Total Synthesis of Motuporin (Nodularin-V)

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Abstract: The serine/threonine phosphatase (protein phosphatase 1 and 2A) inhibitors constitute a biologically and structurally interesting class of natural products. Among this class of inhibitors are cyclic pentapeptides (nodularins) and cyclic heptapeptides (microcystins), both of which inhibit at the nanomolar level and are the only peptide inhibitors of these enzymes. Described herein is the total synthesis of motuporin, which utilizes an Ugi four-component condensation (4CC) reaction to synthesize the 2-(*N*)-methylaminobutenyl residue, Matteson's dihalomethyllithium insertion methodology for the construction of a key fragment, and an overall synthetic strategy amenable to the synthesis of analogues.

Introduction

Inhibitors of protein phosphatase 1 and 2A (PP1 and PP2A) comprise a structurally diverse class of natural products including the calyculins,[3] tautomycin,[4] okadaic acid,[5] the microcystins,[6] and the nodularins (Figure 1).[7] The last two examples are both cyclic peptides of seven and five residues, respectively, and contain similar functionality including the (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (ADDA) residue that is unique to this class of peptides. Motuporin was isolated in 1992 by Andersen and co-workers from the Paupa New Guinea sponge *Theonella swinhoei* Gray and is one of the most potent inhibitors of PP1 known, inhibiting at subnanomolar concentrations and showing strong in vitro cytotoxicity against a number of cancer cell lines.[8] It had also received attention from the synthetic community prior to our efforts in the form of a completed total synthesis from the laboratory of Stuart Schreiber.[9] The work herein describes the successful total synthesis of motuporin, a member of the nodularin class of inhibitors.

Our interest in the total synthesis of motuporin was motivated not only by the varied functionality of the molecule, but also by the synthetic and biological studies of a number of the inhibitors in this class currently ongoing in our laboratory.[10] Thus, we planned a synthetic route that was amenable to analogue studies of the molecule, specifically near the 2-(*N*)-methylaminobutenyl moiety as this is known to be contained within the active site in the microcystin class of inhibitors from a microcystin·protein phosphatase-1 cocrystal structure.[11] With this in mind, we hypothesized that in the corresponding pentapeptide structure this residue should also be in the active site and hence would be a good choice for modification and analogue studies.

Retrosynthetic Analysis

Motuporin contains three sites of functionality which require protection for chemical synthesis: two carboxylic acids and a dehydroamino acid. For the protection of the carboxylic acid functionality we chose a methyl ester protection strategy based on the variety of conditions available for deprotection.[12] Base-catalyzed saponification requires a minimum of reagents which would interfere with the purification of the highly polar natural product, a further benefit of this choice. It was also shown by Schreiber and Valentekovich[8] in their total synthesis of motuporin that the saponification conditions also result in dehydration of threonine to afford the dehydroamino acid residue and the natural product.

With the protection scheme decided upon it was proposed to effect cyclization of the 19-membered pentapeptide macrocycle at the ADDA (*S*)-valine amide bond (Scheme 1). This point of cyclization was based on the reported isolation of a similar acyclic peptide by Reinhart and co-workers and subsequent feeding studies which support the theory that this is the point of cyclization in the biosynthesis of the natural product.[13] For

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(3) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc*. **1986**, *108*, 2780−2781.

(4) Cheung, X. C.; Kihara, T.; Kusakabe, H.; Magae, J.; Kobayashi, Y.; Fang, R. P.; Ni, Z. F.; Shen, Y. C.; Ko, K.; Yamaguchi, I.; Kono, K. *J. Antibiotics* **1987**, *40*, 907−909.

(5) Tachibana, K.; Scheuer, J.; Tsukitani, Y.; Kikuchi, H.; Van Egan, D.; Clardy, J.; Gopichand, Y.; Schmita, F. J. *J. Am. Chem. Soc*. **1981**, *103*, 2469−2471.

(6) Honkanen, R. E.; Zwiller, J.; Moore, R. E.; Daily, S. L.; Khatra, B. S.; Dukelow, M.; Boynton, A. L. *J. Biol. Chem.* **1990**, *265*, 19401−19404..

(7) Hankanen, R. E.; Dukelow, M.; Zwiller, J.; Moore, R. E.; Khatra, B. S.; Boynton, A. L. *Mol. Pharm*. **1991**, *40*, 577−583.

(8) Dilip de Silva, E.; Williams, D. E.; Andersen, R. J.; Klix, H.; Holmes, C. F. B.; Allen, T. M. *Tetrahedron Lett*. **1992**, *33*, 1561−1564.

(9) Valentekovich, R. J.; Schreiber, S. L. *J. Am. Chem. Soc*. **1995**, *117*, 9069−9070.

(10) Total synthesis of calyculin C: (a) Scarlato, G. R.; Dematteі J. A.; Chong L. S.; Ogawa A. K.; Lin, M. R.; Armstrong R. W. *J Org. Chem*. **1996**, *61*, 6139−6152. (b) Ogawa A. K.; DeMattei, J. A.; Scarlato, G. R.; Tellew, J. E.; Chong, L. S.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6153−6161. (c) Ogawa, A. K.; Armstrong, R. W. *J. Am. Chem. Soc*. **1998**, *120*, 12435−12442. Synthetic efforts toward Tautomycin: (d) Maurer K. W.; Armstrong R. W. *J. Org. Chem.* **1996**, *61*, 3106−3116. Biological activity and binding: (e) Gupta, V.; Ogawa, A. K.; Du, X. H.; Houk, K. N.; Armstrong, R. W. *J. Med. Chem.* **1997**, *40*, 3199−3206.

(11) Goldberg, J.; Huang, H.; Kwon, Y.; Greengard, P.; Nairn, A. C.; Kuriyan, J. *Nature*, **1995**, *36*, 745−753.

(12) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991.

(13) Choi, B. W.; Namikoshi, F. S.; Rinehart, K. L.; Carmichael, W. W.; Kaup, A. M.; Evans, W. R.; Beasley, V. R. *Tetrahedron Lett*. **1993**, *34*, 7881−7884.

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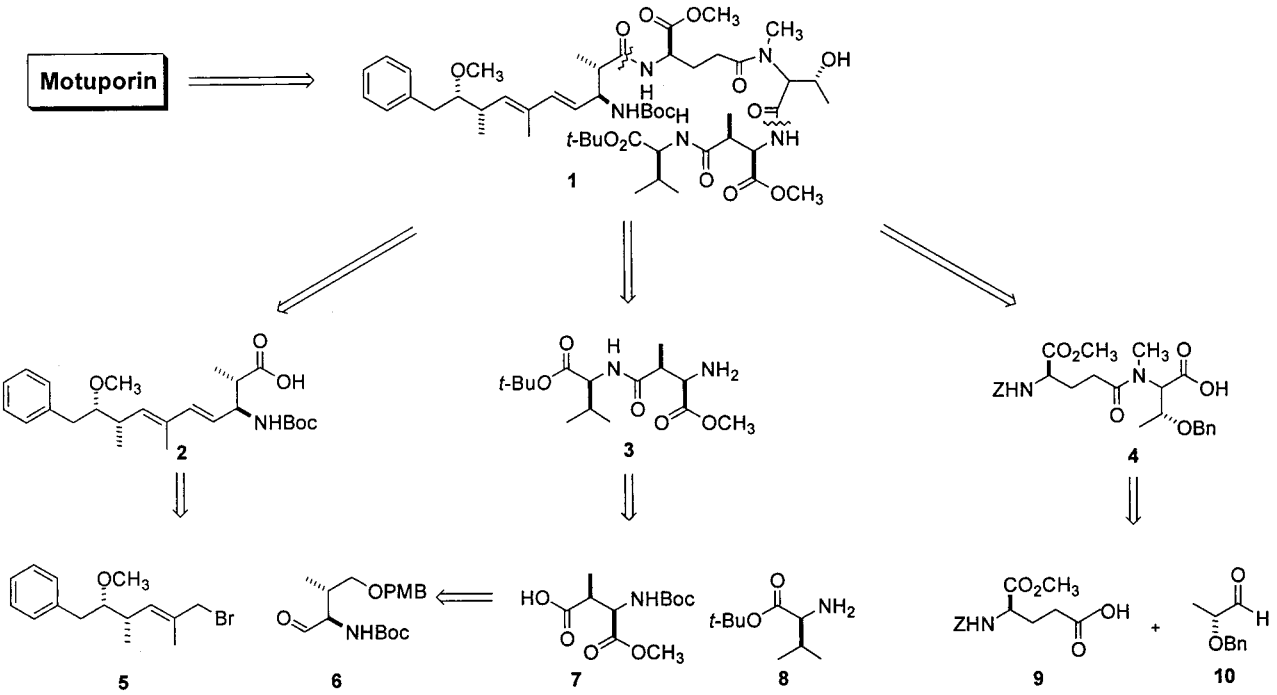
Scheme 1



protection of the amine and acid functionality involved in the cyclization we chose the *tert*-butoxycarbonyl carbamate (Boc) and the *tert*-butyl ester, respectively, because of the relatively mild trifluoroactic acid (TFA) deprotection conditions and the generally high purity and minimum of epimerization of the crude product from these reactions.

Further disconnection of linear peptide **1** affords Boc-protected ADDA (**2**) and a tetrapeptide which can be further disconnected to give dipeptides **3** and **4**. The ADDA synthesis was envisioned from the coupling of a Wittig or Horner-Emmons reagent derived from bromide **5** with aldehyde **6**.[14] While this method for constructing the diene moiety of this molecule has been reported previously,[13b,c] our studies and final success represents a considerable improvement over the earlier attempts. This same intermediate, **6**, can be elaborated by manipulation of the terminal groups to afford the 3-methyl-aspartyl (MeAsp) residue in dipeptide **3**.

For the synthesis of aldehyde **6** we proposed to use the dihalomethyllithium insertion method of Matteson.[15] This methodology offers a unique approach to the construction of a series of contiguous stereocenters and proceeds with extremely high stereoselectivity resulting in material that is enantiomerically and diastereomerically pure. From previous work in our laboratories we have found this method is amenable to large-scale synthesis, a necessity as it affords four of the eight stereogenic centers in the molecule.

Finally, we proposed that dipeptide **4** could be made from the Ugi 4CC of monoprotected glutamic acid **9**,[16] aldehyde **10**, methylamine, and cyclohexenyl isocyanide.[17] The conversion of the resulting cyclohexenamide to the free acid has been shown previously[18] and provides a means of incorporating the valuable MeAsp and ADDA residues late in the synthesis. The use of Ugi technology overcomes the difficulty of coupling a secondary amine and carboxylic acid using standard peptide coupling techniques, which is often a low yielding process. Additionally, the Ugi reaction makes it possible to vary the functionality at the dehydroaminoamide position easily, thus offering another degree of flexibility in the synthesis of analogues. In practice, while this route was quite successful in providing material, the mixture of diastereomers (and resulting rotamers from the tertiary amide) made characterization difficult. Thus, we also synthesized dipeptide **4** using protected amino acids and conventional coupling technology. It is worth noting that the mixture of diastereomers at this center is inconsequential for purposes of synthesizing motuporin as this carbon becomes part of the dehydroamino residue.

Synthesis of Aldehyde 6

The synthesis of **6** began with the transmetalation of chloroiodomethane with *n*-butyllithium in the presence of triisopropyl borate **11** to give diisopropyl chloromethylborate.[19] This was then transesterified with (*1R,2R,3S,5R*)-(+)-pinanediol and the chloride displaced in S_N2 fashion with lithium *p*-methoxybenzyloxide (LiOPMB) in tetrahydrofuran (THF) to produce protected alcohol **13** ready for the first insertion. Chain extension of **13** with dichloromethyllithium followed by addition of 3.7 equiv of $ZnCl_2$ to affect rearrangement of the ate-complex gave α-chloroborate ester **13** as a single diastereomer. Stereospecific displacement of the chloride with methylmagnesium chloride afforded the α-methyl borate ester ready for the next iteration.

(14) For other syntheses of ADDA see: (a) Namakoshi, M.; Rinehart, K. L.; Dahlem, A. M.; Beasley, V. R.; Carmichael, W. W. *Tetrahedron Lett.* **1989**, *30*, 4349. (b) Chakraborty, T. K.; Joshi, T. P. *Tetrahedron Lett.* **1990**, *31*, 2043. (c) Beatty, M. F.; Jennings-White, C.; Avery, M. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1637. (d) Kim, H. Y.; Toogood, P. L. *Tetrahedron Lett.* **1996**, *37*, 2349−2352. (e) Sin, N.; Kallmerten, J. *Tetrahedron Lett.* **1996**, *37*, 5645−5648. (f) D'Aniello, F.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 4870. (g) D'Aniello, F.; Mann, A.; Schoenfelder, A.; Taddei, M. *Tetrahedron* **1997** *53*, 1447−1456. (h) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4914−4915.

(15) Matteson D. S. *Pure Appl. Chem.* **1991**, *63*, 339−344.

