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Convergent synthesis of the HIJKLM ring fragment of ciguatoxin CTX3C

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In honor of Professor Yoshito Kishi on the occasion of his award of the prestigious Tetrahedron Prize

Abstract—Ciguatoxin CTX3C is a representative congener of the ciguatoxins, which are known to be the principal causative agents of ciguatera food poisoning. The structure of CTX3C spans more than 3 nm and is characterized by 13 ether rings. To attain a practical construction of this molecule, efficient supplies of the structural fragments are crucial. Herein we report the convergent synthesis of the HIJKLM ring fragment and present a new carbonyl olefination protocol to cyclize the J ring using low-valent titanium.

1. Introduction

Ciguatera is a major source of food poisoning in tropical and subtropical regions, and often causes long-lasting health problems with diverse symptoms.[1] The causative toxins, such as ciguatoxin (CTX, **1**)[2] and CTX3C (**2**),[3] are produced by the marine dinoflagellate *Gambierdiscus toxicus* and accumulate in fish of many species through the food chain (Scheme 1).[4] More than 20 congeners of ciguatoxin have been identified to date,[5] and most exhibit potent toxicity against mice (LD_{50}=0.25–4 μg/kg). Since ciguateric fish look, taste, and smell normal, immunochemical methods for detecting ciguatoxins prior to consumption have been in demand for a long time.[6] Biological studies have revealed that ciguatoxins exert their toxicity through the activation of voltage-sensitive sodium channels (VSSC).[7] However, detailed biological studies at the molecular level as well as the preparation of anti-ciguatoxin antibodies have been hampered by the extremely low availability of the causative agents. Chemical synthesis is therefore the only plausible solution. Here, we choose CTX3C (**2**) as the prime target for total synthesis, which has very recently been achieved.[8]

The chemical construction of ciguatoxins that possess 13 ether rings and 30 stereogenic centers has received considerable attention due to the interesting structure of the toxins and their biologically important activities.[9–11] We planned a flexible and convergent synthetic route to construct the highly complex polycyclic structure, in which the final stage of the total synthesis would involve the coupling of the ABCDE ring fragment **3**[9e,f] and the HIJKLM ring fragment **4** with the simultaneous construction of the central FG ring system (Scheme 1).[8,9d] This strategy is particularly suitable for the synthesis of various ciguatoxins because the FG ring system is a common structure to all ciguatoxins. In this full account, we report the development of our synthetic route to the right half of CTX3C (**2**), the HIJKLM ring moiety **4**, useful for the total synthesis of **2**.[8,12]

2. Results and discussion

Retrosynthetically, the tetrahydropyran ring H in **4** should be readily constructed by a 6-*endo* selective cyclization as we have previously demonstrated for the HIJ ring system of ciguatoxin (Scheme 1).[13] The IJKLM ring system **5** can be dissected into two parts, the I ring **6** and the LM ring **7**, which may be assembled back into **5** by construction of the JK ring moiety. The J ring is expected to be built through the ring-closing olefin metathesis reaction (RCM),[14,15] providing for the subsequent reductive etherification of the K ring.[16] The 8-membered ring of **6** may be constructed by RCM, deriving the C36–C40 carbons from D-2-deoxyribose. It is expected that the stereocenters of C43 and C44 of **7** can be installed using a stereoselective crotylmetal addition method.[17] Retrosynthetic removal of the ketal M ring of **7** further simplifies the intermediate to lactone **8**. The

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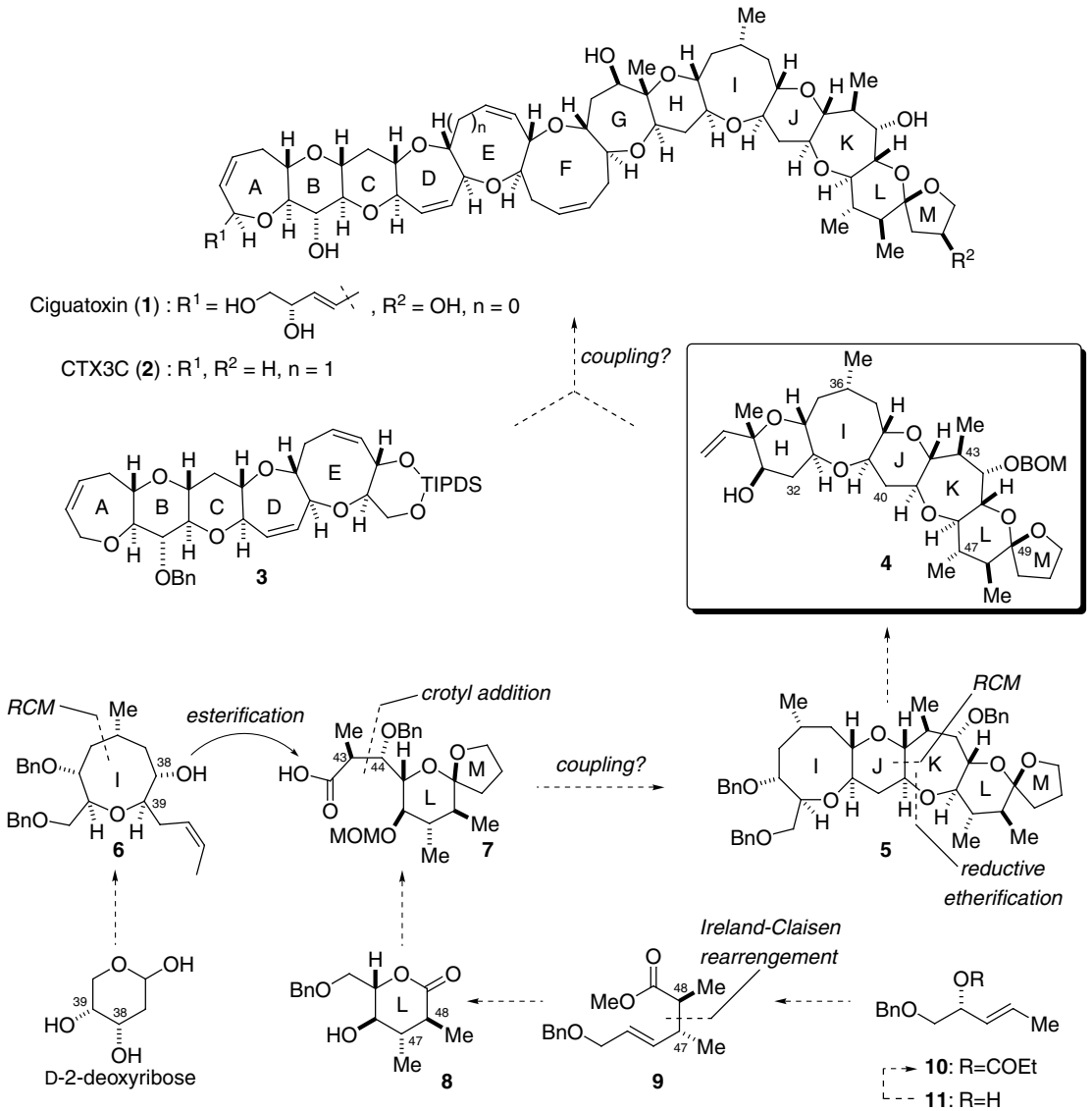


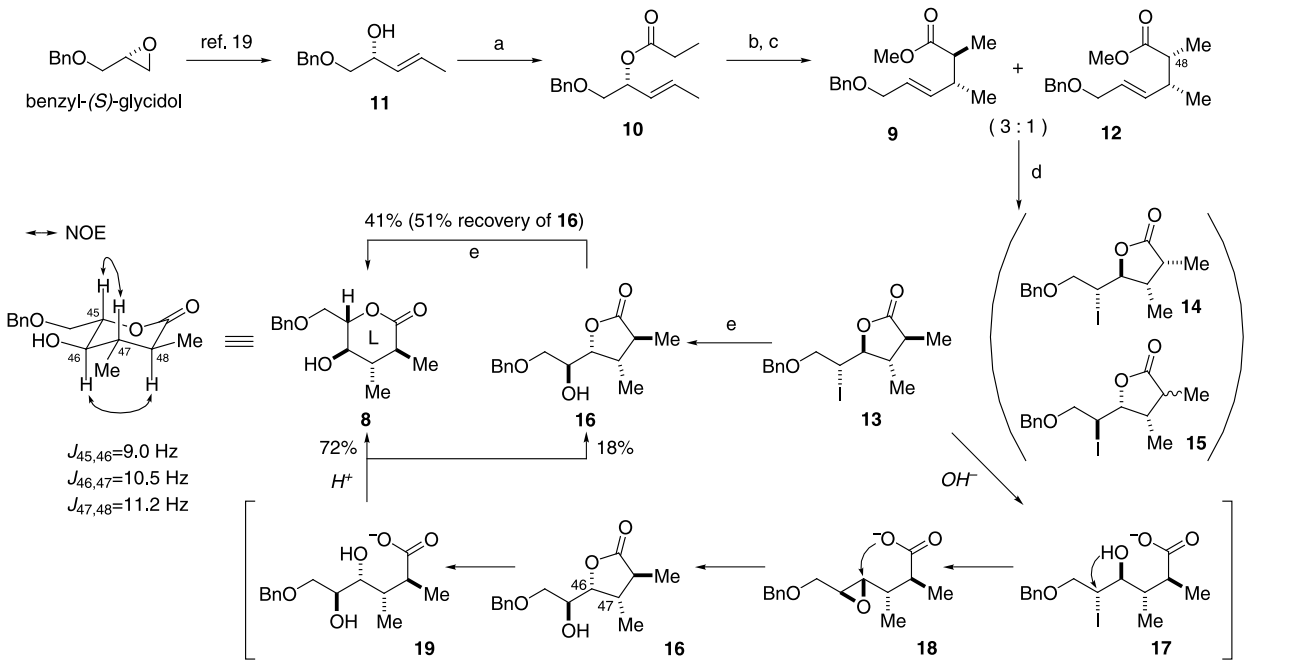
Scheme 1. Structure of ciguatoxins and synthetic strategy for the total synthesis of CTX3C. Bn=benzyl; BOM=benzyloxy methyl; MP=*p*-methoxyphenyl; MPM=*p*-methoxybenzyl; RCM=ring closing olefin metathesis; TIPDS=tetraisopropyl disiloxyl.

contiguous dimethyl groups of **8** will then correspond to the product of the Ireland–Claisen rearrangement (**10**→**9**).[18] In the synthetic direction, successive intramolecular reactions to **9** are expected to reliably introduce the stereocenters into **8**. Thus, the known allylic alcohol **11**[19] was chosen as an appropriate starting material for the synthesis of the LM ring portion.

2.1. Synthesis of the LM ring fragment[12a]

As shown in Scheme 2, synthesis of the L ring lactone **8** started from a glycidol derivative. The allylic ether **11**, prepared from benzyl-(*S*)-glycidol[20] according to the protocol of Ogasawara et al.,[19] was converted to propionate **10** in 90% yield. Enol silyl ether formation from **10** at −78°C and subsequent warming to room temperature resulted in the Ireland–Claisen rearrangement product,[18] which was directly treated with diazomethane to yield a mixture of the desired ester **9** and its C48-epimer **12** (3:1, 88% combined yield). Iodolactonization of this mixture gave the desired lactone **13** as the major product, which was chromatographically separated from other 3 diastereomers (62% yield).[21] Conversion of iodolactone **13** to δ-lactone **8** was achieved through saponification of **13** followed by treatment with acetic acid at 60°C, affording the desired product in 72% yield along with γ-lactone **16** in 18% yield. The isolated γ-lactone **16** was equilibrated under the same conditions to provide a mixture of **8** (41%) and **16** (51%). For large-scale synthesis (100 g), it was more convenient to prepare **8** without the separation of the mixture of **13**–**15** (39% yield from **9** and **12**). The structure of **8** was determined with the NOEs and the coupling constants indicated in Scheme 2.

The mechanism of conversion of iodolactone **13** to the L ring lactone **8** is shown in Scheme 2. Hydroxy carboxylate **17**, formed by saponification of **13**, transforms to epoxide **18**,[22] which undergoes intramolecular attack by the carboxylate group to give γ-lactone **16** with the stereochemical inversion of the C46 center. A second saponification affords the dihydroxy carboxylate **19**, acidic treatment of which leads to γ-lactone **16** and δ-lactone **8**. Since it was



Scheme 2. *Reagents and conditions*: (a) propionyl chloride, pyridine, 0°C to rt, 90%; (b) LDA, TMSCl, THF-HMPA, −80°C to rt; (c) CH_2N_2, 88% (2 steps); (d) I_2, CH_3CN, rt, 62%; (e) NaOH aq., EtOH, rt, then AcOH, 60°C, 1 h. Bn=benzyl; HMPA=hexamethylphosphoramide; LDA=lithium diisopropylamide; TMS=trimethylsilyl.

found that **8** isomerizes into its γ-form **16** after extended exposure to acid, **8** appears to be a kinetic product under these conditions.

The synthesis of the LM ring fragment **7** was continued as illustrated in Scheme 3. After protection of the C46-alcohol of **8** as its MOM ether, the addition of allyl magnesium bromide to **20** introduced the carbon chain corresponding to the M ring, to yield ketal **21**. A hydroboration–oxidation sequence on the terminal olefin of **21** followed by acid treatment afforded the thermodynamically stable spiroketal **22** in 75% overall yield from **20**. The liberation of the primary alcohol of **22** by hydrogenolysis and subsequent oxidation under Swern conditions led to the aldehyde **24**. Then, treatment of **24** with (*R*,*R*)-diisopropyl tartrate (*Z*)-crotylboronate **25**[23] resulted in the stereoselective introduction of both the C43-methyl and C44-hydroxyl groups. After benzylation of the newly formed secondary alcohol, **26** was isolated as a single isomer in 52% yield over the 3 steps. Finally, oxidative cleavage of the olefin of **26** and subsequent oxidation provided the LM carboxylic acid **7** quantitatively.

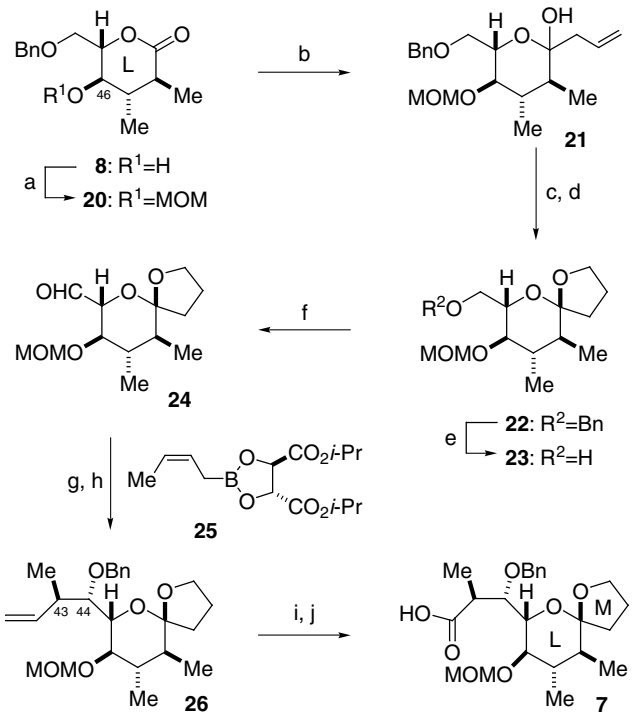
2.2. Synthesis of the I ring fragment[12c]

Synthesis of the 8-membered I ring moiety is illustrated in Scheme 4. Although we have previously prepared the I ring based on a ring-expansion method,[24] a more practical route has been developed based on an aldol–RCM strategy.[9e,f,25] The Wittig reaction of D-2-deoxyribose and subsequent protection of the 1,3-diol gave the *p*-methoxybenzylidene acetal **27**, which was converted to glycolate **28** by *O*-alkylation with *t*-butyl bromoacetate. Aldol reaction of the ester **28** with acrolein gave the adduct **29** as an epimeric mixture of C34-alcohols (44%) along with 33*S*-diastereomers **30** (44%). The chromatographically isolated **29** was submitted to the RCM reaction with Grubbs catalyst[14] to provide the 8-membered cyclic ether **31** in 75% yield. The ester of **31** was reduced by $LiAlH_4$, and the newly formed primary alcohol was protected selectively as its TBDPS ether to give **32** (74%, 2 steps). The secondary alcohol of **32** was converted to ketone **33** by Swern oxidation. Stereoselective introduction of the C36-methyl group was successfully achieved by conjugate addition of $Me_2Cu(CN)Li_2$ to enone **33**, resulting in a single isomer **34** in 69% yield (2 steps). As shown in Fig. 1, the stereoselectivity can be explained by examining the three-dimensional structure of **33**, where one face of the olefin is blocked by the projecting H38. Removal of the TBDPS ether from **34** using TBAF buffered with AcOH, followed by stereoselective reduction with $NaBH(OAc)_3$,[26] led to diol **35** with the correct stereochemistry (92% yield). Through these synthetic procedures, over 10 g of **35** was provided.

Functional group manipulations of **35** were performed in order to couple **35** with the LM ring fragment **7** (Scheme 4). Benzyl protection of **35** and removal of the *p*-methoxybenzylidene acetal provided diol **37** in 83% overall yield (2 steps). The one-carbon homologation of **37** via two-step sequence led to cyanide **39** in 84% yield. Finally, DIBAL-reduction of nitrile **39** and Wittig olefination gave olefin **6** (*Z*/*E*=4:1, 76%, 2 steps).

