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Asymmetric Synthesis of Antimicrotubule Biaryl Hybrids of Allocolchicine and Steganacin

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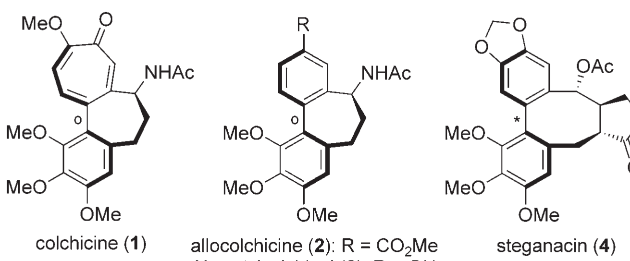
Abstract: The asymmetric synthesis of novel axially chiral biaryl compounds **5a**–**f** containing a seven- or eight-membered heterocyclic medium ring is described. These molecules can be considered to be structural hybrids of allocolchicine- and steganacin-type natural products. The synthesis featured an atropo–diastereoselective biaryl Suzuki coupling in which a benzylic stereocenter efficiently transferred its stereochemical information to the biaryl axis. The coupling conditions were optimized, and two biphenylphosphane ligands (DavePhos and S-Phos) were found to give the highest yields and diastereoselectivities. A three-element stereochemical model was proposed to explain the observed diastereoselectivities. In a second key step, the medium ring of the target molecules was formed by a stereoselective S_N1-type cyclodehydration that probably involved a configurationally stable carbocationic intermediate, as supported by calculations. Alternatively, S_N2-type cyclizations were employed on the same Suzuki coupling products to give the target molecules in a stereodivergent or stereoconvergent manner. These cyclization methods furnished the target hybrid analogues **5a**–**f** with *ee* values above 94%. All analogues were evaluated as antimicrotubule agents and against a panel of cancer-cell lines using colchicine (**1**) and *N*-acetylcolchinol (**3**) as references. Promising activities were found for *R*,a*R*-configured compounds **5a**,**b** and **5f**; in particular, ethyl analogue **5b** showed a twofold antimicrotubule activity relative to colchicine.

Keywords: antimicrotubule agents · asymmetric synthesis · atropisomerism · carbocations · Suzuki coupling

Introduction

Colchicine (**1**; C) is the oldest known natural product that binds to tubulin and inhibits its assembly into microtubules (Scheme 1).[1] Over recent decades, several natural biaryl congeners, such as allocolchicine (**2**); semisynthetic derivatives, such as *N*-acetylcolchinol (**3**; NAC); and synthetic ana-



Scheme 1. Natural or semisynthetic molecules that bind to the colchicine site of tubulin. (According to the nomenclature of Bringmann, the configurationally unstable biaryl axis in the allocolchicinoids is noted as "o" and the configurationally stable axis in the steganes is noted as "*".)[10,11]

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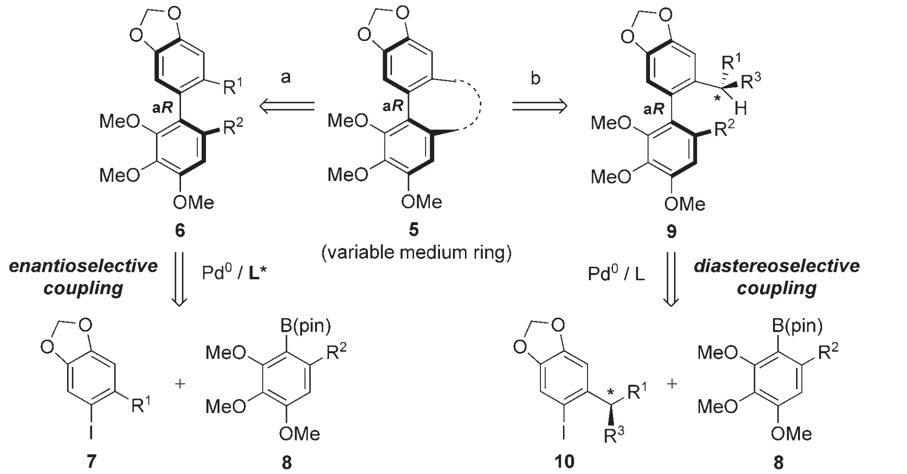
logues have been shown to have similar or even more potent antimicrotubule activity and cytotoxicity toward cancer cells in vitro than colchicine.[2,3] However, the toxicity of these compounds has precluded their medical use as anticancer agents so far, contrary to other tubulin-binding agents, such as vinca alkaloids or taxanes.[4] Recently, molecules that bind to the colchicine site, which is located in β-tubulin at the interface with α-tubulin,[5] have again gained attention as NAC (**3**) and combretastatin derivatives were found to selectively destroy tumor vasculature.[6] Steganacin (**4**) is a naturally occurring dibenzocyclooctadiene (DBCO) lignan, which was isolated in 1973 from *Steganotaenia araliacea*,[7] that also binds to the colchicine site in tubulin and shows weak antitumor activity in vivo.[8] The allocolchicinoid and stegane families of compounds are structurally related as they are both composed of a polyoxygenated biaryl framework bridged by a medium ring, a common feature that is for the most part responsible for their tubulin-binding properties.[9] However, a major structural discrepancy between both families has to be underlined: allocolchicinoids contain a seven-membered medium ring that has enough flexibility to allow free rotation around the biaryl bond (see Scheme 1); thus, they exist as a mixture of interconverting atropisomers at room temperature.[12] In contrast, steganes contain a more rigid eight-membered bridging ring that prevents room-temperature atropisomerization (see Scheme 1).[13] For both series, the absolute configuration of the biaryl axis is a crucial parameter for tubulin binding as a*S* atropisomers do not fit the binding site and therefore are essentially inactive. The unusual structural features and potent antimicrotubule properties of allocolchicinoids and steganes have been the source of numerous synthetic studies.[3,14–16]

Abstract in French: *La synthèse asymétrique de nouveaux biaryles à chiralité axiale **5a–f**, contenant un hétérocycle médian à sept ou huit chaînons, est décrite. Ces molécules peuvent être considérées comme des hybrides structuraux de produits naturels de type allocolchicine et stéganacine. La synthèse met en œuvre un couplage de Suzuki biarylique atropo-diastéréosélectif au cours duquel un centre stéréogène benzylique transfère efficacement son information stéréochimique vers l'axe biarylique. Les conditions du couplage ont été optimisées, et deux ligands de type biphénylphosphines (DavePhos et S-Phos) ont fourni les meilleurs rendements et diastéréosélectivités. Un modèle stéréochimique à trois éléments est proposé afin d'expliquer les diastéréosélectivités observées. Dans une deuxième étape clé, le cycle médian des molécules cibles a été formé par une cyclodéshydratation stéréosélective de type S_N1, qui fait probablement intervenir un intermédiaire carbocationique configurationnellement stable comme indiqué par des calculs de modélisation. Alternativement, des cyclisations de type S_N2 ont été employées à partir des mêmes produits de couplage de Suzuki pour former les molécules cibles de façon stéréodivergente ou stéréoconvergente. Ces méthodes de cyclisation ont permis d'obtenir les analogues hybrides **5a–f** avec des excès énantiomériques supérieurs à 94%. Tous ces analogues ont été évalués comme agents antimicrotubules et sur un panel de lignées de cellules cancéreuses en utilisant la colchicine (**1**) et le N-acétylcolchinol (**3**) comme références. Des activités prometteuses ont été trouvées pour les composés **5a–b** et **5f** de configuration absolue R,aR, en particulier pour l'analogue éthyle **5b** qui a montré une activité antimicrotubule deux fois supérieure à la colchicine.*

Various strategies have been reported to control the absolute configuration of stereogenic biaryl axes within the context of natural product synthesis.[11,17] Among these, only a couple of intermolecular biaryl coupling methods, namely, the Grignard/chiral oxazoline coupling developed by Meyers et al.[18] and the Suzuki coupling of a chiral (arene)chromium tricarbonyl complex,[19] have been successfully used for the asymmetric synthesis of steganes. In contrast, the vast majority of the asymmetric syntheses of allocolchicinoids and DBCO lignans have been based on the control of the axial configuration by the stereogenic centers of the bridging ring.[14–16] We have recently been involved in the development of asymmetric biaryl Suzuki–Miyaura couplings in the context of natural-product synthesis.[20] In particular, we described the asymmetric synthesis of a potent analogue of another axially chiral tubulin-binding biaryl compound, rhazinilam, through an atropo–enantioselective coupling catalyzed by palladium and a chiral phosphane ligand.[21] Herein, we report the synthesis of hybrid analogues of **2** and **4** using a complementary approach, namely, an atropo–diastereoselective Suzuki coupling[20] and the preliminary biological evaluation of these compounds as novel antimicrotubule agents.[22]

Results and Discussion

Retrosynthetic analysis and initial studies: In light of the similar structural properties and antimicrotubule activities of both types of natural products, we envisaged the synthesis of hybrid analogues **5** that retained the polyoxygenated biaryl backbone with the a*R* absolute configuration, namely, the common pharmacophore elements, but with bridging rings of varying size and substitution (Scheme 2). To obtain the desired a*R* axial configuration for the targets **5**, two complementary approaches were devised: The first approach (path a) would use an atropo–enantioselective Suzuki coupling between achiral partners **7** and **8** containing bulky *ortho* R^1 and R^2 groups catalyzed by palladium(0) and a chiral ligand, according to our previous work.[21] In the second approach (path b), the axial configuration would be controlled by chirality induction from a benzylic stereocenter during a diastereoselective Suzuki coupling between chiral non-racemic iodide **10** and boronate **8** catalyzed by palladium(0) and an achiral ligand.[20,23,24] The stereogenic center in **10** should be preferably installed by a catalytic enantioselective reaction to render this synthetic sequence

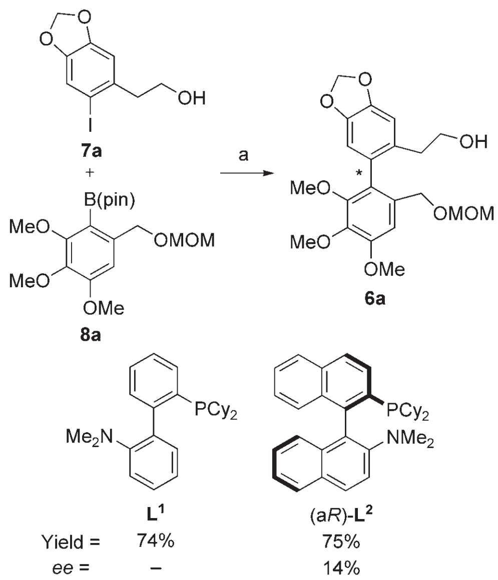


Scheme 2. Retrosynthetic analysis of stegane/allocolchicinoid hybrids (**5**) using an enantio- or diastereoselective Suzuki coupling.

ral biphenylphosphane ligand **L**^{1},[26] which provided (±)-**6a** in 74% yield. Both enantiomers of **6a** could be separated on a small scale by analytical HPLC on a chiral stationary phase (Chiralpak AD, 1 mL min^{-1}, hexane/isopropanol (95:5), t_R=25, 31.5 min), which allowed us to verify their configurational stability under the coupling conditions (0% atropisomerization, as measured by HPLC after heating for 3 h in dioxane at 110 °C). Once this verification had been carried out, the coupling of **7a** and **8a** was performed in the presence of chiral binaphthylphosphane (a*R*)-**L**^{2} under the same conditions.[27] This approach provided **6a** in a similarly good yield, but with a modest enantiomeric excess of 14% in favor of the *levo* enantiomer. This selectivity was rather disappointing and might be ascribed to a lack of steric discrimination between the two *ortho* substituents of the boronic ester (OCH_3 versus $CH_2OCH_2CH_3$), thus necessitating fine-tuning of the structure of the coupling partners and perhaps also of the reaction conditions. While continuing this reoptimization, we studied the diastereoselective Suzuki coupling route (Scheme 2, path b), which was hoped to provide better stereoselectivity.

