Synthesis of Biphenyls Mimicking the Structure of the Antimitotic Rhazinilam

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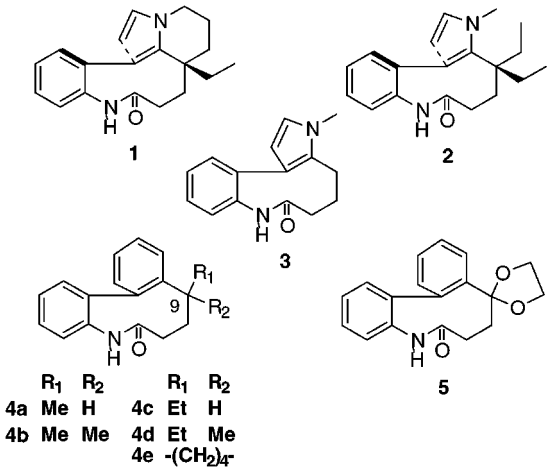
Introduction

(−)-Rhazinilam **1** is an axially chiral phenylpyrrole compound which has been isolated from *Melodinus australis*,[1] *Rhazya stricta*,[2] and *Kopsia singapurensis*.[3] Biological studies have shown that rhazinilam mimics the cellular effects of paclitaxel (Taxol). It induces both microtubules bundling in interphase and blocks mitotic cells in aster-like structure.[4] In vitro, this antimitotic compound induces spiralization of tubulin such as vinblastine and inhibits the cold-induced disassembly of microtubules such as paclitaxel.[4] Structurally, (−)-rhazinilam **1** is characterized by four rings: the phenyl A-ring, the nine-membered lactam B-ring, the pyrrole C-ring, and the piperidine D-ring. According to X-ray data, the A−C dihedral angle of (−)-rhazinilam **1** is 95° and the amide bond possesses a cis conformation.[5] Structure−activity relationship studies suggest that the presence of the phenylpyrrole unit as well as the lactam function are indispensable for antitubulin activity.[6] Moreover, the good interaction of (−)-diethylphenylpyrrole **2**[7,8] with tubulin in comparison to the low activity of phenylpyrrole **3**[8] shows that restricted rotation of the biaryl and/or the presence of the two ethyl groups plays a major role in the biological activity.

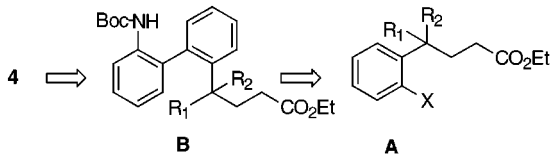
As part of our studies in this series, we considered that the replacement of the phenylpyrrole by a biphenyl unit might be an interesting feature to analyze. Indeed, molecular modeling studies show that biphenyl compounds such as **4** with a quaternary carbon at the 9 position could mimic the conformation of rhazinilam **1** as well as that of phenylpyrrole **2**.[9] Moreover, the biaryl unit is an important moiety present in a number of antimitotic products which act generally as inhibitors of tubulin assembly.[10] Previously, we reported the synthesis of dibenzoazonine **5** from 2-phenylbenzoic acid.[11] This compound does not interact with microtubules, and all our efforts to replace the dioxolane by alkyl chains through alkylation of the corresponding ketone were unsuccessful.[12] In this paper we describe the synthesis of new *ortho*-substituted bridged biphenyls **4a** to **4e**, and we show that the more or less hindered substitution at carbon 9 affects the interaction with tubulin.



Results and Discussion

As shown in Scheme 1, our approach is based on a cross-coupling reaction of a protected aniline derivative with *ortho*-substituted phenyl halides **A**. This would lead to the key biphenyl intermediate **B** which would cyclize into a nine-membered ring after deprotection of the amine and acid groups followed by intramolecular cyclization.

Scheme 1



Commercially available 2-bromophenylacetonitrile was used as starting material to introduce alkyl groups in the *ortho* position of the phenyl ring. Monoalkylation and dialkylation were realized in good yields by reacting 1 or 2 equiv of LDA with the corresponding alkyl halides in THF. This led to nitriles **6a**, **6b**,[13] **6c**, **6d**, and **6e**[14] which were reduced into the corresponding aldehydes **7a**−**e** after treatment with diisobutylaluminum hydride (DIBAH) in toluene and hydrolysis. The unstable aldehydes **7a**−**e** were immediately subjected to the Horner−

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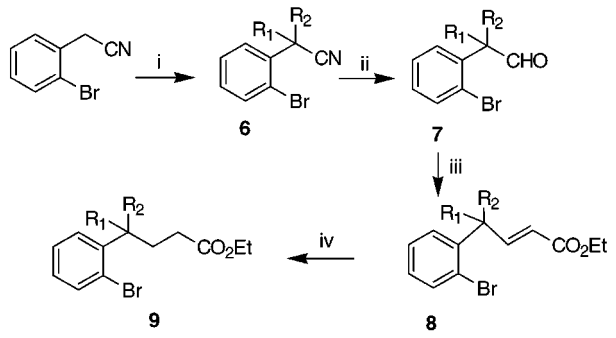
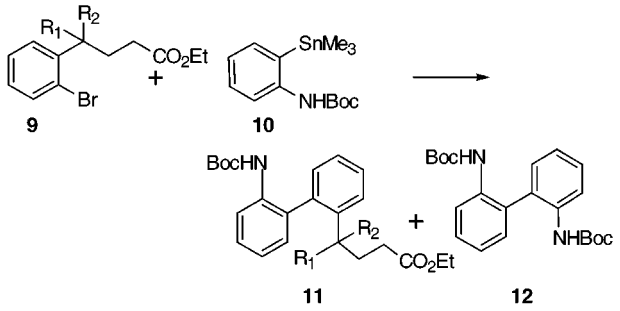
Scheme 2



(i) LDA/MeI or EtI or $Br(CH_2)_4Br$/THF/rt (**6a**, R_1=H, R_2=Me, 90%; **6b**, R_1=R_2=Me, 80%; **6c**, R_1=H, R_2=Et, 88%; **6d**, R_1=R_2=Et, 94%; **6e**, R_1,R_2=-$(CH_2)_4$-, 52%) (ii) DIBAH/toluene/-74°C then HCO_2Et (**7a**, R_1=H, R_2=Me, 44%; **7b**, R_1=R_2=Me, 80%; **7c**, R_1=H, R_2=Et, 69%; **7d**, R_1=R_2=Et, 73%; **7e**, R_1,R_2=-$(CH_2)_4$-, 73%) (iii) NaH/THF/$(EtO)_2P(O)CH_2CO_2Et$/rt (**8a**, R_1=H, R_2=Me, 86%; **8b**, R_1=R_2=Me, 92%; **8c**, R_1=H, R_2=Et, 80%; **8d**, R_1=R_2=Et, 60%; **8e**, R_1,R_2=-$(CH_2)_4$-, 78%) (iv) H_2/PtO_2/EtOH (**9a**, R_1=H, R_2=Me, 47%; **9b**, R_1=R_2=Me, 43%; **9c**, R_1=H, R_2=Et, 92%; **9d**, R_1=R_2=Et, 60%; **9e**, R_1,R_2=-$(CH_2)_4$-, 89%)

Scheme 3



Bromide	R_1	R_2	Product	Yield
9a	Me	H	**11a**	64%
9b	Me	Me	**11b**	19%*
9c	Et	H	**11c**	56%
9d	Et	Et	**11d**	3%*
9d**	Et	Et	**11d**	7%*
9e	-$(CH_2)_4$-		**11e**	6%*

Coupling reactions were conducted with 0.04M phenyl bromides **9** and 1.1 eq. of stannane **10** in toluene with $PdBnCl(PPh_3)_2$ (5 mol%) under reflux. * Yields calculated taking into account the presence of dimer **12** (see experimental part)** With LiCl (4 eq) as additive.