2.3. Construction of the J ring[12b,c]

Having synthesized both fragments, the I ring (**6**) and the LM ring (**7**), we examined the coupling reaction and the ensuing construction of the J ring (Scheme 5). We initially planned to construct the J ring by cyclization using an ester olefination–RCM sequence through the action of Tebbe reagent,[27] according to the method developed by Nicolaou and co-workers.[28] We coupled the I ring alcohol **6** with LM



Scheme 3. *Reagents and conditions*: (a) MOMCl, *i*-Pr_2NEt, $(CH_2Cl)_2$, 50°C, 95%; (b) CH_2=$CHCH_2MgBr$, THF, −70°C; (c) $(Sia)_2BH$, THF, 0°C, then $NaHCO_3$, H_2O_2; (d) CSA, $(CH_2Cl)_2$, rt, 75% (3 steps); (e) H_2, 20% $Pd(OH)_2$/C, AcOEt, rt, 100%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −80 to −60°C; (g) **25**, toluene, −80 to −70°C; (h) BnBr, NaH, DMF, THF, rt, 52% (3 steps); (i) OsO_4, NMO, *t*-BuOH, H_2O, rt, then $NaIO_4$, rt; (j) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH, H_2O, rt, 99% (2 steps). Bn=benzyl; CSA=10-camphorsulfonic acid; MOM=methoxymethyl; NMO=4-methylmorpholine *N*-oxide; Sia=1,2-dimethylpropyl.

carboxylic acid **7** by esterification to afford the olefinic ester **40** in 75% yield, followed by treatment with Tebbe reagent (**41**) to produce the cyclic enol ether **42**. The yield of **42** varied from 0 to 63%, and in the low-yield reactions,

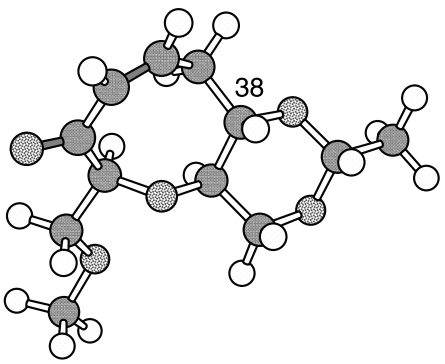
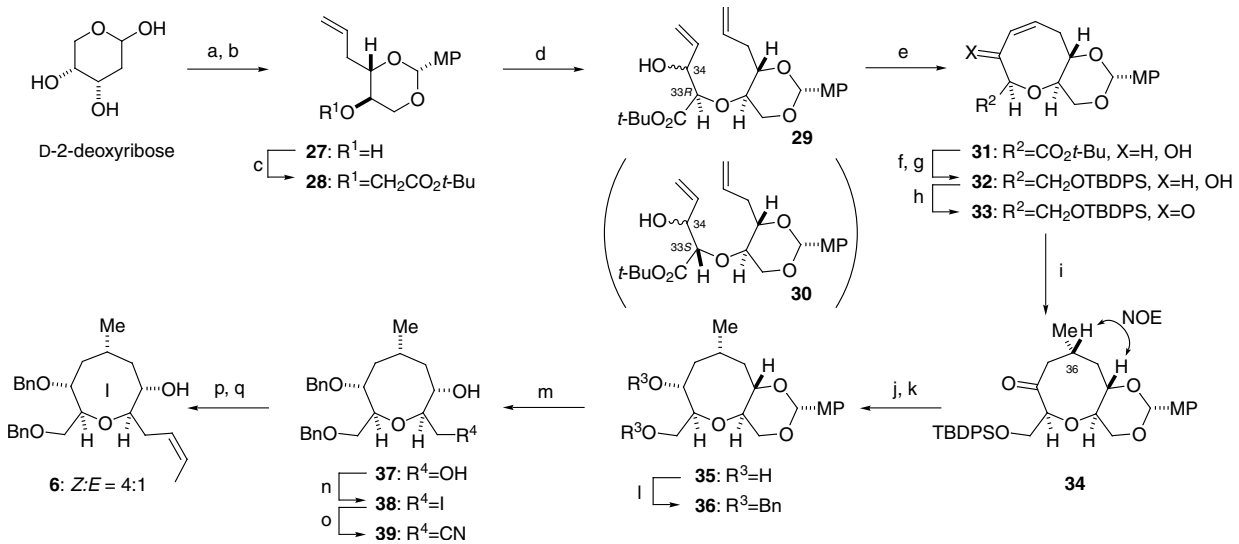


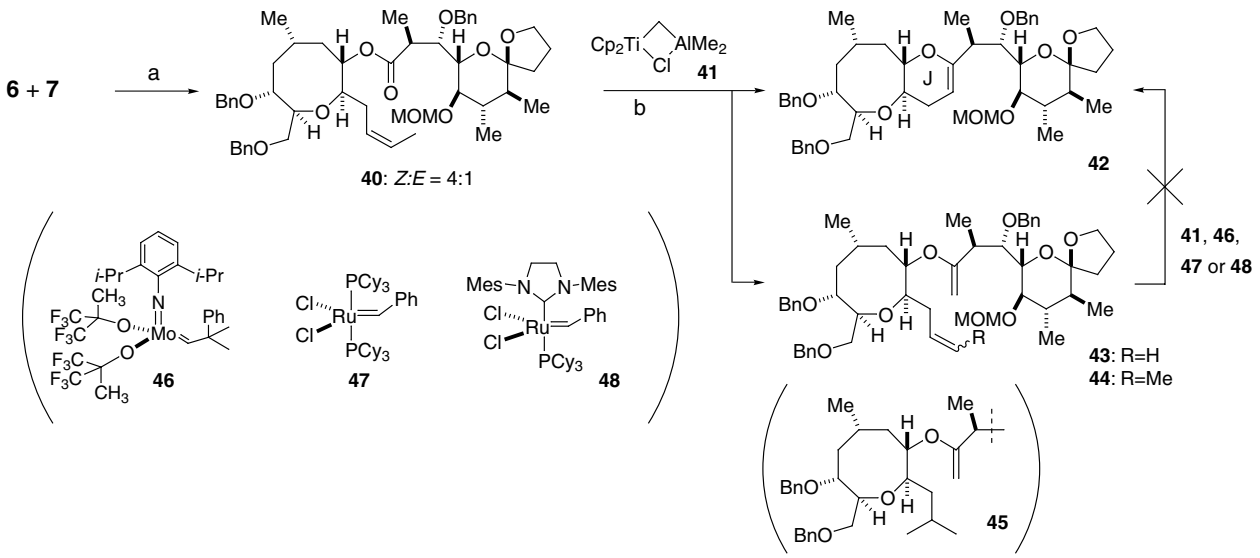
Figure 1. Energy-minimized structure of **33** (MM2*, MacroModel Ver. 6.0). Protecting groups are replaced by methyl groups for clarity.

significant amounts of the *exo*-enol ethers **43**–**45** were produced. Despite extensive investigations, reproducible conditions to form **42** could not be secured. Treatment of the obtained mixture of *exo*-enol ethers (**43**, **44**) with **41**, the Schrock catalyst (**46**),[29] the Grubbs catalyst (**47**)[14] or the *N*-heterocyclic carbene (NHC)-Grubbs catalyst (**48**),[30] did not give the cyclized product **42**,[31] indicating that these RCM catalysts could not induce the cyclization, presumably because of steric hindrance around the *exo*-enol ether.

The unsuccessful cyclizations of diene **44** suggested that the intermediate for the 6-membered ring formation of our substrate might not be the titanium alkylidene complex **49**, in contrast to the literature precedents (**49**→**50**→**42**, Scheme 6).[28,31] There is the possibility that the desired product **42** may be obtained directly by carbonyl olefination of **51**, formed through the addition of the Tebbe reagent to the olefin before *exo*-enol ether formation. In this mechanism, the strong affinity between the titanium and the carbonyl oxygen could favorably drive the reaction to give the oxatitanacyclobutane **52**, despite the steric hindrance, leading to the product **42**. From these considerations, it



Scheme 4. *Reagents and conditions*: (a) Ph_3PMeBr, *t*-BuOK, THF, 0–35°C; (b) $MPCH(OMe)_2$, CSA, CH_2Cl_2, reflux, 76% (2 steps); (c) *t*-BuO_2CCH_2Br, NaH, THF, DMF, 0°C to rt, 82%; (d) LDA, acrolein, THF, −70°C, **29**: 44%, **30**: 44%; (e) $(PCy_3)_2Cl_2Ru$=CHPh (10 mol%), CH_2Cl_2 (0.01 M), reflux, 24 h, 75%; (f) $LiAlH_4$, THF, 0°C to rt; (g) TBDPSCl, Et_3N, CH_2Cl_2, rt, 74% (2 steps); (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −80 to −50°C; (i) $Me_2Cu(CN)Li_2$, Et_2O, −80°C, 69% (2 steps); (j) TBAF, AcOH, THF, rt, 90%; (k) $NaBH(OAc)_3$, AcOH, CH_3CN, −40°C to rt, 92%; (l) BnBr, NaH, THF, DMF, 0°C to rt, quant.; (m) $TsOH{\cdot}H_2O$, MeOH, H_2O, rt, 83%; (n) I_2, PPh_3, imidazole, THF, 0°C to rt, 87%; (o) NaCN, DMSO, 40°C, 97%; (p) DIBAL, CH_2Cl_2, −80 to −60°C; (q) Ph_3PEtBr, *t*-BuOK, THF, 0°C to rt, 76% (2 steps, *Z*/*E*=4:1). Bn=benzyl; CSA=10-camphorsulfonic acid; Cy=cyclohexyl; LDA=lithium diisopropylamide; MP=*p*-methoxyphenyl; TBAF=tetrabutylammonium fluoride; TBDPS=*t*-butyldiphenylsilyl; TsOH=*p*-toluenesulfonic acid.



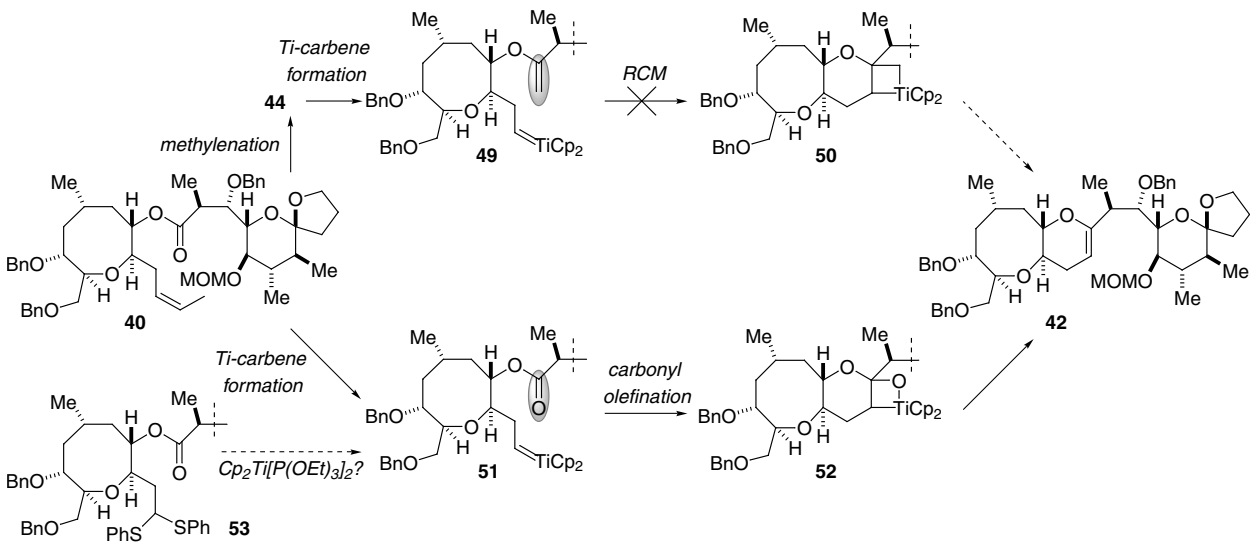
Scheme 5. *Reagents and conditions*: (a) DCC, DMAP, CSA, CH_2Cl_2, 35°C, 1 d, 75%; (b) **41**, THF, 60°C, **42**: trace–63%, **43**–**45**: 18–70%. Cp=cyclopentadienyl; CSA=10-camphorsulfonic acid; Cy=cyclohexyl; DCC=1,3-dicyclohexylcarbodiimide; DMAP=*p*-(dimethylamino)pyridine; Mes=2,4,6-trimethylphenyl.

was anticipated that selective formation of the intermediate **51** would increase both the yield and reproducibility of the cyclization. Very recently, Takeda et al. reported the carbonyl olefination reaction of titanium carbenes, which were selectively generated from bis(phenylthio)acetals by the action of a low-valent titanium complex $Cp_2Ti[P(OEt)_3]_2$ (see **53**→**51**).[32] In light of this, we modified our initial strategy such that the dithioacetal **53** acts as the precursor for **42**.

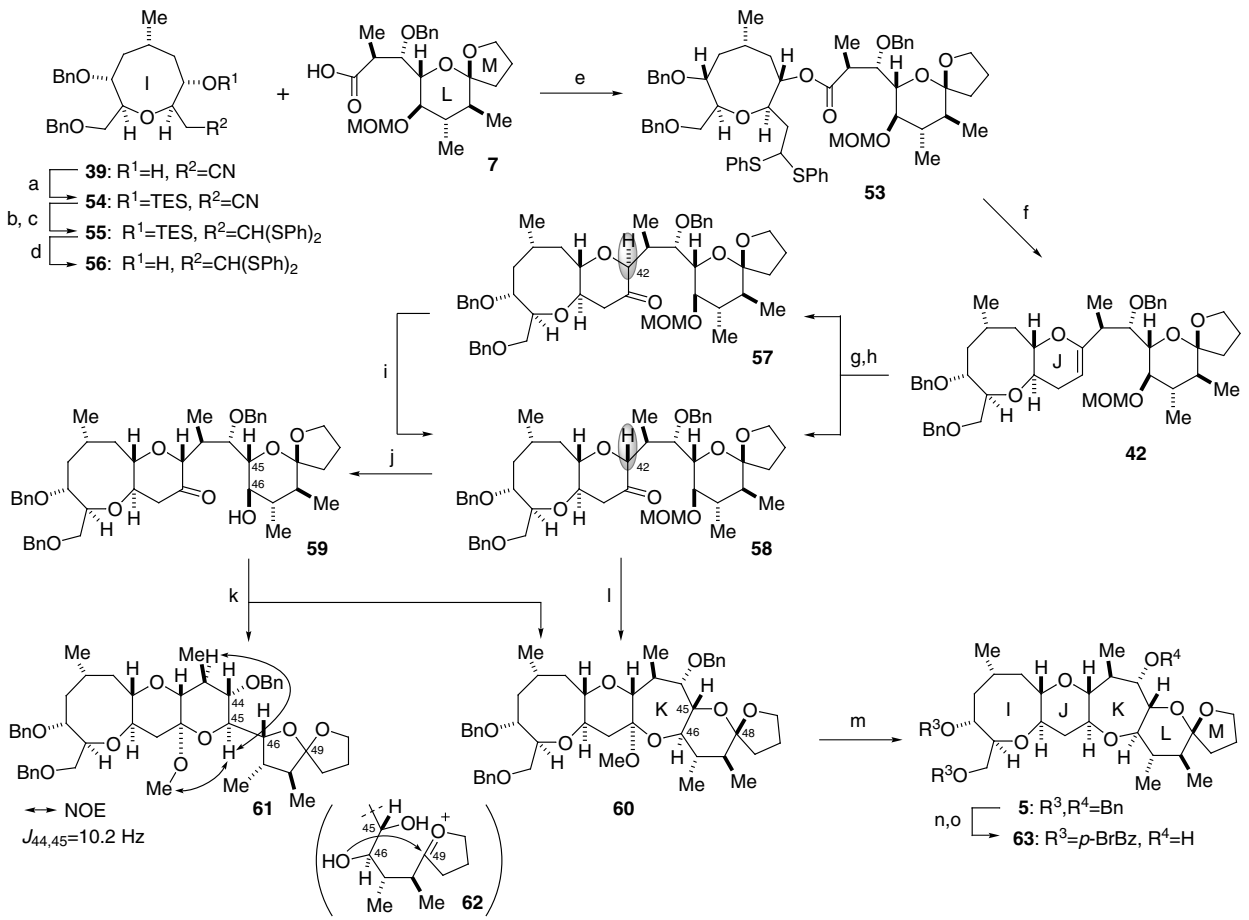
The modified synthetic route to **42** is shown in Scheme 7. The secondary alcohol of **39** was protected as its TES ether to afford **54**. DIBAL reduction of the nitrile of **54** to the aldehyde, followed by treatment with PhSSPh and Bu_3P,[33] gave rise to the dithioacetal **55** in 73% yield over 3 steps. After removal of the TES group of **55**, **56** was coupled with the carboxylic acid **7** to give ester **53** in 76% yield. Fulfilling our expectations, treatment of **53** with the low-valent titanium complex $Cp_2Ti[P(OEt)_3]_2$ in refluxing THF generated the desired enol ether **42** in a reproducible manner (52–67%).[34] This novel methodology based on intramolecular carbonyl olefination routinely supplies multi-gram quantities of **42**, and can be applied to a wide variety of complex substrates.

2.4. Construction of the K ring[12b,c]

The next task in the synthesis was the stereocontrolled construction of the K ring by reductive etherification (Scheme 7).[16] Hydroboration of **42** followed by Swern oxidation produced the C42-epimeric ketones **57** and **58** (2–3:1), which were subsequently separated by silica gel chromatography. Isomerization of the undesired ketone **57** was realized by using DBU in dichloromethane (**57**/**58**=1:1). After three cycles of isomerization, the desired ketone **58** was obtained in 64% combined yield. The subsequent step, transformation of ketone **58** to the 7-membered methylketal **60**, was found to be problematic. For



Scheme 6. Mechanistic considerations of the J ring cyclization.



Scheme 7. *Reagents and conditions*: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, −30 to −20°C, 86%; (b) DIBAL, CH_2Cl_2, −70°C; (c) PhSSPh, Bu_3P, rt, 73% (2 steps); (d) TBAF, THF, rt, 95%; (e) EDC·HCl, DMAP, CSA, 40°C, 2 d, 76%; (f) $Cp_2Ti[P(OEt)_3]_2$, THF, rt to reflux, 1 h, 52–67%; (g) BH_3·THF, THF, 0°C to rt, NaOH, H_2O_2, 75%; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −70 to −40°C, **58**: 31%, **57**: 57%; (i) DBU, CH_2Cl_2, rt (3 cycles), **58**: 58%, **57**: 12%; (j) TMSBr, CH_2Cl_2, −70 to −50°C; (k) TfOH, $CH(OMe)_3$, benzene, rt, 3 h, **60**: ~50%, **61**: ~40%; (l) TfOH, $CH(OMe)_3$, hexane, rt, 20 h, **60**: 84%; (m) Et_3SiH, BF_3·OEt_2, CH_2Cl_2, −50 to −20°C, 1 h, 71%; (n) H_2, $Pd(OH)_2$/C, AcOEt, MeOH, AcOH, rt, 99%; (o) *p*-BrBzCl, DMAP, Et_3N, CH_2Cl_2, rt, 65%. Bn=benzyl; BOM=benzyloxymethyl; Bz=benzoyl; Cp=cyclopentadienyl; DBU=1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL=diisobutylaluminum hydride; DMAP=*p*-(dimethylamino)pyridine; EDC=1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; TBAF=tetrabutylammonium fluoride; TES=triethylsilyl; Tf=trifluoromethanesulfonyl; TMS=trimethylsilyl.

example, removal of the MOM group of **58** using TMSBr provided the C46-alcohol **59**, which when treated with trimethyl orthoformate in the presence of TfOH gave **60** (~50%) along with a considerable amount of the 6-membered methylketal **61** (~40%). The structure of **61** was determined from NOE experiments and coupling values (Scheme 7), and it was revealed that the LM spiroketal partially isomerized into the 5-5 spiroketal under acidic conditions (**59→62**), with subsequent methyl ketal formation affording **61**. As it was anticipated that the spiroketal isomerization could be suppressed without liberation of C46–OH, direct methyl ketalization from the MOM-protected **58** was pursued. This approach proved successful, with the 7-membered ketal **60** obtained in good yield (84%) by treatment of **58** with trimethyl orthoformate and TfOH in hexane. The final reductive etherification of the methylketal **60** was realized by treatment with BF_3·OEt_2 (2 equiv.) in the presence of Et_3SiH at −60°C to −20°C. In this way, the IJKLM ring fragment **5** was isolated in 71% yield. This reductive etherification is particularly sensitive to the reaction conditions: at higher reaction temperature (>−10°C) or with excess BF_3·OEt_2, reductive opening of the C49-spiroketal occurred.

The stereochemistry of the IJKLM ring system **5** was confirmed unambiguously by X-ray crystallography of the bis-*p*-bromobenzoate **63** (Fig. 2),[35] which was prepared by debenzylation of **5** followed by acylation with *p*-bromobenzoyl chloride (Scheme 7).

2.5. Construction of the H ring[12c]

The final task in our synthesis of the HIJKLM ring system was the attachment of the H ring to **5** using the acid-catalyzed epoxide opening reaction as the key step (Scheme 8).[13,36] All of the benzyl groups of **5** were first removed by hydrogenolysis, and the resulting 1,3-diol was protected as its *p*-methoxybenzylidene acetal **64** (76%, 2 steps). After conversion of the remaining C44-alcohol of **64** to the BOM ether **65**, reductive cleavage of the benzylidene acetal with DIBAL regioselectively afforded the MPM ether **66** (100%, 2 steps) without affecting other acetal functionality, such as the C44-BOM ether or the C49-spiroketal. Mesylation of the C32-primary alcohol of **66** and subsequent displacement with cyanide yielded nitrile **67** in 91% over 2 steps. DIBAL reduction of **67** gave an aldehyde, which was subsequently treated with (carbethoxyethylene)triphenylphosphorane to

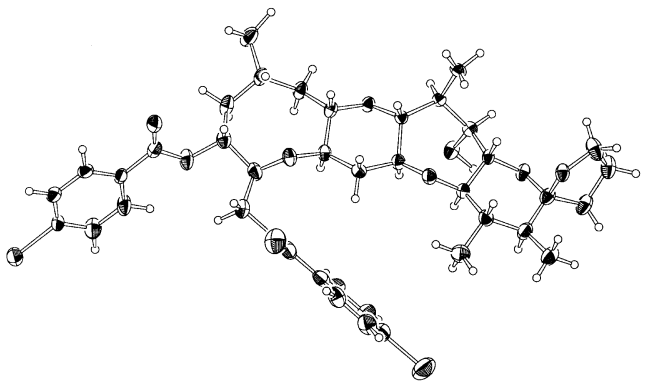


Figure 2. ORTEP drawing of bis-*p*-bromobenzoate **63**.

provide the α,β-unsaturated ester **68** (84% yield, 2 steps). The ester **68** was then reduced to alcohol **69** in 95% yield.