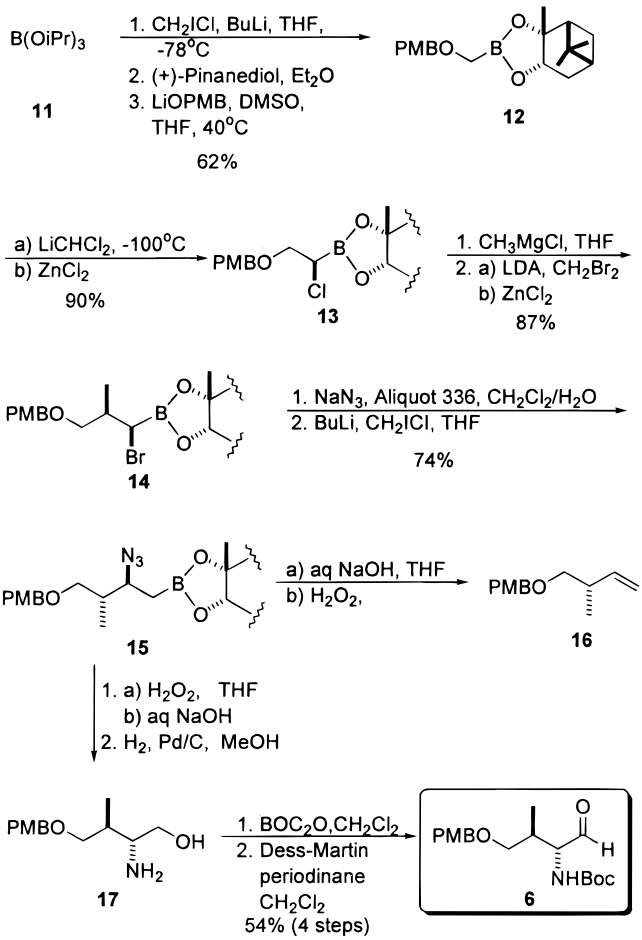
(16) (a) Adams, D. R.; Bailey, P.; Collier, I.; Hefferman, J. D.; Stokes, S. *Chem. Commun.* **1996**, *7*, 349−350. (b) Adams, D. R.; Bailey, P.; Collier, I.; Hefferman, J. D.; Stokes, S. *Chem. Commun.* **1996**, *7*, 886.

(17) Gokel, G.; Lüdke, G.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; pp 145−199.

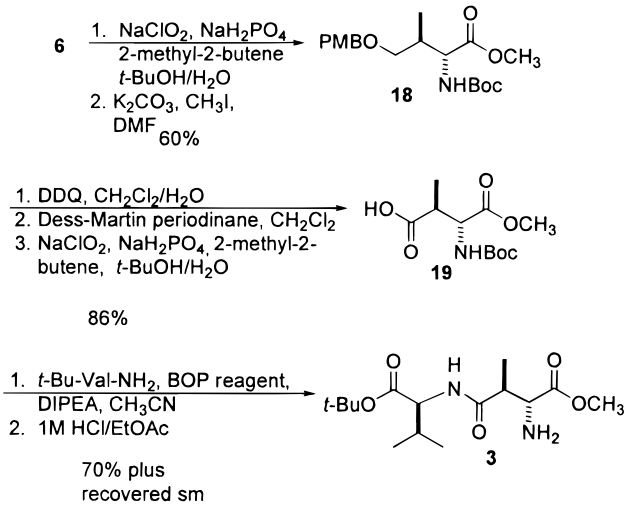
(18) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842−7843.

(19) Matteson, D. S.; Sadhu, K. M. *Organometallics* **1984**, *3*, 614−618.

Scheme 2



Scheme 3



The next step—owing to the comparatively low nucleophilicity of azide and the steric bulk of the substrate—was performed with dibromomethyllithium[20] affording the α-bromo borate (**14**) instead of the usual chloride.[21] Bromide **14** was then converted cleanly to the azide by treatment with sodium azide in CH_2Cl_2/H_2O under phase transfer catalyst conditions.[22] Notably, this was the only reaction in any of our trials using this methodology which has given *any detectable amount* of the diastereomer. This observation is in agreement with Matteson, who also reports a small percentage of the undesired diastereomer when performing azide displacements.[23]

The final chain extension was effected through the use of the transmetalation conditions of the first step and afforded the azido borate in 74% yield from the bromide (3 steps). Oxidative removal of the boron by addition of hydrogen peroxide *followed by* sodium hydroxide gave amino alcohol **17**. Interestingly, reversing the order of addition resulted in a large amount of alkene **16** (presumably by elimination of the azide from the ate-complex) and the desired alcohol as the minor product. Reduction of the azide to amine **17** with standard hydrogenation conditions gave the amine with no concomitant loss of the PMB protecting group. Amine **17** was then protected as the *tert*-Butylcarbamate (Boc) with the pyrocarbonate, and oxidation of the alcohol with the Dess—Martin reagent[24] gave aldehyde **6** in 54% yield for the four steps.

During the course of the synthesis we required a large amount of precursor **6**, and found it could be made quite easily by carrying through material in 20—30 mmol batches, run in parallel. While it is possible to work with larger amounts, the initial deprotonation is exothermic and maintaining a bath temperature of −100 °C was difficult above this quantity. Beyond this minor difficulty, the procedure was quite efficient and afforded a large amount of material in a short period of time.

Synthesis of Val-Methylaspartyl Dipeptide

Elaboration of aldehyde **6** to dipeptide **3** was accomplished as follows: the aldehyde was oxidized with sodium chlorite[25] and the resulting acid protected as the methyl ester (**18**) with methyl iodide in *N*,*N*-dimethylformamide (DMF). The protected primary alcohol was then deprotected with 2,3-dichloro-5,6-dicyano-1,4-diquinone (DDQ)[26] and oxidized with the same two-step protocol as before affording acid **19** in 86% yield. Coupling of the acid to (*D*)-valine with benzotriazol-1-yloxy tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) and diisopropylethylamine (DIPEA) was performed uneventfully, affording the fully protected dipeptide. Given the acid lability of two protecting groups, we anticipated difficulties with the selective deprotection of the Boc-protected amine in the presence of the acid labile *tert*-butyl ester. However, we found that the transformation could be accomplished easily using the conditions of Rapoport[27] affording the aminodipeptide **3** as a single diastereomer, ready to be coupled to dipeptide **4**.

Synthesis of the γ-(D)-Glutamyl-Threonine Dipeptide (4)

As a means of providing diversity for later studies we proposed to use an Ugi 4CC to synthesize the protected threonyl residue which would later be converted to the dehydroamino acid. Thus, Ugi reaction of the carboxylbenzyloxy (Z) protected acid **9**, aldehyde **10**,[28] methylamine **20**, and cyclohexenyl

(20) Matteson, D. S.; Kandil, A. A.; Soundararajan, R. *J. Am. Chem. Soc*. **1990**, *112*, 3964—3969.

(21) Initial attempts with the chloride were successful; however, the reaction only progressed to ca. 50% completion. Given the potential for explosion afforded by the reaction conditions we were reluctant to continue the reaction for a longer duration.

(22) Matteson, D. S.; Beedle, E. C. *Tetrahedron Lett*. **1987**, *28*, 4499—4502.

(23) Matteson, D. S.; Beedle, E. C. *J. Labeled Compd. Radiopharm.* **1988**, *25*, 675—683.

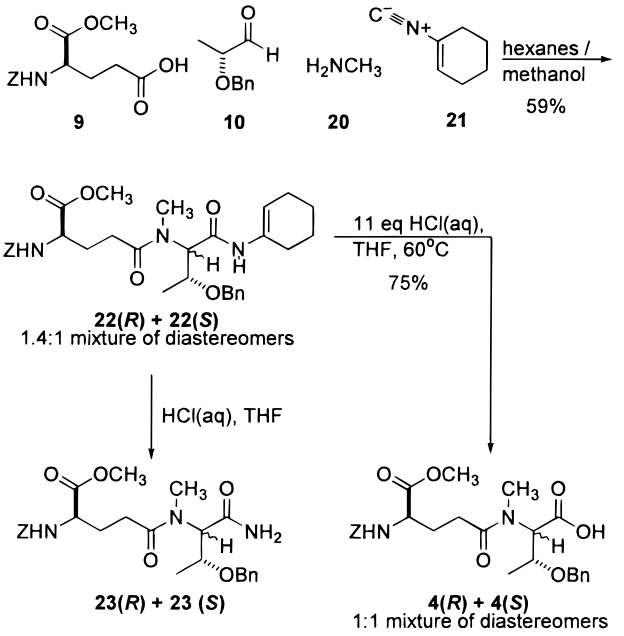
(24) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155—4156.

(25) Bal, B. S.; Childers, W. E.; Pinnick, H. W. T*etrahedron* **1981**, *37*, 2091—2096.

(26) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3651—3654.

(27) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem*. **1994**, *59*, 3216—3218.

Scheme 4

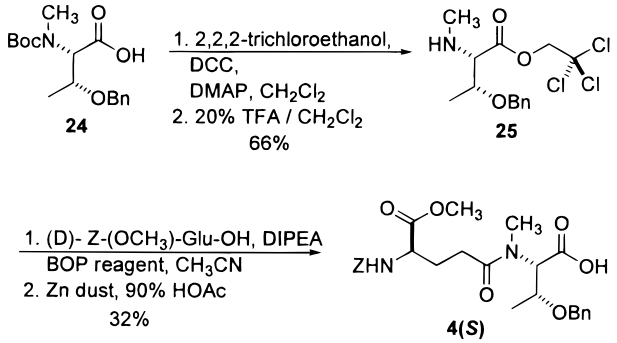


isocyanide **21** afforded cyclohexenamide dipeptide **22** as a mixture of separable diastereomers in reasonable yield. To our surprise, attempted hydrolysis of the cyclohexenyl moiety with standard conditions resulted in exclusive conversion to primary amide **23**. Upon further study of the hydrolysis conditions we found that by increasing the amount of acid and *preheating* the reaction mixture to 60 °C free carboxylic acid **4** was the major product, with only a small amount of the aforementioned amide present.

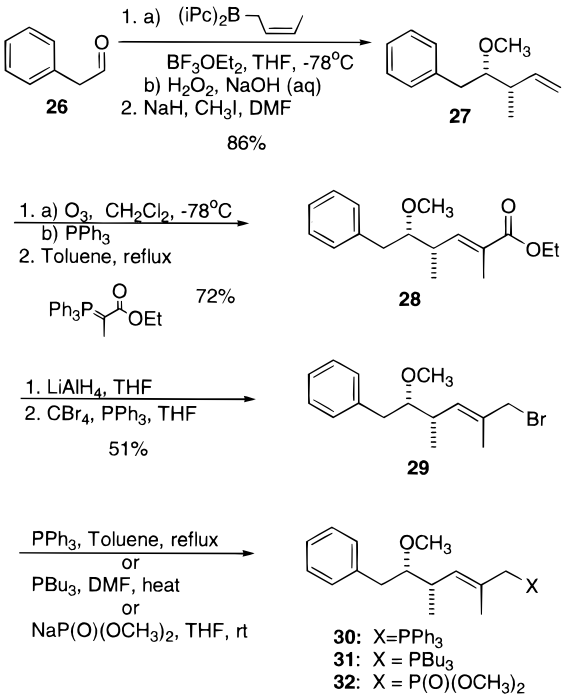
Initially, we noted that the heated conditions also resulted in epimerization of the α-stereocenter, presumably due to formation of the azalactone intermediate. Upon closer observation, however, we realized that the reaction was in fact proceeding through the primary amide that was simply hydrolyzed to the carboxylic acid under the more stringent conditions. This was verified by treating the amide **23** with the revised conditions and obtaining acid **24**. The two diastereomers **4(*R*)** and **4(*S*)** were inseparable by flash chromatography and were carried on as a mixture.

Because of the complexity of the intermediates beyond this point and the fact that many of the compounds exist as a mixture of rotamers we decided to develop a diastereoselective route using standard coupling methods for purposes of characterization. Thus, commercially available diprotected (*S*)-threonine, **24**, was converted to the 2,2,2-trichloroethyl ester with dicyclohexylcarbodiimide (DCC) and catalytic *N*,*N*-(dimethylamino)pyridine (DMAP). The Boc group was then removed with TFA in dichloromethane giving amine **26**, which was then coupled to the aforementioned acid (**24**) with use of the BOP reagent. Finally, the acid was deprotected with Zn dust in aqueous acetic acid (HOAc)[29] overnight affording **4(*S*)** in diastereomerically pure form. This sequence, in addition to providing material for characterization, illustrates the improvement possessed by the Ugi reaction in forming the synthetically challenging tertiary amide bond.

Scheme 5



Scheme 6



Synthesis of Boc-Protected ADDA (2)

Synthesis of the remaining two stereocenters was accomplished by Brown crotylboration[30] of phenylacetaldehyde with the reagent derived from (+)-*B*-(methoxy)diisopinocampheylborane and *cis*-2-butene. This was then converted to the methyl ether **27** and elaborated by using standard conditions to give enoate **28** and finally allylic bromide **29**.

Conversion of **29** to Wittig reagent **30** and deprotonation with *n*-butyllithium in THF afforded **33** in a rather disappointing 17% yield of the desired *trans-trans* product, an observation in agreement with other attempts to form this bond with similar technology.[13b,c] An almost 4-fold increase product was realized when the base was changed to lithium diisopropylamide (LDA). Further attempts at optimization with the tributylphosphonium ylide **31** and LDA as base resulted in coupled material in higher yield, but material which was found to be a 1:1 mixture of diastereomers. Finally, the attempted coupling with Horner-Emmons reagent **32** showed even less success, affording only epimerized aldehyde and recovered **32**.

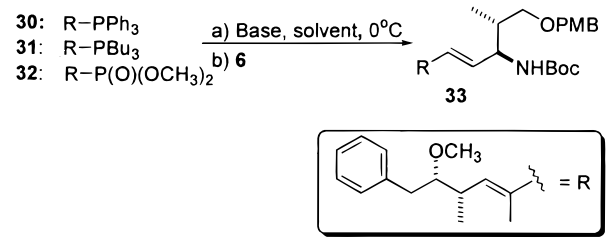
With the diene in hand, attempted deprotection of the PMB ether with DDQ resulted in deprotection of the primary alcohol *and allylic oxidation of the protected amine to the ketone*. We

(28) Prepared in two steps by protecting methyl lactate with benzyl bromide and sodium hydride in DMF followed by reducing the ester to the aldehyde with diisobutylaluminum hydride in toluene at −78 °C.

(29) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramaga, R.; Ranganathan, S.; Vorbrüggen *J. Am. Chem. Soc.* **1966**, *88*, 852−853.

