrogenated

with Lindlar catalyst (49.0 mg, 23 μmol) under 3 kg/cm^2 for 10 hours. The catalyst was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 460 mg (1.10 mmol, 48%) of **21** as colorless needles (hexane), mp 90.5-92.0°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (12H, s), 0.87 (12H, s), 3.43 (2H, ddd, *J*=8.5, 6.5, 5.1 Hz), 3.60 (2H, d, *J*=2.4 Hz), 3.69 (2H, dd, *J*=10.2, 6.5 Hz), 3.82 (2H, dd, *J*=10.2, 5.1 Hz), 4.28 (2H, bd, *J*=8.5 Hz), 5.60 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.61, 18.08, 25.72, 66.29, 73.54, 82.53, 132.32; IR (KBr) ν 3298, 2932, 2860 cm^{-1}. MS (EI, 70 eV) m/z (%) 361 (M^+-^{t}Bu, 77), 284 (15), 211 (21), 199 (12), 187 (10), 169 (47), 117 (100); HRMS (EI, 70 eV) calcd for $C_{16}H_{40}O_3Si_2$ (M^+-^{t}Bu) 361.1867, found 361.1863.

(2*S,7*R**)-2,7-Bis(triisopropylsilyloxymethyl)oxepan-3,6-dione (22).** Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.04 (42H, s), 2.30-2.56 (2H, m, AA'BB'), 3.20-3.45 (2H, m, AA'BB'), 3.91 (2H, t, *J*=3.2 Hz), 4.04-4.13 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.30, 18.32, 38.07, 65.96, 88.94, 212.76; IR (film) 2944, 2870, 1717 cm^{-1}; MS (EI, 70 eV) m/z (%) 457 (M^+-^{i}Pr, 100), 283 (11), 173 (33), 103 (26); HRMS (EI, 70 eV) calcd for $C_{23}H_{45}O_5Si_2$ (M^+-^{i}Pr) 457.2806, found 457.2804; Anal. Calcd for $C_{26}H_{52}O_5Si_2$: C, 62.35; H, 10.46. Found: C, 62.12; H, 10.58.

(2*S,7*R**)-2,7-Bis(triisopropylsilyloxymethyl)-2,7-dihydrooxepin-3,6-dione (23).** To a stirred solution of **22** (506 mg, 1.01 mmol) and TMSCl (641 μL, 5.05 mmol) in THF (30 mL) was added a solution of LDA (0.1M, 26 mL) in THF at -78°C over 30 minutes. The reaction mixture was added a solution of Et_3N (20% in hexane) and warmed to room temperature with stirring. The resulting precipitates were filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in THF (40 mL), then added propyrene oxide (700 μL, 10.1 mmol) and NBS (176 mg, 1.01 mmol) in THF (3 mL) at -78°C. The reaction mixture was stirred for 40 minutes, and then warmed to room temperature. Et_3N (1.5 mL, 10.6 mmol) was added to the reaction mixture and stirred for 12 hours, then quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the organic layer was extracted with EtOAc. The combined organic layer was washed with brine, and dried over $MgSO_4$. Concentration followed by florisil column chromatography gave 409 mg (820 mmol, 81%) of **23** as pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.04 (42H, s), 4.00-4.26 (6H, m), 6.50 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.35, 18.36, 63.51, 88.65, 137. 49, 185.26; IR (film) 2946, 2894, 2870, 1690 cm^{-1}; MS (EI, 70 eV) m/z(%) 455 (M^+-^{i}Pr, 12), 279 (60), 239 (20), 167 (49), 149 (100); HRMS (EI, 70 eV) calcd for $C_{23}H_{43}O_5Si_2$ (M^+-^{i}Pr) 455.2649, found 455.2664.

(2*S,3*R**,6*S**,7*R**)-2,7-Bis(triisopropylsilyloxymethyl)-2,3,6,7-tetrahydrooxepin-3,6-diol (24).** To a stirred solution of **23** (409 mg, 820 μmol) in CH_2Cl_2 (12 mL) was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (2 mL) and Et_3SiH (1.3 mL, 8.2 mmol) at -78°C. The reaction mixture was poured into the vigorously stirred solution of $NaHCO_3$ through cannular. The resulting precipitates was dissolved by the addition of water. The reaction mixture was extracted with EtOAc and the organic layer was washed with saturated aqueous NH_4Cl and brine, and dried over $MgSO_4$. Concentration followed by silica gel column chromatography gave 460 mg (1.10 mmol, 48%) of **24** as colorless needles (hexane), mp 90.5-92.0°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (12H, s), 0.87 (12H, s), 3.43 (2H, ddd, *J*=8.5, 6.5, 5.1 Hz), 3.60 (2H, d, *J*=2.4 Hz), 3.69 (2H, dd, *J*=10.2, 6.5 Hz), 3.82 (2H, dd, *J*=10.2, 5.1 Hz), 4.28 (2H, bd, *J*=8.5 Hz), 5.60 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.61, 18.08, 25.72, 66.29, 73.54 , 82.53, 132.32; IR (KBr) ν 3298, 2932, 2860 cm^{-1}; MS (EI, 70 eV) m/z (%) 361 (M^+-^{t}Bu, 77), 284 (15), 211 (21), 199 (12), 187 (10), 169 (47), 117 (100); HRMS (EI, 70 eV) calcd for $C_{16}H_{40}O_3Si_2$ (M^+-^{t}Bu) 361.1867, found 361.1863.

(4a*R,5a*S**,9a*R**,11a*S**)-2,2,8,8-Tetramethyl-4,4a,5a,6,9a,11a-hexahydro-*m*-dioxino**

[4',5':6,7]oxepino[3,2-*d*]-*m*-dioxin (26). A solution of **24** (10 mg, 24 μmol), *p*-TsOH•H_2O (0.9 mg, 5 μmol), and 2,2-dimethoxypropane (12 μL, 96 μmol) in acetone (0.3 mL) was stirred for 4.5 hours at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The organic layer was washed with aqueous saturated NH_4Cl and brine, and dried over $MgSO_4$. Concentration followed by silica gel column chromatography gave 6.3 mg (23 μmol, 97 %) of **26** as colorless needles (hexane), mp 91.5-92.0°C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83-0.87 (2H, m), 0.85-0.91 (1H, m), 1.15 (3H, d, *J*=5.7 Hz), 1.40 (6H, s), 1.43 (6H, s), 3.24 (2H, ddd, *J*=8.8, 5.5, 2.3 Hz), 3.39 (2H, ddd, *J*=8.8, 8.0, 6.1 Hz), 3.55 (2H, dd, *J*=12.0, 8.0 Hz), (2H, dd, *J*=12.0, 6.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.78, 28.69, 62.48, 73.17, 74.31, 98.39, 132.41; IR (KBr) ν 3036, 3000, 2946, 2892, 2842 cm^{-1}; MS (EI, 70 eV) m/z (%) 270 (M^+, 0.4), 255 (10), 212 (7), 195 (3), 168 (6), 167 (6), 129 (8), 128 (5); HRMS (EI, 70 eV) calcd for $C_{13}H_{19}O_5$ (M^+-Me) 255.1231, found 255.1238.

(1*S,2*S**,3*R**,5*S**,6*R**,7*R**,8*R**)-3,5-Bis(*tert*-butyldimethylsilyloxymethyl)-8-methyl-4-oxabicyclo[5.1.0]octan-2,6-diol (27).** A solution of **21** (22.9 mg, 54.7 μmol) in benzene (5.5mL) was added a 0.98 M solution of Et_2Zn in hexane (375 μL, 383 μmol) and CH_3CHI_2 (51.9 μL, 547 μmol). The reaction mixture was refluxed for 22 hours, then cooled to 0°C. The reaction was quenched with saturated aqueous $NaHCO_3$, and the organic layer was washed with brine, and dried over anhydrous $MgSO_4$. Concentration followed by silica gel column chromatography gave 8.8 mg (19.7 μmol, 36 %) of **26**, and 8.7 mg (20.7 μmol, 38 %) of **21** was recovered. Colorless powder; ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.89 (18H, s), 1.10-1.18 (2H, m), 1.10-1.18 (1H, m), 1.15-1.20 (3H, m), 3.05 (2H, dt, *J*=10.3, 5.9 Hz), 3.16 (2H, d, *J*=3.5 Hz), 3.68 (2H, dd, *J*=10.3, 5.9 Hz), 3.77 (2H, dd, *J*=10.3, 5.9 Hz) 4.01-4.10 (2H, m).

(1*S,2*S**,3*R**,5*S**,6*R**,7*R**,8*R**)-2,6-Bis(acetyloxy)-3,5-bis(triisopropylsilyloxymethyl)-8-methyl-4-oxabicyclo[5.1.0]octane (28).** A solution of **27** (4.3 mg, 9.6 μmol), acetic anhydride (91 μL, 960 μmol), and DMAP (0.1 mg, 1.0 μmol) in pyridine (0.5 mL) was stirred for 15 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give 3.8 mg (7.2 μmol, 75%) of **28** as colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.03 (6H, s), 0.87 (18H, s), 1.04 (3H, d, *J*=5.6 Hz), 1.18-1.23 (1H, m), 1.23-1.26 (2H, m), 3.19 (2H, ddd, *J*=10.0, 4.9, 2.3 Hz), 3.60 (2H, dd, *J*=10.9, 4.9 Hz), 3.68 (2H, dd, *J*=10.9, 2.3 Hz), 5.23 (2H, dt, *J*=10.0, 1.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ -5.45, -5.40, 9.55, 18.27, 19.09, 21.27, 25.85, 64.12, 71.15, 76.79; IR (film) ν 2932, 2860, 1742 cm^{-1}.

