Total Synthesis of Calyculin C

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Abstract: The study of phosphatases continues to flourish given their prominence in signal transduction pathways and the regulation of cell function. Our research efforts in this area focus on the potent inhibition of serine/threonine phosphatases, PP1 and PP2A, by a structurally diverse class of natural products. We herein report the completed total synthesis of the serine/threonine phosphatase inhibitor calyculin C **(1)** as part of an ongoing effort to elucidate key structural requirements for phosphatase inhibition by the aforementioned diverse class of natural products. Synthetic issues addressed include (1) the remote protecting group effect on Brown crotylboration diastereoselectivity during the introduction of the $C_{10}-C_{11}$ stereocenters and (2) the formation of the $C_{25}-C_{26}$ double bond using a fully deprotected $C_{26}-C_{37}$ phosphonium salt **(3)**. In addition, the concurrent synthesis of 34*R*-calyculin C **(29)** clarified our previous C_{34}-stereochemical assignment of $C_{26}-C_{37}$ phosphonium salts (**3** and **27**) (Ogawa, A. K.; DeMattei, J. A.; Scarlato, G. R.; Tellew, J. E.; Chong, L. S.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6153).

The study of phosphatases continues to flourish given their prominence in signal transduction pathways and the regulation of cell function.[3] Our research efforts in this area focus on the potent inhibition of serine/threonine phosphatases, PP1 and PP2A, by a structurally diverse class of natural products.[4] In a previous paper, we proposed a computationally derived enzyme−inhibitor model that identified structural motifs common to all PP1 and PP2A natural product inhibitors.[5] (See Figure 2) Within this class of inhibitors, the calyculins[6] have attracted extensive synthetic interest due to their diverse functionality[7−9] (see Figure 1). We herein report the completed total synthesis of the serine/threonine phosphatase inhibitor calyculin C **(1)** as part of an ongoing effort to elucidate key structural requirements for phosphatase inhibition by the aforementioned diverse class of natural products.

Retrosynthetic analysis yielded an initial disconnection at the $C_{25}-C_{26}$ double bond that subdivided calyculin into two fragments of approximately equal functional complexity **(2** and **3)**[10] (see Scheme 1). Previous synthetic papers outlined a strategy for $C_{25}-C_{26}$ double bond construction via Wittig olefination with a fully deprotected $C_{26}-C_{37}$ phosphonium salt.[7a] Model studies affirmed the viability of this approach which circumvented downstream protecting group manipulations with respect to the $C_{26}-C_{37}$ fragment synthesis. Finally, elaboration

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(3) Wera, S.; Hemmings, B. A. *Biochem. J.* **1995**, *311*, 17, and references therein.

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(10) The structure of **3** was previously assigned in ref 7a as its $C_{34}-$epimer.

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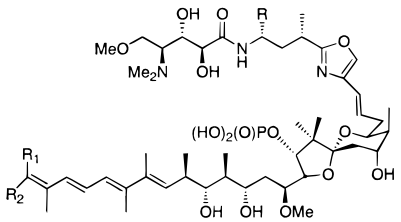
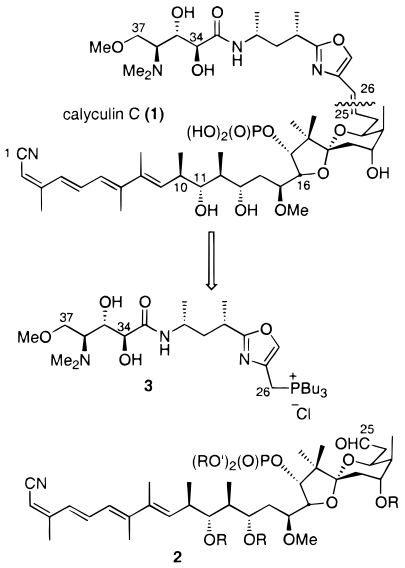


		R_1	R_2	R_3	C_6-geometry
calyculins	A:	CN	H	H	E
	B:	H	CN	H	E
	C:	CN	H	CH_3	E
	D:	H	CN	CH_3	E
	E:	CN	H	H	Z
	F:	H	CN	H	Z
	G:	CN	H	CH_3	Z
	H:	H	CN	CH_3	Z

Figure 1.

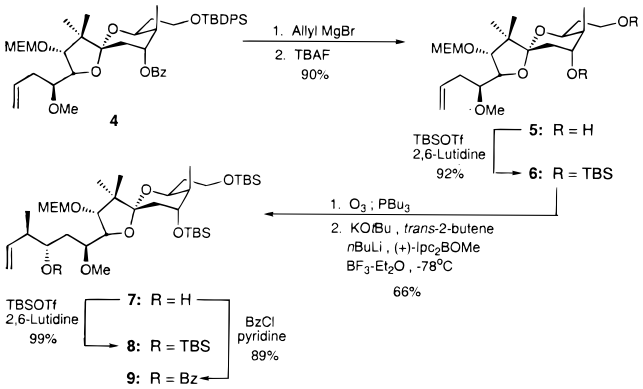
Scheme 1



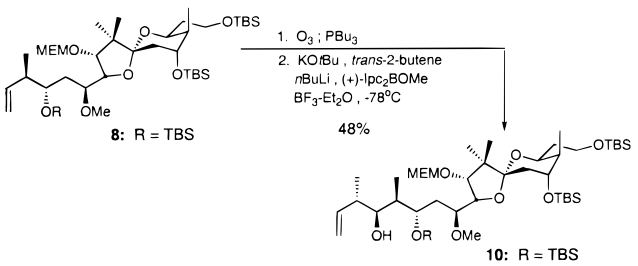
of the C_{17}-hydroxyl late in the C_1-C_{25} fragment synthesis, as precedented by Evans and co-workers,[8a] imparted the requisite flexibility to explore alternate functional groups at this position. Modification at this specific location appealed due to the potential significance of the phosphate toward tertiary structure organization and/or direct active site interactions. Of interest was the apparently conflicting evidence regarding the role of the aforementioned phosphoryl moiety. Examination of the calyculin A crystal structure suggested a significant role in molecular folding, which should logically enhance activity by limiting the entropic cost upon binding. However, Fusetani recently reported that C_{17}-desphosphoryl calyculin A was approximately as equipotent as phosphorylated calyculins,[6e] thus raising an interesting issue regarding the natural selection for such an unusual functionalization.

Prefacing the completion of the total synthesis were efforts to improve our synthesis of the C_1-C_{25} fragment (**2**). Targets of refinement included (1) an upstream conversion to a global silyl protecting group strategy that reduced the number of linear synthetic steps and (2) improving the selectivity during the introduction of the C_{10},C_{11}-propionate unit. The switch to a global silyl protecting group strategy proceeded from spiroketal **4** with the deprotection of both the TPS and benzoate protecting groups to afford diol **5**. Silylation yielded core structure **6** in high yield, thereby completing the protecting group exchange. Ozonolysis afforded an aldehyde intermediate that, upon

Scheme 2



Scheme 3



submission to an asymmetric Brown crotylboration reaction,[11] afforded olefin **7** as the sole reaction product. This result was consistent with the Brown algorithm that predicted an *anti*-stereochemical relationship for the C_{12}-methyl and C_{13}-hydroxyl given *trans*-2-butene as the carbon input. Confirmation of this assignment arose later through comparison with previously characterized intermediates[7b] (see Scheme 2).

The C_{13}-hydroxyl of olefin **7** was readily protected as either a silyl ether **(8)** or benzoate ester **(9)**. Ozonolysis of olefin **8**, again followed by Brown crotylboration,[11] yielded a single alkylated reaction product **(10)**. The drastic change in diastereoselectivity from previous results on this section of calyculin raised suspicion regarding the identity of the newly generated C_{10},C_{11} stereocenters (see Scheme 3).

