Asymmetric Synthesis of Calyculin C. 2. Synthesis of the C_{26}−C_{37} Fragment and Model Wittig Couplings

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We report our synthesis of the C_{26}−C_{37} fragment of serine/threonine protein phosphatase PP1 and PP2A inhibitor calyculin C **(1)**. Outlined in this paper are synthetic approaches to the two components based on disconnection at the C_{33}−N_3 amide bond. We report the successful synthesis of the C_{33}−C_{37} aza-sugar derived from D-lyxose which was coupled onto a C_{26}−C_{32} aminooxazole originating from L-pyroglutamic acid. Elaboration of the resulting amide to a fully deprotected C_{26}−C_{37} fragment of calyculin C completed our synthesis. This provided an appropriate phosphonium salt for use in a Wittig olefination for joining both halves of the natural product.

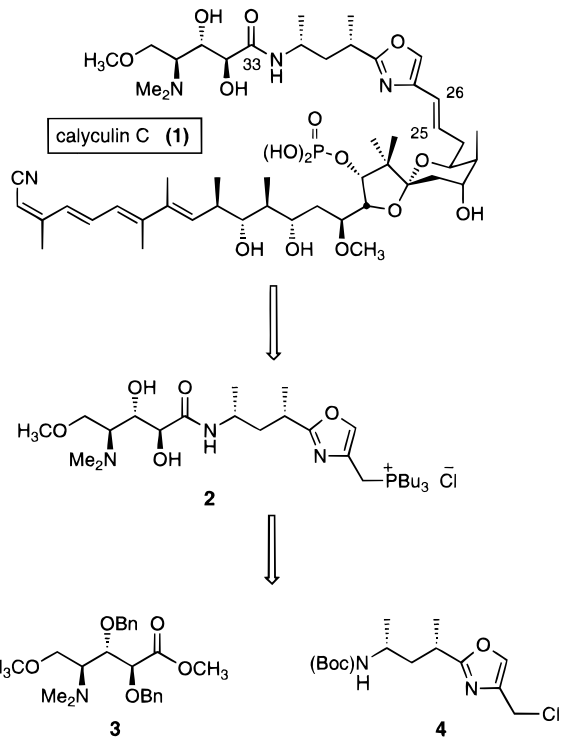
Introduction

In the previous paper, the synthesis of the C_1−C_{25} fragment applicable to calyculins A[3] and C[4] was reported. Herein the focus is on the synthetic efforts directed toward the C_{26}−C_{37} fragment and subsequent couplings to model completion of the carbon skeleton of serine/threonine phosphatase inhibitor calyculin C.

Retrosynthetic analysis of calyculin revealed several possibilities for carbon−carbon bond disconnections. Our strategy centered on an initial disconnection at the C_{25}−C_{26} double bond, dividing the natural product into two fragments of similar functional density. Coupling at this junction was perceived to afford a high degree of convergence. In addition, this strategy was in accord with other synthetic efforts.[5−7]

The introduction of several functionalities within the C_{26}−C_{37} fragment **2** provided concern in establishing our synthetic plan. Formation of the C_{33}−N_3 amide bond in high yield was viewed as critical if efficient use of both fragments **(3** and **4)** was to be maintained (Scheme 1).

Scheme 1



Foremost in our mind was the judicious choice of methodology for introduction and subsequent protection of the amine functionalities at C_{32} and C_{36}. Two possibilites existed and provided a means for stereochemical control of amine introduction. One approach to ester **3** was derived from the preset stereochemistry found in aldopentoses. Reliance on a pentose starting point also precluded any necessity for chain homologation, and controlled introduction of nitrogen at C_{36} could conveniently arise from displacement of oxygen.

The potential for an amino acid-based strategy provided a reasonable alternative to the synthesis of the aza-sugar and offered a stereospecific method for generating the C_{26}−C_{32} oxazole fragment. Synthetic routes originating from amino acids served as the basis for early

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(1) Taken in part from the Ph.D. Thesis of John A. DeMattei, University of California, Los Angeles, 1994.

(2) Taken in part from the Ph.D. Thesis of Gerard R. Scarlato, University of California, Los Angeles, 1990.

(3) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya T. *J. Am. Chem. Soc.* **1986**, *108*, 2780.

(4) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koski, K. *J. Org. Chem.* **1988**, *53*, 3930.

(5) Preliminary communications from this laboratory on this subject, see: (a) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609. (b) Armstrong, R. W.; DeMattei, J. A. *Tetrahedron Lett.* **1991**, *32*, 5749.

(6) For completed total syntheses of both enantiomers of calyculin A, see: (a) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434. (b) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem.* **1994**, *106*, 674.

(7) For other efforts directed toward the synthesis of calyculins, see: (a) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129. (b) Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958. (c) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961. (d) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Org. Chem.* **1992**, *57*, 1964. (e) Duplanter, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357. (f) Vaccaro, H. A.; Levy, D. E.; Sawabe, A.; Jaetsch, T.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1937. (g) Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shiori, T. *Tetrahedron Lett.* **1991**, *32*, 5983. (h) Hara, O.; Hamada, Y.; Shiori, T. *Synlett* **1991**, 283. (i) Yokokawa, F.; Hamada, Y.; Shiori, T. *Synlett* **1992**, 149. (j) Smith, A. B., III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855. (k) Smith, A. B., III; Salvatore, B. A.; Hull, K. G.; Duan, J. J-W. *Tetrahedron Lett.* **1991**, *32*, 4859. (l) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243. (m) Barrett, A. G. M.; Edmunds, J. J.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1236. (n) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1238. (o) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Malecha, J. W.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1240.

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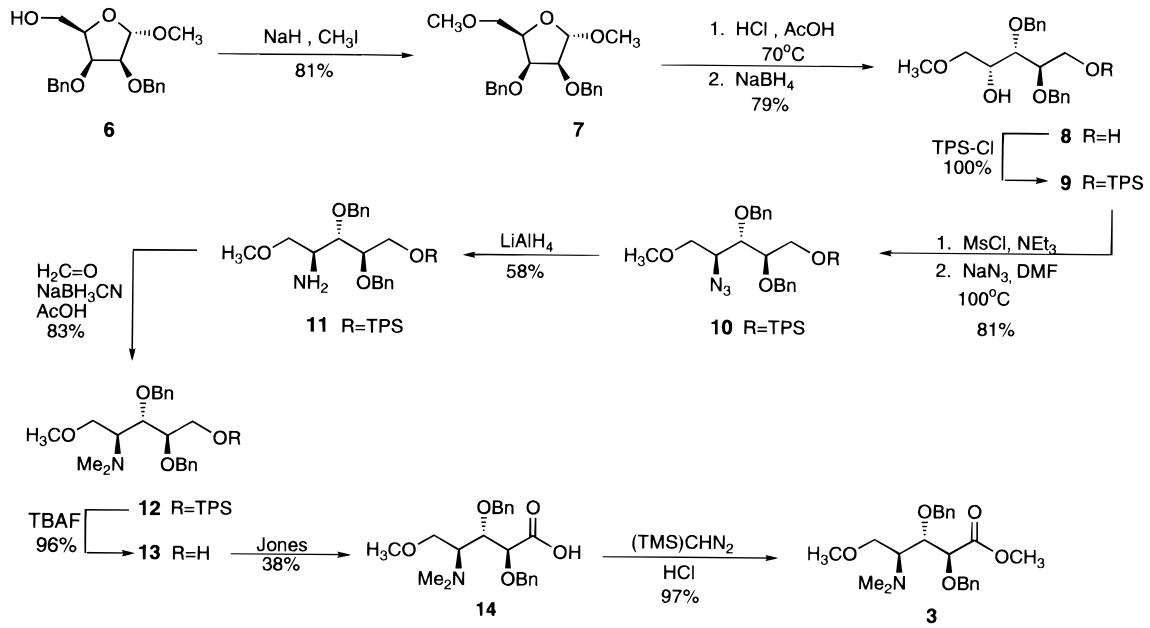
Scheme 2

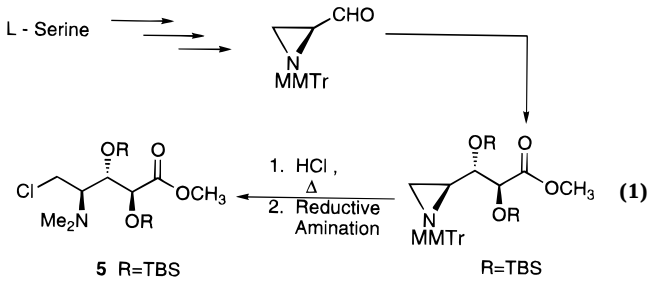


efforts toward the synthesis of the $C_{33}-C_{37}$ aza-sugar **3** and the successful completion of the $C_{26}-C_{32}$ oxazole **4** fragment.

Results and Discussion

Synthesis of the $C_{33}-C_{37}$ Fragment. Several routes were considered for the diversely functionalized $C_{33}-C_{37}$ aza-sugar fragment. As previously indicated, each strategy was founded on decisions affecting the timing for introduction and elaboration of the C_{36} nitrogen.