(4a*R,5a*S**,9a*R**,10*S**,11*S**,12*R**,12a*S**)-2,2,8,8,11-Pentamethyl-*m*-dioxano[4',5':6,7]cyclopropano[1",2":4,5]oxepano[3,2-d]-*m*-dioxane (29).** To a stirred solution of **26** (24.6 mg, 91.0 μmol) and $Pd(OAc)_2$ (2.0 mg, 9.1 μmol) in EtOAc (3.0 mL) was added in dropwise a solution of CH_3CHN_2 in ether (2.0 mL), and stirred for 10 minutes at room temperature. The catalyst was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 10.3 mg (34.5 μmol, 38 %) of **29**, and 15.5 mg (57.4 μmol, 62%) of **26** was recovered. Colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.83-0.87 (2H, m), 0.85-0.91 (1H, m), 1.15 (3H, d, *J*=5.7 Hz), 1.40 (6H, s), 1.43 (6H, s), 3.24 (2H, ddd, *J*=8.8, 5.5, 2.3 Hz), 3.39 (2H, ddd, *J*=8.8, 8.0, 6.1 Hz), 3.55 (2H, dd, *J*=12.0, 8.0 Hz), 3.87 (2H, dd, *J*=12.0, 6.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.35, 19.92, 23.41, 25.71, 27.80, 62.61, 75.81, 76.30, 98.40; IR (film) ν 2996, 2926, 2884 cm^{-1}; MS (EI, 70 eV) m/z (%) 283 (M^+-Me, 17), 240 (4), 182 (33), 139 (18), 112 (18), 97 (11), 70 (100); HRMS (EI, 70 eV) calcd for $C_{15}H_{23}O_5$ (M^+-Me) 283.1544, found 283.1573.

(2*S,3*R**,6*S**,7*R**)-2,7-Bis(triisopropylsilyloxymethyl)-3,6-bis(benzyloxymethyloxy)-2,3,6,7-tetrahydrooxepin (32c).** A solution of diol **24** (940 mg, 1.87 mmol) in CH_2Cl_2 (15 mL) was added $^iPr_2NEt$ (2.28 mL, 13.1 mmol) and BOMCl (1.04 mL, 7.48 mmol). The reaction mixture was stirred for 11 hours at 40°C and diluted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$. Concentration followed by silica gel column chromatography gave 1.39 g (1.87 mmol, quant.) of **32c** as colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00-1.15 (42H, m), 3.70 (2H, dd, *J*=11.7, 5.1 Hz), 3.76 (2H, dd, *J*=11.7, 4.7 Hz), 4.04 (2H, ddd, *J*=6.4, 5.1, 4.7 Hz), 4.34 (2H, brd, *J*=6.4 Hz), 4.56 (2H, d, *J*=11.9 Hz), 4.68 (2H, d, *J*=11.9 Hz), 4.86 (4H, m), 4.86 (2H, m), 5.95 (2H, dd, *J*=2.7, 0.9 Hz), 7.25-7.40 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.95, 17.96, 64.05, 69.44, 75.01, 81.14, 94.05, 127.59, 127.71, 128.36, 130.68, 137.81; IR (film) ν 2946, 2868 cm^{-1}; MS (EI, 70 eV) m/z (%) 699 (M^+-^{i}Pr, 5), 471 (12), 441 (17), 410 (10), 225 (15), 173 (56), 157 (16), 149 (18), 145 (20), 107 (15), 92 (54), 91 (100); HRMS (EI, 70 eV) calcd for $C_{15}H_{23}O_5$ (M^+-^{i}Pr) 699.4109, found 699.4131.

(1*R,2*S**,3*R**,5*S**,6*R**,7*S**,8*R**)-2,6-Bis(benzyloxymethyloxy)-3,5-bis(triisopropylsilyl oxymethyl)-8-methyl-4-oxabicyclo[5.1.0]octane (33c).** To a stirred solution of **32c** (33.0 mg, 44.5 μmol) and $Pd(OAc)_2$ (3.0 mg, 13.4 μmol) in EtOAc (2.5 mL) was added in dropwise a solution of CH_3CHN_2 in Et_2O (1 mL), and stirred for 2 hours at room temperature. The catalyst was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. After repeating this procedure three times, the residue was purified by silica gel column chromatography to give 30.9 mg (40.1 μmol, 90%) of **33c** as colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.76 (2H, td, *J*=5.4, 2.2 Hz), 0.94 (1H, quintet, *J*=5.5 Hz), 1.03-1.12 (9H, m), 1.06 (36H, bs), 3.32 (2H, ddd, *J*=8.3, 5.4, 2.2 Hz), 3.47 (2H, ddd, *J*=8.3, 5.7, 2.5 Hz), 3.79 (2H, dd, *J*=10.6, 5.7 Hz), 4.03 (2H, dd, *J*=10.6, 2.5 Hz), 4.62 (4H, s), 4.81 (2H, d, *J*=6.6 Hz), 4.91 (2H, d, *J*=6.6 Hz), 7.27-7.37 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.06, 17.96, 18.06, 22.89, 26.65, 64.08, 69.34, 78.82, 85.31, 92.69, 127.58, 127.77, 128.37, 137.88; IR (film) ν 2944, 2892, 2868 cm^{-1}; MALDI-TOF MS (alpha) calcd for $C_{44}H_{74}O_7Si_2Na$ ($M+Na^+$) 793.4871, found 793.527.

(1*R,2*S**,3*R**,5*S**,6*R**,7*S**,8*R**)-3,5-Bis(triisopropylsilyloxymethyl)-8-methyl-4-oxabicyclo[5.1.0]octan-2,6-diol (34).** A solution of **33c** (1.38 g, 1.80 mmol) in EtOAc (8 mL) was added 20% $Pd(OH)_2/C$ (192 mg, 180 μmol) and stirred for 30 hours under hydrogen atmosphere (1 kg/cm^2) at room temperature. The catalyst was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to give 716 mg (1.35 mmol, 75 %) of **34** as colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.82 (2H, ddd, *J*=5.6, 5.1, 2.4 Hz), 0.92-0.97 (1H, m), 1.06 (36H, bs), 1.08-1.14 (6H, m), 1.17 (3H, d, *J*=6.0 Hz), 3.33 (2H, dddd, *J*=8.4, 5.6, 2.4, 2.2 Hz), 3.42 (2H, ddd, *J*=8.4, 5.2, 4.3 Hz), 3.86 (2H, dd, *J*=10.6, 5.4 Hz), 3.96 (2H, d, *J*=2.2 Hz), 3.97 (2H, dd, *J*=10.6, 4.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.70, 11.85, 18.51, 23.01, 27.85, 66.56, 77.93, 82.58; IR (film) ν 3438, 2946, 2870 cm^{-1}; MS (EI, 70 eV) m/z (%) 487 (M^+-^{i}Pr, 4), 469 (66), 451 (27), 313 (18), 295 (28), 269 (35), 253 (19), 251 (12); HRMS (FAB) calcd for $C_{28}H_{57}O_4Si_2$ (M^+-OH) 513.3796, found 513.3818.

(2*S,3*R**,5*R**,7*S**,8*R**)-5-Methyl-2,8-bis(triisopropylsilyloxymethyl)oxocan-3,7-diol (35).** A solution of **34** (248 mg, 467 μmol) in cyclohexane (8 mL) was added 5% $Rh\text{-}Al_2O_3$ (57 mg, μmol) and stirred for 6 days under hydrogen atmosphere (5 kg/cm^2). The catalyst was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to give 202 mg (379 μmol, 82 %) of **35** as colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 1.06 (3H, d, *J*=7.2 Hz), 1.07 (36H, s), 1.07-1.17 (6H, m), 1.69 (2H, ddd, *J*=14.3, 10.5, 8.0 Hz), 1.84 (2H, ddd, *J*=14.3, 3.5, 1.8 Hz), 1.86-1.92 (1H, m), 3.45 (2H, ddd, *J*=9.0, 7.4, 4.9 Hz),

3.50 (2H, d, J=1.8 Hz), 3.70 (2H, ddq, J=10.5, 9.0, 1.8 Hz), 3.77 (2H, dd, J=10.1, 7.4 Hz), 3.90 (2H, dd, J=10.1, 4.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.72, 17.89, 27.32, 27.57, 46.53, 67.53, 74.99, 85.11; IR (film) ν 3456, 2948, 2870 cm^{-1}; MS (EI, 70 eV) m/z (%) 489 (M^+-^{i}Pr, 6), 471 (5), 453 (4), 315 (13), 297 (20), 279 (20), 271 (34), 253 (14). **Triacetate derivative of *dl*-36.** ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (3H, d, J=6.5 Hz), 1.53 (1H, dddd, J=14.1, 13.8, 5.0, 1.3 Hz), 1.69 (1H, dd, J=14.1, 4.8 Hz), 1.92 (1H, dd, J=13.8, 5.2 Hz), 1.96 (1H, ddd, J=13.8, 12.0, 1.8 Hz), 2.05 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 2.52-2.59 (1H, m), 4.01 (1H, dd, J=11.6, 9.0,5.2 Hz), 4.04 (1H, dd, J=12.5, 8.3 Hz), 4.08 (1H, dd, J=11.6, 7.1 Hz), 4.13-4.16 (1H, m), 4.23-4.26 (1H, m), 4.28-4.31 (1H, m), 4.30 (2H, dd, J=12.5, 2.7 Hz).