Wadsworth−Emmons (HWE) conditions.[15] Treatment with triethyl phosphonoacetate and NaH afforded selectively *trans*-alkenes **8a**−**e** with good yields. Catalytic hydrogenation with PtO_2 in ethanol led to aryl bromides **9a**−**e** (Scheme 2).

We then performed different cross-coupling reactions with N-(*tert*-butoxycarbonyl)-2-(trimethylstannyl)aniline **10**[16] and the aryl bromides **9a**−**e**. From the palladium catalysts assayed ($PdBnCl(PPh_3)_2$, $PdCl_2(CH_3CN)_2$, or $Pd(PPh_3)_4$), benzyl[bis(triphenylphosphine)]palladium(II) chloride ($PdBnCl(PPh_3)_2$) was found to give the best yield of the cross-coupled products. The reactions were carried out in toluene and were usually complete within 13 h giving **11a**−**e** in yields ranging from 64% to 3% depending on the amount of steric hindrance in the arylbromides **9** (Scheme 3). We varied the conditions of the coupling reaction with the diethyl derivative **9d**. The use of a highly dipolar solvent such as DMF does not improve the Stille coupling (data not shown). LiCl has been reported to accelerate the cross-coupling reaction of organostannanes and aryl bromides.[17] When LiCl was used as an additive in the coupling reaction of aryl bromide **9d**, a slightly higher yield of 7% was obtained. Likewise, copper iodide known to improve yield and rate in the Stille cross-coupling[18] had no effect on the reaction. In all the performed experiments, dimer **12** was also isolated with a yield ranging from 10% (for the coupling reactions with **9a** and **9c**) to about 40% for the coupling reactions with the aryl bromides having a quaternary carbon in the *ortho* position of the phenyl (**9b**, **9d**, and **9e**). The formation of such a homocoupling product was already mentioned in the literature and found to be due to the presence of oxygen in the medium.[19] However, in our hands, the coupling reactions performed under argon after six freeze−thaw cycles as previously described by Farina et al.[19] did not lead to a substantial increase in the yield of the desired compounds.

This study shows that the structure of aryl bromides **9** decisively affects the yield of the Stille coupling reaction going from 64% and 56% with the monoalkyl aryl bromides **9a** and **9c** to less than 10% with the more hindered cyclopentanyl (**9e**) and diethyl (**9d**) derivatives. It should also be noted that the use of the corresponding aryl iodides instead of the aryl bromides **9a**, **9b**, and **9c** in the Stille reaction led to a higher yield in the monoalkylated coupling products **11a** (70% isolated yield) and **11c** (66% isolated yield) (data not shown). Unfortunately, the yield in the dimethyl biphenyl **11b** could not be improved and the synthesis of the diethyl aryl iodide corresponding to **9d** was unsuccessful. As Suzuki couplings are recommended in the case of hindered aryl halides, we studied the reaction of aryl boronic acid with the sterically hindered haloarene **9d** in the presence of base such as Cs_2CO_3 and $Ba(OH)_2$.[20] However, no cross-coupling products could be isolated from the reaction mixture. Because enough quantities of biphenyl products **11a**−**e** were obtained to carry on the synthesis, no further attempts were made to improve the yield of the cross coupling reactions with the hindered aryl halides **9d** and **9e**.[21]

The NMR spectra of the two coupling products **11a** and **11c** clearly show the presence of two diastereoisomers ((*R*,a*S*/*S*,a*R*) and (*R*,a*R*/*S*,a*S*) configuration)[22] whereas compounds **11b**, **11d**, and **11e** have one element of asymmetry and are obtained as racemic atropisomers (a*R* and a*S* configuration). Because of a possible diastereoselectivity during the final cyclization step, no attempts have been made to separate the diastereoisomers of **11a** and **11c**. Removal of the Boc group under acidic condi-

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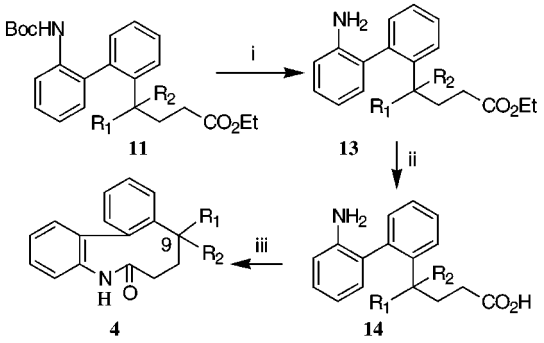
(22) Two distinct signals corresponding to the alkyl groups at C-9 are observed at 1.22 and 1.08 ppm (2d, J = 8 Hz, CH_3) in the NMR spectrum of **11a** and at 0.88 and 0.67 ppm (2t, J = 7 Hz, CH_2CH_3) in the NMR spectra of **11c**.

Scheme 4



(i) TFA,CH_2Cl_2,0°C (**13a** R_1=H, R_2=Me,86%; **13b**, R_1=R_2=Me, 78%;**13c**, R_1=H, R_2=Et,62%; **13d**, R_1=R_2=Et,95%;**13e**, R_1,R_2= -$(CH_2)_4$-,95%) (ii) NaOH,MeOH,reflux (**14a** R_1=H, R_2=Me,100%; **14b**, R_1=R_2=Me,91%; **14c**, R_1=H, R_2=Et,96%; **14d**, R_1=R_2=Et, 77%; **14e**, R_1,R_2=-$(CH_2)_4$-,84%) (iii) EDCI-HOBT(1.1 mM) and **14** (1.1 mM) in CH_2Cl_2 (**4a** R_1=H, R_2=Me,71%, **4b** R_1= R_2=Me,78%, **4c** R_1=H, R_2=Et,81%, **4d** R_1=R_2=Et,74%, **4e** R_1, R_2=-$(CH_2)_4$-,79%)

tions led to the corresponding amino derivatives **13a**−**e** (Scheme 4). Subsequent methanolysis of the ester group gave the amino acids **14a**−**e**, and the synthesis was completed by intramolecular cyclization of **14a**−**e** in the presence of EDCI[23] and HOBT[24] under high dilution conditions to yield the five bridged biphenyl lactams **4a**−**e**.

As expected, cyclization of diastereomeric biphenyls **14a** and **14c** led with good yields to only one isomer, *rac*-**4a** and *rac*-**4c**, respectively. Molecular modeling studies show that the more favorable situation for intramolecular cyclization is with the (*R*,a*R*/*S*,a*S*) isomer which is therefore cyclized.[25] Meanwhile, the unreacted diastereoisomers (*R*,a*S*/*S*,a*R*) **14a** and (*R*,a*S*/*S*,a*R*) **14c** will interconvert into the (*R*,a*R*/*S*,a*S*) isomers by rotation around the phenyl−phenyl bond.

The ^{13}C NMR spectra of **4b** and **4d**, realized at room temperature, show the lack of signals corresponding to some carbons of the B-ring and alkyl groups at C-9. On the other hand, more signals than expected are present in the spectra recorded at 263 K. These results clearly indicate the presence of several conformers, in slow equilibrium, due to the flexibility of the B-ring.

Besides the synthesis of new tricyclic hindered biphenyl lactams, the aim of this study was to show that a biphenyl could replace the phenylpyrrole group of rhazinilam **1** in the interaction with tubulin. The activity of compounds **4a** to **4e** was evaluated on the cold-induced disassembly of microtubules as described earlier.[6] It should be noted that all the compounds have been assayed under their racemic forms and their activities compared to that of (−)-rhazinilam **1**. The results show that compounds **4b**, **4c**, **4d**, and **4e** have the capacity to interact with tubulin in the same fashion as rhazinilam. Compounds **4b**, **4c**, **4d**, and **4e** were respectively 20, 17, 8, and 16 times less active than rhazinilam **1** (IC_{50} = 3μM) and compound **4a** was inactive. Since **4d** is a more active disassembly inhibitor than **4b** and **4c**, this suggests that bulky groups at carbon 9 make an important contribution to tubulin binding. The increase in activity going from compounds **4a**, **4b**, and **4c** to **4d** could thus be due to the decrease of their conformational freedom along the biphenyl axis. But the fact that the cyclopentanyl derivative **4e** is less active than the diethyl biphenyl **4d** rather suggests a direct interaction of the alkyl groups with tubulin. The inactivity of dioxolane **5** in comparison with the activity of the cyclopentanyl derivative **4e** is consistent with the hypothesis of these hydrophobic interactions.