(30) Brown, H. C.; Jadhav, P. K.; Bhat, S. K. *J. Am. Chem. Soc.* **1988**, *110*, 1535−1538.

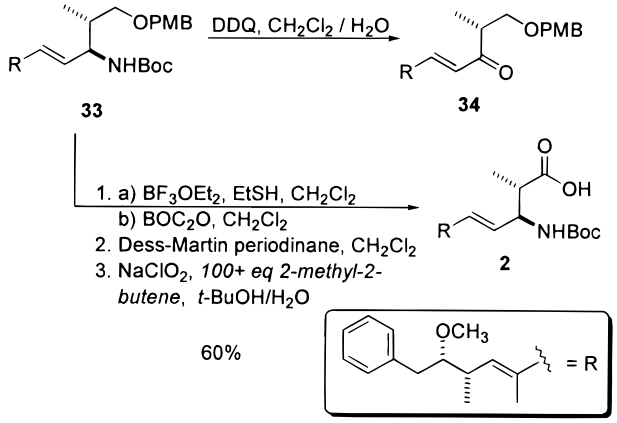
Table I



Starting Material	Base	Solvent	Yield	*cis / trans*
27	n-BuLi	THF	26%	1 : 2
27	LDA	THF	78%	1 : 4
28	LDA	DMF	80%*	<5 : >95
29	n-BuLi	THF	0%**	n / a

*Contained 1:1 ratio of diastereomers
**Recovered sm contained 1:1 ratio of diastereomers

Scheme 7

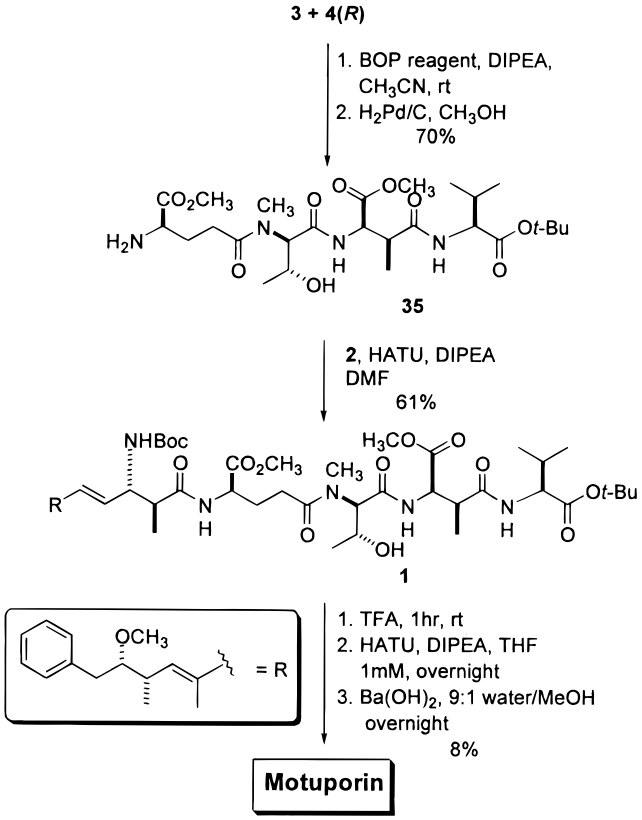


were surprised at this result as allylic oxidation under DDQ conditions is known in the case of allylic alcohols,[31] but to our knowledge unprecedented for amines. Attempts at deprotecting the alcohol with borontrifluoride etherate/ethanethiol [32] or TFA/dichloromethane[33] conditions gave concomitant deprotection of the Boc group—a result that could not be overcome by altering reagent equivalents or varying the temperature—thus necessitating a deprotection/reprotection strategy for this transformation. Oxidation of the alcohol to the acid afforded Boc protected ADDA **2** in 87% yield from the protected alcohol. Notably, initial attempts at oxidation of the aldehyde to the acid afforded only a small amount of the acid, the remainder of the material being baseline by thin-layer chromatography. However, we found that when the amount of 2-methyl-2-butene was increased from 20 to 100+ equiv the yield increased to nearly quantitative, supporting the postulate that the byproducts generated during the reaction was decomposing the more reactive diene rather than reacting with the 2-methyl-2-butene.

Final Coupling and Deprotection

Completion of the synthesis was accomplished as shown in Scheme 8. Amine **3** and acid **4(*S*)** were coupled by using BOP

Scheme 8



reagent affording the fully protected tetrapeptide as a mixture of separable diastereomers, presumably epimerized at the threonyl α-center.[34,35] The protected tetrapeptide was then converted to amino alcohol **35** by hydrogenolysis of the carboxybenzyloxy carbamate and the benzyl ether. This was then immediately coupled to Boc-ADDA, **2**, using O-(7-azabenzotriazol-1-yl)-1,1−3,3-tetramethyluronium pentafluorophosphate (HATU), with DIPEA as base.[36] Notably, both BOP reagent and bis-oxazolidinonyl phosphoryl chloride (BOP chloride)[37] failed in this transformation, though they were successful in model couplings of acid **2** to glutamic acid diesters. The protected pentapeptide was then deprotected with neat TFA, and cyclized with HATU in THF under dilute conditions. This afforded the cyclized material as a mixture of rotamers which were then deprotected by using the conditions of Schreiber and Valentekovich[38] to afford motuporin as a 1:3 mixture of epimers separable by High Performance Thin Layer Chromatography.

During the course of the synthesis, we noted that the yield of the cyclization step varied dramatically with respect to the stereochemistry of the threonyl residue. When material was diastereomeric at this center (derived from the Ugi synthetic route to **4**) the cyclization proceeded in nearly twice the yield

(31) Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc*. **1985**, *107*, 4586−4588.
(32) Daly, S. M.; Armstrong, R. W. *Tetrahedron Lett*. **1989**, *30*, 5713−5715.
(33) Yan, L.; Kahne, D. *Synlett* **1995**, 523−524.
(34) Bodansky, M. *Principles of Peptide Synthesis*; (Reactivity and Structure, Vol. 16; Springer-Verlag: Berlin, Heidelberg, 1984.
(35) The α-center of the threonyl residue was postulated as the site of epimerization as the diastereomers showed opposite but nearly equal optical rotations. This was in agreement with the optical rotations for the separate Ugi derived cyclohexenamide dipeptides **4(*R*)** and **4(*S*)** which were known to be epimers at this center and showed similar optical rotations. While the coupling gave a major and a minor component (presumably due to epimerization via the azalactone), the figures and Experimental Section show the manipulations of the minor diastereomer.
(36) Jou, G.; Gonzalez, I.; Albericio, F.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem*. **1997**, *62*, 354−366.
(37) Diego-Moseguer, J.; Palomo-Coll, A. L.; Fernandez,-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547−551.
(38) Valentekovich, R. J. Personal communication.

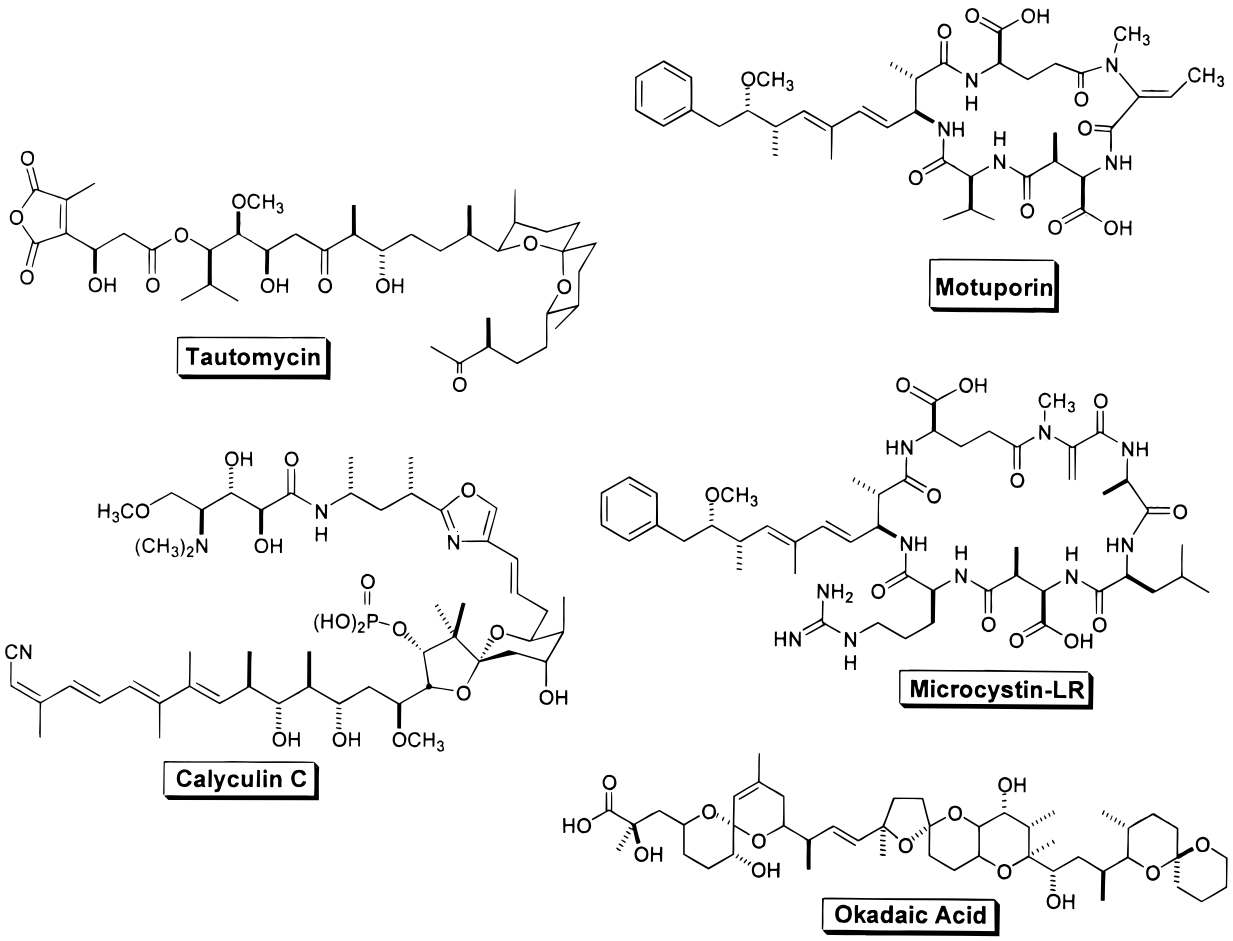


Figure 1.

as reported for the above sequence. This seems to suggest that this stereocenter has a strong effect on the overall conformation of the molecule, a result that is in agreement with the drastically different optical rotations of intermediates epimeric at this center (*vide supra).*

Conclusion

The total synthesis of motuporin provides quantities of the natural product for testing and also proof of our synthetic plan for the synthesis of analogues. In completing the synthesis we showed the utility of Matteson's synthetic methodology through its success in generating the large amount of stereochemically pure material required for the synthesis. By using an Ugi 4CC to synthesize the (*N*)-methyl dehydroamino acid residue we demonstrated the utility of this reaction in forming a tertiary amide bond which proved difficult using standard coupling techniques. Additionally, this strategy also allows for the introduction of varied functionality at this site of the molecule by using different inputs in the 4CC. This synthetic plan affords a novel method of constructing structurally varied dehydroamino acids, and should prove valuable in analogue studies of motuporin.

Experimental Section

All reagents were obtained from commercial suppliers and used without further purification with the following exceptions. $ZnCl_2$ was dried at 100 °C under vacuum overnight then fused, powdered, and placed in sealed ampules. Tetrahydrofuran (THF) was distilled under Ar from sodium benzophenone ketyl. Dichloromethane was distilled from phosphorus pentoxide. Toluene, acetonitrile, dimethyl sulfoxide (DMSO), diisopropylamine, and diisopropylethylamine (DIPEA) were distilled under Ar from calcium hydride. *n*-Butyllithium (2 M in pentane), *N*,*N*-dimethylformamide, and methylmagnesium chloride (1 M in THF) were purchased from Aldrich in Sure Seal bottles. All moisture-sensitive reactions were performed in oven-dried glassware under an Ar atmosphere unless otherwise noted. Reactions were monitored with Merck Silica Gel 60 thin-layer chromatography plates. Flash chromatography was performed with use of flash chromatography silica gel (60A) from ICN Biomedical. Thin Layer Chromatography plates were Merck silica gel 60 and High Performance Thin Layer Chromatography plates were from Bodman Scientific.

(1*S*,2*R*,3*S*,5*S*)-Pinanediol chloromethyl borate. Triisopropylborate (**11**; 24.9 mL (106 mmol) was placed in a flame-dried round-bottom flask under Ar and diluted with 80 mL of THF. The mixture was cooled to −78 °C, and 7.9 mL (110 mmol) of chloroiodomethane was added followed by 50 mL (100 mmol) of *n*-butyllithium (added to the vortex of the stirring solution via syringe pump) over 40 min. The resulting beige suspension was warmed to room temperature and titrated with etherial HCl to the methyl orange endpoint, then concentrated and vacuum distilled (20 Torr, 60−80 °C) affording the diisopropyl chloromethyl borate as a faint orange liquid containing diisopropyl butyl borate as the major impurity.

