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Total Synthesis of the Marine Phosphomacrolide, (−)-Enigmazole A, Exploiting Multicomponent Type I Anion Relay Chemistry (ARC) in Conjunction with a Late-Stage Petasis−Ferrier Union/Rearrangement

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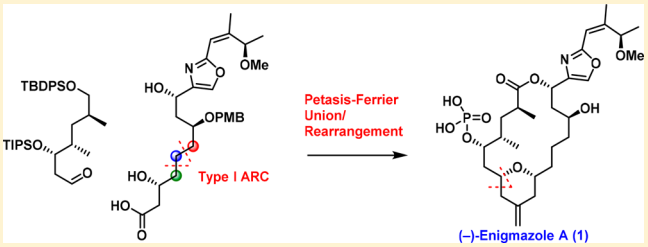
Supporting Information

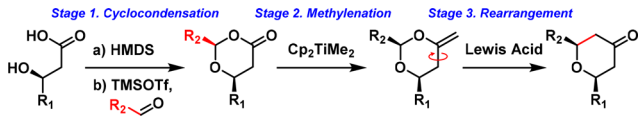
ABSTRACT: An effective late-stage large-fragment union/rearrangement exploiting the Petasis−Ferrier protocol, in conjunction with multicomponent Type I Anion Relay Chemistry (ARC) to access advanced intermediates, permits completion of a convergent, stereocontrolled total synthesis of the architecturally complex phosphomacrolide (−)-enigmazole A (**1**).



INTRODUCTION

The Petasis−Ferrier rearrangement[1] comprises a versatile protocol for the construction of multisubstituted tetrahydropyrans that comprise diverse structural components widely found in bioactive natural products.[2,3] Modification of this reaction sequence early on in our laboratory led to a three-stage protocol for the construction of polyketides[4] that possess *cis*-disubstituted tetrahydropyran rings (Scheme 1).[5]

Scheme 1. Petasis−Ferrier Union/Rearrangement Protocol



Partnering the Petasis−Ferrier union/rearrangement protocol with Anion Relay Chemistry (ARC),[6] also developed in our laboratory, extends considerably this construction paradigm. With these tactics in hand, we initiated a synthetic program to access members of the novel polyketide phosphomacrolide family of marine toxins, known as the enigmazoles. The first member of this family, (−)-enigmazole A (**1**, Figure 1), disclosed by Gustafson et al. at the National Cancer Institute in 2010, exhibited potent activity across the NCI 60-cell line assay with a mean GI50 value of 1.7 μm.[7] Pure enigmazole A (**1**) however did not display the selective inhibition of cells expressing mutant C-Kit as originally observed for the crude extract of the marine sponge, *Cinachyrella enigmatica*.[7] Subsequent extensive chemical investigations of the crude sponge extract by Gustafson et al. suggested that a structurally related metabolite, (−)-enigmazole B (**2**), was responsible for the selective C-Kit inhibition.[7b,c] While sharing the common

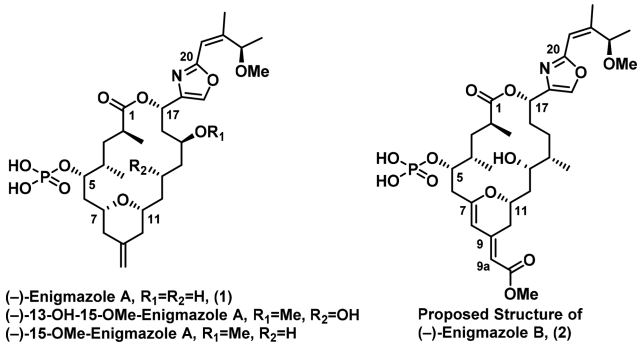


Figure 1. Enigmazole family of molecules.

structural features of (−)-enigmazole A (**1**), including the unprecedented phosphate substituent on the macrolide ring, (−)-enigmazole B (**2**) was found to possess a trisubstituted dihydropyran moiety with a methyl dienoate moiety attached to the dihydropyran core, which may well represent the distinguishing structural feature that contributes to the differential selective C-Kit activity.

Synthetic as well as additional structural interests in the enigmazole family of phosphomacrolides first appeared with back to back publications[8] in 2010 on the total synthesis of (−)-enigmazole A (**1**) by the Molinski group and a full structural account by Gustafson et al. More recently, total syntheses were reported in 2015 by our group,[9] by the Fürstner group in 2016,[10] and by the Fuwa group in 2018.[11] Herein, we provide a full account on the development and execution of the Penn total synthesis of (−)-enigmazole A (**1**) that exploits the

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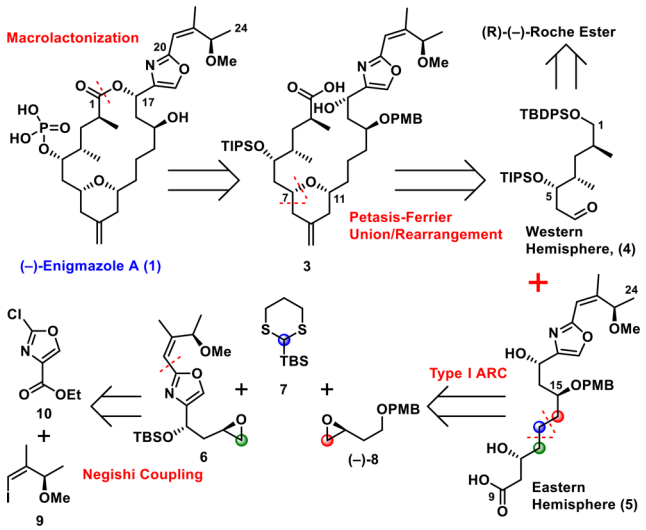
effective combination of a late-stage large fragment Petasis–Ferrier union/rearrangement in conjunction with construction of the requisite advanced acyclic intermediate exploiting Type I Anion Relay Chemistry (ARC).

RESULTS AND DISCUSSION

From the retrosynthetic perspective, our intent for the (−)-enigmazole A (**1**) program was to establish a general strategy leading to the construction of a common enigmazole macrocyclic precursor not only for (−)-enigmazole A (**1**), but also for potential analogues (Scheme 2). Ideal here appeared to

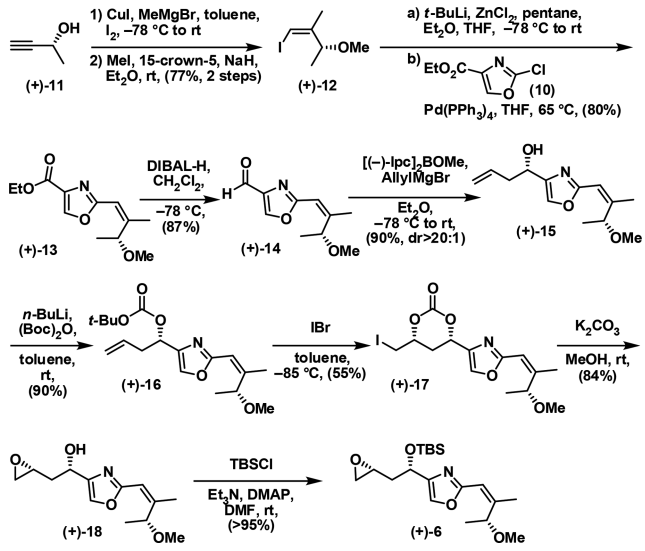
Scheme 2. Retrosynthetic Analysis of (−)-Enigmazole A



be use of the Petasis–Ferrier union/rearrangement tactic comprising an unprecedented late-stage coupling of large fragments to construct the requisite substituted pyran functionality, that would not only lead to (−)-enigmazole A (**1**) after macrolactonization and further elaboration, but to potential analogues. Toward this end, the requisite advanced pyran intermediate **3** was envisioned to be constructed from a western hemisphere aldehyde (**4**) that would arise from commercially available (*R*)-(−)-Roche ester, and a carboxylic acid eastern hemisphere (**5**), comprising the C9–C24 fragment of the (−)-enigmazole A skeleton, which would be constructed via a three-component Type I ARC tactic. The oxazole-containing component **6** in turn would be elaborated via a Negishi cross-coupling[12] employing vinyl iodide **9** and commercially available chloride **10**.

We initiated the synthesis with construction of oxazole **6** for the eastern hemisphere (Scheme 3). Commercially available (*R*)-3-butyn-2-ol [(+)-**11**] was first subjected to a copper-catalyzed carbometalation/iodination reaction[13] followed by methylation to generate *Z*-olefin (+)-**12**. Subsequential Negishi coupling was then achieved via exploiting a finely tuned solvent system that permitted union of an in situ generated zincate with aryl chloride **10** to deliver the desired product (+)-**13** in 80% yield. Following a chelation controlled DIBAL reduction, the derived aldehyde (+)-**14** was subjected to Brown allylation to furnish homoallylic alcohol (+)-**15** with high diastereoselectivity (>20:1). Subsequent carbamation provided (+)-**16** that was submitted to a modified Bartlett iodocarbonate cyclization, via a protocol developed earlier in our laboratory,[14] to furnish iodocarbonate (+)-**17**. Treatment of the latter with potassium

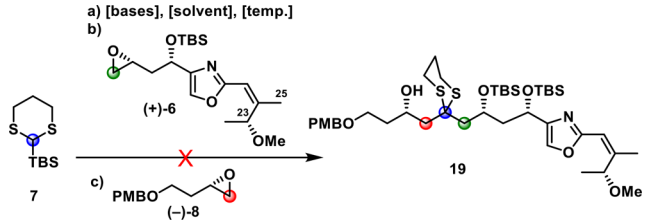
Scheme 3. Synthesis of (+)-Oxazole 6



carbonate in methanol then furnished the *β*-hydroxyl epoxide (+)-**18**, which was protected as the TBS silyl ether to yield the oxazole component (+)-**6** in near quantitative yield.

With the oxazole component (+)-**6** in hand, we next explored the three-component Type I ARC union of commercially available dithiane **7** with enantiomeric enriched epoxide (−)-**8**[15] (Scheme 4). Crucial factors that often dictate

Scheme 4. Initial Study of the Three-Component Type I ARC Union



the success of ARC transformations,[6] such as the solvent system (i.e., Et_2O, Et_2O/HMPA, THF, THF/HMPA, etc.), bases (*n*-BuLi, *t*-BuLi, *t*-BuLi/KO*t*-Bu, etc.), as well as various temperature regimes (−78 °C to rt), were extensively screened. The desired union product **19** however was not observed.

In the event, our typical ARC conditions (e.g., *n*-BuLi, HMPA, Et_2O, −78 °C to rt) resulted in an 80–90% recovery of epoxide (−)-**8**, in conjunction with a complex mixture of products that derive from vinyl oxazole (+)-**6**, presumably due to the acidic protons at C-23 and C-25. We therefore took advantage of one of the significant attributes of the ARC protocol, the ability to reverse the reactivity of the nucleophile and electrophile, recognizing that the oxazole ring might stabilize the requisite negative charge at C-17 and thus lead to the desired alkylation product (Scheme 5). This revision required a revised synthetic plan for the eastern hemisphere **5** to accommodate the acidic protons at the allylic positions.

To this end, disconnection at the C-16/17 junction of **5** would permit construction from the previously available aldehyde (+)-**14** upon conversion to the corresponding dithane **20** and epoxide **21**, again exploiting a three-component Type I ARC tactic with epoxides (−)-**22** and (−)-**23** as electrophiles and dithiane **7** as the nucleophile.

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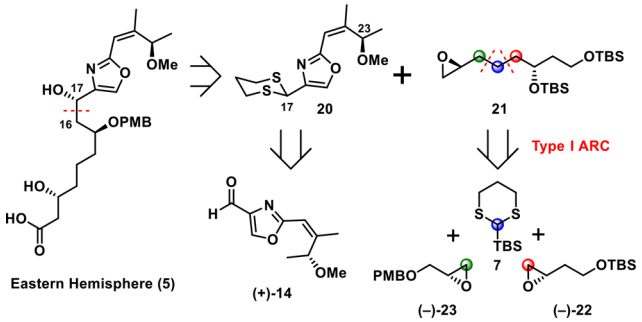
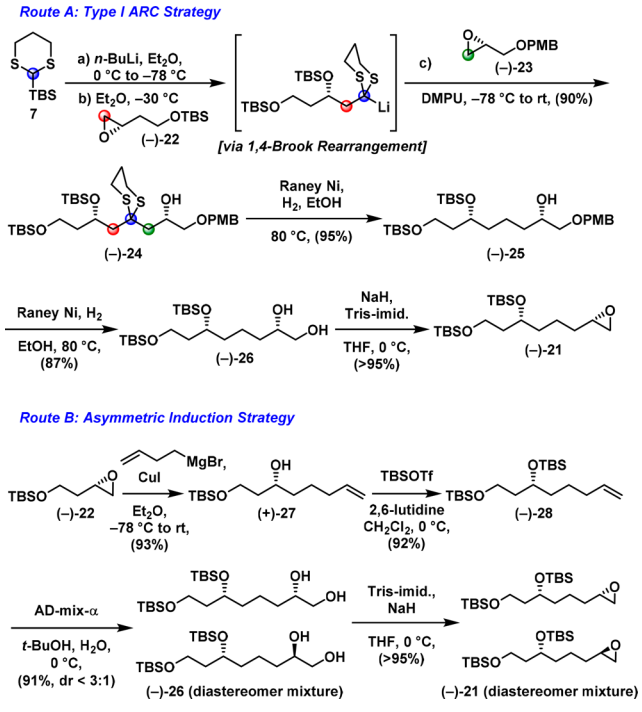
Scheme 5. Revised Retrosynthetic Analysis for the Eastern Hemisphere Intermediate 5



We began with construction of epoxide (−)-**21** (Scheme 6, route A). Deprotonation of dithiane **7** with *n*-BuLi in diethyl ether at 0 °C generated the dithiane anion, which upon addition of epoxide (−)-**22** followed by 1,4-Brook rearrangement triggered by increasing the temperature to −30 °C and addition of the second electrophile epoxide (−)-**23** in DMPU furnished the desired tricomponent adduct (−)-**24** in 90% yield as a single diastereomer. Importantly, this transformation could be carried out on up to the 10 g scale! The dithiane was then removed via Raney nickel hydrogenolysis to deliver (−)-**25**.

Scheme 6. Synthesis of the Epoxide Fragment 21

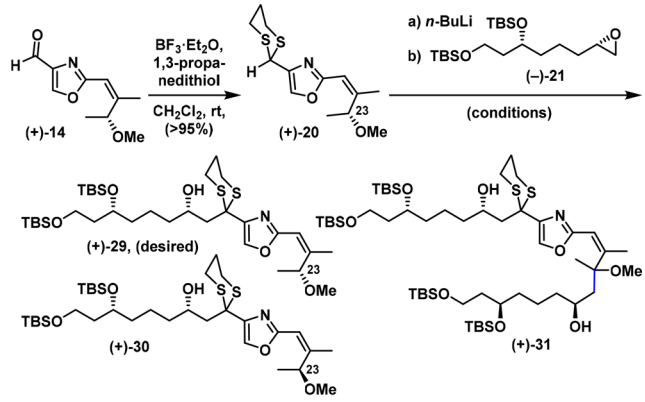


Interestingly, the 4-methoxybenzyl ether (PMB) protection remained intact. However, after purification, the same hydrogenolysis conditions permitted conversion to diol (−)-**26**. Possibly in the first hydrogenolysis the Raney nickel was poisoned by the sulfur from the dithiane. Epoxidation exploiting the one-step Fraser−Reid protocol[16] then furnished fragment (−)-**21** in high yield as a single diastereomer.

As demonstrated above, a major advantage of the ARC strategy is the efficient construction of multiple stereocenters in a fully stereocontrolled manner from simple enantiomeric enriched linchpins. In fact, an earlier devised route to epoxide fragment (−)-**21** (Scheme 6, route B) had resulted in a mixture of diastereomers.[17]

We next turned to construct oxazole **20** (Scheme 7). Aldehyde (+)-**14** was condensed with 1,3-propanedithiol to

Scheme 7. Installation of the Oxazole-Containing Fragment[a]



Entry	*n*-BuLi (eq.)	(–)-21 (eq.)	Conditions	Yield of (+)-29	Yield of (+)-30	Yield of (+)-31
1	1.5	1.5	Et_2O/HMPA, –78 °C	48%	12%	20%
2	1.5	1.5	Et_2O, –78 °C	60%	5%	12%
3	1.5	1.5	THF, –78 °C	32%	3%	--
4	1.5	1.5	Et_2O, –78 to 0 °C	45%	11%	10%
5	2.0	2.0	Et_2O, –78 °C	30%	15%	20%
6	1.0	1.5	Et_2O, –78 °C	42%	--	--
7	1.0	1.5	Et_2O, –78 to 0 °C	51%	--	--
8	1.15	1.5	Et_2O, –78 to 0 °C	73%	--	--
9	1.15	1.0	Et_2O, –78 to 0 °C	77%	--	--

[a]Reactions shown in the table were carried out on ca. 1 mmol scale.

provide dithiane (+)-**20** for the proposed alkylation with epoxide (−)-**21**. Initial attempts (entries 1−5) however only provided moderate yields of the desired union product (+)-**29**, accompanied by the C-23 allylic epimer (+)-**30**, along with the double-alkylated product (+)-**31**. We reasoned that the amount of *n*-BuLi was critical; excess would lead to deprotonation at the C-23 allylic proton and thus a second alkylation with the unreacted epoxide to give (+)-**31** as well as the undesired epimer (+)-**30**. Not surprisingly in our initial synthetic route (Scheme 3), more basic nucleophiles such as alkyl dithiane anions generated via a 1,4-Brook rearrangement had induced decomposition of the vinyl oxazole electrophile (+)-**6**. Pleasingly optimal reaction conditions were obtained upon screening such variables as the electrophile and *n*-BuLi stoichiometry, solvent, and reaction temperature regimes, to furnish the desired union product (+)-**29** in 77% yield (entry 9).