In summary, the synthesis of new *ortho*-substituted bridged biphenyls which mimic the structure of rhazinilam **1** was achieved for the first time. This result is of importance because the stability of biphenyl molecules in comparison to that of phenylpyrroles make these compounds good candidates for structure−activity relationship studies in this series of antimitotic agents. We will present soon the synthesis of other new biphenyl analogues more active than rhazinilam **1**.

Experimental Section

General methods were the same as previously described.[26] All reagents were commercially available except *N*-(*tert*-butoxycarbonyl)-2-(trimethylstannyl)aniline **10** which was prepared according to ref 16.

Alkylation of 2-Bromophenylacetonitrile. 2-(2-Bromophenyl)propionitrile 6a. To a cold (−78 °C) solution of LDA prepared from *n*-BuLi (8.73 mL, 13.9 mmol) and diisopropylamine (2.14 mL, 15.24 mmol) in dry THF (40 mL) under argon was added a solution of 2-bromophenylacetonitrile (1.65 mL, 12.70 mmol) in dry THF (20 mL). This mixture was stirred for 20 min, and iodomethane (0.95 mL, 15 mmol) was added. The solution was allowed to warm to room temperature and stirred for 2.5 h. Addition of aqueous saturated NH_4Cl, extraction with AcOEt, and drying (Na_2SO_4) followed by filtration, concentration, and purification by column chromatography (98:2 heptane−AcOEt) afforded 2.4 g (90%) of 2-(2-bromophenyl)-propionitrile **6a** as a colorless oil: IR ($CHCl_3$) 2250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.36 (t, J = 7.0 Hz, 1H), 7.19 (t, J = 7.0 Hz, 1H), 4.33 (q, J = 7.0 Hz, 1H), 1.61 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.5, 133.4, 129.8, 128.5, 128.3, 122.6, 121.1, 31.4, 20.2 ppm; CIMS *m*/*z* 210−212 ($MH^{+\bullet}$). Anal. Calcd for C_9H_7BrN: C, 51.71; H, 3.37; N, 6.70. Found: C, 51.54; H, 3.27; N, 6.55.

2-(2-Bromophenyl)-2-methylpropionitrile[13] 6b was obtained from 2-bromophenylacetonitrile (1.65 mL, 12.70 mmol) by the above procedure, but using *n*-BuLi (16.7 mL, 26.7 mmol), 27.9 mmol of diisopropylamine (3.9 mL) and 31.8 mmol of iodomethane (2.0 mL). Purified by column chromatography (96:4 heptane−AcOEt): yield 80% of a colorless oil. **6b**: IR ($CHCl_3$) 2240 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.66 (bd, J = 8.0 Hz, 1H), 7.48 (bd, J = 8.0, 1H), 7.34 (bt, J = 8.0 Hz, 1H), 7.19 (bt, J = 8.0 Hz, 1H), 1.91 (s, 6H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.2, 135.7, 129.6, 128.0, 127.3, 123.4, 122.6, 37.4, 27.5 ppm; EIMS *m*/*z* 223−225 ($M^{+\bullet}$), 208−210. Anal. Calcd for $C_{10}H_{10}BrN$: C, 53.57; H, 4.50; N, 6.29. Found: C, 53.84; H, 4.45; N, 6.19.

2-(2-Bromophenyl)butyronitrile 6c was obtained from 2-bromophenylacetonitrile (3.2 mL, 24.6 mmol) by the above procedure, but using *n*-BuLi (17.6 mL, 28.1 mmol), 30.6 mmol of diisopropylamine (4.3 mL), and 51 mmol of iodoethane (4.08 mL). Purified by column chromatography (100:3.5 heptane−AcOEt): yield 88% of a colorless oil. **6c**: IR ($CHCl_3$) 2250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.0 and 1.0 Hz, 1H), 7.58 (dd, J = 8.0 and 1.0 Hz, 1H), 7.38 (bt, J = 8.0, 1H), 7.20 (bt, J = 8.0, 1H), 4.24 (q, J = 8.0 and 5.0 Hz, 1H), 1.93 (m, 2H), 1.14 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.0, 133.4, 129.7, 129.1, 128.2, 123.1, 120.0, 38.7, 27.8, 11.5

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(25) Molecular modeling using MM2 as force field showed that the transition state for the (*R*,a*R*/*S*,a*S*) isomer was 3.6 kcal lower in energy than that of the (*R*,a*S*/*S*,a*R*) isomer.
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ppm; EIMS *m/z* 223−225 ($M^{+\bullet}$). Anal. Calcd for $C_{10}H_{10}BrN$: C, 53.60; H, 4.50; N, 6.25. Found: C, 54.15; H, 4.62; N, 6.08.

2-(2-Bromophenyl)-2-ethylbutyronitrile 6d was obtained from 2-bromophenylacetonitrile (3.3 mL, 25.5 mmol) by the above procedure, but using *n*-BuLi (32 mL, 51 mmol), 51 mmol of diisopropylamine (7.15 mL), and 102 mmol of iodoethane (8.16 mL). Purified by column chromatography (96:4 heptane−AcOEt): yield 94% of a colorless oil. **6d**: IR ($CHCl_3$) 2240 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70 (dd, J = 8.0 and 1.0 Hz, 1H), 7.62 (dd, J = 8.0 and 1.0 Hz, 1H), 7.34 (td, J = 8.0 and 1 Hz, 1H), 7.18 (td, J = 8.0 and 1.0 Hz, 1H), 2.66 (m, 2H), 2.09 (m, 2H), 0.93 (t, J = 7.0 Hz, 6H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.1, 134.7, 131.9, 131.2, 129.4, 127.7, 122.6, 118.7, 52.4, 28.6, 10.4 ppm; CIMS *m/z* 252−254 (MH^+). Anal. Calcd for $C_{12}H_{14}BrN$: C, 57.16; H, 5.60; N, 5.56. Found: C, 57.29; H, 5.63; N, 5.58.

2-(2-Bromophenyl)-2cyclopentanecarbonitrile[14] 6e was obtained from 6-bromo-2-(2-bromophenyl)hexanenitrile prepared from 2-bromophenylacetonitrile (200 μL, 1.54 mmol) by the above procedure, but using *n*-BuLi (2.02 mL, 3.2 mmol), 3.39 mmol of diisopropylamine (475 μL), and 1.54 mmol of 1,4-dibromobutane (190 μL). The crude extract purified by column chromatography (8:2 heptane−AcOEt) led to 285 mg of 6-bromo-2-(2-bromophenyl)hexanenitrile: IR ($CHCl_3$) 2240 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.38 (td, J = 7.0 and 1 Hz, 1H), 7.21 (td, J = 7.0 and 1.0 Hz, 1H), 4.30 (q, J = 9.0 and 6.0 Hz, 1H), 3.42 (t, J = 7.0 Hz, 2H), 1.93 (m, 2H), 1.74 (m, 2H), 1.62 (m, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 135.3, 133.5, 129.9, 129.0, 127.7, 123, 120.3, 37.2, 33.6, 32.8, 25.8 ppm; CIMS *m/z* 386−390 ((MH^+) + 57).

