Transition-Metal-Free Synthesis of a Known Intermediate in the Formal Synthesis of (-)-Steganacin

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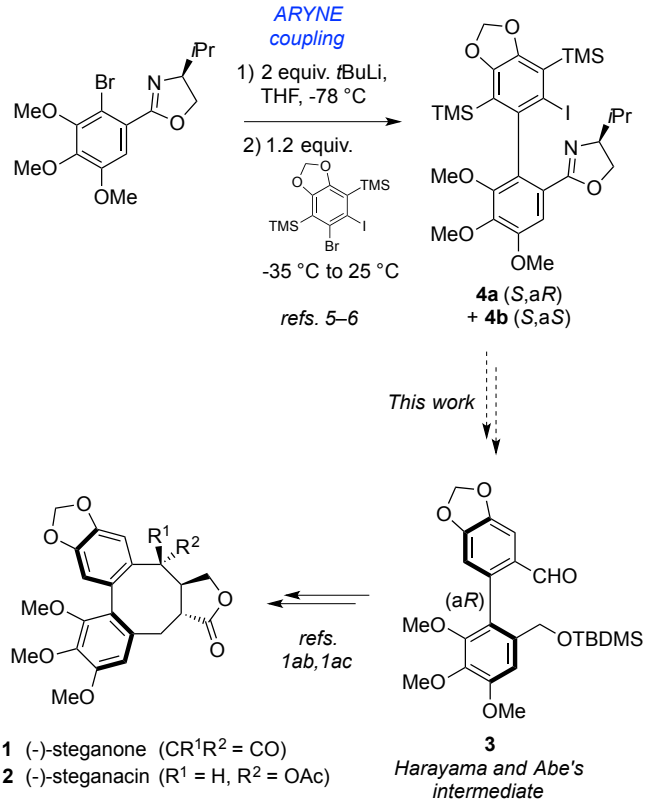
Abstract: The formal synthesis of both enantiomers of a natural axially chiral biaryl, steganacin is reported. The previously developed atropo-diastereoselective coupling of an aryne and an aryllithium (the 'ARYNE coupling') allows for this synthesis. In each step, the axial configuration of the biaryl could be maintained. The key intermediate of literature was accessed without using transition metals, demonstrating the interest of the ARYNE coupling as a complement or an alternative to transition metal-catalyzed couplings.

Introduction

(-)-Steganacin (**2**) (Scheme 1) is a known chiral biaryl-based natural product, which showed potent antimicrotubule *in vivo* activity against mice cancer cell lines and *in vitro* activity against human cancer cell lines, but did not find any medicinal application; however, the early interest for this potential anticancer agent as well as the synthetic challenge explain why (-)-steganacin and its one-step precursor (-)-steganone (**1**), their enantiomers and racemates have been the target of many new synthetic methods.[1] We already described a palladium-catalyzed atropo-diastereoselective Suzuki-Miyaura coupling as a key step to prepare a known synthetic intermediate (**3**) initially described by Harayama, Abe *et al.*[1ab,1ac] in the formal synthesis of (-)-steganone.[2] In the present paper, we report on an alternative transition metal-free, lithium-based synthesis of Harayama and Abe's intermediate **3**, in view of a transition metal-free total synthesis of (-)-steganacin or its derivatives. Indeed, despite their versatile use as catalysts in all sorts of reactions, transition metals might be a concern especially in the pharmaceutical industry, where recommended levels in active pharmaceutical ingredients are very low (permitted daily exposure of patients to palladium: 100 µg/day for oral doses, 10 µg/day for parenterally administered drugs, 1 µg/day by inhalation).[3a,3b] In comparison, the respective permitted daily exposures of patients to lithium are of 560, 280 and 25 µg/day,[3b] which, given the atomic mass of both elements, favours lithium even if it is used in stoichiometric amount while palladium is used in catalytic quantities. Accordingly, the use of transition metals in late-stage synthesis is problematic and requires efficient, but costly, removal of trace metals (e.g. scavenging agents or nanofiltration).[4] Additionally, the price per tonne of palladium, ca. 2000–3000 times more expensive than lithium, has also to be taken in consideration. Consequently, transition metal-free syntheses might offer an appealing solution. We recently described the coupling between an *in situ*-generated aryne and an aryllithium nucleophile bearing a chiral oxazolinyl group *ortho* to lithium; the design of the coupling partners was directed towards the formal synthesis of (-)-steganacin as a model target. Although very moderate selectivity was achieved, we showed that the desired biaryl **4** could be produced with a satisfying 67% yield, given the steric bulk surrounding the newly formed, tetra-*ortho*-substituted aryl-aryl bond, and that both atropo-diastereoisomers could be separated by column chromatography and their absolute configuration determined by X-ray diffraction crystallography.[5] Having created the biaryl backbone of (-)-steganacin, we had now to transform it into intermediate **3**, without using transition metals.



Scheme 1. Planned strategy for the formal synthesis of (-)-steganacin.

Results and Discussion

In order to do so, three kinds of transformations had to be carried out, independently of their order: 1) double desilylation, 2)

