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Total Synthesis of (−)-Reidispongiolide A, an Actin-Targeting Macrolide Isolated from the Marine Sponge *Reidispongia coerulea*

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: A stereocontrolled total synthesis of the microfilament-destabilizing cytotoxic macrolide (−)-reidispongiolide A, isolated from the New Caledonian marine sponge *Reidispongia coerulea*, is described. This synthesis utilizes a convergent aldol-based strategy to construct the 26-membered macrolactone, followed by the late-stage coupling of a derived aldehyde with an *N*-vinylformamide-containing ketone subunit to install the full side chain. Two alternative routes were examined for the introduction of the 2*E*,4*E*-dienoate region, and a complex Mukaiyama aldol coupling was used to connect the northern and southern hemispheres to install the C13 stereocenter. This constitutes the first chemical synthesis of any member of the reidispongiolide/sphinxolide family of marine macrolides and unequivocally establishes the relative and absolute configuration.

Keywords: actin · aldol reaction · antitumor agents · macrolides · natural products

Introduction

Natural products have proven to be a rich source of novel biologically active compounds, with the discovery of lead structures that attenuate the growth of cancer cells being an important contributor to recent progress in cancer chemotherapy.[1] Tubulin-binding natural products, such as taxol, the epothilones, and discodermolide, show potent cytotoxicity through disruption of the microtubule dynamics involved in cell division and inhibit the growth of solid tumours.[2] However, as multidrug resistance often renders current tubulin-targeting therapies ineffective in the clinic, there is an unmet need for the development of novel antimitotic agents with other protein targets. Much like tubulin, actin plays a major role in maintaining the structural integrity of the cytoskeleton of eukaryotic cells and controlling key events in mitosis. Recently, a number of actin-binding macrolides of marine origin have attracted attention as novel antimitotic agents that cause rapid loss of microfilaments in cells without affecting microtubule organization, thus retaining antiproliferative activity towards multidrug-resistant (MDR) cancer cell lines.[3] In particular, the scytophycins,[4] aplyronines,[5] sphinxolides,[6] and reidispongiolides[7] demonstrate pronounced antimicrofilament activity and inhibit the growth of MDR cell lines. Although these preliminary findings highlight their potential, both as leads for new anticancer drugs and as versatile molecular probes of the organization and function of the actin cytoskeleton, their scarcity from natural sources has hampered biological evaluation and preclinical development. Thus, the realization of the chemical synthesis of these rare polyketide natural products is an attractive goal to enable further development and initiate structure–activity relationship studies.[3a,8] In combination with the recently available structural data on actin-bound marine macrolides,[9] the design of simplified analogues with tailored functional properties can also be envisaged.

As part of a programme directed towards the synthesis of antimitotic polyketides, we recently targeted the reidispongiolide/sphinxolide class of complex marine macrolides. At the outset of our work, the relative and absolute configuration of these macrolides was uncertain, requiring the combination of degradation fragment synthesis and detailed NMR

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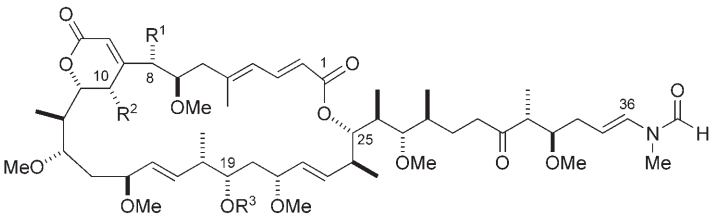
spectroscopic analysis to assign the full stereochemistry progressively, as disclosed previously.[10,11] Herein, we report full details of our recently completed total synthesis of (−)-reidispongiolide A, and provide relevant background material on the evolution of the strategy.[12] Notably, this constitutes the first member of the reidispongiolide/sphinxolide family of cytotoxic marine macrolides to be chemically synthesized and validates our stereochemical assignment.

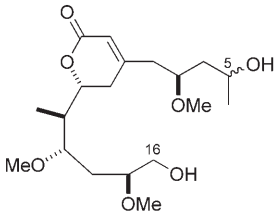
The reidispongolide/sphinxolide family of 26-membered macrolactones (**1**–**6**; Scheme 1) are prominent members of an emerging class of actin-binding cytotoxic macrolides. Originally isolated from an unidentified Pacific nudibranch by Pietra and co-workers in 1989,[6a] sphinxolide A (**1**) is one of the most highly oxygenated members. According to the Pietra report, "the name sphinxolide, from the mysterious Egyptian Sphinx, reflects our difficulties in defining the source and, for some time, the structure of the compound." A subsequent collection of the New Caledonian sponge *Neosiphonia superstes* by D'Auria, Minale, and co-workers led to the re-isolation of sphinxolide A, together with three congeners, designated sphinxolide B (**2**), C (**3**), and D (**4**).[6b] Further investigations of the marine organisms surrounding the New Caledonian coastline resulted in the discovery of two new cytotoxic macrolides, reidispongiolide A (**5**) and B (**6**), isolated from the deep-sea sponge *Reidispongia coerulea*.[7] In 1999, a further collection of the sponges *N. superstes* and *R. coerulea* resulted in the isolation of four related compounds, sphinxolides E–G and reidispongiolide C.[6c] The gross structures of the sphinxolides and reidispongiolides were determined through extensive NMR spectroscopic techniques. These complex macrolides feature a densely functionalized, 26-membered macrolactone core with a flexible side chain and a characteristic *N*-vinylformamide terminus. The macrolactone region contains an α,β-unsaturated δ lactone, four *E* alkenes, and an elaborate oxygenation pattern. Until 2004, the relative and absolute configuration of this family of complex marine macrolides remained elusive. The stereochemical assignments indicated in Scheme 1 are based on our recent synthesis of the three degradation fragments **7**, **8**, and **9** of reidispongiolide A,[10] together with related work reported by the D'Auria[11] and Rayment groups.[13]

Initially, the sphinxolides were found to inhibit potently actin polymerization in vitro and the microfilament-dependent ATPase activity of purified actomyosin. These macrolides displayed promising cytotoxicity profiles (IC_{50} values in the low nM region) associated with the induction of cell-cycle arrest at the G2/M phase leading to apoptosis. Significantly, the sphinxolides were found to be equally cytotoxic toward MCF-7 human breast carcinoma cells and a subline that overexpresses P-glycoprotein. Similarly, overexpression of the multidrug-resistance-associated protein by HL-60 human leukemia cells did not result in resistance to the sphinxolides.[6] Screening of reidispongiolides A and B against various cancer cell lines demonstrated a similar degree of activity to the sphinxolides.[7] Again, no decrease in potency was observed with MDR cell lines.

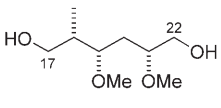
Altogether, these preliminary biological studies showed the sphinxolides and reidispongiolides to be potent antimicrofilament agents that can overcome multidrug resistance, with promise as lead compounds for the development of new chemotherapeutic agents that target actin. As such, they constitute attractive targets for total-synthesis efforts. We now focus on the design and pursuit of our ultimately successful synthetic route to reidispongiolide A that was greatly influenced by new methodology developed in our group, particularly in the area of asymmetric boron aldol reactions for assembling the stereochemically elaborate polyol backbone.



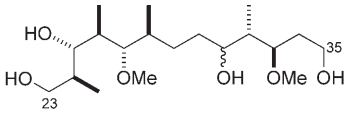
			R^1	R^2	R^3
Sphinxolide	A	**1**	OMe	OH	H
	B	**2**	H	OH	H
	C	**3**	OMe	OH	Me
	D	**4**	H	OH	Me
Reidispongiolide	A	**5**	H	H	Me
	B	**6**	H	H	H



7: C_5–C_{16} fragment



8: C_{17}–C_{22} fragment



9: C_{23}–C_{35} fragment

Scheme 1. Structures of the sphinxolide and reidispongiolide marine macrolides, as well as the degradation fragments **7**, **8**, and **9** of reidispongiolide A used to determine the stereochemistry.

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Results and Discussion

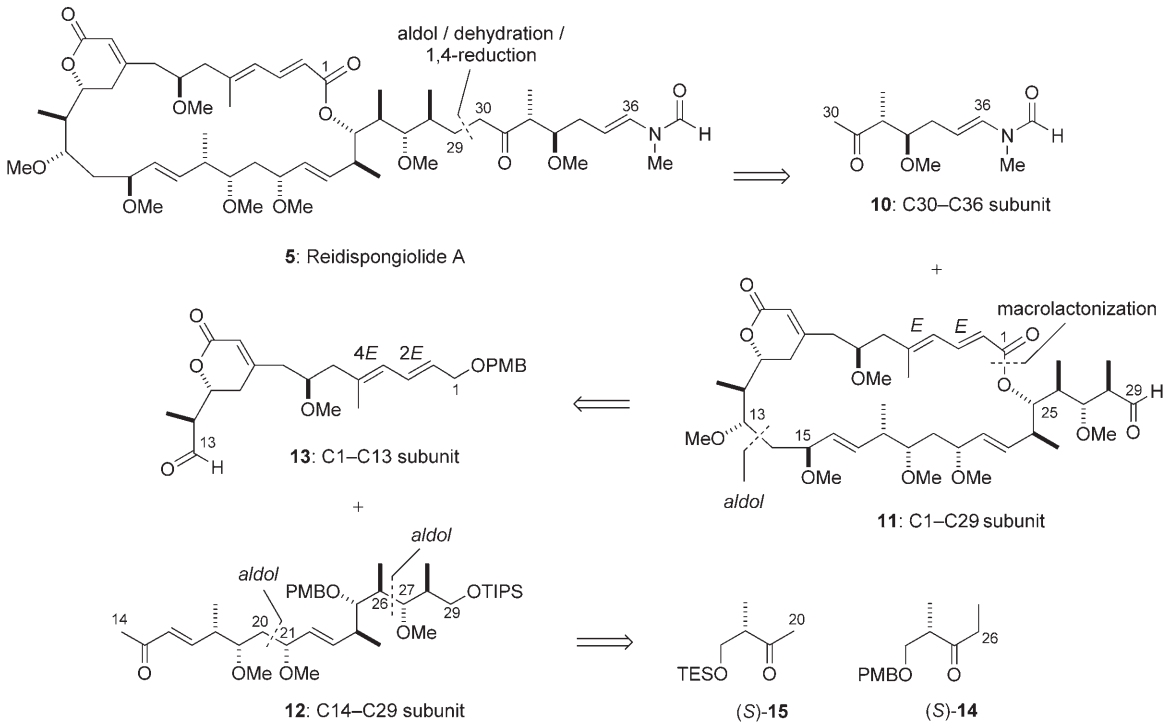
Synthetic Planning

The initial selection of key disconnections for reidispongiolide A was guided by degradation studies using controlled ozonolysis, as performed by D'Auria and co-workers,[11a] which led to three fragments whose stereochemistry was firmly established as indicated in **7**, **8**, and **9** by synthetic studies and detailed NMR correlations performed in our group,[10] as well as related independent studies reported by D'Auria and co-workers.[11] As outlined in Scheme 2, our resulting synthetic strategy for reidispongiolide A (**5**) involved a late-stage introduction of the C30–C36 side-chain segment **10**, which incorporates the sensitive *N*-vinylformamide functionality, by a suitable aldol coupling with the C1–C29 aldehyde subunit **11**, which incorporates the 26-membered macrocyclic lactone. The latter would be accessed by a suitable macrolactonization reaction involving the C25 hydroxy group. In this analysis, the 2*E*,4*E*-diene unit would be introduced at a relatively early stage. Hence, we elected to disassemble the macrolactone **11** further into the key subunits **12** (C14–C29) and **13** (C1–C13) based on an envisaged second aldol coupling to introduce the C13 stereocenter with the required configuration, followed by controlled reduction to set the 1,3-*anti*-related C15 stereocenter. A distinctive structural feature of reidispongiolide A is the seven methyl ethers (C7, C13, C15, C19, C21, C27, and C33), which represents a potential simplification with regard to the identification of suitable hydroxy-protecting groups. Nevertheless, these essential hydroxy-protecting groups were selected with considerable care on the basis of the judicious use of silyl (TES, TBS, TIPS; TBS = *tert*-butyldimethylsilyl) and PMB ethers. Undoubtedly, the most challenging structural feature of reidispongiolide A is the presence of 15 stereocenters, along with the five *E*-configured alkenes, which require controlled introduction as the synthetic route unfolded.

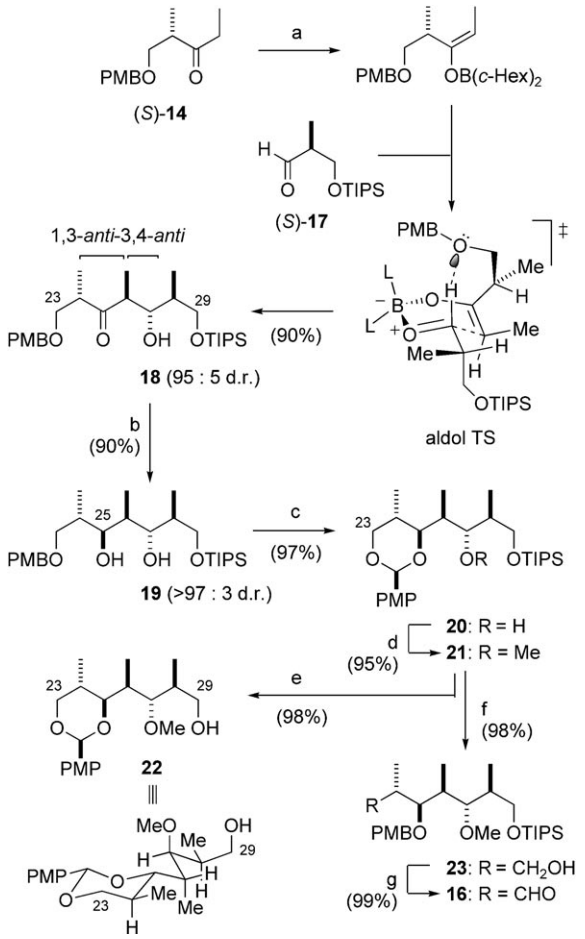
We first address the planned synthesis of the stereochemically most complex subunit **12**, which corresponds to the C14–C29 southern hemisphere. From a structural perspective, this ketone is characterized by a defined sequence of five contiguous stereocenters, spanning C23 to C29, and a further isolated sequence of three stereocenters at C18, C19, and C21, along with two *E*-configured alkenes. On the basis of methodology developed by our group,[14] the former stereopentad should be accessible by a boron-mediated *anti* aldol reaction with the ethyl ketone (*S*)-**14**. We also planned to install the other cluster of stereocenters by using our boron aldol methodology, this time with the corresponding methyl ketone (*S*)-**15**.

Synthesis of the Southern Hemisphere Region

As outlined in Scheme 3, the assembly of the aldehyde **16**, which corresponds to the correctly configured stereopentad of the southern hemisphere segment **12**, commenced with a boron-mediated aldol reaction (*c*-Hex_2BCl, Et_3N) between the ethyl ketone (*S*)-**14**[14a] and the aldehyde (*S*)-**17**. Upon standard oxidative workup, the expected 1,3-*anti*-3,4-*anti* adduct **18**, which resulted from the intermediate *E* enolate, was obtained in 90% yield with high selectivity (d.r. 95:5),



Scheme 2. Retrosynthetic analysis of reidispongiolide A leading to three key building blocks **10**, **12**, and **13**, whereby subunit **12** is further disconnected to ketones (*S*)-**14** and (*S*)-**15**. PMB = *p*-methoxybenzyl, TES = triethylsilyl, TIPS = triisopropylsilyl.



Scheme 3. Installation of the C23–C29 stereopentad in aldehyde **16** with ketone (*S*)-**14**. a) i) *c*-Hex_2BCl, Et_3N, Et_2O, −78→−20 °C; ii) (*S*)-**17**, −78→−20 °C; b) $Me_4NBH(OAc)_3$, MeCN, AcOH, −35→−20 °C; c) DDQ, CH_2Cl_2, 4-Å molecular sieves, −20→−10 °C; d) NaH, MeI, THF, 0 °C→RT; e) TBAF, THF, room temperature; f) DIBAL-H, TBME, room temperature; g) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, room temperature. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride, PMB = *para*-methoxybenzyl, PMP = *para*-methoxyphenyl, TBAF = tetra-*n*-butylammonium fluoride, TBME = *tert*-butyl methyl ether, TS = transition state.

despite this constituting an apparent mismatched pairing.[15] The high level of *E*-enolate π-facial selectivity is governed by the formation of a stabilizing formyl hydrogen bond with the oxygen atom of the PMB ether in the bicyclic aldol transition state shown, which acts in unison with the minimization of allylic strain between the α stereocenter of the enolate and the methyl substituent.[16] This stereoinduction from the boron enolate is somewhat decreased here by the conformational preference of the aldehyde α stereocenter, which in the case of *E*-enolate aldol reactions is matched/reinforcing for the formal Felkin–Anh adduct, thus avoiding *syn*-pentane interactions between the aldehyde substituents and the enolate methyl group.[15]

This aldol adduct **18** provided a suitable substrate for an Evans–Saksena hydroxy-directed reduction[17] to install the required C23–C29 stereopentad in short order. By employing $Me_4NBH(OAc)_3$, the desired 1,3-*anti* diol **19** was obtained cleanly (90%, d.r. > 97:3). With the five contiguous stereocenters now secured in a concise manner, differentiation of the hydroxy groups was required. Treatment of the diol **19** under DDQ-mediated oxidative cyclization conditions[18] resulted in the exclusive formation of the corresponding six-membered PMP acetal **20**, obtained as a single diastereomer in 97% yield. Methylation of the free hydroxy group (NaH, MeI) in **20** then afforded the methyl ether **21** (95%). Although we were confident of the stereochemical assignment, it was rigorously established by silyl ether cleavage with TBAF to generate the crystalline alcohol **22** (98%), whereby single-crystal X-ray diffraction analysis[10a] indicated the preferred conformation shown, which avoids *syn*-pentane interactions.

We were now ready to carry out the regioselective reductive opening of the PMP acetal in **21** to produce the alcohol **23**. Initially, this transformation proved problematic. The use of DIBAL-H in CH_2Cl_2 gave a single alcohol product. However, this was identified as the undesired secondary C25 alcohol, which suggests that the adjacent methoxy group was directing the reduction in an unfavorable manner. However, when the DIBAL-H reduction was carried out in the ethereal solvent TBME, the regioselective acetal opening was facilitated in the required manner to afford only the primary alcohol **23** (98%). Conceivably, TBME forms a solvent cage around the aluminum hydride reagent, thus increasing its size and leading to preferred complexation by the less hindered PMP acetal oxygen atom at C23, cleavage to the corresponding oxonium ion, and reduction to generate the primary alcohol **23**. Dess–Martin oxidation[19] of **23** then completed the preparation of aldehyde **16** (99%).

At this point, we were ready to perform the chain extension of aldehyde **16** to generate the *E* enal **24**, as required for the next aldol addition to introduce the remaining three stereocenters in the southern hemisphere segment. As shown in Scheme 4, aldehyde **16** underwent Horner–Wadsworth–Emmons (HWE) olefination efficiently under LiCl/Et_3N conditions[20] to afford Weinreb amide **25** (97%, *E*/*Z* > 95:5). Reduction of **25** with DIBAL-H in THF then provided the *E* enal **24** (92%), in readiness for a further aldol addition. As the configuration of the C18–C21 stereocluster within reidispongiolide was assigned with confidence in our earlier studies,[10a] installation of these three centers now required a 1,4-*syn*-selective boron aldol reaction of methyl ketone (*S*)-**15**, combined with a reduction in situ to deliver the 1,3-*syn* diol.[21] In practice, the TES-substituted ketone **15** (derived from the Roche ester in 84% yield) proved superior to the analogous PMB and DMB (dimethoxybenzyl) systems in terms of facilitating selective deprotection at a later stage. By using (−)-Ipc_2BCl/Et_3N,[22] a ligand-enhanced addition of ketone (*S*)-**15** to aldehyde **24** proceeded through the bicyclic aldol transition state shown to install the C21 hydroxy-bearing stereocenter, in an analogous fashion to that exploited earlier for the stereopentad assembly. This addition provided the intermediate boron aldolate that was reduced in situ with $LiBH_4$ to give the 1,3-*syn* diol **26** in

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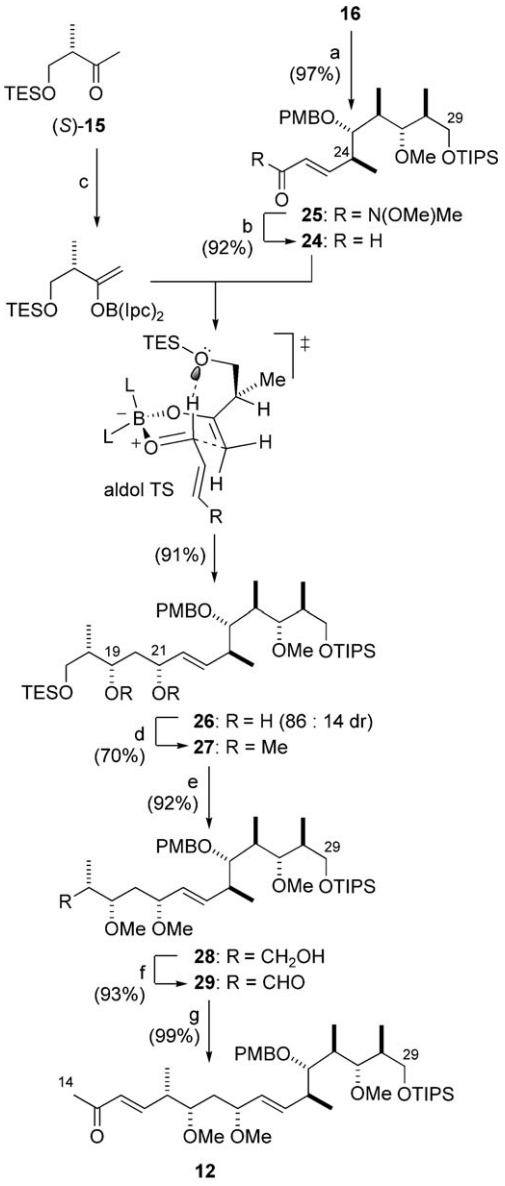
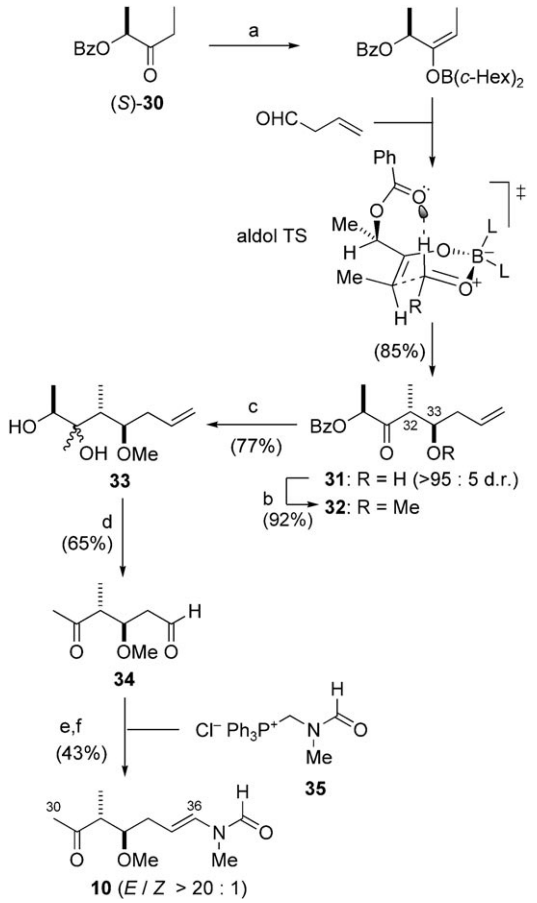


Scheme 4. Synthesis of the C14–C29 subunit **12** with ketone (*S*)-**15**. a) $(MeO)MeNC(O)CH_2P(O)(OEt)_2$, LiCl, Et_3N, MeCN, 0°C→RT; b) DIBAL-H, THF, −78°C; c) i) (−)-Ipc_2BCl, Et_3N, Et_2O, −78→0°C; ii) (*S*)-**15**, −78°C; iii) $LiBH_4$, −78°C; d) NaH, MeI, THF, 0°C→RT; e) PPTS (cat.), MeOH, room temperature; f) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0°C; g) $MeC(O)CH_2P(O)(OMe)_2$, LiCl, Et_3N, MeCN, 0°C→RT. Ipc = isopinocampheyl, PPTS = pyridinium *p*-toluenesulfonate.

