Asymmetric Synthesis

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Biaryl Axis as a Stereochemical Relay for the Enantioselective Synthesis of Antimicrotubule Agents**

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Dedicated to the memory of Pierre Potier

Allocolchicine (**1**) and steganacin (**2**) are two naturally occurring chiral biaryls that inhibit the polymerization of tubulin into microtubules in a similar way to colchicine.[1–3] Recently, colchicine-type antimicrotubule agents got a second wind with the discovery that a prodrug of *N*-acetylcolchinol (**3**; NAC) caused the selective destruction of tumor vasculature.[4] Steganacin (**2**) contains a stereogenic biaryl axis with a stable a*R* configuration, with atropisomerization being prevented by the eight-membered bridging ring conformation.[3] In contrast, the seven-membered ring of allocolchicinoids **1** and **3** allows atropisomerization, and these molecules occur as a mixture of equilibrating atropisomers.[2] The biaryl-axis configuration of **1**–**3** and analogues was shown to be a crucial

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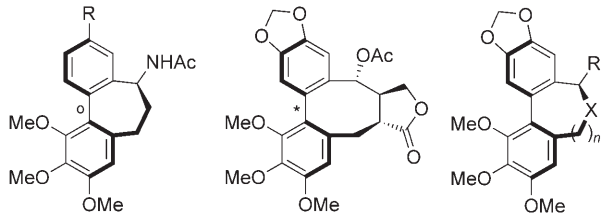
parameter for their tubulin-binding properties, the activity being often restricted to a*R* atropisomers.[1] We report herein a versatile enantioselective synthesis of bioactive biaryls **4**, simple new hybrid analogues of **1**–**3** containing a heterocyclic



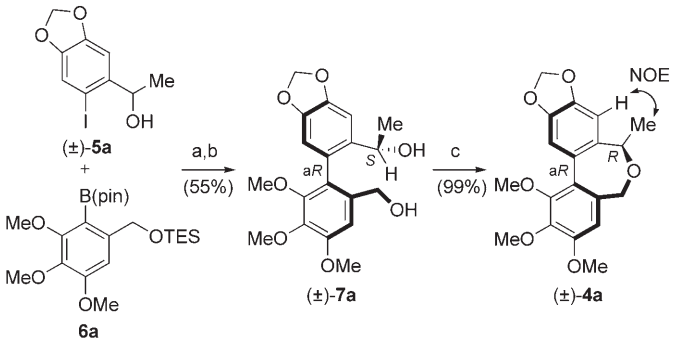
allocolchicine (**1**): R = CO_2Me
N-acetylcolchinol (**3**): R = OH

steganacin (**2**)

4

bridge, by using the biaryl stereogenic axis as a stereochemical relay.[5] First, the biaryl configuration is controlled by a benzylic stereocenter through an atropo-diastereoselective Suzuki coupling,[6] then the biaryl axis relays its stereochemical information to the temporarily destroyed stereocenter in a S_N1-type dehydrative cyclization.

Our synthetic strategy was initially implemented with racemic dibenzoxepine (**4a**; Scheme 1), thus following on from our early investigations.[7] The reoptimized Suzuki coupling of racemic iodide **5a** with boronate **6a** catalyzed by $Pd(OAc)_2$/**L1**[8] followed by removal of the triethylsilyl (TES) group on the major diastereoisomer (d.r. = 87:13 for the Suzuki coupling) gave biphenyl diol **7a** in 55% yield. The *S*,a*R* relative configuration of **7a** was determined by X-ray diffraction analysis.[9] As expected, no atropisomerization of **7a** was detected at temperatures below 160°C. We found that the dehydrative cyclization of **7a** occurred in the presence of CSA in acetone, probably through an intramolecular S_N1 process, thus furnishing racemic **4a** in quantitative yield. The *R*,a*R* relative configuration of **4a** was deduced from NOESY