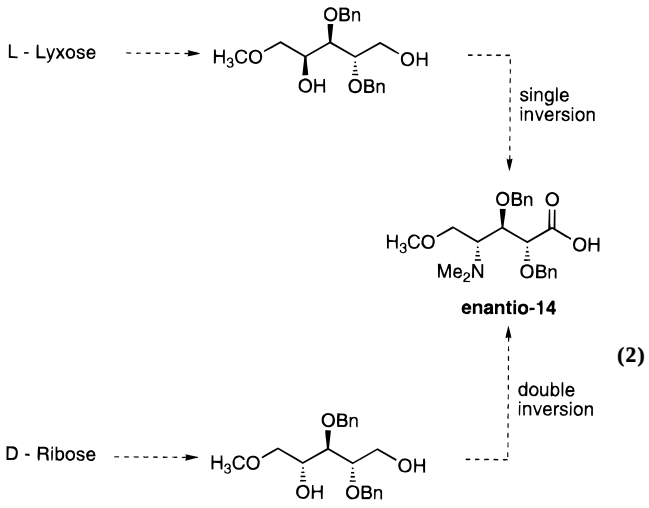
Early efforts were directed toward an approach in which L-serine was converted to an aziridine species representative of $C_{35}-C_{37}$. Subsequent elaboration afforded the desired functionalization for all three stereocenters in the fragment while maintaining a blocked C_{36}-nitrogen. It was envisioned that regioselectve acid-catalyzed ring opening of the aziridine[8] followed by *in situ* reductive amination would provide functionality to account for the completed $C_{33}-C_{37}$ aza-sugar (eq 1). Ring



(1)

opening under acidic conditions proceeded with the expected regiochemistry arising from nucleophilic attack at the less hindered center of an aziridinium intermediate.[8] Reductive amination of the crude ring-opened products afforded fully functionalized aza-sugar compounds bearing a reasonable handle at C_{37} for introduction of the methyl ether moiety (**5**, e.g.). Elaboration of C_{37} proved to be less than trivial while a synthesis of **3** originating from a sugar promised a route of equal efficiency.

The abundant supply of aldopentoses served as the basis for our earliest synthetic efforts toward the synthesis of $C_{33}-C_{37}$ fragment **3**.[2] At the outset of our work in this area, the absolute stereochemistry of the natural product had not yet been established. As a consequence, our early syntheses required double inversion at C_4 of D-ribose for the synthesis of enantiomeric $C_{33}-C_{37}$ fragment (eq 2). The same stereochemical outcome could be effected by a single inversion at C_4 of L-lyxose. The cost of the starting sugar, however, precluded its use in our initial synthetic efforts.



(2)

Confirmation of the absolute configuration of the calyculins by Shiori[7g] suggested that the more efficient approach to the $C_{33}-C_{37}$ aza-sugar from D-lyxose was now a reasonable synthetic possibility. Synthesis of aza-sugar **3** ester proceeded from known alcohol **6**, obtained in four steps from D-lyxose utilizing the elegant work of van

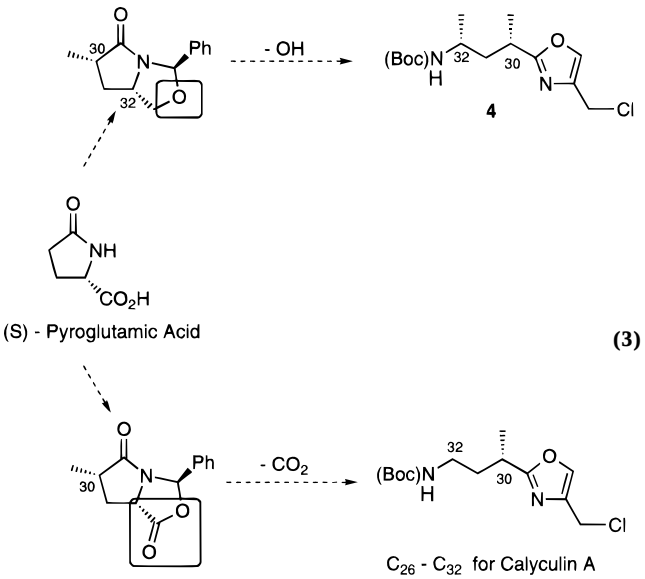
(8) (a) Elderfield, R. C. *Heterocyclic Compounds, Vol. 1*; John Wiley and Sons: New York, 1950; 61. (b) Gabriel, S.; Ohle, H. *Ber.* **1917**, *50*, 804.

Boom.[9] The choice of benzyl protecting groups for the C_{34},C_{35}-diol was required due to the rigor of proposed downstream synthetic steps. This need for stability was demonstrated as 4-methoxybenzyl (PMB) proved labile under conditions necessary for fragment elaboration (Jones oxidation, e.g.).

Methylation of **6** under standard conditions afforded methyl ether **7** in excellent yield. Conversion to diol **8** proceeded *via* initial acidic hydrolysis of the methyl furanoside, which required heat to fully generate the hemiacetal product, followed by mild reduction to give the desired product in excellent overall yield (Scheme 2). Silylation of the 1°-hydroxyl using *tert*-butyldiphenylsilyl chloride would allow for unambiguous introduction of nitrogen upon displacement of the C_{36}-hydroxyl. Silylation to afford alcohol **9** in quantitative yield was followed by mesylation and azide inversion at high temperatures to afford azide **10** which possessed the desired heteroatom substitution and stereochemistry applicable to ester **3**. Azide **10** was reduced to the free amine **11** with lithium aluminum hydride in good yield. Amine **11** was methylated under exhaustive reductive amination conditions which gave dimethylamine **12** in excellent yield. At this time, the remaining synthetic task was oxidation to the C_{33}-carboxylate. Desilylation of **12** with TBAF to give alcohol **13** provided the desired substrate for oxidation to the completed aza-sugar fragment. Conversion of **13** to target fragment **3** *via* Jones oxidation[10] followed by esterification proceeded in modest yield. Despite the apparent shortcomings of the Jones oxidation[10] in this synthesis, other oxidative methods for direct conversion of alcohols to carboxylates proved no more effective. Attempts at effecting stepwise oxidation through the intermediate aldehyde followed by further oxidation to the acid met with similar yields. This observation was attributed to the instability of the intermediate aldehyde. Regardless, the desired ester **3** was in our possession and could be coupled to an aminooxazole, thereby affording a fully protected top half of calyculin C.

Synthesis of the C_{26}−C_{32} Fragment. Work toward the C_{26}−C_{32} fragment originated from a plan for separately generating aminooxazoles compatible with the entire family of calyculins.[4] The important distinction between C_{26}−C_{32} fragments pertaining to calyculins A and C is the presence of a methyl substituent at C_{32} in the latter isomer.

Pyroglutamic acid could represent a versatile chiral template as endo-selective methylation of an acetal intermediate, following the method developed by Meyers,[11] would establish the desired C_{30}-methyl functionality relevant to both calyculins A and C. Differential formation of bicyclic acetal intermediates would facilitate the distinction of functionality at C_{32} for each individual fragment type (eq 3). We supposed that the oxazole fragment of calyculin A could arise from radical decarboxylation of a pyrrolidinone intermediate (boxed carboxylate in the lower path of eq 3). Similarly, endo-methylation of acetal **15**[11] followed by radical deoxygenation would yield a precursor to aminooxazole fragment **4** (boxed heteroatom in the top path of eq 3).



A successful route to oxazole fragment[5b] **4** was established at a time when the absolute configuration of the calyculins was not known. Initial efforts were directed toward a synthetic route derived from (*R*)-pyroglutamic acid *via* the enantiomer of acetal **15**. Establishment of the absolute configuration suggested that the antipode of (*R*)-pyroglutamic acid possessed the correct stereochemistry for use in the synthesis of the C_{26}−C_{32} portion of calyculin C. Lithium enolate formation on known bicyclic *N*,*O*-acetal **15**[12] and subsequent methylation at −78 °C afforded **16a** as the major diastereomer (60% de) (Scheme 3). An interesting result involving clean conversion of lactam **16a** to its C_{30}-epimer **16b** by enolate protonation at −78 °C clearly demonstrated the overwhelming preference for endo-alkylation of these bicyclic acetals. Acid hydrolysis of acetal **16a** was followed by mesylation to afford lactam **17** in reasonable yield. Final elaboration to a fully functionalized C_{29}−C_{32} precursor to the oxazole fragment was accomplished by radical deoxygenation of an *in situ*-generated iodide to give pyrrolidinone **18** in excellent yield. This compound was successfully transformed to an open chain amide intermediate *via N*-Boc-protection to **19**, followed by Weinreb aluminum−amide opening of the butyrolactam to provide amide **20**.[13]

Formation of the oxazole ring presented the next synthetic challenge in the synthesis of fragment **4**. We felt that 1,3-dichloroacetone afforded an excellent synthon in harnessing previous work from our group[5a] to generate the desired oxazole moiety while providing a reactive handle (C_{26}-chloride) for further elaboration.[14] The importance of this functionality was its potential for facile conversion to the phosphonium salt desired for coupling of both halves of the natural product.[5a,6a] The C_{26}-chloride, therefore, eliminated the need for extensive manipulation. To this end, condensation of amide **20** with 1,3-dichloroacetone in chloroform at vigorous reflux successfully yielded the target C_{26}−C_{32} fragment in good yield (Scheme 4). The use of other higher boiling solvents resulted either in generation of inseparable epimers, presumably at C_{30}, or in no observable product formation.

