Application of the Palladium-Catalyzed Borylation/Suzuki Coupling (BSC) Reaction to the Synthesis of Biologically Active Biaryl Lactams

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Received August 30, 2001

The palladium-catalyzed, two-step, one-pot borylation/Suzuki coupling (BSC) reaction was developed to synthesize sterically hindered 2,2′-disubstituted biphenyl and phenyl-indole compounds in a short, simple, and efficient manner from two easily accessible aryl halides. High yields can be obtained by choosing properly both components according to their rough electronic properties. The illustration of the utility of this method was provided by the solution and solid-phase synthesis of seven- or eight-membered biphenyl lactams **5a**−**e**, as well as paullone **3a**. These compounds exhibit moderate albeit significant cytotoxicities and may serve as structural models for future medicinal chemistry developments.

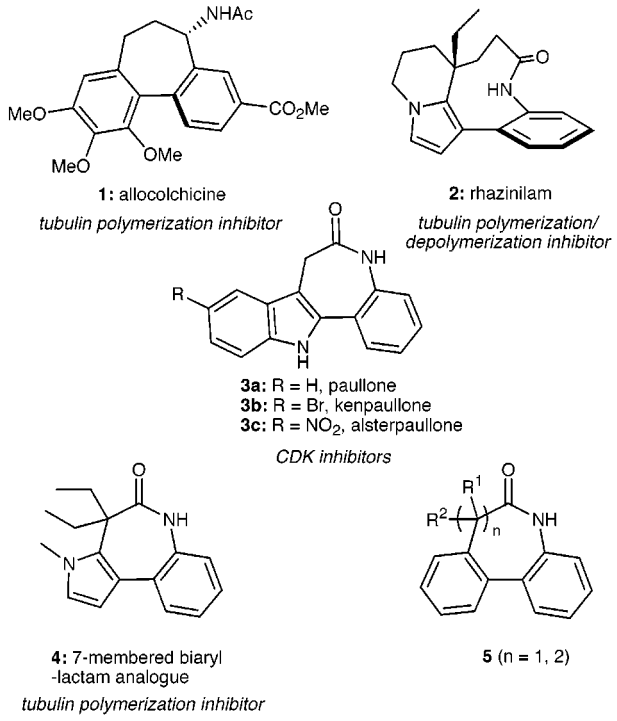
Introduction

Biaryl axis-containing molecules bind to a great diversity of proteins[1] and therefore are found in almost any therapeutic class, for instance, oncolytics, antibiotics, or CNS and cardiovascular agents. In particular, tricyclic biaryls constitute the framework of naturally occurring antimitotic compounds[2] such as colchicinoids (e.g., colchicine and allocolchicine **1**),[3] steganacin, and rhazinilam **2** (Chart 1).[4] These compounds interact with the mitotic spindle: the former bind to tubulin and inhibit the formation of microtubules;[2,3] rhazinilam induces an inhibition of both polymerization and depolymerization of tubulin via the formation of abnormal spirallike structures.[5] Both classes of molecules are configurationally stable due to the presence of the conformationally restrictive 2,2′-bridge between the two aryl moieties and to the possible *ortho*-substitution of these. Remarkable is the fact that their biological activity is restricted to the naturally occurring atropisomer.[3,6]

As part of a program of our group and collaborators directed toward the study of structure−activity relationships of **2**, various phenyl-pyrrole,[7] biphenyl,[8] or phenylpyridine[9] analogues of **2** possessing different median ring sizes have been synthesized and their biological properties assessed. In particular, these studies underlined the effect of the median ring size (six- to nine-membered) on the activity of phenyl-pyrrole analogues.[7] For instance, phenyl-pyrrole **4**, which contains a seven-membered lactam median ring, was shown to interact with tubulin in a different manner from **2**, by inhibiting only microtubule assembly ($IC_{50} = 27\ \mu M$).[7b] Besides, this compound showed an interesting cytotoxicity ($IC_{50} = 7\ \mu M$, KB cell lines).

To further study the role of the size and substitution of the median lactam ring on the nature of the interaction

Chart 1



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10.1021/jo0160726 CCC: $22.00
Published on Web 01/22/2002

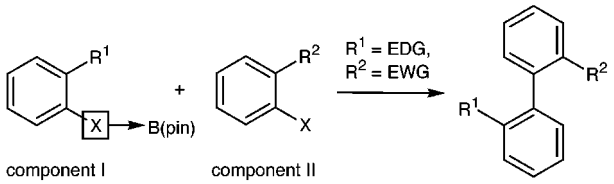
with tubulin, we envisioned a synthesis of biphenyl lactams **5**, possessing possibly different ring sizes and substituents. It was indeed known from our previous data that the pyrrole ring of rhazinilam-type compounds can be replaced by a phenyl ring without notable changes in the activity, which greatly simplifies the synthesis of such compounds.[8] The development of a new versatile and straightforward synthesis of compounds **5** appeared to be necessary in light of the very few existing methods,[10] and in prospect of possible high-throughput synthesis adaptations. Moreover, this method could possibly be applied to the synthesis of other biologically active 2,2′-bridged biaryls structurally close to **5**,[11] including allocolchicine **1** analogues[3] and paullones **3**.[12,13] The latter are seven-membered 2-phenylindole lactams which have been recently discovered as potent inhibitors of cyclin-dependent kinases (CDK).[13] These enzymes constitute a group of serine threonine kinases which control the transmission between successive stages of the cell cycle and therefore represent attractive targets for the development of new antitumor agents.

Recently, we reported a novel one-pot palladium(0)-catalyzed borylation−Suzuki coupling (BSC) reaction for the synthesis of 2,2′-disubstituted biphenyl compounds.[14] Based on the use of the electron-rich, sterically hindered 2-(dicyclohexylphosphino)biphenyl ligand described by Buchwald et al.,[15] as well as on the borylation reaction developed by Masuda et al.,[16] this sequence allows for the rapid and efficient obtention of synthetically useful biphenyls. The reaction conditions tolerate a number of different functional groups, including primary amines, which therefore suppresses the need for additional protecting group chemistry steps. In addition, it is little sensitive to steric hindrance, on the contrary to most existing methods. These features are developed in the present report, and applied to a practical and very short synthesis of biphenyl lactams **5** and unsubstituted paullone **3a**, which currently serve as structural models for the development of new cytotoxic derivatives.

Results and Discussion

The one-pot, two-step BSC reaction allows the direct synthesis of 2,2′-disubstituted biphenyls from two 2-halogenoarene components via the borylation of one component, followed by in situ Suzuki cross-coupling with the other component (Scheme 1).[14,17]

Scheme 1. Electronic Requirements for the Borylation/Suzuki Coupling (BSC) Reaction[a]



[a] Reaction conditions: component I, Et_3N, $Pd(OAc)_2$, PCy_2(*o*-biph), (pin)BH, dioxane, 80 °C, 30 min to 1 h, then H_2O, component II, $Ba(OH)_2 \cdot 8H_2O$, 100 °C, 30 min to 1 h. X = Br or I; EDG = electron-donating group; EWG = electron-withdrawing group; pin = pinacol; PCy_2(*o*-biph) = 2-(dicyclohexylphosphino)biphenyl; (pin)BH = 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (pinacolborane).

The choice of the borylation and cross-coupling component depends on the nature of the substituents present on the aromatic ring. Thus, if R^1 is electron-donating and if R^2 is electron-withdrawing, the borylation should be performed on component I and the coupling of the resulting boronate with component II. Indeed, we found that the borylation reaction gives better yields with electron-rich substrates,[14] and the resulting electron-rich boronate is more reactive for the transmetalation step of the Suzuki coupling. Besides, it is known that Suzuki couplings work better with electron-deficient halides (component II) which undergo easier oxidative insertion to the palladium. On the contrary, if R^1 is rather electron-withdrawing and R^2 electron-donating, the borylation should be performed on component II and the Suzuki coupling with component I.

