General and Stereospecific Route to 9-Substituted, 8,9-Disubstituted, and 9,10-Disubstituted Analogues of Benzolactam-V8

Dawei Ma,*[,†] Wenjun Tang,[†] Alan P. Kozikowski,*[,‡] Nancy E. Lewin,[§] and Peter M. Blumberg[§]

State Key Laboratory of Bio-organic and Natural Product Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China, Drug Discovery Program, Institute for Cognitive & Computational Sciences, Georgetown University Medical Center, 3970 Reservoir Road, NW, Washington, D.C. 20007-2197, and National Cancer Institute, Bethesda, Maryland 20892

Received April 8, 1999

Nitration of the L-tyrosine derivative **9** provides the 3-nitro compound **13**, which is converted into amide **15** by reduction and protection. Nitration of **15** either *ortho* or *para* to the acetamido group gives **16** and **17**. After reduction of the nitro group, the anilines **21b** and **29b** are coupled with triflate **22a**, and then cyclized to afford lactams **24** and **31**, respectively. By means of a Pd-catalyzed coupling reaction, 8-acetamido-9-decynylbenzolactam-V8 (**26**) and 9-decynyl-10-acetamidobenzolactam-V8 (**33**) are obtained. The regioisomers **16** and **17** are transformed into a single isomer, **34**, which is converted into 9-decynylbenzolactam-V8 (**4**). The K_i values for **4**, **26**, and **33** to displace PDBU binding from recombinant PKCα (PKC = protein kinase C) are about 6, 173, and 46 nM. These results demonstrate that while the introduction of a substituent at either the 8- or 10-position of the 9-substituted benzolactam-V8s lowers their binding affinity, these newly generated analogues still retain reasonably good potency for PKC.

Introduction

Protein kinase C (PKC) consists of a growing family of closely related isozymes that mediate a wide range of cellular signal transduction processes.[1,2] Compounds that are able to selectively modulate the individual PKC isozymes can serve as valuable research tools in the elucidation of their physiological roles. Additionally, such compounds hold promise in the development of novel therapeutics for the treatment of human diseases, such as cancer and Alzheimer's dementia.[1−3] Among the known PKC activators, the teleocidins are a family of natural products possessing relatively simple structures, but imbued with a remarkable affinity for PKC.[4] The teleocidins thus offer a chemically manipulable class of molecules that serve as important lead structures in the search for isoform-selective modulators of PKC.[5,6] This class of compounds has indolactam V (ILV)[7] as the core structure, and ^{1}H NMR studies have revealed that ILV exists as two major conformations in solution; these are the *twist* conformer (with a *cis*-amide bond) and the *sofa* conformer (with a *trans*-amide bond) in solution.[8] In seeking to identify the PKC active conformation of ILV, as well as to investigate the possibility to create isoform-selective modulators, Kozikowski and Ma first explored the use of a benzolactam nucleus to replace the indolactam core. They showed that an analogue that mimicked the *sofa* conformation of ILV was incapable of activating PKC.[9] Later, Endo reported that another type of benzolactam, such as the 9-decylbenzolactam-V8 (**5**) (Figure 1), could mimic the twist conformation, and that this compound was a potent PKC activator.[10] The side chain at the 9-position of **5** was important for PKC

† Chinese Academy of Sciences.
‡ Georgetown University Medical Center.
§ National Cancer Institute.

(1) (a) Nishizuka, Y. *Science* **1992**, *258*, 607. (b) Nishizuka, Y. *Nature* **1988**, *334*, 661.

(2) (a) Dekker: L. V.; Parker, P. J. *Trends Biochem. Sci.* **1994**, *19*, 73. (b) *Protein Kinase C, Current Concepts and Future Perspectives*; Lester, D. S.; Epand, R. M., Eds.; Ellis Horwood Ltd.: New York, 1992. (c) Hoffman, J. *FASEB J.* **1997**, *11*, 649.

(3) (a) Stabel, S.; Parker, P. J. *Pharmacol. Ther.* **1991**, *51*, 71. (b) Gescher, A. *Br. J. Cancer* **1992**, *66*, 10. (c) Basu, A. *Pharmacol. Ther.* **1993**, *59*, 257. (d) Wilkinson, S. E.; Hallan, T. J. *Trends Pharmacol. Sci.* **1994**, *15*, 53. (e) O'Brian, C. A. *Oncol. Rep.* **1998**, *5*, 305. (f) Caponigro, F.; French, R. C.; Kaye, S. B. *Anti-Cancer Drugs* **1997**, *8*, 26. (g) Nambi, P.; Amegadzie, B.; Mattern, M. *Pharmacol. Rev. Commun.* **1996**, *8*, 29.

(4) For reviews, see: (a) Rando, R.; Kishi, Y. *Biochemistry* **1992**, *31*, 2211. (b) Wender, P. A.; Cribbs, C. M. Computer assisted molecular design related to the protein kinase C receptor. In *Advances in Medicinal Chemistry*; JAI Press: Greenwich, CT, 1992; Vol. 1, pp 1−53. (c) Kishi, Y.; Rando, R. *Acc. Chem. Res.* **1998**, *31*, 163. (d) Waldmann, H.; Alonsi-Diaz, D.; Hinterding, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 688.

(5) For studies directed toward the synthesis of the teleocidin family, see: (a) Endo, Y.; Shudo, K.; Furuhata, K.; Ogura, H.; Sakai, S.; Aimi, N.; Hitotsuyanagi, Y.; Koyama, Y. *Chem. Pharm. Bull.* **1984**, *32*, 358. (b) Naktsuka, S.; Masuda, T.; Goto, T. *Tetrahedron Lett.* **1987**, *28*, 3671. (c) Okabe, K.; Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 5113. (d) Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, *46*, 6623. (e) Okabe, K.; Natsume, M. *Tetrahedron* **1991**, *47*, 7615. (f) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1395. (g) Quick, J.; Saha, B.; Driedger, P. E. *Tetrahedron Lett.* **1994**, *35*, 8549.

(6) For studies directed toward the modifications of the teleocidin family, see: (a) Irie, K.; Koshimizu, K. *Mem. Coll. Agric., Ktoto Univ.* **1988**, No. 132, 1. (b) Kozikowski, A. P.; Sato, K.; Basu, A.; Lazo, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 6228. (c) Webb II, R. R.; Venuti, M. C.; Eigenbrot, C. *J. Org. Chem.* **1991**, *56*, 4706. (d) Irie, K.; Isaka, T.; Iwata, Y.; Yanai, Y.; Nakamura, Y.; Koizumi, F.; Ohigashi, H.; Wender, P. A.; Satomi, Y.; Nishino, H. *J. Am. Chem. Soc.* **1996**, *118*, 10733.

(7) Irie, I.; Okuno, S.; Kajiyama, S.; Koshimizu, K.; Nishino, H.; Iwashima, A. *Carcinogenesis* **1991**, *12*, 1883 and references therein.

(8) (a) Endo, Y.; Shudo, K.; Itai, A.; Hasegawa, M.; Sakai, S.; *Tetrahedron* **1986**, *42*, 5905. (b) Kawai, T.; Ichinose, T.; Takeda, M.; Tomioka, N.; Endo, Y.; Yamaguchi, K.; Shudo, K.; Itai, A. *J. Org. Chem.* **1992**, *57*, 6150.

(9) Kozikowski, A. P.; Ma, D.; Pang, Y.-P.; Shum, P.; Likic, V.; Mishra, P. K.; Macura, S.; Basu, A.; Lazo, J. S.; Ball, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 3957.