Methyl (2*S,4*R**,7*S**,8*R**)-2,4-bis(*tert*-butyldimethyloxymethyl)-3-oxabicyclo[4.3.0]non-1(5)-ene-7,8-dicarboxylate (37).** A mixture of **14** (18.6 mmol) and maleic anhydride (1.82 g, 18.6 mmol) in Et_2O (150 mL) was refluxed for 5 hours. The solvent was removed under reduced pressure, and the residue was added THF (80 mL) and water (8 mL), and stirred for 11 hours at room temperature. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O and dried over anhydrous $MgSO_4$. The organic phase was cooled to 0°C, then added a solution of CH_2N_2 in Et_2O. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give 7.95g (15 mmol, 81%) of **37** as colorless solid, mp 61-63°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.04 (6H, s), 0.87 (18H, s), 2.38 (2H, bdd, J=16.0, 5.5 Hz), 2.52 (2H, bdd, J=16.0, 5.0 Hz), 3.09 (2H, bt, J=5.5 Hz), 3.61 (2H, dd, J=10.5, 5.0 Hz), 3.67 (2H, dd, J=10.5, 4.5 Hz), 3.69 (6H, s), 4.59 (2H, bs); ^{13}C NMR (150 MHz, $CDCl_3$) δ -5.46, -5.43, 18.22, 23.35, 25.87, 40.26, 51.95, 65.68, 87.12, 132.08, 173.41; IR (film) ν 2956, 2932, 2860, 1742 cm^{-1}; MS (EI, 70 eV) m/z (%) 497 (M^+-OMe, 4), 471 (7), 383 (14), 339 (9), 325 (4), 309 (5), 279 (7), 251 (100); HRMS (FAB) calcd for $C_{26}H_{49}O_7Si_2$ (M^++H) 529.3017, found 529.3019.

Methyl (2*S,5*S**,6*R**,9*R**)-2,9-bis(*tert*-butyldimethyloxymethyl)-3,8-dioxooxonan-5,6-dicarboxylate (38).** To a solution of **37** (11.9 mg, 22.5 μmol) in 1,3-dioxane (2 mL) was added OsO_4 (2.2 mg, 4.5 μmol) and 60% NMO in water (24 μl, 120 μmol), and stirred for 43 hours at 80°C. The reaction was quenched with $Na_2S_2O_5$ (220mg, 1.16 mmol) and stirred for 23 hours at 40°C. The precipitates were removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 12.2 mg (21.7 μmol, 96%) of diol (a mixture of two diastereomers). The diol (16.8 mg, 29.8 μmol) was dissolved in pyridine (1 mL) and added $Pb(OAc)_4$ (22.1 mg, 44.8 μmol), and stirred for 5 minutes at room temperature. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give 15.7 mg (28.0 μmol, 94%) of diketone **38** as colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.05 (6H, s), 0.87 (18H, s), 2.61 (2H, dd, J=14.0, 6.0 Hz), 3.24 (2H, dd, J=14.0, 4.5 Hz), 3.58-3.97 (8H, m), 3.71 (6H, s).

Methyl (2*S,3*S**,5*S**,6*R**,8*R**,9*R**)-2,9-bis(*tert*-butyldimethyloxymethyl)-3,8-dihydroxy oxonan-5,6-dicarboxylate (39).** The diketone **38** (15.7 mg, 28.0 μmol) was dissolved in MeOH (1 mL) and added $NaBH_4$ (3.0 mg, 79 μmol) at 0°C. After stirring for 20 minutes, the reaction was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$. Concentration followed by silica gel column chromatography gave 14.8 mg (26.2 μmol, 94%) of **39** as a single diastereomer. Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.058 (6H, s), 0.062 (6H, s), 0.88 (18H, s), 1.79 (2H, ddd, J=15.5, 7.0, 0.5 Hz), 2.61 (2H, ddd, J=15.5, 8.0, 4.5 Hz), 2.77 (2H, d, J=4.0 Hz), 3.36 (2H, td, J=6.0, 1.0 Hz), 3.66 (6H, s), 3.78 (2H, dd, J=11.0, 6.0 Hz), 3.80 (2H, dd, J=11.0, 6.0 Hz), 3.84 (2H, bs), 4.14 (2H, bd, J=8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ -5.52, -5.46, 18.19, 25.85, 31.46, 40.07, 52.00, 64.76, 68.05, 88.40, 176.19; IR (film) ν 3502, 2956, 2932, 2862, 1736 cm^{-1}; MS (EI,

70 eV) m/z (%) 565 (M^++H, 0.5), 533 (2), 507 (2), 475 (28), 457 (5); HRMS (EI, 70 eV) calcd. for $C_{26}H_{53}O_9Si_2$ (M^++H) 565.3225, found 565.3217.

Methyl (2*S,3*S**,5*S**,6*R**,8*R**,9*R**)-2,9-bis(*tert*-butyldimethyloxymethyl)-3,8-bis(trimethylsilylethoxymethoxy)oxonan-5,6-dicarboxylate (40).** To a mixture of **39** (2.77 g, 4.90 mmol), Bu_4NI (5.43 g, 14.7 mmol), and $^iPr_2NEt$ (8.5 mL, 49 mmol) was added SEMCl (2.8 mL, 16 mmol) at 0°C and stirred for 22 hours at room temperature. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl and brine, then dried over $MgSO_4$. Concentration followed by silica gel column chromatography gave 3.62 g (4.39 mmol, 89%) of **40** as colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 0.00 (18H, s), 0.044 (6H, s), 0.047 (6H, s), 0.85-0.97 (4H, m), 0.88 (18H, s), 1.68 (2H, bq, *J*=8.0 Hz), 2.68 (2H, bs), 3.34 (2H, bt, *J*=6.0 Hz), 3.61 (6H, s), 3.63 (2H, dd, *J*=10.0, 6.5 Hz), 3.66 (2H, dd, *J*=10.0, 6.0 Hz), 3.68 (2H, dd, *J*=10.0, 6.0 Hz), 3.72 (2H, dd, *J*=10.0, 6.5 Hz), 3.75 (2H, bs), 4.04 (2H, bd, *J*=8.5 Hz), 4.61 (2H, d, *J*=7.0 Hz), 4.78 (2H, d, *J*=7.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ -5.23, -5.24, -1.45, -1.42, 14.11, 18.07, 18.19, 25.94, 31.58, 51.68, 63.19, 65.76, 72.02, 89.37, 94.35, 175.37; IR (film) ν 2956, 2934, 2862, 1738 cm^{-1}.

(2*S,3*S**,5*S**,6*R**,8*R**,9*R**)-2,9-Bis(*tert*-butyldimethyloxymethyl)-3,8-bis(trimethylsilyl ethoxymethoxy)oxonan-5,6-dicarboxylic acid (41).** The SEM ether **40** (134 mg, 0.174 mmol) in ^tBuOH (1.4 mL) was added water (0.4 mL), $LiOH•H_2O$ (27.2 mg, 0.648 mmol), and Bu_4NBr (10.7 mg, 33.2 μmol), and stirred for one week at room temperature. The reaction mixture was added saturated aqueous NH_4Cl (pH6), and extracted with EtOAc. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to give 123 mg (0.166 mol, 95%) of **41** as colorless solid; ^1H NMR (200 MHz, $CDCl_3$) δ 0.00 (18H, s), 0.06 (12H, s), 0.89 (18H, s), 0.80-0.98 (4H, m), 1.75 (2H, bs), 2.60 (2H, bs), 3.36 (2H, bt, *J*=7.0 Hz), 3.53-3.80 (10H, m), 4.09 (2H, bd, *J*=8.0 Hz), 4.68 (2H, d, *J*=7.0 Hz), 4.82 (2H, d, *J*=7.0 Hz); IR (film) ν 3600-2300, 2956, 1715 cm^{-1}.

(2*S,3*S**,8*R**,9*R**)-(*Z*)-2,9-Bis(*tert*-butyldimethyloxymethyl)-3,8-bis(trimethylsilylethoxymethoxy)oxon-5-ene (42).** A solution of **41** (3.6 mg, 4.5 μmol) in benzene (1 mL) was added $Pb(OAc)_4$ (6.7 mg, 14 μmol), and the reaction mixture was stirred for 11 hours with irradiation by a tungsten lamp, (100W). The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give 1.1 mg (1.56 μmol, 35%) of **42** and 1.4 mg (1.86 μmol, 40%) of **43**. **42:** colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.00 (18H, s), 0.03 (6H, s), 0.04 (6H, s), 0.87-0.98 (4H, m), 0.88 (18H, s), 2.43 (2H, dddd, *J*=11.5, 6.0, 4.0, 0.5 Hz), 2.98 (2H, bq, *J*=11.5 Hz), 3.18 (2H, bt, *J*=7.0 Hz), 3.49 (2H, ddd, *J*=11.0, 10.0, 6.0 Hz), 3.67-3.72 (4H, m), 3.75 (2H, ddd, *J*=11.5, 10.0, 6.0 Hz), 3.92 (2H, ddd, *J*=9.5, 6.5, 2.5 Hz), 4.68 (2H, d, *J*=7.0 Hz), 4.72 (2H, d, *J*=7.0 Hz), 5.53-5.60 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ -5.34, -1.45, 18.04, 18.25, 25.96, 30.40, 62.72, 64.92, 77.49, 86.41, 95.27, 127.93; IR (film) ν 3012, 2958 cm^{-1}; MS (EI, 70eV) m/z(%) 649(M^+-^{t}Bu, 0.2), 589(0.8), 531(0.4), 501(0.3), 473(0.6), 459(0.7), 443(1.1), 427(0.5), 401(4); HRMS (EI, 70eV) calcd. for $C_{34}H_{74}O_7Si_4$ (M^+) 706.4507, found 706.4493. **43:** colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 0.01 (18H, s), 0.047 (6H, s), 0.051 (6H, s), 0.87-0.96 (4H, m), 0.882 (9H, s), 0.883 (9H, s), 1.91 (1H, ddd, *J*=15.0, 11.5, 0.5 Hz), 2.02 (1H, ddd, *J*=14.5, 11.0, 1.0 Hz), 2.39 (1H, ddd, *J*= 15.0, 7.0, 1.0 Hz), 2.57 (2H, ddd, *J*=14.5, 7.0, 1.0 Hz), 3.25 (1H, ddd, *J*=8.0, 6.0, 2.5 Hz), 3.26 (1H, ddd, *J*=8.0, 5.5, 3.0 Hz), 3.51-3.56 (2H, m), 3.60-3.78 (6H, m), 4.02 (1H, ddd, *J*=7.0, 2.5, 1.0 Hz), 4.10 (1H, bd, *J*=7.0 Hz), 4.36 (1H, ddd, *J*=11.0, 7.0, 1.0 Hz), 4.70 (2H, s), 4.72 (1H, d, *J*=7.0 Hz), 4.76 (1H, d, *J*=7.0 Hz), 5.19 (1H, ddd, *J*=11.0, 6.5, 1.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ -5.41, -5.39, -5.37, -1.48, -1.44, 17.95, 18.00, 18.18, 18.25, 25.89, 25.92, 26.32, 33.07, 48.14, 61.63, 62.35, 65.75, 66.00, 73.75, 74.16, 74.46, 88.27, 88.30, 95.49, 95.88, 174.10; IR (film) ν 2956, 2892, 2862, 1825