Continuing with the synthesis, application of the recently developed iron-mediated oxidative hydrolysis protocol[18] on dithiane (+)-**29** led to ketone (+)-**32** (Scheme 8), which in turn was submitted to the Narasaka−Prasad reduction[19] to provide diol (+)-**33** with high diastereoselectivity (single diastereomer, dr >20:1).

Next, upon formation of the PMP acetal (−)-**34** employing *p*-anisaldehyde dimethyl acetal and CSA, we were pleased to discover that DIBAL reduction led to the secondary alcohol (+)-**35** as a single isomer. Although more sterically hindered, the observed regioselectivity is likely the result of strong chelation of the α-oxygenated oxazole with the aluminum of the DIBAL, thereby permitting delivery of the hydride to the desired site. Following chemoselective formation of the primary TBS ether alcohol (+)-**36** with HF·Py, TEMPO-mediated

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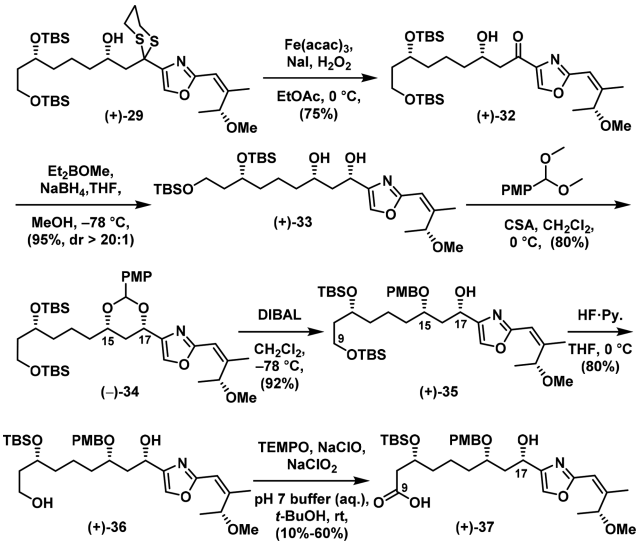
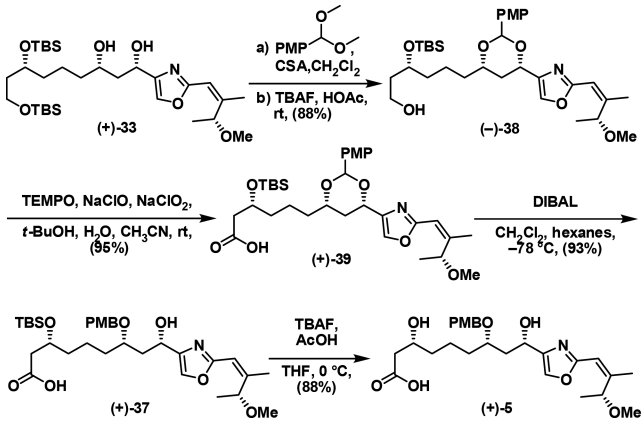
Scheme 8. Elaboration toward the Synthesis of the Eastern Hemisphere (5)



oxidation[20] provided carboxylic acid (+)-**37**, albeit with inconsistent efficiency likely due to competitive oxidation at the C-17 position.

To avoid this inconsistency/chemoselectivity issue, we adjusted the synthetic sequence (Scheme 9). Diol (+)-**33** was

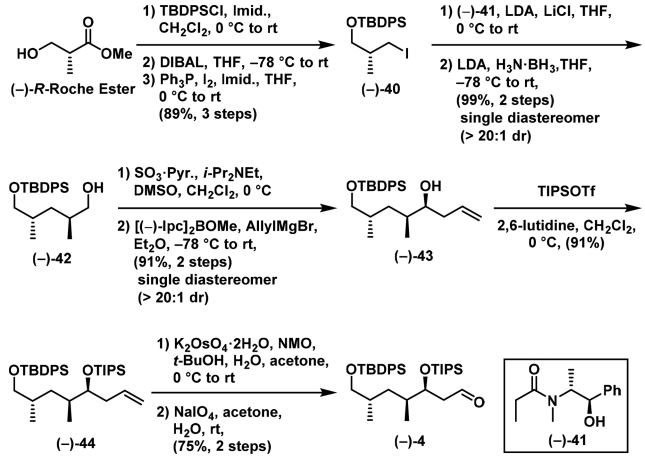
Scheme 9. Adjusted Synthetic Sequence to the Eastern Hemisphere (5)



first converted to the PMP acetal with removal of the TBS group in single flask operation to deliver alcohol (−)-**38** in 88% yield. Subsequent TEMPO-mediated oxidation now consistently led to carboxylic acid (+)-**39** in nearly quantitative yield. A chelation controlled regioselective reduction with DIBAL then permitted access to alcohol (+)-**37** with the carboxylic acid group intact, the latter due to the strength of the chelation of the α-oxygenated oxazole with aluminum hydride. Final deprotection then afforded the desired eastern hemisphere carboxylic acid (+)-**5**. The overall yield for this 12-step sequence was 27%.

We next initiated construction of the western hemisphere **4** (Scheme 10) with commercially available (−)-*R*-Roche ester, employing a three-step protection/reduction/iodination sequence[21] to produce iodide (−)-**40**, which in turn was employed in a two-step Myers alkylation/reduction protocol[22] exploiting pseudoephedrine amide (−)-**41** to furnish the 1,3-

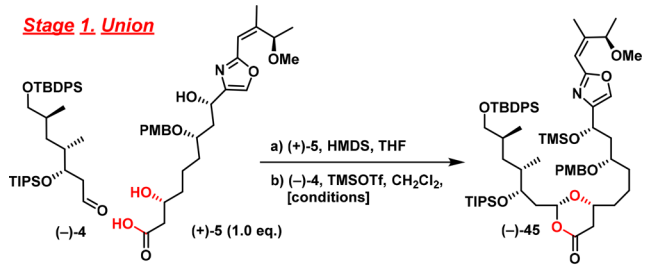
Scheme 10. Synthesis of the Western Hemisphere Fragment (4)



dimethyl alcohol (−)-**42** in near quantitative yield. The diastereoselectivity proved excellent (single diastereomer, dr >20:1). Following in turn a Parikh−Doering oxidation and a Brown allylation, olefin (−)-**43** was produced as a single diastereomer, which was then protected as the TIPS ether to give (−)-**44**. Osmium promoted dihydroxylation in conjugation with oxidative cleavage of the olefin ($NaIO_4$) completed construction of the requisite western hemisphere (−)-**4**.

With both late-stage intermediates (−)-**4** and (+)-**5** secure and readily available, we began exploring the critical strategic level transformation: a three-stage Petasis−Ferrier union/rearrangement to construct the entire carbon skeleton of (−)-engimazole A (**1**). At the outset, union of (−)-**4** and (+)-**5** (i.e., stage 1) employing our standard conditions of HMDS and TMSOTf[5] resulted in only a trace amount of the desired product (entry 1, Scheme 11), along with recovered starting material (−)-**4** and a mixture of silylated (+)-**5**. Increasing the reactivity by elevating the temperature proved detrimental (entries 2−5). However, during these trials, we occasionally obtained a dramatic increase in the yield (ca. 40−80%). This occurred when a frequently employed older sample of the

Scheme 11. Study on the Union Stage[a]



Entry	Temp.	(–)-4 (eq.)	Additives	Time	Recovery of (–)-4	Yield of (–)-45
1	–78 °C	1.35	--	8h	87%	5%
2	–40 °C	1.35	--	8h	80%	5%
3	–40 °C	2.0	--	8h	60%	5%
4	0 °C	1.35	--	2h	0%	10%
5	0 °C	2.0	--	2h	0%	trace
6	–78 °C	1.35	TfOH (0.3 eq.)	2h	0%	trace
7	–78 °C	1.35	TfOH (0.1 eq.)	2h	0%	16%
8	–78 °C	1.35	H_2O (0.25 eq.)	2h	0%	7%
9	–78 °C	1.35	H_2O (trace)	2h	10%	91%
10	–78 °C	1.17	H_2O (trace)	2h	0%	95%

[a]Reactions were carried out on ca. 0.1 mmol scale.

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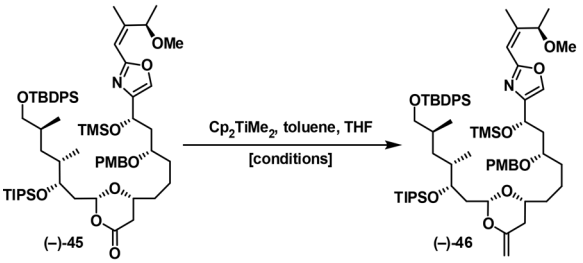
reagent TMSOTf was use. We reasoned that a trace amount of triflic acid in the TMSOTf reagent might facilitate the key union transformation. Such an observation had in fact occurred in our earlier (+)-zampanolide synthesis, where addition of a catalytic amount of TfOH significantly increased the yield, particularly for reactions on a larger scale.[23] In the current case, however, addition of a catalytic amount of TfOH was not profitable (0−16%, entries 6 and 7) with no starting material recovered! Careful NMR analysis of the reaction mixture (entry 6) suggested that the desired dioxanone moiety of (−)-**45** was in fact generated, albeit with removal of both the TMS and the PMB groups presumably due to the strong acidic character of TfOH. Eventually we discovered that introduction of a trace amount of water into the reaction mixture to mimic a frequently used source of TMSOTf dramatically increased the yield (ca. 95%) of (−)-**45** (entries 9 and 10), now in a controlled manner (see Experimental Section).[24]

With dioxanone (−)-**45** now available, we moved to stage 2 of our Petasis−Ferrier union/rearrangement (i.e., olefination; Scheme 12). Initial attempts utilizing 0.05 M Petasis reagent[25]

Scheme 12. Study on the Olefination Stage[a]



Entry	Cp_2TiMe_2 (Conc.)	Temp.	Time	Additives	Heating Conditions	Yield of (−)-46
1	0.05 M	70 °C	15h	2,6-lutidine	conventional	46%
2	0.125 M	70 °C	10h	2,6-lutidine	conventional	55%
3	0.125 M	70 °C	10h	2,6-lutidine, ethyl pivalate	conventional	53%
4	0.2 M	70 °C	10h	2,6-lutidine	conventional	51%
5	0.125 M	90 °C	4h	2,6-lutidine	microwave	72%
6	0.125 M	100 °C	3h	2,6-lutidine	microwave	87%
7	0.125 M	110 °C	3h	2,6-lutidine	microwave	78%

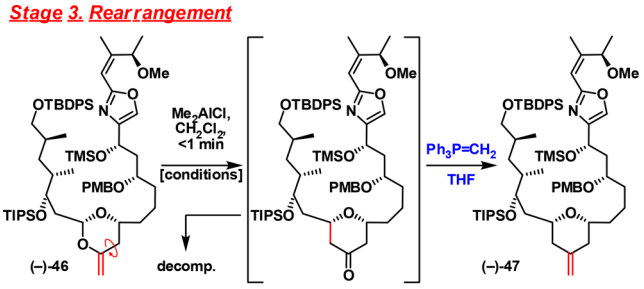
[a]Reactions were carried out on ca. 0.15 mmol scale.

led to enol acetal (−)-**46** in 40−50% yield (entry 1, Scheme 12). Further investigation indicated that the concentration of the Petasis reagent and precise heating (i.e., microwave irradiation) proved critical (entry 6), and as such furnished (−)-**46** in 87% yield.

Turning to stage 3 of the Petasis−Ferrier union/rearrangement protocol, we explored the use of Me_2AlCl, well-known in this venue[5] (Scheme 13, entries 1−7); unfortunately, only decomposition resulted presumably via a retro-Michael fragmentation.[26] Extensive experimentation proved uneventful; we were not able to isolate the desired, standard ketone product. We concluded however that the reaction sequence might proceed to advanced olefin (−)-**47**, via in situ capture of the rearranged/generated ketone with methylene ylide (PPh_3=CH).

Pleasingly under these conditions, an 84% yield of (−)-**47** was obtained for the third stage with complete stereocontrol.[5] The requisite three-stage Petasis−Ferrier union/rearrangement protocol had thus been demonstrated by utilizing highly functionalized late-stage synthetic intermediates (−)-**4** and (+)-**5**, in conjunction with the methyl ylide to deliver advanced

Scheme 13. Study on the Rearrangement Stage[a]



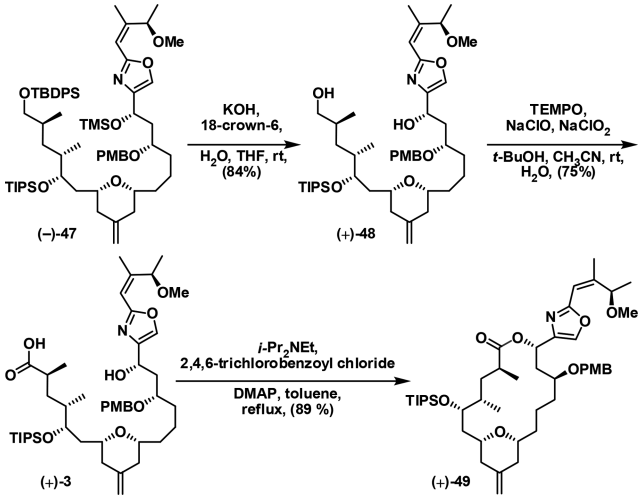
Entry	Temp.	Me_2AlCl	Additives	Quenching Method	Yield of (−)-47
1	0 °C	5.0 eq.	–	$NaHCO_3$ (aq.)	--
2	−78 °C	5.0 eq.	–	$NaHCO_3$ (aq.)	--
3	−78 °C	2.0 eq.	–	$NaHCO_3$ (aq.)	--
4	−30 °C	5.0 eq.	Cs_2CO_3	$NaHCO_3$ (aq.)	--
5	−78 °C	5.0 eq.	4Å MS	$NaHCO_3$ (aq.)	--
6	−78 °C	5.0 eq.	–	Et_3N	--
7	−78 °C	5.0 eq.	–	2,6-lutidine	--
8	−78 °C	5.0 eq.	–	Ph_3P=CH_2, THF	84%

[a]Reactions were carried out on ca. 0.05 mmol scale.

union product (−)-**47** in 69% overall yield with complete stereochemical control for (−)-enigmazole A (**1**).

With all eight stereocenters embedded in (−)-**47**, we advanced to the elaboration of (+)-**48** requiring removal of both the TBDPS and the TMS groups, and then macrocyclization (Scheme 14). Use of KOH/18-crown-6 in water

Scheme 14. Late-Stage Elaboration I of (−)-Enigmazole A



proved highly selective for the latter. The primary hydroxyl group was next oxidized chemoselectively to the carboxylic acid under TEMPO-mediated oxidation conditions to furnish seco-acid (+)-**3**. From initial trials with the Keck macrolactonization condition,[27] although providing the macrolactone (+)-**49**, the yield was only moderate (40−50%). Pleasingly the macrocyclization could be improved to 89% by applying the Yamaguchi protocol.[28]

The next critical issue was selective removal of the TIPS group to install the requisite phosphate group. Initial attempts with various deprotection conditions proved challenging (Scheme 15). Conditions such as HF/acetonitrile, TBAF, TASF, or TBAT in various solvents led to total decomposition, or to δ-lactone (−)-**50** obtained via intramolecular transesterification. The latter unfortunately could not be converted to the desired macrolactone **51** via treatment with various acids

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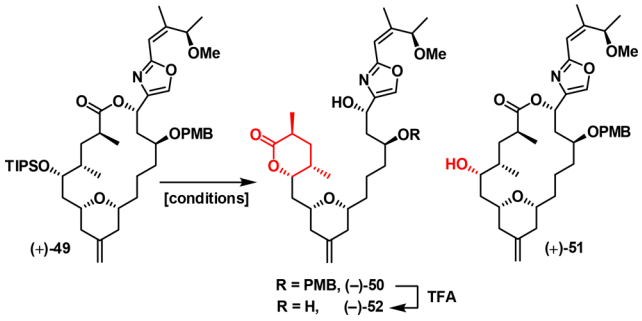
Scheme 15. Late-Stage Elaboration II of (−)-Enigmazole A[a]



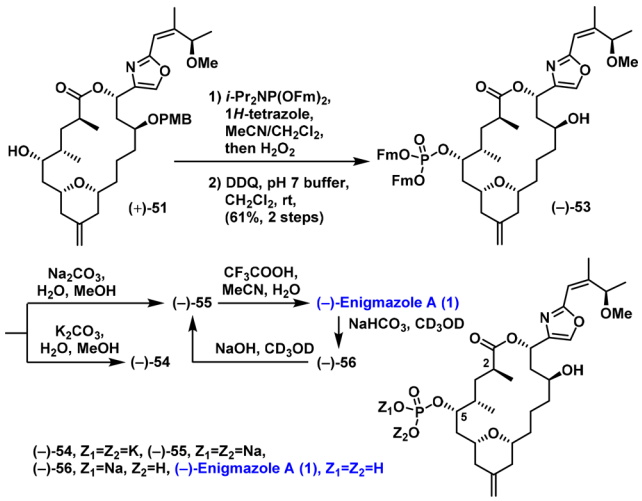
Conditions	Results[b]	Conditions	Results[b]
1. HF in MeCN	(−)-50	6. CSA in CH_2Cl_2	decomp.
2. TBAF/THF/AcOH	no reaction	7. HF/Py./THF (HF:Py. 1:1.5)	(−)-50
3. TBAF in THF	decomp.	8. HF/Py./THF (HF:Py. 1:6)	(−)-50 (+)-51, (70%)
4. TASF in DMF	(−)-50		
5. TBAT in CH_3CN	no reaction		

[a](a) Reactions were carried out on ca. 0.01 mmol scale. (b) Results were determined by NMR and isolation yields.

such as trifluoroacetic acid, but instead provided diol (−)-**52** upon removal of the PMB group. Eventually however we discovered that HF buffered with pyridine (entry 8) led to the successful selective removal of the TIPS group to generate (+)-**51** in 70% yield accompanied by only a small amount of (−)-**50** (<5%).

