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Antimitotic Agents Interacting with Tubulin: Synthesis and Structure-Activity Relationships of Novel *Ortho* Bridged Biphenyls of the Rhazinilam Type.

Cécile Pascal, Joëlle Dubois, Daniel Guénard, Luba Tchertanov, Sylviane Thoret and Françoise Guéritte*

Institut de Chimie des Substances Naturelles, CNRS, 91198- Gif-sur-Yvette Cedex, France

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Abstract Several new *ortho* bridged biphenyls mimicking the structure of (-)-rhazinilam were synthesized and evaluated as cytotoxic compounds and as inhibitors of microtubules disassembly. These included azadibenzo[a,c]cyclononene derivatives having an ester, urea or carbamate function present in the 9-membered ring linking the two phenyl moieties. The compound bearing a carbamate function instead of the amide group of rhazinilam interacts better with tubulin than (-) rhazinilam. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Biaryls; Biologically active compounds; Coupling reactions; Structure-activity

Antimitotic agents interacting with tubulin are one of the most important classes of anticancer drugs used clinically. Examples of these drugs are the taxoids paclitaxel and docetaxel, which stabilize microtubules[1] and the *Vinca* alkaloids vinblastine and vincristine, which are inhibitors of tubulin assembly[1]. Other natural products interact also with tubulin in a manner similar to that of the *Vinca* alkaloids or taxoids[2]. Recently, epothilones[3], discodermolide[4] as well as eleutherobin[5] have been described as new microtubule-stabilizing compounds with a paclitaxel-like activity. Among the inhibitors of tubulin assembly, some such as maytansinoids, rhizoxin and dolastatins, interact at the "*vinca*" site, while others bind to the colchicine site (podophyllotoxin and combretastatins)[2]. In addition to these "spindle poisons", (-)-rhazinilam **1** belongs to a new series of substances interacting with microtubules[6]. This phenylpyrrole compound **1** was initially isolated from *Melodinus australis*[7] and *Rhazia stricta*[8,9] and its structure was elucidated by Abraham *et al.* in 1972[10]. Later on, (-)-rhazinilam **1**, isolated from a Malaysian *Kopsia, K. singapurensis*, was recognized as a microtubule poison in *in vitro* assays, inhibiting tubulin assembly[11] in the same manner as *vinca* alkaloids as well as cold-induced disassembly of microtubules such as taxoids[6]. Because of this peculiar mechanism, the effects of rhazinilam on mammalian cells

* E-mail : gueritte@icsn.cnrs-gif.fr fax : 33(0)169077247

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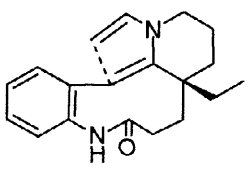
and its interaction with tubulin have been studied in detail[6]. It has thus been shown that the *in vitro* inhibitory effect of rhazinilam on tubulin assembly was due to the formation of abnormal spiral structures, whereas the taxol-like activity could be due to the binding of (-)-rhazinilam **1** at the ends of microtubules thereby resulting in stabilized microtubules. Despite its biological interest, (-)-rhazinilam **1** cannot be considered as a potential pharmacological agent because of its *in vivo* lack of activity. For this reason, analogs have been prepared by structural modifications of (-)-rhazinilam[12] or by synthesis of phenylpyrrole compounds such as **2**[13,14,15]. Evaluation of the activity of these compounds on the disassembly process of microtubules led to the conclusion that the presence of the aromatic units as well as the lactam function is essential for good binding to tubulin[12]. It has also been shown that the size of the lactam ring as well as the bulkiness of the substituents present on this ring have an influence in the interaction with microtubules[13,14,15].



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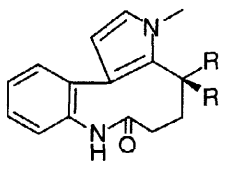
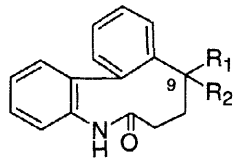
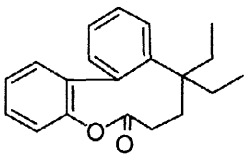


2 R= H or Et



	R_1	R_2		R_1	R_2
3	Et	Et	**5**	Me	H
4	Et	H	**6**	Me	Me



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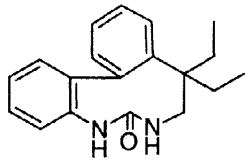

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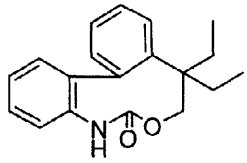

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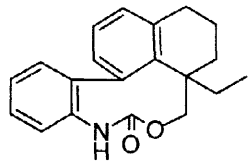

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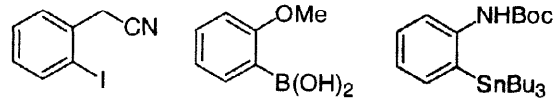
Moreover, absolute configuration is of great importance in the binding since the enantiomer (+)-rhazinilam was inactive on tubulin[12]. In the course of this program, we recently focused on the synthesis of biphenyls mimicking the structure of (-)-rhazinilam **1** with the thought that a phenyl unit could replace the pyrrole ring of rhazinilam without affecting the interaction with tubulin[16,17]. Thus, we found that racemic biphenyl lactam **3**[17] having a diethyl substitution at carbon 9 interacts with tubulin in a similar way as (-)-rhazinilam **1**. Moreover, the monoethyl derivative **4** as well as the monomethyl and dimethyl derivatives **5** and **6** were all less active than **3**[17], showing that the size of the alkyl groups at C-9 exerts marked effects on the interaction with tubulin. This has also been shown in the phenylpyrrole series[15].

Encouraged by these promising results, we next turned to the synthesis of *ortho*-bridged biphenyl compounds in which the lactam function of **3** is replaced by a lactone, a urea or a carbamate group. We report here the synthesis of biphenyls **7-10** and their effects on tubulin and cytotoxicity.

Chemistry

Commercial (2-iodophenyl)acetonitrile **11** served as starting material for the synthesis of compounds **7**, **8**, **9** and **10**. A Suzuki or Stille type coupling was used to form the biphenyl unit from the required halide and (2-methoxyphenyl)boronic acid **12**[18] or (2-tributyl-stannanylphenyl)carbamic acid *tert*-butyl ester **13**[19].

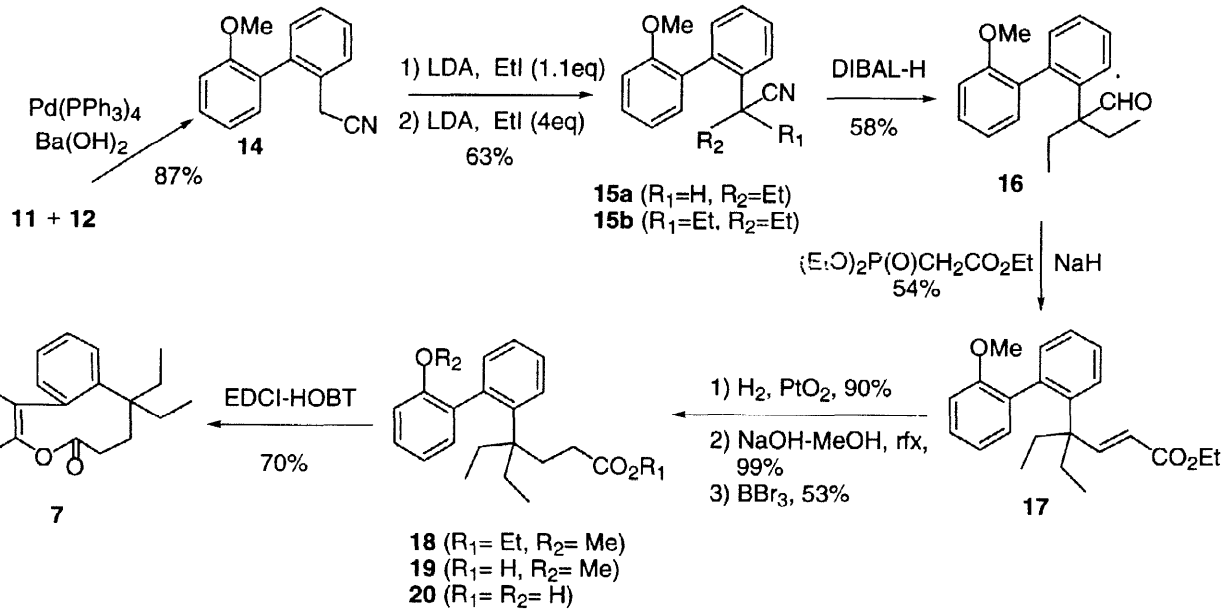


11 12 13

a. *Synthesis of lactone 7*

The Suzuki Pd(0)-catalyzed cross coupling of (2-iodophenyl)acetonitrile **11** with (2-methoxyphenyl)-boronic acid **12** afforded the corresponding biphenyl **14** with a yield of 87% when the reaction was realized in presence of tetrakis(triphenylphosphine)palladium(0) and barium hydroxide in 1,2-dimethoxyethane and ethanol[20] (Scheme 1). It should be noted that compound **14** has been already described as an intermediate in the synthesis of cytotoxic 4,5-dioxoaporphine[21].

Direct dialkylation of nitrile **14** proceeded only slowly. Better results were obtained by performing the alkylation in two steps: the first alkylation, leading to the monoethyl derivative **15a** (85%), was realized with one equivalent of LDA and ethyl iodide. The desired diethyl biphenyl **15b** was then obtained after alkylation of **15a** using 4 equivalents of LDA and ethyl iodide. Reduction of nitrile **15b** was carried out with DIBAL-H to yield **16** which was in turn treated with triethyl phosphonoacetate and NaH[22] to afford *trans*-alkene **17** selectively. Hydrogenation of **17** (to give compound **18**) followed by methanolysis (compound **19**) and deprotection of the methoxy group with BBr_3 furnished biphenyl **20**. Finally, intramolecular cyclization of **20** under high dilution conditions yielded the biphenyl lactone **7**.