These basic rules are illustrated in the synthesis of 2,2′-disubstituted biphenyls **8a**−**c**, hypothetical intermediates in the synthesis of lactams **5** (Table 1, entries 1−6). In these reactions, 1.5 equiv of the borylation substrate (component I, see Scheme 1) were used per Suzuki coupling partner (component II) to account for the uncomplete character of the borylation. Indeed, isolated yields for the borylation itself are 81% for **6a**, 57% for **6b**, 90% for **7a**, and 87% for **7b** (together with the corresponding dehalogenated side-products).[14] The BSC reaction with unprotected 2-bromoaniline **6a** as component I and iodide **7a** as component II furnished biphenyl **8a** in 79% isolated yield (entry 1). In this case, component I is electron-rich and component II rather neutral, thus both borylation and cross-coupling steps are favored. Reversing the sequence, i.e., starting with the borylation of **7a** and performing the cross-coupling with **6a** did not give any coupled material (entry 3). With the much more sterically hindered **7b** as component II, the corresponding biphenyl **8b** is obtained in 81% yield (entry 2). This indicates that the Suzuki reaction, in addition to the borylation reaction,[14] is mostly unsensitive to steric hindrance. This can be ascribed to the unique electronic and steric properties of the phosphine ligand used in both steps.[15] It should be noted that the reverse reaction, i.e., with **7b** as component I and **6a** as component II, did not give any cross-coupling product (entry 4) as observed with

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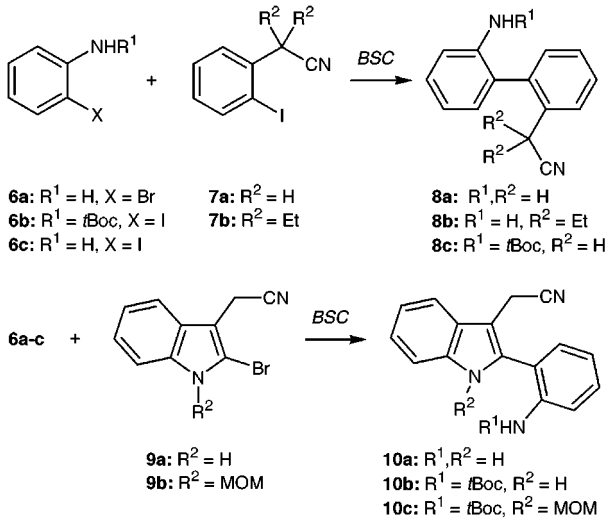
Table 1. Synthesis of Biaryl Intermediates 8a−c and 10a−c Using the BSC Reaction[a]



entry	component I	component II	product (%)[b]
1	**6a**	**7a**	**8a** (79)
2	**6a**	**7b**	**8b** (81)
3	**7a**	**6a**	**8a** (0)
4	**7b**	**6a**	**8b** (0)
5	**6b**	**7a**	**8c** (100)
6	**7a**	**6b**	**8c** (93)
7	**6c**	**9a**	**10a** (62)
8	**6b**	**9a**	**10b** (89)
9	**9a**	**6b**	**10b** (25)
10	**6b**	**9b**	**10c** (76)

[a] Reaction conditions: component I (1.0 equiv), Et_3N (4.0 equiv), $Pd(OAc)_2$ (5 mol %), PCy_2(*o*-biph) (0.2 equiv), (pin)BH (3.0 equiv), dioxane, 80 °C, 30 min-1 h, then H_2O, component II (0.67 equiv for entries 1−6, 0.5 equiv for entries 7−10), $Ba(OH)_2 \cdot 8H_2O$ (3.0 equiv), 100 °C, 1 h. [b] Isolated yields, calculated from component II.

7a (entry 3). As the borylation of **7a** and **7b** is high-yielding as stated above, this behavior can be inferred at least in part to the poor ability of electron-rich **6a** to undergo oxidative insertion to the palladium catalyst in the Suzuki coupling step. Indeed, bromoaniline was recovered unchanged after several hours and no aniline or 2,2′-diaminobiphenyl, which could have been produced as side-products after the oxidative insertion, were observed in the reaction mixture. These data suggest that the borylation and the biaryl coupling steps occur through different mechanisms. The exact mechanism of the borylation itself is not known.[16] The fact that **6a** was converted quantitatively in the borylation reaction (ca. 80% boronate + 20% aniline) but did not react at all in the Suzuki coupling with the same catalyst suggests that the oxidative insertion of palladium in the carbon−halogen bond may not be the rate-determining step of the borylation unlike it is in the biaryl coupling.[18] This is further supported by our observations that phenyl halides bearing electron-donating groups give higher yields of boronates than substrates bearing electron-withdrawing groups. Finally, the BSC reaction of Boc-protected 2-iodoaniline **6b**[19] with iodide **7a** was examined. In this case both halides bear rather electronically neutral *ortho* substituents; thus, the order of reactants should be more or less indifferent according to the above rules. Indeed, using **6b** or **7a** as component I and **7a** or **6b** as component II, respectively, gave in both cases biphenyl **8c** in high yield (entries 5 and 6), despite the steric hindrance introduced by the Boc group.

Next, the synthesis of 2-phenylindoles **10a**−**c**, possible intermediates in the synthesis of paullones **3**, was examined using the preceding method (Table 1, entries 7−10). The borylation of 2-bromo- or 2-iodoaniline (component I), followed by coupling with unprotected 2-bromoindole **9a**,[20] gave biaryl **10a** in 62% yield (entry 7).[21] With Boc-protected **6b**, the bulkier biaryl **10b** was obtained in higher yield (entry 8), which illustrates further the unsensitiveness of the reaction to steric factors. Reversing the reactional sequence, i.e., using **9a** as component I and **6b** as component II gave a much lower yield (25%) of compound **10b** (entry 9). As it was shown that **6b** can react efficiently as component II in the BSC reaction (entry 5), this lower yield is imputable to the use of **9a** as component I: the borylation of **9a** itself gave an isolated yield of 52% of the corresponding pinacolboronate. This boronate is weakly nucleophilic because of the low electronic density of the 2-indole position and fairly unreactive toward the transmetalation step of the Suzuki coupling. By opposition, 2-bromoindoles behave as good components II in the Suzuki reaction due to easy Pd insertion at the electron-deficient 2-indole carbon atom (entries 7, 8, 10). Finally, BSC reaction of **6b** with MOM-protected indole **9b** gave the corresponding phenylindole **10c** in 76% yield (entry 10) despite the presence of bulky substituents on both components.

Thus, by choosing both components according to their rough electronic properties, good to very high yields of biaryls can be obtained through the BSC reaction. Application of this method to the synthesis of the target seven-membered biphenyl lactams **5a**−**d** is shown in Scheme 2. Thus, basic hydrolysis of the nitrile group of **8a** with sodium hydroxide in refluxing methanol and concomitant cyclization gave directly lactam **5a** in 56% yield. The bulkier diethyl derivative **8b** remained intact under the same conditions. Increasing the reaction temperature by using higher-boiling alcohols such as 2-methoxyethanol or switching to acidic hydrolysis with aqueous H_2SO_4 gave the cyclic amidine **11b** in good yield. Applying these acidic conditions to **8a** gave unsubstituted amidine **11a**. These derivatives, arising from dehydration of the putative primary amide or iminoester intermediate, proved resistant to further hydrolysis. As a result, hydrolysis of the Boc-protected biphenyls **8c**−**f** was examined in order to try to avoid the apparently easy amidine formation. Mono- or bis-alkylation of **8c** with LDA and methyl or ethyl iodide gave nitriles **8d**−**f** in good yields. Basic hydrolysis of **8c** with sodium hydroxide in ethanol/water gave a mixture of primary amide (major product)[22] and cyclized product **5a**. **5a** may form by cyclization of the primary amide, followed by in situ deprotection of the resulting base-labile Boc-protected lactam. Total conversion of the mixture in favor of the seven-membered lactam was best effected by treatment

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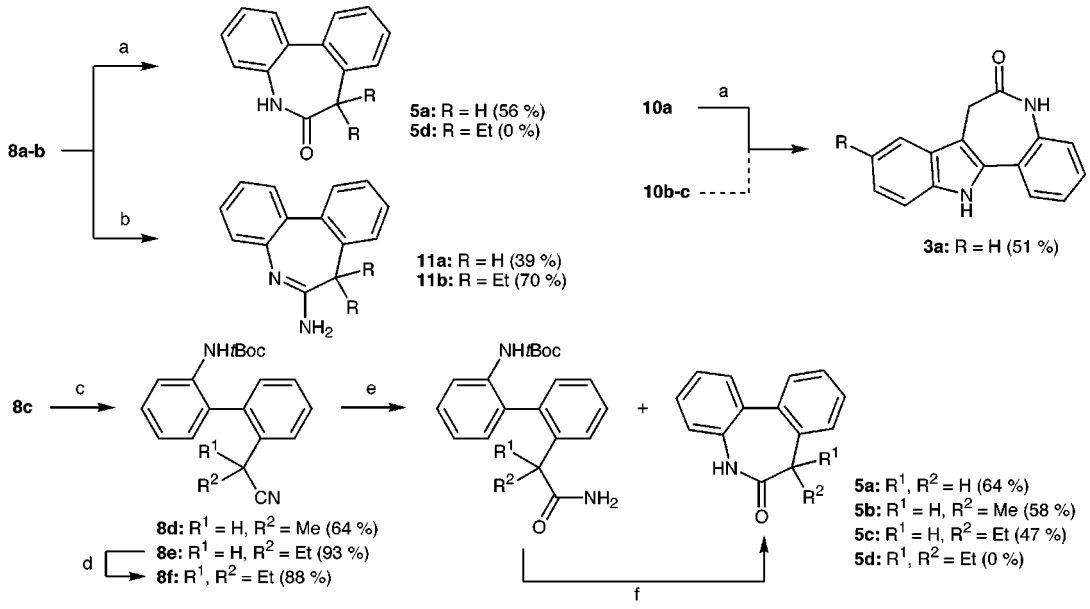
(21) Using **6c** instead of **6a** gave higher isolated yields of **10a** due to easier purification, but conversions were nearly identical.
(22) The primary amide was isolated and characterized by ^1H NMR (amide group: two broad singlets at 5.41 and 5.88 ppm) and mass spectrometry (ESI, $m/z = 349$ for $[M + Na]^+$).