cm^{-1}; MS (EI, 70 eV) m/z(%) 649 (M^+-^{t}Bu-CO_2, 0.5), 619 (0.2), 589 (1), 575(0.7), 531 (0.9), 501 (0.7), 485 (0.7), 473 (2), 443 (3), 427 (2); HRMS (EI, 70 eV) calcd. for $C_{35}H_{74}O_9Si_4$ (M^++H) 750.4405, found 750.4361.

(2*S,3*S**,8*R**,9*R**)-(*Z*)-3,8-Bis(trimethylsilylethoxymethoxy)oxon-5-en-2,9-dimethanol (44).** To a solution of **42** (8.6 mg, 12.0 μmol) in THF (0.3 mL) was added a 1.0M solution of TBAF (30 μL, 30 μmol) at 0°C and stirred for 1.5 hours at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give 5.0 mg (10.4 μmol, 86%) of **44** as colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.007 (18H, s), 0.86-0.96 (4H, m), 2.33 (2H, dddd, *J*=12.4, 6.0, 4.3, 0.5 Hz), 2.94 (2H, bq, *J*=11.0 Hz), 3.39 (2H, btd, *J*=5.7, 3.4 Hz), 3.58 (2H, td, *J*=9.7, 7.8 Hz), 3.64 (2H, bs), 3.66 (2H, td, *J*=9.7, 7.5 Hz), 3.72 (2H, dd, *J*=11.7, 5.4 Hz), 3.83 (2H, dd, *J*=11.7, 6.2 Hz), 3.90 (2H, ddd, *J*=10.1, 6.0, 3.4 Hz), 4.66 (2H, d, *J*=7.0 Hz), 4.70 (2H, d, *J*=7.0 Hz), 5.52-5.58 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ -1.50, 18.03 29.29, 63.77, 65.74, 78.24, 85.28, 94.28, 127.69; IR (film) ν 3366, 3016, 2956 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{22}H_{43}O_5Si_2$ (M^+-2OH) 443.2649, found 443.2670.

(2*S,4*R**,7*R**,8*R**)-2,4-Bis(pivaloyloxymethyl)-7-trimethylsilyl-8-phenylsulfonyl-3-oxabicyclo[4.3.0]non-1(5)-ene (*dl*-46).** A mixture of **45** (24.4 mmol) and (*E*)-2-trimethylsilylvinyl phenylsulfone (8.8 g, 33.6 mmol) in toluene (50 mL) was stirred for 5 days at 100°C. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give 10.2g (18.3 mmol, 75%) of ***dl*-46** as pale yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (9H, s), 1.17 (18H, s), 1.91 (1H, d, *J*=8.0 Hz), 2.02 (1H, d, *J*=17.5 Hz), 2.28 (1H, d, *J*=18.5 Hz), 2.45 (1H, d, *J*=17.5 Hz), 2.64 (1H, d, *J*=18.5 Hz), 3.40 (1H, dt, *J*=7.2, 1.5 Hz), 4.00 (1H, dd, *J*=11.2, 5.7 Hz), 4.03 (1H, dd,*J*=11.2, 5.7 Hz), 4.04 (1H, dd, *J*=11.2, 5.0 Hz), 4.09 (1H, dd, *J*= 11.2, 5.2 Hz), 4.55 (1H, s), 4.66 (1H, s), 7.55-7.59 (2H, m), 7.64-7.68 (1H, m), 7.85-7.89 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ -2.40, 18.85, 19.23, 20.64, 27.20, 60.38, 60.53, 66.12, 66.17, 84.63, 84.95, 128.53, 129.20, 133.77, 134.15, 138.39, 178.25; IR (film) ν 2974, 1734 cm^{-1}; MS (EI, 70 eV) m/z (%) 564 (M^+, 0.5); HRMS (EI, 70 eV) calcd for $C_{29}H_{44}O_7SSi$ (M^+) 564.2577, found 564.2554.

(1*S,2*R**,4*S**,5*R**,7*R**,8*R**)-2,4-Bis(pivaloyloxymethyl)-3-trimethylsilyl-4-phenylsulfonyl-3-oxabicyclo[4.3.0]nonan-1,5-diol (*dl*-47).** To a stirred solution of $K_3Fe(CN)_6$ (32.9 g, 100 mmol), K_2CO_3 (13.8 g, 100 mmol) and DABCO (282 mg, 2.5 mmol) in water (130 mL) was added a solution of ***dl*-46** (5.62g, 10.0 mmol) in ^{t}BuOH (130 mL) and solid OsO_4 (27 mg, 0.1 mmol) at 40-45°C. After stirring for 29 hours, the resulting brown solution was added solid $Na_2S_2O_5$ (19.0 g, 100 mmol) and stirred for 10 hours until the color of the solution turned to green. The organic layer was separated, and the aqueous layer was extracted with Et_2O (30 mLx3). The combined organic layer was washed with saturated aqueous NaCl, and dried over $MgSO_4$. Concentration followed by silica gel column chromatography gave 5.06 g (8.79 mmol, 88%) of ***dl*-47**. colorless solid, mp 176.5-178.0°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (9H, s), 1.14 (9H, s), 1.21 (9H, s), 1.46(1H, td, *J*=9.0, 5.0 Hz), 1.66 (1H, dd, *J*=15.0, 9.5 Hz), 1.70 (1H, dd, *J*=14.0, 4.0 Hz), 1.91 (1H, dd, *J*=14.0, 11.0 Hz), 2.05 (1H, dd, *J*=9.5, 5.0 Hz), 3.31 (1H, td, *J*=11.0, 4.0 Hz), 3.32 (1H, s), 3.50 (1H, s), 3.77 (1H, dd, *J*=6.0, 4.5 Hz), 3.99 (1H, t, *J*= 5.5 Hz), 4.10 (1H, dd, *J*=12.0, 5.5 Hz), 4.14 (1H, dd, *J*=12.0, 6.0 Hz), 4.22 (1H, dd, *J*=12.0, 4.5 Hz), 4.39 (1H, dd, *J*=12.0, 5.5 Hz), 7.56-7.59 (2H, m), 7.64-7.67 (1H, m), 7.84-7.86 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ -1.05, 19.55, 27.08, 27.16, 31.74, 35.80, 59.55, 63.28, 63.64, 77.21, 77.65, 80.23, 82.80, 128.59, 129.32, 133.76, 178.73, 178.98; IR (film) ν 3462, 2972, 1739 cm^{-1}; Anal. Calcd for $C_{29}H_{46}O_9SSi$: C, 58.15: H, 7.76: S, 5.35; Found: C, 58.49; H,7.55; S, 5.26.

(1*S,2*R**,4*S**,5*R**)-2,4-Bis(pivaloyloxymethyl)-3-oxabicyclo[4.3.0]non-7-en-1,5-diol (48).** To a stirred solution of ***dl*-47** (153 mg, 0.26 mmol) in THF (3 mL) was added a 1.0 M solution of TBAF in THF (0.3 mL, 0.3 mmol) and stirred for 12 hours at 40°C. THF was removed under reduced pressure, and the

residue was purified by silica gel column chromatography to give 86.4 mg (0.23 mmol, 88%) of **48** as colorless prisms (hexane/EtOAc), mp 109-111°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (18H, s), 2.39 (2H, d, *J*=17.6 Hz), 2.44 (2H, d, *J*=17.2 Hz), 3.27 (2H, br), 3.82 (2H, dd, *J*=6.4, 4.4 Hz), 4.20 (2H, dd, *J*= 12.0, 6.0 Hz), 4.44 (2H, dd, *J*=12.0, 4.8 Hz), 5.69 (2H, t, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.14, 34.39, 63.77, 78.33, 82.31, 124.39, 178.78; IR (film) ν 3470, 2974, 1729 cm^{-1}; MS (EI, 70 eV) m/z (%) 384 (M^+, 0.4); HRMS (EI, 70 eV) calcd for $C_{20}H_{32}O_7$ (M^+) 384.2148, found 384.2139.