(9) Veeneman, G. H.; Gomes, L. J. F.; van Boom, J. H. *Tetrahedron* **1989**, *45*, 7433.

(10) (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. (b) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lernin, A. J. *J. Chem. Soc.* **1953**, 2548.

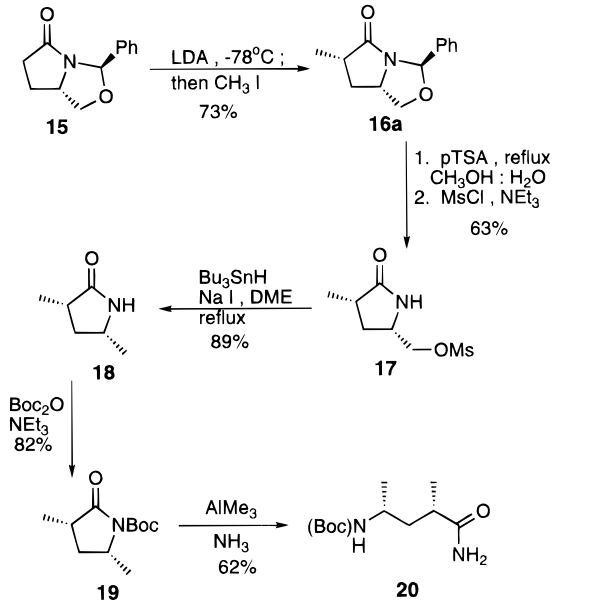
(11) (a) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146. (b) Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *J. Org. Chem.* **1986**, *51*, 1936.

(12) Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissich, T. P. *J. Org. Chem.* **1986**, *51*, 3140.

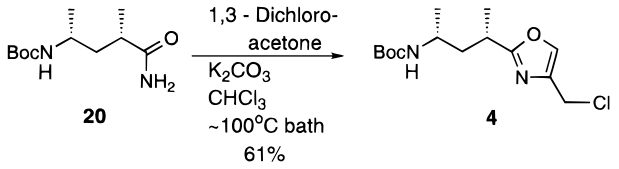
(13) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

(14) (a) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. (b) Lakham, R.; Ternal, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 99.

Scheme 3

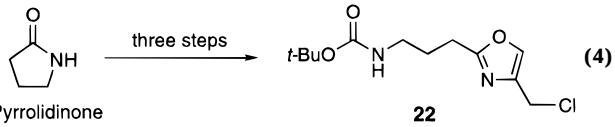


Scheme 4



Completion of the $C_{26}-C_{37}$ Fragment of Calyculin C. With the two fragments from the $C_{26}-C_{37}$ portion of calyculin C in hand, we next sought a viable means of forming the $C_{33}-N_3$ amide bond to yield a fully protected top half segment of the natural product. Numerous unsuccessful attempts were made in an effort to synthesize amide **23** through formation of activated acyl intermediates from the carboxylic acid **14**. Most notable was the isolation of an oxazole−phosphorous adduct from attempted BOP-Cl[15] mediated coupling which suggested an inability of the zwitterionic acid to participate as a nucleophile in generating an activated carboxylate.

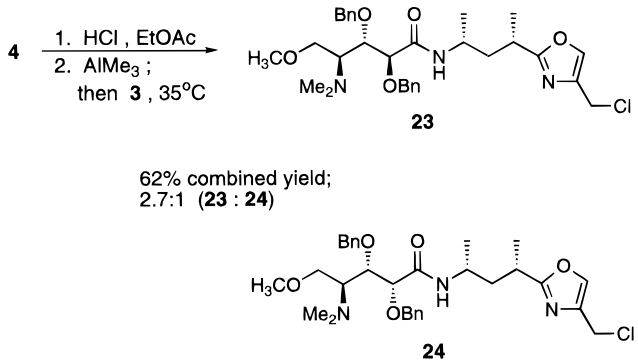
Aluminum-mediated amide formation arising from coupling of amines to esters offered an alternative method for the synthesis of the $C_{33}-N_3$ amide bond.[13,16] Model studies involved the coupling of ester **3** onto an achiral oxazole fragment **22** (eq 4) and established



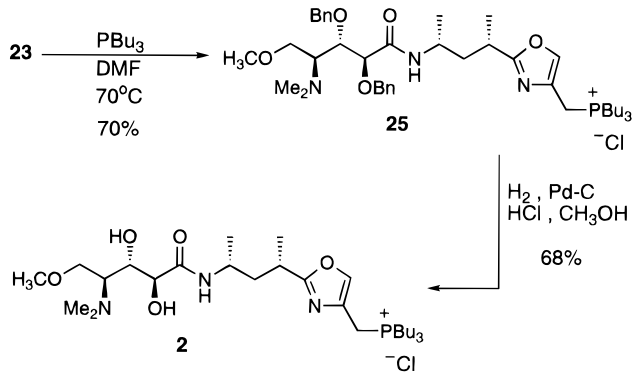
(4)

reaction conditions in which initial formation of an aluminum−amide complex (3 equiv) from the amine-hydrochloride salt was followed by addition of the ester substrate (1 equiv). Heating of the resulting mixture over extended reaction times provided a reliably good yield of amide product while allowing for recycling of unreacted ester starting material. We felt that these model reactions sufficiently mimicked the parent system

Scheme 5



Scheme 6



which provided the impetus to attempt amide formation with more sterically hindered oxazole **4**. The reaction yielded a 2.7:1 separable mixture of diastereomers **23** and **24** (Scheme 5), presumably at C_{34}, in a 62% overall yield.[17] Epimerization at C_{34} was hypothesized to occur prior to amide formation, and supporting evidence came from two separate reactions in which treatment of a single amide diastereomer with excess trimethylaluminum showed no change over extended reaction times (12 hr at 35 °C) while submission of pure ester **3** to similar conditions was met with epimerization.

The remaining obstacle in our efforts toward the synthesis of the $C_{26}-C_{37}$ fragment **1** was the identification of the proper sequence for phosphonium salt formation and debenzylation. Deprotection of the C_{34},C_{35}-diol prior to formation of the phosphonium salt at C_{26} was perceived as ideal. This synthetic sequence would afford flexibility with regard to diol protecting groups in the event that the proposed $C_{25}-C_{26}$ Wittig olefination warranted such manipulation.

Experiments confirming the anticipated lability of the C_{26}-chloride toward hydrogenation suggested the need for an alternative method for debenzylation. The conditions for benzyl removal involving boron trifluoride etherate and ethyl mercaptan[18] were also investigated and were found to be unfruitful, thus relegating our efforts to diol deprotection after formation of the C_{26}-phosphonium salt.

Model studies showed that the C_{26}-phosphonium salt was inert under hydrogenation conditions which prompted conversion of amide **23** to phosphonium salt **25** in good yield (Scheme 6). Successful completion of the $C_{26}-C_{37}$ fragment proceeded as phosphonium salt **25** was submit-

(15) (a) Diago-Messeguer, J.; Palomo-Coll, A. L.; Fernandez-Lisarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547. (b) Cabre, J.; Palomo, A. L. *Synthesis* **1984**, 413.

(16) (a) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (b) Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411.

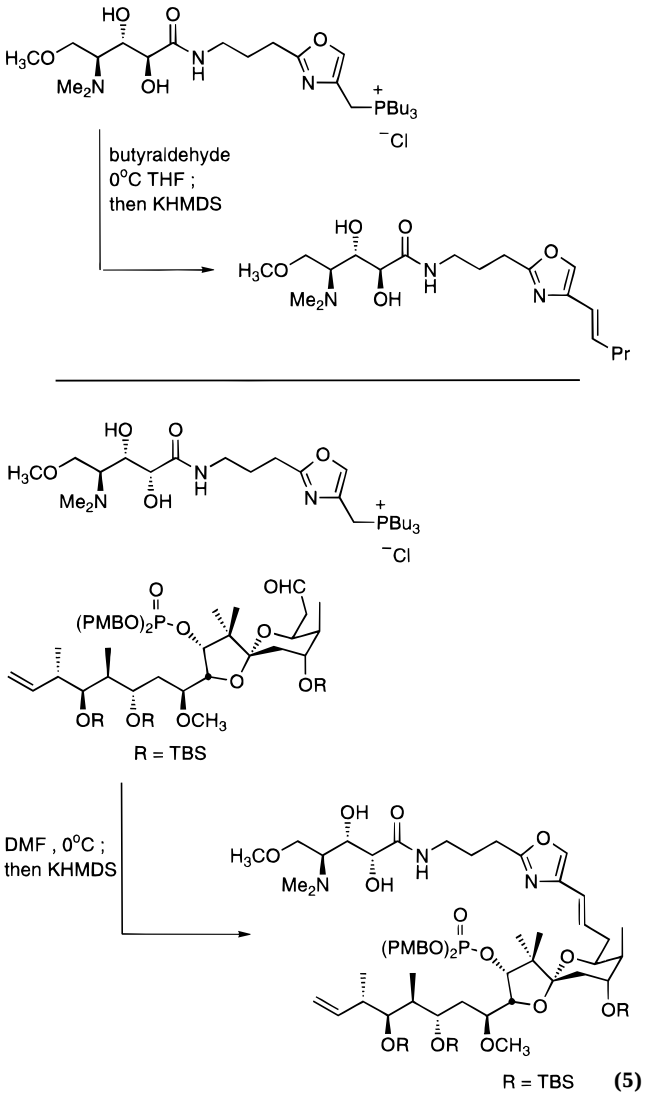
(17) The assignment of stereochemistry is consistent with analysis of 2D-NOESY spectra in conjunction with 1D-^{1}H NMR for each diastereomer.

