Effect of Alteration of the Heterocyclic Nucleus of ILV on Its Isoform Selectivity for PKC. Palladium-Catalyzed Route to Benzofuran Analogues of ILV

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Abstract: The discovery of isoform-selective modulators of protein kinase C (PKC) appears worthwhile in further defining the roles of the individual PKC isoforms in cell type-specific processes. In comparison with the phorbol esters, little information is available regarding the isoform selectivity of the teleocidin family. Blumberg has reported recently that 7-*n*-octylindolactam V exhibits little if any selectivity for the isoforms tested. In order to probe the possibility of developing isotype-selective agents based on the indolactam V (ILV) structure, we sought to explore replacement of the indole nucleus by a benzofuran ring. Herein we describe a novel palladium-catalyzed route to four benzofuran analogues **11a-d** of ILV together with details of their isoform selectivity. Of considerable interest is the unexpected finding that this subtle N to O structural change leads to a compound (**11b**) that is modestly more like 12,13-dibutyrate phorbol and less like *n*-octyl-ILV in its pattern of activity. Moreover, the effect of introducing an additional stereocenter at C-14 into these benzofurans was explored, and a clear preference for *R*-stereochemistry at the C-14 center of the teleocidin family was found, thus providing additional verification of previously published structural correlations between the families of PKC activators. Overall, the present findings provide an important new direction in the quest for isoform-selective activators of PKC.

Introduction

Molecular cloning analysis has revealed that the calcium/phospholipid-dependent protein kinase C (PKC) is comprised of a family of at least ten individual isoforms. According to their structural organization and their sensitivity to Ca^{2+}, these isoforms have been classified into three groups: the classical PKCs (α, βI, βII, and γ) require Ca^{2+} for full activation, while the new PKCs (δ, ϵ, η, and θ) and atypical PKCs (ζ, λ) are Ca^{2+} independent.[1] The different tissue distribution and subtle differences in enzymologic properties and substrate specificities, together with the finding that more than one isoform is expressed at different levels in a single cell type, suggest that each of these different distinct enzymes may play a specific role in cell type-specific processes like endocytosis, secretion, transmission of electric potentials, growth, or differentiation.[1,2] While much attention has focused on the elucidation of the roles of the individual PKC isoforms in the past few years, this research has been hindered by the lack of small molecules that can selectively activate or inhibit either the individual isoforms or a small group of these isoforms.[1,2]

Physiologically, PKC is activated by diacylglycerols (DAGs), which result from the agonist-induced hydrolysis of membrane phospholipids.[1,3] The DAG drives the translocation of the inactive, cytoplasmic PKC to the membrane, where it interacts with other phospholipids such as phosphatidylserine and becomes fully activated. Several complex natural products and their derivatives like the phorbol esters, bryostatins, and teleocidins including indolactam V (ILV) can mimic DAG to activate PKC at low concentrations.[4] However, unlike DAG, these molecules can cause depletion, or down-regulation, of cellular PKC through its prolonged activation.[4]

Preliminary studies have shown that these ligands exhibit some differential isoform selectivity for binding *in vitro* and cause differential isoform translocation and down-regulation *in vivo*.[5,6] For example, the mezerein analogue thymeleatoxin showed 20-fold lower affinity for PKCϵ than for PKCβ. In

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contrast, phorbol 12,13-dibutyrate (PDBu) showed a 5-fold spread in affinities, and DAG showed only a 1.7-fold difference between these isoforms.[6] Bryostatin 1 has been shown to induce the selective translocation of the βII isoform of PKC from cytosol to the nuclear membrane, while phorbol 12,13-dibutyrate (PDBu) fails to translocate either the α or βII isoforms to the nuclear membrane in HL-60 cells.[7] Likewise, bryostatin 1 induces a more rapid down-regulation of PKCα, but not PKCε, than does 12-13-acetate-*O*-tetradecanoylphorbol (TPA) in SH-SY5Y cells,[8a] and in NIH 3T3 fibroblasts, high concentrations of bryostatin 1 both fail to down-regulate PKCδ from the particulate fraction, unlike TPA, and actually protect PKCδ against down-regulation by TPA.[8b] On the basis of its unique pattern of response, bryostatin 1 is now in clinical trials for cancer. The discovery of other isoform-selective agents thus appears worthwhile in further defining the roles of the PKC isoforms as well as in generating new agents for cancer chemotherapy.

In comparison with the phorbol esters, little information is available regarding the isoform selectivity of the teleocidin family. Blumberg has reported recently that 7-*n*-octylindolactam V exhibits little if any selectivity for the isoforms tested.[6] In order to probe the possibility of developing isotype-selective agents based on the ILV structure,[9] we chose to explore the effect of replacing the indole nucleus by a benzofuran ring. Additionally, within this benzofuran series, we felt that it would be of interest to probe the stereochemical consequences of introducing an additional stereocenter at C-14, since previously it has been shown that introduction of a methyl group at the *sn*-3 position of DAG led to an "unanticipated stereospecificity".[4b] While the replacement of the indole ring of ILV by a benzofuran represents a rather minor structural change, it is important to note here that the effect of such a bioisosteric replacement on isotype selectivity in other biological systems has not been widely examined. A recent report does, however, reveal that the N to O change in the case of serotonin leads to altered receptor subtype selectivity.[10]

Furthermore, through the use of computer-assisted molecular modeling studies, several pharmacophore hypotheses have been put forth concerning the key functional groups of the various families of PKC activators that are considered essential for activity. Although there exists some controversy in the modeling area, one of the more reasonable correlations suggests that the indole-ring nitrogen of the teleocidin family, as well as the 19-OH of bryostatin 1, the 9-OH of the phorbol esters, and the oxygen atom of the C-27 carbonyl group of DAT (debromoaplysiatoxin) serve as H-bond acceptors, while the 14-OH group of the teleocidin family as well as the 26-OH of bryostatin I, the 20-OH of the phorbol esters, and the 30-OH of DAT may function as H-bond donors in their interaction with the regulatory domain of PKC (see Figure 1 for the structures of these natural products).[4] While the possibility that the indole nitrogen of teleocidin actually serves as an acceptor can be questioned, it clearly does not function as an essential donor group, since *N*-prenylation or *N*-geranylation have been shown to increase PKC activity.[19] Accordingly, we anticipated that the benzofuran analogue of ILV would still possess PKC activating ability, although perhaps altered subtype selectivity.

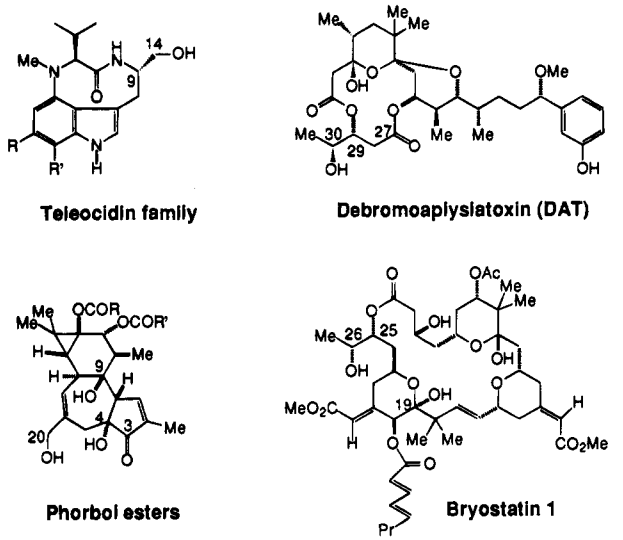

Figure 1. Structures of some known PKC activators.