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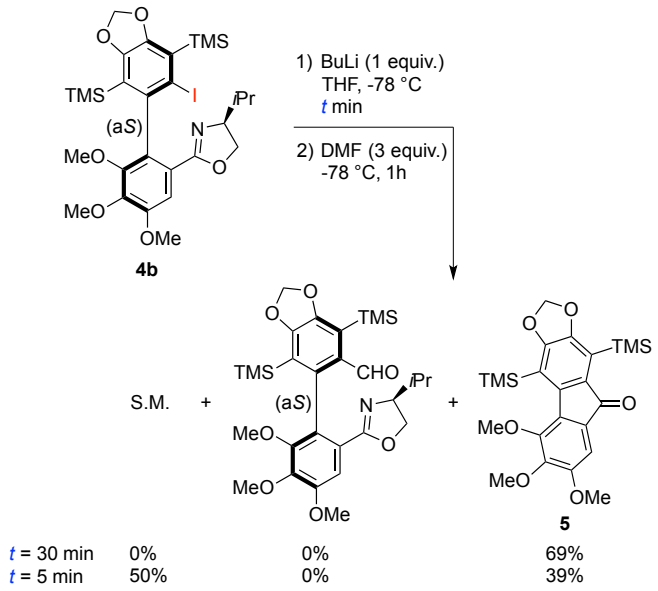
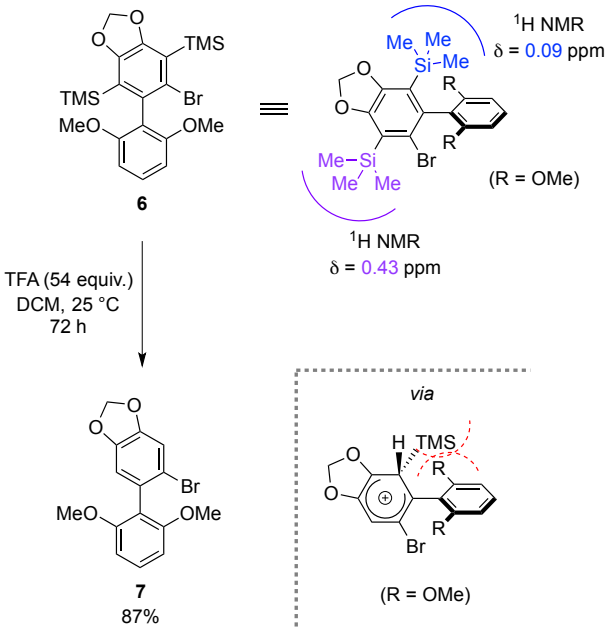
conversion of iodine into a formyl group, 3) reduction of the oxazoline into an alcohol. Starting from iodo-to-formyl conversion by halogen/lithium exchange appeared to be unfruitful (Scheme 2). Indeed, addition of 1 equiv. of butyllithium in THF at -78 °C to **4b** (*S*,a*S*)—as a model in place of the desired **4a** (*S*,a*R*)—followed by trapping with DMF after 30 minutes only led to the undesired fluorenone **5**[5] in 69% yield. When reducing the time before DMF addition to 5 minutes, we surprisingly recovered 50% of starting material, i.e. with untouched iodine, while **5** was still formed in 39% yield. The recovery of unreacted iodobiphenyl can be ascribed to the high steric bulk around iodine, decreasing its reactivity. Anyway, in both cases, no desired aldehyde was obtained after work-up. The fluorenone formation at the detriment of the trapping by DMF was coherent with our previous findings.[5,6] Indeed, cyclisation of the biaryllithium intermediate is favored over trapping with an electrophile when the latter is either slowly reacting or not already present in the reaction medium for *in situ* trapping of the forming biaryllithium.



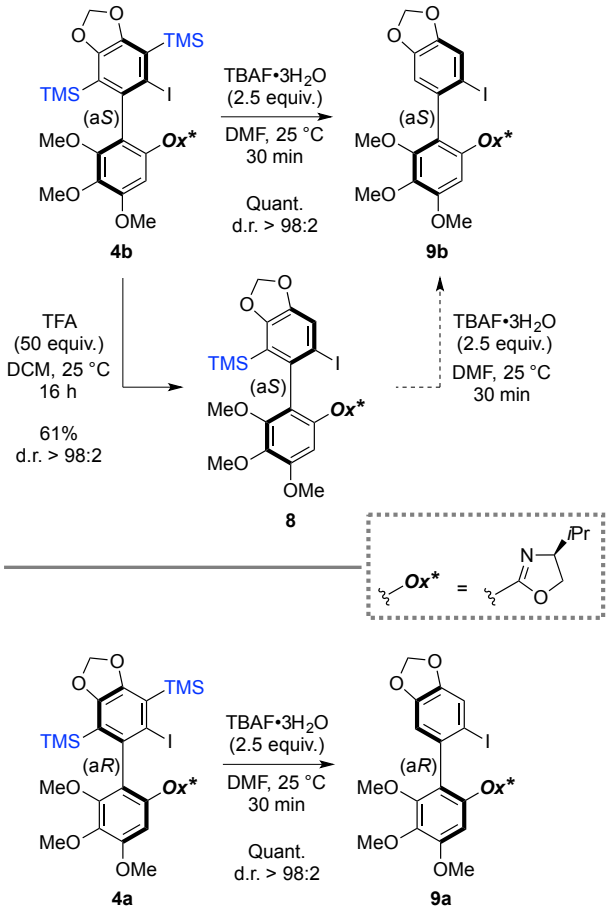
Scheme 2. Attempts of iodine/lithium exchange and trapping with DMF on iodobiaryl **4b**.

Consequently, we rather decided to perform the formylation as a last step, and to investigate on the double desilylation of the biaryl moiety. This transformation was critical from a synthetic point of view, insofar as both TMS groups had to be removed efficiently and without epimerization of the chiral axis. Therefore, we wished to perform the protodesilylation at low temperature if possible. We again started first with a model bis(trimethylsilylated) biaryl, **6** (Scheme 3), that we already described.[5] and treated it with TFA, a known desilylating agent of electron-rich aromatic rings.[7] The reaction proceeded well in the presence of excess TFA at room temperature, although a long reaction time was required to fully remove the TMS group in position 6. Indeed, the latter is quite hindered by the dimethoxyphenyl ring, as observed by ^{1}H NMR where TMS-6 is shielded by 0.34 ppm with regard to TMS-3 due to the anisotropy cone generated by the aforementioned dimethoxyphenyl (Scheme 3). Since the TFA-promoted proto-desilylation —by electrophilic aromatic substitution— requires tetragonalization of the *ipso* carbon, the higher steric hindrance around carbon-6 explains that it is less prone to the latter change of geometry. In the end, the reaction afforded the totally desilylated product **7** in 87% yield after 72 h of reaction at 25 °C (Scheme 3).



Scheme 3. Double protodesilylation of model compound **6**.

