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Efficient synthesis of isoplagiochin D, a macrocyclic bis(bibenzyls), by utilizing an intramolecular Suzuki–Miyaura reaction

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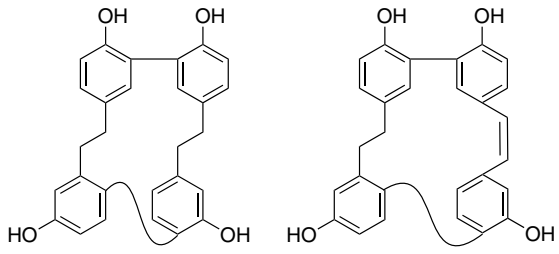
Abstract—Isoplagiochin D, a highly strained macrocyclic bis(bibenzyls) with two biaryl units isolated from the liverwort *Pladiochila fruticosa*, was prepared in 10.6% overall yield for the 11 steps by an efficient synthetic approach involving the construction of two bibenzyl and one biaryl units using Horner–Wadsworth–Emmons and Suzuki–Miyaura protocols.

Macrocyclic bis(bibenzyls) natural products[1] are specific chemical constituents of the liverworts and are presumably biosynthesized by the dimerization of lunularin through several modes of oxidative phenol coupling such as biaryl C–C bond and/or biphenyl ether bond formations. The unique structural characteristics and versatile biological activities[2] have made cyclic bis(bibenzyls) natural products attractive synthetic targets.[3] To date, a few syntheses of cyclic bis(bibenzyls) were reported, for example, reccardin B,[4,5] and plagiochins C and D.[6] Most of them underwent the crucial macrocyclization between two bibenzyl positions by intramolecular Horner–Wadsworth–Emmons reaction or Wurtz type reaction. Independently, we also reported on the successful syntheses[7] of plagiochins A and D by applying the tandem Stille–Kelly reaction[8] for the macrocyclization between two aryl units, which mimicked their proposed biosynthetic route. Although it is the first example to construct the macrocyclic structure of bis(bibenzyls) natural products by the aryl–aryl bond formation, these processes suffer from drawbacks such as low yield of the macrocyclization and being unable to isolate mono-stannyl intermediate requisite for the subsequent Stille reaction.[9] In this paper, we report on the extension of this strategy to the synthesis of isoplagiochin D (**1**), which consists of more strained cyclic system containing two biaryl units than the plagicohin type with one biaryl and one biphenyl ether units.

Compound **1** was isolated together with a structurally similar derivative, isoplagiochin C (**2**), from the liverwort *Pladiochila fruticosa* by Asakawa and co-workers in 1996,[10] and then was first synthesized by Eicher et al. in 1998[11] (Fig. 1).

As described above, our key strategy is the construction of macrocyclic structure **3** from **4a** or **4b** by palladium(0)-catalyzed Stille[12] or Suzuki–Miyaura[13] cross-coupling between positions 14 and 12′ at which some stannyl or boronate group and a triflate are attached, respectively (Scheme 1).



Isoplagiochin D (**1**) Isoplagiochin C (**2**)

Figure 1. Structure of isoplagiochin D (**1**) and C (**2**).

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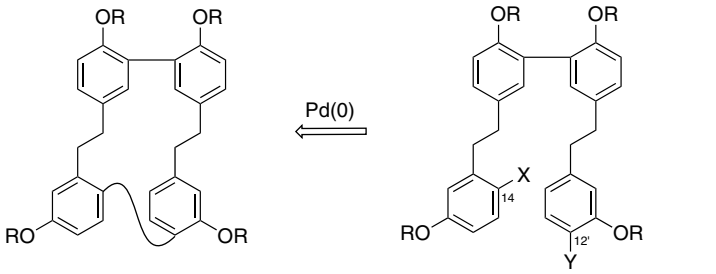


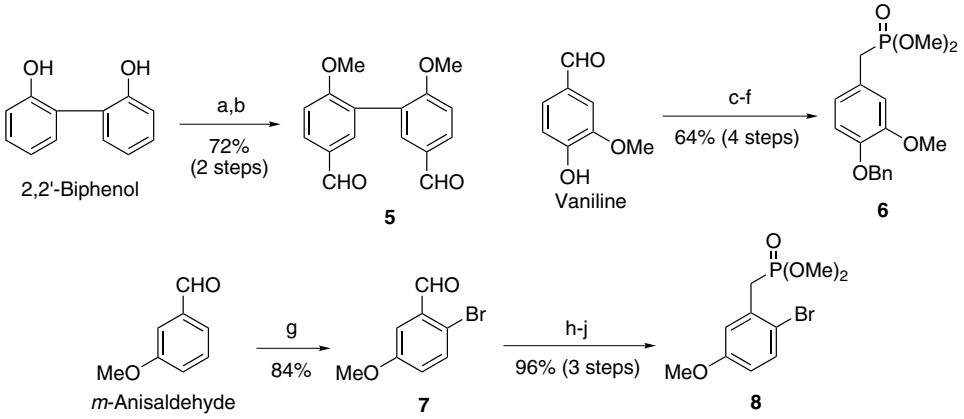
Scheme 1. Key strategy toward synthesis of isoplagiochin D (**1**).