Turning to installation of the phosphate substituent, we employed the conditions of *i*-$Pr_2NP(OFm)_2$/1*H*-tetrazole on (+)-**51** (Scheme 16),[29] followed by DDQ removal of the PMB

Scheme 16. End Game of (−)-Enigmazole A



group to deliver the desired tertiary alcohol (−)-**53**. Final deprotection applying potassium carbonate then furnished the dipotassium phosphate of (−)-enigmazole A (−)-**54**. Surprisingly, multiple inconsistencies in the proton resonances were observed upon comparing the NMR spectrum of synthetic (−)-**54** with the natural product (e.g., H2 and H5, difference >0.11 ppm; see the Supporting Information). We reasoned that different ionic forms (i.e., sodium, potassium, mono- and bis-salt forms) of (−)-enigmazole A may result in different sets of ^{1}H NMR data. We thereby conducted ion exchange experiments in addition to acidification to furnish a series of salts [i.e., (−)-**54**, (−)-**55**, (−)-**56**, and (−)-enigmazole A (**1**)]. Eventually, we were able to determine that the monosodium phosphate of (−)-**56** displayed excellent agreement (^{1}H, ^{13}C, ^{31}P NMR spectra) with the previous reports from both Gustafson[8a] and Molinski.[8b] Thus, the total synthesis of (−)-enigmazole A (**1**) as well as a series of salts had been achieved.

SUMMARY

The total synthesis of the marine phosphomacrolide (−)-enigmazole A (**1**), along with the mono- and disodium phosphate salts, is reported. The overall yield was 4.4%, proceeding in a longest linear sequence of 22 steps from commercially available (*R*)-3-butyn-2-ol. Application of a late-stage Petasis−Ferrier union/rearrangement in conjunction with construction of advanced intermediates via multicomponent Type I Anion Relay Chemistry (ARC) proved highly effective for the total synthesis of (−)-enigmazole A (**1**). Further exploitation of the Petasis−Ferrier union/rearrangement and various ARC tactics continue in our laboratory.

EXPERIMENTAL SECTION

Materials and Methods. All chemicals were purchased from Sigma-Aldrich, Acros, or TCI America, unless otherwise referenced. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and toluene were acquired from a Pure Solve PS-400 system. Triethylamine, diisopropylamine, diisopropylethylamine, and DMPU were freshly distilled from calcium hydride under a nitrogen atmosphere. Commercial *n*-butyllithium (*n*-BuLi) and *tert*-butyllithium (*t*-BuLi) solutions were titrated by using diphenylacetic acid. All reactions that require anhydrous conditions were performed in oven- or flame-dried glassware under N_2 or Ar atmosphere. High vacuum (0.05 Torr) was created by using an oil pump (Nandor model 1400N). All reactions were stirred magnetically unless otherwise mentioned. Ice/water bath created 0 °C reaction temperature; dry ice/acetonitrile bath created −40 °C reaction temperature; dry ice/acetone bath created −78 °C reaction temperature. All yields refer to spectroscopically pure compounds unless otherwise mentioned. Microwave reactions were carried out in a Biotage Initiator microwave reactor with employed vials and septa caps purchased from Biotage (Microwave Reaction Kits), and the temperature was monitored with external surface sensor. Reactions were monitored by thin layer chromatography (TLC) with 250 mm precoated silica gel plates purchased from Silicycle Technology, and C18 silica gel thin layer chromatography (C18 TLC) with 100 mm precoated C18 silica gel plates purchased from Sorbent Technologies. Flash chromatography was conducted by using ACS grade solvents and silica gel, which was purchased from Silicycle Technology. Preparative thin layer chromatography (PTLC) was done with 500 or 1000 mm precoated silica gel plates purchased from Silicycle Technology. High-performance liquid chromatography (HPLC) was conducted by using Gilson 333/334 pumps equipped with a UV−vis dual wavelength detector and a C18 column (Vydac 5 μm C18, 250 × 10 mm). All melting points were obtained on a Thomas−Hoover apparatus and were uncorrected. All infrared spectra were recorded on a Jasco model FT/IR-480 Plus spectrometer. All optical rotations were measured on a Jasco P-2000 polarimeter. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on Bruker Avance III 500 MHz spectrometer equipped with either an Oxford cryomagnet or a Spectrospin/Bruker cryomagnet (500 MHz/52 mm) with a 5 mm dual cryo probe by using either 5 or 3 mm NMR tubes. All chemical shifts (δ, in ppm) reported were referred to chloroform (δ 7.26), benzene (δ 7.16), or methanol (δ 3.30) for ^{1}H NMR and chloroform (δ 77.23), benzene (δ 128.39), or methanol (δ 49.00) for ^{13}C NMR. High-resolution mass spectra (HRMS) were acquired either on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) or on a waters GCT Premier spectrometer at the University of Pennsylvania.

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Preparation of All New Compounds. *Compound (+)-**12**.* To a stirred solution of (*R*)-3-butyn-2-ol (+)-**11** (12.4 g, 177 mmol, 1.0 equiv) in dry toluene (330 mL) at room temperature under a nitrogen atmosphere was added CuI (17.4 g, 88.8 mmol, 0.5 equiv) portionwise. After complete addition, the temperature was decreased to −78 °C before the dropwise addition of MeMgBr solution (1.4 M in THF/toluene, 1:3, 456 mL, 638 mmol, 3.6 equiv) over 2 h. The reaction mixture then was warmed gradually to room temperature and stirred overnight. The reaction was quenched with the dropwise addition of I_2 solution (162 g of I_2 in 250 mL of THF, 638 mmol, 3.6 equiv) at −40 °C. The resulting mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (250 mL). The organic layer was removed, and the aqueous layer was extracted with diethyl ether (50 mL) twice. The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated carefully (volatile!), and the resulting oil was purified using a column chromatography (pentane/Et_2O, 5:1) to afford a hydroxyl vinyl iodide in a mixture with toluene (50 g). The mixture was moved to the next step without further purification. To a stirred suspension of NaH (24.0 g, 600 mmol, 60% in mineral oil, 3.4 equiv) in 250 mL of Et_2O at 0 °C under a nitrogen atmosphere was added slowly a solution of the hydroxyl vinyl iodide [50 g, mixture with toluene made from 177 mmol of (+)-**11**] in 100 mL of Et_2O. After complete addition, the temperature was increased to room temperature, and the reaction mixture was allowed to stir for 20 min before it was recooled to 0 °C. Methyl iodide (96.4 mL, 679 mmol, 3.8 equiv) was added dropwise, followed by very slow addition (over 40 min) of 15-crown-5 (30.5 g, 141 mmol, 0.8 equiv) at 0 °C. The resulted mixture was stirred overnight at room temperature and quenched at 0 °C by very careful addition of saturated aqueous NH_4Cl (100 mL over 1 h). The organic layer was removed, and the aqueous layer was extracted with diethyl ether (50 mL) twice. The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated carefully (volatile!), and the resulting oil was purified by reduced pressure distillation (80 °C at 5 mmHg) to give iodide (+)-**12** (30.7 g, 136 mmol, 76.8%, two steps) as a colorless liquid. $[\alpha]_D^{20}$ = +9.5 (*c* 2.2, $CHCl_3$); IR (film) 2979, 2927, 2900, 2819, 1654, 1443, 1370, 1338, 1281, 1206, 1145, 1115, 1098, 1031, 968, 866, 774, 655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.03 (d, *J* = 1.0 Hz, 1H), 4.27 (q, *J* = 6.5 Hz, 1H), 3.23 (s, 3H), 1.80 (d, *J* = 1.0 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 147.5, 80.9, 75.7, 56.5, 18.6, 18.0; high-resolution mass spectrum (CI) *m*/*z* 225.9852 [$(M)^+$ calcd for $C_6H_{11}IO$, 225.9855].

*Compound (+)-**13**.* To a solution of iodide (+)-**12** (19.0 g, 84.1 mmol, 1.0 equiv) in Et_2O (70 mL) under a nitrogen atmosphere at −78 °C was added *t*-BuLi (99 mL, 1.7 M in pentane, 168.0 mmol, 2.0 equiv) dropwise over 30 min. The resulting heterogeneous mixture was stirred for 1 h at the same temperature, then $ZnCl_2$ solution (100 mL, freshly prepared from solid flame-dried $ZnCl_2$, 1 M in THF, 100.0 mmol, 1.19 equiv) was added dropwise, and the reaction mixture was allowed to warm to room temperature over a 30 min period. At this point, pentane and diethyl ether were removed from the reaction under reduced pressure and nitrogen atmosphere. A solution of oxazolyl chloride **8** (14.9 g, 84.1 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (2.0 g, 1.73 mmol, 0.02 equiv) was separately prepared in THF (80 mL) and was added dropwise. The resulting mixture was vigorously stirred at reflux for 2 h, then cooled to room temperature and quenched by the addition of a saturated aqueous NH_4Cl solution (50 mL). The mixture was diluted with diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (30 mL) twice. The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 15:85, 20:80) to furnish ester (+)-**13** (16.1 g, 67.3 mmol, 80.0%) as a colorless oil. $[\alpha]_D^{20}$ = +43.9 (*c* 0.5, $CHCl_3$); IR (film) 2980, 1743, 1722, 1654, 1576, 1448, 1370, 1316, 1178, 1113, 1025, 839, 770 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ = 8.11 (s, 1H), 6.26 (s, 1H), 5.14 (q, *J* = 6.5 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.23 (s, 3H), 1.93 (d, *J* = 1.0 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.32 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ = 161.4, 161.0, 153.2, 142.8, 134.2, 112.7, 74.8, 61.2, 56.5, 19.4, 17.9, 14.4; high-resolution mass spectrum (ESI) *m*/*z* 262.1051 [$(M + Na)^+$ calcd for $C_{12}H_{17}NO_4Na$, 262.1055].

*Compound (+)-**14**.* A solution of ester (+)-**13** (9.00 g, 37.6 mmol, 1 equiv) in 200 mL of CH_2Cl_2 was treated with DIBAL-H (1 M in hexanes, 75.2 mL, 75.2 mmol, 2.0 equiv) at −78 °C under nitrogen atmosphere, followed by stirring at that temperature for 30 min. The resulted mixture was quenched with MeOH (20 mL) at −78 °C before it was warmed to room temperature. Saturated aqueous Rochelle's salt (80 mL) was then added, and the mixture was stirred vigorously for 1 h. The resulting mixture was diluted with 100 mL of diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (50 mL) twice. The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 15:85, 20:80) to furnish aldehyde (+)-**14** (6.35 g, 32.7 mmol, 87.0%) as a white solid. mp 55.0−57.0 °C; $[\alpha]_D^{20}$ = +25.2 (*c* 1.0, $CHCl_3$); IR (film) 2978, 2924, 1699, 1651, 1562, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.95 (s, 1H), 8.18 (s, 1H), 6.23 (s, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 3.24 (s, 3H), 1.94 (d, *J* = 1.5 Hz, 3H), 1.33 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 184.8, 161.5, 154.8, 143.0, 141.7, 112.2, 75.0, 56.8, 19.4, 18.1; high-resolution mass spectrum (ESI) *m*/*z* 196.0971 [$(M + H)^+$ calcd for $C_{10}H_{14}NO_3$, 196.0974].

*Compound (+)-**15**.* To a solution of (−)-*B*-methoxydiisopinocampheylborane (0.78 g, 2.47 mmol, 3.2 equiv) in Et_2O (10 mL) under argon atmosphere at −5 °C was added allylmagnesium bromide solution (2.1 mL, 1.0 M in Et_2O) dropwise via syringe over 10 min. The resulting mixture was allowed to warm to room temperature and was stirred for 1 h. This mixture was cooled to −78 °C, and a solution of aldehyde (+)-**14** (0.150 g, 0.77 mmol, 1.0 equiv) in Et_2O (3 mL) was added over 15 min. The reaction mixture was stirred at the same temperature for 3 h, and then MeOH (5 mL) was added. The mixture was allowed to warm to room temperature and treated with 0.2 N NaOH (1 mL) and 30% H_2O_2 (2 mL) (exothermic, use water bath). The mixture was stirred for 10 h, and the organic phase was separated. The aqueous part was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification using column chromatography (SiO_2, hexanes/EtOAc, 5:1) gave pure alcohol (+)-**15** (0.164 g, 0.69 mmol, 90.0%). $[\alpha]_D^{20}$ = +27.3 (*c* 1.0, $CHCl_3$); IR (film) 3407 (br), 3052, 2978, 2931, 2821, 1656, 1541, 1446, 1381, 1206, 1153, 1095, 973, 915, 861 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 0.6 Hz, 1H), 6.16 (dq, *J* = 1.4, 0.6 Hz, 1H), 5.81 (dddd, *J* = 17.0, 10.1, 7.1, 7.1 Hz, 1H), 5.14 (dddd, *J* = 17.0, 2.0, 1.4, 1.4 Hz, 1H), 5.12 (dq, *J* = 6.5, 0.6 Hz, 1H), 5.10 (dddd, *J* = 10.1, 2.0, 1.2, 1.2 Hz, 1H), 4.71−4.67 (m, 1H), 3.18 (s, 3H), 2.99 (d, *J* = 3.8 Hz, 1H), 2.62 (ddddd, *J* = 14.3, 7.1, 7.1, 1.4, 1.2 Hz, 1H), 2.53 (ddddd, *J* = 14.3, 7.1, 7.1, 1.4, 1.2 Hz, 1H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.28 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.4, 150.7, 143.8, 133.9, 133.1, 118.3, 113.3, 74.7, 66.4, 56.4, 40.8, 19.1, 17.5; high-resolution mass spectrum (ESI) *m*/*z* 260.1258 [$(M + Na)^+$ calcd for $C_{13}H_{19}NO_3Na$, 260.1263].

*Compound (+)-**16**.* To an ice-cold solution of alcohol (+)-**15** (3.04 g, 12.8 mmol, 1.0 equiv) in dry toluene (60 mL) was dropwise added *n*-BuLi (5.2 mL, 2.5 M in hexanes). After being stirred for 15 min, Boc_2O (3.10 g, 14.2 mmol, 1.1 equiv) was added, and stirring was continued for 2 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the organic phase was separated. The aqueous part was extracted with Et_2O (2 × 100 mL), and the combined organic extracts were dried and concentrated under reduced pressure. Flash chromatography of the residue on silica (hexanes/EtOAc, 20:1) gave 3.89 g (11.53 mmol, 90.1%) of the desired product as yellow oil. $[\alpha]_D^{20}$ = +2.5 (*c* 0.85, $CHCl_3$); IR (neat) 3052, 2979, 2932, 2819, 1741, 1644, 1546, 1449, 1369, 1280, 1254, 1163, 1095, 972, 919, 845, 791, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 0.8 Hz, 1H), 6.18 (dq, *J* = 1.4, 0.6 Hz, 1H), 5.76 (dddd, *J* = 17.0, 10.3, 7.1, 7.1 Hz, 1H), 5.62 (ddd, *J* = 7.1, 6.3, 0.8 Hz, 1H), 5.23 (dq, *J* = 6.5, 0.6 Hz, 1H), 5.16 (dddd, *J* = 17.0, 2.0, 1.4, 1.4 Hz, 1H), 5.07 (dddd, *J* = 10.3, 2.0, 1.0, 1.0 Hz, 1H), 3.21 (s, 3H), 2.78 (ddddd, *J* = 14.3, 6.3, 6.3, 1.4, 1.2 Hz, 1H), 2.71

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(ddddd, J = 14.3, 7.1, 7.1, 1.4, 1.2 Hz, 1H), 1.88 (d, J = 1.4 Hz, 3H), 1.47 (s, 9H), 1.29 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.3, 152.9, 151.0 139.9, 134.8, 132.8, 118.2, 113.2, 82.3, 74.7, 71.0, 56.3, 37.6, 27.8, 19.1, 17.6; high-resolution mass spectrum (ESI) m/z 338.1956 [$(M + H)^+$ calcd for $C_{18}H_{28}NO_5$, 338.1967].

*Compound (+)-**17**.* Iodine monobromide (20 mL, 10.0 equiv, 1.0 M in CH_2Cl_2) was slowly added dropwise to a solution of *tert*-butylcarbonate (+)-**16** (0.68 g, 2.0 mmol, 1.0 equiv) in dry toluene (20 mL) at −85 °C. After 24 h, the mixture was diluted with Et_2O and poured into a mixture of $NaHCO_3/Na_2S_2O_3$ aqueous solutions (1:1). After being stirred for 15 min, the organic phase was separated, and the inorganic part was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated. The crude material was purified using column chromatography on silica (hexanes/EtOAc, 1:1, R_f = 0.5) to give 0.45 g (1.11 mmol, 55.3%) of iodocarbonate (+)-**17**. $[\alpha]_D^{20}$ = +28.5 (c 1.2, $CHCl_3$); IR (film) 3052, 2977, 2930, 2819, 1749, 1653, 1540, 1447, 1383, 1241, 1186, 1112, 971, 856, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.65 (s, 1H), 6.17 (s, 1H), 5.49 (dd, J = 11.7, 3.0 Hz, 1H), 5.14 (q, J = 6.3 Hz, 1H), 4.60 (dddd, J = 11.7, 7.3, 4.0, 4.0 Hz, 1H), 3.44 (dd, J = 10.7, 4.4 Hz, 1H), 3.32 (dd, J = 10.7, 7.3 Hz, 1H), 3.21 (s, 3H), 2.75 (ddd, J = 14.5, 3.0, 3.0 Hz, 1H), 2.15 (ddd, J = 14.5, 11.7, 11.7 Hz, 1H), 1.90 (s, 3H), 1.3 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.9, 152.3, 147.6, 138.1, 134.7, 112.6, 77.2, 74.6, 73.0, 56.4, 32.5, 19.1, 17.6, 5.0; high-resolution mass spectrum (ESI) m/z 408.0302 [$(M + H)^+$ calcd for $C_{14}H_{19}INO_5$, 408.0308].