10.1021/jo990605h CCC: $18.00
Published on Web 08/03/1999

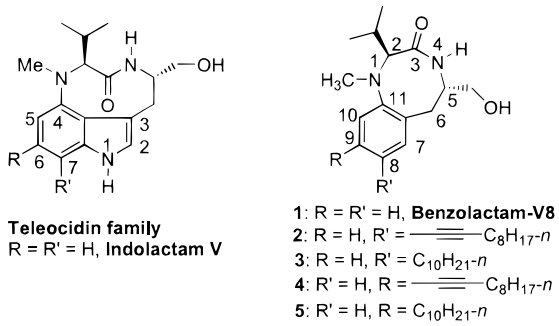


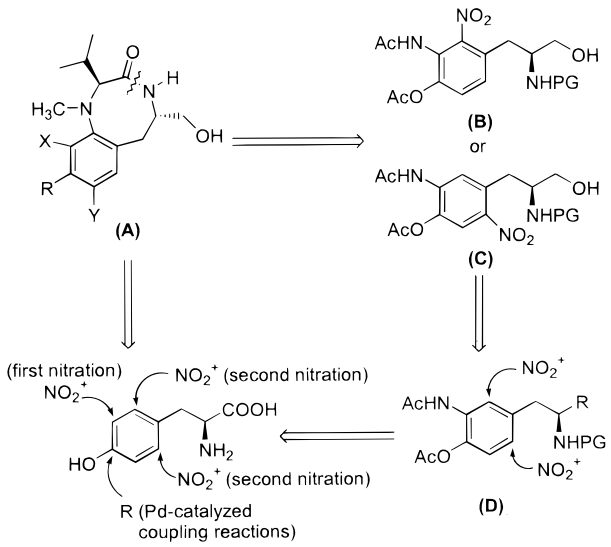
Figure 1. Structures of the teleocidin family and benzolactam-V8 analogues.

activity, since benzolactam-V8 (**1**), without this side chain, demonstrated considerably reduced ability to activate PKC.[10] As it has been reported that different side chain appendages can alter isoform selectivity in the phorbol family,[11] we realized that **1** can be a new core structure for pursuing the design of isoform-selective PKC modulators through side chain variations. In connection with such efforts,[9,12−16] we reported that 8-decynylbenzolactam-V8 (**2**) exhibited improved isozyme selectivity in comparison with its saturated side-chain counterpart, 8-decylbenzolactam-V8 (**3**).[13] Compound **2** also showed isoform selectivity in down-regulating PKCβ and in vivo antitumor activity that indolactam V did not have.[17] These findings promoted us to develop a general route for the synthesis of 9-substituted, 8,9-disubstituted, and 9,10-disubstituted analogues of benzolactam-V8, with the notion to investigate the effects of the aryl ring substitution pattern on PKC isoform selectivity.

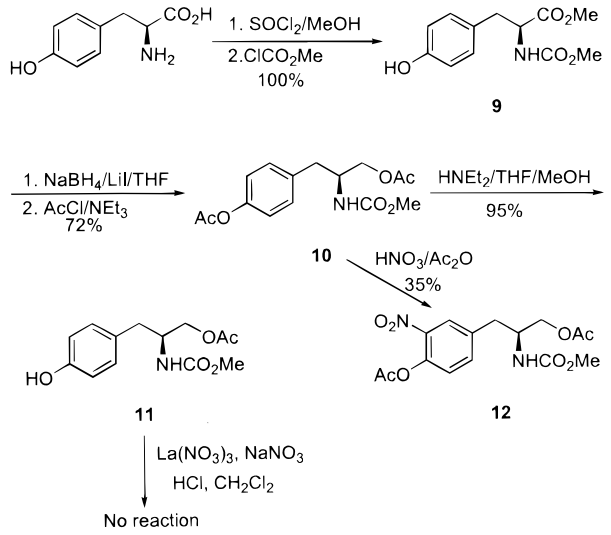
Results and Discussions

Our strategy for synthesizing the desired analogues **A** is shown in Scheme 1. We envisaged that L-tyrosine was a good starting material, because the 4′-hydroxy group of L-tyrosine could be used to introduce various substituents via the corresponding triflate by palladium-catalyzed coupling reactions,[18] while its amino acid moiety could be transformed into the amino alcohol part of the cyclization precursor. The key problem was how to introduce a nitro group at the 2′-position of L-tyrosine, which would in turn allow us to build up the "valine-like" appendage according to a known protocol. As it is obvious that direct nitration of L-tyrosine will take place

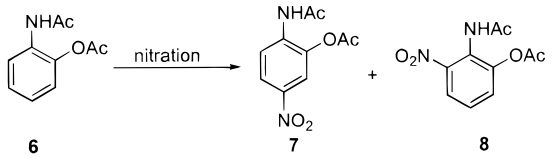
Scheme 1



Scheme 2



in an undesirable manner, we concluded that the electronic distribution of the benzene ring of L-tyrosine must be altered to fit our chemical needs. As the nitration[19] of **6** is known to produce a mixture of **7** and **8** (eq 1), we



(1)

reasoned that our desired products **B** and **C** could be obtained through the nitration of **D**. The acetamido group present in the intermediates **B** and **C** could at a later stage be converted to other substituents through diazotization methods.

As outlined in Scheme 2, we prepared **9** in quantitative yield by esterification of L-tyrosine with thionyl chloride in methanol followed by protection of the amino group with methyl chloroformate in an aqueous $NaHCO_3$ solution. Reduction of **9** with $NaBH_4$/LiI[20] followed by protec-

(10) (a) Ohno, M.; Endo, Y.; Hirano, M.; Itai, A.; Shudo, K. *Tetrahedron Lett.* **1993**, *34*, 8119. (b) Endo, Y.; Ohno, M.; Hirano, M.; Itai, A.; Shudo, K. *J. Am. Chem. Soc.* **1996**, *118*, 1841.

(11) Kazanietz, M. G.; Areces, L. B.; Bahador, A.; Mischak, H.; Goodnight, J.; Mushinski, F.; Blumberg, P. M. *Mol. Pharmacol.* **1993**, *44*, 298.

(12) Kozikowski, A. P.; Ma, D.; Du, L.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1995**, *117*, 6666.

(13) Kozikowski, A. P.; Wang, S.; Ma, D.; Yao, J.; Ahmad, S.; Glazer, R. I.; Bogi, K.; Acs, P.; Modarres, S.; Lewin, N. E.; Blumberg, P. M. *J. Med. Chem.* **1997**, *40*, 1316.

(14) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

(15) Part of the results have been reported as a communication: Ma, D.; Tang, W. *Tetrahedron Lett.* **1998**, *39*, 7369.

(16) Qiao, L.; Wang, S.; George, C.; Lewin, N. E.; Blumberg, P. M.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1998**, *120*, 6629.

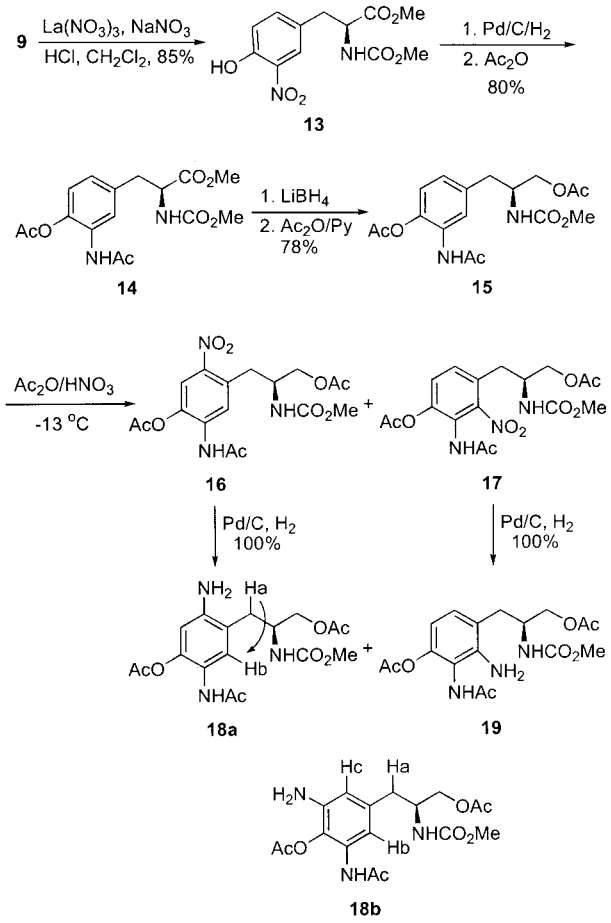
(17) Kozikowski, A. P.; Ma, D.; Glazer, R. I. Unpublished results.

(18) (a) Chen, Q.-Y.; Yang, Z.-Y. *Tetrahedron Lett.* **1986**, *27*, 1171. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (c) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403. (d) Ritter, K. *Synthesis* **1993**, 735. (e) Powell, N. A.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 7901.

(19) Sannie, C.; Lapin, H. *Bull. Soc. Chim. Fr.*, **1952**, 369.

(20) Sudharshan, M.; Hultin, P. G. *Synlett* **1997**, 171.