The above distillate was diluted with diethyl ether and (1*R*,2*R*,3*S*,5*R*)-(+)-pinanediol (7.6 g, 45 mmol) was added slowly to the reaction until a small amount of the diol persisted (TLC). At this time the reaction was concentrated in vacuo and purified by flash chromatography (10% diethyl ether/pentane) affording 9.2 g (40 mmol, 90%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 3H), 1.15 (d, J = 11.1 Hz, 1H), 1.24 (s, 3H), 1.36 (s, 3H), 1.50 (m, 1H), 1.85, (m, 2H), 2.03 (t, J = 5.1 Hz, 1H), 2.18 (m, 1H), 2.30 (m, 1H), 2.93 (s, 2H), 4.31 (dd, J = 1.9, 8.96 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.7, 26.1, 26.8, 28.2, 35.0, 38.0, 39.2, 50.9, 78.4, 86.8; IR (thin film) 2920, 1360, 1029, 846 cm^{-1}; [α] −30.6 (*c* 0.1711, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*)-Pinanediol *p*-Methoxybenzyloxymethyl Borate (12). *n*-Butyllithium (15.1 mL, 30.2 mmol) was slowly added to a stirring solution of *p*-methoxybenzyl alcohol (3.65 mL, 30.3 mmol) in 40 mL of THF at −78 °C. After the addition was complete the mixture was stirred for 15 min, then 2.10 mL (30.2 mmol) of DMSO and 5.393 g (23.4 mmol) of pinanediol chloromethyl borate were added and the mixture was warmed to room temperature until completely dissolved affording a pale yellow solution. The mixture was then warmed to 50 °C, forming a thick white suspension as the reaction progressed, and was stirred until the reaction was complete as shown by TLC. The reaction was cooled to room temperature, diluted with diethyl ether and 0.6 M aqueous HCl, and separated. The aqueous layer was extracted twice with diethyl ether, and the combined organic extracts were dried with saturated NaCl and Na_2SO_4. After concentration in vacuo the crude material was purified by flash chromatography (250 mL of SiO_2, 20% diethyl ether/pentane) affording 5.39 g of a slightly yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.86 (d, J = 10.8 Hz, 1H), 1.30 (s, 3H), 1.44 (s, 3H), 2.24 (m, 1H), 2.35 (m, 1H), 3.31 (d, J = 1.5 Hz, d), 3.82 (s, 3H), 4.33 (dd, J = 1.8, 8.8 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 1.89−1.95 (m, 2H), 2.09 (dd, J = 4.9, 4.1 Hz, 1H), 6.8 (d, 2H), 7.3 (d, 2H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 23.9, 26.4, 27.0, 28.5, 35.1, 38.0, 39.4, 51.0, 53.4, 55.2, 78.1, 86.4, 113.6, 129.8, 130.2, 159.0; IR (thin film) 2911, 1743, 1613, 822 cm^{-1} ; HRMS (FAB, NBA) found 329.1923 (M − H)$^+$, calcd for $C_{19}H_{26}BO_4$ 329.1924.

(1*S*,2*R*,3*S*,5*S*)-Pinanediol (1*R*)-2-(*p*-Methoxybenzyloxy)-1-chloroethyl Borate (13). THF (80 mL) was placed in a flame-dried round-bottom flask purged with Ar that was then cooled to −100 °C and charged with 2.10 mL (33.4 mmol) of dichloromethane. *n*-Butyllithium (15.3 mL, 30.6 mmol) was then added slowly down the side of the flask resulting in the formation of a cloudy yellow suspension. After 30 min of stirring borate ester **12** was added in 17 mL of THF down the side of the flask resulting in a clear yellow solution. After the mixture was stirred for 30 min, a solution of 10.24 g (75.2 mmol) of $ZnCl_2$ in 60 mL of THF was added directly to the solution and the reaction mixture allowed to warm to room temperature until all of the ate-complex had rearranged to **13** as determined by TLC (ca. 17 h). The reaction mixture was diluted with saturated ammonium chloride and diethyl ether and separated, the aqueous layer was extracted twice with diethyl ether, and the combined organic layers were then dried over Na_2SO_4. After concentration of the organic layers the material was purified by flash chromatography (250 mL of SiO_2, 10% diethyl ether/pentane) to afford 7.23 g (70%) of the desired compound as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.23 (d, J = 11 Hz, 1H), 1.29 (s, 3H), 1.41 (s, 3H), 1.80−1.94 (m, 2H), 2.80 (m, 1H), 2.21 (m, 1H), 2.35 (m, 1H), 3.65, dd, J = 5.8, 6.6 Hz, 1H), 3.79 (m, 1H), 3.78 (m, 3H), 4.35 (dd, J = 1.7, 9.1 Hz, 1H), 4.50 (d, J = 11.9 Hz, 2H), 4.55 (d, J = 11.9 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H);^{13}C NMR (90 MHz, $CDCl_3$) δ 23.8, 26.1, 26.8, 28.3, 35.0, 38.0, 39.1, 50.9, 55.0, 71.5, 72.6, 78.5, 86.8, 113.6, 129.1, 129.9, 159.0; IR (thin film) 2934, 2061, 1613, 823 cm^{-1}; HRMS (FAB, NBA) found 378.1767 (M$^+$), calcd for $C_{20}H_{28}BClO_4$ 378.1769; [α] 21.8 (*c* 0.1159, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*)-Pinanediol (1*R*)-2-(*p*-Methoxybenzyloxy)-1-methylethyl Borate. Chloroborate ester **13** (10.25 g) was azeotroped with 5 mL of toluene, then diluted with 120 mL of THF and cooled to −78 °C. Methylmagnesium chloride (9.9 mL, 29.6 mmol) was added slowly to the vortex of the stirring solution until no starting material remained as determined by TLC. The cold bath was then removed and the mixture warmed to room temperature. After 2 h all material had rearranged to the product (TLC) and the mixture was purified via aqueous workup as described above. The organic layers were then concentrated and chromatographed (200 mL of SiO_2, 30% diethyl ether/pentane) affording a quantitative amount (9.7 g) of the desired product as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.82 (s, 3H), 1.06 (d, J = 7.4 Hz, 3H), 1.15 (d, J = 10.9 Hz, 1H), 1.28 (s, 3H), 1.37 (s, 3H), 1.50 (m, 1H), 1.85, (m, 1H), 2.03 (dd, J = 5.2, 5.7 Hz, 1H), 2.15 (m, 1H), 2.31 (m, 1H), 3.45 (t, J = 8.0 Hz, 1H), 3.57 (dd, J = 6.3, 8.7 Hz, 1H), 3.77 (s, 3H), 4.24 (dd, J = 1.6, 8.8 Hz, 1H), 4.43 (s, 3H), 6.85 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 12.5, 23.8, 26.1, 26.9, 28.5, 35.3, 37.9, 39.3, 51.0, 55.0, 72.1, 73.1, 85.3, 113.3, 130.8, 158.8; IR (thin film) 2916, 1613, 1512, 818 cm^{-1}; HRMS (FAB, NBA) found 357.2237 (M−H)$^+$, calcd for $C_{21}H_{30}BO_4$; [α] −14.9 (*c* 0.1585, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*)-Pinanediol (1*R*,2*R*)-1-Bromo-3-(*p*-methoxybenzyloxy)-2-methylpropyl Borate (14). The α-methyl borate ester was azeotroped with toluene, dissolved in 70 mL of THF, and cooled to −78 °C. Dibromomethane (11.3 mL, 161 mmol) was added to the solution followed by 35 mmol of freshly prepared LDA in 20 mL of THF down the side of the flask, the reaction becoming orange as addition progressed. After 1 h of stirring 15.4 g (113 mmol) of $ZnCl_2$ in 95 mL of THF were added directly to the stirring solution and the mixture was allowed to warm to room temperature overnight. The reaction was purified by aqueous workup with saturated ammonium chloride and chromatographed (200 mL of SiO_2, 20% diethyl ether/pentane) to give 11.76 g (96%) of the desired compound as a pale yellow syrup: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.09 (d, J = 6.7 Hz, 3H), 1.33 (s, 3H), 1.38 (s, 3H), 1.38 (d, J = 20.7 Hz, 1H), 1.92, m, 2H), 2.10 (m, 1H), 2.25 (m, 1H), 2.36 (m, 1H), 3.34 (t, J = 8.6 Hz, 1H), 3.44 (dd, J = 5.2, 9.3 Hz, 1H), 3.63 (d, J = 6.6, 1H), 3.82 (s, 3H), 4.37 (dd, J = 2.0, 8.9 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 6.92 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 15.7, 23.8, 26.0, 26.8, 28.0, 35.1, 36.1, 38.1, 39.1, 51.1, 53.3, 55.0, 72.5, 72.9, 78.0, 86.1, 113.6, 129.1, 130.1, 159.0; HRMS (FAB, NBA) found 449.1503 (M−H)$^+$, calcd for 449.1517; [α] −19.07 (*c* 0.1448, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*)-Pinanediol (1*S*,2*S*)-1-azido-3-(*p*-methoxybenzyloxy)-2-methylpropyl Borate. Bromoborate **12** (5.86 g, 12.9 mmol) was diluted with 200 mL of dichloromethane, then 50 mL of water, sodium azide (8.40 g, 129 mmol), and 0.60 mL of Aliquot 336 (1.3 mmol) were added. The biphasic mixture was sealed with a plastic cap and Teflon tape and stirred vigorously overnight. The reaction mixture was then diluted with saturated ammonium chloride and dichloromethane and separated, and the organic layer was dried over Na_2SO_4. The solution was then filtered, concentrated, and chromatographed (220 mL of SiO_2, dichloromethane) affording 5.05 g (94%) of the desired product as a pale yellow oil containing a trace amount of the undesired diastereomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.81 (s, 3H), 0.99 (d, J = 6.9 Hz, 3H), 1.21 (d, J = 10.9 Hz, 1H), 1.28 (s, 3H), 1.32 (s, 3H), 1.78−1.90 (m, 2H), 2.08 (t, J = 5.2 Hz, 1H), 2.13−2.39 (m, 2H), 3.16 (d, J = 4.1 Hz, 1H), 3.32 (m, 1H), 3.80 (s, 3H), 4.29 (dd, J = 2.0, 9.0 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 15.6, 24.0, 26.3, 27.0, 28.4, 35.3, 36.0, 38.1, 39.4, 51.1, 55.2, 71.4, 72.6, 78.2, 86.6, 113.7, 129.3, 130.4, 158.9; IR (thin film) 2871, 2096, 1513, 755 cm^{-1}; HRMS (FAB, NBA) found 414.2564 (M + H)$^+$, calcd for $C_{22}H_{33}BN_3O_4$; [α] 3.38 (*c* 0.0893, CH_2Cl_2).

(2*R*,3*S*)-2-Azido-4-(*p*-methoxybenzyloxy)-3-methyl-1-butanol (14). A 5.07 g (12.2 mmol) sample of the purified α-azidoborate was azeotroped with toluene. It was then diluted with 50 mL of THF and cooled to −78 °C, and 1.10 mL (14.6 mmol) of chloroiodomethane was added. To this was added *n*-butyllithium (6.50 mL, 12.9 mmol), dropwise, directly to the stirring solution taking care to keep the color of the mixture faint yellow (if the addition is too fast it results in a darker color and a significantly lower yield). After the addition was complete the mixture was warmed to room temperature by removal of the bath and stirred until all material had rearranged to the title compound (overnight). It was then worked up as above (saturated ammonium chloride and diethyl ether) and chromatographed (200 mL SiO_2, 10% diethyl ether/pentane) giving 4.11 g (78%) of the desired product as a faint yellow oil that was used immediately for the next step.

(2*R*,3*S*)-2-Azido-4-(*p*-methoxybenzyloxy)-3-methyl-1-butanol. To a solution of **15** (3.868 g, 9.01 mmol) in 90 mL of THF were added aqueous 30% hydrogen peroxide (1.12 mL, 9.91 mmol) followed by 3 N aqueous sodium hydroxide (3.3 mL, 9.91 mmol). The addition of hydrogen peroxide resulted in a cloudy white suspension and evolution of heat. After the reaction was complete (TLC) the mixture was partitioned between diethyl ether and water and separated, the aqueous phase was extracted twice with ether, and the combined organic extracts were dried over Na_2SO_4. After concentration of the crude solution it was chromatographed (150 mL of SiO_2, 66% diethyl ether/pentane) giving 1.866 g (75%) of the desired azido alcohol as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, $J = 7.0$ Hz, 3H), 2.00 (m, 1H), 3.27 (broad s, 1H), 3.38 (dd, $J = 4.8$, 9.4 Hz, 1H), 3.45 (dd, $J = 6.1$, 9.4 Hz, 1H), 3.52 (m, 1H), 3.63 (m, 1H), 3.73 (dd, $J = 4.2$, 11.1 Hz, 1H), 3.77 (s, 3H), 4.42 (s, 2H), 6.88 (ddd, $J = 2.1$, 2.8, 8.7 Hz, 2H), 7.25 (ddd, 2.1, 2.8, 8.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.3, 35.3, 54.9, 62.9, 66.5, 71.2, 72.6, 113.5, 129.1, 129.7, 159.0; IR (thin film) 3410, 2935, 1613, 820 cm $^{-1}$; [α] 8.29, (*c* 0.0607, CH_2Cl_2).

(2*R*,3*S*)-2-Amino-4-(*p*-methoxybenzyloxy)-3-methyl-1-butanol. The azido alcohol (0.723 g, 2.6 mmol) was dissolved in 20 mL of methanol. Palladium on carbon (10%) was added (0.621 g, 0.52 mmol) and the mixture purged and pressurized with H_2 (balloon). After the reaction was complete (ca. 40 min) it was filtered through a short plug of Celite and concentrated to afford a quantitative amount of the polar amino alcohol (**17**) as a colorless oil that was used without purification for the next step.