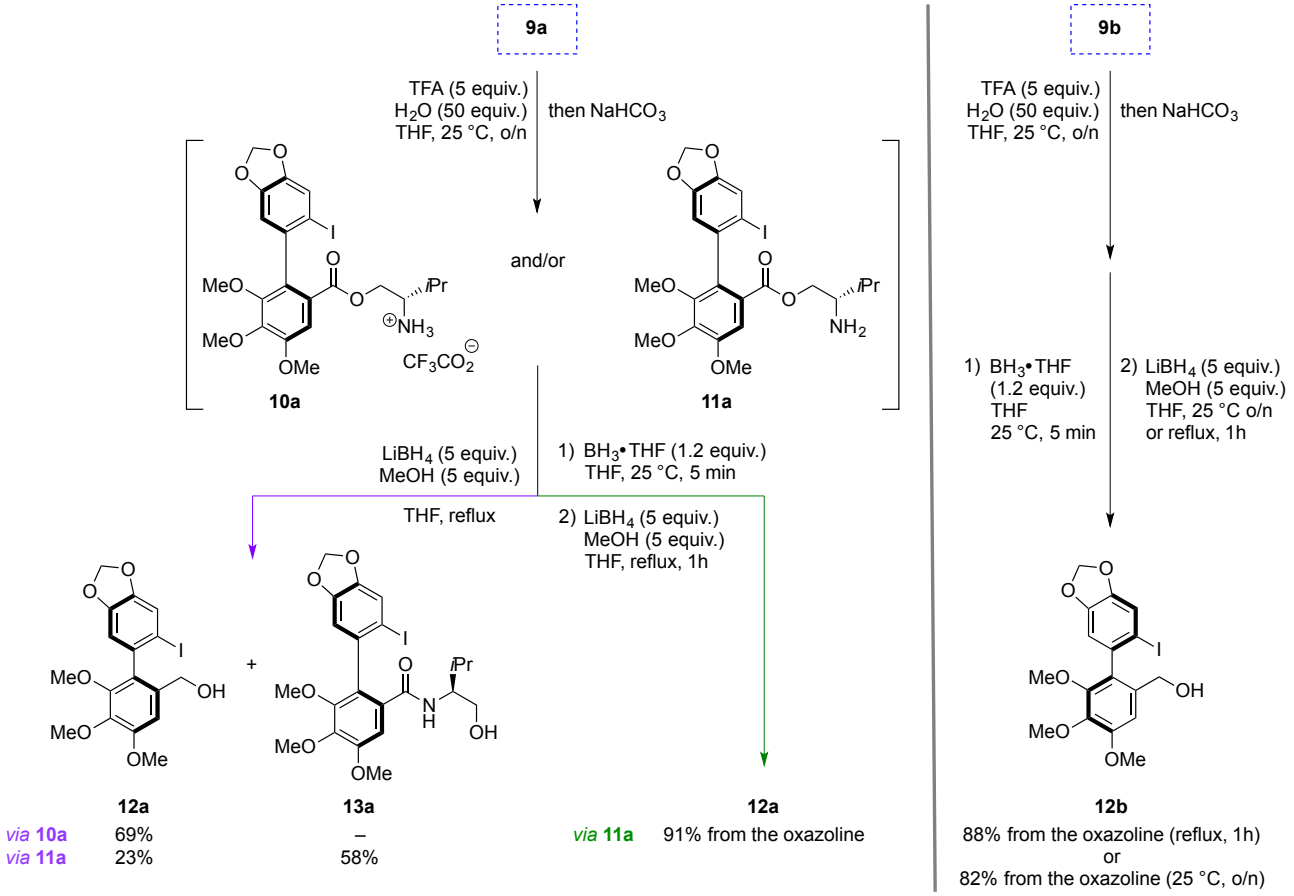
However, when applying these conditions to the (*S*,a*S*) diastereomer **4b**, where the TMS-substituted carbon-6 is much more congested than in **6**, only the mono-desilylated product **8** was obtained in 61% yield, nevertheless with retention of axial stereo-enrichment (Scheme 4). Apart from the characteristic shielded ^{1}H NMR chemical shift of the untouched TMS group, the structure of **8** was confirmed by NOESY, showing a correlation between the signals of the TMS and of the methoxy groups, as well as another between the signals of the TMS and of the aromatic proton located *ortho* to the oxazoline. When other conditions or other acids (HCl, H_2SO_4) were tried, complex mixtures were obtained, from which biphenylcarboxylic acids, coming from hydrolysis of the oxazoline moiety, could sometimes be identified. On the other hand, using a 1M TBAF solution in THF to accomplish the protodesilylation —*via* a different, anion-based mechanistic pathway— revealed completely ineffective.



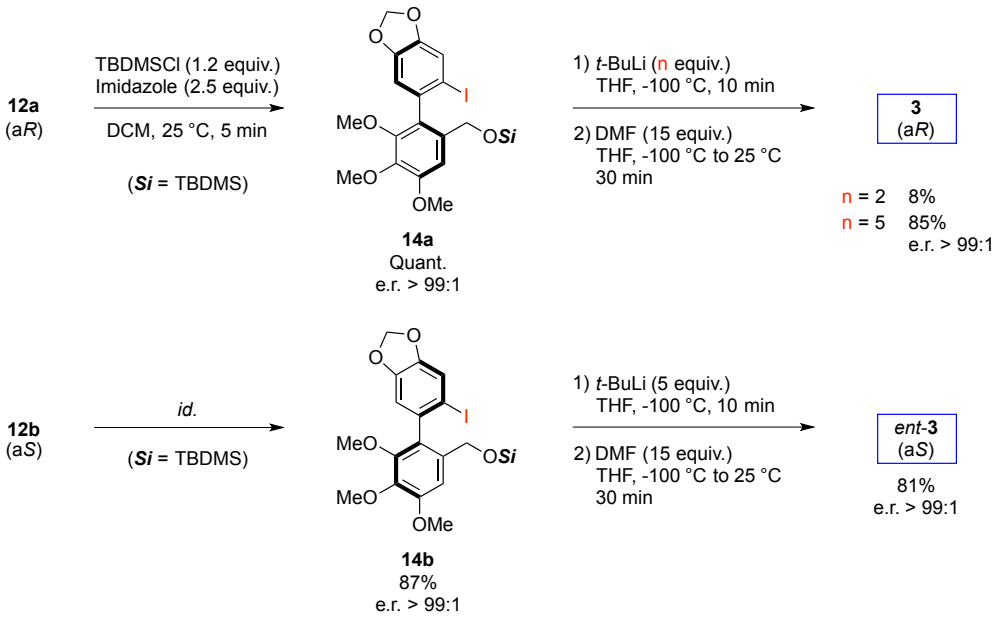
Scheme 4. Single and double protodesilylation of both atropo-isomers of **4**.