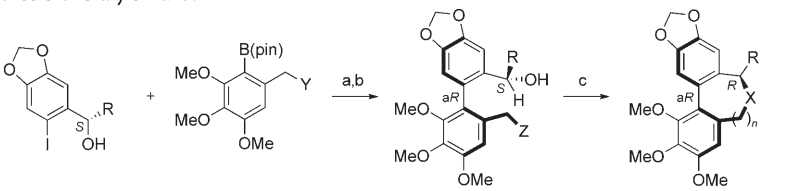


Scheme 1. Synthesis of racemic dibenzoxepine (**4a**). Reagents and conditions: a) (±)-**5a**, **6a** (1.5 equiv), $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), $Ba(OH)_2{\cdot}8H_2O$ (1.1 equiv), dioxane/H_2O (9:1; *c* = 1 M), 100°C (d.r. = 87:13); b) nBu_4NF, THF, 20°C; c) CSA (1.0 equiv), acetone, 20°C (99%). **L1** = 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl, CSA = camphorsulfonic acid, pin = pinacolato.

experiments (Scheme 1). Similar to other allocolchicinoids,[2] **4a** occurred as a 96:4 mixture of interconverting a*R*/a*S* atropisomers in $CDCl_3$, as shown by the presence of exchange correlations on the NOESY spectrum.[10] We were delighted to find that racemic **4a** significantly inhibited the assembly of microtubules in vitro, with an IC_{50} value of 13.1(±2.9) μM versus 8.2(±1.6) μM for (−)-colchicine.

We next embarked on an asymmetric synthesis of (*R*,a*R*)-**4a** and other analogues, on the assumption that only this enantiomer was responsible for the antimicrotubule activity of (±)-**4a**. Our general strategy for the asymmetric synthesis of tricyclic biaryls **4a**–**d** with a seven or eight-membered bridging ring containing an oxygen or nitrogen atom is depicted in Table 1. The *S* enantiomer of **5a** was obtained in 72% yield and 97% *ee* from 3,4-methylenedioxyacetophenone by reduction with catalytic (*R*)-CBS-oxazaborolidine (CBS = Corey, Bakshi, Shibata), followed by electrophilic

Table 1: Enantioselective synthesis of biaryls **4a**–**d**.[a]



(*S*)-**5a**: R = Me
(*R*)-**5a**: R = Me
(*S*)-**5b**: R = Et

6a: Y = OTES
6b: Y = NH*t*Boc
6c: Y = CH_2OTES

7a: R = Me, Z = OH
7b: R = Et, Z = OH
7c: R = Me, Z = NH*t*Boc
7d: R = Me, Z = CH_2OH

4a: *n* = 1, R = Me, X = O
4b: *n* = 1, R = Et, X = O
4c: *n* = 1, R = Me, X = NH
4d: *n* = 2, R = Me, X = O

Entry	Iodide	*ee* [%][b]	Suzuki coupling					Dehydrative cyclization			
			Boronate	Ligand	Product[c]	Yield [%][d]	d.r.[e]	Product[c]	*T* [°C]	Yield [%][g]	*ee* [%][b]
1	(*S*)-**5a**	97	**6a**	**L1**	(*S*, a*R*)-**7a**	54	87:13	(*R*, a*R*)-**4a**[f]	−50	86	96
2	(*R*)-**5a**	96	**6a**	**L1**	(*R*, a*S*)-**7a**	34	87:13	(*S*, a*S*)-**4a**[f]	−50	86	94
3	(*S*)-**5b**	98	**6a**	**L1**	(*S*, a*R*)-**7b**	42	74:26	(*R*, a*R*)-**4b**[f]	−78	77	95
4	(*S*)-**5a**	97	**6b**	**L1**	(*S*, a*R*)-**7c**	39	60:40	(*R*, a*R*)-**4c**	−78	95	88
5	(*S*)-**5a**	97	**6c**	**L2**	(*S*, a*R*)-**7d**	57	81:19	(*R*, a*R*)-**4d**	−50	84	96

[a] Reaction conditions: a) iodide (1 equiv), boronate (1.5 equiv), $Pd(OAc)_2$ (5 mol%), **L1** or **L2** (10 mol%), $Ba(OH)_2{\cdot}8H_2O$ (1.1 equiv), dioxane/H_2O (9:1; *c* = 1 M), 100°C (**L2** = 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl); b) for **7a**–**b** and **7d**: nBu_4NF, THF, 20°C; c) TFA (5 equiv), CH_2Cl_2. [b] Measured by chiral HPLC, using the racemic mixture as a reference. [c] Relative configuration determined by NOESY experiments, absolute configuration confirmed by superimposition of the CD spectrum on an authentic sample of (−)-NAC (**3**; see the Supporting Information). [d] Yield of the isolated major diastereoisomer from steps (a) and (b). [e] Measured by ^{1}H NMR spectroscopic analysis of the crude mixture obtained in step (a). [f] Configuration of the major atropisomer (the compound occurs as a mixture of interconverting atropisomers). [g] Yield of the isolated product.