(18) Daly, S. M.; Armstrong, R. W. *Tetrahedron Lett.* **1989**, *30*, 5713.

ted to hydrogenation conditions, thereby affording phosphonium salt **2** as a white solid.

Model Wittig Couplings. In an effort to test our hypothesis that a fully deprotected $C_{26}-C_{37}$ phosphonium salt could effect coupling to yield a completed calyculin backbone, we carried out model Wittig condensations on a series of systems designed to improve our understanding of the reactivity of diol **2**. We felt that the stabilized ylide generated from **2** would be sufficiently reactive to afford a coupled product with a high degree of stereochemical purity.[5a]

The successful condensation of a phosphonium salt **(26)** derived from our work using achiral oxazole **22** onto an excess of butyraldehyde (eq 5) provided preliminary justification for our approach to formation of the $C_{25}-C_{26}$ double bond. The true test of this strategy, however,

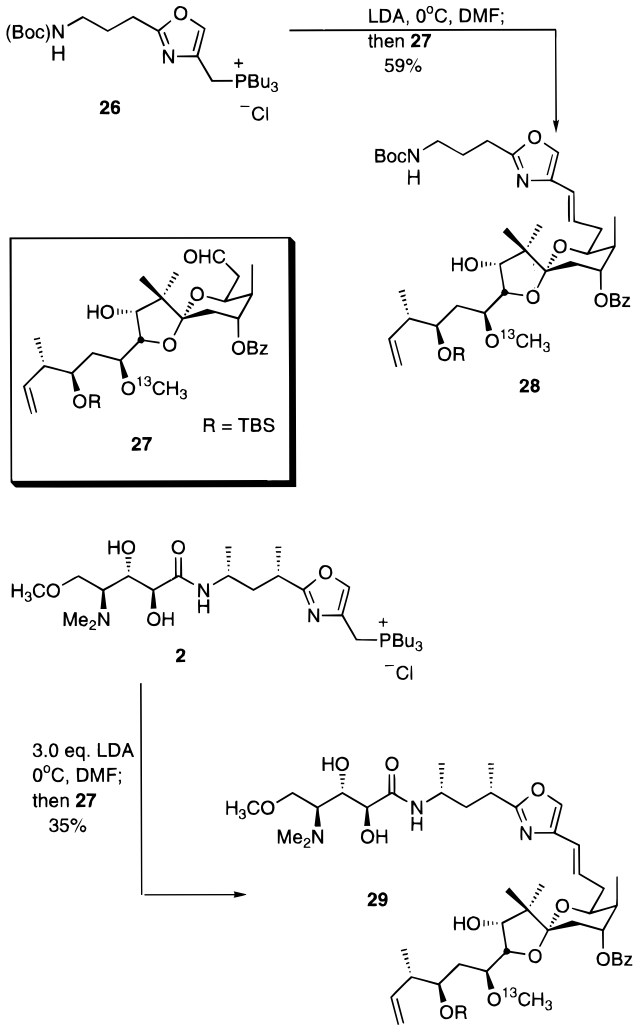


(5)

involved coupling onto more complex aldehyde substrates. Key issues that needed to be addressed included (1) questions involving the kinetics of coupling for two large molecules and (2) the subsequent potential for competitive β-elimination[7d] of the aldehyde given steric constraints related to coupling. Condensation onto a model spiroketal aldehyde (eq 5) yielded the answers to these questions and lent futher support to our overall synthetic strategy.

The de-phospho derivative of calyculin C represents a key analog in our SAR study of phosphatase inhibitors

Scheme 7



of PP1 and PP2A. An inference based on our success in the previous model studies involving a de-phospho C_1-C_{25} aldehyde derivative suggested that the free C_{17}-hydroxyl did not interfere with coupling. The question remained, however, regarding the viability of such a substrate, particularly in reference to the potential for β-elimination. We felt that a conservative approach in which initial Wittig condensations utilized simple model phosphonium salt **26** would more accurately test our initial hypothesis. The successful generation of the desired olefinated product **28** from condensation onto model aldehyde **27** suggested graduation to a structurally more relevant system. Wittig coupling of **2** with the same model aldehyde proceeded to product **29** (Scheme 7). This result confirmed our strategy for $C_{25}-C_{26}$ double bond formation in the synthesis of calyculin C, as well as other relevant analogs.

Conclusions

We have successfully completed synthesis of the $C_{26}-C_{37}$ fragment **2** in our route toward the total synthesis of calyculin C. Our synthetic efforts include a lyxose-based approach to the $C_{33}-C_{37}$ aza-sugar piece **3**, which was coupled onto aminooxazole **4** derived from pyroglutamic acid. We believe that our success in modeling the proposed $C_{25}-C_{26}$ Wittig olefination using a fully deprotected phosphonium salt provides a clear avenue to the total synthesis of calyculin C. Current studies for effect-

ing the established Wittig condensation onto the completed C_1-C_{25} aldehyde[19] and subsequent deprotection to the natural product are ongoing.

Experimental Section

General. Optical rotations were taken at 22 °C. Mass spectra were obtained from the Mass Spectroscopy Facilities at UCLA and UC Riverside. Elemental analyses were obtained from Desert Analysis of Tuscon, AZ. For EI, CI, and FAB mass spectra, $2\sigma = 4$ ppm.

Solvents and reagents were used as supplied from commercial sources with the following exceptions or specific notations. DMF was used as received in Aldrich Sure Seal packing. THF was distilled from sodium benzophenone ketyl. Toluene was distilled from calcium hydride. Methanol was distilled from magnesium turnings, and dichloromethane was distilled from phosphorus pentoxide. All reactions involving moisture-sensitive reagents were performed under either a nitrogen or an argon atmosphere.

Methyl 2,3-Dibenzyl-5-methyl-α-D-lyxofuranoside (7). To a solution of **6** (4.9 g, 14.2 mmol) in DMF (100 mL) was added iodomethane (1.3 mL, 21.4 mmol). Sodium hydride (375 mg, 15.7 mmol) was then added in several portions, and the opaque yellow reaction mixture was stirred at rt. An additional 2.8 mL of iodomethane and 205 mg of sodium hydride were added in three portions. After 12 h, the reaction was quenched by addition of methanol. The resulting mixture was partitioned between CH_2Cl_2–hexane (150 mL total) and H_2O (70 mL). The layers were separated, and the organic layer was washed with H_2O (2 × 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (10–20% ethyl acetate–hexane) afforded methyl ether **7** (4.1 g, 81%): $[\alpha]_D = +26.1$ (*c*, 5.2, $CHCl_3$); IR (thin film) 2932, 1496, 1453, 1346, 1196, 1149, 1101 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.25–7.45 (10H, m), 5.07 (1H, d, $J = 2.0$ Hz), 4.71 (2H, m), 4.62 (1H, d, $J = 12.0$ Hz), 4.56 (1H, d, $J = 12.0$ Hz), 4.38 (1H, ddd, $J = 7.0$, 6.0, 4.0 Hz), 4.25 (1H, dd, $J = 6.0$, 5.0 Hz), 3.93 (1H, dd, $J = 5.0$, 2.0 Hz), 3.75 (1H, dd, $J = 10.0$, 7.0 Hz), 3.69 (1H, dd, $J = 10.0$, 4.0 Hz), 3.42 (3H, s), 3.40 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.8, 137.6, 128.1, 128.1, 127.5, 106.0, 81.7, 77.7, 72.9, 72.2, 72.2, 59.0, 55.0; HRFABMS calcd for MH^+ ($C_{21}H_{27}O_5$) 359.18585, found 359.1866 (error 2.1 ppm).

(2*R*,3*S*,4*R*)-2,3-Bis(benzyloxy)-5-methoxy-1,4-pentanediol (8). To a solution of furanoside **7** (4.1 g, 11.5 mmol) in AcOH (64 mL) and H_2O (10 mL) was added 1.2 N HCl aqueous (1 mL). The resulting opaque reaction mixture was heated at 70 °C for 21 h. The reaction mixture was cooled to rt, and Na_2CO_3 (approximately 2 equiv) was added to quench the HCl. The mixture was concentrated in vacuo, and the resulting crude product was azeotroped with toluene (3 × 30 mL) and eluted in absolute EtOH (100 mL). Sodium borohydride (1.05 g, 27.6 mmol) was added in several small portions over 30 min, at which time the reaction mixture was partitioned between CH_2Cl_2 (100 mL) and H_2O (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography (20–50% ethyl acetate–hexane) afforded diol **8** (3.1 g, 79% two steps): $[\alpha]_D = -14.6$ (*c* 4.8, $CHCl_3$); IR (thin film) 3448, 2921, 1494, 1451, 1397, 1211, 1104 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.25–7.45 (10H, m), 4.78 (1H, d, $J = 11.0$ Hz), 4.65 (2H, s), 4.60 (1H, d, $J = 11.0$ Hz), 4.02 (1H, m), 3.89 (1H, dd, $J = 12.0$, 4.0 Hz), 3.71–3.82 (3H, m), 3.46 (1H, dd, $J = 10.0$, 6.0 Hz), 3.40 (1H, dd, $J = 10.0$, 6.0 Hz), 3.32 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.7, 137.6, 128.1, 128.0, 127.9, 127.5, 127.5, 79.3, 76.8, 73.8, 72.0, 69.2, 60.1, 58.6; HRFABMS calcd for MH^+ ($C_{20}H_{27}O_5$) 347.18585, found 347.1856 (error 0.7 ppm).