Eventually, we succeeded in deprotecting both silylated carbons of **4b** and **4a** by employing TBAF-trihydrate in DMF at 50 °C for 2.5 days. Gratifyingly, no erosion of diastereomeric ratio was observed in product **9**, even at this temperature and reaction time, and quantitative yields were obtained. More gratifyingly, we later found out that the same reaction was complete after 30 min, even at room temperature (Scheme 4). In view of further transformations towards (-)-steganacin or analogues, it is noteworthy that the desilylations can be performed stepwise with first TFA, and then TBAF•3H$_2$O/DMF, making this sequence an interesting tool for controlled deprotection.

Then, to reduce the oxazoline of **9a**, we first hydrolyzed it under conditions similar to Meyers',[8] using TFA in a THF/water mixture, at room temperature to prevent potential epimerization of the chiral axis (Scheme 5). The crude biaryl ester with a pendant ammonium function was then treated with reducing agents. Lithium aluminum hydride was effective, but also reduced the carbon-iodine bond. We therefore turned to lithium borohydride in combination with methanol, which, at first, gave irreproducible results. We soon realized that this was related to the basic work-up of the reaction of **9a**, which was critical as it could either afford the ammonium **10a**, the corresponding amine **11a**, or a mixture of both. Indeed, when the hydrolysis of the oxazoline was followed by simple washing of the organic layer with saturated NaHCO$_3$ and extraction with ether, either **10a** or a mixture of **10a** and **11a**, where ammonium **10a** was largely major, were obtained. On the other hand, when the reaction mixture was quenched with saturated NaHCO$_3$ until evolution of CO$_2$ had ceased, then extracted with diethyl ether, amine **11a** was the sole product, as shown by the absence of fluorine signals in ^{19}F NMR of the crude. Then, as implied above, the nature of the ester to be reduced (**10a**/**11a**) proved influential, as **10a** and **11a** did not behave similarly upon treatment with LiBH$_4$/MeOH[9]. While the crude ammonium **10a** afforded the desired alcohol **12a** in 69% yield, amine **11a** led to a mixture of **12a** (minor) and amide **13a** (major) by rearrangement of the aminoalkyl ester. Accordingly, to prevent formation of the amide **13a** and to increase the yield of the alcohol **12a**, we first reacted the crude **11a** with the borane-THF complex and then treated the mixture with LiBH$_4$/MeOH. We reasoned indeed that borane would coordinate to the free amine, preventing it from attacking the ester. This strategy proved efficient, and we finally obtained 91% yield of alcohol **12a** from oxazoline **9a** (Scheme 5). We then quantitatively protected the compound as a silyl ether **14a**, of which the enantiomeric ratio was measured by chiral HPLC analysis to be higher than 99:1, confirming retention of axial stereoenrichment (Scheme 6). The opposite atropo-isomers **12b** and **14b** were also synthesized from **9b** with similar yields (Scheme 5 and Scheme 6).



Scheme 5. Reduction of the oxazoline moiety.

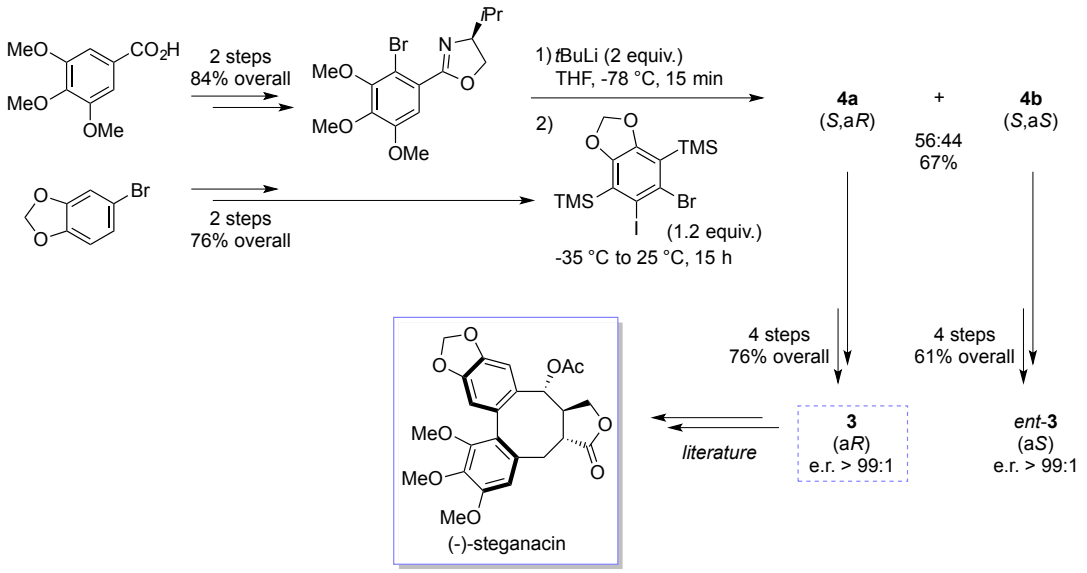


Scheme 6. Protection-iodine/lithium exchange-formylation sequence.

Finally, the most critical step was the iodine/lithium exchange followed by trapping with DMF, which ought to proceed without epimerization of the biaryllithium intermediate to afford the desired aldehyde **3**. We thus carried out the reaction at low temperature (-100 °C) and with *tert*-butyllithium as the base for a clean halogen/metal exchange. Here as well (see Scheme 2), the usual number of equivalents of base (2 in the case of *t*BuLi) appeared insufficient for an effective conversion of the biaryl iodide, as only 8% yield of aldehyde **3** were achieved (Scheme 6). In the end, 5 equiv. of *t*BuLi managed to produce **3** in 85% yield. Again, the same strategy was applied to the opposite atropo-isomer **14b**, giving *ent*-**3** with 81% yield. Both enantiomers were showed to be enantiopure by chiral HPLC (>99:1 e.r.).