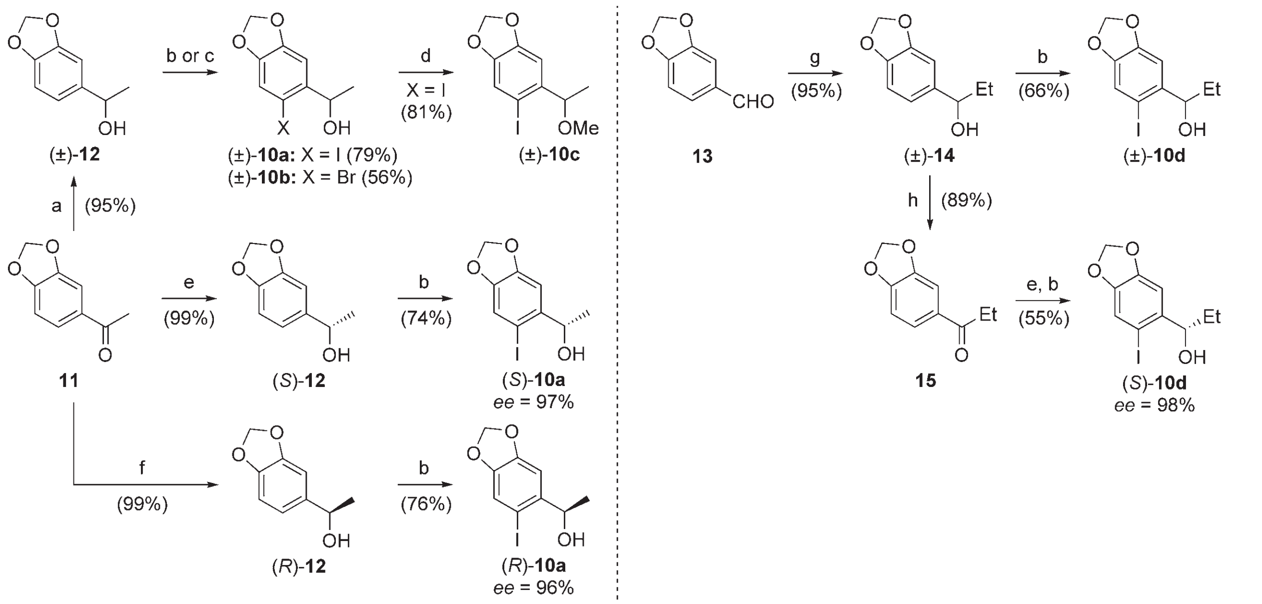
catalytic in chiral material, as in path a. Both approaches would necessitate the appropriate functionalization of coupling products **6** and **9** and subsequent construction of the medium ring. Thus, the benzylic stereogenic center of **9** would not serve as just a temporary agent for the induction of chirality, as it is present in both the allocolchicinoids and steganes.

Our initial studies concentrated on the enantioselective coupling route (path a) under conditions that were previously optimized for the asymmetric synthesis of rhazinilam analogues.[21] The coupling of iodide **7a**[25] and pinacol boronate **8a**[23] was chosen as a model system (Scheme 3). First **7a** and **8a** were coupled in the presence of [Pd_2dba_3] and achi-

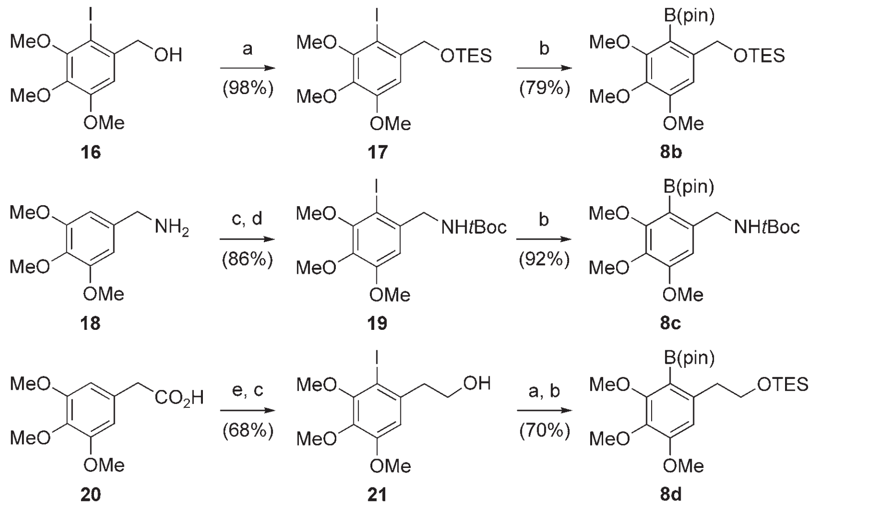


Scheme 3. The initial attempt at enantioselective Suzuki coupling. Reagents and conditions: a) **7a** (1.0 equiv), **8a** (1.5 equiv), [Pd_2dba_3]·$CHCl_3$ (2.5 mol%), **L**^{1} or (a*R*)-**L**^{2} (6 mol%), $Ba(OH)_2 \cdot 8H_2O$ (2 equiv), dioxane/H_2O (9:1), 110 °C, 1 h. dba = *trans,trans*-dibenzylideneacetone, Cy = cyclohexyl, MOM = methoxymethyl, pin = pinacol (2,3-dimethyl-2,3-butanediol).

Racemic diastereoselective Suzuki coupling pathway to allocolchicine/steganacin hybrids: The first task of this approach was finding the right substitution patterns for both Suzuki coupling partners. In preliminary investigations, it was found that the coupling of racemic iodide **10a** (Scheme 4),[28] containing a stereogenic secondary benzylic alcohol, with boronate **8a** (Scheme 3) provided the corresponding MOM-protected biaryl compound in good yield with satisfactory diastereoselectivity in favor of the *S*,a*R*-configured diastereoisomer (d.r. 84:16).[23] However, both diastereoisomers could not be separated, which severely impaired their synthetic interest. Replacement of the MOM group with a triethylsilyl (TES) group (**8b**; Scheme 5) rendered this separation easier, albeit at the expense of the yield of the coupling product. Hence, we reoptimized the coupling of iodide **10a** and boronate **8b** in light of recent work on Suzuki biaryl coupling of sterically hindered substrates. In particular, the efficiency of a variety of bulky and strong σ-donor ligands in these rather difficult cross-coupling reactions was demonstrated.[29] The screening of the ligands was performed under conditions previously developed by us that were found to have a wide applicability to various types of bulky coupling partners:[21,23,30] 1.5 equivalents of boronate, 5 mol% $Pd(OAc)_2$, 10 mol% ligand, and two equivalents of barium hydroxide in dioxane/H_2O (9:1) at 100 °C (Figure 1).



Scheme 4. Preparation of haloarene building blocks. Reagents and conditions: a) $NaBH_4$ (1.6 equiv), $MeOH/CH_2Cl_2$ 5:2, 0°C, 30 min; b) I_2 (1.05 equiv), CF_3CO_2Ag (1.2 equiv), $CHCl_3$, 0°C, 15 min; c) NBS (1.2 equiv), CH_3CN, 20°C, 30 min;[31] d) NaH (1.1 equiv), MeI (2 equiv), THF, 25°C, 15 h; e) (*R*)-2-methyl-CBS-oxazaborolidine (10 mol%), $BH_3{\cdot}SMe_2$ (1.0 equiv), CH_2Cl_2, 20°C, 3 h; f) (*S*)-2-methyl-CBS-oxazaborolidine (10 mol%), $BH_3{\cdot}SMe_2$ (1.0 equiv), CH_2Cl_2, 20°C, 3 h; g) EtMgBr (1.0 equiv), THF, −78°C, 2 h; h) PCC (1.3 equiv), CH_2Cl_2, 20°C, 16 h. NBS = *N*-bromosuccinimide, PCC = pyridinium chlorochromate.



Scheme 5. Preparation of boronate building blocks. Reagents and conditions: a) TESOTf (1.2 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0→20°C, 30 min; b) (pin)BH (2 equiv), Et_3N (3 equiv), $Pd(OAc)_2$ (5 mol%), PCy_2(*o*-biph) (L^3, 10 mol%), dioxane, 80°C, 30 min; c) Boc_2O (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 20°C, 2 h; d) I_2 (1.05 equiv), CF_3CO_2Ag (1.2 equiv), $CHCl_3$, 0°C, 15 min; e) $LiAlH_4$ (10 equiv), Et_2O, reflux, 2.5 h. PCy_2(*o*-biph) = 2-(dicyclohexylphosphino)biphenyl; Boc_2O = di-*tert*-butyldicarbonate.

The following commercially available bulky, strong σ-donor ligands were screened: biphenylphosphanes L^1, L^3, L^4, and L^5 developed by Buchwald and co-workers,[26,32] Q-Phos L^6 developed by Hartwig and co-workers,[33] and L^7, a precursor of the N-heterocyclic carbene (NHC) IPr.[34] Under these reaction conditions, the complete consumption of boronate **8b** was observed within one hour and the TES-protected biaryl product was obtained as a mixture of diastereoisomers **9a**,**b**, with **9a** as the major diastereoisomer. The ratio **9a**/**9b** could not be measured precisely by ^{1}H NMR spectroscopic analysis of the crude mixture as a result of large amounts of by-products. The yields were calculated for the major diastereoisomer for two steps, after deprotection induced by tetrabutylammonium fluoride (TBAF), thus giving biaryl **9c**, to separate **9a** from the coeluted by-product **12**. Together with biaryl compounds **9a**,**b** and starting material **10a**, several by-products were isolated in various amounts: proto-deiodinated compound **12**, the boronate hydrolysis product **22**, and acetophenone (**11**).

The results of this screening are shown in Figure 1 (bar graph, conditions A). The yields for **9c** remained low (but reproducible), with maxima of 25 and 33% for the biphenylphosphanes L^1 and L^5, respectively. As we became aware that hydrolysis of the boronate group was the limiting side reaction (and not the proto-deiodination of the iodide), several modifications of the coupling conditions were attempted with L^1 as the ligand. First, increasing the amount of boronate **8b** to two equivalents—