6-Bromo-2-(2-bromophenyl)hexanenitrile (151 mg, 0.46 mmol) in dry THF (3 mL) was then added dropwise to a solution of *n*-BuLi (0.31 mL) and diisopropylamine (0.80 mL) in dry THF (10 mL) at −72 °C, and the mixture was stirred for 10 min. Addition of aqueous saturated NH_4Cl, extraction with AcOEt, and drying (Na_2SO_4) followed by filtration, concentration and purification by column chromatography (100:6 heptane−AcOEt) afforded 106 mg (92%) of 2-(2-bromophenyl)-cyclopentanecarbonitrile **6e** as a colorless oil: IR ($CHCl_3$) 2243 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.0 and 1.0 Hz, 1H), 7.43 (dd, J = 8.0 and 1.0 Hz, 1H), 7.32 (td, J = 8.0 and 1 Hz, 1H), 7.12 (td, J = 8 and 1 Hz, 1H), 2.74 (m, 2H), 2.20 (m, 2H), 2.03 (m, 2H), 1.96 (m, 2H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.6, 135.3, 129.6, 127.8, 127.6, 123.1, 47.7, 38.3, 23.8 ppm; CIMS *m/z* 250−252 (MH^+).

Preparation of Aldehydes 7a−e. General Procedure. A solution of 1 M DIBAL-H (19 mmol) in hexane was added dropwise to a solution of nitriles **6a**, **6b**, **6c**, **6d**, or **6e** (9.6 mmol) in toluene (30 mL) at −70 °C. The mixture was first stirred at −70 °C for 30 min and then at room temperature for 1 h whereupon ethyl formate was added and stirring was continued for 15 min. The mixture was poured into a saturated ammonium chloride solution, and aqueous sulfuric acid was added. The aqueous phase was extracted with AcOEt, and the organic phase was dried over Na_2SO_4 and filtered. Evaporation to dryness furnished the crude material which was purified by column chromatography leading to aldehydes **7a**, **7b**, **7c**, **7d**, or **7e**.

2-(2-Bromophenyl)propionaldehyde 7a. Purified by column chromatography (100:3 heptane−AcOEt): yield 44% of a colorless oil. **7a**: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.65 (dd, J = 8.0 and 2.0 Hz, 1H), 7.34 (dd, J = 8.0 and 2.0 Hz, 1H), 7.17 (td, J = 8.0 and 2.0 Hz, 1H), 7.12 (dd, J = 8.0 and 2.0 Hz, 1H, 4.18 (q, J = 7.0 Hz, 1H), 1.44 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 200.3, 133.5, 129.3, 129.2, 128.2, 125.2, 52.0, 14.1 ppm; EIMS *m/z* 212−214 ($M^{+\bullet}$).

2-(2-Bromophenyl)-2-methylpropionaldehyde 7b. Purified by column chromatography (100:3 heptane−AcOEt): yield 80% of a colorless oil. **7b**: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.59 (bd, J = 8.0 Hz, 1H), 7.42 (dd, J = 8.0 and 2.0 Hz, 1H), 7.36 (bt, J = 8.0 Hz, 1H), 7.18 (td, J = 8.0 and 2.0 Hz, 1H, 1.50 (s, 6H,) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.0, 142.3, 134.5, 129.2, 128.7, 127.9, 123.5, 51.8, 23.2 ppm; CIMS *m/z* 227−229 (MH^+).

2-(2-Bromophenyl)butyraldehyde 7c. Purified by column chromatography (100:3 heptane−AcOEt): yield 69% of a colorless oil. **7c**: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.64 (dd, J = 8.0 and 2.0 Hz, 1H), 7.33 (dd, J = 8.0 and 2.0 Hz, 1H), 7.17 (td, J = 8.0 and 2.0 Hz, 1H), 7.12 (dd, J = 8.0 and 2.0 Hz, 1H, 4.02 (t, J = 7.0 Hz, 1H), 2.16 (m, 2H), 1.78 (m, 2H), 0.94 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 200.1, 136.4, 133.5, 129.8, 129.1, 128.0, 126.0, 59.1, 22.8, 11.7 ppm; EIMS *m/z* 227−229 ($M^{+\bullet}$).

2-(2-Bromophenyl)-2-ethylbutyraldehyde 7d. Purified by column chromatography (94:6 heptane−AcOEt): yield 73% of a colorless oil. **7d**: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.38 (m, 2H), 7.19 (m, 1H), 2.10 (m, 4H), 0.77 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 139.5, 134.9, 130.7, 129.3, 127.8, 123.8, 24.3, 7.9 ppm; CIMS *m/z* 255−257 (MH^+).

2-(2-Bromophenyl)cyclopentanecarbaldehyde 7e. Purified by column chromatography (100:3 heptane−AcOEt): yield 73% of a colorless oil. **7e**: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.63 (dd, J = 8.0 and 2.0 Hz, 1H), 7.41 (dd, J = 8.0 and 2.0 Hz, 1H), 7.34 (td, J = 8.0 and 2.0 Hz, 1H), 7.18 (dd, J = 8.0 and 2.0 Hz, 1H), 2.40 (m, 2H), 2.29 (m, 2H), 1.78 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.1, 141.6, 134.6, 129.1, 128.8, 127.6, 124.6, 35.5, 34.1, 25.1 ppm; EIMS *m/z* 252−254 ($M^{+\bullet}$).

Preparation of Esters 8a−e via the Horner−Wadsworth−Emmons Reaction. General Procedure. Triethylphosphonoacetate (8.7 mmol) was added to a stirred suspension of NaH (4.26 mmol) in dry THF (25 mL). After 10 min the aldehyde **7a**, **7b**, **7c**, **7d**, or **7e** in dry THF (7 mL) was added. The reaction mixture was stirred at room temperature for 16 h. After hydrolysis and extraction with EtOAc, workup, and chromatography, the corresponding esters were obtained.

4-(2-Bromophenyl)pent-2-enoic Acid Ethyl Ester 8a. Purified by column chromatography (97:3 heptane−AcOEt): yield 86% of a colorless oil. **8a**: IR ($CHCl_3$) 1711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0 and 1.0, 1H), 7.29 (td, J = 8.0 and 1.0 Hz, 1H), 7.19 (dd, J = 8.0 and 1.0 Hz, 1H), 7.12 (dd, J = 16.0 and 5.0 Hz, 1H), 7.11 (td, J = 8 and 1 Hz, 1H), 5.85 (dd, J = 16 and 2 Hz, 1H), 4.19 (q, J = 7.0 Hz, 2H), 4.15 (m, 1H), 1.42 (d, J = 7.0 Hz, 3H), 1.29 (t, J = 7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 151.0, 142.4, 133.1, 128.3, 127.9, 124.0, 120.9, 60.4, 40.6, 19.2, 14.3 ppm; CIMS *m/z* 283−285 (MH^+).

4-(2-Bromophenyl)-4-methylpent-2-enoic Acid Ethyl Ester 8b. Purified by column chromatography (96:4 heptane−AcOEt): yield 92% of a colorless oil. **8b**: IR ($CHCl_3$) 1706 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0 and 1.0 Hz, 1H), 7.43 (dd, J = 8.0 and 1.0 Hz, 1H), 7.39 (td, J = 8.0 and 1.0 Hz, 1H), 7.28 (d, J = 16.0 Hz, 1H), 7.11 (td, J = 8.0 and 1.0 Hz, 1H), 5.70 (d, J = 16 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 1.61 (s, 6H), 1.29 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 157.1, 144.0, 135.5, 128.6, 128.0, 127.4, 123.6, 119.2, 60.3, 42.3, 28.3, 14.3 ppm; CIMS *m/z* 297−299 (MH^+).

4-(2-Bromophenyl)hex-2-enoic Acid Ethyl Ester 8c. Purified by column chromatography (100:3 heptane−AcOEt): yield 80% of a colorless oil. **8c**: IR ($CHCl_3$) 1709 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.62 (dd, J = 8.0 and 2.0 Hz, 1H), 7.35 (td, J = 8.0 and 2.0 Hz, 1H), 7.26 (dd, J = 8.0 and 2.0 Hz, 1H), 7.14 (td, J = 8.0 and 1.0 Hz, 1H), 7.07 (dd, J = 16.0 and 7.0 Hz, 1H), 5.89 (dd, J = 16 and 1, 1H), 4.24 (q, J = 8.0, 2H), 4.01 (m, 1H), 1.88 (m, 2H), 1.33 (t, J = 8.0 Hz, 3H), 0.98 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 150.1, 141.2, 133.1, 128.5, 128.0, 127.9, 125.1, 121.5, 60.3, 48.0, 27.5, 14.3, 11.9 ppm; CIMS *m/z* 297−299 (MH^+).