(2*R*,3*S*)-2-(*tert*-Butyloxycarbonylamino)-4-(*p*-methoxybenzyloxy)-3-methyl-1-butanol. To a solution of amino alcohol **17** (2.09 mmol from the previous step) in 20 mL of dichloromethane were added 2 equiv of Boc anhydride (0.96 g, 4.18 mmol). The resulting solution was stirred overnight, then concentrated and chromatographed (75 mL of SiO_2, 30−50% ethyl acetate/hexanes) giving 0.559 g (88%, two steps) of the carbamate as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.98 (d, $J = 7.0$ Hz, 3H), 1.40 (s, 9H), 1.99 (m, 1H), 3.38 (m, 1H), 3.57 (m, 1H), 3.74 (s, 3H), 4.38 (d, $J = 11.5$ Hz, 1H), 4.40 (d, $J = 11.5$, 1H), 5.42 (broad d, 1H), 6.83 (d, $J = 8.6$ Hz, 2H), 7.19 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 15.2, 28.2, 34.5, 55.0, 55.5, 64.1, 71.8, 72.8, 78.9, 113.6, 129.1, 129.7, 156.5, 159.1; IR (thin film) 3409, 2974, 1514, 823 cm $^{-1}$; HRMS (CI) found 340.2132 (M + H)$^+$, calcd for $C_{18}H_{30}NO_5$ 340.2124; [α] −18.4 (*c* 0.0488, $CDCl_3$).

(2*R*,3*S*)-2-*tert*-Butoxycarbonylamino-4-(*p*-methoxybenzyloxy)-3-methylbutanal (6). The Boc protected amino alcohol (1.38 g, 4.57 mmol) was diluted with 20 mL of dichloromethane and oxidized by addition of the Dess−Martin reagent (2.10 g, 5.02 mmol). During the course of the reaction the mixture changed from an opaque white solution to a thick white suspension. After 1 h it was partitioned between saturated $NaHCO_3$ (10 mL), saturated $Na_2S_2O_3$ (30 mL), and diethyl ether (40 mL), then stirred vigorously until both layers became clear (ca. 5−7 min). The phases were then separated and the aqueous phase extracted twice with ether, dried over Na_2SO_4, and concentrated affording 1.28 g (94%) of the pure aldehyde as a single diastereomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.94 (d, $J = 7.0$ Hz, 3H), 1.41 (s, 9H), 2.52 (m, 1H), 3.19 (distorted t, $J = 9.0$ Hz, 1H), 3.35 (dd, $J = 4.2$, 9.5 Hz, 1H), 3.76 (s, 3H), 4.15 (d, $J = 4.9$ Hz, 1H), 4.27 (d, $J = 11.6$ Hz, 1H), 4.35 (d, $J = 11.4$ Hz, 1H), 5.28 (d, $J = 7.2$, 1H), 6.84 (d, $J = 8.5$ Hz, 2H), 7.16 (d, $J = 8.4$ Hz, 2H), 9.52 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.0, 28.2, 34.6, 55.1, 62.8, 70.7, 72.7, 79.7, 113.7, 129.2, 129.6, 156.1, 159.2, 200.2; IR (thin film) 3340, 2975, 1710, 1514 cm^{-1}; HRMS (CI) found 338.1967 (M + H)$^+$, calcd for $C_{18}H_{28}NO_5$ 338.1967; [α] −82.2 (*c* 0.037, $CDCl_3$).

(2*R*,3*S*)-2-*tert*-Butoxycarbonylamino-4-(*p*-methoxybenzyloxy)-3-methylbutanoic Acid. Aldehyde **6** (1.103 g, 3.66 mmol) was placed in a flask with 75 mL of *tert*-butyl alcohol to which was added 2-methyl-2-butene (2.0 M in THF, 36 mL, 73 mmol) followed by a solution of sodium chlorite (2.98 g, 32.9 mmol) and monobasic sodium phosphate (3.07 g, 25.6 mmol) in 30 mL of water. As the oxidant was added the solution became bright yellow and evolved heat. The reaction was stirred overnight, changing from yellow to colorless. It was then concentrated under vacuum, diluted with saturated $NaHCO_3$, and extracted once with hexanes. The aqueous phase was then acidified with 2 M HCl and extracted twice with ether, the combined ether extracts then dried over Na_2SO_4. The product was concentrated in vacuo affording a quantitative amount of the product as a pale yellow syrup: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.10 (d, $J = 6.9$ Hz, 3H), 1.51 (s, 9H), 2.52 (m, 1H), 3.43 (m, 1H), 3.83 (s, 3H), 4.40 (m, 2H), 4.51 (d, $J = 11.4$ Hz, 1H), 5.76 (d, $J = 8.6$ Hz, 1H), 6.93 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.5$ Hz, 2H), 11.3 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ14.3, 28.2, 30.7, 35.3, 55.0, 56.7, 71.5, 72.8, 79.7, 113.6, 129.1, 156.1, 159.0, 176.7; IR (thin film) 2977, 1715, 1613, 1249 cm^{-1}; HRMS (FAB, NBA) found 354.1913 (M + H)$^+$, calcd for $C_{18}H_{28}NO_6$ 354.1917; [α] −2.35 (*c* 0.2554, CH_2Cl_2).

Methyl (2*R*,3*S*)-2-*tert*-butoxycarbonylamino-4-(*p*-methoxybenzyloxy)-3-methylbutanoate (18). The crude carboxylic acid (0.0676 g, 0.192 mmol) and potassium carbonate (0.029 g, 0.211 mmol) were diluted with DMF (10 mL) and cooled to 0 °C. Iodomethane (0.024 mL, 0.384 mmol) was added slowly to the suspension, which was then stirred for 40 min, partitioned between diethyl ether and water, and separated. The aqueous layer was then extracted thrice with ether and the combined organic extracts were dried with Na_2SO_4. The crude reaction mixture was then concentrated in vacuo and the yellow residue chromatographed (30 mL of SiO_2, 20% ethyl acetate/hexanes) affording the protected product as a colorless syrup (0.0406 g, 60%).

Methyl (2*R*,3*S*)-2-*tert*-butoxycarbonylamino-4-hydroxy-3-methylbutanoate. PMB ether **18** was diluted with 18 mL of 100:1 dichloromethane/water. To this was added DDQ (0.730 g, 0.20 mmol), which resulted in a dark emerald-green solution. The mixture was stirred 75 min over which time it changed to a rust-colored suspension. It was then partitioned between saturated $NaHCO_3$ and dichloromethane and separated. The aqueous phase was then extracted thrice with dichloromethane and the combined organic layers were dried over Na_2SO_4. Concentration of the crude extracts afforded material that was purified by chromatography (40 mL of SiO_2, 40% ethyl acetate/hexanes) yielding the alcohol as a pale yellow syrup (0.4172 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, $J = 7.0$ Hz, 3H), 1.32 (s, 9H), 2.03 (m, 1H), 3.21 (broad s, 1H), 3.39 (dd, $J = 5.6$, 11.1 Hz, 1H), 3.49 (dd, $J = 4.1$, 11.3 Hz, 1H), 3.62 (s, 3H), 4.17 (t, $J = 7.2$ Hz, 1H), 5.61 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.7, 34.1, 43.4, 56.4, 60.2, 67.5, 82.3, 153.6, 169.3; IR (thin film) 3390, 2978, 1694, 734 cm^{-1}; HRMS (FAB, NBA) found 248.1501 (M + H)$^+$, calcd for $C_{11}H_{22}NO_5$ 248.1498; [α] −15.13 (*c* 0.1156, $CDCl_3$).

Methyl (2*S*,3*R*)-3-*tert*-butoxycarbonylamino-4-methoxycarbonyl-3-methylbutanoic Acid (19). The PMB deprotected alcohol (0.4162 g, 1.80 mmol) was oxidized by using the same two-step procedure as above affording a quantitative amount of the acid (0.40 g) as a colorless foaming syrup: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.29 (d, $J = 7.2$ Hz, 3H), 1.46 (s, 9H), 3.31 (m, 1H), 4.54 (dd, $J = 3.6$, 9.7 Hz, 1H), 5.56 (d, $J = 9.7$ Hz, 1H), 11.00 (broad s, 1H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 13.4, 28.0, 41.1, 52.4, 54.9, 80.1, 156.1, 171.4, 178.4; IR (thin film) 3436, 2982, 1715, 1505 cm^{-1}; HRMS (FAB, NBA) found 262.1291 (M + H)$^+$, calcd for $C_{11}H_{20}NO_6$ 262.1291; [α] −19.44 (*c* 0.1451, $CDCl_3$).

***tert*-Butyl (2*S*,3*R*,2′*S*)-3-*tert*-butyloxycarbonylamino-2-methyl-4-methoxycarbonyl-3′-methyl-2′-aminobutanoate.** Acid **19** (0.1115 g, 0.43 mmol) and *t*-Bu-Val-NH_2 (0.23 g, 0.51 mmol) were combined in a flask and azeotroped from toluene. The resulting white solid was dissolved in acetonitrile (5 mL) and DIPEA (0.15 mL, 0.86 mmol) was added followed by BOP reagent (0.23 g, 0.514 mmol). The solution was stirred for 70 min, then partitioned between brine and ethyl acetate and separated. The aqueous phase was then extracted thrice with ethyl acetate and the combined organic layers dried with Na_2SO_4. Concentration of the crude extracts and flash chromatography (20 mL of SiO_2, 0−10% methanol/dichloromethane) afforded 0.1557 g (85%) of a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.78 (d, $J = 7.2$ Hz, 3H), 0.81 (d, $J = 7.7$ Hz, 3H), 1.34 (s, 9H), 1.36 (s, 9H), 3.02 (dq, $J = 6.8$, 11.7 Hz, 1H), 4.06 (dq, $J = 7.0$, 11.1 Hz, 1H), 4.61 (s, 3H), 5.26 (dd, $J = 4.7$, 8.5 Hz, 1H), 5.30 (dd, $J = 3.8$, 9.7 Hz, 1H), 6.81 (d, $J = 9.6$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 15.1, 17.4, 18.6, 27.7, 28.0, 31.0, 41.3, 52.2, 55.8, 57.0, 79.3, 81.8, 156.1, 170.7, 171.8, 173.5; IR (thin film) 3287, 1740, 1699, 1652 cm^{-1}; HRMS (FAB, NBA) found 417.2603 (M + H)$^+$, calcd for $C_{20}H_{36}N_2O_7$ 417.2601; [α] −3.80 (*c* 0.0300, CH_2Cl_2).

***tert*-Butyl (2*S*,3*R*,2′*S*)-3-amino-2-methyl-4-methoxycarbonyl-3′-methyl-2′-aminobutanoate (3).** The fully protected Val-MeAsp dipeptide (0.092 g, 0.217 mmol) was dissolved in 2 mL of 1 M HCl/ethyl acetate and the reaction vessel was sealed with a plastic cap and Teflon tape. After 2 h the reaction mixture was concentrated in vacuo, partitioned between 0.6 M aqueous HCl and dichloromethane, and separated. The aqueous phase was then basified with saturated $NaHCO_3$ and extracted twice with dichloromethane, which was then dried over Na_2SO_4 and concentrated affording 0.046 g (70%) of the desired product as a colorless film. Concentration of the initial organic extract afforded 0.029 g (30%) of recovered starting material. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 0.86 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 1.41 (s, 9H), 1.96 (broad s, 2H), 2.12 (m, 1H), 2.79 (dq, J = 6.0, 7.2 Hz, 1H), 3.61 (m, 1H), 3.70 (s, 3H), 4.37 (dd, J = 4.3, 8.7 Hz, 1H), 7.55 (d, J = 8.5, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.2, 17.4, 18.9, 27.9, 31.0, 56.7, 57.1, 81.6, 171.1, 173.6, 173.8; IR (thin film) 3309, 1738, 1651, 1538 cm^{-1}; HRMS (FAB, NBA) found 317.2076 (M + H)$^+$, calcd for $C_{15}H_{28}N_2O_5$ 317.2076; [α] −11.0 (*c* 0.0911, CH_2Cl_2).

Methyl (*R*)-2-Benzyloxypropionate. (*R*)-Methyl lactate (1.0 mL, 10 mmol) and benzyl bromide (1.7 mL, 0.015 mmol) were diluted with 20 mL of DMF and cooled to 0 °C. NaH (0.24 g, 0.011 mmol) was added over 2 min resulting in a cloudy suspension. This was stirred for 10 min, then warmed to room temperature which resulting in a slightly green cloudy solution that was stirred until all starting material was consumed (TLC). The reaction mixture was quenched with 2 M aqueous HCl and extracted with hexanes, then dried over Na_2SO_4. The dried extracts were then concentrated and the crude residue purified by chromatography (30 mL of SiO_2, 5−15% ether/pentane) affording 1.10 g of the desired product as a colorless oil: ^{1}H NMR δ 1.41 (d, J = 6.84 Hz, 3H), 3.69 (s, 3H), 4.04 (q, J = 6.9 Hz, 1H), 4.40 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 7.20−7.36 (m, 5H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 18.2, 51.4, 71.5, 73.5, 127.4, 127.5, 128.0, 137.2, 173.1; IR (thin film) 3032, 2873, 1749, 739 cm^{-1}; HRMS (EI) found 194.0941 (M)$^+$, calcd for $C_{11}H_{14}O_3$ 194.0921; [α] 78.5 (*c* 0.3653, $CDCl_3$).

(*R*)-2-Benzyloxypropanal (10). Benzyl ether protected methyl lactate (1.10 g, 5.70 mmol) was diluted with 10 mL of toluene and cooled to −78 °C. To this was added DIBAL (1.0 M in hexane, 11 mmol), dropwise, to the stirring solution. After 90 min the reacton was quenched with 2 mL of ice-cold methanol, then partioned with 100 mL of 1 M HCl and hexanes. The biphasic mixture was then separated, washed twice with hexanes, and dried over Na_2SO_4. Concentration at reduced temperature and pressure afforded the aldehyde as a colorless liquid (0.83 g, 5.1 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, J = 7.0 Hz, 3H), 3.95 (dq, J = 1.7, 7.0 Hz, 1H), 4.65 (d, J = 11.8 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 7.30−7.49 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.1, 76.8, 79.2, 127.7, 128.3, 137.2, 203.2; IR (thin film) 2935, 2871, 2712, 1733, 739 cm^{-1}; HRMS (FAB, NBA) found 163.0761 (M − H)$^+$, calcd for $C_{10}H_{11}O_2$ 163.0759; [α] 34.93 (*c* 0.0875, CH_2Cl_2).