Scheme 2. Synthesis of Seven-Membered Biphenyl Lactams 5a−d and Paullone 3a[a]

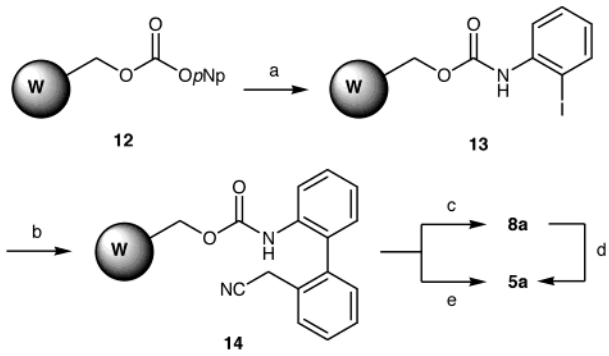


[a] (a) NaOH (10 equiv), MeOH/H_2O 2/1, reflux, 3.5 h; (b) aq H_2SO_4, $MeO(CH_2)_2OH$, reflux, 1−4 h; (c) LDA (2.0−3.0 equiv), MeI (1.0 equiv) or EtI (3.0 equiv), THF, −78 °C to 25 °C, 2 h; (d) LDA (6.0 equiv), EtI (6.0 equiv), THF, −78 °C to 25 °C, 2 h; (e) NaOH (10 equiv), EtOH/H_2O 2/1, reflux, 3−8 h; (f) concd H_2SO_4, 25 °C, 30 min.

of the crude material with concentrated sulfuric acid, providing **5a** in 64% yield from **8c**. The same reaction conditions were applied to monomethyl and ethyl derivatives **8d**−**e**, giving lactams **5b**−**c** in 58% and 47% yields, respectively. Unfortunately, the more sterically hindered nitrile **8f**, when subjected to basic hydrolysis, did not give the expected lactam **5d**. In this case, deprotection of the Boc group occurred and the nitrile group was left unaffected. Exploitation of those results in the synthesis of unsubstituted paullone **3a** is illustrated in Scheme 2. Thus, direct basic hydrolysis of unprotected phenylindole **10a** with alcoholic sodium hydroxide gave **3a** cleanly in 51% yield. Submission of Boc-protected phenylindole **10b** to basic hydrolysis gave a complex mixture of products, which may arise from competitive cyclization of the indole nitrogen on the Boc carbonyl. Indeed, basic hydrolysis of the MOM-protected nitrile **10c** gave the corresponding primary amide, which subsequently failed to give paullone **3a** under acidic conditions. In conclusion, biphenyl **5a** and paullone **3a** were obtained in a convenient and efficient manner: two steps, 44% and 32% overall yields, respectively, from commercially available materials. The BSC method, which was used in the first step, tolerates unprotected nitrogens well, which greatly simplifies the whole sequence by eliminating the need for protection and deprotection chemistry.

The application of the above findings to the solid-phase synthesis of lactam **5a** is shown in Scheme 3. It was anticipated that replacement of the Boc group of **8c** by a resin-bound carbamate could possibly furnish **5a** after cyclization in a similar manner as precedently. Thus, Wang resin (1.0 mmol/g, 200−400 mesh) was treated with *p*-nitrophenyl chloroformate and *N*-methylmorpholine in dichloromethane to give the activated *p*-nitrophenyl carbonate resin **12** (IR: $\nu_{C=O}$ = 1762 cm^{-1}).[23] Deprotonation of 2-iodoaniline with NaHMDS in THF, followed by addition of the resulting anion to resin **12** gave the

Scheme 3. Solid-Phase Synthesis of Biphenyl Lactam 5a[a]



[a] (a) 2-Iodoaniline (3.0 equiv), NaHMDS (6.0 equiv), THF, 25 °C, 30 min, then **12** (1.0 mmol/g), THF, 25 °C, 14 h; (b) **7a** (1.0 equiv), Et_3N (4.0 equiv), $Pd(OAc)_2$ (5 mol %), PCy_2(*o*-biph) (0.2 equiv), (pin)BH (3.0 equiv), dioxane, 80 °C, 30 min, then H_2O, **13** (0.5 equiv), NaOH (4.0 equiv), 100 °C, 1 h; (c) 20% TFA/CH_2Cl_2, 25 °C, 30 min, 60% overall; (d) see Scheme 2; (e) NaOH (20 equiv), toluene/EtOH/H_2O 1/1/1, reflux, 17 h, 25% overall. *p*Np = *p*-nitrophenyl; NaHMDS = sodium hexamethyldisilazane.

resin-bound carbamate **13** (IR: ν_{N-H} = 3387, $\nu_{C=O}$ = 1735 cm^{-1}). BSC reaction using iodide **7a** as component I and resin **13** as component II resulted in the formation of the resin-bound biphenyl **14** (IR: ν_{N-H} = 3418, $\nu_{C\equiv N}$ = 2248, $\nu_{C=O}$ = 1731 cm^{-1}). Practically, **7a** was submitted to the borylation step (80 °C, 30 min), water was added to the reaction medium which was then transferred via cannula or syringe to a suspension of resin **13** in dioxane. Sodium hydroxide was added, and the mixture was heated to 100 °C for 1 h. In this case sodium hydroxide was used instead of barium hydroxide because the latter produces insoluble salts which could not be washed out from the resin. Treatment of resin **14** with TFA in dichloromethane afforded 0.60 mmol of the free amine **8a** per gram of resin (i.e., 60% yield from Wang resin). **8a** can be converted to lactam **5a** in 56% yield through basic hydrolysis according to Scheme 2. Alternatively, treat-

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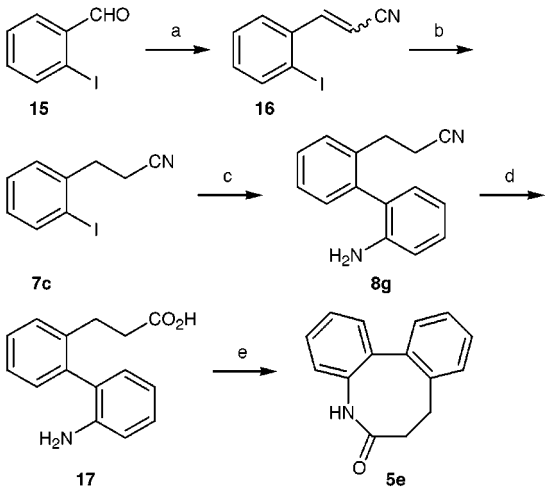
Scheme 4. Synthesis of Eight-Membered Biphenyl Lactam 5e[a]



[a] (a) ($Ph_3P^+CH_2CN,Cl^-$) (1.05 equiv), aq NaOH, CH_2Cl_2, 25 °C, 30 min, 98% (*Z*/*E* 86/14); (b) $NaBH_4$ (1.3 equiv), pyridine/MeOH, reflux, 2 h, 86%; (c) **6a** (1.0 equiv), Et_3N (4.0 equiv), $Pd(OAc)_2$ (5 mol %), PCy_2(*o*-biph) (0.2 equiv), (pin)BH (3.0 equiv), dioxane, 80 °C, 1 h, then H_2O, **7c** (0.67 equiv), $Ba(OH)_2 \cdot 8H_2O$ (3.0 equiv), 100 °C, 1 h, 98% from **7c**; (d) NaOH (10.0 equiv), EtOH/H_2O, reflux, 8 h; (e) Et_3N (2.5 equiv), EDCI·HCl (1.1 equiv), CH_2Cl_2, 25 °C, 24 h, 25% from **8g**. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

ment of resin **14** with sodium hydroxide in refluxing toluene/ethanol/water furnished 0.25 mmol of lactam **5a** per gram of resin (25% yield from Wang resin). The direct formation of **5a** could result from two reactional sequences: releasing of amine **8a** by cleavage of the carbamate and subsequent cyclization to **5a**; or hydrolysis of the nitrile group of **14** to the primary amide, cyclization of the carbamate nitrogen onto the primary amide and subsequent cleavage of the base-labile amide carbamate, releasing **5a** in solution, in an analogous manner as in Scheme 2 ('cyclo-release' hypothesis).[24] No definite proof could be obtained in favor of one or the other hypothesis. We also considered the possibility of performing the borylation on resin-bound iodide **13** as component I, followed by coupling with **7a** as component II, in a reversed manner as above. However, similarly with Boc-protected iodoaniline **6b**, the borylation of **13** gave 30−40% dehalogenated product, which of course remained on the resin, decreasing the overall yield and purity of the target lactam. In the approach shown in Scheme 3 with resin **13** as component II, negligible amounts of aniline resulting from dehalogenation in the Suzuki coupling step were observed, giving good yields and purity of lactam **5a**.