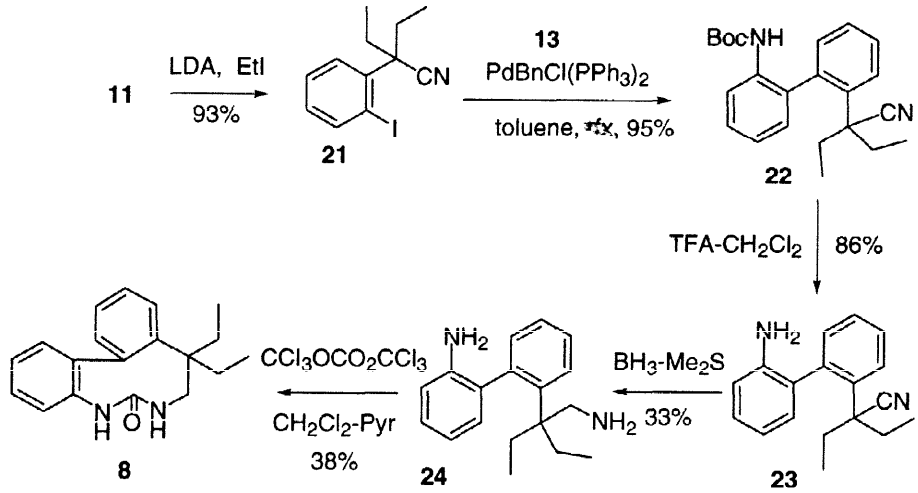


Scheme 1

b. *Synthesis of the urea analog 8*

The urea analog **8** was synthesized by a Stille coupling between stannane **13** and halide **21**. In contrast to the preceding synthesis, the dialkylation was directly realized on (2-iodophenyl)acetonitrile **11** before attempting the cross coupling reaction, in order to avoid the need to protect the carbamate group of **13** (Scheme 2). The diethyl derivative **21**, obtained with good yield from **11**, was coupled with (2-tributylstannanylphenyl)carbamic acid *tert*-butyl ester **13** in the presence of PdBnCl(PPh3)2 in toluene under reflux to give biphenyl **22** (95%

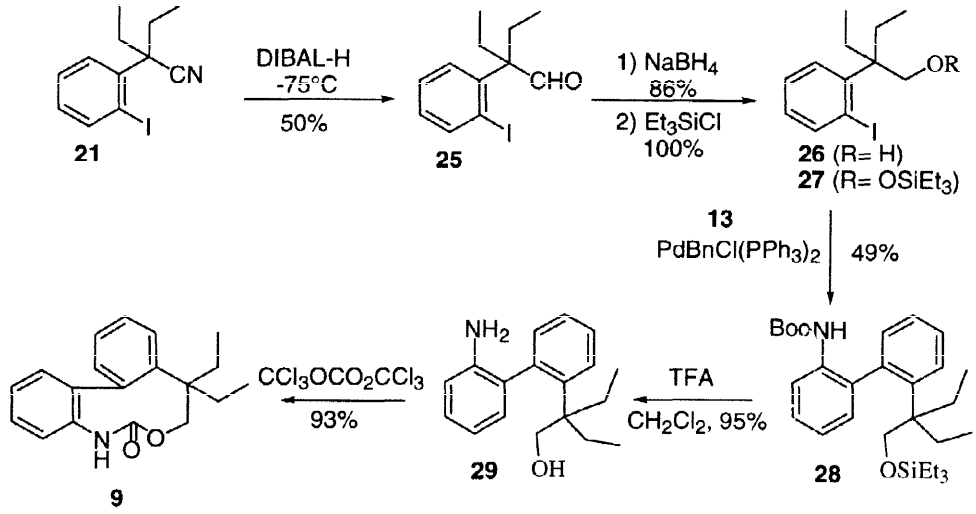
yield). The Boc protecting group of **22** was then removed using trifluoroacetic acid in methylene chloride to give **23**. Reduction of the nitrile group with $Me_2S.BH_3$ produced the diamine **24** which gave the biphenyl urea **8** after treatment with triphosgene.



Scheme 2

c. Synthesis of the urethane analogs 9 and 10

Scheme 3 shows the synthesis of the diethyl urethane analog **9**. Nitrile **21**, obtained in the preceding synthesis, was reduced to aldehyde **25** after treatment with DIBAL-H. Compound **25** was then subjected to reduction with sodium borohydride to give the primary alcohol **26**. We first attempted the Stille cross-coupling between **26** and stannane **13**, but no biphenyl product was obtained when we used the same coupling conditions as above.

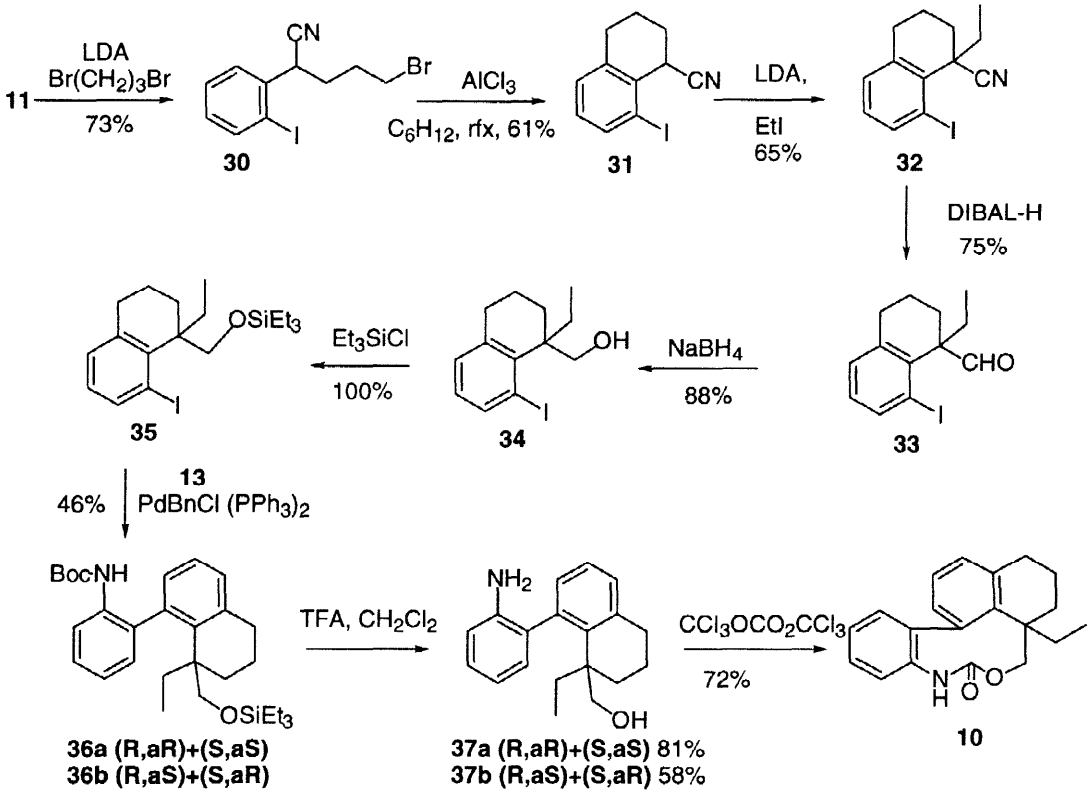


Scheme 3

We therefore decided to attempt the coupling reaction with the protected derivative **27** obtained after treatment of **26** with triethylsilyl chloride. Biphenyl **28** was formed in moderate yield (49%). The lower yield of the coupling product **28** compared to **22** (see scheme 2) may be due to an unfavorable interaction occurring

between the silyloxy group and palladium thus inhibiting the transmetallation process. The two protective groups of **28** were removed in a one pot procedure with trifluoroacetic acid. This led to compound **29** in 95% yield. Finally, compound **29** was converted to the desired urethane derivative **9** by treatment with triphosgene.

As illustrated in Scheme 4, the tetracyclic urethane **10** was synthesized similarly to the tricyclic urethane **9** using the iodo derivative **32** prepared from (2-iodophenyl)acetonitrile **11**.



Scheme 4

Thus, (2-iodophenyl)acetonitrile **11** was first alkylated with 1,3-dibromopropane. Friedel-Crafts intramolecular alkylation of **30** then led to **31** which was again alkylated with ethyl iodide to give the halo derivative **32**. After reduction of the latter to aldehyde **33** and then to primary alcohol **34**, protection of the resulting hydroxyl group using chlorotriethylsilane led to compound **35**. Palladium-catalyzed cross-coupling reaction of **35** with **13** furnished a pair of racemic diastereoisomers **36a** and **36b** which were purified by chromatography. The configuration of the racemic diastereoisomers **36a** and **36b** was assigned on the basis of NOESY data. A NOESY connection of the hydrogen-bonded nitrogen to the methyl protons in the spectra of **36a** indicated that this racemic compound possesses a (R,aR), (S,aS) configuration as shown in figure 1. On the other hand, no NOESY correlation exists between these two groups in the other diastereoisomer **36b** (Figure 1). Removal of the protective groups of **36a** and **36b** led finally to compounds **37a** and **37b**, respectively. The (R,aR)+(S,aS) configuration of **36a** and **37a** and (S,aR)+(R,aS) configuration of **36b** and **37b** were confirmed by the fact that only compound **37b** reacts with triphosgene to give the urethane biphenyl analog **10** (Figure 1).