91% yield, albeit with slightly lower diastereoselectivity (d.r. 86:14) relative to other such one-pot transformations.[10a,21] Conveniently, the diastereomers proved readily separable by flash chromatography following methyl ether formation with NaH and MeI, thus leading to isolation of the stereochemically homogeneous C17–C29 subunit **27** in 70% yield. Cleavage of the TES group in **27** was facilitated by catalytic PPTS in MeOH to give the corresponding primary alcohol **28** (92%). Dess–Martin oxidation of alcohol **28** then gave the aldehyde **29** (93%), which was subjected to HWE olefination with dimethyl (2-oxopropyl)phosphonate to afford the *E* enone **12** (99%, $E/Z > 95:5$). By using this highly scalable and robust reaction sequence, the required C14–C29 subunit **12** was synthesized efficiently on a multigram scale in 35% yield over 13 steps from (*S*)-**14**.

The synthesis of the C30–C36 subunit **10** required for the reidispongiolide side chain is shown in Scheme 5. Conveniently, the route utilized our lactate boron aldol chemistry[23] to install the required C32/C33 *anti* relationship. From our earlier studies to determine the absolute configuration of the side chain,[10a] this called for the use of the ethyl ketone (*S*)-**30**. Thus, enolization of ketone (*S*)-**30** with *c*-Hex_2BCl and Me_2NEt followed by addition of a freshly prepared solution of 3-butenal[24] provided the expected *anti* adduct **31** in 85% yield (d.r. > 95:5) without any detectable isomerization of the sensitive β,γ-unsaturated aldehyde. As in the previous situation, the *E*-enolate π-facial selectivity is presumably governed by the formation of a stabilizing formyl hydrogen bond,[16,23c] which now involves the carbonyl oxygen



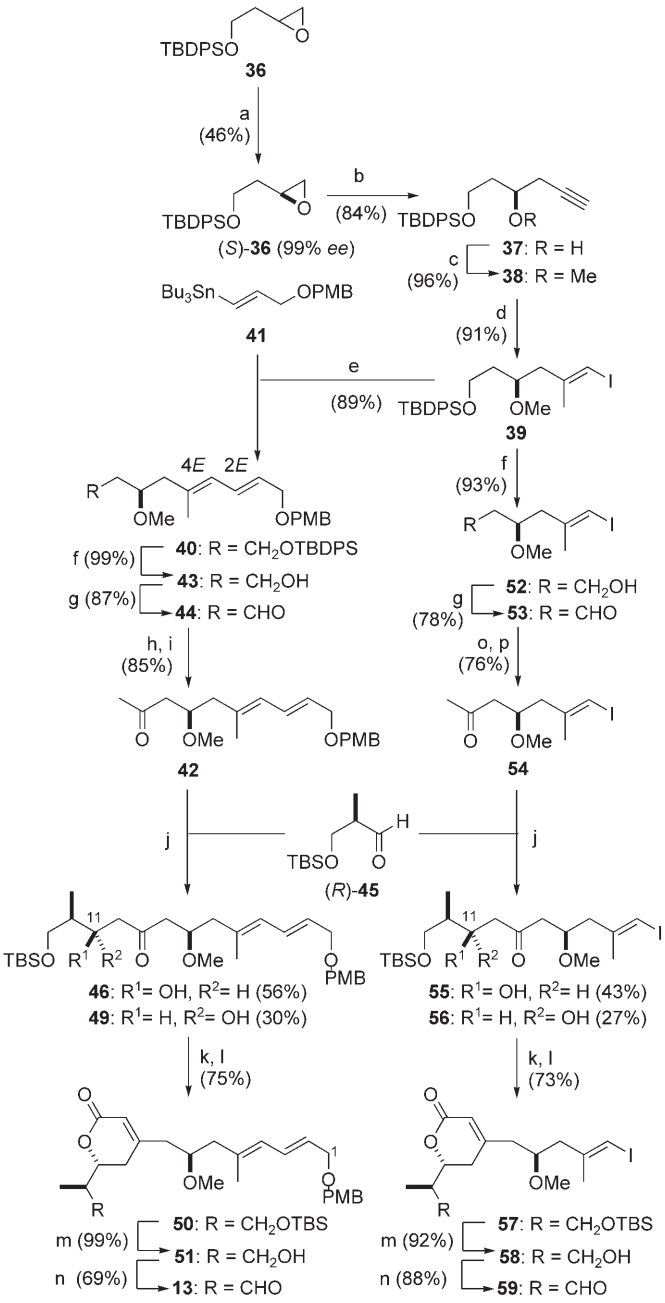
Scheme 5. Synthesis of the C30–C36 subunit **10** with ketone (*S*)-**30**. a) i) *c*-Hex_2BCl, Me_2NEt, −20 to 0°C; ii) 3-butenal, −78→−20°C; b) $Me_3O{\cdot}BF_4$, Proton sponge, CH_2Cl_2, 0°C→RT; c) MeLi, Et_2O, −78→−20°C; d) OsO_4 (cat.), $NaIO_4$, THF, H_2O, 0°C→RT; e) **35**, LiHMDS, THF, −78→0°C; then **34**, −78°C; f) I_2 (cat.), CH_2Cl_2, dark, room temperature. Bz = benzoyl, LiHMDS = lithium hexamethyldisilazide.

atom of the benzoate, in the bicyclic aldol transition state shown, along with minimization of allylic strain between the α stereocenter of the enolate and the methyl substituent. Treatment of aldol adduct **31** with $Me_3O{\cdot}BF_4$ in the presence of Proton sponge® then afforded ketone **32** (92%), which underwent methyl lithium addition with concomitant benzoyl cleavage to generate diol **33** (77%). Dihydroxylation and oxidative cleavage in situ of both 1,2-diols in **33** was achieved readily with $OsO_4/NaIO_4$ to provide the aldehyde **34** (65%). At this point, installation of the sensitive *N*-vinylformamide functionality was required; this can often prove to be a demanding step. By using our established Wittig protocol, as developed in the context of our scytophycin total synthesis,[25] treatment of aldehyde **34** with the ylide obtained from phosphonium salt **35** with LiHMDS delivered the *Z* alkenyl formamide as the predominant isomer (52%, *Z*/*E* = 60:40). Subsequent iodine-mediated isomerization then provided the desired *E* alkenyl formamide **10** cleanly (82%; obtained as a mixture of rotamers by NMR spectroscopic analysis), thus completing the C30–C36 side chain subunit in six steps and 17% overall yield from (*S*)-**30**.

Synthesis of the Northern Hemisphere Region

We now chose to prepare the remaining northern hemisphere segment **13** (Scheme 2), which incorporates a PMB ether at C1, as a projected precursor to the required 2*E*,4*E* dienoate of reidispongiolide. From our earlier work on the aplyronines,[26a] we anticipated that DDQ oxidative conditions would afford the corresponding 2*E*,4*E* dienal, which could then be oxidized to the acid in preparation for macrolactonization. Although this approach was pursued first, complications pertaining to the proposed deprotection/oxidation sequence necessitated a revision of our original strategy.

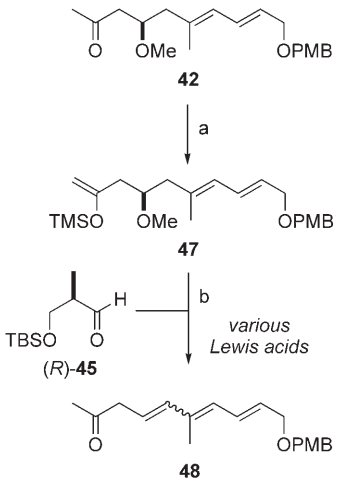
Preparation of the C1–C13 subunit **13** (Scheme 6) began with the epoxide (*S*)-**36**,[27] conveniently prepared in high enantiomeric purity by Jacobsen hydrolytic kinetic resolution.[28] On a multigram scale, the optimized protocol involved activation of the (*S*,*S*)-Co–salen catalyst with AcOH at 40 °C in a melt of racemic epoxide **36** followed by addition of THF and water to provide, after 16 h at 30 °C, the resolved epoxide (*S*)-**36** in 46% yield with consistently excellent levels of enantioselectivity (99% *ee* by HPLC). Treatment of (*S*)-**36** with the lithium anion of trimethylsilylacetylene in THF in the presence of $BF_3{\cdot}Et_2O$ afforded the alcohol **37** in 84% yield after desilylation with K_2CO_3 in MeOH.[27] Subsequent methylation with NaH and MeI in THF then gave methyl ether **38** in 96% yield as a substrate for Negishi carbometalation[29] to introduce the *E* vinyl iodide in **39**. In practice, treatment of alkyne **38** with trimethylaluminum and zirconocene dichloride in 1,2-dichloroethane at 60 °C for 16 h effected regioselective *syn* addition, and reaction of the resulting vinyl alane with iodine provided the desired *E* vinyl iodide **39** in 91% yield.



Scheme 6. Synthesis of the two alternative building blocks **13** (C1–C13) and **59** (C4–C13) for the northern hemisphere. a) (*S*,*S*)-Co–salen (0.5 mol%), AcOH (1 mol%), H_2O, THF, room temperature; b) i) *n*BuLi, HCCTMS, $BF_3{\cdot}Et_2O$, THF, −78 °C; ii) K_2CO_3, MeOH, room temperature; c) NaH, MeI, THF, 0 °C→RT; d) i) $AlMe_3$, [Cp_2ZrCl_2], DCE, 60 °C; ii) I_2, THF, −20 °C→RT; e) CuTC, NMP, room temperature; f) TBAF, THF, 0 °C→RT; g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, −78 °C→RT; h) MeLi, THF, −78→−50 °C; i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, −78 °C→RT; j) i) (−)-Ipc_2BCl, Et_3N, Et_2O, 0 °C; ii) (*R*)-**45**, −100 or −78 °C; k) $(EtO)_2P(O)CH_2CO_2H$, 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, DMAP, PhMe, room temperature; l) $Ba(OH)_2$, wet THF, 0 °C→RT; m) HF·py, py, THF, 0 °C→RT; n) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, room temperature; o) MeMgI, THF, −78→−40 °C; p) PCC, celite, CH_2Cl_2, 0 °C→RT. Cp = cyclopentadienyl, DCE = 1,2-dichloroethane, DMAP = 4-*N*,*N*′-dimethylaminopyridine, DMSO = dimethyl sulfoxide, NMP = 1-methyl-2-pyrrolidinone, PCC = pyridinium chlorochromate, py = pyridine, salen = *N*,*N*′-ethylenebis(salicylideneiminato), TBDPS = *tert*-butyldiphenylsilyl, TC = thiophene-2-carboxylate, TEMPO = 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl, TMS = trimethylsilyl.

To access the 2*E*,4*E* diene **40** with a PMB ether substituent at C1, a Stille-type cross-coupling with the vinyl stannane **41**[30] was examined. Whereas standard Pd-mediated conditions proved unsatisfactory,[31] the use of the Liebeskind protocol, which employs copper(I) thiophene-2-carboxylate (CuTC) in NMP at ambient temperature, was successful.[32] After extensive optimization, slow addition of stannane **41** over 2–3 h to vinyl iodide **39** and CuTC provided the desired 2*E*,4*E* diene **40** in 89% yield. The slow addition was found to be critical to minimize homocoupling of the stannane component **41**. Following the 2*E*,4*E* diene installation, elaboration to the methyl ketone **42** was required. TBDPS ether cleavage of **40** with TBAF and Swern oxidation of the resulting alcohol **43** provided the aldehyde **44** in high yield (86%). Addition of methyl lithium to aldehyde **44** in THF at −50 °C gave the corresponding alcohol, and a further Swern oxidation then afforded the methyl ketone **42** (85%), in readiness for the projected aldol coupling with the aldehyde (*R*)-**45** to give the required adduct **46**.

Initially, introduction of the required C11 hydroxy stereocenter in **46** was envisaged to arise by invoking Felkin–Anh selectivity from aldehyde (*R*)-**45** under Mukaiyama aldol conditions (Scheme 7).[33] Despite considerable experimentation with various Lewis acids, the only product obtained from the attempted reaction of silyl enol ether **47** with aldehyde (*R*)-**45** was the eliminated ketone **48**, with no trace of aldol adducts. With disappointing results obtained even under mild conditions, an alternative was sought by using the corresponding boron-mediated aldol protocol (Scheme 6). In the light of the inherent 1,5-*anti* stereoinduction that the β-methoxy group in ketone **42** would impart in a boron aldol reaction,[34] it proved necessary to employ reagent control to overturn the substrate-based induction.[15,22] Thus, enolization of the methyl ketone **42** with (−)-Ipc_2BCl/Et_3N at 0 °C and reaction with aldehyde (*R*)-**45** at −100 °C for 10 min provided the desired 1,5-*syn* aldol adduct **46** and its C11 epimer **49** in 56 and 30% yield, respectively. Of note are the short reaction time and low temperature required in this reaction, a result of the extraordinary propensity of the intermediate boron aldolate to undergo rapid reduction to the 1,3-diol.



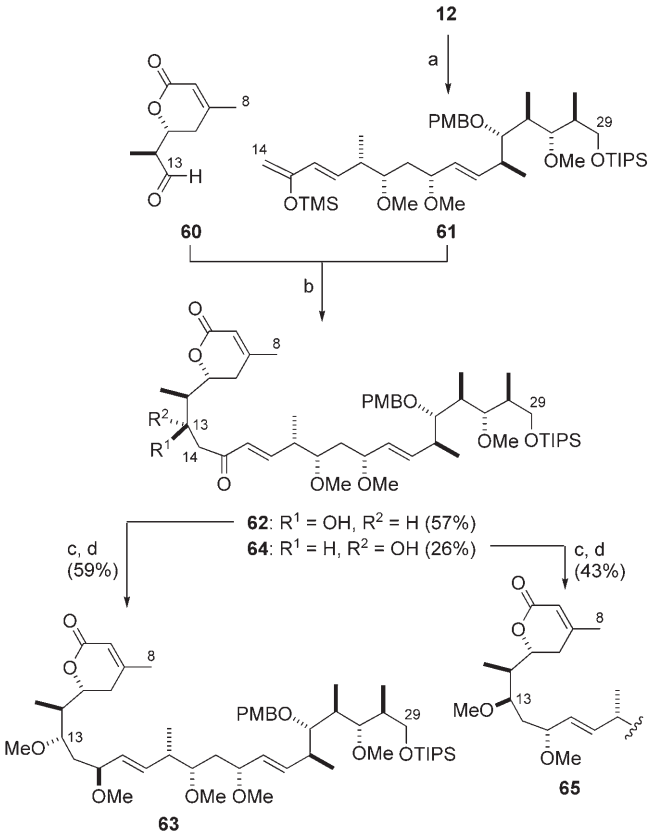
Scheme 7. Attempted Mukaiyama aldol coupling of ketone **42**. a) LDA, TMSCl, Et_3N, THF, −78 °C; b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; alternative Lewis acids examined include $TiCl_4$, $TiCl_2(OiPr)_2$, $Ti(OiPr)_4$, $B(C_6F_5)_3$, ZnI_2. LDA = lithium diisopropylamide.

It now remained to complete the C1–C13 aldehyde **13** by formation of the dihydropyranone and adjustment of the oxidation state at the C13 terminus. By utilizing Yamaguchi conditions,[35] the major β-hydroxy ketone **46** was esterified with diethylphosphonoacetic acid to provide the intermediate phosphonoacetate, followed by exposure to activated $Ba(OH)_2$ in wet THF[36] to result in an intramolecular HWE olefination to afford the dihydropyranone **50** in 75% yield. Cleavage of the primary TBS ether in **50** with HF·py then gave the primary alcohol **51** (99%). Finally, oxidation with TEMPO/$PhI(OAc)_2$[37] provided the northern hemisphere aldehyde **13** (69%).

We also pursued an alternative strategy, whereby the stereodefined 2*E*,4*E*-dienoate region of the northern hemisphere was introduced after the pivotal C13–C14 bond formation by aldol coupling with the southern hemisphere ketone **12**. As shown in Scheme 6 (right column), this commenced with the vinyl iodide **39** already used in the first approach, which was elaborated through a similar sequence involving intermediates **52** and **53** to afford the methyl ketone **54** (55% over 4 steps). By using reagent control with (−)-Ipc_2BCl, the boron aldol coupling of **54** with the aldehyde (*R*)-**45** gave the desired adduct **55** (43%) preferentially, along with the minor C11 epimer **56** (27%), which was removed chromatographically. Esterification of the major β-hydroxy ketone **55** with diethylphosphonoacetic acid and an intramolecular HWE olefination mediated by $Ba(OH)_2$ then afforded the dihydropyranone **57** in 73% yield. TBS ether cleavage with HF·py and oxidation of the resulting alcohol **58** with TEMPO/$PhI(OAc)_2$ completed the C4–C13 subunit **59** in 12 steps and 10% overall yield from (*S*)-**36**.

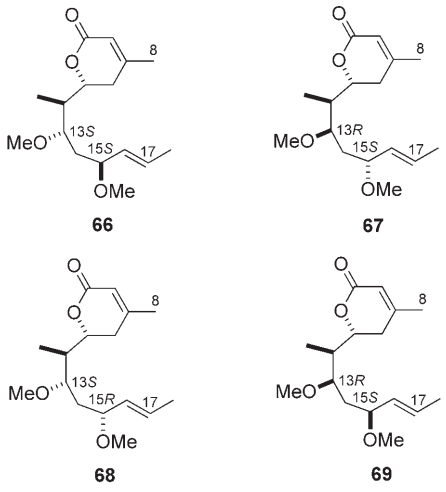
Assembly of the Building Blocks

With the key building blocks in hand, attention was now focused on their union, which began with the exploration of a Mukaiyama aldol reaction[33] of **12** and the truncated model aldehyde **60** to install the C13 stereocenter by relying on Felkin–Anh induction (Scheme 8). Enolization of the methyl ketone **12** with LiHMDS at −78 °C and trapping with TMSCl provided the silyl enol ether **61**. Exposure of **61** and model aldehyde **60** to $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −95 °C then gave a separable 75:25 mixture of epimeric aldol adducts. Conveniently, the C13 configuration could be determined by using our NMR library of fragments,[10b] as previously employed in the stereochemical assignment of reidispongiolide A. The major adduct **62** (assumed to be the 1,2-*syn* Felkin–Anh product) was subjected to Evans–Saksena reduction[17] with $Me_4NBH(OAc)_3$ to give the 1,3-*anti* diol (d.r. > 95:5) followed by O-methylation with trimethyloxonium tetrafluoroborate to afford the methyl ether **63**. Analo-



Scheme 8. Mukaiyama aldol coupling between model aldehyde **60** (C8–C13) and ketone **12** (C14–C29). a) LDA, TMSCl, Et_3N, THF, −78 °C; b) $BF_3{\cdot}OEt_2$, CaH_2, CH_2Cl_2, −95→−78 °C; c) $Me_4NBH(OAc)_3$, MeCN, AcOH, −30 °C; d) $Me_3O{\cdot}BF_4$, Proton sponge, CH_2Cl_2, 0 °C.

gous chemistry was performed in parallel on the minor aldol adduct **64** to provide the methyl ether **65**. The ^{1}H NMR spectra of methyl ethers **63** and **65** were then compared with those for the library of truncated compounds **66–69**, as synthesized previously (Scheme 9).[10b] The major product **63** correlated with the 13*S*,15*S* stereoisomer **66**, whereas the minor product **65** matched best with the 13*R*,15*R* stereoisomer **67**.

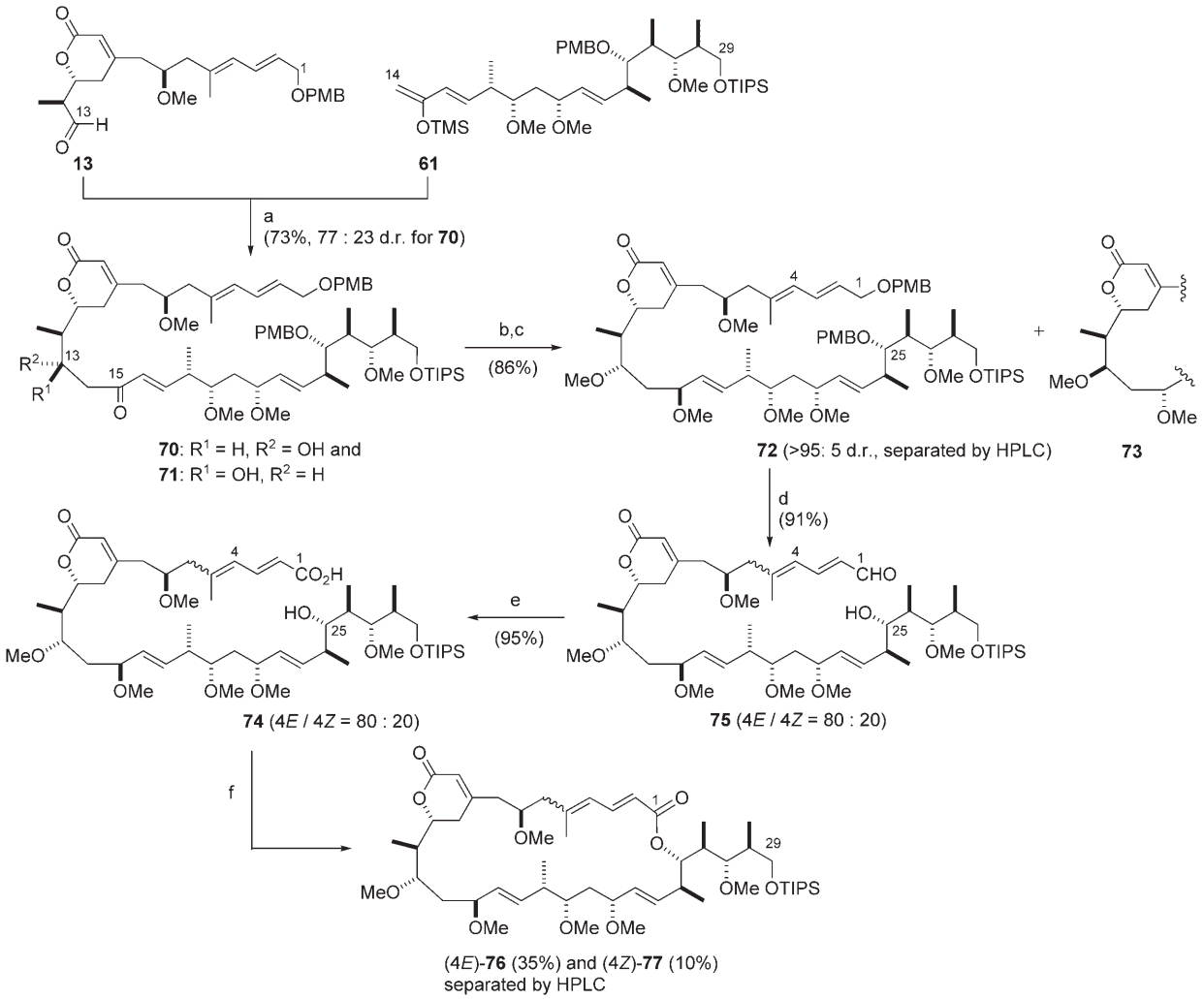


Scheme 9. Reidispongiolide C8–C16 fragment library **66–69** of established stereochemistry for ^{1}H NMR spectroscopic comparison.