In conclusion, seven-membered biphenyl lactam **5a** could be obtained in a straightforward and efficient manner through a solid-phase synthesis involving the BSC reaction in a key step. Although the extension of this model synthetic sequence to the synthesis of libraries of analogues has still to be demonstrated, it may allow, in principle, introduction of chemical diversity in a straightforward fashion for the synthesis of analogues.

Finally, the extension of the preceding results to the synthesis of an eight-membered biphenyl lactam **5e** was examined (Scheme 4). The requisite homologated iodide

(24) For a review on cyclo-release reactions applied to drug discovery, see: Park, K.-H.; Kurth, M. J. *Drugs Future* **2000**, *25*, 1265.

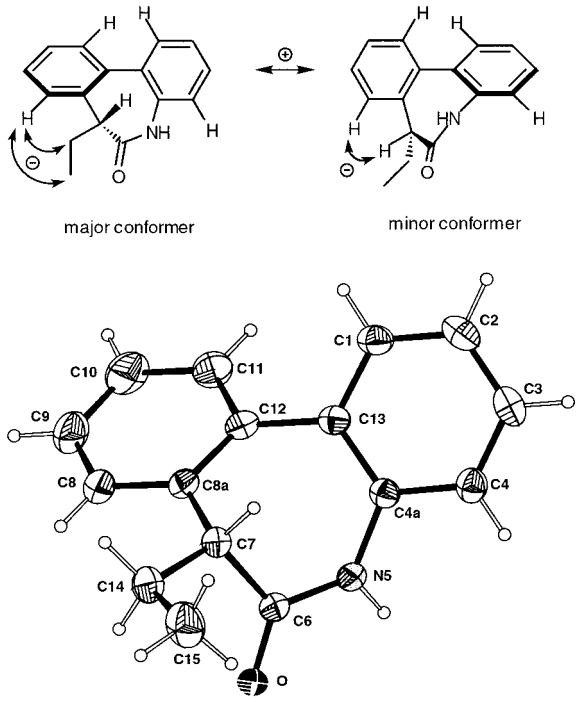


Figure 1. (top) Solution conformers of **5c** with exchange (+) and NOE (−) correlations observed from NOESY spectra ($CDCl_3$, 20 °C); (bottom) X-ray crystal structure of **5c**.

7c was obtained as follows: Wittig olefination[25] of 2-iodobenzaldehyde **15**, obtained from the corresponding benzyl alcohol by PCC oxidation,[26] furnished unsaturated nitrile **16** which was reduced by sodium borohydride in pyridine/methanol[27] to afford **7c** in 84% overall yield. BSC reaction in the usual conditions, with 2-bromoaniline **6a** as component I and **7c** as component II, furnished biphenyl **8g** in 98% yield. When subjected to the previous basic hydrolysis conditions (Scheme 2), **8g** did not cyclize spontaneously to lactam **5e**, but gave carboxylic acid **17** instead. The latter was directly subjected to intramolecular cyclization with EDCI, affording the eight-membered lactam **5e** in 25% yield (unoptimized).

It is interesting to note that monomethyl- and monoethyl-substituted lactams **5b**,**c** exist as a mixture of two conformers in solution at 20 °C as observed from ^1H NMR spectra ($CDCl_3$). The ratio between these conformers was found to be 95/5 and 83/17 for **5b** and **5c**, respectively. These conformers arise from rotation around the biphenyl axis, as shown by NOESY experiments (Figure 1, top) and X-ray crystallographic analysis conducted with compound **5c** (Figure 1, bottom). The fact that these are indeed rotamers and not true diastereoisomers resulting from axial chirality was demonstrated by the presence of exchange correlation spots between the two species on NOESY spectra recorded at 293 K. These spots disappeared on NOESY spectra recorded at 240 K, indicating that rotation around the biphenyl axis is frozen at this temperature. X-ray diffraction data (Figure 1) showed that **5c** crystallizes as the major conformer. Similarly, ^1H NMR spectra ($CDCl_3$) of the open-chain biphenyls **8d**

(25) Daniel, H.; Le Corre, M. *Tetrahedron Lett.* **1987**, *28*, 1165.
(26) Grissom, J. W.; Klingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem.* **1997**, *62*, 603.
(27) Rhodes, R. A.; Boykin, D. W. *Synth. Commun.* **1988**, *18*, 681.
(28) (a) Eagle, H. *Proc. Soc. Exp. Biol. Med.* **1955**, *89*, 362. (b) Tempête, C.; Werner, G. H.; Favre, F.; Roja, A.; Langlois, N. *Eur. J. Chem.* **1995**, *30*, 647.

Table 2. Cytotoxicity of Biaryl Lactams and Amidines (KB cell lines)[28]

compound	**2**	**4**	**5a**	**5b**	**5c**	**5e**	**11a**	**11b**	**3a**
$IC_{50\ (\mu M)}$[a]	1	7	>100	90	32	>100	70	16	90

[a] IC_{50} is the concentration of compound corresponding to 50% growth inhibition after 72 h incubation.

and **8e** show a 63/37 and 60/40 mixture of two nearly identical species, respectively. Nevertheless in this case, the absence of exchange correlation spots between these two species on NOESY spectra recorded at 293 and 330 K indicate that the rotation around the biphenyl axis does not occur even at 330 K, and thus that **8d**,**e** exist as a mixture of configurationally stable diastereoisomers rather than conformers. Finally, the observation of two doublets for the methylene signal of unsubstituted lactam **5a** (J = 11.5 Hz), exchanging on NOESY spectra at 293 K but not at 240 K, indicate that the rotation around the biphenyl bond of **5a** is slow at 293 K and frozen at 240 K. On the contrary, the observation of one singlet for the methylene signal of paullone **3a** at 293 K indicates a faster rotation around the biaryl axis,[12a] which may result from the smaller steric repulsions between the two aryl groups in **3a** compared to **5a**. Molecular modeling studies conducted on seven-membered lactams **5a**−**c** and **3a**, eight-membered lactam **5e**, and nine-membered biphenyl lactam analogues of rhazinilam which were previously synthesized,[8] show that the dihedral angle between the two aryl rings increases with the size of the lactam ring. Thus, approximate biaryl torsion angles of 30°, 45°, 70°, and 90° were found for compounds **3a**, **5a**−**c**, **5e** and nine-membered lactams, respectively, in accordance with available X-ray diffraction data. The modification of these angle values may strongly influence the protein-binding properties of those compounds and thus their biological activities, as suggested in previous studies on rhazinilam analogues.[7,8]

The biaryl lactams **5a**−**e** and amidines **11a**,**b** reported above were evaluated against KB cell lines (Table 2). Biphenyl lactams **5a**−**e** exhibited a weak cytotoxicity toward cancer cell lines, with **5c** > **5b** > **5a** ≈ **5e**, which indicates that increasing the hydrophobicity by adding larger alkyl substituents on the lactam ring improves the cytotoxicity of these compounds. Indeed phenyl-pyrrole **4**, which bears two ethyl groups on the lactam ring, is the most active compounds of this seven-membered biaryl lactam series. Increasing the lactam ring size from seven- to eight-membered (compound **5e**) does not in itself improve the cytotoxicity as already stated previously with phenyl-pyrrole lactams.[7a] Interestingly, biphenyl amidine **11b** was more cytotoxic toward KB cell lines than **11a**, confirming the positive effect of additional alkyl substituents on the median ring. Finally **3a**, which is a known inhibitor of CDK1-cyclin B (IC_{50} value of 7 μM), is weakly cytotoxic (9×10^{-5} M) on KB cell lines, a value consistent with that already reported on HCT cancer cell lines (ca. 10^{-5} M).[13a] Compounds **5a**−**e** and **11a**,**b** were also evaluated on the tubulin assay, and most of them showed no inhibition of assembly nor disassembly of microtubules. Only compound **5c** showed a very weak inhibition of tubulin assembly, with a IC_{50} value of 160 μM. Further studies are under investigation to determine the mode of action of the most cytotoxic compounds **5c** and **11b**. Using the synthetic methodologies reported therein, modifications of the substituents at the benzylic position as well as on the aryl rings are currently underway. Similarly, the synthesis of paullones analogues, among which 10^{-8} M inhibitors of CDK1/cyclin B such as alsterpaullone **3c** (Figure 1) have been described,[13] can be developed in a straightforward fashion as described for unsubstituted paullone **3a**.