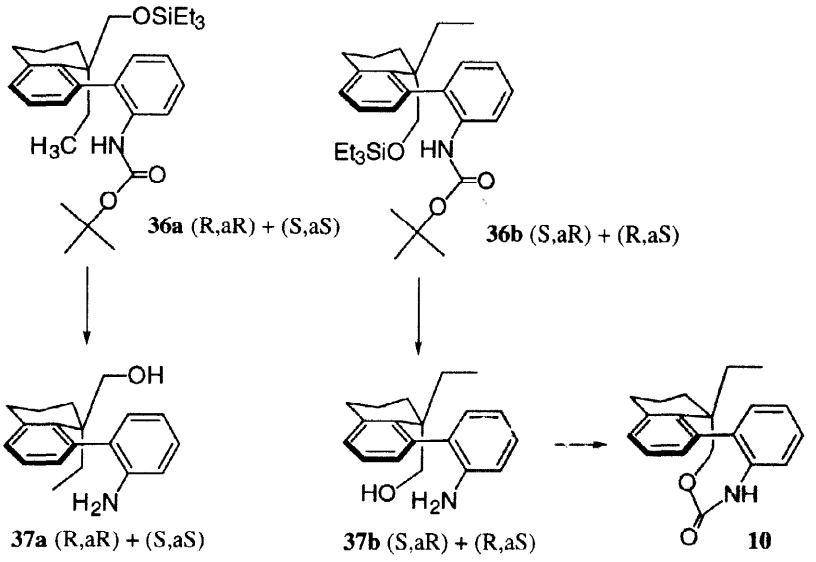


Figure 1

Biological results, conformational study and discussion

The effects of biphenyls **7**, **8**, **9** and **10** on tubulin disassembly and cytotoxicity are summarized in Table I. Inhibition of tubulin disassembly was evaluated using tubulin from bovine brain[12]. Cytotoxicity was examined on the KB human cancer line[23].

Table 1. Cytotoxicity and Antitubulin Activity of Rhazinilam 1 and Biphenyls 3, 7-10

Compound	cytotoxicity (KB cell line) IC_{50} (μM)[a]	inhibition of microtubules disassembly IC_{50} (μM)[b]
(-) rhazinilam **1**	2	3
3	22	24
7	22	inactive
8	80	45
9	5	3
(+)-9	10	inactive
(-)-9	2	1.5
10	21	9

[a] The cytotoxicity IC_{50} values refer to the concentration of compounds corresponding to 50% growth inhibition after 72 h incubation. [b] IC_{50} is the concentration of test compound required to inhibit 50% of the rate of microtubules disassembly

The biological activities of the new biphenyls were compared to those of (-)-rhazinilam **1** and racemic **3**[17]. It should be noted that compounds **7**, **8**, **9** and **10** were first examined in their racemic form. Results of our earlier study showed that the phenyl unit can replace the pyrrole ring without great loss of interaction with microtubules[17]: racemic **3** is only 8 times less active than (-)-rhazinilam **1**. Moreover, we showed that the

bulkiness of the substituents at C-9 is important for anti-tubulin activity: compounds **4**, **5** and **6** are much less active than **3**. Concerning the modifications of the lactam function, the biological results clearly demonstrate the superiority of the urethane group (compounds **9** and **10**) over lactam (compound **3**), lactone (compound **7**) and urea groups (compound **8**). The observed significant loss of antitubulin activity of lactone **7** compared to lactam **3** confirms the fact that the presence of a nitrogen atom is an essential feature for interaction with the receptor as mentioned earlier[12]. Interestingly, racemic **9** has an antitubulin activity superior to that of biphenyl lactam **3** and similar to that of (-)-rhazinilam **1**. Consequently, atropisomers (+)-**9** and (-)-**9** were separated at room temperature by HPLC on a Nucleodex column using methanol-H_2O (70:30) as eluant at 0.8 ml/mn. The superior activity of (-)-**9** over (+)-**9** shows that the binding interaction with microtubules is stereoselective. These results suggest that, for the racemic compounds **8** and **10**, the (-)-isomer is responsible for the inhibition of microtubules disassembly. Regarding the cytotoxicity of the compounds, one observes a rather good correlation with the microtubules disassembly assay. Some discrepancies are, however, observed for compounds (+)-**9** and **7** which possess some cytotoxicity on KB cells but do not show any interaction with microtubules. As table 1 shows, racemic urethane **9** exhibited an 8-fold stronger anti-tubulin activity than racemic lactam **3**. This fact may imply that the conformation of the B-ring which may be different in compounds **3** and **9** plays a role in the binding or that the oxygen atom in urethane **9** stabilizes the interaction with microtubules. It must be emphasized that the ^{13}C NMR spectrum of racemic **3**, realized at room temperature, does not show all the signals corresponding to the carbons of the B-ring[17] This may indicate the presence of several conformers, in slow equilibrium, due to the flexibility of the B-ring[17]. In contrast, the ^{13}C NMR spectrum of **9**, run under the same conditions, displays signals corresponding to every carbon atom of the molecule showing that one unique conformation exists in solution.

The X-ray structure of racemic **9**[24] (figure 2) indicated that the pair of phenyl rings are nearly perpendicular to each other (dihedral angle 86°). The NHC(=O)-O fragment forms a dihedral angle of 53° with the nearest six-membered ring. The NH-C(O)-O-CH_2 torsion angle is -144°. The 9-membered ring of urethane **9** adopts a boat-chair conformation similar to that of (-)-rhazinilam **1**[10], and both compounds clearly show a similar overall three-dimensional structure.

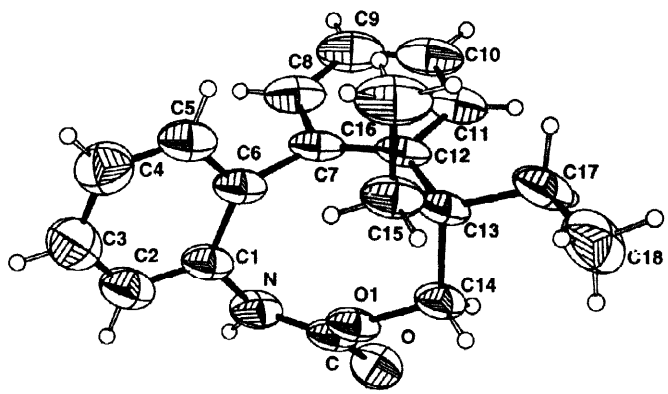


Figure 2. X-ray crystallographic structure of **9**
(the crystallographic numerotation of atoms was used)

The conformations of rhazinilam **1**, lactam **3** and biphenyls **7**-**10** were then studied by molecular modeling. When compared to the X-ray structure, the overall conformations of **1**, **7**, **9** and **10** obtained by

molecular modeling are approximately similar, showing a boat-chair conformation of the B ring. On the other hand, the B ring of biphenyl lactam **3** and urea **8** assumes a boat-boat conformation whereas the biaryl unit adopts a position similar to that of compound **9**. Taking into account that compounds **3** and **8** are less active than urethane **9**, these results strongly suggest that a boat-chair conformation of the B ring may be an essential factor for an optimized interaction with microtubules. Concerning the absolute configuration, the activity of (-)-**9** and the inactivity of (+)-**9** on microtubules disassembly led us to conclude that (-)-**9** possesses the same configuration around the biphenyl axis as (-)-rhazinilam **1**.

In conclusion, we have synthesized four novel biphenyl compounds showing a similar activity on microtubules disassembly as natural (-)-rhazinilam **1**. Among these products, compound (-)-**9** possesses a better interaction with microtubules than (-)-rhazinilam **1** and lactam **3**, showing that the replacement of the lactam by a urethane function is favorable for the binding with tubulin. Considering these results, we are presently attempting to synthesize new substituted biphenyl derivatives as well as phenylpyrrole analogs of rhazinilam possessing a urethane function in the 9-membered ring.

Experimental Section

Mps were measured on a Köfler apparatus. Infrared spectra were recorded on a Nicolet FT-IR 205 and UV spectra on a Elmer-Lambda 5 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Brucker AC-200, AC-250 or AC-300 spectrometers using tetramethylsilane as internal standard. Chemical shifts are expressed in part per million (ppm). s, bs, d, bd, t, dd, q and m indicate singlet, broad singlet, doublet, broad doublet, triplet, doublet of doublet , quartet and multiplet. Mass spectra were measured on a AEI MS-50 spectrometer and elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France. Molecular modeling studies were performed on a Silicon Graphics Indigo II (R10000) workstation, using MacroModel® (version 3.1)[25] and Sybyl (force field: MMFF94) for the analysis of the conformational data. Conformational searches and comparison of conformers were performed with the MonteCarlo[26] procedure using MM2 force field parameters. HPLC analyses were carried out on a Waters apparatus using a Nucleodex column.

Synthesis of lactone 7

(2'-Methoxybiphenyl-2-yl)acetonitrile (14). $Ba(OH)_2.8H_2O$ (223 mg) in ethanol (0.3 mL) and water (1 mL) was added to a mixture of $Pd(PPh_3)_4$ (30 mg), (2-iodophenyl)acetonitrile (85 mg, 0.349 mmol) and (2-methoxyphenyl)boronic acid **12** (84.3 mg, 0.56 mmol) in DME (5 mL). After refluxing for 13 h, the solution was hydrolyzed and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography using heptane-EtOAc (8:2) as eluant to afford **14** (67.3 mg, 87%). The spectral data were identical with those described in ref 21.