Our synthesis of isoplagiochin D (**1**) was commenced with the preparation of three coupling units **5**, **6**, and **8**. Unit **5** was prepared by methylation of 2,2′-biphenol with excess amount of MeI in the presence of K_2CO_3 followed by regioselective formylation with hexamethylenetetramine in TFA in 72% overall yield. Bromination of *m*-anisaldehyde with Br_2 in $CHCl_3$ gave rise to *o*-bromide **7** in 84% yield. Subsequent reduction of **7** with $NaBH_4$, followed by bromination with CBr_4–PPh_3 and Arbuzov reaction, provided unit **8** in 96% yield. Unit **6** was also prepared from vanillin in 67% overall yield by similar procedures (Scheme 2).

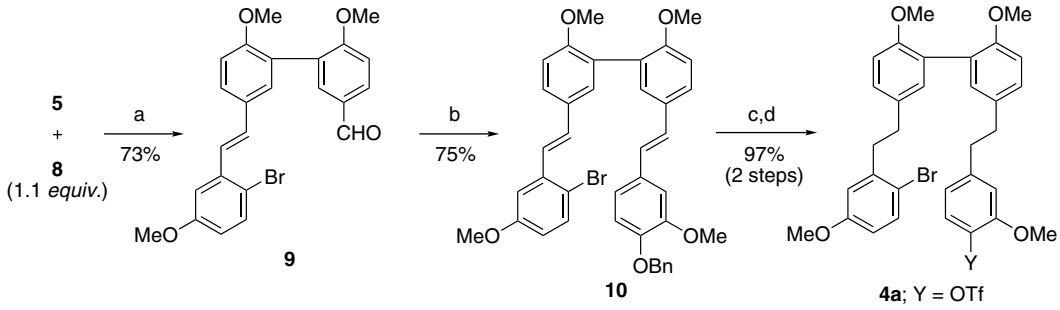
With all the coupling units **5**, **6**, and **8** in hand, next, they were assembled by repeating Horner–Wadsworth–Emmons reaction leading to a precursor **4a** for Pd (0)-catalyzed macrocyclization as following: phosphonate **8** was treated with NaH, and then reacted with dialdehyde **5** to give the desired mono-coupling product **9** in 73% yield contaminated with 10% of the undesired di-coupled product. Coupling reaction between **9** and phosphonate **6** was repeated under similar conditions as above, giving rise to di-(*E*)-olefin **10** in 75% yield. Although hydrogenation of two double bonds in **10** was troublesome in the case of using Pd–C or Lindlar catalysts, giving the complex mixture including over-reduction of benzene rings into cyclohexanes, we were pleased to find that use of PtO_2 catalyst in CH_2Cl_2 under a H_2 atmosphere was able to reduce two double bonds and remove a benzyl group without touching benzene rings, thereby leading to the desired product **4a** in 97% yield after converting the liberated phenol to a triflate with Tf_2O and Et_3N in CH_2Cl_2 (Scheme 3).

Before moving a step forward, we examined the intermolecular version of cross-coupling between trimethylbisbibenzyltin **11** or pinacol boronate ester **12** and a triflate **13** to search for optimal conditions suitable for attempting next intramolecular cross-coupling of **4a**. Namely, the cross-coupling proceeded smoothly between **12** and **13** under Suzuki–Miyaura conditions, 10 mol% of $PdCl_2$(dppf) with K_2PO_4 in 1,4-dioxane, to give rise to **14**, but the Stille coupling between **11** and **13** did not work sufficiently. These results suggest that Stille reaction is not suitable for our purpose. Therefore, we decided to apply the Suzuki–Miyaura protocol for the crucial cyclization of **4a** (Table 1).