In conclusion, this report underlines the usefulness of the BSC reaction for synthesizing sterically hindered 2,2′-disubstituted biaryl compounds in a short, simple, and efficient manner. These are important intermediates which can be easily cyclized to seven- or eight-membered biaryl lactams such as biphenyls **5a**−**e** and paullone **3a**. This synthetic methodology, which tolerates the presence of many functional groups well, may be applicable to the solution- or solid-phase synthesis of libraries of analogues for medicinal chemistry purposes.

Experimental Section

General. Reagents were commercially available and used without further purification unless otherwise stated. THF and dioxane were distilled from sodium/benzophenone, methylene chloride from diphosphorus pentoxide (P_2O_5), and triethylamine from KOH. Methanol and pyridine were analytical grade and stored over 3 or 4 Å molecular sieves, respectively, prior to use. Yields refer to chromatographically and spectroscopically homogeneous materials. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm SDS silica gel coated glass plates (60F254) using UV light as visualizing agent and ethanolic sulfuric molybdate and heat as staining agents. Merck silica gel 60 (particle size 40−63 μM) was used for flash column chromatography. NMR spectra were recorded on Bruker AC-250, AC-300, or AMX-400 instruments and calibrated using tetramethylsilane as an internal reference. The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Nicolet FT-IR 205 spectrometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded under liquid secondary ion (LSIMS), electronic impact (EI), chemical ionization (CI), or electrospray ionization (ESI) conditions at the Laboratoire de Spectrométrie de Masse, ICSN, Gif-sur-Yvette, France or at the Laboratoire Central d′Analyse du CNRS, Vernaison, France. Melting points (mp) are uncorrected and were recorded on a Büchi B-540 capillary melting point apparatus. Molecular modeling studies were conducted on a Silicon Graphics Indigo II (R10000) workstation, using Sybyl 6.7 for the analysis of the conformational data. Conformational searches and comparisons were performed with the Monte Carlo procedure using MMFF94 force field parameters. The physical data of compounds **8a**,[14] **8b**,[8b] **8f**,[8b] and **3a**[12] were previously described. The physical data of compounds **5a** and **5e** were partially described.[10]

General Procedure for the BSC Reaction. To a solution of **6a** (1.06 g, 6.2 mmol) in dioxane (12 mL) at 25 °C under argon were successively added Et_3N (3.4 mL, 24.6 mmol), $Pd(OAc)_2$ (69 mg, 0.31 mmol), PCy_2(*o*-biph) (433 mg, 1.23 mmol), and pinacolborane (2.7 mL, 18.5 mmol) dropwise. The solution was heated to 80 °C for 1 h. After cooling, water (4 mL) was added dropwise, **7a** (1.0 g, 4.1 mmol), dissolved in dioxane (4 mL), and $Ba(OH)_2 \cdot 8H_2O$ (5.84 g, 18.5 mmol) were added, and the solution was heated to 100 °C for 1 h. After cooling, the mixture was filtered through Celite, brine was added (20 mL), and the solution was extracted with methylene chloride. After being dried over magnesium sulfate and evaporation of the solvents under vacuum, the residue was purified by flash chromatography (silica gel, heptane/ethyl acetate 9/1, then 4/1), to afford **8a** as an oil (681 mg, 79%).

(2′-Cyanomethylbiphenyl-2-yl)carbamic acid *tert*-butyl ester 8c: (see general BSC procedure) oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.44 (s, 9 H, *t*Bu), 3.48 (s, 2 H, CH_2), 6.02 (br s, 1 H, N*H*), 7.10 (m, 2 H), 7.26 (m, 1 H), 7.40 (t, J = 7.6 Hz, 1 H), 7.48 (m, 2 H), 7.65 (dd, J = 6.6, 1.8 Hz, 1 H), 8.11 (d,

J = 8.4 Hz, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.4 (*C*H_2), 28.1 (*C*H_3), 80.8 (*C*q), 117.6 (*C*q), 120.1 (*C*H), 123.3 (*C*H), 128.7 (*C*H), 129.1 (*C*H), 129.7 (*C*H), 130.6 (*C*H), 135.6 (*C*q), 137.0 (*C*q), 152.5 (*C*q) ppm; IR (film) υ = 3425, 2979, 2250, 1729 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{21}N_2O_2$ [(M + H)$^+$]: 309.1603; found: 309.1600.

3-(2′-Aminobiphenyl-2-yl)propionitrile 8g: (see general BSC procedure) oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.40 (td, J = 7.2, 1.8 Hz, 2 H, CH_2), 2.83 (td, J = 6.9, 1.7 Hz, 2 H, CH_2), 3.46 (br s, 2 H, NH_2), 6.74 (d, J = 8.1 Hz, 1 H), 6.79 (td, J = 7.5, 1.2 Hz, 1 H), 6.98 (dd, J = 7.5, 1.8 Hz, 1 H), 7.18 (m, 2 H), 7.35 (m, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 18.1 (*C*H_2), 29.0 (*C*H_2), 115.2 (*C*H), 118.2 (*C*H), 119.3 (*C*q), 125.8 (*C*q), 127.7 (*C*H), 128.2 (*C*H), 128.8 (*C*H), 129.6 (*C*H), 129.9 (*C*H), 130.6 (*C*H), 137.0 (*C*q), 138.4 (*C*q), 143.5 (*C*q) ppm; IR (film) υ = 3466, 3370, 2246, 1615 cm^{-1}; HRMS (LSIMS) calcd for $C_{15}H_{15}N_2$ [(M + H)$^+$]: 223.1235; found: 223.1221.

[2-(2-Aminophenyl)indol-3-yl]acetonitrile 10a: (see general BSC procedure) white solid, mp = 127 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 3.75 (s, 2 H, CH_2), 3.82 (br s, 2 H, NH_2), 6.81 (d, J = 7.5 Hz, 1 H), 6.87 (dd, J = 6.8, 1.3 Hz, 1 H), 7.25 (m, 4 H), 7.39 (dd, J = 7.5, 1.0 Hz, 1 H), 7.74 (d, J = 6.5 Hz, 1 H), 8.25 (br s, 1 H, N*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.9, 102.6, 111.3, 116.1, 116.3, 118.3, 118.5, 118.9, 120.7, 123.2, 127.3, 130.6, 131.0, 133.6, 136.0, 145.2 ppm; IR (film) υ = 3379, 2248, 1618 cm^{-1}; HRMS (LSIMS) calcd for $C_{16}H_{14}N_3$ [(M + H)$^+$]: 248.1188; found: 248.1190.

[2-(3-Cyanomethylindol-2-yl)phenyl]carbamic acid *tert*-butyl ester 10b: (see general BSC procedure) oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (s, 9 H, *t*Bu), 3.66 (s, 2 H, CH_2), 6.53 (br s, 1 H, N*H* Boc), 7.14 (t, J = 7.7 Hz, 1 H), 7.27 (m, 3 H), 7.42 (m, 2 H), 7.77 (d, J = 7.2 Hz, 1 H), 8.12 (d, J = 9.0 Hz, 1 H), 8.59 (br s, N*H* indole) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ = 13.5 (*C*H_2), 28.1 (*C*H_3), 81.2 (*C*q), 102.9 (*C*q), 111.5 (*C*H), 117.6 (*C*q), 118.5 (*C*H), 120.3 (*C*H), 120.6 (*C*H), 123.2 (*C*H), 123.4 (*C*H), 126.9 (*C*q), 130.3 (*C*H), 130.9 (*C*H), 132.1 (*C*q), 136.1 (*C*q), 136.7 (*C*q), 153.0 (*C*q) ppm;; IR (film) υ = 3400, 3325, 2979, 2250, 1709 cm^{-1}; HRMS (LSIMS) calcd for $C_{21}H_{21}N_3O_2$ [M^+]: 347.1634; found: 347.1641.