2-(2'-Methoxybiphenyl-2-yl)butyronitrile (15a). To a cold (-78°C) solution of LDA prepared from n-BuLi (2.20 mL, 3.43 mmol) and diisopropylamine (0.5 mL, 3.53 mmol) in dry THF (15 mL) under argon, was added a solution of **14** (740 mg, 3.31 mmol) in dry THF (6 mL). The mixture was stirred for 20 min and iodoethane (0.28 mL, 3.5 mmol) was added. The solution was allowed to warm at room temperature and stirred for 2.20 h. After addition of aqueous saturated NH_4Cl, the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography (91:9 heptane-AcOEt) gave

compound 15a (704 mg, 85%): colorless syrup; IR ($CHCl_3$) 2250, 1237cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.59 (bd, J= 8.0 Hz, 1H, Ar-H), 7.46-7.02 (m, 7H, Ar-H), 3.83 and 3.75 (2s, 3H, OMe), 3.61 (m, 1H, CHCN), 1.84-1.71 (m, 2H, CH_2), 1.01 and 0.82 (2t, J=7.0, 3H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.0 (C-2'), 137.8, 135.2, 135.3 (C), 131.4, 131.11, 130.7 (CH), 129.6 (C), 128.3, 128.1, 127.7, 127.2 (CH), 122 (CN), 120.9, 110.7 (CH), 55.3 (OMe), 35.7 (CH), 29.0, 28.2 (CH_2), 12.0, 11.6 (CH_3) ppm; EIMS *m/z* 251 ($M^{+\cdot}$), 236. HRMS calcd for $C_{17}H_{17}NO$ 251.1310, found 251.1319

2-Ethyl-2-(2'-methoxybiphenyl-2-yl)butyronitrile (15b). To a cold (-78°C) solution of LDA prepared from n-BuLi (2.30 mL, 3.68 mmol) and diisopropylamine (0.56 mL, 3.98 mmol) in dry THF (15 mL) under argon, was added a solution of **15a** (833 mg, 3.32 mmol) in dry THF (6 mL). This mixture was stirred for 20 min and iodoethane (0.29 mL, 3.65 mmol) was added. The solution was allowed to warm to room temperature and stirred for 2 h. After addition of aqueous saturated. NH_4Cl, the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography (91:9 heptane-AcOEt) gave compound **15b** (123 mg, 13%) and a mixture of **15b** and **15a** (658 mg) which was again alkylated as above with n-BuLi (5.9 mL, 9.44 mmol), diisopropylamine (1.35 mL, 9.63 mmol) and iodoethane (0.5 mL, 6.25 mmol). The mixture was purified by column chromatography (93:7 heptane-EtOAc) to give compound **15b** (561 mg, 74%): colorless syrup; IR ($CHCl_3$) 2250 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65 (dd, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.38, 7.11, 6.97 -7.20 (m, 7H, Ar-H), 3.72 (s, 3H, OMe), 1.88 (m, 4H, CH_2), 0.94 (t, J= 7.0, 3H, CH_3) and 0.93 (t, J=7.0, 3H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.3 (C-2'), 138.0, 135.0 (C), 133.2, 131.1 (CH), 130.6 (C), 129.5 , 127.6, 127.1 (CH), 123.1 (CN), 119.8, 110.4 (CH), 55.0 (OMe), 33.5 (CH_2), 10.2, 10.1 (CH_3) ppm; EIMS *m/z* 279 ($M^{+\cdot}$), 250. HRMS calcd for $C_{19}H_{21}NO$ 279.1623, found 279.1615

2-Ethyl-2-(2'-methoxybiphenyl-2-yl)butyraldehyde (16). 1M DIBAL-H (4.9 mmol) in hexane was added dropwise to a solution of nitrile **15b** (683 mg, 2.44 mmol) in toluene (30 mL) at -70°C. The mixture was first stirred at -70°C for 30 min then at room temperature for 1 h. After hydrolysis with 5% H_2SO_4, the solution was extracted with EtOAc. NaOH (50%) was added to the aqueous phase to pH 4-5 which was then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude material was purified by column chromatography (9:1 heptane-EtOAc) leading to aldehyde **16** (401 mg, 58%): colorless syrup; IR ($CHCl_3$) 1718 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.39 (s, 1H, CHO), 7.38 (m, 4H, Ar-H), 7.12 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.05 (dd, J- 7.0 and 1.0 Hz, Ar-H), 6.94 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 6.91 (bd, J= 7.0 Hz, 1H, Ar-H), 3.75 (s, 3H, OMe), 1.82 (m, 4H, CH_2), 0.75 (t, J= 7.0, 3H, CH_3) and 0.72 (t, J=7.0, 3H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203 (CHO), 157.4 (C-2'), 139 and 138.7 (C), 132.4, 131.9 (CH), 130.4 (C), 129.5 , 128.7, 127.4, 126.7, 119.8, 110.6 (CH), 58.9 (C), 55.1 (OMe), 25.0 and 24.9 (CH_2), 8.2 (CH_3) ppm; EIMS *m/z* 282 ($M^{+\cdot}$), 253. HRMS calcd for $C_{19}H_{22}O_2$ 282.1619, found 282.1623.

4-Ethyl-4-(2'-methoxybiphenyl-2-yl)hex-2-enoic acid ethyl ester (17). Triethyl phosphono-acetate (1.45 mL, 7.31 mmol) was added to a stirred suspension of NaH (295 mg, 7.37 mmol) in dry THF (20 mL). After 10 min compound **16** (258 mg, 0.915 mmol) in dry THF (5 mL) was added to the solution. The reaction mixture was

stirred under reflux for 14 h. After hydrolysis and extraction with EtOAc, the organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude material was purified by column chromatography (100:3 hexane-acetone) leading to compound **17** (174 mg, 54%): colorless syrup; IR ($CHCl_3$) 1712 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.35 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.24 (m, 2H, Ar-H), 7.04 (bd, J= 7.0, 1H, Ar-H), 7.00 (d, J= 15.0, 1H, CH), 6.98 (bd, J= 7.0 Hz, 1H, Ar-H), 6.83 (bt, J= 7.0 Hz, 1H, Ar-H), 6.79 (bd, J= 7.0 Hz, 1H, Ar-H), 5.24 (d, J= 15.0, 1H, CH), 4.10 (q, J= 7.0 Hz, 2H, CH_2), 3.07 (s, 3H, OMe), 1.75 (m, 4H, CH_2), 1.28 (t, J= 7.0 Hz, 3H, CH_3), 0.73 (t, J= 7.0, 3H, CH_3) and 0.70 (t, J=7.0, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 ($\underline{C}O_2Et$), 157.1 (C-2'), 156,2 ($\underline{CH}$=$CHCO_2Et$), 141.8, 139.2 (C), 132.4, 132.0, 131.2, 128.5, 128.2, 126.7, 125.8 (CH), 119.0 (CH=$\underline{C}HCO_2Et$), 116.8, 110.1 (CH), 59.7 (CH_2), 54.9 (OMe), 48.6 (C), 29.4, 29.3 (CH_2), 14.3, 8.7 and 8.2 (CH_3) ppm; EIMS *m/z* 352 ($M^{+\cdot}$), 321, 307, 279. HRMS calcd for $C_{23}H_{28}O_3$ 352.2038, found 352.2029.

4-Ethyl-4-(2'-methoxybiphenyl-2-yl)hexanoic acid ethyl ester (18). Ester **17** (174 mg, 0.494 mmol) in ethanol (5 mL) was hydrogenated over PtO_2 (17 mg). After filtration and evaporation of the solvent, the crude extract was chromatographied (100:3, hexane-acetone) to give compound **18** (158 mg, 90%): colorless syrup; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 (bd, J= 7.0 Hz, 1H, Ar-H), 7.30 (m, 2H, Ar-H), 7.19 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.13 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 6.93 (m, 3H, Ar-H), 4.08 (q, J= 7.0 Hz, 2H, CH_2), 3.68 (s, 3H, OMe), 2.04 (m, 2H, CH_2), 1.81 (m, 2H, CH_2), 1.55 (m, 4H, CH_2), 1.23 (t, J= 7.0 Hz, 3H, CH_3), 0.69 (t, J= 7.0, 3H, CH_3) and 0.65 (t, J=7.0, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 ($\underline{C}O_2Et$), 156.9 (C-2'), 143.6, 138.6, 134.0 (C), 133.2, 130.9, 128.7, 128.4, 126.9, 125.1, 119.4 (CH), 110.2 (CH), 60.0 (CH_2), 55.0 (OMe), 45.3 (C), 30.8, 29.6, 27.8 (CH_2), 14.4 and 8.4 (CH_3) ppm; EIMS *m/z* 354 ($M^{+\cdot}$), 309. HRMS calcd for $C_{23}H_{30}O_3$ 354.2194, found 354.2199.

4-Ethyl-4-(2'-methoxybiphenyl-2-yl)hexanoic acid (19). To a solution of ester **18** (80.9 mg, 0.23 mmol) in methanol (1.5 mL) was added 0.5 mL of an aqueous solution of NaOH (50%). After refluxing the mixture for 1h30, the solution was extracted with AcOEt. The aqueous layer was acidified (pH 5) with HCl 1N. After extraction with AcOEt, the organic layers were dried over Na_2SO_4. Removal of the solvent led to acid **19** (73.5 mg, 99%): white amorphous solid; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40 (bd, J= 7.0 Hz, 1H, Ar-H), 7.29 (m, 2H, Ar-H), 7.18 (bt, J= 7.0 Hz, 1H, Ar-H), 7.12 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 6.91 (m, 3H, Ar-H), 3.07(s, 3H, OMe), 2.08 (m, 2H, CH_2), 1.79 (t, J= 7.0 Hz, 2H, CH_2), 1.52 (m, 3H, CH_2), 1.26 (m, 1H, CH_2), 0.68 (t, J= 7.0, 3H, CH_3) and 0.64 (t, J=7.0, 3H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.0 ($\underline{C}O_2H$), 156.8 (C-2'), 143.6, 138.7, 134.0 (C), 133.3, 131.0, 128.8, 128.5, 127.0, 125.3, 119.6, 110.3 (CH), 55.1 (OMe), 45.2 (C), 30.7-27.5 (CH_2), 8.8 and 8.3 (CH_3) ppm; EIMS *m/z* 326 ($M^{+\cdot}$). HRMS calcd for $C_{21}H_{26}O_3$ 326.1882, found 326.1880.