(2*R*,3*S*,4*R*)-2,3-Bis(benzyloxy)-5-methoxy-1-(*tert*-butyldiphenylsiloxy)-4-pentanol (9). To a solution of **8** (1.285 g, 3.70 mmol) in DMF (80 mL) was added TBDPS-Cl (1.05 mL, 4.1 mmol) followed by imidazole (529 mg, 7.4 mmol). The clear reaction mixture was stirred at rt for 12 h. The reaction mixture was concentrated in vacuo, and purification via column chromatography on silica gel (5–15% ethyl acetate–hexane) afforded silyl ether **9** (2.31 g, 100%): $[\alpha]_D = -18.7$ (*c* 10.1, $CHCl_3$); IR (thin film) 3500, 2928, 1454, 1427, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.70 (20H, m), 4.64 (2H, m), 4.50 (2H, m), 4.02 (1H, m), 3.90 (1H, dd, $J = 10.6$, 7.0 Hz), 3.84 (1H, dd, $J = 10.6$, 4.7 Hz), 3.70–3.80 (2H, m), 3.48 (1H, m), 3.40 (1H, dd, $J = 4.9$, 1.4 Hz), 3.30 (3H, s), 1.04 (9H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.1, 138.0, 135.7, 135.6, 134.7, 133.2, 133.0, 129.7, 128.3, 128.0, 127.7, 127.7, 126.6, 126.6, 79.8, 76.6, 73.7, 73.6, 72.7, 69.6, 62.8, 58.9, 26.8, 26.6, 19.1; HRFABMS calcd for MH^+ ($C_{36}H_{45}O_5Si$), 585.3036, found 585.3030 (error 1.0 ppm).

(2*R*,3*S*,4*S*)-4-Azido-2,3-bis(benzyloxy)-5-methoxy-1-(*tert*-butyldiphenyl)siloxy)pentane (10). To a solution of alcohol **9** (2.195 g, 3.71 mmol) in CH_2Cl_2 (80 mL) was added triethylamine (1.6 mL, 11.1 mmol) followed by methanesulfonyl chloride (0.35 mL, 4.45 mmol). The reaction mixture was stirred at rt for 30 min. The reaction mixture was washed with H_2O (2 × 100 mL), dried over Na_2SO_4, filtered, and concentrated. The resulting crude mesylate was eluted in DMF (80 mL). Sodium azide (1.25 g, 18.6 mmol) was added, and the suspension was heated to 100 °C. After 19 h, the reaction mixture was concentrated, and the resulting crude was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 200 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (0–15% ethyl acetate–hexane) afforded azide **10** (10.8 g, 81% two steps): $[\alpha]_D = -18.1$ (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.70 (20H, m), 4.66 (1H, d, $J = 11.1$ Hz), 4.64 (1H, d, $J = 11.7$ Hz,), 4.58 (1H, d, $J = 11.1$ Hz), 4.45 (1H, d, $J = 11.7$ Hz), 3.92 (2H, m), 3.86 (2H, m), 3.63 (1H, m), 3.51 (2H, m), 3.28 (3H, s), 1.06 (9H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.1, 137.9, 135.7, 135.6, 135.5, 135.1, 134.8, 133.3, 133.1, 129.7, 129.6, 129.6, 128.3, 127.9, 127.8, 127.7, 127.6, 79.1, 78.3, 73.9, 72.2, 72.0, 62.5, 62.0, 58.9, 26.7, 19.2; HRFABMS calcd for MH^+ ($C_{36}H_{44}N_3O_4Si$) 610.3101, found 610.3086 (error 2.5 ppm).

(2*R*,3*S*,4*S*)-4-Amino-2,3-bis(benzyloxy)-5-methoxy-1-(*tert*-butyldiphenylsiloxy)pentane (11). To a solution of **10** (11.6 g, 19.0 mmol) in THF (600 mL) was added lithium aluminum hydride (1.08 g, 28.5 mmol) in several portions over 1.5 h. The slurry was stirred at rt for 5.5 h, at which time 0.5 N aqueous NaOH (30 mL) was added dropwise. Upon stirring, a white precipitate formed, and after 15 min, the mixture was neutralized via addition of 1.2 N aqueous HCl. The resulting mixture was filtered, and the precipitate was washed with EtOAc (400 mL). The combined organics were concentrated, and purification via column chromatography on silica gel (20–60% ethyl acetate–hexane) afforded amine **11** (6.42 g, 58%): $[\alpha]_D = -23.7$ (*c* 8.1, $CHCl_3$); IR (thin film) 2930, 1472, 1456, 1428, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.20 (20H, m), 4.69 (1H, d, $J = 11.7$ Hz), 4.68 (1H, d, $J = 11.3$ Hz), 4.56 (1H, d, $J = 11.3$ Hz), 4.54 (1H, d, $J = 11.7$ Hz), 3.99 (1H, dd, $J = 11.2$, 3.8 Hz), 3.92 (1H, dd, $J = 11.2$, 5.3 Hz), 3.79 (1H, m), 3.67 (1H, m), 3.46 (1H, dd, $J = 9.0$, 3.3 Hz), 3.34 (1H, dd, $J = 9.0$, 7.4 Hz), 3.28 (3H, s), 3.18 (1H, m), 1.08 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.4, 135.7, 135.6, 133.3, 133.2, 129.6, 129.6, 128.2, 128.2, 127.7, 127.6, 127.6, 127.6, 127.4, 127.3, 80.6, 80.4, 74.8, 73.7, 72.2, 63.3, 58.7, 52.2, 26.8, 19.1; HRFABMS calcd for MH^+ ($C_{36}H_{46}NO_4Si$) 584.3196, found 584.3195 (error 0.2 ppm).

(2*R*,3*S*,4*S*)-4-(*N*,*N*-Dimethylamino)-2,3-bis(benzyloxy)-5-methoxy-1-(*tert*-butyldiphenyl)siloxy-pentane (12). To a solution of amine **11** (911 mg, 1.56 mmol) in CH_3CN (50 mL) was added formaldehyde (37% wt in H_2O, 2 mL), followed by AcOH (90 μL, 1.56 mmol) and sodium cyanoborohydride (372 mg, 5.92 mmol). The white suspension was stirred at rt for 15 min, at which time saturated aqueous $NaHCO_3$ (0.5 mL) was added to quench the AcOH. The resulting mixture was partitioned between CH_2Cl_2 (200 mL) and saturated aqueous $NaHCO_3$ (70 mL). The layers were separated, and the aqueous

(19) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Len, M. R.; Armstrong, R. W. J. Org. Chem., previous paper in this issue.

layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (20% ethyl acetate−hexane) yielded amine **12** (788 mg, 83%): $[\alpha]_D$ = −21.2 (*c* 7.2, $CHCl_3$); IR (thin film) 2930, 2858, 1455, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19−7.70 (20H, m), 4.74 (1H, d, *J* = 12.0 Hz), 4.70 (1H, d, *J* = 11.3 Hz), 4.60 (1H, d, *J* = 12.0 Hz), 4.49 (1H, d, *J* = 11.2 Hz), 3.82−3.96 (4H, m), 3.52−3.60 (2H, m), 3.25 (3H, s), 2.83 (1H, m), 2.28 (6H, s), 1.06 (9H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ .139.0, 138.8, 135.7, 133.5, 133.5, 129.6, 128.2, 127.6, 127.6, 127.5, 127.3, 127.2, 80.9, 72.8, 72.7, 69.6, 63.6, 63.5, 58.6, 41.8, 26.9, 19.2; HRFABMS calcd for MH^+ ($C_{38}H_{50}NO_4Si$) 612.3509, found 612.3506 (error 0.5 ppm).