*Compound (+)-**18**.* A solution of iodocarbonate (+)-**17** (0.45 g, 1.1 mmol, 1.0 equiv) in dry methanol (7.5 mL) at room temperature was treated with potassium carbonate (0.51 g, 3.7 mmol, 3.4 equiv) and stirred for 2 h. The mixture was diluted with ether and quenched with saturated aqueous NH_4Cl. The aqueous layer was then extracted with Et_2O (3 × 50 mL), and the combined extracts were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. Column chromatography (hexanes/EtOAc, 1:1, R_f = 0.35) provided the desired epoxy alcohol (+)-**18** (0.24 g, 84%). $[\alpha]_D^{20}$ = +45.0 (c 0.5, $CHCl_3$); IR (film) 3433 (br), 3052, 2978, 2925, 2820, 1656, 1590, 1543, 1447, 1369, 1205, 1153, 1093, 971, 855 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 (d, J = 0.8 Hz, 1H), 6.18 (dq, J = 1.6, 0.8 Hz, 1H), 5.16 (dq, J = 6.5, 0.8 Hz, 1H), 4.95−4.88 (m, 1H), 3.19 (s, 3H), 3.1 (br s, 1H), 3.09 (dddd, J = 6.9, 4.2, 4.2, 2.8 Hz, 1H), 2.76 (dd, J = 5.0, 4.2 Hz, 1H), 2.55 (dd, J = 5.0, 2.8 Hz, 1H), 2.22 (ddd, J = 14.5, 4.6, 4.6 Hz, 1H), 1.93 (ddd, J = 14.5, 7.5, 6.9 Hz, 1H), 1.88 (d, J = 1.6, 3H), 1.31 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.6, 151.0, 143.7, 133.2, 113.2, 74.7, 65.7, 56.4, 49.9, 46.7, 39.0, 19.1, 17.6; high-resolution mass spectrum (ESI) m/z 276.1216 [$(M + H)^+$ calcd for $C_{13}H_{19}NO_4Na$, 276.1212].

*Compound (+)-**6**.* To an ice-cold solution of alcohol (+)-**18** (0.24 g, 0.95 mmol, 1.0 equiv) and triethylamine (0.58 mL, 0.42 g, 4.1 mmol) in DMF (10 mL) were added TBSCl (0.58 g, 3.85 mmol, 4.1 equiv) followed by DMAP (10 mg). The resulted mixture was stirred at room temperature overnight and then was poured into ice-cold saturated aqueous NH_4Cl, and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated under reduced pressure, and the residue was purified using flash chromatography on silica (hexanes/EtOAc, 5:1, R_f = 0.5) to give 0.34 g (0.93 mmol, 98%) of product (+)-**6**. $[\alpha]_D^{20}$ = +13.3 (c 1.35, $CHCl_3$); IR (film) 3052, 2953, 2929, 2888, 2857, 2820, 1654, 1592, 1541, 1472, 1447, 1362, 1255, 1206, 1153, 1097, 969, 872, 836, 778 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44 (d, J = 1.0 Hz, 1H), 6.17 (dq, J = 1.4, 0.6 Hz, 1H), 5.19 (dq, J = 6.5, 0.6 Hz, 1H), 4.90 (ddd, J = 5.8, 5.8, 1.0 Hz, 1H), 3.22 (s, 3H), 3.03 (dddd, J = 6.0, 6.0, 4.0, 2.8 Hz, 1H), 2.74 (dd, J = 5.0, 4.0, 1H), 2.49 (dd, J = 5.0, 2.8 Hz, 1H), 2.10 (ddd, J = 14.1, 6.0, 6.0 Hz, 1H), 1.91 (ddd, J = 14.1, 5.8, 5.8 Hz, 1H), 1.68 (d, J = 1.4 Hz, 3H), 1.28 (d, J = 6.5 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.2, 150.5, 144.9, 133.5, 113.4, 74.8, 66.9, 56.4, 49.3, 46.9, 40.5, 25.7, 19.5, 18.1, 17.6, −4.8, −5.0; high-resolution mass spectrum (ESI) m/z 368.2249 [$(M + H)^+$ calcd for $C_{19}H_{34}NO_4Si$, 368.2257].

*Compound (−)-**24**.* A solution of *tert*-butyl(1,3-dithian-2-yl)-dimethylsilane (4.12 g, 17.6 mmol, 1.2 equiv) in diethyl ether (30 mL) was treated dropwise with *n*-BuLi (7.70 mL, 19.3 mmol, 2.5 M in hexanes, 1.3 equiv) at 0 °C under a nitrogen atmosphere. The mixture was kept at 0 °C for 15 min, warmed to room temperature, and then stirred for 18 min before it was cooled to −78 °C. Epoxide (−)-**22** (4.00 g, 19.8 mmol, 1.35 equiv) in 40 mL of diethyl ether was added to the reaction mixture dropwise via a syringe followed by warming to −30 °C and stirring at that temperature for 2 h. The reaction mixture was cooled back to −78 °C, and the epoxide (−)-**24** (2.85 g, 14.7 mmol, 1.0 equiv) in 25 mL of diethyl ether and 5 mL of DMPU was added dropwise via a syringe. The reaction mixture was kept at −78 °C for 30 min and then slowly warmed to room temperature overnight without removing the bath. The resulting mixture was quenched with the addition of saturated aqueous NH_4Cl (20 mL) and diluted with diethyl ether (30 mL). The organic layer was removed, and the aqueous layer was extracted with diethyl ether (15 mL) twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 15:85, 20:80) to furnish dithiane (−)-**24** (8.30 g, 13.2 mmol, 89.8%) as a light yellow oil. $[\alpha]_D^{20}$ = −3.8 (c 4.0, $CHCl_3$); IR (film) 3466, 2954, 2928, 2856, 1613, 1514, 1471, 1250, 1097, 1038, 836, 775, 664 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.50 (s, 2H), 4.28−4.20 (m, 2H), 3.80 (s, 3H), 3.75−3.67 (m, 2H), 3.43 (dd, J = 4.5 Hz, 9.0 Hz, 1H), 3.39 (dd, J = 6.5 Hz, 9.0 Hz, 1H), 3.15 (s, 1H), 2.97−2.91 (m, 1H), 2.89−2.75 (m, 3H), 2.31 (m, 2H), 2.10 (m, 2H), 1.98 (m, 2H), 1.92 (m, 1H), 1.76 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.4, 130.4, 129.5, 112.9, 74.4, 73.0, 68.0, 67.6, 59.8, 55.4, 51.6, 47.1, 43.1, 42.2, 26.7, 26.3, 26.2, 26.1, 24.9, 18.3, 18.2, −3.6, −4.0, −5.1, −5.14; high-resolution mass spectrum (ESI) m/z 653.3168 [$(M + Na)^+$ calcd for $C_{31}H_{58}O_5S_2Si_2Na$, 653.3162].

*Compound (−)-**25**.* Commercially available Raney nickel (19.0 g with water, grade: Raney 2800 nickel from Aldrich) as a slurry in water was weighed into the 200 mL round-bottomed flask and washed with anhydrous ethanol (20 mL) three times under a nitrogen atmosphere. Dithane (−)-**24** (1.00 g, 1.59 mmol, 1.0 equiv) in 35 mL of ethanol was added via syringe to the slurry mixture before hydrogen gas was bubbled through for 20 min. The mixture was heated to 80 °C and kept at that temperature for 2.5 h with stirring under a hydrogen atmosphere before it was brought to room temperature. The liquid phase then was carefully transferred using a pipet to separate the desired product from residual flammable Raney nickel and washed with ethanol (15 mL) four times. The combined liquid was concentrated and purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 15:85, 20:80) to furnish alcohol (−)-**25** (0.79 g, 1.50 mmol, 94.5%) as a colorless oil. $[\alpha]_D^{20}$ = −4.1 (c 5.0, $CHCl_3$); IR (film) 3466, 2953, 2929, 2857, 1613, 1514, 1463, 1388, 1361, 1302, 1251, 1093, 1039, 836, 775, 664 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.25 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.48 (s, 2H), 3.80 (s, 3H), 3.80−3.75 (m, 2H), 3.64 (m, 2H), 3.47 (dd, J = 9.8 Hz, 2.8 Hz, 1H), 3.28 (t, J = 8.8 Hz, 1H), 2.31 (brs, 1H), 1.63 (q, J = 6.5 Hz, 2H) 1.55−1.30 (m, 6H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (s, 9H), 0.03(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.4, 130.2, 129.4, 113.9, 74.4, 73.0, 70.3, 69.2, 60.0, 55.2, 40.1, 37.5, 33.4, 26.1, 26.0, 21.2, 18.3, 18.2, −4.3, −4.5, −5.2; high-resolution mass spectrum (ESI) m/z 549.3394 [$(M + Na)^+$ calcd for $C_{28}H_{54}O_5Si_2Na$, 549.3407].

*Compound (−)-**26**.* Commercially available Raney nickel (9.0 g with water, grade: Raney 2800 nickel from Aldrich) as a slurry in water was weighed out into a 100 mL round-bottomed flask and washed with anhydrous ethanol (10 mL) three times under a nitrogen atmosphere. Alcohol (−)-**25** (0.50 g, 0.95 mmol, 1.0 equiv) in 25 mL of ethanol was added via syringe to the slurry mixture before hydrogen gas was bubbled through over 20 min. The mixture was heated to 80 °C and kept at that temperature for 15 h with stirring under a hydrogen atmosphere before it was allowed to attain room temperature. The liquid phase was transferred carefully using a pipet to separate it from residual flammable Raney nickel and washed with ethanol (8 mL) four times. The combined liquid was concentrated and purified by column chromatography (SiO_2, ethyl acetate/hexanes, 20:80, 30:70, 40:60) to furnish diol (−)-**26** (337 mg, 0.83 mmol, 87.3%) as a colorless oil.

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$[\alpha]_D^{20}$ = −7.5 (*c* 5.0, $CHCl_3$); IR (film) 3379, 2953, 2929, 2857, 1472, 1361, 1255, 1094, 938, 836, 774, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.81 (m, 1H), 3.71 (m, 1H), 3.70−3.63 (m, 3H), 3.43 (dd, *J* = 8.0 Hz, 11.0 Hz, 1H), 1.95−1.75 (brs, 2H), 1.65 (ddd, *J* = 2.3 Hz, 6.5 Hz, 11 Hz, 2H), 1.58−1.42 (m, 5H), 1.42−1.35 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 72.4, 69.3, 66.9, 60.2, 40.2, 37.5, 33.5, 26.2 (3C), 26.1 (3C), 21.3, 18.5, 18.3, −4.2, −4.4, −5.1; high-resolution mass spectrum (ESI) *m*/*z* 429.2844 [(M + Na)$^+$ calcd for $C_{20}H_{46}O_4Si_2Na$, 429.2832].

*Alternative Route for Compound (−)-**26** (Synthesis via Scheme 2, Route B).* To a solution of olefin (−)-**28** (4.70 g, 12.62 mmol, 1.0 equiv) in 80 mL of *t*-BuOH and 80 mL of water was added a mixture of $(DHQ)_2PHAL$ (500 mg, 0.642 mmol, 5 mol %), K_2CO_4 (5.23 g, 37.86 mmol, 3.0 equiv), $K_3Fe(CN)_6$ (12.50 g, 37.86 mmol, 3.0 equiv), and potassium osmate(VI) dehydrate (100 mg, 0.271 mmol, 2 mol %) at 0 °C. The reaction mixture was stirred for 10 h at 0 °C before it was diluted with ethyl acetate (200 mL). The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (50 mL) twice. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate:hexanes 20:90, 30:70) to furnish diol (−)-**26** with its diastereomer (4.66 g, 11.5 mmol, 91.0%) as a colorless oil. The product exists as a mixture of inseparable diastereomers with the same ^1H NMR spectra and slightly different ^{13}C NMR spectra.

*Compound (−)-**21**.* To a solution of diol (−)-**26** (1.57 g, 3.87 mmol, 1.0 equiv) in 40 mL of THF was added 223 mg of NaH (95 wt %, 8.83 mmol, 2.28 equiv) at 0 °C in nitrogen atmosphere, followed by stirring at room temperature for 20 min. The reaction mixture was then cooled to 0 °C, and solid TrisIm (1.54 g, 4.62 mmol, 1.2 equiv) was added in one portion. The resulting mixture was stirred for 1 h before it was quenched with the addition of 10 mL of saturated aqueous NH_4Cl and diluted with diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (15 mL) twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 5:95, 10:90) to furnish epoxide (−)-**21** (1.50 g, 3.86 mmol, quantitative) as a colorless oil. $[\alpha]_D^{20}$ = −10.3 (*c* 4.4, $CHCl_3$); IR (film) 2954, 2929, 2857, 1472, 1388, 1361, 1255, 1095, 1006, 938, 836, 774, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.83 (m, 1H), 3.71 (td, *J* = 6 Hz, 3.5 Hz, 2H), 2.90 (m, 1H), 2.75 (t, *J* = 4.5 Hz, 1H), 2.46 (dd, *J* = 5.2 Hz, 2.8 Hz, 1H), 1.65 (ddd, *J* = 11.0 Hz, 6.5 Hz, 2.3 Hz, 2H), 1.58−1.42 (m, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 69.1, 59.9, 52.3, 47.0, 40.1, 37.3, 32.8, 26.1, 26.0, 21.7, 18.4, 18.2, −4.3, −4.4, −5.2; high-resolution mass spectrum (ESI) *m*/*z* 411.2729 [(M + Na)$^+$ calcd for $C_{20}H_{44}O_3Si_2Na$, 411.2727].

*Compound (+)-**27**.* To a solution of epoxide (−)-**22** (1.80 g, 8.90 mmol, 1.0 equiv) and copper(I) iodide (0.70 g, 3.67 mmol, 0.41 equiv) in 30 mL of Et_2O at −78 °C under a nitrogen atmosphere was added a solution of but-3-en-1-ylmagnesium bromide (1 M in Et_2O, 26.7 mL, 26.7 mmol, 3.0 equiv) dropwise. After complete addition, the temperature was increased to room temperature, and the reaction mixture was continued to stir for 4 h before it was recooled to 0 °C. The resulting mixture was quenched at 0 °C by addition of saturated aqueous NH_4Cl (20 mL). The organic layer was removed, and the aqueous layer was extracted with diethyl ether (30 mL) twice. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate:hexanes 10:90, 15:85, 20:80) to furnish alcohol (+)-**27** (2.14 g, 8.28 mmol, 93.0%) as a colorless oil. $[\alpha]_D^{20}$ = +14.40 (*c* 1.40, $CHCl_3$); IR (film) 3443, 3077 2928, 2858, 1641, 1472, 1463, 1256, 1090, 1005, 910, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 5.77 (m, 1H), 4.97 (d, *J* = 17.0 Hz, 1H), 4.91 (d, *J* = 10.0 Hz, 1H), 3.86 (m, 1H), 3.78 (m, 2H), 3.44 (s, 1H), 2.04 (m, 2H), 1.61 (m, 2H), 1.48−1.60 (m, 2H), 1.39−1.48 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 139.0, 114.6, 72.1, 63.0, 38.5, 37.1, 33.9, 26.0, 25.0, 18.3, −5.39, −5.41; high-resolution mass spectrum (ESI) *m*/*z* 259.2088 [(M + H)$^+$ calcd for $C_{14}H_{31}O_2Si$, 259.2093].

*Compound (−)-**28**.* To a solution of alcohol (+)-**27** (3.70 g, 14.3 mmol, 1.0 equiv) in 80 mL of dichloromethane at 0 °C under a nitrogen atmosphere were added 2,6-lutidine (3.5 mL, 30.1 mmol, 2.1 equiv) followed by TBSOTf (4.0 g, 15.15 mmol, 1.06 equiv). The reaction mixture was stirred for 2 h at 0 °C before it was quenched by addition of saturated aqueous $NaHCO_3$ (20 mL). The organic layer was removed, and the aqueous layer was extracted with dichloromethane (20 mL) twice. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate:hexanes 2:98, 5:95, 10:90) to furnish olefin (−)-**28** (4.93 g, 13.2 mmol, 92.4%) as a colorless oil. $[\alpha]_D^{20}$ = −9.45 (*c* 3.00, $CHCl_3$); IR (film) 2956, 2928, 2858, 1472, 1256, 1094, 839, 833, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 5.80 (m, 1H), 5.00 (d, *J* = 17.0 Hz, 1H), 4.94 (d, *J* = 10.5 Hz, 1H), 3.81 (brs, 1H), 3.66 (m, 2H), 2.04 (d, *J* = 6.5 Hz, 2H), 1.65 (q, *J* = 6.0 Hz, 2H), 1.48−1.52 (m, 4H), 0.89 (s, 18H), 0.04 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 139.1, 114.6, 69.4, 60.2, 40.3, 37.1, 34.1, 26.18, 26.15, 24.7, 18.5, 18.3, −4.2, −4.4, −5.1; high-resolution mass spectrum (ES) *m*/*z* 373.2955 [(M + H)$^+$ calcd for $C_{20}H_{45}O_2Si_2$, 373.2958]

*Compound (+)-**20**.* A solution of aldehyde (+)-**14** (2.30 g, 11.7 mmol, 1.0 equiv) in 60 mL of CH_2Cl_2 was treated with 1,3-propanedithiol (1.75 mL 17.51 mmol, 1.5 equiv) and $BF_3{\cdot}OEt_2$ (0.55 mL, 4.08 mmol, 0.35 equiv), respectively, at 0 °C under a nitrogen atmosphere, followed by stirring at that temperature for 2 h. The resulting mixture was quenched by the addition of a 2 M NaOH aqueous solution (20 mL), and diluted with 30 mL of Et_2O. The organic layer was removed, and the aqueous layer was extracted with Et_2O (30 mL) twice. The combined organic layers were washed with the 2 M aqueous NaOH (15 mL) three times, saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 15:85, 20:80) to furnish dithiane (+)-**14** (3.21 g, 11.2 mmol, 96.1%) as an amorphous white solid. $[\alpha]_D^{20}$ = +43.7 (*c* 4.75, $CHCl_3$); IR (film) 2977, 2931, 2900, 2819, 1654, 1542, 1446, 1422, 1368, 1273, 1204, 1149, 1112, 1095, 971.0, 875, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.60 (s, 1H), 6.21 (s, 1H), 5.16 (q, *J* = 6.5 Hz, 1H), 5.13 (s, 1H), 3.23 (s, 3H), 3.06−2.95 (m, 4H), 2.17 (m, 1H), 2.01 (m, 1H), 1.89 (d, *J* = 1.5 Hz, 3H) 1.31 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.2, 151.1, 140.6, 134.4, 113.2, 74.7, 56.4, 41.3, 30.3, 25.3, 19.2, 17.6; high-resolution mass spectrum (ESI) *m*/*z* 286.0940 [(M + H)$^+$ calcd for $C_{13}H_{20}NO_2S_2$, 286.0935].