Cyclohexenyl (4*R*,2′*R*,3′*R*)-4-Amino-5-methoxycarbonylpentanoyl-3′-benzyloxy-2′-*N*-methylaminobutanamide and Cyclohexenyl (4*R*,2′*S*,3′*R*)-4-Amino-5-methoxycarbonylpentanoyl-3′-benzyloxy-2′-*N*-methylaminobutanamide (22(*R*) + 22(*S*)). (D)-Z-glutamic acid methyl ester **9** (0.114 g, 0.386 mmol) was placed in a flask followed by aldehyde **8** (0.100 g, 0.386 mmol), methylamine (**20**) (2.0 M in methanol, 0.19 mL, 0.39 mmol), and cyclohexenyl isocyanide (**21**) (1.0 M in hexanes, 0.38 mmol). The flask was sealed with a plastic cap and Teflon tape and stirred overnight. The following day the reaction mixture was concentrated by high vacuum and chromatographed (40 mL of SiO_2, 50−100% ether/pentane) affording 0.130 g of the desired product (59%) as a 1.4:1 mixture of diastereomers. Major diastereomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.23 (d, J = 6.1 Hz, 3H), 1.54 (m, 2H), 1.63 (m, 2H), 1.81 (m, 1H), 2.10 (m, 4H), 2.30 (m, 2H), 2.51 (m, 1H), 3.73 (s, 3H), 4.25 (m, 3H), 4.47 (d, J = 11.5 Hz, 1H), 4.50 (m, 1H), 4.59 (d, J = 11.6, 1H), 5.04 (d, J = 12.3, 1H), 5.09 (d, J = 12.3, 1H), 5.12 (m, 1H), 5.72 (d, J = 7.7, 1H), 6.03 (m, 1H), 7.21−7.38 (m, 10H), 7.48 (broad s, 1H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 16.6, 17.0, 21.9, 22.4, 24.0, 27.8, 28.1, 28.9, 32.5, 52.5, 53.1, 61.7, 62.7, 66.9, 70.8, 72.3, 83.1, 114.2, 127.4, 127.5, 127.6, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 132.8, 136.2, 138.6, 156.2, 167.1, 172.7, 173.3; IR (thin film) 3307, 2934, 1716, 1634 cm^{-1}; HRMS (FAB, NBA) found 580.3018 (M + H)$^+$, calcd for $C_{32}H_{41}N_3O_7$ 580.3023; [α] −34.4 (*c* 0.062, $CDCl_3$). Minor diastereomer: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.09 (distorted d, 3H), 1.40−1.59 (m, 4H), 1.89 (m, 3H), 2.00 (m, 2H), 2.18 (m, 1H), 2.31 (m, 3H), 2.88 (s, 3H), 3.66 (s, 3H), 4.08 (m, 1H), 4.30 (m, 1H), 4.41 (d, J = 11.1 Hz, 1H), 4.57 (d, J = 11.2 Hz, 1H), 4.71 (d, J = 9.5 Hz, 1H), 5.01 (s, 2H), 5.68 (d, J = 7.5 Hz, 1H), 6.01 (s, 1H), 7.20−7.31 (m, 10H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 16.4, 16.5, 21.8, 22.3, 23.8, 27.3, 27.6, 27.8, 29.4, 32.5, 52.4, 53.4, 62.1, 66.8, 66.9, 71.6, 71.8, 71.9, 73.5, 73.7, 112.9, 127.7, 127.8, 128.0, 128.3, 128.4, 132.3, 136.2, 137.8, 156.0, 167.2, 172.5, 173.0; IR (thin film) 3316, 1720, 1534, 1453 cm^{-1}; HRMS (FAB, NBA) found 580.3015 (M + H)$^+$, calcd for $C_{32}H_{41}N_3O_7$ 580.3023; [α] +30.1 (*c* 0.071, $CDCl_3$).

2,2,2-Trichloroethyl (2*S*,3*R*)-3-Benzyloxy-2-[*tert*-butoxycarbonyl-(*N*)-methylamino]butanoate. Acid **24** (282.0 mg, 0.872 mmol) and 2,2,2-trichloroethanol (108 μL, 1.13 mmol) were combined with 2 mL of dichloromethane. Dicyclohexylcarbodiimide (216 mg, 1.05 mmol) was added followed by a few crystals of DMAP resulting in an opaque solution that became a white suspension over a few minutes. The mixture was stirred overnight, filtered through a cotton plug, concentrated, then chromatographed (40 mL of SiO_2, 10% ethyl acetate/hexanes) yielding the fully protected ester (262.4 mg, 66%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (m, 3H), 1.48 (s, 2.5H), 1.50 (s, 6.5H), 3.10 (s, 3H), 4.39 (qt, J = 6.2 Hz, 0.8H), 4.31 (qt, J = 5.7 Hz, 0.2H), 4.41 (d, J = 11.6 Hz, 1H), 4.68 (m, 2H), 4.79 (d, J = 11.9 Hz, 1H), 4.81 (m, 1H), 5.14 (d, J = 4.4 Hz, 1H), 7.20−7.31 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) 15.7, 16.0, 28.1, 28.2, 32.8, 33.2, 62.1, 63.4, 71.3, 74.1, 74.2, 74.5, 75.2, 80.0, 80.2, 94.4, 126.9, 127.0, 127.2, 127.3, 128.0, 138.0, 138.2, 155.3, 156.6, 168.3, 168.6; IR (thin film) 3010, 1766, 1694, 723 cm^{-1}; HRMS (FAB, NBA) found 454.0945 (M + H)$^+$, calcd for $C_{19}H_{27}NO_5Cl_3$ 454.0955; [α] +15.25 (*c* 0.2624, CH_2Cl_2).

2,2,2-Trichloroethyl (2*S*,3*R*)-3-Benzyloxy-2-(*N*)-methylaminobutanoate (25). The fully protected Boc threonyl ester (0.3431 g, 0.754 mmol) was diluted with 2 mL of 20% TFA in CH_2Cl_2, the solution immediately changing to pale yellow. The mixture was stirred for 90 min, then concentrated *in vacuo*, azeotroped with toluene (2 × 3 mL), and placed on a vacuum line overnight to give a quantitative amount of the free amine as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (d, J = 5.5 Hz, 3H), 2.83 (s, 3H), 4.14 (m, 1H), 4.24 (s, 1H), 4.46 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.76 (s, 2H), 7.24−7.36 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.9, 32.8, 64.6, 70.6, 71.8, 74.5, 93.1, 127.3, 127.6, 127.9, 136.1, 164.6; IR (thin film) 2877, 1770, 1682, 799 cm^{-1}; HRMS (CI) found 354.04460 (M + H)$^+$, calcd for $C_{14}H_{19}NO_2Cl_3$ 354.04305; [α] −21.20 (*c* 0.1757, $CDCl_3$).

2,2,2-Trichloroethyl (4*R*,2′*S*,3′*R*)-4-Amino-5-methoxycarbonylpentanoyl-3′-benzyloxy-2′-(*N*)-methylaminobutanoate. Acid **9** (260 mg, 0.72 mmol) and the amine derived from threonine (164 mg, 0.56 mmol) were combined with 2 mL of acetonitrile. To the stirring solution was added DIPEA (250 μL, 1.4 mmol) followed by BOP reagent (370 mg, 0.84 mmol), which resulted in a dark yellow color. This solution was stirred overnight, the color changing from yellow to orange, at which time it was determined to have progressed to completion (TLC). The reaction mixture was then partitioned between saturated aqueous NaCl and dichloromethane, separated, and the aqueous phase extracted thrice with dichloromethane. The combined organic layers were dried over Na_2SO_4, then concentrated and chromatographed (60 mL SiO_2, 40% ethyl acetate/hexanes), which gave the product as a slightly brown foam (170.9 mg, 48%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, J = 6.3 Hz, 3H), 2.09 (m, 1H), 2.21 (m, 1H), 2.47 (m, 1H), 2.52 (m, 1H), 3.17 (s, 3H), 3.73 (s, 3H), 4.36 (m, 1H), 4.42 (d, J = 11.3 Hz, 1H), 4.43 (m, 1H), 4.60 (d, J = 11.4 Hz, 1H), 4.61 (d, J = 11.9 Hz, 1H), 4.82 (d, J = 11.9 Hz, 1H), 5.08 (d, J = 12.2 Hz, 1H), 5.11 (d, J = 12.3 Hz, 1H), 5.60 (d, J = 4.1 Hz, 1H), 5.60 (d, J = 4.1 Hz, 1H), 5.76 (d, J = 7.6 Hz, 1H), 7.21−7.40 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.8, 27.0, 29.2, 34.3, 52.3, 43.8, 60.4, 66.8, 71.5, 74.3, 75.2, 94.4, 127.0, 127.5, 128.2, 128.3, 128.4, 136.2, 138.1, 156.0, 168.2, 172.4, 173.7; IR (thin film) 3318, 1748, 1722, 698 cm^{-1}; [α] −25.47 (*c* 0.043, $CDCl_3$).

(4*R*,2′*R*,3′*R*)-4-Amino-5-methoxycarbonylpentanoyl-3′-benzyloxy-2′-(*N*)-methylaminobutanoic Acid and (4*R*,2′*S*,3′*R*)-4-Amino-5-methoxycarbonylpentanoyl-3′-benzyloxy-2′-(*N*)- methylaminobutanoic Acid (4(*R*) and 4(*S*)). 4(*R*) and 4(*S*) were synthesized as a mixture of diastereomers by combining cyclohexenamides (**22**(***R***) and **22**(***S***)) (0.133 g, 0.24 mmol) with 8.5 mL of THF and warming to 60 °C. To this solution was added concentrated HCl (0.22 mL, 2.64 mmol) in one portion and the mixture was stirred for 20 min. After the reaction was determined to be complete (TLC) it was cooled to room temperature, concentrated by high vacuum, and chromatographed (30 mL of SiO_2, 0−10% methanol/dichloromethane) affording 0.090 g of the desired product as a 1:1 mixture of diastereomers (75%).

Synthesized as diastereomerically pure material by reduction of the trichloroethyl ester as follows: the trichloroethyl ester dipeptide (80 mg, 0.13 mmol) was placed in a 10 mL flask and dissolved in 2 mL of 90% aqueous acetic acid. Once the starting material had dissolved completely, Zn dust was added and the resulting gray suspension was stirred overnight. The cloudy silver-gray mixture was partitioned between dichloromethane and water and separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were then dried over $MgSO_4$, concentrated, and chromatographed (10 mL of SiO_2, 0−10% methanol/dichloromethane) affording the acid (38.2 mg, 60%) as a colorless film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 6.2 Hz, 3H), 2.04 (m, 1H), 2.20 (m, 1H), 2.43 (m, 1H), 2.50 (m, 1H), 3.08 (s, 3H), 3.71 (s, 3H), 4.34 (m, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 5.09 (s, 2H), 5.40 (d, J = 3.9 Hz, 1H), 5.84 (d, J = 7.8 Hz, 1H), 7.19−7.38 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.3, 27.1, 29.4, 34.6, 52.5, 53.9, 60.9, 67.1, 71.8, 75.0, 127.4, 127.6, 128.2, 128.3, 128.5, 136.2, 138.3, 156.3, 172.7, 173.4, 174.1; IR (thin film) 3321, 2952, 1720, 1637 cm^{-1}; HRMS (CI) found 501.2235 $(M + H)^+$, calcd for $C_{26}H_{33}N_2O_8$ 501.2237; [α] 20.68 (*c* 0.0382, CH_2Cl_2).

(2*S*,3*S*)-3-Methyl-1-phenyl-4-penten-2-ol. Freshly sublimed potassium *tert*-butoxide (1.467 g, 12 mmol) was placed in a flame-dried round-bottom flask charged with Ar and containing a large magnetic stir-bar. THF (20 mL) was added and the suspension cooled to −78 °C followed by addition of *cis*-2-butene (1 mL). *n*-Butyllithium was slowly added resulting in a bright yellow suspension that was stirred 30 min. At this time, (+)-*B*(OCH_3)(iPc)$_2$ (4.94 g, 15.6 mmol) in 15 mL of THF was added to the stirring mixture resulting in a clear yellow solution. After 30 min, borontrifluoride etherate (1.92 mL, 12.0 mmol) was added followed immediately by phenylacetaldehyde (1.4 mL, 12.0 mmol) in 10 mL of THF. The reaction became very viscous and was stirred 2 h at −78 °C, then slowly warmed to room temperature and quenched by adding 10 mL of 30% H_2O_2 (slowly) and 15 mL of 3 N NaOH. The resulting white biphasic mixture was stirred vigorously for 2 h, until all of the alcohol had been liberated by oxidation. The mixture was then partitioned between brine and dichloromethane and separated, and the aqueous phase was extracted twice with dichloromethane and the combined organic extracts dried over Na_2SO_4. After concentration of the extracts, the crude syrup was chromatographed (170 mL of SiO_2, 0−10% ethyl acetate/hexanes) affording 1.685 g of the desired compound (80%) as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.14 (d, J = 6.8 Hz, 3H), 1.58 (broad s, 1H), 2.63 (dd, J = 9.4, 13.8 Hz, 1H), 2.91 (dd, J = 3.6, 13.8 Hz, 1H), 3.74 (ddd, J = 3.7, 5.5, 9.3 Hz, 1H), 5.11−5.19 (m, 2H), 5.90 (ddd, J = 7.4, 10.6, 18.0 Hz, 1H), 7.20−7.38 (m, 5H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 14.5, 40.8, 43.0, 75.7, 115.4, 126.4, 128.6, 129.3, 138.9, 140.9; IR (thin film) 3425, 2919, 1604, 914 cm^{-1}; HRMS (EI) found 176.1199 (M^+), calcd for $C_{12}H_{16}O$ 176.1201; [α] −43.55 (*c* 0.1233, CH_2Cl_2).

