A Novel 1,3-Central-to-Axial Chirality Induction Approach to Cyclooctadiene Lignans

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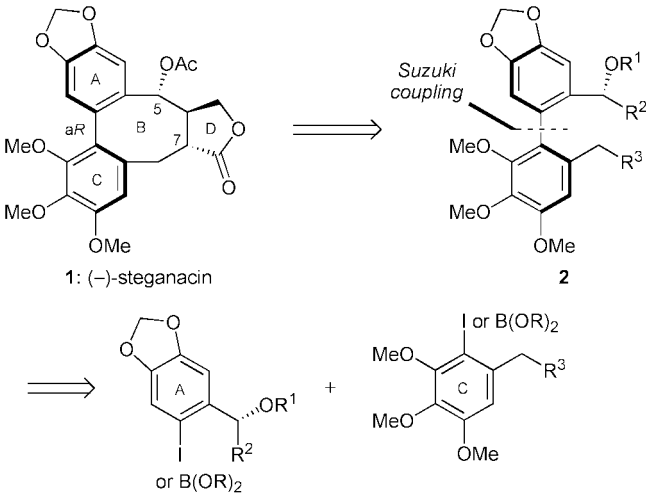
Received 16 July 2003

Abstract: The catalytic asymmetric synthesis of an axially chiral biaryl, potentially useful intermediate in the synthesis of dibenzocyclooctadiene lignans, has been performed. The key step consisted of a diastereoselective Suzuki coupling between a chiral benzylic alcohol and a sterically hindered boronic ester. The 1,3-induction from the benzylic stereocenter to the biaryl axis proceeded with very good diastereoselectivity.

Keywords: axial chirality, Suzuki coupling, chirality induction, cyclooctadiene lignans

Axially chiral biaryls are found in a number of different living organisms and exhibit a great variety of biological activities.[1] These activities are often restricted to one atropisomeric form, and several atroposelective synthetic methodologies have been proposed in order to obtain the bioactive atropisomer.[1,2] Dibenzocyclooctadiene lignans are axially chiral biaryls bridged by a median ring possessing several stereocenters.[3] Among these, (–)-steganacin **1** (Scheme 1) shows antitumor properties originating in the inhibition of microtubule assembly. Several enantioselective syntheses of (–)-steganacin and the related C-5 ketone (–)-steganone have been described via: (a) enantioselective construction of the butyrolactone D-ring and subsequent intramolecular oxidative[4] or intermolecular reductive[5] biaryl coupling; (b) intermolecular diastereoselective biaryl coupling, either following the Meyers chiral oxazoline method,[6] or using a Suzuki coupling with a chiral chromium tricarbonyl-complexed aryl halide,[7] followed by construction of B-D rings. In spite of their efficiency and elegance, the intermolecular coupling approaches necessitate the introduction and removal of a stoichiometric chiral auxiliary. Diastereoselective[8] and enantioselective[9] Suzuki biaryl couplings using chiral phosphines, which have recently been used in other contexts, could provide a straightforward control of the axial chirality in the stegane series. An alternative approach would involve a diastereoselective Suzuki coupling using achiral ligands through chirality induction of the axial configuration by a pre-existing stereocenter such as C-5. Such a method was employed by Lipschutz in his approach to korupensamine A, observing a complete 1,4-induction from a stereocenter attached to a phosphine ligand.[10] In addition, Nicolaou obtained a 33% de using a chiral boronic acid in the Suzuki coupling step of the vancomycin total synthesis.[11]

Our own asymmetric approach to stegane lignans is illustrated in Scheme 1. (–)-Steganacin **1** could arise from a non-bridged precursor **2**, bearing a stereogenic benzylic carbon atom, via construction of the B-D ring system, and **2** could be obtained by a diastereoselective Suzuki coupling. According to our recent work on the palladium(0)-catalyzed synthesis of antimitotic bridged biaryls,[12] the Suzuki coupling should be more efficient if the boronic ester function is placed on the correct ring, presumably ring C. In order to determine the optimal substitution pattern (R^1–R^3) and Suzuki coupling conditions, several precursors were synthesized. With the choice of these precursors, the chemical compatibility of functional groups with the Suzuki coupling conditions and the steric hindrance of *ortho* substituents (R^1–R^3) were taken into account.