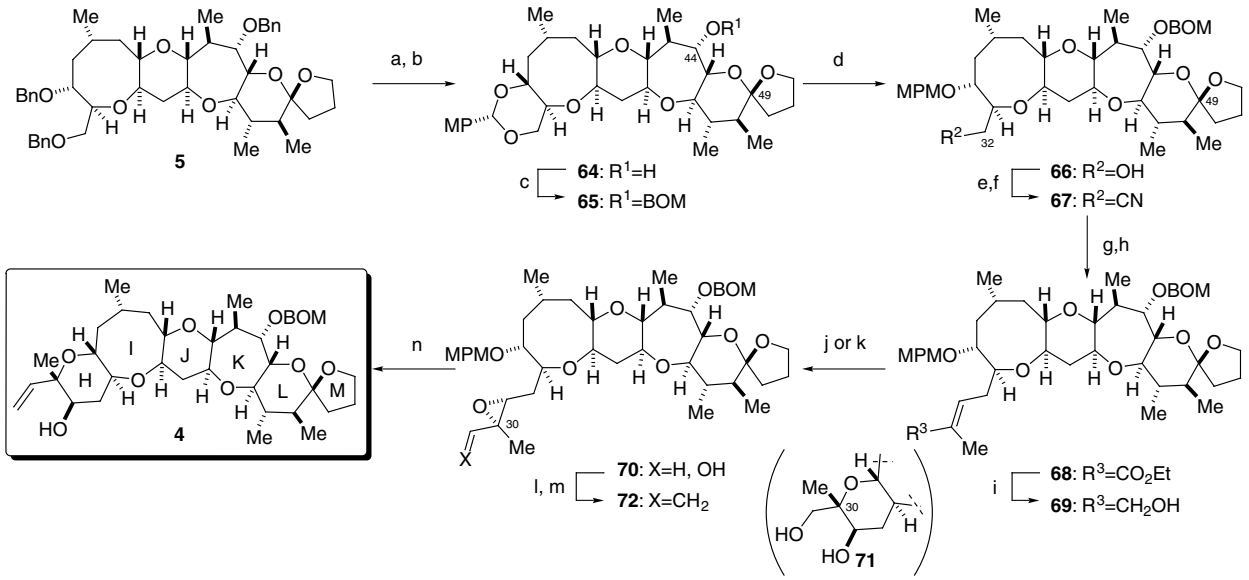
Katsuki–Sharpless epoxidation[37] of **69** at −20°C for 17 h generated only 13% of the epoxy alcohol **70**, while the major product was the 6-membered diol **71** (52%), produced via the 6-*endo* cyclization of **70** with simultaneous removal of the MPM group. Interestingly, the 6-*endo* cyclization was preferred over the 5-*exo* mode, presumably due to the cation-stabilizing ability of the C30-tertiary carbon.[38] In contrast, similar epoxidation at −50 to −40°C gave epoxide **70** in 97% yield without the subsequent cyclization step. The latter epoxidation procedure was therefore employed for production of **70** for further transformation because of the excellent chemical yield. Oxidation of **70** to its aldehyde and subsequent Wittig methylenation gave **72** in 86% yield (2 steps). Finally, treatment of **72** with DDQ in CH_2Cl_2–H_2O (20:1) led to the cleavage of the MPM ether, and in situ cyclization of the resulting epoxy alcohol under the mild acidic reaction conditions afforded the hexacyclic product **4** in 88% yield. Thus, the construction of the H ring was accomplished in 41% overall yield over 13 steps from the IJKLM ring fragment **5**.

3. Conclusion

Firstly, we established concise routes to the I ring fragment **56** and the LM ring fragment **7**: the I ring **56** was constructed via an aldol–RCM sequence, while the LM ring **7** was prepared via Ireland–Claisen rearrangement followed by successive emplacement of its requisite stereocenters. These fragments were then coupled by esterification, and the JK rings were built through a novel intramolecular carbonyl olefination using the Takeda reagent $Cp_2Ti[P(OEt)_3]_2$ to give the J ring, followed by a reductive etherification sequence to give the K ring. Finally, the synthesis of the full HIJKLM ring system **4** was achieved by constructing the H ring through a 6-*endo*-selective epoxide-opening reaction. The longest linear sequence of this synthesis involves 37 steps from the known allylic alcohol **11**, and the route presented here is highly practical to supply material not only for the total synthesis of CTX3C, but also for the preparation of anti-ciguatoxin antibodies. Further studies in the chemistry and biology of ciguatoxins are currently underway in our laboratory.

4. Experimental

All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF was distilled sodium/benzophenone, diethyl ether (Et_2O) from $LiAlH_4$, acetonitrile, benzene, dichloroethane ($(CH_2Cl)_2$), dichloromethane (CH_2Cl_2), diisopropylamine, diisopropylethylamine (*i*-Pr_2NEt), hexane, pyridine,



Scheme 8. *Reagents and conditions*: (a) $Pd(OH)_2/C$, H_2, AcOEt, MeOH, AcOH, rt; (b) $MPCH(OMe)_2$, CSA, THF, rt, 76% (2 steps); (c) BOMCl, *i*-Pr_2NEt, $(CH_2Cl)_2$, 40°C; (d) DIBAL, CH_2Cl_2, −80 to −40°C, 100% (2 steps); (e) MsCl, Et_3N, $(CH_2Cl)_2$, 0°C; (f) NaCN, 18-crown-6, DMF, 50°C, 91% (2 steps); (g) DIBAL, CH_2Cl_2, −80 to −70°C; (h) $Ph_3P{=}CMeCO_2Et$, toluene, rt, 84% (2 steps); (i) DIBAL, CH_2Cl_2, −60°C, 95%; (j) (−)-DET, Ti(O*i*-Pr)$_4$, TBHP, MS4 A, CH_2Cl_2, −20°C, 17 h, **70**: 13%, **71**: 52%; (k) (−)-DET, Ti(O*i*-Pr)$_4$, TBHP, MS4A, CH_2Cl_2, −50 to −40°C, 3 h, **70**: 97%; (l) SO_3·Py, Et_3N, DMSO, $(CH_2Cl)_2$, rt; (m) Ph_3PCH_3Br, NaHMDS, THF, 0°C, 86% (2 steps); (n) DDQ, CH_2Cl_2–H_2O (20:1), rt, 7 h, 88%. Bn=benzyl; BOM=benzyloxymethyl; DET=diethyl tartrate; DDQ=2,3-dichloro-5.6-dicyano-1,4-benzoquinone; DIBAL=diisobutylaluminum hydride; HMDS=bis(trimethylsilyl)amide; MP=*p*-methoxyphenyl; MPM=*p*-methoxybenzyl; Ms=methanesulfonyl; MS=molecular sieves; TBHP=*t*-butylhydroperoxide.

triethylamine (Et_3N), and toluene from calcium hydride, and DMF, DMSO and HMPA from calcium hydride under reduced pressure. All other reagents were used as supplied unless otherwise stated.

Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates. Column chromatography was performed using 100–210 μm Silica Gel 60N (Kanto Chemical Co., Inc.), and for flash column chromatography 40–50 μm Silica Gel 60N (Kanto Chemical Co., Inc.) was used.

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 (200 MHz), a Varian INOVA 500 (500 MHz), or Bruker AM-600 (600 MHz) spectrometer. Chemical shifts are reported in δ (ppm) using residual $CHCl_3$ as an internal standard of δ 7.26 and δ 77.00 for ^1H and ^{13}C NMR, respectively. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Low- and high-resolution mass spectra (MS, HRMS) were recorded on a HITACHI M-2500-S instrument. Time of flight mass spectra (MALDI-TOF MS) were recorded on a PerSeptive Biosystem Voyager DE STR SI-3 instrument. Elemental analysis was conducted with a Yanaco CHN corder MT-5. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus.

4.1. Synthesis of the LM ring fragment

4.1.1. Propionate 10. To a solution of allyl alcohol **11** (228 g, 1.19 mol) in pyridine (300 ml, 3.7 mol) at 0°C were added propionyl chloride (115 ml, 1.32 mol) over 20 min. After 40 min, MeOH (10 ml) was added to the mixture, which was concentrated and subjected to open column chromatography (hexane/EtOAc 1:0–30:1) to give the propionate **10** (266 g, 1.07 mol, 90% yield). R_f=0.70 (hexane/EtOAc 3:1); $[\alpha]_D^{29}$=−16.6 (*c* 1.12, $CHCl_3$); IR (neat) ν 2982, 2944, 2922, 2864, 1738, 1456, 1367, 1274, 1189, 1102, 1029, 967 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 (3H, t, *J*=7.5 Hz), 1.70 (3H, dd, *J*=6.0, 0.9 Hz), 2.35 (2H, q, *J*=7.5 Hz), 3.45–3.60 (2H, m), 4.54 (1H, d, *J*=12.0 Hz), 4.57 (1H, d, *J*=12.0 Hz), 5.40–5.55 (2H, m), 5.65–5.90 (1H, m), 7.23–7.38 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.8, 17.7, 27.7, 71.3, 71.5, 72.9, 73.0, 126.3, 127.4, 128.2, 130.4, 138.0, 173.6; MALDI-TOF MS, calcd for $C_{15}H_{20}O_3Na$ ($M+Na^+$) 271.131, found 271.135.

4.1.2. Methyl esters 9 and 12. *n*-BuLi (103 ml, 1.56 M in hexane, 0.16 mol) was added to a solution of diisopropylamine (30 ml, 0.22 mol) in hexane (100 ml) at 0°C over 15 min, and the solution was concentrated to remove hexane, and dissolved in THF (140 ml). To a solution of propionate **10** (26.7 g, 108 mmol) in THF (280 ml) and HMPA (140 ml) at −80°C was added TMSCl (41 ml, 0.32 mol). The LDA solution was introduced to the reaction mixture over 30 min at −80°C. The solution was allowed to warm to rt over 10 h, and then quenched with saturated aqueous NH_4Cl and 2N HCl at 0°C. The mixture was extracted with Et_2O (×2), and the combined organic layer was extracted with 5% NaOH. The aqueous layer, which contained rearranged carboxylate, was acidified by 2 M H_2SO_4, and extracted with EtOAc. To the solution of rearranged carboxylic acid was added diazomethane at 0°C until the carboxylic acid was consumed. The mixture was stirred overnight at rt, concentrated, and subjected to flash column chromatography (hexane/EtOAc 1:0–5:1) to give a mixture of the methyl esters **9** and **12** (3:1, 24.8 g, 94.5 mmol, 88% combined yield).

4.1.3. Iodolactone 13. A solution of the methyl esters **9** and **12** (3:1, 994 mg, 3.79 mmol) in CH_3CN (25 ml) was added to a solution of I_2 (2.88 g, 11.4 mmol) in CH_3CN (40 ml) at 0°C. After being stirred for 30 min at rt, the mixture was quenched with aqueous $Na_2S_2O_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–4:1) afforded iodolactone **13** (876 mg, 2.34 mmol, 62% yield) and a mixture of the other diastereomers **14** and **15** (153 mg, 0.41 mmol, 11% yield). **13**: IR (neat) ν 3032, 2972, 2936, 2876, 1781, 1547, 1456, 1367, 1317, 1251, 1181, 1075, 1019, 982, 913, 818 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (3H, d, *J*=6.5 Hz), 1.26 (3H, d, *J*=7.0 Hz), 2.12 (1H, ddq, *J*=10.5, 8.2, 6.5 Hz), 2.27 (1H, dq, *J*=10.5, 7.0 Hz), 3.79 (1H, dd, *J*=10.5, 8.0 Hz), 3.86 (1H, dd, *J*=10.5, 5.5 Hz), 4.03 (1H, dd, *J*=8.2, 4.8 Hz), 4.50 (1H, ddd, *J*=8.0, 5.5, 4.8 Hz), 4.54 (1H, d, *J*=12.0 Hz), 4.57 (1H, d, *J*=12.0 Hz), 4.55 (2H, s), 7.28–7.38 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 17.9, 32.4, 43.1, 43.2, 71.9, 73.2, 83.4, 127.8, 128.0, 128.5, 137.3, 177.5.

4.1.4. L ring lactone 8. To a solution of iodolactone **13** (1.62 g, 4.32 mmol) in EtOH (10 ml) at rt was added 15% NaOH (5.1 ml, 4.2 M in H_2O, 22 mmol). After being stirred for 2 h at rt, AcOH (3.5 ml, 60 mmol) was added at 60°C. After additional 1 h at 60°C, the mixture was quenched with saturated aqueous $NaHCO_3$ at rt and extracted with Et_2O (×2). The organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 10:1–4:1) afforded L ring lactone **8** (824 mg, 3.12 mmol, 72% yield) and γ-lactone **16** (206 mg, 0.78 mmol, 18% yield). **8**: white needles; mp 108–110°C; R_f=0.40 (hexane/EtOAc 1:1); $[\alpha]_D^{28}$=−11.1 (*c* 0.59, $CHCl_3$); IR (neat) ν 3428, 2982, 2930, 1734, 1456, 1369, 1243, 1197, 1077, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.12 (3H, d, *J*=6.5 Hz), 1.32 (3H, d, *J*=7.0 Hz), 1.67 (1H, ddq, *J*=11.2, 10.5, 6.5 Hz), 2.13 (1H, dq, *J*=11.2, 7.0 Hz), 2.93 (1H, d, *J*=3.5 Hz), 3.60 (1H, ddd, *J*=10.5, 9.0, 3.5 Hz), 3.69 (1H, dd, *J*=10.2, 5.5 Hz), 3.85 (1H, dd, *J*=10.2, 3.5 Hz), 4.17 (1H, ddd, *J*=9.0, 5.5, 3.5 Hz), 4.56 (1H, d, *J*=11.7 Hz), 4.60 (1H, d, *J*=11.7 Hz), 7.29–7.38 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 15.6, 39.9, 40.8, 70.4, 71.1, 73.9, 80.2, 127.8, 128.1, 128.5, 137.2, 172.7; HRMS (EI), calcd for $C_{15}H_{20}O_4$ 264.1362 (M^+), found 264.1373; Anal. calcd for C, 68.16; H, 7.63, found: C, 68.25; H, 7.69.

4.1.5. Large scale preparation of L ring lactone 8. *n*-BuLi (500 ml, 1.56 M in hexane, 0.78 mol) was added to diisopropylamine (120 ml, 0.86 mol) at 0°C, and the solution was concentrated to remove hexane, and dissolved in THF (600 ml). To a solution of propionate **10** (135 g, 0.54 mol) in THF (1000 ml) and HMPA (680 ml) at −80°C was added TMSCl (215 ml, 1.69 mol). The LDA solution was introduced to the reaction mixture over 30 min at

−80°C. The solution was allowed to warm to rt overnight, and then quenched with water (20 ml) at 0°C. The mixture was extracted with hexane (×4), and the combined organic layer was extracted with 15% NaOH (×2). The combined aqueous layer, which contained rearranged carboxylate, was acidified by 9 M H_2SO_4 and extracted with hexane (×3), and the combined organic layer was washed with 1 M HCl and brine. The same reaction was carried out with the same amount of the propionate **10** (132 g, 0.53 mol), and the crude material was combined. To the solution of rearranged carboxylic acid was added diazomethane (~1200 ml, ~1 M in Et_2O, ~1.2 mol) at 0°C. The mixture was stirred overnight at rt, and then concentrated to give a mixture of the methyl esters **9** and **12** (3:1), which was subjected to the next reaction without further purification.

To a solution of the methyl esters **9** and **12** in CH_3CN (900 ml) at 0°C was added I_2 (341 g, 1.34 mol). After being stirred for 18 h at rt, the additional I_2 (125 g, 0.49 mol) was introduced. After being stirred for 2 d, the additional I_2 (246 g, 1.00 mol) was introduced, again. After 4 h, the mixture was quenched with aqueous $Na_2S_2O_3$ and extracted with hexane/EtOAc (×4). The organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, and concentrated to give a mixture of the iodolactones **13**–**15**, which was subjected to the next reaction without further purification.

To a solution of the iodolactones **13**–**15** in H_2O (600 ml) and EtOH (120 ml) was added 15% NaOH (520 ml, 4.2 M in H_2O, 2.2 mol) at rt. After stirring for 2 d at rt, HCl (290 ml, 6 M in H_2O, 1.7 mol) was added at 0°C. After 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with hexane/EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, concentrated, and recrystalized from hexane/EtOAc (2.5:1, 900 ml) to give the L ring lactone **8**. The mother liquor was concentrated and subjected to flash column chromatography (hexane/EtOAc 10:1–4:1) to afford the products (**8**, **16**, and other diastereomers). A mixture of the γ-lactones was subjected to the saponification–acid treatment sequence, followed by recrystalization and flash column chromatography, to furnish the L ring lactone **8** (total 96.1 g, 0.36 mol, 34%, 4 steps).

4.1.6. MOM ether 20. To a solution of lactone **8** (44.5 g, 169 mmol) and *i*-Pr_2NEt (38 ml, 220 mmol) in $(CH_2Cl)_2$ (80 ml) at rt was added MOMCl (15 ml, 200 mmol), and the reaction mixture was heated to 50°C for 1 d. The mixture was cooled to 0°C and quenched with MeOH (10 ml). The mixture was extracted with hexane/EtOAc (×2), and the organic layer was washed with aqueous saturated NH_4Cl (×2), brine, and dried over $MgSO_4$. Concentration and open column chromatography (hexane/EtOAc 8:1) afforded the MOM ether **20** (49.6 g, 161 mmol) in 95% yield. **20**: white needles; mp 62–63°C; R_f=0.60 (hexane/EtOAc 1:1); $[\alpha]_D^{21}$=−27.7 (*c* 0.598, $CHCl_3$); IR (film) ν 2933, 1731, 1496, 1455, 1383, 1361, 1299, 1236, 1186, 1147, 1074, 1029, 961, 920, 793, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (3H, d, *J*=6.5 Hz, Me56), 1.29 (3H, d, *J*=7.5 Hz, Me57), 1.71–1.80 (1H, m, H47), 2.22 (1H, dq, *J*=11.5, 7.5 Hz, H48), 3.36 (3H, s, MOM), 3.63 (1H, dd, *J*=10.5, 7.5 Hz, H46), 3.71 (1H, dd, *J*=10.5, 2.5 Hz, H44), 3.76 (1H, dd, *J*=11.0, 3.0 Hz, H44), 4.29 (1H, dd, *J*=7.0, 3.0 Hz, H45), 4.53 (1H, d, *J*=12.5 Hz, Bn), 4.59 (1H, d, *J*=12.0 Hz, Bn), 4.62 (1H, d, *J*=7.0 Hz, MOM), 4.71 (1H, d, *J*=6.5 Hz, MOM), 7.26–7.36 (5H, m, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 16.3, 38.8, 39.9, 56.2, 69.3, 73.6, 77.5, 81.6, 97.9, 127.74, 127.76, 128.4, 137.6, 173.6; HRMS (EI), calcd for $C_{17}H_{24}O_5$ 308.1624 (M^+), found 308.1628; Anal. calcd for C, 66.21; H, 7.84, found C, 66.04; H, 7.95.