To assign the newly generated stereocenters, acetonide formation on the C_{11},C_{13}-diol was effected to utilize the Rychnovsky correlation for deducing 1,3-diol stereochemical relationships.[12] The determination of stereochemistry followed from the comparison of the ^{13}C chemical shifts for the 1,3-*O*-acetonide methyl groups of the 1,3-dioxane system, which has been shown to be generally independent of C_2-substitution. To this end, olefin **10** was fully desilylated to afford tetrol **11**. The reaction of tetrol **11** in 2,2-dimethoxypropane in the presence of catalytic acid afforded acetonides **12** and **13**, the latter of which could be readily converted to the desired mono-ketal product via mild acid hydrolysis. Analysis of the ^{13}C spectrum for **12** confirmed an *anti*-stereochemical relationship based on the observed resonances, 23.7 and 24.5 ppm. Evidently, the β-hydroxyl protecting group played a significant role in the asymmetric induction at C_{11} that completely overrode the induction predicted for the Brown crotylboration![11] Indeed, the overwhelming preference for the *anti-syn-anti* relationship

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(12) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

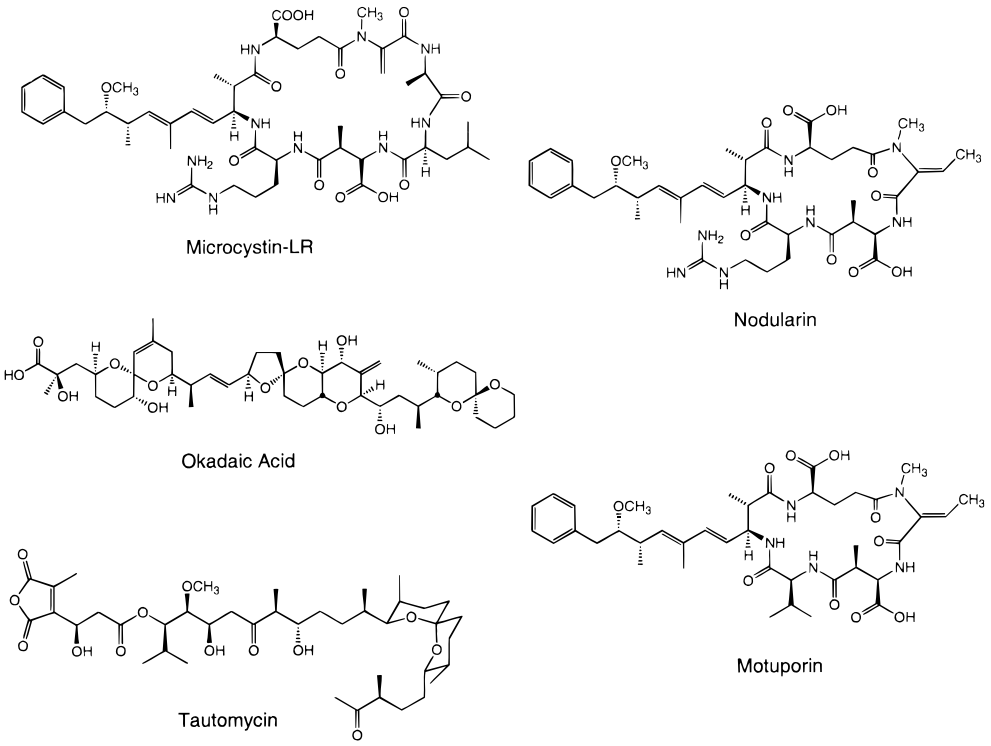


Figure 2.

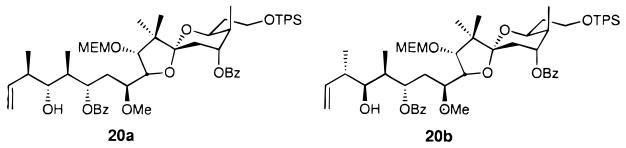
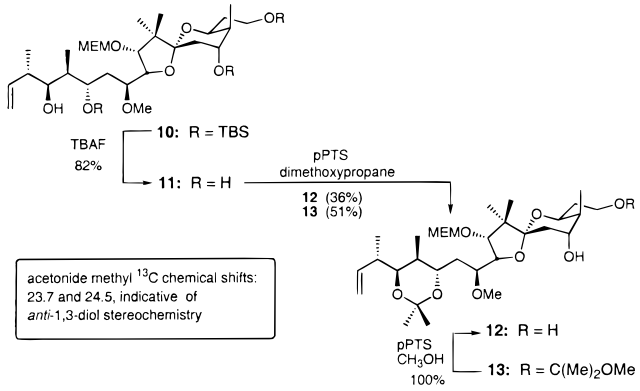


Figure 3.

Scheme 4

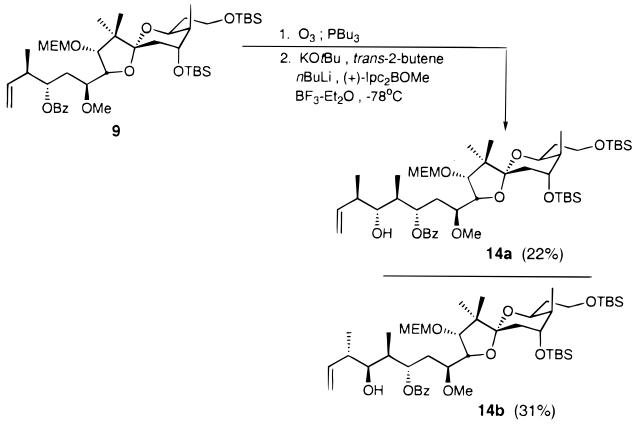


observed for $C_{10}-C_{13}$ in **10** was consistent with the closed transition state model of Roush[13] (see Scheme 4).

This result represented a drastic departure from our previously reported synthesis of the C_1-C_{25} fragment, in which the *anti-anti-anti* isomer was preferentially generated by a 40:30 diastereomeric ratio **(20a:20b**, respectively)[7b] (see Figure 3). The aldehyde used in that Brown crotylboration was benzoyl-protected at C_{13}, which prompted the submission of olefin **9** to a similar ozonolysis-Brown crotylboration sequence. This yielded the desired *anti-anti-anti* diastereomer **14a**, but as the minor component in a 22:31 diastereomeric mixture **(14a** and **14b)** favoring the *anti-syn-anti* isomer. Positive structural assignments were made through the conversion of each dia-

(13) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.

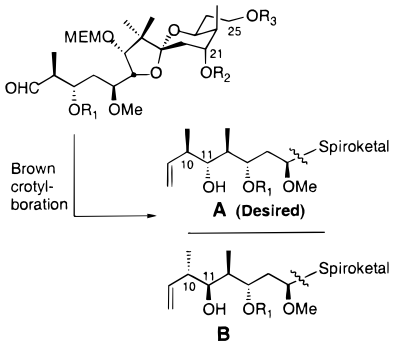
Scheme 5



stereomer to their corresponding tetra-TBS derivatives **(21** and **22)** and comparison to previously reported compound[7b] (see Scheme 7).

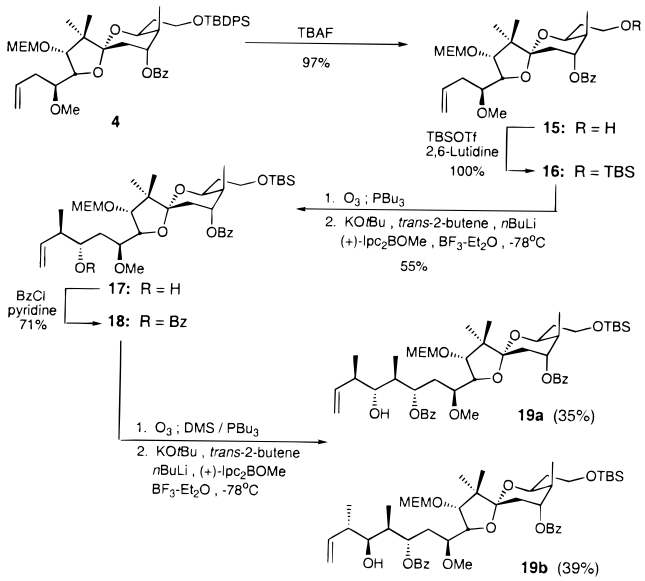
Despite the obvious effect of the β-alkoxy protecting group on stereoselectivity, the discrepancy between the diastereomeric ratios of **14a:14b** and **20a:20b** suggested that the remote protecting groups at C_{21} and C_{25} also impacted the crotylboration diastereoselectivity. This subtle steric effect arose from the *R*-stereochemistry at C_{16}, which projected the reaction site (C_{11}) toward the aforementioned alkoxy groups (protected C_{21} and C_{25}). Illustration of this point derived from the effect of a C_{25}-hydroxyl TBS for TPS exchange on diastereoselectivity at C_{10},C_{11}. Spiroketal **4** was converted to its C_{25}-TBS protected derivative **(16)** in excellent yield. An initial ozonolysis-Brown crotylboration sequence yielded, as expected, a single reaction product **(17)**, the C_{13}-hydroxyl of which was benzoyl-protected **(18)**. The subsequent ozonolysis-Brown crotylboration sequence led to a modest reversal of distereoselectivity to yield homoallylic alcohols **19a** and **19b** in a 35:39 ratio, respectively. Clearly, a definite and remarkable trend exists in which variation

Table 1



	R_1	R_2	R_3	yield of A/B
10	TBS	TBS	TBS	0/48
14	Bz	TBS	TBS	22/31
19	Bz	Bz	TBS	35/39
20	Bz	Bz	TPS	40/30