[2-(3-Cyanomethyl-1-methoxymethylindol-2-yl)phenyl]carbamic acid *tert*-butyl ester 10c: (see general BSC procedure) oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.43 (s, 9 H, *t*Bu), 3.20 (s, 3 H, CH_3O), 3.58 (s, 2 H, NCH_2O), 5.16 (d, J = 10.8 Hz, 1 H, C*H*H′), 5.24 (d, J = 10.8 Hz, 1 H, CH*H*′), 6.53 (br s, 1 H, N*H*), 7.28 (m, 4 H), 7.50 (td, J = 8.1, 1.8 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 7.5 Hz, 1 H), 8.23 (d, J = 8.3 Hz, 1 H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ = 13.5 (*C*H_2), 28.1 (*C*H_3), 56.1 (*C*H_3O), 74.8 (N*C*H_2O), 80.9 (*C*q), 104.9 (*C*q), 110.6 (*C*H), 117.4 (*C*q), 118.2 (*C*q), 118.7 (*C*H), 120.2 (*C*H), 121.3 (*C*H), 123.0 (*C*H), 123.6 (*C*H), 126.8 (*C*q), 130.9 (*C*H), 131.9 (*C*H), 134.5 (*C*q), 137.2 (*C*q), 138.2 (*C*q), 152.5 (*C*q) ppm; IR (film) υ = 3410, 2979, 2248, 1728 cm^{-1}; HRMS (LSIMS) calcd for $C_{23}H_{25}N_3O_3$ [M^+]: 391.1896; found: 391.1899.

[2′-(1-Cyanoethyl)biphenyl-2-yl]carbamic Acid *tert*-Butyl Ester 8d. To a solution of compound **8c** (150 mg, 0.49 mmol) in THF (3 mL) under argon at −78 °C was added dropwise LDA (2 M in THF, 486 μL, 0.97 mmol). After 30 min stirring, iodomethane (30 μL, 0.49 mmol) was added and the mixture was allowed to warm to 25 °C for 2 h. After hydrolysis with a saturated aqueous NH_4Cl solution, the solution was extracted with diethyl ether. The solution was dried over $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by flash chromatography (silica gel, heptane/ethyl acetate 95/5, then 9/1), to afford **8d** as an oil (100 mg, 64%); mixture of two conformers (63/37); ^{1}H NMR (250 MHz, $CDCl_3$) major conformer δ = 1.42 (s, 3H, CH_3), 1.46 (s, 9 H, *t*Bu), 3.67 (q, J = 7.8 Hz, 1 H, C*H*), 6.01 (br s, 1 H, N*H*), 7.11 (m, 2 H), 7.22 (dt, J = 7.8, 1.3 Hz, 1 H), 7.41 (m, 2 H), 7.52 (td, J = 7.8, 1.3 Hz, 1 H), 7.70 (d, J = 7.0 Hz, 1 H), 8.15 (d, J = 8.8 Hz, 1 H) ppm; minor conformer (distinct signals) δ = 3.77 (q, J = 7.0 Hz, 1 H, C*H*), 5.98 (br s, 1 H, N*H*), 8.10 (d, J = 9.0 Hz, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) two conformers δ = 20.4, 21.7, 27.8, 28.1, 80.8, 81.0, 120.0, 121.7, 123.1, 123.3, 127.6, 127.8, 128.4, 128.6, 128.8, 129.2, 129.4, 129.5, 129.9, 130.0, 130.5, 130.9, 135.7, 135.9, 136.2, 136.5, 136.7, 152.4, 152.6 ppm; IR (film) υ = 3425, 2980, 2241, 1731 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{23}N_2O_2$ [(M + H)$^+$]: 323.1760; found: 323.1729.

[2′-(1-Cyanopropyl)biphenyl-2-yl]carbamic Acid *tert*-Butyl Ester 8e. 8e was obtained in the same manner as above for **8d** from **8c** (200 mg, 0.65 mmol), LDA (973 μL, 1.95 mmol), and iodoethane (156 μL, 1.95 mmol): oil (202 mg, 93%); mixture of two conformers (60/40); ^{1}H NMR (250 MHz, $CDCl_3$) major conformer δ = 0.84 (t, J = 7.5 Hz, 3 H, CH_3), 1.46 (s, 9 H, *t*Bu), 1.74 (m, 2 H, CH_2), 3.49 (dd, J = 8.5, 6.8 Hz, 1 H, C*H*), 6.02 (br s, 1 H, N*H*), 7.09 (m, 2 H), 7.22 (m, 1 H), 7.44 (m, 3 H), 7.66 (m, 1 H), 8.16 (d, J = 8.8 Hz, 1 H) ppm; minor conformer (distinct signals) δ = 0.92 (t, J = 7.5 Hz, 3 H, CH_3), 1.43 (s, 9 H, *t*Bu), 3.62 (dd, J = 9.0, 6.0 Hz, 1 H, C*H*), 6.00 (br s, 1 H, N*H*), 8.10 (d, J = 9.0 Hz, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) two conformers δ = 11.4, 11.6, 27.8, 28.1, 29.2, 35.1, 80.7, 80.9, 119.7, 119.9, 120.9, 123.0, 123.2, 128.0, 128.3, 128.4, 128.5, 128.7, 129.1, 129.3, 129.9, 130.0, 130.5, 130.9, 135.1, 135.2, 135.7, 136.3, 136.6, 152.4, 152.6 ppm; IR (film) υ = 3425, 2975, 2239, 1732 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{25}N_2O_2$ [(M + H)$^+$]: 337.1916; found: 337.1915.

[2′-(1-Cyano-1-ethylpropyl)biphenyl-2-yl]carbamic Acid *tert*-Butyl Ester 8f. To a solution of **8c** (150 mg, 0.49 mmol) in THF (5 mL) under argon at −78 °C was added dropwise LDA (730 μL, 1.46 mmol). After 30 min stirring, iodoethane (117 μL, 1.46 mmol) was added and the solution was allowed to warm to 25 °C for 2 h. After recooling to −78 °C, LDA (1.46 mL, 2.92 mmol) was added dropwise and the mixture was stirred for 30 min. Iodoethane (233 μL, 2.92 mmol) was added, and the solution was allowed to warm to 25 °C for 2 h. After hydrolysis with a saturated aqueous NH_4Cl solution, the solution was extracted with diethyl ether. The solution was dried over $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by flash chromatography (silica gel, heptane/ethyl acetate 9/1), to afford **8f** as an oil (156 mg, 88%).

(2-Bromo-1-methoxymethylindol-3-yl)acetonitrile 9b. To a solution of 2-bromo-3-indolylacetonitrile[19] (1.0 g, 4.25 mmol) in THF (15 mL) at 25 °C was added dropwise NaHMDS (2 M in THF, 2.23 mL, 4.47 mmol). After 15 min stirring, the solution was cooled to 0 °C and chloromethyl methyl ether (355 μL, 4.68 mmol) was added dropwise. The mixture was stirred for 5 min at 0 °C and 1 h at 25 °C. A saturated aqueous solution of $NaHCO_3$ was added, and the solution was extracted with diethyl ether. After drying over $MgSO_4$, the solvents were evaporated under vacuum, and the residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate 75/35), to afford **9b** as a yellow oil (776 mg, 65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.28 (s, 3 H, CH_3O), 3.79 (s, 2 H, CH_2-CN), 5.50 (s, 2 H, NCH_2O), 7.21 (td, J = 6.9, 1.5 Hz, 1 H), 7.27 (td, J = 7.2, 1.2 Hz, 1 H), 7.45 (dd, J = 7.5, 1.0 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ = 14.3 (*C*H_3), 56.1 (*C*H_3), 75.3 (*C*H_2), 104.9 (*C*q), 110.2 (*C*H), 113.7 (*C*q), 116.7 (*C*q), 117.8 (*C*H), 121.4 (*C*H), 123.3 (*C*H), 126.3 (*C*q), 136.8 (*C*q) ppm; IR (film) υ = 2942, 2248 cm^{-1}; HRMS (LSIMS) calcd for $C_{12}H_{11}BrN_2O$ [M^+]: 278.0055; found: 278.0050.

