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Synthesis of tubulin-binding bridged biaryls via intermolecular Suzuki coupling

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Abstract

This account summarizes our recent work on the synthesis of bridged biaryls that act on the tubulin–microtubule equilibrium. An emphasis is made on the development of biaryl Suzuki couplings, both in non-asymmetric and asymmetric forms that played a major role in these studies. ***To cite this article: O. Baudoin, C. R. Chimie 11 (2008).***

Résumé

Cette revue résume nos travaux récents sur la synthèse de biaryles pontés agissant sur l'équilibre tubuline–microtubules. Le développement de couplages de Suzuki biaryliques non asymétriques et asymétriques, qui a joué un rôle clé dans ces études, est particulièrement mis en avant. ***Pour citer cet article : O. Baudoin, C. R. Chimie 11 (2008).***

Keywords: Asymmetric synthesis; Biaryls; Palladium; Suzuki couplings; Tubulin

Mots-clés : Synthèse asymétrique ; Biaryles ; Palladium ; Couplages de Suzuki ; Tubuline

1. Introduction

Biaryl-containing molecules bind to a great diversity of proteins and therefore are found in almost any therapeutic class, for instance, oncolytics, antibiotics, or CNS and cardiovascular agents [1,2]. In particular, bridged biaryls constitute the framework of naturally occurring antimitotic compounds such as allocolchicinoids (e.g. allocolchicine **1**), steganes (e.g. steganacin **2**), and rhazinilam **3** [3] (Scheme 1). These molecules interact with the mitotic spindle: allocolchicinoids [4] and steganes [5] bind to tubulin at the colchicine site and inhibit the formation of microtubules, whereas rhazinilam inhibits both the disassembly and the assembly of microtubules via the formation of abnormal spiral-like structures [6]. While being structurally related, a major discrepancy exists between the three families of natural products: allocolchicinoids contain a seven-membered median ring that has enough flexibility to allow free rotation around the biaryl bond (configurationally unstable biaryl axis), thus they exist as a mixture of interconverting atropisomers at room temperature (major a*R*

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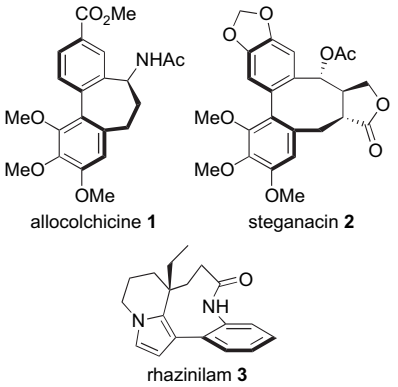
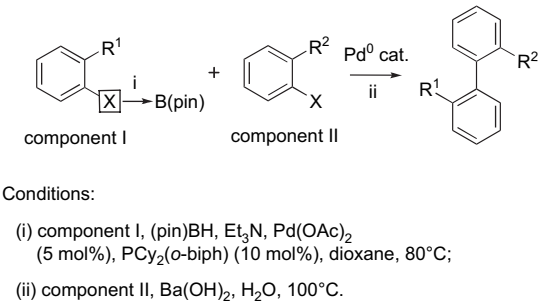


Scheme 1. Structure of allocolchicine, steganacin, and rhazinilam.



Scheme 2. Synthesis of 2,2′-disubstituted biaryls by the one-pot BSC procedure.

atropisomer). In contrast, steganes and rhazinilam-type molecules contain a more rigid eight- and nine-membered bridging ring, respectively, that prevents their room-temperature atropisomerization (configurationally stable axis, a*R* configuration). However, for all three types of compounds, the absolute configuration of the biaryl axis is a crucial parameter for tubulin-binding, since a*S* atropisomers do not fit the binding site and therefore are essentially inactive. The unusual structural features and potent tubulin-binding properties of allocolchicinoids, steganes and rhazinilam have been at the source of numerous synthetic studies [3]. In this account, we report on our own efforts toward the synthesis of these compounds or analogues using Suzuki–Miyaura couplings, both in non-asymmetric [7] and asymmetric [8] variants, to construct their biaryl framework.

