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Towards the enantioselective synthesis of axially chiral cyclic bis(bibenzyls) through sulfoxide-controlled diastereoselective Suzuki coupling

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ABSTRACT

Natural macrocyclic bis(bibenzyls) exhibiting configurationally stable axially chiral biaryls are of high interest from a structural as well as from a synthetic point of view. An enantiopure sulfinyl auxiliary controlling an atropo-diastereoselective biaryl Suzuki coupling reaction has been investigated and promising results for the preparation of the biaryl moiety of cyclic bis(bibenzyls) like isoplagiochins C or D have been obtained. Furthermore, models explaining the stereoselectivity during transition state, and substitution effects including double stereo-differentiation, were discussed.

1. Introduction

'Bis(bibenzyls)' are phenolic natural products that can be isolated with broad diversity from bryophytes.[1] The biosyntheses originate from bibenzyl units[2] which can be dimerized and cyclized by formation of biaryl (C–C) or biarylether bonds (C–O–C). The distribution in liverworts, structure elucidation, and numerous biological activities have been reviewed.[3,4] In this large family of bis(bibenzylic) macrocycles, a twofold C–C connection of two bibenzyl units leads to a subtype represented by isoplagiochin C (**1**)[5] and its dihydro analogue isoplagiochin D (**2**), with two biaryl axes ***a***/***b*** (Fig. 1). The occurrence of axial and/or planar chirality in the series of these macrocyclic bis(bibenzyls) has been discussed earlier[6,7] including for similar representatives containing one biaryl unit and one biaryl ether moiety as in plagiochin G (**3**)[8] as well as for the unique condensed structure of cavicularin (**4**).[9]

The existence of configurationally stable atropisomers as a consequence of axial chirality (two biaryl axes, helical elements) together with ring strain for **1** was first discussed in detail by us[10] and also for its dihydro analogue **2**.[11] For both, the absolute

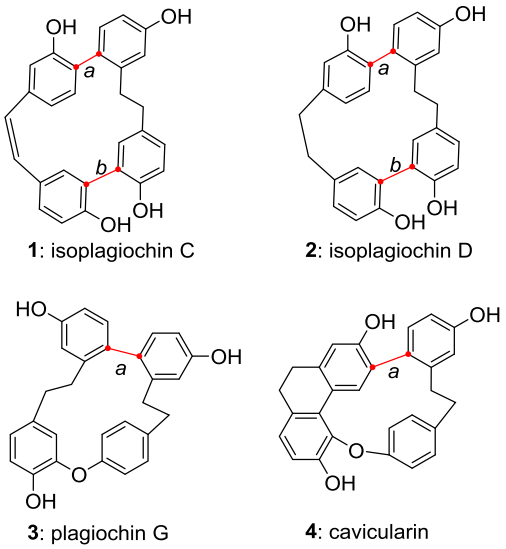

Fig. 1. Cyclic bis(bibenzyls) with axial and/or planar chirality.

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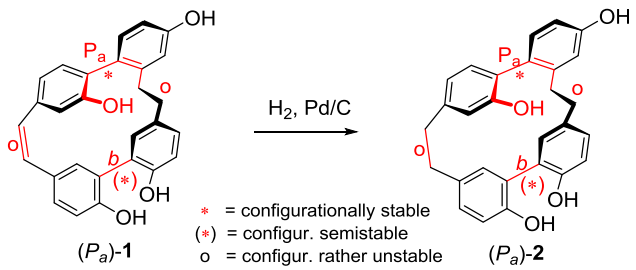
configuration of the natural compound at the stereochemically stable biaryl axis ***a*** (rotational barrier ~ 102 kJ/mol) was determined by quantum chemical CD calculations combined with HPLC-CD coupling[12] of natural and synthetic (racemic) probes (Scheme 1).



Scheme 1. Absolute configuration and chemical correlation of (−)-(**1**) extracted from *Plagiochila deflexa* and (−)-(**2**) extracted from *Bazzania trilobata*.

Two additional aspects are important with respect to synthesis, especially for enantioselective ones: (1) The biaryl axis ***a*** with two *ortho*-substituents is configurationally stable only because of the entire cyclic framework. That means, to ensure conformational stability, an atroposelective formation of this C–C bond must proceed as ring closing step or additional atropo-stabilising *ortho*-substituents are required in open-chained precursors to be removed after cyclization. (2) The biaryl axis ***b*** with two smaller *ortho*-hydroxy substituents is conformationally semistable at ambient temperature (no stable atropo-diastereomers). In case of two methoxy substituents at this position, however, the rotational barrier was determined as ~ 66 kJ/mol causing rotamers detectable at room temperature NMR.[13] Nevertheless, this axis together with more flexible helical elements at the stilbene or ethylene bridge enhance the stability of axis ***a***.

Many members of the bis(bibenzyl) family have been synthesized; the routes and strategies have been recently reviewed.[14] Ring closure proved to be the main challenge because efficiency depends on ring strain, substitution pattern, and concomitant dimerization. In the total syntheses already described for isoplagiochins C (**1**) and D (**2**) or derivatives, ring closure was realized by (a) Wittig reaction,[15] (b) McMurry reaction,[16] both between ring moieties **A** and **D**, (c) Suzuki-Miyaura coupling[17] between **C** and **D**, and otherwise (d) Heck coupling (including asymmetric) between **B** and **C**[18] (Fig. 2).

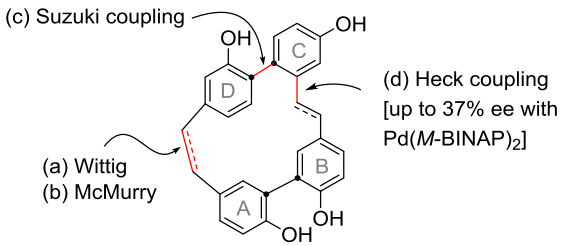


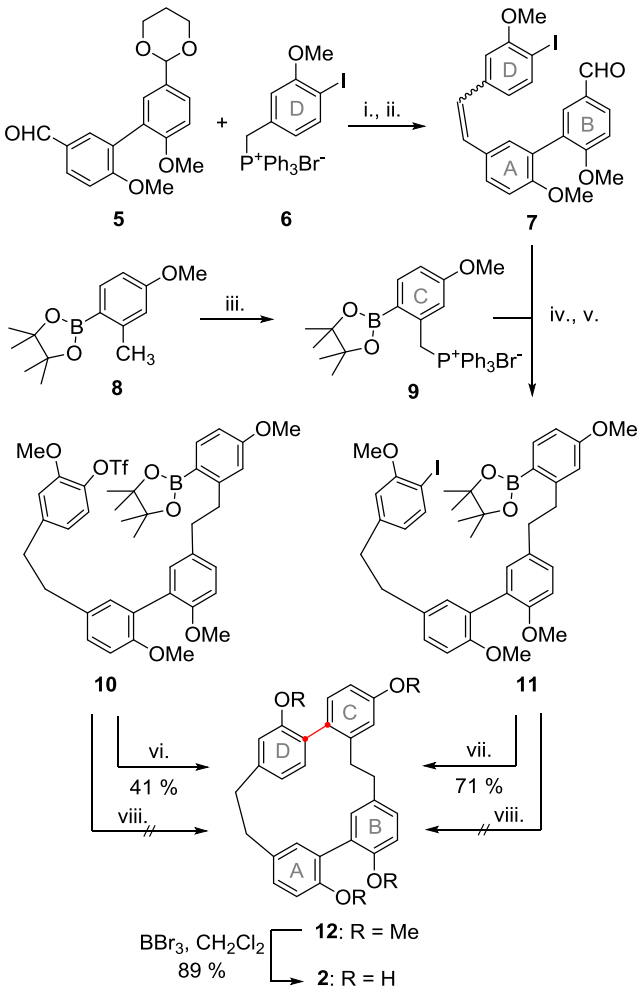
Fig. 2. Ring closing strategies for the total synthesis of isoplagiochins (**1**,**2**).