5,7-Dihydro-dibenz[*b*,*d*]azepin-6-one 5a. Procedure a. A solution of compound **8a** (100 mg, 0.48 mmol) and sodium hydroxide (192 mg, 4.8 mmol) in methanol (3 mL)/water (1.5 mL) was refluxed for 3.5 h. After cooling, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The organic layers were gathered and washed twice with a 1 N HCl aqueous solution and then once with a saturated aqueous solution of NH_4Cl. The solution was dried over $MgSO_4$ and evaporated under vacuum, to afford **5a** as a white powder (56 mg, 56%). **Procedure b.** A solution of compound **8c** (334 mg, 1.08 mmol) and sodium hydroxide (433 mg, 10.8 mmol) in ethanol (8 mL)/water (4 mL) was refluxed for 3 h. After cooling, brine was added and the mixture was extracted with ethyl acetate. The solution was dried over $MgSO_4$ and evaporated under vacuum. The residue was redissolved in 5 mL of concd H_2SO_4, and the solution was stirred for 30 min at 25 °C and then poured into ice. The solution was neutralized with a concd NaOH aqueous solution and extracted with ethyl acetate. The gathered organic layers were dried over $MgSO_4$ and evaporated under vacuum until a

precipitate formed, which was filtered, affording **5a** as a white powder (144 mg, 64%); mp 232 °C (lit.[10] 231−233 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.45 (d, J = 11.4 Hz, 1 H, C*H*H′), 3.57 (d, J = 11.7 Hz, 1 H, CH*H*′), 7.16 (d, J = 8.1 Hz, 1 H), 7.28 (t, J = 7.4 Hz, 1 H), 7.39 (m, 4 H), 7.56 (m, 1 H), 7.63 (d, J = 7.5 Hz, 1 H), 8.99 (br s, 1 H, N*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 41.8 (*C*H_2), 122.0 (*C*H), 125.0 (*C*H), 127.7 (*C*H), 128.4 (*C*H), 128.6 (2*C*H), 128.8 (*C*H), 130.0 (*C*H), 132.0 (*C*q), 134.2 (*C*q), 135.9 (*C*q), 136.6 (*C*q), 173.5 (*C*q) ppm; IR (film) υ = 3175, 1682 cm^{-1}; HRMS (CI) calcd. for $C_{14}H_{12}NO$ [(M + H)$^+$]: 210.0919; found: 210.0938.

5,7-Dihydro-7-methyldibenz[*b,d*]azepin-6-one 5b. Lactam **5b** was synthesized in the same manner as above for **5a** from compound **8d** (100 mg, 0.31 mmol) using procedure b with a reflux time of 6 h. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate 1/1), to afford **5b** as a white powder (40 mg, 58%); two conformers (95/5); ^{1}H NMR (250 MHz, $CDCl_3$) major conformer δ = 1.61 (d, J = 7.2 Hz, 3 H, CH_3), 3.41 (q, J = 6.8 Hz, 1 H, C*H*), 7.15 (dd, J = 8.0, 1.2 Hz, 1 H), 7.27 (td, J = 8.2, 1.5 Hz, 1 H), 7.38 (m, 4 H), 7.52 (d, J = 7.3 Hz, 1 H), 7.63 (dd, J = 8.2, 1.0 Hz, 1 H), 8.84 (br s, 1 H, N*H*) ppm; minor conformer (distinct signals) δ = 3.95 (m, 1 H, C*H*), 9.25 (br s, 1 H, N*H*) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) major conformer δ = 11.8 (*C*H_3), 39.4 (*C*H), 121.7 (*C*H), 123.8 (*C*H), 124.7 (*C*H), 127.1 (*C*H), 128.4 (*C*H), 128.6 (*C*H), 128.8 (*C*H), 129.8 (*C*H), 132.3 (*C*q), 135.9 (*C*q), 137.0 (*C*q), 138.3 (*C*q), 174.9 (*C*q) ppm; IR (film) υ = 3204, 1675 cm^{-1}; HRMS (CI) calcd for $C_{15}H_{14}NO$ [(M + H)$^+$]: 224.1075; found: 224.1075.

5,7-Dihydro-7-ethyldibenz[*b,d*]azepin-6-one 5c. Lactam **5c** was synthesized in the same manner as above for **5a** from compound **8e** (202 mg, 0.60 mmol) using procedure b with a reflux time of 8 h. The residue was purified by flash column chromatography (silica gel, heptane/ethyl acetate 4/1, then 3/2), to afford **5c** as a white powder (67 mg, 47%); two conformers (83/17); mp 174 °C; ^{1}H NMR (250 MHz, $CDCl_3$) major conformer δ = 1.02 (t, J = 7.4 Hz, 3 H, CH_3), 2.01 (m, 1 H, C*H*H′), 2.43 (m, 1 H, CH*H*′), 3.11 (dd, J = 9.0, 6.0 Hz, 1 H, C*H*), 7.16 (dd, J = 8.0, 1.2 Hz, 1 H), 7.25 (td, J = 8.2, 1.3 Hz, 1 H), 7.37 (m, 4 H), 7.52 (m, 1 H), 7.65 (d, J = 7.8, 1.2 Hz, 1 H), 9.02 (br s, 1 H, N*H*) ppm; minor conformer (disctinct signals) δ = 0.76 (t, J = 7.4 Hz, 1 H, CH_3), 1.40 (m, 2 H, CH_2), 3.72 (m, 1 H, C*H*), 9.42 (br s, 1 H, N*H*) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) major conformer δ = 12.4, 19.6, 46.9, 121.8, 124.3, 124.8, 127.0, 128.5, 128.6, 128.9, 129.7, 132.5, 136.0, 137.2, 137.7, 173.8 ppm; IR (film) υ = 3201, 1672 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{16}NO$ [(M + H)$^+$]: 238.1232; found: 238.1262.

7,12-Dihydro-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one (paullone) 3a. Compound **3a** was synthesized in the same manner as above for **5a** from **10a** (200 mg, 0.81 mmol) using procedure a with a reflux time of 6 h. **3a** was obtained as a white powder (103 mg, 51%); mp > 350 °C.[12]

6-Amino-7*H*-dibenz[*b,d*]azepine 11a. A solution of **8a** (53 mg, 0.25 mmol) in 2-methoxyethanol (0.5 mL)/water (0.4 mL)/concd sulfuric acid (0.1 mL) was heated to 120 °C for 1 h. After cooling, the reaction mixture was poured onto ice and neutralized with concd aqueous sodium hydroxide. The resulting aqueous solution was extracted with ethyl acetate, the gathered organic layers were dried over $MgSO_4$, and the solvents were evaporated under vacuum. The residue was purified by preparative thin-layer chromatography (silica gel, dichloromethane/methanol 85/15), to afford **11a** as a white solid (21 mg, 39%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.18 (d, J = 12 Hz, 1 H), 3.27 (d, J = 12.9 Hz, 1 H), 4.61 (br s, 2 H), 7.14 (td, J = 7.7, 1.2 Hz, 1 H), 7.19 (m, 2 H), 7.36 (m, 3 H), 7.61 (dd, J = 8.1, 1.2 Hz, 1 H), 7.64 (dd, J = 7.2, 1.5 Hz, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD) δ = 38.2 (*C*H_2), 122.7 (*C*H), 125.9 (*C*H), 126.9 (*C*H), 127.6 (*C*H), 127.9 (*C*H), 128.2 (*C*H), 128.8 (*C*H), 129.8 (*C*H), 131.6 (*C*q), 135.8 (*C*q), 137.5 (*C*q), 145.4 (*C*q), 159.7 (*C*q) ppm; IR (film) υ = 3460, 1648, 1580 cm^{-1}; HRMS (CI) calcd for $C_{14}H_{13}N_2$ [(M + H)$^+$]: 209.1079; found: 209.1051.

6-Amino-7-diethyl-7*H*-dibenz[*b,d*]azepine 11b. 11b was obtained in the same manner as above for **11a** from **8b** (20 mg, 0.076 mmol), with a heating time of 4 h at 120 °C; white solid (14 mg, 70%); ^{1}H NMR (250 MHz, $CDCl_3$) δ = 0.50 (m, 3 H), 1.17 (m, 3 H), 1.40 (m, 2 H), 2.25 (m, 1 H), 2.37 (m, 1 H), 5.20 (br s, 2 H), 7.10 (td, J = 7.5, 1.0 Hz, 1 H), 7.15 (dd, J = 8.0, 1.0 Hz, 1 H), 7.37 (m, 4 H), 7.60 (dd, J = 7.8, 1.2 Hz, 1 H), 7.68 (m, 1 H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ = 8.9, 9.4, 18.5, 23.8, 51.0, 121.8, 123.5, 125.1, 126.9, 127.5, 128.0, 128.5, 131.0, 132.7, 137.3, 140.1, 144.1, 160.8 ppm; IR (film) υ = 3310, 1648, 1570 cm^{-1}; HRMS (CI) calcd for $C_{18}H_{21}N_2$ [(M + H)$^+$]: 265.1705; found: 265.1682.