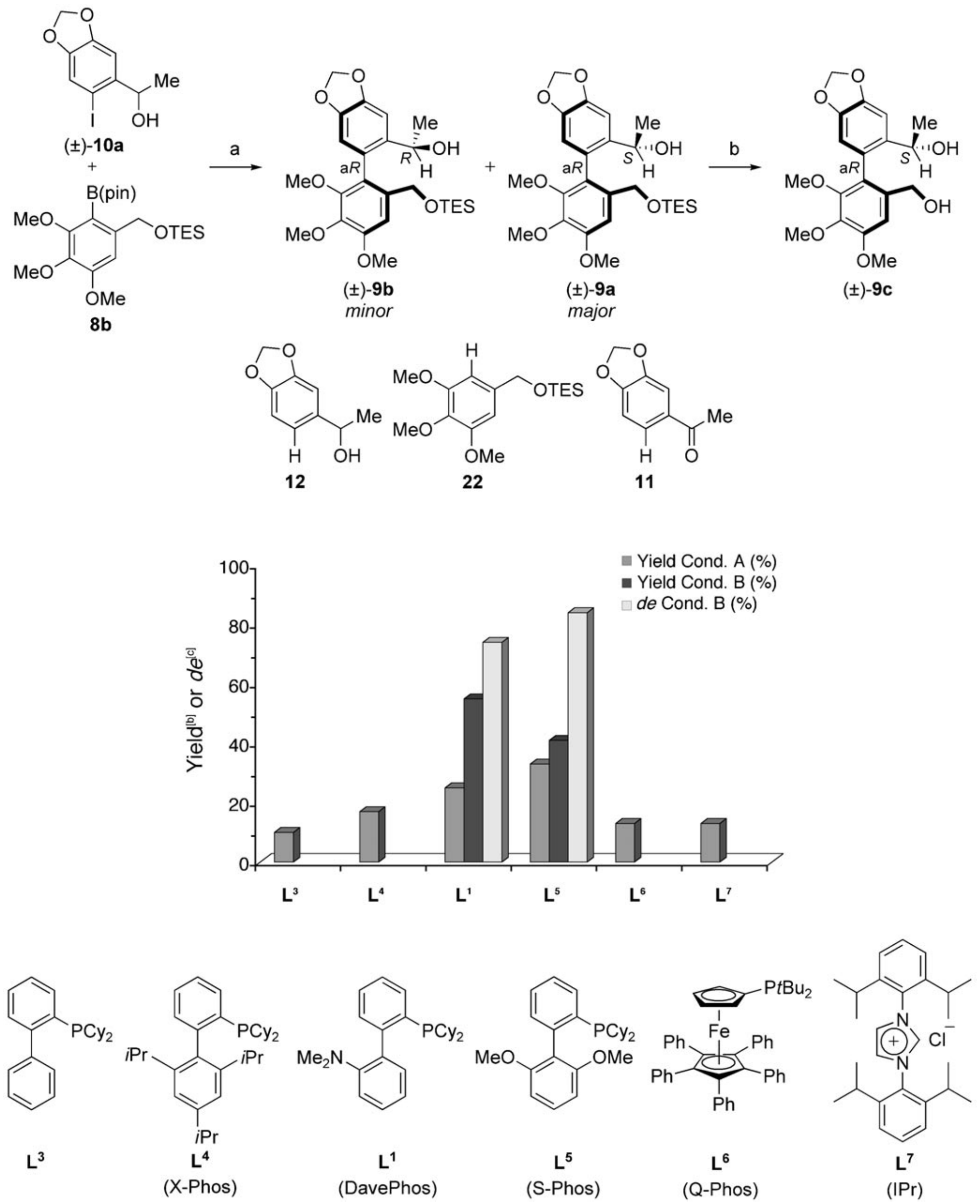
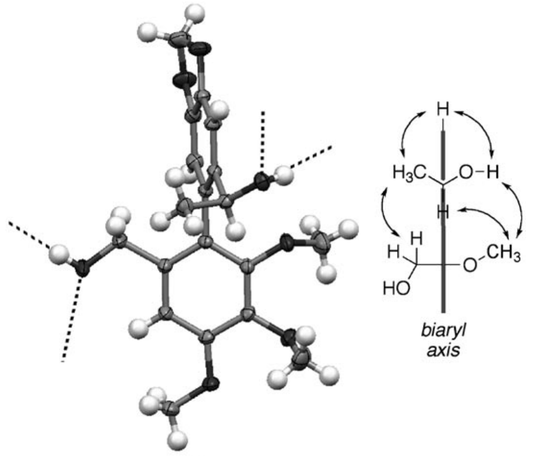


Figure 1. Suzuki coupling optimization for the synthesis of biaryl **9c**.[a] [a] Reagents and conditions: a) Conditions A: **10a** (1.0 equiv), **8b** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), $Ba(OH)_2 \cdot 8H_2O$ (2 equiv), dioxane/H_2O (9:1; c = 0.32 M), 100 °C, 1 h; conditions B: **10a** (1.0 equiv), **8b** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), $Ba(OH)_2 \cdot 8H_2O$ (1.1 equiv), dioxane/H_2O (9:1; c = 1 M), 100 °C, 1 h. b) $n$$Bu_4$NF (1 equiv), THF, 20 °C, 15 min. [b] Yield of the isolated diol **9c** from steps a and b. [c] Diastereomeric excess measured by ^{1}H NMR spectroscopic analysis of the crude mixture obtained in step a.

which is not particularly desirable except for investigational reasons as it can not be recovered—did not significantly increase the yield of biaryl **9c**. A slow addition of a dilute solution of **8b** to the reaction mixture over 30 minutes gave even worse results. Gratifyingly, decreasing the amount of barium hydroxide to 1.1 equivalents gave an increased yield of 45 % relative to 25 % for two equivalents. An optimal yield of 55 % in **9c** was eventually obtained by concentrating the reaction medium to 1 M in **10a** (Figure 1, conditions B). Under the same conditions, $\mathbf{L^5}$ gave a lower yield of 41 %. With this improvement, it was possible to measure the ratio of diastereoisomers **9a**/**9b** from the crude mixture from the coupling reaction (Figure 1). This diastereoisomeric ratio was 87:13 (74 % *de*) with $\mathbf{L^1}$ and 92:8 with $\mathbf{L^5}$ (84 % *de*). Thus, in this coupling reaction S-Phos $\mathbf{L^5}$ gave a better diastereoselectivity, but a lower yield than DavePhos $\mathbf{L^1}$. Finally, a variation in the haloarene coupling partner was examined under these reoptimized conditions (with $\mathbf{L^1}$). The coupling of bromoarene **10b** (Scheme 4) and boronate **8b** gave, after removal of the TES group, a lower yield of 25 % in diol **9c**. On the other hand, the *O*-methyl iodoarene derivative **10c** furnished, after Suzuki coupling with **8b** and desilylation, the corresponding mono-*O*-methylated analogue of **9c** with a yield (51%) and diastereoselectivity (70% *de*) comparable to those obtained from **10a**. These results provide useful indications on the coupling mechanism and will be commented upon later.

The *S*,a*R* relative configuration of the major diastereoisomer **9a** was unambiguously determined by X-ray diffraction studies of diol **9c** (Figure 2). In the solid state, **9c** bonds

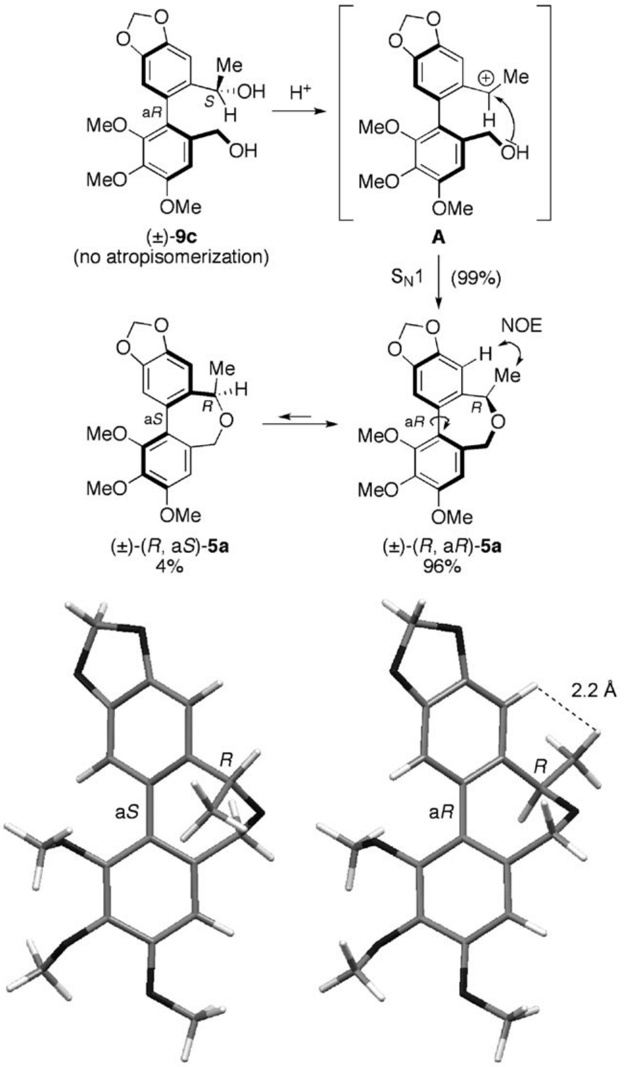


9c

Figure 2. Solid-state (left) and solution (right) structures of biaryl **9c** from X-ray diffraction analysis (30% thermal ellipsoids plot; intermolecular hydrogen bonds are shown as dotted lines) and through-space correlations observed from a NOESY experiment, respectively.

through an intermolecular hydrogen-bonding network. In solution, **9c** seems to adopt a very similar conformation to the solid state, as deduced from through-space NOESY correlations observed in [D$_6$]dimethyl sulfoxide ([D$_6$]DMSO; Figure 2). The TES-protected precursor **9a** showed a similar through-space correlation pattern, which is also the case for all *S*,a*R*-configured Suzuki coupling products in this study. In this common conformation, the hydrogen atom of the stereogenic center eclipses the biaryl axis, which is probably the result of the minimization of $A^{1,3}$ strain (in a benzylic system).

As expected from the presence of the sp^3 benzylic center,[18] **9a** and **9c** showed a very stable axial configuration as no atropisomerization, which would furnish the *S*,a*S* diastereoisomer, was detected by ^{1}H NMR spectroscopic analysis upon heating at temperatures up to 160°C for several hours. Interestingly, we found that **9c**, when treated with a Brønsted acid, such as (+)-camphor-10-sulfonic acid (CSA) or *para*-toluenesulfonic acid (*p*TSA), gave rise to dibenzoxepine **5a** in a quantitative manner (Scheme 6). This cyclodehydration process probably involves the stabilized carbocationic intermediate **A**, which undergoes an intramolecular S$_N$1 reaction with the remaining benzylic alcohol. Compound **5a** was obtained as a 96:4 mixture of a*R*/a*S* atropisomers which, in contrast to diol **9c**, interconverted at room temperature, as evidenced by exchange correlations on the NOESY spectrum. The three-dimensional structure



Scheme 6. Synthesis of racemic dibenzoxepine **5a** and the computed three-dimensional structures of its atropisomers. Reagents and conditions: CSA (1.0 equiv), acetone, 20°C, 3 h.

of **5a** was computed successively by random search (Monte Carlo method with MM2 molecular mechanics optimization) and semiempirical calculations. These calculations furnished the structures of both atropisomers (Scheme 6), with the *R*,a*R* conformer being the most stable by 0.7 kcal. Experimental NOESY correlations observed for the major atropisomer confirmed its *R*,a*R* relative configuration (Scheme 6).[35] The facile atropisomerism in **5a** most probably arises from the lack of rigidity of the seven-membered medium ring, a property that is known in allocolchicinoids[2a] and other medium-ring containing biaryl compounds.[11]

A comparison of the computed three-dimensional structure of dibenzoxepine (**5a**) with available X-ray structures of allocolchicinoids showed strong similarities. In particular, the presence of the oxygen atom in the medium ring of **5a** induces only minimal distortion relative to a carbon atom in the allocolchicinoids. For example, **5a** has a mean biaryl dihedral angle of 45°, whereas this angle is 49° in allocolchicine (**2**)[12] and 54° in NAC (**3**).[36] This finding prompted us to examine the antimicrotubule properties of racemic **5a** (Table 1, entry 3). Compound **5a** showed promising antimicrotubule activity, with an IC_{50} value 1.6 times higher than that of colchicine (**1**; Table 1, entry 1) and five times that of **3** (Table 1, entry 2). Compound **5a** was also tested on a panel of six cancer-cell lines (Table 1) and showed moderate cytotoxicity in the micromolar range. In analogy to allocolchicinoids, it was anticipated that only one enantiomer of **5a**, namely, the one with the a*R* axial configuration, should be responsible for the antimicrotubule activity of the racemic mixture. This hypothesis primarily drove us to develop an asymmetric variation of the synthesis of (*R*,a*R*)-**5a** and (*S*,a*S*)-**5a** that would enable us to test both enantiomers. Besides biological interest, we were driven by the synthetic challenge posed by the transposition of the final S_N1-type cyclization to the enantiomerically pure diol **9c**. Indeed, it is known that the presence of an sp^2 center in the benzylic position (carbocation **A**; Scheme 6) of similar systems considerably facilitates atropisomerization,[18] which in turn should mar the optical purity of the target dibenzoxepine **5a**. Finally, we were aware that such an asymmetric approach should be compatible with the introduction of structural diversity to yield more potent antimicrotubule analogues.