We now applied these Mukaiyama aldol conditions to the coupling of the silyl enol ether **61** and the C1–C13 aldehyde **13** with the 2*E*,4*E*-diene terminus (Scheme 10). This led to the formation of a 77:23 mixture of the epimeric adducts **70** and **71** in 73% yield. The mixture was advanced through the Evans–Saksena reduction and methyl ether formation to lead to the separable diastereomers **72** (major) and **73** (minor). Again, detailed comparison of the ^{1}H NMR spectra of these compounds with those of the fragment library **66–69** enabled the confident assignment of the configuration at C13 and C15.

At this point, we were ready to access the *seco* acid **74** and explore the crucial macrolactonization step to install the 26-membered macrolide core. Exposure of **72** to DDQ led to oxidative conversion[26a] into the dienal **75** with concomitant cleavage of the PMB ether at C25 in 91% yield. Unexpectedly, NMR spectroscopic analysis indicated that the dienal had been produced as an inseparable 80:20 mixture of *E*/*Z* isomers about the trisubstituted alkene, which indicates that some isomerization had occurred under the conditions of reaction. A similar step in our aplyronine work had not been problematic,[26b] thus indicating that the fault here lay with the extra methyl substitution at C5 in the reidispongiolide series. Oxidation under buffered $NaClO_2$ conditions then gave the *seco* acid **74** (95%, again as an inseparable 80:20 mixture of double-bond isomers). With the available material, we could now explore the macrolactonization step, performed under established Yamaguchi conditions.[35] After some optimization, we found that formation of the mixed anhydride and its subsequent slow addition to a solution of DMAP in toluene at ambient temperature generated the 26-membered macrolide core **76** in 35% yield. This was accompanied by a separable minor macrolactone isomer **77**, isolated in 10% yield, from cyclization of the compound with 4*Z*-alkene geometry. Gratifyingly, comparison of the ^{1}H and ^{13}C NMR spectra of the major macrolactone **76** with those for reidispongiolide A[7] indicated an excellent agreement in the C1–C25 region, thus providing timely support for our structural assignment.

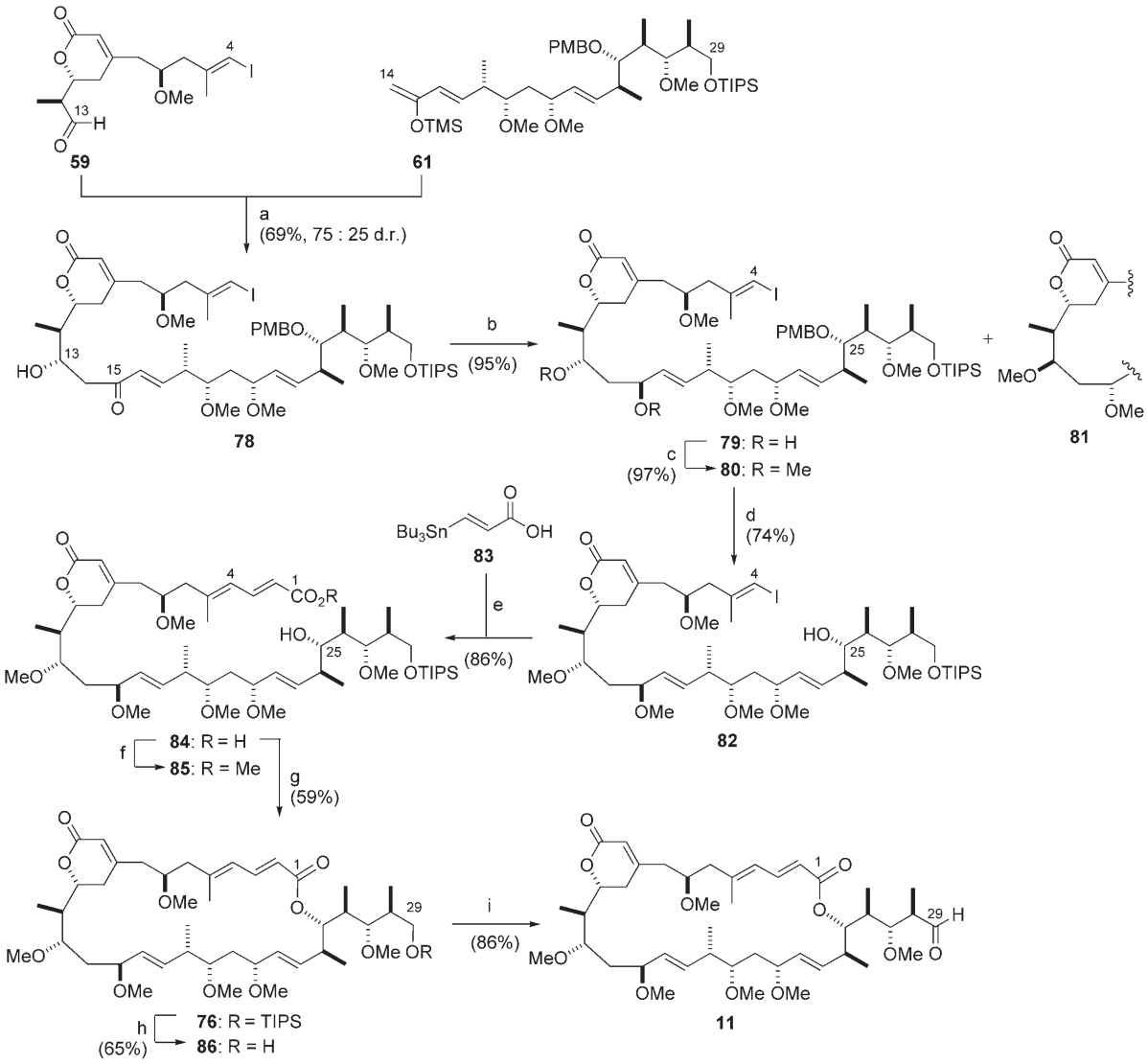
In view of the troublesome diene isomerization experienced in this initial approach, we next examined construction of the macrolide core **76** by using aldol coupling between the C4–C13 aldehyde **59** and the silyl enol ether **61** (Scheme 11). As before, the Mukaiyama aldol reaction afforded a 69% yield of a 75:25 mixture of adducts in favor of the required 13*S* adduct **78**, whereas Evans–Saksena reduction generated the 1,3-*anti* diol **79** (95%). Methyl ether formation with $Me_3O{\cdot}BF_4$ (97%) then enabled chromatographic removal of the minor diastereomer arising from the aldol step to provide stereochemically homogeneous **80** (49% after separation from **81**). In preparation for macrocycle formation, oxidative cleavage of the C25 PMB ether in **80** with DDQ then gave **82** (74%). Installation of a suitable C1–C3 linker subunit was now needed, and the use of the vinyl



Scheme 10. Mukaiyama aldol coupling between **13** (C1–C13) and **61** (C14–C29) followed by elaboration to macrolide core **76**. a) $BF_3{\cdot}OEt_2$, CaH_2, CH_2Cl_2, −95→−78 °C; b) $Me_4NBH(OAc)_3$, MeCN, AcOH, −30→−20 °C; c) $Me_3O{\cdot}BF_4$, Proton sponge, CH_2Cl_2, 0 °C→RT; d) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C; e) $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O, room temperature; f) i) 2,4,6-$Cl_3(C_6H_2)$COCl, Et_3N, PhMe, room temperature; ii) DMAP, PhMe, room temperature.

stannane **83**[38] was examined. In principle, the 26-membered macrolide could be constructed by using either an intramolecular Stille cross-coupling reaction or, as before, a more conventional macrolactonization. Initial studies pursued the former option and focused on the esterification of the C25 hydroxy group in **82** with the acid **83**, but this led to degradation and/or recovery of starting materials under a variety of conditions, including the Yamaguchi protocol. Gratifyingly, reversing the order of this coupling sequence proved successful. In practice, Pd-mediated Stille coupling[31] of vinyl stannane **83** with the vinyl iodide **82** installed the 2*E*,4*E* diene in *seco* acid **84** in 86% yield without any detectable attendant isomerization of the alkenes. The corresponding methyl ester **85** was also prepared to facilitate characterization at this stage. Gratifyingly, by using our previously developed Yamaguchi macrolactonization conditions with pure *seco* acid **84**, the desired 26-membered macrolactone **76** was now obtained cleanly in an improved 59% yield. Cleavage of the C29 TIPS ether in **76** with HF·py and Dess–Martin oxidation of the resulting alcohol **86** then provided the macrocyclic aldehyde **11** (56%), which corresponds to the much anticipated C1–C29 subunit (see Scheme 2), in preparation for the final extension of the side chain.

Attention was now directed to the challenging introduction of the full side chain of reidispongiolide A, thus incorporating the sensitive *N*-vinylformamide terminus. We initially rehearsed this endgame by using a truncated version of the valuable aldehyde **11** in combination with the C30–C36 methyl ketone **10** (Scheme 12). Thus, oxidation of the alcohol **22** by Dess–Martin periodinane afforded the corresponding aldehyde **87**. On the basis of our work on the aplyronines,[39] we decided to examine the use of a boron aldol coupling to install the complete reidispongiolide side chain under mild conditions. After careful optimization, we were able to perform this delicate aldol coupling by using *c*-Hex_2BCl/Et_3N for enolization of **10** followed by enolate addition to the aldehyde **87** to lead to clean formation of a single epimer at C29 in adduct **88** (78%, d.r. > 95:5). The



Scheme 11. Mukaiyama aldol coupling between **59** (C4–C13) and **61** (C14–C29) followed by elaboration to macrocyclic aldehyde **11**. a) $BF_3{\cdot}OEt_2$, CaH_2, CH_2Cl_2, −100 °C; b) $Me_4NBH(OAc)_3$, MeCN, AcOH, −30→−20 °C; c) $Me_3O{\cdot}BF_4$, Proton sponge, CH_2Cl_2, 0 °C→RT; d) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C; e) $[Pd_2(dba)_3]$, iPr_2NEt, NMP, room temperature; f) $TMSCHN_2$, MeOH, room temperature; g) i) 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, PhMe, room temperature; ii) DMAP, PhMe, room temperature; h) HF·py, py, THF, 0 °C→RT; i) Dess–Martin periodinane, CH_2Cl_2, 0 °C→RT. dba = dibenzylideneacetone.

C29 configuration was determined as indicated with the advanced Mosher method.[40] We attribute this formally anti-Felkin result primarily to the high π-facial bias of the boron enolate, which invokes 1,5-*anti* stereoinduction arising from the β-methoxy group in the ketone component.[34]

Completion of the Total Synthesis

At last, we were now ready to perform the real aldol coupling with the precious macrocyclic aldehyde **11**, followed by controlled dehydration of the resulting β-hydroxy ketone and subsequent 1,4-reduction (Scheme 13). Under similar conditions to those above, enolization of the methyl ketone **10** gave the dicylohexylboron enolate, which was then added to the aldehyde **11** in diethyl ether. Following a mild, nonoxidative workup, this afforded a single aldol adduct **89** in 70% yield with the configuration of the temporary C29 stereocenter assigned by analogy with that in the model system **88**. Gratifyingly, controlled dehydration of this β-hydroxy ketone **89** with Burgess reagent ($Et_3NSO_2NCO_2Me$)[41] afforded the *E* enone **90** cleanly (88%). At this stage, all that was required was controlled reduction of the enone without competing reaction of the dienoate. After exploring conditions in appropriate model systems, we identified the Stryker reduction protocol[42] to be the most promising. Thus, treatment of enone **90** with $[Ph_3PCuH]_6$ led to clean 1,4-reduction to give (−)-reidispongiolide A (**5**) in 77% yield (after HPLC purification to remove traces of triphenylphosphine oxide). To our satisfaction, all spectroscopic data (^1H and ^{13}C NMR, IR, MS) for the synthetic material were in excellent agreement with those reported for natural reidispongiolide A[7] and correlated with those of an authentic

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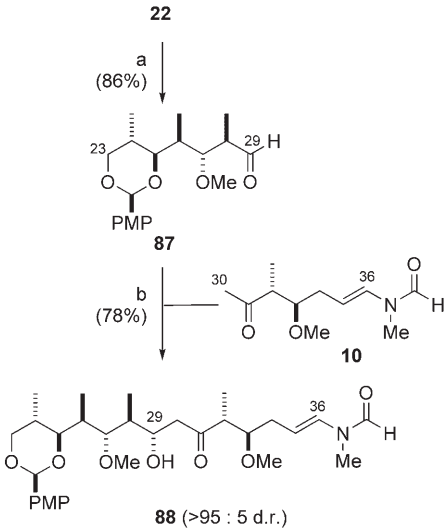
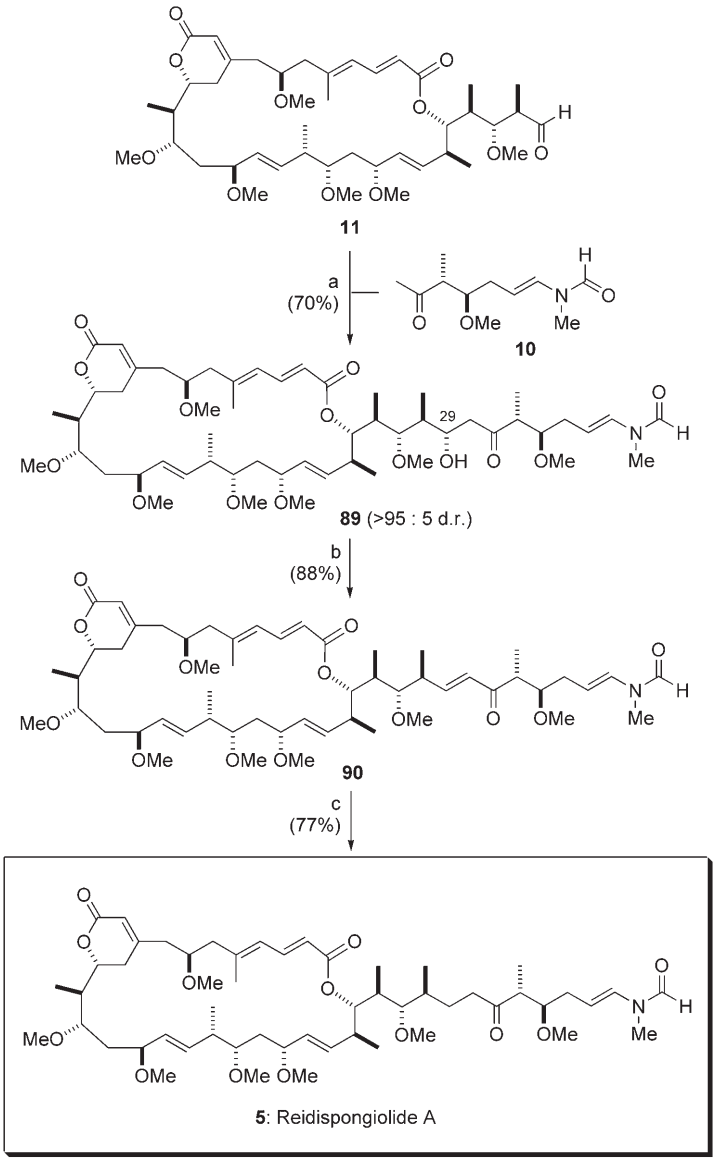


Scheme 12. Boron aldol coupling between **10** (C23–C29) and model aldehyde **87** (C30–C36) for introduction of the full reidispongiolide side chain. a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, room temperature; b) i) *c*-Hex_2BCl, Et_3N, Et_2O, 0 °C; ii) **87**, −78→RT.



Scheme 13. Completion of the total synthesis of (−)-reidispongiolide A. i) *c*-Hex_2BCl, Et_3N, Et_2O, −10→0 °C; ii) **11**, −78→0 °C; b) $Et_3NSO_2NCO_2Me$, THF, room temperature; c) $[Ph_3PCuH]_6$, PhMe, H_2O, room temperature.

sample (provided by Professor D'Auria), including HPLC comparison.[43] As reidispongiolide A has a relatively low magnitude of specific rotation ($[\alpha]_D = -10.0$ ($c = 0.02$, MeOH); compare with lit[7]: $[\alpha]_D = -4.8$), we also carried out a chiroptical correlation with circular dichroism spectra, thereby conclusively defining the relative and absolute configuration. This work also provides strong evidence for the configurational assignment of reidispongiolide B (**6**) and the sphinxolide congeners (**1**–**4**) (Scheme 1).

Conclusions

We have completed a stereocontrolled total synthesis of (−)-reidispongiolide A that proceeds in 1.1% overall yield with a longest linear sequence of 25 steps from (*S*)-**14**. This unequivocally established its relative and absolute configuration as depicted in structure **5**, in agreement with our earlier stereochemical analysis[10b] and the X-ray crystal structure of the reidispongiolide–actin complex reported recently by Rayment and co-workers.[13] Notably, this constitutes the first chemical synthesis of any member of the reidispongiolide/sphinxolide family of complex marine macrolides. Key transformations include a challenging Mukaiyama fragment-coupling reaction to introduce the C13 stereocenter, a Stille cross-coupling to install the 2*E*,4*E* dienoate in a stereodefined manner, a Yamaguchi macrolactonization to construct the 26-membered macrolide, and a late-stage boron aldol reaction to introduce the full side chain, which contains the sensitive *N*-vinylformamide. Furthermore, the effectiveness of our versatile boron aldol methodology allowed the requisite stereochemical motifs in the key subunits **10**, **12**, and **13** to be installed efficiently. Importantly, this modular, convergent synthesis should prove amenable to the production of other congeners of the reidispongiolides and sphinxolides, together with novel analogues of these potent actin-binding agents, thus enabling extensive exploration of their anticancer properties. In combination with the available X-ray structural data on actin-bound reidispongiolide and related marine macrolides, the design of simplified analogues with tailored functional properties can also be envisaged.[9]

Experimental Section

See the Supporting Information for details of instrumentation, purification of reagents and solvents, and chromatography. All non-aqueous reactions were performed under an atmosphere of argon with oven-dried apparatus and standard techniques for handling air-sensitive materials.

18: A solution of (*S*)-**14** (2.20 g, 10.6 mmol) in Et_2O (20 mL) was added to a cold (−78 °C), stirred solution of dicyclohexylboron chloride (2.70 mL, 12.7 mmol) and Et_3N (2.35 mL, 16.9 mmol) in dry Et_2O (25.0 mL). The reaction mixture was allowed to warm to −20 °C for 1.5 h before recooling to −78 °C, followed by addition of (*S*)-**17** (5.07 g, 20.7 mmol) as a solution in Et_2O (20 mL). The reaction mixture was stirred at −78 °C for 3 h and then at −20 °C for 16 h. The resultant solution was partitioned between Et_2O (100 mL) and pH 7 buffer (100 mL), and the organic phase was separated. The aqueous phase was extracted with Et_2O (3×50 mL), and the combined organic phases were concentrated and suspended in MeOH (20 mL) and pH 7 buffer (20 mL) before being cooled to 0 °C. H_2O_2 (30% *v*/*v*, 7 mL) was added, and the reaction mixture was allowed to warm to room temperature for 1 h. It was then poured onto water, and the aqueous phase was extracted with Et_2O (3× 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Analysis of the crude product mixture indicated **18** was obtained with 95:5 d.r. Flash chromatography (5→ 10% EtOAc/PE; PE = petroleum ether) afforded **18** (4.59 g, 90%) as a colorless oil. R_f: 0.13 (10% EtOAc/hexane); $[\alpha]_D^{20} = +17.5$ ($c = 1.5$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3500$, 2940, 1713, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 8.6$ Hz, 2H, Ar), 6.85 (d, $J = 8.6$ Hz, 2H, Ar), 4.41 (d, $J = 11.6$ Hz, 1H, CH_aH_bAr), 4.37 (d, $J = 11.6$ Hz, 1H, CH_aH_bAr), 3.83 (dd, $J = 10.0$, 4.3 Hz, 1H, H_{29a}), 3.78 (s, 3H, ArO*Me*), 3.75 (dd, $J = 9.9$, 4.6 Hz, 1H, H_{29b}), 3.64–3.61 (m, 2H, $H_{23a} + H_{27}$), 3.50 (d, $J = 7.3$ Hz, 1H, OH) 3.42 (dd, $J = 8.9$, 5.4 Hz, 1H, H_{23b}), 3.09–3.03 (m, 2H, $H_{26} + H_{24}$), 1.80 (m, 1H, H_{28}), 1.14–1.03 ppm (m, 30H, $MeC_{28} + MeC_{26} + MeC_{24} + Si(CH(CH_3)_2)_3 + SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 217.7$, 159.2, 130.2, 129.2 (2C), 113.7 (2C), 77.8, 73.0, 72.3, 65.7, 55.2, 49.9, 46.5, 36.7, 18.0 (6C), 15.2, 13.5, 13.4, 11.8 ppm (3C); HRMS (ES+): *m*/*z* calcd for $C_{27}H_{49}O_5Si$: 481.3344 $[M+H]^+$; found: 481.3347. The assigned *S* configuration of the C27 OH center was determined by using the advanced Mosher method[40] following formation of the diastereomeric (*R*)- and (*S*)-MTPA esters.