Solid-Phase Synthesis of Lactam 5a. Carbonate resin **12** was freshly prepared[22] from Wang resin (loading 1.0 mmol/g, 200−400 mesh). **Preparation of Carbamate Resin 13.** To a solution of 2-iodoaniline **6c** (2.62 g, 12.0 mmol) in THF (25 mL) under argon at 25 °C was added NaHMDS (2M in THF, 12.0 mL, 23.9 mmol). After 30 min stirring, the mixture was cannulated into a suspension of resin **12** (3.98 g, ca. 3.98 mmol) in THF (40 mL) and the resulting mixture was stirred for 12 h at 25 °C. The resin was filtered, rinsed thoroughly with DMF, dichloromethane, methanol, and diethyl ether, and dried under vacuum, affording resin **13** (4.29 g); IR (KBr pellet) υ = 3387, 1735 cm^{-1}. **Preparation of Carbamate Resin 14.** To a solution of nitrile **7a** (972 mg, 4.0 mmol) in dioxane (12 mL) at 25 °C under argon were successively added Et_3N (2.23 mL, 16.0 mmol), $Pd(OAc)_2$ (45 mg, 0.20 mmol), PCy_2(*o*-biph) (280 mg, 0.80 mmol), and pinacolborane (1.74 mL, 12.0 mmol) dropwise. The solution was heated to 80 °C for 30 min. After cooling, water (3 mL) was added dropwise, and then the mixture was added to a suspension of resin **13** (2.00 g) in dioxane (8 mL). Sodium hydroxide (640 mg, 16.0 mmol) was added, and the mixture was heated to 100 °C under argon for 1 h. After cooling, the resin was filtered, washed thoroughly with DMF/H_2O, methanol, dichloromethane, and diethyl ether, and dried under vacuum, to afford resin **14** (2.03 g); IR (KBr pellet) υ = 3418, 2248, 1731 cm^{-1}. **Releasing of Biphenyl 8a.** Resin **14** (300 mg) was suspended in dichloromethane (2.4 mL), and TFA (0.6 mL) was added dropwise at 25 °C. After 30 min stirring, the mixture was filtered and the resin was washed with dichloromethane. The filtrate was washed three times with a saturated $NaHCO_3$ aqueous solution, dried over $MgSO_4$, and evaporated under vacuum, affording analytically pure **8a** (37.4 mg, 0.60 mmol per gram of resin). **Releasing of Lactam 5a.** A suspension of resin **14** (200 mg) and sodium hydroxide (160 mg, 4.0 mmol) in toluene (1 mL)/ethanol (1 mL)/water (1 mL) was refluxed for 17 h. The resin was filtered and washed with dichloromethane and methanol. The filtrate was evaporated and redissolved in ethyl acetate, and the solution was washed twice with a 1 N aqueous HCl solution and once with brine. The organic layer was dried over $MgSO_4$ and evaporated under vacuum, to afford analytically pure **5a** (10.5 mg, 0.25 mmol per gram of resin).

3-(2-Iodophenyl)propionitrile 7c. To a solution of 2-iodobenzaldehyde (2.0 g, 5.62 mmol)[24] in dichloromethane (100 mL) at 25 °C were added successively a 30% sodium hydroxide aqueous solution (100 mL) and (cyanomethyl)triphenylphosphonium chloride (3.06 g, 9.05 mmol). After 30 min stirring, 200 mL of water was added, the organic layer was decanted, and the aqueous layer was extracted with dichloromethane. The gathered organic layers were dried over $MgSO_4$ and evaporated under reduced pressure, affording unsaturated nitrile **16** as an oily solid (2.145 g, 98%) which was used directly in the next step without further purification; two diastereoisomers (Z/E = 86/14); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.55 (d, J = 11.4 Hz, 1 H, C*H*═CH *Z*-olefin), 5.78 (d, J = 16.2 Hz, C*H* = CH *E*-olefin), 7.10 (td, J = 7.5, 1.2 Hz, 1 H, *Z*-olefin), 7.34 (d, J = 11.7 Hz, 1 H, CH═C*H* *Z*-olefin), 7.45 (t, J = 7.5 Hz, 1 H, *Z*-olefin), 7.92 (m, 2 H, *Z*-olefin) ppm; IR (film) υ = 3056, 2217, 1610 cm^{-1}; MS (EI) m/z = 255 [$M^{+\bullet}$]. To a solution of **16** (500 mg, 1.96 mmol) in pyridine (30 mL)/methanol (10 mL) was added sodium borohydride (96 mg, 2.55 mmol), and the mixture was refluxed for 2 h under argon. After cooling, the solution was poured into a mixture of 10% aqueous HCl (100 mL) and ice, and concd aqueous HCl was added dropwise until pH = 1−2. The aqueous solution was extracted with diethyl ether, and the gathered organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, heptane/ethyl

acetate 95/5, then 9/1), affording **7c** as a colorless oil (433 mg, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.64 (t, J = 6.9 Hz, 2 H, CH_2), 3.06 (t, J = 7.2 Hz, 2 H, CH_2), 6.97 (td, J = 7.5, 2.1 Hz, 1 H), 7.31 (m, 2 H), 7.83 (dd, J = 8.1, 1.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.7 (*C*H$_2$), 36.4 (*C*H$_2$), 99.7 (*C*q), 118.6 (*C*q), 128.8 (*C*H), 129.1 (*C*H), 129.8 (*C*H), 139.7 (*C*H), 140.3 (*C*q) ppm; IR (film) υ = 3053, 2246 cm^{-1}; HRMS (EI) calcd for C_9H_8IN [$M^{+\bullet}$]: 256.9701; found: 256.9709.

7,8-Dihydro-dibenz[*b*,*d*]azocin-6(5*H*)-one 5e. A solution of compound **8g** (260 mg, 1.17 mmol) and sodium hydroxide (468 mg, 11.7 mmol) in ethanol (8 mL)/water (4 mL) was refluxed for 8 h. After cooling, ethanol was evaporated under vacuum, and the aqueous solution was neutralized (pH = 6−8) with a 1 N aqueous HCl solution and extracted with ethyl acetate, affording crude amino acid **17** (183 mg) as an oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.43 (t, J = 7.0 Hz, 2 H, CH_2), 2.78 (m, 2 H, CH_2), 6.01 (br s, 3 H, NH_2, CO_2H), 6.72 (d, J = 8.0 Hz, 1 H), 6.78 (t, J = 7.4 Hz, 1 H), 6.98 (d, J = 7.5, 1.5 Hz, 1 H), 7.14 (m, 2 H), 7.28 (m, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.1, 34.8, 115.4, 118.4, 126.8, 128.0, 128.5, 129.2, 130.1, 130.4, 138.3, 139.1, 143.3, 178.8 ppm; MS (ESI) m/z 242 [(M + H)$^+$]. To a solution of this oil in dichloromethane (75 mL) at 25 °C under argon were added triethylamine (264 μL, 1.90 mmol) and EDCI·HCl (160 mg, 0.83 mmol). After stirring for 24 h, the solution was concentrated under vacuum and washed twice with a saturated $NaHCO_3$ aqueous solution, twice with a 1 N HCl aqueous solution, and once with a saturated NH_4Cl aqueous solution. After drying over $MgSO_4$, the solvent was evaporated under reduced pressure. The residue was redissolved in ethyl acetate and precipitated with heptane, affording lactam **5e** as a white powder (65 mg, 25%); mp 212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.57 (m, 1 H), 2.74 (m, 1 H), 2.85 (m, 2 H), 7.15 (m, 2 H), 7.31 (m, 6 H), 7.67 (br s, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 29.6 (*C*H$_2$), 34.4 (*C*H$_2$), 126.3 (*C*H), 126.8 (*C*H), 127.8 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 129.5 (*C*H), 129.7 (*C*H), 130.4 (*C*H), 135.8 (*C*q), 138.1 (*C*q), 138.6 (*C*q), 140.7 (*C*q), 174.7 (*C*q) ppm; IR (film) υ = 3172, 1667 cm^{-1}; HRMS (LSIMS) calcd for $C_{15}H_{14}NO$ [(M + H)$^+$]: 224.1075; found: 224.1072.

Acknowledgment. We thank Dr. C. Thal for his constant interest and his helpful comments, S. Thoret for tubulin polymerization and depolymerization assays, Dr. M.-T. Martin for assistance with NOESY experiments, and C. Gaspard for cytotoxicity assays. This work was financially supported by the Centre National de la Recherche Scientifique (France).

Supporting Information Available: X-ray diffraction data for compound **5c** as well as copies of selected ^{1}H, ^{13}C, and NOESY NMR spectra are available free of charge via the Internet at http://pubs.acs.org.

JO0160726