Consequently, selective preparation of boronate **4b** from **4a** was required for this macrocyclization. First, under typical Suzuki–Miyaura conditions,[13] 10 mol% of $PdCl_2$(dppf) and 1,4-dioxane as a solvent at 80 °C, the reaction was carried out to give the desirable boronate **4b** in 27% yield with 23% of starting material **4a**

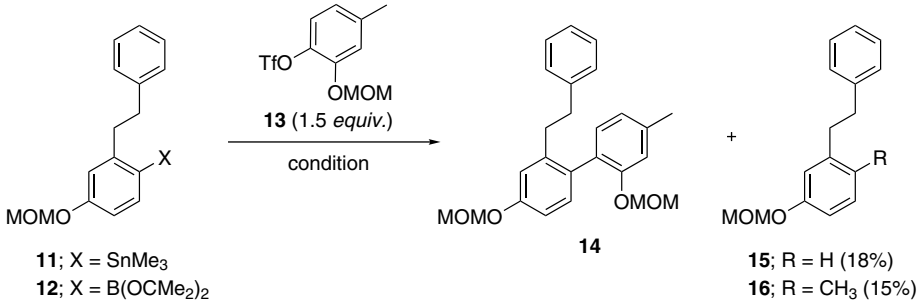


Scheme 2. Preparation of units **5**, **6**, and **8**. Reagents and conditions: (a) MeI, K_2CO_3, acetone, 80 °C, overnight; (b) hexamethylenetetramine, TFA, 0 → 90 °C, overnight; (c) BnBr, K_2CO_3, acetone, rt, 3 h; (d) $LiAlH_4$, THF, 0 °C→rt, 1 h; (e) CBr_4, PPh_3, MeCN, rt, 9 h; (f) $P(OMe)_3$, 90 °C, 3 h; (g) Br_2, $CHCl_3$, 70 °C, 24 h; (h) $NaBH_4$, THF, 0 °C, 4 h; (i) CBr_4, PPh_3, MeCN, rt, overnight; (j) $P(OMe)_3$, 90 °C, 2 h, reflux.



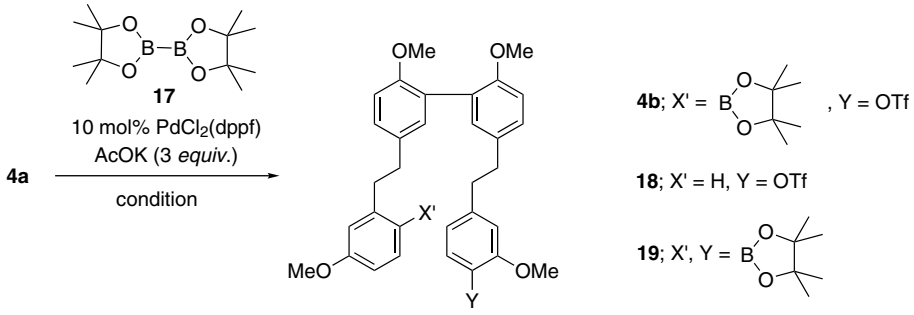
Scheme 3. Preparation of intermediate **4a**. Reagents and conditions: (a) 60% NaH, THF, 0 °C → rt, overnight; (b) **6**, 60% NaH, THF, 0 °C→rt, 3 h; (C) H_2 gas (1 atm), PtO_2 (0.73 equiv), CH_2Cl_2, rt, 6 h; (d) Tf_2O, Et_3N, CH_2Cl_2, 0 °C → rt, 4 h.

Table 1. Model studies for Stille–Kelly reaction and Suzuki–Miyaura reaction



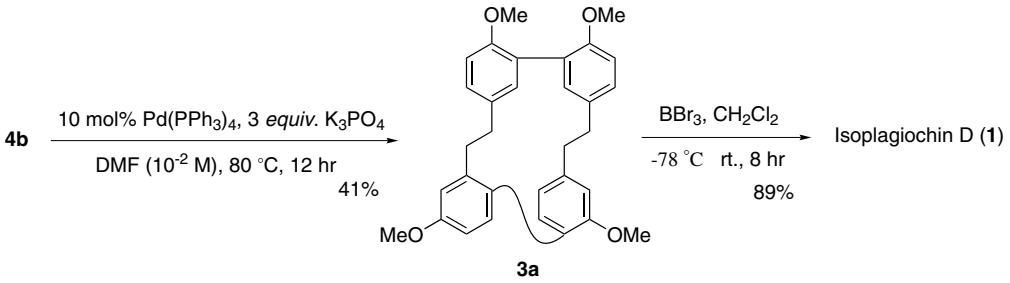
Entry	Substrate	Condition	Yield (%) **14**:**15**:**16**
1	**11**	10 mol% $Pd(PCy_3)_2$, DMF, 70 °C, 40 h	0:18:15
2	**12**	10 mol% $PdCl_2$(dppf), dppf, K_3PO_4, 1,4-dioxane, 80 °C, 29 h	48:0:0