4-(2-Bromophenyl)-4-ethylhex-2-enoic Acid Ethyl Ester 8d. Purified by column chromatography (94:6 heptane−Et_2O): yield 60% of a colorless oil. **8d**: IR ($CHCl_3$) 1706 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 1H), 7.30 (m, 2H), 7.25 (d, J = 16.0 Hz, 1H), 7.09 (td, J = 8.0 and 2.0 Hz, 1H), 5.70 (d, J = 16.0 Hz, 1H), 4.20 (q, J = 8.0 Hz, 2H), 2.21 (m, 2H), 1.99 (m, 2H), 1.30 (t, J = 8.0 Hz, 3H), 0.74 (t, J = 8.0 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 156.1, 142.8, 135.8, 130.5, 128.2, 127.0, 123.7, 120.0, 60.4, 49.6, 28.5, 14.5, 8.7 ppm; CIMS *m/z* 325−327 (MH^+). Anal. Calcd for $C_{16}H_{21}BrO_2$: C, 59.09; H, 6.51; O, 9.84. Found: C, 58.94; H, 7.09; O, 9.48.

3-[1-(2-Bromophenyl)cyclopentyl]acrylic Acid Ethyl Ester 8e. Purified by column chromatography (100:4 heptane−AcOEt): yield 78% of a colorless oil. **8e**: IR ($CHCl_3$) 1706 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0 and 1.0 Hz, 1H),

7.41 (dd, J = 8.0 and 1.0 Hz, 1H), 7.28 (td, J = 8.0 and 1.0 Hz, 1H), 7.18 (d, J = 16.0 Hz, 1H), 7.10 (td, J = 8.0 and 1.0 Hz, 1H), 5.52 (d, J = 16.0 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 2.33 and 2.14 (2m, 4H), 1.75 (m, 4H), 1.26 (t, J = 7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 155.0, 144.6, 135.2, 128.7, 128.3, 127.2, 124.4, 119.7, 60.3, 54.7, 38.4, 23.8, 14.3 ppm; CIMS m/z 323−325 (MH^+).

Hydrogenation of Esters 8a−e. General Procedure. Esters **8a**, **8b**, **8c**, **8d**, and **8e** (0.27 mmol) in ethanol (5 mL) were hydrogenated over PtO_2 (10 mg) for 16 h. After filtration and evaporation of the solvent, the crude extract is chromatographed to give respectively compounds **9a**, **9b**, **9c**, **9d**, and **9e**.

4-(2-Bromophenyl)pentanoic Acid Ethyl Ester 9a. Purified by column chromatography (9:1 heptane−AcOEt): yield 47% of a colorless oil. **9a**: IR ($CHCl_3$) 1725 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.06 (m, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.32 (m, 1H), 2.25 (m, 2H), 1.97 (q, J = 7.0 Hz, 2H), 1.23 (d, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.6, 145.3, 133.0, 127.8, 127.7, 127.3, 122.9, 60.4, 37.6, 32.4, 21.3, 14.3 ppm; CIMS m/z 285−287 (MH^+).

4-(2-Bromophenyl)-4-methylpentanoic Acid Ethyl Ester 9b. Purified by column chromatography (97:3 heptane−AcOEt): yield 43% of a colorless oil. **9b**: IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.62 (dd, J = 8.0 and 1.0 Hz, 1H), 7.39 (dd, J = 8.0 and 1.0 Hz, 1H), 7.28 (td, J = 8.0 and 1.0 Hz, 1H), 7.07 (td, J = 8.0 and 1.0 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 2.43 (m, 2H), 2.03 (m, 2H), 1.53 (s, 6H), 1.24 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 144.0, 135.9, 129.3, 127.9, 125.9, 122.6, 60.3, 39.6, 34.7, 28.8, 28.5, 14.3 ppm; CIMS m/z 299−301 (MH^+).

4-(2-Bromophenyl)hexanoic Acid Ethyl Ester 9c. Purified by column chromatography (97:3 heptane−AcOEt): yield 92% of a colorless oil. **9d**: IR ($CHCl_3$) 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, J = 8.0 and 2.0 Hz, 1H), 7.36 (td, J = 8.0 and 2.0 Hz, 1H), 7.26 (dd, J = 8.0 and 2.0 Hz, 1H), 7.12 (td, J = 8.0 and 2.0 Hz, 1H), 4.15 (q, J = 8.0 Hz, 2H), 3.27 (m, 1H), 2.20 (m, 3H), 1.95 (m, 3H), 1.30 (t, J = 8.0 Hz, 3H), 0.88 (t, J = 8.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 143.7, 132.8, 128.4, 127.8, 127.5, 126.0, 60.3, 44.5, 32.6, 29.3, 14.3, 11.7 ppm; EIMS m/z 298−300 ($M^{+\cdot}$).

4-(2-Bromophenyl)-4-ethylhexanoic Acid Ethyl Ester 9d. Purified by column chromatography (96:4 heptane−AcOEt): yield 60% of a colorless oil. **9e**: IR ($CHCl_3$) 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.0 and 2.0 Hz, 1H), 7.34 (dd, J = 8.0 and 2.0 Hz, 1H), 7.25 (td, J = 8.0 and 2.0 Hz, 1H), 7.03 (td, J = 8.0 and 2.0 Hz, 1H), 4.08 (q, J = 8.0, 2H), 2.33 (m, 2H), 1.99 (m, 6H), 1.29 (t, J = 8, 3H), 0.70 (t, J = 8.0 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 143.3, 136.4, 130.2, 127.7, 127.0, 122.6, 60.3, 44.5, 29.9, 28.8, 26.3, 14.3, 8.5 ppm; CIMS m/z 327−329 (MH^+).

3-[1-(2-Bromophenyl)cyclopentyl]propionic Acid Ethyl Ester 9e. Purified by column chromatography (100:4 heptane−AcOEt): yield 89% of a colorless oil. **9e**: IR ($CHCl_3$) 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.0 and 1.0 Hz, 1H), 7.28 (dd, J = 8.0 and 1.0 Hz, 1H), 7.22 (td, J = 8.0 and 1.0 Hz, 1H), 7.04 (td, J = 8.0 and 1.0 Hz, 1H), 4.02 (q, J = 7.0 Hz, 2H), 2.23 (m, 3H), 1.97 (m, 5H), 1.73 (m, 4H), 1.21 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.8, 145.6, 135.4, 130.1, 127.7, 126.9, 123.2, 60.3, 51.5, 37.5, 23.2, 14.2 ppm; CIMS m/z 325−327 (MH^+).

Stille Coupling between (2-Trimethylstannanylphenyl)-carbamic Acid *tert*-Butyl Ester 10 and Bromides 9a to 9e. General Procedure. In a two-necked round-bottom flask, the bromide **9a**, **9b**, **9c**, **9d**, or **9e** (0.31 mmol) and $PdBnCl(PPh_3)_2$ (0.016 mmol) were stirred in dry toluene (8 mL) at room temperature for 10 min. *N*-(*tert*-Butoxycarbonyl)-2-(trimethylstannyl)aniline **10**[14] (0.34 mmol) was then added. The solution was stirred at 110 °C for 13 h. After cooling, the mixture was hydrolyzed and extracted with EtOAc. The organic layer was further dried with Na_2SO_4 and filtrated. The mixture obtained after removal of the solvent was chromatographed on silica gel. Although most of the dimer **12** could be removed by chromatography, some amount of it remains in the purified fraction of the coupling products **11b**, **11c**, and **11d**. The yield of these coupling products is thus given taking into account the amount of **12** calculated from the ^{1}H NMR spectra.

