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Total Synthesis of Plagiochin D, A Macrocyclic Bis(bibenzyl) from Liverworts by Intramolecular Still-Kelly Reaction

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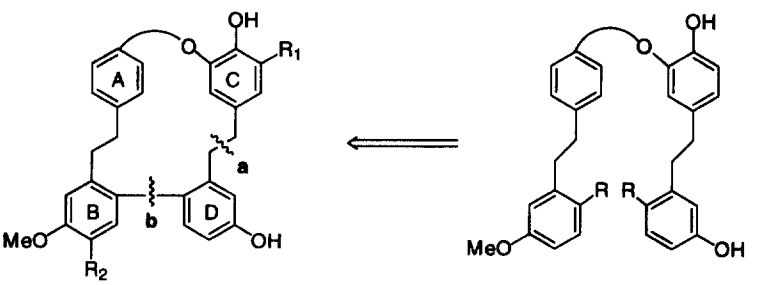
Abstract: Plagiochin D (**4**), a unique macrocyclic bis(bibenzyl) having both a biphenyl ether and a biaryl units isolated from the liverwort *Plagiochila acanthophylla*, was synthesized. The key 16-membered ring closure of a dibromoperrottetin A derivative **13** was realized by Pd(0) catalyzed intramolecular Still-Kelly reaction.

Macrocyclic Bis(bibenzyls) are plant metabolites occurring exclusively in liverworts, and over 30 congeners have been isolated so far.[1] Their unique structures and diversity of their biological activities have attracted much attention.[1, 2] They are categorized into two structural types 1 and 2, which are made up of macrocyclic rings linked via two biphenyl ether C–O bonds, and one biphenyl ether C–O and one biaryl C–C bonds, respectively. These macrocyclic rings are presumably derived by oxidative C-O or C-C coupling of the corresponding open chain bis(bibenzyls) such as perrottetin A (**5**).[3] Among the type 2 of 16-membered ring bis(bibenzyls), plagiochin A (**1**)[4] exhibits an interesting neurotrophic activity in the culture of fetal rat cerebral hemisphere.[5] In order to establish a practical way for the preparation of plagiochin A (**1**), we have investigated the synthesis of plagiochin D (**4**), the simplest member of the plagiochins, as a part of studies on macrocyclic bis(bibenzyls).[6, 7] The synthesis of **4** reported by Nogradi *et al.*[8] involved the Wurtz-type radical coupling at the position **a** for the macrocyclization.



Plagiochin A (**1**) R_1 = OH, R_2 = OH
Plagiochin B (**2**) R_1 = OH, R_2 = H
Plagiochin C (**3**) R_1 = H, R_2 = OH
Plagiochin D (**4**) R_1 =H, R_2 = H

5 R = H
6 R = Br, I

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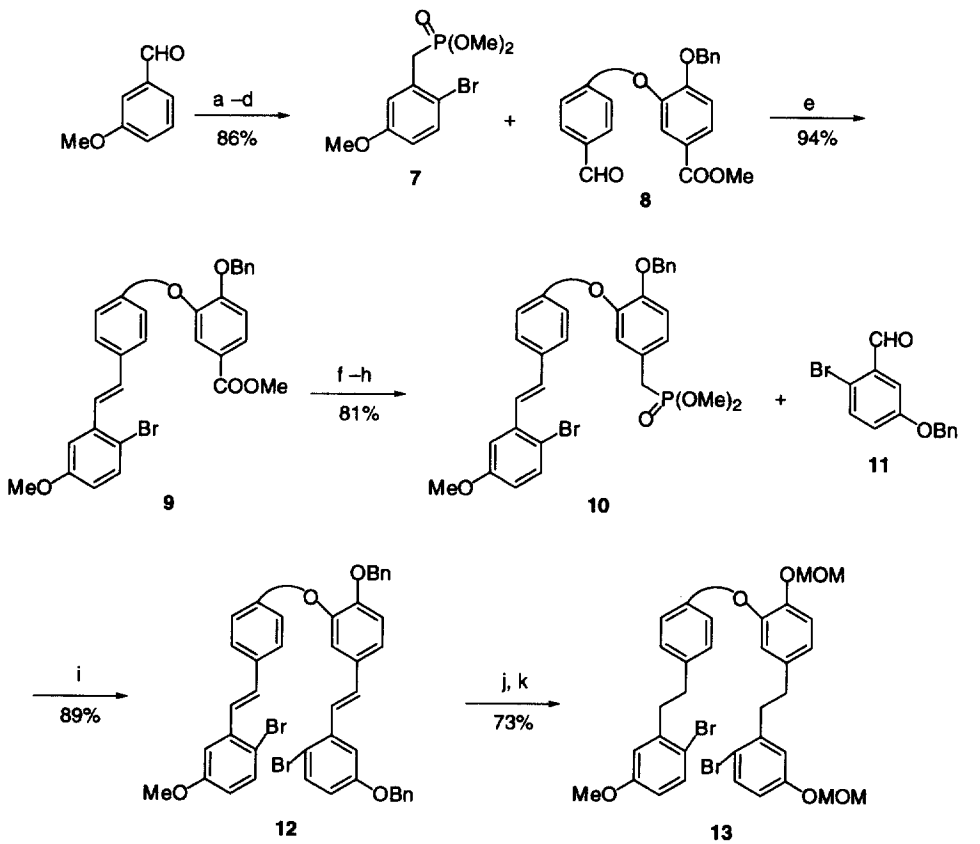
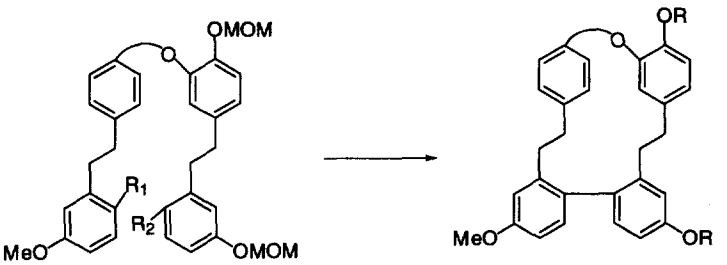
Although we were succeeded in the final ring closure at the position **a** before Nogradi's report,[9] all the attempted procedures for the ring closure at this position suffered considerably poor yield and reproducibility. Therefore, we turned our attention to employ intramolecular C–C cross-coupling at the position **b** in dihalogenated perrottetin A derivatives **6** by using organotransition metals. In this paper, we are pleased to report the synthesis of plagiochin D (**4**) realized by an intramolecular Still-Kelly reaction.[11]