4.1.7. Spiroketal 22. To a solution of the MOM ether **20** (44.3 g, 144 mmol) in THF (700 ml) at −70°C was added allylmagnesium bromide (190 ml, 0.74 M in THF, 140 mmol) over 1 h. After 10 min, additional allylmagnesium bromide (20 ml, 0.74 M in THF, 15 mmol) was introduced to complete the reaction, and the mixture was quenched with aqueous saturated NH_4Cl at −70°C. The mixture was extracted with hexane/EtOAc (×2), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude hemiacetal **21** was subjected to the next step without further purification.

To a solution of the hemiacetal **21** in THF (140 ml) at 0°C was added disiamylborane [$(Sia)_2BH$, 300 ml, 1 M in THF, 300 mmol] dropwise over 1 h. After 10 min, additional $(Sia)_2BH$ (30 ml, 1 M in THF, 30 mmol) was introduced to complete the reaction. MeOH (10 ml) was carefully poured into the reaction mixture, followed by addition of aqueous saturated $NaHCO_3$ (470 ml) and 30% aqueous H_2O_2 (130 ml), while the internal reaction temperature was kept below at 20°C with ice bath. After being stirred overnight at rt, the mixture was treated with aqueous saturated $Na_2S_2O_3$ (30 ml), and extracted with EtOAc (×3). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude alcohol was subjected to the next step without further purification.

To a solution of the alcohol in $(CH_2Cl)_2$ (140 ml) at rt was added CSA (1.0 g, 4.3 mmol). After 3 h, the mixture was quenched with aqueous saturated $NaHCO_3$ and extracted with EtOAc (×3). The organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 25:1–4:1) afforded the desired spiroketal **22** (37.5 g, 107 mmol, 75% yield for 3 steps) and its C49-epimer (7.3 g, 21 mmol, 15% yield for 3 steps). **22**: colorless oil; R_f=0.60 (hexane/EtOAc 3:1); $[\alpha]_D^{31}$=−35.3 (*c* 0.956, $CHCl_3$); IR (film) ν 2973, 2888, 1454, 1364, 1145, 1097, 1041, 921, 870, 734, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, d, *J*=6.5 Hz), 1.03 (3H, d, *J*=6.5 Hz), 1.54–1.70 (2H, m), 1.72–1.83 (1H, m), 1.84–2.06 (3H, m), 3.19 (1H, t, *J*=9.8 Hz), 3.34 (3H, s), 3.60 (1H, dd, *J*=11.0, 2.0 Hz), 3.64 (1H, dd, *J*=11.0, 4.0 Hz), 3.74–3.78 (1H, m), 3.81–3.92 (2H, m), 4.54 (1H, d, *J*=6.0 Hz), 4.55 (1H, d, *J*=12.5 Hz), 4.61 (1H, d, *J*=12.5 Hz), 4.68 (1H, d, *J*=6.5 Hz), 7.25–7.35 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 15.7, 24.3, 34.8, 39.3, 41.9, 56.1, 67.4, 69.6, 72.2, 73.2, 79.5, 98.0, 108.1, 127.4, 127.8, 128.2, 138.3; MALDI-TOF MS, calcd for $C_{20}H_{30}O_5Na$ 373.199 ($M+Na^+$), found 373.196.

4.1.8. Alcohol 23. To a solution of benzyl ether **22** (20.4 g, 58.2 mmol) in EtOAc (60 ml) at rt was added 20% $Pd(OH)_2/C$ (0.93 g, 1.3 mmol), and the mixture was stirred under hydrogen. After 1 d, the catalyst was filtered off, and

the solvent was removed under reduced pressure to give the alcohol **23** (15.1 g, 58.1 mmol) in 100% yield. **23**: colorless oil; R_f=0.40 (hexane/EtOAc 1:1); $[\alpha]_D^{30}=-96.6$ (*c* 1.044, $CHCl_3$); IR (film) ν 3479, 2973, 2887, 1461, 1381, 1302, 1214, 1143, 1098, 1038, 921, 868 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, d, *J*=7.0 Hz), 1.01 (3H, d, *J*=6.0 Hz), 1.54 (1H, dq, *J*=11.0, 6.5 Hz), 1.63–1.71 (1H, m), 1.73–1.87 (2H, m), 1.90–2.03 (2H, m), 2.56 (1H, bs), 3.16 (1H, t, *J*=9.8 Hz), 3.42 (3H, s), 3.59–3.72 (2H, m), 3.76–3.91 (3H, m), 4.68 (1H, d, *J*=6.5 Hz), 4.71 (1H, d, *J*=6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 15.5, 24.3, 34.9, 39.6, 42.1, 56.3, 62.5, 67.6, 72.7, 79.9, 98.8, 108.3; HRMS (EI), calcd for $C_{13}H_{24}O_5$ 260.1624 (M^+), found 260.1625.

4.1.9. Benzyl ether 26. A solution of alcohol **23** (4.68 g, 18.0 mmol) in CH_2Cl_2 (40 ml) was added to a solution of DMSO (2.6 ml, 36 mmol) and $(COCl)_2$ (2.4 ml, 27 mmol) in CH_2Cl_2 (150 ml) at −80°C. After 15 min at the same temperature, Et_3N (10.0 ml, 72 mmol) was added, and the mixture was allowed to warm to −60°C over 2 h, and then quenched with aqueous NH_4Cl at −60°C. The mixture was extracted with Et_2O (×2), and the organic layer was washed with aqueous saturated NH_4Cl and brine, and dried over $MgSO_4$. Concentration and florisil column chromatography afforded aldehyde **24**, which was subjected to the next reaction immediately.

To a solution of aldehyde **24** in toluene (90 ml) at −80°C was added (*R*,*R*)-diisopropyl tartrate (*Z*)-crotylboronate (27 ml, ~0.7 M in toluene, ~19 mmol) dropwise over 20 min. After 15 min at −70°C, $NaBH_4$ (150 mg) and EtOH (25 ml) were added to reduce unreacted aldehyde, and the mixture was allowed to warm to rt. To this solution was introduced 15% aqueous NaOH (10 ml), and the mixture was stirred for 3 d to saponify the tartrate of the reagent, and then extracted with Et_2O (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 15:1–10:1) afforded the homoallyl alcohol (4.8 g), which was subjected to the next reaction without further purification. R_f=0.70 (hexane/EtOAc 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, d, *J*=7.0 Hz), 1.00 (3H, d, *J*=7.0 Hz), 1.03 (3H, d, *J*=7.0 Hz), 1.53 (1H, dq, *J*=13.5, 6.5 Hz), 1.67–1.83 (3H, m), 1.88–2.03 (2H, m), 2.59–2.67 (1H, m), 3.19 (1H, t, *J*=9.8 Hz), 3.28 (1H, d, *J*=4.5 Hz), 3.41 (3H, s), 3.66 (1H, dt, *J*=6.0, 4.5 Hz), 3.73 (1H, dd, *J*=9.5, 6.5 Hz), 3.85–3.91 (1H, m), 4.70 (1H, d, *J*=6.0 Hz), 4.79 (1H, d, *J*=6.0 Hz), 5.03 (1H, bd, *J*=11.0 Hz), 5.07 (1H, bd, *J*=17.5 Hz), 5.93 (1H, ddd, *J*=17.0, 10.5, 7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.7, 13.5, 15.5, 24.5, 35.1, 38.9, 40.3, 42.2, 56.2, 68.2, 71.5, 76.8, 84.8, 98.9, 107.9, 113.8, 142.8; MALDI-TOF MS, calcd for $C_{17}H_{30}O_5Na$ 337.199 ($M+Na^+$), found 337.192.

To a solution of the homoallyl alcohol (4.8 g) in THF (5 ml) and DMF (5 ml) at 0°C were added NaH (1.3 g, 60% oil suspension, 32 mmol) and BnBr (2.8 ml, 23 mmol). After 7 h at rt, MeOH was added to the mixture, and the resultant solution was extracted with hexane/EtOAc (×2). The organic layer was washed with aqueous saturated NH_4Cl and brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–20:1) gave the benzyl ether **26** (3.79 g, 9.36 mmol) in 52% yield over 3 steps. **26**: pale yellow oil; R_f=0.75 (hexane/EtOAc 3:1); $[\alpha]_D^{30}=-50.2$ (*c* 1.158, $CHCl_3$); IR (film) ν 3030, 2974, 2930, 2881, 1497, 1455, 1363, 1097, 1070, 1029, 920, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, d, *J*=6.5 Hz, Me57), 1.04 (3H, d, *J*=6.5 Hz, Me56), 1.09 (3H, d, *J*=6.5 Hz, Me55), 1.51 (1H, dq, *J*=11.0, 7.0 Hz, H48), 1.62–1.70 (1H, m, H47), 1.74–1.81 (2H, m, H50, 51), 1.90–1.94 (1H, m, H50), 1.97–2.04 (1H, m, H51), 2.60 (1H, sextet, *J*=7.5 Hz, H43), 3.25 (1H, t, *J*=10.0 Hz, H46), 3.33 (1H, dd, *J*=8.5, 1.0 Hz, H44), 3.38 (3H, s, MOM), 3.80 (1H, q, *J*=7.5 Hz, H52), 4.02 (1H, dd, *J*=10.0, 1.0 Hz, H45), 4.50 (1H, d, *J*=11.5 Hz, Bn), 4.63 (1H, d, *J*=6.0 Hz, MOM), 4.76 (1H, d, *J*=11.5 Hz, Bn), 4.79 (1H, d, *J*=6.0 Hz, MOM), 4.99 (1H, bd, *J*=10.5 Hz, H41), 5.05 (1H, bd, *J*=17.0 Hz, H41), 5.78 (1H, ddd, *J*=17.0, 10.5, 8.5 Hz, H42), 7.31–7.34 (5H, m, Bn); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 15.8, 17.5, 24.3, 35.0, 40.0, 40.2, 42.1, 56.3, 67.3, 72.9, 73.0, 80.7, 83.6, 98.4, 107.8, 114.5, 127.2, 127.8, 128.1, 139.2, 142.3; MALDI-TOF MS, calcd for $C_{24}H_{36}O_5Na$ 427.246 ($M+Na^+$), found 427.231.

4.1.10. Carboxylic acid 7. To a solution of olefin **26** (420 mg, 1.04 mmol) and NMO (0.65 ml, 50% aqueous solution, 3.12 mmol) in *t*-BuOH (2.5 ml) and H_2O (2.5 ml) at rt was added OsO_4 (550 μl, 19 mM in *t*-BuOH, 10.4 μmol). After 1 d, $NaIO_4$ (440 mg, 2.06 mmol) was added, and the reaction mixture was stirred for additional 1 h, and then diluted with aqueous $NaHCO_3$. The mixture was extracted with Et_2O (×3), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give crude aldehyde, which was immediately subjected to the next reaction without further purification.

To a solution of the aldehyde in *t*-BuOH (8.0 ml) and H_2O (2.0 ml) at rt were added NaH_2PO_4 (600 mg, 3.8 mmol), 2-methyl-2-butene (1.1 ml, 10.4 mmol), and $NaClO_2$ (670 mg, 17.4 mmol). After being stirred for 3 h at rt, the mixture was extracted with EtOAc (×2), and the organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 10:1–1:1) gave the carboxylic acid **7** (437 mg, 1.03 mmol) in 99% yield over 2 steps. **7**: $[\alpha]_D^{31}=-57.1$ (*c* 1.02, $CHCl_3$); IR (film) ν 3400–2800, 2975, 2938, 2888, 1731, 1704, 1497, 1455, 1380, 1097, 1069, 1028, 921, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, d, *J*=6.5 Hz), 1.02 (3H, d, *J*=6.5 Hz), 1.30 (3H, d, *J*=6.5 Hz), 1.52 (1H, dq, *J*=11.0, 6.5 Hz), 1.68 (1H, tq, *J*=10.5, 6.5 Hz), 1.72–1.84 (2H, m), 1.90 (1H, ddd, *J*=13.0, 9.5, 7.0 Hz), 2.01–2.10 (1H, m), 2.86 (1H, quint., *J*=6.5 Hz), 3.09 (1H, t, *J*=10.0 Hz), 3.34 (3H, s), 3.81–3.90 (2H, m), 3.98–4.04 (2H, m), 4.58 (1H, d, *J*=11.5 Hz), 4.65 (1H, d, *J*=6.5 Hz), 4.73 (1H, d, *J*=6.5 Hz), 4.76 (1H, d, *J*=11.5 Hz), 7.25–7.37 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 13.7, 15.7, 24.1, 34.6, 40.0, 41.2, 41.7, 56.2, 67.5, 72.3, 73.5, 79.4, 81.3, 98.5, 108.0, 127.6, 127.7, 128.3, 138.2, 179.3; MALDI-TOF MS, calcd for $C_{23}H_{34}O_7Na$ 445.220 ($M+Na^+$), found 445.232.

4.2. Synthesis of the I ring fragment

4.2.1. *p*-Methoxybenzylidene acetal 27. A mixture of triphenylphosphonium bromide (166 g, 466 mmol) in THF

(1900 ml) was treated with *t*-BuOK (50 g, 447 mmol) at 0°C for 30 min. To the resulting yellow suspension at 0°C was added D-2-deoxyribose (25.0 g, 186 mmol). The mixture was stirred at 35°C for 1 d, and quenched with NH_4Cl (25 g) at 0°C. After 12 h, insoluble salts in the suspension was filtered off, and the resulting solution was concentrated to give a triol, which was subjected to the next reaction without further purification.

To a solution of the triol and anisaldehyde dimethylacetal [$MPCH(OMe)_2$, 52 ml, 280 mmol] in CH_2Cl_2 (370 ml) at rt was added CSA (8.6 g, 37 mmol), and the solution was heated to reflux for 1 d. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C and extracted with hexane/EtOAc. The organic layer was washed with brine, concentrated, and subjected to open column chromatography (hexane/EtOAc 1:0–3:1) to afford *p*-methoxybenzylidene acetal **27** (35.6 g, 142 mmol) in 76% yield over 2 steps. **27**: white solid; mp 38–40°C; R_f=0.48 (hexane/EtOAc 1:1); $[\alpha]_D^{22}$=−23.5 (*c* 0.70, $CHCl_3$); IR (KBr) ν 3417, 3071, 2932, 2845, 1614, 1518, 1429, 1395, 1303, 1251, 1080, 1032, 931, 828, 563 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.40–2.51 (1H, m), 2.58–2.67 (1H, m), 3.54–3.66 (2H, m), 3.81 (1H, s), 4.03–4.25 (2H, m), 5.14 (1H, dd, *J*=10.0, 2.0 Hz), 5.21 (1H, dd, *J*=16.5, 2.0 Hz), 5.45 (1H, s), 5.96–6.05 (1H, m), 6.89–6.91 (2H, m), 7.41–7.43 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.5, 55.2, 65.5, 70.9, 80.9, 100.8, 113.6, 117.4, 127.3, 130.3, 134.3, 159.9.

4.2.2. Glycolate 28. To a solution of the *p*-methoxybenzylidene acetal **27** (12.0 g, 47.9 mmol) and $BrCH_2CO_2t$-Bu (9.2 ml, 62 mmol) in THF (160 ml) and DMF (16 ml) at 0°C was added NaH (2.3 g, 60% oil suspension, 58 mmol). After 18 h at rt, saturated aqueous $NaHCO_3$ was then added to the mixture, and the resultant solution was extracted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 13:1–5:1) gave glycolate **28** (14.3 g, 39.2 mmol) in 82% yield. **28**: white solid; R_f=0.52 (hexane/EtOAc 3:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.48 (9H, s), 2.43 (1H, dtt, *J*=14.5, 7.5, 1.5 Hz), 2.73 (1H, dddt, *J*=14.5, 7.0, 3.5, 1.7 Hz), 3.37 (1H, ddd, *J*=10.5, 9.5, 5.0 Hz), 3.64 (1H, t, *J*=10.5 Hz), 3.72 (1H, ddd, *J*=9.5, 7.0, 3.5 Hz), 3.78 (3H, s), 4.00 (1H, d, *J*=16.0 Hz), 4.07 (1H, d, *J*=16.0 Hz), 4.43 (1H, dd, *J*=10.5, 5.0 Hz), 5.10 (1H, ddt, *J*=10.0, 3.3, 1.6 Hz), 5.16 (1H, ddt, *J*=17.0, 3.3, 1.7 Hz), 5.42 (1H, s), 5.98 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz), 6.86–6.88 (2H, m), 7.38–7.40 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 36.1, 68.3, 69.0, 73.7, 79.8, 81.5, 81.8, 100.6, 100.7, 113.4, 117.1, 127.3, 130.2, 134.2, 159.9, 169.1; MALDI-TOF MS, calcd for $C_{20}H_{28}O_6Na$ ($M+Na^+$) 387.178, found 387.176.

4.2.3. Diene 29. *n*-BuLi (26 ml, 1.56 M in hexane, 41 mmol) was added to diisopropylamine (6.3 ml, 45 mmol) in THF (75 ml) at −70°C, and the solution was stirred for 20 min. A solution of glycolate **28** (10.0 g, 27.4 mmol) in THF (36 ml) was added dropwise to the LDA solution at −70°C over 30 min. After 20 min, acrolein (2.1 ml, 32 mmol) was introduced to the reaction mixture over 20 min at −70°C. After 30 min, the mixture was quenched with saturated aqueous NH_4Cl at −70°C, and extracted with hexane/EtOAc (×2). The organic layer was washed with saturated aqueous NH_4Cl and brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 20:1–5:1) gave diene **29** with 33*R*-stereochemisty as an epimeric mixture of C34-alcohols (5.08 g, 12.1 mmol, 44% yield) and 33*S*-diastereomers **30** (5.12 g, 12.2 mmol, 44% yield).

4.2.4. Eight-membered ring 31. To a solution of diene **29** (23.7 g, 56.4 mmol) in CH_2Cl_2 (1600 ml) at rt was added $(PCy_3)_2Cl_2Ru$=CHPh (920 mg, 1.13 mmol), and the solution was heated to reflux. The additional catalyst (total 3.22 g, 3.91 mmol) was introduced over 4 d. Et_3N (100 ml) was added to this mixture at rt, and the solution was stirred overnight, concentrated, and subjected to flash column chromatography (hexane/EtOAc 19:1–8:1) to afford a C34-epimeric mixture of 8-membered ring **31** (16.6 g, 42.3 mmol) in 75% yield. **31a**: white solid; mp 118–122°C; R_f=0.56 (hexane/EtOAc 1:1); $[\alpha]_D^{26}$=+89.2 (*c* 1.08, $CHCl_3$); IR (KBr) ν 3388, 2974, 2846, 1732, 1614, 1517, 1396, 1367, 1249, 1162, 1102, 1039, 974, 824, 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (9H, s), 2.46 (1H, ddd, *J*=14.0, 7.0, 2.0 Hz), 2.61 (1H, d, *J*=4.0 Hz), 2.81 (1H, ddd, *J*=14.0, 9.5, 5.0 Hz), 3.66 (1H, t, *J*=10.0 Hz), 3.74 (1H, ddd, *J*=10.0, 9.0, 4.5 Hz), 3.76 (1H, d, *J*=9.0 Hz), 3.79 (3H, s), 3.88 (1H, ddd, *J*=9.0, 5.0, 2.0 Hz), 4.20 (1H, dd, *J*=10.0, 4.5 Hz), 4.63 (1H, m), 5.39 (1H, s), 5.81 (1H, dd, *J*=11.0, 5.5 Hz), 5.88 (1H, m), 6.86–6.88 (2H, m), 7.37–7.39 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 30.3, 55.2, 69.1, 70.1, 72.8, 82.1, 82.5, 83.0, 101.6, 113.6, 127.3, 127.4, 129.9, 135.6, 160.0, 169.5; MALDI-TOF MS, calcd for $C_{21}H_{28}O_7Na$ ($M+Na^+$) 415.173, found 415.168. **31b**: white solid; mp 158–160°C; R_f=0.50 (silica, 1:1, hexane/EtOAc); $[\alpha]_D^{26}$=+18.7 (*c* 0.63, $CHCl_3$); IR (KBr) ν 3446, 2978, 2845, 1733, 1614, 1516, 1394, 1369, 1303, 1248, 1173, 1118, 1052, 824, 722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (9H, s), 2.45 (1H, m), 2.60 (1H, ddd, *J*=14.0, 9.5, 3.0 Hz), 2.83 (1H, d, *J*=7.5 Hz), 3.55 (1H, ddd, *J*=10.5, 9.5, 3.0 Hz), 3.67 (1H, d, *J*=10.5 Hz), 3.68 (1H, td, *J*=9.5, 3.0 Hz), 3.79 (3H, s), 4.21 (1H, d, *J*=5.0 Hz), 4.23 (1H, dd, *J*=10.5, 5.0 Hz), 4.79 (1H, m), 5.41 (1H, s), 5.67 (1H, ddd, *J*=10.5, 8.0, 1.5 Hz), 5.92 (1H, tdd, *J*=10.0, 8.0, 1.5 Hz), 6.87–6.89 (2H, m), 7.38–7.40 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 32.9, 55.3, 68.6, 69.3, 74.7, 79.4, 79.9, 82.9, 101.0, 113.6, 127.0, 127.4, 130.0, 132.0, 160.0, 168.3; MALDI-TOF MS, calcd for $C_{21}H_{28}O_7Na$ ($M+Na^+$) 415.173, found 415.155.