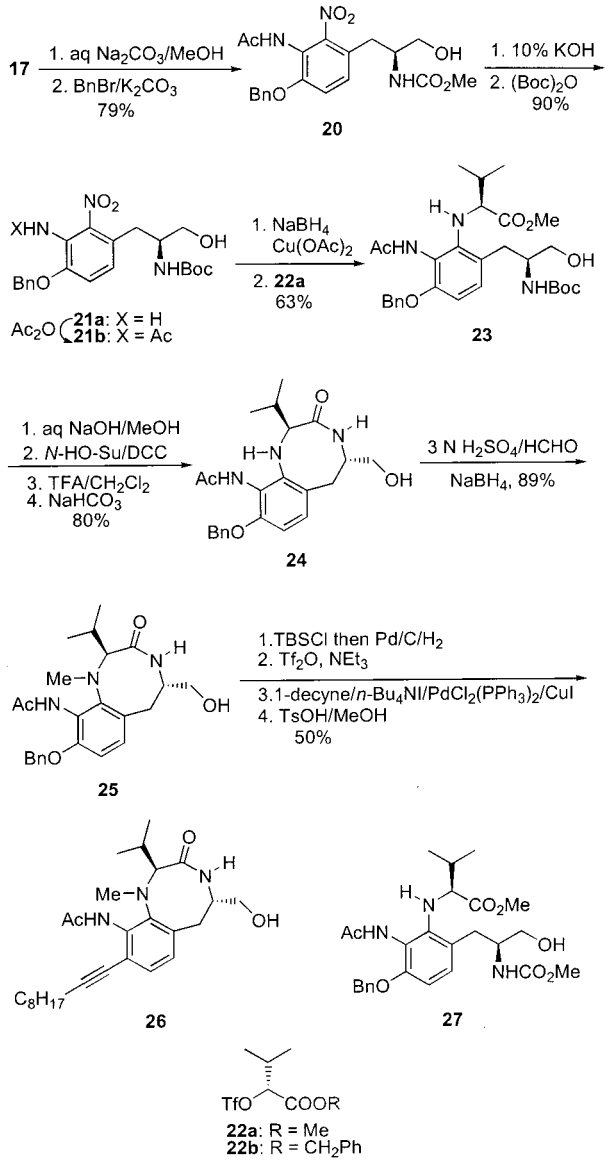
Scheme 3



tion of the two hydroxy groups to their acetates afforded **10** in 72% yield. Unfortunately, nitration of **10** under standard conditions (HNO_3/Ac_2O) provided the desired product **12** in low yield, together with some unidentified products. After a multitude of failures to improve the reaction yield of this step using other nitration conditions such as $HNO_3/Cu(OAc)_2/Ac_2O$[21] and $NaNO_3$/TMSCl/$AlCl_3$,[22] we considered to remove the 4′-acetyl group of **10** to enhance the activity of the substrate, thus allowing the use of other mild nitration conditions. Accordingly, treatment of **10** with diethylamine produced **11**, which was subjected to nitration using $La(NO_3)_3$ as a phase-transfer catalyst and $NaNO_3$/HCl as the nitration reagent.[23] However, no nitration occurred under this condition. After prolonged experimentation, we eventually found that this method was quite workable if compound **9** was used as the substrate. In this way the desired product **13** could be isolated in 85% yield (Scheme 3). The reason for the unexpected difference in reactivity between **9** and **11** was not clear.

Hydrogenation of the nitro group of **13** catalyzed by Pd/C and then protection by *N*-acetylation afforded **14** in 80% yield. Reduction of the amino ester group of **14** to the corresponding amino alcohol using $LiBH_4$ followed by treatment with Ac_2O produced the precursor for second nitration **15** in 78% overall yield. Initial attempts to nitrate **15** using concentrated HNO_3/Ac_2O at 0 °C was

Scheme 4

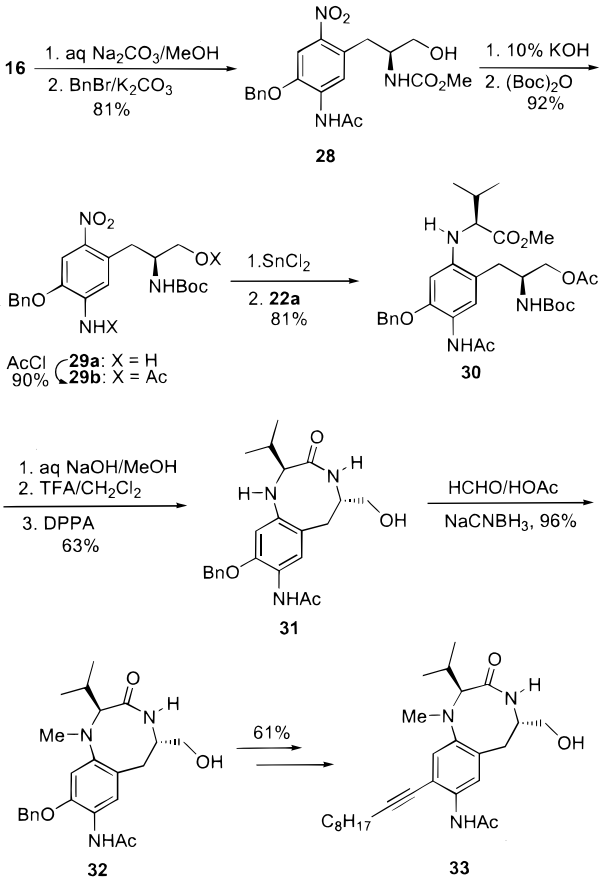


found to give very complex products. However, on lowering the reaction temperature to −13 °C two major separable products in a 1/1 ratio were produced in a total yield of 76%. As the signals in the ^1H NMR spectra of both **16** and **17** are all very broad, we were unable to make a determination of the location of the nitro group in these compounds. Fortunately, their reduction products **18a** and **19** gave clear ^1H NMR spectra, thus permitting us to make regiochemical assignments. The structure of **19** was confirmed by its ^1H NMR spectrum in which clear doublets at 6.64 and 7.17 were observed, while the structure of **18a** was confirmed by its NOESY spectrum in which only one aromatic proton (Hb) has a NOE with Ha. This result ruled out the formation of **18b** and indicated that the regioselectivity of this nitration step was in agreement with our initial proposal.

After confirming the structures of both products, we could transform them to the corresponding disubstituted analogues of benzolactam-V8. First, it was necessary to change the protecting groups in compound **17** (Scheme 4). To avoid any possible problems in subsequent chemical manipulations stemming from the 4′-hydroxy group of **17**, its protecting group was switched to the more stable benzyl group to afford **20**. Also, in consideration

(21) Suzuki, H. *Synthesis* **1977**, 217.
(22) Olah, G. A.; Ramaiah, P.; Sandford, G.; Orlinkov, A.; Prakash, G. K. S. *Synthesis* **1994**, 468.
(23) Ouertani, M.; Girard, P.; Kagan, H. B. *Tetrahedron Lett.* **1982**, *23*, 4315.

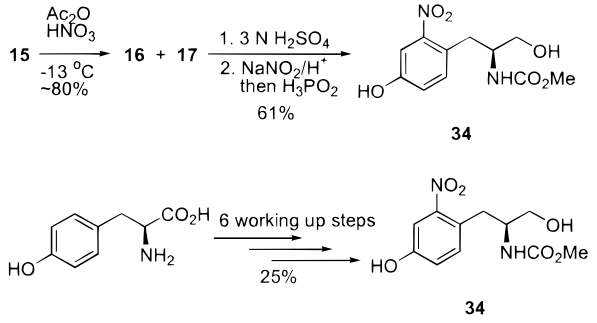
Scheme 5



of the difficulty in cleaving the *N*-methyl carbamate protecting group of **20**, we planned to switch it to an *N*-Boc protecting group. This transformation was confirmed necessary because extensive decomposition was observed when **27** was hydrolyzed to remove the *N*-methyl carbamate protecting group. Hence, treatment of **20** with 10% potassium hydroxide followed by reprotection with di-*tert*-butyl dicarbamate provided a mixture of the 3′-amino product **21a** and 3′-acetamido product **21b**. The former product could be converted into the latter one by reaction with acetyl anhydride. Next, the nitro group of **21b** was reduced with $NaBH_4/Cu(OAc)_2$ to an amino group,[24] which was reacted with the D-valine-derived triflate **22a**[5d] to deliver ester **23**. After compound **23** was transformed into the lactam **24** using a standard activated ester protocol, *N*-methylation was carried out. It was found that the previous procedure[13] for this conversion ($HCHO/NaCNBH_3$/HOAc) did not work well. Some byproducts formed before the starting material disappeared. However, if $NaBH_4$/HCHO/3N H_2SO_4 were employed for methylation, and the reaction were carried out at 50 °C for 15 min, the desired product **25** could be obtained in 89% yield. Finally, the side chain at the 9-position was introduced by the following steps: (i) protection of the hydroxy group with TBSCl and imidazole in DMF; (ii) removal of the benzyl group by hydrogenation followed by transformation of the resultant phenol into its triflate; (iii) coupling the triflate with 1-decyne under the catalysis of $PdCl_2(PPh_3)_2$, CuI, and Bu_4NI;[18] (iv) removal of the silyl group by TsOH/MeOH. The overall yield from **25** to 9-decynyl-10-acetamidobenzolactam-V8 (**26**) was about 80%.

(24) Bellamy, F.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839.