2. Results and discussion

The directed synthesis of enantiopure chiral biaryls has become a challenging tool in organic synthesis.[19] Whereas our previous effective Wittig and McMurry procedures (Fig. 2, connections (a) and (b)) in general lack of enantioselective protocols, we realized (Fig. 2, connection (d) the first atroposelective Heck-cyclization and the first enantioselective approach in the bis(bibenzyl) family, though with moderate ee.[18]

No attempt for an enantioselective approach were mentioned by Esumi et al. in the total synthesis of **2** by a ring closing Suzuki coupling (Fig. 2, connection (c)) from a precursor **10**.[17] Indeed, seminal catalytic enantioselective Suzuki conditions developed concomitantly in 2000 by Buchwald[20] and Cammidge[21] mainly deal with rather simple substrates. Actually described conditions are not a generally approved method to insure the required steric crowding of both coupling partners due to the harsh temperature. To overcome this difficulty, different classes of both mono- and bidentate ligands and Pd-complexes were developed in the past 15 years.[22]

We could successfully reproduce Esumi's general '*racemic*' strategy with **10** or a similar new precursor **11** with 41 and 71% yield, respectively. Deprotection with BBr_3 gave rise to (+/−) isoplagiochin D (**2**) in good yield. However, the up to now best protocol introduced by Buchwald et al.[20] to perform atroposelective Suzuki-Miyaura cross-coupling reaction failed in the presence of the chiral catalyst (*P*)-KenPhos (no conversion or racemic mixtures, see Scheme 2). The open-chained precursor **11** was prepared starting with a known biaryl unit A–B **5**,[15] and a twofold Wittig reaction with a D-unit **6**[18] and a new C-unit **9** (obtained from **8**[23]).



Scheme 2. Attempts to synthesize **2** by intramolecular Suzuki-Miyaura coupling. Reaction conditions: i. K_2CO_3, 18-crown-6, CH_2Cl_2, Δ, 90%; ii. THF, 2 M HCl, 96%; iii. NBS, AIBN, CCl_4, Δ, then Ph_3P, toluene, Δ, 81%; iv. K_2CO_3, 18-crown-6, CH_2Cl_2, Δ, 67%; v. *p*-$TosNHNH_2$, DME, NaOAc, Δ, 84%; vi. $Pd(PPh_3)_4$, K_3PO_4, DMF, 80 °C, 12 h;[17] vii. $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O, 105 °C, 16 h; viii. $Pd_2(dba)_3$, (*P*)-KenPhos, K_3PO_4, toluene, DMF, 80–155 °C, 16–48 h (no conversion or racemate only).

An alternative solution to perform stereoselective biaryl couplings is to introduce a chiral auxiliary on one of the coupling partners. Atropo-diastereoselective Suzuki-Miyaura coupling reactions[19] were initially performed using a planar-chiral chromium complex as chiral coupling partner[24] (chirality transfer planar → axial). Further, a carbon stereogenic center (benzylic alcohols or the

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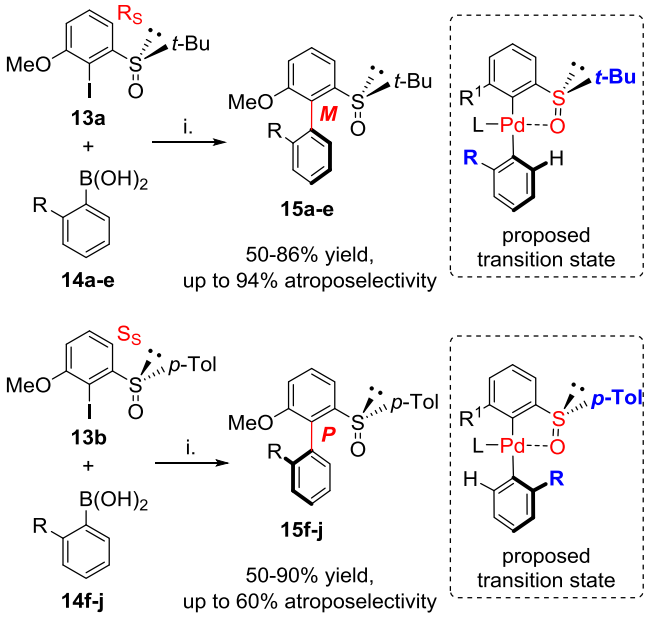
β-hydroxy *p*-tolylsulfinyl group next to the coupling position) proved to be efficient chiral auxiliaries (centro → axial).[25] In 2009, the *t*-butylsulfinyl group directly connected in *ortho* position of aromatic iodides was found to act as an efficient chiral auxiliary allowing the Suzuki-Miyaura coupling of *ortho, ortho'*-disubstituted aryl iodides (e.g., **13a**) with *ortho*-substituted aryl boronic acids **14a**–**e** (Scheme 3) in high yields and atropo-diastereoselectivities.[26] A five-membered palladacycle in which the oxygen atom of the sulfoxide coordinates to palladium is proposed to explain the stereocontrolled transmetallation or a stereodiscriminant reductive elimination. Minimization of steric hindrance led to the formation of the *M* atropisomers **15 a**–**e**. The use of the *p*-tolylsulfinyl group with opposite configuration at sulfur resulted in formation of the *P* atropisomers **15f**–**j**, though in decreased atropo-diastereoselectivities. The key advantages of sulfinyl group are to get it in enantiomerically pure form and to transform it into a myriad of functionalities. Actually, this chiral auxiliary can be readily removed from the products under conservation of the chiral information at the biaryl axis by sulfoxide/lithium exchange followed by electrophilic trapping (various electrophiles are compatible).[27]



Scheme 3. Atropo-diastereoselective Suzuki coupling with sulfinyl group as chiral auxiliary. Reaction conditions: i. $Pd(OAc)_2$, *S*Phos, Cs_2CO_3, dioxane/H_2O, 70 °C.

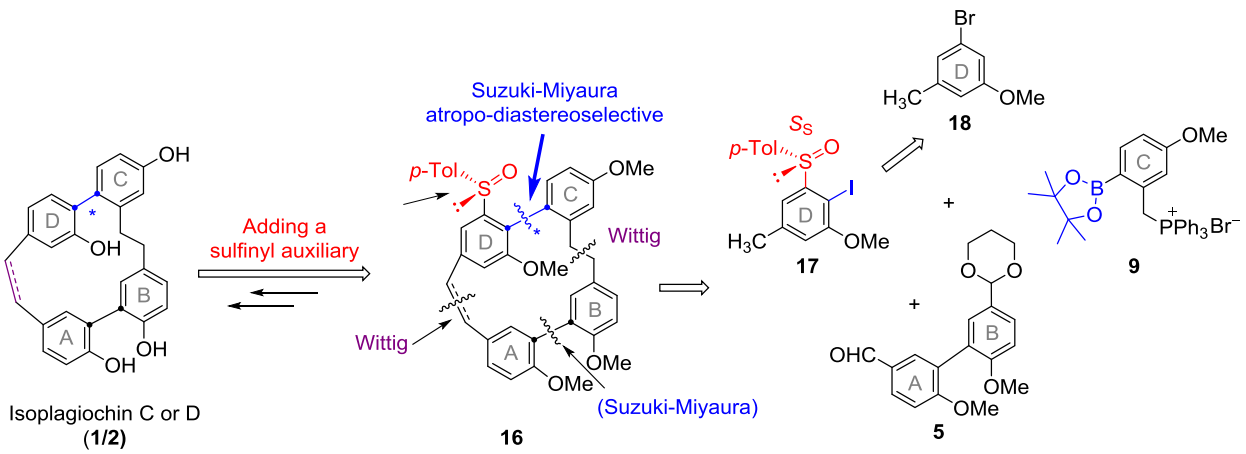
The excellent diastereoselectivities that we have observed in the formation of the biaryl axis prompted us to investigate whether the method developed would also be applicable to the enantioselective synthesis of the configurationally stable biaryl part of bis(bibenzyl) derivatives like isoplagiochins **1**/**2**. It should be noted that the sulfoxide auxiliary group (R=*p*-Tol) was already used in the synthesis of the bis(bibenzyl) riccardin C to accelerate a S_NAr reaction[28] and more recently in the synthesis of cavicularin (**4**) in a symmetrization/asymmetrization approach.[29]

Regarding the foregoing results, we propose the retrosynthetic approach described in Scheme 4. Final macrocyclization could occur by Wittig coupling reaction between rings A and D (most common in known isoplagiochin syntheses) followed by traceless removal of the sulfinyl group and demethylation which could give raise to enantiopure isoplagiochins **1** or **2**. The crucial construction of the C–D biaryl moiety would be considered using a chiral *ortho*-sulfinyl group on the aryl iodide **17** in order (1) to direct the intermolecular atropo-diastereoselective Suzuki-Miyaura cross coupling reaction between **17** and a moiety **9** and (2) to ensure the atropo-stability of this open-chained precursor for isoplagiochins. The aryl iodide **17** would be accessible from the known aryl bromide **18**, the A–B biaryl moiety **5** as twofold Wittig precursor could be taken from known synthesis[15] (see also Scheme 2).