(2*R*,3*S*,4*S*)-4-(*N*,*N*-Dimethylamino)-2,3-bis(benzyloxy)-5-methoxy-1-pentanol (13). To a solution of **12** (72 mg, 0.118 mmol) in THF (10 mL) was added TBAF (200 μL, 1.0 M in THF). The clear, pale yellow reaction mixture was stirred at rt for 8 h. The reaction mixture was concentrated, and purification via column chromatography on silica gel (1% CH_3OH−CH_2Cl_2) afforded alcohol **13** (42 mg, 96%): $[\alpha]_D$ = −25.2 (*c* 4.2, $CHCl_3$); IR (thin film) 3393, 2926, 2872, 1456, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.44 (10H, m), 4.80 (1H, d, *J* = 12.1 Hz), 4.71 (1H, d, *J* = 11.1 Hz), 4.69 (1H, d, *J* = 12.1 Hz), 4.51 (1H, d, *J* = 11.1 Hz), 3.96 (1H, dd, *J* = 11.8, 4.9 Hz), 3.92 (1H, m), 3.77−3.74 (2H, m), 3.68−3.64 (2H, m), 3.35 (3H, s), 3.14 (1H, ddd, *J* = 9.2, 6.6, 2.6 Hz), 2.40 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.3, 128.3, 128.2, 127.8, 127.7, 127.6, 127.4, 80.1, 78.6, 73.0, 71.1, 68.9, 61.8, 60.9, 58.6, 41.7; HRFABMS calcd for MH^+ ($C_{22}H_{32}NO_4$) 374.2331, found 374.2336 (error 1.3 ppm).

(2*S*,3*S*,4*S*)-4-(*N*,*N*-Dimethylamino)-5-methoxy-2,3-bis-(benzyloxy)valeric Acid (14). To a solution of **13** (1.41 g, 3.78 mmol) in acetone (200 mL) was added the Jones reagent (3.65 mL, 2.66 M in CrO_3, 4.14 M in H_2SO_4), and H_2SO_4 (750 μL) was added dropwise in five portions over 4 h. After 5 h total reaction time, the reaction mixture was partitioned between EtOAc (300 mL) and brine (250 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography (0−15% CH_3OH−CH_2Cl_2) afforded acid **14** (553 mg, 38%): IR (thin film) ∼3400 (br), 2928, 1617, 1474, 1387, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.36 (10H, m), 4.78 (1H, d, *J* = 11.5 Hz), 4.62 (1H, d, *J* = 11.4 Hz), 4.48 (1H, d, *J* = 11.5 Hz), 4.38 (1H, d, *J* = 11.3 Hz), 4.35 (1H, s), 3.85 (2H, m), 3.77 (1H, m), 3.58 (1H, dd, *J* = 11.3, 8.8 Hz), 3.27 (3H, s), 2.64 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 137.8, 137.1, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 81.2, 75.8, 71.8, 71.7, 68.3, 62.9, 58.9; HRFABMS calcd for MH^+ ($C_{22}H_{30}NO_5$) 388.2124, found 388.2128 (error 1.0 ppm).

(2*S*,3*S*,4*S*)-4-(*N*,*N*-Dimethylamino)-5-methoxy-2,3-bis-(benzyloxy)valeric Acid Methyl Ester (3). To a solution of acid **14** (18 mg, 0.046 mmol) in CH_2Cl_2 (3 mL) was added 2 N HCl (3 drops), and $TMSCHN_2$ (500 μL total, 2.0 M in hexanes) was added until a yellow color persisted. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL) and EtOAc (2 × 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (1% CH_3OH−CH_2Cl_2) afforded ester **3** (17 mg, 97%): $[\alpha]_D$ = −49.2 (*c* 2.3, $CDCl_3$); IR (thin film) 2930, 1750, 1455, 1281, 1206, 1117 cm^{-1}; ^1H NMR (360 MHz, C_6D_6) δ 7.26−7.40 (10H, m), 4.87 (1H, d, *J* = 12.2 Hz), 4.56 (1H, d, *J* = 11.3 Hz), 4.53 (1H, d, *J* = 12.2 Hz), 4.43 (1H, d, *J* = 11.3 Hz), 4.32 (1H, d, *J* = 2.2 Hz), 3.91 (1H, d, *J* = 8.8 Hz), 3.71 (3H, s), 3.66 (1H, dd, *J* = 10.1, 2.6 Hz), 3.53 (1H, dd, *J* = 10.1, 7.6 Hz), 3.29 (3H, s), 3.12 (1H, m), 2.25 (6H, s); ^{13}C NMR (90 MHz, CD_3CN) δ 171.4, 139.9, 139.5, 129.2, 129.2, 128.9, 128.7, 128.5, 80.5, 78.5, 73.4, 73.2, 70.1, 62.6, 58.8, 51.9, 42.1; HRFABMS calcd for MH^+ ($C_{23}H_{32}NO_5$) 402.22805, found 402.2280 (error 0.1 ppm).

Tetrahydro-3-phenyl-(3*R*-*cis*)-3*H*,5*H*-pyrrolo[1,2-*c*]oxazol-5-one (15). For 15: $[\alpha]_D$ = +247 (*c* 1.0, $CHCl_3$); IR (thin film) 2943, 1702, 1350, 1222, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.46 (5H, m), 6.33 (1H, s), 4.23 (1H, dd, *J* = 8.0, 6.4 Hz), 4.15 (1H, dddd, *J* = 8.0, 7.6, 6.4, 5.5 Hz), 3.48 (1H, dd, *J* = 8.0, 8.0 Hz), 2.80 (1H, ddd, *J* = 14, 10, 9.2 Hz), 2.55 (1H, ddd, *J* = 14.0, 10.0, 5.5 Hz), 2.38 (1H, dddd, *J* = 13.0, 10.0, 7.6, 3.7 Hz), 1.95 (1H, dddd. *J* = 13.0, 10.0, 9.2, 5.5 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.0, 138.7, 128.5, 128.4, 125.9, 87.0, 71.6, 58.7, 33.4, 28.0. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.89; H, 6.45; N, 6.74.

[3*R*-(3a,6a,7aa)]-Tetrahydro-6-methyl-3-phenyl-(3*S*-*cis*)-3*H*,5*H*-pyrrolo[1,2-*c*]oxazol-5-one (16a). A solution of *N*,*N*-diisopropylethylamine (10.2 mL, 72.8 mmol) in THF (200 mL) was cooled to −10 °C. *n*-Butyllithium (36 mL, 1.98 M in pentane) was added slowly dropwise, and the resulting mixture was stirred at −10 °C for 15 min. The clear pale yellow mixture was cooled to −78 °C, and a precooled solution of **15** (13.2 g, 65.0 mmol) in THF (20 mL) was added dropwise down the side of the flask. The resulting dark brown mixture was stirred at −78 °C. After 20 min, iodomethane (20 mL, 325.2 mmol) was added, and the reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched via addition of brine (50 mL) to the cold reaction mixture. The suspension was partitioned between EtOAc (300 mL) and brine (150 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 300 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (0−20% ethyl acetate−hexane) afforded lactam **16a** (10.3 g, 73%): $[\alpha]_D$ = +205 (*c* 1.00, $CHCl_3$); IR (thin film) 2969, 1703, 1452, 1376, 1266, 1223 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.46 (5H, m), 6.33 (1H, s), 4.22 (1H, dd, *J* = 8.36.4 Hz), 4.07 (1H, dddd, *J* = 7.5, 7.2, 6.9, 6.4 Hz), 3.52 (1H, dd, *J* = 8.3, 7.2 Hz), 2.94 (1H, ddq, *J* = 11.3, 8.6 Hz, 6.9 Hz), 2.61 (1H, ddd, *J* = 12.0, 8.6, 6.9 Hz), 1.54 (1H, ddd, *J* = 12.0, 11.0, 7.5 Hz), 1.24 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 179.1, 138.6, 128.4, 128.3, 125.9, 86.7, 72.4, 56.5, 40.0, 34.8, 15.5; HRMS (50 eV EI) calcd for M − H ($C_{13}H_{14}NO_2$) 216.1025, found 216.1017 (error 3.7 ppm). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.85; H, 6.96; N, 6.45, found C, 71.99; H, 6.97; N, 6.70.

(5*R*,3*R*)-5-[(Methanesulfonyl)oxy)methyl]-2-methylpyrrolidin-2-one (17). To a solution of **16a** (10.3 g, 47.4 mmol) in CH_3OH (180 mL) and H_2O (20 mL) was added pTSA (215 mg, 1.13 mmol), and the reaction mixture was heated to reflux (bath temperature ∼80 °C) for 11 h. The mixture was cooled to rt and concentrated to yield a crude white solid which was eluted in CH_2Cl_2 (250 mL). To this mixture were added triethylamine (10 mL, 71.7 mmol) and methanesulfonyl chloride (4.4 mL, 56.9 mmol). The resulting mixture was stirred at rt. After 30 min, the reaction mixture was washed with H_2O (200 mL). The layers were separated, and the organic layer was concentrated to afford a white solid. Multiple recrystallizations from ethyl acetate afforded mesylate **17** (6.19 g, 63% two steps): $[\alpha]_D$ = +17 (*c* 1.1, $CHCl_3$); IR (thin film) 3400 (br), 1701, 1645, 1343, 1170 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (1H, br s), 4.24 (1H, dd, *J* = 10.0, 3.6 Hz), 4.01 (1H, dd, *J* = 10.0, 7.4 Hz), 3.90 (1H, dd, *J* = 7.4, 3.6 Hz), 3.07 (3H, s), 2.49 (1H, m), 2.42 (1H, m), 1.37 (1H, ddd, *J* = 12.0, 9.4, 8.1 Hz), 1.16 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.4, 71.3, 51.0, 37.4, 35.9, 31.4, 16.0.