Scheme 6



Similarly, 8-acetamido-9-decynylbenzolactam-V8 (**33**) was synthesized from nitrate **16** employing the reaction sequence outlined in Scheme 5. Some noteworthy points regarding this scheme are as follows. The *N*-acetyl protecting group of **28** was cleanly removed by hydrolysis with 10% potassium hydroxide. Reduction[25] of the nitro group of **29b** with $SnCl_2$ was found to give higher yields than use of the $NaBH_4/CuSO_4$ method. After hydrolysis of **30** with aqueous NaOH and removal of the Boc group with TFA, the newly generated amino acid salt was directly treated with diphenylphosphoryl azide (DPPA) to give the lactam **31** in 63% overall yield. In this case, use of the previous procedure for *N*-methylation worked well and gave **32** in 96% yield. The divergent chemical behavior of **31** and **24** might result from the differences in the steric accessibility of their nitrogen atoms.

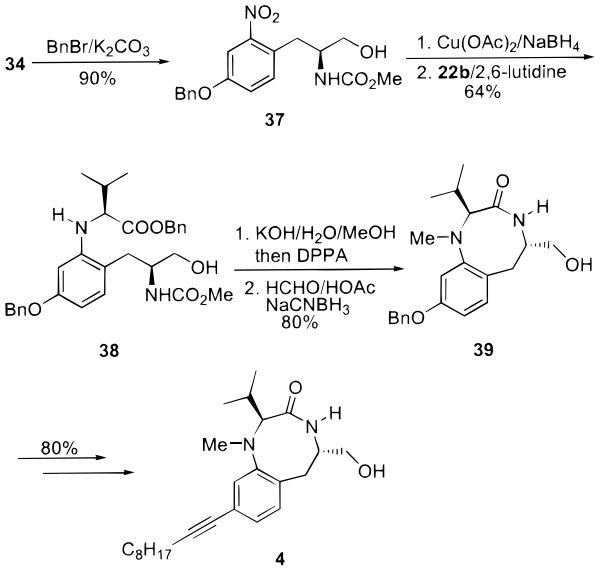
To investigate whether the acetamido group of **16** or **17** could be converted into other substituents by diazotization chemistry, we undertook the studies shown in Scheme 6. After nitration of **15**, the mixture of **16** and **17** was directly treated with 3 N H_2SO_4 at 70 °C to remove the acetyl groups. The resultant aniline salt was subjected to diazotization and then reduction with H_3PO_2 at 70 °C to afford a single nitro compound, **34**, in 61% overall yield. By combining the results indicated in Schemes 2 and 3, we may conclude that the 2′-nitrotyrosine derivative **34** can be obtained from l-tyrosine in 25% overall yield by "six working-up steps" with the key strategy involving introduction of an orientation-directing functional group. This methodology may be useful for preparing various 2′-substituted tyrosine derivatives, compounds which are well-known to be pharmacologically important amino acids as well as building blocks for the synthesis of modified peptides.[26]

With the intermediate **34** in hand, we could synthesize 9-decynylbenzolactam-V8 (**4**) on the basis of the procedure as discussed above (Scheme 7). Protection of phenol **34** with benzyl bromide afforded **37**. Reduction of **37** with $Cu(OAc)_2/NaBH_4$ followed by coupling with triflate **22b** provided **38**. The ester **38** was hydrolyzed in 2 N KOH at 70 °C with simultaneous removal of both the amine protecting groups and the carboxylic acid protecting group, and then neutralized with HCl, concentrated, and dried over P_2O_5. Without any separation, this mixture was directly treated with DPPA and Et_3N in DMF

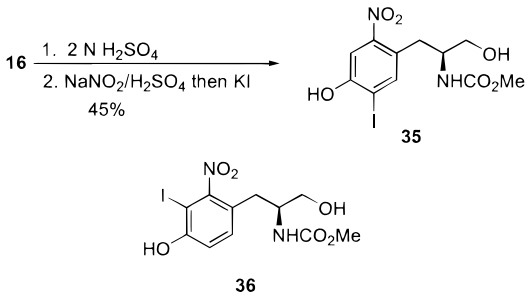
(25) Cowan, J. A. *Tetrahedron Lett.* **1986**, *27*, 1205.

(26) (a) Davis, A. L.; Zaun, J. W.; Reeves, P. C.; Hance, R. L.; McCord, T. J. *J. Med. Chem*, **1966**, *9*, 828. (b) Hara, H.; Inoue, T.; Endoh, M.; Nakamura, H.; Takahashi, H.; Hoshino, O. *Heterocycles* **1996**, *42*, 445. (c) Dugave, C. *J. Org. Chem*. **1995**, *60*, 601. (d) Hinterding, K.; Hagenbuch, P.; Retey, J.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1236. (e) Schmidt, U. Leitenberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248.

Scheme 7



Scheme 8



followed by *N*-methylation to afford benzolactam **39** in 82% overall yield. Finally, the decynyl group was introduced in four steps as described in the synthesis of **26** from **25**. Thus, we have found a convenient and stereospecific route to 9-substituted benzolactam-V8 **4** by using L-tyrosine as the chiral building block. The overall yield of **4** from L-tyrosine was 8.8%.

The acetamido group of **16** and **17** can also be converted into an iodo substituent, which provides flexibility for further modification (Scheme 8) Thus, upon heating a mixture of **16** with 2 N H_2SO_4 in methanol at 70 °C to remove all the acetyl protecting group, the resulting aniline salt was oxidized with $NaNO_2/H_2SO_4$ to afford the diazonium ion. This ion was treated with potassium iodide to provide **35** in 45% yield. In a similar manner, **36** was obtained from **17** in 42% yield.

Compounds **4**, **26**, and **33** were evaluated for their ability to displace phorbol 12,13-dibutyrate (PDBU) binding from recombinant PKCα. The K_i values for these analogues were about 6, 173, and 46 nM. These results demonstrate that while the introduction of a substituent at either the 8- or 10-position of the 9-substituted benzolactam-V8s lowers their binding affinity, these newly generated analogues still retain reasonably good potency for PKC. It is known that certain 5-substituted indolactam-Vs **40** (Figure 2) fail to activate PKC, results that have been explained by the preference of these molecules to adopt a *sofa*-restricted conformation.[6a,d] Thus, the potent activity found for **26** suggests that the 10-substituent of benzolactam-V8 does not play a similar role in altering the conformation. Further modeling-based

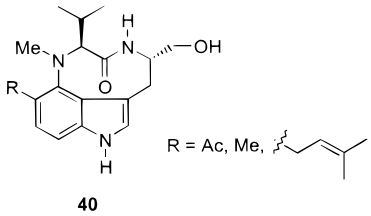


Figure 2. Structures of 5-substituted analogues of indolactam-V.

studies on these benzolactams together with their activity toward other PKC isozymes will be reported in due course.

Experimental Section

(*S*)-3-(4-Hydroxyphenyl)-2-[(methoxycarbonyl)amino]-1-propanoic Acid, Methyl Ester (9). To a suspension solution of L-tyrosine (30 g, 0.17 mol) in 200 mL of methanol was added thionyl chloride (36.5 mL, 0.5 mol) in a dropwise manner at −30 °C. After the addition the solution was allowed to warm to room temperature. The reaction mixture was heated at reflux overnight and then concentrated via rotary evaporator to afford the crude ester, which was dissolved in 200 mL of water. The resultant solution was neutralized with NaOH (6.64 g, 0.17 mol) before $NaHCO_3$ (21 g, 0.25 mol) was added. After the solution was cooled with ice−water, a solution of methyl chloroformate (15.4 mL, 0.2 mol) in 100 mL of $CHCl_3$ was added. The reaction mixture was stirred for 2 h and then extracted with $CHCl_3$ (3 × 150 mL). The combined organic layers were washed with water and dried over Na_2SO_4. After removal of solvent in vacuo, 41.5 g (100%) of **9** was obtained as a pale yellow oil: $[\alpha]^{18}_D$ +9.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, J = 8.1 Hz, 2H), 6.74 (d, J = 8.1 Hz, 2H), 5.22 (br s, 1H), 4.66 (m, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.05 (d, J = 6.4 Hz, 2H); MS (EI) *m*/*z* 254 ($M^+ + H^+$). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.51. Found: C, 56.72; H, 5.96; N, 5.11.