Preliminary attempts (see below, Tables 1 and 3) of the atropo-diastereoselective C–D Suzuki-Miyaura cross-coupling reaction have been investigated with the enantiopure aryl iodide **17** bearing in *ortho* position the *p*-tolylsulfinyl auxiliary and arylboronic moieties **8** and **22** (bearing in *ortho* position either a methyl group or a protected aldehyde, both, in principle, suitable for further C–B coupling). Our objective was to study the Suzuki-Miyaura cross-coupling reaction conditions and to evaluate the atropo-diastereoselectivity.

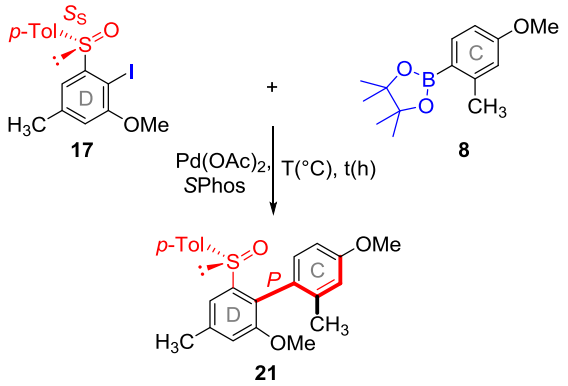
Firstly, we decided to introduce the enantiopure *p*-tolylsulfinyl auxiliary (instead of *t*-butyl-) since it is more easily obtained on multigrams scale from cheap and natural (−) menthol.[30] The D unit **17** is obtained by condensation of the Grignard reagent of methylanisyl bromide **18**[31] with (S_S)-menthyl *p*-toluenesulfinate **19**[30] giving enantiopure sulfoxide **20**, followed by ortholithiation with LDA and addition of diiodine (Scheme 5).

Next, we studied the Suzuki-Miyaura cross-coupling reaction between **17** and boronic ester **8** bearing in *ortho* position the methyl



Scheme 4. Retrosynthetic scheme for the synthesis of isoplagiochins **1**/**2**.

Table 1
Atropo-diastereoselective C–D Suzuki-Miyaura cross-coupling reaction between enantiopure aryl iodide **17** and methylanisyl boronic ester **8**



Entry	$Pd(OAc)_2$ [equiv]	*S*Phos [equiv]	Temp (°C)/time (h)	Yield (%) **21**[a]	dr[b]	de (%)
1	0.1	0.15	70/4	83	64:36	28
2	0.1	0.15	70/16	92	68:32	36
3	0.15	0.2	70/16	98	71:29	42
4	0.1	0.15	50/48	—	—	—
5	0.2	0.30	55/48	72	73:27	45
6	0.1	0.15	60/48	81	71:29	42
7	0.15	0.20	60/48	85	75:25	50

[a] Reaction conditions: Cs_2CO_3 (4 equiv), dioxane/H_2O, 1 mmol of substrate.
[b] Diastereomeric ratio determined by ^1H NMR spectra or by HPLC analysis.

Table 2
Screening for double stereo-differentiation[a]

Entry	Ligand [equiv]	Temp (°C)/time (h)	Yield (%) **21**	dr	de (%)
1	*S*Phos [0.2]	70/48	85	75:25	50
2	(*P*)-BINAP [0.15]	60/48	81	65:35	30[b]
3	(*P*)-BINAP [0.2]	70/48	91	65:35	30[b]
4	(*M*)-BINAP [0.15]	60/48	80	80:20	60[c]
5	(*M*)-BINAP [0.15]	70/48	91	77:23	54[c]
6	(*M*)-BINAP [0.2]	70/48	91	82:18	64[c]

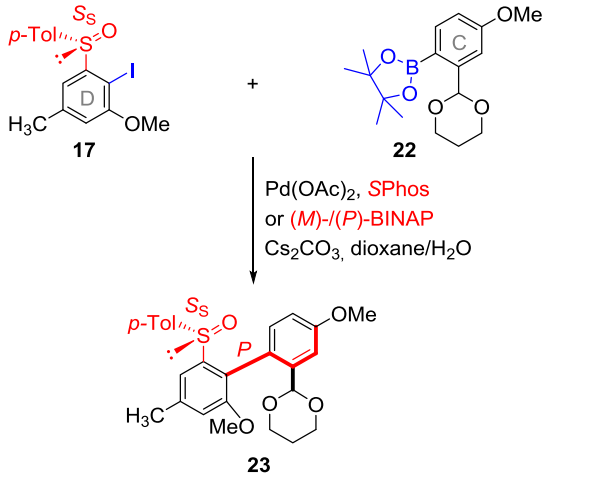
[a] Reaction conditions: $Pd(OAc)_2$ (0.1 equiv), Cs_2CO_3 (4 equiv), dioxane/H_2O, 1 mmol of substrate.
[b] Mismatched pair.
[c] Matched pair.

group (boronic acid gave similar results) (Table 1). As in our previous work,[26] the expected biaryl **21** was obtained with the optimized reaction conditions $Pd(OAc)_2$ (0.1 equiv), *S*Phos (0.15 equiv) and Cs_2CO_3 in dioxane/H_2O (entry 1) with a good 83% yield but a low selectivity of 64:36. A detailed screening of reaction conditions (reaction time, temperature and charge of palladium/ligand) revealed an optimum reaction temperature of 60 °C providing **21** in good yield (85%) and diastereoselectivity (75:25) (entries 2–7).

Furthermore, replacement of *S*-Phos as achiral Pd coordinating ligand by (*P*)- or (*M*)-BINAP clearly revealed a double stereo-differentiation with (*M*)-BINAP as 'matched pair' enhancing the diastereoselectivity up to 82:18 even at slightly higher temperature and with high yield (Table 2).

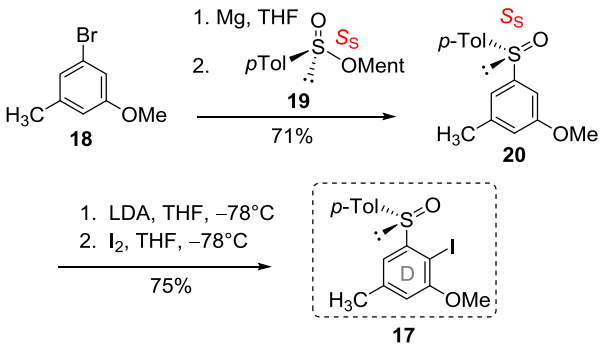
The diastereoselectivity observed in Suzuki-Miyaura cross-coupling reaction using a sulfinyl group as chiral auxiliary was discussed in our previous work.[26] Thus, oxidative insertion of the palladium atom into the C–I bond of the enantiopure aryl iodide **17** would give rise to the five-membered-ring palladacycle **17′** with Pd–O coordination for mainly geometrical reasons.[32] In presence of Cs_2CO_3, approach of the boronate **8** to the complex **17′** in the transmetalation step should take place with minimization of steric hindrance of the *p*-tolyl group in unit D and the *ortho*-substituent R in unit C. Reductive elimination would afford **21** with *P*-configuration of the biaryl axis deduced from the absolute

Table 3
Atropo-diastereoselective Suzuki-Miyaura cross-coupling between **17** and **22**



Entry	Ligand [equiv]	Temp (°C)/time (h)	Yield (%) **23**[a]	dr[b]	de (%)
1	*S*Phos [0.15]	70/16	84	99:1	98
2	(*M*)-BINAP [0.15]	70/16	68	99:1	98
3	(*P*)-BINAP [0.15]	70/16	70	99:1	98
4	none	70/16	—	—	—

[a] Reaction conditions: $Pd(OAc)_2$ (0.1 equiv), Cs_2CO_3 (4 equiv), dioxane/H_2O, 1 mmol of substrate.
[b] Diastereomeric ratio determined by ^1H NMR spectra or by HPLC analysis.



Scheme 5. Synthesis of enantiopure aryl iodide **17**.

configuration *Ss* of the sulfinyl group in accordance with our previous results[25] (Fig. 3).

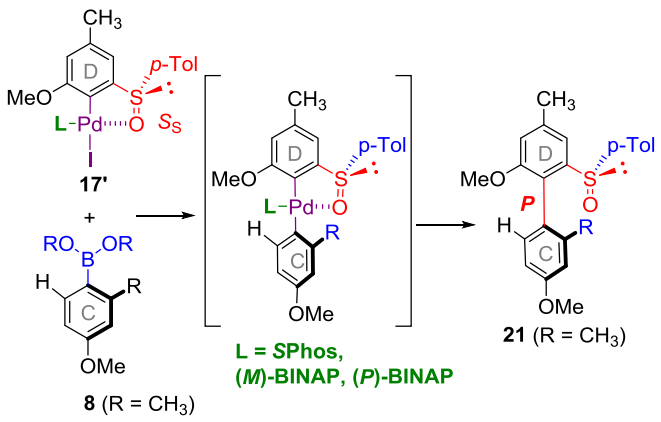


Fig. 3. Model explaining control of atropo-diastereoselectivity during the auxiliary controlled formation of **21**.