Scheme 6

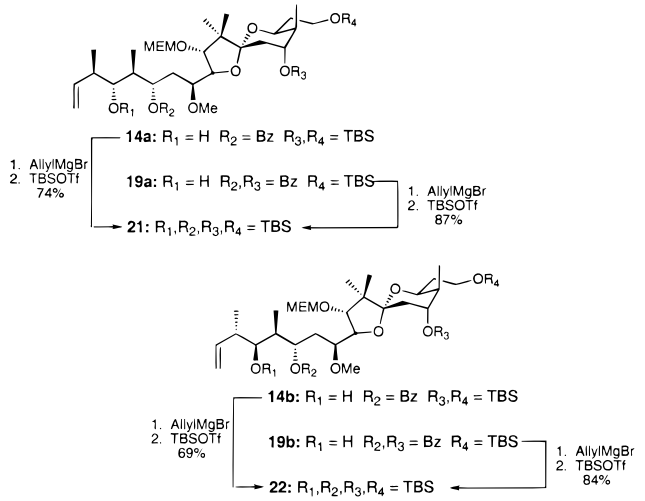


of proximal and remote protecting groups affected the crotylboration diastereoselectivity! (see Table 1)

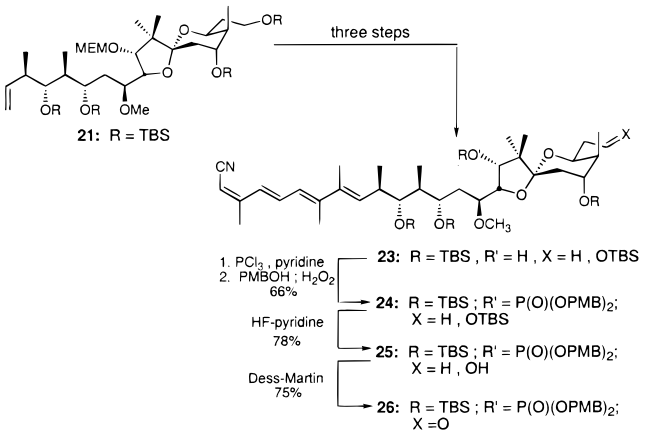
The conversion of *anti-anti-anti* olefin isomers **(14a** and **19a)** to a common tetra-TBS protected compound **(21)** enabled the conclusive assignment of stereochemistry at $C_{10}-C_{13}$ and established the desired global silyl protection scheme. Elaboration to tetraene **23** over four steps followed a previously established route.[7b,8a] Phosphorylation afforded **24** in good yield using the Evans procedure[8a] (see Scheme 2). Selective deprotection of the C_{25}-TBS group **(25)**, followed by Dess−Martin oxidation of the corresponding primary hydroxyl[14] provided aldehyde **26** and completed the C_1-C_{25} fragment synthesis (see Scheme 8).

In our previously reported synthesis of the $C_{26}-C_{37}$ fragment,[7a] Weinreb amidation[15] to generate the $C_{33}-N_3$ amide bond resulted in a C_{34}-epimeric mixture of products,[16] which we were unable to definitively assign. Consequently, both diastereomers were carried on into coupling reactions with the C_1-C_{25}

Scheme 7



Scheme 8



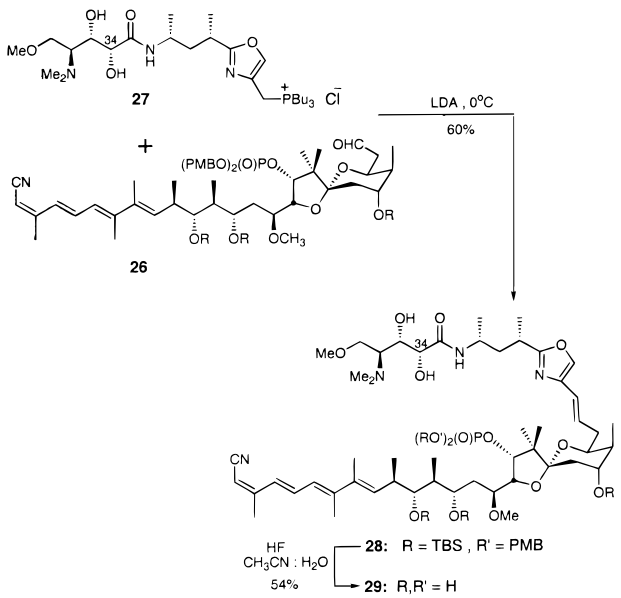
fragment. Condensation of the deprotected phosphonium salt derived from the major amide stereoisomer with aldehyde **26** proceeded in good yield. Submission of the corresponding Wittig adduct to HF-deprotection afforded a TLC spot that failed to coelute with an authentic sample of calyculin C. ^{1}H NMR and HRMS analysis of the resultant product confirmed its identity as a fully deprotected system. This evidence supported our structural assignment of **29** as C_{34}-*epi*-calyculin C and the major Weinreb amidation product as stereoisomer **27** (see Scheme 9).

Condensation of the phosphonium salt from the minor amidation product **(3)** with aldehyde **26** proceeded in acceptable yield to protected calyculin **30**. Deprotection of **30** under the previously employed reaction conditions generated a TLC spot that co-spotted with an authentic sample in multiple solvent systems.[17] ^{1}H NMR[18] and HRMS data were consistent with the aforementioned authentic calyculin C sample, which corroborated our structural assignments of compounds **27**−**30** and represented the completed total synthesis of calyculin C **(1)** (see Scheme 10).

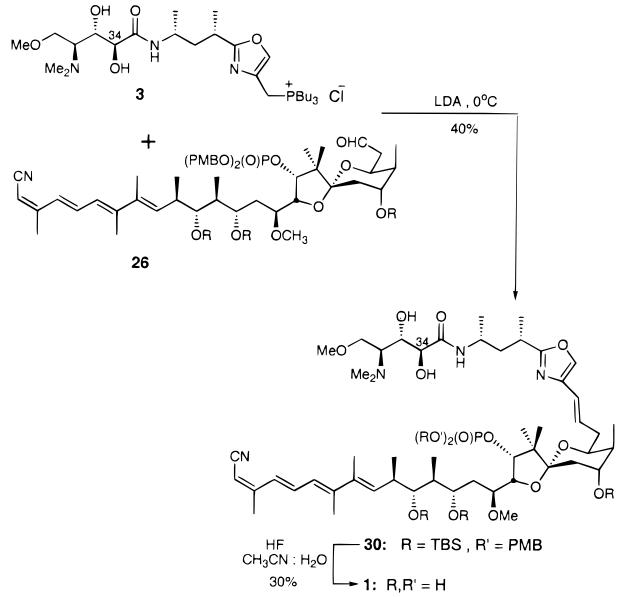
In summary, our pursuit of an improved synthesis for the C_1-C_{25} fragment exposed a remarkable, remote protecting group effect on the diastereoselectivity that was observed during the

(14) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
(15) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.
(16) Noteworthy is our ability to recycle recovered ester from the Weinreb amidation. The diastereoselectivity of the amidation is not affected by the corresponding epimeric mixture present in the ester starting material.
(17) The solvent systems sampled were (a) 10% acetone:ethyl acetate ($R_f = 0.7$), (b) 30% acetone:hexane (double elution; $R_f = 0.3$), (c) 20% acetonitrile:methylene chloride (double elution; $R_f = 0.6$), and (d) 5% methanol:methylene chloride (double elution; $R_f = 0.4$).
(18) 1H NMR data for authentic and synthetic calyculin C were obtained in both $CDCl_3$ and C_6D_6.

Scheme 9



Scheme 10



generation of the C_{10},C_{11}-propionate stereocenters. In addition, we were able to unequivocally assign the stereochemistry at C_{34}. We, therefore, report the total synthesis of calyculin C, a member of a family of structurally diverse serine/threonine phosphatase inhibitors.

Experimental Section

General Methods. NMR spectra were obtained from Bruker AM360, ARX400, and ARX500 spectrometers. IR data was collected on a Nicolet PCIR. Optical rotations were taken at 22 °C on a Perkin-Elmer model 241MC. High-resolution FAB mass spectra were obtained by the Mass Spectroscopy Facilities at UCLA or UC-Riverside. For FAB mass spectra, $2\sigma = 4$ ppm.

Solvents and reagents were used as supplied from commercial sources with the following exceptions. All moisture sensitive reagents not packaged in Aldrich sure seal bottles were distilled prior to use and stored in a desiccated environment. Particularly sensitive reagents, such as dimethyl phosphite and phosphorus trichloride, were freshly distilled prior to each usage. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane was distilled from phosphorus pentoxide. Methanol was distilled from magnesium turnings. Dimethylformamide, dimethyl sulfoxide, and in some cases diisopropylamine were distilled from barium oxide and stored over 4 Å molecular sieves. All reactions involving moisture-sensitive reagents were performed under either a nitrogen or an argon atmosphere.