(*S*)-3-(4-Hydroxy-3-nitrophenyl)-2-[(methoxycarbonyl)amino]-1-propanoic Acid, Methyl Ester (13). $NaNO_3$ (13.8 g, 163 mmol) and $La(NO_3)_3 \cdot 6H_2O$ (0.7 g, 1.6 mmol) were dissolved in 260 mL of 6 N HCl. To this solution was added a solution of **9** (41 g, 163 mmol) in 500 mL of methylene chloride at 0 °C over 2 h. After the addition the solution was warmed to room temperature, and the stirring was continued for 4 h. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residual oil was chromatographed, eluting with 1/4 ethyl acetate/petroleum ether to afford 41 g (85%) of **13**: $[\alpha]^{18}_D$ +83.6 (*c* 3.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.5 (d, J = 3.0 Hz, 1H), 7.86 (s, 1H), 7.36 (dd, J = 8.7, 1.6 Hz, 1H), 7.08 (dd, J = 8.7, 3.0 Hz, 1H), 5.33 (br s, 1H), 4.62 (m, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 3.12 (dd, J = 13.6, 5.1 Hz, 1H), 2.98 (dd, J = 13.6, 9.1 Hz, 1H); MS (EI) *m*/*z* 299 ($M^+ + H^+$); HRMS found *m*/*z* 298.0808 (M^+), $C_{12}H_{14}N_2O_7$ requires 298.0801.

(*S*)-3-(4-Acetoxy-3-acetamidophenyl)-2-[(methoxycarbonyl)amino]-1-propanoic Acid, Methyl Ester (14). A suspension solution of **13** (40 g, 143 mmol) and Pd/C (10%, 1 g) in 400 mL of ethyl acetate was stirred under hydrogen atmosphere (30 atm) until no more hydrogen was taken in. The catalyst was filtered off, and the filtrate was concentrated to afford the crude aniline, which was dissolved in 400 mL of methylene chloride. After triethylamine (70 mL, 0.5 mol) was added, the solution was cooled to −10 °C, and acetyl chloride (20 mL, 280 mmol) was added dropwise. The resultant mixture was stirred for 2 h before it was quenched by adding 200 mL of water. The organic layer was separated, and the aqueous layer was extracted. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated via rotary evaporator. Column chromatography (2/1 ethyl

acetate/petroleum ether as eluent) of the residual oil afforded 36 g (80%) of **14**: $[\alpha]^{19}_D$ +69.1 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.56 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 5.47 (br s, 1H), 4.57 (m, 1H), 3.71 (s, 3H), 3.60 (s, 3H), 3.02 (m, 2H), 2.26 (s, 3H), 2.12 (s, 3H); MS (EI) *m*/*z* 353 ($M^+ + H^+$); HRMS found *m*/*z* 352.1271 (M^+), $C_{16}H_{20}N_2O_7$ requires 352.1271.

***(S)*-*O*-Acetyl-3-(4-acetoxy-3-acetamidophenyl)-2-[(methoxycarbonyl)amino]-1-propanol (15).** To a stirring solution of **14** (15.1 g, 42.6 mmol) in 350 mL of anhydrous THF was added $LiBH_4$ (2.8 g, 128 mmol) at 0 °C. The solution was warmed to room temperature, and the stirring was continued for 5 h. The reaction was quenched by adding HOAc with cooling by ice−water, and then the mixture was concentrated. The residue was partitioned between 300 mL of ethyl acetate and 50 mL of water. The organic layer was separated, washed with brine, and concentrated to dryness to afford the crude reduction product, which was dissolved in 200 mL of dry pyridine. After the solution was cooled to 0 °C, acetic anhydride (16.3 g, 160 mmol) was added dropwise. The reaction mixture was stirred for 8 h at room temperature and then concentrated via rotary evaporator. The residual oil was partitioned between 400 mL of ethyl acetate and 100 mL of water. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed, eluting with 2/1 ethyl acetate/petroleum ether to afford 12.2 g (78%) of **15**: $[\alpha]^{18}_D$ −10.5 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.17 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 4.89 (d, J = 7.5 Hz, 1H), 4.13 (m, 1H), 4.06 (m, 2H), 3.65 (s, 3H), 2.85 (m, 2H), 2.31 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H); MS (EI) *m*/*z* 367 (M^+). Anal. Calcd for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.65. Found: C, 55.50; H, 5.94; N, 7.19.

Nitration of 15. To a suspension of **15** (16.5 g, 45.1 mmol) in 160 mL of acetic anhydride was added HNO_3 (65%, 9.4 mL, 142 mmol) in a dropwise manner at −13 °C. After the addition the reaction mixture was stirred at the same temperature until the starting material disappeared as monitored by TLC. The solution was partitioned between 300 mL of ethyl acetate and 300 mL of water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water and brine and then dried over Na_2SO_4. After removal of solvent the residual oil was chromatographed (2/1 ethyl acetate/petroleum ether as eluent) to afford 6.5 g (36%) of **16** and 7.5 g (40%) of **17**. Data for **16**: $[\alpha]^{21}_D$ −61.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.92 (s, 1H), 7.61 (br s, 1H), 5.20 (br s, 1H), 4.23 (m, 1H), 4.15 (m, 2H), 3.54 (s, 3H), 3.18 (m, 2H), 2.38 (s, 3H), 2.20 (s, 3H), 2.11 (s, 3H); MS (EI) *m*/*z* 412 ($M^+ + H^+$); HRMS found *m*/*z* 411.1278 (M^+), $C_{17}H_{21}N_3O_9$ requires 411.1276. Data for **17**: $[\alpha]^{21}_D$ −50.7 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.28 (m, 2H), 5.28 (br s, 1H), 4.09 (m, 1H), 4.04 (m, 2H), 3.57 (s, 3H), 2.84 (m, 2H), 2.24 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H); MS (EI) *m*/*z* 412 ($M^+ + H^+$); HRMS found *m*/*z* 411.1277 (M^+), $C_{17}H_{21}N_3O_9$ requires 411.1276.

General Procedure for Hydrogenation of 16 and 17. A suspension of **16** (190 mg, 0.5 mmol) and 10 mg of 10% Pd/C in 5 mL of ethyl acetate was stirred under hydrogen at room temperature and ordinary pressure for 3 h. The catalyst was filtered off, and the filtrate was purified by column chromatography (2/1 ethyl acetate/petroleum ether as eluent) to provide 190 mg (100%) of **18a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.57 (s, 1H), 6.33 (s, 1H), 5.48 (m, 1H), 4.13 (m, 1H), 4.38 (dd, J = 12.5, 3.4 Hz, 1H), 3.89 (m, 1H), 3.70 (s, 3H0, 271 (d, J = 12.3 Hz, 1H), 2.39 (dd, J = 12.3, 10.1 Hz, 1H), 2.17 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H); MS (EI) *m*/*z* 381 (M^+). Data for **19**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.17 (d, J = 8.3 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 4.44 (m, 1H), 4.38 (m, 2H), 3.85 (s, 3H), 3.02 (dd, J = 12.4, 5.2 Hz, 1H), 2.92 (dd, J = 12.4, 7.9 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H); MS (EI) *m*/*z* 381 (M^+).

***(S)*-3-(4-Benzoxy-3-acetamido-2-nitrophenyl)-2-[(methoxycarbonyl)-amino]-1-propanol (20).** To a mixture of **17** (3.0 g, 7.2 mmol) in 60 mL of methanol and 40 mL of water was added Na_2CO_3 (2.0 g, 18.8 mmol). After it was stirred for 2 h, the solution was neutralized with HCl to pH 7. Ethyl acetate extraction and workup followed by concentration provided an oil, which was dissolved in 30 mL of dry DMF. To this solution were added anhydrous K_2CO_3 (1.93 g, 14 mmol) and freshly distilled benzyl bromide (1.44 g, 8.4 mmol), respectively. After the reaction mixture was heated at 50 °C for 3 h, DMF was removed at reduced pressure. The residue was partitioned between 100 mL of ethyl acetate and 20 mL of water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (2/1 ethyl acetate/petroleum ether as eluent) of the residual oil afforded 2.4 g (79%) of **20**: $[\alpha]^{19}_D$ −28.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.18 (d, J = 8.7 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 5.31 (br s, 1H), 5.13 (s, 2H), 3.89 (m, 1H), 3.68 (m, 2H), 3.64 (s, 3H), 2.80 (m, 2H), 2.12 (s, 3H); MS (EI) *m*/*z* 418 ($M^+ + H^+$); HRMS found *m*/*z* 417.1542 (M^+), $C_{20}H_{23}N_3O_7$ requires 417.1547.

***(S)*-3-(4-Benzoxy-3-amino-2-nitrophenyl)-2-[(*tert*-butoxycarbonyl)amino]-1-propanol (21a).** A mixture of **20** (2.0 g, 4.8 mmol) in 30 mL of methanol and 30 mL of 10% KOH was stirred at 50 °C until the starting material disappeared as monitored by TLC. After the solution was neutralized with HCl to pH 7, di-*tert*-butyl dicarbonate (1.3 g, 5.8 mmol) and $NaHCO_3$ (1.0 g, 11.9 mmol) were added. The resultant mixture was stirred for 32 h before it was extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (2/1 ethyl acetate/petroleum ether as eluent) to afford 0.92 g (46%) of **21a**, together with 0.88 g (44%) of **21b**. Data for **21a**: $[\alpha]^{18}_D$ −38.4 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H), 6.86 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 5.13 (s, 2H), 3.90 (m, 1H), 3.11 (dd, J = 13.8, 4.4 Hz, 1H), 2.89 (dd, J = 13.8, 9.8 Hz, 1H), 1.37 (s, 9H); MS (EI) *m*/*z* 367 ($M^+ + H^+$). Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.36; H, 6.50; N, 9.94.