4-Ethyl-4-(2'-hydroxybiphenyl-2-yl)hexanoic acid (20). To a solution of acid **19** (66.3 mg, 0.20 mmol) in ethylene chloride (4 mL) was added BBr_3 (0.425 mL, 0.42 mmol). The mixture was stirred at 0°C for 5h. The solution was hydrolyzed and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography using heptane-EtOAc (1:1) as eluant to afford **20**

(33.5 mg, 53%): white amorphous solid; IR ($CHCl_3$) 3550, 1712 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 (bd, J= 7.0 Hz, 1H, Ar-H), 7.32 (bt, J= 7.0 Hz, 1H, Ar-H), 7.20 (m, 2H, Ar-H), 7.09 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.03 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 6.89 (m, 2H, Ar-H), 2.02 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 1.62 (m, 3H, CH_2), 1.45 (m, 1H, CH_2), 0.69 (t, J= 7.0, 3H, CH_3) and 0.63 (t, J=7.0, 3H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.0 (C-OH), 144.9, 136.4 (C), 133.8 (CH), 131.3 (C), 130.5, 129.6, 128.9, 128.1, 126.2, 119.6, 115.6 (CH), 45.4 (C), 31.0, 30.0, 27.6, 27.2 (CH_2), 8.4 and 8.3 (CH_3) ppm; EIMS *m/z* 312 ($M^{+\cdot}$), 294, 239. HRMS calcd for $C_{20}H_{24}O_3$ 312.1725, found 312.1730.

9,9-Diethyl-8,9-dihydro-7*H*-5-oxadibenzo[a,c]cyclononen-6-one (7). Compound **20** (31.4 mg, 0.101 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of EDCI (21.8 mg, 0.114 mmol) and HOBT (15.7 mg, 0.118 mmol) in dry CH_2Cl_2 (80 mL) at 0°C. The mixture was stirred for 16h at room temperature. After evaporation of the solvent, the solid mixture was dissolved in AcOEt and the solution was washed with water. After drying over Na_2SO_4 and filtration, the organic layer was evaporated. The crude extract was then chromatographied to give compound **7** (20.9 mg, 70%): white amorphous solid; IR ($CHCl_3$) 1725 cm^{-1}; U.V (EtOH) λmax (ε) 209 (26637); ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.38 (m, 4H, Ar-H), 7.25 td, J= 7.0 and 1.0, 1H, Ar-H), 7.17 (bd, J= 7.0 Hz, 1H, Ar-H), 6.99 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 2.48 (m, 2H, CH_2), 2.01 (m, 2H, CH_2), 1.67 (m, 2H, CH_2), 1.30 (m, 2H, CH_2), 0.88 (t, J= 7.0, 3H, CH_3) and 0.55 (t, J=7.0, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5 (CO), 150.0 (C-O), 143.4, 138.4, 135.8 (C), 131.9, 130.1, 129.2, 128.9, 128.5, 120.3 (CH), 45.3 (C), 34.4, 32.0, 30.9, 27.8 (CH_2), 8.36 (CH_3) ppm; EIMS *m/z* 294 ($M^{+\cdot}$), 265; HRMS calcd for $C_{20}H_{22}O_2$ 294.1619, found 294.1624.

Synthesis of urea 8

2-Ethyl-2-(2-iodophenyl)butyronitrile (21): To a cold (-78°C) solution of LDA prepared from n-BuLi (7.5 mL, 12.0 mmol) and diisopropylamine (1.74 mL, 12.4 mmol) in dry THF (15 mL) under argon, was added a solution of (2-iodophenyl)acetonitrile **11** (2.48g, 10.2 mmol) in dry THF (7 mL). This mixture was stirred for 20 mn and iodoethane (0.98 mL, 12.24 mmol) was added. The solution was allowed to warm to rt and stirred for 2.20 h. After addition of aqueous saturated NH_4Cl, the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. This crude extract was again alkylated with 10.5 mL of n-BuLi (16.6 mmol), 1.74 mL diisopropylamine (12.4 mmol) and 0.98 mL iodoethane (12.24 mmol). After work-up, the extract was purified by column chromatography (100:5 heptane-EtOAc) to give compound **21** (2.83 g, 93%): colorless syrup; IR ($CHCl_3$) 2237 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.02 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.67 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.38 (td, J= 7.0 and 1.0 Hz, Ar-H), 6.99 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 2.74 (m, 2H, CH_2), 2.03 (m, 2H, CH_2), 0.92 (t, J= 7.0 Hz, 6H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.9 (CH), 137.0 (C), 132.7, 129.5, 128.4 (CH), 122.7 (C), 91.8 (C), 52.2 (C), 30.1 (CH_2), 9.9 (CH_3) ppm; EIMS *m/z* 299 ($M^{+\cdot}$), 270, 172. Anal. Calcd for $C_{12}H_{14}IN$: C, 48.18; H, 4.72; N, 4.68; I, 42.42 . Found: C, 48.16; H, 4.75; N, 4.71; I, 42.28.

[2'-(1-Cyano-1-ethylpropyl)biphenyl-2-yl]carbamic acid *tert*-butyl ester (22). In a two-necked round-bottom flask, the iodide **21** (300 mg, 1.0 mmol) and $PdBnCl(PPh_3)_2$ (31.5 mg, 0.041 mmol) were stirred in dry toluene (17 mL) at room temperature for 10 min. N-(*tert*-butoxycarbonyl)-2-(tributylstannyl) aniline **13** (530 mg, 1.1 mmol) was then added. The solution was stirred at 110°C for 18 h. After cooling, the mixture was hydrolyzed and extracted with EtOAc. The organic layer was further dried with Na_2SO_4 and filtrated. After removal of the solvent, the mixture was purified by chromatography (100:8 heptane-EtOAc) to give biphenyl **22** (344.4 mg, 95%): colorless syrup; IR ($CHCl_3$) 3431, 2250, 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.13 (bd, J= 7.0 Hz, 1H, Ar-H), 7.80 (bd, J= 8.0 Hz, 1H, Ar-H), 7.42 (m, 3H, Ar-H), 7.07 (m, 3H, Ar-H), 5.89 (s, 1H, NH), 1.99-1.72 (m, 4H, CH_2), 1.42 (s, 9H, CH_3), 0.92 (t, J= 7.0, 6H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152 (C), 136.5, 135.8, 135.7 (C), 133.3 (CH), 131 (C), 130.6, 130.1, 129.2, 128.9, 128.3 (CH), 122.6 (C), 122.0, 119.2 (CH), 80.7 (C), 52.0 (C), 33.1, 32.7 (CH_2), 28.3 (CH_3), 10.5 and 10.2 (CH_3) ppm; EIMS *m/z* 364 ($M^{+\cdot}$), 264, 235. HRMS calcd for $C_{23}H_{28}N_2O_2$ 364.2150, found 364.2153.

2-(2'-Aminobiphenyl-2-yl)-2-ethylbutyronitrile (23). To a solution of biaryl **22** (161 mg, 0.442 mmol) in methylene chloride (1 mL) was added trifluoroacetic acid (1 mL) at 0°C. The mixture was stirred at 0°C for 15 min. After neutralization with aqueous saturated Na_2CO_3, extraction with AcOEt, the organic phase was dried, filtrated and the solvent was removed to give the crude extract which was purified by column chromatography (87:13, heptane-EtOAc) to give **23** (100 mg, 86%): IR ($CHCl_3$) 3693-3580, 2237, 1618 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.73 (bd, J= 7.0 Hz, 1H, Ar-H), 7.39 (m, 2H, Ar-H), 7.20 (td, J= 7.0 and 1.0 Hz, Ar-H), 7.13 (dd, J= 7.0 and 1.0 Hz), 6.99 (bd, J= 7.0, 1H, Ar-H), 6.77 (m, 2H, Ar-H), 3.40 (s, 2H, NH_2), 1.94 (m, 4H, CH_2), 0.95 (t, J= 7.0, 6H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.6, 137.2, 136.1 (C), 133.5, 130.5, 130.1, 129.2, 128.2, 128.1 (CH), 126.8 (C), 122.6 (C), 117.6, 115.3 (CH), 51.8 (C), 33.1, 32.6 (CH_2), 10.5 and 10.3 (CH_3) ppm; EIMS *m/z* 264 ($M^{+\cdot}$), 235. HRMS calcd for $C_{18}H_{20}N_2$ 264.1626, found 264.1622.

2'-(1-Aminomethyl-1-ethylpropyl)biphenyl-2-yl-amine (24). An argon purged solution of **23** (37 mg, 0.141 mmol) in dry THF (3 mL) was refluxed before dropwise addition of $BH_3.Me_2S$ (0.21 mL, 0.42 mmol). The mixture was refluxed for 30 min. After cooling, HCl (6N) was added and the mixture was refluxed for 30 min. The solution was ice cooled and 50% NaOH was added to pH 12. After extraction with EtOAc, the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude extract was purified by column chromatography to give **24** (12.4 mg, 33%): IR ($CHCl_3$) 3387, 1612 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.48 (bd, J= 7.0 Hz, 1H, Ar-H), 7.34 (td, J= 7.0 and 1.0 Hz, 1H Ar-H), 7.25 (bt, J= 7.0 Hz, 1H, Ar-H), 7.14 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.02 (bd, J= 7.0 Hz, 2H, Ar-H), 6.76 (m, 2H, Ar-H), 3.66 (q, J= 4.0 Hz, 2H, CH_2), 2.78 (s, 4H, NH_2), 1.62 (m, 4H, CH_2), 0.74 (t, J= 7.0 Hz, 3H, CH_3), 0.64 (t, J= 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 145.0, 143.0, 139.0(C), 133.3 (CH), 130.1 (C), 130.0, 128.4, 127.7, 126.6, 126.0 , 117.8, 115.6 (CH), 47.6 (C), 45.8 (CH_2), 26.2, 25.8 (CH_2), 8.4 (CH_3) ppm; EIMS *m/z* 268 ($M^{+\cdot}$). HRMS calcd for $C_{18}H_{24}N_2$ 268.1939, found 268.1937.