We also studied the Suzuki-Miyaura cross-coupling reaction between **17** and a C unit bearing a dioxolane group **22**[33] (Table 3). To our delight, a close to perfect atropo-diastereoselectivity (>99:1)[34] was observed for **23** even with *S*Phos as achiral ligand (Table 3, entry 1). This – according to Fig. 3 – might be due to the bulkier dioxanyl-substituent present in *ortho*-position. Surprisingly, no mismatched effect was observed using (*P*)-BINAP (entry 3). To rationalize the observed diastereoselectivity, we propose that an additional coordination dioxane-O→Pd can replace the external ligand ensuring a higher stereodiscrimination (Fig. 4). Nevertheless, *S*Phos is necessary at least for the oxidative addition step (compare entry 4).

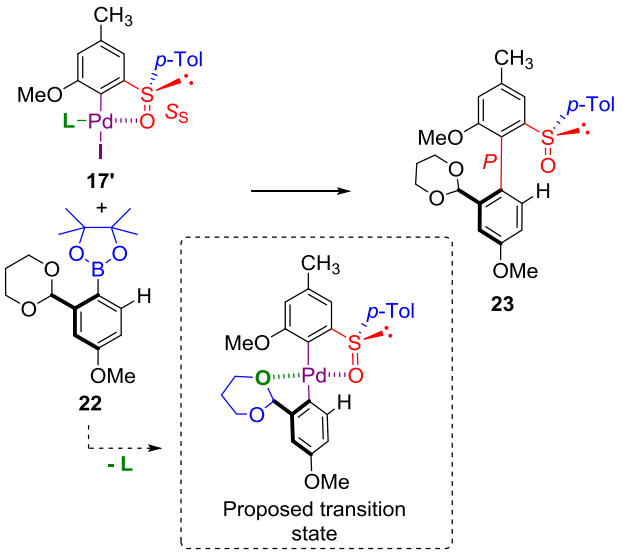


Fig. 4. Proposed TS during the sulfinyl-controlled formation of **23**.

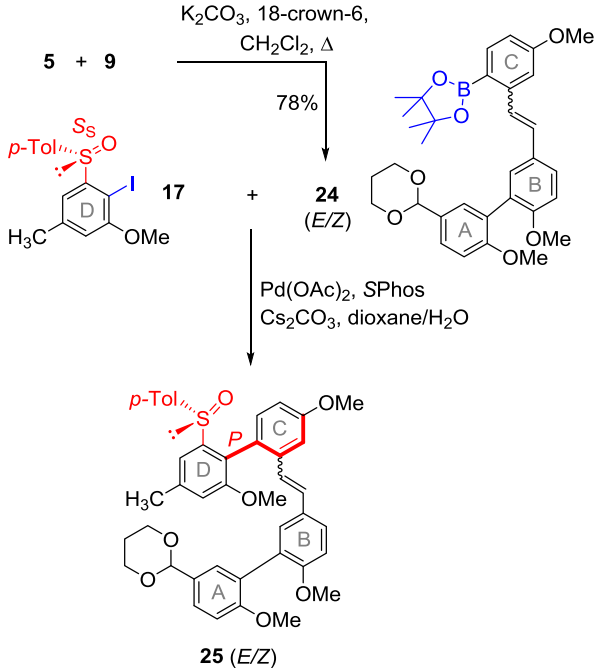
In conclusion of these preliminary studies to insure a high atropo-diastereoselectivity during the Suzuki-Miyaura cross coupling, the best conditions are $Pd(OAc)_2$ (0.15 equiv), *S*Phos (0.15 equiv) and Cs_2CO_3 (4 equiv) in dioxane/H_2O with or without an additional chiral ligand such as (*M*)- or (*P*)-BINAP depending on the presence or not of a coordinating substituent in *ortho* position of the biaryl axis formed.

Following our principal objective which was the synthesis of isoplagiochins **1** or **2** in enantiomerically pure form as described in Scheme 4, we synthesized the boronic ester **24**, starting from biaryl **5** and boronic ester **9**, to be able to perform the Suzuki-Miyaura cross coupling reaction with **17**.

Using previous optimized conditions, the A–B–C–D unit **25**, a feasible straight forward open chained candidate for cyclic bis(-bibenzyls) like **1**/**2**, was obtained in fair yields with an excellent 99:1 atropo-diastereoselectivity, surprisingly, with or without adding (*M*)-BINAP (Table 4). One explanation would be again the presence of considerable bulky *ortho*-substituent (see Figs. 3 and 4). It should be noted that the *E*/*Z*-ratio shifted to *E*, presumably due to the presence of the Pd-catalyst.[35]

Surprisingly, we were not able to transform **25** into a precursor for cyclization to obtain **1** or **2**. Actually, different hydrogenation protocols and conditions gave no conversion or resulted in a mixture of the sulfinyl compound **26** and the corresponding thioether **27**,[36] which of course could be used alternatively. Likewise, Wohl-Ziegler bromination on the verge of a Wittig-cyclization with **28**[15,37] resulted in concomitant side reactions with the sulfinyl moiety leading to the impossibility to perform some specific transformation (Scheme 6).[38]

Table 4
Atropo-diastereoselective Suzuki-Miyaura cross-coupling to **25**[a]



Entry	**24**: *E*/*Z*	Ligand [equiv]	Temp (°C)/ time (h)	Yield (%) **25**[a]	**25**: *E*/*Z*	de (%)[b]
1	65:35	*S*Phos [0.15]	70/48	61	80:20	98[c]
2	55:45	(*M*)-BINAP [0.15]	70/48	78	80:20	98[c]
3	55:45	*S*Phos [0.2]	70/48	75	65:35	98[c]
4	95:5	(*M*)-BINAP [0.2]	70/48	80	95:5	98[c]

[a] Reaction conditions: $Pd(OAc)_2$ (0.1 equiv), Cs_2CO_3 (4 equiv), dioxane/H_2O, 1 mmol of substrate.
[b] Diastereomeric ratio determined by ^1H NMR spectra or by HPLC analysis.
[c] For *E* and *Z*.

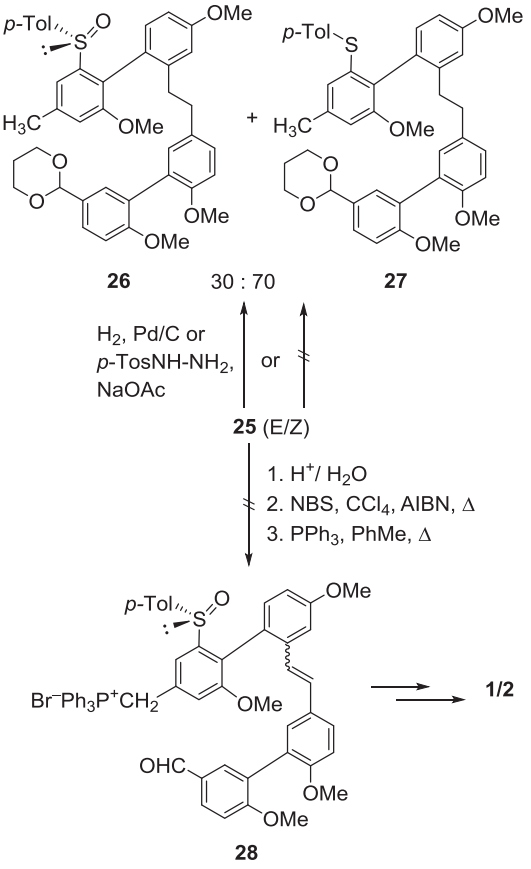
3. Conclusion

In summary, an enantiopure sulfinyl group in *ortho* position of an aryl iodide was enabled to control atropo-diastereoselective Suzuki coupling reaction with excellent diastereomeric excess (up to 98%) and this methodology was efficiently applied for the preparation of the biaryl C–D part of bis(bibenzyls) such as isoplagiochin C **1** or D **2**. Furthermore, we get deeper insight into mechanistic aspects of stereocontrol including double stereodifferentiation. As the final bromination, required for the envisioned macrocyclization by Wittig reaction, was not successful, we turn now our attention to a ring closing through an atropo-diastereoselective Suzuki coupling always with the sulfinyl part as chiral inductor and stabiliser. These investigations will be reported in due course.