(2*S*,3*S*)-2-Methoxy-3-methyl-1-phenyl-4-pentene (27). The alcohol derived from the crotylboration of phenylacetaldehyde (0.376 g, 2.13 mmol) was diluted with DMF (8 mL) and cooled to 0 °C. NaH (0.43 g, 5.3 mmol) was added slowly to the mixture resulting in a gray suspension. After 20 min of stirring iodomethane (0.33 mL, 5.3 mmol) was added and the mixture warmed to room temperature. After 60 min the reaction was quenched by careful addition of water, then the solution was partitioned between dichloromethane, separated, dried with Na_2SO_4, and purified by chromatography (60 mL SiO_2, dichloromethane) affording 0.387 g of clear oil (95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, J = 6.9 Hz, 3H), 2.46 (m, 1H), 2.76 (dd, J = 8.0, 14.0 Hz, 1H), 2.85 (dd, J = 4.4, 14.0 Hz, 1H), 3.29 (s, 3H), 3.31 (m, 1H), 5.12 (m, 2H), 5.93 (m, 1H), 7.21−7.38 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.0, 37.8, 40.8, 58.2, 86.4, 114.5, 125.9, 128.1, 129.2, 139.6, 141.0; IR (thin film) 3028, 2929, 1605, 700 cm^{-1}; HRMS (EI) found 190.1360 (M^+), calcd for $C_{13}H_{18}O$ 190.1358; [α] −23.6 (*c* 0.1480, CH_2Cl_2).

(2*S*,3*S*)-3-Methoxy-2-methyl-4-phenylbutanal. Alkene **27** (2.01 g, 10.5 mmol) was diluted with 30 mL of dichloromethane and cooled to −78 °C. Ozone was then bubbled into the solution until a faint blue color persisted, the solution was then purged with air, and triphenylphosphine (2.90 g, 11.1 mmol) was added in one portion. The cooling bath was then removed and the solution stirred until all of the ozonide disappeared as shown by TLC. The mixture was concentrated and purified by flash chromatography (100 mL of SiO_2, 10% ethyl acetate/hexanes) affording 1.717 g (85%) of the aldehyde as a clear oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.26 (d, J = 7.1 Hz, 3H), 2.45 (dddd, J = 3.4, 7.1, 14.2, 21.2 Hz, 1H), 2.80 (dd, J = 7.3, 13.7 Hz, 1H), 3.10 (dd, J = 6.5, 13.7 Hz, 1H), 3.38 (s, 3H), 3.98 (m, 1H), 7.25−7.42 (m, 5H), 9.75 (s, 1H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 7.2, 37.2, 48.7, 57.6, 81.3, 126.3, 128.3, 129.0, 137.8, 203.8; IR (thin film) 2827, 2719, 1726, 701 cm^{-1}; HRMS (EI) found 192.1075 (M^+), calcd for $C_{12}H_{16}O_2$ 192.1150; [α] −24.61 (*c* 0.138, $CDCl_3$).

Ethyl (2*E*,4*S*,5*S*)-5-Methoxy-2,4-dimethyl-6-phenyl-2-hexenoate (28). The methoxy aldehyde derived from **27** (1.71 g, 8.93 mmol) was diluted with 50 mL of toluene and $Ph_3PCH(CH_3)CO_2CH_2CH_3$ (3.74 g, 10.3 mmol) was added resulting in a yellow suspension that persisted until heating. The mixture was refluxed overnight, affording a slightly darker yellow solution that was partitioned between diethyl ether and water, and the organic phase was separated. The aqueous phase was then extracted with ether and the combined organic extracts dried with Na_2SO_4. After concentration the crude yellow residue was chromatographed (70 mL of SiO_2, 20% ethyl acetate/hexanes) affording 2.102 g (85%) of the desired product as a faint yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.22 (d, J = 6.8 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H), 1.88 (s, 3H), 2.76 (m, 1H), 2.85 (dd, J = 7.2, 13.9 Hz, 1H), 2.95 (dd, J = 4.9, 14.0 Hz, 1H), 3.39 (s, 3H), 3.40 (m, 1H), 4.33, (q, J = 7.2 Hz, 2H), 6.84 (d, J = 10.2 Hz, 1H), 7.29−7.43 (m, 5H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 12.2, 14.0, 15.0, 36.8, 37.8, 56.3, 60.2, 85.8, 125.9, 127.3, 128.0, 129.2, 143.8, 167.8; IR (thin film) 2827, 1714, 1455, 1241 cm^{-1}; HRMS (FAB, NBA) found 277.1805 $(M + H)^+$, calcd for $C_{17}H_{25}O_3$ 277.1804; [α] −28.86 (*c* 0.1465, $CDCl_3$).

(2*S*,3*S*,4*E*)-2-Methoxy-3,5-dimethyl-1-phenyl-4-hexen-6-ol. Ester **28** (2.102 g, 7.60 mmol) was diluted with 10 mL of THF and added to a suspension of $LiAlH_4$ (0.29 g, 7.6 mmol) in 40 mL of THF in a round-bottom flask equipped with a reflux condenser. After the mixture was stirred at room temperature for 60 min the reaction was quenched by slow addition of 0.3 mL of water (caution, exothermic), followed by 0.3 mL of 15% aqueous NaOH, and finally 0.9 mL of water. The suspension was stirred until a fine gray suspension formed, which was then vacuum filtered, and the supernatant was dried over Na_2SO_4. The solution was filtered, concentrated, and chromatographed (150 mL of SiO_2, 20% ethyl acetate/hexanes) affording 1.540 g (86%) of a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (d, J = 6.8 Hz, 3H), 1.59 (s, 3H), 2.60 (m, 1H), 2.70 (dd, J = 7.8, 14.0 Hz, 1H), 2.83 (dd, J = 4.4, 14.0 Hz, 1H), 3.22 (m, 1H), 3.23 (s, 3H), 3.97 (s, 2H), 5.35 (d, J = 9.9 Hz, 1H), 7.16−7.30 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.6, 16.2, 35.6, 37.7, 58.2, 68.2, 86.9, 125.7, 127.9, 129.1, 134.7, 139.3; IR (thin film) 3396, 2928, 1453, 700 cm^{-1}; HRMS (CI) found 252.1959 $(M + NH_4)^+$, calcd for $C_{15}H_{26}NO_2$ 262.1964; [α] −11.94 (*c* 0.1057, $CDCl_3$).

(2*S*,3*S*,4*E*)-6-Bromo-2-methoxy-3,5-dimethyl-1-phenyl-4-hexene (29). The alcohol from reduction of ethyl ester **28** (1.08 g, 4.61 mmol) was diluted with 25 mL of THF. To this was added carbon tetrabromide (3.05 g, 9.21 mmol) followed by triphenylphosphine (2.66 g, 10.1 mmol) in 30 mL of THF, which resulted in an orange solution. The mixture was stirred for 60 min, and the insoluble triphenylphosphine oxide which precipitated from the solution was then removed by vacuum filtration. The solution was then concentrated and chromatographed (75 mL of SiO_2, 0−5% ethyl acetate/hexanes) affording 0.819 g (60%) of the allylic bromide as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.02, d, J = 6.8 Hz, 3H), 1.64 (d, J = 1.3 Hz, 3H), 2.45 (m, 1H), 2.68 (dd, J = 7.2, 13.9 Hz, 1H), 2.80 (dd, J = 4.7, 13.9 Hz, 1H), 3.19 (ddd, J = 4.8, 6.5, 11.2 Hz, 1H), 3.24 (s, 3H), 3.93 (d, J = 9.4 Hz, 1H), 3.97 (d, J = 9.4 Hz, 1H), 5.51 (d, J = 9.8 Hz, 1H), 7.14−7.30 (m, 5H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 14.8, 15.6, 36.5, 37.9, 41.5, 58.4, 86.4, 125.9, 128.0, 129.4, 131.7, 134.0, 139.0; IR (thin film) 2966, 1930, 1206, 701 cm^{-1}; HRMS (CI) found 314.1130 $(M + NH_4)^+$, calcd for $C_{15}H_{25}BrNO$ 314.1120; [α] −4.35 (*c* 0.1159, CH_2Cl_2).

(2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-*tert*-Butoxycarbonylamino-9-methoxy-2,6,8-trimethyl-1-*p*-methoxybenzyloxy-4, 6-decadiene (30). The allylic bromide **29** (0.073 g, 0.25 mmol) was diluted with toluene (20 mL) and treated with triphenylphosphine (0.065 g, 0.25 mmol). The mixture

was refluxed overnight, then concentrated in vacuo and used immediately for the next step.

The above phosphonium salt was evaporated from toluene (1 × 3 mL), dissolved in 2 mL of THF, and cooled to 0 °C. Freshly prepared lithium diisopropylamide (0.25 mmol) in 1 mL of THF was added slowly to the stirring solution, which became dark red as the addition progressed. After the mixture was stirred for 10 min, aldehyde **6** was added in 1 mL of THF resulting in a pale yellow solution after the addition was complete. After the solution was stirred for 10 min the ice bath was removed and the reaction partitioned between ether and water and separated, and the organic layer was dried over Na_2SO_4. The mixture was then concentrated by rotary evaporation and chromatographed (20 mL of SiO_2, 10% ethyl acetate/hexanes) affording 0.075 g (67%) of the desired *trans-trans* diene and 0.014 g (16%) of the undesired *trans-cis* diene both as clear oils: ^{1}H NMR (360 MHz, $CDCl_3$) 1.03 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.47 (s, 9H), 1.61 (s, 3H), 1.93 (m, 1H), 2.61 (m, 1H), 2.69 (dd, J = 7.4, 13.8 Hz, 1H), 2.82 (dd, J = 4.3, 13.9 Hz, 1H), 3.20 (m, 1H), 3.24 (s, 3H), 3.36, dd, J = 5.2 9.0 Hz, 1H), 3.48, (dd, J = 5.0, 8.9 Hz, 1H), 6.17 (d, J = 15.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.15−7.30 (m, 7H); ^{13}C NMR (91 MHz, $CDCl_3$) δ 12.6, 14.4, 16.1, 28.3, 36.5, 37.7, 38.1, 55.0, 58.4, 72.0, 72.7, 78.8, 86.9, 113.6, 125.8, 126.4, 128.0, 129.0, 129.3, 130.2, 132.5, 135.0, 135.1, 139.2, 155.3, 159.0; IR (thin film) 3412, 2974, 1514, 701 cm^{-1}; HRMS (FAB, NBA) found 538.3527 (M + H)$^+$, calcd for $C_{33}H_{46}NO_5$ 538.3532; [α] −17.1 (*c* 0.0830, $CDCl_3$).

(2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-*tert*-Butoxycarbonylamino-9-methoxy-2,6,8-trimethyl-4,6-decadien-1-ol. The protected alcohol **33** (0.247 g, 0.47 mmol) was diluted with 2 mL of dichloromethane. Ethanethiol (1 mL) was added followed by borontrifluoride etherate (0.46 mL, 3.76 mmol), which resulted in a pale yellow solution. After 30 min, all material had been totally deprotected and the mixture was partitioned between water and dichloromethane and separated, and the aqueous phase was then extracted with ethyl acetate. The combined organic layers were then concentrated in vacuo and diluted with dichloromethane. Boc anhydride (0.13 mL, 0.56 mmol) was added to the solution and the mixture was stirred until all starting material was consumed, then concentrated and chromatographed (50 mL of SiO_2, 20% ethyl acetate/hexanes) affording the desired alcohol (0.106 g, 60%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 1.62 (s, 3H), 2.59 (m, 1H), 2.68 (dd, J = 9.09, 16.5 Hz, 1H), 2.79 (dd, J = 4.6, 14.0 Hz, 1H), 3.19 (ddd, J = 4.9, 7.0, 11.3 Hz, 1H), 3.23 (s, 3H), 3.25 (dd, J = 2.9 14.9 Hz, 1H), 3.47 (m, 1H), 3.71 (d, J = 10.6 Hz, 1H), 4.09 (q, J = 7.3 Hz, 1H), 4.97 (d, J = 7.9 Hz, 1H), 5.40 (d, J = 9.9 Hz, 1H), 5.43 (dd, J = 7.3, 15.6 Hz, 1H), 6.20 (d, J = 15.6 Hz, 1H), 7.15−7.29 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.6, 14.2, 16.1, 22.1, 18.33, 28.3, 36.6, 58.8, 79.8, 87.2, 124.1, 125.3, 128.1, 129.1, 129.3, 132.4, 135.7, 136.7, 139.2, 156.3; IR (thin film) 3377, 2931, 1682, 1014 cm^{-1}; HRMS (FAB, NBA) found 418.2956 (M + H)$^+$, calcd for $C_{25}H_{39}NO_4$ 418.2957; [α] −13.6 (*c* 0.0719, $CDCl_3$).