LiCl Procedure. A round-bottom flask containing a solution of **9c** (40 mg, 0.12 mmol in dry THF (4 mL) was degassed under argon. To this solution was added *N*-(*tert*-butoxycarbonyl)-2-(trimethylstannyl)aniline **10** (43.6 mg, 0.13 mmol), $PdBnCl(PPh_3)_2$ (4.6 mg, 0.006 mmol), and LiCl (20.6 mg, 0.49 mmol). The resulting solution was allowed to stir at 110 °C for 16 h. The reaction was then diluted in AcOEt and washed with NH_4OH (10%). The organic fraction was dried and concentrated to give a mixture which was chromatographed.

4-(2′-*tert*-Butoxycarbonylaminobiphenyl-2-yl)pentanoic Acid Ethyl Ester 11a (*R*,a*S*/*S*,a*R* and *R*,a*R*/*S*,a*S*). Purified by preparative thin-layer chromatography (9:1 heptane−AcOEt): white amorphous solid (yield 64% from **9a**). **11a**: IR ($CHCl_3$) 3400, 1725 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.19 and 8.11 (2d, J = 8.0 Hz, 1H), 7.47−7.28 (m, 4H), 7.14 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.19 and 6.08 (2s, 1H), 4.04 and 3.99 (2q, J = 7 Hz, 2H), 2.56 (m, 1H), 2.10 (m, 1H), 1.94 (m, 2H), 1.79 (m, 1H), 1.45 (s, 9H), 1.22 and 1.08 (2d, J = 7.0 Hz, 3H), 1.19 and 1.17 (2t, J = 7 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.6, 152.6, 145.3, 137.0, 136.8, 136.1, 130.6, 130.4, 130.2, 129.1, 128.5, 128.4, 126.7, 126.6, 126.4, 126.1, 122.7, 122.5, 118.7, 80.5, 60.3, 35.3, 34.6, 35.0, 34.0, 32.9, 32.5, 28.4, 28.3, 23.6, 22.1, 14.3 ppm; CIMS m/z 398 (MH^+). Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.71; H, 8.12; N, 3.51.

4-(2′-*tert*-Butoxycarbonylaminobiphenyl-2-yl)-4-methylpentanoic Acid Ethyl Ester 11b (a*S*/a*R*). Purified by preparative thin-layer chromatography (9:1 heptane−AcOEt): yellow oil containing **11b** (19% from **9b**) and **12**. **11b**: IR ($CHCl_3$) 3418, 1725 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.35 (m, 3H), 7.08 (m, 3H), 5.99 (bs, 1H), 4.09 (q, J = 7.0 Hz, 2H), 2.12−1.78 (m, 4H), 1.45 (s, 9H), 1.21 (t, J = 7.0 Hz, 3H), 1.20 and 1.07 (s, 6H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.9, 152.7, 146.0, 136.6, 136.2, 134.0, 133.4, 132.9, 130.3, 128.9, 128.5, 126.5, 122.0, 119.1, 80.5, 60.4, 39.6, 39.1, 30.7, 29.7, 28.4, 14.3 ppm; CIMS m/z 412 (MH^+).

4-(2′-*tert*-Butoxycarbonylaminobiphenyl-2-yl)hexanoic Acid Ethyl Ester 11c (*R*,a*S*/*S*,a*R* and *R*,a*R*/*S*,a*S*). Purified by preparative thin-layer chromatography (8:2 heptane−AcOEt): yield 56% (from **9c**) of a white amorphous solid. **11c**: IR ($CHCl_3$) 3410, 1725 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.17 (t, J = 8.0 Hz, 1H), 7.30 (m, 5H), 7.12 (m, 1H), 7.04 (m, 1H), 6.19 and 6.05 (2s, 1H), 4.02 (q, J = 7.0 Hz, 2H), 2.35 (m, 1H), 2.09−1.50 (m, 6H), 1.42 (s, 9H), 1.16 (t, J = 7.0 Hz, 3H), 0.88 and 0.67 (2t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.1, 174.0, 152.5, 144.1, 143.9, 137.6, 136.0, 135.1, 130.6, 129.0, 128.9, 128.4, 126.6 122.4, 122.3, 118.4, 80.4, 60.3, 41.8, 41.7, 32.7, 32.3, 31.8, 30.4, 29.9, 28.9, 28.30, 28.27, 14.3, 12.5, 11.8 ppm; CIMS m/z 412 (MH^+). Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40. Found: C, 73.24; H, 8.25; N, 3.35.

4-(2′-*tert*-Butoxycarbonylaminobiphenyl-2-yl)-4-ethylhexanoic Acid Ethyl Ester 11d (a*S*/a*R*). LiCl procedure. Purified by preparative thin-layer chromatography (7:3 hexanes−Et_2O): yellow oil containing **11d** (7% from **9d**)) and **12**. **11d**: IR ($CHCl_3$) 3250, 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (bd, J = 8.0 Hz, 1H), 7.51 (bd, J = 8 Hz, 1H), 7.20 (m, 6H), 6.02 (s, 1H), 4.09 (q, J = 8.0 Hz, 2H), 1.70 (m, 4H), 1.50 (m, 4H), 1.42 (s, 9H), 1.22 (t, J = 8.0 Hz, 3H), 0.69 and 0.60 (t, J = 8.0 Hz, 6H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.1, 153.0, 144.7, 137.2, 133.4, 133.3, 130.6, 130.1, 128.3, 128.2, 126.4, 121.7, 118.6, 80.4, 60.4, 45.9, 31.2, 29.7, 28.5, 28.38, 28.3, 14.4, 8.7 ppm; CIMS m/z 440 (MH^+).

4-[1-(2′-*tert*-Butoxycarbonylaminobiphenyl-2-yl)cyclopentylpropionic Acid Ethyl Ester 11e (a*S*/a*R*). Purified by column chromatography (100:7 heptane−AcOEt): yellow oil containing **11e** (6% from **9e**) and **12**. **11e**: IR ($CHCl_3$) 3419, 1725 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 1H), 7.30 (m, 4H), 7.15 (bd, J = 8.0 Hz, 1H), 7.04 (m, 2H), 6.06 (bs, 1H), 4.04 (q, J = 7.0 Hz, 2H), 2.12−1.40 (m, 12H), 1.42 (s, 9H), 1.22 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.0, 152.8, 146.5, 136.9, 136.4, 132.3, 130.5, 130.1, 128.3, 127.9, 126.5, 121.8, 119.1, 80.6, 60.4, 51.8, 37.5, 36.6, 32.8, 30.9, 28.4, 22.7, 21.9, 14.3 ppm; EIMS m/z 437 ($M^{+\cdot}$).

2,2′-(Bis(*N*-*tert*-butoxycarbonylamine)biphenyl 12. Isolated as a white amorphous solid from the above purifications. yield: 10% from the cross-coupling reaction of **9a** with **10**, 40% from the cross coupling reaction of **9b**, **9d**−**9e** with **10**. **12**: IR

($CHCl_3$) 3412, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 7.0 Hz, 2H), 7.43 (m, 2H), 7.15 (m, 4H), 6.26 (s, 2H), 1.54 (s, 18H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 136.6, 130.6, 129.6, 129.1, 126.5, 123.4, 120.1, 80.8, 28.4 ppm; EIMS m/z 384 ($M^{+\bullet}$).

Preparation of Amines 13a−e. General Procedure. To a solution of biaryl **11a**, **11b** (87%), **11c**, **11d** (90%), or **11e** (96%) (0.136 mmol) in methylene chloride (1 mL) was added at 0 °C 1 mL of trifluoroacetic acid. The mixture was stirred at 0 °C for 15 min. After neutralization with aqueous saturated Na_2CO_3 and extraction with AcOEt, the organic phase was dried and filtered and the solvent was removed to give the crude extract which was chromatographed.