9,9-Diethyl-5,7,8,9-tetrahydro-5,7-diazadibenzo[a,c]cyclononen-6-one (8). A solution of **24** (29.6 mg, 0.106 mmol) and triphosgene (31.2 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) and pyridine (0.080 mL) was stirred at -74°C under argon for 1h30. After hydrolysis with a saturated aqueous solution of Na_2CO_3, the mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (96:4 CH_2Cl_2-MeOH) to give urea **8** (12.3 mg, 38%): white amorphous solid; IR ($CHCl_3$) 3460, 1656 cm^{-1}; U.V (EtOH) λmax (ε) 210 (29356); ^1H NMR (250 MHz, $CDCl_3$) δ 7.35-7.11 (m, 6H, Ar-H), 7.07 (bd, J= 7.0 Hz, 1H, Ar-H), 6.95 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 6.90 (s, 1H, NH), 4.89 (q, J= 11.0 and 4.0 Hz, 1H, NH), 3.66 (q, J= 11.0 and 15.0, 1H, CH_2), 2.85 (q, J= 4.0 and 15.0 Hz, 1H, CH_2), 2.02 (m, 2H, CH_2), 1.22 (m, 2H, CH_2), 0.89 (t, J= 7.0 Hz, 3H, CH_3) and 0.54 (t, J=7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1 (C-O), 142.9, 140.6, 138.6, 137.1 (C), 131.4, 128.6, 127.8, 126.3, 125.3, 124.1 (CH), 45.5 (C), 45.4 (CH_2), 27.8, 25.5 (CH_2), 8.4 and 8.1 (CH_3) ppm; EIMS *m/z* 294 ($M^{+\cdot}$); HRMS calcd for $C_{19}H_{22}N_2O$ (M^+) 294.1732, found 294.1734.

Synthesis of urethane 9

2-Ethyl-2-(2-iodophenyl)butyraldehyde (25). 1M DIBAL-H (0.34 mmol) in hexane was added dropwise to a solution of nitrile **21** (52 mg, 0.174 mmol) in toluene (1 mL) at -70°C. The mixture was first stirred at -70°C for 30 min then at room temperature for 1 h. After hydrolysis with 5% H_2SO_4, the solution was extracted with EtOAc. NaOH was added to the aqueous phase to pH 4-5 which was then extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The crude material was purified by preparative thin layer chromatography (85:15 heptane-EtOAc) leading to aldehyde **25** (26.2 mg, 50%): colorless syrup; IR ($CHCl_3$) 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.03 (s, 1H, CHO), 7.97 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.42 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.31 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 6.99 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 2.12 (m, 4H, CH_2), 0.77 (t, J= 7.0, 6H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 204.9 (C), 142.5, 142.3 (C), 130.6, 129.1, 128.0, (CH), 98.2 (C), 59.6 (C), 25.1 (CH_2), 8.1 (CH_3) ppm; EIMS *m/z* 302 ($M^{+\cdot}$), 175. HRMS calcd for $C_{12}H_{15}IO$ 302.0167, found 302.0170.

2-Ethyl-2-(2-iodophenyl)butan-1-ol (26). To a solution of aldehyde **25** (1.01 g, 3.34 mmol) in methanol (15 mL) was added $NaBH_4$ (384.7 mg, 10.2 mmol). After stirring for 40 min at room temperature, the solvent was evaporated, and H_2O and HCl 0.1N were added to pH 6. Extraction with EtOAc, drying the organic layer with Na_2SO_4 and evaporation afforded a residue which was purified by column chromatography. Compound **26** was obtained as a white amorphous solid (862 mg, 86%): IR ($CHCl_3$) 3600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.04 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.28 (m, 2H, Ar-H), 6.86 (m, 1H, Ar-H), 4.09 (bd, J= 4.0 Hz, 2H, CH_2), 2.20 (m, 2H, CH_2), 1.96 (m, 2H, CH_2), 1.37 (s, 1H, OH), 0.71 (t, J= 7.0, 6H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 146.0 (C, Ar-H), 144.2, 130.2, 128.0, 127.8 (CH), 94.8 (C), 64.4 (CH_2), 47.9 (C), 24.9 (CH_2), 8.7 (CH_3) ppm; EIMS *m/z* 304 ($M^{+\cdot}$), 273, 177 Anal. Calcd for $C_{12}H_{17}IO$: C, 47.38; H, 5.63; O, 5.26 . Found: C, 47.81; H, 5.85; O, 5.39.

Triethyl-[2-ethyl-2-(2-iodophenyl)butoxy] silane (27). To a solution of alcohol **26** (202 mg, 0.66 mmol) in pyridine (1 mL) was added triethylsilyl chloride (0.23 mL, 1.37 mmol). After stirring for 30 min at room temperature, the solvent was evaporated, and H_2O was added. Extraction with EtOAc, drying the organic layer with Na_2SO_4 and evaporation afforded compound **27** (280 mg, 100%): colorless syrup; IR ($CHCl_3$) 1462, 1418 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.01 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.28 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.12 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 6.81 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 3.98 (s, 2H, CH_2), 2.31 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 0.95 (m, 9H, CH_3), 0.60 (m, 12H, CH_2) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 144.8 (C, Ar-H), 143.5, 130.4, 127.3 (CH), 91.0 (C), 63.6 (CH_2), 47.6 (C), 24.6 (CH_2), 8.5 (CH_3), 6.6 (CH_3), 4.3 (CH_2) ppm; EIMS *m/z* 419($M^{+\cdot}$), 291; Anal. Calcd for $C_{18}H_{32}IOSi$: C, 51.54; H, 7.69; I, 30.25 . Found: C, 51.63; H, 7.47; I, 30.11.

[2'-(1-triethylsilanyloxymethyl-1-ethylpropyl)biphenyl-2-yl] carbamic acid *tert*-butyl ester (28). In a two-necked round-bottom flask, the iodide **27** (80.7 mg, 0.19 mmol) and $PdBnCl(PPh_3)_2$ (5.6 mg, 0.0074 mmol) were stirred in dry toluene (4 mL) at room temperature for 10 min. N-(*tert*-butoxycarbonyl)-2-(tributylstannyl) aniline **13** (106.7 mg, 0.22 mmol) was then added. The solution was stirred at 110°C for 10 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 purified on preparative thin layer chromatography (96:4 heptane-EtOAc) to give biphenyl **28** (45.0 mg, 49%): white amorphous solid; IR ($CHCl_3$) 3418, 1725, 1518 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.14 (bd, J= 8.0 Hz, 1H, Ar-H), 7.45 (dd, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.39 (td, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.33 (td, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.23 (td, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.08 (dd, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.00 (td, J= 8.0 and 1.0 Hz, 1H, Ar-H), 6.95 (dd, J= 8.0 and 1.0 Hz, 1H, Ar-H), 6.50 (s, 1H, NH), 3.41 (s, 2H, CH_2), 1.83-1.55 (2m, 4H, CH_2), 1.41 (s, 9H, CH_3), 0.84 (t, J= 7.0 Hz, 9H, CH_3), 0.64-0.62 (2t, J= 7.0, 6H, CH_3), 0.43 (q, J= 7.0, 6H, CH_2) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153 (C), 143.8, 137.2, 136.4, 133.6 (C), 133.5, 132.6, 130.1, 129.6, 128.3, 128.2, 126.0, 121.5, 118.5 (CH), 80.3 (C), 62.3 (CH_2), 49.6 (C), 30.1, 29.0 (CH_2), 28.3 (CH_3), 9.0, 8.9 (CH_3), 6.8 (CH_3) and 4.3 (CH_2) ppm; EIMS *m/z* 483($M^{+\cdot}$), 436, 382, 367; Anal. Calcd for $C_{29}H_{45}INO_3Si$: C, 72.00; H, 9.38; N, 2.90. Found: C, 71.82; H, 9.39; N, 2.81.

2-(2'-Aminobiphenyl-2-yl)-2-ethylbutan-1-ol (29). To a solution of biaryl **28** (79.6 mg, 0.165 mmol) in methylene chloride (1 mL) was added trifluoroacetic acid (1 mL) at 0°C. The mixture was stirred at 0°C for 15 min. After neutralization with aqueous saturated Na_2CO_3, extraction with AcOEt, the organic layer was dried, filtrated and the solvent was removed to give the crude extract which was purified by preparative thin layer chromatography (100:1, CH_2Cl_2-MeOH)) to give **29** (42.2 mg, 95%): white amorphous solid; IR ($CHCl_3$) 3431, 3343, 1612 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.56 (bd, J= 8.0 Hz, 1H, Ar-H), 7.37 (td, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.28 (td, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.19 (td, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.07 (m, 2H, Ar-H), 6.86 (td, J= 8.0 and 1.0 Hz, 1H, Ar-H), 6.79 (dd, J= 8.0 and 1.0 Hz, 1H, Ar-H), 3.48 (q, J= 11.0, 2H, CH_2), 3.42 (s, 3H, CH_3), 1.89 (m, 2H, CH_2), 1.40 (m, 2H, CH_3), 0.87 (t, J= 7.0, 3H, CH_3), 0.61 (t, J= 7.0, 3H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 143.7, 143.4, 138.4 (C), 132.4 (CH), 131.8

(C), 130.5, 130.1, 128.4, 127.8, 126.5, 119.0, 115.9 (CH), 66.2 (CH_2), 48.6 (C), 26.5, 26.2 (CH_2), 8.6 and 8.2 (CH_3) ppm; EIMS *m/z* 269($M^{+\cdot}$), 252. HRMS calcd for $C_{18}H_{23}NO$ 269.1779, found 269.1776.