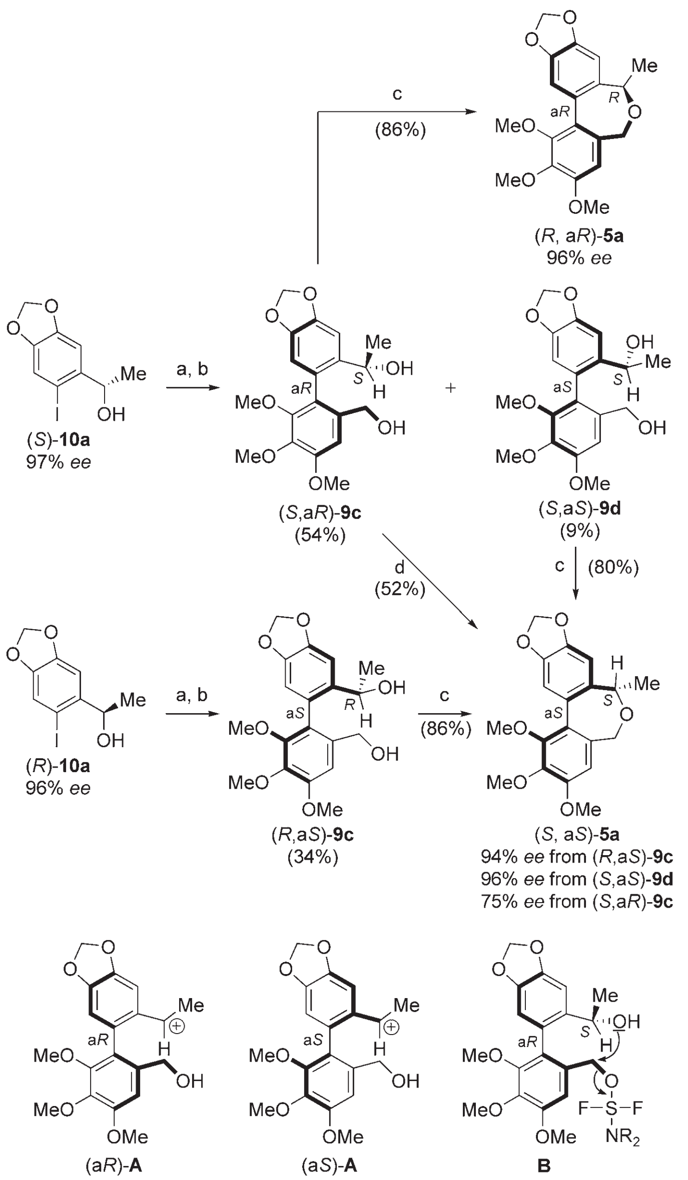
Enantioselective synthesis of both enantiomers of 5a: The required non-racemic iodoarene building blocks (*S*)-**10a** and (*R*)-**10a** were obtained in two steps in good yield (73–75%) with high enantiomeric excess (96–97% *ee*) from commercially available **11** (Scheme 4). In the first step, the Corey–Bakshi–Shibata (CBS) reduction[37] of ketone **11** with the borane–dimethylsulfide complex in the presence of 10 mol% (*R*)-2-methyloxazaborolidine was best performed at 20 °C[38] and afforded the known[39] alcohol (*S*)-**12** quantitatively. Regioselective iodination of the latter with iodine and silver trifluoroacetate provided iodoarene (*S*)-**10a** in 72% yield. An enantiomeric excess of 97% was measured for (*S*)-**10a** by HPLC on a chiral phase with (±)-**10a** as the reference. The same sequence employing (*S*)-2-methyloxazaborolidine in the first step provided the *R* enantiomer (*R*)-**10a** in 96% *ee* (Scheme 4).

The coupling of (*S*)-**10a** with boronate **8b** under the reoptimized conditions furnished, after removal of the TES group, diastereoisomeric diols (*S*,a*R*)-**9c** and (*S*,a*S*)-**9d** in 54 and 9% yield of the isolated product, respectively (Scheme 7; after the coupling step the measured diastereomeric ratio was again 87:13, as in the racemic synthesis). The stereochemically crucial cyclodehydration of (*S*,a*R*)-**9c** (step c) was then attempted in the presence of CSA in acetone. To our surprise, this approach furnished the desired dibenzoxepine (*R*,a*R*)-**5a** as the major enantiomer in 74% *ee* (measured by HPLC on a chiral phase), thus with a relatively small loss of optical purity. A quick optimization of the cyclization conditions led us to conduct the reaction at −50 °C, with the dropwise addition of a dilute ($c = 0.35$ M) solution of trifluoroacetic acid (TFA) in dichloromethane to maintain a constant temperature. This procedure furnished (*R*,a*R*)-**5a** with a reproducible yield of 86% with 96% *ee*, hence with conservation of the optical purity of the starting alcohol (*S*)-**10a**. Below −50 °C, no reaction took place, whereas the enantiomeric excess decreased above that temperature. The same reaction sequence applied to (*R*)-**10a** (96% *ee*) furnished the *S*,a*S* enantiomer of dibenzoxepine **5a** in 94% *ee* (Scheme 7). It was anticipated that the cyclodehydration of enantiomeric diols (*S*,a*R*)-**9c** and (*R*,a*S*)-**9c** involved the configurationally stable carbocationic intermediates (a*R*)-**A** and (a*S*)-**A**, respectively.[40] This proposal was confirmed by submitting diastereomeric diol (*S*,a*S*)-**9d**, obtained as minor diastereoisomer of the Suzuki coupling from (*S*)-**10a** (Scheme 7), to the cyclodehydration conditions. Enantiomer (*S*,a*S*)-**5a** was obtained in 96% *ee*, thus showing that diastereoisomeric diols with the same a*S* axial configuration but a different central configuration (namely, (*R*,a*S*)-**9c** and (*S*,a*S*)-**9d**) evolve toward the same a*S*-configured carbocationic intermediate.

Table 1. Antimicrotubule activity and cytotoxicity of target biaryl compounds **5a–f**.

Entry	Compound	Inhibition of microtubule assembly[a,c] IC_{50}(cpd)/IC_{50}(**1**)	Cytotoxicity[b,c] IC_{50} [μM] B16F10	HCT-116	A549	U87	MDA-MB-435	MDA-MB-231
1	**1**	1	0.03	0.04	0.04	0.03	0.04	0.07
2	**3**	0.3	0.07	0.10	0.25	0.20	0.14	0.70
3	(±)-**5a**	1.6	0.80	2.0	3.2	3.2	2.0	5.0
4	(*R*,a*R*)-**5a**	1.5	0.18	0.75	0.9	1.3	1.8	2.5
5	(*S*,a*S*)-**5a**	In	7.5	10	In	In	In	In
6	(±)-**5b**	0.7	0.79	1.4	2.0	1.6	1.0	4.0
7	(*R*,a*R*)-**5b**	0.6	0.70	0.90	1.0	1.4	0.85	3.5
8	(±)-**5c**	In	In	In	In	In	In	In
9	(*R*,a*R*)-**5c**	In	In	In	In	In	In	In
10	(±)-**5d**	In	In	In	In	In	In	In
11	(±)-**5e**	In	In	In	In	In	In	In
12	(±)-**5f**	3.1	4.0	4.5	3.8	6.8	5.0	8.0
13	(*R*,a*R*)-**5f**	1.3	1.8	2.1	3.0	3.5	2.2	6.0

[a] IC_{50} is the concentration of compound required to inhibit 50% of the rate of microtubule assembly, average of three experiments; IC_{50}(**1**) = 8.2 μM. [b] IC_{50} is the concentration of compound corresponding to 50% growth inhibition after 72 h incubation, average of three experiments; cell lines: B16F10 = murine melanoma, HCT-116 = human colorectal cancer, A549 = human nonsmall cell lung cancer, U87 = human glioblastoma, MDA-MB-435 and MDA-MB-231 = human breast cancers. [c] In = inactive (or IC_{50} not measurable).



Scheme 7. Enantioselective synthesis of both enantiomers of dibenzoxepine **5a**. Reagents and conditions: a) **10a** (1.0 equiv), **8b** (1.5 equiv), Pd$(OAc)_2$ (5 mol%), **L**^{1} (10 mol%), $Ba(OH)_2{\cdot}8H_2O$ (1.1 equiv), dioxane/H_2O (9:1; $c=1$ M), 100 °C, 1 h; b) nBu_4NF (1 equiv), THF, 20 °C, 15 min; c) TFA (0.35 M in CH_2Cl_2, 5 equiv), CH_2Cl_2, −50 °C, 18 h; d) $(CH_3OCH_2CH_2)_2NSF_3$ (2.5 equiv), CH_2Cl_2, −78 °C, 50 min.

At this point, we could thus access both enantiomers of the target dibenzoxepine **5a** starting from enantiomeric alcohols (*S*)- and (*R*)-**10a**. We considered the possibility of developing a shorter route to these enantiomers, in a stereodivergent manner using diol **9c** as a common precursor. This approach necessitated regioselectively activating the primary alcohol of **9c** and performing an intramolecular S_N2 reaction of the secondary alcohol onto the activated benzylic position. Attempts at regioselective mesylation or tosylation of (*S*,a*R*)-**9c** with one equivalent of mesyl or tosyl chloride proved unsuccessful. On the other hand, treatment of this diol with (diethylamino)sulfur trifluoride (DAST) at −78 °C provided (*S*,a*S*)-**5a** as the major enantiomer in 58% yield with 44% *ee*. This process presumably involves intermediate **B** (Scheme 7). S_N2 cyclization of **B** furnishes (*S*,a*R*)-**5a**, which atropisomerizes to the more stable conformer (*S*,a*S*)-**5a** (as shown before in Scheme 6). This approach is a rare example of DAST used as a cyclodehydrating agent for diols.[41,42] The observed incomplete stereoselectivity might be ascribed either to incomplete regioselectivity in the activation of the primary alcohol or, more probably, to a mixture of S_N2/S_N1 reactions as a result of the residual acidity of DAST. This behavior prompted us to perform the reaction with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor), which is known to decompose less rapidly than DAST.[41] Compound (*S*,a*S*)-**5a** was furnished with an improved enantiomeric excess of 75% (Scheme 7, step d). Further optimization of this process is underway.

To confirm the expected absolute configuration of the enantiomers of **5a**, circular dichroism spectra were recorded and compared to that of an authentic sample of **3**, which was obtained from colchicine by the described procedure (Figure 3).[43] The *levo* enantiomer of **5a**, ascribed the *R*,a*R* configuration, showed similar Cotton effects to **3**, as these two molecules have a quasi-superimposable biaryl framework (compare the structures of (*R*,aR)-**5a** and **3** in Scheme 6 and Figure 3). Consistently, (*S*,a*S*)-(+)-**5a** showed opposite Cotton effects (Figure 3).

We undertook calculations using semiempirical methods to understand better the stereoselectivity observed during the cyclodehydration of diol **9c** to furnish dibenzoxepine **5a** (Scheme 8).