In conclusion, we carried out the synthesis of Harayama and Abe's intermediate **3** in 9 steps, 22% overall yield, excellent control of chirality (>98% e.e., with retention of axial stereoenrichment at each stage of the process), and in the absence of transition metals (Scheme 7). Interestingly, the enantiomer *ent*-**3** of the target compound could be obtained with similar efficiency. This transition metal-free synthetic pathway is an efficient alternative to Harayama and Abe's synthesis of **3**[1ab,ac] (10 steps from piperonyl alcohol, 25% overall yield, 83% e.e.) or our previous Pd-catalyzed strategy[2] (15 steps from piperonyl alcohol, 9% overall yield, 94% e.e.), which both involved palladium-promoted steps and stoichiometric chromium-mediated transformations. The current work enforces the interest in heavy metal-free biaryl synthesis applied to the preparation of potential pharmaceutically relevant ingredients.

Conclusions



Scheme 7. Formal synthesis of (-)-steganacin.

Experimental Section

See the Supporting Information for further information. The preparation of compounds **4a**, **4b**, **5** and **6** was already described.[5]

5-Bromo-6-(2,6-dimethoxyphenyl)benzo[*d*][1,3]dioxole (7)

To a stirred solution of bis(trimethylsilyl)biarylbromide **6** (0.20 g, 0.42 mmol, 1 equiv.) in dry dichloromethane (9 mL), was added trifluoroacetic acid (1.68 mL) at 25 °C. The reaction mixture was stirred for 3 d at 25 °C. The mixture was concentrated and the residue was taken up in $CHCl_3$ (40 mL), washed with $NaHCO_3$ (40 mL), water (40 mL), then brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **7** as a yellow solid; yield = 0.12 g (0.36 mmol, 87%); R_f = 0.38 (cyclohexane/CH_2Cl_2 = 1:1); M.p. = 119-121 °C; $\tilde{\nu}$ = 294.7, 2902.7, 2838.2, 1593.4, 1473.5, 1243.0 (C-O), 1098.5 (C-O), 1018.6, 926.4 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (t, 1 H, ^3J = 8.4 Hz, Ar-*H*), 7.12 (s, 1 H, Ar-*H*), 6.72 (s, 1 H, Ar-*H*), 6.65 (d, 2 H, ^3J = 8.4 Hz, Ar-*H*), 6.00 (s, 2 H, OCH_2O), 3.76 (s, 6 H, OCH_3) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.97 (C), 147.63 (C), 147.15 (C), 129.53 (CH^{Ar}), 128.96 (C), 118.86 (C), 115.78 (*C*-Br), 112.67 (CH^{Ar}), 111.93 (CH^{Ar}), 104.21 (CH^{Ar}), 101.79 (OCH_2O), 56.16 (OCH_3) ppm; $C_{15}H_{13}BrO_4$ (335.99): calcd. C 53.43, H 3.89; found C 53.27, H 4.04.

(*S*)-2-(2-(a*S*)-(6-Iodo-4-(trimethylsilyl)benzo[*d*][1,3]dioxol-5yl)-3,4,5-trimethoxyphenyl)-4-isoproyl-4,5-dihydrooxazole (8)

To a stirred solution of **4b** (220 mg, 0.33 mmol, 1 equiv.) in dry dichloromethane (4 mL), was added trifluoroacetic acid (1.22 mL, 16.43 mmol, 50 equiv.) at 25 °C. The reaction mixture was stirred at 25 °C for 16 h. Saturated aqueous $NaHCO_3$ was added portionwise to the stirred mixture until no more carbon dioxide evolution was observed and the mixture was extracted thrice with Et_2O. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under vacuum to give the

crude, which was purified by column chromatography on silica gel, eluting with a cyclohexane/AcOEt gradient to yield **8** as a pale yellow oil; yield = 120 mg (0.20 mmol, 61%); R_f = 0.21 (cyclohexane/AcOEt = 90:10); $[\alpha]_D^{20}$ = -2.1 (*c* = 1.00, $CHCl_3$); $\tilde{\nu}$ = 2956.2, 2933.0, 1653.9 (C=N), 1589.8, 1398.2, 1359.3, 1196.8, 1099.2, 1019.5, 839.7 ($Si(CH_3)_3$), 765.3, 692.8, 630.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.25 (s, 1 H, Ar-*H*), 7.23 (s, 1 H, Ar-*H*), 5.95 (ABq, 2 H, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 1.3 Hz, O-CH_2-O), 4.13-4.05 (m, 1 H, O-CH_2-C), 3.94 (s, 3 H, Ar-OCH_3), 3.90 (s, 3 H, Ar-OCH_3), 3.88-3.80 (m, 2 H, O-CH_2-C + NCH), 3.72 (s, 3 H, Ar-OCH_3), 1.57 (sept.d, 1 H, ^3J = 6.6 Hz, ^3J = 6.6 Hz, CH^{iPr}), 0.78 (d, 3 H, ^3J = 6.7 Hz, CH_3^{iPr}), 0.77 (d, 3 H, ^3J = 6.8 Hz, CH_3^{iPr}), -0.07 (s, 9 H, $Si(CH_3)_3$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.43 (*C*=N), 153.03 (C), 152.83 (C), 151.87 (C), 145.65 (C), 144.26 (C), 139.58 (C), 134.13 (C), 124.30 (C), 122.25(C), 118.14 (CH^{Ar}), 108.05 (CH^{Ar}), 100.69 (OCH_2O), 91.59 (C-I), 72.77 (NCH), 70.27 (OCH_2), 60.68 (Ar-OCH_3), 60.56 (Ar-OCH_3), 56.16 (Ar-OCH_3), 33.12 (CH^{iPr}), 18.69 (CH_3^{iPr}), 18.61 (CH_3^{iPr}), -0.34 ($Si(CH_3)_3$) ppm; HRMS ES *m/z* $[M+Na]^+$ calcd. for $C_{22}H_{24}INaNO_6$: 620.0941, found 620.0938.

(*S*,a*R*)- and (*S*,a*S*)-2-[2-(6-iodo-2*H*-1,3-benzodioxol-5-yl)-3,4,5-trimethoxyphenyl]-4-(propan-2-yl)-4,5-dihydro-1,3-oxazole (9a and 9b)

The desired atropo-diastereomer of **4** (1 equiv.) was dissolved in DMF (0.3 M). Tetrabutylammonium fluoride trihydrate (2.5 equiv.) was added and the mixture was stirred for 30 min at RT. The reaction mixture was taken up in brine and extracted twice with Et_2O. The organic layers were combined, washed thrice with H_2O, dried over Na_2SO_4, filtrated and concentrated under vacuum to give the desired product.