19: A suspension of $Me_4NBH(OAc)_3$ (740 mg, 3.13 mmol) in MeCN/AcOH (1:1, 4 mL) was stirred at room temperature for 1 h. The resulting clear solution was cooled to −35 °C, and **18** (100 mg, 0.21 mmol) was added as a solution in MeCN (1.0 mL). After 3 h, the reaction mixture was warmed to −20 °C and stored for 16 h (freezer), then warmed to room temperature for 2 h. Decomplexation of the boron was facilitated by vigorous stirring with saturated aqueous sodium/potassium tartrate (10 mL) and $NaHCO_3$ (10 mL) for 1 h at room temperature. The aqueous phase was then extracted with Et_2O (3×10 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (10→20% EtOAc/PE) afforded **19** (91 mg, 90%, >97:3 d.r.) as a colorless oil. R_f: 0.08 (10% EtOAc/hexane); $[\alpha]_D^{20} = +2.3$ ($c = 1.0$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3421$, 2930, 1514, 1461 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.6$ Hz, 2H, Ar), 6.87 (d, $J = 8.6$ Hz, 2H, Ar), 4.67 (br s, 1H, OH), 4.49 (d, $J = 11.6$ Hz, 1H, CH_aH_bAr), 4.45 (d, $J = 11.6$ Hz, 1H, CH_aH_bAr), 4.29 (br s, 1H, OH), 3.86 (dd, $J = 9.7$, 4.5 Hz, 1H, H_{29a}), 3.83 (app d, $J = 10.0$ Hz, 1H, H_{25}), 3.80 (s, 3H, ArO*Me*), 3.76 (dd, $J = 9.7$, 7.8 Hz, 1H, H_{29b}), 3.65 (dd, $J = 8.9$, 5.5 Hz, 1H, H_{23a}), 3.56 (dd, $J = 8.6$, 3.1 Hz, 1H, H_{27}), 3.46 (dd, $J = 8.9$, 6.4 Hz, 1H, H_{23b}), 2.02 (m, 1H, H_{28}), 1.94 (m, 1H, H_{24}), 1.80 (m, 1H, H_{26}), 1.15–1.09 (m, 3H, $Si(CH)_3$), 1.08–1.03 (m, 21H, $Si(CH(CH_3)_2)_3 + MeC_{26}$), 0.86 (d, $J = 6.6$ Hz, 3H, MeC_{24}), 0.84 ppm (d, $J = 6.8$ Hz, 3H, MeC_{28}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 159.1, 130.6, 129.4 (2C), 113.7 (2C), 82.2, 74.1, 73.6, 72.9, 69.5, 55.2, 37.5, 36.5, 34.8, 18.0 (6C), 13.5, 13.4, 11.7 (3C), 10.4 ppm; HRMS (ES+): *m*/*z* calcd for $C_{27}H_{51}O_5Si$: 483.3500 $[M+H]^+$; found: 483.3503. The assigned 1,3-*anti* diol stereochemistry was confirmed by the Rychnovsky ^{13}C NMR spectroscopic method[44] following formation of the corresponding acetonide (2,2-dimethoxypropane, PPTS).

20: A solution of **19** (1.10 g, 2.28 mmol) in CH_2Cl_2 (40 mL) was added to a cold (−20 °C), stirred solution of powdered activated 4-Å molecular sieves (≈100 mg) and DDQ (780 mg, 3.42 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at −20 °C for 10 min before being warmed to −10 °C for 1 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (50 mL) and Et_2O (3×30 mL). The combined organic extracts were washed with $NaHCO_3$ (2×50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (10% EtOAc/PE) afforded **20** (1.06 g, 97%) as a colorless oil. R_f: 0.20 (10% EtOAc/hexane); $[\alpha]_D^{20} = +31.9$ ($c = 1.15$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3509$, 2865, 1518, 1460 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) $\delta = 7.37$ (d, $J = 8.6$ Hz, 2H, Ar), 6.86 (d, $J = 8.6$ Hz, 2H, Ar), 5.50 (s, 1H, O_2CHAr), 4.11 (dd, $J = 11.1$, 4.6 Hz, 1H, H_{23a}), 4.02 (dd, $J = 10.2$, 1.6 Hz, 1H, H_{25}), 3.95 (dd, $J = 9.7$, 4.4 Hz, 1H, H_{29a}), 3.85 (dd, $J = 9.7$, 2.9 Hz, 1H, H_{29b}), 3.79 (s, 3H, ArO*Me*), 3.54 (app t, $J = 11.1$ Hz, 1H, H_{23b}), 3.47 (m, 1H, H_{27}), 3.22 (d, $J = 9.1$ Hz, 1H, OH), 2.10 (m, 1H, H_{24}), 1.98 (app dquint, $J = 7.2$, 1.5 Hz, 1H, H_{26}), 1.82 (m, 1H, H_{28}), 1.14 (d, $J = 7.0$ Hz, 3H, MeC_{28}), 1.15–1.09 (m, 3H, $Si(CH)_3$), 1.08–1.03 (m, 18H, $Si(CH(CH_3)_2)_3$), 1.02 (d, $J = 7.0$ Hz, 3H, MeC_{26}), 0.75 ppm (d, $J = 6.7$ Hz, 3H, MeC_{24}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.8$, 131.4, 127.4 (2C), 113.5 (2C), 101.0, 82.3, 76.4, 73.2, 65.8, 55.3, 36.8, 36.5, 30.3, 18.0 (6C), 15.4, 12.0, 11.8 (3C), 10.5 ppm; HRMS (ES+): *m*/*z* calcd for $C_{27}H_{49}O_5Si$: 481.3344 $[M+H]^+$; found: 481.3348. The assigned PMP acetal configuration was determined by NOE analysis.

21: A solution of **20** (4.88 g, 10.15 mmol) in THF (50 mL) was added to a cold (0 °C), stirred suspension of NaH (60% dispersion in oil, 4.06 g, 101.5 mmol) in THF (150 mL). After 30 min, MeI (9.48 mL, 152.3 mmol) was added, and the reaction mixture allowed to warm to room temperature for 18 h before the reaction was quenched with MeOH (30 mL). The reaction mixture was poured into brine (100 mL), the aqueous phases were extracted with Et_2O (3×100 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (5% EtOAc/PE) afforded **21** (4.77 g, 95%) as a colorless oil. R_f: 0.30 (10% EtOAc/hexane); $[\alpha]_D^{20} = +28.9$ ($c = 1.5$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2941$, 2666, 1516, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.42$ (d, $J =$ 8.6 Hz, 2H, Ar), 6.89 (d, $J = 8.6$ Hz, 2H, Ar), 5.47 (s, 1H, O_2CHAr), 4.12 (dd, $J = 11.1$, 4.6 Hz, 1H, H_{23a}), 3.84 (dd, $J = 9.6$, 6.5 Hz, 1H, H_{29a}), 3.81 (s, 3H, ArO*Me*), 3.77 (app d, $J = 10.0$ Hz, 1H, H_{25}), 3.53 (app t, $J =$ 11.1 Hz, 1H, H_{23b}), 3.47 (dd, $J = 9.6$, 7.4 Hz, 1H, H_{29b}), 3.44 (s, 3H, OMe), 3.22 (app d, $J = 9.9$ Hz, 1H, H_{27}), 2.10–1.99 (m, 3H, $H_{24} + H_{26} +$ H_{28}), 1.11–1.03 (m, 24H, $Si(CH(CH_3)_2)_3 + Si(CH)_3 + MeC_{28}$), 0.95 (d, $J =$ 6.9 Hz, 3H, MeC_{26}), 0.74 ppm (d, $J = 6.7$ Hz, 3H, MeC_{24}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.8$, 131.7, 127.3 (2C), 113.5 (2C), 100.8, 84.8, 82.0, 73.4, 64.1, 61.6, 55.3, 38.2, 36.7, 30.4, 18.1 (7C), 16.1, 11.9 (3C), 10.2 ppm; HRMS (ES+): *m*/*z* calcd for $C_{28}H_{51}O_5Si$: 495.3500 $[M+H]^+$; found: 495.3507.

22: Pyridinium hydrofluoride (0.4 mL) prebuffered with pyridine (0.80 mL) was added to a stirred solution of **21** (200 mg, 0.404 mmol) in THF (5.0 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature for 24 h before the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was then diluted with Et_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (50% EtOAc/PE) gave **22** (134 mg, 98%) as white needles. R_f: 0.40 (50% EtOAc/hexane); m.p.: 104–105 °C; $[\alpha]_D^{20} = +72.1$ ($c = 0.19$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3439$, 2931, 1615, 1518 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.40$ (d, $J = 8.7$ Hz, 2H, Ar), 6.89 (d, $J = 8.7$ Hz, 2H, Ar), 5.46 (s, 1H, O_2CHAr), 4.13 (dd, $J = 11.1$, 4.6 Hz, 1H, H_{23a}), 3.91 (app d, $J =$ 11.1 Hz, 1H, H_{25}), 3.81 (s, 3H, ArO*Me*), 3.77 (dd, $J = 10.1$, 1.5 Hz, 1H, H_{29a}), 3.58–3.51 (m, 2H, $H_{23b} + H_{27}$), 3.49 (s, 3H, OMe), 3.30 (dd, $J = 10.1$, 1.7 Hz, 1H, H_{29b}), 2.89 (br d, $J = 8.5$ Hz, 1H, OH), 2.09 (m, 1H, H_{24}), 2.01 (m, 1H, H_{26}), 1.87 (m, 1H, H_{28}), 1.21 (d, $J = 7.1$ Hz, 3H, MeC_{28}), 0.91 (d, $J = 7.0$ Hz, 3H, MeC_{26}), 0.76 ppm (d, $J = 6.7$ Hz, 3H, MeC_{24}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.9$, 131.5, 127.3 (2C), 113.6 (2C), 100.9, 87.6, 81.6, 73.4, 64.2, 62.1, 55.3, 37.2, 35.6, 30.4, 16.2, 12.0, 10.1 ppm; HRMS (EI+): *m*/*z* calcd for $C_{19}H_{30}O_5Na$: 361.1985 $[M+Na]^+$; found: 361.1991.

23: A solution of DIBAL-H (24.1 mL, 1 M in CH_2Cl_2, 24.1 mmol) in TBME (60 mL) was added to a stirred solution of **21** (4.77 g, 9.64 mmol) in dry TBME (100 mL) at room temperature, and the reaction mixture was stirred for 20 min before the reaction was quenched with saturated aqueous sodium/potassium tartrate (50 mL) at 0 °C. Decomplexation of the aluminum was facilitated by stirring with further saturated aqueous sodium/potassium tartrate (50 mL) for 45 min at room temperature before dilution with CH_2Cl_2 (100 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The com-

bined organic phases were then washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford **23** (4.77 g, 98%) as a colorless oil. A small sample was purified by flash chromatography (20% EtOAc/hexane) for characterization purposes. R_f: 0.25 (20% EtOAc/hexane); $[\alpha]_D = +13.1$ ($c = 0.63$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3500$, 2930, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 8.5$ Hz, 2H, Ar), 6.87 (d, $J = 8.5$ Hz, 2H, Ar), 4.63 (d, $J = 10.6$ Hz, 1H, CH_aH_bAr), 4.50 (d, $J = 10.6$ Hz, 1H, CH_aH_bAr), 3.80 (s, 3H, Ar-OMe), 3.78 (dd, $J = 9.7$, 5.6 Hz, 1H, H_{29a}), 3.67–3.60 (m, 4H, $H_{29b}+H_{25}+H_{23a}+H_{23b}$), 3.44 (s, 3H, OMe), 3.13 (dd, $J = 7.8$, 4.2 Hz, 1H, H_{27}), 2.03 (m, 1H, H_{26}), 1.95–1.89 (m, 2H, $H_{24}+H_{28}$), 1.14–1.05 (m, 21H, $Si(CH(CH_3)_2)_3+Si(CH)_3$), 1.01 (d, $J = 7.0$ Hz, 6H, $MeC_{26}+MeC_{28}$), 0.90 ppm (d, $J = 7.0$ Hz, 3H, MeC_{24}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.2$, 130.9, 129.3 (2C), 113.8 (2C), 86.0, 83.1, 73.9, 66.7, 65.0, 60.0, 55.3, 38.9, 38.5, 38.3, 18.1 (6C), 14.9, 14.7, 12.0 ppm (4C); HRMS (ES+): m/z calcd for $C_{28}H_{53}O_5Si$: 497.3657 $[M+H]^+$; found: 497.3663.

16: A solution of **23** (10 mg, 0.02 mmol) in CH_2Cl_2 (1.0 mL) was added to a stirred suspension of Dess–Martin periodinane (26 mg, 0.06 mmol) and pyridine (16 μL, 0.20 mmol) in CH_2Cl_2 (1.0 mL). After 1.5 h, hexane (5 mL) was added, and the resulting suspension was stirred for a further 15 min. The solid material was filtered off, and the filtrate was concentrated in vacuo. Flash chromatography (15% EtOAc/PE) afforded **16** (10 mg, 99%) as a colorless oil. R_f: 0.50 (20% EtOAc/hexane); $[\alpha]_D = -5.3$ ($c = 0.40$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2941$, 2866, 1725, 1514, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.79$ (d, $J = 2.7$ Hz, 1H, H_{23}), 7.23 (d, $J = 8.7$ Hz, 2H, Ar), 6.86 (d, $J = 8.7$ Hz, 2H, Ar), 4.55 (d, $J = 10.7$ Hz, 1H, CH_aH_bAr), 4.44 (d, $J = 10.7$ Hz, 1H, CH_aH_bAr), 3.94 (dd, $J = 7.7$, 2.1 Hz, 1H, H_{25}), 3.80 (s, 3H, ArO*Me*), 3.78 (dd, $J = 9.7$, 5.8 Hz, 1H, H_{29a}), 3.61 (dd, $J = 9.7$, 6.7 Hz, 1H, H_{29b}), 3.44 (s, 3H, OMe), 3.18 (dd, $J = 7.9$, 4.0 Hz, 1H, H_{27}), 2.68 (app dquint, $J = 7.1$, 2.7 Hz, 1H, H_{24}), 2.04 (m, 1H, H_{26}), 1.92 (m, 1H, H_{28}), 1.12–1.05 (m, 21H, $Si(CH(CH_3)_2)_3+Si(CH)_3$), 1.05 (d, $J = 7.1$ Hz, 3H, MeC_{24}), 1.02 (d, $J = 6.8$ Hz, 3H, MeC_{26}), 1.01 ppm (d, $J = 6.9$ Hz, 3H, MeC_{28}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 205.0$, 159.1, 130.8, 129.0 (2C), 113.7 (2C), 85.3, 79.9, 77.2, 73.4, 64.9, 60.1, 55.3, 50.3, 38.5, 18.1 (6C), 15.1, 12.0 (3C), 11.7, 11.5 ppm; HRMS (ES+): m/z calcd for $C_{28}H_{54}O_5SiN$: 512.3766 $[M+NH_4]^+$; found: 512.3771.

25: A solution of diethyl (*N*-methoxy-*N*-methyl-carbomoylmethyl)-phosphonate (167 μL, 0.81 mmol), Et_3N (113 μL, 0.81 mmol), and **16** (160 mg, 0.32 mmol) in MeCN (8.0 mL) was added to a cold (0°C), stirred suspension of LiCl (34 mg, 0.81 mmol) in MeCN (4.0 mL). The reaction mixture was allowed to warm to room temperature over 18 h, then it was partitioned between saturated aqueous NH_4Cl (5 mL) and CH_2Cl_2 (5 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (20→30% EtOAc/PE) afforded **25** (180 mg, 97%) as a colorless oil. R_f: 0.25 (20% EtOAc/hexane); $[\alpha]_D = -19.6$ ($c = 1.4$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2938$, 1664, 1634, 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) $\delta = 7.25$ (d, $J = 8.6$ Hz, 2H, Ar), 7.11 (dd, $J = 15.4$, 8.7 Hz, 1H, H_{23}), 6.84 (d, $J = 8.6$, 2H, Ar), 6.43 (d, $J = 15.4$ Hz, 1H, H_{22}), 4.50 (d, $J = 10.7$ Hz, 1H, CH_aH_bAr), 4.46 (d, $J = 10.7$ Hz, 1H, CH_aH_bAr), 3.79 (s, 3H, ArO*Me*), 3.79 (dd, $J = 9.3$, 5.3 Hz, 1H, H_{29a}), 3.63 (s, 3H, MeNO*Me*), 3.61–3.57 (m, 2H, $H_{29b}+H_{25}$), 3.40 (s, 3H, OMe), 3.23 (s, 3H, *Me*NOMe), 3.14 (dd, $J = 7.7$, 3.9 Hz, 1H, H_{27}), 2.64 (app sext, $J = 7.2$ Hz, 1H, H_{24}), 1.99 (m, 1H, H_{28}), 1.92 (app dquint, $J = 7.1$, 2.2 Hz, 1H, H_{26}), 1.12–1.04 (m, 24H, $Si(CH(CH_3)_2)_3+Si(CH)_3+MeC_{24}$), 1.03 (d, $J = 7.1$ Hz, 3H, MeC_{28}), 0.96 ppm (d, $J = 7.0$ Hz, 3H, MeC_{26}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.6$, 158.9, 150 .8, 131.4, 128.9 (2C), 118.4, 113.6 (2C), 85.4, 82.1, 73.6, 64.9, 61.6, 60.1, 55.3, 41.4, 38.5, 38.3, 32.2, 18.1 (6C), 17.1, 15.3, 12.0 (3C), 11.3 ppm; HRMS (ES+): m/z calcd for $C_{32}H_{58}NO_6Si$: 580.4028 $[M+H]^+$; found: 580.4031.

24: DIBAL-H (35 μL, 1.5 M solution in THF, 0.05 mmol) was added to a cold (−78°C), stirred solution of **25** (30 mg, 0.05 mmol) in THF (0.4 mL). After a further 10 min, the reaction was quenched by vigorous stirring with saturated aqueous sodium/potassium tartrate (2 mL) at room temperature for 1 h. After dilution with CH_2Cl_2 (5 mL), the organic phase was separated, and the aqueous layer was subsequently extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (10% EtOAc/PE) afforded **24** (24 mg, 92%) as a colorless oil. R_f: 0.20 (10% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.48$ (d, $J = 7.8$ Hz, 1H, H_{21}), 7.24 (d, $J = 8.5$ Hz, 2H, Ar), 6.95 (dd, $J = 15.7$, 7.8 Hz, 1H, H_{23}), 6.87 (d, $J = 8.4$ Hz, 2H, Ar), 6.13 (dd, $J = 15.7$, 7.7 Hz, 1H, H_{22}), 4.56 (d, $J = 10.8$ Hz, 1H, CH_aH_bAr), 4.45 (d, $J = 10.8$ Hz, 1H, CH_aH_bAr), 3.80 (s, 3H, ArO*Me*), 3.77 (dd, $J = 9.7$, 5.5 Hz, 1H, H_{29a}), 3.66–3.60 (m, 2H, $H_{25}+H_{29b}$), 3.41 (s, 3H, OMe), 3.13 (dd, $J = 7.0$, 4.5 Hz, 1H, H_{27}), 2.71 (app sext, $J = 6.9$ Hz, 1H, H_{24}), 1.98 (m, 1H, H_{28}), 1.91 (m, 1H, H_{26}), 1.13–1.05 (m, 24H, $Si(CH(CH_3)_2)_3+Si(CH)_3+MeC_{24}$), 1.01 (d, $J = 7.1$ Hz, 3H, MeC_{28}), 0.99 ppm (d, $J = 7.1$ Hz, 3H, MeC_{26}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 194.1$, 161.8, 159.1, 132.4, 129.1 (2C), 127.4, 113.8 (2C), 85.4, 81.9, 73.8, 65.0, 60.0, 55.2, 41.8, 38.9, 38.5, 18.0 (6C), 16.8, 15.1, 12.0 (3C), 11.9 ppm; HRMS (ES+): m/z calcd for $C_{30}H_{53}O_5Si$ 521.3657: $[M+H]^+$; found: 521.3664.

26: A solution of (*S*)-**15** (1.50 g, 6.94 mmol) in Et_2O (30 mL) was added to a cold (−78°C), stirred solution of (−)-Ipc_2BCl (2.45 g, 7.63 mmol) and Et_3N (1.25 mL, 9.02 mmol) in dry Et_2O (50 mL). The reaction mixture was allowed to warm to 0°C for 1 h before recooling to −78°C followed by addition of **24** (1.81 g, 3.47 mmol) in Et_2O (30 mL). After the mixture was stirred at −78°C for 1.5 h, $LiBH_4$ (8.67 mL, 2 M in THF, 17.4 mmol) was added. After a further 30 min, the reaction mixture was partitioned between Et_2O (250 mL) and saturated aqueous NH_4Cl (250 mL), the organic phase was separated, and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic phases were concentrated and suspended in MeOH (70 mL) and NaOH (10 mol%, 70 mL) before being cooled to 0°C. H_2O_2 (30% *v*/*v*, 35 mL) was added dropwise, the reaction mixture was warmed to room temperature for 30 min then poured into water, and the aqueous phase was extracted with Et_2O (3×130 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Analysis of the crude product mixture indicated **26** was obtained with 6:1 d.r. Flash chromatography (10→20% EtOAc/PE) afforded **26** (2.32 g, 91%) as a colorless oil. R_f: 0.10 (20% EtOAc/hexane); $[\alpha]_D = -8.9$ ($c = 1.0$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3417$, 2956, 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.27$ (m, 2H, Ar), 6.85 (d, $J = 8.6$ Hz, 2H, Ar) 5.76 (dd, $J = 15.5$, 8.4 Hz, 1H, H_{23}), 5.53 (dd, $J = 15.5$, 6.8 Hz, 1H, H_{22}), 4.55 (d, $J = 11.0$ Hz, 1H, CH_aH_bAr), 4.49 (d, $J = 11.0$ Hz, 1H, CH_aH_bAr), 4.33 (m, 1H, H_{21}), 4.03 (m, 1H, H_{19}), 3.84 (d, $J = 3.8$ Hz, 1H, OH), 3.79 (s, 3H, ArO*Me*), 3.77 (dd, $J = 9.6$, 5.0 Hz, 1H, H_{29a}), 3.71 (dd, $J = 9.7$, 4.3 Hz, 1H, H_{29b}), 3.63–3.59 (m, 2H, $H_{17a}+H_{17b}$), 3.46 (dd, $J = 6.7$, 3.0 Hz, 1H, H_{25}), 3.39 (s, 3H, OMe), 3.11 (dd, $J = 7.1$, 4.5 Hz, 1H, H_{27}), 2.42 (m, 1H, H_{24}), 1.95 (m, 1H, H_{28}), 1.90 (m, 1H, H_{26}), 1.74 (m, 1H, H_{18}), 1.66 (app dt, $J = 14.1$, 10.3 Hz, 1H, H_{20a}), 1.38 (app dt, $J = 14.1$, 2.1 Hz, 1H, H_{20b}), 1.12–1.05 (m, 21H, $Si(CH(CH_3)_2)_3+Si(CH)_3$), 1.02 (d, $J = 7.0$ Hz, 3H, MeC_{24}), 1.02 (d, $J = 6.9$ Hz, 3H, MeC_{28}), 0.96 (t, $J = 8.0$ Hz, 9H, $Si(CH_2CH_3)_3$), 0.95 (m, 3H, MeC_{26}) 0.85 (d, $J = 7.0$ Hz, 3H, MeC_{18}), 0.61 ppm (q, $J = 8.0$ Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.8$, 134.2, 132.5, 131.7, 128.7 (2C), 113.6 (2C), 85.5, 82.5, 75.8, 73.8, 73.4, 67.4, 65.0, 60.0, 55.2, 41.0, 39.9, 39.5, 38.5, 38.3, 18.1 (6C), 17.8, 15.3, 12.0 (3C), 11.6, 11.0, 6.7 (3C), 4.2 ppm (3C); HRMS (ES+): m/z calcd for $C_{41}H_{82}O_7Si_2N$: 756.5624 $[M+NH_4]^+$; found: 756.5637.