(2*S,9*R**)-(*Z*)-2,9-Bis(pivaloyloxymethyl)oxon-5-en-3,8-dione (49).** To a stirred solution of **48** (665 mg, 1.73 mmol) in pyridine (8.7 mL) was added solid $Pb(OAc)_4$ (1.15 g, 2.6 mmol), and stirred for 15 minutes at room temperature. The pyridine was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give 628 mg (1.65 mmol, 95%) of **49** as colorless needles (hexane/Et_2O), mp 68-89°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (18H, s), 2.93 (2H, dd, *J*=11.0, 5.2 Hz), 4.11 (2H, dd, *J*=5.4, 3.2 Hz), 4.21 (2H, dd, *J*=11.0, 3.7 Hz), 4.23 (2H, dd, *J*=11.7, 5.4 Hz), 4.57 (2H, dd, *J*=11.7, 3.2 Hz), 5.59-5.77 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.15, 40.98, 64.99, 84.07, 125.66, 177.87, 205.48; IR (film) ν 2976, 1734 cm^{-1}; MS (EI, 70 eV) m/z (%) 382 (M^+,100); HRMS (EI, 70 eV) cacld for $C_{20}H_{30}O_7$ (M^+) 382.1992, found 382.1994.

(2*S,3*R**,8*S**,9*R**)-(*Z*)-2,9-Bis(pivaloyloxymethyl)oxon-5-en-3,8-diol (50).** To a stirred solution of **49** (155 mg, 0.41 mmol) and Et_3SiH (650 μL, 4.1 mmol) in CH_2Cl_2 (4 mL) was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (1.3 mL, 1.3 mmol) at -78°C under the argon atmosphere, and allowed warmed to -15°C. The reaction mixture was poured into the vigorously stirred solution of saturated aqueous $NaHCO_3$ and EtOAc through cannular. The resulting precipitates was dissolved by the addition of water. The reaction mixture was extracted with EtOAc and the organic layer was washed with saturated aqueous NH_4Cl and brine, and dried over $MgSO_4$. Concentration followed by silica gel column chromatography gave 134 mg (0.35 mmol, 86%) of **50** as a single diastereomer. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (18H, s), 2.17 (2H, ddd, *J*=13.6, 4.0, 3.1 Hz), 2.75 (2H, ddd, *J*=13.6, 5.7, 3.6 Hz), 2.85-2.96 (2H, br), 3.31 (2H, ddd, *J*=8.5, 4.5, 3.0 Hz), 3.75 (2H, ddd, *J*=8.5, 3.6, 3.1 Hz), 4.22 (2H, dd, *J*=12.0, 4.5 Hz), 4.33 (2H, dd, *J*=12.0, 3.0 Hz), 5.77-5.85 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.11, 31.80, 65.81,70.42, 85.16, 127.84, 179.07; IR (film) ν 3456, 2972, 2922, 1731 cm^{-1}; MS (EI, 70 eV) m/z (%) 386 (M^+, 23); HRMS (EI, 70 eV) cacld for $C_{20}H_{34}O_7$ (M^+) 386.2341, found 386.2303. **51:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (9H, s), 1.21 (9H, s), 2.18 (1H, d, *J*=8.0 Hz), 2.24 (1H, m), 2.37 (1H, d, *J*=4.0 Hz), 2.41 (1H, ddd, *J*=11.8, 6.3, 5.6 Hz), 2.67 (1H, dt, *J*=12.6, 10.3 Hz), 2.90 (1H, m), 3.29 (1H, ddd, *J*=8.2, 4.2, 3.3 Hz), 3.51 (1H, ddd, *J*=7.3, 5.2, 2.2 Hz), 3.84 (1H, m), 4.23 (1H, dd, *J*=11.3, 5.2 Hz), 4.26 (1H, dd, *J*=11.7, 4.2 Hz), 4.34 (1H, dd, *J*=11.7, 3.3 Hz), 4.40 (1H, dd, *J*=11.3, 7.3 Hz), 5.63 (1H, td, *J*=10.3, 5.6 Hz), 5.84 (1H, td, *J*=10.3, 6.3 Hz). **52:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (18H, s), 2.40 (2H, ddd, *J*=12.5, 6.0, 4.7 Hz), 2.47 (2H, d, *J*=7.3 Hz), 2.83 (2H, ddd, *J*=18.6, 9.2, 2.6 Hz), 3.38 (2H, br), 3.86 (2H, br), 4.18 (2H, ddd, *J*=11.4, 5.7 Hz), 4.47 (2H, dd, *J*=11.4, 7.0 Hz), 5.61 (2H, m).

(2*S,3*R**,6*S**,7*R**)-2,7-Bis(benzyloxymethyl)-2,3,6,7-dihydrooxepin-3,6-diol (53).** To a stirred solution of **24** (346 mg, 688 μmol) in THF (2.5 mL) and water (650 μL) was added CF_2CO_2H (265 μL, 3.44 mmol) and stirred for 30 hours at room temperature. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (EtOAc/EtOH=25/1~20/1) to give 77.1 mg (405 μmol, 59%) of tetraol. A solution of the tetraol (143 mg, 750 μmol) and Bu_2SnO (411 mg, 1.65 mmol) in toluene (5 mL) was refluxed with azeotropy for 5 hours. The solvent was removed under reduced pressure, and the residue was dissolved in DMF (4 mL). The mixture was added CsF (456 mg, 3.00 mmol) and BnBr (196 μL, 1.65 mmol), and stirred for 17 hours at room temperature. Concentration followed by silica gel column chromatography gave

142 mg (383 μmol, 51%) of **53** as colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.92 (2H, d, *J*=Hz), 3.50-3.80 (6H, m), 4.36 (2H, dd, *J*=8.0, 2.5 Hz), 4.56 (4H, dd, *J*=2.5 Hz), 3.73 (H, dd, *J*=10.5, 5.0 Hz), 3.67 (2H, dd, *J*=10.5, 4.5 Hz), 3.69 (6H, s), 4.59 (2H, bs); ^{13}C NMR (50 MHz, $CDCl_3$) δ 72.24, 72.52, 73.64, 82.37, 127.27, 127.92, 128.50, 132.54, 137.44; IR (film) ν 3422, 3066, 2870 cm^{-1}.

(2*S*,3*R*,6*S*,7*R*)-2,7-Bis(tert-butyldimethylsilyloxymethyl)-3-acetoxy-2,3,6,7-dihydrooxepin-6-ol (54). To a solution of diol **21** (15.5 mg, 37.0 μmol) and vinyl acetate (0.1 mL) in CH_3CN (0.5 mL) was added lipase AK (15 mg), and stirred for 6 days at 30°C. The enzyme was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 11.1 mg (24.1 μmol, 65 %) of **21** and recovered 5.5 mg (13.1 μmol, 35 %) of **54** as colorless needles, mp 50-51°C; $[\alpha]^{23}_D$ -48.4° (*c*, 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.033 (3H, s), 0.039 (3H, s), 0.103 (3H, s), 0.109 (3H, s), 0.883 (9H, s), 0.903 (9H, s), 3.50-3.59 (2H, m), 3.60 (1H, dd, *J*=10.5, 3.5 Hz), 3.67 (1H, ddd, *J*=9.0, 6.5, 3.5 Hz), 3.71 (1H, d, *J*=2.5 Hz), 3.73 (1H, dd, *J*=10.5, 7.5 Hz), 3.95 (1H, dd, *J*=10.5, 4.5 Hz), 3.39 (1H, dq, *J*=9.0, 2.5 Hz), 5.33 (1H, dq, *J*=9.0, 2.5 Hz), 5.51 (1H, dt, *J*=12.5, 2.5 Hz), 5.70 (1H, dt, *J*=12.5, 2.5 Hz); IR (KBr) 3514, 2930, 2860, 2862, 1723 cm^{-1}; HRMS (EI, 70 eV) calcd. for $C_{22}H_{44}O_6Si_2$ (M^+) 460.2677, found 460.2676.

(2*S*,3*R*,6*S*,7*R*)-2,7-Bis(triisoproylsilyloxymethyl)-3-Acetoxy-2,3,6,7-dihydrooxepin-6-ol (55). A mixture of diol **24** (1.24 g, 2.48 mmol) in vinyl acetate was added lipase AK (496 mg), and stirred for 6 days at 30°C. The lipase was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 1.03 g (1.90 mmol, 77%) of **55** as colorless oil; $[\alpha]^{22}_D$ -36.4° (*c*, 1.09, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (21H, bs), 1.05 (21H, bs), 2.02 (3H, s), 3.50-3.74 (3H, m), 3.63 (1H, s), 3.78 (1H, dd, *J*=9.6, 8.3 Hz), 3.95 (2H, m), 4.37 (1H, dt, *J*=8.9, 2.1 Hz), 5.32 (1H, dd, *J*=8.1, 2.4 Hz), 5.48 (1H, dt, *J*=12.9, 2.4 Hz), 5.66 (1H, dt, *J*=12.9, 2.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.61, 11.89, 17.82, 17.89, 21.06, 64.17, 67.35, 71.35, 74.79, 81.08, 84.23, 127.89, 134.09, 169.75; IR (film) 3490, 2946, 2868, 1748 cm^{-1}; HRMS (EI, 70 eV) calcd. for $C_{25}H_{49}O_6Si_2$ (M^+-^{i}Pr) 501.3065, found 501.3084. The enantiomeric excess was determined by HPLC analysis of the corresponding benzoate using CHIRALCEL OD: (hexane/2-propanol=99/1, 1.0 mL/min).