(5*S*,3*S*)-2,5-Dimethylpyrrolidin-2-one (18). A solution of **17** (1.100 g, 5.31 mmol) in DME (60 mL) was degassed via a stream of argon. To this solution were added sodium iodide (1.53g, 10.2 mmol), tributyltin hydride (2.15 mL, 8.0 mmol), and AIBN (17 mg, 0.11 mmol). The cloudy white reaction mixture was heated to reflux (bath temperature ∼100 °C) for 5 h. The reaction mixture was cooled to rt, filtered, and concentrated. Purification via column chromatography on silica gel (0−5% CH_3OH−CH_2Cl_2) afforded lactam **18** (533 mg, 89%): $[\alpha]_D$ = −18 (*c* 0.57, $CHCl_3$); IR (thin film) 3238, 2962, 1711, 1654, 1456, 1427, 1307, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (1H, br s), 3.59 (1H, m), 2.44−2.33 (2H, m), 1.18 (1H, m), 1.16 (3H, d, *J* = 6.1 Hz), 1.12 (3H, d, *J* = 5.3 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 180.6, 48.0, 38.7, 37.2, 22.0, 15.9; HRMS (20 eV CI) calcd for M^+ ($C_6H_{11}NO$) 113.0841, found 113.0836 (error 4.4 ppm). Anal. Calcd for $C_6H_{11}NO$: C, 63.67; H, 9.8; N, 12.38. Found: C, 63.42; H, 9.97; N, 12.27.

(5*S*,3*S*)-*N*-(*tert*-Butoxycarbonyl)-2,5-dimethylpyrrolidin-2-one (19). To a solution of **18** (54 mg, 0.48 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (200 μL, 1.44 mmol), DMAP (76 mg, 0.62 mmol), and Boc_2O (265 μL, 1.15 mmol). The clear yellow reaction mixture was stirred at rt for 12 h. The reaction mixture was partitioned against H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 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 lactam **19** (84 mg, 82%): $[\alpha]_D = -51$ (*c* 1.3, $CHCl_3$); IR (thin film) 2975, 1784, 1748, 1752, 1507, 1304, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.01 (1H, m), 2.50 (1H, m), 2.40 (1H, m), 1.51 (9H, s), 1.36 (3H, d, J = 6.1 Hz), 1.23 (1H, m), 1.22 (3H, d, J = 7.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 177.1, 150.4, 82.7, 52.2, 37.6, 34.3, 28.8, 22.0, 16.8. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 8.98; N, 6.57. Found: C, 62.08; H, 8.99; N, 6.29.

(2*S*,4*R*)-4-[(*tert*-Butoxycarbonyl)amino]-2,4-dimethylbutanamide (20). Through a solution of **19** (668 mg, 3.13 mmol) in CH_2Cl_2 was bubbled NH_3(g) for ∼3 min. Trimethylaluminum (2.35 mL, 2.0 M in toluene) was added rapidly dropwise, and the reaction mixture was stirred for 2 h at rt. The reaction was quenched via dropwise addition of 0.1 N aqueous HCl (3 mL), and the resulting suspension was stirred for 5 min, filtered, and concentrated. Purification via column chromatography on silica gel (0−5% $CH_3OH-CH_2Cl_2$) afforded amide **20** (449 mg, 62%) and lactam **19** (210 mg, 31%). **20**: $[\alpha]_D = +6.7$ (*c* 1.4, $CHCl_3$); IR (thin film) 3384, 3352, 3027, 2971, 1602, 1643, 1618, 1530, 1275, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.11 (1H, br s), 5.72 (1H, br s), 4.53 (1H, br d), 3.68 (1H, br m), 2.35 (1H, br m), 1.86 (1H, br m), 1.41 (9H, s), 1.18 (3H, d, J = 6.9 Hz), 1.12 (3H, d, J = 6.5 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 179.3, 156.8, 79.2, 45.5, 41.4, 38.4, 28.4,.21.9, 18.8; HRMS (NH_3/CI) calcd for MH^+ ($C_{11}H_{23}N_2O_3$) 231.1709, found 231.1715 (error 2.6 ppm). Anal. Calcd for $C_{11}H_{22}N_2O_3$: C, 57.37; H, 9.63; N, 12.16. Found: C, 57.77; H, 9.54; N, 12.03.

[2(1*S*,3*R*)]-4-(Chloromethyl)-2-[3-[(*tert*-butoxycarbonyl)amino]-1,3-dimethylpropyl]oxazole (4). To a solution of **20** (70 mg, 0.304 mmol) in distilled $CHCl_3$ (7.5 mL) were added K_2CO_3 (298 mg, 2.1 mmol) and 1,3-dichloroacetone (250 mg, 1.9 mmol). The reaction mixture was heated to reflux at a bath temperature of >100 °C. After 9 h at reflux, the reaction mixture was cooled to rt and partitioned between $CHCl_3$ (20 mL) and brine/H_2O (10 mL/10 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (5−20% ethyl acetate−hexane) afforded oxazole **4** (56 mg, 61%), and amide **20** (4 mg, 6%). $[\alpha]_D = 21.6$ (*c* 4.0, $CHCl_3$); IR (thin film) 3438 (br), 2978, 1705, 1505, 1367, 1250, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, s), 4.43 (2H, s), 3.73 (1H, m), 3.01 (1H, m), 1.89 (1H, m), 1.65 (1H, m), 1.36 (9H, s), 1.31 (3H, d, J = 6.9 Hz), 1.09 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 155.2, 136.9, 135.6, 79.0, 44.3, 42.0, 36.9, 30.8, 28.2, 21.9, 18.1 HRFABMS calcd for MH^+, $C_{14}H_{24}N_2O_3Cl$: 303.1475, found 303.1490 (error 4.9 ppm).

[2*S*,3*S*,4*S*,N(1*R*,3*S*)]-4-(*N*,*N*-Dimethylamino)-*N*-[1-methyl-3-(4-(chloromethyl)-2-oxazoyl)butyl]-5-methoxy-2,3-bis(benzyloxy)valeramide (23). A solution of **4** (94 mg, 0.310 mmol) in EtOAc (11 mL) was cooled to 0 °C, and HCl(g) was bubbled through for 2 min. The cloudy reaction mixture was stirred at 0 °C for 15 min. The excess HCl was purged via a stream of argon (5 min), and a white precipitate formed. The suspension was concentrated and azeotroped with CH_2Cl_2 (2 × 2 mL) to afford a white solid which was eluted in CH_2Cl_2 (6 mL). Trimethylaluminum (260 μL, 2.0 M in toluene) was added, and the clear yellow-brown mixture was stirred for 25 min, at which time a solution of **3** (46 mg, 0.115 mmol) in CH_2Cl_2 (1.0 mL and 2 × 0.5 mL rinses) was added. The resulting clear brown reaction mixture was heated to 35 °C for 9.5 h. The reaction mixture was quenched via addition of CH_3OH (∼1 mL), followed by 0.1 N aqueous HCl (2 mL). The mixture was partitioned between EtOAc (20 mL) and brine (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (0−5% $CH_3OH-CH_2Cl_2$) afforded amide **23** (30 mg, 46%), **24** (11 mg, 16%), and epimerized ester starting material (8 mg, 17%). For **23**: $[\alpha]_D = -37.4$ (*c* 1.6, $CHCl_3$); IR (thin film) 3401, 2928, 1671, 1653, 1522, 1456, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (1H, t, J = 1.0 Hz), 7.19−7.35 (10H, m), 6.62 (1H, br d, J = 11.3 Hz), 4.72 (1H, d, J = 14.3 Hz), 4.55 (1H, d, J = 14.8 Hz), 4.52 (1H, d, J = 14.4 Hz), 4.48 (2H, d, J = 1.1 Hz), 4.46 (1H, d, J = 14.3 Hz), 4.44 (1H, d, J = 2.2 Hz), 4.18 (1H, dd, J = 12.5, 1.9 Hz), 4.07 (1H, m), 3.65 (1H, dd, J = 12.7, 2.8 Hz), 3.56 (1H, dd, J = 12.7, 7.6 Hz), 3.25 (3H, s), 2.96 (1H, m), 2.72 (1H, m), 2.35 (6H, s), 1.79 (1H, ddd, J = 18.0, 11.7, 6.7 Hz), 1.56 (1H, ddd, J = 17.9, 11.3, 6.2 Hz), 1.33 (3H, d, J = 8.6 Hz), 1.02 (3H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 168.6, 138.5, 137.4, 137.1, 135.7, 128.6, 128.6, 128.2, 128.6, 127.7, 127.4, 79.8, 79.1, 74.9, 74.5, 68.3, 62.8, 58.5, 42.2, 42.0, 41.8, 37.1, 30.5, 21.2, 17.9; HRFABMS calcd for MH^+ ($C_{31}H_{43}N_3O_5Cl$) 572.2891, found 572.2892 (error 0.2 ppm).