27: A solution of **26** (2.32 g, 3.14 mmol) in THF (50 mL) was added to a cold (0°C), stirred suspension of NaH (1.26 g, 60% in mineral oil, 31.4 mmol) in THF (100 mL). After 30 min, MeI (1.95 mL, 31.4 mmol) was added, and the reaction mixture was allowed to warm to room temperature for 4 h, after which the reaction was quenched with saturated aqueous NH_4Cl (200 mL) and the phases separated. The aqueous phase was extracted with Et_2O (3×200 mL), and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (3→5% EtOAc/PE) afforded **27** (1.69 g, 70%) as a colorless oil (385 mg of the minor diastereomer). R_f: 0.62 (20% EtOAc/hexane) (minor diastereomer: R_f: 0.58 (20% EtOAc/hexane)); $[\alpha]_D = -3.6$ ($c = 0.14$, $CHCl_3$); IR (neat): $\tilde{\nu} = 2936$, 2867, 1514, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.27$ (d, $J = 8.7$ Hz, 2H, Ar), 6.86 (d, $J = 8.7$ Hz, 2H, Ar), 5.81 (dd, $J = 15.6$, 7.8 Hz, 1H, H_{23}), 5.30 (dd, $J = 15.6$, 8.3 Hz, 1H, H_{22}), 4.55 (d, $J = 11.0$ Hz, 1H, CH_aH_bAr), 4.50 (d, $J = 11.0$ Hz, 1H, CH_aH_bAr), 3.80 (s, 3H, ArO*Me*), 3.77 (dd, $J = 9.5$, 5.0 Hz, 1H, H_{29a}), 3.66–3.54 (m, 3H, $H_{17a}+H_{29b}+H_{21}$), 3.50 (dd, $J = 5.8$, 3.0 Hz,

1H, H_{25}), 3.41 (dd, J=9.8, 7.3 Hz, 1H, H_{17b}), 3.39 (s, 3H, OMe), 3.35 (dt, J=6.5, 3.0 Hz, 1H, H_{19}), 3.28 (s, 3H, OMe), 3.22 (s, 3H, OMe), 3.10 (dd, J=6.9, 4.9 Hz, 1H, H_{27}), 2.46 (m, 1H, H_{24}), 1.97–1.88 (m, 2H, H_{28}+H_{26}), 1.85–1.77 (m, 2H, H_{20a}+H_{18}), 1.48 (app dt, J=13.9, 6.2 Hz, 1H, H_{20b}), 1.11–1.05 (m, 24H, Si(CH(CH_3)$_2$)$_3$+Si(CH)$_3$+MeC$_{24}$), 1.02 (d, J=7.0 Hz, 3H, MeC$_{28}$), 0.97 (d, J=7.0 Hz, 3H, MeC$_{26}$), 0.96 (t, J=8.0 Hz, 9H, Si-(CH_2CH_3)$_3$), 0.83 (d, J=6.8 Hz, 3H, MeC$_{18}$), 0.59 ppm (q, J=8.0 Hz, 6H, Si(CH_2CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.9 137.6, 131.6, 129.9, 128.7 (2C), 113.6 (2C), 85.6, 82.3, 80.1, 78.2, 73.4, 64.9, 64.8, 60.1, 57.4, 55.9, 55.3, 41.1, 38.7 (2C), 38.6, 37.1, 18.0 (7C), 15.3, 12.0 (3C), 11.9, 11.2, 6.7 (3C), 4.4 (3C) ppm; HRMS (ES+): m/z calcd for $C_{43}H_{86}O_7Si_2N$: 784.5937 $[M+NH_4]^+$; found: 784.5944.

28: A catalytic amount of PPTS (3 mg) was added to a stirred solution of **27** (260 mg, 0.35 mmol) in MeOH (25 mL). After 10 min at room temperature, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL), and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (30% EtOAc/PE) afforded **28** (210 mg, 92%) as a colorless oil. R_f: 0.55 (1:1 EtOAc/hexane); $[\alpha]_D$=+3.8 (c=0.79, $CHCl_3$); IR (neat): $\tilde{\nu}$=3748, 2940, 2866, 1514, 1463 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26 (d, J=8.7 Hz, 2H, Ar), 6.86 (d, J=8.7 Hz, 2H, Ar), 5.81 (dd, J=15.6, 7.8 Hz, 1H, H_{23}), 5.28 (dd, J=15.6, 8.4 Hz, 1H, H_{22}), 4.55 (d, J=11.0 Hz, 1H, CH_aH$_b$Ar), 4.52 (d, J=11.0 Hz, 1H, CH$_a$$H_b$Ar), 3.80 (s, 3H, ArO$Me$), 3.77 (dd, J=9.8, 5.0 Hz, 1H, H_{29a}), 3.68–3.53 (m, 4H, H_{17a}+H_{29b}+H_{21}+H_{17b}), 3.51 (dd, J=5.8, 3.0 Hz, 1H, H_{25}), 3.40 (s, 3H, OMe), 3.34 (ddd, J=4.9, 7.5, 3.5 Hz, 1H, H_{19}), 3.29 (s, 3H, OMe), 3.23 (s, 3H, OMe), 3.10 (dd, J=6.9, 4.8 Hz, 1H, H_{27}), 2.70 (app t, J=5.3 Hz, 1H, OH), 2.46 (m, 1H, H_{24}), 2.01 (m, 1H, H_{28}), 1.97–1.86 (m, 3H, H_{18}+H_{26}+H_{20a}), 1.52 (ddd, J=14.3, 6.6, 5.1 Hz, 1H, H_{20b}), 1.12–1.04 (m, 24H, Si(CH(CH_3)$_2$)$_3$+Si(CH)$_3$+MeC$_{24}$), 1.02 (d, J=7.0 Hz, 3H, MeC$_{28}$), 0.98 (d, J=7.0 Hz, 3H, MeC$_{26}$), 0.81 (d, J=7.0 Hz, 3H, MeC$_{18}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.9 138.0, 131.5, 129.8, 128.6 (2C), 113.6 (2C), 85.7, 82.2, 81.7, 80.0, 73.4, 66.3, 65.0, 60.1, 57.1, 55.8, 55.3, 41.2, 38.7, 38.5, 36.3, 35.8, 18.5, 18.1 (6C), 15.5, 12.1 (3C), 12.0, 11.8 ppm; HRMS (ES+): m/z calcd for $C_{37}H_{72}O_7SiN$: 670.5073 $[M+NH_4]^+$; found: 670.5075.

29: A solution of **28** (215 mg, 0.33 mmol) in CH_2Cl_2 (2.0 mL) was added to a cold (0°C), stirred suspension of Dess–Martin periodinane (215 mg, 0.50 mmol) and pyridine (140 μL, 1.70 mmol) in CH_2Cl_2 (3 mL). After 1 h, hexane was added, and the resulting precipitate was filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (25% EtOAc/PE) to afford **29** (200 mg, 93%) as a colorless oil. R_f: 0.25 (20% EtOAc/hexane); $[\alpha]_D$=−14.1 (c=0.29, $CHCl_3$); IR (neat): $\tilde{\nu}$=2943, 1735, 1514 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.72 (d, J=0.8 Hz, 1H, H_{17}), 7.26 (d, J=8.7 Hz, 2H, Ar), 6.86 (d, J=8.7 Hz, 2H, Ar), 5.81 (dd, J=15.6, 7.9 Hz, 1H, H_{23}), 5.30 (dd, J=15.6, 8.3 Hz, 1H, H_{22}), 4.53 (app s, 2H, CH_2Ar), 3.80 (s, 3H, ArOMe), 3.78–3.71 (m, 2H, H_{29a}+H_{19}), 3.62 (dd, J=9.6, 7.0 Hz, 1H, H_{29b}), 3.59 (m, 1H, H_{21}), 3.51 (dd, J=5.8, 3.0 Hz, 1H, H_{25}), 3.40 (s, 3H, OMe), 3.25 (s, 3H, OMe), 3.22 (s, 3H, OMe), 3.10 (dd, J=7.0, 4.8 Hz, 1H, H_{27}), 2.52–2.44 (m, 2H, H_{18}+H_{24}), 1.98–1.88 (m, 3H, H_{20a}+H_{28}+H_{26}), 1.53 (app dt, J=14.1, 6.1 Hz, 1H, H_{20b}), 1.12–1.05 (m, 24H, Si(CH(CH_3)$_2$)$_3$+Si(CH)$_3$+MeC$_{18}$), 1.04 (m, 3H, MeC$_{24}$), 1.02 (d, J=7.0 Hz, 3H, MeC$_{28}$), 0.98 ppm (d, J=7.0 Hz, 3H, MeC$_{26}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.3, 158.9 138.1, 131.5, 129.4, 128.6 (2C), 113.6 (2C), 85.6, 82.2, 79.5, 77.3, 73.4, 65.0, 60.1, 57.2, 55.8, 55.3, 49.1, 41.2, 38.7, 38.5, 37.0, 18.3, 18.1 (6C), 15.3, 12.0 (3C), 11.9, 7.8 ppm; HRMS (ES+): m/z calcd for $C_{37}H_{70}O_7SiN$: 668.4916 $[M+NH_4]^+$; found: 668.4922.

12: A solution of dimethyl (2-oxo-propyl)phosphonate (100 μL, 0.70 mmol), Et_3N (100 μL, 0.70 mmol), and **29** (185 mg, 0.28 mmol) in MeCN (4.0 mL) was added to a cold (0°C), stirred suspension of LiCl (30 mg, 0.70 mmol) in MeCN (2.0 mL). The reaction mixture was allowed to warm to room temperature for 18 h before being partitioned between saturated aqueous NH_4Cl (5 mL) and CH_2Cl_2 (5 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (15% EtOAc/PE) afforded **12** (195 mg, 99%) as a colorless oil. R_f: 0.17 (20% EtOAc/hexane); $[\alpha]_D$=−33.8 (c=0.07, $CHCl_3$); IR (neat): $\tilde{\nu}$=2945, 1674, 1466 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26 (d, J=8.6 Hz, 2H, Ar), 6.86 (d, J=8.7 Hz, 2H, Ar), 6.82 (dd, J=16.2, 6.9 Hz, 1H, H_{17}), 6.04 (dd, J=16.2, 1.3 Hz, 1H, H_{16}), 5.82 (dd, J=15.6, 7.8 Hz, 1H, H_{23}), 5.25 (dd, J=15.6, 8.4 Hz, 1H, H_{22}), 4.55 (d, J=11.0 Hz, 1H, CH_aH$_b$Ar), 4.51 (d, J=11.0 Hz, 1H, CH$_a$$H_b$Ar), 3.80 (s, 3H, ArO$Me$), 3.76 (dd, J=9.6, 5.0 Hz, 1H, H_{29a}), 3.65–3.59 (m, 2H, H_{29b}+H_{21}), 3.51 (dd, J=5.8, 3.0 Hz, 1H, H_{25}), 3.40 (s, 3H, OMe), 3.27 (s, 3H, OMe), 3.22 (s, 3H, OMe), 3.18 (app dt, J=8.6, 4.3 Hz, 1H, H_{19}), 3.10 (dd, J=6.9, 4.7 Hz, 1H, H_{27}), 2.63 (m, 1H, H_{18}), 2.47 (m, 1H, H_{24}), 2.24 (s, 3H, H_{14}), 1.97–1.88 (m, 2H, H_{28}+H_{26}), 1.75 (ddd, J=14.1, 8.6, 5.8 Hz, 1H, H_{20a}), 1.48 (ddd, J=14.0, 7.8, 4.1 Hz, 1H, H_{20b}), 1.12–1.04 (m, 24H, Si(CH(CH_3)$_2$)$_3$+Si(CH)$_3$+MeC$_{24}$), 1.02 (d, J=7.0 Hz, 3H, MeC$_{28}$), 0.99 (d, J=6.9 Hz, 3H, MeC$_{18}$), 0.98 ppm (d, J=7.0 Hz, 3H, MeC$_{26}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.6, 158.9 149.9, 138.3, 131.5, 131.2, 129.6, 128.6 (2C), 113.6 (2C), 85.6, 82.2, 80.9, 79.9, 73.4, 65.0, 60.1, 57.2, 55.8, 55.3, 41.2, 38.8, 38.6, 38.6, 37.1, 26.7, 18.2, 18.1 (6C), 15.3, 14.1, 12.0 (3C), 12.0 ppm; HRMS (ES+): m/z calcd for $C_{40}H_{74}O_7SiN$: 708.5229 $[M+NH_4]^+$; found: 708.5235.

31: A solution of (*S*)-**30** (2.00 g, 9.70 mmol) in Et_2O (10 mL) was added to a cold (−20°C), stirred solution of dicyclohexylboron chloride (2.75 mL, 12.6 mmol) and Me_2NEt (1.58 mL, 14.55 mmol) in Et_2O (10.0 mL). The reaction mixture was allowed to warm to 0°C for 1 h before being cooled to −78°C. A solution of 3-butenal (23.3 mL, ≈1 M in CH_2Cl_2, 23.3 mmol) was then added dropwise. The reaction mixture was stirred at −78°C for 2 h, then at −20°C for 16 h, after which the reaction was quenched at 0°C with MeOH (20 mL), pH 7 buffer (20 mL), and H_2O_2 (30% v/v, 10 mL), and the mixture was stirred for 1 h at room temperature. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (10% EtOAc/PE) afforded **31** (2.28 g, 85%) as a white solid. R_f: 0.18 (25% EtOAc/hexane); m.p.: 70–71°C; $[\alpha]_D^{20}$=+24.9 (c=0.55, $CHCl_3$); IR (neat): $\tilde{\nu}$=3453, 2983, 2938, 1717, 1453, 1270, 1119, 1003, 715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.08 (app dd, J=8.3, 1.3 Hz, 2H, Ar), 7.59 (tt, J=7.5, 1.3 Hz, 1H, Ar), 7.46 (t, J=7.5 Hz, 2H, Ar), 5.84 (m, 1H, CH=CH$_2$), 5.44 (q, J=7.0 Hz, 1H, BzOCH), 5.17–5.11 (m, 2H, CH=CH_2), 3.85 (m, 1H, CHOH), 2.92 (app quint, J=7.3 Hz, 1H, CHMe), 2.42 (d, J=5.5 Hz, 1H, OH), 2.39 (m, 1H, CH_aH$_b$), 2.18 (app dt, J=14.4, 7.8 Hz, 1H, CH$_a$$H_b$), 1.57 (d, J=7.0 Hz, 3H, Me), 1.26 ppm (d, J=7.0 Hz, 3H, Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ=212.3, 165.8, 134.2, 133.3, 129.8, 129.5 (2C), 128.5 (2C), 118.3, 74.7, 72.5, 47.5, 39.9, 15.8, 14.1 ppm; HRMS (ES+): m/z calcd for $C_{16}H_{21}O_4$: 277.1434 $[M+H]^+$; found: 277.1438.

32: Proton sponge (9.86 g, 46.0 mmol) and trimethyloxonium tetrafluoroborate (4.26 g, 28.8 mmol) were added to a stirred solution of **31** (3.63 g, 13.14 mmol) in CH_2Cl_2 (80 mL) at 0°C. After 30 min, the reaction mixture was allowed to warm to room temperature for 16 h before the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (80 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with citric acid (50 mL, 10 wt%) and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (10% EtOAc/PE) afforded **32** (3.50 g, 92%) as a colorless oil. R_f: 0.60 (20% EtOAc/hexane); $[\alpha]_D^{20}$=−25.8 (c=2.23, $CHCl_3$); IR (neat): $\tilde{\nu}$=2980, 2936, 1718, 1452, 1266, 1115, 1094, 711 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.08 (app dd, J=8.4, 1.4 Hz, 2H, Ar), 7.56 (tt, J=7.5, 1.3 Hz, 1H, Ar), 7.44 (t, J=7.5 Hz, 2H, Ar), 5.83 (m, 1H, CH=CH$_2$), 5.38 (q, J=7.0 Hz, 1H, BzOCH), 5.14–5.07 (m, 2H, CH=CH_2), 3.50 (dt, J=9.4, 4.5 Hz, 1H, CHOMe), 3.24 (s, 3H, OMe), 3.02 (dq, J=9.5, 7.0 Hz, 1H, CHMe), 2.51 (m, 1H, CH_aH$_b$), 2.14 (m, 1H, CH$_a$$H_b$), 1.53 (d, J=7.0 Hz, 3H, Me), 1.10 ppm (d, J=7.0 Hz, 3H, Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ=209.8, 165.6, 133.3, 133.0, 129.6 (3C), 128.2 (2C), 117.4, 81.6, 74.9, 57.5, 45.7, 33.9, 15.1, 13.2 ppm; HRMS (ES+): m/z calcd for $C_{17}H_{23}O_4$: 291.1591 $[M+H]^+$; found: 291.1582.

33: Methyllithium (42 mL, 1.6 M in Et_2O, 67.5 mmol) was added dropwise to a stirred solution of **32** (3.92 g, 13.50 mmol) in Et_2O (120 mL) at −78°C over 10 min. The reaction mixture was allowed to warm to

−20 °C for 2 h before the reaction was quenched by sequential addition of EtOAc (10 mL) and saturated aqueous NH_4Cl (30 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 50 mL). The combined organic extracts were washed with saturated aqueous sodium/potassium tartrate (40 mL) and brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (66% EtOAc/PE) afforded **33** (2.10 g, 77%) as a colorless oil (obtained as a 3:2 mixture of diastereomers). R_f: 0.21 (20% EtOAc/hexane); IR (neat): $\tilde{\nu}$ = 3438, 2979, 2938, 1458, 1370, 1081, 913 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.84 (m, 1H, C*H*=CH_2), 5.14–5.08 (m, 2H, CH=C*H*$_2$), 4.82 (s, 1H, *OH), 3.86 (s, 1H, OH), 3.74 (br m, 1H, C*H*Me), 3.50 (br m, 1H, *C*H*Me), 3.42 (m, 1H, C*H*O), 3.39 (s, 3H, *OMe), 3.35 (s, 3H, OMe), 2.93 (br s, 1H, OH), 2.58 (m, 1H, CH_aH_b), 2.41 (br d, J = 9.8 Hz, 1H, *OH), 2.21 (m, 1H, CH_aH_b), 1.91 (m, 1H, C*H*Me), 1.84 (m, 1H, *C*H*Me), 1.20 (s, 3H, *Me), 1.17–1.13 (m, 3H, Me), 1.04 (s, 3H, Me), 0.90 (d, J = 7.1 Hz, 3H, Me), 0.71 ppm (d, J = 7.0 Hz, 3H, *Me) (distinguishable diastereomeric resonances of the minor component are denoted with an asterisk); HRMS (ES+): m/z calcd for $C_{11}H_{22}O_3Na$: 225.1461 $[M+Na]^+$; found: 225.1466.

34: A solution of **33** (900 mg, 4.45 mmol) in THF/H_2O (1:1, 30 mL) was added to a stirred suspension of $NaIO_4$ (7.61 g, 35.6 mmol) and OsO_4 (2.5 wt% in *t*BuOH, 0.65 mL, 49 μmol) in THF/H_2O (1:1, 30 mL) at 0 °C. The reaction mixture was stirred for 2 h then allowed to warm to room temperature for 20 h before the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (20 mL). The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (30% EtOAc/PE) afforded **34** (457 mg, 65%) as a colorless oil. R_f: 0.39 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = −24.8 (c = 2.42, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2939, 1710, 1458, 1357, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.82 (dd, J = 2.5, 1.5 Hz, 1H, C*H*O), 3.99 (dt, J = 6.9, 4.3 Hz, 1H, C*H*OMe), 3.34 (s, 3H, OMe), 2.89 (app q, J = 7.1 Hz, 1H, C*H*Me), 2.61 (ddd, J = 16.7, 4.3, 1.5 Hz, 1H, CH_aH_b), 2.54 (ddd, J = 16.7, 6.8, 2.5 Hz, 1H, CH_aH_b), 2.20 (s, 3H, MeCO), 1.06 ppm (d, J = 7.2 Hz, 3H, Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.6, 200.7, 77.1, 57.6, 49.5, 44.9, 29.8, 11.7 ppm; HRMS (ESI+): m/z calcd for $C_8H_{15}O_3$: 159.1016 $[M+H]^+$; found: 159.1016.

10: LiHMDS (3.76 mL, 1 M in THF, 3.76 mmol) was added dropwise to a stirred solution of **35** (1.60 g, 4.33 mmol) in THF (10 mL) at −78 °C over 10 min. The reaction mixture was allowed to warm to 0 °C and was maintained for 30 min to produce a bright-yellow solution. After cooling to −78 °C, a solution of **34** (457 mg, 2.89 mmol) in THF (10 mL) was added. After 1 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL), and the mixture was diluted with EtOAc (20 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in hot Et_2O/hexane (1:2, 40 mL), and the resulting suspension cooled in an ice bath for 1 h (Ph_3PO precipitated as a white crystalline solid). The supernatant liquid was transferred into another flask and concentrated in vacuo. Flash chromatography (50% EtOAc/CH_2Cl_2) afforded the *N*-vinylformamide (320 mg, 52%) as a 1.5:1 mixture of *Z*/*E* isomers by ^1H NMR spectroscopic analysis. This mixture was dissolved in CH_2Cl_2 (50 mL), and a solution of iodine (9.9 mg, 0.039 mmol) in CH_2Cl_2 (40 mL) was added. The reaction mixture was stirred in the dark for 96 h, and the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (30 mL). The layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (30 mL) and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (50% EtOAc/CH_2Cl_2) afforded **10** (263 mg, 82%) as a colorless oil. R_f: 0.47 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = −74.6 (c = 1.78, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2934, 1696, 1658, 1387, 1354, 1077, 955 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.28 (s, 1H, NC*H*O), 8.06 (s, 1H, *NC*H*O), 7.18 (d, J = 14.5 Hz, 1H, *H_{36}), 6.51 (d, J = 13.9 Hz, 1H, H_{36}), 5.14–5.04 (m, 1H, H_{35}), 3.45 (m, 1H, H_{33}), 3.32 (s, 3H, OMe), 3.31 (s, 3H, *OMe), 3.07 (s, 3H, *N*Me*), 3.03 (s, 3H, N*Me*), 2.79–2.70 (m, 1H, H_{32}), 2.50 (dt, J = 15.0, 5.2 Hz, 1H, *H_{34a}), 2.43 (dt, J = 15.0, 5.2 Hz, 1H, H_{34a}), 2.23–2.12 (m_{obs}, 1H, H_{34b}), 2.18 (s, 3H, H_{30}), 2.17 (s, 3H, *H_{30}), 1.01 ppm (app t, J = 7.4 Hz, 3H, *Me*C_{32}+**Me*C_{32}) (distinguishable resonances of the minor rotamer are denoted with an asterisk); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.4 *(211.5), 162.0 *(160.7), 130.3 *(126.3), 105.4 *(107.0), 82.2, 57.5 *(57.3), 49.5 *(49.4), 30.4 *(30.2), 29.9 *(29.7), 27.4 *(32.9), 12.3 *(12.5) ppm; HRMS (ES+): m/z calcd for $C_{11}H_{20}NO_3$: 214.1438 $[M+H]^+$; found: 214.1449.