4. Experimental section

4.1. General

NMR data were recorded on a *Bruker Avance 2* Spectrometer (AVII400, 400 or 100 MHz). Chemical shifts are reported relative to TMS. High resolution mass analyses were conducted with a *Finnigan MAT 95* instrument (CI). Flash chromatography was performed using silica gel (35–70 μm). Analytical HPLC was performed



Scheme 6. Further transformation of the A–B–C–D unit **25**.

on a *Merck-Hitachi L-6200 Intelligent Pump* equipped with a *Merck-Hitachi L-4200 UV–vis* detector; DataApex Clarity Chromatography Station. As analytical columns were used: Daicel Chiralcel OD-H (4.6×250 mm) or Phenomenex Lux Amylose-2 (4.6×250 mm); eluent: 2-propanol/n-hexane; detection: UV 275 nm. Both columns proved to be suitable for HPLC analyses of enantiomers (e.g., compound **17**) as well as diastereomers (**21**, **23**, **25**). The solvents used were dried using common laboratory methods. All moisture-sensitive reactions were carried out in flame-dried glassware under nitrogen or argon atmosphere. Hydrogenation was conducted in a Parr 5500 Compact Micro Reactor, 4836 Controller. Melting points were determined with a Büchi melting point apparatus (Dr. Tottoli). Optical rotatory values were determined on a *Perkin Elmer 241* polarimeter.

4.2. Synthetic procedures

*4.2.1. 5′-(4-Iodo-3-methoxystyryl)-2′,6-dimethoxy-[1,1′-biphenyl]-3-carbaldehyde (**7**).* Part (i): A mixture of the aldehyde **5** (9.20 g, 28.0 mmol), the phosphonium salt **6** (16.5 g, 28.0 mmol), anhydrous K_2CO_3 (13.8 g, 0.10 mol) and a catalytic amount of 18-crown-6 in CH_2Cl_2 (200 mL) was heated at reflux for 24 h. After cooling to rt the mixture was filtered, concentrated and purified by flash chromatography (SiO_2, *n*-hexane/EtOAc 3:1); 14.0 g (90%), colourless solid, *E*/*Z* mixture (73:27), mp. 84–85 °C. ^{1}H NMR ($CDCl_3$): δ (ppm)=7.69 (d, *J*=8.0 Hz, 0.73H), 7.61 (d, *J*=8.0 Hz, 0.27H), 7.47–7.41 (m, 2H), 7.37 (d, *J*=2.3 Hz, 0.73H), 7.20 (d, *J*=2.3 Hz, 0.73H), 7.15 (dd, *J*=2.3 Hz, 0.27H), 7.09 (d, J_{trans}=16.3 Hz, 0.73H, (*E*)-CH=CH), 6.95 (d, *J*=8.5 Hz, 0.73H), 6.93 (d, *J*=1.5 Hz, 0.73H), 6.92 (d, *J*=2.0 Hz, 1H), 6.89 (d, *J*=3.3 Hz, 0.27H), 6.84 (dd, *J*=8.0, 1.8 Hz, 0.73H), 6.80 (d, *J*=8.5 Hz, 0.27H), 6.78 (d, *J*=1.8 Hz, 0.27H), 6.67 (dd, *J*=8.0, 1.5 Hz, 0.27H), 6.59 (d, J_{cis}=12.3 Hz, 0.27H, (*Z*)-CH=CH), 6.40 (d, *J*=12.1 Hz, 0.27H, (*Z*)-CH=CH), 5.50 (s, 0.73H, OCHO), 5.47 (s, 0.27H, OCHO), 4.27–4.24 (m, 2H, OCH_2), 4.02–3.94 (m, 2H, OCH_2), 3.92 (s, 2.2H, OCH_3), 3.77 (s, 2.2H, OCH_3), 3.76 (s, 2.2H, OCH_3), 3.72 (s, 0.8H, OCH_3), 3.71 (s, 0.8H, OCH_3), 3.67 (s, 0.8H, OCH_3), 2.27–2.18 (m, 1H, CH_2), 1.41 (m, 1H, CH_2). ^{13}C NMR ($CDCl_3$): δ (ppm)=158.2, 157.6, 157.5, 157.4, 157.3, 156.6, 139.6, 139.4, 139.2, 139.0, 132.0, 131.0, 130.9, 130.9, 129.4, 129.3, 129.2, 129.1, 129.1, 129.0, 128.4, 127.9, 127.8, 127.5, 127.3, 126.5, 126.4, 125.6, 123.4, 120.5, 111.4, 111.0, 110.7, 110.7, 110.7, 108.5, 101.6 (OCHO), 101.5 (OCHO), 83.90 (C_{Ar}–I), 83.86 (C_{Ar}–I), 67.37, 67.35, 56.25 (OCH_3), 56.02 (OCH_3), 55.89 (OCH_3), 55.79 (OCH_3), 55.76 (OCH_3), 55.68 (OCH_3), 25.80, 25.77. HR-MS (Cl): calcd for $C_{27}H_{27}IO_5$ 558.0903; found 558.0906.

Part (ii): The acetal from part (i) (10.0 g, 17.9 mmol) was dissolved in THF/2 M HCl (1:1; 180 mL) and stirred for 16 h at rt. The mixture was taken up in EtOAc (270 mL) and satd. NaCl solution (90 mL) was added. The organic layer was separated and washed with satd. $NaHCO_3$ solution (2×50 mL) and satd. NaCl solution (2×50 mL), dried ($MgSO_4$) and concentrated; yield 8.60 g (96%) **7**, colourless solid, mp. 164–167 °C. The NMR was recorded from an analytical sample of the *E*-stilbene, obtained from flash chromatography (SiO_2, *n*-hexane/EtOAc 3:1). ^{1}H NMR ($CDCl_3$): δ (ppm)= 9.93 (s, 1H, CHO), 7.91 (dd, *J*=8.5, 2.3 Hz, 1H), 7.81 (d, *J*=2.0 Hz, 1H), 7.71 (d, *J*=8.3 Hz, 1H), 7.49 (dd, *J*=8.5, 2.3 Hz, 1H), 7.42 (d, *J*=2.3 Hz, 1H), 7.10 (d, J_{trans}=15.8 Hz, 1H, (*E*)–CH=CH), 7.08 (d, *J*=8.0 Hz, 1H), 6.98 (d, *J*=8.5 Hz, 1H), 6.93 (d, J_{trans}=15.8 Hz, 1H, (*E*)-CH=CH), 6.92 (d, *J*=2.0 Hz, 1H), 6.86 (dd, *J*=8.3, 2.0 Hz, 1H), 3.92 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ (ppm)=190.9 (CHO), 162.2, 158.3, 157.0, 139.4, 133.1, 131.7, 131.2, 129.6, 129.5, 129.3, 128.9, 127.8, 126.9, 126.1, 120.5, 111.3, 110.9, 108.6, 84.18 (C_{Ar}–I), 56.28 (OCH_3), 56.03 (OCH_3), 55.84 (OCH_3). HR-MS (Cl): calcd for $C_{24}H_{22}IO_4$ 500.0485 found 500.0416.

*4.2.2. (5-Methoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2yl) benzyl)triphenyl-phosphonium bromide (**9**).* The methylarene **8** (20.0 g, 80.6 mmol), NBS (15.8 g, 88.7 mmol) and a trace of AIBN in CCl_4 (350 mL) were heated at reflux for 6 h with additional irradiation with a 300 W daylight lamp. The resulting suspension was cooled, filtered and concentrated. The crude benzyl bromide was taken up in toluene (400 mL) and heated at reflux for 12 h together with triphenyl phosphane (23.3 g, 88.7 mmol). The phosphonium salt precipitated and was filtered and washed with petroleum ether; yield 38.0 g (81%) **9**, colourless solid, mp. 248 °C. ^{1}H NMR ($CDCl_3$): δ (ppm)=7.82–7.78 (m, 3H), 7.69 (m, 1H), 7.67–7.61 (m, 6H), 7.55–7.49 (m, 6H), 6.88–6.82 (m, 2H), 5.57 (d, $J_{P,H}$=14.8 Hz, 2H, Ar-CH_2), 3.56 (s, 3H, OCH_3), 1.07 (s, 12H, $OC(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ (ppm)=162.31/162.27, 138.61/138.51, 135.92/135.83, 135.11/135.08, 134.58/134.49, 130.12/130.00, 118.29, 117.43, 115.95/ 115.90, 115.09/115.06, 83.79 (B–O–C), 55.41 (OCH_3), 30.65 (d, $J_{P,C}$=46.2 Hz, Ar-CH_2), 24.81 (CH_3)$_2$).