(2*S*,3*R*,6*S*,7*R*)-2,7-Bis(benzyloxymethyl)-3-acetoxy-2,3,6,7-dihydrooxepin-6-ol (56). A mixture of diol **53** (46.1 mg, 124 μmol), vinyl acetate (500 μL), and lipase AK (1.6 mg, 4%w/w) was stirred for 2 days at 35°C. The lipase was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 41.5 mg (101 μmol, 81 %) of **56** as colorless oil; $[\alpha]^{26}_D$ -58.0° (*c*, 1.03, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.96 (3H, s), 3.18 (1H, bs), 3.47-3.56 (2H, m), 3.62-3.88 (4H, m), 4.40 (1H, bd, *J*=7.5 Hz), 4.48 (1H, d, *J*=11.5 Hz), 4.56 (1H, d, *J*=11.5 Hz), 4.60 (1H, d, *J*=11.5 Hz), 4.63 (1H, d, *J*=11.5 Hz), 4.49-5.51 (1H, m), 5.47 (1H, dt, *J*=12.5, 2.5 Hz), 5.72 (1H, dt, *J*=12.5, 2.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.95, 70.33, 71.32, 72.22, 72.49, 73.37, 73.65, 82.04, 82.16, 127.56, 127.70, 127.74, 127.87, 128.20, 128.27, 128.45, 134.10, 169.68; IR (film) ν 3472, 3034, 2872, 1740 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{17}H_{21}O_6$ (M^+-Bn) 321.1300, found 321.1337. The enantiomeric excess was determined by HPLC analysis of the corresponding benzoate using CHIRALCEL OD: (hexane/2-propanol=100/1, 1.0 mL/min).

(2*S,3*R**,5*R**,7*S**,8*R**)-3,7-Bis(benzoyloxy)-5-methyloxocan-2,8-dimethanol (59).** To a solution of **35** (45 mg, 84 μmol) and DMAP (2.1 mg, 17 μmol) in pyridine (0.85 mL) was added BzCl (97 μL, 0.840 mmol), and stirred for 17 hours at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography. The resulting benzoate was dissolved in

CH_3CN, and treated with 10 % HF solution in CH_3CN (0.4 ml) for 3.5 hours at room temperature. The reaction mixture was diluted with ether (20 mL), quenched with saturated aqueous $NaHCO_3$ at 0 °C and stirred for 30 minutes. The organic phase was washed with brine, and dried over $MgSO_4$. Concentration followed by silica gel column chromatography gave 27 mg (64 μmol, 76 %) of **59** as colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 1.09 (3H, d, *J*=7.2 Hz), 1.90 (2H, ddd, *J*=14.3, 10.4, 8.1 Hz), 2.03 (2H, ddd, *J*=14.3, 10.4, 8.1 Hz), 3.64 (2H, dd, *J*=11.3, 9.0 Hz), 3.86 (2H, dd, *J*=11.3, 2.6 Hz), 4.04 (2H, ddd, *J*=14.3, 3.5, 2.0 Hz), 2.16-2.20 (1H, m), 3.64 (2H, dd, *J*=11.5, 9.2 Hz), 3.85 (2H, dd, *J*=11.5, 2.5 Hz), 4.01 (2H, td, *J*=9.2, 2.5 Hz), 4.97 (2H, ddd, *J*=10.4, 9.2, 3.5 Hz), 7.44-7.48 (4H, m), 7.55-7.58 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.14, 27.64, 43.22, 64.90, 73.36, 86.57, 128.46, 129.59, 129.88, 133.26, 165.41; IR (film) ν 3324, 3020, 2960, 1719, 1603, 1586 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{24}H_{28}O_7$ (M^+) 428.1833, found 428.1844.

(2*S*,3*R*,5*R*,7*S*,8*R*)-2-Acetoxymethyl-3,7-bis(benzoyloxy)-5-methyloxocan-8-methanol (60). To a solution of diol **59** (27 mg, 64 μmol) in vinyl acetate (2.5 mL) was added lipase AK (50 mg), and stirred for 6 days at 30 °C. The lipase was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 27 mg (58 μmol, 92 %) of **60** as colorless oil; $[\alpha]^{22}_D$ -12.8° (*c*, 1.01, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 1.09 (3H, d, *J*=7.2 Hz), 1.90 (1H, ddd, *J*=14.6, 9.7, 4.9 Hz), 1.92 (1H, ddd, *J*=14.4, 9.8, 4.6 Hz), 2.05 (1H, ddd, *J*=14.6, 3.3, 2.5 Hz), 2.09 (1H, ddd, *J*=14.4, 3.4, 2.4 Hz), 2.10 (3H, s), 2.18-2.27 (1H, m), 3.30 (1H, dd, *J*=10.4, 3.5 Hz), 3.55 (1H, ddd, *J*=11.8, 8.1, 3.5 Hz), 3.75 (1H, ddd, *J*=11.8, 10.4, 2.6 Hz), 3.92 (1H, ddd, *J*=9.7, 8.1, 2.6 Hz), 4.00 (1H, dd, *J*=11.8, 6.3 Hz), 4.12 (1H, ddd, *J*=9.0, 6.3, 2.2 Hz), 4.65 (1H, dd, *J*=11.8, 2.2 Hz), 5.01 (1H, ddd, *J*=9.8, 9.0, 3.4 Hz), 5.10 (1H, ddd, *J*=9.8, 9.0, 3.4 Hz), 7.44-7.48 (4H, m), 7.57-7.61 (2H, m), 8.00-8.04 (4H, m); IR (film) ν 3538, 2964, 1719, 1603 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{26}H_{30}O_8$ (M^+) 470.1941, found 470.1954. The enantiomeric excess was determined by HPLC analysis using CHIRALCEL OD: (hexane/2-propanol=10/1, 0.5 mL/min).

(2*S,3*S**,8*R**,9*R**)-(*Z*)-2,9-Bis(hydroxymethy)-5-oxonen-3,8-diol (61).** A solution of **44** (37.9 mg, 53.6 μmol) in THF (1.5 mL) was added water (1.5 mL) and trifluoroacetic acid (0.3 mL), and stirred for 6.5 hours at 50°C. After evaporation, the residue was purified by silica gel column chromatography to give 8.4 mg (38.5 μmol, 72%) of **61** as colorless oil; ^1H NMR (600 MHz, pyridine-d_5) δ 2.50 (2H, ddd, *J*=12.2, 6.2, 4.3 Hz), 3.40 (2H, bq, *J*=11.0 Hz), 3.86 (2H, ddd, *J*=7.0, 3.5, 2.9 Hz), 4.36 (2H, ddd, *J*=10.2, 6.2, 2.9 Hz), 4.43 (2H, dd, *J*=11.6, 3.5 Hz), 4.64 (2H, dd, *J*=11.6, 7.0 Hz), 5.63-5.69 (2H, m), 5.95 (4H, br); ^{13}C NMR (150 MHz, pyridine-d_5) δ 33.61, 65.71, 72.84, 88.52, 128.36; IR (film) ν 3308, 2924, 1686 cm^{-1}; MS (EI, 70 eV) m/z (%) 219 (M^++H, 2), 200 (16), 182 (4), 170 (18), 139 (23); HRMS (EI, 70 eV) calcd for $C_{10}H_{19}O_5$ (M^++H) 219.1231, found 219.1206.

(2*S*,3*S*,8*R*,9*R*)-(*Z*)-2-Hydroxymethy-9-acetyloxymethyl-5-oxonen-3,8-diol (62). Tetraol **61** (5.5 mg, 25.0 μmol) in acetonitrile (2 mL) was added vinyl acetate (0.2 mL) and lipase AK (Amano, 1.6 mg), and stirred for 5 days at 30°C. The lipase was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 6.0 mg (23.1 μmol, 91%) of **62** as colorless prisms, mp 176°C; $[\alpha]^{28}_D$ +9.3° (*c*, 0.45, MeOH); ^1H NMR (600 MHz, pyridine-d_5) δ 1.99 (3H, s), 2.51-2.56 (2H, m), 3.40 (1H, bq, *J*=10.5 Hz), 3.42 (1H, bq, *J*=10.5 Hz), 3.71 (1H, td, *J*=5.9, 3.2 Hz), 3.78 (1H, td, *J*=6.4, 3.0 Hz), 4.33 (1H, br), 4.42 (1H, dd, *J*=10.8, 5.6 Hz), 4.48 (1H, dd, *J*=10.8, 6.2 Hz), 4.54 (1H, ddd, *J*=9.4, 6.2, 3.2 Hz), 4.84 (1H, dd, *J*=10.9, 6.7 Hz), 5.00 (1H, dd, *J*=10.9, 6.2 Hz), 5.62-5.70 (2H, m), 6.37 (1H, bs), 6.43 (1H, bs), 6.61 (1H, bs); ^{13}C NMR (150 MHz, pyridine-d_5) δ 20.83, 33.34, 33.48, 63.50, 65.79, 71.22, 71.94 , 84.37, 87.99,

128.09, 128.63, 170.74; IR (film) ν 3386, 3014, 2924, 1734, 1655 cm^{-1}; MS (EI, 70 eV) m/z (%) 261 (M^++H, 0.9), 242 (5), 224 (1), 212 (4), 199 (4), 182 (6), 169 (7).