37: *n*BuLi (80.5 mL, 1.4 M in hexane, 112.7 mmol) was added to a stirred solution of trimethylsilylacetylene (14.9 mL, 106 mmol) in THF (150 mL) at −78 °C. After 30 min, a solution of (*S*)-**36** (11.5 g, 35.2 mmol) in THF (50 mL) was added, followed by the addition of $BF_3{\cdot}Et_2O$ (4.9 mL, 38.7 mmol). After 1.5 h, the reaction mixture was partitioned between saturated aqueous NH_4Cl (50 mL) and CH_2Cl_2 (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2×50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude extracts were then dissolved in MeOH (150 mL), followed by the addition of K_2CO_3 (34.0 g, 246 mmol). After 4 h, the reaction mixture was partitioned between CH_2Cl_2 (200 mL) and H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2×150 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (10→15% EtOAc/PE) afforded **37** (10.4 g, 84%) as a colorless oil. R_f: 0.46 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = −0.5 (c = 3.80, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3422, 3298, 2932, 2858, 1589, 1472, 1111, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 4H, SiPh), 7.48–7.37 (m, 6H, SiPh), 4.08 (m, 1H, C*H*OH), 3.92 (app dt, J = 10.5, 5.0 Hz, 1H, CH_aH_bOSi), 3.86 (ddd, J = 10.5, 7.5, 4.5 Hz, 1H, CH_aH_bOSi), 3.36 (d, J = 3.2 Hz, 1H, OH), 2.45 (ddd, J = 16.8, 6.3, 2.6 Hz, 1H, CH_aH_b), 2.40 (ddd, J = 16.8, 6.3, 2.6 Hz, 1H, CH_aH_b), 2.02 (t, J = 2.6 Hz, 1H, alkyne C-H), 1.87–1.76 (m, 2H, CH_aH_b), 1.06 ppm (s, 9H, SiC(*CH*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5 (4C), 133.0, 132.9, 129.8 (2C), 127.8 (4C), 81.0, 70.3, 69.9, 62.9, 37.3, 27.1, 26.8 (3C), 19.0 ppm; HRMS (ES+): m/z calcd for $C_{22}H_{29}O_2Si$: 353.1931 $[M+H]^+$; found: 353.1930.

38: NaH (1.16 g, 60 wt% dispersion in oil, 28.9 mmol) was added to a stirred solution of **37** (8.5 g, 24.1 mmol) in THF (100 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 h, then it was cooled to 0 °C, and MeI (4.5 mL, 72.2 mmol) was added. After 30 min, the reaction mixture was warmed to room temperature for 4 h, recooled to 0 °C, and the reaction was quenched with methanol (6.0 mL). After partitioning between saturated aqueous NH_4Cl (50 mL) and CH_2Cl_2 (200 mL), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (5% EtOAc/PE) afforded **38** (8.48 g, 96%) as a colorless oil. R_f: 0.40 (10% Et_2O/hexane); $[\alpha]_D^{20}$ = −17.2 (c = 4.30, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3306, 2930, 2858, 1589, 1478, 1428, 1105, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 4H, SiPh), 7.45–7.36 (m, 6H, SiPh), 3.83 (ddd, J = 10.2, 8.2, 5.1 Hz, 1H, CH_aH_bOSi), 3.75 (dt, J = 10.2, 5.4 Hz, 1H, CH_aH_bOSi), 3.60 (m, 1H, C*H*OMe), 3.37 (s, 3H, OMe), 2.46 (ddd, J = 16.8, 6.1, 2.6 Hz, 1H, CH_aH_b), 2.40 (ddd, J = 16.8, 4.9, 2.6 Hz, 1H, CH_aH_b), 1.99 (t, J = 2.6 Hz, 1H, alkyne C-H), 1.90 (m, 1H, CH_aH_b), 1.81 (m, 1H, CH_aH_b), 1.06 ppm (s, 9H, SiC(*CH*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6 (4C), 133.9 (2C), 129.6 (2C), 127.6 (4C), 81.0, 76.0, 69.9, 60.2, 57.1, 36.6, 26.9 (3C), 23.3, 19.2 ppm; HRMS (ES+): m/z calcd for $C_{23}H_{31}O_2Si$: 367.2088 $[M+H]^+$; found: 367.2100.

39: Trimethylaluminum (15.4 mL, 2.0 M in hexane, 30.8 mmol) was added to a stirred solution of **38** (2.26 g, 6.16 mmol) in 1,2-dichloroethane (30 mL) at room temperature. After 15 min, zirconocene dichloride (3.60 g, 12.3 mmol) was added, and the reaction mixture was heated to 60 °C for 16 h. After cooling to −20 °C, a solution of iodine (2.50 g, 9.86 mmol) in THF (15 mL) was added, the reaction mixture was allowed to warm to room temperature, and the reaction was quenched with saturated aqueous NH_4Cl (20 mL). Acidification with aqueous HCl (1 M, 10 mL) gave a clear solution, which was extracted with CH_2Cl_2 (3× 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (5% EtOAc/PE) afforded **39** (2.85 g, 91%) as a colorless oil. R_f: 0.58 (15% EtOAc/hexane); $[\alpha]_D^{20}$ = −17.5 (c = 4.0, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2930, 2857, 1472, 1428, 1105, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.70–7.63 (m, 4H, SiPh), 7.44–7.36 (m, 6H, SiPh), 5.94 (app d, J = 1.0 Hz, 1H, H_4), 3.80 (ddd, J = 10.2, 7.8, 5.4 Hz, 1H, H_{9a}), 3.71 (app dt, J = 10.2, 5.4 Hz, 1H, H_{9b}), 3.57 (m, 1H, H_7), 3.30 (s, 3H, OMe), 2.45 (dd, J = 14.0, 6.4 Hz, 1H, H_{6a}), 2.30 (dd, J = 14.0, 6.1 Hz, 1H, H_{6b}), 1.87 (app d, J = 1.0 Hz, 3H,

MeC_5), 1.70–1.59 (m, 2H, $H_{8a}+H_{8b}$), 1.06 ppm (s, 9H, SiC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 135.6 (4C), 133.8 (2C), 129.6 (2C), 127.7 (4C), 76.9, 75.9, 60.2, 56.9, 43.9, 36.8, 26.9 (3C), 24.4, 19.2 ppm; HRMS (ES+): *m*/*z* calcd for $C_{24}H_{34}IO_2Si$: 509.1367 $[M+H]^+$; found: 509.1301.

52: TBAF (13 mL, 1 M in THF, 12.98 mmol) was added to a stirred solution of **39** (5.5 g, 10.81 mmol) in THF (120 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature for 2 h before being partitioned between CH_2Cl_2 (150 mL) and saturated aqueous NH_4Cl (120 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (10→40% EtOAc/PE) afforded **52** (2.71 g, 93%) as a colorless oil. R_f: 0.06 (20% Et_2O/hexane); $[\alpha]_D^{20}$ = −23.3 (*c* = 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3390, 2930, 2830, 1620, 1110, 1070 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.98 (d, *J* = 1.0 Hz, 1H, H_4), 3.79–3.69 (m, 2H, $H_{9a}+H_{9b}$), 3.54 (m, 1H, H_7), 3.36 (s, 3H, OMe), 2.53 (dd, *J* = 13.9, 5.8 Hz, 1H, H_{6a}), 2.33 (dd, *J* = 13.9, 6.6 Hz, 1H, H_{6b}), 1.86 (d, *J* = 1.0 Hz, 3H, *Me*C_5), 1.72 (m, 1H, H_{8a}), 1.63 ppm (m, 1H, H_{8b}); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.5, 78.6, 77.3, 60.4, 56.9, 43.4, 35.8, 24.3 ppm; HRMS (ES+): *m*/*z* calcd for $C_8H_{16}IO_2$: 271.0189 $[M+H]^+$; found: 271.0193.

53: A solution of dimethyl sulfoxide (1.76 mL, 24.74 mmol) in CH_2Cl_2 (6.0 mL) was added to a cold (−78 °C), stirred solution of oxalyl chloride (1.06 mL, 12.37 mmol) in CH_2Cl_2 (17.0 mL). After 15 min, a solution of **52** (2.57 g, 9.51 mmol) in CH_2Cl_2 (9.0 mL) was added. After 15 min, Et_3N (6.9 mL, 49.48 mmol) was added, and the solution was warmed to −50 °C followed by 20 min at room temperature. The reaction mixture was then partitioned between saturated aqueous NH_4Cl (50 mL) and CH_2Cl_2 (3× 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (20% EtOAc/PE) afforded **53** (2.0 g, 78%) as a colorless oil. R_f: 0.40 (30% EtOAc/hexane); $[\alpha]_D^{20}$ = −19.0 (*c* = 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2930, 2830, 2730, 1700, 1110, 1080 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ = 9.40 (s, 1H, H_9), 5.78 (s, 1H, H_4), 3.48 (app quint, *J* = 6.0 Hz, 1H, H_7), 2.99 (s, 3H, OMe), 2.16–2.10 (m, 2H, $H_{6a}+H_{8a}$), 1.97 (dd, *J* = 13.9, 6.0 Hz, 1H, H_{6b}), 1.92 (dd, *J* = 16.7, 4.8 Hz, 2H, H_{8b}), 1.74 ppm (s, 3H, *Me*C_5); ^{13}C NMR (125 MHz, C_6D_6): δ = 199.2, 144.5, 78.2, 74.6, 56.7, 47.7, 43.5, 24.4 ppm; HRMS (ES+): *m*/*z* calcd for $C_8H_{14}IO_2$: 269.0033 $[M+H]^+$; found: 268.9933.

54: MeMgI (7.46 mL, 3 M in Et_2O, 22.38 mmol) was added to a stirred solution of **53** (2.0 g, 7.46 mmol) in THF (60 mL) at −78 °C. After 1 h, the reaction mixture was warmed to −40 °C for 1 h then partitioned between saturated aqueous NH_4Cl (50 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (2×50 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (30→50% Et_2O/PE) afforded the alcohol (1.69 g, 80%) as a colorless oil (obtained as a 1:1 mixture of diastereomers). R_f: 0.06 (30% Et_2O/hexane); $[\alpha]_D^{20}$ = −32.7 (*c* = 1.27, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3420, 2970, 2930, 2830, 1620, 1460, 1370, 1270, 1080 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.98 (s, 1H, H_4), 4.06 (m, 0.5H, H_9), 3.94 (m, 0.5H, *H_9), 3.62 (m, 0.5H, H_7), 3.54 (m, 0.5H, *H_7), 3.38 (s, 1.5H, OMe), 3.37 (s, 1.5H, *OMe), 2.60–2.50 (m, 2H, OH+H_{6a}), 2.36–2.30 (m, 1H, H_{6b}), 1.86 (s, 3H, *Me*C_5), 1.60 (ddd, *J* = 14.6, 9.1, 3.4 Hz, 1H, H_{8a}), 1.54–1.46 (m, 1.5H, *$H_{8a}+H_{8b}$), 1.18 (d, *J* = 6.3 Hz, 1.5H, H_{10}), 1.16 ppm (d, *J* = 6.2 Hz, 1.5H, *H_{10}) (distinguishable diastereomeric resonances of the minor component are denoted with an asterisk); HRMS (ES+): *m*/*z* calcd for $C_9H_{18}IO_2$: 285.0346 $[M+H]^+$; found: 285.0348. Pyridinium chlorochromate (2.28 g, 10.56 mmol) was added to a stirred suspension of the preceding alcohol (1.5 g, 5.28 mmol) and celite (2.28 g), dried under high vacuum, in CH_2Cl_2 (60 mL) at 0 °C. After 2 h, the reaction mixture was maintained at room temperature for 16 h then partitioned between saturated aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2×20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (20% EtOAc/PE) afforded **54** (1.41 g, 95%) as a colorless oil. R_f: 0.50 (30% EtOAc/Hexane); $[\alpha]_D^{20}$ = −21.0 (*c* = 1.01 $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3060, 2930, 2830, 1710, 1360, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.97 (s, 1H, H_4), 3.82 (app quint, *J* = 6.4 Hz, 1H, H_7), 3.31 (s, 3H, OMe), 2.63 (dd, *J* = 16.5, 7.3 Hz, 1H, H_{8a}), 2.47 (dd, *J* = 13.9, 6.1 Hz, 1H, H_{6a}), 2.42 (dd, *J* = 16.5, 4.9 Hz, 1H, H_{8b}), 2.31 (dd, *J* = 13.9, 6.3 Hz, 1H, H_{6b}), 2.15 (s, 3H, H_{10}), 1.86 ppm (s, 3H, *Me*C_5); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.9, 144.6, 77.5, 75.3, 57.2, 47.7, 43.6, 31.1, 24.3 ppm; HRMS (ES+): *m*/*z* calcd for $C_9H_{16}IO_2$: 283.0189 $[M+H]^+$; found: 283.0190.

55 and **56**: Et_3N (0.20 mL, 1.42 mmol) was added to a stirred solution of (−)-Ipc_2BCl (432 mg, 1.35 mmol, dried under vacuum for 1.5 h) in Et_2O (3.0 mL) at 0 °C, followed by the addition of a solution of **54** (200 mg, 0.71 mmol) in Et_2O (3.0 mL). After 1 h, the reaction mixture was cooled to −78 °C, and a solution of (*R*)-**45** (337 mg, 1.77 mmol) in Et_2O (3 mL) was added. After 20 min at −78 °C, the reaction was quenched by addition of MeOH (3.2 mL) and pH 7 buffer (3.2 mL), and the mixture was allowed to warm to 0 °C. Hydrogen peroxide (1.6 mL, 30% aqueous) was added dropwise, and stirring continued for 40 min, then the reaction mixture was partitioned between water (10 mL) and CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (5→10% EtOAc/PE) afforded epimeric adducts **55** (148 mg, 43%) and **56** (92 mg, 27%) as colorless oils. Major adduct **55**: R_f: 0.46 (40% EtOAc/hexane); $[\alpha]_D^{20}$ = −2.60 (*c* = 1.0, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3494, 2929, 2857, 1709, 1463, 1361, 1098 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ = 5.80 (s, 1H, H_4), 4.26 (m, 1H, H_{11}), 3.65 (dd, *J* = 9.7, 7.7 Hz, 1H, H_{13a}), 3.46 (d, *J* = 1.7 Hz, 1H, OH), 3.45 (dd, *J* = 9.7, 5.3 Hz, 1H, H_{13b}), 3.35 (m, 1H, H_7), 2.94 (s, 3H, OMe), 2.54 (dd, *J* = 17.3, 7.9 Hz, 1H, H_{10a}), 2.51 (m, 1H, H_{12}), 2.43 (dd, *J* = 17.3, 4.3 Hz, 1H, H_{10b}), 2.13 (dd, *J* = 14.0, 6.1 Hz, 1H, H_{8a}), 2.06 (dd, *J* = 14.0, 5.6 Hz, 1H, H_{8b}), 1.73 (s, 3H, *Me*C_5), 1.60 (ddd, *J* = 14.2, 8.3, 7.9 Hz, 1H, H_{6a}), 1.41 (ddd, *J* = 14.2, 5.0, 3.3 Hz, 1H, H_{6b}), 0.92 (s, 9H, SiC(CH_3)$_3$), 0.87 (d, *J* = 7.0 Hz, 3H, *Me*C_{12}), 0.00 ppm (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, C_6D_6): δ = 212.8, 145.1, 78.5, 77.6, 66.4, 65.8, 56.2, 50.2, 49.2, 43.4, 40.7, 26.1 (3C), 24.5, 18.5, 12.9, −5.3 ppm (2C); HRMS (ES+): *m*/*z* calcd for $C_{19}H_{38}IO_4Si$: 485.1579 $[M+H]^+$; found: 485.1582. Minor adduct **56**: R_f: 0.50 (40% EtOAc/hexane); $[\alpha]_D^{20}$ = −22.2 (*c* = 7.5, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3486, 2929, 2857, 1709, 1471, 1362, 1256, 1100, 837 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ = 5.82 (d, *J* = 0.9 Hz, 1H, H_4), 4.36 (m, 1H, H_{11}), 3.60 (dd, *J* = 9.7, 7.7 Hz, 1H, H_{13a}), 3.55 (m, 1H, H_7), 3.42 (dd, *J* = 9.7, 5.2 Hz, 1H, H_{13b}), 3.36 (d, *J* = 3.3 Hz, 1H, OH), 3.10 (s, 3H, OMe), 2.44 (m, 1H, H_{12}), 2.40 (dd, *J* = 17.3, 9.1 Hz, 1H, H_{10a}), 2.23 (dd, *J* = 17.3, 3.0 Hz, 1H, H_{10b}), 2.21 (dd, *J* = 14.0, 5.9 Hz, 1H, H_{8a}), 2.08 (dd, *J* = 14.1, 6.3 Hz, 1H, H_{8b}), 1.76 (d, *J* = 0.9 Hz, 3H, *Me*C_5), 1.44 (ddd, *J* = 14.1, 10.1, 2.8 Hz, 1H, H_{6a}), 1.29 (m, 1H, H_{6b}), 0.92 (s, 9H, SiC(CH_3)$_3$), 0.82 (d, *J* = 6.9 Hz, 3H, *Me*C_{12}), 0.00 ppm (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, C_6D_6): δ = 213.8, 145.4, 77.4, 76.4, 65.8, 64.9, 57.2, 49.9, 49.2, 43.8, 41.6, 26.1 (3C), 24.5, 18.5, 12.8, −5.4 ppm (2C); HRMS (ES+): *m*/*z* calcd for $C_{19}H_{38}IO_4Si$: 485.1579 $[M+H]^+$, found: 485.1589.

57: Et_3N (0.21 mL, 1.52 mmol) and 2,4,6-trichlorobenzoylchloride (0.243 mL, 1.52 mmol) were added to a stirred solution of diethylphosphonoacetic acid (0.24 mL, 1.52 mmol) in PhMe (30 mL) at room temperature. After 5 min, a solution of **55** (210 mg, 0.43 mmol) in PhMe (20 mL) was added by cannula, followed by DMAP (106 mg, 0.87 mmol). After 1 h, the reaction mixture was partitioned between pH 7 buffer (20 mL) and EtOAc (3×30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting residue was dissolved in THF (12 mL) and cooled to 0 °C before addition of water (0.63 mL) and barium hydroxide octahydrate (340 mg, 1.08 mmol, dried under vacuum (0.5 mm Hg/150 °C/4 h)). After 20 min, the reaction mixture was warmed to room temperature for 2 h before being partitioned between CH_2Cl_2 (30 mL), pH 7 buffer (15 mL), and citric acid (5 mL, 10 wt%). The layers were separated, and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (10→20% EtOAc/PE) afforded **57** (161 mg, 73%) as a colorless oil. R_f: 0.52 (40% EtOAc/hexane); $[\alpha]_D^{20}$ = +20.0 (*c* = 1.0, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2929, 2858, 1718, 1471, 1390, 1252, 1103, 838, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.01 (s, 1H, H_4), 5.82 (br s, 1H, H_{39}), 4.46 (dt, *J* = 12.9, 3.9 Hz, 1H, H_{11}), 3.66–3.58 (m, 2H, $H_{13a}+H_{13b}$), 3.49 (m, 1H, H_7), 3.32 (s, 3H, OMe), 2.53–2.45 (m, 2H, $H_{10a}+H_{6a}$), 2.35 (app d, *J* = 6.0 Hz, 2H, $H_{8a}+H_{8b}$), 2.32 (dd, *J* = 14.1, 6.2 Hz, 1H, H_{6b}), 2.22 (dd, *J* = 17.9, 3.4 Hz, 1H, H_{10b}), 1.87 (br d, *J* = 0.6 Hz, 4H, *Me*C_5), 1.87 (m, 1H, H_{12}), 1.00 (d, *J* = 6.9 Hz, 3H, *Me*C_{12}), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.04 ppm (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3, 158.3, 144.1, 117.8,

77.8, 77.8, 77.5, 64.2, 57.1, 43.6, 41.0, 39.5, 32.0, 25.9 (3C), 24.4, 18.2, 11.5, −5.5 ppm (2C); HRMS (ES+): *m/z* calcd for $C_{21}H_{38}IO_4Si$: 509.1579 $[M+H]^+$; found: 504.1584.

58: Pyridinium hydrofluoride buffered with pyridine (1.06 mL, 4.2 mmol) was added to a stirred solution of **57** (100 mg, 0.20 mmol) in THF (7.0 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature for 16 h before being partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (40→60% EtOAc/PE) afforded **58** (77 mg, 92%) as a colorless oil. R_f: 0.08 (40% EtOAc/PE); $[\alpha]_D^{20}=+38.7$ ($c=1.00$, $CHCl_3$); IR (neat): $\tilde{\nu}=3450$, 2934, 2830, 1710, 1258, 1102, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=6.00$ (s, 1H, H_4), 5.80 (br s, 1H, H_{39}), 4.54 (dt, $J=12.8$, 3.7 Hz, 1H, H_{11}), 3.72 (m, 1H, H_{13a}), 3.64 (br s, 1H, H_{13b}), 3.51 (app quint, $J=6.1$ Hz, 1H, H_7), 3.32 (s, 3H, OMe), 2.55–2.46 (m, 2H, $H_{10a}+H_{6a}$), 2.37–2.34 (m, 2H, $H_{8a}+H_{8b}$), 2.31 (dd, $J=14.1$, 6.2 Hz, 1H, H_{6b}), 2.21 (dd, $J=17.9$, 3.4 Hz, 1H, H_{10b}), 2.15 (br s, 1H, OH), 1.92 (m, 1H, H_{12}), 1.86 (s, 3H, MeC_5), 1.01 (d, $J=7.1$ Hz, 3H, MeC_{12}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=165.1$, 158.5, 144.0, 117.5, 77.8 (2C), 77.4, 64.0, 57.0, 43.5, 40.8, 39.1, 31.7, 24.4, 11.2 ppm; HRMS (ES^+): *m/z* calcd for $C_{15}H_{23}IO_4Na$: 417.0533 $[M+Na]^+$; found: 417.0535.

59: TEMPO (3.2 mg, 0.020 mmol) was added to a stirred solution of **58** (40 mg, 0.13 mmol) in CH_2Cl_2 (2.5 mL) at room temperature, followed by iodobenzene diacetate (98 mg, 0.304 mmol). After 3 h, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (2.0 mL), NaS_2O_3 (2.0 mL), and CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (50% EtOAc/PE) afforded **59** (35 mg, 88%) as a colorless oil that was used directly in the subsequent aldol coupling step. R_f: 0.12 (40% EtOAc/hexane); ^1H NMR (500 MHz, $CDCl_3$): $\delta=9.78$ (d, $J=0.9$ Hz, 1H, H_{13}), 6.03 (br d, $J=1.0$ Hz, 1H, H_4), 5.86 (s, 1H, H_{39}), 4.72 (dt, $J=9.9$, 5.8 Hz, 1H, H_{11}), 3.52 (m, 1H, H_7), 3.34 (s, 3H, OMe), 2.73 (m, 1H, H_{12}), 2.52 (dd, $J=13.9$, 6.0 Hz, 1H, H_{6a}), 2.43–2.40 (m, 2H, $H_{10a}+H_{10b}$), 2.39–2.34 (m, 2H, $H_{8b}+H_{10b}$), 2.33 (dd, $J=13.9$, 6.3 Hz, 1H, H_{6b}) 1.88 (d, $J=0.9$ Hz, 3H, MeC_5), 1.30 ppm (d, $J=7.2$ Hz, 3H, MeC_{12}).

61: TMSCl (1.0 mL) and Et_3N (1.0 mL) were mixed in a dry centrifuge tube fitted with a septum. The mixture was centrifuged, and the resulting supernatant liquid was used immediately. LDA (0.85 mL, 1 M in THF, 0.85 mmol) was added to a stirred solution of **12** (146 mg, 0.21 mmol) in THF (7.5 mL) containing powdered CaH_2 (100 mg) at −78 °C. After 30 min, the prepared solution of TMSCl and Et_3N (584 μL) was added. After 1 h, the reaction was quenched by the addition of pH 7 buffer (5 mL), and the mixture was diluted with PE (10 mL). The layers were separated, and the aqueous layer was extracted with PE (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford **61** (161 mg, ≈100%) that was used directly in the subsequent aldol coupling step.