(2*S*)-*N*-[2-Acetamido-3-benzoxy-6-[(*S*)-2-(*tert*-butoxycarbonyl)amino-3-hydroxypropyl]phenyl]valine Methyl Ester (23). To a solution of **21b** (780 mg, 1.7 mmol) in 30 mL of methanol was added 10 mL of $Cu(OAc)_2$-saturated methanol. The resultant solution was cooled with ice−water while $NaBH_4$ (1.0 g, 26 mmol) was added in four partitions. The stirring was continued for 30 min, and then the reaction mixture was passed over a short column of silica gel. The filtrate was concentrated before it was partitioned between 100 mL of ethyl acetate and 20 mL of water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to provide the crude aniline, which was dissolved in 20 mL of 1,2-dichloroethane. To the resulting solution were added 2,6-lutidine (310 μL, 2.7 mmol) and **22a** (520 mg, 2.0 mmol). The mixture was heated at 70 °C for 72 h before the solvent was evaporated. The residual oil was chromatographed (1/1 ethyl acetate/petroleum ether as eluent) to provide 581 mg (63%) of **23**: $[\alpha]^{19}_D$ −78.2 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.36 (m, 5H), 7.11 (d, J = 8.4 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 5.29 (br s, 1H), 5.04 (AB q, J = 11.1, 2H), 3.67 (d, J = 5.4 Hz, 1H), 3.57 (s, 3H), 3.48 (m, 2H), 3.00 (m, 1H), 2.85 (m, 1H), 2.21 (s, 3H), 1.46 (m, 9H), 1.09 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H); MS (EI) *m*/*z* 544 ($M^+ + H^+$); HRMS found *m*/*z* 543.2945 (M^+), $C_{29}H_{41}N_3O_7$ requires 543.2949.

Lactam 24. A mixture of **23** (350 mg, 0.64 mmol) in 3 mL of methanol and 3 mL of 10% NaOH was stirred overnight. The solution was neutralized with 10% aqueous citric acid to pH 5 before it was extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated to afford the crude acid. This product and *N*-hydroxysuccinimide (89 mg, 0.77 mmol) were dissolved in 15 mL of methylene chloride. To this solution was added a solution of DCC (159 mg, 0.77 mmol) in 2 mL of methylene chloride. After it was stirred for 2 h, the mixture was filtered. The filtrate was purified by passing it over a short column of silica gel to afford the corresponding activated ester.

The above product was dissolved in 5 mL of methylene chloride. With cooling by ice−water, 5 mL of TFA was added slowly. After the stirring was continued for 2 h at 0 °C, the solvents were evaporated at reduced pressure. The residue was

dissolved in 60 mL of ethyl acetate and 6 mL of saturated aqueous $NaHCO_3$. After the resultant mixture was stirred for 10 min at room temperature, it was heated at reflux for 30 min. The cooled mixture was separated, and the organic layer was washed with brine and dried over Na_2SO_4. After removal of solvent, the residual oil was chromatographed (4/1 ethyl acetate/petroleum ether as eluent) to provide 210 mg (80%) of **24**: $[\alpha]^{21}_D$ −47.3 (*c* 0.13, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 7.28 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.59 (br s, 1H), 5.01 (s, 2H), 4.91 (m, 1H), 3.72 (dd, J = 11.3, 3.4 Hz, 1H), 3.57 (dd, J = 11.3, 5.2 Hz, 1H), 3.53 (d, J = 6.6 Hz, 1H), 3.01 (dd, J = 13.8, 4.4 Hz, 1H), 2.89 (dd, J = 13.8, 9.8 Hz, 1H), 2.17 (s, 3H), 2.16 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H); MS (EI) *m*/*z* 411 (M^+); HRMS found *m*/*z* 411.2140 (M^+), $C_{23}H_{29}N_3O_4$ requires 411.2158.

(*S*,*S*)-9-Benzoxy-10-acetamidobenzolactam-V8 (25). The lactam **24** (130 mg, 0.32 mmol) and $NaBH_4$ (60 mg, 1.58 mmol) were mixed in 5 mL of THF. The resultant suspension solution was added dropwise into a freshly prepared mixture of formalin (0.6 mL, 7.4 mmol) and 3 N H_2SO_4 (1.0 mL, 0.32 mmol) with vigorous stirring. During the addition the reaction temperature should be kept below 20 °C by cooling with ice−water. After the addition the stirring was continued for 5 min. NaOH powder was added to quench the reaction, and then the mixture was partitioned between 50 mL of ethyl acetate and 10 mL of water. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (4/1 ethyl acetate/petroleum ether as eluent) to afford 120 mg (89%) of **25**: $[\alpha]^{21}_D$ −193 (*c* 0.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.92 (br s, 2H), 6.89 (d, J = 7.7 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 5.01 (s, 2H), 3.74 (m, 1H), 3.57 (m, 2H), 3.45 (m, 1H), 2.88 (m, 1H), 2.73 (s, 3H), 2.41 (m, 1H), 2.16 (s, 3H), 1.00 (d, J = 6.8 Hz, 6H); MS (EI) *m*/*z* 425 (M^+); HRMS found *m*/*z* 425.2299 (M^+), $C_{24}H_{31}N_3O_4$ requires 425.2314.

(*S*,*S*)-9-Decynyl-10-acetamidobenzolactam-V8 (26). To a solution of **25** (80 mg, 0.19 mmol) in 5 mL of DMF were added imidazole (26 mg, 0.38 mmol) and *tert*-butyldimethylsilyl chloride (58 mg, 0.38 mmol), respectively. After the mixture was stirred overnight, DMF was removed in vacuo. The residue was partitioned between 20 mL of ethyl acetate and 5 mL of water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. After column chromatography (1/2 ethyl acetate/petroleum ether as eluent), the silyl ether was obtained. This product was dissolved in 5 mL of ethyl acetate, and then 5 mg of 10% Pd/C was added. The resultant suspension was stirred under hydrogen atmosphere (ordinary pressure) until no more starting material was determined by TLC. Pd/C was filtered off, and the filtrate was concentrated to dryness to provide an oil, which was dissolved in 1 mL of dry methylene chloride. To this solution was added triethylamine (84 μL, 0.6 mmol) before trifluoromethanesulfonic anhydride (86 mg, 0.3 mmol) was added at −78 °C. After the solution was stirred for 10 min at the same temperature, the reaction was quenched by adding water. Methylene chloride extraction and workup followed by column chromatography afforded 77 mg (70% from **25**) of the corresponding triflate.

The above triflate (50 mg, 0.086 mmol), 1-decyne (78 mL, 0.43 mmol), and 1 mL of triethylamine were dissolved in 5 mL of DMF. Under nitrogen $PdCl_2(PPh_3)_2$ (24 mg, 0.017 mmol), CuI (6.5 mg, 0.034 mmol), and *n*-Bu_4NI (95 mg, 0.17 mmol) were added, respectively. The mixture was heated at 70 °C for 2 days under nitrogen before it was passed over a short column of silica gel. The filtrate was mixed with a solution of 10 mg of TsOH in 2 mL of methanol, and then the mixture was stirred for 3 h. The solvents were removed in vacuo, and the residue was chromatographed (1/3 ethyl acetate/petroleum ether as eluent) to afford 28 mg (71% from the triflate) of **26**: $[\alpha]^{21}_D$ −168 (*c* 0.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (m, 1H), 6.84 (m, 1H), 6.66 (m, 1H), 3.79 (m, 1H), 3.50 (m, 3H), 2.79 (m, 2H), 2.64 (s, 3H), 2.30 (m, 1H), 2.29 (t, J = 7.0 Hz, 2H), 2.12 (s, 3H), 1.87 (m, 1H), 1.48 (m, 2H), 1.32 (m, 2H), 1.19 (m, 8H), 0.94 (d, J = 6.6 Hz, 6H), 0.79 (t, J = 6.4 Hz, 3H); MS (EI) *m*/*z* 455 (M^+); HRMS found *m*/*z* 455.3147 (M^+), $C_{27}H_{41}N_3O_3$ requires 455.3148.