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-Hydroxy-7-(2-hydroxyethyl)-2-[(1*S*)-methoxy-but-3ene]-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (5). To a solution of benzoate **4** (1.60 g, 2.06 mmol, 1.0 equiv) in CH_2Cl_2 (45 mL) at −78 °C was added allylmagnesium bromide (1.0 M in diethyl ether, 15 mL, 7.25 equiv) rapidly dropwise. The cloudy white reaction mixture was warmed to room temperature over 30 min. The reaction was quenched via addition of H_2O (10 mL), and the resulting suspension was filtered. The solid residue was washed with CH_2Cl_2 (3 × 40 mL), and the filtrate was partitioned between CH_2Cl_2 (20 mL) and brine (60 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated.

The resulting crude, yellow oil was eluted in THF (50 mL), and TBAF (1.0 M in THF, 2.5 mL, 1.2 equiv) was added. After 16 h, the reaction mixture was concentrated, and column chromatography on silica gel (70−100% ethyl acetate−hexane) afforded diol **5** (804 mg, 90%). $[\alpha]_D = -64.5$ (*c* 5.0, $CHCl_3$). IR (thin film) 3501, 2924, 1472, 1419 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (1H, m), 5.10 (1H, dd, $J = 17.2$, 1.2 Hz), 5.06 (1H, m), 4.71 (2H, s), 4.47 (1H, dt, $J = 11.2$, 2.0 Hz), 4.16 (1H, dd, $J = 9.1$, 4.9 Hz), 4.06 (1H, dd, $J = 11.1$, 1.1 Hz), 3.80 (2H, m), 3.71 (4H, m), 3.52, (3H, s), 3.48 (2H, m), 3.33 (3H, s), 2.47 (1H, m), 2.17 (1H, m), 1.91 (1H, m), 1.78 (1H, d, $J = 13.7$ Hz), 1.63 (1H, m), 1.57 (1H, m, $J = 14.2$ Hz), 1.38 (1H, m), 1.06 (3H, s), 0.90 (3H, s), 0.84 (3H, d, $J = 7.1$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 117.3, 108.2, 97.3, 86.7, 83.4, 80.0, 71.5, 70.5, 69.9, 68.5, 63.5, 59.0, 58.9, 50.5, 38.1, 34.8, 34.4, 28.8, 22.9, 17.5, 10.8. HRFABMS calcd for (M + H) $C_{22}H_{41}O_8$: 433.2801, found: 433.2807.

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-*tert*-Butyldimethylsiloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-[(1*S*)-methoxy-but-3ene]-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (6). To a solution of diol **5** (50 mg, 0.116 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C was added 2,6-lutidene (81 μL, 0.693 mmol, 6 equiv). TBSOTf (80 μL, 0.347 mmol, 3 equiv) was added dropwise, and the clear reaction mixture was stirred at 0 °C for 15 min. Saturated aqueous $NaHCO_3$ (2 mL) was added, and the resulting mixture was partitioned between CH_2Cl_2 (20 mL) and brine (15 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (10% ethyl acetate−hexane) afforded silyl ether **6** (70 mg, 92%). $[\alpha]_D = -75.8$ (*c* 3.6, $CHCl_3$). IR (thin film) 2928, 1471, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, m), 5.07 (1H, dd, $J = 17.2$, 1.7 Hz), 5.00 (1H, m), 4.70 (1H, d, $J = 13.1$ Hz), 4.67 (1H, d, $J = 13.1$ Hz), 4.34 (1H, dt, $J = 10.6$, 2.3 Hz), 4.02 (1H, dd, $J = 9.2$, 5.2 Hz), 3.90 (1H, ddd, $J = 15.5$, 10.4, 5.1 Hz), 3.78 (1H, m), 3.62−3.70 (4H, m), 3.59 (3H, s), 3.49 (2H, m), 3.38 (1H, dd, $J = 9.3$, 2.3 Hz), 3.35 (3H, s), 2.34 (1H, m), 2.04 (1H, m), 1.72 (1H, m), 1.60 (1H, dd, $J = 14.3$, 3.8 Hz), 1.36−1.44 (3H, m), 1.00 (3H, s), 0.88 (9H, s), 0.85 (9H, s), 0.78 (3H, d, $J = 7.1$ Hz), 0.04 (3H, s), 0.03 (3H, s), 0.02 (3H, s), −0.02 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 116.1, 106.8, 97.6, 87.7, 84.1, 81.0, 71.6, 71.2, 68.1, 63.5, 62.1, 60.4, 59.0, 50.5, 38.7, 36.5, 35.7, 30.6, 26.1, 25.8, 23.0, 18.4, 18.1, 17.7, 10.5, −4.7, −5.1, −5.2 (2 carbons). HRFABMS calcd for (M + H) $C_{34}H_{69}O_8Si_2$: 661.4531, found: 661.4529.

(2*R*,2(1*S*,3*S*,4*S*),3*R*,5*R*,7*S*,8*R*,9*R*)-9-*tert*-Butyldimethylsiloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-(3-hydroxy-1-methoxy-4-methyl-5-hexenyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (7). Ozone was bubbled through a solution of olefin **6** (993 mg, 1.51 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) at −78 °C until a light blue endpoint was achieved. The excess ozone was purged via a stream of argon (until colorless). Tributylphosphine (350 μL, 1.47 mmol, 0.97 equiv) was added dropwise, and the clear colorless reaction mixture was warmed slowly to room temperature. After 12.5 h, the reaction mixture was concentrated to afford a crude aldehyde which

was carried on without purification. It should be noted that, although the aldehyde generally withstood column chromatography, purification did not improve the yields of the subsequent crotylboration reactions.

To a cloudy solution of KOtBu (676 mg, 6.02 mmol, 4.0 equiv) and *trans*-2-butene (~1 mL, excess) in THF (9 mL) at −78 °C was added dropwise 2.14 M *n*BuLi (2.4 mL, 5.13 mmol, 3.4 equiv). Upon initial addition of *n*BuLi, the reaction mixture became yellow. After, 15 min, a solution of (+)-*B*-Methoxydiisopinocampheylborane (2.18 g, 6.89 mmol, 4.6 equiv) in THF (2.5 mL) was added dropwise. Addition of the borane solution resulted in a clear colorless reaction mixture. After 30 min, BF_3-Et_2O (820 μL, 6.66 mmol, 4.4 equiv) was added rapidly, followed immediately by a solution of the crude aldehyde in THF (2 mL + 0.7 mL rinse). The resulting cloudy, colorless reaction mixture was stirred at −78 °C for 4 h. Then 3 N NaOH (3 mL) and 30% H_2O_2 (1.5 mL) were added, and the cold bath was removed. After 3 h, the mixture was diluted with ethyl acetate (20 mL), poured into brine (20 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 40 mL), and the combined organics were dried over Na_2SO_4, filtered and concentrated. Purification via column chromatography on silica gel (5% ethyl acetate−hexane) afforded olefin **7** (714 mg, 66%). $[\alpha]_D = -61.7$ (*c* 7.7, $CHCl_3$). IR (thin film) 3503, 2928, 1472, cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (1H, ddd, J = 18.6, 10.7, 7.8 Hz), 5.05 (1H, s), 5.03 (1H, m), 4.70 (1H, d, J = 6.4 Hz), 4.63 (1H, d, J = 6.4 Hz), 4.36 (1H, m), 4.12 (1H, dd, J = 9.4, 5.1 Hz), 3.88 (1H, m), 3.77−3.80 (2H, m), 3.62−3.72 (6H, m), 3.51 (3H, m), 3.36 (3H, s), 2.82 (1H, d, J = 5.0 Hz), 2.18 (1H, m), 1.70 (1H, m), 1.57−1.64 (2H, m), 1.38−1.48 (4H, m), 1.02 (3H, d, J = 7.0 Hz), 1.01 (3H, s), 0.89 (9H, s), 0.88 (9H, s), 0.80 (3H, d, J = 7.2 Hz), 0.04 (3H, s), 0.03 (3H, s), 0.03 (3H, s), −0.01 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0. 115.0, 106.9, 98.1, 88.3, 84.3, 79.4, 71.8, 71.6, 71.2, 68.0, 63.5, 61.8, 60.6, 59.0, 50.5, 44.4, 38.6, 36.5, 35.4, 30.6, 26.0, 25.8, 23.0, 18.3, 18.2, 17.6, 16.0, 10.5, −4.7, −5.1, −5.2, −5.2. HRFABMS calcd for (M + H) $C_{37}H_{75}O_9Si_2$: 719.4949, found: 719.4953.