[2*S*,3*S*,4*S*,N(1*R*,3*S*)]-4-(*N*,*N*-Dimethylamino)-*N*-[1-methyl-3-(4-((tributylphosphino)methyl)-2-oxazoyl)butyl]-5-methoxy-2,3-bis(benzyloxy)valeramide (25). To a solution of **23** (15 mg, 0.026 mmol) in distilled DMF (3 mL) was added tributylphosphine (31 μL, 0.131 mmol). The clear yellow mixture was heated to 70 °C for 3 h, at which time the reaction mixture was cooled and concentrated. Purification via column chromatography on silica gel (1−15% $CH_3OH-CH_2Cl_2$) afforded phosphonium salt **25** (14 mg, 70%): $[\alpha]_D = -4.56$ (*c* 1.6, $CHCl_3$); IR (thin film) 3403, 2961, 2934, 1669, 1653, 1522, 1456, 1277, 1098 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 7.88 (1H, d, J = 4.0 Hz), 7.29−7.44 (10H, m), 4.61−4.66 (2H, m), 4.48−4.55 (2H, m), 4.33 (1H, s), 4.13 (1H, m), 4.00 (1H, m), 3.59−3.73 (2H, m), 3.58 (2H, dd, J = 14.5, 0.6 Hz), 3.29 (3H, s), 2.94−3.10 (1H, m), 2.18−2.33 (12H, m), 1.44−1.65 (14H, m), 1.31 (3H, d, J = 6.9 Hz), 1.10 (3H, d, J = 6.5 Hz), 0.95 (9H, t, J = 7.3 Hz); ^{13}C NMR (125 MHz, CD_3CN) δ 169.9, 139.8, 138.9, 138.6, 138.6, 129.7, 129.6, 129.6, 129.4, 129.1, 128.9, 128.6, 128.4, 80.4, 79.8, 75.2, 74.8, 68.9, 63.7, 58.7, 43.1, 42.7, 42.3, 31.6, 24.6, 24.4, 23.9, 23.8, 19.5, 19.1, 18.4, 13.6; HRFABMS calcd for M^+ ($C_{43}H_{69}N_3O_5P$) 738.4975, found 738.4974 (error 0.1 ppm).

[2*S*,3*S*,4*S*,N(1*R*,3*S*)]-4-(*N*,*N*-Dimethylamino)-*N*-[1-methyl-3-(4-((tributylphosphino)methyl)-2-oxazoyl)butyl]-2,3-dihydroxy-5-methoxyvaleramide (2). To a solution of **25** (40 mg, 0.052 mmol) in CH_3OH (18 mL) was added 3 N HCl (anhydrous in CH_3OH, 0.52 mL), followed by 10% Pd−C (36 mg). Hydrogen gas was bubbled through the suspension for 5 min, and the reaction mixture was stirred at rt under H_2. After 10 h, an additional 42 mg of 10% Pd−C was added. After 15 h, the mixture was filtered through a plug of Celite which was rinsed with CH_3OH (50 mL), EtOAc (50 mL), and CH_2Cl_2 (50 mL). The combined organics were concentrated, and purification via column chromatography on silica gel (5−30% $CH_3OH-CH_2Cl_2$) afforded diol **2** (21 mg, 68%): $[\alpha]_D = -72.9$ (*c* 0.8, $CHCl_3$); IR (thin film) 3223 (br), 2963, 2934, 1653, 1566, 1464, 1262, 1098 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 7.91 (1H, d, J = 3.8 Hz), 4.50 (1H, s), 4.36 (1H, br s), 4.09 (1H, br s), 3.68−3.91 (5H, m), 3.39 (3H, s), 3.13 (1H, m), 2.82 (6H, br s), 2.22 (6H, m), 2.08 (1H, m), 1.73 (1H, m), 1.59 (6H, m), 1.49 (6H, m), 1.32 (3H, d, J = 6.9 Hz), 1.19 (3H, d, J = 6.6 Hz), 0.96 (9H, t, J = 3.8 Hz); ^{13}C NMR (125 MHz, CD_3CN) δ 173.5, 170.0, 139.1, 139.0, 129.2, 129.1, 72.5, 69.9, 68.6, 66.7, 59.4, 44.8, 42.1, 32.3, 24.6, 24.5, 23.9, 23.9, 21.8, 19.4, 19.1, 18.8, 18.4, 12.7; HRFABMS calcd for M^+ ($C_{29}H_{57}N_3O_5P$) 558.4036, found 558.4041 (error 0.9 ppm).

***tert*-Butyl [3-[4-[(1*E*)-3-[(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-2-[(1*S*,3*R*,4*S*)-3-(*tert*-butyl dimethylsiloxy)-1-methoxy-4-methyl-5-hexenyl]-9-(benzoyloxy)-3-hydroxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-7-yl]propenyl]-2-oxazolyl]propyl]carbamate (28).** To a solution of phosphonium salt **26** (11 mg, 0.022 mmol) in DMF (0.44 mL) at 0 °C was added LDA (88 μL, 0.25M in THF). The yellow mixture was stirred at 0 °C for 10 min, at which time a solution of aldehyde **27** (7 mg, 0.011 mmol) in DMF (0.2 mL + 0.2 mL rinse) was added

dropwise. The reaction mixture was stirred at 0 °C for 45 min, at which time the reaction mixture was partitioned between 5% aqueous $NaHCO_3$ (10 mL) and ether (10 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via preparative thin layer chromatography (35% ethyl acetate−hexane) afforded coupled product **28** (5.3 mg, 59%): IR (thin film) 3500, 3350 (br), 2957, 2928, 1717, 1472, 1453, 1366, 1277, 1260, 1175, 1101 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.13 (2H, m), 7.54 (1H, m), 7.42 (2H, m), 7.37 (1H, s), 6.26 (2H, m), 5.69 (1H, ddd, J = 17.6, 10.3, 7.6 Hz), 5.14 (1H, m), 4.83−4.93 (3H, m), 4.60 (1H, m), 4.03 (1H, dd, J = 8.5, 4.2 Hz), 3.77 (1H, m), 3.49 (1H, dd, J = 12.2, 4.2 Hz), 3.44 (3H, d, J = 134.5 Hz), 3.27 (2H, m), 3.17 (1H, m), 2.74 (2H, m), 2.15−2.40 (3H, m), 1.85−1.95 (3H, m), 1.73 (1H, m), 1.14 (3H, s), 1.02 (3H, d, J = 6.9 Hz), 0.99 (3H, d, J = 7.0 Hz), 0.88 (3H, s), 0.84 (9H, s), 0.02 (3H, s), 0.00 (3H, s); HRFABMS DCM/NBA calcd for MH^+ ($C_{45}{}^{13}CH_{73}N_2O_{10}Si$) 842.5068, found 842.5071 (error 0.3 ppm).

(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*R*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-1-methoxy-4-methyl-5-hexenyl]-9-(benzoyloxy)-3-hydroxy-4,4,8-trimethyl-4,6-dioxaspiro[4.5]dec-2-yl]propenyl]-2-oxazolyl]-1-methylbutyl]-4-(dimethylamino)-2,3-dihydroxy-5-methoxyvaleramide (29). To a solution of phosphonium salt **2** (13 mg, 0.022 mmol) in DMF (0.3 mL) at 0 °C was added LDA (88 μL, 0.25M in THF). The yellow mixture was stirred at 0 °C for 10 min, at which time a solution of aldehyde **27** (9.1 mg, 0.015 mmol) in DMF (0.2 mL + 0.1 mL rinse) was added. The reaction mixture was stirred at 0 °C, and portions of LDA (4 × 44 μL, 2 equiv total) were added over the course of 1.5 h. The reaction was quenched via addition of saturated aqueous $NaHCO_3$ (3 mL). The reaulting mixture 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 (20% ethyl acetate−hexanes to 10% CH_3OH−CH_2Cl_2) afforded coupled product **29** (5 mg, 35%): IR (thin film) 3500, 3350(br), 2928, 1717, 1645, 1464, 1277, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (2H, m), 7.60 (1H, m), 7.48 (2H, m), 7.46 (1H, s), 7.10 (1H, m), 6.29−6.35 (2H, m), 5.77 (1H, ddd, J = 17.7, 10.4, 7.8 Hz), 5.21 (1H, m), 4.94−4.98 (2H, m), 4.68 (1H, m), 4.15−4.30 (2H, m), 4.11 (1H, dd, J = 8.2, 4.3 Hz), 3.79−3.90 (3H, m), 3.70 (1H, m), 3.59 (1H, dd, J = 12.1, 4.3 Hz), 3.52 (3H, d, J = 137.0 Hz), 3.30−3.45 (4H, m), 2.90−3.10 (3H, m), 2.30−2.50 (9H, m), 1.95−2.10 (2H, m), 1.70−1.90 (3H, m), 1.45 (1H, m), 1.38 (3H, d, J = 6.9 Hz), 1.26 (3H, d, J = 6.6 Hz), 1.21 (3H, s), 1.06 (3H, d, J = 7.1 Hz), 1.03 (3H, d, J = 6.9 Hz), 0.95 (3H, s), 0.91 (9H, s), 0.09 (3H, S), 0.07 (3H, s); HRFABMS DCM/NBA calcd for MH^+ ($C_{50}{}^{13}CH_{84}N_3O_{12}Si$) 959.5858, found 959.5903 (error 4.7 ppm).

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Supporting Information Available: Procedures and characterization data for **5**, **16b**, **21**, **22**, **24**, **26**, and **27** and NMR spectra of all new compounds to indicate purity (65 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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