2. Synthesis of rhazinilam analogues

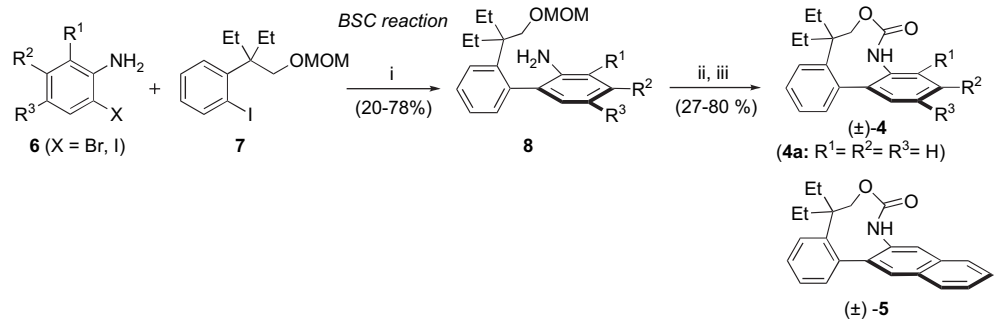
2.1. The borylation–Suzuki coupling (BSC) approach to biaryls

Starting from two ortho-substituted aryl halides (Scheme 2), a variety of 2,2′-disubstituted biaryls were synthesized by a one-pot borylation–Suzuki coupling (BSC) procedure using the same palladium(0) catalyst [9]. The choice of borylation and cross-coupling components 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 best 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, 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) due to an acceleration of the oxidative addition step [7]. 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. It was found that the palladium ligand played a crucial role on the efficiency of both steps, with Buchwald's (2-dicyclohexylphosphino)biphenyl [PCy_2-(*o*-biph)] [10] giving the best results in combination to palladium(II) acetate as the metal source. In addition, a specific base had to be employed for each step, with triethylamine being suitable for the borylation step and barium hydroxide for the Suzuki coupling step.

The BSC procedure was applied to the synthesis of racemic analogues of rhazinilam [11] (Scheme 3). The borylation of 2-haloanilines **6**, followed by coupling with iodoarene **7** (obtained in four steps from commercially available material [12]) furnished biaryls **8** that were converted in two steps into biarylcarbamate analogues of rhazinilam **4**–**5** bearing various electron-donating or -withdrawing R^1–R^3 groups. Although these molecules have a simplified structure compared to rhazinilam (**3**), they have very similar three-dimensional shapes. The unsubstituted racemic analogue **4a** showed comparable antitubulin properties and cytotoxicities toward cancer cells to those of rhazinilam. After separation of both atropisomers of **4a** on a small scale, it was shown that this biological activity is restricted to the a*R* atropisomer, that is twice more active than rhazinilam on the inhibition of microtubule disassembly. With this activity, (a*R*)-**4a** is still the most potent rhazinilam-type antitubulin compound known to date.

*2.2. Catalytic enantioselective synthesis of rhazinilam analogue (aR)-**4a***

HPLC separation of **4a** racemate could provide only mg-scale quantities of (a*R*)-**4a**, that were insufficient for



Conditions:

(i) **6**, (pin)BH, Et_3N, $Pd(OAc)_2$ (5 mol%), PCy_2(*o*-biph) (10 mol%), dioxane, 80°C, then **7**, $Ba(OH)_2$, H_2O,100°C;

(ii) HCl aq., MeOH;

(iii) $(Cl_3CO)_2C{=}O$, pyridine, CH_2Cl_2, –78°C.

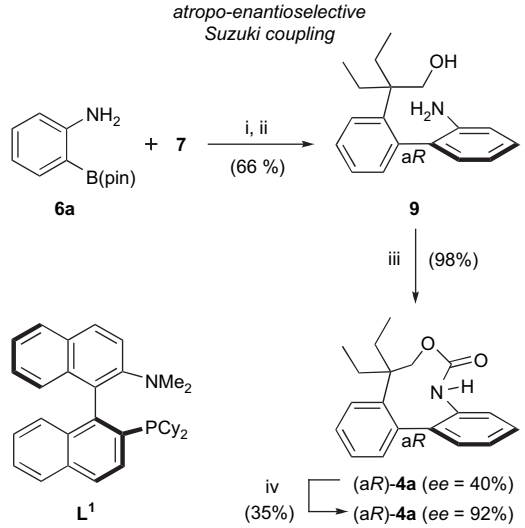
Scheme 3. Synthesis of rhazinilam analogues by the BSC procedure.