(2*S,3*R**,8*S**,9*R**)-(*Z*)-3,8-Bis(*p*-methoxybenzyloxy)-5-oxonen-2,9-dimethanol (64).** A solution of **50** (441 mg, 1.14 mmol) and trichloroacetoimidate (967 mg, 3.42 mmol) in Et_2O (7 mL) was added a 0.1 M solution of CF_3SO_3H (68.4 μL, 6.84 μmol) in Et_2O, and stirred for 30 minutes at room temperature. The reaction mixture was added saturated aqueous $NaHCO_3$, and the organic layer was separated, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was dissolved in Et_2O. This solution was added $LiAlH_4$ (146 mg, 3.86 mmol) at 0°C and stirred for an hour at room temperature. The reaction was quenched with water (150 μL), 8% NaOH (300 μL), and water (300 μL). The resulting precipitates were removed by filtration through a glassflitted filter packed with Celite, and the filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography gave 332 mg (780 μmol, 68%) of **64** as colorless prisms (hexane/ Et_2O), mp 78-85°C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.38 (2H, ddd, *J*=13.6, 3.8 3.0 Hz), 2.64 (2H, ddd, *J*=13.6, 9.5, 3.0 Hz), 3.01 (2H,br), 3.36 (2H, ddd, *J*=8.8, 5.1, 3.0 Hz), 3.52 (2H, dt, *J*=8.8, 3.0 Hz), 3.59 (2H, dd, *J*=11.6, 5.1 Hz), 3.76 (2H, dd, *J*=11.6, 3.0 Hz), 3.80 (6H, s), 4.35 (2H, d, *J*=11.0 Hz), 4.60 (2H, d, *J*=11.0 Hz), 5.82-5.73 (2H, m), 6.87 (4H, AA'BB'), 7.24 (4H, AA'BB'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.09, 55.26, 64.14, 70.99, 77.81, 85.48, 113.87, 127.68, 129.47, 130.15, 159.30; IR (film) ν 3364, 2924 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{26}H_{34}O_7$ (M^+) 458.2305, found 458.2307.

(2*S*,3*R*,8*S*,9*R*)-(*Z*)-2-Acetoxymethyl-3,8-bis(*p*-methoxybenzyloxy)-5-oxonen-9-methanol (65). A solution of diol **64** (29.4 mg, 68.7 μmol) in benzene (8 mL) was added vinyl acetate (2 mL) and lipase AK (6.0 mg), and stirred for 5 days at 37°C. The lipase was removed by filtration through a glassfritted filter packed with Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 20.7 mg (43.9 μmol, 68%) of **65** as colorless oil; $[\alpha]^{24}_D$ -13.3° (*c*, 1.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.04 (3H, s), 2.38 (2H, m), 2.61 (2H, m), 3.25 (1H, dt, *J*=9.0, 3.1 Hz), 3.39 (1H, ddd, *J*=9.0, 3.7, 2.3 Hz), 3.60 (1H, dd, *J*=9.0, 3.1 Hz), 3.65 (1H, dt, *J*=9.0, 3.1 Hz), 3.70 (1H, dt, *J*=9.0, 3.2 Hz), 3.78 (1H, dd, *J*=9.0, 3.1 Hz), 3.79 (3H, s), 3.80 (3H, s), 4.02 (1H, dd, *J*=12.0, 3.9 Hz), 4.36 (1H, d, *J*=11.0 Hz), 4.39 (1H, d, *J*=11.2 Hz), 4.52 (1H, dd, *J*=12.0, 2.4 Hz), 4.60 (1H, d, *J*=11.2 Hz), 4.61 (1H, d, *J*=11.0 Hz), 5.79 (2H, m), 6.87 (4H, AA'BB'), 7.25 (4H, AA'BB'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.98, 26.88, 27.23, 55.28, 62.06, 65.01, 71.02, 71.27 , 76.95, 77.38, 83.35, 86.07, 113.87, 127.64, 128.23, 129.23, 130.00, 130.07, 159.30, 159.35, 171.39; IR (film) ν 3364, 2924, 1738, 1613 cm^{-1}; Enantiomeric excess was determined by HPLC analysis using CHIRALCEL OD: (hexane/2-propanol=10/1, 0.5 mL/min).

(2*R*,4a*R*,6*S*,7*R*,11a*S*)-(*Z*)-2-(*p*-Methoxyphenyl)-6-acetoxymethyl-*m*-dioxano[5,4-b]oxon-9-en-7-ol (71). A solution of **65** (113 mg, 241 μmol) in CH_2Cl_2 (2.4 mL) was added DDQ (87.4 mg, 385 μmol) in portionwise and stirred for 13 minutes at room temperature. The reaction mixture was added water (100 μL), then DDQ (54.7 mg, 241 μmol) in portionwise. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, then dried over $MgSO_4$. Concentration followed by silica gel column chromatography gave 66 mg (196 μmol, 81%) of **71**. $[\alpha]^{24}_D$ +14.9° (*c*, 0.97, $CHCl_3$); ^1H NMR (600 MHz, C_6D_6) δ 1.43 (1H, dd, *J*=5.7 Hz), 1.63 (3H, s), 2.11 (1H, br), 2.34 (1H, br), 2.46 (1H, br), 2.67 (1H, br), 3.13 (1H, ddd, *J*=9.3, 7.1, 2.2 Hz), 3.25-3.29 (1H, m), 3.42 (1H, td, *J*=10.2, 4.5 Hz), 3.48 (1H, t, *J*=10.2 Hz), 3.50 (1H, dt, *J*=10.3, 5.0 Hz), 3.99 (1H, ddd, *J*=11.7, 7.1 Hz), 4.23 (1H, dd, *J*=11.7, 2.2 Hz), 4.40 (1H, dd, *J*=10.2, 4.5 Hz), 5.68 (1H, bq, *J*=10.0 Hz), 5.75 (1H, bq, *J*=10.0 Hz), 6.83 (2H, AA'BB'), 7.60 (2H, AA'BB'); ^{13}C NMR (150 MHz, C_6D_6) δ 20.83, 33.34, 33.48, 63.50, 65.79, 71.22, 71.94 , 84.37, 87.99, 128.09, 128.63, 170.74; IR (film) ν

3466, 3018, 2938, 2862, 1742, 1615 cm^{-1}; MS (EI, 70 eV) m/z (%) 378 (M^+, 93), 272 (15), 212 (6), 199 (7), 163 (8), 136 (100); HRMS (EI, 70 eV) calcd for $C_{20}H_{26}O_7$ (M^+) 378.1679, found 378.1678.

(*S*)-MTPA ester of 55: ^1H NMR (500 MHz, $CDCl_3$) δ 1.01-1.10 (42H, bs), 1.94 (3H, s), 3.52 (3H, s), 3.61 (1H, dd, *J*=11.0, 4.0 Hz), 3.65 (1H, dd, *J*=10.0, 5.0 Hz), 3.68 (1H, dd, *J*=11.0, 5.5 Hz), 3.75 (1H, dd, *J*=10.5, 5.0 Hz), 3.92 (1H, ddd, *J*=7.0, 5.0, 4.0 Hz), 4.05 (1H, dt, *J*=6.0, 5.0 Hz), 5.34 (1H, m), 5.66 (1H, m), 5.89 (2H, m), 7.35-7.51 (5H, m).

(*R*)-MTPA ester of 55: ^1H NMR (500 MHz, $CDCl_3$) δ 1.02-1.08 (42H, bs), 1.98 (3H, s), 3.54 (3H, s), 3.55 (1H, dd, *J*=11.0, 5.0 Hz), 3.61 (1H, dd, *J*=10.5, 4.5 Hz), 3.65 (1H, dd, *J*=11.0, 5.0 Hz), 3.70 (1H, dd, *J*=10.5, 5.0 Hz), 3.96 (1H, dt, *J*=6.5, 5.0 Hz), 4.02 (1H, ddd, *J*=6.0, 5.0 Hz), 5.41 (1H, m), 5.64 (1H, m), 5.97 (2H, m), 7.35-7.52 (5H, m).

(*S*)-MTPA ester of 56: ^1H NMR (600 MHz, $CDCl_3$) δ 1.87 (3H, s), 3.43 (3H, s), 3.48 (1H, dd, *J*=11.0, 4.0 Hz), 3.50 (1H, dd, *J*=11.0, 4.0 Hz), 3.50 (1H, dd, *J*=11.0, 5.0 Hz), 3.54 (1H, dd, *J*=11.0, 5.0 Hz), 3.95 (1H, dt, *J*=7.0, 4.0 Hz), 4.06 (1H, ddd, *J*=8.0, 5.0, 3.5 Hz), 4.49 (1H, d, *J*=12.0 Hz), 4.54 (2H, s), 4.57 (1H, d, *J*=12.0 Hz), 5.42 (1H, ddt, *J*=7.0, 4.0, 1.0 Hz), 5.67 (1H, ddt, *J*=8.0, 4.2, 1.0 Hz), 5.75 (1H, ddd, *J*=12.0, 5.0, 1.0 Hz), 5.77 (1H, ddd, *J*=12.0, 4.0, 1.0 Hz), 7.25-7.41 (13H, m), 7.45-7.48 (2H, m).

(*R*)-MTPA ester of 56: ^1H NMR (600 MHz, $CDCl_3$) δ 1.91 (3H, s), 3.40 (1H, dd, *J*=10.0, 5.0 Hz), 3.42 (1H, dd, *J*=11.0, 4.0 Hz), 3.47 (1H, dd, *J*=11.0, 4.5 Hz), 3.51 (1H, dd, *J*=11.0, 5.0 Hz), 3.51 (3H, s), 3.98 (1H, ddd, *J*=8.0, 4.5, 4.0 Hz), 4.04 (1H, ddd, *J*=8.0, 5.0, 4.0 Hz), 4.46 (1H, d, *J*=12.0 Hz), 4.48 (1H, d, *J*=12.0 Hz), 4.49 (1H, d, *J*=12.0 Hz), 4.57 (1H, d, *J*=12.0 Hz), 5.44 (1H, ddt, *J*=7.0, 4.5, 1.0 Hz), 5.68 (1H, ddt, *J*=8.0, 4.0, 1.0 Hz), 5.82 (1H, m), 5.84 (1H, m), 7.25-7.42 (13H, m), 7.47-7.55 (2H, m).