(*S*)-3-(5-Acetamido-4-benzoxy-2-nitrophenyl)-2-[(methoxycarbonyl)amino]-1-propanol (28). Following the procedure for preparing **20** from **17**, **28** was obtained in 81% yield from **16**: $[\alpha]^{19}_D$ −53.2 (*c* 0.64, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.89 (s, 1H), 7.67 (s, 1H), 7.43 (m, 5H), 5.38 (m, 1H), 5.17 (s, 2H), 4.03 (m, 1H), 3.75 (m, 2H), 3.67 (s, 3H), 3.15 (dd, J = 13.8, 4.4 Hz, 1H), 3.08 (dd, J = 13.8, 9.8 Hz, 1H), 2.19 (s, 3H); MS (EI) *m*/*z* 418 ($M^+ + H^+$); HRMS found *m*/*z* 417.1540 (M^+), $C_{20}H_{23}N_3O_7$ requires 417.1547.

(*S*)-*O*-Acetyl-3-(5-acetamido-4-benzoxy-2-nitrophenyl)-2-[(*tert*-butoxycarbonyl)amino]-1-propanol (29b). Following the procedure for synthesizing **21a** for **20**, **29a** was prepared from **28** in 81% yield. To a mixture of **29a** (0.81 g, 1.94 mmol) and 30 mL of pyridine was added acetyl chloride (0.37 g, 4.66 mmol) at 50 °C. After the addition the stirring was continued for 10 min at the same temperature. The solvent was removed in vacuo, and the residue was partitioned between 70 mL of ethyl acetate and 20 mL of water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (1/2 ethyl acetate/petroleum ether as eluent) of the residual oil afforded 870 mg (90%) of **29b**: $[\alpha]^{17}_D$ −29.5 (*c* 0.76, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.89 (s, 1H), 7.70 (s, 1H), 7.43 (m, 5H), 5.15 (s, 2H), 4.87 (d, J = 9.3 Hz, 1H), 4.19 (m, 1H), 4.11 (m, 2H), 3.22 (dd, J = 13.2, 4.8 Hz, 1H), 3.02 (dd, J = 13.3, 9.4 Hz, 1H), 2.19 (s, 3H), 2.13 (s, 3H), 1.37 (s, 9H); MS (EI) *m*/*z* 502 ($M^+ + H^+$). Anal. Calcd for $C_{25}H_{31}N_3O_8$: C, 59.87; H, 6.27; N, 8.38. Found: C, 59.68; H, 6.20; N, 8.18.

(2*S*)-*N*-[5-Benzoxy-4-acetamido-(*S*)-2-[2-(*tert*-butoxycarbonyl)amino-3-acetoxypropyl]phenyl]valine Methyl Ester (30). To a solution of **29b** (670 mg, 1.33 mmol) in 30 mL of ethanol was added $SnCl_2$ (1.27 g, 6.71 mmol). The resulting solution was refluxed for 1 h before it was cooled and poured onto ice−water. The mixture was neutralized with saturated $NaHCO_3$ to pH 8 and then extracted with ethyl acetate. After the extraction the product was purified by column chromatography (1/2 ethyl acetate/petroleum ether as eluent) to afford the corresponding aniline. This aniline was coupled with **22a** according to the procedure for preparing **23** to provide **30** in 81% overall yield: $[\alpha]^{19}_D$ −114.5 (*c* 0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.38 (m, 6H), 6.28 (s, 1H), 5.18 (d, J = 7.1 Hz, 1H), 5.04 (s, 2H), 4.06 (d, J = 5.6 Hz, 2H), 3.90 (m, 1H), 3.75 (d, J = 7.0 Hz, 1H), 3.61 (s, 3H), 2.98 (m, 1H), 2.52 (m, 1H), 2.23 (m, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 1.44 (s, 9H), 1.13 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H); MS (EI) *m*/*z* 585 (M^+); HRMS found *m*/*z* 585.3045 (M^+), $C_{31}H_{43}N_3O_8$ requires 585.3050.

Lactam 31. A mixture of **30** (250 mg, 0.43 mmol), 5 mL of methanol, and 5 mL of 2 N NaOH was stirred overnight. After the solution was neutralized with 10% aqueous citric acid to pH 6, it was extracted with methylene chloride. The organic layer was cooled to −10 °C, and 6 mL of TFA was added dropwise. The resultant solution was stirred for 1 h at the same temperature before it was concentrated. The residue was dried in vacuo and then dissolved in 60 mL of DMF. At 0 °C triethylamine (91 mg, 0.91 mmol) and DPPA (141 mg, 0.51 mmol) were added. The solution was stirred for 1 h at 0 °C and 17 h at room temperature. DMF was removed in vacuo, and the residual oil was partitioned between 50 mL of ethyl acetate and 20 mL of water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (4/1 ethyl acetate/petroleum ether as eluent) of the residual oil afforded 110 mg (63%) of **31**: $[\alpha]^{21}_D$ −22.9 (*c* 0.36, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.49 (s, 1H), 7.31 (m, 5H), 6.33 (s, 1H), 6.30 (d, J = 7.3 Hz, 1H), 4.89 (s, 2H), 3.98 (m, 1H), 3.73 (d, J = 8.4 Hz, 1H), 3.65 (dd, J = 11.3, 4.3 Hz, 1H), 3.56 (dd, J = 11.3, 6.2 Hz, 1H), 3.03 (dd, J = 14.2, 11.6 Hz, 1H), 2.79 (dd, J = 14.2, 6.5 Hz, 1H), 2.15 (m, 1H), 2.09 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H); MS (EI) *m*/*z* 411 (M^+); HRMS found *m*/*z* 411.2189 (M^+), $C_{23}H_{29}N_3O_4$ requires 411.2158.

(*S*,*S*)-8-Acetamindo-9-benzoxybenzolactam-V8 (32). To a mixture of **31** (100 mg, 0.24 mmol) in 5 mL of CH_3CN were

added 0.2 mL of formalin, $NaCNBH_3$ (46 mg, 0.73 mmol), and 23 μM HOAc at 0 °C, sequentially. After the stirring was continued for 30 min at the same temperature, the reaction mixture was partitioned between 50 mL of ethyl acetate and 10 mL of water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (4/1 ethyl acetate/petroleum ether as eluent) to afford 100 mg (96%) of **32**: $[\alpha]^{21}_D$ −244 (*c* 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.62 (s, 1H), 7.39 (m, 5H), 6.77 (d, J = 4.1 Hz, 1H), 6.61 (s, 1H), 5.08 (AB q, J = 11.7 Hz, 2H), 4.89 (s, 2H), 3.98 (m, 1H), 3.73 (d, J = 8.4 Hz, 1H), 3.65 (dd, J = 11.3, 4.3 Hz, 1H), 3.56 (dd, J = 11.3, 6.2 Hz, 1H), 3.03 (dd, J = 14.2, 11.6 Hz, 1H), 2.79 (dd, J = 14.2, 6.5 Hz, 1H), 2.15 (m, 1H), 2.09 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H); MS (EI) *m*/*z* 425 (M^+); HRMS found *m*/*z* 425.2306 (M^+), $C_{24}H_{31}N_3O_4$ requires 425.2314.

(*S*,*S*)-8-Acetamindo-9-decynylbenzolactam-V8 (33). Following the procedure for preparing **26** from **25**, **33** was obtained from **32** in 61% overall yield: $[\alpha]^{21}_D$ −153 (*c* 0.34, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.76 (s, 1H), 7.03 (s, 1H), 6.53 (d, J = 3.6 Hz, 1H), 4.22 (m, 1H), 3.68 (dd, J = 10.8, 3.8 Hz, 1H), 3.50 (dd, J = 10.9, 8.1 Hz, 1H), 3.38 (d, J = 8.0 Hz, 1H), 2.95 (dd, J = 15.3, 8.2 Hz, 1H), 2.85 (dd, J = 15.4, 2.1 Hz, 1H), 2.73 (s, 3H), 2.48 (d, J = 7.3 Hz, 2H), 2.37 (m, 1H), 2.18 (s, 3H), 1.66 (m, 2H), 1.47 (m, 2H), 1.30 (m, 8H), 1.06 (d, J = 6.6 Hz, 6H), 0.90 (m, 6H); MS (EI) *m*/*z* 455 (M^+); HRMS found *m*/*z* 455.3146 (M^+), $C_{27}H_{41}N_3O_3$ requires 455.3148.