9a (*S*,a*R*): light orange oil; yield = 572 mg (1.09 mmol, 99 %) from **4a** (734 mg, 1.10 mmol); R_f = 0.1 (cyclohexane/AcOEt = 9/1); $[\alpha]_D^{20}$ = -7.72 (c = 1.05, $CHCl_3$); $\tilde{\nu}$ = 2964.0, 2930.5, 2901.2, 1635.6 (C=N), 1440.0, 1415.1, 1340.6 (C-O), 1205.3 (C-O), 1101.7, 1037.0, 970.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.26 (s, 1 H, Ar-*H*), 7.22 (s, 1 H, Ar-*H*), 6.69 (s, 1 H, Ar-*H*), 5.97 (s, 2 H, O-CH_2-O), 4.09 (dd, 1 H, ^3J = 9.1 Hz, ^2J = 8.2 Hz, O-CH_2-C), 3.93 (s, 3 H, Ar-OCH_3), 3.91 (s, 3 H, Ar-OCH_3), 3.86 (ddd, 1 H, ^3J = 9.1 Hz, ^3J = 8.2 Hz, ^3J = 6.7 Hz, N-C*H*), 3.77 (dd, 1 H, ^3J = 8.2 Hz, ^2J = 8.2 Hz, O-CH_2-C), 3.70 (s, 3 H, Ar-OCH_3), 1.66 (sept.d, 1 H, ^3J = 6.7 Hz, ^3J = 6.7 Hz, CH^{iPr}), 0.86 (d, 3 H, ^3J = 6.7 Hz, CH_3^{iPr}), 0.81 (d, 3 H, ^3J = 6.7 Hz, CH_3^{iPr}) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.09 (C_{IV}, *C*=N), 152.99 (C_{IV}, C^{Ar}), 151.36 (C_{IV}, C^{Ar}), 147.70 (C_{IV}, C^{Ar}), 147.38 (C_{IV}, C^{Ar}), 144.33 (C_{IV}, C^{Ar}), 135.99 (C_{IV}, C^{Ar}), 131.97 (C_{IV}, C^{Ar}), 123.61 (C_{IV}, C^{Ar}), 117.63 (CH^{Ar}), 110.53 (CH^{Ar}), 108.52 (CH^{Ar}), 101.58 (O-CH_2-O), 89.70 (C_{IV}, *C*-I), 72.61 (N-CH), 70.42 (O-CH_2-C), 61.11 (Ar-OCH_3), 61.00 (Ar-OCH_3), 56.15 (Ar-OCH_3), 32.78 (CH^{iPr}), 18.95 (CH_3^{iPr}), 18.40 (CH_3^{iPr}) ppm; HRMS ES *m/z* $[M+ Na]^+$ calcd. for $C_{22}H_{24}INaNO_6$: 548.0546, found 548.0541.

9b (*S*,a*S*): light yellow oil; yield = 440 mg (0.84 mmol, 99 %) from **4b** (561 mg, 0.84 mmol); R_f = 0.1 (cyclohexane/AcOEt = 9/1); $[\alpha]_D^{20}$ = -5.60 (c = 0.94, $CHCl_3$); $\tilde{\nu}$ = 2963.0, 2928.5, 2900.2, 1633.6 (C=N), 1440.0, 1415.1, 1340.6 (C-O), 1204.3 (C-O), 1100.7, 1036.0, 968.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.25 (s, 1 H, Ar-*H*), 7.19 (s, 1 H, Ar-*H*), 6.76 (s, 1 H, Ar-*H*), 5.97 (ABq, 2 H, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 1.3 Hz, O-CH_2-O), 4.15 (dd, 1 H, ^3J = 8.7 Hz, ^2J = 7.3 Hz, O-CH_2-C), 3.93 (s, 3 H, Ar-OCH_3), 3.92 (s, 3 H, Ar-OCH_3), 3.91-3.84 (m, 1 H, N-C*H*), 3.82 (dd, 1 H, ^3J = 7.8 Hz, ^2J = 7.8 Hz, O-CH_2-C), 3.68 (s, 3 H, Ar-OCH_3), 1.62 (sept.d, 1 H, ^3J = 6.7 Hz, ^3J = 6.7 Hz, CH^{iPr}), 0.81 (d, 3 H, ^3J = 6.7 Hz, CH_3^{iPr}), 0.80 (d, 3 H, ^3J = 6.7 Hz, CH_3^{iPr}) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.93 (C_{IV}, *C*=N), 152.96 (C_{IV}, C^{Ar}), 151.38 (C_{IV}, C^{Ar}), 147.80 (C_{IV}, C^{Ar}), 147.44 (C_{IV}, C^{Ar}), 144.38 (C_{IV}, C^{Ar}), 135.86 (C_{IV}, C^{Ar}), 132.02 (C_{IV}, C^{Ar}), 123.78 (C_{IV}, C^{Ar}), 117.70 (CH^{Ar}), 111.03 (CH^{Ar}), 108.44 (CH^{Ar}), 101.61(O-CH_2-O), 89.31 (C_{IV}, *C*-I), 72.80 (N-CH), 70.41 (O-CH_2-C), 61.05 (Ar-OCH_3), 61.04 (Ar-OCH_3), 56.14 (Ar-OCH_3), 32.98 (CH^{iPr}), 18.85 (CH_3^{iPr}), 18.54 (CH_3^{iPr}) ppm.