4.2.5. TBPS ether 32. To a solution of ester **31** (29.2 g, 80.4 mmol) in Et_2O (350 ml) at 0°C was added a suspension of $LiAlH_4$ (3.66 g, 96.5 mmol) in Et_2O (30 ml) over 10 min. The mixture was allowed to warm to rt over 3 h, then quenched with saturated aqueous $NaHCO_3$ (80 ml) at 0°C, and diluted with EtOAc. The aqueous layer was adjusted to pH 7 by the addition of 2 M HCl (~50 ml), and extracted with EtOAc. The organic layer was concentrated to afford diol (23.7 g), which was subjected to the next reaction without further purification. The diol: white solid; mp 146–147°C; R_f=0.52 (EtOAc); IR (KBr) ν 3330, 2935, 2855, 1614, 1586, 1515, 1249, 1101, 1057, 1032, 826, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.19 (1H, brt, *J*=6.0 Hz), 2.26 (1H, brd, *J*=4.0 Hz), 2.46 (1H, ddd, *J*=14.5, 6.3, 2.0 Hz), 2.78 (1H, ddd, *J*=14.5, 8.2, 5.0 Hz), 3.47 (1H, ddd,

J=8.5, 5.2, 4.0 Hz), 3.61 (1H, t, J=10.0 Hz), 3.74–3.83 (2H, m), 3.76 (1H, dd, J=10.0, 5.2 Hz), 3.79 (3H, s), 3.88 (1H, ddd, J=10.5, 6.8, 4.0 Hz), 4.17 (1H, dd, J=10.0, 5.0 Hz), 4.47 (1H, dd, J=8.5, 4.0 Hz), 5.39 (1H, s), 5.80–5.88 (2H, m), 6.86–6.89 (2H, m), 7.36–7.39 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.4, 55.3, 64.2, 69.4, 70.4, 72.3, 82.0, 83.1, 101.6, 113.7, 126.8, 127.5, 130.0, 136.9, 160.1; MALDI-TOF MS, calcd for $C_{17}H_{22}O_6Na$ (M+Na^+) 345.131, found 345.123; Anal. calcd for $C_{17}H_{22}O_6$ C, 63.34; H, 6.88, found C, 63.05; H, 6.72.

To a solution of the diol (23.7 g) and Et_3N (30.8 ml, 221 mmol) in CH_2Cl_2 (74 ml) at rt was added TBPSCl (12.9 ml, 73.5 mmol). After 11 h at rt, additional TBPSCl (2.6 ml, 14.7 mmol) was introduced. After 19 h, the mixture was quenched with MeOH and extracted with EtOAc (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–10:1) afforded TBPS ether **32** (33.57 g, 60.0 mmol) in 74% yield over 2 steps. **32**: viscous oil; R_f=0.30 (hexane/EtOAc 3:1); IR (KBr) ν 3469, 3014, 2932, 2857, 1615, 1517, 1463, 1428, 1391, 1302, 1250, 1172, 1105, 1085, 1036, 972, 826, 759, 704, 610 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (9H, s), 2.46 (1H, ddd, J=14.0, 5.0, 1.5 Hz), 2.78 (1H, ddd, J=14.0, 8.0, 5.0 Hz), 3.09 (1H, d, J=2.5 Hz), 3.44 (1H, dt, J=9.0, 5.0 Hz), 3.51 (1H, t, J=9.5 Hz), 3.71 (1H, td, J=9.5, 5.0 Hz), 3.75 (1H, ddd, J=9.5, 5.0, 1.5 Hz), 3.80 (3H, s), 3.91 (2H, dd, J=10.5, 5.0 Hz), 4.06 (1H, dd, J=9.5, 5.0 Hz), 4.60 (1H, dt, J=9.0, 2.5 Hz), 5.38 (1H, s), 5.82–5.84 (2H, m), 6.87–6.91 (2H, m), 7.37–7.47 (8H, m), 7.68–7.72 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 26.8, 30.4, 55.2, 66.3, 69.5, 71.4, 72.0, 82.1, 82.3, 101.5, 113.6, 126.3, 127.4, 127.67, 127.75, 129.83, 129.9, 130.1, 132.7, 132.9, 135.5, 135.6, 136.9, 160.0; MALDI-TOF MS, calcd for $C_{33}H_{40}O_6SiNa$ (M+Na^+) 583.249, found 583.218.

4.2.6. Ketone 34. A solution of allyl alcohol **32** (13.9 g, 24.7 mmol) in CH_2Cl_2 (100 ml) was added to a solution of DMSO (5.3 ml, 74 mmol) and $(COCl)_2$ (4.4 ml, 49 mmol) in CH_2Cl_2 (150 ml) at −80°C. After 1 h at the same temperature, Et_3N (20 ml, 140 mmol) was added, and the mixture was allowed to warm to −50°C over 1 h, and then quenched with aqueous NH_4Cl at −50°C. The mixture was extracted with hexane−EtOAc (×3), and the organic layer was washed with aqueous saturated NH_4Cl and brine, and dried over $MgSO_4$. Concentration and florisil column chromatography (hexane/EtOAc 12:1–4:1) afforded enone **33**, which was used in the next reaction without further purification. **33**: colorless viscous oil; R_f=0.50 (hexane/EtOAc 3:1); IR (KBr) ν 2931, 1673, 1615, 1517, 1428, 1392, 1251, 1112, 1034, 910, 825, 737, 704, 614 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (9H, s), 2.62 (1H, dd, J=13.5, 10.0 Hz), 2.87 (1H, dddd, J=13.5, 10.0, 8.5, 1.5 Hz), 3.70–3.74 (2H, m), 3.78 (1H, td, J=9.0, 4.5 Hz), 3.82 (3H, s), 3.87 (1H, dd, J=11.0, 7.5 Hz), 4.06 (1H, dd, J=11.0, 3.3 Hz), 4.35 (1H, dd, J=11.0, 4.5 Hz), 4.38 (1H, dd, J=7.5, 3.3 Hz), 5.49 (1H, s), 5.89 (1H, brd, J=12.0 Hz), 6.48 (1H, ddd, J=12.0, 10.0, 8.5 Hz), 6.91–6.93 (2H, m), 7.40–7.46 (8H, m), 7.69–7.72 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 26.7, 33.9, 55.1, 65.0, 69.5, 77.7, 88.2, 101.3, 113.6, 127.3, 127.6, 127.7, 129.65, 129.73, 130.8, 133.0, 135.4, 135.5, 136.0, 160.0, 201.5; MALDI-TOF MS, calcd for $C_{33}H_{38}O_6SiNa$ (M+Na^+) 581.234, found 581.183.

CuCN (3.66 g, 40.8 mmol) was dried using heat gun under vacuo, and suspended in Et_2O (150 ml). To this suspension was added MeLi (68 ml, 1.14 M in Et_2O, 78 mmol) over 15 min at −70°C. The mixture was warmed to 0°C for 15 min before being cooled to −80°C. A solution of enone **33** in Et_2O (100 ml) was added to the $Me_2Cu(CN)Li_2$ solution over 20 min at −80°C. The mixture was allowed to warm to −60°C over 1 h, quenched with saturated aqueous NH_4Cl/concentrated NH_3 (5:1, 30 ml), and extracted with hexane/EtOAc (×2). The organic layer was washed with saturated aqueous NH_4Cl–concentrated NH_3 (5:1) and brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 18:1–7:1) afforded ketone **34** (9.71 g, 17.0 mmol) in 69% yield over 2 steps. **34**: colorless viscous oil; R_f=0.45 (hexane/EtOAc 3:1); $[\alpha]_D^{29}$=−102 (c 1.01, $CHCl_3$); IR (KBr) ν 2931, 2857, 2359, 2341, 1715, 1615, 1588, 1517, 1458, 1427, 1373, 1296, 1249, 1172, 1136, 1112, 1035, 976, 941, 824, 795, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.11 (3H, d, J=6.5 Hz), 1.53 (1H, ddd, J=15.5, 13.0, 9.0 Hz), 1.96 (1H, brd, J=11.0 Hz), 2.01 (1H, dd, J=15.5, 5.0 Hz), 2.29–2.36 (1H, m), 3.33 (1H, td, J=9.0, 4.5 Hz), 3.62 (1H, dd, J=11.0, 6.5 Hz), 3.76 (1H, dd, J=4.5, 2.5 Hz), 3.77 (1H, t, J=10.5 Hz), 3.81 (3H, s), 3.82 (1H, t, J=9.0 Hz), 3.85 (1H, dd, J=10.5, 2.5 Hz), 3.93 (1H, dd, J=10.5, 4.5 Hz), 4.30 (1H, dd, J=10.5, 4.5 Hz), 5.46 (1H, s), 6.90–6.92 (2H, m), 7.39–7.46 (8H, m), 7.65–7.67 (2H, m), 7.71–7.73 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 21.8, 26.7, 30.7, 41.8, 42.3, 55.3, 66.6, 69.6, 79.3, 81.2, 89.9, 101.1, 113.7, 127.4, 127.65, 127.71, 129.8, 130.0, 133.0, 133.1, 135.6, 135.7, 160.1, 215.4; MALDI-TOF MS, calcd for $C_{34}H_{42}O_6SiNa$ (M+Na^+) 597.265, found 597.265.

4.2.7. Diol 35. To a solution of TBPS ether **34** (50.5 g, 87.8 mmol) in THF (100 ml) at 0°C was added a solution of TBAF (131 ml, 1 M in THF, 131 mmol) and AcOH (7.53 ml, 131 mmol). After being stirred for 1 d at rt, the solution was concentrated, and the residue was subjected to flash column chromatography (hexane/EtOAc 3:1–1:2) to afford the hydroxy ketone (26.8 g, 79.6 mmol) in 90% yield. The hydroxy ketone: white solid; mp 157–158°C; R_f=0.40 (hexane/EtOAc 1:1); $[\alpha]_D^{24}$=−186 (c 0.93, $CHCl_3$); IR (KBr) ν 3372, 2969, 2851, 1709, 1613, 1521, 1455, 1285, 1252, 1172, 1132, 1098, 1009, 972, 846, 817, 553 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, d, J=7.0 Hz), 1.93 (1H, brd, J=11.0 Hz), 2.01 (1H, dd, J=15.0, 4.5 Hz), 2.19 (1H, brs), 2.26–2.32 (1H, m), 3.35 (1H, ddd, J=11.0, 10.0, 5.5 Hz), 3.47 (1H, dd, J=11.0, 6.8 Hz), 3.70 (1H, t, J=11.0 Hz), 3.69–3.79 (4H, m), 3.79 (3H, s), 4.28 (1H, dd, J=11.0, 5.5 Hz), 5.42 (1H, s), 6.87–6.89 (2H, m), 7.38–7.40 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 30.6, 41.6, 41.9, 55.2, 64.2, 69.3, 79.3, 81.0, 89.3, 101.1, 113.6, 127.4, 129.8, 160.1, 215.0; MALDI-TOF MS, calcd for $C_{18}H_{24}O_6Na$ (M+Na^+) 359.147, found 359.155; Anal. calcd for $C_{18}H_{24}O_6$ C, 64.27; H, 7.19, found C, 64.45; H, 7.08.

A solution of the hydroxy ketone (26.8 g, 79.6 mmol) in CH_3CN (100 ml) was added to a solution of $NaBH(OAc)_3$ (84.3 g, 398 mmol) and AcOH (68.4 ml, 1.19 mol) in

CH_3CN (600 ml) at −40°C, which was allowed to warm to rt over 4 h. K_2CO_3 (150 g) was added to the mixture, and the resultant solution was extracted with EtOAc (×2). The organic layer was washed with saturated aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated. Recrystallization and open column chromatography (hexane/EtOAc 5:1–0:1) afforded diol **35** (24.7 g, 73.1 mmol) in 92% yield. **35**: white solid; mp 169°C; R_f=0.10 (hexane/EtOAc 1:1); $[\alpha]_D^{24}$=−6.56 (*c* 1.01, $CHCl_3$); IR (KBr) ν 3292, 2920, 2853, 1617, 1521, 1450, 1399, 1255, 1118, 1089, 1029, 977, 832, 818 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (3H, d, *J*=7.0 Hz), 1.75 (1H, dt, *J*=14.0, 10.0 Hz), 1.80–1.88 (2H, m), 1.93–1.98 (1H, m), 1.98 (1H, ddd, *J*=14.0, 4.0, 1.5 Hz), 2.08 (1H, m), 3.40 (1H, dt, *J*=9.5, 4.0 Hz), 3.53 (1H, t, *J*=9.5 Hz), 3.53–3.58 (1H, m), 3.63 (1H, td, *J*=10.0, 4.0 Hz), 3.67–3.72 (2H, m), 3.80 (3H, s), 3.82 (1H, dd, *J*=11.0, 4.0 Hz), 4.25 (1H, dd, *J*=9.5, 4.0 Hz), 5.39 (1H, s), 6.87–6.89 (2H, m), 7.38–7.40 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.8, 45.1, 47.7, 55.3, 65.2, 69.8, 73.0, 78.5, 80.7, 87.8, 100.7, 100.8, 113.7, 127.4, 130.2, 160.0; MALDI-TOF MS, calcd for $C_{18}H_{26}O_6Na$ ($M+Na^+$) 361.163, found 361.164; Anal. calcd for $C_{18}H_{26}O_6$ C, 63.89; H, 7.74, found C, 63.94; H, 7.65.

4.2.8. Diol 37. To a solution of diol **35** (208 mg, 613 μmol) in THF (3.0 ml) and DMF (0.6 ml) at 0°C were added NaH (147 mg, 60% oil suspension, 3.7 mmol) and BnBr (0.29 ml, 2.5 mmol). After 10 h at rt, MeOH was added to the mixture, and the mixture was diluted with Et_2O and aqueous NH_4Cl, and extracted with Et_2O (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 10:0–8:1) gave the benzyl ether **36** (378 mg, quant.).

To a solution of the benzyl ether **36** (834 mg, 1.61 mmol) in MeOH (8 ml) and H_2O (10 drops) at rt was added *p*-TsOH·H_2O (31 mg, 0.16 mmol). After 3 h at rt, Et_3N was added, and the mixture was concentrated and subjected to flash column chromatography (hexane/EtOAc 3:0–0:1) to give diol **37** (533 mg, 1.33 mmol) in 83% yield. **37**: white solid; mp 96–97°C; R_f=0.35 (hexane/EtOAc 1:1); $[\alpha]_D^{28}$=−40.3 (*c* 1.04, $CHCl_3$); IR (film) ν 3429, 3030, 2923, 2866, 1496, 1454, 1208, 1122, 1097, 1071, 1028, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, d, *J*=6.5 Hz), 1.62 (1H, dt, *J*=14.0, 10.5 Hz), 1.69 (1H, ddd, *J*=15.0, 11.0, 6.5 Hz), 1.79–1.95 (3H, m), 3.13–3.19 (1H, m), 3.39 (1H, t, *J*=9.5 Hz), 3.49 (1H, td, *J*=10.0, 4.0 Hz), 3.53–3.60 (2H, m), 3.76 (1H, td, *J*=9.5, 2.0 Hz), 3.83 (1H, dd, *J*=9.5, 2.5 Hz), 3.89–3.95 (1H, m), 4.29 (1H, d, *J*=11.0 Hz), 4.55 (1H, d, *J*=11.0 Hz), 4.56 (1H, d, *J*=11.5 Hz), 4.59 (1H, d, *J*=11.5 Hz), 7.18–7.39 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.3, 27.6, 42.3, 48.7, 65.6, 71.0, 71.9, 72.5, 73.4, 79.4, 85.7, 88.5, 127.7, 127.8, 127.9, 128.0, 128.36, 128.44, 137.1, 137.8; MALDI-TOF MS, calcd for $C_{24}H_{32}O_5Na$ 423.215 ($M+Na^+$), found 423.200.

4.2.9. Iodide 38. To a solution of diol **37** (5.35 g, 13.4 mmol) in THF (70 ml) at 0°C were added imidazole (1.83 g, 26.7 mmol), PPh_3 (3.51 g, 13.4 mmol), and I_2 (3.04 g, 12.0 mmol). The stirred mixture was allowed to warm to rt, and additional reagents [PPh_3 (0.35 g, 1.4 mmol) and I_2 (0.34 g, 1.3 mmol)] were introduced twice. After 21 h, aqueous NH_4Cl was added to the mixture, and the resultant mixture was extracted with hexane/EtOAc (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–5:1) gave iodide **38** (5.97 g, 11.7 mmol) in 87% yield. **38**: pale yellow oil; R_f=0.70 (hexane/EtOAc 1:1); $[\alpha]_D^{29}$=−44.3 (*c* 0.974, $CHCl_3$); IR (neat) ν 3445, 3063, 3030, 2921, 1496, 1454, 1371, 1304, 1096, 909, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, d, *J*=7.0 Hz), 1.49 (1H, bs), 1.64 (1H, ddd, *J*=15.0, 9.0, 7.5 Hz), 1.78–1.86 (2H, m), 1.91–2.01 (2H, m), 3.23 (1H, ddd, *J*=8.5, 5.0, 3.0 Hz), 3.42 (1H, dd, *J*=10.0, 4.5 Hz), 3.48 (1H, td, *J*=8.5, 3.0 Hz), 3.55 (1H, dd, *J*=10.0, 6.5 Hz), 3.58–3.65 (1H, m), 3.64 (1H, dd, *J*=10.5, 3.0 Hz), 3.72 (1H, ddd, *J*=9.0, 6.0, 2.5 Hz), 3.80 (1H, dd, *J*=10.0, 3.0 Hz), 4.37 (1H, d, *J*=11.0 Hz), 4.56 (1H, d, *J*=11.5 Hz), 4.58 (2H, s), 7.20–7.40 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.5, 27.3, 27.6, 41.4, 46.8, 71.4, 71.5, 73.6, 74.0, 78.5, 84.8, 85.6, 127.5, 127.6, 127.8, 128.3, 128.4, 138.1, 138.4; MALDI-TOF MS, calcd for $C_{24}H_{31}IO_4Na$ 533.117 ($M+Na^+$), found 533.116.