9,9-Diethyl-8,9-dihydro-5*H*-7-oxa-5-azadibenzo[a,c]cyclononen-6-one 9. A solution of **29** (25.3 mg, 0.106 mmol) and triphosgene (31.2 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) and pyridine (0.08 mL) was stirred at -74°C under argon for 30 min. After hydrolysis with a saturated aqueous solution of Na_2CO_3, the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (6:4 heptane-EtOAc) to give **9** (25.8 mg, 93%): white solid that crystallized in heptane-CH_2Cl_2; mp 140°; IR ($CHCl_3$) 3450, 1725 cm^{-1}; U.V (EtOH) λmax (ε) 209 (40208); ^1H NMR (250 MHz, $CDCl_3$) δ 7.52 (bd, J= 8.0, 1H, Ar-H), 7.38 (dd, J= 8.0 and 1.0 Hz, 1H, Ar-H), 7.28 (m, 4H, Ar-H), 7.12 (bd, J= 8.0, 1H, Ar-H), 6.84 (dd, J= 8.0 and 1.0 Hz, 1H, Ar-H), 6.09 (s, 1H, NH), 4.26 (d, J= 11.0, 1H, CH_2), 3.83 (d, J= 11.0, 1H, CH_2), 1.85 and 1.60 (m, 4H, CH_2), 0.95 (t, J= 7.0, 3H, CH_3) and 0.68 (t, J=7.0, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4 (C-O), 144.9, 142.0, 139.7, 137.2 (C), 132.9, 130.0, 128.6, 128.2, 127.9, 126.3, 125.7, 124.8 (CH), 74.5 (CH_2), 49.1 (C), 25.7, 24.5 (CH_2), 9.0 and 8.9 (CH_3) ppm; EIMS *m/z* 295 ($M^{+\cdot}$), 266, 222; HRMS calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1563.

X-ray structure determination of compound **9**: Mr= 295.37, triclinic, space group: P-1 (No.2), a=8.302 (5), b=8.730 (4),)°, c=12.156 (9) Å, α=96.84 (5), β=95.69 (6), γ = 111.42 (5)°, V=804.6 (9) $Å^3$, Z=2, ρ=1.219 Mg/m^3. Of the 5356 reflections collected, 2111 reflections ($F>\sigma(Fo)$) were used for the refinement. The final residuals were R1=0.056, wR2=0.150, and GOF=1.086. Structure was solved by direct methods with SHELX86[27] and refined by the full-matrix least squares approximation based on F^2 with SHELXL93[28] programs. Refinement was anisotropic for all non-H atoms. Hydrogen atoms were located from a difference map and refined isotropically.

Atropisomeric biphenyls **9** were separated at room temperature by HPLC on a nucleodex column using methanol-H_2O (70:30) as solvent at 0.8 mL/min. Retention time of the enantiomers were 6 min for (+)-**9** ($[\alpha]_D^{22°C}$ = +235 (c= 0.246, $CHCl_3$)) and 7.5 min for (-)-**9** ($[\alpha]_D^{22°C}$ = -234 (c= 0.244, $CHCl_3$)).

Synthesis of urethane 10

5-Bromo-2-(2-iodophenyl) pentanenitrile (30). To a cold (-78°C) solution of LDA prepared from n-BuLi (7.3 mL, 11.7 mmol) and diisopropylamine (1.8 mL, 12.8 mmol) in dry THF (30 mL) under argon, was added a solution of **11** (2.54 g, 10.5 mmol) in dry THF (15 mL). This mixture was stirred for 20 min and 1,3-dibromopropane (2.7 mL, 26.6 mmol) was added. The solution was allowed to warm at room temperature and stirred for 2 h. After addition of aqueous saturated NH_4Cl, the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography (93:7 heptane-EtOAc) gave compound **30** (2.78 g, 73%): colorless syrup; IR ($CHCl_3$) 2249 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.86 (bd, J= 7.0 Hz, 1H, Ar-H), 7.57 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.42 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 7.03 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 4.20 (m, 1H, CHCN), 3.45 (t, J= 7.0 Hz, 2H,

CH_2Br), 2.05 (m, 4H, CH_2) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 140.2 (CH), 138.1 (C), 130.1, 129.3, 128.3 (CH), 119.0 (C), 99.0 (C), 41.0 (CH), 33.4, 33.3, 32.1, 29.9 (CH_2) ppm; EIMS *m/z* 363-365 ($M^{+\cdot}$), 283, 242. HRMS calcd for $C_{11}H_{11}BrIN$ 362.9119, found 362.9117.

8-Iodo-1,2,3,4-tetrahydronaphtalene-1-carbonitrile (31). To a solution of nitrile **30** (764 mg, 2.1 mmol) in cyclohexane was added $AlCl_3$ (848 mg, 6.3 mmol). After stirring for 45 min under reflux, the mixture was hydrolyzed and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography (90:10 heptane-EtOAc) gave compound **31** (364 mg, 61%) that crystallized in heptane-EtOAc; m.p. 109-110°C; IR ($CHCl_3$) 2250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.74 (d, J= 7.0 Hz, 1H, Ar-H), 7.14 (d, J= 7.0 Hz, 1H, Ar-H), 6.95 (t, J= 7.0 Hz, 1H, Ar-H), 4.08 (m, 1H, CHCN), 2.87 (m, 2H, CH_2), 2.37 (m, 1H, CH_2), 1.95 (m, 3H, CH_2) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 139.5 (CH), 137.8 (CH), 132.5 (C), 130.3, 129.8 (CH), 120.3 (C), 102.4 (C), 37.0 (CH), 29.9-19.9 (CH_2) ppm; EIMS *m/z* 283 ($M^{+\cdot}$), 156. Anal. Calcd for $C_{11}H_{10}IN$: C, 46.67; H, 3.56; N, 4.95 . Found: C, 46.45; H, 3.85; N, 4.95.

1-Ethyl-8-iodo-1,2,3,4-tetrahydronaphtalene-1-carbonitrile (32). To a cold (-78°C) solution of LDA prepared from n-BuLi (0.6 mL, 0.96 mmol) and diisopropylamine (0.15 mL, 1 mmol) in dry THF (20 mL) under argon, was added compound **31** (61 mg, 0.216 mmol). This mixture was stirred for 20 min and ethyl iodide (0.2 mL, 0.25 mmol) was added. The solution was allowed to warm at room temperature and stirred for 2 h. The mixture was hydrolyzed with aqueous saturated NH_4Cl, and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to dryness. Purification by preparative TLC chromatography (80-20 heptane-EtOAc) gave compound **32** (43.4 mg, 65%) that crystallized in heptane-EtOAc; m.p. 94-95°C; IR ($CHCl_3$) 2250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.87 (bd, J= 7.0 Hz, 1H, Ar-H), 7.13 (dd, J= 7.0 and 1.0 Hz, 1H, Ar-H), 6.85 (t, J= 7.0 Hz, 1H, Ar-H), 2.84 (m, 2H, CH_2), 2.37 (m, 3H, CH_2), 1.84 (m, 3H, CH_2), 1.16 (t, J= 7 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2 (CH), 139.4, 135.4 (C), 130.3, 129.0 (CH), 122.5 (C), 98.5 (C), 43.4 (C), 36.7 (CH_2), 31.1, 29.7, 18.2 (CH_2), 9.4 (CH_3) ppm; EIMS *m/z* 311 ($M^{+\cdot}$), 282, 184. Anal. Calcd for $C_{13}H_{14}IN$: C, 50.18; H, 4.53; N, 4.50. Found: C, 50.54; H, 4.73; N, 4.40.

1-Ethyl-8-iodo-1,2,3,4-tetrahydronaphtalene-1-carbaldehyde (33). To an argon purged solution of nitrile **32** (280 mg, 0.9 mmol) in toluene (6 mL) was added dropwise at -78°C a solution of 1M DIBAL-H (1.8 mL, 1.8 mmol) in hexane. After stirring for 30 min., the solution is warmed at room temperature and stirred for 1 h. Ethyl formate (2 mL) was added and stirring was continued for 1 h. After addition of aqueous saturated NH_4Cl (5 mL) and 20% H_2SO_4 (7 mL), the solution was extracted with EtOAc. The aqueous phase was diluted with 50% NaOH to pH 5 and extracted with EtOAc. The organic layers were dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography (97:3 heptane-EtOAc) gave compound **33** as a colorless syrup (211 mg, 75%); IR ($CHCl_3$) 1713 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.00 (s, 1H, CHO), 7.77 (d, J= 7.0 Hz, 1H, Ar-H), 7.15 (d, J= 7.0 Hz, 1H, Ar-H), 6.86 (t, J= 7.0 Hz, 1H, Ar-H), 2.83 (t, J= 5.0 Hz, 2H, CH_2), 2.54 (m, 1H, CH_2), 2.10 (m, 1H, CH_2), 1.82 (m, 4H, CH_2), 0.86 (t, J= 7 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9 (C), 142.1 (CH), 140.0 (CH), 139.8 (C), 130.1 (CH), 128.6 (CH), 99.1 (C), 55.5 (C),

32.1 (CH_2), 31.5 (CH_2), 27.7 (CH_2), 18.8 (CH_2) , 9.4 (CH_3) ppm; EIMS *m/z* 314 ($M^{+\cdot}$), 285, 187. HRMS calcd for $C_{13}H_{15}IO$ 314.0167, found 314.0164.

(1-Ethyl-8-iodo-1,2,3,4-tetrahydronaphatalen-1-yl)methanol (34). To a solution of aldehyde **33** (246 mg, 0.78 mmol) in methanol (8 mL) was added sodium borohydride (91 mg, 2.39 mmol). After stirring at room temperature for 40 min, the methanol was removed in vacuo. The mixture was diluted with water and 0.1N HCl was added to pH 6. After extraction with EtOAc, the organic layer was dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography (87:13 heptane-EtOAc) gave compound **34** as an amorphous white solid (218 mg, 88%); IR ($CHCl_3$) 3437 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.86 (d, J= 7.0 Hz, 1H, Ar-H), 7.08 (d, J= 7.0 Hz, 1H, Ar-H), 6.72 (t, J= 7.0 Hz, 1H, Ar-H), 4.45 (m, 1H, CH_2), 3.82 (m, 1H, CH_2), 2.81 (m, 2H, CH_2), 2.67 (m, 1H, CH_2), 2.07 (m, 1H, CH_2), 1.79 (m, 3H, CH_2), 1.56 (m, 1H, CH_2), 1.41 (s, 1H, OH), 0.72 (t, J= 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 143.4 (CH), 142.1 (CH), 140.2 (C), 130.5 (CH), 127.7 (CH), 95.9 (C), 67.6 (CH_2), 44.8 (C), 33.3 (CH_2), 27.7 (CH_2), 19.2 (CH_2) , 8.6 (CH_3) ppm; EIMS *m/z* 316 ($M^{+\cdot}$), 285, 189. HRMS calcd for $C_{13}H_{17}IO$ 316.0324, found 364.0327.