As shown earlier (Figure 2), in the solid state and solution, diol (*S*,a*R*)-**9c** adopts the most stable conformation **9c1**, in which the C4−H bond eclipses the biaryl C1−C2 bond to minimize the $A^{1,3}$ strain. The calculated rotation barrier around C1−C2 was very high (23.4 kcal mol^{-1}), which confirms our observations on the great stability of the axial configuration of this compound. From conformation **9c1**, TFA-induced formation of carbocation (*E*,a*R*)-**A** should occur stereoselectively to maintain the $A^{1,3}$ eclipsed conformation of the C4−H bond. The *E* stereodescriptor in this intermediate can be used to describe the C3−C4 bond configuration as it has a marked double-bond character through conjugation with the aromatic ring. The calculated rotation barriers for the C1−C2 and C3−C4 bonds (15.0 and 21.8 kcal mol^{-1}, respectively) were much higher than the cyclization activation energy (7.2 kcal mol^{-1}, **TS1**), which indicates that this carbocation should undergo cyclization faster than isomerization. This behavior concords with experimental observations that the optical purity of (*R*,a*R*)-**5a** remains high (74% *ee*) at room temperature. A tentative mechanism for the observed racemization of (*R*,a*R*)-**5a** at cyclodehydration temperatures above −50 °C could be also proposed on the basis of these calculations. The first possibility would be that the (*S*,a*S*)-**5a** enantiomer was formed by isomerization of carbocation (*E*,a*R*)-**A**. In this case, the difference in the rotation barriers of the C1−C2 and C3−C4 bonds indicates that this process should occur by atropisomerization to the

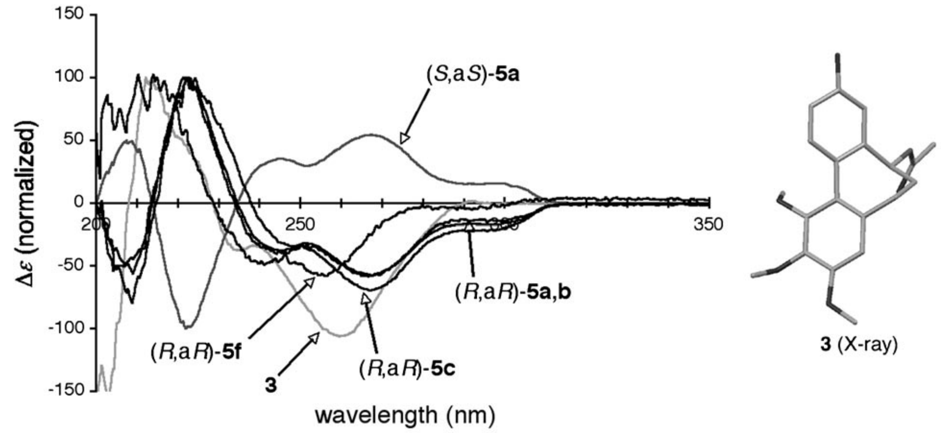
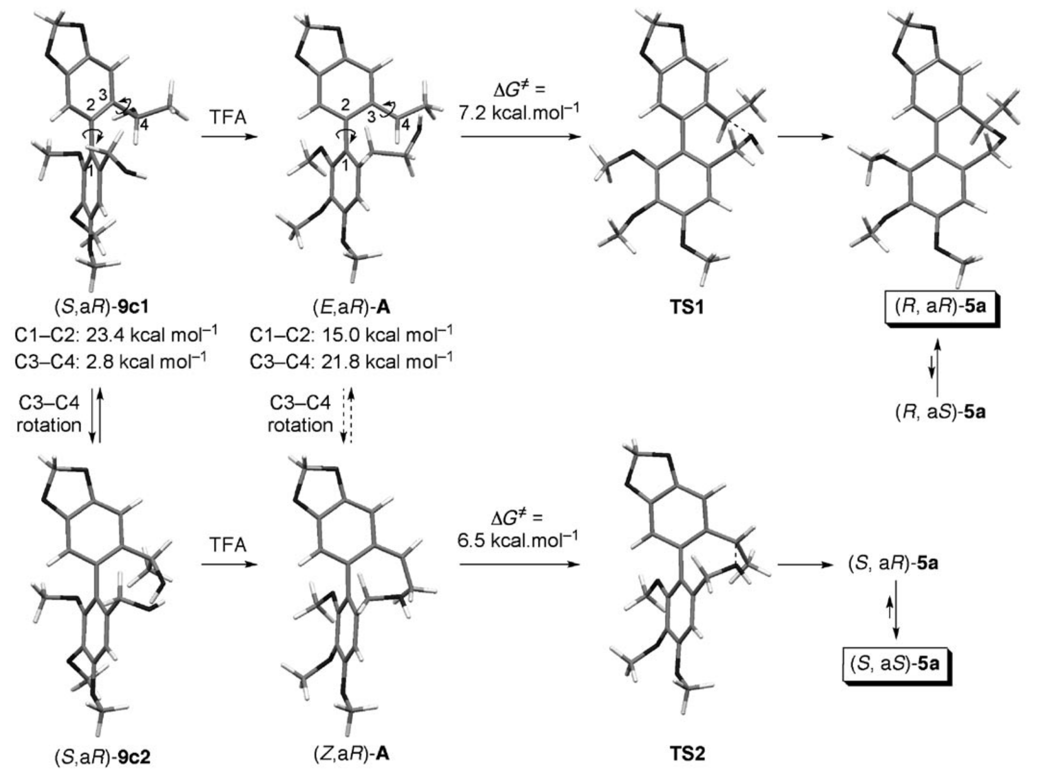


Figure 3. Normalized circular dichroism spectra of NAC (**3**) and target biaryl compounds **5a–d**.

(*E*,a*S*)-**A** carbocation (not shown), rather than isomerization to the (*Z*,a*R*)-**A** carbocation (Scheme 8). The second and more likely possibility involves the formation of the other $A^{1,3}$ eclipsed diol conformer **9c2** by rotation around the C3–C4 bond. Reaction of **9c2** with TFA would produce carbocation (*Z*,a*R*)-**A** again stereoselectively, and this species should immediately undergo cyclization to give (*S*,a*R*)-**5a** via transition state **TS2**. Compound (*S*,a*R*)-**5a** would then atropisomerize to give a thermodynamic mixture in favor of the most stable conformer (*S*,a*S*)-**5a**. The calculated rotation barrier of 2.8 kcal mol^{-1} for C3–C4 in diol **9c1** is much lower than the rotation barriers of C1–C2 and C3–C4 in (*E*,a*R*)-**A**; thus, this second epimerization pathway should be favored over the first one.

Racemic and enantioselective syntheses of other heterocyclic steganacin/allocolchicine hybrids: The asymmetric synthetic sequence that furnished (*R*,a*R*)-**5a** was applied to other starting materials to both test its versatility and study structure–activity relationships. Achieving these goals necessitated the synthesis of heterocyclic biaryl compounds in both racemic and enantiomerically enriched forms, thus allowing us to determine the enantioselectivities unambiguously and to gain a better understanding of the impact of the optical purity on their biological activity. To this purpose, various Suzuki coupling partners were prepared. First, to test the influence of a different alkyl benzylic substituent, both the racemic and the *S*-configured ethyl alcohols **10d** were prepared in a straightforward manner from commercially available aldehyde **13** (Scheme 4). The CBS reduction of ethyl ketone **15** proceeded again with high enantioselectivity to furnish (*S*)-**10d** with 98% *ee* after iodination. To vary the nature of the heteroatom in the target heterocyclic biaryl compounds, a nitrogen-containing boronate **8c** was synthe-



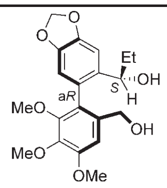
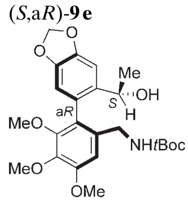
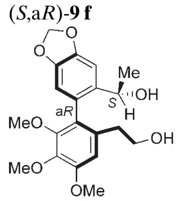
Scheme 8. Mechanistic rationale for the stereoselective cyclodehydration of (*S*,a*R*)-**9c** based on semiempirical calculations (AM1 method).

sized (Scheme 5). Protection with a *tert*-butyloxycarbonyl (*t*Boc) group was chosen for the amine, as it was anticipated that this group would be cleaved during the final cyclodehydration and liberate the free secondary amine. Boronate **8c** was obtained in three steps and 79% overall yield from benzylamine **18** in a similar manner to boronate **8b**, namely, through protection with a *t*Boc group, iodination, and catalytic borylation under conditions optimized in our laboratory (with $Pd(OAc)_2$/$\mathbf{L^3}$ as the catalyst).[30]

Finally, pinacol boronate **8d** was chosen as a Suzuki coupling partner to obtain an analogue of **5a** bearing an eight-membered medium ring, thus becoming structurally closer to stegane-type compounds. This homologous boronate was obtained in four steps and 48% yield from phenylacetic acid **20** by a similar reaction sequence (Scheme 5). We next performed Suzuki couplings with both racemic and non-racemic iodides **10a** and **10d** as new coupling partners (Table 2). Following our optimization studies with iodide **10a** and boronate **8b**, we decided to test the two most efficient ligands DavePhos ($\mathbf{L^1}$) and S-Phos ($\mathbf{L^5}$) in each type of coupling (either with the racemic or the non-racemic iodide). For couplings with boronates **8b** and **8d** (Table 2, entries 1–3 and 7–9), the yields are reported for the isolated major diastereoisomer (**9e** and **9g**) after removal of the TES group, as before, whereas in the case of boronate **8c** (Table 2, entries 4–6) the major diastereoisomer **9f** could be directly isolated in pure form. In all cases the diastereomeric ratio was recorded by ^{1}H NMR spectroscopic analysis of the crude coupling mixture. The relative configuration of the major diastereoisomers **9e–g** was determined to be identical to that of **9c** (namely, *S*,a*R* configuration) by NOESY or ROESY experiments. The coupling of racemic iodide **10d** with boronate **8b** was higher yielding with $\mathbf{L^1}$ than $\mathbf{L^5}$ (Table 2, entry 1 versus 2), although the diastereoselectivity seemed to be higher with $\mathbf{L^5}$. In a somewhat counterintuitive manner, the diastereoselectivity observed with this iodide (d.r. 74:26) was lower than with the methyl analogue **10a** (d.r. 87:13). Repeating the coupling with (*S*)-**10d** using $\mathbf{L^1}$ furnished (*S*,a*R*)-**9e** in 42% yield with a diastereoisomer ratio of 74:26 again (Table 2, entry 3). The coupling of (±)-**10a** with the nitrogen-containing boronate **8c** furnished biaryl **9f** in good yield (50%) but with poor diastereoselectivity (d.r. 3:2; Table 2, entry 4). This result probably originates in the diminished steric hindrance of the *t*Boc carbamate **8c** relative to the TES ether **8b**. The ligand effect on this coupling was evaluated using non-racemic iodide (*S*)-**10a** (Table 2, entries 5 and 6). Although comparable yields were obtained with $\mathbf{L^1}$ and $\mathbf{L^5}$, the diastereoselectivity was again slightly improved with S-Phos (Table 2, entry 6). Finally, the coupling of (±)-**10a** with homologous boronate **8d** provided diol **9g** in comparable (d.r. 4:1) diastereoselectivity with $\mathbf{L^1}$ and $\mathbf{L^5}$ (Table 2, entries 7 and 8); however, S-Phos gave a much better yield in this case. This result was repeated with (*S*)-**10a**, thus giving the *S*,a*R* enantiomer of **9g** in 57% yield with d.r. 81:19 (Table 2, entry 9).