4.2.10. Nitrile 39. To a solution of iodide **38** (1.64 g, 3.21 mmol) in DMSO (6.4 ml) at rt was added NaCN (0.31 g, 6.4 mmol). After 19 h at 40°C, H_2O was then added to the mixture, the resultant mixture was extracted with EtOAc (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and open column chromatography (hexane/EtOAc 10:0–3:1) gave nitrile **39** (1.27 g, 3.10 mmol) in 97% yield. **39**: colorless oil; R_f=0.50 (hexane/EtOAc 1:1); $[\alpha]_D^{29}$=−61.7 (*c* 0.920, $CHCl_3$); IR (neat) ν 3467, 3064, 3031, 2924, 2866, 2251, 1496, 1455, 1362, 1295, 1208, 1112, 1068, 1027, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, d, *J*=7.5 Hz), 1.40 (1H, d, *J*=5.0 Hz), 1.61 (1H, ddd, *J*=14.5, 10.0, 7.5 Hz), 1.72–1.80 (1H, m), 1.81–1.85 (1H, m), 1.92–2.01 (2H, m), 2.65 (1H, dd, *J*=16.5, 5.0 Hz), 2.85 (1H, dd, *J*=16.5, 3.5 Hz), 3.44 (1H, td, *J*=9.0, 3.5 Hz), 3.52 (1H, dd, *J*=10.0, 6.5 Hz), 3.63–3.71 (3H, m), 3.78 (1H, dd, *J*=9.5, 2.5 Hz), 4.35 (1H, d, *J*=11.5 Hz), 4.54 (1H, d, *J*=11.5 Hz), 4.55 (1H, d, *J*=11.5 Hz), 4.58 (1H, d, *J*=11.5 Hz), 7.21–7.35 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.7, 27.4, 27.5, 41.7, 47.6, 71.5 (×2), 72.6, 73.5, 78.5, 82.7, 86.3, 118.3, 127.6, 127.7, 127.8 (×4), 128.3 (×4), 138.0, 138.2; MALDI-TOF MS, calcd for $C_{25}H_{31}NO_4Na$ 432.215 ($M+Na^+$), found 432.180.

4.2.11. TES ether 54. To a solution of nitrile **39** (1.27 g, 3.10 mmol) and 2,6-lutidine (0.54 ml, 4.7 mmol) in CH_2Cl_2 (6.2 ml) at −30°C was added TESOTf (0.77 ml, 3.4 mmol). After being stirred for 1.5 h at −20°C, the mixture was quenched with aqueous saturated NH_4Cl and extracted with hexane/EtOAc (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–10:1) gave TES ether **54** (1.40 g, 2.67 mmol) in 86% yield. **54**: colorless oil; R_f=0.70 (hexane/EtOAc 1:1); $[\alpha]_D^{28}$=−32.1 (*c* 1.034, $CHCl_3$); IR (neat) ν 3064, 3031, 2953, 2875, 2249, 1496, 1454, 1415, 1373, 1302, 1239, 1092, 1009, 811, 735, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.61 (6H, q, *J*=8.0 Hz), 0.95 (9H, t, *J*=8.0 Hz), 1.03 (3H, d, *J*=7.5 Hz), 1.56–1.64 (1H, m), 1.71 (1H, dt, *J*=14.0, 9.0 Hz), 1.77–

1.82 (1H, m), 1.90–1.97 (2H, m), 2.55 (1H, dd, J=16.5, 4.5 Hz), 2.79 (1H, dd, J=16.5, 3.5 Hz), 3.44 (1H, td, J=9.5, 3.5 Hz), 3.53 (1H, dd, J=9.5, 6.0 Hz), 3.61–3.69 (3H, m), 3.80 (1H, dd, J=9.5, 2.0 Hz), 4.34 (1H, d, J=11.0 Hz), 4.53 (1H, d, J=12.0 Hz), 4.55 (1H, d, J=11.0 Hz), 4.58 (1H, d, J=12.0 Hz), 7.21–7.35 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 4.9, 6.8, 22.5, 27.2, 27.6, 42.0, 47.5, 71.36, 71.40, 73.37, 73.41, 78.2, 83.5, 86.3, 118.3, 127.5, 127.56, 127.68, 127.73, 128.3, 138.0, 138.2; MALDI-TOF MS, calcd for $C_{31}H_{45}NO_4SiNa$ 546.302 (M+Na^+), found 546.297.

4.2.12. Dithioacetal 55. To a solution of nitrile **54** (4.78 g, 9.13 mmol) in CH_2Cl_2 (32 ml) at −70°C was added DIBAL (18.5 ml, 0.95 M in hexane, 17.6 mmol) over 10 min. After being stirred for 40 min, the reaction mixture was quenched with EtOAc at −70°C, diluted with EtOAc, and stirred with saturated Rochelle's salt (20 ml) at rt for 2 h. The mixture was extracted with hexane/EtOAc (×3), and the organic layer was washed with brine and dried over $MgSO_4$. Concentration and purification through a pad of florisil column afforded the aldehyde, which was used immediately.

To the aldehyde and PhSSPh (2.20 g, 10.0 mmol) at rt was added Bu_3P (3.0 ml, 12.0 mmol) over 5 min. After being stirred for 1 d at rt, the mixture was directly subjected to flash column chromatography (deactivated with 1% Et_3N/hexane, hexane/EtOAc 50:1–30:1) gave dithioacetal **55** (4.83 g, 6.63 mmol) in 73% yield for 2 steps. **55**: colorless oil; R_f=0.70 (hexane/EtOAc 3:1); $[\alpha]_D^{28}$=−22.0 (c 1.00, $CHCl_3$); IR (neat) ν 3061, 3030, 2953, 2875, 1583, 1481, 1454, 1438, 1362, 1239, 1090, 1006, 809, 736, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.47–0.53 (6H, m), 0.89 (9H, t, J=8.0 Hz), 1.02 (3H, d, J=7.0 Hz), 1.64–1.98 (6H, m), 2.15–2.22 (1H, m), 3.42–3.52 (3H, m), 3.55 (1H, dd, J=10.0, 1.5 Hz), 3.87–3.91 (1H, m), 3.95–4.00 (1H, m), 4.34 (1H, d, J=11.0 Hz), 4.36 (1H, d, J=12.5 Hz), 4.41 (1H, d, J=12.5 Hz), 4.53 (1H, d, J=11.5 Hz), 5.07 (1H, dd, J=12.0, 2.5 Hz), 7.16–7.32 (16H, m), 7.43–7.46 (2H, m), 7.50–7.53 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 4.9, 6.9, 26.6, 28.0, 39.5, 41.1, 45.3, 52.6, 71.1, 71.2, 73.1, 75.4, 78.5, 83.2, 83.3, 127.1, 127.37, 127.41, 127.5, 127.66, 127.71, 128.2, 128.3, 128.61, 128.64, 132.2, 132.7, 133.2, 134.4, 138.2, 138.6; MALDI-TOF MS, calcd for $C_{43}H_{56}O_4S_2SiNa$ 751.329 (M+Na^+), found 751.337.

4.2.13. Alcohol 56. To dithioacetal **55** (5.73 g, 7.86 mmol) at rt was added TBAF (8.7 ml, 1 M in THF, 8.7 mmol). After being stirred for 3 h at rt, the mixture was concentrated and subjected to flash column chromatography (deactivated with 1% Et_3N/hexane, hexane/EtOAc 10:1–4:1) gave alcohol **56** (4.61 g, 7.01 mmol) in 95% yield. **56**: colorless oil; R_f=0.45 (hexane/EtOAc 3:1); $[\alpha]_D^{24}$=−68.6 (c 1.25, $CHCl_3$); IR (film) ν 3448, 3060, 3029, 2922, 2864, 1582, 1481, 1453, 1438, 1090, 1069, 1026, 738, 695 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, d, J=7.0 Hz), 1.22 (1H, d, J=6.0 Hz), 1.71 (1H, dt, J=15.0, 8.0 Hz), 1.76–1.94 (3H, m), 1.95–2.02 (1H, m), 2.08 (1H, ddd, J=14.0, 9.0, 3.0 Hz), 2.28 (1H, ddd, J=14.0, 11.5, 2.5 Hz), 3.42–3.50 (3H, m), 3.54 (1H, dd, J=10.0, 2.5 Hz), 3.85–3.90 (1H, m), 3.94–3.99 (1H, m), 4.35 (1H, d, J=11.5 Hz), 4.40 (2H, s), 4.54 (1H, d, J=11.0 Hz), 5.09 (1H, dd, J=10.5, 4.0 Hz), 7.18–7.32 (16H, m), 7.41–7.44 (2H, m), 7.51–7.54 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 27.9, 39.2, 41.0, 45.4, 52.3, 71.17, 71.19, 73.0, 74.3, 78.6, 82.7, 83.3, 126.8, 127.40, 127.43, 127.6, 128.18, 128.21, 128.6, 128.7, 131.3, 132.6, 133.1, 134.7, 138.0, 138.2; MALDI-TOF MS, calcd for $C_{37}H_{42}O_4S_2Na$ 637.242 (M+Na^+), found 637.266.

4.3. Construction of the J ring

4.3.1. Ester 53. To a mixture of alcohol **56** (1.54 g, 2.50 mmol) and carboxylic acid **7** (768 mg, 1.82 mmol) at rt were added EDC·HCl (540 mg, 2.8 mmol), DMAP (22 mg, 0.18 mmol), and CSA (44 mg, 0.18 mmol). After being stirred 2 d at 40°C, the reaction mixture was directly subjected to flash column chromatography (deactivated with 1% Et_3N/hexane, hexane/EtOAc 20:1–10:1) gave ester **53** (1.41 g, 1.38 mmol) in 76% yield. **53**: colorless oil; R_f=0.65 (hexane/EtOAc 3:1); $[\alpha]_D^{27}$=−69.2 (c 1.040, $CHCl_3$); IR (film) ν 3062, 3030, 2929, 1731, 1583, 1496, 1455, 1373, 1175, 1097, 1069, 1028, 920, 737, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, d, J=6.5 Hz), 1.02 (6H, d, J=7.0 Hz), 1.20 (3H, d, J=7.0 Hz), 1.45–2.09 (13H, m), 2.79 (1H, quint., J=7.5 Hz), 3.06 (1H, t, J=10.0 Hz), 3.36 (3H, s), 3.43–3.53 (3H, m), 3.79–3.89 (4H, m), 3.90–3.95 (1H, m), 4.24–4.30 (1H, m), 4.33 (1H, d, J=12.5 Hz), 4.34 (1H, d, J=11.5 Hz), 4.36 (1H, d, J=12.5 Hz), 4.52 (1H, d, J=12.5 Hz), 4.54 (1H, d, J=11.5 Hz), 4.61 (1H, d, J=7.0 Hz), 4.59–4.65 (1H, m), 4.72 (1H, d, J=12.0 Hz), 4.75 (1H, d, J=6.0 Hz), 5.10 (1H, dd, J=9.5, 4.5 Hz), 7.17–7.36 (21H, m), 7.36–7.39 (2H, m), 7.52–7.55 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 14.6, 15.8, 24.4, 25.9, 28.1, 35.1, 38.0, 39.8, 40.3, 40.4, 41.6, 42.1, 52.1, 56.5, 67.5, 71.3, 72.6, 73.1, 73.7, 75.7, 78.7, 79.9, 80.0, 81.0, 83.1, 98.5, 107.9, 126.8, 127.3, 127.5, 127.65, 127.71, 128.19, 128.29, 128.33, 128.75, 128.80, 131.2, 132.5, 133.4, 136.3, 138.3, 139.0, 174.5; MALDI-TOF MS, calcd for $C_{60}H_{74}O_{10}S_2$ 1041.462 (M+Na^+), found 1041.441.

4.3.2. Cyclic enol ether 42. Mg turnings (58 mg, 2.4 mmol), powdered MS4A (200 mg), and Cp_2TiCl_2 (500 mg, 2.0 mmol) were placed in a flask and dried with a heat gun under reduced pressure. THF (4.0 ml) and $P(OEt)_3$ (0.69 ml, 4.0 mmol) were added to this flask successively under argon at rt, and the reaction mixture was stirred for 3 h. Then a solution of ester **53** (504 mg, 494 μmol) in THF (6 ml) was added dropwise at rt. After being heated to reflux for 1 h, the reaction mixture was quenched with 1 M NaOH (15 ml) at rt and the resulting insoluble materials were filtered off. The mixture was extracted with Et_2O (×2), and the organic layer was washed with brine. The violet organic layer was left overnight to give a colorless solution, which was dried over K_2CO_3. Concentration and flash column chromatography (deactivated with 1% Et_3N/hexane, hexane/EtOAc 20:1–10:1) afforded the cyclic enol ether **42** (260 mg, 331 μmol) in 67% yield. **42**: colorless oil; R_f=0.40 (hexane/EtOAc 6:1); IR (film) ν 2928, 1728, 1497, 1454, 1374, 1098, 1028, 736, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, d, J=6.0 Hz, Me57), 0.94 (3H, t, J=7.5 Hz, Me41), 1.02 (3H, d, J=6.5 Hz, Me56), 1.03 (3H, d, J=7.0 Hz, Me54), 1.23 (3H, d, J=7.5 Hz, Me55), 1.39 (1H, dq, J=14.0, 7.0 Hz, H40), 1.47 (1H, dq, J=11.0, 6.5 Hz, H48), 1.60–2.01 (10H, m, H35×2, 37×2, 40, 47, 50×2, 51×2), 2.02–2.10 (1H, m, H36), 2.82 (1H, dq, J=8.0, 7.0 Hz, H43), 3.12 (1H, t,

J=10.0 Hz, H46), 3.36 (3H, s, MOM), 3.50–3.57 (2H, m, H34, 39), 3.57 (1H, dd, J=9.5, 5.0 Hz, H32), 3.65 (1H, dd, J=9.5, 2.5 Hz, H32), 3.71 (1H, ddd, J=8.5, 5.0, 2.5 Hz, H33), 3.77–3.87 (4H, m, H44, 45, 52×2), 4.36 (1H, d, J=11.5 Hz, Bn), 4.51 (1H, d, J=11.5 Hz, Bn), 4.52 (1H, d, J=12.5 Hz, Bn), 4.56 (1H, d, J=12.0 Hz, Bn), 4.58 (1H, d, J=11.0 Hz, Bn), 4.63 (1H, d, J=6.0 Hz, MOM), 4.69–4.75 (1H, m, H38), 4.74 (1H, d, J=12.0 Hz, Bn), 4.78 (1H, d, J=6.5 Hz, MOM), 7.20–7.36 (15H, m, Bn×3); MALDI-TOF MS, calcd for $C_{48}H_{66}O_{10}Na$ 825.455 ($M+Na^+$), found 825.369.

4.4. Construction of the K ring

4.4.1. Ketone 58. To a solution of the cyclic enol ether **42** (1.24 g, 1.58 mmol) in THF (16 ml) at 0°C was added BH_3·THF complex (1.75 ml, 1 M in THF, 1.75 mmol). After 2.5 h at rt, additional BH_3·THF complex (0.16 ml, 1 M in THF, 0.16 mmol) was introduced at 0°C to complete the hydroboration reaction. After additional 1 h at rt, 15% aqueous NaOH (1.9 ml, 7.9 mmol) was added to the reaction mixture at 0°C, followed by addition of 30% aqueous H_2O_2 (1.8 ml, 16 mmol). After being stirred overnight at rt, the mixture was diluted with aqueous saturated NH_4Cl, extracted with EtOAc (×2), and the organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 10:1–3:1) afforded a diastereomer mixture of the alcohols (950 mg, 1.18 mmol) in 75% combined yield.

The mixture of the alcohols (1.11 g, 1.39 mmol) in CH_2Cl_2 (6 ml) was added to a solution of DMSO (0.49 ml, 6.9 mmol) and $(COCl)_2$ (0.38 ml, 4.2 mmol) in CH_2Cl_2 (10 ml) at −70°C. After 30 min at the same temperature, Et_3N (2.0 ml, 14 mmol) was added, and the reaction mixture was allowed to warm to −40°C over 1 h, and then quenched with aqueous NH_4Cl at −40°C. The mixture was extracted with hexane/EtOAc (×2), and the organic layer was washed with aqueous saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated. The residue was purified through a pad of silica gel and the resulting ketones were separated by medium pressure column chromatography (MPLC, Ultra Pack SI-40B, Yamazen, hexane/Et_2O 10:1–5:1) to give the desired ketone **58** (346 mg, 432 μmol, 31%) and the C42-epimer **57** (628 mg, 784 μmol, 57%).

To a solution of the C-42 epimeric ketone **57** (628 mg, 784 μmol) in CH_2Cl_2 (5 ml) at rt was added DBU (0.25 ml). After being stirred for 4 h, the mixture was diluted with EtOAc and aqueous saturated NH_4Cl and then extracted with hexane/EtOAc (×2). The organic layer was washed with aqueous saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated. The residue was purified through a pad of flash column and the resulting ketones were separated by MPLC to give the desired ketone **58** and the C42-epimer **57**. The undesired C42-epimer **57** was subjected to additional two cycles of the isomerization–separation sequence to afford the desired ketone **58** (367 mg, 458 μmol, 58% yield for 3 cycles) and the C42-epimer **57** (75 mg, 94 μmol, 12% yield for 3 cycles). **58**: colorless oil; R_f=0.45 (pentane/Et_2O 3:2); $[\alpha]_D^{28}$=−31.4 (c 0.876, $CHCl_3$); IR (film) ν 3088, 3063, 3030, 2926, 2061, 1723, 1641, 1605, 1548, 1496, 1454, 1379, 1324, 1099, 1069, 1028, 943, 921, 736, 698, 607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (6H, d, J=6.5 Hz, Me55, 57), 1.05 (3H, d, J=6.2 Hz, Me56), 1.10 (3H, d, J=7.0 Hz, Me54), 1.50–2.07 (11H, m, H35×2, 36, 37×2, 47, 48, 50×2, 51×2), 2.36–2.46 (1H, m, H52), 2.41 (1H, dd, J=17.0, 9.5 Hz, H40), 2.93 (1H, dd, J=17.0, 6.0 Hz, H40), 3.23 (1H, t, J=10.0 Hz, H46), 3.35 (3H, s, MOM), 3.35–4.00 (10H, m, H32×2, 33, 34, 38, 39, 44, 45, 52×2), 3.51 (1H, d, J=9.0 Hz, H42), 4.32 (1H, d, J=11.0 Hz, Bn), 4.49 (1H, d, J=11.5 Hz, Bn), 4.53 (2H, s, Bn×2), 4.60 (1H, d, J=11.0 Hz, Bn), 4.60 (1H, d, J=6.9 Hz, MOM), 4.81 (1H, d, J=11.5 Hz, Bn), 4.85 (1H, d, J=6.9 Hz, MOM), 7.20–7.36 (15H, m, Bn×3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.2, 13.6, 15.8, 24.3, 26.3, 28.4, 35.0, 36.1, 38.8, 39.9, 42.1, 43.3, 46.8, 56.2, 67.2, 71.4, 71.8, 72.8, 73.3, 73.5, 78.9, 79.9, 80.8, 81.8, 82.8, 84.1, 84.9, 98.8, 107.9, 127.1, 127.4, 127.5, 127.6, 127.7, 128.1, 128.3, 138.1, 138.3, 139.3, 207.5; HRMS (EI, 70 eV), calcd for $C_{48}H_{64}O_{10}$ 800.4500 (M^+), found 800.4504. **57**: colorless oil; R_f=0.50 (pentane/Et_2O 3:2); $[\alpha]_D^{28}$=−97.4 (c 1.007, $CHCl_3$); IR (film) ν 3030, 2927, 1721, 1496, 1454, 1380, 1323, 1099, 1069, 1028, 921, 751, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, d, J=6.7 Hz, Me55), 0.93 (3H, d, J=6.2 Hz, Me57), 1.07 (3H, d, J=6.2 Hz, Me56), 1.10 (3H, d, J=7.0 Hz, Me54), 1.50–2.06 (11H, m, H35×2, 36, 37×2, 47, 48, 50×2, 51×2), 2.45–2.60 (1H, m, H43), 2.53 (1H, dd, J=14.3, 11.4 Hz, H40), 2.87 (1H, dd, J=14.3, 5.0 Hz, H40), 3.12 (1H, t, J=10.0 Hz, H46), 3.37 (3H, s, MOM), 3.37–3.93 (10H, m, H32×2, 33, 34, 38, 39, 42, 44, 52×2), 4.15 (1H, dd, J=10.0, 2.5 Hz, H45), 4.31 (1H, d, J=11.0 Hz, Bn), 4.50 (1H, d, J=11.5 Hz, Bn), 4.50–4.60 (2H, m, MOM), 4.57 (1H, d, J=11.0 Hz, Bn), 4.64 (2H, s, Bn×2), 4.73 (1H, J=11.5 Hz, Bn), 7.20–7.36 (15H, m, Bn×3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.6, 13.6, 16.0, 24.3, 26.7, 28.0, 32.4, 35.0, 38.4, 40.2, 42.4, 43.7, 45.7, 56.2, 67.7, 71.4, 71.5, 72.0, 72.5, 73.0, 73.3, 78.0, 78.6, 80.7, 83.2, 83.8, 85.7, 95.9, 107.7, 127.2, 127.48, 127.55, 127.64, 127.8, 128.1, 128.3, 138.1, 138.2, 139.0, 206.9; HRMS (EI, 70 eV), calcd for $C_{48}H_{64}O_{10}$ 800.4500 (M^+), found 800.4487.