(a*R*)- and (a*S*)-[2-(6-iodo-2*H*-1,3-benzodioxol-5-yl)-3,4,5-trimethoxyphenyl]methanol (12a and 12b)

The desired atropo-diastereomer of **9** (1 equiv.) was dissolved in THF (0.12 M). Trifluoroacetic acid (5 equiv.) and water (50 equiv.) were then added and the mixture was stirred overnight at r.t. (LCMS monitoring). Saturated aqueous $NaHCO_3$ was added portionwise to the stirred mixture until no more carbon dioxide evolution was observed and the mixture was extracted thrice with DCM. The combined organic layers were dried over Na_2SO_4, filtrated and concentrated under vacuum to give the crude amino-ester intermediate that was then directly engaged into the reduction step. Under an argon atmosphere, a solution of borane-THF complex (1.2 equiv., 1 M in THF) and methanol (5 equiv.) were added to a solution of the previous crude (1 equiv.) in dry THF (0.12 M). Lithium borohydride (5 equiv.) was then added in one portion as a solid (CAUTION: hydrogen evolution). The mixture was refluxed for 1 h and quenched with 2 M HCl once cooled down (CAUTION: hydrogen evolution). Once there was no more hydrogen degassing, the mixture was extracted thrice with DCM. The organic layers were combined, dried over Na_2SO_4, filtrated and concentrated under vacuum. The crude was purified by flash chromatography on silica gel, eluting with a cyclohexane/AcOEt mixture, to give the purified alcohol as a colorless foam.

12a (a*R*): yield = 255 mg (0.57 mmol, 91 %) from **9a** (330 mg, 0.63 mmol; $[\alpha]_D^{20}$ = +8.5 (c = 1, CH_2Cl_2)

12b (a*S*): yield = 319 mg (0.72 mmol, 88 %) from **9b** (430 mg, 0.82 mmol); $[\alpha]_D^{20}$ = -8.8 (c = 1, CH_2Cl_2)

R_f = 0.25 (cyclohexane/AcOEt = 6/4); $\tilde{\nu}$ = 3423.9 (O-H), 2934.6, 1598.0, 1471.8, 1456.8, 1413.2, 1317.1, 1223.6, 1141.7, 1117.9, 1034.6, 1014.8, 731.6, 556.1 (C-I) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (s, 1 H, Ar-*H*), 6.91 (s, 1 H, Ar-*H*), 6.70 (s, 1 H, Ar-*H*), 6.01 (s, 2 H, O-CH_2-O), 4.30 (ABq, 2 H, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 13.0 Hz, Ar-CH_2-OH), 3.92 (s, 3 H, Ar-OCH_3), 3.89 (s, 3 H, Ar-OCH_3), 3.73 (s, 3 H, Ar-OCH_3), 1.73 (bs, 1 H, O*H*) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.7 (C_{IV}, C^{Ar}), 151.1 (C_{IV}, C^{Ar}), 148.5 (C_{IV}, C^{Ar}), 148.0 (C_{IV}, C^{Ar}), 141.5 (C_{IV}, C^{Ar}), 135.0 (C_{IV}, C^{Ar}), 134.5 (C_{IV}, C^{Ar}), 130.1 (C_{IV}, C^{Ar}), 118.3 (CH^{Ar}), 110.7 (CH^{Ar}), 106.6 (CH^{Ar}), 101.9 (O-CH_2-O), 89.9 (C_{IV}, *C*-I), 63.1 (Ar-CH_2-OH), 61.1 (Ar-OCH_3), 61.0 (Ar-OCH_3), 56.1 (Ar-OCH_3) ppm; $C_{17}H_{17}IO_6$ (444,01): calcd. C 45.97, H 3.86, found C 45.57, H 3.99.

(a*R*)- and (a*S*)-*tert*-butyl({[2-(6-iodo-2*H*-1,3-benzodioxol-5-yl)-3,4,5-trimethoxyphenyl]meth-oxy})dimethylsilane (14a and 14b)

Under an argon atmosphere, the desired atropo-enantiomer of **12** (1 equiv.) was dissolved in dry DCM (0.1 M) and imidazole (2.5 equiv.) was added in one portion. Once dissolved, *tert*-butyldimethylsilyl chloride (1.2 equiv.) was added in one portion and the mixture was stirred at RT for 5 min. Saturated aqueous NH_4Cl was added to the reaction mixture that was then extracted thrice with DCM. The organic layers were combined, dried over Na_2SO_4, filtrated and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel, eluting with a cyclohexane/AcOEt mixture, to give the purified silylated alcohol as a colorless oil. The enantiomeric ratio of the product was determined by chiral HPLC on a Chiralpak IB column (hexane/isopropanol = 80/20; 0.5 mL/min; t_R = 8.00 min (a*S*), 8.78 min (a*R*)).

14a (a*R*): yield = 293 mg (0.52 mmol, 99 %, *e.r.* > 99:1) from **12a** (236 mg, 0.53 mmol); $[\alpha]_D^{20}$ = +15.0 (c = 1, CH_2Cl_2)

14b (a*S*): yield = 350 mg (0.63 mmol, 87 %, *e.r.* > 99:1) from **12b** (319 mg, 0.72 mmol); $[\alpha]_D^{20}$ = -15.3 (c = 1, CH_2Cl_2)

R_f = 0.25 (cyclohexane/AcOEt = 9/1); $\tilde{\nu}$ = 2930.1, 1598.6, 1472.4, 1457.3, 1224.6, 1142.9, 1119.2, 1084.9, 1039.3, 1017.4, 836.2 (Si(CH_3)$_3$), 776.3 (Si(CH_3)$_3$), 555.8 (C-I) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (s, 1 H, Ar-*H*), 6.98 (s, 1 H, Ar-*H*), 6.68 (s, 1 H, Ar-*H*), 6.02 (ABq, 2H, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 1.1 Hz, O-C*H*$_2$-O), 4.30 (ABq, 2H, $\Delta\delta_{AB}$ = 0.08, J_{AB} = 14.0 Hz, Ar-C*H*$_2$-OTBS), 3.92 (s, 3 H, Ar-OC*H*$_3$), 3.88 (s, 3 H, Ar-OC*H*$_3$), 3.73 (s, 3 H, Ar-OC*H*$_3$), 0.92 (s, 9 H, C(C*H*$_3$)$_3$), 0.04 (s, 3 H, C*H*$_3$), 0.02 (s, 3 H, C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.44 (C_{IV}, *C*^{Ar}), 150.83 (C_{IV}, *C*^{Ar}), 148.47 (C_{IV}, *C*^{Ar}), 147.85 (C_{IV}, *C*^{Ar}), 140.73 (C_{IV}, *C*^{Ar}), 135.07 (C_{IV}, *C*^{Ar}), 134.98 (C_{IV}, *C*^{Ar}), 128.64 (C_{IV}, *C*^{Ar}), 118.32 (*C*H^{Ar}), 110.54 (*C*H^{Ar}), 105.20 (*C*H^{Ar}), 101.86 (O-*C*H$_2$-O), 89.66 (C_{IV}, *C*-I), 62.74 (Ar-*C*H$_2$-OTBS), 61.14 (Ar-O*C*H$_3$), 61.02 (Ar-O*C*H$_3$), 55.92 (Ar-O*C*H$_3$), 26.08 (C(*C*H$_3$)$_3$), 18.48 (C_{IV}, *C*(CH$_3$)$_3$), -5.10 (Si-*C*H$_3$), -5.15 (Si-*C*H$_3$) ppm; $C_{23}H_{31}IO_6Si$ (558,09): calcd. C 49.46, H 5.60, found C 49.84, H 5.61.