further biological (in vivo) evaluation. This prompted us to devise an asymmetric variant for the synthesis of the active enantiomer. In addition to the biological interest, it became clear that this would constitute a good opportunity to assess the synthetic value of enantioselective biaryl Suzuki couplings, that had not been developed to a great extent, neither in methodological studies nor in multi-step synthesis (Scheme 4) [8].

Aryl iodide **7** was coupled with pinacolboronate **6a** under conditions similar to those used in the racemic synthesis of **4a**, in the presence of 5 mol% Pd^0 and 6 mol% of a chiral phosphine ligand to give, after MOM-group cleavage, aminoalcohol **9**. Compound **9** and its MOM-protected precursor bear only two substituents in their 2 and 2′ positions and have therefore limited configurational stability. However, under the described conditions, the coupling was sufficiently fast (45–60 min at 80 °C) to avoid thermal epimerization of the product. Several chiral ligands were tested in this reaction, including those previously reported in other enantioselective Suzuki couplings. From this screen, Buchwald's binaphthyl-monophosphine (a*S*)-L^1 [13] gave the highest enantioselectivity, and aminoalcohol **9** was obtained in a moderate 40% ee (and 66% yield for two steps). Cyclization with triphosgene at low temperature gave the target enantiomer (a*R*)-**4a** quantitatively and again in 40% ee. Gratifyingly, a single crystallization improved the ee to 92%, providing compound quantities suitable for further biological evaluation.

3. Asymmetric synthesis of hybrids of allocolchicine and steganacin

Allocolchicine (**1**) and steganacin (**2**) are antimicrotubule agents that both bind to tubulin at the colchicine site (Scheme 1). We envisioned to structurally combine these two families of natural products so as to obtain simple but potent inhibitors of tubulin polymerization. We took benefit of the expertise gained with the synthesis of rhazinilam analogues to design an asymmetric synthesis of such hybrid molecules. After unsuccessful attempts with enantioselective Suzuki couplings, we



Conditions:

(i) 2.5 mol% $Pd_2(dba)_3$, 6 mol% L^1, $Ba(OH)_2$,dioxane/water 9:1, 80 °C;

(ii) concd. HCl/MeOH 1:4, 35 °C;

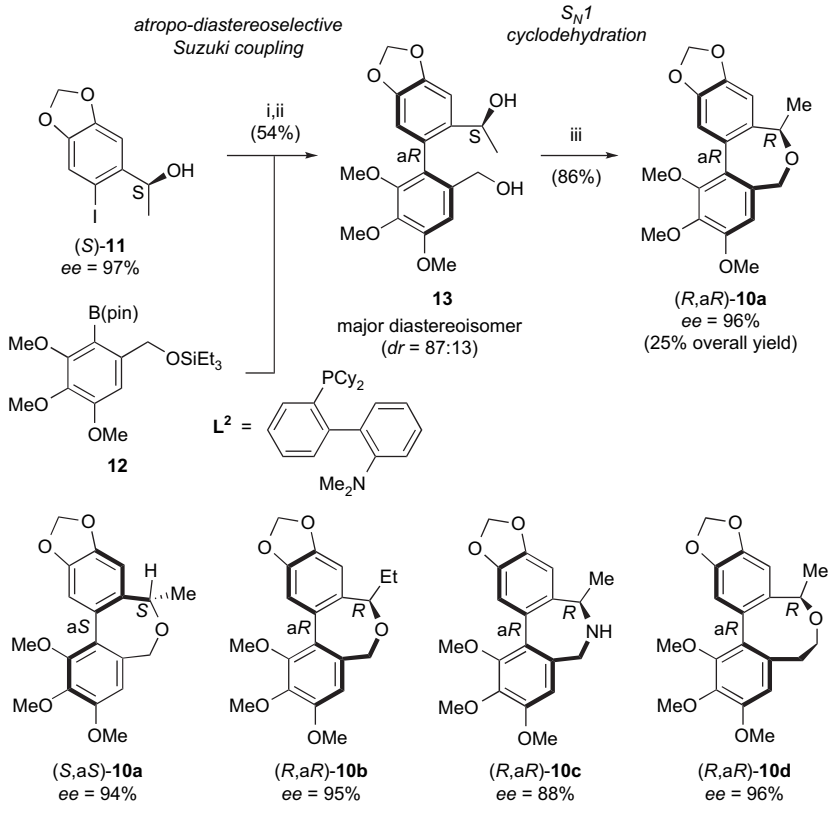
(iii) $(Cl_3CO)_2C{=}O$, pyridine, CH_2Cl_2, –78 °C;