4.4.2. Methyl ketal 60. To a solution of ketone **58** (281 mg, 295 μmol) and $CH(OMe)_3$ (0.35 ml) in hexane (3.5 ml) at rt was added TfOH (42 μl, 0.25 M in CH_2Cl_2, 11 μmol). After being stirred for 19 h at rt, the mixture was quenched with aqueous saturated $NaHCO_3$, extracted with hexane/EtOAc (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–15:1) afforded the methyl ketal **60** (227 mg, 295 μmol) in 84% yield. **60**: colorless oil; R_f=0.70 (pentane/Et_2O 3:2); $[\alpha]_D^{29}$=−25.8 (c 0.752, $CHCl_3$); IR (film) ν 3064, 3030, 2926, 1496, 1462, 1455, 1360, 1206, 1069, 1028, 972, 752, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, d, J=6.2 Hz, Me57), 1.05 (3H, d, J=7.0 Hz, Me55), 1.06 (3H, d, J=6.0 Hz, Me56), 1.08 (3H, d, J=7.0 Hz, Me54), 1.40–2.40 (13H, m, H35×2, 36, 37×2, 40, 43, 47, 48, 50×2, 51×2), 2.57 (1H, dd, J=14.0, 4.0 Hz, H40), 2.89 (1H, d, J=9.2 Hz, H42), 3.04–3.12 (1H, m, H38), 3.09 (3H, s, OMe), 3.25–3.32 (2H, m, H39, 44), 3.38 (1H, td, J=9.0, 3.0 Hz, H34), 3.43 (1H, dd, J=10.0, 7.0 Hz, H32), 3.52–3.58 (2H, m, H45, 46), 3.60–3.65 (1H, m, H33), 3.74 (1H, dd, J=10.0, 3.0 Hz, H32), 3.82 (1H, bq, J=7.0 Hz, H52), 3.86–3.92 (1H, m, H52), 4.31

(1H, d, J=11.2 Hz, Bn), 4.51 (1H, d, J=11.5 Hz, Bn), 4.54 (1H, d, J=11.5 Hz, Bn), 4.58 (1H, d, J=11.2 Hz, Bn), 4.63 (2H, s, Bn×2), 7.20–7.36 (15H, m, Bn×3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 16.6, 20.2, 24.6, 26.8, 28.1, 35.0, 37.2, 38.5, 39.0, 40.2, 40.7, 43.9, 48.3, 67.6, 68.7, 71.4, 72.4, 72.6, 72.9, 73.4, 79.0, 80.8, 81.5, 83.9, 85.4, 85.9, 98.9, 107.7, 126.8, 127.26, 127.31, 127.39, 127.46, 127.50, 127.59, 127.7, 127.9, 128.2, 128.3, 138.2, 138.5, 140.0; HRMS (EI, 70 eV), calcd for $C_{47}H_{62}O_9$ 770.4394 (M^+), found 770.4399.

4.4.3. IJKLM ring fragment 5. To a solution of the methyl ketal **60** (104 mg, 134 μmol) and Et_3SiH (0.48 ml, 3.0 mmol) in CH_2Cl_2 (1.1 ml) at −50°C was added $BF_3{\cdot}OEt_2$ (0.33 ml, 10% solution in CH_2Cl_2, 0.27 mmol). The reaction was allowed to warm to −20°C over 1 h, and then quenched with 1% Et_3N/hexane and aqueous $NaHCO_3$ at −20°C. The mixture was extracted with hexane/EtOAc (×2), and the organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–15:1) gave the IJKLM ring fragment **5** (70.9 mg, 95.7 μmol) in 71% yield. **5**: colorless oil; R_f=0.75 (pentane/Et_2O 3:2); $[\alpha]_D^{29}$=−41.2 (*c* 0.807, $CHCl_3$); IR (film) ν 2954, 2925, 2854, 1454, 1377, 1260, 1098, 1072, 1027, 974, 803, 733, 697 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (3H, d, J=6.3 Hz, Me57), 1.02 (3H, d, J=6.0 Hz, Me56), 1.08 (3H, d, J=7.1 Hz, Me54), 1.11 (3H, d, J=7.7 Hz, Me55), 1.41 (1H, q, J=11.7 Hz, H40), 1.50–1.57 (2H, m, H47, 48), 1.63 (1H, bdt, J=14.2, 10.2 Hz, H37), 1.68 (1H, bddd, J=15.2, 9.5, 6.4 Hz, H35), 1.73–1.81 (2H, m, H50, 51), 1.83–1.88 (1H, m, H37), 1.90–1.98 (4H, m, H35, 36, 50, 51), 2.15 (1H, qdd, J=7.7, 4.6, 3.5 Hz, H43), 2.40 (1H, bdt, J=12.0, 4.8 Hz, H40), 2.87 (1H, dd, J=9.3, 4.6 Hz, H42), 3.06 (1H, btd, J=9.6, 3.0 Hz, H38), 3.23 (1H, ddd, J=11.3, 9.0, 4.4 Hz, H39), 3.35 (1H, t, J=9.5 Hz, H46), 3.41 (1H, btd, J=9.2, 2.8 Hz, H34), 3.43 (1H, bdd, J=3.5, 1.0 Hz, H41), 3.44 (1H, dd, J=10.0, 6.5 Hz, H32), 3.60 (1H, bddd, J=9.3, 6.5, 2.1 Hz, H33), 3.64 (1H, dd, J=9.5, 1.0 Hz, H45), 3.68 (1H, dd, J=10.0, 2.1 Hz, H32), 3.75 (1H, bq, J=7.5 Hz, H52), 3.82 (1H, ddd, J=11.2, 9.3, 5.0 Hz, H41), 3.87 (1H, btd, J=7.8, 4.5 Hz, H52), 4.32 (1H, d, J=11.1 Hz, Bn), 4.55 (2H, s, Bn×2), 4.58 (1H, d, J=11.1 Hz, Bn), 4.63 (1H, d, J=12.2 Hz, Bn), 4.68 (1H, d, J=12.2 Hz, Bn), 7.20–7.40 (15H, m, Bn×3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 15.8, 20.0, 22.7, 24.4, 28.2, 29.7, 30.3, 35.0, 38.6, 39.6, 40.3, 41.8, 71.4, 71.9, 72.0, 72.1, 73.4, 74.3, 77.2, 77.5, 78.1, 79.0, 80.3, 82.7, 84.7, 86.9, 108.3, 127.1, 127.4, 127.58, 127.63, 127.9, 128.1, 128.29, 128.33, 138.6; HRMS (EI, 70 eV), calcd for $C_{46}H_{60}O_8$ 740.4288 (M^+), found 740.4304.

4.4.4. Bis-*p*-bromobenzoate 63. To a solution of the tribenzyl ethers **5** (11.3 mg, 15.3 μmol) in EtOAc (1 ml), MeOH (1 ml), and AcOH (30 μl) at rt was added 20% $Pd(OH)_2$/C (4.3 mg, 8 μmol), and the mixture was stirred under hydrogen. After 2 d, additional 20% $Pd(OH)_2$/C (4.3 mg, 8 μmol) was introduced to the reaction mixture. After 1 d, the catalyst was filtered off, and the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexane/EtOAc 3:1–0:1) to give the triol (7.1 mg, 15.1 μmol) in 99% yield.

To a solution of the triol (3.3 mg, 7.0 μmol) in CH_2Cl_2 (0.4 ml) and Et_3N (0.1 ml) at rt were added DMAP (0.7 mg, 6 μmol) and *p*-BrBzCl (6.8 mg, 31 μmol). Additional *p*-BrBzCl (6.8 mg, 31 μmol) was introduced to complete the reaction. MeOH was added to the mixture, and the resultant solution was diluted with EtOAc and aqueous saturated NH_4Cl, and extracted with hexane/EtOAc (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–6:1) gave bis-*p*-bromobenzoate **63** (3.8 mg, 4.5 μmol, 65% yield), which was recrystallized from hexane/CH_2Cl_2 and subjected to X-ray crystallography. **63**: prisms; R_f=0.70 (hexane/EtOAc 1:1); IR (film) ν 3440, 2959, 2924, 1727, 1715, 1591, 1455, 1398, 1264, 1175, 1116, 1069, 1013, 976, 847, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88–0.91 (6H, m), 1.07 (3H, d, J=7.0 Hz), 1.15 (3H, d, J=7.5 Hz), 1.40 (1H, q, J=11.5 Hz), 1.46–2.07 (12H, m), 2.16 (1H, bs), 2.24 (1H, dt, J=12.5, 4.5 Hz), 2.87 (1H, dd, J=9.5, 4.5 Hz), 3.07–3.13 (1H, m), 3.15 (1H, t, J=9.5 Hz), 3.32 (1H, ddd, J=11.5, 8.5, 4.5 Hz), 3.61–3.67 (2H, m), 3.72 (1H, bs), 3.79 (1H, q, J=7.0 Hz), 3.88 (1H, td, J=8.0, 4.0 Hz), 4.00–4.05 (1H, m), 4.24 (1H, dd, J=11.5, 8.0 Hz), 4.42 (1H, dd, J=11.5, 3.0 Hz), 5.07 (1H, td, J=9.5, 2.5 Hz), 7.53–7.58 (4H, m), 7.83–7.90 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.4, 15.5, 19.8, 24.3, 26.9, 27.9, 34.9, 38.4, 39.4, 41.7, 42.0, 42.2, 44.3, 66.4, 67.6, 71.6, 74.2, 75.4, 77.3, 78.7, 80.2, 82.7, 83.3, 86.4, 108.7, 128.2, 128.4, 128.8 (×2), 131.06 (×2), 131.11 (×2), 131.79 (×2), 131.81 (×2), 164.7, 165.5; MALDI-TOF MS, calcd for $C_{39}H_{48}Br_2O_{10}Na$ 857.151 (M+Na^+), found 857.134.

4.5. Construction of the H ring

4.5.1. *p*-Methoxybenzylidene acetal 64. To a solution of the tribenzyl ethers **5** (290 mg, 390 μmol) in EtOAc (1 ml), MeOH (1 ml), and AcOH (30 μl) at rt was added 20% $Pd(OH)_2$/C (37 mg, 53 μmol), and the mixture was stirred under hydrogen. After 1 d, additional 20% $Pd(OH)_2$/C (11 mg, 16 μmol) was introduced to the reaction mixture. After 1.5 d, the catalyst was filtered off, and the solvent was removed under reduced pressure to give the triol, which was used in the next reaction without further purification. The triol: white solid; R_f=0.30 (hexane/EtOAc 1:3); IR (film) ν 3452, 2957, 2926, 1455, 1379, 1274, 1072, 1027, 976, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, d, J=6.5 Hz), 1.03 (3H, d, J=6.5 Hz), 1.06 (3H, d, J=7.0 Hz), 1.15 (3H, d, J=7.5 Hz), 1.41 (1H, q, J=11.5 Hz), 1.46–2.06 (14H, m), 2.19 (1H, bs), 2.33 (1H, dt, J=12.0, 5.0 Hz), 2.87 (1H, dd, J=9.5, 4.5 Hz), 2.99–3.06 (1H, m), 3.24 (1H, t, J=9.5 Hz), 3.22–3.29 (1H, m), 3.36 (1H, dt, J=9.5, 5.0 Hz), 3.60–3.75 (5H, m), 3.79 (1H, q, J=7.5 Hz), 3.78–3.82 (1H, m), 3.88 (1H, td, J=7.5, 4.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.4, 15.7, 19.7, 24.3, 27.7, 27.8, 35.0, 38.5, 39.9, 42.1, 42.2, 44.9, 47.6, 65.1, 67.6, 71.7, 72.9, 75.5, 77.2, 78.6, 80.7, 82.9, 86.3, 87.3, 108.7; MALDI-TOF MS, calcd for $C_{25}H_{42}O_8Na$ 493.278 (M+Na^+), found 493.259.

To a solution of the triol and anisaldehyde dimethylacetal (100 μl, 540 μmol) in THF (2 ml) at rt was added CSA (4.2 mg, 18 μmol). After being stirred for 1 h, the mixture was quenched with aqueous saturated $NaHCO_3$ and extracted with hexane/EtOAc (×3). The organic layer was

washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 20:1–3:1) gave the *p*-methoxybenzylidene acetal **64** (174 mg, 296 μmol) in 76% yield. **64**: white solid; R_f=0.30 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, d, *J*=7.0 Hz), 1.04 (3H, d, *J*=6.5 Hz), 1.07 (3H, d, *J*=7.5 Hz), 1.16 (3H, d, *J*=7.5 Hz), 1.42 (1H, q, *J*=12.0 Hz), 1.46–2.07 (12H, m), 2.16 (1H, d, *J*=2.0 Hz), 2.25 (1H, dt, *J*=12.0, 5.0 Hz), 2.87 (1H, dd, *J*=9.5, 5.0 Hz), 2.97–3.03 (1H, m), 3.19 (1H, ddd, *J*=12.0, 8.5, 5.0 Hz), 3.25 (1H, t, *J*=10.0 Hz), 3.43 (1H, td, *J*=9.0, 5.0 Hz), 3.50 (1H, t, *J*=10.5 Hz), 3.56–3.62 (1H, m), 3.65 (1H, dd, *J*=9.5, 1.0 Hz), 3.69–3.76 (2H, m), 3.79 (3H, s), 3.79 (1H, q, *J*=7.5 Hz), 3.89 (1H, td, *J*=7.5, 5.0 Hz), 4.16 (1H, td, *J*=10.5, 5.0 Hz), 5.36 (1H, s), 6.85–6.88 (2H, m), 7.36–7.39 (2H, m).

4.5.2. Alcohol 66. To a solution of alcohol **64** (182 mg, 309 μmol) and *i*-Pr_2NEt (0.54 ml, 3.1 mmol) in $(CH_2Cl)_2$ (1 ml) at rt was added BOMCl (0.13 ml, 0.93 mmol), and the reaction mixture was heated to 40°C for 14 h. The reaction mixture was cooled to rt, and quenched with Et_3N (0.5 ml) and MeOH (0.3 ml). The solution was diluted with aqueous NH_4Cl and extracted with EtOAc (×3), and the organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–5:1) afforded the BOM ether **65** (222.5 mg), which was used in the next reaction without further purification. **65**: colorless viscous oil; R_f=0.60 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, d, *J*=6.0 Hz), 1.05 (3H, d, *J*=5.5 Hz), 1.07 (3H, d, *J*=7.5 Hz), 1.16 (3H, d, *J*=7.5 Hz), 1.42 (1H, q, *J*=11.5 Hz), 1.46–1.98 (11H, m), 2.09–2.15 (1H, m), 2.25 (1H, dt, *J*=12.5, 4.5 Hz), 2.88 (1H, dd, *J*=9.5, 4.5 Hz), 2.97–3.02 (1H, m), 3.13–3.20 (1H, m), 3.32 (1H, t, *J*=9.5 Hz), 3.44 (1H, td, *J*=9.0, 5.0 Hz), 3.50 (1H, t, *J*=10.5 Hz), 3.56–3.62 (1H, m), 3.66 (1H, d, *J*=9.0 Hz), 3.73–3.83 (2H, m), 3.77 (1H, q, *J*=7.5 Hz), 3.79 (3H, s), 3.87 (1H, td, *J*=7.5, 5.0 Hz), 4.17 (1H, td, *J*=10.5, 5.5 Hz), 4.63 (1H, d, *J*=11.5 Hz), 4.69 (1H, d, *J*=11.5 Hz), 4.82 (1H, d, *J*=7.0 Hz), 4.85 (1H, d, *J*=7.0 Hz), 5.37 (1H, s), 6.85–6.88 (2H, m), 7.26–7.41 (7H, m).

To a solution of the BOM ether **65** (222.5 mg) in CH_2Cl_2 (6.0 ml) at −80°C was added DIBAL (8.5 ml, 0.93 M in hexane, 7.7 mmol) over 5 min. The solution was allowed to warm to −40°C over 1.5 h, and then the mixture was quenched with aqueous saturated NH_4Cl at −40°C, diluted with EtOAc, and stirred with saturated Rochelle's salt for 2 h. The mixture was extracted with EtOAc (×2), and the organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 10:1–3:1) afforded alcohol **66** (220 mg, 309 μmol) in 100% yield over 2 steps. **66**: colorless oil; R_f=0.30 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, d, *J*=6.0 Hz), 1.03 (3H, d, *J*=6.0 Hz), 1.08 (3H, d, *J*=7.0 Hz), 1.15 (3H, d, *J*=7.5 Hz), 1.39 (1H, q, *J*=11.5 Hz), 1.45–1.77 (6H, m), 1.84–1.96 (5H, m), 2.00–2.17 (2H, m), 2.33 (1H, dd, *J*=12.0, 4.5 Hz), 2.87 (1H, dd, *J*=9.5, 4.5 Hz), 3.00–3.06 (1H, m), 3.25 (1H, ddd, *J*=11.0, 9.5, 5.0 Hz), 3.31 (1H, t, *J*=9.5 Hz), 3.34 (1H, td, *J*=9.0, 2.5 Hz), 3.42–3.51 (2H, m), 3.56 (1H, d, *J*=9.0 Hz), 3.72–3.81 (4H, m), 3.79 (3H, s), 3.87 (1H, td, *J*=7.5, 4.5 Hz), 4.29 (1H, d, *J*=11.0 Hz), 4.55 (1H, d, *J*=11.0 Hz), 4.62 (1H, d, *J*=11.0 Hz), 4.68 (1H, d, *J*=11.0 Hz), 4.81 (1H, d, *J*=7.0 Hz), 4.84 (1H, d, *J*=7.0 Hz), 6.84–6.89 (2H, m), 7.19–7.23 (2H, m), 7.26–7.38 (5H, m); MALDI-TOF MS, calcd for $C_{41}H_{58}O_{10}Na$ 733.393 ($M+Na^+$), found 733.605.

4.5.3. Nitrile 67. To a solution of alcohol **66** (220 mg, 309 μmol) in $(CH_2Cl)_2$ (3.0 ml) and Et_3N (0.18 ml, 1.3 mmol) at 0°C was added MsCl (50 μl, 0.62 mmol). After 40 min, aqueous NH_4Cl was added to the mixture, which was extracted with hexane/EtOAc (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 3:1) gave a mesylate, which was used in the next reaction without further purification.