(2*R*,2(1*S*,3*S*,4*S*),3*R*,5*R*,7*S*,8*R*,9*R*)-9-*tert*-Butyldimethylsiloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-(1-methoxy-4-methyl-3-(benzoyl)oxy-5-hexenyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (9). To a solution of alcohol **7** (99 mg, 0.138 mmol, 1 equiv) in pyridine (2 mL) was added benzoyl chloride (32 μL, 0.276 mmol, 2.0 equiv). The clear yellow mixture was heated to 50 °C for 24 h. Concentration in vacuo, followed by purification via column chromatography on silica gel (0−5% ethyl acetate/(1:1) methylene chloride/hexane) afforded spirocycle **9** (101 mg, 89%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (2H, d, J = 7.4 Hz), 7.52 (1H, m), 7.41 (2H, m), 5.84 (1H, ddd, J = 17.6, 9.7, 7.4 Hz), 5.48 (1H, m), 5.03 (2H, m), 4.70 (1H, d, J = 6.9 Hz), 4.65 (1H, d, J = 6.9 Hz), 4.31 (1H, m), 4.01 (1H, dd, J = 8.9, 4.9 Hz), 3.78 (1H, d, J = 2.3 Hz), 3.70 (1H, m), 3.55−3.65 (6H, m), 3.43−3.50 (3H, m), 3.36 (4H, m), 2.52 (1H, m), 1.78 (1H, dd, J = 13.1, 10.8 Hz), 1.60 (1H, dd, J = 14.2, 3.7 Hz), 1.45−1.56 (2H, m), 1.30−1.42 (3H, m), 1.05 (3H, d, J = 8.6 Hz), 1.02 (3H, s), 0.84 (12H, m), 0.76 (12H, m), 0.02 (3H, s), −0.03 (3H, s), −0.15 (3H, s), −0.16 (3H, s). ^{13}CNMR (125 MHz, $CDCl_3$) δ 166.1, 139.3, 132.6, 130.8, 129.6, 128.2, 115.6, 106.8, 98.0, 88.1, 84.9, 77.9, 74.0, 71.7, 71.1, 67.9, 63.8, 61.1, 60.9, 59.0, 50.4, 42.5, 38.1, 34.1, 30.7, 25.8, 25.8, 23.2, 18.1, 18.0, 17.8, 15.8, 10.4, −4.7, −5.2, −5.4, −5.4, −5.4.

(2*R*,2(1*S*,3*S*,4*S*,5*R*,6*R*),3*R*,5*R*,7*S*,8*R*,9*R*)-9-*tert*-Butyldimethylsiloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-(5-hydroxy-1-methoxy-4,6-dimethyl-3-benzoyloxy-8-nonenyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (14a). Ozone was bubbled through a solution of olefin **9** (500 mg, 0.609 mmol, 1 equiv) in CH_2Cl_2 (25 mL) at −78 °C until a light blue color persisted. The excess ozone was purged via a stream of argon (until colorless), at which time DMS (2.3 mL, >50 equiv) was added. The reaction mixture was warmed to room temperature slowly. After 14 h, triphenylphosphine (84 mg total, ~0.6 equiv) was added in three portions over 3 h. The reaction mixture was concentrated after 19 h, and the resulting crude aldehyde was carried on without purification.

To a cloudy solution of KOtBu (352 mg, 3.14 mmol, 5.1 equiv) and *trans*-2-butene (~1 mL, excess) in THF (4 mL) at −78 °C was added dropwise 2.02 M *n*BuLi (1.35 mL, 2.74 mmol, 4.5 equiv). Upon initial addition of *n*BuLi, the reaction mixture became yellow. After, 15 min, a solution of (+)-*B*-Methoxydiisopinocampheylborane (1.03 g, 3.26 mmol, 5.4 equiv) in THF (1.2 mL) was added dropwise. Addition of the borane solution resulted in a clear colorless reaction mixture. After 30 min, BF_3-Et_2O (350 μL, 2.85 mmol, 4.7 equiv) was added rapidly, followed immediately by a solution of the crude aldehyde from above in THF (1.2 mL + 0.5 mL rinse). The resulting cloudy, colorless reaction mixture was stirred at −78 °C for 4 h. Then 3 N NaOH (4 mL) and 30% H_2O_2 (2 mL) were added, and the cold bath was removed. After 13 h, the mixture was diluted with ethyl acetate (20 mL) and poured into brine (20 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 25 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The resultant crude was eluted in THF (8 mL), 3 N NaOH (2 mL), and 30% H_2O_2 (1 mL) to complete oxidation of the borane intermediate. After 2 h, the mixture was worked-up as previously mentioned. The excess isopinocamphol was removed via Kugelrohr distillation (high vacuum pressure at 80 °C). Purification via column chromatography on silica gel (5−20% ethyl acetate−hexane) afforded olefins **14a** (118 mg, 22%) and **14b** (163 mg, 31%) (53% overall for both steps). For **14a**: $[\alpha]_D = -59.1$ (*c* 2.4, $CHCl_3$). IR (thin film) 3443, 2928, 1719, 1377 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (2H, m), 7.54 (1H, m), 7.42 (2H, m), 5.87 (1H, ddd, J = 17.1, 8.6, 6.6 Hz), 5.64 (1H, m), 5.06 (2H, m), 4.70 (1H, d, J = 6.8 Hz), 4.65 (1H, d, J = 6.8 Hz), 4.34 (1H, m), 4.05 (1H, dd, J = 9.0, 4.9 Hz), 3.80 (1H, m), 3.69 (3H, s), 3.35−3.75 (9H, m), 3.33 (3H, s), 2.96 (1H, br d, J = 5.1 Hz), 4.41 (1H, m), 2.12 (1H, ddd, J = 9.0, 6.9, 3.4 Hz), 1.77 (2H, m), 1.62 (1H, m), 1.42 (3H, m), 1.16 (3H, d, J = 6.9 Hz), 1.04 (3H, s), 0.95 (3H, d, J = 6.9 Hz), 0.89 (3H, s), 0.88 (3H, s), 0.86 (9H, s), 0.80 (9H, s), 0.79 (3H, d, J = 5.1 Hz), 0.03 (3H, s), −0.01 (3H, s), −0.09 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 139.3, 132.7, 130.9, 129.6, 128.3, 115.8, 107.0, 98.1, 88.1, 84.9, 79.2, 76.6, 73.3, 71.7, 71.2, 68.0, 63.8, 61.3, 60.9, 59.0, 50.4, 40.6, 39.6, 38.3, 36.3, 32.2, 30.8, 29.7, 26.1, 25.9 (two carbons), 23.2, 18.2, 18.2, 18.0, 17.8, 11.6, 10.5, −4.6, −5.1, −5.3 (two carbons). HRFABMS calcd for (M + Na) $C_{47}H_{84}O_{11}Si_2Na$: 903.5450, found: 903.5459.

(2*R*,2(1*S*,3*S*,4*S*,5*S*,6*S*),3*R*,5*R*,7*S*,8*R*,9*R*)-9-*tert*-Butyldimethylsiloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-(5-hydroxy-1-methoxy-4,6-dimethyl-3-benzoyloxy-8-nonenyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (14b). $[\alpha]_D = -57.7$ (*c* 3.4, $CHCl_3$). IR (thin film) 3492, 2928, 1717, 1472 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (2H, m), 7.56 (1H, m), 7.43 (2H, m), 5.85 (1H, ddd, J = 17.6, 10.3, 7.9 Hz), 5.47 (1H, ddd, J = 9.5, 6.9, 2.2 Hz), 5.08 (2H, m), 4.76 (1H, d, J = 6.9 Hz), 4.72 (1H, d, J = 6.9 Hz), 4.31 (1H, ddd, J = 7.9, 5.2, 2.0 Hz), 4.06 (1H, dd, J = 9.0, 5.0 Hz), 3.79 (1H, d, J = 2.8 Hz), 3.74 (2H, m), 3.55 (3H, s), 3.37 (3H, s), 3.35−3.65 (7H, m), 2.64 (1H, d, J = 3.7 Hz), 2.32 (1H, m), 1.95 (2H, m), 1.76 (1H, m), 1.63 (1H, dd, J = 14.3, 3.9 Hz), 1.51 (1H, m), 1.41 (3H, m), 1.04 (3H, s), 0.98 (3H, d, J = 6.9 Hz), 0.94 (3H, d, J = 6.8 Hz), 0.87 (3H, s), 0.82 (9H, s), 0.79 (9H, s), 0.78 (3H, d, J = 7.2 Hz), 0.02 (3H, s), −0.02 (3H, s), −0.11 (3H, s), −0.12 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 141.9, 132.9, 130.4, 129.7, 128.4, 115.1, 106.9, 98.0, 87.7, 84.9, 78.2, 74.4, 73.8, 71.8, 71.2, 68.1, 64.0, 61.1, 60.9, 59.0, 50.5, 41.0, 39.4, 38.0, 36.0, 33.9, 30.7, 26.1, 25.9, 25.9, 23.2, 18.2, 18.1, 17.8, 16.5, 10.4, 8.7, −4.7, −5.1, −5.3, −5.3. HRFABMS calcd for (M + H) $C_{47}H_{85}O_{11}Si_2$: 881.5630, found: 881.5630.