78: $BF_3{\cdot}OEt_2$ (1.20 mL, 1 M in CH_2Cl_2, 1.20 mmol) was added to a stirred solution of **59** (64 mg, 0.16 mmol) and **61** in CH_2Cl_2 (3.6 mL) containing powdered CaH_2 (100 mg) at −100 °C. After 40 min, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (20→50% EtOAc/PE) afforded a mixture of epimeric aldol adducts as a colorless oil (122 mg, 69%, 3:1 d.r.). HPLC (10% *i*PrOH/hexane) separation of a sample provided pure major adduct **78**. R_f: 0.60 (80% EtOAc/hexane); t_R(HPLC)=16.0 min (10% *i*PrOH); $[\alpha]_D^{20}=-7.8$ ($c=0.30$, $CHCl_3$); IR (neat): $\tilde{\nu}=3525$, 2932, 2830, 1716, 1514, 1462, 1248, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.28$–7.25 (m, 2H, Ar), 6.92 (dd, $J=16.1$, 6.8 Hz, 1H, H_{17}), 6.86 (d, $J=8.7$ Hz, 2H, Ar), 6.09 (dd, $J=16.1$, 1.1 Hz, 1H, H_{16}), 6.02 (s, 1H, H_4), 5.85–5.80 (m, 2H, $H_{23}+H_{39}$), 5.26 (dd, $J=15.5$, 8.4 Hz, 1H, H_{22}), 4.57–4.48 (m, 3H, CH_2Ar+H_{11}), 4.30 (m, 1H, H_{13}), 3.80 (s, 3H, ArO*Me*), 3.77 (dd, $J=9.6$, 5.0 Hz, 1H, H_{29a}), 3.65–3.60 (m, 2H, $H_{21}+H_{29b}$), 3.55–3.49 (m, 2H, H_7+H_{25}), 3.40 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.27 (s, 3H, OMe), 3.22 (s, 3H, OMe), 3.20 (dt, $J=8.6$, 4.3 Hz, 1H, H_{19}), 3.10 (dd, $J=6.9$, 4.7 Hz, 1H, H_{27}), 2.79–2.76 (m, 2H, $H_{14a}+H_{14b}$), 2.64 (m, 1H, H_{18}), 2.58–2.45 (m, 3H, $H_{10a}+H_{8a}+H_{24}$), 2.38–2.31 (m, 4H, $H_{8b}+H_{10b}+H_{6a}+H_{6b}$), 1.94 (m, 1H, H_{28}), 1.88 (s, 3H, MeC_5), 1.88–1.84 (m, 2H, $H_{26}+H_{12}$), 1.73 (ddd, $J=14.0$, 8.3, 5.8 Hz, 1H, H_{20a}), 1.48 (ddd, $J=14.0$, 7.8, 4.4 Hz, 1H, H_{20b}), 1.10–1.04 (m, 27H, $MeC_{12}+MeC_{24}+Si(CH(CH_3)_2)_3+Si(CH)_3$), 1.02 (d, $J=7.0$ Hz, 3H, MeC_{28}), 1.00 (d, $J=7.0$ Hz, 3H, MeC_{18}), 0.98 (d, $J=7.1$ Hz, 3H, MeC_{26}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=201.3$, 165.1, 158.9, 158.5, 150.6, 144.1, 138.4, 131.5, 130.1, 129.4, 128.6 (2C), 117.4, 113.6 (2C), 85.6, 82.2, 80.8, 79.9, 78.8, 77.9, 77.2, 73.4, 67.4, 64.9, 60.1, 57.2, 57.1, 55.8, 55.3, 43.5, 43.2, 41.3, 41.1, 41.0, 38.7, 38.5, 38.4, 36.9, 31.7, 24.4, 18.2, 18.1 (6C), 15.3, 13.9, 12.0 (4C), 9.5 ppm; HRMS (ES+): *m/z* calcd for $C_{55}H_{91}IO_{11}SiNa$: 1105.5268 $[M+Na]^+$; found: 1105.5230.

79: AcOH (1.0 mL) was added to a stirred solution of $Me_4NBH(OAc)_3$ (21 mg, 0.37 mmol) in MeCN (2.0 mL) at room temperature. After 30 min, the reaction mixture was cooled to −30 °C followed by the addition of **78** (21 mg, 19.0 μmol) in MeCN (1.05 mL). The resultant solution was then stirred at −20 °C for 3 h before the addition of saturated aqueous sodium/potassium tartrate (5.0 mL). After 15 min, the resultant suspension was partitioned between saturated aqueous $NaHCO_3$ (15 mL), Et_2O (2×10 mL), and CH_2Cl_2 (2×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (60% EtOAc/PE) afforded **79** (20 mg, 95%, >95:5 d.r.) as a colorless oil. R_f: 0.3 (50% EtOAc/hexane); $[\alpha]_D^{20}=-11.0$ ($c=0.10$, $CHCl_3$); IR (neat): $\tilde{\nu}=3427$, 2929, 1714, 1613, 1514, 1463, 1382, 1248, 1090, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.28$–7.24 (m, 2H, Ar), 6.86 (d, $J=8.6$ Hz, 2H, Ar), 6.02 (s, 1H, H_4), 5.84–5.79 (m, 2H, $H_{23}+H_{39}$), 5.68 (dd, $J=15.7$, 7.4 Hz, 1H, H_{17}), 5.56 (dd, $J=15.7$, 6.4 Hz, 1H, H_{16}), 5.26 (dd, $J=15.6$, 8.4 Hz, 1H, H_{22}), 4.56 (d, $J=11.0$ Hz, 1H, CH_aH_bAr), 4.51 (d, $J=11.0$ Hz, 1H, CH_aH_bAr), 4.49 (m, 1H, H_{11}), 4.40 (m, 1H, H_{15}), 4.16 (m, 1H, H_{13}), 3.80 (s, 3H, ArO*Me*), 3.77 (dd, $J=9.6$, 4.9 Hz, 1H, H_{29a}), 3.65–3.60 (m, 2H, $H_{21}+H_{29b}$), 3.54–3.49 (m, 3H, H_7+OH+H_{25}), 3.39 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.25 (s, 3H, OMe), 3.22 (s, 3H, OMe), 3.11–3.06 (m, 2H, $H_{27}+H_{19}$), 2.59–2.43 (m, 3H, $H_{18}+H_{10a}+H_{24}$), 2.37–2.20 (m, 5H, $H_{6a}+H_{6b}+H_{8a}+H_{8b}+H_{10b}$), 1.96–1.84 (m, 2H, $H_{26}+H_{28}+H_{14a}$) 1.88 (s, 1H, MeC_5), 1.80–1.70 (m, 2H, $H_{12}+H_{20a}$), 1.58 (m, 1H, H_{14b}), 1.49 (m, 1H, H_{20b}), 1.10–1.04 (m, 27H, $MeC_{12}+MeC_{24}+Si(CH(CH_3)_2)_3+Si(CH)_3$), 1.02 (d, $J=7.0$ Hz, 3H, MeC_{28}), 0.98 (d, $J=7.0$ Hz, 3H, MeC_{26}), 0.93 ppm (d, $J=6.9$ Hz, 3H, MeC_{18}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=165.0$, 158.9, 158.5, 144.0, 138.2, 133.5, 132.4, 131.5, 129.7, 128.7 (2C), 117.3, 113.6 (2C), 85.6, 82.2, 81.3, 80.2, 79.9, 77.9, 77.2, 73.4, 71.0, 69.3, 64.9, 60.1, 57.1, 56.9, 55.8, 55.3, 43.5, 42.0, 41.1, 40.9, 40.4, 38.7, 38.5, 38.0, 36.8, 31.9, 24.4, 18.2, 18.1 (6C), 15.3, 15.2, 12.0 (4C), 8.8 ppm; HRMS (ES+): *m/z* calcd for $C_{55}H_{93}IO_{11}SiNa$: 1107.5424 $[M+Na]^+$; found: 1107.5469.

80: Proton sponge (166 mg, 0.784 mmol) and trimethyloxonium tetrafluoroborate (58 mg, 0.39 mmol) were added to a stirred solution of **79** together with its minor diastereomer (21 mg, 19.6 μmol) in CH_2Cl_2 (2.4 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature for 4 h before being partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with citric acid (10 mL, 10 wt%), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (5→10% *i*PrOH/PE) afforded **80** and its minor diastereomer (20 mg, 97%, 3:1 d.r.) as a colorless oil. Separation of the diastereomers was performed by HPLC (5% *i*PrOH/hexane, 9.0 mL min^{-1}, SiO_2 semipreparative) to provide **80** (9.8 mg, 49%) and the minor diastereomer **81** (3.3 mg, 16%). **80**: R_f: 0.64 (60% EtOAc/hexane); $t_R=61$ min (5% *i*PrOH/hexane, 9 mL min^{-1}); $[\alpha]_D^{20}=-3.1$ ($c=0.1$, $CHCl_3$); IR (neat): $\tilde{\nu}=2925$, 2867, 1720, 1514, 1463, 1379, 1248, 1100, 883, 821, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.26$ (d, $J=8.4$ Hz, 2H, Ar), 6.86 (d, $J=8.6$ Hz, 2H, Ar), 6.01 (s, 1H, H_4), 5.82 (dd, $J=15.6$, 7.7 Hz, 1H, H_{23}), 5.81 (s, 1H, H_{39}), 5.63 (dd, $J=15.6$, 7.4 Hz, 1H, H_{17}), 5.29–5.21 (m, 2H, $H_{22}+H_{16}$), 4.56 (d, $J=11.0$ Hz, 1H, CH_aH_bAr), 4.51 (d, $J=11.0$ Hz, 1H, CH_aH_bAr), 4.38 (ddd, $J=12.1$, 5.4, 3.8 Hz, 1H, H_{11}), 3.79 (s, 3H, ArO*Me*), 3.77 (dd, $J=9.7$, 5.1 Hz, 1H, H_{29a}), 3.67–3.58 (m, 3H, $H_{15}+H_{21}+H_{29b}$), 3.53–3.45 (m, 3H, $H_7+H_{13}+H_{25}$), 3.39 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.32 (s, 3H, OMe), 3.25 (s, 3H, OMe), 3.23 (s, 3H, OMe), 3.22 (s, 3H, OMe), 3.11–3.05 (m, 2H, $H_{19}+H_{27}$), 2.52–2.41 (m, 4H, $H_{10a}+H_{18}+H_{24}+H_{8a}$), 2.39–

2.28 (m, 4H, $H_{6a}+H_{6b}+H_{8b}+H_{10b}$), 1.98 (m, 1H, H_{12}), 1.96–1.89 (m, 2H, $H_{26}+H_{28}$), 1.87 (s, 3H, *Me*C_5), 1.79–1.67 (m, 2H, $H_{14a}+H_{20a}$), 1.58 (m, 1H, H_{14b}), 1.50 (ddd, $J=13.9$, 8.2, 3.7 Hz, 1H, H_{20b}), 1.10–1.03 (m, 27H, *Me*$C_{12}+Me C_{24}+$Si(CH(CH_3)$_2$)$_3+$Si(CH)$_3$), 1.02 (d, $J=6.9$ Hz, 3H, *Me*C_{28}), 0.98 (d, $J=6.9$ Hz, 3H, *Me*C_{26}), 0.92 ppm (d, $J=6.9$ Hz, 3H, *Me*C_{18}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=165.2$, 158.9, 158.2, 144.1, 138.2, 136.0, 131.6, 130.3, 129.8, 128.6 (2C), 117.6, 113.6 (2C), 85.7, 82.2, 81.5, 80.2, 79.1, 78.8, 78.4, 77.9, 77.4, 73.4, 65.0, 60.2, 57.9, 57.1, 57.0, 55.8 (2C), 55.3, 43.5, 41.1, 40.8, 39.7, 38.7, 38.5, 38.2, 37.7, 36.9, 32.6, 24.4, 18.2, 18.1 (6C), 15.3, 15.3, 12.0 (4C), 10.8 ppm; HRMS (ES+): *m/z* calcd for $C_{57}H_{97}IO_{11}SiNa$: 1135.5737 $[M+Na]^+$; found: 1135.5792.

82: DDQ (3.15 mg, 13.9 μmol) was added to a stirred solution of **80** (10.3 mg, 9.25 μmol) in CH_2Cl_2 (0.5 mL) and pH 7 buffer (0.05 mL) at 0 °C. After 1 h, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (5.0 mL) and CH_2Cl_2 (15 mL). The aqueous phase was extracted with CH_2Cl_2 (2×10 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (20→50% EtOAc/PE) afforded **82** (6.8 mg, 74%) as a colorless oil. R_f: 0.40 (50% EtOAc/hexane); $[\alpha]_D^{20}=-5.1$ ($c=1.0$, $CHCl_3$); IR (neat): $\tilde{\nu}=3747$, 2931, 2867, 1718, 1460, 1381, 1253, 1100, 883, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.01$ (s, 1H, H_4), 5.81 (s, 1H, H_{39}), 5.72 (dd, $J=15.5$, 7.7 Hz, 1H, H_{23}), 5.66 (dd, $J=15.6$, 7.4 Hz, 1H, H_{17}), 5.30–5.22 (m, 2H, $H_{16}+H_{22}$), 4.38 (ddd, $J=11.9$, 5.7, 3.9 Hz, 1H, H_{11}), 3.77 (app d, $J=4.3$ Hz, 2H, $H_{29a}+H_{29b}$), 3.69 (ddd, $J=8.3$, 8.4, 5.2 Hz, 1H, H_{21}), 3.65–3.58 (m, 2H, $H_{15}+H_{25}$), 3.54–3.45 (m, 2H, H_7+H_{13}), 3.50 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.32 (s, 3H, OMe), 3.24 (s, 3H, OMe), 3.23 (s, 3H, OMe), 3.22–3.21 (m_{obs}, 1H, H_{27}), 3.17 (m, 1H, H_{19}), 2.55–2.40 (m, 3H, $H_{10a}+H_{18}+H_{8a}$), 2.39–2.26 (m, 5H, $H_{10b}+H_{8b}+H_{6a}+H_{6b}+H_{24}$), 1.99 (m, 1H, H_{12}), 1.95–1.86 (m, 2H, $H_{26}+H_{28}$), 1.88 (s, 3H, *Me*C_5), 1.81–1.67 (m, 2H, $H_{14a}+H_{20a}$), 1.62–1.51 (m, 2H, $H_{14b}+H_{20b}$), 1.12–1.03 (m, 27H, *Me*$C_{12}+Me C_{26}+$Si(CH-(CH_3)$_2$)$_3+$Si(CH)$_3$), 0.96 (d, $J=7.0$ Hz, 3H, *Me*C_{18}), 0.94 (d, $J=6.9$ Hz, 3H, *Me*C_{28}), 0.93 ppm (d, $J=6.8$ Hz, 3H, *Me*C_{24}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=165.2$, 158.2, 144.1, 139.2, 136.1, 130.2, 129.5, 117.6, 88.6, 81.5, 80.3, 79.1, 78.7, 78.5, 77.9, 77.4, 74.1, 65.0, 61.9, 57.9, 57.2, 57.1, 55.8, 55.7, 43.5, 40.8, 40.0, 39.7, 38.7, 38.4, 37.7, 36.8, 34.7, 32.5, 24.4, 18.1 (6C), 16.7, 15.5, 14.8, 12.0 (3C), 11.2, 10.8 ppm; HRMS (ES+): *m/z* calcd for $C_{49}H_{89}IO_{10}SiNa$: 1015.5162 $[M+Na]^+$; found: 1015.5130.

84: A solution of (*E*)-3-(tributylstannyl)acrylic acid (**83**; 4.9 mg, 13.7 μmol), **82** (6.8 mg, 6.8 μmol), and *N,N*-diisopropylethylamine (6.0 μL, 34 μmol) in NMP (250 μL) was degassed by three freeze–pump–thaw cycles. The resulting solution was then cannulated into a stirred solution of tris(dibenzylideneacetone)dipalladium(0) (0.7 mg, 0.7 μmol) in NMP (50 μL) at room temperature. After 16 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL), and the reaction was quenched by the addition of aqueous citric acid (1 M, 6 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (20% EtOAc/PE→80% EtOAc then 80% EtOAc/PE+1% MeOH→80% EtOAc/PE+6% MeOH) afforded **84** (5.5 mg, 86%) as a colorless oil. R_f: 0.32 (80:16:4 EtOAc/hexane/CH_2Cl_2); $[\alpha]_D^{20}=-8.2$ ($c=1.0$, $CHCl_3$); IR (neat): $\tilde{\nu}=2937$, 2867, 1707, 1460, 1260, 1096, 910, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.58$ (dd, $J=15.1$, 11.6 Hz, 1H, H_3), 6.04 (d, $J=11.6$ Hz, 1H, H_4), 5.85–5.80 (m, 1H, H_2), 5.83 (s, 1H, H_{39}), 5.69 (dd, $J=15.8$, 8.0 Hz, 1H, H_{23}), 5.66 (dd, $J=15.8$, 7.6 Hz, 1H, H_{17}), 5.29–5.23 (m, 2H, $H_{16}+H_{22}$), 4.32 (m, 1H, H_{11}), 3.79 (dd, $J=9.5$, 5.0 Hz, 1H, H_{29a}), 3.76 (dd, $J=9.5$, 3.5 Hz, 1H, H_{29b}) 3.70–3.55 (m, 4H, $H_7+H_{15}+H_{21}+H_{25}$), 3.52 (s, 3H, OMe), 3.43 (dt, $J=8.1$, 4.0 Hz, 1H, H_{13}), 3.33 (s, 6H, OMe), 3.31 (s, 3H, OMe), 3.26–3.22 (m_{obs}, 1H, H_{27}), 3.24 (s, 3H, OMe), 3.23 (s, 3H, OMe), 3.18 (dt, $J=8.6$, 4.3 Hz, 1H, H_{19}), 2.49–2.43 (m_{obs}, 1H, H_{18}), 2.46 (dd, $J=13.8$, 5.8 Hz, 1H, H_{6a}), 2.40–2.31 (m, 5H, $H_{8a}+H_{8b}+H_{10a}+H_{10b}+H_{24}$), 2.25 (dd, $J=13.8$, 6.5 Hz, 1H, H_{6b}), 2.00 (m, 1H, H_{12}), 1.93 (s, 3H, *Me*C_5), 1.92–1.87 (m, 2H, $H_{26}+H_{28}$), 1.78 (ddd, $J=14.2$, 8.6, 5.7 Hz, 1H, H_{20a}), 1.73 (m, 1H, H_{14a}), 1.59–1.52 (m, 2H, $H_{14b}+H_{20b}$), 1.12–1.04 (m, 27H, *Me*$C_{12}+Me C_{26}+$Si(CH(CH_3)$_2$)$_3+$Si(CH)$_3$), 0.96–0.92 ppm (m, 9H, *Me*$C_{18}+Me C_{24}+Me C_{28}$); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta=169.5$, 165.2, 158.0, 145.8, 141.3, 139.2, 136.7, 130.2, 129.8, 126.1, 119.6, 117.7, 88.8, 81.4, 80.3, 79.1, 78.9, 78.8, 77.6, 74.5, 65.1, 62.0, 57.6, 57.2, 57.0, 55.8, 55.6, 44.3, 40.7, 40.1, 39.5, 38.7 (2C), 36.9, 36.8, 34.4, 32.6, 18.1 (6C), 18.0, 16.9, 15.6, 14.7, 12.0 (3C), 11.3, 11.2 ppm; HRMS (ES+): *m/z* calcd for $C_{52}H_{92}O_{12}SiNa$: 959.6250 $[M+Na]^+$; found: 959.6237.

76: Et_3N (2.2 μL, 15.9 μmol) and 2,4,6-trichlorobenzoyl chloride (1.6 μL, 10.6 μmol) were added to a stirred solution of **84** (5.5 mg, 5.9 μmol) in PhMe (0.3 mL) at room temperature. After 1 h, the reaction mixture was diluted with PhMe (3.0 mL) and added over 2 h by syringe pump to a stirred solution of DMAP (8.6 mg, 70.4 μmol) in PhMe (5.0 mL). After a further 2 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×10.0 mL). The combined organic phases were washed with aqueous citric acid (10.0 mL, 10% *w/w*) followed by brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (20→60% EtOAc/PE) afforded **76** (3.2 mg, 59%) as a colorless oil. R_f: 0.57 (40% EtOAc/hexane); $[\alpha]_D^{20}=+18.3$ ($c=0.18$, $CHCl_3$); IR (neat): $\tilde{\nu}=2926$, 1713, 1635, 1581, 1463, 1382, 1271, 1096, 980 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.52$ (dd, $J=15.1$, 11.7 Hz, 1H, H_3), 6.01 (d, $J=11.7$ Hz, 1H, H_4), 5.87 (s, 1H, H_{39}), 5.83 ($J=15.1$ Hz, 1H, d, H_2), 5.59 (dd, $J=15.6$, 5.8 Hz, 1H, H_{17}), 5.51 (dd, $J=15.2$, 9.6 Hz, 1H, H_{23}), 5.22 (dd, $J=15.6$, 8.8 Hz, 1H, H_{16}), 5.19 (app d, $J=10.1$ Hz, 1H, H_{25}), 5.14 (dd, $J=15.2$, 8.9 Hz, 1H, H_{22}), 4.28 (ddd, $J=12.0$, 8.5, 3.5 Hz, 1H, H_{11}), 3.76 (dd, $J=9.7$, 6.1 Hz, 1H, H_{29a}), 3.56 (dd, $J=9.7$, 6.7 Hz, 1H, H_{29b}), 3.51 (m, 1H, H_{15}), 3.49–3.44 (m_{obs}, 1H, H_7), 3.43 (m, 1H, H_{21}), 3.36 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.27 (m, 1H, H_{13}), 3.24 (s, 3H, OMe), 3.19 (s, 3H, OMe), 3.17 (s, 3H, OMe), 3.11 (app dd, $J=10.9$, 6.6 Hz, 1H, H_{19}), 2.87 (dd, $J=8.8$, 2.9 Hz, 1H, H_{27}), 2.55 (dd, $J=13.4$, 5.0 Hz, 1H, H_{6a}), 2.47 (m, 1H, H_{24}), 2.39–2.29 (m, 3H, $H_{18}+H_{8a}+H_{10a}$), 2.26–2.18 (m, 2H, $H_{8b}+H_{10b}$), 2.15 (dd, $J=13.4$, 7.9 Hz, 1H, H_{6b}), 2.05–1.99 (m, 2H, $H_{26}+H_{28}$), 1.95 (ddd, $J=13.6$, 8.6, 4.8 Hz, 1H, H_{14a}), 1.90 (s, 3H, *Me*C_5), 1.83 (m, 1H, H_{12}), 1.76 (ddd, $J=13.6$, 9.5, 4.4 Hz, 1H, H_{14b}), 1.73 (m, 1H, H_{20a}), 1.31 (m, 1H, H_{20b}), 1.11 (d, $J=6.7$ Hz, 3H, *Me*C_{12}), 1.08–1.03 (m, 24H, *Me*$C_{24}+$Si(CH(CH_3)$_2$)$_3+$Si(CH)$_3$), 1.01 (d, $J=7.0$ Hz, 3H, *Me*C_{26} or *Me*C_{28}), 0.98 (d, $J=6.9$ Hz, 3H, *Me*C_{26} or *Me*C_{28}), 0.85 ppm (d, $J=6.9$ Hz, 3H, *Me*C_{18}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=166.7$, 165.2, 157.6, 145.1, 140.1, 139.1, 138.7, 130.6, 130.1, 126.2, 120.8, 117.6, 84.9, 80.7, 79.5, 79.3, 78.9, 78.0, 77.2, 75.3, 64.6, 61.0, 57.2, 56.9, 56.8, 55.8, 55.6, 44.4, 41.0, 40.7, 39.3, 38.3, 37.7, 36.8, 36.5, 33.6, 31.3, 18.1 (6C), 18.0, 17.6, 15.4, 14.2, 12.0 (3C), 10.5, 10.0 ppm; HRMS (ES+): *m/z* calcd for $C_{52}H_{90}O_{11}SiNa$: 941.6145 $[M+Na]^+$; found: 941.6160.