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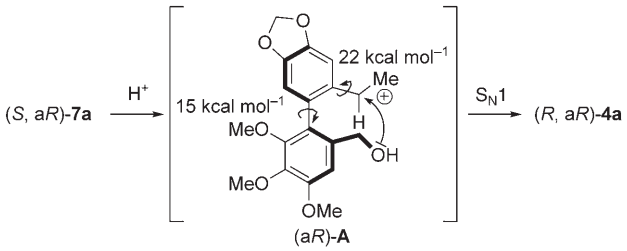
iodination. Atropo-diastereoselective Suzuki coupling with boronate **6a** followed by removal of the TES group on the major diastereoisomer provided (*S*,a*R*)-**7a** in 54% yield (entry 1). The stereochemically crucial dehydration of this compound was first attempted under the same conditions as the racemic mixture at 20°C. This step gave **4a** with 74% *ee* in favor of the putative *R*,a*R* enantiomer. Gratifyingly, carrying out the cyclization at −50°C with trifluoroacetic acid (TFA) in CH_2Cl_2 allowed almost complete conservation of the optical purity (96% *ee*, 86% yield). The *R*,a*R* absolute configuration of the product was confirmed by the superimposition of its CD spectrum on that of an authentic sample of (−)-NAC (**3**). Repeating the same reaction sequence from enantiomeric (*R*)-**5a** (synthesized in 96% *ee*) furnished (*S*, a*S*)-**4a** in 94% ee (entry 2). Introduction of another alkyl group on the oxepine ring proved feasible, as illustrated by the synthesis of the ethyl analogue (*R*,a*R*)-**4b** (entry 3). This analogue was obtained with 95% *ee* from (*S*)-**5b** (98% *ee*).[11] The dibenzazepine analogue (*R*,a*R*)-**4c** could be obtained accordingly, starting from (*S*)-**5a** and boronate **6b** (entry 4). In this case, a small loss of optical purity was observed (88% *ee*), although the dehydration occurred at −78°C. Cleavage of the *tert*-butyloxycarbonyl (*t*Boc) group was observed upon warming the reaction mixture to room temperature. Finally, dibenzoxocine (*R*,a*R*)-**4d** (eight-membered median ring) was synthesized with 96% *ee* from (*S*)-**5a** and boronate **6c** containing a homologated side chain. In this case, **L2** (S-Phos)[12] gave a better yield than **L1** in the Suzuki coupling. Compound **4d** occurred as a single atropisomer in solution, contrary to **4a**,**b**, because of the presence of the larger bridging ring, similar to stegane-type molecules.[3]

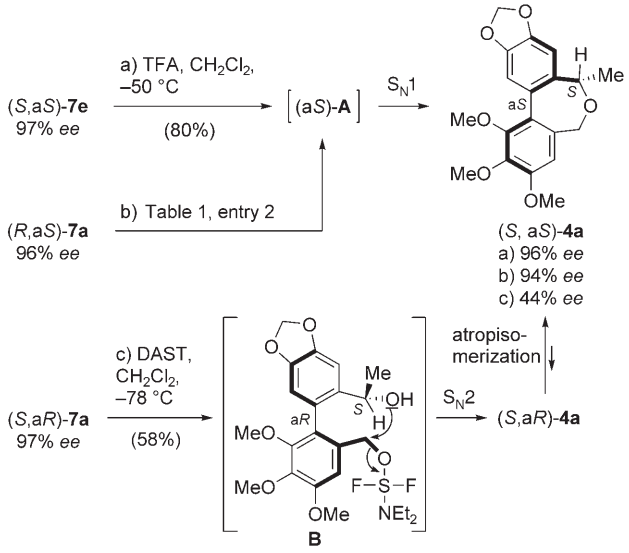
The stereoselectivity of the dehydrative cyclization of diol (*S*,a*R*)-**7a** can be rationalized by the formation of chiral benzylic cation (*aR*)-**A**,[13] in which the C^+–H bond eclipses the biaryl axis to minimize $A^{1,3}$ allylic strain (Scheme 2). At