(2*S*,3*S*,8*S*,9*S*,4*E*,6*E*)-3-*tert*-Butoxycarbonylamino-9-methoxy-2,6,8-trimethyl-4, 6-decadienoic Acid (2). The Boc protected amino alcohol (0.0883 g, 0.22 mmol) was oxidized by using the two-step procedure above affording a quantitative amount (0.0907 g, 0.22 mmol) of the desired acid as a colorless foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.1 Hz, 3H), 1.45 (s, 9H), 1.61 (s, 3H), 2.60 (m, 1H), 2.68 (dd, J = 7.3, 21.3 Hz, 1H), 2.79 (dd, J = 4.5, 14.0 Hz, 1H), 3.19 (m, 2H), 3.23 (s, 3H), 4.40 (m, 1H), 5.35 (m, 1H), 5.39 (d, J = 9.8 Hz, 1H), 5.49 (m, 1H), 6.20 (d, J = 15.6 Hz, 1H), 7.10−7.30 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 14.5, 16.1, 21.1, 23.4, 28.3, 36.6, 38.2, 44.2, 54.2, 58.5, 87.1, 125.1, 125.9, 128.1, 129.3, 132.5, 135.9, 136.4, 139.3; IR (thin film) 3425, 2977, 1715, 701 cm^{-1}; HRMS (FAB, NBA) found 432.2743 (M + H)$^+$, calcd for $C_{25}H_{37}NO_5$ 432.2750; [α] −19.10 (*c* 0.0547, $CDCl_3$).

tert*-Butyl (4*R*,2′*R*,3′*R*,2″*S*,3″*R*,2‴*S*)-4-benzyloxycarbonylamino-5-methoxycarbonylpentanoyl-3′-benzyloxy-2′-(*N*)-methylaminobutanoyl-3″-amino-4″-methoxycarbonyl-2″methylbutanoyl-2‴-amino-3‴-methylbutanoate.** Amine **3** (19 mg, 0.059 mmol) and acid **4** (R***) (38.2 mg, 0.076 mmol) were azeotroped with 2 mL of toluene. The resulting foam was then dissolved in 1 mL of acetonitrile and DIPEA (26 μL, 0.15 mmol) and BOP reagent (39 mg, 0.088 mmol) were added. The solution was stirred for 2 h, changing from pale yellow to light orange over the course of the reaction. The mixture was then partitioned between saturated aqueous NaCl and ethyl acetate and separated, the aqueous phase was extracted twice with ethyl acetate, and the combined organic layers were dried over $MgSO_4$. The suspension was filtered, concentrated to a brown oil, then chromatographed (15 mL SiO_2, 50−100% ethyl acetate/hexanes) to give the tetrapeptide (40 mg, 85%) as two diastereomers, both slightly yellow oils. Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 6H), 1.12 (d, J = 6.8 Hz, 6H), 1.48 (s, 9H), 2.15 (m, 2H), 2.31 (m, 1H), 2.42 (m, 1H), 2.60 (m, 1H), 3.04 (s, 3H), 3.10 (ddd, J = 4.1, 6.9, 7.0 Hz, 1H), 3.63 (s, 3H), 3.72 (s, 3H), 4.34 (m, 3H), 4.49 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.68 (dd, J = 3.8, 8.8 Hz, 1H), 5.09 (s, 2H), 5.32 (d, J = 5.4 Hz, 1H), 5.90 (d, J = 7.7 Hz, 1H), 6.20 (d, J = 8.3 Hz, 1H), 7.20−7.40 (m, 10H), 7.48 (d, J = 8.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.4, 16.9, 17.5, 18.7, 26.7, 27.9, 29.2, 31.2, 33.3, 41.1, 52.3, 52.4, 53.6, 54.2, 57.1, 60.9, 66.7, 71.2, 73.2, 82.1, 127.2, 127.3, 127.7, 128.1, 128.4, 136.4, 138.7, 156.1, 169.7, 170.7, 171.1, 172.5, 173.6; IR (thin film) 2936, 1732, 1660, 1506 cm^{-1}; HRMS (FAB, NBA/NaI) found 821.3902 (M + Na)$^+$, calcd for $C_{41}H_{58}N_4O_{12}Na$ 821.3949; [α] −67.6 (*c* 0.0306, $CDCl_3$). Major diastereomer: ^{1}H NMR (500 MHz, CD_3OD) δ 0.88−0.91 (m, 6H), 1.12 (d, J = 7.2 Hz, 3H), 1.16 (d, J = 6.1 Hz, 3H), 1.43 (s, 9H), 2.10−1.73 (m, 4H), 2.47 (m, 1H), 2.91 (s, 3H), 3.18 (m, 1H), 3.64 (s, 3H), 3.69 (s, 3H), 4.11 (d, 6.2, 1H), 4.08 (m, 1H), 4.25 (m, 1H), 4.57 (m, 1H), 4.60 (d, J = 7.4 Hz, 1H), 4.68 (d, J = 5.8 Hz, 1H), 4.93 (d, J = 8.3 Hz, 1H), 5.04 (d, 12.6 Hz, 1H), 5.08 (d, J = 12.5 Hz, 1H), 7.18−7.36 (m, 10H); ^{13}H NMR (126 MHz, CD_3OD) δ 44.5, 15.5, 17.0, 18.0, 26.6, 26.8, 28.2, 30.3, 32.0, 51.3, 51.5, 53.2, 54.1, 58.0, 61.3, 66.2, 70.8, 73.4, 81.3, 127.0, 127.2, 127.3, 127.5, 127.7, 128.0, 138.2, 139.4, 155.4, 170.1, 170.7, 170.8, 171.6, 173.0, 174.6; IR (thin film) 2977, 1727, 1650, 848 cm^{-1}; [α] −2.6 (*c* 0.0325, $CDCl_3$).

***tert*-Butyl (2*S*,3*S*,8*S*,9*S*,4*E*,6*E*,4′*R*,2″*R*,3″*R*,2‴*S*,3‴*R*,2⁗*S*)-3-*tert*-Butoxycarbonylamino-9-methoxy-2,6,8-trimethyl-4, 6-decadienoyl-4′-benzyloxycarbonylamino-5′-methoxycarbonylpentanoyl-3″-benzyloxy-2″-(*N*)-methylaminobutanoyl-3‴-amino-4‴-methoxycarbonyl-2‴-methylbutanoyl-2⁗-amino-3⁗-methylbutanoate (1).** The protected tetrapeptide was diluted with methanol (7 mL) and 20 mg of 10% Pd/C was added to the solution. The black suspension was then purged and pressurized with H_2 (balloon), and stirred for 16 h. After stirring, the reaction mixture was filtered through a short pad of Celite (0.4 mL) that was then washed exhaustively with methanol. The filtrate was then concentrated affording 0.013 g (82%) of amine **3** as a clear film, which was used immediately for the next step.

Boc-ADDA (**2**; 0.024 g, 0.057 mmol) and tetrapeptide **35** (0.0291 g, 0.052 mmol) were evaporated from toluene (containing a few drops of dichloromethane for solubility), then diluted in 0.5 mL of DMF. The stirring solution was treated with HATU (0.025 g, 0.062 mmol) followed by DIPEA (0.022 mL, 0.124 mmol) which resulted in a faint yellow-green solution. The mixture was stirred overnight, then partitioned between water and ethyl acetate (with a small amount of brine to break the emulsion) and separated, and the aqueous phase was extracted thrice with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a pale brown oil that was then chromatographed (10 mL of SiO_2, 0−10% methanol/dichloromethane) affording 0.030 g (61%) of the desired compound (colorless film) as rotamers: (500 MHz, CD_3OD) 0.92 (m, 6H), δ 1.02 (d, J = 6.7 Hz, 3H), 1.10 (d, J = 6.8 Hz, 1.4H), 1.13 (d, J = 6.8 Hz, 1.6H), 1.19 (m, 6H), 1.42 (s, 9H), 1.45 (s, 9H), 1.61 (s, 3H), 1.90−2.20 (m, 2H), 2.20−2.50 (m, 2H), 2.61 (m, 2H), 2.70−3.00 (m, 2H), 3.07 (s, 1.6 H), 3.08 (s, 1.4H), 3.19 (m, 2H), 3.21 (s, 1.6H), 3.22 (s, 1.4H), 3.66 (s, 1.5H), 3.68 (s, 1.5H), 3.69 (s, 1.5H), 3.70 (s, 1.5), 4.14 (d, J = 6.1 Hz, 1H), 4.15 (m, 1H), 4.29 (q, J = 6.0 Hz, 1H), 4.44 (dd, J = 5.3, 9.0 Hz, 1H), 4.57 (t, J = 5.8 Hz, 1H), 5.00 (m, 1H), 5.39 (d, J = 9.8 Hz, 1H), 5.51 (m, 1H), 6.18 (d, J = 15.5 Hz, 1H), 7.10−7.30 (m, 5H); ^{13}C NMR (126 MHz, CD_3OD) δ 11.5, 12.9, 14.6, 15.0, 16.9, 18.0, 19.3, 19.4, 26.8, 27.6, 29.1, 30.3, 31.9, 32.0, 35.4, 36.1, 37.5, 39.3, 40.1, 51.1, 51.2, 51.4, 51.7, 53.2, 54.2, 57.2, 58.0, 60.0, 61.6, 64.5, 81.2, 86.9, 125.5, 127.7, 129.0, 132.3, 135.3, 135.4, 159.0, 156.1, 170.5, 170.8, 171.1, 172.1, 174.2, 174.4, 174.6, 174.7, 175.7, 176.4; IR (thin film) 2975, 1738, 1651, 1248 cm^{-1}; HRMS (FAB, NBA, Ultra)

found 1010.5736 $(M + Na)^+$, calcd for $C_{51}H_{81}N_5O_{14}Na$ 1010.5678; [α] −30.5 (*c* 0.0084, EtOAc).

cyclo (2*S*,3*S*,8*S*,9*S*,4*E*,6*E*,4′*R*,2″*R*,3″*R*,2‴*S*,3‴*R*,2⁗*S*)-3-amino-9-methoxy-2,6,8-trimethyl-4,6-decadienoyl-4′-benzyloxycarbonyl-amino-5′-methoxycarbonylpentanoyl-3″-benzyloxy-2″-(*N*)-methyl-aminobutanoyl-3‴-amino-4‴-methoxycarbonyl-2‴methylbutanoyl-2⁗amino-3⁗-methylbutanamide. Pentapeptide **1** (0.024 g, 0.025 mmol) was dissolved in 1 mL of TFA and stirred for 60 min over which time the appearance changed from colorless to faint orange. It was then concentrated by high vacuum and azeotroped from toluene (2 mL) affording a white solid.

The pentapeptide amino acid was then dissolved in 25 mL of THF and treated with DIPEA (0.013 mL, 0.075 mmol) followed by HATU (0.014 g, 0.075 mmol). The slightly cloudy solution was stirred overnight, then partitioned between water (10 mL), brine (5 mL), and ethyl acetate (20 mL). The layers were separated and the aqueous phase extracted twice with ethyl acetate; the combined organic layers were then dried over $MgSO_4$. After filtration, the organic layers were concentrated and chromatographed (5 mL of SiO_2, 20% acetone/dichloromethane), then purified by High Performance TLC (using 5%:5%:90% ethyl acetate/methanol/dichloromethane) affording ca. 5.0 mg of the desired product as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 0.88 (m, 6H), 0.98 (d, *J* = 6.7 Hz, 2H), 0.99 (d, *J* = 5.7 Hz, 1H), 1.07 (d, *J* = 7 Hz, 2H), 1.08 (d, *J* = 7.0 Hz, 1H), 1.16−1.25 (m, 6H), 1.60 (s, 3H), 1.97−2.20 (m, 5H), 2.20−2.42 (m, 2H), 2.58 (m, 1H), 2.66 (m, 1H), 2.80 (m, 1H), 2.88 (s, 1H), 3.03 (s, 2H), 3.18−3.25 (m, 3H), 3.20 (s, 1H), 3.21 (s, 2H), 3.70 (s, 3H), 3.72 (s, 3H), 4.00−4.70 (m, 10H), 5.32 (m, 0.3H), 5.41 (m, 1H), 5.60 (dd, *J* = 8.6, 15.7 Hz, 0.7H), 5.67 (dd, *J* = 8.1, 15.8 Hz, 0.3H), 6.22 (d, *J* = 15.6 Hz, 1H), 7.10−7.40 (m, 5H); IR (thin film) 2928, 1738, 1653, 845 cm^{-1}; HRMS (FAB, NBA/NaCl) found 836.4441 $(M + Na)^+$, calcd for $C_{42}H_{63}N_5O_{11}Na$ 836.4422; [α] −16 (*c* 0.0028, $CDCl_3$).

Motuporin. The protected motuporin diester (2.8 mg) was deprotected by using 0.2 mL of saturated $Ba(OH)_2$ in 1 mL of 9:1 water/methanol. The solution was stirred overnight resulting in no visible change, then acidified with 2 M aqueous HCl and extracted thrice with ethyl acetate; the combined organic extracts were dried over $MgSO_4$. After concentration, the material was purified by high performance prep plate (50% methanol/dichloromethane) affording 1.0 mg of motuporin as a white solid and ca. 0.4 mg of epimeric material: ^{1}H NMR (500 MHz, CD_3OD) δ 0.74 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.60 (d, *J* = 1.0 Hz, 3H), 1.72 (d, *J* = 7.2 Hz, 3H), 2.03 (m, 1H), 2.29 (m, 1H), 2.48 (m, 1H), 2.55 (m, 1H), 2.64 (dd, *J* = 7.3, 14.0 Hz, 1H), 2.75 (m, 1H), 2.79 (dd, *J* = 4.6, 9.2 Hz, 1H), 3.04 (dd, *J* = 6.2, 10.9 Hz, 1H), 3.05 (s, 3H), 3.18 (m, 1H), 3.21 (s, 3H), 4.16 (m, 1H), 4.17 (d, *J* = 3.0, 1H), 4.40 (m, 1H), 4.46 (t, *J* = 4.2 Hz, 1H), 4.59 (dd, *J* = 8.9, 10.6 Hz, 1H), 5.37 (d, *J* = 9.5 Hz, 1H), 5.60 (dd, *J* = 8.9, 15.5 Hz, 1H), 6.01 (d, *J* = 15.6 Hz, 1H), 6.90 (q, *J* = 7.2 Hz, 1H), 7.20−7.31 (m, 5H), 7.35 (m, 2H), 7.70 (dd, *J* = 1.6, 7.5 Hz, 1H), 8.60 (s, 1H); IR (thin film) 2924, 1734, 1458, 656 cm^{-1}; HRMS (FAB, NBA/NaCl) found 790.3967 $(M + Na)^+$, calcd for $C_{40}H_{57}NO_{10}Na$ 790.400313; [α] −51 (*c* 0.0009, CD_3OD).

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Supporting Information Available: ^{1}H and ^{13}C spectra for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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