4-(2′-Aminobiphenyl-2-yl)pentanoic Acid Ethyl Ester 13a (*R*,a*S*/*S*,a*R* and *R*,a*R*/*S*,a*S*). Purified by preparative thin-layer chromatography (8:2 heptane−AcOEt): yield 86% of a white amorphous solid. **13a**: IR ($CHCl_3$) 3450, 3350, 1725, 1620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40−7.19 (m, 6H), 7.09 (d, J = 8.0, 1H), 6.95 (t, J = 8.0, 1H), 4.06 (q, J = 7.0, 2H), 3.87 (bs, 2H), 2.63 (m, 1H), 2.07−1.82 (m, 4H), 1.15 (m, 6H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.9, 145.4, 144.0, 135.8, 131.2, 130.6, 130.4, 128.4, 126.6, 126.4, 126.3, 126.1, 118.2, 117.9, 115.1, 114.9, 61.1, 60.4, 35.0, 34.8, 33.6, 33.0, 32.6, 32.5, 23.2, 22.3, 14.2, 14.0 ppm; EIMS m/z 297 ($M^{+\bullet}$).

4-(2′-Aminobiphenyl-2-yl)-4-methylpentanoic Acid Ethyl Ester 13b (a*S*/a*R*). Purified by column chromatography (6:4 heptane−AcOEt): yield 78% of a white amorphous solid. **13b**: IR ($CHCl_3$) 3494, 3394, 1725, 1613 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.0 and 1.0 Hz, 1H), 7.33 (td, J = 8.0 and 1.0 Hz, 1H), 7.22 (td, J = 8.0 and 1.0 Hz, 1H), 7.16 (td, J = 8.0 and 1.0 Hz), 1H, 7.04 (2dd, J = 8.0 and 1.0 Hz, 2H), 6.78 (td, J = 8.0 and 1.0 Hz, 1H), 6.72 (bd, J = 8.0 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 3.42 (bs, 2H), 2.09 (m, 3H), 1.82 (m, 1H), 1.28 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H), 1.18 (s, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.6, 146.1, 144.1, 138.2, 133.1, 130.7, 130.6, 128.6, 127.8, 126.5, 126.0, 117.5, 115.1, 60.3, 39.5, 38.9, 30.9, 29.9, 29.4, 14.3 ppm; CIMS m/z 312 (MH^+).

4-(2′-Aminobiphenyl-2-yl)hexanoic Acid Ethyl Ester 13c (*R*,a*S*/*S*,a*R* and *R*,a*R*/*S*,a*S*). Purified by column chromatography (7:3 heptane−AcOEt): yield 62% of a white amorphous solid. **13c**: IR ($CHCl_3$) 34580, 3400, 1725, 1618 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.98 (m, 1H), 6.79 (m, 2H), 4.02 (2q, J = 7.0 Hz, 2H), 3.49 (bs, 2H), 2.52 (m, 1H), 2.18−1.58 (m, 6H), 1.20 (2t, J = 7.0 Hz, 3H), 0.80 (2t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.0, 144.1, 139.0, 130.9, 130.8, 130.5, 130.4, 128.4, 128.2, 126.8, 126.3, 117.9, 117.8, 115.0, 60.2, 41.6, 32.9, 32.5, 31.5, 30.6, 30.1, 29.1, 14.2, 12.3, 12.0 ppm; CIMS m/z 312 (MH^+).

4-(2′-Aminobiphenyl-2-yl)-4-ethylhexanoic Acid Ethyl Ester 13d (a*S*/a*R*). Purified by column chromatography (8:2 hexanes−Et_2O): yield 95% of a white amorphous solid. **13d**: IR ($CHCl_3$) 3488, 3400, 1725, 1613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, J = 8.0 and 2.0 Hz, 1H), 7.33 (td, J = 8.0 and 2.0 Hz, 1H), 7.23 (td, J = 8.0 and 2.0 Hz, 1H), 7.14 (td, J = 8.0 and 2.0 Hz, 1H), 7.02 (m, 2H), 6.72 (m, 2H), 4.10 (q, J = 8.0 Hz, 2H), 3.42 (s, 2H), 1.89 (m, 4H), 1.63 (m, 4H), 1.24 (t, J = 8.0 Hz, 3H), 0.69 (t, J = 8.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 144.8, 144.3, 139.0, 133.7, 130.5, 129.7, 128.4, 127.7, 126.4, 117.5, 115.3, 60.4, 45.8, 31.2, 30.1, 28.1, 27.8, 14.5, 8.7 ppm; CIMS m/z 340 (MH^+).

4-(2′-Aminobiphenyl-2-yl)cyclopentylpropionic Acid Ethyl Ester 13e (a*S*/a*R*). Purified by preparative thin-layer chromatography (8:2 heptane−AcOEt): yield 95% of a white amorphous solid. **13e**: IR ($CHCl_3$) 3488, 3394, 1725, 1612 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (td, J = 8.0 and 1.0 Hz, 1H), 7.29 (dd, J = 8.0 and 1.0 Hz, 1H), 7.24 (td, J = 8.0 and 1.0 Hz, 1H), 7.17 (td, J = 8.0 and 1.0 Hz, 1H), 7.08 (m, 2H), 6.78 (td, J = 8.0 and 1.0 Hz, 1H), 6.72 (bd, J = 8.0 Hz, 1H), 4.04 (q, J = 8.0, 2H), 3.46 (bs, 2H), 2.10−1.42 (m, 12H), 1.24 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 138.0, 130.8, 129.9, 129.7, 128.4, 127.3, 126.4, 117.4, 115.1, 60.3, 51.7, 37.9, 35.9, 32.9, 31.0, 22.7, 22.1, 14.3; CIMS m/z 338 (MH^+).

Preparation of Acids 14a−e. General Procedure. To a solution of amine **13a**, **13b**, **13c**, **13d** or **13e** (0.1 mmol) in methanol (1 mL) was added an aqueous solution of NaOH (50%). After refluxing the mixture for 3 h, the solution was extracted with AcOEt. The aqueous phase was acidified (pH = 5) with 1 N HCl. After extraction with AcOEt, the organic layers were dried over Na_2SO_4. After removal of the solvent, the crude extracts were chromatographed if necessary.

4-(2′-Aminobiphenyl-2-yl)pentanoic Acid 14a (*R*,a*S*/*S*,a*R* and *R*,a*R*/*S*,a*S*). Yield: 100% of a white amorphous solid. **14a**: IR ($CHCl_3$) 3488, 3394, 1713, 1612 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 6.98 (d, J = 8.0 Hz, 1H), 6.64 (m, 2H), 5.12 (bs, 3H), 2.61 (m, 1H), 2.09 (m, 2H), 1.80 (m, 2H), 1.17 and 1.15 (2d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 145.1, 144.0, 143.7, 138.4, 130.6, 130.4, 128.5, 127.2, 126.9, 126.3, 126.6, 126.4, 126.1, 118.2, 115.4, 115.0, 34.9, 34.5, 33.4, 32.7, 32.0, 23.2, 22.4 ppm; CIMS m/z 270 (MH^+).

4-(2′-Aminobiphenyl-2-yl)-4-methylpentanoic Acid 14b (a*S*/a*R*). Purified by preparative thin-layer chromatography (92:8 CH_2Cl_2−MeOH): yield 91% of a white amorphous solid. **14b**: IR ($CHCl_3$) 3394, 1730, 1612 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 1H), 7.32 (J = 8.0 and 1.0 Hz, 1H), 7.23 (bt, J = 8.0 Hz, 1H), 7.16 (bt, J = 8.0 Hz, 1H), 7.03 (2bd, J = 8.0 Hz, 2H), 6.79 (bt, J = 8.0 Hz, 1H), 6.73 (bd, J = 8.0 Hz, 1H), 5.10 (bs, 3H), 2.01 (m, 4H), 1.22 (s, 3H), 1.19 (s, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 181, 146.0, 143.6, 138.1, 133.0, 130.9, 130.6, 128.6, 128.5, 128.0, 126.6, 118.1, 115.6, 50.9, 39.5, 31.3, 30.2, 29.5 ppm; CIMS m/z 284 (MH^+).