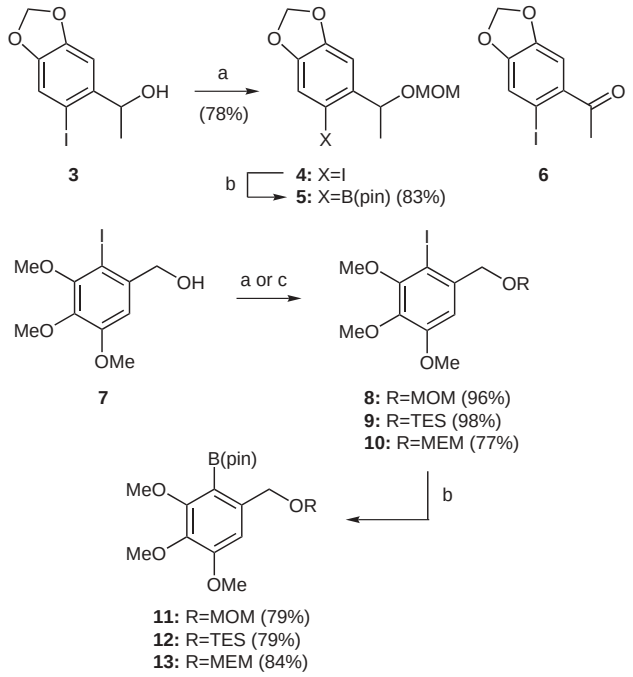


Scheme 1

The A-ring building block **3**[13] was obtained from commercially available 3,4-methylenedioxyacetophenone in 77% yield by $NaBH_4$ reduction and regioselective iodination (I_2, CF_3CO_2Ag)[14] (Scheme 2). This secondary alcohol was protected with a MOM group and submitted to our modified Pd(0)-catalyzed borylation conditions[15] to give the corresponding sterically hindered boronic ester **5** in good yield. Ketone **6** was obtained by PCC oxidation of **3**.[13] C-Ring building blocks were synthesized from the known iodide **7** (Scheme 2).[13] After introduction of a

SYNLETT 2003, No. 13, pp 2009–2012
Advanced online publication: 08.10.2003
DOI: 10.1055/s-2003-42039; Art ID: D17603ST.pdf

MOM (compound **8**), TES (compound **9**) or MEM (compound **10**) protecting group, the borylation was performed as above in good yield in spite of the steric hindrance, giving boronic esters **11**–**13**.

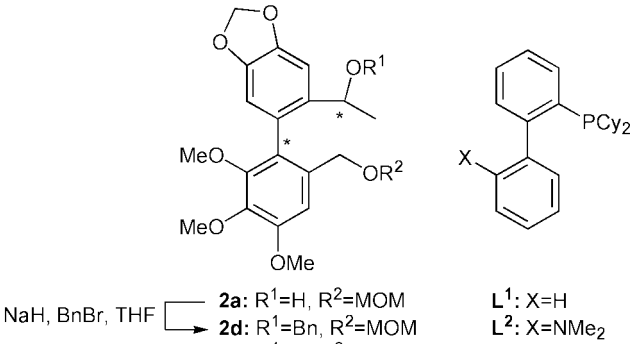


Scheme 2 *Reagents and conditions*: a. MOMCl or MEMCl (2 equiv), EtN(*i*-Pr)$_2$ (3 equiv), CH_2Cl_2; 0 °C to 25 °C, 15 h; b. (pin)BH (2 equiv), Et_3N (3 equiv), Pd(OAc)$_2$ (5 mol%), PCy$_2$(*o*-biph) (10 mol%), dioxane, 80 °C, 30 min; c. TESOTf (1.2 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0 °C to 25 °C, 30 min. pin = pinacol, PCy$_2$(*o*-biph) = 2-(dicyclohexylphosphino)biphenyl

The Suzuki coupling reaction between these A-ring and C-ring synthons was subsequently examined (Table 1). Boronic esters and iodides were initially coupled using our standard conditions,[12,15] in the presence of barium hydroxide, palladium acetate and biphenyl ligand **L**^{1} or **L**^{2},[16] in dioxane–water. Indeed we found that the combination of this particular base and catalyst gives good yields and short reaction times with sterically hindered substrates.