Herein we describe syntheses of four benzofuran analogues of *n*-hexyl-ILV and the results of their biological evaluation including isotype selectivity.

Chemical Synthesis

As detailed in the accompanying schemes, the benzofuran analogues **11a−d** were assembled enantioselectively, starting from the *N*-pivaloyl derivative of *m*-anisidine (**1**), which was converted to the bromide **2** through the directed *ortho*-metalation reaction.[12] The Friedel−Crafts reaction of **2** with *n*-hexanoyl chloride at 70 °C for 2 days was accompanied by *O*-demethylation and afforded ketone **3** in 41% yield, together with ester **4** (44% yield) as the major side product. After failure to reduce the acyl group to an alkyl group by use of H_2/catalyst or LAH/$AlCl_3$, we found that treatment of **3** with ethyl chloroformate followed by reduction with $NaBH_4$ gave the desired product **5** in excellent yield.[13] The pivaloyl protecting group was then removed by refluxing **5** in HCl/ethanol to afford **6b**. On the other hand, the hydrolysis of ester **4** provided 2-bromo-3-aminophenol (**6a**) (Scheme 1). Next, these aminophenol derivatives were reacted with the D-serine- or D-threonine-derived allyl alcohols **7a** or **7b** under the Mitsunobu conditions to produce **8** in 63−78% yield. Preparation of the required allylic alcohols **7a** and **7b** was carried out starting from the aldehydes **12a** and **12b**[14] by the standard sequence of operations detailed in Scheme 2. Subjection of the ether derivatives **8a−c** to Larock's intramolecular cyclization protocol employing Jeffrey's palladium catalyst system and sodium formate as the reducing agent led in turn to the benzofurans **9a−c** in 79−83% yield (Scheme 3).[15] This key operation proceeds markedly well and provides an important strategy for assembling optically pure benzofurans. Next, the reaction of **9a−c** with the D-valine-derived triflate **13** was carried out under basic conditions to afford compounds **10a−c** in ~76% yield.[16] Lastly, the three

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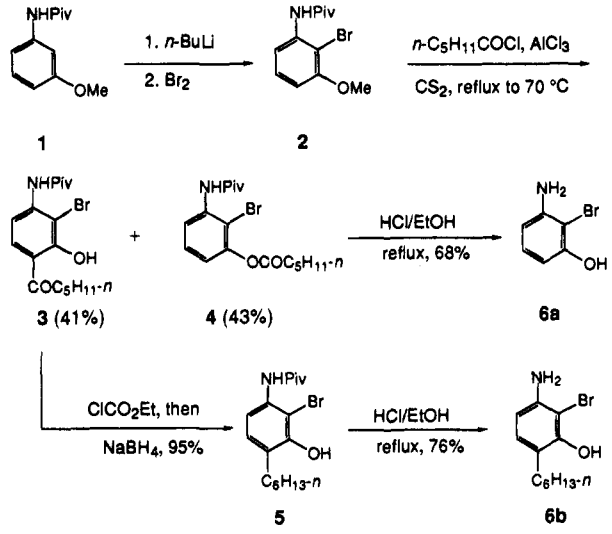
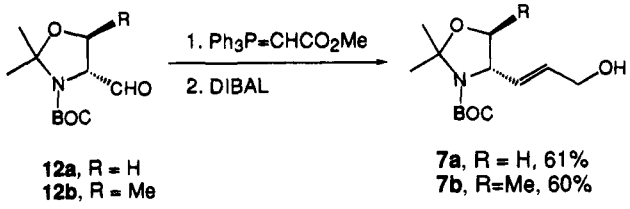
Scheme 1. Synthesis of the Aminophenol Precursors **6a** and **6b**



Scheme 2. Synthesis of the Amino Acid Derived Allylic Alcohols **7a** and **7b**



protecting groups of **10a**–**c** were removed in a one-pot operation by Pd/C-catalyzed hydrogenation and hydrolysis with a 1:1 mixture of concentrated HCl and ethanol. The resulting amino acid hydrochlorides were immediately treated with (benzotriazol-1-yloxy)(tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent), 1-hydroxybenzotriazole hydrate (HOBt), and *N*-methylmorpholine in DMF to generate the lactam ring, and then the amine nitrogen was *N*-methylated to furnish the final structures **11a**–**c**. Application of the Mitsunobu inversion protocol to **11b** using acetate as the nucleophile followed by base hydrolysis provided access to the C-14-inverted isomer **11d** (Scheme 4).

Owing to their biological activity, ILV and its analogues have over the past decade served as attractive synthetic targets.[11] Although several stereospecific routes to ILV have been completed,[11,16] syntheses of the more potent 7-substituted ILV analogues have only been accomplished by using ethyl 3-bromo-2-hydroxyiminopropanoate to introduce the aminopropanol side chain at the 3-position of the indole ring. This reaction proceeds in modest yield (50–60%) and requires reduction of the imino group, which leads to a mixture of epimers in a 1:1 ratio.[11] In comparison, the chemistry detailed above for the synthesis of the 7-substituted benzofuran analogues of ILV is relatively efficient, for only eight operations requiring workup are needed. Both asymmetric centers present in these analogues are introduced with the correct absolute stereochemistry by using amino acids as starting materials. Moreover, the use of threonine in place of serine provides ready access to the C-14 methyl-bearing analogues **11c** and **11d**, thus allowing us to explore the importance of this additional stereocenter to PKC activity.[4b] While we had previously attempted to prepare the analogous C-14 methyl-bearing analogues of ILV through oxidation of its hydroxyl group to aldehyde followed by addition of a methyl organometallic, the aldehyde intermediate proved difficult to work with due to its instability.[17]

Biological Evaluation and Discussion. Compound **11a** was evaluated for its ability to displace [^{3}H]PDBu binding to recombinant PKCα using the same protocols described elsewhere.[6] It was found to exhibit a potency nearly identical to that of ILV; the K_i of **11a** was 17.30 ± 3.70 nM, compared to 10.96 ± 1.32 nM for ILV.[6] In view of the high affinity found for the parent structure **11a**, its 7-substituted counterpart **11b** was evaluated more extensively for its ability to inhibit [^{3}H]-PDBu binding to recombinant PKCα, PKCβ, PKCγ, PKCδ, and PKCε employing the standard experimental protocols.[6] Compound **11b** exhibited modestly weaker affinity for PKCδ (12.3 ± 3.4 nM, n = 3), PKCε (8.0 ± 2.1 nM, n = 3), and PKCγ (6.4 ± 0.5 nM, n = 3) than for PKCα (4.0 ± 0.7 nM, n = 6) and PKCβI (2.3 ± 0.5 nM, n = 3). The comparative K_i values for (−)-*n*-octyl-ILV[6] are 0.53 ± 0.06 (PKCα), 0.39 ± 0.06 (PKCβI), 1.19 ± 0.33 (PKCγ), 0.77 ± 0.08 (PKCδ), and 0.95 ± 0.09 (PKCε); for PDBu, these values are 0.15 ± 0.02 (PKCα), 0.14 ± 0.01 (PKCβI), 0.37 ± 0.03 (PKCγ), 0.71 ± 0.10 (PKCδ), and 0.63 ± 0.07 (PKCε).[6] Compound **11b** was also shown to stimulate PKC enzymatic activity to the same maximal extent as PDBu.