Several conclusions can be drawn from the four different Suzuki couplings in this study (Figure 1 and Table 2): First, the ligand effect on the coupling yield is not clear, and it seems necessary to test different ligands for each substrate. In addition, the diastereoselectivity was slightly, but significantly, higher with $\mathbf{L^5}$ than $\mathbf{L^1}$. Second, there is a clear effect of the size of the benzylic alkyl group of the two different iodides (Me, Et) on the yield (increased size gave, quite logically, a lower yield) and diastereoselectivity (increased size gave a lower diastereoselectiv-

Table 2. Suzuki coupling in the synthesis of other steganacin/allocolchicine hybrids.[a]

Entry	Iodide	Boronate	Ligand	Product(s)	Yield [%][b]	d.r.[c]
1	(±)-**10d**	**8b**	$\mathbf{L^1}$	 (±)-**9e**	34	74:26
2	(±)-**10d**	**8b**	$\mathbf{L^5}$	(±)-**9e**	<10	80:20
3	(*S*)-**10d**	**8b**	$\mathbf{L^1}$	(*S*,a*R*)-**9e**	42	74:26
4	(±)-**10a**	**8c**	$\mathbf{L^1}$	 (±)-**9f**	50	60:40
5	(*S*)-**10a**	**8c**	$\mathbf{L^1}$	(*S*,a*R*)-**9f**	39	60:40
6	(*S*)-**10a**	**8c**	$\mathbf{L^5}$	(*S*,a*R*)-**9f**	43	65:35
7	(±)-**10a**	**8d**	$\mathbf{L^1}$	 (±)-**9g**	28	80:20
8	(±)-**10a**	**8d**	$\mathbf{L^5}$	(±)-**9g**	63	81:19
9	(*S*)-**10a**	**8d**	$\mathbf{L^5}$	(*S*,a*R*)-**9g**	57	81:19

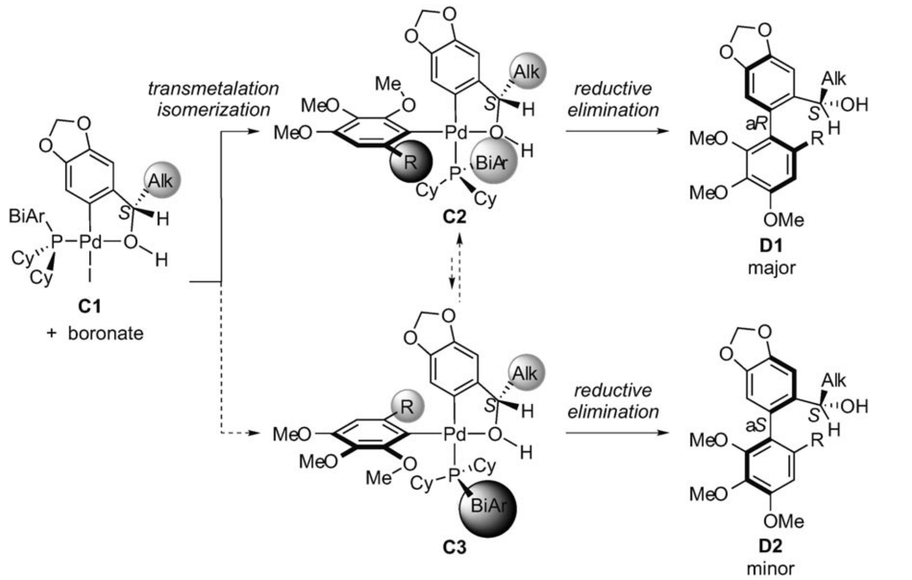
[a] Reagents and conditions: a) iodide (1.0 equiv), boronate (1.5 equiv), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), $Ba(OH)_2 \cdot 8H_2O$ (1.1 equiv), dioxane/H_2O (9:1; c=1 M), 100°C, 1 h; b) for **9e** and **9g**: $n\text{Bu}_4\text{NF}$ (1 equiv), THF, 20°C, 15 min. [b] Yield of the isolated major diastereoisomer from steps (a) and (b) (**9e**, **9g**) or step (a) (**9f**). [c] Measured by ^{1}H NMR spectroscopic analysis of the crude mixture obtained in step (a).

ity), but the latter effect was rather unexpected. The coupling was also performed with the *n*-propyl and isopropyl analogues of **10a** and **10d**, but the yield was lower (<20–30%) than with **10d**, which thus has the same trend for the yield but prevented us from measuring a precise diastereoselectivity. Third, the effect of the boronate size on the diastereoselectivity is quite coherent, with lower diastereoisomer ratios being observed with progressively smaller ($CH_2OTES > CH_2CH_2OTES > CH_2NH$*t*Boc) ortho substituents. However, a more comprehensive study with a larger number of iodides and boronates would be necessary to allow a better rationalization of this reaction.

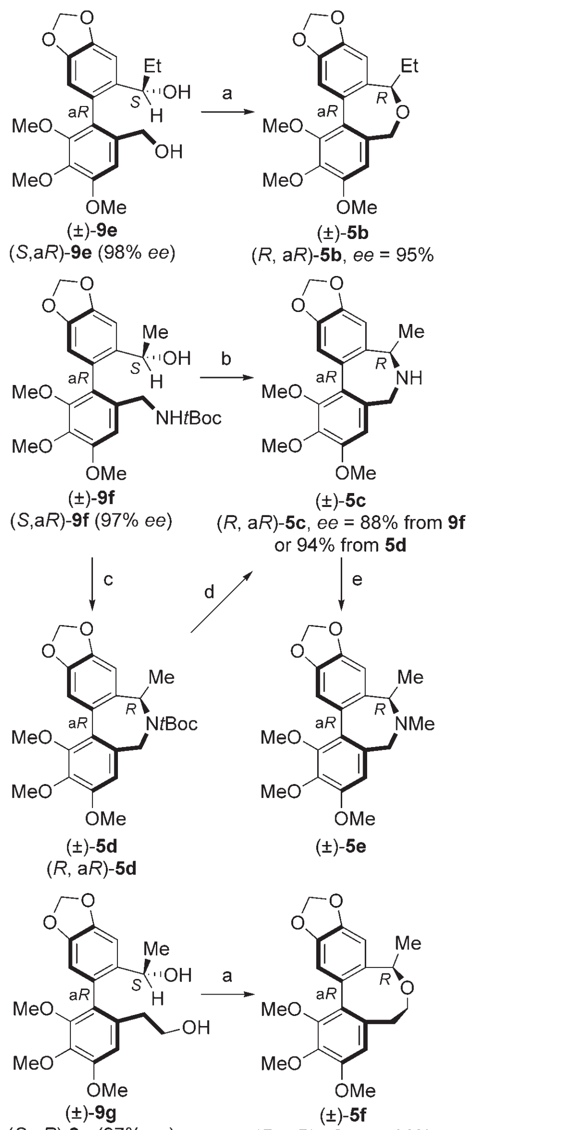
The stereochemical model that we proposed earlier[23] was modified to rationalize the diastereoselectivities observed herein (Scheme 9). The oxidative addition of aryl iodides **10a,d** to a palladium(0) species is likely to generate phosphane-bound oxapalladacycle **C1**, according to literature precedents.[44] This conjecture was indirectly confirmed by the isolation of ketone **11** (Figure 1) as a coupling by-product that probably arises from **C1** by β-H elimination, as proposed previously.[44a] In oxapalladacycle **C1**, which has an *S* configuration, the alkyl group (Me, Et) introduces a moderate steric bulk to the α face. The transmetalation of a boronate, followed by *trans* to *cis* isomerization would produce complexes **C2** and **C3**, which may be in equilibrium. In these proposed intermediates, one bulky element is present on each of the three Pd ligands, namely, in order of increasing volume: the alcohol alkyl group (Alk), the boronate *ortho* substituent (R), and the phosphane biaryl moiety (BiAr). These three bulky groups repulse each other, and their relative position would determine the stereochemical outcome of the reaction. The strongest steric repulsion should take place between the two largest groups, BiAr and R. Thus, in the proposed two lowest energy complexes **C2** and **C3**, the R group is positioned on the face opposite to the BiAr group. Reductive elimination from **C2** would produce the observed *S*,a*R* major diastereoisomer **D1**, whereas reductive elimination from **C3** would furnish the *S*,a*S* minor diastereoisomer **D2**. This behavior implies that intermediate **C2** would be favored over **C3** as a result of the steric repulsion between the R and Alk groups in **C3**, which would be stronger than the repulsion between the BiAr and Alk groups in **C2**. This three-element stereocontrol model may account for the effect of the Alk-group size observed in this study.[45] Thus, when the Alk group changes from Me to Et, **C2** might be disfavored as a result of the increased steric repulsion between Et and the phosphane BiAr moiety. It is also clear that the nature of the phosphane BiAr group should also influence the stereoselectivity according to this model. Finally, replacing the free alcohol with a methoxy group (iodide **10c**; Scheme 4) should have a very limited impact on the stereoselectivity according to this model, as observed.

Eventually, the conversion of racemic and non-racemic coupling products **9e–g** into heterocyclic biaryl compounds **5b–d** was performed like the synthesis of **5a** (Scheme 10). The optical purities of the final non-racemic products were determined by HPLC on a chiral phase, with the racemates as references. Their relative configurations were determined by NOESY experiments as for **5a**. First, a TFA-induced cyclodehydration of (±)-**9e** furnished ethyldibenzoxepine (±)-**5b** in 70% yield. The cyclodehydration of (*S*,a*R*)-**9e** (98% *ee* based on (*S*)-**10d**) occurred at −78°C to give (*R*,a*R*)-**5b** in 77% yield with 95% *ee*, thus with only a slight decrease in the optical purity of the starting material. The stronger electron-donating character of the benzyl ethyl group relative to a methyl group probably accelerated the formation of the carbocationic intermediate, as the reaction could be run at −78°C, whereas no reaction occurred below −50°C for **5a**. Similar to **5a**, **5b** was obtained as a 91:9 mixture of a*R*/a*S* atropisomers in equilibrium. Next, racemic dibenzazepine **5c** was obtained from biaryl **9f** in 90% yield. The treatment of (±)-**9f** with concentrated TFA in dichloromethane at −78°C induced cyclodehydration of the carbamate, and the *t*Boc group was cleaved upon warming to room temperature. This process was evidenced by the isolation of *t*Boc-protected dibenzazepine **5d** upon quenching the reaction at low temperature. Contrary to **5a** and **5b**, the nitrogen analogue **5c** occurred only as the a*R* atropisomer.

Repeating this process starting from non-racemic biaryl (*S*,a*R*)-**9f** (97% *ee* based on (*S*)-**10a**) furnished *R*,a*R*-con-



Scheme 9. Proposed three-element stereocontrol model for the diastereoselective Suzuki coupling.



Scheme 10. Racemic and enantioselective synthesis of steganacin/allocolchicine hybrids **5b**–**f**. Reagents and conditions: a) TFA (0.35 M in CH_2Cl_2, 5 equiv), CH_2Cl_2, 20 °C (for (±)-**5b**), −78 °C (for (*R*,a*R*)-**5b**), or −50 °C (for (±)-**5f** and (*R*,a*R*)-**5f**), yields: 70% (±)-**5b**, 77% (*R*,a*R*)-**5b**, 80% (±)-**5f**, 84% (*R*,a*R*)-**5f**; b) TFA/CH_2Cl_2 (0.75:2), −78 °C then 20 °C, yield: 90% (±)-**5c**, 95% (*R*,a*R*)-**5c**; c) CH_3SO_2Cl (1.5 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C then 20 °C, 1 h, yield: 70% (±)-**5d**, 77% (*R*,a*R*)-**5d**; d) TFA/CH_2Cl_2 (1:2), 20 °C, 45 min, yield: 93% (±)-**5c**, 97% (*R*,a*R*)-**5c**; e) HCHO (37% in H_2O, 12 equiv), $NaBH_3CN$ (5 equiv), CH_3CN, 20 °C, 1.5 h, 97%.

figured dibenzazepine **5c** in 95% yield with 88% *ee*. The significant loss of optical purity is probably imputable to the excess TFA added to cleave the *t*Boc group in the same pot, which caused undesirable warming of the reaction mixture. An alternative route was thus envisaged to obtain **5c** with better and more reproducible optical purity. Taking advantage of the presence of only one free alcohol group in **9f**, a S_N2-type cyclization was effected simply by treating racemic or non-racemic **9f** with mesyl chloride (MsCl) and triethylamine. This approach furnished *t*Boc-protected **5d** in racemic and enantio-enriched forms in good yields. Treatment of these species with TFA furnished (±)-**5c** and (*R*,a*R*)-**5c** with an improved enantiomeric excess of 94%. For biological evaluation purposes, the *N*-Me analogue (±)-**5e** was also synthesized from (±)-**5c** in 97% yield by reductive amination with formaldehyde and $NaBH_3CN$. Finally, dibenzoxocine **5f**, containing an eight-membered medium ring, was obtained in both racemic and enantiomerically enriched (96% *ee*) forms from biaryl **9g** in the same manner as dibenzoxepine **5a**. However, in this case, treatment of (±)-**9g** with TFA at 20 °C afforded a 95:5 mixture of (±)-**5f** and its *R*,a*S* diastereoisomer, which did not interconvert (as shown by the absence of exchange correlations in the NOESY spectrum of the mixture). Indeed the eight-membered medium ring of **5f** is more rigid than the seven-membered ring of **5a**,**b**, thus preventing atropisomerization. Gratifyingly, by performing the cyclodehydration at −50 °C only the *R*,a*R* diastereoisomer was obtained, which presumably arises from the same type of carbocationic intermediate as **5a** (see Schemes 7 and 8).