To a solution of the mesylate and 18-crown-6 (25 mg, 95 μmol) in DMF (1.0 ml) at rt was added NaCN (90 mg, 1.84 mmol). After 2 d at 50°C, aqueous $NaHCO_3$ was added to the mixture, which was extracted with EtOAc (×2). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–3:1) gave nitrile **67** (202 mg, 280 μmol) in 91% over 2 steps. **67**: colorless oil; R_f=0.40 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, d, *J*=6.0 Hz), 1.03 (3H, d, *J*=6.0 Hz), 1.11 (3H, d, *J*=7.5 Hz), 1.14 (3H, d, *J*=7.5 Hz), 1.41 (1H, q, *J*=11.5 Hz), 1.45–1.77 (6H, m), 1.84–2.01 (5H, m), 2.07–2.13 (1H, m), 2.31 (1H, dd, *J*=16.5, 8.5 Hz), 2.50 (1H, dt, *J*=12.5, 5.0 Hz), 2.71 (1H, dd, *J*=16.5, 2.5 Hz), 2.87 (1H, dd, *J*=9.5, 4.5 Hz), 2.99–3.04 (1H, m), 3.21–3.28 (2H, m), 3.32 (1H, t, *J*=9.5 Hz), 3.65 (1H, d, *J*=10.0 Hz), 3.67 (1H, td, *J*=9.0, 3.0 Hz), 3.73 (1H, d, *J*=3.5 Hz), 3.76 (1H, q, *J*=7.5 Hz), 3.80 (3H, s), 3.78–3.84 (1H, m), 3.86 (1H, td, *J*=7.5, 4.5 Hz), 4.26 (1H, d, *J*=11.5 Hz), 4.57 (1H, d, *J*=11.5 Hz), 4.62 (1H, d, *J*=11.0 Hz), 4.67 (1H, d, *J*=11.0 Hz), 4.81 (1H, d, *J*=7.0 Hz), 4.84 (1H, d, *J*=7.0 Hz), 6.85–6.89 (2H, m), 7.18–7.21 (2H, m), 7.25–7.38 (5H, m); MALDI-TOF MS, calcd for $C_{42}H_{57}NO_9Na$ 742.3931 ($M+Na^+$), found 742.4296.

4.5.4. α,β-Unsaturated ester 68. To a solution of nitrile **67** (80.8 mg, 112 μmol) in CH_2Cl_2 (1.1 ml) at −80°C was added DIBAL (0.36 ml, 0.95 M in hexane, 0.34 mmol) dropwise. After 30 min, the reaction mixture was quenched with EtOAc at −70°C, diluted with EtOAc and aqueous saturated NH_4Cl, and stirred with aqueous saturated Rochelle's salt at rt for 30 min. The mixture was extracted with EtOAc (×2), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated to afford an aldehyde, which was used in the next reaction immediately.

To a solution of the aldehyde in toluene (1.2 ml) at rt was added (carbethoxyethylene)triphenylphosphorane (123 mg, 0.34 mmol). After being stirred for 3 h, the mixture was subjected directly to flash column chromatography (hexane/EtOAc 20:1–10:1) to give the α,β-unsaturated ester **68** (75.7 mg, 93.8 μmol) in 84% over 2 steps. **68**: colorless oil; R_f=0.60 (hexane/EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, d, *J*=6.0 Hz), 1.02 (3H, d, *J*=6.0 Hz), 1.07 (3H, d, *J*=7.0 Hz), 1.14 (3H, d, *J*=7.0 Hz), 1.28 (3H, t, *J*=7.5 Hz), 1.44–1.77 (6H, m), 1.82 (3H, s), 1.81–1.95 (6H, m), 2.07–2.14 (1H, m), 2.18 (1H, dt, *J*=15.0, 8.5 Hz),

2.27 (1H, dt, *J*=12.0, 5.0 Hz), 2.58–2.64 (1H, m), 2.85 (1H, dd, *J*=9.5, 4.5 Hz), 2.98–3.04 (1H, m), 3.17 (1H, ddd, *J*=11.0, 9.0, 5.0 Hz), 3.23 (1H, dd, *J*=9.0, 3.0 Hz), 3.29 (1H, t, *J*=9.5 Hz), 3.45 (1H, td, *J*=9.0, 3.0 Hz), 3.65 (1H, d, *J*=10.0 Hz), 3.69–3.76 (2H, m), 3.76 (1H, q, *J*=8.0 Hz), 3.79 (3H, s), 3.86 (1H, td, *J*=8.0, 5.0 Hz), 4.14–4.21 (2H, m), 4.29 (1H, d, *J*=11.0 Hz), 4.55 (1H, d, *J*=11.0 Hz), 4.62 (1H, d, *J*=11.5 Hz), 4.68 (1H, d, *J*=11.5 Hz), 4.81 (1H, d, *J*=6.5 Hz), 4.84 (1H, d, *J*=6.5 Hz), 6.81–6.88 (3H, m), 7.20–7.24 (2H, m), 7.25–7.38 (5H, m); MALDI-TOF MS, calcd for $C_{47}H_{66}O_{11}Na$ 829.450 ($M+Na^+$), found 829.459.

4.5.5. Allyl alcohol 69. To a solution of the α,β-unsaturated ester **68** (194 mg, 240 μmol) in CH_2Cl_2 (2.4 ml) at −60°C was added DIBAL (0.8 ml, 0.93 M in hexane, 0.74 mmol) over 10 min. After being stirred for 20 min at −60°C, the reaction mixture was quenched with EtOAc at −60°C, diluted with EtOAc, and stirred with aqueous saturated Rochelle's salt for 2 h. The mixture was extracted with EtOAc (×3), and the combined organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–5:1) afforded the allyl alcohol **69** (175 mg, 229 μmol) in 95% yield. **69**: colorless oil; R_f=0.25 (hexane/EtOAc 3:1); $[\alpha]_D^{30}=-36.0$ (*c* 0.985, $CHCl_3$); IR (film) ν 3469, 2927, 2873, 1612, 1514, 1454, 1249, 1178, 1101, 1074, 1038, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, d, *J*=6.5 Hz, Me57), 1.03 (3H, d, *J*=6.0 Hz, Me56), 1.07 (3H, d, *J*=7.5 Hz, Me54), 1.14 (3H, d, *J*=7.0 Hz, Me55), 1.30 (1H, q, *J*=11.5 Hz, H40), 1.66 (3H, s, Me53), 1.45–1.95 (11H, m, H35×2, 36, 37×2, 47, 48, 50×2, 51×2), 2.03–2.14 (2H, m, H32, 43), 2.26 (1H, dt, *J*=12.0, 5.0 Hz, H40), 2.45–2.51 (1H, m, H32), 2.85 (1H, dd, *J*=9.0, 4.5 Hz, H42), 3.01 (1H, td, *J*=9.5, 3.5 Hz, H38), 3.16 (1H, ddd, *J*=11.5, 9.0, 5.0 Hz, H39), 3.23 (1H, td, *J*=9.0, 2.0 Hz, H34), 3.31 (1H, t, *J*=9.5 Hz, H46), 3.37 (1H, td, *J*=9.0, 2.5 Hz, H33), 3.65 (1H, d, *J*=9.0 Hz, H45), 3.69–3.75 (2H, m, H41, 44), 3.76 (1H, q, *J*=7.5 Hz, H52), 3.79 (3H, s, MPM), 3.86 (1H, td, *J*=7.5, 4.5 Hz, H52), 3.98–4.04 (2H, m, H29×2), 4.29 (1H, d, *J*=11.0 Hz, MPM), 4.55 (1H, d, *J*=11.0 Hz, MPM), 4.62 (1H, d, *J*=11.5 Hz, BOM), 4.68 (1H, d, *J*=11.5 Hz, BOM), 4.81 (1H, d, *J*=6.5 Hz, BOM), 4.84 (1H, d, *J*=6.5 Hz, BOM), 5.48 (1H, t, *J*=7.0 Hz, H31), 6.84–6.87 (2H, m, MPM), 7.20–7.38 (7H, m, MPM, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 14.0, 15.7, 20.0, 24.2, 26.5, 28.1, 32.6, 34.9, 38.5, 39.3, 39.5, 40.5, 41.8, 44.2, 55.2, 67.3, 68.9, 69.0, 70.9, 71.2, 74.4, 78.3, 80.3, 81.8, 81.9, 82.0, 86.0, 86.7, 93.5, 108.3, 113.7, 122.9, 127.5, 128.0, 128.2, 129.5, 130.4, 136.5, 138.1, 159.1; MALDI-TOF MS, calcd for $C_{45}H_{64}O_{10}Na$ 787.440 ($M+Na^+$), found 787.445.

4.5.6. Epoxy alcohol 70. To a solution of allyl alcohol **69** (175 mg, 229 μmol), D-(−)-DET (40 μl, 230 μmol), and activated powdered MS4 A (100 mg) in CH_2Cl_2 (3.0 ml) at −50°C was added Ti(O*i*-Pr)$_4$ (50 μl, 170 μmol). After 10 min, TBHP (0.8 ml, 3 M in CH_2Cl_2, 2.4 mmol) was added to the mixture, and the reaction temperature kept below −40°C for 3 h. The mixture was diluted with Et_2O (8 ml), and 30% aqueous NaOH saturated with NaCl (4 ml) were added. The mixture was stirred overnight at rt, and then diluted with aqueous saturated NH_4Cl and extracted with EtOAc (×3). The organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 12:1–3:1) gave the epoxy alcohol **70** (174 mg, 223 μmol) in 97% yield. **70**: colorless oil; R_f=0.70 (hexane/EtOAc 1:1); $[\alpha]_D^{29}=-31.6$ (*c* 0.994, $CHCl_3$); IR (film) ν 3479, 2929, 2873, 1613, 1514, 1455, 1380, 1249, 1176, 1101, 1073, 1037, 822, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, d, *J*=6.5 Hz, Me57), 1.03 (3H, d, *J*=6.0 Hz, Me56), 1.08 (3H, d, *J*=7.0 Hz, Me54), 1.14 (3H, d, *J*=7.5 Hz, Me55), 1.27 (3H, s, Me53), 1.39 (1H, q, *J*=11.5 Hz, H40), 1.45–1.61 (3H, m, H37, 47, 48), 1.64–1.99 (10H, m, H32×2, 35×2, 36, 37, 50×2, 51×2), 2.09–2.14 (1H, m, H43), 2.32 (1H, dt, *J*=12.0, 5.0 Hz, H40), 2.87 (1H, dd, *J*=9.5, 4.5 Hz, H42), 3.06 (1H, td, *J*=9.5, 4.5 Hz, H38), 3.20 (1H, t, *J*=6.0 Hz, H31), 3.22–3.28 (1H, m, H39), 3.31 (1H, t, *J*=9.5 Hz, H46), 3.30–3.35 (1H, m, H34), 3.49–3.54 (1H, m, H33), 3.56 (1H, dd, *J*=12.5, 8.0 Hz, H29), 3.65 (1H, d, *J*=9.5 Hz, H45), 3.68 (1H, dd, *J*=12.5, 4.0 Hz, H29), 3.72–3.81 (3H, m, H41, 44, 52), 3.79 (3H, s, MPM), 3.86 (1H, td, *J*=8.0, 4.5 Hz, H52), 4.31 (1H, d, *J*=11.0 Hz, MPM), 4.54 (1H, d, *J*=11.0 Hz, MPM), 4.62 (1H, d, *J*=11.5 Hz, BOM), 4.68 (1H, d, *J*=11.5 Hz, BOM), 4.81 (1H, d, *J*=7.0 Hz, BOM), 4.85 (1H, d, *J*=7.0 Hz, BOM), 6.84–6.87 (2H, m, MPM), 7.20–7.38 (7H, m, MPM, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 14.2, 15.6, 19.9, 24.2, 26.2, 27.9, 33.2, 34.8, 38.4, 38.7, 39.5, 40.5, 41.7, 44.0, 55.1, 57.6, 59.9, 65.5, 67.2, 69.0, 70.9, 71.1, 74.2, 78.2, 80.0, 81.7, 81.8, 81.9, 83.6, 86.7, 93.4, 108.2, 113.6, 127.4, 127.9, 128.2, 129.5, 130.3, 138.0, 159.1; MALDI-TOF MS, calcd for $C_{45}H_{64}O_{11}Na$ 803.435 ($M+Na^+$), found 803.439.

4.5.7. Vinyl epoxide 72. To a solution of epoxy alcohol **70** (174 mg, 223 μmol) and Et_3N (0.6 ml, 4.4 mmol) in $(CH_2Cl)_2$ (0.6 ml) and DMSO (0.6 ml) at 0°C was added SO_3·pyridine complex (220 mg, 1.4 mmol). After being stirred for 40 min at rt, the mixture was diluted with EtOAc and aqueous NH_4Cl, and extracted with EtOAc (×3). The organic layer was washed with brine and dried over $MgSO_4$, and concentrated. The residue was purified by florisil column chromatography to afford the aldehyde, which was subjected to the next reaction without further purification. A mixture of triphenylphosphonium bromide (394 mg, 1.10 mmol) in THF (0.6 ml) was treated with NaHMDS (0.9 ml, 1 M in THF, 0.9 mmol) at 0°C for 15 min. To the resultant yellow suspension at 0°C was added dropwise a solution of the aldehyde in THF (2.3 ml). The reaction mixture was stirred at 0°C for 45 min, quenched with aqueous saturated NH_4Cl, and extracted with EtOAc (×3). The organic layer was washed with brine and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 1:0–10:1) gave the vinyl epoxide **72** (148 mg, 191 μmol) in 86% yield over 2 steps. **72**: colorless oil; R_f=0.60 (hexane/EtOAc 3:1); $[\alpha]_D^{29}=-45.0$ (*c* 1.070, $CHCl_3$); IR (film) ν 2929, 2874, 1612, 1514, 1455, 1249, 1176, 1102, 1074, 1038, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, d, *J*=6.5 Hz, Me57), 1.03 (3H, d, *J*=6.0 Hz, Me56), 1.06 (3H, d, *J*=6.5 Hz, Me54), 1.14 (3H, d, *J*=7.0 Hz, Me55), 1.35 (1H, q, *J*=11.5 Hz, H40), 1.39 (3H, s, Me53), 1.45–1.97 (13H, m, H32×2, 35×2, 36, 37×2, 47, 48, 50×2, 51×2), 2.10–2.14 (1H, m, H43), 2.30 (1H, dt, *J*=12.5, 5.0 Hz, H40), 2.87 (1H, dd, *J*=9.0, 4.5 Hz, H42), 3.02 (1H, t, *J*=6.5 Hz, H31), 3.03–3.08 (1H, m, H38), 3.23 (1H, ddd, *J*=9.0, 7.0, 4.5 Hz, H39),

3.29 (1H, t, J=9.5 Hz, H46), 3.27–3.32 (1H, m, H34), 3.47 (1H, td, J=8.0, 3.5 Hz, H33), 3.65 (1H, d, J=10.0 Hz, H45), 3.69–3.75 (2H, m, H41, 44), 3.76 (1H, q, J=8.0 Hz, H52), 3.79 (3H, s, MPM), 3.87 (1H, td, J=8.0, 5.0 Hz, H52), 4.31 (1H, d, J=11.0 Hz, MPM), 4.53 (1H, d, J=11.0 Hz, MPM), 4.62 (1H, d, J=11.5 Hz, BOM), 4.68 (1H, d, J=11.5 Hz, BOM), 4.81 (1H, d, J=6.5 Hz, BOM), 4.85 (1H, d, J=6.5 Hz, BOM), 5.18 (1H, dd, J=11.0, 1.0 Hz, H28), 5.33 (1H, dd, J=17.5, 1.0 Hz, H28), 5.66 (1H, dd, J=17.5, 11.0 Hz, H29), 6.84–6.87 (2H, m, MPM), 7.20–7.38 (7H, m, MPM, BOM); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 14.9, 15.7, 20.0, 24.3, 26.5, 27.8, 33.7, 34.9, 38.5, 39.48, 39.53, 40.5, 41.8, 44.4, 55.2, 58.5, 62.7, 67.3, 69.1, 71.0, 71.2, 74.3, 78.4, 80.0, 81.9, 82.0, 82.0, 83.9, 86.7, 93.6, 108.3, 113.7, 115.9, 127.5, 128.0, 128.3, 129.6, 130.3, 138.1, 141.0, 159.2; MALDI-TOF MS, calcd for $C_{46}H_{64}O_{10}Na$ 799.440 ($M+Na^+$), found 799.439.

4.5.8. HIJKLM ring system 4. To a solution of vinyl epoxide **72** (148 mg, 191 μmol) in CH_2Cl_2 (4.0 ml) and H_2O (0.2 ml) at rt was added DDQ (42 mg, 0.19 mmol). After 3.5 h, additional DDQ (4 mg, 18 μmol) was introduced to complete the reaction. After additional 3.5 h, the mixture was diluted with EtOAc and aqueous saturated $NaHCO_3$, and extracted with EtOAc (×3). The organic layer was washed with brine, and dried over $MgSO_4$. Concentration and flash column chromatography (hexane/EtOAc 20:1–3:1) gave the HIJKLM ring system **4** (110 mg, 167 μmol) in 88% yield. **4**: colorless oil; R_f=0.40 (hexane/EtOAc 3:1); $[\alpha]_D^{28}$=−4.9 (c 0.612, $CHCl_3$); IR (film) ν 3470, 2929, 2883, 1454, 1379, 1103, 1071, 1038, 921, 753, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, d, J=6.0 Hz, Me57), 1.04 (3H, d, J=7.0 Hz, Me54), 1.04 (3H, d, J=6.0 Hz, Me56), 1.14 (3H, d, J=8.0 Hz, Me55), 1.26 (3H, s, Me53), 1.43 (1H, q, J=12.0 Hz, H40), 1.47–1.96 (12H, m, H32, 35×2, 36, 37×2, 47, 48, 50×2, 51×2), 2.09–2.15 (1H, m, H43), 2.17 (1H, dt, J=12.5, 5.0 Hz, H32), 2.28 (1H, dt, J=12.0, 5.0 Hz, H40), 2.87 (1H, dd, J=9.5, 4.5 Hz, H42), 2.97–3.02 (1H, m, H38), 3.14 (1H, ddd, J=11.5, 9.0, 4.5 Hz, H39), 3.22 (1H, td, J=10.0, 4.5 Hz, H33), 3.31 (1H, t, J=9.5 Hz, H46), 3.41 (1H, td, J=10.0, 3.5 Hz, H34), 3.44 (1H, dd, J=12.0, 4.0 Hz, H31), 3.66 (1H, d, J=9.0 Hz, H45), 3.72–3.80 (3H, m, H41, 44, 52), 3.87 (1H, td, J=8.0, 4.5 Hz, H52), 4.63 (1H, d, J=11.5 Hz, BOM), 4.68 (1H, d, J=11.5 Hz, BOM), 4.81 (1H, d, J=7.0 Hz, BOM), 4.85 (1H, d, J=7.0 Hz, BOM), 5.17 (1H, bd, J=10.5 Hz, H28), 5.29 (1H, bd, J=17.5 Hz, H28), 5.89 (1H, dd, J=17.5, 10.5 Hz, H29), 7.27–7.38 (5H, m, BOM); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.4, 13.5, 15.8, 20.0, 24.3, 27.7, 28.2, 34.9, 36.6, 38.5, 40.48, 40.54, 41.8, 45.6, 46.3, 67.4, 69.1, 71.0, 71.2, 73.3, 74.5, 76.5, 78.4, 81.0, 81.9, 83.6, 83.8, 86.8, 93.6, 108.3, 114.5, 127.5, 128.0, 128.3, 138.1, 143.0; HRMS (EI, 70 eV), calcd for $C_{38}H_{56}O_9$ 656.3924 (M^+), found 656.3922.

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