(*S*)-MTPA ester of 66: ^1H NMR (600 MHz, $CDCl_3$) δ 1.080 (3H, d, *J*=7.2 Hz), 1.356 (3H, s), 1.450 (3H, s), 1.52-1.58 (1H, m), 1.77-1.82 (1H, m), 1.834 (1H, ddd, *J*=14.4, 9.9, 6.8 Hz), 1.940 (1H, ddd, *J*=14.4, 2.8, 2.0 Hz), 1.98-2.04 (1H, m), 2.035 (3H, s), 3.339 (1H, td, *J*=9.6, 5.8 Hz), 3.540 (1H, dd, *J*=11.5, 9.6 Hz), 3.540 (3H, s), 3.656 (1H, ddd, *J*=9.9, 7.3, 2.4 Hz), 3.686 (1H, ddd, *J*=10.4, 9.6, 3.9 Hz), 3.760 (1H, dd, *J*=11.6, 7.3 Hz), 3.787 (1H, ddd, *J*=11.5, 5.8 Hz), 3.830 (1H, dd, *J*=11.6, 2.4 Hz), 4.929 (1H, td, *J*=9.9, 2.8 Hz), 7.40-7.47 (5H, m).

(*R*)-MTPA ester of 66: ^1H NMR (600 MHz, $CDCl_3$) δ 1.036 (3H, d, *J*=7.2 Hz), 1.355 (3H, s), 1.452 (3H, s), 1.519 (1H, dt, *J*=14.2, 10.2 Hz), 1.725 (1H, ddd, *J*=14.3, 10.3, 6.7 Hz), 1.76-1.79 (1H, m), 1.842 (1H, ddd, *J*=14.3, 2.8, 2.0 Hz), 1.95-2.00 (1H, m), 2.064 (3H, s), 3.350 (1H, ddd, *J*=9.9, 9.6, 5.9 Hz), 3.490 (3H, s), 3.558 (1H, dd, *J*=11.4, 9.9 Hz), 3.680 (1H, ddd, *J*=10.2, 9.6, 3.9 Hz), 3.692 (1H, ddd, *J*=10.3, 7.5, 2.3 Hz), 3.812 (1H, dd, *J*=11.4, 5.9 Hz), 3.903 (1H, dd, *J*=11.6, 7.5 Hz), 4.057 (1H, dd, *J*=11.6, 2.3 Hz), 4.908 (1H, dt, *J*=10.3, 2.8 Hz), 7.40-7.47 (5H, m).

(*S*)-MTPA ester of 68: ^1H NMR (500 MHz, $CDCl_3$) δ 1.023 (3H, d, *J*=7.2 Hz), 1.357 (3H, s), 1.443 (3H, s), 1.522 (1H, dt, *J*=14.0, 10.0 Hz), 1.729 (1H, ddd, *J*=15.0, 10.0, 6.0 Hz), 1.765 (1H, ddd, *J*=14.0, 4.0, 1.5 Hz), 1.850 (1H, dt, *J*=15.0, 2.5 Hz), 1.97-2.03 (1H, m), 3.373 (1H, td, *J*=10.0, 5.5 Hz), 3.458 (1H, dd, *J*=11.0, 6.5 Hz), 3.465 (3H, s), 3.556 (1H, dd, *J*=10.5, 3.0 Hz), 3.616 (1H, ddd, *J*=9.5, 6.5, 2.5 Hz), 3.697 (1H, td, *J*=10.0, 4.0 Hz), 3.860 (1H, dd, *J*=11.0, 5.5 Hz), 4.561 (2H, s), 4.982 (1H, td, *J*=10.0, 2.5 Hz), 7.30-7.39 (8H, m), 7.50-7.52 (2H, m).

(*R*)-MTPA ester of 68: ^1H NMR (500 MHz, $CDCl_3$) δ 1.069 (3H, d, *J*=7.0 Hz), 1.354 (3H, s), 1.439 (3H, s), 1.52-1.59 (1H, m), 1.788 (1H, ddd, *J*=13.5, 4.0, 1.5 Hz), 1.828 (1H, ddd, *J*=13.5, 10.0, 6.5 Hz), 1.939 (1H, dt, *J*=14.0, 2.5 Hz), 1.97-2.03 (1H, m), 3.275 (1H, dd, *J*=10.5, 6.0 Hz), 3.341 (1H, dd, *J*=10.5, 3.0 Hz), 3.359 (1H, td, *J*=10.0, 5.5 Hz), 3.537 (3H, s), 3.545 (1H, t, *J*=10.0 Hz), 3.568 (1H, ddd, *J*=10.0,

6.0, 3.0 Hz), 3.700 (1H, td, *J*=10.5, 4.0 Hz), 3.838 (1H, dd, *J*=11.5, 5.5 Hz), 4.513 (2H, s), 4.974 (1H, td, *J*=10.0, 3.0 Hz), 7.27-7.40 (8H, m), 7.46-7.52 (2H, m).

(*S*)-MTPA ester of 69: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.349 (3H, s), 1.384 (3H, s), 2.028 (3H, s), 2.141 (1H, dddd, *J*=12.1, 5.1, 4.9, 0.5 Hz), 2.472 (1H, dddd, *J*=11.7, 6.2, 5.0, 0.5 Hz), 2.960 (1H, ddd, *J*=12.1, 11.2, 10.8 Hz), 3.048 (1H, ddd, *J*=11.7, 10.8, 10.6 Hz), 3.236 (1H, ddd, *J*=6.4, 6.3, 4.2 Hz), 3.451 (1H, ddd, *J*=7.6, 5.2, 3.5 Hz), 3.590 (3H, s), 3.684 (1H, dd, *J*=12.1, 6.4 Hz), 3.741 (1H, dd, *J*=11.5, 7.6 Hz), 3.800 (1H, dd, *J*=11.5, 5.2 Hz), 3.903 (1H, dd, *J*=12.1, 6.3 Hz), 4.044 (1H, ddd, *J*=11.2, 4.9, 4.2 Hz), 5.267 (1H, ddd, *J*=10.6, 6.2, 3.5 Hz), 5.573 (1H, tdd, *J*=10.8, 5.0, 0.5 Hz), 5.623 (1H, tdd, *J*=10.8, 5.1, 0.5 Hz), 7.39-7.43 (3H, m), 7.51-7.55 (2H, m).

(*R*)-MTPA ester of 69: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.348 (3H, s), 1.378 (3H, s), 2.051 (3H, s), 2.104 (1H, dtd, *J*=12.1, 4.8, 0.5 Hz), 2.389 (1H, dddd, *J*=11.4, 6.1, 5.2, 0.5 Hz), 2.889 (1H, ddd, *J*=11.4, 10.7, 10.6 Hz), 2.898 (1H, ddd, *J*=12.1, 11.3, 10.7 Hz), 3.255 (1H, ddd, *J*=6.3, 6.2, 4.2 Hz), 3.506 (1H, ddd, *J*=7.1, 5.7, 3.4 Hz), 3.530 (3H, s), 3.710 (1H, dd, *J*=12.1, 6.3 Hz), 3.930 (1H, dd, *J*=12.1, 6.2 Hz), 3.998 (1H, dd, *J*=11.4, 7.1 Hz), 4.023 (1H, dd, *J*=11.4, 5.7 Hz), 4.035 (1H, ddd, *J*=11.3, 4.8, 4.2 Hz), 5.256 (1H, ddd, *J*=10.6, 6.1, 3.4 Hz), 5.564 (1H, tdd, *J*=10.7, 5.2, 0.5 Hz), 5.608 (1H, tdd, *J*=10.7, 4.8, 0.5 Hz), 7.40-7.45 (3H, m), 7.47-7.53 (2H, m).

(*S*)-MTPA ester of 71: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.07 (3H, s), 2.46 (1H, br), 2.56 (1H, br), 2.79 (1H, br), 3.52-3.57 (2H, m), 3.57 (3H, s), 3.63 (1H, ddd, *J*=9.4, 6.8, 2.1 Hz), 3.73 (1H, br), 3.76 (1H, ddd, *J*=12.0, 6.8 Hz), 3.80 (3H, s), 3.90 (1H, dd, *J*=12.0, 2.1 Hz), 4.30 (1H, dd, *J*=5.8, 2.4 Hz), 5.11 (1H, br), 3.37 (1H, s), 5.72 (1H, ddd, *J*=10.3, 8.8, 7.5 Hz), 5.90 (1H, ddd, *J*=10.3, 9.2, 8.0 Hz), 6.88 (2H, AA'BB'), 7.37 (2H, AA'BB'), 7.41-7.46 (3H, m), 7.48-7.52 (2H, m).

(*R*)-MTPA ester of 71: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.09 (3H, s), 2.43 (2H, br), 2.70 (1H, br), 2.80 (1H, br), 3.54 (3H, s), 3.54-3.59 (2H, m), 3.64-3.68 (1H, m), 3.74 (1H, br), 3.78 (3H, s), 3.88 (1H, dd, *J*=12.0, 7.1 Hz), 4.11 (1H, dd, *J*=12.0, 2.2 Hz), 4.33 (1H, dd, *J*=10.0, 4.0 Hz), 5.08 (1H, br), 5.37 (1H, s), 5.53 (1H, ddd, *J*=10.2, 9.0, 6.8 Hz), 5.84 (1H, td, *J*=10.2, 7.2 Hz), 6.87 (2H, AA'BB'), 7.37 (2H, AA'BB'), 7.41-7.44 (3H, m), 7.49-7.52 (2H, m).

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