(iv) crystallization from CH_2Cl_2/heptane.

Scheme 4. Enantioselective synthesis of the rhazinilam analogue (a*R*)-**4a**.

designed a diastereoselective variant, making use of a simple chirality induction from a benzylic stereogenic alcohol (Scheme 5) [14].

Alcohol (*S*)-**11** was obtained in 97% ee by a Corey–Bakshi–Shibata catalytic enantioselective reduction. The coupling of (*S*)-**11** with boronate **12** was conducted under reoptimized conditions using palladium acetate and ligand $\mathbf{L^2}$ as pre-catalyst. This furnished, after TES-group removal with TBAF, diol **13** as the major diastereoisomer with *S*,a*R* absolute configuration in 54% isolated yield. A good diastereoselectivity was observed in the biaryl coupling step (dr = 87:13 in favor of the *S*,a*R* diastereoisomer). A S_N1-type cyclodehydration performed at −50 °C produced dibenzoxepine (*R*,a*R*)-**10a** with configuration inversion at the benzylic stereocenter and conservation of the optical purity of alcohol (*S*)-**11**. This can be rationalized by the formation of a configurationally stable a*R*-configured benzylic carbocation intermediate. Using this reaction sequence, compound (*R*,a*R*)-**10a**, which is very similar to allocolchicine (**1**) in three-dimensions, was obtained in 96% ee and 25% overall yield. As could be expected from this structural similarity, (*R*,a*R*)-**10a** showed colchicine-type antimicrotubule activity, which was only slightly (1.5×) inferior to that of colchicine itself. Variations in the structure of either Suzuki coupling partners **11** and **12** and in the synthetic sequence allowed the synthesis of enantiomer (*S*,a*S*)-**10a** and analogues (*R*,a*R*)-**10b–d** with similar efficiency and enantioselectivity. It could thus be checked that only the *R*,a*R* enantiomer of **10a** had antimicrotubule activity, similar to other allocolchicine-type molecules. Other analogues showed interesting activities, for instance the ethyl analogue (*R*,a*R*)-**10b** was 1.7 times more potent than colchicine as antimicrotubule agent. In addition, analogue (*R*,a*R*)-**10d**, having an eight-membered median ring conformationally closer to that of steganacin-type compounds, showed a similar



Conditions:

(i) 5 mol% $Pd(OAc)_2$, 10 mol% L^2, $Ba(OH)_2$, dioxane/water 9:1, 100 °C;
(ii) *n*-Bu_4NF, THF, 20°C;
(iii) TFA, CH_2Cl_2, –50°C.

Scheme 5. Enantioselective synthesis of allocolchicine/steganacin hybrids.

potency to its seven-membered ring analogue **10a**. This synthetic sequence, powered by the use of an efficient and stereoselective biaryl Suzuki coupling paves the way for further structural optimization of these new types of allocolchicine/steganacin hybrids and their evaluation as new antimitotics.

4. Conclusion

We have designed modified reaction conditions for the biaryl Suzuki coupling that are specifically adapted to the synthesis of 2,2′-bridged biaryls of biological interest. Both non-asymmetric and asymmetric variants of this approach were found to be viable for the production of small libraries of molecules that act on the tubulin–microtubule equilibrium and therefore arrest mitosis. It is our hope that these studies will contribute to improve the synthesis of biaryls, that are both synthetically challenging and biologically important molecular motifs.

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