In accordance to the procedure used for the synthesis of marchantin A and riccardin B[7] belonging to type 1 macrocyclic bis(bibenzyls), dibromoperrottetin A (**13**), a key precursor for the crucial C–C ring closure step, was prepared as follows. The A–C ring segment **8**[7] and the phsophonate **7** readily derivable from *m*-anisaldehyde were effectively combined by Wardworth-Emmons reaction using sodium hydride to give rise to **9** in 94 % yield. The ester group of **9** was then reduced with lithium aluminum hydride to the alcohol, which was brominated with tetrabromomethane followed by treatment of trimethyl phosphite to afford the phsophonate **10** in 81 % yield. The Wardworh-Emmons reaction between **10** and **11**[12] smoothly proceeded to yield the bis(dibromostilbene) **12** in 89 % yield. Next catalytic hydrogenation of the double bonds in **12** was troublesome



Reagents and conditions: a) Br_2, $CHCl_3$, 70°C; b) $NaBH_4$, THF, 0°C; c) CBr_4, Ph_3P, MeCN; d) $P(OMe)_3$, 90°C; e) NaH, THF, O°C; f) $LiAlH_4$, THF, 0°C; g) CBr_4, Ph_3P, MeCN; h) $P(OMe)_3$, 90°C; i) NaH, THF, 0°C; j) H_2, PtO_2, CH_2Cl_2; k) NaH, MOMCl, DMF.

due to being accompanied by an unanticipated debromination. After several attempts, **12** was cleanly hydrogenated using PtO_2 as catalyst and methylene chloride as solvent, thereby giving rise to the key intermediate **13** in 73 % yield after the protection of the liberated hydroxy group on the C ring as a MOM ether. We are now ready for performing the key intramolecular C–C ring closure step for the construction of the 16-membered ring.



13 $R_1 = R_2 = Br$
14 $R_1 = R_2 = I$
15 $R_1 = Br$, $R_2 = SnMe_3$ or $R_1 = SnMe_3$, $R_2 = Br$
16 $R_1 = R_2 = H$

17 R =MOM
4 R = H

As first of all, Ni(0) mediated intramolecular coupling[13] which was recently utilized for the construction of the 12-membered vancomysin-type biaryl ring system[14] and the 17-membered ring biaryl system[15] was applied to **13** and **14**[16] but failed to give the cyclized product **17**. Only the reduction product **16** was obtained, while the intramolecular Suzuki-Miyaura Pd(0) catalyzed reaction on **13** using bis(pinacolate)diboron[17] made no C-C bond formation. In contrast, the intramolecular version of Still-Kelly reaction led to the crucial cyclization of **13**. A 0.01 M toluene solution of **13** was heated at 120°C with 1.1 equivalent of hexamethylditin and 5 mol% tetrakis(triphenylphosphine)palladium in the sealed tube to give the cyclized product **17** in 17 % yield along with a trimethylstannyl compound **15** (9 %) and the recovery **13** (45 %). The cyclization of diiodide **14** under the same conditions was comparable to that of **13**. The key intermediate for this ring closure was regarded as the isolated trimethylstannyl compound **15.** In fact, a diluted solution of **15** in toluene, upon treatment of 5 mol% tetrakis(triphenylphosphine)palladium in the sealed tube at 120°C, resulted in the formation of biaryl system **17** in 20 % yield. Finally, removal of the MOM groups in **17** by treatment of 47% HBr in MeOH afforded plagiochin D (**4**) in 87 % yield, all spectral data of which were superimposable with those of natural one.

In conclusion, the intramolecular Still-Kelly reaction was demonstrated to be quite useful for the crucial 16-membered ring formation at the position **b** of **13** in moderate and reproducible yield in spite of accompanying the formation of the dimmers (about 15 %). Thus, we have developed a new approach for the construction of the rigid macrocyclic biaryl ring system of the plagiochins. Further work toward total synthesis of the most biologically intriguing plagiochin A (**1**) is in progress.

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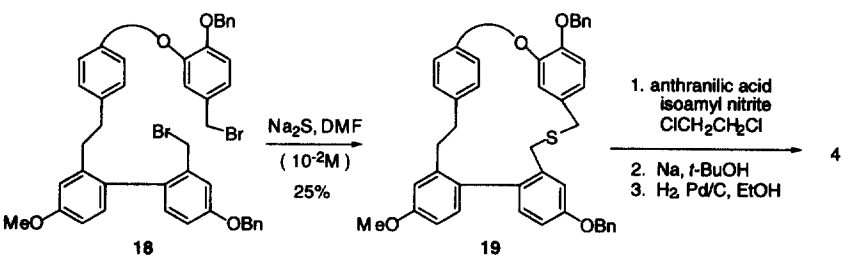

18 **19**

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