On the other hand, the 14-(*S*)-analogue **11c** exhibited relatively poor affinity for PKCα (5710 ± 260 nM), while its 14-(*R*)-epimer **11d** displayed a binding affinity (9.56 ± 1.52 nM, n = 3) comparable to that of the parent compound **11b**. The binding affinities of **11d** for the other isoforms are the following: 11.24 ± 1.56 (PKCβI, n = 3), 23.36 ± 0.20 (PKCγ, n = 3), 41.37 ± 0.11 (PKCδ, n = 3), and 30.20 ± 4.07 (PKCε, n = 3). The binding of **11c** to PKCδ and ε was also examined and found to be 33.2 ± 8.7 μM (n = 3) and 20.7 ± 3.9 μM (n = 3), respectively.

The relative affinities of benzofurans **11b** and **11d**, PDBu, and (−)-7-*n*-octyl-ILV for the different PKC isoforms are shown in graphical form in Figure 2. These results indicate that the benzofuran analogues exhibit a *pattern of activity* which is modestly more like that for PDBu and less like that for 7-*n*-octyl-ILV and ILV.[6] Thus, our idea of pursuing further structural modifications of ILV in order to obtain agents exhibiting improved levels of isoform selectivity appears to be reasonably well founded.

Through both computer modeling studies and experimental findings, the putative pharmacophoric elements responsible for the binding of various families of PKC activators to PKCs regulatory domain have been identified. In some of this work, it has been suggested that the indole-ring nitrogen of the teleocidin family constitutes one of the key hydrophilic atoms essential for PKC activation.[4] However, in view of our work and the recent work reported by Endo *et al.* regarding the activity of an 8-membered benzolactam analogue of ILV which lacks this particular heteroatom, it is clear that the indole nitrogen cannot be viewed as entirely essential for PKC activation. Our results taken together with those of Endo would suggest that the ring heteroatom plays some sort of accessory role in its interaction with PKC and in particular that it has a (modest) role in isoform selectivity. While this result is somewhat unexpected and may be related to differences in the hydrogen bond donor/acceptor character of N and O, a more complete understanding of the subtleties of the molecular recognition

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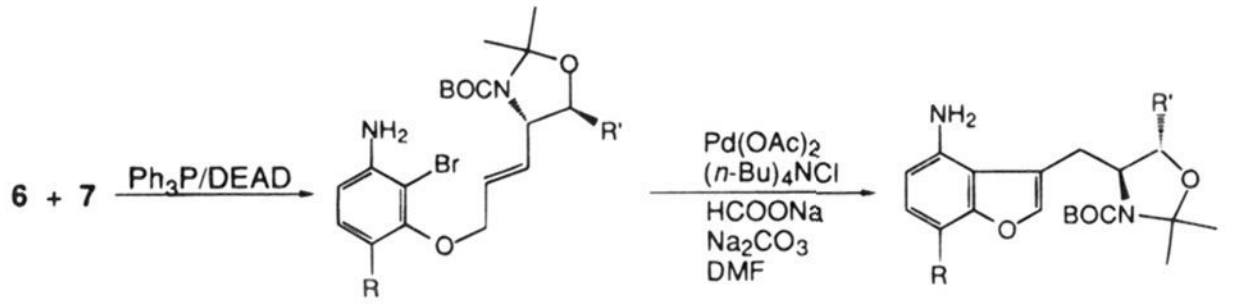
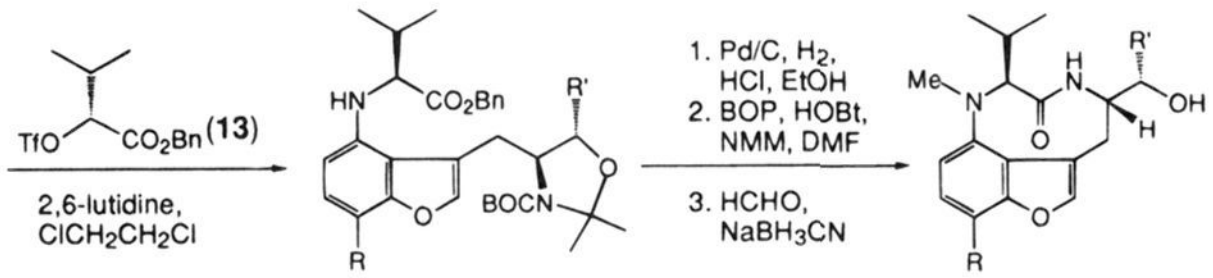
Scheme 3. Completion of the Palladium-Catalyzed Benzofuran Synthesis



8a, R = R' = H, 78%
8b, R = *n*-hexyl, R' = H, 75%
8c, R = *n*-hexyl, R' = Me, 63%

9a, R = R' = H, 79%
9b, R = *n*-hexyl, R' = H, 83%
9c, R = *n*-hexyl, R' = Me, 81%



10a, R = R' = H, 76%
10b, R = *n*-hexyl, R' = H, 76%
10c, R = *n*-hexyl, R' = Me, 75%

11a, R = R' = H, 61%
11b, R = *n*-hexyl, R' = H, 63%
11c, R = *n*-hexyl, R' = Me, 61%

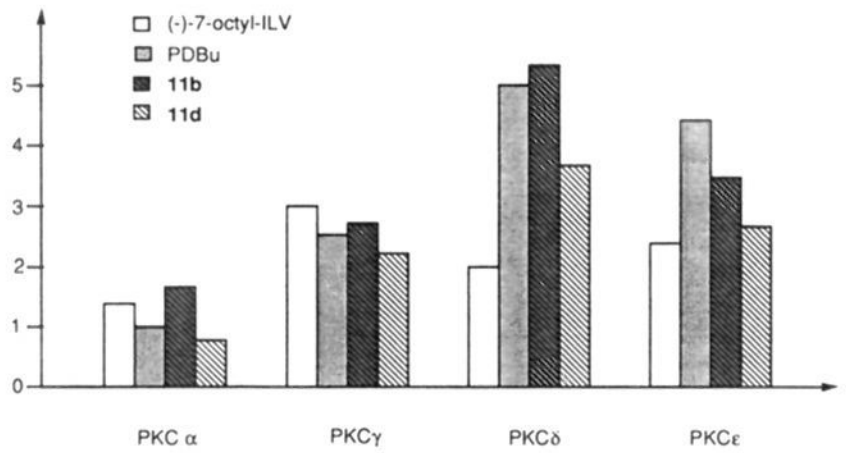
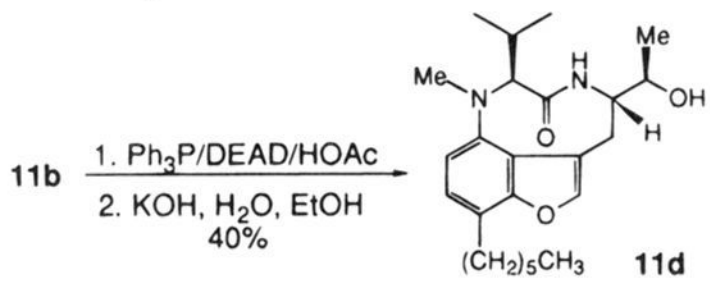


Figure 2. Relative affinities of PKC ligands for the different PKC isoforms. Affinities of the different ligands for each PKC isoform are expressed as the ratio to those for PKCβI.