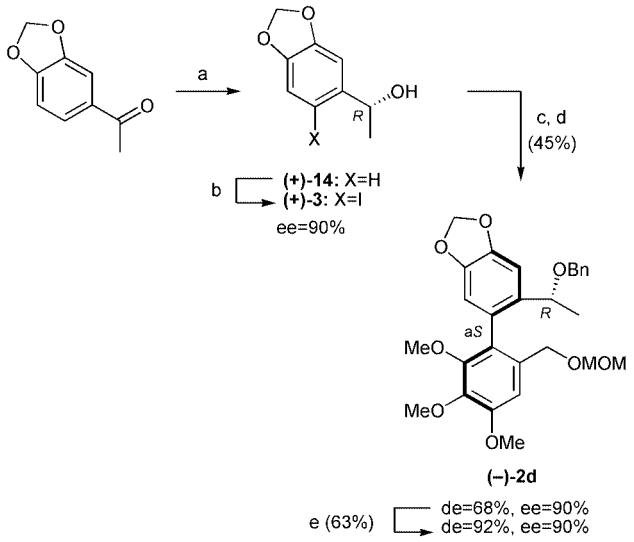
The coupling of ring A boronic ester **5** with ring C iodide **7** (entry 1) gave only protodeiodinated or protodeboronated products, as gave other coupling trials in this sense. When the sense of the reaction was reversed, starting from an A-ring iodide and a C-ring boronate, the desired biphenyls were formed in low to moderate yields (entries 2–7). The coupling of boronate **11** with iodide **3** in the presence of ligand **L**^{1} (entry 2) gave the coupling product **2a** in ca 50% yield, as an inseparable mixture with the pinacol. For purification and analysis purposes, the less polar biphenyl **2d** was synthesized by treatment with NaH and benzyl bromide, in 38% isolated yield from iodide **3**. Examination of the ^{1}H NMR spectra of **2a**,**d** indicated a 84:16 mixture of two diastereoisomers (68% de), resulting from a chirality induction from the benzylic position to the biaryl axis. Heating **2d** in DMSO-d_6 up to 140 °C did not modify the diastereomeric ratio, which indicates that this compound has a high atropisomerization energy barrier. The yield of the Suzuki coupling was improved using biphenyl ligand **L**^{2} (entry 3), giving **2d** in 53% isolated yield after benzylation, with identical diastereoselectivity. When the more sterically hindered boronate **12** was coupled to iodide **3** (entry 4) in the presence of ligand **L**^{1}, the desired biphenyl **2b** was obtained in low yield (ca. 15%), together with the protodeiodinated by-product. In order to resolve this mixture, the TES group was removed with TBAF giving diol **2e** in 10% isolated yield from **3** and as a single diastereoisomer. The use of ligand **L**^{2} instead of **L**^{1} (entry 5) again gave an improved yield of 31% for **2e**, also with complete diastereoselectivity. The coupling of MEM-protected boronate **13** with iodide **3** (entry 6) furnished, after protection with BnBr, the corresponding biphenyl **2f** in 31% yield and with a 70% de. This result indicates that a subtle adjustment of the size of the R^2 group is necessary to combine a satisfying yield with a high diastereoselectivity. Finally, the coupling between boronate **11** and ketone **6** (entry 7) gave less than 10% yield of the corresponding biphenyl, indicating that the presence of the alcohol group is crucial. Other coupling trials with

Table 1 Suzuki Coupling Study to Form the A-C Ring System of Steganes[a]



Entry	Boronate	Iodide	Ligand	Product	Yield (%)[b]	de (%)[c]
1	**5**	**7**	**L**^{1}		0	
2	**11**	**3**	**L**^{1}	**2d**	38	68
3	**11**	**3**	**L**^{2}	**2d**	53	68
4	**12**	**3**	**L**^{1}	**2e**	10	>96
5	**12**	**3**	**L**^{2}	**2e**	31	>96
6	**13**	**3**	**L**^{2}	**2f**	31	70
7	**11**	**6**	**L**^{1}		<10	

[a] *Reagents and conditions*: iodide (1 equiv), boronic ester (1.5 equiv), Pd(OAc)$_2$ (5 mol%), **L**^{1} or **L**^{2} (10 mol%), Ba(OH)$_2$ (2 equiv), dioxane–water (9:1), 100 °C, 1 h.
[b] Isolated yield for 2 steps.
[c] Diastereomeric ratio, from ^{1}H NMR.



Scheme 3 *Reagents and conditions*: a. (*S*)-2-Methyl-CBS-oxazaborolidine (10 mol%), $BH_3{\cdot}SMe_2$ (1.0 equiv), CH_2Cl_2, –20 °C, 5 h; b. I_2 (1.05 equiv), CF_3CO_2Ag (1.05 equiv), $CHCl_3$, 0 °C, 15 min; c. (+)-**3** (1.0 equiv), **11** (1.5 equiv), $Pd(OAc)_2$ (5 mol%), $\mathbf{L^2}$ (10 mol%), $Ba(OH)_2$ (2 equiv), dioxane–water 9:1, 100 °C, 1 h; d. NaH (1.5 equiv), BnBr (1.5 equiv), THF, 25 °C, 4 h; e. crystallization from heptane

bulkier boronic acids and iodides failed, giving only protodeiodinated or deboronated products.