*Compound (+)-**29**.* To a solution of dithiane (+)-**20** (3.30 g, 11.6 mmol, 1.0 equiv) in 40 mL of Et_2O at −78 °C under a nitrogen atmosphere was added a solution of *n*-BuLi (2.30 M in hexanes, 5.79 mL, 13.3 mmol, 1.15 equiv) over a 5 min period. After complete addition, the reaction mixture was stirred for 20 min at −78 °C. Epoxide (−)-**21** (4.50 g, 11.57 mmol, 1.0 equiv) in 20 mL of Et_2O was added to the reaction mixture dropwise at the same temperature over 5 min. The resulting mixture was gradually allowed to come to 0 °C over 2 h before it was quenched by addition of saturated aqueous NH_4Cl (20 mL). The organic layer was removed, and the aqueous layer was extracted with Et_2O (30 mL) twice. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 15:85, 20:80, 30:70) to furnish dithiane (+)-**29** (6.01 g, 8.92 mmol, 77.0%) as a colorless oil. $[\alpha]_D^{20}$ = +16.0 (*c* 1.7, $CHCl_3$); IR (film) 2928, 2856, 1468, 1255, 1096, 836, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 6.21 (s, 1H), 5.11 (q, *J* = 6.5 Hz, 1H), 3.89 (brs, 1H), 3.78 (m, 1H), 3.64, (dd, *J* = 10.5 Hz, 6.5 Hz, 2H), 3.49 (s, 1H), 3.23 (s, 3H), 2.78−2.92 (m, 4H), 2.22−2.35 (m, 2H), 2.01 (m, 2H), 1.90 (s, 3H), 1.45 (m, 2H), 1.47−1.52 (m, 6H), 1.31 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.9, 152.1, 143.9, 136.5, 113.3, 75.1, 69.4, 68.5, 60.2, 56.8, 49.5, 40.2, 37.9, 37.7, 27.8, 27.6, 26.2, 26.1, 25.0, 21.4, 19.4, 18.5, 18.3, 17.9, −4.2, −4.4, −5.09, −5.10; high-resolution mass spectrum (ESI) *m*/*z* 674.3765

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[(M + H)$^+$ calcd for $C_{33}H_{64}NO_5S_2Si_2$, 674.3764]. In an earlier condition screening, side product (+)-**30** was inseparable from the desired product (+)-**29**. The approximate yield shown in Scheme 7 was calculated on the basis of crude NMR spectra. Side product (+)-**31** exists as a mixture of two inseparable diastereomers with multiple other minor side products. The structure was proposed on the basis of the absence of C-23 proton (5.1−5.2 ppm, q) in ^{1}H NMR spectra as well as high resolution mass spectra (ESI) *m*/*z* 1062.6581 [(M + H)$^+$ calcd for $C_{53}H_{108}NO_8S_2Si_4$, 1062.6593].

Note: Similar yield (75%−77%) was achieved when the reaction was carried out on ca. 1 mmol scale.

*Compound (+)-**32***. To a solution of dithiane (+)-**29** (2.55 g, 3.77 mmol, 1.0 equiv) in ethyl acetate (40 mL) and water (40 mL) were added $Fe(acac)_3$ (271 mg, 0.757 mmol, 0.2 equiv), sodium iodide (848 mg, 5.66 mmol, 1.5 equiv), and 30% hydrogen peroxide (1.3 mL aqueous solution, 11.31 mmol, 3.0 equiv) sequentially at 0 °C under an air atmosphere. The reaction mixture was stirred for 30 min at the same temperature before it was quenched by the addition of saturated aqueous $Na_2S_2O_3$. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) three times. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate:hexanes 15:85, 20:80, 30:70) to furnish ketone (+)-**32** (1.65 g, 2.83 mmol, 75.0%) as a colorless oil. $[\alpha]_D^{20}$ = +24.6 (*c* 1.4, $CHCl_3$); IR (film) 3465, 2928, 2856, 1686, 1562, 1463, 1386, 1255, 1096, 968, 836, 774, 664 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 1.5 Hz, 1H), 6.24 (s, 1H), 5.19 (q, *J* = 6.5 Hz, 1H), 4.19 (brs, 1H), 3.83 (brs, 1H), 3.67 (brs, 2H), 3.25 (s, 3H), 3.13 (d, *J* = 17.5 Hz, 2H), 3.01 (d, *J* = 17.5 Hz, 9.0 Hz, 1H), 1.95 (s, 3H), 1.66 (q, *J* = 6.0 Hz, 2H), 1.35−1.68 (m, 6H), 1.34 (dd, *J* = 6.5 Hz, 1.0 Hz, 3H), 0.891 (s, 9H), 0.887 (s, 9H), 0.05 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 196.1, 160.7, 154.2, 141.4, 141.2, 112.4, 75.1, 69.4, 67.9, 60.2, 56.8, 46.9, 40.2, 37.5, 37.2, 26.2, 26.1, 21.3, 19.4, 18.5, 18.3, 18.1, −4.2, −4.4, −5.1; high-resolution mass spectrum (ESI) *m*/*z* 584.3802 [(M + H)$^+$ calcd for $C_{30}H_{58}NO_6Si_2$, 584.3803].

*Compound (+)-**33***. To a solution of ketone (+)-**32** (1.70 g, 2.91 mmol, 1.0 equiv) in 30 mL of THF/MeOH (4:1) was added a solution of Et_2BOMe (1 M in THF, 6.11 mL, 6.11 mmol, 2.1 equiv) dropwise at −78 °C under a nitrogen atmosphere. After the reaction mixture was stirred for 15 min at the same temperature, $NaBH_4$ (250 mg, 6.58 mmol, 2.25 equiv) was added in one portion. The resulting mixture was stirred for 2 h before it was diluted by MeOH (20 mL). The temperature was then allowed to increase to 0 °C followed by the addition of saturated aqueous Rochelle's salt solution (30 mL). The resulting mixture was stirred at room temperature for 30 min before it was diluted by ethyl acetate (50 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) three times. The combined organic layers were washed with 2 M aqueous NaOH (20 mL) three times, saturated aqueous NH_4Cl (20 mL), and brine (20 mL), then dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 20:80, 30:70, 50:50) to furnish diol (+)-**33** (1.62 g, 2.76 mmol, 95.0%) as a colorless oil. $[\alpha]_D^{20}$ = +12.8 (*c* 1.0, $CHCl_3$); IR (film) 3388, 2929, 2857, 1655, 1472, 1363, 1255, 1095, 836, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.48 (s, 1H), 6.18 (s, 1H), 5.13 (q, *J* = 6.5 Hz, 1H), 4.93 (d, *J* = 7.0 Hz, 1H), 3.95 (brs, 1H), 3.81 (brs, 2H), 3.66 (brs, 2H), 3.21 (s, 3H), 3.13 (brs, 1H), 1.98 (d, *J* = 14.5 Hz, 1H), 1.88 (s, 3H), 1.86 (m, 1H), 1.64 (q, *J* = 6.0 Hz, 2H), 1.32−1.58 (m, 6H), 1.29 (dd, *J* = 6.5 Hz, 3H), 0.874 (s, 9H), 0.868 (s, 9H), 0.03 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.7, 151.1, 144.7, 133.1, 113.5, 75.0, 72.4, 69.4, 68.5, 60.2, 56.7, 43.0, 40.2, 38.5, 37.5, 26.2, 26.1, 21.0, 19.5, 18.5, 18.3, 17.9, −4.2, −4.4, −5.1; high-resolution mass spectrum (ESI) *m*/*z* 586.3953 [(M + H)$^+$ calcd for $C_{30}H_{60}NO_6Si_2$, 586.3959].

*Compound (−)-**34***. To a solution of diol (+)-**33** (610 mg, 1.04 mmol, 1.0 equiv) in 20 mL of dichloromethane was added CSA (20 mg, 0.086 mmol, 0.083 equiv) as one portion followed by addition of *p*-methoxybenzaldehyde dimethyl acetate (304 mg, 1.67 mmol, 1.60 equiv) at 0 °C under an air atmosphere. The resulting mixture was stirred for 20 min at the same temperature before it was quenched by saturated aqueous $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (10 mL) twice. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate:hexanes 5:95, 10:90, 20:80) to furnish PMP acetal (−)-**34** (585 mg, 0.83 mmol, 80.0%) as a colorless oil. $[\alpha]_D^{20}$ = −1.62 (*c* 0.77, $CHCl_3$); IR (film) 2929, 2856, 1616, 1518, 1463, 1362, 1251, 1097, 1037, 835, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.54 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 7.8 Hz, 2H), 6.21 (s, 1H), 5.65 (s, 1H), 5.17 (q, *J* = 6.5 Hz, 1H), 4.92 (d, *J* = 11.0 Hz, 1H), 3.93 (brs, 1H), 3.81 (brs, 1H), 3.80 (s, 3H), 3.66 (d, *J* = 3.5 Hz, 2H), 3.23 (s, 3H), 2.00 (d, *J* = 12.5 Hz, 1H), 1.89 (s, 3H), 1.73 (m, 2H), 1.65 (q, *J* = 6.0 Hz, 2H), 1.39−1.61 (m, 5H), 1.31 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 18H), 0.04 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.5, 160.1, 150.7, 142.5, 134.0, 131.4, 127.7, 113.8, 113.7, 101.1, 75.0, 73.1, 69.4, 60.2, 56.7, 55.5, 40.3, 37.6, 36.6, 36.3, 26.2, 26.1, 20.9, 19.5, 18.5, 18.3, 17.8, −4.2, −4.3, −5.1; high-resolution mass spectrum (ESI) *m*/*z* 704.4380 [(M + H)$^+$ calcd for $C_{38}H_{66}NO_7Si_2$, 704.4378].

*Compound (+)-**35***. To a solution of PMP acetal (−)-**34** (250 mg, 0.355 mmol, 1.0 equiv) in 10 mL of dichloromethane was added a DIBAL-H solution (1 M in hexanes, 1.24 mL, 1.24 mmol, 3.5 equiv) dropwise at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 100 min at the same temperature before it was quenched with MeOH at −78 °C. The temperature was then allowed to increase to 0 °C, at which point a saturated aqueous Rochelle's salt solution (10 mL) was added. The resulting mixture was stirred at room temperature for 30 min before it was diluted with ethyl acetate (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate: hexanes 10:90, 30:70) to furnish acid (+)-**35** (230 mg, 0.327 mmol, 92.0%) as a colorless oil. $[\alpha]_D^{20}$ = +27.72 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 1.0 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.19 (s, 1H), 5.16 (q, *J* = 6.5 Hz, 1H), 4.84 (d, *J* = 9.5 Hz, 1H), 4.61 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 9.0 Hz, 1H), 3.95 (s, 1H), 3.85−3.74 (m, 2H), 3.82 (s, 3H), 3.67 (m, 2H), 3.22 (s, 3H), 2.07 (dt, *J* = 11.0 Hz, 3.5 Hz, 1H), 1.93−1.89 (m, 1H), 1.89 (s, 3H), 1.65 (m, 4H), 1.51−1.37 (m, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H) 0.06 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.5, 159.6, 150.3, 144.9, 133.3, 130.2, 129.8, 114.2, 113.7, 79.5, 74.9, 70.6, 69.3, 68.3, 60.1, 56.6, 55.4, 41.1, 40.2, 37.9, 33.9, 26.11, 26.07, 20.3, 19.4, 18.4, 18.3 17.7, −4.2, −4.4, −5.1; high-resolution mass spectrum (ESI) *m*/*z* 706.4501 [(M + H)$^+$ calcd for $C_{38}H_{68}NO_7Si_2$, 706.4534].

*Compound (+)-**36***. To a solution of alcohol (+)-**35** (227 mg, 0.322 mmol, 1.0 equiv) in 5 mL of THF in a 50 mL plastic container was added 4.7 mL of the mixture of HF-pyridine complex/pyridine/THF (1:1.5:2.5) dropwise at 0 °C. The reaction mixture was allowed to stir at the same temperature for 45 min before it was slowly quenched by saturated aqueous $NaHCO_3$. After dilution with ethyl acetate (20 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate:hexanes 20:80, 30:70, 40:60) to furnish diol (+)-**36** (152 mg, 0.258 mmol, 80.0%) as a colorless oil. $[\alpha]_D^{20}$ = +21.11 (*c* 1.33, $CHCl_3$); IR (film) 3407, 2929, 2856, 1613, 1514, 1250, 1095, 1036, 856, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.19 (s, 1H), 5.16 (q, *J* = 6.5 Hz, 1H), 4.83 (dd, *J* = 8.9 Hz, 2.9 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.02−3.92 (m, 2H), 3.79 (s, 3H), 3.78 (m, 2H), 3.72 (m, 1H), 3.21 (s, 3H), 2.07 (dt, *J* = 11.0 Hz, 3.5 Hz, 1H), 1.92 (m, 1H), 1.88 (s, 3H), 1.77 (m, 1H), 1.55 (m, 2H), 1.63 (m, 4H), 1.38 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.5, 159.6, 150.4, 144.8, 133.3, 130.2, 129.7, 114.2, 113.7, 79.0, 74.9, 71.5, 70.6, 67.9, 60.2, 56.6, 55.4, 41.0, 38.1, 37.3, 33.8, 26.0, 20.5, 19.4, 18.1, 17.7,

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−4.2, −4.5; high-resolution mass spectrum (ES) *m*/*z* 592.3652 [(M + H)$^+$ calcd for $C_{32}H_{54}NO_7Si$, 592.3670].

*Compound (−)-**38***. To a solution of diol (+)-**33** (790 mg, 1.35 mmol, 1.0 equiv) in 20 mL of dichloromethane was added CSA (30 mg, 0.13 mmol, 0.096 equiv) in one portion followed by addition of *p*-methoxybenzaldehyde dimethyl acetate (345 mg, 1.89 mmol, 1.4 equiv) at 0 °C under an air atmosphere. The resulting mixture was stirred for 10 min at the same temperature before addition of TBAF (1.0 M in THF, 10.80 mL, 10.80 mmol, 8.0 equiv) and acetic acid (473 mg, 6.75 mmol, 5.0 equiv). The resulting mixture was allowed to increase to room temperature and was allowed to stir for 16 h before it was quenched with brine. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 5:95, 10:90, 20:80) to furnish alcohol (−)-**38** (700 mg, 1.19 mmol, 88.0%) as a colorless oil. $[\alpha]_D^{20}$ = −3.4 (*c* 1.6, $CHCl_3$); IR (film) 3435, 2929, 2856, 1615, 1518, 1463, 1368, 1336, 1250, 1171, 1112, 1035, 835, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.54 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 7.8 Hz, 2H), 6.20 (s, 1H), 5.64 (s, 1H), 5.17 (q, *J* = 6.5 Hz, 1H), 4.92 (d, *J* = 11.0 Hz, 1H), 3.93 (brs, 2H), 3.81 (brs, 1H), 3.80 (s, 3H), 3.72 (brs, 1H), 3.22 (d, *J* = 1.0 Hz, 3H), 2.34 (brs, 1H), 2.00 (d, *J* = 12.8 Hz, 1H), 1.89 (s, 3H), 1.81 (m, 1H), 1.75 (m, 1H), 1.68 (m, 2H), 1.58 (m, 4H), 1.42 (m, 1H), 1.30 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.5, 160.1, 150.6, 142.4, 133.9, 131.2, 127.6, 113.7, 113.6, 101.1, 76.8, 74.8, 72.9, 71.6, 60.3, 56.6, 55.4, 38.0, 36.9, 36.5, 36.1, 26.0, 21.0, 19.4, 18.1, 17.7, −4.3, −4.5; high-resolution mass spectrum (ESI) *m*/*z* 590.3506 [(M + H)$^+$ calcd for $C_{32}H_{52}NO_7Si$, 590.3513].

*Compound (+)-**39***. To a solution of alcohol (−)-**38** (184 mg, 0.312 mmol, 1.0 equiv) in 2.5 mL of *t*-BuOH and 0.25 mL of pH 7 buffer solution was added TEMPO solution (0.025 M in CH_3CN, 5 mL, 0.125 mmol, 0.4 equiv) at room temperature under an air atmosphere. The resulting mixture was stirred for 20 min at the same temperature before the subsequent addition of $NaClO_2$ (1 M in water, 0.624 mL, 0.624 mmol, 2.0 equiv) and NaClO (0.025 M in water, 12.5 mL, 0.312 mmol, 1.0 equiv) solution. The reaction was stirred at room temperature for 3 h before it was quenched by saturated aqueous Na_2SO_3 (10 mL). After dilution with ethyl acetate (20 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 5:95, 10:90, 20:80, 30:70) to furnish carboxylic acid (+)-**39** (184 mg, 0.296 mmol, 95.0%) as a colorless oil. $[\alpha]_D^{20}$ = +4.8 (*c* 1.0, $CHCl_3$); IR (film) 2930, 1711, 1518, 1250, 1114, 834, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.23 (s, 1H), 5.64 (s, 1H), 5.15 (q, *J* = 6.5 Hz, 1H), 4.93 (d, *J* = 10.5 Hz, 1H), 4.14 (t, *J* = 5.4 Hz, 1H), 3.93 (brs, 1H), 3.80 (s, 3H), 3.23 (s, 3H), 2.50 (d, *J* = 6.1 Hz, 2H), 2.00 (d, *J* = 12.8 Hz, 1H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.72 (m, 1H), 1.70 (m, 1H), 1.59 (m, 4H), 1.45 (brs, 1H), 1.30 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.4, 160.5, 160.0, 150.8, 142.3, 134.0, 131.2, 127.6, 113.7, 113.6, 101.1, 76.7, 75.0, 72.8, 69.4, 56.6, 55.4, 42.1, 37.4, 36.4, 36.0, 25.9, 20.8, 19.4, 18.1, 17.7, −4.4, −4.7; high-resolution mass spectrum (ESI) *m*/*z* 626.3118 [(M + Na)$^+$ calcd for $C_{32}H_{49}NO_8SiNa$, 626.3125].