Scheme 4. Preparation of the C-14-Inverted Stereoisomer



11d

process at the atomic level will require detailed NMR/X-ray studies of the individual complexes formed from these small molecules and the various isotypes of PKC.[6]

As mentioned above, the 14-(*S*)-analogue **11c** exhibited relatively poor affinity for PKCα, while its 14-(*R*)-epimer **11d** displayed a binding affinity comparable to that of the parent compound **11b**. This result establishes the stereochemical requirement for PKC binding at the C-14 position of the teleocidin family as *R*. The difference between the affinities of the 14-(*S*) and 14-(*R*) isomers is thus substantial, namely approximately 600-fold. Interestingly, this stereochemistry matches that of the C-30 center of debromoaplysiatoxin, the C-26 position of bryostatin 1, and the *sn*-3 position of 3-methyl-DAG,[4b] thus providing further evidence for the correlation of these centers in their interaction with PKC.

Conclusions

The present study reveals that the benzofuran analogues of ILV activate PKC with a slightly different pattern of isotype selectivity than ILV or 7-*n*-octyl-ILV. Additionally, this work establishes a clear preference for *R*-stereochemistry at the C-14 center of the teleocidin family, thus providing additional verification of previously published structural correlations between the families of PKC activators. Further efforts aimed at the development of isotype-selective PKC activators will be reported in due course.

Experimental Section

2-Bromo-*N*-pivaloyl-3-methoxyaniline (2). To a solution of *N*-pivaloyl-3-methoxyaniline (**1**, 20.0 g, 96.6 mmol) in 200 mL of THF was added dropwise *n*-BuLi (2.5 M in *n*-hexane, 250 mmol) at 0 °C. The resulting solution was stirred at this temperature for 2.5 h and then cooled to −78 °C. Bromine (19.8 g, 125 mmol) was added dropwise over 45 min. After the addition was completed, the solution was stirred for 1 h at −78 °C and then slowly warmed to room temperature. The mixture was partitioned between 300 mL of water and 500 mL of ether, and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation under reduced pressure followed by column chromatography eluting with 10% ethyl acetate/*n*-hexane afforded 22.5 g (76%) of **2** as a yellow oil: IR (neat) 3318, 1695, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00 (s, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.29 (dd, J = 7.5, 7.6 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 3.89 (s, 3H), 1.37 (s, 9H); MS *m/z* 287 (M^+, ^{81}Br), 285 (M^+, ^{79}Br), 244, 242, 206, 173, 158, 121, 106, 57.

Friedel−Crafts Reaction of 2. To a stirred solution of **2** (10.5 g, 36.9 mmol) and hexanoyl chloride (14.8 g, 110.6 mmol) in 100 mL of carbon disulfide was added anhydrous aluminum chloride (19.7 g, 147.5 mmol) in four portions over 10 min. The suspension was heated at reflux for 3 h, the reflux condenser was turned downward, and the carbon disulfide was distilled off. The remaining mixture was heated

at 70 °C for 2 days. After being cooled to room temperature, the thickened mixture was poured onto 300 g of ice containing 30 mL of concentrated hydrochloric acid, and 500 mL of ether was added. The organic layer was separated, washed with water (3 × 200 mL), 0.5 N NaOH (100 mL), and brine, and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the remaining oil was loaded onto a silica gel column. The column was eluted with 10% ethyl acetate/*n*-hexane, and the solvent was evaporated under reduced pressure to afford 6.03 g (41%) of ketone **3** together with 6.11 g (44%) of ester **4**.

Ketone 3: IR (neat) 3374, 3327, 2957, 1669, 1639, 1535, 1506 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 12.05 (s, 1H), 8.39 (s, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 2.96 (t, J = 7.4 Hz, 2H), 1.38 (m, 2H), 1.36 (s, 9H), 1.33 (m, 4H), 0.91 (t, 3H); MS *m/z* 371 (M^+, ^{81}Br), 369 (M^+, ^{79}Br), 298, 290, 234, 186, 158, 106, 57; HRMS calcd for $C_{17}H_{24}NO_3Br$ (M^+, ^{79}Br) 369.094, found 369.092.

Ester 4: IR (neat) 3418, 3294, 2958, 2877, 1770, 1698, 1586, 1521, 1489 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (d, J = 7.6 Hz, 1H), 8.05 (br s, 1H), 7.29 (dd, J = 7.6, 7.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 2.64 (t, J = 7.8 Hz), 1.82 (m, 2H), 1.56−1.12 (m, 4H), 1.35 (s, 9H), 0.89 (t, 3H); MS *m/z* 371 (M^+, ^{81}Br), 369 (M^+, ^{79}Br), 301, 299, 246, 220, 206, 162, 136, 108, 57.

2-Bromo-4-*n*-hexyl-3-hydroxy-*N*-pivaloylaniline (5). To a solution of ketone **3** (2.53 g, 6.85 mmol) and triethylamine (1.15 mL, 8.22 mmol) in 40 mL of THF was added at 0 °C ethyl chloroformate (0.78 mL, 8.2 mmol) dropwise from a syringe over 15 min. The resulting suspension was stirred for an additional 30 min at this temperature and then filtered with suction. The salt was washed with THF (2 × 10 mL), and the combined filtrates were added to a solution of sodium borohydride (1.0 g, 26.4 mmol) in 30 mL of water at 5−15 °C over 40 min. After the solution was stirred for 3 h at room temperature, THF was removed by rotary evaporation, and the residue was partitioned between 200 mL of ether and 50 mL of 2 N HCl. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Removal of solvent followed by column chromatography eluting with 5% ethyl acetate/*n*-hexane afforded 2.11 g (87% yield) of **5** as a yellow oil: IR (neat) 3420, 3338, 2957, 1682, 1520 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 8.4 Hz, 1H), 7.74 (br s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 5.49 (s, 1H), 2.62 (t, J = 7.5 Hz, 1H), 1.57 (m, 2H), 1.30 (s, 9H), 1.25 (m, 6H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 176.6, 149.9, 133.8, 129.3, 126.1, 113.9, 103.3, 40.2, 30.4, 29.6, 29.1, 27.7, 22.6, 14.2; MS *m/z* 357 (M^+, ^{81}Br), 355 (M^+, ^{79}Br), 228, 226, 202, 200, 174, 148, 93, 57, 41; HRMS calcd for $C_{17}H_{26}NO_2Br$ (M^+, ^{79}Br) 355.115, found 355.113.