The three-dimensional structures of target biaryl compounds **5b**, **5c**, and **5f** were calculated in the same manner as **5a** (Figure 4). For **5b** and **5c**, the *R*,a*R* conformer was found to be more stable by 0.6 and 1.6 kcal mol^{-1}, respectively, over its *R*,a*S* atropisomer. This result correlates well with the fact that for **5c** only the a*R* atropisomer was experimentally observed, whereas **5a** and **5b** occurred as atropisomeric mixtures (major a*R* atropisomer). For dibenzoxocine **5f**, the a*R* atropisomer was more stable by 2.9 kcal mol^{-1} than the a*S* atropisomer, in addition to the experimental observation of the blocked biaryl bond rotation. The medium ring of the lowest energy structure of **5f** (Figure 4) shows a twist-boat–chair-type conformation, with a biaryl dihedral angle of 59° (relative to 45° for seven-membered ring analogues **5a**–**c**), and thus this compound is structurally closer to stegane-type molecules.[8] The circular dichroism spectra of (*R*,a*R*)-**5b, 5c**, and **5f** were compared to those of **5a** and NAC (**3**), which confirmed their major a*R* biaryl configuration (Figure 3). The antimicrotubule properties and the cytotoxicities of the racemic and non-racemic compounds were

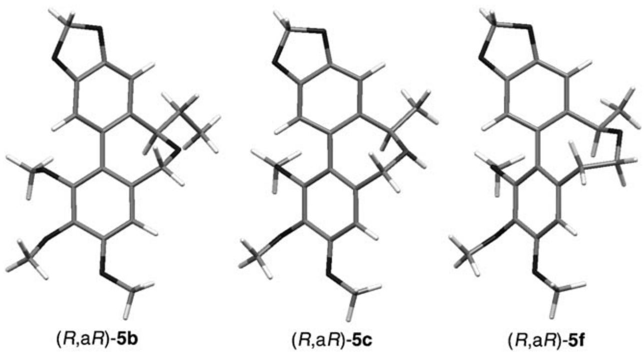


Figure 4. Computed three-dimensional structures of dibenzoxepine **5b**, dibenzazepine **5c**, and dibenzoxocine **5f** (lowest-energy structures).

also evaluated (Table 1). Ethyldibenzoxepine (**5b**) had the most potent antimicrotubule activity, as it was approximately twofold that of colchicine (**1**) for the *R*,a*R* enantiomer (Table 1, entry 7), and showed interesting cytotoxicities. Curiously, all nitrogen-containing analogues **5c–e** were completely inactive on all assays whatever the *N*-substitution (H, *t*Boc, Me; Table 1, entries 8–11). On the other hand, dibenzoxocine (*R*,aR)-**5f** showed an antimicrotubule activity comparable to its dibenzoxepine analogue (*R*,aR)-**5a** (Table 1, entry 13), while being significantly less cytotoxic. In summary, compounds **5a,b** and **5f** have potent antimicrotubule activities that are within the range of those of allocolchicinoids and steganacin (**4**).[46] These results are thus very encouraging and structural modifications are underway to further increase the antimicrotubule activity of these allocolchicine/steganacin hybrids.

Conclusion

We have reported the asymmetric synthesis of novel axially chiral biaryl compounds containing a seven- or eight-membered heterocyclic medium ring. These molecules can be considered as structural hybrids of allocolchicine and steganacin-type natural products. The synthesis featured an atropo-diastereoselective biaryl Suzuki coupling in which the benzylic stereocenter efficiently transferred its stereochemical information to the biaryl axis. The coupling conditions were optimized, and two biphenylphosphane ligands (DavePhos and S-Phos) were found to give the highest yields and diastereoselectivities. A three-element stereochemical model was proposed to explain the observed diastereoselectivities. In a second key step, the medium ring of the target molecules was formed during a stereoselective cyclodehydration that probably involves a configurationally stable, axially chiral carbocationic intermediate as supported by calculations. During this step, the biaryl axis transferred back its stereochemical information to the benzylic stereocenter in a new type of stereochemical relaying.[47] The overall synthetic sequence was shown to be quite general, with the production of structurally varied analogues that could be evaluated as antimicrotubule agents. This sequence was also shown to be flexible, with the possibility to use stereoconvergent and stereodivergent pathways. Finally, this study could pave the way for the synthesis of new vascular-targeting agents structurally related to NAC (**3**).

Experimental Section

General: The reagents were commercially available and used without further purification unless otherwise stated. All solvents were distilled from the appropriate drying agents immediately before use. Yields refer to chromatographically and spectroscopically homogeneous materials. Merck silica gel 60 (particle size: 40–63 mm) was used for flash column chromatography, 1- and 2-mm SDS glass plates coated with silica gel (60F254) were used for preparative TLC using UV light as the visualizing agent. Products that had been reported previously were isolated in greater than 95% purity, as determined by ^{1}H NMR spectroscopic analysis. NMR spectra were recorded on Bruker Avance 300 or Avance 500 instruments at 295 K with tetramethylsilane or residual protiated solvent used as an internal reference for the ^{1}H and ^{13}C NMR spectra. The following abbreviations were used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Assignments were made on the basis of DQF-COSY, NOESY or ROESY, HMQC, and HMBC experiments. IR spectra were recorded on a Perkin–Elmer Spectrum BX spectrometer. Mass spectra and high-resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI) conditions at the Laboratoire de Spectrométrie de Masse, ICSN (Gif-sur-Yvette, France). Melting points (m.p.) are uncorrected and were recorded on a Büchi B-540 capillary melting-point apparatus. Optical rotations were recorded on a JASCO P-1010 polarimeter. Circular dichroism spectra were recorded on a JASCO J-810 apparatus at 20 °C. HPLC analyses were performed on a Waters system equipped with a photodiode array detector (monitoring at 200–400 nm) using a Chiracel OD or a Chiralpak AD column (25 × 0.46 cm; Daicel Chemical Ind., Ltd). The *ee* values of all the compounds were determined after injection of the racemic mixture and were reproducible over two runs (error margin = 0.5%).

(*S*)-(−)-α-Methyl-2-iodo-4,5-methylenedioxybenzyl alcohol [(*S*)-10a]: (*R*)-2-Methyl-CBS-oxazaborolidine (1 M in toluene, 323 μL, 0.32 mmol, 0.1 equiv) and BH_3–Me_2S (10 M in Me_2S, 323 μL, 3.23 mmol, 1 equiv) were added to a solution of dichloromethane (5 mL) under argon at 20 °C. After stirring for 30 min at 20 °C, a solution of 3,4-methylenedioxyacetophenone (**11**; 530 mg, 3.23 mmol, 1 equiv) in dichloromethane (5 mL) was added dropwise over 2 h. The solution was stirred for another 3 h, methanol was then added dropwise, and the solvents evaporated in vacuo. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate 8:2) to give alcohol (*S*)-**12** as an oil (532 mg, 3.20 mmol, 99%). $[\alpha]_D^{22} = -46$ ($c = 0.99$, $CHCl_3$).[39] Silver trifluoroacetate (825 mg, 3.73 mmol) and iodine (829 mg, 3.27 mmol) were added in one portion to a solution of (*S*)-**12** (517 mg, 3.11 mmol) in $CHCl_3$ (17 mL) at 0 °C. After stirring for 15 min at 0 °C, the reaction mixture was filtered through celite and washed with a saturated aqueous Na_2SO_3 solution. The organic layer was dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, dichloromethane) to give (*S*)-**10a** as a white powder with 97% *ee* (669 mg, 74%). $[\alpha]_D^{22} = -44$ ($c = 0.99$, $CHCl_3$); m.p. 73 °C (lit. 72–73 °C for (±)-**10a**);[28] HPLC (Chiracel OD, hexane/ethanol (95:5), 1.0 mL min^{-1}) $t_R = 10.2$ min (major enantiomer), 13.6 min (minor enantiomer).

General Suzuki coupling procedure (Figure 1, Table 2): A sealed tube was charged with the aryl halide (1 equiv), the aryl boronate (1.5 equiv), $Pd(OAc)_2$ (5 mol%), phosphane ligand (**L^1** or **L^5**, 10 mol%), $Ba(OH)_2 \cdot 8H_2O$ (1.1 equiv), and dioxane/water (9:1; [aryl halide] = 1 M). The tube was sealed and placed in an oil bath preheated at 100 °C and stirred for 2.5 h. After cooling to room temperature, the reaction mixture was filtered through celite and $MgSO_4$. The filtrate was concentrated, and the diastereomeric ratio of the coupling product was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The residue was then purified by flash chromatography (silica gel, heptanes/ethyl acetate) to give an inseparable mixture of the expected product and a by-product of the reaction (the proto-deiodination product or pinacol). The coupling product was characterized by ^{1}H and ^{13}C NMR spectroscopic analysis. For **9c**, **9e**, and **9g**, the general procedure includes cleavage of the TES group: TBAF (1 M in THF, 1 equiv) was added to a solution of this product mixture in THF ($c = 0.1$ M) at room temperature, and the solution was stirred for 15 min. A saturated aqueous $NaHCO_3$ solution was added and the aqueous layer extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate).

Biaryl (*S*,a*R*)-9c (Scheme 7, Figure 1): The above general Suzuki coupling procedure from iodide (*S*)-**10a** (162 mg, 0.55 mmol), boronate **8b** (372 mg, 0.83 mmol), and ligand **L^1** (19.7 mg, 0.05 mmol) in dioxane (0.45 mL) and water (0.05 mL) gave, after flash chromatography (heptanes/ethyl acetate 9:1 then 7:3), a mixture of the major diastereoisomer (*S*,a*R*)-**9a** and the proto-deiodination product **12** (154 mg). Treatment of this mixture (154 mg) with TBAF in THF (3 mL) gave, after flash chromatography (silica gel, heptanes/ethyl acetate 1:1), biaryl (*S*,a*R*)-**9c** as a white solid (108 mg, 54% from (*S*)-**10a**). $[\alpha]_D^{22}=+53$ ($c=1.15$, $CHCl_3$); m.p. 179 °C; ^1H NMR (300 MHz, [D$_6$]DMSO) $\delta=7.08$ (s, 1H), 6.97 (s, 1H), 6.52 (s, 1H), 6.03 (s, 2H), 5.03 (t, $J=5.1$ Hz, 1H), 4.79 (d, $J=4.5$ Hz, 1H), 4.30 (m, 1H), 4.11 (dd, $J=13.4$, 5.3 Hz, 1H), 3.92 (dd, $J=13.4$, 5.3 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.50 (s, 3H), 0.99 (d, $J=6.3$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, [D$_6$]DMSO) $\delta=152.4$, 149.9, 146.7, 145.3, 140.1, 139.6, 136.3, 125.8, 124.3, 109.8, 106.3, 105.3, 100.8, 65.2, 60.6, 60.5, 60.4, 55.6, 25.2 ppm; IR (neat): $\tilde{\nu}=3392$, 2935, 1479 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}O_7Na$ $[M+Na^+]$: 385.1263; found: 385.1260.