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-Benzoyloxy-7-(2-hydroxyethyl)-2-[(1*S*)-methoxy-but-3ene]-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (15). To a solution of silyl ether **4** (1.100 g, 1.42 mmol, 1 equiv) in THF (15 mL) was added 1.0 M TBAF (3.5 mL, 3.55 mmol, 2.5 equiv). After 2.5 h, the reaction mixture was concentrated. Purification via column chromatography on silica gel (30−50% ethyl acetate−hexane) afforded alcohol **15** (736 mg, 97%). $[\alpha]_D = -52.0$ (*c* 28.0, $CHCl_3$). IR (thin film) 3497, 2924, 1713, 1453 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, m), 7.49 (1H, m), 7.37 (2H, m), 5.87 (1H, m), 5.11 (1H, m), 5.07 (1H, dd, J = 17.2, 1.0 Hz), 5.02 (1H, d, 10.0 Hz), 4.71 (2H, s), 4.58 (1H, m), 4.19 (1H, m), 4.14 (1H, dd, J = 9.1, 4.8 Hz), 3.83 (1H, m), 3.65−3.74 (4H, m), 3.53 (4H, m), 3.46 (2H, m), 3.30 (3H, s), 2.43 (1H, m), 2.15 (1H, m), 1.89 (1H, m), 1.84 (1H, dd, J = 15.0, 4.1 Hz), 1.74 (2H, m), 1.35 (1H, dd,

J = 14.5, 4.0 Hz), 1.08 (3H, s), 0.97 (3H, d, J = 7.1 Hz), 0.88 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 134.6, 132.7, 130.6, 129.8, 128.1, 116.7, 106.6, 97.2, 87.2, 83.1, 80.3, 73.4, 71,4, 69.9, 68.3, 63.0, 59.1, 58.8, 50.6, 35.2, 34.8, 34.7, 27.3, 22.7, 17.4, 10.2. HRFABMS calcd for (M + H) $C_{29}H_{45}O_9$: 537.3064, found: 537.3066.

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-Benzoyloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-[(1*S*)-methoxy-but-3ene]-3-(2-methoxyethoxy methyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (16). To a solution of alcohol **15** (736 mg, 1.37 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at 0 °C was added 2,6-lutidine (390 μL, 3.34 mmol, 2.4 equiv), followed by TBSOTf (380 μL, 1.65 mmol, 1.2 equiv). After 10 min, the reaction mixture was partitioned between CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (5−15% ethyl acetate−hexane) afforded silyl ether **16** (924 mg, 103%, contaminated with TBS-OH). $[\alpha]_D$ = −77.7 (*c* 20.2, $CHCl_3$). IR (thin film) 2928, 1715, 1453 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (2H, m), 7.48 (1H, m), 7.38 (2H, m), 5.88 (1H, dddd, J = 17.7, 7.8, 4.3, 2.1 Hz), 5.13 (1H, m), 5.07 (1H, dd, J = 17.1, 1.2 Hz), 5.01 (1H, d, J = 10.2 Hz), 4.69 (2H, m), 4.42 (1H, m), 4.07 (1H, dd, J = 9.3, 5.2 Hz), 3.90 (1H, m), 3.68 (3H, m), 3.62 (1H, d, J = 5.2 Hz), 3.51 (3H, s), 3.49 (5H, m), 3.33 (3H, s), 2.40 (1H, m), 2.11 (1H, m), 1.81 (1H, dd, J = 11.1, 4.0 Hz), 1.68−1.78 (3H, m), 1.46 (1H, m), 1.07 (3H, s), 0.94 (3H, d, J = 7.1 Hz), 0.86 (3H, s), 0.84 (9H, s), 0.01 (3H, s), 0.00 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 135.1, 132.5, 130.7, 129.8, 128.0, 116.2, 106.3, 97.5, 87.2, 83.1, 80.6, 72.9, 71.5, 68.0, 63.8, 61.4, 59.2, 58.8, 50.5, 36.0, 34.9, 34.8, 27.5, 25.9, 22.8, 18.2, 17.5, 10.0, −5.4, −5.4. HRFABMS calcd for (M + Na) $C_{35}H_{58}O_9SiNa$: 673.3748, found: 673.3775.

(2*R*,2(1*S*,3*S*,4*S*),3*R*,5*R*,7*S*,8*R*,9*R*)-9-Benzoyloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-(3-hydroxy-1-methoxy-4-methyl-5-hexenyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]-decane (17). Ozone was bubbled through a solution of olefin **16** (653 mg, 1.00 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) at −78 °C until a light blue endpoint was achieved. The excess ozone was purged via a stream of argon (until colorless). Tributylphosphine (250 μL, 1.05 mmol, 1.05 equiv) was added dropwise, and the clear, colorless reaction mixture was warmed slowly to room temperature. After 10 h, the reaction mixture was concentrated to afford a crude aldehyde that was carried on without purification.

To a cloudy solution of KOtBu (560 mg, 4.99 mmol, 5.0 equiv) and *trans*-2-butene (∼1.5 mL, excess) in THF (6 mL) at −78 °C was added dropwise 2.02 M *n*BuLi (2.3 mL, 4.65 mmol, 4.6 equiv). Upon initial addition of *n*BuLi, the reaction mixture became yellow. After, 15 min, a solution of (+)-*B*-Methoxydiisopinocampheylborane (1.72 g, 5.42 mmol, 5.4 equiv) in THF (2 mL) was added dropwise. Addition of the borane solution resulted in a clear, colorless reaction mixture. After 30 min, BF_3-Et_2O (590 μL, 4.79 mmol, 4.8 equiv) was added rapidly, followed immediately by a solution of the crude aldehyde in THF (2.4 mL + 1 mL rinse). The resulting cloudy colorless reaction mixture was stirred at −78 °C for 3 h. Then 3 N NaOH (4 mL) and 30% H_2O_2 (2 mL) were added, and the cold bath was removed. After 5 h, the mixture was diluted with ethyl acetate (50 mL) and poured into brine (20 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 50 mL), and the combined organics were dried over Na_2SO_4, filtered and concentrated. Purification via column chromatography on silica gel (5% ethyl acetate−hexane) afforded olefin **17** (390 mg, 55%). $[\alpha]_D$ = −87.3 (*c* 12.9, $CHCl_3$). IR (thin film) 3500 (br), 2930, 1713 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, m), 7.50 (1H, m), 7.40 (2H, m), 5.82 (1H, ddd, J = 17.0, 10.7, 7.8 Hz), 5.14 (1H, m), 5.06 (1H, s), 5.03 (1H, d, J = 8.1 Hz), 4.73 (1H, d, J = 6.3 Hz), 4.65 (1H, d, J = 6.4 Hz), 4.45 (1H, m), 4.18 (1H, dd, J = 9.5, 5.0 Hz), 3.88 (1H, m), 3.79 (1H, m), 3.65−3.75 (3H, m), 3.64 (1H, m), 3.58 (3H, s), 3.57 (1H, m), 3.51 (2H, m), 3.37 (3H, s), 2.82 (1H, s br), 2.18 (1H, m), 1.83 (1H, dd, J = 15.0, 4.0 Hz), 1.72−1.79 (3H, m), 1.62 (1H, m), 1.45−1.50 (2H, m), 1.07 (3H, s), 1.02 (3H, d, J = 6.8 Hz), 0.96 (3H, d, J = 7.1 Hz), 0.89 (3H, s), 0.84 (9H, s), 0.01 (3H, s), 0.00 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 140.8, 132.7, 130.7, 129.9, 128.1, 115.1, 106.5, 98.1, 87.9, 83.7, 79.3, 73.1, 71.8, 71.4, 68.0, 64.0, 61.3, 60.1, 58.9, 50.6, 44.4, 36.1, 35.0, 34.8, 27.8, 25.9, 22.8, 18.2, 17.6, 15.9, 10.1, −5.3, −5.4. HRFABMS calcd for (M + Na) $C_{38}H_{64}O_{10}SiNa$: 731.4166, found: 731.4205.