(a*R*)- and (a*S*)-6-(6-{[(*tert*-butyldimethylsilyl)oxy]methyl}-2,3,4-trimethoxyphenyl)-2*H*-1,3-benzodioxole-5-carbaldehyde (3 and *ent*-3)

Under an argon atmosphere, a solution of *tert*-butyllithium (5 equiv., 1.5 M in pentane) was added to dry THF (0.2 M) at -78 °C. This solution was cooled down to -100 °C after 10 min stirring. A solution of the desired atropoenantiomer of the silylated alcohol **14** (1 equiv.) in dry THF (0.2 M) was cooled down to -100 °C and was then cannulated onto the first one at -100 °C. The mixture was stirred for 10 min at this temperature before being quickly quenched with dry dimethylformamide (15 equiv.). The mixture was stirred for 30 min from -100 °C to RT. Saturated aqueous NH_4Cl was added and the mixture was extracted thrice with Et_2O. The organic layers were combined, washed thrice with water, dried over Na_2SO_4, filtrated and concentrated under vacuum. The crude was purified by flash chromatography on silica gel, eluting with a cyclohexane/AcOEt mixture, to give the purified aldehyde as a colorless oil. The enantiomeric ratio of the product was determined by chiral HPLC on a Chiralpak IB column (hexane/isopropanol = 95/5; 0.5 mL/min; t_R = 11.40 min (a*S*), 11.94 min (a*R*)).

3a (a*R*): yield = 204 mg (0.44 mmol, 85 %, *e.r.* > 99:1) from **14a** (290 mg, 0.52 mmol); $[\alpha]_D^{20}$ = - 2.8 (c = 1, CH_2Cl_2)

3b (a*S*): yield = 166 mg (0.36 mmol, 81 %, *e.r.* > 99:1) from **14b** (250 mg, 0.45 mmol); $[\alpha]_D^{20}$ = + 2.6 (c = 1, CH_2Cl_2)

R_f = 0.12 (cyclohexane/AcOEt = 9/1); $\tilde{\nu}$ = 2930.8, 1682.5 (C=O), 1612.2, 1598.2, 1475.4, 1462.3, 1239.5, 1139.0, 1102.0, 1058.8, 1035.4, 996.4, 835.2 (Si(CH_3)$_3$), 776.7 (Si(CH_3)$_3$), 507.9 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.50 (s, 1 H, C*H*O), 7.46 (s, 1 H, Ar-*H*), 6.96 (s, 1 H, Ar-*H*), 6.67 (s, 1 H, Ar-*H*), 6.10 (ABq, 2 H, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 0.9 Hz, O-C*H*$_2$-O), 4.30 (ABq, 2 H, $\Delta\delta_{AB}$ = 0.09, J_{AB} = 13.2 Hz, Ar-C*H*$_2$-OTBS), 3.92 (s, 3 H, Ar-OC*H*$_3$), 3.87 (s, 3 H, Ar-OC*H*$_3$), 3.61 (s, 3 H, Ar-OC*H*$_3$), 0.87 (s, 9 H, C(C*H*$_3$)$_3$), -0.03 (s, 3 H, C*H*$_3$), -0.04 (s, 3 H, C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 190.46 (*C*HO), 153.73 (C_{IV}, *C*^{Ar}), 152.38 (C_{IV}, *C*^{Ar}), 151.35 (C_{IV}, *C*^{Ar}), 148.05 (C_{IV}, *C*^{Ar}), 140.90 (C_{IV}, *C*^{Ar}), 137.20 (C_{IV}, *C*^{Ar}), 135.54 (C_{IV}, *C*^{Ar}), 129.65 (C_{IV}, *C*^{Ar}), 121.75 (C_{IV}, *C*^{Ar}), 110.95 (*C*H^{Ar}), 106.39 (*C*H^{Ar}), 106.07 (*C*H^{Ar}), 102.20 (O-*C*H$_2$-O), 62.96 (Ar-*C*H$_2$-OTBS), 61.06 (Ar-O*C*H$_3$), 60.96 (Ar-O*C*H$_3$), 56.04 (Ar-O*C*H$_3$), 25.98 (C(*C*H$_3$)$_3$), 18.42 (C_{IV}, *C*(CH$_3$)$_3$), -5.29 (Si-*C*H$_3$), -5.33 (Si-*C*H$_3$) ppm; HRMS ESI *m/z* $[M+Na]^+$ calcd. for $C_{24}H_{32}NaO_7Si$: 483.1815, found 483.1810.

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Keywords: Aryne • Asymmetric synthesis • Transition metal-free • Organolithium • Chirality

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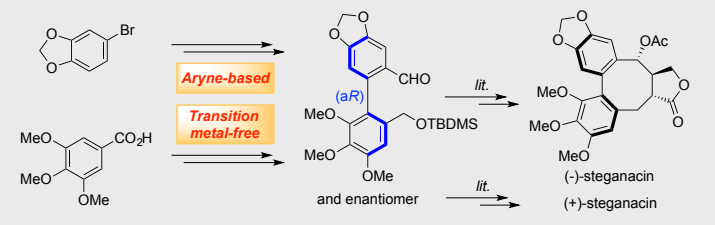

The formal synthesis of both enantiomers of a natural axially chiral biaryl, steganacin with excellent enantiomeric ratio and without transition metals is presented.

Transition metal-free synthesis

David Augros, Boubacar Yalcouye, Sabine Choppin, Matthieu Chessé, Armen Panossian and Frédéric R. Leroux**

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Transition metal-free synthesis of a known intermediate in the formal synthesis of (-)-steganacin