Biaryl (*S*,a*S*)-9d (Scheme 7, Figure 1): From the preceding Suzuki coupling of iodide (*S*)-**10a** and boronate **8b**, a small amount (30.5 mg) of a mixture of the minor diastereomer (*S*,a*S*)-**9b** and by-products was isolated. This reaction mixture (27.5 mg) was treated with TBAF in THF (1.5 mL) to give, after flash chromatography (heptanes/ethyl acetate 1:1), biaryl (*S*,a*S*)-**9d** as an oil (15.8 mg, 9%). ^1H NMR (300 MHz, $CDCl_3$) $\delta=7.06$ (s, 1H), 6.79 (s, 1H), 6.53 (s, 1H), 6.00 (s, 2H), 4.48 (q, 1H, $J=6.3$ Hz), 4.23 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.65 (s, 3H), 2.90 (br s, 1H), 1.39 (d, $J=6.3$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=152.3$, 151.6, 147.8, 146.7, 141.9, 137.8, 134.8, 128.1, 127.0, 109.8, 108.7, 105.8, 101.3, 66.2, 63.1, 61.0, 56.2, 22.9 ppm.

General cyclodehydration procedure (Schemes 6, 7, 10): A solution of diol (1 equiv) in dichloromethane ($c=0.02$ M) was cooled down to the appropriate temperature, a solution of TFA (5 equiv) in dichloromethane (0.35 M) was then added dropwise and the reaction was run until complete conversion of the starting material (followed by TLC: an aliquot of the reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate before being spotted on the TLC plate). A saturated aqueous $NaHCO_3$ solution was added and the aqueous layer extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by preparative TLC (silica gel, heptanes/ethyl acetate).

Dibenzoxepine (*R*,a*R*)-5a (Scheme 7): The above general cyclodehydration procedure from diol (*S*,a*R*)-**9c** (44.0 mg, 0.12 mmol) in dichloromethane (4 mL) at −50 °C gave, after preparative TLC (heptanes/ethyl acetate 1:1), dibenzoxepine (*R*,a*R*)-**5a** as a white solid with 96% *ee* (35.5 mg, 86%, 96:4 mixture of interconverting atropisomers). $[\alpha]_D^{24}=-117$ ($c=1.09$, $CHCl_3$); HPLC (Chiralpak AD, hexane/ethanol 99:1, 1.0 mL.min^{-1}) $t_R=17.4$ min (major enantiomer), 29.2 min (minor enantiomer); m.p. 104 °C ; ^1H NMR (300 MHz, $CDCl_3$) $\delta=7.14$ (s, 1H), 7.00 (s, 1H), 6.74 (s, 1H), 6.04 (d, $J=1.5$ Hz, 1H), 6.02 (d, $J=1.5$ Hz, 1H), 4.24 (d, $J=11.3$ Hz, 1H), 4.24 (q, $J=6.6$ Hz, 1H), 3.98 (d, $J=11.3$ Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.72 (s, 3H), 1.56 (d, $J=6.6$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=153.1$, 150.5, 147.3, 146.9, 142.7, 131.7, 131.4, 130.9, 126.3, 109.8, 108.3, 105.5, 101.3, 68.7, 68.1, 61.2, 61.0, 56.2, 18.2 ppm; IR (neat): $\tilde{\nu}=2936$, 1483 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{20}O_6Na$ $[M+Na^+]$: 367.1158; found: 367.1140.

Synthesis of dibenzoxepine (*S*,a*S*)-5a by cyclodehydration with Deoxofluor (Scheme 7): A solution of Deoxofluor (12.5 µL, 0.065 mmol) in dichloromethane (60 µL) was added dropwise to a stirred solution of diol (*S*,a*R*)-**9c** (9.5 mg, 0.026 mmol) in dichloromethane (1 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 50 min, warmed to room temperature and treated with a saturated aqueous $NaHCO_3$ solution. After extraction of the aqueous layer with dichloromethane, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by preparative TLC (silica gel, heptanes/ethyl acetate 3:2) to give (*S*,a*S*)-**5a** as a white powder in 75% *ee* (4.7 mg, 52%). $[\alpha]_D^{23}=+119$ ($c=1.0$, $CHCl_3$); HPLC (Chiralpak AD, hexane/ethanol 99:1, 1.0 mL min^{-1}) $t_R=15.2$ min (minor enantiomer), 24.1 min (major enantiomer).

Dibenzazepine (*R*,a*R*)-5c (Scheme 10): A solution of TFA (0.75 mL) in dichloromethane (1 mL) was added dropwise over 1.5 h to a solution of (*S*,a*R*)-**9f** (11 mg, 0.024 mmol) in dichloromethane (1 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C and then allowed to warm up to room temperature over 30 min. An aqueous solution of NaOH (1 M) was added dropwise until the aqueous phase reached pH 12. The aqueous layer was then extracted with dichloromethane and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, dichloromethane/methanol 95:5 then 9:1) to give dibenzazepine (*R*,a*R*)-**5c** as an oil in 88% *ee* (7.7 mg, 95%). $[\alpha]_D^{25}=-47$ ($c=0.87$, $CHCl_3$); HPLC (Chiralpak AD, hexane/*i*PrOH 95:5 + 0.1% Et_3N, 1.0 mL min^{-1}) $t_R=27.5$ min (major enantiomer), 34.4 min (minor enantiomer); ^1H NMR (300 MHz, $CDCl_3$) $\delta=7.06$ (s, 1H), 7.00 (s, 1H), 6.75 (s, 1H), 6.05 (d, $J=1.8$ Hz, 1H), 6.02 (d, $J=1.8$ Hz, 1H), 4.36 (br s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.85–3.77 (m, 2H), 3.71 (s, 3H), 3.45 (d, $J=12.6$ Hz, 1H), 1.63 (d, $J=6.6$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=153.4$, 150.8, 147.6, 147.3, 142.9, 130.4, 130.0, 129.2, 125.9, 110.3, 108.7, 105.7, 101.5, 61.2, 61.1, 56.2, 50.2, 48.0, 17.2 ppm; IR (neat): $\tilde{\nu}=2929$, 1484, 1457, 1409 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}NO_5$ $[M+H^+]$: 344.1498; found: 344.1505.

Synthesis of dibenzazepine (*R*,a*R*)-5c by mesylation (Scheme 10): Triethylamine (7.2 µL, 0.052 mmol) and methanesulfonyl chloride (3 µL, 0.039 mmol) were added dropwise to a solution of (*S*,a*R*)-**9f** (12 mg, 0.026 mmol) in dichloromethane (1 mL) at 0 °C. After stirring for 1 h at room temperature, water was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by preparative TLC (silica gel, heptanes/ethyl acetate 7:3) to give *t*Boc-protected dibenzazepine (*R*,a*R*)-**5d** as an oil (8.9 mg, 77%). ^1H NMR (300 MHz, $CDCl_3$) $\delta=7.13$ (s, 1H), 6.83–6.63 (m, 2H), 6.02 (d, $J=1.4$ Hz, 1H), 6.02 (d, $J=1.4$ Hz, 1H), 5.07–4.66 (m, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.64–3.50 (m, 4H), 1.51 (s, 9H), 0.89 (d, $J=6.9$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=153.9$, 153.1, 150.7, 146.9, 142.7, 133.0, 131.6, 128.7, 126.5, 111.7, 110.3, 108.5, 101.4, 79.9, 61.4, 60.6, 56.9, 56.3, 46.7, 28.8, 21.1 ppm; IR (neat): $\tilde{\nu}=2930$, 1681, 1395 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{29}NO_7Na$ $[M+Na^+]$: 466.1842; found: 466.1812. A mixture of (*R*,a*R*)-**5d** (8.9 mg, 0.02 mmol), dichloromethane (1 mL), and TFA (0.5 mL) was stirred for 45 min at 20 °C. An aqueous solution of NaOH (1 M) was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (silica gel, dichloromethane/methanol 95:5 then 9:1) to give dibenzazepine (*R*,a*R*)-**5c** as an oil in 94% *ee* (6.7 mg, 97%).

Calculations: Three-dimensional structures of 5a–c and 5f (Scheme 6, Figure 4): One thousand conformations of each compound were generated by random search Monte Carlo method and optimized by molecular mechanics PRCG minimization method using the Macromodel (version 5.5) program with the MM2 force field.[48] The search was carried out on blocks of 100 Monte Carlo steps until no additional conformation was found to be of lower energy than the current minimum. From these conformational searches, all possible conformations within 3 kcal mol^{-1} from the global minimum were analyzed. For each compound, the geometries of the most stable conformations were retained. These geometries were used for building the three-dimensional structures in the calculations of the formation enthalpy using a molecular-orbital semiempirical method. Geometries were optimized by means of a gradient technique at RHF/AM1 level,[49] using the MOPAC program (version 5.0).[50]

Cyclodehydration mechanism (Scheme 8): The energy barriers for C1−C2 and C3−C4 bond rotations were determined by rotating in steps of 15°. Only the corresponding dihedral angles were fixed, all the other parameters were optimized. RHF/AM1 transition structures **TS1** and **TS2** were located using the procedures implemented in MOPAC 5.0. All variables were optimized by minimizing the sum of the squared scalar gradients (NLLSQ and SIGMA).[51] Force calculations were carried out to ensure that the transition structures located had one imaginary frequency. Final values of the gradient norms were <1 kcal Å^{-1} and each transition structure had one negative eigenvalue in the Hessian matrix as required. The activation enthalpies were obtained by the difference between the formation enthalpy of the fully optimized reactant in the ground state with the formation enthalpy of the corresponding transition structures.

Inhibition of the microtubule assembly: The drug was dissolved in DMSO at different concentrations and preincubated with a solution of tubulin at 37 °C for 10 min, then the solution was cooled to 0 °C for 5 min to achieve complete tubulin depolymerization. The solution was then placed in a temperature-controlled cell at 37 °C (microtubule assembly) and the increase of the optical density was monitored in a UV spectrophotometer at 350 nm for 1 min. The maximum rate of assembly was recorded and compared to a sample without the drug. The IC_{50} value is the concentration of the compound required to inhibit 50 % of the rate of microtubule assembly. It was calculated from the effect of several concentrations and compared to the IC_{50} value of colchicine obtained within the same day with the same tubulin preparation. The reported values are averages of three experiments.

Cell culture and proliferation assay: Cancer-cell lines were obtained from the American Type Culture Collection (Rockville, MD, USA) and were cultured according to the supplier's instructions. All cell lines were maintained at 37 °C in a humidified atmosphere containing 5 % CO_2. Cell viability was assessed using the Promega CellTiter-Blue reagent (Promega, WI, USA) according to the manufacturer's instructions. Briefly, the cells were seeded in 96-well plates (5×103 cell well^{-1}) containing 50 µL of growth medium. After 24 h of culture, the cells were supplemented with 50 µL of drug dissolved in DMSO (less than 0.1 % in each preparation). After 72 h of incubation, 20 µL of resazurin were added and after 2 h the fluorescence was recorded (560 nm Ex/590 nm Em) using a Victor microtiter plate fluorimeter (Perkin–Elmer, USA). The IC_{50} value corresponds to the concentration of drug that caused a decrease of 50 % in fluorescence of drug-treated cells relative to untreated cells.

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