(2*R*,2(1*S*,3*S*,4*S*),3*R*,5*R*,7*S*,8*R*,9*R*)-9-Benzoyloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-(3-benzoyloxy-1-methoxy-4-methyl-5-hexenyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]-decane (18). To a solution of alcohol **17** (712 mg, 1.00 mmol, 1 equiv) in pyridine (10 mL) was added DMAP (32 mg, 0.26 mmol, 0.26 equiv), followed by benzoyl chloride (190 μL, 1.64 mmol, 1.6 equiv). The clear yellow-brown reaction mixture was heated at 58 °C for 14.5 h, at which time concentration afforded a brown slurry. Purification via column chromatography on silica gel (10−20% ethyl acetate−hexane) afforded dibenzoate **18** (578 mg, 71%), as well as a tribenzoate byproduct (101 mg, 13%). $[\alpha]_D$ = −76.0 (*c* 12.0, $CHCl_3$). IR (thin film) 2930, 1719 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (2H, m), 8.02 (2H, m), 7.51 (1H, m), 7.47 (1H, m), 7.39 (2H, m), 7.35 (2H, m), 5.82 (1H, ddd, J = 17.4, 9.7, 7.1 Hz), 5.48 (1H, m), 5.11 (1H, m), 5.04 (2H, m), 4.71 (1H, d, J = 6.9 Hz), 4.67 (1H, d, J = 6.9 Hz), 4.41 (1H, m), 4.06 (1H, dd, J = 9.1, 4.9 Hz), 3.72 (1H, ddd, J = 9.0, 5.3, 3.4 Hz), 3.63 (1H, ddd, J = 10.1, 6.2, 4.2 Hz), 3.60 (1H, d, J = 4.9 Hz), 3.53 (3H, s), 3.40−3.50 (4H, m), 3.35 (3H, s), 2.53 (1H, m), 1.81 (2H, m), 1.75 (2H, m), 1.60 (1H, m), 1.52 (1H, ddd, J = 12.5, 10.3, 2.2 Hz), 1.41 (1H, m), 1.07 (3H, s), 1.04 (3H, d, J = 6.9 Hz), 0.92 (3H, d, J = 7.2 Hz), 0.89 (3H, s), 0.71 (9H, s), −0.18 (3H, s), −0.19 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 166.0, 139.2, 132.6, 130.7, 130.6, 129.8, 129.5, 128.2, 128.0, 115.7, 106.5, 97.9, 87.6, 84.5, 77.8, 73.8, 73.1, 71.6, 67.9, 64.2, 60.6, 60.5, 58.9, 50.4, 42.5, 35.7, 34.4, 33.8, 27.8, 25.7, 23.0, 17.9, 17.7, 15.7, 10.0, −5.5, −5.6.

(2*R*,2(1*S*,3*S*,4*S*,5*R*,6*R*),3*R*,5*R*,7*S*,8*R*,9*R*)-9-benzoyloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-(5-hydroxy-1-methoxy-4,6-dimethyl-3-benzoyloxy-8-nonenyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro [4.5]decane (19a). Ozone was bubbled through a solution of olefin **18** (841 mg, 1.03 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at −78 °C until a light blue color persisted. The excess ozone was purged via a stream of argon (until colorless), at which time DMS (3.6 mL, ∼50 equiv) was added. The reaction mixture was warmed to room temperature slowly. After 11 h, triphenylphosphine (105 mg total, ∼0.4 equiv) was added in two portions over 3 h. The reaction mixture was concentrated after 16 h (total reaction time), and the resulting crude aldehyde was carried on without purification.

To a cloudy solution of KOtBu (600 mg, 5.35 mmol, 5.2 equiv) and *trans*-2-butene (∼2 mL, excess) in THF (6 mL) at −78 °C was added dropwise 2.02 M *n*BuLi (2.30 mL, 4.65 mmol, 4.5 equiv). Upon initial addition of *n*BuLi, the reaction mixture became yellow. After, 15 min, a solution of (+)-*B*-Methoxydiisopinocampheylborane (1.74 g, 5.49 mmol, 5.3 equiv) in THF (2 mL) was added dropwise. Addition of the borane solution resulted in a clear, colorless reaction mixture. After 30 min, BF_3-Et_2O (600 μL, 4.86 mmol, 4.7 equiv) was added rapidly, followed immediately by a solution of the crude aldehyde in THF (2.2 mL + 1.2 mL rinse). The resulting cloudy, colorless reaction mixture was stirred at −78 °C for 3.5 h. Then 3 N NaOH (4 mL) and 30% H_2O_2 (2 mL) were added, and the cold bath was removed. After 1 h, the mixture was diluted with ethyl acetate (20 mL) and poured into brine (20 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (5 × 30 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The resultant crude was eluted in THF (10 mL), 3 N NaOH (3 mL), and 30% H_2O_2 (1.5 mL) to complete oxidation of the borane intermediate. After 1 h, the mixture was worked-up as previously mentioned. The excess isopinecamphol was removed via Kugelrohr distillation (high vacuum pressure at 65 °C). Purification via column chromatography on silica gel (5−20% ethyl acetate−hexane) afforded olefins **19a** (315 mg, 35%) and **19b** (351 mg, 39%) (74% overall for both steps). For **19a**: $[\alpha]_D$ = 71.9 (*c* 10.5, $CHCl_3$). IR (thin film) 3500 (br), 2930, 1717, 1453 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03−8.13 (4H, m), 7.47−7.55 (2H, m), 7.35−7.42 (4H, m), 5.83 (1H, ddd, J = 17.0, 10.5, 8.5 Hz), 5.68 (1H, m), 5.12 (1H, m), 5.06 (2H, m), 4.71 (1H, d, J = 6.7 Hz), 4.68 (1H, d, J = 6.7 Hz), 4.43 (1H, ddd, J = 6.3, 4.1, 2.1 Hz), 4.10 (1H, dd, J = 9.1, 4.9 Hz), 3.69 (2H, m), 3.64 (1H, d, J = 4.8 Hz), 3.60 (3H, s), 3.36−3.58 (6H, m), 3.33 (3H, s), 3.30 (1H, m), 2.60

(1H, br), 2.41 (1H, m), 2.11 (1H, m), 1.57−1.90 (6H, m), 1.45 (1H, m), 1.14 (3H, d, J = 6.9 Hz), 1.09 (3H, s), 0.96 (3H, d, J = 7.3 Hz), 0.94 (3H, d, J = 7.4 Hz), 0.91 (3H, s), 0.75 (9H, s), −0.14 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 165.8, 139.2, 132.7, 132.7, 130.8, 130.6, 129.8, 129.5, 128.2, 128.1, 116.0, 106.6, 97.9, 87.5, 84.6, 79.0, 76.6, 73.2, 72.6, 71.7, 68.0, 64.3, 60.8, 60.7, 58.9, 40.6, 39.6, 35.9, 34.6, 31.8, 27.8, 25.7, 23.0, 18.0, 17.8, 17.7, 11.2, 10.0, −5.4, −5.5. HRFABMS calcd for (M + Na) $C_{48}H_{74}O_{12}SiNa$: 893.4847, found: 893.4817.

(2*R*,2(1*S*,3*S*,4*S*,5*S*,6*S*),3*R*,5*R*,7*S*,8*R*,9*R*)-9-benzoyloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-(5-hydroxy-1-methoxy-4,6-dimethyl-3-benzoyloxy-8-nonenyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro [4.5]decane (19b). $[\alpha]_D = -70.3$ (c 10.9, $CHCl_3$). IR (thin film) 3500 (br), 2930, 1713, 1453 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (4H, m), 7.32−7.56 (6H, m), 5.83 (1h, ddd, J = 17.8, 10.3, 7.9 Hz), 5.46 (1H, m), 5.04−5.14 (3H, m), 4.75 (2H, m), 4.40 (1H, ddd, J = 7.6, 5.1, 1.8 Hz), 4.10 (1h, dd, J = 9.0, 4.9 Hz), 3.0.39−3.77 (12H, m), 3.35 (3H, s), 3.34 (1H, m), 2.50 (1H, br), 2.31 (1H, m), 1.97 (2H, m), 1.83 91H, dd, J = 15.2, 4.2 Hz), 1.76 (3H, m), 1.57 (1H, m), 1.41 (1H, m), 1.09 (3H, s), 0.97 (3H, d, J = 6.9 Hz), 0.93 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 7.1 Hz), 0.91 (3H, s), 0.71 (9H, s), −0.17 (3H, s), −0.19 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 166.1, 141.6, 132.9, 132.6, 130.6, 130.3, 129.8, 129.6, 128.3, 128.0, 115.3, 106.6, 97.8, 87.3, 84.5, 78.0, 74.1, 73.8. 71.7, 68.1, 64.2, 60.6, 60.5, 59.0, 50.4, 40.9, 39.4, 35.6, 34.3, 33.6, 27.8, 25.7, 23.0, 17.9, 17.7, 16.4, 10.0, 8.6, −5.5, −5.6. HRFABMS calcd for (M + Na) $C_{48}H_{74}O_{12}SiNa$: 893.4847, found: 893.4860.