2-Bromo-4-*n*-hexyl-3-hydroxyaniline (6b). A solution of amide **5** (5.38 g, 15.1 mmol) in 75 mL of saturated ethanolic HCl solution was heated at 80 °C for 12−18 h until no starting material was detected by TLC. The solvent was removed by rotary evaporation, and the residual oil was poured into 100 mL of water. $NaHCO_3$ powder was added with caution to neutralize the solution, and then 500 mL of ether was added. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography eluting with 10% ethyl acetate/*n*-hexane followed by evaporation of the solvent under reduced pressure afforded 3.05 g (74%) of **6b** as a yellow oil: IR (neat) 3522, 3379, 2926, 2858, 1620, 1499, 1249, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.85 (d, J = 8.1 Hz, 1H), 6.32 (d, J = 8.1 Hz, 1H), 5.43 (br s, 1H), 3.95 (br s, 2H), 2.55 (t, J = 7.4 Hz, 2H), 1.55 (m, 2H), 1.26−1.31 (m, 6H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 150.4, 142.5, 129.2, 119.6, 107.4, 99.2, 31.8, 30.0, 29.1, 22.7, 14.1; MS *m/z* 273 (M^+, ^{81}Br), 271 (M^+, ^{79}Br), 202, 200, 174, 172, 135, 93, 65, 41; HRMS calcd for $C_{12}H_{18}NOBr$ (M^+, ^{79}Br) 271.057, found 271.056.

2-Bromo-3-hydroxyaniline (6a). A solution of ester **4** (8.37 g, 15.1 mmol) in 75 mL of saturated ethanolic HCl was heated at 80 °C for 6 to 12 h until no more starting material was detected by TLC. The solvent was removed by rotary evaporation, and the residual oil was poured into 100 mL of water. $NaHCO_3$ powder was added with caution to neutralize the solution, and then 500 mL of ether was added. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography eluting with 10% ethyl acetate/*n*-hexane followed by evaporation of the solvent under reduced pressure afforded 2.51 g (61%) of **6a** as a yellow oil: IR (neat) 3528, 3381, 2926, 2858, 1623, 1499, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.93 (t, J = 7.8 Hz, 1H), 6.42 (d, J = 7.8 Hz, 1H), 6.36 (d, J = 7.8 Hz, 1H), 5.3 (br s, 1H), 4.3 (br s, 2H); MS *m/z* 189 (M^+, ^{81}Br), 187 (M^+, ^{79}Br), 158, 108, 80.

Wittig Reaction of Aldehyde 12. A mixture of aldehyde **12a** (14.2 g, 62.0 mmol) and methyl (triphenylphosphoranylidene)acetate (20.7 g, 62.0 mmol) in 300 mL of benzene was stirred for 8−12 h at room temperature. The solution was concentrated to ca. 100 mL, and the residue was loaded onto a column of silica gel. Elution with 10% ethyl acetate/*n*-hexane followed by evaporation afforded 15.4 g (86%) of the unsaturated ester as a mixture of trans and cis isomers (ca. 94/6): $[\alpha]^{22}_D$ +62° (*c* 0.27, $CHCl_3$); IR (neat) 2982, 1730, 1697, 1456, 1384, 1281 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.85 (m, 1H), 5.93 (m, 1H), 4.56−4.41 (m, 1H), 4.08 (dd, J = 6.1, 9.2 Hz), 3.07 (dd, J = 2.2, 9.1 Hz, 1H), 3.75 (br s, 3H), 1.64−1.41 (m, 15H); MS *m/z* 270 (M^+ − Me), 229, 214, 170, 128, 96, 57.

Following a similar procedure, the ester was obtained from aldehyde **12b** in 84% yield as a mixture of trans and cis isomers (ca. 94/6): $[\alpha]^{22}_D$ +46° (*c* 0.21, EtOAc); IR (neat) 2981, 2727, 1698, 1381 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.76 (m, 1H), 5.88 (m, 1H), 3.88−3.79 (m, 2H), 3.73 (s, 3H), 1.60 (s, 3H), 1.51 (s, 3H), 1.38 (br s, 9H), 1.27 (d, J = 7.6 Hz); MS *m/z* 284 (M^+ − Me), 228, 184, 142, 110, 57.

Preparation of the Allylic Alcohol 7a. To a stirred solution of the above ester derived from **12a** (15.2 g, 53.3 mmol) in 200 mL of toluene was added dropwise diisobutylaluminum hydride (1 M in *n*-hexane, 175 mmol) at −60 °C. After the addition was completed, the resulting solution was stirred for 3 h at −60 to −40 °C and then cooled to −78 °C. MeOH (10 mL) was added slowly to destroy the excess of the reagent. The cooled solution was poured into 500 mL of ice water containing 50 mL of concentrated HCl. Ether extraction (3 × 400 mL) followed by column chromatography eluting with 33% ethyl acetate/*n*-hexane afforded 8.32 g (61%) of the allylic alcohol **7a** as a mixture of trans and cis isomers (ca. 93/7): $[\alpha]^{22}_D$ +23.1° (*c* 0.74, EtOAc); IR (neat) 3445, 2980, 1696, 1392, 1255, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.78−5.63 (m, 2H), 4.40−4.28 (m, 1H), 4.11 (m, 2H), 4.02 and 3.72 (ABq, J = 9.0 Hz, 2H, A part split into d with J = 6.3 Hz, B part split into d with J = 2.1 Hz), 3.91 (br s, 1H), 1.58−1.42 (m, 15 H); MS *m/z* 242 (M^+ − Me), 201, 186, 142, 124, 83, 57.

Following a similar procedure, **7b** was prepared form the corresponding ester in 61% yield as a mixture of trans and cis isomers (ca. 93/7): $[\alpha]^{22}_D$ +10.5° (*c* 0.54, EtOAc); IR (neat) 3435, 2980, 2935, 1696, 1479, 1367, 1255, 1172, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.72 and 5.50 (ABq, J = 15.0 Hz, 2H, B part split into d with J = 7.5 Hz), 4.10 (m, 2H), 3.93−3.74 (m, 3H), 1.46−1.40 (m, 15 H), 1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 152.3, 131.8, 130.0, 93.9, 80.1, 75.3, 66.1, 61.8, 28.4, 25.8, 17.4; MS *m/z* 256 (M^+ − Me), 200, 171, 156, 114, 96, 57.

Coupling of Phenols 6 and Allylic Alcohols 7. To an ice water cooled solution of triphenylphosphine (306 mg, 1.17 mmol) in 5 mL of dry THF was added sequentially diethyl azodicarboxylate (173 mg, 1.10 mmol), 2-bromo-4-*n*-hexyl-3-hydroxyaniline (**6b**) (143 mg, 0.52 mmol), and the allylic alcohol **7a** (203 mg, 0.78 mmol). The resulting solution was stirred for approximately 24 h at room temperature until **6b** was no longer detected by TLC. The solvent was removed by rotary evaporation, and the residual oil was loaded onto a column of silica gel. Elution with 10% ethyl acetate/*n*-hexane followed by solvent evaporation under reduced pressure afforded 214 mg (75%, containing ca. 5−7% of an impurity) of **8b** as a yellow oil: IR (neat) 3465, 3387, 2979, 1693, 1398 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.62 (d, J = 7.8 Hz, 1H), 6.25 (d, J = 7.8 Hz, 1H), 5.94−5.80 (m, 2H), 4.45−4.34 (m, 3H), 4.07 (dd, J = 6.1, 9.0 Hz, 1H), 3.79 (dd, J = 2.1, 9.0 Hz, 1H), 2.48 (t, J = 7.2 Hz, 2H), 1.61 (s, 3H), 1.59 (s, 1H), 1.46 (s, 9H), 1.17 (m, 8H), 0.85 (t, J = 7.3 Hz, 3H).