*Compound (+)-**37***. To a solution of PMP acetal (+)-**39** (1.25 g, 2.07 mmol, 1.0 equiv) in 50 mL of dichloromethane was added a DIBAL-H solution (1 M in hexanes, 9.93 mL, 9.93 mmol, 4.8 equiv) dropwise at −78 °C under nitrogen atmosphere. The resulting mixture was stirred for 100 min at the same temperature before it was quenched with MeOH at −78 °C. The temperature was then allowed to increase to 0 °C followed by the addition of saturated aqueous Rochelle's salt (30 mL). The resulting mixture was stirred at room temperature for 30 min before it was diluted by ethyl acetate (50 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (30 mL) six times. The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 20:80, 30:70, 50:50, 80:20) to furnish carboxylic acid (+)-**37** (1.17 g, 1.93 mmol, 93.0%) as a colorless oil. $[\alpha]_D^{20}$ = +32.4 (*c* 1.0, $CHCl_3$); IR (film) 2930, 1712, 1514, 1245, 1096, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.19 (s, 1H), 5.11 (q, *J* = 6.5 Hz, 1H), 4.83 (dd, *J* = 9.5 Hz, 2.9 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.12 (m, 1H), 3.79 (s, 3H), 3.75 (m, 1H), 3.21 (s, 3H), 2.28 (d, *J* = 6.1 Hz, 2H), 2.05 (dt, *J* = 11.0 Hz, 3.5 Hz, 1H), 1.95 (m, 1H), 1.88 (s, 3H), 1.73 (m, 2H), 1.67 (m, 2H), 1.42 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.9, 160.7, 159.6, 150.8, 144.6, 133.5, 130.2, 129.8, 114.2, 113.6, 78.8, 75.0, 70.7, 69.4, 67.6, 56.6, 55.5, 42.2, 40.8, 37.7, 33.6, 26.0, 20.3, 19.5, 18.2, 17.8, −4.3, −4.6; high-resolution mass spectrum (ESI) *m*/*z* 606.3466 [(M + H)$^+$ calcd for $C_{32}H_{52}NO_8Si$, 606.3462].

*Alternative Route for Compound (+)-**37** (Scheme 5)*. To a solution of diol (+)-**36** (58 mg, 0.098 mmol, 1.0 equiv) in 0.775 mL of *t*-BuOH and 0.5 mL of pH 7 buffer solution was added a TEMPO solution (0.025 M in CH_3CN, 1.18 mL, 0.029 mmol, 0.3 equiv) at room temperature. The resulting mixture was stirred for 20 min at the same temperature before the subsequent addition of $NaClO_2$ (1 M in water, 0.196 mL, 0.196 mmol, 2.0 equiv) and NaClO (0.025 M in water, 4.0 mL, 0.1 mmol, 1.0 equiv). The reaction was stirred at room temperature for 3 h before it was quenched with saturated aqueous Na_2SO_3 solution (5 mL). After dilution with ethyl acetate (10 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate:hexanes 20:80, 30:70, 50:50, 80:20) to furnish acid (+)-**37** (36 mg, 0.059 mmol, 60.0%) as a colorless oil. (Note: The yield for this TEMPO oxidation is not always reproducible due to competitive oxidation at the C-17 position.)

*Compound (+)-**5***. To a solution of carboxylic acid (+)-**37** (800 mg, 1.32 mmol, 1.0 equiv) in 30 mL of THF was added TBAF (1.0 M in THF, 9.24 mL, 9.24 mmol, 7.0 equiv) dropwise followed by acetic acid (400 mg, 6.60 mmol, 5.0 equiv) at room temperature. The resulting mixture was stirred for 8 h before it was quenched with brine. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) six times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 50:50, 80:20 then ethyl acetate:acetic acid 99:1) to furnish β-hydroxy acid (+)-**5** (569 mg, 1.16 mmol, 87.7%) as a colorless oil. $[\alpha]_D^{20}$ = +56.2 (*c* 1.47, $CHCl_3$); IR (film) 3421, 2934, 1719, 1612, 1514, 1443, 1249, 1177, 1094, 1035, 822 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.21 (s, 1H), 5.03 (q, *J* = 6.5 Hz, 1H), 4.86 (dd, *J* = 9.3 Hz, 2.6 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.04 (brs, 1H), 3.80 (s, 3H), 3.75 (brs, 1H), 3.21 (s, 3H), 2.50 (m, 2H), 2.13 (d, *J* = 14.3 Hz, 1H), 1.89 (m, 1H), 1.89 (s, 3H), 1.72 (m, 1H), 1.63 (m, 1H), 1.38−1.58 (m, 4H), 1.29 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.1, 160.9, 159.5, 151.5, 144.2, 133.8, 130.2, 129.7, 114.1, 113.2, 79.1, 75.1, 70.5, 68.0, 67.4, 56.6, 55.4, 41.4, 40.7, 36.8, 33.3, 21.0, 19.5, 17.8; high-resolution mass spectrum (ESI) *m*/*z* 490.2440 [(M − H)$^-$ calcd for $C_{26}H_{36}NO_8$, 490.2441].

*Compound (−)-**42***. To a suspended solution of diisopropylamine (7.81 g, 77.2 mmol, 4.3 equiv) and flame-dried LiCl (9.59 g, 226 mmol, 12.6 equiv) in 80 mL of THF was added a *n*-BuLi solution (2.33 M in hexanes, 30.8 mL, 71.8 mmol, 4.0 equiv) dropwise over 15 min at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 10 min at the same temperature before it was cooled to −78 °C. To the resulting mixture was then added amide (−)-**41** (8.35 g, 37.7 mmol, 2.1 equiv) in 80 mL of THF dropwise at −78 °C over 30 min. The reaction mixture was then warmed to room temperature before the addition of iodide (−)-**40** (7.87g, 18.0 mmol, 1.0 equiv) in 30 mL of THF over 20 min. The resulting mixture was stirred overnight at room temperature before it was quenched by saturated

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aqueous NH_4Cl (30 mL) and diluted by EtOAc (200 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (50 mL) twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate:hexanes 90:10, 80:20, 60:40) to furnish the amide with a small amount of (−)-**41** derived impurity as an amorphous solid. The mixture was moved to the next step without further purification. To a solution of diisopropylamine (10.6 mL, 75.4 mmol, 4.2 equiv) in 60 mL of THF was added a *n*-BuLi solution (2.33 M in hexanes, 30 mL, 70.0 mmol, 3.9 equiv) dropwise over 10 min at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 15 min at the same temperature before the addition of ammonium-borane solid (2.22 g, 71.8 mmol, 4.0 equiv) in one portion at 0 °C. The temperature was increased to room temperature, and the reaction mixture was stirred for 30 min before it was recooled to 0 °C. A solution of the amide [made from 18.0 mmol of iodide (−)-**40**] in 90 mL of THF was then added dropwise, and the temperature was allowed to increase to room temperature after the addition. The resulting mixture was stirred at the same temperature for 2 h before it was slowly quenched with 100 mL of 3 N HCl aqueous solution over 20 min at 0 °C. The resulting mixture was stirred at 0 °C for a further 30 min before the dilution with Et_2O (200 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (50 mL) twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 90:10, 80:20, 60:40) to furnish alcohol (−)-**42** (6.60 g, 17.81 mmol, 99.2% over two steps) as a colorless oil. $[\alpha]_D^{20} = -15.7$ (*c* 3.2, $CHCl_3$); IR (film) 3342, 2929, 2857, 1417, 1427, 1389, 1112, 1036, 824, 740, 701, 613.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.72−7.65 (m, 4H), 7.45−7.35 (m, 6H), 3.52−3.47 (m, 3H), 3.40 (m, 1H), 1.79 (m, 1H), 1.70 (m, 1H), 1.22 (ddd, *J* = 13.5 Hz, 9.0 Hz, 4.0 Hz, 1H), 1.14 (ddd, *J* = 13.5 Hz, 9.0 Hz, 4.5 Hz, 1.0H), 1.08 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 135.8, 134.3, 134.2, 129.7, 127.8, 68.8, 69.2, 37.0, 33.31, 33.26, 27.1, 19.5, 16.8, 16.6; high-resolution mass spectrum (ESI) *m*/*z* 371.2390 [(M + H)$^+$ calcd for $C_{23}H_{35}O_2Si$, 371.2406].

*Compound (−)-**43**.* To a solution of alcohol (−)-**42** (6.50 g, 17.5 mmol, 1.0 equiv) in 70 mL of dichloromethane were added diisopropylethylamine (9.15 mL, 52.5 mmol, 3.0 equiv) and DMSO (6.21 mL, 87.5 mmol, 5.0 equiv) followed by portionwise addition of SO_3·pyridine (8.36 g, 52.5 mmol, 3.0 equiv) at 0 °C under an air atmosphere. The resulting mixture was stirred for 1 h at the same temperature before it was quenched by 2 M $NaHSO_4$ aqueous solution (30 mL). The organic layer was separated, and the aqueous phase was extracted with Et_2O (50 mL) twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting aldehyde was moved to the next step as a colorless oil without further purification. To a solution of (−)-*B*-methoxydiisopinocampheylborane (9.41 g, 29.8 mmol, 1.7 equiv) in 50 mL of Et_2O was added allylmagnesium bromide solution (1.0 M in Et_2O, 21.87 mL, 21.87 mmol, 1.25 equiv) dropwise over 20 min at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 1 h at the same temperature. The temperature was allowed to increase to room temperature, and the reaction mixture was stirred for 1 h before it was recooled to −78 °C. A solution of corresponding aldehyde of alcohol (−)-**42** (17.5 mmol, 1.0 equiv, crude) in 35 mL of Et_2O was then added dropwise to the reaction mixture at −78 °C over 20 min. The resulting mixture was stirred at the same temperature for 1 h before the temperature was allowed to increase to 0 °C. A pH 7 buffer solution (30 mL) was then added followed by the careful addition of 30% aqueous H_2O_2 (7 mL) over 20 min at 0 °C. The resulting mixture was then stirred at room temperature overnight before it was diluted by Et_2O. The organic layer was separated, and the aqueous phase was extracted with Et_2O (60 mL) twice. The combined organic layers were washed with saturated aqueous NaS_2O_3 (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 10:90, 20:80, 30:70) to furnish olefin (−)-**43** (6.53 g, 15.93 mmol, 91.0% over two steps) as a colorless oil. $[\alpha]_D^{20} = -13.4$ (*c* 2.86, $CHCl_3$); IR (film) 3325, 3071, 2959, 2930, 2858, 1709, 1640, 1589, 1471, 1428, 1389, 1112, 914, 824, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.68−7.62 (m, 4H), 7.41−7.31 (m, 6H), 5.81 (dddd, *J* = 17.5 Hz, 9.7 Hz. 7.2 Hz, 6.5 Hz, 1H), 5.18−5.08 (m, 2H), 3.53−3.48 (m, 3H), 2.31−2.25 (m, 1H), 2.15 (m, 1H), 1.76 (brs, 1H), 1.62 (brs, 1H), 1.35−1.25 (m, 1H), 1.21−1.11 (m, 1H), 1.07 (s, 9H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 135.9, 135.7, 134.29, 134.27, 129.7, 127.8, 118.0, 74.7, 69.8, 39.2, 36.8, 35.3, 33.4, 27.1, 19.5, 16.7, 14.1; high-resolution mass spectrum (ESI) *m*/*z* 411.2717 [(M + H)$^+$ calcd for $C_{26}H_{39}O_2Si$, 411.2719].

*Compound (−)-**44**.* To a solution of olefin (−)-**43** (1.03 g, 2.51 mmol, 1.0 equiv) in 20 mL of dichloromethane at 0 °C under a nitrogen atmosphere was added 2,6-lutidine (0.7 mL, 6.02 mmol, 2.4 equiv), followed by the dropwise addition of TIPSOTf (0.80 g, 3.01 mmol, 1.2 equiv). The reaction mixture was stirred for 2 h at 0 °C before it was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The organic layer was removed, and the aqueous layer was extracted with dichloromethane (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 2:98, 5:95, 10:90) to furnish olefin (−)-**44** (1.29 g, 2.28 mmol, 90.7%) as a colorless oil. $[\alpha]_D^{20} = -10.0$ (*c* 2.22, $CHCl_3$); IR (film) 3072, 2942, 2865, 1463, 1428, 1388, 1112, 882, 824, 784, 701, 678, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.71−7.68 (m, 4H), 7.43−7.36 (m, 6H), 5.78 (dddd, *J* = 17.2 Hz, 9.8 Hz, 7.2 Hz, 6.5 Hz, 1H), 5.04 (dd, *J* = 17.2 Hz, 1.8 Hz, 1H), 4.99 (dt, *J* = 9.8 Hz, 1.0 Hz, 1H), 3.79 (m,1H), 3.49 (m, 2H), 2.28 (m, 2H), 1.80−1.68 (m, 2H), 1.41 (td, *J* = 9.8 Hz, 4.0 Hz, 1H), 1.37 (td, *J* = 9.8 Hz, 4.0 Hz, 1H), 1.12−1.02 (m, 30H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 136.1 135.87, 135.86, 134.39, 134.37, 129.7, 127.8, 116.6, 76.7, 70.0, 39.3, 36.4, 34.9, 33.5, 27.1, 19.5, 18.6, 18.5, 16.6, 13.9, 13.2; high-resolution mass spectrum (ESI) *m*/*z* 589.3871 [(M + Na)$^+$ calcd for $C_{35}H_{58}O_2Si_2Na$, 589.3873].

*Compound (−)-**4**.* To a solution of olefin (−)-**44** (570 mg, 1.01 mmol, 1.0 equiv) in 35 mL of acetone/*tert*-butanol/water (3:3:1) was added NMO (357 mg, 3.0 mmol, 3.0 equiv) as one portion followed by potassium osmate(VI) dihydrate (30 mg, 0.08 mmol, 0.08 equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature before it was quenched with 10 g of solid $Na_2S_2O_3$. The resulting heterogeneous mixture was stirred for a further 30 min before it was diluted by ethyl acetate (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (30 mL) three times. The combined organic layers were washed with saturated aqueous NH_4Cl (10 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting diol was moved to the next step as a black oil without further purification. To a solution of the corresponding diol of (−)-**44** (1.01 mmol, crude) in 25 mL of acetone/water (4:1) was added $NaIO_4$ (750 mg, 3.50 mmol, 3.50 equiv) as one portion at room temperature under air atmosphere. The resulting mixture was stirred at the same temperature for 3 h before it was diluted with ethyl acetate (30 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 2:98, 5:95, 10:90) to furnish aldehyde (−)-**4** (436 mg, 0.75 mmol, 75.0% over two steps) as a colorless oil. $[\alpha]_D^{20} = -21.7$ (*c* 1.75, $CHCl_3$); IR (film) 2943, 2865, 1727, 1463, 1427, 1389, 1112, 882, 824, 740, 702, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.87 (t, *J* = 2.2 Hz, 1H), 7.71−7.68 (m, 4H), 7.46−7.39 (m, 6H), 4.34 (m, 1H), 3.51 (d, *J* = 6.0 Hz, 2H), 2.54 (m, 2H), 1.82 (m, 1H), 1.73 (m, 1H), 1.39 (td, *J* = 13.0 Hz, 2.5 Hz, 1H), 1.27 (m, 1H), 1.09 (m, 30H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 202.4, 135.8, 134.17, 134.15, 129.7, 127.3, 72.6, 70.0, 47.7, 36.8, 34.4, 33.3, 27.0, 19.4, 18.4, 18.3, 16.1, 15.2, 12.9; high-resolution mass (ESI) *m*/*z* 591.3664 [(M + Na)$^+$ calcd for $C_{34}H_{56}O_3Si_2Na$, 591.3666].