(2*R*,2(1*S*,3*S*,4*S*,5*R*,6*R*),3*R*,5*R*,7*S*,8*R*,9*R*)-9-*tert*-Butyldimethylsiloxy-7-(2-*tert*-butyldimethylsiloxyethyl)-2-(1-methoxy-4,6-dimethyl-3,5-bis(*tert*-butyldimethylsiloxy)-8-nonenyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (21). $[\alpha]_D = -41.9$ (c 1.7, $CHCl_3$). IR (thin film) 2928, 1472 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (1H, ddd, J = 17.4, 10.4, 7.1 Hz), 4.98 (2H, m), 4.80 (1H, d, J = 7.3 Hz), 4.57 (1H, d, J = 7.3 Hz), 4.38 (1H, m), 4.30 (1H, m), 3.96 (1H, dd, J = 9.1, 4,7 Hz), 3.75−3.85 (3H, m), 3.62 (3H, s), 3.47−3.67 (6H, m), 3.38−3.41 (1H, m), 3.38 (3H, m), 2.42 (1H, m), 1.86 (1H, m), 1.71 (1H, m), 1.64 (1H, dd, J = 14.2, 4.0 Hz), 1.40−1.53 (3H, m), 1.25 (2H, m), 1.05 (3H, s), 1.04 (3H, d, J = 6.9 Hz), 0.91 (3H, s), 0.89 (9H, s), 0.88 (9H, s), 0.87 (18H, s), 0.81 (3H, d, J = 7.1 Hz), 0.74 (3H, d, J = 7.1 Hz), 0.13 (3H, s), 0.10 (3H, s), 0.07 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.03 (6H, s), 0.01 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 113.6, 106.8, 98.7, 89.6, 86.4, 77.6, 77.4, 71.8, 71.4, 68.1, 67.8, 64.0, 61.3, 60.3, 59.0, 50.1, 43.7, 42.6, 37.9, 36.1, 33.9, 31.2, 29.7, 26.3, 26.1, 26.0, 25.9, 25.7, 23.3, 18.4, 18.3, 18.2, 18.1, 17.9, 15.4, 10.6, 10.4, −3.0, −3.8, −4.0, −4.0, −4.6, −5.0 (3 carbons).

(2*R*,3*S*,4*S*)-*N*-[(1*R*,3*S*)-3-[4-(1*E*)-3[(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-2-[(1*S*,-3*S*,4*S*,5*R*,6*R*,7*E*,9*E*,11*E*,13*Z*)-3,5-Bis(*tert*-butyldimethylsiloxy)-14-cyano-1-methoxy-4,6,8,9,13-pentamethyl-7,9,11,13-tetradecatetraenyl]-9-(*tert*-butyldimethylsiloxy)-3-[bis(*p*-methoxybenzyl)phosphatyl]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-7-yl]propenyl]-2-oxazolyl]-1-methylbutyl]-2,3-dihydroxy-4-(dimethylamino)-5-methoxy Valeramide (28). To a solution of aldehyde **26** (9.6 mg, 0.015 mmol) and phosphonium salt **27** (10.4 mg, 0.008 mmol) in DMF (200 μL) at 0 °C was added LDA (32 μL, 0.5 M in THF, 1 equiv). Four successive portions of LDA (3 × 32 μL, then 15 μL, 0.5 M in THF) were added over 30 min, at which time the reaction mixture was partitioned between ethyl acetate (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (2−6% $CH_3OH-CH_2Cl_2$) afforded aldehyde **26** (6 mg, 58%) and olefin **28** (3 mg, 23%, 55% based on recovered starting material, **26**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (1H, s), 6.99−7.08 (4H, m), 6.77−6.85 (5H, m), 6.36 (1H, d, J = 11.1 Hz), 6.16 (2H, m), 6.07 (1H, d, J = 8.9 Hz), 5.06 (1H, s), 5.01 (1H, dd, J = 20.9, 11.6 Hz), 4.91 (1H, dd, J = 25.6, 13.6 Hz), 4.80 (1H, dd, J = 11.2, 5.3 Hz), 4.67 (1H, dd, J = 11.0, 5.8 Hz), 4.56 (2H, m), 4.38 (1H, br d), 4.29 (1H, br), 4.09 (3H, m), 3.84 (1H, br), 3.76−3.79 (9H, m), 3.66 (4H, m), 3.58 (1H, m), 3.48 (1H, m), 3.35 (3H, s), 2.99 (1H, m), 2.73 (7H, br m), 2.65 (2H, m), 2.07 (3H, s), 2.01 (3H, s), 1.88 (3H, s), 1.40−1.85 (8H, m), 1.33 (3H, d, J = 6.8 Hz), 1.25 (3H, s), 1.19 (3H, d, J = 6.5 Hz), 1.16 (3H, s), 1.03 (3H, d, J = 6.9 Hz), 0.94 (9H, s), 0.88 (3H, d, J = 9.0 Hz), 0.86 (9H, s), 0.85 (9H, s), 0.82 (3H, d, J = 7.0 Hz), 0.20 (3H, s), 0.08 (3H, s), 0.07 (3H, s), 0.05 (3H, s), 0.04 (3H, s), −0.01 (3H, s).

34*R*-Calyculin C (29). To a Nalgene tube (2 mL) containing protected calyculin **28** (3 mg, 1.8 μmol) and a magnetic stirbar was added an HF stock solution (130 μL; composed of 215 μL of CH_3CN, 45 μL of H_2O, and 23 μL of 48% aqueous HF). After a total reaction time of 65 h, the entire reaction mixture was chromatographed directly on silica gel (0−12% $CH_3OH-CH_2Cl_2$) to afford 34*R*-calyculin C **29** (1 mg, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (1H, m), 7.33 (1H, s), 6.99 (1H, dd, J = 14.9, 11.1 Hz), 6.88 (1H, m), 6.81 (1H, d, J = 14.9 Hz), 6.32 (1H, d, J = 11.5 Hz), 6.13 (1H, d, J = 16.1 Hz), 6.01 (1H, J = 9.8 Hz), 5.05 (1H, s), 4.57 (1H, m), 4.45 (1H, s), 4.35 (1H, m), 4.26 (1H, dd, J = 10.3, 3.5 Hz), 4.24 (1H, m), 4.05 (1H, m), 3.97 (2H, m), 3.87 (1H, m), 3.78 (1H, dd, J = 9.7, 9.4 Hz), 3.56 (2H, m), 3.54 (3H, s), 3.39 (3H, s), 3.16 (1H, m), 2.85 (6H, s), 2.73 (1H, m), 2.49 (1H, m), 2.07 (3H, d, J = 1.0 Hz), 1.97 (3H, s), 1.84 (3H, s), 1.45−2.10 (8H, m), 1.32 (3H, d, J = 6.6 Hz), 1.29 (3H, d, J = 6.9 Hz), 1.23 (3H, s), 1.03 (3H, d, J = 6.9 Hz), 0.95 (3H, s), 0.88 (3H, d, J = 7.1 Hz), 0.71 (3H, d, J = 6.8 Hz). HRFABMS calcd for $C_{51}H_{84}N_4O_{15}P$ (MH^+): 1023.5671, found: 1023.5690.

(2*S*,3*S*,4*S*)-*N*-[(1*R*,3*S*)-3-[4-(1*E*)-3[(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-2-[(1*S*,3*S*,-4*S*,5*R*,6*R*,7*E*,9*E*,11*E*,13*Z*)-3,5-Bis(*tert*-butyldimethylsiloxy)-14-cyano-1-methoxy-4,6,8,9,13-pentamethyl-7,9,11,13-tetradecatetraenyl]-9-(*tert*-butyldimethylsiloxy)-3-[bis(p-methoxybenzyl)phosphatyl]-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-7-yl]propenyl]-2-oxazolyl]-1-methylbutyl]-2,3-dihydroxy-4-(dimethylamino)-5-methoxy Valeramide (30). To a solution of aldehyde **26** (9 mg, 0.007 mmol) and phosphonium salt **3** (10 mg, 0.017 mmol) in DMF (120 μL) at 0 °C was added LDA (37 μL, 0.5M in THF, 1 equiv). Six successive portions of LDA (6 × 37 μL, 0.5M in THF) were added over 1 h, at which time the reaction mixture was partitioned between ethyl acetate (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (2−6% $CH_3OH-CH_2Cl_2$) afforded aldehyde **26** (4 mg, 44%) and olefin **30** (2.7 mg, 24%, 41% based on recovered starting material, **26**). HRFABMS calcd for $C_{85}H_{142}N_4O_{17}PSi_3$ (MH^+): 1605.9415, found: 1605.9381.

Calyculin C (1). To a Nalgene tube (2 mL) containing protected calyculin **30** (2.5 mg, 1.5 μmol) was added an HF stock solution (100 μL; composed of 215 μL of CH_3CN, 45 μL of H_2O, and 23 μL of 48% aqueous HF). After a total reaction time of 60 h, the entire reaction mixture was chromatographed directly on silica gel (0−5% $CH_3OH-CH_2Cl_2$) to afford calyculin C **(1)** (0.4 mg, 30%). Thin-layer chromatography of **1** was performed in multiple solvent systems against an authentic sample of calyculin C.[17] For ^{1}HNMR of **1** and authentic calyculin C, see Supporting Information. HRFABMS calcd for $C_{51}H_{84}N_4O_{15}P$ (MH^+): 1023.5671, found: 1023.5723.

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Supporting Information Available: Experimental procedures and/or data for compounds **8**, **10**−**12**, and **22**, as well as copies of ^{1}H NMR for compounds **1**, **5**−**19b**, **21**−**22**, and **28**−**29** are provided. Mass spectral data for compounds **1** and **30** are also provided (36 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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