At this stage, the question regarding the relative configuration at both stereogenic elements had to be addressed. The Suzuki coupling was repeated starting with alcohol **3** in an enantiomerically enriched form (Scheme 3). The catalytic enantioselective reduction of 3,4-methylenedioxyacetophenone with (*S*)-CBS-oxazaborolidine[17] gave alcohol (+)-**14** which was converted to iodide (+)-**3** in 59% overall yield and 90% ee as determined by chiral HPLC.[18] The absolute (*R*) configuration of (+)-**14** was deduced from literature data.[19] The Pd(0)-catalyzed coupling of (+)-**3** and **11** proceeded as before to give biphenyl (–)-**2d** after benzyl protection in 45% yield and 68% de. Crystallization from heptane afforded compound (–)-**2d** in 92% de and 90% ee as measured by chiral HPLC.[20]

Crystals of (–)-**2d** suitable for X-ray analysis were obtained after slow crystallization from EtOH. The analysis of the X-ray diffraction data provided evidence for the (*R*, a*S*) absolute configuration of the molecule (Figure 1).[21] In the crystal, proton H-19 eclipses the biaryl axis, which is probably the more sterically favored arrangement for subsituents at C-19. ROESY correlations (Figure 1) were in agreement with the solid-state structure. NOESY experiments conducted with racemic diol **2e** showed similar 2D correlations, arguing for the same (*R*, a*S*) relative configuration.

From this, it can be deduced that the enantiomer (–)-**3** should be employed instead of (+)-**3** in the Suzuki coupling step in order to obtain the (a*R*) configuration of natural (–)-steganacin.

A tentative explanation for the diastereoselectivity observed in the Suzuki coupling between **3** and **11**–**13** is illustrated in Figure 2. The oxidative insertion of the palladium complex in the C–I bond of **3** could give, under basic reaction conditions, the oxapalladacycle complex **A**.[22] The transmetalation by the 'ate' complex **B** should occur with the bulky C-16 substituent (R^2 = MOM, MEM, TES) taking position in the face opposite to the C-20 methyl group. This would furnish *trans*-palladium complex

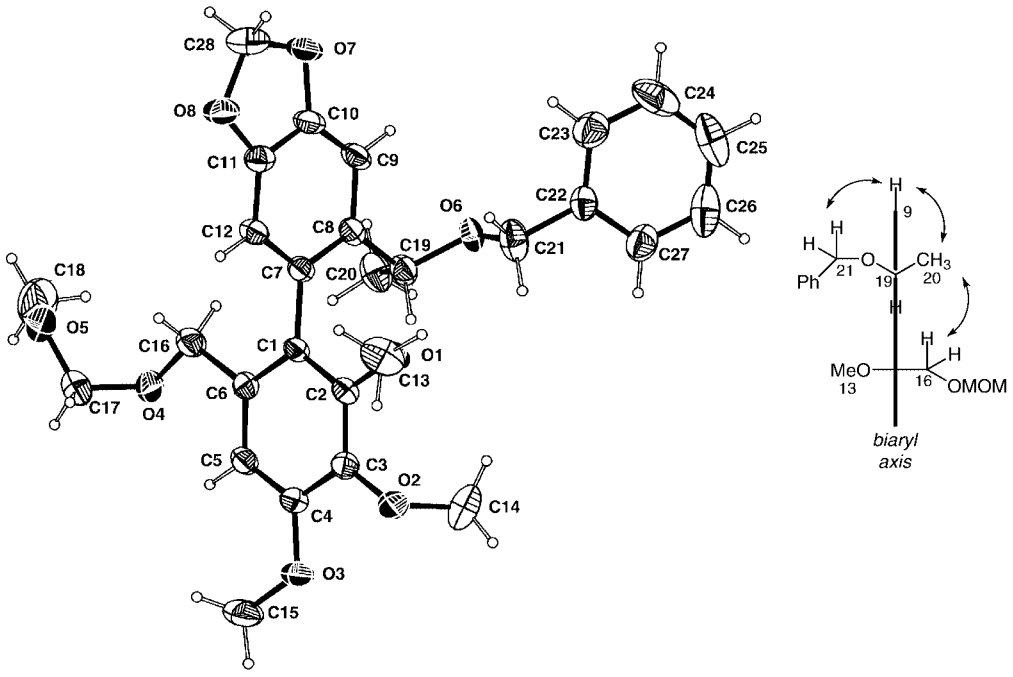


Figure 1 X-ray crystal structure (left) and selected ROESY correlations (right) of biphenyl (–)-**2d**

C and, after isomerization to the *cis* complex and reductive elimination, biphenyls **2a**–**c** having the (*R*, a*S*) relative configuration. The transmetalation of **B** in the opposite orientation, i.e. with the C-16 substituent in the same face as the C-20 methyl group, which would furnish **2a**–**c** with the (*R*, a*R*) relative configuration, should be disfavored. This model accounts in particular for the better diastereoselectivity observed with boronate **12** having a bulkier protecting group than **11**.