(*S*)-3-(4-Hydroxy-2-nitrophenyl)-2-[(methoxycarbonyl)amino]-1-propanol (34). After nitration of **15** according to the procedure as described above, the generated mixture of **16** and **17** (1.5 g, 3.6 mmol) was dissolved in 30 mL of methanol and 30 mL of 1 N H_2SO_4. The resultant solution was heated at 70 °C for 1 day, and then methanol was removed via rotavapor. The aqueous solution was cooled to 0 °C, and $NaNO_2$ (262 mg, 3.8 mmol) was added. After the stirring was continued for 30 min, 0.5 mL of 30% H_3PO_2 was added. The solution was heated at 70 °C for 5 h, and then the cooled solution was extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (2/1 ethyl acetate/petroleum ether as eluent) of the residual oil afforded 601 mg (61%) of **34**: $[\alpha]^{21}_D$ −17.1 (*c* 0.62, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.51 (d, J = 2.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.4, 2.6 Hz, 1H), 4.09 (m, 1H), 3.75 (m, 2H), 3.70 (s, 3H), 3.15 (dd, J = 13.8, 4.4 Hz, 1H), 2.71 (dd, J = 13.8, 9.8 Hz, 1H); MS (EI) *m*/*z* 271 (M^+ + H^+); HRMS found *m*/*z* 270.0852 (M^+), $C_{11}H_{14}N_2O_6$ requires 270.0851.

(*S*)-3-(5-Iodo-4-hydroxy-2-nitrophenyl)-2-[(methoxycarbonyl)amino]-1-propanol (35). A mixture of **16** (100 mg, 0.24 mmol), 5 mL of methanol, and 3 mL of 2 N H_2SO_4 was heated at 70 °C for 16 h. Methanol was removed by rotavapor, and the remaining aqueous solution was cooled to 0 °C. To this stirring solution was added $NaNO_2$ (20 mg, 0.28 mmol). After the stirring was continued for 30 min, KI (120 mg, 0.72 mmol) was added, and the resultant mixture was heated at 70 °C for 5 h. Extraction workup followed by column chromatography (2/1 ethyl acetate/petroleum ether as eluent) afforded 43 mg (45%) of **35**: $[\alpha]^{21}_D$ −55 (*c* 0.35, CH_3OH); ^{1}H NMR (300 MHz, CD_3COCD_3) δ 7.91 (s, 1H), 7.47 (s, 1H), 6.28 (d, J = 9.2 Hz, 1H), 3.92 (m, 1H), 3.60 (d, J = 5.0 Hz, 2H), 3.47 (s, 3H), 3.25 (dd, J = 14.0, 4.3 Hz, 1H), 2.80 (dd, J = 13.9, 10.0 Hz, 1H); MS (EI) *m*/*z* 396 (M^+); HRMS found *m*/*z* 395.9808 (M^+), $C_{11}H_{13}N_2O_6I$ requires 395.9818.

(*S*)-3-(4-Hydroxy-3-iodo-2-nitrophenyl)-2-[(methoxycarbonyl)amino]-1-propanol (36). Following the procedure for preparing **35** from **16**, **36** was obtained from **17** in 42% yield: $[\alpha]^{21}_D$ −29.3 (*c* 0.35, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.51 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.18 (dd, J = 8.4, 2.4 Hz, 1H), 4.08 (m, 1H), 3.73 (m, 2H), 3.70 (s, 3H), 3.38 (dd, J = 13.8, 4.5 Hz, 1H), 2.71 (dd, J = 13.8, 9.5 Hz, 1H); MS (EI) *m*/*z* 396 (M^+); HRMS found *m*/*z* 395.9821 (M^+), $C_{11}H_{13}N_2O_6I$ requires 395.9818.

(*S*)-3-(4-Benzoxy-2-nitrophenyl)-2-[(methoxycarbonyl)amino]-1-propanol (37). To a solution of **34** (600 mg, 2.22 mmol) and K_2CO_3 (612 mg, 4.44 mmol) in 20 mL of DMF was added benzyl bromide (456 mg, 2.67 mmol) in a dropwise manner. After the reaction mixture was heated at 50 °C for 2 h, DMF was removed in vacuo. The residue was partitioned between 100 mL of ethyl acetate and 20 mL of water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography (2/1 ethyl acetate/petroleum ether as eluent) to provide 720 mg (90%) of **37**: $[\alpha]^{18}_D$ +9.3 (*c* 0.2, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 2.6 Hz, 1H), 7.38 (m, 6H), 7.17 (dd, J = 8.4, 2.6 Hz, 1H), 5.24 (d, J = 7.6 Hz, 1H), 5.10 (s, 2H), 3.98 (m, 1H), 3.70 (m, 2H), 3.60 (s, 3H), 3.11 (dd, J = 13.8, 6.1 Hz, 1H), 2.73 (dd, J = 13.8, 9.1 Hz, 1H); MS (EI) *m*/*z* 361 (M^+ + H^+). Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 7.77; N,5.59. Found: C, 59.75; H, 7.49; N, 5.64.

(2*S*)-*N*-[5-Benzoxy-2-[(*S*)-2-(*tert*-butoxycarbonyl)amino-3-hydroxypropyl] phenyl]valine Benzyl Ester (38). Following the procedure for synthesizing **23** from **21b**, **38** was obtained from **37** in 64% yield: $[\alpha]^{21}_D$ −92.2 (*c* 0.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 5H), 7.29 (m, 5H), 7.00 (d, J = 8.2 Hz, 1H), 6.33 (dd, J = 8.2, 2.4 Hz, 1H), 6.24 (d, J = 2.4 Hz, 1H), 5.34 (d, J = 8.2 Hz, 1H), 5.10 (AB q, J = 12.0 Hz, 2H), 4.94 (AB q, J = 11.6 Hz, 2H), (d, J = 8.5 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 3.76 (m, 1H), 3.49 (m, 2H), 3.42 (s, 3H), 3.53 (d, J = 8.1 Hz, 1H), 3.44 (d, J = 8.7 Hz, 1H), 2.79 (dd, J = 13.8, 4.8 Hz, 1H), 2.70 (dd, J = 13.8, 9.8 Hz, 1H), 2.12 (m 1H), 1.04 (d, J = 7.1 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H); MS (EI) *m*/*z* 520 (M^+); HRMS found *m*/*z* 520.2545 (M^+), $C_{30}H_{36}N_2O_6$ requires 520.2574.

(*S*,*S*)-9-Benzoxybenzolactam-V8 (39). A mixture of **38** (180 mg, 0.35 mmol), 6 mL of methanol, and 3 mL of 2 N KOH was heated at 70 °C for 1 day. The cooled solution was neutralized with 2 N HCl to pH 7 and then concentrated. The residual solid was dried in vacuo for 1 day before it was dissolved in 10 mL of DMF. To this solution were added triethylamine (97 μM, 0.73 mmol) and DPPA (90 μM, 0.42 mmol) at 0 °C. After the stirring was continued for 1 h at 0 °C and 17 h at room temperature, DMF was evaporated at reduced pressure. The residue was partitioned between 50 mL of ethyl acetate and 10 mL of water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residual oil was chromatographed (2/1 ethyl acetate/petroleum ether as eluent) to provide 100 mg (82%) of cyclization product, which was subjected to reduction methylation following the procedure for preparing **32** from **31** to provide **39** in 95% yield: $[\alpha]^{21}_D$ −279.2 (*c* 0.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H), 6.94 (d, J = 8.3 Hz, 1H), 6.61 (m, 2H), 6.49 (dd, J = 8.3, 2.5 Hz, 1H), 5.02 (s, 2H), 3.92 (m, 1H), 3.68 (m, 1H), 3.52 (m, 1H), 3.49 (d, J = 9.1 Hz, 1H), 3.03 (m, 1H), 2.98 (m, 1H), 2.76 (s, 3H), 2.68 (m, 1H), 2.41 (m, 1H), 1.04 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); MS (EI) *m*/*z* 368 (M^+); HRMS found *m*/*z* 368.2101 (M^+), $C_{22}H_{28}N_2O_3$ requires 368.2105.

(*S*,*S*)-9-Decynylbenzolactam-V8 (4). Following the procedure for preparing **26** from **25**, **4** was obtained from **39** in 80% overall yield: $[\alpha]^{19}_D$ = −140.6 (*c* 0.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 1.3 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.89 (dd, J = 7.8, 1.3 Hz, 1H), 6.51 (m, 1H), 3.95 (br s, 1H), 3.71 (dd, J = 10.6, 3.9 Hz, 1H), 3.53 (dd, J = 10.6, 9.1 Hz, 1H), 3.09 (dd, J = 17.0 Hz, 7.8 Hz, 1H), 2.79 (s, 3H), 2.74 (m, 1H), 2.51 (m, 1H), 2.38 (t, J = 7.1 Hz, 2H), 1.60 (m, 2H), 1.45 (m, 2H), 1.29 (m, 8H), 1.05 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H). MS (EI) *m*/*z* 398 (M^+); HRMS found *m*/*z* 398.2928 (M^+), $C_{25}H_{38}N_2O_2$ requires 398.2934.

Acknowledgment. We are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (Grant 29725205), and Qiu Shi Science & Technologies Foundation for their financial support.

Supporting Information Available: ^{1}H NMR spectra of compounds **4**, **16**, **24**, **26**, **32**−**36**, and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990605H