Following a similar procedure, **8a** was obtained from **6a** and **7a** in 78% yield: IR (neat) 3461, 3375, 2978, 1681, 1483, 1397, 1282 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.00 (t, J = 8.1 Hz, 1H), 6.40 (d, J = 8.1 Hz, 1H), 6.27 (d, J = 8.1 Hz, 1H), 5.86 (br s, 2H), 4.57 (br s, 2H), 4.31 (m, 1H), 4.15 (br s, 2H), 3.96 and 3.78 (AB q, d, J = 9.0 Hz, A part split into d with J = 6.3 Hz, B part split into d with J = 1.1 Hz), 1.63−1.43 (m, 15 H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 155.8, 151.9, 145.7, 132.7, 128.3, 126.7, 108.6, 102.7, 99.3, 68.7, 68.1, 58.8, 28.5; HRMS calcd for $C_{19}H_{27}N_2O_4Br$ (M^+, ^{79}Br) 426.115, found 426.115

8c was obtained in 63% yield (containing ca. 5−7% of an impurity) as a yellow oil from **6b** and **7b**: IR (neat) 3422, 3368, 2978, 1689, 1397 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.61 (d, J = 8.1 Hz, 1H), 6.26 (d, J = 8.1 Hz, 1H), 5.96−5.67 (m, 2H), 4.46 (m, 2H), 4.01−3.78 (m, 2H), 2.48 (t, J = 7.6 Hz, 2H), 1.63−1.37 (m, 15 H), 1.31−1.23 (m, 11H), 0.76 (t, J = 7.3 Hz, 3H); MS *m/z* 526 (M^+, ^{81}Br), 524 (M^+, ^{79}Br), 505, 424, 409, 367, 353, 291, 277, 210, 158, 114; HRMS calcd for $C_{26}H_{41}N_2O_4Br$ (M^+, ^{79}Br) 524.225, found 524.226.

Palladium-Catalyzed Ring Closure of 8. A mixture of palladium acetate (2.8 mg, 0.011 mmol), **8b** (182 mg, 0.36 mmol), sodium formate (24.4 mg, 0.36 mmol), sodium carbonate (76.2 mg, 0.72 mmol), tetrabutylammonium chloride (99.7 mg, 0.36 mmol), and 5 mL of DMF was heated at 80 °C for 36 h under a nitrogen atmosphere. The cooled solution was partitioned between 100 mL of ethyl acetate and 20 mL of water. The organic layer was washed with water (20 mL) and brine (20 mL) and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residual oil was chromatographed (silica gel, 10% ethyl acetate/*n*-hexane as eluent) to afford 128.3 mg (83%) of **9b** as a pale yellow oil: $[\alpha]^{22}_D$ −23.3° (*c* 0.12, EtOAc); IR (neat) 3460, 3372, 2976, 1684, 1484, 1391, 1279 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (s, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.35 (d, J = 7.5 Hz, 1H), 4.70 (br s, 2H), 4.19 (m, 1H), 3.80 (m, 2H), 3.34 (br d, J = 14.1 Hz, 1H), 2.74−2.65 (m, 3H), 1.70−1.59 (m, 8H), 1.40 (m, 9H), 1.31 (m, 6H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 155.8, 152.6, 140.3, 139.9, 125.3, 116.5, 116.0, 107.6, 93.9, 66.5, 65.5, 58.1, 31.8, 30.2, 29.3, 28.5, 27.9, 27.8, 24.3, 22.7, 14.1; MS *m/z* 430 (M^+), 405, 371, 316, 272, 245, 230, 184, 160, 111, 100, 83; HRMS calcd for $C_{25}H_{38}N_2O_4$ (M^+) 430.283, found 430.281.

Following the same procedure as described above, **9a** was prepared from **8a** in 79% yield: $[\alpha]^{22}_D$ −9.2° (*c* 0.12, EtOAc); IR (neat) 3431, 3378, 2976, 1684, 1484, 1391, 1279 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (s, 1H), 7.04 (t, J = 8.1 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.39 (d, J = 8.1 Hz, 1H), 4.98 (br s, 2H), 4.18 (m, 1H), 3.83−3.71 (m, 2H), 3.36 and 2.70 (ABq, 2H, J = 13.8 Hz, B part split into d with J = 11.4 Hz), 1.63−1.41 (m, 15H); ^{13}C NMR ($CDCl_3$, 75.46 Hz) δ 157.6, 152.6, 142.1, 140.3, 127.3, 125.6, 116.4, 107.5, 100.9, 93.9, 80.9, 68.5, 65.5, 58.1, 28.5, 27.8, 24.3; HRMS calcd for $C_{19}H_{26}N_2O_4$ (M^+) 346.189, found 346.189.

9c: 81% yield, $[\alpha]^{22}_D$ −53.9° (*c* 1.16, EtOAc); IR (neat) 3455, 3367, 2985, 1691, 1401 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (s, 1H), 6.85 (d, J = 7.8 Hz), 6.36 (d, J = 7.8 Hz), 4.86 (br s, 2H), 4.14 (m, 1H), 3.86 (m, 1H), 3.56 (br d, J = 14.2 Hz, 1H), 2.72 (t, J = 7.3 Hz), 2.67 (m, 1H), 1.72−1.35 (m, 23H), 1.07 (d, J = 6.3 Hz), 0.86 (t, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75.46 MHz, two isomers) δ 155.8, 152.8, 140.0, 139.8, 127.9, 125.2, 116.1, 116.0, 114.3, 107.6, 103.0, 93.9, 80.6, 76.0, 75.5, 66.6, 63.8, 31.8, 30.2, 29.3, 28.9, 28.5, 28.3, 27.8, 22.7, 21.7, 17.7, 17.4, 14.2; MS *m/z* 444 (M^+), 405, 330, 269, 242, 230, 215, 172, 160, 114, 83; HRMS calcd for $C_{26}H_{40}N_2O_4$ (M^+) 444.298, found 444.299.