Table 2. $PdCl_2$(dppf) catalyzed borylation of **4a**



Entry	**17** (equiv)	Ligand (mol%)	Solvent (10^{-2} M)	Temperature (°C)	Time (h)	Yield 4b (%) **4a**:**4b**:**18**:**19**
1	1.2	dppf (10)	1,4-Dioxane	80	48	23:27:0:0
2	1.2	dppf (10)	1,4-Dioxane	110	24	0:33:34:0
3	1.2	dppf (10)	DMSO	80	12	0:0:50:0
4	1.2	—	DMF	80	12	0:24:11:0
5	2.4	—	DMF	80	3	0:56:0:40
6	2.4	—	DMF	80	2	0:63:0:19
7	2.4	—	DMF	80	1.5	17:63:0:0

(Table 2, entry 1). Although elevating the reaction temperature (110 °C) enhanced a boronate–bromine exchange, the protonated product **18** was produced in 34% yield (Table 2, entry 2). Changing the solvent to more polar one,[14] DMF was found to be suitable solvent for this reaction (Table 2, entry 4). Additionally, when the reaction was carried out in DMF using 2.4 equiv of bis(pinacol)diborate for 2–3 h, the conversion of the



Scheme 4. Macrocyclization of **18** and completion of total synthesis of isoplagiochin D (**1**).

desired product **4b** was increased up to 56–63% yield together with the generation of bis(pinacolate) **19** (Table 2, entries 5 and 6). In the shorter reaction time (1.5 h) the desired product **4b** was obtained in 63% yield with starting material **4a** in 17% yield. (Table 2, entry 7) Eventually, the pinacolborate **4b** was obtained in 76% yield after repeating the same reaction three times. However, no generation of cyclized product was observed under these conditions.[15]

Now, we address the issue of the final macrocyclization in this synthesis. In this case, the intramolecular Suzuki–Miyaura reaction of **18** with 10 mol% of $Pd(PPh_3)_4$ in DMF in the presence of 3 equiv K_3PO_4[13c,16] proceeded smoothly and afforded the expected macrocyclic product **21** in 41% yield. Finally, Removal of all methyl groups in **21** with BBr_3 led to the total synthesis of isoplagiochin D (**1**) (Scheme 4), which was identical in all the spectra data[17] (^{1}H NMR, ^{13}C NMR, EIMS, IR) with the natural product.

In conclusion, we could improve the yield of palladium-catalyzed macrocyclization between two aryl units in the synthesis of cyclic bis(bibenzyls) natural products more significantly than the previously used tandem Stille–Kelly protocol[7] by utilizing intramolecular Suzuki–Miyaura reaction, and thereby achieve the efficient synthesis of isoplagiochin D (**1**) in 10.6% overall yield for the 11 steps. Further application of this methodology is currently underway in our laboratory in an attempt to synthesize riccarrdin A and cavicularin, the most complex cyclic bis(bibenzyls).[18]

Acknowledgements

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9. The intramolecular cross-coupling of **4c** under the previous Stille–Kelly conditions gave the cyclized product **3b** in 9% yield.
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15. It is well known that use of the weak bases such as AcOK does not afford the cross-coupling products. See Ref. 14a.
16. First, we applied the same conditions for the macrocyclization as used in the model study. However, the reaction did not occur.
17. Spectra data of isoplagiochin D (**1**): ^{1}H NMR (300 MHz, acetone-d_6): δ 2.78–3.08 (8H, m), 6.39 (1H, d, J = 2.2 Hz), 6.50 (1H, d, J = 2.2 Hz), 6.71 (1H, dd, J = 2.5, 8.2 Hz), 6.74 (1H, d, J = 2.5 Hz), 6.75 (1H, dd, J = 2.5, 8.0 Hz), 6.78 (1H, d, J = 8.2 Hz), 6.84 (1H, d, J = 2.7 Hz), 6.89 (1H, d, J = 8.2 Hz), 6.99 (1H, d, J = 8.0 Hz), 7.00 (1H, dd, J = 2.2, 8.2 Hz), 7.07 (1H, d, J = 7.7 Hz), 7.13 (1H, dd,

J = 2.2, 8.2 Hz); ^{13}C NMR (75 MHz, acetone-d_6): δ 36.2, 38.1, 38.6, 39.1, 113.3, 116.0, 116.1, 117.0, 117.4, 121.5, 126.0, 127.2, 127.6, 128.1, 129.4, 129.5, 132.0, 132.4, 133.9, 133.9, 134.3, 136.0, 142.6, 144.0, 151.7, 152.2, 155.2, 157.4; HREIMS calcd 424.1674 for $C_{28}H_{24}O_4$, found 424.1660 (M^+); IR (KBr) 3389, 1419, 1255 cm^{-1}.

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