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*Compound (−)-**45***. To a solution of β-hydroxy acid (+)-**5** (58.0 mg, 0.118 mmol, 1.0 equiv) in 0.9 mL of THF was added 0.6 mL of HMDS as one portion at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 22 h at 40−45 °C before the HMDS/THF was removed under high vacuum (pressure <5 Torr). The mixture was then azeotropically purified with toluene to remove the residual amount of HMDS, applying high vacuum with no access of air followed by stirring overnight at 40−45 °C under the same high vacuum conditions. The resulting tris-silylated ester was dissolved in 2 mL of dichloromethane before the addition of aldehyde (−)-**4** (80.0 mg, 0.138 mmol, 1.17 equiv) solution in 2 mL of dichloromethane at −78 °C under nitrogen atmosphere. TMSOTf (50.0 mg, 0.225 mmol, 1.90 equiv of a newly opened bottle purchased from Sigma-Aldrich) was then added to the reaction mixture at −78 °C. The resulting mixture was stirred for 1 h at −78 °C under a nitrogen atmosphere before allowing access to air via insertion of a needle (1.2 mm diameter) at −78 °C for 10 min to introduce a small amount of moisture (H_2O). The reaction mixture was then stirred at −78 °C under a nitrogen atmosphere for 50 min before it was slowly diluted with 5 mL of dichloromethane at the same temperature. The resulting mixture was then quenched with 100 mg of 2,6-lutidine and attached to the high vacuum to partially remove solvent at 5−10 °C. The resulting solution (1 mL) was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 10:90, 20:80) to furnish dioxanone (−)-**45** (125 mg, 0.112 mmol, 95.1%) as a colorless oil. $[\alpha]_D^{20}$ = −3.3 (*c* 1.15, $CHCl_3$); IR (film) 2930, 2864, 1752, 1513, 1463, 1428, 1388, 1250, 1112, 883, 824, 740, 702 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ = 7.81−7.79 (m, 4H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.27−7.24 (m, 7H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.16 (s, 1H), 5.58 (q, *J* = 6.5 Hz, 1H), 5.29 (q, *J* = 6.8 Hz, 1H), 5.08 (t, *J* = 6.4 Hz, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.13 (m, 1H), 3.67 (m, 1H), 3.63−3.53 (m, 2H), 3.34 (s, 3H), 3.30−3.25 (m, 1H), 3.12 (s, 3H), 2.40−2.33 (m, 1H), 2.20−2.10 (m, 2H), 2.06−1.96 (m, 2H), 1.87−1.81 (m, 1H), 1.74 (d, *J* = 1.1 Hz, 3H), 1.48−1.25 (m, 6H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.19 (s, 9H), 1.17−1.13 (m, 21H), 1.12−1.05 (m, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.92−0.89 (s, 1H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ = 166.7, 161.3, 160.4, 152.3, 146.9, 136.7, 135.0, 134.3, 132.3, 130.6, 130.1, 129.2, 114.7, 113.9, 102.0, 76.0, 75.7, 75.1, 73.7, 71.4, 70.9, 66.9, 56.9, 55.4, 43.3, 40.1, 37.1, 36.9, 36.6, 35.22, 35.18, 34.3, 27.8, 21.4, 20.2, 20.0, 19.21, 19.15, 18.2, 16.9, 15.4, 13.0, 0.9; high-resolution mass (ESI) *m*/*z* 1114.6652 [(M + H)$^+$ calcd for $C_{63}H_{100}NO_{10}Si_3$, 1114.6655]. Note: Employing similar reaction conditions (HMDS, newly purchased/opened bottle of TMSOTf, −78 °C), without introduction of air, gave the desired product in very low yield (<5%), with most of the starting materials, aldehyde (−)-**4** and a mixture of silylated (+)-**5** (mono-, bis-, or tris-) being recovered. Interestingly, the yield of the union reaction significantly increased (ca. 40−80%) through utilizing TMSOTf from frequently used bottles. This observation suggested that a trace amount of TfOH derived from TMSOTf facilitated the union. We therefore added a catalytic amount of either TfOH or H_2O to our reaction mixture at −78 °C. Unfortunately, the yield of desired product was unsatisfactory (5−25%); moreover, no starting material could be recovered. The NMR analysis of multiple major side products suggested that, although the dioxanone moiety had been generated, an undesired loss of the TMS group or both the TMS and the PMB groups had also occurred. The derived alcohol or diol then underwent further reactions with aldehyde (−)-**4** to form multiple complex side products. This result confirmed that addition of TfOH was necessary, but the substrates were sensitive under the acidic conditions utilizing a measurable amount of TfOH or H_2O. Surprisingly, however, slow introduction of moisture (H_2O) via simple exposure of the −78 °C reaction mixture to room temperature air via the insertion of a needle (1.2 mm diameter) for 5−10 min proved successful, and remarkably led to the desired product (−)-**45** in excellent yield (95%) as a single diastereomer, with no side products observed! The possibilities of the involvement of other components of the introduced wet air, N_2 and O_2 gas, had been excluded through attempts of the union reaction in either dry N_2 or dry O_2 atmosphere (yield <5%).

*Compound (−)-**46***. To a solution of dioxanone (−)-**45** (200 mg, 0.180 mmol, 1.0 equiv) in 2.3 mL of THF in a glass microwave vial (2−5 mL) were added 0.08 mL of 2,6-lutidine followed by 2.4 mL of Petasis reagent (0.25 M in THF/toluene, freshly prepared, 0.60 mmol, 3.35 equiv) at room temperature under an air atmosphere. The resulting mixture was sealed and stirred for 3 h at 100 °C in microwave at the "high" level of absorption setting before it was cooled (three levels of absorption in Biotage microwave reactor: medium, high, very high). The resulting mixture was diluted with 20 mL of hexanes and stirred for 10 min before it was filtered and concentrated. The resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 5:95, 10:90) to furnish enol acetal (−)-**46** (174 mg, 0.157 mmol, 87.2%) as a colorless oil. $[\alpha]_D^{20}$ = −0.9 (*c* 1.43, $CHCl_3$); IR (film) 2930, 2864, 1512, 1462, 1428, 1388, 1249, 1112, 883, 738, 702, 666 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ = 7.81−7.77 (m, 4H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.26−7.22 (m, 7H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.15 (s, 1H), 5.59 (q, *J* = 6.5 Hz, 1H), 5.08 (q, *J* = 5.4 Hz, 1H), 4.93 (t, *J* = 5.9 Hz, 1H), 4.64 (s, 1H), 4.53−4.43 (m, 2H), 4.24 (brs, 1H), 4.10 (s, 1H), 3.72−3.67 (m, 1H), 3.61−3.53 (m, 2H), 3.48−3.44 (m, 1H), 3.31 (s, 3H), 3.12 (s, 3H), 2.40−2.33 (m, 1H), 2.17−2.06 (m, 3H), 1.91−1.85 (m, 2H), 1.74 (s, 3H), 1.64−1.46 (m, 6H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.21−1.12 (m, 33H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.98−0.94 (m, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ = 161.2, 160.3, 158.0, 152.1, 146.9, 136.7, 135.0, 134.2, 132.4, 130.5, 130.0, 129.1, 114.6, 113.9, 101.7, 93.6, 77.3, 76.2, 75.7, 74.0, 71.3, 70.8, 66.9, 56.8, 55.3, 43.3, 40.2, 37.1, 36.8, 35.87, 35.83, 35.3, 34.3, 27.8, 21.6, 20.2, 20.0, 19.24, 19.19, 18.2, 17.1, 15.2, 14.0, 0.9; high-resolution mass (ESI) *m*/*z* 1112.6841 [(M + H)$^+$ calcd for $C_{64}H_{102}NO_9Si_3$, 1112.6862].

*Compound (−)-**47***. To a solution of methyltriphenylphosphonium bromide (475 mg, 1.33 mmol) in 8 mL of THF was added 2 mL of KO*t*-Bu solution (1.0 M solution in THF, 2.0 mmol) dropwise at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 min at the same temperature to give the ylide solution (0.133 M in THF, 10 mL). To a solution of enol acetal (−)-**46** (70 mg, 0.0629 mmol, 1.0 equiv) in 7 mL of THF was added 0.31 mL of dimethylaluminum chloride solution (1.0 M in hexanes, newly opened, 0.31 mmol, 4.9 equiv) over 3 s at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 s at −78 °C before the addition of freshly prepared ylide solution (0.133 M in THF, 4.2 mL, 0.559 mmol, 8.9 equiv) at the same temperature. The resulting mixture was stirred for a further 10 min at −78 °C before it was quenched by 10 mL of saturated aqueous NH_4Cl solution. The resulting mixture was diluted with 20 mL of ethyl acetate. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 2:98, 5:95, 10:90) to furnish methylene tetrahydropyran (−)-**47** (59 mg, 0.0531 mmol, 84.4%) as a colorless oil. $[\alpha]_D^{20}$ = −4.1 (*c* 0.83, $CHCl_3$); IR (film) 2930, 2864, 1589, 1513, 1462, 1428, 1388, 1249, 1112, 883, 740, 702 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ = 7.83−7.80 (m, 4H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.28−7.23 (m, 7H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.16 (s, 1H), 5.63 (q, *J* = 6.5 Hz, 1H), 5.14 (t, *J* = 6.2 Hz, 1H), 4.76 (d, *J* = 4.3 Hz, 2H), 4.53 (d, *J* = 5.9 Hz, 2H), 4.28−4.25 (m, 1H), 3.80−3.73 (m, 1H), 3.66−3.56 (m, 3H), 3.32 (s, 3H), 3.32−3.29 (m, 1H), 3.13 (s, 3H), 2.44−2.37 (m, 1H), 2.25−2.19 (m, 1H), 2.14 (d, *J* = 13.1 Hz, 2H), 2.01 (d, *J* = 11.7 Hz, 1H), 1.92 (t, *J* = 11.7 Hz, 2H), 1.82−1.70 (m, 3H), 1.75 (d, *J* = 1.2 Hz, 3H), 1.72−1.62 (m, 2H), 1.60−1.53 (m, 2H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.25−1.12 (m, 34H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.95−0.91 (m, 1H), 0.91 (d, *J* = 7.3 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ = 160.6, 159.7, 151.5, 146.5, 145.6, 136.1, 134.6, 133.7, 132.0, 130.0, 129.5, 128.6, 114.0, 113.4, 108.4, 78.6, 75.8, 75.5, 75.2, 74.5, 70.8, 70.6, 66.4, 56.3, 54.8, 42.9, 42.2, 41.3, 40.4, 37.3 36.8, 35.0, 34.1, 33.8, 27.2, 21.8, 19.6, 19.5, 18.8, 18.7, 17.7, 16.3, 15.5, 13.6, 0.4; high-resolution mass (ESI) *m*/*z* 1110.7103 [(M + H)$^+$ calcd for $C_{65}H_{104}NO_8Si_3$, 1110.7070].

*Compound (+)-**48***. To a solution of methylene tetrahydropyran (−)-**47** (47.0 mg, 0.0424 mmol, 1.0 equiv) in 16.5 mL of THF/H_2O

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(45:1) were added 18-crown-6 (550 mg, 2.08 mmol, 49.0 equiv) followed by KOH (420 mg, 7.49 mmol, 177 equiv) at room temperature. The resulting mixture was stirred for 3 h at the same temperature before it was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). The resulting mixture was diluted with 20 mL of ethyl acetate. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 30:70, 40:60, 50:50) to furnish diol (+)-**48** (28.4 mg, 0.0355 mmol, 83.7%) as a colorless oil. $[\alpha]_D^{20}$ = +3.1 (*c* 1.5, $CHCl_3$); IR (film) 2932, 2864, 1727, 1514, 1463, 1249, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.44 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.18 (s, 1H), 5.12 (q, *J* = 6.5 Hz, 1H), 4.83 (d, *J* = 8.7 Hz, 1H), 4.68 (s, 2H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.39 (d, *J* = 10.9 Hz, 1H), 3.98 (brs, 1H), 3.79 (s, 3H), 3.79−3.77 (brs, 1H), 3.52−3.47 (m, 1H), 3.42−3.39 (m, 1H), 3.34 (t, *J* = 10.1 Hz, 1H), 3.20 (s, 3H), 3.20−3.17 (m, 1H), 2.18 (d, *J* = 12.6 Hz, 1H), 2.15−2.03 (m, 2H), 1.99−1.87 (m, 3H), 1.87 (s, 3H), 1.80−1.73 (brs, 1H), 1.70−1.59 (m, 4H), 1.59−1.50 (m, 2H), 1.49−1.40 (m, 3H), 1.32−1.25 (m, 1H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.20 (m, 1H), 1.11−0.99 (m, 21H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.6, 159.6, 150.4, 145.2, 144.8, 133.4, 130.2, 129.8, 114.2, 113.8, 108.4, 79.3, 78.3, 75.6, 75.0, 74.1, 70.5, 69.4, 68.3, 56.6, 55.5, 41.9, 41.0, 40.3, 36.9, 36.2, 34.3, 33.7, 33.4, 20.9, 19.5, 18.6, 18.51, 18.48, 17.8, 16.2, 15.0, 13.3; high-resolution mass (ESI) *m*/*z* 800.5486 [(M + H)$^+$ calcd for $C_{46}H_{78}NO_8Si$, 800.5497].

*Compound (+)-**3**.* To a solution of diol (+)-**48** (15.8 mg, 0.0199 mmol, 1.0 equiv) in 0.5 mL of *t*-BuOH and 0.2 mL of pH 7 buffer solution was added TEMPO solution (0.025 M in CH_3CN, 0.88 mL, 0.022 mmol, 1.1 equiv) at room temperature under an air atmosphere. The resulting mixture was stirred for 20 min at the same temperature before the subsequent addition of $NaClO_2$ (1 M in water, 0.068 mL, 0.0677 mmol, 3.4 equiv) and NaClO (0.025 M in water, 1.44 mL, 0.036 mmol, 1.8 equiv) solution. The reaction was stirred at room temperature for 3 h before it was quenched by saturated aqueous $Na_2S_2O_3$ solution (3 mL); after dilution with ethyl acetate (5 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (5 mL) twice. The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_2, ethyl acetate/hexanes 20:80, 30:70, 50:50, 80:20) to furnish acid (+)-**3** (12.1 mg, 0.0149 mmol, 74.7%) as a colorless oil. $[\alpha]_D^{20}$ = +3.1 (*c* 0.3, $CHCl_3$); IR (film) 2926, 2865, 1735, 1707, 1514, 1463, 1381, 1248, 883, 821, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.46 (s, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.22 (s, 1H), 5.03 (q, *J* = 6.5 Hz, 1H), 4.89 (d, *J* = 8.8 Hz, 1H), 4.68 (d, *J* = 6.0 Hz, 2H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 3.98 (m, 1H), 3.80 (s, 3H), 3.80−3.77 (brs, 1H), 3.27−3.20 (m, 1H), 3.21 (s, 3H), 3.20−3.13 (m, 1H), 2.48 (m, 1H), 2.21−2.10 (m, 3H), 2.01−1.97 (m, 1H), 1.89 (s, 3H), 1.89−1.87 (m, 1H), 1.78−1.65 (m, 5H), 1.61−1.50 (m, 5H), 1.48−1.35 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.30−1.25 (m, 1H), 1.20−1.14 (m, 4H) 1.11−1.03 (m, 19H), 1.02−0.93 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 180.4, 160.9, 159.5, 151.1, 145.0, 144.5, 133.7, 130.1, 129.7, 114.1, 113.4, 108.4, 79.7, 78.6, 75.9, 75.0, 73.3, 70.5, 68.0, 56.6, 55.4, 42.0, 41.2, 41.0, 40.8, 37.9, 36.8, 36.6, 36.3, 33.7, 21.6, 19.5, 18.5, 18.4, 18.0, 17.8, 14.6, 13.3; high-resolution mass (ESI) *m*/*z* 814.5298 [(M + H)$^+$ calcd for $C_{46}H_{76}NO_9Si$, 814.5289].

*Compound (+)-**49**.* To a solution of carboxylic acid (+)-**3** (24 mg, 0.030 mmol, 1.0 equiv) in 0.75 mL of THF were added Hunig's base (0.06 mL) followed by 2,4,6-trichlorobenzoyl chloride (54 mg, 0.22 mmol, 7.5 equiv) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 3 h at the same temperature before it was diluted by toluene (3 mL). This resulting activated macrolide precursor solution was stored at room temperature for further use. To a solution of DMAP (120 mg, 0.98 mmol, 33 equiv) in 30 mL of toluene was slowly added the activated macrolide precursor solution using a syringe pump over 5 h at reflux temperature under a nitrogen atmosphere. The resulting mixture was stirred for a further 12 h at the same temperature before it was cooled to room temperature. The resulting mixture was filtered and concentrated, and purified by column chromatography (SiO_2, ethyl acetate:hexanes 5:95, 10:90, 20:80) to give the crude macrolide, which was then purified by PTLC (SiO_2, ethyl acetate:hexanes 10:90) to furnish macrolide (+)-**49** (20.8 mg, 0.0261 mmol, 88.5%) as a colorless oil. $[\alpha]_D^{20}$ = +10.3 (*c* 0.33, $CHCl_3$); IR (film) 2927, 2856, 1750, 1653, 1613, 1577, 1548, 1513, 1464, 1378, 1248, 1160, 1097, 883, 820, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.44 (s, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.20 (s, 1H), 5.96 (dd, *J* = 12.6 Hz, 2.6 Hz, 1H), 5.20 (q, *J* = 6.5 Hz, 1H), 4.70 (s, 2H), 4.64 (d, *J* = 10.9 Hz, 1H), 4.43 (d, *J* = 10.9 Hz, 1H), 4.12 (dd, *J* = 11.1 Hz, 4.1 Hz, 1H), 3.81 (s, 3H), 3.42 (t, *J* = 10.0 Hz, 1H), 3.30 (t, *J* = 11.1 Hz, 1H), 3.21 (s, 3H), 3.10 (t, *J* = 9.2 Hz, 1H), 2.73 (td, *J* = 13.3 Hz, 3.5 Hz, 1H), 2.69−2.63 (m, 1H), 2.13−2.03 (m, 3H), 1.99−1.93 (m, 1H), 1.91 (d, *J* = 1.3 Hz, 3H), 1.89−1.85 (m, 1H), 1.83−1.70 (m, 4H), 1.66−1.58 (m, 4H), 1.50−1.55 (m, 1H), 1.48−1.35 (m, 2H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.30−1.25 (m, 2H), 1.14 (d, *J* = 6.8 Hz, 3H) 1.12−1.05 (m, 18H), 0.95−0.90 (m, 1H), 0.85 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.0, 160.7, 159.5, 151.4, 145.0, 141.3, 134.0, 130.9, 129.7, 114.1, 113.4, 108.7, 76.1, 75.9, 75.0, 74.5, 71.8, 71.3, 65.0, 56.7, 55.5, 42.5, 41.8, 41.5, 39.2, 38.6, 37.6, 35.2, 34.5, 31.6, 20.8, 19.4, 18.6, 18.5, 18.1, 17.9, 14.3, 13.4; high-resolution mass (ESI) *m*/*z* 796.5194 [(M + H)$^+$ calcd for $C_{46}H_{74}NO_8Si$, 796.5184].