Coupling of Amines 9 and Triflate 13. A solution of **9b** (104 mg, 0.24 mmol), 2,6-lutidine (0.3 mL, 2.57 mmol), and benzyl (*R*)-2-[(trifluoromethanesulfonyl)oxy]-3-methylbutanoate (82.3 mg, 0.24 mmol) in 3 mL of dichloroethane was heated at 80 °C for 28 h. After cooling, the mixture was directly loaded onto a column of silica gel. Elution with 10% ethyl acetate/hexane followed by evaporation under reduced pressure afforded 113 mg (76%) of **10b**: $[\alpha]^{22}_D$ −42.7° (*c* 1.14, EtOAc); IR (neat) 3367, 2981, 1742, 1687, 1520, 1376 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (s, 1H), 7.27−7.21 (m, 5H), 6.85 (d, J = 7.8 Hz, 1H), 6.35 (d, J = 7.8 Hz, 1H), 5.37 (br d, J = 9.3 Hz, 1H), 5.13 and 5.05 (ABq, J = 12.3 Hz, 2H), 4.19 (m, 1H), 3.89−3.74 (m, 3H), 3.49 and 2.52 (ABq, J = 15.3 Hz, 2H, B part split into d with J = 11.5 Hz), 2.72 (m, 2H), 2.51 (m, 1H), 1.67 (m, 2H), 1.61 (s, 3H), 1.58 (s, 3H), 1.49 (s, 9H), 1.35−1.29 (m, 6H), 1.12 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 174.2, 155.7, 152.2, 140.9, 140.7, 139.9, 136.0, 128.4, 128.1, 128.0, 125.2, 116.5, 115.1, 104.5, 93.7, 80.3, 66.5, 66.2, 65.5, 64.9, 58.2, 31.8, 31.5, 30.4, 30.1, 29.3, 28.5, 27.8, 27.4, 24.5, 23.3, 22.7, 20.8, 19.7, 19.4, 14.2; MS *m/z* 620 (M^+), 564, 477, 442, 385, 371, 242, 211; HRMS calcd for $C_{37}H_{52}N_2O_6$ (M^+) 620.383, found 620.383.

Following a similar procedure as described above, **10a** was prepared from **9a** in 76% yield: $[\alpha]^{22}_D$ −58.4° (*c* 0.11, EtOAc); IR (neat) 3443, 3364, 2976, 1681, 1482, 1391, 1279 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.23 (m, 6H), 7.05 (t, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 5.53 (d, J = 9.3 Hz, 1H), 5.14 and 5.06 (ABq, J = 12.6 Hz, 2H), 4.19 (m, 1H), 3.93−3.71 (m, 2H), 3.50 and 2.65 (ABq, J = 14.1 Hz, 2H, B part split into d with J = 11.7 Hz), 2.56 (m, 1H), 1.70−1.36 (m, 15H), 1.06 (d, J = 7.3 Hz, 3H), 0.96 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.46 Hz) δ 173.9, 157.3, 152.2, 142.9, 140.7, 135.9, 128.4, 128.0, 127.2, 125.7, 116.2, 115.1, 104.3, 101.9, 93.7, 80.3, 66.3, 65.4, 64.8, 58.1, 30.3, 28.5, 28.4, 27.8, 27.4, 24.5, 20.8, 19.7; HRMS calcd for $C_{31}H_{40}N_2O_6$ (M^+) 536.289, found 536.288.

10c: 75% yield; $[\alpha]^{22}_D$ −74.2° (*c* 0.12, EtOAc); IR (neat) 3391, 2974, 1740, 1682, 1518, 1377 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29−7.21 (m, 6H), 6.86 (d, J = 7.8 Hz, 1H), 6.33 (d, J = 7.8 Hz, 1H), 5.46 (br d, J = 9.0 Hz, 1H), 5.15 and 5.07 (ABq, J = 12.4 Hz, 2H), 4.09 (m, 1H), 3.94−3.77 (m, 3H), 2.72 (t, J = 7.5 Hz, 1H), 2.59 (m, 1H), 2.48 (m, 1H), 1.77−1.62 (m, 8H), 1.49 (br s, 9H), 1.27 (m, 9H), 1.08 (d, J = 7.2 Hz, 3H), 0.99 (d, J = 7.2 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ 174.5, 155.9, 152.3, 140.8, 140.2, 135.8, 128.4, 125.2, 116.5, 116.0, 115.4, 104.3, 93.5, 80.2, 76.1, 66.2, 64.7, 63.7, 31.8, 30.4, 30.1, 29.2, 28.6, 28.4, 27.7, 27.5, 27.4, 22.7, 21.2, 20.6, 19.6, 14.1; MS *m/z* 634 (M^+), 605, 513, 481, 399, 326, 280, 242, 216; HRMS calcd for $C_{38}H_{54}N_2O_6$ (M^+) 634.398, found 634.398.

(2*S*,5*S*)-9-Hexyl-1,2,5,6-tetrahydro-5-(hydroxymethyl)-1-methyl-2-(1-methylethyl)furo[4,3,2-*gh*]-1,4-benzodiazonin-3(4*H*)-one (11b). A mixture of **10b** (98.4 mg, 0.16 mmol) and 5 mg of 10% Pd/C in 5 mL of ethanol and 0.5 mL of trifluoroacetic acid was hydrogenated with concomitant hydrolysis at 50 °C under ordinary pressure for 8 h. The catalyst was filtered off, and the filtrate was concentrated to dryness in vacuo. The crude amino acid was dissolved in 5 mL of DMF, and 1-hydroxybenzotriazole (36.4 mg, 0.24 mmol), *N*-methylmorpholine (0.15 mL, 1.36 mmol), and (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (105.2 mg, 0.6 mmol) were added sequentially at 0 °C. The resulting solution was warmed to room temperature, stirred for 56 h, and partitioned between 100 mL of ethyl acetate and 20 mL of water. The organic layer was separated, washed with water (2 × 20 mL) and brine (20 mL), and concentrated to dryness. The remaining oil was dissolved in 10 mL of acetonitrile, and then 37% formalin (0.14 mL), sodium cyanoborohydride (123 mg), and acetic acid (0.02 mL) were added sequentially at 0 °C. After the addition was completed, the mixture was stirred for 3 h at 0 °C. Ether extraction followed by column chromatography eluting with 33% ethyl acetate/hexane afforded 38.9 mg (63%) of **11b**, which according to spectroscopy is comprised of an approximately 3.5:1 mixture of two conformers: $[\alpha]^{22}_D$ −175.8° (*c* 0.24, EtOAc); IR (KBr) 3385, 2979, 1689, 1461 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.97 (br s, 1H, minor), 7.55 (br s, 1H, major), 7.33 (s, 1H, major), 7.06 (s, 1H, minor), 6.95 (d, J = 7.8 Hz, 1H, both), 6.53 (d, J = 7.8 Hz, 1H, both), 4.74 (br d, J = 9.6 Hz, 1H, minor), 4.43 (m, 1H, minor), 4.23 (m, 1H, major), 4.18 (d, J = 9.8 Hz, 1H, major), 3.75 and 3.59 (ABq, J = 11.7 Hz, 2H, major, A part split into d with J = 2.7 Hz, B part split into d with J = 7.2 Hz) overlapping 3.76 and 3.46 (ABq, J = 7.6 Hz, 2H, minor), 3.09−2.91 (m, 2H, both), 2.84 (s, 3H, major), 2.74 (m, 2H, major), 2.68 (s 3H, minor), 2.58 (m, 1H, major) overlapping 2.61 (m, 2H, minor), 2.31 (m, 1H, minor), 1.64 (m, 2H, both), 1.30 (m, 6H, both), 1.20 (d, J = 6.6 Hz, 3H, minor), 0.92 (d, J = 6.7 Hz, 3H, major) overlapping 0.90 (d, 3H, minor), 0.87 (m, 3H, both), 0.63 (d, J = 6.7 Hz, 3H, major); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (major conformer only) 174.1, 157.6, 150.8, 141.3, 132.6, 128.7, 119.6, 118.2, 98.8, 63.3, 62.6, 60.5, 31.8, 30.7, 30.1, 29.8, 29.1, 28.5, 22.6, 14.5, 14.4, 14.1; MS *m/z* 386 (M^+), 381, 331, 300, 269, 225, 191, 149, 125, 111, 97; HRMS calcd for $C_{23}H_{34}N_2O_3$ (M^+) 386.257, found 386.257.