4-(2′-Aminobiphenyl-2-yl)hexanoic Acid 14c (*R*,a*S*/*S*,a*R* and *R*,a*R*/*S*,a*S*). Purified by preparative thin-layer chromatography (91:9 CH_2Cl_2−MeOH): yield 96% of a white amorphous solid. **14c**: IR ($CHCl_3$) 3400, 1720, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5H), 7.05 (d, J = 8.0 Hz, 1H), 6.84 (m, 2H), 6.40 (s, 3H), 2.61 (m, 1H), 2.19 (m, 2H), 1.95 (m, 2H), 1.63 (2q, J = 7.0 Hz, 2H), 0.84 and 0.82 (2t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 138.6, 130.4, 130.3, 130.1, 129.9, 128.0, 127.8, 126.6, 126.0, 125.9, 117.6, 114.9, 114.7, 41.1, 30.9, 30.2, 29.6, 28.5, 12.4, 11.8, 11.5 ppm; CIMS m/z 284 (MH^+).

4-(2′-Aminobiphenyl-2-yl)-4-ethylhexanoic Acid 14d (a*S*/a*R*). Purified by preparative thin-layer chromatography (92:8 CH_2Cl_2−MeOH): yield 77% of a white amorphous solid. **14d**: IR ($CHCl_3$) 3400, 1712, 1612 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.59 (bd, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.14 (m, 2H), 6.91 (m, 2H), 5.40 (bs, 3H), 2.12−1.64 (m, 8H), 0.85 and 0.75 (t, J = 7.0 Hz, 6H) ppm; ^{13}C NMR (60 MHz, $CDCl_3$) δ 144.5, 143.3, 138.3, 133.3, 131.0, 130.4, 129.7, 128.4, 127.8, 126.4, 118.4, 115.9, 45.4, 31.2, 30.8, 27.8, 27.2, 8.5, 8.3 ppm; EIMS m/z 311 ($M^{+\bullet}$).

3-[1-(2′-Aminobiphenyl-2-yl)cyclopentyl)]propionic Acid 14e (a*S*/a*R*). Purified by preparative thin-layer chromatography (92:8 CH_2Cl_2−MeOH): yield 84% of a white amorphous solid. **14e**: IR ($CHCl_3$) 3400, 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.05 (m, 2H), 6.78 (t, J = 8.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 5.52 (bs, 3H), 2.01−1.57 (3m, 12H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 146.5, 143.8, 138.2, 132.4, 131.0, 130.0, 129.8, 128.4, 127.4, 126.5, 118.0, 115.6, 51.7, 38.6, 36.0, 33.0, 31.7, 22.6, 22.4 ppm; CIMS m/z 310 (MH^+).

Cyclization of Amino Acids 14a−e. General Procedure. A solution of **14a**, **14b**, **14c**, **14d**, or **14e** (0.177 mmol) and NEt_3 (0.177 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of EDCI (0.177 mmol) and HOBT (0.177 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C. The mixture was stirred for 84 h. After evaporation of the solvent, the solid mixture was dissolved in AcOEt and the solution was washed with aqueous saturated Na_2CO_3 and water. After drying over Na_2SO_4 and filtration, the organic phase was evaporated. The crude extract was then chromatographed to give compound **4a**, **4b**, **4c**, **4d**, or **4e**.

9-Methyl-5,7,8,9-tetrahydro-5-azadibenzo[*a*,*c*]cyclononen-6-one 4a (*R*,a*R*/*S*,a*S*). Purified by preparative thin-layer chromatography (97:3 CH_2Cl_2−MeOH): yield 71% of a white amorphous solid. **4a**: IR ($CHCl_3$) 3381, 1665 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40 (m, 7H), 6.96 (d, J = 8.0 Hz, 1H), 6.60 (bs, 1H), 2.42 (m, 1H), 2.14 (m, 2H), 1.81 (m, 2H), 1.23 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.4, 144.0, 129.3, 129.0, 128.7, 127.7, 126.1, 126.0, 37.0, 36.4, 33.9, 23.1 ppm; EIMS m/z 251 ($M^{+\bullet}$); HRMS calcd for $C_{17}H_{17}NO$ (MH^+) 251.1310, found 251.1319.

9,9-Dimethyl-5,7,8,9-tetrahydro-5-azadibenzo[*a*,*c*]cyclononen-6-one 4b (a*R*/a*S*). Purified by preparative thin-layer chromatography (97:3 CH_2Cl_2−MeOH): yield 78% of a white amorphous solid. **4b**: IR ($CHCl_3$) 3381, 1662 cm^{-1}; ^1H NMR

(250 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 1H), 7.40 (m, 2H), 7.34 (bt, J = 8.0 Hz, 1H), 7.23 (m, 2H), 7.20 (t, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.84 (bs, 1H), 2.42 (m, 2H), 1.79 (m, 2H), 1.48 (s, 3H), 0.92 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, 263 K) δ 177.0, 145.5, 135.6, 130.4, 129.1, 128.4, 128.2, 127.9, 127.8, 127.4, 42.3, 39.3−34.7, 29.5−27.5 ppm; CIMS *m*/*z* 266 (MH^+); HRMS calcd for $C_{18}H_{19}NO$ (MH^+) 265.1467, found 265.1473.

9-Ethyl-5,7,8,9-tetrahydro-5-azadibenzo[*a*,*c*]cyclononen-6-one 4c (*R*,a*R*/*S*,a*S*). Purified by preparative thin-layer chromatography (95:5 CH_2Cl_2−MeOH): yield 81% of a white amorphous solid. **4c**: IR ($CHCl_3$) 3400, 1662 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40 (m, 5H), 7.28 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.02 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 2.10−1.55 (3m, 7H), 0.65 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.5, 143.2−136.5, 129.3−125.9, 45.0, 35.0, 34.2, 29.6, 12.4 ppm; CIMS *m*/*z* 266 (MH^+); HRMS calcd for $C_{18}H_{19}NO$ (MH^+) 265.1467, found 265.1473

9,9-Diethyl-5,7,8,9-tetrahydro-5-azadibenzo[*a*,*c*]cyclononen-6-one 4d (a*R*/a*S*). Purified by preparative thin-layer chromatography (97:3 CH_2Cl_2−MeOH): yield 74% of a white amorphous solid. **4d**: IR ($CHCl_3$) 3380, 1662 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 1H), 7.39 (m, 3H), 7.33 (m, 1H), 7.20 (m, 2H), 6.84 (d, J = 8.0 Hz, 1H), 6.68 (s, 1H), 2.39−1.78 (m, 6H), 1.27 (m, 2H), 0.82 (t, J = 7.0 Hz, 3H), 0.71 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 263 K) δ 177.4, 138.5, 135.7, 130.9, 129.5, 128.7, 128.5, 128.1, 127.9, 127.7, 125.9, 45.3, 38.1−24.1, 8.3, 8.2 ppm; EIMS *m*/*z* 293 ($M^{+\bullet}$); HRMS calcd for $C_{20}H_{23}NO$ (MH^+) 293.1780, found 293.1782.

9,9-Tetramethylene-5,7,8,9-tetrahydro-5-azadibenzo[*a*,*c*]-cyclononen-6-one 4e (a*R*/a*S*). Purified by preparative thin-layer chromatography (97:3 CH_2Cl_2−MeOH): yield 79% of a white amorphous solid. **4e**: IR ($CHCl_3$) 3378, 1662 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40 (m, 4H), 7.32 (td, J = 8.0 and 1.0 Hz, 1H), 7.32 (td, J = 8.0 and 1.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.17 (bt, J = 8.0 Hz, 1H), 6.85 (dd, J = 8.0 Hz, 1H), 6.77 (s, 1H), 2.30−1.08 (m, 12H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.9, 147.7, 145.2, 138.2, 136.2, 131.1, 129.7, 129.3, 128.6, 128.3, 127.7, 125.8, 52.0, 42.5, 36.6, 34.8, 29.7, 23.2, 21.0 ppm; CIMS *m*/*z* 292 (MH^+); HRMS calcd for $C_{20}H_{21}NO$ (MH^+) 291.1623, found 291.1624.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **6a**−**e** to **11a**−**e**, **12**, **13a**−**e**, **14a**−**e**, and **4a**−**e** (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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