*4.2.3. 2-(2-(2-(5′-(4-Iodo-3-methoxyphenethyl)-2′,6-dimethoxy-[1,1′-biphenyl]-3-yl)ethyl)-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11**).* Part (iv.): A mixture of the aldehyde 7 (10.5 g, 21.0 mmol), the phosphonium salt 9 (16.1 g, 27.3 mmol), anhydrous K_2CO_3 (29.0 g, 0.21 mol) and a catalytic amount of 18-crown-6 in CH_2Cl_2 (400 mL) was heated at reflux for 24 h. After cooling to rt, the mixture was filtered, concentrated and purified by flash chromatography (SiO_2, *n*-hexane/EtOAc 3:1); yellowish solid (10.3 g, 67%), mp 84–85 °C; complex NMR data because of double *E*/*Z* mixture. HR-MS (Cl): calcd for $C_{38}H_{40}BIO_6$ 730.1963 found 730.1942.

Part (v.). The stilbene mixture from iv. (3.65 g, 5.00 mmol) and *p*-toluenesulfonic acid hydrazide (13.9 g, 75.0 mmol) in DME (140 mL) was heated at reflux while adding a solution of NaOAc (10.2 g, 0.125 mol) in H_2O (210 mL) within 4 h. Heating was continued for

12 h. After cooling to rt, H_2O (250 mL) was added and the mixture was extracted with CH_2Cl_2 (3×250 mL). The combined organic layers were washed with H_2O (2×200 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (SiO_2, *n*-hexane/EtOAc 3:1) gave **11** as a pale yellow oil (2.88 g, 84%). ^{1}H NMR ($CDCl_3$): δ (ppm)=7.78 (d, *J*=8.0 Hz, 1H), 7.64 (d, *J*=7.8 Hz, 1H), 7.24 (dd, *J*=8.3, 2.3 Hz, 1H), 7.12 (d, *J*=2.3 Hz, 1H), 7.08–7.06 (m, 2H), 6.90 (d, *J*=8.3 Hz, 1H), 6.87 (d, *J*=8.3 Hz, 1H), 6.73 (dd, *J*=8.3, 2.3 Hz, 1H), 6.70 (d, *J*=2.3 Hz, 1H), 6.59–6.56 (m, 2H), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.18–3.14 (m, 2H, CH_2–CH_2), 2.90–2.80 (m, 6H, CH_2–CH_2), 1.35 (s, 12H, $OC(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ (ppm)=161.8, 157.9, 155.5, 155.3, 151.6, 144.1, 139.1, 138.3, 134.6, 133.0, 133.5, 131.5, 129.4, 128.4, 128.3, 128.2, 127.7, 122.8, 115.1, 113.7, 111.7, 111.1, 111.1, 110.7, 83.19 ($\underline{O}C(CH_3)_2$), 82.49 (C_{Ar}–I), 56.19 (OCH_3), 55.91 (OCH_3), 55.87 (OCH_3), 55.02 (OCH_3), 39.04, 38.94, 37.96, 36.94, 24.89 ($OC(\underline{C}H_3)_2$). HR-MS (Cl): calcd for $C_{38}H_{40}BIO_6$ 734.2276 found 734.2269.

*4.2.4. Isoplagiochin D tetramethylether (**12**) and isoplagiochin D (**2**).* The iodoboronic ester **11** (100 mg, 0.14 mmol) was dissolved in a mixture of toluene (2 mL), EtOH (1 mL) and 2 M Na_2CO_3 solution (1 mL). The mixture was degassed with a stream of argon. $Pd(PPh_3)_4$ (5.00 mg, ~4.3 mmol) was added and the mixture was heated at 105 °C for 16 h. After cooling to rt, the mixture was filtered through a short pad of SiO_2 with elution with EtOAc. After evaporation of the solvents, the residue was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc 3:1), colourless solid (47.8 mg, 71%) **12**. The spectroscopic data were identical with those reported in the literature.[15]

For the preparation of **2** from **12** we applied the procedure given in the literature.[15,17] The spectroscopic data were identical with those reported therein.

*4.2.5. (S_S)-1-Methoxy-3-methyl-5-(p-tolylsulfinyl) benzene (**20**).* To magnesium turnings (635 mg, 26.2 mmol) and a trace of diiodine under inert gas atmosphere was added dropwise 1/10 of a solution of 1-bromo-3-methoxy-5-methylbenzene (**18**, 5.27 g, 26.2 mmol) in anhydrous THF (20 mL). After initiation, the addition was continued keeping the temperature between 50 and 55 °C and stirring was continued for 1 h. This Grignard solution freshly prepared was slowly transferred into a solution of (S_S)-menthyl-*p*-tolylsulfinate **23** (7.00 g, 23.8 mmol) in toluene (20 mL) at 0 °C. Stirring was continued for 2 h at 0 °C, satd. NH_4Cl solution was added (10 mL) ant the mixture was extracted with EtOAc (2×60 mL). The combined organic layers were washed with satd. NaCl solution (2×30 mL), dried ($MgSO_4$) and concentrated in vacuum. The crude product was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc 1:1), yellowish viscous oil **20** (4.13 g, 67%); $[\alpha]_D^{23}$=+4.0 (*c*=0.70, acetone). ^{1}H NMR ($CDCl_3$): δ (ppm)=7.53 (d, *J*=8.0 Hz, 2H), 7.24 (d, *J*=8.0 Hz, 2H), 7.01 (s, 1H), 6.99 (s, 1H), 6.74 (s, 1H), 3.78 (s, 3H, OCH_3), 2.35 (s, 3H, *p*-C_6H_4–CH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm)=160.2, 146.8, 142.5, 141.6, 140.8, 130.0, 124.9, 117.9, 117.4, 106.3, 55.46 (OCH_3), 21.47 (CH_3), 21.38 (CH_3). HR-MS (Cl): calcd for $C_{15}H_{16}O_2S$ 260.0871 found 260.0875.

*4.2.6. (S_S)-2-Iodo-1-methoxy-5-methyl-3-(p-tolyl-sulfinyl)benzene (**17**).* (S_S)-3-Methyl-5-(*p*-tolyl-sulfinyl)anisol (**20**) (2.00 g, 7.68 mmol) was dissolved in anhydrous THF (10 mL). At −78 °C a solution of LDA (4.86 g, 12.0 mmol; 6.00 mL of a 2 M solution in THF/*n*-heptane/ethylbenzene) was added dropwise and stirring was continued for 1 h. Diiodine (2.34 g, 9.23 mmol) in anhydrous THF (15 mL) was added at −78 °C with additional stirring for 12 h. The mixture was quenched with satd. $Na_2S_2O_3$ solution (10 mL) and extracted with Et_2O (2×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc/CH_2Cl_2 2:1:1), colourless solid **17** (2.11 g, 71%), mp. 122 °C; $[\alpha]_D^{23}$=−143.3 (*c*=0.49, acetone), ee>99%. ^{1}H NMR ($CDCl_3$): δ (ppm)=7.67 (d, *J*=8.2 Hz, 2H), 7.44 (d, *J*=1.0 Hz, 1H), 7.22 (d, *J*=8.2 Hz, 2H), 6.72 (d, *J*=1.0 Hz, 1H), 3.87 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3), 2.34 (s, 3H, *p*-C_6H_4–CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm)=158.0, 148.9, 141.9, 141.6, 141.2, 129.9, 126.9, 119.2, 114.2, 81.66 (C_{Ar}–I), 56.67 (OCH_3), 21.66 (CH_3), 21.47 (CH_3). HR-MS (Cl): calcd for $C_{15}H_{15}IO_2S$ 385.9837 found 385.9830.