86: A solution of HF·py/py was prepared by addition of pyridinium hydrofluoride (0.1 mL) to a stirred solution of pyridine (0.3 mL) in THF (2 mL) at 0 °C, followed by warming to room temperature for 30 min before use. This solution of HF·py/py (100 μL) was added to a stirred solution of **76** (2.6 mg, 2.83 μmol) in THF (100 μL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature for 27 h before the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (0.5 mL). The mixture was then diluted with CH_2Cl_2 (3 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (70% EtOAc/PE→70% EtOAc/PE+3% MeOH) afforded **86** (1.4 mg, 65%) as a colorless oil. R_f: 0.25 (70% EtOAc/hexane); $[\alpha]_D^{20}=+25.0$ ($c=0.14$, $CHCl_3$); IR (neat): $\tilde{\nu}=3445$, 2925, 1712, 1634, 1464, 1380, 1270, 1102, 1026, 975 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.54$ (dd, $J=15.1$, 11.6 Hz, 1H, H_3), 6.02 (d, $J=11.6$ Hz, 1H, H_4), 5.87 (s, 1H, H_{39}), 5.83 (d, $J=15.1$ Hz, 1H, H_2), 5.60 (dd, $J=15.6$, 5.8 Hz, 1H, H_{17}), 5.50 (dd, $J=15.1$, 9.6 Hz, 1H, H_{23}), 5.23 (dd, $J=15.6$, 8.8 Hz, 1H, H_{16}), 5.18 (app d, $J=10.1$ Hz, 1H, H_{25}), 5.16 (dd, $J=15.1$, 8.9 Hz, 1H, H_{22}), 4.28 (ddd, $J=11.9$, 8.4, 3.5 Hz, 1H, H_{11}), 3.83 (dd, $J=11.0$, 3.5 Hz, 1H, H_{29a}), 3.57 (dd, $J=11.1$, 4.5 Hz, 1H, H_{29b}), 3.51 (m, 1H, H_{15}), 3.49–3.40 (m_{obs}, 2H, H_7+H_{21}), 3.46 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.27 (m, 1H, H_{13}), 3.24 (s, 3H, OMe), 3.19 (s, 3H, OMe), 3.18 (s, 3H, OMe), 3.12 (app dd, $J=10.8$, 6.5 Hz, 1H, H_{19}), 2.89 (dd, $J=8.8$, 2.9 Hz, 1H, H_{27}), 2.77 (br s, 1H, OH), 2.54 (dd, $J=13.4$, 5.0 Hz, 1H, H_{6a}), 2.49 (m, 1H, H_{24}), 2.40–2.29 (m, 3H, $H_{18}+H_{8a}+H_{10a}$), 2.26–2.19 (m, 2H, $H_{8b}+H_{10b}$), 2.16 (dd, $J=13.5$, 7.8 Hz, 1H, H_{6b}), 2.07–1.99 (m, 2H, $H_{26}+H_{28}$), 1.94 (m, 1H, H_{14a}), 1.91 (s, 3H, *Me*C_5), 1.83 (m, 1H, H_{12}), 1.79–1.70 (m, 2H, $H_{14b}+H_{20a}$), 1.30 (m_{obs}, 1H, H_{20b}), 1.15 (d, $J=7.1$ Hz, 3H, *Me*C_{28}), 1.11 (d, $J=6.8$ Hz, 3H, *Me*C_{12}),

1.06 (d, $J=6.7$ Hz, 3H, MeC_{24}), 0.95 (d, $J=7.0$ Hz, 3H, MeC_{26}), 0.85 ppm (d, $J=6.9$ Hz, 3H, MeC_{18}); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=166.7$, 165.2, 157.6, 145.6, 140.5, 139.2, 138.3, 130.8, 130.1, 126.1, 120.4, 117.6, 88.5, 80.7, 79.4, 79.3, 78.9, 77.9, ($C7_{obsc}$) 74.9, 64.7, 62.2, 57.1, 56.9, 56.8, 55.8, 55.6, 44.4, 41.0, 40.8, 39.3, 37.6, 37.2, 36.7, 36.2, 33.4, 31.3, 18.0, 17.6, 16.3, 14.1, 10.4, 9.9 ppm; HRMS (ES+): m/z calcd for $C_{43}H_{70}O_{11}Na$: 785.4810 $[M+Na]^+$; found: 785.4827.

11: A solution of **86** (1.40 mg, 1.83 μmol) in CH_2Cl_2 (200 μL) was added to a stirred suspension of Dess–Martin periodinane (2.3 mg, 5.5 μmol) and $NaHCO_3$ (1.5 mg, 18.3 μmol) in CH_2Cl_2 (100 μL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to room temperature for 1 h, after which hexane was added, and the resulting precipitate was filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (80 % EtOAc/PE) on florisil to afford **11** (1.2 mg, 86 %) as a colorless oil. R_f: 0.45 (80 % EtOAc/hexane); $[\alpha]_D^{20}=+14.0$ ($c=0.12$, $CHCl_3$); IR (neat): $\tilde{\nu}=2972$, 2928, 2820, 1715, 1635, 1460, 1382, 1271, 1099, 1027, 979 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=9.75$ (s, 1H, H_{29}), 7.55 (dd, $J=15.1$, 11.5 Hz, 1H, H_3), 6.03 (d, $J=11.5$ Hz, 1H, H_4), 5.87 (s, 1H, H_{39}), 5.84 (d, $J=15.0$ Hz, 1H, H_2), 5.59 (dd, $J=15.6$, 5.8 Hz, 1H, H_{17}), 5.48 (dd, $J=15.0$, 9.5 Hz, 1H, H_{23}), 5.25 (app d, $J=10.1$ Hz, 1H, H_{25}), 5.23 (dd, $J=15.6$, 8.8 Hz, 1H, H_{16}), 5.17 (dd, $J=15.0$, 8.9 Hz, 1H, H_{22}), 4.28 (ddd, $J=12.0$, 8.3, 3.6 Hz, 1H, H_{11}), 3.54–3.41 (m, 3H, $H_{15}+H_7+H_{21}$), 3.37 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.28 (m, 1H, H_{13}), 3.24 (s, 3H, OMe), 3.20 (m_{obs}, 1H, H_{27}), 3.20 (s, 3H, OMe), 3.17 (s, 3H, OMe), 3.10 (app dd, $J=11.0$, 6.6 Hz, 1H, H_{19}), 2.72 (m, 1H, H_{28}), 2.54 (dd, $J=13.4$, 5.0 Hz, 1H, H_{6a}), 2.47 (m, 1H, H_{24}), 2.40–2.29 (m, 3H, $H_{18}+H_{8a}+H_{10a}$), 2.27–2.20 (m, 2H, $H_{8b}+H_{10b}$), 2.17 (dd, $J=13.3$, 7.9 Hz, 1H, H_{6b}), 2.01 (m, 1H, H_{26}), 1.94 (m, 1H, H_{14a}), 1.92 (s, 3H, MeC_5), 1.84 (m, 1H, H_{12}), 1.78–1.69 (m, 2H, $H_{14b}+H_{20a}$), 1.31 (m_{obs}, 1H, H_{20b}), 1.19 (d, $J=6.9$ Hz, 3H, MeC_{28}), 1.11 (d, $J=6.7$ Hz, 3H, MeC_{12}), 1.04 (d, $J=6.7$ Hz, 3H, MeC_{24}), 0.85 ppm (app t, $J=6.7$ Hz, 6H, $MeC_{18}+MeC_{26}$); HRMS (ES+): m/z calcd for $C_{43}H_{68}O_{11}Na$: 783.4654 $[M+Na]^+$; found: 783.4665.

89: A stock solution (0.059 M in Et_2O) of the boron enolate of **10** was prepared by addition of Et_3N (6.5 μL, 0.0468 mmol) and dicyclohexylboron chloride (5.1 μL, 0.0234 mmol) to a solution of **10** (5.0 mg, 0.0234 mmol) in Et_2O (0.4 mL) at −10 °C. The resulting suspension was stirred for 1 h at 0 °C before use. Aldehyde **11** (1.20 mg, 1.58 μmol) was dissolved in Et_2O (100 μL), and this solution was stirred over powdered CaH_2 for 30 min at room temperature before being cooled to −78 °C. A solution of the enolate (100 μL, 5.9 μmol) was added dropwise to this cooled solution, and the reaction mixture was stirred at −78 °C for 30 min, then at −6 °C for 1 h. After warming to 0 °C, the reaction was quenched by addition of pH 7 buffer (0.3 mL) and MeOH (0.05 mL). The resulting mixture was stirred at room temperature for 30 min then diluted with CH_2Cl_2 (3 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (70 % EtOAc/PE→70 % EtOAc/PE+3 % MeOH) on florisil afforded **89** (1.08 mg, 70 %) as a colorless oil. R_f: 0.11 (80 % EtOAc/PE); $[\alpha]_D^{20}=-12.0$ ($c=0.10$, $CHCl_3$); IR (neat): $\tilde{\nu}=3448$, 2971, 2922, 1710, 1659, 1460, 1382, 1271, 1098, 1080 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.29$ (s, 1H, NC*H*O), 8.07 (s, 1H, *NC*H*O), 7.52 (dd, $J=15.1$, 11.6 Hz, 1H, H_3), 7.19 (d, $J=15.0$ Hz, 1H, *H_{36}), 6.52 (d, $J=14.0$ Hz, 1H, H_{36}), 6.02 (d, $J=11.6$ Hz, 1H, H_4), 5.87 (s, 1H, H_{39}), 5.83 (d, $J=15.1$ Hz, 1H, H_2), 5.59 (dd, $J=15.6$, 5.8 Hz, 1H, H_{17}), 5.49 (dd, $J=15.1$, 9.5 Hz, 1H, H_{23}), 5.22 (ddd, $J=15.6$, 8.7, 1.1 Hz, 1H, H_{16}), 5.19 (app d, $J=10.8$ Hz, 1H, H_{25}), 5.15 (dd, $J=15.2$, 9.1 Hz, 1H, H_{22}), 5.12 (m_{obs}, 1H, *H_{35}), 5.08 (m, 1H, H_{35}), 4.28 (ddd, $J=12.0$, 8.2, 3.6 Hz, 1H, H_{11}), 4.19 (m, 1H, H_{29}), 4.09 (br s, 1H, OH), 3.53–3.44 (m, 3H, $H_{15}+H_7+H_{33}$), 3.43 (m, 1H, H_{21}) 3.39 (s, 3H, OMe), 3.38 (s, 3H, *OMe), 3.34 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.30 (s, 3H, OMe), 3.29 (s, 3H, *OMe), 3.28 (m, 1H, H_{13}), 3.24 (s, 3H, OMe), 3.19 (s, 3H, OMe), 3.17 (s, 3H, OMe), 3.11 (m, 1H, H_{19}), 3.07 (s, 3H, *N*Me*), 3.04 (s, 3H, N*Me*), 2.90 (dd, $J=8.7$, 3.2 Hz, 1H, H_{27}), 2.83–2.74 (m, 2H, $H_{30a}+H_{32}$), 2.59 (m, 1H, H_{30b}), 2.54 (dd, $J=13.1$, 5.0 Hz, 1H, H_{6a}), 2.51–2.44 (m, 2H, $H_{34a}+H_{24}$), 2.40–2.29 (m, 3H, $H_{18}+H_{8a}+H_{10a}$), 2.27–2.13 (m, 4H, $H_{8b}+H_{10b}+H_{34b}+H_{6b}$), 2.03 (m, 1H, H_{26}), 1.96 (m, 1H, H_{28}), 1.94 (m, 1H, H_{14a}), 1.90 (s, 3H, MeC_5), 1.83 (m, 1H, H_{12}), 1.79–1.70 (m, 2H, $H_{14b}+H_{20a}$), 1.31 (m_{obs}, 1H, H_{20b}), 1.11 (d, $J=6.8$ Hz, 3H, MeC_{12}), 1.04–0.96 (m, 12H, $MeC_{24}+MeC_{32}+MeC_{26}+MeC_{28}$), 0.85 ppm (d, $J=6.9$ Hz, 3H, MeC_{18}) (distinguishable resonances of the minor rotamer are denoted with an asterisk); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=215.0$ *(215.2), 166.7, 165.2, 162.1 *(160.8), 157.6, 145.4, 140.3, 139.1, 138.4, 130.8, 130.5, 130.1 *(126.5), 126.2, 120.6, 117.5, 105.1 *(106.7), 86.4, 82.5, 80.7, 79.4, 79.3, 78.9, 78.0 ($C7_{obs}$), 74.9 *(75.0), 68.5 *(68.4), 61.2 *(61.2), 57.7 *(57.4), 57.2, 56.9, 56.8, 55.7, 55.6, 49.4 *(49.5), 47.9 *(47.7), 44.4, 41.0, 40.7, 40.3 *(40.2), 39.3, 37.6, 37.3 *(37.2), 36.7, 33.6, 31.3, 30.4 *(30.2), 27.5 *(33.0), 17.9, 17.6, 14.5 *(14.4), 14.2, 12.6 *(12.7), 10.5, 10.0 ppm; HRMS (ES+): m/z calcd for $C_{54}H_{91}N_2O_{14}$: 991.6465 $[M+NH_4]^+$; found: 991.6509.

90: A stock solution (0.042 M in HF) of Burgess reagent ($Et_3NSO_2NCO_2Me$) was prepared by dissolving Burgess reagent (10 mg, 0.0420 mmol) in THF (1.0 mL) at room temperature. The resulting solution was stored under argon for 1 h before use. The stock solution of Burgess reagent (43 μL, 1.81 μmol) was added to a stirred solution of **89** (0.352 mg, 0.361 μmol) in THF (100 μL), and the reaction mixture was stirred at room temperature for 48 h before the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (0.5 mL). The resulting mixture was stirred for 30 min then diluted with CH_2Cl_2 (3 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (80 % EtOAc/PE) on florisil afforded **90** (0.304 mg, 88 %) as a colorless oil. R_f: 0.24 (80 % EtOAc/PE); $[\alpha]_D^{20}=-4.0$ ($c=0.03$, $CHCl_3$); IR (neat): $\tilde{\nu}=2925$, 2854, 1712, 1659, 1464, 1262, 1162, 1099, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.28$ (s, 1H, NC*H*O), 8.07 (s, 1H, *NC*H*O), 7.54 (dd, $J=15.1$, 11.6 Hz, 1H, H_3), 7.18 (d, $J=14.5$ Hz, 1H, *H_{36}), 6.92 (dd, $J=15.9$, 8.2 Hz, 1H, H_{29}), 6.52 (d, $J=14.0$ Hz, 1H, H_{36}), 6.16 (dd, $J=15.9$, 4.8 Hz, 1H, H_{30}), 6.02 (d, $J=11.6$ Hz, 1H, H_4), 5.87 (s, 1H, H_{39}), 5.83 (d, $J=15.1$ Hz, 1H, H_2), 5.60 (dd, $J=15.6$, 5.6 Hz, 1H, H_{17}), 5.48 (dd, $J=15.1$, 9.6 Hz, 1H, H_{23}), 5.22 (dd, $J=15.6$, 9.0 Hz, 1H, H_{16}), 5.17 (app d, $J=10.5$ Hz, 1H, H_{25}), 5.14 (dd, $J=15.2$, 9.0 Hz, 1H, H_{22}), 5.12 (m_{obs}, 1H, *H_{35}), 5.09 (m, 1H, H_{35}), 4.29 (ddd, $J=12.1$, 8.2, 3.5 Hz, 1H, H_{11}), 3.53–3.45 (m, 3H, $H_{15}+H_7+H_{33}$), 3.41 (m_{obs}, 1H, H_{21}) 3.41 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.29 (s, 3H, OMe), 3.28 (s, 3H, *OMe), 3.28 (m_{obs}, 1H, H_{13}), 3.24 (s, 3H, OMe), 3.18 (s, 3H, OMe), 3.16 (s, 3H, OMe), 3.11 (m, 1H, H_{19}), 3.08 (s, 3H, *N*Me*), 3.04 (s, 3H, N*Me*), 2.83 (dd, $J=9.6$, 2.3 Hz, 1H, H_{27}), 2.76 (m, 1H, H_{32}), 2.65 (m, 1H, H_{28}), 2.56 (dd, $J=13.3$, 4.8 Hz, 1H, H_{6a}), 2.50–2.41 (m, 2H, $H_{34a}+H_{24}$), 2.39–2.28 (m, 3H, $H_{18}+H_{8a}+H_{10a}$), 2.26–2.17 (m, 3H, $H_{8b}+H_{10b}+H_{34b}$), 2.16 (dd, $J=13.4$, 8.0 Hz, 1H, H_{6b}), 1.95 (m, 1H, H_{14a}), 1.91 (s, 3H, MeC_5), 1.82 (m, 1H, H_{12}), 1.80 (m, 1H, H_{26}), 1.78–1.69 (m, 2H, $H_{14b}+H_{20a}$), 1.30 (m_{obs}, 1H, H_{20b}), 1.18 (d, $J=6.8$ Hz, 3H, MeC_{28}), 1.11 (d, $J=6.7$ Hz, 3H, MeC_{12}), 1.03–0.99 (m, 6H, $MeC_{32}+MeC_{24}$), 0.87 (d, $J=7.0$ Hz, 3H, MeC_{26}) 0.85 ppm (d, $J=6.8$ Hz, 3H, MeC_{18}) (distinguishable resonances of the minor rotamer are denoted with an asterisk); HRMS (ES+): m/z calcd for $C_{54}H_{85}NO_{13}Na$: 978.5913 $[M+Na]^+$; found: 978.5947.

5: Enone **90** (0.220 mg, 0.230 μmol) was dissolved in degassed wet PhMe (100 μL, 99:1 PhMe/H_2O). The resulting solution was transferred to a flask containing $[Ph_3PCuH]_6$ (0.90 mg, 0.46 μmol). The reaction mixture was stirred at room temperature for 1 h before the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (0.3 mL). The resulting mixture was stirred at room temperature for 15 min then diluted with CH_2Cl_2 (2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2/MeOH (9:1, 2×1 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (50 % EtOAc/PE→80 % EtOAc/PE+3 % MeOH) on florisil afforded reidispongiolide A (**5**; 79 % by ^{1}H NMR) as a colorless oil (with a trace amount of Ph_3PO present as a minor contaminant). Further purification was performed by analytical HPLC (10 % H_2O/MeOH, 1.0 mL min^{-1}, reversed phase C-18, ODS 5 μm×4.6 mm) to afford **5** (165 μg, 77 %) as a colorless amorphous solid. R_f: 0.15 (80 % EtOAc/PE); $t_R=6.07$ min; $[\alpha]_D^{20}=-10.0$ ($c=0.02$, $CHCl_3$); IR (neat): $\tilde{\nu}=2973$, 2932, 2826, 1711, 1659, 1463, 1382, 1271, 1098, 1079, 980 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.29$ (s, 1H, NC*H*O), 8.07 (s, 1H, *NC*H*O), 7.53 (dd, $J=15.2$, 11.6 Hz, 1H, H_3), 7.18 (d, $J=14.8$ Hz, 1H, *H_{36}), 6.52 (d, $J=14.1$ Hz, 1H, H_{36}), 6.02 (d, $J=11.7$ Hz, 1H, H_4), 5.87 (s, 1H, H_{39}), 5.84 (d, $J=15.2$ Hz, 1H, H_2), 5.60 (dd, $J=15.7$, 5.8 Hz, 1H, H_{17}), 5.49 (dd, $J=$

15.1, 9.5 Hz, 1H, H_{23}), 5.22 (ddd, J=15.6, 9.0, 1.2 Hz, 1H, H_{16}), 5.17 (app d, J=10.5 Hz, 1H, H_{25}), 5.15 (dd, J=15.1, 8.8 Hz, 1H, H_{22}), 5.12 (m_{obs}, 1H, *H_{35}), 5.08 (m, 1H, H_{35}), 4.28 (ddd, J=12.0, 8.4, 3.5 Hz, 1H, H_{11}), 3.51 (m, 1H, H_{15}), 3.48–3.44 (m, 2H, H_7+H_{33}), 3.42 (m, 1H, H_{21}) 3.39 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.29 (s, 3H, OMe), 3.29 (s, 3H, *OMe), 3.28 (m, 1H, H_{13}), 3.24 (s, 3H, OMe), 3.19 (s, 3H, OMe), 3.17 (s, 3H, OMe), 3.12 (m, 1H, H_{19}), 3.07 (s, 3H, *N*Me*), 3.03 (s, 3H, N*Me*), 2.73 (m, 1H, H_{32}), 2.70 (dd, J=7.1, 2.3 Hz, 1H, H_{27}), 2.61–2.52 (m, 2H, H_{30a}+H_{6a}), 2.51–2.43 (m, 3H, H_{24}+H_{30b}+H_{34a}), 2.40–2.29 (m, 3H, H_{18}+H_{8a}+H_{10a}), 2.26–2.18 (m, 2H, H_{8b}+H_{10b}), 2.15 (dd, J=13.3, 7.8, 1H, H_{6b}), 2.14 (m, 1H, H_{34b}), 1.98–1.92 (m, 2H, H_{26}+H_{14a}), 1.90 (s, 3H, *Me*C_5), 1.82 (m, 1H, H_{12}), 1.79–1.66 (m, 4H, H_{14b}+H_{29a}+H_{20a}+H_{28}), 1.40 (m, 1H, H_{29b}), 1.31 (m, 1H, H_{20b}), 1.11 (d, J=6.8 Hz, 3H, *Me*C_{12}), 1.05 (d, J=6.8 Hz, 3H, *Me*C_{24}), 0.99 (d, J=6.9 Hz, 3H, *Me*C_{28}), 0.97 (d, J=6.9 Hz, 3H, *Me*C_{32}), 0.93 (d, J=6.9 Hz, 3H, *Me*C_{26}), 0.85 ppm (d, J=6.9 Hz, 3H, *Me*C_{18}) (distinguishable resonances of the minor rotamer are denoted with an asterisk); ^{13}C NMR (125 MHz, $CDCl_3$): δ= 213.6, 166.8, 165.2, 162.1 *(160.8), 157.6, 145.3, 140.3, 139.2, 138.6, 130.6 *(126.3), 130.4, 130.0, 126.2, 120.6, 117.6, 105.3 *(107.0), 87.2, 82.3, 80.7, 79.4, 79.3, 78.9, 77.9 ($C7_{obs}$), 75.4, 61.6 *(61.5), 57.7 *(57.5), 57.1, 56.9, 56.8, 55.7, 55.6, 48.9 *(49.1), 44.4, 41.0 (2C), 40.8, 39.3, 37.6, 36.7, 36.5, 34.4 *(34.3), 33.5, 31.3, 30.4 *(30.2), 27.5 *(33.0), 23.3 *(23.2), 18.0, 17.6, 17.5, 14.1, 12.7 *(12.9), 10.0, 9.9 ppm; HRMS (ES+): m/z calcd for $C_{54}H_{87}NO_{13}Na$: 980.6070 $[M+Na]^+$; found: 980.6081. These data is in accord with those reported by D'Auria et al.[7,43]

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