Scheme 2. Proposed cationic cyclization intermediate.

low temperature, this intermediate is configurationally stable and trapped by the internal nucleophile, thus giving (*R*,a*R*)-**4a** with inversion of configuration at the benzylic stereocenter. An atropisomerization barrier of 15 kcal mol^{-1} was calculated for **A** (AM1 method), whereas the rotation barrier of the C(Ar)–C^+ bond was significantly higher (22 kcal mol^{-1}), as expected from conjugation with the aromatic ring. This behavior indicates that the observed racemization of (*R*,a*R*)-**4a** at higher temperatures might occur preferably by atropisomerization. Overall, the biaryl axis, therefore, functions as a stereochemical relay for the benzylic stereocenter that is temporarily destroyed in intermediate **A**.

Additional evidence of a chiral carbocationic intermediate in the dehydrative cyclization was provided by the reaction of the minor diastereoisomer (*S*,a*S*)-**7e** obtained in a small amount after Suzuki coupling of (*S*)-**5a** with **6a** and deprotection (Scheme 3, path a). This reaction furnished



Scheme 3. Stereoconvergent syntheses of (*S*,a*S*)-**4a**.

(*S*,a*S*)-**4a** with 96% *ee*, most likely through the same carbocationic intermediate (a*S*)-**A** as that formed from (*R*,a*S*)-**7a** (path b). A third stereoconvergent pathway could be devised for the synthesis of (*S*,a*S*)-**4a** (path c). When diol (*S*,a*R*)-**7a**, which was previously converted into (*R*,a*R*)-**4a** with TFA (Table 1, entry 1), was treated with (diethylamino)sulfur trifluoride (DAST) in CH_2Cl_2 at −78°C, (*S*,a*S*)-**4a** was obtained as the major enantiomer in 44% *ee*. This result can be best rationalized by the regioselective reaction of the primary alcohol of **7a** with DAST to give intermediate **B**, followed by intramolecular S_N2.[14] This reaction would produce (*S*,a*R*)-**4a**, which interconverts into the more stable atropisomer (*S*,a*S*)-**4a**. The loss of optical purity could be ascribed either to incomplete regioselectivity in the reaction of the diol with DAST or to a mixed S_N2/S_N1 mechanism.

The antimicrotubule activity of biaryls **4a–d** was examined and compared to that of (−)-colchicine and (−)-NAC (**3**). First, no activity was found for (*S*,a*S*)-**4a**, as expected. The IC_{50} values for the inhibition of the microtubule assembly for the target compounds and the reference compounds were: 2.9(±0.7) μM for NAC (**3**); 8.2(±1.6) μM for colchicine; 12.3(±2.5) μM for (*R*, a*R*)-**4a**; 4.9(±0.4) μM for (*R*, a*R*)-**4b**; 11.1(±2.0) μM for (*R*, a*R*)-**4d**. Dibenzazepine (*R*,a*R*)-**4c** was found to be inactive. Thus, all oxygen-containing analogues were strong inhibitors of tubulin polymerization, with (*R*,a*R*)-**4b** being the most active (1.7× more active than colchicine).[15]

In conclusion, we have reported a general and efficient enantioselective synthesis of potent antimicrotubule biaryls

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by using a novel type of asymmetry relay by a biaryl stereogenic axis. These molecules could represent promising new leads for the development of vascular-targeting agents.

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[10] The structures of both atropisomers were computed using random search calculations. The NOE interactions observed for the major a*R* atropisomer (Scheme 1) corresponds to a H(Ar)–CH_3 distance of 2.2 Å, whereas this distance is 3.6 Å in the a*S* atropisomer.
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