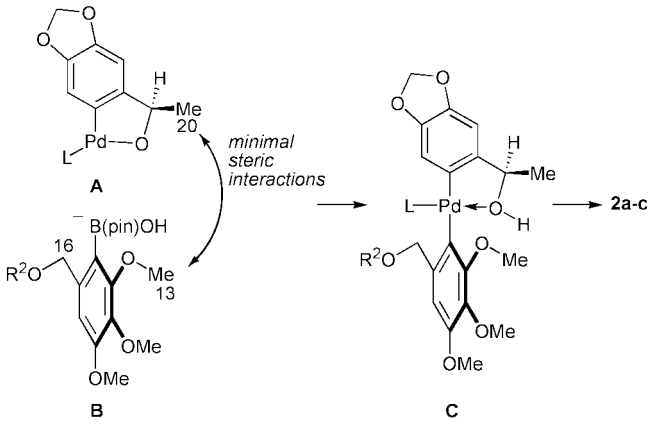


Figure 2 Proposed stereochemical course of the Suzuki coupling

In conclusion, a novel atropo-diastereoselective Suzuki coupling has been discovered in the synthesis of biaryl lignans. In this process, a 1,3-chirality induction was performed from an oxygen-bearing benzylic stereogenic center to the biaryl axis. This benzylic stereocenter was in turn generated by a catalytic enantioselective reduction. Therefore, this methodology provides a unique catalytic asymmetric access to axially chiral molecules having a benzylic stereocenter. The elaboration of stegane-type dibenzocyclooctadiene lignans using these findings will be reported in due course.

Acknowledgment

We thank M.-T. Adeline and B. Dumontet for HPLC analyses and Dr. M.-T. Martin for NMR experiments. This work was financially supported by the Centre National de la Recherche Scientifique (CNRS).

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(18) (+)-**3**: $[\alpha]_D^{23}$ +38.8 (*c* 1.1, $CHCl_3$); HPLC (Chiracel OD, hexane–EtOH, 95:5, 1.0 mL/min) t_R 7.8 min (minor enantiomer), 9.2 min (major enantiomer).

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(20) Compound (–)-**2d**: mp 70 °C; $[\alpha]_D^{24}$ –21.4 (*c* 1.0, $CHCl_3$); HPLC (C_{18} Symmetry column, H_2O–CH_3CN, 35:65, 1.0 mL/min) t_R 16.6 min (diastereoisomer 1, 4%), 17.9 min (diastereoisomer 2, 96%); HPLC (Chiralpak AD, heptane–*i*-PrOH, 98:2, 1.0 mL/min) diastereoisomer 2: t_R 10.8 min (enantiomer 1, 5%), 24.5 min (enantiomer 2, 95%), diastereoisomer 1: t_R 11.4 min (enantiomer 1, 95%), 13.0 min (enantiomer 2, 5%). ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ = 1.15 (d, *J* = 6.3 Hz, 3 H), 3.23 (s, 3 H), 3.61 (s, 3 H), 3.74 (s, 3 H), 3.89 (s, 3 H), 4.15 (d, *J* = 12.0 Hz, 1 H), 4.21 (d, *J* = 12.0 Hz, 1 H), 4.25 (q, *J* = 6.5 Hz, 1 H), 4.33 (d, *J* = 12.3 Hz, 1 H), 4.45 (d, *J* = 12.3 Hz, 1 H), 4.57 (s, 2 H), 6.04 (s, 1H), 6.06 (s, 1 H), 6.63 (s, 1 H), 6.98 (s, 1 H), 7.12 (s, 1 H), 7.20–7.32 (m, 5 H) (major diastereoisomer). ^{13}C NMR [75.5 MHz, $(CD_3)_2CO$] δ = 23.9, 55.3, 56.2, 60.9, 61.0, 67.7, 70.8, 74.9, 96.7, 102.1, 105.9, 108.7, 111.0, 126.6, 127.7, 127.9, 128.5, 128.9, 133.5, 138.4, 140.7, 142.5, 147.2, 148.6, 151.2, 154.1 (major diastereoisomer). HRMS (ESI): *m*/*z* for $[(M + Na)^+]$ calcd for $C_{28}H_{32}NaO_8$: 519.1995; found: 519.1982.

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