Triethyl-(1-ethyl-8-iodo-1,2,3,4-tetrahydronaphtalen-1-yl-methoxy)silane (35). To a solution of alcohol **34** (111 mg, 0.35 mmol) in pyridine (1 mL) was added triethylsilyl chloride (0.10 mL, 0.60 mmol). After stirring for 30 min at room temperature, the solvent was evaporated, and H_2O was added. Extraction with EtOAc, drying the organic layer with Na_2SO_4 and evaporation afforded compound **35** (154.5 mg, 100%): colorless syrup; IR ($CHCl_3$) 2956, 2875, 1462 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.83 (d, J= 7.0 Hz, 1H, Ar-H), 7.06 (d, J= 7.0 Hz, 1H, Ar-H), 6.70 (t, J= 7.0 Hz, 1H, Ar-H), 4.02 (q, J= 9.0, 2H, CH_2), 2.95 (m, 2H, CH_2), 2.80 (m, 2H, CH_2), 2.18 (m, 1H, CH_2), 1.71 (m, 2H, CH_2), 1.59 (m, 1H, CH_2), 1.39 (m, 1H, CH_2), 0.92 (m, 12H, CH_3), 0.55 (m, 6H, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0 (C, Ar-H), 142.0, 140.5, 130.2 (CH), 127.4 (CH), 86.5 (C), 66.5 (CH_2), 44.9 (C), 30.5 (CH), 32.2 (CH), 27.3 (CH), 19.1 (CH), 8.9 (CH_3), 6.9 (CH_3), 4.7 (CH_2) ppm; EIMS *m/z* 430($M^{+\cdot}$), 401, 303, 285. HRMS calcd for $C_{19}H_{31}IOSi$ 430.2274, found 430.2270.

2-(8-Ethyl-8-triethylsilanyloxymethyl-5,6,7,8-tetrahydronaphtalen-1-yl)phenylamine (36a and 36b). In a two-necked round-bottom flask, the iodide **34** (165 mg, 0.38 mmol) and $PdBnCl(PPh_3)_2$ (16.6 mg, 0.0022 mmol) were stirred in dry toluene (7 mL) at room temperature for 10 min. N-(*tert*-butoxycarbonyl)-2-(tributylstannyl) aniline **13** (202.5 mg, 0.42 mmol) was then added. The solution was stirred at 110°C for 12 h. After cooling, the mixture was hydrolyzed and extracted with EtOAc. The organic layer was further dried over Na_2SO_4 and filtrated. The mixture obtained after removal of the solvent was purified by column chromatography (100:2 heptane-EtOAc) to give a mixture (87.0 mg, 46%) of biphenyls **36a** and **36b** as white amorphous solid. The diastereoisomers were separated by preparative TLC (96:4, hexane-ether). **36a** (32.0 mg) IR ($CHCl_3$) 3425, 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.12 (d, J= 7.0 Hz, 1H, Ar-H), 7.31 (t, J= 7.0 Hz, 1H, Ar-H), 7.14 (m, 3H, Ar-H), 6.97 (t, J= 7.0 Hz, 1H, Ar-H), 6.77 (dd, J= 7.0 and 1.5 Hz, 1H, Ar-H), 6.15 (s, 1H, NH), 3.62 (s, 2H, CH_2), 2.89 (m, 2H, CH_2), 2.02 (m, 1H, CH_2), 1.77 (m, 3H, CH_2), 1.43 (s, 9H, CH_3),

1.37 (m, 2H, CH_2), 0.86 (t, J= 7.0 Hz, 9H, CH_3), 0.66 (t, J= 7.0 Hz, 3H, CH_3), 0.49 (q, J= 7.0 Hz, 6H, CH_2) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.6 (C, CO), 141.7-133.6 (C), 131.2-118.7 (CH), 80.3 (C), 69.5 (CH_2), 45.2 (C), 33.2 CH_2), 31.0 CH_2), 28.4 (CH_3), 19.4 (CH_2), 9.8 (CH_3), 6.9 (CH_3), 4.5 (CH_2) ppm; EIMS *m/z* 495($M^{+\cdot}$), 394. HRMS calcd for $C_{30}H_{45}NO_3Si$ 495.4254, found 495.4253. **36b** (36.1 mg) IR ($CHCl_3$) 3425, 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.98 (d, J= 8.0 Hz, 1H, Ar-H), 7.15 (m, 5H, Ar-H), 6.74 (m, 1H, Ar-H), 6.31 (s, 1H, NH), 3.40 (q, J= 10 Hz, 2H, CH_2), 2.88 (m, 2H, CH_2), 1.99 (m, 1H, CH_2), 1.78 (m, 3H, CH_2), 1.43 (s, 9H, CH_3), 1.33 (m, 2H, CH_2), 0.84 (t, J= 7.0 Hz, 9H, CH_3), 0.70 (t, J= 7.0 Hz, 3H, CH_3), 0.49 (q, J= 7.0 Hz, 6H, CH_2) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.1 (C, CO), 140.9-135.3 (C), 130.9-120.6 (CH), 80.1 (C), 68.7 (CH_2), 44.8 (C), 33.0-30.3 (CH_2), 28.4 (CH_3), 19.5 (CH_2), 9.3 (CH_3), 6.9 (CH_3), 4.5 (CH_2) ppm; EIMS *m/z* 495($M^{+\cdot}$), 394. HRMS calcd for $C_{30}H_{45}NO_3Si$ 495.4254, found 495.4252.

[8-(2-Aminophenyl)-1-ethyl-1,2,3,4-tetrahydronaphtalen-1-yl]methanol (37a and 37b). To a solution of biaryl **36a** (46 mg, 0.093 mmol) in methylene chloride (1 mL) was added at 0°C trifluoroacetic acid (0.5 mL). The mixture was stirred at 0°C for 15 min. After neutralization with aqueous saturated Na_2CO_3, extraction with AcOEt, the organic phase was dried, filtrated and the solvent was removed to give the crude extract which was purified by preparative thin layer chromatography (100:1, CH_2Cl_2-MeOH)) to give **37a** (21 mg, 81%). Similarly, compound **37b** was obtained with a yield of 58% from **36b. 37 a**: IR ($CHCl_3$) 3587, 3487, 3400, 1612 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.15 (m, 4H, Ar-H), 6.87 (m, 1H, Ar-H), 6.76 (td, J= 7.0 and 1.0 Hz, 1H, Ar-H), 6.72 (bd, J= 7 Hz, 1H, NH), 3.59 (q, J= 10 Hz, 2H, CH_2), 2.90 (m, 2H, CH_2), 1.90 (m, 4H, CH_2), 1.55 (m, 2H, CH_2), 0.73 (t, J= 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2 (C), 141.8 (C), 139.2 (C), 139.0 (C), 131.5 (CH), 130.2 (CH), 128.4 (CH), 126.3 (CH), 117.5 (CH), 115.2 (CH), 70.7 (CH_2), 44.9 (C), 33.2 (CH_2), 19.7 (CH_2), 9.7 (CH_3) ppm; EIMS *m/z* 281($M^{+\cdot}$), 250. HRMS calcd for $C_{19}H_{23}NO$ 281.1779, found 281.1775. **37b**: IR ($CHCl_3$) 3583, 3431, 3350, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (m, 4H, Ar-H), 6.89 (td, J= 7 and 1 Hz, 1H, Ar-H), 6.82 (m, 2H, Ar-H), 3.31 (q, J= 11 Hz, 2H, CH_2), 2.91 (m, 2H, CH_2), 2.08 (m, 1H, CH_2), 1.88 (m, 2H, CH_2), 1.74 (m, 1H, CH_2), 1.53 (m, 2H, CH_2), 0.69 (t, J= 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5 (C), 141.6 (C), 140.6 (C), 138.3 (C), 132.7 (CH), 130.3 (CH), 130.2 (CH), 129.7 (CH), 128.3 (CH), 126.1 (CH), 119.6 (CH), 116.3 (CH), 71.4 (CH_2), 45.3 (C), 34.0 (CH_2), 19.6 (CH_2), 8.9 (CH_3) ppm; EIMS *m/z* 281($M^{+\cdot}$), 250. HRMS calcd for $C_{19}H_{23}NO$ 281.1779, found 281.1778.

Compound 10. A solution of **37b** (14.5 mg, 0.051 mmol) and triphosgene (16.6 mg, 0.056 mmol) in CH_2Cl_2 (2 mL) and pyridine (0.04 mL) was stirred at -74°C under argon for 30 min. After hydrolysis with a saturated aqueous solution of Na_2CO_3, the mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (99:1, CH_2Cl_2-MeOH) to give **10** (11.2 mg, 72%): IR ($CHCl_3$) 3431, 1725 cm^{-1}; U.V (EtOH) λmax (ε) 208 (36165); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 2H, Ar-H), 7.10 (m, 4H, Ar-H), 6.62 (dd, J= 7 and 1, Ar-H), 6.15 (s, 1H, NH), 4.75 (d, J= 11 Hz, 1H, CH_2), 3.45 (d, J= 11 Hz, 1H, CH_2), 2.93 (m, 2H, CH_2), 1.90

(m, 3H, CH_2), 1.76 (m, 1H, CH_2), 1.45 (m, 1H, CH_2), 1.18 (m, 1H, CH_2), 0.76 (t, J= 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.8 (CO), 143.5 (C), 144.7 (C), 139.5 (C), 139.4 (C), 136.5 (C), 136.4 (C), 130.9 (CH), 130.6 (CH), 129.8 (CH), 127.7 (CH), 125.9 (CH), 124.9 (CH), 75.3 (CH_2), 44.7 (C), 32.7-19.16 (CH_2), 8.9 (CH_3) ppm; EIMS *m/z* 307($M^{+\cdot}$); HRMS calcd for $C_{20}H_{21}NO_2$ (MH^+) 307.1572, found 307.1578.

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