*Compound (−)-**50**.* δ-Lactone (−)-**50** was isolated as a side product of TIPS removal reaction of macrolide (+)-**49**. $[\alpha]_D^{20}$ = −3.5 (*c* 0.7, $CHCl_3$); IR (film) 2923, 2852, 1738, 1553, 1514, 1463, 1379, 1249, 1174, 1099, 1036, 804 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.45 (s, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.18 (s, 1H), 5.13 (q, *J* = 6.5 Hz, 1H), 4.83 (d, *J* = 9.0 Hz, 1H), 4.71 (s, 2H), 4.62 (d, *J* = 5.5 Hz, 1H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.41 (d, *J* = 10.9 Hz, 1H), 3.98 (s, 1H), 3.80 (s, 4H), 3.57 (t, *J* = 10.4 Hz, 1H), 3.30−3.24 (m, 1H), 3.21 (s, 3H), 2.63−2.57 (m, 1H), 2.22−2.18 (m, 2H), 2.07 (d, *J* = 14.3 Hz, 1H), 2.06−1.98 (m, 1H), 1.98−1.82 (m, 3H), 1.90 (s, 3H), 1.75−1.52 (m, 5H), 1.51−1.42 (m, 4H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.8, 160.6, 159.6, 150.5, 144.9, 144.3, 133.4, 130.2, 129.8, 114.2, 113.8, 109.1, 80.3, 79.2, 78.2, 75.0, 74.2, 70.5, 68.2, 56.7, 55.5, 41.5, 41.02, 40.98, 40.0, 36.7, 36.0, 33.5, 31.5, 30.6, 20.7, 19.5, 18.1, 17.8, 11.9; high-resolution mass (ESI) *m*/*z* 640.3859 [(M + H)$^+$ calcd for $C_{37}H_{54}NO_8$, 640.3849].

*Compound (+)-**51**.* To a solution of TIPS ether (+)-**49** (9.0 mg, 0.0113 mmol, 1.0 equiv) in 3.5 mL of THF in a plastic container was added pyridine (3.9 mL) followed by HF/pyridine complex (1.0 mL) at room temperature in an air atmosphere. The resulting mixture was stirred for 48 h at 45 °C before it was quenched slowly with saturated aqueous $NaHCO_3$ (12.0 mL) at room temperature. The resulting mixture was diluted with ethyl acetate (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (8 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting mixture was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 30:70, 40:60, 50:50) to furnish alcohol (+)-**51** (5.1 mg, 0.0080 mmol, 70.5%) as a colorless oil. $[\alpha]_D^{20}$ = +4.9 (*c* 0.42, $CHCl_3$); IR (film) 2917.8, 2849.3, 1708.1, 1552.4, 1513.4, 1463.2, 1378.4, 1149.9, 1096.8, 807.1, 720.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.49 (s, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.20 (s, 1H), 5.84 (dd, *J* = 12.6 Hz, 2.6 Hz, 1H), 5.16 (q, *J* = 6.5 Hz, 1H), 4.68 (s, 2H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.41 (d, *J* = 10.9 Hz, 1H), 3.80 (s, 4H), 3.47 (t, *J* = 10.4 Hz, 1H), 3.30 (q, *J* = 10.4 Hz, 2H), 3.23 (s, 3H), 2.75 (td, *J* = 12.6 Hz, 3.2 Hz, 1H), 2.70−2.64 (m, 1H), 2.13 (d, *J* = 13.5 Hz, 2H), 2.04−1.95 (m, 2H), 1.90 (s, 3H), 1.86−1.76 (m, 3H), 1.76−1.60 (m, 5H), 1.48−1.33 (m, 4H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 175.9, 160.6, 159.4, 151.2, 145.0, 140.6, 134.7, 130.7, 129.7, 114.0, 113.4, 108.5, 76.1, 75.7, 75.03, 74.95, 71.0, 68.9, 65.8, 56.7, 55.4, 41.9, 41.7, 41.5, 38.0, 37.0, 36.5, 35.4, 33.8, 31.6, 21.1, 19.4, 17.8, 16.7, 13.1; high-resolution mass (ESI) *m*/*z* 640.3849 [(M + H)$^+$ calcd for $C_{37}H_{54}NO_8$, 640.3849].

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*Compound (−)-**52**.* To a solution of PMB ether (−)-**50** (4.0 mg, 0.0063 mmol, 1.0 equiv) in 1.5 mL of dichloromethane was added a mixture of TFA/H_2O (0.4 mL, TFA:H_2O 1:1) dropwise at room temperature. The resulting mixture was stirred for 1 h at the same temperature before it was quenched with saturated aqueous $NaHCO_3$ (5.0 mL) at room temperature. The resulting mixture was diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (5 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting mixture was purified by column chromatography (SiO_2, ethyl acetate:hexanes, 40:60, 50:50, 70:30) to furnish δ-lactone (−)-**52** (2.2 mg, 0.00419 mmol, 67.0%) as a colorless oil. $[\alpha]_D^{20}$ = −12.58 (*c* 0.20, $CHCl_3$); IR (film) 2920, 1727, 1649, 1551, 1449, 1379, 1323, 1204, 1097 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ = 7.69 (s, 1H), 6.23 (s, 1H), 5.23 (q, *J* = 6.4 Hz, 1H), 4.82 (m, 1H), 4.73 (d, *J* = 1.5 Hz, 2H), 4.68 (ddd, *J* = 9.5, 2.5, 2.5 Hz, 1H), 3.68 (m, 1H), 3.46 (t, *J* = 10.5 Hz, 1H), 3.24 (m, 1H), 3.21 (s, 3H), 2.64 (m, 1H), 2.24 (s, 1H), 2.22 (s, 1H), 2.10−2.00 (m, 2H), 1.95−1.85 (m, 4H), 1.89 (s, 3H), 1.78−1.72 (m, 2H), 1.65 (m, 1H), 1.60 (m, 1H), 1.52−1.42 (m, 5H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.24 (d, *J* = 7.3 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ = 177.0, 161.5, 151.7, 145.7, 145.6, 135.3, 114.1, 108.8, 81.8, 79.4, 75.9, 75.5, 70.5, 66.2, 56.5, 44.1, 42.0, 41.6, 40.2, 38.3, 37.0, 36.2, 32.3, 31.4, 22.3, 19.3, 17.9, 17.3, 11.8; high-resolution mass (ES) *m*/*z* 520.3254 [(M + H)$^+$ calcd for $C_{29}H_{46}NO_7$, 520.3274].

*Compound (−)-**53**.* To a solution of alcohol (+)-**51** (3.5 mg, 0.0055 mmol, 1.0 equiv) in 0.2 mL of acetonitrile were added 1*H*-tetrazole solution (0.45 M in acetonitrile, 0.195 mL, 0.088 mmol, 16.0 equiv) followed by *i*-$Pr_2NP(OFm)_2$ solution (57.5 mg in 0.2 mL of dichloromethane, 0.110 mmol, 20.0 equiv) at room temperature in an argon atmosphere. The resulting mixture was stirred for 50 min at the same temperature before it was cooled to 0 °C. 0.2 mL of H_2O_2 solution (50% in water) was added to the reaction mixture at 0 °C, allowing the resulting mixture to be stirred at the same temperature for 30 min. The resulting mixture was quenched by saturated aqueous $NaHCO_3$ (3.0 mL) at room temperature. The resulting mixture was diluted by ethyl acetate (5 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 mL) twice. The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting mixture was purified by column chromatography (SiO_2, ethyl acetate:hexanes, 40:60, 50:50, 60:40) to furnish the phosphorus ester together with inseparable phosphate impurity as a colorless oil. The mixture was moved to the next step without further purification. To a solution of this phosphoric ester [made from 0.0055 mmol of alcohol (+)-**51**] in CH_2Cl_2/pH 7 aqueous buffer solution (4.4 mL, 10:1) was added DDQ (8.0 mg) in one portion at room temperature. The resulting mixture was stirred for 30 min at the same temperature before it was diluted with diethyl ether (10 mL). The organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 mL) twice. The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated, and the resulting mixture was purified by column chromatography (SiO_2, ethyl acetate:hexanes, 50:50, 60:40, 80:20) to furnish alcohol (−)-**53** (3.2 mg, 0.00334 mmol, 61.0% over two steps) as a colorless oil. $[\alpha]_D^{20}$ = −4.00 (*c* 0.6, $CHCl_3$); IR (film) 2925, 2853, 1729, 1555, 1451, 1381, 1252, 1076, 1012, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.76−7.68 (m, 4H), 7.56−7.49 (m, 3H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.41−7.31 (m, 4H), 7.39 (s, 1H), 7.30−7.20 (m, 4H), 6.16 (s, 1H), 5.98 (dd, *J* = 11.8, 3.1 Hz, 1H), 5.18 (q, *J* = 6.5 Hz, 1H), 4.72 (d, *J* = 3.1 Hz, 2H), 4.60 (m, 1H), 4.30−4.23 (m, 2H), 4.23−4.15 (m, 2H), 4.15−4.10 (m, 2H), 3.63 (brt, *J* = 9.2 Hz, 1H), 3.30 (t, *J* = 10.7 Hz, 1H), 3.22 (s, 1H), 3.07 (t, *J* = 9.1 Hz, 1H), 2.71 (m, 1H), 2.49 (m, 1H), 2.10 (d, *J* = 13.5 Hz, 1H), 2.03 (d, *J* = 13.5 Hz, 1H), 1.94−1.82 (m, 2H), 1.89 (s, 3H), 1.75 (dd, *J* = 13.5, 4.4 Hz, 2H), 1.72−1.60 (m, 4H), 1.86−1.76 (m, 3H), 1.47−1.39 (m, 2H), 1.39−1.30 (m, 2H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.09 (m, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.4, 160.7, 151.6, 144.6, 143.38, 143.35, 143.32, 143.29, 141.5, 141.2, 133.9, 128.13, 128.11, 128.09, 127.38, 127.36, 127.31, 125.4, 125.3, 125.24, 125.22, 120.32, 120.27, 120.25, 113.2, 108.9, 78.81, 78.75, 75.1, 75.0, 74.6, 69.55, 69.48, 69.43, 69.21, 69.17, 64.9, 56.7, 48.23, 48.21, 48.18, 48.14, 42.0, 41.5, 41.4, 39.0, 38.4, 38.2, 35.2, 33.8, 33.7, 33.1, 20.9, 19.4, 17.9, 17.8, 14.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ = −1.53; high-resolution mass (ESI) *m*/*z* 956.4521 [(M + H)$^+$ calcd for $C_{57}H_{67}NO_{10}P$, 956.4503].

*Dipotassium Phosphate Form of Enigmazole A (−)-**54**.* To a solution of phosphoric ester (−)-**53** (1 mg, 0.001 mmol, 1.0 equiv) in 0.33 mL of MeOH/H_2O (10:1) was added 2.9 mg of K_2CO_3 at room temperature. The resulting mixture was stirred for 6 h at the same temperature, at which time C18 TLC indicated the completion of the reaction. The mixture was diluted with H_2O (0.7 mL) before it was extracted with pentane (0.5 mL) three times. The resulting mixture was purified by C18 silica column chromatography (0.4 g of 40−75 μm, 70 Å, C18 silica gel, purchased from Sorbent Technology, was packed into a Fisherbrand 9-in. Pasteur pipet, 100% H_2O, then 2:3 H_2O/MeOH) to give 0.3 mg of enigmazole A (−)-**54** (dipotassium phosphate form). $[\alpha]_D^{20}$ = −0.8 (*c* 0.03, MeOH). Dipotassium phosphate (−)-**54** displayed the same ^1H NMR spectrum as did the disodium phosphate (−)-**55** [see the NMR data for (−)-**55**].

*Free Acid Form of Enigmazole A (−)-**1**.* To a solution of phosphorus ester (−)-**53** (2.0 mg, 0.0021 mmol, 1.0 equiv) in 0.4 mL of MeOH/H_2O (2:1) was added 6 mg of Na_2CO_3 at room temperature. The resulting mixture was stirred for 24 h at the same temperature before the addition of CD_3COOD (15 mg). The resulting mixture was then stirred at the same temperature for 10 min before it was extracted with pentane (0.5 mL) for three times. The solvent and CD_3COOD were removed under high vacuum from the mixture to furnish enigmazole A (−)-**1** together with CD_3COONa. Further purification was achieved by RP HPLC (Vydac 5 μm C18, 250 × 10 mm, 5% MeCN/95% H_2O with 0.1% TFA to 40% MeCN/60% H_2O with 0.1% TFA linear gradient over 15 min, then 40% MeCN/60% H_2O with 0.1% TFA for 15 min, 10 mL/min, λ = 261 nm) to give enigmazole A free acid form (−)-**1** (1.4 mg, 0.0020 mmol, 95.0%) as a colorless oil. $[\alpha]_D^{20}$ = −1.7 (*c* 0.2, MeOH); UV (MeCN/H_2O, 0.5% TFA) λ_{max} 261 nm; ^1H NMR (500 MHz, CD_3OD) δ = 7.70 (s, 1H), 6.21 (s, 1H), 5.97 (dd, *J* = 12.8, 2.2 Hz, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 4.72 (s, 2H), 4.58 (m, 1H), 3.58 (td, *J* = 10.1 Hz, 3.0 Hz, 1H), 3.20 (s, 3H), 3.14 (m, 1H), 2.87 (m, 1H), 2.51 (td, J = 13.7 Hz, 3.8 Hz, 1H), 2.20−2.13 (m, 2H), 2.01−1.94 (m, 3H), 1.89 (d, *J* = 1.2 Hz, 3H), 1.86−1.83 (m, 1H), 1.78−1.70 (m, 4H), 1.69−1.60 (m, 2H), 1.48 (q, *J* = 12.4 Hz, 1H), 1.44−1.37 (m, 1H), 1.37−1.30 (m, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.05−1.01 (m, 1H), 0.98 (d, *J* = 5.9 Hz, 3H). Note: H11 was overlapped by CD_3OD. ^{13}C NMR (125 MHz, CD_3OD) δ = 176.2, 161.9, 152.8, 146.2, 142.2, 136.0, 114.0, 109.0, 77.8 (d, *J* = 5.8 Hz), 76.9, 76.2, 75.9, 69.8, 65.9, 56.8, 43.0, 42.6, 42.4, 40.1, 39.6, 39.2, 36,1, 34.6 (d, *J* = 5.2 Hz), 33.6, 21.9, 19.5, 18.1, 17.7, 15.6.

*Monosodium Phosphate Form of Enigmazole A (−)-**56**.* To the neat phosphoric acid (−)-**1** (1.4 mg) in a 3 mm glass NMR tube was added 0.2 mL of saturated $NaHCO_3$/CD_3OD solution to furnish monophosphate (−)-**56** in CD_3OD solution. $[\alpha]_D^{20}$ = −2.1 (*c* 0.2, MeOH); IR (film) 3411 (br) 2934, 2851, 1681, 1538, 1438, 1382, 1208, 1139, 1080, 967, 909, 726, 653 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ = 7.68 (s, 1H), 6.21 (s, 1H), 5.95 (dd, *J* = 12.8, 2.5 Hz, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 4.70 (d, *J* = 1.5 Hz, 1H), 4.69 (d, *J* = 1.5 Hz, 1H), 4.42 (m, 1H), 3.62 (td, *J* = 10.1 Hz, 2.9 Hz, 1H), 3.20 (s, 3H), 3.12 (dd, *J* = 10.2 Hz, 8.9 Hz, 1H), 2.98 (m, 1H), 2.50 (td, *J* = 13.4 Hz, 3.9 Hz, 1H), 2.21 (d, *J* = 12.8 Hz, 1H), 2.13 (d, *J* = 12.8 Hz, 1H), 2.10 (m, 1H), 1.97 (t, *J* = 12.2, 1H), 1.89 (s, 3H), 1.88−1.83 (m, 3H), 1.80−1.72 (m, 3H), 1.66−1.60 (m, 2H), 1.54 (q, *J* = 12.4 Hz, 1H), 1.39 (t, *J* = 11.3 Hz, 1H), 1.37 (t, *J* = 11.1 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.02 (td, *J* = 12.0 Hz, 2.6 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 3H). Note: H11 was overlapped by CD_3OD. ^{13}C NMR (125 MHz, CD_3OD) δ = 176.5, 161.9, 152.7, 146.6, 142.4, 136.0, 113.9, 108.6, 77.6, 76.2, 75.7, 75.2 (d, *J* = 6.4 Hz), 69.8, 65.7, 56.8, 43.0, 42.6, 42.5, 40.1, 39.6, 39.3, 36,2, 34.7 (d, *J* = 6.6 Hz), 33.6, 21.8, 19.4, 18.3, 17.7, 15.0; ^{31}P (202 MHz, CD_3OD) δ = 1.45; high-resolution mass (ESI) *m*/*z* 598.2759 [(M − H)$^-$ calcd for $C_{29}H_{45}NO_{10}P$, 598.2781].

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*Disodium Phosphate Form of Enigmazole A (−)-**55***. To a solution of enigmazole A (monophosphate form) (−)-**56** (1.4 mg) in 0.2 mL of saturated $NaHCO_3$ CD_3OD solution in a 3 mm glass NMR tube was added 0.02 mL of 1 M NaOH CD_3OD solution to furnish enigmazole A (disodium phosphate form) (−)-**55** in CD_3OD solution. $[\alpha]_D^{20}$ = −1.8 (*c* 0.2, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ = 7.68 (s, 1H), 6.21 (s, 1H), 5.93 (dd, *J* = 13.1, 2.9 Hz, 1H), 5.23 (q, *J* = 6.5 Hz, 1H), 4.67 (s, 2H), 4.31 (m, 1H), 3.64 (td, *J* = 10.8 Hz, 2.8 Hz, 1H), 3.20 (s, 3H), 3.14 (m, 1H), 3.09 (m, 1H), 2.50 (td, J = 12.3 Hz, 3.1 Hz, 1H), 2.25 (m, 1H), 2.14−2.09 (m, 1H), 2.06−1.95 (m, 2H), 1.88 (d, *J* = 1.2 Hz, 3H), 1.87−1.78 (m, 2H), 1.78−1.70 (m, 2H), 1.78−1.67 (m, 2H), 1.63−1.51 (m, 2H), 1.48 (q, *J* = 12.4 Hz, 1H), 1.40−1.47 (m, 2H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.06−0.99 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H). Note: H11 was overlapped by CD_3OD. ^{13}C NMR (125 MHz, CD_3OD) δ = 177.4, 161.9, 152.6, 147.0, 142.5, 135.9, 114.0, 108.3, 78.0, 76.3, 75.7, 73.6, 69.8, 65.7, 56.8, 43.2, 42.7, 42.6, 40.3, 39.8, 39.5, 36,3, 34.9 (d, *J* = 6.8 Hz), 33.7, 21.8, 19.5, 18.6, 17.7, 15.4. Note: Na_2CO_3 peak is shown in 161.5.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00899.

Spectroscopic and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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