Following a similar procedure as described above, **11a** was prepared from **10a** in 61% yield: $[\alpha]^{22}_D$ −183.3° (*c* 0.53, chloroform); IR (KBr) 3378, 2981, 1667, 1568, 1498 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) showed the presence of two conformers in a ratio of 1/5.8, δ (major conformer only) 7.33 (s, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.06 (br s, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 4.23 (d, J = 8.1 Hz), 4.20 (m, 1H), 3.75 and 3.56 (ABq, J = 11.4, 2H, A part split into d with J = 3.9 Hz, B part split into d with J = 8.4 Hz), 3.01 (m, 2H), 2.90 (s, 3H), 2.59 (m, 1H), 0.90 (d, J = 6.7 Hz, 3H), 0.62 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.46 Hz) δ (major conformer only) 174.0,

158.2, 148.3, 140.4, 125.3, 118.6, 117.7, 109.0, 104.2, 71.6, 64.8, 54.9, 36.0, 32.8, 31.2, 28.4, 21.5, 19.5; HRMS calcd for $C_{17}H_{23}N_2O_3$ (M + H^+) 303.171, found 303.170.

11c: 61% yield; $[\alpha]^{22}_D$ −276.4° (*c* 0.11, EtOAc); IR (KBr) 3397, 2985, 1685, 1467 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) showed the presence of two conformers in a ratio of 1/5.3; δ 7.43 (s, 1H, minor), 7.39 (s, 1H, major), 7.07 (br s, 1H, both), 6.95 (d, *J* = 8.1 Hz, 1H, both), 6.95 (d, *J* = 8.1 Hz, 1H, both), 4.98 (d, *J* = 10.5 Hz, 1H, minor), 4.17 (d, *J* = 10.1 Hz, 1H, major), 3.93 (m, 1H, major), 3.79 (m, 1H, major), 3.76−3.55 (m, 2H, minor), 3.45 (br s, 1H, major), 3.08 (br s, 2H, major), 2.86 (s, 3H, major), 2.82 (m, 2H, minor), 2.77 (t, *J* = 7.8 Hz, 2H, major), 2.67 (s, 3H, minor), 2.61 (m, 1H, major) overlapping 2.53 (m, 1H, minor), 2.39 (m, 1H, minor), 1.63 (m, 2H, both), 1.31 (m, 6H, both) overlapping 1.32 (d, 3H, minor), 1.28 (d, *J* = 6.7 Hz, 3H, major) overlapping 1.29 (d, 3H, minor), 0.94 (d, *J* = 6.8 Hz, 3H, major) overlapping 0.92 (d, 3H, minor), 0.84 (m, 3H, both), 0.63 (d, *J* = 6.8 Hz, 3H, major); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (major conformer) 173.7, 156.5, 146.4, 139.8, 124.6, 119.3, 119.0, 117.8, 109.2, 71.8, 70.2, 58.8, 32.9, 31.8, 30.0, 29.3, 28.5, 22.7, 21.6, 20.2, 19.6, 14.2, (minor conformer) 172.2, 156.0, 143.8, 142.7, 127.9, 126.3, 125.8, 125.3, 114.7, 71.9, 67.9, 61.9, 58.5, 36.1, 29.8, 29.5, 27.7, 24.5, 20.4, 19.4; MS *m/z* 400 (M^+), 357, 314, 270, 256, 184, 128, 97, 83; HRMS calcd for $C_{24}H_{36}N_2O_3$ (M^+) 400.273, found 400.273.

[2*S*-[2*R,5*R**(*S**)]]-9-Hexyl-1,2,5,6-tetrahydro-5-(1-hydroxyethyl)-1-methyl-2-(1-methylethyl)furo[4,3,2-*gh*]-1,4-benzodiazonin-3(4*H*)-one (11d).** To a solution of **11c** (25.7 mg, 0.064 mmol), triphenylphosphine (33.6 mg, 0.128 mmol), and THF (1 mL) were added sequentially diethyl azodicarboxylate (20.0 mg, 0.114 mmol) and acetic acid (6 μL, 0.096 mmol) at 0 °C. The resulting solution was stirred for 36 h at room temperature and then concentrated under reduced pressure. The residual oil was loaded onto a column of silica gel eluting with 50% ethyl acetate/*n*-hexane followed by rotary evaporation to afford 15.1 mg of the acetate of **11d**, together with 5.2 mg of recovered starting material. The acetate was dissolved in 3 mL of EtOH, and 1 mL of 2 N KOH was added. This mixture was stirred for 5 h at room temperature. Ether extraction followed by rotary evaporation and chromatography (silica gel, 75% ethyl acetate/*n*-hexane as eluent) provided 10.3 mg of **11d** as a pale yellow solid: $[\alpha]^{22}_D$ −165° (*c* 0.11, EtOAc); IR (KBr) 3399, 2989, 1687, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) showed the presence of two conformers in a ratio of 1/5.6; δ 7.91 (br s, 1H, both), 7.77 (s, 1H, minor), 7.49 (s, 1H, major), 6.95 (d, *J* = 8.1 Hz, 1H, both), 6.55 (d, *J* = 8.1 Hz, 1H, both), 4.64 (d, *J* = 10.8 Hz, 1H, minor), 4.17 (d, *J* = 8.7 Hz, 1H, major), 4.13 (m, 2H, both), 3.64 (m, 1H, minor), 3.49−3.37 (m, 2H, major), 3.16 (m, 1H, minor), 2.93 (m, 2H, minor), 2.82 (s, 3H, major), 2.74 (t, *J* = 7.4 Hz, 2H, major), 2.68 (s, 3H, minor), 2.60 (m, 1H, major), 2.36 (m, 1H, minor), 1.58 (m, 2H, both), 1.41−1.28 (m, 6H, both), overlapping 1.27 (d, *J* = 7.3 Hz, 3H, minor), 1.25 (d, *J* = 7.2 Hz, 3H, minor), 1.19 (d, *J* = 7.3 Hz, 3H, major), 0.92 (d, *J* = 7.3 Hz, 3H, major), 0.78 (t, *J* = 7.3 Hz, 3H, both) overlapping 0.80 (d, 3H, minor), 0.63 (d, *J* = 7.3 Hz, major); ^{13}C NMR ($CDCl_3$, 75.46 MHz) δ (major conformer only) 174.2, 156.4, 146.3, 139.9, 124.5, 120.0, 119.1, 117.9, 109.1, 71.6, 69.4, 59.2, 33.0, 31.8, 30.0, 29.3, 29.0, 28.5, 22.7, 21.6, 19.3, 18.2, 14.1; HRMS calcd for $C_{24}H_{36}N_2O_3$ (M^+) 400.273, found 400.273.

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