*4.2.7. (P,M)-2,4′-Dimethoxy-2′,4-dimethyl-6-((S_S)-p-tolylsulfinyl)-1,1′-biphenyl (**21**).* Suzuki coupling between (S_S)-iodoarene **17** and boronic ester **8**:

(a) Procedure with $Pd(OAc)_2$/*S*Phos (see Table 1): To a solution of the (S_S)-iodoarene **17** (386 mg, 1.00 mmol) and the boronic ester **8** (298 mg, 1.20 mmol) in 1,4-dioxane (15 mL) were added *S*Phos (0.15–0.30 equiv, M=410.54), $Pd(OAc)_2$ (0.1–0.2 equiv, M=224.51) and Cs_2CO_3 (1.30 g, 4.00 mmol, 4.0 equiv). The reaction was initiated by adding H_2O (2.5 mL) and heating (temperature/time see Table 1). After cooling to rt, H_2O (20 mL) was added and the mixture was filtered and extracted with EtOAc (2×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (SiO_2, n-hexane/EtOAc 1:1), yellow viscous liquid **21**. ^{1}H NMR ($CDCl_3$): δ (ppm)=7.68 (s, 0.65H), 7.58 (s, 0.35H), 7.20 (d, *J*=8.3 Hz, 0.65H), 7.14–7.08 (m, 1.3H), 7.01 (d, *J*=7.8 Hz, 1.3H), 6.90 (d, *J*=8.0 Hz, 1.3H), 6.86–6.82 (m, 2H), 6.59 (d, *J*=2.5 Hz, 0.65H), 6.55 (dd, *J*=2.5, 8.0 Hz, 0.35H), 6.33 (d, *J*=8.5 Hz, 0.35H), 3.85 (s, 2H, OCH_3), 3.83 (s, 1H, OCH_3), 3.69 (s, 3H, OCH_3), 2.51 (s, 2H, CH_3), 2.49 (s, 1H, CH_3), 2.32 (s, 1H, CH_3), 2.29 (s, 2H, *p*-C_6H_4–CH_3), 2.15 (s, 1H, *p*-C_6H_4–CH_3), 1.20 (s, 2H, *p*-C_6H_4–CH_3); (entry 1). ^{13}C NMR ($CDCl_3$): δ (ppm)=159.7, 159.4, 156.9, 154.8, 145.3, 142.1, 141.5, 141.4, 141.1, 140.3, 139.9, 139.7, 138.3, 132.7, 131.8, 129.5, 129.3, 126.4, 126.2, 125.2, 125.1, 124.8, 116.0, 115.6, 115.5, 115.1, 114.2, 113.5, 111.1, 110.5, 56.98 (OCH_3), 55.83 (OCH_3), 55.21 (OCH_3), 55.16 (OCH_3), 21.98 (CH_3), 21.94 (CH_3), 21.43 (CH_3), 21.40 (CH_3), 20.40 (CH_3), 18.96 (CH_3). HR-MS (Cl): calcd for $C_{23}H_{24}O_3S$ 380.1446 found 380.1456

(b) Procedure using BINAP instead of *S*Phos (see Table 2): In a Schlenck tube (argon atmosphere), $Pd(OAc)_2$ and (*M*)- or (*P*)-BINAP (for equiv see Table 2) were pre-incubated in 1,4-dioxane (15 mL) and H_2O (2.5 mL) for 30 min at 50 °C. The (S_S)-iodoarene **17** (386 mg, 1.00 mmol), the boronic ester **8** (298 mg, 1.20 mmol) and Cs_2CO_3 (1.30 g, 4.00 mmol, 4.0 equiv) were added and the mixture was stirred for 48 h (60–70 °C, see Table 2). After cooling to rt, the reaction mixture was quenched with H_2O (20 mL), filtered and extracted with EtOAc (2×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc 1:1), yellow viscous liquid **21**; analytical data see above.

*4.2.8. 2-((P)-2′,4-Dimethoxy-4′-methyl-6′-((S_S)-p-tolylsulfinyl)-[1,1′-biphenyl]-2-yl)-1,3-dioxane (**23**).* The Suzuki coupling reactions (with 1.00 mmol of **17** and 1.20 mmol of **22**) were performed according to the procedures described for the preparation of **21**, for details see Table 3, pale-yellow solid **23**, mp. 136–138 °C; $[\alpha]_D^{23}$=−109.3 (*c*=0.19, acetone), measured for entry 1. ^{1}H NMR ($CDCl_3$): δ (ppm)=7.42 (s, 1H), 7.26 (d, *J*=8.4 Hz, 1H), 7.22 (d, *J*=2.8 Hz, 1H), 7.16 (d, *J*=8.3 Hz, 2H), 7.09 (d, *J*=8.3 Hz, 2H), 7.00 (dd, *J*=8.4, 2.8 Hz, 1H), 6.79 (s, 1H), 4.52 (s, 1H, OCHO), 4.14–4.06 (m, 1H, OCH_2), 3.88 (s, 3H, OCH_3), 3.85–3.82 (m, 0.6H, OCH_2), 3.68 (s, 3H, OCH_3), 3.52 (td, *J*=12.3, 2.3 Hz, 1H), 3.23 (td, *J*=12.3, 2.3 Hz, 1H), 2.45 (s, 3H, *p*-C_6H_4–CH_3), 2.31 (s, 3H, CH_3), 2.14–2.05 (m, 1H, HCH), 1.19 (d, *J*=13.3 Hz, 1H, HCH). ^{13}C NMR ($CDCl_3$): δ (ppm)=159.9, 157.1, 146.1, 141.4, 140.9, 140.3, 139.5, 132.0, 129.6, 125.3, 124.7, 124.0,

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116.6, 115.2, 113.6, 111.2, 100.0 (OCHO), 67.28 (OCH_2), 66.82 (OCH_2), 56.82 (OCH_3), 55.35 (OCH_3), 25.56, 21.91 (CH_3), 21.41 (CH_3). HR-MS (Cl): calcd for $C_{26}H_{28}O_5S$ 452.1657 found 452.1652.

*4.2.9. Preparation of **24**: Wittig reaction between **5** and **9**.* A mixture of the aldehyde **5** (6.56 g, 20.0 mmol), the phosphonium salt **9** (15.3 g, 26.0 mmol), anhydrous K_2CO_3 (13.8 g, 0.10 mol) and a catalytic amount of 18-crown-6 in CH_2Cl_2 (200 mL) was heated at reflux for 24 h. After cooling to rt the mixture was filtered, concentrated and purified by flash chromatography (SiO_2, *n*-hexane/EtOAc 3:1); 8.72 g (78%), colourless solid **24**, *E*/*Z* mixture (typical 55:45), mp 145–146 °C. ^{1}H NMR ($CDCl_3$): δ (ppm)=7.96 (d, J_{trans}=16.3 Hz, 0.45H, (*E*)-CH=CH), 7.75 (d, *J*=8.3 Hz, 0.45H), 7.73 (d, *J*=8.3 Hz, 0.55H), 7.49 (dd, *J*=8.5, 2.3 Hz, 0.55H), 7.45 (dd, *J*=8.0, 2.3 Hz, 0.55H), 7.42 (d, *J*=2.3 Hz, 0.55H), 7.39 (d, *J*=2.3 Hz, 0.25H), 7.38 (d, *J*=2.3 Hz, 0.5H), 7.21 (d, *J*=2.3 Hz, 0.55H), 7.19 (d, *J*=2.3 Hz, 0.45H), 7.11 (dd, *J*=2.3, 8.5 Hz, 0.45H), 7.07 (d, *J*=2.3 Hz, 0.45H), 7.00 (d, J_{cis}=12.3 Hz, 0.55H, (*Z*)-CH=CH), 6.98 (d, J_{trans}=16.3 Hz, 0.45H, (*E*)-CH=CH), 6.96 (d, *J*=3.0 Hz, 0.45H), 6.94 (d, *J*=3.0 Hz, 0.55H), 6.90–6.88 (m, 1H), 6.78 (dd, *J*=2.5, 8.3 Hz, 0.55H), 6.74–6.71 (m, 1H), 6.52 (d, J_{cis}=12.3 Hz, 0.55H, (*Z*)-CH=CH), 5.49 (s, 0.55H, OCHO), 5.44 (s, 0.45H, OCHO), 4.26–4.22 (m, 2H, CH_2), 3.99–3.92 (m, 2H, CH_2), 3.86 (s, 1.7H, OCH_3), 3.77 (s, 1.7H, OCH_3), 3.76 (s, 1.7H, OCH_3), 3.70 (s, 1.3H, OCH_3), 3.67 (s, 1.3H, OCH_3), 3.60 (s, 1.3H, OCH_3), 2.26–2.14 (m, 1H), 1.44–1.40 (m, 1H), 1.33 (s, 6.7H, $OC(CH_3)_2$), 1.29 (s, 5.3H, $OC(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ (ppm)=161.9, 161.2, 157.6, 157.5, 156.9, 156.2, 146.0, 145.9, 138.0, 137.8, 132.6, 131.1, 130.9, 130.5, 130.2, 130.1, 129.7, 129.3, 129.3, 129.2, 129.2, 129.0, 128.1, 127.8, 127.8, 127.7, 127.6, 126.8, 126.3, 126.2, 113.6, 113.1, 112.4, 111.2, 110.8, 110.7, 110.6, 109.2, 101.6 (OCHO), 101.6 (OCHO), 83.39 ($OC(CH_3)_2$), 83.27 ($OC(CH_3)_2$), 67.33, 55.92 (OCH_3), 55.82 (OCH_3), 55.76 (OCH_3), 55.71 (OCH_3), 55.12 (OCH_3), 54.87 (OCH_3), 25.81, 24.94 ($OC(CH_3)_2$), 24.88 ($OC(CH_3)_2$). HR-MS (Cl): calcd for $C_{33}H_{39}O_7$ 558.2789 found 558.2804.

*4.2.10. Preparation of **25**: Suzuki coupling between the (S_S)-iodoarene **17** and the stilbene **24** (see Table 4).* The Suzuki coupling reactions (with 1.00 mmol of **17** and 1.20 mmol of **24**) were performed according to the procedures described for the preparation of **21** (b), for details see Table 4. The crude product was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc/CH_2Cl_2 2:1:1), pale-yellow solid **25**, mp. 98–100 °C. complex NMR data. HR-MS (Cl): calcd for $C_{42}H_{42}O_7S$ 690.2651 found 690.2704.

Supplementary data

Supplementary data (Experimental procedures and full spectroscopic data for all new compounds; details of HPLC.) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.12.052.

References and notes

1. Asakawa, Y. In *Progress in the Chemistry of Organic Natural Products*; Herz, E., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer: Wien – New York, 1995; p 5.
2. Friederich, S.; Rueffer, M.; Asakawa, Y.; Zenk, M. H. *Phytochemistry* **1999**, *52*, 1195–1202.
3. Asakawa, Y.; Toyota, M.; Tori, M.; Hashimoto, T. *Spectroscopy* **2000**, *14*, 149–175.
4. Asakawa, Y.; Ludwiczuk, A.; Nagashima, F.; Toyota, M.; Hashimoto, T.; Tori, M.; Fukuyama, Y.; Harinantenaina, L. *Heterocycles* **2009**, *77*, 99–150.
5. Hashimoto, T.; Kanayama, S.; Kan, Y.; Tori, M.; Asakawa, Y. *Chem. Lett.* **1996**, 741–742.
6. Keserü, G. M.; Kolossváry, I.; Nógrádi, M. *J. Mol. Struct.* **1995**, *356*, 143–148.
7. Hashimoto, T.; Irita, H.; Takaoka, S.; Tanaka, M.; Asakawa, Y. *Tetrahedron* **2000**, *56*, 3153–3159.
8. Schaumlöffel, A.; Groh, M.; Knauer, M.; Speicher, A.; Bringmann, G. *Eur. J. Org. Chem.* **2012**, 6878–6887.
9. Toyota, M.; Yoshida, T.; Kan, Y.; Takaoka, S.; Asakawa, Y. *Tetrahedron Lett.* **1996**, *37*, 4745–4748.
10. Bringmann, G.; Mühlbacher, J.; Reichert, M.; Dreyer, M.; Kolz, J.; Speicher, A. *J. Am. Chem. Soc.* **2004**, *126*, 9283–9290.
11. Scher, J. M.; Zapp, J.; Becker, H.; Kather, N.; Kolz, J.; Speicher, A.; Dreyer, M.; Maksimenka, K.; Bringmann, G. *Tetrahedron* **2004**, *60*, 9877–9881.
12. Bringmann, G.; Gulder, T. A. M.; Reichert, M.; Gulder, T. *Chirality* **2008**, *20*, 628–642.
13. Speicher, A.; Backes, T.; Hesidens, K.; Kolz, J. *Beilstein J. Org. Chem.* **2009**, *5*, 71.
14. Harrowven, D. C.; Kostiuk, S. L. *Nat. Prod. Rep.* **2012**, *29*, 223–242.
15. Eicher, T.; Fey, S.; Puhl, W.; Buchel, E.; Speicher, A. *Eur. J. Org. Chem.* **1998**, 877–888.
16. Speicher, A.; Kolz, J.; Sambanje, R. P. *Synthesis* **2002**, 2503–2512.
17. Esumi, T.; Wada, M.; Mizushima, E.; Sato, N.; Kodama, M.; Asakawa, Y.; Fukuyama, Y. *Tetrahedron Lett.* **2004**, *45*, 6941–6945.
18. Groh, M.; Meidlinger, D.; Bringmann, G.; Speicher, A. *Org. Lett.* **2012**, *14*, 4548–4551.
19. (a) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427; (b) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. *Chem. Soc. Rev.* **2015**, *44*, 3418–3430; (c) Gulder, T.; Baran, P. S. *Nat. Prod. Rep.* **2012**, *29*, 899–934.
20. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052.
21. Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun.* **2000**, 1723–1724.
22. (a) Wang, S.; Li, J.; Miao, T.; Wu, W.; Li, Q.; Zhuang, Y.; Zhou, Z.; Qiu, L. *Org. Lett.* **2012**, *14*, 1966–1969; (b) Zhou, Y.; Wang, S.; Wu, W.; Li, Q.; He, Y.; Zhuang, Y.; Li, L.; Pang, J.; Zhou, Z.; Qiu, L. *Org. Lett.* **2013**, *15*, 5508–5511; (c) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M.-H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Gao, J. J.; Li, W.; Rodriguez, S.; Lu, B. Z.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2012**, *14*, 2258–2261; (d) Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 11278–11287; (e) Ros, A.; Estepa, B.; Bermejo, A.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **2012**, *77*, 4740–4750; (f) Bermejo, A.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 15798–15799; (g) Zhang, S.-S.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 5546–5549; (h) Genov, M.; Almorín, A.; Espinet, P. *Chem.—Eur. J.* **2006**, *12*, 9346–9352; (i) Yamamoto, T.; Akai, Y.; Nagata, Y.; Suginome, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8844–8847; (j) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2708–2710.
23. Cao, S.; Christiansen, R.; Peng, X. *Chem.—Eur. J.* **2013**, *19*, 9050–9058.
24. Uemura, M.; Nishimura, H.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 107–110.
25. (a) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223–4229; (b) Broutin, P.-E.; Colobert, F. *Org. Lett.* **2003**, *5*, 3281–3284; (c) Broutin, P.-E.; Colobert, F. *Org. Lett.* **2005**, *7*, 3737–3740; (d) for the application of a related approach to the synthesis of the biaryl part of vancomycin, steganacin and dibenzoxepine derivatives see: Leermann, T.; Broutin, P.-E.; Leroux, F. R.; Colobert, F. *Org. Biomol. Chem.* **2012**, *10*, 4095–4102; (e) Yalcouye, B.; Choppin, S.; Panossian, A.; Leroux, F. R.; Colobert, F. *Eur. J. Org. Chem.* **2014**, 6285–6294 and; (f) Joncour, A.; Decor, A.; Thoret, S.; Chiaroni, A.; Baudoin, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 4149–4152.
26. Colobert, F.; Valdivia, V.; Choppin, S.; Leroux, F. R.; Fernandez, I.; Alvarez, E.; Khiar, N. *Org. Lett.* **2009**, *11*, 5130–5133.
27. (a) Leroux, F. R.; Berthelot, A.; Bonnafoux, L.; Panossian, A.; Colobert, F. *Chem.—Eur. J.* **2012**, *18*, 14232–14236 and references cited herein; (b) Leroux, F. R.; Panossian A. Ed. J. Mortier, John Wiley & Sons; 2015; 813–833.
28. Takiguchi, H.; Ohmori, K.; Suzuki, K. *Chem. Lett.* **2011**, *40*, 1069–1071.
29. Takiguchi, H.; Ohmori, K.; Suzuki, K. *Angew. Chem.* **2013**, *125*, 10666–10670.
30. (a) Andersen, K. K.; Gaffied, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637–5646; (b) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987** 173–173.
31. (a) Coleman, R.; Guernon, J.; Roland, J. *Org. Lett.* **2000**, 277–280; (b) Chan, J. H.; Hong, J. S.; Hunter, R. N.; Orr, G. F.; Cowan, J. R.; Sherman, D. B. *J. Med. Chem.* **2001**, *44*, 1866–1882.
32. Nonoyama, M.; Nakajima, K. *Polyhedron* **1998**, *18*, 533–543.
33. Speicher, A.; Groh, M.; Zapp, J.; Schaumlöffel, A.; Knauer, M.; Bringmann, G. *Synlett* **2009**, 1852–1858.
34. No trace of the other atropodiastereomer was detected by ^{1}H and ^{13}C NMR spectra.
35. Tan, E. H. P.; Lloyd-Jones, G. C.; Harvey, J. N.; Lennox, A. J. J.; Mills, B. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 9602–9606.
36. Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Synthesis* **1975**, 385–387.
37. Chen, G.; Gui, J.; Li, L.; Liao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7681–7685.
38. Surendra, K.; Srilakshmi Krishnaveni, N.; Pavan Kumar, V.; Sridhar, R.; Rama Rao, K. *Tetrahedron Lett.* **2005**, *46*, 4581–4583.